VYSOKÁ ŠKOLA
CHEMICKO-TECHNOLOGICKÁ
V PRAZE

Fakulta potravinářské a biochemické technologie

Ústav chemie přírodních látek

Syntéza *C*-glykosidů a *C*-disacharidů

HABILITAČNÍ PRÁCE

pro obor ORGANICKÁ CHEMIE

VYPRACOVAL | **Ing. Kamil Parkan, Ph.D.**

ROK | **2021**

Prohlašuji, že jsem tuto habilitační práci vypracoval samostatně. Veškeré literární prameny a informace, které jsem v práci využil jsou uvedeny v seznamu použité literatury. Prohlašuji rovněž, že na všech výsledcích, které uvádím ve své habilitační práci, mám svůj autorský podíl. Tyto výsledky by však nemohly být získány bez spolupráce a pomoci kolegů a studentů, kteří jsou uvedeni jako spoluautoři a kterým tímto děkuji.

…….

V Praze 2.7. 2021 Ing. Kamil Parkan, Ph.D.

PODĚKOVÁNÍ

Rád bych na tomto místě poděkoval celému kolektivu Ústavu chemie přírodních látek za vytvoření příjemného pracovního prostředí, a zvláště nedávno zesnulé prof. Ing. Jitce Moravcové, CSc. za odborné vedení během mého studia i následné práci. Dále bych rád poděkoval všem, se kterými jsem na výzkumu uvedeném v této práci spolupracoval. Zejména pak mým studentům, kteří vynikali pracovitostí a nezbytnou horlivostí, dále i spolupracovníkům z Ústavu organické chemie a biochemie AV ČR, v.v.i., především Ing. Radku Pohlovi, PhD., za podporu, inspiraci a možnost spolupracovat na zajímavých tématech. Rovněž děkuji své rodině a svým blízkým za podporu a pochopení.

OBSAH

1 ÚVOD

Sacharidy jsou nejrozšířenější skupinou biomolekul na Zemi. Přestože v minulém století hlavní pozornost poutaly nukleové kyseliny a proteiny, postupem času se sacharidy staly hlavním cílem biologického a biochemického výzkumu. Kromě strukturní a metabolické funkce mají totiž i důležitou úlohu v procesech buněčného rozpoznávání, a to zejména ve formě glykokonjugátů. Buňky na svém povrchu nesou komplexní oligosacharidy, které jsou kovalentně vázány k proteinům a lipidům a specificky kódují informaci, která je rozpoznána proteiny druhé buňky pomocí nekovalentních vazeb. Tato komunikace na buněčné úrovni se uplatňuje v řadě klíčových biologických procesů jako jsou např. virová a bakteriální infekce, vznik a růst nádorů a septický šok, které přímo souvisí se smrtelnými onemocněními 21. století jako jsou rakovina, AIDS, meningitida a sepse[1].

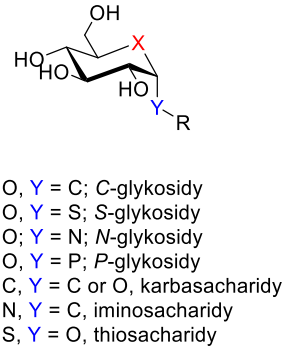
Vzhledem k tomu, že příroda vytvořila neuvěřitelné množství mono-, di- a oligosacharidů, je studium jimi řízených procesů problematické, zejména kvůli omezené dostupnosti syntetických metod pro přípravu glykoproteinů a glykolipidů s dobře definovanou cukernou sekvenci[2, 3].

Dalším faktorem, který zatím brání širšímu využití sacharidů jako potenciálních terapeutik, je jejich vysoká hydrofilita, která umožňuje sacharidům se vázat ke svým receptorům převážně pomocí nevazebných interakcí, jako je vodíková vazba, asociace s kovy, nepolární anebo iontová vazba. Dále vysoká hydrofilita neumožňuje použití terapeutik perorálně. Limitujícím faktorem sacharidů je i jejich glykosidová vazba (*O*-acetalová vazba), která za fyziologických podmínek snadno podléhá hydrolýze a terapeutikum je pak v organismu nestabilní. Nedávné pokroky však ukázaly, že některé z těchto problémů lze řešit použitím tzv. glykomimetik[4], což jsou látky, které napodobují strukturu a funkci sacharidu, a přitom jsou hydrolyticky stabilnější.

1.1 Glykomimetika

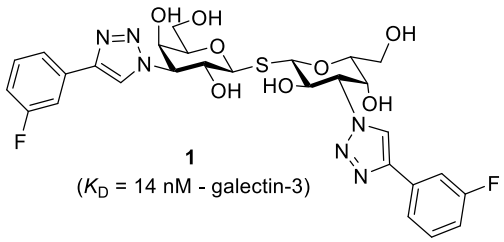
Stejně jako peptidomimetika jsou stabilní vůči proteasam, tak i glykomimetika jsou analogy přírodních sacharidů, které jsou odolné vůči glykosidasam a glykosyltransferasam, ale také většinou vykazují větší stabilitu v kyselém prostředí. Byly vyvinuty různé syntetické přístupy, které se dokážou vypořádat s labilitou obcházejí glykosidové vazby. Na **obrázku 1** je schematicky naznačeno, že toho lze dosáhnout buď náhradou kyslíku pyranosového kruhu

(iminosacharidy[5], karbasacharidy[6, 7], thiosacharidy[8]) nebo náhradou anomerního kyslíku (*C*--glykosidy, *N*-glykosidy, *S*-glykosidy, *P*-glykosidy)[9].



Obrázek 1: Glykomimetika získaná modifikací *O*-glykosidů

Nejběžnějšími modifikacemi jsou *S*-, *N*- a *C*-glykosidy. Jako příklad stabilního *S*-glykomimetika, které je specifickým nanomolárním inhibitorem galektinu-3, lze uvést TD139 (**1**), který prošel v roce 2017 první fází klinického testováním jako lék proti idiopatické pulmonální fibróze[10, 11]. (**Obr. 2**) Pokud porovnáme stabilitu těchto glykomimetik s přírodními *O*-glykosidy, náhrada anomerního kyslíku atomem síry nebo dusíkem vede k odlišné reaktivitě a stabilitě těchto analogů. Pokud však nahradíme anomerní spojení vazbou C-C nebo methylenovou spojkou, zůstane nám pouze etherová vazba, a tím tvorba stálých analogů, které se souhrnně nazývají *C*-glykosidy.

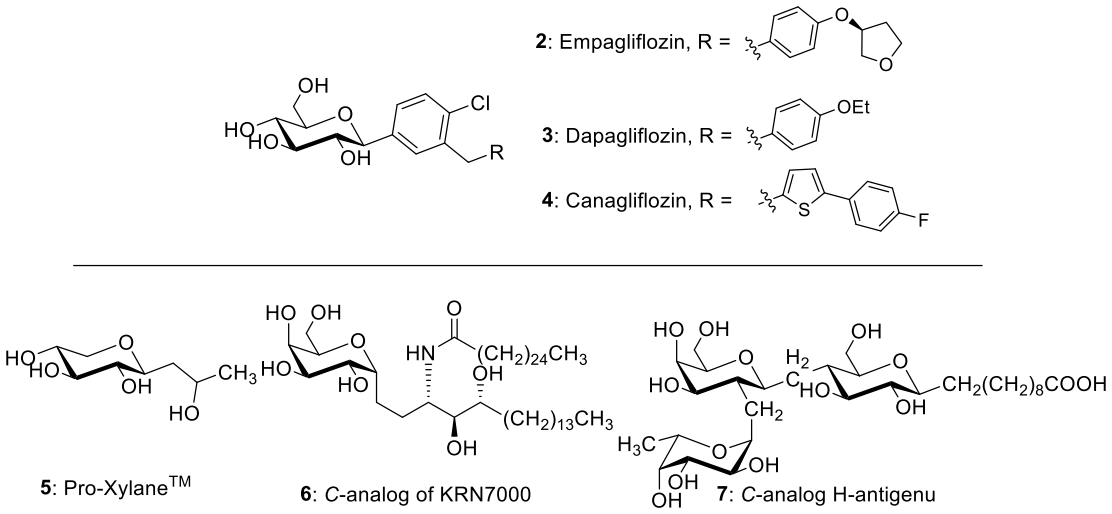


Obrázek 2: Stabilní *S*-glykomimetikum TD139 (**1**)

1.2 Přírodní a syntetické *C*-glykosidy

C-Glykosidy resp. *C*-disacharidy jsou analogy přírodních sacharidů, u kterých je C-O glykosidová/*O*-acetalová vazba mezi sacharidovou jednotkou a aglykonem nebo další sacharidovou jednotkou nahrazena C-C vazbou resp. methylenovou spojkou (CH_2). Díky tomu jsou *C*-glykosidy stálé vůči hydrolytickým enzymům *in vivo* i vůči kyselé hydrolýze, a jsou

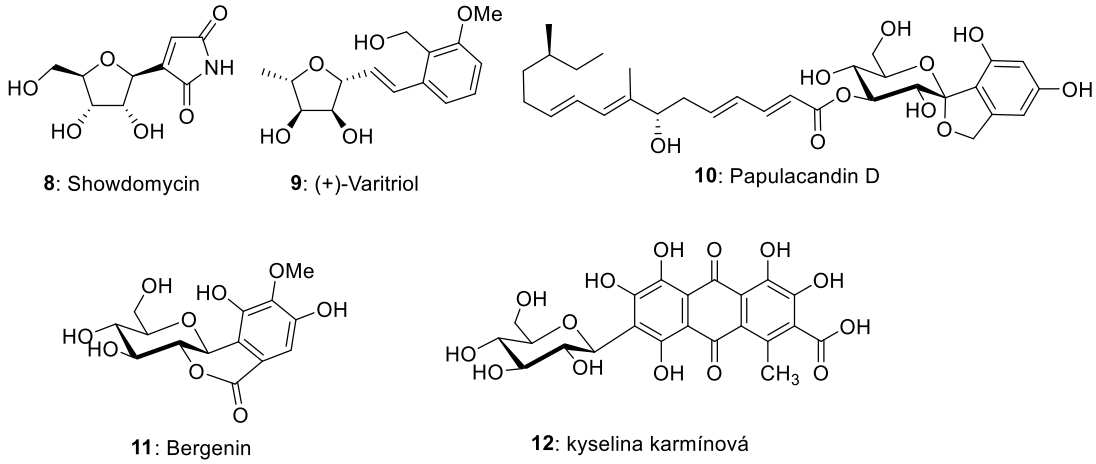
proto často obvyklou volbou syntézy analogů přirozených *O*-glykosidů jako potencionálních terapeutik[9, 12-17]. Jako úspěšný příklad z posledních let lze uvést objevení série antidiabetik (např. empagliflozin **2**, dapagliflozin **3**, canagliflozin **4**)[18-22], které jsou SGLT2 inhibitory a způsobují glykosurii blokováním zpětné resorpce glukosy v proximálním tubulu ledvin. Dalším komerčně používaným *C*-glykosidem je Pro-Xylane™ **5** [23, 24], který byl vyvinut firmou L´Oréal a je využíván jako populární kosmetická látka proti stárnutí. Jako příklad *C*-oligosacharidů, které jsou enzymaticky stálé, a přesto jsou biologicky aktivní lze uvést *C*-analog KRN7000 (**6**) [16, 17] a *C*-mimetikum H-antigenu **7** [25] krevní skupiny 0. (**Obr. 3**)



Obrázek 3: Příklady *C*-analogů se zajímavými biologickými vlastnostmi

Na druhou stranu, celá řada *C*-glykosidů jsou přírodní produkty převážně sekundárního metabolismu bakterií a rostlin s významnou biologickou aktivitou[26]. Jako příklady lze uvést některé, které se z důvodu studia jejich aktivity podařilo připravit pomocí organické syntézy. Jako první bych uvedl přírodní antibiotikum showdomycin **8** [27], který byl izolován z bakterie *Streptomyces showdoensis* a vykazuje antivirální, antibakteriální, ale i protirakovinové účinky. Dále lze zmínit například cytotoxický (+)-varitriol **9** [28, 29], který byl izolován[30] z kmene mořské houby *Emricella variecolor* nebo fungicidní papulacandin D **10** [31]. Dalším zajímavým přírodním *C*-glykosidem je bergenin **11**, jehož první totální syntéza je popsána v **Příloze IV** [32]. Tento *C*-glykosid je derivátem kyseliny gallové a vykazuje zajímavé farmakologické vlastnosti, jako jsou hepatoprotektivní ale i hepatotoxické, antiulcerogenní, fungicidní, anti-HIV, antiarytmické, neuroprotektivní, protizánětlivé a imunomodulační účinky. Byl izolován z celé řady rostlin. Jako příklad lze uvést extrakt z rostliny *Macaranga peltata*, který obsahuje bergenin, a je běžně používán v indické lidové medicíně při léčbě

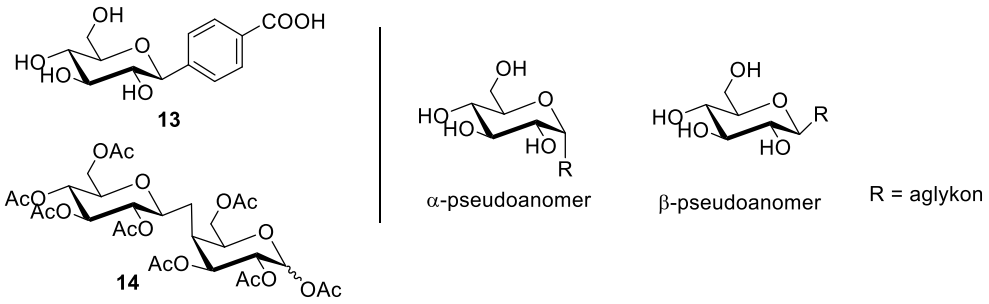
pohlavních chorob[33]. Bergenin samotný je také aktivní farmakologickou složkou léků proti kašli a bronchitidě v čínské medicíně[34]. Dalším příkladem může být i kyselina karmínová **12**, která se pod označením E120 používá jako potravinářské barvivo. Tato kyselina má živočišný původ a získává se extrakcí z vysušených tělíček samiček červce nopálového (*Dactylopius coccus*). Na tomto místě bych rád zmínil, že o optimalizaci její výroby se v roce 1985 zasloužili i pracovníci našeho Ústavu chemie přírodních látek[35]. (**Obr. 4**)



Obrázek 4: Příklady přírodních *C*-glykosidů, které byly syntetizovány

1.3 Nomenklatura *C*-glykosidů

Protože v této práci jsou používány termíny jako *C*-glykosid a *C*-disacharid, je třeba si tyto a další související pojmy definovat. Přestože výrazy *C*-glykosid a *C*-disacharid se v odborné literatuře běžně používají, podle platné nomenklatury správné nejsou. Protože tyto sloučeniny formálně vznikají ztrátou anomerní hydroxylové skupiny sacharidu a vytvořením vazby k uhlíku jiné sloučeniny, jsou nazývány s použitím příslušné předpony typu glykosyl-. Proto podle platné nomenklatury[36] je pro látku **13** správný název kyselina 4-β-D--glukopyranosylbenzoová a nikoliv 4-kaboxyfenyl-*C*-β-D-glukopyranosid. (**Obr. 5**). U *C*--disacharidu **14** je situace ještě komplikovanější a podle této nomenklatury je možné použít název 1,2,3,6-tetra-*O*-acetyl-4-deoxy-4-(3,4,5,7-tetra-*O*-acetyl-2,6-anhydro-1-deoxy-D--*glycero*-D-*gulo*-heptitol-1-yl)-α,β-D-galaktopyranosa a dále uznávaný je i název 1,2,3,6-tetra--*O*-acetyl-4-deoxy-4-*C*-(2,3,4,6-tetra-*O*-acetyl-β-D-glukopyranosylmethyl)-α,β-D--galaktopyranosa. (**Obr. 5**)



Obrázek 5: Příklady *C*-glykosidů

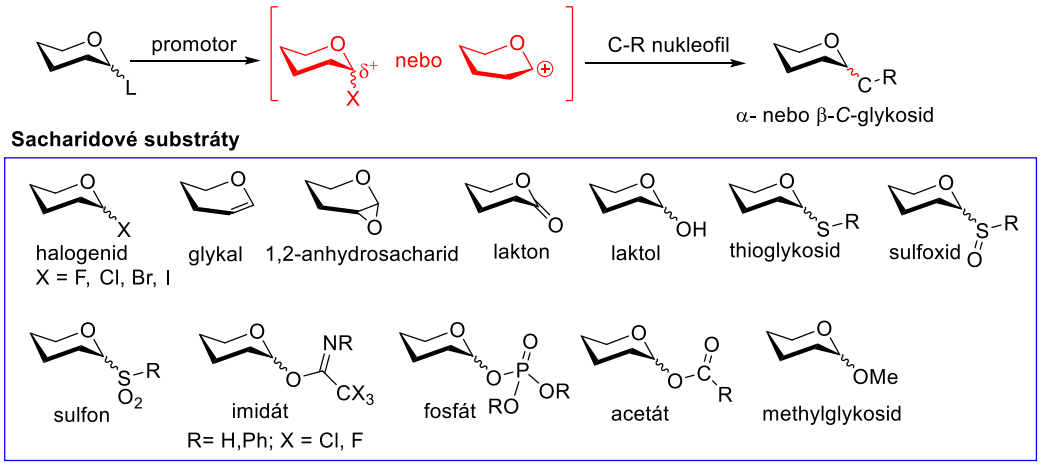
Pokud se zmiňuji o *C*-glykosidech a *C*-disacharidech, je zapotřebí vysvětlit i to co znamenají termíny pseudoanomerní uhlík, α- a β-pseudoanomer. Jako anomerní se u aldos označuje uhlík nacházející se v poloze 1, který je acetalovou vazbou vázán k exocyklickému atomu kyslíku. Používat stejné označení i v případě *C*-glykosidů resp. *C*-disacharidů však není zcela správné, neboť uhlíkový atom C-1 je vázán k exocyklickému uhlíkovému atomu. Proto je vhodnější používat termíny pseudoanomerní uhlík a příslušné epimery nazývat jako α- a β--pseudoanomer. (**Obr. 5**)

1.4 Syntéza *C*-glykosidů

Vůbec první syntéza *C*-glykosidů se datuje do období 1945-1950, kdy prof. Hurd využil reaktivitu Grignardových činidel s glykosyl halogenidy[37, 38]. Od této doby bylo pro syntézu rozmanitých *C*-glykosidů, *C*-disacharidů, ale i *C*-oligosacharidů, nalezeno velké množství různých syntetických přístupů, jejichž plný výčet přesahuje rozsah této práce. Případné zájemce o tuto problematiku bych odkázal na přehledné články z posledního období[39-59]. Tyto syntetické přístupy lze podle použitého glykosyl donoru (prekursoru) rozdělit do 6 hlavních skupin. (**Obr. 6-11**)

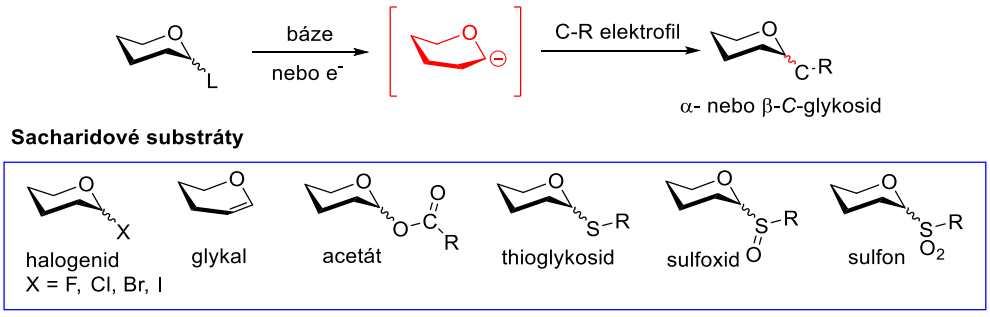
Protože povaha anomerního centra je z hlediska reaktivity elektrofilní a jeho elektrofilita může být navýšena převedením anomerní hydroxylové skupiny na lépe odstupující skupinu (např. halogen, acetát, imidát atd.), je nejrozšířenější přístup pro tvorbu *C*-glykosidické vazby založen na ataku nukleofilního uhlíku na anomerní centrum elektrofiního glykosyl donoru. Na **obrázku 6** je elektrofilní anomerní centrum naznačeno karbokationtem, ale *C*-glykosidy lze připravit i pomocí mechanismu S_N2 substituce, popřípadě přes iontový pár v závislosti na povaze nukleofilu. Karbanionty jsou například malonáty, nitromethan, kyanidové anionty a organokovová činidla jako jsou např. Grignarova činidla, která s výše zmíněnými glykosyl donory tvoří *C*-glykosidy. Alternativně lze anomerní kation generovat např. pomocí Lewisovy

kyseliny, a ten může následně reagovat s dvojnou vazbou např. allyl-, vinyl- a propargylsilanu, silylenoletheru, enaminů, ale také s jednoduchými alkeny a aktivovanými aromatickými sloučeninami. Pro přípravu *C*-glykosidů mohou být použity i laktony. V tomto případě lakton reaguje s organolithnou sloučeninou za vzniku laktolu, který může být následně redukován na odpovídající *C*-glykosid za katalýzy Lewisovou kyselinou v přítomnosti triethylsilanu. Dále je možné příslušné *C*-glykosidy tvořit nukleofilní atakem oxiranového kruhu v 1,2--anhydrocukrech.



Obrázek 6: Syntéza *C*-glykosidů za využití anomerního glykosyl elektrofilu/kationtu

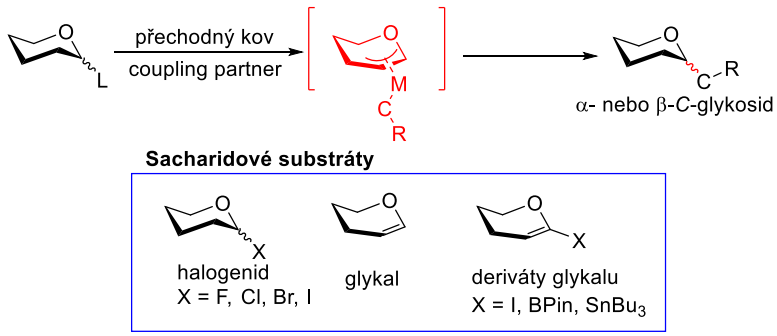
U některých vhodně chráněných sacharidových donorů, lze pomocí organolithných sloučenin (silných bází) generovat *in situ* na anomerním centru karbanion, který se může chovat jako nukleofil. (**Obr. 7**) Pak se jako C-R elektrofil hojně používají různé deriváty aldehydů, ketonů nebo oxid uhličitý. Tento syntetický přístup, je asi jednou z nejefektivnějších cest přípravy *C*-glykosidů.



Obrázek 7: Syntéza *C*-glykosidů za využití anomerního glykosyl aniontu

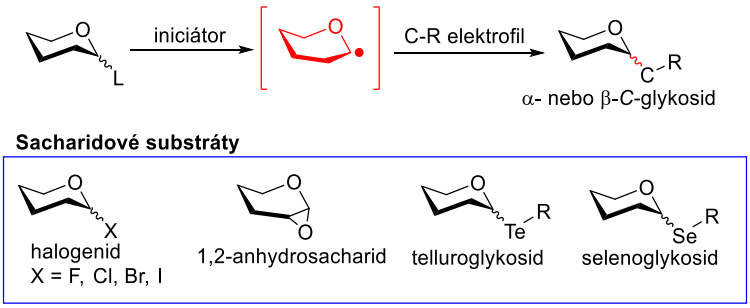
Takto *in situ* generované karbanionty jsou také často využívány i pro přípravu glykosyl donorů, které se využívají pro syntézu *C*-glykosidů za katalýzy přechodnými kovy. Tyto

syntetické přístupy využívají různé „cross-coupling“ reakce, jako je například Heckova, Stilleho, Sonogashirova, Suzukiho-Miyaurova reakce, které jsou převážně katalyzovány přechodnými kovy (Pd, Ni, atd.). Tyto reakce lze dále rozdělit z hlediska reagentů na sp^2-sp^2 „cross-coupling“ reakce, které jsou založeny na reakci elektronově bohatých glykosyl donorů s elektronově bohatými elektrofily (např. aryl, heteroaryl nebo alkenyl halogenidy) (**Příloha IV** a **IX-X**). Na druhou stranu pro přípravu *C*-glykosidů, lze využít ze syntetického hlediska i mnohem obtížnější sp^2-sp^3 „cross-coupling“ reakci, kdy jedním z partnerů je elektronově chudý alkyl halogenid. (**Příloha V**) (**Obr. 8**)



Obrázek 8: Syntéza *C*-glykosidů pomocí přechodných kovových komplexů

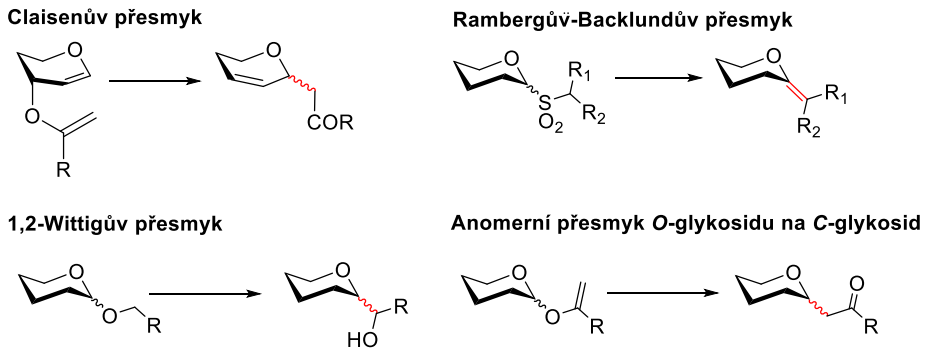
Dále může být anomerní centrum také převedeno na radikál. Jako výchozí prekursory jsou převážně využívány opět glykosyl halogenidy, ale i seleno-, telluroglykosidy a 1,2--anhydrosacharidy. Příslušné radikály mohou být generovány buď ozářením nebo použitím vhodného promotoru jako je. například AIBN. Vzniklý radikál pak obvykle reaguje buď s allylstanany, allylthioethery, anebo s různými alkeny, které jsou aktivovány elektronakceptorními skupinami.



Obrázek 9: Syntéza *C*-glykosidů pomocí glykosyl radikálu

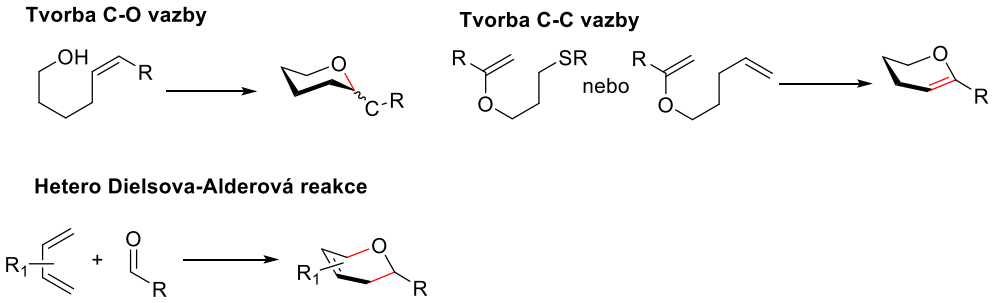
Další neméně zajímavé, jsou syntetické přístupy, které využívají pro přípravu různých *C*--glykosidů sigmatropní přesmyky předem připravených sloučenin. Jako příklady lze uvést

Claisenův, Ramergův-Bäklundův a 1,2-Wittigův přesmyk. (**Obr. 10**) Na tomto místě je nutné zmínit, že tyto přesmyky většinou probíhají za retence konfigurace na anomerním centru.



Obrázek 10: Příprava *C*-glykosidů za využití přesmyků

Pro přípravu *C*-glykosidů byly využity i postupy využívající intra- nebo intermolekulární cyklizační reakce, které tvoří pyranový/furanový kruh *C*-glykosidů tzv. *de novo* z vhodných acyklických syntonů. (**Obr. 11**) Jako příklad lze uvést např. oxa-Michaelovu cyklizaci δ-hydroxylkenů nebo γ-hydroxyalkenů v přítomnosti různých promotorů reakce. V tomto případě vzniká pyranový kruh vznikem C-O vazby. Velice populární je i tvorba dihydropyranového kruhu za použití intramolekulární „cross-metateze" acyklických alkenů. Za těchto podmínek dihydropyranový kruh vzniká tvorbou C-C vazby. Na tomto místě nelze zapomenout ani na syntetické přístupy, které pro tvorbu dihydropyranového kruhu využívají stereoselektivní hetero-Dielsovu-Alderovu reakci připraveného dienu s vhodným dienofilem. (**Obr. 11**) Jak bude ukázáno dále, i tento přístup jsem využil při syntéze (1→3)-*C*-vázaných disacharidů. (**Přílohy I-III** a **VII**)



Obrázek 11: Příprava *C*-glykosidů za tvorby sacharidového kruhu *de novo*

Na závěr této kapitoly bych rád zmínil, že kontrola stereochemie při tvorbě *C*-glykosidové vazby je obvykle velice obtížná a závisí nejen na použitém syntetickém postupu, ale také na

typu a povaze substrátu. Obecně ale lze říci, že těmito postupy lze stereoselektivně připravit jak α- tak i β-*C*-glykosidy.

2 SOUHRN VLASTNÍCH VÝSLEDKŮ

V průběhu posledních let se věnuji problematice nalezení nových a zefektivnění stávajících streoselektivních syntéz *C*-glykosidů a *C*-disacharidů. Jak již bylo zmíněno v úvodu, syntéza těchto glykomimetik není triviální záležitostí. Především z důvodu rozmanitosti a různé reaktivity stavebních bloků (monosacharidových jednotek) a možných typů vazeb mezi nimi. Problémem při jejich syntéze je často také stereoselektivita tvorby pseudoglykosidové vazby a také volba vhodných chránících skupin.

Soubor vybraných experimentálních výsledků, který je předmětem této habilitační práce, chronologicky reflektuje tématiku řešenou v rámci mého doktorského studia a nezávislé vědecko-pedagogické činnosti na VŠCHT v Praze. Lze je tematicky rozdělit do dvou hlavních skupin:

1. Stereoselektivní syntéza *C*-disacharidů a *C*-glykosidů za využití α- a β-glykopyranosylpropenu.
2. Stereoselektivní syntéza *C*-glykosidů a *C*-disacharidů pomocí „cross-coupling“ reakcí.

2.1 Stereoselektivní syntéza *C*-disacharidů a *C*-glykosidů za využití α- a β-glykopyranosylpropenu

Pro přípravu *C*-glykosidů popř. *C*-disacharidů lze využít široké spektrum syntetických přístupů. Obecně lze ale říci, že pro přípravu *C*-disacharidů se využívá hlavně dvou postupů. Buď se jedná o stereoselektivní spojení dvou cukerných jednotek (monosacharidů, popřípadě synthonů odvozených od těchto monosacharidu), nebo se na daný výchozí monosacharid připojí uhlíkový řetězec a z něj se stereoselektivně vystaví druhý monosacharid (tzv. syntéza *C*-disacharidu *de novo*).

Ve své první publikované práci (**Příloha I**) jsem se zaměřil na přípravu (1→3)-*C*--disacharidů **15ab** a **16ab**, jejichž syntéza byla založena právě na *de novo* syntéze druhé cukerné jednotky pomocí hetero-Dielsovy-Alderovy reakce (HDA reakce) z α-D-galaktopyranosyl propenu **17**. Tato práce vycházela z předchozích výsledků[60, 61] naší laboratoře a mým hlavním cílem bylo obejít slabiny těchto dříve publikovaných postupů. (**Schéma 1**)

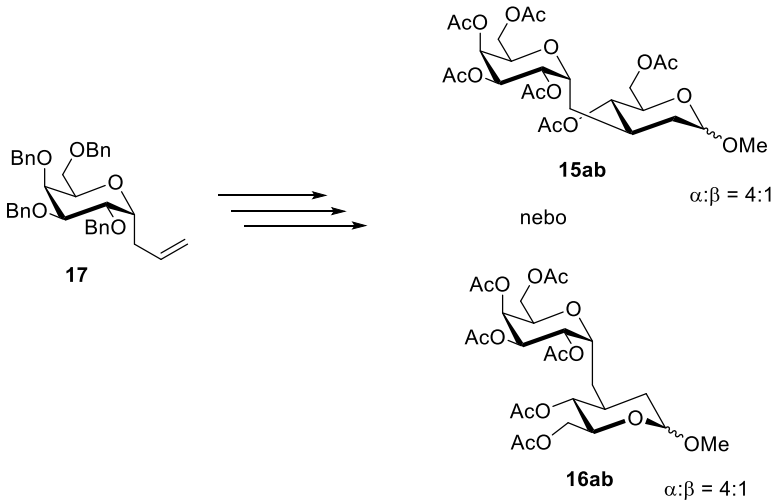


Schéma 1

Volba přípravy těchto *C*-analogů přírodních disacharidů byla volena cíleně, neboť vazba α-D-galaktopyranosylu vázaného glykosidovou vazbou (1→3) k oligosacharidovému řetězci se vyskytuje v řadě přírodních epitopů. Jako příklad lze uvést pentasacharidový α--galaktosylovaný antigen krevní skupiny B (Galα1-3Galβ1-4GlcNAcβ1-3Galβ1-4Glcβ-R), který je odpovědný za hyperakutní odmítnutí orgánu při xenotransplantacích[62]. Syntézou podobného stereoisomerního *C*-analogu přírodních disacharidů β-D-Gal*p*(1→3)-D-Gal*p* se například zabýval profesor Vogel, který pro přípravu tohoto *C*-disacharidu využil mnohem pracnější cestu vycházející z isolevoglukosenonu[63].

Syntetickým přístupem k *C*-disacharidům se v naší laboratoři zabývali i mí spolupracovníci, ale pokud byl při HDA reakci (*E*)-(4-tetra-*O*-benzyl-α-D-galaktopyranosyl)--1-thiazol-2-yl)-but-2-en-1-onu **18** použit achirální vinylether vznikala nedělitelná směs dvou diasteromerních *endo* cykloaduktů, v poměru 1:1. Proto jsem pro HDA reakci použil enantiomerně čisté chirální vinylethery **19** a **20**, které lze snadno připravit[64-66] z D- a L--enantiomerů kyseliny mandlové. Při použití chirálních vinyletherů byla cykloadiční reakce vysoce stereoselektivní a při použití *R*-epimeru **19** za katalýzy Lewisovou kyselinou $Eu(fod)_3$ vznikal pouze cykloadukt **21**. Na druhou stranu, pokud byl použit chirální vinylether s *S*-konfigurací **20**, byl získán cykloadukt **22**. (**Schéma 2**) Cykloadiční reakce byla výlučně *endo* selektivní, což bylo potvrzeno pomocí NOE NMR experimentů. Absolutní konfigurace 2*R*,4*R* na stereogenních centrech nově vznikajícího dihydropyranového kruhu cykloaduktu **22** byla zpětně určena pomocí X-ray analýzy[61] krystalického derivátu, který byl získán z derivátu **22**.

Z toho vyplývá, že cykloadukt **21**, který vznikl po cykloadici chirálního vinyletheru s opačnou konfigurací (tj. **19**), musí obsahovat dihydropyranový kruh s konfigurací 2*S*,4*S*.

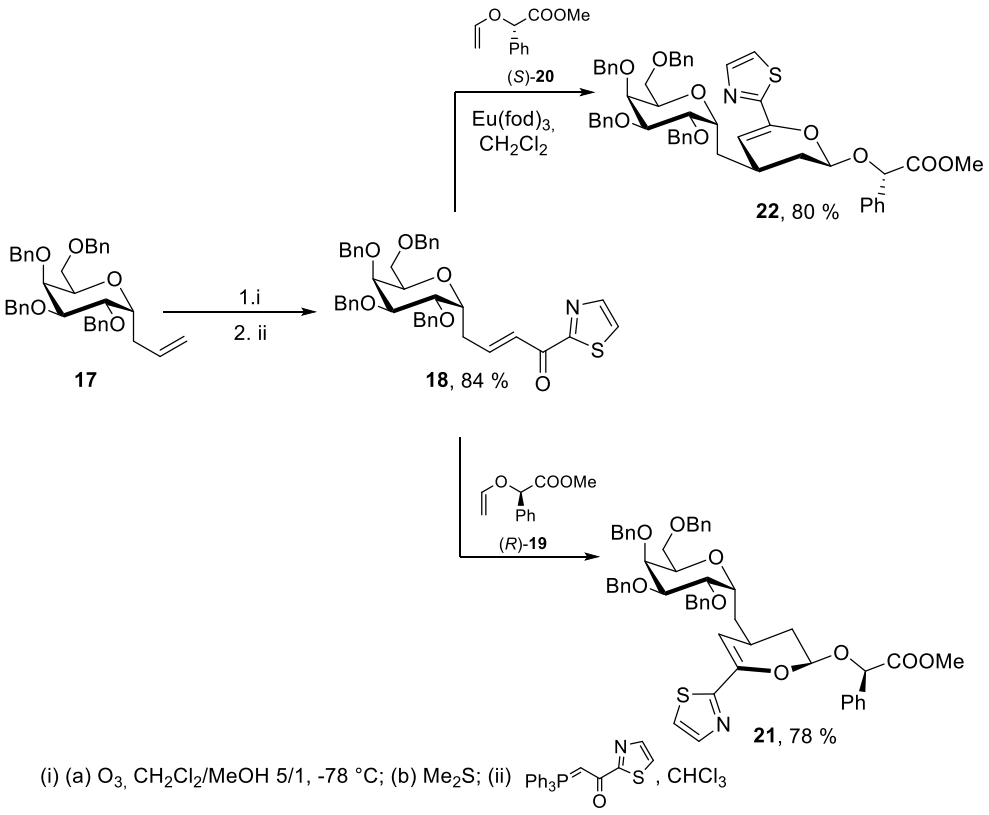
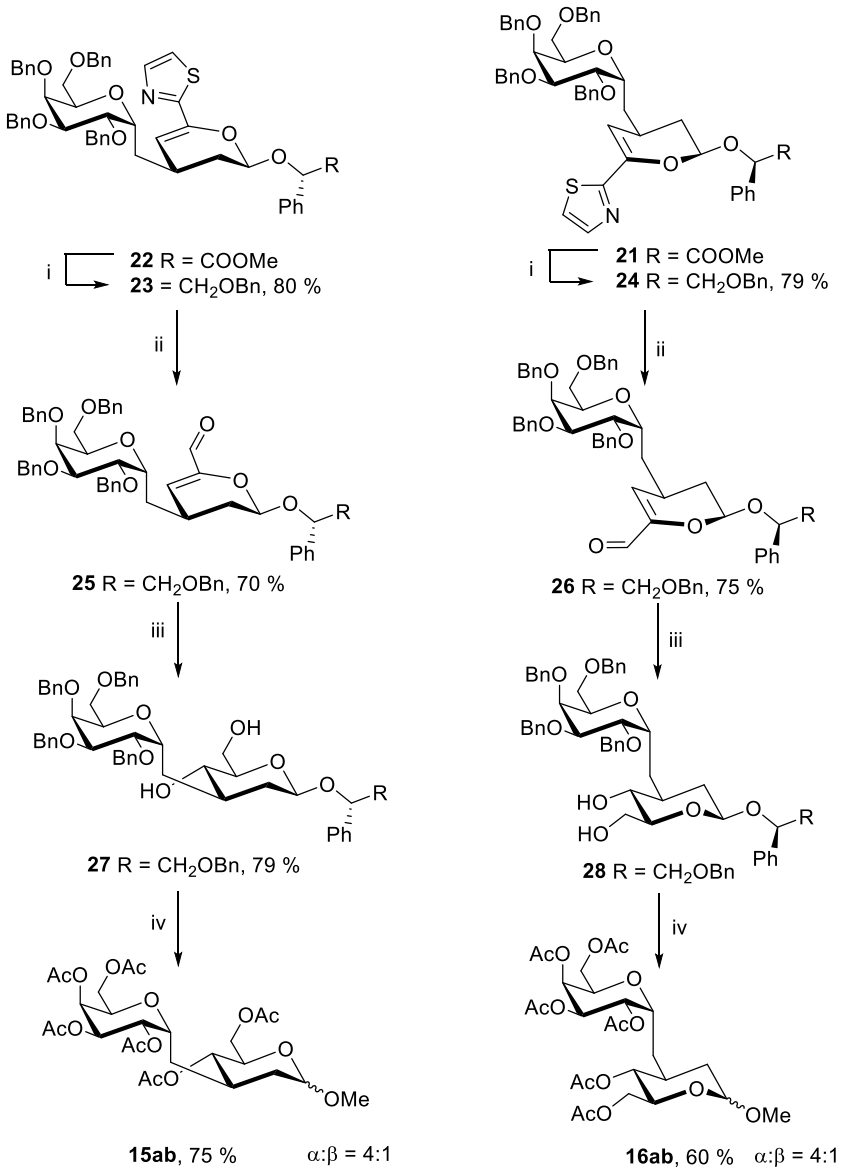


Schéma 2

Dále bylo nutné optimalizovat i následnou transformaci dihydropyranového kruhu, protože při transformaci thiazolového kruhu na aldehyd docházelo k vzniku nedělitelné směsi produktů. Tyto problémy byly překonány redukcí methylesterů a následnou benzylací volné hydroxylové skupiny obou cykloaduktů za vzniku látek **23** a **24**. Pak již bylo možné bez problému transformovat thiazolový kruh na aldehydy **25** a **26**. (**Schéma 3**)



(i) 1. $LiAlH_4$, THF, 2. 60% NaH, BnBr, TBAI, THF; (ii) 1. TfOMe, MeCN, 2. $NaBH_4$, MeOH, 3. $AgNO_3$, H_2O, MeCN; (iii) 1. a) $BH_3.Me_2S$, THF, b) 30% H_2O_2, 30% $NaOH_{aq}$, 2. 60% NaH, BnBr, TBAI, THF; (iv) 1. MeOH, 3M HCl, THF, 2. H_2, Pd/C, 3. Ac_2O, pyridin

Schéma 3

Následná redukce aldehydové skupiny a současná stereoselektivní hydroborace nadbytkem komplexu boranu s dimethylsulfidem ($BH_3.Me_2S$) vedla ke vzniku *C*-disacharidů **27** a **28**. Pro potvrzení konfigurace připravených látek NMR experimenty byly pomocí tří reakčních kroků připraveny *C*-analogy methyl glykosidů **15ab** a **16ab** s konfigurací α-D-Gal*p*--(1→3)-D-2-deoxy-Ara*p*OMe a α-D-Gal*p*-(1→3)-L-2-deoxy-Ara*p*OMe, které vznikaly jako směsi α- a β-anomerů v poměru 4:1. (**Schéma 3**)

Na základě těchto výsledků jsem se dále rozhodl ověřit, zda je nově nalezený postup možné využít i pro přípravu dalších (1→3)-*C*-disacharidů z glykosylpropenů **29** a **30** s konfigurací β-D-*gluko*, α-6-deoxy-L-*galacto*. (**Příloha II**) Dalším cílem bylo nalezení syntetického postupu, který by umožnil vzniklé dihydropyranové kruhy cykloaduktů **31**-**33** transformovat až na D- a L- 1,5-anhydro-2,3,-dideoxy-*arabino*-hex-1-enitoly **34**-**36** (D- a L--glukaly), které by byly vhodnými substráty v syntéze sacharidů a umožnily by pak pomocí jedno- nebo dvoukrokové syntézy připravit gluko-[67, 68] nebo mannopyranosylglykosidy[69], glykosidy glukosaminu[70], nebo mannosaminu[71] nebo i jiného *C*-glykosidu[72, 73]. Lze také předpokládat, že by mělo být možné připojit takto připravená α- nebo β-(1→3)-*C*-disacharidová mimetika i k oligosacharidovému, peptidovém nebo lipidovém derivátu, jak pomocí glykosidové, tak i C-C vazby, což by umožnilo připravit různé stabilní nehydrolyzovatelné glykokonjugáty.

Jako výchozí látky jsem využil snadno připravitelné glykopyranosylpropeny **29ab** a **30**. Příslušný diastereomerně čistý α-L-fukopyranosylpropen **30** byl připraven pomocí publikovaného postupu[74]. Následnou Wittigovou reakcí aldehydu **37** se stabilizovaným ylidem **38** byl získán oxadien **39**. (**Schéma 4**)

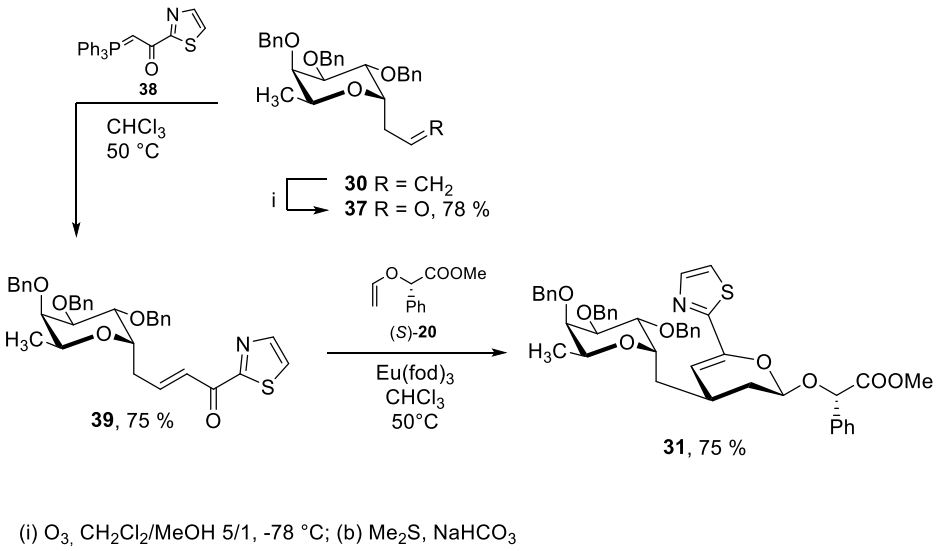
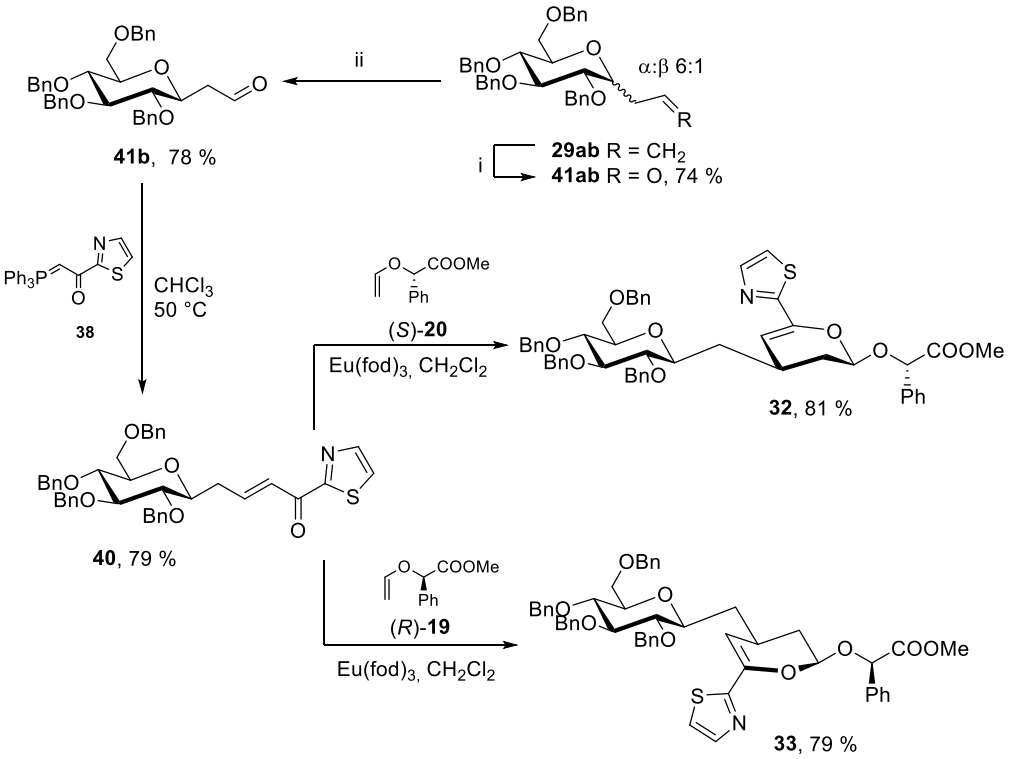


Schéma 4

Pro přípravu oxadienu **40** byla použita epimerní směs α- a β-pseudoanomerů D--glukopyranosylpropenu **29ab** v poměru 6:1, která byla ozonolýzou převedena na pseudoanomerní směs D-glukopyranosylethanalu **41ab** ve stejném poměru. V této fázi bylo možné pomocí 1% K_2CO_3 v methanolu tuto směs epimerizovat a získat pouze termodynamicky

stabilnější β-pseudoanomer **41b**, který byl jako v předchozích případech převeden pomocí Wittigovy reakce s ylidem **38** na příslušný oxadien **40** s *trans*-konfigurací. (**Schéma 5**) Takto připravené oxadieny **39** a **40** byly následně podrobeny HDA reakci s enantiomerně čistými chirálními vinylethery **19** a **20** a byly získány tři očekávané cykloadukty **31**-**33** s vysokou stereoselektivitou. (**Schéma 4** a **5**)



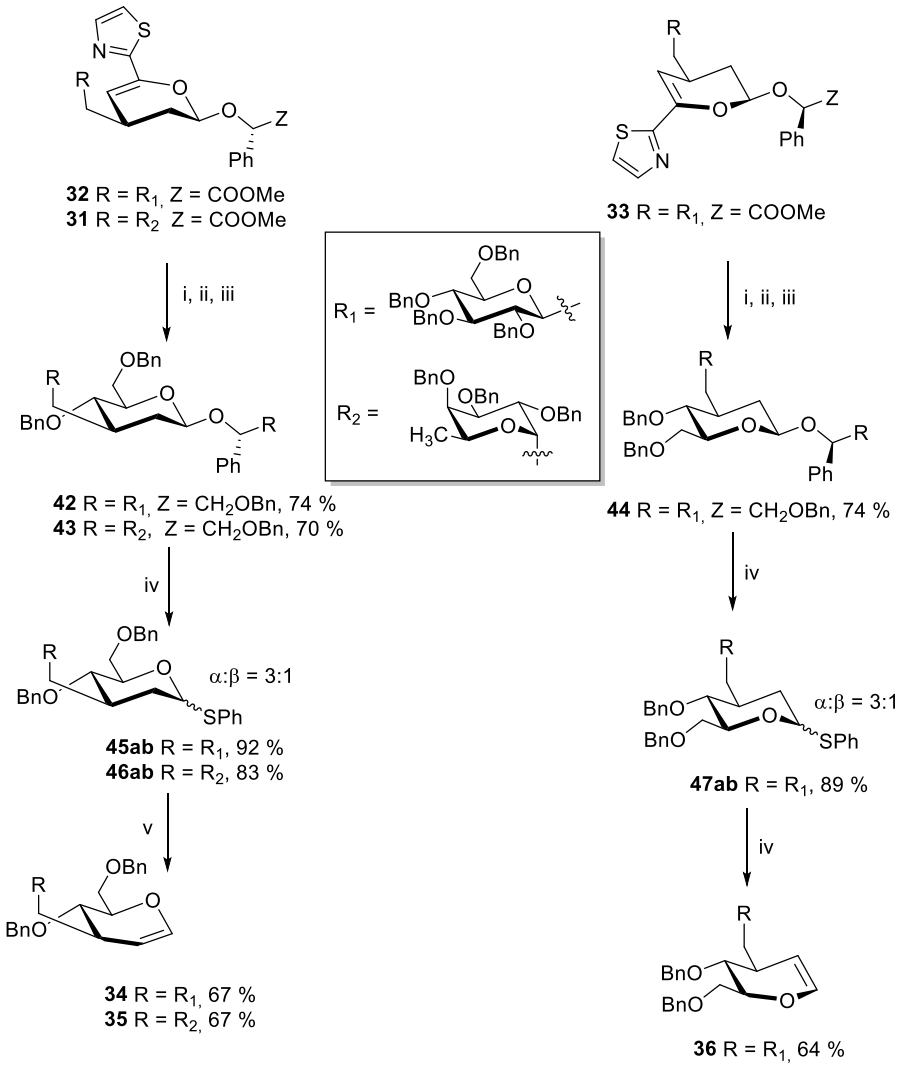
(i) (a) O_3, CH_2Cl_2/MeOH 5/1, -78 °C; (b) Me_2S, $NaHCO_3$, (ii) 1% K_2CO_3/MeOH

Schéma 5

Jak je naznačeno ve **schématu 6**, připravené deriváty **31**-**33** byly dříve optimalizovaným postupem (**Příloha I**) postupně transformovány na deriváty **42**, **43** a **44**. Protože cílem této práce bylo připravit substituované D- a L-glykaly **34**-**36**, bylo nutné nalézt syntetický přístup, který by to umožnil. Proto byl u všech *C*-disacharidů **42**-**44** chirální aglykon nejprve substituován thiofenolem, za vzniku směsi thioglykosidů **45ab**, **46ab**, **47ab** v poměru α:β 3:1. (**Schéma 6**)

Anomerní směs látek **45ab**-**47ab** byla následně podrobena reakci s *N*--bromsukcinimidem ve vodném acetonu za vzniku anomerní směsi *C*-disacharidů s volnou OH skupinou. Vzniklý anomerní hydroxyl byl následně mesylován a vzniklý mesyl byl

v přítomnosti silné báze *in situ* eliminován za vzniku D- popř. L-glukalů **34**, **35** a **36**. (**Schéma 6**)

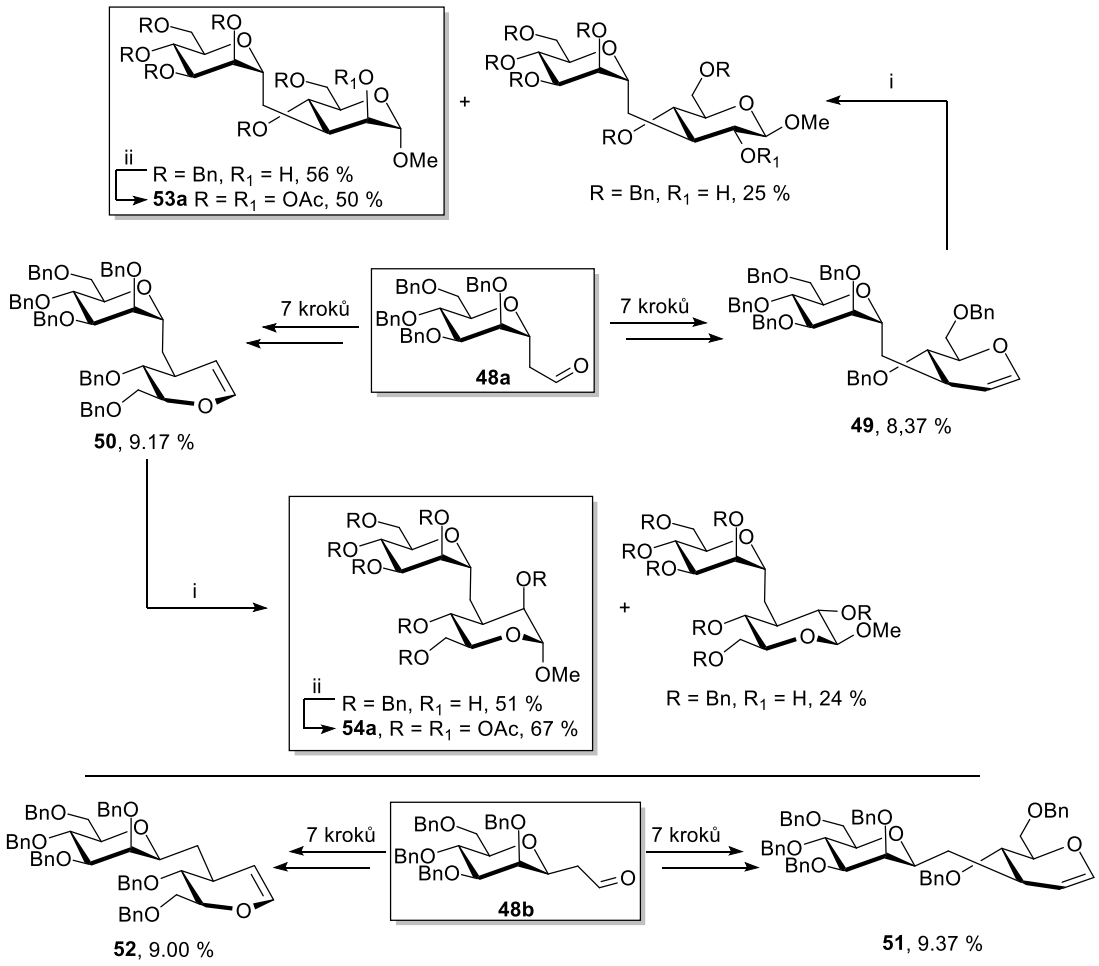


(i) (a) 1. $LiAlH_4$, THF, 2. 60% NaH, BnBr, TBAI, THF, 40 °C; (ii) 1. TfOMe, MeCN, 2. $NaBH_4$, MeOH, 3. $AgNO_3$, H_2O, MeCN; (iii) 1. a) $BH_3.Me_2S$, THF, b) 30% H_2O_2, 30% $NaOH_{aq}$, 2. 60% NaH, BnBr, TBAI, THF, 40 °C; (iv) PhSH, $BF_3.Et_2O$, CH_2Cl_2, -78-25 °C; (iv) (a) NBS, 1% H_2O v acetonu, -15 °C; (b) Ms_2O, *s*-kolidin, CH_2Cl_2, 0 °C

Schéma 6

V další práci (**Příloha III**) je popsán syntetický přístup, který umožňuje z výchozího α--D-mannopyranosylethenalu **48a** připravit opět za pomocí HDA reakce s již dříve zmíněnými chirálními vinyl ethery příslušné 3-*C*-α-D-mannopyranosylované 1,2-glukaly **49** a **50** jak s konfigurací D- tak i L-. Dále se mi podařilo potvrdit, že epimerizací α-aldehydu **48a** lze připravit příslušný β-pseudoanomer **48b**, který lze opět pomocí stejného postupu využít pro přípravu i 3-*C*-β-D-mannopyranosylovaného D- a L-glukalů **51** a **52**. Konformace připravených D- a L-glukalů **49** a **50** byla následně potvrzena pomocí NMR experimentu po transformaci na

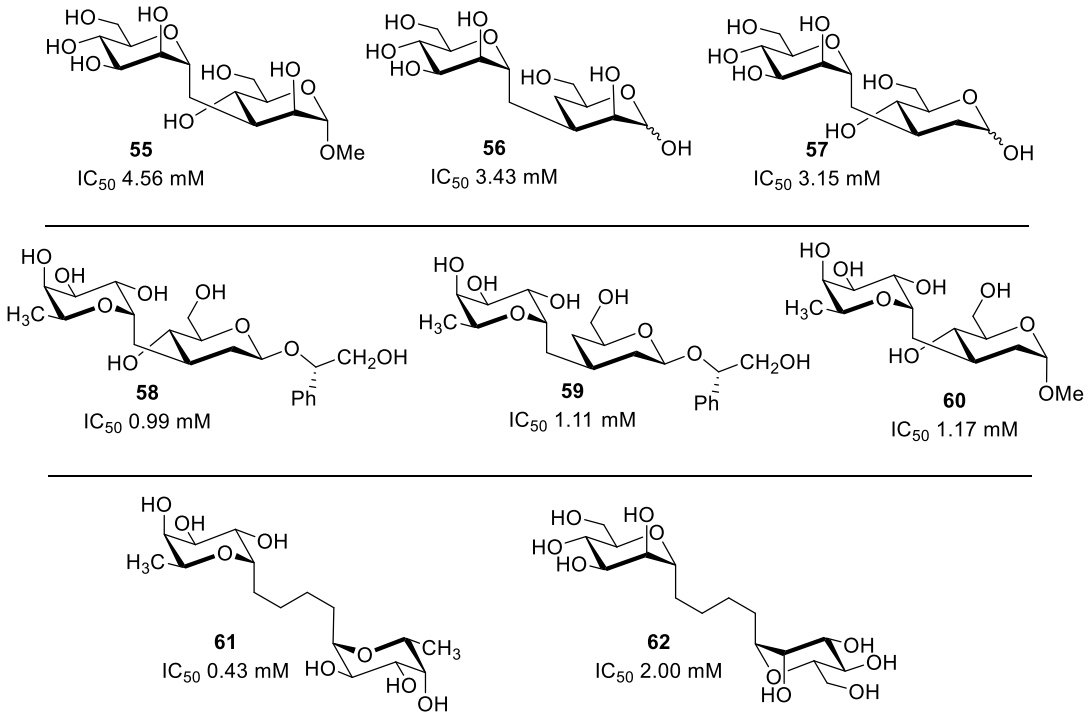
příslušné peracetylované analogy methyl glykosidů s konfigurací α-D-Man*p*(1→3)-*C*-α-D--Man*p*OMe **53a** a α-D-Man*p*(1→3)-*C*-α-L-Man*p*OMe **54a**. (**Schéma 7**)



(i) mCPBA, MeOH, CH_2Cl_2; (ii) (a) Pd/C, H_2, Pd, MeOH, AcOH; (b) Ac_2O, pyridin

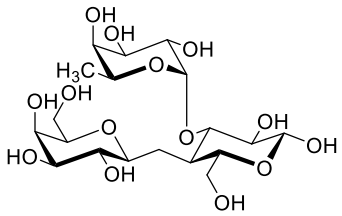
Schéma 7

Další dvě publikované práce (**Příloha VII-VIII**) jsou výsledkem spolupráce na evropském projektu CARMUSYS, kdy se mi podařilo otestovat připravené (1→3)-vázané *C*-disacharidy **55-60** (**Obr. 11**) pro jejich afinitu k DC-SIGN receptoru. Současně byly připraveny pomocí „cross-metateze" i další dva dimery **61** a **62** odvozené od příslušných α-L--fuko a α-D-mannopyranosylpropenů. Pomocí kompetitivní SPR techniky[75], byly získány příslušné hodnoty IC_{50}. (**Obr. 12**)



Obrázek 12: Inhibiční aktivita připravených *C*-glykosidů **55-62** vůči DC-SIGN lektinu

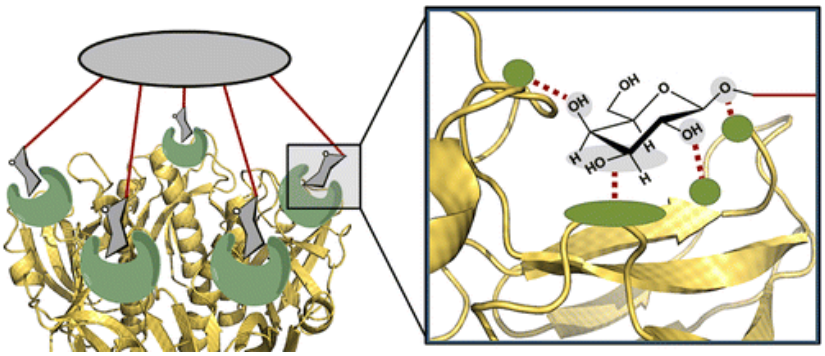
DC-SIGN (Dentritic Cell-Specific ICAM-3 Grabbing Non-integrin) je transmembránový protein typu II obsahující C-koncovou doménu, která specificky váže sacharidy[76]. DC-SIGN [77, 78] byl poprvé klonován v roce 1992 a v roce 2000 byla popsána jeho úloha, jako transreceptoru, který se účastní interakce s proteinem gp120 viru HIV. Dále bylo zjištěno, že tento lektin je schopný rozpoznat široké spektrum glykosylovaných struktur na povrchu viru a že je schopný se specificky vázat k virům jako je HIV, virus Ebola, virus hepatitidy C a SARS a dále i k bakteriím jako jsou *Mycobacterium tuberculosis*, *Helicobacter pylori*, kvasinkám jako je *Candida albicans* a parazitům jako jsou např. *Leishmania pifanoi* a *Schistosoma*. Tento živočišný transmembránový C-lektin se nachází na povrchu nezralé dendritické buňky, která se vyskytuje nejčastěji v mukose. Po navázaní patogenu dentritická buňka dozrává a putuje do lymfatického systému, kde se naváže na T-lymfocyty vazbou k ICAM-3 (InterCellular Adhesion Molecule) a zahájí tak imunitní odpověď organismu. Část dentritických buněk s navázaným patogenem se této cestě vyhne a putuje v organismu dále, čímž podporuje šíření infekce. V současné době je DC-SIGN považován za univerzální receptor pro patogeny a je cílem při vývoji antiifekčních látek[79]. DC-SIGN je specifickým receptorem především pro glykany, které obsahují D-mannosu nebo L-fukosu. Jako příklad lze uvést pentasacharid lakto-*N*-fukopentosu, který obsahuje Lewis^X trisacharid **63** [80]. (**Obr. 13**)



Obrázek 13: Lewis-X trisacharid

Na základě biologických výsledků, lze říci, že připravené *C*-analogy **55-62** vykazovaly podobnou aktivitu jako referenční látky (D-mannosa IC_{50} = 3,42 mM; L-fukosa IC_{50} = 2,52 mM; Manα(1-2)Man IC_{50} = 0,91 mM; Manα(1-3)Man IC_{50} = 2,29 mM), a některé z nich vykazovaly podobnou afinitu jako přírodní ligand $Lewis^X$.[80] Nejdůležitějším zjištěním je, že připravené *C*-disacharidy můžou být perspektivními ligandy DC-SIGN receptoru, protože naše výsledky spíše naznačují, že volnější konformační chování v porovnání s *O*-glykosidy není na překážku.

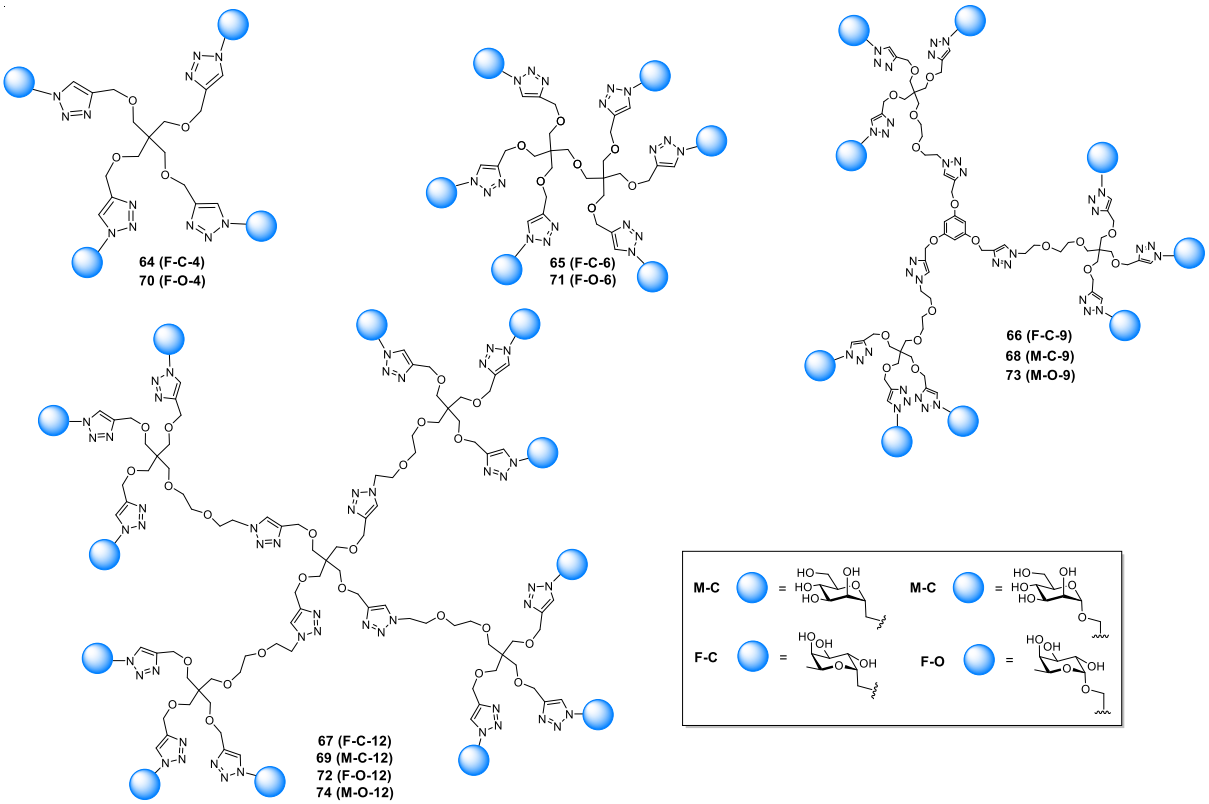
Je známo, že interakce mezi CRD doménou lektinů a příslušným sacharidem jsou zprostředkovány převážně nevazebnými interakcemi (vodíková vazba, asociace s kovy, nepolární nebo iontová interakce). Obecně jsou tyto interakce s monosacharidovými epitopy slabé. Pokud se však specifické interakce účastní několik receptorů na povrchu buňky s několika epitopy (např. sacharidové dendrimery), pak se jedná o tzv. „multi-valency effect“ a vazba je obvykle silnější[81]. (**Obr. 14**)



Obrázek 14: Příklad ideální multivalentní vazby glykodendrimeru s vazebnými místy lektinu[81]

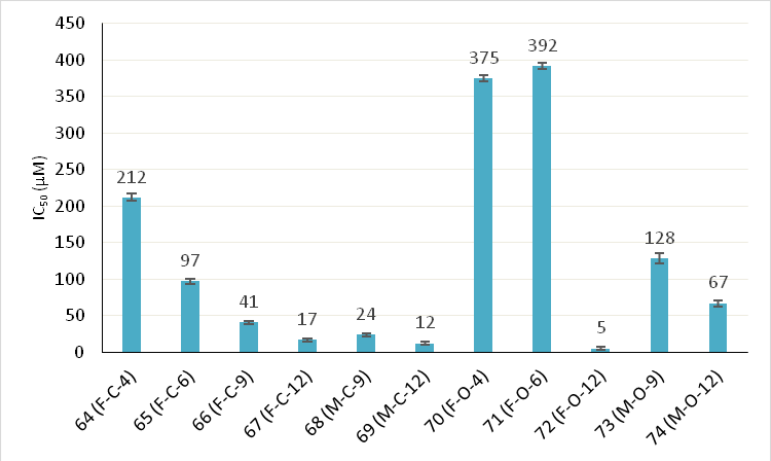
Protože výše zmíněné mono- a divalentní *C*-glykosidy **55-62** odvozené od D-mannosy a L-fukosy se jevily jako perspektivní DC-SIGN ligandy, v dalším projektu jsme se spolu s prof. Jitkou Moravcovou pokusili připravit i multivalentní *C*-glykosidové dendrimery **64-67**, které obsahovaly čtyři, šest, devět a dvanáct α-L-fukopyranosylových jednotek, a současně i

dendrimery **68**-**69** s devíti a dvanácti α-D-mannopyranosylovými jednotkami. Pro porovnání (jako slepý standard) byly připraveny i *O*-glykosidové dendrimery s α-D-mannosou a L-fukosou **70**-**72**. Všechny připravené dendrimery byly syntetizovány pomocí Cu(I) katalyzované azid--alkyn cykloadice (CuAAc) polypropargyl derivátu s azidy *C*- a *O*-glykosidů. (**Obr. 15**)



Obrázek 15: Testované *O*- a *C*-glykosylované dendrimery

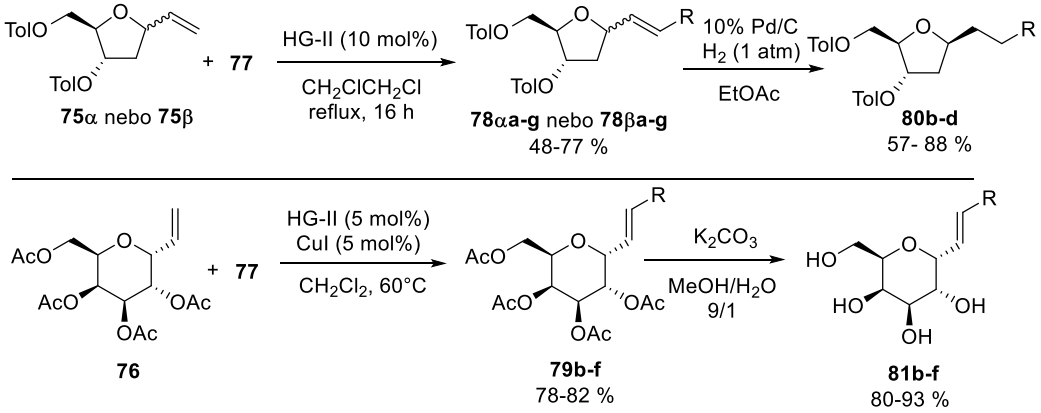
Celkem bylo připraveno jedenáct sacharidových dendrimerů, které byly stejně jako v předešlé práci testovány na jejich afinitu k DC-SIGN pomocí SPR techniky[75].



Obrázek 16: Inhibiční aktivita studovaných glykodendrimerů pomocí SPR

V závěru kapitoly ještě zmíním publikaci, která vznikla ve spolupráci s prof. Martinem Kotorou z Přírodovědecké fakulty Univerzity Karlovy. V tomto projektu jsem opět využil znalosti přípravy α-glykopyranosylpropenů pro přípravu α- a β-*C*-glykosidů za použití „cross--metateze“ s různými alkeny. (**Příloha VI**)

Přestože již dříve byla publikována práce[82] zabývající se využitím glykopyranosyl propenu pro „cross-metateze“, rozhodli jsme se ověřit, zda je možné tento typ reakcí využít i pro vinyl *C*-glykosidy. Jako modelové výchozí látky jsme použili jak čisté epimery **75α** a **75β** odvozené od 2-deoxy-D-ribofuranosy, tak i vinyl α-*C*-glykosid **76** odvozený D-galaktosy, které byly podrobeny „cross-metatezi“ s různými alkeny **77a**-**77g**. Jako katalyzátor byl ve všech reakcích využit běžně používaný a stabilnější Hoveyda-Grubbs II generace, který se ukázal jako nejlepší volba. Protože je známo, že při této reakci mohou vznikat jak „cross-coupling“, tak i „homo-coupling“ produkty výchozích látek, bylo nutné podmínky reakce optimalizovat. Dále bylo potvrzeno, že za námi zvolených podmínek byla konfigurace na dvojné vazbě připravených *C*-glykosidů **78αa-g** a **78βa-g** a **79b-f** vždy pouze *trans*. (**Schéma 8**)



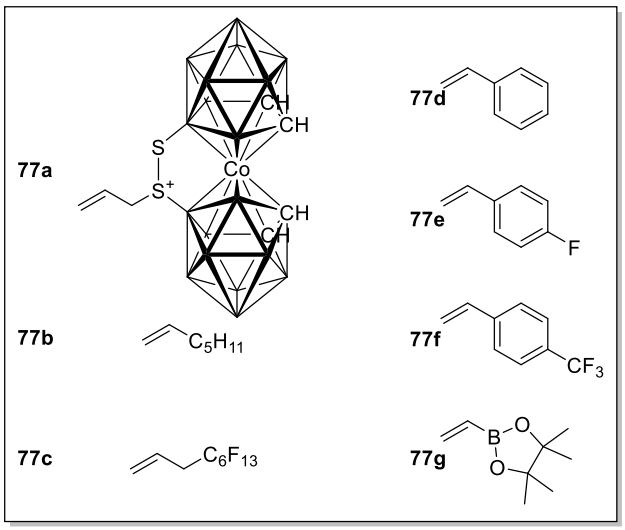


Schéma 8

Po různých optimalizacích bylo zjištěno, že nejlepších výsledků lze v případě vinyl α- a β-*C*-glykosidů **75α** a **75β** dosáhnout za refluxu v 1,2-dichlorethanu. Pokud byl jako výchozí *C*-glykosid použit vinyl derivát **76**, bylo nejlepších výtěžků dosaženo při refluxu v dichlormethanu v přítomnosti katalytického množství CuI, který má zásadní vliv na stabilitu použitého katalyzátoru[83]. (**Schéma 8**) V rámci této práce byla u vybraných derivátů otestována i možnost redukce dvojné vazby za vzniku látek **80b-d** a dále byly připraveny volné *C*-glykosidy **81b-f**.

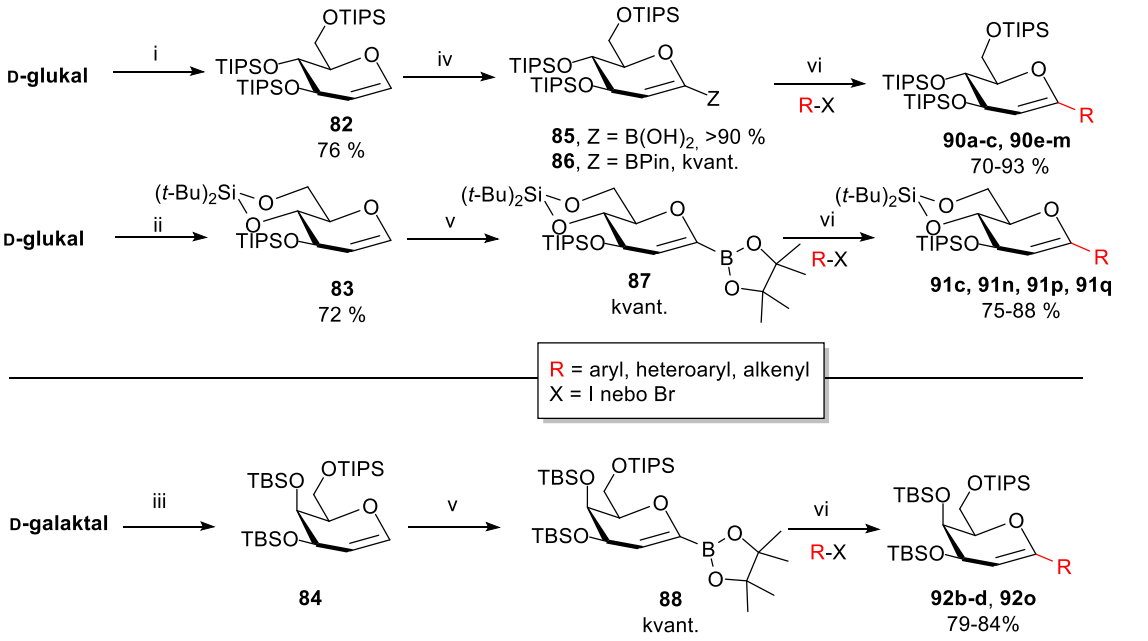
2.2 Stereoselektivní syntéza *C*-glykosidu a *C*-disacharidů pomocí přechodných kovů.

Jak bylo ukázáno v předchozí kapitole (**kap. 2.1**), syntetický přístup k (1→3)-*C*--disacharidům byl vysoce stereoselektivní a umožnil připravit příslušné nehydrolyzovatelné

deriváty jak α- tak i β-glykopyranosyl propenů. Na druhou stranu tento přístup bylo možné využít pouze pro syntézu (1→3)-vázaných *C*-disacharidů a vyžadoval vždy 7 a více reakčních kroků, a tím byly finální *C*-analogy syntetizovány v celkových výtěžcích, které se pohybovaly v rozmezí 3-10 %. Proto jsem se snažil najít nový syntetický přístup, který by syntézu *C*-glykosidů zjednodušil a navýšil celkové výtěžky.

Při hledání modulárního a přímého syntetického přístupu, který by umožnil připravit jak α- a β-*C*-glykosidy, tak i *C*-disacharidy, jsem se zaměřil na využití populární Suzukiho--Miyaurovy reakce, za kterou byla v roce 2010 prof. A. Suzukimu udělena Nobelova cena za chemii[84]. Můj syntetický přístup přípravy *C*-analogů přírodních glykosidů je založen na reakci glykosyl pinakol-boronátů s různými elektrofily za katalýzy Pd- nebo Ni-katalyzátory. (**Příloha IV** a **V**) Jak bude ukázáno dále, výhodou je, že připravené „cross-coupling" produkty lze v jednom nebo dvou krocích stereoselektivně převést na α- tak i β-*C*-glykosidy s konfigurací jak D-*gluko*, D-*manno*, 2-deoxy-D-*arabino* a D-*galakto*.

Protože většina publikací zabývajících se syntézou *C*-glykosidů pomocí „cross--coupling" reakce byla založena na Stilleho a Sonogashirově reakci, při které je nutné použit vysoce toxické deriváty stannanu, bylo nutné nalézt postup, který by umožnil snadno a ve vysokém výtěžku získat cukerné pinakol-boronáty z komerčně dostupných sacharidů. Jako výchozí látky byly použity komerčně dostupný D-glukal a D-galaktal, které byly ochráněny silylovými chránícími skupinami, které jsou stále za silně bazických podmínek. Připravené glykaly **82**-**84** byly následně převedeny na boronovou kyselinu **85** a pinakol-boronáty **86**-**88** pomocí esterů kyseliny boronové po lithiaci *t*-BuLi. Po optimalizaci podmínek se podařilo tyto deriváty boronové kyseliny **84**-**85** získat v kvantitativním výtěžku a excelentní čistotě, hned po extrakci mezi toluen a vodu. (**Schéma 9**)



(i) TIPSCl, imidazol, DMF, 60 °C; (ii) (a) *t*-$Bu_2Si(OTf)_2$, pyridin, DMF, -45-0 °C; (b) TIPSCl, imidazol, DMF, 60 °C; (iii) (a) TIPSCl, imidazol, DMF, 0-4 °C, (b) TBSCl, imidazol, 80 °C; (iv) (a) *t*-BuLi, THF, -78-0 °C; (b) $B(OEt)_3$ nebo $B(OMe)_3$ nebo $B(OiPr)_3$, -78-25 °C; (iii) (a) *t*-BuLi, THF, -78-0 °C; (b) 2-isopropoxy-4,4,5,5-tetramethyl-1,3,2-dioxaborolan; (iv) $Pd(PPh_3)Cl_2$, 2M $Na_2CO_{3(H2O)}$ nebo AcOK, DME, 80 °C

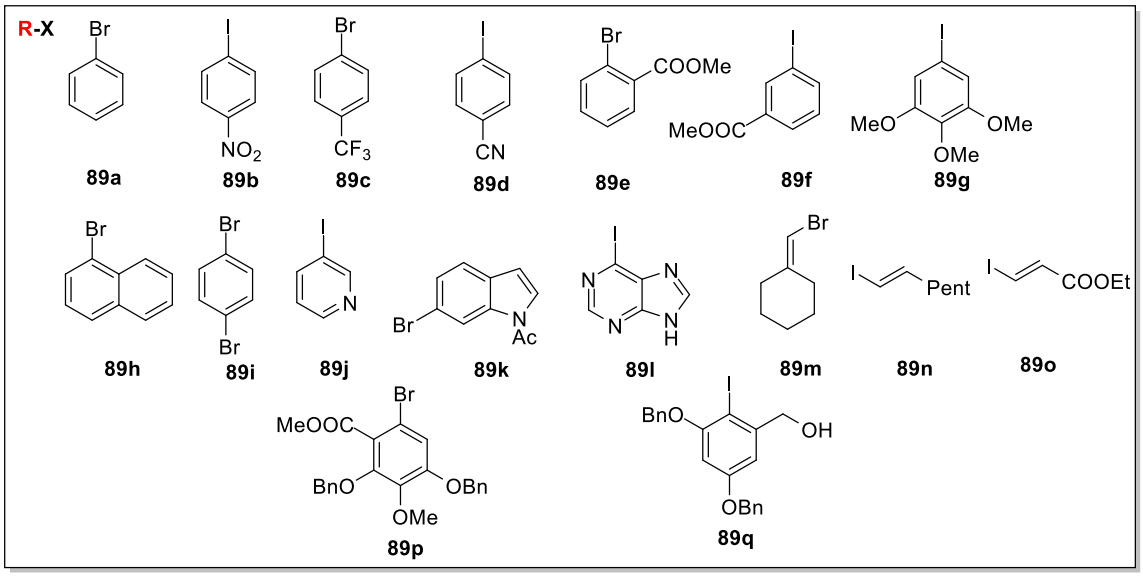


Schéma 9

Jak již jsem zmínil, klíčovým krokem syntézy *C*-glykosidů byla Pd-katalyzovaná „cross--coupling“ reakce pinakol-boronátů **85-88** s různými aryl-, heteroaryl, ale i alkenyl-bromidy nebo jodidy **89a-q**. Po nalezení optimálních podmínek, tedy vhodného rozpouštědla, katalyzátoru, ligandu a báze, byly připraveny příslušné „cross-coupling“ produkty **90-92a-q** ve vysokých výtěžcích 70-93 %. (**Schéma 9**)

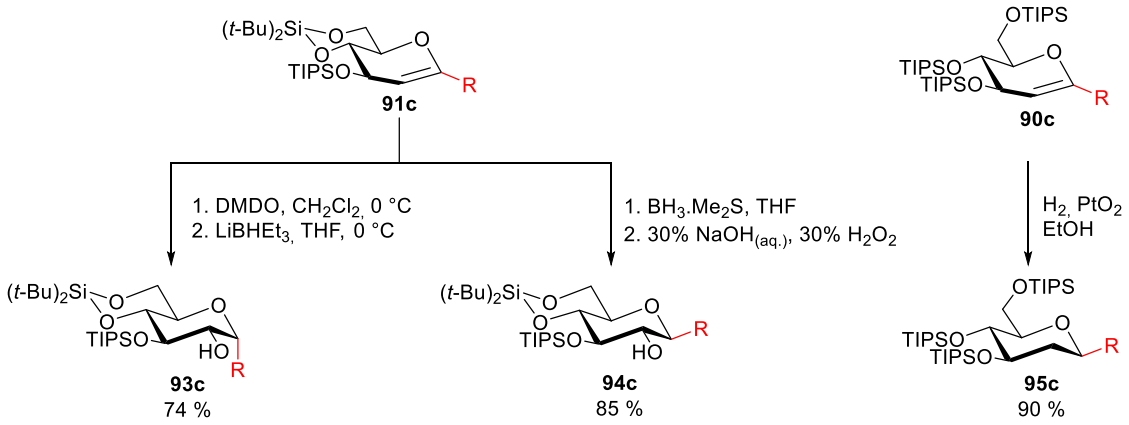
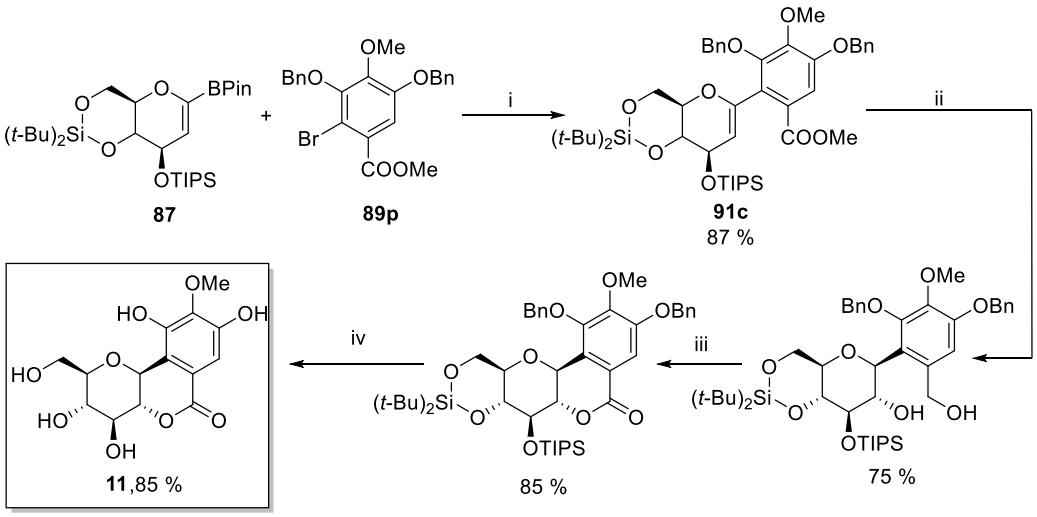


Schéma 10

Následně byly hledány elegantní stereoselektivní syntetické postupy, které by umožnily připravit příslušné *C*-glykosidy. Látka **93c** s D-*gluko* konfigurací byla získána po stereoselektivní epoxidaci endocyklické dvojné vazby derivátu **90c** dimetyldioxiranem (DMDO) a vytvořený α-epoxidový kruh byl následně otevřen pomocí nukleofilního hydridového aniontu Super-hydridu®. Pro stereoselektivní syntézu β-*C*-glykosidů **94c** byla použita hydroborace a β-2-deoxy-*C*-glykosid **95c** byl získán katalytickou hydrogenací „cross--coupling" produktu **90c** za použití Adamsova katalyzátoru. (**Schéma 10**)

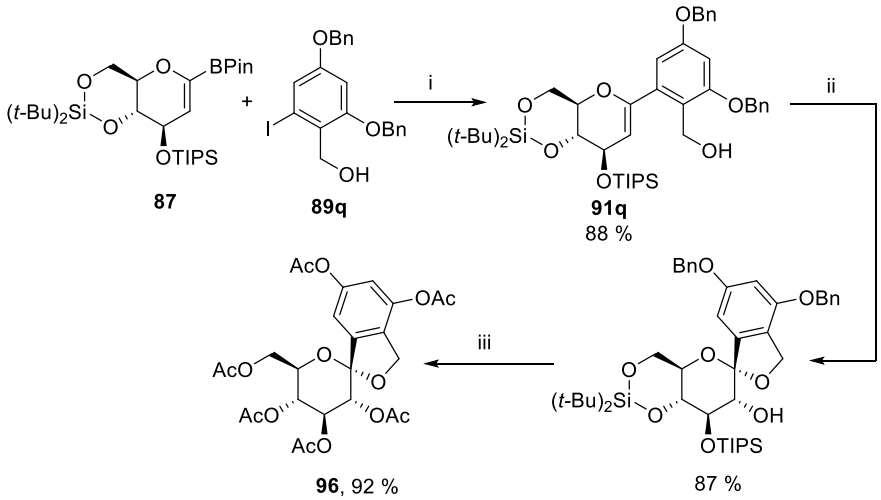


(i) $Pd(Ph_3P)_2Cl_2$, 2M Na_2CO_3(aq.), DMF, 80 °C; (ii) (a) $BH_3.Me_2S$, THF; (b) 30% NaOH, H_2O_2;
(iii) TEMPO, BAIB, CH_2Cl_2; (iv) (a) TBAF.3H_2O, THF, 45°C; (b) $SOCl_2$, MeOH; (c) Pd/C, H_2, EtOH

Schéma 11

Použitelnost nově nalezeného postupu byla následně otestována při přípravě dvou přírodních *C*-glykosidů **11** a **96**. (**Schéma 11** a **12**) Nejprve jsem se pokusil o první totální syntézu bergeninu **11**, neboť tento *C*-glykosid kyseliny gallové, vykazuje zajímavé

farmakologické vlastnosti (viz **kap. 1.2**). Jak je naznačeno ve **schématu 11**, tento *C*-glykosid se podařilo připravit v celkovém 40% výtěžku za použití pouze šesti reakčních kroků z příslušného bromidu **89p**. (**Schéma 11**)



(i) $Pd(Ph_3P)_2Cl_2$, 2M $Na_2CO_3(H_2O)$, DME, 80 °C; (ii) a) DMDO, CH_2Cl_2, 0-20 °C; (iii) (a) Pd/C, H_2, $NaHCO_3$, THF; (b) TBAF, THF; (c) Ac_2O, pyridin

Schéma 12

Potenciál nalezeného postupu se mi podařilo demonstrovat i při alternativní syntéze sacharidové části papulacandinu D **96**, opět ve vysokém 64% výtěžku. (**Schéma 12**)

V další práci (**Příloha V**) je popsána v chemii sacharidů první aplikace obtížnější Suzukiho-Miyaurovy sp^2-sp^3 „cross-coupling" reakce pro modulární syntézu (1→2)-*C*--disacharidů. Tento přístup umožňuje spojení dvou cukerných jednotek pinakol-boronátu **87** a cukerných jednotek **97** a **98** pomocí C-C vazby. Suzukiho-Miyaurova reakce[85] je jednou z nejoblíbenějších a nejefektivnějších metod tvorby C-C vazby v organické chemii. Ačkoliv její využití pro syntézu aktivovaných sp^2 substrátů je dobře popsáno (viz **Příloha IV**), použití sp^3 hybridizovaných elektrofilů v „cross-coupling" reakcích je obecně obtížné, protože přítomnost β-vodíku v molekule elektrofilu umožňuje průběh nežádoucí β-hydridové eliminace. Tato konkurenční reakce se může uplatňovat po oxidativní adici a je za běžných podmínek rychlejší než transmetalace, což je často zdrojem špatných výtěžků „cross-coupling" produktů[86]. Tento mechanismus vede ke tvorbě alkenu a organokovového komplexu, kde je odstupující skupina OR´ zaměněna za atom vodíku pocházející původně z molekuly elektrofilu. Komplex po reduktivní eliminaci poskytuje produkt protodeboronace a regenerovaný katalyzátor. Mezi další komplikace spojené s použitím alkyl elektrofilů lze zmínit poměrně pomalou oxidativní adici

kovu do X-(sp^3) vazby, nežádoucí jednoelektronovou oxidaci atomu kovu (SET) a také náchylnost ke klasické eliminaci HX v bazickém prostředí[87]. (**Schéma 13**)

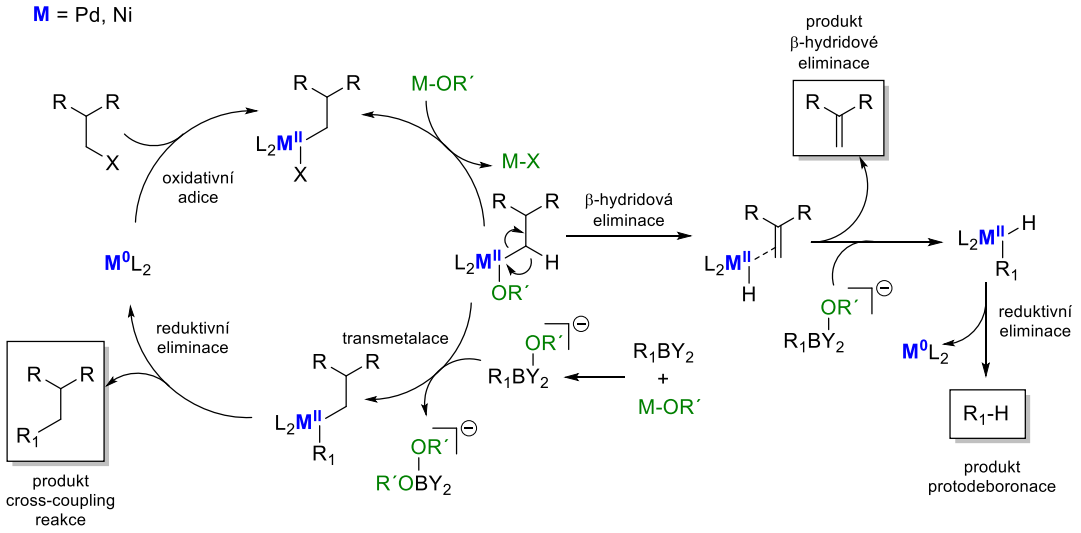


Schéma 13

Největšího pokroku v použití tohoto typu „cross-coupling" reakce neaktivovaných substrátů (alkenyl-alkyl, ale i alkyl-alkyl) dosáhl Fu[88-91] za pomoci nikelnatých katalyzátorů s objemnými dusíkatými elektrodonorními ligandy. Ty jsou většinou nezbytné, protože aktivací organokovového komplexu zvýhodňují vznik „cross-coupling" produktu na úkor nežádoucího produktu β-hydridové eliminace.

Pro tento typ Suzukiho reakce bylo nejprve zapotřebí připravit cukerné alkyl halogenidy **97** a **98**. Komerčně dostupný D-glukal byl nejprve benzylován, následně byl pomocí Simmonsovy-Smithovy reakce s vysokou stereoselektivitou připraven derivát **99** s cyklopropanovým kruhem. V dalším kroku, byl cyklopropanový kruh stereoselektivně otevřen pomocí *N*-brom- ale i *N*-jód-sukcinimidu za vzniku methyl glykosidu **97** nebo **98**. (**Schéma 14**)

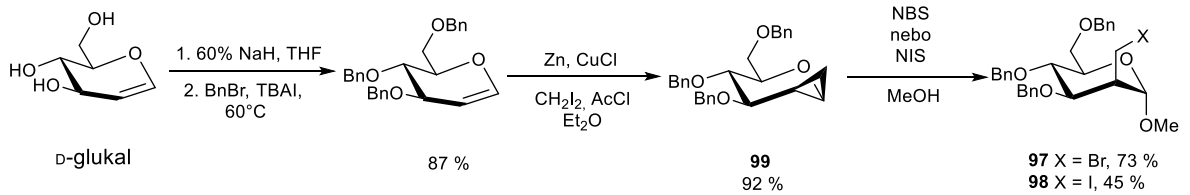


Schéma 14

Pro Suzukiho sp^2-sp^3 „cross-coupling" reakci s dříve připraveným pinakol-boronátem **87** s halogenidy **97**-**98** bylo testováno několik palladnatých a nikelnatých katalyzátorů

s různými ligandy, basemi a rozpouštědly. Pečlivé optimalizace nakonec vedly k nalezení reakčních podmínek, které poskytly „cross-coupling“ produkt **100** v dobrém 72-78% výtěžku. (**Schéma 15**)

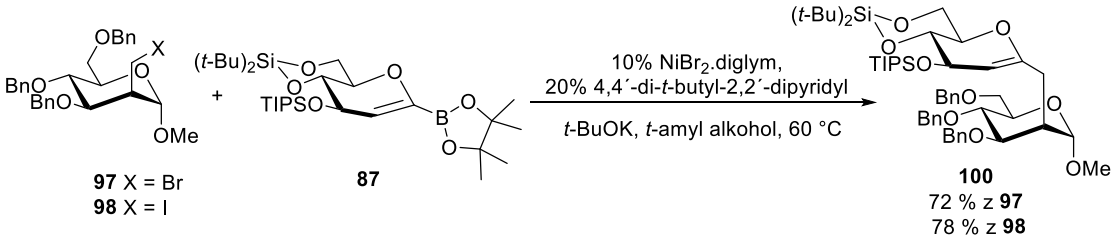


Schéma 15

Stejně jako v předchozím případě (**Příloha IV**), endocyklická dvojná vazba látky **100** umožnila využít stereoselektivní oxidativně-reduktivní transformace a připravit tak různé *C*-disacharidy. Jak je naznačeno ve **schématu 16**, za použití dříve diskutovaných stereoselektivních reakcí, které jsou detailně popsány v publikaci, bylo z jednoho „cross--coupling“ produktu **100** připraveno pět α- a β-(1→2)-*C*-disacharidů **101**-**105** ve vysokém celkovém výtěžku. (**Schéma 16**)

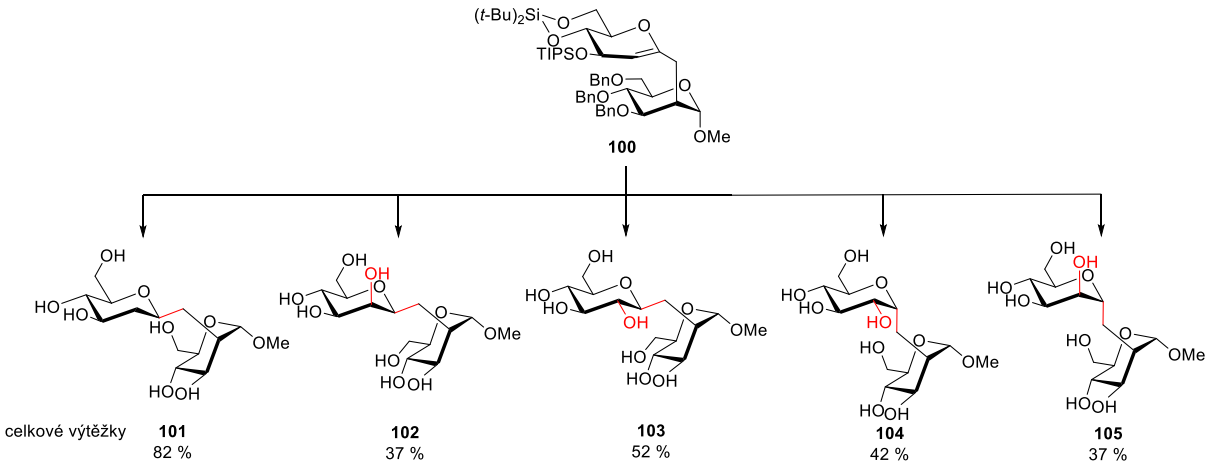
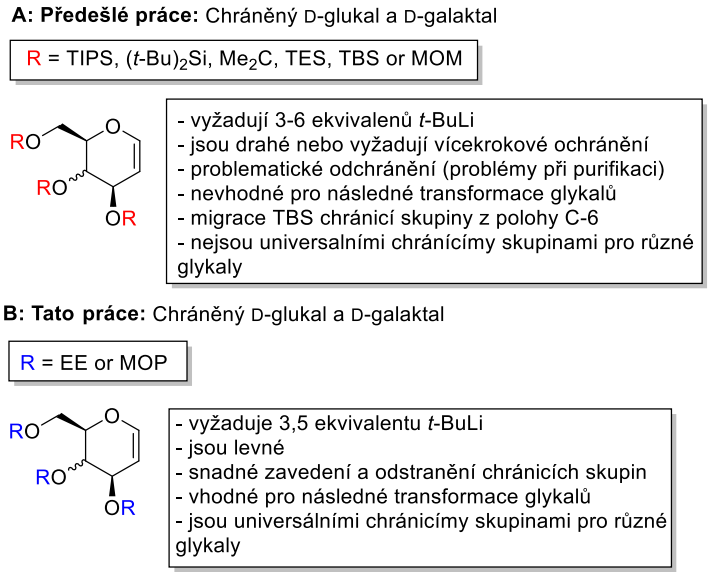


Schéma 16

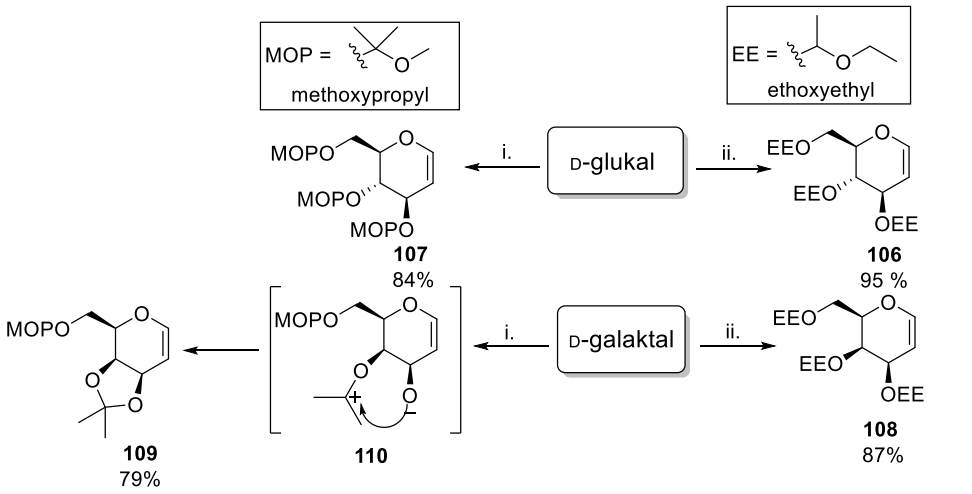
V další práci (**Příloha IX**) jsem se zaměřil na nalezení efektivnějších chránících skupin D-glykalů, které lze využít pro přípravu aryl *C*-glykosidů. Pro syntézu *C*-glykosidů lze využít D-glykaly, které lze pomocí lithiace převést na látky, které mohou vstupovat do reakce s různými elektrofily jako nukleofily. Protože deprotonace glykalů na uhlíku C-1 vyžaduje vždy silně bazické organolithné sloučeniny, je zapotřebí výchozí glykaly vhodně chránit. Klasické benzyl (Bn) a *t*-butyldimetylsilyl (TBS) etherové chránicí skupiny nejsou vhodné, protože se

při deprotonaci samy lithiují, což vede ke vzniku nežádoucích vedlejších produktů. Na druhou stranu byly nalezeny chránící skupiny, které tvrdé lithiační podmínky sice přežijí, a jsou použitelné (TIPS, TBDPS, TES, MOM a isopropyliden), bohužel i tyto chránicí skupiny mají své slabiny, které brání jejich širšímu využití. (**Obr. 17**) Protože i v dřívějších pracích (**Příloha IV** a **V**), jsem se musel potýkat s některými z těchto nevýhod, pokusil jsem se pro syntézu *C*-glykosidů nalézt vhodné chránicí skupiny D-glukalu a D-galaktalu.



Obrázek 17: Chránicí skupiny, které jsou vhodné pro lithiaci D-glukalu a D-galaktalu

Jako vhodné se ukázaly ethoxyethyl (EE) a methoxypropyl (MOP) acetylové chránicí skupiny, které se v cukerné chemii využívají jen zřídka a většinou pouze pro ortogonální chránění některých hydroxylových skupin sacharidů. Bylo prokázáno, že za použití 2-methoxypropenu a ethylvinyletheru lze v přítomnosti Py.TsOH získat plně chráněné glykaly **106-108** ve vysokém výtěžku. (**Schéma 17**) Zajímavé však bylo zjištění, že při reakci 2-methoxypropenu s *cis*-3,4-diolem D-galaktalu vznikala látka **109** s isopropyliden acetalem na sekundárních hydroxylových skupinách, zatímco za stejných podmínek *trans*-3,4-diol D-glukalu vedl k plně MOP chráněnému derivátu **108**. To lze vysvětlit pravděpodobnou intramolekulární reakcí karbokationtu meziproduktu **110** se druhou sekundární hydroxylovou skupinou. (**Schéma 17**)

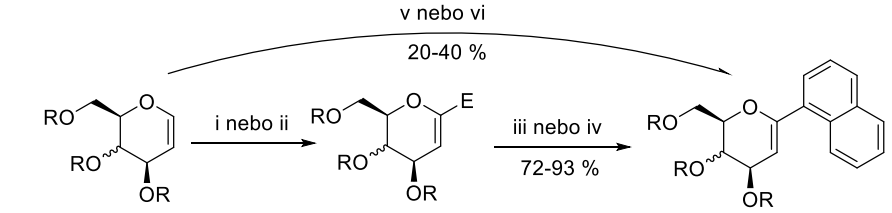


i. 2-methoxypropen, Py.TsOH, CH_2Cl_2 nebo DMF, 0-25 °C; ii. ethylvinylether, Py.TsOH, CH_2Cl_2, 0-25 °C

Schéma 17

Následně byly glykaly **106**-**108** podrobeny lithiaci s 3,5 ekvivalety *t*-BuLi. Za optimalizovaných podmínek probíhala lithiace glykalu **106**-**108** standardně, a při následném použití elektrofilů (Bu_3SnCl a *i*PrOBPin) byly získány očekávané deriváty **110a,b**-**112a,b** opět ve vysokých výtěžcích v rozmezí 69-94 %. Bohužel při lithiaci chráněného D-galaktalu **109**, docházelo v přítomnosti *t*-BuLi k otevření dihydropyranového kruhu a vzniku racemátu **113**, což bylo potvrzeno pomocí NMR experimentu s (*S*)-Mosherovou solí. (**Schéma 18**)

Při studiu použitelnosti EE a MOP chránících skupin byla testována také stabilita těchto chránicích skupin při různých „cross-coupling" reakcích. Jako modelové reakce byly vybrány Suzukiho-Miyaurova a Stilleho reakce s 1-jódnaftalenem. Pro Suzukiho reakci byly použity již dříve objevené podmínky (**Příloha IV**) a příslušné 1-pinakol-boronáty **110a**-**112a** poskytly „cross-coupling" produkty **114**-**116** ve výtěžcích 72-93 %. Pro Stilleho reakci byly použity standartní podmínky[92] a očekávané naftyl-*C*-glykosidy **114**-**116** byly získány ve výtěžcích 72-86 %. Dále jsem se rozhodl, otestovat kompatibilitu připraveného EE chráněného D-glukalu **106** i při Negishiho[93] a In-zprostředkované[94] „cross-coupling" reakci opět s 1-jódnaftalenem. V obou případech však příslušné „cross-coupling" produkty **114** vznikaly v nízkých 20-43 % výtěžcích, což bylo pravděpodobně způsobeno nestabilitou EE chránících skupin v přítomnosti Lewisových kyselin ($ZnCl_2$ a $InCl_3$) po vodném zpracovaní reakcí. (**Schéma 18**)

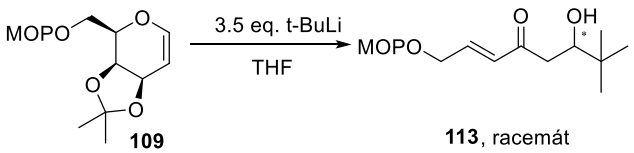


106 D-glukal, R = EE
107 D-glukal, R = MOP
108 D-galaktal, R = EE

110a D-glukal, R = EE, E = BPin, 81 %
110b D-glukal, R = EE, E = $SnBu_3$, 90 %
111a D-glukal, R = MOP, E = BPin, 94 %
111b D-glukal, R = MOP, E = $SnBu_3$, 93 %
112a D-galaktal, R = EE, E = BPin, 90 %
112b D-galaktal, R = EE, E = $SnBu_3$, 90 %

114 D-glukal, R = EE
115 D-glukal, R = MOP
116 D-galaktal, R = EE

(i) a) 3,5 ekv. *t*-BuLi, THF, -78 - 0 °C; b) *i*PrOBPin, THF -78 - 25 °C; (ii) a) 3,5 ekv. *t*-BuLi, THF, -78 - 0 °C; b) Bu_3SnCl, THF, -78 - 25 °C; (iii) $Pd(PPh_3)_2Cl_2$, 1,2-dimethoxyethan (DME), Na_2CO_3, 80 °C; (iv) $Pd(PPh_3)_4$, toluen, 120 °C; (v) a) *t*-BuLi, $InCl_3$, THF; b) $Pd(PPh_3)_2Cl_2$, reflux; (v) a) *t*-BuLi, $ZnCl_2$, THF; b) $Pd(Ph_3P)_4$



109

113, racemát
81 %

Schéma 18

Plně EE-chráněné glykaly **106** a **108** vznikaly jako směs osmi možných diastereomerů, a proto bylo nutné najít jednoduchou a efektivní metodu pro určení struktury připravených derivátu pomocí NMR experimentů. To se mi podařilo, pokud jsem glykaly **106**, **108** a deriváty z nich připravené (**114**, **116**) kompletně odchránil přímo v NMR kyvetě pomocí 10% deuterované kyseliny octové (CD_3COOD) v MeOH-d_4.

