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Synthesis of a stable, storable and differentially protected acyclic precursor of D-amicetose and its conversion to 4-*O*-benzyl-protected D-amicetose

Indrapal Singh Aidhen* & N Satyamurthi

Department of Chemistry, Indian Institute of Technology Madras, Chennai 600 036, India
E-mail: isingh@iitm.ac.in

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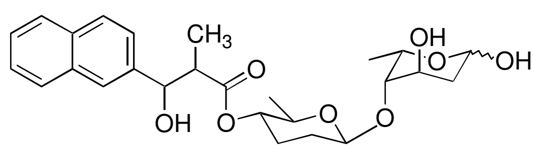
Two carbon chain homolgation of enantiopure four carbon *erythro* configured iodo derivative **5** with *N*-methoxy-*N*-methyl-2-phenylsulfonylacetamide **6** affords for the first time a stable and storable precursor **3** of D-amicetose in the acyclic form, wherein the sensitive aldehyde is masked as a Weinreb amide. The differential protection in this acyclic derivative offers all the potential to exclusively arrive at the pyranose form of the target dideoxy-sugar.

Keywords: Lactone, homologation, amide, deoxysugar

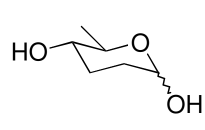
Deoxy sugar moieties and oligosaccharides derived from them are more and more being recognised as structural elements contributing to the general mechanism of action of bioactive drugs. They are widespread substructure units of microbial secondary metabolites *e.g.*: macrolides, anthracyclines or angucyclines. For instance, axenomycin **1** is an antibiotic produced by *Streptomyces lysandri* n. sp. and has activity against plateworms and yeasts[1]. In axenomycin, axenose is glycosylated at the fourth position with the trideoxy sugar D-amicetose **2** (**Figure 1**). D-Amicetose, 2, 3, 6-trideoxy-D-erythro-hexose is a constituent of antibiotics such as amicetin[2] isolated from *Streptomyces plicatus* and *Streptomyces vinaceus-drappus*. Deoxyhexoses, have therefore continued to remain valuable and important targets for synthesis[3].

D-Amicetose and its derivatives have been prepared previously by a number of synthetic routes[4]. These routes either use carbohydrate precursors such as derivatives of glucose[4a-e,4g,4i] and mannose[4k] and few non-carbohydrate precursors such as L-glutamic acid[4f,4i] and (*S*)-glycidyl sulfide[4g]. Despite the high stereoselectivity reported from the synthetic routes involving the non-carbohydrate precursors, the products are contaminated by the undesired stereoisomers and demand further purification. In fact, two syntheses starting from achiral precursors[4h,4n] and involving Diels-Alder reaction followed by asymmetric hydroboration reaction lead to a racemic mixture of D-L isomers thereby necessitating separation by optical resolution, chromatographic or enzymatic methods. While two syntheses have been reported involving one carbon homologation of substituted γ-butyrolactone obtained from L-glutamic acid[4f,4i], the other synthesis involves stepwise chain extension by four carbons and later excision by one carbon on (*S*)-glycidyl sulfide[4g], thereby making the synthesis cumbersome, indirect and very lengthy.

Realizing the fact that there is no availability of a stable and storable precursor of this important sugar, which would enable convenient and immediate access to pyranose or furanose form at will, the synthesis of **3** was aimed at fulfilling the same objective. The Weinreb amide functionality in **3** provides a robust



1
Axenomycin



2
Amicetose

Figure 1

equivalence to the sensitive aldehyde group and the orthogonal protection at C_4 and C_5 allows for the exclusive obtainement of either furanose or pyranose form of the target dideoxy-sugar, respectively. The present work disclosed herein therefore constitutes first synthesis of differentially protected acyclic derivative of D-amicetose (**Figure 2**). The successful transformation of **3** to 4-*O*-benzyl-D-amicetose **4**, fully demonstrates the usefulness of the proposed acyclic precursor **3**. The strategy for the synthesis of **3** relies on chain extension of the iodo derivative **5** with two carbon homologating agent **6** developed by this group[5]. The inbuilt *erythro* configuration and enantiopurity of **5** ensures complete enantiopurity of the homologated product **3**. Apparently, chain extension of D-*erythro*-2,3-dihydroxybutanal carrying similar protection as in **5** with *N*-methoxy-*N*-methyl-2-(triphenylphosphoranylidene) acetamide[6] or its Horner-Wadsworth-Emmons variant[7] would appear to be an attractive alternative for the synthesis of **3**. However, iodo derivative **5** was chosen for chain extension because there were reports in literature indicating epimerization at the α-stereocenter during Wittig reactions with aldehydes bearing heteroatom at the α carbon[8]. The apparent attractiveness of Wittig approach gets marred by these factual observations. No fear of any epimerization would exist with the use of iodo-derivative **5**.

