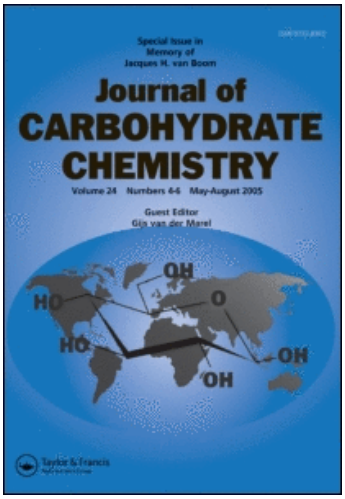

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The Synthesis of a New Class of Potential Inhibitors for Glycoside Hydrolases

Robert V. Stick[a]; Keith A. Stubbs[a]

[a] Chemistry M313, School of Biomedical and Chemical Sciences, University of Western Australia, Crawley, WA, Australia

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The Synthesis of a New Class of Potential Inhibitors for Glycoside Hydrolases

Robert V. Stick and Keith A. Stubbs

Chemistry M313, School of Biomedical and Chemical Sciences, University of Western Australia, Crawley, WA, Australia

Some attempts toward the synthesis of novel inhibitors of glycosyl transferases are described. More successfully, the synthesis of an activated cyclopropacyclohexene and an amide and an amine of a cyclopropa-fused pyranose are described. None of these three novel compounds proved to be a significant inhibitor of a retaining α-glucosidase from barley.

Keywords Glycoside hydrolases, Glycosyl transferases, Cyclopropanes, Inhibitors

The design and subsequent synthesis of inhibitors for the major carbohydrate-processing enzymes, namely the glycosyl transferases and the glycoside hydrolases, have attracted much attention over the past few decades. Although great strides have been made toward the successful inhibition of the glycoside hydrolases,[1] things have not progressed nearly as well with the glycosyl transferases.[2]

It occurred to us that a molecule such as **1** (Fig. 1) could offer the potential to label a glycosyl transferase covalently at the active site; related to this design would be the cyclopropane **2** (Fig. 2). This paper, then, describes our efforts toward the synthesis of **1** and **2** and the carbocyclic counterpart **3**. Along the way we diverted to syntheses of the dinitrophenyl ether **4**, the amide **5**, and the amine **6**. Whereas the amine **6** (in its protonated form) could only ever act as a reversible inhibitor of a glycoside hydrolase, there was some hope

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This paper is dedicated to the memory of Jacques H. van Boom.
Address correspondence to Robert V. Stick, Chemistry M313, School of Biomedical and Chemical Sciences, University of Western Australia, Crawley, WA 6009, Australia. E-mail: rvs@chem.uwa.edu.au

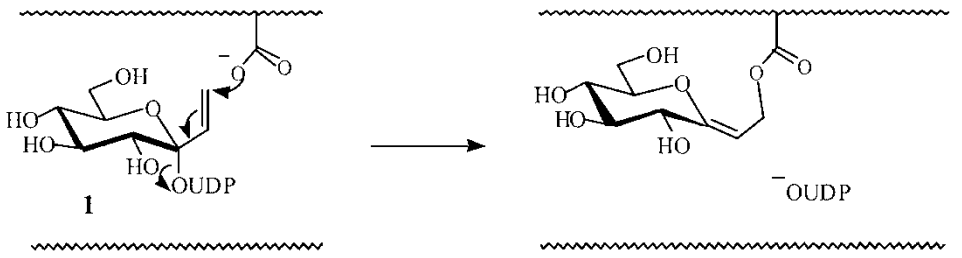


Figure 1: The alkene **1** as a potential inhibitor of a glycosyl transferase; 'OUDP' is uridine diphosphate.

that the molecules **4** and **5** could provide a covalent label for such an enzyme (Figs. 3 and 4). We were well aware that Vasella and coworkers had prepared a range of spirocyclic cyclopropylamines that were found to be very weak inhibitors of several glycoside hydrolases.[3]

Toward a synthesis of the alkene **1**, we treated the readily available alkene **7**[4–6] with diphenyl chlorophosphonate and pyridine; not too surprisingly, only the diene **8** was isolated, and in good yield (Sch. 1). Presumably, the desired phosphate **9** is formed but rapidly decomposes through a favored carbenium ion intermediate.

We immediately turned our attention to the cyclopropane derivative **2**. Penta-*O*-acetyl-β-D-glucopyranose was converted into the trisilyl D-glucal **10** (Sch. 2).[7] Cyclopropanation of **10** then gave the ester **11**,[8] and a subsequent reduction gave the primary alcohol **12**.[9] Treatment of **12** with diphenyl chlorophosphonate and pyridine again failed to give the desired phosphate **13**—the activated cyclopropane ring caused immediate formation of the diene **14** (Sch. 3). The instability of both the purported phosphates **9** and **13** undoubtedly resided in the endocyclic oxygen atom; we therefore turned to a synthesis of the carbocyclic analog of **2**, namely the cyclopropacyclohexene **3**. The obvious precursor to **3** is the phosphate **15**.

Methyl α-D-glucopyranoside was easily converted into the alkene **16** (Sch. 4).[10–12] Acetolysis of **16** then gave the tetraacetate **17** that was the direct precursor, using our VO(salen)-catalyzed procedure,[13] of the glycals

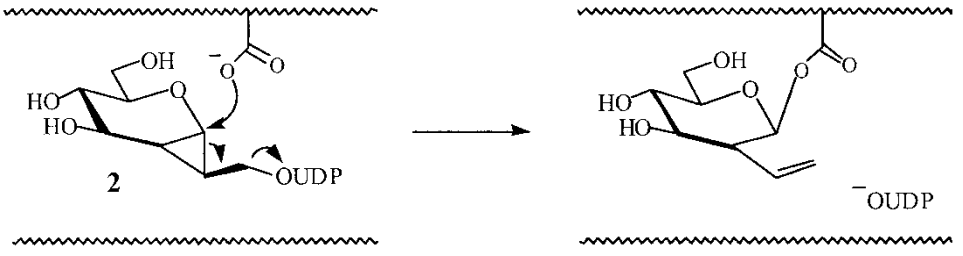


Figure 2: The cyclopropane **2** as a potential inhibitor of glycosyl transferase.

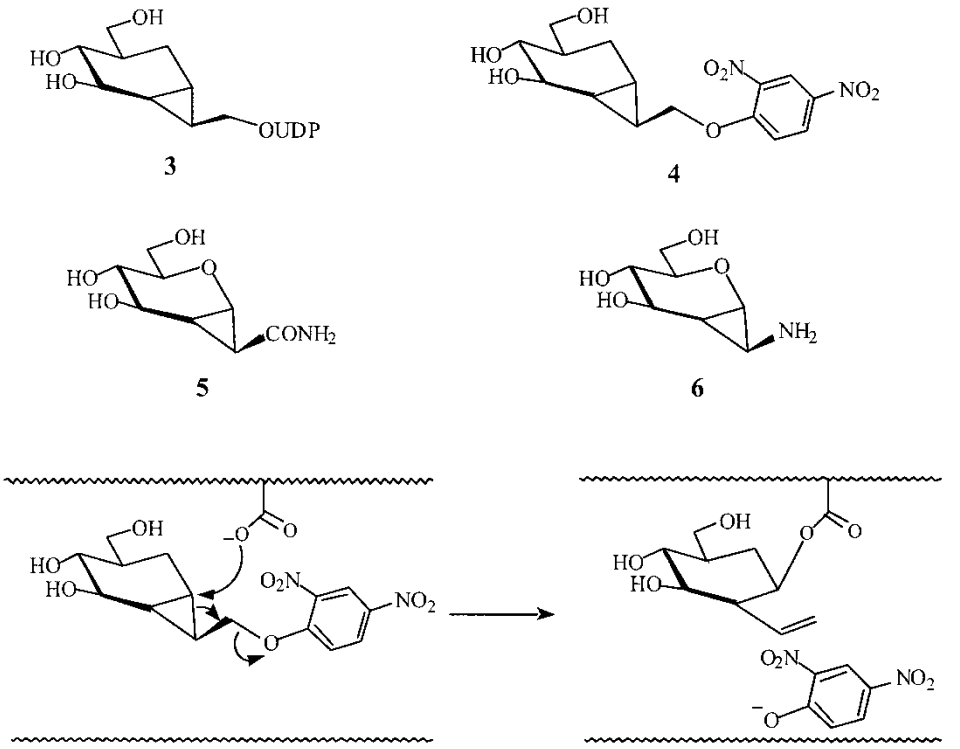


Figure 3: The cyclopropane **4** as a potential inhibitor of a glycoside hydrolase.

18, **19**, and **20**. A Claisen rearrangement on the glycal **19** in 1,2-dichlorobenzene heated to 240°C in a sealed tube is reported to give the aldehyde **21** in 84% yield[14]; we found it simpler to heat the glycal **19** in boiling diphenyl ether (210°C) (Sch. 5). After a subsequent reduction, the unsaturated alcohol was obtained in good yield; a similar rearrangement was performed on the glycal **20**, with both the unsaturated alcohols being protected as the appropriate ether (**22** and **23**).

Cyclopropanation of the tribenzyl ether **22** gave the ethyl ester **24** in a modest yield (Sch. 6); however, a similar treatment of the trisilyl ether **23** gave the ethyl ester **25** in good yield (71%). The stereochemical assignment of the three new stereogenic centers in **24** and **25** was based on an analysis of their ^{1}H NMR NOESY spectra—interactions between H1 and H3 confirmed the orientation of the cyclopropane rings, and interactions between H4 and H7 defined the configuration in both molecules as 7*R*.