Pro ověření použitelnosti EE a MOP chránících skupin, bylo nutné otestovat, zda je možné připravené „cross-coupling" produkty **114**-**116** transformovat na příslušné α- a β-*C*--glykosidy s konfigurací *gluko* a *galakto*. To se mi opět podařilo za obdobných podmínek jako v předchozích pracích (**Příloha IV** a **V**) a příslušné *C*-glykosidy **117**-**119** byly získány v dobrých celkových výtěžcích, které se pohybovaly v rozmezí 64-84 %. Problém nastal pouze při transformaci pseudo-*C*-glykosidu **116** na příslušný naftyl-α-*C*-glykosid, neboť při otevírání oxiranového kruhu vznikal vždy acyklický derivát **120**. β-*C*-Glykosidy **117** a **119** bylo možné připravit i z volných naftyl-*C*-glykalů **121** a **122** opět v dobrých celkových výtěžcích. (**Schéma 19**)

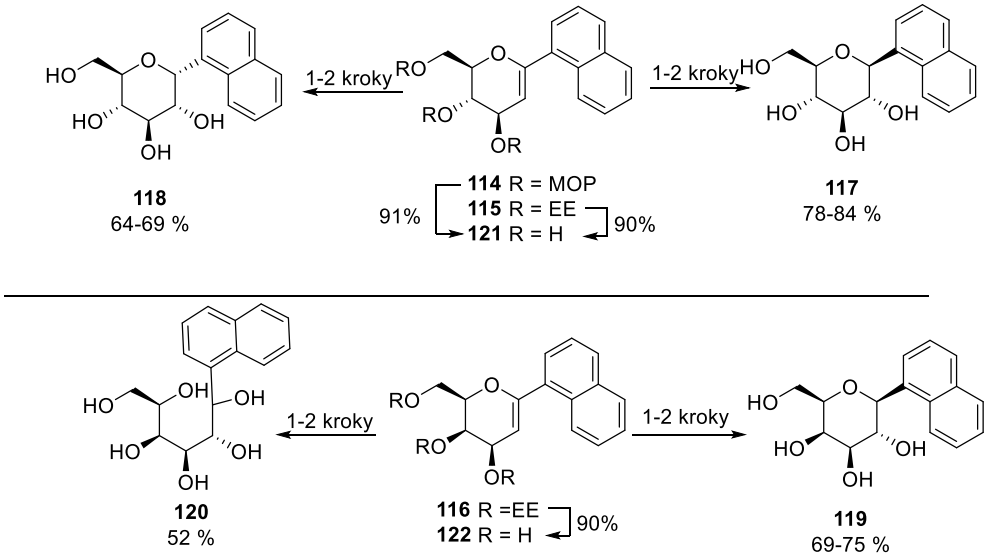


Schéma 19

V roce 2021 se mi podařilo publikovat nový syntetický přístup přípravy (hetero)aryl-*C*--glykosidů, který značně zjednodušuje využití glykalů (glykosyl donorů) pro arylační reakce katalyzované přechodnými kovy, protože umožnuje připravit příslušné *C*-analoga přírodních glykosidů, bez nutnosti chránit reaktivní hydroxylové skupiny. (**Příloha X**)

Jak již bylo naznačeno výše (viz **Příloha IX**), MOP acetalové chránicí skupiny D--glukalů se ukázaly jako vhodné chránicí skupiny, pro přípravu různých glykosyl donorů. Proto jsem pro přípravu nového glykosyl donoru **124** využil již dříve připravený MOP-D-glukal **107**. Ten byl následně převeden za použití ekvivalentního nadbytku *t*-BuLi na 1-lithiovaný meziprodukt, který reagoval s diisopropylsilylchloridem za vzniku derivátu **123**. Po extrakci, byl surový **123** jemnou kyselou hydrolýzou transformován na volný 1-diisopropylsilyl-D-glukal **124**, který byl získán jako stabilní krystalická látka v celkovém výtěžku 93 %. (**Schéma 20**)

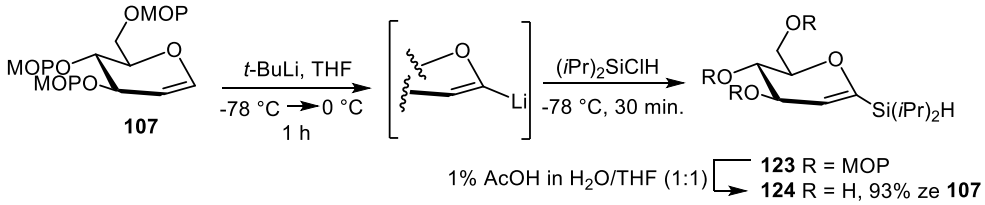
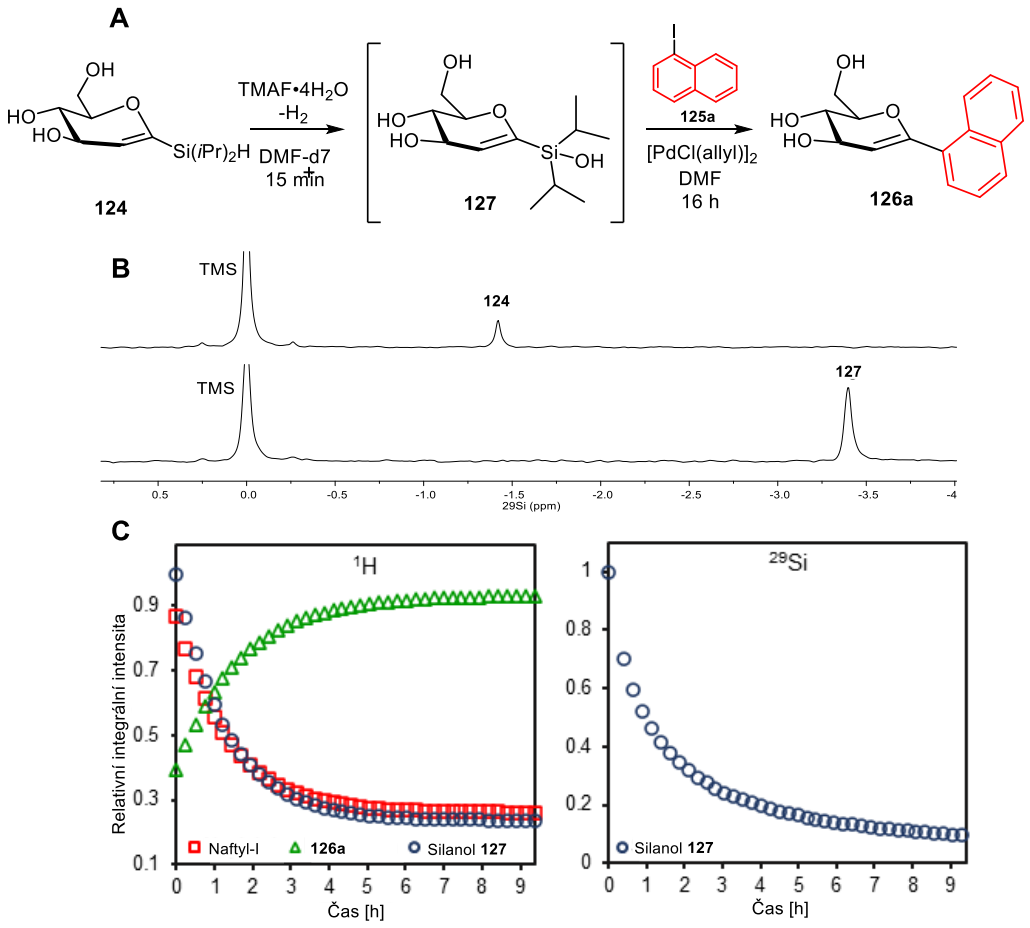


Schéma 20

Klíčovým krokem syntézy *C*-glykosidů byla Pd-katalyzovaná Hiyamova „cross--coupling“ reakce nechráněného 1-diisopropylsilyl-D-glukalu **124** s různými aryl- a heteroaryl halogenidy. Pro nelezení optimálních podmínek Hiyamovy reakce[95] byl jako modelový aryl

halogenid použit 1-jodnaftalen **125a**. Počáteční studie začala použitím katalyzátoru [PdCl(allyl)$_2$] a 1M roztoku tetrabutylamonium fluoridu (TBAF) v THF jako zdroje fluoridových aniontů. Úplná konverze výchozího materiálu **124** na produkt **126a** byla pozorována během 1 hodiny a reakční podmínky se jevily jako vyhovující. Bohužel, problémem se stala purifikace produktu kvůli přítomnosti tetrabutylamoniových solí, které se nepodařilo odstranit jak sloupcovou chromatografií na silikagelů, tak ani při čištění pomocí HPLC na reverzní fázi. Z tohoto důvodu bylo nutné najít vhodnější zdroj fluoridových aniontů. Bylo zjištěno, že nejvyšších výtěžku arylace glukalu **124** a vzniku 1-naftyl-D-glukalu **126a** je možné dosáhnout při použití tetrahydrátu tetramethylamonium fluoridu (TMAF•4H$_2$O) za katalýzy [PdCl(allyl)$_2$] v DMF. (**Obr. 18A**).



Obrázek 18: Sledování Hiyamovi reakce pomocí NMR. **A**: Reakční schéma; **B**: Dekaplované ^{29}Si NMR spektrum látky **124** (horní spektrum) a po přidání TMAF•4H$_2$O (dolní spektrum); **C**: Kinetika arylačního kroku z ^{1}H (vlevo) a ^{29}Si (vpravo) NMR dat

Při sledování reakce pomocí NMR, byla potvrzena i úloha derivátu silylhydridu jako maskovaného silanolu a jeho hydrolytická aktivace, která je klíčovým mechanistickým krokem

pro transmetalaci glykalové části na palladiu. Bylo totiž zjištěno, že přídavek hydratovaného TMAF k roztoku látky **124** vede ke vzniku silanolu **127**. Tato hydrolýza je pravděpodobně urychlována i přítomnosti vody v TMAF•4H_2O, protože pokud jsem jako zdroj fluoridu použil bezvodý TMAF, Hiyamova arylace neběžela. (**Obr. 18B** a **18C**)

Jak je naznačeno ve **schématu 21**, optimalizované reakční podmínky pro Hiyamovu reakci 1-diisopropylsilyl-D-glukalu **124** byly otestovány pro různě substituované (hetero)aryl halogenidy a byly získány příslušné pseudo-*C*-glukosidy **125a-n** ve výtěžcích, které se pohybovaly v závislosti na substituci aromatického jádra v rozmezí 25-96 %.

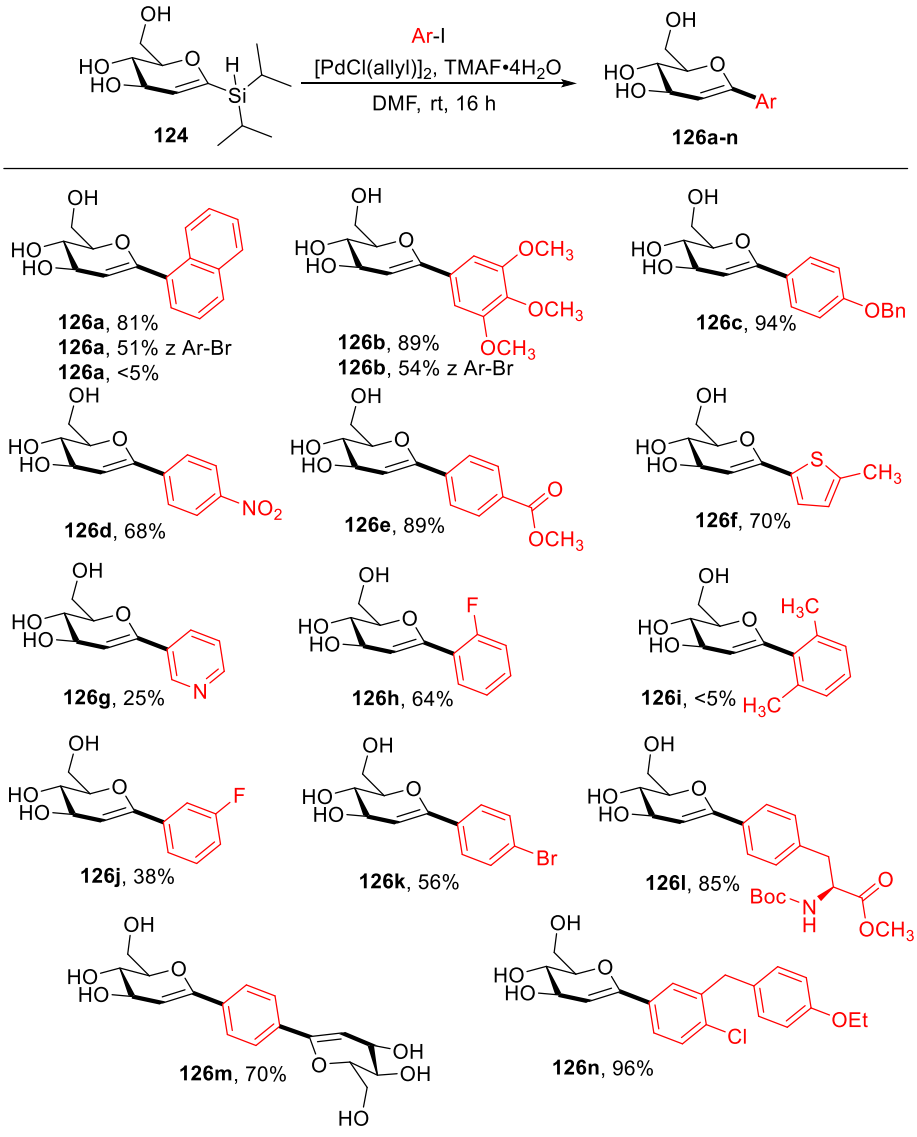


Schéma 21

Následně jsem se snažil ověřit, zda je možné připravené nechráněné „cross-coupling“ produkty s endocyklickou dvojnou vazbou i v tomto případě stereoselektivně transformovat na

příslušné *C*-glykosidy. Pro stereoselektivní přípravu β-*C*-glykosidů **128a-d** s D-*gluko* jsem opět použil hydroboraci komplexem BH_3.THF s následnou bazickou oxidací. (**Schéma 22**)

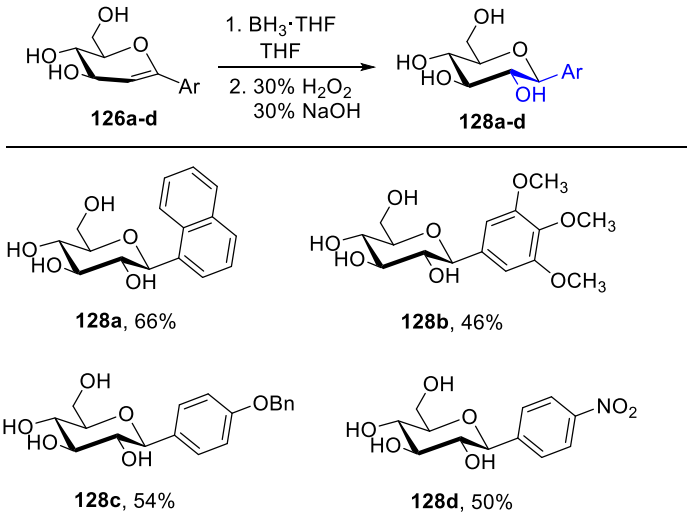


Schéma 22

Dále se ukázalo, že katalytická hydrogenace dvojné vazby vybraných „cross-coupling" produktů **126b** a **126h** v přítomnosti Adamsova katalyzátoru vede ke vzniku pouze β-*C*--glykosidů **129b** a **129h** s konfigurací 2-deoxy-D-*arabino*. (**Schéma 23**)

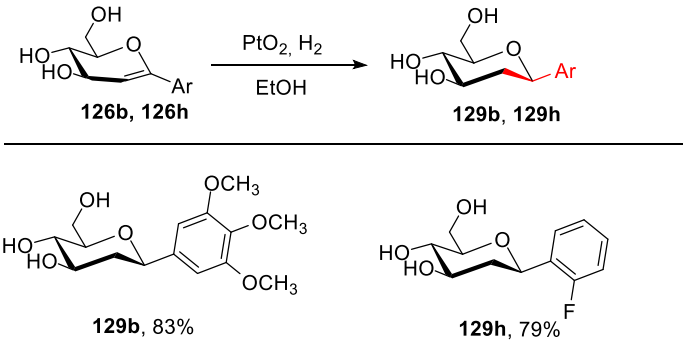


Schéma 23

Použitelnost nově nalezeného postupu byla ověřena i při dvoukrokové syntéze celosvětově používaného antidiabetika dapagliflozinu **3**, který byl získán ve vysokém 79% celkovém výtěžku. (viz **kap. 1.2.**) Jak je naznačeno ve **schématu 24**, příslušný „cross-couping" produkt **126n** (**Schéma 21**), byl bez nutnosti chránit reaktivní hydroxylové skupiny převeden přímo na dapagliflozin **3**.

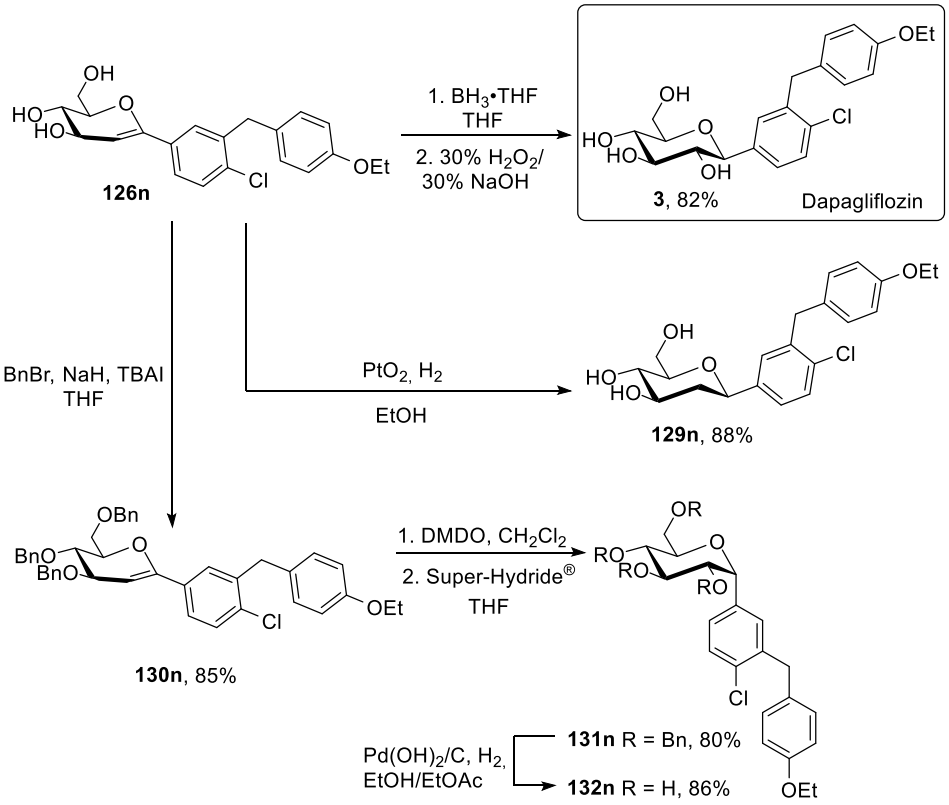


Schéma 23

Pro úplnost jsem se rozhodl universálnost syntetického přístupu ověřit přípravou i dalších dvou analogů dapagliflozinu **129n** a **132n**. Pokud byl pseudo-*C*-glykosid **126n** podroben katalytické hydrogenaci v přítomnosti Adamsova katalyzátoru byl získán β-analog **128n** s konfigurací 2-deoxy-D-*arabino* opět ve vysokém 88% výtěžku. Pro přípravu nového α-analogu dapagliflozinu **132n** jsem využil stereoselektivní transformaci endocyklické dvojné vazby látky **126n**, která je podrobně popsána v publikacích (**Příloha IV** a **V**). V tomto případě však bylo nutné nejprve ochránit volné hydroxylové skupiny, aby při následné oxidaci nedošlo ke vzniku nežádoucích meziproduktů. Proto byl pseudo-*C*-glykosid **126n** nejprve benzylován, za vzniku derivátu **130n**. Následná epoxidace dvojné vazby a stereoselektivní otevření vzniklého epoxidu Super-hydridem® vedlo ke vzniku pseudo-α-anomeru **131n**. Volný α-analog dapagliflozinu **131n** byl získán po katalytické debenzylaci za použití $Pd(OH)_2/C$. Výhodou použití tohoto katalyzátoru bylo, že za těchto podmínek nebyl pozorován vznik nežádoucího produktu dehalogenace a příslušný α-analog **131n** vznikal ve vysokém 86% výtěžku.

Pokud porovnáme tento syntetický přístup s dříve diskutovanými (**Příloha IV** a **IX**), tak se mi opět podařilo zjednodušit syntézu *C*-glykosidů, protože *C*-analoga přírodních glykosidů bylo možné připravit bez nutnosti chránit reaktivní hydroxylové skupiny.

3 ZÁVĚR A VÝHLED

Tato práce je zaměřena na vývoj a optimalizaci stereoselektivních metod pro přípravu *C*--glykosidů a *C*-disacharidů. Jak bylo naznačeno v úvodní kapitole 1.4 pro syntézu těchto stabilních glykomimetik se obecně využívají dva syntetické postupy. První spočívá v připojení výchozího sacharidu na uhlíkový řetězec, který lze následně použit pro připojení různých aglykonů (syntéza *C*-glykosidů) nebo se na něm vystaví druhá monosacharidová jednotka (tzv. *de novo* syntéza *C*-disacharidů). Této problematice je věnována **kapitola 2.1.**, ve které je popsáno:

1. využití různých α- a β-glykopyranosylpropenů pro stereoselektivní syntézu α- i β--(1→3)-*C*-disacharidů za použití hetero-Dielsovy-Alderovy reakce s chirálními vinylethery
2. v rámce spolupráce na evropském projektu CARMUSYS byly otestovány připravené *C*-glykosidy, *C*-disacharidy a cukerné glykodenrimery na afinitu k DC-SIGN receptoru
3. využití těchto cukerných synthonů (glykopyranosyl propenů) pro syntézu *C*-glykosidů za využití „cross-metateze“ s různými alkeny.

Kapitola 2.2, je věnována druhému syntetickému přístupu, který je založen na spojení jedné cukerné jednotky s aglykonem (*C*-glykosidů) nebo druhou cukernou jednotkou (*C*--disacharidů). Uvedené práce popisují:

1. vývoj nové modulární metody pro stereoselektivní syntézu α- a β-*C*-glykosidů za využití Suzukiho-Miyaurovy sp^2-sp^2 „cross-coupling“ reakce
2. první aplikace Suzukiho-Miyaurovy sp^2-sp^3 „cross-coupling“ reakce pro stereoselektivní přípravu α- a β-(1→2)-*C*-disacharidů
3. využití nových ethoxyethyl a methoxypropyl acetalových chránících skupin pro přímou a stereoselektivní syntézu α- a β-aryl-*C*-glykosidů
4. vývoj jednoduché syntézy *C*-glukosidů za využití Hiyamovi „cross-coupling“ reakce bez chránicích skupin

Vedle vývoje těchto syntetických postupů, byly vybrané metody aplikovány i pro přípravu přírodních látek (bergeninu a cukerné části papulacandinu D) a celosvětově používaného léčiva dapagliflozinu včetně jeho dvou analogů. Nalezené metody se snažím dále rozvíjet. Díky tomu, že jsem se stal členem týmu orientovaného na hledání stabilních glykomimetik inhibujících galektiny, začal jsem se věnovat i syntéze *S*- a *N*-glykomimetik. Vedle aplikace známých

syntetických postupů je mým plánem při výzkumu využít v současnosti se rozvíjející fotokatalýzu.

4 LITERATURA

1. Gabius, H. J. *The Sugar Code: Fundamentals of Glycosciences*; Wiley-VCH: Weinheim, 2009.
2. Seeberger, P. H.; Werz, D. B. Automated synthesis of oligosaccharides as a basis for drug discovery. *Nat. Rev. Drug Discov.* **2005**, *4*, (9), 751-763.
3. Panza, M.; Pistorio, S. G.; Stine, K. J.; Demchenko, A. V. Automated Chemical Oligosaccharide Synthesis: Novel Approach to Traditional Challenges. *Chem. Rev.* **2018,** *118* (17), 8105-8150.
4. Nicotra, F.; Cipolla, L.; La Ferla, B.; Araújo, A. C. Blocking the anomeric reactivity, how and why. In *Carbohydrate Chemistry: Volume 35*, The Royal Society of Chemistry: 2009; Vol. 35, pp 260-289.
5. Compain, P.; Martin O. R. Iminosugars: From Synthesis to Therapeutic Applications. Weinheim: Wiley-VCH, **2008**.
6. Ren, W.; Pengelly, R.; Farren-Dai, M.; Shamsi Kazem Abadi, S.; Oehler, V.; Akintola, O.; Draper, J.; Meanwell, M.; Chakladar, S.; Świderek, K.; Moliner, V.; Britton, R.; Gloster, T. M.; Bennet, A. J. Revealing the mechanism for covalent inhibition of glycoside hydrolases by carbasugars at an atomic level. *Nat. Commun.* **2018**, *9* (1), 3243.
7. Arjona, O.; Gómez, A. M.; López, J. C.; Plumet, J. Synthesis and Conformational and Biological Aspects of Carbasugars. *Chem. Rev.* **2007**, *107* (5), 1919-2036.
8. Hideya, Y.; Masayuki, I.; Hironobu, H., Thiasugars: Potential Glycosidase Inhibitors. *Curr. Top. Med. Chem.* **2009**, *9* (1), 76-86.
9. Koester, D. C.; Holkenbrink, A.; Werz, D. B. Recent Advances in the Synthesis of Carbohydrate Mimetics. *Synthesis* **2010**, *2010* (19), 3217-3242.
10. Mackinnon, A. C.; Gibbons, M. A.; Farnworth, S. L.; Leffler, H.; Nilsson, U. J.; Delaine, T.; Simpson, A. J.; Forbes, S. J.; Hirani, N.; Gauldie, J.; Sethi, T. Regulation of transforming growth factor-β1-driven lung fibrosis by galectin-3. *Am. J. Respir. Crit. Care Med.* **2012**, *185* (5), 537-546.

11. Hirani, N.; MacKinnon, A. C.; Nicol, L.; Ford, P.; Schambye, H.; Pedersen, A.; Nilsson, U. J.; Leffler, H.; Sethi, T.; Tantawi, S.; Gavelle, L.; Slack, R. J.; Mills, R.; Karmakar, U.; Humphries, D.; Zetterberg, F.; Keeling, L.; Paul, L.; Molyneaux, P. L.; Li, F.; Funston, W.; Forrest, I. A.; Simpson, A. J.; Gibbons, M. A.; Maher, T. M. Target-inhibition of Galectin-3 by Inhaled TD139 in Patients with Idiopathic Pulmonary Fibrosis. *Eur. Resp. J.* **2020**, 2002559.

12. Dondoni, A.; Marra, A. Methods for Anomeric Carbon-Linked and Fused Sugar Amino Acid Synthesis: The Gateway to Artificial Glycopeptides. *Chem. Rev.* **2000**, *100* (12), 4395-4422.

13. Leclerc, E.; Pannecoucke, X.; Ethève-Quelquejeu, M.; Sollogoub, M., Fluoro-*C*--glycosides and fluoro-carbasugars, hydrolytically stable and synthetically challenging glycomimetics. *Chem. Soc. Rev.* **2013**, *42* (10), 4270-4283.

14. Wei, Z. *C*-Glycosides and Aza-*C*-Glycosides as Potential Glycosidase and Glycosyltransferase Inhibitors. *Curr. Top. Med. Chem.* **2005**, *5* (14), 1363-1391.

15. Compain, P.; Martin, O. R. Carbohydrate mimetics-based glycosyltransferase inhibitors. *Bioorg. Med. Chem.* **2001**, *9* (12), 3077-3092.

16. Yang, G.; Schmieg, J.; Tsuji, M.; Franck, R. W. The *C*-Glycoside Analogue of the Immunostimulant α-Galactosylceramide (KRN7000): Synthesis and Striking Enhancement of Activity. *Angew. Chem., Int. Ed.* **2004**, *43* (29), 3818-3822.

17. Franck, R. W.; Tsuji, M. α-*C*-Galactosylceramides: Synthesis and Immunology. *Accounts Chem. Res.* **2006**, *39* (10), 692-701.

18. Chao, E. C.; Henry, R. R., SGLT2 inhibition - a novel strategy for diabetes treatment. *Nat. Rev. Drug Discov.* **2010**, *9*, 551-559.

19. Wang, X.-J.; Zhang, L.; Byrne, D.; Nummy, L.; Weber, D.; Krishnamurthy, D.; Yee, N.; Senanayake, C. H. Efficient Synthesis of Empagliflozin, an Inhibitor of SGLT-2, Utilizing an $AlCl_3$-Promoted Silane Reduction of a β-Glycopyranoside. *Org. Lett.* **2014**, *16* (16), 4090-4093.

20. Henschke, J. P.; Lin, C.-W.; Wu, P.-Y.; Tsao, W.-S.; Liao, J.-H.; Chiang, P.-C. β--Selective *C*-Arylation of Diisobutylaluminum Hydride Modified 1,6-

Anhydroglucose: Synthesis of Canagliflozin without Recourse to Conventional Protecting Groups. *J. Org. Chem.* **2015**, *80* (10), 5189-5195.

21. Guo, C.; Hu, M.; DeOrazio, R. J.; Usyatinsky, A.; Fitzpatrick, K.; Zhang, Z.; Maeng, J.-H.; Kitchen, D. B.; Tom, S.; Luche, M.; Khmelnitsky, Y.; Mhyre, A. J.; Guzzo, P. R.; Liu, S. The design and synthesis of novel SGLT2 inhibitors: *C*-glycosides with benzyltriazolopyridinone and phenylhydantoin as the aglycone moieties. *Bioorg. Med. Chem.* **2014**, *22* (13), 3414-3422.

22. Wenqing, C.; Linlin, J.; Yafei, X.; Yuqiang, L.; Wei, L.; Guilong, Z. Design of SGLT2 Inhibitors for the Treatment of Type 2 Diabetes: A History Driven by Biology to Chemistry. *Med. Chem.* **2015**, *11* (4), 317-328.

23. Cavezza, A.; Boulle, C.; Guéguiniat, A.; Pichaud, P.; Trouille, S.; Ricard, L.; Dalko-Csiba, M. Synthesis of Pro-XylaneTM: A new biologically active C-glycoside in aqueous media. *Bioorg. Med. Chem. Lett.* **2009,** *19* (3), 845-849.

24. Leseurre, L.; Merea, C.; Duprat de Paule, S.; Pinchart, A. Eco-footprint: a new tool for the "Made in Chimex" considered approach. *Green Chem.* **2014**, *16* (3), 1139-1148.

25. Wei, A.; Boy, K. M.; Kishi, Y. Biological Evaluation of Rationally Modified Analogs of the H-Type II Blood Group Trisaccharide. A Correlation between Solution Conformation and Binding Affinity. *J. Am. Chem. Soc.* **1995**, *117* (37), 9432-9436.

26. Philip, G. H. Bioactive *C*-Glycosides from Bacterial Secondary Metabolism. *Curr. Top. Med. Chem.* **2005,** *5* (14), 1299-1331.

27. Hungerford, N. L.; Armitt, D. J.; Banwell, M. G. Syntheses of Showdomycin andits Anomer Using *N*-(Triisopropylsilyl)pyrrole asa Synthetic Equivalent for the Maleimide C3-Anion. *Synthesis* **2003**, *2003* (12), 1837-1843.

28. Kumar, V.; Shaw, A. K. First Total Synthesis of (+)-Varitriol. *J. Org. Chem.* **2008**, *73* (19), 7526-7531.

29. Zeng, J.; Vedachalam, S.; Xiang, S.; Liu, X.-W., Direct *C*-Glycosylation of Organotrifluoroborates with Glycosyl Fluorides and Its Application to the Total Synthesis of (+)-Varitriol. *Org. Lett.* **2011**, *13* (1), 42-45.

30. Malmstrøm, J.; Christophersen, C.; Barrero, A. F.; Oltra, J. E.; Justicia, J.; Rosales, A. Bioactive Metabolites from a Marine-Derived Strain of the Fungus Emericella variecolor. *J. Nat. Prod.* **2002**, *65* (3), 364-367.

31. Denmark, S. E.; Regens, C. S.; Kobayashi, T., Total Synthesis of Papulacandin D. *J. Am. Chem. Soc.* **2007**, *129* (10), 2774-2776.

32. Parkan, K.; Pohl, R.; Kotora, M. Cross-Coupling Reaction of Saccharide-Based Alkenyl Boronic Acids with Aryl Halides: The Synthesis of Bergenin. *Chem.-Eur. J.* **2014**, *20* (15), 4414-4419.

33. Ramaiah, P. A.; Row, L. R.; Reddy, D. S.; Anjaneyulu, A. S. R.; Ward, R. S.; Pelter, A. Isolation and characterisation of bergenin derivatives from Macaranga peltata. *J. Chem. Soc.-Perkin Trans. 1* **1979**, 2313-2316.

34. Li, Y. F.; Liu, J.; Song, G.; Li, K. J.; Zhang, K.; Ye, B. X. Sensitive voltammetric sensor for bergenin based on poly(L-lysine)/graphene modified glassy carbon electrode. *Anal. Methods* **2013**, *5* (16), 3895-3902.

35. Staněk, J.; Heřmánková, V.; Ineman V.; Kefurtová, Z.; Jarý, J. Způsob výroby kyseliny karmínové. CZ Patentový spis 228582, 1984, GB Patent 2094797, 1985.

36. McNaught, A. D. Nomenclature of carbohydrates (IUPAC Recommendations 1996). *Pure Appl. Chem.* **1996**; *68* (10), 1919-2008.

37. Hurd, C. D.; Bonner, W. A. The Glycosylation of Hydrocarbons by Means of the Grignard Reagent. *J. Am. Chem. Soc.* **1945**, *67* (11), 1972-1977.

38. Hurd, C. D.; Holysz, R. P. Reactions of Polyacylglycosyl Halides with Grignard Reagents. *J. Am. Chem. Soc.* **1950**, *72* (4), 1732-1735.

39. Kitamura, K.; Ando, Y.; Matsumoto, T.; Suzuki, K. Total Synthesis of Aryl *C*--Glycoside Natural Products: Strategies and Tactics. *Chem. Rev.* **2018**, *118* (4), 1495-1598.

40. Yang, Y.; Yu, B. Recent Advances in the Chemical Synthesis of *C*-Glycosides. *Chem. Rev.* **2017**, *117* (19), 12281-12356.

41. Levy, D. E.; Tang. C. *The chemistry of C-Glycosides*; Pergamon Press: Oxford, U.K. 1995.

42. Postema, M. *C-Glycoside Synthesis*; CRC Press: Boca Raton FL 1995.

43. Du, Y.; Linhardt, R. J.; Vlahov, I. R. Recent advances in stereoselective *C*-glycoside synthesis. *Tetrahedron* **1998**, *54* (34), 9913-9959.

44. Postema, M. H. D. Recent developments in the synthesis of *C*-glycosides. *Tetrahedron* **1992**, *48* (40), 8545-8599.

45. Taillefumier, C.; Chapleur, Y. Synthesis and Uses of *exo*-Glycals. *Chem. Rev.* **2004**, *104* (1), 263-292.

46. Xuejun, Y.; Robert, J. L. Recent Advances in the Synthesis of *C*-oligosaccharides. *Curr. Top. Med. Chem.* **2005**, *5* (14), 1393-1430.

47. Lei, L.; Michael, M.; Maarten, H. D. P., Synthesis of *C*-Saccharides and Higher Congeners. *Curr. Org. Chem.* **2001**, *5* (12), 1133-1167.

48. Elisabeth v, M.; Robert, N. B. Recent Advances in the Synthesis of *C*-linked Glycoconjugates. *Curr. Top. Med. Chem.* **2005**, *5* (14), 1351-1361.

49. David, Y. W. L.; Minsheng, H. Recent Advances in Aryl *C*-Glycoside Synthesis. *Curr. Top. Med. Chem.* **2005**, *5* (14), 1333-1350.

50. Bokor, É.; Kun, S.; Goyard, D.; Tóth, M.; Praly, J.-P.; Vidal, S.; Somsák, L. *C*-Glycopyranosyl Arenes and Hetarenes: Synthetic Methods and Bioactivity Focused on Antidiabetic Potential. *Chem. Rev.* **2017**, *117* (3), 1687-1764.

51. Štambaský, J.; Hocek, M.; Kočovský, P. *C*-Nucleosides: Synthetic Strategies and Biological Applications. *Chem. Rev.* **2009**, *109* (12), 6729-6764.

52. Mauro, F. A. A.; Roberto, P. Synthesis and Medicinal Properties of 2-deoxyribose and ribose *C*-Nucleosides. *Curr. Org. Chem.* **2008**, *12* (18), 1544-1569.

53. Choumane, M.; Banchet, A.; Probst, N.; Gérard, S.; Plé, K.; Haudrechy, A. The synthesis of D-*C*-mannopyranosides. *C. R. Chim.* **2011**, *14* (2), 235-273.

54. Lalitha, K.; Muthusamy, K.; Prasad, Y. S.; Vemula, P. K.; Nagarajan, S. Recent developments in β-*C*-glycosides: synthesis and applications. *Carbohydr. Res.* **2015**, *402*, 158-171.

55. Beau, J.-M.; Gallagher, T. Nucleophilic *C*-glycosyl donors for *C*-glycoside synthesis. In *Glycoscience Synthesis of Substrate Analogs and Mimetics*; Driguez, H.; Thiem, J., Eds. Springer: Berlin Heidelberg, 1998; pp 1-54.

56. Togo, H.; He, W.; Waki, Y.; Yokoyama, M. *C*-Glycosidation Technology With Free Radical Reactions. *Synlett* **1998**, *1998* (07), 700-717.

57. Somsák, L. Carbanionic Reactivity of the Anomeric Center in Carbohydrates. *Chem. Rev.* **2001**, *101* (1), 81-136.

58. Pedro, M.; Tomas, T.; Eduardo, M.; Fernando, G.-B.; Ignacio, D.; Rosa, M. CROSS--COUPLING REACTIONS FOR THE SYNTHESIS OF *C*-GLYCOSIDES AND RELATED COMPOUNDS. *Heterocycles* **2012**, *86*, 791-820.

59. Wellington, K. W.; Benner, S. A. A Review: Synthesis of Aryl *C*-Glycosides Via the Heck Coupling Reaction. *Nucleosides Nucleotides Nucleic Acids* **2006**, *25* (12), 1309--1333.

60. Štěpánek, P.; Vích, O.; Kniežo, L.; Dvořáková, H.; Vojtíšek, P. A short and efficient synthesis of α-*C*-(1→3)-linked disaccharides containing deoxyhexopyranoses. *Tetrahedron-Asymmetry* **2004**, *15* (6), 1033-1041.

61. Stepanek, P.; Vich, O.; Werner, L.; Kiezo, L.; Dvorakova, H.; Vojtisek, P. Stereoselective preparation of precursors of alpha-*C*-(1→3)-disaccharides. *Collect. Czech. Chem. Commun.* **2005**, *70* (9), 1411-1428.

62. Fang, J.; Li, J.; Chen, X.; Zhang, Y.; Wang, J.; Guo, Z.; Zhang, W.; Yu, L.; Brew, K.; Wang, P. G. Highly Efficient Chemoenzymatic Synthesis of α-Galactosyl Epitopes with a Recombinant α(1→3)-Galactosyltransferase. *J. Am. Chem. Soc.* **1998**, *120* (27), 6635-6638.

63. Demange, R.; Awad, L.; Vogel, P. Synthesis of *C*-linked analogues of β-D--galactopyranosyl-(1→3)-D-galactopyranosides and of β-D-galactopyranosyl-(1→3)--D-galactal. *Tetrahedron-Asymmetry* **2004**, *15* (22), 3573-3585.

64. Dujardin, G.; Rossignol, S.; Brown, E. An Improved Dienophile-Induced Access to Enantiopure 2,4-Dideoxysugar Lactones via Hetero Diels-Alder Reaction: Synthesis of the (+)-Lactone Moiety of Compactin. *Synthesis* **1998**, *1998* (05), 763-770.

65. Dujardin, G.; Molato, S.; Brown, B. Asymmetric syntheses of substituted dehydropyrans by Diels-Alder heterocycloadditions involving chiral vinyl ethers as dienophiles. *Tetrahedron-Asymmetry* **1993**, *4* (2), 193-196.

66. Dujardin, G.; Rossignol, S.; Brown, E. Chiral enol ethers in carbohydrate chemistry: De novo synthesis of protected L-2-deoxy hexoses. *Tetrahedron Lett.* **1996**, *37* (23), 4007-4010.

67. Tiwari, P.; Misra, A. K. An Efficient Stereoselective Dihydroxylation of Glycals using a Bimetallic System, $RuCl_3/CeCl_3/NaIO_4$. *J. Org. Chem.* **2006**, *71* (7), 2911-2913.

68. Di Bussolo, V.; Kim, Y.-J.; Gin, D. Y. Direct Oxidative Glycosylations with Glycal Donors. *J. Am. Chem. Soc.* **1998**, *120* (51), 13515-13516.

69. Kim, J.-Y.; Bussolo, V. D.; Gin, D. Y. Stereoselective Synthesis of 2-Hydroxy-α--mannopyranosides from Glucal Donors. *Org. Lett.* **2001**, *3* (2), 303-306.

70. Liu, J.; Gin, D. Y. C2-Amidoglycosylation. Scope and Mechanism of Nitrogen Transfer. *J. Am. Chem. Soc.* **2002**, *124* (33), 9789-9797.

71. Liu, J.; Di Bussolo, V.; Gin, D. Y. C2-Acetamidomannosylation. Synthesis of 2-*N*--acetylamino-2-deoxy-α-D-mannopyranosides with glucal donors. *Tetrahedron Lett.* **2003,** *44* (21), 4015-4018.

72. Parrish, J. D.; Little, R. D., Preparation of α-*C*-Glycosides from Glycals. *Org. Lett.* **2002**, *4* (9), 1439-1442.

73. Codée, Jeroen D. C.; Marel, Gijsbert A. van d.; Boeckel, Constant A. A. v.; Boom, Jacques H. v. Probing the Heparin−Antithrombin III Interaction Using Synthetic Pentasaccharides Bearing Positively Charged Groups. *Eur. J. Org. Chem.* **2002**, *2002* (23), 3954-3965.

74. Uchiyama, T.; Woltering, T. J.; Wong, W.; Lin, C.-C.; Kajimoto, T.; Takebayashi, M.; Wéitz-Schmidt, G.; Asakura, T.; Noda, M.; Wong, C.-H. Design and synthesis of *C*-linked fucosides as inhibitors of E-selectin. *Bioorg. Med. Chem.* **1996**, *4* (7), 1149--1165.

75. Doknic, D.; Abramo, M.; Sutkeviciute, I.; Reinhardt, A.; Guzzi, C.; Schlegel, M. K.; Potenza, D.; Nieto, P. M.; Fieschi, F.; Seeberger, P. H.; Bernardi, A. Synthesis and

Characterization of Linker-Armed Fucose-Based Glycomimetics. *Eur. J. Org. Chem.* **2013**, *2013* (24), 5303-5314.

76. Banchereau, J.; Briere, F.; Caux, C.; Davoust, J.; Lebecque, S.; Liu, Y.-J.; Pulendran, B.; Palucka, K. Immunobiology of Dendritic Cells. *Annu. Rev. Immunol.* **2000**, *18* (1), 767-811.

77. Khoo, U.-S.; Chan, K. Y. K.; Chan, V. S. F.; Lin, C. L. DC-SIGN and L-SIGN: the SIGNs for infection. *J. Mol. Med.* **2008**, *86* (8), 861-874.

78. Rojo, J.; Delgado, R. Glycodendritic structures: promising new antiviral drugs. *J. Antimicrob. Chemother.* **2004**, *54* (3), 579-581.

79. Anderluh, M.; Jug, G.; Svajger, U.; Obermajer, N. DC-SIGN Antagonists, a Potential New Class of Anti-Infectives. *Curr. Med. Chem.* **2012**, *19* (7), 992-1007.

80. Guo, Y.; Feinberg, H.; Conroy, E.; Mitchell, D. A.; Alvarez, R.; Blixt, O.; Taylor, M. E.; Weis, W. I.; Drickamer, K. Structural basis for distinct ligand-binding and targeting properties of the receptors DC-SIGN and DC-SIGNR. *Nat. Struct. Mol. Biol.* **2004**, *11*, 591-598.

81. Cecioni, S.; Imberty, A.; Vidal, S. Glycomimetics versus Multivalent Glycoconjugates for the Design of High Affinity Lectin Ligands. *Chem. Rev.* **2015,** *115* (1), 525-561.

82. Eignerová, B.; Dračínský, M.; Kotora, M. Perfluoroalkylation through Cross--Metathesis between Alkenes and (Perfluoroalkyl)propenes. *Eur. J. Org. Chem.* **2008**, *2008* (26), 4493-4499.

83. Voigtritter, K.; Ghorai, S.; Lipshutz, B. H. Rate Enhanced Olefin Cross-Metathesis Reactions: The Copper Iodide Effect. *J. Org. Chem.* **2011**, *76* (11), 4697-4702.

84. Johansson Seechurn, C. C. C.; Kitching, M. O.; Colacot, T. J.; Snieckus, V., Palladium-Catalyzed Cross-Coupling: A Historical Contextual Perspective to the 2010 Nobel Prize. *Angew. Chem.-Int. Edit.* **2012**, *51* (21), 5062-5085.

85. Miyaura, N.; Suzuki, A. Palladium-Catalyzed Cross-Coupling Reactions of Organoboron Compounds. *Chem. Rev.* **1995**, *95* (7), 2457-2483.

86. Jana, R.; Pathak, T. P.; Sigman, M. S. Advances in Transition Metal (Pd,Ni,Fe)--Catalyzed Cross-Coupling Reactions Using Alkyl-organometallics as Reaction Partners. *Chem. Rev.* **2011**, *111* (3), 1417-1492.

87. Hu, X. Nickel-catalyzed cross coupling of non-activated alkyl halides: a mechanistic perspective. *Chem. Sci.* **2011,** *2* (10), 1867-1886.

88. Lu, Z.; Fu, G. C., Alkyl–Alkyl Suzuki Cross-Coupling of Unactivated Secondary Alkyl Chlorides. *Angew. Chem.-Int. Edit.* **2010**, *49* (37), 6676-6678.

89. Netherton, M. R.; Dai, C.; Neuschütz, K.; Fu, G. C. Room-Temperature Alkyl−Alkyl Suzuki Cross-Coupling of Alkyl Bromides that Possess β Hydrogens. *J. Am. Chem. Soc.* **2001**, *123* (41), 10099-10100.

90. Saito, B.; Fu, G. C., Alkyl−Alkyl Suzuki Cross-Couplings of Unactivated Secondary Alkyl Halides at Room Temperature. *J. Am. Chem. Soc.* **2007**, *129* (31), 9602-9603.

91. Zhou, J.; Fu, G. C. Suzuki Cross-Couplings of Unactivated Secondary Alkyl Bromides and Iodides. *J. Am. Chem. Soc.* **2004**, *126* (5), 1340-1341.

92. Dubois, E.; Beau, J.-M. Formation of *C*-glycosides by a palladium-catalysed coupling reaction of tributylstannyl glycals with organic halides. *J. Chem. Soc., Chem. Commun.* **1990**, (17), 1191-1192.

93. Boucard, V.; Larrieu, K.; Lubin-Germain, N.; Uziel, J.; Augé, J. *C*-Glycosylated Phenylalanine Synthesis by Palladium-Catalyzed Cross-Coupling Reactions. *Synlett* **2003**, *2003* (15), 2444-2444.

94. Lehmann, U.; Awasthi, S.; Minehan, T. Palladium-Catalyzed Cross-Coupling Reactions between Dihydropyranylindium Reagents and Aryl Halides. Synthesis of *C*-Aryl Glycals. *Org. Lett.* **2003**, *5* (14), 2405-2408.

95. Foubelo, F.; Nájera, C.; Yus, M. The Hiyama Cross-Coupling Reaction: New Discoveries. *Chem. Rec.* **2016**, *16* (6), 2521-2533.

5 SEZNAM ZKRATEK

Ac	acetyl
AIBN	2,2'- azobisisobutyronitril
aq.	vodný roztok
Ar	aryl
Bn	benzyl
B(pin)	pinakol-boronát
Bu	butyl
COD	1,5-cyklooktadien
CRD	sacharid rozpoznávající doména (carbohydrate recognition domain)
dba	dibenzylidenaceton
DMAP	*N*,*N*-dimetylpyridin-4-amin
DMDO	dimethyldioxiran
DME	1,2-dimethoxyethan
DMF	*N*,*N*-dimethylformamid
DMP	Dess-Martinovo činidlo
DMSO	dimetylsulfoxid
EE	ethoxyethyl
ekv.	ekvivalent
Et_3N (TEA)	triethylamin
fod	6,6,7,7,8,8,8-heptafluor-2,2-dimethyl-3,6-oktandionát
HDA	hetero-Dielsova-Alderova reakce
HG-II	katalyzátor Hoveyda-Grubbs 2. generace
IC_5	poloviční maximální inhibiční koncentrace (half maximal inhibitory concentration)
*i*Pr	isopropyl
L-selektrid	lithium tri-*sek*-butylborohydrid lithný
mCPBA	kyselina *m*-chlorperoxybenzoová
Me	methyl
MOP	methoxypropyl
Ms	mesyl, methansulfonyl

NBS	*N*-bromsukcinimid
NIS	*N*-jodsukcinimid
NMR	nukleární magnetická rezonance
NOE	nukleární Overhauserův efekt
Ph	fenyl
py.	pyridin
Super-hydrid	lithium triethylborohydrid
p-TsOH	*p*-toluensulfonová kyselina
TBA	tetrabutylamonium
TMA	tetramethylamonium
TBDMS, TBS	*tert*-butyldimetylsilyl
TBDPS	*tert*-butyldifenylsilyl
Tf	trifluormethansulfonát
TIPS	triisopropylsilyl
THF	tetrahydrofuran
X-ray	krystalografická analýza

6 PŘÍLOHY

PŘÍLOHA I

Parkan, K.; Vich, O.; Dvorakova, H.; Kniezo, L. Stereoselective preparation of 2,3-dideoxy-3--*C*-[(α-D-galactopyranosyl)methyl]-D-arabino-hexopyranose and 2,3-dideoxy-3-*C*-[(α-D--galactopyranosyl)methyl]-L-arabino-hexopyranose. *Collect. Czech. Chem. Commun.* **2008**, *73* (5), 690-700. IF 1.137; počet citací 2

PŘÍLOHA II

Parkan, K.; Werner, L.; Lovyova, Z.; Prchalova, E.; Kniezo, L. An approach to stereoselective preparation of 3-*C*-glycosylated D- and L-glucals. *Carbohydr. Res.* **2010**, *345* (3), 352-362. IF 2,104; počet citací 5

PŘÍLOHA III

Lovyova, Z.; Parkan, K.; Kniezo, L. Stereoselective preparation of four 3-*C*-mannosylated D- and L-glucals from a single starting compound. *Tetrahedron* **2011**, *67* (27), 4967-4979. IF 2,457; počet citací 5

PŘÍLOHA IV

Parkan, K.; Pohl, R.; Kotora, M. Cross-Coupling Reaction of Saccharide-Based Alkenyl Boronic Acids with Aryl Halides: The Synthesis of Bergenin, *Chem.-Eur. J.* **2014**, *20* (15), 4414-4419. IF 5,236; počet citací 32

PŘÍLOHA V

Oroszová, B.; Choutka, J.; Pohl, R.; Parkan, K. Modular Stereoselective Synthesis of (1→2)--*C*-Glycosides based on the sp^2–sp^3 Suzuki–Miyaura Reaction. *Chem.-Eur. J.* **2015**, *21* (19), 7043-7047. IF 5,236; počet citací 10

PŘÍLOHA VI

Šnajdr, I.; Parkan, K.; Hessler, F.; Kotora, M. Cross-metathesis Reaction of α- and β-Vinyl *C*-glycosides with Alkenes. *Beilstein J. Org. Chem.* **2015**, *11*, 1392-1397. IF 2,883; počet citací 6

PŘÍLOHA VII

Bertolotti, B.; Oroszová, B.; Sutkeviciute, I.; Kniežo, L.; Fieschi, F.; Parkan, K.; Lovyová, Z.; Kašáková, M.; Moravcová, J. Nonhydrolyzable *C*-disaccharides, a new class of DC-SIGN ligands. *Carbohydr. Res.* **2016**, *435*, 7-18. IF 2,104; počet citací 4

PŘÍLOHA VIII

Bertolotti, B.; Sutkeviciute, I.; Ambrosini, M.; Ribeiro-Viana, R.; Rojo, J.; Fieschi, F.; Dvořáková, H.; Kašáková, M.; Parkan, K.; Hlaváčková, M.; Nováková, K.; Moravcová, J. Polyvalent *C*-glycomimetics based on L-fucose or D-mannose as potent DC-SIGN antagonists. *Org. Biomol. Chem.* **2017**, *15* (18), 3995-4004. IF 3,876; počet citací 18

PŘÍLOHA IX

Choutka, J.; Pohl, R.; Parkan, K. MOP and EE Protecting Groups in Synthesis of α- or β-Aryl--*C*-Glycosides from Glycals. *ACS Omega* **2018**, *3* (7), 7875-7887. IF 3,512, počet citací 6

PŘÍLOHA X

Vaňková K., Rahm M., Choutka J., Pohl R., Parkan K.: Facile Approach to *C*-glucosides by Using a Protecting-Group-Free Hiyama Cross-Coupling Reaction: High-Yielding Dapagliflozin Synthesis. *Chem.-Eur. J.*, **2021**, DOI: 10.1002/chem.202101052**.** IF 5,236; počet citací 0.

PŘÍLOHA I

Parkan, K.; Vich, O.; Dvorakova, H.; Kniezo, L. Stereoselective preparation of 2,3-dideoxy-3--*C*-[(α-D-galactopyranosyl)methyl]-D-arabino-hexopyranose and 2,3-dideoxy-3-*C*-[(α-D--galactopyranosyl)methyl]-L-arabino-hexopyranose. *Collect. Czech. Chem. Commun.* **2008**, *73* (5), 690-700.

STEREOSELECTIVE PREPARATION OF 2,3-DIDEOXY-3-*C*-[(α-D-GALACTOPYRANOSYL)METHYL]-D-*arabino*-HEXOPYRANOSE AND 2,3-DIDEOXY-3-*C*-[(α-D-GALACTOPYRANOSYL)METHYL]-L-*arabino*-HEXOPYRANOSE

Kamil PARKAN[a1], Ondřej VÍCH[a2], Hana DVOŘÁKOVÁ[b] and Ladislav KNIEŽO[a3,*]

[a] *Department of Chemistry of Natural Compounds, Institute of Chemical Technology, Prague, Technická 5, 166 28 Prague 6, Czech Republic; e-mail:* [1] *kamil.parkan@vscht.cz,* [2] *ondrej.vich@vscht.cz,* [3] *ladislav.kniezo@vscht.cz*

[b] *NMR Laboratory, Institute of Chemical Technology, Prague, Technická 5, 166 28 Prague 6, Czech Republic; e-mail: hana.dvorakova@vscht.cz*

Received May 23, 2008
Accepted July 2, 2008
Published online July 25, 2008

The diastereomeric substituted 2*H*-dihydropyran derivatives **2b** and **3b** were obtained by the stereoselective cycloaddition of (*E*)-4-(tetra-*O*-benzyl-α-D-galactopyranosyl)-1-(thiazol-2-yl)but-2-en-1-one (**1**) with either of the enantiomeric chiral vinyl ethers (*R*)-**4** or (*S*)-**4**. Reduction of the ester group, transformation of the thiazole ring into an aldehyde group and reaction with an excess of borane afforded the final *C*-(1→3)-disaccharide structures. The obtained *C*-(1→3)-disaccharides, containing an L- or D-deoxy-*arabino*-hexopyranose moiety at the reducing end, were characterized as peracetylated methyl glycosides **9a**, **9b** and **12a**, **12b**.
Keywords: *C*-Disaccharides; Stereoselective synthesis; Saccharide chemistry.

As a result of their great structural variability, saccharides represent very suitable "structural units" for the construction of the so-called sugar codes[1]. The interactions of sugar codes with protein receptors play a key role in cell/cell or cell/pathogen communication and, inter alia, even control such important processes as cell adhesion, fertilization, inflammation, immune response and cancer metastasis. A deeper understanding of molecular details of these recognition processes has led to the discovery of various saccharide derivatives of significant therapeutic potential[2]. However, the search for new carbohydrate-based therapeutics or vaccines is often complicated by the fact that oligosaccharides used in forming the sugar codes are labile compounds in vivo, because they undergo hydrolysis by ubiquitous glycosidases. The solution to this problem may rest in the use of stable carbohydrate mimicks, such as *C*-disaccharides, which nominally preserve the

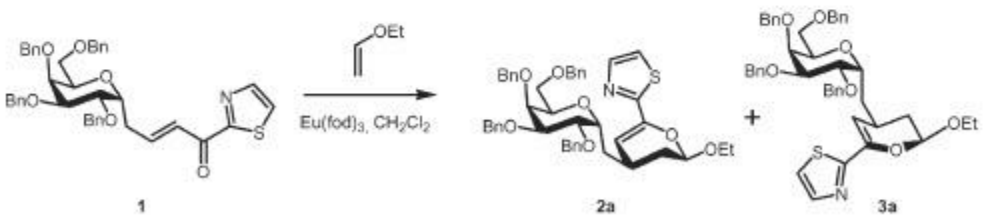
Collect. Czech. Chem. Commun. 2008, Vol. 73, No. 5, pp. 690–700

doi:10.1135/cccc20080690

structural information of natural disaccharides but are chemically as well as enzymatically non-hydrolyzable[3].

Recently we described a short and efficient synthesis of α-*C*-(1→3)-disaccharides in which D-glucopyranose was linked to an L- or D-2-deoxy-*arabino*-hexopyranose moiety[4]. Later on, we found that the stereoselectivity of the key step in our synthesis, namely the cycloaddition of the substituted oxadiene with ethyl vinyl ether, can be markedly increased by the use of chiral vinyl ethers. This has made possible the facile stereoselective preparation of further *C*-(1→3)-disaccharide derivatives[5]. As an example of this approach we now report the preparation of previously unknown disaccharide mimetics, in which the α-D-galactopyranosyl moiety is linked by a methylene bridge to C-3 of an L- or D-2-deoxy-*arabino*-hexopyranose. The α-D-galactopyranosyl moiety, attached by a (1→3) glycosidic bond to the oligosaccharide chain, is present as the terminal monosaccharide, e.g., in the B blood group antigen and in the so-called α-galactosyl epitope, which is responsible for the hyperacute rejection of organs in xenotransplantation[6]. The synthesized compounds represent non-hydrolyzable mimetics of this structural motif, and further synthetic transformations of the deoxy-*arabino*-hexopyranose ring (i.e., via the corresponding glycals) make possible their linkage into oligosaccharide chains and the synthesis of non-hydrolyzable analogs of natural epitopes. A stereoisomeric compound, 2,3-dideoxy-3-*C*-[(β-D-galactopyranosyl)methyl]D-*lyxo*-hexopyranose, was recently prepared from isolevoglucosen, using a longer and more laborious procedure[7].

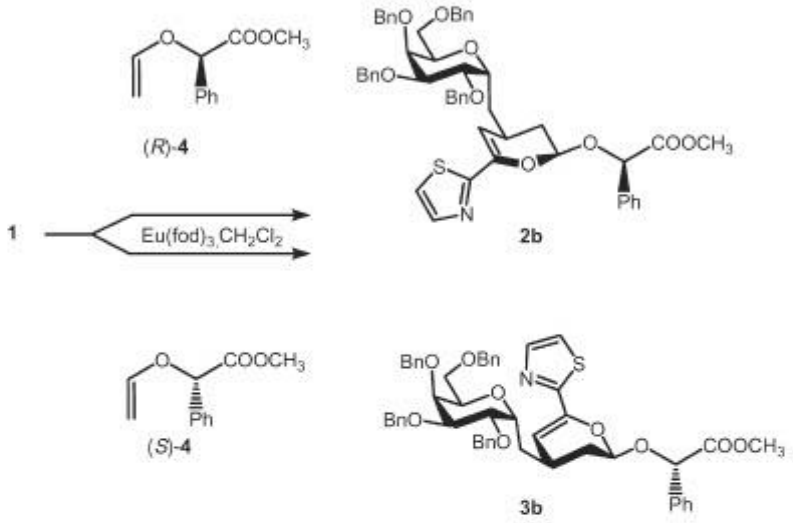
Using our original procedure[4], the reaction of (*E*)-4-(tetra-*O*-benzyl-α-D-galactopyranosyl)-1-(thiazol-2-yl)but-2-en-1-one (**1**) with ethyl vinyl ether led to a 1:1 mixture of two diastereomeric endo cycloadducts **2a** and **3a** which were inseparable by preparative chromatography (Scheme 1).



SCHEME 1

Collect. Czech. Chem. Commun. 2008, Vol. 73, No. 5, pp. 690–700

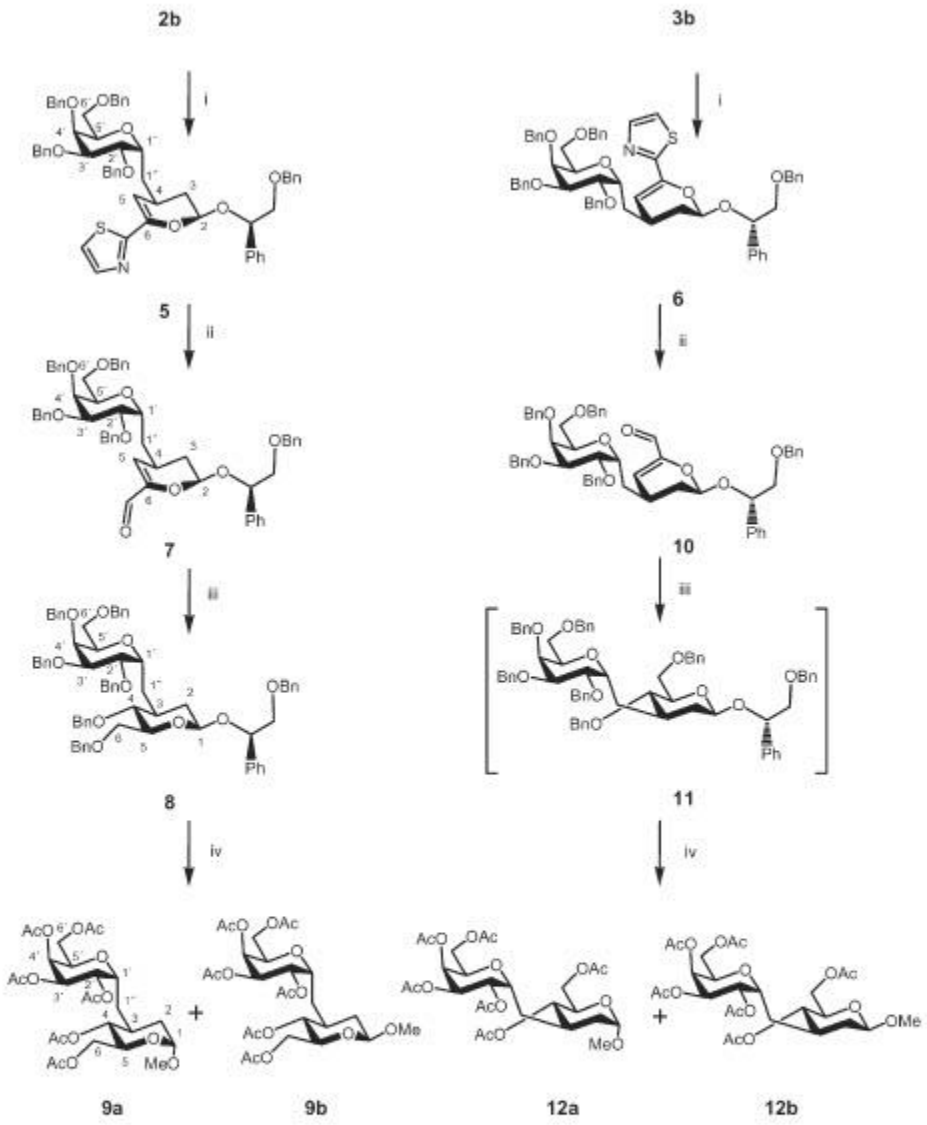
On the contrary, cycloaddition with the enantiopure vinyl ethers (*R*)-**4** and (*S*)-**4**, easily obtainable from the cheap and commercially accessible enantiomers of mandelic acid, was highly stereoselective[5]. The reaction with enantiomer (*R*)-**4** afforded almost pure cycloadduct **2b**, while the reaction with enantiomer (*S*)-**4** led to almost pure cycloadduct **3b** (Scheme 2).



SCHEME 2

Unfortunately, preliminary experiments demonstrated that the subsequent transformation of the thiazole ring in cycloadducts **2b** and **3b** into an aldehyde functionality (unlike the similar conversion in cycloadducts **2a** and **3a**) proceeded with problems. The desired aldehydes were obtained in only low yields and were accompanied by other unidentified compounds. Originally, we intended to circumvent this synthetic problem by replacing the chiral moiety of mandelic acid in cycloadducts **2b** and **3b** with simpler substituents (e.g., methoxy or ethoxy). However, all such attempts led only to mixtures of several compounds. The attempted acid-catalyzed transglycosidation was probably accompanied by cleavage of the unsaturated dihydropyran ring and subsequent decomposition of the intermediates.

To avoid this problem, we reduced the ester group in cycloadducts **2b** and **3b** with $LiAlH_4$ and protected the resulting primary alcohols by benzylation (Scheme 3). The benzyl ethers **5** and **6** then underwent transformation of the thiazole ring to an aldehyde in the usual manner without difficulty. Compound **5** gave pure aldehyde **7** (yield 70%) which, on reaction with excess of borane and benzylation of the newly generated hydroxy



(i) 1. $LiAlH_4$, THF, 2. NaH, BnBr, THF; (ii) 1. TfOMe, MeCN, 2. $NaBH_4$, MeOH, 3. $AgNO_3$, H_2O, MeCN; (iii) 1. $BH_3{\cdot}Me_2S$, THF, 30% NaOH, 30% H_2O_2, 2. NaH, BnBr, THF; (iv) 1. MeOH, 3 M HCl, THF, 2. H_2, Pd/C, 3. Ac_2O, pyridine

SCHEME 3
Synthesis of (1→3)-*C*-disaccharides

Collect. Czech. Chem. Commun. 2008, Vol. 73, No. 5, pp. 690–700

groups, afforded the desired structure, *C*-disaccharide **8**, as the sole reaction product. Although the mass spectrum of the compound obtained agreed with the assumed structure **8**, it was not possible to confirm the relative configuration of the new deoxypyranose directly from its complex ^{1}H NMR spectrum. However, the chiral aglycon was easily exchanged by treatment of compound **8** in tetrahydrofuran with methanolic solution of HCl, the reaction afforded a mixture of only two anomers, which, after exchange of the benzyl protecting groups for acetates, was characterized as a mixture of the peracetyl methyl glycosides **9a** and **9b**. As determined from the NMR spectra, the anomeric methyl glycosides **9a** and **9b** were formed in the 4:1 ratio (as estimated by integration of the ^{1}H NMR signals of the methoxy group at 3.27 ppm in the major anomer and at 3.41 ppm in the minor one). The coupling constants of the major anomer **9a** unequivocally show that the substituents on carbon atoms 4 and 5 of the new deoxyhexopyranose are in the equatorial positions (J(H-4,H-5) = 9.9 Hz). The configurations of the remaining carbon atoms in this compound were determined using NOE experiments: a marked NOE was observed between protons H-3 and H-5, but there was no interaction with proton H-1. On the contrary, protons H-3 and H-5 showed a strong NOE with the methoxy group in the anomeric position. These results confirm that the substituents at positions 3, 4 and 5 are equatorial whereas the anomeric methoxy group is axial. This means that the major stereoisomer **9a** is the α-methyl glycoside of the substituted 2-deoxy-*arabino*-hexopyranose. As follows from the coupling constants of the ^{1}H NMR spectrum of the minor anomer **9b**, the substituents on carbon atoms 1, 4 and 5 of this deoxyhexopyranose are in equatorial position (J(H-1,H-2ax) = 9.4 Hz, J(H-1,H-2eq) = 1.8 Hz, J(H-4,H-5) = 9.6 Hz). Moreover, the spectrum of this anomer displayed marked NOEs between protons H-1, H-3 and H-5; thus confirming that in this case all the substituents are equatorial and thus **9b** is the β-methyl glycoside of the substituted 2-deoxy-*arabino*-hexopyranose. Since the absolute configuration of the starting compound **2b** was unequivocally determined by X-ray diffraction in our previous study[5], the deoxy-*arabino*-hexopyranose in methyl glycosides **9a** and **9b** must have the L-configuration.

Using the same reaction scheme as above, we converted the diastereoisomeric compound **6** into aldehyde **10**, which, via intermediate **11** (in this case not isolated), was converted into a mixture of peracetylated methyl glycosides **12a** and **12b**. The NMR spectra of the obtained mixture of **12a** and **12b** were almost identical with those of compounds **9a** and **9b**. Also in this case, the two methyl glycosides were formed in the ca. 4:1 ratio (as determined by integration of ^{1}H NMR signals of OMe at 3.34 ppm for the

major anomer and at 3.49 ppm for the minor one). As in the preceding case, the interaction constants and NOE experiments unequivocally confirm that the major stereoisomer **12a** is the α-methyl glycoside of the substituted 2-deoxy-*arabino*-hexopyranose whereas the minor stereoisomer **12b** is the β-methyl glycoside. As follows from the absolute configuration[5] of the starting compound **3b**, the new deoxy-*arabino*-hexopyranose in the methyl glycosides **12a**, **12b** must have the D-configuration.

In conclusion, we have demonstrated that stereoselective cycloaddition of the enantiomeric vinyl ethers (*R*)-**4** and (*S*)-**4** with the suitably substituted oxadiene **1** enables a facile and simple preparation of the previously unknown (1→3)-disaccharide mimetics, containing an α-D-galactopyranosyl moiety at the non-reducing end and a 2-deoxy-*arabino*-hexopyranose moiety of L- or D-configuration at the reducing end. Compounds **12a** and **12b** may serve as precursors for the synthesis of non-hydrolyzable glycoprotein or glycolipid epitopes containing the α-D-galactopyranosyl-(1→3)-structural motif.

EXPERIMENTAL

The synthesis of compounds **2b** and **3b** has already been described in our previous paper[5].

The melting points are uncorrected. TLC was performed on HF_{254} plates (Merck), detection was by UV light or by spraying with a solution of $Ce(SO_4)_2(H_2O)_4$ (5 g) in 10% H_2SO_4 (500 ml) and subsequent heating. Flash column chromatography was performed on silica gel (MERCK, 100–160 μm) in solvents, distilled prior to use. Optical rotations were measured at 25 °C on a JASCO DIP-370 spectropolarimeter. ^1H and ^{13}C NMR spectra were taken on a Bruker DRX 500 Avance spectrometer at 500.132 MHz (^1H NMR) and at 125.767 MHz (^{13}C NMR) using tetramethylsilane as internal standard. Chemical shifts in the ^1H and ^{13}C NMR spectra are given in ppm (δ-scale), coupling constants (*J*) in Hz. ^1H and ^{13}C NMR signal assignments were confirmed by 2D COSY and HMQC when necessary. NOE connectivities were obtained using the 1D ^1H DPFGSE-NOE experiment. For numbering of atoms see Scheme 3. Mass spectra and HPLC were performed on a 250 × 4.6 mm column packed with 5 μm Supelco BDS Hypersil C-18, mobile phase methanol–water, using an HP 1100 instrument equipped with a gradient pump, column thermostat, and in addition to a UV detector, also with an Agilent G1956B single quadrupole system as an MS detector.

(2*S*,4*S*)-2-[(2*R*)-2-(Benzyloxy)-1-phenylethoxy]-4-[(2,3,4,6-tetra-*O*-benzyl-α-D-galacto pyranosyl)methyl]-6-(thiazol-2-yl)-3,4-dihydro-2*H*-pyran (**5**)

Lithium aluminum hydride (0.3 g, 7.95 mmol) was added portionwise under nitrogen to a solution of compound **2b** (2.3 g, 2.65 mmol) in tetrahydrofuran (50 ml), cooled to 0 °C, and the reaction mixture was stirred at room temperature for 2 h. The mixture was then quenched by the cautious addition of 1 M NaOH (5 ml), the solid salts were removed by filtration and the filtrate was taken down. The residue was partitioned between ethyl acetate and water. The organic phase was dried, the solvent evaporated and the residue flash-

chromatographed on a short column of silica gel in petroleum ether–ethyl acetate (5:1). A solution of the obtained alcohol (2.1 g, R_F 0.4 in petroleum ether–ethyl acetate (2:1), *m/z* 841.8 $[M + H]^+$) in tetrahydrofuran (60 ml) was stirred with NaH (0.2 g, 5 mmol; 60% suspension in mineral oil) at room temperature for 1 h. Benzyl bromide (0.49 ml, 3.75 mmol) and tetrabutylammonium iodide (0.23 g, 0.63 mmol) were added, and the reaction mixture was stirred at 40 °C for 15 min and then at room temperature for 14 h. After the addition of methanol (3 ml), the solvent was evaporated in vacuo and the residue was partitioned between dichloromethane and saturated solution of $NaHCO_3$. The organic phase was dried and then evaporated. The residue was chromatographed on silica gel in petroleum ether–ethyl acetate (4:1). Yield 1.97 g (80%) of compound 5, R_F 0.65 (petroleum ether–ethyl acetate 2:1). $[\alpha]_D$ +52.2 (*c* 1.02, $CHCl_3$). ^{1}H NMR ($CDCl_3$): 1.78 m, 1 H (H-1″a); 1.92 ddd, 1 H, *J*(3ax,3eq) = 13.7, *J*(3ax,4) = 6.8, *J*(3ax,2) = 6.8 (H-3ax); 2.00 ddd, 1 H, *J*(1″a,1″b) = 15.1, *J*(1″b,1′) = 10.3, *J*(1″b,4) = 5.5 (H-1″b); 2.24 ddd, 1 H, *J*(3eq,3ax) = 13.7, *J*(3eq,4) = 6.6, *J*(3eq,2) = 1.4 (H-3eq); 2.62 m, 1 H (H-4); 3.59–3.75 m, 5 H (BnOC**H**$_2$CHPh, H-2′, H-3′, H-6a′); 3.92 m, 1 H (6b′); 4.02 m, 1 H (H-4′); 4.11 m, 1 H (H-5′); 4.25 bd, 1 H, *J*(1″b,1′) = 10.3 (H-1′); 4.47–4.80 m, 10 H (5 × OC**H**$_2$Ph); 5.00 dd, 1H, *J* = 8.1, 3.6 (BnOCH$_2$C**H**Ph); 5.50 dd, 1 H, *J*(2,3eq) = 1.4, *J*(2,3ax) = 6.8 (H-2); 6.01 d, 1 H, *J*(5,4) = 3.4 (H-5); 7.12 d, 1 H, *J* = 3.2 (H-thiazole); 7.19–7.41 m, 30 H (6 × Ph); 7.71 d, 1 H, *J* = 3.2 (H-thiazole). ^{13}C NMR ($CDCl_3$): 27.61 (C-4), 34.15 (C-1″), 34.17 (C-3), 67.61 (C-6′), 72.40 (C-1′), 72.95, 73.07, 73.27, 73.34, 73.52 (5 × O**C**H$_2$Ph), 74.35, 76.78, 77.01, 77.24 (C-2′, C-3′, C-4′, C-5′), 76.92 (BnO**C**H$_2$CHPh), 81.16 (BnOCH$_2$**C**HPh), 100.78 (C-2), 103.76 (C-5), 118.49 (CH-thiazole), 126.56–128.29 (25 × C$_6$H$_5$), 138.16, 138.32, 138.41, 138.50, 139.75 (5 × *ipso* C$_6$H$_5$), 142.79 (CH-thiazole); 143.58 (C-6) 164.46 (C-2 thiazole). For $C_{58}H_{59}NO_8S$ calculated relative molecular mass 930.16. MS (ESI), *m/z*: 931.4 $[M + H]^+$.

(2*S*,4*S*)-2-[(2*R*)-2-(Benzyloxy)-1-phenylethoxy]-4-[(2,3,4,6-tetra-*O*-benzyl-α-D-galacto pyranosyl)methyl]-6-formyl-3,4-dihydro-2*H*-pyran (7)

Molecular sieves (4Å, 1.5 g) were added to a solution of compound 5 (1.5 g, 1.6 mmol) in acetonitrile (10 ml), and methyl triflate (0.24 ml, 2.1 mmol) was added dropwise. After stirring at room temperature for 15 min, methanol (3 ml) was added and the solvent was evaporated in vacuo. The residue was treated with methanol (20 ml) and then $NaBH_4$ (0.20 g, 5.2 mmol) was added in portions. After stirring at room temperature for 15 min, acetone (5 ml) was added, the reaction mixture was filtered through Supercel and the filtrate was evaporated in vacuo. The residue was dissolved in acetonitrile (15 ml) and a solution of $AgNO_3$ (0.41 g, 2.4 mmol) in water (1.5 ml) was added under vigorous stirring. After stirring for 10 min, phosphate buffer (10 ml, pH 7) was added and after an additional 10 min the acetonitrile was evaporated in vacuo and the residue was partitioned between dichloromethane and phosphate buffer (pH 7). The organic phase was dried and evaporated. The resulting residue was flash-chromatographed through a short column of silica gel in petroleum ether–ethyl acetate (4:1). Yield 1.14 g (70%) of aldehyde 7, R_F 0.4 (petroleum ether–ethyl acetate 3:1). $[\alpha]_D$ +33.6 (*c* 1.03, $CHCl_3$). ^{1}H NMR ($CDCl_3$): 1.92–2.07 m, 4 H (H-1″a, H-1″b, H-3ax, H-3eq); 2.57 m, 1 H (H-4); 3.54–3.65 m, 3 H (BnOC**H**$_2$CHPh, H-6a′); 3.71–3.78 m, 2 H (H-2′, H-3′); 3.87 m, 1 H (H-6b′); 3.99 m, 1 H (H-4′); 4.02–4.10 m, 2 H (H-1′, H-5′); 4.45–4.77 m, 10 H (5 × OC**H**$_2$Ph); 4.94 dd, 1 H, *J* = 8.0, 3.4 (BnOCH$_2$C**H**Ph); 5.56 m, 1 H (H-2); 5.81 d, 1 H, *J*(5,4) = 4.2 (H-5), 7.14–7.37 m, 30 H (6 × Ph); 8.74 s, 1 H (CHO). ^{13}C NMR ($CDCl_3$): 26.54 (C-4), 32.11 (C-1″), 32.15 (C-3), 67.68 (C-6′), 72.01 (C-1′), 72.8, 73.04, 73.21, 73.24, 73.34 (5 ×

OCH_2Ph), 74.31, 76.78, 77.01, 77.26 (C-2′, C-3′, C-4′, C-5′), 76.84 ($BnOCH_2CHPh$), 79.60 ($BnOCH_2CHPh$), 98.30 (C-2), 125.66 (C-5), 127.39–128.36 (25 × C_6H_5), 138.13, 138.20, 138.38, 139.47, 139.34 (5 × *ipso* C_6H_5), 148.72 (C-6), 186.40 (CHO). For $C_{56}H_{58}O_9$ calculated relative molecular mass 875.05. MS (ESI), *m/z*: 876.1 $[M + H]^+$.

(2*R*)-2-(Benzyloxy)-1-phenylethyl 2,3-Dideoxy-3-*C*-[(2,3,4,6-tetra-*O*-benzyl-α-D-galacto pyranosyl)methyl]-4,6-di-*O*-benzyl-β-L-*arabino*-hexopyranoside (**8**)

A 2 M solution of $BH_3 \cdot Me_2S$ in tetrahydrofuran (2.1 ml, 4.1 mmol) was added dropwise to a cool (0 °C) solution of aldehyde **7** (1.03 g, 1.18 mmol) in tetrahydrofuran (35 ml) and the reaction mixture was stirred at room temperature for 16 h. The mixture was quenched by the gradual addition of 30% NaOH (2.2 ml) and 30% H_2O_2 (2.2 ml), and stirred at room temperature for 30 min. The reaction mixture was partitioned between dichloromethane and a saturated aqueous NaCl solution. The organic phase was dried and evaporated in vacuo. The residue was dissolved in tetrahydrofuran (20 ml) and stirred with NaH (60% suspension in mineral oil; 0.21 g, 5.3 mol) at room temperature for 1 h. Benzyl bromide (0.56 ml, 4.7 mmol) and tetrabutylammonium iodide (0.13 g, 0.35 mmol) were added, and the reaction mixture was heated to 40 °C for 15 min. After stirring at room temperature for 14 h, methanol (3 ml) was added and the solvent was evaporated in vacuo. The residue was partitioned between dichloromethane and a saturated solution of $NaHCO_3$. The organic layer was dried, evaporated in vacuo, and chromatographed on silica gel in petroleum ether–ethyl acetate (5:1). Yield 1 g (79%) of compound **8**, R_F 0.4 (petroleum ether–ethyl acetate 3:1). $[\alpha]_D$ +45.6 (*c* 0.26, $CHCl_3$). ^1H NMR ($CDCl_3$): 1.31–1.55 m, 2 H (H-1″a, H-2ax); 2.02–2.35 m, 3 H (H-1″b, H-2eq, H-3); 3.40 m, 1 H (H-5), 3.49–3.58 m, 2 H ($BnOCH_2aCHPh$, H-6a); 3.60–3.79 m, 6 H ($BnOCH_2bCHPh$, H-2′, H-3′, H-6′a, H-6b, H-5); 3.86 m, 1 H (H-6′b); 3.97 m, 1 H (H-4′); 4.10 m, 1 H (H-5′); 4.15 m, 1 H (H-1′); 4.34–4.84 m, 15 H (7 × OCH_2Ph, H-1); 4.93 dd, 1 H, *J* = 8.2, 3.5 ($BnOCH_2CHPh$); 7.10–7.43 m, 40 H (8 × Ph). ^{13}C NMR ($CDCl_3$): 29.70 (C-1″), 35.44 (C-3), 35.68 (C-2), 69.35 (C-6′), 69.58 (C-6), 71.27 (C-1′), 72.85, 72.99, 73.05, 73.18, 73.36, 73.43, 73.53 (7 × OCH_2Ph), 74.18, 74.26, 74.49 (C-2′, C-3′, C-4′), 74.72 ($BnOCH_2CHPh$), 76.79 (C-5), 76.85 (C-5′), 78.32 (C-4), 78.36 ($BnOCH_2CHPh$), 93.90 (C-1), 127.18–128.46 (40 × C_6H_5), 138.11, 138.22, 138.26, 138.29, 138.32, 138.41, 138.51, 138.53 (8 × *ipso* C_6H_5). For $C_{70}H_{74}O_{10}$ calculated relative molecular mass 1075.33. MS (ESI), *m/z*: 1076.6 $[M + H]^+$.

Methyl 2,3-Dideoxy-3-*C*-[(2,3,4,6-tetra-*O*-acetyl-α-D-galactopyranosyl)methyl]-4,6-di-*O*-acetyl-α-L-*arabino*-hexopyranoside (**9a**) and
Methyl 2,3-Dideoxy-3-*C*-[(2,3,4,6-tetra-*O*-acetyl-α-D-galactopyranosyl)methyl]-4,6-di-*O*-acetyl-β-L-*arabino*-hexopyranoside (**9b**)

Methanol (30 ml) and 3 M HCl (3.6 ml) were successively added to a solution of compound **8** (0.6 g, 0.56 mmol) in tetrahydrofuran (15 ml) and the reaction mixture was stirred at room temperature for 23 h. A saturated solution of $NaHCO_3$ (10 ml) was added cautiously and the resulting mixture was concentrated in vacuo. The residue thus obtained was partitioned between dichloromethane and a saturated solution of $NaHCO_3$. After drying and evaporation of the solvent, the residue was chromatographed on silica gel in petroleum ether–ethyl acetate (8:1). The obtained mixture of methyl glycosides (425 mg), R_F 0.3 (petroleum ether–ethyl acetate 3:1), *m/z* 879.4 $[M + H]^+$, was dissolved in methanol (10 ml) and hydrogenated over Pd/C (10%; 100 mg) at room temperature for 2 h. The catalyst was re-

Collect. Czech. Chem. Commun. 2008, Vol. 73, No. 5, pp. 690–700

moved by filtration, the solvent was evaporated and the residue dissolved in pyridine (2 ml). Acetic anhydride (2 ml) was added and the mixture was stirred at room temperature for 1 h. The reaction mixture was poured onto ice and then partitioned between water and ethyl acetate. The organic phase was dried and evaporated in vacuo. Chromatography of the residue on silica gel in petroleum ether–ethyl acetate (2:1) afforded 248 mg (75%) of product as a mixture of two anomers **9a** and **9b** in the ratio 4:1, R_F 0.7 (petroleum ether–ethyl acetate 2:1).

Anomer **9a**: ^{1}H NMR ($CDCl_3$): 1.37 m, 1 H (H-1″a); 1.49–1.58 m, 2 H (H-2ax, H-1″b); ca. 1.95 m, overlapped by Ac, 1 H (H-2eq); 1.95 s, 3 H (1 × Ac); 1.98 s, 3 H (1 × Ac); 2.00 s, 3 H (1 × Ac); 2.01 s, 3 H (1 × Ac); 2.02 s, 3 H (1 × Ac); 2.05 s, 3 H (1 × Ac); 2.19 m, 1 H (H-3); 3.27 s, 3 H (OCH_3); 3.77 ddd, 1 H, *J*(5,6a) = 2.3, *J*(5,6b) = 4.8, *J*(5,4) = 9.9 (H-5); 3.91 dd, 1 H, *J*(6a,5) = 2.3, *J*(6a,6b) = 12.1 (H-6a); 3.93–4.03 m, 2 H (H-5′, H-6a′); 4.13–4.16 m, 2 H (H-1′, H-6b′); 4.18 dd, overlapped, 1 H, *J*(6b,5) = 4.8, *J*(6b,6a) = 12.1 (H-6b); 4.61–4.71 m, 2 H (H-1, H-4); 5.04 dd, 1 H, *J*(3′,4′) = 3.2, *J*(3′,2′) = 9.6 (H-3′); 5.10 dd, 1 H, *J*(2′,1′) = 5.0, *J*(2′,3′) = 9.6 (H-2′); 5.31 dd, 1 H, *J*(4′,3′) = 3.2, *J*(4′,5′) = 5.5 (H-4′). ^{13}C NMR ($CDCl_3$): 20.48, 20.57, 20.62, 20.63, 20.74, 20.76 (6 × **C**H_3CO), 28.22 (C-1″), 32.33 (C-3), 36.07 (C-2), 54.36 (OCH_3), 61.67 and 62.73 (C-6 and C-6′), 67.48 and 67.57 (C-3′ and C-4′), 68.02 and 68.22 (C-2′ and C-5′), 68.53 (C-5), 71.35 (C-1′), 71.94 (C-4), 97.46 (C-1), 169.82, 169.88, 169.96, 170.43, 170.60, 170.74 (6 × CH_3**C**O). For $C_{26}H_{38}O_{15}$ calculated relative molecular mass 590.57. MS (ESI), *m/z*: 591.3 $[M + H]^+$.

Anomer **9b**: ^{1}H NMR ($CDCl_3$): 1.82 m, 1 H (H-3); 3.41 s, 3 H (OCH_3); 3.49 ddd, 1 H, *J*(5,6a) = 2.5, *J*(5,6b) = 4.9, *J*(4,5) = 9.6 (H-5); 4.35 dd, 1 H, *J*(1,2ax) = 9.4, *J*(1,2eq) = 1.8 (H-1), other resonances are overlapped by signals of the major isomer. For $C_{26}H_{38}O_{15}$ calculated relative molecular mass 590.57. MS (ESI), *m/z*: 591.3 $[M + H]^+$.

(2*R*,4*R*)-2-[(2*S*)-2-(Benzyloxy)-1-phenylethoxy]-4-[(2,3,4,6-tetra-*O*-benzyl-α-D-galacto pyranosyl)methyl]-6-(thiazol-2-yl)-3,4-dihydro-2*H*-pyran (**6**)

Compound **3b** (5 g) was treated in the same manner as described for the preparation of compound **5**, yielding 4.235 g (79%) of compound **6**, R_F 0.45 (petroleum ether–ethyl acetate 3:1). $[\alpha]_D$ +29.5 (*c* 1.0, $CHCl_3$). ^{1}H NMR ($CDCl_3$): 1.73 m, 1 H (H-1″a); 1.87 ddd, 1 H, *J*(3ax,3eq) = 13.7, *J*(3ax,4) = 6.9, *J*(3ax,2) = 6.9 (H-3_{ax}); 1.95 ddd, 1 H, *J*(1″a,1″b) = 15.2, *J*(1″b,1′) = 10.3, *J*(1″b,4) = 5.4 (H-1″b); 2.19 ddd, 1 H, *J*(3eq,3ax) = 13.7, *J*(3eq,4) = 6.8, *J*(3eq,2) = 1.2 (H-3eq); 2.62 m, 1 H (H-4); 3.59–3.75 m, 5 H (BnOCH_2CHPh, H-2′, H-3′, H-6a′); 3.87 m, 1 H (H-6b′); 3.98 m, 1 H (H-4′); 4.06 m, 1 H (H-5′); 4.20 bd, 1 H, *J*(1″b,1′) = 10.3 (H-1′); 4.45–4.75 m, 10 H (5 × OCH_2Ph); 4.95 dd, 1 H, *J* = 7.9, 3.4 (BnOCH_2CHPh); 5.45 dd, 1 H, *J*(2,3eq) = 1.4, *J*(2,3ax) = 6.8 (H-2); 6.01 d, 1 H, *J*(5,4) = 3.2 (H-5); 7.12 d, 1 H, *J* = 3.1 (H-thiazole); 7.19–7.35 m, 30 H (6 × Ph); 7.66 d, 1 H, *J* = 3.1 (H-thiazole). ^{13}C NMR ($CDCl_3$): 27.65 (C-4), 34.15 (C-1″), 34.17 (C-3), 67.61 (C-6′), 72.40 (C-1′), 72.95, 73.07, 73.27, 73.34, 73.52 (5 × O**C**H_2Ph), 74.35, 76.78, 77.01, 77.24 (C-2′, C-3′, C-4′, C-5′), 76.92 (BnO**C**H_2CHPh), 81.16 (BnOCH_2**C**HPh), 100.78 (C-2), 103.76 (C-5), 118.49 (CH-thiazole), 126.56–128.29 (25 × C_6H_5), 138.16, 138.32, 138.41, 138.50, 139.75 (5 × *ipso* C_6H_5), 142.79 (CH-thiazole), 143.58 (C-6), 164.46 (C-2 thiazole). For $C_{58}H_{59}NO_8S$ calculated relative molecular mass 930.16. MS (ESI), *m/z*: 931.4 $[M + H]^+$.

(2*R*,4*R*)-2-[(2*S*)-2-(Benzyloxy)-1-phenylethoxy]-4-[(2,3,4,6-tetra-*O*-benzyl-α-D-galacto pyranosyl)methyl]-6-formyl-3,4-dihydro-2*H*-pyran (**10**)

Compound **6** (2.25 g) was treated in the same manner as described for the preparation of compound **7**, yielding 1.60 g (75%) of aldehyde **10**, R_F 0.4 (petroleum ether–ethyl acetate 3:1). $[\alpha]_D$ + 23.8 (*c* 0.92, $CHCl_3$). ^{1}H NMR ($CDCl_3$): 1.90–2.06 m, 4 H (H-1″a, H-1″b, H-3ax, H-3eq); 2.57 m, 1 H (H-4); 3.50–3.65 m, 3 H (BnOC**H**$_2$CHPh, H-6a′); 3.73–3.80 m, 2 H (H-2′, H-3′); 3.87 m, 1 H (H-6b′); 3.99 m, 1 H (H-4′); 4.02–4.11 m, 2 H (H-1′, H-5′); 4.45–4.75 m, 10 H (5 × OC**H**$_2$Ph); 4.94 dd, 1 H, *J* = 8.1, 3.5 (BnOCH$_2$C**H**Ph); 5.56 m, 1 H (H-2); 5.81 d, 1 H, *J*(5,4) = 4.2 (H-5); 7.12–7.40 m, 30 H (6 × Ph); 8.74 s, 1 H (CHO). ^{13}C NMR ($CDCl_3$): 26.54 (C-4), 32.11 (C-1″), 32. 15 (C-3), 67.68 (C-6′), 72.01 (C-1′), 72.8, 73.04, 73.21, 73.24, 73.34 (5 × **C**H$_2$Ph), 74.31, 76.78, 77.01, 77.26 (C-2′, C-3′, C-4′, C-5′), 76.84 (BnO**C**H$_2$CHPh), 79.60 (BnOCH$_2$**C**HPh), 98.30 (C-2), 125.66 (C-5), 127.39–128.36 (25 × C$_6$H$_5$), 138.13, 138.20, 138.38, 139.47, 139.34 (5 × *ipso* C$_6$H$_5$), 148.72 (C-6), 186.40 (CHO). For $C_{56}H_{58}O_9$ calculated relative molecular mass 875.05. MS (ESI), *m/z*: 876.1 $[M + H]^+$.

Methyl 2,3-Dideoxy-3-*C*-[(2,3,4,6-tetra-*O*-acetyl-α-D-galactopyranosyl)methyl]-4,6-di-*O*-acetyl-α-D-*arabino*-hexopyranoside (**12a**) and
Methyl 2,3-Dideoxy-3-*C*-[(2,3,4,6-tetra-*O*-acetyl-α-D-galactopyranosyl)methyl]-4,6-di-*O*-acetyl-β-D-*arabino*-hexopyranoside (**12b**)

Compoud **10** (1.60 g) was treated in the same manner as described for the preparation of compound **8**, yielding compound **11** (1.69 g), R_F 0.45 (petroleum ether–ethyl acetate 3:1), *m/z* 1076.6 $[M + H]^+$, which was immediately processed as described for the preparation of compounds **9a** and **9b**, yielding 650 mg (60%) of a mixture of anomers **12a** and **12b** in the ratio 4:1, R_F 0.7 (petroleum ether–ethyl acetate 2:1).

Anomer **12a**: ^{1}H NMR ($CDCl_3$): 1.47 m, 1 H (H-1″a); 1.56–1.66 m, 2 H (H-2ax, H-1″b); ca. 2.00 m, overlapped by Ac, 1 H (H-2eq); 2.02 s, 3 H (1 × Ac); 2.05 s, 3 H (1 × Ac); 2.06 s, 3 H (1 × Ac); 2.07 s, 3 H (1 × Ac); 2.08 s, 3 H (1 × Ac); 2.12 s, 3 H (1 × Ac); 2.26 m, 1 H (H-3); 3.34 s, 3 H (OCH_3); 3.84 ddd, 1 H, *J*(5,6a) = 2.1, *J*(5,6b) = 4.6, *J*(5,4) = 9.7 (H-5); 3.99 dd, 1 H, *J*(6a,5) = 2.1, *J*(6a,6b) = 12.2 (H-6a); 4.01–4.09 m, 2 H (H-5′, H-6a′); 4.20–4.25 m, 2 H (H-1′, H-6b′); 4.27 dd, overlapped, 1 H, *J*(6b,5) = 4.6, *J*(6a,6b) = 12.2 (H-6b), 4.71–4.77 m, 2 H (H-1, H-4); 5.10 dd, 1 H, *J*(3′,4′) = 3.2, *J*(3′,2′) = 9.5 (H-3′); 5.17 dd, 1 H, *J*(2′,1′) = 5.1, *J*(2′,3′) = 9.5 (H-2′); 5.38 m, 1 H (H-4′). ^{13}C NMR ($CDCl_3$): 20.48, 20.52, 20.57, 20.62, 20.64, 20.76 (6 × **C**H$_3$CO), 28.25 (C-1′), 32.34 (C-3), 36.07 (C-2), 54.54 (CH_3O), 61.64 and 62.73 (C-6 and C-6′), 67.49 and 67.55 (C-3′ and C-4′), 68.04 and 68.23 (C-2′ and C-5′), 68.54 (C-5), 71.35 and 71.94 (C-4 and C-1′), 97.47 (C-1), 169.83, 169.90, 169.97, 170.45, 170.62, 170.77 (6 × CH$_3$**C**O). For $C_{26}H_{38}O_{15}$ calculated relative molecular mass 590.57. MS (ESI), *m/z*: 591.3 $[M + H]^+$.

Anomer **12b**: ^{1}H NMR ($CDCl_3$): 1.86 m, 1 H (H-3); 3.49 s, 3 H (OCH_3); 3.56 ddd, 1 H, *J*(5,6a) = 2.4, *J*(5,6b) = 5.0, *J*(4,5) = 9.6 (H-5); 4.42 dd, 1 H, *J*(1,2ax) = 9.5, *J*(1,2eq) = 1.9 (H-1), other resonances are overlapped by signals of the major isomer. For $C_{26}H_{38}O_{15}$ calculated relative molecular mass 590.57. MS (ESI), *m/z*: 591.3 $[M + H]^+$.

This work was supported by the Ministry of Education, Youth and Sports of the Czech Republic (Grant No. 6046137305) and by the Czech Science Foundation (Grant No. 203/08/1124).

Collect. Czech. Chem. Commun. 2008, Vol. 73, No. 5, pp. 690–700

REFERENCES

1. Gabius H.-J.: *Naturwissenschaften* **2000**, *87*, 108.
2. Wong Ch.-H. (Ed.): *Carbohydrate-Based Drug Discovery*. Wiley, Weinheim 2003.
3. For recent approaches to *C*-disaccharides see: a) Postema M. H. D., Piper J. L., Betts R. L.: *Synlett* **2005**, 1345; b) Awad L., Demange R., Zhu Y.-U., Vogel P.: *Carbohydr. Res.* **2006**, *341*, 1235; c) Taylor R. J. K., McAllister G. D., Franck R. W.: *Carbohydr. Res.* **2006**, *341*, 1298; and references therein.
4. a) Štěpánek P., Kniežo L., Dvořáková H., Vojtíšek P.: *Synlett* **2003**, 963; b) Štěpánek P., Vích O., Kniežo L., Dvořáková H., Vojtíšek P.: *Tetrahedron: Asymmetry* **2004**, *15*, 1033.
5. Štěpánek P., Vích O., Werner L., Kniežo L., Dvořáková H., Vojtíšek P.: *Collect. Czech. Chem. Commun.* **2005**, *70*, 1411.
6. Fang J., Li J., Chen X., Zhang Y., Wang J., Guo Z., Zhang W., Yu L., Brew K., Wang P. G.: *J. Am. Chem. Soc.* **1998**, *120*, 6635.
7. Demange R., Awad L., Vogel P.: *Tetrahedron: Asymmetry* **2004**, *15*, 3573.

Collect. Czech. Chem. Commun. 2008, Vol. 73, No. 5, pp. 690–700

PŘÍLOHA II

Parkan, K.; Werner, L.; Lovyova, Z.; Prchalova, E.; Kniezo, L. An approach to stereoselective preparation of 3-*C*-glycosylated D- and L-glucals. *Carbohydr. Res.* **2010**, *345* (3), 352-362.

Carbohydrate Research 345 (2010) 352–362

Contents lists available at ScienceDirect

Carbohydrate Research

journal homepage: www.elsevier.com/locate/carres

An approach to stereoselective preparation of 3-*C*-glycosylated D- and L-glucals

Kamil Parkan, Lukáš Werner, Zuzana Lövyová, Eva Prchalová, Ladislav Kniežo *

Department of Chemistry of Natural Compounds, Institute of Chemical Technology, Technická 5, 166 28 Prague 6, Czech Republic

ARTICLE INFO

Article history:
Received 7 October 2009
Accepted 18 November 2009
Available online 4 December 2009

Keywords:
C-Disaccharides
Glucal derivatives
Stereoselective synthesis

ABSTRACT

An approach to stereoselective synthesis of α- or β-3-*C*-glycosylated L- or D-1,2-glucals starting from the corresponding α- or β-glycopyranosylethanals is described. The key step of the approach is the stereoselective cycloaddition of chiral vinyl ethers derived from both enantiomers of mandelic acid. The preparation of 1,5-anhydro-4,6-di-*O*-benzyl-2,3-dideoxy-3-*C*-[(2,3,4,6-tetra-*O*-benzyl-β-D-glucopyranosyl)methyl]-L-*arabino*-hex-1-enitol, 1,5-anhydro-4,6-di-*O*-benzyl-2,3-dideoxy-3-*C*-[(2,3,4,6-tetra-*O*-benzyl-β-D-glucopyranosyl)methyl]-D-*arabino*-hex-1-enitol, and 1,5-anhydro-4,6-di-*O*-benzyl-2,3-dideoxy-3-*C*-[(2,3,4-tri-*O*-benzyl-α-L-fucopyranosyl)methyl]-D-*arabino*-hex-1-enitol serves as an example of this approach.

1. Introduction

Glycoproteins on the cell surface form specific ligands that are recognized by receptors on the surface of other cells or by surface receptors of pathogenic microorganisms. These processes mediate a variety of biological events that range from cell to cell interaction (signaling and recognition), host–pathogen interactions, immune responses, and cancer metastasis. A key player in these communications is the structure of the oligosaccharide portion of glycoproteins synthesized in the endoplasmatic reticulum and Golgi's apparatus of the cell.[1] Cell surface carbohydrate–receptor binding events can be investigated with synthetic oligosaccharides, glycoconjugates, and their analogues. In the study of these processes, an important role can also be played by *C*-disaccharides, which nominally preserve the structural information of natural disaccharides but are chemically as well as enzymatically non-hydrolyzable. Moreover, the synthesized *C*-disaccharides can also be utilized in another way. Their attachment as non-hydrolyzable disaccharide mimetics, mimicking the structure of natural saccharide epitopes to suitable dendrimers or to a suitable peptide chain, may lead to the preparation of therapeutically useful glycoconjugates or vaccines, neither of which will be hydrolyzed by ubiquitous glycosidases in the organism. It is therefore important to look for stereoselective methods for the synthesis of precursors for a simple preparation of glycoconjugates containing non-hydrolyzable disaccharide mimetics. Such precursors may be derivatives of 1,5-anhydro-2,3-dideoxy-*arabino*-hex-1-enitol (1,2-glucal).[2]

In our previous study, we described a short and efficient synthesis of α-*C*-(1→3)-disaccharides in which D-glucopyranose was linked to an L- or D-2-deoxy*arabino*-hexopyranose moiety starting from α-glucopyranosylethanal.[3] Later, we found that the stereoselectivity of the key step in our synthesis, namely the cycloaddition of substituted oxadiene with ethyl vinyl ether, can be markedly increased by the use of chiral vinyl ethers, the high stereoselectivity of the cycloaddition being influenced neither by the configuration of the starting monosaccharide nor by the character of the protecting group used.[4] This procedure enables a facile stereoselective preparation of a series of α-*C*-(1→3)-disaccharide derivatives **1** and **2** (Fig. 1) containing any monosaccharide (at least D-glucose, D-galactose, D-mannose, or L-fucose) at the non-reducing end and D- or L-2-deoxyarabinohexopyranose at the reducing end (e.g., see Ref. 5). Moreover, the range of compounds obtainable by this method can be further extended to include the corresponding β-*C*-(1→3)-disaccharides **3** and **4** because it is known that in the presence of amines or other bases, the starting α-pyranosylethanals easily undergo epimerization to the corresponding β-pyranosylethanals.[6] Thus, from a single starting compound such as α-pyranosylpropene, one can prepare pure α-pyranosylethanal, which is either converted to two diastereoisomeric *C*-(1→3)-disaccharides **1** and **2**, or epimerized to give pure β-pyranosylethanal which affords further two diastereoisomeric *C*-(1→3)-disaccharides **3** and **4** (For recent synthesis of other *C*-(1→3)-disaccharides, see Ref. 19).

In the present study, we would like to show that *C*-(1→3)-disaccharides **1**–**4**, obtained by this approach, can easily be transformed further to derivatives of D- or L-1,5-anhydro-2,3-dideoxy-*arabino*-hex-1-enitol (D- or L-glucal) **5**–**8**. So far, only the preparation of a similar D-galactal has been described in the literature, namely a C-linked analogue of β-D-galactopyranosyl-(1→3)-D-galactal.[2c] 1,2-Glucals are extremely useful intermediates in the synthesis of saccharide derivatives and they enable one- or two-step stereoselective preparation of gluco-[7] or mannopyranosylglycosides,[8] glycosides of glucosamine[9], or mannosamine,[10] as well as some of

* Corresponding author. Tel.: +420 220 444 265; fax: +420 220 444 422.
E-mail address: Ladislav.Kniezo@vscht.cz (L. Kniežo).

0008-6215/$ - see front matter © 2009 Elsevier Ltd. All rights reserved.
doi:10.1016/j.carres.2009.11.025

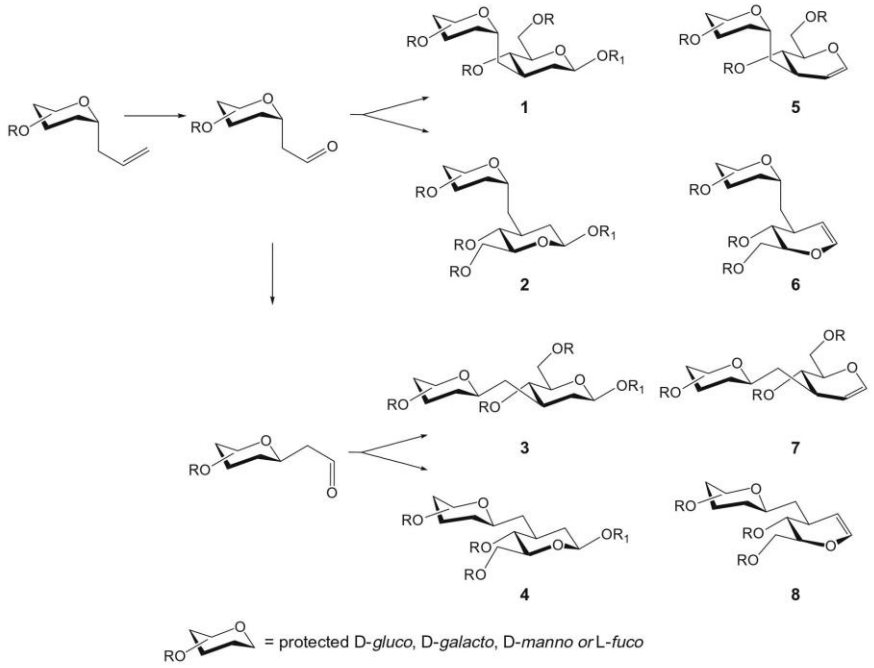
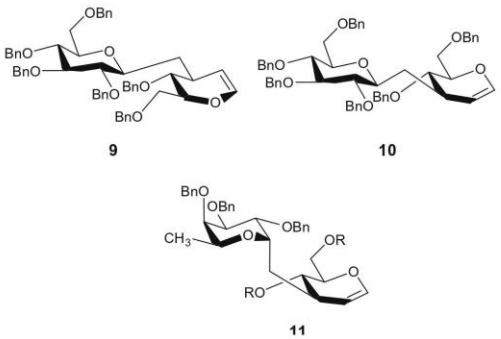


Figure 1. Synthetic route to 3-*C*-glycosylated glucals.

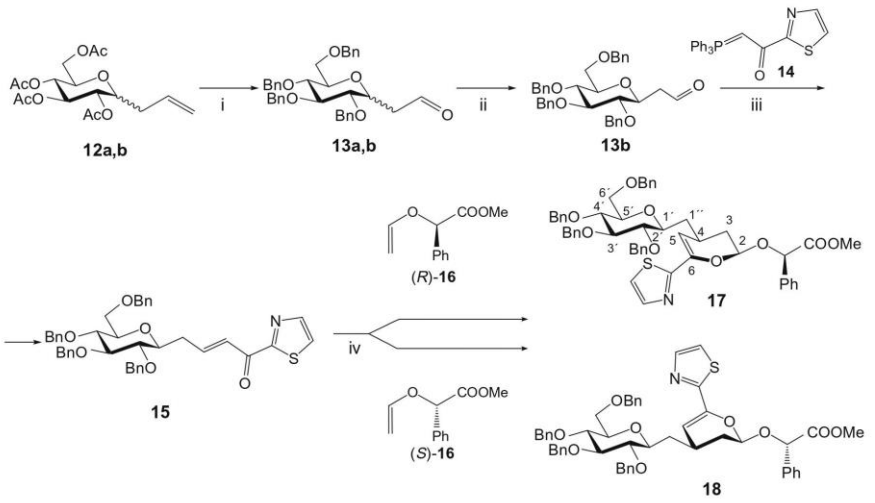
C-glycosides.[11] One can envisage that these or similar reactions may also be utilized for attachment of α- or β-*C*-(1→3)-disaccharide mimetics **5**–**8** to an oligosaccharide, peptide, or lipid moiety, either by glycosidic or by C–C bonding, thus enabling the synthesis of various stable, non-hydrolyzable, glycoconjugates.

2. Results and discussion

As examples of this approach, we now report the preparation of C-substituted L-glucal **9** or D-glucal **10**, mimicking the β-glycoside bond in which the β-D-glucopyranosyl moiety is linked by a methylene bridge to C-3 of L- or D-1,5-anhydro-2,3-dideoxy-*arabino*-hex-1-enitol, and of C-substituted D-glucal **11**, mimicking the α-glycoside bond in which the α-L-fucopyranosyl moiety is linked by a methylene bridge to C-3 of D-1,5-anhydro-2,3-dideoxy-*arabino*-hex-1-enitol.



As the starting compound for the preparation of *C*-(1→3)-disaccharides **9** and **10**, containing the β-D-glucopyranosyl moiety, we employed a mixture of tetra-*O*-acetyl-α- and tetra-*O*-acetyl-β-D-glucopyranosylpropenes **12a**,**b** in the ratio of about 6:1 (Scheme 1), obtained by reaction of allyltrimethylsilane with peracetylated glucose in boiling acetonitrile (Scheme 1). Deacetylation and benzylation afforded a mixture of tetra-*O*-benzyl-α- and tetra-*O*-benzyl-β-D-glucopyranosylpropenes which on ozonolysis afforded a mixture of tetra-*O*-benzyl-α- and tetra-*O*-benzyl-β-D-glucopyranosylethanals **13a**,**b** in the same ratio as in the starting **12a**,**b**. The epimerization of protected α-D-glucopyranosylethanals to the corresponding β-diastereoisomers has been hitherto described only in two cases. Zhou et al. described epimerization of methanolic solution of 2-*O*-acetyl-3,4,6-tri-*O*-benzyl-α-D-glucopyranosylethanal by a mixture of MeONa/$Zn(OAc)_2$ (Ref. 6a) or by MeONa alone (Ref. 6b) however, in both of these cases, the β-D-glucopyranosylethanal formed was not isolated instead, it was in situ reduced to the corresponding alcohol. Dondoni et al.[6d] described an alternative method of epimerization of tetra-*O*-benzyl-α-D-glucopyranosylethanal using L-proline in a microwave reactor. Although the arising tetra-*O*-benzyl-β-D-glucopyranosylethanal was isolated, the reaction was performed only in a small vial with 0.4 mmol of the aldehyde. We have found that epimerization of larger amounts of the aldehyde can advantageously be performed using a 1% methanolic solution of K_2CO_3; in this way, in a single batch, a mixture of tetra-*O*-benzyl-α- and tetra-*O*-benzyl-β-D-glucopyranosylethanals **13a**,**b** afforded pure tetra-*O*-benzyl-β-D-glucopyranosylethanal **13b** in an amount greater than 10 g. This product in a subsequent Wittig reaction with ((2-thiazolylcarbonyl)-methylen)triphenylphosphorane **14** (Ref. 13) afforded substituted oxadiene **15** as the sole product. Unlike the case of similar and previously prepared substituted oxadienes,[3–5] the H-2 proton signal in the ^{1}H NMR

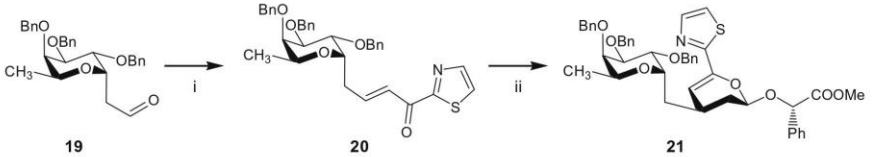


Scheme 1. Stereoselective synthesis of **17** and **18**. Reagents and conditions: (i) (a) MeONa/MeOH, rt, 20 h; (b) NaH, BnBr, Bu_4NI, THF, 50 °C, 2 h, then rt 15 h; (c) O_3, CH_2Cl_2, −78 °C, 2 h; (d) Me_2S, $NaHCO_3$, rt, 2 days; (ii) 1% K_2CO_3/MeOH, rt, 2 days; (iii) **14**, $CHCl_3$, 50 °C, 30 h; (iv) (*R*)-**16** or (*S*)-**16**, Eu(fod)$_3$ (6 mol %), CH_2Cl_2, rt, 3 days.