The requisite orthogonally protected iodo derivative **5** for the synthesis was obtained as depicted in **Scheme I**. The dihydroxy ester **7** (Ref. 9) was monobenzylated under the non-basic conditions [BnBr (1.2 equiv)/ Ag_2O] to prevent epimerization at C-2 carbon. Although the described monobenzylation conditions afforded the product as a mixture of regioisomers **8a**, **8b** in the ratio 3.7:1, the two can be readily separated using silica-gel column chromatography[10]. The β-hydroxyl group in **8a** is now protected as silyl ether under standard conditions to furnish **9** in 76% yields. Subsequent $LiAlH_4$ reduction of **9** led to the desired alcohol **10a**, however in a low yield of 36% only. The major product in this reaction was the desilylated compound **10b** in 49% yield. No improvement occurred by changes in the reaction conditions and work-up procedure. Finally, a change of reducing agent from $LiAlH_4$ to $NaBH_4$ in ethanol, led to substantial advantage of convenience and also moderate increase in the yield of **10a**. Tosylation of the alcohol **10a** followed by conventional displacement of the tosylate group in **11** by the iodide ion led to the requisite iodo derivative **5**.

The iodo derivative **5** was two carbon homologated using **6** to give **12** as a diastereomeric mixture under mild conditions using K_2CO_3 in DMF (**Scheme II**). Clean desulfonylation of **12**, which ensued under sodium-amalgam conditions, led to the synthesis of **3**, which is the first stable and storable precursor of differentially protected D-amicetose in its acyclic form. The usefulness of this derivative was fully demonstrated by its successful conversion to 4-O-benzyl protected D-amicetose **4** in excellent yields. The amide derivative **3** on desilylation with Bu_4NF afforded **13**, and subsequent reduction with $LiAlH_4$ furnished the target **4**.

In summary, synthesis of a potential precursor for enantiopure synthesis of 4-O-benzyl protected D-amicetose has been realized. The most attractive feature being that, the final precursor is stable and storable wherein the sensitive aldehyde group is masked as a robust amide group and the differential

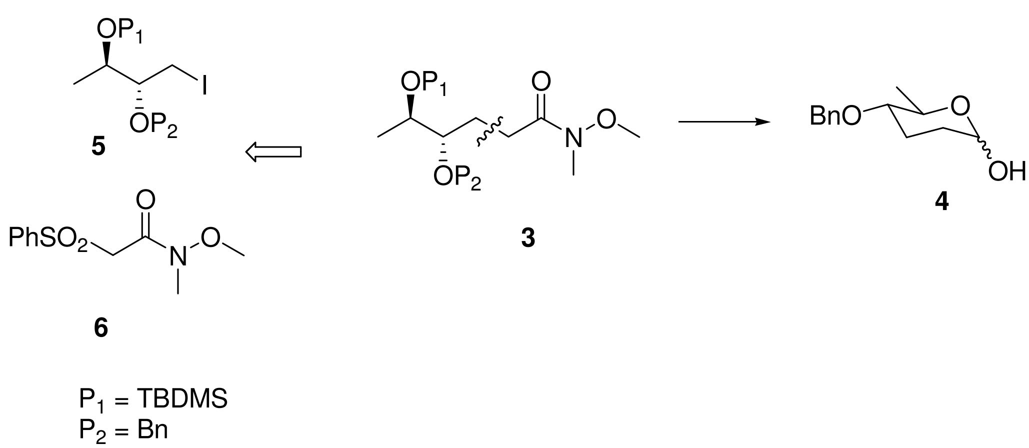
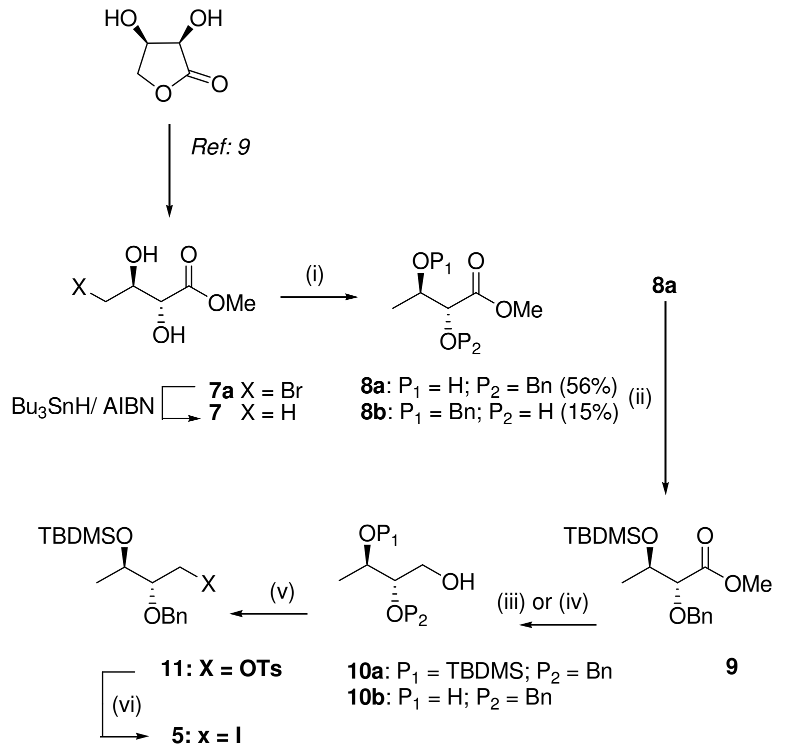


