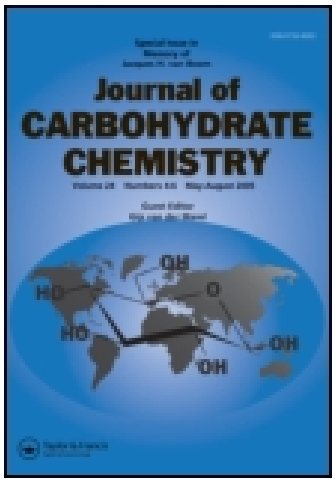

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SYNTHESIS OF CARBASUGARS FROM NUCLEOPHILIC ADDITION–RING CLOSURE (NARC)–DERIVED CYCLOALKENES

Patrick Perlmutter [a] & Mark Rose [a]
[a] School of Chemistry , Monash University , P.O. Box 23, Victoria, 3800, Australia
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SYNTHESIS OF CARBASUGARS FROM NUCLEOPHILIC ADDITION—RING CLOSURE (NARC)—DERIVED CYCLOALKENES

Patrick Perlmutter* and Mark Rose

School of Chemistry, Monash University, P.O. Box 23, Victoria, 3800, Australia

ABSTRACT

A short, enantioselective synthesis of carbasugars 4a-carba-α-L-xylofuranose **15**, 4-*epi*-validatol **16** and their corresponding carboxylic acids **11** and **12** is reported. These compounds were prepared via a four-step sequence of nucleophilic addition, ring closure (NARC), dihydroxylation and reduction.

INTRODUCTION

Carbasugars, including carbanucleosides, constitute a rapidly developing family of therapeutically important carbohydrate analogues.[1–3] Their importance is largely due to their stability in vivo. Examples include carbovir,[4] BMS200475,[5] mannostatin,[6] and (+)-cyclophellitol.[7] We have initiated a program intended to develop new, rapid approaches to the synthesis of enantiomerically pure compounds. One such approach (the ''NARC'' approach) involves the combination of a Nucleophilic Addition immediately followed by a Ring Closure as the key synthetic sequence in the preparation of a range of cyclic target molecules.[8]

In this paper we show how one such sequence, employing a *syn*-selective aldol reaction followed by ring closing metathesis,[9] provides a rapid route to enantiomerically pure cycloalkenes. These were then converted into carba-α-L-xylofuranose **15**,[10] 4-*epi*-validatol **16**[11,12] and their carboxylic acid derivatives **11** and **12**.[13]

*Corresponding author. Fax: +61-3-9905-4597; E-mail: patrick.perlmutter@sci.monash.edu.au

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RESULTS AND DISCUSSION

The NARC sequence used in this work involved a *syn*-aldol reaction for the nucleophilic addition (NA) and ring closing metathesis for the ring closure (RC). Thus, addition of the Z-boron enolate of acyl sultam **1**[14,15] or its homologue **2**,[16] to cinnamaldehyde **3** gave *syn* aldol adducts **4** and **5** in 88% and 60% yields, respectively. In each case the diastereoselectivity was excellent (dr > 95:5). Subsequent ring closing metathesis with Grubbs' catalyst[17] gave good yields of the highly crystalline cycloalkenes **6** and **7** (83% and 74% respectively).

Dihydroxylation of **6** using potassium osmate/*N*-methyl morpholine oxide [18,19] in a mixture of *t*-butyl alcohol and DMF gave, in 90% yield, **9** as a single diastereoisomer. Triol **9** proved to be highly crystalline and its x-ray structure is shown in Figure 1. As is evident from the figure, dihydroxylation occurred exclusively from the face remote to the two ring substituents. Dihydroxylation of **7** proceeded in a similar fashion to that for **6**. Again only one diastereoisomer, **10**, was obtained, although in significantly lower yield, 50%, due to incomplete reaction. The crystal structure of **10** is also shown in Figure 1.

Although **9** and **10** are relatively polar compounds it was found that they could be manipulated in a straightforward fashion. Due to the hydrophobic nature of the auxiliary it proved possible to efficiently recover each triol from water by extraction with organic solvents. In addition both were amenable to chromatography on silica.

Some attempts were made to reverse the stereoselectivity of the dihydroxylations. Reaction of **6** with either of the Sharpless ADα or ADβ ligand catalyst mixtures[21,22] yielded only **9**. No evidence for the production of **8** was found. This strongly suggests that the ring substituents control the selectivity in these dihydroxylations, overriding any reagent control that the AD mixes normally provide.

Reduction of **9** and **10** with $NaBH_4$ gave the carbasugars, 4a-carba-α-L-xylofuranose **15** and 4-*epi*-validatol **16** in 52% and 95% yields, respectively. Both compounds were obtained as oils. These highly polar compounds were purified by a sequence of (i) evaporation of the crude aqueous extracts of the reaction mixture, (ii) extraction of the residue into ethanol and chromatography on silica gel or celite.

