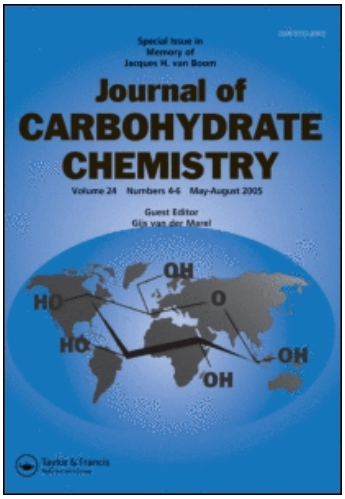

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COMMUNICATION

A NEW APPROACH TO THE SYNTHESIS OF ENANTIOMERICALLY PURE 4-DEOXY SUGARS[1]

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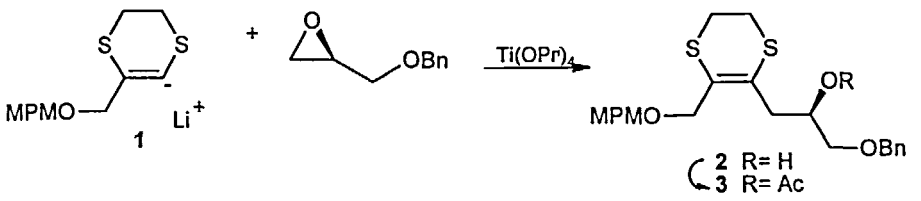
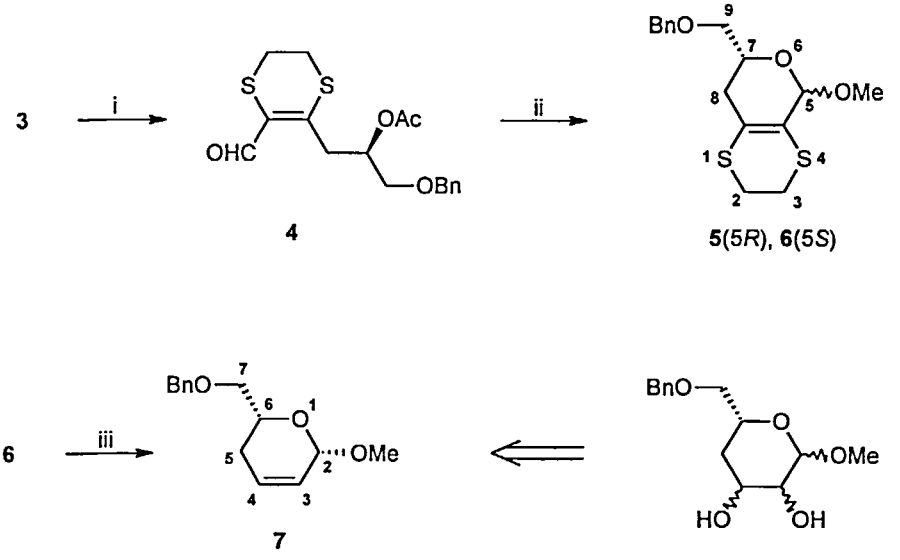
In a recent paper[2] we have reported the design and synthesis of 3-*C*-lithiated 5,6-dihydro-1,4-dithiin-2-yl[(4-methoxybenzyl)oxy]methane (**1**) which can be utilized as an allylic alcohol anion equivalent and leads to three-carbon elongations of various electrophiles by introduction of a fully protected hydroxypropenyl moiety. The latter contains a double bond, which can be unravelled to the *cis* configuration by diastereoselective removal[3] of the dimethylene-disulfur bridge, as well as a protected primary hydroxyl group that, depending on the deprotection conditions used (DDQ/$NaBH_4$ or DDQ), may either lead to the free allylic alcohol or to an α,β-unsaturated aldehyde.



Scheme 1. Coupling reaction with (*R*)-benzyl glycidyl ether.

We report now a new versatile synthesis of a precursor of 4-deoxy-L-sugars that is in fact initiated by coupling of **1** with (*R*)-benzyl glycidyl ether.

The coupling product **2** derived from (*R*)-benzyl glycidyl ether, after acetylation of the free hydroxyl group to give **3**, was selectively deprotected *via* oxidative removal of the *p*-methoxybenzyl ether by DDQ to afford carbaldehyde **4** as shown in Scheme 2. Cyclization of carbaldehyde by treatment with TMSOTf and TEA in methanol led to a diastereomeric mixture of dihydropyrans **5** and **6**. The latter was then desulfurised by treatment with Raney-Ni (W2) in glacial acetic acid to give the final compound **7**. This is a formal 2,3-dehydro-2,3,4-trideoxy L-sugar which can be hydroxylated in a stereocontrolled manner[4] to give 4-deoxy-L-sugars.



