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# Stereo-controlled approach to pyrrolidine iminosugar C-glycosides and 1,4-dideoxy-1,4-imino-L-allitol using a D-mannose-derived cyclic nitrone

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ABSTRACT

Intramolecular N-alkylation of 2,3-*O*-isopropylidene-5-*O*-methanesulfonyl-6-*O*-*t*-butyldimethylsilyl-D-mannofuranose-oxime **7** afforded a five-membered cyclic nitrone **9**, which on *N*–*O* bond reductive cleavage followed by deprotection of *–OTBS* and acetonide functionalities gave 1,4-dideoxy-1,4-imino-L-allitol (DIA) **3**. Addition of allylmagnesium chloride to nitrone **9** afforded α-allylated product **10a** in high diastereoselectivity providing an easy entry to *N*-hydroxy-C1-α-allyl-substituted pyrrolidine iminosugar **4a** after removal of protecting group, while *N*–*O* bond reductive cleavage in **10a** afforded C1-α-allyl-pyrrolidine iminosugar **4b**.



Enantiopure five-membered hydroxylated cyclic nitrones are precursors of chiral pyrrolidine, pyrrolizidine, and indolizidine iminosugars by exploiting 1,3-dipolar cycloaddition,[1] 1,3-addition of organometallics,[2] and $SmI_2$-mediated reductive coupling reactions.[3] Amongst iminosugars, five-membered pyrrolidine compounds such as 2,5-dideoxy-2,5-imino-D-mannitol (DMDP) **1** (Fig. 1) and 2,5-dideoxy-2,5-imino-D-glycero-D-manno-heptitol (homo DMDP) **2** are selective inhibitors of α- and β-glucosidases.[4] The 1,4-dideoxy-1,4-imino-L-allitol (DIA) **3** is a moderately good inhibitor of human liver α-D-mannosidase and a weak inhibitor of α-L-fucosidase, *N*-acetyl-β-D-hexosaminidase, and β-D-mannosidase.[5] In addition, much interest is now focused on C1-alkyl, vinyl, and allyl-substituted pyrrolidine and piperidine iminosugars[6,7] which were found to be more selective inhibitors of glycosidases. In particular, the C1-allylated iminosugars have found significant importance due to the synthetic versatility of the C=C bond (as a precursor for further functionalities) and its use in the synthesis of neoglycoconjugates and *C*-disaccharides.[7] As a part of our efforts in use of nitrones toward the synthesis of iminosugars,[8] we now report the intramolecular N-alkylation of D-mannose-derived oxime **7**[9] in the synthesis of five-membered cyclic nitrone **9** that was exploited in the synthesis of DIA **3** and the hitherto unknown C1-α-allylated pyrrolidine iminosugars **4a** and **4b**.

The required 1-*O*-benzoyl-2,3-*O*-isopropylidene-6-*O*-*t*-butyldimethylsilyl-α-D-mannofuranose **5** was prepared from D-mannose as reported earlier.[10] Treatment of **5** with mesyl chloride in the presence of triethyl amine in $CH_2Cl_2$ afforded mesylated product **6**[11] in 98% yield (Scheme 1). Debenzoylation of **6** using potassium carbonate in methanol afforded a mixture of hemiacetals (α/β anomers = 3:1) which on treatment with hydroxylamine hydrochloride and sodium bicarbonate in methanol–water at room temperature for 2 h afforded a mixture of *syn*- and *anti*-oxime **7**.[12] In the subsequent step, reaction of oxime **7** with hydroxylamine hydrochloride[13] and sodium bicarbonate in methanol–water at reflux for 12 h afforded five-membered cyclic nitrones **8** and **9** in the ratio of 2:8. The structure of five-membered nitrone

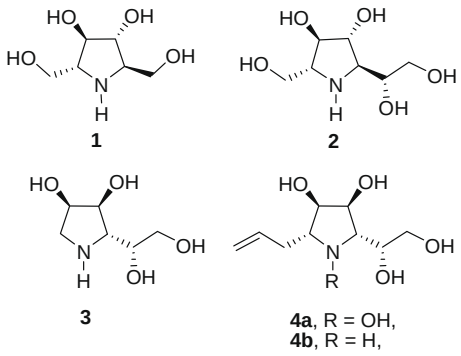


**Figure 1.** Iminosugars and analogues.

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**8** was established by the spectral data and the single crystal X-ray analysis[14] (Fig. 2).

