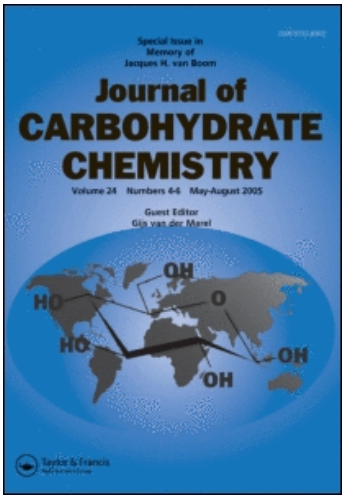


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# A Synthesis of the 4-Alkylamino-2,4-Dideoxy-l-*threo*-pentopyranose Components of the Calicheamicins and Esperamicins

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# A SYNTHESIS OF THE 4-ALKYLAMINO-2,4-DIDEOXY-L-*threo*-PENTOPYRANOSE COMPONENTS OF THE CALICHEAMICINS AND ESPERAMICINS

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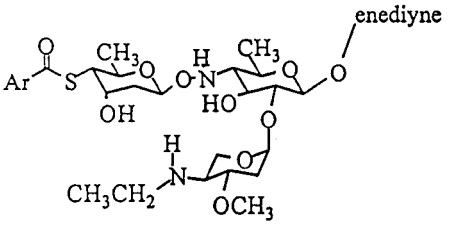
## ABSTRACT

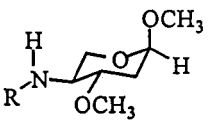
A general synthetic approach to enantiomerically pure 4-substituted 2,4-dideoxy-pentopyranosides has been developed which provides access to the 4-alkylamino-2,4-dideoxy-L-*threo*-pentopyranose components of the calicheamicins and esperamicins.

## INTRODUCTION

There has been much recent effort toward synthesizing the oligosaccharide components (c.f. 1) of the calicheamicins and the esperamicins.[1] These structurally remarkable enediyne-containing antitumor agents function by site-directed DNA strand scission.




**1**




| R | |
|---|---|
| **2a** | $CH_3$ |
| **2b** | $CH_2CH_3$ |
| **2c** | $CH(CH_3)_2$ |

In principle, aminosugars **2** might be synthesized from an appropriate chiron or by *de novo* synthesis. Previous syntheses of derivatives of the 4-ethylamino-2,4-dideoxy-α-L-*threo*-pentopyranose **2b** from L-serine and of the 4-isopropylamino-2,4-dideoxy-α-L-*threo*-pentopyranose **2c** from 2-deoxy-D-ribose have established the absolute configurations of

compounds **2** as 3*S*,4*S*.[2-4] Golik and co-workers described a preparation of the *p*-bromophenylurea derivative of **2c** based on methyl 2-deoxy-β-D-*erythro*-pentopyranoside (**3**) as starting material.[4] This synthesis, carried out as a proof of structure, afforded a low overall yield. As pyranoside **3** is readily available and is an obvious starting material for the synthesis of **2**, we have reinvestigated its use.[5]

## RESULTS AND DISCUSSION

The initial plan to differentiate between the C-3 and C-4 hydroxyl groups by alkylation of the *O*-stannylene acetal derivative of **3** was thwarted by a decided lack of regioselectivity (Scheme 1). Methyl 2-deoxy-β-D-*erythro*-pentopyranoside (**3**)[6,7] was allowed to react with dibutyltin oxide in refluxing toluene to produce the corresponding *O*-stannylene acetal,[8] which was not normally isolated. Alkylation with benzyl bromide provided the regioisomeric monobenzyl ethers **4** and **5** in 43% and 47% yields, respectively, after separation by column chromatography. Fortunately, both **4** and **5** could separately be converted to key tosylate **8** in a convergent approach.

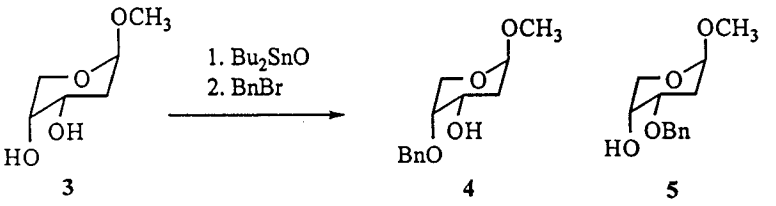
The less polar regioisomeric alcohol **4** was deprotonated using sodium hydride and alkylated with iodomethane to give ether **6** in 94% yield (Scheme 2). Debenzylation of **6** using hydrogen and palladium on carbon provided alcohol **7** which was tosylated to give pyranoside **8** in 91% yield.

A change in step order permitted conversion of the more polar regioisomeric alcohol **5** to the key tosylate **8** (Scheme 2). Tosylation of **5** produced pyranoside **9** in 95% yield, and debenzylation using hydrogen and palladium on carbon gave alcohol **10** in 84% yield. While treatment of **10** with sodium hydride and iodomethane resulted in decomposition, methylation of **10** using iodomethane and silver oxide[9] in DMF provided pyranoside **8** in 96% yield. The combined yield of tosylate **8** from **3** by these convergent routes was 73%.

