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Expeditious synthesis of seven-membered iminocyclitols

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Abstract—A concise synthesis of an azepanetriol and an octahydropyrrolo[1,2-*a*]azepinepentol, by nitrone addition to a pent-4-enofuranoside derived from D-ribose, followed by reductive opening of the isoxazolidine ring formed, is reported.

Natural and synthetic iminocyclitols, frequently known as 'aza-sugars' show specific inhibition against glycosidases and glycosyltransferases, being potential therapeutic agents for viral, proliferative and metabolic diseases.[1] As a consequence, intensive work has been focused on their synthesis, usually directed towards the five- and six-membered iminocyclitols. However, little attention has been given to the azepane analogues, in spite of some reports that several tetra- and tri-hydroxy seven-membered iminocyclitols such as **1** and **2** (Fig. 1) show significant activity as glycosidase inhibitors.[2] In addition, azepanediol **3** has been used for the synthesis of balanol, a popular synthetic target with remarkable inhibitory activity against protein kinase C, which has an azepane ring in its structure.[3] Further to our recent synthetic approach to hydroxylated pyrrolizidines and hydroxylated carbocycles from enofurano(pyrano)-sides,[4] we now report a concise method for the synthesis of azepanetriol **4** and octahydropyrrolo[1,2-*a*]-azepinepentol **5**, in their protected form.

Addition of the nitrone CH_2=N(→O)Bn to pent-4-enofuranoside **6** (Scheme 1), readily available from D-ribose in three steps,[5] afforded cycloadduct **7** as a single

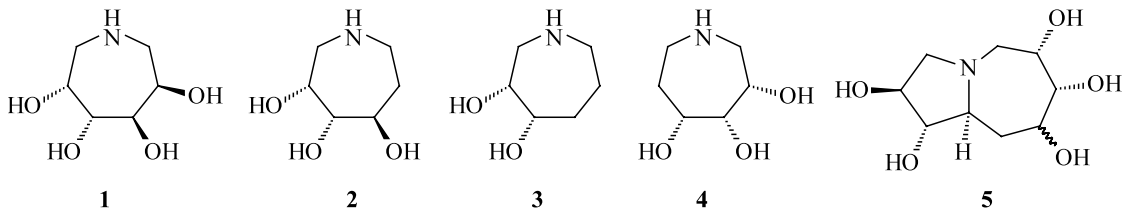
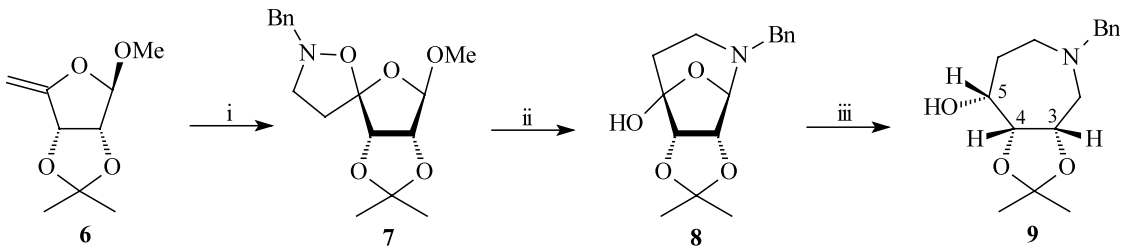


Figure 1.



Scheme 1. *Reagents and conditions*: (i) CH_2=N(→O)Bn, toluene, reflux, 72 h, 59% (30% of **6** recovered); (ii) Raney Ni, H_2, MeOH, H_3BO_3 (20 equiv.), $MgSO_4$, 20°C, 2 h, 56%; (iii) $NaBH_3CN$, AcOH (gl.), 20°C, 24 h, 49%.

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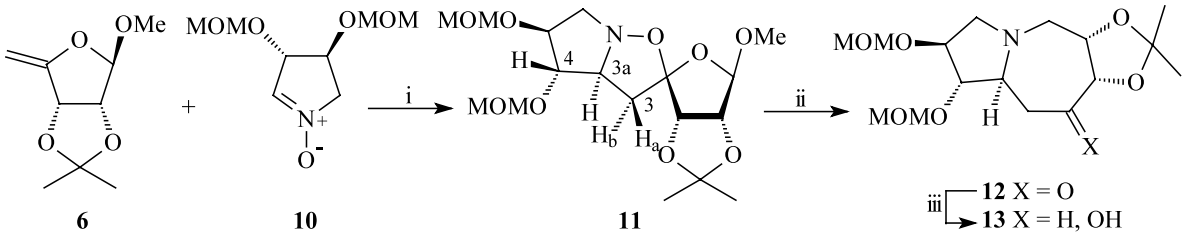

