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An expeditious synthesis of a (3*S*,4*S*,5*R*)-trihydroxyazepane

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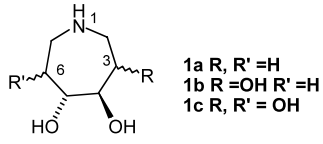
Abstract—A practical approach for the synthesis of the (2*S*,3*S*,4*R*)-trihydroxyazepane **1d** has been reported. Starting from α-D-*xylo*-pentodialdose, readily available from D-glucose, the sequence involves Wittig olefination and reductive amination as key steps.

Amongst polyhydroxylated imino-sugars, the seven-membered azepane compounds **1** play an important role as DNA minor groove binding ligands (MGBL) and as glycosidase inhibitors.[1] The primary advantage of these compounds is their high water solubility, allowing them to circumvent the problem of poor bio-availability seen with many other MGBL's. In addition, the pseudo-rotating conformations in the seven-membered ring (as compared to five or six-membered imino-sugars) render the ability of azepanes to point into the minor groove of DNA. This effect of adopting different conformations is augmented due to the probability of hydrogen bonding between the hydroxyl groups with the nitrogen of various bases. In the search for structure–activity relationship, attempts are being made to correlate the MGBL and glycosidase inhibitory activities for each hydroxyl substituent in azepanes.[2] This has led to the discovery of di-, tri- and tetra-hydroxylated azepane derivatives **1a**, **1b** and **1c** (Fig. 1), respectively, either by chemoenzymatic or chemical synthesis.[1,3] A number of synthetic approaches to tetrahydroxy-azepanes are known, however only limited synthetic strategies are reported for the trihydroxy derivatives. As a part of our ongoing interest in the synthesis of polyhydroxylated imino-sugars using the chiron approach,[4] we describe here a new efficient method for the synthesis of trihydroxyazepane **1d**.[5] Our approach hinges on the reductive amination of suitably protected 5-amino-5-deoxy-α-D-*xylo*-hexodialdo-1,4-furanose which can be obtained by a one carbon homologation of α-D-*xylo*-pentodialdose **2** using the Wittig olefination.



1a R, R' =H
1b R =OH R' =H
1c R, R' = OH

Figure 1.

Thus, reaction of 3-*O*-benzyl-1,2-*O*-isopropylidene-α-D-*xylo*-pentodialdose[6] **2** with the Wittig reagent, prepared from methoxymethyltriphenylphosphonium chloride and potassium-*t*-butoxide in *t*-butanol–THF, afforded a geometrical mixture of **3** (*E*:*Z* = 3:1) which on mild acid hydrolysis gave 5-deoxy-3-*O*-benzyl-1,2-*O*-isopropylidene-α-D-*xylo*-hexodialdo-1,4-furanose **4**[7] in 82% yield (Scheme 1).[8] Reductive amination of **4** using *N*-benzylamine and sodium cyanoborohydride afforded amino derivative **5**.[8] Hydrogenolytic removal of the *N*- and *O*-benzyl protecting groups in **5** with ammonium formate and 10% Pd–C in methanol gave an amino alcohol, which was directly subjected to selective *N*-Cbz protection with benzyl chloroformate to give 5,6-dideoxy-6-(*N*-benzyloxycarbonyl) amino-1,2-*O*-isopropylidene-α-D-*gluco*-furanose **6**. Treatment of **6** with TFA–water afforded an anomeric mixture of hemiacetals, which on hydrogenation using 10% Pd–C in methanol afforded trihydroxyazepane **1d** as a thick oil. The ^{1}H and ^{13}C NMR spectra and analytical data were in agreement with the proposed structure **1d**. The compound **1d** was treated with acetic anhydride in pyridine for three days to obtain the tetra-acetyl derivative **1e** as a solid. The melting point, analytical data and the optical rotation value[8] of **1e** was found to be in good agreement with those reported.[5]