With the ready availability of the ester **25**, subsequent transformations gave the alcohol **26** and the phosphate **27** (Sch. 7). Unfortunately, we were unable to deprotect **27** successfully to form the triol **15**, the precursor of **3**; the treatment of **27** with tetrabutylammonium fluoride gave a complex

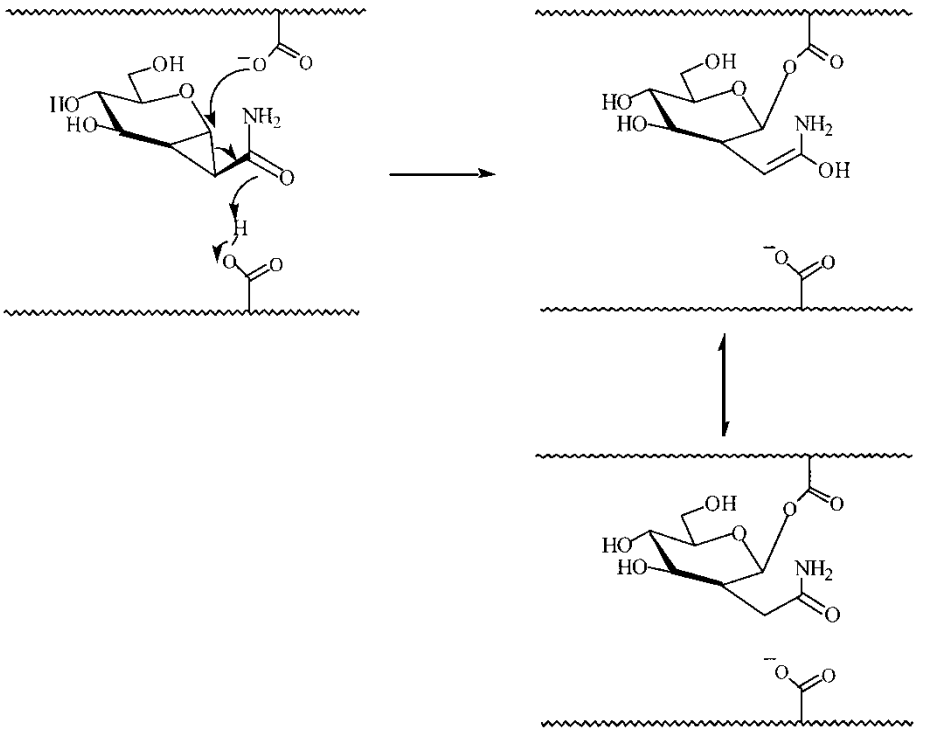
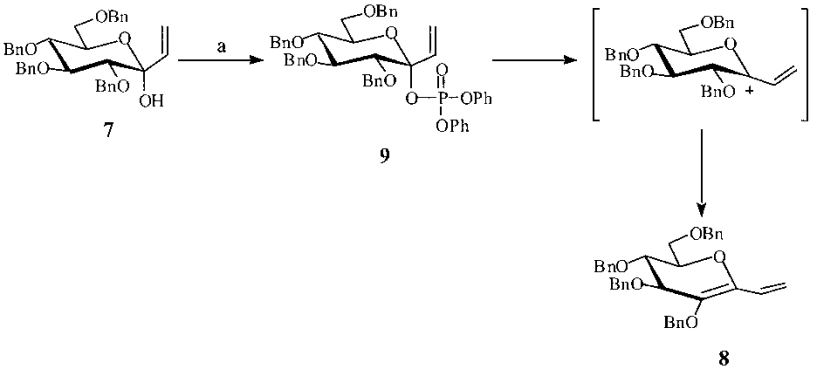


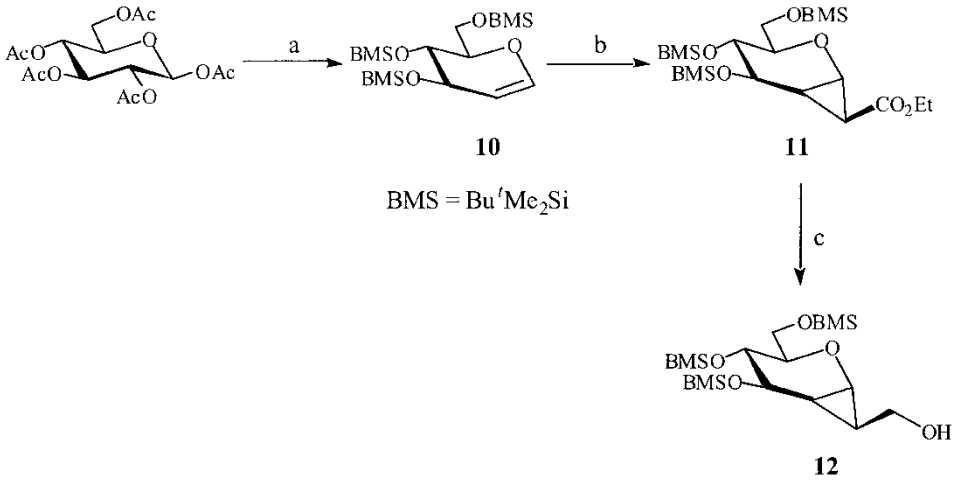
Figure 4: The cyclopropane **5** as a potential inhibitor of a glycoside hydrolase.

mixture, with some apparent loss of the phenyl groups,[15] and treatment of **27** with hydrogen and platinum(IV) oxide again gave a complex mixture.

We next considered the preparation of the dibenzyl phosphate **28** but encountered problems with the preparation and use of dibenzyl chlorophosphonate.[16] Instead, we prepared the diethyl phosphate **29**; however, treatment of

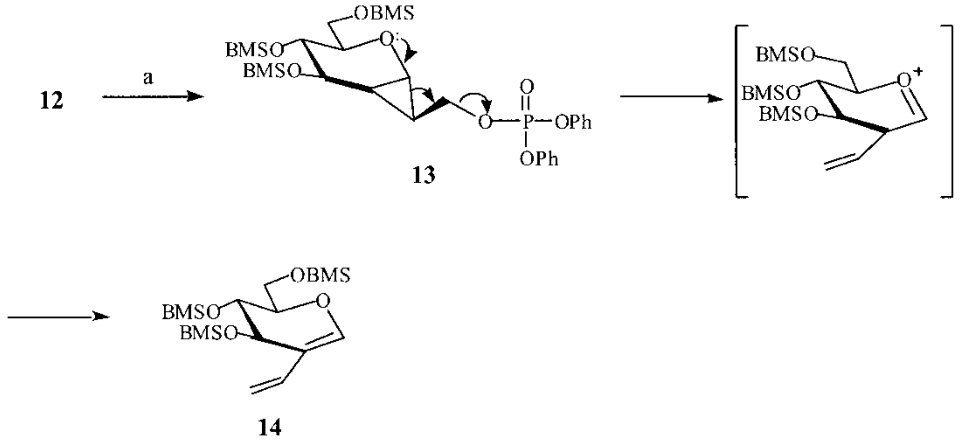


Scheme 1: a) $ClPO(OPh)_2$, pyridine, CH_2Cl_2.

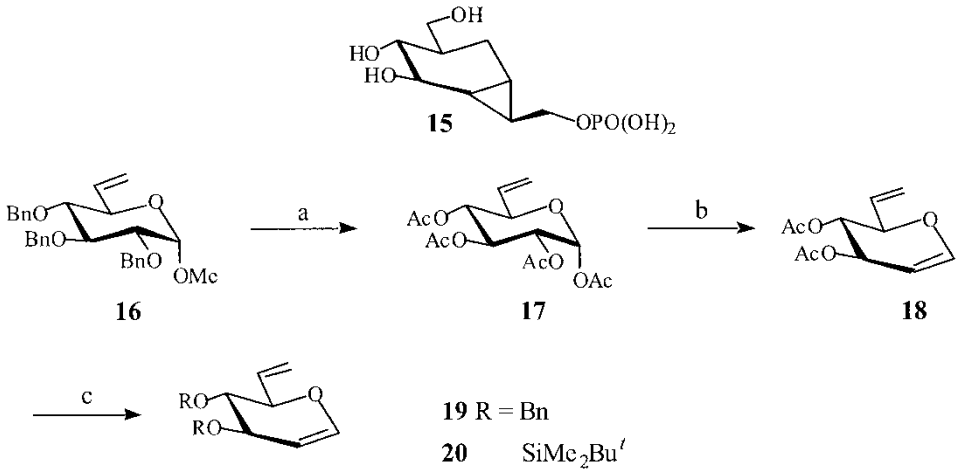


Scheme 2: a) i. HBr, AcOH; ii. Zn, NH_4Cl, VO(salen), MeOH; iii. NaOMe, MeOH; iv. BMSCl, imidazole, DMF; b) $Rh_2(OAc)_4$, N_2CHCO_2Et, CH_2Cl_2; c) $LiAlH_4$, THF.

29 with tetrabutylammonium fluoride or hydrochloric acid in ethanol[17] again gave complex mixtures. Finally, we prepared the bis(trichloroethyl) phosphate **30**; again, treatment of **30** with tetrabutylammonium fluoride[18] gave a complex mixture. However, hydrochloric acid in ethanol did cause a poor conversion of **30** into the triol **31**, along with what appeared to be a mixture of the ethyl ethers **32**, **33**, and **34**. At this stage we curtailed our investigations into the synthesis of **3**, but not the prospect of using the cyclopropane moiety in inhibitor design. Treatment of the alcohol **26** with 2,4-dinitrofluorobenzene



Scheme 3: a) $ClPO(OPh)_2$, pyridine, CH_2Cl_2.

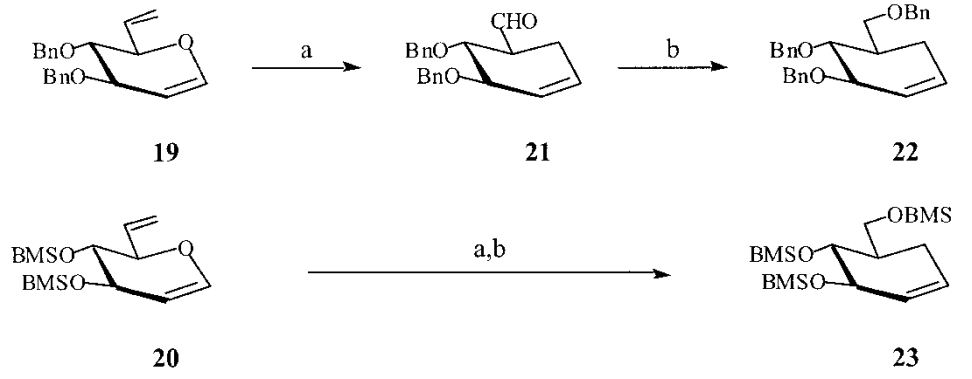


Scheme 4: a) TMSOTf, Ac_2O; b) i. HBr, HOAc; ii. Zn, VO(salen), with NH_4Cl, MeOH or HOAc, MeCN; c) i. NaOMe, MeOH; ii. NaH, BnBr, DMF for **19**; BMSCl, imidazole, DMF for **20**.

