42. A New Synthesis of (2*S*,3*R*,4*R*)-2-(Hydroxymethyl)pyrrolidine-3,4-diol

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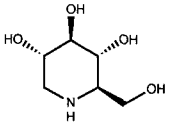
The title compound **6** was synthesized from 2,3,5-tri-*O*-benzyl-D-arabinofuranose (**7**) in three steps and 48% overall yield. Moreover, it was shown, in the case of γ-hydroxy amide **9**, that the *Mitsunobu* reaction is not suitable for the preparation of γ-lactams, because *O*-alkylation is predominant.

Introduction. – A variety of sugar-like N-containing compounds, naturally occurring and synthetic, *e.g.* deoxynojirimycin (**1**) and castanospermine (**2**), are potent glycosidase inhibitors [1]. More interestingly, recent studies suggest that aminosugar derivatives which inhibit glycoprotein processing have potential anti-AIDS-virus activity [2]. *E.g.*, **2** inhibits AIDS-virus syncytium formation and virus replication [2a].



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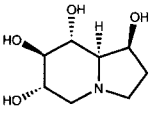

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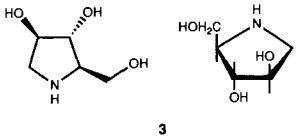

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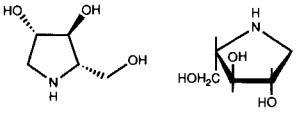

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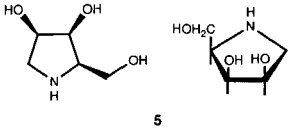

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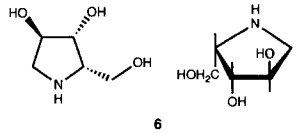

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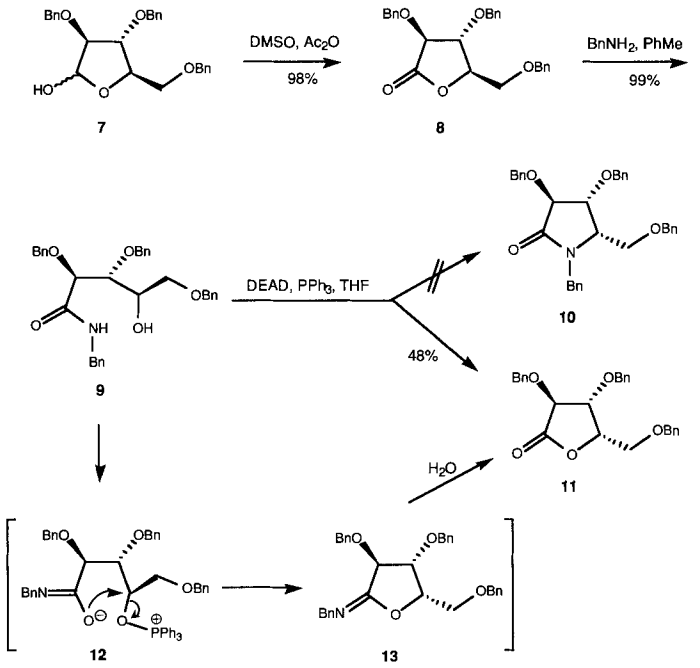
Several stereoisomers of 2-(hydroxymethyl)pyrrolidine-3,4-diol have been reported to be potent glycosidase and/or AIDS-virus inhibitors. The (2*R*,3*R*,4*R*)-isomer, 1,4-dideoxy-1,4-imino-D-arabinitol (DAB1; **3**), is an α-glucosidase inhibitor [3] and potential AIDS-virus replication inhibitor [4]. The (2*S*,3*S*,4*S*)-isomer, 1,4-dideoxy-1,4-imino-L-arabinitol (LAB1; **4**), which also inhibits α-glucosidase, though to a lesser extent [3], is a powerful inhibitor of the cytopathic effect of AIDS virus at non-cytotoxic concentrations [2c][4]. The