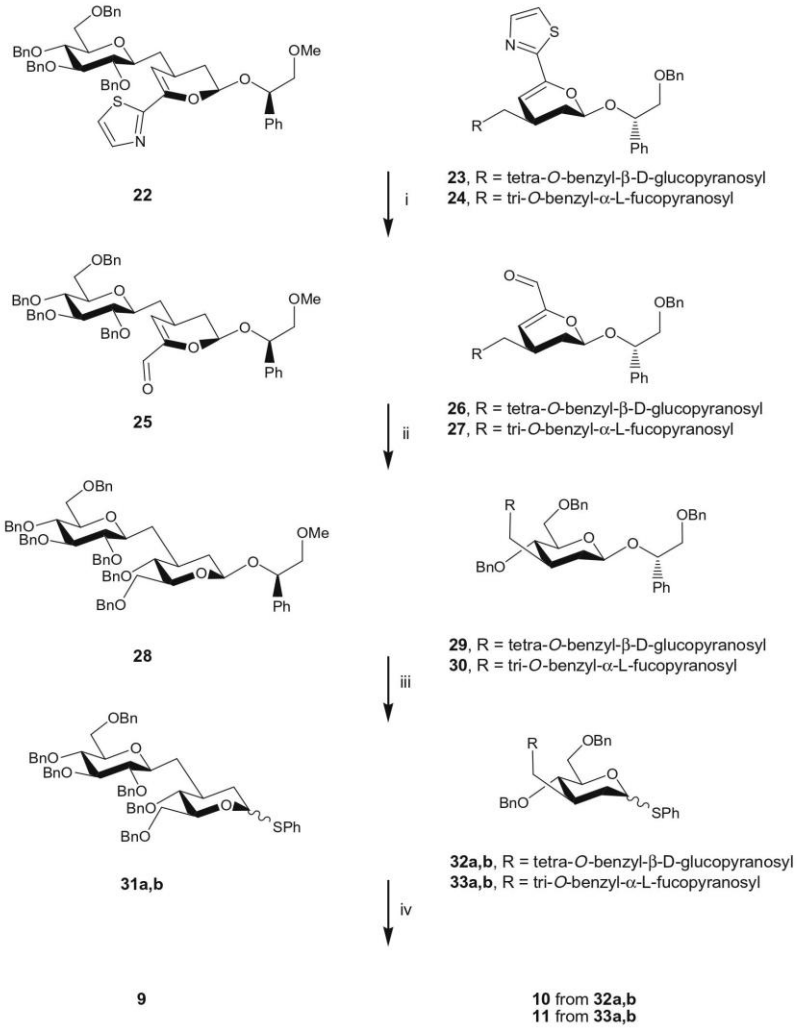
spectrum of compound **15** was not overlapping with the aromatic proton signals and from its coupling constant ($J_{2,3}$ = 15.6 Hz) we were able to directly assign *trans*-configuration of the C=C bond. Cycloaddition reaction of **15** with both enantiomers of methyl (ethenyloxy)(phenyl)acetate, (*R*)-**16** and (*S*)-**16** (Refs. 4,12), stereoselectively afforded two different products: **17** and **18** (the first was an oil whereas the second was a crystalline compound, mp 67–68 °C), with almost identical NMR spectra. In both cases, NOE experiments confirmed the *cis*-relation of substituents at C-2 and C-4 in the dihydropyran ring. Therefore, similar to previous cases,[3–5] compounds **17** and **18** are two diastereoisomers of the same relative but different absolute configuration of the newly arisen dihydropyran ring. Unfortunately, the crystalline diastereoisomer **18** did not afford any crystals suitable for X-ray analysis; however, since our previous paper[4] confirmed that neither the configuration of the saccharide substituent nor the character of the protecting groups in the starting oxadiene affects the selectivity of cycloaddition with chiral vinyl ethers (*R*)-**16** and (*S*)-**16**, in this case we can assume with a great deal of certainty that vinyl ether (*R*)-**16** afforded cycloadduct **17** with configuration 2*S*,4*S*, and vinyl ether (*S*)-**16** afforded cycloadduct **18** with configuration 2*R*,4*R* on the dihydropyran ring.

In the preparation of substituted D-glucal **11**, containing the α-L-fucopyranosyl moiety, we started from tri-*O*-benzyl-α-L-fucopyranosylethanal **19**, which, in turn, was prepared from L-fucose according to Ref. 14. The procedure was slightly modified, in that pure α-L-fucopyranosylprop-2-ene was isolated from the α- and β-diastereoisomeric mixture by crystallization from isopropyl alcohol instead of ethyl acetate, and the desired α-stereoisomer, mp 157–158 °C (Ref. 14, mp 153 °C), was obtained in high purity after a single crystallization. Similar to the preceding case, fucopyranosylethanal **19** was converted into substituted oxadiene **20**. Its cycloaddition reaction with vinyl ether (*S*)-**16** afforded cycloadduct **21** as the sole product (Scheme 2). Judging from analogy with previous results,[4,5] we can assume that the configuration at the newly arisen dihydropyran ring almost certainly is 2*R*,4*R*.

The obtained cycloadducts **17**, **18**, and **21** were converted to the final L- or D-glucal derivatives **9** or **10** and **11** as described in Scheme 3. For reasons described in our previous paper,[5] we first reduced the ester group. For protection of the arising primary alcohol we used two ways: the alcohol, prepared by reduction of the ester group of cycloadduct **17**, was methylated by the formation of compound **22**, and the alcohol, prepared from cycloadduct **18** or **21**, was benzylated to compounds **23** or **24**. Both protection procedures were equivalent giving the same yields of the protected products. The known transformation of the thiazole ring to an aldehyde group[3–5,15] afforded compounds **25**–**27**, which on hydroboration and simultaneous reduction of the aldehyde group, followed by benzylation of the arising hydroxyl goups,[3,5] yielded *C*-(1→3)-disaccharides **28**–**30** as the sole reaction products. As confirmed by the coupling constants in the ^{1}H NMR spectra, in all the synthesized compounds, the new pyranose has the 2-deoxy-*arabino*-



Scheme 2. Stereoselective synthesis of **21**. Reagents and conditions: (i) **14**, $CHCl_3$, 50 °C, 30 h; (ii) (*S*)-**16**, Eu(fod)$_3$ (6 mol %), CH_2Cl_2, rt, 3 days.



Scheme 3. Synthesis of **9**–**11**. Reagents and conditions: (i) (a) MeOTf, MeCN, rt, 15 min; (b) $NaBH_4$, MeOH, rt, 15 min; (c) $AgNO_3$, $MeCN/H_2O$, rt, 20 min; (ii) (a) $Me_2S{\cdot}BH_3$, THF, rt, 16 h; (b) NaOH, H_2O_2, rt, 30 min; (c) NaH, BnBr, Bu_4NI, THF, 40 °C, 15 min, then rt 14 h; (iii) PhSH, $BF_3{\cdot}Et_2O$, CH_2Cl_2, −78 °C, then to rt 2 h; (iv) (a) NBS, moist acetone (1% H_2O), −15 °C, 1 h, exclusion of light; (b) Ms_2O, s-collidine, CH_2Cl_2, 0 °C, 4 h.

hexopyranose configuration (compound **28**: $J_{1,2ax}$ = 9.6 Hz, $J_{3,4}$ = $J_{4,5}$ = 9.1 Hz, compound **29**: $J_{3,4} = J_{4,5}$ = 9.1 Hz, and compound **30**: $J_{1,2ax}$ = 11.7 Hz, $J_{3,4} = J_{4,5}$ = 9.6 Hz). The reaction of thiophenol with disaccharides **28**–**30** afforded anomeric mixtures of thioglycosides **31a**,**b**, **32a**,**b**, and **33a**,**b** (in a ratio α:β of about 3:1). The mixtures of anomeric thioglycosides were subjected to a reaction with *N*-bromosuccinimide in aqueous acetone under the formation of β-C-(1→3)-disaccharides with a free OH group in the anomeric position[16] and the compounds obtained were, without isolation, reacted with methanesulfonic anhydride in the presence of s-collidine.[17] In this way, we obtained the substituted L- glucal **9** or D-glucals **10** and **11** as the sole reaction products.

3. Conclusion

In conclusion, using the three selected examples, we have demonstrated that from an α- or β-pyranosylethanal one can stereoselectively prepare a 3-*C*-glycosylated D- or L-glucal. In general, the starting α-pyranosylpropenes are easily available compounds[4,14,18] that, on ozonolysis, can be transformed in a single step to α-pyranosylethanals which, after epimerization, can be converted to pure β-pyranosylethanals.[6] We have shown that the configuration of the starting monosaccharide does not affect the stereoselectivity of the individual steps of the synthesis, therefore, one can assume that this approach may be used for preparation of any of the substi-

tuted glucals **5**–**8**, depicted in Figure 1. Substituted glucals, obtainable by this method, may then serve as useful intermediates, for the synthesis of either various (1→3)-disaccharide mimetics using reactions described in the literature,[7–11] or non-hydrolyzable glycoprotein or glycolipid epitopes containing α- or β-pyranosyl-(1→3)-pyranosyl structural motifs.

4. Experimental

4.1. General

The melting points are uncorrected. TLC was performed on HF_{254} plates (Merck), detection utilized either UV light or spraying with $Ce(SO_4)_2$ solution (5 g) in 10% H_2SO_4 (500 ml), and subsequent heating. Flash column chromatography was performed on a silica gel (Merck, 100–160 μm) in solvents which had been distilled prior to use. Optical rotations were measured at 25 °C on a JASCO DIP-370 spectropolarimeter. ^1H and ^{13}C NMR spectra were taken on a Bruker DRX 500 Avance spectrometer at 500.132 MHz (^1H NMR) and at 125.767 MHz (^{13}C NMR) using tetramethylsilane as an internal standard. ^1H and ^{13}C NMR signal assignments were confirmed by 2D COSY and HMQC when necessary. NOE connectivities were obtained using 1D ^1H DPFGSE-NOE experiments. Mass spectra and HPLC were performed on a 250 × 4.6 mm column packed with 5 μm Supelco BDS Hypersil C-18, mobile phase of MeOH/water, using an HP 1100 instrument equipped with a gradient pump, a column thermostat and, in addition to a UV detector, an Agilent G1956B single quadrupole system as an MS detector.

4.2. (2,3,4,6-Tetra-*O*-acetyl-α-D-glucopyranosyl)-prop-2-ene (12a) and (2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranosyl)-prop-2-ene (12b)

Allyltrimethylsilane (16.3 ml; 100 mmol) and $BF_3{\cdot}Et_2O$ (13.2 ml; 100 mmol) were added to a solution of 1,2,3,4,6-penta-*O*-acetyl-α-D-glucopyranose (10 g; 25.64 mmol) in dry CH_3CN (160 ml). The mixture was refluxed for 2.5 h and then another portion of allyltrimethylsilane (16.3 ml; 100 mmol) and $BF_3{\cdot}Et_2O$ (13.2 ml; 100 mmol) was added. This procedure was then repeated twice at 2.5 h intervals, so that the total amount of allyltrimethylsilane added was 65.2 ml (400 mmol) and the total amount of $BF_3{\cdot}Et_2O$ was 52.8 ml (400 mmol). Two hours after the last addition, the reaction mixture was cooled to room temperature, diluted with CH_2Cl_2 (350 ml), and washed with 1 M NaOH to persisting alkaline reaction of the aqueous phase. The organic layer was dried over $MgSO_4$ and the solvent was evaporated. Chromatography of the residue (PE/AcOEt = 4:1) afforded a mixture of two diastereoisomeric products **12a**,**b** (6.87 g; 72%), R_f = 0.63 (PE/AcOEt 2:1) in the ratio α:β = 6:1 (integration of H-1′ signals in ^1H NMR spectrum; diastereoisomer α as ddd at 4.20 ppm, diastereoisomer β as ddd at 3.50 ppm).

4.3. (2,3,4,6-Tetra-*O*-benzyl-β-D-glucopyranosyl)-ethanal (13b)

A 0.1 M solution of MeONa in MeOH was added dropwise to a mixture of compounds **12a**,**b** (23 g; 61.76 mmol) in MeOH (500 ml) to allow the alkaline reaction to persist and the reaction mixture was stirred at room temperature. After 20 h, no starting compound was detected (TLC) in the reaction mixture which was then neutralized with Dowex 50 (5 g) and filtered. Evaporation of the solvent and chromatography on a silica gel (chloroform/MeOH 5:1) afforded 11 g (87%) of a mixture of α and β D-glucopyranosyl-prop-2-enes, R_f = 0.4 (chloroform/MeOH 5:1). ESIMS *m*/*z*: calcd for ($C_9H_{16}O_5$): 204.2. Found, 205.7 $[M+H]^+$. The obtained mixture of D-glucopyranosylprop-2-enes (10.1 g; 49.4 mmol) was dissolved in dry THF (400 ml), to this solution we added 11.8 g (296.7 mmol) of 60% suspension of NaH in mineral oil and the reaction mixture was stirred at room temperature for 1 h. Then, tetrabutylammonium iodide (4.56 g; 12.3 mmol) was added, followed by dropwise addition of benzyl bromide (35.3 ml; 296.7 mmol), the reaction mixture was heated at 50 °C for 2 h, and then stirred at room temperature for another 15 h. The excess hydride was decomposed by the addition of MeOH (5 ml), the solvent was evaporated, and the residue was partitioned between CH_2Cl_2 and H_2O. The organic phases were combined, dried, stripped of solvent, and the residue was chromatographed on silica gel (light petroleum/ethyl acetate 12:1→9:1). This yielded 19.5 g (70%) of a mixture of α and β perbenzylated glucopyranosylprop-2-enes; R_f = 0,35 (light petroleum/ethyl acetate 9:1). ESIMS *m*/*z*: calcd for ($C_{37}H_{40}O_5$): 564.7. Found, 565.8 $[M+H]^+$. The mixture obtained was dissolved in dry dichloromethane (150 ml) and, after addition of anhydrous MeOH (30 ml) and cooling to −78 °C, it was ozonized. After 2 h, the solution turned blue permanently and the reaction was terminated by passing nitrogen through the mixture for 5 min. Then $NaHCO_3$ (4 g) (to prevent an acetalization), followed by dimethyl sulfide (25.4 ml; 345 mmol), was added successively and the stirred mixture was allowed to warm to room temperature. After stirring the mixture for 2 days at room temperature, the $NaHCO_3$ was filtered off, the solvent was evaporated, and the residue was chromatographed on a silica gel (light petroleum/ethyl acetate, 10:1). This yielded 14.48 g (74%) of a mixture of aldehydes **13a**,**b**; R_f = 0.18 (light petroleum/ethyl acetate, 6:1) in 6:1 ratio (integration of ^1H NMR aldehyde group signals; α-diastereoisomer as t at 9.65 ppm, β-diastereoisomer as t at 9.69 ppm). The mixture of aldehydes **13a**,**b** (14 g; 24.7 mmol) was dissolved in a 1% methanolic solution of K_2CO_3 (270 ml) and stirred at room temperature. According to ^1H NMR, after 2 days, the reaction mixture was already completely free of α-diastereoisomer **13a**. The reaction was quenched by neutralization with acetic acid, the solvent was evaporated, and the residue was partitioned between CH_2Cl_2 and a saturated NaCl solution. The organic phase was dried, the solvent evaporated, and the residue chromatographed on a silica gel (light petroleum/ethyl acetate 9:1→5:1), affording 10.9 g (78%) of pure aldehyde **13b**, R_f = 0.3 (light petroleum/ethyl acetate 3:1). $[\alpha]_D$ −2.3 (*c* 0.70, $CHCl_3$); ^1H NMR ($CDCl_3$): 2.54 (ddd, 1H, $J_{2a,2b}$ = 16.2 Hz, $J_{2a,1'}$ = 7.9 Hz, $J_{2a,CHO}$ = 2.5 Hz, H-2_a), 2.69 (ddd, 1H, $J_{2b,2a}$ = 16.2 Hz, $J_{2b,1'}$ = 4.3 Hz, $J_{2b,CHO}$ = 2.5 Hz, H-2_b), 3.33 (dd, 1H, $J_{2',1'} = J_{2',3'}$ = 9.1 Hz, H-2′), 3.47 (ddd, 1H, $J_{5',4'} = J_{5',6a'}$ = 9.6 Hz, $J_{5',6b'}$ = 2.9 Hz, H-5′), 3.62–3.70 (m, 3H, H-4′, H-6_a′, H-6_b′), 3.73 (dd, 1H, $J_{3',2'} = J_{3',4'}$ = 9.1 Hz, H-3′), 3.81 (ddd, 1H, $J_{1',2'}$ = 9.1 Hz, $J_{1',2a}$ = 7.9 Hz, $J_{1',2b}$ = 4.3 Hz, H-1′), 4.45–4.96 (m, 8H, 4 × CH_2Ph), 7.10–7.40 (m, 20H, 4 × C_6H_5), 9.69 (t, *J* = 2.5 Hz, *CH*O). ^{13}C NMR ($CDCl_3$): 45.9 (C-2), 68.6 (C-6′), 74.4 (C-1′), 73.4, 74. 9, 74.9, 75.4 (4 × CH_2Ph), 78.2 (C-4′), 79.1 (C-5′), 81.1 (C-2′), 87.0 (C-3′), 127.5–128.4 (4 × C_6H_5), 137.5, 137.9, 137.9, 138.3 (4 × *ipso* C_6H_5), 200. 0 (*C*HO). ESIMS *m*/*z*: calcd for ($C_{36}H_{38}O_6$): 566.7. Found, 567.4 $[M+H]^+$. Anal. Calcd for $C_{36}H_{38}O_6$: C, 76.30; H, 6.76. Found: C, 76.42; H, 6. 88.

4.4. (*E*)-4-(2,3,4,6-Tetra-*O*-benzyl-β-D-glucopyranosyl)-1-(thiazol-2-yl)-but-2-en-1-one (15)

Ylide **14** (Ref. 13; 13.7 g, 35.3 mmol) was added to a solution of aldehyde **13b** (10 g, 17.6 mmol) in $CHCl_3$ (50 ml) and the mixture was heated at 50 °C. After 30 h the reaction mixture did not show an aldehyde proton signal (9.69 ppm) in the ^1H NMR spectrum. The solvent was evaporated and the residue chromatographed on a silica gel (light petroleum/ethyl acetate 5:1→3:1) affording 9.42 g (79%) of compound **15**; R_f = 0.3 (light petroleum/ethyl acetate 3:1). $[\alpha]_D$ −3.79 (*c* 1.08, $CHCl_3$); ^1H NMR ($CDCl_3$): 2.56 (ddd, 1H, $J_{4a,4b}$ = 15.3 Hz, $J_{4a,1}$ = 7.8 Hz, $J_{4a,3}$ = 6.2 Hz,

H-4a), 2.85 (ddd, 1H, $J_{4b,4a}$ = 15.3 Hz, $J_{4b,1'}$ = 5.7 Hz, $J_{4b,3}$ = 3.4 Hz, H-4b), 3.36 (dd, 1H, $J_{3',4'} = J_{4',5'}$ = 9.1 Hz, H-4′), 3.41–3.51 (m, 2H, H-1′, H-5′), 3.62–3.76 (m, 4H, H-6′a, H-6′b, H-2′, H-3′), 4.50–4.98 (m, 8H, 4 × CH_2Ph), 7.10–7.42 (m, 21H, 4 × C_6H_5, H-3) 7.43 (d, $J_{2,3}$ = 15.6 Hz, H-2), 7.64 (d, 1H, J = 3.0 Hz, C*H*-thiazole) 7.97 (d, 1H, J = 3.0 Hz, C*H*-thiazole). ^{13}C NMR ($CDCl_3$): 35.2 (C-4), 68.7 (C-6′), 73.5, 75.0, 75.1, 75.5 (4 × CH_2Ph), 77.8 (C-1′), 78.4 (C-3′), 79.1 (C-5′), 81.5 (C-4′), 87.2 (C-2′), 126.2 (C-3), 126.4 (*C*H-thiazole), 127.5–128.5 (20 × C_6H_5), 137.9, 138.1, 138.2, 138.5 (4 × *ipso* C_6H_5), 144.6 (CH-thiazole), 147.4 (C-2), 168.2 (*C*-thiazole), 181.4 (C-1). ESIMS *m/z*: calcd for ($C_{41}H_{41}NO_6S$): 675.8. Found, 693.7 $[M+NH_4]^+$. Anal. Calcd for $C_{41}H_{41}NO_6S$: C, 72.86; H, 6.11. Found: C, 72.83; H, 6.17.

4.5. (*E*)-4-(2,3,4-Tri-*O*-benzyl-α-L-fucopyranosyl)-1-(thiazol-2-l)-but-2-en-1-one (20)

Similar to the preceding experiment, aldehyde **19** (Ref. 14; 6.2 g, 13.5 mmol) and ylide **14** (11.5 g; 29.7 mmol) afforded 5.74 g (75%) of compound **20**; R_f = 0.6 (light petroleum/ethyl acetate 3:1). $[\alpha]_D$ −43.0 (*c* 0.74, $CHCl_3$); ^{1}H NMR ($CDCl_3$): 1.30 (d, 3H, J = 6.5 Hz, CH_3), 2.55 (m, 1H, H-4b), 2.68 (m, 1H, H-4a), 3.74–3.84 (m, 3H, H-2′, H-3′, H-4′), 3.96 (m, 1H, H-5′), 4.23 (m, 1H, H-1′), 4.46–4.80 (m, 6H, 3 × CH_2Ph), 7.21–7.40 (m, 17H, 3 × C_6H_5, H-2, H-3), 7.58 (d, 1H, J = 2.9 Hz, C*H*-thiazole), 7.95 (d, 1H, J = 2.9 Hz, C*H*-thiazole). ^{13}C NMR ($CDCl_3$): 15.0 (C-6′), 31.7 (C-4), 68.8, 69.6 (C-1′, C-5′), 72.1, 72.5, 72.9 (3 × $PhCH_2$), 76.3, 75.5, 74.1 (C-2′, C-3′, C-4′), 125.1 (C-3), 126.1 (*C*H-thiazole), 128.3–127.3 (3 × C_6H_5), 137.9, 138.3, 138.4 (3 × *ipso* C_6H_5), 144.5 (*C*H-thiazole), 148.1 (C-2), 168.1 (*C*-thiazole), 181.1 (C-1). ESIMS *m/z*: calcd for ($C_{34}H_{35}NO_5S$): 569.7. Found, 587.2 $[M+NH_4]^+$. Anal. Calcd for $C_{34}H_{35}NO_5S$: C, 71.68; H, 6.19. Found: C, 71.51; H, 6.22.

4.6. Methyl (*R*)-2-phenyl-2-((2*S*, 4*S*)-4-((2,3,4,6-tetra-*O*-benzyl-β-D-glucopyranosyl)methyl-6-(thiazol-2-yl)-3,4-dihydro-2*H*-pyran-2-yl)oxy)acetate (17)

$Eu(fod)_3$ (0.46 g, 0.44 mmol) was added to a solution of compound **15** (5 g, 7.3 mmol) and chiral vinyl ether (*R*)-**16** (Refs. 4,12) (3.6 g, 18.4 mmol) in dichloromethane (200 ml) and the reaction mixture was stirred at room temperature. After 3 days, the mixture did not contain (TLC) any starting compound **15**. Evaporation of solvent and chromatography of the residue on silica gel (light petroleum/ethyl acetate 7:1) afforded 5.1 g (79%) of compound **17**; R_f = 0.35 (light petroleum/ethyl acetate 6:1). $[\alpha]_D$ +96.7 (*c* 0.54, $CHCl_3$). ^{1}H NMR ($CDCl_3$): 1.75 (ddd, 1H, $J_{1a'',1b''}$ = 14.2 Hz, $J_{1''a,4}$ = 10.1 Hz, $J_{1a'',1'}$ = 4.6 Hz, H-1a″); 1.81 (ddd, 1H, $J_{3ax,3eq}$ = 13.3 Hz, $J_{3ax,4}$ = 8.0 Hz, $J_{2,3ax}$ = 7.3 Hz, H-3_{ax}); 1.96 (ddd, 1H, $J_{1a'',1b''}$ = 14.2 Hz, $J_{1b'',4}$ = 10.1 Hz, $J_{1b'',1'}$ = 2.1 Hz, H-1b″); 2.34 (ddd, $J_{3ax,3eq}$ = 13.3 Hz, $J_{3eq,4}$ = 6.4 Hz, $J_{2,3eq}$ = 2.1 Hz, H-3_{eq}); 2.85 (m, 1H, H-4); 3.25 (t, 1H, J = 8.8 Hz, H-4′); 3.36–3.43 (m, 2H, H-5′, H-1′); 3.62–3.78 (m, 4H, H-2′, H-3′, H-6′a, H-6′b); 3.73 (s, 3H, PhCHCOOCH_3); 4.52–4.68, 4.78–4.93 (m, 8H, 4 × $PhCH_2$); 5.38 (dd, 1H, $J_{2,3ax}$ = 7.3 Hz, $J_{2,3eq}$ = 2.1 Hz, H-2); 5.52 (s, 1H, PhC*H*COOCH$_3$); 5.99 (d, 1H, $J_{4,5}$ = 3.2 Hz, H-5); 7.14–7.44 (m, 25H, 5 × C_6H_5), 7.45 (d, 1H, J = 3.2 Hz, CH-thiazole), 7.75 (d, 1H, J = 3.2 Hz, C*H*-thiazole). ^{13}C NMR ($CDCl_3$): 27.7 (C-4); 33.0 (C-3); 37.9 (C-1″); 52.4 (CH–COOCH_3); 69.0 (C-6′); 73.6, 74.9, 75.2, 75.5 (4 × $PhCH_2$); 77.1 (C-1′); 77.7 (*C*H–COOCH$_3$); 78.4 (C-3′); 79.0 (C-5′); 82.67 (C-4′); 87.2 (C-2′); 98.9 (C-2); 106.6 (C-5); 118.53 (*C*H-thiazole); 127.3–128.6 (25 × C_6H_5); 136.1, 138.0, 138.2, 138.3, 138.6 (5 × *ipso* C_6H_5); 143.1 (*C*H-thiazole); 143.4 (C-6); 164.1 (*C*-thiazole); 171.0 (CH–*C*OOCH$_3$). ESIMS *m/z*: calcd for ($C_{52}H_{53}NO_9S$): 868.0. Found, 869.0 $[M+H]^+$. Anal. Calcd for $C_{52}H_{53}NO_9S$: C, 71.95; H, 6.15. Found: C, 72.01; H, 6.18.

4.7. Methyl (*S*)-2-phenyl-2-((2*R*,4*R*)-4-((2,3,4,6-tetra-*O*-benzyl-β-D-glucopyranosyl)methyl-6-(thiazol-2-yl)-3,4-dihydro-2*H*-pyran-2-yl)oxy)acetate (18)

According to the same procedure described for the preparation of compound **17**, compound **15** (3.51 g; 5.2 mmol) and chiral vinyl ether (*S*)-**16** (Refs. 4,12) (2.5 g, 13.0 mmol) afforded 3.65 g (81%) of compound **18**, mp 67–68 °C (ethyl acetate/light petroleum). R_f = 0.32 (light petroleum/ethyl acetate 6:1). $[\alpha]_D$ +56.9 (*c* 0.048, $CHCl_3$). ^{1}H NMR ($CDCl_3$): 1.76 (ddd, 1H, $J_{1a'',1b''}$ = 14. 6 Hz, $J_{1a'',4}$ = 10.3 Hz, $J_{1a'',1'}$ = 5.0 Hz, H-1a″); 1.83 (ddd, 1H, $J_{3ax,3eq}$ = 13.5 Hz, $J_{3ax,4}$ = 8.0 Hz, $J_{2,3ax}$ = 7.3 Hz, H-3_{ax}); 1.96 (ddd, 1H, $J_{1a'',1b''}$ = 14.6 Hz, $J_{1b'',4}$ = 10.3 Hz, $J_{1b'',1'}$ = 2.5 Hz, H-1b″); 2.33 (ddd, 1H, $J_{3ax,3eq}$ = 13.5 Hz, $J_{3eq,4}$ = 6.7 Hz, $J_{2,3eq}$ = 1.8 Hz, H-3_{eq}); 2.85 (m, 1H, H-4); 3.25 (m, 1H, J = 8.7 Hz, H-4′); 3.35–3.43 (m, 2H, H-5′, H-1′); 3.61–3.79 (m, 4H, H-2′, H-3′, H-6′a, H-6′b); 3.72 (s, 3H, PhCHCOOCH_3); 4.53–4.67, 4.78–4.92 (m, 8H, 4 × Ph**C**H_2); 5.39 (dd,1H, $J_{2,3ax}$ = 7.3 Hz, $J_{2,3eq}$ = 1.8 Hz, H-2); 5.52 (s, 1H, PhC*H*COOCH$_3$); 5.98 (d, 1H, $J_{4,5}$ = 3.2 Hz, H-5); 7.10–7.43 (m, 25H, 5 × C_6H_5) 7.45 (1H, J = 3.2 Hz, C*H*-thiazole); 7.75 (d, 1H, J = 3.2 Hz, C*H*-thiazole). ^{13}C NMR ($CDCl_3$): 27.7 (C-4); 32.95 (C-3); 37.9 (C-1″); 52.4 (CH–COOCH_3); 69.0 (C-6′); 73.6, 74.9, 75.2, 75.5 (4 × $PhCH_2$); 77.1 (C-1′); 77.7 (*C*H–COOCH$_3$); 78.4 (C-3′); 79.0 (C-5′); 82.7 (C-4′); 87.2 (C-2′); 98.9 (C-2); 106.5 (C-5); 118.5 (C*H*-thiazole); 127.3–128.6 (25 × C_6H_5); 136.1, 138.0, 138.2, 138.3, 138.6 (5 × *ipso* C_6H_5); 143.2 (*C*H-thiazole); 143.4 (C-6); 164.1 (*C*-thiazole); 171.0 (CH–*C*OOCH$_3$). ESIMS *m/z*: calcd for ($C_{52}H_{53}NO_9S$): 868.1. Found, 869.6 $[M+H]^+$. Anal. Calcd for $C_{52}H_{53}NO_9S$: C, 71.95; H, 6.15. Found: C, 71.99; H, 6.12.

4.8. Methyl (*S*)-2-phenyl-2-(((2*R*, 4*R*)-4-((2,3,4-tri-*O*-benzyl-α-L-fucopyranosyl)methyl)-6-(thiazol-2-yl)-3,4-dihydro-2*H*-pyran-2-yl)oxy)acetate (21)

According to the same procedure described for the preparation of compound **17**, compound **20** (4.9 g; 8.6 mmol) and chiral vinyl ether (*S*)-**16** (Refs. 4,12) (3.3 g; 17.2 mmol) afforded 4.93 g (75%) of compound **21**. R_f = 0.3 (light petroleum/ethyl acetate 2:1). $[\alpha]_D$ ~0 (*c* 3.24, $CHCl_3$). ^{1}H NMR ($CDCl_3$): 1.22 (d, 3H, J = 6.4 Hz, CH_3); 1.59 (ddd, 1H, $J_{1a'',1b''}$ = 14.2 Hz, $J_{1a'',4}$ = 9.6 Hz, $J_{1a'',1'}$ = 2.8 Hz, H-1a″); 1.87 (ddd, 1H, $J_{3ax,3eq}$ = 13.7 Hz, $J_{3ax,4}$ = 6.9 Hz, $J_{2,3ax}$ = 6.0 Hz, H-3_{ax}); 2.06 (ddd, 1H, $J_{1b'',1a''}$ = 14.2 Hz, $J_{1b'',1'}$ = 11.6 Hz, $J_{1b'',4}$ = 6.0 Hz, H-1b″); 2.26 (ddd, 1H, $J_{3eq,3ax}$ = 13.7 Hz, $J_{3eq,4}$ = 6.8 Hz, $J_{3eq,2}$ = 2.2 Hz, H-3_{eq}); 2.59 (m, 1H, H-4); 3.65 (s, 3H, PhCH-COOCH_3); 3.69–3.81 (m, 4H, H-2′, H-3′, H-4′, H-5′); 4.15 (ddd, 1H, $J_{1',1b''}$ = 11.6 Hz, $J_{1',2'}$ = 6.0 Hz, $J_{1',1a''}$ = 2.8 Hz, H-1′) 4.48–4.79 (m, 6H, 3 × $PhCH_2$); 5.43 (dd, 1H, $J_{2,3ax}$ = 6.0 Hz, $J_{2,3eq}$ = 2.2 Hz, H-2); 5.49 (s, 1H, PhC*H*COOCH$_3$); 6.00 (d, 1H, $J_{4,5}$ = 3.7 Hz, H-5); 7.20–7.45 (m, 21H, 4 × C_6H_5, C*H*-thiazole); 7.74 (d, 1H, J = 3.2 Hz, C*H*-thiazole). ^{13}C NMR ($CDCl_3$): 15.0 (C-6′); 27.2 (C-4); 31.8 (C-3); 32.5 (C-1″); 52.2 (CH–COOCH_3); 68.2 (C-1′); 68.2 (C-5′); 72.9, 76.6, 77.1 (3 × $PhCH_2$); 75.8 75.8, 76.9, 77.3 (*C*H–COOCH$_3$, C-4′, C-3′, C-2′); 98.0 (C-2); 106.5 (C-5); 118.2 (C*H*-thiazole); 127.1–128.4 (4 × C_6H_5); 136.1, 138.1, 138.4, 138.6 (4 × *ipso* C_6H_5); 142.7 (C-6); 143.1 (*C*H-thiazole); 163.9 (*C*-thiazole); 170.7 (CH–*C*OOCH$_3$). ESIMS *m/z*: calcd for ($C_{45}H_{47}NO_8S$): 761.9. Found, 763.1 $[M+H]^+$. Anal. Calcd for $C_{45}H_{47}NO_8S$: C, 70.94; H, 6.22. Found: C, 70.89; H, 6.32.

4.9. (2*S*,4*S*)-2-[(2*R*)-2-Methoxy-1-phenylethoxy]-4-[(2,3,4,6-tetra-*O*-benzyl-β-D-glucopyranosyl)methyl]-6-(thiazol-2-yl)-3,4-dihydro-2*H*-pyran (22)

Lithium aluminum hydride (0.5 g; 13.8 mmol) was added portionwise to a solution of compound **17** (4.01 g, 4.61 mmol) in tetrahydrofuran (200 ml), pre-cooled to 0 °C, and the reaction

mixture was stirred at room temperature for 2 h. After cautious addition of 1 M solution of NaOH (10 ml), the salts were removed by filtration, washed with ethyl acetate, and the solvent was evaporated. The residue was partitioned between ethyl acetate and water, the organic layer was dried and taken down, and the residue was chromatographed through a short silica gel column in light petroleum/ethyl acetate (5:1). The obtained alcohol (3.8 g, R_f = 0.35 in light petroleum/ethyl acetate 2:1, *m/z* 841.6 $[M+H]^+$) was dissolved in tetrahydrofuran (250 ml) and the solution was stirred with potassium *tert*-butoxide (1.4 g, 12.5 mmol) at room temperature for 15 min, the mixture was then treated with methyl iodide (1.04 ml, 16.6 mmol) and stirred at room temperature for 15 h. After the addition of saturated aqueous NH_4Cl (100 ml), the reaction mixture was concentrated in vacuo and the residue was partitioned between dichloromethane and a saturated solution of NH_4Cl. The organic layer was dried, the solvent evaporated, and the residue chromatographed on silica gel in light petroleum/ethyl acetate (6:1) affording 2.95 g (75%) of compound **22**; R_f = 0.71 (light petroleum/ethyl acetate 2:1). $[\alpha]_D$ +48.8 (*c* 0.86, $CHCl_3$). ^1H NMR ($CDCl_3$): 1.74–1.84 (m, 2H, H-1a″, H-3_{ax}); 2.03 (m, Hz, 1H, H-1b″); 2.23 (m, 1H, H-3_{eq}); 2.85 (m, 1H, H-4); 3.29 (dd, 1H, $J_{3',4'} = J_{4',5'}$ = 8.7 Hz, H-4′); 3.37 (s, 3H, $PhCHCH_2OCH_3$); 3.32–3.44 (m, 2H, H-1′, H-5′); 3.47 (dd, 1H, *J* = 10.8 Hz, *J* = 3.7 Hz, $PhCHCH_{2a}OCH_3$); 3.57 (dd, 1H, *J* = 10.5 Hz, *J* = 8.5 Hz, H-6′$_a$); 3.65–3.78 (m, 4H, H-3′, $PhCHCH_{2b}OCH_3$, H-6′$_b$, H-2′); 4.54–4.68 (m, 4H, 2 × $PhCH_2$); 4.76–4.95 (m, 4H, 2 × $PhCH_2$); 4.91 (m, 1H, $PhCHCH_2OCH_3$); 5.42 (dd, 1H, $J_{2,3ax}$ = 7.3 Hz, $J_{2,3eq}$ = 1.8 Hz, H-2); 5.91 (d, 1H, $J_{4,5}$ = 3.0 Hz, H-5); 7.12 (d, 1H, *J* = 3.2 Hz, C*H*-thiazole); 7.13–7.44 (m, 25H, 5 × C_6H_5); 7.66 (d, *J* = 3.2 Hz, C*H*-thiazole). ^{13}C NMR ($CDCl_3$): 27.6 (C-4); 32.9 (C-3); 37.8 (C-1″); 59.3 ($PhCHCH_2OCH_3$); 69.0 (C-6′); 73.4, 73.5, 74.9, 75.3, 75.5 (4 × $PhCH_2$, $PhCHCH_2OCH_3$); 76.8 (C-1′); 78.5 (C-3′); 79.0 (C-5′); 81.5 ($PhCHCH_2OCH_3$); 82.8 (C-4′); 87.2 (C-2′); 101.3 (C-2); 105.4 (C-5); 118.5 (*C*H-thiazole); 126.1–128.4 (25 × C_6H_5); 138.0, 138.2, 138.2, 138.6, 139.8 (5 × *ipso* C_6H_5); 142.8 (*C*H-thiazole); 143.7 (C-6); 164.4 (*C*-thiazole). ESIMS *m/z*: calcd for ($C_{52}H_{55}NO_8S$): 854.1. Found, 872.4 $[M+NH_4]^+$. Anal. Calcd for $C_{52}H_{55}NO_8S$: C, 73.13; H, 6.49. Found: C, 73.23; H, 6.56.

4.10. (2*R*,4*R*)-2-[(2*S*)-2-Benzyloxy-1-phenylethoxy]-4-[(2,3,4,6-tetra-*O*-benzyl-β-D-glucopyranosyl)methyl]-6-(thiazol-2-yl)-3,4-dihydro-2*H*-pyran (23)

Lithium aluminum hydride (0.5 g, 22.14 mmol) was added portionwise under argon to a solution of compound **18** (6.41 g, 7.38 mmol) in tetrahydrofuran (250 ml), pre-cooled to 0° C, and the reaction mixture was stirred at room temperature for 2 h. After cautious addition of 1 M solution of NaOH (10 ml), the salts were removed by filtration, terahydrofuran was evaporated and the residue was partitioned between ethyl acetate and water. The organic layer was dried, the solvent evaporated and the residue was subjected to flash chromatography through a short column of silica gel in light petroleum/ethyl acetate (5:1). The obtained alcohol (5.248 g, R_f = 0.4 in light petroleum/ethyl acetate = 4:1, *m/z* 839.6 $[M+H]^+$) was dissolved in tetrahydrofuran (300 ml) and the solution was stirred at room temperature for 1 h with a 60% suspension of NaH v mineral oil (1 g, 41.6 mmol). Then benzyl bromide (2.23 ml, 18.7 mmol) and tetrabutylammonium iodide (0.58 g, 1.56 mmol) were added, the reaction mixture was heated at 40 °C for 20 min and then stirred at room temperature for 14 h. MeOH (5 ml) was added, the solvent was evaporated in vacuo and the residue partitioned between dichloromethane and a saturated solution of $NaHCO_3$. The organic layer was dried, the solvent was taken down and the residue was chromatographed on a silica gel in light petroleum/ethyl acetate (6:1). This procedure yielded 5.07 g (74%) of compound **23**, mp 107–108 °C (from ethyl acetate/light petroleum), R_f = 0.5 (light petroleum/ethyl acetate 4:1). $[\alpha]_D$ +33.8 (*c* 1.03, $CHCl_3$). ^1H NMR ($CDCl_3$): 1.75–1.85 (m, 2H, H-1a″, H-3_{ax}); 2.07 (m, 1H, H-1b″); 2.20 (m, 1H, H-3_{eq}); 2.84 (m, 1H, H-4); 3.29 (dd, 1H, $J_{3',4'} = J_{4',5'}$ = 8.9 Hz, H-4′); 3.35–3.46 (m, 2H, H-1′, H-5′); 3.57 (dd, 1H, *J* = 11.0 Hz, *J* = 3.7 Hz, $PhCHCH_{2a}OBn$); 3.60–3.71 (m, 3H, $PhCHCH_{2b}OBn$, H-3′, H-6′$_a$); 3.71–3.77 (m, 2H, H-6′$_b$, H-2′); 4.45–4.92 (m, 10H, 5 × $PhCH_2$); 4.95 (dd, 1H, *J* = 8.0 Hz, *J* = 3.7 Hz, $PhCHCH_2OBn$), 5.46 (dd, 1H, $J_{2,3ax}$ = 6.9 Hz, $J_{2,3eq}$ = 1.6 Hz, H-2); 5.94 (d, 1H, $J_{4,5}$ = 3.0 Hz, H-5); 7.12 (d, 1H, *J* = 3.2 Hz, C*H*-thiazole); 7.13–7.40 (m, 30H, 6 × C_6H_5); 7.66 (d, *J* = 3.2 Hz, C*H*-thiazole). ^{13}C NMR ($CDCl_3$): 27.4 (C-4); 32.7 (C-3); 37.7 (C-1″); 69.0 (C-6′); 73.5, 73.5, 74.9, 75.0, 75.3 (5 × $PhCH_2$); 75.5 ($PhCHCH_2OBn$) 76.9 (C-1′); 78.5 (C-3′); 79.0 (C-5′), 81.7 ($PhCHCH_2OBn$); 82.8 (C-4′); 87.2 (C-2′); 101.2 (C-2); 105.4 (C-5); 118.5 (*C*H-thiazole); 126.6–128.4 (30 × C_6H_5); 138.0, 138.2, 138.3, 138.6, 139.8, 139.8 (6 × *ipso* C_6H_5); 142.7 (*C*H-thiazole); 143.6 (C-6); 164.5 (*C*H-thiazole). ESIMS *m/z*: calcd for ($C_{58}H_{59}NO_8S$): 930.2. Found, 948.3 $[M+NH_4]^+$. Anal. Calcd for $C_{58}H_{59}NO_8S$: C, 74.89; H, 6.39. Found: C, 74.97; H, 6.56.

4.11. (2*R*,4*R*)-2-[(2*S*)-2-Benzyloxy-1-phenylethoxy]-4-(2,3,4-tri-*O*-benzyl-α-L-fucopyranosyl)methyl]-6-(thiazol-2-yl)-3,4-dihydro-2*H*-pyran (24)

Using the same procedure as described for the preparation of compound **23**, compound **21** (4.27 g; 5.6 mmol) was converted to compound **24** (2.65 g; 69%), R_f = 0.65 (light petroleum/ethyl acetate 9:1). $[\alpha]_D$ −20.8 (*c* 1.26, $CHCl_3$). ^1H NMR ($CDCl_3$): 1.27 (d, 3H, *J* = 6.2 Hz, CH_3), 1.62 (m, 1H, H-1a″), 1.78 (m, 1H, H-3_{ax}), 2.08 (ddd, 1H, $J_{1b'',1a''}$ = 14.6 Hz, *J* = 9.6 Hz, *J* = 5.0 Hz, H-1b″), 2.22 (m,1H, H-3_{eq}), 2.60 (m, 1H, H-4), 3.60 (dd, 1H, *J* = 11.00, *J* = 3.7 Hz, $PhCHCH_{2a}OBn$), 3.65–3.90 (m, 5H, H-2′, H-3′, H-4′, H-5′, $PhCHCH_{2b}OBn$), 4.20 (m, 1H, H-1′), 4.42–4.80 (m, 8H, 4 × CH_2Ph), 4.98 (1H, *J* = 8.3 Hz, *J* = 3.7 Hz, $PhCHCH_2OBn$), 5.49 (dd, 1H, $J_{2,3ax}$ = 6.9 Hz, $J_{2,3eq}$ = 1.8 Hz, H-2), 5.92 (d, 1H, $J_{5,4}$ = 3.2 Hz, H-5), 7.05 (d, 1H, *J* = 3.2 Hz, C*H*-thiazole), 7.13–7.38 (m, 25H, 5 × C_6H_5), 7.08 (d, 1H, *J* = 3.2 Hz, C*H*-thiazole).^{13}C NMR ($CDCl_3$): 15.6 (C-6′), 27.3 (C-4), 32.2 (C-3), 32.3 (C-1″), 68.2, 68.3 (C-1′, C-5′), 72.8, 72.9, 73.0, 73.2 (4 × $PhCH_2$), 74.7 ($PhCHCH_2OBn$), 75.9, 76.7, 76.9 (C-2′, C-3′, C-4′), 80.8 ($PhCHCH_2OBn$), 100.7 (C-2), 105.3 (C-5), 118.3 (*C*H thiazole), 126.4–128.2 (5 × C_6H_5), 138.0, 138.1, 138.4, 138.6, 139.5 (5 × *ipso* C_6H_5), 142.7 (*C*H tiazol), 143.4 (C-6), 164.2 (thiazole C-2). ESIMS *m/z*: calcd for ($C_{51}H_{53}NO_7S$): 823.4. Found, 824.3 $[M+H]^+$. Anal. Calcd for $C_{51}H_{53}NO_7S$: C, 74.34; H, 6.48. Found: C, 74.53; H, 6.59.

4.12. (2*S*,4*S*)-2-[(2*R*)-2-Methoxy-1-phenylethoxy]-4-[(2,3,4,6-tetra-*O*-benzyl-β-D-glucopyranosyl)methyl]-6-formyl-3,4-dihydro-2*H*-pyran (25)

Molecular sieves (4 Å; 3.5 g) were added to a solution of compound **22** (2.8 g, 3.28 mmol) in acetonitrile (40 ml), and methyl triflate (0.48 ml, 4.26 mmol) was added dropwise. After stirring at room temperature for 15 min, MeOH (5 ml) was added and the solvent was evaporated in vacuo. The residue was treated with MeOH (40 ml) and then $NaBH_4$ (0.37 g, 9.83 mmol) was added in portions. After stirring at room temperature for 15 min, acetone (8 ml) was added, the reaction mixture was filtered through a supercel and the filtrate was evaporated in vacuo. The residue was dissolved in acetonitrile (40 ml) and a solution of $AgNO_3$ (1.11 g, 6.56 mmol) in water (4.4 ml) was added under vigorous stirring. After stirring for 10 min, phosphate buffer (30 ml, pH 7) was added and after 10 min, the acetonitrile was evaporated in vacuo and the residue was partitioned between dichloromethane and a phosphate buffer (pH 7). The organic phase was dried, the solvent evaporated, and the residue flash-chromatographed through a short silica gel

column in light petroleum/ethyl acetate (4:1). This resulted in a yield of 1.83 g (70%) of crystalline aldehyde **25**, mp 113–114 °C (ethyl acetate/light petroleum), R_f = 0.3 (light petroleum/ethyl acetate, 3:1). $[\alpha]_D$ −19.0 (*c* 0.19, $CHCl_3$). ^1H NMR ($CDCl_3$): 1.70 (ddd, 1H, $J_{1a'',1b''}$ = 13.8 Hz, *J* = 10.2 Hz, *J* = 4.6 Hz, H-1a″); 1.92 (ddd, 1H, *J 3ax,3eq* = 14.0 Hz, $J_{3ax,4}$ = 9.2 Hz, $J_{2,3ax}$ = 4.6 Hz, H-3_{ax}); 2.03 (ddd, 1H, $J_{3ax,3eq}$ = 14.0 Hz, $J_{3eq,4}$ = 7.3 Hz, $J_{2,3eq}$ = 2.6 Hz, H-3_{eq}); 2.20 (ddd, 1H, $J_{1a'',1b''}$ = 13.8 Hz, *J* = 8.7 Hz, *J* = 2.2 Hz, H-1b″); 2.73 (m, 1H, H-4); 3.28 (dd, 1H, $J_{3',4'} = J_{4',5'}$ = 9.2 Hz, H-4′); 3.32 (s, 3H, PhCHCH$_2$OC*H*$_3$); 3.37–3.47 (m, 3H, H-1′, H-5′, PhCHC*H*$_{2a}$OCH$_3$); 3.50 (dd, 1H, *J* = 10.54 Hz, *J* = 8.25 Hz, PhCHC*H*$_{2b}$OCH$_3$); 3.63 (dd, 1H, $J_{2',3'} = J_{3',4'}$ = 9.2 Hz, H-3′); 3.66 (dd, 1H, *J* = 10.54 Hz, *J* = 4.6 Hz, H-6′$_a$); 3.69–3.75 (m, 2H, H-6′b, H-2′); 4.51–4.95 (m, 8H, 4 × PhC*H*$_2$); 4.90 (m, 1H, PhC*H*CH$_2$OCH$_3$); 5.49 (dd, 1H, $J_{2,3ax}$ = 4.6 Hz, $J_{2,3eq}$ = 2.6 Hz, H-2); 5.87 (d, 1H, $J_{5,4}$ = 4.1 Hz, H-5); 7.16–7.37 (m, 25H, 5 × C$_6$*H*$_5$); 8.79 (s, 1H, *CHO*). ^{13}C NMR ($CDCl_3$): 27.7 (C-4); 31.4 (C-3); 36.9 (C-1″); 59.2 (CHCH$_2$OCH$_3$); 69.2 (C-6′); 73.5, 75.0, 75.2, 75.6, 77.2 (4 × PhCH$_2$, PhCHCH$_2$OCH$_3$); 77.5 (C-1′); 78.6 (C-3′), 78.9 (C-5′); 79.8 (PhCHCH$_2$OCH$_3$); 82.6 (C-4′); 87.2 (C-2′); 98.8 (C-2); 126.6 (C-5); 127.5–128.5 (25 × *C*$_6$H$_5$); 138.0, 138.1, 138.2, 138.5, 139.3 (5 × *ipso* *C*$_6$H$_5$); 148.7 (C-6); 186.3 (*C*HO). ESIMS *m/z*: calcd for ($C_{50}H_{54}O_9$): 799.0. Found, 817.1 $[M+NH_4]^+$. Anal. Calcd for $C_{50}H_{54}O_9$: C, 75.16; H, 6.81. Found: C, 75.23; H, 6.93.

4.13. (2*R*,4*R*)-2-[(2*S*)-2-Benzyloxy-1-phenylethoxy]-4-[(2,3,4,6-tetra-*O*-benzyl-β-D-glucopyranosyl)methyl]-6-formyl-3,4-dihydro-2*H*-pyran (26)

Using the same procedure as described for the preparation of compound **25**, compound **23** (3.39 g; 3.64 mmol) was converted to aldehyde **26**, (2.36 g; 74%), R_f = 0.5 (light petroleum/ethyl acetate, 3:1). $[\alpha]_D$ −83.8 (*c* 0.66, $CHCl_3$). ^1H NMR ($CDCl_3$): 1.70 (ddd, 1H, $J_{1a'',1b''}$ = 13.8 Hz, *J* = 10.3 Hz, *J* = 5.7 Hz, H-1″a); 1.94 (m, 1H, $J_{3ax,3eq}$ = 14.2 Hz, $J_{3ax,4}$ = 9.6 Hz, $J_{3ax,2}$ = 4.6 Hz, H-3_{ax}); 2.03 (m, 1H, $J_{3eq,3ax}$ = 14.2 Hz, $J_{3eq,4}$ = 6.4 Hz, $J_{3eq,2}$ = 2.8 Hz Hz, H-3_{eq}); 2.24 (ddd, 1H, $J_{1b'',1a''}$ = 13.8 Hz, *J* = 8.7 Hz, *J* = 2.1 Hz, H-1″b); 2.73 (m, 1H, H-4); 3.30 (dd, 1H, $J_{3',4'} = J_{4',5'}$ = 9.2 Hz, H-4′); 3.36–3.47 (m, 2H, H-1′, H-5′); 3.50–3.58 (m, 2H, PhCHC*H*$_{2a}$OBn, H-6′a); 3.63 (dd, 1H, $J_{2',3'} = J_{3',4'}$ = 9.1 Hz, H-3′); 3.66–3.74 (m, PhCHC*H*$_{2b}$OBn, H-6′b, H-2′); 4.43–4.93 (m, 10H, 5 × PhC*H*$_2$); 4.94 (dd, 1H, *J* = 7.6 Hz, *J* = 4.1 Hz, PhC*H*CH$_2$OBn); 5.55 (dd, 1H $J_{2,3ax}$ = 4.6 Hz, $J_{2,3eq}$ = 2.8 Hz, H-2); 5.89 (d, 1H, $J_{5,4}$ = 4.1 Hz, H-5); 7.10–7.39 (m, 30H, 6 × C$_6$*H*$_5$); 8.82 (s, 1H, *CHO*). ^{13}C NMR ($CDCl_3$): 27.6 (C-4); 31.1 (C-3); 36.8 (C-1″); 69.1 (C-6′); 73.3, 73.4, 74.8, 74.9, 75.2 (5 × PhCH$_2$); 75.6 (PhCHCH$_2$OBn); 77.4 (C-1′); 78.5 (C-3′), 78.8 (C-5′); 80.1 (PhCHCH$_2$OBn); 82.5 (C-4′); 87.2 (C-2′); 98.8 (C-2); 126.5 (C-5); 127.3–128.4 (6 × C$_6$H$_5$); 137.9, 138.0, 138.1, 138.3, 138.4, 139.2 (5 × *ipso* C$_6$H$_5$); 148.7 (C-6); 186.4 (*C*HO). ESIMS *m/z*: calcd for ($C_{56}H_{58}O_9$): 875.1. Found, 893.6 $[M+NH_4]^+$. Anal. Calcd for $C_{56}H_{58}O_9$: C, 76.86; H, 6.68. Found: C, 76.82; H, 6.75.

4.14. (2*R*,4*R*)-2-[(2*S*)-2-Benzyloxy-1-phenylethoxy]-4-[(2,3,4-tri-*O*-benzyl-α-L-fucopyranosyl)methyl]-6-formyl-3,4-dihydro-2*H*-pyran (27)

Using the same procedure as described for the preparation of compound **25**, compound **24** (2.65 g; 3.22 mmol) was converted to aldehyde **27** (1.79 g; 72%), R_f = 0.65 (light petroleum/ethyl acetate, 2:1). $[\alpha]_D$ −21.2 (*c* 0.79, $CHCl_3$). ^1H NMR ($CDCl_3$): 1.12 (d, 3H, *J* = 6.3 Hz, CH_3), 1.72 (m, 1H, H-1a″), 1,95 (m, 1H, H-3_{ax}), 2.01 (ddd, 1H, $J_{3eq,3ax}$ = 14.2 Hz, $J_{3eq,4}$ = 7.3 Hz, $J_{3eq,2}$ = 2.7 Hz, H-3_{eq}), 2.12 (ddd, 1H, $J_{1b'',1a''}$ = 14.2 Hz, *J* = 9.6 Hz, *J* = 6.9 Hz, H-1b″), 2.46 (m, 1H, H-4), 3.56 (m, 1H, H-5′), 3.57 (dd, *J* = 11.00 Hz, *J* = 3.7 Hz, PhCHC*H*$_{2a}$OBn), 3.63 (m, 1H, H-4′), 3.64–3.70 m (m, 2H, H-2′, PhCHC*H*$_{2b}$OBn), 3.85 (m, 1H, H-3′), 4.15 (m, 1H, H-1′), 4.43–4.83 (m, 8H, 4 × O-C*H*$_2$-Ph), 4.98 (dd, *J* = 8.3 Hz, *J* = 3.7 Hz, 1H, PhC*H*CH$_2$OBn), 5.60 (d, 1H, *J* = 2.7 Hz, H-2), 5.90 (d, 1H, *J* = 4.6 Hz, H-5), 7.10–7.40 (m, 25H, 5 × C$_6$*H*$_5$), 8.85 (s, 1H, *CHO*). ^{13}C NMR ($CDCl_3$): 15,6 (C-6′), 28.0 (C-4), 31.1 (C-1″), 30.9 (C-3), 67.9 (C-5′), 70.3 (C-1′), 72.9, 73.0, 73.1, 73.4 (4 × PhCH$_2$), 74.3 (PhCHCH$_2$OBn), 76.5 (C-4′), 76.8 (C-3′), 77.3 (C-2′), 78.9 (PhCHCH$_2$OBn), 98.0 (C-2), 126.5–128.3 (5 × C$_6$H$_5$, C-5), 138.0, 138.2, 138.4, 138.6, 139.2 (5 × *ipso* C$_6$H$_5$), 148.3 (C-6), 186.3 (*C*HO). ESIMS *m/z*: calcd for ($C_{49}H_{52}O_8$): 768.9. Found, 787.1 $[M+NH_4]^+$. Anal. Calcd for $C_{49}H_{52}O_8$: C, 76.54; H, 6.82. Found: C, 76.73; H, 7.01.

4.15. (2*R*)-2-Methoxy-1-phenylethyl 2,3-dideoxy-3-*C*-[(2,3,4,6-tetra-*O*-benzyl-β-D-glucopyranosyl)methyl]-4,6-di-*O*-benzyl-β-L-arabinohexopyranoside (28)

A 2 M solution of $BH_3{\cdot}Me_2S$ in tetrahydrofuran (3.94 ml, 7.88 mmol) was added dropwise to a solution of aldehyde **25** (1.8 g, 2.23 mmol) in tetrahydrofuran (40 ml) pre-cooled to 0 °C, and the reaction mixture was stirred at room temperature for 16 h. Then, a 30% NaOH solution (4 ml) and 30% H_2O_2 (4 ml) were added in succession. The mixture was stirred at room temperature for 30 min and partitioned between dichloromethane and a saturated NaCl solution. The organic phase was dried, the dichloromethane evaporated in vacuo, and the residue was dissolved in tetrahydrofuran (60 ml). After addition of a 60% suspension of NaH in mineral oil (0.72 g, 30.03 mmol), the mixture was stirred at room temperature for 1 h. Benzyl bromide (1.04 ml, 9.01 mmol) and tetrabutylammonium iodide (0.21 g, 0.56 mmol) were added and the reaction mixture was heated at 40 °C for 15 min. After stirring at room temperature for 14 h, MeOH (5 ml) was added, the solvent was evaporated in vacuo, and the residue was partitioned between dichloromethane and a saturated solution of $NaHCO_3$. The organic layer was dried, the solvent removed in vacuo, and the residue chromatographed on silica gel in light petroleum/ethyl acetate (5:1) to give 1.69 g (75%) of compound **28**, R_f = 0.35 (light petroleum/ethyl acetate, 3:1). $[\alpha]_D$ −6.3 (*c* 0.19, $CHCl_3$). ^1H NMR ($CDCl_3$): 1.34 (m, 1H, H-2_{ax}), 1.45 (m, 1H, H-1a″), 1.71 (m, 1H, H-3), 2.04 (m, 1H-1b″), 2.12 (m, 1H, H-2_{eq}), 3.12 (m, 1H, H-1′), 3.17 (m, 1H, H-5), 3.29 (dd, 1H, $J_{3,4} = J_{4,5}$ = 9.1 Hz, H-4), 3.34 (s, 3H, PhCHCH$_2$OC*H*$_3$), 3.32–3.40 (m, 2H, PhCHC*H*$_{2a}$OCH$_3$, H-4′), 3.47–3.56 (m, 2H, PhCHC*H*$_{2b}$OCH$_3$, H-5′), 3.58 (m, 1H, H-6a); 3.58-3.68 (m, 4H, H-6′a, H-3′, H-2′, H-6′a), 3.71 (m, 1H, H-6b), 4.30–4.92 (m, 12H, 6 × C*H*$_2$Ph), 4.75 (dd, 1H, $J_{1,2ax}$ = 9.6 Hz, $J_{1,2eq}$ = 1.60 Hz, H-1), 4.84 (m, 1H, PhC*H*CH$_2$OCH$_3$) 7.15–7.40 (m, 35H, 7 × C$_6$H$_5$). ^{13}C NMR ($CDCl_3$): 34.5 (C-1″), 35.8 (C-2), 36.0 (C-3), 59.2 (PhCHCH$_2$OCH$_3$), 69.0, 69.3 (C-6′, C-6), 70.3, 73.4, 73.5, 73.6, 75.0, 75.1, 75.5 (PhCHC*H*$_2$OCH$_3$, 6 × C*H*$_2$Ph), 75.4 (C-5′), 77.9 (C-4), 78.0 (C-1′), 78.6 (C-3′), 78.7 (C-5), 79.0 (PhCHCH$_2$OMe), 82.6 (C-4′), 87.3 (C-2′), 101.8 (C-1), 126.7–128.5 (35 × C$_6$H$_5$), 138.1, 138.2, 138.3, 138.4, 138.5, 138.6, 140.3 (7 × *ipso* C$_6$H$_5$). ESIMS *m/z*: calcd for ($C_{64}H_{70}O_{10}$): 999.2. Found, 1000.6 $[M+H]^+$. Anal. Calcd for $C_{64}H_{70}O_{10}$: C, 76.93; H, 7.06. Found: C, 77.25; H, 6.98.

4.16. (2*S*)-2-Methoxy-1-phenylethyl 2,3-dideoxy-3-*C*-[(2,3,4,6-tetra-*O*-benzyl-β-D-glucopyranosyl)methyl]-4,6-di-*O*-benzyl-β-D-arabinohexopyranoside (29)

Using the same procedure as described for the preparation of compound **28**, aldehyde **26** (2.36 g, 2.7 mmol) was converted to compound **29** (2.21 g; 76%), R_f = 0.4 (light petroleum/ethyl acetate, 3:1). $[\alpha]_D$ −45.24 (*c* 1.25, $CHCl_3$). ^1H NMR ($CDCl_3$): 1.36 (m, 1H, H-2_{ax}), 1.48 (m, 1H, H-1″$_a$), 1.83 (m, 1H, H-3) 2.05 (m, 1H-2_{eq}), 2.14 (m, 1H, H-1″$_a$), 3.14 (m, 1H, H-1′), 3.19 (m, 1H, H-5), 3.29 (dd, 1H, $J_{3,4} = J_{4,5}$ = 9.1 Hz, H-4), 3.37 (m, 2H, PhCHC*H*$_a$OBn, H-4′), 3.47 (m, 1H, H-5′), 3.54 (m, 1H, H-6a), 3.58–3.74 (m, 6H, H-6′a, PhCHC*H*$_b$OMe, H-6b, H-3′, H-2′, H-6′b), 4.42–4.92 (m, 14H, 7 × C*H*$_2$Ph) 4.79 (m, 1H, H-1), 4.92 (m, 1H, PhC*H*CH$_2$OBn), 4.73–

4.93 (m, 6H, H-1, 2 × CH_2Ph,) 7.14–7.41 (m, 40H, 8 × C_6H_5). ^{13}C NMR ($CDCl_3$): 34.4 (C-1″), 35.8 (C-2), 35.9 (C-3), 69.0, 69.3 (C-6′, C-6), 73.2, 73.3, 73.4, 73.6, 74.6, 74.9, 75.1, 75.5, (PhCHCH$_2$OCH$_3$, 7 × CH_2Ph), 75.5 (C-5′), 78.0 (C-4), 78.5 (C-1′), 79.0 (C-3′), 79.3 (C-5), 79.4 (PhCHCH$_2$OBn), 82.5 (C-4′), 87.3 (C-2′), 101.8 (C-1), 126.8–128.4 (40 × C_6H_5), 138.1, 138.2, 138.2, 138.3, 138.4, 138.5, 138.6, 140.3 (8 × *ipso* C_6H_5). ESIMS *m/z*: calcd for ($C_{64}H_{70}O_{10}$): 1075.3. Found, 1076.1 [M+H]$^+$. Anal. Calcd for $C_{70}H_{74}O_{10}$: C, 78.19; H, 6.94. Found: C, 78.38; H, 7.21.

4.17. (2*S*)-2-Methoxy-1-phenylethyl 2,3-dideoxy-3-*C*-[(2,3,4-tri-*O*-benzyl-α-L-fucopyranosyl)methyl]-4,6-di-*O*-benzyl-β-D-arabinohexopyranoside (30)

Using the same procedure as described for the preparation of compound **28**, aldehyde **27** (1.79 g, 2.33 mmol) was converted to compound **30** (1.63 g; 72%), R_f = 0.65 (light petroleum/ethyl acetate, 9:1). $[\alpha]_D$ −11.5 (*c* 0.41, $CHCl_3$). ^{1}H NMR ($CDCl_3$): 1.14 (d, 3H, *J* = 6.4 Hz, CH_3), 1.2–1.4 (m, 2H, H-1″b, H-2$_{ax}$), 1.82 (m, 1H, H-3), 2.2 (m, 2H, H-1″a, H-2$_{eq}$), 3.18 (dd, 1H, $J_{3,4} = J_{4,5}$ = 9.6 Hz, H-4), 3.35 (m, 1H, H-5), 3.52–3.59 (m, 2H, H-6a, H-4′, H-3′), 3.60–3.69 (m, 4H, H-5′, PhCHCH_{2a}OBn, H-6b), 3.72 (dd, 1H, *J* = 11.9 Hz, *J* = 3.7 Hz,, PhCHCH_{2b}OBn), 3.95 (m, 1H, H-2′), 4.12 (ddd, 1H, *J* = 12.4 Hz, *J* = 7.8 Hz, *J* = 3.2 Hz, H-1′), 4.3–4.75 (m, 12H, 6 × CH_2Ph), 4.82 (dd, 1H, $J_{1,2ax}$ = 11.7 Hz, $J_{1,2eq}$ = 7.4 Hz, H-1), 4.93 (dd, 1H, *J* = 3.7 Hz, *J* = 7.7 Hz, PhC*H*CH$_2$OBn), 7.1–7.4 (m, 35H, 7 × C_6H_5). ^{13}C NMR ($CDCl_3$): 16.1 (C-6′), 28.0 (C-1″), 35.4 (C-2), 35.7 (C-3), 67.2 (C-5′), 67.3 (C-1′), 69.2 (C-6), 72.8, 72.9, 73.0, 73.3, 73.8, 74.3, (6 × PhCH_2), 74.6 (PhCHCH_2OBn), 76.6 (C-4′), 76.7 (C-3′), 76.8 (C-2′), 78.1 (C-5), 78.5 (C-4), 79.3 (PhCHCH$_2$OBn), 101.6 (C-1), 126.7–128.3 (7 × C_6H_5), 138.1, 138.3, 138.4, 138.5, 138.6, 138.7, 140.1 (7 × *ipso* C_6H_5). ESIMS *m/z*: calcd for ($C_{63}H_{68}O_9$): 969.2. Found, 987.5 [M+NH$_4$]$^+$. Anal. Calcd for $C_{63}H_{68}O_9$: C, 78.07; H, 6.94. Found: C, 78.56; H, 7.46.

4.18. Phenyl-1-thio 2,3-dideoxy-3-*C*-[(2,3,4,6-tetra-*O*-benzyl-β-D-glucopyranosyl)methyl]-4,6-di-*O*-benzyl-α-L-arabinohexopyranoside (31a) and phenyl-1-thio 2,3-dideoxy-3-*C*-[(2,3,4,6-tetra-*O*-benzyl-β-D-glucopyranosyl)methyl]-4,6-di-*O*-benzyl-β-L-arabinohexopyranoside (31b)

$BF_3{\cdot}Et_2O$ (0.31 ml, 2.4 mmol) and thiophenol (0.82 ml, 8.0 mmol) were added in an inert atmosphere to a solution of compound **28** (1.6 g, 1.60 mmol) in dichloromethane (100 ml), pre-cooled to −78° C. The stirred reaction mixture was allowed to warm spontaneously to room temperature and after 2 h, the reaction was quenched by cautious addition of aqueous $NaHCO_3$. The reaction mixture was partitioned between dichloromethane and a saturated $NaHCO_3$ solution, the combined organic phases were dried and the residue was chromatographed on a silica gel (light petroleum/ethyl acetate 7:1) affording 1.36 g (89%) of a mixture of thioglycosides **31a**,**b** in a ratio α:β = 3:1 (integration of H-1 in NMR spectrum). R_f = 0.4 (light petroleum/ethyl acetate, 3.5:1).

Major α-diastereoisomer **31a**: ^{1}H NMR ($CDCl_3$): 1.49 (m, 1H, H-1a″), 1.84 (m, 1H, H-2$_{ax}$), 1.96 (m, 1H, H-1b″), 2.18 (m, 1H, H-2$_{eq}$), 2.40 (m, 1H, H-3), 3.16–3.32 (m, 3H, H-1′, H-5, H-4,), 3.35 (m, 1H, H-4′), 3.55 (dd, 1H, *J* = 9.62 Hz, *J* = 3.21 Hz, H-6a), 3.59–3.67 (m, 4H, H-3′, H-6b, H-5′, H-2′), 3.73 (m, 1H, H-6′a), 3.83 (dd, 1H, *J* = 10.9 Hz, *J* = 3.2 Hz, H-6′b), 4.34–4.93 (m, 12H, 6 × CH_2Ph), 5.60 (d, 1H, $J_{1,2}$ = 5.3 Hz, H-1), 7.14–7.53 (m, 35H, 7 × C_6H_5). ^{13}C NMR ($CDCl_3$): 33.9 (C-1″), 35.3 (C-3), 35.5 (C-2), 69.0, 69.3 (C-6′, C-6), 72.1, 72.6, 73.5, 74.9, 75.2, 75.7, (6 × CH_2Ph), 75.6 (C-5′), 78.1 (C-4), 78.6 (C-1′), 79.2 (C-3′), 80.0 (C-5), 82.5 (C-4′), 84.8 (C-1), 87.4 (C-2′), 126.1–128.7 (35 × C_6H_5), 138.0, 138.1, 138.2, 138.3, 138.3, 138.6, 138.6, (7 × *ipso* C_6H_5). ESIMS *m/z*: calcd for ($C_{61}H_{64}O_8S$): 957.2. Found, 973.5 [M+NH$_4$]$^+$.

Minor β-diastereoisomer **31b**: ^{1}H NMR, 4.75 (dd, $J_{1,2ax}$ = 11.7 Hz, $J_{1,2eq}$ = 1.6 Hz, H-1). Further signals were overlapped by those of the major diastereoisomer.

4.19. Phenyl-1-thio 2,3-dideoxy-3-*C*-[(2,3,4,6-tetra-*O*-benzyl-β-D-glucopyranosyl)methyl]-4,6-di-*O*-benzyl-α-D-arabinohexopyranoside (32a) and phenyl-1-thio 2,3-dideoxy-3-*C*-[(2,3,4,6-tetra-*O*-benzyl-β-D-glucopyranosyl)methyl]-4,6-di-*O*-benzyl-β-D-arabinohexopyranoside (32b)

Using the same procedure as described for the preparation of compounds **31a**,**b**, compound **29** 2.1 g (1.95 mmol) was converted to a mixture of thioglycosides **32a**,**b** (1.72 g; 92%), R_f = 0.45 (light petroleum/ethyl acetate, 3:1).

Major α-diastereoisomer **32a**: ^{1}H NMR ($CDCl_3$): 1.49 (m, 1H, H-1a″), 1.86 (m, 1H, H-2$_{ax}$), 1.98 (m, 1H, H-1b″), 2.16 (m, 1H, H-2$_{eq}$), 2.41 (m, 1H, H-3), 3.15–3.32 (m, 3H, H-1′, H-4, H-5′), 3.32–3.39 (m, 1H, H-4′), 3.51 (m, 1H, H-6a), 3.57–3.71 (m, 4H, H-3′, H-6b, H-5, H-2′), 3.75 (m, 1H, H-6′a), 3.83 (m, 1H, H-6′b), 4.37–4.97 (m, 12H, 6 × CH_2Ph), 5.61 (d, 1H, $J_{1,2}$ = 5.1 Hz, H-1), 7.14–7.53 (m, 35H, 7 × C_6H_5). ^{13}C NMR ($CDCl_3$): 33.4 (C-1″), 34.0 (C-3), 34.2 (C-2), 69.0, 69.3 (C-6′, C-6), 72.1, 72.8, 73.4, 74., 75.2, 75.7, (6 × CH_2Ph), 75.6 (C-5′), 78.3 (C-4), 79.0 (C-1′), 79.2 (C-3′), 80.0 (C-5), 82.5 (C-4′), 84.8 (C-1), 87.4 (C-2′), 126.2–128.7 (35 × C_6H_5), 138.0, 138.0, 138.1, 138.2, 138.2, 138.3, 138.6, (7 × *ipso* C_6H_5). ESIMS *m/z*: calcd for ($C_{61}H_{64}O_8S$): 957.2. Found, 973.5 [M+NH$_4$]$^+$.

Minor β-diastereoisomer **32b**: ^{1}H NMR, 4.75 (dd, $J_{1,2ax}$ = 11.5 Hz, $J_{1,2eq}$ = 1.7 Hz, H-1). Further signals were overlapped by those of the major diastereoisomer.

4.20. Phenyl-1-thio 2,3-dideoxy-3-*C*-[(2,3,4-tri-*O*-benzyl-α-L-fucopyranosyl)methyl]-4,6-di-*O*-benzyl-α-D-arabinohexopyranoside (33a) and phenyl-1-thio 2,3-dideoxy-3-*C*-[(2,3,4-tri-*O*-benzyl-α-L-fucopyranosyl)methyl]-4,6-di-*O*-benzyl-β-D-arabinohexopyranoside (33b)

Using the same procedure as described for the preparation of compounds **31a**,**b**, compound **30** (1.63 g; 1.68 mmol) was converted to a mixture of thioglycosides **33a**,**b**, (1.1 g; 83%). R_f = 0.55 (light petroleum/ethyl acetate, 3:1).

Major α-diastereoisomer **33a**: ^{1}H NMR ($CDCl_3$): 1.11 (m, 1H, H-1a″), 1.22 (d, 3H, *J* = 6.4 Hz, CH_3), 1.76 (m, 1H, H-2$_{ax}$), 2.12 (m, 1H, H-3), 2.15–2.27 (m, 2H, H-1b″, H-2$_{eq}$), 3.35 (dd, 1H, $J_{3,4}$ = $J_{4,5}$ = 9.6 Hz, H-4), 3.48 (m, 1H, H-5), 3.57–3.65 (m, 3H, H-6a, H-4′, H-3′), 3.66–3.78 (m, 2H,, H-5′, H-6b), 3.91 (m, 1H, H-2′), 4.06 (m, 1H, H-1′), 4.42–4.86 (m, 12H, 6 × CH_2Ph), 5.61 (dd, 1H, *J* = 1 Hz, *J* = 5.0 Hz, H-1), 7.12–7.54 (m, 35H, 6 × C_6H_5). ^{13}C NMR ($CDCl_3$): 15.9 (C-6′), 29.6 (C-1″), 33.8 (C-3), 35.0 (C-2), 67.7 (C-5′), 67.7 (C-1′), 69.2 (C-6), 72.7, 72.8, 73.2, 74.3, 75.7 (5 × PhCH_2), 76.6 (C-4′), 76.7 (C-3′), 76.8 (C-2′), 78.6 (C-5), 81.2 (C-4), 84.7 (C-1), 126.6–127.3 (6 × C_6H_5), 137.9, 138.3, 138.5, 138.6, 138.8, 140.2 (6 × *ipso* C_6H_5). ESIMS *m/z*: calcd for ($C_{54}H_{58}O_7S$): 850.4. Found, 868.3 [M+NH$_4$]$^+$.

Minor β-diastereoisomer **33b**: ^{1}H NMR, 4.93 (dd, $J_{1,2ax}$ = 9.2 Hz, $J_{1,2eq}$ = 3.2 Hz, H-1). Further signals were overlapped by those of the major diastereoisomer.

4.21. 1,5-Anhydro-4,6-di-*O*-benzyl-2,3-dideoxy-3-*C*-[(2,3,4,6-tetra-*O*-benzyl-β-D-glucopyranosyl)methyl]-L-*arabino*-hex-1-enitol (9)

N-Bromosuccinimide (0.06 g, 0.34 mmol) was added to a solution of anomers **31a**,**b** (0.24 g, 0.25 mmol) in acetone (12 ml) containing 1% water. The reaction mixture was stirred at −15 °C under exclusion of light and the reaction course was monitored by TLC (light petroleum/ethyl acetate 3:1). After 1 h, the reaction mixture

did not contain the starting compound and the reaction was quenched by the addition of a $NaHCO_3$ solution to pH 8. After partitioning between dichloromethane and aqueous $NaHCO_3$, the organic phase was dried, the solvent evaporated, and the residue chromatographed on a short silica gel column in light petroleum/ethyl acetate (2:1) affording 0.20 g of 2,3-dideoxy-3-*C*-[(2,3,4,6-tetra-*O*-benzyl-β-D-glucopyranosyl)methyl]-4,6-di-*O*-benzyl-L-*arabino*-hexopyranose (R_f 0.3, light petroleum/ethyl acetate (2:1), *m/z* 865.7 $[M+H]^+$). The obtained compound (0.23 mmol) was dissolved in dichloromethane (5 ml) and the solution was treated in an inert atmosphere at 0 °C with s-collidine (0.415 g, 3.43 mmol) and mesyl anhydride (0.08 g, 0.458 mmol). The reaction mixture was stirred at 0 °C and its course was monitored by TLC (light petroleum/ethyl acetate 3:1). After 4 h, the reaction mixture was partitioned between dichloromethane and aqueous $NaHCO_3$. The organic phase was dried, the solvent evaporated, and the residue chromatographed on silica gel in light petroleum/ethyl acetate (7:1→4:1), affording 0.145 g (64%) of compound **9**, R_f = 0.65 (light petroleum/ethyl acetate, 3:1). $[\alpha]_D$ +35.1 (*c* 0.43, $CHCl_3$). ^1H NMR ($CDCl_3$): 1.50 (m, 1H, H-1a″), 1.76 (ddd, 1H, $J_{1a'',1b''}$ = 13.3 Hz, J = 10.1 Hz, J = 3.2 Hz, H-1b″), 2.65 (m, 1H, H-3), 3.19 (dd, 1H, $J_{3',4'} = J_{4',5'}$ = 8.9 Hz, H-4′), 3.30–3.38 (m, 2H, H-1′, H-5′), 3.44 (dd, 1H, $J_{3,4} = J_{4,5}$ = 8.8 Hz, H-4), 3.56–3.76 (m, 4H, H-3′, H-6$_a$′, H-6$_b$′, H-2′), 3.77–3.81 (m, 1H, H-6$_a$), 3.82–3.86 (m, 2H, H-5, H-6$_b$), 4.47–4.67 (m, 8H, 4 × CH_2Ph), 4.69 (dd, 1H, J = 5.9 Hz, J = 2.0 Hz, H-2), 4.75–4.92 (m, 4H, 2 × CH_2Ph), 6.30 (dd, 1H, J = 5.9 Hz, J = 1.8 Hz, H-1), 7.16–7.38 (m, 30H, 6 × C_6H_5). ^{13}C ($CDCl_3$): 34.5 (C-1″), 35.3 (C-3), 68.7, 69.0 (C-6′, C-6), 73.4, 73.6, 73.8, 74.9, 75.2, 75.6 (6 × CH_2Ph), 76.0, 76.2 (C-4′, C-4), 77.9 (C-5), 78.6 (C-3′), 79.1 (C-1′), 82.4 (C-5′), 87.3 (C-2′), 102.1 (C-2), 127.5–128.4 (6 × C_6H_5), 138.0, 138.1, 138.2, 138.3, 138.4, 138.6 (6 × *ipso* C_6H_5), 142.4 (C-1). ESIMS *m/z*: calcd for ($C_{55}H_{58}O_8$): 847.0. Found, 848.3 $[M+H]^+$. Anal. Calcd for $C_{55}H_{58}O_8$: C, 77.99; H, 6.90. Found: C, 78.36; H, 7. 7.06.

4.22. 1,5-Anhydro-4,6-di-*O*-benzyl-2,3-dideoxy-3-*C*-[(2,3,4,6-tetra-*O*-benzyl-β-D-glucopyranosyl)methyl]-D-*arabino*-hex-1-enitol (10)

Using the same procedure as described for the preparation of compound **9**, the mixture of compounds **32a**,**b** (1.6 g; 1.11 mmol) was converted to compound **10** (0.63 g; 67%), R_f = 0.65 (light petroleum/ethyl acetate, 3:1). $[\alpha]_D$ +7.4 (*c* 0.99, $CHCl_3$). ^1H NMR ($CDCl_3$): 1.53 (m, 1H, H-1″), 1.77 (m, 1H, H-1″), 2.67 (m, 1H, H-3), 3.21 (dd, 1H, $J_{3',4'} = J_{4',5'}$ = 9.0 Hz, H-4′), 3.31–3.38 (m, 2H, H-1′, H-5′), 3.45 (dd, 1H, $J_{3,4} = J_{4,5}$ = 8.9 Hz, H-4), 3.56–3.74 (m, 4H, H-3′, H-6$_a$′, H-6$_b$′, H-2′), 3.76–3.82 (m, 1H, H-6$_a$), 3.82–3.88 (m, 2H, H-5, H-6$_b$), 4.37–4.68 (m, 8H, 4 × CH_2Ph), 4.70 (dd, 1H, J = 5.9 Hz, J = 1.6 Hz, H-2), 4.76–4.95 (m, 4H, 2 × CH_2Ph), 6.32 (dd, 1H, J = 5.9 Hz, J = 2.0 Hz, H-1), 7.05–7.45 (m, 30H, 6 × C_6H_5). ^{13}C ($CDCl_3$): 34.4 (C-1″), 35.2 (C-3), 68.6, 68.9 (C-6′, C-6), 73.3, 73.4, 73.5, 73.7, 74.9, 75.1, (6 × CH_2Ph), 75.9, 76.1 (C-4′, C-4), 77.8 (C-5), 78.5 (C-3′), 79.0 (C-1′), 82.3 (C-5′), 87.3 (C-2′), 102.0 (C-2), 127.4–128.3 (6 × C_6H_5), 138.1, 138.2, 138.2, 138.4, 138.3, 138.6 (6 × *ipso* C_6H_5), 142.4 (C-1). ESIMS *m/z*: calcd for ($C_{55}H_{58}O_8$): 847.1. Found, 848.3 $[M+H]^+$. Anal. Calcd for $C_{55}H_{58}O_8$: C, 77.99; H, 6.90. Found: C, 78.29; H, 7.12.

4.23. 1,5-Anhydro-4,6-di-*O*-benzyl-2,3-dideoxy-3-*C*-[(2,3,4-tri-*O*-benzyl-α-L-fucopyranosyl)methyl]-D-*arabino*-hex-1-enitol (11)

Using the same procedure as described for the preparation of compound **9**, the mixture of compounds **33a**,**b** (0.69 g; 0.81 mmol) was converted to compound **11** (0.26 g; 67%), R_f = 0.75 (light petroleum/ethyl acetate, 3:1). $[\alpha]_D$ −43.0 (*c* 0.74, $CHCl_3$). ^1H NMR ($CDCl_3$): 1.13 (d, 3H, J = 6.4 Hz, CH_3), 1.19 (dt, 1H, $J_{1a'',1b''}$ = 14.2 Hz, J = 2.8 Hz, H-1″b), 2.04 (dt, 1H, $J_{1b'',1a''}$ = 14.2 Hz, J = 2.8 Hz, H-1″a), 2.39 (dt, 1H, J = 11.00 Hz, J = 1.9 Hz, H-3), 3.48 (dd, 1H, $J_{3,4} = J_{4,5}$ = 9.2 Hz, H-4), 3.54 (m, 1H, H-3′), 3.56–3.63 (m, 2H, H-4′, H-5′), 3.75–3.87 (m, 3H, H-5, H-6a, H-6b), 3.92 (m, 1H, H-2′), 4.11 (ddd, 1H, J = 13.3 Hz, J = 7.8 Hz, J = 3.2 Hz, H-1′), 4.47–4.86 (m, 11H, 5 × CH_2Ph, H-2), 6.32 (dd, 1H, J = 2.3 Hz, J = 5.9 Hz, H-1), 7.1–7.45 (m, 25H, 5 × C_6H_5). ^{13}C NMR ($CDCl_3$): 16.0 (C-6′), 29.6 (C-1″), 35.1 (C-3), 67.4 (C-5′), 68.6 (C-6), 69.0 (C-1′), 72.8, 73.0, 73.8, 73.5, 74.3 (5 × $PhCH_2$), 76.7 (C-4′), 76.7 (C-2′), 76.9 (C-4), 77.8 (C-5), 78.2 (C-3′), 101.7 (C-2), 127.3–128.3 (5 × C_6H_5), 138.2, 138.3, 138.4, 138.5, 138.8 (5 × *ipso* C_6H_5), 142.4 (C-1). ESIMS *m/z*: calcd for ($C_{48}H_{52}O_7$): 740.9. Found, 758.1 $[M+NH_4]^+$. Anal. Calcd for $C_{48}H_{52}O_7$: C, 77.81; H, 7.07. Found: C, 77.95; H, 7.68.

Acknowledgments

This work was supported by the Grant Agency of the Czech Republic (Grant No. 203/08/1124) and by the Ministry of Education, Youth and Sport of the Czech Republic (Grant No. 6046137305).

References

1. Bertozzi, C. R.; Kiessling, L. L. *Science* **2001**, *291*, 2357–2364.
2. (a) Danishefsky, S. J.; Allen, J. R. *Angew. Chem., Int. Ed.* **2000**, *39*, 836–863; (b) Galonic, D. P.; Gin, D. Y. *Nature* **2007**, *446*, 1000–1007; (c) Demange, R.; Awad, L.; Vogel, P. *Tetrahedron: Asymmetry* **2004**, *15*, 3573–3585.
3. (a) Štěpánek, P.; Kniežo, L.; Dvořáková, H.; Vojtíšek, P. *Synlett* **2003**, 963–966; (b) Štěpánek, P.; Vích, O.; Kniežo, L.; Dvořáková, H.; Vojtíšek, P. *Tetrahedron: Asymmetry* **2004**, *15*, 1033–1041.
4. Štěpánek, P.; Vích, O.; Werner, L.; Kniežo, L.; Dvořáková, H.; Vojtíšek, P. *Coll. Czech. Chem. Commun.* **2005**, *70*, 1411–1428.
5. Parkan, K.; Vích, O.; Dvořáková, H.; Kniežo, L. *Coll. Czech. Chem. Commun.* **2008**, *73*, 690–700.
6. (a) Shao, H.; Wang, Z.; Lacroix, E.; Wu, S. H.; Jennings, H. J.; Zhou, W. *J. Am. Chem. Soc.* **2002**, *124*, 2130–2131; (b) Wang, Z.; Shao, H.; Lacroix, E.; Wu, S. H.; Jennings, H. J.; Zhou, W. *J. Org. Chem.* **2003**, *68*, 8097–8105; (c) Zhou, W.; Shao, H.; Wu, S. H. *Carbohydr. Res.* **2004**, *339*, 2475–2485; (d) Massi, A.; Nuzzi, A.; Dondoni, A. *J. Org. Chem.* **2007**, *72*, 10279–10282.
7. (a) Di Bussolo, V.; Kim, Y.-J.; Gin, D. Y. *J. Am. Chem. Soc.* **1998**, *120*, 13515–13516; (b) Tiwari, P.; Misra, A. K. *J. Org. Chem.* **2006**, *71*, 2911–2913.
8. Kim, Y.-J.; Di Bussolo, V.; Gin, D. Y. *Org. Lett.* **2001**, *3*, 303–306.
9. Liu, J.; Gin, D. Y. *J. Am. Chem. Soc.* **2002**, *124*, 9789–9797.
10. Liu, J.; Gin, D. Y. *Tetrahedron Lett.* **2003**, *44*, 4015–4018.
11. (a) Parrish, J. D.; Little, R. D. *Org. Lett.* **2002**, *4*, 1439–1442; (b) Allwein, S. P.; Cox, J. M.; Howard, B. E.; Johnson, H. W. B.; Rainier, J. D. *Tetrahedron* **2002**, *58*, 1997–2009; (c) Codeé, J. D. C.; van der Marel, G. A.; van Boeckel, C. A. A.; van Boom, J. H. *Eur. J. Org. Chem.* **2002**, 3954–3965.
12. Dujardin, G.; Rossignol, S.; Brown, E. *Tetrahedron Lett.* **1995**, *36*, 1653–1656.
13. Dondoni, A.; Marra, A.; Merino, P. *J. Am. Chem. Soc.* **1994**, *116*, 3324–3336.
14. Uchiyama, T.; Woltering, J. T.; Wong, W.; Lin, C.-C.; Kajimoto, T.; Takebayashi, M.; Weitz-Schmidt, G.; Asakura, T.; Noda, M.; Wong, C.-H. *Bioorg. Med. Chem.* **1996**, *4*, 1149–1165.
15. Dondoni, A.; Marra, A.; Scherrmann, M.-Ch.; Bertolasi, V. *Chem. Eur. J.* **2001**, *7*, 1371–1382.
16. (a) Martín-Lomaz, M.; Khiar, N.; García, S.; Koessler, J.-L.; Nieto, P. M.; Rademacher, T. W. *Chem. Eur. J.* **2000**, *6*, 3608–3621; (b) Werner, L.; Kniežo, L.; Dvořáková, H. *Tetrahedron Lett.* **2007**, *48*, 609–612.
17. Charette, A. B.; Côté, B. *J. Org. Chem.* **1993**, *58*, 933–936.
18. (a) Giannis, A.; Sandhoff, K. *Tetrahedron Lett.* **1985**, *26*, 1479–1482; (b) Hosomi, A.; Sakata, Y.; Sakurai, H. *Carbohydr. Res.* **1987**, *171*, 223–232; (c) Allevi, P.; Anastasia, M.; Ciuffreda, P.; Fiecchi, A.; Scala, A. *J. Chem. Soc., Chem. Commun.* **1987**, 1245–1246; (d) Bombard, S.; Maillet, M.; Capmau, M.-L. *Carbohydr. Res.* **1995**, *275*, 433–440; (e) Marron, T. G.; Woltering, T. J.; Weitz-Schmidt, G.; Wong, C.-H. *Tetrahedron Lett.* **1996**, *37*, 9037–9040; (f) McDevitt, J. P.; Lansbury, P. T. *J. Am. Chem. Soc.* **1996**, *118*, 3818–3828; (g) Lucero, C. G.; Woerpel, K. A. *J. Org. Chem.* **2006**, *71*, 2641–2647; (h) McGarvey, G. J.; LeClair, Ch. A.; Schmidtmann, B. A. *Org. Lett.* **2008**, *10*, 4727–4730.
19. (a) Ref. 2c; (b) Zhu, Y.-H.; Demange, R.; Vogel, P. *Tetrahedron:Asymmetry* **2000**, *11*, 263–282; (c) Pasquarello, C.; Picasso, S.; Demange, R.; Malissard, M.; Berger, E. G.; Vogel, P. *J. Org. Chem.* **2000**, *65*, 4251–4260; (d) Zhu, Y.-H.; Vogel, P. *Synlett* **2001**, 79–81; (e) Demange, R.; Bühlmann, C.; Vogel, P. *Helv. Chim. Acta* **2003**, *86*, 361–376; (f) Avad, L.; Riedner, J.; Vogel, P. *Chem. Eur. J.* **2005**, *11*, 3565–3573; (g) Vauzeilles, B.; Sinaÿ, P. *Tetrahedron Lett.* **2001**, *42*, 7269–7272; (h) Notz, W.; Hartel, Ch.; Waldscheck, B.; Schmidt, R. R. *J. Org. Chem.* **2001**, *66*, 4250–4260; (i) Mikkelsen, L. M.; Krintel, S. L.; Jiménez-Barbero, J.; Skrydstrup, T. *J. Org. Chem.* **2002**, *67*, 6297–6308; (j) Liu, L.; Postema, M. H. D. *J. Am. Chem.*

Soc. **2001**, *123*, 8602–8603; (k) Postema, M. H. D.; Piper, J. L.; Liu, L.; Shen, J.; Faust, M.; Andreana, P. *J. Org. Chem.* **2003**, *68*, 4748–4754; (l) Wan, Q.; Lubineau, A.; Guillot, R.; Scherrmann, M.-Ch. *Carbohydr. Res.* **2008**, *343*, 1754–1765; (m) Hirai, G.; Watanabe, T.; Yamaguchi, K.; Miyagi, T.; Sodeoka, M. *J. Am. Chem. Soc.* **2007**, *129*, 15420–15421; (n) Watanabe, T.; Hirai, G.; Kato, M.; Hashizume, D.; Miyagi, T.; Sodeoka, M. *Org. Lett.* **2008**, *10*, 4167–4170.

PŘÍLOHA III

Lovyova, Z.; Parkan, K.; Kniezo, L. Stereoselective preparation of four 3-*C*-mannosylated D- and L-glucals from a single starting compound. *Tetrahedron* **2011**, *67* (27), 4967-4979.

Tetrahedron 67 (2011) 4967–4979

Contents lists available at ScienceDirect

Tetrahedron

journal homepage: www.elsevier.com/locate/tet

Stereoselective preparation of four 3-*C*-mannosylated D- and L-glucals from a single starting compound

Zuzana Lövyova, Kamil Parkan, Ladislav Kniežo *

Department of Chemistry of Natural Compounds, Institute of Chemical Technology, Technická 5, 166 28 Prague 6, Czech Republic

ARTICLE INFO

Article history:
Received 14 February 2011
Received in revised form 29 March 2011
Accepted 12 April 2011
Available online 20 April 2011

Keywords:
C-Disaccharides
Glucal derivatives
Stereoselective synthesis

ABSTRACT

The corresponding oxadiene, prepared from the starting perbenzylated α-D-mannopyranosylethanal was subjected to stereoselective cycloaddition reactions with *R* and *S* methyl (ethenyloxy)(phenyl)acetates. From the two obtained diastereoisomeric cycloadducts, 3-*C*-α-D-mannosylated 1,2-D-glucal and 3-*C*-α-D-mannosylated 1,2-L-glucal were prepared. A simple epimerisation of the starting α-D-mannopyranosylethanal afforded perbenzylated β-D-mannopyranosylethanal, which was converted to 3-*C*-β-D-mannosylated 1,2-D-glucal or to 3-*C*-β-D-mannosylated 1,2-L-glucal by the same procedure. The structure of the obtained 3-*C*-α-D-mannosylated 1,2-D-glucal has been confirmed independently by its transformation to the known peracetylated methyl α-*C*-(1→3)-mannobioside. The prepared glucals are suitable precursors for the synthesis of stable glycoconjugates with non-hydrolyzable mannose-containing epitopes.

1. Introduction

Communication systems used on a molecular level by living organisms, are not limited to only the four letters of the genetic alphabet. A detailed study of the role played by saccharides in living organisms revealed that in addition to the two well-known 'alphabet' types (represented by amino acids and nucleotides), another 'alphabet' type that is utilized in biological recognition processes may also be formed by monosaccharides.[1] Using this alphabet, the cell surface carbohydrates mediate interactions between themselves and other cells (including immunodifferentiation, cell adhesion, cell differentiation, and regulation of cell growth) as well as between cells and antibodies, viruses, bacteria, peptide hormones or toxins. Among these interactions, mannose-containing ligands occupy a significant position because they are present on the surface of a large number of pathogens, such as viruses (including HIV), bacteria, fungi, and parasites. Aside from other lectins, they are also recognized by the carbohydrate recognition domain of lectin DC-SIGN, principally expressed by dendritic cells in genital and intestinal mucosa.[2] It has been shown that the inhibition of the recognition process between the mannose-containing ligands present, e.g., in HIV glycoprotein gp 120 and lectin DC-SIGN, may inhibit an infection process at one of the earliest stages.[3] In the studies of these and similar processes, it could be useful to obtain *C*-glycoside or *C*-oligosaccharide analogs of saccharides, which can mimic the structure of natural saccharide epitopes but are by far more stable in the organism because of their resistance to the ubiquitous glycosidases. The quest for effective synthetic methods leading to glycoconjugates with non-hydrolyzable saccharide mimetics is therefore very desirable. For the synthesis of the glycoconjugates mentioned, one might advantageously utilize the reactivity of the C=C bond in 1,2-glucals[4] because of its reactivity, which enables one- or two-step stereoselective preparations of *gluco*-[5] or mannopyranosyl glycosides,[6] glycosides of glucosamine[7] or mannosamine,[8] and some *C*-glycosides.[9] One can envisage that these or similar reactions of *C*-mannosylated 1,2-glucals may also be utilized for their attachment to an oligosaccharide, peptide or lipid moieties, either by glycosidic or C–C bonding, thus enabling the synthesis of various stable glycoconjugates with non-hydrolyzable mannose-containing epitopes. Therefore, we decided to prepare diastereoisomeric 3-*C*-mannosylated 1,2-glucals **1**–**4** as precursors for the synthesis of non-hydrolyzable glycoconjugates, using an approach to the preparation of 3-*C*-glycosylated D- and L-1,2-glucals that was recently published by our group.[10]

Thus, in the present paper, we describe a method enabling the conversion of the starting perbenzylated α-D-mannopyranosylethanal **5** into either of the two 3-*C*-α-D-mannosylated 1,2-glucals, namely 1,5-anhydro-4,6-di-*O*-benzyl-2,3-dideoxy-3-*C*-[(2,3,4,6-tetra-*O*-benzyl-α-D-mannopyranosyl)methyl]-D-*arabino*-hex-1-enitol **1** or 1,5-anhydro-4,6-di-*O*-benzyl-2,3-dideoxy-3-*C*-[(2,3,4,6-tetra-*O*-benzyl-α-D-mannopyranosyl)methyl]-L-*arabino*-hex-1-enitol **2**. Following facile epimerization of aldehyde **5** to β-D-mannopyranosylethanal **6**, it is possible to obtain any of the two 3-*C*-β-D-mannosylated 1,2-glucals by the same procedure, namely

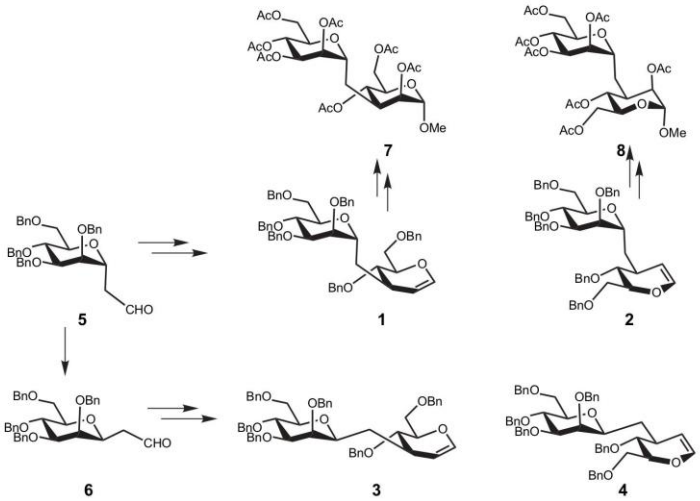
* Corresponding author. Tel.: +420 220 444 265; fax: +420 220 444 422; e-mail address: Ladislav.Kniezo@vscht.cz (L. Kniežo).

0040-4020/$ – see front matter © 2011 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tet.2011.04.044

1,5-anhydro-4,6-di-*O*-benzyl-2,3-dideoxy-3-*C*-[(2,3,4,6-tetra-*O*-benzyl-β-D-mannopyranosyl)methyl]-D-*arabino*-hex-1-enitol **3** and 1,5-anhydro-4,6-di-*O*-benzyl-2,3-dideoxy-3-*C*3,4,6-tetra-*O*-[(2,-benzyl-β-D-mannopyranosyl)methyl]-L-*arabino*-hex-1-enitol **4**. The structure of the obtained glucal **1** has been confirmed independently by its transformation to the known peracetylated methyl α-*C*-mannobioside **7**.[11] By the same manner, glucal **2** was converted to the diastereomeric *C*-disaccharide **8** with L-mannopyranose at the reducing end (Scheme 1).

mixture of peracetylated α- and β-D-mannopyranosylpropenes.[14] Although this mixture is not separable by simple column chromatography, our preliminary experiments have shown that replacement of the acetyl protecting groups by benzyl groups and subsequent ozonolysis of the C=C bond leads to a mixture of perbenzylated α- and β-D-mannopyranosylethanals **5** and **6** that are separable (as shown by TLC) by chromatography on silica gel.

We prepared the mixture of peracetylated α- and β-D-mannopyranosylpropenes using a slight modification of the original procedure.[14]

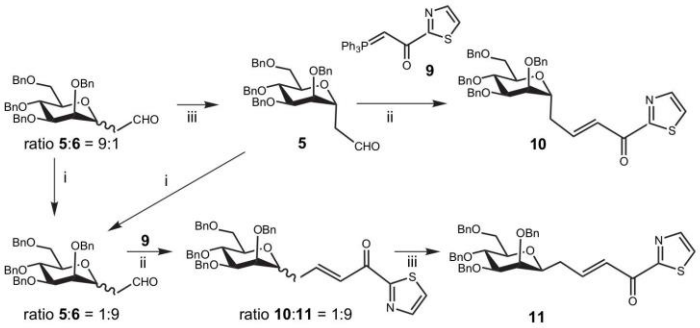


Scheme 1. Synthetic route to 3-*C*-mannosylated glucals **1**–**4**.

2. Results and discussion

The starting perbenzylated α-D-mannopyranosylethanal **5** is a known compound,[12] and the best method of its preparation is ozonolysis or dihydroxylation of the C=C bond (and its subsequent oxidative cleavage) of perbenzylated α-D-mannopyranosylpropene, accessible by stereoselective allylation of the D-mannopyranosyl cation generated from suitable precursors.[13] Because we required a greater amount (more than 10 g) of pure α-D-mannopyranosylethanal **5** and its β-isomer **6**, stereoselective synthesis of multigram amounts of pure perbenzylated α-D-mannopyranosylpropene did not appear to be practical. Therefore, we tried to obtain the aldehyde **5** through a more economic approach, from the readily accessible

A solution of peracetylated D-mannose, 4 equiv of allyltrimethylsilane, and 5.5 equiv of $BF_3 \cdot Et_2O$ was refluxed in acetonitrile for 5 h. Following a workup of the reaction mixture, an unseparable mixture of peracetylated α- and β-D-mannopyranosylpropenes was afforded in 75% yield. Replacement of the acetyl protecting groups by benzyl groups and the subsequent ozonolysis gave a mixture of perbenzylated α- and β-D-mannopyranosylethanals **5** and **6** in the ratio of 9:1 (as determined by integration of the –CHO protons in the ^{1}H NMR spectrum; α anomer: triplet at 9.71 ppm, β anomer: triplet at 9.56 ppm). Chromatography of this mixture on silica gel afforded pure perbenzylated α-D-mannopyranosylethanal **5** in good yield, which in the Wittig reaction with ((2-thiazolylcarbonyl)methylen)triphenylphosphorane **9**[15] gave the only product substituted oxadiene **10**, which is



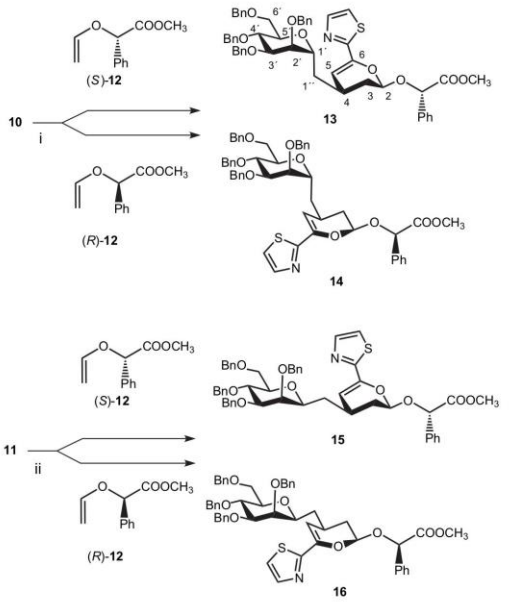
Scheme 2. Synthesis of **10** and **11**. Reagents and conditions: (i) 1% K_2CO_3/MeOH, rt, sonication, 6 h; (ii) **9**, $CHCl_3$, 50 °C, 48 h; (iii) flash chromatography.

the intermediate for the synthesis of glucal **1** or **2** (Scheme 2). It is evident that, alternatively, the described processes[13] may be used for the preparation of pure perbenzylated α-mannopyranosylpropene, which can be converted to aldehyde **5** by ozonolysis and subsequently converted to oxadiene **10** by reaction with phosphorane **9**.

To synthesize the substituted oxadiene **11**, which is an intermediate for the synthesis of glucals **3** and **4**, we made use of the epimerization of α-D-mannopyranosylethanal **5**. This epimerization was described to proceed in methanolic solution with either MeONa[16] or proline in a microwave oven.[17] In the first case, however, the arising β-D-mannopyranosylethanal **6** was not isolated but was reduced in situ to the corresponding alcohol. In the second case, the reaction was performed with only 0.4 mmol of aldehyde **5**. For epimerization of multigram amounts of the aldehyde **5**, a 1% methanolic solution of K_2CO_3 proved to be useful. After adding smaller amounts (≤0.5 g) of pure aldehyde **5** into a stirred solution of 1% methanolic K_2CO_3 at room temperature, equilibrium was achieved after about 2 days, and according to the ^{1}H NMR, the equilibrium mixture consisted of aldehydes **5** and **6** in the ratio of 1:12. Epimerization of greater amounts of the aldehyde was slower, and moreover, signals of other products began to appear in the ^{1}H NMR spectrum. However, the epimerization can be markedly accelerated by sonication. Thus, when 7 g of the starting aldehyde (or a mixture of aldehydes 5:6=9:1) was sonicated for 6 h at room temperature, the equilibrium mixture contained solely compounds **5** and **6** in the ratio of 1:9, whereas after longer periods of sonication, traces of the side product began to appear. Attempts to separate β-D-mannopyranosylethanal **6** from the remnants of the starting α-D-mannopyranosylethanal **5** by chromatography on silica gel were not very successful, and we isolated the pure β-D-mannopyranosylethanal **6** in a maximum yield of about 35%. The low yield is most likely due to relatively rapid decomposition of **6** (unlike **5**) on silica gel. Therefore, we abandoned purification attempts at this step and directly subjected the mixture of aldehydes **5** and **6** (1:9) to the Wittig reaction with ((2-thiazolylcarbonyl)-methylen)triphenylphosphorane **9**. The minor α-epimer **10** in the obtained mixture of oxadienes **10** and **11** was then removed by chromatography on silica gel, affording pure intermediate **11** in a good yield.

The obtained intermediates **10** and **11** were subjected to cycloaddition reactions with both enantiomers of methyl (ethenyloxy)(phenyl)acetate, (*R*)-**12** and (*S*)-**12**, easily obtainable from cheap and commercially accessible enantiomers of mandelic acid.[18] The cycloadditions were accelerated by sonication and proceeded at room temperature in the presence of 0.15 equiv of Eu(fod)$_3$ .The reaction time was 48 h for the α-D-mannopyranosyl derivative **10** and 24 h for the β-D-mannopyranosyl derivative **11**. NOE experiments confirmed the cis-relation of substituents on the C-2 and C-4 atoms of the 3,4-dihydro-2*H*-pyran ring in all of the obtained cycloadducts **13**–**16**. On the basis of analogy with similar cycloadditions that we had studied earlier,[10,18b,19] we can assume with great certainty that, similar to all preceding cases, the vinyl ether (*S*)-12 afforded cycloadducts **13** and **15** with 2*R*,4*R*-configuration and the vinyl ether (*R*)-**12** gave cycloadducts **14** and **16** with 2*S*,4*S*-configuration on the 3,4-dihydro-2*H*-pyran ring (Scheme 3).

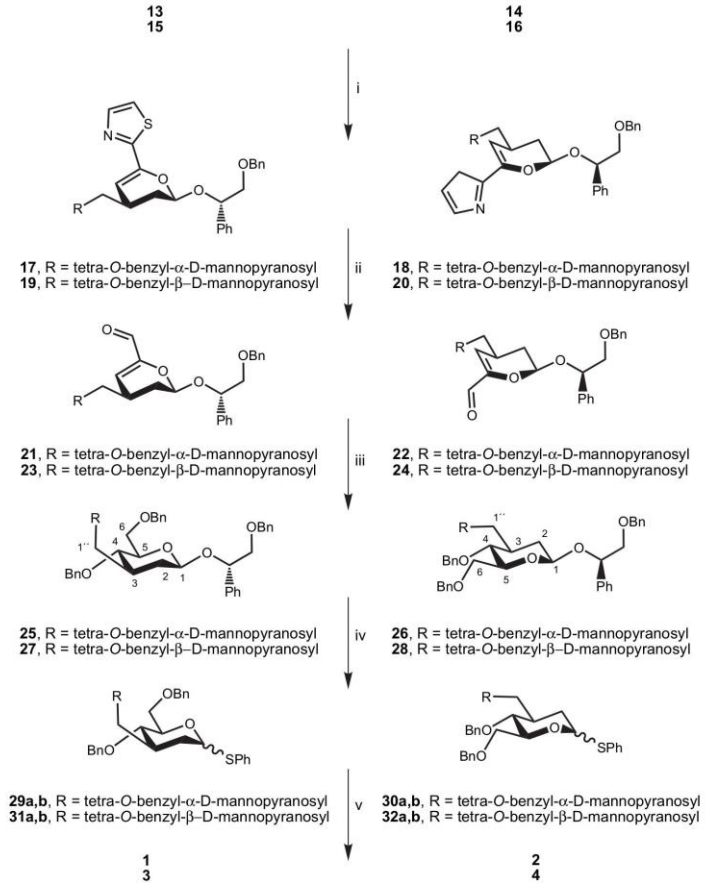
All four synthesized cycloadducts **13**–**16** were converted into the final glucal derivatives **1**–**4** using a procedure that was recently published by our group,[10] shown in Scheme 4. Reduction of the ester group in **13**–**16**, followed by benzylation of the resultant hydroxy group, afforded compounds **17**–**20**, which gave aldehydes **21**–**24** after transformation of the thiazole ring. Simultaneous reduction of the aldehyde group and hydroboration of the double bond by $BH_3\cdot Me_2S$ led to *C*-(1→3)-disaccharides **25**–**28**, having 2-deoxy-*arabino*-hexopyranose (compound **25**: $J_{3,4}$ 9.5 Hz, $J_{4,5}$ 9.7 Hz, compound **26**: $J_{3,4}$=$J_{4,5}$ 9.7 Hz, compound **27**: $J_{3,4}$=$J_{4,5}$ 9.7 Hz, and compound **28**: $J_{3,4}$=$J_{4,5}$ 9.4 Hz) at the reducing end, and these



Scheme 3. Stereoselective synthesis of **13**–**16**. Reagents and conditions: (i) (*R*)-**12** or (*S*)-**12**, Eu(fod)$_3$ (15 mol %), CH_2Cl_2, rt, sonication 48 h; (ii) (*R*)-**12** or (*S*)-**12**, Eu(fod)$_3$ (15 mol %), CH_2Cl_2, rt, sonication 24 h.

disaccharides were treated with thiophenol to give anomeric mixtures of thioglycosides **29a**,**b**–**32a**,**b**. Hydrolysis of the thioglycosides and subsequent mesylation and elimination of the formed hydroxy group led to glucals **1**–**4**. It is worth mentioning that in the synthesized structures with the α-D-mannopyranosyl moiety (e.g., **13**, **14**, **25**, **26**, and **2**), this non-reducing D-mannohexopyranose showed deviation from the normal $^4C_1$ conformation, as follows from lower values (6.4–7.3 Hz) of vicinal diaxial interactions between H-3′ and H-4′ and between H-4′ and H-5′ in the NMR spectra of these compounds. The same effect was also observed for α-*C*-(1→3)-mannobioside[11] and was explained by the steric congestion between the two monosaccharide moieties. In structures containing the β-D-mannopyranosyl moiety (**15**, **16**, **19**, **20**, **23**, **24**, **27**, **28**, **31a**, **3**, and **4**), this steric congestion is evidently not present because their β-D-mannohexopyranose moieties have 'normal' values of vicinal diaxial interactions between H-3′ and H-4′ and between H-4′ and H-5′ (in the range 9.2–9.7 Hz).

