Ring Enlargement of Polyhydroxylated Pyrrolidines to Piperidines by Mitsunobu Reaction: A Fortuitous Synthesis of 1-Deoxy-L-allonojirimycin

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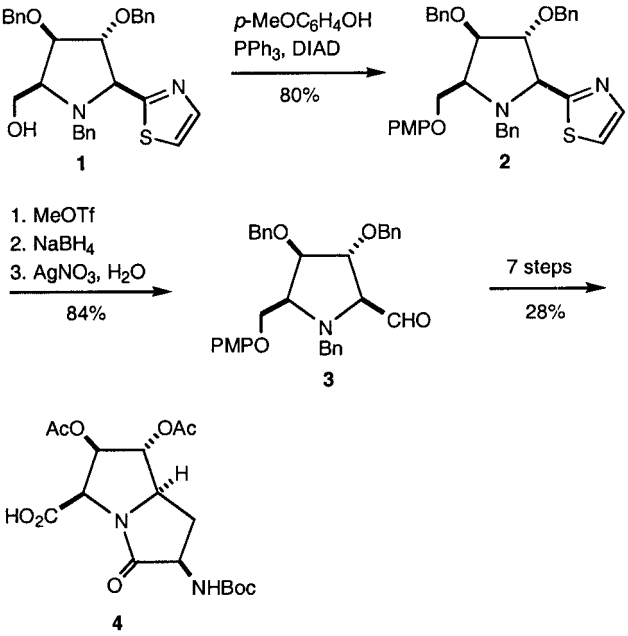
Abstract: Chiral 3,4-dibenzyloxy-5-hydroxymethyl-2-thiazolyl-pyrrolidines under Mitsunobu conditions (R-OH, Ph_3P, DIAD in THF, 80 °C) afforded the corresponding R-protected pyrrolidines and 2-deoxy-piperidines in different ratios depending on the stereochemistry of the starting pyrrolidine and the nature of the acid R-OH. A mechanistic scheme is proposed involving the formation of an aziridinium ion as an intermediate. A piperidine derivative obtained in 74% yield was converted in four steps into the title allonojirimycin.

Key words: azasugars, 1-deoxynojirimycin, piperidines, pyrrolidines, ring expansion

In a recent publication from this laboratory,[1] we reported on an effective synthesis of the 6,7-diacetoxy azabicyclo[3.3.0]octanone amino acid (**4**, pyrrolizidinone amino acid, Scheme 1). This hydroxylated rigidified Pro-Ala dipeptide belongs to the class of fused bicyclic dipeptides[2] that simulate the bioactive conformation of the β-turn sites.[3] A rigidified dipeptide of type **4** but lacking the hydroxy groups was employed[4] as scaffold for the preparation of a cyclopeptide by insertion of the pharmacophoric tripeptide Arg-Gly-Asp (RGD) sequence which is implicated in several diseases including angiogenesis and osteoporosis.[5] The synthesis of **4** represented the initial step in our program directed toward the preparation of stereodiversified libraries of densely hydroxylated rigidified peptidomimetics constituted of azabicyclo[X.Y.0]alkanone amino acids. We have briefly discussed[1] the potential of these systems as tools for biological studies and for improving the delivery and selectivity of drugs in several diseases, such as inflammation and cancer, where integrins are implicated. A simple yet important operation in the synthetic scheme leading to **4** from the *N*-benzyl pyrrolidine **1** (prepared via the nitrone route from D-arabinose),[6] entailed the protection of the primary hydroxyl group as *p*-methoxyphenyl (PMP) ether via Mitsunobu reaction with *p*-methoxyphenol in the presence of PPh_3 and diisopropylazodicarboxylate (DIAD). Then, the product **2** (80% isolated yield) was transformed into the orthogonally protected polyhydroxylated formyl pyrrolidine **3** via thiazole-to-formyl conversion. The formyl group in the latter compound served as the starting point for the construction of the condensed five-member ring of **4** bearing the carbonyl and amino groups while the PMP-protected primary alcohol was transformed into the carboxylic group.