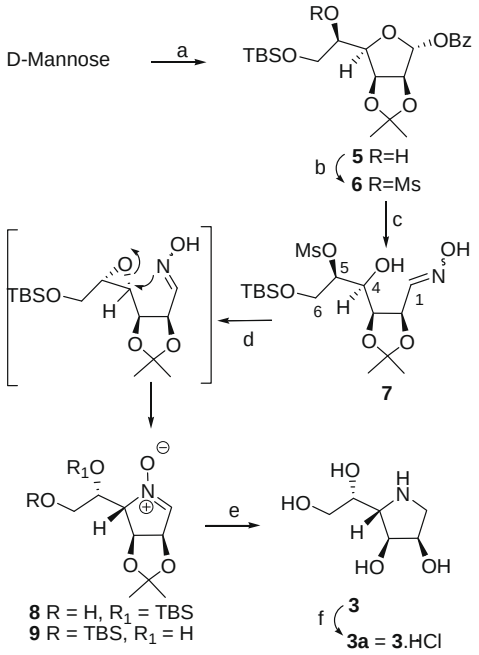
The $^{1}H$ and $^{13}C$ NMR data[15] of nitrone **9** were found to be nearly identical to those of **8** (slight difference in the $\delta$ and $J$ values), indicating formation of five-membered nitrone **9** whose structure was confirmed in subsequent steps by single crystal X-ray analysis (vide supra). The formation of nitrone **9** probably involves in situ generation of an epoxide by intramolecular $S_N2$ displacement of C5-mesyl group by C4-hydroxyl group. The intramolecular 5-*exo-tet* epoxide ring opening by nucleophilic attack of the nitrogen atom (from the side opposite to epoxide ring) afforded nitrone **9** as a major product, as expected on the basis of Baldwin rules,[16] with inversion of configuration at C4 and C5 (Scheme 1). No trace of six-membered nitrone derived from the less favored 6-*endo-tet* ring closure mode was observed. Under reflux conditions, migration of the *t*-butyldimethylsilyl (TBS) group from primary (C6) to secondary (C5) hydroxyl functionality occurred,[17] affording nitrone **8** as a minor product.

The utility of nitrone **9** was first demonstrated in the synthesis of the known pyrrolidine iminosugar DIA **3**. Thus, one pot *N–O* bond reductive cleavage and reduction of *C=N* bond in nitrone **9** (or a mixture of **8** and **9**) by hydrogenation ($H_2$/10% Pd/C in methanol) followed by cleavage of 2,3-*O*-isopropylidene functionality and desilylation with TFA–$H_2O$ (9:1), afforded **3** in good yield. The spectral and analytical data[18] were found to be in agreement with structure **3** which was further confirmed by converting it into known hydrochloride salt (MeOH–HCl). Thus, treatment of DIA **3** with MeOH–HCl gave hydrochloride salt **3a**. The spectral and analytical data of **3a** were found to be in consonance with those reported[5b] {mp 110–112 °C, $[\alpha]_D^{20}$ −26.0 (*c* 1.0, $H_2O$), [lit[5b] mp 112–113 °C, $[\alpha]_D^{20}$ −24.6 (*c* 1.12, $H_2O$)]}.