Hydrolysis of **9** and **10** provided the highly polar, water-soluble trihydroxy acids **11** and **12** in good yield. The cyclohexane derivative **12** was characterized as its methyl ester **14** after treatment of the crude hydrolysate with acidic methanol. Unlike **12**, **11** resisted all attempts at esterification. To our surprise it was unreactive to diazomethane or acidic methanol. This may be due to strong intramolecular hydrogen bonding. For

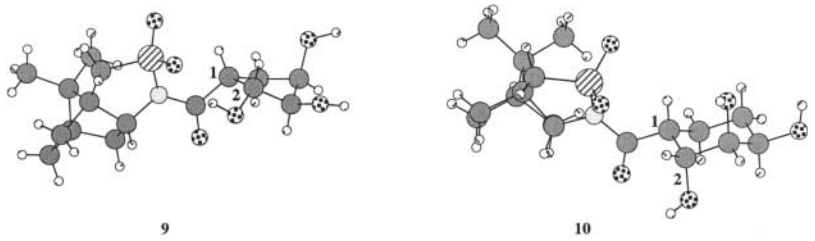
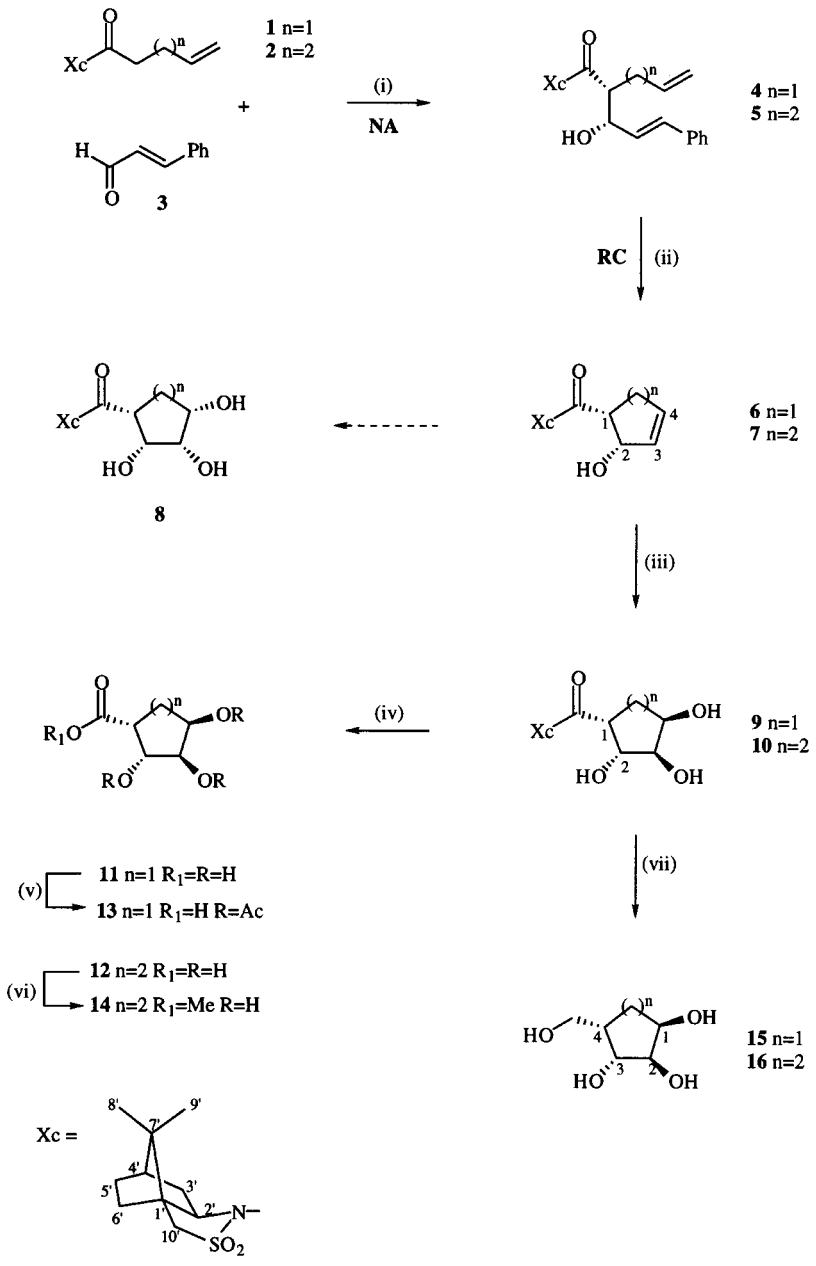


Figure 1. X-ray crystal structures of **9** and **10**.



Scheme. (i) (a) **1** or **2**, Et_2BOTf, $(iPr)_2NEt$, CH_2Cl_2 (b) **3**; (ii) $RuCl_2(=CHPh)(PCy_3)_2$, CH_2Cl_2; (iii) $K_2OsO_4.2H_2O$, tBuOH, DMF, NMO; (iv) LiOH, H_2O_2, H_2O, THF; (v) Ac_2O, H_2SO_4; (vi) MeOH, H_2SO_4; (vii) $NaBH_4$, EtOH.

this reason **11** was isolated and characterized as its triacetate, **13**, obtained in 41% overall yield from **9**.

