EurJOC
European Journal of Organic Chemistry

A Journal of
ChemPubSoc Europe

Accepted Article

Title: Synthesis of carba-cyclophellitols: a new class of carbohydrate mimetics

Authors: Thomas J.M. Beenakker, Dennis P.A. Wander, Jeroen D.C. Codee, Johannes M.F.G. Aerts, Gijsbert A. van der Marel, and Hermen S. Overkleeft

To be cited as: *Eur. J. Org. Chem.* 10.1002/ejoc.201701601

Link to VoR: http://dx.doi.org/10.1002/ejoc.201701601

Supported by
ACES Asian Chemical Editorial Society

WILEY-VCH

Synthesis of carba-cyclophellitols: a new class of carbohydrate mimetics

Thomas J. M. Beenakker,[a][‡] Dennis P. A. Wander,[a][‡] Jeroen D. C. Codée,[a] Johannes M. F. G. Aerts,[b] Gijsbert A. van der Marel,[a] and Herman S. Overkleeft*[a]

Abstract: Cyclophellitol and cyclophellitol aziridine are potent and irreversible retaining β-glucosidase inhibitors. They preferentially adopt a $^4H_3$ half-chair conformation, thereby mimicking the transition state conformation that characterizes retaining β-glucosidase-mediated substrate processing. As a consequence, both compounds bind tightly to the enzyme active site, after which attack of the catalytic nucleophile onto the epoxide/aziridine results in enzyme deactivation. Substitution of the epoxide oxygen in cyclophellitol for (substituted) carbon yielded carba-cyclophellitols as a conceptually new class of retaining β-glucosidase inhibitors, as we demonstrated in a recent communication. Here, in-depth synthesis studies towards this class of compounds are described, and the preparation of a comprehensive set of structurally and configurationally new carba-cyclophellitols is presented.

Introduction

Cyclophellitol (**1**, Figure 1), isolated in 1990 from the mushroom *Phellinus* sp., is a potent mechanism-based covalent retaining β-glucosidase inhibitor.[1] Following protonation of the epoxide oxygen by the acid-base catalyst residing within β-glucosidase active sites and subsequent S_N2 displacement by the active site nucleophile, a covalent enzyme-inhibitor adduct is formed.[2,3] This adduct is stable over time, leading to irreversible retaining β-glucosidase inhibition. Cyclophellitol aziridine (**2**), the cyclophellitol analogue in which the epoxide oxygen in cyclophellitol (**1**) is substituted by nitrogen, proved to inhibit retaining β-glucosidases covalently and irreversibly as well.[4] Structural studies have revealed that cyclophellitol and cyclophellitol aziridine employ a similar mode of action.

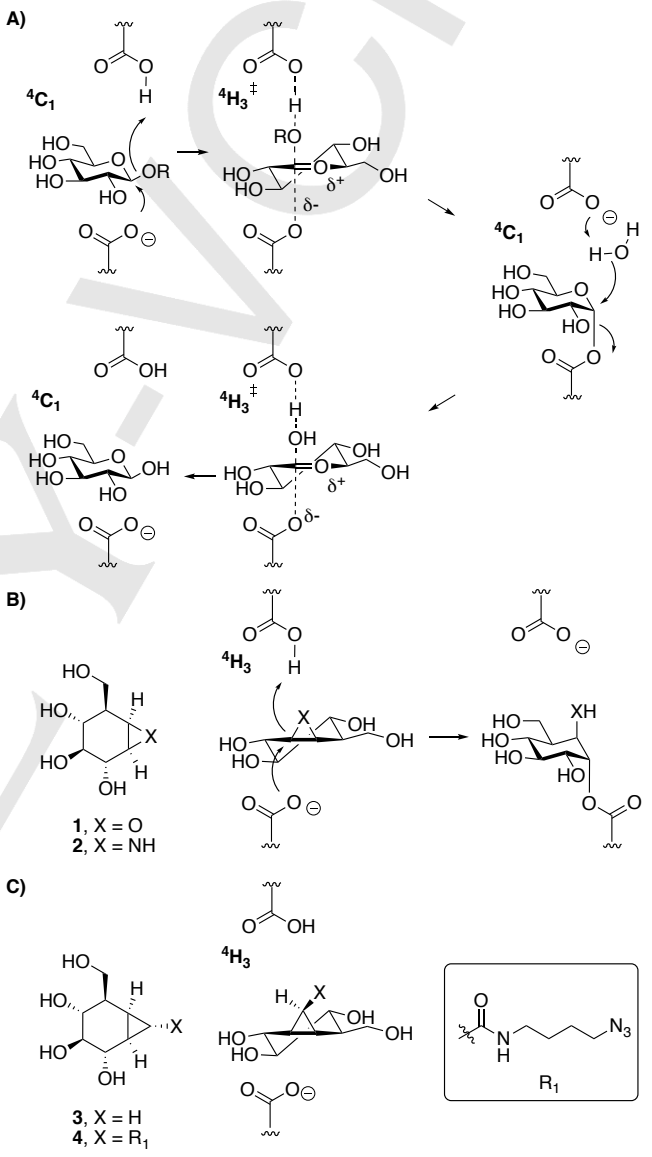


Figure 1. A) Proposed mechanism of retaining β-glucosidases.[5] B) Cyclophellitol (**1**) and cyclophellitol aziridine (**2**) inhibit retaining β-glucosidases covalently by initial binding in $^4H_3$ conformation, followed by S_N2 displacement of the (protonated) epoxide-oxygen or aziridine-nitrogen. C) Structure of carba-cyclophellitols **3** and **4**. Carba-cyclophellitol **4** is a potent competitive inhibitor of retaining β-glucosidases and binds to the active site in a $^4H_3$ conformation.[6]

Cyclophellitol and cyclophellitol aziridine are configurational analogues of β-glucopyranosides, the substrates of retaining β-glucosidases, but their conformational behavior is different. Whereas β-glucopyranoses preferably adopt a $^4C_1$ conformation,

[a] T. J. M. Beenakker, D. P. A. Wander, J. D. C. Codée, G. A. van der Marel, H. S. Overkleeft
Department of Bio-Organic Synthesis
Leiden Institute of Chemistry, Leiden University
Einsteinweg 55, 2300 RA Leiden, The Netherlands
E-Mail: h.s.overkleeft@lic.leidenuniv.nl
[b] J. M. F. G. Aerts
Department of Medical Biochemistry
Leiden Institute of Chemistry, Leiden University
Einsteinweg 55, 2300 RA Leiden, The Netherlands
[‡] T.J.M. Beenakker and D.P.A. Wander contributed equally to this work.

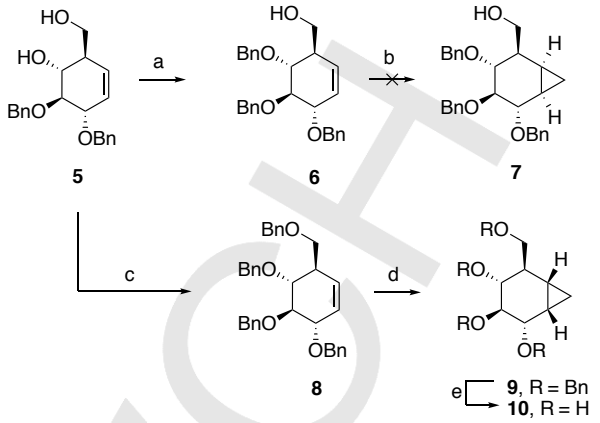
Supporting information for this article is given via a link at the end of the document.

the epoxide annulation in **1** (and aziridine annulation in **2**) enforces a preferred $^4H_3$ half-chair conformation onto the cyclitol moiety. A similar half-chair conformation[5] is thought to occur during hydrolysis of β-glucosidic linkages as effected by retaining β-glucosidases (Figure 1A) and for this reason, cyclophellitol and cyclophellitol aziridine are thought to bind well within β-glucosidase active sites (Figure 1B). This mode of action of cyclophellitol and cyclophellitol aziridine led us to postulate that configurational isomeric compounds that would adopt the $^4H_3$ half-chair conformation but would not present an electrophile to the retaining β-glucosidase active site nucleophile, would act as competitive inhibitors. Substitution of the cyclophellitol epoxide-oxygen for carbon, as in carba-cyclophellitol **3**, and attachment of an azidoacyl chain (**3** to **4**) indeed yielded a remarkably effective competitive retaining β-glucosidase inhibitor (8.20 nM, *Thermotoga maritima Tm*GH1[6]) (Figure 1C). Emboldened by these initial results, and realizing that in fact carba-cyclophellitols represent a conceptually new class of glycosidase inhibitors, and also carbohydrate mimetics, we decided to investigate broadening the scope of these class of compounds, starting with investigating their synthetic accessibility. Here, we report on our in-depth synthesis and structural analysis studies on carba-cyclophellitols. This work, besides reporting details on the synthesis of carba-cyclophellitol **4** and some β-glucopyranose-configured isosters, also presents the synthesis of their α-congeners as well as a set of α- and β-galactopyranose-configured carba-cyclophellitols.

Results and Discussion

In designing a library for this new class of compounds, we envisioned to include a variety of substituents onto the carba-cyclophellitol core, varying the electron density on the cyclopropane ring, steric factors, as well as hydrogen-bonding capability. For this reason, we selected the ketone, hydroxymethyl, hydroxymethyl-ethyl ether and carboxamide functional groups. The latter was appended with an azido-alkyl tail to allow for further functionalization through click-chemistry.

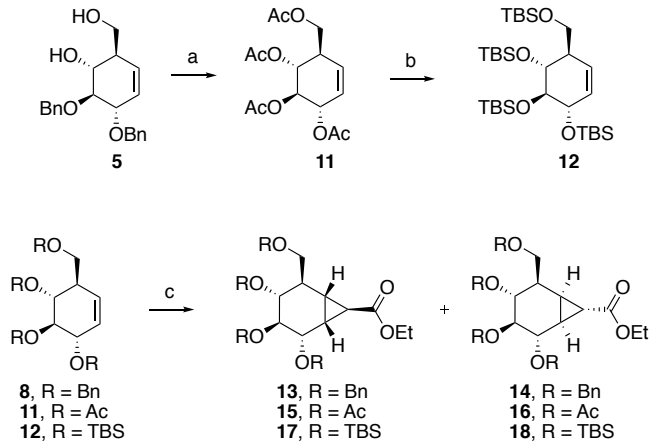
Hashimoto and co-workers[7] were the first to report on the synthesis of carba-cyclophellitols, specifically carba-cyclophellitols **3** and **10**. The key step in their synthesis procedure entails a Simmons-Smith cyclopropanation (Et_2Zn, CH_2I_2 in DCM) on partially benzylated cyclohexene **6** (prepared through standard protecting group manipulations from diol **5**). The β-product was reported to emerge as the predominant isomer when adding DME and MeOH to the standard conditions. In our hands, however, this did not lead to any conversion of the cyclohexene. Application of the reported α-selective conditions (DME and $BF_3{\cdot}OEt_2$ as additives) on the fully benzylated cyclohexene **8** did give us the fully benzylated α-carba-cyclophellitol **9**. This was then debenzylated under palladium-catalyzed hydrogenolysis, followed by acetylation and de-acetylation to finally give α-carba-cyclophellitol **10**.



Scheme 1. Reagents and conditions: a) (*i*) TBS-Cl, imidazole, DMF, rt, 1 h (*ii*) BnBr, NaH, TBAI, DMF, 0 °C to rt, overnight, (*iii*) TBAF, THF, rt, 2 h, 83% over 3 steps; b) Et_2Zn, CH_2I_2, 1,2-dimethoxyethane, MeOH, CH_2Cl_2, rt; c) BnBr, NaH, TBAI, DMF, 0 °C to rt, overnight, 94%; d) Et_2Zn, CH_2I_2, 1,2-dimethoxyethane, boron trifluoride diethyl etherate, CH_2Cl_2, rt, 3 h, 46%; e) (*i*) Pd/C, H_2, MeOH, rt, overnight, (*ii*) Ac_2O, pyridine, rt, 48 h; (*iii*) NaOMe, MeOH, rt, 2 h, 66% over three steps.

We then turned our attention to ethyl diazoacetate (EDA)[10,11] as the cyclopropanating agent for the synthesis of functionalized carba-cyclophellitols, employing perbenzylated cyclohexene **8** as the substrate. When the conditions developed for cyclopropanation of glucals with $Rh_2(OAc)_4$ as catalyst[12-14] were applied to **8**, only trace amounts of cyclopropanes **15** and **16** were formed, as detected by TLC-MS analysis of the reaction mixture. Instead, several other products with higher molecular masses were detected, corresponding to additional molecules of EDA having reacted with cyclohexene **8**, as compared to the desired product. We concluded this to be the result of Büchner-type ring expansion[15,16], in which the benzyl ethers in **8** have reacted with EDA.[17]

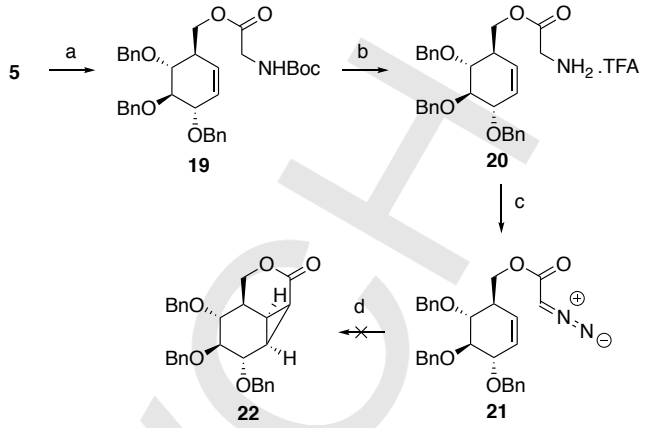
Based on these initial discouraging results we conducted a comparative study in which a number of transition metal cyclopropanation catalysts that employ EDA as the cyclopropanylating agents were compared side-by-side (Scheme 2). $Rh_2(OAc)_4$, $Cu(acac)_2$ and $Pd(OAc)_2$[18] are oft-used catalysts for EDA-mediated cyclopropanation of various substrates[19-21], and were employed in this study. Bearing in mind the electrophilic character of copper and rhodium carbenes[22], the influence of the electron density of the alkene was studied by comparing peracetyl-cyclohexene **13**, per-*tert*-butyldimethylsilyl-cyclohexene **14** (which were prepared by means of standard protective group manipulations from **11** – see Scheme 2) and perbenzyl-cyclohexene **8**.



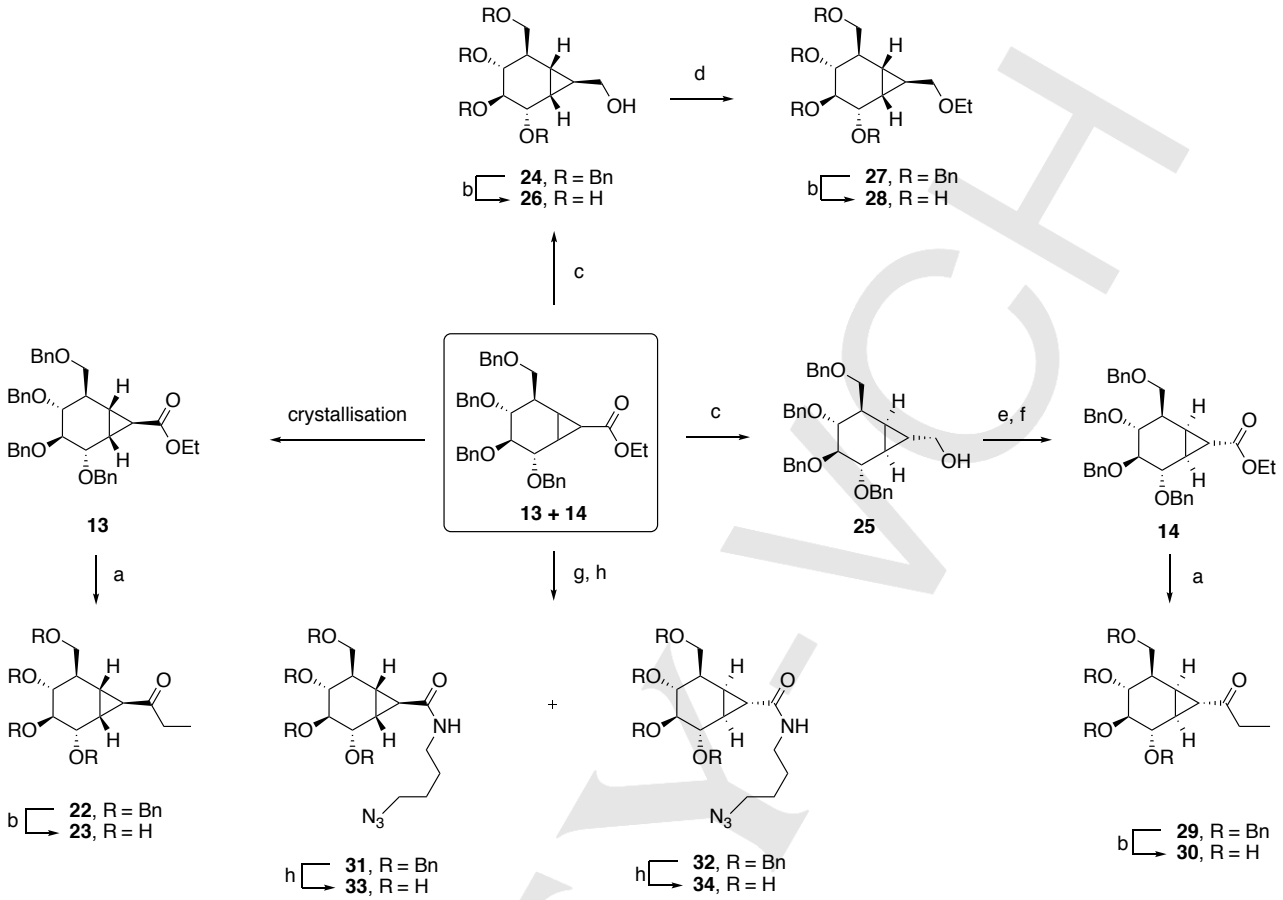
Scheme 2. Reaction conditions: a) (*i*) Li (s), NH_3 (l), THF, -60 °C, 35 min, (*ii*) Ac_2O, pyridine, rt, overnight, 79% over two steps; b) (*i*) NaOMe, MeOH, rt, overnight, (*ii*) TBS-Cl, imidazole, DMF, rt to reflux temperature, 7 days, 35% over 2 steps; c) to 0.1 mmol of substrate (**8**, **11** or **12**) and 5 mol% of ($Rh(OAc)_2$, $Cu(acac)_2$ or $Pd(OAc)_2$) in DCE (200 µL) at reflux was added EDA (0.3 mmol) in DCE (150 µL) over 6 h.