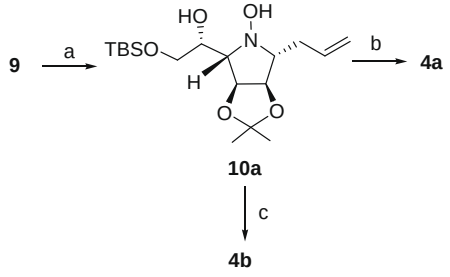
Targeting toward pyrrolidine iminosugar C-glycosides, we explored the 1,3-addition of allylmagnesium chloride to nitrone **9** (Scheme 2). This reaction in THF at 0–25 °C for 2.5 h afforded C1-α-allylated *N*-hydroxy pyrrolidine iminosugar **10a** and its C1-epimer **10b** in the ratio 92:08, respectively, as evident from the $^{1}H$ NMR spectrum of crude product. Our attempts to separate the mixture by column chromatography were unsuccessful. However, crystallization with hexane/ethyl acetate (9:1) gave pure α-allylated diastereomer **10a** in 75% yield.[19] The absolute configuration at newly generated C1-stereocenter in **10a** was firmly established as 1*R* based on the single crystal X-ray analysis[20] (Fig. 3) which also confirms the structure of five-membered cyclic nitrone **9**.[21]

In the next step, reaction of **10a** with TFA–$H_2O$ (9:1) at 0–25 °C for 6 h afforded N-hydroxylated pyrrolidine C-glycoside **4a** in 88% yield.[22] Alternatively, **10a** was subjected to *N–O* bond reductive cleavage using *Zn*–acetic acid which on treatment with TFA–$H_2O$ (9:1) at 0–25 °C gave C1-α-allylated pyrrolidine C-glycoside **4b**.[23]

In conclusion, we have reported a new chiral cyclic nitrone **9** from D-mannose in 34% overall yield and demonstrated its utility in the synthesis of DIA **3**. In addition, we have reported our preliminary results on the 1,3-addition of allylmagnesium chloride to nitrone **9** which was found to be highly stereoselective. The resulting C1-α-allyl-substituted pyrrolidine is easily converted into C-




**Scheme 1.** Reagents and conditions: (a) Ref. 10; (b) MsCl, $Et_3N$, DCM, 3 h, 98%; (c) (i) $K_2CO_3$, MeOH, 25 °C, 0.5 h, 98%, (ii) hydroxylamine hydrochloride, $NaHCO_3$, MeOH–$H_2O$, rt for 3 h, 90%; (d) hydroxylamine hydrochloride, $NaHCO_3$, MeOH–$H_2O$, reflux for 12 h, 80% in the 2:8 ratio; (e) (i) $H_2$, Pd/C, 12 h, (ii) TFA, $H_2O$, (9:1), 0–25 °C, 6 h, 75%; (f) MeOH, HCl, 25 °C, 2 h. 98%.




**Scheme 2.** Reagents and conditions: (a) allylmagnesium chloride, THF, 0–25 °C, 75%; (b) TFA–$H_2O$, 9:1 ratio, 0–25 °C, 6 h, 80%; (c) (i) Zn, MeOH–acetic acid 20:1 ratio, reflux 3 h, (ii) TFA–$H_2O$, 9:1 ratio, 0–25 °C, 6 h, 82%.