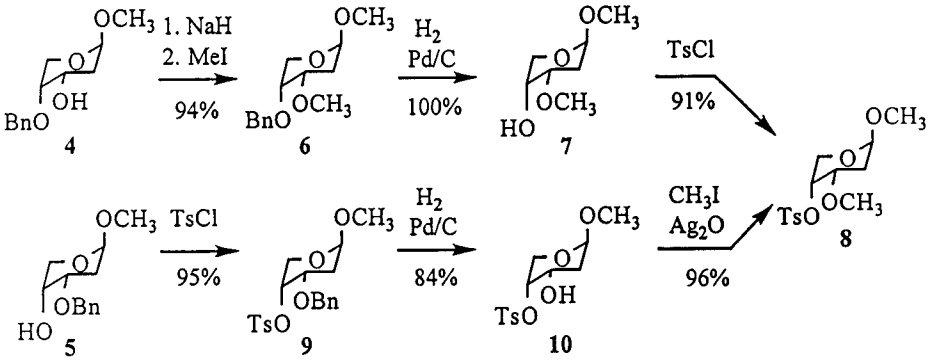
When tosylate **8** was dissolved in 70% aqueous ethylamine at room temperature, no reaction was observed. At elevated temperature considerable decomposition resulted. However, the tosylate was cleanly displaced from **8** by the use of sodium azide in DMSO[10] at 120-130 °C, providing **11** as an oil in 93% yield after chromatography (Scheme 3). Azide reduction and concomitant *N*-acetylation[11] produced pyranoside **12** in 87% yield. Amide **12** was subsequently reduced using $LiAlH_4$ to give methyl 4-ethylamino-3-*O*-methyl-2,4-dideoxy-α-L-*threo*-pentopyranoside (**2b**) in 91% yield. The overall yield of **2b** from **3** was 54%.

The structure of **2b** is based on comparison of its NMR spectra to those found in the literature.[3] Further confirmation of structure and purity was obtained by conversion of **2b** in 90% yield to the *N*-acetyl derivative **13** (Scheme 4). NMR spectra obtained for **13** were in accord with those of an authentic sample.[12]

The *N*-CBZ derivative **15** of the 4-methylamino sugar **2a** was also prepared (Scheme 5). Reduction of azide **11** using hydrogen and 10% palladium on carbon, followed by carbonylation with benzyl chloroformate, produced urethane **14** in 53% yield. Methylation using iodomethane and silver oxide afforded **15** in 82% yield.

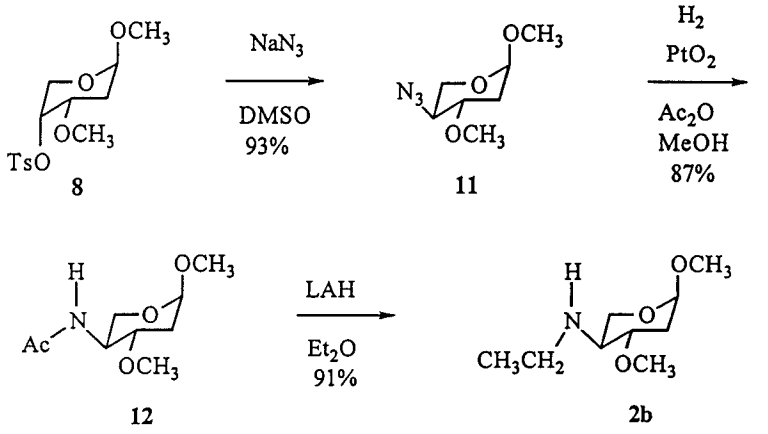



Scheme 1. Synthesis of regioisomers **4** and **5** from methyl 2-deoxy-β-D-*erythro*-pentopyranoside(**3**).

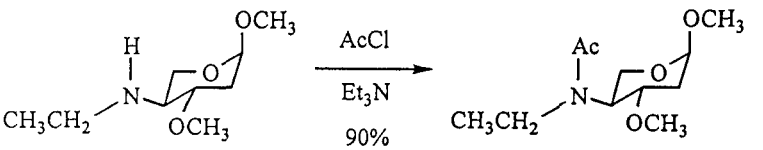



Scheme 2. Convergent synthesis of key tosylate **8** from regioisomers **4** and **5**.



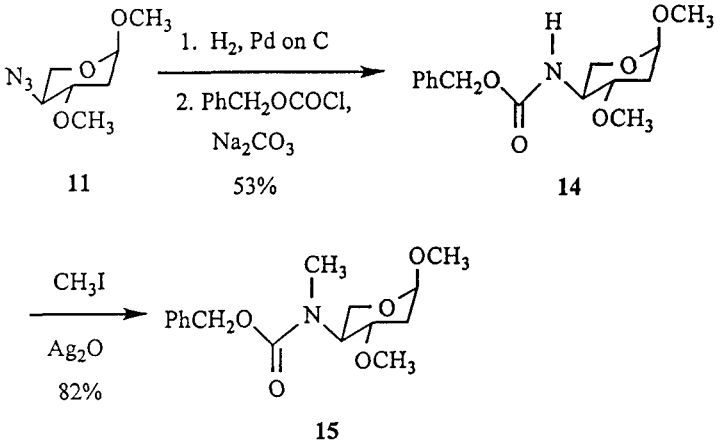



Scheme 3. Conversion of tosylate **8** to methyl 4-ethylamino-3-*O*-methyl-2,4-dideoxy-α-L-*threo*-pentopyranoside (**2b**).




