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Stereoselective Synthesis

SPECIAL ISSUE

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 inhibitors of retaining β-glucosidases. They preferentially adopt a $^4H_3$ half-chair conformation, thereby mimicking the substrate-transition-state conformation characteristic of retaining β-glucosidases. As a consequence, both compounds bind tightly to the enzyme active site, and attack of the catalytic nucleophile onto the epoxide/aziridine results in enzyme deactivation. Replacement of the epoxide oxygen in cyclophellitol by a (substituted) carbon yielded carba-cyclophellitols, a conceptually new class of inhibitors of retaining β-glucosidases, as we demonstrated in a recent communication. In this paper, in-depth synthetic studies of 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 inhibitor of retaining β-glucosidases.[1] Protonation of the epoxide oxygen by the acid–base catalyst residing within the β-glucosidase active site and subsequent S_N2 displacement by the active-site nucleophile leads to the formation of a covalent enzyme–inhibitor adduct.[2,3] This adduct is stable over time, resulting in irreversible inhibition of retaining β-glucosidases. Cyclophellitol aziridine (**2**), the cyclophellitol analogue in which the epoxide oxygen of cyclophellitol (**1**) is replaced by a nitrogen, was also shown to act as an irreversible covalent inhibitor of retaining β-glucosidases.[4] Structural studies have revealed that cyclophellitol and cyclophellitol aziridine use similar modes of action.

Cyclophellitol and cyclophellitol aziridine are configurational analogues of β-glucopyranosides, the substrates of retaining β-glucosidases, but their conformational behavior is different. β-Glucopyranoses preferentially adopt a $^4C_1$ conformation, whereas 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 form during hydrolysis of β-glucosidic linkages as effected

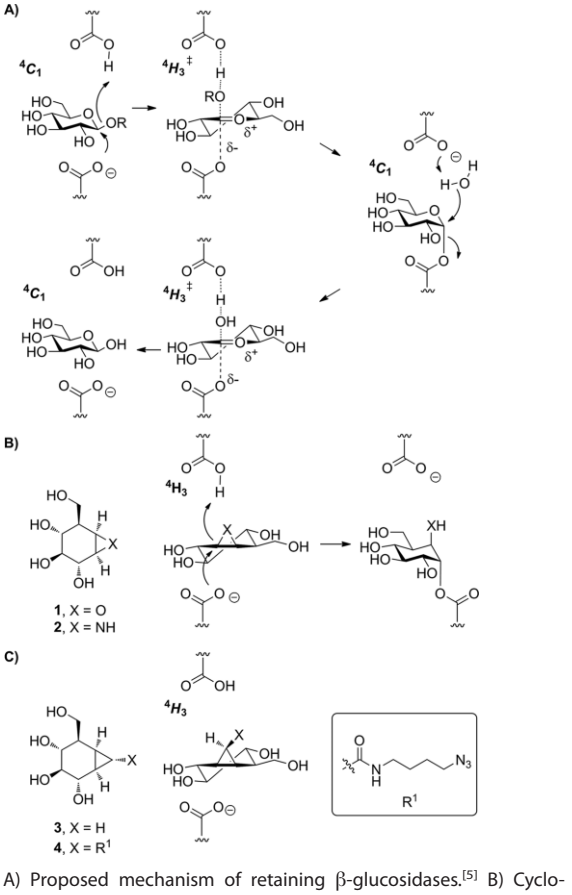


Figure 1. A) Proposed mechanism of retaining β-glucosidases.[5] B) Cyclophellitol (**1**) and cyclophellitol aziridine (**2**) inhibit retaining β-glucosidases covalently by initial binding in a $^4H_3$ conformation, followed by S_N2 displacement of the (protonated) epoxide oxygen or aziridine nitrogen. 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].

[a] *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
https://www.universiteitleiden.nl/en/science/chemistry/biosyn
[b] *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 and ORCID(s) from the author(s) for this article are available on the WWW under https://doi.org/10.1002/ejoc.201701601.

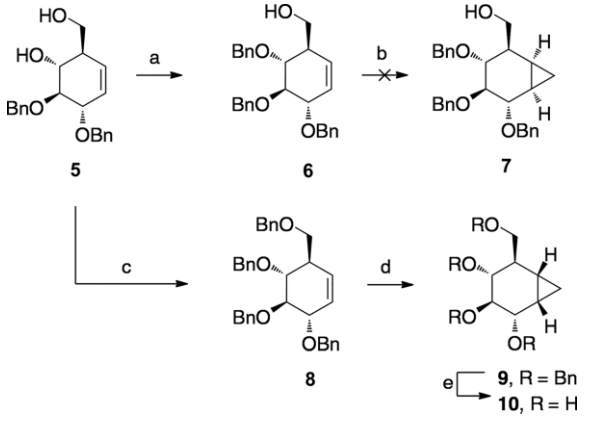
by retaining β-glucosidases (Figure 1A); it is thought that cyclophellitol and cyclophellitol aziridine bind well within β-glucosidase active sites for this reason (Figure 1B). This mode of action of cyclophellitol and cyclophellitol aziridine led us to postulate that configurationally isomeric compounds that would adopt a $^4H_3$ half-chair conformation but would not present an electrophile to the active-site nucleophile of retaining β-glucosidases, would act as competitive inhibitors. We found that substitution of the cyclophellitol epoxide oxygen for carbon, as in carba-cyclophellitol **3**, and attachment of an azidoacyl chain (**3** to **4**) did indeed yield a remarkably effective competitive inhibitor of retaining β-glucosidases (8.20 nM, *Thermotoga maritima Tm*GH1[6]; Figure 1C). Emboldened by these initial results, and realising that in fact carba-cyclophellitols represent a conceptually new class of glycosidase inhibitors, and also carbohydrate mimetics, we decided to investigate this class of compounds further, starting with an investigation of their synthetic accessibility. In this paper, we report the results of our in-depth studies on the synthesis and structural analysis of carba-cyclophellitols. In this paper, we report the details of the synthesis of carba-cyclophellitol **4** and some β-glucopyranose-configured analogues. We also describe 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 of this new class of, we planned to include a variety of substituents on the carba-cyclophellitol core, varying the electron density on the cyclopropane ring, as well as steric factors and hydrogen-bonding capabilities. For this reason, we selected ketone, hydroxymethyl, ethoxymethyl, and carboxamide functional groups. The latter was appended with an azidoalkyl tail to allow further functionalisation through click chemistry.

Hashimoto and coworkers[7] were the first to report the synthesis of carba-cyclophellitols, specifically carba-cyclophellitols **3** and **10**. The key step in their synthesis was a Simmons–Smith cyclopropanation reaction (Et_2Zn, CH_2I_2 in CH_2Cl_2) of a partially benzylated cyclohexene **6** (prepared by standard protecting-group manipulations from diol **5**). The β product was reported to emerge as the predominant isomer when DME (1,2-dimethoxyethane) and MeOH were added to the standard conditions. In our hands, however, this did not lead to any conversion of the cyclohexene. Using the reported α-selective conditions (with DME and BF_3•OEt_2 as additives) on fully benzylated cyclohexene **8** did give us fully benzylated α-carba-cyclophellitol **9**. This was then debenzylated by palladium-catalysed hydrogenolysis, and subsequent acetylation and deacetylation finally gave α-carba-cyclophellitol **10** (Scheme 1).

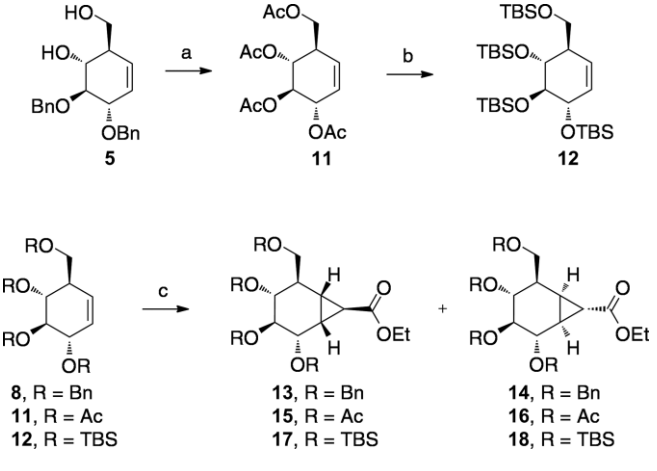
We then turned our attention to ethyl diazoacetate (EDA)[10,11] as a cyclopropanating agent for the synthesis of functionalised carba-cyclophellitols, using perbenzylated cyclohexene **8** as the substrate. When conditions developed for the cyclopropanation of glucals, with $Rh_2(OAc)_4$ as catalyst,[12–14] were applied to **8**, only trace amounts of cyclopropanes **15** and **16** were formed, as detected by TLC–MS analysis of the reaction



Scheme 1. Reagents and conditions: a) (i) TBS-Cl (*tert*-butyldimethylsilyl chloride), imidazole, DMF, room temp., 1 h; (ii) BnBr, NaH, TBAI (tetrabutylammonium iodide), DMF, 0 °C to r.t., overnight; (iii) TBAF (tetrabutylammonium fluoride), THF, r.t., 2 h, 83 % over three steps; b) Et_2Zn, CH_2I_2, 1,2-dimethoxyethane, MeOH, CH_2Cl_2, r.t.; c) BnBr, NaH, TBAI, DMF, 0 °C to r.t., overnight, 94 %; d) Et_2Zn, CH_2I_2, DME, BF_3•OEt_2, CH_2Cl_2, r.t., 3 h, 46 %; e) (i) Pd/C, H_2, MeOH, r.t., overnight; (ii) Ac_2O, pyridine, r.t., 48 h; (iii) NaOMe, MeOH, r.t., 2 h, 66 % over three steps.

mixture. Instead, we detected several other products with higher molecular masses, corresponding to products formed by the reaction of more than one molecule of EDA with cyclohexene **8**. We concluded that this was the result of Büchner-type ring expansion,[15,16] in which the benzyl ethers in **8** reacted with the EDA.[17]

Based on these initial discouraging results, we carried out a comparative study in which a number of transition-metal cyclopropanation catalysts that use EDA as the cyclopropanylating agent were compared side by side (Scheme 2). $Rh_2(OAc)_4$, $Cu(acac)_2$, and $Pd(OAc)_2$[18] are often used as catalysts for the EDA-mediated cyclopropanation of various substrates,[19–21] and were tested in this study. Bearing in mind the electrophilic character of copper and rhodium carbenes,[22] the influence of

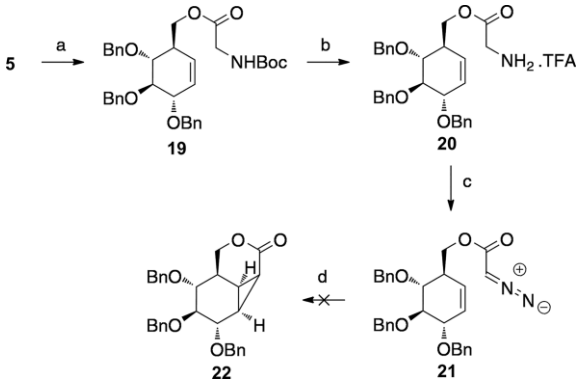


Scheme 2. Reaction conditions: a) (i) Li (s), NH_3 (l), THF, –60 °C, 35 min; (ii) Ac_2O, pyridine, room temp., overnight, 79 % over two steps; b) (i) NaOMe, MeOH, r.t., overnight; (ii) TBS-Cl, imidazole, DMF, r.t. to reflux temperature, 7 d, 35 % over two steps; c) Substrate (**8**, **11**, or **12**; 0.1 mmol), catalyst [$Rh(OAc)_2$, $Cu(acac)_2$, or $Pd(OAc)_2$; 5 mol-%], DCE (1,2-dichloroethane; 200 μL), reflux; EDA (0.3 mmol) in DCE (150 μL) added over 6 h.

the electron density of the alkene was studied by comparing peracetyl cyclohexene **11** (prepared from **11** by standard protecting-group manipulations; see Scheme 2), and perbenzyl cyclohexene **8**.