(2*R*,3*S*,4*R*)-isomer, 1,4-dideoxy-1,4-imino-D-lyxitol (**5**), is an α-galactosidase inhibitor [3]. Compound **3** has been isolated from *Angylocalyx boutiqueanus* TOUSS. and *Arachniodes standishii* (MOORE) OHWI[1]) [3][5]. Almost all the stereoisomers of 2-(hydroxymethyl)-pyrrolidine-3,4-diol have been synthesized, mostly from sugar templates [3][5c][6] and, in one *de novo* case, by enzymatic aldol condensation [7].

Because of the biological interest in 2-(hydroxymethyl)pyrrolidine-3,4-diols, especially stimulation of the immune response, it is desirable to develop very efficient synthetic approaches to all stereoisomers. Here, we report an efficient synthesis of the (2*S*,3*R*,4*R*)-isomer, 1,4-dideoxy-1,4-imino-L-xylitol (**6**). Compound **6** has been previously synthesized from 2-amino-2-deoxy-D-glucose in nine steps [6b] and from D-mannose by using a Fe^{III}-catalyzed photoreaction [6f]. During the preparation of this paper, other workers reported the synthesis of **6** using the same starting material as we did but employing a different route [6i].

Results and Discussion. – Our first (unsuccessful) approach to the synthesis of **6** implied the preparation of the key intermediate **10** from which **6** can be obtained by conventional procedures (*Scheme 1*). Intermediate **10** should be accessible by a *Mitsunobu* reaction [8] of γ-hydroxy amide **9**. The *Mitsunobu* reaction has been widely employed to construct β-lactams from the corresponding linear β-hydroxy amides [9], but, to the authors' knowledge, has not been applied to the synthesis of γ-lactams.

Scheme 1

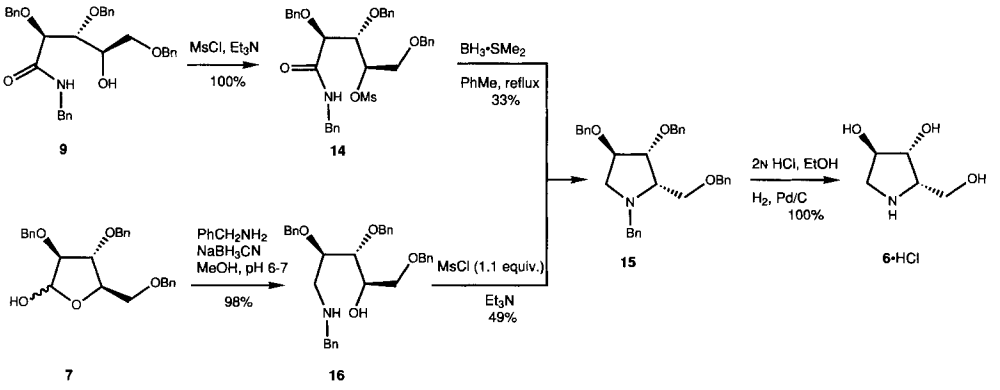


[1]) The configuration of the component of *A. standishii* was originally assigned differently [5b] and corrected later [5c].

Hydroxy amide **9** was prepared *via* **8** from the D-arabinofuranose **7** in 97% total yield according to the procedure in [10]. Hovever, subjection of **9** to the *Mitsunobu* reaction resulted in lactone **11** instead of lactam **10**. Since **11** was indistinguishable from lactone **8** under several different TLC conditions, we first assumed that lactonization by nucleophilic attack of the OH group on the amide C=O group, with retention of configuration, had occurred (→**8**), and that this process was accelerated under *Mitsunobu* conditions. However, the specific rotation of the product **11** ($[\alpha]_D^{22} = -75.1$) was very different from that of **8** ($[\alpha]_D^{22} = +6.6$), and several other runs using either diethyl azodicarboxylate (DEAD) or diisopropyl azodicarboxylate and Ph_3P confirmed that **11** was always the predominant product (*ca.* 50% yield). Thus, the *Mitsunobu* reaction of **9** involves an *O*-alkylation, probably *via* intermediates **12** and **13** instead of the *N*-alkylation. This finding can be further developed into a useful method to invert the γ-configuration of γ-lactones. There are several other known examples of *Mitsunobu O*-alkylation [9a][11].