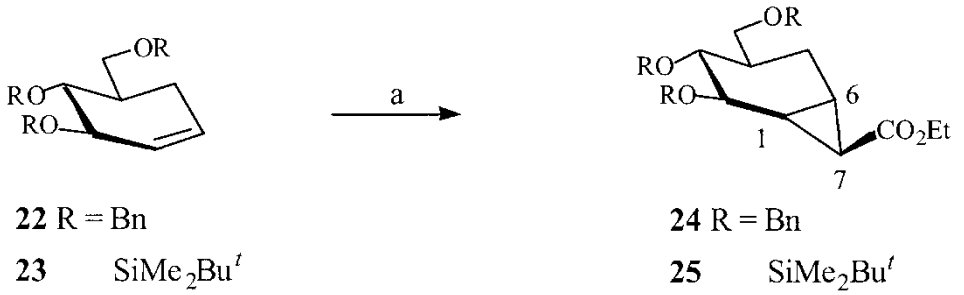
gave the ether **35**, and deprotection the desired putative inhibitor (of glycoside hydrolases) **4** (Sch. 8).

Our final efforts were toward a synthesis of **5** and **6**. Thus, the ester **11** was converted into the amide **36** (Sch. 9), but a subsequent treatment with ethanol under acidic conditions gave only the ethyl glycoside **37** (perhaps a good sign for potential inhibition of a glycoside hydrolase). However, **36** was efficiently converted into the triol **5** under basic conditions. It was gratifying to observe a successful Hofmann reaction[19] on the amide **5**, to yield the amine **6**.

None of the compounds **4**, **5**, and **6** was found to be a significant inhibitor of the retaining α-glucosidase from barley (family 31). Only the amine **6** showed



Scheme 5: a) Ph_2O, 210°C; b) i. $NaBH_4$, THF; NaH, BnBr, DMF for **22**; BMSCl, imidazole, DMF for **23**.



22 R = Bn
23 $SiMe_2Bu^t$

24 R = Bn
25 $SiMe_2Bu^t$

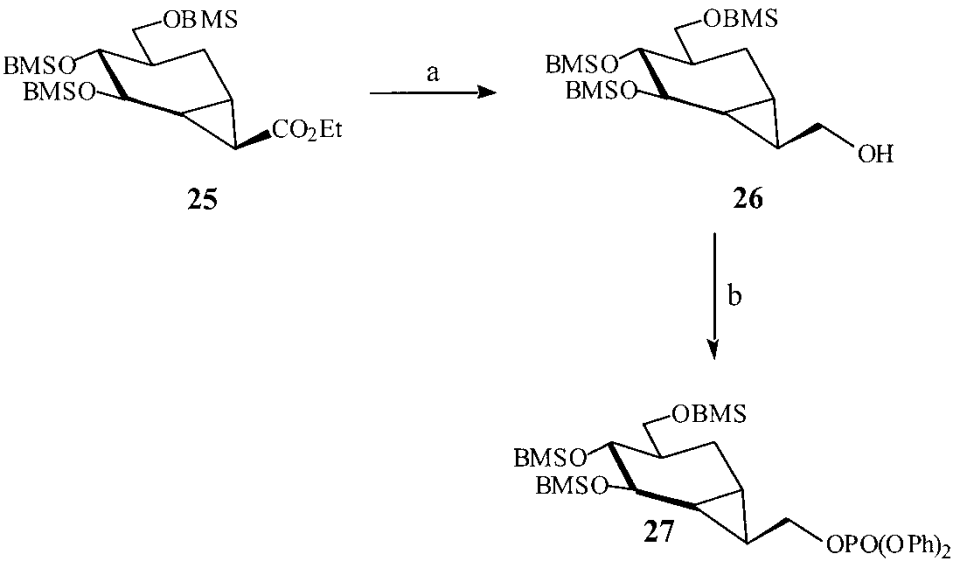
Scheme 6: a) $Rh_2(OAc)_4$, N_2CHCO_2Et, CH_2Cl_2.

any (competitive) inhibition (K_i 18 mM), with maltose (K_M 1.5 mM) as substrate.

EXPERIMENTAL

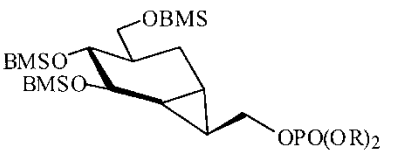
General experimental procedures have been given previously.[20]

***1,5-Anhydro-tetra-O-benzyl-1-C-vinyl-D-gluc-1-enitol* 8.** Diphenyl chlorophosphonate (0.2 mL, 0.8 mmol) was added to the alkene **7**[6] (160 mg, 0.30 mmol) and pyridine (0.03 mL, 0.4 mmol) in CH_2Cl_2 (5 mL) and the solution was stirred (rt, 12 hr). Concentration of the mixture followed by flash chromatography (EtOAc/petrol 1:19) gave the diene **8** as a colorless oil (100 mg, 80%). ^1H NMR

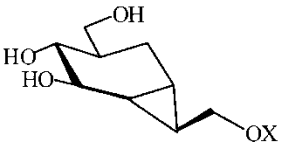


25 **26** **27**

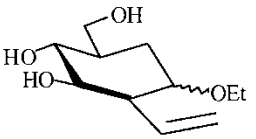
Scheme 7: a) $LiAlH_4$, THF; b) $ClPO(OPh)_2$, pyridine, CH_2Cl_2.



28 R = Bn
29 Et
30 CH_2CCl_3



31 X = $PO(OCH_2CCl_3)_2$
32 Et



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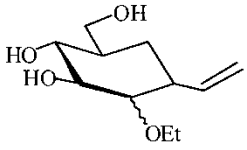

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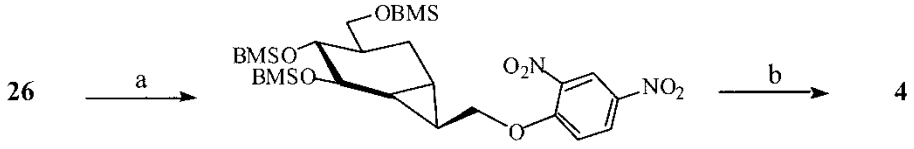

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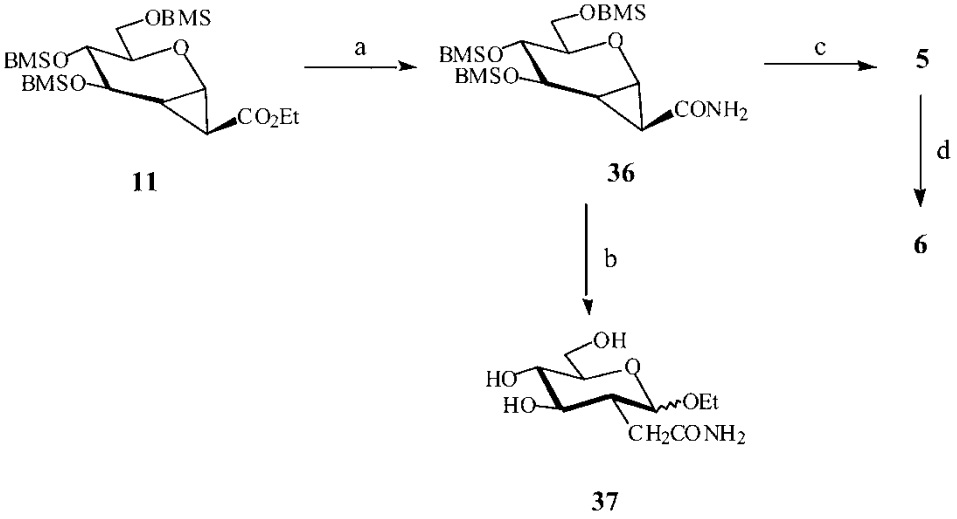
Scheme 8: a) 2,4-dinitrofluorobenzene, Et_3N, $ClCH_2CH_2Cl$; b) conc. HCl, EtOH.



11 **36** **37**

Scheme 9: a) NaCN, NH_3, MeOH; b) conc. HCl, EtOH; c) i. TBAF, THF; ii. Ac_2O, pyridine; iii. NaOMe, MeOH; (d) NaOCl, NaOH, H_2O.

(500 MHz) δ 3.80, dd, $J_{5,6}$ 3.9, $J_{6,6}$ 10.9 Hz, H6; 3.84, dd, $J_{5,6}$ 5.4 Hz, H6; 4.03, dd, $J_{3,4}$ 4.7, $J_{4,5}$ 6.8 Hz, H4; 4.15, ddd, H5; 4.44, d, H_3; 4.57–4.80, m, 8H, C**H**$_2$Ph; 5.17, dd, J 1.9, 11.0 Hz, 1H, =CH_2; 5.63, dd, J 17.4 Hz, 1H, =CH_2; 6.66, dd, =CH; 7.28–7.36, m, 20H, Ph. ^{13}C NMR (125.7 MHz) δ 68.16, C6; 70.54, 72.74, 73.43, 74.32, 4C, **C**H_2Ph; 73.50, 75.29, 76.32, C3,4,5; 115.03, =CH_2; 125.82–138.22, C1,2,=CH,Ph. HRMS (FAB) m/z 548.2577 [$C_{36}H_{36}O_5$ $(M)^+$. requires 548.2563].