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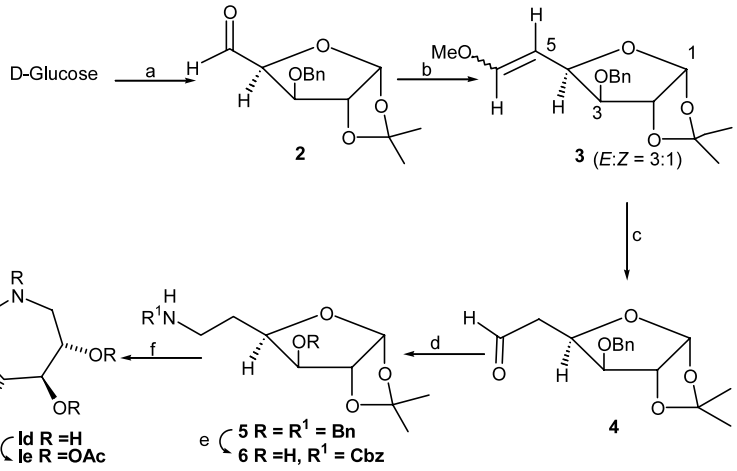

Scheme 1. *Reagents and conditions*: (a) Ref. 4; (b) potassium *t*-butoxide (1.5 equiv.), $H_3COCH_2PPh_3Cl$ (1.2 equiv.), *t*-BuOH–THF, −40°C, 2 h, 78%; (c) 3N HCl–THF (1:10), 25°C, 3 h, 88%; (d) $BnNH_2$ (1.1 equiv.), $NaCNBH_3$ (1.5 equiv.), cat. CH_3COOH, MeOH, −78°C, 2 h then 25°C, 24 h, 86%; (e) i. $HCOONH_4$ (7 equiv.), 10% Pd–C, MeOH, reflux, 40 min, ii. ClCOOBn (1.5 equiv.), $NaHCO_3$ (2.8 equiv.), MeOH–H_2O, 0–25°C, 2 h, 76%; (f) i. TFA–H_2O (3:2), 25°C, 2 h, ii. 10% Pd–C, MeOH, H_2, 80 psi, 25°C, 24 h, 85%; (g) Ac_2O, pyridine, 25°C, 72 h, 45%.

In summary, we have developed a simple and concise synthesis of trihydroxyazepane **1d**. The readily available starting material, low cost of reagents and high yields make our synthetic route practicable and workable on multigram scale.