Scheme 1

We now report that when the Mitsunobu reaction with *p*-methoxyphenol as the nucleophile was applied to the 5-hydroxymethyl pyrrolidine **5**[7] (prepared via the nitrone route from D-ribose),[6] two products were obtained in 1.3:1 ratio (from NMR analysis), the major one being characterized as the piperidine **7a**, and the other the expected pyrrolidine **6a** (Scheme 2).[8] The ratio between the piperidine and pyrrolidine products increased significantly (**7b**:**6b** = 2.3:1) by the use of benzoic acid[8] and became quite substantial (**7c**:**6c** = 4.1:1) with diphenyl acetic acid.[8] The yields of isolated products **6** and **7** confirmed the above product distributions. With pivalic acid the reaction was very sluggish since only 13% of **5** appeared to have reacted after three hours while affording exclusively the piperidine **7d**. The ring size and the configuration of the 5-*O*-protected piperidines **7** were readily assigned by ^1H NMR analysis. The two H-6 protons of **7a**–**c** resonate at much higher field (δ = 2.7–3.0 ppm) than those of the pyrrolidine isomers **6a**–**c** (δ = 4.5–5.0 ppm), as expected

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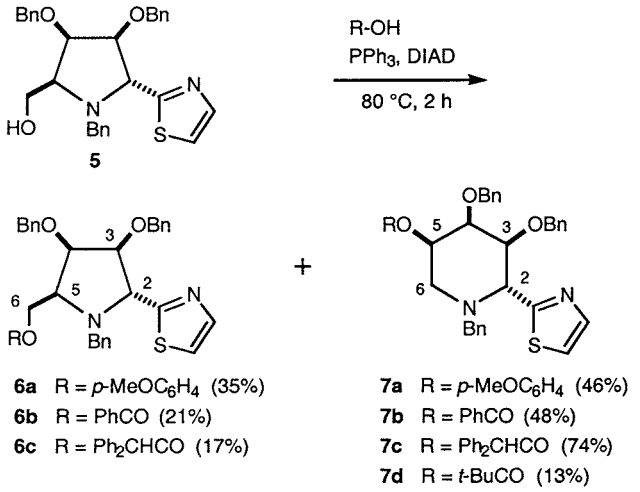
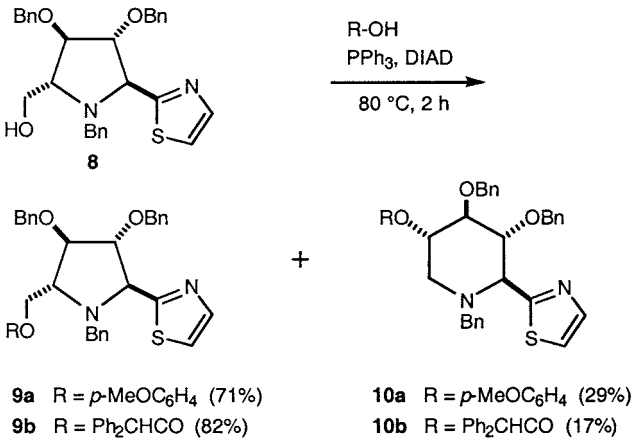
for a methylene group linked to a nitrogen rather than an oxygen atom. Moreover, a significant NOE between H-3 and H-5 of **7a–c** indicates that these protons are in a *cis*-relationship.



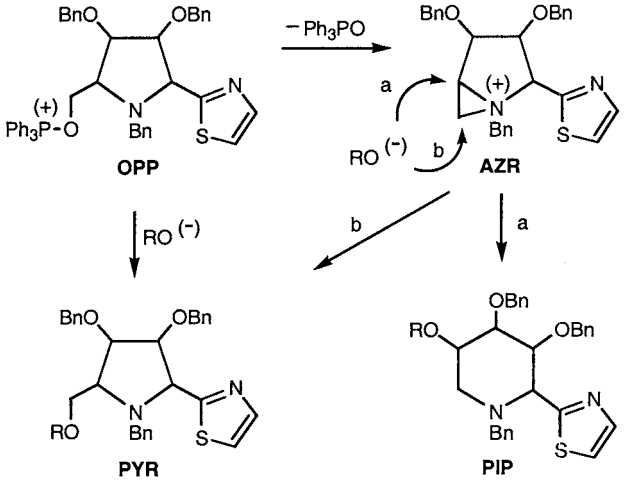
Scheme 2

Since diphenyl acetic acid was the most effective reagent favoring the ring enlargement of **5**, this carboxylic acid was employed to see whether the same process occurred with the pyrrolidine **1** (see Scheme 1). Quite surprisingly, no formation of the corresponding piperidine was observed in this case. Hence, we explored the Mitsunobu reaction of another stereoisomer of **1**, namely the 5-hydroxymethyl pyrrolidine **8**[9] (Scheme 3) prepared via the nitrone route from L-xylose.[6] The use of *p*-methoxyphenol-Ph_3P-DIAD system furnished a mixture of the pyrrolidine **9a** and piperidine **10a** in 2.5:1 ratio[9] by NMR analysis and, in contrast to our expectation, the substitution of the phenol with diphenyl acetic acid increased the above ratio to give products **9b** and **10b** in 4.8:1 ratio.[9] Also in these reactions the yields of isolated products **9** and **10** confirmed the ratios determined by NMR analysis.