In summary, we have prepared four carbasugar derivatives using a highly stereoselective NARC sequence followed by a completely diastereoselective dihydroxylation. Noteworthy also is that this approach obviated the need for any hydroxy group protection during the synthesis.

EXPERIMENTAL

General Procedures. ^{1}H NMR spectra are assigned according to the type of proton e.g. CH_3, CHN, C*H* = CH_2 or according to numbering as shown in the text. ^{13}C NMR spectra are assigned in a similar fashion with the exception of the sultam carbons which are numbered $1'-10'$. Dichloromethane, tetrahydrofuran (THF) and toluene were dried and distilled before use. Solvents used for metathesis reactions were degassed by bubbling a stream of argon through them for at least 20 min prior to use. Grubbs' catalyst was purchased from Aldrich Chemical Company. Compounds characterized without elemental analyses were found to be pure by nmr spectroscopy.

For the x-ray structure determination of **9** and **10** a suitable single crystal was mounted on a glass fibre and data collected on a Nonius Kappa CCD area detector. The structures were solved by direct methods and refined by the full matrix least-squares method: for **9** the programs used were—Texan: Crystal Structure Analysis Package, Molecular Structure Corporation (1992), and for **10** ShelocS-97 and ShelocL-97: G.M.Sheldrick, Universität Göttingon, 1997. All nonhydrogen atoms were refined anisotropically. The hydrogens were put into theoretical positions and refined using the riding model.

Further details of data collection: Diffractometer; Nonius Kappa CCD; Radiation: $\lambda = 0.71069$ Å (Mo–Kα) with graphite monochromator;

9: crystal size: $0.24\times0.14\times0.14$ mm; formula: $C_{16}H_{25}NO_6S$; formula weight: 359.44; temperature: 123(2)K; crystal system: orthorhombic; space group $P2_12_12_1$; unit cell dimensions: a = 8.0585(1)Å, b = 13.8941(3)Å, c = 14.5160(3)Å; volume: 1625.29(4)Å^{-3}; z = 4; density (Calcd): 1.469 Mg/m^3; absorption coefficient: 0.233 mm^{-1}; F(000):768; Max θ value for data collection: 30.0 °C ; index ranges: $-11 \le h \le 11$, $-19 \le k < 19$, $-20 \le l \le 20$; reflections collected: 24 155; independent; 2734; R(int) 0.034; completeness to $\theta = 27.5$ °C, 99.7%; data/restraints/parameters: 2067/0/217; goodness-of-fit on F: 2.19; final R indicies [$I > 3\sigma(I)$]: $R_1 = 0.040$, $R_w = 0.033$; absolute structures parameter: 0.03(3); longest diff. peak and hole: 0.45 and -0.44 e/Å^3.

10: crystal size: $0.20\times0.16\times0.19$ mm; formula: $C_{35}H_{60}N_2O_{14}S_2$; formula weight: 796.97; temperature: 123(2)K; crystal system: orthorhombic; space group $P2_12_12_1$; unit cell dimensions: a = 28.1405(9)Å, b = 11.0610(3)Å, c = 11.9020(3)Å; volume: 3704.6(2)Å^{-3}; z = 4; density (Calcd): 1.429 Mg/m^3; absorption coefficient: 0.216 mm^{-1}; F(000):1712; Max θ value for data collection: 30.0 °C ; index ranges: $-39 \le h \le 39$, $-15 \le k < 15$, $-15 \le l \le 15$; reflections collected: 34 181; independent; 10 280; R(int) 0.072; completeness to $\theta = 27.5$ °C, 96.3%; data/restraints/parameters: 10 280/2/429; goodness-of-fit on F^2: 1.028; final R indicies [$I > 2\sigma(I)$]: $R_1 = 0.060$, $wR_2 = 0.103$; absolute structures parameter: 0.04(7); longest diff. peak and hole: 0.42 and -0.43 e/Å^3. Crystallographic data for the structures reported in this paper have been deposited with the Cambridge Crystallographic data Centre as supplementary publication nos. CCDC-172515 and 172516.

Copies of the data can be obtained free of charge an application to The Director. CCDC, 12 Union Road, Cambridge CB2 1EZ, UK (fax: Int.code + (1223) 336-033; e-mail: deposit@ccdc.cam.ac.uk).