2b 13

Scheme 4. Conversion of **2b** to amide **13.**




11 14 15

Scheme 5. Conversion of azide **11** to the *N*-CBZ derivative **15** of **2a.**



In summary, the above synthesis provides a relatively short and efficient route to the 4-alkylamino-2,4-dideoxy-L-*threo*-pentopyranose targets. The enantiomers of the aminosugars described would also be available from methyl 2-deoxy-β-L-*erythro*-pentopyranoside, which can be prepared from L-arabinose.[4]

## EXPERIMENTAL SECTION

Dichloromethane was distilled from calcium hydride. Diethyl ether and tetrahydrofuran were distilled from sodium/benzophenone ketyl under an inert atmosphere. Melting points are uncorrected. $^1H$ and $^{13}C$ NMR spectra were recorded at 250 and 62.9 MHz, respectively. Thin layer chromatographic analyses were performed on Merck silica gel 60 plates (0.25 mm, 70-230 mesh ASTM). Column chromatography was performed on either Merck silica gel 60 (70-230 mesh ASTM, gravity driven) or Merck silica gel 60 (230-400 mesh ASTM, flash). The purity of all title compounds was judged to be >95% by analytical thin layer chromatography and $^1H$ and

$^{13}C$ NMR spectral determinations. High resolution mass spectra were recorded at the Nebraska Center for Mass Spectrometry, Lincoln, NE. Elemental analyses were performed by Desert Analytics, Tucson, AZ.

**Methyl 4-*O*-Benzyl-2-deoxy-β-D-*erythro*-pentopyranoside (4) and Methyl 3-*O*-Benzyl-2-deoxy-β-D-*erythro*-pentopyranoside (5).** A mixture of methyl 2-deoxy-β-D-*erythro*-pentopyranoside (3) (1.00 g, 6.75 mmol) and dibutyltin oxide (1.74 g, 7.01 mmol) in toluene (200 mL) was refluxed under a Dean-Stark trap for 12 h. After removal of 50 mL of the solvent via the trap, benzyl bromide (1.39 g, 8.10 mmol) and tetrabutylammonium bromide (1.31 g, 4.08 mmol) were added and the resulting mixture was refluxed for 48 h. The solvent was removed *in vacuo* and the residue was chromatographed twice on flash silica gel (200 g) eluted with 30% EtOAc/hexanes to give the less polar regioisomer **4** (683 mg, 2.88 mmol, 43%) as a white solid, mp 37-39 °C, homogenous by TLC ($R_f$ 0.18, 30% EtOAc/hexanes). $[\alpha]_D^{21}$ -126.0° (*c* 7.26, $CH_3OH$); IR ($CH_2Cl_2$) $cm^{-1}$ 3429, 2930, 1060; $^1H$ NMR ($CDCl_3$) δ 1.85 (1, dt, J = 13 Hz, J = 4 Hz), 1.98 (1, ddd, J = 13 Hz, J = 9.5 Hz, J = 3 Hz), 2.39 (1, br s), 3.36 (3, s), 3.60 (1, m), 3.71 (1, dd, J = 12 Hz, J = 2 Hz), 3.81 (1, dd, J = 12 Hz, J = 4 Hz), 4.06 (1, m), 4.54 (1, d, J = 12 Hz), 4.72 (1, d, J = 12 Hz), 4.76 (1, t, J = 3 Hz), and 7.29-7.36 (5, m); $^{13}C$ NMR ($CDCl_3$) δ 35.1 ($CH_2$), 55.2 ($CH_3$), 60.0 ($CH_2$), 65.0 (CH), 71.2 ($CH_2$), 75.8 (CH), 98.7 (CH), 127.5 (CH), 127.8 (CH), 128.2 (CH), and 137.3 (C); EIMS (70 eV) *m/z* (rel intensity) 238 ($M^+$, 0.04), 207 (0.5), 206 (2), 189 (0.5), 178 (0.5), 177 (4), 163 (0.5), 150 (1), 147 (0.5), 135 (2), 134 (7), 121 (2), 117 (1), 115 (1), 114 (5), 108 (3), 107 (5), 105 (3), 103 (3), 100 (2), 99 (7), 92 (10), 91 (100), 87 (6), 85 (3), 71 (4), 65 (7), 61 (5), 59 (10); HRMS calcd for $C_{13}H_{18}O_4$ 238.1205, found 238.1208.