Figure 2



(iii) **10a**: 36%; **10b**: 49%
(iv) **10a**: 56%; **10b**: 31%

(i) Ag_2O, 1.2 equ BnBr, ether 24hr (ii) TBDMSiCl, NEt_3, DMAP, CH_2Cl_2, 0 °C, 48hr, 76% (iii) $LiAlH_4$, THF, 0°C, 45 min
(iv) $NaBH_4$, EtOH, RT, 48hr (v) *p*-TsCl, NEt_3, DMAP, CH_2Cl_2, RT, 24hr, 93%
(vi) NaI, acetone reflux, 24hr, 90 %

Scheme I

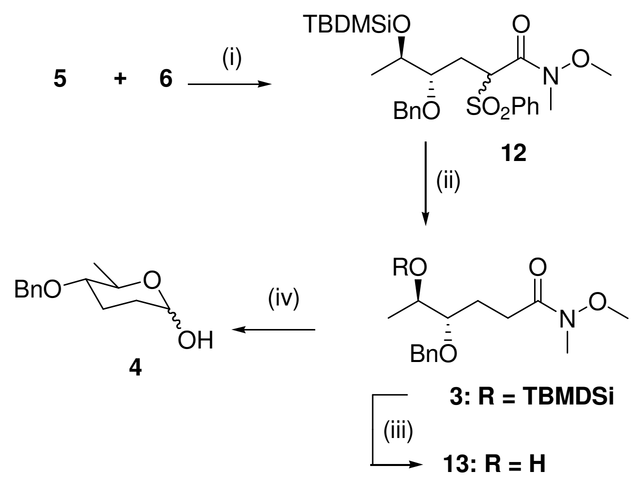
protection allowed for the exclusive obtainment of the sugar in the desired pyranose form.

Experimental Section

All solvents were distilled and dried using the usual recommended procedures. ^1H NMR (300 MHz) and ^{13}C NMR (75 MHz) spectra were recorded using deuteriochloroform ($CDCl_3$) as solvent and tetramethylsilane (TMS) as a reference. For selected compounds, the ^1H NMR was obtained on 400 MHz Bruker machine. For monitoring progress of reactions TLC's were performed on pre-coated silica-gel plates obtained from Merck. The TLC plates were developed by dipping in a solution prepared by adding ammonium ceric sulfate (1 g), and ammonium molybdate (21 g) to concentrated sulfuric acid (31 mL) and diluted to 500 mL with distilled water. The TLC plates were later heated upto 100°C on hot plate for development.

Methyl (2*R*, 3*R*)-2, 3-dihydroxybutanoate, 7

A solution of D-erythronolactone[11] (2 g, 16.9 mmol) in methanol (10 mL) was saturated with HBr at 0°C and stirred for 48 hr, after which the solution was evaporated and the residue subjected to silica-gel chromatography. The isolated yield of the 4-bromo-2,3-dihydroxy butanoate **7a**, was 2.5 g (69%). The bromo derivative **7a** was immediately subjected to radical reduction using tributyltinhydride. To a solution of compound **7a** (1.6 g, 5 mmol) in benzene (25 mL) was added Bu_3SnH (1.6 mL, 6 mmol) and the mixture was heated to reflux at 80°C. Catalytic amount of AIBN dissolved in benzene (1 mL) was



(i) K_2CO_3, DMF, 70°C 48hr, 76% (ii) Na(Hg), Na_2HPO_4, MeOH, 0°C,15hr, 85% (iii) 1M Bu_4NF in THF, 14hr, 75% (iv)$LiAlH_4$, THF, -78°C, 15 min, 81%

