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SYNTHESES OF TRI- AND TETRAHYDROXYLATED 1-AMINO-HEPTANES+

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ABSTRACT

Syntheses of tri- and tetrahydroxylated 1-amino-heptanes from α-D-glucose are described.

Polyfunctional aminoalkanols represent a pharmacophore which is of great concern for medicinal chemists. For example, ethambutol, an antituberculor drug,[1] sphingosines,[2] sphingomyelins[3] and cerebrosides[4] with wide variety of enzyme inhibitory activities and recently reported cytotoxicity and antiinflammatory activity of long chain 3-amino 1,2-diols,[5] all possess the basic amino alkanol substructural unit. Moreover, 2-amino alcohol is implicated as the minimum essential structure for immunosuppressive activity of ISP-1 (myriocin)[6] and their N-acyl derivatives are useful for the treatment of mammalian pathologies induced by mast cell degranulation.[7] Thus, the main concern for designing bioactive amino alkanols rests on the following: the nature

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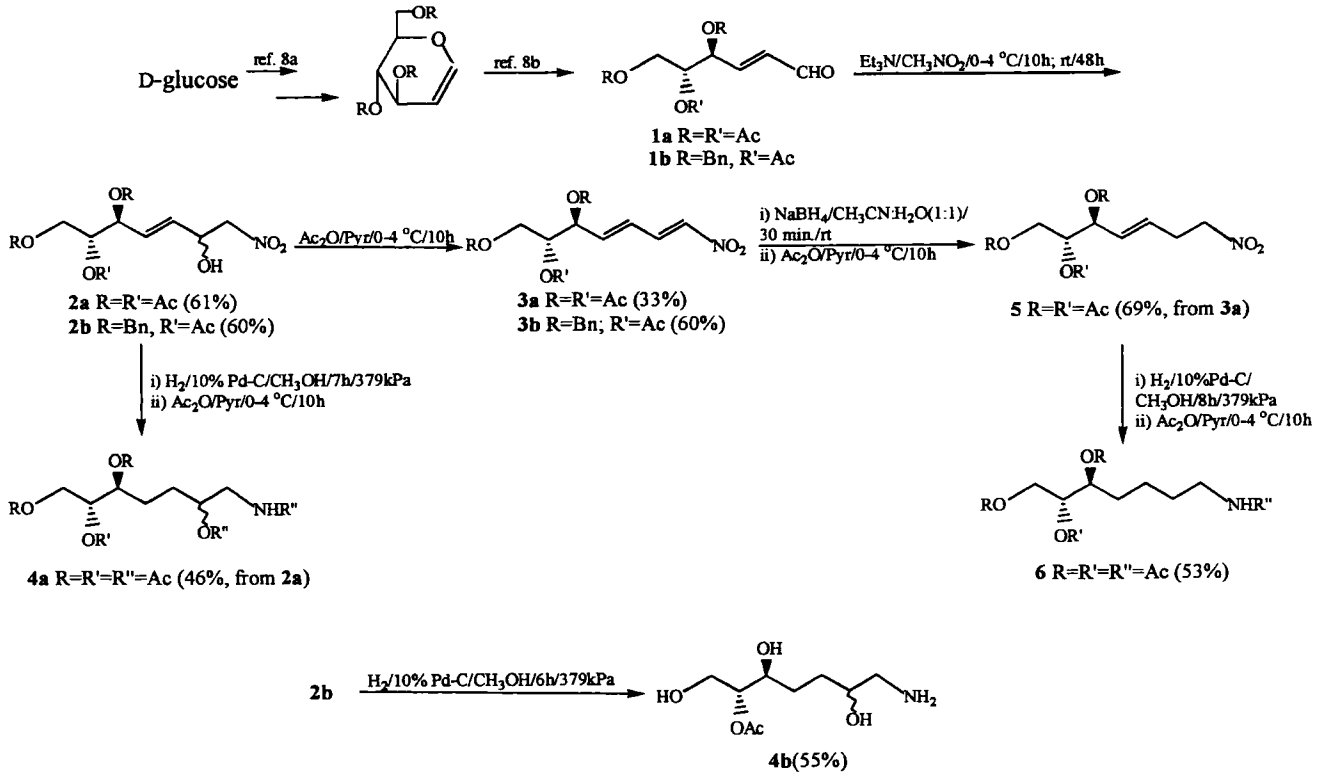
of substituent on the nitrogen atom, orientation and number of additional hydroxy groups and their spacing with respect to the nitrogen atom. On the basis of these requirements, a number of synthetic strategies for amino alkanols have been developed earlier but to the best of our knowledge a simple synthetic strategy for obtaining tri- and tetrahydroxy derivatives of 1-amino-heptane has not been reported. Such 1-amino-heptanes involve the generation of a number of chiral centres and a convenient synthetic strategy demands the possibility of preparing the compounds with well defined stereochemistry. The present communication aims towards this objective.