(2*R*)-*N*-[(2*R*)-2-((1*S*,2*E*)-1-Hydroxy-3-phenyl-2-propen-1-yl)-4-penten-1-oyl]-bornane-10,2-sultam (4). A solution of diethylboron triflate was generated by dropwise addition of freshly distilled triflic acid (340 μL, 3.8 mmol) to triethylborane (1 M in hexane, 3.8 mL, 3.8 mmol). The solution was stirred at rt for 20 min. (Note: if not homogeneous warm at approx. 40 °C for 20 min.) The above solution was cooled to −5 °C and a solution of **1** (530 mg, 1.8 mmol) in dichloromethane (5 mL), followed by a solution of *N*,*N*-diisopropylethylamine (1 M in dichloromethane, 4 mL, 4.0 mmol) were added. After stirring at −5 °C for 20 min the solution was cooled to −78 °C and a solution of **3** (0.5 mL, 4.0 mmol) in dichloromethane (1 mL) was added. After stirring for 2 h the reaction was quenched by addition of 0.5 M pH 7 phosphate buffer (8 mL) and left to warm to rt. The mixture was then taken up in ether (30 mL), the aqueous layer separated and the organic layer washed with satd aq NH_4Cl (2×50 mL). After drying ($MgSO_4$) and removal of solvent in vacuo (at ambient temperature), **4** was purified by column chromatography (hexane/ethyl acetate, 4:1). The aldol adduct **4** (680 mg, 88%) was obtained as a colorless foam. $[\alpha]_D^{25}$ −86 °C (*c* 0.8, CH_2Cl_2). R_f (0.27) in hexane/ethyl acetate (3:1). IR (nujol/CH_2Cl_2): 3539, 2923, 2853, 1671, 1461, 1377, 1339, 1271, 1241, 1217, 1163, 1134, 1065, 970, 922, 721 cm^{-1}. ^1H NMR (300 mHz, $CDCl_3$) δ 0.97 (s, 3H, CH_3), 1.16 (s, 3H, CH_3), 1.32–1.45 (m, 2H, CH_2), 1.92–1.97 (m, 3H, CH_2 and CH), 2.02–2.04 (m, 2H, CH_2), 2.44–2.60 (m, 2H, 2×H-3), 3.42 (m, 1H, H-2), 3.47 and 3.53 (AB quartet, 2H, J = 13.9 Hz, CH_2SO_2), 3.93 (t, 1H, J = 6.3 Hz, CHN), 4.70 (m, 1H, H-1), 5.02 (m, 2H, CH = CH_2), 5.82 (m, 1H, CH = CH_2), 6.23 (dd, 1H, J = 5.8, 16.0 Hz, CH = CHPh), 6.69 (d, 1H, J = 16.0 Hz, CH = CHPh), 7.20–7.44 (m, 5H, Ph). ^{13}C NMR (75 mHz, $CDCl_3$) δ 20.0(C-8′), 20.9(C-9′), 26.4(C-5′). 32.6(C-6′), 32.9(C-3), 38.4(C-3′), 44.7(C-4′), 47.7(C-7′), 48.2(C-1′), 49.6(C-2), 53.2(C-10′), 65.3(C-2′), 71.6(C-1), 117.4(CH$_2$ = C), 126.5(Ph), 127.4(C = HC), 128.3 (C = HC and Ph), 131.4(Ph), 134.8(CH = C), 136.5(Ph), 174.5(CO). [M + Na^+] *m*/*z* 452.2 (100%), [M−OH]*m*/*z* 412.2 (50%).

Anal. Calcd for $C_{24}H_{31}NO_4S$: C, 67.10; H, 7.27; N, 3.26: Found: C, 67.44; H, 7.17; N, 3.14.

(2*R*)-*N*-[(2*R*)-2-((1*S*,2*E*)-1-Hydroxy-3-phenyl-2-propen-1-yl)-5-hexen-1-oyl]-bornane-10,2-sultam (5). A solution of diethylboron triflate was generated from triflic acid (240 μL, 2.7 mmol) and triethylborane (1 M in hexane, 2.7 mL, 2.7 mmol). To this solution was added, at −5 °C, **2** (398 mg, 1.3 mmol) in dichloromethane (5 mL), followed by a solution of *N*,*N*-diisopropylethylamine (1 M in dichloromethane, 3 mL, 3.0 mmol). After cooling to −78 °C, a solution of **3** (2.65 mmol) in dichloromethane (1 mL) was added. The reaction was quenched by addition of 0.5 M pH 7 phosphate buffer (5.4 mL), taken up in ether (30 mL) and the aqueous layer separated. The organic layer was washed with satd aq NH_4Cl (2×50 mL), dried ($MgSO_4$) and concentrated in vacuo (at ambient temperature). The resulting mixture was purified by column chromatography (hexane/ethyl acetate, 4:1) to yield the aldol adduct **5** (340 mg, 60%) as an oil. $[\alpha]_D^{25}$ − 89 °C (*c* 0.9, CH_2Cl_2). R_f (0.31) in hexane/ethyl acetate (3:1). IR (nujol/CH_2Cl_2): 3502, 2924, 2854, 1684, 1461, 1378, 1338, 1264, 1237, 1214, 1165, 1135, 1066, 9687, 744 cm^{-1}. ^1H

