Chemistry of Epoxysulfones: A New Route to Polyhydroxylated Pyrrolidines

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Abstract: A new methodology for the synthesis of polyhydroxylated pyrrolidines using epoxysulfones is described. The synthesis of two natural glycosidase inhibitors, 1,4-dideoxy-1,4-imino-D-lyxitol and 1,4-dideoxy-1,4-imino-D-mannitol (DIM), is reported.

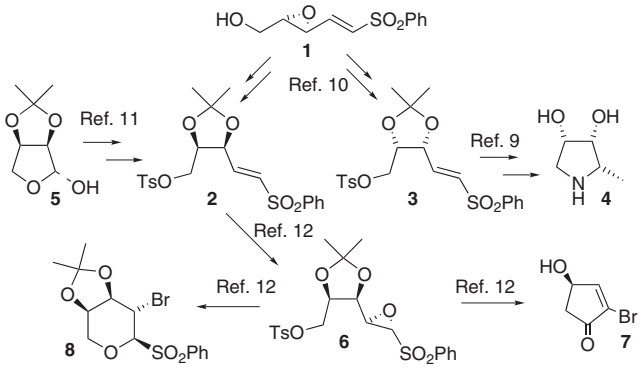
Key words: epoxysulfones, iminosugars, 1,4-dideoxy-1,4-imino-D-lyxitol, 1,4-dideoxy-1,4-imino-D-mannitol

The synthesis of iminosugars has been the subject of much continued effort in recent years.[1] These compounds are known as glycosidase inhibitors,[2] and more recently have been shown to be inhibitors of other enzymes such as glycosyltransferases[3] and nucleoside phosporylases.[4] Many natural and unnatural polyhydroxylated pyrrolidines or piperidines (commonly referred to as azasugars or iminocyclitols) are potent glycosidase inhibitors[5] and hence could be applied in the treatment of numerous pathologies such as diabetes,[6] viral infections[7] or even cancer.[8]

In our previous work, we reported the synthesis of the enantiomerically pure vinyl sulfones **2** and **3**, with complete stereoselection, from the same epoxide, **1**.[9] Compound **3** was further elaborated to the pyrrolidine **4**,[9,10] inhibitor of glycosidases. The key step is the synthesis of the pyrrolidines by SN_2 displacement of the tosylate and intramolecular Michael addition to the vinyl sulfone. Although the method described for the synthesis of **2** is very versatile, multigram quantities of **2** are better obtained from 2,3-*O*-isopropylidene-D-erythronolactol (**5**) in only two steps[11] (Scheme 1).

Very recently we have described a stereoselective epoxidation of **2** and its use for the synthesis of the versatile chiral building blocks **7** and **8**, among others[12] (Scheme 1).

Due to the ease with which compound **6** and its enantiomer could be obtained on a multigram scale, we decided to extend this methodology to the asymmetric synthesis of more functionalized pyrrolidines. It is known that the attack of a nucleophile on an epoxysulfone leads to the elimination of the sulfone group, producing a carbonyl moiety.[13] We therefore anticipated that a cyclization analogous to that used to prepare pyrrolidine **4**, but using an epoxysulfone such as **6**, would give polyhydroxylated pyrrolidines in one step, with a hydroxymethyl group at C-2.



Scheme 1

Treatment of compound **6** with benzylamine in MeOH at reflux gave pyrrolidine **9** (Scheme 2). The reaction occurred as expected, with further reaction of the aldehyde due to the excess of benzylamine. Pyrrolidine **9** was hydrolyzed on silica gel to give aldehyde **10** [an unstable compound, which has been transformed by Ikota et al. into (–)-swansonine[14]], which was reduced straightforwardly with sodium borohydride under the usual conditions to give the known alcohol **11**.[15] The enantiomer of this compound has been transformed by Kim et al. via ring expansion, into piperidines.[16] Finally, hydrogenolysis and acetonide deprotection gives 1,4-dideoxy-1,4-imino-D-lyxitol (**12**), which has previously been synthesized by several authors[17] and has been shown to be a reversible inhibitor of α-galactosidase from green coffee beans.[18]

Having opened a new route to polyhydroxylated pyrrolidines, we decided to apply the method to a more challenging target, such as 1,4-dideoxy-1,4-imino-D-mannitol (DIM), a potent α-mannosidase inhibitor[19] that has been synthesized by Fleet et al.,[20] Jäger et al.,[21] and Díaz-de-Villegas and Gálvez et al.[22]

