New entry for asymmetric deoxyazasugar synthesis: syntheses of deoxymannojirimycin, deoxyaltrojirimycin and deoxygalactostatin

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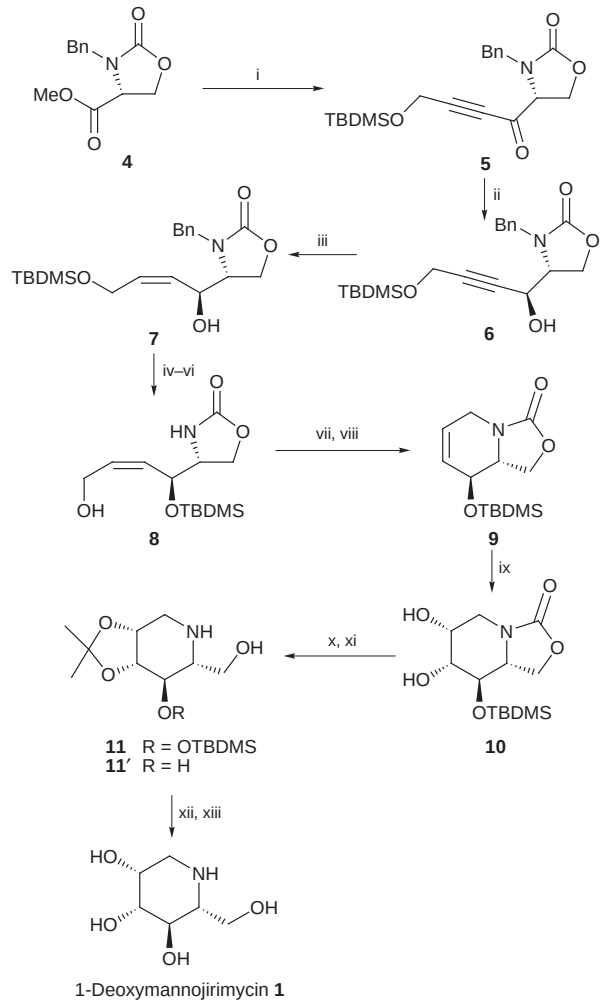
Deoxyazasugars such as deoxymannojirimycin, deoxyaltrojirimycin and deoxygalactostatin were stereoselectively synthesized starting from (*R*)-(+)-4-methoxycarbonyloxazolidinone *via* a bicyclic oxazolidinylpiperidine as a common synthetic intermediate.

Recently, polyhydroxylated piperidine alkaloids have received much attention due to their importance as glycosidase inhibitors.[1] Among them, deoxymannojirimycin **1** isolated from *Lonchocarpus* sp.,[2] deoxyaltrojirimycin **2**[3] and deoxygalactostatin **3**[4] can be regarded as deoxyazasugars based on their structural relationship to deoxysugars. Deoxy compound **1** is a moderate inhibitor of α-mannosidases and a good inhibitor of mammalian α-fucosidase, compound **2** is known as an analogue of **1** and is named in the relation with altrose, and compound **3** is a potent inhibitor of galactosidase. Because of the significant biological activities of these compounds as well as their characteristic structure, a number of synthetic efforts have been reported.[5]†

We previously developed both enantiomers of 4-methoxycarbonyloxazolidinone **4** as a chiral building block for the synthesis of natural amino alcohols, and realized the stereoselective syntheses of both γ-hydroxy-β-amino alcohols[6] and sphingolipids.[7] As part of our continuing interest in the synthetic utility of **4**, we have applied this methodology to the synthesis of deoxyazasugars. As a new flexible deoxyazasugar synthesis, we now report the stereoselective asymmetric syntheses of deoxymannojirimycin **1**, deoxyaltrojirimycin **2** and deoxygalactostatin **3** from common intermediate **9**.

Synthesis of deoxymannojirimycin **1** *via* the common intermediate **9** is shown in Scheme 1. Reaction of (*R*)-(+)-ester **4** with the lithium anion of propargyl alcohol silyl ether at −100 °C in THF gave ketone **5** [mp 31.0–32.0 °C; $[\alpha]_D^{23}$ +32.2 (*c* 0.88, $CHCl_3$)]. The successful stereoselective reduction of the ketone to produce the desired *anti* alcohol **6** was achieved with diisobutylaluminium 2,6-di-*tert*-butyl-4-methylphenoxide in 92% yield; the *anti*:*syn* selectivity was 11:1 by ^{1}H NMR analysis. Reduction with $NaBH_4$ and L-Selectride® gave a 5:3 and 1:2 mixture of *anti*- and *syn*-derivatives, respectively, and triisobutylaluminium reduction showed 9:1 selectivity. The obtained stereoselectivity can be understood by considering the reaction intermediates as shown in Fig. 1. In the case of diisobutylaluminium 2,6-di-*tert*-butyl-4-methylphenoxide reduction, two possible conformers **A** and **B** in the transition state were considered based on an intramolecular fashion of this reagent. Compared to intermediate **A**, intermediate **B** is disfavored due to steric interactions between the bulky aluminium reagent and the methylene group of the oxazolidinone ring, and hence this reaction resulted in high *anti*-selectivity. On the other hand, conformers **C** and **D** were anticipated in sodium borohydride and L-Selectride® reduction. There was considered to be no significant difference in steric interactions between these conformers due to the intermolecular fashion of the hydride attack of these reagents, and they resulted in poor selectivity, despite the fact that the L-Selectride® is sterically more demanding than $NaBH_4$.