Because the assignment of the D- or L-configuration in glucals **1**–**4** is based only on analogy with similar previously studied cycloadditions,[10,18b,19] we decided to confirm the assignment unequivocally by transforming glucal **1** to the known peracetyl methyl α-*C*-(1→3)-mannobioside **7** that has already been prepared by coupling two D-mannohexopyranoses in an Sm_2I-promoted C-glycosylation.[11] The simplest way to transform glucal **1** to methyl *C*-mannobioside **7** is to perform an epoxidation with *m*-chloroperoxybenzoic acid in methanol, where formation of the α-epoxide should give rise to the corresponding methyl glucopyranoside derivative, whereas epoxidation from the β-face of the double bond should lead to the desired methyl mannopyranoside **7**. As indicated by the literature data, the diastereoselectivity of this epoxidation may depend significantly on the structure and substitution of the starting unsaturated saccharide. Thus, for example, epoxidation of 4-*O*-glycosylated glucal, namely hexa-*O*-methylmaltal, with *m*-chloroperoxybenzoic acid in

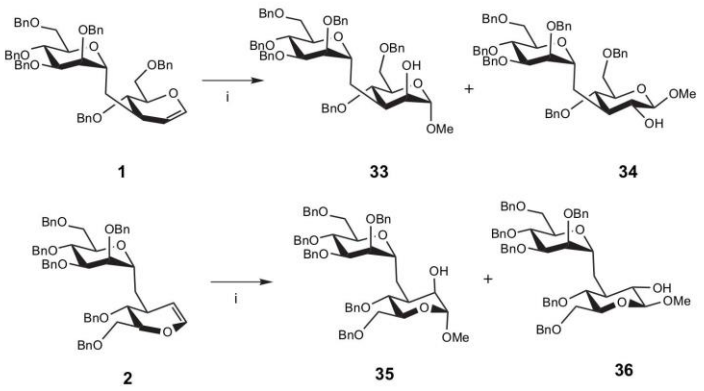


Scheme 4. Synthesis of glucals **1**–**4**. Reagents and conditions. (i) (a) $LiAlH_4$, THF, rt, 1 h; (b) NaH, BnBr, Bu_4NI, THF, 40 °C, 4 h, then rt 14 h; (ii) (a) MeOTf, MeCN, rt, 15 min; (b) $NaBH_4$, MeOH, rt, 15 min; (c) $AgNO_3$, $MeCN/H_2O$, rt, 20 min; (iii) (a) $Me_2S{\cdot}BH_3$, THF, rt, 16 h; (b) NaOH, H_2O_2, rt, 30 min; (c) NaH, BnBr, Bu_4NI, THF, 40 °C, 4 h, then rt 14 h; (iv) PhSH, $BF_3{\cdot}Et_2O$, CH_2Cl_2, −78 °C, then to rt 2 h; (v) (a) NBS, moist acetone (1% H_2O), −15 °C, 1 h, exclusion of light; (b) Ms_2O, *s*-collidine, CH_2Cl_2, 0 °C, 4 h.

methanol proceeded selectively from the α-face, affording solely methyl hexa-*O*-methyl-β-maltoside.[20] The same epoxidation of 3-*C*-glycosylated galactal, i.e., 4,6-di-*O*-benzyl-3-*C*-[(1*R*)-1,3,4,5,7-penta-*O*-benzyl-2,6-anhydro-D-*glycero*-L-*manno*-heptitol-1-*C*-yl]-3-deoxy-D-galactal, took place predominantly from the β-face under formation of methyl 4,6-di-*O*-benzyl-1,3-*C*-[(1*R*)-1,3,4,5,7-penta-*O*-benzyl-2,6-anhydro-D-*glycero*-L-*manno*-heptitol-1-*C*-yl]-3-deoxy-α-D-*talo*-pyranoside as the principal reaction product.[21]

We performed this simple epoxidation with glucal **1** and found that the reaction also proceeded preferentially from the β-face and that stereoselectivity of the epoxidation is practically the same as in the case of the *C*-glycosylated galactal.[21] The epoxidation afforded a mixture of two methyl glycosides **33** and **34**, which were easily separable by chromatography on silica gel (Scheme 5). The major product **33** was isolated chromatographically in 56% yield, and the minor product **34** was isolated in 20% yield. Both products had the same molecular weight (MS), corresponding to the expected methyl glycosides. In the ^1H NMR spectrum of **33**, the H-1 proton appeared as a broad singlet at 4.29 ppm, which corresponds to the methyl α-mannopyranoside structure, whereas in the spectrum of **34**, the H-1 proton appeared as a doublet at 4.13 ppm ($J_{1,2}$ 7.6 Hz), corresponding to methyl β-glucopyranoside. Moreover, debenzylation, followed by acetylation of the major product **33**, afforded a compound whose NMR spectra were identical with those published for peracetylated methyl α-*C*-(1→3)-mannobioside 7.[11] The only significant difference was the chemical shift of the methylene protons of the *C*-glycoside bond (H-1″a,b), described in the original paper as a multiplet at 1.40 to 1.24 ppm, which we found to be a multiplet at 1.88 to 1.83 ppm, partly overlapped with signals of acetyl groups. Chemical shifts of these protons were confirmed by using COSY and HMQC spectra. Because the chemical shifts and multiplicities of other protons were identical with the published values, we assume that the chemical shift of the *C*-glycoside methylene protons was assigned erroneously in the original paper.

By analogy, the same epoxidation of glucal **2** afforded a mixture of two methyl glycosides **35** and **36**, which were isolated by chromatography on silica gel in the yields of 51% and 20%, respectively. Similar to the preceding case, the H-1 proton in the major methyl



Scheme 5. Epoxidation of glucals **1** and **2**. Reagents and conditions: (i) MCPBA, MeOH, CH_2Cl_2, rt, 1.5 h.

glycoside **35** exhibited a broad singlet at 4.59 ppm, whereas in the methyl glycoside **36**, it appeared as a doublet at 4.11 ppm ($J_{1,2}$ 7.6 Hz). Debenzylation of methyl glycoside **35** followed by acetylation afforded *C*-disaccharide **8**, whose ^{1}H NMR spectrum was similar to that of compound **7**. However, it exhibited significant differences in chemical shifts or coupling constants for some protons. The most significant chemical shift differences (more than 0.1 ppm) were found for the protons H-1, H-2, H-3, and H-4 and for the methylene protons of the *C*-glycoside bond, which appeared as two discrete multiplets at 1.92 and 1.77 ppm. In regard to the coupling constants, the most significant deviations were observed for the H-3 proton.

Comparison of the NMR spectra of the obtained methyl glycosides **7** and **8** with the published spectra of methyl α-*C*-(1→3)-mannobioside showed convincing evidence that compound **7** is identical to the known methyl α-*C*-(1→3)-mannobioside, whereas compound **8** is its diastereoisomer. The differences in the H-3 proton coupling constants (for **7**: *J* 11.0, 5.5, 5.5, 3.0 Hz, and for **8**: *J* 11.2, 11.2, 3.1, 3.1 Hz) agree with the fact that *C*-disaccharides **7** and **8** differ in the absolute configuration of mannohexopyranose at the reducing end, which manifests itself in different conformational preferences of the *C*-aglycone bond. Thus, as follows from the obtained NMR spectra, the configuration for the cycloadducts **13** and **14** have been assigned correctly and compounds **1** and **3** are 3-*C*-mannosylated glucals with D-configuration, whereas compounds **2** and **4** are 3-*C*-mannosylated glucals with L-configuration.

3. Conclusion

In summary, we have reported a stereoselective synthesis of any of the four diastereoisomeric 3-*C*-mannosylated 1,2-glucals (1,5-anhydro-2,3-dideoxy-*arabino*-hex-1-enitols) **1**–**4** starting from the known α-D-mannopyranosylethanal **5**. The key step of the synthetic protocol is the cycloaddition of substituted oxadienes, prepared from starting aldehyde **5**, with chiral vinyl ethers derived from both enantiomers of mandelic acid. The final compounds were obtained in seven steps with overall yields 8.37% (for **1**), 9.17% (for **2**), 9.37% (for **3**), and 9.00% (for **4**). Epoxidation of glucals **1** or **2** in methanol afforded as the principal reaction products methyl glycosides of *C*-disaccharides **33** or **35** in 56% and 51% isolated yields, respectively. The obtained methyl glycoside **33** is a non-hydrolyzable analog of disaccharide α-D-Man-(1→3)-D-Man, which is significantly present in cell surface carbohydrates as the core branching region of asparagine-linked oligosaccharides. The simple epoxidation of glucal **1** and the subsequent facile chromatographic isolation of *C*-disaccharide **33** represent a good alternative to the published preparation of this structure.[11] Moreover, the prepared 3-*C*-mannosylated 1,2-glucals **1**–**4** are useful intermediates for preparation of various non-hydrolyzable mannose—containing (1→3)-disaccharide mimetics, which may serve either as tools for study of recognition processes with lectins or for synthesis of non-hydrolyzable glycoprotein or glycolipid epitopes.

4. Experimental

4.1. General methods

All solvents were purified by standard procedures. TLC was performed on HF_{254} plates (Merck), and the detection utilized either UV light or spraying with $Ce(SO_4)_2$ solution (5 g) in 10% H_2SO_4 (500 mL), with subsequent heating. Flash column chromatography was performed on silica gel (Merck, 100–160 μm) with solvents that had been distilled prior to use. Optical rotations were measured at 20 °C on a spectropolarimeter Autopol VI. ^{1}H (300 and 500 MHz) and ^{13}C (75 and 125.7 MHz) NMR spectra were recorded on Varian Oxford 300 and Bruker DRX 500 Avance spectrometers, using tetramethylsilane as an internal standard. The assignments of ^{1}H and ^{13}C signals were confirmed by homonuclear COSY and heteronuclear 2D correlated spectra, respectively. NOE connectivities were obtained using 1D ^{1}H DPFGSE-NOE experiments. Infrared spectra were recorded as $CHCl_3$ solutions on Nicolet 750 FT-IR spectrometer and are reported in wave numbers (cm^{-1}). Mass spectra and HPLC were performed on a 250×4.6 mm column packed with 5 μm Supelco BDS Hypersil C-18, with a mobile phase of MeOH/water, using an HP 1100 instrument equipped with a gradient pump, a column thermostat and, in addition to a UV detector, an Agilent G1956B single quadrupole system as an MS detector.

*4.1.1. (2,3,4,6-Tetra-O-benzyl-α-D-mannopyranosyl)-ethanal (**5**).* Allyltrimethylsilane (60 mL, 368 mmol) and $BF_3{\cdot}Et_2O$ (65 mL, 492 mmol) were portionwise added to a solution of 1,2,3,4,6-penta-*O*-acetyl-D-mannopyranose (35 g, 93 mmol) in dry CH_3CN (500 mL). The mixture was refluxed for 5 h, then cooled to room temperature, and after concentration diluted with CH_2Cl_2 (500 mL). The solution was washed with 2 M NaOH under vigorous stirring to persisting alkaline reaction of the aqueous phase. The organic layer was washed with $NaHCO_3$ solution, dried over $MgSO_4$, and the solvent

was evaporated. Chromatography of the residue (light petroleum/ethyl acetate, 3:1) afforded an unseparable mixture of α and β (2,3,4,6-tetra-*O*-acetyl-D-mannopyranosyl)-prop-2-enes (25 g, 75%); R_f=0.5 (light petroleum/ethyl acetate, 2:1). ESIMS: MH^+ found: 373.7. $C_{17}H_{25}O_9$ requires 373.2. The spectroscopic data were consistent with those reported.[14] A 0.1 M solution of MeONa in MeOH was added dropwise to the obtained mixture of peracetylated D-mannopyranosylprop-2-enes in MeOH (500 mL) to allow the alkaline reaction to persist, and the reaction mixture was stirred at room temperature. After 20 h, no starting compound was detected (TLC) in the reaction mixture, and the reaction was then neutralized with Dowex 50 (5 g) and filtered. Evaporation of the solvent and chromatography on silica gel (chloroform/MeOH, 5:1) afforded 13 g of a mixture of α and β D-mannopyranosylprop-2-enes; R_f=0.4 (chloroform/MeOH, 5:1). ESIMS: MH^+ found: 205.7. $C_9H_{17}O_5$ requires 205.2. The obtained mixture of D-mannopyranosylprop-2-enes was dissolved in dry tetrahydrofuran (400 mL). To this solution, we added 11.8 g (296.7 mmol) of a 60% suspension of NaH in mineral oil, and the reaction mixture was stirred at room temperature for 1 h. Then, tetrabutylammonium iodide (4.56 g, 12.3 mmol) was added, followed by dropwise addition of benzyl bromide (35.3 mL, 296.7 mmol). The reaction mixture was heated at 50 °C for 2 h and then stirred at room temperature for another 15 h. The excess hydride was decomposed by the addition of MeOH (5 mL), the solvent was evaporated, and the residue was partitioned between CH_2Cl_2 and H_2O. The organic phases were combined, dried, and stripped of solvent, and the residue was chromatographed on silica gel (light petroleum/ethyl acetate, 12:1→9:1). This procedure yielded 33 g of a mixture of α and β perbenzylated D-mannopyranosylprop-2-enes; R_f=0.35 (light petroleum/ethyl acetate, 9:1). ESIMS: MH^+ found: 565.8. $C_{37}H_{41}O_5$ requires 565.7. The mixture obtained was dissolved in dry dichloromethane (200 mL) and was subsequently ozonized, after addition of anhydrous MeOH (40 mL) and cooling to −78 °C. After 20 min, the mixture did not contain (TLC) any starting compound, and the reaction was terminated by passing nitrogen through the mixture for 5 min. Then $NaHCO_3$ (4 g) (to prevent an acetalization) and then dimethyl sulfide (43 mL, 587 mmol) were added successively, and the stirred mixture was allowed to warm to room temperature. After stirring the mixture for 3 days at room temperature, the $NaHCO_3$ was filtered off, and the solvent was evaporated. ^{1}H NMR of the crude product showed the presence of a mixture of α and β perbenzylated D-mannopyranosylethanals **5** and **6** in a 9:1 ratio (aldehyde proton of the α-diastereoisomer as a triplet at 9.71 ppm and that of the β-diastereoisomer as a triplet at 9.56 ppm). Chromatography on a silica gel column (light petroleum/ethyl acetate, 9:1→5:1) afforded 23 g (60% from mixture of peracetylated D-mannopyranosylprop-2-enes) of (2,3,4,6-tetra-*O*-benzyl-α-D-mannopyranosyl)-ethanal **5**; R_f=0.35 (light petroleum/ethyl acetate, 3:1) and 6.5 g of a mixture of α and β of perbenzylated D-mannopyranosylethanals **5** and **6**; R_f=0.30 (light petroleum/ethyl acetate, 3:1). The spectroscopic data obtained for compound **5** were identical to those reported.[12b]

*4.1.2. (E)-4-(2,3,4,6-Tetra-O-benzyl-α-D-mannopyranosyl)-1-(thiazol-2-yl)-but-2-en-1-one (**10**).* Ylide **9**[15] (17.2 g, 44.5 mmol) was added to a solution of aldehyde **5** (11.5 g, 20.3 mmol) in $CHCl_3$ (130 mL), and the mixture was stirred and heated at 50 °C. After 48 h, the reaction mixture did not show an aldehyde proton signal (9.71 ppm) in the ^{1}H NMR spectrum. The solvent was evaporated, and the residue was chromatographed on silica gel (light petroleum/ethyl acetate, 5:1→3:1), affording 9.6 g (70%) of compound **10** as a yellow viscous oil; [Found: C, 72.66; H, 5.96. $C_{41}H_{41}NO_6S$ requires C, 72.86; H, 6.11%]; R_f=0.3 (light petroleum/ethyl acetate, 3:1); $[\alpha]_D^{20}$ +9.5 (*c* 0.74, $CHCl_3$); ν_{max} 3011, 1671, 1625, 1454, 1390, 1094, 1028 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) 7.89 (d, 1H, *J* 3.0 Hz, H-thiazol), 7.52 (d, 1H, *J* 3.0 Hz, H-thiazol), 7.15–7.40 (m, 22H, 4× C_6H_5, H-2, H-3), 4.64–4.44 (m, 8H, 4× O–CH_2–Ph), 4.16 (m, 1H, H-1′), 3.96 (dd, 1H, $J_{4',5'}$ 10.4 Hz, $J_{5',6'b}$ 5.0 Hz, H-5′), 3.91–3.76 (m, 3H, H-3′, H-6′a, H-4′), 3.72 (dd, 1H, $J_{6'a,6'b}$ 10.3 Hz, $J_{6'b,5'}$ 5.0 Hz, H-6′b), 3.62 (dd,1H, $J_{3',2'}$ 6.3 Hz, $J_{2',1'}$ 2.7 Hz, H-2′), 2.73–2.52 (m, 2H, H-4a, H-4b); ^{13}C NMR (125 MHz, $CDCl_3$) 180.9 (*C*-1), 167.8 (thiazol *C*-2), 146.7 (C-2), 144.4 (*C*–H thiazol), 138.1, 137.9, 137.7, 137.6 (4× *ipso* C_6H_5), 128.2–127.2 (20× C_6H_5), 126.3 (C-3), 126.0 (*C*–H thiazol), 75.4 (C-2′), 75.1, 74.3 (C-3′, C-4′), 73.9 (C-5′), 72.9, 72.7, 72.0, 71.2 (4× CH_2–Ph), 70.3 (C-5′), 68.4 (C-6′), 34.1 (C-4). ESIMS: MH^+, found: 676.4. $C_{41}H_{42}NO_6S$ requires 676.8.

*4.1.3. (E)-4-(2,3,4,6-Tetra-O-benzyl-β-D-mannopyranosyl)-1-(thiazol-2-yl)-but-2-en-1-one (**11**).* Aldehyde **5** (or the mixture of aldehydes **5** and **6** in a ratio of 9:1) (7.0 g, 12.3 mmol) was dissolved in a 1% methanolic solution of K_2CO_3 (270 mL) and was sonicated at room temperature. According to ^{1}H NMR, the reaction mixture contained the mixture of aldehydes **5** and **6** in a ratio of 1:9 after 6 h. The reaction was quenched by neutralization with acetic acid, the solvent was evaporated, and the residue was partitioned between CH_2Cl_2 and a saturated NaCl solution. The organic phase was dried, the solvent evaporated, and the residue dissolved in $CHCl_3$. Ylide **9**[15] (10.5 g, 27.2 mmol) was added to the solution, and the mixture was heated at 50 °C. After 30 h, the reaction mixture did not show any aldehyde proton signals in the ^{1}H NMR spectrum. The solvent was evaporated, and the residue was chromatographed on silica gel (light petroleum/ethyl acetate, 5:1→3:1), affording 3.8 g (60%) of compound **11** as a yellow viscous oil; [Found: C, 72.64; H, 6.25. $C_{41}H_{41}NO_6S$ requires C, 72.86; H, 6.11%]; R_f=0.32 (light petroleum/ethyl acetate, 3:1); $[\alpha]_D^{20}$ +7.4 (*c* 0.74, $CHCl_3$); ν_{max} 3009, 1675, 1627, 1453, 1390, 1095, 1028 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) 7.99 (d, 1H, H-thiazol, *J* 2.9 Hz), 7.65 (d, 1H, H-thiazol, *J* 2.9 Hz), 7.15–7.42 (m, 22H, 4× C_6H_5, H-2, H-3), 4.5–5.1 (m, 8H, 4× O–CH_2–Ph), 3.95 (dd, 1H, $J_{4',5'}$ 10.0 Hz, $J_{4',H-3'}$ 9.5 Hz, H-4′), 3.77 (m, 2H, H-2′, H-6′a), 3.70 (dd, 1H, $J_{6'a,6'b}$ 10.9 Hz, $J_{6'b,5'}$ 5.3 Hz, H-6′b), 3.64 (dd,1H, $J_{3',4'}$ 9.5 Hz, $J_{3',2'}$ 2.2 Hz, H-3′), 3.49 (m, 2H, H-1′, H-5′), 2.78 (m, 1H, H-4a), 2.49 (m, 1H, H-4b); ^{13}C NMR (125 MHz, $CDCl_3$) 181.4 (C-1), 168.1 (thiazol *C*-2), 147.0 (C-2), 144.7 (*C*–H thiazol), 138.4, 138.3, 138.2 (4× *ipso* C_6H_5), 128.5–127.4 (20× C_6H_5), 126.4 (*C*–H thiazol), 126.3 (C-3), 85.2 (C-3′), 79.9, 77.1 (C-1′, C-5′), 74.9 (C-2′, C-4′), 74.3, 73.5, 72.6 (4× CH_2–Ph), 69.5 (C-6′), 34.9 (C-4). ESIMS: MNH_4^+, found, 693.2. $C_{41}H_{42}N_2O_6S$ requires 693.3.

*4.1.4. Methyl (S)-2-phenyl-2-{[(2R,4R)-4-(2,3,4,6-tetra-O-benzyl-α-D-mannopyranosyl)methyl-6-(thiazol-2-yl)-3,4-dihydro-2H-pyran-2-yl]oxy}acetate (**13**).* Eu(fod)$_3$ (2.10 g, 2.06 mmol) was added to a solution of compound **10** (9.0 g, 13.3 mmol) and chiral vinyl ether (*S*)-**12**[18] (3.9 g, 20.3 mmol) in dichloromethane (200 mL), and the reaction mixture was sonicated at room temperature. After 48 h, the mixture did not contain (TLC) any starting compound **10**. Evaporation of solvent and chromatography of the residue on silica gel (light petroleum/ethyl acetate, 3:1→2:1) afforded 8.7 g (75%) of compound **13** as a colorless foam; [Found: C, 71.78; H, 6.05. $C_{52}H_{53}NO_9S$ requires C, 71.95; H, 6.15%]; R_f=0.30 (light petroleum/ethyl acetate, 2:1); $[\alpha]_D^{20}$ +21.1 (*c* 1.36, $CHCl_3$); ν_{max} 3010, 1736, 1496, 1454, 1272, 1095, 1028 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) 7.73 (d, 1H, H-thiazol, *J* 3.2 Hz), 7.45–7.15 (m, 26H, 5× C_6H_5, H-thiazol), 6.05 (d, INS> 1H, $J_{5,4}$ 3.7 Hz, H-5), 5.46 (s, 1H, Ph*CH*$COOCH_3$), 5.42 (dd, 1H, $J_{2,3ax}$ 5.5 Hz, $J_{2,3eq}$ 2.2 Hz, H-2), 4.73–4.42 (m, 8H, 4× O–CH_2–Ph), 4.18 (m, 1H, H-1′), 3.92–3.81 (m, 3H, H-4′, H-5′, H-6′a), 3.76 (dd, 1H, $J_{6'a,6'b}$ 10.5 Hz, $J_{6',5'}$ 3.3 Hz, H-6′b), 3.71 (dd, 1H, $J_{3',4'}$ 6.7 Hz, $J_{3',2'}$ 2.7 Hz, H-3′), 3.68 (s, 3H, $COOCH_3$), 3.49 (dd, 1H, $J_{2',1'}$ 4.3 Hz, $J_{3',2'}$ 2.7 Hz, H-2′), 2.67 (m, 1H, H-4), 2.23 (ddd, 1H, $J_{3eq,3ax}$ 13.7 Hz, $J_{3eq,4}$ 6.8 Hz, $J_{3eq,2}$ 2.2 Hz, H-3_{eq}), 2.04 (ddd, 1H, $J_{3eq,3ax}$ 13.7 Hz, $J_{3ax,4}$ 5.9 Hz, $J_{3ax,2}$ 5.5 Hz, H-3_{ax}), 1.89 (m, 1H, H-1″a), 1.70 (m, 1H, H-1″b); ^{13}C NMR (125 MHz, $CDCl_3$) 170.8 ($COOCH_3$), 163.9 (thiazol C-2), 143.1 (*C*–H thiazol), 143.0 (C-6), 138.4, 138.3, 138.2,

138.1, 136.1 (5× *ipso* C_6H_5), 128.4–127.1 (25× C_6H_5), 118.5 (C–H thiazol), 104.6 (C-5), 97.9 (C-2), 77.6 (PhCHCOOCH$_3$), 77.3 (C-3′), 76.6 (C-2′), 74.8, 73.4 (C-4′, C-5′), 73.6, 73.2, 72.0, 71.6 (4× CH_2–Ph), 71.1 (C-1′), 69.2 (C-6′), 52.2 (COOCH$_3$), 35.4 (C-1″), 32.8 (C-3), 27.1 (C-4). ESIMS: MH$^+$, found, 869.3. $C_{52}H_{54}NO_9S$ requires 869.1.

*4.1.5. Methyl (R)-2-phenyl-2-{[(2S,4S)-4-(2,3,4,6-tetra-O-benzyl-α-D-mannopyranosyl)methyl-6-(thiazol-2-yl)-3,4-dihydro-2H-pyran-2-yl]oxy}acetate (**14**).* According to the same procedure described for the preparation of compound **13**, compound **10** (8.0 g, 11.8 mmol) and chiral vinyl ether (*R*)-**12**[18] (3.4 g, 17.8 mmol) afforded 8.2 g (80%) of compound **14** as a colorless foam; [Found: C, 71.75; H, 5.95. $C_{52}H_{53}NO_9S$ requires C, 71.95; H, 6.15%]; R_f=0.30 (light petroleum/ethyl acetate, 2:1); $[\alpha]_D^{20}$ −9.1 (*c* 0.99, CHCl$_3$); ν_{max} 3011, 1747, 1496,1454, 1272, 1096, 1028 cm^{-1}; ^{1}H NMR (500 MHz, CDCl$_3$) 7.73 (d, 1H, H-thiazol, *J* 3.2 Hz), 7.45–7.13 (m, 26H, 5× C_6H_5, H-thiazol), 5.95 (d,1H, $J_{5,4}$ 3.9 Hz, H-5), 5.46 (s, 1H, PhC*H*COOCH$_3$), 5.41 (dd, 1H, $J_{2,3ax}$ 6.0 Hz, $J_{2,3eq}$ 2.3 Hz, H-2), 4.73–4.42 (m, 8H, 4× O–C*H*$_2$–Ph), 4.18 (m, 1H, H-1′), 3.86 (dd, 1H, $J_{4',5'}$=$J_{4',3'}$ 6.4 Hz, H-4′), 3.82–3.74 (m, 2H, H-3′, H, 6′a), 3.70 (m,5H, COOC*H*$_3$, H-5′, H-6′b), 3.52 (dd, 1H, $J_{2',3'}$ 4.8 Hz, $J_{2',1'}$ 3.0 Hz, H-2′), 2.71 (m, 1H, H-4), 2.18 (ddd, 1H, $J_{3eq,3ax}$ 13.6 Hz, $J_{3eq,4}$ 6.8 Hz, $J_{3eq,2}$ 2.3 Hz, H-3$_{eq}$), 1.98–1.79 (m, 2H, H-3, H-1″), 1.63 (m, 1H, H-1″); ^{13}C NMR (125 MHz, CDCl$_3$) 170.8 (*C*OOCH$_3$), 163.9 (thiazol C-2), 143.2, 143.1 (C-6, *C*–H thiazol), 138.4, 138.2, 138.1, 136.2 (5× *ipso* C_6H_5), 128.5–127.1 (25× C_6H_5), 118.4 (*C*–H thiazol), 106.1 (C-5), 98.3 (C-2), 77.7 (Ph*C*HCOOCH$_3$), 77.1 (C-4′), 76.5 (C-2′), 74.8 (C-5′), 73.6, 73.3, 72.1, 71.6 (4× PhCH$_2$), 73.5 (C-3′), 70.1 (C-1′), 68.9 (C-6′), 52.2 (COOCH$_3$), 35.1 (C-1″), 31.5 (C-3), 26.9 (C-4). ESIMS: MH$^+$, found, 869.3. $C_{52}H_{54}NO_9S$ requires 869.1.

*4.1.6. Methyl (S)-2-phenyl-2-{[(2R,4R)-4-(2,3,4,6-tetra-O-benzyl-β-D-mannopyranosyl)methyl-6-(thiazol-2-yl)-3,4-dihydro-2H-pyran-2-yl]oxy}acetate (**15**).* According to the same procedure described for the preparation of compound **13** after 24 h of sonification, compound **11** (9.25 g, 13.69 mmol) and chiral vinyl ether (*S*)-**12** (3.94 g, 20.54 mmol) afforded 9.2 g (77%) of compound **15** as a colorless foam; [Found: C, 80.05; H, 6.25. $C_{52}H_{53}NO_9S$ requires C, 71.95; H, 6.15%]; R_f=0.30 (light petroleum/ethyl acetate, 2:1); $[\alpha]_D^{20}$ +15.0 (*c* 1.02, CHCl$_3$); ν_{max} 3015, 1745, 1497, 1456, 1272, 1096, 1028 cm^{-1}; ^{1}H NMR (300 MHz, CDCl$_3$) 7.77 (d, 1H, H-thiazol, *J* 2.6 Hz); 7.48–7.16 (m, 26H, 5× C_6H_5, H-thiazol), 5.96 (d,1H, $J_{5,4}$ 3.5 Hz, H-5), 5.49 (s, 1H, PhC*H*COOCH$_3$), 5.38 (dd, 1H, $J_{2,3ax}$ 6.4 Hz, $J_{2,3eq}$ 2.3 Hz, H-2), 4.51–5.15 (m, 8H, 4× O–C*H*$_2$–Ph), 3.95 (dd, 1H, $J_{4',5'}$ 10.0 Hz, $J_{4',3'}$ 9.5 Hz, H-4′), 3.77 (m, 2H, H-2′, H-6′a), 3.75 (s, 3H, COOC*H*$_3$), 3.70 (dd, 1H, $J_{6'a,6'b}$ 10.9 Hz, $J_{6'b,5'}$ 5.3 Hz, H-6′b), 3.64 (dd,1H, $J_{3',4'}$ 9.5 Hz, $J_{3',2'}$ 2.2 Hz, H-3′), 3.50–3.45 (m, 2H, H-1′, H-5′), 2.55 (m, 1H, H-4), 2.20–2.15 (m, 2H, H-3$_{eq}$, H-1″), 1.85 (m, 1H, H-3$_{ax}$), 1.57 (m, 1H, H-1″); ^{13}C NMR (75 MHz, CDCl$_3$) 171.2 (*C*OOCH$_3$), 164.3 (thiazol C-2), 143.6, 143.5 (C-6, *C*–H thiazol), 138.8, 138.7, 136.4 (5× *ipso* C_6H_5), 128.9–127.5 (25×C_6H_5), 118.9 (*C*–H thiazol), 106.0 (C-5), 98.7 (C-2), 85.7 (C-3′), 77.9 (Ph*C*HCOOCH$_3$), 76.0, 75.8, 75.7 (C-5′, C-2′, C-1′), 75.8 (C-4′), 74.7, 73.7, 72.8 (4× PhCH$_2$), 70.0 (C-6′), 52.7 (*C*OOCH$_3$), 36.9 (C-1″), 32.3 (C-3), 27.1 (C-4). ESIMS: MH$^+$, found, 869.2. $C_{52}H_{54}NO_9S$ requires 869.1.

*4.1.7. Methyl (R)-2-phenyl-2-{[(2S,4S)-4-(2,3,4,6-tetra-O-benzyl-β-D-mannopyranosyl)methyl-6-(thiazol-2-yl)-3,4-dihydro-2H-pyran-2-yl]oxy}acetate (**16**).* According to the same procedure described for the preparation of compound **15**, compound **11** (9.0 g, 13.3 mmol) and chiral vinyl ether (*R*)-**12** (3.9 g, 20.3 mmol) afforded 9.3 g (80%) of compound **16** as a colorless foam; [Found: C, 71.70; H, 5.95. $C_{52}H_{53}NO_9S$ requires C, 71.95; H, 6.15%]; R_f=0.30 (light petroleum/ethyl acetate, 2:1); $[\alpha]_D^{20}$ −27.5 (*c* 1.48, CHCl$_3$); ν_{max} 3020, 1748, 1497, 1454, 1268, 1096, 1028 cm^{-1}; ^{1}H NMR (500 MHz, CDCl$_3$) 7.72 (d, 1H, H-thiazol, *J* 3.1 Hz), 7.48–7.10 (m, 26H, 5× C_6H_5, H-thiazol), 6.00 (d,1H, $J_{5,4}$ 3.5 Hz, H-5), 5.48 (s, 1H, PhC*H*COOCH$_3$), 5.42 (dd, 1H, $J_{2,3ax}$ 6.5 Hz, $J_{2,3eq}$ 2.0 Hz, H-2), 4.90–4.48 (m, 8H, 4× O–C*H*$_2$–Ph), 3.94 (dd, 1H, $J_{4',5'}$=$J_{4',3'}$ 9.3 Hz, H-4′), 3.78–3.69 (m, 2H, H-6′a, H-6′b), 3.68 (s, 3H, COOC*H*$_3$), 3.62–3.56 (m, 2H, H-3′, H-2), 3.50 (m, 1H, H-1′), 3.45 (m, 1H, H-5′), 2.70 (m, 1H, H-4), 2.27 (ddd, 1H, $J_{3eq,3ax}$ 13.5 Hz, $J_{3eq,4}$ 7.1 Hz, $J_{2,3eq}$ 2.0 Hz, H-3$_{eq}$), 2.11 (m, 1H, H-1″a), 1.88 (ddd, 1H, $J_{3eq,3ax}$ 13.5 Hz, $J_{3ax,4}$ 6.9 Hz, $J_{2,3ax}$ 6.5 Hz, H-3$_{ax}$), 1.52 (m, 1H, H-1″b); ^{13}C NMR (125 MHz, CDCl$_3$) 170.7 (*C*OOCH$_3$), 163.9 (thiazol C-2), 143.1 (C-6), 143.1 (*C*–H thiazol), 138.5, 138.4, 138.3, 13.2, 136.0 (5× *ipso* C_6H_5), 128.4–127.0 (25× C_6H_5), 118.5 (*C*–H thiazol), 104.2 (C-5), 98.1 (C-2), 85.0 (C-3′), 79.6 (C-5′), 77.4 (C-2′), 76.3 (Ph*C*HCOOCH$_3$), 75.4 (C-4′), 75.3 (C-1′), 74.9, 74.4, 73.2, 72.3 (4× PhCH$_2$), 69.5 (C-6′), 52.2 (*C*OOCH$_3$), 37.6 (C-1″), 33.5 (C-3), 26.42 (C-4). ESIMS: MH$^+$, found, 869.2. $C_{52}H_{54}NO_9S$ requires 869.1.

*4.1.8. (2R,4R)-2-[(S)-2-(Benzyloxy)-1-phenylethoxy]-4-[(2,3,4,6-tetra-O-benzyl-α-D-mannopyranosyl)methyl]-6-(thiazol-2-yl)-3,4-dihydro-2H-pyran (**17**).* Lithium aluminum hydride (0.9 g, 23.7 mmol) was added portionwise under argon to a solution of compound **13** (6.9 g, 7.9 mmol) in tetrahydrofuran (120 mL) that was pre-cooled to 0 °C, and the reaction mixture was stirred at room temperature for 1 h. After cautious addition of a 1 M solution of NaOH (10 mL), the reaction mixture was concentrated and partitioned between a 0.5 M solution of HCl and CH_2Cl_2. The organic layer was washed with $NaHCO_3$ solution and dried. The solvent was subsequently evaporated, and the residue was subjected to flash chromatography through a short column of silica gel in light petroleum/ethyl acetate (5:1). The obtained alcohol (6.34 g, R_f=0.4 in light petroleum/ethyl acetate, 4:1, *m/z* 839.6 [M+H]$^+$) was dissolved in tetrahydrofuran (300 mL), and the solution was stirred at room temperature for 1 h with a 60% suspension of NaH in mineral oil (1.9 g, 47.5 mmol). Then, benzyl bromide (2.7 mL, 18.7 mmol) and tetrabutylammonium iodide (0.71 g, 1.9 mmol) were added, and the reaction mixture was heated at 40 °C for 4 h and then stirred at room temperature for 14 h. MeOH (5 mL) was added, the solvent was evaporated in vacuo, and the residue was partitioned between dichloromethane and a saturated solution of $NaHCO_3$. Then, the organic layer was dried, the solvent was taken down, and the residue was chromatographed on silica gel in light petroleum/ethyl acetate (12:1 →3:1). This procedure yielded 5.2 g (70%) of compound **17** as a pale yellow viscous oil; [Found: C, 74.75; H, 6.55. $C_{58}H_{59}NO_8S$ requires C, 74.89; H, 6.39%]; R_f=0.35 (light petroleum/ethyl acetate, 3:1); $[\alpha]_D^{20}$ +12.4 (*c* 1.43, CHCl$_3$); ν_{max} 3011, 1722,1700, 1496, 1454, 1363, 1265, 1094, 1028 cm^{-1}; ^{1}H NMR (500 MHz, CDCl$_3$) 7.63 (d, 1H, H-thiazol, *J* 3.2 Hz), 7.38–7.09 (m, 30H, 6× C_6H_5), 7.04 (d, 1H, *J* 3.2 Hz, H-thiazol), 6.01 (d,1H, $J_{5,4}$ 3.7 Hz, H-5), 5.48 (dd, 1H, $J_{2,3eq}$ 2.2 Hz, $J_{2,3ax}$ 5.8 Hz, H-2), 4.94 (dd, 1H, *J* 8.2 Hz, *J* 3.5 Hz, PhC*H*CH$_2$OBn), 4.70–4.47 (m, 10H, 5× O–C*H*$_2$–Ph), 4.23 (ddd, 1H, $J_{1',1''a}$ 10.5 Hz, $J_{1',1''b}$ 4.5 Hz, $J_{1',2'}$ 3.0 Hz, H-1′), 3.95–3.86 (m, 2H, H-4′, H-5′), 3.85–3.72 (m, 3H, H-3′, H-6′a, H-6′b), 3.66 (dd, 1H, *J* 10.6 Hz, *J* 8.2 Hz, PhCHC*H*$_{2a}$OBn), 3.58 (dd, 1H, *J* 10.6 Hz, *J* 3.5 Hz, PhCHC*H*$_{2b}$OBn), 3.54 (dd, 1H, $J_{2',3'}$ 4.8 Hz, $J_{2',1'}$ 3.0 Hz, H-2′), 2.66 (m, 1H, H-4), 2.15 (ddd, 1H, $J_{3eq,3ax}$ 13.5 Hz, $J_{3eq,4}$ 6.9 Hz, $J_{2,3eq}$ 2.2 Hz, H-3$_{eq}$), 2.00–1.85 (m, 2H, H-1″a, H-3$_{ax}$), 1.80 (m, 1H, H-1″b); ^{13}C NMR (125 MHz, CDCl$_3$) 164.2 (thiazol C-2), 143.5 (C-6), 142.6 (*C*–H thiazol), 139.6, 138.3, 138.2, 138.1, 138.1, 138.0 (6× *ipso* C_6H_5), 128.2–126.3 (30×C_6H_5), 118.3 (*C*–H thiazol), 103.5 (C-5), 100.2 (C-2), 80.9 (PhCHCH$_2$OBn), 76.9 (C-3′), 76.5 (C-2′), 74.7, 73.4 (C-4′, C-5′), 74.7 (PhCHCH$_2$OBn), 73.4, 73.1, 73.1, 71.9, 71.4 (5× PhCH$_2$, PhCHCH$_2$OBn), 70.8 (C-1′), 69.7 (C-1′), 69.0 (C-6′), 35.5 (C-1″), 33.4 (C-3), 27.3 (C-4). ESIMS: MH$^+$, found, 931.2. $C_{58}H_{60}NO_8S$ requires 931.2.

*4.1.9. (2S,4S)-2-[(R)-2-(Benzyloxy)-1-phenylethoxy]-4-[(2,3,4,6-tetra-O-benzyl-α-D-mannopyranosyl)methyl]-6-(thiazol-2-yl)-3,4-dihydro-2H-pyran (**18**).* Using the same procedure as described for the preparation of compound **17**, compound **14** (6.1 g, 7.03 mmol) was converted to compound **18** (pale yellow viscous oil, 4.6 g, 70%); [Found: C, 74.98; H, 6.25. $C_{58}H_{59}NO_8S$ requires C, 74.89; H, 6.39%];

R_f=0.35 (light petroleum/ethyl acetate, 3:1); $[\alpha]_D^{20}$ −0.7 (*c* 1.57, $CHCl_3$); ν_{max} 3011, 1723,1699, 1496, 1454, 1363, 1266, 1099, 1028 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) 7.63 (d, 1H, H-thiazol, *J* 3.2 Hz), 7.36–7.14 (m, 30H, 6× C_6H_5), 7.07 (d, 1H, H-thiazol, *J* 3.2 Hz), 5.88 (d,1H, $J_{5,4}$ 3.5 Hz, H-5), 5.47 (dd, 1H, $J_{2,3ax}$ 6.5 Hz, $J_{2,3eq}$ 1.9 Hz, H-2), 4.95 (dd, 1H, *J* 8.0 Hz, *J* 3.5 Hz, PhC*H*CH_2OBn), 4.70–4.47 (m, 10H, 5× O–CH_2–Ph), 4.17 (m, 1H, H-1′), 3.90–3.83 (m, 2H, H-4′, H-5′), 3.83–3.76 (m, 2H, H-6′a, H-3′), 3.73 (dd, 1H, $J_{6'a,6'b}$ 10.2 Hz, $J_{6'b,5'}$ 3.6 Hz, H-6′b), 3.68 (dd, 1H, *J* 10.7 Hz, *J* 8.0 Hz, PhCHCH_{2a}OBn), 3.60 (dd, 1H, *J* 10.7 Hz, *J* 3.5 Hz, PhCHCH_{2b}OBn), 3.55 (dd, 1H, $J_{2',3'}$ 4.9 Hz, $J_{2',1'}$ 3.0 Hz, H-2′), 2.72 (m, 1H, H-4), 2.23 (ddd, 1H, $J_{3eq,3ax}$ 13.3 Hz, $J_{3eq,4}$ 6.7 Hz, $J_{2,3eq}$ 1.9 Hz, H-3_{eq}), 1.93 (m, 1H, H-1″a), 1.83 (ddd, 1H, $J_{3eq,3ax}$ 13.3 Hz, $J_{3ax,4}$ 7.5 Hz, $J_{2,3ax}$ 6.5 Hz, H-3_{ax}), 1.69 (m, 1H, H-1″b); ^{13}C NMR (125 MHz, $CDCl_3$) 164.2 (thiazol C-2), 143.6 (C-6), 142.8 (C–H thiazol), 139.6, 138.3, 138.2, 138.1, 138.1, 138.1 (6× *ipso* C_6H_5), 128.3–126.5 (30× C_6H_5), 118.4 (C–H thiazol), 105.0 (C-5), 100.7 (C-2), 81.0 (PhCHCH_2OBn), 77.0, 74.7, 73.5 (C-3′, C-4′, C-5′), 76.6 (C-2′), 74.8, 73.4, 73.3, 73.1, 72.1, 71.5 (5× PhCH_2, PhCHCH_2OBn), 69.7 (C-1′), 68.8 (C-6′), 35.4 (C-1″), 32.1 (C-3), 27.1 (C-4). ESIMS: MH^+, found, 931.2. $C_{58}H_{60}NO_8S$ requires 931.2.

*4.1.10. (2R,4R)-2-[(S)-2-(Benzyloxy)-1-phenylethoxy]-4-[(2,3,4,6-tetra-O-benzyl-β-D-mannopyranosyl)methyl]-6-(thiazol-2-yl)-3,4-dihydro-2H-pyran (**19**).* Using the same procedure as described for the preparation of compound **17**, compound **15** (7.1 g, 8.2 mmol) was converted to compound **19** (pale yellow viscous oil, 5.3 g, 70%); [Found: C, 75.05; H, 6.55. $C_{58}H_{59}NO_8S$ requires C, 74.89; H, 6.39%]; R_f=0.35 (light petroleum/ethyl acetate, 3:1); $[\alpha]_D^{20}$ +6.3 (*c* 1.81, $CHCl_3$); ν_{max} 3011, 1722, 1700, 1496, 1454, 1363, 1257, 1116, 1028 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) 7.63 (d, 1H, *J* 3.2 Hz, H-thiazol,), 7.42–7.14 (m, 30H, 6× C_6H_5), 7.03 (d, 1H, *J* 3.2 Hz, H-thiazol,), 5.89 (d,1H, $J_{5,4}$ 3.2 Hz, H-5), 5.39 (dd, 1H, $J_{2,3ax}$ 7.1 Hz, $J_{2,3eq}$ 2.3 Hz, H-2), 4.98 (d, 1H, *J* 10.8 Hz, O–CH_2–Ph), 4.94 (dd, 1H, *J* 8.3 Hz, *J* 3.4 Hz, PhC*H*CH_2OBn), 4.89 (d, 1H, *J* 10.8 Hz, O–CH_2–Ph), 4.78–4.43 (m, 8H, 4× O–CH_2–Ph), 3.97 (dd, 1H, $J_{4',5'}$=$J_{4',3'}$ 9.5 Hz, H-4′), 3.80–3.55 (m, 6H, PhCHCH_{2a}OBn, PhCHCH_{2b}OBn, H-6′a, H-6′b, H-2′, H-3′), 3.52–3.42 (m, 2H, H-1′, H-5′), 2.49 (m, 1H, H-4), 2.16 (m, 1H, H-1″a), 2.07 (ddd, 1H, $J_{3eq,3ax}$ 13.1 Hz, $J_{3eq,4}$ 6.9 Hz, $J_{2,3eq}$ 2.3 Hz, H-3_{eq}), 1.75 (ddd, 1H, $J_{3eq,3ax}$ 13.1 Hz, $J_{3ax,2}$ 7.1 Hz, $J_{3ax,4}$ 6.7 Hz, H-3_{ax}), 1.58 (m, 1H, H-1″b); ^{13}C NMR (125 MHz, $CDCl_3$) 164.1 (thiazol C-2); 143.5 (C-6), 142.6 (C–H thiazol), 139.4, 138.3, 138.2, 138.1, 138.1, 137.9 (6× *ipso* C_6H_5), 128.2–126.3 (30×C_6H_5), 118.5 (C–H thiazol), 104.2 (C-5), 100.7 (C-2), 85.2 (C-3′), 81.2 (PhCHCH_2OBn), 79.7 (C-5′), 75.3, 75.1, 74.9 (C-1′, C-2′, C-4′), 74.9, 74.6, 74.0, 73.2, 73.1, 72.3 (5× PhCH_2, PhCHCH_2OBn), 69.4 (C-6′), 36.5 (C-1″), 32.7 (C-3), 27.0 (C-4). ESIMS: MH^+, found, 931.2. $C_{58}H_{60}NO_8S$ requires 931.2.

*4.1.11. (2S,4S)-2-[(R)-2-(Benzyloxy)-1-phenylethoxy]-4-[(2,3,4,6-tetra-O-benzyl-β-D-mannopyranosyl)methyl]-6-(thiazol-2-yl)-3,4-dihydro-2H-pyran (**20**).* Using the same procedure as described for the preparation of compound **17**, compound **16** (6.1 g, 7.03 mmol) was converted to compound **20** (pale yellow viscous oil, 4.6 g, 70%); [Found: C, 74.78; H, 6.25. $C_{58}H_{59}NO_8S$ requires C, 74.89; H, 6.39%]; R_f=0.35 (light petroleum/ethyl acetate, 3:1); $[\alpha]_D^{20}$ −13.8 (*c* 1.26, $CHCl_3$); ν_{max} 3011, 1722, 1699, 1497, 1454, 1363, 1266, 1098, 1028 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) 7.66 (d, 1H, H-thiazol, *J* 3.2 Hz), 7.42–7.16 (m, 30H, 8× C_6H_5), 7.13 (d, 1H, H-thiazol, *J* 3.2 Hz), 5.87 (d,1H, $J_{5,4}$ 3.2 Hz, H-5), 5.47 (dd, 1H, $J_{2,3ax}$ 6.7 Hz, $J_{2,3eq}$ 1.9 Hz, H-2), 5.10–4.95 (m, 2H, PhC*H*CH_2OBn, O–CH_2–Ph), 4.88 (d, 1H, *J* 10.8 Hz, O–CH_2–Ph), 4.90–4.48 (m, 8H, 4× O–CH_2–Ph), 3.94 (dd, 1H, $J_{4',5'}$=$J_{4',3'}$ 9.4 Hz, H-4′), 3.80–3.68 (m, 4H, PhCHCH_{2a}OBn, PhCHCH_{2b}OBn, H-6′a, H-6′b), 3.67–3.57 (m, 2H, H-2′, H-3′), 3.53 (m, 1H, H-1′), 3.44 (ddd, 1H, $J_{4',5'}$ 9.4 Hz, $J_{5',6'b}$ 5.0 Hz, $J_{5',6'a}$ 1.7 Hz, H-5′), 2.68 (m, 1H, H-4), 2.21 (ddd, 1H, $J_{3eq,3ax}$ 13.3 Hz, $J_{3eq,4}$ 6.6 Hz, $J_{3eq,2}$ 1.9 Hz, H-3_{eq}), 2.11 (m, 1H, H-1″a), 1.75 (ddd, 1H, $J_{3eq,3ax}$ 13.3 Hz, $J_{3ax,4}$ 8.5 Hz, $J_{3ax,2}$ 6.7 Hz, H-3_{ax}), 1.42 (m, 1H, H-1″b); ^{13}C NMR (125 MHz, $CDCl_3$) 164.5 (thiazol C-2), 143.7 (C-6), 142.9 (C–H thiazol), 139.7, 138.6, 138.5, 138.5, 138.4, 138.2 (6× *ipso* C_6H_5), 128.4–126.6 (30× C_6H_5), 118.7 (C–H thiazol), 103.3 (C-5), 100.9 (C-2), 85.3 (C-3′), 81.1 (PhCHCH_2OBn), 79.8 (C-5′), 76.2, 75.6 (C-2′, C-4′), 75.2 (C-1′), 75.1, 74.9, 74.4, 73.4, 73.3, 72.6 (5× PhCH_2, PhCHCH_2OBn), 69.7 (C-6′), 37.7 (C-1″), 34.5 (C-3), 27.2 (C-4). ESIMS: MH^+, found, 931.2. $C_{58}H_{60}NO_8S$ requires 931.2.

*4.1.12. (2R,4R)-2-[(S)-2-(Benzyloxy)-1-phenylethoxy]-4-[(2,3,4,6-tetra-O-benzyl-α-D-mannopyranosyl)methyl]-6-formyl-3,4-dihydro-2H-pyran (**21**).* Molecular sieves (4 Å; 7.2 g) were added to a solution of compound **17** (5.3 g, 5.68 mmol) in acetonitrile (160 mL), and methyl triflate (0.96 mL, 8.45 mmol) was added dropwise. After stirring at room temperature for 15 min, MeOH (5 mL) was added, and the solvent was evaporated in vacuo. The residue was treated with MeOH (80 mL), and then, $NaBH_4$ (0.7 g, 18.6 mmol) was added in portions. After stirring at room temperature for 15 min, acetone (15 mL) was added, the reaction mixture was filtered through Super Cel and the filtrate was evaporated in vacuo. The residue was dissolved in acetonitrile (60 mL), and a solution of $AgNO_3$ (2.1 g, 12.36 mmol) in water (6 mL) was added under vigorous stirring. After stirring for 10 min, phosphate buffer (20 mL; pH 7) was added, and after 10 min, the acetonitrile was evaporated in vacuo, and the residue was partitioned between dichloromethane and phosphate buffer (pH 7). The organic phase was dried, the solvent was evaporated, and the residue was flash-chromatographed through a short silica gel column in light petroleum/ethyl acetate (7:1→5:1). This procedure resulted in a yield of 3.7 g (73%) of aldehyde **21** as a viscous oil; [Found: C, 76.74; H, 6.52. $C_{56}H_{58}O_9$ requires C, 76.86; H, 6.68%]; R_f=0.3 (light petroleum/ethyl acetate, 3:1); $[\alpha]_D^{20}$ +5.7 (*c* 1.2, $CHCl_3$); ν_{max} 3011, 2926, 2865, 1697, 1496, 1454, 1364, 1093, 1028, 986 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) 8.75 (s, 1H, *H*CO), 7.40–7.10 (m, 30H, 6× C_6H_5), 5.81 (d, 1H, $J_{5,4}$ 4.3 Hz, H-5), 5.55 (m, 1H, H-2), 4.93 (dd, 1H, *J* 8.1, 3.5 Hz, PhC*H*CH_2OBn), 4.71–4.45 (m, 10H, 5× O–CH_2–Ph), 4.06 (ddd, 1H, $J_{1',1''a}$ 10.1 Hz, $J_{1',1''b}$ 5.2 Hz, $J_{1',2'}$ 2.8 Hz, H-1′), 3.98–3.73 (m, 4H, H-3′, H-4′, H-5′, H-6′a), 3.68 (dd, 1H, $J_{6'a,6'b}$ 10.2 Hz, $J_{6'b,5'}$ 3.7 Hz, H-6′b), 3.62 (m, 1H, PhCHCH_{2a}OBn), 3.57–3.48 (m, 2H, H-2′, PhCHCH_{2b}OBn), 2.64 (m, 1H, H-4), 2.10–1.91 (m, 3H, H-1″a, H-3_{eq}, H-3_{ax}), 1.85 (m, 1H, H-1″b); ^{13}C NMR (125 MHz, $CDCl_3$) 186.3 (*H*CO); 148.7 (C-6), 139.3, 138.2, 138.1, 138.1 (6× *ipso* C_6H_5), 128.4–126.5 (30× C_6H_5), 125.2 (C-5), 98.3 (C-2), 79.8 (PhCHCH_2OBn), 76.8, 74.8, 73.7 (C-3′, C-4′, C-5′), 76.4 (C-2′), 74.6 (PhCHCH_2OBn), 73.3, 73.2, 73.1, 72.4, 71.8 (5× Ph*C*H_2), 69.1 (C-1′), 68.8 (C-6′), 35.7 (C-1″), 32.1 (C-3), 26.5 (C-4). ESIMS: MNH_4^+, found 892.6. $C_{56}H_{62}NO_9$ requires 892.4.

*4.1.13. (2S,4S)-2-[(R)-2-(Benzyloxy)-1-phenylethoxy]-4-[(2,3,4,6-tetra-O-benzyl-α-D-mannopyranosyl)methyl]-6-formyl-3,4-dihydro-2H-pyran (**22**).* Using the same procedure as described for the preparation of compound **21**, compound **18** (5.3 g, 5.68 mmol) was converted to aldehyde **22** (viscous oil, 3.8 g, 75%); [Found: C, 76.65; H, 6.56. $C_{56}H_{58}O_9$ requires C, 76.86; H, 6.68%]; R_f=0.3 (light petroleum/ethyl acetate, 3:1); $[\alpha]_D^{20}$ +10.0 (*c* 1.05, $CHCl_3$); ν_{max} 3019, 2925, 2865, 1696, 1496, 1454, 1364, 1096, 1028, 986 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) 8.75 (s, 1H, *H*CO), 7.39–7.08 (m, 30H, 6× C_6H_5); 5.94 (d, 1H, $J_{5,4}$ 4.3 Hz, H-5); 5.56 (m,1H, H-2); 4.95 (dd, 1H, *J* 8.1, 3.6 Hz, PhC*H*CH_2OBn), 4.71–4.45 (m, 10H, 5× O–CH_2–Ph), 4.15 (ddd,1H, $J_{1',1''a}$ 11.0 Hz, $J_{1',1''b}$ 4.8 Hz, $J_{1',2'}$ 2.7 Hz, H-1′), 3.86–3.71 (m, 4H, H-3′, H-4′, H-5′, H-6′a), 3.69–3.60 (m, 2H, H-6′b, PhCHCH_{2a}OBn), 3.60–3.53 (m, 2H, H-2′, PhCHCH_{2b}OBn), 2.59 (m, 1H, H-4), 2.03–1.87 (m, 3H, H-1″a, H-3_{eq}, H-3_{ax}), 1.78 (m, 1H, H-1″b); ^{13}C NMR (125 MHz, $CDCl_3$) 186.3 (*H*CO), 148.4 (C-6), 139.0, 138.0, 138.0, 137.9, 137.8 (6× *ipso* C_6H_5), 128.2–127.2 (30× C_6H_5), 126.4 (C-5), 98.1 (C-2) 79.3 (PhCHCH_2OBn), 76.4, 76.3 (C-2′, C-3′),

74.8, 73.3 (C-4′, C-5′), 74.5 (PhCHCH$_2$OBn), 73.4, 73.1, 72.0, 71.4 (5× PhCH$_2$), 71.0 (C-1′), 68.9 (C-6′), 34.8 (C-1″), 30.9 (C-3), 27.7 (C-4). ESIMS: MNH$_4^+$, found 892.6. $C_{56}H_{62}NO_9$ requires 892.4.

*4.1.14. (2R,4R)-2-[(S)-2-(Benzyloxy)-1-phenylethoxy]-4-[(2,3,4,6-tetra-O-benzyl-β-D-mannopyranosyl)methyl]-6-formyl-3,4-dihydro-2H-pyran (**23**).* Using the same procedure as described for the preparation of compound **21**, compound **19** (5.1 g, 5.45 mmol) was converted to aldehyde **23** (viscous oil, 3.5 g, 73%); [Found: C, 76.74; H, 6.88. $C_{56}H_{58}O_9$ requires C, 76.86; H, 6.68%]; R_f=0.3 (light petroleum/ethyl acetate, 3:1); $[\alpha]_D^{20}$ +5.2 (*c* 1.24, $CHCl_3$); ν_{max} 3020, 2928, 2863, 1697, 1497, 1454, 1364, 1088, 1028, 986 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) 8.78 (s, 1H, *H*CO), 7.43–7.15 (m, 30H, 6× C$_6$*H*$_5$), 5.84 (d, 1H, $J_{H\text{-}5,H\text{-}4}$ 4.10 Hz, H-5), 5.5 (m, 1H, H-2), 4.98 (d, 1H, *J* 11.7 Hz, O–C*H*$_2$–Ph), 4.95 (dd, 1H, *J* 7.7, 3.8 Hz, PhC*H*CH$_2$OBn), 4.89 (d, 1H, *J* 10.8 Hz, O–C*H*$_2$–Ph), 4.78–4.47 (m, 8H, 4× O–C*H*$_2$–Ph), 3.92 (dd, 1H, $J_{4',5'}$=$J_{4',3'}$ 9.5 Hz, H-4′), 3.79–3.55 (m, 6H, H-2′, H-3′, H-6′a, H-6′b, PhCHC*H*$_{2a}$OBn, PhCHC*H*$_{2b}$OBn), 3.48–3.41 (m, 2H, H-1′, H-5′), 2.56 (m, 1H, H-4), 2.15 (ddd, 1H, $J_{1''a,1''b}$ 13.4, *J* 9.9, *J* 6.0 Hz, H-1″a), 1.95 (ddd, 1H, $J_{3eq,3ax}$ 13.9 Hz, $J_{4,3eq}$ 7.1 Hz, $J_{2,3eq}$ 2.2 Hz, H-3$_{eq}$), 1.84 (ddd, 1H, $J_{3eq,3ax}$ 13.9 Hz, $J_{2,3ax}$=$J_{4,3ax}$ 4.1 Hz, H-3$_{ax}$), 1.57 (ddd, 1H, $J_{1''a,1''b}$ 13.4 Hz, *J* 8.6, 2.3 Hz, H-1″b); ^{13}C NMR (125 MHz, $CDCl_3$) 186.3 (*H*CO), 148.6 (C-6), 139.2, 138.5, 138.4, 138.3, 138.1 (6× *ipso* C$_6$H$_5$), 128.4–127.2 (30× C$_6$H$_5$), 126.6 (C-5), 98.5 (C-2), 85.3 (C-3′), 79.8 (PhCHCH$_2$OBn), 79.8 (C-5′), 76.2, 76.1, 75.4 (C-1′, C-2′, C-4′), 75.1, 74.7, 74.4, 73.4, 73.2 (5× PhCH$_2$), 72.6 (PhCHCH$_2$OBn), 69.8 (C-6′), 36.3 (C-1″), 31.1 (C-3), 27.5 (C-4). ESIMS: MNH$_4^+$, found 892.6. $C_{56}H_{62}NO_9$ requires 892.4.

*4.1.15. (2S,4S)-2-[(R)-2-(Benzyloxy)-1-phenylethoxy]-4-[(2,3,4,6-tetra-O-benzyl-β-D-mannopyranosyl)methyl]-6-formyl-3,4-dihydro-2H-pyran (**24**).* Using the same procedure as described for the preparation of compound **21**, compound **20** (4.8 g, 5.16 mmol) was converted to aldehyde **24** (viscous oil, 3.4 g, 75%); [Found: C, 76.59; H, 6.75. $C_{56}H_{58}O_9$ requires C, 76.86; H, 6.68%]; R_f=0.3 (light petroleum/ethyl acetate, 3:1); $[\alpha]_D^{20}$ −1.9 (*c* 1.13, $CHCl_3$); ν_{max} 3020, 2928, 2861, 1697, 1497, 1454, 1363, 1097, 1028, 987 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) 8.82 (s, 1H, *H*CO); 7.43–7.15 (m, 30H, 6× C$_6$*H*$_5$), 5.71 (d, 1H, $J_{5,4}$ 4.1 Hz, H-5); 5.57 (m, 1H, H-2), 5.10 (d, 1H, *J* 11.7 Hz, O–C*H*$_2$–Ph), 4.95 (dd, 1H, *J* 8.1, 3.5 Hz, PhC*H*CH$_2$OBn), 4.89 (d, 1H, *J* 10.8 Hz, O–C*H*$_2$–Ph), 4.82–4.46 (m, 8H, 4× O–C*H*$_2$–Ph), 3.92 (dd, 1H, $J_{4',5'}$=$J_{4',3'}$ 9.2 Hz, H-4′), 3.75 (dd, 1H, $J_{6'a,6'b}$ 10.7 Hz, $J_{6'a,5'}$ 1.4 Hz, H-6′a), 3.71–3.64 (m, 2H, H-6′b, PhCHC*H*$_{2a}$OBn), 3.64–3.56 (m, 3H, H-2′, H-3′, PhCHC*H*$_{2b}$OBn), 3.42–3.34 (m, 2H, H-1′, H-5′), 2.59 (m, 1H, H-4), 2.15 (m, 1H, H-1″a), 2.03 (ddd, 1H, $J_{3eq,3ax}$ 13.8 Hz, $J_{3eq,4}$ 7.4 Hz, $J_{3eq,2}$ 2.4 Hz, H-3$_{eq}$), 1.88 (ddd, 1H, $J_{3eq,3ax}$ 13.8 Hz, $J_{3eq,4}$=$J_{3eq,2}$ 4.0 Hz, H-3$_{ax}$), 1.78 (m, 1H, H-1″b); ^{13}C NMR (125 MHz, $CDCl_3$) 186.5 (*H*CO), 148.9 (C-6), 139.1, 138.5, 138.4, 138.3, 138.2 (6× *ipso* C$_6$H$_5$); 128.4–126.6 (30× C$_6$H$_5$), 125.2 (C-5), 98.5 (C-2), 85.2 (C-3′), 79.9 (C-5′), 79.2 (PhCHCH$_2$OBn), 76.1 (C-2′), 75.7 (C-1′), 75.4 (C-4′), 75.1, 74.7, 74.4, 73.4, 73.3, 72.6 (5× PhCH$_2$, PhCHCH$_2$OBn), 69.8 (C-6′), 36.8 (C-1″), 32.4 (C-3), 26.6 (C-4). ESIMS: MNH$_4^+$, found 892.6. $C_{56}H_{62}NO_9$ requires 892.4.

*4.1.16. (S)-2-Benzyloxy-1-phenylethyl 2,3-dideoxy-3-C-[(2,3,4,6-tetra-O-benzyl-α-D-mannopyranosyl)methyl]-4,6-di-O-benzyl-β-D-arabino-hexopyranoside (**25**).* A 2 M solution of $BH_3 \cdot Me_2S$ in tetrahydrofuran (7.4 mL, 14.7 mmol) was added dropwise to a solution of aldehyde **21** (3.7 g, 4.2 mmol) in tetrahydrofuran (80 mL) that was pre-cooled to 0 °C, and the reaction mixture was stirred at room temperature for 16 h. Then, a 30% NaOH solution (4.6 mL) and a 30% H_2O_2 (4.6 mL) were added in succession. The mixture was stirred at room temperature for 30 min and partitioned between ethyl acetate and a saturated NaCl solution. The organic phase was dried, the ethyl acetate evaporated in vacuo, and the residue was dissolved in tetrahydrofuran (150 mL). After addition of a 60% suspension of NaH in mineral oil (1 g, 25 mmol), the mixture was stirred at room temperature for 1 h. Benzyl bromide (3.1 mL, 25.8 mmol) and tetrabutylammonium iodide (0.49 g, 1.3 mmol) were added, and the reaction mixture was heated at 40 °C for 4 h. After stirring at room temperature for 14 h, MeOH (5 mL) was added, the solvent was evaporated in vacuo, and the residue was partitioned between dichloromethane and a saturated solution of $NaHCO_3$. The organic layer was dried, the solvent was removed in vacuo, and the residue was chromatographed on silica gel in light petroleum/ethyl acetate (12:1→8:1) to give 2.7 g (60%) of compound **25** as a viscous oil; [Found: C, 78.26; H, 6.75. $C_{70}H_{74}O_{10}$ requires C, 78.19; H, 6.94%]; R_f=0.56 (light petroleum/ethyl acetate, 3:1); $[\alpha]_D^{20}$ +2.5 (*c* 0.73, $CHCl_3$); ν_{max} 3011, 2922, 2867, 1496, 1454, 1364, 1087, 1028 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) 7.42–7.13 (m, 40H, 8× C$_6$*H*$_5$); 4.91 (dd, 1H, *J* 7.8, 4.1 Hz, PhC*H*CH$_2$OBn), 4.73 (dd, 1H, $J_{1,2ax}$ 9.4 Hz, $J_{1,2eq}$ 1.6 Hz, H-1), 4.69 (d, 1H, H-1, *J* 11.2 Hz, O–C*H*$_2$–Ph), 4.60–4.30 (m, 13H, O–C*H*$_2$–Ph), 4.08 (ddd, 1H, $J_{1',1''a}$ 7.8 Hz, $J_{1',1''a}$ 4.4 Hz, $J_{1',2'}$ 3.1 Hz, H-1′), 3.85 (dd, 1H, $J_{4',5'}$=$J_{3',4'}$ 6.7 Hz, H-4′), 3.76–3.58 (m, 7H, H-3′, H-5′, H-6a, H-6b, H-6′a, H-6′b, PhCHC*H*$_{2a}$OBn, PhCHC*H*$_{2b}$OBn), 3.53 (dd, 1H, $J_{6'b,6'a}$ 11.2 Hz, $J_{6'b,5'}$ 1.6 Hz, H-6′b), 3.46 (dd, 1H, $J_{2',3'}$ 4.2 Hz, $J_{2',1'}$ 3.1 Hz, H-2′), 3.30 (ddd, 1H, $J_{4,5}$ 9.4 Hz, $J_{5,6a}$ 3.9 Hz, $J_{5,6b}$ 1.8 Hz, H-5), 3.16 (dd, 1H, $J_{4,5}$=$J_{3,4}$ 9.4 Hz, H-4), 2 0.18 (ddd, 1H, $J_{2eq,2ax}$ 12.6 Hz, $J_{2eq,3}$ 3.7 Hz, $J_{2eq,1}$ 1.6 Hz, H-2$_{eq}$), 1.86 (ddd, 1H, $J_{1''a,1''b}$ 13.8 Hz, $J_{1''a,1'}$ 4.4 Hz, $J_{1''a,3}$ 3.9 Hz, 1″a), 1.62 (m, 1H, H-3), 1.42 (ddd, 1H, $J_{2eq,2ax}$ 12.8 Hz, $J_{2ax,3}$=$J_{2ax,1}$ 9.4 Hz, H-2$_{ax}$), 1.33 (ddd, 1H, $J_{1''a,1''b}$ 13.8 Hz, $J_{1''b,3}$ 8.3 Hz, $J_{1''b,1'}$ 7.8 Hz, H-1″b); ^{13}C NMR (125 MHz, $CDCl_3$) 140.3, 138.6, 138.5, 138.4, 138.3, 138.2, 138.1, 138.0 (8× *ipso* C$_6$H$_5$), 128.3–126.7 (40× C$_6$H$_5$), 101.5 (C-1), 79.3 (PhCHCH$_2$OBn), 78.3, 78.2 (C-5, C-4), 77.3 (C-3′), 75.9 (C-2′), 74.9 (C-4′), 74.7, 74.1, 73.7, 73.4, 73.3, 73.2, 72.2, 71.4 (7× PhCH$_2$, PhCHCH$_2$OBn), 73.4 (C-5′), 72.5 (C-1′), 69.2 (C-6′, C-6), 38.7 (C-3), 36.9 (C-2), 32.3 (C-1″). ESIMS: MNH$_4^+$, found 1092.7. $C_{70}H_{78}NO_{10}$ requires 1092.6.

*4.1.17. (R)-2-(Benzyloxy)-1-fenylethyl 2,3-dideoxy-3-C-[(2,3,4,6-tetra-O-benzyl-α-D-mannopyranosyl)methyl]-4,6-di-O-benzyl-β-L-arabino-hexopyranoside (**26**).* Using the same procedure as described for the preparation of compound **25**, aldehyde **22** (1.9 g, 2.17 mmol) was converted to compound **26** (viscous oil, 1.4 g, 60%); [Found: C, 78.05; H, 7.05. $C_{70}H_{74}O_{10}$ requires C, 78.19; H, 6.94%]; R_f=0.58 (light petroleum/ethyl acetate, 3:1); $[\alpha]_D^{20}$ +8.6 (*c* 1.03, $CHCl_3$); ν_{max} 3010, 2918, 2866, 1496, 1454, 1363, 1089, 1028 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) 7.40–7.12 (m, 40H, 8× C$_6$*H*$_5$), 4.88 (dd, 1H, *J* 7.5, 4.0 Hz, PhC*H*CH$_2$OBn), 4.78 (dd, 1H, $J_{1,2ax}$ 9.4 Hz, $J_{1,2eq}$ 1.8 Hz, H-1), 4.77 (d, 1H, *J* 11.5 Hz, O–C*H*$_2$–Ph), 4.63–4.32 (m, 13H, O–C*H*$_2$–Ph), 4.08 (ddd, 1H, $J_{1',1''b}$ 11.9 Hz, $J_{1',2'}$=$J_{1',1''a}$ 3.2 Hz, H-1′), 3.88 (dd, 1H, $J_{4',5'}$=$J_{3',4'}$ 7.3 Hz, H-4′), 3.77–3.57 (m, 7H, H-3′, H-5′, H-6a, H-6b, H-6′a, PhCHC*H*$_{2a}$OBn, PhCHC*H*$_{2b}$OBn), 3.52 (dd, 1H, $J_{6'a,6'b}$ 11.1 Hz, $J_{6',5'}$ 1.5 Hz, H-6′b), 3.43 (dd, 1H, $J_{2',3'}$ 3.4 Hz, $J_{2',1'}$ 3.2 Hz, H-2′), 3.30 (ddd, 1H, $J_{5,4}$ 9.6 Hz, $J_{5,6a}$ 3.9 Hz, $J_{5,6b}$ 2.1 Hz, H-5), 3.14 (dd, 1H, $J_{4,5}$=$J_{3,4}$ 9.6 Hz, H-4), 2.21 (ddd, 1H, $J_{2eq,2ax}$ 12.8 Hz, $J_{2eq,3}$ 3.9 Hz, $J_{2eq,1}$ 1.8 Hz, H-2$_{eq}$), 2.06 (m, 1H, H-1″a), 1.90 (m, 1H, H-3), 1.30 (ddd, 1H, $J_{2eq,2ax}$=$J_{2ax,3}$ 12.8 Hz $J_{2ax,1}$ 9.4 Hz, H-2$_{ax}$), 0.85 (m, 1H, H-1″b); ^{13}C NMR (125 MHz, $CDCl_3$) 140.3, 138.6, 138.5, 138.5, 138.3, 138.3, 138.1, 138.1 (8× *ipso* C$_6$H$_5$), 128.4–126.7 (40× C$_6$H$_5$), 101.6 (C-1), 79.3 (PhCHCH$_2$OBn), 78.1 (C-5, C-3′), 77.7 (C-4), 76.5 (C-2′), 75.0 (C-4′), 74.4, 73.9, 73.8, 73.4, 73.2, 72.9, 71.9, 71.4 (7× PhCH$_2$, PhCHCH$_2$OBn), 72.5 (C-5′), 69.4 (C-1′), 69.2 (C-6′, C-6), 35.7 (C-3), 35.6 (C-2), 31.2 (C-1″). ESIMS: MNH$_4^+$, found 1092.7. $C_{70}H_{78}NO_{10}$ requires 1092.6.

*4.1.18. (S)-2-(Benzyloxy)-1-fenylethyl 2,3-dideoxy-3-C-[(2,3,4,6-tetra-O-benzyl-β-D-mannopyranosyl)methyl]-4,6-di-O-benzyl-β-D-arabino-hexopyranoside (**27**).* Using the same procedure as described for the preparation of compound **25**, aldehyde **23** (3.4 g, 3.9 mmol) was converted to compound **27** (viscous oil, 2.9 g, 70%); [Found: C, 78.35; H, 6.74. $C_{70}H_{74}O_{10}$ requires C, 78.19; H, 6.94%]; R_f=0.6 (light

petroleum/ethyl acetate, 3:1); $[\alpha]_D^{20}$ −4.9 (*c* 0.78, $CHCl_3$); ν_{max} 3011, 2921, 2864, 1497, 1454, 1364, 1086, 1028 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) 7.40–7.10 (m, 40H, 8× C_6H_5), 4.80 (d, 1H, *J* 11.8 Hz, O–CH_2–Ph), 4.90 (dd, 1H, *J* 7.6, 3.9 Hz, PhCHCH$_2$OBn), 4.86 (d, 1H, *J* 11.8 Hz, O–CH_2–Ph), 4.75 (dd, 1H, $J_{1,2ax}$ 9.5 Hz, $J_{1,2eq}$ 1.9 Hz, H-1), 4.72–4.29 (m, 12H, 6× O–CH_2–Ph), 3.95 (dd, 1H, $J_{4',5'}=J_{3',4'}$ 9.5 Hz, H-4′), 3.78–3.66 (m, 4H, H-2′, H-6a, H-6b, PhCHCH_{2a}OBn), 3.66–3.57 (m, 2H, H-6′a, PhCHCH_{2b}OBn), 3.56–3.48 (m, 2H, H-3′, H-6′b), 3.42–3.36 (m, 2H, H-1′, H-5′), 3.34 (ddd, 1H, $J_{5,4}$ 9.7 Hz, $J_{5,6b}$ 4.0 Hz, $J_{5,6a}$ 2.1 Hz, H-5), 3.14 (dd, 1H, $J_{4,5}=J_{3,4}$=9.7 Hz, H-4), 2.37 (m, 1H, H-1″a), 2.0 (ddd, 1H, $J_{2eq,2ax}$ 12.8 Hz, $J_{2eq,3}$ 3.9 Hz, $J_{1,2eq}$ 1.9 Hz, H-2_{eq}), 1.87 (m, 1H, H-3), 1.35 (ddd, 1H, $J_{2eq,2ax}$ 12.8 Hz, $J_{1,2ax}$ 9.5 Hz, $J_{3,2ax}$ 1.6 Hz, H-2_{ax}), 1.15 (m, 1H, H-1″b); ^{13}C NMR (125 MHz, $CDCl_3$) 140.1, 138.7, 138.6, 138.4, 138.4, 138.3, 138.1, 138.0 (8× *ipso* C_6H_5); 128.3–126.6 (40× C_6H_5), 101.4 (C-1), 85.3 (C-3′), 79.9 (C-5′), 79.2 (PhCHCH$_2$OBn), 78.4 (C-4), 77.8 (C-5), 76.0 (C-2′), 75.3, 74.8 (C-4′, C-1′), 74.9, 74.6, 74.2, 73.5, 73.3, 73.3, 73.1, 72.4 (7× PhCH$_2$, PhCHCH$_2$OBn), 69.6 (C-6), 69.2 (C-6′), 36.3 (C-2), 35.9 (C-3), 34.7 (C-1″). ESIMS: MNH_4^+, found 1092.7. $C_{70}H_{78}NO_{10}$ requires 1092.6.

*4.1.19. (S)-2-(Methoxy)-1-fenylethyl 2,3-dideoxy-3-C-[(2,3,4,6-tetra-O-benzyl-β-D-mannopyranosyl)methyl]-4,6-di-O-benzyl-β-L-arabino-hexopyranoside (**28**).* Using the same procedure as described for the preparation of compound **25**, aldehyde **24** (1.3 g, 1.5 mmol) was converted to compound **28** (viscous oil, 0.9 g, 60%); [Found: C, 77.99; H, 7.04. $C_{70}H_{74}O_{10}$ requires C, 78.19; H, 6.94%]; R_f=0.6 (light petroleum/ethyl acetate, 3:1); $[\alpha]_D^{20}$ −9.6 (*c* 0.85, $CHCl_3$); ν_{max} 3010, 2923, 2865, 1497, 1454, 1363, 1095,1028 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): 7.50–7.05 (m, 40H, 8× C_6H_5), 4.94 (d, 1H, *J* 11.7 Hz, O–CH_2–Ph), 4.92 (dd, 1H, *J* 8.0, 3.7 Hz, PhCHCH$_2$OBn), 4.85 (d, 1H, *J* 10.8 Hz, O–CH_2–Ph), 4.79 (dd, 1H, $J_{1,2ax}$ 9.5 Hz, $J_{1,2eq}$ 1.6 Hz, H-1), 4.74–4.28 (m, 12H, 6× O–CH_2–Ph), 3.95 (dd, 1H, $J_{4',5'}=J_{3',4'}$ 9.5 Hz, H-4′), 3.75–3.65 (m, 3H, H-6a, H-6b, PhCHCH_{2a}OBn), 3.65–3.58 (m, 2H, H-6′a, PhCHCH_{2b}OBn), 3.57 (br s, 1H, H-2′), 3.55–3.48 (m, 2H, H-3′, H-6′b), 3.42–3.36 (m, 2H, H-1′, H-5′), 3.33 (ddd, 1H, $J_{4,5}$ 9.4 Hz, $J_{5,6b}$ 4.4 Hz, $J_{5,6a}$ 1.8 Hz, H-5), 3.24 (dd, 1H, $J_{4,5}=J_{3,4}$ 9.4 Hz, H-4), 2.08 (ddd, 1H, $J_{2eq,2ax}$ 12.8 Hz, $J_{2eq,3}$ 4.1 Hz, $J_{2eq,1}$ 1.6 Hz, H-2_{eq}), 1.82–1.66 (m, 3H, H-3, H-1″a, H-1″b), 1.49 (ddd, 1H, $J_{2ax,2eq}$ 12.8 Hz, $J_{2ax,3}$ 12.6, $J_{2ax,1}$ 9.5 Hz, H-2_{ax}); ^{13}C NMR (125 MHz, $CDCl_3$) 140.2, 138.7, 138.6, 138.5, 138.4, 138.4, 138.3, 138.2 (8× *ipso* C_6H_5), 128.4–126.8 (40× C_6H_5), 101.7 (C-1), 85.4 (C-3′), 79.6 (C-5′), 79.4 (PhCHCH$_2$OBn), 78.6 (C-4), 78.5 (C-5), 77.1 (C-1′), 75.9 (C-2′), 75.5 (C-4′), 75.1, 74.8, 74.4, 74.3, 73.4, 73.3, 73.3, 72.6 (7× PhCH$_2$, PhCHCH$_2$OBn), 69.8 (C-6), 69.4 (C-6′), 38.2 (C-2), 36.9 (C-3), 33.9 (C-1″). ESIMS: MNH_4^+, found 1092.7. $C_{70}H_{78}NO_{10}$ requires 1092.6.

*4.1.20. Phenyl-1-thio 2,3-dideoxy-3-C-[(2,3,4,6-tetra-O-benzyl-α-D-mannopyranosyl)methyl]-4,6-di-O-benzyl-α-D-arabino-hexopyranoside (**29a**) and phenyl-1-thio 2,3-dideoxy-3-C-[(2,3,4,6-tetra-O-benzyl-α-D-mannopyranosyl)methyl]-4,6-di-O-benzyl-β-D-arabino-hexopyranoside (**29b**).* $BF_3{\cdot}Et_2O$ (0.50 mL, 3.76 mmol) and thiophenol (1.3 mL, 12.5 mmol) were added in an inert atmosphere to a solution of compound **25** (2.70 g, 2.50 mmol) in dichloromethane (150 mL) that was pre-cooled to −78 °C. The stirred reaction mixture was allowed to warm spontaneously to room temperature, and after 2 h, the reaction was quenched by cautious addition of 1 M NaOH. The reaction mixture was partitioned between dichloromethane and a saturated $NaHCO_3$ solution, the combined organic phases were dried and evaporated, and the residue was chromatographed on silica gel (light petroleum/ethyl acetate, 8:1), affording 1.9 g (80%) of a mixture of thioglycosides **29a**,**b** in a ratio α/β=3:1 (determined by integration of H-1 in ^1H NMR spectrum; for the α anomer d at 5.53 ppm, and for the β anomer dd at 4.65 ppm); R_f=0.35 (light petroleum/ethyl acetate, 4:1). Repeated chromatography afforded an analytical sample of the major α-diastereoisomer **29a** as a viscous oil; [Found: C, 76.38; H, 6.89. $C_{61}H_{64}O_8S$ requires C, 76.54; H, 6.69%]; ν_{max} 3011, 2913, 2868, 1585, 1497, 1454, 1364, 1088, 1028 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) 7.47–7.13 (m, 35H, 7× C_6H_5), 5.53 (d, 1H, $J_{1,2ax}$ 5.4 Hz, H-1), 4.73–4.40 (m, 12H, 6× O–CH_2–Ph), 4.26 (m, 1H, H-5), 4.10 (m, 1H, H-1′), 3.85–3.73 (m, 3H, H-4′, H-5′, H-6a), 3.72–3.64 (m, 2H, H-3′, H-6′a), 3.61 (dd, 1H, *J* 1.4, 10.7 Hz, H-6′b), 3.50 (dd, 1H, *J* 3.3, 4.1 Hz, H-2′), 3.31 (dd, 1H, $J_{4,5}$ 9.7 Hz, $J_{3,4}$ 9.5 Hz, H-4), 2.41 (ddd, 1H, $J_{2eq,2ax}$ 13.9 Hz, $J_{2eq,3}$ 3.9 Hz, $J_{2eq,1}$ ~0 Hz, H-2_{eq}), 2.04 (m, 1H, H-3), 1.94 (m, 1H, H-1″a), 1.86 (ddd, 1H, $J_{2eq,2ax}$ 13.9 Hz, $J_{2ax,3}$ 12.6 Hz, $J_{2ax,1}$ 5.4 Hz, H-2_{ax}); 1.27 (m, 1H, H-1″b); ^{13}C NMR (125 MHz, $CDCl_3$) 138.4, 138.3, 138.3, 138.2, 138.1, 137.9, 135.7 (7× *ipso* C_6H_5), 130.8–126.5 (35× C_6H_5), 84.7 (C-1), 78.4 (C-4), 77.2 (C-3′), 77.3 (C-3′), 76.1 (C-2′), 74.9 (C-4′), 73.9, 73.8, 73.4, 73.3, 72.0, 71.4 (6× PhCH$_2$), 73.5 (C-5′), 72.6 (C-5), 72.2 (C-1′), 69.4 (C-6), 69.3 (C-6′), 37.1 (C-3), 36.4 (C-2), 31.6 (C-1″). ESIMS: MNH_4^+, found 974.8. $C_{61}H_{68}NO_8S$ requires 974.5.

*4.1.21. Phenyl-1-thio 2,3-dideoxy-3-C-[(2,3,4,6-tetra-O-benzyl-α-D-mannopyranosyl)methyl]-4,6-di-O-benzyl-α-L-arabino-hexopyranoside (**30a**) and phenyl-1-thio 2,3-dideoxy-3-C-[(2,3,4,6-tetra-O-benzyl-α-D-mannopyranosyl)methyl]-4,6-di-O-benzyl-β-L-arabino-hexopyranoside (**30b**).* Using the same procedure as described for the preparation of compounds **29a**,**b**, compound **26** (1.4 g, 1.30 mmol) was converted to a mixture of thioglycosides **30a**,**b** (viscous oil 1.2 g, 80%) in a ratio α/β=1.3:1 (integration of H-1 in ^1H NMR spectrum; for the α anomer d at 5.58 ppm, for the β anomer dd at 4.75 ppm); R_f=0.4 (light petroleum/ethyl acetate, 4:1). ESIMS: MNH_4^+, found 974.8. $C_{61}H_{68}NO_8S$ requires 974.5. The obtained mixture was sufficiently pure to use in the next step without further purification.

*4.1.22. Phenyl-1-thio 2,3-dideoxy-3-C-[(2,3,4,6-tetra-O-benzyl-β-D-mannopyranosyl)methyl]-4,6-di-O-benzyl-α-D-arabino-hexopyranoside (**31a**) and phenyl-1-thio 2,3-dideoxy-3-C-[(2,3,4,6-tetra-O-benzyl-β-D-mannopyranosyl)methyl]-4,6-di-O-benzyl-β-D-arabino-hexopyranoside (**31b**).* Using the same procedure as described for the preparation of compounds **29a**,**b**, compound **27** (2.9 g, 2.7 mmol) was converted to a mixture of thioglycosides **31a**,**b** (2.1 g, 81%), in a ratio α/β=3:1 (integration of H-1 in ^1H NMR spectrum; for the α anomer d at 5.56 ppm, for the β anomer dd at 4.67 ppm); R_f=0.46 (light petroleum/ethyl acetate, 4:1). Repeated chromatography afforded an analytical sample of the major α-diastereoisomer **31a** as a viscous oil; [Found: C, 76.38; H, 6.89. $C_{61}H_{64}O_8S$ requires C, 76.54; H, 6.69%]; ν_{max} 3011, 2915, 2867, 1585, 1497, 1454, 1363, 1086, 1028 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) 7.46–7.10 (m, 35H, 7× C_6H_5), 5.58 (d, 1H, $J_{1,2ax}$ 5.3 Hz, H-1), 5.02 (d, 1H, *J* 11.6 Hz, O–CH_2–Ph), 4.86 (d, 1H, *J* 11.6 Hz, O–CH_2–Ph), 4.76–4.42 (m, 10H, 5× O–CH_2–Ph), 4.29 (m, 1H, H-5), 3.94 (dd, 1H, $J_{4',5'}=J_{3',4'}$ 9.5 Hz, H-4′), 3.81 (dd, 1H, $J_{6'a,6'b}$ 10.8 Hz, $J_{6'a,5'}$ 3.6 Hz, H-6′a), 3.80–3.71 (m, 2H, H-6a, H-6b), 3.69 (m, 1H, H-2′), 3.63 (dd, $J_{6'a,6'b}$ 10.8 Hz, 1H, $J_{6'a,5'}$ 1.6 Hz, H-6′$_b$), 3.53 (dd, 1H, $J_{3',4'}$ 9.4 Hz, $J_{3',2'}$ 2.4 Hz, H-3′), 3.42–3.37 (m, 2H, H-1′, H-5′), 3.34 (dd, 1H, $J_{4,5}=J_{4,3}$ 9.7 Hz, H-4), 2.38–2.22 (m, 2H, H-3, H-1″a), 2.05 (ddd, 1H, $J_{2eq,2ax}$ 13.8 Hz, $J_{2eq,3}$ 3.5 Hz, $J_{2eq,1}$ ~0 Hz, H-2_{eq}), 1.96 (ddd, 1H, $J_{2eq,2ax}$ 13.8 Hz, $J_{2ax,3}$ 12.6 Hz, $J_{2ax,1}$ 5.3 Hz, H-2_{ax}), 1.25 (m, 1H, H-1″b); ^{13}C NMR (125 MHz, $CDCl_3$) 138.8, 138.7, 138.5, 138.5, 138.1, 138.0, 135.6 (7× *ipso* C_6H_5), 130.0–126.6 (35× C_6H_5), 85.4 (C-3′), 84.7 (C-1), 80.0 (C-5′), 78.4 (C-4), 76.3 (C-2′), 75.4, 75.2 (C-4′, C-1′), 75.0, 74.5, 73.6, 73.5, 73.4, 72.5 (6× PhCH$_2$, PhCHCH$_2$OBn), 72.2 (C-5), 69.7 (C-6), 69.3 (C-6′), 36.0 (C-2), 34.2 (C-1″), 34.1 (C-3). ESIMS: MNH_4^+, found 974.8. $C_{61}H_{68}NO_8S$ requires 974.5.

*4.1.23. Phenyl-1-thio 2,3-dideoxy-3-C-[(2,3,4,6-tetra-O-benzyl-α-D-mannopyranosyl)methyl]-4,6-di-O-benzyl-β-L-arabino-hexopyranoside (**32a**) and phenyl-1-thio 2,3-dideoxy-3-C-[(2,3,4,6-tetra-O-benzyl-β-D-mannopyranosyl)methyl]-4,6-di-O-benzyl-β-L-arabino-hexopyranoside (**32b**).* Using the same procedure as described for the preparation of compounds **29a**,**b**, compound **28** (0.9 g, 0.84 mmol) was converted to a mixture of thioglycosides **32a**,**b** (viscous oil,

0.7 g, 85%), in a ratio α/β=1.2:1 (integration of H-1 in ^{1}H NMR spectrum; for α anomer d at 5.64 ppm, for β anomer dd at 4.71 ppm); R_f=0.4 (light petroleum/ethyl acetate, 4:1). ESIMS: MNH_4^+, found 974.8. $C_{61}H_{68}NO_8S$ requires 974.5. The obtained mixture was sufficiently pure to use in the next step without further purification.

*4.1.24. 1,5-Anhydro-4,6-di-O-benzyl-2,3-dideoxy-3-C-[(2,3,4,6-tetra-O-benzyl-α-D-mannopyranosyl)methyl]-D-arabino-hex-1-enitol (**1**).* *N*-Bromosuccinimide (0.27 g, 1.5 mmol) was added to a solution of anomers **29a**,**b** (1.1 g, 1.1 mmol) in acetone (12 mL) containing 1% water. The reaction mixture was stirred at −15 °C under exclusion of light, and the reaction course was monitored by TLC (light petroleum/ethyl acetate, 3:1). After 40 min, the reaction mixture did not contain the starting compound, and the reaction was quenched by the addition of a $NaHCO_3$ solution to pH 8. After partitioning between dichloromethane and aqueous $NaHCO_3$, the organic phase was dried, the solvent was evaporated, and the residue was chromatographed on a short silica gel column in light petroleum/ethyl acetate (2:1), affording 0.83 g of 2,3-dideoxy-3-*C*-[(2,3,4,6-tetra-*O*-benzyl-α-D-mannopyranosyl)methyl]-4,6-di-*O*-benzyl-D-*arabino*-hexopyranose (R_f 0.3, light petroleum/ethyl acetate (2:1); ESMSI: MH^+, found 865.7. $C_{55}H_{61}O_9$ requires 865.4.). The obtained compound was dissolved in dichloromethane (20 mL), and the solution was treated in an inert atmosphere at 0 °C with *s*-collidine (1.9 mL, 14.4 mmol) and mesyl anhydride (0.33 g, 1.9 mmol). The reaction mixture was stirred at 0 °C, and the reaction course was monitored by TLC (light petroleum/ethyl acetate, 3:1). After 4 h, the reaction mixture was partitioned between dichloromethane and aqueous $NaHCO_3$. The organic phase was dried, the solvent was evaporated, and the residue was chromatographed on silica gel in light petroleum/ethyl acetate (8:1), affording 0.63 g (65%) of compound **1** as a colorless syrup; [Found: C, 78.10; H, 6.80. $C_{55}H_{58}O_8$ requires C, 77.99; H, 6.90%]; R_f=0.5 (light petroleum/ethyl acetate, 4:1); $[\alpha]_D^{20}$ −10.3 (*c* 1.28, $CHCl_3$); ν_{max} 3011, 1650, 1497, 1454, 1364, 1096, 1028, 914 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) 7.40–7.14 (m, 30H, 6× C_6H_5); 6.24 (dd, 1H, $J_{1,2}$ 6.0 Hz, $J_{1,3}$ 2.3 Hz, H-1), 4.75 (dd, 1H, $J_{1,2}$ 6.0 Hz, $J_{2,3}$ 2.0 Hz, H-2); 4.73–4.44 (m, 12H, O–CH_2–Ph), 4.10 (ddd, 1H, $J_{1',1''b}$ 8.3 Hz, $J_{2',1'}$ 4.2 Hz, $J_{1',1''a}$ 4.1 Hz, H-1′), 3.86–3.71 (m, 6H, H-4′, H-5′, H-5, H-6′a, H-6a, H-6b), 3.70–3.62 (m, 2H, H-3′, H-6′b), 3.50 (dd, 1H, $J_{4,5}$=$J_{4,3}$ 8.9 Hz, H-4), 3.47 (dd, 1H, $J_{2',1'}$,4.2 Hz, $J_{2',3'}$,3.2 Hz, H-2′), 2.33 (m, 1H, H-3), 1.67 (ddd, 1H, $J_{1''a,1''b}$ 14.2 Hz, $J_{1''a,1'}$ 4.1 Hz, $J_{1''a,3}$ 3.9 Hz, H-1″a), 1.45 (ddd,1H, $J_{1''a,1''b}$ 14.2 Hz, $J_{1''b,3}$ 8.4 Hz, $J_{1''b,1'}$ 8.3 Hz, H-1″b); ^{13}C NMR (125 MHz, $CDCl_3$) 142.6 (C-1), 138.4, 138.4, 138.3, 138.3, 138.2, 137.9 (6× *ipso* C_6H_5), 128.4–127.4 (30× C_6H_5), 102.9 (C-2), 78.0, 75.0, 73.4 (C-4′, C-5′, C-5), 77.6 (C-3′), 76.2, 75.9 (C-2′, C-4), 72.6 (C-1′), 74.1, 73.9, 73.6, 73.3, 72.1, 71.5 (6× $PhCH_2$), 69.3, 68.7 (C-6, C-6′), 38.6 (C-3), 31.8 (C-1″). ESIMS: MNH_4^+, found, 864.8. $C_{55}H_{62}NO_8$ requires 864.4.

*4.1.25. 1,5-Anhydro-4,6-di-O-benzyl-2,3-dideoxy-3-C-[(2,3,4,6-tetra-O-benzyl-α-D-mannopyranosyl)methyl]-L-arabino-hex-1-enitol (**2**).* Using the same procedure as described for the preparation of compound **1**, the mixture of compounds **30a**,**b** (0.8 g, 0.8 mmol) was converted to compound **2** (colorless syrup, 0.48 g, 65%); [Found: C, 77.75; H, 6.65. $C_{55}H_{58}O_8$ requires C, 77.99; H, 6.90%]; R_f=0.5 (light petroleum/ethyl acetate, 4:1); $[\alpha]_D^{20}$ +6.8 (*c* 0.45, $CHCl_3$); ν_{max} 3009, 1651, 1496, 1454, 1363, 1096, 1028, 914 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) 7.39–7.14 (m, 30H, 6× C_6H_5), 6.30 (dd, 1H, $J_{1,2}$ 6.0 Hz, $J_{1,3}$ 2.3 Hz, H-1), 4.74 (d, 1H, *J* 11.4 Hz, O–CH_2–Ph), 4.66 (d, 1H, *J* 12.0 Hz, O–CH_2–Ph), 4.62 (dd, 1H, $J_{1,2}$ 6.0 Hz, $J_{2,3}$ 1.8 Hz, H-2), 4.61–4.43 (m, 10H, O–CH_2–Ph), 4.09 (ddd, $J_{1',1''b}$ 11.5 Hz, $J_{1',1''a}$=$J_{1',2'}$ 3.3 Hz, H-1′), 3.88 (dd, 1H, $J_{4',3'}$=$J_{4',5'}$ 7.0 Hz, H-4′), 3.85–3.67 (m, 6H, H-5′, H-5, H-6′a, H-6′b, H-6a, H-6b), 3.63 (dd, 1H, $J_{4',3'}$ 7.3 Hz, $J_{3',2'}$ 3.2 Hz, H-3′), 3.46–3.39 (m, 2H, H-2′, H-4), 2.50 (m, 1H, H-3), 1.91 (ddd, 1H, $J_{1''a,1''b}$ 13.8 Hz, $J_{1''a,3}$ 11.1 Hz, $J_{1''a,1'}$ 3.3 Hz, H-1″a), 0.96 (ddd, 1H, $J_{1''b,1''a}$ 13.8 Hz, $J_{1''b,1'}$ 11.5 Hz, $J_{1''b,3}$ 2.6 Hz, H-1″b); ^{13}C NMR (125 MHz, $CDCl_3$) 142.6 (C-1), 138.7, 138.5, 138.3, 138.3, 138.2, 137.9 (6× *ipso* C_6H_5), 128.5–127.4 (30× C_6H_5), 101.8 (C-2), 77.9 (C-5′or C-5), 77.8 (C-3′), 76.6, 76.1 (C-4, C-2′), 75.0 (C-4′), 72.9 (C-5′or C-5), 73.9, 73.8, 73.7, 73.2, 72.1, 71.6 (6× $PhCH_2$), 69.8 (C-1′), 69.2, 68.7 (C-6, C-6′), 35.2 (C-3), 3.8 (C-1″). ESIMS: MNH_4^+, found, 864.8. $C_{55}H_{62}NO_8$ requires 864.4.

*4.1.26. 1,5-Anhydro-4,6-di-O-benzyl-2,3-dideoxy-3-C-[(2,3,4,6-tetra-O-benzyl-β-D-mannopyranosyl)methyl]-D-arabino-hex-1-enitol (**3**).* Using the same procedure as described for the preparation of compound **1**, the mixture of compounds **31a**,**b** (1.4 g, 1.4 mmol) was converted to compound **3** (colorless syrup, 0.87 g, 70%); [Found: C, 77.85; H, 6.75. $C_{55}H_{58}O_8$ requires C, 77.99; H, 6.90%]; R_f=0.5 (light petroleum/ethyl acetate, 4:1); $[\alpha]_D^{20}$ −5.9 (*c* 1.03, $CHCl_3$); ν_{max} 3011, 1650, 1497, 1454, 1363, 1086, 1028, 914 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) 7.38–7.15 (m, 30H, 6× C_6H_5), 6.31 (dd, 1H, $J_{1,2}$ 6.0 Hz, $J_{1,3}$ 2.3 Hz, H-1), 5.00 (d, 1H, *J* 11.7 Hz, O–CH_2–Ph), 4.86 (d, 1H, *J* 10.9 Hz, O–CH_2–Ph), 4.73–4.50 (10H, O–CH_2–Ph), 4.63 (dd, 1H, $J_{2,1}$ 6.0 Hz, $J_{2,3}$ 1.5 Hz, H-2), 3.94 (dd, 1H, $J_{4',3'}$=$J_{4',5'}$ 9.5 Hz, H-4′), 3.85–3.67 (m, 6H, H-5, H-6a, H-6b, H-6′a, H-6′b, H-2′), 3.54 (dd, 1H, $J_{3',4'}$ 9.5 Hz, $J_{2',3'}$ 2.7 Hz, H-3′), 3.47–3.35 (m, 3H, H-1′, H-4, H-5′), 2.51 (m, 1H, H-3), 2.29 (ddd, 1H, $J_{1''a,1''b}$ 14.0 Hz, *J* 9.2 Hz, *J* 5.3 Hz, H-1″a), 1.19 (ddd, 1H, $J_{1''a,1''b}$ 14.0 Hz, *J* 8.9 Hz, *J* 4.1 Hz, H-1″b); ^{13}C NMR (125 MHz, $CDCl_3$) 142.6 (C-1), 138.8, 138.7, 138.5, 138.5, 138.1, 137.9 (6× *ipso* C_6H_5), 128.4–127.3 (30× C_6H_5), 102.6 (C-2), 85.4 (C-3′), 80.1 (C-5′), 77.9 (C-5), 76.7, 76.2, 75.3 (C-1′, C-4, C-2′), 75.4 (C-4′), 75.1, 74.4, 73.8, 73.6, 73.5, 72.4 (6× $PhCH_2$), 69.7, 68.7 (C-6, C-6′), 35.6 (C-3), 35.1 (C-1″). ESIMS: MNH_4^+, found, 864.8. $C_{55}H_{62}NO_8$ requires 864.4.

*4.1.27. 1,5-Anhydro-4,6-di-O-benzyl-2,3-dideoxy-3-C-[(2,3,4,6-tetra-O-benzyl-β-D-mannopyranosyl)methyl]-L-arabino-hex-1-enitol (**4**).* Using the same procedure as described for the preparation of compound **1**, the mixture of compounds **32a**,**b** (0.7 g, 0.7 mmol) was converted to compound **4** (colorless syrup, 0.43 g, 70%); [Found: C, 77.79; H, 7.10. $C_{55}H_{58}O_8$ requires C, 77.99; H, 6.90%]; R_f=0.5 (light petroleum/ethyl acetate, 4:1); $[\alpha]_D^{20}$ +10.9 (*c* 0.39, $CHCl_3$); ν_{max} 3010, 1650, 1497, 1454, 1363, 1087, 1028, 915 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) 7.40–7.09 (m, 30H, 6× C_6H_5), 6.29 (dd, 1H, $J_{1,2}$ 5.9 Hz, $J_{1,3}$ 2.0 Hz, H-1), 4.95 (d, 1H, *J* 11.7 Hz, O–CH_2–Ph), 4.86 (d, 1H, *J* 10.9 Hz, O–CH_2–Ph), 4.73 (dd, 1H, 1H, $J_{2,1}$ 5.9 Hz, $J_{2,3}$ 1.8 Hz, H-2), 4.66–4.45 (m, 10H, 5× O–CH_2–Ph), 3.88 (dd, 1H, $J_{4',3'}$=$J_{4',5'}$ 9.5 Hz, H-4′), 3.84–3.76 (m, 3H, H-6a, H-6b, H-5), 3.73 (dd, 1H, $J_{6'a,6'b}$ 10.8 Hz, $J_{6'a,5'}$ 1.8 Hz, H-6′a), 3.67 (dd, 1H, $J_{6'a,6'b}$ 10.8 Hz, $J_{6'b,5'}$ 5.8 Hz, H-6′b), 3.62 (br s, 1H, H-2′), 3.60–3.53 (m, 2H, H-4, H-3′), 3.45–3.35 (m, 2H, H-1′, H-5′), 2.39 (m, 1H, H-3), 1.83 (ddd, 1H, $J_{1''a,1''b}$ 14.1 Hz, $J_{1',1''a}$=$J_{3,1''a}$ 8.2 Hz, H-1″a), 1.64 (ddd, 1H, $J_{1''a,1''b}$ 14.1 Hz, $J_{1''b,1'}$=$J_{1''b,3}$ 3.9 Hz, H-1″b); ^{13}C NMR (125 MHz, $CDCl_3$) 142.5 (C-1), 138.8, 138.8, 138.5, 138.4, 138.3, 137.9 (6× *ipso* C_6H_5), 128.4–127.4 (30× C_6H_5), 103.3 (C-2), 85.3 (C-3′), 79.5 (C-5), 78.1 (C-5′), 77.5 (C-1′), 76.3, 76.2 (C-2′, C-4), 75.5 (C-4′), 75.1, 74.3, 74.3, 73.6, 73.4, 72.5 (6× $PhCH_2$), 69.9, 68.9 (C-6′, C-6), 38.1 (C-3), 34.1 (C-1″). ESIMS: MNH_4^+, found, 864.8. $C_{55}H_{62}NO_8$ requires 864.4.

*4.1.28. Methyl 3-deoxy-3-C-[(2,3,4,6-tetra-O-benzyl-α-D-mannopyranosyl)methyl]-4,6-di-O-benzyl-α-D-mannopyranoside (**33**) and methyl 3-deoxy-3-C-[(2,3,4,6-tetra-O-benzyl-α-D-mannopyranosyl)methyl]-4,6-di-O-benzyl-β-D-glucopyranoside (**34**).* *m*-Chloroperoxybenzoic acid (77%) (150 mg, 0.67 mmol) was added, with stirring in an inert atmosphere, to a solution of **1** (470 mg, 0.56 mmol) in anhydrous MeOH (8 mL) and CH_2Cl_2 (2 mL) at room temperature. TLC showed that the reaction was complete after 1.5 h. The excess of peroxyacid was reduced by addition of aqueous $NaHCO_3$ (to pH=8), and the reaction mixture was partitioned between CH_2Cl_2 and H_2O. The

organic layer was dried and concentrated, and the residue was chromatographed on silica gel (light petroleum/ethyl acetate, 3:1) to yield **33** as a viscous oil (270 mg, 56%), R_f=0.36 (light petroleum/ethyl acetate, 2:1) and **34** as a viscous oil (120 mg, 25%), R_f=0.30 (light petroleum/ethyl acetate, 2:1). Compound **33**: [Found: C, 74.93; H, 6.75. $C_{56}H_{62}O_{10}$ requires C, 75.13; H, 6.93%]; $[\alpha]_D^{20}$ +6.3 (*c* 0.92, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) 7.37–7.09 (m, 30H, 6× C_6H_5), 4.78–4.31 (m, 12H, O–CH_2–Ph), 4.28 (br s, 1H, H-1), 4.09–4.02 (m, 2H, H-1′, H-2), 3.94 (dd, 1H, $J_{4',3'}$=$J_{4',5'}$ 7.8 Hz, H-4′), 3.75–3.64 (m, 4H, H-5, H-6a, H-6b, H-6′a), 3.62 (dd, 1H, $J_{3',4'}$ 7.8 Hz, $J_{3',2'}$ 2.3 Hz, H-3′), 3.60–3.50 (m, 2H, H-5′, H-6′b), 3.50–3.40 (m, 2H, H-4, H-2′), 3.31 (s, 3H, OCH_3), 1.98 (m, 1H, H-3), 1.81 (ddd, 1H, $J_{1''a,1''b}$ 14.0 Hz, $J_{1''a,1'}$=$J_{1''a,3}$ 11.0 Hz, H-1″a), 1.56 (m, 1H, H-1″b); ^{13}C NMR (125 MHz, $CDCl_3$) 138.3, 138.3, 138.2, 138.1, 138.1, 137.4 (6× *ipso* C_6H_5), 128.4–127.5 (30× C_6H_5), 100.9 (C-1), 78.2 (C-3′), 77.5 (C-4), 75.7 (C-5′), 75.0 (C-2′), 74.8 (C-2), 72.6 (C-4′), 77.7 (C-5), 74.2, 74.1, 73.5, 73.4, 72.1, 71.7 (6× $PhCH_2$), 70.1, 69.7 (C-6, C-6′), 67.8 (C-1′), 54.5 (OCH_3), 42.7 (C-3), 29.7 (C-1″). ESIMS: MNH_4^+, found 912.2. $C_{56}H_{66}NO_{10}$ requires 912.5. Compound **34**: $[\alpha]_D^{20}$ −3.8 (*c* 0.85, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) 7.40–7.10 (m, 30H, 6× C_6H_5), 4.68–4.43 (m, 12H, 6× O–CH_2–Ph), 4.22–4.17 (m, 1H, H-1′), 4.11 (dd, 1H, $J_{1,2}$ 7.5 Hz, H-1), 3.98 (m, 1H, H-5′), 3.82 (dd, 1H, $J_{3',4'}$=$J_{4',5'}$ 5.8 Hz, H-4′), 3.79–3.68 (m, 5H, H-3′, H-6′a, H-6′b, H-6a, H-6b), 3.57–3.52 (m, 4H, H-2′, OCH_3), 3.45 (m, 1H, H-5), 3.35 (dd, 1H, $J_{3,4}$=$J_{4,5}$ 9.5 Hz, H-4), 3.21 (dd, 1H, $J_{2,3}$ 9.6 Hz, $J_{1,2}$ 7.5 Hz, H-2), 2.08 (m, 1H, H-1″a), 1.80–1.67 (m, 2H, H-1″b, H-3); ^{13}C NMR (125 MHz, $CDCl_3$) 138.2, 138.2, 138.1, 138.1, 137.9, 137.8 (6× *ipso* C_6H_5), 128.3–127.4 (30× C_6H_5), 105.4 (C-1), 77.6 (C-5), 77.2 (C-4), 76.5 (C-2′), 76.1 (C-3′), 74.6 (C-4′), 74.1 ($PhCH_2$), 73.6 (C-5′), 73.5 (2× $PhCH_2$), 73.2 ($PhCH_2$), 72.8 (C-2), 72.2 ($PhCH_2$), 71.9 (C-1′), 71.3 ($PhCH_2$), 69.1, 68.7 (C-6, C-6′), 56.7 (OCH_3), 46.3 (C-3), 30.7 (C-1″). ESIMS: MNH_4^+, found 912.2. $C_{56}H_{66}NO_{10}$ requires 912.5.

*4.1.29. Methyl 3-deoxy-3-C-[(2,3,4,6-tetra-O-benzyl-α-D-mannopyranosyl)methyl]-4,6-di-O-benzyl-α-L-mannopyranoside (**35**) and methyl 3-deoxy-3-C-[(2,3,4,6-tetra-O-benzyl-α-D-mannopyranosyl) methyl]-4,6-di-O-benzyl-β-L-glucopyranoside (**36**).* Using the same procedure as in the previous case, the glucal **2** (290 mg, 0.34 mmol) was converted to compounds **35** (viscous oil, 160 mg, 51%), R_f=0.30 (light petroleum/ethyl acetate, 2:1) and **36** (viscous oil, 76 mg, 24%), R_f=0.36 (light petroleum/ethyl acetate, 2:1). Compound **35**: [Found: C, 74.93; H, 6.75. $C_{56}H_{62}O_{10}$ requires C, 75.13; H, 6.93%]; $[\alpha]_D^{20}$ −4.2 (*c* 0.56, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) 7.40–7.10 (m, 30H, 6× C_6H_5), 4.69 (d, 1H, *J* 11.4 Hz, O–CH_2–Ph), 4.65 (d, 1H, *J* 11.4 Hz, O–CH_2–Ph), 4.59 (br s, 1H, H-1), 4.57–4.34 (m, 10H, O–CH_2–Ph), 4.19 (m, 1H, H-1′), 3.87–3.82 (m, 2H, H-2, H-6a), 3.81–3.65 (m, 7H, H-5, H-3′, H-4′, H-5′, H-6b, H-6′a, H-6′b), 3.58–3.53 (m, 2H, H-2′, H-4), 3.3 (s, 3H, OCH_3), 2.19 (m, 1H, H-3), 1.93 (m, 1H, H-1″a), 1.64 (m, 1H, H-1″b); ^{13}C NMR (125 MHz, $CDCl_3$) 138.5–138.1 (6× *ipso* C_6H_5), 128.3–127.3 (30× C_6H_5), 100.6 (C-1), 76.7 (C-3′), 76.1, 74.9, 73.8 (C-4, C-2′, C-2), 74.1, 73.5, 73.5, 73.2, 72.1, 71.5 (6× $PhCH_2$), 73.3, 72.0, 69.3 (C-4′, C-5, C-4′), 69.4, 69.0 (C-6, C-6′), 54.7 (OCH_3), 37.9 (C-3), 26.5 (C-1″). ESIMS: MNH_4^+, found 912.2. $C_{56}H_{66}NO_{10}$ requires 912.5. Compound **36**: $[\alpha]_D^{20}$ +5.6 (*c* 0.56, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) 7.40–7.14 (m, 30H, 6× C_6H_5), 4.73–4.39 (m, 11H, O–CH_2–Ph), 4.33 (ddd, 1H, $J_{1',1''b}$ 10.4 Hz, $J_{1',1''a}$ 3.9 Hz, $J_{1',2'}$ 2.2 Hz, H-1′), 4.23 (d, 1H, 1H, *J* 11.0 Hz, O–CH_2–Ph), 4.10 (d, 1H, $J_{1,2}$ 7.7 Hz, H-1), 3.94 (ddd, 1H, $J_{5',4'}$=$J_{5',6'a}$ 7.4 Hz, $J_{5',6'b}$ 2.8 Hz, H-5′), 3.77–3.65 (m, 5H, H-3′, H-4′, H-6a, H-6b, H-6′a), 3.63–3.56 (m, 2H, H-6′b, H-2), 3.53–3.48 (m, 4H, H-2′, OCH_3), 3.45 (ddd, 1H, $J_{4,5}$ 9.6 Hz, $J_{5,6a}$=$J_{5,6b}$ 3.3 Hz, H-5), 3.38 (dd, 1H, $J_{4,3}$ 10.5 Hz, $J_{4,5}$ 9.6 Hz, H-4), 2.16 (m, 1H, H-1″a), 1.84 (m, 1H, H-3), 1.56 (m, 1H, H-1″b); ^{13}C NMR (125 MHz, $CDCl_3$) 138.1–137.8 (6× *ipso* C_6H_5), 128.3–127.5 (30×C_6H_5), 105.6 (C-1), 77.8, 77.7 (C-5, C-3′), 76.4 (C-2′), 75.3 (C-4′), 74.9 (C-4), 73.9, 73.8, 73.5, 73.3 (4× $PhCH_2$), 72.8 (C-5′), 72.3, 71.6 (2× $PhCH_2$), 71.2 (C-2), 71.0 (C-1′), 69.6, 69.2 (C-6, C-6′), 56.7 (OCH_3), 45.0 (C-3), 25.5 (C-1″). ESIMS: MNH_4^+, found 912.2. $C_{56}H_{66}NO_{10}$ requires 912.5.