Treatment of **10** with potassium hexamethyldisilazide (KHMDS) and methylenetriphenylphosphorane gave the olefin **13** in good yield. Dihydroxylation of **13** under the usual conditions led to diol **14**, only one diastereoisomer being observed. In order to establish the stereochemistry obtained at C-1′, compound **14** was protected as its acetonide, giving pyrrolidine **15** in good yield; the structure of this compound was confirmed by synthesis via a differ-

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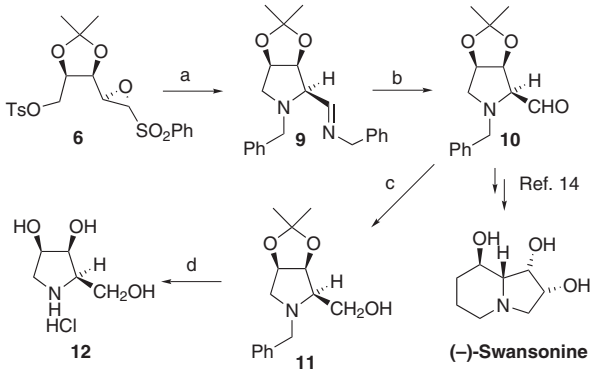
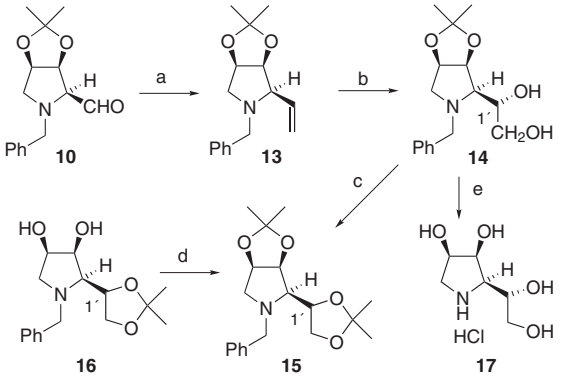


Scheme 2 *Reaction conditions*: a) $BnNH_2$, MeOH, reflux; b) silica gel, 79% (from compound **6**); c) $NaBH_4$, MeOH, 90%; d) 1. H_2, Pd/C, MeOH; 2. HCl (6 M), 68%

ent route. Thus, starting with (*R*)-2,3-*O*-isopropylideneglyceraldehyde and following the procedure of Díaz-de-Villegas and Galvez,[22] compound **16** was obtained, in which the C-1′ stereochemistry was derived from the starting material. Protection of **16** as its acetonide gives a compound identical to **15**, confirming the stereochemistry assigned to **14** at C-1′. Final removal of all the protecting groups from **14** led to **17** in excellent yield, whose physical properties were identical to those described by Fleet et al. for DIM[20] and to an authentic sample purchased from Aldrich (Scheme 3).



Scheme 3 *Reaction conditions*: a) $CH_3Ph_3P^+Br^-$, KHMDS, THF, –78 °C, 89%; b) OsO_4, dioxane–H_2O (6:4), 76%; c) 2,2-DMP, *p*-TsOH, acetone, 94%; d) 2,2-DMP, *p*-TsOH, acetone, 97%; e) 12 M HCl, H_2, 3 atm., $Pd(OH)_2$/C, MeOH, 96%.

In conclusion, in this paper a new route to polyhydroxylated pyrrolidines is described, exploiting the reactivity of epoxysulfones. Due to the accessibility of **6** and its enantiomer on a multigram scale, this provides a new and very versatile strategy for the synthesis of pyrrolidine glycosidase inhibitors.

^{1}H NMR spectra were recorded in $CDCl_3$ (ref. δ = 7.26) at 200 MHz on a Varian 200 VX spectrometer. ^{13}C NMR spectra were recorded in $CDCl_3$ (ref. δ = 77.0) at 50 MHz on a Varian 200 VX spectrometer, and multiplicities were determined by DEPT experiments. IR spectra were recorded on a BOMEM 100 FT IR spectrophotometer. Optical Rotations were determined using a Perkin-Elmer 241 polarimeter in 1 dm cells. EI mass spectra were run on a VG-TS 250 spectrometer at 70 eV. HRMS were recorded in a VG Platform (Fisons) spectrometer using Chemical Ionization (ammonia as gas) or Fast Atom Bombardment (FAB) techniques. Column chromatography was performed with Merck silica gel 60 (70–230 mesh). Solvents and reagents were generally distilled immediately prior to use: THF from sodium benzophenone ketyl; CH_2Cl_2 and diisopropylamine from CaH_2; pyridine from KOH. 1,4-Dideoxy-1,4-imino-D-mannitol hydrochloride was purchased from Aldrich.