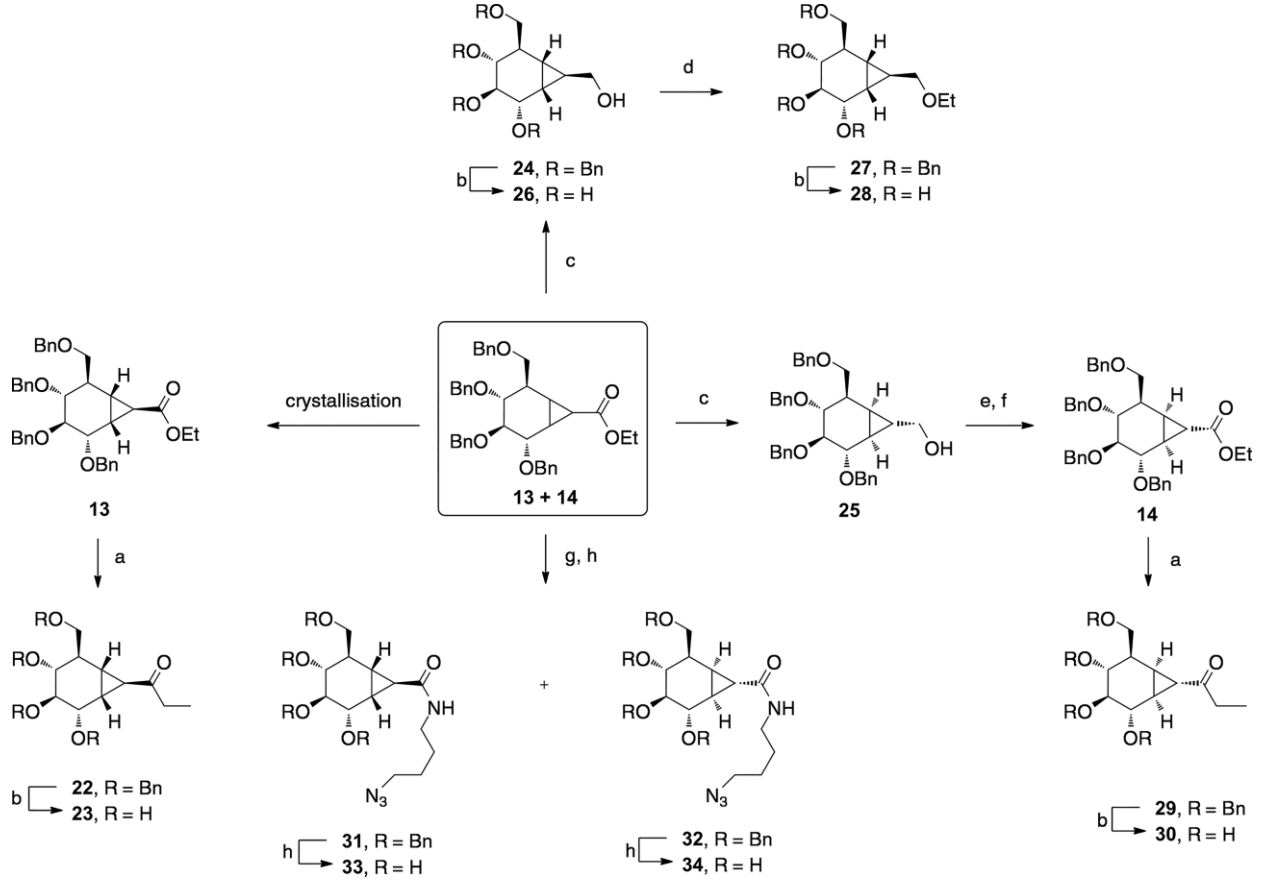
The combination of $Cu(acac)_2$ as catalyst and tetra-*O*-benzyl-cyclohexene **8** as substrate was optimal, based on TLC–MS analysis, even though, unlike compounds **11** and **12**, cyclohexene **8** can undergo the aforementioned Büchner-type reactions. Such side reactions were minimised when the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

We investigated an alternative strategy for the synthesis of bicyclic compounds involving an intramolecular cyclopropanation strategy (Scheme 3). In this approach, an intramolecular tether would deliver the carbene to the β face of the alkene to give a lactone derivative of the carba-cyclophellitol.



Scheme 3. Reagents and conditions: a) *N*-Boc-glycine (Boc = *tert*-butoxycarbonyl), DIC (*N*,*N*′-diisopropylcarbodiimide), DMAP (4-dimethylaminopyridine), room temp., overnight, quant.; b) TFA (trifluoroacetic acid), CH_2Cl_2, r.t., 45 min, quant.; c) $NaNO_2$, monosodium citrate, CH_2Br_2, H_2O, 0 °C, 1 h, 99 %; d) $Cu(acac)_2$ (acac = acetylacetone) or Cu(*N*-*tert*-butylsalicylaldiminato)$_2$, toluene, EtOAc or DCE, reflux.

For this purpose, alcohol **5** (derived from cyclohexene **7**[8,9] through standard protecting-group manipulations) was condensed with *N*-Boc-glycine to give **19**. Treatment with TFA gave amine **20**, which was subsequently subjected to biphasic



Scheme 4. Reagents and conditions: a) *N*,*O*-dimethylhydroxylamine hydrochloride, EtMgBr, THF, −5 °C, then EtMgBr, THF, room temp., overnight, **15** (56 %), **22** (45 %); b) $Pd(OH)_2/C$, H_2, MeOH, r.t., overnight, **23** (96 %), **26** (90 %), **28** (94 %), **30** (58 %); c) DIBAL, THF, 30 min at 0 °C and then 1 h at r.t., **24** and **25** (2:1; 41 %); d) EtBr, NaH, TBAI, DMF, 0 °C to r.t., 4 h, 59 %; e) Jones reagent, acetone, 0 °C, 3 h, 53 %; f) EtOH, *N*,*N*′-diisopropylcarbodiimide, 4-dimethylaminopyridine, toluene, r.t., 4 h, 62 %; g) (i) LiOH, THF, MeOH, H_2O, r.t., overnight, 82 %; (ii) 1-azido-4-aminobutane, HCTU [*O*-(1*H*-6-chlorobenzotriazole-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate], DIPEA (diisopropylethylamine), CH_2Cl_2, r.t., overnight, 78 %; h) BCl_3, CH_2Cl_2, −78 °C, 5 h, **33** (88 %), **34** (99 %).

diazotisation to give diazoester **21**. Based on the literature report of a similar intramolecular cyclopropanation by Corey's group,[23,24] we attempted the cyclisation under their conditions of Cu^{II}(*N-tert*-butylsalicylaldiminato)$_2$ in toluene, and also under our previously used conditions of Cu(acac)$_2$ in EtOAc. However, the major identified product proved to be the product of carbene dimerisation. The desired product **23** could not be detected (TLC, LC–MS) in these experiments.

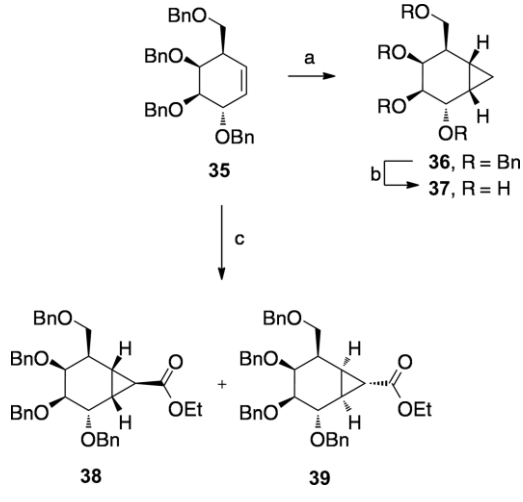
We then explored the versatility of carba-cyclophellitol esters **13** and **14** (Scheme 2) as intermediates for further elaboration (Scheme 4). Attempted separation of the stereoisomers **13** and **14** by silica gel column chromatography or HPLC was not successful. Crystallisation of the mixture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

With this versatile functionalised carba-cyclophellitol derivative in hand, the ester was converted into ketone **22**. This was accomplished through direct Weinreb-amide formation from the ester, using ethylmagnesium bromide as a base at low temperature, followed by Grignard addition at room temperature. Subsequently, ketone **22** was subjected to palladium-catalysed hydrogenolysis in MeOH to give compound **23**.

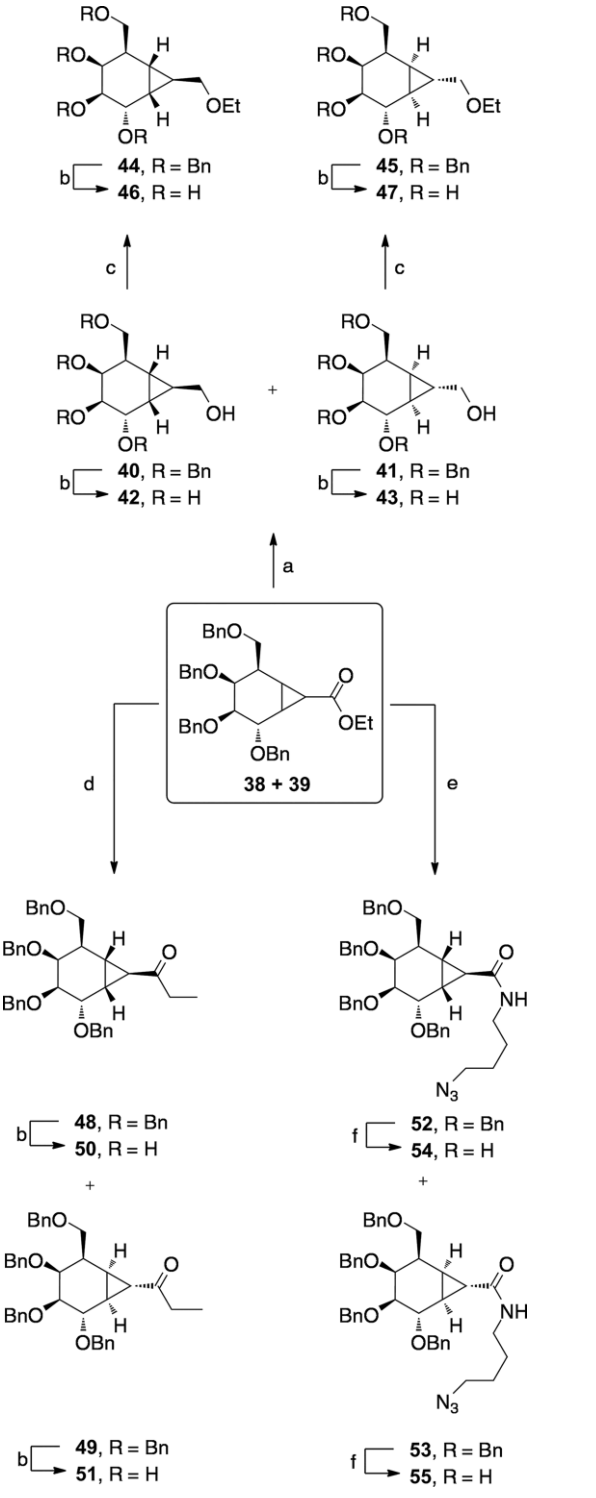
The mixture of esters **13** and **14** was reduced with diisobutylaluminum hydride (DIBAL)[25] to give alcohols **24** and **25**, which were carefully separated by column chromatography. Subjection of alcohol **24** to palladium-catalysed hydrogenolysis in MeOH gave compound **26**. Ether **28** was 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 oxidised using aqueous sodium dichromate/sulfuric acid (Jones reagent), followed by esterification to give enantiopure **14**. This was then converted into the corresponding ketone, as described for its diastereomer, followed by debenzylation to give **30**.

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



Scheme 5. Reagents and conditions: a) DME, BF_3·OEt_2, 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 %).



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

As our next research objective, we set out to investigate whether the synthetic strategies we had identified for the construction of glucopyranose-configured cyclophellitol cyclopropanes could also be used for the construction of some galactopyranose-configured analogues, potential inhibitors of α- and β-galactosidases. For this purpose, *galacto*-configured cyclohexene **35** was synthesised in large quantities following our previously reported strategy,[27] based on chemistry developed by Llebaria and coworkers.[28] Simmons–Smith cyclopropanation of this cyclohexene derivative as described above for its diastereomer followed by global debenzylation gave α-cyclopropane **37** (Scheme 5).

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

DIBAL-mediated reduction of the mixture of esters **38** and **39** gave alcohols **40** and **41** (Scheme 6), which could be separated by silica gel column chromatography. Palladium-catalysed hydrogenolysis of these alcohols gave compounds **42** and **43**, respectively. The free alcohols in **40** and **41** were alkylated with ethyl bromide, and subsequent debenzylation gave ethers **44** and **45**.

The mixture of esters **38** and **39** was converted into the corresponding ketones **48** and **49** under the Weinreb conditions described above; these compounds were then separated by HPLC. Deprotection by palladium-catalysed hydrogenation gave compounds **50** and **51**. Finally, a mixture of **38** and **39** was saponified, followed by condensation with 1-azido-4-aminobutane. The resulting mixture of amides was separated by HPLC, and then each was treated with BCl_3 to give **54** and **55**.

The configuration of the carba-cyclophellitol products was determined by nuclear Overhauser effect spectroscopy (NOESY), as exemplified for compounds **13** and **14** (Figure 2). Correlations between 1-H and 3-H, and between 4-H and 8-H were observed for compound **13**. For compound **14**, the β isomer of **13**, through-space correlations were observed between 1-H and 6-H, and between 3-H and 8-H. These observations were consistent throughout the series of compounds reported in this paper; further NOESY data for the final compounds can be found in the Supporting Information.

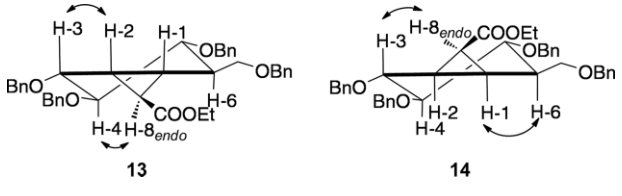


Figure 2. Determination of configuration of compounds **13** and **14** by through-space correlations observed by nuclear Overhauser effect spectroscopy (NOESY) experiments.

Conclusions

We have reported full details of the synthesis of a new class of carbohydrate mimetics: cyclophellitol cyclopropanes (see Figure 3 for a full list of the structures prepared). We believe such compounds to be of interest as potential inhibitors of glycoprocessing enzymes, but also as glycomimetics in general. We note that the carboxylate-containing compounds could undergo oligomerisation, 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 family of densely functionalised molecules that can be derived from nature's most diverse class of compounds: carbohydrates.

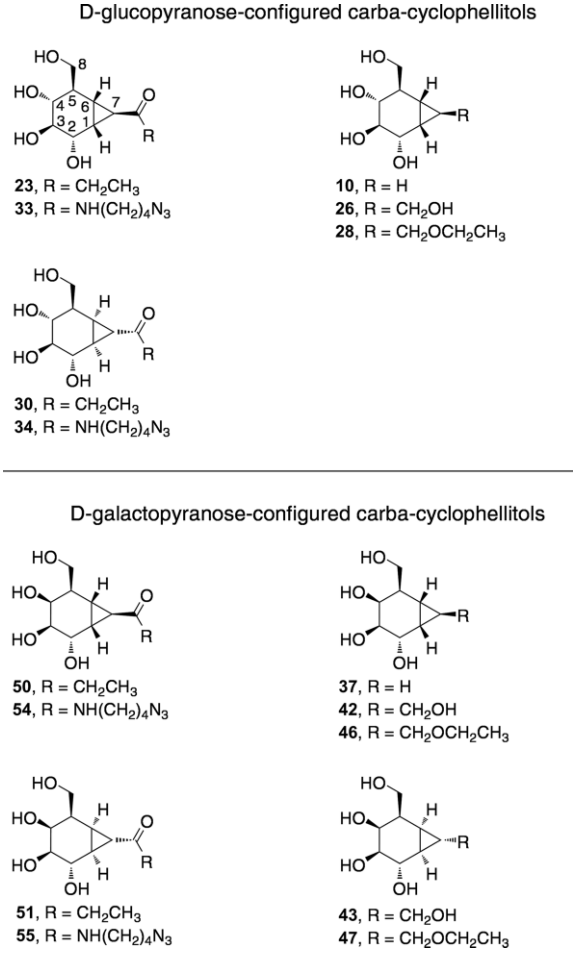


Figure 3. Structures of the carba-cyclophellitols described in this synthetic study.