Scheme 3

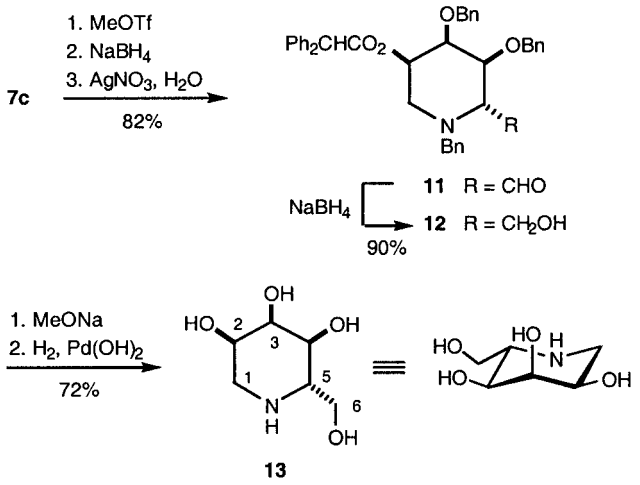
From the above results it appears that the pyrrolidine–piperidine ratio in the Mitsunobu reaction of chiral 3,4-dibenzyloxy-5-hydroxymethyl-2-thiazolyl-pyrrolidines depends on both their stereochemistry and the nature of the nucleophile R-OH. However in view of the limited set of data so far collected it is premature to speculate on those effects. Instead, a mechanistic rationale for the pyrrolidine to piperidine ring enlargement can be advanced on the basis of previous observations of neighboring group effects in nitrogen, oxygen, and sulfur containing compounds subjected to Mitsunobu reactions.[10] Stereochemical outcomes and/or ring size variations were in fact explained by invoking aziridinium, oxonium, and thiirenium ion intermediates. Hence, we suggest that also in the present cases after the oxyphosphonium (OPP) salt formation through the agency of DIAD, the reaction proceeds through a condensed aziridinium (AZR) ion intermediate,[11] which undergoes the nucleophilic attack by $R\text{-}O^-$ at the tertiary carbon atom (route a) to give the enlarged piperidine (PIP) system (Scheme 4). On the other hand the pyrrolidine (PYR) should be formed by attack of the nucleophile at the methylene carbon atom of the aziridinium ring (route b) although it cannot be excluded its direct formation from the oxyphosphonium salt OPP. A mechanistic scheme involving the initial formation of the protected pyrrolidine and then its partial transformation into the piperidine system through the AZR ion intermediate seems unlikely because we found that the molar ratio between **6c** and **7c** did not change during the reaction (NMR analysis of samples withdrawn from the reaction mixture after 5, 10, 20, and 120 min). Moreover, pure compounds **6c** and **9b** were recovered unaltered upon heating for two hours at 80 °C in dry THF.



Scheme 4

While extensive investigations are needed to gain more insight on the steric and electronic factors determining the kinetic of the above concurrent reactions, we envisaged the implementation of this chemistry for the synthesis of rare six-member ring 1-deoxy iminosugars, which are eventually hardly accessible by more common routes.

This class of polyhydroxylated piperidines has gained great importance due to their superior activity as specific glycosidase inhibitors.[12] Since such inhibition has significance to both viral expression and tumor growth,[13] the potential of these compounds as leads for the development of new drugs has became quite apparent. Thus, given the good selectivity by which the piperidine **7c** was obtained from **5**, we considered the elaboration of this compound as an example for iminosugar synthesis (Scheme 5). Succinctly, application of the silver-based thiazole-to-formyl conversion protocol[14] to **7c** furnished the aldehyde[15] **11**, which in turn was readily reduced to the alcohol[16] **12**. Removal of the *O*- and *N*-protective groups by standard methods afforded 1-deoxy-L-allonojirimycin[17] **13**, an iminosugar whose synthesis has been previously reported in one instance only[18] while the antipode was prepared in various manners by chemical and enzymatic means.[19] While the latter product has been proved[19a] to act as an inhibitor of rat intestine isomaltase and cellobiase, and bovine liver cytosolic β-galactosidase, the biological properties of the enantiomer **13** have not been studied so far. Application of the same reaction sequence to the thiazole-substituted piperidine **10b** would give the 1-deoxynojirimycin, a well-known potent glycosidase inhibitor.[12]