The retrosynthetic analysis of compound **4a**, (5*S*,6*R*)-1-acetamido 2,5,6,7-tetraacetoxy(erythro/threo)-heptane and **6**, (5*S*,6*R*)-1-acetamido 5,6,7-triacetoxy-heptane indicated that these can be obtained by 1,2 addition of nitromethane to α, β-unsaturated sugar aldehyde **1a**. Thus, the synthesis was initiated with (2*E*,4*S*,5*R*)-4,5,6-triacetoxy-2-hexenal **1a** which was easily prepared from α-D-glucose.[8]

Dropwise addition of a solution of **1a** in nitromethane at 0 °C under N_2 to a solution of nitromethane and triethylamine yielded the inseparable diastereomeric mixture **2a**, 61%. Similar result was obtained when the reaction was carried out in presence of DBU. Dehydration of **2a** with acetic anhydride and pyridine furnished the conjugated nitro olefin **3a**, 33%. Its low yield was attributed to the parallel reverse aldol reaction of **2a** to furnish the starting material **1a**. The regioselective reduction of C_1 - C_2 double bond in **3a** was accomplished with sodium borohydride to yield **5**, 69%. To obtain the terminal amine, several reduction

methods like $LiAlH_4$,[9] Zn-AcOH,[10] hydrogen transfer by $HCOONH_4$ over Pd-C,[11] Zn-HCl[12] were tried but the best method was found to be hydrogenation, under pressure, over 10% Pd-C. The amines, thus, obtained after hydrogenation of nitro compounds were isolated as their acetate derivatives. **2a** and **5** on hydrogenation over Pd-C (10%) at 379 kPa gave the resulting amines **4a** as inseparable diastereomeric mixture and **6** in 46% and 53% yield respectively. The compound **6** was also prepared directly from **3a** by hydrogenation over 10% Pd-C at 379 kPa but the yield was found to be less than that obtained from **5**. The reason for the low yield of compound **6** from **3a** may be explained on the basis of earlier report[13] that buta-1,3-diene are very strongly adsorbed to the catalyst surface during hydrogenation and therefore compound **3a** will generate a number of amines during hydrogenation which will facilitate catalytic poisoning, side reactions and polymerisation. Reactions were also carried out with the benzyl protected unsaturated aldehyde **1b** to furnish nitro aldol derivative **2b**, 60%. During the conversion of **2b** to **3b** (conjugated nitro olefin) the reverse aldol reaction was not observed and therefore the yield of **3b** (60%) was found better. Catalytic hydrogenation of **2b** over 10% Pd-C at 379 kPa for 6h gave **4b**, 55% which on subsequent acetylation yielded **4a** (Scheme 1).

In conclusion, looking towards the importance of chiral tri- and tetrahydroxylated amino alcohols in the biological system, a simple strategy has been developed for an easy access of such compounds starting from α, β-unsaturated aldehydo sugars which in turn can be easily obtained from the corresponding glycals.