The combination of $Cu(acac)_2$ as catalyst and tetra-*O*-benzyl-cyclohexene **8** as substrate was optimal based on TLC-MS analysis, even though, in contrast to compounds **11** and **12**, cyclohexene **8** can undergo the aforementioned Büchner-type reactions. Minimizing such side reactions is best achieved when EDA is added over time to a mixture of **8** and the copper(II) catalyst in ethyl acetate. Upon TLC-MS detection of Büchner-type adducts, the reaction mixture is then concentrated, the desired product isolated, the side products removed and the remainder of starting material reused. In this manner and over two reaction cycles, compounds **13** and **14** were obtained as a mixture (2:1 α:β, both *exo* only) in 35% yield. Formation of the *endo*-cyclopropanes was not observed, as these place the largest cyclopropane substituent over/under the carbacycle ring.

An alternative strategy towards bicyclic constructs we investigated invokes an *intra*-molecular cyclopropanation strategy (Scheme 3). This would entail an intramolecular tether to deliver the carbene to the beta-face of the alkene, to yield a lactone derivative of the carba-cyclophellitol.
For this purpose, alcohol **5** (derived from cyclohexene **7**[8,9] through standard protecting group manipulations) was condensed with *N*-Boc-glycine to obtain **19**. Treatment with TFA gave amine **20**, which was subsequently subjected to biphasic diazotization to give diazoester **21**. Following literature precedents regarding similar intramolecular cyclopropanation by Corey's group[23,24], we attempted the cyclisation catalyzed by their condition of Cu(II)(*N-tert*-butylsalicylaldiminato)$_2$ in toluene or our previously used condition of $Cu(acac)_2$ in EtOAc. However, the major identified product proved to be that of carbene dimerization. The desired product **23** could not be detected (TLC, LC/MS) in these experiments.



Scheme 3. Reagents and conditions: a) *N*-Boc-glycine, DIC, DMAP, rt, overnight, quant.; b) TFA, CH_2Cl_2, rt, 45 min, quant.; c) $NaNO_2$, monosodium citrate, CH_2Br_2, H_2O, 0 °C, 1 h, 99%; d) $Cu(acac)_2$ or Cu(*N-tert*-butylsalicylaldiminato)$_2$, toluene, EtOAc or DCE, reflux.



Scheme 4. Reagents and conditions: a) *N,O*-dimethylhydroxylamine hydrochloride, EtMgBr, THF, -5 °C, then EtMgBr, THF, rt, overnight, 56% for **15**, 45% for **22**; b) $Pd(OH)_2/C$, H_2, MeOH, rt, overnight, **23** (96%), **26** (90%), **28** (94%), **30** (58%); c) DIBAL, THF, 30 min at 0 °C and then 1 h at rt, (41%, 2:1 **24** and **25**); d) EtBr, NaH, TBAI, DMF, 0 °C to rt, 4 h, 59%; e) Jones reagent, acetone, 0 °C, 3 h, 53%; f) EtOH, *N,N'*-diisopropylcarbodiimide, 4-dimethylaminopyridine, toluene, rt, 4 h, 62%; g) (*i*) LiOH, THF, MeOH, H_2O, rt, overnight, 82%; (*ii*) 1-azido-4-aminobutane, HCTU, DIPEA, DCM, rt, overnight, 78%; h) BCl_3, DCM, -78°C, 5h, **33** (88%), **34** (99%).

We then explored the versatility of carba-cyclophellitol esters **13** and **14** (Scheme 2) as intermediates for further elaboration (Scheme 4). Separation of the stereoisomers **13** and **14** by silica gel column chromatography or HPLC was not successful. Crystallization of the mixture of compounds from ethanol, however, resulted in isolation of the pure α-*endo* ester **13**.

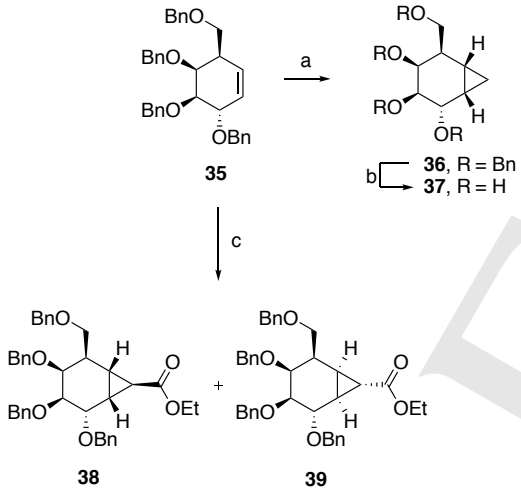
Having this versatile functionalized carba-cyclophellitol construct in hand, the ester was converted into ketone **22**. This was accomplished through direct Weinreb amide formation from the ester, using ethylmagnesium bromide as the base at low temperature, followed by Grignard addition at room temperature. Subsequently, it was subjected to palladium-catalyzed hydrogenolysis in MeOH to obtain compound **23**.

Upon diisobutylaluminum hydride (DIBAL-H)-mediated reduction of the mixture of esters **13** and **14**[25], alcohols **24** and **25** were obtained and could be carefully separated by column chromatography. Subjection of alcohol **24** to palladium-catalyzed hydrogenolysis in MeOH gave compound **26**. Ether **28** was obtained by alkylation of alcohol **24** with ethyl bromide followed by global debenzylation.

Pure β-*exo* alcohol **25** was then used to provide pure ester **14** for further transformations. To this end, **25** was oxidized using aqueous sodium dichromate-sulfuric acid (Jones reagent) and esterified to give enantiopure **14**. Then, conversion into the corresponding ketone, as described for its diastereomer, followed by debenzylation gave **30**.

Finally, we prepared the carba-cyclophellitol carboxamides. Upon saponification of the mixture of **13** and **14** we obtained the corresponding carboxylic acids, which were subsequently condensed with 1-azido-4-aminobutane[26]. This resulted into a mixture of **31** and **32**, which were separated by means of HPLC. The thus purified compounds were treated with BCl_3 in dichloromethane to afford **33** and **34**, respectively.

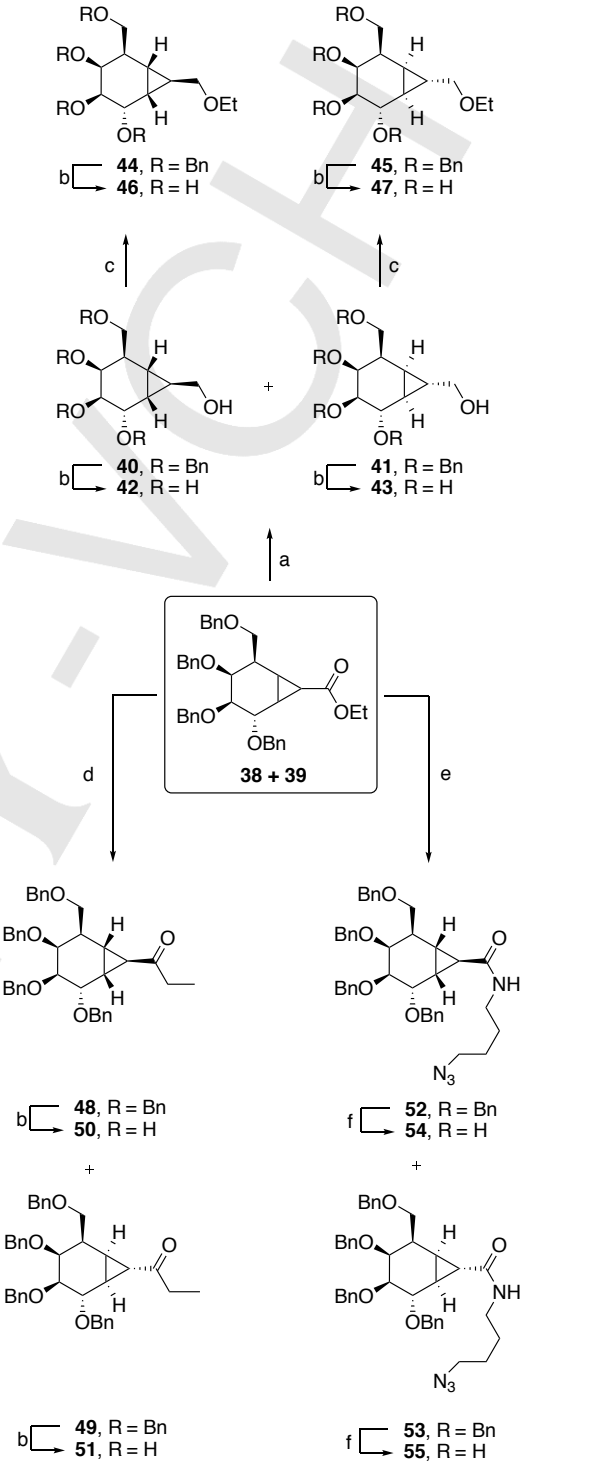
As the next research objective, we set out to investigate whether the synthesis strategies we identified for the construction of glucopyranose-configured cyclophellitol cyclopropanes could also be applied for the construction of some *galacto*pyranose-configured isosters, as potential inhibitors for α- and β galactosidases. For this purpose, galacto-configured cyclohexene **35** was synthesized in large quantities following our previously reported strategy[27], which was based on chemistry developed by Llebaria and co-workers.[28] Simmons-Smith cyclopropanation of this cyclohexene as described for its diastereomer afforded α-cyclopropane **37** after global debenzylation (Scheme 5).



Scheme 5. Reagents and conditions: a) 1,2-dimethoxyethane, boron trifluoride diethyl etherate, Et_2Zn, CH_2I_2, CH_2Cl_2, 84%; b) $Pd(OH)_2/C$, H_2, MeOH, (99%); c) EDA, $Cu(acac)_2$, EtOAc, **38** and **39** (2:1, 29%).

The optimized conditions for EDA-mediated cyclopropanation of **8** as described before were applied to cyclohexene **35**, yielding **38** and **39** after a single cyclopropanation cycle as an inseparable mixture (29%, 2:1 α:β, both *exo* only).

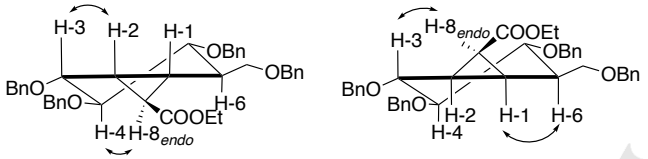
DIBAL-mediated reduction of a mixture of esters **38** and **39** provided alcohols **40** and **41** (Scheme 6), which could now be separated by silica gel column chromatography. Palladium-catalyzed hydrogenolysis of these alcohols resulted in compound **42** and **43**, respectively. The free alcohols in **40** and **41** were alkylated with ethyl bromide to afford ethers **44** and **45** after debenzylation.



Scheme 6. Reagents and conditions: a) DIBAL, CH_2Cl_2, **40** (40%) and **41** (36%); b) Pd/C, H_2, MeOH, rt, overnight, **42** (quant.), **43** (quant.), **46** (87%), **47** (quant.), **50** (80%), **51** (88%); c) EtBr, NaH, TBAI, DMF, 0 °C to rt, **44** (80%) **45** (74%); d) *N,O*-dimethylhydroxylamine hydrochloride, EtMgBr, THF, -8 °C to rt, overnight, **48** (16%) and **49** (21%); e) (*i*) LiOH, THF, EtOH, H_2O, rt, overnight; (*ii*) 1-azido-4-aminobutane, HCTU, DIPEA, DCM, rt, overnight, **52** (24%) and **53** (18%); f) BCl_3, DCM, **54** (quant.), **55** (70%).

A mixture of esters **38** and **39** was converted into their corresponding ketones **48** and **49** according to the previously described Weinreb conditions and subsequently separated by HPLC. Deprotection by palladium-catalyzed hydrogenation then gave compounds **50** and **51.** Finally, a mixture of **38** and **39** was saponified and condensed with 1-azido-4-aminobutane. The obtained mixture of amides was separated by HPLC to afford **54** and **55** after BCl_3 treatment.

The configuration of the obtained carba-cyclophellitol products was determined by Nuclear Overhauser Effect SpectroscopY (NOESY), as exemplified for compounds **13** and **14** (Figure 2). Spatial couplings between H-1 and H-3, and between H-4 and H-8 were observed in compound **13**. The observed couplings through space in compound **14**, the β-isomer of **13**, are between H-1 and H-6, and between H-3 and H-8. These observations were consistent throughout the series of compounds reported herein, and further NOESY data for the final compounds can be found in the Supporting Information.



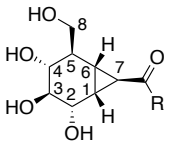
13 **14**

Figure 2. Configuration determination by spatial couplings of Nuclear Overhauser Effect spectroscopY (NOESY) experiments allowed the assignment of the absolute configuration of compounds **13** and **14**.

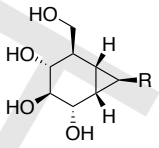
Conclusion

In this work, we reveal in full detail the synthesis of a new class of carbohydrate mimetics: cyclophellitol cyclopropanes (see Figure 3 for a full list of the structures prepared here). We believe such compounds to be of interest as potential inhibitors of glycoprocessing enzymes, but also as glycomimetics in general, and we observe that those carboxylate-containing analogues allow for oligomerization as we and others have shown in the past for another class of glycomimetics: sugar amino acids.[29] Thus, our cyclophellitol cyclopropanes represent yet another addition to the rich and ever-growing, densely functionalized molecules one can derive from nature's most diverse class of compounds: carbohydrates.

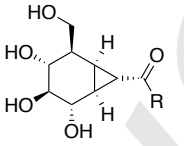
D-glucopyranose-configured carba-cyclophellitols



23, R = CH_2CH_3
33, R = $NH(CH_2)_4N_3$

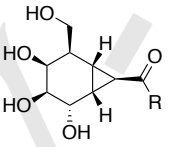


10, R = H
26, R = CH_2OH
28, R = $CH_2OCH_2CH_3$

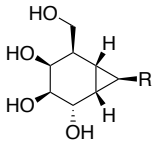


30, R = CH_2CH_3
34, R = $NH(CH_2)_4N_3$

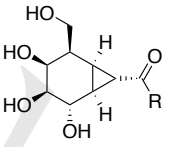
D-galactopyranose-configured carba-cyclophellitols



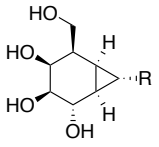
50, R = CH_2CH_3
54, R = $NH(CH_2)_4N_3$



37, R = H
42, R = CH_2OH
46, R = $CH_2OCH_2CH_3$



51, R = CH_2CH_3
55, R = $NH(CH_2)_4N_3$



43, R = CH_2OH
47, R = $CH_2OCH_2CH_3$

Figure 3. Structures of the carba-cyclophellitols that are described in the here presented synthetic studies.

Experimental Section

General: All chemicals were purchased from Acros, Sigma Aldrich, Biosolve, VWR, Fluka, Merck and Fisher Scientific and used as received unless stated otherwise. *N*,*N*-Dimethylformamide (DMF) and toluene were stored over flame-dried 4 Å molecular sieves before use. Traces of water from reagents were removed by co-evaporation with toluene in reactions that require anhydrous conditions. All moisture and/or oxygen sensitive reactions were performed under inert atmosphere. TLC analysis was conducted using Merck aluminium sheets (Silica gel 60 F_{254}) with detection by UV absorption (254 nm), by spraying with a solution of $(NH_4)_6Mo_7O_{24}{\cdot}4H_2O$ (25 g/L) and $(NH_4)_4Ce(SO_4)_4{\cdot}2H_2O$ (10 g/L) in 10% sulfuric acid or a solution of $KMnO_4$ (20 g/L) and K_2CO_3 (10 g/L) in water, followed by charring at ~150 ˚C. Column chromatography was performed using Screening Device BV Silica Gel (particle size of 40 – 63 µm, pore diameter of 60 Å) in the indicated solvent systems. For reversed-phase HPLC purifications, an Agilent Technologies 1200 series instrument equipped with a semi-prep column (Gemini C18, 250 x 10 mm, 5 µm particle size, Phenomenex) was used. LC/MS analysis was performed on a Surveyor HPLC system (Thermo Finnigan) equipped with a C_{18} column (Gemini, 4.6 mm x 50 mm, 5 µm particle size, Phenomenex), coupled to a LCQ Advantage Max (Thermo Finnigan) ion-trap spectrometer (ESI^+). The applied buffers were H_2O, MeCN and 1% aqueous TFA. ^1H NMR and ^{13}C NMR spectra were recorded on a Brüker AV-400 (400 and 101 MHz respectively), a Brüker DMX-600 (600 and 151 MHz respectively) or a Bruker AV-850 (850 and 214 MHz respectively) spectrometer in the given solvent. Chemical shifts are given in ppm (δ) relative to the residual solvent peak or to tetramethylsilane (0 ppm) as internal standard. Coupling constants are given in Hz. High-resolution mass spectrometry (HRMS) analysis was performed with a LTQ Orbitrap mass spectrometer (Thermo Finnigan), equipped with an electronspray ion source in positive mode (source voltage 3.5 kV, sheath gas flow 10 mL/min, capillary temperature 250 °C) with resolution R = 60000 at m/z 400 (mass range m/z = 150 – 2000) and dioctyl phthalate (m/z = 391.28428) as a "lock mass". The high-resolution mass spectrometer was calibrated prior to measurements with a calibration mixture (Thermo Finnigan).

General procedure for global debenzylation
To a solution of the benzyl ether in MeOH was added a catalytic amount of 10% Pd on carbon or $Pd(OH)_2$ on carbon. The reaction vessel was purged with hydrogen gas and the mixture was vigorously stirred overnight. After TLC analysis showed full conversion to a lower running spot, the palladium catalyst was filtered off over a pad of Celite, followed by concentration *in vacuo*, which gave the corresponding product.

(1*R*,2*R*,5*S*,6*S*)-5,6-bis(benzyloxy)-2-(((*tert*-butyldimethylsilyl)oxy) methyl)cyclohex-3-en-1-ol (6)
Diol **5** (0.558 g, 1.64 mmol) was dissolved in DMF (8.2 mL), after which TBS-Cl (0.271 g, 1.80 mmol, 1.1 eq.) and imidazole (0.279 g, 4.10 mmol, 2.5 eq.) were added. The reaction mixture was stirred at room temperature for 1 h and was then partitioned between Et_2O (40 mL) and H_2O (40 mL). The organic layer was separated, washed with H_2O (2x), dried over $MgSO_4$, filtered and concentrated *in vacuo* to give the crude silyl ether, which was continued without further purification. HRMS: calculated for $[C_{27}H_{39}O_4Si]^+$ 455.26121, found 455.26129.

This was then dissolved in DMF (8.0 mL) at 0 °C, after which TBAI (catalytic amount), BnBr (0.23 mL, 1.97 mmol, 1.2 eq.) and NaH (60% dispersion in mineral oil, 79.2 mg, 1.98 mmol, 1.21 eq.) were added. After stirring at room temperature overnight, the reaction mixture was concentrated *in vacuo* and partitioned between Et_2O (25 mL) and H_2O (25 mL). The organic layer was washed with H_2O (3x) and the resulting aqueous layers were extracted with Et_2O. The combined organic layers were dried over $MgSO_4$, filtered and concentrated *in vacuo* to give the crude fully protected cyclohexene, which was continued without further purification. HRMS: calculated for $[C_{34}H_{44}O_4SiNa]^+$ 567.29011, found 567.28989.

