Access to New Cyclitol Thiirane Analogs from Oxa-Pseudosaccharides

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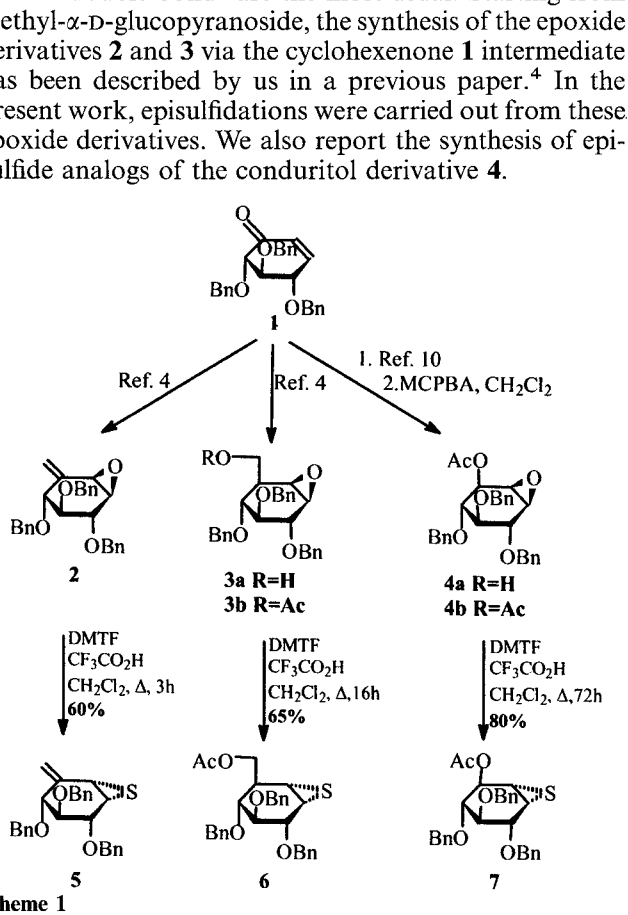
The synthesis of new cyclitol thiirane analogs, from the corresponding epoxides, is reported.

Among the naturally occurring glycosidase inhibitors,[1] aminocyclitols[2] have been extensively studied due to their antibiotic properties.[2] As part of our investigation on the synthesis of potential enzyme inhibitors,[3] we have recently prepared some new analogs which exhibited an activity against the chitine synthetase.[4]

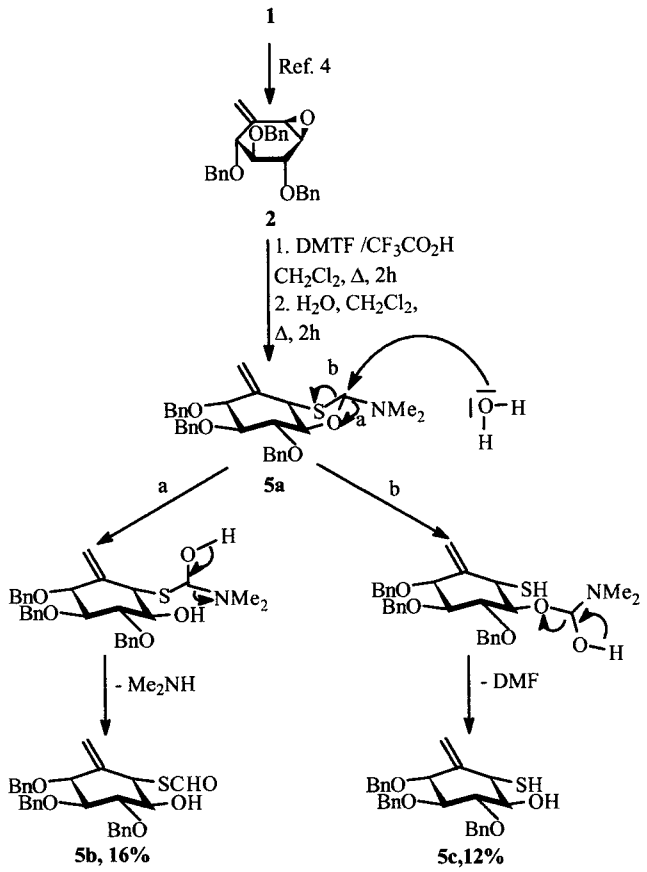
Another important class of glycosidase inhibitors are conduritol epoxides and cyclophellitols.[1] According to Legler's proposition,[1] the activity of such derivatives is attributed to their half chair conformation, which favours the transition state formation between the substrate and the enzyme.