NMR (200 mHz, $CDCl_3$) δ 0.99 (s, 3H,CH_3), 1.18 (s, 3H, CH_3), 1.40 (m, 2H, CH_2), 1.60 (m, 2H, CH_2), 1.80–2.20 (m, 8H, 3×CH_2, CH and OH), 3.33 (pent, 1H, J = 4.1 Hz, H-2), 3.49 and 3.56 (AB quartet, 2H, J = 13.8 Hz, CH_2SO_2), 3.95 (t, 1H, J = 6.3 Hz, CHN), 4.65 (m, 1H, H-1), 4.90 (m, 2H, CH = CH_2), 5.70 (m, 1H, CH = CH_2), 6.25 (dd, 1H, J = 5.8, 16.0 Hz, CH = CHPh), 6.68 (d, 1H, J = 16.0 Hz, CH = CHPh), 7.20–7.50 (m, 5H, Ph). ^{13}C NMR (75 mHz, $CDCl_3$) δ 19.6(C-8′), 20.9(C-9′), 26.4(C-5′), 27.5(C-3), 31.3(C-4), 33.0(C-6′), 38.6(C-3′), 44.7(C-4′), 47.8(C-7′), 48.2(C-1′), 50.1(C-2), 53.2(C-10′), 65.4(C-2′), 71.9(C-1), 115.0(CH$_2$ = C), 126.5(Ph), 127.4(CH = C), 128.3(Ph), 128.5(Ph), 131.2(CH = C), 136.6(Ph), 137.5(CHC), 174.9(CO). Exact mass m/z calcd for $C_{25}H_{32}NSO_3$ (M−OH) 426.2103, found 426.2083.

(2*R*)-*N*-[(1*R*,2*S*)-2-Hydroxy-3-cyclopenten-1-oyl]bornane-10,2-sultam (6). The aldol adduct **4** (680 mg, 1.6 mmol) was dissolved in degassed dichloromethane (60 mL) under argon. A solution of Grubbs' catalyst (130 mg, 0.16 mmol) in dichloromethane (5 mL) was added and the reaction stirred overnight. Evaporation of the solvent, followed by chromatography (hexane/ethyl acetate, 2:1), gave **6** (415 mg, 83%) as colorless crystals, mp 141–143 °C. $[\alpha]_D^{25}$ + 13 °C (c 1.0, CH_2Cl_2). R_f (0.13) in hexane/ethyl acetate (4:1). IR (nujol/CH_2Cl_2): 3514, 2924, 2854,1686, 1458, 1378, 1360, 1321, 1274, 1249, 1208, 1166, 1134, 1119, 1059, 1040, 1001, 964, 802, 788, 721 cm^{-1}. ^{1}H NMR (200 mHz, $CDCl_3$) δ 0.98 (s, 3H,CH_3), 1.17 (s, 3H,CH_3), 1.30–1.45 (m, 2H, CH_2), 1.70–2.10 (m, 8H, 3×CH_2, CH and OH), 2.55 (m, 1H, H-5), 2.90 (m, 1H, H-5), 3.51 and 3.53 (AB quartet, 2H, J = 13.9 Hz, CH_2SO_2), 3.85 (m, 1H, H-1), 3.96 (dd, 1H, J = 5.3, 5.3 Hz, CHN), 5.20 (m, 1H, H-2), 5.75 (m, 1H, H-4), 5.95 (m, 1H, H-3). ^{13}C NMR (50 mHz, $CDCl_3$) δ 20.0(C-8′), 21.1(C-9′), 26.5(C-5′), 32.9(C-6′), 36.0(C-5), 38.8(C-3′), 44.7(C-4′), 47.1(C-1), 47.9(C-7′), 48.4(C-1′), 53.3(C-10′), 65.7(C-2′), 78.2(C-2), 131.7(C-4), 133.7(C-3), 171.7(CO). Exact mass m/z Calcd for $C_{16}H_{23}NSO_4Na$ (M + Na$^+$) 348.1245, found 348.1231.

