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Synthesis of bis(2-tetrahydropyranyl)methanes – new potential precursors for cyclic polyethers[†]

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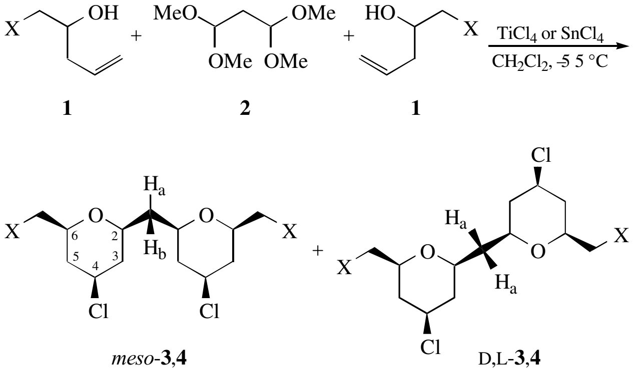
The $TiCl_4$- or $SnCl_4$-promoted cyclization of homoallylic alcohols with malonaldehyde bis(dimethylacetal) affords bis(2-tetrahydropyranyl)methane derivatives, which are potential precursors of *C*-(1→1)-disaccharides and other cyclic polyethers.

Lewis acid promoted cyclization of homoallylic alcohols with aldehydes or their acetals was suggested for the preparation of 2,6-disubstituted tetrahydropyran derivatives.[1] Later we developed the cyclization of this type for preparing synthetic intermediates for aminomethyl *C*-glycosides.[2] Here we report the first one-step synthesis of structures containing two of these rings – bis(2-tetrahydropyranyl)methane derivatives **3** and **4**, which may serve as convenient precursors for various *C*-(1→1)-disaccharides and as building blocks for the total synthesis of natural products such as polyether antibiotics and toxins.



1 **2** **1**

meso-**3**,**4** D,L-**3**,**4**

3 X = H (93%)
4 X = phthalimido (phtN) (73%)

By $TiCl_4$- or $SnCl_4$-promoted cyclization of homoallylic alcohols **1** with malonaldehyde bis(dimethylacetal) **2** in the molar ratio 2:1, compounds **3** and **4** were prepared as a mixture of diastereomers, which was separated by flash chromatography.[‡]

The signals in well-resolved ^1H NMR spectra of compounds DL-**3**, *meso*-**3** and DL-**4** (300 MHz, $CDCl_3$) were assigned using the COSY and homonuclear decoupling technique.[§] The large spin–spin coupling constants H(2)–H(3), H(3)–H(4), H(4)–H(5) and H(5)–H(6) proved the *trans*-diaxial orientation of these pairs of protons and, consequently, the thermodynamically most stable equatorial position of all substituents in these stereoisomers.

The assignment of stereoisomers was also based on ^1H NMR data. The identity of signals of the methylene bridge protons H_a pointed to the molecular C_2 symmetry for the racemic mixtures of compounds D,L-**3** or D,L-**4**. The methylene bridge protons H_a and H_b of the second stereoisomer **3** showed different signals thus proving the *meso*-configuration.

Interestingly, DL-**3** has a strong fresh odour, while *meso*-**3** practically does not smell.

Compounds **3** and **4** potentially can be functionalised in different ways[2] providing an approach to various useful products, *e.g.*, *C*-(1→1)-disaccharides.

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[†] Part of this work was reported at the 19th International Carbohydrate Symposium, San Diego, USA, 1998.

[‡] *5-Phthalimido-1-penten-4-ol* **1** (X = phtN) was prepared by the treatment of phthalimidoacetaldehyde[3] with allyltrimethylsilane and $SnCl_4$ in CH_2Cl_2 (–55 °C) using a procedure described earlier.[4]

Bis(4-chloro-6-methyl-2-tetrahydropyranyl)methane **3**. A solution of $TiCl_4$ (25.0 g, 0.132 mol) in CH_2Cl_2 (200 ml) was added dropwise in 2 h to a stirred cold (–55 °C) solution of 4-penten-2-ol[1,2] (9.5 g, 0.11 mol) and malonaldehyde bis(dimethylacetal) (Aldrich; 8.2 g, 0.05 mol) in CH_2Cl_2 (300 ml) under N_2. The mixture was stirred for 24 h at room temperature, cooled (0 °C) and quenched by dropwise addition of cold 1 M HCl (250 ml). The aqueous layer was extracted with CH_2Cl_2 (2×50 ml). The standard procedure gave 13.9 g of slightly brown crystals containing approximately equal amounts of DL-**3** and *meso*-**3** (^1H, ^{13}C NMR). Separation by flash chromatography (silica gel, $CHCl_3$) of a 5 g aliquot portion afforded 1.5 g of DL-**3** (mp 122 °C, yield 30%), 1.56 g of a mixture of DL-**3** and *meso*-**3** (yield 31%), and 1.65 g of *meso*-**3** (mp 112 °C, yield 33%). Found for DL-**3** (%): C, 55.43; H, 7.89. Found for *meso*-**3** (%): C, 55.71; H, 7.97. Calc. for $C_{13}H_{22}Cl_2O_2$ (%): C, 55.52; H, 7.89.