It was obvious to us that although these compounds have been extensively studied, there was a lack of investigation about episulfide analogs.[5] Therefore, we now report the synthesis of new cyclitol thiirane analogs. Among various procedures to introduce an episulfide group, nucleophilic displacement of an oxa group[6] and sulfur addition to an olefinic double bond[7] are the most usual. Starting from methyl-α-D-glucopyranoside, the synthesis of the epoxide derivatives **2** and **3** via the cyclohexenone **1** intermediate has been described by us in a previous paper.[4] In the present work, episulfidations were carried out from these epoxide derivatives. We also report the synthesis of episulfide analogs of the conduritol derivative **4**.



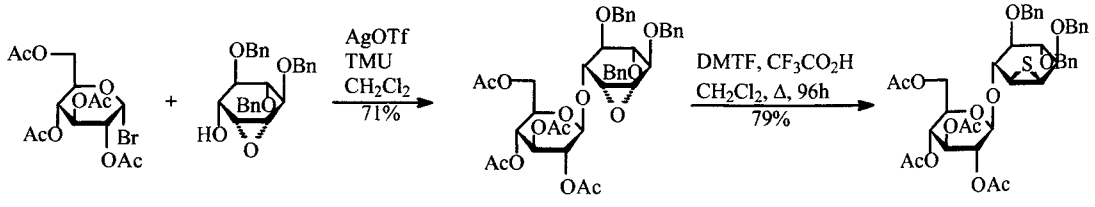
Scheme 1

An efficient enzyme inhibitor activity for compounds which bear a heteroatom (e.g. nitrogen) in an allylic position[4,8] led us to convert epoxide **2** into its thiirane analog **5**. Previous attempts by treatment with thiourea or potassium thiocyanate being unsuccessful in our hands, we used the *N*,*N*-dimethylthioformamide (DMTF)/trifluoroacetic acid (TFA) system. Treatment of **2** with 2.4 equivalents of DMTF and 1.2 equivalents of TFA in refluxing dichloromethane under argon atmosphere for 3 hours led to **5** in 60% yield. The ^{1}H NMR spectrum of **5** ($J_{1,2}$ = 6.4 Hz) as well as the chemical shift of both C-1 and C-2 in ^{13}C NMR spectrum respectively from δ = 55.85 to 38.09 and δ = 57.70 to 38.44 clearly indicate the thiirane formation. Because of the flattened structure of **5**, the confirmation that the C-1 and C-2 configuration were inverted was difficult to establish. Therefore, we carried out the hydrolysis of the cyclic intermediate **5a**[9] by addition of 0.2% of water in dichloromethane. Under these conditions, **5** is obtained in 30% yield and the hydrolysis of **5a** led to **5b** (16%) which shows *trans* diaxial coupling constants ($J_{1,2}$ = 7.7 Hz and $J_{2,3}$ = 9.1 Hz) and to **5c** (12%) which also exhibits *trans* diaxial coupling constants ($J_{1,2}$ = 10.2 Hz and $J_{2,3}$ = 8.5 Hz). The pathways to both **5b** and **5c** from **5a** are depicted in Scheme 2.