Scheme 1

EXPERIMENTAL

General methods and materials. All the reactions were carried out using anhydrous solvents or as stated and monitored by thin layer chromatography over silica gel (E. Merck) coated TLC plates. The spots were visualised by warming the $CeSO_4$ (1% in 2N H_2SO_4) sprayed plates in oven at 100 °C or as mentioned otherwise. Column chromatography was performed using silica gel (60-120 mesh). IR spectra were recorded on Perkin Elmer 881 infrared spectrophotometer. NMR spectra were determined on AVANCE DPX200 Bruker Robotics spectrometer operating at 200 MHz for ^1H NMR and 50 MHz for ^{13}C NMR using TMS and $CDCl_3$ [$\delta(CDCl_3)$ = 77.0 ppm with respect to TMS] as internal references respectively. Mass spectra were recorded on a Jeol JMS-D-300 and Jeol SX 102/DA 6000 mass spectra using Argon/Xenon (6KV, 10MA) as the FAB gas. The electrospray mass spectrum was recorded on a MICROMASS QUATTRO II triple quadrupole mass spectrometer. Specific rotations were determined with Rudolph Autopol - III polarimeter at 28 °C. Elemental analyses were carried out on Carlo-Erba-1108 CHN elemental analyser.

Mixture of (3*E*,5*S*,6*R*)-5,6,7-triacetoxy-2-hydroxy-1-nitro(erythro)-hept-3-ene and (3*E*,5*S*,6*R*)-5,6,7-triacetoxy-2-hydroxy-1-nitro(threo)-hept-3-ene (2a). To a stirred solution of nitromethane (5 mL) and triethylamine (0.25 mL, 1.8 mmol) was added the solution of **1a** (500 mg, 1.8 mmol) in nitromethane (1.8 mL) during half an hour at 0 °C under N_2. The reaction was carried out at the same temperature for 10 h followed at room temperature for 48 h. The reaction mixture was concentrated in vacuo and the residue was chromatographed (eluent

hexane/ethylacetate=4:1, v/v) to furnish **2a** (374 mg, 61.2%) as yellow oil: R_f=0.50 (hexane/ethyl acetate=3:2, v/v); IR (neat, cm^{-1}) 3462, 1746, 1556, 1430, 1224, 972; ^1H NMR ($CDCl_3$) δ 2.06, 2.09 (2 × s, 9H, 3 × COC*H*$_3$), 2.94 (brs, *OH*), 4.16 (dd, 1H, $J_{6,7a}$=3.5 Hz, $J_{7a,7b}$=12.1Hz, H-7a), 4.26 (dd, 1H, $J_{6,7b}$=6.7 Hz, H-7b), 4.37 - 4.45 (m, 2H, H-1), 4.91 (m,1H, H-2), 5.20 (m, 1H, H-6), 5.50 (t, 1H, $J_{4,5}$=$J_{5,6}$=5.1 Hz, H-5), 5.80 (ddd,1H, $J_{2,3}$=4.5 Hz, $J_{3,4}$=15.5 Hz, $J_{3,5}$=1.3 Hz, H-3), 5.93 (dd, 1H, H-4); ^{13}C NMR ($CDCl_3$) δ 20.37, 20.63, 20.70, 20.77, 20.81 (COC*H*$_3$), 61.63 and 61.79 (C-7), 68.30 (C-2), 71.40 and 71.43 (C-6), 71.49 (C-5), 79.53 and 80.35 (C-1), 127.20 and 127.29 (C-3), 131.72 and 131.80 (C-4), 169.48, 169.75, 170.04, 170.25, 170.59, 170.81 (*C*OCH$_3$) ; FABMS m/z 356 $(M + Na)^+$.

Anal. Calcd. for $C_{13}H_{19}NO_9$ (333.29): C, 46.85; H, 5.75; N, 4.20. Found: C, 47.17; H, 6.06; N, 4.00.