This was was then dissolved in THF (8.2 mL), after which TBAF (1 M in THF, 9.8 mL, 9.8 mmol, 6.0 eq.) was added. After the mixture was stirred at room temperature for 2 h, it was quenched with 4 drops of H_2O and concentrated *in vacuo*. Purification by column chromatography (30% EtOAc in pentane → 50% EtOAc in pentane) gave title compound **6** as a yellow oil (0.585 g, 1.36 mmol, 83% over 3 steps). ^1H NMR (400 MHz, $CDCl_3$): δ (ppm) 7.45 – 7.07 (m, 15H, H_{arom}Bn), 5.72 (dt, *J* = 10.0, 3.0 Hz, 1H, H1/6), 5.53 (dt, *J* = 10.2, 2.6 Hz, 1H, H1/6), 5.03 – 4.84 (m, 3H, CH_2Bn), 4.74 – 4.57 (m, 3H, CH_2Bn), 4.28 – 4.17 (m, 1H, H-3), 3.83 (dd, *J* = 10.6, 7.4 Hz, 1H, H-2), 3.68 – 3.50 (m, 3H, H-4 and H-7), 2.46 (ddd, *J* = 14.3, 7.4, 3.7 Hz, 1H, H-5). ^{13}C NMR (100 MHz, $CDCl_3$: δ (ppm) 138.8, 138.5, 138.4 (4 x C_q Bn), 128.6, 128.5, 128.5, 128.4, 128.3, 128.0, 128.0, 127.9, 127.7, 127.7 (CH_{arom}, C-1 and C-6), 85.2 (C-3), 80.8 (C-2), 78.7 (C-4), 75.3, 75.2, 72.1 (3 x CH_2 Bn), 63.1 (H-7), 45.8 (H-5). HRMS: calculated for $[C_{28}H_{31}O_4]^+$ 431.22169, found 431.22174.

((((1*R*,2*R*,3*S*,6*R*)-6-((benzyloxy)methyl)cyclohex-4-ene-1,2,3-triyl)tris (oxy))tris(methylene)) tribenzene (8)
Diol **7** (2.21 g, 6.50 mmol) was dissolved in DMF (33 mL) at 0 °C. TBAI (22.0 mg, 60 µmol, 0.01 eq.), BnBr (1.86 mL, 15.6 mmol, 2.4 eq.) and NaH (60% dispersion in mineral oil, 0.629 g, 15.7 mmol, 2.4 eq.) were added. After stirring overnight, additional BnBr (0.93 mL, 7.80 mmol, 1.2 eq.) and NaH (60% dispersion in mineral oil, 0.315 g, 7.68 mmol, 1.0 eq.) were added at 0 °C. After the mixture was stirred for 4 h, it was quenched with MeOH (2 mL) and concentrated *in vacuo*. The crude residue was redissolved in Et_2O (100 mL) and washed with H_2O (1 x 100 mL, 3 x 50 mL). The aqueous layers were extracted with Et_2O (50 mL) and the combined organic layers were dried over $MgSO_4$, filtered and concentrated *in vacuo*. Purification by column chromatography (3% EtOAc in pentane → 6% EtOAc in pentane) gave fully benzylated **8** as a yellow oil (3.17 g, 6.08 mmol, 94%). ^1H NMR (400 MHz, $CDCl_3$): δ (ppm) 7.56 – 7.00 (m, 20H, H_{arom}Bn), 5.83 – 5.56 (m, 2H, H-1, H-6), 4.98 – 4.86 (m, 3H, CH_2Bn), 4.70 (s, 2H, CH_2Bn), 4.53 – 4.36 (m, 3H, CH_2Bn), 4.31 – 4.22 (m, 1H, H-3), 3.81 (dd, *J* = 10.1, 7.8 Hz, 1H, H-4), 3.67 (t, *J* = 9.8 Hz, 1H, H-2), 3.52 (d, *J* = 4.4 Hz, 2H, H-8), 2.64 – 2.42 (m, 1H, H-5). ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 129.3, 128.5, 128.2, 128.1, 128.0, 127.9, 127.8, 127.7, 127.0 (CH_{arom}, C-1 and C-6), 85.5 (C-3), 81.0 (C-2), 78.5 (C-4), 75.5, 75.5, 73.2 72.2 (CH_2 Bn), 69.3 (C-8), 44.5 (C-5). HRMS: calculated for $[C_{35}H_{37}O_4]^+$ 520.14791, found 521.26883.

(1*S*,2*S*,3*R*,4*R*,5*R*,6*R*)-2,3,4-tris(benzyloxy)-5-((benzyloxy)methyl) bicyclo[4.1.0]heptane (9)
To a solution of 1,2-dimethoxyethane (72 µL) in DCM (0.35 mL) was added boron trifluoride ethyl etherate (43 µL) and diethyl zinc (1 M in hexane, 0.7 mL, 0.7 mmol) at room temperature. After stirring for 5 min, diiodomethane (112 µL, 1.4 mmol) was added and the reaction mixture was stirred an additional 5 min. Compound **8** (36.3 mg, 70 µmol) was dissolved in DCM (0.85 mL) and added dropwise to the reaction mixture. After stirring for 3 h, the reaction mixture was quenched with a saturated aqueous NH_4Cl solution and diluted with EtOAc. The aqueous layer was extracted with EtOAc (3x) and the combined organic layers were dried over $MgSO_4$, filtered and concentrated *in vacuo*. Purification by column chromatography (pentane → 8% EtOAc in pentane) gave cyclopropane **26** (17.3 mg, 32 µmol, 46%) as a yellow oil. ^1H NMR (400 MHz, $CDCl_3$): δ (ppm) 7.40 (d, *J* = 7.0 Hz, 2H, H_{arom}Bn), 7.37 – 7.27 (m, 16H, H_{arom}Bn), 7.18 – 7.12 (m, 2H, H_{arom}Bn), 4.89 – 4.75 (m, 4H, CH_2Bn), 4.69 (d, *J* = 12 Hz, 1H, CH_2Bn), 4.55 – 4.36 (m, 3H, CH_2Bn), 4.14 – 4.04 (m, 1H, H-2), 3.59 (d, *J* = 4.2 Hz, 2H, H-8), 3.46 – 3.24 (m, 2H, H-3 and H-4), 1.93 – 1.85 (m, 1H, H-5), 1.44 – 1.34 (m, 1H, H-1), 1.17 – 1.07 (m, 1H, H-6). 0.82 – 0.74 (m, 1H, H-7), 0.40 – 0.35 (m, 1H, H-7) ^{13}C NMR (101 MHz,

$CDCl_3$): δ (ppm) 128.5, 128.5, 128.2, 128.1, 128.0, 127.8, 127.7, 127.6 (CH_{arom}), 84.4 (C-3), 80.5 (C-2), 79.5 (C-4), 75.6, 75.3, 73.3, 71.4 (4 x CH_2 Bn), 71.0 (C-8), 44.1 (C-5), 16.2, 14.2 (C-1 and C-6), 10.4 (C-7).

(1*S*,2*S*,3*R*,4*R*,5*R*,6*R*)-5-(hydroxymethyl)bicyclo[4.1.0]heptane-2,3,4-triol (10)

Compound **9** (760 mg, 1.4 mmol) was dissolved in MeOH (20 mL). The reaction mixture was purged with argon gas and 10% palladium on carbon (373 mg) was added. After the reaction vessel was purged with hydrogen gas and vigorously stirring overnight, the palladium catalyst was filtered off over a pad of Celite followed by concentration *in vacuo*. Purification by column chromatography (EtOAc → 30% MeOH in EtOAc) gave a crude product which was dissolved in pyridine (4.2 mL) and acetic anhydride (0.67 mL, 7.1 mmol) was added. After stirring for 2 days at room temperature, the reaction mixture was diluted with EtOAc (30 mL) and washed with H_2O (3x). The combined water layers were extracted with EtOAc (2x) and the combined organic layers were dried over $MgSO_4$, filtered, concentrated *in vacuo*. Purification by column chromatography (pentane → 20% EtOAc in pentane) gave the corresponding acetylated product **10** (0.36 g, 1.0 mmol, 71%) as a clear oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 5.39 (dd, *J* = 8.7, 6.2 Hz, 1H, H-2), 5.00 – 4.84 (m, 2H, H-3 and H-4), 4.18 – 4.05 (m, 2H, H-8), 2.19 – 2.13 (m, 1H, H-5), 2.09 (s, 3H, Ac), 2.06 (s, 3H, Ac) 2.00 (s, 6H, 2 x Ac), 1.68 – 1.56 (m, 1H, H-6), 1.10 – 1.02 (m, 1H, H-1), 0.93 – 0.85 (m, 1H, H-7), 0.57 – 0.47 (m, 1H, H-7) ^{13}C NMR (101 MHz, $CDCl_3$): δ (ppm) 171.2, 170.8, 170.2, 169.9 (4 x C_q Ac), 72.9 (C-3), 71.6 (C-4), 70.2 (C-2), 64.6 C-8), 41.0 (C-5), 21.2, 21.0, 20.8, 20.8 (4 x CH_3 Ac), 15.9 (C-6), 13.6 (C-1), 10.7 (C-7). HRMS: calculated for $[C_{16}H_{22}O_8Na]^+$ 365.12069, found 365.12048. The acetylated product (25 mg, 73 µmol) was dissolved in MeOH (10 mL) and a catalytic amount of NaOMe was added. After TLC analysis showed full conversion to a lower running spot, the reaction mixture was neutralized with Amberlite-H^+ IR-120, filtered and concentrated *in vacuo* to obtain compound **10** (12 mg, 68 µmol, 93%). ^{1}H NMR (400 MHz, D_2O): δ (ppm) 3.99 (dd, *J* = 8.8, 5.9 Hz, 1H, H-2), 3.83 (dd, *J* = 10.9, 3.5 Hz, 1H, H-8), 3.70 (dd, *J* = 10.9, 6.3 Hz, 1H, H-8), 3.18 (t, *J* = 10.2 Hz, 1H, H-4), 3.09 (dd, *J* = 10.2, 8.9 Hz, 1H, H-3), 1.77 – 1.66 (m, 1H, H-5), 1.39 – 1.31 (m, 1H, H-6), 1.05 – 0.93 (m, 1H, H-1), 0.79 – 0.72 (m, 1H, C-7), 0.35 – 0.25 (m, 1H, C-7). ^{13}C NMR (101 MHz, D_2O): δ (ppm) 74.5 (C-3), 72.1 (C-4), 71.0 (C-2), 63.1 (C-8), 45.1 (C-5), 17.6 (C-6), 12.6 (C-1), 9.2 (C-7). HRMS: calculated for $[C_8H_{14}O_4Na]^+$ 197.07843, found 197.07845.

(1*R*,2*R*,3*S*,6*R*)-6-(acetoxymethyl)cyclohex-4-ene-1,2,3-triyl triacetate (11)

NH_3 (20 mL) was condensed at -60 °C. Lithium (250 mg) was added and the reaction mixture was stirred until the lithium was completely dissolved. To this solution was added a solution of compound **7** (340 mg, 1.00 mmol) in THF (22.5 mL). The reaction mixture was stirred for 30 min at -60 °C and subsequently quenched with MeOH (10 mL). The solution was allowed to come to room temperature and stirred until all NH_3 had evolved. The resulting crude was then dissolved in pyridine (6.0 mL) and acetic anhydride (5.0 mL) was added. After stirring overnight, additional acetic anhydride (9.0 mL) was added. The reaction mixture was partitioned between EtOAc (25 mL) and H_2O (10 mL). The organic layer was washed with H_2O (3x), dried over $MgSO_4$ and concentrated *in vacuo*. The residue was taken up in pyridine (3.0 mL) and Ac_2O (2.0 mL). After stirring overnight at room temperature, the reaction mixture was partitioned between EtOAc (25 mL) and H_2O (10 mL). The organic layer was washed with H_2O (3x), dried over $MgSO_4$, filtered and concentrated *in vacuo*. Purification by column chromatography (10% EtOAc in pentane → 40% EtOAc in pentane) and coevaporation with toluene (to remove any residual pyridine) gave title compound **11** as a yellow oil (0.258 g, 0.786 mmol, 79% over 2 steps). ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 5.72 – 5.68 (m, 1H, H-1/H-6), 5.67 – 5.61 (m, 1H, H-1/H-6), 5.58 – 5.54 (m, 1H, H-2), 5.32 (dd, *J* = 10.6, 7.9 Hz, 1H, H-3), 5.28 – 5.18 (m, 1H, H-4), 4.15 (dd, *J* = 11.3, 4.1 Hz, 1H, H-7), 4.02 (dd, *J* = 11.3, 5.1 Hz, 1H, H-7), 2.83 – 2.76 (m, 1H, H-5), 2.03 (s, 12H, 4 x CH_3). ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 170.9, 170.5, 170.3, 170.1 (4 x C_q acetyl), 128.5, 126.5 (C-1 and C-6), 72.8 (C-4), 72.2 (C-3), 69.2 (C-5), 63.1 (C-7), 41.4 (C-5), 21.0, 20.8, 20.8, 20.8 (4 x CH_3). HRMS: calculated for $[C_{15}H_{21}O_8]^+$ 329.12309, found 329.12336.

(((1*R*,2*R*,3*S*,6*R*)-6-(((*tert*-butyldimethylsilyl)oxy)methyl)cyclohex-4-ene-1,2,3-triyl)tris(oxy))tris(*tert*-butyldimethylsilane) (12)

Compound **11** (69.5 mg, 0.434 mmol) was dissolved in MeOH (4.0 mL) and NaOMe (catalytic amount) was added. After stirring overnight, the reaction mixture was concentrated *in vacuo* and dissolved in DMF (3.1 mL). After addition of imidazole (0.708 g, 10.4 mmol, 24 eq.) and a solution of TBS-Cl (0.864 g, 5.73 mmol, 13.2 eq.) in DMF (2.0 mL) the mixture was stirred at room temperature for 5 days and subsequently refluxed over 2 nights. The reaction mixture was partitioned between Et_2O (10 mL) and H_2O (10 mL). The organic layer was separated, washed with H_2O (2x), dried over $MgSO_4$, filtered and concentrated *in vacuo*. Purification by column chromatography (10% toluene in pentane) gave title compound **12** as a slightly yellow oil (94.0 mg, 0.152 mmol, 35% over 2 steps). ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 5.74 (d, *J* = 3.6 Hz, 1H, H-1/H-6), 5.73 (d, *J* = 3.6 Hz, 1H, H-1/H-6), 3.93 (d, *J* = 2.5 Hz, 1H, H-2), 3.90 (d, *J* = 2.0 Hz, H-4), 3.83 (d, *J* = 3.2 Hz, 1H, H-3), 3.61 (dd, *J* = 9.6, 8.0 Hz, 1H, H-7), 3.52 (dd, *J* = 9.2, 7.2, 1H, H-7), 2.35 – 2.30 (m, 1H, H-5), 0.87 (s, 18H, TBS), 0.86 – 0.83 (m, 18H, TBS), 0.10 – 0.05 (m, 18H, TBS), 0.01 (s, 3H, TBS), 0.00 (s, 3H, TBS). ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 127.3, 127.2 (C-1 and C-2), 76.0 (C-3), 70.5 (C-4), 69.2 (C-2), 65.4 (C-7), 46.4 (C-5), 26.3, 26.3, 26.2, 26.1 (TBS), 18.6, 18.5, 18.2 (C_q TBS), -3.9, -4.1, -4.2, -4.5, -4.6, -5.0, -5.1 (TBS). HRMS: calculated for $[C_{31}H_{69}O_8Si_4]^+$ 617.42674, found 617.42689.

ethyl (1*R*,2*S*,3*R*,4*R*,5*R*,6*R*,7*R*)-2,3,4-tris(benzyloxy)-5-((benzyloxy) methyl) bicyclo[4.1.0]heptane-7-carboxylate (13) and ethyl (1*S*,2*S*,3*R*,4*R*,5*R*,6*S*,7*S*)-2,3,4-tris(benzyloxy)-5-((benzyloxy)methyl) bicycle[4.1.0]heptane-7-carboxylate (14)

EtOAc was dried over flame dried 4 Å molsieves overnight before use. To a solution of cyclic alkene **8** (1.57 g, 3.01 mmol) in EtOAc (2.7 mL) in a 2-necked pear flask, was added $Cu(acac)_2$ (79.0 mg, 0.301 mmol, 0.1 eq.). The reaction mixture was stirred at 90 °C and a solution of ethyl diazoacetate (13 wt% DCM, 4.52 mmol, 0.55 mL, 1.5 eq.) in EtOAc (9.0 mL) was added by syringe pump over 6 h. TLC-MS analysis indicated the presence of starting material, so an equal batch of ethyl diazoacetate diluted with EtOAc was added. After addition of a total of 6 eq. of ethyl diazoacetate, the formation of a product with m/z 715 $[M + Na]^+$ was detected by TLC-MS analysis. The reaction was concentrated *in vacuo* and purification by column chromatography (3% EtOAc in pentane → 7% EtOAc in pentane) to give the desired product as a crude mixture of 2 isomers. In addition, recovered starting material **25** (0.433 g, 0.832 mmol, 28%) was obtained and was subjected to the same conditions as stated above. After addition of 4.5 eq. of ethyl diazoacetate, significant byproduct formation was observed by TLC-MS analysis. After this cycle was repeated a second time a total crude mixture of α-*exo*-ester **13** and β-exo-ester **14** (0.642 g, 1.06 mmol, 35%, 2:1, as a mixture of α/β) was obtained as a light yellow oil. Crystallization of the combined crude isomeric product mixture from ethanol gave **13** as a white solid (0.274 g, 0.452 mmol, 15%) and a mixture of **13** and **14** as a light yellow oil (0.368 g, 0.606 mmol, 20**%).** Analytical data for **13:** ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 7.30 (m, 16H, H_{arom}Bn), 7.14 (m, 2H, H_{arom}Bn), 4.89 – 4.69 (m, 4H, CH_2Bn), 4.64 (d, *J* = 11.8 Hz, 1H, CH_2Bn), 4.53 – 4.34 (m, 3H, CH_2Bn), 4.22 – 4.03 (m, 3H, C*H*$_2$CH$_3$ and H-2), 3.66 – 3.52 (m, 2H, 2 x H-8), 3.40 (t, *J* = 10.2 Hz, 1H, H-4), 3.25 (dd, *J* = 10.1, 8.3 Hz, 1H, H-3), 2.05 – 1.97 (m, 1H, H-1), 1.94 – 1.88 (m, 1H, H-5), 1.76 (ddd, *J* = 9.5, 4.7, 2.3 Hz, 1H, H-6), 1.67 (t, *J* = 4.7 Hz, 1H, H-7), 1.27 (t, *J* = 7.1 Hz, 3H, CH_3). ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 173.4 (C_q carbonyl),

139.0, 138.6, 136.6, 138.3 (4 x C_q Bn), 128.5, 128.5, 128.5, 128.4, 128.2, 128.0, 128.0, 127.8, 127.7, 127.6, 127.5 (CH_{arom}), 84.1 (C-3), 79.2 (C-2), 78.5 (C-4), 75.7, 75.4, 73.3, 71.6 (4 x CH_2 Bn), 70.2 (C-8), 60.8 (CH_2CH_3), 43.1 (C-5), 26.9 (C-1), 25.0, 25.0 (C-6 and C-7), 14.4 (CH_3). HRMS: calculated for $[C_{39}H_{43}O_7]^+$ 607.30542, found 607.30589.