***1,5-Anhydro-tri*-O-(t-*butyldimethylsilyl*)-2-*deoxy*-2-C-*vinyl*-D-*gluc*-1-*enitol* 14.** Diphenyl chlorophosphonate (0.2 mL, 0.8 mmol) was added to the alcohol **12**[9] (140 mg, 0.30 mmol) and pyridine (0.03 mL, 0.4 mmol) in CH_2Cl_2 (5 mL) and the solution was stirred (rt, 1 hr). Concentration of the mixture followed by flash chromatography (EtOAc/petrol 1:19) gave the diene **14** as a colorless oil (92 mg, 83%). ^{1}H NMR (200 MHz) δ 0.05, 0.07, 0.09, 0.11, 4s, 18H, CH_3; 0.89, 0.91, 2s, 27H, C(CH_3)3; 3.72, dd, $J_{5,6}$ 3.5, $J_{6,6}$ 7.6 Hz, H6; 3.89–4.11, m, H3,4,5,6; 4.79, dd, J1.1, 11.0 Hz, 1H, =CH_2; 4.99, dd, J16.9 Hz, 1H,=CH_2; 6.18, dd, =CH; 6.49, s, H1. HRMS (FAB) m/z 515.3411 [$C_{26}H_{55}O_4Si_3$ $(M+H)^+$ requires 515.3408].

***Tetra*-O-*acetyl*-6,7-*dideoxy*-α-D-gluco-*hept*-6-*enopyranose* 17.** Trimethylsilyl trifluoromethanesulfonate (1 mL, 5 mmol) was added to the alkene **16** (8.0 g, 19 mmol) in Ac_2O (40 mL) and the solution was stirred (rt, 24 hr). The mixture was quenched by the addition of saturated $NaHCO_3$ solution (5 mL). Concentration of the mixture followed by a standard work-up (EtOAc) and flash chromatography (EtOAc/petrol 1:4) gave the *alkene* **17** as colorless needles (2.5 g, 83%), m.p. 98–100°C (Et_2O/petrol), $[\alpha]_D + 7.8°$ (Found: C, 52.6; H, 5.6. $C_{15}H_{20}O_9$ requires C, 52.5; H, 5.6%). ^{1}H NMR (500 MHz) δ 1.97, 1.98, 2.13, 3s, 12H, CH_3; 4.27–4.31, m, $J_{4,5}$ 10.0 Hz, H5; 4.91, dd, $J_{3,4}$ 10.0 Hz, H4; 5.05, dd, $J_{1,2}$ 3.7, $J_{2,3}$ 10.0 Hz, H2; 5.24, ddd, $J_{5,7}$ 1.3, $J_{6,7}$ 10.4, $J_{7,7}$ 1.2 Hz, H7; 5.32, ddd, $J_{6,7}$ 17.2 Hz, H7; 5.44, dd, H3; 5.65–5.70, m, H6; 6.30, d, H1. ^{13}C NMR (125.7 MHz) δ 20.33, 20.50, 20.55, 20.77, 4C, CH_3; 69.36, 69.42, 71.04, C2,3,4; 72.95, C5; 88.87, C1; 120.11, C7; 132.59, C6; 168.74, 169.29, 169.58, 170.06, 4C, C=O. HRMS (FAB) m/z 344.1107 [$C_{15}H_{20}O_9$ $(M)^+$. requires 344.1107].

***Di*-O-*acetyl*-1,5-*anhydro*-2,6,7-*trideoxy*-D-arabino-*hept*-1,6-*dienitol* 18.** (i) 30% HBr in AcOH (3.0 mL, 15 mmol) was added to the tetraacetate **17** (5.0 g, 14 mmol) and the solution was stirred (rt, 1 hr). Standard work-up (EtOAc) gave a light yellow oil that crystallized upon standing to give tri-*O*-acetyl-6,7-dideoxy-α-D-*gluco*-hept-6-enopyranosyl bromide as needles (4.8 g, 90%), m.p. 93–99°C (Et_2O/petrol), $[\alpha]_D + 175°$. ^{1}H NMR (500 MHz) δ 2.01, 2.02, 2.09, 3s, 9H, CH_3; 4.48, ddd, $J_{4,5}$ 10.1, $J_{5,6}$ 7.1, $J_{5,7}$ 0.7 Hz, H5; 4.81, dd, $J_{1,2}$ 4.0, $J_{2,3}$ 9.8 Hz, H2; 4.98, dd, $J_{3,4}$ 9.8 Hz, H4; 5.32, ddd, $J_{6,7}$ 10.4, $J_{7,7}$ 1.0 Hz, H7; 5.40, ddd, $J_{6,7}$ 17.1 Hz, H7; 5.57, dd, H3; 5.75, ddd, H6; 6.61, d,

H1. ^{13}C NMR (125.7 MHz) δ 20.60, 20.62, CH_3; 69.83, 70.47, 70.85, C2,3,4; 75.19, C5; 86.52, C1; 121.07, C7; 131.67, C6; 169.45, 169.75, 169.78, 3C, C=O. HRMS (FAB) m/z 365.0236 [$C_{13}H_{18}^{81}BrO_7$ $(M+H)^+$ requires 365.0204].

(ii) (a) Powdered Zn (2.0 g, 30 mmol), NH_4Cl (1.8 g, 6 mmol), and VO(salen) (10 mg) were added to the bromide from (i) (2.2 g, 6.0 mmol) in MeOH (30 mL) and the mixture was stirred (10 min). Filtration, followed by concentration of the filtrate, standard work-up (EtOAc), and flash chromatography (EtOAc/petrol 1:4), gave the diene **18** as a colorless oil (1.2 g, 92%), $[\alpha]_D$ − 81.7°. ^{1}H NMR (500 MHz) δ 2.03, 2.05, 2s, 6H, CH_3; 4.41, dd, $J_{4,5}$ 7.9, $J_{5,6}$ 7.3 Hz, H5; 4.82, dd, $J_{1,2}$ 6.2, $J_{2,3}$ 3.1 Hz, H2; 5.11, dd, $J_{3,4}$ 6.0 Hz, H4; 5.30, ddd, $J_{5,7} \approx J_{7,7}$ 2.3, $J_{6,7}$ 10.3 Hz, H7; 5.36–5.39, m, H3; 5.39, ddd, $J_{6,7}$ 17.2 Hz, H7; 5.87, ddd, H6; 6.48, dd, $J_{1,3}$ 1.4 Hz, H1. ^{13}C NMR (125.7 MHz) δ 20.91, 21.03, 2C, CH_3; 67.63, 70.03, C3,4; 77.44, C5; 98.92, 119.88, C2,7; 132.50, C6; 145.82, C1; 169.73, 170.52, 2C, C=O. HRMS (FAB) m/z 227.0910 [$C11H_{15}O_5$ $(M+H)^+$ requires 227.0919].

(b) Powdered Zn (4.0 g, 60 mmol), AcOH (35 mg, 0.60 mmol), and VO(salen) (10 mg) were added to the bromide from (i) (2.2 g, 6 mmol) in MeCN (30 mL) and the mixture was stirred (80 min). Filtration, followed by neutralization with resin (Amberlite IRA 400, OH^-) and another filtration, gave a green residue. Flash chromatography (EtOAc/petrol 1:4) then gave the diene **18** as a colorless oil (1.1 g, 90%). The ^{1}H and ^{13}C NMR spectra were consistent with those reported in (a).

***1,5-Anhydro-di-O-benzyl-2,6,7-trideoxy-D-arabino-hept-1,6-dienitol* 19.** 10% NaOMe in MeOH was added to the diene **18** (1.0 g, 4.4 mmol) in MeOH (10 mL) and the solution was stirred (rt, 30 min). Concentration of the solution gave a yellow residue that was dissolved in DMF (20 mL), and NaH (60% dispersion in mineral oil, 220 mg, 9.0 mmol) and BnBr (1.0 mL, 9.0 mmol) were added and the mixture stirred (rt, 1 hr). The mixture was quenched with MeOH (5 mL) and concentration followed by a standard work-up (EtOAc) and flash chromatography (EtOAc/petrol 1:19) gave the diene **19** as a colorless oil (1.3 g, 95%), $[\alpha]_D$ −32.9°. ^{1}H NMR (600 MHz) δ 3.69, dd, $J_{3,4}$ 6.1, $J_{4,5}$ 8.5 Hz, H4; 4.28–4.30, m, H3; 4.40–4.43, m, H5; 4.65, 4.71, AB, J 11.8 Hz, C**H**$_2$Ph; 4.77, 4.85, AB, J 11.3 Hz, C**H**$_2$Ph; 4.96, dd, $J_{1,2}$ 2.7, $J_{2,3}$ 6.1 Hz, H2; 5.38, ddd, $J_{5,7} \approx J_{7,7}$ 1.3, $J_{6,7}$ 10.6 Hz, H7; 5.51, ddd, $J_{6,7}$ 17.2 Hz, H7; 6.14, ddd, $J_{5,6}$ 6.5 Hz, H6; 6.49, d, H1; 7.33–7.41, m, 10H, Ph. ^{13}C NMR (150.8 MHz) δ 70.54, 73.68, 2C, **C**H$_2$Ph; 75.32, 77.88, 78.18, C3,4,5; 100.23, C2; 118.14, C7; 127.52, 127.61, 127.66, 128.27, 137.99, 138.31, Ph; 134.26, C6; 144.42, C1. HRMS (FAB) m/z 321.1491 [$C21H_{21}O_3$ $(M-H)^+$ requires 321.1514].

***1,5-Anhydro-di-O-(t-butyldimethylsilyl)-2,6,7-trideoxy-D-arabino-hept-1,6-dienitol* 20.** 10% NaOMe in MeOH was added to the diene **18** (1.0 g, 4.4 mmol) in MeOH (10 mL) and the solution was stirred (rt, 30 min.).