Scheme 2. *Reagents and conditions*: (i) toluene, reflux, 48 h, 96%; (ii) Raney Ni, H_2, MeOH, H_3BO_3 (20 equiv.), $MgSO_4$, 20°C, 24 h, 43% of **12** and 56% of **13** (as a ca. 1:1 mixture of epimers); (iii) $NaBH_4$, EtOH, 20°C, 4 h, 98% (as a ca. 1:1 mixture of epimers)

diastereomer.[6] Although the diastereoselectivity of this reaction is of no importance, since the spiro carbon loses its chirality in the next step, the assigned structure was analogous to the cycloadducts obtained from the nitrile oxide and nitrosoalkene additions to **6**.[4] This diastereoselectivity results from addition of the nitrone to the less hindered face of the double bond. Raney Ni hydrogenation of **7** in MeOH at 20°C in the presence of 20 equiv. of H_3BO_3, led to the formation of compound **8**, isolated in good yield. Evidently, N–O bond cleavage by hydrogenolysis was followed by MeOH elimination to an aminoketoaldehyde, which spontaneously cyclised to the *N*,*O*-acetal-*O*,*O*-hemiacetal **8**. Treatment of **8** with $NaBH_3CN$ in glacial AcOH at 20°C, gave the protected azepanetriol **9** as a single diastereomer in good yield,[2h] resulting from further reduction of the ketone intermediate. A bicyclic compound analogous to **8** has been previously isolated as a by-product in the Raney Ni hydrogenation of a nitrile oxide adduct to **6**.[4c]

It was apparent that a bicyclic iminocyclitol with an azepane fused ring could be prepared by using a cyclic nitrone and applying the above reaction sequence. Indeed, 3,4-dihydro-2*H*-pyrrole-1-oxide was smoothly added to **6**, but the diastereoselectivity of the reaction was poor. A most satisfactory diastereoselection was achieved by adding the chiral nitrone **10**[7] to the ribose derivative **6**, where cycloadduct **11** was isolated in good yield, together with the C-3a epimer, in a ratio ca. 8.5:1 (Scheme 2). Further, Raney Ni hydrogenation in MeOH at 20°C in the presence of 20 equiv. of H_3BO_3 gave directly the desired protected octahydropyrrolo[1,2-*a*]azepinepentol **13** (56%), together with its ketone precursor **12** (43%). The latter was quantitatively reduced to **13** with $NaBH_4$. Compound **13** was isolated as an inseparable mixture of epimers in ca. 1:1 ratio, due to the non-selective reduction of the carbonyl group of **12** by Raney Ni or $NaBH_4$.

The different reactivity of cycloadducts **7** and **11** towards Raney Ni hydrogenation could be attributed to the *N*-benzyl group of **7**, which reduces the reactivity of the secondary amine generated by N–O bond cleavage and its addition to the aldehyde, formed at the same time, stops with the formation of the *N*,*O*-acetal-*O*,*O*-hemiacetal **8**. In the case of **11**, it is plausible that an intermediate similar to **8** was formed, which then underwent spontaneous elimination of water after protonation of the hydroxyl group, followed by hydrogenation of the C=N bond thus generated. In the case of **8**, the presence of $NaCNBH_3$ in AcOH was necessary to complete the reaction.

With the exception of **12**, all new compounds were characterized on the basis of their spectroscopic and analytical data, which were consistent with the given structures.[6] Compound **12** was relatively unstable and could not be isolated in pure form, but the signal at δ 203.1 in the ^{13}C NMR spectrum as well as the measured exact molecular mass leaves little doubt of its structure. Especially for compounds **9** and **11** (and therefore **12** and **13**), NOE experiments confirmed the assigned absolute configuration of the newly formed stereocenters, resulting from the reduction of the carbonyl group and the addition of nitrone to **6**, respectively. The significant signal enhancements of the 3-H and 5-H protons when irradiating the 4-H proton of **9** confirms its expected all-*cis* stereochemistry. In the case of **11**, the strong signal enhancement of 3a-H upon saturation of 3-H_b and the considerable enhancement of the 3-H_a signal caused by the saturation of 4-H confirm the configuration of the newly formed chiral center in the major epimer of **11**. Regarding compound **13**, as already mentioned, it is an inseparable mixture of epimers in ca. 1:1 ratio, the epimers being different in the absolute configuration of the stereocenter resulting from reduction of the carbonyl group of **12**.

In conclusion, a new method for the synthesis of hydroxylated azepanes, either monocyclic or fused with a pyrrolidine ring from readily available pent-4-enofuranoside has been developed, utilizing cheap and easily available reagents, applying simple and convenient methods. Further work in the synthesis of some other azepanol analogues is in progress.

