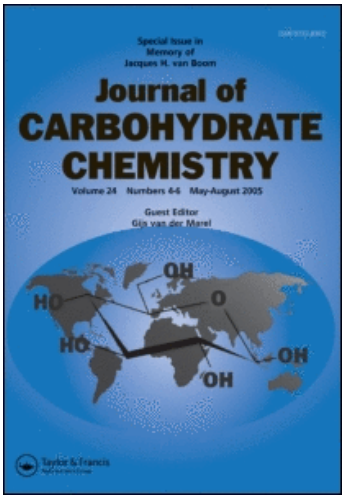

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A Convenient Synthesis of Methyl 2,3-Di-*O*- Benzyl-4-Deoxy-α-D-*Xylo*-Hexodialdo-1,5-Pyranoside and its Stereospecific Ethynylation

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A CONVENIENT SYNTHESIS OF METHYL 2,3-DI-O-BENZYL-4-DEOXY-α-D-XYLO-HEXODIALDO-1,5-PYRANOSIDE AND ITS STEREOSPECIFIC ETHYNYLATION.

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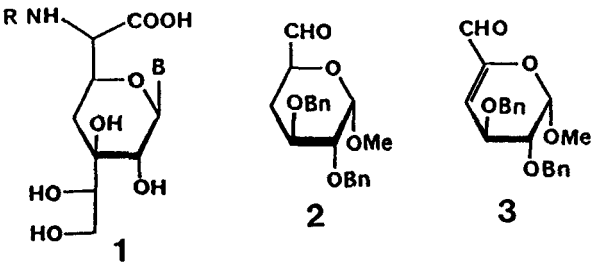
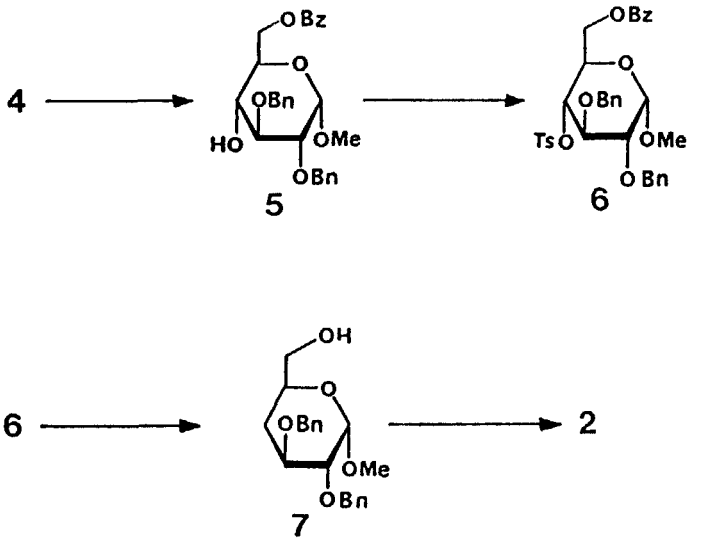
ABSTRACT

The title compound was synthesized in three steps from methyl 2,3-di-O-benzyl- α-D-glucopyranoside in 42 % overall yield. Further ethynylation in the presence of magnesium bromide occurred in a stereospecific way in 75 % yield.

Since R. M. Giuliano and J. H. Buzby guessed[1] that amipurimycin 1[2] was one of our target molecules wnen we disclosed a mild and efficient methodology for cyano-amination of dialdohexose derivatives,[3] we decided to report herein the synthesis of the protected dialdosugar 2 that could be a precursor of this antibiotic (Scheme 1).



SCHEME 1



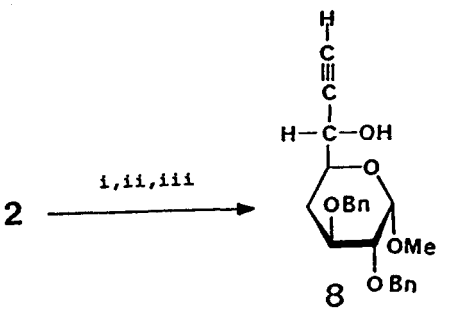
SCHEME 2

Furthermore since 2 is deoxygenated at C-4 it may serve as a good model substrate for enlarging the scope of our recent stereoselective ethynylation procedure. [4]

In contrast to the above mentioned authors' report who obtained 2 together with its L-epimer by reduction of 3, pure 2 was prepared in 42 % overall yield from methyl 2,3-di-O-benzyl-α-D-glucopyranoside 4[5] by the reaction sequence depicted in scheme 2.