*4.1.30. Methyl 3-deoxy-3-C-[(2,3,4,6-tetra-O-acetyl-α-D-mannopyranosyl)methyl]-2,4,6-tri-O-acetyl-α-D-mannopyranoside (**7**).* 10% Pd/C (30 mg) were added to a solution of *C*-disaccharide **33** (150 mg, 0.17 mmol) in MeOH (15 mL) and glacial acetic acid (3 mL), and the reaction was stirred overnight under an atmosphere of hydrogen, then filtered through a pad of Celite and coevaporated three times with toluene. The obtained compound (methyl 3-deoxy-3-*C*-[(α-D-mannopyranosyl)methyl]-α-D-mannopyranoside, ESIMS: MNH_4^+, found 372.1. $C_{14}H_{30}NO_{10}$ requires 372.2) was dissolved in pyridine (16 mL) and Ac_2O (8 mL) and stirred overnight at room temperature. The reaction mixture was concentrated and coevaporated three times with toluene, and column chromatography (light petroleum/ethyl acetate, 2:1→1:2) yielded 55 mg (50%) of **7** as a viscous oil; [Found: C, 51.60; H, 6.05. $C_{28}H_{40}O_{17}$ requires C, 51.83; H, 6.17%]; R_f=0.67 ($CHCl_3$/MeOH, 15:1); $[\alpha]_D^{20}$ +10.7 (*c* 0.68, $CHCl_3$); ν_{max} 3034, 2932, 1744, 1371, 1142, 1048 cm^{-1}; ^{1}H NMR (500 MHz, C_6D_6) 5.56 (dd, 1H, $J_{3',4'}$ 6.0 Hz, $J_{2',3'}$ 3.2 Hz, H-3′), 5.41 (dd, 1H, $J_{4,3}$=$J_{4,5}$ 10.5 Hz, H-4), 5.29 (dd, 1H, $J_{2',1'}$ 6.9 Hz, $J_{2',3'}$ 3.2 Hz, H-2′), 5.26 (dd, 1H, $J_{2,3}$ 3.0 Hz, $J_{2,1}$ 1.3 Hz, H-2), 5.18 (dd, 1H, $J_{3',4'}$ 6.0 Hz, $J_{4',5'}$ 4.4 Hz, H-4′), 4.76 (dd, 1H, $J_{6'a,6'b}$ 11.9 Hz, $J_{5',6'a}$ 8.0 Hz, H-6′a), 4.71 (d, 1H, $J_{2,1}$ 1.3 Hz, H-1), 4.41 (dd, 1H, $J_{6a,6b}$ 12.1 Hz, $J_{5,6a}$ 5.2 Hz, H-6a), 4.21–4.12 (m, 2H, H-1′, H-6b) 4.06 (ddd, 1H, $J_{5',6'a}$ 8.0 Hz, $J_{5',4'}$ 4.4 Hz, $J_{5',6'b}$ 3.7 Hz, H-5′), 4.02 (dd, 1H, $J_{6'a,6'b}$ 11.9 Hz, $J_{5',6'b}$ 3.7 Hz, H-6′b), 3.89 (ddd, 1H, $J_{5,4}$ 10.5 Hz, $J_{5,6a}$ 5.2 Hz, $J_{5,6b}$ 2.5 Hz, H-5), 3.0 (s, 3H, OCH_3), 2.58 (dddd, 1H, $J_{4,3}$ 10.5 Hz, $J_{1''a,3}$=$J_{1''b,3}$ 5.5 Hz, $J_{3,2}$ 3.0 Hz, H-3), 1.87 (s, 3H, $COOCH_3$), 1.86–1.84 (m, 2H, H-1″a, H-1″b), 1.82 (s, 3H, $COOCH_3$), 1.75 (s, 3H, $COOCH_3$), 1.71 (s, 3H, $COOCH_3$), 1.65 (s, 3H, $COOCH_3$), 1.57 (s, 3H, $COOCH_3$), 1.53 (s, 3H, $COOCH_3$); ^{13}C NMR (125 MHz, C_6D_6) 170.1–169.1 (7× $COOCH_3$), 97.8 (C-1), 73.0 (C-5′), 72.4 (C-2), 71.0 (C-1′), 70.3 (C-2′), 69.6 (C-5), 68.6 (C-4), 68.2 (C-4′), 68.1 (C-3′), 63.1 (C-6), 60.9 (C-6′), 54.5 (OCH_3), 37.1 (C-3), 29.1 (C-1″), 20.4–20.1 (7× $COOCH_3$). ESIMS: MNH_4^+, found 665.9. $C_{28}H_{44}NO_{17}$ requires 666.2.

*4.1.31. Methyl 3-deoxy-3-C-[(2,3,4,6-tetra-O-acetyl-α-D-mannopyranosyl)methyl]-2,4,6-tri-O-acetyl-α-L-mannopyranoside (**8**).* Using the same procedure as for the preparation of **7**, compound **35** (160 mg, 0.18 mmol) was converted to *C*-disaccharide **8** (viscous oil, 80 mg, 67%); [Found: C, 51.55; H, 6.35. $C_{28}H_{40}O_{17}$ requires C, 51.83; H, 6.17%]; R_f=0.67 ($CHCl_3$/MeOH, 15:1); $[\alpha]_D^{20}$ −6.9 (*c* 0.75, $CHCl_3$); ν_{max} 3011, 1671, 1625, 1454, 1390, 1094, 1028 cm^{-1}; ^{1}H NMR (500 MHz, C_6D_6) 5.57 (dd, 1H, $J_{3',4'}$ 6.1 Hz, $J_{3',2'}$ 3.2 Hz, H-3′), 5.37 (br s, 1H, H-2), 5.30 (dd, 1H, $J_{4,3}$ 11.2 Hz, $J_{4,5}$ 10.5 Hz, H-4), 5.27 (dd, 1H, $J_{2',1'}$ 6.2 Hz, $J_{2',3'}$ 3.2 Hz, H-2′), 5.17 (dd, 1H, $J_{4',3'}$ 6.1 Hz, $J_{4',5'}$ 5.0 Hz, H-4′), 4.60 (br s, 1H, H-1), 4.61 (dd, 1H, $J_{6'a,6'b}$ 12.1 Hz, $J_{5',6'a}$ 8.7 Hz, H-6′a), 4.35 (dd, 1H, $J_{6a,6b}$ 12.2 Hz, $J_{5,6a}$ 5.3 Hz, H-6a), 4.25 (dd, 1H, $J_{6'a,6'b}$ 12.1 Hz, $J_{5',6'b}$ 3.4 Hz, H-6′b), 4.22–4.10 (m, 3H, H-1′, H-5′, H-6b), 3.88 (m, 1H, H-5), 2.98 (s, 3H, OCH_3), 2.73 (dddd, 1H, $J_{3,4}$=$J_{3,1''a}$ 11.2 Hz, $J_{3,1''b}$=$J_{3,2}$ 3 Hz, H-3), 1.92 (m, 1H, H-1″a), 1.87 (s, 3H, $COOCH_3$), 1.78 (m, 1H, H-1″b), 1.74 (s, 3H, $COOCH_3$), 1.73 (s, 3H, $COOCH_3$), 1.68 (s, 3H, $COOCH_3$), 1.66 (s, 3H, $COOCH_3$), 1.61 (s, 3H, $COOCH_3$), 1.58 (s, 3H, $COOCH_3$); ^{13}C NMR (125 MHz, C_6D_6) 170.1–169.3 (7× $COOCH_3$), 98.2 (C-1), 72.7 (C-5′), 70.5 (C-2′), 69.4, 69.3 (C-2, C-5), 68.6 (C-4′), 68.1 (C-3′), 67.9 (C-4), 67.3 (C-1′), 63.2 (C-6), 61.4 (C-6′), 54.4 (OCH_3), 35.1 (C-3), 27.0 (C-1″), 20.3–20.1 (7× $COOCH_3$). ESIMS: MNH_4^+, found 665.9. $C_{28}H_{44}NO_{17}$ requires 666.2.

Acknowledgements

This work was supported by the Grant Agency of the Czech Republic (Grant No. 203/08/1124) and by the Ministry of Education, Youth and Sport of the Czech Republic (Grant No. 6046137305).

Supplementary data

Supplementary data associated with this article can be found in the online version, at doi:10.1016/j.tet.2011.04.044. These data include MOL file and InChIKey of the most important compounds described in this article.

References and notes

1. (a) Reuter, G.; Gabius, H.-J. *Cell. Mol. Life Sci.* **1999**, *55*, 368–422; (b) Gabius, H.-J. *Naturwissenschaften* **2000**, *87*, 108–121; (c) Gabius, H.-J.; André, S.; Kaltner, H.; Siebert, H.-C. *Biochim. Biophys. Acta* **2002**, *1572*, 165–177; (d) Rüdiger, H.; Gabius, H.-J. In *The Sugar Code*; Gabius, H.-J., Ed.; Wiley: Weinheim, 2009; pp 3–13.
2. (a) Švajger, U.; Anderluh, M.; Jeras, M.; Obermajer, N. *Cell. Signalling* **2010**, *22*, 1397–1405; (b) Guo, Y.; Feinberg, H.; Conroy, E.; Mitchell, D. A.; Alvarez, R.; Blixt, O.; Taylor, M. E.; Weis, W. I.; Drickamer, K. *Nat. Struct. Mol. Biol.* **2004**, *11*, 591–598.
3. (a) Tabarani, G.; Reina, J. J.; Ebel, C. H.; Vivès, C.; Lortat-Jacob, H.; Rojo, J.; Fieschi, F. *FEBS Lett.* **2006**, *580*, 2402–2408; (b) Sattin, S.; Daghetti, A.; Thépaut, M.; Berzi, A.; Sánchez-Navarro, M.; Tabarani, G.; Rojo, J.; Fieschi, F.; Clerici, M.; Bernardi, A. *ACS Chem. Biol.* **2010**, *5*, 301–312.
4. (a) Danishefsky, S. J.; Allen, J. R. *Angew. Chem., Int. Ed.* **2000**, *39*, 836–863; (b) Warren, J. D.; Geng, X.; Danishefsky, S. *J. Top. Curr. Chem.* **2007**, *267*, 109–141; (c) Galonic, D. P.; Gin, D. Y. *Nature* **2007**, *446*, 1000–1007.
5. (a) Di Bussolo, V.; Kim, Y.-J.; Gin, D. Y. *J. Am. Chem. Soc.* **1998**, *120*, 13515–13516; (b) Tiwari, P.; Misra, A. K. *J. Org. Chem.* **2006**, *71*, 2911–2913.
6. Kim, Y.-J.; Di Bussolo, V.; Gin, D. Y. *Org. Lett.* **2001**, *3*, 303–306.
7. Liu, J.; Gin, D. Y. *J. Am. Chem. Soc.* **2002**, *124*, 9789–9797.
8. Liu, J.; Gin, D. Y. *Tetrahedron Lett.* **2003**, *44*, 4015–4018.
9. (a) Parrish, J. D.; Little, R. D. *Org. Lett.* **2002**, *4*, 1439–1442; (b) Allwein, S. P.; Cox, J. M.; Howard, B. E.; Johnson, H. W. B.; Rainier, J. D. *Tetrahedron* **2002**, *58*, 1997–2009; (c) Codee, J. D. C.; van der Marel, G. A.; van Boeckel, C. A. A.; van Boom, J. H. *Eur. J. Org. Chem.* **2002**, 3954–3965.
10. Parkan, K.; Werner, L.; Lövyová, Z.; Prchalová, E.; Kniežo, L. *Carbohydr. Res.* **2010**, *345*, 352–362.
11. (a) Krintel, S. L.; Jiménez-Barbero, J.; Skrydstrup, T. *Tetrahedron Lett.* **1999**, *40*, 7565–7568; (b) Mikkelsen, L. M.; Krintel, S. L.; Jiménez-Barbero, J.; Skrydstrup, T. *J. Org. Chem.* **2002**, *67*, 6297–6308.
12. (a) Panek, J. S.; Sparks, M. A. *J. Org. Chem.* **1989**, *54*, 2034–2038; (b) Bertozzi, C. R.; Bednarski, M. D. *J. Org. Chem.* **1991**, *56*, 4326–4329; (c) Giguère, D.; Cloutier, P.; Roy, R. *J. Org. Chem.* **2009**, *74*, 8480–8483.
13. (a) Lucero, C. G.; Woerpel, K. A. *J. Org. Chem.* **2006**, *71*, 2641–2647 and references therein; (b) McGarvey, G. J.; LeClair, C. A.; Schmidtmann, B. A. *Org. Lett.* **2008**, *10*, 4727–4730.
14. Nicolau, K. C.; Hwang, C. K.; Duggan, M. E. *J. Am. Chem. Soc.* **1989**, *111*, 6682–6690.
15. Dondoni, A.; Marra, A.; Merino, P. *J. Am. Chem. Soc.* **1994**, *116*, 3324–3336.
16. (a) Shao, H.; Wang, Z.; Lacroix, E.; Wu, S. H.; Jennings, H. J.; Zhou, W. *J. Am. Chem. Soc.* **2002**, *124*, 2130–2131; (b) Wang, Z.; Shao, H.; Lacroix, E.; Wu, S. H.; Jennings, H. J.; Zhou, W. *J. Org. Chem.* **2003**, *68*, 8097–8105.
17. Massi, A.; Nuzzi, A.; Dondoni, A. *J. Org. Chem.* **2007**, *72*, 10279–10282.
18. (a) Dujardin, G.; Rossignol, S.; Brown, E. *Tetrahedron Lett.* **1995**, *36*, 1653–1656; (b) Štěpánek, P.; Vích, O.; Werner, L.; Kniežo, L.; Dvořákova, H.; Vojtíšek, P. *Collect. Czech. Chem. Commun.* **2005**, *70*, 1411–1428.
19. Parkan, K.; Vích, O.; Dvořákova, H.; Kniežo, L. *Collect. Czech. Chem. Commun.* **2008**, *73*, 690–700.
20. Aspinall, G. O.; Capek, P.; Carpenter, R. C.; Szafranek, J. *Carbohydr. Res.* **1991**, *214*, 95–105.
21. Demange, R.; Awad, L.; Vogel, P. *Tetrahedron: Asymmetry* **2004**, *15*, 3573–3585.

PŘÍLOHA IV

Parkan, K.; Pohl, R.; Kotora, M. Cross-Coupling Reaction of Saccharide-Based Alkenyl Boronic Acids with Aryl Halides: The Synthesis of Bergenin, *Chem.-Eur. J.* **2014**, *20* (15), 4414-4419.

ChemPubSoc Europe

DOI: 10.1002/chem.201304304

CHEMISTRY A European Journal Full Paper

C–C Coupling

Cross-Coupling Reaction of Saccharide-Based Alkenyl Boronic Acids with Aryl Halides: The Synthesis of Bergenin

Kamil Parkan,*[a] Radek Pohl,[b] and Martin Kotora*[c]

Abstract: A convenient synthetic pathway enabling D-glucal and D-galactal pinacol boronates to be prepared in good isolated yields was achieved. Both pinacol boronates were tested in a series of cross-coupling reactions under Suzuki–Miyaura cross-coupling conditions to obtain the corresponding aryl, heteroaryl, and alkenyl derivatives in high isolated yields. This methodology was applied to the formal synthesis of the glucopyranoside moiety of papulacandin D and the first total synthesis of bergenin.

Introduction

C-Arylglycosides are an interesting and important class of natural compounds possessing appealing biological properties that may have potential application in many areas of medicinal chemistry. The saccharide moiety of such compounds is usually composed of D-glucose scaffolds and vitexin, orientin etc.,[1] with bergenin[2] and papulacandin D[3] serving as typical examples (Figure 1). However, compounds possessing ribo, manno, and other scaffolds also exist.[4] Despite the fact that numerous synthetic procedures based on a range of methodologies have been described, the development of new and more synthetically robust procedures is still desirable.[5] This interest is driven by the weakness of the available methodologies with respect either to the required reaction conditions or to the substrate scope.

One approach to *C*-arylglycosides is based on the use of the corresponding 1-alkenylboronic acids or their pinacol esters in the Suzuki–Miyaura cross-coupling reaction[6] with suitable substituted aryl and heteroaryl halides, and with alkenyl halides. During the course of our work on that subject, a report on a synthetic procedure for the synthesis of *C*-arylglycosides based on cross-coupling reaction of glucal boronate with aryl(heteroaryl) bromides was published.[7] The report clearly demonstrated the advantages of this approach; however, the scope of this investigation was limited to just six examples. In our report we would like to show that the use of pinacol boronates of D-glucal and also D-galactal offers an improved synthetic protocol and extends the scope of the reaction. Finally, we would like to demonstrate that this methodology can provide synthetic access to various natural *C*-aryl glycosides that have been isolated from a variety of medicinal plants.[8] One such compound of interest is bergenin,[9] which has interesting pharmacological properties such as antihepatotoxic, antiulcerogenic, anti-HIV, antifungal, hepatotoxic, hepatoprotective, antiarrhythmic, neuroprotective, anti-inflammatory, and immunomodulatory activity. Bergenin-containing extracts from *Macaranga peltata* are used in Indian folk medicine for treatment of venereal diseases[10] and bergenin itself is an active pharmaceutical ingredient of a Chinese drug[11] described to be effective against coughs and bronchitis. Due to its broad spectrum

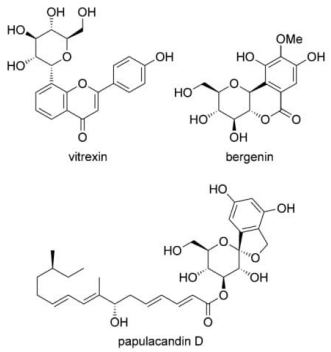


Figure 1. Selected natural *C*-glycosides.

[a] Dr. K. Parkan
Department of Chemistry of Natural Compounds
Institute of Chemical Technology
Technická 5, 166 28 Praha 6 (Czech Republic)
Fax: (+420) 220444422
E-mail: parkank@vscht.cz

[b] Dr. R. Pohl
Institute of Organic Chemistry and Biochemistry
Academy of Sciences of the Czech Republic, v. v. i.
Flemingovo 2, 166 10 Prague 6 (Czech Republic)

[c] Prof. Dr. M. Kotora
Department of Organic Chemistry
Faculty of Science, Charles University in Prague
Hlavova 8, 128 43 Praha 2 (Czech Republic)
Fax: (+420)211-951-326
E-mail: kotora@natur.cuni.cz

Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/chem.201304304.

ChemPubSoc Europe

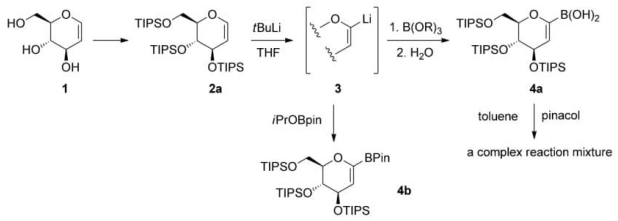
CHEMISTRY A European Journal Full Paper

of biological activities, the development of new and efficient synthetic pathway for its preparation is highly desirable. In this report we would like to show that the approach mentioned above allows the flexible synthesis of various substituted saccharide derivatives and can be applied to the first total synthesis of bergenin.

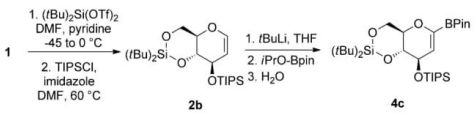
Results and Discussion

Synthesis of the starting boronic acid derivatives

Our initial attention focused on the synthesis of protected D-glucal boronic acid and its pinacol esters (Scheme 1 and Scheme 2). Although boronation of the double bond in D-glucals with B_2Pin_2 catalyzed by an Ir-complex could be used for the synthesis of D-glucal pinacol boronates,[12] we were looking for a more economical method that was also suitable for larger scale syntheses.



Scheme 1. Synthesis of D-glucal boronic acid **4a** and D-glucal pinacol boronate **4b**.

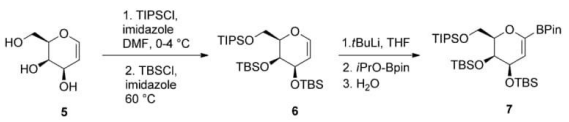


Scheme 2. Synthesis of D-glucal pinacol boronate **4c**.

Initially, we decided to explore pathways for the preparation of boronic acid **4a** (Scheme 1). Because an alkenyl sugar derivative is exposed to *t*BuLi during the course of the reaction, suitable protective groups that were not affected by strong bases during the course of reactions had to be chosen for the saccharide moiety (e.g., methoxymethyl ether (MOM),[13,14] *tert*-butyldiphenylsilyl (TBDPS),[13,15,16,17,18] triisopropylsilyl (TIPS),[13,19,20] di-*tert*-butylsilylene,[13,21] and *tert*-butyldimethylsilyl (TBS)[22,23]. Tri-TIPS-protected glucal **2**, prepared by protection of commercially available D-glucal **1** with TIPS chloride and imidazole, was converted into 1-lithiated intermediate **3** by treatment with 4.0 equivalents of *t*BuLi. A number of trialkyl borates $B(OR)_3$ (R = Me, Et, *i*Pr) were added followed by hydrolysis. In all cases, the boronic acid **4a** was isolated in 75–80% yields, however, although it was obtained with a reasonable purity (ca. 90%), it was difficult to obtain in higher quality due to its instability. Attempts to protect the boronic acid function of **4a** with pinacol under published conditions[6] to obtain tri-TIPS glucal pinacol boronate **4b** were not successful and resulted in the formation of complex reaction mixtures. Interestingly, its formation in high yield was claimed,[7] but its spectral characterization was not reported. In view of the aforementioned results, we decided to approach the synthesis of TIPS-protected glucal boronate **4b** by other means (Scheme 1). The procedure was based on a similar approach, that is, on the reaction of the 1-lithiated glycal **3** with 2-isopropoxy-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (*i*PrOBpin). The reaction proceeded cleanly, providing the desired compound **4b** in an almost quantitative yield. The successful isolation strongly depended on appropriate work-up procedure of the formed reaction mixture, and it was essential to carry out the extraction by using a mixture of toluene and water (for details see the Supporting Information).

In addition to **4b**, boronate **4c** was also prepared by the reaction sequence described above (Scheme 2), that is, D-glucal **1** was converted into the bridged-silyl protected glucal **2b** with $(t\text{Bu})_2\text{Si(OTf)}_2$[24] followed by silylation of the free hydroxyl group at position C-3 with TIPS chloride and imidazole. Compound **2b** was then treated with *t*BuLi followed by reaction with *i*PrOBpin to give the stable bicyclic boronate **4c** as a crystalline solid, again in almost quantitative yield.

In the next step we wanted to prepare the corresponding fully protected D-galactal pinacol boronate **7** (Scheme 3). However, the primary hydroxyl functionality required protection with a more bulky silyl protective group, because it is known that the TBS-protected galactal tends to succumb to competing α-silyl deprotonation at the 6-position.[16,25,26] To avoid this undesirable competing reaction, we protected the 6-hydroxyl group of commercially available D-galactal **5** with TIPS chloride and imidazole followed by in situ installation of the less bulky TBS groups at the 3- and 4-positions providing the protected derivative **6** in good yield. An analogous approach based on C-1 lithiation of galactal **6** with 3.5 equivalents of *t*BuLi and



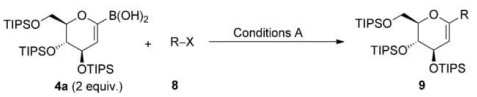
Scheme 3. Synthesis of D-galactal pinacol boronate **7**.

ChemPubSoc Europe

CHEMISTRY A European Journal Full Paper

subsequent excess of *i*PrOBpin was used (Scheme 3). The desired product, the pinacol ester of (1,5-anhydro-2-deoxy-3,4-*O*-di-(*tert*-butyldimethylsilyl)-6-*O*-triisopropylsilyl-D-*lyxo*-hex-1-enitolyl)boronic acid (**7**) was obtained in an almost quantitative yield. All starting boronic acid derivatives **4a–c** and **7** were fully characterized by means of NMR spectroscopy. In the ^{13}C NMR spectra of these compounds, the signal of C-1 is broad and usually absent due to $^{13}C–^{11}B$ spin-spin coupling interaction and additional $^{10}B/^{11}B$ isotope induced chemical shift of C-1 signal. This difficulty can be overcome by acquiring H,C-HMBC spectra for which H-2/C-1, H-5/C-1, and H-3/C-1 cross-peaks can be observed, providing an assignment of the C-1 signal. In addition, NMR spectra of *galacto*-derivatives **7** and **11** measured at ambient temperature provide generally broad signals, likely due to conformational flexibility. Therefore, it is advisable to acquire NMR spectra of these derivatives at higher temperatures (55 °C in $CDCl_3$, 80 °C in CD_3CN).

Table 1. Cross-coupling reaction of **4a** with **8**.



4a (2 equiv.) **8** **9**

A: $[Pd(PPh_3)_2Cl_2]$ (5 mol%), Na_2CO_3 (2 equiv.), DME, 60 °C, 12 h

Entry	Halide **8**	Conditions	Yield of **9** [%][a]
1	**8a**	A	89
2	**8b**	A	84
3	**8c**	A	93
4	**8e**	A	72
5	**8f**	A	76
6	**8g**	A	88
7	**8i**	A	70
8	**8j**	A	78
9	**8k**	A	74
10	**8l**	A	74
11	**8m**	A	71

[a] Isolated yield.

Cross-coupling reactions of 4 with aryl halides 8

Cross-coupling reactions of **4a–c** were performed with a range of aryl, heteroaryl, and alkenyl halides (Figure 2). After extensive screening of various reaction conditions, the best results were achieved with $[Pd(PPh_3)_2Cl_2]$ in the presence of 2 M aqueous solution of Na_2CO_3 in dimethoxyethane at 80 °C (conditions A). The results are summarized in Table 1.

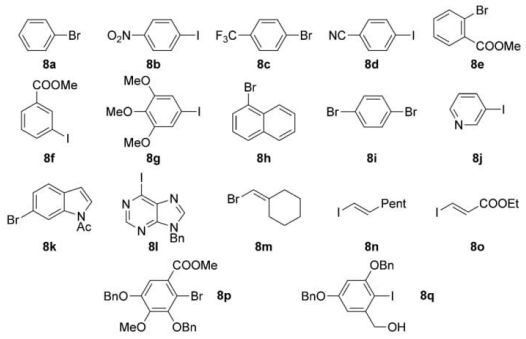


Figure 2. Aryl, heteroaryl, and alkenyl halides **8** tested in the cross-coupling reactions.

Initially, the Suzuki–Miyaura cross-coupling reactions of **4a** with aryl halides were carried out under conditions A (see Table 1) by using Na_2CO_3 as the base. The reactions proceeded well with *para*-substituted aryl bromides and halides **8a–c**, giving the corresponding products **9a–c** in good isolated yields of 89, 84 and 93%, respectively (entries 1–3). Furthermore, the use of *meta*- and *ortho*-substituted aryl halides **8e–g** provided the expected products **9e–g** in good yields of 72, 76, and 88%, respectively (entries 4–6). The reaction with 1,4-dibromobenzene **8i** gave the double-substituted product **9i** in a good 70% yield (entry 7). The Pd-catalyzed cross-coupling reactions with heteroaryl halides **8j–l** proceeded in a similar manner, providing compounds **9j–l** in 78, 74, and 74% isolated yields, respectively (entries 8–10). Finally, the cross-coupling reaction with vinyl bromide **8m** was performed to give **9m** in 71% isolated yield (entry 11). To achieve high conversions of starting material and high yields of the corresponding products, the use of 2.1 equivalents of the boronic acid **4a** was required. Perhaps because of this, partial dimerization of **4a** to dimer **4d** (Figure 3) was observed.[27]

Cross-coupling reactions of **4b** were initially also tested under conditions A. Again, a 1.8-fold excess of **4b** was used to ensure good conversions and yields. Although the cross-coupling reactions with **8b**, **8c**, **8g**, and **8l** provided the corresponding products **9b**, **9c**, **9g**, and **9l** in high isolated yields (88, 87, 88, and 77%, respectively; Table 2, entries 1, 3, 6, and 10), the formation of dimer **4d** in various amounts was again observed (5–20%). To suppress the formation of the latter, conditions B using KOAc as the base were tested.[28] Thus, the reaction of **8b**, **8c**, **8e**, and **8h–j** gave rise to the corresponding products **9b**, **9c**, **9e**, and **9h–j** in good yields (86, 85, 80, 87, 76, and 80%; entries 2, 4, 5, 7, and 8). Although, the reaction rate was considerably slower, the formation of dimer **4d** was not observed.

Cross-coupling reactions of **4c** were carried out under conditions A only (Table 3). Thus, reaction with **8c** to give **10c** pro-

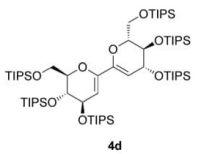
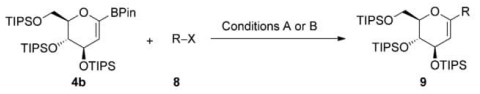


Figure 3. Dimer **4d**.

ChemPubSoc Europe

CHEMISTRY A European Journal Full Paper

Table 2. Cross-coupling reaction of **4b** with **8**.

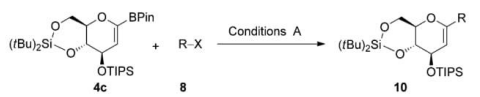


A: $[Pd(PPh_3)_2Cl_2]$ (5 mol%), Na_2CO_3 (2 equiv.), DME, 60 °C, 12 h
B: $[Pd(PPh_3)_2Cl_2]$ (5 mol%), KOAc (1.5 equiv.), DME, 80 °C, 12 h

Entry	Halide **8**	Conditions	Yield of **9** [%][a]
1	**8b**	A	88
2		B	86
3	**8c**	A	87
4		B	85
5	**8e**	B	80
6	**8g**	A	88
7	**8h**	B	87
8	**8i**	B	76
9	**8j**	B	80
10	**8l**	A	77

[a] Isolated yield.

Table 3. Cross-coupling reaction of **4c** with **8**.



A: $[Pd(PPh_3)_2Cl_2]$ (5 mol%), Na_2CO_3 (2 equiv.), DME, 60 °C, 12 h

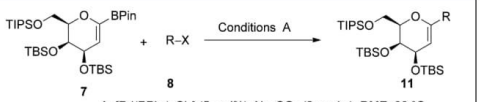
Entry	Halide **8**	Conditions	Yield of **10** [%][a]
1	**8c**	A	87
2	**8n**	A	75
3	**8p**	A	88
4	**8q**	A	87

[a] Isolated yield.

ceeded in good 87% isolated yield (entry 1). This result is comparable to results obtained for **4a** and **4b**. The reaction with **8n** proceeded in a similar manner, providing **10n** in good 75% isolated yield (entry 2). Next, the reactions with sterically hindered aryl halides **8p** and **8q** were attempted (entries 3 and 4). A synthesis of aryl bromide **8p**, which is a potential intermediate for the bergenin synthesis (see below), has not been previously reported and had to be synthesized starting from methyl ester of gallic acid through a reaction sequence involving acetylation, methylation, benzylation, and bromination (for synthetic details see the Supporting Information). Aryl iodide **8q**, a known intermediate in the papulacandin synthesis, was synthesized according to a known procedure.[29] Gratifyingly, in both cases, the cross-coupling reactions proceeded smoothly to give the corresponding products **10p** and **10q** in very good isolated yields of 88 and 87%, respectively.

Finally, we focused on the Pd-catalyzed cross-coupling reactions of fully protected D-galactal pinacol boronate **7** with several aryl halides (Table 4). The reactions of **7** with aryl halides **8b–d** proceeded well, with high isolated yields (80, 85, and 79%, respectively) of the corresponding products **11b–d** (entries 1–3). A similar result was also obtained with methyl (*E*)-3-

Table 4. Cross-coupling reaction of **7** with **8**.



A: $[Pd(PPh_3)_2Cl_2]$ (5 mol%), Na_2CO_3 (2 equiv.), DME, 60 °C

Entry	Halide **8**	Conditions	Yield of **11** [%][a]
1	**8b**	A	80
2	**8c**	A	85
3	**8d**	A	79
4	**8o**	A	84

[a] Isolated yield.

iodopropenoate **8o**, providing the product **11o** in 84% isolated yield (entry 4). Because, to the best of our knowledge, there have not been any reports on cross-coupling of galactal boronates with organyl halides, these results indicate that this methodology could also be applied to saccharide pinacol boronates with other scaffolds.

Synthesis of the papulacandin D glucopyranoside moiety

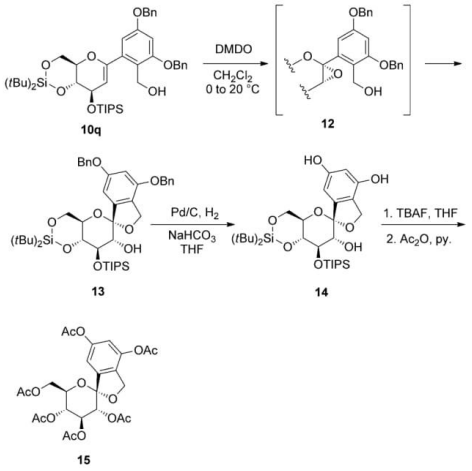
In the last couple of years several approaches to the papulacandin D glucopyranoside moiety have been reported. These methods were based on organolithium addition to gluconolactone,[30,31,32] reductive aromatization of quinols,[33] transformation of arylvinylfurans,[34] or cross-coupling of a vinylstannane[35] or a vinylsilanol with aryl halides.[29,36,37] We envisioned that the papulacandin D glucopyranoside moiety could be also prepared by a cross-coupling reaction of a suitably substituted aryl halide with boronate **4c**. Because we have shown that cross-coupling between boronate **4c** and iodobenzene **8q** (Table 3, entry 3) proceeded successfully to give **10q** with high isolated yield (88%), further conversion of this intermediate was undertaken (Scheme 4). In the next step, the double bond was oxidized with dimethyldioxirane (DMDO)[35] under mild conditions. The epoxidation proceeded stereoselectively to provide α-epoxide **12**, which was immediately opened by intramolecular attack of the pendant benzylic hydroxyl to furnish the desired spiroketal **13** as a single anomer. The previous synthesis of **13** led to a mixture of α and β-anomers, which had to be epimerized under acidic conditions[37] to obtain the required anomer. We assume that the formation of the single diastereoisomer was caused by the fixed conformation of the bicyclic derivative that would not cause axial-equatorial flip on the pyranose ring. Debenzylation of **13** led to the formation of compound **14** in 93% isolated yield. Subsequent desilylation followed by peracetylation provided **15** in 89% yield, which is a known intermediate in synthesis of papulacandin D.[38]

Synthesis of bergenin

Prior to the synthetic endeavors that would lead to the synthesis of bergenin, transformations of the cross-coupling products into stereoselectively pure arylglycosides were attempted.

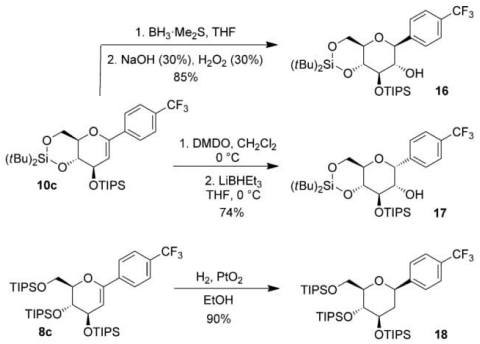
ChemPubSoc Europe

CHEMISTRY A European Journal Full Paper



Scheme 4. Synthesis of the papulacandin D glycopyranoside moiety **15**.

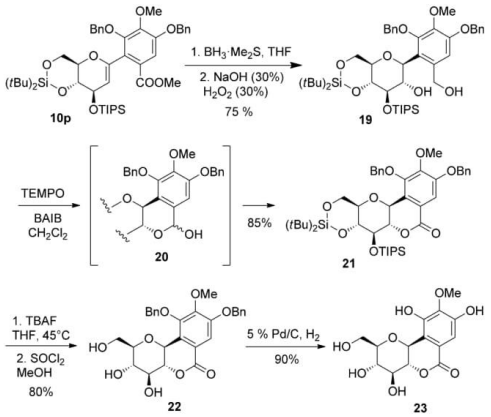
Compound **10c**, with the bridged-silyl protecting group to keep the molecule locked in one conformation, served as a model (Scheme 5). It was found that hydroboration[39] of the double bond in **10c** with BH_3·Me_2S complex followed by oxidation with alkaline hydrogen peroxide gave aryl-β-*C*-glycoside



Scheme 5. Transformations of the glucal double bond in **8c** and **10c**.

16 as a single stereoisomer (4.32 ppm (br. d, $J_{1,2}$ = 9.4 Hz, 1H, H-1)). The formation of the opposite anomer (5.16 ppm (br. d, $J_{1,2}$ = 3.8 Hz, 1H, H-1)), aryl-α-*C*-glycoside **17**, was achieved by epoxidation of the double bond with DMDO[40] followed by subsequent cleavage of the formed epoxide ring with lithium triethylborohydride.[41] It should be added that the reactions mentioned above were also carried out with the tri-TIPS-protected derivative **8c**, but this led to the formation of intractable reaction mixtures. This is clearly the result of conformational flexibility of the starting material **8c**. On the other hand, hydrogenation[42] of **8c** with H_2 on PtO_2 also proceeded stereoselectively to give aryl-β-*C*-2-deoxy-glycoside **18** (4.60 ppm (dd, $J_{1,2}$ = 11.2 Hz, $J_{1,3}$ 2.6 Hz, 1H, H-1)).

In view of the aforementioned results, the synthesis of bergenin was executed as follows (Scheme 6). The cross-coupling product **10p** was hydroborated with BH_3·Me_2S, followed by oxidation of the C–B bond to furnish arylglucoside **19** as a single



Scheme 6. Synthesis of bergenin **23**.

diastereoisomer. ^1H and ^{13}C NMR spectra of **19** measured at 0 °C in $CDCl_3$ revealed the existence of two isomers. Because vicinal coupling constants of sugar protons in both isomers were similar, we concluded that the isomerism is caused by hindered rotation of the aryl moiety. Unfortunately, NOE measurements did not provide more detailed information on the orientation of the aryl part for individual isomers. Subsequent selective oxidation of the benzyl alcohol moiety was accompanied by cyclization to lactol **20**, which was further oxidized to give lactone **21** in 85% isolated yield. The silyl protecting group was then removed to give **22** (80%) and, finally, reductive debenzylation provided bergenin **23** in 90% isolated yield. Thus, bergenin was synthesized in six steps from bromide **8p** in 40% overall yield.

Conclusion

We have developed an efficient method for preparation of aryl- or alkenyl-*C*-glucals and -*C*-galactals by using glucal or galactal boronates as the key synthons in cross-coupling reactions performed under Suzuki–Miyaura conditions. Partial dimerization of the boronates observed when K_2CO_3 was used as the base could be prevented by the use of KOAc. A possibility of further functionalization of the double bond in the cross-coupling products (1-aryl-*C*-glycals) was explored and resulted in diastereoselective syntheses of α- or β-glycosides in good yields. These results enabled the synthetic potential of this

ChemPubSoc Europe

CHEMISTRY A European Journal Full Paper

methodology to be demonstrated in two syntheses. First, it was applied in an alternative synthesis of papulacandin D glucopyranoside intermediate **15** in 64% overall yield. Second, the cross-coupling reaction was utilized as a crucial step for the first total synthesis of bergenin **23** in 40% overall yield in only six steps from bromide **8p**.

Acknowledgements

This work was supported by the Grant Agency of the Czech Republic (grant No. P207/12/P713 and 13-15915S).

Keywords: C–C coupling · glycosides · natural products · protecting groups · synthetic methods

[1] Y. Zhang, J. Jiao, C. Liu, X. Wu, Y. Zhang, *Food Chem.* **2008**, *107*, 1326–1336.
[2] W. R. Carruthers, J. E. Hay, L. J. Haynes *Chem. Ind.* **1957**, 76–77.
[3] P. Traxler, J. Gruner, J. A. Auden, *J. Antibiot.* **1977**, *30*, 289–296.
[4] a) A. Garcia, L. Lenis, C. Jiménez, C. Debitus, E. Quinoá, R. Riguera *Org. Lett.* **2000**, *2*, 2765–2767; b) T. Nishikawa, Y. Koide, A. Kanakudo, H. Yoshimura, M. Isobe, *Org. Biomol. Chem.* **2006**, *4*, 1268–1277; c) K. P. Kaliappan, A. V. Subrahmanyam, *Org. Lett.* **2007**, *9*, 1121–1124.
[5] For reviews, see: a) D. Y. W. Lee, M. He, *Curr. Top. Med. Chem.* **2005**, *5*, 1333–1350; b) T. Bililign, B. R. Griffith, J. S. Thorson, *Nat. Prod. Rep.* **2005**, *22*, 742–760; c) C. Len, M. Mondon, J. Lebreton, *Tetrahedron* **2008**, *64*, 7453–7475; d) J. Štambaský, M. Hocek, P. Kočovský, *Chem. Rev.* **2009**, *109*, 6729–6764.
[6] a) A. Suzuki, *Pure Appl. Chem.* **1991**, *63*, 419–422; b) N. Miyaura, A. Suzuki, *Chem. Rev.* **1995**, *95*, 2457–2483; c) A. Suzuki, *J. Organomet. Chem.* **1999**, *576*, 147–168.
[7] S. Sakamaki, E. Kawanishi, S. Nomura, T. Ishikawa, *Tetrahedron* **2012**, *68*, 5744–5753.
[8] a) K. Dhalwal, M. V. Shinde, S. Y. Biradar, R. K. Mahadik, *J. Food Compos. Anal.* **2008**, *21*, 496–500; b) A. Wibowo, N. Ahmat, A. S. Hamzah, A. S. Sufian, N. H. Ismail, R. Ahmad, F. M. Jaafar, H. Takayama, *Fitoterapia* **2011**, *82*, 676–681; c) H.-K. Lim, H.-S. Kim, H.-S. Choi, S. Oh, J. Choi, *J. Ethnopharmacol.* **2000**, *72*, 469–474.
[9] D. K. Patel, K. Patel, R. Kumar, M. Gadewar, V. Tahilyani, *Asian Pac. J. Trop. Dis.* **2012**, *2*, 163–167.
[10] R. N. Chopra, S. L. Maya, I. C. Chopra, *Glossary of Indian Medicinal Plants*; Council of Scientific and Industrial Research, New Delhi **1956**, p. 156.
[11] Y. Li, J. Liu, G. Song, K. Li, K. Zhanga, B. Ye, *Anal. Methods* **2013**, *5*, 3895–3902.
[12] T. Kikuchi, J. Takagi, H. Isou, T. Ishiyama, N. Miyaura, *Chem. Asian J.* **2008**, *3*, 2082–2090.
[13] P. Steunenberg, V. Jeanneret, Y.-H. Zhu, P. Vogel, *Tetrahedron: Asymmetry* **2005**, *16*, 337–346.
[14] L. A. Paquette, J. A. Oplinger, *Tetrahedron* **1989**, *45*, 107–124.
[15] K. A. Parker, D.-S. Su, *J. Carbohydr. Chem.* **2005**, *24*, 187–197.
[16] R. W. Friesen, C. F. Sturino, A. K. Daljeet, A. Kolaczewska, *J. Org. Chem.* **1991**, *56*, 1944–1947.
[17] U. Majumder, J. M. Cox, H. W. B. Johnson, J. D. Rainier, *Chem. Eur. J.* **2006**, *12*, 1736–1746.
[18] R. W. Friesen, R. W. Loo, C. F. Sturino, *Can. J. Chem.* **1994**, *72*, 1262–1272.
[19] K. H. Dötz, F. Otto, M. J. Nieger, *Organomet. Chem.* **2001**, *621*, 77.
[20] C. Jäkel, K. H. Dötz, *Tetrahedron* **2000**, *56*, 2167–2173.
[21] V. Boucard, K. Larrieu, N. Lubin-Germain, J. Uziel, J. Auge, *Synlett* **2003**, *12*, 1834–1837.
[22] M. A. Tius, J. Gomez-Galeno, X.-q. Z. Gu, H. Javid, *J. Am. Chem. Soc.* **1991**, *113*, 5775–5783.
[23] K. A. Parker, C. A. Coburn, P. D. Johnson, P. Aristoff, *J. Org. Chem.* **1992**, *57*, 5547–5550.
[24] O. J. Hoberg, *Carbohydr. Res.* **1997**, *300*, 365–368.
[25] W. R. Friesen, A. L. Trimble, *J. Org. Chem.* **1996**, *61*, 1165–1168.
[26] D. Crich, T. J. Ritchie, *Tetrahedron* **1988**, *44*, 2319–2328.
[27] U. Lehmann, S. Awasthi, T. Minehan, *Org. Lett.* **2003**, *5*, 2405–2408.
[28] L. K. Billingsley, E. T. Barder, L. S. Buchwald, *Angew. Chem.* **2007**, *119*, 5455–5459; *Angew. Chem. Int. Ed.* **2007**, *46*, 5359–5363.
[29] S. E. Denmark, Ch. S. Regens, T. Kobayashi, *J. Am. Chem. Soc.* **2007**, *129*, 2774–2776.
[30] S. B. Rosenblum, R. Bihovsky, *J. Am. Chem. Soc.* **1990**, *112*, 2746–2748.
[31] S. Czernecki, M.-C. Perlat, *J. Org. Chem.* **1991**, *56*, 6289–6292.
[32] a) A. M. G. Barrett, M. Peña, J. A. Willardsen, *J. Chem. Soc. Chem. Commun.* **1995**, 1147–1148; b) A. M. G. Barrett, M. Peña, J. A. Willardsen, *J. Org. Chem.* **1996**, *61*, 1082–1100.
[33] K. A. Parker, A. T. Georges, *Org. Lett.* **2000**, *2*, 497–499.
[34] D. Balachari, G. A. O'Doherty, *Org. Lett.* **2000**, *2*, 4033–4036.
[35] R. W. Friesen, C. F. Sturino, *J. Org. Chem.* **1990**, *55*, 5808–5810.
[36] S. E. Denmark, C. S. Regens, T. Kobayashi, *Tetrahedron* **2010**, *66*, 4745–4759.
[37] For synthesis of papulacandin derivatives, see: M. van der Kaaden, E. Breukink, R. J. Pieters, *Beilstein J. Org. Chem.* **2012**, *8*, 732–737.
[38] E. Dubois, J.-M. Beau, *Carbohydr. Res.* **1992**, *223*, 157167.
[39] N. Khan, X. Cheng, D. R. Mootoo, *J. Am. Chem. Soc.* **1999**, *121*, 4918–4919.
[40] For facial selective and reactivity of DMDO reactions, see: a) A. Düfert, D. B. Werz, *J. Org. Chem.* **2008**, *73*, 5514–5519; b) L. Alberch, G. Cheng, S.-K. Seo, X. Li, F. P. Boulineau, A. Wei, *J. Org. Chem.* **2011**, *76*, 2532–3547.
[41] a) D. C. Koester, E. Kriemen, D. B. Werz, *Angew. Chem. Int. Ed.* **2013**, *52*, 2985–2989; b) D. C. Koester, D. B. Werz, *Beilstein J. Org. Chem.* **2012**, *8*, 675–682; c) D. B. Koester, M. Leibeling, R. Neufeld, D. B. Werz, *Org. Lett.* **2010**, *12*, 3934–3937.
[42] D. E. Kaelin, O. D. Lopez, S. F. Martin, *J. Am. Chem. Soc.* **2001**, *123*, 6937–6938.

Received: November 3, 2014
Published online on March 3, 2014

Please note: Minor changes have been made to this manuscript since its publication in *Chemistry—A European Journal* Early View. The Editor.

PŘÍLOHA V

Oroszová, B.; Choutka, J.; Pohl, R.; Parkan, K. Modular Stereoselective Synthesis of (1→2)--*C*-Glycosides based on the sp^2–sp^3 Suzuki–Miyaura Reaction. *Chem.-Eur. J.* **2015**, *21* (19), 7043-7047.

ChemPubSoc Europe

DOI: 10.1002/chem.201304304

CHEMISTRY A European Journal Full Paper

C–C Coupling

Cross-Coupling Reaction of Saccharide-Based Alkenyl Boronic Acids with Aryl Halides: The Synthesis of Bergenin

Kamil Parkan,*[a] Radek Pohl,[b] and Martin Kotora*[c]

Abstract: A convenient synthetic pathway enabling D-glucal and D-galactal pinacol boronates to be prepared in good isolated yields was achieved. Both pinacol boronates were tested in a series of cross-coupling reactions under Suzuki–Miyaura cross-coupling conditions to obtain the corresponding aryl, heteroaryl, and alkenyl derivatives in high isolated yields. This methodology was applied to the formal synthesis of the glucopyranoside moiety of papulacandin D and the first total synthesis of bergenin.

Introduction

C-Arylglycosides are an interesting and important class of natural compounds possessing appealing biological properties that may have potential application in many areas of medicinal chemistry. The saccharide moiety of such compounds is usually composed of D-glucose scaffolds and vitexin, orientin etc.,[1] with bergenin[2] and papulacandin D[3] serving as typical examples (Figure 1). However, compounds possessing ribo, manno, and other scaffolds also exist.[4] Despite the fact that numerous synthetic procedures based on a range of methodologies have been described, the development of new and more synthetically robust procedures is still desirable.[5] This interest is driven by the weakness of the available methodologies with respect either to the required reaction conditions or to the substrate scope.

One approach to *C*-arylglycosides is based on the use of the corresponding 1-alkenylboronic acids or their pinacol esters in the Suzuki–Miyaura cross-coupling reaction[6] with suitable substituted aryl and heteroaryl halides, and with alkenyl halides. During the course of our work on that subject, a report on a synthetic procedure for the synthesis of *C*-arylglycosides based on cross-coupling reaction of glucal boronate with aryl(heteroaryl) bromides was published.[7] The report clearly demonstrated the advantages of this approach; however, the scope of this investigation was limited to just six examples. In our report we would like to show that the use of pinacol boronates of D-glucal and also D-galactal offers an improved synthetic protocol and extends the scope of the reaction. Finally, we would like to demonstrate that this methodology can provide synthetic access to various natural *C*-aryl glycosides that have been isolated from a variety of medicinal plants.[8] One such compound of interest is bergenin,[9] which has interesting pharmacological properties such as antihepatotoxic, antiulcerogenic, anti-HIV, antifungal, hepatotoxic, hepatoprotective, antiarrhythmic, neuroprotective, anti-inflammatory, and immunomodulatory activity. Bergenin-containing extracts from *Macaranga peltata* are used in Indian folk medicine for treatment of venereal diseases[10] and bergenin itself is an active pharmaceutical ingredient of a Chinese drug[11] described to be effective against coughs and bronchitis. Due to its broad spectrum

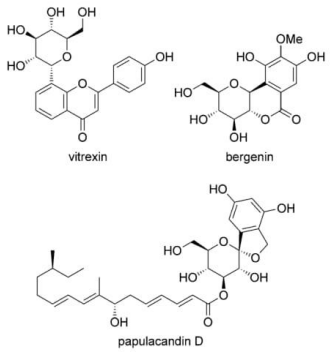


Figure 1. Selected natural *C*-glycosides.

[a] Dr. K. Parkan
Department of Chemistry of Natural Compounds
Institute of Chemical Technology
Technická 5, 166 28 Praha 6 (Czech Republic)
Fax: (+420) 220444422
E-mail: parkank@vscht.cz

[b] Dr. R. Pohl
Institute of Organic Chemistry and Biochemistry
Academy of Sciences of the Czech Republic, v. v. i.
Flemingovo 2, 166 10 Prague 6 (Czech Republic)

[c] Prof. Dr. M. Kotora
Department of Organic Chemistry
Faculty of Science, Charles University in Prague
Hlavova 8, 128 43 Praha 2 (Czech Republic)
Fax: (+420)211-951-326
E-mail: kotora@natur.cuni.cz

Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/chem.201304304.

ChemPubSoc Europe

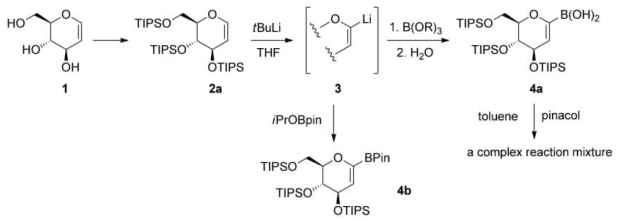
CHEMISTRY A European Journal Full Paper

of biological activities, the development of new and efficient synthetic pathway for its preparation is highly desirable. In this report we would like to show that the approach mentioned above allows the flexible synthesis of various substituted saccharide derivatives and can be applied to the first total synthesis of bergenin.

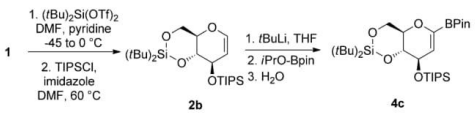
Results and Discussion

Synthesis of the starting boronic acid derivatives

Our initial attention focused on the synthesis of protected D-glucal boronic acid and its pinacol esters (Scheme 1 and Scheme 2). Although boronation of the double bond in D-glucals with B_2Pin_2 catalyzed by an Ir-complex could be used for the synthesis of D-glucal pinacol boronates,[12] we were looking for a more economical method that was also suitable for larger scale syntheses.



Scheme 1. Synthesis of D-glucal boronic acid **4a** and D-glucal pinacol boronate **4b**.

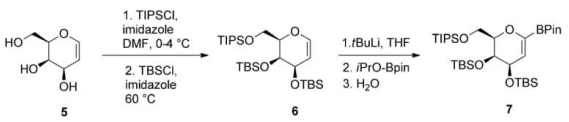


Scheme 2. Synthesis of D-glucal pinacol boronate **4c**.

Initially, we decided to explore pathways for the preparation of boronic acid **4a** (Scheme 1). Because an alkenyl sugar derivative is exposed to *t*BuLi during the course of the reaction, suitable protective groups that were not affected by strong bases during the course of reactions had to be chosen for the saccharide moiety (e.g., methoxymethyl ether (MOM),[13,14] *tert*-butyldiphenylsilyl (TBDPS),[13,15,16,17,18] triisopropylsilyl (TIPS),[13,19,20] di-*tert*-butylsilylene,[13,21] and *tert*-butyldimethylsilyl (TBS)[22,23]. Tri-TIPS-protected glucal **2**, prepared by protection of commercially available D-glucal **1** with TIPS chloride and imidazole, was converted into 1-lithiated intermediate **3** by treatment with 4.0 equivalents of *t*BuLi. A number of trialkyl borates $B(OR)_3$ (R = Me, Et, *i*Pr) were added followed by hydrolysis. In all cases, the boronic acid **4a** was isolated in 75–80% yields, however, although it was obtained with a reasonable purity (ca. 90%), it was difficult to obtain in higher quality due to its instability. Attempts to protect the boronic acid function of **4a** with pinacol under published conditions[6] to obtain tri-TIPS glucal pinacol boronate **4b** were not successful and resulted in the formation of complex reaction mixtures. Interestingly, its formation in high yield was claimed,[7] but its spectral characterization was not reported. In view of the aforementioned results, we decided to approach the synthesis of TIPS-protected glucal boronate **4b** by other means (Scheme 1). The procedure was based on a similar approach, that is, on the reaction of the 1-lithiated glycal **3** with 2-isopropoxy-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (*i*PrOBpin). The reaction proceeded cleanly, providing the desired compound **4b** in an almost quantitative yield. The successful isolation strongly depended on appropriate work-up procedure of the formed reaction mixture, and it was essential to carry out the extraction by using a mixture of toluene and water (for details see the Supporting Information).

In addition to **4b**, boronate **4c** was also prepared by the reaction sequence described above (Scheme 2), that is, D-glucal **1** was converted into the bridged-silyl protected glucal **2b** with $(tBu)_2Si(OTf)_2$[24] followed by silylation of the free hydroxyl group at position C-3 with TIPS chloride and imidazole. Compound **2b** was then treated with *t*BuLi followed by reaction with *i*PrOBpin to give the stable bicyclic boronate **4c** as a crystalline solid, again in almost quantitative yield.

In the next step we wanted to prepare the corresponding fully protected D-galactal pinacol boronate **7** (Scheme 3). However, the primary hydroxyl functionality required protection with a more bulky silyl protective group, because it is known that the TBS-protected galactal tends to succumb to competing α-silyl deprotonation at the 6-position.[16,25,26] To avoid this undesirable competing reaction, we protected the 6-hydroxyl group of commercially available D-galactal **5** with TIPS chloride and imidazole followed by in situ installation of the less bulky TBS groups at the 3- and 4-positions providing the protected derivative **6** in good yield. An analogous approach based on C-1 lithiation of galactal **6** with 3.5 equivalents of *t*BuLi and



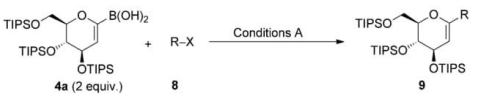
Scheme 3. Synthesis of D-galactal pinacol boronate **7**.

ChemPubSoc Europe

CHEMISTRY A European Journal Full Paper

subsequent excess of *i*PrOBpin was used (Scheme 3). The desired product, the pinacol ester of (1,5-anhydro-2-deoxy-3,4-*O*-di-(*tert*-butyldimethylsilyl)-6-*O*-triisopropylsilyl-D-*lyxo*-hex-1-enitolyl)boronic acid (**7**) was obtained in an almost quantitative yield. All starting boronic acid derivatives **4a–c** and **7** were fully characterized by means of NMR spectroscopy. In the ^{13}C NMR spectra of these compounds, the signal of C-1 is broad and usually absent due to $^{13}C–^{11}B$ spin-spin coupling interaction and additional $^{10}B/^{11}B$ isotope induced chemical shift of C-1 signal. This difficulty can be overcome by acquiring H,C-HMBC spectra for which H-2/C-1, H-5/C-1, and H-3/C-1 cross-peaks can be observed, providing an assignment of the C-1 signal. In addition, NMR spectra of *galacto*-derivatives **7** and **11** measured at ambient temperature provide generally broad signals, likely due to conformational flexibility. Therefore, it is advisable to acquire NMR spectra of these derivatives at higher temperatures (55 °C in $CDCl_3$, 80 °C in CD_3CN).

Table 1. Cross-coupling reaction of **4a** with **8**.



4a (2 equiv.) **8** **9**

A: $[Pd(PPh_3)_2Cl_2]$ (5 mol%), Na_2CO_3 (2 equiv.), DME, 60 °C, 12 h

Entry	Halide **8**	Conditions	Yield of **9** [%][a]
1	**8a**	A	89
2	**8b**	A	84
3	**8c**	A	93
4	**8e**	A	72
5	**8f**	A	76
6	**8g**	A	88
7	**8i**	A	70
8	**8j**	A	78
9	**8k**	A	74
10	**8l**	A	74
11	**8m**	A	71

[a] Isolated yield.

Cross-coupling reactions of 4 with aryl halides 8

Cross-coupling reactions of **4a–c** were performed with a range of aryl, heteroaryl, and alkenyl halides (Figure 2). After extensive screening of various reaction conditions, the best results were achieved with $[Pd(PPh_3)_2Cl_2]$ in the presence of 2 M aqueous solution of Na_2CO_3 in dimethoxyethane at 80 °C (conditions A). The results are summarized in Table 1.

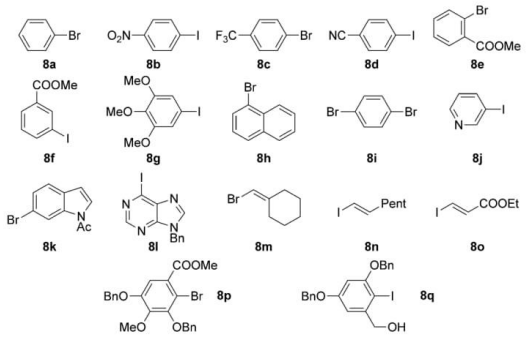


Figure 2. Aryl, heteroaryl, and alkenyl halides **8** tested in the cross-coupling reactions.

Initially, the Suzuki–Miyaura cross-coupling reactions of **4a** with aryl halides were carried out under conditions A (see Table 1) by using Na_2CO_3 as the base. The reactions proceeded well with *para*-substituted aryl bromides and halides **8a–c**, giving the corresponding products **9a–c** in good isolated yields of 89, 84 and 93%, respectively (entries 1–3). Furthermore, the use of *meta*- and *ortho*-substituted aryl halides **8e–g** provided the expected products **9e–g** in good yields of 72, 76, and 88%, respectively (entries 4–6). The reaction with 1,4-dibromobenzene **8i** gave the double-substituted product **9i** in a good 70% yield (entry 7). The Pd-catalyzed cross-coupling reactions with heteroaryl halides **8j–l** proceeded in a similar manner, providing compounds **9j–l** in 78, 74, and 74% isolated yields, respectively (entries 8–10). Finally, the cross-coupling reaction with vinyl bromide **8m** was performed to give **9m** in 71% isolated yield (entry 11). To achieve high conversions of starting material and high yields of the corresponding products, the use of 2.1 equivalents of the boronic acid **4a** was required. Perhaps because of this, partial dimerization of **4a** to dimer **4d** (Figure 3) was observed.[27]

Cross-coupling reactions of **4b** were initially also tested under conditions A. Again, a 1.8-fold excess of **4b** was used to ensure good conversions and yields. Although the cross-coupling reactions with **8b**, **8c**, **8g**, and **8l** provided the corresponding products **9b**, **9c**, **9g**, and **9l** in high isolated yields (88, 87, 88, and 77%, respectively; Table 2, entries 1, 3, 6, and 10), the formation of dimer **4d** in various amounts was again observed (5–20%). To suppress the formation of the latter, conditions B using KOAc as the base were tested.[28] Thus, the reaction of **8b**, **8c**, **8e**, and **8h–j** gave rise to the corresponding products **9b**, **9c**, **9e**, and **9h–j** in good yields (86, 85, 80, 87, 76, and 80%; entries 2, 4, 5, 7, and 8). Although, the reaction rate was considerably slower, the formation of dimer **4d** was not observed.

Cross-coupling reactions of **4c** were carried out under conditions A only (Table 3). Thus, reaction with **8c** to give **10c** pro-

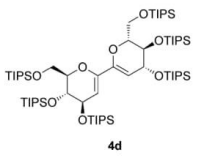
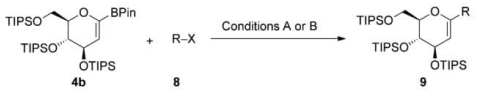


Figure 3. Dimer **4d**.

ChemPubSoc Europe

CHEMISTRY A European Journal Full Paper

Table 2. Cross-coupling reaction of **4b** with **8**.

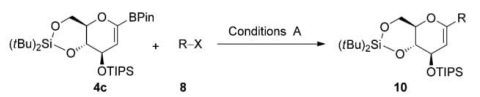


A: $[Pd(PPh_3)_2Cl_2]$ (5 mol%), Na_2CO_3 (2 equiv.), DME, 60 °C, 12 h
B: $[Pd(PPh_3)_2Cl_2]$ (5 mol%), KOAc (1.5 equiv.), DME, 80 °C, 12 h

Entry	Halide **8**	Conditions	Yield of **9** [%][a]
1	**8b**	A	88
2		B	86
3	**8c**	A	87
4		B	85
5	**8e**	B	80
6	**8g**	A	88
7	**8h**	B	87
8	**8i**	B	76
9	**8j**	B	80
10	**8l**	A	77

[a] Isolated yield.

Table 3. Cross-coupling reaction of **4c** with **8**.



A: $[Pd(PPh_3)_2Cl_2]$ (5 mol%), Na_2CO_3 (2 equiv.), DME, 60 °C, 12 h

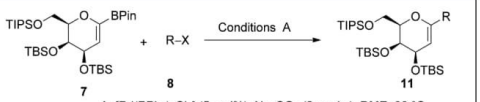
Entry	Halide **8**	Conditions	Yield of **10** [%][a]
1	**8c**	A	87
2	**8n**	A	75
3	**8p**	A	88
4	**8q**	A	87

[a] Isolated yield.

ceeded in good 87% isolated yield (entry 1). This result is comparable to results obtained for **4a** and **4b**. The reaction with **8n** proceeded in a similar manner, providing **10n** in good 75% isolated yield (entry 2). Next, the reactions with sterically hindered aryl halides **8p** and **8q** were attempted (entries 3 and 4). A synthesis of aryl bromide **8p**, which is a potential intermediate for the bergenin synthesis (see below), has not been previously reported and had to be synthesized starting from methyl ester of gallic acid through a reaction sequence involving acetylation, methylation, benzylation, and bromination (for synthetic details see the Supporting Information). Aryl iodide **8q**, a known intermediate in the papulacandin synthesis, was synthesized according to a known procedure.[29] Gratifyingly, in both cases, the cross-coupling reactions proceeded smoothly to give the corresponding products **10p** and **10q** in very good isolated yields of 88 and 87%, respectively.

Finally, we focused on the Pd-catalyzed cross-coupling reactions of fully protected D-galactal pinacol boronate **7** with several aryl halides (Table 4). The reactions of **7** with aryl halides **8b–d** proceeded well, with high isolated yields (80, 85, and 79%, respectively) of the corresponding products **11b–d** (entries 1–3). A similar result was also obtained with methyl (*E*)-3-

Table 4. Cross-coupling reaction of **7** with **8**.



A: $[Pd(PPh_3)_2Cl_2]$ (5 mol%), Na_2CO_3 (2 equiv.), DME, 60 °C

Entry	Halide **8**	Conditions	Yield of **11** [%][a]
1	**8b**	A	80
2	**8c**	A	85
3	**8d**	A	79
4	**8o**	A	84

[a] Isolated yield.

iodopropenoate **8o**, providing the product **11o** in 84% isolated yield (entry 4). Because, to the best of our knowledge, there have not been any reports on cross-coupling of galactal boronates with organyl halides, these results indicate that this methodology could also be applied to saccharide pinacol boronates with other scaffolds.

Synthesis of the papulacandin D glucopyranoside moiety

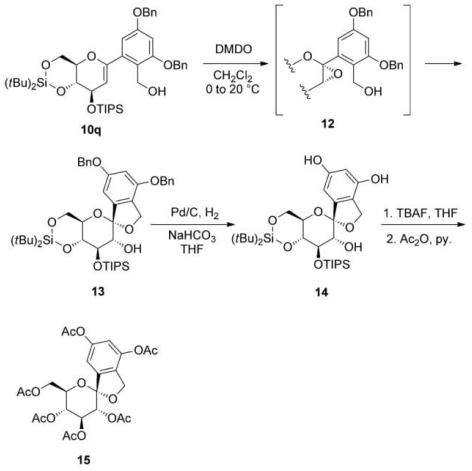
In the last couple of years several approaches to the papulacandin D glucopyranoside moiety have been reported. These methods were based on organolithium addition to gluconolactone,[30,31,32] reductive aromatization of quinols,[33] transformation of arylvinylfurans,[34] or cross-coupling of a vinylstannane[35] or a vinylsilanol with aryl halides.[29,36,37] We envisioned that the papulacandin D glucopyranoside moiety could be also prepared by a cross-coupling reaction of a suitably substituted aryl halide with boronate **4c**. Because we have shown that cross-coupling between boronate **4c** and iodobenzene **8q** (Table 3, entry 3) proceeded successfully to give **10q** with high isolated yield (88%), further conversion of this intermediate was undertaken (Scheme 4). In the next step, the double bond was oxidized with dimethyldioxirane (DMDO)[35] under mild conditions. The epoxidation proceeded stereoselectively to provide α-epoxide **12**, which was immediately opened by intramolecular attack of the pendant benzylic hydroxyl to furnish the desired spiroketal **13** as a single anomer. The previous synthesis of **13** led to a mixture of α and β-anomers, which had to be epimerized under acidic conditions[37] to obtain the required anomer. We assume that the formation of the single diastereoisomer was caused by the fixed conformation of the bicyclic derivative that would not cause axial-equatorial flip on the pyranose ring. Debenzylation of **13** led to the formation of compound **14** in 93% isolated yield. Subsequent desilylation followed by peracetylation provided **15** in 89% yield, which is a known intermediate in synthesis of papulacandin D.[38]

Synthesis of bergenin

Prior to the synthetic endeavors that would lead to the synthesis of bergenin, transformations of the cross-coupling products into stereoselectively pure arylglycosides were attempted.

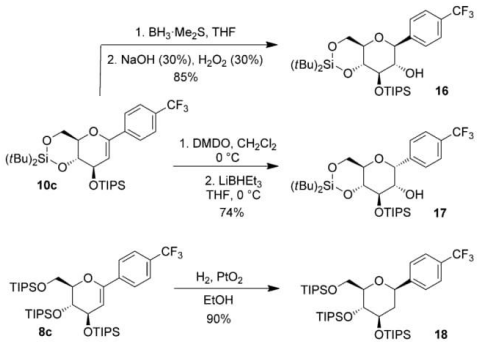
ChemPubSoc Europe

CHEMISTRY A European Journal Full Paper



Scheme 4. Synthesis of the papulacandin D glycopyranoside moiety **15**.

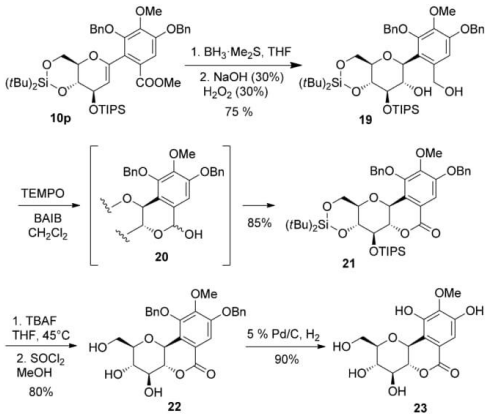
Compound **10c**, with the bridged-silyl protecting group to keep the molecule locked in one conformation, served as a model (Scheme 5). It was found that hydroboration[39] of the double bond in **10c** with $BH_3{\cdot}Me_2S$ complex followed by oxidation with alkaline hydrogen peroxide gave aryl-β-*C*-glycoside



Scheme 5. Transformations of the glucal double bond in **8c** and **10c**.

16 as a single stereoisomer (4.32 ppm (br. d, $J_{1,2}=9.4$ Hz, 1H, H-1)). The formation of the opposite anomer (5.16 ppm (br. d, $J_{1,2}=3.8$ Hz, 1H, H-1)), aryl-α-*C*-glycoside **17**, was achieved by epoxidation of the double bond with DMDO[40] followed by subsequent cleavage of the formed epoxide ring with lithium triethylborohydride.[41] It should be added that the reactions mentioned above were also carried out with the tri-TIPS-protected derivative **8c**, but this led to the formation of intractable reaction mixtures. This is clearly the result of conformational flexibility of the starting material **8c**. On the other hand, hydrogenation[42] of **8c** with H_2 on PtO_2 also proceeded stereoselectively to give aryl-β-*C*-2-deoxy-glycoside **18** (4.60 ppm (dd, $J_{1,2}=11.2$ Hz, $J_{1,3}$ 2.6 Hz, 1H, H-1)).

In view of the aforementioned results, the synthesis of bergenin was executed as follows (Scheme 6). The cross-coupling product **10p** was hydroborated with $BH_3{\cdot}Me_2S$, followed by oxidation of the C–B bond to furnish arylglucoside **19** as a single



Scheme 6. Synthesis of bergenin **23**.

diastereoisomer. ^1H and ^{13}C NMR spectra of **19** measured at 0 °C in $CDCl_3$ revealed the existence of two isomers. Because vicinal coupling constants of sugar protons in both isomers were similar, we concluded that the isomerism is caused by hindered rotation of the aryl moiety. Unfortunately, NOE measurements did not provide more detailed information on the orientation of the aryl part for individual isomers. Subsequent selective oxidation of the benzyl alcohol moiety was accompanied by cyclization to lactol **20**, which was further oxidized to give lactone **21** in 85% isolated yield. The silyl protecting group was then removed to give **22** (80%) and, finally, reductive debenzylation provided bergenin **23** in 90% isolated yield. Thus, bergenin was synthesized in six steps from bromide **8p** in 40% overall yield.

Conclusion

We have developed an efficient method for preparation of aryl- or alkenyl-*C*-glucals and -*C*-galactals by using glucal or galactal boronates as the key synthons in cross-coupling reactions performed under Suzuki–Miyaura conditions. Partial dimerization of the boronates observed when K_2CO_3 was used as the base could be prevented by the use of KOAc. A possibility of further functionalization of the double bond in the cross-coupling products (1-aryl-*C*-glycals) was explored and resulted in diastereoselective syntheses of α- or β-glycosides in good yields. These results enabled the synthetic potential of this

ChemPubSoc Europe

CHEMISTRY A European Journal Full Paper

methodology to be demonstrated in two syntheses. First, it was applied in an alternative synthesis of papulacandin D glucopyranoside intermediate **15** in 64% overall yield. Second, the cross-coupling reaction was utilized as a crucial step for the first total synthesis of bergenin **23** in 40% overall yield in only six steps from bromide **8p**.

Acknowledgements

This work was supported by the Grant Agency of the Czech Republic (grant No. P207/12/P713 and 13-15915S).

Keywords: C–C coupling · glycosides · natural products · protecting groups · synthetic methods

[1] Y. Zhang, J. Jiao, C. Liu, X. Wu, Y. Zhang, *Food Chem.* **2008**, *107*, 1326–1336.
[2] W. R. Carruthers, J. E. Hay, L. J. Haynes *Chem. Ind.* **1957**, 76–77.
[3] P. Traxler, J. Gruner, J. A. Auden, *J. Antibiot.* **1977**, *30*, 289–296.
[4] a) A. Garcia, L. Lenis, C. Jiménez, C. Debitus, E. Quinoá, R. Riguera *Org. Lett.* **2000**, *2*, 2765–2767; b) T. Nishikawa, Y. Koide, A. Kanakudo, H. Yoshimura, M. Isobe, *Org. Biomol. Chem.* **2006**, *4*, 1268–1277; c) K. P. Kaliappan, A. V. Subrahmanyam, *Org. Lett.* **2007**, *9*, 1121–1124.
[5] For reviews, see: a) D. Y. W. Lee, M. He, *Curr. Top. Med. Chem.* **2005**, *5*, 1333–1350; b) T. Bililign, B. R. Griffith, J. S. Thorson, *Nat. Prod. Rep.* **2005**, *22*, 742–760; c) C. Len, M. Mondon, J. Lebreton, *Tetrahedron* **2008**, *64*, 7453–7475; d) J. Štambaský, M. Hocek, P. Kočovský, *Chem. Rev.* **2009**, *109*, 6729–6764.
[6] a) A. Suzuki, *Pure Appl. Chem.* **1991**, *63*, 419–422; b) N. Miyaura, A. Suzuki, *Chem. Rev.* **1995**, *95*, 2457–2483; c) A. Suzuki, *J. Organomet. Chem.* **1999**, *576*, 147–168.
[7] S. Sakamaki, E. Kawanishi, S. Nomura, T. Ishikawa, *Tetrahedron* **2012**, *68*, 5744–5753.
[8] a) K. Dhalwal, M. V. Shinde, S. Y. Biradar, R. K. Mahadik, *J. Food Compos. Anal.* **2008**, *21*, 496–500; b) A. Wibowo, N. Ahmat, A. S. Hamzah, A. S. Sufian, N. H. Ismail, R. Ahmad, F. M. Jaafar, H. Takayama, *Fitoterapia* **2011**, *82*, 676–681; c) H.-K. Lim, H.-S. Kim, H.-S. Choi, S. Oh, J. Choi, *J. Ethnopharmacol.* **2000**, *72*, 469–474.
[9] D. K. Patel, K. Patel, R. Kumar, M. Gadewar, V. Tahilyani, *Asian Pac. J. Trop. Dis.* **2012**, *2*, 163–167.
[10] R. N. Chopra, S. L. Maya, I. C. Chopra, *Glossary of Indian Medicinal Plants*; Council of Scientific and Industrial Research, New Delhi **1956**, p. 156.
[11] Y. Li, J. Liu, G. Song, K. Li, K. Zhanga, B. Ye, *Anal. Methods* **2013**, *5*, 3895–3902.
[12] T. Kikuchi, J. Takagi, H. Isou, T. Ishiyama, N. Miyaura, *Chem. Asian J.* **2008**, *3*, 2082–2090.
[13] P. Steunenberg, V. Jeanneret, Y.-H. Zhu, P. Vogel, *Tetrahedron: Asymmetry* **2005**, *16*, 337–346.
[14] L. A. Paquette, J. A. Oplinger, *Tetrahedron* **1989**, *45*, 107–124.
[15] K. A. Parker, D.-S. Su, *J. Carbohydr. Chem.* **2005**, *24*, 187–197.
[16] R. W. Friesen, C. F. Sturino, A. K. Daljeet, A. Kolaczewska, *J. Org. Chem.* **1991**, *56*, 1944–1947.
[17] U. Majumder, J. M. Cox, H. W. B. Johnson, J. D. Rainier, *Chem. Eur. J.* **2006**, *12*, 1736–1746.
[18] R. W. Friesen, R. W. Loo, C. F. Sturino, *Can. J. Chem.* **1994**, *72*, 1262–1272.
[19] K. H. Dötz, F. Otto, M. J. Nieger, *Organomet. Chem.* **2001**, *621*, 77.
[20] C. Jäkel, K. H. Dötz, *Tetrahedron* **2000**, *56*, 2167–2173.
[21] V. Boucard, K. Larrieu, N. Lubin-Germain, J. Uziel, J. Auge, *Synlett* **2003**, *12*, 1834–1837.
[22] M. A. Tius, J. Gomez-Galeno, X.-q. Z. Gu, H. Javid, *J. Am. Chem. Soc.* **1991**, *113*, 5775–5783.
[23] K. A. Parker, C. A. Coburn, P. D. Johnson, P. Aristoff, *J. Org. Chem.* **1992**, *57*, 5547–5550.
[24] O. J. Hoberg, *Carbohydr. Res.* **1997**, *300*, 365–368.
[25] W. R. Friesen, A. L. Trimble, *J. Org. Chem.* **1996**, *61*, 1165–1168.
[26] D. Crich, T. J. Ritchie, *Tetrahedron* **1988**, *44*, 2319–2328.
[27] U. Lehmann, S. Awasthi, T. Minehan, *Org. Lett.* **2003**, *5*, 2405–2408.
[28] L. K. Billingsley, E. T. Barder, L. S. Buchwald, *Angew. Chem.* **2007**, *119*, 5455–5459; *Angew. Chem. Int. Ed.* **2007**, *46*, 5359–5363.
[29] S. E. Denmark, Ch. S. Regens, T. Kobayashi, *J. Am. Chem. Soc.* **2007**, *129*, 2774–2776.
[30] S. B. Rosenblum, R. Bihovsky, *J. Am. Chem. Soc.* **1990**, *112*, 2746–2748.
[31] S. Czernecki, M.-C. Perlat, *J. Org. Chem.* **1991**, *56*, 6289–6292.
[32] a) A. M. G. Barrett, M. Peña, J. A. Willardsen, *J. Chem. Soc. Chem. Commun.* **1995**, 1147–1148; b) A. M. G. Barrett, M. Peña, J. A. Willardsen, *J. Org. Chem.* **1996**, *61*, 1082–1100.
[33] K. A. Parker, A. T. Georges, *Org. Lett.* **2000**, *2*, 497–499.
[34] D. Balachari, G. A. O'Doherty, *Org. Lett.* **2000**, *2*, 4033–4036.
[35] R. W. Friesen, C. F. Sturino, *J. Org. Chem.* **1990**, *55*, 5808–5810.
[36] S. E. Denmark, C. S. Regens, T. Kobayashi, *Tetrahedron* **2010**, *66*, 4745–4759.
[37] For synthesis of papulacandin derivatives, see: M. van der Kaaden, E. Breukink, R. J. Pieters, *Beilstein J. Org. Chem.* **2012**, *8*, 732–737.
[38] E. Dubois, J.-M. Beau, *Carbohydr. Res.* **1992**, *223*, 157167.
[39] N. Khan, X. Cheng, D. R. Mootoo, *J. Am. Chem. Soc.* **1999**, *121*, 4918–4919.
[40] For facial selective and reactivity of DMDO reactions, see: a) A. Düfert, D. B. Werz, *J. Org. Chem.* **2008**, *73*, 5514–5519; b) L. Alberch, G. Cheng, S.-K. Seo, X. Li, F. P. Boulineau, A. Wei, *J. Org. Chem.* **2011**, *76*, 2532–3547.
[41] a) D. C. Koester, E. Kriemen, D. B. Werz, *Angew. Chem. Int. Ed.* **2013**, *52*, 2985–2989; b) D. C. Koester, D. B. Werz, *Beilstein J. Org. Chem.* **2012**, *8*, 675–682; c) D. B. Koester, M. Leibeling, R. Neufeld, D. B. Werz, *Org. Lett.* **2010**, *12*, 3934–3937.
[42] D. E. Kaelin, O. D. Lopez, S. F. Martin, *J. Am. Chem. Soc.* **2001**, *123*, 6937–6938.

Received: November 3, 2014
Published online on March 3, 2014

Please note: Minor changes have been made to this manuscript since its publication in *Chemistry—A European Journal* Early View. The Editor.

PŘÍLOHA VI

Šnajdr, I.; Parkan, K.; Hessler, F.; Kotora, M. Cross-metathesis Reaction of α- and β-Vinyl *C*-glycosides with Alkenes. *Beilstein J. Org. Chem.* **2015**, *11*, 1392-1397.

BEILSTEIN JOURNAL OF ORGANIC CHEMISTRY

Cross-metathesis reaction of α- and β-vinyl *C*-glycosides with alkenes

Ivan Šnajdr[1], Kamil Parkan[2], Filip Hessler[1] and Martin Kotora[*1]

Full Research Paper

Open Access

Address:
[1]Department of Organic Chemistry, Charles University in Prague, Hlavova 8, 153 00 Praha 2, Czech Republic, Fax: (+) 420 221 951 326 and [2]Department of Chemistry of Natural Compounds, University of Chemistry and Technology, Prague, Technická 5, 160 00 Praha 6, Czech Republic

Email:
Martin Kotora* - martin.kotora@natur.cuni.cz

* Corresponding author

Keywords:
C-glycosides; catalysis; carbohydrates; cross-metathesis; ruthenium

Beilstein J. Org. Chem. **2015,** *11,* 1392–1397.
doi:10.3762/bjoc.11.150

Received: 17 April 2015
Accepted: 20 July 2015
Published: 10 August 2015

This article is part of the Thematic Series "Progress in metathesis chemistry II".

Guest Editor: K. Grela

Abstract

Cross-metathesis of α- and β-vinyl *C*-deoxyribosides and α-vinyl *C*-galactoside with various terminal alkenes under different conditions was studied. The cross-metathesis of the former proceeded with good yields of the corresponding products in $ClCH_2CH_2Cl$ the latter required the presence of CuI in CH_2Cl_2 to achieve good yields of the products. A simple method for the preparation of α- and β-vinyl *C*-deoxyribosides was also developed. In addition, feasibility of deprotection and further transformations were briefly explored.

Introduction

Natural and unnatural *C*-substituted glycosides are important compounds with a plethora of attractive biological properties and they often have been used as artificial DNA components [1]. Among various synthetic procedures providing *C*-deoxyribosides the one based on the use of a protected *C*-(2-deoxyribofuranosyl)ethyne, easily accessed by a coupling of a protected D-ribosyl halide and ethynylmagnesium chloride [2], offers a considerable synthetic flexibility since the triple bond could be transformed directly into various functional groups [3-13]. Thus the ethyne moiety was used in [2 + 2 + 2] cyclotrimerization to yield aryl *C*-deoxyribosides [3] and in a Sonogashira reaction for the synthesis of butenolidyl *C*-deoxyribosides [4]. Substituted alkynyl *C*-deoxyribosides [5,10,11] were used in other types of cycloaddition reactions providing indolyl *C*-deoxyribosides [6], cyclopentenonyl *C*-deoxyribosides [9], triazolyl *C*-deoxyribosides [12,13], carboranyl *C*-deoxyribosides [7], and finally also in Diels–Alder reaction with cyclobutadiene derivatives [8]. Despite of the above mentioned transformations, alkynyl *C*-deoxyribosides could also be used as a suitable starting material for hitherto rarely studied transformations.

One such a potential transformation is their hydrogenation to the corresponding vinyl *C*-deoxyribosides that could serve as

intermediates for further functionalization. Interestingly, just a couple of reports regarding synthesis of vinyl *C*-deoxyribosides have been published so far. Among them is the Lindlar catalyst mediated hydrogenation of ethynyl β-*C*-deoxyriboside (prepared by a rather lengthy synthetic procedure) that provided vinyl β-*C*-deoxyribofuranosides [9]. Another procedure leading to pure vinyl β-*C*-deoxyribofuranoside was based on transformation of 6-*O*-*tert*-butyldiphenylsilyl-3,5-dideoxy-5-iodo-L-lyxo-hexofuranose [14]. A reaction sequence relying on Horner–Wadsworth–Emmons/ring closure–halogenation/Ramberg–Bäcklund/Wittig reaction gave rise to the equimolar mixture of styryl α- and β-*C*-deoxyribosides [15].

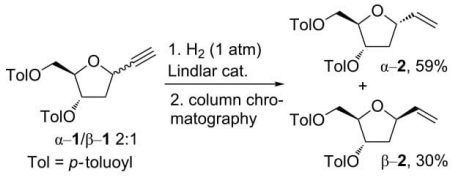
Finally, there is also a method utilizing an excess of vinylmagnesium bromide in the reaction with 3,5-bis-*O*-TBDPS-protected 2-deoxy-D-ribofuranose giving rise to a mixture of diastereoisomeric diols. The diasteroisomers were separated and cyclized in the presence of MsCl to the corresponding vinyl α-*C*-deoxyriboside α-**2** and β-*C*-deoxyriboside β-**2** [16]. As far as further transformation of vinyl *C*-deoxyribosides relying on the metathesis reaction is concerned, only one paper dealing with successful cross-metathesis with 4-vinyl-5-methyl-2-oxazolone has been reported [16]. This finding is rather surprising, because the metathesis reaction has been frequently used as a tool for chain elongation of various saccharides [17].

In view of the aforementioned, it is obvious that a development of a new and simple route to anomerically pure α- and β-vinyl *C*-deoxyribosides is desirable as well as to study the scope of their participation in cross-metathesis reactions. This procedure could thus open a new pathway for preparation of a number of alkenyl and alkyl *C*-deoxyriboside derivatives.

Results and Discussion

Synthesis of vinyl α- and β-*C*-deoxyribosides **2**

Although the simplest pathway for the preparation of vinyl α-*C*-deoxyriboside α-**2** and β-*C*-deoxyriboside β-**2** seems the reaction of a halogenose with ethynylmagnesium chloride followed by hydrogenation, this approach has not been reported yet (to the best of our knowledge). Presumably, difficulties regarding separation of a mixture of ethynyl α-*C*-deoxyriboside α-**1** and β-*C*-deoxyriboside β-**1** precluded any attempts. Notwithstanding this, we decided to test this approach. We found that hydrogenation of the epimeric mixture of ethynyl α-*C*-deoxyriboside α-**1** and β-*C*-deoxyriboside β-**1** on Lindlar catalyst at 1 atm of H_2 provided, as expected, a mixture of the corresponding vinyl α-*C*-deoxyriboside α-**2** and vinyl β-*C*-deoxyriboside β-**2**. The mixture was easily separated into pure epimers (59% for α-**2** and 30% β-**2**) just by using a simple column chromatography (Scheme 1). Their identity was confirmed by comparison of the obtained spectral data with the published ones for related compounds [9,14,16]. This two-step reaction sequence is very simple and provides access to both epimers from a simply available starting material.



Scheme 1: Synthesis of vinyl *C*-deoxyribosides α-**2** and β-**2**.

Cross-metathesis reactions with vinyl α- and β-*C*-deoxyribosides **2**

There is a general interest in synthesis of borylated [18] or carboranylated [8,19] saccharides and derivatives thereof because of their interesting properties. Bearing this in mind, we decided to explore the possibility of attaching the carborane moiety by using a cross-metathesis reaction. Cross-metathesis of α-**2** with the allylated carborane **3a** (Figure 1) was used as a model reaction [20-22]. Since it has been shown that the solvent [23] may profoundly affect the course of the cross-metathesis reaction in terms of activity and selectivity, we screened various reaction conditions to secure the highest yield of the desired cross-product of the reaction between α-**2** and **3a** (Table 1). The reactions were carried out in the presence of Hoveyda–Grubbs 2nd generation catalyst (HG II), which has been shown to be the best catalyst for cross-metathesis reactions [24]. Running the reaction under the standard conditions in dichloromethane or toluene under reflux, the desired cross-metathesis product α-**4a** was isolated in low 10% and 3% yields (Table 1, entries 1 and 2). Although it has been observed that the use of octafluorotoluene [23,25-27] as the solvent had a positive effect on yields, its use provided α-**4a** in a low 12% yield (Table 1, entry 3), but its use under microwave irradiation [26,28-30] gave rise to α-**4a** in 33% isolated yield (Table 1, entry 4). A similar result (36% yield) was obtained with a 1:1 octafluorotoluene/$ClCH_2CH_2Cl$ mixture (Table 1, entry 5). Although microwave irradiation had a positive effect on the cross-metathesis reaction, see examples above, carrying out the reaction in a mixture of 1:1 octafluorotoluene/$ClCH_2CH_2Cl$ under irradiation provided α-**4a** in only 3% (Table 1, entry 6). Finally, carrying out the reaction in pure $ClCH_2CH_2Cl$ under reflux furnished the product in a nice 70% isolated yield (Table 1, entry 7), while microwave irradiation resulted in decreased yield of 58% (Table 1, entry 8). According to the obtained data in some cases microwave irradiation had a positive effect on the course of the

Beilstein J. Org. Chem. **2015,** *11,* 1392–1397.

reaction (Table 1, entry 4), whereas as in some cases it had a detrimental effect (Table 1, entries 6 and 8). Currently we do not know how to account for these observations; however, decomposition of the catalyst under these conditions cannot be excluded. In all of the above mentioned cases the unreacted starting material was recovered from the reaction mixtures.

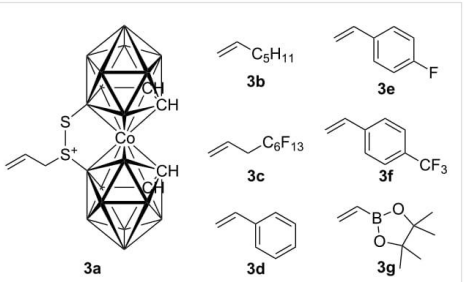
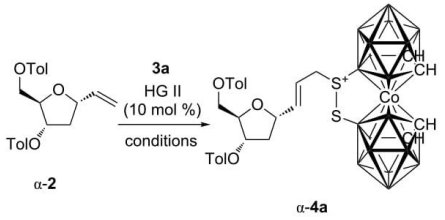


Figure 1: Alkenes **3** used in cross-metathesis reactions with **2**.

Table 1: Conditions tested for cross-metathesis of α-**2** with **3a**.

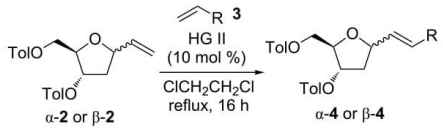


Entry	Reaction conditions[a]	Yield (%)[b]
1	CH_2Cl_2, reflux, 24 h	10
2	toluene, reflux, 24 h	3
3	$C_6F_5CF_3$, reflux, 16 h	12
4	$C_6F_5CF_3$, mw[c]	33
5	$C_6F_5CF_3$/$ClCH_2CH_2Cl$ 1:1, 16 h	36
6	$C_6F_5CF_3$/$ClCH_2CH_2Cl$ 1:1, mw[c]	3
7	$ClCH_2CH_2Cl$, reflux, 12 h	70
8	$ClCH_2CH_2Cl$, mw, 110 °C, 2 h[c]	58

[a]α-**2** (0.26 mmol), solvent (5 mL). [b]Isolated yields. [c]mw = microwave irradiation.

With these results in hand we decided to screen the scope of cross-metathesis reactions with other terminal alkenes **3b**–**3g** (Figure 1, Table 2). Our first choice was 1-heptene (**3b**), which reacted under the above mentioned conditions (i.e., with HG II in $ClCH_2CH_2Cl$ under reflux) to give the corresponding product α-**4b** in 59% isolated yield (Table 2, entry 2). We also carried out the reaction with perfluorohexylpropene (**3c**), because of our long term interest in the synthesis of perfluoroalkylated compounds [21,30-34] and their application [35]. The reaction furnished the desired compound α-**4c** in a good 50% isolated yield (Table 2, entry 3). Next we switched our attention to styrenes **3d**–**3f**. In all cases the corresponding products α-**4d**–α-**4f** were obtained in good 68, 60, and 59% isolated yields, respectively (Table 2, entries 4–6). Finally, cross-metathesis with vinylboronic acid pinacol ester (**3g**) was attempted. Once again the reaction proceeded well, furnishing boronate α-**4g** in 66% isolated yield (Table 2, entry 7). Then we turned to reactions of the above mentioned terminal alkenes with β-**2**. In all cases the corresponding products were obtained in good isolated yields in the range similar to α-**2**. The metathesis with the allylated carborane **3a** provided β-**4a** in 77% yield (Table 2, entry 8). The reaction with 1-heptene (**3b**) and perfluorohexylpropene (**3c**) gave the corresponding products β-**4b** and β-**4c** in 64 and 48% yields (Table 2, entries 9 and 10). In a similar manner also the styrenes **3d**–**3f** furnished the desired products β-**4d**–β-**4f** in 69, 58, and 61% yields, respectively (Table 2, entries 11–13). Similarly compound **3g** reacted well providing the boronate β-**4g** in a nice 64% yield (Table 2, entry 14). The latter boronate was subjected to coupling with iodobenzene under Suzuki conditions and the corresponding product β-**4d** was obtained in 51% isolated yield.

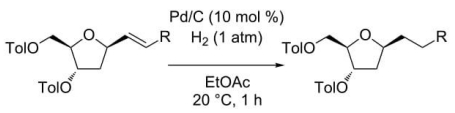
Table 2: Cross-coupling of **2α** and β-**2** with alkenes **3**.



Entry	**2**	**3**	**4**	Yield (%)[a]
1	α-**2**	**3a**	α-**4a**	74
2		**3b**	α-**4b**	59
3		**3c**	α-**4c**	50
4		**3d**	α-**4d**	68
5		**3e**	α-**4e**	60
6		**3f**	α-**4f**	59
7		**3g**	α-**4g**	66
8	β-**2**	**3a**	β-**4a**	77
9		**3b**	β-**4b**	64
10		**3c**	β-**4c**	48
11		**3d**	β-**4d**	69
12		**3e**	β-**4e**	58
13		**3f**	β-**4f**	61
14		**3g**	β-**4g**	64

[a]Isolated yields.

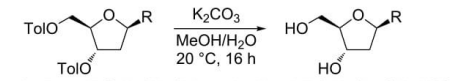
With the *C*-deoxyribosides on hand, the feasibility of catalytic hydrogenation was also briefly explored. Compounds possessing the heptenyl side chain (β-**4b**), tridecafluorononenyl side chain (β-**4c**), and the styryl side chain (β-**4d**) were chosen as substrates. In all cases the hydrogenation by using Pd/C under low pressure of hydrogen (1 atm) proceeded uneventfully to give rise to products with the saturated side chain β-**5b**, β-**5c**, and β-**5d** in good isolated yields of 88, 57, and 87% (Scheme 2). In addition, deprotection of the toluoyl groups was tested on compounds bearing an unsaturated side chain such as β-**4e** and a saturated side chain such as β-**5b** by using K_2CO_3 in a mixture of MeOH/H_2O. In both cases the reaction proceeded almost quantitatively providing the corresponding *C*-deoxyribosides β-**6e** and β-**7b** in 89 and 93% isolated yields (Scheme 3).



β-**4b**, R = *n*-pentyl
β-**4c**, R = $CF_3(CF_2)_5CH_2$
β-**4d**, R = Ph

β-**5b**, R = *n*-pentyl, 88%
β-**5c**, R = $CF_3(CF_2)_5CH_2$, 57%
β-**5d**, R = Ph, 87%

Scheme 2: Hydrogenation of β-**4b**–β-**4d** to β-**5b**–β-**5d**.



β-**4e**, R = 4-F-C_6H_4CH=CH
β-**5b**, R = *n*-heptyl

β-**6e**, R = 4-F-C_6H_4CH=CH, 89%
β-**7b**, R = *n*-heptyl, 93%

Scheme 3: Deprotection of β-**4e** and β-**5b** to β-**6e** and β-**7b**.

Cross-metathesis reactions with 1-(tetra-*O*-acetyl-α-D-galactopyranosyl)ethene (**8**)

There have been, to the best of our knowledge, just a handful of reports of cross-metathesis reactions of other vinyl *C*-glycosides. Among these reports metatheses of 1-(D-glucopyranosyl)prop-2-ene derivatives with various alkenes [36-40] and one report regarding a 1-(α-D-galactopyranosyl)ethene derivative with allyl amines [41]. Because of our interest in the synthesis of various D-galactose derivatives, we decided to explore the scope of their metathesis reaction with several different alkenes.

The starting material – 1-(tetra-*O*-acetyl-α-D-galactopyranosyl)ethene (**8**) – was prepared according to the previously reported procedure. A solution of penta-*O*-acetyl-D-galactose, allyltrimethylsilane and $BF_3{\cdot}Et_2O$ was refluxed in acetonitrile giving a 6:1 mixture of α- and β-epimers of 1-(tetra-*O*-acetyl-D-galactopyranosyl)prop-2-ene in 98% yield. Zemplén deacetylation afforded quantitatively the same mixture of epimeric 1-(D-galactopyranosyl)prop-2-enes that were dissolved in ethanol and treated with ether. This allowed the α-epimer to precipitate and it could afterwards be isolated as a pure crystalline product in 60% yield [42]. Its acetylation afforded 1-(tetra-*O*-acetyl-α-D-galactopyranosyl)prop-2-ene in high yield and purity. It was then isomerized [43] to 1-(tetra-*O*-acetyl-α-D-galactopyranosyl)prop-1-ene (80% yield) that was subjected to cross-metathesis with ethene to give the desired compound **8** in 82% yield [41].

The above mentioned metathesis conditions – HG II, reflux in 1,2-dichloroethane – were also tested in the reactions of **8** with alkenes **3d**–**3f** (Table 3). However, the yields of the corresponding products **9d**–**9f** were around 60% (Table 3, entries 1–3, column IV). Switching the solvent to dichloromethane did not have any substantial effect on the yields of the corresponding products (57–70%) (Table 3, entries 1–3, column V). Moreover, in all above mentioned cases the starting material remained partially unreacted and could not be easily separated from the desired products.

Table 3: Cross-metathesis of **8** with alkenes **3**.

Entry	**3**	**9**	Yield (%)[a] (in $ClCH_2CH_2Cl$)	Yield (%)[a] (in CH_2Cl_2)
1	**3d**	**9d**	58	70
2	**3e**	**9e**	61	57
3	**3f**	**9f**	56	58

[a]Isolated yield.

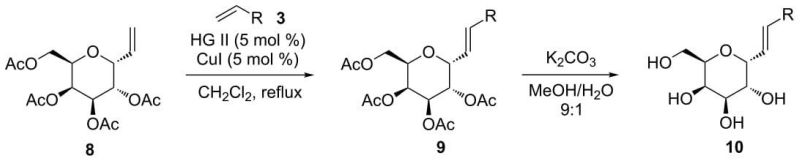
A considerable improvement was observed when the metatheses were run in dichloromethane and in the presence of CuI (Table 4) [44]. In all cases the reactions provided the corresponding products in very good isolated yields. The first metatheses were carried out with 1-heptene (**3b**) and perfluorohexylpropene (**3c**) furnishing **9b** and **9c** in nice 80 and 79% isolated yields, respectively (Table 4, entries 1 and 2). Then we switched our attention to styrenes **3d**–**3f**. In all cases the corresponding products **9d**–**9f** were obtained in good 82, 79, and 78% isolated yields, respectively (Table 4, entries 3–5). In addition, in all cases deprotection under basic conditions provided the corresponding *C*-alkenylated D-galactoses in very good isolated yields (86–93%).

Conclusion

In conclusion, the cross-metathesis reaction of anomerically pure vinyl *C*-deoxyriboses (easily accessible from a mixture of ethynyl α/β-*C*-deoxyribosides) with alkenes bearing various

Beilstein J. Org. Chem. **2015,** *11,* 1392–1397.

Table 4: Cross-metathesis of **8** with alkenes **3** in the presence of CuI.



Entry	3	9	Yield (%)[a]	10	Yield (%)[a]
1	**3b**	**9b**	80	**10b**	88
2	**3c**	**9c**	79	**10c**	80
3	**3d**	**9d**	82	**10d**	93
4	**3e**	**9e**	79	**10e**	90
5	**3f**	**9f**	78	**10f**	87

[a]Isolated yield.

functional groups proceeded in the presence of a catalytic amount of HG II catalysts in refluxing 1,2-dichloroethane giving rise to the corresponding alkenylated derivatives in good yields and without loss of stereochemical information. Deprotection as well as hydrogenation is also feasible providing the desired compounds as exemplified in selected examples. In addition, this methodology is also applicable to vinyl α-*C*-D-galactopyranoside, albeit the best results were obtained when the reaction was carried out in refluxing dichloromethane and in the presence of CuI. Deprotection of the prepared alkenylated derivatives proceeded without any problems.

Since homodimerization of the starting alkenes **2** and **8** has not been observed under the reaction conditions used (however, we cannot exclude that minor undetected amounts of homodimers of **2** or **8** were formed), they could be preliminarily considered as type II or III olefins according to the Grubbs classification of olefins [45].

Supporting Information

Supporting Information File 1

Detailed experimental procedures for all compounds, characterization of the synthesized compounds, and copies of $^{1}H/^{13}C$ NMR spectra for all compounds.
[http://www.beilstein-journals.org/bjoc/content/supplementary/1860-5397-11-150-S1.pdf]

Acknowledgements

This work was supported by Czech Science Foundation (grant No. 13-15915S and 15-17572S).

References

1. Teo, Y. N.; Wilson, J. N.; Kool, E. T. *J. Am. Chem. Soc.* **2009,** *131,* 3923–3933. doi:10.1021/ja805502k
2. Wamhoff, H.; Warnecke, H. *ARKIVOC* **2001,** *9,* 5–100.
3. Novák, P.; Čihalová, S.; Otmar, M.; Hocek, M.; Kotora, M. *Tetrahedron* **2008,** *64,* 5200–5207. doi:10.1016/j.tet.2008.03.046
4. Novák, P.; Pour, M.; Špulák, M.; Votruba, I.; Kotora, M. *Synthesis* **2008,** 3465–3472. doi:10.1055/s-0028-1083181
5. Bobula, T.; Hocek, M.; Kotora, M. *Tetrahedron* **2010,** *66,* 530–536. doi:10.1016/j.tet.2009.11.030
6. Nečas, D.; Hidasová, D.; Hocek, M.; Kotora, M. *Org. Biomol. Chem.* **2011,** *9,* 5934–5937. doi:10.1039/c1ob05844d
7. Šnajdr, I.; Janoušek, Z.; Takagaki, M.; Císařová, I.; Hosmane, N. S.; Kotora, M. *Eur. J. Med. Chem.* **2014,** *83,* 389–397. doi:10.1016/j.ejmech.2014.06.005
8. Hessler, F.; Kulhavá, L.; Císařová, I.; Otmar, M.; Kotora, M. *Synth. Commun.* **2014,** *44,* 1232–1239. doi:10.1080/00397911.2013.848896
9. Takase, M.; Morikawa, T.; Abe, H.; Inouye, M. *Org. Lett.* **2003,** *5,* 625–628. doi:10.1021/ol027210w
10. Adamo, M. F. A.; Pergoli, R. *Org. Lett.* **2007,** *9,* 4443–4446. doi:10.1021/ol701794u
11. Heinrich, D.; Wagner, T.; Diederichsen, U. *Org. Lett.* **2007,** *9,* 5311–5314. doi:10.1021/ol7025334
12. Nakahara, M.; Kuboyama, T.; Izawa, A.; Hari, Y.; Imanishi, T.; Obika, S. *Bioorg. Med. Chem. Lett.* **2009,** *19,* 3316–3319. doi:10.1016/j.bmcl.2009.04.063
13. Kaliappan, K. P.; Kalanidhi, P.; Mahapatra, S. *Synlett* **2009,** 2162–2166. doi:10.1055/s-0029-1217570
14. Egron, D.; Durand, T.; Roland, A.; Vidal, J.-P.; Rossi, J.-C. *Synlett* **1999,** *4,* 435–437. doi:10.1055/s-1999-3157
15. Jeanmart, S.; Taylor, R. J. K. *Tetrahedron Lett.* **2005,** *46,* 9043–9048. doi:10.1016/j.tetlet.2005.10.099
16. Rothman, J. H. *J. Org. Chem.* **2009,** *74,* 925–928. doi:10.1021/jo801910u
17. Aljarilla, A.; López, J. C.; Plumet, J. *Eur. J. Org. Chem.* **2010,** 6123–6143. doi:10.1002/ejoc.201000570

18. Martin, A. R.; Mohanan, K.; Luvino, D.; Floquet, N.; Baraguey, C.; Smietana, M.; Vasseur, J.-J. *Org. Biomol. Chem.* **2009,** *7,* 4369–4377. doi:10.1039/b912616c
19. Tietze, L. F.; Griesbach, U.; Schubert, I.; Bothe, U.; Marra, A.; Dondonni, A. *Chem. – Eur. J.* **2003,** *9,* 1296–1302. doi:10.1002/chem.200390148
20. Wei, X.; Carroll, P. J.; Sneddon, L. G. *Organometallics* **2006,** *25,* 609–621. doi:10.1021/om050851l
21. Eignerová, B.; Janoušek, Z.; Dračínský, M.; Kotora, M. *Synlett* **2010,** 885–888. doi:10.1055/s-0029-1219546
22. Sedlák, D.; Eignerová, B.; Dračínský, M.; Janoušek, Z.; Bartůněk, P.; Kotora, M. *J. Organomet. Chem.* **2013,** *747,* 178–183. doi:10.1016/j.jorganchem.2013.06.013
23. Rost, D.; Porta, M.; Gessler, S.; Blechert, S. *Tetrahedron Lett.* **2008,** *49,* 5968–5971. doi:10.1016/j.tetlet.2008.07.161
24. Vougioukalakis, G. C.; Grubbs, R. H. *Chem. Rev.* **2010,** *110,* 1746–1787. doi:10.1021/cr9002424
25. Samojłowicz, C.; Bienek, M.; Zarecki, A.; Kadyrov, R.; Grela, K. *Chem. Commun.* **2008,** *47,* 6282–6284. doi:10.1039/b816567j
26. Samojłowicz, C.; Borré, E.; Maudit, M.; Grela, K. *Adv. Synth. Catal.* **2011,** *353,* 1993–2002. doi:10.1002/adsc.201100053
27. Samojłowicz, C.; Bienik, M.; Pazio, A.; Makal, A.; Woźniak, K.; Poater, A.; Cavallo, L.; Wójcik, J.; Zdanowski, K.; Grela, K. *Chem. – Eur. J.* **2011,** *17,* 12981–12993. doi:10.1002/chem.201100160
28. Bargiggia, F. C.; Murray, W. V. *J. Org. Chem.* **2005,** *70,* 9636–9639. doi:10.1021/jo0514624
29. Michaut, A.; Boddaert, T.; Coquerel, Y.; Rodriguez, J. *Synthesis* **2007,** 2867–2871. doi:10.1055/s-2007-983825
30. Prchalová, E.; Votruba, I.; Kotora, M. *J. Fluorine Chem.* **2012,** *141,* 49–57. doi:10.1016/j.jfluchem.2012.06.005
31. Eignerová, B.; Dračínský, M.; Kotora, M. *Eur. J. Org. Chem.* **2008,** 4493–4499. doi:10.1002/ejoc.200800230
32. Eignerová, B.; Slavíková, B.; Buděšínský, M.; Dračínský, M.; Klepetářová, B.; Šťastná, E.; Kotora, M. *J. Med. Chem.* **2009,** *52,* 5753–5757. doi:10.1021/jm900495f
33. Eignerova, B.; Sedlák, D.; Dračínský, M.; Bartůněk, P.; Kotora, M. *J. Med. Chem.* **2010,** *53,* 6947–6953. doi:10.1021/jm100563h
34. Řezanka, M.; Eignerová, B.; Jindřich, J.; Kotora, M. *Eur. J. Org. Chem.* **2010,** 6256–6262. doi:10.1002/ejoc.201000807
35. Prchalová, E.; Štěpánek, O.; Smrček, S.; Kotora, M. *Future Med. Chem.* **2014,** *6,* 1201–1229. doi:10.4155/fmc.14.53
36. Dondoni, A.; Giovannini, P. P.; Marra, A. *J. Chem. Soc., Perkin Trans. 1* **2001,** 2380–2388. doi:10.1039/b106029p
37. Postema, M. H. D.; Piper, J. L. *Tetrahedron Lett.* **2002,** *43,* 7095–7099. doi:10.1016/S0040-4039(02)01617-9
38. Dominique, R.; Das, S. K.; Liu, B.; Nahra, J.; Schmor, B.; Gan, Z.; Roy, R. *Methods Enzymol.* **2003,** *362,* 17–28. doi:10.1016/S0076-6879(03)01002-4
39. Nolen, N. G.; Kurish, A. J.; Wong, K. A.; Orlando, M. D. *Tetrahedron Lett.* **2003,** *44,* 2449–2453. doi:10.1016/S0040-4039(03)00350-2
40. Lin, Y. A.; Chalker, J. M.; Davis, B. G. *J. Am. Chem. Soc.* **2010,** *132,* 16805–16811. doi:10.1021/ja104994d
41. Chen, G.; Schmieg, J.; Tsuji, M.; Franck, R. W. *Org. Lett.* **2004,** *6,* 4077–4080. doi:10.1021/ol0482137
42. Štěpánek, P.; Vích, O.; Werner, L.; Kniežo, L.; Dvořáková, H.; Vojtíšek, P. *Collect. Czech. Chem. Commun.* **2005,** *70,* 1411–1428. doi:10.1135/cccc20051411
43. Liu, S.; Ben, R. N. *Org. Lett.* **2005,** *7,* 2385–2388. doi:10.1021/ol050677x
44. Voigtritter, K.; Ghorai, S.; Lipshutz, B. H. *J. Org. Chem.* **2011,** *76,* 4697–4702. doi:10.1021/jo200360s
45. Chatterjee, A. K.; Choi, T.-L.; Sanders, D. P.; Grubbs, R. H. *J. Am. Chem. Soc.* **2003,** *125,* 11360–11370. doi:10.1021/ja0214882

PŘÍLOHA VII

Bertolotti, B.; Oroszová, B.; Sutkeviciute, I.; Kniežo, L.; Fieschi, F.; Parkan, K.; Lovyová, Z.; Kašáková, M.; Moravcová, J. Nonhydrolyzable *C*-disaccharides, a new class of DC-SIGN ligands. *Carbohydr. Res.* **2016**, *435*, 7-18.