(2*R*)-*N*-[(1*R*,2*S*)-2-Hydroxy-3-cyclohexen-1-oyl]bornane-10,2-sultam (7). The aldol adduct **5** (690 mg, 1.5 mmol) was dissolved in degassed dichloromethane (55 mL) under argon. A solution of Grubbs' catalyst (125 mg, 0.15 mmol) in dichloromethane (10 mL) was added and the reaction stirred overnight. Evaporation of the solvent, followed by chromatography (hexane/ethyl acetate, 2:1), gave **7** (393 mg, 74%) as colorless crystals, mp 176–178 °C. $[\alpha]_D^{25}$ − 58 °C (c 1.6, CH_2Cl_2). R_f (0.25) in hexane/ethyl acetate (4:1). IR (nujol/CH_2Cl_2): 3424, 2924, 2854, 1689, 1665, 1461, 1377, 1330, 1264, 1237, 1213, 1166, 1131, 1051, 1000, 939, 829, 743 cm^{-1}. ^{1}H NMR (200 mHz, $CDCl_3$) δ 0.98 (s, 3H, CH_3), 1.16 (s, 3H, CH_3), 1.20–1.60 (m, 5H, 2×CH_2 and CH), 1.70–2.20 (m, 7H, 3×CH_2, and OH), 3.10 (m, 1H, H-1), 3.49 and 3.50 (AB quartet, 2H, J = 13.9 Hz, CH_2SO_2), 3.92 (t, 1H, J = 6.0 Hz, CHN), 4.45 (m, 1H, H-2), 5.89 (m, 2H, H-3 and H-4). ^{13}C NMR (50 mHz, $CDCl_3$) δ 19.8(C-8′), 20.7(C-9′), 21.4(C-5), 25.4(C-6), 26.4(C-5′), 32.7(C-6′), 38.4(C-3′), 44.5(C-4′), 44.9(C-1), 47.8(C-7′), 48.4(C-1′), 53.0(C-10′), 63.1(C-2), 64.9(C-2′), 127.1(C-4), 130.9(C-3), 176.3(CO). [M + 1] m/z 340.2 (100%), [M + 1−H_2O] m/z 322.2 (65%).

Anal. Calcd for $C_{17}H_{25}NSO_4$: C, 60.15; H, 7.42; N, 4.13: Found: C, 59.90; H, 7.62; N, 4.12.

(2*R*)-*N*-[(1*R*,2*S*,3*R*,4*R*)-2,3,4-Trihydroxycyclopentan-1-oyl]bornane-10,2-sultam (9). A solution of **6** (180 mg, 0.57 mmol) in *t*-butyl alcohol (3 mL) and DMF (3

mL) was added to $K_2OsO_4.2H_2O$ (20 mg, 0.06 mmol) and 4-methyl morpholine *N*-oxide (134 mg, 1.14 mmol) under N_2. The reaction was left stirring at rt overnight, then quenched with 20% aq. $Na_2S_2O_5$ solution (1 mL) and left stirring for 30 min. The solution was poured into water (30 mL) and extracted with ethyl acetate (3×20 mL). Drying ($MgSO_4$) and removal of solvent gave **9** (180 mg, 90%) as colorless crystals. Recrystallization from ethyl acetate gave material suitable for x-ray crystallography, mp 187–189 °C. R_f (0.31) in ethyl acetate. $[\alpha]_D^{25} - 46$ °C (*c* 0.4, CH_3OH). IR (nujol/CH_2Cl_2): 3420, 3313, 2925, 2854, 1693, 1459, 1413, 1376, 1320, 1283, 1271, 1237, 1216, 1164, 1129, 1100, 1063, 1038, 1000, 882, 774 cm^{-1}. ^1H NMR (300 mHz, $CDCl_3$) δ 0.98 (s, 3H, CH_3), 1.14 (s, 3H, CH_3), 1.35 (m, 2H, CH_2), 1.80–2.20 (m, 6H, H-5, 2×CH_2, CH), 2.36 (pent., 1H, *J* = 6.5 Hz, H-5), 3.48 and 3.55 (AB quartet, 2H, *J* = 13.7 Hz, CH_2SO_2), 3.82–3.96 (m, 2H, H-1 and CHN), 4.11 (t, 1H, *J* = 6.2 Hz, H-4), 4.29 (m, 1H, H-2), 4.45 (t, 1H, *J* = 7.3 Hz, H-3). ^{13}C NMR (50 mHz, $CDCl_3$) δ 20.0(C-8′), 21.1(C-9′). 26.5(C-5′), 33.0(C-6′), 33.8(C-5), 38.7(C-3′), 44.7(C-4′), 44.8(C-1), 47.9(C-7′), 48.4(C-1′), 53.4(C-10,), 65.7(C-2′), 70.8(C-4), 77.7(C-2), 78.3(C-3), 172.9(CO). Exact mass *m/z* calcd for $C_{16}H_{25}NSO_6Na$ ($M + Na^+$) 382.1300, found 382.1303.