First, slow addition of benzoyl chloride to a cold pyridine solution of the starting diol allowed selective esterification at C-6. Treatment of the resulting crude monobenzoate with p-toluenesulfonyl chloride in pyridine at 50 °C followed by classical work-up readily afforded the tosylate 6 in 78 % isolated yield from 4. Further reaction with lithium tetrahydroaluminate was carried out in THF under reflux and smoothly gave in 64 % yield the 4-deoxy derivative 7 directly deprotected at C-6.

Usually secondary sulfonyl groups are not displaced by lithium tetrahydroaluminate but O-S cleavage is observed,[6] unless there is a suitably located hydroxyl or ester group (6-O-benzoate in this case) from which an alkoxyaluminium hydride is generated allowing intramolecular reduction of the sulfonate.[7,8]



Reagents: i, $MgBr_2$-Et_2O; ii, Me_3Si-C≡CMgBr,Et_2O,-30°C;
iii, $AgNO_3$,EtOH-H_2O then KCN-H_2O

SCHEME 3

Several attempts were made to oxidize the primary hydroxyl group by means of either dimethylsulfoxide-dicyclohexyl carbodiimide[9] or pyridinium dichromate[10] as reagents. Finally the Swern oxidation[11] proved to be the best method to obtain the dialdose derivative 2 in 85 % yield as the sole product. As shown by both TLC and ^{1}H-NMR spectroscopy, the crude compound contained no trace of L-epimer and was used without purification in the next step.

Ethynylation of 2 was performed in ether by means of trimethylsilylethynyl magnesium bromide in the presence of magnesium bromide,[4] and further desilylation provided a sirupy compound homogeneous on TLC in 75 % yield. ^{1}H-NMR spectrum examination clearly indicated the presence of a single product identified as 8. Significantly, the signal of axially oriented H-4 was a doublet of doublet (δ 1.55 $J_{3,4}$ = 11.2 Hz, $J_{4,5}$ = 12.0 Hz) indicating a trans diaxial relationship with H-3 and H-5, thus precluding C-5 epimerization. The L-glycero-configuration of C-6 was initially assigned on a mechanistic basis.[4]

The stereochemical outcome of the ethynylation was confirmed by a test experiment which was carried out with trimethylsilylethynyl lithium in ether without magnesium bromide. The same work-up afforded in similar yield (68 %) a compound, still homogeneous on TLC, whose ^{1}H NMR spectrum clearly demonstrated the presence of two epimers as shown by different chemical shifts for nearly all protons.

In conclusion, dialdosugar 2, synthesized in six steps from methyl α-D-glucopyranoside, was stereospecifically ethynylated in high yield, affording a highly functionalized precursor of higher-carbon sugars deoxygenated at C-4.[12]

EXPERIMENTAL

General procedures are the same as indicated before.[3]

Methyl 6-O-Benzoyl-2,3-di-O-benzyl-4-O-p-toluenesulfonyl-α-D-glucopyranose (6). Benzoyl chloride (4.5 mL, 5.45 g, 38.7 mmol) was very slowly added to a stirred solution of 4 (12 g, 32 mmol) in dry pyridine (60 mL) at O °C. The complete introduction required 2 h 30 min. After 15 h at + 4 °C the mixture was poured into cold water (500 mL) under continuous stirring. The precipitate thus obtained was filtered, washed with cold water (60 mL) and dried to yield crude 5 (15 g, 98 %) mp 65 °C homogeneous on TLC, R_F 0.54 (petroleum ether : ether 1:2) which was pure enough for further transformation. Recrystallization (benzene) afforded an analytical sample mp 78-79 °C.