Mixture of (3*E*,5*S*,6*R*)-6-acetoxy-5,7-dibenzyloxy-2-hydroxy-1-nitro(erythro)-hept-3-ene and (3*E*,5*S*,6*R*)-6-acetoxy-5,7-dibenzyloxy-2-hydroxy-1-nitro(threo)-hept-3-ene (2b). Preparation procedure (in 110 mg scale, 0.26 mmol) was the same as above. Pale yellow oil (77.3 mg, 60.3%) was obtained by column chromatography (eluent hexane/ethyl acetate=17:3, v/v); R_f=0.5 (hexane/ethyl acetate=7:3, v/v); IR (neat, cm^{-1}) 3676, 3024, 1736, 1554, 1436, 926, 668; ^1H NMR ($CDCl_3$) δ 1.71 (brs, O*H*), 2.04 (s, 3H, COC*H*$_3$), 3.61 (dd, 1H, $J_{6,7a}$=4.5 Hz, $J_{7a,7b}$=10.5 Hz, H-7a), 3.68 (dd, 1H, $J_{6,7b}$=5.4 Hz, H-7b), 4.08 (t, 1H, $J_{4,5}$=$J_{5,6}$=6.1 Hz, H-5), 4.33 - 4.56 (m, 4H, 2 × C*H*$_2$Ph), 4.43 (m, 2H, H-1), 4.81 (m, 1H, H-2), 5.09 (m, 1H, H-6), 5.71 (dd, 1H, $J_{3,4}$=15.9 Hz, H-4),

5.78 (dd, 1H, $J_{2,3}$=4.5 Hz, H-3), 7.25 - 7.26 (m, 10H, aromatic); ^{13}C NMR ($CDCl_3$) δ 21.08 ($COCH_3$), 67.88 (C-7), 68.58 and 68.62 (C-2), 71.20, 73.19 (CH_2Ph), 73.42 and 73.46 (C-5), 77.43 (C-6), 79.62 (C-1), 127.73 and 128.37 (C-3), 131.02 and 131.08 (C-4), 128.81 - 138.07 (aromatic), 170.57 and 170.61 ($COCH_3$). EIMS m/z 231 [M^+- (BnOH +CH_3NO_2+$^{\cdot}$CHO)].

(1*E*,3*E*,5*S*,6*R*)-5,6,7-Triacetoxy-1-nitro-hepta-1,3-diene (3a). To a solution of **2a** (1.10 g, 3.3 mmol) in pyridine (5 mL), acetic anhydride (15 mL) was added at 0 °C and the resulting reaction mixture was left overnight at 0-4 °C. Crude reaction mixture was poured in acidurated (1N HCl, 50 mL) ice, extracted with chloroform (3 × 20 mL), washed with $NaHCO_3$, brine, dried over anhydrous Na_2SO_4 and concentrated in vacuo to give a dark syrup which was purified by column chromatography (eluent benzene/ether=47:3, v/v) to furnish **3a** (350 mg, 33.6%) as yellow oil: R_f=0.50 (benzene/ether=9:1, v/v; $KMnO_4$ as spray reagent); $[\alpha]_D$ +30.9^0 (c 0.11, methanol); IR (neat, cm^{-1}) 3026, 1744, 1648, 1520, 1346, 1222; ^{1}H NMR ($CDCl_3$) δ 2.06, 2.09, 2.12 (3 × s, 9H, 3 × $COCH_3$), 4.15 (dd, 1H, $J_{6,7a}$=4.3 Hz, $J_{7a,7b}$=12.7 Hz, H-7a), 4.23 (dd, 1H, $J_{6,7b}$=6.7 Hz, H-7b), 5.25 (m, 1H, H-6), 5.62 (dd~t, 1H, $J_{4,5}$=6 Hz, $J_{5,6}$ =5.3 Hz, H-5), 6.28 (dd, 1H, $J_{3,4}$=15.3 Hz, H-4), 6.44 (dd, 1H, $J_{2,3}$=10.5 Hz, H-3), 7.14 (d, 1H, $J_{1,2}$=13 Hz, H-1), 7.54 (dd, 1H, H-2); ^{13}C NMR ($CDCl_3$) δ 20.68 - 20.80 (3 × $COCH_3$), 61.54 (C-7), 71.33 (C-6), 71.81 (C-5), 126.42 (C-4), 136.53 (C-3), 140.10 (C-1), 140.51 (C-2), 169.51, 170.01, 170.50 (3 × $COCH_3$); FABMS m/z 354 $(M+K)^+$.

Anal. Calcd. for $C_{13}H_{17}NO_8$ (315.28): C, 49.52; H, 5.43; N, 4.44. Found: C, 49.05; H, 5.44; N, 4.29.