Scheme 2

The 3,4,5-tri-*O*-benzylcyclophellitol (**3**) was treated, after acetylation under analogous conditions, to afford after 16 hours, the episulfide **6** in 65% yield. In vitro assays of the unprotected **6** derivative synthesized from L-glucose,[9] showed an interesting inhibitor activity against baker's yeast α-glucosidase. The conduritol B epoxide derivative **4a** was prepared in two steps from **1**.[10] The acetylation of **4a** gave **4b** which was converted into **7** by treatment with DMTF in 88% yield. When the same treatment was carried out on the unacetylated products **3a** and **4a**, no reaction was observed.



4a **8** **9**

Scheme 3

To modify the hydrophilic / lipophilic balance of **7**, the epoxide **4a** was coupled with 2,3,4,6-tetra-*O*-acetyl-α-D-glucopyranosyl bromide (3 equiv) in the presence of silver trifluoromethanesulfonate (3 equiv) and 1,1,3,3-tetramethylurea (3 equiv) in dichloromethane to afford **8** in 70% yield. The ^1H NMR spectrum of **8** showed a coupling constant $J_{1',2'} = 7.8$ Hz involving a β-glycoside configuration. By the use of the same episulfidation procedure, **8** was converted into **9** in 79% yield (Scheme 3)

Melting points were determined with a Buchi apparatus and are uncorrected. Optical rotations were recorded at r.t. on $CHCl_3$ solutions with a Perkin-Elmer 241 polarimeter using a 1 dm cell. ^1H NMR spectra were recorded in $CDCl_3$/TMS at 300.13 MHz (Bruker AM300). Chromatography was performed on Merck silica gel (230–400 mesh) and precoated Merck silica gel plates (60 F-254) were used for TLC.

1*R*(1,2,4,6/3,5)-1,2-Anhydro-3,4,5-tri-*O*-benzylcyclohexane-1,2,3,4,5,6-hexol (4a):
To a solution of 1*R*-1,2,3-tri-*O*-benzyl-(1,3/2,4)-5-cyclohexene-1,2,3,4-tetrol[10] (2 g, 4.81 mmol) in CH_2Cl_2 (100 mL) was added 3-chloroperoxybenzoic acid (MCPBA, 2.42 g, 55%, 7.71 mmol). After stirring at r.t. for 2 d, CH_2Cl_2 (100 mL) was added and the solution washed with aq 10% $Na_2S_2O_3$ solution (100 mL). After drying (Na_2SO_4) and evaporation of the solvent under reduced pressure, the residue was chromatographed on silica gel (hexane/EtOAc, 7:3) to give **7** (1.74 g, 84%); $[\alpha]_D + 75$ ($c = 0.5$, $CHCl_3$); mp 146–149°C (Lit.[10] mp 147–150°C).

^1H NMR ($CDCl_3$/TMS): $\delta = 3.24$ (d, 1H, $J_{1,2} = 3.8$ Hz, H-1), 3.42 (m, 1H, H-2), 3.52 (m, 2H, H-4, H-5), 3.96 (d, 1H, $J_{5,6} = 7.5$ Hz, H-6), 4.06 (dd, 1H, $J_{2,3} = 1.8$ Hz, $J_{3,4} = 8.2$ Hz, H-3), 4.65–5.00 (m, 6H, 3 × CH_2Ph), 7.2–7.4 (m, 15H, 3 × C_6H_5).

1*R*(1,2,4,6/3,5)-6-*O*-Acetyl-1,2-anhydro-3,4,5-tri-*O*-benzylcyclohexane-1,2,3,4,5,6-hexol (4b):
A solution of **4a** (2 g, 4.59 mmol), and Ac_2O (0.7 mL, 7.17 mmol) in pyridine (20 mL) was stirred overnight at r.t. After evaporation of the solvents, the crude product was chromatographed on silica gel (hexane / EtOAc, 9:1) to afford **4b** (91 g, 88%); $[\alpha]_D + 141.8$ ($c = 1$, $CHCl_3$); mp 75–77°C.