Carbohydrate Research 435 (2016) 7–18

Contents lists available at ScienceDirect

Carbohydrate Research

journal homepage: www.elsevier.com/locate/carres

Nonhydrolyzable *C*-disaccharides, a new class of DC-SIGN ligands

Benedetta Bertolotti [a], Beáta Oroszová [a], Ieva Sutkeviciute [b, c, d, 1], Ladislav Kniežo [a], Franck Fieschi [b, c, d], Kamil Parkan [a], Zuzana Lovyová [a], Martina Kašáková [a], Jitka Moravcová [a, *]

[a] Department of Chemistry of Natural Compounds, University of Chemistry and Technology, Technická 5, 166 28 Prague, Czech Republic
[b] University Grenoble Alpes, Institut de Biologie Structurale, F-38044 Grenoble, France
[c] CNRS, IBS, F-38044, Grenoble, France
[d] CEA, IBS, F-38044 Grenoble, France

ARTICLE INFO

Article history:
Received 18 July 2016
Received in revised form
5 September 2016
Accepted 6 September 2016
Available online 9 September 2016

Keywords:
DC-SIGN ligands
Glycomimetics
C-Disaccharides
Surface plasmon resonance

ABSTRACT

The discovery of effective ligands for DC-SIGN receptor is one of the most challenging concepts of antiviral drug design due to the importance of this *C*-type lectin in infection processes. DC-SIGN recognizes mannosylated and fucosylated oligosaccharides but glycosidic linkages are accessible to both chemical and enzymatic degradations. To avoid this problem, the synthesis of stable glycoside mimetics has attracted increasing attention. In this work we establish for the first time mono- and divalent *C*-glycosides based on D-*manno* and L-*fuco* configurations as prospective DC-SIGN ligands. In particular, the L-fucose glycomimetics were more active than the respective D-mannose ones. The highest affinity was assessed for simple 1,4-bis(α-L-fucopyranosyl)butane (SPR: IC_{50} 0.43 mM) that displayed about twice higher activity than natural ligand Le^x. Our results make *C*-glycosides attractive candidates for multivalent presentations.

1. Introduction

The interactions between oligosaccharide chains of glycolipids/glycoproteins and carbohydrate-binding protein receptors, termed lectins, mediate many biological recognition events that are of vital importance in many normal and pathological processes [1]. In the immune system, such carbohydrate-protein interactions are particularly important for pathogen recognition. Dendritic cells (DCs) of the innate immunity survey peripheral tissues, such as skin and mucosa, to capture invading pathogens, which eventually leads to pathogen-specific adaptive immune response initiation. The pathogen recognition receptors (PRRs) expressed on the surface of DCs, including Toll-like receptors (TLRs) and *C*-type lectin receptors (CLRs), are instrumental in pathogen recognition. Among a diverse repertoire of CLRs on DCs, DC-SIGN (Dendritic Cell-Specific ICAM-3 Grabbing Non-integrin) is abundantly expressed on immature DCs and has been attributed many various roles. Apart from its function as a PRR, DC-SIGN is known to bind several self-antigens [2–7]. Indeed, this lectin, initially discovered as an intercellular adhesion molecule-3 (ICAM-3) binding protein [2] mediates several functions other than PRR, such as DC transmigration from blood to lymphoid tissues [3] and immunological synapse initiation [2]. Probably due to the latter property of self-antigen recognition, many pathogens have evolved to exploit this CLR in order to evade immune responses and instead to promote their infection. Such pathogens include viruses (HIV, Ebola, Dengue, cytomegalovirus, Phlebovirus, and hepatitis C virus), bacteria (*Helicobacter pylori*, *Klebsiella pneumonia*, and *Mycobacteria tuberculosis*), parasites (*Leishmania pifanoi* and *Schistosoma mansoni*) and yeast (*Candida albicans*) [8–11]. Hence, blocking DC-SIGN interaction with pathogen surface glycans seems to be a plausible concept of infection prevention, and glycomimetic DC-SIGN antagonists are promising candidates for new antimicrobial drug development [12,13].

DC-SIGN is a type II membrane protein with an extracellular domain (ECD) composed of a neck and a C-terminal carbohydrate recognition domains (CRD). The neck domain is responsible for oligomerization of the lectin to functional tetramers, and hence the presentation of CRDs on the cell surface in a tetravalent manner [14]. DC-SIGN CRD displays the specificity to mannose- and fucose-containing glycans that are bound in a Ca^{2+}-dependent manner

* Corresponding author.
E-mail address: Jitka.Moravcova@vscht.cz (J. Moravcová).
[1] Present address: Laboratory for GPCR Biology, Department of Pharmacology & Chemical Biology, University of Pittsburgh School of Medicine, Pittsburgh, PA, USA.

http://dx.doi.org/10.1016/j.carres.2016.09.005
0008-6215/

[15]. Furthermore, the lectin preferentially recognizes internal D-mannose of high-mannose glycans and binds L-fucose within the blood group antigens [16–18].

The mannose-type sugar residues bind DC-SIGN CRD through equatorial 3-OH and 4-OH groups, and alternatively, L-fucose residue interacts through equatorial 3-OH and axial 4-OH groups. In both cases, these hydroxyl groups are coordinated to Ca^{2+} in a conventional sugar binding site (primary binding site) of the lectin's CRD. However, in case of fucosylated structures such as Lewis-type blood group antigen Le^x, the terminal galactose residue interacts with the CRD at a secondary binding site suggesting that other fucose-containing oligosaccharides may also make additional contacts with the protein at other sites [19]. The X-ray crystallography as well as solution NMR studies of disaccharide Manα(1-2) Man interaction with DC-SIGN revealed that this sugar binds the primary site of DC-SIGN CRD in at least two possible ways, where reducing or non-reducing end mannose moieties, respectively, are coordinated to Ca^{2+}0.20 Multiple binding modes were also identified by docking and NMR studies of mannosyl trisaccharide ligands [21].

The presence of multiple binding modes as well as additional contacts with the protein side chains lead to an enhanced affinity of the ligands. Indeed, a survey of immune-related mannose/fucose-binding C-type lectin receptors demonstrated that DC-SIGN has an enhanced binding of Manα(1-2)Man over D-mannose and binds Le^x trisaccharide structure stronger than L-fucose itself [22]. However, DC-SIGN displays a low binding affinity to monosaccharide ligands (K_D in mM range), a common feature shared among all C-type lectins. The DC-SIGN inhibition constant K_i determined for D-mannose in solid-phase radioligand binding assay was 13.1 mM, while L-fucose displayed higher apparent affinity (K_i 6.7 mM) in the same assay [23]. Our previous SPR competition assays indicated IC_{50} of about 2 mM for D-mannose, [24,25] and 1.2 mM for L-fucose [24].

To address their low affinity, the strategy of designing monovalent glycomimetics with different chemical moieties to mediate formation of additional contacts with DC-SIGN CRD may yield promising lead compounds. Apart from relatively few efforts to design the non-carbohydrate ligands of DC-SIGN [26], the concept of glycomimetics is most widely used in this quest. A good affinity improvement was observed for simple structure of 2-*C*-amino(-azido)methyl-D-mannose, which bound DC-SIGN with significantly higher affinity than D-mannose itself [27].

Our groups pursue the development of DC-SIGN inhibitors based on either L-fucose or D-mannose anchors to enable the ligand accommodation [28–31] into the primary binding site of DC-SIGN CRD, whereas the rest of the molecule is designed to enhance binding affinity and specificity to DC-SIGN.

Most of the compounds within the libraries of Le^x mimics were built using an α-fucosylamides of general structure **1** (Fig. 1) that had but slightly higher binding affinity than the natural Le^x (IC_{50} 0.80 mM) as determined by surface plasmon resonance (SPR) competition assay. Compound **2** with IC_{50} of 0.33 mM was the most active of all ligands tested [24,28,29].

The Manα(1-2)Man- and Manα(1-2)Manα(1-6)Man-based glycomimetics have been studied more intensively in our groups. For the pseudodisaccharide **3**, IC_{50} of 0.62 mM was established using an infection model based on pseudotype Ebola virus and Jurkat cells expressing DC-SIGN [32]. In this pursuit, the linear pseudomannnotrioside **4** appeared to be the most active compound (IC_{50} 0.13 mM) with high selectivity to DC-SIGN in SPR competition assay (Fig. 1) [33]. However, later structural studies revealed that the relatively high affinity of **4** was an artefact resulting from its unexpected property to bridge DC-SIGN tetramers within the conditions of the competition test [30]. Moreover, once presented on polyvalent scaffolds, compound **4** as well as its shorter analogue **3** had similar activities towards DC-SIGN receptor [34]. To improve binding affinities of monovalent glycomimetics, a series of bis-benzylamides was synthesized and their affinity assessed in SPR competition assay. Among them compound **5** showed the best inhibitory potency and selectivity to DC-SIGN [35]. An assay measuring the ability of molecules to inhibit dendritic cell adhesion to mannan-coated plates revealed that bis-amide **6** was the most potent inhibitor with IC_{50} of 6.86 μM [36].

Majority of glycomimetic DC-SIGN ligands reported so far at least partly retain oligosaccharide structure with metabolically unstable glycosidic bond. The *C*-glycosidic carbohydrate mimics, in which the anomeric oxygen has been replaced by a methylene or a substituted methylene unit, exhibit stability against chemical and enzymatic hydrolysis but their conformational behaviour differs from those of *O*-glycosides due to the lack of *exo*- and *endo*-anomeric effects [37]. Because the activity can significantly depend on the conformation in solution, affinity of *C*-glycoside mimetics can be diminished, retained or even enhanced in comparison to *O*-

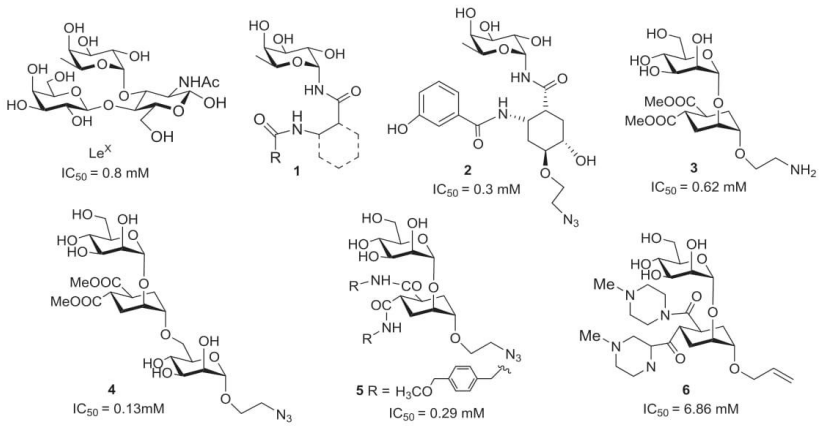


Fig. 1. Structures of the most potent monovalent ligands for DC-SIGN receptor.

glycoside. Nevertheless, the *C*-glycoside mimics design has not yet been explored, and here we for the first time demonstrate our efforts to develop *C*-glycosidic pseudosaccharides as DC-SIGN ligands. We have designed and synthesized a small library of *C*-disaccharides containing at least one D-mannose or L-fucose unit. These compounds were examined for DC-SIGN binding properties in SPR competition assay.

2. Results and discussion

In parallel to the ongoing development of Manα(1-2)Man glycomimics [25,32,35,38], we have set out to take an alternative approach and to explore the possibility of *C*-glycosidic Manα(1-3)Man glycomimics (type I, Fig. 2B) as DC-SIGN ligands. Our choice was dictated by the earlier finding that the α(1-3)-linked D-mannose (*Man1*, Fig. 2A) of the branched trimannoside Manα(1-3)[Manα(1-6)]Man binds DC-SIGN CRD in the primary binding site by the conventional coordination of 3- and 4-OH groups to the Ca^{2+}, while the internal mannose moiety (*Man2*, Fig. 2A) makes additional contacts with the protein.[16] Similarly, interaction between Le^x (Fig. 1) and the Ca^{2+} site is mediated by the α(1-3)-linked L-fucose residue [19].

The design of type II glycomimetics (Fig. 2C) was inspired by the structure of Le^x where four-atom long linker connects C1 of L-fucose to C1 of D-galactose (Fig. 1), which was found to make additional contacts with the protein at the secondary site [19].

2.1. Synthesis of α-(1-3)-C-disaccharides (type I)

We have recently elaborated the stereoselective synthesis of α-*C*-(1-3) disaccharide precursors based on the *de novo* construction of L- or D-2-deoxy-*arabino*-hexopyranose moiety starting from respective α-hexopyranosylethanal [39]. Later, we found that the stereoselectivity of the key cycloaddition of substituted oxadiene can be markedly increased by the use of chiral vinyl ethers [40]. The feasibility of our approach was verified by the preparation of 3-*C*-fucosylated [41] and mannosylated [42] D- and L-glucals. Moreover, the methyl glycoside **7** as a non-hydrolyzable analogue of disaccharide Manα(1-3)Man (Fig. 2) was synthesized in our group previously [42]. Thus, our experience in the synthesis of α-*C*-(1-3) disaccharides prompted us to prepare model compounds **8**–**12** (Fig. 3).

As the starting compound for the preparation of α-(1-3)-mannopyranosyl pseudodisaccharides **8** and **9** we employed previously described glycan **13** (Scheme 1) [42]. The known transformation of the thiazole ring to an aldehyde group [43] afforded compound **14**, which on simultaneous reduction of both carbonyl functions gave diol **15**. Catalytic hydrogenation in methanol yielded methyl glycoside **16** as a mixture of anomers in a ratio α:β of about 3:1 (^{1}H NMR: α, 4.79 ppm, d, $J_{1,2}$ = 3.2 Hz, H-1; β, 4.43 ppm, dd, $J_{1,2eq}$ = 2.1 Hz, $J_{1,2ax}$ = 9.5 Hz, H-1). The mixture of anomers **16** was subjected to an acidic hydrolysis and target disaccharide **8** with a free OH group in the anomeric position (α:β of about 1:2; ^{1}H NMR: α, 5.39 ppm, d, $J_{1,2}$ = 3.4 Hz, H-1; β, 4.86 ppm, dd, $J_{1,2eq}$ = 2.2 Hz, $J_{1,2ax}$ = 9.7 Hz, H-1) was isolated and identified also as anomeric acetate **17**. For the preparation of 4-hydroxy-α-(1-3)-mannopyranosyl pseudodisaccharide **9**, the diol **15** was benzylated prior to the BH_3. Me_2S hydroboration of the double bond in **18**. The new pyranose in **19** has the 2-deoxy-*arabino*-hexopyranose configuration according to ^{1}H NMR spectrum ($J_{1,2ax}$ = 9.4 Hz, $J_{3,4} = J_{4,5}$ = 9.5 Hz) and comparison with the literature [41]. During the catalytic hydrogenation of **19**, we found that a mixture of both methyl and 1-benzyloxy-2-fenyl-ethyl glycosides was formed if methanol was used as a solvent. Therefore, the product of debenzylation was directly hydrolysed to free pseudodisaccharide **9** obtained as a 1:1 mixture of anomers (^{1}H NMR: α, 5.32 ppm, d, $J_{1,2}$ = 2.6 Hz, H-1; β, 4.94 ppm, dd, $J_{1,2eq}$ = 2.0 Hz, $J_{1,2ax}$ = 9.8 Hz, H-1) and identified also as acetate **20**. The partial or total methanolysis observed during hydrogenolysis of compounds **15** and **19** could be attributed to a trace acidity of the catalyst. Later on, we prepended methanolysis to debenzylation (**24** → **26**→**12**) to obtain pure methyl glycosides and compound **11** was prepared with a new batch of the catalyst.

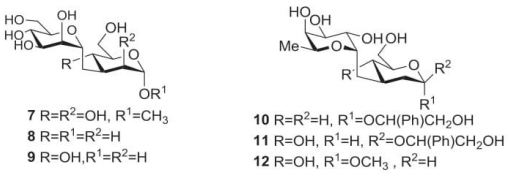


Fig. 3. Target *C*-disaccharides of type I.

The synthetic route to α(1-3)-fucopyranosyl pseudodisaccharides **10** - **12** was analogous to this one developed for **8** and **9** (Scheme 1). Starting glycan **21** was prepared using literature procedure [40] and its thiazolyl moiety was transformed into carbonyl by Dondoni protocol [43]. The crude product of subsequent reduction of **22** with $LiAlH_4$ was directly benzylated to give fully protected fucopyranosyl glycan **23**. Subsequent hydroboration of a double bond gave stereoselectively 4-hydroxy hexopyranoside **24** having 2-deoxy-*arabino* configuration (^{1}H NMR: $J_{1,2ax}$ = 9.5 Hz, $J_{3,4} = J_{4,5}$ = 9.6 Hz) [40] that was converted to an anomeric mixture of methyl glycosides **25** from which pure α-anomer **26** was isolated by chromatography. The final step was catalytic hydrogenation of benzyl derivatives **23**, **24** and **26** providing fucosyl pseudodisaccharides **10**, **11** and **12**, respectively.

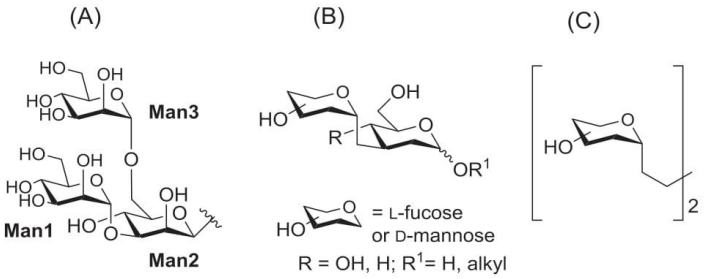
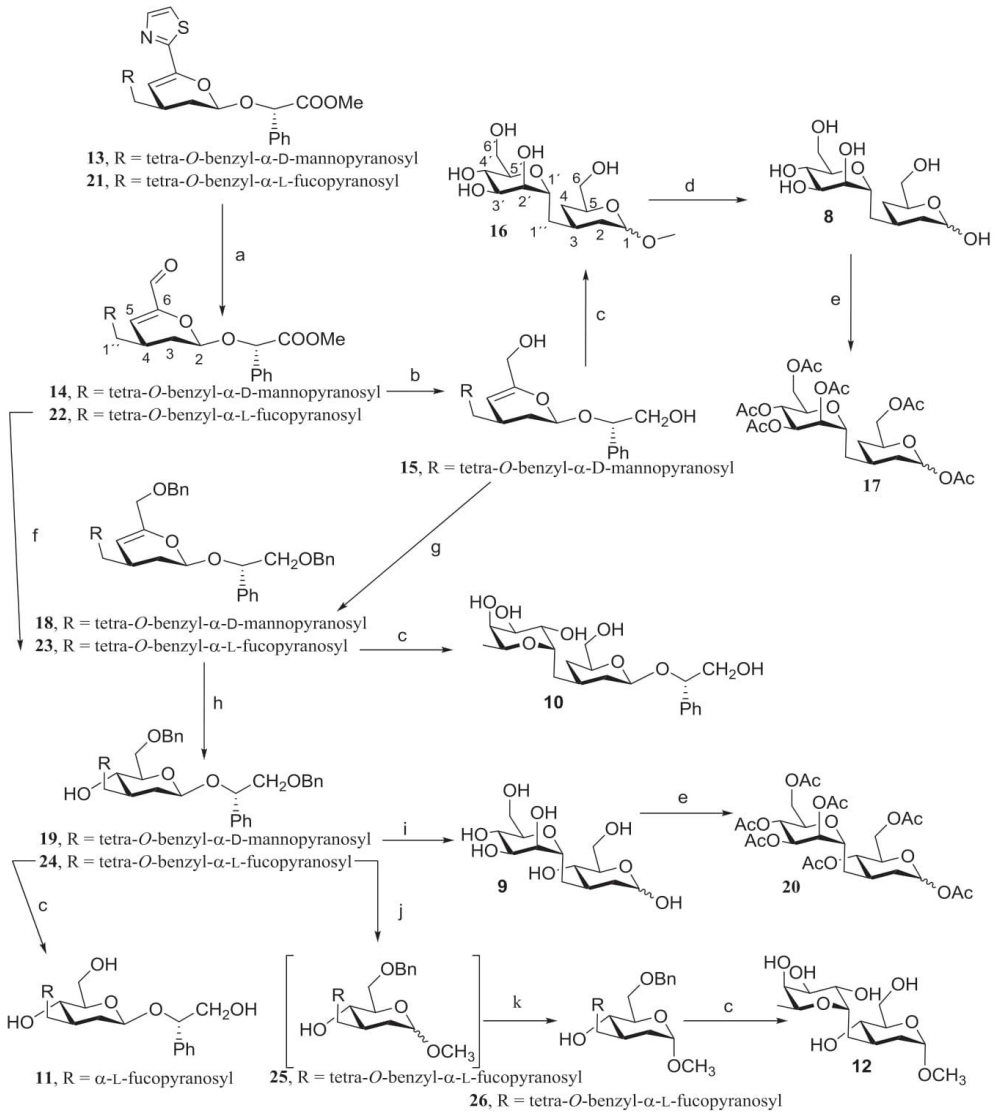


Fig. 2. Structure of Manα(1-3)[Manα(1-6)]Man trimannoside (A), *C*-disaccharides type I (B) and II (C).

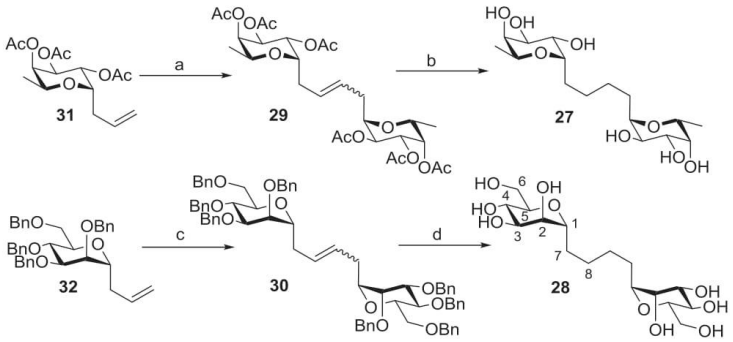


Scheme 1. Synthesis of **8**–**12**. Reagents and conditions: a) MeOTf, CH_3CN, rt; $NaBH_4$, MeOH, rt; $AgNO_3$, CH_3CN/H_2O; b) $LiAlH_4$, THF, rt; c) H_2, Pd/C, MeOH; d) 10% CF_3COOH, rt, 2 h; e) Ac_2O, Py; f) $LiAlH_4$, THF, rt, BnBr, THF, TBAI, NaH, 40 °C, 24 h; g) BnBr, THF, TBAI, NaH, 40 °C, 24 h; h) 2M BH_3 Me_2S, THF, 25 °C; 30% NaOH, 30% H_2O_2, 30 min; i) H_2, Pd/C, MeOH, 10% CF_3COOH, rt, 2 h; j) 3M HCl, MeOH, THF; k) separation.

2.2. Synthesis of 1,4-bis(hexopyranosyl)butanes (type II)

For the preparation of target diglycosyl butanes **27** and **28** we used the transition metal catalyzed olefin metathesis, which provides versatile strategy for the preparation of hydrolytically stable C-glycosides and neoglycoconjugates [44,45]. Our decision to employ Grubbs' catalysts for the synthesis of target intermediates **29** and **30** (Scheme 2) was prompted by previous reports on their application to self-methatesis [45–47] of tetra-*O*-benzyl-α-D-mannopyranosylprop-2-ene (**23**) and tri-*O*-acetyl-α-L-fucopyranosylprop-2-ene (**24**) [44].

Pure α-L-fucopyranosyl propene **31** was prepared by crystallization [41] from an α,β-diastereoisomeric mixture arising after deacetylation of per-*O*-acetyl derivative [48], and by repeated acetylation of the α-anomer. 3-(2,3,4,6-Tetra-*O*-acetyl-α-D-mannopyranosyl)prop-1-ene was synthesized stereoselectively from



Scheme 2. Synthesis of **27** and **28**. Reagents and conditions: a) 2nd generation Grubbs catalyst, 5 mol%, 6 days, 40 °C, 84%; b) H_2, Pd/C, MeOH; 98%; c) 1st generation Grubbs catalyst, 10 mol%, 3 h, 40 °C, MW, 24%; d) MeONa, MeOH, 87%.

methyl α-D-mannopyranoside using silylation-reductive cleavage-deprotection protocol developed for methyl α-D-glucopyranoside [49] and adapted for methyl 2,3,4,6-tetra-*O*-benzyl-α-D-mannopyranoside [50]. Zemplén deacetylation provided 3-(α-D-mannopyranosyl)prop-1-ene and its common benzylation afforded known benzylether **32** [51].

Keeping the conditions described for the self-metathesis of **31** (1st generation Grubbs' catalyst, 10 mol%, 3 days, 40 °C)[45], the yield of **29** was only 50% instead of 95% reported. If the 2nd generation Grubbs' catalyst (5 mol%, 3 d, 40 °C) was used, the isolated yield of **29** increased up to 84%. The next two reactions, hydrogenation and deacetylation, were carried out without purification of the respective intermediate and disaccharide **27** was isolated in 85% yield over these two steps. Whilst no significant differences between the reactivity of acetate versus benzyl protected *C*-allyl glycosides were reported [52], in our case only benzyl ether **32** gave homodimer **30** in a low yield of 24% under optimized conditions (1st generation Grubbs' catalyst, 10 mol%, 3 h, 40 °C, microwave) although 83% yield was reported [45]. The efforts made to optimize this reaction did not significantly improve the overall yield of **28**, but did produce enough material for its full characterization and biological test.

2.3. SPR competition assay

In this study, we aimed to evaluate the glycomimetics **7**–**12**, **27**, and **28** for their activity to inhibit the binding of DC-SIGN ECD to mannosylated bovine serum albumin (Man-BSA) and to compare their apparent affinity (in terms of IC_{50} value) with natural ligands D-mannose, L-fucose, and disaccharides Manα(1-2)Man and Manα(1-3)Man. For this purpose, we used the previously described SPR competition assay [24], where the decrease of soluble DC-SIGN ECD binding to Man-BSA surface is measured as a function of compound concentration. Hence, Man-BSA, bearing on average 12 copies of branched trisaccharide Man(α1-3)[Man(α1-6)]Man, was covalently attached to a carboxymethyldextran-functionalized gold SPR sensor chip, over which DC-SIGN ECD was injected in the absence or presence of tested compounds. Plotting the normalized DC-SIGN binding response decrease against the increasing compound concentrations allowed calculating the IC_{50} values for each compound tested.

The reference monosaccharides D-mannose and L-fucose were found to exhibit IC_{50} values of 3.42 and 2.52 mM, respectively (Fig. 4A), those are consistent with previous results [25,28,29]. As expected, the disaccharides Manα(1-2)Man and Manα(1-3)Man had greater apparent affinity in terms of IC_{50} (0.91 and 2.29 mM, respectively) than D-mannose. Although the interaction of Manα(1-2)Man with DC-SIGN has been well characterized previously [20], there is virtually no data on Manα(1-3)Man interaction with DC-SIGN, with an exception of the initial structural study [16]. Thus here we for the first time report the apparent affinity of

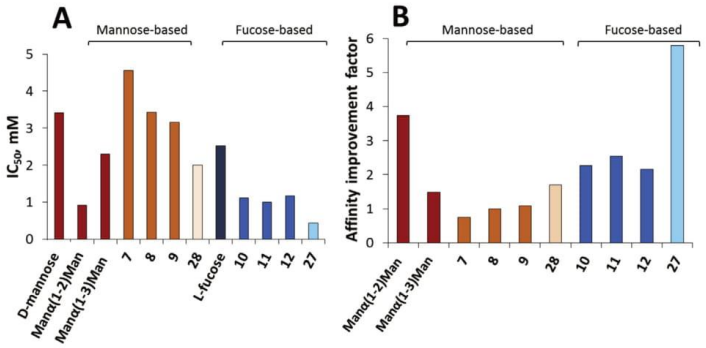


Fig. 4. Inhibition activity of studied ligands and reference compounds assessed by SPR. A, The IC_{50} values for mannose- (orange-shaded bars) and fucose-based (blue-shaded bars) compounds. B, Affinity improvement of tested compounds with respect to corresponding natural monosaccharide D-mannose (red shades) or L-fucose (blue shades). (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

disaccharide Manα(1-3)Man to DC-SIGN, which appeared to be approximately twice lower than that of Manα(1-2)Man.

To our surprise, the *C*-disaccharide **7**, which was designed as a direct mimics of Manα(1-3)Man (with the only exception of methyl group instead of hydrogen attached to the oxygen of C1 of reducing mannose), displayed not only a twice lower apparent affinity (IC_{50} 4.56 mM) than its natural counterpart Manα(1-3)Man, but also had lower affinity than D-mannose (Fig. 4A). This observation suggests that *C*-glycosidic bond between two mannose moieties of **7** negatively impacts the disaccharide's conformation in solution, which most likely interferes with the van der Waals contact establishment with Phe325 as well as water-mediated hydrogen bond formation with Ser372 of the lectin's side chain [16], and in addition, destabilizes the binding of non-reducing D-mannose in the primary binding site. Although slightly more active than **7**, the pseudomannosides **8** and **9** were still less potent than the natural Manα(1-3)Man with IC_{50} values of 3.43 and 3.15 mM, respectively, being very close to the one of D-mannose, suggesting that only the non-reducing D-mannose residue interacts with the protein, while the reducing moiety had virtually no effect to binding.

On the contrary, in the series of L-fucose-bearing type I *C*-disaccharides, the reducing end moieties linked by *C*-glycosidic bond markedly increased the overall affinity of the resulting compounds as compared to L-fucose. All three pseudodisaccharides **10**, **11** and **12** have the same apparent affinity to DC-SIGN as indicated by very similar IC_{50} values of 1.11, 0.99 and 1.17 mM, respectively (Fig. 4A). This finding suggests that the α-(1-3) substitutes to L-fucose participate in binding to the protein. The overall comparison of *manno* (**7** - **9**) and *fuco* (**10** - **12**) type I *C*-disaccharide potencies, normalized to corresponding natural monosaccharide activity (Fig. 4B, affinity improvement factor = $IC_{50,monosaccharide}/IC_{50,compound}$), illustrates well that modification of L-fucose by α-(1-3) substitutions results in significant affinity improvement, reaching the activity of the trisaccharide Le^x, and thus is the suitable approach for further development of this type DC-SIGN ligands. Meanwhile, the analogous modifications of D-mannose either have no or slightly negative effect. Even the natural Manα(1-3)Man has a similar activity as D-mannose, compared to its "cousin" Manα(1-2)Man, which has almost 4-fold higher activity than D-mannose most like resulting from multiple binding modes of this disaccharide. However, the interest of further development *C*-disaccharides using Manα(1-3)Man as a template may lie in an exceptional selectivity of this sugar to DC-SIGN, as described below.

The issue of compound selectivity to DC-SIGN is particularly important considering another related CLR Langerin, which has similar sugar specificity, but has been demonstrated to have a proactive role against HIV-1 infection [53,54]. Therefore, the disaccharide Manα(1-3)Man and its direct mimic **7** were tested for the selectivity to DC-SIGN versus Langerin using SPR competition assay as described previously [32,38]. Interestingly, while previous results showed that related disaccharide Manα(1-2)Man is capable to inhibit Langerin ECD binding to Man-BSA surface with an IC_{50} of 1.6 mM [38], virtually no binding inhibition was observed with both Manα(1-3)Man and **7** (Fig. 5).

The type II glycomimetics, the bis(hexopyranosyl)butans **27** and **28**, were the most potent compounds within the studied library of DC-SIGN ligands. The affinity of **28** (IC_{50} 2.00 mM) was comparable with the one of Manα(1-3)Man and almost two times higher than the affinity of D-mannose. This could be explained by a 2-fold increase of local concentration of D-mannose as a result of linking two sugar moieties, which in turn increases the (re)binding probability.

Interestingly, the bis(fucopyranosyl)butan **27** displayed the highest apparent affinity (IC_{50} 0.43 mM) among all the tested compounds. Furthermore, it achieved almost a 6-fold affinity improvement compared to simple L-fucose and displayed about twice higher activity than Le^x. This result suggests that apart from the affinity enhancement due to the increased local concentration of L-fucose, the additional contacts with the protein are likely to contribute to affinity improvement.

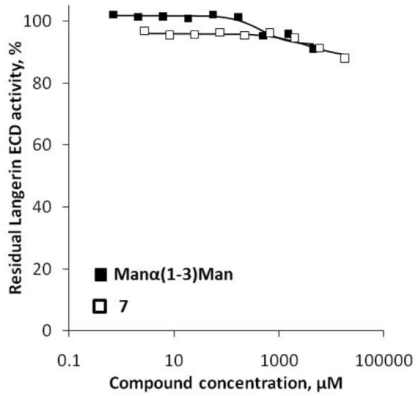


Fig. 5. The dependence of Langerin ECD activity on compound concentration.

3. Conclusion

In this work we have demonstrated for the first time that divalent *C*-disaccharides based on D-mannose or L-fucose scaffold can be prospective ligands for the DC-SIGN receptor. In particular, L-fucose glycomimetics open the space for versatile derivatization in the development of stronger binding ligands. The advantage presented by *C*-glycoside ligands in terms of stability and solubility makes them attractive candidates for the construction of multivalent systems.

4. Experimental

4.1. General methods

Optical rotations were measured with an Autopol VI (Rudolph Research Analytical, USA) digital polarimeter in appropriate solvents, at temperature 20 °C and 589 nm sodium line, in 1 dm cuvette and are given at 10^{-1}.deg.cm^2.g^{-1}. Concentrations (*c*) are given in g/100 ml.

NMR spectra were recorded with a Bruker DRX 500 Avance spectrometer operating at 500.0 MHz for ^{1}H, and 125.7 MHz for ^{13}C, or with a Varian Gemini 300HC spectrometer operating at 299.9 MHz for ^{1}H, and 75 MHz for ^{13}C, as indicated. ^{1}H and ^{13}C resonances were fully assigned using H,H-COSY, H,H-ROESY, H,C-HSQC and H,C-HMBC techniques. All chemical shifts are quoted on the δ scale in ppm and referenced using residual ^{1}H solvent signal in ^{1}H NMR spectra ($\delta(CDCl_3)$ = 7.26 ppm; $\delta(CD_3OD)$ = 3.31 ppm) and ^{13}C solvent signal in ^{13}C NMR spectra ($\delta(CDCl_3)$ = 77.0 ppm; $\delta(CD_3OD)$ = 49.0 ppm). Coupling constants (*J*) are reported in Hz with the following splitting abbreviations: s = singlet, d = doublet, t = triplet, q = quartet.

Mass spectra were measured with a Q-Tof Micro (Waters, USA) or LTQ Velos Orbitrap (Thermo Fisher Scientific, UK) instruments equipped with LockSpray in ES+ and ES- modes with mobile phase of methanol and flow rate of 100 μL min^{-1}. Nominal and exact *m/z* values are reported in Daltons.

HPLC-MS system consisted of a Hewlett-Packard HP/Agilent

Technologies (USA) 1100HPLC system which was coupled on line to HP mass selective single quadrupole detector (model G1946 A) and controlled by ChemStation software (revision B.02.01). Column RP C18 (30 × 2.1 mm) Zorbax SB-C18 (3.5 μm particle size) was used with mobile phases of 50% methanol (A) and 100% methanol (B), each containing 5 mmol ammonium formiate, and flow rate 0.3 mL min^{-1}. Capillary voltage for electrospray ionization was set at 3.5 kV. Pressure reactor Parr® 4848 was used for catalytic hydrogenations. The mixture was irradiated in Microwave reactor Biotage 355301.

Solvents were evaporated at 40 °C and 2 kPa, and compounds were dried at 60 °C and 2 kPa. Reactions were monitored by thin-layer chromatography (TLC) on the silica gel plates with Merck Stahl 10–40 μm or on Merck aluminium backed sheets coated with 60F 254 silica gel. Visualization of the silica plates was achieved using a UV lamp Spektroline-ENF-240/F (Spectronics Corporation Westbury, USA) (λ_{max} = 254 nm) and/or by spraying with cerium(IV)sulfate (1% in 10% H_2SO_4) solution followed by charring. Silica gel (100–160 μm, Merck) was used for flash column chromatography, C-18 silica gel (200–400 mesh, Sigma Aldrich) for reversed-phase chromatography. 'Hexane' refers to the fraction of hexane boiling in the range 68–72 °C. All reactions were carried out under anhydrous conditions using flame-dried apparatus under an atmosphere of argon. Brine refers to a saturated solution of NaCl. Anhydrous $MgSO_4$ was used as drying agents after reaction workup, as indicated.

Methyl (*S*)-2-phenyl-2-{[(2*R*,4*R*)-4-(2,3,4,6-tetra-*O*-benzyl-α-D-mannopyranosyl)methyl-6-(thiazol-2-yl)-3,4-dihydro-2H-pyran-2-yl]oxy}acetate (**13**) [41] and methyl (*S*)-2-phenyl-2-{[(2*R*,4*R*)-4-(2,3,4-tri-*O*-benzyl-α-L-fucopyranosyl)methyl-6-(thiazol-2-yl)-3,4-dihydro-2H-pyran-2-yl]oxy}acetate (**21**) [40] were prepared according to the previously reported method. ^1H and ^{13}C NMR spectral data matched that reported.

4.2. General procedure for the catalytic hydrogenation

A compound (1 eq.) in MeOH was placed into pressure reactor, Pd/C (10%; 5 eq.) was added to the solution and the reactor was purged with vacuum. Afterwards hydrogen was charged up 110 bar and stirring continued for 16 h, and finally, the system was purged again. The suspension was filtered through a Celite® pad, which was washed with MeOH. The filtrate was concentrated under reduced pressure and column chromatography of the residue on silica gel was used for the purification.

4.3. Preparation of 3-(2,3,4,6-tetra-O-acetyl-α-D-mannopyranosyl) prop-1-ene

Methyl α-D-mannopyranoside (5.0 g; 25.8 mmol) was stirred in MeCN (24 mL) and BSA (19.0 mL; 78 mmol) was added dropwise at rt. The stirring was continuing for 2–3 h up to dissolution of the starting glycoside. Then allyltrimethylsilane (20.6 mL; 77.8 mmol) and TMSOTf (23.5 mL, 0.13 mol) were added and the mixture was stirred for 3 h. The reaction was monitored by TLC (R_f 0.96; hexan/EtOAc 2:1) and after completion the mixture was cooled to 0 °C, water (30 mL) and Et_3N (19 mL) were added. Evaporation of the volatiles to dryness provided a residue that was acetylated by stirring in a mixture of pyridine/Ac_2O (2:1; 66 mL) overnight at rt. The reaction was quenched with water (66 mL) and extracted with CH_2C1_2. Organic layer was washed successively with 1 M HCl, satd. aq. solution of $NaHCO_3$ and water. After drying over $MgSO_4$ the CH_2Cl_2 solution was evaporated and the residue was purified on silica gel using hexan EtOAc (2:1) as a mobile phase. 3-(2,3,4,6-Tetra-*O*-acetyl-α-D-mannopyranosyl)prop-1-ene was isolated exclusively as α-anomer (8.9 g; 92%); R_f 0.67 ($CHCl_3$/MeOH 5:1); $[\alpha]_D^{25}$ 1.6 (*c* 1.2; $CHCl_3$). ^1H and ^{13}C NMR spectral data matched that reported [55].

4.4. 2,3,4-Trideoxy-3-C-[(α-D-mannopyranosyl)methyl]-α,β-D-threo-hexopyranose (8)

Compound **16** (20 mg; 0.13 mmol; 1 eq.) was dissolved in CF_3COOH (10% aq. solution, 5 mL), after 2 h the reaction was quenched with Na_2CO_3, The solvent was evaporated and the residue purified by flash silica gel chromatography (MeCN/H_2O 8:1) to give **8** (18 mg, 98%) as a colorless syrup; R_f 0.45 (MeCN/H_2O 8:1); ratio α:β = 0.3:0.7. ^1H NMR (600 MHz, D_2O): δ 5.39 (d, 0.3H, $J_{1,2}$ 3.4 Hz, H-1α), 4.86 (dd, 0.7H, $J_{1,2ax}$ 9.7, $J_{1,2eq}$ 2.2 Hz, H-1β), 4.09 (m, 1H, H-5α, H-5β), 3.91–3.84 (m, 2H, H-1'α, H-1'β, H-6aα, H-6aβ), 3.75 (dd, 1H, $J_{6b,6a}$ 12.2, $J_{6b,5}$ 6.1 Hz, H-6bα, H-6bβ), 3.71–3.55 (m, 6H, H-2'α, H-2'β, H-3'α, H-3'β, H-4'α, H-4'β, H-5'α, H-5'β, 2 x H-6'α, 2 x H-6'β), 2.09 (m, 1H, H-3α, H-3β), 2.02–1.71 (m, 3H, H-1″α, H-1″β, H-2aα, H-2aβ, H-4aα, H-4aβ), 1.48–1.33 (m, 2H, H-2bα, H-2bβ, H-4bα, H-4bβ), 1.09 (m, 0.3H, H-1″bα) 0.92 (m, 0.7H, H-1″bβ); ^{13}C-NMR (151 MHz, D_2O): δ 95.38 (C-1β), 91.32 (C-1α), 75.91 (C-5α, C-5β), 75.48, 75.59, 71.77, 70.75, 67.39 (C-1'β, C-2'β, C-3'β, C-4'β, C-5'β), 75.31, 73.54, 71.77, 69.47, 67.42 (C-1'α, C-2'α, C-3'α, C-4'α, C-5'α), 64.26 (C-6'β), 64.50 (C-6'α), 61.25 (C-6β), 61.32 (C-6α), 38.63, 33.63, 31.42 (C-2β, C-4β, C-1″β), 36.22, 33.88, 31.42 (C-2α, C-4α, C-1″α), 29.68 (C-3β), 24.63 (C-3α); HRESIMS (*m/z*): Calcd for $C_{13}H_{24}NaO_8Na$ $[M+Na]^+$ 331.1369. Found 331.1366.

4.5. 2,3-Dideoxy-3-C-[(α-D-mannopyranosyl)methyl]-α,β-D-arabino-hexopyranose (9)

Compound **19** (60 mg; 0.06 mmol) was dissolved in MeOH (2 mL) and debenzylated (10% Pd/C; 57 mg; 0.54 mmol) according to the procedure 4.2. Crude mixture of glycosides was dissolved in CF_3COOH (10% aq solution; 5 mL) and stirred at rt for 2 h. Hydrolysis was quenched with Na_2CO_3 (satd. aq. solution), volatiles were evaporated and the residue purified on silica gel (MeCN/H_2O 8:1) to give **9** (19 mg; 98%) as a colorless syrup. R_f 0.36 (MeCN/H_2O 4:1); ratio α:β = 0.4:0.6; ^1H NMR (600 MHz, D_2O): δ 5.32 (d, 0.4H, $J_{1,2}$ 2.6 Hz, H-1α), 4.94 (dd, 0.6H, $J_{1,2ax}$ 9.8, $J_{1,2eq}$ 2.0 Hz, H-1β), 4.12 (m, 1H, H-5α, H-5β), 3.87–3.42 (m, 8H, H-1'α, H-1'β, H-6aα, H-6aβ, H-6bα, H-6bβ, H-2'α, H-2'β, H-3'α, H-3'β, H-4'α, H-4'β, 2 x H-6'α, 2 x H-6'β), 3.47–3.43 (m, 2H, H-5'α, H-5'β), 3.30 (t, 0.4H, $J_{4,5}$ 9.7 Hz, $J_{4,3}$ 9.7 Hz, H-4α), 3.22 (t, 0.6H, $J_{4,5}$ 9.8 Hz, $J_{4,3}$ 9.8 Hz, H-4β), 2.17 (m, 0.6H, H-2aβ), 2.06 (m, 0.4H, H-2aα), 2.03–1.92 (m, 1.4H, H-3α, H-1″aα, H-1″aβ), 1.83–1.71 (m, 1.6H, H-1″bα, H-1″bβ, H-3β), 1.63 (m, 0.4H, H-2bα) 1.36 (m, 0.6H, H-2bβ); ^{13}C-NMR (151 MHz, D_2O): δ 94.81 (C-1β), 90.46 (C-1α), 79.01 (C-5'α, C-5'β), 77.56 (C-5α, C-5β), 75.14, 73.79, 71.44, 70.55, 69.42, 67.37 (C-1'α, C-2'α, C-3'α, C-4'α, C-5'α, C-4α), 74.84, 73.79, 71.49, 70.57, 69.42, 67.37 (C-1'β, C-2'β, C-3'β, C-4'β, C-5'β, C-4β), 67.53 (m, C-6'β, C-6'α), 61.09 (C-6β), 61.31 (C-6α), 37.09 (C-2β), 34.97 (C-2α), 38.37 (C-3β), 34.06 (C-2α), 30.12 (C-1″β), 30.09 (C-1″α); HRESIMS (*m/z*): Calcd for $C_{13}H_{24}O_9Na$ $[M+Na]^+$ 347.1318. Found: 347.1314.

4.6. 4(S)-2-Hydroxy-1-phenylethyl 2,3,4-trideoxy-3-C-[(α-L-fucopyranosyl)methyl]-β-D-threo-hexopyranoside (10)

Compound **23** (77 mg; 0.09 mmol) in MeOH (20 mL) was hydrogenated (Pd/C, 10%; 50 mg; 0.45 mmol; 5 eq.) according to the procedure 4.2. Column chromatography on silica gel (CH_2Cl_2/MeOH 8:1) furnished **10** (26 mg, 71%) as a colorless solid; $[\alpha]_D^{25}$-45.6 (*c* 0.4, MeOH); R_f 0.25 (CH_2Cl_2/MeOH 3:1); ^1H NMR (500 MHz, MeOD): δ 7.41–7.24 (m, 5H, C_6H_5), 4.83 (dd, 1H, $J_{CH,CH2a}$ 7.3 Hz, $J_{CH,CH2b}$ 4.8 Hz, PhC*H*CH_2OH), 4.80 (dd, 1H, $J_{1,2ax}$ 9.4 Hz, $J_{1,2eq}$ 1.9 Hz, H-1), 4.07 (ddd, 1H, $J_{1',1b''}$ 11.1 Hz, $J_{1',2'}$ 5.7 Hz, $J_{1',1a''}$ 3.2 Hz, H-1′), 3.89 (dd, 1H, $J_{2',3''}$9.1 Hz, $J_{2',1''}$5.6 Hz, H-2′), 3.82 (qd, 1H, $J_{5',6'}$ 6.5 Hz, $J_{5',4'}$ 2.1 Hz, H-5′), 3.73 (dd, 1H, $J_{CH2a,CH}$ 11.8 Hz, $J_{CH2a,CH}$ 7.2 Hz, PhCHCH_{2a}OH), 3.72–3.68 (m, 2H, PhCHCH_{2b}OH, H-4′), 3.66 (dd, 1H, $J_{3',2'}$ 9.2 Hz, $J_{3',4'}$ 3.5 Hz, H-3′), 3.51–3.43 (m, 3H, H-5, H-6a, H-6b),

2.11 (ddd, 1H, $J_{2eq,2ax}$ 12.7 Hz, $J_{2eq,3}$ 3.7 Hz, $J_{2eq,1}$ 1.6 Hz, H-2_{eq}), 1.78 (m, 1H, H-4a), 1.65 (ddd, 1H, $J_{1a'',1b''}$ 11.5 Hz, $J_{1a'',1'}$ 3.9 Hz, $J_{1a'',3}$ 1.9 Hz, H-1″a), 1.47 (m, 1H, H-4b), 1.32 (m, 1H, H-3), 1.24 (d, 3H, $J_{6',5'}$ 6.5 Hz, H-6′), 1.08 (m, 1H, H-2_{ax}), 0.94 (m, 1H, H-1″b); ^{13}C NMR (125 MHz, MeOD): δ 141.8 (ipso C_6H_5), 129.0, 128.4, 128.0 (C_6H_5), 103.5 (C-1), 82.1 (PhCHCH$_2$OH), 77.4 (C-5), 72.6 (C-1′), 72.2 (C-3′, C-4′), 69.9 (C-2′), 68.9 (C-5′), 67.4 (PhCHCH$_2$OH), 66.1 (C-6), 38.2 (C-2), 35.5 (C-1″), 32.1 (C-4), 32.1 (C-3), 16.6 (C-6′).

HRESIMS (*m/z*). Calcd for $C_{21}H_{32}O_8Na$ $[M+Na]^+$ 435.1989. Found: 435.1989.

4.7. (S)-2-Hydroxy-1-phenylethyl 2,3-dideoxy-3-C-[(α-L-fucopyranosyl)methyl]-β-D-arabino-hexopyranoside (11)

Starting **24** (93 mg; 0.11 mmol) in MeOH (20 mL) was hydrogenated on Pd/C (10%; 56 mg; 0.54 mmol) according to the procedure 4.2. Column chromatography of the residue on silica gel (CH_2Cl_2/MeOH 8:1) furnished **11** (20 mg, 60%) as a colorless solid; $[\alpha]_D^{25}$ -19.0 (*c* 0.2, MeOH); R_f 0.38 (CH_2Cl_2/MeOH 3:1); ^{1}H NMR (500 MHz, MeOD): δ 7.21–7.24 (m, 5H, C_6H_5), 4.89 (dd, 1H, $J_{1,2ax}$ 9.5 Hz, $J_{1,2eq}$ 1.9 Hz, H-1), 4.83 (dd, 1H, $J_{CH,CH2a}$ 7.0 Hz, $J_{CH,CH2b}$ 4.5 Hz, PhC*H*CH$_2$OH), 4.06 (ddd, 1H, $J_{1',1a''}$ 12.4 Hz, $J_{1',2'}$ 5.9 Hz, $J_{1',1b''}$ 3.0 Hz, H-1′), 3.95 (dd, 1H, $J_{2',3'}$ 8.8 Hz, $J_{2',1'}$ 5.9 Hz, H-2′), 3.86 (dd, 1H, $J_{5',6'}$ 6.5 Hz, $J_{5',4'}$ 1.6 Hz, H-5′), 3.75 (dd, 1H, $J_{6a,6b}$ 11.7 Hz, $J_{6a,5}$ 2.7 Hz, H-6a), 3.73–3.66 (m, 4H, PhCHC*H*$_2$OH, H-3′, H-4′), 3.59 (dd, 1H, $J_{6b,6a}$ 11.6 Hz, $J_{6b,5}$ 5.9 Hz, H-6b), 3.24 (ddd, $J_{5,4}$ 9.5 Hz, $J_{5,6b}$ 5.8 Hz, $J_{5,6a}$ 2.7 Hz, H-5), 3.05 (t, 1H, $J_{4,5}$ 9.7 Hz, $J_{4,3}$ 9.7 Hz, H-4), 2.30 (ddd, 1H, $J_{1a'',1b''}$ 15.2 Hz, $J_{1a'',1''}$12.4 Hz, $J_{1a'',3}$ 3.4 Hz, H-1″a), 2.21 (ddd, 1H, $J_{2eq,2ax}$ 12.8 Hz, $J_{2eq,3}$ 4.3 Hz, $J_{2eq,1}$ 2.0 Hz, H-2eq), 1.67 (m, 1H, H-3), 1.37–1.20 (m, 2H, H-1″a, H-2_{ax}), 1.24 (d, 3H, $J_{6',5'}$ 6.4 Hz, H-6′); ^{13}C NMR (125 MHz, MeOD): δ 141.7 (ipso C_6H_5), 129.1, 128.5, 128.0 (C_6H_5), 102.9 (C-1), 82.2 (PhCHCH$_2$OBn), 80.9 (C-5), 73.0 (C-1′), 72.1, 71.3 (C-3′, C-4′, C-4), 69.7 (C-2′), 68.5 (C-5′), 67.4 (PhCHCH$_2$OH), 63.4 (C-6), 38.6 (C-3), 36.6 (C-2), 27.9 (C-1″), 16.8 (C-6′); HRESIMS (*m/z*): Calcd for $C_{21}H_{32}O_9Na$ $[M+Na]^+$ 451.1939. Found: 451.1938.

4.8. Methyl 2,3-dideoxy-3-C-[(α-L-fucopyranosyl)methyl]-α-D-arabino-hexopyranoside (12)

Starting **26** (40 mg; 0.59 mmol) in MeOH (20 mL) was hydrogenated on Pd/C (10%; 31 mg) according to the procedure 4.2. Column chromatography of the residue on silica gel (CH_2Cl_2/MeOH 8:1) furnished **12** (12 mg; 64%) as a colorless solid; $[\alpha]_D^{25}$ -17.3 (*c* 0.3, MeOH); R_f 0.2 (CH_2Cl_2/MeOH 3:1); ^{1}H NMR (500 MHz, MeOD): δ 4.72 (d, 1H, $J_{1,2}$ 3.3 Hz, H-1), 4.01 (ddd, 1H, $J_{1',1a''}$ 12.3 Hz, $J_{1',2'}$ 5.8 Hz, $J_{1',1b''}$ 2.9 Hz, H-1′), 3.92 (dd, 1H, $J_{2',3'}$ 9.0 Hz, $J_{2',1'}$ 5.8 Hz, H-2′), 3.88 (qd, $J_{5'6'}$ 6.5 Hz, $J_{5',4'}$ 1.8 Hz, H-5′), 3.84 (dd, 1H, $J_{6a,6b}$ 11.7 Hz, $J_{6a,5}$ 2.6 Hz, H-6a), 3.72–3.66 (s, 3H, H-4′, H-3′, H-6b), 3.54 (ddd, 1H, $J_{5,4}$ 9.8 Hz, $J_{5,6b}$ 5.8 Hz, $J_{5,6a}$ 2.6 Hz, H-5), 3.37 (s, 3H, OCH_3), 3.13 (t, 1H, $J_{4,5}$ 9.8 Hz, $J_{4,3}$ 9.8 Hz, H-4), 2.29 (ddd, 1H, $J_{1a'',1b''}$ 14.9 Hz, $J_{1a'',1'}$ 12.2 Hz, $J_{1a'',3}$ 3.4 Hz, H-1″a), 1.92–2.03 (m, 2H, H-2_{ax}, H-3), 1.36 (ddd, 1H, $J_{2eq,2ax}$ 13.3 Hz, $J_{2eq,1}$ 0.9 Hz, $J_{2eq,3}$ 3.6 Hz, H-2eq), 1.27–1.21 (m, 1H, H-1″b), 1.24 (d, 3H, $J_{6',5'}$ 6.4 Hz, H-6′); ^{13}C NMR (125 MHz, MeOD): δ 99.1 (C-1), 74.5 (C-5), 72.9 (C-1′), 72.1, 71.6 (C-3′, C-4′, C-4), 69.8 (C-2′), 68.6 (C-5′), 63.3 (C-6), 54.8 (OCH_3), 35.4 (C-2), 34.5 (C-3), 28.0 (C-1″), 16.7 (C-6′); HRESIMS (*m/z*): Calcd for $C_{14}H_{26}O_8Na$ $[M+Na]^+$ 345.1520. Found: 345.1521.

4.9. (2R,4R)-2-[(S)-2-Methyloxycarbonyl-1-phenyl]ethoxy-4-[(2,3,4,6-tetra-O-benzyl-α-D-mannopyranosyl)methyl]-6-formyl-3,4-dihydro-2H-pyrane (14)

Molecular sieves (4 Å; 1.35 g) were added to a solution of compound **13** (1.78 g; 2.05 mmol) in dry MeCN (40 mL), and MeOTf (0.35 mL; 3.08 mmol) was added dropwise. After stirring at room temperature for 1 h, MeOH (4 mL) was added and the solvent was evaporated in vacuo. The residue was treated with MeOH (30 mL) and then $NaBH_4$ (0.256 g; 6.77 mmol) was added in portions. After stirring at room temperature for 1 h, acetone (4 mL) was added, the reaction mixture was filtered through a Celite® pad, which was washed with acetone (70 mL) and the filtrate was evaporated in vacuo. The residue was dissolved in MeCN (35 mL) and a solution of $AgNO_3$ (708 mg; 4.17 mmol) in H_2O (2.1 mL) was added under vigorous stirring. After stirring for 20 min at room temperature, phosphate buffer (7 mL; pH 7) was added. After a further 15 min, the solvent was evaporated in vacuo and the residue was partitioned between CH_2Cl_2 (150 mL) and a phosphate buffer (150 mL, pH 7). The organic layers were dried over $MgSO_4$, filtered and concentrated under reduce pressure. Column chromatography of residue on silica gel (hexane/EtOAc, 3:1 → 2:1) furnished **14** (1.07 g; 64%) as a colorless oil; $[\alpha]_D^{25}$+27.8 (*c* 1.0, $CHCl_3$); R_f 0.22 (hexane/EtOAc 2:1); ^{1}H NMR (500 MHz, $CDCl_3$): δ 9.00 (s, C*H*O), 7.38–7.16 (m, 25H, 5 x C_6H_5), 5.90 (d, 1H, $J_{4,5}$ 4.4 Hz, H-5), 5.42 (m, 1H, H-2), 5.41 (s, 1H, C*H*COOCH$_3$), 4.62 (d, 1H, *J* 11.6 Hz, OCH_2Ph), 4.59 (d, 1H, *J* 12.2 Hz, OCH_2Ph), 4.52–4.45 (m, 6H, OCH_2Ph), 4.00 (ddd, 1H, $J_{1',1''a}$ 9.9 Hz, $J_{1',1''b}$ 4.5 Hz, $J_{1',2'}$ 2.9 Hz, H-1′), 3.91 (dd, 1H, $J_{5',4'}$ 6.1 Hz, $J_{5',6'a}$ 6.1 Hz, $J_{5',6'b}$ 3.8 Hz, H-5′), 3.85 (dd, 1H, $J_{6'a,6'b}$ 10.3 Hz, $J_{6'a,5'}$ 6.4 Hz, H-6'a), 3.78–3.64 (m, 3H, H-3′, H-6'b, H-4′), 3.68 (s, 3H, OCH_3), 3.45 (dd, 1H, $J_{2',1'}$ 2.9 Hz, $J_{2',3'}$ 5.6 Hz, H-2′), 2.73–2.70 (m, 1H, H-4), 2.12 (m, 1H, $J_{3ax,3eq}$ 14.3 Hz, $J_{3ax,4}$ 7.3 Hz, $J_{3ax,2}$ 2.9 Hz, H-3ax), 2.05 (ddd, 1H, $J_{3eq,3ax}$ 14.1 Hz, $J_{3eq,2}$ 3.8 Hz, $J_{3eq,4}$ 3.8 Hz, H-3eq), 1.91–1.81 (m, 2H, H-1″ax, H-1″eq); ^{13}C-NMR (125 MHz, $CDCl_3$): 186.6 (CH=O), 170.9 (COOCH$_3$), 148.5 (C-6), 138.2, 138.1, 138.0, 136.0 (4 x ipso C_6H_5), 128.6–127.2 (4 x C_6H_5), 126.8 (C-5), 96.5 (C-2), 76.9 (CHCOOCH$_3$), 76.5 (C2′, C-3′), 74.64 (C-4′), 73.57 (C-5′), 73.3, 73.2, 72.4, 71.8 (4 x PhCH$_2$), 69.9 (C-1′), 68.7 (C-6′), 52.2 (OCH$_3$), 35.5 (C-1″), 31.8 (C-3), 26.50 (C-4); HRESIMS (*m/z*): Calcd for $C_{50}H_{52}O_{10}Na$ $[M+Na]^+$ 835.3453. Found 835.3458.

4.10. (2R,4R)-2-[(S)-2-hydroxy-1-phenylethoxy]-4-[(2,3,4,6-tetra-O-benzyl-α-D-mannopyranosyl)methyl]-6-hydroxymethyl-3,4-dihydro-2H-pyrane (15)

Aldehyde **14** (0.50 g; 0.62 mmol) was dissolved in dry THF (10 mL) and $LiAlH_4$ (70 mg; 1.85 mmol) was added in portions at 0 °C. The reaction mixture was stirred at rt for 1 h and then NaOH (1M aq. solution; 11 mL) was added at 0 °C. The salts were removed through a Celite® pad, which was washed with THF (50 mL) and the filtrate was evaporated. The residue was portioned between EtOAc (50 mL) and HCl. (0.5M aq. solution; 50 mL) and then the organic layer was washed with $NaHCO_3$ (satd aq; 50 mL) solution. The organic layers were dried over $MgSO_4$, filtered and concentrated. Column chromatography of residue on silica gel (hexane/EtOAc, 2:1) afforded **15** (0.47 g; 95%) as a light yellow oil; $[\alpha]_D^{25}$-10.6 (*c* 1.2, $CHCl_3$); R_f 0.31 (hexane/EtOAc 1:1); ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.38–7.21 (m, 25H, 5 x C_6H_5), 5.14 (dd, 1H, $J_{2.3ax}$ 3.9 Hz, $J_{2,3eq}$ 2.8 Hz, H-2), 4.74 (d, 1H, *J* 11.5 Hz, CH_aH_bPh), 4.71 (d, 1H, $J_{5,4}$ 4.3 Hz, H-5), 4.65 (d, 1H, *J* 12.2 Hz, CH_aH_bPh), 4.62 (d, 1H, *J* 12.2 Hz, CH_aH_bPh), 4.60–4.55 (m, 4H, 3x CH_aH_bPh, PhC*H*CH$_2$OH); 4.54 (d, 1H, *J* 11.5 Hz, CH_aH_bPh), 4.52 (d, 1H, *J* 11.7 Hz, CH_aH_bPh), 4.11 (ddd, 1H, $J_{1',1''a}$ 10.7 Hz, $J_{1',1''b}$ 4.4 Hz, $J_{1',2''}$2.5 Hz, H-1′), 4.04 (td, 1H, $J_{5',6'a}$ 10.0 Hz, $J_{5',4'}$ 7.1 Hz, $J_{5',6'b}$ 3.1 Hz, H-5′), 3.81–3.75 (m, 3H, H-3′, H-4′, PhCHCH_{2a}OH), 3.72 (dd, 1H, J_{gem} 10.1 Hz, $J_{CH2b,CH}$ 7.1 Hz, PhCHCH_{2b}OH), 3.63 (dd, 1H, $J_{6'a,6'b}$ 11.8 Hz, $J_{6'a,5'}$ 9.6 Hz, H-6a'), 3.54–3.50 (m, 1H, H-6b'), 3.55 (s, 1H, $J_{2',3'}$ 4.4 Hz, $J_{2',1''}$2.4 Hz, H-2′), 3.39 (dd, 1H, $J_{7b,7a}$ 13.5 Hz, $J_{7b,OH}$ 4.3 Hz, H-7), 3.33 (dd, 1H, $J_{7a,7b}$ 12.9 Hz, $J_{7a,OH}$ 3.7 Hz, H-7a), 3.10 (bd, *J* 9.7 Hz, PhCHCH$_2$O*H*), 2.36–2.26 (m, 2H, H-3eq, H-4), 2.11 (ddd, $J_{1''a,1''b}$ 14.2 Hz, $J_{1''a,1'}$ 10.7 Hz, $J_{1''a,4}$ 8.1 Hz, H-1″a), 1.85 (ddd, $J_{3ax,3eq}$ 13.6 Hz, $J_{3ax,4}$ 6.9 Hz, $J_{3ax,2}$ 2.8 Hz, H-3ax), 1.48 (ddd, 1H, $J_{1''b,1''a}$ 14.4 Hz, $J_{1''b,4}$ 6.1 Hz, $J_{1''b,1'}$

2.5 Hz, H-1″b), 0.91 (m, 1H, 7-O*H*); ^{13}C-NMR (125 MHz, $CDCl_3$): 148.9 (C-6), 140.3, 138.4, 138.38, 138.3, 137.1 (5x ipso C_6H_5), 128.5–127.8 (4 x C_6H_5), 102.0 (C-5), 100.0 (C-2), 84.1 (PhCHCH$_2$OH), 77.9, 75.3 (C-3′, C-4′), 76.9 (C-2′), 73.2, 73.1 (C-1′,C-5′), 74.1, 73.7, 72.3, 71.8 (4 x PhCH$_2$), 70.1 (PhCHCH$_2$OH), 67.3 (C-6′), 63.0 (C-7), 34.5 (C-1″), 31.0 (C-3), 27.9 (C-4); HRESIMS (*m/z*): Calcd for $C_{49}H_{54}O_9Na$ $[M+Na]^+$ 809.3666. Found 809.3662.

4.11. Methyl 2,3,4-trideoxy-3[(α-D-manopyranosyl)methyl]-α,β-D-threo-hexopyranoside (16)

A solution of compound **15** (0.104 g; 0.13 mmol) in MeOH (20 mL) was hydrogenated on Pd/C (10%; 70.4 mg; 0.66 mmol) according to the procedure 4.2. Column chromatography of the residue on silica gel ($CHCl_3$/MeOH 7:3) furnished **16** (48 mg; 82%) as a colorless solid; $[\alpha]_D^{25}$-10.6 (*c* 1.2, $CHCl_3$); R_f 0.31 ($CHCl_3$/MeOH 7:3); ratio α:β = 0.7:0.3; ^{1}H NMR (600 MHz, MeOD): δ 4.79 (d, 0.7H, $J_{1,2}$ 3.2 Hz, H-1α), 4.43 (dd, 0.3H, $J_{1,2ax}$ 9.5 Hz, $J_{1,2eq}$ 2.1 Hz, H-1β), 4.02 (ddd, 1H, *J* 10.7 Hz, *J* 4.2 Hz, *J* 2.4 Hz, H-5α, H-5β), 3.84–3.77 (m, 2H, H-1′α, H-1′aβ, H-6aα, H-6aβ), 3.75 (dd, 1H, $J_{6b,6a}$ 11.8 Hz, $J_{6b,5}$ 5.6 Hz, H-6bα, H-6bβ), 3.72–3.42 (m, 6H, H-2′α, H-2′β, H-3′α, H-3′β, H-4′α, H-4′β, H-5′α, H-5′β, 2 x H-6′α, 2 x H-6′β), 3.50 (s, 0.9H, OCH_3-β), 3.37 (s, 2.1H, OCH_3-α), 2.12 (m, 1H, H-3α, H-3β), 1.89–1.73 (m, 3H, H-1″α, H-1″β, H-2aα, H-2aβ, H-4aα, H-4aβ), 1.38–1.23 (m, 2H, H-2bα, H-2bβ, H-4bα, H-4bβ), 0.97 (m, 1H, H-1″bα, H-1″bβ); ^{13}C NMR (151 MHz, MeOD): δ 104.3 (C-1β), 99.7 (C-1α), 77.2 (C-5α, C-5β), 75.83, 73.37, 72.79, 70.71, 69.33 (C-1′α, C-2′α, C-3′α, C-4′α, C-5′α), 75.86, 73.31, 72.79, 70.80, 69.46 (C-1′β, C-2′β, C-3′β, C-4′β, C-5′β), 66.49 (C-6′α), 66.15 (C-6′β), 63.02 (C-6α), 63.08 (C-6β), 56.46 (OCH_3-β), 53.76 (OCH_3-α), 37.89, 36.64, 34.14 (C-2α, C-4α, C-1″α), 39.44, 36.34, 33.89 (C-2β, C-4β, C-1″β), 31.5 (C-3β), 27.2 (C-3α); HRESIMS (*m/z*): Calcd for $C_{14}H_{26}O_8Na$ $[M+Na]^+$ 345.1525. Found 345.1524.

4.12. 1,6-Di-O-Acetyl-2,3,4-trideoxy-3[(2,3,4,6-tetra-O-acetyl-α-D-manopyranosyl)methyl]-α,β-D-threo-hexopyranose (17)

Compound **8** (20 mg; 0.06 mmol) was dissolved in pyridine/Ac_2O (2:1, 2 mL). After 8 h, the volatiles were evaporated and the residue was purified by flash column chromatography (hexane/EtOAc 1.5:1) to give **17** (35 mg; 96%) as a colorless syrup; R_f 0.28 (hexane/EtOAc 1.5:1); ratio α:β = 0.3:0.7; ^{1}H NMR (600 MHz, $CDCl_3$): δ 6.21 (d, 0.3H, $J_{1,2}$ 3.2 Hz, H-1α), 5.66 (dd, 0.7H, $J_{1,2ax}$ 9.9 Hz, $J_{1,2eq}$ 2.2 Hz, H-1β), 5.22 (m, 1H, $J_{3,4}$ 8.7 Hz, $J_{3,2}$ 3.1 Hz, H-3′α, H-3′β), 5.17 (m, 1H, $J_{4,5}$ 8.7 Hz, $J_{4,3}$ 8.7 Hz, H-4′α, H-4′β), 5.09 (m,12H, H-2′α, H-2′β), 4.36 (dd, 1H, $J_{6a,6b}$ 12.1 Hz, $J_{6a,5}$ 6.7 Hz, H-6′a-α, H-6′a-β), 4.12–4.04 (m, 4H, H-6′b-α, H-6′b-β, 2 x H-6-α, 2 x H-6-β, H-1′α, H-1′β), 3.87 (m, 1H, H-5′α, H-5′β), 3.76 (m, 1H, H-5α, H-5β), 2.13, 2.12, 2.10, 2.09, 2.078, 2.080, 2.07, 2.06, 2.03 (9 x s, 9H, 12 x Ac-α+β), 1.96–1.72 (m, 4H, H-3α, H-3β, H-4aα, H-4aβ, H-2aα, H-2aβ, H-1″a-α, H-1″a-β), 1.49–1.27 (m, 2H, H-2bα, H-2bβ, H-1″b-α, H-1″b-β), 1.16–0.97 (m, 1H, H-4bα, H-4bβ); ^{13}C-NMR (151 MHz, $CDCl_3$): 171.03, 171.00, 170.68, 170.64, 170.36, 170.08, 169.73, 169.57, 169.29 (12 x CH_3CO-α+β), 94.1 (C-1β), 97.1 (C-1α), 73.9 (C-5α+β), 72.03 (C-1′α+β), 70.98, 70.94, 70.83 (C-5′α+β, C-4′α+β), 68.85 (C-3′α), 68.80 (C-3′β), 67.16 (C-2′α), 67.14 (C-2′β), 66.61 (C-6α), 66.25 (C-6β), 62.52 (C-6′α), 62.44 (C-6′β), 36.64, 35.14, 32.46 (C-4β, C-2β, C-1″β), 36.64, 35.32, 32.69 (C-4α, C-2α, C-1″α), 30.54 (C-3α+β), 21.32, 21.07, 21.04, 21.02, 20.89, 20.85 (12 x CH_3CO α+β); HRESIMS (*m/z*). Calcd for $C_{25}H_{36}O_{14}Na$ $[M+Na]^+$ 583.2002. Found 583.1999.

4.13. (2R,4R)-2-[(S)-2-benzyloxy-1-phenylethoxy]-4-[(2,3,4,6-tetra-O-benzyl-α-D-mannopyranosyl)methyl]-6-benzyloxymethyl-3,4-dihydro-2H-pyrane (18)

Compound **15** (0.256 g; 0.33 mmol) was dissolved in dry THF (15 mL). After addition of NaH (47 mg; 1.96 mmol; 60% suspension in mineral oil), the mixture was stirred at rt for 1 h. Benzyl bromide (0.66 mL; 1.96 mmol) and TBAI (30 mg; 0.08 mmol) were added and the solution was stirred at rt for 19 h. The reaction was quenched by addition of MeOH (5 mL) and the volatiles were evaporated. The residue was diluted with CH_2Cl_2 (50 mL), extracted with $NaHCO_3$ (satd aq solution; 50 mL) and brine (50 mL). The organic layer was dried over $MgSO_4$, and concentrated. Column chromatography of the residue on silica gel (hexane/EtOAc 8:1 → 5:1) provided **18** (0.143 g; 45%) as a colorless oil; $[\alpha]_D^{25}$ -0.5 (*c* 5.1, $CHCl_3$); R_f 0.24 (hexane/EtOAc 4:1); ^{1}H NMR (600 MHz, CD_2Cl_2): δ 7.45–7.27 (m, 35H, 7 x C_6H_5), 5.47 (dd, 1H, $J_{2,3eq}$ 2.7 Hz, $J_{2,3ax}$ 4.8 Hz, H-2), 4.96 (dd, 1H, $J_{CH,CH2a}$ 7.9 Hz, $J_{CH,CH2b}$ 3.8 Hz, PhC*H*CH$_2$OBn), 4.93 (d, 1H, $J_{5,3}$ 3.8 Hz, H-5), 4.83 (d, 1H, *J* 11.1 Hz, C*Ha*HbPh), 4.69 (d, 1H, *J* 11.1 Hz, CHa*Hb*Ph), 4.68–4.54 (m, 8H, 4 x CH$_2$Ph), 4.38 (d, 1H, *J* 12.0 Hz, C*Ha*HbPh), 4.35 (d, 1H, *J* 12.0 Hz, CHa*Hb*Ph), 4.20 (ddd, 1H, $J_{1',1''a}$ 11.0 Hz, $J_{1',1''b}$ 3.7 Hz, $J_{1',2'}$ 3.7, H-1′), 3.95 (t, 1H, $J_{4',5'}$ $J_{4',3'}$ 7.3 Hz, H-4′), 3.90–3.84 (m, 3H, H-6a', H-3′, H-5′), 3.75 (dd, 1H, $J_{6'b,5'}$5.1 Hz, $J_{6'b,6'a}$ 12.6 Hz, H-6b'), 3.70 (dd, 1H, $J_{CH2a,CH}$ 8.1 Hz, $J_{CH2a,CH2b}$ 10.5 Hz, PhCHC*H$_{2a}$*OBn), 3.66 (dd, 1H, $J_{2',1'}$ 3.6 Hz, $J_{2',3'}$ 3.6 Hz, H-2′), 3.63 (dd, 1H, $J_{CH2b,CH}$ 3.8 Hz, $J_{CH2b,CH2a}$ 10.5 Hz, PhCHC*H$_{2b}$*OBn), 3.51 (d, 1H, J_{gem} 12.2 Hz, H-7), 3.41 (d, 1H, J_{gem} 12.3 Hz, H-7), 2.49 (m, 1H, H-4), 2.12 (ddd, 1H, $J_{3eq,3ax}$ 13.4 Hz, $J_{3eq,4}$ 7.0 Hz, $J_{3eq,2}$ 2.6 Hz, H-3eq), 1.97 (m, 1H, H-1″a), 1.92 (ddd, 1H, $J_{3ax,3eq}$ 13.6 Hz, $J_{3ax,2}$ 4.7 Hz, $J_{3ax,4}$ 4.8 Hz, H-3ax), 1.79 (ddd,1H, $J_{1''b,1''a}$ 13.4 Hz, $J_{1''b,4}$ 9.3 Hz, $J_{1''b,1'}$ 3.2 Hz, H-1″); ^{13}C NMR (151 MHz, CD_2Cl_2): δ 147.5 (C-6), 140.8, 139.0, 138.93, 138.91, 138.88, 138.88, 138.84 (7 x ipso C_6H_5), 128.8–127.0 (7 x C_6H_5), 103.3 (C-5), 99.5 (C-1), 80.3 (PhCHCH$_2$OBn), 78.6 (C-3′), 77.3 (C-2′), 75.3 (C-4′), 75.2 (PhCHCH$_2$OBn), 74.4, 73.5, 72.4, 72.2, 72.1, 70.2 (6 x PhCH$_2$), 73.5 (C-5′), 71.9 (C-1′), 70.2 (C-7), 69.6 (C-6′), 35.7 (C-1″), 33.3 (C-3), 26.7 (C-4); HRESIMS (*m/z*): Calcd for $C_{63}H_{66}NaO_9$ $[M+Na]^+$ 989.4599. Found 989.4609.

4.14. (2R,4R)-2-[(S)-2-benzyloxy-1-phenylethoxy] 2,3-dideoxy-3-C-[(2,3,4,6-tetra-O-benzyl-α-D-mannopyranosyl)methyl]-6-O-benzyl-β-D-arabino-hexopyranoside (19)

To a solution of compound **18** (143 mg; 0.15 mmol) in THF (3 mL) at 0 °C was added drop wise 2 M solution of BH_3.Me_2S in THF (0.26 mL; 0.52 mmol). The reaction mixture was stirred at rt for 20 h and then 30% NaOH solution (0.23 mL) and 30% H_2O_2 (0.23 mL) were added in succession. The mixture was stirred at rt for further 30 min and partitioned between EtOAc (15 mL) and saturated $NaHCO_3$ (15 mL) solution. The organic phase was dried, the solution evaporated, and the residue chromatographed on silica gel in hexane/EtOAc (2:1) to give **19** (56 mg; 38%) as a colorless oil; $[\alpha]_D^{25}$ 4.2 (*c* 2.9, CH_2Cl_2); R_f 0.32 (hexane/EtOAc 2:1); ^{1}H NMR (600 MHz, $CDCl_3$): δ 7.38–7.18 (m, 35H, 7 x C_6H_5), 4.93 (dd, 1H, $J_{CH,CH2b}$ 3.8 Hz, $J_{CH,CH2a}$ 7.9 Hz, PhC*H*CH$_2$OBn), 4.79 (dd, 1H, $J_{1,2ax}$ 9.4 Hz, $J_{1,2eq}$ 2.0 Hz, H-1), 4.67 (d, 1H, *J* 11.1 Hz, C*Ha*HbPh), 4.66–4.35 (m, 10 H, 5 x CH$_2$Ph), 4.48 (d, 1H, *J* 11.4 Hz, CHa*Hb*Ph), 4.22 (ddd, 1H, $J_{1',1''a}$ 9.5 Hz, $J_{1',1''b}$ 5.0 Hz, $J_{1',2'}$ 3.0 Hz, H-1′), 3.90 (dt, 1H, $J_{5',6'a}$ 7.2 Hz, $J_{5',4'}$ 7.2 Hz, $J_{5',6'b}$ 3.3 Hz, H-5′), 3.75 (dd, 1H, $J_{3',4'}$ 6.9 Hz, $J_{3',2'}$ 3.0 Hz, H-3′), 3.72–3.54 (m, 7H, H-6a', H-6'b, H-4′, H-6a, H-2′, PhCHC*H$_{2a}$*OBn, PhCHC*H$_{2b}$*OBn), 3.47 (dd, 1H, $J_{6b,6a}$ 10.6 Hz, $J_{6b,5}$ 5.8 Hz, H-6b), 3.32 (t, 1H, $J_{4,5}$ 9.5 Hz, $J_{4,3}$ 9.5 Hz, H-4), 3.27 (ddd, 1H, $J_{5,4}$ 9.3 Hz, $J_{5,6b}$ 5.8 Hz, $J_{5,6a}$ 3.6 Hz, H-5), 1.92–1.86 (m, 2H, H-1″a, H-2eq), 1.68 (m, 1H, H-3), 1.50–1.43 (m, 2H, H-1″b, H-2ax); ^{13}C NMR (151 MHz, $CDCl_3$): δ 140.1, 138.7, 138.4, 138.29, 138.26, 138.2, 137.9 (7 x ipso C_6H_5), 128.5–126.9 (6 x C_6H_5), 101.5 (C-1), 79.2 (PhCHCH$_2$OBn), 78.2 (C-5), 76.7 (C-3′), 75.3 (C-2′), 74.9 (C-6′), 73.8, 73.5, 73.43, 73.38, 72.4, 71.6 (6 x PhCH$_2$), 73.36 (C-5′), 71.1 (C-6), 70.9, 70.76 (C-4, C-4′, C-1′), 69.3 (PhCHCH$_2$OBn), 38.7 (C-3), 36.7 (C-2), 32.1 (C-1″); HRESIMS (*m/z*): Calcd for $C_{63}H_{68}NaO_{10}$ $[M+Na]^+$ 1007.4710, Found 1007.4760.

4.15. 1,4,6-Tri-O-acetyl-2,3-dideoxy-3-C-[(2,3,4,6-tetra-O-acetyl-α-D-mannopyranosyl)methyl]-α,β-D-arabino-hexopyranose (20)

Compound **9** (7 mg; 0.02 mmol) was dissolved in pyridine/Ac_2O (2:1, 2 mL) After 8 h, the volatiles were evaporated and the residue was purified by flash chromatography (hexane/EtOAc 1:1) to give **20** (12 mg; 95%) as a colorless syrup; R_f 0.21 (hexane/EtOAc 1:1); ratio α:β = 0.2:0.8; ^{1}H NMR (600 MHz, $CDCl_3$): δ 6.15 (dd, 0.2H, $J_{1,2ax}$ 3.6 Hz, $J_{1,2eq}$ 1.2 Hz, H-1α), 5.72 (dd, 0.8H, $J_{1,2ax}$ 10.0 Hz, $J_{1,2eq}$ 2.3 Hz, H-1β), 5.16 (m, 1H, $J_{3,4}$ 9.2 Hz, $J_{3,2}$ 3.7 Hz, H-3'α, H-3'β), 5.17 (m, 1H, $J_{4,5}$ 8.4 Hz, $J_{4,3}$ 8.4 Hz, H-4'α, H-4'β), 5.06 (m, 0.2H, H-2'α), 5.03 (m, 0.8H, H-2'β), 4.81 (t, 0.8H, $J_{4,5}$ 10.2 Hz, $J_{4,3}$ 10.2 Hz, H-4β), 4.64 (t, 0.2H, $J_{4,5}$ 9.9 Hz, $J_{4,3}$ 9.9 Hz, H-4α), 4.35 (dd, 1H, $J_{6'a,6'b}$ 12.1 Hz, $J_{6'a,5'}$ 7.1 Hz, H-6'a+β), 4.31 (m, 0.2H, H-6'a-α), 4.25 (dd, 0.8H, $J_{6a,6b}$ 12.3 Hz, $J_{6a,5}$ 4.8 Hz, H-6a-β), 4.22 (m, 0.2H, H-6a-α), 4.09 (dd, 0.8H, $J_{6'b,6'a}$ 12.1 Hz, $J_{6'b,5'}$ 3.0 Hz, H-6'b-β), 4.05 (m, 0.2H, H-6'b-α), 4.01 (dd, 0.8H, $J_{6b,6a}$ 12.4 Hz, $J_{6b,5}$ 2.3 Hz, H-6b-β), 3.98 (m, 0.2H, H-6a-α), 3.95 (m, 1H, H-1'α, H-1'β), 3.91–3.84 (m, 1H, H-5'α, H-5'β), 3.68 (ddd, 0.8H, $J_{5,4}$ 9.6 Hz, $J_{5,6}$ 4.8 Hz, $J_{5,6b}$ 2.3 Hz, H-5β), 3.48 (m, 0.2H, H-5α), 2.30–2.17 (m, 2H, H-2aα, H-2aβ, H-1″aα, H-1″aβ), 2.13, 2.12, 2.11, 2.10, 2.091, 2.088, 2.082, 2.07, 2.06, 2.03, 2.024, 2.016, 1.99 (13 x s, 9H, 14 x Ac-α+β), 1.95 (m, 1H, H-3α, H-3β), 1.74–1.64, 1.62–1.47 (m, 2H, H-2bα, H-2bβ, H-1″b-α, H-1″b-β); ^{13}C-NMR (151 MHz, $CDCl_3$): δ 170.9–169.1 (14 x CH_3CO-α+β), 93.1 (C-1β), 90.8 (C-1α), 75.7 (C-5α+β), 73.7 (C-1'α+β), 71.29, 71.13, 71.01, 70.82, 70.40, 70.14 (C-5'α+β, C-4'α+β, C-4α+β), 68.60 (C-3'α), 68.43 (C-3'β), 67.05 (C-2'α), 67.20 (C-2'β), 66.57, 62.37 (C-6'β, C-6β), 62.59, 62.51 (C-6'α, C-6α), 38.04 (C-3α), 37.8 (C-3β), 35.19 (C-2β), 34.15 (C-2α), 31.14 (C-1″β), 30.82 (C-3α), 21.21–20.81 (m, 14 x CH_3CO α+β); HRESIMS (*m/z*): Calcd for $C_{27}H_{38}O_{16}Na$ $[M+Na]^+$ 641.2052. Found 641.2053.

4.16. (2R,4R)-2-[(S)-2-methyloxycarbonyl-1-phenylethoxy]-4-[(2,3,4-tri-O-benzyl-α-L-fucopyranosyl)methyl]-6-formyl-3,4-dihydro-2H-pyrane (22)

Molecular sieves (4 Å; 1.35 g) were added to a solution of compound **21** (1.0 g; 1.3 mmol) in dry MeCN (25 mL), and MeOTf (0.23 mL; 1.9 mmol) was added dropwise. After stirring at rt for 20 min, MeOH (2.5 mL) was added and the solvent was evaporated. The residue was treated with MeOH (25 mL) and then $NaBH_4$ (0.16 g; 4.3 mmol; 3.3 eq.) was added in portions. After stirring at rt for 10 min, acetone (2.5 mL) was added, the reaction mixture was filtered through a Celite® pad, which was washed with acetone (50 mL) and the filtrate was evaporated. The residue was dissolved in MeCN (25 mL) and a solution of $AgNO_3$ (0.36 g; 2.1 mmol) in H_2O (1.2 mL) was added under vigorous stirring. After stirring for 30 min at rt, phosphate buffer (5 mL; pH 7) was added. After 15 min, the solvent was evaporated and the residue was partitioned between CH_2Cl_2 (100 mL) and a phosphate buffer (100 mL, pH 7). The organic layers were dried over $MgSO_4$, filtered and concentrated. Column chromatography of residue on silica gel (PE/EtOAc, 5:1) furnished **22** (0.65 g; 70%) as colorless oil; $[\alpha]_D^{25}$ -6.8 (*c* 1.2, $CHCl_3$); R_f 0.35 (PE/EtOAc 3:1); ^{1}H NMR ($CDCl_3$, 500 MHz): δ 9.06 (s, 1H, C*H*O), 7.14–7.38 (m, 20H, 4 x C_6H_5), 6.06 (d, 1H, $J_{5,4}$ 4.6 Hz, H-5), 5.47 (dd, 1H, $J_{2,3ax}$ 3.7 Hz, $J_{2,3eq}$ 2.7 Hz, H-2), 5.39 (s, 1H, PhC*H*COOMe), 4.43–4.78 (m, 6H, 3 x PhCH_2), 4.10 (ddd, 1H, $J_{1',1b''}$ 7.3 Hz, $J_{1',2'}$ 4.5 Hz, $J_{1',1a''}$ 2.4 Hz, H-1′), 3.78 (m, 1H, H-2′), 3.69 (s, 3H, OCH_3), 3.51 (dd, 1H, $J_{3',2'}$ 7.7 Hz, $J_{3',4'}$ 3.0 Hz, H-3′), 3.49 (t, 1H, $J_{4',5'}$ 3.1 Hz, $J_{4',3'}$ 3.1 Hz, H-4′), 3.41 (m, 1H, H-5′), 2.51 (m, 1H, H-4), 2.12 (ddd, 1H, $J_{1''b,1''a}$ 14.5 Hz, $J_{1''b,1'}$ 7.3 Hz, $J_{1''b,4}$ 2.9 Hz, H-1″b), 2.08 (ddd, 1H, $J_{3ax,3eq}$ 14.2 Hz, $J_{3ax,4}$ 7.9 Hz $J_{3ax,2}$ 3.7 Hz, H-3ax), 2.02 (ddd, 1H, $J_{3eq,3ax}$ 14.2, $J_{3eq,2}$ 2.7 Hz, $J_{3eq,4}$ 1.2 Hz, H-3eq), 1.68 (ddd, 1H, $J_{1''a,1b''}$ 14.5 Hz, $J_{1''a,4}$ 7.6 Hz, $J_{1''a,1'}$ 2.4 Hz, H-1″a), 1.06 (d, 3H, $J_{6',5'}$ 6.5 Hz, H-6′); ^{13}C NMR (126 MHz, $CDCl_3$): δ 186.8 (CHO), 171.1 ($COOCH_3$), 148.2 (C-6), 139.0, 138.7, 138.5136.5 (4 x ipso C_6H_5), 129.7 (C-5), 127.4–128.7 (4 x C_6H_5), 96.4 (C-2), 77.1, 76.6, 76.6 (C-3′, C-4′, C-5′), 76.3 (C-2′, PhCHCOOMe), 73.6, 73.5, 73.3 (3 x PhCH_2), 68.1 (C-1′), 52.4 (OCH_3), 31.2, 31.2 (C-3, C-1″), 28.6 (C-4), 15.7 (C-6′); HRESIMS (*m/z*): Calcd for $C_{43}H_{46}O_9Na$ $[M+Na]^+$ 729.3034. Found: 729.3034.

4.17. (2R,4R)-2-[(S)-2-benzyloxy-1-phenylethoxy]-4-[(2,3,4-tri-O-benzyl-α-L-fucopyranosyl)methyl]-6-benzyloxymethyl-3,4-dihydro-2H-pyrane (23)

Aldehyde **22** (0.65 g; 0.92 mmol) was dissolved in dry THF (10 mL) and $LiAlH_4$ (0.1 g; 2.8 mmol) was added in portions at 0 °C. The reaction mixture was stirred at rt for 1 h and then NaOH (1M aq solution; 12 mL) was added at 0 °C. The salts were removed through a Celite® pad, which was washed with THF (50 mL) and the filtrate was evaporated. The residue was portioned between EtOAc (50 mL) and HCl. (0.5M aq solution; 50 mL) and then the organic layer was washed with $NaHCO_3$ (satd aq; 50 mL) solution. The organic layers were dried over $MgSO_4$, filtered and concentrated. Column chromatography of residue on silica gel (PE/EtOAc, 2:1) afforded (2*R*,4*R*)-2-[(*S*)-2-hydroxy-1-phenylethoxy]-4-[(2,3,4-tri-*O*-benzyl-α-L-fucopyranosyl)(methyl)-6-hydroxymethyl-3,4-dihydro-2*H*-pyrane as light yellow oil, which was directly used for the next reaction step. The residue was dissolved in dry THF (25 mL). After addition of NaH (0.27 g; 9.3 mmol; 60% suspension in mineral oil), the mixture was stirred at rt for 1 h. Benzyl bromide (0.66 mL; 5.5 mmol) and TBAI (0.08 g; 0.23 mmol) were added and the solution was stirred at rt for 19 h. The reaction was quenched by addition of MeOH (5 mL) and the volatiles were evaporated. The residue was diluted with CH_2Cl_2 (50 mL), washed with $NaHCO_3$ (satd aq solution; 50 mL) and brine (50 mL). The organic layer was dried over $MgSO_4$, and concentrated. Column chromatography of the residue on silica gel (PE/EtOAc 12:1) provided **23** (0.55 g; 70%) as a light yellow oil; $[\alpha]_D^{25}$ −31.2 (*c* 0.05, $CHCl_3$); R_f 0.53 (PE/EtOAc 4:1); ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.17–7.37 (m, 30H, 6 x C_6H_5), 5.37 (dd, 1H, $J_{2,3ax}$ 6.1 Hz, $J_{2,3eq}$ 2.5 Hz, H-2), 4.91 (dd, 1H, $J_{CH,CH2a}$ 8.0 Hz, $J_{CH,CH2b}$ 3.8 Hz, PhC*H*CH_2OBn), 4.80–4.31 (m, 10H, 5 x PhCH_2), 4.77 (m, 1H, H-5), 4.15 (dt, 1H, $J_{1',1''b}$ 11.3 Hz, $J_{1',1a''}$ 3.6 Hz, $J_{1',2'}$ 3.6 Hz, H-1′), 3.84–3.77 (m, 2H, H-2′, H-5′), 3.70–3.74 (m, 2H, H-3′, H-4′), 3.64 (dd, 1H, $J_{CH2a,CH2b}$ 10.6 Hz, $J_{CH2a,CH}$ 8.0 Hz, PhCHCH_{2a}OBn), 3.58 (dd, 1H, $J_{CH2b,CH2a}$ 10.6 Hz, $J_{CH2b,CH}$ 3.8 Hz, PhCHCH_{2b}OBn), 3.52 (d, 1H, $J_{7a,7b}$ 12.5 Hz, H-7a), 3.47 (d, 1H, $J_{7b,7a}$ 12.5 Hz, H-7b), 2.35 (m, 1H, H-4), 2.07 (ddd, 1H, $J_{3eq,3ax}$ 13.4 Hz, $J_{3eq,4}$ 6.9 Hz, $J_{3eq,2}$ 2.5 Hz, H-3$_{eq}$), 1.91 (ddd, 1H, $J_{1''b,1''a}$ 14.3 Hz, $J_{1''b,1'}$ 11.2 Hz, $J_{1''b,4}$ 5.7 Hz, H-1″b), 1.71 (dt, 1H, $J_{3ax,3eq}$ 13.0 Hz, $J_{3ax,4}$ 6.2 Hz, $J_{3ax,2}$ 6.2 Hz, H-3$_{ax}$), 1.59 (dd, 1H, $J_{1''a,1''b}$ 14.3 Hz, $J_{1''a,4}$ 9.3 Hz, $J_{1''a,1'}$ 2.8 Hz, H-1″a), 1.21 (d, 3H, $J_{6',5'}$ 6.6 Hz, H-6′); ^{13}C NMR (126 MHz, $CDCl_3$): δ 147.3 (C-6), 140.3, 139.0, 138.8, 138.5, 138.5, 138.4 (6 x ipso C_6H_5), 126.8–128.5 (6 x C_6H_5), 104.9 (C-5), 99.6 (C-2), 79.9 (PhC*H*CH_2OBn), 75.0 (PhCHCH_2OBn), 73.5, 73.5, 73.2, 73.1, 72.2 (5 x PhCH_2), 69.9 (C-7), 76.9, 68.4 (C-2′, C-5′), 78.3, 76.5 (C-3′, C-4′), 32.4 (C-3, C-1″), 27.1 (C-4), 15.7 (C-6′); HRESIMS (*m/z*): Calcd for $C_{56}H_{60}O_8Na$ $[M+Na]^+$ 883.4180. Found: 883.4176.

4.18. (S)-2-Benzyloxy-1-phenylethyl 2,3-dideoxy-3-C-[(2,3,4-tri-O-benzyl-α-L-fucopyranosyl)methyl]-6-O-benzyl-β-D-arabino-hexopyranoside (24)

BH_3.Me_2S (2M solution; 1.1 mL; 2.2 mmol) was added to the solution of **23** (0.55 g; 0.64 mmol) in anhydrous THF (7 mL) at 0 °C. The reaction mixture was stirred at rt for 20 h. Then 30% aq. NaOH (0.69 mL) and 30% H_2O_2 (0.69 mL) were added in succession and the reaction mixture was stirred at rt for additional 30 min. The mixture was diluted with EtOAc (50 mL), the organic layer was washed successively with NH_4Cl (satd. aq. solution; 50 mL), H_2O (50 mL), brine (50 mL), dried over $MgSO_4$ and concentrated.

Column chromatography of the residue on silica gel (PE/EtOAc 6:1) yielded **24** (0.33 g, 59%) as a colorless oil; $[\alpha]_D^{25}$-18.6 (*c* 0.4, $CHCl_3$); R_f 0.75 (PE/EtOAc 2:1); ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.20–7.39 (m, 30H, 6 x C_6H_5), 4.92 (dd, 1H, $J_{CH,CH2a}$ 7.9 Hz, $J_{CH,CH2b}$ 3.8 Hz, PhC*H*CH_2OBn), 4.83 (dd, 1H, $J_{1,2ax}$ 9.5 Hz, $J_{1,2eq}$ 2.0 Hz, H-1), 4.77 (d, 1H, *J* 11.8 Hz, C*Ha*HbPh), 4.74 (d, 1H, *J* 12.0 Hz, C*Ha*HbPh), 4.69 (d, 1H, *J* 12.0 Hz, CHa*Hb*Ph), 4.64 (d, 1H, *J* 11.8 Hz, C*Ha*HbPh), 4.60 (d, 1H, *J* 8.9 Hz, CHa*Hb*Ph), 4.58 (d, 1H, *J* 9.3 Hz, CHa*Hb*Ph), 4.55 (d, 1H, *J* 12.3 Hz, C*Ha*HbPh), 4.50 (d, 1H, *J* 11.6 Hz, CHa*Hb*Ph), 4.45 (d, 1H, *J* 12.2 Hz, C*Ha*HbPh), 4.42 (d, 1H, *J* 12.2 Hz, CHa*Hb*Ph), 4.12 (ddd, 1H, $J_{1',1''a}$ 11.5 Hz, $J_{1',2'}$ 4.3 Hz, $J_{1',1''b}$ 2.2 Hz, H-1′), 3.96 (dd, 1H, $J_{5',6'}$ 6.7 Hz, $J_{5',4'}$ 3.1 Hz, H-5′), 3.83 (m, 1H, H-3′), 3.78–3.73 (m, 2H, H-2′, H-3′), 3.71 (dd, 1H, J_{gem} 10.5 Hz, $J_{CH2a,CH}$ 7.9 Hz, PhCHC$H_a$$H_b$OBn), 3.66–3.61 (m, 2H, PhCHC$H_a$$H_b$OBn, H-6a), 3.59 (dd, 1H, $J_{6b,6a}$ 10.3 Hz, $J_{6b,5}$ 5.3 Hz, H-6b), 3.35 (dt, 1H, $J_{5,4}$ 9.6 Hz, $J_{5,6a}$ 4.9 Hz, $J_{5,6b}$ 4.9 Hz, H-5), 3.14 (dt, 1H, $J_{4,5}$ 9.3 Hz, $J_{4,3}$ 9.3 Hz, *J* 2.0 Hz, H-4), 2.04 (m, 1H, H-1″a), 1.99 (m, 1H, H-2_{eq}), 1.60 (m, 1H, H-3), 1.38–1.29 (m, 2H, H-1″a, H-2_{ax}), 1.27 (d, 3H, $J_{6',5'}$ 6.7 Hz, H-6′); ^{13}C NMR (125 MHz, $CDCl_3$): δ 140.1, 138.9, 138.7, 138.6, 138.4, 138.4, 138.3 (6 x ipso C_6H_5), 128.5–126.9 (6 x C_6H_5), 101.5 (C-1), 79.3 (Ph*C*HCH$_2$OBn), 77.4, 77.4, 77.3, 76.2 (C-2′, C-3′, C-4′, C-5), 74.9 (PhCHCH_2OBn), 73.6, 73.6, 73.5, 73.3, 73.3, 73.2 (5 x PhCH_2), 72.5 (C-4), 71.4 (C-6), 69.7 (C-1′), 68.8 (C-5′), 39.3 (C-3), 36.8 (C-2), 31.7 (C-1″), 15.6 (C-6′); HRESIMS (*m/z*): Calcd for $C_{56}H_{62}O_9Na$ $[M+Na]^+$ 901.4286. Found: 901.4286.

4.19. Methyl 2,3-dideoxy-3-C-[(2,3,4-tri-O-benzyl-α-L-fucopyranosyl)methyl]-6-O-benzyl-α-D-arabino-hexopyranoside (26)

The glycoside **24** (0.20 g; 0.23 mmol) was dissolved in THF (13 mL) and MeOH (12.3 mL), and then HCl (1.5 mL; 3M aq. solution) was added dropwise. The reaction mixture was stirred at rt for 19 h. After cautious addition of $NaHCO_3$ (satd. aq. solution) the solvent was evaporated. The residue was diluted with CH_2Cl_2 (30 mL), washed with $NaHCO_3$ (satd. aq. solution; 30 mL) and brine (30 mL). The organic layer was dried over $MgSO_4$ and concentrated. Column chromatography of the anomeric methyl glycosides **25** on silica gel (PE/EtOAc 15:1 → 7:1) provided α-anomer **26** (0.13 g; 85%) as a light yellow oil; $[\alpha]_D^{25}$+15.9 (*c* 0.3, $CHCl_3$); R_f 0.5 (PE/EtOAc 2:1); ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.38–7.23 (m, 25H, 5 x C_6H_5), 4.74 (d, *J* 12.0 Hz, C*Ha*HbPh), 4.73–4.68 (m, 2H, CH_2Ph, H-1), 4.66–4.56 (m, 6H, CH_2Ph), 4.47 (d, 1H, *J* 11.8 Hz, CHa*Hb*Ph), 4.12–4.04 (m, 1H, H-1′, H-5′), 3.79 (dd, $J_{4',3'}$ 4.0 Hz, $J_{4',5'}$ 2.9 Hz, H-4′), 3.77–3.68 (m, 5H, H-2′, H-3′, H-5, H-6b), 3.65 (m, 1H, H-6b), 3.34 (s, 3H, OCH_3), 3.23–3.31 (t, 1H, $J_{4,5}$ 9.4 Hz, $J_{4,3}$ 9.4 Hz, H-4), 1.90 (m, 1H, H-3), 1.83 (m, 1H, H-1″a), 1.73 (m, 1H, $J_{2eq,2ax}$ 13.5 Hz, *J* 4.3 Hz, *J* 1.3 Hz, H-2_{eq}), 1.42–1.50 (dd, 1H, $J_{2eq,2ax}$ 13.5 Hz, *J* 3.7 Hz, H-2_{ax}), 1.33 (d, 3H, $J_{6',5'}$ 6.7 Hz, H-6′), 1.32–1.25 (m, 1H, H-1″a); ^{13}C NMR (125 MHz, $CDCl_3$): δ 138.8, 138.7, 138.5, 138.2 (4 x ipso C_6H_5), 128.5–127.5 (4 x C_6H_5), 97.7 (C-1), 73.6, 73.3, 73.2, 73.1 (4 x PhCH_2), 77.6, 76.7, 75.5, 71.6, (C-2′, C-3′, C-4′, C-5), 71.5 (C-4), 70.5 (C-6), 70.0 (C-1′), 69.5 (C-5′), 54.6 (OCH_3), 36.7 (C-3), 36.3 (C-2), 33.7 (C-1″), 15.0 (C-6′); HRESIMS (*m/z*): Calcd for $C_{42}H_{50}O_8Na$ $[M+Na]^+$ 705.3398. Found: 705.3396.

4.20. 1,4-Bis(α-L-fucopyranosyl)butan (27)

To a solution of **29** (0.274 g; 0.46 mmol) in MeOH (10 mL), Pd/C (10%; 0.186 g; 1.74 mmol) was added and hydrogenation was carried out according to the procedure 4.2. The residue was dissolved in MeOH (5 mL) and solid NaOMe was added till pH 10. The solution was stirred at rt for 8 h. An excess of base was neutralized with Dowex 50Wx8, solids were removed and filtrate concentrated to afford **27** (142 mg; 87%) as a white powder; $[\alpha]_D^{25}$-79.0 (*c* 0.3, DMSO); R_f 0.17 ($CHCl_3$/MeOH 4:1); ^{1}H NMR (600 MHz, DMSO-*d6*): δ 4.59 (s, 2H, 2 x OH-3), 4.45 (s, 2H, 2 x OH-4), 4.26 (s, 2H, 2 x OH-2), 3.69–3.58 (m, 6H, 2 x H-5, 2 x H-3, 2 x H-1), 3.51 (t, 2H, $J_{4,3}$ 3.0 Hz, $J_{4,5}$ 3.0 Hz, 2 x H-4), 3.48 (dd, 2H, $J_{2,3}$ 8.3 Hz, $J_{2,1}$ 3.4 Hz, 2 x H-2), 1.54 (dtd, 2H, *J* 14.1 Hz, *J* 9.9 Hz, *J* 4.4 Hz, 2 x H-7a), 1.42 (ddt, 2H, *J* 14.0 Hz, *J* 9.5 Hz, *J* 4.4 Hz, 2 x H-7b), 1.32 (m, 2H, 2 x H-8a), 1.23 (m, 2H, 2 x H-8b), 1.09 (d, 6H, $J_{6,5}$ 6.5 Hz, 2 x H-6); ^{13}C-NMR (151 MHz, DMSO-*d6*): δ 73.2 (2 x C-5), 70.7 (2 x C-2), 70.1 (2 x C-4), 68.5 (2 x C-3), 67.2 (2 x C-1), 25.7 (2 x C-8), 24.8 (2 x C-7), 16.2 (2 x C-6); HRESIMS (*m/z*): Calcd for $C_{16}H_{30}O_8Na$ $[M+Na]^+$ 373.1833. Found 373.1834.

4.21. 1,4-Bis(α-D-mannopyranosyl)butan (28)

To a solution of **30** (160 mg; 0.14 mmol) in MeOH (10 mL) was added Pd/C (10%; 60 mg; 0.56 mmol) and hydrogenation was carried out according to the procedure 4.2. Purification by column chromatography ($CHCl_3$/MeOH 7:3) afforded **28** (47 mg; 98%) as a colorless syrup; $[\alpha]_D^{25}$+14.2 (*c* 1.2, MeOH); R_f 0.14 ($CHCl_3$/MeOH 7:3); ^{1}H NMR (600 MHz, MeOD): δ 3.93–3.59 (m, 12H, 2 x H-1, 2 x H-2, 2 x H-3, 2 x H-4, 4 x H-6), 3.43 (m, 2H, *J* 8.8 Hz, *J* 5.7 Hz, *J* 2.7 Hz, 2 x H-5), 1.85–1.73 (m, 2H, 2 x H-7a), 1.59–1.36 (m, 6H, 2 x H-7, 4 x H-8). ^{13}C-NMR (151 MHz, MeOD): δ 78.9 (2 x C-1), 75.6 (2 x C-5), 73.1, 72.8 (2 x C-2, 2 x C-3), 69.3 (2 x C-4), 63.0 (2 x C-6), 29.4 (2 x C-7), 26.6 (2 x C-8). HRESIMS (*m/z*): Calcd for $C_{16}H_{30}O_1Na$ $[M+Na]^+$ 405.1731. Found 405.1735.

4.22. 1,4-Bis(2,3,4-tri-O-acetyl-α-L-fucopyranosyl)but-2-en (29)

To a solution of **31** (0.200 g; 0.64 mmol) in CH_2Cl_2 (5 mL), Grubbs catalyst 2nd generation (27 mg; 0.03 mmol; 5% mol) was added. The solution was stirred at 40 °C for 3 d. The solvent was evaporated and the residue was purified by silica gel chromatography (hexane/EtOAc 2:1) to afford **29** (163 mg; 84%) as a colorless syrup; $[\alpha]_D^{25}$-79.7 (*c* 0.7, $CHCl_3$); R_f 0.14 (hexane/EtOAc 2:1); ratio of isomers A:B 0.2:0.8; ^{1}H NMR (600 MHz, $CDCl_3$): δ 5.53 (m, 0.4H, $J_{8,7}$ 4.4 Hz, H-8-A) 5.50 (m, 1.6H, $J_{8,7}$ 3.7 Hz, $J_{8,7}$ 1.8 Hz, H-8-B), 5.33–5.27 (m, 2H, H-4-A, H-4-B, H-2-A, H-2-B), 5.25 (dd, 0.4H, $J_{3,2}$ 9.9 Hz, $J_{3,4}$ 3.4 Hz, H-3-A), 5.22 (dd, 1.6H, $J_{3,2}$ 9.9 Hz, $J_{3,4}$ 3.4 Hz, H-3-B), 4.25 (m, 0.4H, $J_{1,7a}$ 16.5 Hz, $J_{1,7b}$ 10.4 Hz, $J_{1,2}$ 4.7 Hz, H-1-A), 4.22 (m, 1.6H, $J_{1,7a}$ 16.5 Hz, $J_{1,7b}$ 10.4 Hz, $J_{1,2}$ 4.7 Hz, H-1-B), 3.98 (dd, 1.6H, $J_{5,6}$ 6.5 Hz, $J_{5,4}$ 1.9 Hz, H-5-B), 3.95 (dd, 0.4H, $J_{5,6}$ 6.5 Hz, $J_{5,4}$ 1.9 Hz, H-5-A), 2.54–2.45 (m, 2H, H-7a-A, H-7a-B), 2.32–2.21 (m, 2H, H-7b-A, H-7b-B), 2.16, 2.07, 2.03 (3 x s, 2.4H, 3 x OAc-B), 2.17, 2.10, 2.04 (3 x s, 0.6H, 3 x OAc-A), 1.17 (d, 0.6H, $J_{6,5}$ 6.5 Hz, H-6-A), 1.16 (d, 2.4H, $J_{6,5}$ 6.5 Hz C-6-B); ^{13}C-NMR (151 MHz, $CDCl_3$): δ 170.54, 170.14, 169.88 (3 x CH_3*C*O-B), 170.51, 170.09, 169.95 (3 x CH_3*C*O-A), 128.2 (C-8-B), 127.0 (C-8-A), 72.27 (C-1-A), 72.10 (C-1-B), 70.64 (C-2-B), 70.52 (C-2-A), 68.50 (C-3-B), 68.48 (C-3-A), 68.25 (C-4-B), 68.43 (C-4-A), 65.98 (C-5-A), 65.89 (C-5-B), 29.29 (C-7-B), 24.50 (C-7-A), 20.83, 20.73.20.68 (*C*H_3CO-A, *C*H_3CO-B), 15.91 (C-6-A, C-6-B); HRESIMS (*m/z*): Calcd for $C_{28}H_{40}O_{14}Na$ $[M+Na]^+$ 623.2310. Found 623.2314.

4.23. 4-Bis(2,3,4,6-tetra-O-benzyl-α-D-mannopyranosyl)but-2-en (30)

To a solution of **32** (0.200 mg; 0.35 mmol) in CH_2Cl_2 (2 mL), Grubbs catalyst 1st generation (29 mg; 0.035 mmol; 10% mol) was added. The mixture was stirred at 40 °C for 3 h under microwave irradiation. The solvent was evaporated and the residue was purified by silica gel chromatography (hexane/EtOAc 6:1) to afford **30** (93 mg; 24%) as a colorless syrup; $[\alpha]_D^{25}$+32.1 (*c* 1.1, $CHCl_3$); R_f 0.26 (hexane/EtOAc 6:1); ratio of isomers A:B 0.5:0.5; ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.47–7.44 (m, 40H, 8 x C_6H_5-A, 8 x C_6H_5-B), 5.43 (m, 1H, $J_{8,7}$ 4.5 Hz, H-8-A), 5.35 (m, 1H, $J_{8,7}$ 4.5 Hz, H-8-B), 4.77–4.44 (m, 8H, 8 x PhCH_2O-A, 8 x PhCH_2O-B), 4.03–3.92 (m, 2H, H-1-A, H-1-B), 3.93–3.82 (m, 2H, H-4-A, H-4-B), 3.82–3.63 (m, 8H, 2 x H-6-A, 2 x H-6-B, H-3-A, H-3-B, H-5-A, H-5-B), 3.62–3.52 (m,

2H, H-2-A, H-2-B), 2.47–2.14 (m, 4H, H-7-A, H-7-B); ^{13}C-NMR (125 MHz, $CDCl_3$): δ 138.6–138.3 (16 x ipso C_6H_5), 128.9–127.4 (16 x C_6H_5, C-8-A, C-8-B), 75.4 (m, C-2-A, C-2-B), 75.3 (m, C-4-A, C-4-B) 75.0, 73.7 (m, C-3-A, C-3-B, C-5-A, C-5-B), 74.0,73.4, 72.2, 71.6 (8 x OCH_2Ph), 72.8 (m, C-1-A, C-1-B), 69.3 (C-6-A, C-6-B), 33.5 (C-7-A), 29.8 (C-7-B); HRESIMS (*m/z*): Calcd for $C_{72}H_{76}O_{10}Na$ $[M+Na]^+$ 1123.5331. Found 1123.5325.

Acknowledgement

Financial support by the EU-ITN CARMUSYS (PITN-GA-2008-213592) is gratefully acknowledged. For DC-SIGN ECD production, this work used the Multistep Protein Purification Platform (MP3) and the SPR platform for the competition test of the Grenoble Instruct centre (ISBG; UMS 3518 CNRS-CEA-UJF-EMBL) with support from FRISBI (ANR-10-INSB-05-02) and GRAL (ANR-10-LABX-49-01) within the Grenoble Partnership for Structural Biology.