(2*S*,3*S*,4*R*)-*N*-Benzyl-2-formyl-3,4-(isopropylidenedioxy)pyrrolidine (10)

To a solution of epoxysulfone **6** (370 mg, 0.86 mmol) in MeOH (7 mL) was added benzylamine (297 mL, 2.72 mmol). The mixture was refluxed for 12 h, then allowed to cool to r.t., and the solvent was concentrated. The residue was diluted with H_2O (11 mL) and extracted with EtOAc. The combined organic layers were washed with H_2O and brine, then dried (Na_2SO_4). Removal of solvent gave the imine **9**. The unstable imine **9** hydrolyzed on silica gel (*n*-hexane–EtOAc, 8:2) to give aldehyde **10** (224 mg, 79%).

IR (film): 2936, 2810, 1728, 1373, 1209, 1096, 858 cm^{-1}.

^{1}H NMR ($CDCl_3$, 200 MHz): δ = 9.42 (1 H, d, *J* = 3.4 Hz, CHO), 7.34–7.25 (5 H, m, Ar), 4.92 (1 H, dd, *J* = 5.6, 6.2 Hz, H-3), 4.69 (1 H, dd, *J* = 4.4, 6.2 Hz, H-4), 3.76 (1 H, d, *J* = 13.2 Hz, H_A of C*H*$_2$Ph), 3.52 (1 H, d, *J* = 13.2 Hz, H_B of C*H*$_2$Ph), 3.25 (1 H, d, *J* = 11.0 Hz, H_A-5), 2.81 (1 H, m, H-2), 2.25 (1 H, dd, *J* = 4.4, 11.0 Hz, H_B-5), 1.54 (3 H, s, CH_3-acetonide), 1.28 (3 H, CH_3-acetonide).

(2*R*,3*S*,4*R*)-*N*-Benzyl-2-hydroxymethyl-3,4-(isopropylidenedioxy)pyrrolidine (11)

To a solution of aldehyde **10** (200 mg, 0.75 mmol) in MeOH (25 mL) was added $NaBH_4$ (30 mg, 0.75 mmol) and the mixture was stirred for 15 min. The reaction was quenched by the addition of H_2O and the mixture was extracted with EOtAc. The combined organic layers were washed with H_2O and brine, then dried (Na_2SO_4). Concentration of the organic layers after filtration gave an oil, which was purified by column chromatography on silica gel (eluent: *n*-hexane–EtOAc, 8:2) to furnish the alcohol **11** (175 mg, 90%). The physical data are in agreement with those given in the literature.[15] Extra data is given for completion of the information.

^{13}C NMR ($CDCl_3$, 50 MHz): δ = 139.1 (C-*ipso*), 128.9 (2 CH-*meta*), 128.5 (2 CH-*ortho*), 127.2 (CH-*para*), 111.2 (C-acetonide), 82.1 (CH-3), 78.1 (CH-4), 67.3 (CH-2), 59.9 (CH_2-1′), 58.9 (CH_2-5), 56.9 (CH_2-1″), 26.4 (CH_3-acetonide), 25.2 (CH_3-acetonide).

HRMS (EI): *m*/*z* calcd for $C_{15}H_{21}NO_3$ (M^+): 263.1521; found: 263.1524.

(2*R*,3*S*,4*R*)-*N*-Benzyl-3,4-dihydroxy-2-hydroxymethyl-pyrrolidine Hydrochloride (12)

A solution of alcohol **11** (150 mg, 0.55 mmol) in MeOH (5 mL) containing a catalytic amount of Pd/C was flushed with H_2 and stirred under an atmosphere of H_2 at 1 bar for 24 h. The mixture was filtered over Celite and solvent was concentrated to 1.5 mL. Aq 6 M HCl (three drops) were added and the mixture was stirred for 12 h. Concentration gave a residue, which was washed with cold Et_2O and MeOH to give a white solid **12** (55 mg, 68%) whose physical data are in agreement with those given in the literature.[17]

(2*R*,3*S*,4*R*)-*N*-Benzyl-3,4-(isopropylidenedioxy)-2-vinyl-pyrrolidine (13)