Since the *Mitsunobu* reaction was not suitable, we turned our attention to a stepwise cyclization of **9**. Treatment with MsCl and Et_3N afforded the mesylate **14** quantitatively (*Scheme 2*), but in contrast to known analogs [12], **14** could not be reduced by $BH_3 \cdot Me_2S$ in refluxing THF. Under more vigorous conditions (5 h reflux in toluene), however, cyclized product **15** was obtained in 33% yield, This yield could not be improved under a variety of other conditions.

Scheme 2



A more straightforward route to the target compound **6** is as follows: reductive amination of 2,3,5-tri-*O*-benzyl-D-arabinofuranose (**7**) with $PhCH_2NH_2$ and sodium cyanoborohydride at pH 6–7 afforded amino alcohol **16** in 98% yield. The crucial step of this route, cyclization of **16** to **15**, involves selective mesylation of the OH over the secondary benzylamino group. The optimal yield of **15** (49%) was obtained with 1.1 equiv. of MsCl at –23°. At –78°, no reaction occurred, but after slow warming to room temperature, **15** was obtained in 43% yield. The yield was only 28%, when the reaction was run at 0°. Comparison of the ^{1}H-NMR spectra of **15** with those of the sample obtained from **9** *via* **14** established their

identity. Finally, catalytic hydrogenolysis of **15** with Pd/C in 2N HCl in EtOH afforded the hydrochloride of (2*S*,3*R*,4*R*)-2-(hydroxymethyl)pyrrolidine-3,4-diol (**6**) quantitatively. Therefore, the total synthesis of **6** has been accomplished in 48% overall yield from **7**. The spectroscopic data of **6** · HCl are in accordance with the published data [6f, i]. It is noteworthy to mention that the $[M + 1]^+$ peak of **6** could not be observed by CI-MS using isobutane as a carrier gas, whereas it was easily accessable, when NH_3 was used.

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Experimental Part

General. All reagents and solvents except 2,3,5-tri-*O*-benzyl-D-arabinofuranose (**7**) were from *Fluka*. Air-sensitive reactions were conducted under Ar. Solns. were dried over anh. $MgSO_4$ before evaporation. Column chromatography: silica gel *60* (230–400 mesh, *Merck*). M.p.: *Mettler FP5/FP52*. Specific rotations: *Perkin-Elmer 241*. IR spectra (in cm^{-1}): *Perkin-Elmer 297*. ^{1}H-NMR spectra (δ in ppm rel. to TMS; *J* in Hz): *Bruker AC-300* (300 MHz) or *Bruker AM-400* (400 MHz). ^{13}C-NMR spectra (δ in ppm rel. to TMS; *J* in Hz): *Varian XL-200* (50 MHz). MS: *Varian MAT 112S* or *Finnigan MAT-90*. Carbohydrate numbering is used in spectral assignments.