Experimental Section

General Remarks: All chemicals were purchased from Acros, Sigma Aldrich, Biosolve, VWR, Fluka, Merck, and Fisher Scientific, and were used as received unless otherwise stated. *N*,*N*-Dimethylformamide (DMF) and toluene were stored over flame-dried molecular sieves (4 Å) before use. Traces of water were removed from reagents by coevaporation with toluene in reactions that required anhydrous conditions. All moisture- and/or oxygen-sensitive reactions were carried out under an inert atmosphere. TLC analysis was carried out using Merck aluminium sheets (silica gel 60 F_{254}); visualisation was achieved by UV absorption (254 nm), and/or 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 sulfuric acid (10 % methanolic) or a solution of $KMnO_4$

(20 g/L) and K_2CO_3 (10 g/L) in water, followed by charring at ca. 150 °C. Column chromatography was carried out using Screening Device BV Silica Gel (40–63 μm particle size, 60 Å pore diameter) in the solvent systems indicated. For reverse-phase HPLC purifications, an Agilent Technologies 1200 series instrument equipped with a semi-preparative column (Gemini C18, 250 × 10 mm, 5 μm particle size, Phenomenex) was used. LC–MS analysis was carried out with a Surveyor HPLC system (Thermo Finnigan) equipped with a C18 column (Gemini, 4.6 mm × 50 mm, 5 μm particle size, Phenomenex), coupled to a LCQ Advantage Max (Thermo Finnigan) ion-trap spectrometer (ESI^+). The buffers used were H_2O, MeCN, and aqueous TFA (1 %). ^1H and ^{13}C NMR spectra were recorded with Bruker AV-400 (400 and 101 MHz, respectively), Bruker DMX-600 (600 and 151 MHz, respectively) or Bruker AV-850 (850 and 214 MHz, respectively) spectrometers in the given solvent. Chemical shifts are given in ppm (δ), and spectra were calibrated using the residual solvent or tetramethylsilane (δ = 0 ppm) as an internal standard. Coupling constants are given in Hz. High-resolution mass spectrometry (HRMS) analysis was carried out with a LTQ Orbitrap mass spectrometer (Thermo Finnigan) equipped with an electrospray 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), using dioctyl phthalate (m/z = 391.28428) as a lock mass. The high-resolution mass spectrometer was calibrated using a calibration mixture (Thermo Finnigan) before measurements were taken.

General Procedure for Global Debenzylation: A catalytic amount of Pd on carbon (10 %) or $Pd(OH)_2$ on carbon was added to a solution of the benzyl ether in MeOH. The reaction vessel was purged with hydrogen gas, and the mixture was stirred vigorously overnight. When TLC analysis showed full conversion to a lower-running spot, the palladium catalyst was removed by filtration through a pad of Celite. The filtrate was concentrated in vacuo to give 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), and then TBS-Cl (0.271 g, 1.80 mmol, 1.1 equiv.) and imidazole (0.279 g, 4.10 mmol, 2.5 equiv.) were added. The reaction mixture was stirred at room temperature for 1 h, and then it was partitioned between Et_2O (40 mL) and H_2O (40 mL). The organic layer was separated, washed with H_2O (2 ×), dried with $MgSO_4$, filtered, and concentrated in vacuo. The resulting crude silyl ether was used without further purification. HRMS: calcd. for $[C_{27}H_{39}O_4Si]^+$ 455.26121; found 455.26129.

The residue was then dissolved in DMF (8.0 mL) at 0 °C, and then TBAI (catalytic amount), BnBr (0.23 mL, 1.97 mmol, 1.2 equiv.), and NaH (60 % dispersion in mineral oil; 79.2 mg, 1.98 mmol, 1.21 equiv.) were added. The mixture was stirred at room temperature overnight, then it was concentrated in vacuo. The residue was partitioned between Et_2O (25 mL) and H_2O (25 mL). The organic layer was washed with H_2O (3 ×), and the resulting aqueous layers were extracted with Et_2O. The combined organic layers were dried with $MgSO_4$, filtered, and concentrated in vacuo. The resulting crude fully protected cyclohexene was used without further purification. HRMS: calcd. for $[C_{34}H_{44}O_4SiNa]^+$ 567.29011; found 567.28989.

The residue was then dissolved in THF (8.2 mL), and then TBAF (1 M in THF; 9.8 mL, 9.8 mmol, 6.0 equiv.) was added. The mixture was stirred at room temperature for 2 h, then it was quenched with H_2O (4 drops), and concentrated in vacuo. The residue was purified by column chromatography (30 % EtOAc in pentane → 50 % EtOAc in pentane) to give compound **6** (0.585 g, 1.36 mmol, 83 % over three steps) as a yellow oil. ^1H NMR (400 MHz, $CDCl_3$): δ = 7.45–7.07 (m, 15 H, $H_{arom}Bn$), 5.72 (dt, J = 10.0, 3.0 Hz, 1 H, 1-H or 6-H), 5.53 (dt, J = 10.2, 2.6 Hz, 1 H, 1-H or 6-H), 5.03–4.84 (m, 3 H, CH_2Bn), 4.74–4.57 (m, 3 H, CH_2Bn), 4.28–4.17 (m, 1 H, 3-H), 3.83 (dd, J = 10.6, 7.4 Hz, 1 H, 2-H), 3.68–3.50 (m, 3 H, 4-H, 7-H), 2.46 (ddd, J = 14.3, 7.4, 3.7 Hz, 1 H, 5-H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 138.8, 138.5, 138.4 (4 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, C-6), 85.2 (C-3), 80.8 (C-2), 78.7 (C-4), 75.3, 75.2, 72.1 (3 CH_2 Bn), 63.1 (C-7), 45.8 (C-5) ppm. HRMS: calcd. 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 equiv.), BnBr (1.86 mL, 15.6 mmol, 2.4 equiv.), and NaH (60 % dispersion in mineral oil; 0.629 g, 15.7 mmol, 2.4 equiv.) were added. The mixture was stirred overnight, then additional BnBr (0.93 mL, 7.80 mmol, 1.2 equiv.) and NaH (60 % dispersion in mineral oil; 0.315 g, 7.68 mmol, 1.0 equiv.) were added at 0 °C. The mixture was stirred for a further 4 h, then 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 × 100 mL, 3 × 50 mL). The aqueous layers were extracted with Et_2O (50 mL), and the combined organic layers were dried with $MgSO_4$, filtered, and concentrated in vacuo. The residue was purified by column chromatography (3 % EtOAc in pentane → 6 % EtOAc in pentane) to give fully benzylated derivative **8** (3.17 g, 6.08 mmol, 94 %) as a yellow oil. ^1H NMR (400 MHz, $CDCl_3$): δ = 7.56–7.00 (m, 20 H, $H_{arom}Bn$), 5.83–5.56 (m, 2 H, 1-H, 6-H), 4.98–4.86 (m, 3 H, CH_2Bn), 4.70 (s, 2 H, CH_2Bn), 4.53–4.36 (m, 3 H, CH_2Bn), 4.31–4.22 (m, 1 H, 3-H), 3.81 (dd, J = 10.1, 7.8 Hz, 1 H, 4-H), 3.67 (t, J = 9.8 Hz, 1 H, 2-H), 3.52 (d, J = 4.4 Hz, 2 H, 8-H), 2.64–2.42 (m, 1 H, 5-H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 129.3, 128.5, 128.2, 128.1, 128.0, 127.9, 127.8, 127.7, 127.0 (CH_{arom}, C-1, 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) ppm. HRMS: calcd. 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): Boron trifluoride ethyl etherate (43 μL) and diethylzinc (1 M in hexane; 0.7 mL, 0.7 mmol) were added to a solution of 1,2-dimethoxyethane (72 μL) in CH_2Cl_2 (0.35 mL) at room temperature. The mixture was stirred for 5 min, then diiodomethane (112 μL, 1.4 mmol) was added. The reaction mixture was stirred for a further 5 min. Compound **8** (36.3 mg, 70 μmol) was dissolved in CH_2Cl_2 (0.85 mL), and the solution was added dropwise to the reaction mixture. The mixture was stirred for 3 h, then it was quenched with a saturated aqueous NH_4Cl solution, and diluted with EtOAc. The aqueous layer was extracted with EtOAc (3 ×), and the combined organic layers were dried with $MgSO_4$, filtered, and concentrated in vacuo. The residue was purified by column chromatography (pentane → 8 % EtOAc in pentane) to give cyclopropane **26** (17.3 mg, 32 μmol, 46 %) as a yellow oil. ^1H NMR (400 MHz, $CDCl_3$): δ = 7.40 (d, J = 7.0 Hz, 2 H, $H_{arom}Bn$), 7.37–7.27 (m, 16 H, $H_{arom}Bn$), 7.18–7.12 (m, 2 H, $H_{arom}Bn$), 4.89–4.75 (m, 4 H, CH_2Bn), 4.69 (d, J = 12 Hz, 1 H, CH_2Bn), 4.55–4.36 (m, 3 H, CH_2Bn), 4.14–4.04 (m, 1 H, 2-H), 3.59 (d, J = 4.2 Hz, 2 H, 8-H), 3.46–3.24 (m, 2 H, 3-H, 4-H), 1.93–1.85 (m, 1 H, 5-H), 1.44–1.34 (m, 1 H, 1-H), 1.17–1.07 (m, 1 H, 6-H), 0.82–0.74 (m, 1 H, 7-H), 0.40–0.35 (m, 1 H, 7-H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$): δ = 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 CH_2 Bn), 71.0 (C-8), 44.1 (C-5), 16.2, 14.2 (C-1, C-6), 10.4 (C-7) ppm.

(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 resulting solution was purged with argon gas, and palladium on carbon (10 %; 373 mg) was added. The reaction vessel was then purged with hydrogen gas, and the mixture was stirred vigorously overnight. The palladium catalyst was then removed by filtration through a pad of Celite, and the filtrate was concentrated in vacuo. The residue was purified by column chromatography (EtOAc → 30 % MeOH in EtOAc) to give a crude product.

This material was dissolved in pyridine (4.2 mL), and acetic anhydride (0.67 mL, 7.1 mmol) was added. The mixture was stirred for 2 d at room temperature, then it was diluted with EtOAc (30 mL), and washed with H_2O (3 ×). The combined aqueous layers were extracted with EtOAc (2 ×). The combined organic layers were dried with $MgSO_4$, filtered, concentrated in vacuo. The residue was purified by column chromatography (pentane → 20 % EtOAc in pentane) to give the corresponding acetylated product **10** (0.36 g, 1.0 mmol, 71 %) as a colourless oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 5.39 (dd, *J* = 8.7, 6.2 Hz, 1 H, 2-H), 5.00–4.84 (m, 2 H, 3-H, 4-H), 4.18–4.05 (m, 2 H, 8-H), 2.19–2.13 (m, 1 H, 5-H), 2.09 (s, 3 H, Ac), 2.06 (s, 3 H, Ac), 2.00 (s, 6 H, 2 Ac), 1.68–1.56 (m, 1 H, 6-H), 1.10–1.02 (m, 1 H, 1-H), 0.93–0.85 (m, 1 H, 7-H), 0.57–0.47 (m, 1 H, 7-H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$): δ = 171.2, 170.8, 170.2, 169.9 (4 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 CH_3 Ac), 15.9 (C-6), 13.6 (C-1), 10.7 (C-7) ppm. HRMS: calcd. 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. When TLC analysis showed full conversion to a lower-running spot, the reaction mixture was neutralised with Amberlite-H^+ IR-120, filtered, and concentrated in vacuo to give compound **10** (12 mg, 68 µmol, 93 %). ^{1}H NMR (400 MHz, D_2O): δ = 3.99 (dd, *J* = 8.8, 5.9 Hz, 1 H, 2-H), 3.83 (dd, *J* = 10.9, 3.5 Hz, 1 H, 8-H), 3.70 (dd, *J* = 10.9, 6.3 Hz, 1 H, 8-H), 3.18 (t, *J* = 10.2 Hz, 1 H, 4-H), 3.09 (dd, *J* = 10.2, 8.9 Hz, 1 H, 3-H), 1.77–1.66 (m, 1 H, 5-H), 1.39–1.31 (m, 1 H, 6-H), 1.05–0.93 (m, 1 H, 1-H), 0.79–0.72 (m, 1 H, C-7), 0.35–0.25 (m, 1 H, C-7) ppm. ^{13}C NMR (101 MHz, D_2O): δ = 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) ppm. HRMS: calcd. 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. A solution of compound **7** (340 mg, 1.00 mmol) in THF (22.5 mL) was then added. The reaction mixture was stirred for 30 min at –60 °C, and then it was quenched with MeOH (10 mL). The solution was allowed to come to room temperature, and it was stirred until all the NH_3 had evaporated.