((1*R*,4*S*,5*R*,6*R*)-4,5,6-tris(benzyloxy)cyclohex-2-en-1-yl)methyl (*tert*-butoxycarbonyl) glycinate (19)

Compound **6** (51.9 mg, 0.120 mmol), N-Boc-glycine (31.5 mg, 0.18 mmol, 1.5 eq.) and DMAP (catalytic amount) were dissolved in toluene (0.6 mL) and DIC (38 µL, 2 eq.) was subsequently added dropwise. After stirring overnight at room temperature, the reaction mixture was filtered over Celite, concentrated *in vacuo* and purified by column chromatography (8% EtOAc in pentane → 25% EtOAc in pentane) to give compound **19** as a yellow oil (69.4 mg, 0.120 mmol, quant.). ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 7.42 – 7.21 (m, 15H, H_{arom}Bn), 5.72 (dt, *J* = 10.2, 2.4 Hz, 1H, H1/6), 5.58 – 5.46 (m, 1H, H1/6), 5.04 – 4.49 (m, 6H, CH_2Bn), 4.28 (dd, *J* = 10.8, 3.2 Hz, 1H, H-8), 4.23 (ddd, *J* = 7.7, 3.3, 1.9 Hz, 1H, H-2), 4.14 (dd, *J* = 10.9, 5.0 Hz, 1H, H-8), 3.80 (td, *J* = 13.3, 11.6, 7.5 Hz, 3H, H-3 and CH_2-Glyc), 3.53 (t, *J* = 9.8 Hz, 1H, H-4), 2.71 – 2.52 (m, 1H, H-5), 1.45 (d, *J* = 2.5 Hz, 9H, Boc-*t*Bu). ^{13}C NMR (75 MHz, $CDCl_3$): δ (ppm) 170.5 (C=O ester), 138.9, 138.4, 138.0 (3 x C_q Bn), 128.6, 128.6, 128.5, 128.2, 128.0, 128.0, 127.9, 127.8, 127.5 (CH_{arom}), 104.8 (C-1/6), 101.9 (C-1/6), 85.4 (C-3), 80.8 (C-2), 75.4, 75.3, 75.3 (CH_2Bn), 72.3 (C-4), 64.5 (C-8), 43.3 (C-5), 42.4 (CH_2-Glyc), 28.5 (Boc-CH_3). HRMS: calculated for $[C_{35}H_{42}NO_7]^+$ 588.29558, found 588.29600.

(1*R*,4*S*,5*R*,6*R*)-4,5,6-tris(benzyloxy)cyclohex-2-en-1-yl)methyl 2-diazoacetate (21)

To a solution of compound **19** (69.4 mg, 0.120 mmol) in DCM (0.3 mL) was added TFA (0.3 mL). After stirring for 45 min at room temperature, the reaction mixture was concentrated *in vacuo* to give compound **20** as a light yellow solid which was used without further purification (72.2 mg, 0.120 mmol, quant.). HRMS (as the free amine): calculated for $[C_{30}H_{34}NO_5]^+$ 488.24315, found 488.24285. Compound **20** (60.0 mg, 0.0990 mmol) was suspended in H_2O (0.4 mL), after which monosodium citrate (31.7 mg, 0.149 mmol, 1.5 eq.) and CH_2Br_2 (0.5 mL) were added. The reaction was cooled to 0 °C and $NaNO_2$ (8.19 mg, 0.119 mmol, 1.2 eq.) was added. After stirring at 0 °C for 1 h, the reaction mixture was warmed up to room temperature and the organic layer was removed by syringe. Additional CH_2Br_2 was added (0.5 mL) and after stirring for 10 min the organic layer was removed again by syringe. The combined organic layers were combined and concentrated *in vacuo* to give compound **21** as a bright yellow oil (49 mg, 98.0 µmol, 99%). ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 7.45 – 7.16 (m, 15H, H_{arom}), 5.73 (d, *J* = 10.2 Hz, 1H, H-1/H-6), 5.55 (d, *J* = 10.2 Hz, 1H, H-1/H-6), 4.96 (d, *J* = 10.8 Hz, 1H, CH_2 Bn), 4.93 – 4.88 (m, 2H, CH_2 Bn), 4.69 – 4.62 (m, 3H, CH_2 Bn and H-diazocarbonyl), 4.56 (d, *J* = 9.2 Hz, 1H, CH_2 Bn), 4.33 (dd, *J* = 10.8, 3.0 Hz, 1H, H-2), 4.23 – 4.18 (m, 2H, H-8), 3.82 (t, *J* = 8.4 Hz, 1H, H-3), 3.54 (t, *J* = 9.8 Hz, 1H, H-4), 2.61 (bs, 1H, H-5). ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 138.9, 138.5, 138.4 (3 x $C_{q\text{-}arom}$), 128.6, 128.6, 128.4, 128.1, 128.0, 127.9, 127.8, 127.7 (CH_{arom}), 85.3 (C-3), 80.9 (C-2), 77.9 (C-4), 75.5, 74.4, 72.3 (3 x CH_2 Bn), 63.9 (C-8), 46.4 (C=N), 43.6 (C-5).

Bis(*N*-tert-butylsalicylaldiminato)copper(II)

$Cu(OAc)_2$ (0.399 g, 2.00 mmol) was dissolved in H_2O (5 mL) and a solution of salicylaldehyde (435 µL, 4.00 mmol, 2 eq.) in EtOH (2 mL) was added. After stirring for 1h at 55 °C, the precipitate was filtered off and subsequently suspended in EtOH (2 mL). After addition of tert-butylamine (525 µL, 5.00 mmol, 2.25 eq.), the reaction mixture was refluxed for 1.5 h and concentrated *in vacuo* to give the title compound as black crystals (0.680 g, 1.64 mmol, 82%). m.p.: 185 °C (literature values 185-186 °C).[30]

1-((1*R*,2*S*,3*R*,4*R*,5*R*,6*R*,7*R*)-2,3,4-tris(benzyloxy)-5-((benzyloxy) methyl)bicyclo[4.1.0]heptan-7-yl)propan-1-one (22)

Ester **13** (60.8 mg, 0.100 mmol) was added to Me(MeO)NH.HCl (12.2 mg, 0.125 mmol, 1.25 eq.) in THF (0.5 mL). After addition of EtMgBr (0.5 M in THF, 0.840 mmol, 8.4 eq.) over 2 h at -5 – 0 °C, the reaction mixture was stirred overnight, quenched with aqueous HCl (3 M, 3 mL) and extracted with EtOAc (10 mL). The organic layer was dried, concentrated *in vacuo* and redissolved in THF (0.8 mL). After addition of EtMgBr (1 M in THF, 0.300 mmol, 3 eq.) over 2 min at -20 °C, the reaction mixture was allowed to come to room temperature and was stirred for 75 min before quenching with aqueous HCl (3 M, 3 mL). The reaction mixture was extracted with EtOAc (10 mL) after which the organic layer was dried and concentrated *in vacuo*. Purification by column chromatography (6% EtOAc in pentane → 8% EtOAc in pentane) gave compound **22** as a white solid (32.8 mg, 55.6 µmol, 56%). ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 7.39 – 7.18 (m, 18H, H_{arom}), 7.15 – 7.12 (m, 2H, H_{arom}), 4.92 – 4.76 (m, 3H, CH_2 Bn), 4.74 – 4.57 (m, 2H, CH_2 Bn), 4.50 – 4.38 (m, 3H, CH_2 Bn), 4.06 (dd, *J* = 7.9, 5.8 Hz, 1H, H-2), 3.61 – 3.50 (m, 2H, H-8), 3.39 (t, *J* = 10.0 Hz, 1H, H-4), 3.34 – 3.24 (m, 1H, H-3), 2.58 (dd, *J* = 14.4, 7.6 Hz, 2H, CH_2CH_3), 2.09 – 2.00 (m, 1H, H-1), 1.98 (t, *J* = 4.5 Hz, 1H, H-7), 1.95 – 1.89 (m, 1H, H-5), 1.86 – 1.78 (m, 1H, H-6), 1.08 (t, *J* = 7.3 Hz, 3H, CH_3). ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 209.6 (C=O), 139.1, 138.7, 138.6, 138.4 (4 x $C_{q\text{-}arom}$), 128.6, 128.5, 128.5, 128.2, 128.0, 127.9, 127.8, 127.7 (CH_{arom}), 84.3 (C-3), 79.4 (C-2), 78.7 (C-4), 75.7, 75.5, 73.5, 71.6 (4 x CH_2 Bn), 70.4 (C-8), 43.5 (C-5), 37.3 (CH_2CH_3), 32.6 (C-7), 29.6 (C-1), 27.4 (C-6), 8.2 (CH_3). HRMS: calculated for $[C_{39}H_{42}O_5Na]^+$ 613.29245, found 613.29242.

1-((1*R*,2*S*,3*R*,4*R*,5*R*,6*R*,7*R*)-2,3,4-trihydroxy-5-(hydroxymethyl) bicyclo[4.1.0]heptan-7-yl)propan-1-one (23)

Compound **22** (32.8 mg, 55.6 µmol) was treated according to General procedure for global debenzylation with $Pd(OH)_2$/C to obtain title compound **23** as a clear oil (12.3 mg, 53.4 µmol, 96%). ^{1}H NMR (400 MHz, D_2O): δ (ppm) 4.04 (dd, *J* = 8.6, 5.5 Hz, 1H, H-2), 3.84 (dd, *J* = 11.0, 3.6 Hz, 1H, H-8), 3.72 (dd, *J* = 11.0, 6.2 Hz, 1H, H-8), 3.37 – 3.09 (m, 2H, H-3 and H-4), 2.72 (dd, *J* = 7.2, 14.8 Hz, 2H, CH_2CH_3), 2.25 (t, *J* = 4.5 Hz, 1H, H-7), 2.11 – 1.98 (m, 1H, H-1), 1.90 – 1.83 (m, 1H, H-5), 1.68 – 1.61 (m, 1H, H-6), 1.04 (t, *J* = 7.3 Hz, 3H, CH_3). ^{13}C NMR (100 MHz, D_2O): δ (ppm) 216.1 (C=O), 74.4 (C-3), 70.7 (C-2), 70.4 (C-4), 62.5 (C-8), 44.3 (C-5), 36.6 (CH_2CH_3), 32.1 (C-7), 31.9 (C-1), 26.8 (C-6), 7.4 (CH_3). HRMS: calculated for $[C_{11}H_{19}O_5]^+$ 231.12270, found 231.12270.

((1*R*,2*S*,3*R*,4*R*,5*R*,6*R*,7*R*)-2,3,4-tris(benzyloxy)-5-((benzyloxy)methyl) bicyclo[4.1.0]heptan-7-yl)methanol (24) and ((1*S*,2*S*,3*R*,4*R*, 5*R*,6*S*,7*S*)-2,3,4-tris(benzyloxy)-5-((benzyloxy)methyl)bicyclo [4.1.0]heptan-7-yl)methanol (25)

A crude mixture of **13** and **14** (0.142 g, 0.234 mmol) was dissolved in THF (1 mL) at 0 °C, after which DIBAL (1 M in hexanes, 2.1 mL, 2.1 mmol, 9.0 eq.) was added dropwise. After the mixture was stirred for 30 min at 0 °C followed by 1 h at room temperature, the reaction was quenched with EtOAc. The mixture was concentrated *in vacuo* and the residue was partitioned between EtOAc (20 mL) and 1 M aqueous HCl (20 mL). The aqueous layer was extracted with EtOAc (20 mL) and the combined organic layers were dried over $MgSO_4$, filtered and concentrated *in vacuo*. Purification by column chromatography (20% EtOAc in pentane → 25% EtOAc in pentane) gave title compounds **24** (36.6 mg, 64.8 µmol, 28%) and **25** (17.1 mg, 30.2 µmol, 13%) as white solids. Analytical data for **24:** ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 7.46 – 7.20 (m, 18H, CH_{arom}), 7.19 – 7.11 (m, 2H, CH_{arom}), 4.96 – 4.64 (m, 5H, CH_2 Bn), 4.55 – 4.29 (m, 3H, CH_2 Bn), 4.06 (dd, *J* = 7.9, 6.2 Hz, 1H, H-2), 3.59 (d, *J* = 4.1 Hz, 1H, H-8), 3.51 (dd, *J* = 11.2, 6.3 Hz, 1H, C*H*HOH), 3.40 – 3.18 (m, 3H, CH*H*OH, H-3, H-4), 1.93 – 1.89 (m, 1H, H-5), 1.30 – 1.20 (m, 1H, H-1), 1.12 – 1.03 (m, 2H, H-6 and H-7). ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 139.2, 139.1, 138.8, 138.5 (4 x $C_{q\text{-}arom}$), 128.6, 128.5,

128.5, 128.2, 128.1, 128.1, 128.0, 127.9, 127.8, 127.8, 127.7 (CH_{arom}), 84.8 (C-3), 80.1 (C-2), 79.3 (C-4), 75.7, 75.4, 73.4, 71.7 (4 x CH_2 Bn), 70.9 (C-8), 66.5 (CH_2OH), 43.6 (C-5), 26.4 (C-7), 22.0 (C-1), 19.8 (C-6). HRMS: calculated for $[C_{37}H_{41}O_6]^+$ 565.29485, found 565.29462. Analytical data for **25:** ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 7.63 – 6.95 (m, 20H, CH_{arom}), 4.95 – 4.60 (m, 5H, CH_2 Bn), 4.53 – 4.31 (m, 3H, CH_2 Bn), 3.75 – 3.62 (m, 3H, CH*H*OH, H-2, H-8), 3.58 – 3.42 (m, 2H, H-3 and H-8), 3.07 – 2.99 (m, 2H, C*H*HOH and H-4), 2.41 – 2.30 (m, 1H, H-5), 1.14 (dd, *J* = 8.2, 4.7 Hz, 1H, H-6), 1.02 (dd, *J* = 8.9, 4.8 Hz, 1H, H-1), 0.97 – 0.78 (m, 1H, H-7). ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 139.0, 138.6, 138.5, 138.2 (4 x C_q arom) 128.7, 128.6, 128.6, 128.5, 128.3, 128.2, 128.1, 128.1, 128.0, 127.9, 127.9, 127.7, 127.7 (CH_{arom}), 86.4 (C-3), 82.3 (C-2), 75.5, 75.3, 73.5, 72.5 (4 x CH_2 Bn), 71.4 (C-8), 66.7 (CH_2OH, 40.2 (C-5), 22.9 (C-7), 21.2 (C-6), 20.6 (C-1). HRMS: calculated for $[C_{37}H_{41}O_6]^+$ 565.29485, found 565.29526.

(1*R*,2*S*,3*R*,4*R*,5*R*,6*R*,7*R*)-5,7-bis(hydroxymethyl)bicyclo[4.1.0] heptane-2,3,4-triol (26)

Compound **24** (25.6 mg, 45.1 µmol) was treated according to General procedure for global debenzylation with $Pd(OH)_2$/C to obtain title compound **26** as a clear oil (8.30 mg, 40.6 µmol, 90%). ^{1}H NMR (400 MHz, D_2O): δ (ppm) 4.03 (dd, *J* = 8.7, 6.0 Hz, 1H, H-2), 3.90 (dd, *J* = 10.9, 3.5 Hz, 1H, H-8), 3.78 (dd, *J* = 10.9, 6.1 Hz, 1H, H-8), 3.62 (dd, *J* = 11.6, 6.1 Hz, 1H, CH_2-OH), 3.33 (dd, *J* = 11.5, 7.7 Hz, 1H, CH_2-OH), 3.25 (t, *J* = 10.1 Hz, 1H, H-4), 3.21 – 3.11 (m, 1H, H-3), 1.86 – 1.77 (m, 1H, H-5), 1.35 (dt, *J* = 9.0, 5.5 Hz, 1H, H-1/6), 1.13 (dt, *J* = 11.3, 5.3 Hz, 1H, H-7), 1.05 – 0.97 (m, 1H, H-1/H-6). ^{13}C NMR (100 MHz, D_2O): δ (ppm) 70.5 (C-3), 67.0 (C-2), 66.5 (C-4), 60.8 (CH_2-OH), 58.6 (C-8), 40.2 (C-5), 20.2 (C-7), 18.8 (C-1), 14.1 (C-6). HRMS: calculated for $[C_9H_{17}O_6]^+$ 205.10705, found 205.10701.

(1*R*,2*S*,3*R*,4*R*,5*R*,6*R*,7*R*)-2,3,4-tris(benzyloxy)-5-((benzyloxy)methyl)-7-(ethoxymethyl)bicyclo[4.1.0]heptane (27)

Compound **24** (18.0 mg, 32.0 µmol), TBAI (catalytic amount) and NaH (60%, 2.55 mg, 2.0 eq.) were dissolved in DMF (0.3 mL) at 0 °C. After stirring for 5 min, ethyl bromide (21 µL, 0.287 mmol, 9.0 eq.) was added and the reaction mixture was allowed to stir at room temperature for 4 h. The reaction mixture was partitioned between H_2O (10 mL) and EtOAc (10 mL) and the organic layer was washed with H_2O (2x) and all the aqueous layers were extracted with EtOAc (1x). The combined organic layers were dried over $MgSO_4$, filtered and concentrated *in vacuo*. Purification by column chromatography (10% EtOAc in pentane → 20% EtOAc in pentane) gave title compound **27** as a clear oil (11.1 mg, 18.7 µmol, 59**%**). ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 7.48 – 7.11 (m, 20H, H_{arom}Bn), 4.91 – 4.72 (m, 4H, CH_2Bn), 4.66 (d, *J* = 11.7 Hz, 1H, CH_2Bn), 4.55 – 4.36 (m, 3H, CH_2Bn), 4.07 (dd, *J* = 8.0, 6.2 Hz, 1H, H-2), 3.66 – 3.60 (m, 2H, H-8), 3.56 – 3.42 (m, 2H, CH_2CH$_3$), 3.42 – 3.32 (m, 2H, H-4 and C*H*HO), 3.32 – 3.22 (m, 2H, H-3, C*H*HO), 1.89 (dd, *J* = 6.6, 3.5 Hz, 1H, H-5), 1.34 – 1.28 (m, 1H, H-1), 1.17 (t, *J* = 7.0 Hz, 3H, CH_3), 1.12 – 1.04 (m, 2H, H-6 and H-7). ^{13}C NMR (101 MHz, $CDCl_3$): δ (ppm) 139.3, 139.2, 138.9, 138.6 (4 x $C_{q\text{-}arom}$),128.6, 128.5, 128.5, 128.2, 128.2, 128.1, 128.0, 127.9, 127.8, 127.7, 127.6, 127.1 (CH_{arom}), 84.9 (C-3), 80.2 (C-2), 79.3 (C-4), 75.7, 75.3 (2 x CH_2 Bn), 74.1 (CH_2O), 73.3, 71.1 (2 x CH_2 Bn), 70.9 (C-8), 65.8 (CH_2CH_3), 43.6 (C-5), 23.5 (C-7), 21.6 (C-1), 20.4 (C-6), 15.5 (CH_3). HRMS: calculated for $[C_{39}H_{45}O_5]^+$ 593.32615, found 593.32647.