Scheme II

added and the mixture refluxed for 1.25 hr, after which the solution was evaporated over rotary evaporator and the obtained residue was subjected to silica-gel chromatography. The isolated yield of compound **7** was 0.560 g, 83%, as colorless syrup. R_f 0.16 (Hexane/Ethyl acetate, 1:1). $[\alpha]_D$ = -15.8° (c = 1.1, MeOH), Lit[12]: $[\alpha]_D$ = -16° (c = 1.1, MeOH); ^{1}H NMR ($CDCl_3$, 300MHz): δ 1.18 (d, *J* = 6Hz, 3H, C*H*$_3$); 3.46 (bs, 2H, O*H*), 3.80 (s, 3H, COOC*H*$_3$), 4.06-4.10 (m, 1H, -C*H*OH), 4.24 (d, *J* = 6 Hz, 1H, C*H*OH); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 17.7 (-*C*H$_3$), 53.0 (-COO*C*H$_3$), 69.5 (-*C*HOH), 74.9 (-*C*HOH), 173.5 (-*C*OOCH$_3$); IR (neat): 3418, 2935, 1736 cm^{-1}; HRMS (CI): *m/z* M+H$^+$, Found 135.0659. Calcd 135.0658.

Methyl (2*R*, 3*R*)-2-*O*-benzyl-3-hydroxybutanoate, 8a

To a suspension of silver oxide (0.56 g, 2.4 mmol) in diethyl ether (4 mL) was added the ester **7** (Ref. 9) (0.27 g, 2.0 mmol) and benzyl bromide (0.28 mL, 2.4 mmol) and the solution was stirred at RT for a period of 24 hr. The reaction mixture was filtered through celite pad, the filtrate evaporated and the residue subjected to silica-gel chromatography using hexane/ethyl-acetate (9:1) as eluent to give 0.25 g of **8a** (56%) and 0. 067 g of **8b** (15%).

R_f: 0.36 (Hexane/Ethyl acetate 1:1). Nature: colourless gum; $[\alpha]_D$: 80.0° (c =1, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 300MHz): δ 1.22 (d, *J* = 6.3 Hz, 3H, C*H*$_3$), 2.40 (bs, 1H, OH), 3.78 (s, 3H, -OC*H*$_3$), 3.96 (d, *J* = 4.5 Hz, 1H, C*H*OBn), 4.09-4.13 (m, 1 H, C*H*OH), 4.61 (AB quartet, *J* = 11.7 Hz, 2H, -OC*H*$_2$Ph), 7.29-7.37 (m, 5H, Ar-*H*); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 18.8 (CH_3), 52.4 (-OCH_3), 68.7 (CHOH), 73.2 (OC*H*$_2$Ph) 82.3 (CHOBn), 128.0, 128.5, 128.9, 137.4 (Ar-C), 171.6 (COOMe); IR (neat): 3426(b), 1743, 1606, 1402 cm^{-1}; HRMS (ESI): *m/z* (M+Na), Found: 247.0956. Calcd for $C_{12}H_{16}O_4$ + Na: 247.0946.

Data for the minor product **8b**: R_f: 0.45 (Hexane/Ethyl acetate 1:1). Nature: colourless gum; $[\alpha]_D$: -17.9° (c =1, $CHCl_3$); ^{1}H NMR($CDCl_3$, 300 MHz): δ 1.20 (d, *J* = 6.6 Hz, 3H, C*H*$_3$), 3.15 (b d, *J* = 5.7 Hz, 1H, OH), 3.76 (s, 3H, -OC*H*$_3$), 3.83-3.89 (m, 1H, C*H*OBn), 4.33 (dd, *J* = 5.7 and 3.3, 1 H, C*H*OH), 4.58 (AB quartet, *J* = 11.7 Hz, 2H, -OC*H*$_2$Ph), 7.23-7.33 (m, 5H, Ar-*H*); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 15.3 (CH_3), 52.9 (-OCH_3), 71.5 (CHOH), 73.7 (OC*H*$_2$Ph) 76.6 (CHOBn), 128.0, 128.1, 128.8, 138.4 (Ar-C), 173.4 (COOMe); IR (neat): 3420(b), 2930, 1751, 1597 cm^{-1}.

Methyl (2*R*, 3*R*)-2-*O*-benzyl-3-*O*-*tert*-butyldimethylsilyl-butanoate, 9

To a solution of ester **8a** (0.338 g, 1.50 mmol) in dichloromethane (3 mL) was added *tert*-butyldimethylsilyl chloride (0.272 g, 1.8 mmol), triethylamine (0.40 mL, 3 mmol) and 4-dimethylaminopyridine (catalytic) at 0°C and the solution was stirred for 48 hr at RT. The reaction mixture was poured into water (10 mL) and the solution extracted with dichloromethane (3×5 mL). The combined organic layers was washed with brine solution (10 mL), dried over sodium sulphate and the residue subjected to silica-gel column chromatography to afford **9** (0.388 g, 76%) as a colourless oil.