(1*E*,5*S*,6*R*)-6-Acetoxy-5,7-dibenzyloxy-1-nitro-hepta-1,3-diene (3b). Preparation procedure (in 50 mg scale, 0.12 mmol) was the same as above. Pale yellow oil (28.7 mg, 60%). ^{1}H NMR ($CDCl_3$) δ 2.08 (s, 3H, COC*H*$_3$), 3.62 (dd, 1H, $J_{6,7a}$=4.5 Hz, $J_{7a,7b}$=10.5 Hz, H-7a), 3.72 (dd, 1H, $J_{6,7b}$=5.4 Hz, H-7b), 4.28 (t, 1H, $J_{4,5}$= $J_{5,6}$=5.4 Hz, H-5), 4.44 - 4.61 (m, 4H, 2 × C*H*$_2$Ph), 5.16 (m, 1H, H-6), 6.36-6.39 (m, 2H, H-3 and H-4), 7.10 (d, 1H, $J_{1,2}$=13.2 Hz, H-1), 7.21 - 7.36 (m, 10H, aromatic), 7.56 (dd, 1H, $J_{2,3}$=9.3 Hz, H-2).

Mixture of (5*S*,6*R*)-1-acetamido-2,5,6,7-tetraacetoxy(erythro)-heptane and (5*S*,6*R*)-1-acetamido-2,5,6,7-tetraacetoxy(threo)-heptane (4a). To a solution of **2a** (1 g, 3 mmol) in methanol (25 mL) was added 10% Pd-C (2 g). The mixture was hydrogenated at 379 kPa for 7 h. It was filtered through celite pad and the residue obtained after solvent evaporation in vacuo was acetylated. The worked up product after column chromatography (eluent benzene/methanol=24:1, v/v) gave **4a** (540 mg, 46.2%), yellow oil: R_f=0.45 (benzene/methanol=9:1, v/v; iodine as developer); IR (neat, cm^{-1}) 3314, 1734, 1648, 1542, 1244; ^{1}H NMR ($CDCl_3$) δ 1.62-1.63 (m, 4H, H-3 and H-4), 1.98 (s, 3H, NHCOC*H*$_3$), 2.06, 2.07 (2 × s, 12H, 4 × COC*H*$_3$), 3.35 (m, 2H, H-1), 4.12 (dd, 1H, $J_{6,7a}$=4.3 Hz, $J_{7a,7b}$=12.7 Hz, H-7a), 4.28 (dd, 1H, $J_{6,7b}$=6.7 Hz, H-7b), 4.88 (m, 1H, H-6), 5.11 (m, 2H, H-2 and H-5), 5.84 (brs, N*H*Ac); ^{13}C NMR ($CDCl_3$) δ 20.63 - 21.00 (CO*C*H$_3$), 23.04 (NHCO*C*H$_3$), 25.69 and 25.82 (C-4), 27.23 and 27.34 (C-3), 42.38 and 42.47 (C-1), 61.72 (C-7), 71.07 and 71.31 (C-6), 71.46 (C-2), 72.35 and 72.73 (C-5), 169.93, 170.07, 170.13, 170.17, 170.24, 170.60, 170.91 and 170.94 (*C*OCH$_3$); ESMS m/z 390 (M^+ + 1).

Anal. Calcd. for $C_{17}H_{27}NO_9$ (389.40): C, 52.44; H, 6.99; N, 3.60. Found: C, 52.78; H, 7.48; N, 3.82.

Mixture of (5*S*,6*R*)-6-acetoxy-1-amino-2,5,7-trihydroxy(erythro)-heptane and (5*S*,6*R*)-6-acetoxy-1-amino-2,5,7-trihydroxy(threo)-heptane (4b). To a solution of **2b** (70 mg, 0.16 mmol) in methanol (6 mL), 10% Pd-C (150 mg) was added and the mixture was hydrogenated at 379 kPa pressure for 6 h. Filtration through celite pad and the solvent evaporation in vacuo furnished **4b** (20 mg, 55.5%) as yellow oil which on subsequent acetylation gave **4a**.