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References

1. (a) Horita, K.; Yoshioka, T.; Tanaka, T.; Oikawa, Y.; Yonemitsu, O. *Tetrahedron* **1986**, *42*, 3021; (b) Winchester, B.; Fleet, G. W. J. *Glycobiology* **1992**, *2*, 199; (c) Wong, C. H.; Halcomb, R. L.; Ichikawa, Y.; Kajimato, T. *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 521; (d) Moris-Varas, F.; Qian, X.; Wong, C. H. *J. Am. Chem. Soc.* **1996**, *118*, 7647; (e) Qian, X.; Moris-Varas, F.; Fitzgerald, M. C.; Wong, C. H. *Bioorg. Med. Chem.* **1996**, *4*, 2055; (f) Le Merrer, Y.; Poitout, L.; Depazy, J.-C.; Dosbaa, I.; Geoffroy, S.; Foglietti, M. *Bioorg. Med. Chem.* **1997**, *5*, 519.
2. Johnson, H. A.; Thomas, N. R. *Bioorg. Med. Chem. Lett.* **2002**, *12*, 237.
3. (a) Poitout, L.; Le Merrer, Y.; Depazy, J.-C. *Tetrahedron Lett.* **1994**, *35*, 3293; (b) Lohray, B. B.; Jayamma, Y.; Chatterjee, M. *J. Org. Chem.* **1995**, *60*, 5958; (c) Poitout, L.; Merrer, Y. L.; Depazy, J.-C. *Tetrahedron Lett.* **1996**, *37*, 1613; (d) Herdeis, C.; Mohareb, R. M.; Neder, R. B.; Schwabenlander, F.; Tesler, J. *Tetrahedron: Asymmetry* **1999**, *10*, 4521; (e) Lohray, B. B.; Bhushan, V.; Prasuna, G.; Jayamma, Y.; Raheem, M. A.; Papireddiy, P.; Umadevi, B.; Premkumar, M.; Lakshmi, N. S.; Narayanreddy, K. *Indian J. Chem.* **1999**, *38B*, 1311–1321; (f) Painter, G. F.; Falshaw, A. *J. Chem. Soc., Perkin Trans. 1* **2000**, 1157; (g) Armbruster, J.; Stelzer, F.; Landenberger, P.; Wieber, C.; Hunkler, D.; Keller, M.; Prinzbach, H. *Tetrahedron Lett.* **2000**, *41*, 5483.
4. (a) Dhavale, D. D.; Desai, V. N.; Sindkhedkar, M. D.; Mali, R. S.; Castellari, C.; Trombini, C. *Tetrahedron: Asymmetry* **1997**, *9*, 1475; (b) Dhavale, D. D.; Saha, N. N.; Desai, V. N. *J. Org. Chem.* **1997**, *62*, 7482; (c) Dhavale, D. D.; Desai, V. N.; Saha, N. N. *Chem. Commun.* **1999**, 1719; (d) Patil, N. T.; Tilekar, J. N.; Dhavale, D. D. *J. Org. Chem.* **2001**, *66*, 1065; (e) Saha, N. N.; Desai, V. N.; Dhavale, D. D. *Tetrahedron* **2001**, *57*, 39; (f) Patil, N. T.; Tilekar, J. N.; Dhavale, D. D. *Tetrahedron Lett.* **2001**, *42*, 747; (g) Patil, N. T.; John, S.; Sabharwal, S. G.; Dhavale, D. D. *Bioorg. Med. Chem.* **2002**, *10*, 2155.
5. For the first synthesis of the tetra-acetylated derivative **1e** see: Paulsen, H.; Todt, K. *Chem. Ber.* **1967**, *100*, 512. No other synthesis of **1d** has been reported so far.
6. Wolfrom, M. L.; Hanessian, S. *J. Org. Chem.* **1962**, *27*, 1800.
7. Compound **4** is reported as unpublished results: Tronchet, J. M. J.; Bonenfant, A. P. *Helv. Chim. Acta* **1980**, *63*, 1644.
8. All new compounds were obtained in analytically pure form. Data of significant chemical shifts of major *E*-isomer **3**: ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.33 (s, 3H), 1.52 (s, 3H), 3.59 (s, 3H), 3.78 (d, $J=3.0$ Hz, 1H), 4.54–4.75 (m, 4H), 5.05 (dd, $J=12.9$ and 9.4 Hz, 1H), 5.92 (d, $J=3.9$ Hz, 1H), 6.67 (d, $J=12.9$ Hz, 1H), 7.25–7.36 (m, 5H). Anal. calcd for $C_{17}H_{22}O_5$: C, 66.65%; H, 7.23%. Found C, 66.43%; H, 7.37%. Data for **4**: $[\alpha]_D^{25}$ −40.21 (*c* 0.15, $CHCl_3$). IR (neat): 2733, 1722 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.33 (s, 3H), 1.51 (s, 3H), 2.85 (m, 2H), 3.99 (d, $J=3.02$ Hz, 1H), 4.53 (d, $J=11.8$ Hz, 1H), 4.50–4.73 (m, 3H), 5.90 (d, $J=3.57$ Hz, 1H), 7.25–7.36 (m, 5H), 9.73 (t, $J=1.3$, 1H); ^{13}C NMR (75 MHz $CDCl_3$): δ 26.26, 26.80,