(1*R*,2*S*,3*R*,4*R*,5*R*,6*R*,7*R*)-7-(ethoxymethyl)-5-(hydroxymethyl)bicyclo [4.1.0]heptane-2,3,4-triol (28)

Compound **27** (11.1 mg, 18.7 µmol) was treated according to General procedure for global debenzylation with $Pd(OH)_2$/C to obtain title compound **28** as a clear oil oil (4.1 mg, 17.7 µmol, 94%). ^{1}H NMR (400 MHz, D_2O): δ (ppm) 4.00 (dd, *J* = 8.8, 6.0 Hz, 1H, H-2), 3.87 (dd, *J* = 10.9, 3.5 Hz, 1H, H-8), 3.75 (dd, *J* = 10.9, 6.0 Hz, 1H, H-8), 3.65 – 3.55 (m, 3H, CH_2CH$_3$, C*H*HOEt), 3.24 – 3.16 (m, 2H CH*H*OEt and H-4), 3.16 – 3.10 (m, 1H, H-3) 1.83 – 1.72 (m, 1H, H-5), 1.36 – 1.30(m, 1H, H-1), 1.20 (t, *J* = 7.1 Hz, 3H, CH_3), 1.13 – 1.05 (m, 1H, H-7), 1.08 – 0.95 (m, 1H, H-6). ^{13}C NMR (100 MHz, D_2O): δ (ppm) 79.3 (C-3), 78.2 (CH_2OEt), 75.8 (C-2), 75.3 (C-4), 70.5 (CH_2CH_3), 67.3 (C-8), 49.0 (C-5), 27.6 (C-1), 26.6 (C-7), 23.4 (C-6), 18.5 (CH_3). HRMS: calculated for $[C_{11}H_{21}O_6]^+$ 233.13835, found 233.13843.

ethyl (1*S*,2*S*,3*R*,4*R*,5*R*,6*S*,7*S*)-2,3,4-tris(benzyloxy)-5-((benzyloxy) methyl)bicyclo[4.1.0]heptane-7-carboxylate (14)

Chromic acid stock solution (1.0 M) was prepared (*Caution:* Chromic acid is corrosive, toxic and carcinogenic). Concentrated H_2SO_4 (2.25 mL, 40.5 mmol) is taken up in H_2O (12.5 mL). To this solution was added CrO_3 (2.50 g, 25.0 mmol) and the resulting bright red solution was stirred until all solids were completely dissolved. The solution was then diluted with H_2O to a total volume of 25 mL. Compound **31** (261 mg, 0.462 mmol) was dissolved in acetone (9.2 mL) and cooled to 0 °C, after which the chromic acid stock solution (0.92 mL, 0.920 mmol, 2 eq.) was added. After stirring for 3 h, the reaction mixture was diluted with EtOAc (150 mL) and washed with aqueous HCl (3 M, 2 x 150 mL) and brine (150 mL). The organic layer was dried over $MgSO_4$, filtered and concentrated *in vacuo*. Purification by column chromatography (15% EtOAc in pentane → 35% EtOAc in pentane) gave the corresponding carboxylic acid as a white solid (141 mg, 0.244 mmol, 53%). ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 7.44 – 7.10 (m, 20H, H_{arom}), 4.90 – 4.71 (m, 4H, CH_2 Bn), 4.69 – 4.57 (m, 1H, CH_2 Bn), 4.54 – 4.34 (m, 3H, CH_2 Bn), 3.75 (d, *J* = 8.1 Hz, 1H, H-2), 3.65 (dd, *J* = 8.9, 2.7 Hz, 1H, H-8), 3.60 – 3.51 (m, 2H, H-3 and H-8), 3.11 (t, *J* = 10.2 Hz, 1H, H-4), 2.45 – 2.33 (m, 1H, H-5), 2.03 – 1.98 (m, 1H, H-6), 1.80 (dd, *J* = 9.5, 4.5 Hz, 1H, H-1), 1.60 (t, *J* = 4.6 Hz, 1H, H-8). ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 179.4 (C=O), 138.9, 138.6, 138.5, 138.1 (4 x $C_{q\text{-}arom}$), 128.7, 128.6, 128.6, 128.5, 128.5, 128.2, 128.2, 128.1, 128.0, 127.9, 127.7 (CH_{arom}), 85.8 (C-3), 81.3 (C-2), 76.2 (C-4), 75.5, 75.4, 73.3, 72.5 (4 x CH_2 Bn), 70.2 (C-8), 40.6 (C-5), 27.3 (C-6), 26.0 (C-1), 22.0 (C-7). HRMS: calculated for $[C_{37}H_{39}O_6]^+$ 579.27412, found 579.27438.

To a solution of the carboxylic acid (141 mg, 0.244 mmol) in toluene (1.2 mL) was added ethanol (66 µL, 0.488 mmol, 2 eq.) and DMAP (catalytic amount). After DIC (75 µL, 0.484 mmol, 2.0 eq.) was added dropwise, the reaction mixture was stirred for 4 h at room temperature. The reaction mixture was filtered over Celite, concentrated *in vacuo* and purification by column chromatography (7% EtOAc in pentane → 10% EtOAc in pentane) gave title compound **14** as a white solid (91.4 mg, 0.151 mmol, 62%). ^{1}H NMR (400 MHz, $CDCl_3$: δ (ppm) 7.44 – 7.14 (m, 20H, H_{arom}), 4.89 – 4.72 (m, 4H, CH_2 Bn), 4.64 (d, *J* = 11.6 Hz, 1H, CH_2 Bn), 4.52 – 4.36 (m, 3H, CH_2 Bn), 4.15 (d, *J* = 7.2 Hz, 1H, C*H*HCH$_3$), 4.12 (d, *J* = 7.2, CH*H*CH$_3$), 3.75 (d, *J* = 7.8 Hz, 1H, H-2), 3.65 (dd, *J* = 8.9, 2.7 Hz, 1H, H-8), 3.61 - 3.48 (m, 2H, H-3 and H-8), 3.14 (t, *J* = 10.2 Hz, 1H, H-4), 2.45 – 2.29 (m, 1H, H-6), 1.96 - 1.84 (m, 1H, H-6), 1.74 (dd, *J* = 9.3, 4.5 Hz, 1H, H-1), 1.61 (t, *J* = 4.7 Hz, 1H, H-7), 1.26 (t, *J* = 7.1 Hz, 3H, CH_3). ^{13}C NMR (101 MHz, $CDCl_3$): δ (ppm) 173.5 (C=O), 138.9, 138.7, 138.6, 138.2 (4 x $C_{q\text{-}arom}$), 128.6, 128.5, 128.5, 128.4, 128.2, 128.1, 128.0, 128.0, 127.9, 127.8, 127.8, 127.7, 127.6, 127.5 (CH_{arom}), 85.9 (C-3), 81.5 (C-2), 76.3 (C-4), 75.4, 75.4, 73.3, 72.4 (4 x CH_2 Bn), 70.4 (C-8), 60.8 (CH_2CH_3), 40.6 (C-5), 26.4 (C-6), 24.9 (C-1), 22.2 (C-7), 14.4 (CH_3). HRMS: calculated for $[C_{39}H_{43}O_7]^+$ 607.30542, found 607.30589.

1-((1*S*,2*S*,3*R*,4*R*,5*R*,6*S*,7*S*)-2,3,4-tris(benzyloxy)-5-((benzyloxy) methyl)bicyclo[4.1.0]heptan-7-yl)propan-1-one (29)

Ethyl ester **14** (60.8 mg, 0.100 mmol) was added to Me(MeO)NH.HCl (12.2 mg, 0.125 mmol, 1.25 eq.) in THF (0.5 mL). Subsequently, EtMgBr (0.5 M in THF, 0.840 mmol, 8.4 eq.) was added over 2 h at -5 to 0 °C. After stirring overnight, the reaction mixture was quenched with aqueous HCl (3 M, 3 mL). The reaction mixture was extracted with EtOAc (10 mL), after which the organic layer was dried and concentrated *in vacuo*. Purification by column chromatography (15% EtOAc in pentane) gave compound **29** as a white solid (29.4 mg, 47.9 µmol, 48%). ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 7.42 – 7.14 (m, 20H, H_{arom}), 4.95 – 4.69 (m, 4H, CH_2 Bn), 4.60 (d, *J* = 11.5 Hz, 1H, CH_2 Bn), 4.52 – 4.30 (m, 3H, CH_2 Bn), 3.72 (d, *J* = 7.8 Hz, 1H, H-2), 3.69 – 3.46 (m, 3H, H-3 and H-8), 3.26 (t, *J* = 10.2 Hz, 1H, H-4), 2.38 (dd, *J* = 8.7, 7.4 Hz, 2H, CH_2CH_3), 2.36 – 2.29 (m, 1H, H-5), 1.89 (t, *J* = 4.7 Hz, 1H, H-7), 1.84 – 1.82 (m, 1H, H-6), 1.82 – 1.79 (m, 1H, H-1), 1.00 (t, *J* = 7.3 Hz, 3H, CH_3). ^{13}C NMR (101 MHz, $CDCl_3$): δ (ppm) 209.7 (C=O), 139.0, 138.7, 138.6, 138.2 (4 x $C_{q\text{-}arom}$), 128.6, 128.6, 128.5, 128.5, 128.2, 128.2, 128.1, 127.9, 127.9, 127.8, 127.8, 127.7, 127.6 (CH_{arom}), 86.1 (C-3), 81.6 (C-2), 76.3 (C-4), 75.4, 73.4, 72.2 (4 x CH_2 Bn), 70.3 (C-8), 40.7 (C-5), 37.0 (CH_2CH_3), 29.8 (C-7), 29.3 (C-6), 26.4 (C-1), 8.0 (CH_3). HRMS: calculated for $[C_{39}H_{42}O_5Na]^+$ 613.29245, found 613.29257.

1-((1*S*,2*S*,3*R*,4*R*,5*R*,6*S*,7*S*)-2,3,4-trihydroxy-5-(hydroxymethyl) bicyclo[4.1.0]heptan-7-yl)propan-1-one (30)

Compound **29** (29.4 mg, 49.8 µmol) was treated according to General procedure for global debenzylation with $Pd(OH)_2$/C to obtain title compound **30** as a clear oil (6.70 mg, 29.1 µmol, 58%). ^{1}H NMR (400 MHz, D_2O): δ (ppm) 3.92 (dd, *J* = 11.2, 4.0 Hz, 1H, H-8), 3.89 (dd, *J* = 0.8 Hz, 8.6 Hz, 1H, H-2), 3.60 (dd, *J* = 10.8, 8.2 Hz, 1H, H-8), 3.28 (dd, *J* = 10.2, 8.6 Hz, 1H, H-3), 3.05 (t, *J* = 10.0 Hz, 1H, H-4), 2.69 (dd, *J* = 14.6, 7.4 Hz, 2H, CH_2CH_3), 2.21 – 2.15 (m, 1H, H-5), 2.13 (t, *J* = 4.2 Hz, 1H, H-7), 1.93 (ddd, *J* = 9.7, 5.0, 5.0, 1H, H-6), 1.67 (dd, *J* = 9.2, 4.4 Hz, 1H, H-1), 1.03 (t, *J* = 7.2 Hz, 3H, CH_3). ^{13}C NMR (100 MHz, D_2O): δ (ppm) 216.2 (C=O), 77.3 (C-3), 72.4 (C-2), 68.2 (C-4), 62.7 (C-8), 42.1 (C-5), 36.6 (CH_2CH_3), 30.1 (C-1), 29.2 (C-7), 28.4 (C-6), 7.4 (CH_3). HRMS: calculated for $[C_{11}H_{19}O_5]^+$ 231.12270, found 231.12276.

(1*R*,2*S*,3*R*,4*R*,5*R*,6*R*,7*R*)-*N*-(4-azidobutyl)-2,3,4-tris(benzyloxy)-5-((benzyloxy)methyl)bicyclo[4.1.0]heptane-7-carboxamide (31) and (1*S*,2*S*,3*R*,4*R*,5*R*,6*S*,7*S*)-*N*-(4-azidobutyl)-2,3,4-tris(benzyloxy)-5-((benzyloxy)methyl)bicyclo[4.1.0]heptane-7-carboxamide (32)

To a mixture of **13** and **14** (0.142 g, 0.234 mmol) in THF (8 mL), was added MeOH (2 mL), H_2O (1 mL) and LiOH (22.4 mg, 0.94 mmol, 4 eq.). After stirring overnight at room temperature, 1 M aqueous HCl solution was used to acidify the reaction mixture to pH 2. The reaction mixture was diluted with EtOAc (20 mL) and washed with brine (10 mL). The aqueous layer was extracted with EtOAc (10 mL) and the combined organic layers were dried over $MgSO_4$, filtered and concentrated *in vacuo*. Purification by column chromatography (30% EtOAc in pentane) gave the carboxylic acid derivatives as a mixture of α- and β-isomers (119 mg, 0.206 mmol, 82%) as a clear oil. The carboxylic acid derivatives (0.346 g, 0.600 mmol) were dissolved in DCM (6.0 mL) and 4-azidobutan-1-amine (82.2 mg, 0.720 mmol, 1.2 eq.) was added. After addition of DIPEA (364 µL, 2.10 mmol, 3.5 eq.) and HCTU (298 mg, 0.720 mmol, 1.2 eq.), the reaction mixture was stirred overnight at room temperature. The reaction mixture was concentrated *in vacuo*, dissolved in EtOAc (40 mL) and subsequently washed with aqueous HCl (1 M, 2 x 40 mL), saturated aqueous $NaHCO_3$ (40 mL) and brine (2 x 40 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo*. Purification by column chromatography (30% EtOAc in pentane) gave the mixture of α-*exo* isomer **31** and β-exo-isomer **32** (0.341 g, 0.505 mmol, 78%) as a white solid, which were separated by HPLC purification (C18, linear gradient: 50-90% B in A, solutions used A: H_2O, B: acetonitrile, 0.5% TFA, 15 min). Analytical data for **31:** ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 7.38 – 7.10 (m, 20H, H_{arom}Bn), 5.66 (t, *J* = 5.8 Hz, 1H, NH), 4.90 – 4.69 (m, 4H, CH_2Bn), 4.61 (d, *J* = 11.6 Hz, 1H, CH_2Bn), 4.53 – 4.32 (m, 3H, CH_2Bn), 4.10 (dd, *J* = 8.2, 5.9 Hz, 1H, H-2), 3.59 (qd, *J* = 8.8, 3.8 Hz, 2H, H-8), 3.42 (t, *J* = 10.1 Hz, 1H, H-4), 3.30 (t, *J* = 6.1 Hz, 4H, NHC*H*$_2$, C*H*$_2$N$_3$), 3.26 – 3.20 (m, 1H, H-3), 2.04 (dt, *J* = 10.0, 5.2 Hz, 1H, H-1), 1.94 – 1.85 (m, 1H, H-5), 1.82 (ddd, *J* = 9.2, 4.4, 2.2 Hz, 1H, H-6), 1.65 – 1.57 (m, 4H, NHCH$_2$C*H*$_2$, CH$_2$C*H*$_2$N$_3$), 1.35 (t, *J* = 4.5 Hz, 1H, H-7). ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 172.1 (C=O), 139.1, 138.6 ($C_{q\text{-}}$Bn), 128.6, 128.6, 128.6, 128.5, 128.3, 128.1, 128.0, 127.9, 127.9, 127.7 ($C_{arom\text{-}}$Bn), 84.4 (C-3), 79.4 (C-2), 78.8 (C-4), 75.7, 75.5, 73.5, 71.6 (CH_2-Bn), 70.5 (C-8), 51.3 (CH_2N_3), 43.4 (C-1), 39.4 ($NHCH_2$), 27.3 (NHCH$_2$C*H*$_2$), 27.1 (C-5), 26.5 ($CH_2CH_2N_3$), 25.7 (C-6), 23.8 (C-7). HRMS: calculated for $[C_{41}H_{47}N_4O_5]^+$ 675.35410, found 675.35411. Analytical data for **32:** ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 7.45 – 7.12 (m, 20H, CH_{arom}), 5.22 (t, *J* = 5.8 Hz, 1H, NH), 4.87 (d, *J* = 12.3 Hz, 2H, CH_2), 4.83 – 4.74 (m, 2H, CH_2), 4.60 (d, *J* = 11.5 Hz, 1H, CH_2), 4.50 (d, *J* = 11.0 Hz, 1H, CH_2), 4.37 (d, *J* = 2.4 Hz, 2H, CH_2), 3.83 (dd, *J* = 9.1, 3.6 Hz, 1H, H-2), 3.75 (d, *J* = 7.6 Hz, 1H, H-3), 3.66 – 3.52 (m, 2H, H-8), 3.34 (t, *J* = 10.2 Hz, 1H, H-4), 3.23 (t, *J* = 6.7 Hz, 2H, CH_2N_3), 3.19 – 3.10 (m, 1H, NHC*H*H), 3.10 – 3.00 (m, 1H, NHCH*H*), 2.29 – 2.24 (m, 1H, H-5), 1.79 (dd, *J* = 9. 1, 4.8 Hz, 1H, H-6), 1.70 – 1.63 (m, 1H, H-1), 1.55 – 1.44 (m, 2H, NHCH$_2$C*H*$_2$), 1.43 – 1.30 (m, 3H, C*H*$_2$CH$_2$N$_3$, H-7). ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 172.1 (C=O), 139.0, 139.0, 138.7, 138.3 ($C_{q\text{-}arom}$), 128.7, 128.6, 128.5, 128.3, 128.1, 128.1, 127.9, 127.9, 127.8, 127.7, 127.4 (CH_{arom}), 86.3 (C-3), 81.6 (C-2), 75.9 (C-4), 75.4, 75.4, 73.2, 71.9 (4 x CH_2 arom), 70.3 (C-8), 51.2 (CH_2N_3), 40.5 (C-1), 39.2 ($NHCH_2$), 27.1 (NHCH$_2$C*H*$_2$), 26.3 (*C*H$_2$CH$_2$N$_3$), 25.2 (C-5), 24.5 (C-6), 21.5 (C-7). HRMS: calculated for $[C_{41}H_{47}N_4O_5]^+$ 675.35410, found 675.35436.