R_f: 0.45 (Hexane/Ethyl acetate 9:1). $[\alpha]_D$: 23.6° (c =1, $CHCl_3$); ^{1}H NMR($CDCl_3$, 300MHz): δ 0.04 (s, 3H, Si-C*H*$_3$), 0.07 (s, 3H, Si-C*H*$_3$), 0.90 (s, 9H, -C(C*H*$_3$)$_3$), 1.22 (d, *J* = 6.3 Hz, 3H, C*H*$_3$), 3.70 (s, 3 H, -COOC*H*$_3$), 3.78-3.81 (m 1H, C*H*O-Si), 4.20 (d, *J* = 5.4 Hz, 1H, C*H*OBn), 4.56 (AB quartet, *J* = 11.7 Hz, 2H, -OC*H*$_2$Ph), 7.25-7.32 (m, 5H, ArH); ^{13}C NMR ($CDCl_3$, 75 MHz): δ -4.71 (-SiCH_3), 0.41 (-SiCH_3), 16.2 (CH_3), 18.6 (-Si*C*(CH$_3$)$_3$), 26.0 (-C(*C*H$_3$)$_3$), 52.2 (-COO*C*H$_3$), 71.6 (O*C*H$_2$Ph), 75.8 (*C*HOSi), 77.0 (*C*HOBn), 127.9, 128.0, 128.7, 138.7 (Ar-C), 173.1 (COOMe); IR (neat): 3403(b), 2931, 2857, 1753, 1605 cm^{-1}; HRMS (EI): *m/z* (M$^+$), Found: 338.1909. Calcd for $C_{18}H_{30}O_4Si$: 338.1913.

2-*O*-Benzyl-3-*O*-*tert*-butyldimethylsilyl-4-deoxy-D-erythritol, 10a

To a solution of the ester **11** (0.738 g, 2.18 mmol) in dry ethanol (4 mL) was added sodium borohydride (0.082 g, 2.18 mmol) and the solution was stirred at RT for 48 hr. The solvent was removed from the reaction-mixture over rotary evaporator and the residue was subjected to silica-gel column chromatography to give 0.348 g (56%) of the product **10a** and 0.134 g (31%) of **10b**.

Data for **10a**: R_f: 0.7 (Hexane/Ethyl acetate 1:1). $[\alpha]_D$: -6.0° (c =1, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 300MHz): δ 0.07 (s, 3H, Si-C*H*$_3$), 0.08 (s, 3H, Si-C*H*$_3$), 0.89 (s, 9H, -C(C*H*$_3$)$_3$), 1.22 (d, *J* = 6.3 Hz, 3H, C*H*$_3$), 2.17 (bs, 1 H, -OH), 3. 28-3.47 (m, 1H, -OCH), 3.73-3.80 (m 2H, C*H*$_2$OH), 3.93-4.20 (m, 1H, OC*H*), 4.65 (dd, *J* = 11.5 Hz, 2H, -OC*H*$_2$Ph), 7.25-7.36 (m, 5H, ArH); ^{13}C NMR ($CDCl_3$, 75 MHz): δ -4.90 (-SiCH$_3$), -4.40 (-SiCH$_3$), 17.9 (-Si*C*(CH$_3$)$_3$), 20.5 (CH$_3$), 25.9 (-C(*C*H$_3$)$_3$), 61.0 (-CH$_2$OH), 69.5 (*C*HOSi), 72.4 (O*C*H$_2$Ph), 83.3 (*C*HOBn), 127.6, 127.7, 128.4, 138.3 (Ar-C); IR (neat): 3421, 2931, 1629, 1461 cm^{-1}; HRMS (CI): *m/z* (M+H), Found: 311.2038. Calcd for $C_{17}H_{30}O_3Si$ + H: 311.2042.

1-*p*-Toluenesulfonyl-2-*O*-benzyl-3-*O*-*tert*-butyl-dimethylsilyl-4-deoxy-D-erythritol, 11

To a solution of the alcohol **12a** (0.672 g, 2.16 mmol) in dichloromethane (4 mL) was added *p*-toluenesulfonylchloride (0.493 g, 2.59 mmol), triethylamine (0.57 mL, 4.32 mmol) and catalytic amount of 4-dimethylaminopyridine, and the solution was stirred at RT for 24 hr. The reaction mixture was then poured into cold water (10 mL) and extracted with dichloromethane (3×5 mL). The combined organic layers were dried over anhydrous sodium sulphate, evaporated and the residue was subjected to silica-gel column chromatography to furnish 0.933 g (93%) of the product **11**.