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6. All new compounds gave spectral and analytical data consistent with the proposed structures. Compound **7**: oil, $[\alpha]_D$ +49.9 (*c* 4.62, $CHCl_3$); ^1H NMR ($CDCl_3$, 50°C): δ 1.31 (s, 3H), 1.43 (s, 3H), 2.35 (m, 2H), 2.95 (m, 2H), 3.30 (s, 3H), 4.01 (d, 1H, $J=12.2$ Hz), 4.05 (d, 1H, $J=12.2$ Hz), 4.63 (s, 2H), 4.96 (s, 1H), 7.3 (m, 5H); ^{13}C NMR ($CDCl_3$, 50°C): δ 25.3, 26.4, 36.3, 53.7, 54.7, 63.4, 84.1, 84.8, 108.30, 108.31, 112.7, 127.4, 128.3, 129.2, 137.2; HRMS (MALDI-FTMS) calcd ($C_{17}H_{24}NO_5$) 322.1649 (M+H), found 322.1651, σ 0.6 ppm. Compound **8**: oil, $[\alpha]_D$ +1.0 (*c* 0.5, $CHCl_3$); ^1H NMR ($CDCl_3$): δ 1.37 (s, 3H), 1.47 (m, 1H), 1.51 (s, 3H), 2.23 (dt, 1H, $J=6.7$, 6.2 Hz), 2.82 (m, 2H), 3.81 (d, 1H, $J=13.3$ Hz), 3.96 (d, 1H, $J=13.3$ Hz), 3.98 (s br, 1H), 4.32 (d, 1H, $J=5.5$ Hz), 4.60 (s, 1H), 4.69 (d, 1H, $J=5.5$ Hz), 7.3 (m, 5H); ^{13}C NMR ($CDCl_3$): δ 25.1, 26.0, 28.7, 43.3, 55.9, 79.6, 82.8, 92.4, 102.0, 112.9, 127.3, 128.4, 128.9, 138.2; HRMS (MALDI-FTMS) calcd ($C_{16}H_{22}NO_4$) 292.1543 (M+H), found 292.1535, σ 2.7 ppm. Compound **9**: oil, $[\alpha]_D$ −10.7 (*c* 2.8, $CHCl_3$); ^1H NMR ($CDCl_3$): δ 1.33 (s, 3H), 1.43 (s, 3H), 1.83 (m, 2H), 2.40 (m, 2H), 2.50 (s br, 1H), 2.95 (m, 2H), 3.54 (d, 1H, $J=13.2$ Hz), 3.70 (d, 1H, $J=13.2$ Hz), 3.85 (ddd, 1H, $J=9.6$, 7.5, 2.3 Hz), 4.10 (dd, 1H, $J=8.7$, 7.5 Hz), 4.32 (ddd, 1H, $J=10.7$, 7.5, 5.4 Hz), 7.3 (m, 5H); ^{13}C NMR ($CDCl_3$): δ 24.7, 27.5, 33.3, 55.4, 55.7, 63.6, 71.4, 75.1, 82.9, 108.7, 127.2, 128.3, 128.7, 138.4; HRMS (MALDI-FTMS) calcd ($C_{16}H_{24}NO_3$) 278.1751 (M+H), found 278.1747, σ 1.4 ppm. Compound **11**: oil, $[\alpha]_D$ +44.6 (*c* 1.07, $CHCl_3$); ^1H NMR ($CDCl_3$): δ 1.32 (s, 3H), 1.45 (s, 3H), 2.62 (dd, 1H, $J=13.8$, 8.1 Hz), 2.83 (dd, 1H, $J=13.8$, 6.2 Hz), 3.37 (s, 3H), 3.38 (s, 3H), 3.41 (s, 3H), 3.42 (dd, 1H, $J=13.8$, 3.2 Hz), 3.56 (dd, 1H, $J=13.8$, 5.7 Hz), 3.78 (ddd, 1H, $J=8.1$, 6.2, 3.5 Hz), 4.09 (dd as t, 1H, $J=3.5$ Hz), 4.23 (ddd as dt, 1H, $J=5.7$, 3.5 Hz), 4.65 (m, 6H), 4.99 (s, 1H); ^{13}C NMR ($CDCl_3$): δ 25.0, 26.2, 41.4, 54.7, 55.4 (two MeO from MOM overlapping), 60.0, 69.2, 83.1, 83.5, 84.5, 87.1, 95.9, 96.0, 107.8, 112.6, 116.4; HRMS (MALDI-FTMS) calcd ($C_{17}H_{30}NO_9$) 392.1915 (M+H), found 392.1918, σ 0.8 ppm. Compound **12**: oil; HRMS (MALDI-FTMS) calcd ($C_{16}H_{28}NO_7$) 346.186 (M+H), found 346.1856, σ 1.2 ppm. Compound **13**: oil; ^1H NMR ($CDCl_3$): δ 1.32 (s, 3H), 1.46 (s, 3H), 1.65 (m, 2H), 2.2–3.2 (several m, 5H), 3.34 (s, 3H), 3.35 (s, 3H), 3.42 (m, 1H), 3.73 (m, 1H), 3.98 (m, 1H), 4.18 (m, 1H), 4.6–4.75 (m, 6H); ^{13}C NMR ($CDCl_3$): δ 26.4/26.5, 27.2/27.3, 29.6/29.7, 55.55/55.59, 55.63/55.68, 55.70/55.77, 61.1/61.5, 63.9/65.1, 70.5/70.7, 72.1/74.1, 78.3/78.9, 83.0/83.1, 88.0/89.4, 95.2/95.3, 95.7/95.9, 108.6/109.3; HRMS (MALDI-FTMS) calcd ($C_{16}H_{30}NO_7$) 348.2017 (M+H), found 348.2023, σ 1.7 ppm.
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