Also isolated was the more polar regioisomer **5** (762 mg, 3.21 mmol, 47%) as a colorless oil homogenous by TLC ($R_f$ 0.16, 30% EtOAc/hexanes). $[\alpha]_D^{26.5}$ -81.6° (*c* 15.4, $CH_2Cl_2$); $^1H$ NMR ($CDCl_3$) δ 1.88-2.10 (2, m), 2.39 (1, br s), 3.34 (3, s), 3.74 (2, d, J = 2 Hz), 3.85-3.93 (2, m), 4.59 (2, s), 4.81 (1, t, J = 2.5 Hz), and 7.34 (5, m); $^{13}C$ NMR ($CDCl_3$) δ 30.8 ($CH_2$), 55.5 ($CH_3$), 62.2 ($CH_2$), 65.8 (CH), 70.1 ($CH_2$), 71.9 (CH), 98.8 (CH), 127.6 (CH), 127.8 (CH), 128.5 (CH), and 137.9 (C); EIMS (70 eV) *m/z* (rel intensity) 238 ($M^+$, 0.5), 207 (1), 206 (3), 189 (0.5), 188 (0.5), 178 (1), 177 (8), 163 (2), 134 (2), 117 (3), 108 (2), 107 (4), 105 (4), 100 (4), 99 (4), 92 (14), 91 (100), 87 (11), 65 (10), 59 (18); HRMS calcd for $C_{13}H_{18}O_4$ 238.1205, found 238.1199.

**Methyl 4-*O*-Benzyl-3-*O*-methyl-2-deoxy-β-D-*erythro*-pentopyranoside (6).** To a suspension of NaH (497 mg, 20.7 mmol) in dry THF (10 mL) at 0-5 °C was added a solution of alcohol **4** (1.82 g, 7.66 mmol) in THF (15 mL). After 1 h, iodomethane (1.88 g, 13.2 mmol) was added and the mixture allowed to attain room temperature. After 17.5 h, the mixture was cooled in an ice bath and the reaction was quenched by careful addition of water (20 mL). The mixture was extracted with ether (6 x 50 mL) and the combined organic phases were dried ($MgSO_4$), filtered, and concentrated *in vacuo* to give methyl ether **6** (1.82 g, 7.21 mmol, 94%) as a pale yellow oil homogenous by TLC ($R_f$ 0.42, 40% EtOAc/hexanes). $[\alpha]_D^{26}$ -89.0° (*c* 0.76, $CH_2Cl_2$); IR ($CHCl_3$) $cm^{-1}$ 2904, 1205, 1060; $^1H$ NMR ($CDCl_3$ ) δ 1.87 (1, dm, J = 13 Hz), 2.15 (1, ddd, J = 13 Hz, J = 10 Hz, J = 3 Hz), 3.33 (3, s), 3.34 (3, s), 3.60-3.85 (4, m), 4.72 (2,

s), 4.81 (3, t, J = 3 Hz), and 7.26-7.41 (5,m); $^{13}C$ NMR ($CDCl_3$) δ 31.4 ($CH_2$), 55.0 ($CH_3$), 55.9 ($CH_3$), 60.6 ($CH_2$), 71.2 ($CH_2$), 71.8 (CH), 74.2 (CH), 99.0 (CH), 127.5 (CH), 127.7 (CH), 128.2 (CH), and 138.4 (C); EIMS (70 eV) *m/z* (rel intensity) 252 ($M^+$, 0.1), 221 (1), 220 (5), 189 (1), 181 (1), 180 (0.5), 177 (1), 164 (0.5), 159 (0.5), 135 (4), 134 (3), 114 (5), 107 (2), 105 (3), 103 (9), 101 (23), 91 (100), 88 (7), 87 (7), 75 (7), 71 (9), 65 (7), 58 (6), 54 (7); HRMS calcd for $C_{14}H_{20}O_4$ 252.1362, found 252.1356.

**Methyl 3-*O*-Methyl-2-deoxy-β-D-*erythro*-pentopyranoside (7).** A solution of benzyl ether **6** (277 mg, 1.10 mmol) in absolute ethanol (50 mL) was stirred with 10% palladium on carbon catalyst (50 mg) at room temperature under hydrogen (1 atm, balloon). After 12 h, the catalyst was removed by centrifugation and volatiles removed *in vacuo*. Chromatography of the residue on silica gel 60 (25 g) eluted with 50% EtOAc/hexanes afforded alcohol **7** (179 mg, 1.10 mmol, 100%) as an oil homogenous by TLC ($R_f$ 0.15, 40% EtOAc/hexanes). $[\alpha]_D^{27}$ -204.9° (*c* 2.65, $CH_3OH$); IR ($CDCl_3$) $cm^{-1}$ 3568, 2932, 1059, 1001; $^1H$ NMR ($CDCl_3$) δ 1.80-2.05 (2, m), 2.77 (1, s), 3.34 (3, s), 3.35 (3, s), 3.60-3.70 (1, m) 3.75 (2, m), 3.93 (1, br s), and 4.79 (1, t, J = 3 Hz); $^{13}C$ NMR ($CDCl_3$) δ 30.1 ($CH_2$), 54.7 ($CH_3$), 55.4 ($CH_3$), 62.2 ($CH_2$), 65.1 (CH), 73.6 (CH), and 98.6 (CH).