The resulting crude material was dissolved in pyridine (6.0 mL), and acetic anhydride (5.0 mL) was added. The mixture was stirred overnight, then 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 (3 ×), dried with $MgSO_4$, and concentrated in vacuo. Pyridine (3.0 mL) and Ac_2O (2.0 mL) were added to the residue. The mixture was stirred overnight at room temperature, then it was partitioned between EtOAc (25 mL) and H_2O (10 mL). The organic layer was washed with H_2O (3 ×), dried with $MgSO_4$, filtered and concentrated in vacuo. The residue was purified by column chromatography (10 % EtOAc in pentane → 40 % EtOAc in pentane) and coevaporation with toluene (to remove any residual pyridine) to give compound **11** (0.258 g, 0.786 mmol, 79 % over two steps) as a yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 5.72–5.68 (m, 1 H, 1-H or 6-H), 5.67–5.61 (m, 1 H, 1-H or 6-H), 5.58–5.54 (m, 1 H, 2-H), 5.32 (dd, *J* = 10.6, 7.9 Hz, 1 H, 3-H), 5.28–5.18 (m, 1 H, 4-H), 4.15 (dd, *J* = 11.3, 4.1 Hz, 1 H, 7-H), 4.02 (dd, *J* = 11.3, 5.1 Hz, 1 H, 7-H), 2.83–2.76 (m, 1 H, 5-H), 2.03 (s, 12 H, 4 CH_3) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 170.9, 170.5, 170.3, 170.1 (4 C_q acetyl), 128.5, 126.5 (C-1, 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 CH_3) ppm. HRMS: calcd. 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. The mixture was stirred overnight, then it was concentrated in vacuo.

The residue was dissolved in DMF (3.1 mL), and imidazole (0.708 g, 10.4 mmol, 24 equiv.) was added, followed by a solution of TBS-Cl (0.864 g, 5.73 mmol, 13.2 equiv.) in DMF (2.0 mL). The mixture was stirred at room temperature for 5 d and then it was heated at reflux for a further 2 d. The reaction mixture was partitioned between Et_2O (10 mL) and H_2O (10 mL). The organic layer was separated, washed with H_2O (2 ×), dried with $MgSO_4$, filtered, and concentrated in vacuo. The residue was purified by column chromatography (10 % toluene in pentane) to give compound **12** (94.0 mg, 0.152 mmol, 35 % over two steps) as a slightly yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 5.74 (d, *J* = 3.6 Hz, 1 H, 1-H or 6-H), 5.73 (d, *J* = 3.6 Hz, 1 H, 1-H or 6-H), 3.93 (d, *J* = 2.5 Hz, 1 H, 2-H), 3.90 (d, *J* = 2.0 Hz, 4-H), 3.83 (d, *J* = 3.2 Hz, 1 H, 3-H), 3.61 (dd, *J* = 9.6, 8.0 Hz, 1 H, 7-H), 3.52 (dd, *J* = 9.2, 7.2 Hz, 1 H, 7-H), 2.35–2.30 (m, 1 H, 5-H), 0.87 (s, 18 H, TBS), 0.86–0.83 (m, 18 H, TBS), 0.10–0.05 (m, 18 H, TBS), 0.01 (s, 3 H, TBS), 0.00 (s, 3 H, TBS) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 127.3, 127.2 (C-1, 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) ppm. HRMS: calcd. 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 with flame-dried molecular sieves (4 Å) overnight before use. Cyclic alkene **8** (1.57 g, 3.01 mmol) was dissolved in EtOAc (2.7 mL) in a two-necked pear-shaped flask, and $Cu(acac)_2$ (79.0 mg, 0.301 mmol, 0.1 equiv.) was added. The reaction mixture was stirred at 90 °C, and a solution of ethyl diazoacetate (containing 13 wt.-% CH_2Cl_2; 4.52 mmol, 0.55 mL, 1.5 equiv.) 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 dissolved in EtOAc was added. This was repeated until a total of 6 equiv. of ethyl diazoacetate was added, and the formation of a product with *m/z* = 715 $[M + Na]^+$ was detected by TLC–MS analysis. The reaction mixture was concentrated in vacuo. The residue was purified by column chromatography (3 % EtOAc in pentane → 7 % EtOAc in pentane) to give the desired product as a crude mixture of two isomers. In addition, recovered starting material **25** (0.433 g, 0.832 mmol, 28 %) was obtained, which was subjected to the same conditions described above. After the addition of a total of 4.5 equiv. of ethyl diazoacetate, significant by-product formation was observed by TLC–MS analysis. After this second reaction cycle, and a total crude mixture of α-*exo*-ester **13** and β-*exo*-ester **14** (0.642 g, 1.06 mmol, 35 %, 2:1 α/β mixture) was obtained as a pale yellow oil. Crystallisation of the combined crude isomeric product mixture from ethanol gave **13** (0.274 g, 0.452 mmol, 15 %) as a white solid, and a mixture of **13** and **14** (0.368 g, 0.606 mmol, 20 %) as a pale yellow oil. Analytical data for **13**: ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.30 (m, 16 H, H_{arom}Bn), 7.14 (m, 2 H, H_{arom}Bn), 4.89–4.69 (m, 4 H, CH_2Bn), 4.64 (d, *J* = 11.8 Hz, 1 H, CH_2Bn), 4.53–4.34 (m, 3 H,

CH_2Bn), 4.22–4.03 (m, 3 H, CH_2CH_3, 2-H), 3.66–3.52 (m, 2 H, 2 8-H), 3.40 (t, J = 10.2 Hz, 1 H, 4-H), 3.25 (dd, J = 10.1, 8.3 Hz, 1 H, 3-H), 2.05–1.97 (m, 1 H, 1-H), 1.94–1.88 (m, 1 H, 5-H), 1.76 (ddd, J = 9.5, 4.7, 2.3 Hz, 1 H, 6-H), 1.67 (t, J = 4.7 Hz, 1 H, 7-H), 1.27 (t, J = 7.1 Hz, 3 H, CH_3) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 173.4 (C_q carbonyl), 139.0, 138.6, 136.6, 138.3 (4 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 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, C-7), 14.4 (CH_3) ppm. HRMS: calcd. 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 equiv.), and DMAP (catalytic amount) were dissolved in toluene (0.6 mL), and then DIC (38 µL, 2 equiv.) was added dropwise. The mixture was stirred overnight at room temperature, then it was filtered through Celite, and the filtrate was concentrated in vacuo. The residue was purified by column chromatography (8 % EtOAc in pentane → 25 % EtOAc in pentane) to give compound **19** (69.4 mg, 0.120 mmol, quant.) as a yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.42–7.21 (m, 15 H, H_{arom}Bn), 5.72 (dt, J = 10.2, 2.4 Hz, 1 H, 1-H or 6-H), 5.58–5.46 (m, 1 H, 1-H or 6-H), 5.04–4.49 (m, 6 H, CH_2Bn), 4.28 (dd, J = 10.8, 3.2 Hz, 1 H, 8-H), 4.23 (ddd, J = 7.7, 3.3, 1.9 Hz, 1 H, 2-H), 4.14 (dd, J = 10.9, 5.0 Hz, 1 H, 8-H), 3.80 (td, J = 13.3, 11.6, 7.5 Hz, 3 H, 3-H, CH_2-Glyc), 3.53 (t, J = 9.8 Hz, 1 H, 4-H), 2.71–2.52 (m, 1 H, 5-H), 1.45 (d, J = 2.5 Hz, 9 H, Boc-*t*Bu) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 170.5 (C=O ester), 138.9, 138.4, 138.0 (3 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 or C-6), 101.9 (C-1 or C-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-Gly), 28.5 (Boc-CH_3) ppm. HRMS: calcd. 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): TFA (0.3 mL) was added to a solution of compound **19** (69.4 mg, 0.120 mmol) in CH_2Cl_2 (0.3 mL). The mixture was stirred for 45 min at room temperature, then it was concentrated in vacuo to give compound **20** (72.2 mg, 0.120 mmol, quant.) as a pale yellow solid that was used without further purification. HRMS (as the free amine): calcd. 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), and then monosodium citrate (31.7 mg, 0.149 mmol, 1.5 equiv.) and CH_2Br_2 (0.5 mL) were added. The reaction mixture was cooled to 0 °C, and $NaNO_2$ (8.19 mg, 0.119 mmol, 1.2 equiv.) was added. The mixture was stirred at 0 °C for 1 h, then it was warmed up to room temperature. The organic layer was removed by syringe. Additional CH_2Br_2 was added (0.5 mL), and the mixture was stirred for 10 min. The organic layer was then again removed by syringe. The combined organic layers were combined and concentrated in vacuo to give compound **21** (49 mg, 98.0 µmol, 99 %) as a bright yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.45–7.16 (m, 15 H, H_{arom}), 5.73 (d, J = 10.2 Hz, 1 H, 1-H or 6-H), 5.55 (d, J = 10.2 Hz, 1 H, 1-H or 6-H), 4.96 (d, J = 10.8 Hz, 1 H, CH_2 Bn), 4.93–4.88 (m, 2 H, CH_2 Bn), 4.69–4.62 (m, 3 H, CH_2 Bn and H-diazocarbonyl), 4.56 (d, J = 9.2 Hz, 1 H, CH_2 Bn), 4.33 (dd, J = 10.8, 3.0 Hz, 1 H, 2-H), 4.23–4.18 (m, 2 H, 8-H), 3.82 (t, J = 8.4 Hz, 1 H, 3-H), 3.54 (t, J = 9.8 Hz, 1 H, 4-H), 2.61 (br. s, 1 H, 5-H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 138.9, 138.5, 138.4 (3 $C_{q\text{-}arom}$), 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 CH_2 Bn), 63.9 (C-8), 46.4 (C=N), 43.6 (C-5) ppm.

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 equiv.) in EtOH (2 mL) was added. The mixture was stirred for 1 h at 55 °C, then the precipitate was collected by filtration. The precipitate was suspended in EtOH (2 mL), and *tert*-butylamine (525 µL, 5.00 mmol, 2.25 equiv.) was added. The reaction mixture was heated at reflux for 1.5 h and then it was concentrated in vacuo to give bis(*N*-*tert*-butylsalicylaldiminato)copper(II) (0.680 g, 1.64 mmol, 82 %) as black crystals. M.p. 185 °C (lit.[30] m.p. 185–186 °C).

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 a solution of Me(MeO)NH•HCl (12.2 mg, 0.125 mmol, 1.25 equiv.) in THF (0.5 mL). EtMgBr (0.5 M in THF; 0.840 mmol, 8.4 equiv.) was then added over 2 h at –5 to 0 °C, and then the reaction mixture was stirred overnight. The mixture was quenched with aqueous HCl (3 M; 3 mL), and extracted with EtOAc (10 mL). The organic layer was dried, and concentrated in vacuo. The residue was redissolved in THF (0.8 mL), and then EtMgBr (1 M in THF; 0.300 mmol, 3 equiv.) was added over 2 min at –20 °C. The reaction mixture was allowed to come to room temperature, and was stirred for 75 min. The mixture was quenched with aqueous HCl (3 M; 3 mL). The reaction mixture was extracted with EtOAc (10 mL), and the organic layer was dried and concentrated in vacuo. The residue was purified by column chromatography (6 % EtOAc in pentane → 8 % EtOAc in pentane) to give compound **22** (32.8 mg, 55.6 µmol, 56 %) as a white solid. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.39–7.18 (m, 18 H, H_{arom}), 7.15–7.12 (m, 2 H, H_{arom}), 4.92–4.76 (m, 3 H, CH_2 Bn), 4.74–4.57 (m, 2 H, CH_2 Bn), 4.50–4.38 (m, 3 H, CH_2 Bn), 4.06 (dd, J = 7.9, 5.8 Hz, 1 H, 2-H), 3.61–3.50 (m, 2 H, 8-H), 3.39 (t, J = 10.0 Hz, 1 H, 4-H), 3.34–3.24 (m, 1 H, 3-H), 2.58 (dd, J = 14.4, 7.6 Hz, 2 H, CH_2CH_3), 2.09–2.00 (m, 1 H, 1-H), 1.98 (t, J = 4.5 Hz, 1 H, 7-H), 1.95–1.89 (m, 1 H, 5-H), 1.86–1.78 (m, 1 H, 6-H), 1.08 (t, J = 7.3 Hz, 3 H, CH_3) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 209.6 (C=O), 139.1, 138.7, 138.6, 138.4 (4 $C_{q\text{-}arom}$), 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 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) ppm. HRMS: calcd. 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 with $Pd(OH)_2$/C according to the general procedure for global debenzylation to give compound **23** (12.3 mg, 53.4 µmol, 96 %) as a colourless oil. ^{1}H NMR (400 MHz, D_2O): δ = 4.04 (dd, J = 8.6, 5.5 Hz, 1 H, 2-H), 3.84 (dd, J = 11.0, 3.6 Hz, 1 H, 8-H), 3.72 (dd, J = 11.0, 6.2 Hz, 1 H, 8-H), 3.37–3.09 (m, 2 H, 3-H, 4-H), 2.72 (dd, J = 7.2, 14.8 Hz, 2 H, CH_2CH_3), 2.25 (t, J = 4.5 Hz, 1 H, 7-H), 2.11–1.98 (m, 1 H, 1-H), 1.90–1.83 (m, 1 H, 5-H), 1.68–1.61 (m, 1 H, 6-H), 1.04 (t, J = 7.3 Hz, 3 H, CH_3) ppm. ^{13}C NMR (100 MHz, D_2O): δ = 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) ppm. HRMS: calcd. 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, and then DIBAL (1 M in hexanes; 2.1 mL, 2.1 mmol, 9.0 equiv.) was added dropwise. The mixture was stirred for 30 min at 0 °C, and then for 1 h at room temperature, and the reaction was quenched with EtOAc. The mixture was concentrated in vacuo, and the residue was partitioned between EtOAc (20 mL) and aqueous HCl (1 M; 20 mL). The aqueous layer was extracted with EtOAc (20 mL), and the combined organic layers were dried with $MgSO_4$,

filtered, and concentrated in vacuo. The residue was purified by column chromatography (20 % EtOAc in pentane → 25 % EtOAc in pentane) to give compounds **24** (36.6 mg, 64.8 μmol, 28 %) and **25** (17.1 mg, 30.2 μmol, 13 %) as white solids.