(3*E*,5*S*,6*R*)-5,6,7-Triacetoxy-1-nitro-hept-3-ene (5). To a stirred solution of **3a** (50 mg, 0.15 mmol) in 50% aqueous acetonitrile (1.5 mL), sodium borohydride (50 mg) was added and the mixture was stirred for 30 min. at room temperature. 10% acetic acid was added to decompose the excess of reductant. Evaporation of the solvent, extraction of the residue with acetone and evaporation of the solvent followed by acetylation at 0-4 °C with acetic anhydride (5 mL) and pyridine (1 mL), after usual work up, furnished **5** (35 mg, 69.5%), as yellow oil: R_f=0.55 (benzene/ether=9:1, v/v; $KMnO_4$ as spray reagent); $[\alpha]_D$ +26.08° (c 0.07, methanol); IR (neat, cm^{-1}) 1740, 1550, 1436, 1224, 868; ^1H NMR ($CDCl_3$) δ 2.06, 2.07, 2.08 (3 × s, 9H, 3 × COC*H*$_3$), 2.75 (q, 2H, $J_{1,2}$=$J_{2,3}$= 6.6 Hz, H-2), 4.15 (dd, 1H, $J_{6,7a}$=4.3 Hz, $J_{7a,7b}$=12.7 Hz, H-7a), 4.23 (dd, 1H, $J_{6,7b}$=6.7 Hz, H-7b), 4.43 (t, 2H, $J_{1,2}$=6.7 Hz , H-1), 5.19 (m, 1H, H-6), 5.41 (dd~t, 1H, $J_{4,5}$=6.4 Hz, $J_{5,6}$=5.3 Hz, H-5), 5.58 (dd, 1H, $J_{3,4}$=15.3 Hz, H-3), 5.81 (dd, 1H, H-4); ^{13}C NMR ($CDCl_3$) δ 20.57, 20.70, 20.82 (3 × COC*H*$_3$), 29.80 (C-2), 61.65 (C-7), 71.23 (C-1), 71.75 (C-6), 74.26 (C-5), 127.88 (C-4), 129.94 (C-3), 169.47, 169.97, 170.46 (3 × *C*OCH$_3$); EIMS m/z 258 (M^+ - OAc).

Anal. Calcd. for $C_{13}H_{19}NO_8$ (317.29): C, 49.21; H, 6.03; N, 4.41. Found: C, 48.26; H, 5.73; N, 3.52.

(5*S*,6*R*)-1-Acetamido-5,6,7-triacetoxy-heptane (6). To a solution of **5** (360 mg, 1.13 mmol) in methanol (40 mL), 10% Pd-C (1 g) was added and the mixture was hydogenated at 379 kPa pressure for 8 h. The product was worked up followed by acetylation resulting in **6** (200 mg, 53.2%) as a yellow oil: R_f=0.40 (benzene/methanol=9:1, v/v; iodine as developer); $[\alpha]_D$ +17.87° (c 0.17, methanol); IR (neat, cm^{-1}) 3382, 1750, 1670, 1536, 1234; ^1H NMR ($CDCl_3$) δ 1.29 - 1.60 (m, 6H, H-2 , H-3, and H-4), 1.97 (s, 3H, NHCOC*H*$_3$), 2.06, 2.07, 2.11 (3 × s, 9H, 3 × COC*H*$_3$), 3.22 (q, 2H, $J_{1,2}$=$J_{1,NHAc}$=6.6 Hz, H-1)[14], 4.12 (dd, 1H, $J_{6,7a}$=4.3 Hz, $J_{7a,7b}$=12.7 Hz, H-7a), 4.28 (dd, 1H, $J_{6,7b}$=6.7 Hz, H-7b), 5.12 (m, 2H, H-5 and H-6), 5.73 (brs, N*H*Ac); ^{13}C NMR ($CDCl_3$) δ 20.64 - 20.81 (3 × CO*C*H$_3$), 22.32 (C-2), 23.13 (NHCO*C*H$_3$), 28.94 (C-3), 29.77 (C-4), 39.11 (C-1), 61.85 (C-7), 71.59 (C-6), 71.81 (C-5), 169.99, 170.28, 170.48, 170.62 (4 × *C*OCH$_3$); EIMS m/z 329 (M^+ - 2).

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