**Methyl 3-*O*-Methyl-4-*O*-*p*-toluenesulfonyl-2-deoxy-β-D-*erythro*-pentopyranoside (8).** From methyl 3-*O*-methyl-2-deoxy-β-D-*erythro*-pentopyranoside (**7**): To a solution of alcohol **7** (977 mg, 6.02 mmol) in dry pyridine (14 mL) at 0-5 °C was added *p*-toluenesulfonyl chloride (3.57 g, 18.7 mmol). The reaction mixture was stirred at 0-5 °C for 0.5 h, kept at -5 °C for 48 h, then diluted with ether (200 mL) and washed with water (50 mL), cold aqueous 10% HCl (2 x 50 mL), water (50 mL), and saturated aqueous $NaHCO_3$ (2 x 50 mL). The organic phase was dried ($MgSO_4$), filtered, and volatiles were removed *in vacuo*. The residue was chromatographed on silica gel 60 (250 g) eluted with 30% EtOAc/hexanes to afford tosylate **8** (1.74 g, 5.51 mmol, 91%) as an oil homogenous by TLC ($R_f$ 0.36, 40% EtOAc/hexanes).

From methyl 4-*O*-*p*-toluenesulfonyl-2-deoxy-β-D-*erythro*-pentopyranoside (**10**): To a solution of tosylate **10** (102 mg, 0.34 mmol) and iodomethane (424 mg, 3.0 mmol) in DMF (1 mL) at room temperature was added silver(I) oxide (151 mg, 0.650 mmol) in one portion. The solution was stirred for 27 h, then diluted with chloroform (10 mL), filtered, and volatiles removed *in vacuo*. The residue was taken up in ether (40 mL), and the solution washed with water (2 x 10 mL), dried ($MgSO_4$), filtered, and volatiles removed *in vacuo*. The residue was chromatographed on silica gel 60 (25 g) eluted with 20% EtOAc/hexanes to afford **8** (103 mg, 0.326 mmol, 96%) as an oil homogenous by TLC ($R_f$ 0.36, 40% EtOAc/hexanes). $[\alpha]_D^{26}$ -137.6° (*c* 4.45, $CH_3OH$); IR ($CDCl_3$) $cm^{-1}$ 2981, 2932, 1363, 1176; $^1H$ NMR ($CDCl_3$) δ 1.81-2.04 (2, m), 2.43 (3, s), 3.14 (3, s), 3.32 (3, s), 3.61 (1, dt, J = 11 Hz, J = 3 Hz), 3.72 (1, d, J = 13 Hz), 3.80 (1, dd, J = 13 Hz, J = 3 Hz), 4.79 (2, br s), 7.31 (2, d, J = 8 Hz), and 7.85 (2, d, J = 8 Hz); $^{13}C$ NMR ($CDCl_3$) δ 21.5 ($CH_3$), 31.2 ($CH_2$), 55.0 ($CH_3$), 55.8 ($CH_3$), 60.7 ($CH_2$), 71.9 (CH), 74.5 (CH), 98.5 (CH), 127.8 (CH), 129.5 (CH), 134.0 (C), and 144.5 (C); EIMS (70 eV) *m/z* (rel intensity) 316 ($M^+$, 0.5), 315 (1), 286 (0.5), 285 (2), 254 (1), 253 (9), 228 (3), 225 (1), 215 (3), 199 (5), 198 (8), 156 (9), 155 (100), 144 (11), 139 (9), 134 (3), 129 (2), 117 (2), 114 (2), 113 (16), 112 (7), 111 (2), 103 (50), 101 (23), 99 (4), 92 (6), 91 (70), 87 (6), 85 (5), 84 (9), 81 (15), 75 (22), 71 (17), 65 (16), 58 (19); HRMS calcd for $C_{14}H_{20}O_6S$ 316.0980, found 316.0981.

**Methyl 3-*O*-Benzyl-4-*O*-*p*-toluenesulfonyl-2-deoxy-β-D-*erythro*-pentopyranoside (9).** To a solution of alcohol **5** (557 mg, 2.34 mmol) in dry pyridine (6 mL) at 0-5 °C was added *p*-toluenesulfonyl chloride (1.38 g, 7.24 mmol). The reaction mixture was stirred at 0-5 °C for 0.5 h and at -5 °C for 72 h, then diluted with ether (200 mL) and washed with water (50 mL), cold 10% aqueous HCl (2 x 50 mL), water (50 mL), and saturated aqueous $NaHCO_3$ (2 x 50 mL). The organic phase was dried ($MgSO_4$), filtered, and volatiles were removed *in vacuo*. The residue was chromatographed on silica gel 60 (50 g) and eluted with 30% EtOAc/hexanes to afford tosylate **9** (871 mg, 2.22 mmol, 95%) as a white solid, mp 115-116 °C, homogenous by TLC ($R_f$ 0.50, 40% EtOAc/hexanes). $[\alpha]_D^{24.5}$ -72.8° (*c* 0.8, $CH_2Cl_2$); $^1H$ NMR ($CDCl_3$) δ 1.85-1.95 (1, m), 2.00-2.13 (1, m), 2.38 (3, s), 3.30 (3, s), 3.73 (1, d, J = 13 Hz), 3.80-3.90 (1, m), 3.87 (1, dd, J = 13 Hz, J = 3 Hz), 4.36 (1, d, J = 12 Hz), 4.42 (1, d, J =12 Hz), 4.80 (2, br s), 7.17-7.33 (7, m), and 7.80 (2, d, J = 8 Hz); $^{13}C$ NMR ($CDCl_3$) δ 21.6 ($CH_3$), 31.7 ($CH_2$), 55.1 ($CH_3$), 61.0 ($CH_2$), 70.1 (CH), 70.1 ($CH_2$), 75.2 (CH), 98.7 (CH), 127.5 (CH), 127.6 (CH), 127.9 (CH), 129.3 (CH), 129.6 (CH), 133.8 (C), 136.7 (C), and 143.9 (C).