Data for **24**: ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.46–7.20 (m, 18 H, CH_{arom}), 7.19–7.11 (m, 2 H, CH_{arom}), 4.96–4.64 (m, 5 H, CH_2 Bn), 4.55–4.29 (m, 3 H, CH_2 Bn), 4.06 (dd, *J* = 7.9, 6.2 Hz, 1 H, 2-H), 3.59 (d, *J* = 4.1 Hz, 1 H, 8-H), 3.51 (dd, *J* = 11.2, 6.3 Hz, 1 H, C*H*HOH), 3.40–3.18 (m, 3 H, CH*H*OH, 3-H, 4-H), 1.93–1.89 (m, 1 H, 5-H), 1.30–1.20 (m, 1 H, 1-H), 1.12–1.03 (m, 2 H, 6-H, 7-H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 139.2, 139.1, 138.8, 138.5 (4 $C_{q\text{-}arom}$), 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 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) ppm. HRMS: calcd. for $[C_{37}H_{41}O_6]^+$ 565.29485; found 565.29462.

Data for **25**: ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.63–6.95 (m, 20 H, CH_{arom}), 4.95–4.60 (m, 5 H, CH_2 Bn), 4.53–4.31 (m, 3 H, CH_2 Bn), 3.75–3.62 (m, 3 H, CH*H*OH, 2-H, 8-H), 3.58–3.42 (m, 2 H, 3-H, 8-H), 3.07–2.99 (m, 2 H, C*H*HOH, 4-H), 2.41–2.30 (m, 1 H, 5-H), 1.14 (dd, *J* = 8.2, 4.7 Hz, 1 H, 6-H), 1.02 (dd, *J* = 8.9, 4.8 Hz, 1 H, 1-H), 0.97–0.78 (m, 1 H, 7-H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 139.0, 138.6, 138.5, 138.2 (4 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 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) ppm. HRMS: calcd. 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 with $Pd(OH)_2$/C according to the general procedure for global debenzylation to give compound **26** (8.30 mg, 40.6 μmol, 90 %) as a colourless oil. ^{1}H NMR (400 MHz, D_2O): δ = 4.03 (dd, *J* = 8.7, 6.0 Hz, 1 H, 2-H), 3.90 (dd, *J* = 10.9, 3.5 Hz, 1 H, 8-H), 3.78 (dd, *J* = 10.9, 6.1 Hz, 1 H, 8-H), 3.62 (dd, *J* = 11.6, 6.1 Hz, 1 H, CH_2-OH), 3.33 (dd, *J* = 11.5, 7.7 Hz, 1 H, CH_2-OH), 3.25 (t, *J* = 10.1 Hz, 1 H, 4-H), 3.21–3.11 (m, 1 H, 3-H), 1.86–1.77 (m, 1 H, 5-H), 1.35 (dt, *J* = 9.0, 5.5 Hz, 1 H, 1-H or 6-H), 1.13 (dt, *J* = 11.3, 5.3 Hz, 1 H, 7-H), 1.05–0.97 (m, 1 H, 1-H or 6-H) ppm. ^{13}C NMR (100 MHz, D_2O): δ = 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) ppm. HRMS: calcd. 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 equiv.) were dissolved in DMF (0.3 mL) at 0 °C. The mixture was stirred for 5 min, then ethyl bromide (21 μL, 0.287 mmol, 9.0 equiv.) was added. The reaction mixture was stirred at room temperature for 4 h. The mixture was partitioned between H_2O (10 mL) and EtOAc (10 mL), and the organic layer was washed with H_2O (2 ×). The aqueous layers were extracted with EtOAc (1 ×). The combined organic layers were dried with $MgSO_4$, filtered, and concentrated in vacuo. The residue was purified by column chromatography (10 % EtOAc in pentane → 20 % EtOAc in pentane) to give compound **27** (11.1 mg, 18.7 μmol, 59 %) as a colourless oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.48–7.11 (m, 20 H, H_{arom}Bn), 4.91–4.72 (m, 4 H, CH_2Bn), 4.66 (d, *J* = 11.7 Hz, 1 H, CH_2Bn), 4.55–4.36 (m, 3 H, CH_2Bn), 4.07 (dd, *J* = 8.0, 6.2 Hz, 1 H, 2-H), 3.66–3.60 (m, 2 H, 8-H), 3.56–3.42 (m, 2 H, CH_2CH_3), 3.42–3.32 (m, 2 H, 4-H, C*H*HO), 3.32–3.22 (m, 2 H, 3-H, C*H*HO), 1.89 (dd, *J* = 6.6, 3.5 Hz, 1 H, 5-H), 1.34–1.28 (m, 1 H, 1-H), 1.17 (t, *J* = 7.0 Hz, 3 H, CH_3), 1.12–1.04 (m, 2 H, 6-H, 7-H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$): δ = 139.3, 139.2, 138.9, 138.6 (4 $C_{q\text{-}arom}$), 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 CH_2 Bn), 74.1 (CH_2O), 73.3, 71.1 (2 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) ppm. HRMS: calcd. 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 with $Pd(OH)_2$/C according to the general procedure for global debenzylation to give compound **28** (4.1 mg, 17.7 μmol, 94 %) as a colourless oil. ^{1}H NMR (400 MHz, D_2O): δ = 4.00 (dd, *J* = 8.8, 6.0 Hz, 1 H, 2-H), 3.87 (dd, *J* = 10.9, 3.5 Hz, 1 H, 8-H), 3.75 (dd, *J* = 10.9, 6.0 Hz, 1 H, 8-H), 3.65–3.55 (m, 3 H, CH_2CH_3, C*H*HOEt), 3.24–3.16 (m, 2 H CH*H*OEt, 4-H), 3.16–3.10 (m, 1 H, 3-H), 1.83–1.72 (m, 1 H, 5-H), 1.36–1.30 (m, 1 H, 1-H), 1.20 (t, *J* = 7.1 Hz, 3 H, CH_3), 1.13–1.05 (m, 1 H, 7-H), 1.08–0.95 (m, 1 H, 6-H) ppm. ^{13}C NMR (100 MHz, D_2O): δ = 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) ppm. HRMS: calcd. 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 as follows (CAUTION: Chromic acid is corrosive, toxic and carcinogenic). Concentrated H_2SO_4 (2.25 mL, 40.5 mmol) was added to H_2O (12.5 mL). CrO_3 (2.50 g, 25.0 mmol) was then added, and the resulting bright red solution was stirred until all the 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 the solution was cooled to 0 °C. Chromic acid stock solution (0.92 mL, 0.920 mmol, 2 equiv.) was then added. The mixture was stirred for 3 h, then it was diluted with EtOAc (150 mL), and washed with aqueous HCl (3 M; 2 × 150 mL) and brine (150 mL). The organic layer was dried with $MgSO_4$, filtered, and concentrated in vacuo. The residue was purified by column chromatography (15 % EtOAc in pentane → 35 % EtOAc in pentane) to give the corresponding carboxylic acid (141 mg, 0.244 mmol, 53 %) as a white solid. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.44–7.10 (m, 20 H, H_{arom}), 4.90–4.71 (m, 4 H, CH_2 Bn), 4.69–4.57 (m, 1 H, CH_2 Bn), 4.54–4.34 (m, 3 H, CH_2 Bn), 3.75 (d, *J* = 8.1 Hz, 1 H, 2-H), 3.65 (dd, *J* = 8.9, 2.7 Hz, 1 H, 8-H), 3.60–3.51 (m, 2 H, 3-H, 8-H), 3.11 (t, *J* = 10.2 Hz, 1 H, 4-H), 2.45–2.33 (m, 1 H, 5-H), 2.03–1.98 (m, 1 H, 6-H), 1.80 (dd, *J* = 9.5, 4.5 Hz, 1 H, 1-H), 1.60 (t, *J* = 4.6 Hz, 1 H, 8-H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 179.4 (C=O), 138.9, 138.6, 138.5, 138.1 (4 $C_{q\text{-}arom}$), 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 CH_2 Bn), 70.2 (C-8), 40.6 (C-5), 27.3 (C-6), 26.0 (C-1), 22.0 (C-7) ppm. HRMS: calcd. for $[C_{37}H_{39}O_6]^+$ 579.27412; found 579.27438.

The carboxylic acid (141 mg, 0.244 mmol) was dissolved in toluene (1.2 mL), and ethanol (66 μL, 0.488 mmol, 2 equiv.) and DMAP (catalytic amount) were added. DIC (75 μL, 0.484 mmol, 2.0 equiv.) was added dropwise, and the reaction mixture was stirred for 4 h at room temperature. The reaction mixture was then filtered through Celite, and concentrated in vacuo. The residue was purified by column chromatography (7 % EtOAc in pentane → 10 % EtOAc in pentane) to give compound **14** (91.4 mg, 0.151 mmol, 62 %) as a white solid. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.44–7.14 (m, 20 H, H_{arom}), 4.89–4.72 (m, 4 H, CH_2 Bn), 4.64 (d, *J* = 11.6 Hz, 1 H, CH_2 Bn), 4.52–4.36 (m, 3 H, CH_2 Bn), 4.15 (d, *J* = 7.2 Hz, 1 H, C*H*HCH$_3$), 4.12 (d, *J* = 7.2 Hz, CH*H*CH$_3$), 3.75 (d, *J* = 7.8 Hz, 1 H, 2-H), 3.65 (dd, *J* = 8.9, 2.7 Hz, 1 H, 8-H), 3.61–3.48 (m, 2 H, 3-H, 8-H), 3.14 (t, *J* = 10.2 Hz, 1 H, 4-H), 2.45–2.29 (m, 1 H, 6-H), 1.96–1.84 (m, 1 H, 6-H), 1.74 (dd, *J* = 9.3, 4.5 Hz, 1 H, 1-H), 1.61 (t, *J* = 4.7 Hz, 1 H, 7-H), 1.26 (t, *J* =

7.1 Hz, 3 H, CH_3) ppm. ^{13}C NMR (101 MHz, $CDCl_3$): δ = 173.5 (C=O), 138.9, 138.7, 138.6, 138.2 (4 $C_{q\text{-}arom}$), 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 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) ppm. HRMS: calcd. 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 equiv.) in THF (0.5 mL). Subsequently, EtMgBr (0.5 M in THF; 0.840 mmol, 8.4 equiv.) was added over 2 h at –5 to 0 °C. The mixture was stirred overnight, then it was quenched with aqueous HCl (3 M; 3 mL). The mixture was extracted with EtOAc (10 mL), after which the organic layer was dried and concentrated in vacuo. The residue was purified by column chromatography (15 % EtOAc in pentane) to give compound **29** (29.4 mg, 47.9 µmol, 48 %) as a white solid. ^1H NMR (400 MHz, $CDCl_3$): δ = 7.42–7.14 (m, 20 H, H_{arom}), 4.95–4.69 (m, 4 H, CH_2 Bn), 4.60 (d, *J* = 11.5 Hz, 1 H, CH_2 Bn), 4.52–4.30 (m, 3 H, CH_2 Bn), 3.72 (d, *J* = 7.8 Hz, 1 H, 2-H), 3.69–3.46 (m, 3 H, 3-H, 8-H), 3.26 (t, *J* = 10.2 Hz, 1 H, 4-H), 2.38 (dd, *J* = 8.7, 7.4 Hz, 2 H, CH_2CH_3), 2.36–2.29 (m, 1 H, 5-H), 1.89 (t, *J* = 4.7 Hz, 1 H, 7-H), 1.84–1.82 (m, 1 H, 6-H), 1.82–1.79 (m, 1 H, 1-H), 1.00 (t, *J* = 7.3 Hz, 3 H, CH_3) ppm. ^{13}C NMR (101 MHz, $CDCl_3$): δ = 209.7 (C=O), 139.0, 138.7, 138.6, 138.2 (4 $C_{q\text{-}arom}$), 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 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) ppm. HRMS: calcd. 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 with $Pd(OH)_2$/C according to the general procedure for global debenzylation to give compound **30** (6.70 mg, 29.1 µmol, 58 %) as a colourless oil. ^1H NMR (400 MHz, D_2O): δ = 3.92 (dd, *J* = 11.2, 4.0 Hz, 1 H, 8-H), 3.89 (dd, *J* = 0.8, 8.6 Hz, 1 H, 2-H), 3.60 (dd, *J* = 10.8, 8.2 Hz, 1 H, 8-H), 3.28 (dd, *J* = 10.2, 8.6 Hz, 1 H, 3-H), 3.05 (t, *J* = 10.0 Hz, 1 H, 4-H), 2.69 (dd, *J* = 14.6, 7.4 Hz, 2 H, CH_2CH_3), 2.21–2.15 (m, 1 H, 5-H), 2.13 (t, *J* = 4.2 Hz, 1 H, 7-H), 1.93 (ddd, *J* = 9.7, 5.0, 5.0 Hz, 1 H, 6-H), 1.67 (dd, *J* = 9.2, 4.4 Hz, 1 H, 1-H), 1.03 (t, *J* = 7.2 Hz, 3 H, CH_3) ppm. ^{13}C NMR (100 MHz, D_2O): δ = 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) ppm. HRMS: calcd. 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): MeOH (2 mL), H_2O (1 mL), and LiOH (22.4 mg, 0.94 mmol, 4 equiv.) were added to a mixture of **13** and **14** (0.142 g, 0.234 mmol) in THF (8 mL). The mixture was stirred overnight at room temperature, then aqueous HCl (1 M) 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 with $MgSO_4$, filtered, and concentrated in vacuo. The residue was purified by column chromatography (30 % EtOAc in pentane) to give the carboxylic acid derivatives as a mixture of α and β isomers (119 mg, 0.206 mmol, 82 %) as a colourless oil.