^1H NMR ($CDCl_3$/TMS): $\delta = 3.10$ (d, 1H, $J_{1,2} = 3.8$Hz, H-2), 3.26 (dd, $J_{1,6} = 1.6$, $J_{1,2} = 3.8$ Hz, 1H, H-1), 3.45 (t, 1H, $J = 8.2$ Hz, H-4), 3.50 (t, 1H, $J = 8.4$ Hz, H-5), 3.80 (d, 1H, $J_{3,4} = 7.2$ Hz, H-3), 5.20 (dd, 1H, $J_{5,6} = 8.4$ Hz, H-6), 1.90 (s, 3H, CH_3CO), 4.45–4.75 (m, 6H, 3 × C_6H_5).

6-*O*-(2',3',4',6'-Tetra-*O*-acetyl-β-D-glucopyranoside)-1*R*(1,2,4,6/3,5)-1,2-anhydro-3,4,5-tri-*O*-benzylcyclohexane-1,2,3,4,5,6-hexol (8):
To a stirred solution of AgOTf (900 mg, 3.5 mmol) in CH_2Cl_2 (15 mL) at −30°C in the dark, was added a solution of **4a** (500 mg, 1.16 mmol) and 2,3,4,6-tetra-*O*-acetyl-α-D-glucopyrannosyl bromide (1.45 g, 3.53 mmol). At the end of the addition, the solution was allowed to warm to r.t. for 2.5 h, filtered and washed with an aqueous solution of $NaHCO_3$. The organic layer was dried (Na_2SO_4) and concentrated under reduced pressure. The residual syrup was chromatographed on silica gel (hexane / EtOAc, 8:2) to afford **8** in 71% yield (620 mg); $[\alpha]_D + 76.6$ ($c = 1$, $CHCl_3$); mp 121–124°C.

^1H NMR ($CDCl_3$/TMS): $\delta = 3.19$ (d, 1H, H-1), 3.42 (d, 1H, $J_{1,2} = 3.7$ Hz, H-2), 3.47 (t, 1H, $J_{4,5} = 10.2$ Hz, H-5), 3.58 (t, H, $J_{3,4} = 7.9$ Hz, H-4), 3.65 (m, 1H, $J_{4',5'} = 6.3$ Hz, H-5'), 3.85 (d, 1H, $J_{3,4} = 7.5$ Hz, H-3), 4.08 (d, 1H, $J_{1,6} = 8$ Hz, H-6), 4.16 (d, 2H, $J_{5',6'} = J_{5',6''} = 3.5$ Hz, H-6', 6''), 4.95 (d, 1H, $J_{1',2'} = 7.8$ Hz, H-1'), 5.03 (t, 1H, $J_{2',3'} = 9.1$ Hz, H-2'), 5.15 (t, 1H, $J_{3',4'} = 9.1$ Hz, H-3'), 1.80, 1.90, 2.00, 2.10 (4 s, 12H, 4 × CH_3CO), 4.60–4.80 (m, 6H, 3 × CH_2Ph), 7.20–7.40 (m, 15H, 3 × C_6H_5).

Thiirane Derivatives 5-7,9; General Procedure:
To a stirred mixture of the protected epoxide **2**, **3b**, **4b** or **8** (0.45 mmol) in CH_2Cl_2 (20 mL) refluxing under argon was added dropwise CF_3CO_2H (0.54 mmol) and *N*,*N*-dimethylthioformamide (1.08 mmol). The mixture was stirred magnetically under reflux until TLC monitoring indicated that all starting material had disappeared. The solvent was removed under vacuum and the crude product was dissolved in Et_2O (30 mL) and washed with water (2 × 10 mL). The organic phase was dried (Na_2SO_4) and concentrated under reduced pressure. The residual syrup was chromatographed on silica gel (140 g) using hexane/EtOAc (95:5) as eluent.