Anal. Calcd for $C_{20}H_{24}O_6S$: C 61.20, H 6.16; found: C 61.40, H 5.95.

**Methyl 4-*O*-*p*-Toluenesulfonyl-2-deoxy-β-D-*erythro*-pentopyranoside (10).** A solution of tosylate **9** (211 mg, 0.538 mmol) in ethyl acetate (20 mL) was stirred at room temperature with 10% palladium on carbon catalyst (50 mg) under hydrogen (1 atm, balloon) for 16 h. The flask was flushed with argon and the volatiles were removed *in vacuo*. The residue was resuspended in dry absolute ethanol (20 mL), the flask was flushed repeatedly with hydrogen, and the mixture stirred under hydrogen (1 atm, balloon) for 17 h. The catalyst was removed by centrifugation and volatiles were removed *in vacuo*. Chromatography of the residue on silica gel 60 (25 g) eluted with 30% EtOAc/hexanes afforded alcohol **10** (136 mg, 0.450 mmol, 84%) as a white solid, mp 115-116 °C, homogenous by TLC ($R_f$ 0.29, 40% EtOAc/hexanes). $[\alpha]_D^{26}$ -113.9° (*c* 1.6, $CHCl_3$); IR ($CHCl_3$) $cm^{-1}$ 3618, 1597, 1475, 1365, 1175, 1064, 929; $^1H$ NMR ($CDCl_3$) δ 1.88-1.95 (2, m), 2.08 (1, d, J = 8 Hz), 2.45 (3, s), 3.31 (3, s), 3.73 (2, d, J = 3 Hz), 4.05-4.20 (1, m), 4.66-4.72 (1, m), 4.77 (1, t, J = 3 Hz), 7.35 (2, d, J = 8 Hz) and 7.84 (2, d, J = 8 Hz); $^{13}C$ NMR ($CDCl_3$) δ 21.5 ($CH_3$), 33.9 ($CH_2$), 55.1 ($CH_3$), 60.2 ($CH_2$), 63.3 (CH), 78.4 (CH), 98.5 (CH), 127.7 (CH), 129.8 (CH), 133.4 (C), and 144.9 (C).

Anal. Calcd for $C_{13}H_{18}O_6S$: C 51.65, H 6.00; found: C 51.36, H 5.81.

**Methyl 4-Azido-3-*O*-methyl-2,4-deoxy-α-L-*threo*-pentopyranoside (11).** A suspension of tosylate **8** (969 mg, 3.41 mmol) and sodium azide (1.18 g, 18.1 mmol) in dimethyl sulfoxide (30 mL) was stirred at 130-140 °C for 1 h. The reaction mixture was cooled to room temperature, poured into a mixture of ice cold water (150 mL) and saturated aqueous $NaHCO_3$ (30 mL), and extracted with hexanes (3 x 150 mL). The combined extracts were dried ($MgSO_4$), filtered, and volatiles removed *in vacuo*. The residue was chromatographed on silica gel 60 (30 g) eluted with 50% EtOAc/hexanes to afford azide **11** (0.594 g, 3.17 mmol, 93%) as an oil homogenous by TLC ($R_f$ 0.43, 40% EtOAc/hexanes). $[\alpha]_D^{25}$ -12.5° (*c* 0.4, $CHCl_3$); IR ($CDCl_3$) $cm^{-1}$ 2109; $^1H$ NMR ($CDCl_3$) δ 1.55 (1, ddd, J = 13 Hz, J = 11 Hz, J = 4 Hz), 2.25 (1, ddd, J = 13 Hz, J = 5 Hz, J = 2 Hz), 3.32 (3, s), 3.42-3.67 (4, m), 3.43 (3, s), and 4.77 (1, dd, J = 4 Hz, J = 2 Hz); $^{13}C$ NMR ($CDCl_3$) δ 34.4 ($CH_2$), 54.8 (CH), 56.6 ($CH_3$), 60.2 ($CH_2$), 61.2 (CH), 76.8 (CH), and 98.6 (CH).