The carboxylic acid derivatives (0.346 g, 0.600 mmol) were dissolved in CH_2Cl_2 (6.0 mL), and 4-azidobutan-1-amine (82.2 mg, 0.720 mmol, 1.2 equiv.) was added. DIPEA (364 µL, 2.10 mmol, 3.5 equiv.) and HCTU (298 mg, 0.720 mmol, 1.2 equiv.) were then added, and the reaction mixture was stirred overnight at room temperature. The reaction mixture was concentrated in vacuo. The residue was dissolved in EtOAc (40 mL). The organic phase was washed with aqueous HCl (1 M; 2 × 40 mL), saturated aqueous $NaHCO_3$ (40 mL), and brine (2 × 40 mL), dried with $MgSO_4$, filtered, and concentrated in vacuo. The residue was purified by column chromatography (30 % EtOAc in pentane) to give a mixture of α-*exo* isomer **31** and β-*exo* isomer **32** (0.341 g, 0.505 mmol, 78 %) as a white solid. The isomers were separated by HPLC purification [C18; linear gradient: 50–90 % B in A over 15 min; solutions used: A = H_2O; B = acetonitrile (0.5 % TFA,)].

Data for **31**: ^1H NMR (400 MHz, $CDCl_3$): δ = 7.38–7.10 (m, 20 H, H_{arom}Bn), 5.66 (t, *J* = 5.8 Hz, 1 H, NH), 4.90–4.69 (m, 4 H, CH_2Bn), 4.61 (d, *J* = 11.6 Hz, 1 H, CH_2Bn), 4.53–4.32 (m, 3 H, CH_2Bn), 4.10 (dd, *J* = 8.2, 5.9 Hz, 1 H, 2-H), 3.59 (qd, *J* = 8.8, 3.8 Hz, 2 H, 8-H), 3.42 (t, *J* = 10.1 Hz, 1 H, 4-H), 3.30 (t, *J* = 6.1 Hz, 4 H, NHC*H*$_2$, C*H*$_2$N$_3$), 3.26–3.20 (m, 1 H, 3-H), 2.04 (dt, *J* = 10.0, 5.2 Hz, 1 H, 1-H), 1.94–1.85 (m, 1 H, 5-H), 1.82 (ddd, *J* = 9.2, 4.4, 2.2 Hz, 1 H, 6-H), 1.65–1.57 (m, 4 H, NHCH$_2$C*H*$_2$, CH$_2$C*H*$_2$N$_3$), 1.35 (t, *J* = 4.5 Hz, 1 H, 7-H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 172.1 (C=O), 139.1, 138.6 (C_q-Bn), 128.6, 128.6, 128.6, 128.5, 128.3, 128.1, 128.0, 127.9, 127.9, 127.7 (C_{arom}-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$_2$*C*H$_2$N$_3$), 25.7 (C-6), 23.8 (C-7) ppm. HRMS: calcd. for $[C_{41}H_{47}N_4O_5]^+$ 675.35410; found 675.35411.

Data for **32**: ^1H NMR (400 MHz, $CDCl_3$): δ = 7.45–7.12 (m, 20 H, CH_{arom}), 5.22 (t, *J* = 5.8 Hz, 1 H, NH), 4.87 (d, *J* = 12.3 Hz, 2 H, CH_2), 4.83–4.74 (m, 2 H, CH_2), 4.60 (d, *J* = 11.5 Hz, 1 H, CH_2), 4.50 (d, *J* = 11.0 Hz, 1 H, CH_2), 4.37 (d, *J* = 2.4 Hz, 2 H, CH_2), 3.83 (dd, *J* = 9.1, 3.6 Hz, 1 H, 2-H), 3.75 (d, *J* = 7.6 Hz, 1 H, 3-H), 3.66–3.52 (m, 2 H, 8-H), 3.34 (t, *J* = 10.2 Hz, 1 H, 4-H), 3.23 (t, *J* = 6.7 Hz, 2 H, CH_2N_3), 3.19–3.10 (m, 1 H, NHC*H*H), 3.10–3.00 (m, 1 H, NHCH*H*), 2.29–2.24 (m, 1 H, 5-H), 1.79 (dd, *J* = 9. 1, 4.8 Hz, 1 H, 6-H), 1.70–1.63 (m, 1 H, 1-H), 1.55–1.44 (m, 2 H, NHCH$_2$C*H*$_2$), 1.43–1.30 (m, 3 H, C*H*$_2$CH$_2$N$_3$, 7-H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 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 CH_2 arom), 70.3 (C-8), 51.2 (CH_2N_3), 40.5 (C-1), 39.2 ($NHCH_2$), 27.1 ($NHCH_2CH_2$), 26.3 ($CH_2CH_2N_3$), 25.2 (C-5), 24.5 (C-6), 21.5 (C-7) ppm. HRMS: calcd. 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): BCl_3 (1 M in CH_2Cl_2; 0.400 mL, 0.40 mmol, 20 equiv.) was added slowly to a cooled (–78 °C) solution of benzylated **31** (12.7 mg, 18.8 µmol) in CH_2Cl_2 (0.2 mL). The mixture was stirred for 5 h at –78 °C, then the reaction was quenched with MeOH (5 mL), and the mixture was warmed to room temperature overnight. The mixture was concentrated in vacuo and coevaporated with toluene (3 ×). The residue was purified by column chromatography (20 % MeOH in CH_2Cl_2) to give compound **33** (5.20 mg, 16.5 µmol, 88 %) as a white solid. ^1H NMR (400 MHz, [D_4]methanol): δ = 3.81 (dd, *J* = 8.7, 5.7 Hz, 1 H, 2-H), 3.72 (dd, *J* = 10.6, 3.9 Hz, 1 H, 8-H), 3.55 (dd, *J* = 10.5, 6.5 Hz, 1 H, 8-H), 3.34–3.30 (m, 2 H, CH_2N_3), 3.09 (t, *J* = 6.6 Hz, 2 H, CH_2N), 3.03 (t, *J* = 10.1 Hz, 1 H, 4-H), 2.97–2.85 (m, 1 H, 3-H), 1.85–1.80 (m, 1 H, 1-H), 1.74–1.70 (m, 1 H, 5-H), 1.63–1.54 (m, 5 H, 2 CH_2, 7-H), 1.53–1.49 (m, 1 H, 6-H) ppm. ^{13}C NMR (100 MHz, [D_4]methanol): δ = 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) ppm. HRMS: calcd. 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): BCl_3 (1 M in CH_2Cl_2; 0.400 mL, 0.40 mmol, 20 equiv.) was slowly added to a cooled (–78 °C) solution of benzylated **32** (12.7 mg, 18.8 μmol) in CH_2Cl_2 (0.2 mL). The mixture was stirred for 3 h at –78 °C, then additional BCl_3 (1 M in CH_2Cl_2; 0.400 mL, 0.376 mmol, 20 equiv.) was added. The mixture was stirred overnight at –20 °C, then the reaction was quenched with MeOH (5 mL), and the mixture was warmed to room temperature. The mixture was concentrated in vacuo and coevaporated with MeOH (3 ×). The residue was purified by column chromatography (20 % MeOH in CH_2Cl_2) to give compound **34** (5.9 mg, 18.6 μmol, 99 %) as a slightly yellow solid. ^{1}H NMR (400 MHz, [D$_4$]methanol): δ = 3.80 (d, *J* = 6.3 Hz, 1 H, 8-H), 3.53–3.44 (m, 2 H, 2-H, 8-H), 3.17–3.01 (m, 3 H, 3-H, NHC*H*$_2$), 2.83 (t, *J* = 9.7 Hz, 1 H, 4-H), 2.07–1.90 (m, 1 H, 5-H), 1.76–1.61 (m, 1 H, 1-H), 1.54–1.44 (m, 4 H, NHCH$_2$C*H*$_2$, and C*H*$_2$CH$_2$N$_3$), 1.44–1.38 (m, 1 H, 7-H), 1.34–1.28 (m, 1 H, 6-H) ppm. ^{13}C NMR (100 MHz, [D$_4$]methanol): δ = 79.6 (C-3), 74.5 (C-2), 70.7 (C-4), 65.1 (C-8), 52.3 (CH$_2$N$_3$), 43.8 (C-5), 40.2 (NHCH$_2$), 27.9, 27.9 (*C*H$_2$CH$_2$N$_3$ and NHCH$_2$*C*H$_2$), 27.5 (C-7), 25.0 (C-1), 24.5 (C-6) ppm. HRMS: calcd. 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): Boron trifluoride ethyl etherate (62 μL) and diethylzinc (1 M in hexane; 1.0 mL, 1.0 mmol) were added sequentially to a solution of CH_2Cl_2 (0.5 mL) and 1,2-dimethoxyethane (100 μL) at room temperature. The mixture was stirred for 5 min, then diiodomethane (161 μL, 2.0 mmol) was added, and the mixture was stirred for a further 5 min. Compound **35** (52.0 mg, 0.100 mmol) was dissolved in CH_2Cl_2 (1.0 mL), and the resulting solution was added dropwise to the reaction mixture. The mixture was stirred overnight, then it was quenched with saturated aqueous NH_4Cl solution, and diluted with EtOAc. The aqueous layer was extracted with EtOAc (3 ×), and the combined organic layers were washed with brine, dried with $MgSO_4$, filtered, and concentrated in vacuo. The residue was purified by column chromatography (pentane → 8 % EtOAc in pentane) to give benzylated cyclopropane **36** (45.1 mg, 84.3 μmol, 84 %) as a colourless oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.47–7.21 (m, 20 H, H$_{arom}$ Bn), 4.86 (dd, *J* = 27.0, 11.7 Hz, 2 H, CH$_2$ Bn), 4.76–4.62 (m, 3 H, CH$_2$ Bn), 4.58 (d, *J* = 11.7 Hz, 1 H, CH$_2$ Bn), 4.47 (d, *J* = 4.4 Hz, 2 H, CH$_2$ Bn), 4.39 (dd, *J* = 8.4, 6.6 Hz, 1 H, 2-H), 3.90 (s, 1 H, 4-H), 3.66–3.52 (m, 2 H, 8-H), 3.19 (dd, *J* = 8.4, 1.1 Hz, 1 H, 3-H), 1.90–1.85 (m, 1 H, 5-H), 1.55–1.40 (m, 1 H, 1-H), 0.84–0.69 (m, 2 H, 6-H, 7-H), 0.30 (q, *J* = 5.2 Hz, 1 H, 7-H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$): δ = 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) ppm. HRMS: calcd. 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 with Pd(OH)$_2$/C according to the general procedure for global debenzylation to give compound **37** (13.0 mg, 74.7 μmol, 99 %) as a colourless oil. ^{1}H NMR (400 MHz, D$_2$O): δ = 4.20 (dd, *J* = 9.0, 6.6 Hz, 1 H, 2-H), 3.80 (s, 1 H, 4-H), 3.76–3.62 (m, 2 H, 8-H), 3.17 (dd, *J* = 9.1, 1.7 Hz, 1 H, 3-H), 1.83–1.78 (m, 1 H, 5-H), 1.42–1.32 (m, 1 H, 1-H), 0.82–0.75 (m, 2 H, 6-H, 7-H), 0.25–0.18 (m, 1 H, 7-H) ppm. ^{13}C NMR (101 MHz, D$_2$O): δ = 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) ppm. HRMS: calcd. 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 two-necked pear-shaped flask was loaded with cyclic alkene **35** (2.94 g, 5.65 mmol), Cu(acac)$_2$ (153 mg, 0.57 mol, 0.1 equiv.), and EtOAc [dried over activated molecular sieves (4 Å) overnight; 10 mL]. The mixture was stirred at reflux at 90 °C, then a solution of ethyl diazoacetate (containing 13 wt.-% CH_2Cl_2; 17.1 mmol, 1.46 mL, 3 equiv.) in EtOAc (38 mL) was added by syringe pump over 12 h. The reaction mixture was concentrated in vacuo. The residue was purified by column chromatography (5 % → 7 % EtOAc in pentane) to give a mixture of the desired products **38** (666 mg, 1.10 mmol, 19 %) and **39** (333 mg, 0.55 mmol, 10 %). Spectroscopic data was obtained from analytical samples of both products.

Data for **38**: ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.34–7.23 (m, 20 H, H$_{arom}$Bn), 4.88 (d, *J* = 11.6 Hz, 1 H, CH$_2$Bn), 4.81–4.60 (m, 4 H, CH$_2$Bn), 4.56 (d, *J* = 11.6 Hz, 1 H, CH$_2$Bn), 4.50–4.40 (m, 2 H, CH$_2$Bn), 4.37 (dd, *J* = 8.2, 6.4 Hz, 1 H, 2-H), 4.14–4.08 (m, 2 H, C*H*$_2$CH$_3$), 3.91 (s, 1 H, 4-H), 3.64 (t, *J* = 9.0 Hz, 1 H, 8-H), 3.56 (dd, *J* = 8.6, 6.3 Hz, 1 H, 8-H), 3.15 (d, *J* = 8.2 Hz, 1 H, 3-H), 2.13–2. 04 (m, 1 H, 1-H), 1.99–1.93 (m, 1 H, 5-H), 1.62–1.58 (m, 1 H, 7-H), 1.40–1.34 (m, 1 H, 6-H), 1.28–1.25 (m, 3 H, CH$_3$) ppm. ^{13}C NMR (101 MHz, $CDCl_3$): δ = 173.50 (C$_q$ carbonyl), 139.2, 139.0, 139.0, 138.4 (4 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 CH$_2$ Bn), 70.5 (C-8), 60.7 (*C*H$_2$CH$_3$), 41.4 (C-5), 27.1 (C-1), 26.0 (C-7), 24.5 (C-6), 14.4 (CH$_3$) ppm. HRMS: calcd. for $[C_{39}H_{43}O_6]^+$ 607.30542; found 607.30560.