(1*R*,2*S*,3*R*,4*R*,5*R*,6*R*,7*R*)-*N*-(4-azidobutyl)-2,3,4-trihydroxy-5-(hydroxymethyl)bicyclo[4.1.0]heptane-7-carboxamide (33)

To a cooled (-78 °C) solution of benzylated **31** (12.7 mg, 18.8 µmol) in DCM (0.2 mL) was added slowly BCl_3 (1 M in DCM, 0.400 mL, 0.40 mmol, 20 eq.). After stirring for 5 h at -78 °C, the reaction was quenched with MeOH (5 mL) and allowed to warm to room temperature overnight. Concentration *in vacuo*, co-evaporation with toluene (3x) and purification by column chromatography (20% MeOH in DCM) gave compound **33** as a white solid (5.20 mg, 16.5 µmol, 88%). ^{1}H NMR (400 MHz, MeOD): δ (ppm) 3.81 (dd, *J* = 8.7, 5.7 Hz, 1H, H-2), 3.72 (dd, *J* = 10.6, 3.9 Hz, 1H, H-8), 3.55 (dd, *J* = 10.5, 6.5 Hz, 1H, H-8), 3.34 – 3.30 (m, 2H, CH_2N_3), 3.09 (t, *J* = 6.6 Hz, 2H, CH_2N), 3.03 (t, *J* = 10.1 Hz, 1H, H-4), 2.97 – 2.85 (m, 1H, H-3), 1.85 – 1.80 (m, 1H, H-1), 1.74 – 1.70 (m, 1H, H-5), 1.63 – 1.54 (m, 5H, 2 x CH_2 and H-7), 1.53 – 1.49 (m, 1H, H-6). ^{13}C NMR (100 MHz, MeOD): δ (ppm) 174.8 (C=O), 76.5 (C-3), 72.6 (C-4), 72.2 (C-2), 64.7 (C-8), 52.2 (CH_2N_3), 46.4 (C-5), 40.1 (CH_2N), 28.7 (C-1), 27.9 (CH_2), 27.3 (CH_2), 27.2 (C-7), 23.2 (C-6). HRMS: calculated for $[C_{13}H_{22}N_4O_5]^+$ 315.16630, found 315.16635.

(1*S*,2*S*,3*R*,4*R*,5*R*,6*S*,7*S*)-*N*-(4-azidobutyl)-2,3,4-trihydroxy-5-(hydroxymethyl)bicyclo[4.1.0]heptane-7-carboxamide (34)

To a cooled (-78 °C) solution of benzylated **32** (12.7 mg, 18.8 µmol) in DCM (0.2 mL) was added slowly BCl_3 (1 M in DCM, 0.400 mL, 0.40 mmol, 20 eq.). After stirring for 3 h at -78 °C, additional BCl_3 (1 M in DCM, 0.400 mL, 0.376 mmol, 20 eq.) was added. After stirring overnight at -20 °C, the reaction was quenched with MeOH (5 mL) and allowed to warm to room temperature. Concentration *in vacuo*, co-evaporation with MeOH (3 x) and purification by column chromatography (20% MeOH in DCM) gave compound **34** as a slightly yellow solid (5.9 mg, 18.6 µmol, 99%). ^{1}H NMR (400 MHz, MeOD): δ (ppm) 3.80 (d, *J* = 6.3 Hz, 1H, H-8), 3.53 – 3.44 (m, 2H, H-2 and H-8), 3.17 – 3.01 (m, 3H, H-3 and NHC*H*$_2$), 2.83 (t, *J* = 9.7 Hz, 1H, H-4), 2.07 – 1.90 (m, 1H, H-5), 1.76 – 1.61 (m, 1H, H-1), 1.54 – 1.44 (m, 4H, NHCH$_2$C*H*$_2$, and C*H*$_2$CH$_2$N$_3$), 1.44 – 1.38 (m, 1H, H-7), 1.34 – 1.28 (m, 1H, H-6). ^{13}C NMR (100 MHz, MeOD): δ (ppm)

79.6 (C-3), 74.5 (C-2), 70.7 (C-4), 65.1 (C-8), 52.3 (CH_2N_3), 43.8 (C-5), 40.2 ($NHCH_2$), 27.9, 27.9 ($CH_2CH_2N_3$ and $NHCH_2CH_2$), 27.5 (C-7), 25.0 (C-1), 24.5 (C-6). HRMS: calculated for $[C_{13}H_{22}N_4O_5]^+$ 315.16630, found 315.16635.

(1*S*,2*S*,3*R*,4*S*,5*R*,6*R*)-2,3,4-tris(benzyloxy)-5-((benzyloxy)methyl) bicyclo[4.1.0]heptane (36)

To a solution of DCM (0.5 mL) and 1,2-dimethoxyethane (100 µL) was added consecutively boron trifluoride ethyl etherate (62 µL) and diethylzinc (1 M in hexane, 1.0 mL, 1.0 mmol) at room temperature. After stirring for 5 min, diiodomethane (161 µL, 2.0 mmol) was added and the reaction mixture was stirred for additional 5 min. Compound **35** (52.0 mg, 0.100 mmol) was dissolved in DCM (1.0 mL) and added dropwise to the reaction mixture. After stirring overnight, the reaction mixture was quenched with a saturated aqueous NH_4Cl solution and diluted with EtOAc. The aqueous layer was extracted with EtOAc (3x) and the combined organic layers were washed with brine, dried over $MgSO_4$, filtered and concentrated *in vacuo*. Purification by column chromatography (pentane → 8% EtOAc in pentane) gave benzylated cyclopropane **36** (45.1 mg, 84.3 µmol, 84%) as a clear oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 7.47 – 7.21 (m, 20H, H_{arom} Bn), 4.86 (dd, *J* = 27.0, 11.7 Hz, 2H, CH_2 Bn), 4.76 – 4.62 (m, 3H, CH_2 Bn), 4.58 (d, *J* = 11.7 Hz, 1H, CH_2 Bn), 4.47 (d, *J* = 4.4 Hz, 2H, CH_2 Bn), 4.39 (dd, *J* = 8.4, 6.6 Hz, 1H, H-2), 3.90 (s, 1H, H-4), 3.66 – 3.52 (m, 2H, H-8), 3.19 (dd, *J* = 8.4, 1.1 Hz, 1H, H-3), 1.90 – 1.85 (m, 1H, H-5), 1.55 – 1.40 (m, 1H, H-1), 0.84 – 0.69 (m, 2H, H-6 and H-7), 0.30 (q, *J* = 5.2 Hz, 1H, H-7). ^{13}C NMR (101 MHz, $CDCl_3$): δ (ppm) 139.4, 139.4, 139.2, 138.4 (C_q Bn), 128.5, 128.4, 128.4, 128.3, 128.1, 128.0, 127.9, 127.8, 127.5, 127.5, 127.4 (C_{arom} Bn), 83.3 (C-3), 76.8 (C-2), 76.3 (C-4), 74.0, 73.3, 72.8, 71.3 (CH_2 Bn), 42.4 (C-5), 16.3 (C-1), 14.0 (C-6), 11.5 (C-7). HRMS: calculated for $[C_{36}H_{39}O_4]^+$ 557.26623, found 557.26551.

(1*S*,2*S*,3*R*,4*S*,5*R*,6*R*)-5-(hydroxymethyl)bicyclo[4.1.0]heptane-2,3,4-triol (37)

Compound **36** (40.0 mg, 74.8 µmol) was treated according to General procedure for global debenzylation with $Pd(OH)_2$/C to obtain title compound **37** as a clear oil (13.0 mg, 74.7 µmol, 99%). ^{1}H NMR (400 MHz, D_2O): δ (ppm) 4.20 (dd, *J* = 9.0, 6.6 Hz, 1H, H-2), 3.80 (s, 1H, H-4), 3.76 – 3.62 (m, 2H, H-8), 3.17 (dd, *J* = 9.1, 1.7 Hz, 1H, H-3), 1.83 – 1.78 (m, 1H, H-5), 1.42 – 1.32 (m, 1H, H-1), 0.82 – 0.75 (m, 2H, H-6 and H-7), 0.25 – 0.18 (m, 1H, H-7). ^{13}C NMR (101 MHz, D_2O): δ (ppm) 73.6 (C-3), 71.8 (C-4), 69.4 (C-2), 62.9 (C-8), 43.3 (C-5), 17.6 (C-1), 12.5 (C-6), 10.4 (C-7). HRMS: calculated for $[C_8H_{14}O_4Na]^+$ 197.07843, found 197.07839.

(1*R*,2*S*,3*R*,4*S*,5*R*,6*R*,7*R*)-ethyl 2,3,4-tris(benzyloxy)-5-((benzyloxy) methyl)bicyclo[4.1.0]heptane-7-carboxylate (38) and (1*S*,2*S*,3*R*,4*S*, 5*R*,6*S*,7*S*)-ethyl 2,3,4-tris(benzyloxy)-5-((benzyloxy)methyl)bicyclo [4.1.0]heptane-7-carboxylate (39)

A 2-necked pear flask was charged with cyclic alkene **35** (2.94 g, 5.65 mmol), $Cu(acac)_2$ (153 mg, 0.57 mol, 0.1 eq.) and EtOAc (10 mL, dried over activated 4 Å molsieves overnight). After stirring under reflux at 90 °C a solution of ethyl diazoacetate (13 wt% DCM, 17.1 mmol, 1.46 mL, 3 eq.) in EtOAc (38 mL) was added by syringe pump over 12 h. The reaction was concentrated *in vacuo* and purification by column chromatography (5% → 7% EtOAc in pentane) gave a mixture of the desired products **38** (666 mg, 1.10 mmol, 19%) and **39** (333 mg, 0.55 mmol, 10%). Spectral data was obtained from analytical samples of both products. **38:** ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 7.34 – 7.23 (m, 20H, H_{arom}Bn), 4.88 (d, J = 11.6 Hz, 1H, CH_2Bn), 4.81 – 4.60 (m, 4H, CH_2Bn), 4.56 (d, J = 11.6 Hz, 1H, CH_2Bn), 4.50 – 4.40 (m, 2H, CH_2Bn), 4.37 (dd, J = 8.2, 6.4 Hz, 1H, H-2), 4.14 – 4.08 (m, 2H, C*H*$_2$CH$_3$), 3.91 (s, 1H, H-4), 3.64 (t, J = 9.0 Hz, 1H, H-8), 3.56 (dd, J = 8.6, 6.3 Hz, 1H, H-8), 3.15 (d, J = 8.2 Hz, 1H, H-3), 2.13 – 2. 04 (m, 1H, H-1), 1.99 – 1.93 (m, 1H, H-5), 1.62 – 1.58 (m, 1H, H-7), 1.40 – 1.34 (m, 1H, H-6), 1.28 – 1.25 (m, 3H, CH_3). ^{13}C NMR (101 MHz, $CDCl_3$) δ (ppm) 173.50 (C_q carbonyl), 139.2, 139.0, 139.0, 138.4 (4 x C_q Bn), 128.6, 128.4, 128.3, 128.0, 128.0, 127.9, 127.6, 127.5 (CH_{arom}), 82.9 (C-3), 76.2 (C-2), 75.7 (C-4), 74.1, 73.4, 73.0, 71.6 (4 x CH_2 Bn), 70.5 (C-8), 60.7 (CH_2CH_3), 41.4 (C-5), 27.1 (C-1), 26.0 (C-7), 24.5 (C-6), 14.4 (CH_3). HRMS: calculated for $[C_{39}H_{43}O_6]^+$ 607.30542, found 607.30560. Analytical data for **39:** ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 7.40 – 7.24 (m, 20H, H_{arom}Bn), 4.87 (d, *J* = 11.6 Hz, 1H, CH_2Bn) 4.78 – 4.65 (m, 4H, CH_2Bn), 4.53 – 4.40 (m, 3H, CH_2Bn), 4.14 – 4.08 (m, 2H, C*H*$_2$CH$_3$), 4.08 – 4.02 (m, 1H, H-4), 4.00 (d, *J* = 8.8 Hz, 1H, H-2), 3.66 – 3.58 (m, 1H, H-8), 3.57 – 3.51 (m, 1H, H-8), 3.47 (dd, *J* = 8.8, 1.7 Hz, 1H, H-3), 2.47 – 2.38 (m, 1H, H-5), 2.09 (t, *J* = 4.6 Hz, 1H, H-7), 1.72 (dd, *J* = 9.4, 4.4 Hz, 1H, H-1/H-6), 1.59 – 1.52 (m, 1H, H-1/H-6), 1.22 (s, 3H, CH_3). ^{13}C NMR (101 MHz, $CDCl_3$): δ (ppm) 174.0 (C_q carbonyl), 139.2, 138.9, 138.6, 138.3 (4 x C_q Bn), 128.6, 128.5, 128.4, 128.3, 128.0, 127.8, 127.8, 127.7, 127.6, 127.6, 127.6, 127.4 (CH_{arom}), 84.3 (C-3), 77.7 (C-2), 74.9 (CH_2 Bn), 74.8 (C-4), 73.4, 72.9, 72.7 (3 x CH_2 Bn), 70.4 (C-8), 60.7 (CH_2CH_3), 38.4 (C-5), 26.1, 23.1 (C-1 and C-6), 22.6 (C-7), 14.4 (CH_3). HRMS: calculated for $[C_{39}H_{43}O_6]^+$ 607.30542, found 607.30550.

((1*R*,2*S*,3*R*,4*S*,5*R*,6*R*,7*R*)-2,3,4-tris(benzyloxy)-5-((benzyloxy)methyl) bicyclo[4.1.0]heptan-7-yl)methanol (40) and ((1*S*,2*S*,3*R*,4*S*,5*R*,6*S*, 7*S*)-2,3,4-tris(benzyloxy)-5-((benzyloxy)methyl)bicyclo[4.1.0]heptan-7-yl)methanol (41)

A mixture of **38** and **39** (0.254 g, 0.420 mmol) was dissolved in DCM (2.1 mL) at 0 °C, after which DIBAL (1 M in hexanes, 1.05 mmol, 2.5 eq.) was added dropwise. After the mixture was stirred for 1 h at 0 °C the reaction was quenched with EtOAc, diluted with DCM and washed with 1 M aqueous HCl. The layers were separated and the aqueous layer was extracted three times with DCM. The combined organic layers were washed with saturated aqueous $NaHCO_3$ and brine, dried over $MgSO_4$, filtered and concentrated *in vacuo*. Purification by column chromatography (pentane → 30% EtOAc in pentane) yielded compound **40** (94.5 mg, 0.167 mmol, 40%) and **41** (85.7 mg, 0.152 mmol, 36%) as yellow oils. Analytical data for **40:** ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 7.42 – 7.21 (m, 20H, CH_{arom}), 4.88 (d, *J* = 11.6 Hz, 1H, CH_2 Bn), 4.78 (d, *J* = 11.6 Hz, 1H, CH_2 Bn), 4.73 – 4.64 (m, 3H, CH_2 Bn), 4.57 (d, 11.6 Hz, 1H, CH_2 Bn), 4.52 – 4.40 (m, 2H, CH_2 Bn), 4.35 (t, *J* = 8.0 Hz, 1H, H-2), 3.89 (s, 1H, H-4), 3.65 – 3.51 (m, 2H, H-8), 3.44 (dd, *J* = 11.2, 6.7 Hz, 1H, C*H*HOH), 3.35 (dd, *J* = 11.2, 6.8 Hz, 1H, CH*H*OH), 3.17 (d, *J* = 8.3 Hz, 1H, H-3), 1.93 – 1.79 (m, 1H, H-5), 1.36 – 1.30 (m, 1H, H-1) 1.07 – 0.99 (m, 1H, H-7), 0.72 – 0.63 (m, 1H, H-6). ^{13}C NMR (101 MHz, $CDCl_3$): δ (ppm) 139.3, 139.3, 139.0, 138.3 (4 x $C_{q\text{-}arom}$), 128.5, 128.5, 128.4, 128.3, 128.1, 128.0, 127.9, 127.8, 127.6, 127.5, 127.5 (CH_{arom}), 83.6 (C-3), 76.9 (C-2), 76.1 (C-4), 74.0, 73.3, 72.9, 71.7 (4 x CH_2 Bn), 71.1 (C-8), 66.6 (*C*H$_2$OH), 41.8 (C-5), 27.4 (C-7), 22.1 (C-1), 19.5 (C-6). HRMS: calculated for $[C_{37}H_{41}O_5]^+$ 565.29485, found 565.29480. Analytical data for **41:** ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 7.41 – 7.20 (m, 20H, CH_{arom}), 4.85 (d, *J* = 11.6 Hz, 1H, CH_2 Bn), 4.78 – 4.67 (m, 4H, CH_2 Bn), 4.53 – 4.41 (m, 3H, CH_2 Bn), 4.01 – 3.92 (m, 2H, H-2 and H-4), 3.64 – 3.52 (m, 2H, H-8), 3.50 – 3.41 (m, 2H, H-3 and C*H*HOH), 3.16 (dd, *J* = 11.1, 7.7 Hz, 1H, CH*H*OH), 2.47 – 2.38 (m, 1H, H-5), 1.51 – 1.48 (m, 1H, H-7), 1.01 – 0.95 (m, 1H, H-1), 0.86 – 0.79 (m, 1H, H-6). ^{13}C NMR (101 MHz, $CDCl_3$) δ (ppm) 139.3, 139.1, 139.0, 138.4 (4 x $C_{q\text{-}arom}$), 128.6, 128.5, 128.4, 128.3, 128.0, 127.9, 127.8, 127.7, 127.6, 127.6, 127.5, 127.4 (CH_{arom}), 84.4 (C-3), 78.2 (C-2), 75.4 (C-4), 74.7, 73.5, 72.8, 72.8 (4 x CH_2 Bn), 71.0 (C-8), 67.0 (*C*H$_2$OH), 37.9 (C-5), 23.2 (C-7), 21.5 (C-1), 18.3 (C-6). HRMS: calculated for $[C_{37}H_{41}O_5]^+$ 565.29485, found 565.29472.