**Methyl 4-(*N*-Acetyl)amino-3-*O*-methyl-2,4-deoxy-α-L-*threo*-pentopyranoside (12).** A solution of azide **11** (594 mg, 3.17 mmol) in methanol (132 mL) containing acetic anhydride (4.3 mL) was stirred with platinum(IV) oxide (200 mg) under hydrogen (1 atm, balloon) for 39 h. After the catalyst was removed by centrifugation, triethylamine (10 mL) was added, and volatiles were removed *in vacuo*. The residue was chromatographed on silica gel 60 (50 g) eluted with ethyl acetate to give **12** as a yellowish solid. Recrystallization from ether (30 mL) gave **12** (603 mg, 2.967 mmol, 93%) as a white solid, mp 105-106 °C, homogenous by TLC ($R_f$ 0.12, EtOAc). $[a]_D^{26.5}$ -79.2° (c 0.5, $CH_2Cl_2$); IR ($CH_2Cl_2$) $cm^{-1}$ 3430, 1674; $^1H$ NMR ($CDCl_3$) δ 1.70-1.90 (2, m), 1.95 (3, s), 3.37 (3, s), 3.34 (3, s), 3.45-3.55 (2, m), 3.85-4.00 (2, m), 3.96 (1, br s), and 5.78 (1, br s); $^{13}C$ NMR ($CDCl_3$) δ 23.2 ($CH_3$), 33.0 ($CH_2$), 47.9 (CH), 55.6 ($CH_3$), 56.2 ($CH_3$), 62.6 ($CH_2$), 75.2 (CH), 99.3 (CH), and 170.0 (C).

**Methyl 4-Ethylamino-3-*O*-methyl-2,4-deoxy-α-L-*threo*-pentopyranoside (2b).** In a dry, 250 mL flask equipped with a reflux condenser was suspended $LiAlH_4$ (124 mg, 3.26 mmol) in THF (10 mL). The mixture was heated to reflux for 20 min, external heating was discontinued, and amide **12** (254 mg, 1.25 mmol) in THF (35 mL) was added dropwise over 0.5 h. The mixture was heated to reflux for 11 h, then cooled to 0 °C and the reaction quenched by addition of water (129 μL), 4N NaOH (129 μL), and water (382 μL). The precipitated salts were removed by filtration and extracted with ether using a sohxlet apparatus. The extracts were combined and volatiles were removed *in vacuo*. The residue was chromatographed on silica gel 60 (25 g) eluted with ethyl acetate to give amine **2b** (215 mg, 1.14 mmol, 91%) as an oil homogenous by TLC ($R_f$ 0.23, 10% methanol/EtOAc). $[\alpha]_D^{25}$ -56.8° (*c* 1.4, $CHCl_3$), lit.[3] $[\alpha]_D^{23}$ -56.7° (*c* 1.0, $CHCl_3$); $^1H$ NMR ($CDCl_3$) δ 1.12 (3, t, J = 7 Hz), 1.52 (1, dm, J = 13 Hz), 1.95 (1, br s), 2.11 (1, dm, J = 13 Hz), 2.50-2.80 (3, m), 3.20-3.55 (2, m), 3.32 (3, s), 3.34-3.49 (4, m), 3.35 (3,s), 3.73-3.78 (1, m), and 4.79 (1, br s); $^{13}C$ NMR ($CDCl_3$) δ 15.5 ($CH_3$), 33.6 ($CH_2$), 41.9 ($CH_2$), 54.5 ($CH_3$), 55.9 ($CH_3$), 58.9 (CH), 61.8 ($CH_2$), 76.7 (CH), and 98.8 (CH).

**Methyl 4-(*N*-Acetyl)ethylamino-3-*O*-methyl-2,4-deoxy-α-L-*threo*-pentopyranoside (13).** To a well-stirred solution of amine **2b** (129 mg, 0.682 mmol) in triethylamine (10 mL) at 0-5 °C was added acetyl chloride (242 μL, 3.41 mmol) dropwise. The mixture was allowed to attain room temperature and stirred for 4 h. The mixture was poured into water (50 mL) and extracted with $CH_2Cl_2$ (3 x 20 mL). The organic extracts were dried ($MgSO_4$), filtered, and volatiles removed *in vacuo*. The residue was chromatographed on silica gel 60 (25 g) eluted with ethyl acetate to give the *N*-acetylated sugar **13** (142 mg, 0.614 mmol, 90%) as an oil homogenous by TLC ($R_f$ 0.20, EtOAc). $[\alpha]_D^{25}$ -98° (*c* 0.4, $CHCl_3$), lit.[3] $[\alpha]_D^{25}$ -99.0° (*c* 0.96, $CHCl_3$), lit.[2] $[\alpha]_D^{20}$ -96.0° (*c* 0.9, $CHCl_3$); $^1H$ NMR ($CDCl_3$) δ 1.09-1.25 (4, m), 1.48-1.60 (1, m), 2.08-2.15 (3, m), 2.29-2.40 (1, m), 3.09-4.06 (11, m), and 4.81 (1, br s); $^{13}C$ NMR ($CDCl_3$) δ 14.7 and 15.4 ($CH_3$), 22.3 and 22.4 ($CH_3$), 35.3 and 36.8 ($CH_2$), 54.7 and 54.9 ($CH_3$), 55.5 and 56.4 ($CH_3$), 59.8 and 59.8 ($CH_2$), 59.7 (CH), 71.8 and 72.7 (CH), 98.8 and 98.9 (CH), and 170.9 and 171.3 (C); EIMS (70 eV) *m/z* (rel intensity) 231 ($M^+$, 0.3), 216 (1), 200 (4), 184 (1), 171 (1), 170 (1), 169 (2), 168 (12), 167 (2), 156 (5), 144 (13), 143 (3), 142 (1), 140 (2), 139 (2), 130 (2), 129 (6), 128 (3), 126 (21), 114 (6), 113 (33), 112 (37), 103 (16), 101 (19), 88 (55), 87 (11), 86 (21), 84 (12), 73 (11), 72 (11), 71 (100), 70 (12), 59 (13), 56 (33); HRMS calcd for $C_{11}H_{21}NO_4$ 231.1470, found 231.1469.