Anal. Calcd for $C_{28}H_{30}O_7$ (478.54) : C, 70.28 ; H, 6.32. Found : C, 70.05 ; H, 6.25.

The above crude 5 (12 g, 25 mmol) was dissolved in dry pyridine (65 mL) and allowed to react with p-toluene sulfonyl chloride (7.63 g, 40 mmol, 1.6 equiv.) at 50 °C during 12 h. The reaction mixture was transferred to a separatory funnel containing chloroform (125 mL) and cold water (550 mL). After decantation, the aqueous phase was extracted with chloroform (2 x 100 mL) and the combined organic layers were washed successively with 10 % aqueous HCl (100 mL), 10 % aqueous sodium hydrogencarbonate (100 mL), water (100 mL) and dried over Na_2SO_4. Evaporation of the solvent under reduced pressure afforded the crude tosylate 6 (15.4 g, 97 %) as a solid. Recrystallization (ethanol) yielded pure 6 (12.6 g, 80 %) : mp 121 °C ; TLC R_F 0.49 (toluene : ethylacetate 7:2) ; $[\alpha]^{25}$ + 32.1 (c 1.1, $CHCl_3$) ; IR (KBr) 3070, 3030, 1720, 1595 cm^{-1} ; ^1H NMR (C_6D_6) δ 8.26, 7.73, 7.15 - 7.0 and 6.57 (m, 19H, ArH) ; 5.08 (dd, 1H, J_{3-4} = 9.25 Hz, J_{4-5} = 10.1 Hz, H - 4) ; 4.76, 4.58 and 4.24 (2 ABq, 4H, $PhCH_2$) ; 4.40 - 4.28 (m, 3H, H - 1, H - 6 and H - 6') ; 4.00 (dd, J_{2-3} = 9.45 Hz, H - 3) ; 3.84 (m, 1H, H - 5) ; 3.39 (dd, J_{1-2} = 3.6 Hz, H - 2) ; 2.98 (s, 3H,OCH_3) ; 1.78 (s, 3H, $ArCH_3$).

Anal. Calcd for $C_{35}H_{36}O_9S$ (632.7) : C, 66.43 ; H, 5.73 ; S, 5.06. Found : C, 66.25 ; H, 5.97 ; S, 4.88.

Methyl 2,3-di-O-Benzyl-4-deoxy-α-D-xylo-hexopyranoside (7). A solution of 6 (7.3 g, 11.5 mmol) in dry THF (15 mL) was added dropwise to a suspension of lithium tetrahydridoaluminate (4.4 g, 116 mmol, 10 equiv.) in dry THF (100 mL) under argon. The mixture was heated at reflux overnight then cooled down to O °C and the excess of hydride was destroyed by careful successive additions of ethyl acetate (5 mL) dissolved in THF (10 mL) and cold water (250 mL). The inorganic materials were filtered off, rinsed with THF (2 x 25 mL) and the filtrate reduced to ca. 100 mL by concentration under reduced pressure. The residue was extracted with ether (3 x 75 mL) and the organic layers dried over Na_2SO_4. Evaporation of the solvent left the crude product (4.05 g) which was purified by chromatography to yield pure 7 (2.63 g, 64 %) as a syrup : TLC R_F 0.50 (ether) ; $[\alpha]^{20}$ + 81.5 (c 2.0, CH_2Cl_2) ; Lit.[1] $[\alpha]_D$ + 75.4 (c 1.425, CH_2Cl_2) ; ^1H NMR (C_6D_6) δ 7.40 - 7.30 and 7.17 (m + b.s., 10H, ArH) ; 4.71, 4.62, 4.55 and 4.53 (2 ABq, 4H, Ph CH_2) ; 4.63 (d, 1H, J_{1-2} = 3.5 Hz, H - 1) ; 3.95 (ddd, 1H, J_{3-4a} = 12 Hz, J_{2-3} = 9.35 Hz, J_{3-4e} = 5.2 Hz, H - 3) ; 3.53 (m, 1H, J_{4a-5} = 12 Hz, $J_{5-6'}$= 3.5 Hz, J_{4e-5} = 2.4 Hz, H - 5) ; 3.42 (dd, 1H, H - 2) ; 3.32 (m, 2H, H - 6 and H - 6') ; 3.13 (s, 3H, OCH_3) ; 1.67 (ddd, 1H, J_{4e-4a} = 12.5 Hz, H - 4e) ; 1.6 (b.s., 1H, OH) ; 1.37 (q, 1H, H - 4a).