1R(1,2,3,5/4)-3,4,5-Tri-O-benzyl-1,2-epithio-6-methylenecyclohexane-3,4,5-triol **(5)**:
The foregoing procedure applied to 1*S*(1,2,4/3,5)-1,2-anhydro-3,4,5-tri-*O*-benzyl-6-methylenecyclohexane-1,2,3,4,5-pentol (**2**) gave after 3 h the corresponding episulfide **5** in 60% yield as a colorless syrup; $[\alpha]_D + 12.4$ ($c = 0.8$, $CHCl_3$).

^1H NMR ($CDCl_3$/TMS): $\delta = 3.45$ (dd, 1H, $J_{2,3} = 3.4$ Hz, H-2), 3.80 (d, 1H, $J_{1,2} = 6.4$ Hz, H-1), 4.01 (m, 2H, H-4,5), 4.09 (m, 1H, H-3), 5.57 (s, 1H, H-7), 5.60 (s, 1H, H-7'), 4.55–4.90 (m, 6H, 3 × CH_2Ph), 7.15–7.40 (m, 15H, 3 × C_6H_5).
Compounds **5b** and **5c** were isolated from the reaction of **2** with DMTF by hydrolysis with 0.2% water in CH_2Cl_2 by addition of 0.2% water into the solution after 1 h. The solution was refluxed for a further 2 h. The workup is the same as described in the general procedure; **5b** eluted after **5** and was followed by **5c**.

5b: yield: 16%; $[\alpha]_D -38.6$ ($c = 0.8$, $CHCl_3$); mp 78–80°C.

^1H NMR $CDCl_3$ / TMS: $\delta = 1.70$ (d, 1H, $J_{1,2} = 7.7$ Hz, H-1,) 3.41 (dd, 1H,$J_{2,3} = 9.1$ Hz, H-2), 3.50 (t, 1H, $J_{4,5} = 8.9$ Hz, H-4), 3.61 (t, 1H, $J_{3,4} = 9.1$ Hz, H-3), 3.95 (d, 1H, $J_{4,5} = 8.5$ Hz, H-5), 5.05 (s, 1H, H-7), 5.10 (s, 1H, H-7'), 8.05 (s, SCHO), 4.55–4.96 (m, 6H, 3 × CH_2Ph), 7.20–7.30 (m, 15H, 3 × C_6H_5).

5c: yield: 12%; $[\alpha]_D$ −47.2, (c = 0.6, $CHCl_3$); mp 83–85°C.

^1H NMR $CDCl_3$ / TMS: δ = 1.85 (d, 1H, $J_{1,5H}$ = 6.8 Hz, SH), 2.71 (s, 1H, OH), 3.15 (dd, 1H, $J_{2,3}$ = 8.5 Hz, H-2), 3.24 (dd, 1H, $J_{1,2}$ = 10.2 Hz, $J_{1,5H}$ = 6.8 Hz, H-1), 3.41 (m, 2H, $J_{3,4}$ = 8.2 Hz, H-3,4), 3.87 (d, 1H, $J_{4,5}$ = 8.2 Hz, H-5), 5.37 (s, 1H, H-7), 5.44 (s, 1H, H-7′), 4.51–4.96 (m, 6H, 3 × CH_2Ph), 7.25–7.35 (m, 15H, 3 × C_6H_5).

1S(1,2,3,5/4,6)-7-O-Acetyl-3,4,5-tri-O-benzyl-1,2-epithio-6-hydroxymethylcyclohexane-3,4,5-triol **(6)**:

The foregoing procedure applied to 1*R*(1,2,4,6/3,5)-7-O-acetyl-1,2-anhydro-3,4,5-tri-*O*-benzyl-6-hydroxymethylcyclohexane-1,2,3,4,-5 pentol (**3b**) gave after 16 hours the corresponding episulfide **6** in 65% yield as a pate yellow syrup; $[\alpha]_D$ −4.3 (c = 0.5, $CHCl_3$).