R_f: 0.6 (Hexane/Ethyl acetate 4:1). ^{1}H NMR ($CDCl_3$, 300MHz): δ -0.07 (s, 3H, Si-C*H*$_3$), -0.04 (s, 3H, Si-C*H*$_3$), 0.82 (s, 9H, -C(C*H*$_3$)$_3$), 1.16 (d, *J* = 6.3 Hz, 3H, C*H*$_3$), 2.43 (s, 3 H, -ArCH$_3$), 3. 39-3.43 (m, 1H, -OCH), 3.81-3.85 (m 1H, OCH), 4.07 (dd, *J* = 10.5, 6.2 Hz, 1H, OC*H*H′OTs), 4.10 (dd, *J* = 10.5, 3 Hz, 1H, - OCH*H*′OTs), 4.55 (AB quartet, *J* = 11.4 Hz, 2H, OCH$_2$Ph), 7.25-7.34(m, 2H, ArH), 7.78 (d, *J* = 8.2 Hz, 2H, ArH); ^{13}C NMR ($CDCl_3$, 75 MHz): δ -4.60 (-SiCH$_3$), -4.0 (-SiCH$_3$), 18.2 (-Si*C*(CH$_3$)$_3$), 20.7(CH$_3$), 22.0 (-Ar-CH$_3$) 26.1(-C(*C*H$_3$)$_3$), 68.4 (-CHOSi), 70.3 (*C*H$_2$OTs), 73.4 (O*C*H$_2$Ph), 81.8 (*C*HOBn), 128.0, 128.2, 128.4, 130.2, 133.2, 138.3, 145.1 (Ar-C).

1-Iodo-2-*O*-benzyl-3-*O*-*tert*-butyldimethylsilyl-1,4-dideoxy-D-erythritol, 5

To a solution of the tosylate **11**, (0.883 g, 1.9 mmol) in acetone (4 mL) was added sodium iodide (4.27 g, 28.5 mmol) and the solution was heated to reflux for 24 hr. The acetone was evaporated, water (10 mL) was added and the aq solution extracted with ethyl acetate (3×5 mL). The combined organic layers was dried over sodium sulphate, evaporated and the residue subjected to silica-gel column chromatography to give 0.723 g (90%) of the compound **5**.

R_f: 0.62 (Hexane/Ethyl acetate 9:1). $[\alpha]_D$: 5.8° (c =1, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 300MHz): δ -0.06 (s, 3H, Si-C*H*$_3$), -0.03 (s, 3H, Si-C*H*$_3$), 0.89 (s, 9H, -C(C*H*$_3$)$_3$), 1.22 (d, *J* = 6.3 Hz, 3H, C*H*$_3$), 2.86-2.89 (m, 1 H, C*H*H′I), 3. 30-3.36 (m, 2H, -OCH, -CH*H*′I), 3.72-3.76 (m 1H, OCH) 4.51 (AB quartet, *J* = 11.3 Hz, 2H, OCH$_2$Ph), 7.17-7.32(m, 5H, ArH); ^{13}C NMR ($CDCl_3$, 75 MHz): δ -4.60 (-SiCH$_3$), -4.1 (-SiCH$_3$), 8.5 (-CH$_2$I), 17.8 (-Si*C*(CH$_3$)$_3$), 19.9 (CH$_3$), 25.8 (-C(*C*H$_3$)$_3$), 70.0 (-CHOSi), 72.1 (-O*C*H$_2$Ph), 81.7 (*C*HOBn), 127.6, 127.7, 128.0, 137.7, (Ar-C); IR (neat): 2929, 2856, 1598 cm^{-1}; HRMS (CI): *m/z* (M+H), Found: 421.1047. Calcd for $C_{17}H_{29}IO_2Si$ + H: 421.1060.

***N*-methoxy-*N*-methyl-2, 3, 6-trideoxy-4-*O*-benzyl-5-*O*-*tert*-butyldimethylsilyl-D-eryt- hrohexonamide, 3**

The iodo compound **5** (0.745 g, 1.6 mmol) and *N*-methoxy-*N*-methyl-2-phenylsulfonylacetamide **6** (0.466 g, 1.92 mmol) were stirred with anhydrous K_2CO_3 (0.662 g, 4.8 mmol) in dry DMF (3.2 mL) at 70°C for 48 hr. Water (5 mL) was added, the solution was extracted with EtOAc (3×5 mL) and the combined organic layer was evaporated after drying with Na_2SO_4. The crude product was column chromatographed to give 0.716 g (76%) of compound **12** as diastereomeric mixture (colorless syrup, R_f: 0.46, Hexane/Ethyl acetate 2:1).