*2,3,5-Tri-*O*-benzyl-*D*-arabinono-1,4-lactone* (**8**). *2,3,5-Tri-*O*-benzyl-*D*-arabinofuranose* (**7**; 6.0 g, 14.27 mmol; from *Sigma*) was dissolved in DMSO (18 ml)/Ac_2O (12 ml). After stirring overnight, the resulting soln. was poured into ice-water (200 ml) and stirred for 1 h. The precipitate was filtered out, washed with H_2O, and crystallized from hexane/AcOEt: **8** (5.83 g, 98%, colorless needles). M.p. 67.5–68.5° ([10]: 63–65°). $[\alpha]_D^{22} = +6.6$ (*c* = 1.650, $CHCl_3$). IR ($CHCl_3$): 1790 (γ-lactone), 1205, 1115, 785, 730, 670. ^{1}H-NMR (300 MHz, $CDCl_3$): 3.59 (*dd*, *J* = 3, 12, 1 H–C(5)); 3.71 (*dd*, *J* = 2, 12, 1 H–C(5)); 4.29–4.37 (*m*, H–C(2), H–C(3), H–C(4)); 4.50, 4.52, 4.56, 4.64, 4.77, 5.07 (6 *d*, each *J* = 12, 1 H, PhCH_2); 7.30–7.39 (*m*, 15 arom. H). ^{13}C-NMR (50 MHz, $CDCl_3$): 67.9 (*t*, C(5)); 72.4, 72.7, 73.5 (3*t*, 3 PhCH_2); 78.8, 79.1, 79.2 (3*d*, C(2), C(3), C(4)); 127.7, 127.8, 127.9, 128.1, 128.2, 128.4, 128.45, 128.5 (15*d*, 15 arom. CH); 136.7, 137.0, 137.4 (3 *s*, 3 arom. C); 172.4 (*s*, C(1)). CI-MS: 419 (13, $[M + 1]^+$), 417 (15), 327 (30), 271 (34), 239 (40), 182 (15), 181 (100), 179 (14), 91 (36). Anal. calc. for $C_{26}H_{26}O_5$ (418.488): C 74.62, H 6.26; found: C 74.59, H 6.41.

*1-*N*,2-*O*,3-*O*,5-*O*-Tetrabenzyl-*D*-arabinonamide* (**9**). To a soln. of **8** (3.10 g, 7.407 mmol) in toluene (50 ml) was added $PhCH_2NH_2$ (8 ml), and the resulting soln. was stirred at r.t. for 12 h. Then, the soln. was washed succesively with 1N HCl, sat. aq. $NaHCO_3$ soln., and H_2O (each 30 ml), dried, and evaporated to a syrup. Crystallization (hexane/AcOEt): **9** (3.84 g, 99%). M.p. 96.5–97°. $[\alpha]_D^{22} = +45.2$ (*c* = 0.157, $CHCl_3$; [10]: $[\alpha]_D$ = + 37.6). IR ($CHCl_3$): 3405, 3005, 1720, 1520, 1455, 1070. ^{1}H-NMR (300 MHz, $CDCl_3$): 2.50 (br. *s*, OH); 3.57 (*dd*, *J* = 4, 10, 1 H–C(5)); 3.64 (*dd*, *J* = 3, 10, 1 H–C(5)); 3.94 (*m*, H–C(4)); 4.06 (*dd*, *J* = 2, 9, H–C(3)); 4.31 (*dd*, *J* = 6, 15, 1 H, PhCH_2N); 4.37 (*d*, *J* = 11, 1 H, PhCH_2N); 4.38 (*d*, *J* = 2, H–C(2)); 4.45 (*d*, *J* = 15, 1 H, PhCH_2N); 4.46 (*d*, *J* = 12, 1 H, PhCH_2O); 4.48 (*d*, *J* = 11, 1 H, PhCH_2O); 4.51 (*d*, *J* = 12, 1 H, PhCH_2O); 4.54 (*d*, *J* = 11, 1 H, PhCH_2O); 4.67 (*d*, *J* = 11, 1 H, PhCH_2O); 7.07–7.19 (*m*, 4 arom. H, 1 NH); 7.27–7.37 (*m*, 16 arom. H). ^{13}C-NMR (50 MHz, $CDCl_3$): 43.2 (*t*); 69.3 (*d*); 70.5, 73.3, 74.5, 74.6 (4 *t*); 79.7, 79.8 (2 *d*); 127.4, 127.6, 127.7, 127.8, 127.9, 128.0, 128.18, 128.2, 128.4, 128.5, 128.6 (20 *d*); 136.8, 137.61, 137.64, 137.8 (4 *s*); 171.3 (*s*). CI-MS: 526 (100, $[M + 1]^+$), 181 (29), 108 (70), 107 (12), 91 (45). Anal. calc. for $C_{33}H_{35}NO_5$ (525.643): C 75.41, H 6.71, N 2.66; found: C 75.55, H 6.84, N 2.55.