Concentration of the mixture gave a yellow residue that was dissolved in DMF (20 mL), Bu^tMe_2SiCl (2.0 g, 9.0 mmol) and imidazole (3.1 g, 44 mmol) were added, and the solution was stirred (60°C, 24 hr). Concentration of the mixture followed by a standard work-up (EtOAc) and flash chromatography (PhMe/petrol 1:4) gave the diene **20** as a colorless oil (1.5 g, 92%), $[\alpha]_D$ −47.6°. ^{1}H NMR (600 MHz) δ 0.08, 0.09, 0.10, 0.11, 4s, 12H, CH_3; 0.90, s, 18H, $C(CH_3)_3$; 3.69, dd, $J_{3,4} \approx J_{4,5}$ 4.6 Hz, H4; 4.06, dd, $J_{1,3}$ 1.0, $J_{2,3}$ 4.5 Hz, H3; 4.26–4.29, m, H5; 4.71, dd, $J_{1,2}$ 6.2 Hz, H2; 5.17, ddd, $J_{5,7} \approx J_{7,7}$ 1.6, $J_{6,7}$ 10.7 Hz, H7; 5.28, ddd, $J_{6,7}$ 18.8 Hz, H7; 6.08, ddd, $J_{5,6}$ 7.2 Hz, H6; 6.35, dd, H1. ^{13}C NMR (150.8 MHz) δ −4.21, −4.16, −4.13, −3.91, 4C, CH_3; 18.04, $\mathbf{C}(CH_3)_3$; 25.91, $C(\mathbf{C}H_3)_3$; 68.29, C3; 73.62, C4; 80.07, C5; 102.75, C2; 117.02, C7; 134.94, C6; 143.06, C1. HRMS (FAB) m/z 369.2283 [$C_{19}H_{37}O_3Si_2$ $(M-H)^+$ requires 369.2281].

***(3R,4R,5R)-3,4-Dibenzyloxy-5-(benzyloxymethyl)cyclohexene* 22.** (i) The diene **19** (1.0 g, 3.2 mmol) in Ph_2O (15 mL) was heated (210°C, 2 hr). Concentration of the solution gave a colorless residue, presumably the aldehyde **21**. This residue was dissolved in THF (5 mL), $NaBH_4$ (450 mg, 12 mmol) was added and the mixture was stirred (rt, 1 hr). The mixture was quenched by the addition of AcOH (5 mL). Concentration of the mixture followed by a standard work-up (EtOAc) and flash chromatography (EtOAc/petrol 1:19) gave *(3*R,*4*R,*5*R*)-3,4-dibenzyloxy-5-(hydroxymethyl)cyclohexene* as a colorless oil (850 mg, 84%), $[\alpha]_D$ −23.4° (Found: C, 77.5; H, 7.7. $C_{21}H_{24}O_3$ requires C, 77.7; H, 7.5%). ^{1}H NMR (600 MHz) δ 1.89–1.95, m, H6; 2.03–2.08, m, H5; 2.13–2.17, m, H6; 2.69, s, OH; 3.62, dd, $J_{3,4}$ 10.7, $J_{4,5}$ 2.8 Hz, H4; 3.67–3.69, m, CH_2OH; 4.25, m, $J_{1,3}$ 1.3, $J_{2,3}$ 3.8 Hz, H3; 4.66, 4.75, AB, J 11.6 Hz, $C\mathbf{H}_2Ph$; 4.66, 4.75, AB, J 11.3 Hz, $C\mathbf{H}_2Ph$; 5.73, m, $J_{1,2}$ 10.3 Hz, H1; 5.78–5.79, m, H2; 7.30–7.40, m, 10H, Ph. ^{13}C NMR (150.8 MHz) δ 27.95, C6; 40.48, C5; 65.43, CH_2OH; 71.18, 74.22, 2C, $\mathbf{C}H_2Ph$; 81.06, C3; 81.93, C4; 125.81, C1; 128.16, C2; 127.39–138.33, Ph. HRMS (FAB) m/z 325.1804 [$C_{21}H_{25}O_3$ $(M+H)^+$ requires 325.1811].

(ii) Sodium hydride (60% dispersion in mineral oil, 80 mg, 3.0 mmol) was added to (3*R*,4*R*,5*R*)-3,4-dibenzyloxy-5-(hydroxymethyl)cyclohexene (800 mg, 2.6 mmol) in DMF (10 mL) at 0°C and the mixture was stirred (10 min). Benzyl bromide (0.3 mL, 3 mmol) was then added and the mixture was stirred (rt, 1 hr). The mixture was quenched with MeOH (5 mL), followed by concentration, standard work-up (EtOAc), and flash chromatography (EtOAc/petrol 1:19) to give the alkene **22** as a colorless oil (900 mg, 89%), $[\alpha]_D$+3.4°. ^{1}H NMR (500 MHz) δ 2.13–2.18, m, H5; 2.30–2.35, m, 2H, H6; 3.65, dd, $J_{5,H}$ 3.2, J 9.0 Hz, 1H, CH_2O; 3.73, dd, $J_{5,H}$ 5.8 Hz, 1H, CH_2O; 3.77, dd, $J_{3,4}$ 10.8, $J_{4,5}$ 7.2 Hz, H4; 4.25–4.26, m, H3; 4.55, s, $C\mathbf{H}_2Ph$; 4.69, 4.95, AB, J 11.1 Hz, $C\mathbf{H}_2Ph$; 4.73, 4.75, AB, J 11.2 Hz, $C\mathbf{H}_2Ph$; 5.75–5.78, m, H1; 5.83–5.84, m, H2; 7.30–7.43, m, 15H, Ph. ^{13}C NMR (125.7 MHz) δ 28.72, C6; 39.30, C5; 70.39, CH_2O; 71.34, 73.01, 74.31, 3C, $\mathbf{C}H_2Ph$; 79.46, C4; 81.01, C3;

126.00, C1; 127.38–138.91, Ph; 128.45, C2. HRMS (FAB) m/z 415.2273 [$C_{28}H_{31}O_3$ $(M+H)^+$ requires 415.2308].

***(3R,4R,5R)-3,4-Di-(t-butyldimethylsilyloxy)-5-(t-butyldimethylsilyloxymethyl)cyclohexene* 23.** (i) According to the procedure described for the preparation of (3*R*,4*R*,5*R*)-3,4-dibenzyloxy-5-(hydroxymethyl)cyclohexene, the diene **20** (1.4 g) gave (3*R*,4*R*,5*R*)-3,4-di-(*t*-butyldimethylsilyloxy)-5-(hydroxymethyl)cyclohexene as colorless crystals (1.2 g, 86%), m.p. 74–77°C (CH_2Cl_2/petrol), $[\alpha]_D$ −90.2°. ^{1}H NMR (600 MHz) δ 0.06, 0.07, 0.11, 0.12, 4s, 12H, CH_3; 0.86, 0.89, 2s, 18H, $C(CH_3)_3$; 1.85–1.88, m, H6; 2.00–2.03, m, H5; 2.35–2.38, m, H6; 2.90, s, OH; 3.66–3.68, m, CH_2OH; 3.86–3.88, m, H3,4; 5.56–5.59, m, H2; 5.84–5.86, m, H1. ^{13}C NMR (150.8 MHz) δ −4.78, −4.71, −4.58, −4.56, 4C, CH_3; 17.95, **C**$(CH_3)_3$; 23.76, C6; 25.74, C(**C**$H_3)_3$; 39.60, C5; 64.5, CH_2OH; 69.21, 73.00, C3,4; 125.11, C1; 130.14, C2. HRMS (FAB) m/z 373.2580 [$C_{19}H_{41}O_3Si_2$ $(M+H)^+$ requires 373.2594].

(ii) Imidazole (400 mg, 5.4 mmol) and Bu^{t}Me$_2$SiCl (760 mg, 5.4 mmol) were added to the alkene from (i) (1.0 g, 2.7 mmol) in DMF (10 mL) and the solution was stirred (rt, 30 min). The mixture was quenched with MeOH (5 mL) and concentration followed by a standard work-up (EtOAc) and flash chromatography (PhMe/petrol 1:19) gave the alkene **23** as a colorless oil (1.2 g, 91%), $[\alpha]_D$ −40.4°. ^{1}H NMR (600 MHz) δ 0.03, 0.04, 0.06, 0.07, 0.08, 0.09, 6s, 18H, CH_3; 0.87, 0.88, 0.89, 3s, 27H, $C(CH_3)3$; 1.95–2.01, m, H5,6; 2.25–2.30, m, H6; 3.63, dd, $J_{5,H} \approx J$ 9.7 Hz, 1H, CH_2O; 3.68, m, H4,CH_2O; 3.86–3.89, m, H3; 5.53–5.55, m, H2; 5.68–5.71, m, H1. ^{13}C NMR (150.8 MHz) δ −5.31, −4.63, −4.37, −4.29, −4.20, CH_3; 18.02, 18.07, 18.39, 3C, **C**$(CH_3)_3$; 24.14, C6; 25.91, 26.03, C(**C**$H_3)_3$; 41.73, C5; 63.33, CH_2O; 70.76, C3; 73.12, C4; 127.00, C2; 127.27, C1. HRMS (FAB) m/z 487.3436 [$C_{25}H_{55}O_3Si_3$ $(M+H)^+$ requires 487.3459].

***(1R,2R,3R,4R,6S,7R)-2,3-Dibenzyloxy-4-(benzyloxymethyl)bicyclo[4.1.0]heptane-7-carboxylic acid, ethyl ester* 24.** Ethyl diazoacetate (0.7 mL, 4.4 mmol) in CH_2Cl_2 (1 mL) was added dropwise to the alkene **22** (900 mg, 2.2 mmol) and $Rh_2(OAc)_4$ (5 mg) in CH_2Cl_2 (3 mL) and the mixture was stirred (rt, 10 hr). A further amount of N_2CHCO_2Et (0.7 mL) in CH_2Cl_2 (1 mL) was then added dropwise and the solution was stirred (rt, 10 hr). The mixture was concentrated and flash chromatography (EtOAc/petrol 1:9) gave the *ester* **24** as a colorless oil (450 mg, 40%), $[\alpha]_D$+14.4° (Found: C, 76.6; H, 7.3. $C_{32}H_{36}O_5$ requires C, 76.8; H, 7.2%). ^{1}H NMR (600 MHz) δ 1.27, t, J 7.1 Hz, CH_2C**H**$_3$; 1.45–1.47, m, H4,6; 1.71–1.77, m, H1,7; 2.01–2.12, m, 2H, H5; 3.40, dd, $J_{2,3}$ 7.5, $J_{3,4}$ 10.8 Hz, H3; 3.49, dd, $J_{4,8}$ 3.1, $J_{8,8}$ 8.9 Hz, H8*;

*The designation H8/C8 has been arbitrarily assigned to the hydrogen and carbon atoms of the substituent at C-4 of the cyclohexane.