**Methyl 4-(*N*-Carbobenzyloxy)amino-3-*O*-methyl-2,4-deoxy-α-L-*threo*-pentopyranoside (14).** A solution of azide **11** (460 mg, 2.46 mmol) in ethyl alcohol (4 mL) was stirred with 10% palladium on carbon catalyst (50 mg) at room temperature under hydrogen (1 atm, balloon) for 15 h. The catalyst was removed by centrifugation and volatiles were removed *in vacuo*. The residue was taken up in THF (10 mL), mixed with sodium carbonate (520 mg), and cooled to 0 °C. Benzyl chloroformate (0.526 mL, 3.69 mmol) was added dropwise and the reaction mixture stirred for 3 h. The reaction was quenched by addition of $NaHCO_3$ (100 mg), ether (100 mL), and water (15 mL). The organic phase was separated, dried ($MgSO_4$), filtered, and volatiles were removed *in vacuo*. The residue was chromatographed on silica gel 60 (25g) eluted with ethyl acetate to give urethane **14** (386 mg, 53%) as an oil homogenous by TLC ($R_f$ 0.61, EtOAc). $[\alpha]_D^{26.5}$ -48.9° (*c* 2.5, $CH_2Cl_2$); IR ($CDCl_3$) $cm^{-1}$ 3433, 1718; $^1H$ NMR ($CDCl_3$) δ 1.73 (1, m), 1.98-2.03 (2, m), 3.36 (3, s), 3.44 (3, s), 3.48-3.93 (4, m), 4.68 (1, t, J = 3 Hz), 5.21 (2, s), 5.23 (1, br s), and 7.33 (5, s); $^{13}C$ NMR ($CDCl_3$) δ 33.2 ($CH_2$), 50.1 (CH), 55.3 ($CH_3$), 56.2 ($CH_3$), 62.2 ($CH_2$), 66.7 ($CH_2$), 75.6 (CH), 99.0 (CH), 128.0 (CH), 128.0 (CH), 128.4 (CH), 136.2 (C), and 155.9 (C).

Anal. Calcd for $C_{14}H_{21}NO_5$: C 61.00, H 7.17; found: C 60.91, H 7.04.

**Methyl 4-(*N*-Carbobenzyloxy)methylamino-3-*O*-methyl-2,4-deoxy-α-L-*threo*-pentopyranoside (15).** To a solution of **14** (123 mg, 0.416 mmol) and iodomethane (261 mg, 1.84 mmol) in DMF (1.5 mL) at room temperature was added silver oxide (344 mg, 1.48 mmol) in one portion. The solution was stirred for 20 h, then diluted with chloroform (20 mL), filtered, and volatiles were removed *in vacuo*. The residue was partitioned between water (200 mL) and ether (3 x 100 mL). The organic extracts were combined, dried ($MgSO_4$), filtered, and volatiles removed *in vacuo*. The residue was dissolved in ethyl acetate (5 mL), filtered through a silica gel plug, and volatiles removed *in vacuo* to give **15** (105 mg, 0.339 mmol, 82%) as an oil homogenous by TLC ($R_f$ 0.51, EtOAc). $[\alpha]_D^{25.5}$ -40.4° (*c* 0.75, $CH_2Cl_2$); IR ($CH_2Cl_2$) $cm^{-1}$ 1720; $^1H$ NMR ($CDCl_3$) δ 1.45-1.50 (1, m), 2.19-2.26 (1, m), 2.80-2.84 (3, m), 3.22-3.28 (6, m), 3.50-3.74 (4, m), 4.69 (1, br s), 5.03-5.09 (2, m) and 7.26-7.30 (5, m); $^{13}C$ NMR ($CDCl_3$) δ 34.8 ($CH_2$), 54.6 (CH), 55.5 and 55.7 ($CH_3$), 57.0 ($CH_3$), 58.7 and 59.0 ($CH_2$), 67.0 ($CH_2$), 71.7 and 72.0 (CH), 98.7 (CH), 127.6 and 127.7 (CH), 128.3 (CH), 136.6 (C), and 156.4 (C).



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