Bis(4-chloro-6-phthalimidomethyl-2-tetrahydropyranyl)methane **4**: $SnCl_4$ was used as a reagent. A mixture containing DL-**4**, *meso*-**4** and two minor stereoisomers with the axial position of chlorine atoms (^1H, ^{13}C NMR) was obtained in 73% yield. Found (%): C, 61.12; H, 5.01; N, 4.86. Calc. for $C_{29}H_{28}Cl_2N_2O_6$ (%): C, 60.95; H, 4.94; N, 4.90. A sample of DL-**4** was isolated from the mixture by flash chromatography (silica gel, CH_2Cl_2 + 5% MeOH; mp 213–215 °C).

[§] DL-**3**: ^1H NMR, δ: 1.19 (d, 6H, Me, *J* 6.2 Hz), 1.47 [dt, 4H, $H(3)_{ax}$ + + $H(5)_{ax}$, *J* 12.6 and 11.6 Hz], 1.58 (dd, 2H, CH_2-bridge, *J* 5.5 and 6.8 Hz), 2.09 [m, 4H, $H(3)_{eq}$ + $H(5)_{eq}$], 3.45 [ddq, 2H, H(6), *J* 1.8, 11.3 and 6.2 Hz], 3.53 [dddd, 2H, H(2), *J* 1.8, 5.4, 6.8 and 11.5 Hz], 4.00 [tt, 2H, H(4), *J* 4.5 and 11.7 Hz]. ^{13}C NMR, δ: 21.79 (Me), 42.60 (CH_2-bridge), 42.89, 44.32 (CH_2), 55.79 [C(4)], 72.76, 73.02 [C(2)/C(6)].

meso-**3**: ^1H NMR, δ: 1.20 (d, 6H, Me, *J* 6.3 Hz), 1.50 [dt, 4H, $H(3)_{ax}$ + + $H(5)_{ax}$, *J* 12.7 and 11.5 Hz], 1.55 (dt, 1H, CH_2-bridge, *J* 13.9 and 6.0 Hz), 1.92 (dt, 1H, CH_2-bridge, *J* 14.1 and 7.1 Hz), 2.13 [m, 4H, $H(3)_{eq}$ + $H(5)_{eq}$, *J* 12.9 Hz], 3.44 [ddq, 2H, H(6), *J* 1.9, 11.0 and 6.2 Hz], 3.48 [dddd, 2H, H(2), *J* 1.9, 6.0, 7.0 and 11.5 Hz], 4.01 [tt, 2H, H(4), *J* 4.5 and 11.8 Hz]. ^{13}C NMR, δ: 21.74 (Me), 41.82 (CH_2-bridge), 42.07 (CH_2), 44.21 (CH_2), 55.77 [C(4)], 72.82, 73.06 [C(2)/C(6)].

DL-**4**: ^1H NMR, δ: 1.42 [q, 2H, $H(3)_{ax}$/$H(5)_{ax}$, *J* 12.1 Hz], 1.47 [q, 2H, $H(5)_{ax}$/$H(3)_{ax}$, *J* 12.0 Hz], 1.49 (dd, 2H, CH_2-bridge, *J* 5.8 and 6.6 Hz), 1.96 [m, 2H, $H(3)_{eq}$], 2.02 [m, 2H, $H(5)_{eq}$], 3.16 [m, 4H, H(2) + H(6)], 3.53 (dd, 2H, CH_2N, *J* 4.1 and 13.7 Hz), 3.67 [tt, 2H, H(4), *J* 4.4 and 11.8 Hz], 3.72 (dd, 2H, CH_2N, *J* 8.3 and 13.7 Hz) 7.76 (m, 4H, Ar), 7.89 (m, 4H, Ar). ^{13}C NMR, δ: 39.91 (CH_2), 41.63 (CH_2-bridge), 42.13 (CH_2), 42.40 (CH_2), 54.94 [C(4)], 72.94, 73.7 [C(2)/C(6)], 123.43, 131.99, 134.06 (C_{Ar}), 167.94 (CO).