To a solution of $CH_3Ph_3P^+Br^-$ (1.46 g, 4.09 mmol) in anhyd THF (20 mL) was added a solution 0.5 M KHMDS in toluene (8.8 mL) at –78 °C under argon. The mixture was stirred for 30 min at this temperature and then compound **10** (224 mg, 0.86 mmol) dissolved in anhyd THF (2 mL) was added via cannula. The reaction mixture

was stirred for 12 h, quenched with aq sat. NH_4Cl and extracted with Et_2O. The combined organic layers were washed with H_2O and brine, and dried (Na_2SO_4). Concentration followed by flash chromatography on silica gel gave **13** (198 mg, 89%); $[\alpha]_D^{20}$ –17.6 (c = 0.61, $CHCl_3$).

IR (film): 2930, 1456, 1379, 1209, 1101, 995 cm^{-1}.

^1H NMR ($CDCl_3$, 200 MHz): δ = 7.24–7.30 (5 H, m, Ar), 5.87 (1 H, ddd, J = 8.6, 10.2, 16.9 Hz, H-1′), 5.39–5.29 (2 H, m, H-2′), 4.69–4.54 (2 H, m, H-3, H-4), 3.99 (1 H, d, J = 13.6, H_A-1″), 3.08 (1 H, d, J = 11.6 Hz, H_A-5), 3.07 (1 H, d, J = 13.6, H_B-1″), 2.64 (1 H, m, H-2), 1.98 (1 H, dd, J = 4.8, 11.6 Hz, H_B-5), 1.57 (3 H, s, CH_3-acetonide), 1.31 (3H, s, CH_3-acetonide).

^{13}C NMR ($CDCl_3$, 50 MHz): δ = 140.0 (C-*ipso*), 135.8 (CH-1′), 128.8 (2 CH-*meta*), 128.4 (2 CH-*ortho*), 126.9 (CH-*para*), 119.5 (CH_2-2′), 111.6 (C-acetonide), 82.9 (CH-3), 78.7 (CH-4), 72.1 (CH-2), 58.9 (CH_2-5), 56.7 (CH_2-1″), 26.5 (CH_3-acetonide), 25.7 (CH_3-acetonide).

EIMS: m/z (%) = 259 (M^+, 52), 159 (52), 91 (100), 68 (60).

HRMS (EI): m/z calcd for $C_{16}H_{21}NO_2$ (M^+): 259.1572; found: 259.1591.

(2*R*,3*S*,4*R*)-*N*-Benzyl-2-[(1′*S*)-1,2-dihydroxyethyl]-3,4-(isopropylidenedioxy)pyrrolidine (14)

To a solution of compound **13** (198 mg, 0.77 mmol) in a dioxane–H_2O mixture (6:4, 8 mL) was added NMO (72 mg, 0.77 mmol) and 10 drops of a solution of 2.5% OsO_4 in *t*-BuOH. The mixture was heated at 60 °C for one day. The resulting mixture was cooled and a sat. aq solution of Na_2SO_3 was added (3 mL). After stirring for 30 min, the mixture was extracted with EtOAc, the organic extract was washed with brine and dried (Na_2SO_4). Concentration followed by chromatography (*n*-hexane–EtOAc, 7:3) gave **14** (172 mg, 76%); $[\alpha]_D^{20}$ –27.9 (c = 0.73, $CHCl_3$).

IR (film): 3500, 1717, 1559, 1456, 1373, 1262, 1098 cm^{-1}.

^1H NMR ($CDCl_3$, 200 MHz): δ = 7.30–7.26 (5 H, m, Ar), 4.77–4.47 (3 H, m, H-3, H-4, H-1′), 4.25 (1 H, d, J = 13.2 Hz, H_A-1″), 3.89 (1 H, dd, J = 8.0, 11.0 Hz, H_A-2′), 3.79 (1 H, dd, J = 4.4, 11.0 Hz, H_B-2′), 3.20 (1 H, d, J = 13.2 Hz, H_B-1″), 3.08 (1 H, d, J = 11.4 Hz, H_A-5), 2.34 (1 H, m, H-2), 2.05 (1 H, m, H_B-5), 1.54 (3 H, s, CH_3-acetonide), 1.29 (3 H, s, CH_3-acetonide).