With *anti*-alcohol **6** in hand, our attention turned to the construction of the bicyclic oxazolidinylpiperidine. Reduction of **6** along with its stereoisomer with Lindlar catalyst produced *cis*-allyl alcohol **7**,‡ which was isolated, then treated with sodium in liquid ammonia followed by acid to give the corresponding diol. Unfortunately, cyclization attempts utilizing the obtained diol *via* the tosylate of the primary alcohol were unsuccessful. The secondary hydroxy group of **7** was then protected with a TBDMS group, and the terminal silyl group was selectively removed by treatment with aq. HF in MeCN to give allyl alcohol **8**.[9] The cyclization proceeded successfully upon treatment of **8** with MsCl followed by NaH to produce



Scheme 1 *Reagents and conditions*: i, $TBDMSOCH_2C{\equiv}CLi$, THF, −100 °C (82%); ii, diisobutylaluminium 2,6-di-*tert*-butyl-4-methylphenoxide, toluene, 0 °C (92%); iii, Lindlar catalyst, H_2, MeOH (90%); iv, Na, liquid NH_3, −78 °C; v, TBDMSCl, imidazole, DMF (67% for 2 steps), vi, 55% aq. HF, MeCN, −20 °C (98%); vii, MsCl, Et_3N, DMAP, DMF; viii, NaH, DMF, 0 °C (80% for 2 steps); ix, OsO_4, NMO, Bu^tOH, H_2O (86%); x, $Me_2C(OMe)_2$, PPTS, acetone (92%); xi, 6 M aq. NaOH, dioxane, reflux, 24 h (71%); xii, conc. HCl, MeOH, reflux, 4 h (quant.); xiii, basic ion-exchange resin.

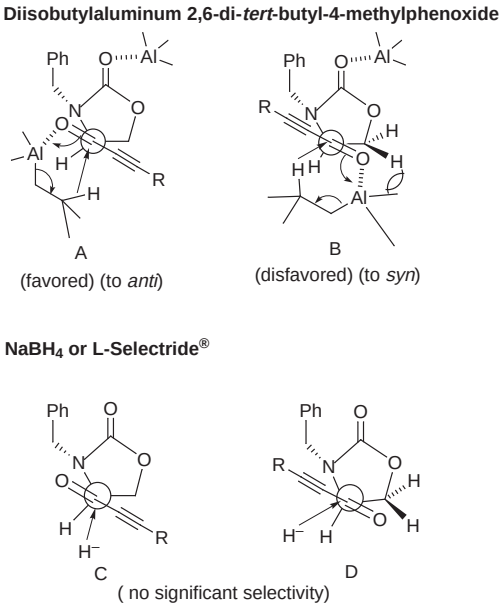
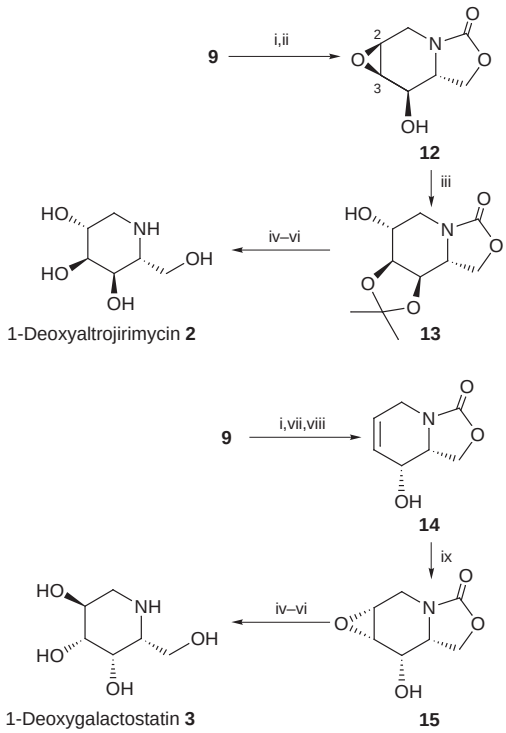


Fig. 1

bicyclic oxazolidinylpiperidine **9**§. This compound was used as the common intermediate for the present deoxyazasugar synthesis. Oxidation of **9** with OsO_4 yielded diol **10** as the sole product, the stereochemistry of which was assumed to be *anti* to the neighbouring siloxy group at this stage. Acetonide formation followed by cleavage of the oxazolidinone ring with aq. NaOH in dioxane gave a mixture of monosilyl ether **11** and diol **11′**. Upon treatment of the mixture with acid, deoxymannojirimycin **1** was quantitatively obtained after purification with basic ion-exchange resin.¶