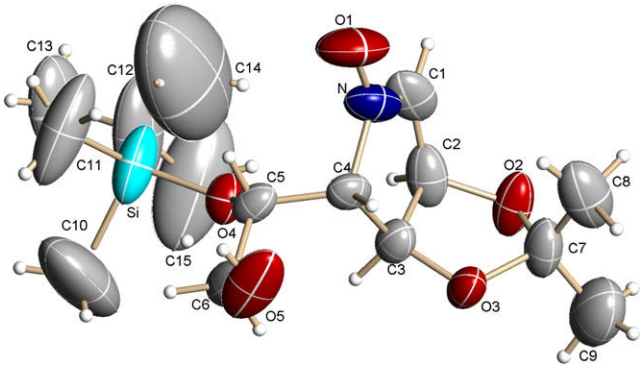



**Figure 2.** ORTEP diagram of compound **8**.

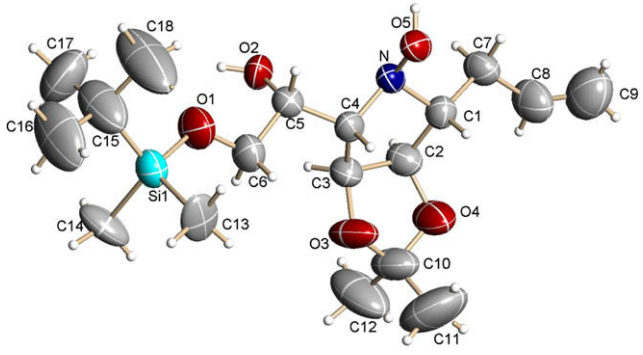



**Figure 3.** ORTEP diagram of compound **10a**.

glycosided pyrrolidine iminosugars **4a** and **4b**. The present approach is general and is useful for the synthesis of a variety of *C1*-alkyl, vinyl, and aryl glycosides of pyrrolidine iminosugars.