(1*R*,2*S*,3*R*,4*S*,5*R*,6*R*,7*R*)-5,7-bis(hydroxymethyl)bicyclo[4.1.0] heptane-2,3,4-triol (42)

Alcohol **40** (30.0 mg, 53 µmol) was treated according to General procedure for global debenzylation with 10% Pd on carbon to obtain the title compound **42** (10.9 mg, 53 µmol, quant.) as a clear oil. ^{1}H NMR (400 MHz, D_2O): δ (ppm) 4.20 (dd, *J* = 9.1, 6.6 Hz, 1H, H-2), 3.85 – 3.82 (m, 1H, H-4), 3.78 – 3.66 (m, 2H, H-8), 3.58 (dd, *J* = 11.6, 6.1 Hz, 1H, C-*H*HOH), 3.27 (dd, *J* = 11.6, 7.8 Hz, 1H, CH*H*OH), 3.20 (dd, *J* = 9.1, 1.8 Hz, 1H, H-3), 1.90 – 1.82 (m, 1H, H-5), 1.36 – 1.29 (m, 1H, H-1), 1.05 – 0.97 (m, 1H, H-7), 0.77 – 0.70 (m, 1H, H-6). ^{13}C NMR (101 MHz, D_2O): δ (ppm) 74.0 (C-3), 71.6 (C-4), 68.6 (C-2), 65.3 (CH_2OH), 62.7 (C-8), 42.7 (C-5), 25.8 (C-7), 23.2 (C-1), 18.3 (C-6). HRMS: calculated for $[C_9H_{16}O_5Na]^+$ 227.08899, found 227.08899.

(1*S*,2*S*,3*R*,4*S*,5*R*,6*S*,7*S*)-5,7-bis(hydroxymethyl)bicyclo[4.1.0] heptane-2,3,4-triol (43)

Alcohol **41** (35 mg, 62 µmol) was treated according to General procedure for global debenzylation with 10% Pd on carbon to obtain the title compound **43** (11.2 mg, 54 µmol, 87%) as a clear oil. ^{1}H NMR (400 MHz, D_2O): δ (ppm) 4.01 – 3.95 (m, 1H, H-4), 3.83 (d, *J* = 8 Hz 1H, H-2), 3.78 – 3.64 (m, 2H, H-8), 3.41 – 3.31 (m, 3H, CH_2OH and H-3), 2.29 – 2.20 (m, 1H, H-5), 1.31 – 1.21 (m, 1H, H-7), 1.02 – 0.92 (m, 1H, H-6), 0.92 – 0.84 (m, 1H, H-1). ^{13}C NMR (101 MHz, D_2O): δ (ppm) 76.0 (C-3), 69.6, 69.5 (C-2 and C-4), 65.6 (CH_2OH), 62.4 (C-8), 38.8 (C-5), 22.6 (C-7), 21.9 (C-1), 17.8 (C-6). HRMS: calculated for $[C_9H_{17}O_5]^+$ 205.10705, found 205.10753.

(1*R*,2*S*,3*R*,4*S*,5*R*,6*R*,7*R*)-2,3,4-tris(benzyloxy)-5-((benzyloxy)methyl)-7-(ethoxymethyl)bicyclo[4.1.0]heptane (44)

To a solution of alcohol **40** (33.9 mg, 60.0 µmol) and TBAI (10 mg) in DMF (0.8 mL) was added NaH (60% dispersion in mineral oil, 19.2 mg, 0.480 mmol 8 eq.) at 0 °C. After stirring the reaction mixture for 5 min, ethyl bromide (20 µL, 0.36 mmol, 6 eq.) was added and the reaction mixture was stirred overnight at room temperature. The reaction mixture was quenched with H_2O (3 mL) and diluted with EtOAc (20 mL). The organic layer was separated and washed with saturated aqueous $NaHCO_3$, H_2O (3x) and brine. The combined aqueous layers were extracted with EtOAc and the combined organic layers were dried over $MgSO_4$, filtered and concentrated *in vacuo*. Purification by column chromatography (pentane → 20% EtOAc in pentane) gave ether **44** as a yellow oil (28.5 mg, 48.1 µmol, 80%). ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 7.43 – 7.21 (m, 20H, H_{arom}), 4.88 (d, *J* = 11.6 Hz, 1H, CH_2 Bn), 4.83 (d, *J* = 11.6 Hz, 1H, CH_2 Bn), 4.77 – 4.61 (m, 3H, CH_2 Bn), 4.58 (d, *J* = 11.7 Hz, 1H, CH_2 Bn), 4.52 – 4.40 (m, 2H, CH_2 Bn), 4.39 – 4.33 (m, 1H, H-2), 3.90 (s, 1H, H-4), 3.68 – 3.53 (m, 2H, H-8), 3.52 – 3.37 (m, 2H, C*H*$_2$CH$_3$), 3.35 – 3.22 (m, 2H, CH_2O), 3.18 (d, *J* = 8.3 Hz, 1H, H-3), 1.97 – 1.87 (m, 1H, H-5), 1.41 – 1.35 (m, 1H, H-1), 1.15 (t, *J* = 7.0 Hz, 3H, CH_3), 1.04 (p, *J* = 6.2 Hz, 1H, H-7), 0.70 – 0.64 (m, 1H, H-6). ^{13}C NMR (101 MHz, $CDCl_3$): δ (ppm) 139.5, 139.4, 139.2, 138.4 (4 x $C_{q\text{-}arom}$), 128.5, 128.4, 128.3, 128.3, 128.1, 127.9, 127.8, 127.5, 127.5, 127.4 (CH Bn), 83.6 (C-3), 76.9 (C-2), 76.2 (C-4), 74.2, 74.0, 73.3, 72.9 (3 x CH_2 Bn and CH_2O), 71.1, 71.0 (CH_2 Bn and C-8), 65.8 (*C*H$_2$CH$_3$), 41.8 (C-5), 24.5 (C-7), 21.6 (C-1), 20.0 (C-6), 15.4 (CH_3). HRMS: calculated for $[C_{39}H_{45}O_5]^+$ 593.32615, found 593.32617.

(1*S*,2*S*,3*R*,4*S*,5*R*,6*S*,7*S*)-2,3,4-tris(benzyloxy)-5-((benzyloxy)methyl)-7-(ethoxymethyl)bicyclo[4.1.0]heptane (45)

To a solution of alcohol **41** (38.0 mg, 67.3 µmol) and a catalytic amount of TBAI in DMF (0.8 mL) was added NaH (60% dispersion in mineral oil, 21.4 mg, 0.536 mmol 8 eq.) at 0 °C. After stirring the reaction mixture for 5 min, ethyl bromide (50 µL, 0.66 mmol, 10 eq.) was added and the reaction mixture was stirred overnight. The reaction mixture was quenched with H_2O (3 mL) and diluted with EtOAc (20 mL). The organic layer was separated and washed with saturated aqueous $NaHCO_3$, H_2O (3x) and brine. The combined aqueous layers were extracted with EtOAc and the combined organic layers were dried over $MgSO_4$, filtered and concentrated *in vacuo*. Purification by column chromatography (pentane → 20% EtOAc in pentane) gave ether **45** as a yellow oil (29.6 mg, 50.0 µmol, 74%). ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 7.40 – 7.22 (m, 20H, H_{arom}), 4.87 (d, *J* = 11.6 Hz, 1H, CH_2 Bn), 4.80 – 4.67 (m, 4H, CH_2 Bn), 4.49 – 4.44 (m, 3H, CH_2 Bn), 4.03 (dd, *J* = 3.8, 1.7 Hz, 1H, H-4), 3.99 (d, *J* = 8.7 Hz, 1H, H-2), 3.68 – 3.61 (m, 1H, H-8), 3.59 – 3.50 (m, 1H, H-8), 3.47 – 3.40 (m, 3H, H-3 and C*H*$_2$CH$_3$), 3.20 (d, *J* = 6.8 Hz, 2H, CH_2O), 2.40 – 2.37 (m, 1H, H-5), 1.51 – 1.43 (m, 1H, H-7), 1.17 (t, *J* = 7.0 Hz, 3H, CH_3), 0.99 (dd, *J* = 8.9, 4.4 Hz, 1H, H-6), 0.85 – 0.77 (m, 1H, H-1). ^{13}C NMR (101 MHz, $CDCl_3$): δ (ppm) 139.5, 139.2, 139.0, 138.5 (4 x $C_{q\text{-}arom}$), 128.5, 128.4, 128.4, 128.3, 128.3, 128.2, 128.1, 127.9, 127.9, 127.7, 127.6, 127.5, 127.5, 127.5, 127.4, 127.3 (CH Bn), 84.8 (C-3), 78.3 (C-2), 75.4 (C-4), 74.8 (CH_2 Bn), 74.4 (CH_2O), 73.5, 72.7, 72.4 (3 x CH_2 Bn), 71.0 (C-8), 65.6 (*C*H$_2$CH$_3$), 38.6 (C-5), 21.3 (C-6), 20.5 (C-7), 18.4 (C-1), 15.4 (CH_3). HRMS: calculated for $[C_{39}H_{45}O_5]^+$ 593.32615, found 593.32603.

(1*R*,2*S*,3*R*,4*S*,5*R*,6*R*,7*R*)-7-(ethoxymethyl)-5-(hydroxymethyl)bicyclo [4.1.0]heptane-2,3,4-triol (46)

Ether **44** (20 mg, 34 µmol) was treated according to General procedure for global debenzylation with 10% Pd on carbon to obtain the title compound **46** (8.0 mg, 35 µmol, quant.) as a clear oil. ^{1}H NMR (400 MHz, D_2O): δ (ppm) 4.22 – 4.18 (dd, *J* = 6.4, 9.2 Hz, 1H, H-2), 3.83 (s, 1H, H-4), 3.75 – 3.67 (m, 2H, H-8), 3.63 – 3.51 (m, 3H, C*H*HO and C*H*$_2$CH$_3$), 3.23 – 3.13 (m, 2H, CH*H*O and H-3), 1.91 – 1.83 (m, 1H, H-5), 1.38 – 1.28 (m, 1H, H-1), 1.17 (t, *J* = 7.1 Hz, 3H, CH_3), 1.05 – 0.96 (m, 1H, H-7), 0.80 – 0.73 (m, 1H, H-6). ^{13}C NMR (101 MHz, D_2O): δ (ppm) 73.9, 73.8 (C-3 and CH_2O), 71.5 (C-4), 68.6 (C-2), 66.1 (*C*H$_2$CH$_3$), 62.6 (C-8), 42.6 (C-5), 23.3, 23.2 (C-1 and C-7), 18.7 (C-6), 14.1 (CH_3). HRMS: calculated for $[C_{11}H_{20}O_5Na]^+$ 255.12029, found 255.12034.

(1*S*,2*S*,3*R*,4*S*,5*R*,6*S*,7*S*)-7-(ethoxymethyl)-5-(hydroxymethyl)bicyclo [4.1.0]heptane-2,3,4-triol (47)

Ether **45** (23.0 mg, 39 µmol) was treated according to General procedure for global debenzylation with 10% Pd on carbon to obtain the title compound **47** (9.0 mg, 39 µmol, quant.) as a clear oil. ^{1}H NMR (400 MHz, D_2O): δ (ppm) 4.02 – 3.95 (m, 1H, H-4), 3.84 (d, *J* = 8.9 Hz, 1H, H-2), 3.75 – 3.67 (m, 2H, H-8), 3.62 – 3.52 (m, 2H, C*H*$_2$CH$_3$), 3.42 – 3.33 (m, 2H, H-3 and C*H*HO), 3.29 – 3.22 (m, 1H, CH*H*O), 2.31 – 2.21 (m, 1H, H-5), 1.32 – 1.26 (m, 1H, H-7), 1.18 (t, *J* = 7.1 Hz, 3H, CH_3), 1.02 – 0.96 (m, 1H, H-6), 0.93 – 0.86 (m, 1H, H-1). ^{13}C NMR (101 MHz, D_2O): δ (ppm) 75.9 (C-3), 74.2 (CH_2O), 69.5, 69.4 (C-2 and C-4), 65.9 (*C*H$_2$CH$_3$), 62.3 (C-8), 38.9 (C-5), 22.3 (C-1), 20.1 (C-7), 17.9 (C-6), 14.1 (CH_3). HRMS: calculated for $[C_{11}H_{21}O_5]^+$ 233.13835, found 233.13951.

(1*R*,2*S*,3*R*,4*S*,5*R*,6*R*,7*S*)-1-(2,3,4-tris(benzyloxy)-5-((benzyloxy) methyl)bicyclo[4.1.0]heptan-7-yl)propan-1-one (48) and (1*S*,2*S*,3*R*, 4*S*,5*R*,6*S*,7*S*)-1-(2,3,4-tris(benzyloxy)-5-((benzyloxy)methyl)bicyclo [4.1.0]heptan-7-yl)propan-1-one (49)

To a mixture of **38** and **39** (126 mg, 0.207 mmol) in THF (2.7 mL) was added Me(MeO)NH.HCl (26.3 mg, 0.270 mmol, 1.3 eq.) at -8 °C. Subsequently, EtMgBr (1 M in THF, 1.7 mL, 1.7 mmol, 8.4 eq.) was added over 2 h. After the mixture had stirred overnight, it was quenched with NaOH (0.5 M). The reaction mixture was extracted with EtOAc (10 mL), after which the organic layer was washed with aqueous HCl (3 M). The organic layer was dried over $MgSO_4$, filtered, concentrated *in vacuo* and co-evaporated with toluene (3x). The residue was dissolved in THF (1 mL) and EtMgBr (1 M in THF, 0.60 mmol, 3 eq.) was added over 2 min at -20 °C. After the reaction was allowed to come to room temperature and stirred for 3 h, the reaction was quenched with a saturated aqueous NH_4Cl solution. After extraction with EtOAc (10 mL), the organic layer was dried over $MgSO_4$, filtered and concentrated *in vacuo*. Purification by

column chromatography (8% EtOAc in pentane → 10% EtOAc in pentane) followed by purification by HPLC (C18, linear gradient: 50-90% B in A, solutions used A: H2O, B: acetonitrile, 0.1% TFA, 15 min) gave compound **48** (19.4 mg, 32.8 µmol, 16%) and compound **49** (25.2 mg, 42.6 µmol, 21%). Analytical data for **48:** ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 7.39 – 7.22 (m, 20 H, H_{arom}), 4.88 (d, *J* = 11.6 Hz, 1H, CH_2Bn), 4.76 – 4.52 (m, 5H, CH_2Bn), 4.44 (d, *J* = 3.1 Hz, 2H, CH_2Bn), 4.35 (dd, *J* = 8.3, 6.3 Hz, 1H, H-2), 3.92 (s, 1H, H-4), 3.63 (t, *J* = 9.0 Hz, 1H, H-8), 3.57 – 3.50 (m, 1H, H-8), 3.19 (d, *J* = 7.6 Hz, 1H, H-3), 2.56 (d, *J* = 8.0 Hz, 1H, C*H*HCH$_3$), 2.52 (d, *J* = 8.0 Hz, 1H, CH*H*CH$_3$), 2.14 – 2.07 (m, 1H, H-1), 1.98 – 1.87 (m, 2H, H-5 and H-7), 1.48 – 1.39 (m, 1H, H-6), 1.06 (t, *J* = 7.3 Hz, 3H, CH_3). ^{13}C NMR (101 MHz, $CDCl_3$) δ (ppm) 209.81 (C_q carbonyl), 139.2, 139.0, 138.9, 138.2 (4 x $C_{q\text{-}arom}$), 128.6, 128.5, 128.4, 128.3, 128.0, 127.9, 127.9, 127.9, 127.7, 127.5, 127.5 (CH Bn), 83.2 (C-3), 76.5 (C-2), 75.6 (C-4), 74.1, 73.5, 72.9, 71.6 (4 x CH_2 Bn), 70.6 (C-8), 41.7 (C-5), 37.1 (*C*H$_2$CH$_3$), 33.7 (C-7), 29.9 (C-1), 26.6 (C-6), 8.1 (CH_3). HRMS: calculated for $[C_{39}H_{43}O_5]^+$ 591.31050, found 591.31043. Analytical data for **49:** ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 7.39 – 7.22 (m, 20H, H_{arom}), 4.90 (d, *J* = 11.6 Hz, 1H, CH_2Bn), 4.80 – 4.60 (m, 4H, CH_2Bn), 4.53 – 4.38 (m, 3H, CH_2Bn), 4.07 – 4.01 (m, 1H, H-4), 3.96 (d, *J* = 8.7 Hz, 1H, H-2), 3.58 (t, *J* = 8.8 Hz, 1H, H-8), 3.54 – 3.44 (m, 2H, H-3 and H-8), 2.50 – 2.39 (m, 3H, C*H*$_2$CH$_3$, H-7), 1.78 (dd, *J* = 9.2, 4.4 Hz, 1H, H-1/H-6), 1.60 – 1.5 (m, 1H, H-1/H-6), 1.03 (t, *J* = 7.3 Hz, 3H, CH_3). ^{13}C NMR (101 MHz, $CDCl_3$): δ (ppm) 210.38 (C_q carbonyl), 139.4, 138.9, 138.5, 138.3 (4 x $C_{q\text{-}arom}$), 128.6, 128.5, 128.4, 128.4, 128.0, 127.9, 127.8, 127.7, 127.6, 127.5, 127.4 (CH Bn), 84.2 (C-2), 77.9 (C-3), 75.1 (C-4), 74.9, 73.5, 72.9, 72.5 (4 x CH_2 Bn), 70.4 (C-8), 38.5 (C-5), 37.1 (CH_2CH_3), 30.0 (C-7), 28.1, 25.9 (C-1 and C-6), 8.2 (CH_3). HRMS: calculated for $[C_{39}H_{43}O_5]^+$ 591.31050, found 591.31025.

(1*R*,2*S*,3*R*,4*S*,5*R*,6*R*,7*R*)-1-(2,3,4-trihydroxy-5-(hydroxymethyl) bicyclo[4.1.0]heptan-7-yl)propan-1-one (50)

Ethyl ketone **48** (14.8 mg, 25 µmol) was treated according to General procedure for global debenzylation with 10% Pd on carbon to obtain the title compound **50** (4.6 mg, 20 µmol, 80%) as a white solid. ^{1}H NMR (400 MHz, D_2O): δ (ppm) 4.26 (dd, *J* = 9.0, 6.1 Hz, 1H, H-2), 3.89 (s, 1H, H-4), 3.81 – 3.65 (m, 2H, H-8), 3.29 (dd, *J* = 9.1, 1.6 Hz, 1H, H-3), 2.74 (d, *J* = 8.0 Hz, 1H, C*H*HCH$_3$), 2.70 (d, *J* = 8.0 Hz, 1H, CH*H*CH$_3$), 2.18 (t, *J* = 4.6 Hz, 1H, H-7), 2.11 – 2.04 (m, 1H, H-1), 2.03 – 1.96 (m, 1H, H-5), 1.50 – 1.42 (m, 1H, H-6), 1.04 (t, *J* = 7.3 Hz, 3H, CH_3). ^{13}C NMR (101 MHz, D_2O): δ (ppm) 216.2 (C=O), 73.4 (C-3), 71.1 (C-4), 68.0 (C-2), 62.3 (C-8), 42.4 (C-5), 36.5 (*C*H$_2$CH$_3$), 33.2 (C-7), 31.8 (C-1), 26.5 (C-6), 7.4 (CH_3). HRMS: calculated for $[C_{11}H_{19}O_5]^+$ 231.12270, found 231.12260.