(2*R*)-*N*-[(1*R*,2*R*,3*R*,4*R*)-2,3,4-Trihydroxycyclohexan-1-oyl]bornane-10,2-sultam (10). A solution of **7** (220 mg, 0.65 mmol) in *t*-butyl alcohol (3 mL) and DMF (3 mL) was added to $K_2OsO_4.2H_2O$ (29 mg, 0.08 mmol) and 4-methylmorpholine *N*-oxide (157 mg, 1.34 mmol) under N_2. The reaction was left stirring at rt overnight, then quenched with 20% aq $Na_2S_2O_5$ solution (1 mL) and left stirring for 30 min. The solution was poured into water (30 mL) and extracted with ethyl acetate (3×20 mL). Drying ($MgSO_4$), removal of solvent and column chromatography (eluting with 100% ethyl acetate), gave **10** (121 mg, 50%) as colorless crystals, mp 183–185 °C. Recrystallization from methanol/water gave material suitable for x-ray crystallography. R_f (0.65) in ethyl acetate. $[\alpha]_D^{25} - 91$ °C (*c* 0.4, CH_3OH). IR (CH_2Cl_2): 3443, 2962, 1671, 1456, 1413, 1394, 1334, 1267, 1237, 1217, 1166, 1135, 1066, 1001, 912, 736, 649 cm^{-1}. ^1H NMR (300 mHz, $CDCl_3$) δ 0.97 (s, 3H, CH_3), 1.13 (s, 3H, CH_3), 1.38 (m, 2H, CH_2), 1.70–2.05 (m, 9H, 4×CH_2 and CH), 2.40 (bs, 3H, 3×OH), 3.42 (m, 1H, H-1), 3.47 and 3.52 (AB quartet, 2H, *J* = 13.6 Hz, CH_2SO_2), 3.90 (t, 1H, *J* = 5.9 Hz, CHN), 4.05 (bs, 2H, H-2 and H-4), 4.21 (bs, 1H, H-3). ^{13}C NMR (75 mHz, $CDCl_3$) δ 19.9(C-8′), 20.9(C-9′), 22.6(C-6), 26.5(C-5′), 27.3(C-5), 32.8(C-6′), 38.4(C-3′), 42.6(C-1), 44.6(C-4′), 47.8(C-7′), 48.4(C-1′), 53.0(C-10′), 64.9(C-2′), 67.7(C-4), 70.3(C-2), 71.1(C-3), 175.3(CO). Exact mass *m/z* calcd for $C_{17}H_{27}NSO_6Na$ ($M + Na^+$) 396.1457, found 396.1459.

(1*R*,2*S*,3*R*,4*R*)-2,3,4-Triacetoxycyclopentanoic acid (13). To a chilled solution of **9** (456 mg, 1.3 mmol) in THF (20 mL) and water (5 mL) was added lithium hydroxide (111 mg, 2.6 mmol) followed by 30% aqueous H_2O_2 solution (350 μL, 4.5 mmol). The reaction mixture was allowed to warm to rt and stirred for a further 3 h, after which it was acidified with 1 M HCl. The solvent was removed in vacuo, and the residue was taken up in ethyl acetate/water (20 mL/20 mL) and the aqueous layer separated to give a solution of **11** in water. A portion of this solution (4 mL, 0.26 mmol) was concentrated, taken up in acetic anhydride (1 mL), treated with 3 drops of conc. H_2SO_4 and stirred at rt overnight. Most of the acetic anhydride was removed in vacuo and the residue was taken up in ethyl acetate/water (5 mL/5 mL). The organic phase was separated and dried ($MgSO_4$). Column chromatography (hexane/ethyl acetate,1:1, then 1:3) gave **13** (31 mg,

41%) as an oil. R_f (0.4) in hexane/ethyl acetate (1:3). $[\alpha]_D^{25}$ −30 °C (*c* 1.0, CH_2Cl_2). IR (CH_2Cl_2): 3600–2700, 1750, 1430, 1375, 1231, 1049, 938, 899, 736 cm^{-1}. ^1H NMR (300 mHz, $CDCl_3$) δ 2.04 (m, 10H, 3×CH_3 and H-5), 2.60 (pent., 1H, *J* = 6.7 Hz, H-5), 3.48 (m, 1H, H-1), 5.28 (dd, 1H, *J* = 4.7, 6.7 Hz, H-4), 5.42 (m, 1H, H-2), 5.51 (dd, 1H, *J* = 6.7, 8.4 Hz, H-3). ^{13}C NMR (75 mHz, $CDCl_3$) δ 20.6(CH_3), 20.8(CH_3), 20.9(CH_3), 30.2(C-5), 42.2(C-1), 70.4(C-4), 74.6(C-2), 75.1(C-3), 169.5(CO), 169.7(CO), 169.8(CO), 175.8(CO). Exact mass *m*/*z* calcd for $C_{12}H_{16}O_8Na$ ($M+Na^+$) 311.0743 found 311.0737.