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11. *Spectral data for* **6**: thick liquid; $[\alpha]_D^{25}$ +48.92 (*c* 0.32, $CHCl_3$). IR (Nujol): 1728, 1217 $cm^{-1}$; $^1H$ NMR (300 MHz, $CDCl_3$): $\delta$ 0.01 (s, 3H), 0.06 (s, 3H), 0.80 (s, 9H), 1.38 (s, 3H), 1.56 (s, 3H), 3.11 (s, 3H), 3.91 (dd, *J* = 12.0, 4.2 Hz, 1H), 4.12 (dd, *J* = 12.0, 1.8 Hz, 1H), 4.51 (dd, *J* = 7.5, 3.3 Hz, 1H), 4.82–4.89 (m, 2H), 4.94 (dd, *J* = 6.0, 3.3 Hz, 1H), 6.39 (s, 1H), 7.43 (t, *J* = 7.5 Hz, 2H), 7.58 (t, *J* = 7.5 Hz, 2H), 7.98 (d, *J* = 8.7 Hz, 1H); $^{13}C$ NMR (75 MHz, $CDCl_3$): $\delta$ −5.5, −5.3, 18.2, 25.0, 25.7 (s), 26.1, 38.6, 62.4, 78.9(s), 80.0, 84.8, 100.8, 113.3, 128.3(s), 129.1 (s), 133.4, 164.5. Anal. Calcd for $C_{23}H_{36}NO_9SSi$: C, 53.47; H, 7.03. Found: C, 53.53; H, 7.23.
12. *Selected data of major syn oxime* **7**: $^1H$ NMR (300 MHz, $CDCl_3$): $\delta$ 0.04 (s, 3H), 0.06 (s, 3H), 0.81 (s, 9H), 1.27 (s, 3H), 1.44 (s, 3H), 3.01 (s, 3H), 3.71 (br d, *J* = 6.9 Hz, 1H), 3.99 (dd, *J* = 12.3, 3.6 Hz, 1H), 4.08 (dd, *J* = 12.3, 2.4 Hz, 1H), 4.30 (br s, 1H, exchangeable with $D_2O$), 4.38–4.48(m, 1H), 4.53 (d, *J* = 7.8 Hz, 1H), 5.18 (dd, *J* = 7.8, 3.9 Hz, 1H), 6.95 (d, *J* = 3.9 Hz, 1H), 9.25(br s, 1H, exchangeable with $D_2O$); $^{13}C$ NMR (75 MHz, $CDCl_3$): $\delta$ −5.2, −5.0, 18.6, 24.4, 25.8, 26.2(s), 38.2, 63.0, 66.7, 721, 76.7, 82.3, 109.4, 151.6. Anal. Calcd for $C_{16}H_{33}NO_8SSi$: C, 44.94; H, 7.78. Found: C, 44.63; H, 7.98. The $^1H$ and $^{13}C$ NMR spectrum showed additional signals (∼15%) corresponding to other isomer.
13. Oxime **7** in the presence of hydroxylamine hydrochloride offered better results in terms of yields and reproducibility. An analogous observation is reported, see: Refs. 3 and 9d.
14. Crystallographic data for compound **8** have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication No. CCDC 742578. Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK. Fax: +44 1223 336033. E-mail: deposit@ccdc.cam.ac.uk.
15. *Spectral data for* **8**: white solid, mp 140–142 °C; $[\alpha]_D^{25}$ +39.29 (*c* 0.24, $CHCl_3$). IR (Nujol): 3540–3200, 1728, 1217 $cm^{-1}$; $^1H$ NMR (300 MHz, $CDCl_3$+$D_2O$): $\delta$ 0.02 (s, 3H), 0.06 (s, 3H), 0.81 (s, 9H), 1.33 (s, 3H), 1.40 (s, 3H), 3.67 (dd, *J* = 11.1, 6.9 Hz, 1H), 3.8 (dd, *J* = 11.1, 4.8 Hz, 1H), 4.20 (br s, 1H), 4.44 (dd, *J* = 6.9, 4.8 Hz, 1H), 4.98 (d, *J* = 6.3 Hz, 1H), 5.10 (d, *J* = 6.3 Hz, 1H), 6.87 (s, 1H); $^{13}C$ NMR (75 MHz, $CDCl_3$+$D_2O$): $\delta$ −5.1, −4.8, 17.9, 25.3(s), 27.3, 64.1, 69.3, 74.7, 79.0, 81.9, 111.6, 133.2. Anal. Calcd for $C_{15}H_{29}NO_5Si$: C, 54.35; H, 8.82. Found: C, 54.53; H, 8.98. Data for **9**: white solid, mp = 145–147 °C; $[\alpha]_D^{25}$ +12.5 (*c* 0.05, $CHCl_3$); IR (Nujol): 3450–3050, 1725, 1583 $cm^{-1}$; $^1H$ NMR (300 MHz, $CDCl_3$+$D_2O$) $\delta$ 0.10 (s, 6H), 0.91 (s, 9H), 1.35 (s, 3H), 1.44 (s, 3H), 3.5–3.8 (m, 2H), 4.13 (br s, 1H), 4.33 (dt, *J* = 6.0, 1.5 Hz, 1H), 4.70 (d, *J* = 6.3 Hz, 1H), 5.29 (d, *J* = 6.3 Hz, 1H), 6.95 (s, 1H); $^{13}C$ NMR (75 MHz, $CDCl_3$+$D_2O$) $\delta$ −5.4, −5.3, 18.3, 25.6, 25.8 (s), 27.2, 64.2, 68.1, 75.0, 79.0, 81.3, 111.5, 133.2; Anal. Calcd for $C_{15}H_{29}NO_5Si$: C, 54.35; H, 8.82. Found: C, 54.54; H, 8.60.