^{13}C NMR ($CDCl_3$, 50 MHz): δ = 132.2 (C-*ipso*), 129.1 (2 CH-*meta*), 128.6 (2 CH-*ortho*), 127.4 (CH-*para*), 111.7 (C-acetonide), 81.5 (CH-3), 77.8 (CH-4), 69.9 (CH-2), 67.1 (CH-1′), 65.5 (CH_2-2′), 58.4 (CH_2-5), 56.2 (CH_2-1″), 26.3 (CH_3-acetonide), 24.8 (CH_3-acetonide).

EIMS: m/z (%) = 293 (M^+, 1), 247 (20), 232 (80), 91 (100), 73 (20).

HRMS (EI): m/z calcd for $C_{16}H_{23}NO_4$ (M^+): 293.1627; found: 293.1628.

(2*R*,3*S*,4*R*)-*N*-Benzyl-2-[(1′*S*)-1,2-(isopropylidenedioxy)ethyl]-3,4-(isopropylidenedioxy)pyrrolidine (15)

To a solution of compound **14** (86 mg, 0.29 mmol) in acetone (3 mL) was added 2,2-dimethoxypropane (2,2-DMP; 100 mL, 0.87 mmol) and a catalytic amount of *p*-TsOH. The mixture was stirred at r.t. for 48 h. The mixture was then neutralized with aq 5% N aHCO$_3$ and extracted with EtOAc. The combined organic layers were washed with H_2O and brine, then dried (Na_2SO_4) before concentration to give **15** (91 mg, 94%); $[\alpha]_D^{20}$ +62.8 (c = 0.53, $CHCl_3$).

IR (film): 2928, 1456, 1379, 1209, 1098, 1038, 860 cm^{-1}.

^1H NMR ($CDCl_3$, 200 MHz): δ = 7.30–7.26 (5 H, m, Ar), 4.64–4.39 (4 H, m, H-4, H-1′, H-2′, H_A-1″), 4.07 (1 H, dd, J = 7.4, 7.8 Hz, H-3), 3.18 (1 H, d, J = 13.6 Hz, H_B-1″), 3.07 (1 H, d, J = 11.2 Hz, H_A-5), 2.35 (1 H, dd, J = 5.8, 7.4 Hz, H-2), 2.07 (1 H, dd, J = 4.6, 11.2 Hz, H_B-5), 1.46 (3 H, s, CH_3-acetonide), 1.43 (3 H, s, CH_3-acetonide), 1.36 (3 H, s, CH_3-acetonide), 1.26 (3 H, s, CH_3-acetonide).

^{13}C NMR ($CDCl_3$, 50 MHz): δ = 133.0 (C-*ipso*), 128.9 (2 CH-*meta*), 128.4 (2 CH-*ortho*), 127.0 (CH-*para*), 113.3 (C-acetonide), 107.5 (C-acetonide), 81.2 (CH-3), 77.3 (CH-4), 75.6 (CH-1′), 68.2 (CH_2-2′), 67.3 (CH-2), 59.2 (CH_2-5), 58.4 (CH_2-1″), 29.0 (CH_3), 26.4 (CH_3), 26.0 (CH_3), 24.9 (CH_3).

EIMS: m/z (%) = 333 (M^+, 1), 318 (10), 232 (100), 91 (100).

HRMS (EI): m/z calcd for $C_{19}H_{27}NO_4$ (M^+): 333.1940; found: 333.1954.

Compound 15

To a solution of compound **16** (200 mg, 0.68 mmol) (synthesized following the procedure of Díaz-de-Villegas and Gálvez[22]) in acetone (6 mL) was added 2,2-DMP (250 mL, 2.04 mmol) and a catalytic amount of *p*-TsOH and the mixture was stirred at r.t. for 48 h. The mixture was then neutralized with aq 5% $NaHCO_3$ and extracted with EtOAc. The combined organic layers were washed with H_2O and brine, then dried (Na_2SO_4) before concentration to give **15** (221 mg, 97%). The physical properties were identical to the compound prepared according to the route described above.

1,4-Dideoxy-1,4-imino-D-mannitol Hydrochloride (17)

Aminodiol **14** (86 mg, 0.29 mmol) was dissolved in MeOH (9 mL). A catalytic amount of $Pd(OH)_2$ (20%) and 12 M HCl (0.04 mL) was added. After flushing with H_2 and stirring under 3 atm of H_2 for 24 h, the mixture was filtered over Celite and concentrated to give **17** (55 mg, 96%). The physical properties were identical to an authentic sample of **17** purchased from Aldrich .

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