(1*S*,2*S*,3*R*,4*S*,5*R*,6*S*,7*S*)-1-(2,3,4-trihydroxy-5-(hydroxymethyl)bicycle [4.1.0]heptan-7-yl)propan-1-one (51)

Ethyl ketone **49** (12.0 mg, 20 µmol) was treated according to General procedure for global debenzylation with 10% Pd on carbon to obtain the title compound **51** (4.0 mg, 18 µmol, 88%) as a white solid. ^{1}H NMR (400 MHz, D_2O): δ (ppm) 3.93 (t, *J* = 2.8 Hz, 1H, H-4), 3.81 (d, *J* = 9.2 Hz, 1H, H-2), 3.72 – 3.55 (m, 2H, H-8), 3.36 (dd, *J* = 9.0, 2.3 Hz, 1H, H-3), 2.64 – 2.54 (m, 2H, C*H*$_2$CH$_3$), 2.37 (t, *J* = 4.6 Hz, 1H, H-7), 2.30 – 2.21 (m, 1H, H-5), 1.66 – 1.56 (m, 2H, H-1 and H-6), 0.96 (t, *J* = 7.4 Hz, 3H, CH_3). ^{13}C NMR (101 MHz, D_2O): δ (ppm) 217.1 (C=O), 75.4 (C-3), 69.0, 68.8 (C-2 and C-4), 62.0 (C-8), 38.8 (C-5), 36.5 (*C*H$_2$CH$_3$), 30.4 (C-1/C-2 and C-8), 26.6 (C-1/C-2), 7.6 (CH_3). HRMS: calculated for $[C_{11}H_{19}O_5]^+$ 231.12270, found 231.12283.

(1*R*,2*S*,3*R*,4*S*,5*R*,6*R*,7*R*)-*N*-(4-azidobutyl)-2,3,4-tris(benzyloxy)-5-((benzyloxy)methyl)bicyclo[4.1.0]heptane-7-carboxamide (52) and (1*S*,2*S*,3*R*,4*S*,5*R*,6*S*,7*S*)-*N*-(4-azidobutyl)-2,3,4-tris(benzyloxy)-5-((benzyloxy)methyl)bicyclo[4.1.0]heptane-7-carboxamide (53)

To a mixture of **38** and **39** (0.260 g, 0.428 mmol) in THF (16 mL), EtOH (4 mL), H_2O (3 mL) and MeOH (0.5 mL), was added LiOH (150 mg, 6.3 mmol, 14.7 eq.). After the mixture was stirred overnight at room temperature, 1 M aqueous HCl solution was used to acidify to pH 1, and the reaction mixture was partitioned between EtOAc (125 mL) and brine (30 mL). The aqueous layer was extracted with EtOAc (50 mL) and the combined organic layers were dried over MgSO4, filtered and concentrated *in vacuo*, resulting in a yellow oil. The crude acid was used without further purification. HRMS: calculated for $[C_{37}H_{39}O_6]^+$ 579.27412, found 579.27384. The crude acid was dissolved in DCM (7.6 mL) to this were added 4-azidobutan-1-amine (52 mg, 0.456 mmol, 1.1 eq.), *N*,*N*-diisopropylethylamine (230 µL, 1.33 mmol, 3.1 eq.) and HCTU (188 mg, 0.456 mmol, 1.1 eq.). After stirring overnight at room temperature, the reaction mixture was concentrated *in vacuo*, redissolved in EtOAc (40 mL), washed with 1 M aqueous HCl and saturated aqueous $NaHCO_3$, dried over $MgSO_4$, filtered and concentrated *in vacuo*. Purification by column chromatography (pentane → 30% EtOAc in pentane) followed by purification by HPLC (C18, linear gradient: 70-90% B in A, solutions used A: H2O, B: acetonitrile, 0.1% TFA, 15 min) afforded compound **52** (68.9 mg, 0.102 mmol, 24%) and compound **53** (51.0 mg, 75.6 µmol, 18%) as white solids. Analytical data for **52:** ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 7.39 – 7.21 (m, 20H, H_{arom}), 5.70 – 5.63 (m, 1H, NH), 4.88 (d, *J* = 11.6 Hz, 1H, CH_2 Bn), 4.75 – 4.55 (m, 5H, CH_2 Bn), 4.44 (d, *J* = 2.7 Hz, 2H, CH_2 Bn), 4.39 (dd, *J* = 8.3, 6.5 Hz, 1H, H-2), 3.93 (s, 1H, H-4), 3.66 (t, *J* = 8Hz, 1H, H-8), 3.58 – 3.54 (m, 1H, H-8), 3.31 –3.22 (m, 4H, 2 x CH_2 amide), 3.13 (d, *J* = 8.4 Hz, 1H, H-3), 2.15 – 2.05 (m, 1H, H-1), 1.93 – 1.85 (m, 1H, H-5), 1.64 – 1.48 (m, 4H, 2 x CH_2 amide), 1.45 – 1.36 (m, 1H, H-6), 1.31 – 1.23 (m, 1H, H-7). ^{13}C NMR (101 MHz, $CDCl_3$): δ (ppm) 172.1 (C=O), 139.2, 138.9, 138.8, 138.2 (4 x C_q), 128.5, 128.4, 128.4, 128.3, 128.1, 127.9, 127.9, 127.7, 127.5, 127.5 (CH_{arom}), 83.1 (C-3), 76.4 (C-2), 75.5 (C-4), 74.1, 73.5, 72.7, 71.5 (4 x CH_2 Bn), 70.6 (C-8), 51.1 (CH_2 amide), 41.6 (C-5), 39.2 (CH_2 amide), 28.1 (C-7), 27.2, 26.3 (2 x CH_2 amide), 26.0 (C-1), 23.0 (C-6). HRMS: calculated for $[C_{41}H_{47}N_4O_5]^+$ 675.35410, found 675.35401. Analytical data for **53** ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 7.40 – 7.24 (m, 20H, H_{arom}), 5.56 (t, *J* = 5.6 Hz, 1H, NH), 4.86 (d, *J* = 11.2 Hz, 1H, CH_2 Bn), 4.81 – 4.61 (m, 4H, CH_2 Bn), 4.54 – 4.42 (m, 3H, CH_2 Bn), 4.06 – 4.05 (m, 1H, H-4), 3.96 (d, *J* = 14.8 Hz, 1H, H-2), 3.60 (t, *J* = 9.0 Hz, 1H, H-8), 3.56 – 3.52 (m, 1H, H-8), 3.49 (dd, *J* = 8.7, 1.6 Hz, 1H, H-3), 3.31 – 3.16 (m, 4H, 2 x CH_2 amide), 2.51 – 2.42 (m, 1H, H-5), 1.77 – 1.72 (m, 2H, H-1 and H-7), 1.60 – 1.51 (m, 5H, H-6 and 2 x CH_2 amide). ^{13}C NMR (101 MHz, $CDCl_3$): δ (ppm) 172.77 (C=O), 139.4, 138.9, 138.6, 138.3 (4 x C_q), 128.5, 128.4, 128.4, 128.4, 128.0, 128.0, 127.9, 127.9, 127.8, 127.8, 127.6, 127.5 (CH_{arom}), 84.3 (C-3), 77.7 (C-2), 75.2 (C-4), 75.1, 73.4, 72.9, 72.2 (4 x CH_2 Bn), 70.3 (C-8, 51.1 (CH_2 amide), 39.3 (CH_2 amide), 38.1 (C-5), 27.1, 26.3 (2 xCH_2 amide), 24.5, 24.4 (C-1 and C-7), 21.7 (C-6). HRMS: calculated for $[C_{41}H_{47}N_4O_5]^+$ 675.35410, found 675.35385.

(1*R*,2*S*,3*R*,4*S*,5*R*,6*R*,7*R*)-*N*-(4-azidobutyl)-2,3,4-trihydroxy-5-(hydroxy methyl)bicyclo[4.1.0]heptane-7-carboxamide (54)

To a solution of benzylated **52** (62.5 mg, 93 µmol) in DCM (0.46 mL) was added slowly BCl_3 (1 M in DCM, 1.9 mL, 1.9 mmol, 20 eq.) at -78 °C. After stirring for 4 h at -78 °C, the reaction mixture was quenched with MeOH (3 mL). concentrated *in vacuo* and co-evaporated with toluene (3x). Purification by column chromatography (EtOAc → 20% MeOH in EtOAc) gave title compound **54** (29.0 mg, 93 µmol, quant.) as a white solid. ^{1}H NMR (400 MHz, D_2O): δ (ppm) 4.25 (dd, *J* = 9.1, 6.3 Hz, 1H, H-2), 3.85 (s, 1H, H-4), 3.77 – 3.65 (m, 2H, H-8), 3.33 (t, *J* = 6.2 Hz, 2H, CH_2 amide), 3.28 – 3.14 (m, 3H, CH_2 amide and H-3), 1.97 – 1.87 (m, 2H, H-1 and H-5), 1.66 – 1.52 (m, 5H, 2 x CH_2 amide and H-7), 1.31 –

1.25 (m, 1H, H-6). ^{13}C NMR (101 MHz, D_2O): δ (ppm) 174.6 (C_q), 73.5 (C-3), 71.1 (C-4), 67.8 (C-2), 62.3 (C-8), 50.8 (CH_2 amide), 42.2 (C-5), 39.1 (CH_2 amide), 27.0, 27.0 (C-1 and C-7), 25.8 (CH_2 amide), 25.4 (CH_2 amide), 21.8 (C-6). HRMS: calculated for $[C_{13}H_{23}N_4O_5]^+$ 315.16630, found 315.16638.

(1*S*,2*S*,3*R*,4*S*,5*R*,6*S*,7*S*)-*N*-(4-azidobutyl)-2,3,4-trihydroxy-5-(hydroxyl methyl)bicyclo[4.1.0]heptane-7-carboxamide (55)

To a solution of benzylated **53** (45.0 mg, 66 µmol) in DCM (0.50 mL) was added slowly BCl_3 (1 M in DCM, 1.5 mL, 1.5 mmol, 23 eq.). After stirring for 4 h at -78 °C, the reaction mixture was quenched with MeOH (3 mL). concentrated *in vacuo* and co-evaporated with toluene (3x). Purification by column chromatography (EtOAc → 20% MeOH in EtOAc) gave title compound **55** (14.6 mg, 46.4 µmol, 70%) as a white solid. ^{1}H NMR (400 MHz, D_2O): δ (ppm) 3.98 (t, *J* = 4.0 Hz, 1H, H-4), 3.84 (d, *J* = 9.0 Hz, 1H, H-2), 3.74 – 3.62 (m, 2H, H-8), 3.41 (dd, *J* = 9.0, 2.3 Hz, 1H, H-3), 3.31 (t, *J* = 6.4 Hz, 2H, CH_2 amide), 3.18 (t, *J* = 6.3 Hz, 2H, CH_2 amide), 2.34 – 2.25 (m, 1H, H-5), 1.91 (t, *J* = 4.7 Hz, 1H, H-7), 1.64 – 1.43 (m, 6H, 2 x CH_2 amide, H-1 and H-6). ^{13}C NMR (101 MHz, D_2O): δ (ppm) 175.3 (C=O), 75.5 (C-3), 69.0, 68.9 (C-2 and C-4), 61.9 (C-8), 50.7, 38.9 (2 x CH_2 amide), 38.5 (C-5), 25.8 (CH_2 amide), 25.7 (C-6), 25.3 (CH_2 amide), 24.0 (C-7), 21.4 (C-1). HRMS: calculated for $[C_{13}H_{23}N_4O_5]^+$ 315.16630, found 315.16615.

Supporting Information (see footnote on the first page of this article): ^{1}H NMR and ^{13}C APT NMR spectra for all new compounds.

Acknowledgements: We thank The Netherlands Organization for Scientific Research (NWO-CW, ChemThem grant to J.M.A. and H.S.O.) and the European Research Council (ERC-2011-AdG- 290836 "Chembiosphing" to H.S.O.

Keywords: cyclophellitol • cyclopropanation • conformational analysis • carbohydrate mimetic • glucosidase

References:

[1] S. Atsumi, K. Umezawa, H. Iinuma, H. Naganawa, H. Nakamura, Y. Iitaka, T. Takeuchi, *J. Antibiot.* **1990**, *43*, 49–53.

[2] S. G. Withers, K. Umezawa, *Biochem. Biophys. Res. Commun.* **1991**, *177*, 532–537.

[3] T. M. Gloster, R. Madsen, G. J. Davies, *Org. Biomol. Chem.* **2007**, *5*, 444–446.

[4] W. W. Kallemeijn, K.-Y. Li, M. D. Witte, A. R. A. Marques, J. Aten, S. Scheij, J. Jiang, L. I. Willems, T. M. Voorn-Brouwer, C. P. A. A. van Roomen, R. Ottenhoff, R. G. Boot, H. van den Elst, M. T. C. Walvoort, B. I. Florea, J. D. C. Codée, G. A. van der Marel, J. M. F. G. Aerts, H. S. Overkleeft, *Angew. Chem. Int. Ed.* **2012**, *51*, 12529–12533.

[5] Speciale, G., Thompson, A. J., Davies, G. J., & Williams, S. J.. *Current Opinion in Structural Biology*, **2014,** *28*, 1–13.

[6] T. J. M. Beenakker, D. P. A. Wander, W. A. Offen, M. Artola, L. Raich, M. J. Ferraz, K.-Y. Li, J. H. P. M. Houben, E. R. van Rijssel, T. Hansen, G. A. van der Marel, J. D. C. Codée, J. M. F. G. Aerts, C. Rovira, G. J. Davies, H. S. Overkleeft *J. Am. Chem. Soc.* **2017**, *139*, 6534–6537.

[7] N. Akiyama, S. Noguchi, M. Hashimoto, *Biosci. Biotech. Bioch.* **2011**, *75*, 1380–1382.

[8] F. G. Hansen, E. Bundgaard, R. Madsen, *J. Org. Chem.* **2005**, *70*, 10139–10142.

[9] K.-Y. Li, J. Jiang, M. D. Witte, W. W. Kallemeijn, H. van den Elst, C.-S. Wong, S. D. Chander, S. Hoogendoorn, T. J. M. Beenakker, J. D. C. Codée, J. M. F. G. Aerts, G. A. van der Marel, H. S. Overkleeft, *Eur. J. Org. Chem.* **2014**, *2014*, 6030–6043.

[10] T. Ye, M. A. McKervey, *Chem. Rev.* **1994**, *94*, 1091–1160.

[11] A. Caballero, A. Prieto, M. M. Diaz-Requejo, P. J. Pérez, *Eur. J. Inorg. Chem.* **2009**, *2009*, 1137–1144.

[12] C. M. Timmers, M. A. Leeuwenburgh, J. C. Verheijen, G. A. van der Marel, J. H. van Boom, *Tetrahedron Asymm.* **1996**, *7*, 49–52.

[13] M. D. P. Risseeuw, R. J. B. H. N. van den Berg, W. E. Donker-Koopman, G. A. van der Marel, J. M. F. G. Aerts, M. Overhand, H. S. Overkleeft, *Bioorg. Med. Chem. Lett.* **2009**, *19*, 6600–6603.

[14] M. D. P. Risseeuw, G. A. van der Marel, H. S. Overkleeft, M. Overhand, *Tetrahedron Asymm.* **2009**, *20*, 945–951.

[15] A. J. Anciaux, A. Demonceau, A. F. Noels, *J. Org. Chem.* **1981**, *46*, 873–876.

[16] E. Buchner, T. Curtius, *Ber. Dtsch. Chem. Ges.* **1885**, *18*, 2377–2379.

[17] W. D. Mackay, J. S. Johnson, *Org. Lett.* **2016**, *18*, 536–539.

[18] S. Chen, J. Ma, J. Wang, *Tetrahedron Lett.* **2008**, *49*, 6779–6781.

[19] M. P. Doyle, *Chem. Rev.* **1986**, *86*, 919–939.

[20] A. J. Anciaux, A. J. Hubert, A. F. Noels, N. Petiniot, P. Teyssie, *J. Org. Chem.* **1980**, *45*, 695–702.

[21] L. Remen, A. Vasella, *Helv. Chim. Acta* **2002**, *85*, 1118–1127.

[22] Fructos, M. R.; Belderrain, T. R.; Nicasio, M. C.; Nolan, S. P.; Kaur, H.; Díaz-Requejo, M. M.; Pérez, P. J., *J. Am. Chem. Soc.* **2004**, *126*, 10846–1084

[23] E. J. Corey, A. G. Myers, *Tetrahedron Lett.* **1984**, *25*, 3559–3562.

[24] E. J. Corey, A. G. Myers, *J. Am. Chem. Soc.* **1985**, *107*, 5574–5576.

[25] S. Zhou, E. R. Kern, E. Gullen, Y.-C. Cheng, J. C. Drach, S. Tamiya, H. Mitsuya, J. Zemlicka, *J. Med. Chem.* **2006**, *49*, 6120–6128.

[26] Q. Ma, H. Yang, J. Hao, Y. Tan, *J. Disper. Sci. Technol.* **2012**, *33*, 639–646.

[27] L. I. Willems, T. J. M. Beenakker, B. Murray, B. Gagestein, H. van den Elst, E. R. van Rijssel, J. D. C. Codée, W. W. Kallemeijn, J. M. F. G. Aerts, G. A. van der Marel, H. S. Overkleeft, *Eur. J. Org. Chem.* **2014**, 6044–6056.

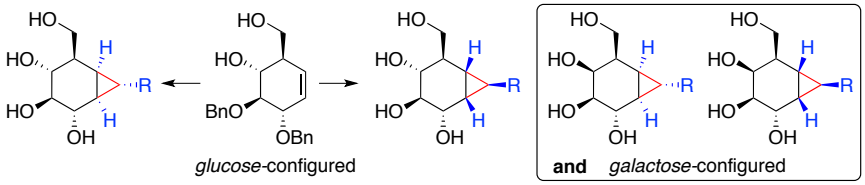
[28] Y. Harrak, C. M. Barra, A. Delgado, A. R. Castano, A. Llebaria, *J. Am. Chem. Soc.* **2011**, *133*, 12079–12084.

[29] S. A. W. Gruner, E. Locardi, E. Lohof, H. Kessler, *Chem. Rev.* **2002**, *102*, 491–514.

[30] L. Sacconi, M. Ciampolini, *J. Chem. Soc.* **1964**, *0*, 276–280.

Entry for the Table of Contents

FULL PAPER



Key Topic* Stereoselective synthesis

*Thomas J. M. Beenakker[‡], Dennis P. A. Wander[‡], Jeroen D. C. Codée, Johannes M. F. G. Aerts, Gijsbert A. van der Marel and Herman S. Overkleeft**

Page No. – Page No.

Synthesis of carba-cyclophellitols: a new class of cyclophellitol derivatives

The synthesis towards a new class of glycosidase inhibitors, carba-cyclophellitols, is described. In these cyclophellitol derivatives the characteristic cyclophellitol epoxide has been replaced by a stable (substituted) methylene group through the generation of a cyclopropyl moiety. The challenging cyclopropanation of *gluco*- and *galacto*-configured cycloalkenes was achieved using copper catalysis.