3.58, dd, $J_{4,8}$ 5.8 Hz, H8; 3.69, d, H2; 4.14, dq, C**H**$_2$CH$_3$; 4.46, s, C**H**$_2$Ph; 4.54, 4.84, AB, J 11.0 Hz, C**H**$_2$Ph; 4.61, 4.77, AB, J 11.5 Hz, C**H**$_2$Ph; 7.23–7.38, m, 15H, Ph. ^{13}C NMR (150.8 MHz) δ 14.25, CH$_2$**C**H$_3$; 22.58, 26.17, C1,7; 22.88, 35.48, C4,6; 25.65, C5; 60.58, **C**H$_2$CH$_3$; 70.54, C8; 71.75, 73.09, 74.45, 3C, **C**H$_2$Ph; 80.32, C3; 81.59, C2; 127.44–138.81, Ph; 173.71, C=O. HRMS (FAB) m/z 501.2649 [$C_{32}H_{37}O_5$ $(M+H)^+$ requires 501.2641].

***(1R,2R,3R,4R,6S,7R)-2,3-Di-(t-butyldimethylsilyloxy)-4-(t-butyldimethylsilyloxy)methylbicyclo[4.1.0]heptane-7-carboxylic acid, ethyl ester* 25.** According to the procedure described for the preparation of **24**, the alkene **23** (1.0 g) gave the ester **25** as a colorless oil (830 mg, 71%), $[\alpha]_D$+11.9°. ^{1}H NMR (500 MHz) δ 0.03, 0.04, 0.05, 0.06, 0.07, 0.09, 6s, 18H, CH$_3$; 0.88, 0.89, 0.91, 3s, 27H, C(CH$_3$)3; 1.24, t, J 7.0 Hz, CH$_2$C**H**$_3$; 1.53–1.57, m, H1,4,6; 1.83, dd, $J_{1,7} \approx J_{6,7}$ 4.5 Hz, H7; 1.86, ddd, $J_{4,5}$ 2.4, $J_{5,5}$ 14.6, $J_{5,6}$ 5.5 Hz, H5; 1.99, ddd, $J_{4,5}$ 4.8, $J_{5,6}$ 7.6 Hz, H5; 3.44, dd, $J_{2,3} \approx J_{3,4}$ 4.3 Hz, H3; 3.58, dd, $J_{4,8}$ 4.2, $J_{8,8}$ 9.7 Hz, H8; 3.59, dd, $J_{4,8}$ 9.7 Hz, H8; 3.80, d, H2; 4.10, dq, C**H**$_2$CH$_3$. ^{13}C NMR (125.7 MHz) δ −5.31, −5.29, −4.81, −4.77, −4.55, −4.43, 6C, CH$_3$; 14.32, CH$_2$**C**H$_3$; 17.91, 17.92, **C**(CH$_3$)$_3$; 18.40, 27.54, 40.66, C1,4,6; 19.42, C5; 24.59, CH$_2$**C**H$_3$; 25.84, 26.02, C(**C**H$_3$)$_3$; 26.25, C7; 60.25, **C**H$_2$CH$_3$; 63.77, C8; 70.01, C2; 73.05, C3; 174.41, C=O. HRMS (FAB) m/z 573.3804 [$C_{29}H_{61}O_5Si_3$ $(M+H)+$ requires 573.3827].

***[(1R,2R,3R,4R,6S,7R)-2,3-Di-(t-butyldimethylsilyloxy)-4-(t-butyldimethylsilyloxy)methylbicyclo[4.1.0]hept-7-yl]methanol* 26.** Lithium aluminium hydride (220 mg, 6.0 mmol) was added to the ester **25** (700 mg, 1.2 mmol) in THF (5 mL) at 0°C and the solution was stirred (5 min). The mixture was quenched with EtOAc (5 mL) and preadsorption onto silica gel followed by flash chromatography (EtOAc/petrol 1:19) furnished the *alcohol* **26** as a colorless oil (560 mg, 87%), $[\alpha]_D$+12.3° (Found: C, 61.0; H, 11.1. $C_{27}H_{58}O_4Si_3$ requires C, 61.1; H, 11.0%). ^{1}H NMR (600 MHz) δ 0.02, 0.04, 0.05, 0.07, 0.09, 5s, 18H, CH$_3$; 0.70, dd, $J_{1,6}$ 8.8, $J_{1,7}$ 4.9 Hz, H1; 0.79–0.84, m, H6; 0.88, 0.89, 0.91, 3s, 27H, C(CH$_3$)$_3$; 1.21–1.24, m, H7; 1.57–1.59, m, H4; 1.81, ddd, $J_{4,5}$ 5.3, $J_{5,5}$ 14.2, $J_{5,6}$ 2.9 Hz, H5; 1.94, ddd, $J_{4,5}$ 8.2, $J_{5,6}$ 3.9 Hz, H5; 3.30, dd, $J_{7,H}$ 7.6, J 11.1 Hz, 1H, C**H**$_2$OH; 3.39, dd, $J_{2,3} \approx J_{3,4}$ 4.3 Hz, H3; 3.54, dd, $J_{7,H}$ 6.4 Hz, ^{1}H, C**H**$_2$OH; 3.60–3.63, m, 2H, H8; 3.78, d, H2. ^{13}C NMR (150.8 MHz) δ −5.30, −5.21, −4.79, −4.55, −4.41, −4.39, 6C, CH$_3$; 13.34, C6; 17.93, 17.96, 18.43, 3C, **C**(CH$_3$)$_3$; 21.28, C5; 22.28, C1; 25.32, C7; 25.90, 26.04, C(**C**H$_3$)$_3$; 40.91, C4; 64.00, C8; 67.24, CH$_2$OH; 71.19, C2; 73.51, C3. HRMS (FAB) m/z 531.3674 [$C_{27}H_{59}O_4Si_3$ $(M+H)^+$ requires 531.3721].

***[(1R,2R,3R,4R,6S,7R)-2,3-Di-(t-butyldimethylsilyloxy)-4-(t-butyldimethylsilyloxy)methylbicyclo[4.1.0]hept-7-yl]methyl Diphenyl Phosphate* 27.** Diphenyl chlorophosphonate (0.1 mL, 0.4 mmol) was added to the alcohol

26 (100 mg, 0.2 mmol) and pyridine (0.03 mL, 0.4 mmol) in CH_2Cl_2 (5 mL) and the solution was stirred (rt, 10 min). Concentration of the mixture followed by flash chromatography (EtOAc/petrol 1:19) gave the phosphate **27** as a colorless oil (130 mg, 90%), $[\alpha]_D$+11.1°. ^{1}H NMR (500 MHz) δ 0.01, 0.03, 0.04, 0.05, 0.07, 5s, 18H, CH_3; 0.85–0.90, m, 29H, H1,6,C$(CH_3)_3$; 1.38–1.42, m, H7; 1.54–1.56, m, H4; 1.75, ddd, $J_{4,5}$ 5.3, $J_{5,5}$ 11.7, $J_{5,6}$ 2.9 Hz, H5; 1.93, ddd, $J_{4,5}$ 4.6, $J_{5,6}$ 8.8 Hz, H5; 3.41, dd, $J_{2,3} \approx J_{3,4}$ 3.8 Hz, H3; 3.55, dd, $J_{4,8}$ 4.1, $J_{8,8}$ 11.0 Hz, H8; 3.63, dd, $J_{4,8}$ 10.0 Hz, H8; 3.78, d, H2; 4.00, ddd, $J_{7,H} \approx J_{H,P}$ 8.0, J 10.0 Hz, 1H, CH_2O; 4.15, $J_{7,H}$ 6.4, $J_{H,P}$ 8.6 Hz, 1H, CH_2O; 7.15–7.23, 7.30–7.34, 2 m, 10H, Ph. ^{13}C NMR (125.7 MHz) δ −5.28, −4.84, −4.68, −4.57, −4.42, CH_3; 13.81, C6; 17.86, 17.90, 18.41, 3C, **C**$(CH_3)_3$; 20.41, C5; 22.46, C1; 22.71, C7; 25.83, 26.04, C(**C**$H_3)_3$; 40.75, C4; 63.73, C8; 70.23, C2; 73.18, C3; 73.75, $J_{C,P}$ 25 Hz, CH_2O; 120.04, 125.18, 129.70, 150.62, Ph. HRMS (FAB) m/z 763.4005 [$C_{39}H_{68}O_7PSi_3$ $(M + H)^+$ requires 763.4010].

***[(1R,2R,3R,4R,6S,7R)-2,3-Di-(t-butyldimethylsilyloxy)-4-(t-butyldimethylsilyloxy)methylbicyclo[4.1.0]hept-7-yl]methyl Diethyl Phosphate* 29.** According to the procedure described for the preparation of **27**, the alcohol **26** (100 mg, 0.2 mmol) and diethyl chlorophosphonate (70 mg, 0.4 mmol) yielded the phosphate **29** as a colorless oil (100 mg, 85%), $[\alpha]_D$+26.3°. ^{1}H NMR (500 MHz) δ 0.02, 0.04, 0.05, 0.06, 0.09, 5s, 18H, CH_3; 0.80–0.87, m, 29H, H1,6,C$(CH_3)_3$; 1.32–1.34, m, 7H, H7,CH_2C**H**$_3$; 1.57–1.58, m, H4; 1.79, ddd, $J_{4,5}$ 5.3, $J_{5,5}$ 11.9, $J_{5,6}$ 2.7 Hz, H5; 1.95, ddd, $J_{4,5}$ 4.9, $J_{5,6}$ 8.6 Hz, H5; 3.40, dd, $J_{2,3} \approx J_{3,4}$ 4.0 Hz, H3; 3.56, dd, $J_{4,8}$ 3.9, $J_{8,8}$ 10.6 Hz, H8; 3.63, dd, $J_{4,8}$ 9.9 Hz, H8; 3.76–3.79, m, 2H, H2,CH_2O; 3.94, ddd, $J_{7,H} \approx J_{H,P}$ 8.0, J 10.0 Hz, 1H, CH_2O; 4.06–4.12, m, 4H, C**H**2CH_3. ^{13}C NMR (125.7 MHz) δ −5.31, −5.29, −4.80, −4.66, −4.50, −4.38, 6C, CH_3; 13.71, C6; 16.13, d, $J_{C,P}$ 26 Hz, CH_2**C**H_3; 17.89, 17.92, 18.42, 3C, **C**$(CH_3)_3$; 20.72, C5; 22.52, C1; 22.63, C7; 25.85, 26.03, C(**C**$H_3)_3$; 40.80, C4; 63.53, d, $J_{C,P}$ 28 Hz, **C**H_2CH_3; 63.83, C8; 70.56, C2; 71.89, $J_{C,P}$ 20 Hz, CH_2O; 73.34, C3. HRMS (FAB) m/z 667.4015 [$C_{31}H_{68}O_7PSi_3$ $(M + H)^+$ requires 667.4010].