References

[1] A. Varki, Glycobiology 3 (1993) 97. Dwek, R. A. *Chem. Rev.* 1996, 96, 683; Lis, H.; Sharon, N. Chem. Rev. 1998, 98, 637.
[2] T.B.H. Geijtenbeek, R. Torensma, S.J. van Vliet, G.C.F. van Duijnhoven, J. AdemaG, Y. van Kooyk, C.G. Figdor, Cell 100 (2000) 575–585.
[3] T.B.H. Geijtenbeek, D.J. Krooshoop, D.A. Bleijs, S.J. van Vliet, G.C.F. van Duijnhoven, V. Grabovsky, C.G. Figdor, Y. van Kooyk, Nat. Immunol. 1 (2000) 353–357.
[4] K.P. van Gisbergen, M. Sanchez-Hernandez, T.B.H. Geijtenbeek, Y. van Kooyk, J. Exp. Med. 201 (2005) 1281–1292.
[5] K.P. van Gisbergen, I.S. Ludwig, T.B.H. Geijtenbeek, Y. van Kooyk, FEBS Lett. 579 (2005) 6159–6168.
[6] K.P. van Gisbergen, C.A. Aarnoudse, G.A. Meijer, T.B.H. Geijtenbeek, Y. van Kooyk, Cancer Res. 65 (2005) 5935–5944.
[7] J. Sabatte, W. Faigle, A. Ceballos, W. Morelle, C. Rodríguez Rodrígues, F. Remes Lenicov, M. Thépaut, F. Fieschi, E. Malchiodi, M. Fernández, F. Arenzana-Seisdedos, H. Lortat-Jacob, J.C. Michalski, J. Geffner, S. Amigorena, J. Immunol. 187 (2011) 5299–5309.
[8] Y. van Kooyk, T.B.H. Geijtenbeek, Nat.Rev. Immunol. 3 (2003) 697–709.
[9] U.S. Khoo, K.Y.K. Chan, V.S.F. Chan, C.L.S. Chan, J. Mol. Med. 86 (2008) 861–874.
[10] C.P. Alvarez, F. Lasala, J. Carillo, O. Muñiz, A.L. Corbì, R. Delgrado, J. Virol. 73 (2002) 6841–6844.
[11] P.Y. Lozach, R. Kühbacher, R. Meier, R. Mancini, D. Bitto, M. Bouloy, A. Helenius, Cell Host Microbe 10 (2011) 75–88.
[12] U.S. Khoo, K.Y. Chan, V.S. Chan, C.L. Lin, J. Mol. Med. 86 (2008) 861–874.
[13] M. Anderluh, G. Jug, U. Švajger, N. Obermajer, Curr. Med. Chem. 19 (2012) 992–1007.
[14] U. Svajger, M. Anderluh, M. Jeras, N. Obermajer, Cell. Signall 22 (2010) 1397–1405.
[15] B.J. Appelmelk, I. van Die, S.J. van Vliet, C.M. Vandenbroucke-Grauls, T.B. Geijtenbeek, Y. van Kooyk, J. Immunol. 170 (2003) 1635–1639.
[16] H. Feinberg, D.A. Mitchell, K. Drickamer, W. Weis, Science 294 (2001) 2163–2166.
[17] A. Holla, A. Skerra, Protein Eng. Design. Selection 24 (2011) 659–669.
[18] Y. van Kooyk, A. Engering, A.N. Lekkerkerker, I.S. Ludwig, T.B.H. Geijtenbeek, Curr. Opin. Immunol. 16 (2004) 488–493.
[19] Y. Guo, H. Feinberg, E. Conroy, D.A. Mitchell, R. Alvarez, O. Blixt, M.E. Taylor, W.I. Weis, K. Drickamer, Nat. Struct. Mol. Biol. 11 (2004) 591–598.
[20] J. Angulo, I. Díaz, J.J. Reina, G. Tabarani, F. Fieschi, J. Rojo, P.M. Nieto, ChemBioChem 9 (2008), 225–2227.
[21] J.J. Reina, I. Díaz, P.M. Nieto, N.E. Campillo, J.A. Páez, G. Tabarani, F. Fieschi, J. Rojo, Org. Biomol. Chem. 6 (2008) 2743–2754.
[22] R.T. Lee, T.L. Hsu, S.K. Huang, S.L. Hsich, C.H. Wong, Y.C. Lee, Glycobiology 21 (2011) 512–520.
[23] D.A. Mitchell, A.J. Fadden, K. Drickamer, J. Biol. Chem. 276 (2001) 28939–28945.
[24] G. Timpano, G. Tabarani, M. Anderluh, D. Invernizzi, F. Vasile, D. Potenza, P.M. Nieto, J. Rojo, F. Fieschi, A. Bernardi, ChemBioChem 9 (2008) 1921–1930.
[25] S. Sattin, A. Daghetti, M. Thepaut, A. Berzi, M. Sanchez-Navarro, G. Tabarani, J. Rojo, F. Fieschi, M. Clerici, A. Bernardi, ACS Chem. Biol. 5 (2010) 301–312.
[26] K.C.A. Garber, K. Wangkanont, E.E. Carlson, L.L. Kiessling, Chem. Commun. 46 (2010) 6747–6749.
[27] D.A. Mitchell, N.A. Jones, S.J. Hunter, J.M.D. Cook, S.F. Jenkinson, M.R. Wormald, R.A. Dwek, G.W.J. Fleet, Tetrahedron-Asymmetry 18 (2007) 1502–1510.
[28] M. Andreini, D. Doknic, I. Sutkeviciute, J.J. Reina, J.X. Duan, E. Chabrol, M. Thepaut, E. Moroni, F. Doro, L. Belvisi, J. Weiser, J. Rojo, F. Fieschi, A. Bernardi, Org. Biomol. Chem. 9 (2011) 5778–5786.
[29] D. Doknic, M. Abramo, I. Sutkeviciute, A. Reinhardt, C. Guzzi, M.K. Schlegel, D. Potenza, P.M. Nieto, F. Fieschi, P.H. Seeberger, A. Bernardi, Eur. J. Org. Chem. 24 (2013) 5303–5314.
[30] I. Sutkeviciute, M. Thepaut, S. Sattin, A. Berzi, J. McGeagh, S. Grudinin, J. Weiser, A. Le Roy, J.J. Reina, J. Rojo, M. Clerici, A. Bernardi, C. Ebel, F. Fieschi, ACS Chem. Biol. 9 (2014) 1377–1385.
[31] C. Guzzi, P. Alfarano, I. Sutkeviciute, S. Sattin, R. Ribeiro-Viana, F. Fieschi, A. Bernardi, J. Weiser, J. Rojo, J. Angulo, P.M. Nieto, Org. Biomol. Chem. 14 (2016) 335–344.
[32] J.J. Reina, S. Sattin, D. Invernizzi, S. Mari, L. Martínez-Prats, G. Tabarani, F. Fieschi, R. Delgado, P.M. Nieto, J. Rojo, A. Bernardi, ChemMedChem 2 (2007) 1030–1036.
[33] S. Sattin, A. Daghetti, M. Thepaut, A. Berzi, M. Sanchez-Navarro, G. Tabarani, J. Rojo, F. Fieschi, M. Clerici, A. Bernardi, ACS Chem. Biol. 5 (2010) 301–312.
[34] J. Luczkowiak, S. Sattin, I. Sutkeviciute, J.J. Reina, M. Sanchez-Navarro, M. Thepaut, L. Martínez-Prats, A. Daghetti, F. Fieschi, R. Delgado, A. Bernardi, J. Rojo, Bioconjugate Chem. 22 (2011) 1354–1365.
[35] N. Varga, I. Sutkeviciute, C. Guzzi, J. McGeagh, I. Petit-Haertlein, S. Gugliotta, J. Weisser, J. Angulo, F. Fieschi, A. Bernardi, Chem. Eur. J. 19 (2013) 4786–4797.
[36] N. Obermajer, S. Sattin, C. Colombo, M. Bruno, U. Svajger, M. Anderluh, A. Bernardi, Mol. Divers 15 (2011) 347–360.
[37] J. Jimenez-Barbero, J.F. Espinosa, J.K. Asensio, F.J. Canada, A. Poveda, Adv. Carbohydr. Chem. Biochem. 56 (2001) 235–284.
[38] M. Thepaut, C. Guzzi, I. Sutkeviciute, S. Sattin, R. Ribeiro-Viana, N. Varga, E. Chabrol, J. Rojo, A. Bernardi, J. Angulo, P.M. Nieto, F. Fieschi, J. Am. Chem. Soc. 135 (2013) 2518–2529.
[39] P. Štěpánek, L. Kniežo, H. Dvořáková, P. Vojtíšek, Synlett (2003) 963–966. Štěpánek, P.; Vích, O.; Werner, L.; Kniežo, L.; Dvořáková, H.; Vojtíšek, P. Tetrahedron:Asymmetry 2004, 15, 1033–1041.
[40] P. Štěpánek, O. Vích, L. Werner, L. Kniežo, H. Dvořáková, P. Vojtíšek, Coll. Czech. Chem. Commun. 70 (2005) 1411–1428.
[41] K. Parkan, L. Werner, Z. Lövyova, E. Prchalova, L. Kniežo, Carbohydr. Res. 345 (2010) 352–362.
[42] Z. Lövyova, K. Parkan, L. Kniežo, Tetrahedron 67 (2011) 4967–4979.
[43] A. Dondoni, A. Marra, M.C. Scherrmann, V. Bertolasi, Chem. Eur. J. 7 (2001) 1371–1382.
[44] M.A. Leeuwenburgh, G.A. van der Marel, H.S. Overkleeft, Curr. Opin. Chem. Biol. 7 (2003) 757–765.
[45] R. Roy, S.K. Das, Chem. Commun. (2000) 519–529.
[46] R. Roy, S.K. Das, R. Dominique, M.C. Trono, F. Hernandez-Mateo, F. Santoyo-Gonzalez, Pure Appl. Chem. 71 (1999) 565–571.
[47] S.K. Das, R. Dominique, C. Smith, J. Nahra, R. Roy, Carbohydr. Lett. 3 (1999) 361.
[48] T. Uchiyama, V.P. Vassilev, T. Kajimoto, W. Wong, H. Huang, C.C. Lin, C.H. Wong, J. Am. Chem. Soc. 117 (1995) 5395–5396.
[49] J.A. Bennek, G.R. Gray, J. Org. Chem. 52 (1987) 892–897.
[50] J. Beignet, J. Tiernan, C.H. Woo, B.M. Kariuki, L.R. Coy, J. Org. Chem. 69 (2004) 6341–6356.
[51] A. Hosomi, Y. Sakata, H. Sakura, Carbohydr. Res. 171 (1987) 223–232.
[52] E.G. Nolen, A.J. Kurish, K.A. Wong, M.D. Orlando, Tetrahedron Lett. 44 (2003) 2449–2453.
[53] L. de Witte, A. Nabatov, M. Pion, D. Fluitsma, M.A.W.P. de Jong, T. de Gruijl, V. Piguet, Y. van Kooyk, T.B.H. Geijtenbeek, Nat. Med. 13 (2007) 347–371.
[54] L. de Witte, A. Nabatov, T.B.H. Geijtenbeek, Trends Mol. Med. 14 (2008) 12–19.
[55] P. Czechura, R.Y. Tam, E. Dimitrijevic, A.V. Murphy, R.N. Ben, J. Am. Chem. Soc. 130 (2008) 2928–2929.

PŘÍLOHA VIII

Bertolotti, B.; Sutkeviciute, I.; Ambrosini, M.; Ribeiro-Viana, R.; Rojo, J.; Fieschi, F.; Dvořáková, H.; Kašáková, M.; Parkan, K.; Hlaváčková, M.; Nováková, K.; Moravcová, J. Polyvalent *C*-glycomimetics based on L-fucose or D-mannose as potent DC-SIGN antagonists. *Org. Biomol. Chem.* **2017**, *15* (18), 3995-4004.

Organic & Biomolecular Chemistry

PAPER

View Article Online
View Journal | View Issue

Cite this: *Org. Biomol. Chem.*, 2017, **15**, 3995

Polyvalent *C*-glycomimetics based on L-fucose or D-mannose as potent DC-SIGN antagonists†

Benedetta Bertolotti,[a] Ieva Sutkeviciute,[‡b] Martino Ambrosini,[c] Renato Ribeiro-Viana,[§d] Javier Rojo,[d] Franck Fieschi,[b] Hana Dvořáková,[e] Martina Kašáková,[a] Kamil Parkan,[a] Martina Hlaváčková,[a] Kateřina Nováková[f] and Jitka Moravcová*[a]

Received 10th February 2017,
Accepted 10th April 2017

DOI: 10.1039/c7ob00322f

rsc.li/obc

The *C*-type lectin DC-SIGN expressed on immature dendritic cells is a promising target for antiviral drug development. Previously, we have demonstrated that mono- and divalent *C*-glycosides based on D-*manno* and L-*fuco* configurations are promising DC-SIGN ligands. Here, we described the convergent synthesis of *C*-glycoside dendrimers decorated with 4, 6, 9, and 12 α-L-fucopyranosyl units and with 9 and 12 α-D-mannopyranosyl units. Their affinity against DC-SIGN was assessed by surface plasmon resonance (SPR) assays. For comparison, parent *O*-glycosidic dendrimers were synthesized and tested, as well. A clear increase of both affinity and multivalency effect was observed for *C*-glycomimetics of both types (mannose and fucose). However, when dodecavalent *C*-glycosidic dendrimers were compared, there was no difference in affinity regarding the sugar unit (L-*fuco*, IC_{50} 17 μM; D-*manno*, IC_{50} 12 μM). For the rest of glycodendrimers with L-fucose or D-mannose attached by the *O*- or *C*-glycosidic linkage, *C*-glycosidic dendrimers were significantly more active. These results show that in addition to the expected physiological stability, the biological activity of *C*-glycoside mimetics is higher in comparison to the corresponding *O*-glycosides and therefore these glycomimetic multivalent systems represent potentially promising candidates for targeting DC-SIGN.

Introduction

Interactions between carbohydrates and *C*-type lectin receptors (CLRs) are vital to immune responses initiated by dendritic cells (DCs). Complex molecular information contained in glycan structures is read out by CLRs through highly selective recognition processes. These carbohydrate–CLR complexes must exist at least as long as the reading of the message requires. Paradoxically, a single monosaccharide binding to a single carbohydrate recognition domain (CRD) of a CLR typically is transient with affinity in the mM range. Nature overcomes this problem by introducing the avidity, or multivalency, phenomenon whereby multiple monosaccharide moieties connected into a complex glycan, that covers the pathogen particle, interact with several CRDs of a single CLR, thus enhancing interaction affinity from the mM to nM range.[1]

Although most CLR/pathogen interactions result in protective effects from infections, the opposite outcomes have been proven for some particular lectin–pathogen interactions. The most relevant CLR in this context is the dendritic cell-specific intercellular adhesion molecule-3-grabbing nonintegrin (DC-SIGN). This type II tetrameric CLR is overexpressed on the surface of immature DCs that survey mucosal surfaces.[2] DC-SIGN is implicated in promoting some pathogen infections, including HIV-1 or Ebola.[3] Indeed, the discovery[4,5] that DCs act as local facilitators of productive *trans*-infection of T-cells due to DC-SIGN-mediated capture and protection of

[a]*Department of Chemistry of Natural Compounds, University of Chemistry and Technology, Prague, Technická 5, 166 28 Prague, Czech Republic. E-mail: Jitka.Moravcova@vscht.cz*
[b]*Institut de Biologie Structurale (IBS), Univ. Grenoble Alpes, CEA, CNRS, 38044 Grenoble, France*
[c]*Department of Molecular Cell Biology and Immunology, VU University Medical Center (VUmc), Amsterdam, The Netherlands*
[d]*Glycosystems Laboratory, Instituto de Investigaciones Químicas (IIQ), CSIC – Universidad de Sevilla, Sevilla, Spain*
[e]*Laboratory of NMR, Central Laboratories, University of Chemistry and Technology, Prague, Technická 5, 166 28 Prague, Czech Republic*
[f]*The Institute of Organic Chemistry and Biochemistry of the Czech Academy of Sciences, Flemingovo nám. 2, 166 10 Prague 6, Czech Republic*

† Electronic supplementary information (ESI) available: MS and NMR characterization of new compounds, SPR sensorgrams, inhibition curves, and IC_{50} values. See DOI: 10.1039/c7ob00322f

‡ Present address: Laboratory for G Protein-Coupled Receptor Biology, Department of Pharmacology and Chemical Biology, School of Medicine, University of Pittsburgh, Pittsburgh, PA 15261.
§ Present address: Departamento Academico de Química, Universidade Tecnologica Federal do Paraná. Av dos Pioneiros, 3131. Londrina, PR, Brazil.

HIV-1 virions within DCs has opened a new perspective for DC-SIGN in the rational anti-infective drug development.[6]

In order to compete with multivalent CLR/pathogen interactions successfully, multivalent antagonists have become promising targets to be developed. Numerous glycoclusters have already been designed to achieve high affinity binding to lectins.[7] The design of DC-SIGN high affinity antagonists is primarily inspired by the structure of its natural ligand, the branched high-mannose oligosaccharide $(Man)_9(GlcNAc)_2$, that is present in pathogen envelope glycoproteins, such as the gp120 of HIV. DC-SIGN can also recognize Lewis antigens such as the branched trisaccharide $Lewis^x$ (Galβ(1-4)[Fucα(1-3)]GlcNAc).[8]

The first multivalent ligands for DC-SIGN were prepared in 2003.[9] A glycodendrimer structure was based on the hyperbranched commercially available polymer BoltornH30 presenting at the periphery 32 mannose units linked through a succinyl spacer. This polyfunctional glycomimetic exhibited a high antiviral activity (IC_{50} = 0.3 μM) in an artificial Ebola virus infection model. The polydispersity of the Boltorn polymer was a major drawback of this strategy, so a divergent synthesis starting from pentaerythritol as a central core was developed.[10] Glycomimetics with an average of 30–32 units of pseudodi- or trimannosides were then tested using pseudotyped viral particles presenting the EboGP envelope glycoprotein and a Jurkat cell line expressing DC-SIGN on the surface. The IC_{50} values were found to be in the nanomolar range in both *cis* and *trans* infection assays. A strong difference in the IC_{50} values for the starting pseudodimannosides disappeared when presented on dendrimers. This fact has been clarified later by a clustering effect.[11]

The convergent synthesis of dendrimers offers a convenient approach to well defined polyvalent systems. However, in general terms, dendrimers made in this way are not as large as those made by divergent methods because of the major limitation imposed by the crowding around the core due to steric effects when dendrons have to be conjugated on the core. In addition, the coupling step must be very efficient to enable complete reactions, especially when involving sterically demanding higher generation dendrons avoiding structural defects. In this respect, the click chemistry reaction based on the Cu(I) catalyzed azide–alkyne cycloaddition (CuAAC) introduced by Sharpless and Meldal[12] met the synthetic requirements to achieve this goal. Several reviews covering the scope of the cycloaddition reaction can be found in the literature.[13]

This strategy was previously employed by some of us for the synthesis of glycodendrons having 3 and 9 α-L-fucopyranosyl or α-D-mannopyranosyl units.[14] The nonavalent glycodendrons present an azido group at the focal point allowing coupling with a BODIPY derivative in order to fluorescently label the systems for internalization and endocytic routing analysis of these dendrons in DCs.[14] Using the convergent approach, tri- and nonavalent *manno* dendrons were incorporated also into virus-like particles bearing up to 1620 glycans.[15] These glycodendrimer-protein particles were found to be very active from low nanomolar up to high picomolar concentrations inhibiting the infection of Ebola pseudotype virus through competitive blockage of the DC-SIGN receptor.

Our ongoing research was focused on the development of a very efficient click chemistry approach to conjugate different carbohydrate and glycomimetic ligands to a variety of multimeric scaffolds with different valences.[16] With this approach, a library of polyvalent constructs was synthesized and the SPR competition assay revealed a gradual increase of activity against DC-SIGN when the valence increased.[16] For example, the nonavalent dendrimer **M-O-9** displaying nine copies of α-D-mannopyranose had the IC_{50} = 128 μM while the IC_{50} = 67 μM was assessed for dodecavalent dendrimer **M-O-12** (Fig. 1).

An important issue to be considered when designing ligands for targeting lectins is their stability under physiological conditions. In particular, the stability against glycolytic enzymes arises because the majority of ligand structures have

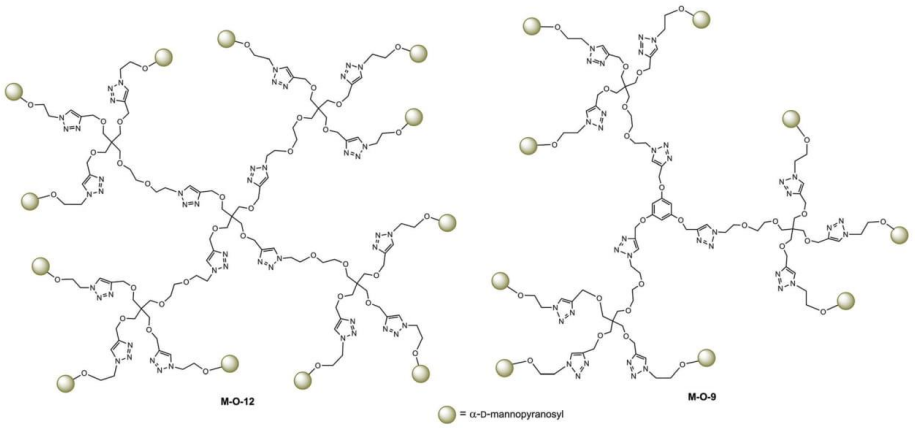


Fig. 1 Structure of mannopyranosyl glycodendrimers.[16]

been derived from *O*-glycosides. To overcome this important drawback, one approach lies in the replacement of the exocyclic oxygen with a carbon to provide *C*-glycosidic analogues, which have a high resistance to degradation by glycosidases.[17] Recently we have demonstrated for the first time that divalent *C*-disaccharides based on the D-mannose or L-fucose scaffold can be prospective ligands for the DC-SIGN receptor.[18] To verify if *C*-pseudoglycosides are adequate candidates for the construction of multivalent systems, we present here a new class of potentially stable pseudoglycodendrimers with different valences. The affinities of these constructs for DC-SIGN were evaluated by SPR competition assays and compared with their parent *O*-glycosidic dendrimers.

Results and discussion

The general synthetic strategy was based on the Cu(I) catalyzed azide–alkyne cycloaddition (CuAAC) reaction[12] of polypropargyl core compounds **A**, **B** and **C** with 2-(α-D-mannopyranosyl) ethylazide (**1**), 2-(α-L-fucopyranosyl)ethylazide (**2**), 2-azidoethyl α-D-mannopyranoside (**3**) or 2-azidoethyl α-L-fucopyranoside (**4**) (Fig. 2). These cores **A**, **B**, **C** as well as **D** have been prepared according to the procedures described previously.[16] The structure of **D** allows subsequent functionalization by CuAAC reaction with three copies of a carbohydrate azide derivative followed by substitution of the chloride attached to the focal position with an azide. Then, it can be clicked again by CuAAC on polyalkyned cores **A**, **B**, or **C** giving more complex structures with a higher valency.

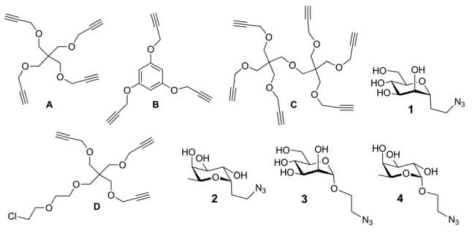
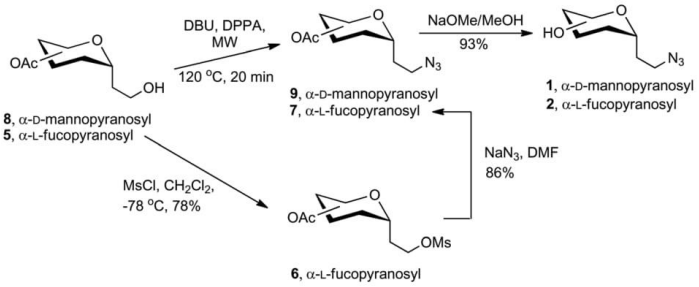


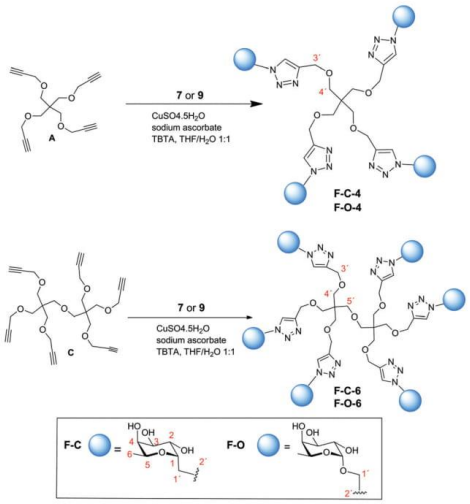
Fig. 2 Structure of core polypropargyl compounds and azides used.

2-(α-L-Fucopyranosyl)ethylazide (**2**) was synthesized from 2-(2,3,4-tri-*O*-acetyl-α-L-fucopyranosyl)ethanol (**5**) obtained on a multi-gram scale from L-fucose by a multistep pathway already described (Scheme 1).[19] For the incorporation of the azido group, two procedures were tested. A traditional two-step process *via* intermediate mesylate **6** gave fucopyranosyl azide **7** in 67% overall yield while direct azidation of **5** with diphenyl phosphoryl azide and 1,8-diazabicyclo[5.4.0]undec-7-ene under microwave irradiation afforded **7** in excellent yield (90%).[20] 2-(α-D-Mannopyranosyl)ethylazide (**1**) was synthesized according to the published protocol starting from 2-(2,3,4,6-tetra-*O*-acetyl-α-D-mannopyranosyl)ethanol (**8**).[21] The only modification in regard to the published approach was the first step where the 2-(2,3,4,6-tetra-*O*-acetyl-α-D-mannopyranosyl)prop-1-ene was obtained from methyl α-D-mannopyranoside using a silylation-reductive cleavage-deprotection strategy[22] adapted for the *manno* configuration.[18] The alcohol **8** was converted to the azide **9** by a direct azidation as described above in 84% yield. The final Zemplén's deacetylation of both **7** and **9** produced unprotected azides **2** and **1**, respectively. 2-Azidoethyl glycosides **3**[23] and **4**[24] were synthesized according to the known procedures.

The general design of our target dendrimers was based on two important facts. Firstly, it was already published that glycodendrons containing up to nine copies of carbohydrate ligands interact efficiently with the DC-SIGN receptor at the surface of DCs.[14] Therefore we primarily focused on dendrimers having at least nine *C*-glycosidic D-mannose or L-fucose units attached. Secondly, biological tests carried out with our monovalent and divalent *C*-glycosidic ligands were completed indicating L-*fuco* configuration as a more active ligand in comparison with D-*manno* configuration.[18] Moreover, a very minor affinity improvement of tetra- and hexavalent dendrimers based on the *O*-mannopyranosylated scaffold was found.[16] In this context, a full series of L-*fuco* dendrimers carrying 4, 6, 9, and 12 units were prepared whilst only two constructs with 9 and 12 D-*manno* units attached were made.



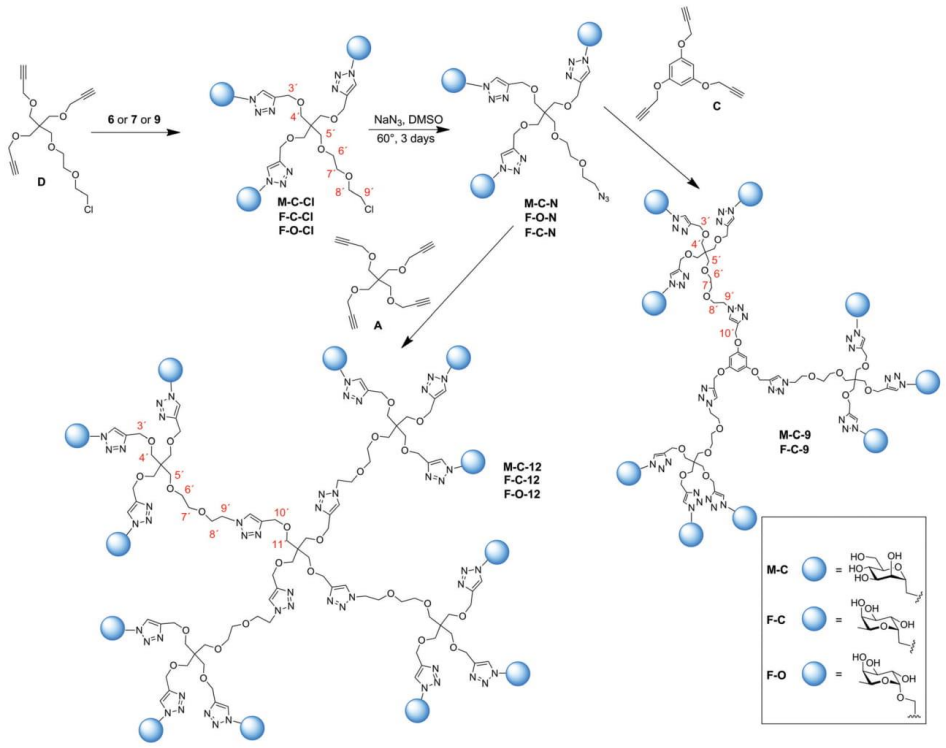
Scheme 1 Preparation of azides **1** and **2**.



Scheme 2 Synthesis of tetra- and hexavalent *fuco* dendrimers.

The previously developed conditions for these Cu(I) catalyzed azide–alkyne cycloadditions[16] were initially applied to the preparation of tetra- and hexavalent dendrimers (Scheme 2). Constructs having L-fucose units attached either by *O*-glycosidic (**F-O-4**, **F-O-6**) or *C*-glycosidic bonds (**F-C-4**, **F-C-6**) were isolated in 95% yield. Later on, we found that a combination of copper(I)bromide with TBTA under microwave irradiation was more effective for achieving the preparation of these glycodendrimers with yields in the range of 84–95% within a reasonable reaction time in the *C*-manno series (Scheme 3).[14] Trivalent fucosylated chloro dendron **F-O-Cl**, azido dendron **F-O-N**, mannosylated chloro dendron **M-O-Cl** and azido dendron **M-O-N**[14,15] as well as mannosylated nona- (**M-O-9**) and dodecavalent (**M-O-12**) dendrimers[16] have been previously described. The affinity of both dendrimers **M-O-9** and **M-O-12** against DC-SIGN was already assessed and published.[16]

All the pseudoglycodendrimers synthesized and the azido derivatives **6** and **7** were tested by SPR, using a previously described procedure.[26] The SPR competition assay was carried out to estimate the potency of the pseudoglycodendrimers to inhibit the binding of the tetrameric DC-SIGN extracellular



Scheme 3 Synthesis of nona- and dodecavalent *fuco* and *manno* dendrimers.

domain (ECD) to mannosylated bovine serum albumin immobilized on the sensor chip surface. The assay allows the determination of the apparent affinity in terms of the IC_{50} value and thus, the comparison of test compounds with parent glycodendrimers and natural ligands D-mannose and L-fucose. Furthermore, an affinity improvement factor β was calculated as the relationship $IC_{50,monosaccharide}$/valency × $IC_{50,dendrimer}$ to assess the contribution of valency to the affinity increase.[27]

The reference monosaccharides D-mannose and L-fucose were found to exhibit IC_{50} values of 3.39 and 2.06 mM respectively which are consistent with our previous results.[18,25,26] Initially the affinity of azides **1** and **2** was tested in order to check if the affinity of *C*-glycosides could be comparable to those of the parent hexoses. Manno azide **1** (IC_{50} = 3.95 mM) has the same apparent affinity for DC-SIGN ECD as its counterpart D-mannose, so the attachment of the azido ethyl chain at the anomeric position had no effect on D-mannose binding properties in **1**. In contrast, fuco azide **2** (IC_{50} = 1.05 mM) shows two-times stronger affinity to DC-SIGN ECD than its counterpart L-fucose. We can only speculate that the more hydrophobic character of the C-1 substituent may be responsible for the increased affinity in the case of fuco azide **2**.

All *C*-fucosyl dendrimers **F-C-4** – **F-C-12** showed a proportional increase of both affinity and multivalency effect in the β term (Fig. 3). In contrast, *O*-fucosylated dendrimers did not show such a trend and the tetra- and hexavalent dendrimers present approximately the same affinity. Surprisingly, the system with 12 fucoses (**F-O-12**) showed an enormous increase in both affinity and multivalency effect. This observation could be explained by a clustering capacity of **F-O-12**. The best improvement of relative inhibitory potency β values[27] was obtained for **F-C-12**. Comparing the activities of the constructs with L-fucose attached by an *O*- or *C*-glycosidic bond with the same valency, the higher affinities were found for *C*-glycomimetics. The only exception was the dodecavalent system **F-O-12** displaying 3 times higher affinity than **F-C-12**.

With respect to the mannosylated series, significantly higher activities of mannose *C*-glycoside-based constructs were observed as compared to the corresponding *O*-mannosides. A gradual improvement effect was discovered in both cases; however, it was more substantial in the *C*-mannose series.

Comparing the same scaffolds with L-fucose or D-mannose attached by the *O*- or *C*-glycosidic linkage, it seems that *C*-glycosidic dendrimers present an advantage, which could be attributed to the free rotation around the C1–CH_2 bond that caused more flexible conformations on the periphery of the dendrimer. Among dodecavalent *C*-glycosidic dendrimers (**F-C-12** and **M-C-12**), there is no difference in affinity if the configuration of the sugar is L-*fuco* or D-*manno*.

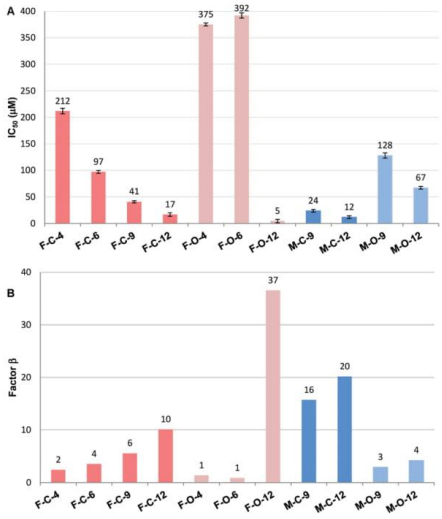


Fig. 3 Inhibition activity of studied dendrimers assessed by SPR (A). Affinity improvement of tested compounds with respect to the corresponding natural monosaccharide D-mannose (β = 1) or L-fucose (β = 1) (B).

Conclusions

In conclusion, this work represents a step further in the design of novel multivalent glycomimetics. We introduced fully non-hydrolyzable dendrimeric DC-SIGN antagonists having L-fucose and D-mannose attached by *C*-glycosidic bonds to overcome the potential limitation of low physiological stability of polyvalent glycoside-based constructs. We extended the scope of the Cu(I) catalyzed azide–alkyne cycloaddition to the reaction of novel (L-fuco/D-manno)pyranosylethylazides and their dendrons with polypropargylated scaffolds. The SPR assessment proved that the binding properties of these *C*-glycosidic ligands against DC-SIGN have been improved substantially in comparison with parent *O*-glycosidic constructs. These results could be the starting point for the synthesis of new stable ligands for different lectins in the near future.

Experimental part

General methods

^1H, ^{13}C, COSY, HMQC and HMBC spectra were recorded on a Bruker DPX-300, DRX-400, DRX-500, or Bruker Advance III 600 (Bruker Corporation, Germany) spectrometer. All spectra were acquired at 298 K. Chemical shifts are given in δ-units (ppm) and are referenced to TMS. Coupling constants (J) are reported in Hz. Numbering of atoms is placed in schemes. Optical rotations were measured with an Autopol VI (Rudolph Research Analytical, USA) digital polarimeter in appropriate solvents, at temperature 25 °C and 589 nm sodium line, in a 1 dm cuvette and are given as 10^{-1} deg cm^2 g^{-1}. Concentrations (c) are given in g per 100 mL. Low resolution ESI-MS was

carried out using an Esquire 6000 ESI-Ion Trap from Bruker Daltonics. ESI high resolution mass spectra were recorded with an LTQ Velos Orbitrap XL (Thermo Fisher Scientific, UK) instrument equipped with a LockSpray in ES+ and ES− modes with a mobile phase of 80% methanol. MALDI high resolution mass analysis was carried out in positive reflectron mode using a MALDI TOF UltrafleXtremeTM MALDI TOF/TOF (Bruker Daltonics, Germany) instrument equipped with a 1 kHz smartbeam II laser. 2,5-Dihydroxybenzoic acid was a matrix substance. Nominal and exact *m*/*z* values are reported in daltons.

General procedure for the CuAAC reaction

In the optimized procedure, the alkynyl compound (1 eq.), tris [(1-benzyl-1*H*-1,2,3-triazol-4-yl)methyl]amine (TBTA) (1 eq.), a copper salt (CuBr or $CuSO_4 \cdot 5H_2O$) (0.1 eq.), sodium ascorbate (0.4 eq. if Cu(II) salt was used), and the azide derivative (1.1 eq. per alkyne) were dissolved in THF/H_2O (1 : 1) or CH_3CN/H_2O (1 : 1). The reaction mixture was either stirred at room temperature under a nitrogen atmosphere and protected from light or heated in a microwave oven (MW) (Table 1). A copper scavenger resin, Quadrasil MP, was added to the reaction solution and stirred for 5 min. After that, the mixture was filtered, and the resulting solution was loaded directly on a Sephadex LH-20 column (MeOH as the eluent) to purify the product by size exclusion chromatography.

General procedure for deacetylation

A 0.1 M solution of NaOMe in MeOH (1 eq.) was added to a solution of the respective acetate. The reaction mixture was stirred for 1 h at room temperature and then the pH was adjusted to 7 by the addition of Dowex 50 × 8 (H^+) resin, which was removed by filtration. The solvent was evaporated and the residue was purified by column flash chromatography on silica.

General procedure for substitution of chloro by an azido group

Sodium azide (large excess) and the corresponding dendrons (**F-O-Cl**, **F-C-Cl**, **M-C-Cl**) were dissolved in dimethylformamide (DMF). The mixture was stirred at 60 °C for 3–4 days after the reaction was complete. After evaporation of the solvent, the residue was purified on a Sephadex G25 (H_2O/MeOH 9/1).

General procedure for SPR competition assay

DC-SIGN extracellular domain (ECD) was expressed in *E. coli* as inclusion bodies, refolded and purified as described previously.[27] SPR competition experiments were performed using a Biacore 3000 instrument, at 25 °C as described previously.[16,25] Briefly, using a Biacore amino coupling kit and a standard amino coupling procedure, the interaction flow cell of a sensor chip CM4 was covalently functionalized with BSA-Manα1-3[Manα1-6]Man (Man-BSA), while the reference flow cell was EDC/NHS-activated and ethanolamine-deactivated carboxymethyldextran. DC-SIGN ECD alone (20 μM) or in the presence of increasing concentrations of test compounds was injected over reference and interaction surfaces at a 20 μL min^{-1} flow rate. All samples were prepared in a running buffer consisting of 25 mM Tris-HCl pH 8, 150 mM NaCl, 4 mM $CaCl_2$ and 0.005% surfactant P20. Binding of DC-SIGN ECD to the Man-BSA surface was recorded in sensorgrams. After reference surface correction, DC-SIGN ECD binding responses for each injection were extracted and normalized to the DC-SIGN ECD alone binding response. Normalized binding responses were plotted against the compound concentration and IC_{50} values were calculated from the resulting competition curves using a 4-parameter logistic model.[16,25] Each run was repeated twice using two different ManBSA surfaces.

Table 1 Reaction conditions for the preparation of dendrons and dendrimers

Product	Catalyst	Solvent	Reaction conditions
F-C-Cl, **M-C-Cl**,	Cu^+	CH_3CN/H_2O	r.t., 4 h
F-C-4, **F-C-6**, **F-O-4**, **F-O-6**, **F-O-12**	Cu^{2+}	THF/H_2O	r.t., 4 h
F-C-9, **F-C-12**,	Cu^+	CH_3CN/H_2O	MW, 20 min
M-C-9, **M-C-12**	Cu^{2+}	CH_3CN/H_2O	MW, 20 min

Synthesis and characterization of compounds

2-(2,3,4,6-Tetra-*O*-acetyl-α-L-fucopyranosyl)ethylazide (7). A solution of **5** (1.30 g, 4.1 mmol), diphenylphosphoryl azide (1.3 mL, 5.7 mmol), and 1,8-diazabicyclo[5.4.0]undec-7-ene (852 μL, 5.7 mmol) in DMF (12 mL) was treated under microwave irradiation at 120 °C for 20 min. The solvent was evaporated and the residue was purified by column chromatography on silica gel (hexane/EtOAc 4/1 to 2/1) to afford azide **7** (1.0 g, 90%).

$[\alpha]_D^{25}$ −94.3 (*c* 1.0, $CHCl_3$), IR ($CHCl_3$) ν_{max}/cm^{-1} 2096 (N_3).

δ ^{1}H NMR (600.1 MHz, $CDCl_3$): 5.32 (1 H, dd, $J_{1,2}$ 5.6, $J_{2,3}$ 9.7, H-2), 5.27 (1 H, b dd, H-4), 5.17 (1 H, dd, $J_{3,4}$ 3.6, H-3), 4.30 (1 H, ddd, $J_{1,1'a}$ 11.5, $J_{1,1'b}$ 3.3, H-1), 3.96 (1 H, dq, $J_{5,4}$ 2.6, H-5), 3.45–3.35 (2 H, m, H-2′), 2.16, 2.08, 2.02 (9 H, 3 s, CH_3-Ac), 2.03–1.95 (1 H, m, H-1′$_a$), 1.72 (1 H, dddd, $J_{1'b,1'a}$ 15.1, H-1′$_b$), 1.18 (3 H, d, $J_{5,6}$ 6.5, H-6).

δ ^{13}C-NMR (125 MHz, $CDCl_3$): 170.4, 170.1, 169.8 (CO), 70.2 (CH-4), 69.6 (CH-1), 68.5 (CH-3), 68.0 (CH-4), 66.1 (CH-5), 48.0 (CH_2-1′), 25.2 (CH_2-2′), 20.8, 20.7, 20.6 (CH_3-Ac), 15.8 (CH_3-6).

HRMS (ESI) for $C_{14}H_{21}N_3O_7Na$: calc. 366.1272; found 366.1276.

2-(α-L-Fucopyranosyl)ethylazide (2). Deacetylation of **7** (500 mg, 1.45 mmol) followed by purification by column chromatography on silica gel ($CHCl_3$/MeOH 4/1) afforded azide **2** (294 mg, 93%).

$[\alpha]_D^{25}$ −84.6 (*c* 1.0, MeOH). IR (MeOH) ν_{max}/cm^{-1} 2081 (N_3).

δ ^{1}H NMR (600.1 MHz, D_2O): δ [ppm] 4.05 (1 H, ddd, $J_{1,2}$ 6.1, $J_{1,1'a}$ 11.2, $J_{1,1'b}$ 3., H-1), 3.92 (1 H, dd, $J_{2,3}$ 9.5, H-2), 3.86–3.83 (1 H, m, H-5), 3.73–3.70 (2 H, m, H-3, H-4), 3.44–3.39 (1 H, m, H-2′), 3.36–3.31 (1 H, m, H-2′), 1.99–1.93 (1 H, m, $J_{1'a,1'b}$ 15.0, H-1′$_a$), 1.80–1.76 (1 H, m, H-1′$_b$), 1.14 (3 H, d, H-6).

δ ^{13}C-NMR (125 MHz, D_2O): 73.2 (C-1), 71.7 (C-4), 69.8 (C-3), 67.6 (C-2), 67.3 (C-5), 48.0 (C-2′), 23.0 (C-1′), 15.6 (C-6).

HRMS (ESI) for $C_8H_{15}N_3O_4Na$: calc. 240.0955; found 240.0953.

2-(2,3,4,6-Tetra-*O*-acetyl-α-D-mannopyranosyl)ethylazide (9). A solution of **8** (1.54 g, 4.1 mmol), diphenylphosphoryl azide (1.3 ml, 5.7 mmol), and 1,8-diazabicyclo[5.4.0]undec-7-ene (852 μL, 5.7 mmol) in DMF (12 mL) was treated under microwave irradiation at 120 °C for 20 min. The solvent was evaporated and the residue was purified by column chromatography on silica gel (hexane/EtOAc 4/1 to 2/1) to afford azide **9** (1.22 g, 74%) containing 6% of the β-anomer.

IR (MeOH) ν_{max}/cm^{-1} 2102 (N_3).

δ ^{1}H NMR (major **9**, 600.1 MHz, $CDCl_3$): 5.26 (1 H, dd, $J_{3,2}$ 3.4, $J_{3,4}$ 7.7, H-3), 5.17–5.13 (2 H, m, H-4, H-2), 4.45 (1 H, dd, $J_{6a,5}$ 7.0, $J_{6a,6b}$ 12.1, H-6a), 4.14 (1 H, dd, $J_{6b,5}$ 3.3, H-6b), 4.13–4.08 (1 H, m, H-1), 3.94–3.91 (1 H, m, H-5), 3.49–3.42 (2 H, m, H-2′), 2.13, 2.12, 2.10, 2.08 (12 H, H-Ac), 2.00–1.95 (1H, m, H-1′), 1.85–1.80 (1 H, m, H-1′).

δ ^{13}C-NMR (125 MHz, $CDCl_3$): 170.6, 170.1, 169.8, 169.6 (C═O), 71.4 (CH-5), 70.6 (CH-1), 70.0 (CH-2), 68.3(CH-3), 67.2 (CH-4), 62.0 (CH_2-6), 47.5 (CH_2-2′), 28.6 (CH_2-1′), 20.9, 20.8, 20.8, 20.7 (CH_3-Ac).

HRMS (ESI) for $C_{16}H_{23}O_9N_3Na$: calc. 424.1332; found 424.1320.

2-(α-D-Mannopyranosyl)ethylazide (1). Deacetylation of **9** (857 mg, 2.14 mmol) followed by purification by column chromatography on silica gel ($CHCl_3$/MeOH 4/1) afforded azide **1** (465 mg, 93%).

$[\alpha]_D^{25}$ −1.2 (*c* 1.0, MeOH). IR (MeOH) ν_{max}/cm^{-1} 2093 (N_3).

δ ^{1}H NMR (600.1 MHz, D_2O): 4.01–3.97 (1 H, m, H-1), 3.86–3.83 (1 H, m, H-2), 3.80 (1 H, dd, $J_{6a,5}$ 1.9, $J_{6a,6b}$ 12.1, H-6a), 3.76 (1 H, dd, $J_{3,2}$ 3.2, $J_{3,4}$ 9.3, H-3), 3.69 (1H, dd, $J_{6b,5}$ 6.1, H-6b), 3.60 (1 H, dd, $J_{4,5}$ 9.3, H-4), 3.50–3.46 (1 H, m, H-5), 3.45 –3.33 (2 H, m, H-2′), 2.10–2.02 (1 H, m, H-1′), 1.76–1.69 (1 H, m, H-1′).

δ ^{13}C-NMR (125 MHz, D_2O): 75.6 (CH-1), 73.9 (CH-5), 71.3 (CH-2), 70.7 (CH-3), 67.3 (CH-4), 61.2 (CH_2-6), 47.7 (CH_2-2′), 26.7 (CH_2-1′).

HRMS (ESI) for $C_8H_{15}N_3O_5Na$: calc. 256.0904; found 256.0907.

Dendron F-C-Cl. Cycloaddition of 2-(2-chloroethoxy)ethoxymethyl tris(2-propynyloxymethyl)methane (**D**) (64 mg, 0.18 mmol) with fucopyranosyl azide **2** (128 mg, 0.59 mmol) afforded dendron **F-C-Cl** (157 mg, 87%).

$[\alpha]_D^{25}$ −88.4 (*c* 0.4, MeOH).

δ ^{1}H NMR (600.1 MHz, D_2O): 8.00 (3H, br s, triazolyl-H), 4.35–4.59 (12 H, m, 2′-, 3′-CH_2), 3.83–3.97 (6 H, m, H-1, H-2), 3.65–3.75 (11 H, m, H-3, H-4, H-5, 8′-CH_2), 3.59–3.63 (2 H, m, 9′-CH_2), 3.54–3.59 (2 H, m, 7′-CH_2), 3.46–3.50 (2 H, m, 6′-CH_2), 3.38–3.46 (6 H, m, 4′-CH_2), 3.29–3.37 (2H, m, 5′-CH_2), 2.26–2.37 (3 H, m, 1′a-CH_2), 1.07–2.19 (3 H, m, 1′b-CH_2), 1.01 (9 H, d, $J_{5,6}$ 6.5, H-6).

δ ^{13}C NMR (150.9 MHz, D_2O):[29] 73.5 (CH-1), 71.5 (CH-4), 70.8 (CH_2-8′), 70.3 (CH_2-6′), 69.8 (CH-3), 69.5 (CH_2-7′), 69.2 (CH_2-5′), 68.5 (CH_2-4′), 67.4 (CH-2 and CH-5), 63.9 (CH_2-3′), 48.0 (CH_2-2′), 44.7 (C-centre), 43.4 (CH_2-9′), 24.2 (CH_2-1′), 15.6 (6-CH_3).

HRMS (ESI) for $C_{42}H_{70}ClN_9O_{17}Na$: calc. 1030.4470; found 1030.4475

Dendron F-C-N. A reaction of dendron **F-C-Cl** (208 mg, 0.21 mmol) with NaN_3 (137 mg, 2.1 mmol) in DMSO (1.5 mL) gave the dendron **F-C-N** (224 mg, 100%).

$[\alpha]_D^{25}$ −56.2 (*c* 3.1, MeOH).

δ ^{1}H NMR (600.1 MHz, D_2O): 7.93 (3H, br s, triazolyl-H), 4.49 (6 H, s, 3′-CH_2), 4.45 (6 H, t, *J* 7.0, 2′-CH_2), 3.85–3.95 (6 H, m, H-1, H-2), 3.66–3.76 (9 H, m, H-3, H-4, H-5), 3.58–3.62 (2 H, m, 8′-CH_2), 3.54–3.57 (2 H, m, 7′-CH_2), 3.46–3.50 (2 H, m, 6′-CH_2), 3.35–3.40 (8 H, m, 4′-CH_2, 9′-CH_2), 3.34 (2H, s, 5′-CH_2), 2.26–2.37 (3 H, m, 1′a-CH_2), 2.07–2.19 (3 H, m, 1′b-CH_2), 1.02 (9 H, d, $J_{5,6}$ 6.4, 6-CH_3).

δ ^{13}C NMR (150.9 MHz, D_2O): 144.1 (C-triazolyl), 125.2 (CH-triazolyl), 73.5 (CH-1), 71.5 (CH-4), 70.5 (CH_2-6′), 69.8 (CH-3), 69.6 (CH_2-7′), 69.3 (CH_2-8′), 69.3 (CH_2-5′), 68.4 (CH_2-4′), 67.4 (CH-2 and CH-5), 63.5 (CH_2-3′), 50.2 (CH_2-9′), 47.8 (CH_2-2′), 44.7 (C-centre), 24.3 (CH_2-1′), 15.6 (6-CH_3).

HRMS (ESI) for $C_{42}H_{70}N_{12}O_{17}Na$: calc. 1037.4874; found 1037.4875.

Dendron M-C-Cl. Cycloaddition of 2-(2-chloroethoxy)ethoxymethyl tris(2-propynyloxymethyl)methane (**D**) (139 mg, 0.39 mmol) with mannopyranosyl azide **1** (229 mg, 1.28 mmol) afforded dendron **M-C-Cl** (353 mg, 85%).

$[\alpha]_D^{25}$ +37.4 (*c* 0.7, MeOH).

δ ^{1}H NMR (600.1 MHz, D_2O): 7.96 (3H, br s, triazolyl-H), 4.42–4.54 (12 H, m, 2′-, 3′-CH_2), 3.76–3.82 (6 H, m, H-1, H-2), 3.69–3.76 (5 H, m, 8′-CH_2, CH_2-6a), 3.63–3.69 (6 H, m, CH_2-6b, H-3), 3.57–3.63 (5 H, m, H-4, 9′-CH_2), 3.53–3.57 (2 H, m, 7′-CH_2), 3.43–3.49 (5 H, m, H-5, 6′-CH_2), 3.37 (6 H, br s, 4′-CH_2), 3.33 (2 H, br s, 5′-CH_2), 2.32–2.41 (3 H, m, 1′a-CH_2), 1.97–2.08 (3 H, m, 1′b-CH_2).

δ ^{13}C NMR (150.9 MHz, D_2O): 144.1 (C-triazolyl), 125.3 (CH-triazolyl), 75.0 (CH-1), 74.1 (CH-5), 71.1 (CH-2), 70.7 (CH_2-8′), 70.7 (CH-3), 70.3 (CH_2-6′), 69.5 (CH_2-7′), 69.2 (CH_2-5′), 68.4 (CH_2-4′), 67.2 (CH-4), 63.5 (CH_2-3′), 61.0 (CH_2-6), 47.0 (CH_2-2′), 44.6 (C-centre), 43.4 (CH_2-9′), 28.0 (CH_2-1′).

HRMS (MALDI) for $C_{42}H_{71}ClN_9O_{20}Na$: calc. 1078.4318; found 1078.4323.

Dendron M-C-N. A reaction of dendron **M-C-Cl** (353 mg, 0.33 mmol) with NaN_3 (214 mg, 3.3 mmol) gave dendron **M-C-N** (361 mg, 100%).

$[\alpha]_D^{25}$ +29.0 (*c* 4, MeOH).

δ ^{1}H NMR (600.1 MHz, D_2O): 7.96 (3H, br s, triazolyl-H), 4.49 (6 H, s, 3′-CH_2), 4.47 (6 H, t, *J* 6.8, 2′-CH_2), 3.76–3.82 (6 H, m, H-1, H-2), 3.70–3.76 (5H, m, H-3, CH_2-6b), 3.67 (3H, dd, *J* 12.2, *J* 6.0, CH_2-6a), 3.57–3.63 (5 H, m, H-4, 8′-CH_2), 3.53–3.57 (2 H, m, 7′-CH_2), 3.43–3.50 (5 H, m, 6′-CH_2, H-5), 3.34–3.40 (8 H, m, 4′-CH_2, 9′-CH_2), 3.34 (2H, s, 5′-CH_2), 2.33–2.42 (3 H, m, 1′a-CH_2), 1.99–2.09 (3 H, m, 1′b-CH_2).

δ ^{13}C NMR (150.9 MHz, D_2O): 144.1 (C-triazolyl), 125.3 (CH-triazolyl), 75.0 (CH-1), 74.1 (CH-5), 71.1 (CH-2), 70.7 (CH-3), 70.5 (CH_2-6′), 69.6 (CH_2-7′), 69.3 (CH_2-8′), 69.2 (CH_2-5′), 68.4 (CH_2-4′), 67.2 (CH-4), 63.5 (CH_2-3′), 61.0 (CH_2-6), 50.2 (CH_2-9′), 47.1 (CH_2-2′), 44.6 (C-centre), 28.0 (CH_2-1′).

HRMS (ESI) for $C_{42}H_{70}N_{12}O_{20}Na$: calc. 1085.4722; found 1085.4720.

Dendrimer F-O-4. The reaction of 2-azidoethyl α-L-fucopyranoside[14] (20 mg, 0.08 mmol) with tetrakis(2-propinyloxymethyl)methane (**A**) (5.6 mg, 0.019 mmol) gave dendrimer **F-O-4** (19 mg, 95%).

$[\alpha]_D^{25}$ −71 (*c* 1, MeOH/H_2O 1/1).

δ ^{1}H NMR (500 MHz, D_2O): δ 8.08 (4 H, s, triazolyl-H), 4.85 (4 H, d, $J_{1,2}$ 3.5, H-1), 4.70–4.66 (8 H, m, 2′-CH_2), 4.55 (8 H, m, 3′-CH_2), 4.08–4.02 (4H, m, 1′-CH_2), 3.97–3.92 (4 H, m, 1′-CH_2), 3.72 (4 H, dd, $J_{2,3}$ 10, $J_{2,1}$ 3.5, H-2), 3.65 (4 H, dd, $J_{3,2}$ 10, $J_{3,4}$ 3, H-3) 3.62–3.59 (4 H, m, H-4), 3.42 (8 H, s, 4′-CH_2), 3.07–3.02 (4 H, m, H-5), 0.99 (12 H, d, $J_{6,5}$ 6.5, H-6).

δ ^{13}C NMR (125 MHz, D_2O): 144.3 (C-triazole), 125.4 (CH-triazole), 97.8 (CH-1), 71.5 (CH-4), 69.42 (CH-3), 68.2 (CH_2-4′), 67.7 (CH-2), 66.4 (CH-5), 65.8 (CH_2-1′), 63.4 (CH_2-3′), 50.1 (CH_2-2′), 44.7 (C-centre), 15.2 (CH_3-6).

MS (ESI) for $C_{49}H_{80}N_{12}O_{24}Na$: calc. 1243.8; found 1244.0.

Dendrimer F-O-6. The reaction of 2-azidoethyl α-L-fucopyranoside[14] (20 mg, 0.08 mmol) with hexapropinyloxymethyl bispentaerythritol (**C**) (6 mg, 0.013 mmol) afforded dendrimer **F-O-6** (15 mg, 75%).

$[\alpha]_D^{25}$ −62 (*c* 1, MeOH/H_2O 1/1).

δ ^{1}H NMR (500 MHz, D_2O): 8.06 (6 H, s, triazolyl-H), 4.83 (6 H, d, $J_{1,2}$ 4.0, H-1), 4.67–4.62 (12 H, m, 2′-CH_2), 4.51 (12 H, m, 3′-CH_2), 4.04–3.98 (6 H, m, 1′-CH_2), 3.95–3.89 (6 H, m, 1′-CH_2), 3.71 (6 H, dd, $J_{2,3}$ 10.4, $J_{2,1}$ 4.0, H-2), 3.64 (6 H, dd, $J_{3,2}$ 10.4, $J_{3,4}$ 3, H-3), 3.59–3.56 (6 H, m, H-4), 3.37 (12 H, s, 4′-CH_2), 3.24 (4 H, s, 4H, 5′-CH_2), 3.05–3.00 (6 H, m, H-5), 0.97 (18 H, d, $J_{6,5}$ 6.5, H-6).

δ ^{13}C NMR (125 MHz, D_2O): 144.3 (C-triazole), 125.4 (CH-triazole), 98.0 (CH-1), 71.5 (CH-4), 69.4 (CH-3), 68.9, 68.4 (CH_2-4′, CH_2-5′), 67.8 (CH-2), 66.4 (CH-5), 65.9 (CH_2-1′), 63.6 (CH_2-3′), 50.1 (CH_2-2′), 45.1 (C-centre), 15.3 (CH_3-6).

MS (ESI) for $C_{76}H_{123}N_{18}O_{37}$: calc. 1880.9; found 1880.3.

Dendrimer F-O-12. The reaction of dendron **F-O-N**[14] (30 mg, 0.02 mmol) with tetrakis(2-propinyloxymethyl)methane (**A**) (2.1 mg, 0.007 mmol) gave dendrimer **F-O-12** (15 mg, 75%).

$[\alpha]_D^{25}$ −47 (*c* 1, MeOH/H_2O 1 : 1).

δ ^{1}H NMR (500 MHz, D_2O): 8.08 (12 H, s, triazolyl-H), 7.96 (4 H, s, triazolyl-H), 4.85 (12 H, s, H-1), 4.69–4.64 (24 H, m, 2′-CH_2), 4.58–4.51 (32 H, m, 3′-CH_2, 9′-CH_2), 4.45 (8 H, s, 10′-CH_2), 4.07–3.99 (12 H, m, 1′-CH_2), 3.97–3.88 (20 H, m, 1′-CH_2, 8′-CH_2), 3.74 (12 H, dd, $J_{2,1}$ 4.5, $J_{2,3}$ 10.3, H-2), 3.66 (12 H, dd, $J_{3,4}$ 3.0, $J_{2,3}$ 10.3, H-3), 3.62–3.59 (12 H, m, H-4), 3.57–3.52 (8 H, m, 7′-CH_2), 3.49–3.45 (8 H, m, 6′-CH_2), 3.42–3.35 (32 H, m, 4′-CH_2, 11′-CH_2), 3.33 (8 H, s, 5′-CH_2), 3.10–3.05 (12 H, m, H-5), 1.00 (36 H, d, $J_{5,6}$ 6.5, H-6).

δ ^{13}C NMR (D_2O, 125 MHz): 144.3 (C-triazole), 125.4 (CH-triazole), 98.1 (CH-1), 71.5 (CH-4), 70.5 (CH_2-6′), 69.6 (CH_2-7′), 69.5 (CH-3), 68.7 (CH_2-5′), 68.4 (CH_2-8′), 68.1 (CH_2-4′, CH_2-11′), 67.7 (CH-2), 66.4 (CH-5), 65.9 (CH_2-1′), 63.2 (CH_2-3′, CH_2-10′), 50.1 (CH_2-2′, CH_2-9′), 44.8 (2 × C-centre), 15.3 (CH_3-6).

MS (ESI) for $C_{185}H_{300}N_{48}O_{84}$: calc. 4538.0; found 2291.7 $[M + 2Na]^{2+}$, 1540.7 $[M + 3Na]^{3+}$, 1157.4 $[M + 4Na]^{4+}$.

Dendrimer F-C-4. Cycloaddition of 2-(α-L-fucopyranosyl) ethylazide (**2**) (25 mg, 0.115 mmol) with tetrakis(2-propinyloxymethyl)methane (**A**) (7.5 mg, 0.026 mmol) gave dendrimer **F-C-4** (29 mg, 96%).

$[\alpha]_D^{25}$ −87.2 (*c* 1.0, MeOH).

δ ^{1}H NMR (600.1 MHz, D_2O): 7.98 (4 H, br s, triazolyl-H), 4.43 (16 H, br s, 2′-, 3′-CH_2), 3.85–3.95 (8 H, m, H-1, H-2), 3.64–3.75 (12 H, m, H-3, H-4, H-5), 3.35 (8 H, br s, 4′-CH_2), 2.25–2.35 (4 H, m, 1′a-CH_2), 2.08–2.17 (4 H, m, 1′b-CH_2), 1.00 (12 H, d, $J_{5,6}$ 6.4, H-6).

δ ^{13}C NMR (150.9 MHz, D_2O):[28] 73.5 (CH-1), 71.5 (CH-4), 69.8 (CH-3), 68.2 (CH_2-4′), 67.4 and 67.4 (CH-2 and CH-5), 63.9 (CH_2-3′), 48.0 (CH_2-2′), 44.6 (C-centre), 24.2 (CH_2-1′), 15.6 (CH_3-6).

HRMS (ESI) for $C_{49}H_{80}N_{12}O_{20}Na$: calc. 1179.5504; found 1179.5506.

Dendrimer F-C-6. Cycloaddition of 2-(α-L-fucopyranosyl) ethylazide (**2**) (25 mg, 0.115 mmol) with hexapropinyloxymethyl bispentaerythritol (**C**) (12.5 mg, 0.012 mmol) afforded dendrimer **F-C-6** (22 mg, 95%).

$[\alpha]_D^{25}$ −88.6 (*c* 1.0, MeOH).

δ ^{1}H NMR (600.1 MHz, D_2O): 7.95 (6 H, br s, triazolyl-H), 4.38–4.52 (24 H, m, 2′-, 3′-CH_2), 3.84–3.96 (12 H, m, H-1, H-2), 3.65–3.74 (18 H, m, H-3, H-4, H-5), 3.26–3.45 (12 H, m, 4′-CH_2), 3.13–3.45 (4 H, br m, 5′-CH_2), 2.23–2.36 (6 H, m, 1′a-CH_2), 2.06–2.19 (6 H, m, 1′b-CH_2), 1.00 (18 H, d, $J_{5,6}$ 6.3, 6-CH_3).

δ ^{13}C NMR (150.9 MHz, D_2O):[28] 125.2 (CH – triazolyl, from HMQC), 73.5 (CH-1), 71.5 (CH-4), 69.8 (CH-3), 68.8 (CH_2-5′), 68.2 (CH_2-4′), 67.4 and 67.4 (CH-2 and CH-5), 63.7 (CH_2-3′), 47.9 (CH_2-2′), 45.0 (C-centre), 24.3 (CH_2-1′), 15.6 (CH_3-6).

HRMS (MALDI) for $C_{76}H_{124}N_{18}O_{31}Na$: calc. 1807.8572; found 1807.8546.

Dendrimer F-C-9. The reaction of dendron **F-C-N** (25 mg, 0.025 mmol) with 1,3,5-tris(2-propyn-1-yl)oxybenzene (**B**) (1.8 mg, 0.0076 mmol) gave dendrimer **F-C-9** (22 mg, 89%). A Sephadex G50 (eluent H_2O/MeOH 9/1) was used for the purification.

$[\alpha]_D^{25}$ −80.7 (*c* 0.4, MeOH).

δ ^{1}H NMR (600.1 MHz, D_2O):[29] 8.03, 7.94 and 7.84 (12 H, br s, triazolyl-H), 6.19 (3 H, br s, Ph), 5.00 (6 H, br s, 10′-CH_2), 4.53 (6 H, br s, 9′-CH_2), 4.51–4.31 (36 H, m, 3′-CH_2, 2′-CH_2), 3.95–3.72 (24 H, m, H-1, H-2, 8′-CH_2), 3.77–3.62 (27 H, m, H-3, H-4, H-5), 3.61–3.58 (m), 3.58–3.53 (m), 3.50–3.43 (m), 3.41–3.31 (m), 3.25 (brs) and 3.19 (brs) (36 H, 7′-CH_2, 6′-CH_2, 4′-CH_2, 5′-CH_2), 2.37–2.03 (18 H, m, 1′a-CH_2 and 1′b-CH_2), 1.02 and 0.98 (27 H, 2 × d, $J_{6,5}$ 6.3, 6-CH_3).

δ ^{13}C NMR (150.9 MHz, D_2O):[28] 159.7 (C-Ph), 125.2 and 125.1 (2 × CH-triazolyl, from HMQC), 95.3 (CH-Ph), 73.5 (CH-1), 71.5 (CH-4), 70.4 (CH_2-6′), 69.82 and 69.78 (CH-3), 69.6 and 69.3 (CH_2-7′), 69.2 and 69.0 (CH_2-5′), 68.6 (CH_2-8′), 68.43 and 68.36 (CH_2-4′), 67.4 and 67.3 (CH-2 and CH-5), 63.6 and 63.5 (CH_2-3′), 61.2 (CH_2-10′), 50.3 and 50.2 (CH_2-9′), 47.8 (CH_2-2′), 44.8 and 44.7 (C-centre), 24.3 and 24.2 (CH_2-1′), 15.61 and 15.55 (6-CH_3).

HRMS (MALDI) for $C_{141}H_{222}N_{36}O_{54}Na$: calc. 3306.5624; found 3306.5729.

Dendrimer F-C-12. Cycloaddition of dendron **F-C-N** (25 mg, 0.025 mmol) with tetrakis(2-propinyloxymethyl)methane (**A**) (1.6 mg, 0.006 mmol) afforded dendrimer **F-C-12** (26 mg, 100%). The reaction was performed under microwave

irradiation (20 min at 60 °C, then 15 min at 80 °C) and a Sephadex G50 (eluent H_2O/MeOH 9 : 1) was used for the purification.

$[\alpha]_D^{25}$ −95.2 (*c* 0.3, MeOH).

δ ^{1}H NMR (600.1 MHz, D_2O): 7.91 (12 H, br s, triazolyl-H), 7.88 (4 H, br s, triazolyl-H), 4.30–4.55 (64 H, m, 9′-CH_2, 3′-CH_2, 2′-CH_2, 10′-CH_2,), 3.84–3.95 (24 H, m, H-1, H-2), 3.81 (8 H, br t, 8′-CH_2), 3.62–3.75 (36 H, m, H-3, H-4, H-5), 3.45 (8 H, br s, 7′-CH_2), 3.37 (8 H, br s, 6′-CH_2), 3.30 (24 H, br s, 4′-CH_2), 3.22 (8 H, br s, 5′-CH_2), 2.21–2.33 (12 H, m, 1′a-CH_2), 2.04–2.17 (12 H, m, 1′b-CH_2), 1.00 (36 H, d, *J* 6.3, 6-CH_3).

δ ^{13}C NMR (150.9 MHz, D_2O):[28] 125.2 (2 × CH-triazolyl, from HMQC), 73.5 (CH-1), 71.5 (CH-4), 70.4 (CH_2-6′), 69.8 (CH-3), 69.7 (CH_2-7′), 69.1 (CH_2-5′), 68.7 (CH_2-8′), 68.4 (CH_2-4′), 67.4 (CH-2 and CH-5), 63.8 (CH_2-10′), 63.7 (CH_2-3′), 50.1 (CH_2-9′), 47.8 (CH_2-2′), 44.8 (2 × C-centre), 24.3 (CH_2-1′), 15.6 (6-CH_3).

HRMS (MALDI) for $C_{185}H_{301}N_{48}O_{72}$: calc. 4347.1362; found 4347.1236.

Dendrimer M-C-9. The reaction of dendron **M-C-N** (25 mg, 0.023 mmol) with 1,3,5-tris(2-propyn-1-yl)oxybenzene (**B**) (1.7 mg, 0.0071 mmol) afforded dendrimer **M-C-9** (20 mg, 82%). The reaction was performed under microwave irradiation (20 min at 60 °C) and a Sephadex G50 (eluent H_2O/MeOH 9/1) was used for the purification.

$[\alpha]_D^{25}$ +12.3 (*c* 0.15, MeOH).

δ ^{1}H NMR (600.1 MHz, D_2O): 8.05 (3 H, br s, triazolyl-H), 7.90 (9 H, br s, triazolyl-H), 6.15 (3 H, br s, Ph), 5.00 (6 H, br s, 10′-CH_2), 4.53 (6 H, br s, 9′-CH_2), 4.27–4.46 (36 H, m, 3′-CH_2, 2′-CH_2), 3.84 (6 H, br s, 8′-CH_2), 3.62–3.81 (45 H, m, H-1, H-2, H-3, 6a-CH_2, 6b-CH_2), 3.60 (9H, dd, *J* 9.0, *J* 9.0, H-4), 3.39–3.50 (15 H, m, 7′-CH_2, H-5), 3.35 (6 H, br s, 6′-CH_2), 3.25 (18 H, br s, 4′-CH_2), 3.19 (6H, br s, 5′-CH_2), 2.25–2.41 (9 H, m, 1′a-CH_2), 1.88–2.01 (9 H, m, 1′b-CH_2).

δ ^{13}C NMR (150.9 MHz, D_2O):[28] 159.6 (C-Ph), 125.7 and 125.4 (2 × CH-triazolyl, from HMQC), 95.3 (CH-Ph), 75.0 (CH-1), 74.1 (CH-5), 71.1 (CH-2), 70.7 (CH-3), 70.4 (CH_2-6′), 69.8 (CH_2-7′), 68.9 (CH_2-5′), 68.6 (CH_2-8′), 68.4 (CH_2-4′), 67.2 (CH-4), 63.7 (CH_2-3′), 61.3 (CH_2-10′), 61.0 (6-CH_2), 50.1 (CH_2-9′), 47.0 (CH_2-2′), 44.8 (C-centre), 28.1 (CH_2-1′).

HRMS (MALDI) for $C_{141}H_{223}N_{36}O_{63}$: calc. 3428.5347; found 3428.5295.

Dendrimer M-C-12. The reaction of dendron **M-C-N** (25 mg, 0.023 mmol) with tetrakis(2-propinyloxymethyl)methane (**A**) (1.5 mg, 0.0053 mmol) gave dendrimer **M-C-12** (21 mg, 85%). The reaction was performed under microwave irradiation (20 min at 60 °C) and a Sephadex G50 (eluent H_2O/MeOH 9/1) was used for the purification.

$[\alpha]_D^{25}$ +10.5 (*c* 0.1, MeOH).

δ ^{1}H NMR (600.1 MHz, D_2O): 7.93 (12 H, br s, triazolyl-H), 7.88 (4 H, br s, triazolyl-H), 4.30–4.55 (64 H, m, 9′-CH_2, 3′-CH_2, 2′-CH_2, 10′-CH_2,), 3.77–3.82 (20 H, m, 8′-CH_2, H-1), 3.74–3.77 (12 H, m, 6a-CH_2), 3.73–3.74 (12 H, m, H-2), 3.70–3.73 (12 H, m, H-3), 3.68–3.71 (8 H, m, 11′-CH_2), 3.65 (12 H, dd, *J* 12.4, *J* 6.3, 6b-CH_2), 3.60 (12 H, dd, *J* 9.0, *J* 9.0, H-4), 3.41–3.49 (20 H, m, 7′-CH_2, H-5), 3.36 (8 H, br s, 6′-CH_2), 3.29 (24 H, br s, 4′-CH_2), 3.21 (8 H, br s, 5′-CH_2), 2.29–2.39 (12 H, m, 1′a-CH_2), 1.95–2.05 (12 H, m, 1′b-CH_2).

δ ^{13}C NMR (150.9 MHz, D_2O): 125.2 (2 × CH-triazolyl, from HMQC), 75.0 (CH-1), 74.1 (CH-5), 71.1 (CH-2), 70.7 (CH-3), 70.4 (CH_2-6′), 69.7 (CH_2-7′), 69.0 (CH_2-5′), 68.7 (CH_2-8′), 68.3 (CH_2-4′), 67.2 (CH-4), 63.7 (CH_2-10′), 63.6 (CH_2-3′), 61.3 (CH_2-11′), 61.0 (6-CH_2), 50.1 (CH_2-9′), 47.0 (CH_2-2′), 44.7 and 44.8 (2 × C-centre), 28.1 (CH_2-1′).

HRMS (MALDI) for $C_{185}H_{301}N_{48}O_{84}$: calc. 4539.0752; found 4539.0891.

Acknowledgements

Financial support by the EU-ITN CARMUSYS (PITN-GA-2008-213592) and MINECO (CTQ2014-52328P) co-financed by European Regional Development Funds (ERDF) is gratefully acknowledged. For DC-SIGN ECD production, this work used the Multistep Protein Purification Platform (MP3) and the SPR platform for the competition test of the Grenoble Instruct Centre (ISBG; UMS 3518 CNRS-CEA-UJF-EMBL) with support from FRISBI (ANR-10-INSB-05-02) and GRAL (ANR-10-LABX-49-01) within the Grenoble Partnership for Structural Biology.

Notes and references

1 M. Reynolds and S. Pérez, *C. R. Chim.*, 2011, **14**, 74.
2 Y. van Kooyk and T. B. H. Geijtenbeek, *Nat. Rev. Immunol.*, 2003, **3**, 697.
3 E. A. Koppel, K. P. J. M. van Gisbergen, T. B. H. Geijtenbeek and Y. van Kooyk, *Cell. Microbiol.*, 2005, **7**, 157.
4 T. B. Geijtenbeek, D. S. Kwon, R. Torensma, S. J. Vliet, G. C. van Duijnhoven, J. Middel, I. L. Cornelissen, H. S. Nottet, V. N. Kewal-ramani, D. R. Littman, C. G. Figdor and Y. van Kooyk, *Cell*, 2000, **100**, 587.
5 Y. van Kooyk, A. Engering, A. N. Lekkerkerker, I. S. Ludwig and T. B. H. Geijtenbeek, *Curr. Opin. Immunol.*, 2004, **16**, 488.
6 M. Anderluh, G. Jug, U. Švajger and N. Obermajer, *Curr. Med. Chem.*, 2012, **19**, 992.
7 (*a*) M. Sánchez-Navarro and J. Rojo, *Drugs News Perspect.*, 2010, **23**, 557; (*b*) A. Bernardi, J. Jiménez-barbero, A. Casnati, C. De Castro, T. Darbre, F. Fieschi, J. Finne, H. Funken, K. E. Jaeger, M. Lahmann, T. K. Lindhorst, M. Marradi, P. Messner, A. Molinaro, P. V. Murphy, C. Nativi, S. Oscarson, S. Penadés, F. Peri, R. J. Pieters, O. Renaudet, J. L. Reymond, B. Richichi, J. Rojo, F. Sansone, C. Schäffer, W. B. Turnbull, T. Velasco-torrijos, S. Vidal, S. Vincent, M. Wennekes, H. Zuilhofxy and A. Imberty, *Chem. Soc. Rev.*, 2013, **42**, 4709; (*c*) J. J. Reina and J. Rojo, *Braz. J. Pharm. Sci.*, 2013, **49**, 109; (*d*) B. Lepenies, J. Lee and S. Sonkaria, *Adv. Drug Delivery Rev.*, 2013, **65**, 1271; (*e*) S. Cecioni, A. Imberty and S. Vidal, *Chem. Rev.*, 2015, **115**, 525; (*f*) C. T. Varner, T. Rosen, J. T. Martin and R. S. Kane, *Biomacromolecules*, 2015, **16**, 43; (*g*) S. Sattin and A. Bernardi, *Trends Biotechnol.*, 2016, **34**, 483.

8 Y. Guo, H. Feinberg, E. Conroy, D. A. Mitchell, R. Alvarez, O. Blixt, M. E. Taylor, W. I. Weis and K. Drickamer, *Nat. Struct. Mol. Biol.*, 2004, **11**, 591.
9 F. Lasala, E. Arce, J. R. Otero, J. Rojo and R. Delgado, *Antimicrob. Agents Chemother.*, 2003, **47**, 3970.
10 J. Luczkowiak, S. Sattin, I. Sutkeviciute, J. J. Reina, M. Sanchez-navarro, M. Thepaut, L. Martínez-prats, A. Daghetti, F. Fieschi, R. Delgado, A. Bernardi and J. Rojo, *Bioconjugate Chem.*, 2011, **22**, 1354.
11 (*a*) I. Sutkeviciute, M. Thépaut, S. Sattin, A. Berzi, J. Mcgeagh, S. Grudinin, J. Weiser, A. Le Roy, J. J. Reina, J. Rojo, M. Clerici, A. Bernardi, C. Ebel and F. Fieschi, *ACS Chem. Biol.*, 2014, **9**, 1377; (*b*) C. Guzzi, P. Alfarano, I. Sutkeviciute, S. Sattin, R. Ribeiro-viana, F. Fieschi, A. Bernardi, J. Weiser, J. Rojo, J. Angulo and P. M. Nieto, *Org. Biomol. Chem.*, 2016, **14**, 335.
12 (*a*) V. V. Rostovtsev, L. G. Green, V. V. Fokin and K. B. Sharpless, *Angew. Chem., Int. Ed.*, 2002, **41**, 2596; (*b*) C. W. Tornøe, C. Christensen and M. Meldal, *J. Org. Chem.*, 2002, **67**, 3057; (*c*) M. Meldal and C. W. Tornøe, *Chem. Rev.*, 2008, **108**, 2952.
13 (*a*) J. F. Lutz, *Angew. Chem., Int. Ed.*, 2007, **46**, 1018; (*b*) J. E. Moses and A. D. Moorhouse, *Chem. Soc. Rev.*, 2007, **36**, 1249; (*c*) C. D. Hein, X. M. Liu and D. Wang, *Pharm. Res.*, 2008, **25**, 2216; (*d*) M. van Dijk, D. T. Rijkers, R. M. Liskamp, C. F. van Nostrum and W. E. Hennink, *Bioconjugate Chem.*, 2009, **20**, 2001; (*e*) G. Franc and A. K. Kakkar, *Chem. Soc. Rev.*, 2010, **39**, 1536; (*f*) E. Lallana, F. Fernandez-trillo, A. Sousa-herves, R. Riguera and E. Fernandez-megia, *Pharm. Res.*, 2012, **29**, 902; (*g*) K. Kempe, A. Krieg, C. R. Becer and U. S. Schubert, *Chem. Soc. Rev.*, 2012, **41**, 176; (*h*) V. K. Tiwari, B. B. Mishra, K. B. Mishra, N. Mishra, A. S. Singh and X. Chen, *Chem. Rev.*, 2016, **116**, 3086.
14 R. Ribeiro-viana, J. J. García-vallejo, D. Collado, E. Pérez-Inestrosa, K. Bloem, I. van Kooyk and J. Rojo, *Biomacromolecules*, 2012, **13**, 3209.
15 R. Ribeiro-viana, M. Sánchez-Navarro, J. Luczkowiak, J. R. Koeppe, R. Delgado, J. Rojo and B. G. Davis, *Nat. Commun.*, 2012, **3**, 1303.
16 N. Varga, I. Sutkeviciute, R. Ribeiro-viana, A. Berzi, R. Ramdasi, A. Daghetti, G. Vettoretti, A. Amara, M. Clerici, J. Rojo, F. Fieschi and A. Bernardi, *Biomaterials*, 2014, **35**, 4175.
17 S. Mari, H. Posteri, G. Marcou, D. Potenza, F. Micheli, F. J. Canada, J. Jimenez-barbero and A. Bernardi, *Eur. J. Org. Chem.*, 2004, 5119.
18 B. Bertolotti, B. Oroszová, I. Sutkeviciute, L. Kniežo, F. Fieschi, K. Parkan, Z. Lovyova, M. Kašáková and J. Moravcová, *Carbohydr. Res.*, 2016, **435**, 7.
19 (*a*) T. Uchiyama, T. J. Woltering, W. Wong, C. C. Lin, T. Kajimoto, M. Takebaashi, G. Weitz-schmidt, T. Asakura, M. Noda and C. H. Wong, *Bioorg. Med. Chem.*, 1996, **4**, 1149; (*b*) T. Uchiyama, V. P. Vassilev, T. Kajimoto, W. Wong, H. Huang, C. C. Lin and C. H. Wong, *J. Am. Chem. Soc.*, 1995, **117**, 5395.
20 P. Cheshev, L. Morelli, M. Marchesi, Č. Podlipnik, M. Bergström and A. Bernardi, *Chem. – Eur. J.*, 2009, **16**, 1951.
21 C. G. Francisco, R. Freire, A. J. Herrera, I. Perez-martın and E. Suarez, *Tetrahedron*, 2007, **63**, 8910.
22 J. A. Bennek and G. R. Gray, *J. Org. Chem.*, 1987, **52**, 892.
23 T. K. Lindhorst, S. Kötter, U. Krallmann-wenzel and S. Ehlers, *J. Chem. Soc., Perkin Trans. 1*, 2001, 823.
24 A. Patel and T. K. Lindhorst, *Eur. J. Org. Chem.*, 2002, 79.
25 M. Andreini, D. Doknic, I. Sutkeviciute, J. J. Reina, J. Duan, E. Chabrol, M. Thepaut, E. Moroni, F. Doro, L. Belvisi, J. Weiser, J. Rojo, F. Fieschi and A. Bernardi, *Org. Biomol. Chem.*, 2011, **9**, 5778.
26 D. Doknic, M. Abramo, I. Sutkeviciute, A. Reinhardt, C. Guzzi, M. K. Schlegel, D. Potenza, P. M. Nieto, F. Fieschi, P. H. Seeberger and A. Bernardi, *Eur. J. Org. Chem.*, 2013, 5303.
27 G. Tabarani, M. Thépaut, D. Stroebel, C. Ebel, C. Vivès, P. Vachette, D. Durand and F. Fieschi, *J. Biol. Chem.*, 2009, **284**, 21229.
28 Signal of triazolyl carbons is missing in the ^{13}C spectrum due to some dynamic process.
29 Mixture of two stereoisomers of **F-C-9**; most of the carbons and some of the proton resonances are doubled.

PŘÍLOHA IX

Choutka, J.; Pohl, R.; Parkan, K. MOP and EE Protecting Groups in Synthesis of α- or β-Aryl--*C*-Glycosides from Glycals. *ACS Omega* **2018**, *3* (7), 7875-7887.

ACS OMEGA

Article

Cite This: ACS Omega 2018, 3, 7875−7887

MOP and EE Protecting Groups in Synthesis of α- or β-Naphthyl-C-Glycosides from Glycals

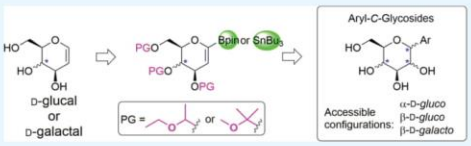
Jan Choutka,[†] Radek Pohl,[‡] and Kamil Parkan*[,†]

[†]Department of Chemistry of Natural Compounds, University of Chemistry and Technology, Prague, Technická 5, 166 28 Prague, Czech Republic

[‡]Institute of Organic Chemistry and Biochemistry, Czech Academy of Sciences, Gilead Sciences & IOCB Research Center, Flemingovo nám. 2, 166 10 Prague, Czech Republic

Supporting Information

ABSTRACT: The development of effective protection strategies is essential in the synthesis of complex carbohydrates and glycomimetics. This article describes a versatile four-stage protocol for the synthesis of α- or β-aryl-C-glycosides from unprotected D-glycals using two acetal protecting groups, ethoxyethyl and methoxypropyl, which are stable under harsh basic conditions and convenient for the C-1 metalation of glycals. Their stability was investigated in subsequent cross-coupling reactions with 1-iodonaphthalene followed by oxidative/reductive transformations to naphthyl-C-glycosides.



INTRODUCTION

Recent development of glycobiology[1] has increased the need for the synthesis of structurally defined carbohydrates and their analogues. Among them, C-glycosides[2] are important analogues of carbohydrates, which exhibit high stability toward chemical and enzymatic hydrolysis and include many bioactive natural products[3] and commercial drugs.[4] Because of their stability and broad range of biological activities, access to C-glycosides is of great importance.

Several common synthetic approaches,[2e,f,3b] including methods using cationic, anionic, or radical sugar species, as well as methods using de novo construction of the sugar or aromatic moiety for the synthesis of aryl-C-glycoside scaffolds, were used in the past. However, these methods are often hard to carry out stereoselectively and are not universal across sugar substrates. Therefore, alternative approaches including transition-metal-mediated cross-coupling reactions[2e,f,3b] (Heck, Suzuki, Stille, and Negishi-type reactions) have been developed for the synthesis of C-glycosides employing metalated glycals and aromatic electrophiles as key starting materials. Nevertheless, the preparation of 1-metalated glycals usually relies upon the lithiation of the C-1 position of protected glycals by a strong base. Lithiation conditions are harsh, and some common protecting groups such as benzyl[5a] or *tert*-butyldimethylsilyl (TBS)[5b,c] ethers compete for lithiation. Several protecting groups that survive the metalation of glycals by *t*-BuLi have been gradually developed (triisopropylsilyl,[6] di-*tert*-butylsilylene,[6b,c,7] TBS,[5,6c,8] *tert*-butyldiphenylsilyl,[5a,9] triethylsiyl,[10] methoxymethyl (MOM),[7,11] and isopropylidene[11,12]), but they all suffer from one or more disadvantages, which precludes their general applicability (Figure 1). These include, for example, the requirement of 3−6 equiv of *t*-BuLi for glycal deprotonation, presumably due to complexation effects. Besides that, the deprotection of silyl ethers with tetra-*n*-butylammonium fluoride is usually complicated by problems in separating the product from tetrabutylammonium salts. Moreover, silyl ethers are not universal protecting groups across pyranoid substrates (D-glucal, D-galactal, etc.), which makes it necessary to discover the efficient combination of

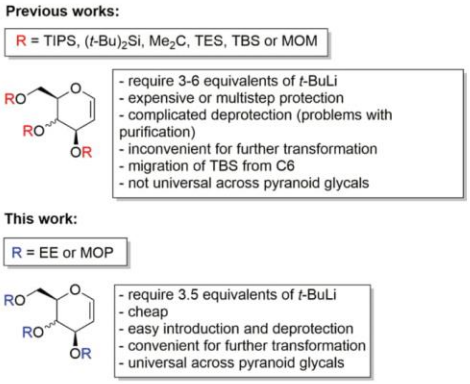
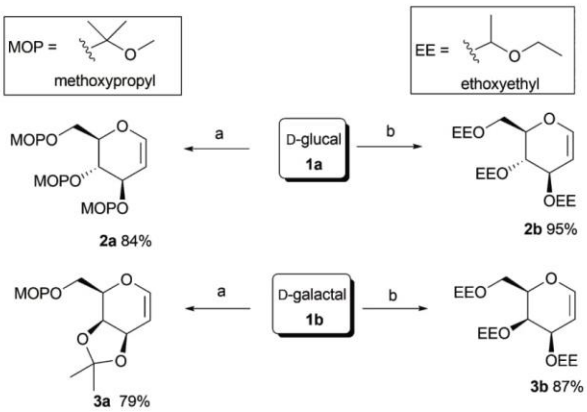


Figure 1. Protecting groups that survive metalation of D-glucal and D-galactal by *t*-BuLi.

Received: May 4, 2018
Accepted: June 20, 2018
Published: July 16, 2018

DOI: 10.1021/acsomega.8b00901
ACS Omega 2018, 3, 7875−7887

Scheme 1. Preparation of MOP- and EE-Protected D-Glycals 2a–b and 3a–b[a,b]



[a]2-Methoxypropene, Py·TsOH, dichloromethane (DCM), or dimethylformamide (DMF); 0–25 °C; 1–12 h. [b]Ethyl vinyl ether, Py·TsOH, DCM; 0–25 °C; 1.5–12 h.

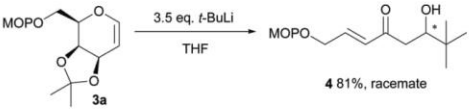
protecting groups for each application. Next, silyl groups are quite expensive for multigram synthesis and the combination of MOM and isopropylidene groups requires multistep protection. Finally, silyl ether-protected cross-coupling products are often inconvenient for further transformation to α- or β-*C*-glycosides, presumably due to the bulkiness of the protecting groups and for ring-strain reasons.[6b,13] In view of the aforementioned, it is obvious that the development of alternative protection strategies would facilitate progress in the synthesis of aryl-*C*-glycosides from glycals.

■ RESULTS AND DISCUSSION

We have found that the utilization of rarely used ethoxyethyl[14] (EE) or methoxypropyl[15] (MOP) acetal protecting groups (Figure 1) offers several advantages. Although these protecting groups have been used for orthogonal protection in carbohydrate chemistry, their use for glycals has not yet been described. Specifically, EE and MOP protecting groups are cheap and enable mild conditions for their introduction and removal. Nevertheless, they are stable under strong basic conditions. This article suggests that EE and MOP can be universal protecting groups across pyranoid glycals and convenient for further transformation of cross-coupling products to the corresponding α- or β-*C*-glycosides.

First, we investigated the reaction conditions for the preparation of fully protected glycals **2a–b** and **3a–b**. Specifically, we investigated commercially available D-glucal **1a** and D-galactal **1b**, which reacted under standard conditions with 2-methoxypropene[16] or ethyl vinyl ether[17] in the presence of pyridinium tosylate, yielding fully protected glycals **2a–b** and **3a–b** in 79–95% yields. Remarkably, the reaction of 2-methoxypropene with *cis*-1,2-diol such as D-galactal **1b** leads to the formation of isopropylidene acetal on the secondary hydroxyls (**3a**), whereas the reaction with *trans*-1,2-diol such as D-glucal **1a** introduces MOP groups selectively. In the reaction with ethyl vinyl ether, no such selectivity has been observed and per-EE products have been obtained in both cases (Scheme 1). Surprisingly, the subsequent reaction of **3a** with *t*-BuLi formed racemic open-chain enone **4** in 81% yield (the enantiomeric composition was determined by derivatization by (*S*)-Mosher's acid and NMR analysis (see Supporting Information (SI) Chapter 2, Scheme 2)).

Scheme 2. Reaction of 3a with *t*-BuLi

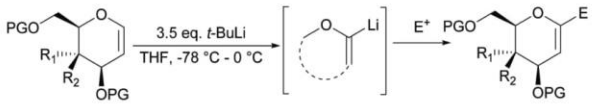


Next, since the protection of glycals with ethyl vinyl ether produced fully protected glycals as a mixture of eight possible diastereoisomers, it was crucial to find a simple and efficient method to prove the structure of these compounds by NMR. Therefore, we first attempted to deprotect EE glycals **2b** and **3b** using 5% (v/v) trifluoroacetic acid (TFA) in MeOH-d_4 directly in the NMR tube; however, this method suffered from partial decomposition of substrates. Fortunately, switching the 5% TFA to 10% (v/v) CD_3COOD in MeOH-d_4 and heating the mixture to 50 °C for 0.75–2 h in the NMR tube enabled the complete cleavage of EE groups. Using this in situ deprotection protocol, we were able to confirm the structure of EE-protected compounds by NMR (for details, see the SI, Chapter 4).

Since our interest was focused on the synthesis of *C*-glycosides using Suzuki and Stille reactions, fully protected D-glucals **2a–b** and D-galactal **3b** were converted into 1-lithiated intermediates by treatment with *t*-BuLi and then reacted with Bu_3SnCl or *i*PrOBPin, followed by quenching with water. In all cases (Table 1, entries 1–6), the reaction proceeded cleanly, providing the desired compounds **5a–b**, **6a–b**, **7**, and **8** in almost quantitative yields (Table 1). The deprotonation of vinylic C1–H by *t*-BuLi usually requires 3–6 equiv of base.[18] Therefore, it was important to find the optimal lithiation conditions for the preparation of organometalated glycals with EE and MOP protecting groups. We performed a series of lithiation experiments on protected D-glucals **2a–b** with *t*-

DOI: 10.1021/acsomega.8b00901
ACS Omega 2018, 3, 7875–7887

Table 1. Preparation of Metalated Glycals 5a−b or 6a−b and 7−8



D-glucal **2a-b** R_1 = OPG, R_2 = H
D-galactal **3b** R_1 = H, R_2 = OPG

5a-b R_1 = OPG, R_2 = H
6a-b R_1 = OPG, R_2 = H
7-8 R_1 = H, R_2 = OPG

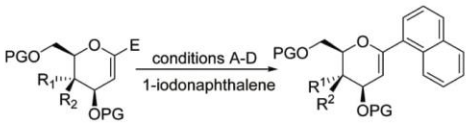
entry	derivative	PG	E^+	E	product, yield (%)
1	D-glucal, **2a**	MOP	*i*PrOBPin	BPin	**5a**, (94)[a]
2	D-glucal, **2a**	MOP	Bu_3SnCl	$SnBu_3$	**6a**, (93)[b]
3	D-glucal, **2b**	EE	*i*PrOBPin	BPin	**5b**, (81)[a]
4	D-glucal, **2b**	EE	Bu_3SnCl	$SnBu_3$	**6b**, (90)[b]
5	D-galactal, **3b**	EE	*i*PrOBPin	BPin	**7**, (90)[a]
6	D-galactal, **3b**	EE	Bu_3SnCl	$SnBu_3$	**8**, (69)[b]

[a]Crude product. [b]Isolated yield.

BuLi, followed by deuteration with D_2O. In both cases, direct deprotonations of C1−H required 3.5 equiv of *t*-BuLi (see the SI, Chapter 1). No evidence of competing deprotonation on MOP or EE protecting groups was observed.

In our systematic study of EE and MOP protecting groups, we also tested the performance of the substituted glycals **5a−b**, **6a−b**, **7**, and **8** in cross-coupling reactions. As model reactions, we investigated Suzuki−Miyaura and Stille reactions with 1-iodonaphthalene (Table 2). The Suzuki−Miyaura reaction of

Table 2. Preparation of Protected 1-Naphthyl-*C*-glycals 9a−b and 10



5a-b R_1 = OPG, R_2 = H
6a-b R_1 = OPG, R_2 = H
7,8 R_1 = H, R_2 = OPG

9a-b R_1 = OPG, R_2 = H
10 R_1 = H, R_2 = OPG

entry	derivative	PG	E	conditions	product, yield (%)[a]
1	**5a**	MOP	BPin	A	**9a**, (86)
2	**6a**	MOP	$SnBu_3$	B	**9a**, (76)
3	**5b**	EE	BPin	A	**9b**, (79)
4	**6b**	EE	$SnBu_3$	B	**9b**, (93)
5	**7**	EE	BPin	A	**10**, (72)
6	**8**	EE	$SnBu_3$	B	**10**, (87)
7	**2b**	EE	H	C	**9b**, (43)
8	**2b**	EE	H	D	**9b**, (20)

[a]Isolated yield; reaction conditions: (A) $Pd(PPh_3)_2Cl_2$, 1,2-dimethoxyethane (DME), Na_2CO_3, 80 °C; (B) $Pd(PPh_3)_4$, toluene, 120 °C; (C) (1) *t*-BuLi, $InCl_3$, tetrahydrofuran (THF), (2) $Pd(Ph_3P)_2Cl_2$, reflux; (D) (1) *t*-BuLi, $ZnCl_2$, THF, (2) $Pd(Ph_3P)_4$.

1-pinacolboronates **5a**, **5b**, and **7** was performed under our previously published conditions[6c] (conditions A). In all cases, the expected cross-coupling products **9a**, **9b**, and **10** were obtained in high yields of 72−93% (Table 2, entries 1, 3, and 5).

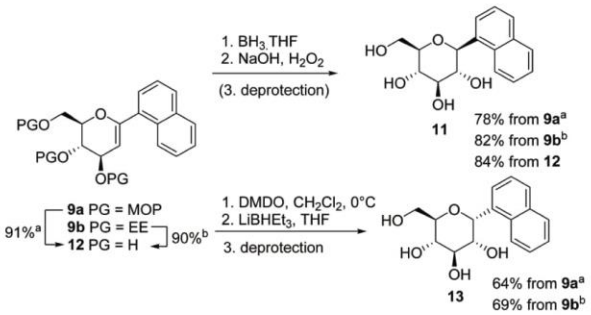
The Stille reaction was carried out under standard conditions.[19] Specifically, $Pd(PPh_3)_4$ was used as a catalyst and the reaction was heated at 120 °C for 12 h in toluene as the solvent. In these cases, the corresponding 1-stannylglycals **6a**, **6b**, and **8** were again converted to naphthyl-*C*-glycals **9a**, **9b**, and **10** in high yields of 72−86% (Table 2, entries 2, 4, and 6). Finally, we decided to prove the compatibility of the EE protecting groups of **2b** in Negishi-type[20] and In-mediated[6a] coupling reactions with 1-iodonaphthalene (Table 2, entries 7 and 8). In both cases, the cross-coupling product **9b** was isolated in 20−43% yields. These low yields were probably caused by the instability of EE protecting groups in the presence of zinc and indium Lewis acids after quenching with water.

In the next step, we investigated whether these protected cross-coupling products **9a**, **9b**, and **10** with a reactive endocyclic double bond can be deprotected without damaging the glycal double bond. To our surprise, the fully protected gluco derivative **9a** with MOP protecting groups was converted to free enol ether **12** by stirring in the mixture of 1% acetic acid and THF overnight. Similarly, the free cross-coupling product **12** was achieved after the treatment of the EE-protected derivative **9b** with a mixture of 20% aqueous acetic acid and THF (Scheme 3).

Since the control of the stereochemistry of *C*-glycosides is essential for the preparation of the desired stereoisomer, it was necessary to confirm that the EE- and MOP-protected derivatives **9a−b** are stable during stereoselective transformations,[6c,21] leading to *α*- or *β*-aryl-*C*-glycosides. Compounds **9a** and **9b** with MOP and EE protecting groups served as model compounds. It was found that hydroboration of the double bond in **9a** and **9b** with the BH_3·THF complex followed by oxidation with alkaline hydrogen peroxide and deprotection with diluted acetic acid in THF gave directly aryl-*β*-*C*-glycoside **11** as a single stereoisomer in high overall yields (Scheme 3). The opposite anomer, naphthyl-*α*-*C*-glycoside **13**, was obtained by epoxidation of the double bond with dimethyldioxirane (DMDO), followed by the cleavage of the formed epoxide ring with lithiumtriethylborohydride (Li-BEt_3H). The stereochemical outcome of these transformations is consistent with results previously reported on the substituted glucal unit bearing benzyl ether[21,22b] or silyl ether[6b,c] protection. The reactions mentioned above were also carried out with the free cross-coupling product **12**; after hydroboration, *β*-*C*-glycoside **11** was obtained in high 84% yield

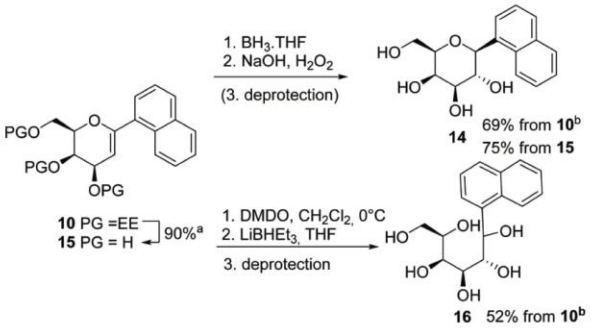
DOI: 10.1021/acsomega.8b00901
ACS Omega 2018, 3, 7875−7887

Scheme 3. Transformations of the Glucal Double Bond to α- or β-Aryl-C-glucosides 11 or 13[a,b]



[a]1% AcOH/THF (1:1). [b]20% AcOH/THF (1:1).

Scheme 4. Preparation of Aryl-C-galactosides 14 and 16[a,b]



[a]10% AcOH in MeOH. [b]20% AcOH/MeOH (1:1).

(Scheme 3). On the other hand, the transformation of **12** to α-anomer **13** failed.

Finally, the protected 1-naphthylgalactal **10** was subjected to subsequent stereoselective transformation. As we assumed, hydroboration of derivative **10** with the BH_3.THF complex and deprotection with a mixture of 20% aqueous acetic acid and THF provided free aryl-β-C-glycoside **14** in 69% overall yield (Scheme 4).

Additionally, we also tested the Werz protocol,[22] which was supposed to lead to β-aryl-C-galactoside **14** using DIBAL-H and $LiAlH_4$ for the opening of the epoxide ring. In both of these cases, the expected derivative **14** was obtained after deprotection. The free aryl-β-C-glycoside **14** was also obtained by the hydroboration of the free cross-coupling product **15**. As before, we decided to transform the coupled product **10** to the opposite naphthyl-α-C-glycoside. Although the product of the DMDO epoxidation of derivative **10** was confirmed, the subsequent opening of the formed epoxide ring with lithiumtriethylborohydride failed and derivative **16** with an opened galactose ring was isolated under the standard deprotection conditions. Even though various attempts to modify reaction conditions, workup procedures, and hydride sources were made, the desired α-C-galactoside with a closed sugar ring was not obtained (Scheme 4).

CONCLUSIONS

In conclusion, we have introduced ethoxyethyl and methoxypropyl acetals as effective protecting groups for a straightforward and stereoselective synthesis of α- or β-naphthyl-C-glycosides. We have established that uniformly EE- and MOP-protected D-glycals are compatible with harsh basic conditions and are universal protecting groups for both D-glucal and D-galactal. Their stability was also proven in the subsequent Pd-catalyzed cross-coupling reactions and the ensuing oxidative−reductive transformation. We have also found that the complete removal of all EE or MOP groups is high yielding and effective under mild acidic conditions. We assume that this work can be extended to the synthesis of a wide range of aryl-C-glycosides.

EXPERIMENTAL SECTION

General Experiment. All reactions using anhydrous conditions were performed using flame-dried apparatus under an atmosphere of argon. Standard inert techniques were used in handling all air and moisture sensitive reagents. Anhydrous THF and CH_2Cl_2 were obtained by distillation using CaH_2 as a drying agent. Other anhydrous solvents were used directly as received from commercial suppliers. All other solvents were used as supplied (Analytical or high-performance liquid chromatography grade), without prior purification. Reagents

DOI: 10.1021/acsomega.8b00901
ACS Omega 2018, 3, 7875−7887

were purchased from various commercial suppliers and used as supplied, unless otherwise indicated. Distilled water was used for chemical reactions. "Hexane" refers to the fraction of hexane boiling in the range 68−72 °C. Brine refers to a saturated solution of sodium chloride. Anhydrous magnesium sulfate ($MgSO_4$) was used as a drying agent after reaction workup, as indicated.

Solution of DMDO in acetone was obtained according to a literature procedure,[23] stored at −20 °C under argon atmosphere, and used in 2 days after distillation at the latest. Column chromatography was carried out using Material Harvest silica gel (pore size 60 Å, mesh 230−400 (40−63 μm)). Thin-layer chromatography (TLC) was carried out using Merck TLC Silica gel 60 F_{254} aluminum plates. Visualization of the TLC plates was achieved using a UV lamp Spektroline-ENF-240/F (Spectronics Corporation Westbury) (λ_{max} = 254 nm) and/or by spraying with cerium(IV) sulfate solution (1% in 10% H_2SO_4). Mobile phases are reported in relative composition (e.g., hexane/EtOAc 1:1 *v*/*v*). All ^{1}H and ^{13}C NMR spectra were recorded using a Bruker Avance III 400 (401.0 MHz for ^{1}H; 100.8 MHz for ^{13}C) or Bruker Avance III 500 (500.0 MHz for ^{1}H; 125.7 MHz for ^{13}C) spectrometers. ^{1}H and ^{13}C resonances were fully assigned using H,H-COSY, H,C-HSQC, and H,C-HMBC techniques. All chemical shifts are quoted on the δ scale in ppm and referenced using residual ^{1}H solvent signal in ^{1}H NMR spectra ($\delta(CHCl_3)$ = 7.26 ppm, $\delta(CD_2HOD)$ = 3.31 ppm, $\delta(CD_2HCOCD_3)$ = 2.05 ppm, and $\delta(CD_2HSOCD_3)$ = 2.50 ppm) and ^{13}C solvent signal in ^{13}C NMR spectra ($\delta(CDCl_3)$ = 77.0 ppm, $\delta(CD_3OD)$ = 49.0 ppm, $\delta(CD_3COCD_3)$ = 29.8 ppm, and $\delta((CD_3)_2SO)$ = 29.7 ppm). Coupling constant (*J*) is reported in Hz with the following splitting abbreviations: s = singlet, d = doublet, t = triplet, q = quartet, and m = multiplet. IR spectra were recorded on a Thermo Scientific Nicolet 6700 spectrometer. Absorption maxima (υ_{max}) are reported in wavenumbers (cm^{-1}).

High-resolution mass spectra were measured on a LTQ Orbitrap XL (Thermo Fisher Scientific) spectrometer using electrospray ionization technique. Nominal and exact *m*/*z* values are reported in Daltons.

Optical rotations were measured on an AUTOPOL IV (Rudolph Research Analytical,) polarimeter at temperature 20 °C and 589 nm sodium line with a path length *l* of 1.0 dm. Concentration *c* is given in g/100 mL. Specific rotation values are reported as a unitless number with implied units of (deg mL)/(g dm). Melting points (mp) were recorded on a Kofler hot-stage microscope and are reported uncorrected in degrees Celsius (°C).

1,5-Anhydro-3,4,6-tri-O-(2-methoxypropan-2-yl)-D-arabino-hex-1-enitol (**2a**). To a stirred solution of D-glucal **1a** (5 g, 34.21 mmol, 1 equiv) in anhydrous CH_2Cl_2 (50 mL) were added 2-methoxypropene (19.66 mL, 205.28 mmol, 6 equiv) and Pyr·TsOH (860 mg, 3.42 mmol, 0.10 equiv) at 0 °C under an argon atmosphere. The resulting heterogeneous reaction mixture was stirred for 3 h at the same temperature, during which it turned homogeneous. Et_3N (5 mL) was added, and the resulting mixture was stirred for another 20 min at room temperature (RT) and then diluted with CH_2Cl_2 (300 mL). The organic layer was washed with H_2O (3 × 200 mL), dried over $MgSO_4$, filtered, and concentrated in vacuo. The residue was purified by column chromatography on silica gel (hexane/EtOAc 15:1, 1% Et_3N) to give MOP-glucal **2a** (10.46 g, 84%) as a colorless oil: R_f = 0.47 (hexane/EtOAc 4:1); $[\alpha]_D^{20}$ −28.6 (*c* 0.3, $CHCl_3$); ^{1}H NMR (401.0 MHz, DMSO-d_6): 1.24, 1.245, 1.25, 1.29, 1.30 (5 × s, 18H, $(CH_3)_2C$); 3.09, 3.15 (2 × s, 9H, CH_3O); 3.47 (dd, 1H, $J_{6b,6a}$ = 10.7, $J_{6b,5}$ = 4.3, H-6b); 3.67 (dd, 1H, $J_{6a,6b}$ = 10.7, $J_{6a,5}$ = 8.2, H-6a); 3.80 (dt, 1H, $J_{3,2}$ = 5.3, $J_{3,4}$ = $J_{3,5}$ = 2.0, H-3); 3.94 (td, 1H, $J_{4,3}$ = $J_{4,5}$ = 2.0, $J_{4,2}$ = 1.6, H-4); 4.14 (ddt, 1H, $J_{5,6a}$ = 8.2, $J_{5,6b}$ = 4.3, $J_{5,4}$ = 2.0, H-5); 4.75 (ddd, 1H, $J_{2,1}$ = 6.4, $J_{2,3}$ = 5.3, $J_{2,4}$ = 1.6, H-2); 6.38 (d, 1H, $J_{1,2}$ = 6.4, H-1); ^{13}C NMR (100.8 MHz, DMSO-d_6): 24.3, 24.5, 25.0, 25.05, 25.08, 25.2 ($(\mathbf{C}H_3)_2C$); 47.8, 48.7, 49.0 (CH_3O); 58.9 (CH_2-6); 61.6 (CH-3); 67.2 (CH-4); 76.9 (CH-5); 99.5, 100.3 ($(CH_3)_2\mathbf{C}$); 100.4 (CH-2); 101.0 ($(CH_3)_2\mathbf{C}$); 143.5 (CH-1); IR ($CHCl_3$): ν_{max} 3069, 2996, 2945, 2832, 1647, 1464, 1382, 1373, 1250, 1184, 1151, 1097, 1070, 1044, 1027, 1014, 909, 864, 839, 572, 528, 505 cm^{-1}; HRMS (ESI) *m*/*z* $[M + Na]^+$ calcd for $C_{18}H_{34}O_7Na$ 385.2197, found 385.2198.

1,5-Anhydro-3,4,6-tri-O-(ethoxyethyl)-D-arabino-hex-1-enitol (**2b**). To a stirred solution of D-glucal **1a** (2 g, 13.69 mmol, 1 equiv) in anhydrous CH_2Cl_2 (30 mL) were added ethyl vinyl ether (7.86 mL, 82.11 mmol, 6 equiv) and Pyr·TsOH (344 mg, 1.37 mmol, 0.10 equiv) at 0 °C under an argon atmosphere. The resulting heterogeneous reaction mixture was stirred for 20 h at room temperature, during which it turned homogeneous. The resulting mixture was diluted with CH_2Cl_2 (250 mL). The organic layer was washed with H_2O (3 × 200 mL), dried over $MgSO_4$, filtered, and concentrated in vacuo. The residue was purified by column chromatography on silica gel (hexane/EtOAc 6:1 to 3:1) to give EE-glucal **2b** (4.7 g, 95%) as a colorless oil: R_f = 0.53 (hexane/EtOAc 3:1); ^{1}H NMR (401.0 MHz, $CDCl_3$): 1.16−1.21 (m, 9H, $C\mathbf{H}_3CH_2O$); 1.28−1.34 (m, 9H, $C\mathbf{H}_3CH$); 3.43−3.94 (m, 8H, H-4,6, $CH_3C\mathbf{H}_2O$); 4.03−4.20 (m, 2H, H-3,5); 4.69−5.00 (m, 4H, H-2, $CH_3C\mathbf{H}$); 6.35−6.43 (m, 1H, H-1); ^{13}C NMR (100.8 MHz, $CDCl_3$): 15.19, 15.22, 15.24, 15.27, 15.28, 15.30, 15.31 ($\mathbf{C}H_3CH_2O$); 19.73, 19.76, 19.77, 19.78, 19.80, 19.83, 20.30, 20.31, 20.33, 20.34, 20.42, 20.44, 20.51, 20.55, 20.57, 20.58, 20.60 ($\mathbf{C}H_3CH$); 59.84, 59.87, 59.88, 60.41, 60.43, 60.57, 60.81, 60.84, 60.86, 60.97, 61.03, 61.06, 61.18, 61.26, 61.27, 61.29, 61.35, 61.40, 61.54, 61.79 (CH_3CH_2O); 62.68, 63.14, 63.16, 63.22, 63.31, 63.86, 63.89 (CH_2-6); 67.47, 67.80, 69.18, 69.32, 70.26, 70.63, 70.73, 70.85, 71.12, 71.14, 71.18, 71.37, 71.38, 72.22, 72.49 (CH-3,4); 76.38, 76.41, 76.47, 76.81, 76.84, 76.98 (CH-5); 97.31, 97.32, 97.50, 98.63, 98.83, 99.05, 99.12, 99.43, 99.45, 99.56, 99.58, 99.63, 99.68, 99.73, 99.77, 99.82, 99.85, 99.93, 99.95, 100.05, 100.11, 100.17, 100.28, 100.35, 100.52, 100.79, 100.86, 100.93 (CH-2, CH_3CH); 144.00, 144.09, 144.24 (CH-1); IR ($CHCl_3$): ν_{max} 3070, 2981, 2933, 2898, 2886, 1948, 1445, 1383, 1341, 1239, 1131, 1096, 1084, 1055, 971, 949, 930, 877, 844, 819 cm^{-1}; HRMS (ESI) *m*/*z* $[M + Na]^+$ calcd for $C_{18}H_{34}O_7Na$ 385.2197, found 385.2198.