^{1}H NMR ($CDCl_3$, 400MHz): δ -0.04, -0.02, -0.01, 0.05, (4 s, 6H, Si-C*H*$_3$), 0.82 and 0.84 (2 s, 9H, -C(C*H*$_3$)$_3$), 1.09 and 1.22 (2 d, *J* = 6.3 Hz, 3H, -C*H*$_3$), 1.96-2.15 (m, 2H, -C*H*$_2$CHSO$_2$Ph), 2.85 and 3.06 (2 s, 3H, -NC*H*$_3$), 3.10 – 3.14 (m, 0.4H, -C*H*OBn), 3.54 and 3.57 (2s, 3H, OC*H*$_3$), 3.55-3.63 (m, 0.6H, -C*H*OBn), 3.80-3.90 (m, 1H, -C*H*-OSi-), 4.44 and 4.58 (2×AB quartet, *J* = 11.2 Hz, 2H, -OC*H*$_2$Ph), 4.88 (dd, *J* = 7.3 Hz, 5.8 Hz, 0.4H, -C*H*SO_2Ph), 4.93 (dd, *J* = 10.7 Hz, 3.4 Hz, 0.6H, -C*H*SO_2Ph), 7.20-7.27 (m, 5H, Ar-*H*), 7.49 -7.57 (m, 2H, Ar-*H*), 7.60 – 7.66 (m, 1H, Ar-*H*), 7.83 -7.91 (m, 2H, Ar-*H*); ^{13}C NMR ($CDCl_3$, 100MHz): δ -4.5, -4.2, -4.1 (Si-*C*H_3), 18.1 (Si-*C*$(CH_3)_3$), 19.5 (-*C*H_3), 19.8 (-*C*H_3), 26.0 (-*C*H_3), 28.8 (-*C*H_2CO), 30.1 (-*C*H_2CO), 32.2 (-N*C*H_3), 32.5 (-N*C*H_3), 61.5 (-O*C*H_3), 61.7 (-O*C*H_3), 62.4 (-*C*HSO_2Ph), 63.2 (-*C*HSO_2Ph), 69.7 (-*C*HOSi), 70.6 (-*C*HOSi), 72.4 (-O*C*H_2Ph), 72.6 (-O*C*H_2Ph), 81.3 (-*C*HOBn), 82.2 (-*C*HOBn), 127.5, 127.6, 127.7, 128.4, 128.8, 128.9, 129.6, 130.0, 130.2, 134.1, 137.2, 137.5, 138.7, 138.9 (Ar-*C*'s), 166.1 (-CH_2*C*O), 166.5 (-CH_2*C*O).

A solution of alkylated product **12** (0.505 g, 0.94 mmol) in MeOH (9.4 mL) cooled to 0°C was treated with Na_2HPO_4 (0.531 g, 3.77 mmol) and 6% Na (Hg) (1.41 g). The reaction mixture was stirred for 1.5 hr after which H_2O (10 mL) was added and the solution extracted with EtOAc (3×10 mL). The combined organic layers were dried over Na_2SO_4, the solvent evaporated and the residue column chromatographed to give 0.317 g (85%) of the product **3** as syrup. R_f: 0.5 (hexane/EtOAc, 3:2). $[\alpha]^D_{24}$ = -33.1° (c=1, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 400MHz): δ -0.07 (s, 3H, Si-C*H*$_3$), -0.03 (s, 3H, Si-C*H*$_3$), 0.82 (s, 9H, C(C*H*$_3$)$_3$), 1.12 (d, *J* = 6.4 Hz, 3H, C*H*$_3$), 1.65-1.84 (m, 2H, -C*H*$_2$$CH_2$CO), 2.33-2.60 (m, 2H, -C*H*$_2$CO), 3.07 (s, 3H, -NC*H*$_3$), 3.54 (s, 3H, -OC*H*$_3$), 3.28-3.32 (m, 1H, -C*H*OBn), 3.78-3.84 (m, 1H, -C*H*OSi), 4.56 (AB quartet, *J* = 11.7 Hz, 2H, -OC*H*$_2$Ph), 7.17-7.29 (m, 5H, Ar-*H*); ^{13}C NMR ($CDCl_3$, 100MHz): δ -4.7 (Si-*C*H_3), -4.4 (Si-*C*H_3), 18.0 (Si-*C*$(CH_3)_3$), 19.2 (*C*H_3), 25.3 (-*C*$H_2$$CH_2$CO), 25.8 (-C(*C*$H_3$)$_3$), 27.9 (-*C*$H_2$CO), 32.0 (-N*C*$H_3$), 61.1 (-O*C*$H_3$), 70.7 (-*C*HOSi), 72.6 (-O*C*H_2Ph), 83.0 (-*C*HOBn), 127.3, 127.8, 128.2, 139.0 (Ar-*C*), 174.5 (-CH_2*C*O); IR (Neat): 2929, 1667, 1594 cm^{-1}; HRMS (CI): *m/z* (MH+), Found: 396.2574. Calcd for $C_{21}H_{38}NO_4Si$: 396.2570.

N-Methoxy-*N*-methyl-2,3,6-trideoxy-4-*O*-benzyl-D-*erythro*-hexonamide, 13

The solution of the amide **3** (0.365 g, 0.92 mmol) was treated with 1M solution of tetrabutylammonium fluoride (1.8 mL) and the solution was stirred for 14 hr at RT. The reaction mixture was evaporated and a small silca-gel filtration column chromatography performed to afford 0.192 g (75%) of the compound **13**.