Methyl (1*R*,2*S*,3*R*,4*R*)-2,3,4-Trihydroxycyclohexanoate (14). To a chilled solution of **10** (121 mg, 0.3 mmol) in THF (4.8 mL) and water (1.2 mL) was added lithium hydroxide (27 mg, 0.6 mmol) followed by 30% aqueous H_2O_2 solution (140 μL, 1.2 mmol). The reaction was allowed to warm to rt and stirred for a further 4 h, after which it was acidified with 1 M HCl. The solvent was removed in vacuo and the residue was taken up in ethyl acetate/water (6 mL/6 mL) and the aqueous layer separated, concentrated in vacuo and dissolved in methanol (20 mL). A few drops of concd H_2SO_4 were added and the mixture refluxed overnight. Following removal of solvent, adsorption onto silica and chromatography (6:1 CH_2Cl_2, 2-propanol) **14** (45 mg, 74%) was obtained as an oil. R_f(0.66) in CH_2Cl_2/2-propanol (3:1). $[\alpha]_D^{25}$+5 °C (*c* 1.0, CH_3OH). IR (neat): 3500–3000, 2951, 2840, 1720, 1650, 1452, 1223, 1113, 1063, 1026, 775 cm^{-1}. ^1H NMR (300 mHz, CD_3OD) δ 1.60–1.90 (m, 4H, H-5 and H-6), 2.75 (dq, 1H, *J* = 2.9, 11.3 Hz, H-1), 3.68 (s, 3H, CH_3), 3.85 (m, 2H, H-2 and H-3), 4.21 (t, 1H, *J* = 3.2 Hz, H-4). ^{13}C NMR (75 mHz, CD_3OD) δ 21.4(C-6), 28.0(C-5), 43.3(CH_3), 52.1(C-1), 68.7(C-4), 72.6(C-2), 73.4(C-3), 176.1(CO). Exact mass *m*/*z* calcd for $C_8H_{14}O_5Na$ ($M+Na^+$) 213.0739, found 213.0736.

(1*R*,2*R*,3*R*,4*S*)-4-Hydroxymethyl-1,2,3-trihydroxycyclopentane or 4a-carba-α-L-xylofuranose (15). To a solution of **9** (50 mg, 0.14 mmol) in ethanol (4 mL) was added $NaBH_4$ (50 mg, 1.3 mmol). After stirring at rt for 1 hour the reaction was acidified to pH 4 by dropwise addition of 2 M H_2SO_4. Following removal of solvent in vacuo, the residue was taken up in water/ethyl acetate (5 mL/5 mL) and the aqueous layer was separated and concentrated. The residue was extracted by stirring in methanol (10 mL) for 20 min and the solution was filtered through Celite. Removal of solvent, adsorption onto silica and chromatography (CH_2Cl_2/2-propanol, 1:1) gave **15** (11 mg, 52%) as an oil. $[\alpha]_D^{25}$ −15 °C (*c* 1.0, CH_3OH). IR (neat): 3419, 2941, 2137, 1652, 1416, 1337, 111, 1037, 979 cm^{-1}. ^1H NMR (300 mHz, CD_3OD) δ 1.75 (m, 2H, 2×H-5), 2.44 (m, 1H, H-4), 3.56 (dd, 1H, *J* = 6.5, 10.9 Hz, *H*CHOH), 3.68 (dd, 1H, *J* = 6.5, 10.9 Hz, *H*CHOH), 3.80 (t, 1H, *J* = 4.4 Hz, H-1), 4.14 (m, 2H, H-2 and H-3). ^{13}C NMR (75 mHz, CD_3OD) δ 34.0(C-5), 41.8(C-4), 63.3(CH_2OH), 72.3(C-1), 78.1(C-3), 80.3(C-2) Exact mass *m*/*z* calcd for $C_6H_{12}O_4Na$ ($M+Na^+$) 171.0633, found 171.0629.

(1*R*,2*R*,3*R*,4*S*)-4-Hydroxymethyl-1,2,3-trihydroxycyclohexane or 4-*epi*-validitol (16). To a solution of **10** (46 mg, 0.12 mmol) in ethanol (4 mL) was added $NaBH_4$ (45 mg, 1.2 mmol). After stirring at rt for 2 h the reaction was acidified to pH 4 by dropwise addition of 2 M H_2SO_4. Following removal of solvent in vacuo, the residue was taken up in water/ethyl acetate (5 mL/5 mL) and the aqueous layer was separated and concentrated. The residue was extracted by stirring in 2-propanol (10 mL) for 20 min and

the solution was successively filtered through silica and Celite. Evaporation of solvent gave **16** (19 mg, 95%) as an oil. $[\alpha]_D^{25} + 16$ °C (*c* 1.0, CH_3OH). IR (neat): 3386, 2948, 1648, 1560, 1458, 1114, 1019 cm^{-1}. ^1H NMR (300 mHz, CD_3OD) δ 1.32–1.72 (m, 4H, 2×H-5 and 2×H-6), 1.85 (m, 1H, H-4), 3.50 (dd, 1H, *J* = 6.7, 10.7 Hz, *H*CHOH), 3.62 (dd, 1H, *J* = 6.7, 10.7 Hz, *H*CHOH), 3.78 (t, 1H, *J* = 3.4 Hz, H-1), 3.85 (m, 1H, H-3), 3.95 (t, 1H, *J* = 3.4 Hz, H-2). ^{13}C NMR (75 mHz, CD_3OD) δ 22.3 (C-5), 28.6 (C-6), 39.0 (C-4), 64.7 (CH_2OH), 69.4 (C-1), 72.4 (C-3), 73.8 (C-2). Exact mass *m/z* calcd for $C_7H_{14}O_4Na$ ($M + Na^+$) 185.0790, found 185.0783.

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