Data for **39**: ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.40–7.24 (m, 20 H, H$_{arom}$Bn), 4.87 (d, *J* = 11.6 Hz, 1 H, CH$_2$Bn), 4.78–4.65 (m, 4 H, CH$_2$Bn), 4.53–4.40 (m, 3 H, CH$_2$Bn), 4.14–4.08 (m, 2 H, C*H*$_2$CH$_3$), 4.08–4.02 (m, 1 H, 4-H), 4.00 (d, *J* = 8.8 Hz, 1 H, 2-H), 3.66–3.58 (m, 1 H, 8-H), 3.57–3.51 (m, 1 H, 8-H), 3.47 (dd, *J* = 8.8, 1.7 Hz, 1 H, 3-H), 2.47–2.38 (m, 1 H, 5-H), 2.09 (t, *J* = 4.6 Hz, 1 H, 7-H), 1.72 (dd, *J* = 9.4, 4.4 Hz, 1 H, 1-H or 6-H), 1.59–1.52 (m, 1 H, 1-H or 6-H), 1.22 (s, 3 H, CH$_3$) ppm. ^{13}C NMR (101 MHz, $CDCl_3$): δ = 174.0 (C$_q$ carbonyl), 139.2, 138.9, 138.6, 138.3 (4 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 CH$_2$ Bn), 70.4 (C-8), 60.7 (*C*H$_2$CH$_3$), 38.4 (C-5), 26.1, 23.1 (C-1, C-6), 22.6 (C-7), 14.4 (CH$_3$) ppm. HRMS: calcd. 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 CH_2Cl_2 (2.1 mL) at 0 °C, and then DIBAL (1 M in hexanes; 1.05 mmol, 2.5 equiv.) was added dropwise. The mixture was stirred for 1 h at 0 °C, then the reaction was quenched with EtOAc. The mixture was diluted with CH_2Cl_2, and washed with aqueous HCl (1 M). The layers were separated, and the aqueous layer was extracted with CH_2Cl_2 (3 ×). The combined organic layers were washed with saturated aqueous $NaHCO_3$ and brine, dried with $MgSO_4$, filtered, and concentrated in vacuo. The residue was purified by column chromatography (pentane → 30 % EtOAc in pentane) to give compounds **40** (94.5 mg, 0.167 mmol, 40 %) and **41** (85.7 mg, 0.152 mmol, 36 %) as yellow oils.

Data for **40**: ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.42–7.21 (m, 20 H, CH$_{arom}$), 4.88 (d, *J* = 11.6 Hz, 1 H, CH$_2$ Bn), 4.78 (d, *J* = 11.6 Hz, 1 H, CH$_2$ Bn), 4.73–4.64 (m, 3 H, CH$_2$ Bn), 4.57 (d, *J* = 11.6 Hz, 1 H, CH$_2$ Bn), 4.52–4.40 (m, 2 H, CH$_2$ Bn), 4.35 (t, *J* = 8.0 Hz, 1 H, 2-H), 3.89 (s, 1 H, 4-H), 3.65–3.51 (m, 2 H, 8-H), 3.44 (dd, *J* = 11.2, 6.7 Hz, 1 H, C*H*HOH), 3.35 (dd, *J* = 11.2, 6.8 Hz, 1 H, CH*H*OH), 3.17 (d, *J* = 8.3 Hz, 1 H, 3-H), 1.93–1.79 (m, 1 H, 5-H), 1.36–1.30 (m, 1 H, 1-H), 1.07–0.99 (m, 1 H, 7-H), 0.72–0.63 (m, 1 H, 6-H) ppm. ^{13}C NMR (101 MHz,

$CDCl_3$): δ = 139.3, 139.3, 139.0, 138.3 (4 $C_{q\text{-}arom}$), 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 CH_2 Bn), 71.1 (C-8), 66.6 (CH_2OH), 41.8 (C-5), 27.4 (C-7), 22.1 (C-1), 19.5 (C-6) ppm. HRMS: calcd. for $[C_{37}H_{41}O_5]^+$ 565.29485; found 565.29480.

Data for **41**: ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.41–7.20 (m, 20 H, CH_{arom}), 4.85 (d, J = 11.6 Hz, 1 H, CH_2 Bn), 4.78–4.67 (m, 4 H, CH_2 Bn), 4.53–4.41 (m, 3 H, CH_2 Bn), 4.01–3.92 (m, 2 H, 2-H, 4-H), 3.64–3.52 (m, 2 H, 8-H), 3.50–3.41 (m, 2 H, 3-H, C*H*HOH), 3.16 (dd, J = 11.1, 7.7 Hz, 1 H, CH*H*OH), 2.47–2.38 (m, 1 H, 5-H), 1.51–1.48 (m, 1 H, 7-H), 1.01–0.95 (m, 1 H, 1-H), 0.86–0.79 (m, 1 H, 6-H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$): δ = 139.3, 139.1, 139.0, 138.4 (4 $C_{q\text{-}arom}$), 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 CH_2 Bn), 71.0 (C-8), 67.0 (CH_2OH), 37.9 (C-5), 23.2 (C-7), 21.5 (C-1), 18.3 (C-6) ppm. HRMS: calcd. 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 with Pd on carbon (10 %) according to the general procedure for global debenzylation to give compound **42** (10.9 mg, 53 µmol, quant.) as a colourless oil. ^{1}H NMR (400 MHz, D_2O): δ = 4.20 (dd, J = 9.1, 6.6 Hz, 1 H, 2-H), 3.85–3.82 (m, 1 H, 4-H), 3.78–3.66 (m, 2 H, 8-H), 3.58 (dd, J = 11.6, 6.1 Hz, 1 H, C*H*HOH), 3.27 (dd, J = 11.6, 7.8 Hz, 1 H, CH*H*OH), 3.20 (dd, J = 9.1, 1.8 Hz, 1 H, 3-H), 1.90–1.82 (m, 1 H, 5-H), 1.36–1.29 (m, 1 H, 1-H), 1.05–0.97 (m, 1 H, 7-H), 0.77–0.70 (m, 1 H, 6-H) ppm. ^{13}C NMR (101 MHz, D_2O): δ = 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) ppm. HRMS: calcd. 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 with Pd on carbon (10 %) according to the general procedure for global debenzylation to give compound **43** (11.2 mg, 54 µmol, 87 %) as a colourless oil. ^{1}H NMR (400 MHz, D_2O): δ = 4.01–3.95 (m, 1 H, 4-H), 3.83 (d, J = 8 Hz, 1 H, 2-H), 3.78–3.64 (m, 2 H, 8-H), 3.41–3.31 (m, 3 H, CH_2OH, 3-H), 2.29–2.20 (m, 1 H, 5-H), 1.31–1.21 (m, 1 H, 7-H), 1.02–0.92 (m, 1 H, 6-H), 0.92–0.84 (m, 1 H, 1-H) ppm. ^{13}C NMR (101 MHz, D_2O): δ = 76.0 (C-3), 69.6, 69.5 (C-2, 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) ppm. HRMS: calcd. 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): NaH (60 % dispersion in mineral oil; 19.2 mg, 0.480 mmol 8 equiv.) was added to a solution of alcohol **40** (33.9 mg, 60.0 µmol) and TBAI (10 mg) in DMF (0.8 mL) at 0 °C. The mixture was stirred for 5 min, then ethyl bromide (20 µL, 0.36 mmol, 6 equiv.) was added. The reaction mixture was stirred overnight at room temperature. The reaction was quenched with H_2O (3 mL), and the mixture was diluted with EtOAc (20 mL). The organic layer was separated, and washed with saturated aqueous $NaHCO_3$, H_2O (3 ×), and brine. The combined aqueous layers were extracted with EtOAc, and the combined organic layers were dried with $MgSO_4$, filtered, and concentrated in vacuo. The residue was purified by column chromatography (pentane → 20 % EtOAc in pentane) to give ether **44** (28.5 mg, 48.1 µmol, 80 %) as a yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.43–7.21 (m, 20 H, H_{arom}), 4.88 (d, J = 11.6 Hz, 1 H, CH_2 Bn), 4.83 (d, J = 11.6 Hz, 1 H, CH_2 Bn), 4.77–4.61 (m, 3 H, CH_2 Bn), 4.58 (d, J = 11.7 Hz, 1 H, CH_2 Bn), 4.52–4.40 (m, 2 H, CH_2 Bn), 4.39–4.33 (m, 1 H, 2-H), 3.90 (s, 1 H, 4-H), 3.68–3.53 (m, 2 H, 8-H), 3.52–3.37 (m, 2 H, CH_2CH$_3$), 3.35–3.22 (m, 2 H, CH_2O), 3.18 (d, J = 8.3 Hz, 1 H, 3-H), 1.97–1.87 (m, 1 H, 5-H), 1.41–1.35 (m, 1 H, 1-H), 1.15 (t, J = 7.0 Hz, 3 H, CH_3), 1.04 (p, J = 6.2 Hz, 1 H, 7-H), 0.70–0.64 (m, 1 H, 6-H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$): δ = 139.5, 139.4, 139.2, 138.4 (4 $C_{q\text{-}arom}$), 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 CH_2 Bn and CH_2O), 71.1, 71.0 (CH_2 Bn and C-8), 65.8 (CH_2CH_3), 41.8 (C-5), 24.5 (C-7), 21.6 (C-1), 20.0 (C-6), 15.4 (CH_3) ppm. HRMS: calcd. 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): NaH (60 % dispersion in mineral oil, 21.4 mg, 0.536 mmol 8 equiv.) was added to a solution of alcohol **41** (38.0 mg, 67.3 µmol) and a catalytic amount of TBAI in DMF (0.8 mL) at 0 °C. The mixture was stirred for 5 min, then ethyl bromide (50 µL, 0.66 mmol, 10 equiv.) was added. The reaction mixture was stirred overnight. The reaction was quenched with H_2O (3 mL), and the mixture was diluted with EtOAc (20 mL). The organic layer was separated, and washed with saturated aqueous $NaHCO_3$, H_2O (3 ×), and brine. The combined aqueous layers were extracted with EtOAc, and the combined organic layers were dried with $MgSO_4$, filtered, and concentrated in vacuo. The residue was purified by column chromatography (pentane → 20 % EtOAc in pentane) to give ether **45** (29.6 mg, 50.0 µmol, 74 %) as a yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.40–7.22 (m, 20 H, H_{arom}), 4.87 (d, J = 11.6 Hz, 1 H, CH_2 Bn), 4.80–4.67 (m, 4 H, CH_2 Bn), 4.49–4.44 (m, 3 H, CH_2 Bn), 4.03 (dd, J = 3.8, 1.7 Hz, 1 H, 4-H), 3.99 (d, J = 8.7 Hz, 1 H, 2-H), 3.68–3.61 (m, 1 H, 8-H), 3.59–3.50 (m, 1 H, 8-H), 3.47–3.40 (m, 3 H, 3-H, CH_2CH$_3$), 3.20 (d, J = 6.8 Hz, 2 H, CH_2O), 2.40–2.37 (m, 1 H, 5-H), 1.51–1.43 (m, 1 H, 7-H), 1.17 (t, J = 7.0 Hz, 3 H, CH_3), 0.99 (dd, J = 8.9, 4.4 Hz, 1 H, 6-H), 0.85–0.77 (m, 1 H, 1-H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$): δ = 139.5, 139.2, 139.0, 138.5 (4 $C_{q\text{-}arom}$), 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 CH_2 Bn), 71.0 (C-8), 65.6 (CH_2CH_3), 38.6 (C-5), 21.3 (C-6), 20.5 (C-7), 18.4 (C-1), 15.4 (CH_3) ppm. HRMS: calcd. 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 with Pd on carbon (10 %) according to the general procedure for global debenzylation to give compound **46** (8.0 mg, 35 µmol, quant.) as a colourless oil. ^{1}H NMR (400 MHz, D_2O): δ = 4.22–4.18 (dd, J = 6.4, 9.2 Hz, 1 H, 2-H), 3.83 (s, 1 H, 4-H), 3.75–3.67 (m, 2 H, 8-H), 3.63–3.51 (m, 3 H, C*H*HO and CH_2CH$_3$), 3.23–3.13 (m, 2 H, CH*H*O, 3-H), 1.91–1.83 (m, 1 H, 5-H), 1.38–1.28 (m, 1 H, 1-H), 1.17 (t, J = 7.1 Hz, 3 H, CH_3), 1.05–0.96 (m, 1 H, 7-H), 0.80–0.73 (m, 1 H, 6-H) ppm. ^{13}C NMR (101 MHz, D_2O): δ = 73.9, 73.8 (C-3, CH_2O), 71.5 (C-4), 68.6 (C-2), 66.1 (CH_2CH_3), 62.6 (C-8), 42.6 (C-5), 23.3, 23.2 (C-1, C-7), 18.7 (C-6), 14.1 (CH_3) ppm. HRMS: calcd. 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 with Pd on carbon (10 %) according to the general procedure for global debenzylation to give compound **47** (9.0 mg, 39 µmol, quant.) as a colourless oil. ^{1}H NMR (400 MHz, D_2O): δ = 4.02–3.95 (m, 1 H, 4-H), 3.84 (d, J = 8.9 Hz, 1 H, 2-H), 3.75–3.67 (m, 2 H, 8-H), 3.62–3.52 (m, 2 H, CH_2CH$_3$), 3.42–3.33 (m, 2 H, 3-H, C*H*HO), 3.29–3.22 (m, 1 H, CH*H*O), 2.31–2.21 (m, 1 H, 5-H), 1.32–1.26 (m, 1 H, 7-H), 1.18 (t, J = 7.1 Hz, 3 H, CH_3), 1.02–0.96 (m, 1 H, 6-H), 0.93–0.86 (m, 1 H, 1-H) ppm. ^{13}C NMR (101 MHz, D_2O): δ = 75.9 (C-3), 74.2 (CH_2O), 69.5, 69.4 (C-2, C-4), 65.9 (CH_2CH_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) ppm. HRMS: calcd. 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): Me(MeO)NH•HCl (26.3 mg, 0.270 mmol, 1.3 equiv.) was added to a mixture of **38** and **39** (126 mg, 0.207 mmol) in THF (2.7 mL) at –8 °C. Subsequently, EtMgBr (1 M in THF; 1.7 mL, 1.7 mmol, 8.4 equiv.) was added over 2 h. The mixture was stirred overnight, then it was quenched with NaOH (0.5 M aq.). The reaction mixture was extracted with EtOAc (10 mL), then the organic layer was washed with aqueous HCl (3 M). The organic layer was dried with $MgSO_4$, filtered, concentrated in vacuo, and coevaporated with toluene (3 ×). The residue was dissolved in THF (1 mL), and EtMgBr (1 M in THF; 0.60 mmol, 3 equiv.) was added over 2 min at –20 °C. The reaction mixture was allowed to come to room temperature and stirred for 3 h, then the reaction was quenched with a saturated aqueous NH_4Cl solution. The mixture was extracted with EtOAc (10 mL). The organic layer was dried with $MgSO_4$, filtered, and concentrated in vacuo. The residue was purified by column chromatography (8 % EtOAc in pentane → 10 % EtOAc in pentane) followed by HPLC [C18; linear gradient: 50–90 % B in A over 15 min; solutions used: A = H_2O; B = acetonitrile (0.1 % TFA)] to give compound **48** (19.4 mg, 32.8 μmol, 16 %) and compound **49** (25.2 mg, 42.6 μmol, 21 %).