Anal. Calcd for $C_{21}H_{26}O_5$ (358.42) : C,70.37 ; H, 7.31. Found : C, 70.24 ; H, 7.33.

Methyl 2,3-Di-O-benzyl-4-deoxy-α-D-xylo-hexodialdo-1,5-pyranoside (2). The Swern oxidation was used as previously described on a similar substrate.[3] Starting from 7 (1.79 g, 5 mmol) the procedure yielded 2 (1.519 g, 85 %) as a colourless syrup chromatographically homogeneous, pure enough for further ethynylation. Flash chromatography afforded the pure dialdose (1.105 g , 62 %) : TLC R_F 0.36 (petroleum ether : ether 1:3) ; $[\alpha]_D$ + 23 (c 1.2, $CHCl_3$) ; ^1H NMR (C_6D_6) δ 9.37 (s, 1H, H - 6) ; 7.30 - 7.03 (m, 10 H, ArH) ; 4.57 (ABq, 2H, Ph CH_2) ; 4.62 (d, 1H, J_{1-2} = 3,5 Hz, H - 1) ; 4.49 (S, 2H, $PhCH_2$) ; 3.86 (ddd, 1H, J_{3-4a} = 11.0 Hz, J_{2-3} = 9.45 Hz, J_{3-4e} = 5.0 Hz, H - 3) ; 3.70 (dd, 1H, J_{4a-5} = 12.25 Hz, J_{4e-5} = 2.8 Hz, H - 5) ; 3.34 (dd, 1H, H - 2) ; 3.05 (s, 3H, OCH_3) ; 2.08 (ddd, 1H, J_{4a-4e} = 12.5 Hz, H - 4e) ; 1.29 (q, 1H, H - 4a).

Anal. Calcd for $C_{21}H_{24}O_5$ (356.40) : C, 70.76 ; H, 6.78. Found : C, 70.84 ; H, 6.67.

Methyl-2,3-Di-O-benzyl-4,7,8,-trideoxy-α-L-ido-oct-7-ynopyranoside (8). The dialdose 2 (335 mg, 0.94 mmol) first complexed with freshly prepared anhydrous $MgBr_2$ (8 mmol) was allowed to react at - 30 °C with trimethylsilylmagnesium bromide as previously described.[4] After desilylation,[13] usual processing left a syrup (270 mg, 75 %)

: TLC R_F = 0.56 (toluene : ethyl acetate 7 : 3) ; $[\alpha]_D$ + 67 (c 0.95, $CHCl_3$) ; ^1H NMR (C_6D_6) δ 7.33 - 7.1 (m, 10 H, C_6H_5), 4.73 - 4.51 (ABq + S, 4H, $PhCH_2$), 4.61 (d, 1H, J_{1-2} = 3.6 Hz, H - 1), 4.10 (dd, 1H, J_{5-6} = 5.3 Hz, J_{6-8} = 2.2 Hz, H - 6), 3.95 (m, 1H, J_{2-3} = 9.4 Hz, J_{3-4e} = 5.15 Hz, J_{3-4a} = 11.2 Hz, H - 3), 3.65 (ddd, 1H, J_{4e-5} = 2.2 Hz, J_{4a-5} = 12 Hz, H - 5), 3.40 (dd, 1H, H - 2), 3.17 (s, 3H, OCH_3), 2.9 (d, 1H, H - 8), 2.05 (ddd, 1H, J_{4a-4e} = 12.7 Hz, H - 4e), 1.55 (q, 1H, H - 4a), 2.35 (bs, 1H, OH).

Anal. Calcd for $C_{23}H_{26}O_5$ (382.43) : C, 72.23 ; H, 6.85. Found : C, 72.17 ; H, 6.98.

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