***[(1R,2R,3R,4R,6S,7R)-2,3-Di-(t-butyldimethylsilyloxy)-4-(t-butyldimethylsilyloxy)methylbicyclo[4.1.0]hept-7-yl]methyl Bis(trichloroethyl) Phosphate* 30.** According to the procedure described for the preparation of **27**, the alcohol **26** (100 mg, 0.2 mmol) and bis(trichloroethyl) chlorophosphonate (130 mg, 0.40 mmol) yielded the phosphate **30** as a colorless oil (140 mg, 88%), $[\alpha]_D$+42.3° ^{1}H NMR (600 MHz) δ 0.02, 0.03, 0.04, 0.05, 0.06, 0.09, 6s, 18H, CH_3; 0.87, m, 10H, H1,C$(CH_3)_3$; 0.88, 0.89, 2s, 18H, C$(CH_3)_3$; 0.98–1.00, m, H6; 1.39–1.43, m, H7; 1.56–1.61, m, H4; 1.79, ddd, $J_{4,5}$ 5.3, $J_{5,5}$ 14.3, $J_{5,6}$ 2.7 Hz, H5; 2.03, ddd, $J_{4,5}$ 8.1, $J_{5,6}$ 4.8 Hz, H5; 3.42, dd, $J_{2,3} \approx J_{3,4}$ 3.9 Hz, H3; 3.56, dd, $J_{4,8}$ 4.0, $J_{8,8}$ 10.0 Hz, H8; 3.63, dd, $J_{4,8}$ 9.9 Hz, H8; 3.83,

d, H2; 4.00–4.04, m, CH_2O; 4.61, dd, $J_{H,P} \approx J_{H,H}$ 1.9 Hz, CH_2CCl_3; 4.62, dd, CH_2CCl_3. ^{13}C NMR (150.8 MHz) δ −5.30, −5.28, −4.78, −4.60, −4.49, −4.38, 6C, CH_3; 13.91, C6; 17.88, 17.94, 18.41, 3C, $\mathbf{C}(CH_3)_3$; 20.55, C5; 22.33, d, $J_{C,P}$ 7.5 Hz, C7; 22.84, C1; 25.84, 25.87, 26.03, 3C, $C(\mathbf{C}H_3)_3$; 40.76, C4; 63.75, C8; 70.30, C2; 73.16, C3; 73.94, d, $J_{C,P}$ 6.2 Hz, CH_2O; 77.10, d, $J_{C,P}$ 4.5 Hz, $\mathbf{C}H_2CCl_3$; 94.70, d, $J_{C,P}$ 10.5 Hz, CCl_3. HRMS (FAB) m/z 873.1594 [$C_{31}H_{62}^{35}Cl_5^{37}ClO_7PSi_3$ $(M+H)^+$ requires 873.1642].

***[(1R,2R,3R,4R,6S,7R)-2,3-Dihydroxy-4-(hydroxymethyl)bicyclo[4.1.0]hept-7-yl]methyl Bis(trichloroethyl) Phosphate* 31.** Conc. HCl (1 drop) was added to the phosphate **30** (50 mg) in EtOH (5 mL) and the solution kept (12 hr). Concentration of the mixture gave a yellow residue that was subjected to flash chromatography ($MeOH/CHCl_3$ 1:19), yielding the triol **31** as an unstable, colorless solid (3 mg, 11%). ^1H NMR (600 MHz, CD_3OD) δ 1.06, dd, $J_{1,6}$ 8.6, $J_{1,7}$ 4.4 Hz, H1; 1.15–1.24, m, H4,6,7; 1.70, ddd, $J_{4,5}$ 10.4, $J_{5,5}$ 13.6, $J_{5,6}$ 5.0 Hz, H5; 2.03, ddd, $J_{4,5}$ 1.2, $J_{5,6}$ 4.4 Hz, H5; 3.10, dd, $J_{2,3}$ 8.2, $J_{3,4}$ 10.1 Hz, H3; 3.50–3.55, m, 2H, H2,8; 3.64, dd, $J_{4,8}$ 4.6, $J_{8,8}$ 12.1 Hz, H8; 4.11–4.15, m, CH_2O; 4.75, dd, $J_{H,P} \approx J_{H,H}$ 1.3 Hz, CH_2CCl_3; 4.76, dd, CH_2CCl_3. ^{13}C NMR (150.8 MHz, CD_3OD) δ 18.90, 38.46, C4,6; 22.33, d, $J_{C,P}$ 6.0 Hz, C7; 25.04, C1; 26.94, C5; 64.87, C8; 75.00, d, $J_{C,P}$ 6.2 Hz, CH_2O; 75.68, C2; 77.24, C3; 78.38, d, $J_{C,P}$ 4.5 Hz, $\mathbf{C}H_2CCl_3$; 96.14, d, $J_{C,P}$ 10.5 Hz, CCl_3. Next to elute was what appeared to be a mixture (^1H NMR) of the ethyl ethers **32**, **33**, and **34** as a colorless oil (7 mg, 56%).

***[(1R,2R,3R,4R,6S,7R)-2,3-Di-(t-butyldimethylsilyloxy)-4-(t-butyldimethylsilyloxy)methylbicyclo[4.1.0]hept-7-yl]methyl 2,4-Dinitrophenyl Ether* 35.** 2,4-Dinitrofluorobenzene (0.2 mL, 2 mmol) was added to the alcohol **26** (100 mg, 0.2 mmol) in $ClCH_2CH_2Cl$ (5 mL) and Et_3N (0.3 mL, 2 mmol) and the solution was stirred (40°C, 24 hr). Concentration of the mixture followed by standard work-up (CH_2Cl_2) and flash chromatography (EtOAc/petrol 1:19) furnished the ether **35** as a colorless oil (130 mg, 91%), $[\alpha]_D$+25.7°. ^1H NMR (600 MHz) δ 0.01, 0.03, 0.04, 0.06, 0.07, 0.08, 6s, 18H, CH_3; 0.84, 0.89, 0.90, 3s, 27H, $C(CH_3)_3$; 0.95, dd, $J_{1,6}$ 8.9, $J_{6,7}$ 4.7 Hz, H1; 0.99–1.04, m, H6; 1.50–1.53, m, H7; 1.61–1.64, m, H4; 1.79, ddd, $J_{4,5}$ 5.5, $J_{5,5}$ 14.3, $J_{5,6}$ 2.6 Hz, H5; 2.03, ddd, $J_{4,5}$ 8.5, $J_{5,6}$ 3.7 Hz, H5; 3.44, dd, $J_{2,3} \approx J_{3,4}$ 3.3 Hz, H3; 3.56, dd, $J_{4,8}$ 3.9, $J_{8,8}$ 10.3 Hz, H8; 3.67, dd, $J_{4,8}$ 10.2, H8; 3.83, d, H2; 3.94, dd, $J_{7,H}$ 7.7, J 10.3 Hz, 1H, CH_2O; 4.29, dd, $J_{7,H}$ 6.3 Hz, 1H, CH_2O; 7.15, 8.37, 8.72, 3 m, 3H, Ar. ^{13}C NMR (150.8 MHz) δ −5.30, −5.27, −4.85, −4.83, −4.65, −4.55, 6C, CH_3; 13.62, C6; 17.86, 17.88, 18.42, 3C, $\mathbf{C}(CH_3)_3$; 20.13, C5; 20.92, C7; 22.95, C1; 25.78, 25.80, 26.04, 3C, $C(\mathbf{C}H_3)_3$; 40.81, C4; 63.67, C8; 69.73, C2; 72.95, C3; 74.83, CH_2O; 114.55, 121.86, 128.78, 139.22, 139.83, 156.75, 6C, Ar. HRMS (FAB) m/z 697.3702 [$C_{33}H_{61}N_2O_8Si_3$ $(M+H)^+$ requires 697.3735].

***[(1R,2R,3R,4R,6S,7R)-2,3-Dihydroxy-4-(hydroxymethyl)bicyclo[4.1.0]hept-7-yl]methyl 2,4-Dinitrophenyl Ether* 4.** Conc. HCl (1 drop) was added to the ether **35** (120 mg) in EtOH (5 mL) and the solution kept (rt, 6 hr). Concentration of the mixture followed by coevaporation with PhMe left a colorless solid that was subjected to flash chromatography ($MeOH/CHCl_3$ 1:19), yielding the *triol* **4** as colorless needles (58 mg, 94%), m.p. 125–129°C (CH_2Cl_2/petrol), $[\alpha]_D$+43.9° (CH_3OH) (Found: C, 50.9; H, 5.0. $C_{15}H_{18}N_2O_8$ requires C, 50.8; H, 5.1%). ^{1}H NMR (500 MHz, CD_3OD) δ 1.06, dd, $J_{1,6}$ 8.6, $J_{1,7}$ 4.6 Hz, H1; 1.15–1.23, m, H4,6,7; 1.71, ddd, $J_{4,5}$ 12.4, $J_{5,5}$ 12.9, $J_{5,6}$ 5.1 Hz, H5; 2.03, ddd, $J_{4,5}$ 1.2, $J_{5,6}$ 4.4 Hz, H5; 3.10, dd, $J_{2,3}$ 8.0, $J_{3,4}$ 10.0 Hz, H3; 3.54–3.59, m, H2,8; 3.66, dd, $J_{4,8}$ 4.5, $J_{8,8}$ 11.1 Hz, H8; 4.16, dd, $J_{7,H}$ 6.7, J 10.3 Hz, ^{1}H, CH_2O; 4.28, dd, $J_{7,H}$ 6.7, 1H, CH_2O; 7.45, 8.45, 8.70, 3 m, 3H, Ar. ^{13}C NMR (125.7 MHz, CD_3OD) δ 18.54, 21.04, 38.40, C4,6,7; 24.91, C1; 26.85, C5; 64.94, C8; 75.32, CH_2O; 75.82, C2; 77.34, C3; 116.51, 122.32, 130.01, 140.57, 141.37, 157.82, 6C, Ar. HRMS (FAB) m/z 355.1120 [$C_{15}H_{19}N_2O_8$ $(M+H)^+$ requires 355.1141].