^1H NMR ($CDCl_3$/TMS) δ = 3.07 (m, 1H, H-6), 3.27 (t, 1H, $J_{1,2} = J_{1,6}$ = 6.5 Hz, H-1), 3.42 (dd, 1H, $J_{2,3}$ = 4.3 Hz, H-2), 3.45 (dd, 1H, $J_{5,6}$ = 7.6 Hz, H-5), 3.72 (dd, 1H, $J_{4,5}$ = 9.6 Hz, H-4), 4.03 (dd, 1H, $J_{3,4}$ = 8.5 Hz, H-3), 4.16 (t, 1H, $J_{7,6} = J_{7,7}$ = 10 Hz, H-7), 4.51 (dd, 1H, $J_{6,7'}$ = 5.1 Hz, H-7′).

1S(1,2,3,5/4,6)-6-O-Acetyl-3,4,5-tri-O-benzyl-1,2-epithiocyclohexane-3,4,5,6-tetrol (**7**):

The foregoing procedure applied to **4b** gave after 72 h the corresponding episulfide **7** in 80% yield as a colorless syrup; $[\alpha]_D$ +91.4 (c = 0.7, $CHCl_3$).

^1H NMR ($CDCl_3$ / TMS: δ = 3.04 (d, 1H, $J_{1,2}$ = 6.2 Hz, H-1), 3.42 (dd, 1H, $J_{2,3}$ = 3.8 Hz, H-2), 3.57 (dd, 1H, $J_{5,6}$ = 6.9 Hz, H-5), 3.89 (t, 1H, $J_{4,5}$ = 9.2 Hz, H-4), 4.20 (dd, 1H, $J_{3,4}$ = 9.2 Hz, H-3), 5.44 (d, 1H, H-6), 2.0 (s, 3H, CH_3CO), 4.60–5.00 (m, 6H, 3 × CH_2Ph), 7.30–7.50 (m, 15H, 3 × C_6H_5).

6-O-(2′,3′,4′,6′-Tetra-O-acetyl-β-D-glucopyranoside)-1R(1,2,3,5/4,6)-3,4,5-tri-O-benzyl-1,2-epithiocyclohexane-3,4,5,6-tetrol (**9**):

The foregoing procedure applied to **8** gave after 96 h the corresponding episulfide **9** in 79% yield; $[\alpha]_D$ +71.5 (c = 1, $CHCl_3$); mp 128–131°C.

^1H NMR ($CDCl_3$/TMS): δ = 3.35 (dd, 1H, $J_{2,3}$ = 3.6 Hz, H-2), 3.37 (dd, 1H, $J_{1,2}$ = 6.4 Hz, $J_{1,6}$ = 1.2 Hz, H-1), 3.40 (dd, 1H, $J_{5,6}$ = 7.6 Hz, H-5), 3.70 (m, 2H, $J_{4,5}$ = 10 Hz, H-4, H-5′), 4.10 (2 × dd, 2H, $J_{3,4}$ = 8.6 Hz, H-3, $J_{5',6'}$ = 3.8 Hz, H-6′), 4.25 (dd, 1H,) $J_{5',6''}$ = 5.9 Hz, $J_{6',6''}$ = 12.2 Hz, H-6″), 4.30 (dd, 1H, $J_{1,6}$ = 1.2, $J_{5,6}$ = 7.5 Hz, H-6), 4.75 (d, 1H, $J_{1',2'}$ = 8.2 Hz, H-1′), 5.05 (t, 1H, $J_{4',5'}$ = 9.6 Hz, H-4′), 5.10 (t, 1H, $J_{2',3'}$ = 9.4 Hz, H-2′), 5.20 (t, 1H, $J_{3,4'}$ = 9.4 Hz, H-3′), 1.75, 1.90, 2.00, 2.10 (4 s, 12H, 4 × CH_3CO), 4.55–4.85 (m, 6H, 3 × CH_2Ph), 7.20–7.40 (m, 15H, 3 × C_6H_5).

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