42.61, 71.95, 75.39, 82.07, 82.25, 104.57, 111.57, 127.66, 127.96, 128.39, 128.41, 137.01, 199.71. Anal. calcd for $C_{16}H_{20}O_5$: C, 65.75%; H, 6.85%. Found C, 65.83%; H, 6.72%. Data for **5**: $[\alpha]_D^{25}$ −25.05 (*c* 0.2, $CHCl_3$). IR(neat): 3600–3300 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 1.32 (s, 3H), 1.49 (s, 3H), 1.72–1.92 (broad, 2H), 1.96–2.10 (m, 1H), 2.62–2.80 (m, 2H), 3.75 (AB quartet, $J=11.7$ Hz, 2H), 3.78 (d, $J=3.02$ Hz, 1H), 4.16–4.27 (m, 1H), 4.43 (d, $J=11.8$ Hz, 1H), 4.60 (d, $J=3.9$ Hz, 1H), 4.68 (d, $J=11.8$ Hz, 1H), 5.90 (d, $J=3.9$ Hz, 1H), 7.25–7.36 (m, 10H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 26.17, 26.66, 28.48, 46.35, 53.85, 71.56, 78.95, 82.03, 82.17, 104.53, 111.11, 126.74, 127.57, 127.73, 127.96, 128.20, 128.28, 128.37, 128.41, 137.29, 140.02. Anal. calcd for $C_{23}H_{29}NO_4$: C, 72.06%; H, 7.57%. Found C, 72.33%; H, 7.21%. Data for **6**: $[\alpha]_D^{25}$ 13.33 (*c* 0.15, $CHCl_3$). IR (neat): 3354, 1701 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 1.32 (s, 3H), 1.47 (s, 3H), 1.70–1.98 (m, 2H), 2.62–2.80 (broad 1H, exchangeable with D_2O), 3.18–3.40 (m, 2H), 3.95–4.20 (m, 2H), 4.50 (d, $J=3.9$ Hz, 1H), 5.06 (bs, 2H), 5.31 (broad 1H, exchangeable with D_2O), 5.87 (d, $J=3.9$ Hz, 1H), 7.25–7.40 (m, 5H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 26.16, 26.67, 28.10, 66.78, 75.47, 77.18, 78.72, 85.15, 104.27, 111.40, 128.02, 128.40, 136.29, 157.48. Anal. calcd for $C_{17}H_{23}NO_6$: C, 60.53%; H, 6.82%. Found C, 60.87%; H, 7.05%. Data for **1d**: $[\alpha]_D^{25}$ 16.36 (*c* 0.33, MeOH). ^1H NMR (300 MHz, D_2O): δ 1.72–2.20 (m, 2H), 2.95–3.20 (m, 2H), 3.27–3.37 (m, 2H), 3.40–3.52 (m, 1H), 3.55–3.70 (m, 1H), 3.72–3.87 (m, 1H); ^{13}C NMR (75 MHz, D_2O): δ 27.8, 53.0, 53.4, 68.0, 72.5, 78.7. Anal. calcd for $C_6H_{13}NO_3 \cdot H_2O$: C, 43.63%; H, 9.14%. Found C, 43.87%; H, 9.35%. Data of **1e**: mp = 108–110°C, lit.[5] 112–114°C, $[\alpha]_D^{25}$ 4.0 (*c* 0.5, $CHCl_3$), 4.6 (*c* 1, MeOH), lit.[5] $[\alpha]_D^{25}$ 4.8 (*c* 1, MeOH). IR (Nujol): 1740, 1642 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 1.80–2.62 (m, 14H), 3.32–3.65 (m, 2H), 3.67–3.82 (dd, $J=3.8$, 15.3 Hz, 1H), 3.84–4.02 (m, 1H), 4.84–4.96 (m, 1H), 4.96–5.08 (m, 1H), 5.13–5.28 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 20.6, 20.8, 21.3, 21.6, 28.8, 41.7, 47.1, 72.6, 74.2, 74.3, 169.4 (strong), 169.8, 171.0. The ^1H and ^{13}C NMR spectra of **1e** showed doubling of signals. This was due to the isomerisation by restricted rotation around C=N in the *N*-$COCH_3$ group. see: *Applications of NMR Spectroscopy in Organic Chemistry*; Jackman, L. M.; Sternhell, S., Eds.; Pergamon Press: Elmsford, NY, 1978; p. 361. An analogous observation was also noticed by us and others (Ref. 4d). Anal. calcd for $C_{14}H_{21}NO_7$: C, 53.34%; H, 6.70%. Found C, 53.63%; H, 7.01%.