Data for **48**: ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.39–7.22 (m, 20 H, H_{arom}), 4.88 (d, J = 11.6 Hz, 1 H, CH_2Bn), 4.76–4.52 (m, 5 H, CH_2Bn), 4.44 (d, J = 3.1 Hz, 2 H, CH_2Bn), 4.35 (dd, J = 8.3, 6.3 Hz, 1 H, 2-H), 3.92 (s, 1 H, 4-H), 3.63 (t, J = 9.0 Hz, 1 H, 8-H), 3.57–3.50 (m, 1 H, 8-H), 3.19 (d, J = 7.6 Hz, 1 H, 3-H), 2.56 (d, J = 8.0 Hz, 1 H, C*H*HCH$_3$), 2.52 (d, J = 8.0 Hz, 1 H, CH*H*CH$_3$), 2.14–2.07 (m, 1 H, 1-H), 1.98–1.87 (m, 2 H, 5-H, 7-H), 1.48–1.39 (m, 1 H, 6-H), 1.06 (t, J = 7.3 Hz, 3 H, CH_3) ppm. ^{13}C NMR (101 MHz, $CDCl_3$): δ = 209.81 (C_q carbonyl), 139.2, 139.0, 138.9, 138.2 (4 $C_{q\text{-}arom}$), 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 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) ppm. HRMS: calcd. for $[C_{39}H_{43}O_5]^+$ 591.31050; found 591.31043.

Data for **49**: ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.39–7.22 (m, 20 H, H_{arom}), 4.90 (d, J = 11.6 Hz, 1 H, CH_2Bn), 4.80–4.60 (m, 4 H, CH_2Bn), 4.53–4.38 (m, 3 H, CH_2Bn), 4.07–4.01 (m, 1 H, 4-H), 3.96 (d, J = 8.7 Hz, 1 H, 2-H), 3.58 (t, J = 8.8 Hz, 1 H, 8-H), 3.54–3.44 (m, 2 H, 3-H, 8-H), 2.50–2.39 (m, 3 H, C*H*$_2$CH$_3$, 7-H), 1.78 (dd, J = 9.2, 4.4 Hz, 1 H, 1-H or 6-H), 1.60–1.5 (m, 1 H, 1-H or 6-H), 1.03 (t, J = 7.3 Hz, 3 H, CH_3) ppm. ^{13}C NMR (101 MHz, $CDCl_3$): δ = 210.38 (C_q carbonyl), 139.4, 138.9, 138.5, 138.3 (4 $C_{q\text{-}arom}$), 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 CH_2 Bn), 70.4 (C-8), 38.5 (C-5), 37.1 (*C*H$_2$CH$_3$), 30.0 (C-7), 28.1, 25.9 (C-1, C-6), 8.2 (CH_3) ppm. HRMS: calcd. 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 with Pd on carbon (10 %) according to the general procedure for global debenzylation to give compound **50** (4.6 mg, 20 μmol, 80 %) as a white solid. ^{1}H NMR (400 MHz, D_2O): δ = 4.26 (dd, J = 9.0, 6.1 Hz, 1 H, 2-H), 3.89 (s, 1 H, 4-H), 3.81–3.65 (m, 2 H, 8-H), 3.29 (dd, J = 9.1, 1.6 Hz, 1 H, 3-H), 2.74 (d, J = 8.0 Hz, 1 H, C*H*HCH$_3$), 2.70 (d, J = 8.0 Hz, 1 H, CH*H*CH$_3$), 2.18 (t, J = 4.6 Hz, 1 H, 7-H), 2.11–2.04 (m, 1 H, 1-H), 2.03–1.96 (m, 1 H, 5-H), 1.50–1.42 (m, 1 H, 6-H), 1.04 (t, J = 7.3 Hz, 3 H, CH_3) ppm. ^{13}C NMR (101 MHz, D_2O): δ = 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) ppm. HRMS: calcd. 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)bicyclo[4.1.0]heptan-7-yl]propan-1-one (51): Ethyl ketone **49** (12.0 mg, 20 μmol) was treated with Pd on carbon (10 %) according to the general procedure for global debenzylation to give compound **51** (4.0 mg, 18 μmol, 88 %) as a white solid. ^{1}H NMR (400 MHz, D_2O): δ = 3.93 (t, J = 2.8 Hz, 1 H, 4-H), 3.81 (d, J = 9.2 Hz, 1 H, 2-H), 3.72–3.55 (m, 2 H, 8-H), 3.36 (dd, J = 9.0, 2.3 Hz, 1 H, 3-H), 2.64–2.54 (m, 2 H, C*H*$_2$CH$_3$), 2.37 (t, J = 4.6 Hz, 1 H, 7-H), 2.30–2.21 (m, 1 H, 5-H), 1.66–1.56 (m, 2 H, 1-H, 6-H), 0.96 (t, J = 7.4 Hz, 3 H, CH_3) ppm. ^{13}C NMR (101 MHz, D_2O): δ = 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-6 and C-7), 26.6 (C-1), 7.6 (CH_3) ppm. HRMS: calcd. 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): LiOH (150 mg, 6.3 mmol, 14.7 equiv.) was added 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). The mixture was stirred overnight at room temperature, then aqueous HCl (1 M) was used to acidify to pH 1. The 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 with $MgSO_4$, filtered, and concentrated in vacuo to give a yellow oil. The crude acid was used without further purification. HRMS: calcd. for $[C_{37}H_{39}O_6]^+$ 579.27412; found 579.27384.

The crude acid was dissolved in CH_2Cl_2 (7.6 mL), and 4-azidobutan-1-amine (52 mg, 0.456 mmol, 1.1 equiv.), *N*,*N*-diisopropylethylamine (230 μL, 1.33 mmol, 3.1 equiv.), and HCTU (188 mg, 0.456 mmol, 1.1 equiv.) were added. The mixture was stirred overnight at room temperature, then it was concentrated in vacuo. The residue was redissolved in EtOAc (40 mL), and the resulting solution was washed with aqueous HCl (1 M) and saturated aqueous $NaHCO_3$, dried with $MgSO_4$, filtered, and concentrated in vacuo. The residue was purified by column chromatography (pentane → 30 % EtOAc in pentane) followed by HPLC [C18; linear gradient: 70–90 % B in A over 15 min; solutions used: A = H_2O; B = acetonitrile (0.1 % TFA)] to give compound **52** (68.9 mg, 0.102 mmol, 24 %) and compound **53** (51.0 mg, 75.6 μmol, 18 %) as white solids.

Data for **52**: ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.39–7.21 (m, 20 H, H_{arom}), 5.70–5.63 (m, 1 H, NH), 4.88 (d, J = 11.6 Hz, 1 H, CH_2 Bn), 4.75–4.55 (m, 5 H, CH_2 Bn), 4.44 (d, J = 2.7 Hz, 2 H, CH_2 Bn), 4.39 (dd, J = 8.3, 6.5 Hz, 1 H, 2-H), 3.93 (s, 1 H, 4-H), 3.66 (t, J = 8 Hz, 1 H, 8-H), 3.58–3.54 (m, 1 H, 8-H), 3.31–3.22 (m, 4 H, 2 CH_2 amide), 3.13 (d, J = 8.4 Hz, 1 H, 3-H), 2.15–2.05 (m, 1 H, 1-H), 1.93–1.85 (m, 1 H, 5-H), 1.64–1.48 (m, 4 H, 2 CH_2 amide), 1.45–1.36 (m, 1 H, 6-H), 1.31–1.23 (m, 1 H, 7-H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$): δ = 172.1 (C=O), 139.2, 138.9, 138.8, 138.2 (4 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 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 CH_2 amide), 26.0 (C-1), 23.0 (C-6) ppm. HRMS: calcd. for $[C_{41}H_{47}N_4O_5]^+$ 675.35410; found 675.35401.

Data for **53** ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.40–7.24 (m, 20 H, H_{arom}), 5.56 (t, J = 5.6 Hz, 1 H, NH), 4.86 (d, J = 11.2 Hz, 1 H, CH_2 Bn), 4.81–4.61 (m, 4 H, CH_2 Bn), 4.54–4.42 (m, 3 H, CH_2 Bn), 4.06–4.05 (m, 1 H, 4-H), 3.96 (d, J = 14.8 Hz, 1 H, 2-H), 3.60 (t, J = 9.0 Hz, 1 H, 8-H), 3.56–3.52 (m, 1 H, 8-H), 3.49 (dd, J = 8.7, 1.6 Hz, 1 H, 3-H), 3.31–3.16 (m, 4 H, 2 CH_2 amide), 2.51–2.42 (m, 1 H, 5-H), 1.77–1.72 (m, 2 H, 1-H, 7-H), 1.60–1.51 (m, 5 H, 6-H, 2 CH_2 amide) ppm. ^{13}C NMR (101 MHz, $CDCl_3$): δ = 172.77 (C=O), 139.4, 138.9, 138.6,

138.3 (4 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 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, C-7), 21.7 (C-6) ppm. HRMS: calcd. 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-(hydroxymethyl)bicyclo[4.1.0]heptane-7-carboxamide (54): BCl_3 (1 M in CH_2Cl_2; 1.9 mL, 1.9 mmol, 20 equiv.) was slowly added to a solution of benzylated **52** (62.5 mg, 93 μmol) in CH_2Cl_2 (0.46 mL) at –78 °C. The mixture was stirred for 4 h at –78 °C, then it was quenched with MeOH (3 mL). The mixture was concentrated in vacuo, and coevaporated with toluene (3 ×). The residue was purified by column chromatography (EtOAc → 20 % MeOH in EtOAc) to give compound **54** (29.0 mg, 93 μmol, quant.) as a white solid. ^{1}H NMR (400 MHz, D_2O): δ = 4.25 (dd, *J* = 9.1, 6.3 Hz, 1 H, 2-H), 3.85 (s, 1 H, 4-H), 3.77–3.65 (m, 2 H, 8-H), 3.33 (t, *J* = 6.2 Hz, 2 H, CH_2 amide), 3.28–3.14 (m, 3 H, CH_2 amide, 3-H), 1.97–1.87 (m, 2 H, 1-H, 5-H), 1.66–1.52 (m, 5 H, 2 CH_2 amide, 7-H), 1.31–1.25 (m, 1 H, 6-H) ppm. ^{13}C NMR (101 MHz, D_2O): δ = 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, C-7), 25.8 (CH_2 amide), 25.4 (CH_2 amide), 21.8 (C-6) ppm. HRMS: calcd. 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-(hydroxylmethyl)bicyclo[4.1.0]heptane-7-carboxamide (55): BCl_3 (1 M in CH_2Cl_2; 1.5 mL, 1.5 mmol, 23 equiv.) was slowly added to a solution of benzylated **53** (45.0 mg, 66 μmol) in CH_2Cl_2 (0.50 mL) at –78 °C. The mixture was stirred for 4 h at –78 °C, then it was quenched with MeOH (3 mL). The mixture was concentrated in vacuo and coevaporated with toluene (3 ×). The residue was purified by column chromatography (EtOAc → 20 % MeOH in EtOAc) to give compound **55** (14.6 mg, 46.4 μmol, 70 %) as a white solid. ^{1}H NMR (400 MHz, D_2O): δ = 3.98 (t, *J* = 4.0 Hz, 1 H, 4-H), 3.84 (d, *J* = 9.0 Hz, 1 H, 2-H), 3.74–3.62 (m, 2 H, 8-H), 3.41 (dd, *J* = 9.0, 2.3 Hz, 1 H, 3-H), 3.31 (t, *J* = 6.4 Hz, 2 H, CH_2 amide), 3.18 (t, *J* = 6.3 Hz, 2 H, CH_2 amide), 2.34–2.25 (m, 1 H, 5-H), 1.91 (t, *J* = 4.7 Hz, 1 H, 7-H), 1.64–1.43 (m, 6 H, 2 CH_2 amide, 1-H, 6-H) ppm. ^{13}C NMR (101 MHz, D_2O): δ = 175.3 (C=O), 75.5 (C-3), 69.0, 68.9 (C-2, C-4), 61.9 (C-8), 50.7, 38.9 (2 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) ppm. HRMS: calcd. 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.

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