R_f: 0.30 (hexane/EtOAc, 2:3). $[\alpha]^D_{24}$ = 15.3° (c=0.8, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 400MHz): δ 1.14 (d, *J* = 6.4 Hz, 3H, -C*H*$_3$), 1.83-1.93 (m, 2H, -C*H*$_2$$CH_2$CO), 2.37-2.70 (m, 2H, -C*H*$_2$CO), 2.72 (bs, 1H, O*H*) 3.09 (s, 3H, -NC*H*$_3$), 3.29-3.33 (m, 1H, -OC*H*) 3.57 (s, 3H, -OC*H*$_3$), 3.76-3.82 (m, 1H, -C*H*OH), 4.50 (AB quartet, *J* = 11.7 Hz, 2H, -OC*H*$_2$Ph), 7.19-7.30 (m, 5H, Ar-*H*); ^{13}C NMR ($CDCl_3$, 100MHz): δ 18.2 (-*C*H_3), 22.5 (-*C*$H_2$$CH_2$CO), 26.6 -*C*$H_2$CO), 32.0 (-N*C*$H_3$), 61.6 (-O*C*$H_3$), 67.3 (-*C*HOH), 71.7 (-O*C*H_2Ph), 82.1 (-*C*HOBn), 127.6, 127.7, 128.3, 138.3 (Ar-*C*), 174.7 (-*C*H_2CO); IR (Neat): 3429 (b), 2925, 1666 cm^{-1}; HRMS (CI): *m/z* (MH+), Found: 282.1700. Calcd for [$C_{15}H_{23}NO_4$ + H]: 282.1704.

2, 3, 6-Trideoxy-4-*O*-benzyl-D-*erythro*-hexopyranose, 4

To a suspension of the lithium aluminum hydride (0.024 g, 0.6 mmol) in anhydrous THF (2 mL) was added the amide **13** (0.170 g, 0.6 mmol) dissolved in THF (2 mL) and stirred at -78°C for 15 min. The excess LAH was then quenched with EtOAc (0.5 mL) and the mixture was subsequently treated with H_2O (0.1 mL), 15% NaOH solution (0.3 mL) and again with H_2O (0.1 mL). The mixture was then filtered through a celite pad, the filtrate dried over anhydrous Na_2SO_4, evaporated and the residue subjected to silica-gel column chromatography to give 0.107 g (81%) of the cyclized product **4**. Solid (low melting). R_f: 0.38 (hexane/EtOAc, 1:1). $[\alpha]^D_{22}$ = +63.9° (c=1, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 400 MHz): δ (α: β = 1: 1.21), 1.24 (d, *J* = 6.4 Hz, 3H, -C*H*$_3$, α-anomer), 1.31 (d, *J* = 6.4 Hz, 3H, C*H*$_3$, β-anomer), 1.39-2.20 (m, 4H, -C*H*$_2$C*H*$_2$, both anomers), 3.03-3.09 (m, 1H, -C*H*OBn, both anomers), 3.44-3.51 (m, 1H, -C*H*(CH_3), β anomer), 3.60 (bs, 1H, OH, α-anomer), 3.95-4.02(m, 1H, -C*H*(CH_3), α-anomer), 4.26 (bd, *J* = 6.0 Hz, 1H, OH, β-anomer), 4.44-4.48 (m, 1H, -OC*H*$_2$Ph, both anomers), 4.60-4.66 (m, 1H, -OC*H*$_2$Ph, both anomers), 4.74-4.81 (bm, 1H, H_1, β-anomer), 5.16-5.19 (bm, 1H, H_1, α-anomer), 7.24-7.35 (m, 5H, Ar-*H*); ^{13}C NMR ($CDCl_3$, 100MHz): δ 18.3 (-*C*H_3 α-anomer), 18.4 (-*C*H_3 β-anomer), 23.1 (-CH_2 C_2 or C_3 α-anomer), 27.3 (-CH_2 C_2 or C_3 β-anomer), 29.3 (CH_2 C_2 or C_3 α-anomer), 31.7 (-CH_2 C_2 or C_3 β-anomer), 68.0 (-OCH C_4 or C_5 α-anomer), 70.6 (-O*C*H_2Ph α-anomer), 71.2 (-O*C*H_2Ph β-anomer), 74.8 (-OCH C_4 or C_5 β-anomer), 78.1 (-*C*HOBn β-anomer), 78.8 (-*C*HOBn α-anomer), 90.7 (-OCH C_1 α anomer), 95.7 (-OCH C_1 β anomer), 127.6, 127.7, 128.3, 128.4, 138.2, 138.4 (Ar-*C* mixture of α and β anomers); IR

(Neat): 3342 (b), 2925, 1595 cm^{-1}; HRMS (CI): *m/z* (MH+), Found: 223.1334. Calcd for $C_{13}H_{18}O_3$ +H: 223.1334.

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