Next is the synthesis of deoxyaltrojirimycin **2** (Scheme 2). Epoxidation of bicyclic compound **9** after removal of the silyl group gave epoxy alcohol **12**, which was treated with BF_3–Et_2O in acetone to produce acetonide **13** [mp 123.0–124.0 °C; $[\alpha]_D^{22}$ +49.9 (*c* 0.48, $CHCl_3$)] resulting from diaxial opening of the epoxide ring. Synthesis of **2** from **13** was achieved by the same procedures as those in the deoxymannojirimycin synthesis (6 M aq. NaOH, conc. HCl; 85% for two steps).¶



Scheme 2 *Reagents and conditions*: i, TBAF, THF (98%); ii, MCPBA, CH_2Cl_2 (78%); iii, BF_3–OEt_2, acetone, 0 °C (70%); iv, 6 M aq. NaOH, dioxane, reflux, 24 h; v, conc. HCl, MeOH, reflux, 4 h (85% for 2 steps); vi, basic ion-exchange resin; vii, PDC, 4 Å molecular sieves, CH_2Cl_2 (73%); viii, L-Selectride®, $CeCl_3$, THF (77%); ix, MCPBA, $CHCl_3$, 3 d (65%).

The synthetic strategy for deoxyaltrojirimycin was applied to the synthesis of deoxygalactostatin **3** (Scheme 2), which is not a natural product but was synthesized as an analogue of deoxygalactose. Oxidation of **9** with PDC after removal of the silyl group gave the corresponding ketone. Reduction of the ketone obtained with L-Selectride® in the presence of cerium chloride produced *syn* alcohol **14** with a high degree of stereoselectivity (20:1 by ^{1}H NMR analysis; 77%). Although epoxidation of **14** with MCPBA was very slow (room temp., 3 days, $CHCl_3$), we obtained the desired α-oriented epoxide **15** in 65% conversion yield. The synthesis of deoxygalactostatin **3** was achieved from **15** by the same procedure employed in the synthesis of deoxyaltrojirimycin. Thus, formation of acetonide (52%), hydrolysis of oxazolidinone (67%), and then acid treatment (quant.) yielded deoxygalactostatin **3**.¶

In conclusion, 4-methoxycarbonyloxazolidinone **4** has been proved to be a versatile chiral building block for the syntheses of deoxyazasugars *via* bicyclic oxazolidinylpiperidine **9** as a common synthetic intermediate.

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Notes and references

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‡ *Selected data* for **7**: mp 83.0–84.0 °C; $[\alpha]_D^{24}$ −23.9 (*c* 0.19, $CHCl_3$); ν(KBr)/cm^{-1} 3262, 1778, 1119; δ_H(400 MHz, $CDCl_3$) 0.067 (3H, s), 0.073 (3H, s), 0.90 (9H, s), 3.10 (1H, br s), 3.61–3.65 (1H, a pair of ddd, *J* 2.9, 6.1, 9.0), 4.26 (5H, m), 4.58 (1H, br d, *J* 6.1), 4.82 (1H, d, *J* 15.1), 5.37 (1H, ddt, *J* 1.7, 7.3, 11.5), 5.72 (1H, m), 7.34 (5H, m).

§ *Selected data* for **9**: mp 92.5–93.0 °C; $[\alpha]_D^{23}$ +26.0 (*c* 1.00, $CHCl_3$); ν(KBr)/cm^{-1} 2953, 1786, 1630; δ_H(400 MHz, $CDCl_3$) 0.11 (3H, s), 0.13 (3H, s), 0.90 (9H, s), 3.51 (1H, ddd, *J* 4.2, 8.1, 8.1), 3.65 (1H, m), 4.09 (1H, m), 4.15 (1H, m), 4.22 (1H, dd, *J* 4.2, 8.9), 4.51 (1H, dd, *J* 8.1, 8.9), 5.72 (2H, s); δ_C(100 MHz, $CDCl_3$) −4.68, −4.20, 17.86, 25.61, 40.82, 56.42, 67.21, 68.37, 123.83, 130.48, 157.24.

¶ *Selected data* for **1**: mp 186.0–186.5 °C; $[\alpha]_D^{27}$ −35.7 (*c* 0.07, MeOH) [lit.,[5a] mp 183–185 °C; $[\alpha]_D^{20}$ −36.2 (*c* 0.342, MeOH)]. For **2**: $[\alpha]_D^{23}$ +16.3 (*c* 0.8, H_2O) [lit. (of enantiomer),[3b] $[\alpha]_D^{20}$ −14.5(*c* 0.7, $CHCl_3$)]. For **3**: $[\alpha]_D^{27}$ +40.3 (*c* 0.38, H_2O) [lit.,[5c] $[\alpha]^{25}_D$ +44.6(*c* 1.1, H_2O)].

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