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17. (a) Hiller, M. C.; Meyers, A. I. *Tetrahedron Lett.* **2001**, *42*, 5145; (b) Rucker, C. *Chem. Rev.* **1995**, *95*, 1009.
18. *Data for* **3**: thick liquid, $[\alpha]_D^{25}$ −63.4 (*c* 0.20, MeOH). IR (neat) 3650–3150 $cm^{-1}$; $^1H$ NMR (300 MHz, $D_2O$): $\delta$ 3.35 (dd, *J* = 12.9, 2.1 Hz, 1H), 3.46 (dd, *J* = 12.9, 3.6 Hz, 1H), 3.67 (dd, *J* = 8.1, 3.3 Hz, 1H), 3.72–3.79 (m, 2H); 1.3 (apperant q, *J* = 5.4 Hz, 1H), 4.33–4.40 (m, 1H), 4.42 (dd, *J* = 8.1, 4.2 Hz, 1H); $^{13}C$ NMR (75 MHz, $D_2O$): $\delta$ 50.0, 61.8, 62.4, 68.6, 70.0, 70.3; Anal. Calcd for $C_6H_{13}NO4$: C, 44.16; H, 8.03. Found: C, 44.30; H, 8.25.
19. *Data for compound* **10a**: white solid, mp 89–91 °C; $[\alpha]_D^{25}$ +2.76 (*c* 0.11, $CHCl_3$); IR (neat) 3676–3250 $cm^{-1}$; 1215, 759; $^1H$ NMR (300 MHz, $CDCl_3$): $\delta$ 0.05 (s, 6H), 0.09 (s, 9H), 1.25 (s, 3H), 1.50 (s, 3H), 2.30–2.45 (m, 1H), 2.46–2.62 (m, 1H), 2.94 (dd, *J* = 5.7, 2.7 Hz, 1H), 3.01 (apperent q, *J* = 6.9 Hz, 1H), 3.04–3.20 (1H, exchangeable with $D_2O$), 3.67 (dd, *J* = 10.4, 7.4 Hz, 1H), 3.73 (dd, *J* = 10.4, 4.8 Hz, 1H), 3.95–4.04 (m, 1H), 4.13 (t, *J* = 6.9 Hz, 1H), 4.53 (dd, *J* = 6.9, 5.7 Hz, 1H), 5.04–5.22 (m, 2H), 5.50–5.80 (1H, exchangeable with $D_2O$), 5.80–6.00 (m, 1H); $^{13}C$ NMR (75 MHz, $CDCl_3$) $\delta$ −5.25, −5.20, 18.3, 25.2, 25.9 (s), 27.2, 35.9, 64.5, 69.2, 72.3, 74.0, 74.8, 79.5, 113.3, 117.1, 134.4; Anal. Calcd for $C_{18}H_{35}NO_5Si$: C, 57.87; H, 9.44. Found: C, 57.71; H, 9.29.
20. Crystallographic data for compound **10a** have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication No. CCDC 742579. Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK. Fax: +44 1223 336033. E-mail: deposit@ccdc.cam.ac.uk.
21. The observed diastereoselectivity was found to be analogous to earlier report in which addition of vinylmagnesium chloride to five-membered cyclic nitrone afforded major product from the face opposite to the 2-*O*-Bn group, see: Ref. 2a.
22. *Data for* **4a**: thick liquid, $[\alpha]_D^{25}$ +1.7 (*c* 0.11, MeOH). IR (neat) 3600–3250 $cm^{-1}$; $^1H$ NMR (300 MHz, $D_2O$): $\delta$ 2.38−2.54 (m, 2H), 2.88 (t, *J* = 4.2 Hz, 1H), 2.97 (dt, *J* = 6.0, 5.7 Hz, 1H), 3.60–3.72(m, 2H), 3.75 (dd, *J* = 11.7, 3.9 Hz, 1H), 3.93 (quin, *J* = 3.9 Hz, 1H), 4.03 (t, *J* = 5.7 Hz, 1H), 5.04–5.28 (m, 2H); 5.86–6.06 (m, 1H); $^{13}C$ NMR (75 MHz, $D_2O$): $\delta$ 34.9, 63.4, 67.7, 70.4, 70.9, 71.0, 75.2, 117.2, 135.0; Anal. Calcd for $C_9H_{17}NO_5$: C, 49.31; H, 7.82. Found: C, 49.59; H, 7.65.
23. *Data for* **4b**: thick liquid, $[\alpha]_D^{25}$ +13.0 (*c* 0.13, MeOH). IR (Neat) 3770–3050 $cm^{-1}$; $^1H$ NMR (300 MHz, $D_2O$): $\delta$ 2.40–2.59 (m, 1H), 2.60–2.75 (m, 1H), 3.67 (dt, *J* = 9.0, 6.0 Hz, 1H), 3.72–3.79 (m, 3H), 4.05–4.12 (m, 2H), 4.45 (t, *J* = 5.14 Hz, 1H), 5.25–5.38 (m, 2H), 5.78–5.95 (m, 1H); $^{13}C$ NMR (75 MHz, $D_2O$): $\delta$ 33.6, 61.9, 62.7, 64.9, 68.2, 68.9, 73.4, 120.0, 132.0; Anal. Calcd for $C_9H_{17}NO_4$: C, 53.19; H, 8.43. Found: C, 53.40; H, 8.31.