***(1S,3R,4R,5R,6S,7R)-4,5-Di-(t-butyldimethylsilyloxy)-3-(t-butyldimethylsilyloxy)methyl-2-oxabicyclo[4.1.0]heptane-7-carboxylic acid, amide* 36.** Sodium cyanide (2 mg) was added to the ester **11**[8] (600 mg) in 9 M NH_3/MeOH (10 mL) and the solution was stirred at 50°C in a pressure bottle (4 d). The ammonia was then allowed to evaporate and concentration of the mixture followed by flash chromatography (EtOAc/petrol 1:4) gave the amide **36** as a colorless oil (470 mg, 82%), $[\alpha]_D$+43.1°. ^{1}H NMR (500 MHz) δ 0.05, 0.06, 0.07, 0.08, 0.09, 0.11, 6s, 18H, CH_3; 0.88, 0.89, 2s, 27H, $C(CH_3)_3$; 1.74, ddd, $J_{1,6}$ 7.1, $J_{5,6}$ 1.3, $J_{6,7}$ 6.1 Hz, H6; 2.06, dd, $J_{1,7}$ 1.7 Hz, H7; 3.54–3.56, m, H3,5; 3.64, dd, $J_{3,8}$ 4.0, $J_{8,8}$ 11.4 Hz, H8; 3.75, dd, H1; 3.88–3.92, m, H4,8; 6.14, 6.20, 2s, NH_2. ^{13}C NMR (125.7 MHz) δ −5.31, −5.23, −4.87, −4.81, −4.73, CH_3; 17.80, 17.90, 18.33, 3C, **C**$(CH_3)_3$; 25.69, 25.76, 25.93, 3C, C(**C**$H_3)_3$; 26.08, 26.25, C6,7; 55.07, C1; 62.34, C8; 66.27, 71.17, 78.91, C3,4,5; 173.35, C=O. HRMS (FAB) m/z 545.3401 [$C_{26}H_{55}NO_5Si_3$ $(M)^+$. requires 545.3388].

***Ethyl 2*-C-*Carbamoylmethyl-2-deoxy*-D-*glucopyranoside* 37.** Conc. HCl (1 drop) was added to the amide **36** (200 mg) in EtOH (5 mL) and the solution kept (rt, 8 hr). Concentration of the mixture followed by coevaporation with PhMe left a colorless solid that was subjected to flash chromatography ($MeOH/CHCl_3$ 1:3), yielding the triol **37** as a colorless solid (60 mg, 90%). ^{1}H NMR (600 MHz, CD_3OD) δ 1.16–1.19, m, CH_3; 1.85–1.94, m, H2β; 2.05–2.09, m, H2α; 2.31, dd, $J_{2,H}$ 9.7, J 15.0 Hz, 1H, $CH_2CO\alpha$; 2.36, dd, $J_{2,H}$ 5.8, J 14.7 Hz, 1H, $CH_2CO\beta$; 2.51, dd, $J_{2,H}$ 4.2 Hz, 1H, $CH_2CO\beta$; 2.61, dd, $J_{2,H}$ 4.5 Hz, 1H, $CH_2CO\alpha$; 3.24–3.33, m, H3β,4,5α; 3.40–3.42, 3.53–3.57, 3.71–3.73, 3.91–3.95, 4 m, C**H**$_2$CH$_3$,5β; 3.48, dd, $J_{2,3} \approx J_{3,4}$ 9.3 Hz, H3α;

3.66–3.85, 2 m, 2H, H6; 4.35, d, $J_{1,2}$ 8.7 Hz, H1β; 4.79, d, $J_{1,2}$ 3.1 Hz, H1α. ^{13}C NMR (150.8 MHz, CD_3OD) δ 15.23, 15.29, CH_3; 34.82, **C**$H_2CO\alpha$; 34.86, **C**$H_2CO\beta$; 44.53, C2α; 46.39, C2β; 62.91, 62.93, C6; 64.04, 66.15, **C**H_2CH_3; 72.89, 73.04, 76.34, 77.82, C3β,4,5α; 73.80, 73.82, C3α,5β; 99.56, C1α; 104.24, C1β; 173.28, 173.45, C=O. HRMS (FAB) m/z 250.1291 [$C_{10}H_{20}NO_6$ $(M + H)^+$ requires 250.1290].

***(1S,3R,4R,5R,6R,7S)-4,5-Dihydroxy-3-hydroxymethyl-2-oxabicyclo[4.1.0]-heptane-7-carboxylic acid, amide* 5.** (i) Tetrabutylammonium fluoride trihydrate (340 mg, 1.1 mmol) was added to the amide **36** (160 mg, 0.3 mmol) in THF (5 mL) and the solution was stirred (rt, 1 hr). The solution was concentrated and the residue was dissolved in pyridine (5 mL), and then Ac_2O (2 mL) was added and the solution stirred (rt, 1 hr). The mixture was quenched with MeOH (5 mL), and concentration of the mixture followed by standard work-up (CH_2Cl_2) and flash chromatography (EtOAc/petrol 7:3) gave (1*S*,3*R*,4*R*,5*R*,6*S*,7*S*)-4,5-diacetoxy-3-acetoxymethyl-2-oxabicyclo[4.1.0] heptane-7-carboxylic acid amide as a colorless oil (90 mg, 94%), $[\alpha]_D$+43.7°. ^{1}H NMR (500 MHz) δ 1.68, ddd, $J_{1,6}$ 6.8, $J_{5,6}$ 2.3, $J_{6,7}$ 4.6 Hz, H6; 1.91, dd, $J_{1,7}$ 1.9 Hz, H7; 2.00, 2.03, 2.05, 3s, 9H, CH_3; 3.79, ddd, $J_{3,4}$ 5.4, $J_{3,8}$ 3.9, 7.5 Hz, H3; 3.83, dd, H1; 4.09, dd, $J_{8,8}$ 12.1 Hz, H8; 4.37, dd, H8; 4.80, dd, $J_{4,5}$ 5.4 Hz, H4; 4.94, dd, H5; 6.16, 6.24, 2s, NH_2. ^{13}C NMR (125.7 MHz) δ 20.57, 20.60, 20.71, 3C, CH_3; 22.30, 25.91, C6,7; 55.32, C1; 61.86, C8; 67.65, 68.55, 72.77, C3,4,5; 169.37, 169.67, 170.47, 171.92, 4C, C=O. HRMS (FAB) m/z 330.1178 [$C_{14}H_{20}NO_8$ $(M + H)^+$ requires 330.1188].

(ii) 10% NaOMe in MeOH (5 mL) was added to the diacetate from (i) (80 mg) in MeOH (5 mL) and the solution was stirred (rt, 30 min). The solution was quenched by the addition of resin (Amberlite IR-120, H^+). Concentration of the mixture followed by flash chromatography (MeOH/EtOAc 1:4) gave the *triol* **5** as a colorless solid (45 mg, 92%), $[\alpha]_D + 78.1°$ (H_2O) (Found: C, 47.4; H, 6.6. $C_8H_{13}NO_5$ requires C, 47.3; H, 6.4%). ^{1}H NMR (500 MHz, D_2O) δ 1.49, ddd, $J_{1,6}$ 7.4, $J_{5,6}$ 2.4, $J_{6,7}$ 5.8 Hz, H6; 1.98, dd, $J_{1,7}$ 2.3 Hz, H7; 3.33–3.37, m, H4,8; 3.58, dd, $J_{3,8}$ 1.1, $J_{8,8}$ 12.4 Hz, H8; 3.68–3.73, m, H3,5; 3.80, dd, H1. ^{13}C NMR (125.7 MHz, D_2O) δ 24.72, 25.21, C6,7; 56.85, C1; 60.82, C8; 69.58, 69.96, 76.66, C3,4,5; 176.01, C=O. HRMS (FAB) m/z 204.0881 [$C_8H_{14}NO_5$ $(M + H)^+$ requires 204.0871].

***(1S,3R,4R,5R,6R,7S)-7-Amino-3-hydroxymethyl-2-oxabicyclo[4.1.0]heptane-4,5-diol* 6.** Sodium hypochlorite (1.6 M, 5 mL, 8 mmol) was added to the amide **5** (100 mg, 0.5 mmol) in 2 M NaOH solution (2 mL) and the solution was stirred at 50°C (1 hr). Concentration of the mixture left a yellow residue that was dissolved in water and applied to a column of resin (Amberlite IR-120, H^+). Elution with water followed by 1 M NH_3 solution gave the *amine* **6** as a colorless oil (69 mg, 81%), $[\alpha]_D$+46.8° (H_2O) (Found: C, 47.7; H, 7.3. $C_7H_{13}NO_4$ requires

C, 47.9; H, 7.5%). ^{1}H NMR (300 MHz, D_2O) δ 0.88, ddd, $J_{1,6}$ 7.2, $J_{5,6}$ 4.2, $J_{6,7}$ 5.6 Hz, H6; 2.39–2.41, m, H7; 3.24, dd, $J_{3,4}$ 6.7, $J_{4,5}$ 8.2 Hz, H4; 3.35–3.40, m, H1,3; 3.49, dd, H5; 3.53, dd, $J_{3,8}$ 2.9, $J_{8,8}$ 12.4 Hz, H8; 3.71, dd, $J_{3,8}$ 7.6 Hz, H8. ^{13}C NMR (75.5 MHz, D_2O) δ 27.34, C6; 37.05, C7; 57.95, C1; 63.40, C8; 72.39, 72.69, 82.06, C3,4,5. HRMS (FAB) m/z 176.0921 [$C_7H_{14}NO_4$ $(M + H)^+$ requires 176.0921].

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