Scheme 5

Acknowledgment

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(6) (a) Dondoni, A.; Giovannini, P. P.; Perrone, D. *J. Org. Chem.* **2002**, *62*, 7203. (b) This article dealt with the preparation of *O*- and *N*-benzyl-protected 3,4-dihydroxy-5-hydroxymethyl-2-thiazolyl-pyrrolidines. The selective debenzylation of the primary hydroxy group to give compound **1** has been described (ref.[1]). Under the same conditions, the 5-hydroxymethyl pyrrolidines **5** (Scheme 2) and **8** (Scheme 3) were obtained from the corresponding perbenzylated precursors.
(7) Analytical data for compound **5**. $[\alpha]_D$ = –4.1 (*c* 1.0, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$ + D_2O): δ = 7.80 (d, 1 H, *J* = 3.3 Hz, Th), 7.46–7.22 (m, 16 H, 3 Ph, Th), 4.97 and 4.75 (2 d, 2 H, *J* = 11.6 Hz, PhCH_2O), 4.85 (d, 1 H, $J_{2,3}$ = 1.5 Hz, H-2), 4.53 and 4.40 (2 d, 2 H, *J* = 11.7 Hz, PhCH_2O), 4.31 (dd, 1 H, $J_{3,4}$ = 6.1, $J_{4,5}$ = 7.2 Hz, H-4), 4.14 and 3.98 (2 d, 2 H, *J* = 13.9 Hz, PhCH_2N), 4.06 (dd, 1 H, H-3), 3.82–3.76 (m, 2 H, 2 H-6), 3.40 (ddd, 1 H, $J_{5,6a}$ = $J_{5,6b}$ = 2.7 Hz, H-5).
(8) **General Procedure for the Mitsunobu Reaction:** To a refluxing solution of 6-OH thiazolylpyrrolidine (150 mg, 0.30 mmol), PPh_3 (120 mg, 0.45 mmol), and phenol or carboxylic acid derivative (0.60 mmol) in anhyd THF (6 mL) was added DIAD (90 μL, 0.45 mmol). The reaction mixture was stirred at 80 °C for 2 h and then concentrated. The residue was eluted from a column of silica gel (cyclohexane–EtOAc) to give the pyrrolidine **6** and the piperidine **7**. Compound **6a**. $[\alpha]_D$ = +6.8 (*c* 0.9, $CHCl_3$). Compound **7a**. $[\alpha]_D$ = –32.0 (*c* 1.4, $CHCl_3$). Compound **6b**. $[\alpha]_D$ = –13.7 (*c* 1.0, $CHCl_3$). Compound **7b**. $[\alpha]_D$ = –25.5 (*c* 0.8, $CHCl_3$). Compound **6c**. $[\alpha]_D$ = –39.2 (*c* 1.0, $CHCl_3$). ^1H NMR (400 MHz, C_6D_6): δ = 7.57 and 6.55 (2 d, 2 H, *J* = 3.3 Hz, Th), 7.34–6.90 (m, 25 H, 5 Ph), 5.04 (dd, 1 H, $J_{5,6a}$ = 2.4, $J_{6a,6b}$ = 12.5 Hz, H-6a), 4.78 (s, 1 H, Ph_2CH), 4.65 and 4.60 (2 d, 2 H, *J* = 12.2 Hz, PhCH_2O), 4.58 (dd, 1 H, $J_{5,6b}$ = 7.2 Hz, H-6b), 4.54 (d, 1 H, $J_{2,3}$ = 1.5 Hz, H-2), 4.18 and 4.08 (2 d, 2 H, *J* = 11.9 Hz, PhCH_2O), 4.10 (dd, 1 H, $J_{3,4}$ = 5.2, $J_{4,5}$ = 6.6 Hz, H-4), 3.86 (dd, 1 H, H-3), 3.78 (ddd, 1 H, H-5), 3.68 (s, 2 H, PhCH_2N). Compound **7c**. $[\alpha]_D$ = –36.0 (*c* 0.4, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$): δ = 7.76 (d, 1 H, *J* = 3.2 Hz, Th), 7.32–7.13 and 6.93–6.89 (2 m, 26 H, 5 Ph, Th), 5.06 (ddd, 1 H, $J_{4,5}$ = 1.8, $J_{5,6a}$ = 4.7, $J_{5,6b}$ = 10.5 Hz, H-5), 4.97 (s, 1 H, Ph_2CH), 4.55 and 4.33 (2 d, 2 H, *J* = 11.8 Hz, PhCH_2O), 4.29 and 4.07 (2 d, 2 H, *J* = 11.9 Hz, PhCH_2O), 4.29 (d, 1 H, $J_{2,3}$ = 9.5 Hz, H-2), 4.10 (dd, 1 H, $J_{3,4}$ = 1.7 Hz, H-4), 3.73 and 3.17 (2 d, 2 H, *J* = 13.8 Hz, PhCH_2N), 3.71 (dd, 1 H, H-3), 2.78 (dd, 1 H, $J_{6a,6b}$ = 10.3 Hz, H-6a), 2.72 (dd, 1 H, H-6b).