*2,3,5-Tri-*O*-benzyl-*L*-xylono-1,4-lactone* (**11**). To a soln. of **9** (375.8 mg, 0.715 mmol) and Ph_3P (224.9 mg, 1.2 equiv.) in THF (20 ml) was added DEAD (0.14 ml, 1.5 equiv.) slowly. The resultant soln. was stirred at r.t. for 12 h and evaporated to a syrup. Chromatography (hexane/AcOEt 15:1): **11** (144.5 mg, 48%, syrup). $[\alpha]_D^{22} = -75.1$ (*c* = 0.430, $CHCl_3$). IR ($CHCl_3$): 3020, 2925, 2870, 1790, 1500, 1455, 1375, 1330, 1240, 1170, 1105, 1060. ^{1}H-NMR (300 MHz, $CDCl_3$): 3.70 (*dd*, *J* = 3, 11, 1 H–C(5)); 3.77 (*dd*, *J* = 3, 11, 1 H–C(5)); 4.37 (*t*, *J* = 7, 1 H); 4.53–4.61 (*m*, 5 H); 4.67 (*t*, *J* = 12, 2 H, PhCH_2O); 5.05 (*d*, *J* = 12, 1 H, PhCH_2O); 7.28–7.34 (*m*, 15 arom. H). ^{13}C-NMR (50 MHz, $CDCl_3$): 67.0 (*t*); 72.4, 72.5, 73.4 (3 *t*); 77.2 (2*d*); 79.2 (*d*); 127.4, 127.5, 127.7, 127.9, 128.0, 128.1, 128.2, 128.3, 128.4 (15 *d*); 137.0, 137.1, 137.5 (3 *s*); 173.1 (*s*). CI-MS: 419 (4, $[M + 1]^+$), 417 (6), 361 (19), 327 (16), 271 (37), 182 (15), 181 (100), 179 (16), 91 (61). Anal. calc. for $C_{26}H_{26}O_5$ (418.488): C 74.62, H 6.26; found C 73.25, H 6.81.

In his Ph. D. thesis, *R. Meuwly* (University of Zürich, 1986) has reported on the synthesis of some compounds, somehow similar to **13**, by different methods.

*1-N,2-O,3-O,5-O-Tetrabenzyl-4-O-mesyl-*D*-arabinonamide* (**14**). To a soln. of **9** (2.48 g, 4.718 mmol) and Et_3N (6 ml) in CH_2Cl_2 (50 ml) was added MsCl (0.5 ml, 4 equiv.) at 0°. The resultant soln. was stirred at 0° for 0.5 h and then washed consecutively with sat. $NaHCO_3$ soln. (50 ml), 5% citric acid (50 ml), and H_2O (2 x 50 ml), dried, and evaporated: **14** (2.85 g). Syrup. IR ($CHCl_3$): 3410, 3010, 1675, 1525, 1455, 1355, 1175, 1100, 925. ^{1}H-NMR (300 MHz, $CDCl_3$): 3.00 (*s*, MsO); 3.71 (*dd*, *J* = 6, 11, 1 H–C(5)); 3.88 (*dd*, *J* = 2, 11, 1 H–C(5)); 4.22–4.30 (*m*, 3 H); 4.44–4.51 (*m*, 6 H); 4.71 (*d*, *J* = 11, 1 H, PhCH_2O); 5.06–5.11 (*m*, 1 H); 7.12 (br. *t*, *J* = 1, NH); 7.14–7.19 (*m*, 5 arom. H); 7.24–7.34 (*m*, 15 H). ^{13}C-NMR (50 MHz, $CDCl_3$): 39.1 (*q*); 43.4, 68.7, 73.3, 74.6, 75.2 (5 *t*); 78.9, 79.7, 79.8 (3 *d*); 127.6–128.9 (20 *d*); 136.6, 137.37, 137.42, 137.6 (4 *s*); 170.1 (*s*). CI-MS: 603 (0, M^+), 382 (33), 293 (23), 292 (100), 181 (13), 91 (84).