1,5-Anhydro-2-deoxy-3,4-O-isopropylidene-6-O-(2-methoxypropan-2-yl)-D-lyxo-hex-1-enitol (**3a**). To a stirred solution of D-galactal **1b** (2 g, 13.69 mmol, 1 equiv) in anhydrous DMF (15 mL) were added 2-methoxypropene (3.93 mL, 41.06 mmol, 3 equiv) and Pyr·TsOH (172 mg, 684 μmol, 0.05 equiv) at 0 °C under an argon atmosphere. The resulting mixture was stirred for 1 h at the same temperature, and then another portion of 2-methoxypropene (2.62 mL, 27.37 mmol, 2 equiv) was added. The reaction mixture was stirred for another 2 h at 0 °C. Et_3N (3 mL) was added, and the resulting mixture was diluted with EtOAc (200 mL) and then washed with H_2O (300 mL). The aqueous phase was washed with EtOAc (3 × 150 mL), and the combined organic

DOI: 10.1021/acsomega.8b00901
ACS Omega 2018, 3, 7875−7887

phases were dried over $MgSO_4$, filtered, and concentrated in vacuo. The residue was purified by column chromatography on silica gel (hexane/EtOAc 15:1 to 10:1, 1% Et_3N) to give product **3a** (2.78 g, 79%) as a pale yellow oil: R_f = 0.65 (hexane/EtOAc 3:1); $[\alpha]_D^{20}$ −3.2 (*c* 0.4, $CHCl_3$); ^{1}H NMR (401.0 MHz, DMSO-d_6): 1.26 (q, 3H, ^4J = 0.6, $(CH_3)_2C$); 1.27 (s, 6H, $(CH_3)_2C$); 1.34 (q, 3H, ^4J = 0.6, $(CH_3)_2C$); 3.11 (s, 3H, CH_3O); 3.50−3.62 (m, 2H, H-6); 3.99 (ddd, 1H, $J_{5,6}$ = 7.0, 5.7, $J_{5,4}$ = 1.5, H-5); 4.29 (dtd, 1H, $J_{4,3}$ = 6.1, $J_{4,2}$ = $J_{4,5}$ = 1.5, $J_{4,1}$ = 0.4, H-4); 4.63 (dd, 1H, $J_{3,4}$ = 6.1, $J_{3,2}$ = 2.9, H-3); 4.71 (ddd, 1H, $J_{2,1}$ = 6.2, $J_{2,3}$ = 2.9, $J_{2,4}$ = 1.5, H-2); 6.41 (dd, 1H, $J_{1,2}$ = 6.2, $J_{1,4}$ = 0.4, H-1); ^{13}C NMR (100.8 MHz, DMSO-d_6): 24.39, 24.40, 26.9, 28.3 ($(CH_3)_2C$); 60.7 (CH_2-6); 68.1 (CH-3); 72.3 (CH-4); 73.7 (CH-5); 99.8 ($(CH_3)_2C$); 102.8 (CH-2); 109.6 ($(CH_3)_2C$); 144.5 (CH-1); IR ($CHCl_3$): ν_{max} 3442, 3065, 2989, 2940, 2892, 2831, 1727, 1648, 1459, 1437, 1380, 1371, 1260, 1239, 1214, 1185, 1164, 1153, 1126, 1088, 1068, 1054, 1032, 993, 868, 843, 755, 720, 676, 661, 597, 560, 536, 500 cm^{-1}; HRMS (ESI) *m*/*z* $[M + Na]^+$ calcd for $C_{13}H_{22}O_5Na$ 281.1359, found 281.1360.

*1,5-Anhydro-2-deoxy-3,4,6-tri-O-(ethoxyethyl)-D-lyxo-hex-1-enitol (**3b**).* To a stirred solution of D-galactal **1a** (5 g, 34.21 mmol, 1 equiv) in anhydrous CH_2Cl_2 (40 mL) were added ethyl vinyl ether (26.21 mL, 273.71 mmol, 8 equiv) and Pyr·TsOH (860 mg, 3.42 mmol, 0.10 equiv) at 0 °C under an argon atmosphere. The resulting heterogeneous reaction mixture was stirred for 20 h at room temperature, during which it turned homogeneous. The resulting mixture was diluted with CH_2Cl_2 (200 mL). The organic layer was washed with H_2O (3 × 150 mL), dried over $MgSO_4$, filtered, and concentrated in vacuo. The residue was purified by column chromatography on silica gel (hexane/EtOAc 10:1 to 4:1) to give EE-galactal **3b** (10.75 g, 87%) as a colorless oil: R_f = 0.41 (hexane/EtOAc 4:1); ^{1}H NMR (500.0 MHz, $CDCl_3$): 1.16−1.21 (m, 9H, CH_3CH_2O); 1.29−1.36 (m, 9H, CH_3CH); 3.43−4.00 (m, 8H, H-6, CH_3CH_2O); 4.00−4.38 (m, 3H, H-3,4,5); 4.68−4.87 (m, 3H, CH_3CH); 4.88−5.06 (m, 1H, H-2); 6.29−6.37 (m, 1H, H-1); ^{13}C NMR (125.7 MHz, $CDCl_3$): 15.22, 15.23, 15.24, 15.25, 15.27, 15.28, 15.31, 15.32, 15.34, 15.36, 15.39, 15.41 (CH_3CH_2O); 19.81, 19.82, 19.84, 19.88, 19.90, 19.94, 19.99, 20.00, 20.01, 20.06, 20.08, 20.13, 20.15, 20.17, 20.24, 20.29, 20.37, 20.39, 20.41, 20.42 (CH_3CH); 59.48, 59.49, 59.68, 59.80, 59.84, 60.01, 60.17, 60.57, 60.67, 60.69, 61.03, 61.06, 61.12, 61.19, 61.21, 61.33, 61.34 (CH_3CH_2O); 61.62, 61.74, 61.82, 62.00, 62.58, 62.63, 63.66, 64.18 (CH_2-6); 66.71, 68.04, 68.34, 68.52, 69.56, 69.67, 69.93 (CH-3,4); 75.61, 75.77, 75.82, 76.06, 76.34, 76.40, 76.57, 76.70 (CH-5); 98.13, 98.15, 99.59, 99.63, 99.73, 99.70, 99.73, 99.76, 99.80, 99.91, 99.93, 99.97, 100.01, 100.07, 100.11, 100.16, 100.21, 100.31, 100.87, 100.92, 100.97, 100.98 (CH-2, CH_3CH); 143.64, 143.80, 143.81, 143.87, 144.04, 144.05 (CH-1); IR ($CHCl_3$): ν_{max} 3069, 2980, 2933, 2898, 1644, 1484, 1454, 1445, 1394, 1383, 1340, 1298, 1254, 1235, 1134, 1094, 1082, 1055, 1030, 950, 931, 880, 844, 819, 698; HRMS (ESI) *m*/*z* $[M + Na]^+$ calcd for $C_{18}H_{34}O_7Na$ 385.2197, found 385.2197.

*rac-(E)-6-Hydroxy-1-((2-methoxypropan-2-yl)oxy)-7,7-dimethyloct-2-en-4-one (**4**).* To a stirred solution of compound **3a** (0.5 g, 1.94 mmol, 1 equiv) in anhydrous THF (10 mL) was added *t*-BuLi (3.99 mL, 6.77 mmol, 3.5 equiv, 1.7 M in pentane) dropwise over 15 min at −78 °C under an argon atmosphere. The reaction mixture was stirred for 10 min at −78 °C and then for 2 h at 0 °C. After warming to RT, Et_3N (2 mL) was added and the resulting mixture was diluted with EtOAc (100 mL). The organic phase was washed with sat. aq $NaHCO_3$ (200 mL) and H_2O (2 × 200 mL), dried over $MgSO_4$, filtered, and concentrated in vacuo. The residue was purified by column chromatography on silica gel (hexane/EtOAc 8:1 to 5:1, 1% Et_3N) to give enone **4** (854 mg, 81%) as racemic mixture of enantiomers: R_f = 0.44 (hexane/EtOAc 3:1); $[\alpha]_D^{20}$ 9.4 (*c* 0.3, $CHCl_3$); ^{1}H NMR (500.0 MHz, DMSO-d_6): 0.83 (s, 9H, $((CH_3)_3)C$); 1.29 (s, 6H, $(CH_3)_2C$); 2.52 (dd, 1H, ^2J = 15.3, ^3J = 2.7, CH_aH_bCHOH); 2.60 (dd, 1H, ^2J = 15.3, ^3J = 9.5, CH_aH_bCHOH); 3.08 (s, 3H, CH_3O); 3.60 (ddd, 1H, ^3J = 9.5, 5.9, 2.8, CH_2CHOH); 4.09 (dd, 2H, ^3J = 4.3, ^4J = 2.1, $CH_2-CH=CH$); 4.54 (d, 1H, ^3J = 5.9, CH_2CHOH); 6.32 (dt, 1H, ^3J = 16.0, ^4J = 2.1, $CH_2-CH=CH$); 6.84 (dt, 1H, ^3J = 16.0, 4.3, $CH_2-CH=CH$); ^{13}C NMR (125.7 MHz, DMSO-d_6): 24.4 ($(CH_3)_3C$); 26.0 ($(CH_3)_2C$); 35.0 ($(CH_3)_3C$); 42.9 (CH_2CHOH); 48.2 (CH_3O); 59.7 ($CH_2-CH=CH$); 74.5 (CH_2CHOH); 100.1 ($(CH_3)_2C$); 129.2 ($CH_2-CH=CH$); 143.7 ($CH_2-CH=CH$); 199.8 (CO); IR ($CHCl_3$): ν_{max} 3054, 2989, 2956, 2909, 2879, 2873, 1690, 1665, 1634, 1480, 1466, 1381, 1368, 1292, 1192, 1065, 969 cm^{-1}; HRMS (ESI) *m*/*z* $[M + Na]^+$ calcd for $C_{14}H_{26}O_4Na$ 281.1723, found 281.1723.

*(1,5-Anhydro-2-deoxy-3,4,6-tri-O-(2-methoxypropan-2-yl)-D-arabino-hex-1-enitolyl)boronic Acid Pinacol Ester (**5a**).* To a stirred solution of MOP-glucal **2a** (1 g, 2.76 mmol, 1 equiv) in anhydrous THF (20 mL) was added *t*-BuLi (5.68 mL, 9.66 mmol, 3.5 equiv, 1.7 M in pentane) dropwise over 10 min at −78 °C under argon atmosphere. The reaction mixture was stirred for 10 min at −78 °C and then for 1 h at 0 °C. Subsequently, the resulting mixture was again cooled to −78 °C and iPrOBpin (2.25 mL, 11.04 mmol, 4 equiv) was added dropwise over 10 min. The mixture was allowed to warm gradually to RT over 3 h and stirred overnight. The reaction was quenched by the addition of H_2O (5 mL) and extracted between EtOAc (200 mL) and H_2O (200 mL). The organic layer was washed with H_2O (2 × 200 mL), dried over $MgSO_4$, filtered, and concentrated in vacuo to give crude product **5a** (1.27 g, 94%) as a pale yellow oil, which was used without further purification for the next step: $[\alpha]_D^{20}$ −17.9 (*c* 0.3, $CHCl_3$); IR ($CHCl_3$): ν_{max} 2995, 2985, 2957, 2833, 1644, 1468, 1447, 1402, 1391, 1381, 1373, 1330, 1235, 1144, 1144, 1099, 1099, 1079, 1049, 1027, 966, 866 cm^{-1}; HRMS (ESI) *m*/*z* $[M + Na]^+$ calcd for $C_{24}H_{45}O_9BNa$ 511.3049, found 511.3051.

*(1,5-Anhydro-2-deoxy-3,4,6-tri-O-(ethoxyethyl)-D-arabino-hex-1-enitolyl)boronic Acid Pinacol Ester (**5b**).* To a stirred solution of EE-glucal **2b** (3 g, 8.28 mmol, 1 equiv) in anhydrous THF (20 mL) was added *t*-BuLi (17.04 mL, 28.97 mmol, 3.5 equiv, 1.7 M in pentane) dropwise over 10 min at −78 °C under argon atmosphere. The reaction mixture was stirred for 10 min at −78 °C and then for 1 h at 0 °C. Subsequently, the resulting mixture was again cooled to −78 °C and iPrOBpin (6.75 mL, 33.11 mmol, 4 equiv) was added dropwise over 5 min. The mixture was allowed to warm gradually to RT over 3 h and stirred overnight. The reaction was quenched by the addition of H_2O (5 mL) and extracted between EtOAc (150 mL) and H_2O (100 mL). The organic layer was washed with H_2O (2 × 100 mL), dried over $MgSO_4$, filtered, and concentrated in vacuo to give crude product **5b** (3.26 g, 81%) as a pale yellow oil, which was used without further purification for the next step: IR ($CHCl_3$): ν_{max} 3614, 3574, 2982, 2935, 1732, 1642, 1480, 1405, 1396, 1382, 1374,

DOI: 10.1021/acsomega.8b00901
ACS Omega 2018, 3, 7875−7887

1340, 1141, 1135, 1095, 1084, 1055, 1055, 962, 861 cm^{-1}; HRMS (ESI) m/z $[M + Na]^+$ calcd for $C_{24}H_{45}O_9BNa$ 511.3049, found 511.3055.

*1,5-Anhydro-2-deoxy-3,4,6-tri-O-(2-methoxypropan-2-yl)-1-(tri-n-butylstannyl)-D-arabino-hex-1-enitol (**6a**).* To a stirred solution of MOP-glucal **2a** (3 g, 8.28 mmol, 1 equiv) in anhydrous THF (20 mL) was added *t*-BuLi (17.04 mL, 28.97 mmol, 3.5 equiv, 1.7 M in pentane) dropwise over 15 min at −78 °C under argon atmosphere. The reaction mixture was stirred for 10 min at −78 °C and then for 1 h at 0 °C. Subsequently, the resulting mixture was again cooled to −78 °C and Bu_3SnCl (8.98 mL, 31.11 mmol, 4 equiv) was added dropwise over 10 min. The mixture was allowed to warm gradually to RT over 3 h and stirred for 2 h. Et_3N (5 mL) was added, and the resulting mixture was stirred for another 20 min at RT and then diluted with EtOAc (250 mL). The organic layer was washed with $NaHCO_3$ (250 mL), H_2O (250 mL), and brine (250 mL), dried over $MgSO_4$, and filtered and concentrated in vacuo. The residue was purified by column chromatography on silica gel (hexane/EtOAc 20:1, 1% Et_3N) to give product **6a** (5.02, 93%) as a light-yellow oil: R_f = 0.69 (hexane/EtOAc 3:1); $[\alpha]_D^{20}$ −44.6 (c 0.3, $CHCl_3$); ^1H NMR (401.0 MHz, DMSO-d_6): 0.86 (t, 9H, J_{vic} = 7.3, $CH_3CH_2CH_2CH_2Sn$); 0.85−0.94 (m, 6H, $CH_3CH_2CH_2CH_2Sn$); 1.21−1.34 (m, 24H, $(CH_3)_2C$, $CH_3CH_2CH_2CH_2Sn$); 1.40−1.62 (m, 6H, $CH_3CH_2CH_2CH_2Sn$); 3.08, 3.14 (2 × s, 9H, CH_3O); 3.52 (dd, 1H, $J_{6b,6a}$ = 10.3, $J_{6b,5}$ = 5.1, H-6b); 3.59 (dd, 1H, $J_{6a,6b}$ = 10.3, $J_{6a,5}$ = 7.5, H-6a); 3.72 (dt, 1H, $J_{3,2}$ = 5.1, $J_{3,4}$ = $J_{3,5}$ = 2.1, H-3); 3.91 (td, 1H, $J_{4,3}$ = $J_{4,5}$ = 2.1, $J_{4,2}$ = 1.6, H-4); 4.07 (ddt, 1H, $J_{5,6a}$ = 7.5, $J_{5,6b}$ = 5.2, $J_{5,3}$ = $J_{5,4}$ = 2.1, H-5); 4.79 (dd, 1H, $J_{2,3}$ = 5.1, $J_{2,4}$ = 1.6, H-2); ^{13}C NMR (100.8 MHz, DMSO-d_6): 9.4 ($CH_3CH_2CH_2CH_2Sn$); 13.8 ($CH_3CH_2CH_2CH_2Sn$); 24.6, 24.4, 25.0, 25.1, 25.1, 25.3 ($(CH_3)_2C$); 26.7 ($CH_3CH_2CH_2CH_2Sn$); 28.6 ($CH_3CH_2CH_2CH_2Sn$); 47.8, 48.5, 48.8 (CH_3O); 59.2 (CH_2-6); 61.9 (CH-3); 67.6 (CH-4); 76.8 (CH-5); 99.4; 100.2, 100.8 ($(CH_3)_2C$); 111.5 (CH-2); 162.3 (C-1); IR ($CHCl_3$): ν_{max} 2994, 2958, 2932, 2827, 1465, 1433, 1381, 1373, 1151, 1104, 1072, 1011, 891, 870, 857, 843, 824, 515 cm^{-1}; HRMS (ESI) m/z $[M + Na]^+$ calcd for $C_{30}H_{60}O_7NaSn$ 675.3253, found 675.3260.

*1,5-Anhydro-2-deoxy-3,4,6-tri-O-(ethoxyethyl)-1-(tri-n-butylstannyl)-D-arabino-hex-1-enitol (**6b**).* To a stirred solution of EE-glucal **2b** (2 g, 5.52 mmol, 1 equiv) in anhydrous THF (15 mL) was added *t*-BuLi (11.36 mL, 19.31 mmol, 3.5 equiv, 1.7 M in pentane) dropwise over 10 min at −78 °C under argon atmosphere. The reaction mixture was stirred for 20 min at −78 °C and then for 3 h at 0 °C. Subsequently, the resulting mixture was again cooled to −78 °C and Bu_3SnCl (5.99 mL, 22.07 mmol, 4 equiv) was added dropwise over 10 min. The mixture was allowed to warm gradually to RT over 3 h and stirred for 1 h. Et_3N (5 mL) was added, and the resulting mixture was stirred for another 30 min at RT and then diluted with EtOAc (100 mL). The organic layer was washed with sat. aq $NaHCO_3$ (50 mL), H_2O (100 mL), and brine (250 mL), dried over $MgSO_4$, filtered, and concentrated in vacuo. The residue was purified by column chromatography on silica gel (hexane/EtOAc 20:1, 1% Et_3N) to give product **6b** (2.89, 81%) as a yellow oil: R_f = 0.65 (hexane/EtOAc 4:1); ^1H NMR (401.0 MHz, $CDCl_3$): 0.83−0.96 (m, 15H, $CH_3CH_2CH_2CH_2Sn$); 1.16−1.21 (m, 9H, CH_3CH_2O); 1.26−1.35 (m, 15H, CH_3CH, $CH_3CH_2CH_2CH_2Sn$); 1.42−1.61 (m, 6H, $CH_3CH_2CH_2CH_2Sn$); 3.41−4.00 (m, 10H, H-4,5,6, CH_3CH); 4.03−4.24 (m, 1H, H-3); 4.65−5.05 (m, 1H, H-2); ^{13}C NMR (100.8 MHz, $CDCl_3$): 9.57, 9.60, 9.62 ($CH_3CH_2CH_2CH_2Sn$); 13.65, 13.66 ($CH_3CH_2CH_2CH_2Sn$); 15.28, 15.30, 15.31, 15.35, 15.38 (CH_3CH_2O); 19.83, 19.85, 19.90, 19.93, 19.96, 20.00, 20.40, 20.44, 20.57, 20.59, 20.60, 20.71, 20.75, 20.80, 20.82, 20.84, 20.97, 21.01 (CH_3CH); 27.19, 27.20 ($CH_3CH_2CH_2CH_2Sn$); 28.88 ($CH_3CH_2CH_2CH_2Sn$); 59.67, 59.73, 59.76, 59.82, 60.37, 60.40, 60.44, 60.47, 60.63, 60.64, 60.65, 60.68, 60.80, 60.82, 60.99, 61.09, 61.41, 61.49, 61.59, 61.62, 61.82, 61.93, 62.34 (CH_3CH_2O); 63.35, 63.46, 64.03, 64.21, 64.26, 64.85, 65.03 (CH_2-6); 69.26, 70.05, 71.15, 71.38, 71.60, 71.72, 71.74, 71.93, 72.00, 72.10, 72.24, 72.40, 73.25, 74.12, 75.27, 75.66, 76.56, 76.75, 76.92, 77.05, 77.20, 77.25, 77.29, 77.36 (CH-3,4,5); 97.29, 97.31, 97.48, 97.51, 99.59, 99.83, 99.86, 99.91, 99.92, 99.96, 99.99, 100.01, 100.23, 100.27, 100.30, 100.33, 100.41, 100.55, 100.58 (CH_3CH); 109.87, 110.18, 110.26, 110.32, 111.83, 111.95, 112.14, 112.36 (CH-2); 163.90, 164.07, 164.16, 164.22, 164.25, 164.27, 164.36 (C-1); IR ($CHCl_3$): ν_{max} 2979, 2931, 2897, 2852, 1606, 1464, 1457, 1379, 1246, 1131, 1097, 1097, 1055, 1055, 1030 cm^{-1}; HRMS (ESI) m/z $[M + Na]^+$ calcd for $C_{30}H_{60}O_7NaSn$ 675.3253, found 675.3255.

*(1,5-Anhydro-2-deoxy-3,4,6-tri-O-(ethoxyethyl)-D-lyxo-hex-1-enitolyl)boronic Acid Pinacol Ester (**7**).* To a stirred solution of EE-galactal **3b** (2 g, 5.52 mmol, 1 equiv) in anhydrous THF (15 mL) was added *t*-BuLi (11.36 mL, 19.31 mmol, 3.5 equiv, 1.7 M in pentane) dropwise over 5 min at −78 °C under argon atmosphere. The reaction mixture was stirred for 5 min at −78 °C and then for 30 h at 0 °C. Subsequently, the resulting mixture was again cooled to −78 °C and iPrOBpin (4.50 mL, 22.07 mmol, 4 equiv) was added dropwise over 5 min. The mixture was allowed to warm gradually to RT over 3 h and stirred overnight. The reaction was quenched by the addition of H_2O (5 mL) and extracted between EtOAc (100 mL) and H_2O (100 mL). The organic layer was washed with H_2O (2 × 200 mL), dried over $MgSO_4$, filtered, and concentrated in vacuo to give crude product **7** (2.42 g, 90%) as a red-brown oil, which was used without further purification for the next step: IR ($CHCl_3$): ν_{max} 2981, 2936, 1477, 1471, 1402, 1391, 1391, 1382, 1374, 1296, 1167, 1138, 1112, 1094, 1083, 1008, 866, 851, 851 cm^{-1}; HRMS (ESI) m/z $[M + Na]^+$ calcd for $C_{24}H_{45}O_9BNa$ 511.3049, found 511.3051.

*1,5-Anhydro-2-deoxy-3,4,6-tri-O-(ethoxyethyl)-1-(tri-n-butylstannyl)-D-lyxo-hex-1-enitol (**8**).* To a stirred solution of EE-galactal **3b** (2.5 g, 6.90 mmol, 1 equiv) in anhydrous THF (15 mL) was added *t*-BuLi (14.20 mL, 24.14 mmol, 3.5 equiv, 1.7 M in pentane) dropwise over 5 min at −78 °C under argon atmosphere. The reaction mixture was stirred for 5 min at −78 °C and then for 30 min at 0 °C. Subsequently, the resulting mixture was again cooled to −78 °C and Bu_3SnCl (7.48 mL, 27.59 mmol, 4 equiv) was added dropwise over 10 min. The mixture was allowed to warm gradually to RT over 3 h and stirred for 2 h. The resulting mixture was diluted with EtOAc (150 mL) and washed with sat. aq $NaHCO_3$ (100 mL), H_2O (100 mL), and brine (100 mL), dried over $MgSO_4$, filtered, and concentrated in vacuo. The residue was purified by column chromatography on silica gel (hexane/EtOAc 15:1, 1% Et_3N) to give product **8** (3.10, 69%) as a red-brown oil: R_f = 0.80 (hexane/EtOAc 3:1); ^1H NMR (401.0 MHz, acetone-d_6): 0.90 (t, 9H, J_{vic} = 7.3, $CH_3CH_2CH_2CH_2Sn$); 0.94−1.01 (m,

DOI: 10.1021/acsomega.8b00901
ACS Omega 2018, 3, 7875−7887

6H, $CH_3CH_2CH_2CH_2Sn$); 1.10−1.18 (m, 9H, CH_3CH_2O); 1.22−1.29 (m, 9H, CH_3CH); 1.30−1.40 (m, 6H, $CH_3CH_2CH_2CH_2Sn$); 1.47−1.69 (m, 6H, $CH_3CH_2CH_2CH_2Sn$); 3.40−3.91 (m, 8H, H-6, CH_3CH_2O); 3.94−4.38 (m, 3H, H-3,4,5); 4.65−5.13 (m, 4H, H-2, CH_3CH); ^{13}C NMR (100.8 MHz, acetone-d_6): 10.10, 10.12, 10.13, 10.14 ($CH_3CH_2CH_2CH_2Sn$); 13.94, 13.96, 13.97 ($CH_3CH_2CH_2CH_2Sn$); 15.71, 15.73, 15.75, 15.78, 15.82 (CH_3CH_2O); 20.29, 20.30, 20.45, 20.50, 20.53, 20.61, 20.66, 20.72, 20.76, 20.79, 20.83, 20.87, 20.93, 21.08, 21.09 (CH_3CH); 27.79, 27.80, 27.82, 27.84 ($CH_3CH_2CH_2CH_2Sn$); 29.60, 29.61 ($CH_3CH_2CH_2CH_2Sn$); 60.19, 60.24, 60.62, 60.75, 60.78, 60.93, 60.98, 61.11, 61.21, 61.22, 61.26, 61.31, 61.35, 61.39, 62.04, 62.08, 62.14 (CH_3CH_2O); 63.68, 64.29, 64.79, 64.81, 65.29, 65.55, 65.73 (CH_2-6); 69.93, 69.98, 70.05, 70.98, 71.22, 71.40, 76.82, 76.94, 77.12, 77.28, 77.37, 77.75, 77.81 (CH-3,4,5); 99.34, 99.47, 100.18, 100.25, 100.27, 100.35, 100.39, 100.45, 100.62, 100.72, 100.77, 100.79, 100.88, 100.92, 101.00 (CH_3CH); 112.10, 112.29, 112.33, 112.91, 112.95, 113.11 (CH-2); 163.08, 163.11, 163.28, 163.31, 163.32 (C-1); IR ($CHCl_3$): ν_{max} 3040, 2978, 2959, 2931, 2920, 2900, 2872, 1855, 1600, 1483, 1465, 1457, 1445, 1417, 1395, 1379, 1293, 1176, 1133, 1096, 1096, 1082, 1068, 1056, 843, 650, 599, 510 cm^{-1}; HRMS (ESI) m/z $[M + Na]^+$ calcd for $C_{30}H_{60}O_7NaSn$ 675.3253, found 675.3254.

General Procedure A: Suzuki Reactions of MOP- and EE-Protected Glycal Pinacol Boronates. To a stirred solution of pinacol boronate (2 equiv) in 1,2-dimethoxyethane (DME) were added 1-iodonaphthalene (1 equiv), $Pd(PPh_3)_2Cl_2$ (0,05 equiv), and 2 M Na_2CO_3 (DME/2 M Na_2CO_3 4:1) under argon atmosphere. The reaction mixture was heated to 80 °C and stirred for 3 h. After TLC analysis showed complete consumption of the starting material, the mixture was cooled to RT, diluted with EtOAc, extracted with H_2O and brine, dried over $MgSO_4$, filtered, and concentrated in vacuo. The residue was purified by column chromatography on silica gel (hexane/EtOAc 10:1 to 6:1).

General Procedure B: Stille Reactions of MOP- and EE-Protected Glycal Stannanes. To a solution of stannane (1 equiv) in anhydrous toluene were added 1-iodonaphthalene (1.5 equiv) and $Pd(PPh_3)_4$ (0.05 equiv) under an argon atmosphere. The reaction mixture was stirred under reflux at 125 °C for 5 h. After TLC analysis showed complete consumption of the starting material, the mixture was cooled to RT, filtered through a short plug of celite, and evaporated in vacuo. The residue was purified by column chromatography on silica gel (hexane/EtOAc 10:1 to 6:1).

*(1,5-Anhydro-2-deoxy-3,4,6-tri-O-(2-methoxypropan-2-yl)-D-arabino-hex-1-enitolyl)naphthalene (**9a**).* From **5a**: Following the general procedure A, boronate **5a** (1.5 g, 3.07 mmol, 2 equiv), 1-iodonaphthalene (0.22 mL, 1.53 mmol, 1 equiv), $Pd(PPh_3)_2Cl_2$ (54 mg, 77 μmol, 0.05 equiv) in DME (12 mL), and 2 M Na_2CO_3 (3 mL) were used. The reaction mixture was stirred at 80 °C for 3 h. After completion of the reaction, the residue was purified by column chromatography on silica gel (hexane/EtOAc 10:1 to 6:1) to give product **9a** (568 mg, 76%) as a pale yellow oil.

From **6a**: Following the general procedure B, stannane **6a** (220 mg, 338 μmol, 1 equiv), 1-iodonaphthalene (74 μL, 507 μmol, 1.5 equiv), and $Pd(PPh_3)_4$ (20 mg, 17 μmol, 0.05 equiv) in toluene (7 mL) were used. The reaction mixture was stirred at 125 °C for 5 h. After completion of the reaction, the residue was purified by column chromatography on silica gel (hexane/EtOAc 10:1 to 6:1) to give product **9a** (142 mg, 86%) as a pale yellow oil: R_f = 0.51 (hexane/EtOAc 3:1); $[\alpha]_D^{20}$ −27.6 (*c* 0.3, $CHCl_3$); ^1H NMR (401.0 MHz, DMSO-d_6): 1.26, 1.31, 1.32, 1.36, 1.42 (5 × s, 18H, $(CH_3)_2C$); 3.05, 3.20, 3.23 (3 × s, 3 × 3H, CH_3O); 3.63 (dd, 1H, $J_{6b,6a}$ = 10.9, $J_{6b,5}$ = 3.6, H-6b); 3.97 (dd, 1H, $J_{6a,6b}$ = 10.9, $J_{6a,5}$ = 8.5, H-6a); 4.07−4.13 (m, 2H, H-3,); 4.45 (ddt, 1H, $J_{5,6}$ = 8.5, 3.6, $J_{5,3}$ = $J_{5,4}$ = 1.9, H-5); 5.06 (dd, 1H, $J_{2,3}$ = 5.5, $J_{2,4}$ = 1.5, H-2); 7.45−7.57 (m, 4H, H-2,3,6,7-naphth); 7.87−7.97 (m, 2H, H-4,5-naphth); 8.31−8.40 (m, 1H, H-8-naphth); ^{13}C NMR (100.8 MHz, DMSO-d_6): 24.39, 24.50, 25.11, 25.19, 25.26 ($(CH_3)_2C$); 47.99, 48.79, 49.10 (CH_3O); 59.03 (CH_2-6); 62.95 (CH-3); 66.77 (CH-4); 78.29 (CH-5); 99.63, 100.47 ($(CH_3)_2C$); 100.69 (CH-2); 101.08 ($(CH_3)_2C$); 125.43, 126.10, 126.12, 126.13, 126.33 (CH-2,3,6,7-naphth); 128.21, 129.02 (CH-4,5-naphth); 130.95 (C-8a-naphth); 133.29 (C-4a-naphth); 134.75 (C-1-naphth); 152.26 (C-1); IR ($CHCl_3$): ν_{max} 3049, 2995, 2962, 2945, 2886, 2832, 1662, 1508, 1463, 1435, 1435, 1382, 1373, 1258, 1151, 1105, 1095, 1071, 1015, 958, 901, 864, 853, 853, 835, 819, 527, 499 cm^{-1}; HRMS (ESI) m/z $[M + Na]^+$ calcd for $C_{28}H_{40}O_7Na$ 511.2666, found 511.2667.

*(1,5-Anhydro-2-deoxy-3,4,6-tri-O-(ethoxyethyl)-D-arabino-hex-1-enitolyl)naphthalene (**9b**).* From **5b**: Following the general procedure A, boronate **5b** (2.01 g, 4.11 mmol, 2 equiv), 1-iodonaphthalene (0.3 mL, 2.05 mmol, 1 equiv), $Pd(PPh_3)_2Cl_2$ (72 mg, 103 μmol, 0.05 equiv) in DME (16 mL), and 2 M Na_2CO_3 (4 mL) were used. The reaction mixture was stirred at 80 °C for 3 h. After completion of the reaction, the residue was purified by column chromatography on silica gel (hexane/EtOAc 10:1 to 6:1) to give product **9b** (931 mg, 93%) as a pale yellow oil.

From **6b**: Following the general procedure B, stannane **6b** (2 g, 3.07 mmol, 1 equiv), 1-iodonaphthalene (0.67 mL, 4.60 mmol, 1.5 equiv), and $Pd(PPh_3)_4$ (177 mg, 153 μmol, 0.05 equiv) in toluene (15 mL) were used. The reaction mixture was stirred at 125 °C for 5 h. After completion of the reaction, the residue was purified by column chromatography on silica gel (hexane/EtOAc 10:1 to 6:1) to give product **9b** (1.19 g, 79%) as a pale yellow oil.

Preparation of 9b Using Indium Cross-Coupling Reaction. To a stirred solution of EE-glucal **2b** (200 mg, 552 μmol, 1 equiv) in anhydrous THF (5 mL) was added *t*-BuLi (0.49 mL, 828 μmol, 1.7 M in pentane, 1.5 equiv) dropwise over 5 min at −78 °C under argon. The reaction mixture was stirred for 15 min at −78 °C and then for 1 h at 0 °C. Subsequently, the resulting mixture was again cooled to −78 °C and transferred via cannula to the solution of $InCl_3$ (61 mg, 276 μmol, 0.5 equiv) in THF (4 mL) at −78 °C. The reaction was stirred for 30 min at −78 °C and then allowed to warm to RT. 1-Iodonaphthalene (0.12 mL, 828 μmol, 1.5 equiv) and $Pd(Ph_3P)_2Cl_2$ (12 mg, 17 μmol, 0.03 equiv) were added, and the resulting mixture was heated to reflux at 70 °C overnight. The mixture was diluted with toluene (10 mL), MeOH (5 mL), filtered over a plug of Celite, and evaporated in vacuo. The residue was purified by column chromatography on silica gel (toluene/acetone 20:1) to give product **9b** (115 mg, 43%) as a pale yellow oil.

Preparation of 9b Using Negishi Cross-Coupling Reaction. To a stirred solution of EE-glucal **2b** (200 mg, 552 μmol, 1 equiv) in anhydrous THF (5 mL) was added *t*-BuLi (1.14 mL, 1.93 mmol, 1.7 M in pentane, 3.5 equiv) dropwise over 5 min at −78 °C under argon. The reaction mixture was stirred for 15 min at −78 °C and then for 1 h at 0

DOI: 10.1021/acsomega.8b00901
ACS Omega 2018, 3, 7875−7887

°C. Then, a solution of freshly fused $ZnCl_2$ (301 mg, 2.21 mmol, 4 equiv) in THF (4 mL) was added at 0 °C. In a separate flask, $Pd(PPh_3)_4$ (32 mg, 28 μmol, 0.05 equiv) and 1-iodonaphthalene (97 μL, 662 μmol, 1.2 equiv) were dissolved in THF (1 mL), giving a red-brown solution. To this solution was transferred the solution containing the organozinc compound via cannula at RT and stirred for 2 h. The reaction mixture was diluted with EtOAc (50 mL) and filtered over a plug of Celite. The filtrate was washed with H_2O (2 × 50 mL) and brine (50 mL), dried over $MgSO_4$, filtered, and evaporated in vacuo. The residue was purified by column chromatography on silica gel (hexane/EtOAc 6:1) to give product **9b** (54 mg, 20%) as a pale yellow oil: R_f = 0.37 (hexane/EtOAc 4:1); ^1H and ^{13}C NMR spectra of **9b** were analyzed after in situ deprotection by 10% CD_3COOD in CD_3OD (see SI Chapter 4), and NMR spectra were compared with the spectra of unprotected derivative **12**; IR ($CHCl_3$): ν_{max} 3061, 3050, 2980, 2933, 2899, 2887, 2875, 2860, 2855, 1662, 1593, 1580, 1508, 1484, 1466, 1445, 1397, 1382, 1241, 1130, 1096, 1084, 1056, 868, 844, 694 cm^{-1}; HRMS (ESI) m/z $[M + Na]^+$ calcd for $C_{28}H_{40}O_7Na$ 511.2666, found 511.2666.

*(1,5-Anhydro-2-deoxy-3,4,6-tri-O-(ethoxyethyl)-D-lyxo-hex-1-enitolyl)naphthalene (**10**).* From **7**: Following the general procedure A, boronate **7** (1.35 g, 2.76 mmol, 2 equiv), 1-iodonaphthalene (0.20 mL, 1.38 mmol, 1 equiv), $Pd(PPh_3)_2Cl_2$ (48 mg, 69 μmol, 0.05 equiv) in DME (12 mL), and 2 M Na_2CO_3 (3 mL) were used. The reaction mixture was stirred at 80 °C for 3 h. After completion of the reaction, the residue was purified by column chromatography on silica gel (hexane/EtOAc 8:1, 1% Et_3N) to give product **10** (584 mg, 87%) as a pale yellow oil.

From **8**: Following the general procedure B, stannane **8** (800 mg, 1.23 mmol, 1 equiv), 1-iodonaphthalene (0.27 mL, 1.84 mmol, 1.5 equiv), and $Pd(PPh_3)_4$ (71 mg, 61 μmol, 0.05 equiv) in toluene (15 mL) were used. The reaction mixture was stirred at 125 °C for 5 h. After completion of the reaction, the residue was purified by column chromatography on silica gel (hexane/EtOAc 8:1, 1% Et_3N) to give product **10** (432 mg, 72%) as a pale yellow oil: R_f = 0.38 (hexane/EtOAc 4:1); ^1H and ^{13}C NMR spectra of **10** were analyzed after in situ deprotection by 10% CD_3COOD in CD_3OD (see SI Chapter 4), and NMR spectra were compared with the NMR of unprotected derivative **15**; IR ($CHCl_3$): ν_{max} 3090, 3062, 3049, 2981, 2933, 2898, 2874, 1661, 1621, 1593, 1581, 1508, 1483, 1456, 1446, 1395, 1381, 1134, 1112, 1100, 1084, 1056, 861, 804, 640 cm^{-1}; HRMS (ESI) $[M + Na]^+$ m/z calcd for $C_{28}H_{40}O_7Na$ 511.2666, found 511.2667.

*(1,5-Anhydro-2-deoxy-D-arabino-hex-1-enitolyl)-naphthalene (**12**).* From **9a**: The derivative **9a** (250 mg, 512 μmol) was dissolved in the mixture of THF (5 mL) and 1% AcOH (5 mL). The reaction mixture was stirred at RT overnight. The reaction mixture was diluted with EtOAc (100 mL) and washed with H_2O (2 × 50 mL). The organic layer was dried over $MgSO_4$, filtered, and concentrated in vacuo. The residue was purified by column chromatography on silica gel ($CHCl_3$/MeOH 8:1) to give product **12** (127 mg, 91%) as a colorless oil.

From **9b**: The derivative **9b** (180 mg, 368 μmol) was dissolved in the mixture of THF (5 mL) and 20% AcOH (5 mL). The reaction mixture was stirred at RT overnight. The reaction mixture was diluted with EtOAc (100 mL) and washed with H_2O (2 × 50 mL). The organic layer was dried over $MgSO_4$, filtered, and concentrated in vacuo. The residue was purified by column chromatography on silica gel ($CHCl_3$/MeOH 8:1) to give product **12** (90 mg, 90%) as a colorless oil: R_f = 0.61 ($CHCl_3$/MeOH 3:1); $[\alpha]_D^{20}$ −11.9 (c 0.3, MeOH); ^1H NMR (401.0 MHz, CD_3OD): 3.84 (dd, 2H, $J_{4,5}$ = 9.8, $J_{4,3}$ = 7.1, H-4); 3.93 (dd, 1H, $J_{6b,6a}$ = 12.3, $J_{6b,5}$ = 5.3, H-6b); 4.00 (dd, 1H, $J_{6a,6b}$ = 12.3, $J_{6a,5}$ = 2.6, H-6a); 4.10 (ddd, 1H, $J_{5,4}$ = 9.8, $J_{5,6}$ = 5.3, 2.6, H-5); 4.37 (dd, 1H, $J_{3,4}$ = 7.1, $J_{3,4}$ = 2.5, H-3); 5.02 (d, 1H, $J_{2,3}$ = 2.5, H-2); 7.43 (dd, 1H, $J_{3,4}$ = 8.3, $J_{3,2}$ = 7.0, H-3-naphth); 7.44−7.52 (m, 2H, H-6,7-naphth); 7.55 (dd, 1H, $J_{2,3}$ = 7.0, $J_{2,4}$ = 1.3, H-2-naphth); 7.82−7.87 (m, 2H, H-4,5-naphth); 8.23 (m, 1H, H-8-naphth); ^{13}C NMR (100.8 MHz, CD_3OD): 62.3 (CH_2-6); 71.0 (CH-4); 71.5 (CH-3); 81.3 (CH-5); 105.4 (CH-2); 126.0 (CH-3-naphth); 126.9, 127.00, 127.2 (CH-6,7,8-naphth); 127.8 (CH-2-naphth); 129.2 (CH-5-naphth); 130.2 (CH-4-naphth); 132.6 (C-8a-naphth); 135.0, 135.1 (C-1,4a-naphth); 155.0 (C-1); IR ($CHCl_3$): ν_{max} 3278, 1659, 1621, 1590, 1509, 1400, 1253, 1108, 1067, 1067, 1047, 800 cm^{-1}; HRMS (ESI) m/z $[M + Na]^+$ calcd for $C_{16}H_{16}O_4Na$ 295.0941, found 295.0941.

*(1,5-Anhydro-2-deoxy-D-lyxo-hex-1-enitolyl)naphthalene (**15**).* EE-protected derivative **10** (186 mg, 381 μmol) was dissolved in 10% AcOH in MeOH (10 mL). The reaction mixture was heated to 40 °C and stirred for 1.5 h. After cooling to RT, toluene (30 mL) was added and the solution was evaporated in vacuo. The residue was purified by column chromatography on silica gel ($CHCl_3$/MeOH 12:1 to 10:1, 1% Et_3N) to give product **15** (61 mg, 59%) as a colorless oil: R_f = 0.68 ($CHCl_3$/MeOH 5:1); $[\alpha]_D^{20}$ −6.2 (c 0.4, MeOH); ^1H NMR (401.0 MHz, CD_3OD): 3.90 (dd, 1H, $J_{6b,6a}$ = 11.5, $J_{6b,5}$ = 5.8, H-6b); 3.94 (dd, 1H, $J_{6a,6b}$ = 11.5, $J_{6a,5}$ = 6.6, H-6a); 4.06 (ddd, 1H, $J_{4,3}$ = 4.7, $J_{4,2}$ = 1.9, $J_{4,5}$ = 1.1, H-4); 4.24 (ddt, 1H, $J_{5,6}$ = 6.6, 5.8, $J_{5,3}$ = $J_{5,4}$ = 1.1, H-5); 4.59 (dd, 1H, $J_{3,4}$ = 4.7, $J_{3,2}$ = 2.4, H-3); 4.93 (dd, 1H, $J_{2,3}$ = 2.4, $J_{2,1}$ = 1.9, H-2); 7.43 (dd, 1H, $J_{3,4}$ = 8.4, $J_{3,2}$ = 7.0, H-3-naphth); 7.43−7.50 (m, 2H, H-6,7-naphth); 7.55 (dd, 1H, $J_{2,3}$ = 7.0, $J_{2,4}$ = 1.4, H-2-naphth); 7.82−7.87 (m, 2H, H-4,5-naphth); 8.28 (m, 1H, H-8-naphth); ^{13}C NMR (100.8 MHz, CD_3OD): 62.6 (CH_2-6); 66.1 (CH-4); 66.6 (CH-3); 79.6 (CH-5); 104.6 (CH-2); 126.0 (CH-3-nphth); 126.8 (CH-6-naphth); 127.0 (CH-7-naphth); 127.3 (CH-8-naphth); 127.6 (CH-2-naphth); 129.0 (CH-5-naphth); 130.0 (CH-4-naphth); 132.8 (C-8a-naphth); 135.1 (C-4a-naphth); 135.5 (C-1-naphth); 155.0 (C-1); IR ($CHCl_3$): ν_{max} 3361, 1060, 1592, 1508, 1085, 959, 893, 852 cm^{-1}; HRMS (ESI) m/z $[M + Na]^+$ calculated for $C_{16}H_{16}O_4Na$ 295.0941, found 295.0941.

Transformations of Endocyclic Double Bond: General Procedure C: Hydroboration. To a stirred solution of 1-naphthylglycal (1 equiv) in anhydrous THF was added BH_3·THF (1 M in THF, 10 equiv) dropwise at 0 °C under argon atmosphere. The reaction mixture was stirred for 2.5 h and 30% NaOH and 30% H_2O_2 were added slowly, and the resulting mixture was stirred for 1 h at 0 °C and then for another 2 h at RT. The reaction mixture was diluted with EtOAc and washed with H_2O (3×). The organic layer was dried over $MgSO_4$, filtered, and evaporated in vacuo. The residue was dissolved in the mixture of hexane/EtOAc (3:1) and filtered over a plug of silica gel and evaporated in vacuo. The protected alcohol was confirmed by HRMS and used directly for deprotection (general procedure E or F).

General Procedure D: Epoxidation/LiBHEt$_3$ Opening. To a stirred solution of 1-naphthylglycal (1 equiv) in CH_2Cl_2 was added freshly distilled solution of DMDO[23] (approx. 0.06 M in acetone, 1.1 equiv) at 0 °C under argon atmosphere. The

DOI: 10.1021/acsomega.8b00901
ACS Omega 2018, 3, 7875−7887

reaction mixture was stirred for 30 min at 0 °C. Thereafter, the solvent was removed under reduced pressure without heating, codistilled with toluene (3 × 20 mL), and dried for 1 h under vacuum. The residue was dissolved in anhydrous THF, and $LiBHEt_3$ (1 M in THF, 40 equiv) was added at 0 °C under argon atmosphere. The reaction mixture was stirred for 30 min at 0 °C and then for 1.5 h at RT. The resulting mixture was diluted with Et_2O and washed with H_2O (3×). The organic layer was dried over $MgSO_4$, filtered, and evaporated in vacuo. The protected alcohol was confirmed by HRMS and used directly for deprotection (general procedure E or F).

General Procedure E: Deprotection for MOP. MOP-protected derivative was dissolved in the mixture of THF and 1% aqueous AcOH (1:1) and stirred at RT overnight. The solution was diluted with H_2O (10 mL) and evaporated in vacuo. The residue was purified by column chromatography on silica gel ($CHCl_3$/MeOH) to give corresponding *C*-glycoside.

General Procedure F: Deprotection for EE. EE-protected derivative was dissolved in the mixture of THF and 20% aqueous AcOH (1:1) and stirred at RT overnight. The solution was diluted with H_2O (10 mL) and evaporated in vacuo. The residue was purified by column chromatography on silica gel ($CHCl_3$/MeOH) to give corresponding *C*-glycoside.

*1-(β-D-Glucopyranosyl)naphthalene (**11**).* From **9a**: Following the general procedure C, the MOP-protected derivative **9a** (100 mg, 205 μmol, 1 equiv), BH_3·THF (2.05 mL, 2.05 mmol, 1 M in THF, 10 equiv), and THF (5 mL) were used. The mixture was stirred for 2.5 h at 0 °C. Then, 30% NaOH (2 mL) and 30% H_2O_2 (2 mL) were used and resulting mixture was stirred for 1 h at 0 °C and then for 2 h at RT. After completion of the reaction, crude 1-(3,4,6-tri-*O*-(2-methoxypropan-2-yl)-β-D-glucopyranosyl)naphthalene (R_f = 0.71 ($CHCl_3$/MeOH 5:1); HRMS (ESI) *m*/*z* [M + Na]$^+$ calcd for $C_{28}H_{42}O_8Na$ 529.2772, found 529.2772) was obtained. Following the general procedure E, the MOP-*C*-glycoside, THF (5 mL), and 1% AcOH (5 mL) were used. After completion of the reaction, the residue was purified by column chromatography on silica gel ($CHCl_3$/MeOH 6:1) to give product **11** (107 mg, 78%) as a colorless foam.

From **9b**: Following the general procedure C, the MOP-protected derivative **9b** (230 mg, 471 μmol, 1 equiv), BH_3·THF (4.71 mL, 4.71 mmol, 1 M in THF, 10 equiv), and THF (7 mL) were used. The mixture was stirred for 2.5 h at 0 °C. Then, 30% NaOH (5 mL) and 30% H_2O_2 (5 mL) were used and resulting mixture was stirred for 1 h at 0 °C and then for 2 h at RT. After completion of the reaction, crude 1-(3,4,6-tri-*O*-(ethoxyethyl)-β-D-glucopyranosyl)naphthalene (R_f = 0.57 (hexane/EtOAc 2:1); HRMS (ESI) *m*/*z* [M + Na]$^+$ calcd for $C_{28}H_{42}O_8Na$ 529.2772, found 529.2772) was obtained. Following the general procedure E, the EE-*C*-glycoside, THF (10 mL), and 20% AcOH (10 mL) were used. After completion of the reaction, the residue was purified by column chromatography on silica gel ($CHCl_3$/MeOH 6:1) to give product **11** (49 mg, 82%) as a colorless foam.

From **12**: Following the general procedure C, the derivative **12** (150 mg, 551 μmol, 1 equiv), BH_3·THF (5.51 mL, 5.51 mmol, 1 M in THF, 10 equiv), and THF (5 mL) were used. The mixture was stirred for 2.5 h at 0 °C. Then, 30% NaOH (3 mL) and 30% H_2O_2 (3 mL) were used and the resulting mixture was stirred for 1 h at 0 °C and then for 2 h at RT. The reaction mixture was diluted with acetone (10 mL) and stirred for 10 min. Then, the formed solid was filtered over a plug of Celite, the plug was washed with MeOH (20 mL), and the filtrate was evaporated in vacuo. The residue was purified by column chromatography on silica gel ($CHCl_3$/MeOH 6:1) to give **11** (134 mg, 84%) as a colorless foam: R_f = 0.22 ($CHCl_3$/MeOH 5:1); $[\alpha]_D^{20}$ 9.1 (*c* 0.3, MeOH); ^{1}H NMR (401.0 MHz, CD_3OD): 3.51−3.60 (m, 2H, H-4,5); 3.64 (t, 1H, $J_{3,2}$ = $J_{3,4}$ = 8.6, H-3); 3.74 (dd, 1H, $J_{6b,6a}$ = 12.0, $J_{6b,5}$ = 5.6, H-6b); 3.82 (dd, 1H, $J_{2,1}$ = 9.6, $J_{2,3}$ = 8.6, H-2); 3.91 (dd, 1H, $J_{6a,6b}$ = 12.0, $J_{6a,5}$ = 1.9, H-6a); 4.94 (d, 1H, $J_{1,2}$ = 9.6, H-1); 7.42−7.55 (m, 3H, H-3,6,7-naphth); 7.67 (dd, 1H, $J_{2,3}$ = 7.2, $J_{2,4}$ = 1.4, H-2-naphth); 7.83 (dt, 1H, $J_{4,3}$ = 8.4, $J_{4,2}$ = $J_{4,5}$ = 1.4, H-4-naphth); 7.86 (m, 1H, H-5); 8.31 (m, 1H, H-8); ^{13}C NMR (100.8 MHz, CD_3OD): 63.2 (CH_2-6); 72.0 (CH-4); 75.8 (CH-2); 80.1 (CH-3); 80.4 (CH-1); 82.5 (CH-5); 125.6 (CH-8-naphth); 126.2 (CH-3-naphth); 126.4 (CH-6-naphth); 126.77 (CH-2-naphth); 126.80 (CH-7-naphth); 129.5, 129.6 (CH-4,5-naphth); 133.5 (C-8a-naphth); 135.4 (C-4a-naphth); 136.3 (C-1-naphth); IR (KBr): ν_{max} 3375, 2924, 1618, 1598, 1512, 1398, 1084, 1084, 1043, 1027, 802 cm^{-1}; HRMS (ESI) *m*/*z* [M + Na]$^+$ calcd for $C_{16}H_{18}O_5Na$ 313.1046, found 313.1048. Previously published NMR data were measured in $CDCl_3$.

*1-(β-D-Galactopyranosyl)naphthalene (**14**).* From **10**: Following the general procedure C, the EE-protected derivative **10** (100 mg, 205 μmol, 1 equiv), BH_3·THF (2.05 mL, 2.05 mmol, 1 M in THF, 10 equiv), and THF (5 mL) were used. The mixture was stirred for 2.5 h at 0 °C. Then, 30% NaOH (5 mL) and 30% H_2O_2 (5 mL) were used and the resulting mixture was stirred for 1 h at 0 °C and then for 2 h at RT. After completion of the reaction, crude 1-(3,4,6-tri-*O*-(ethoxyethyl)-β-D-galactopyranosyl)naphthalene (R_f = 0.32 (hexane/EtOAc 2:1); HRMS (ESI) *m*/*z* [M + Na]$^+$ calcd for $C_{28}H_{42}O_8Na$ 529.2772, found 529.2773) was obtained. Following the general procedure F, the EE-*C*-glycoside, THF (5 mL), and 20% AcOH (5 mL) were used. After completion of the reaction, the residue was purified by column chromatography on silica gel ($CHCl_3$/MeOH 6:1) to give product **14** (41 mg, 69%) as a white solid.

From **15**: Following the general procedure C, the derivative **15** (100 mg, 367 μmol, 1 equiv), BH_3·THF (3.67 mL, 3.67 mmol, 1 M in THF, 10 equiv), and THF (5 mL) were used. The mixture was stirred for 2.5 h at 0 °C. Then, 30% NaOH (3 mL) and 30% H_2O_2 (3 mL) were used and the resulting mixture was stirred for 1 h at 0 °C and then for 2 h at RT. The reaction mixture was diluted with acetone (10 mL) and stirred for 10 min. Then, the formed solid was filtered over a plug of Celite, the plug was washed with MeOH (20 mL), and the filtrate was evaporated in vacuo. The residue was purified by column chromatography on silica gel ($CHCl_3$/MeOH 6:1) to give **14** (80 mg, 75%) as a white solid: R_f = 0.20 ($CHCl_3$:MeOH 5:1); mp 106−112 °C (acetone) $[\alpha]_D^{20}$ 12.2 (*c* 0.3, MeOH); ^{1}H NMR (401.0 MHz, CD_3OD): 3.72 (dd, 1H, $J_{3,2}$ = 9.2, $J_{3,4}$ = 3.3, H-3); 3.75−3.86 (m, 3H, H-5,6); 4.08 (dd, 1H, $J_{4,3}$ = 3.3, $J_{4,5}$ = 0.9, H-4); 4.20 (dd, 1H, $J_{2,1}$ = 9.6, $J_{2,3}$ = 9.2, H-2); 4.81 (d, 1H, $J_{1,2}$ = 9.6, H-1); 7.41−7.53 (m, 3H, H-3,6,7-naphth); 7.68 (dd, 1H, $J_{2,3}$ = 7.2, $J_{2,4}$ = 1.3, H-2-naphth); 7.83 (dt, 1H, $J_{4,3}$ = 8.2, $J_{4,2}$ = $J_{4,5}$ = 1.3, H-4-naphth); 7.86 (m, 1H, H-5); 8.46 (m, 1H, H-8); ^{13}C NMR (100.8 MHz, CD_3OD): 63.1 (CH_2-6); 71.2 (CH-4); 72.6 (CH-2); 76.8 (CH-3); 80.8 (CH-5); 82.0 (CH-1); 126.08 (CH-8-naphth); 126.11 (CH-3-naphth); 126.40 (CH-6-naphth); 126.71 (CH-7-naphth); 127.4 (CH-2-naphth); 129.5 (CH-5-naphth); 129.6 (CH-4-naphth); 133.5 (C-8a-naphth); 135.5 (C-4a-naphth); 136.4 (C-1-naphth); IR (MeOH): ν_{max} 3361,

DOI: 10.1021/acsomega.8b00901
ACS Omega 2018, 3, 7875−7887

1599, 1512, 1179, 1083, 1048, 1013, 950, 847 cm^{-1}; HRMS (ESI) m/z $[M + Na]^+$ calcd for $C_{16}H_{18}O_5Na$ 313.1046, found 313.1047.

*1-(α-D-Glucopyranosyl)naphthalene (**13**).* From **9a**: Following the general procedure D, the MOP-protected derivative **9a** (200 mg, 409 μmol, 1 equiv), DMDO (7.50 mL, 450 μmol, 0.06 M in acetone, 1.1 equiv), and CH_2Cl_2 (5 mL) were used. The mixture was stirred for 30 min at 0 °C. After completion of the epoxidation step, the residue $LiBHEt_3$ (16.37 mL, 16.37 mmol, 1 M in THF, 40 equiv) and THF (5 mL) were used. The reaction mixture was stirred for 30 min at 0 °C and then for 1.5 h at RT. After completion of the reaction, crude 1-(3,4,6-tri-*O*-(2-methoxypropan-2-yl)-α-D-glucopyranosyl)-naphthalene (R_f = 0.47 (hexane/EtOAc 3:1); HRMS (ESI) $[M + Na]^+$ m/z calcd for $C_{28}H_{42}O_8Na$ 529.2772, found 529.2772) was obtained. Following the general procedure E, the MOP-*C*-glycoside, THF (5 mL), and 1% AcOH (5 mL) were used. After completion of the reaction, the residue was purified by column chromatography on silica gel ($CHCl_3$/MeOH 8:1) to give product **13** (76 mg, 64%) as a colorless oil.

From **9b**: Following the general procedure D, the EE-protected derivative **9b** (140 mg, 287 μmol, 1 equiv), DMDO (5.25 mL, 315 μmol, 0.06 M in acetone, 1.1 equiv), and CH_2Cl_2 (5 mL) were used. The mixture was stirred for 30 min at 0 °C. After completion of the epoxidation step, the residue $LiBHEt_3$ (11.46 mL, 11.46 mmol, 1 M in THF, 40 equiv) and THF (5 mL) were used. The reaction mixture was stirred for 30 min at 0 °C and then for 1.5 h at RT. After completion of the reaction, crude 1-(3,4,6-tri-*O*-(ethoxyethyl)-α-D-glucopyranosyl)naphthalene (R_f = 0.53 ($CHCl_3$/MeOH 3:1); HRMS (ESI) m/z $[M + Na]^+$ calcd for $C_{28}H_{42}O_8Na$ 529.2772, found 529.2773) was obtained. Following the general procedure F, the EE-*C*-glycoside, THF (5 mL), and 20% AcOH (5 mL) were used. After completion of the reaction, the residue was purified by column chromatography on silica gel ($CHCl_3$/MeOH 8:1) to give product **13** (57 mg, 69%) as a colorless oil: R_f = 0.63 ($CHCl_3$/MeOH 3:1); $[\alpha]_D^{20}$ 42.4 (*c* 0.3, $CHCl_3$); ^1H NMR (401.0 MHz, CD_3OD): 3.51 (ddd, 1H, $J_{5,4}$ = 6.9, $J_{5,6}$ = 6.1, 3.3, H-5); 3.61−3.69 (m, 2H, H-4,6b); 3.88 (dd, 1H, $J_{6a,6b}$ = 12.0, $J_{6a,5}$ = 6.1, H-6a); 4.08 (dd, 1H, $J_{2,3}$ = 7.1, $J_{2,1}$ = 4.2, H-2); 4.23 (dd, 1H, $J_{3,2}$ = 7.1, $J_{3,4}$ = 6.4, H-3); 5.89 (d, 1H, $J_{1,2}$ = 4.2, H-1); 7.42−7.57 (m, 3H, H-3,6,7-naphth); 7.82 (d, 1H, $J_{4,3}$ = 8.2, H-4-naphth); 7.88 (m, 1H, H-5-naphth); 7.98 (dt, 1H, $J_{2,3}$ = 7.3, $J_{2,4}$ = $J_{2,5}$ = 1.1, H-2-naphth); 8.28 (m, 1H, H-8-naphth); ^{13}C NMR (100.8 MHz, CD_3OD): 62.1 (CH_2-6); 71.7 (CH-4); 72.3 (CH-1); 73.8 (CH-2); 74.4 (CH-3); 77.9 (CH-5); 125.2 (CH-8-naphth); 125.6 (CH-3-naphth); 126.4 (CH-6-naphth); 126.9 (CH-7-naphth); 128.1 (CH-2-naphth); 129.2 (CH-4-naphth); 129.8 (CH-5-naphth); 133.0 (C-8a-naphth); 134.4 (C-1-naphth); 135.5 (CH-4-naphth); IR ($CHCl_3$): ν_{max} 3606, 3530, 3412, 2928, 1626, 1600, 1592, 1509, 1463, 1401, 1059, 811 cm^{-1}; HRMS (ESI) m/z $[M - H]^-$ calcd for $C_{16}H_{17}O_5$ 289.1082, found 289.1080.

*(2S,3R,4S,5R)-1-(Naphthalen-1-yl)hexane-1,2,3,4,5,6-hexaol (**16**).* Following the general procedure D, the EE-protected derivative **10** (180 mg, 368 μmol, 1 equiv), DMDO (6.75 mL, 405 μmol, 0.06 M in acetone, 1.1 equiv), and CH_2Cl_2 (5 mL) were used. The mixture was stirred for 30 min at 0 °C. After completion of the epoxidation step, the residue $LiBHEt_3$ (14.74 mL, 14.74 mmol, 1 M in THF, 40 equiv) and THF (5 mL) were used. The reaction mixture was stirred for 30 min at 0 °C and then for 1.5 h at RT. After completion of the reaction, crude (2*S*,3*R*,4*S*,5*R*)-1-(naphthalen-1-yl)hexane-(3,4,6-tri-*O*-(ethoxyethyl)-1,2,3,4,5,6-hexaol) (R_f = 0.26 (hexane/EtOAc 5:1); HRMS (ESI) m/z $[M + Na]^+$ calcd for $C_{28}H_{44}O_9Na$ 547.2878, found 547.2880) was obtained. Following the general procedure F, the hexanol, THF (5 mL), and 20% AcOH (5 mL) were used. After completion of the reaction, the residue was purified by column chromatography on silica gel ($CHCl_3$/MeOH 5:1) to give product **16** (59 mg, 52%) as a colorless oil: R_f = 0.15 ($CHCl_3$/MeOH 5:1); ^1H NMR (500.0 MHz, DMSO-d_6): 3.31−3.42 (m, 2H, H-6, overlapped with water signal); 3.49 (bd, 1H, $J_{3,4}$ = 9.5, H-3); 3.74 (bt, 1H, $J_{5,6}$ = 6.2, H-5); 3.90 (d, 1H, $J_{4,3}$ = 9.5, H-4); 4.01 (bd, 1H, $J_{2,1}$ = 7.8, H-2); 4.15 (bs, 1H, OH-3); 4.21 (bs, 2H, OH-2,5); 4.51 (bs, 1H, OH-6); 4.69 (bs, 1H, OH-4); 5.37 (d, 1H, $J_{1,2}$ = 7.8, H-1); 5.68 (bs, 1H, OH-1); 7.43−7.53 (m, 3H, H-3,6,7-naphth); 7.64 (dd, 1H, $J_{2,3}$ = 7.3, $J_{2,4}$ = 1.3, H-2-naphth); 7.79 (d, 1H, $J_{4,3}$ = 8.2, H-4-naphth); 7.89 (m, 1H, H-5-naphth); 8.26 (m, 1H, H-8-naphth); ^{13}C NMR (125.7 MHz, DMSO-d_6): 63.5 (CH_2-6); 69.1 (CH-4); 69.3 (CH-3); 70.2 (CH-5); 71.2 (CH-1); 72.4 (CH-2); 124.7 (CH-2-naphth); 124.8 (CH-8-naphth); 125.3, 125.4, 125.5 (CH-3,6,7-naphth); 127.1 (CH-4-naphth); 128.5 (CH-5-naphth); 131.7 (C-8a-naphth); 133.4 (CH-4a-naphth); 140.9 (C-1-naphth); HRMS (ESI) m/z $[M + Na]^+$calcd for $C_{16}H_{20}O_6Na$ 331.1152, found 331.1152.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acsomega.8b00901.

Experimental details and analytical data of the new compounds and their ^1H and ^{13}C NMR spectra (PDF)

■ AUTHOR INFORMATION

Corresponding Author

*E-mail: parkank@vscht.cz.

ORCID

Kamil Parkan: 0000-0001-7585-6004

Author Contributions

All authors have given approval to the final version of the manuscript.

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

This work was supported by the Czech Science Foundation (reg. No. 15-17572S) and in part by financial support from specific university research (MSMT No. 20-SVV/2017). We also appreciate the support from Gilead Sciences, Inc. provided under the program "Molecules for Life" at the Gilead Sciences & IOCB Prague Research Center.

■ REFERENCES

(1) Dingjan, T.; Yuriev, E.; Ramsland, A. P. Computational Approaches for Studying Carbohydrate-Lectin Interactions in Infection. In *Glycobiology and Human Diseases*, 1st ed.; Wiederschain, G., Ed.; CRC Press: Boca Raton, 2016; pp 129−147.
(2) (a) Du, Y.; Linhardt, R. J.; Vlahov, I. R. Recent advances in stereoselective *C*-glycoside synthesis. *Tetrahedron* **1998**, *54*, 9913−9959. (b) Lee, D.; He, M. Recent advances in aryl *C*-glycoside synthesis. *Curr. Top. Med. Chem.* **2005**, *5*, 1333−1350. (c) Bililign, T.;

DOI: 10.1021/acsomega.8b00901
ACS Omega 2018, 3, 7875−7887

Griffith, B. R.; Thorson, J. S. Structure, activity, synthesis and biosynthesis of aryl-*C*-glycosides. *Nat. Prod. Rep.* **2005**, *22*, 742−760. (d) Hocek, M. *C*-nucleosides: Synthetic strategies and biological applications. *Chem. Rev.* **2009**, *109*, 6729−6764. (e) Bokor, É; Kun, S.; Goyard, D.; Tóth, M.; Praly, J.-P.; Vidal, S.; Somsák, L. *C*-glycopyranosyl arenes and hetarenes: Synthetic methods and bioactivity focused on antidiabetic potential. *Chem. Rev.* **2017**, *117*, 1687−1764. (f) Yang, Y.; Yu, B. Recent advances in the chemical synthesis of *C*-glycosides. *Chem. Rev.* **2017**, *117*, 12281−12356.

(3) (a) Kharel, M. K.; Pahari, P.; Shepherd, M. D.; Tibrewal, N.; Nybo, S. E.; Shaaban, K. A.; Rohr, J. Angucyclines: Biosynthesis, mode-of-action, new natural products, and synthesis. *Nat. Prod. Rep.* **2012**, *29*, 264−325. (b) Kitamura, K.; Ando, Y.; Matsumoto, T.; Suzuki, K. Total synthesis of aryl *C*-glycoside natural products: Strategies and tactics. *Chem. Rev.* **2017**, *118*, 1495−1598.

(4) (a) Meng, W.; Ellsworth, B. A.; Nirschl, A. A.; McCann, P. J.; Patel, M.; Girotra, R. N.; Wu, G.; Sher, P. M.; Morrison, E. P.; Biller, S. A.; Zahler, R.; Deshpande, P. P.; Pullockaran, A.; Hagan, D. L.; Morgan, N.; Taylor, J. R.; Obermeier, M. T.; Humphreys, W. G.; Khanna, A.; Discenza, L.; Robertson, J. G.; Wang, A.; Han, S.; Wetterau, J. R.; Janovitz, E. B.; Flint, O. P.; Whaley, J. M.; Washburn, W. N. Discovery of dapagliflozin: A potent, selective renal sodium-dependent glucose cotransporter 2 (SGLT2) inhibitor for the treatment of type 2 diabetes. *J. Med. Chem.* **2008**, *51*, 1145−1149. (b) Nomura, S.; Sakamaki, S.; Hongu, M.; Kawanishi, E.; Koga, Y.; Sakamoto, T.; Yamamoto, Y.; Ueta, K.; Kimata, H.; Nakayama, K.; Tsuda-Tsukimoto, M. Discovery of canagliflozin, a novel *C*-glucoside with thiophene ring, as sodium-dependent glucose cotransporter 2 inhibitor for the treatment of type 2 diabetes mellitus. *J. Med. Chem.* **2010**, *53*, 6355−6360. (c) De Clercq, E. *C*-nucleosides to be revisited. *J. Med. Chem.* **2016**, *59*, 2301−2311.

(5) (a) Cox, P.; Lister, S.; Gallagher, T. Regiospecific enolates from tetrahydropyran-3-one. Synthetic equivalents of a thermodynamically and kinetically disfavoured enolate isomer. *J. Chem. Soc., Perkin Trans. 1* **1990**, 3151−3157. (b) Friesen, R. W.; Sturino, C. F.; Daljeet, A. K.; Kolaczewska, A. Observation of α-silyl carbanions in the metalation of 3,4,6-tri-*O*-(*tert*-butyldimethylsilyl)-D-glucal. *J. Org. Chem.* **1991**, *56*, 1944−1947. (c) Friesen, R. W.; Trimble, L. A. Selectivity in the α-silyl lithiation of 3,4,6-tris-*O*-(*tert*-butyldimethylsilyl)-D-glucal and 3,4-bis-*O*-(*tert*-butyldimethylsilyl)-6-deoxy-L-glucal with *tert*-butyllithium. *J. Org. Chem.* **1996**, *61*, 1165−1168.

(6) (a) Lehmann, U.; Awasthi, S.; Minehan, T. Palladium-catalyzed cross-coupling reactions between dihydropyranylindium reagents and aryl halides. synthesis of *C*-aryl glycals. *Org. Lett.* **2003**, *5*, 2405−2408. (b) Sakamaki, S.; Kawanishi, E.; Nomura, S.; Ishikawa, T. Aryl-β-*C*-glucosidation using glucal boronate: application to the synthesis of tri-*O*-methylnorbergenin. *Tetrahedron* **2012**, *68*, 5744−5753. (c) Parkan, K.; Pohl, R.; Kotora, M. Cross-coupling reaction of saccharide-based alkenyl boronic acids with aryl halides: The synthesis of bergenin. *Chem. - Eur. J.* **2014**, *20*, 4414−4419.

(7) Steunenberg, P.; Jeanneret, V.; Zhu, Y.-H.; Vogel, P. C(1→4)-linked disaccharides through carbonylative Stille cross-coupling. *Tetrahedron: Asymmetry* **2005**, *16*, 337−346.

(8) Tius, M. A.; Gomez-Galeno, J.; Gu, X. Q.; Zaidi, J. H. *C*-glycosylanthraquinone synthesis: Total synthesis of vineomycinone B2 methyl ester. *J. Am. Chem. Soc.* **1991**, *113*, 5775−5783.

(9) (a) Barnes, N. J.; Probert, M. A.; Wightman, R. H. Synthesis of 2-deoxy-α- and -β-D-arabino-hexopyranosyl phosphonic acids and related compounds; analogues of early intermediates in the shikimate pathway. *J. Chem. Soc., Perkin Trans. 1* **1996**, 431−438. (b) Majumder, U.; Cox, J. M.; Rainier, J. D. Synthesis of an F−H gambierol subunit using a *C*-glycoside-centered strategy. *Org. Lett.* **2003**, *5*, 913−916.

(10) Denmark, S. E.; Regens, C. S.; Kobayashi, T. Total synthesis of papulacandin D. *J. Am. Chem. Soc.* **2007**, *129*, 2774−2776.

(11) Dubbaka, S. R.; Steunenberg, P.; Vogel, P. Aryl and arylmethyl *C*-glycosides through desulfitative Stille and carbonylative Stille cross-coupling of tinglycals and sulfonyl chlorides. *Synlett* **2004**, 1235−1238.

(12) (a) Jäkel, C.; Dötz, K. H. Organotransition metal modified sugars: Part 22. Direct metalation of glycals: short and efficient routes to diversely protected stannylated glycals. *J. Organomet. Chem.* **2001**, *624*, 172−185. (b) Otto, F.; Dötz, K. H. Diastereoselective cyclopropanation of electron-deficient alkenes via metal glycal Carbenes. *Synthesis* **2008**, 2183−2190.

(13) Koester, D. C.; Werz, D. B. Sonogashira−Hagihara reactions of halogenated glycals. *Beilstein J. Org. Chem.* **2012**, *8*, 675−682.

(14) (a) Wolfrom, M. L.; Bhattacharjee, S. S.; de Lederkremer, R. M. Reaction of carbohydrates with vinyl ethers; a differential hydrolysis. *Carbohydr. Res.* **1969**, *11*, 148−150. (b) Lehmann, J.; Ziser, L. Irreversible product-inhibition of green-coffee α-D-galactosidase by 2-bromo- and 2-iodo-1-methoxyethyl α-D-galactopyranoside. *Carbohydr. Res.* **1988**, *183*, 301−309. (c) Mootoo, D. R.; Date, V.; Fraser-Reid, B. *n*-Pentenyl glycosides permit the chemospecific liberation of the anomeric center. *J. Am. Chem. Soc.* **1988**, *110*, 2662−2663. (d) Takahashi, T.; Ebata, S.; Yamada, H. Highly stereoselective hydroformylation of olefins possessing chiral sugar templates. *Synlett* **1998**, 381−382. (e) Hughes, K. D.; Nguyen, T.-L. N.; Dyckman, D.; Dulay, D.; Boyko, W. J.; Giuliano, R. M. Synthesis of vinyl glycosides and carbohydrate vinyl ethers from mixed acetals: a hetero-Diels−Alder approach to deoxygenated disaccharides. *Tetrahedron: Asymmetry* **2005**, *16*, 273−282. (f) Crucho, C.; Petrova, K.; Pinto, R.; Barros, M. Unsaturated sucrose ethers and their application as monomers. *Molecules* **2008**, *13*, 762−770.

(15) (a) Pozsgay, V.; Jennings, H. J. Synthesis of a di-, tri-, and tetrasaccharide unit of the group B streptococcal common antigen. *Carbohydr. Res.* **1988**, *179*, 61−75. (b) Barili, P. L.; Berti, G.; Bertozzi, D.; Catelani, G.; Colonna, F.; Corsetti, T.; D'Andrea, F. Meta-chloroperbenzoic acid as a selective reagent for the removal of *O*-propenyl groups. Its use in the synthesis of some d-galactopyranoside and 4-deoxy-L-threo-4-hexenopyranoside derivatives. *Tetrahedron* **1990**, *46*, 5365−5376. (c) Attolino, E.; Catelani, G.; D'Andrea, F. Regiospecific synthesis of 4-deoxy-D-*threo*-hex-3-enopyranosides by simultaneous activation−elimination of the talopyranoside axial 4-OH with the NaH/Im_2SO_2 system: Manifestation of the stereoelectronic effect. *Eur. J. Org. Chem.* **2006**, 5279−5292. (d) Xia, C.; Zhou, D.; Liu, C.; Lou, Y.; Yao, Q.; Zhang, W.; Wang, P. G. Thio-isoglobotrihexosylceramide, an agonist for activating invariant natural killer T cells. *Org. Lett.* **2006**, *8*, 5493−5496. (e) Mensah, E.; Camasso, N.; Kaplan, W.; Nagorny, P. Chiral phosphoric acid directed regioselective acetalization of carbohydrate-derived 1,2-diols. *Angew. Chem., Int. Ed.* **2013**, *52*, 12932−12936.

(16) Morihira, K.; Hara, R.; Kawahara, S.; Nishimori, T.; Nakamura, N.; Kusama, H.; Kuwajima, I. Enantioselective total synthesis of taxol. *J. Am. Chem. Soc.* **1998**, *120*, 12980−12981.

(17) Fukuzawa, A.; Sato, H.; Masamune, T. Synthesis of (±)-prepinnaterpene, a bromoditerpene from the red alga Laurencia Pinnata Yamada. *Tetrahedron Lett.* **1987**, *28*, 4303−4306.

(18) Jarowicki, K.; Kilner, C.; Kocienski, P. J.; Komsta, Z.; Milne, J. E.; Wojtasiewicz, A.; Coombs, V. Synthesis of 1-lithiated glycals and 1-tributylstannyl glycals from 1-phenylsulfinyl glycals via sulfoxide-lithium ligand exchange. *Synthesis* **2008**, 2747−2763.

(19) Dubois, E.; Beau, J.-M. Formation of *C*-glycosides by a palladium-catalysed coupling reaction of tributylstannyl glycals with organic halides. *J. Chem. Soc., Chem. Commun.* **1990**, 1191−1192.

(20) Boucard, V.; Larrieu, K.; Lubin-Germain, N.; Uziel, J.; Augé, J. C-glycosylated phenylalanine synthesis by palladium-catalyzed cross-coupling reactions. *Synlett* **2003**, No. 2444.

(21) Oroszova, B.; Choutka, J.; Pohl, R.; Parkan, K. Modular stereoselective synthesis of (1→2)-*C*-glycosides based on the sp^2−sp^3 Suzuki−Miyaura reaction. *Chem. - Eur. J.* **2015**, *21*, 7043−7047.

(22) (a) Koester, D. C.; Leibeling, M.; Neufeld, R.; Werz, D. B. A Pd-catalyzed approach to (1→6)-linked C-glycosides. *Org. Lett.* **2010**, *12*, 3934−3937. (b) Koester, D. C.; Kriemen, E.; Werz, D. B. Flexible synthesis of 2-deoxy-*C*-glycosides and (1→2)-, (1→3)-, and (1→4)-linked *C*-glycosides. *Angew. Chem., Int. Ed.* **2013**, *52*, 2985−2989.

DOI: 10.1021/acsomega.8b00901
ACS Omega 2018, 3, 7875−7887

(23) Taber, D. F.; DeMatteo, P. W.; Hassan, R. A. Simplified preparation of dimethyldioxirane (DMDO). *Org. Synth.* **2013**, *90*, 350−357.

DOI: 10.1021/acsomega.8b00901
ACS Omega 2018, 3, 7875−7887

PŘÍLOHA X

Vaňková K., Rahm M., Choutka J., Pohl R., Parkan K.: Facile Approach to *C*-glucosides by Using a Protecting-Group-Free Hiyama Cross-Coupling Reaction: High-Yielding Dapagliflozin Synthesis. *Chem.-Eur. J.,* **2021**, DOI: 10.1002/chem.202101052**.**


Check for updates
Chemistry A European Journal
Chemistry Europe
European Chemical Societies Publishing
Front Cover:
K. Parkan et al.
Facile Approach to C-Glucosides by Using a Protecting-Group-Free Hiyama Cross-Coupling Reaction: High-Yielding Dapagliflozin Synthesis
Aryl-C-glycosides
C-Glycopeptides
Dapagliflozin
00/2021
WILEY-VCH

COVER

A silyl hydride derivative of d-glucal was used conveniently as a bench-stable precursor for the construction of *C*-glycosidic bond. After activation by fluoride-mediated dehydrogenative hydrolysis, an intermediate silanol species was used for Hiyama arylation. Various aryl and heteroaryl *C*-glycosides, *C*-glycopeptides, as well as both a- and b-isomers of Dapagliflozin could be constructed rapidly and without the need for protecting groups. The cover image was designed by Tomáš Belloň at IOCB Prague. More information can be found in the Full Paper by K. Parkan et al. (DOI: 10.1002/chem.202101052).

*K. Vaňková, M. Rahm, J. Choutka, Dr. R. Pohl, Dr. K. Parkan**

1 – 2

Facile Approach to *C*-Glucosides by Using a Protecting-Group-Free Hiyama Cross-Coupling Reaction: High-Yielding Dapagliflozin Synthesis

Chemistry–A European Journal | Cover Profile
doi.org/10.1002/chem.202101995
Chemistry Europe
European Chemical Societies Publishing

Facile Approach to C-glucosides by Using a Protecting-Group-Free Hiyama Cross-Coupling Reaction: High-Yielding Dapagliflozin Synthesis





Karolína Vaňková Michal Rahm Jan Choutka Radek Pohl Kamil Parkan

UNIVERSITY OF CHEMISTRY AND TECHNOLOGY PRAGUE

ÚOCHB IOCB PRAGUE

Invited for the cover of this issue is Kamil Parkan and co-workers at University of Chemistry and Technology and Institute of Organic Chemistry and Biochemistry, Prague. The cover graphic depicts a schematic representation of the assembly of aryl-*C*-glycosides based on a protecting-group-free Hiyama reaction. Read the full text of the article at 10.1002/chem.202101052.

What is the most significant result of this study?

This work represents another step in the effort to use glycals (1,2-unsaturated derivatives of carbohydrates) as donor synthons for transition metal-catalyzed arylation reactions. We have employed a novel 1-silyl derivative of d-glucal, which was obtained as a bench-stable solid and could therefore be used conveniently. For its preparation, we have used a transient protection with MOP groups, which we developed previously, and therefore we could access the key synthon in its unprotected form. Taking advantage of this, we have carried out a range of Hiyama arylation reactions without the need for protection. We have also spectroscopically confirmed the role of the silyl hydride derivative as a masked silanol and its hydrolytic activation, which is a key mechanistic step for transmetalation of the glycal moiety to palladium. Moreover, we have used this strategy to develop a very short synthesis of Dapagliflozin, an important commercial drug.

What was the inspiration for this cover design?

We have depicted the sugar moiety as a cube of sugar. To match the overall "sweet" tone of the cover, we have placed the sugar assembly line into the surroundings inspired by the Tim Burton's bizzare adaptation of the novel Charlie and the Chocolate Factory. The only thing missing on the cover are the Oompa Loompas.

How did each team member/collaborator contribute to the work?

I would like to emphasize the role of both of the first authors of this paper, as both of them worked on this project during their undergraduate stay in our group. Given the early stage of their academic career, publication in Chemistry - A European Journal is a welcome encouragement into their upcoming successes.

These are not the final page numbers! ↗↗

Chemistry–A European Journal | Full Paper
doi.org/10.1002/chem.202101052
Chemistry Europe
European Chemical Societies Publishing

VIP Facile Approach to *C*-Glucosides by Using a Protecting-Group-Free Hiyama Cross-Coupling Reaction: High-Yielding Dapagliflozin Synthesis

Karolína Vaňková,[a] Michal Rahm,[a] Jan Choutka,[a] Radek Pohl,[b] and Kamil Parkan*[a]

Abstract: Access to unprotected (hetero)aryl pseudo-*C*-glucosides via a mild Pd-catalysed Hiyama cross-coupling reaction of protecting-group-free 1-diisopropylsilyl-D-glucal with various (hetero)aryl halides has been developed. In addition, selected unprotected pseudo-*C*-glucosides were stereoselectively converted into the corresponding α- and β-*C*-glucosides, as well as 2-deoxy-β-*C*-glucosides. This methodology was applied to the efficient and high-yielding synthesis of dapagliflozin, a medicament used to treat type 2 diabetes mellitus. Finally, the versatility of our methodology was proved by the synthesis of other analogues of dapagliflozin.

Introduction

In the field of carbohydrate chemistry, aryl *C*-glycosides are an important class of natural products[1] and synthetic drugs.[2] Structurally, they can be viewed as mimetics of aryl *O*-glycosides, in which their labile *O*-glycosidic bond is replaced with a stable C–C bond. This modification increases their stability towards chemical and enzymatic hydrolysis substantially, providing them with great potential as drug candidates. Various *C*-glycosides such as papulacandin D,[3] bergenin,[4] thailanstatin A,[5] and vicenin-2,[6] have been isolated from natural sources and show significant biological activities. The major use of aryl *C*-glycosides includes the inhibition of the sodium-glucose cotransporter-2 (SGLT-2). In recent years, these inhibitors have attracted much attention due to their effective, safe and well-tolerated control and regulation of type 2 diabetes.[2b] Accordingly, the FDA has approved SGLT-2 inhibitors, such as dapagliflozin (Forxiga), empagliflozin (Jardiance), and canagliflozin (Invokana).[7]

Consequently, many successful strategies to provide a synthetic access to aryl *C*-glycosides in a direct or *de novo* manner have been already developed.[1] Notable strategies to construct these saccharide mimetics by transition-metal-mediated coupling reactions include Heck,[8] Stille,[9] Suzuki-Miyaura,[4,9a,10] Negishi[10b,11] and Hiyama-Denmark cross-coupling reactions (Figure 1).[12] All of these methodologies were applied almost exclusively to *O*-protected (mostly benzylated and silylated) 1-substituted glycals except for the Stille cross-coupling reaction of aryl halides with glycosyl stannanes, described by Walczak et al.[13] The use of protecting groups suppresses problems with solubility in organic solvents and purification as well as side reactivity.[13–14] Nevertheless, depending on the sensitivity of the introduced functional group, the deprotection of the obtained saccharide mimetics can become challenging. Therefore, a straightforward access to unprotected aryl *C*-glycosides in high yield is advantageous. In continuation of our interest in the synthesis of *C*-glycosides,[4,9a,15] we report access to diverse (hetero)aryl *C*-glycosides via a key Hiyama cross-coupling reaction of 1-diisopropylsilyl-D-glucal **4** with different (hetero)aryl halides under mild conditions. Herein, to the best of our knowledge, the most suitable and practical synthesis of dapagliflozin **8n** and its derivatives **7n** and **10n** is also described.

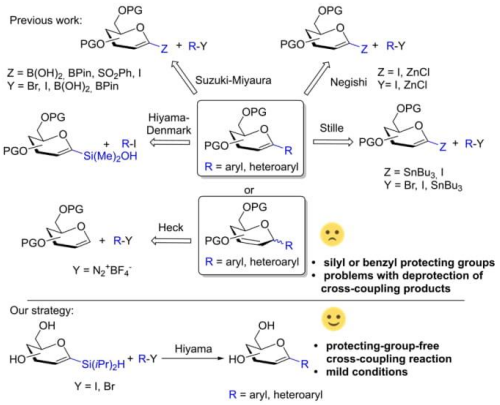


Figure 1. Cross-coupling approaches for the synthesis of aryl *C*-glycosides.

[a] *K. Vaňková, M. Rahm, J. Choutka, Dr. K. Parkan*
Department of Chemistry of Natural Compounds
University of Chemistry and Technology Prague
Technická 5, 166 28 Prague 6 (Czech Republic)
E-mail: parkank@vscht.cz

[b] *Dr. R. Pohl*
Institute of Organic Chemistry and Biochemistry of the Czech Academy of Sciences
Gilead Sciences & IOCB Research Centre
Flemingovo nám. 2, 166 10, Prague (Czech Republic)

Supporting information for this article is available on the WWW under https://doi.org/10.1002/chem.202101052

Chemistry–A European Journal | Full Paper doi.org/10.1002/chem.202101052 | Chemistry Europe European Chemical Societies Publishing

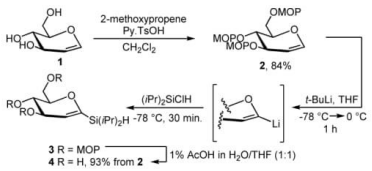
Results and Discussion

The first step was the preparation of 1-diisopropylsilyl-D-glucal **4** from commercially available D-glucal **1**, which was fully protected with 2-methoxyprop-2-yl (MOP) groups (Scheme 1). The reaction of 2-methoxypropene in the presence of pyridinium tosylate afforded MOP-D-glucal **2** in an excellent yield of 84%. As we reported before,[9a] MOP acetal protecting groups represent an efficient strategy for transient protection of glycals. Their use is favourable for several reasons, such as their easy introduction and removal, compatibility with silyl groups, low cost, and stability under harsh basic conditions, which are required for C-1 derivatization. In the next step, MOP-D-glucal **2** was converted into a 1-lithiated intermediate by treatment with *t*-BuLi (3.5 equiv.) in THF at −78 °C and then this intermediate was reacted with $(iPr)_2SiClH$ to give compound **3**. The subsequent mildly acidic hydrolysis (THF/1% aqueous AcOH in the ratio 1:1, *v*/*v*) of **3** resulted in the formation of bench-stable solid 1-diisopropylsilyl-D-glucal **4** in a notable yield of 78% over three steps.

The reaction of the unprotected 1-diisopropylsilyl-D-glucal **4** with 1-iodonaphthalene was chosen as a model reaction for the Hiyama cross-coupling.[16] To optimize the reaction conditions, the fluoride source and its quantity was screened, as summarized in the Table 1. Other parameters such as the temperature and the reaction time were varied. The formation of the desired 1-naphthyl-D-glucal **5a** was monitored by ^{1}H NMR with an internal standard (1,3,5-trimethoxybenzene).

The initial study began with tetrabutylammonium fluoride (TBAF) as a fluoride source in anhydrous THF at 0 °C (Table 1, entry 1). A complete conversion of the starting material **4** to product **5a** was observed within 1 h and the reaction conditions appeared to be satisfactory. Unfortunately, the purification of the product became problematic because of the presence of tetrabutylammonium salts, which we were not able to remove by column chromatography, ion-exchange on DOWEX 50X8 in Et_3N cycle or HPLC. For this reason, it was necessary to find a more convenient source of fluoride ions.

We first turned our attention to KF in the presence of a catalytic amount of 18-crown-6 (0.2 equiv.).[17] We tested different amounts of KF (2.2, 4.4, and 6.6 equiv.) under constant conditions in anhydrous THF at room temperature for 4 h. As shown in Table 1, the product **5a** was detected in all cases, although in low yields (17–36%) (Table 1, entries 2–4). Moreover, the conversion of the starting 1-diisopropylsilyl-D-glucal **4** was incomplete, and the addition of a Pd catalyst, crown ether, an extension of the reaction time or higher temperature did not lead to increased conversion. Therefore, CsF was used as a fluoride ion (Table 1, entries 5–12), because of its greater ionic character compared to KF. In this case, DMF and DMSO were tested as solvents. To our delight, the complete conversion of **4** was observed in all reactions (Table 1, entry 5–12). However, besides the desired cross-coupling product, D-glucal **1** was identified as a by-product. Its origin can be explained by competitive protodesilylation,[18] in which the diisopropylsilyl group is replaced by a hydrogen atom. In an attempt to prevent its formation, several reactions with different timing t_2 between



Scheme 1. The preparation of 1-diisopropylsilyl-D-glucal **4** from D-glucal **1**.

Table 1. The optimisation of the Hiyama cross-coupling reaction.

Entry	R^+F^- (equiv.)	Solvent	t_R [h]/t_2 [min]	T [°C]	Yieldof **1**/**5a** [%][a]	Conversion of **4** [%][a]
1	**TBAF (2.2)**	**THF**	**1/10**	**0–rt**	**0/80**[b]	**100**
2[d]	KF (2.2)	THF	4/10	rt	ND/24	ND
3[d]	KF (4.4)	THF	4/10	rt	0/36	ND
4[d]	KF (6.6)	THF	4/10	rt	0/17	63
5[d]	CsF (2.2)	DMF	16/0	rt	53/20	100
6[d]	CsF (4.4)	DMF	16/0	rt	52/14	100
7[d]	CsF (4.4)	DMF	16/0	60	68/16	100
8[d]	CsF (4.4)	DMF	16/20	60	ND/38	100
9[d]	CsF (4.4)	DMF	16/60	60	26/40	100
10[d]	CsF (4.4)	DMSO	16/0	60	ND/ND	ND
11[d]	CsF (4.4)	DMSO	16/20	60	26/40	100
12[d]	CsF (4.4)	DMSO	16/60	60	ND/ND	ND
13	NH_4F (2.2)	THF	16/10	rt	0/0	0
14	**TMAF·4H$_2$O (2.2)**	**DMF**	**16/10**	**rt**	**0/81**[c]	**100**
15	TMAF·4H$_2$O (2.2)	THF	16/10	rt	0/40[c]	50

[a] All yields and conversions were determined by ^{1}H NMR with an internal standard, 1,3,5-trimethoxybenzene. [b] Product contained traces of tetrabutylammonium salts. [c] Isolated yield. [d] 18-crown-6 (0.2 equiv.) was added; t_R = reaction time; t_2 = time between the addition of fluoride and the addition of 1-iodonaphthalene with a Pd catalyst; ND = not determined.

Chemistry–A European Journal | Full Paper doi.org/10.1002/chem.202101052 | Chemistry Europe European Chemical Societies Publishing

the addition of CsF and the addition of 1-iodonaphthalene along with the catalyst were performed. Unfortunately, the presence of D-glucal **1** was still apparent.

Additionally, NH_4F was also tested as a source of fluoride ions (Table 1, entry 13), but no reactivity of the starting material was observed, which was attributed to the insufficient ionic character of this salt. Ideal conditions (Table 1, entry 14) were found using tetramethylammonium fluoride tetrahydrate ($TMAF \cdot 4H_2O$) in DMF. This quaternary ammonium salt provided almost the same reaction yield as the experiment using TBAF; in this case, the cross-coupling product **5a** was observed in 81% yield. Its main advantage lays in the purification step, in which the quaternary ammonium salts were easily separated from the product by column chromatography. Based on these facts, $TMAF \cdot 4H_2O$ could have become an alternative source of fluoride ions to the more problematic TBAF. It is also important to note that the use of THF as a solvent (Table 1, entry 15) instead of DMF decreased the yield to 40%. This could be explained by the lower solubility of $TMAF \cdot 4H_2O$ in THF.

Monitoring of the reaction progress by NMR revealed, that the addition of hydrated TMAF to the solution of **4** leads to dehydrogenative hydrolysis to silanol **6** (Figure 2). This observation confirms the role of silyl hydride **4** as a masked silanol, as described before for silacyclobutanes[19] as well as for 2-thienyl[20] and 2-pyridyl[21] silanes. This hydrolysis is likely promoted by water present in the TMAF hydrate, as the cross-coupling reactions were otherwise carried out under anhydrous conditions. The *in situ* formation of silanol **6** from **4** was evidenced by upfield shift of the singlet in decoupled ^{29}Si NMR spectra (from −1.42 to −3.40 ppm) and the disappearance of $^{1}J_{Si\text{-}H}$ coupling in the silyl hydride signal in proton-coupled ^{29}Si spectra (Figure 2B). The formation of silanol **6** was also observed in ESI-MS of the reaction mixture after the addition of $TMAF \cdot 4H_2O$ ($[M+Na]^+$ 299.1287).

The addition of 1-iodonaphthalene and $[PdCl(allyl)]_2$ led to the conversion of silanol **6** to the arylated product **5a** overnight, as observed by the decay of the silanol signal at −3.40 ppm in ^{29}Si NMR and corresponding arylation kinetics in ^{1}H NMR (pseudo-first order rate, $k = 1.8 \times 10^{-4}\ s^{-1}$) (Figure 2C, see Supporting Information (chapter S3) for details).

As shown in Table 2, various aromatic partners were tested with 1-diisopropylsilyl-D-glucal **4** under optimized conditions. In general, electron-rich aryl iodides were found to provide better results. Especially, 5-iodo-1,2,3-trimethoxybenzene and 1-benzyloxy-4-iodobenzene provided the expected products (**5b** and **5c**) in excellent yields (89% and 94%). Compared to aromatic iodides, the identical bromides provided lower yields as demonstrated by the yields of products **5a** (81% vs. 51%) and **5b** (89% vs. 54%). Similarly, aryl triflates, which are also commonly used as suitable donors for cross-coupling reactions, are not able to compete with identical iodides as is illustrated by no formation of the product **5a**.

Electron-poor aromatic iodides, such as 1-iodo-4-nitrobenzene and methyl 4-iodobenzoate were also well tolerated substrates and their products **5d** and **5e** were isolated in high

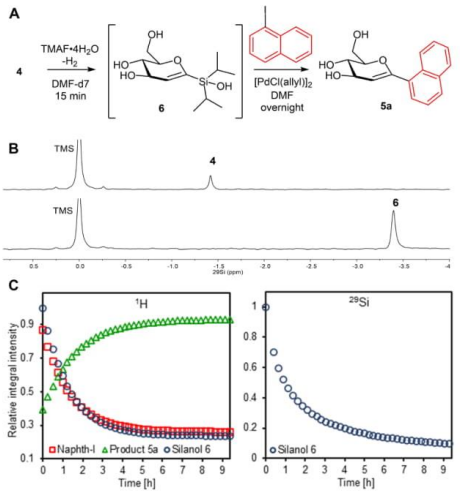
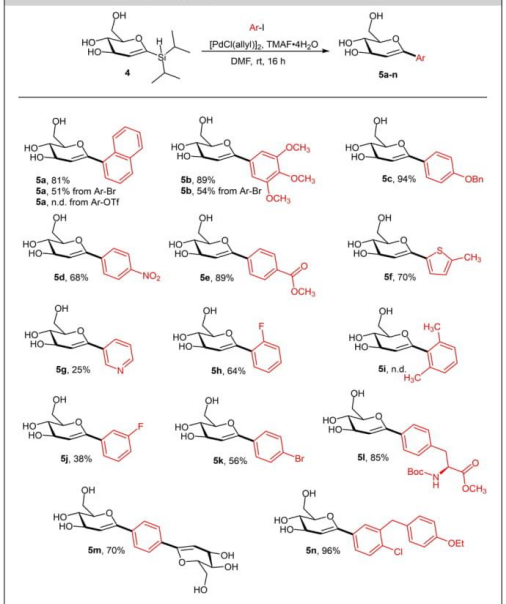


Figure 2. Reaction monitoring by NMR. **A**: Reaction scheme **B**: Decoupled ^{29}Si NMR spectra of **4** before (upper spectrum) and after (lower spectrum) the addition of $TMAF \cdot 4H_2O$ **C**: Kinetics of the arylation step from ^{1}H (left) and ^{29}Si (right) NMR data. Displayed are relative integral intensities after fitting to pseudo-first order kinetic equation.

Table 2. The substrate scope of the Pd-catalysed Hiyama cross-coupling reaction of 1-diisopropylsilyl-D-glucal **4** with different aryl halides.[a]



[a] Reaction conditions: **4** (0.6 mmol, 1.2 equiv.), Aryl-X (0.5 mmol, 1 equiv.), $[PdCl(allyl)]_2$ (2.5 mol%), $TMAF \cdot 4H_2O$ (1.1 mmol, 2.2 equiv.), 25 °C, DMF (5 mL), 16 h. Isolated yields. n.d. = not detected.

Chemistry–A European Journal | Full Paper doi.org/10.1002/chem.202101052 | Chemistry Europe European Chemical Societies Publishing

yields (68% and 89%). Thereafter, we probed whether the *C*-glycosidic bond could be formed with heteroaromatic compounds containing nitrogen or sulfur. The utilisation of 2-iodo-5-methylthiophene provided **5f** in 70% yield. However, the reaction of the starting silylhydride **4** with 3-iodopyridine afforded **5g** in lowered 25% yield. Further study of *ortho*-substituted 1-fluoro-2-iodobenzene with **4** gave the corresponding coupling product **5h** in good 64% yield, whereas bulky 2-iodo-1,3-dimethylbenzene failed to provide any product. To expand the substrate scope, a reaction with *meta*-substituted arene was performed. 1-Fluoro-3-iodobenzene underwent the coupling reaction to give **5j** in 38% yield. Due to the lower reactivity of aryl bromides, we also performed a reaction with 1-bromo-4-iodobenzene. As expected, the reaction resulted in a mixture of mono- and bis-glycosylated products **5k** and **5m**, but the major product **5k** was successfully isolated in 56% yield. Besides, we also wondered whether our method would be suitable for the synthesis of glycopeptides *C*-analogues, as the attachment of saccharide to peptides and proteins is a common post-translational modification. The reaction of **4** with *N*-(*tert*-butoxycarbonyl)-4-iodo-L-phenylalanine methyl ester afforded the glycoconjugate **5l** in a high yield of 85%. Lastly, we showed that 1,4-diiodobenzene can be employed in this transformation with 2.2 equivalents of **4**, affording the bis-glycosylated product **5m** in 70% yield.

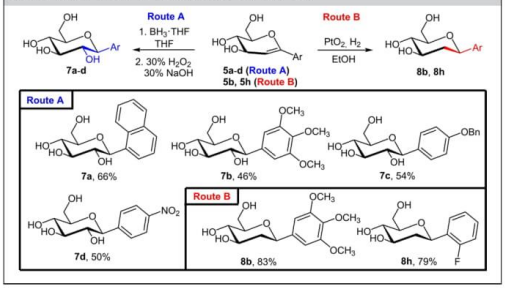
As we published before,[4,9a,15a] the protected unsaturated pseudo-*C*-glycosides are suitable substrates for further stereoselective transformations, which produced α- or β-*C*-glycosides and 2-deoxy-β-*C*-glycosides in high yields. As most of the naturally occurring aryl *C*-glycosides exist with β-configuration at the pseudoanomeric centre, selected unprotected cross-coupling products **5a–d** were directly converted to β-*C*-glucosides **7a–d** (Table 3. Route A).

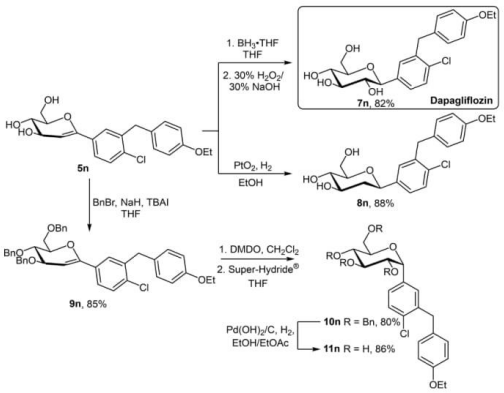
For efficiency reasons, we aimed for a one-pot sequence[9a] of hydroboration followed by oxidation with alkaline hydrogen peroxide. The resulting products **7a–d** were obtained in moderate yields (46–66%) with only β-selectivity. Moreover, the direct transformation of unprotected cross-coupling products to aryl 2-deoxy-β-*C*-glucosides was examined. In this case, the choice of the catalyst played a crucial role in the reactivity. The unprotected pseudo-*C*-glycosides **5b** and **5h** were used as the starting materials. Unfortunately, the hydrogenation of their endocyclic double bonds in the presence of 10% Pd/C in ethanol resulted in a mixture of the expected products and sugar ring-opened product. Due to their very similar R_F values, these products could not be separated. Therefore, several conditions were tested (Pd/C in THF, methanol and ethyl acetate,[10a] $Pd(OH)_2/C$ in ethanol[22] and Pt_2O in ethanol[4]). It turned out that the hydrogenation of the double bond of **5b** and **5h** with Adams' catalyst in ethanol successfully led to the desired aryl 2-deoxy-β-*C*-glucosides **8b** and **8h** in high yields (83% and 79%) (Table 3. Route B). These results might be explained by the coordination of palladium catalysts to endocyclic oxygen and the subsequent reductive sugar-ring opening.

The compatibility with various aromatic electrophiles enabled us to apply this Hiyama coupling reaction to the synthesis of dapagliflozin, a worldwide approved inhibitor for the treatment of type 2 diabetes. The required acceptor for the cross-coupling reaction was prepared via a published three-step synthesis.[23] According to the general procedure, 1-diisopropylsilyl-D-glucal **4** underwent the Hiyama cross-coupling reaction with the prepared 1-chloro-2-(4-ethoxybenzyl)-4-iodobenzene and the desired pseudo-*C*-glycoside **5n** (Table 2) was obtained in excellent 96% yield. For the synthesis of dapagliflozin, **5n** was simply used for hydroboration-oxidation, which resulted in a molecule of dapagliflozin **7n** in 82% isolated yield with exclusive β-anomeric stereoselectivity (Scheme 2). Next, the pseudo-*C*-glycoside **5n** was subjected to catalytic hydrogenation in the presence of Adams' catalyst. As we assumed, the *syn*-addition of hydrogen successfully led to the desired 2-deoxy analogue of dapagliflozin **8n** in 88% yield (Scheme 2).

For completeness, we probed previously published two-step synthetic procedure[15a,24] for the first stereoselective preparation of the α-anomer analogue of dapagliflozin **11n**. Firstly, the pseudo-*C*-glycoside **5n** was benzylated to prevent side reaction of free hydroxyl groups during the oxidation in

Table 3. A. The preparation of aryl β-*C*-glucosides **7a–d. B**. The preparation of aryl 2-deoxy-β-*C*-glucosides **8b** and **8h**.





Scheme 2. The preparation of dapagliflozin **7n** and its analogues **8n** and **11n**.

Chemistry–A European Journal | Full Paper doi.org/10.1002/chem.202101052 | Chemistry Europe European Chemical Societies Publishing

the following step. The benzylation of **5n** with BnBr and NaH in the presence of tetrabutylammonium iodide (TBAI) in THF provided the benzylated derivative **9n** in high 85% yield. The corresponding pseudo-α-anomer **10n** was obtained by the epoxidation of the endocyclic double bond with dimethyldioxirane (DMDO),[25] followed by the subsequent cleavage of the formed epoxide ring with lithium triethylborohydride (Super-Hydride®). The α-*C*-glycoside **10n** was successfully isolated in 80% yield as the only isomer. The final catalytic debenzylation of **10n** in the presence of $Pd(OH)_2$/C furnished a free analogue of dapagliflozin **11n** with α-D-*gluco* configuration. The advantage of using $Pd(OH)_2$/C was that no dehalogenation product was observed and **11n** was obtained in high 86% yield (Scheme 2).

Conclusion

In summary, we have developed a new strategy for the synthesis of (hetero)aryl *C*-glycosides via the Pd-catalysed Hiyama reaction of unprotected 1-diisopropylsilyl-D-glucal **4** with iodo- or bromo- (hetero)arenes under mild conditions. It enables the straightforward synthesis of a variety of (hetero)aryl *C*-glycosides, providing access to products that are otherwise difficult to prepare by known methods and offers a tool for late-stage modifications of drug molecules. We also report a new practical two-step strategy for the synthesis of pharmaceutically important dapagliflozin in the overall yield of 79%. Next, we have verified that our stereoselective procedure is also useful for the preparation of dapagliflozin analogues with 2-deoxy-β-D-*gluco* and α-D-*gluco* configuration in good overall yields (84% and 56%) from 1-diisopropylsilyl-D-glucal **4**.

Experimental Section

General procedure A for Hiyama cross-coupling reaction

$TMAF \cdot 4H_2O$ (2.2 equiv.) was added to a 0.24 M solution of 1-diisopropylsilyl-D-glucal **4** (1.2 equiv.) in anhydrous DMF at room temperature under an argon atmosphere. After 15 min, $[PdCl(allyl)]_2$ catalyst (0.025 equiv.) and the corresponding aryl halide (1 equiv.) were subsequently added, and the reaction mixture was stirred for 16 h. After consumption of the starting material, the reaction mixture was concentrated *in vacuo* and the resulting residue was purified by column chromatography on silica to afford the desired product **5a–n**. In some cases, the obtained compounds were additionally purified by prep-HPLC on Phenomenex (Luna C_{18}) column.

General procedure B for hydroboration-oxidation

To a 0.025 M solution of corresponding coupling product **5a–d** and **5n** (1 equiv.) in anhydrous THF, $BH_3 \cdot THF$ complex solution (1.0 M in THF, 10 equiv.) was added dropwise at 0 °C. The resulting mixture was stirred for 10 min at this temperature and then warmed to room temperature and stirred for next 16 h (overnight). Then the mixture was cooled to 0 °C again and 30% solution of H_2O_2 and 30% solution of NaOH (2 mL, 1:1) were added simultaneously dropwise. After a slow transition to room temperature (approx. 20 min), the reaction mixture was filtered through Celite® and concentrated *in vacuo*. The residue was purified by column chromatography on silica to provide the desired aryl β-*C*-glycoside **7a–d** and **7n**. In some cases, the obtained compounds were additionally purified prep-HPLC on Phenomenex (Luna C_{18}) column.

General procedure C for hydrogenation

To a 0.016 M solution of corresponding coupling products **5b**, **5h**, and **5n** (1 equiv.) in ethanol PtO_2 (0.05 mmol, 0.5 equiv.) was added. The resulting mixture was stirred for 40 min under a hydrogen atmosphere for 2 h. The mixture was filtered through Celite® and concentrated *in vacuo*. The residue was purified by column chromatography on silica to provide the desired aryl 2-deoxy-β-*C*-glycosides **8b**, **8h**, and **8n**.

Acknowledgements

This work was financially supported from specific university research (grant No. A1_FPBT_2021_002). We also appreciate the support from Gilead Sciences, Inc., provided under the program 'Molecules for Life' at the Gilead Sciences & IOCB Prague Research Centre.

Conflict of Interest

The authors declare no conflict of interest.

Keywords: aryl *C*-glycosides · cross-coupling · dapagliflozin · Hiyama reaction · protecting-group-free

[1] K. Kitamura, Y. Ando, T. Matsumoto, K. Suzuki, *Chem. Rev.* **2018**, *118*, 1495–1598.
[2] a) E. De Clercq, *J. Med. Chem.* **2016**, *59*, 2301–2311; b) D. S. Hsia, O. Grove, W. T. Cefalu, *Curr. Opin. Endocrinol. Diabetes Obes.* **2017**, *24*, 73–79.
[3] S. E. Denmark, C. S. Regens, T. Kobayashi, *J. Am. Chem. Soc.* **2007**, *129*, 2774–2776.
[4] K. Parkan, R. Pohl, M. Kotora, *Chem. Eur. J.* **2014**, *20*, 4414–4419.
[5] A. K. Ghosh, A. M. Veitschegger, S. Nie, N. Relitti, A. J. MacRae, M. S. Jurica, *J. Org. Chem.* **2018**, *83*, 5187–5198.
[6] T. C. Ho, H. Kamimura, K. Ohmori, K. Suzuki, *Org. Lett.* **2016**, *18*, 4488–4490.
[7] A. R. Aguillón, A. Mascarello, N. D. Segretti, H. F. Z. de Azevedo, C. R. W. Guimaraes, L. S. M. Miranda, R. O. M. A. de Souza, *Org. Process Res. Dev.* **2018**, *22*, 467–488.
[8] a) K. W. Wellington, S. A. Benner, *Nucleosides Nucleotides Nucleic Acids* **2006**, *25*, 1309–1333; b) F. Otte, B. Schmidt, *J. Org. Chem.* **2019**, *84*, 14816–14829.
[9] a) J. Choutka, R. Pohl, K. Parkan, *ACS Omega* **2018**, *3*, 7875–7887; b) E. Dubois, J.-M. Beau, *Carbohydr. Res.* **1992**, *228*, 103–120.
[10] a) L. Gong, H.-B. Sun, L.-F. Deng, X. Zhang, J. Liu, S. Yang, D. Niu, *J. Am. Chem. Soc.* **2019**, *141*, 7680–7686; b) R. W. Friesen, R. W. Loo, *J. Org. Chem.* **1991**, *56*, 4821–4823.
[11] M. A. Tius, X. Q. Gu, J. Gomez-Galeno, *J. Am. Chem. Soc.* **1990**, *112*, 8188–8189.
[12] S. E. Denmark, T. Kobayashi, C. S. Regens, *Tetrahedron* **2010**, *66*, 4745–4759.
[13] F. Zhu, J. Rodriguez, T. Yang, I. Kevlishvili, E. Miller, D. Yi, S. O'Neill, M. J. Rourke, P. Liu, M. A. Walczak, *J. Am. Chem. Soc.* **2017**, *139*, 17908–17922.
[14] K. H. Shaughnessy, *Molecules* **2015**, *20*, 9419–9454.

Chemistry–A European Journal | Full Paper doi.org/10.1002/chem.202101052 | Chemistry Europe European Chemical Societies Publishing

[15] a) B. Oroszova, J. Choutka, R. Pohl, K. Parkan, *Chem. Eur. J.* **2015**, *21*, 7043–7047; b) I. Snajdr, K. Parkan, F. Hessler, M. Kotora, *Beilstein J. Org. Chem.* **2015**, *11*, 1392–1397.
[16] a) F. Foubelo, C. Nájera, M. Yus, *Chem. Rec.* **2016**, *16*, 2521–2533; b) S. E. Denmark, L. Neuville, *Org. Lett.* **2000**, *2*, 3221–3224.
[17] D. J. Sam, H. E. Simmons, *J. Am. Chem. Soc.* **1974**, *96*, 2252–2253.
[18] I. Fleming, J. A. Langley, *J. Chem. Soc. Perkin Trans. 1* **1981**, 1421–1423.
[19] S. E. Denmark, D. Wehrli, J. Y. Choi, *Org. Lett.* **2000**, *2*, 2491–2494.
[20] K. Hosoi, K. Nozaki, T. Hiyama, *Proc. Jpn. Acad. Ser. B* **2002**, *78*, 154–160.
[21] K. Itami, T. Nokami, Y. Ishimura, K. Mitsudo, T. Kamei, J.-i. Yoshida, *J. Am. Chem. Soc.* **2001**, *123*, 11577–11585.
[22] B. Oroszova, J. Choutka, R. Pohl, K. Parkan, *Chem. Eur. J.* **2015**, *21*, 7043–7047.
[23] S. Hu, W. Sun, Y. Wang, H. Yan, *Med. Chem. Res.* **2019**, *28*, 465–472.
[24] D. C. Koester, M. Leibeling, R. Neufeld, D. B. Werz, *Org. Lett.* **2010**, *12*, 3934–3937.
[25] H. Mikula, D. Svatunek, D. Lumpi, F. Glöcklhofer, C. Hametner, J. Fröhlich, *Org. Process Res. Dev.* **2013**, *17*, 313–316.

Manuscript received: March 23, 2021
Accepted manuscript online: May 28, 2021
Version of record online: ■■, ■■