(9) Analytical data: compound **8**: $[\alpha]_D$ = +16.4 (*c* 0.6, $CHCl_3$). Compound **9a**: $[\alpha]_D$ = –4.6 (*c* 0.6, $CHCl_3$). Compound **10a**: $[\alpha]_D$ = +10.0 (*c* 0.7, $CHCl_3$). Compound **9b**: $[\alpha]_D$ = +10.9 (*c* 0.7, $CHCl_3$). Compound **10b**: $[\alpha]_D$ = +20.0 (*c* 0.7, $CHCl_3$).
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(15) A mixture of **7c** (40 mg, 0.06 mmol), activated 4 Å powdered molecular sieves (140 mg), and anhyd MeCN (0.7 mL) was stirred at r.t. for 10 min, then methyl triflate (13 μL, 0.12 mmol) was added. The suspension was stirred at r.t. for 15 min and then concentrated to dryness without filtering off the molecular sieves. To a cooled (0 °C), stirred suspension of the crude *N*-methylthiazolium salt in MeOH (0.7 mL) was added $NaBH_4$ (5 mg, 0.13 mmol). The mixture was stirred at r.t. for additional 10 min, diluted with acetone, filtered through a pad of Celite, and concentrated. A solution of the residue in Et_2O (30 mL) was washed with H_2O, dried (Na_2SO_4), and concentrated. To a vigorously stirred solution of the thiazolidines in MeCN (1 mL) was added H_2O (0.1 mL) and then $AgNO_3$ (12 mg, 0.07 mmol). The mixture was stirred at r.t. for 5 min, then diluted with 1 M phosphate buffer at pH 7 (10 mL) and partially concentrated to remove MeCN (bath temperature not exceeding 40 °C). The suspension was extracted with Et_2O (3 × 20 mL), the combined organic phases were dried (Na_2SO_4), and concentrated to give a yellow syrup. A solution of the residue in Et_2O (ca. 30 mL) was filtered through a pad of Celite and concentrated to afford **11** (30 mg, 82%) as a colorless syrup ca. 95% pure by ^1H NMR analysis. ^1H NMR (400 MHz, $CDCl_3$): δ = 9.41 (d, 1 H, *J* = 4.7 Hz, CHO), 7.35–7.20 and 7.12–7.07 (2 m, 25 H, 5 Ph), 4.96 (s, 1 H, Ph_2CH), 4.91 (ddd, 1 H, $J_{4,5}$ = 2.4, $J_{5,6a}$ = 4.9, $J_{5,6b}$ = 10.7 Hz, H-5), 4.50 and 4.30 (2 d, 2 H, *J* = 11.9 Hz, $PhCH_2O$), 4.44 and 4.32 (2 d, 2 H, *J* = 11.3 Hz, $PhCH_2O$), 4.12 (dd, 1 H, $J_{3,4}$ = 2.0 Hz, H-4), 3.72 and 3.34 (2 d, 2 H, *J* = 13.8 Hz, $PhCH_2N$), 3.71 (dd, 1 H, $J_{2,3}$ = 9.7 Hz, H-3), 3.34 (dd, 1 H, H-2), 2.71 (dd, 1 H, $J_{6a,6b}$ = 10.6 Hz, H-6a), 2.60 (dd, 1 H, H-6b).