*2,3,5-Tri-*O*-benzyl-1-(benzylamino)-1-deoxy-*D*-arabitol* (**16**). To a soln. of **7** (1.808 g, 4.300 mmol) and $PhCH_2NH_2$ in MeOH (50 ml) was added $NaBH_3CN$ (85%, 381.2 mg, 1.2 equiv.), and the resultant soln. was adjusted to pH 6–7 with conc. HCl. After stirring at r.t. for 48 h, the soln. was poured into CH_2Cl_2, washed with sat. $NaHCO_3$ soln. and H_2O, dried, and evaporated to a syrup. Chromatography (CH_2Cl_2/MeOH 40:1): **16** (2.16 g, 98%). Syrup. $[\alpha]_D^{22} = +8.9$ (*c* = 1.173, $CHCl_3$). IR ($CHCl_3$): 3035, 3005, 2920(sh), 2870 (br.), 1500, 1455, 1250, 1095 (br.), 1075 (br.). ^{1}H-NMR (300 MHz, $CDCl_3$): 2.90 (*d*, *J* = 4, 2 H–C(1)); 3.65–3.70 (*m*, 3 H); 3.75–3.80 (*m*, 3 H); 3.95–3.98 (*m*, 1 H); 4.49–4.51 (*m*, 1 H); 4.51 (*d*, *J* = 12, 1 H, PhCH_2O); 4.53 (*d*, *J* = 1, 2 H, PhCH_2O); 4.58 (*s*, 2 H, PhCH_2O); 4.61 (*d*, *J* = 12, 1 H, PhCH_2O); 7.21–7.36 (*m*, 20 arom. H). ^{13}C-NMR (50 MHz, $CDCl_3$): 47.6 (*t*); 53.4 (*t*); 70.3 (*d*); 71.4 (*t*); 72.3 (*t*); 73.0 (2 *t*); 78.3 (*d*); 79.1 (*d*); 126.8–128.1 (20 *d*); 137.8, 138.0, 138.1, 139.1 (4 *s*). CI-MS: 512 (100, $[M + 1]^+$), 181 (14), 136 (24), 120 (14), 108 (13), 91 (53). Anal. calc. for $C_{33}H_{37}NO_4$ (511.660): C 77.47, H 7.29, N 2.74; found C 75.68, H 7.17, N 3.16.

*2,3,5-Tri-*O*-benzyl-1,4-(benzylimino)-1,4-dideoxy-*L*-xylitol* (**15**). *Method A.* To a soln. of **16** (643.5 mg, 1.259 mmol) and Et_3N (1.5 ml) in CH_2Cl_2 (50 ml) cooled to –23° was slowly added MsCl (158.7 mg, 1.1 equiv.) in CH_2Cl_2 (5 ml). The resultant soln. was stirred at the same temp. for 4 h, then allowed to warm to r.t., washed with sat. $NaHCO_3$ soln. and H_2O, dried, and evaporated to an oil. Chromatography (hexane/AcOEt 10:1): **15** (301.6 mg, 49%). Colorless syrup.

Method B. To a soln. of **14** (189.1 mg, 0.314 mmol) in THF (20 ml) was added $BH_3 \cdot Me_2S$ (0.3 ml, 3 mmol) at r.t. and the resultant soln. was stirred under reflux for 24 h. Almost no reaction occurred. Then toluene (40 ml) was added and the soln. stirred under reflux at 130° for 5 h. AcOEt (50 ml) was added and the soln. washed with H_2O, sat. $NaHCO_3$ soln., and H_2O, dried, and evaporated to an oil. Compound **15** was obtained after chromatography (33%). $[\alpha]_D^{22} = +30.5$ (*c* = 0.950, $CHCl_3$). IR ($CHCl_3$): 3005, 1500, 1455, 1365, 1080 (br.), 1075. ^{1}H-NMR (300 MHz, $CDCl_3$): 2.32 (*dd*, *J* = 5, 11, 1 H); 3.14 (*dd*, *J* = 6, 11, 1 H); 3.27 (*dd*, *J* = 3, 10, 1 H); 3.48 (*d*, *J* = 13, 1 H, PhCH_2N); 3.65 (*dd*, *J* = 5, 10, 1 H); 3.86 (*dd*, *J* = 6, 10, 1 H); 3.98–4.03 (*m*, 1 H); 4.08 (*dd*, *J* = 3, 5, 1 H); 4.12 (*d*, *J* = 13, 1 H, PhCH_2N); 4.43 (*s*, 2 H, PhCH_2O); 4.53 (*s*, 2 H, PhCH_2O); 4.56 (*d*, *J* =12, 1 H, PhCH_2O); 4.62 (*d*, *J* = 12, 1 H, PhCH_2O); 7.28–7.33 (*m*, 20 arom. H). ^{13}C-NMR (50 MHz, $CDCl_3$): 57.0 (*t*); 59.2 (*t*); 65.0 (*d*); 69.3, 71.2, 71.9, 73.2 (4 *t*); 81.9 (*d*); 83.4 (*d*); 126.6, 127.3, 127.35, 127.4, 127.5, 127.8, 127.9 (9 *d*); 128.1, 128.3, 128.7, 128.8 (20 *d*); 138.0 (*s*); 138.3 (2 *s*); 138.9 (*s*). CI-MS: 494 (76, $[M + 1]^+$), 373 (10), 372 (37), 313 (12), 181 (28), 133 (11), 91 (100), 89 (43). Anal. calc. for $C_{33}H_{35}NO_3$ (493.644): C 80.29, H 7.15, N 2.84; found C 80.02, H 7.13, N 2.73.

*(2S,3R,4R)-2-(Hydroxymethyl)pyrrolidine-3,4-diol (=1,4-Dideoxy-1,4-imino-*L*-xylitol*, **6**). A mixture of **15** (89.5 mg, 0.182 mmol) and 10% Pd/C (41.5 mg) in 2N HCl in EtOH (5 ml) was stirred under H_2 at r.t./1 atm for 18 h. The mixture was filtered and the filtrate evaporated. The syrup was dried under high vacuum, whereupon it solidified spontaneously (attempt to crystallize it failed.): **6** · HCl (31.3 mg, 100%). $[\alpha]_D^{22} = -1.3$ (*c* = 0.540, H_2O;. [6i]: $[\alpha]_D = -9.9$ (*c* = 0.71, H_2O/ crystalline sample)).^{1}H-NMR (400 MHz, (D_6)DMSO): 2.97 (*d*, *J* = 12, H_β–C(1)); 3.35 (*dd*, *J* = 4, 12, H_α–C(1)); 3.55 (br. *s*, H–C(4)); 3.67, 3.75 (each *q*, *J* = 6, 11, *ABX*, 2 H–C(5)); 4.01 (*s*, H–C(3)); 4.08 (*d*, *J* = 3, H–C(2)). ^{13}C-NMR (50 MHz, CD_3OD): 51.8 (*t*); 58.6 (*t*); 64.4 (*d*); 75.5 (*d*); 75.6 (*d*). CI-MS: 169 (21, $[M + HCl]^+$), 134 (62, $[M + 1]^+$), 102 (100), 85 (15). By ^{1}H-NMR, no other diastereoisomer has been detected.

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