(16) To a cooled (0 °C), stirred solution of **11** (30 mg, 0.05 mmol) in 5:2 Et_2O–MeOH (1 mL) was added $NaBH_4$ (5 mg, 0.13 mmol). The mixture was stirred at r.t. for 5 min, diluted with acetone (0.1 mL) and then 1 M phosphate buffer at pH 7 (5 mL), and partially concentrated to remove the organic solvents. The suspension was extracted with CH_2Cl_2 (3 × 20 mL), the combined organic phases were dried (Na_2SO_4), and concentrated. The residue was eluted from a column of silica gel with 3:1 cyclohexane–EtOAc to give **12** (27 mg, 90%) as a syrup; $[\alpha]_D$ = +2.7 (*c* 0.6, $CHCl_3$). ^1H NMR (400 MHz, C_6D_6): δ = 7.32–6.92 (m, 25 H, 5 Ph), 4.94 (ddd, 1 H, $J_{1a,2}$ = 10.6, $J_{1b,2}$ = 4.2, $J_{2,3}$ = 2.3 Hz, H-2), 4.92 (s, 1 H, Ph_2CH), 4.52 and 4.36 (2 d, 2 H, *J* = 11.6 Hz, $PhCH_2O$), 4.24 and 4.19 (2 d, 2 H, *J* = 11.5 Hz, $PhCH_2O$), 4.06 (dd, 1 H, $J_{3,4}$ = 2.4 Hz, H-3), 3.92 (ddd, 1 H, $J_{5,6a}$ = 1.8, $J_{6a,6b}$ = 11.0, $J_{6a,OH}$ = 9.7 Hz, H-6a), 3.73 and 2.87 (2 d, 2 H, *J* = 14.0 Hz, $PhCH_2N$), 3.73 (dd, 1 H, $J_{5,6b}$ = 1.8 Hz, H-6b), 3.54 (dd, 1 H, $J_{4,5}$ = 9.6 Hz, H-4), 2.83 (dd, 1 H, $J_{1a,1b}$ = 10.4 Hz, H-1a), 2.77 (dd, 1 H, H-1b), 2.76 (ddd, 1 H, H-5), 2.01 (br d, 1 H, OH).

(17) A solution of **12** (31 mg, 0.05 mmol) in freshly prepared 0.1 M CH_3ONa in CH_3OH (2 mL) was kept at r.t. for 2 h, then neutralized with HOAc, and concentrated. A solution of the residue in CH_2Cl_2 was washed with 1 M phosphate buffer at pH 7, dried (Na_2SO_4), and concentrated. The residue was eluted from a short column of silica gel with EtOAc (containing 0.5% of Et_3N) to give the 2-OH derivative (17 mg). A vigorously stirred mixture of the alcohol, 20% $Pd(OH)_2$ on carbon (20 mg), and HOAc (2 mL) was degassed under vacuum and saturated with hydrogen (by a H_2-filled balloon) five times. The suspension was stirred at r.t. for 5 h under a slightly positive pressure of hydrogen (balloon), then filtered through a plug of cotton and concentrated. A solution of the crude tetrol in H_2O was eluted from a column (0.5 × 3 cm, d × h) of freshly activated Dowex 1X8-200 (HO^- form) to give pure **13** (6 mg, 72%); $[\alpha]_D$ = –28.6 (*c* 0.2, H_2O); lit.[18] $[\alpha]_D$ = –35.2 (*c* 0.025, MeOH). *ent*-**13**: lit.[19a] $[\alpha]_D$ = +25.7 (*c* 0.65, H_2O); lit.[19b] $[\alpha]_D$ = +28.1 (*c* 0.8, H_2O). ^1H NMR (400 MHz, D_2O): δ = 3.92 (dd, 1 H, $J_{2,3}$ = $J_{3,4}$ = 2.8 Hz, H-3), 3.62 (dd, 1 H, $J_{5,6a}$ = 3.0, $J_{6a,6b}$ = 11.6 Hz, H-6a), 3.52 (ddd, 1 H, $J_{1a,2}$ = 5.1, $J_{1b,2}$ = 11.2 Hz, H-2), 3.46 (dd, 1 H, $J_{5,6b}$ = 5.8 Hz, H-6b), 3.30 (dd, 1 H, $J_{4,5}$ = 10.3 Hz, H-4), 2.67 (dd, 1 H, $J_{1a,1b}$ = 12.4 Hz, H-1a), 2.56 (ddd, 1 H, H-5), 2.50 (dd, 1 H, H-1b).

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