(i) DDQ in CH_2Cl_2/H_2O; (ii) TMSOTf, NEt_3 in MeOH; (iii) Raney-Ni in glacial acetic acid

Scheme 2. Formal synthesis of 4-deoxy-L-sugars.

The same procedure reported in Schemes 1 and 2 applied to (*S*)-benzyl glycidyl ether led, as expected, to the formation of the D analog of **7**. Work is now in progress to achieve 4-deoxy L- and D-sugars by stereocontrolled hydroxylations of the double bond in **7** and its D analog.

EXPERIMENTAL

General methods. ^{1}H NMR spectra were recorded in $CDCl_3$ solutions: chemical shifts were reported in ppm (δ) downfield from internal tetramethylsilane (TMS). Optical rotations were measured in $CHCl_3$ solutions (1.0 dm cell). Thin-layer chromatography (TLC) analyses were performed on silica gel Merck 60 F_{254} plates (0.2 mm layer thickness). Column chromatography was carried out with Merck Kieselgel 60 (70-230 mesh).

(5*R*,7*R*)- and (5*S*,7*R*)-[(Benzyloxy)methyl]-5-methoxy-3,5,7,8-tetrahydro-2H-[1,4]dithiino[2,3-c]pyran (5 and 6). To a stirred solution of aldehyde **4**[2] (1.0 g; 2.8 mmol) in methanol (5 mL) at room temperature, TEA (1.95 mL; 14.0 mmol) and TMSOTf (2.2 mL; 14.0 mmol) were added slowly over 1 h. After 2 h, most of the solvent was evaporated under reduced pressure and replaced by AcOEt (10 mL). The organic phase was washed with brine until neutral, then dried (Na_2SO_4) and concentrated under reduced pressure. Chromatography of the crude residue on silica gel (hexane-AcOEt, 8:2) afforded the pure diastereomeric dihydropyrans **5** and **6** (0.83 g, 90% yield; diastereomer ratio 1.6:8.4). Higher R_f compound **5**: (0.14 g), oil; $[\alpha]_D^{25}$ +18 (*c* 0.9); ^{1}H NMR (200 MHz) δ 1.98 (dd, 1H, $J_{8a,7}$ = 3.3Hz, $J_{8a,8b}$ = 16.6 Hz, H-8a), 2.44 (dd, 1H, $J_{8b,7}$ = 11.4 Hz, $J_{8b,8a}$ = 16.6 Hz, H-8b), 3.00-3.38 (m, 2H, H-2), 3.18-3.31 (m, 2H, H-3), 3.54 (dd, 1H, $J_{9a,7}$ = 4.2 Hz, $J_{9a,9b}$ = 10.3 Hz, H-9a), 3.57 (dd, 1H, $J_{9b,7}$ = 5.1 Hz, $J_{9b,9a}$ = 10.3 Hz, H-9b), 3.83 (s, 3H, OCH_3), 4.26-4.37 (m, 1H, H-7), 4.57 (d, 1H, $J_{Ha,Hb}$ = 12.1 Hz, Ha_{Bn}), 4.61 (d, 1H, $J_{Hb,Ha}$ = 12.1 Hz, Hb_{Bn}), 4.85 (s, 1H, H-5), 7.35-7.39 (m, 5H, H_{Ar}).

Anal. Calcd for $C_{16}H_{20}O_3S_2$ (324.46): C, 59.23; H, 6.21. Found C, 59.58; H, 6.17.

Lower R_f compound **6**: (0.69 g), oil; $[\alpha]_D^{25}$ +39 (*c* 1.4); ^{1}H NMR (400 MHz) δ 1.93 (dd, 1H, $J_{8a,7}$ = 3.4 Hz, $J_{8a,8b}$ = 16.5 Hz, H-8a), 2.39 (dd, 1H, $J_{8b,7}$ = 11.6 Hz, $J_{8b,8a}$ = 16.5 Hz, H-8b), 3.05-3.15 (m, 2H, H-2), 3.18-3.31 (m, 2H, H-3), 3.43 (s, 3H, OCH_3), 3.53 (dd, 1H, $J_{9a,7}$ = 4.6 Hz, $J_{9a,9b}$ = 10.6 Hz, H-9a), 3.58 (dd, 1H, $J_{9b,7}$ = 5.2 Hz, $J_{9b,9a}$ = 10.6 Hz, H-9b), 4.23-4.32 (m, 1H, H-7), 4.57 (d, $J_{Ha,Hb}$ = 12.1 Hz, 1H, Ha_{Bn}), 4.61 (d, 1H, $J_{Hb,Ha}$ = 12.1 Hz, Hb_{Bn}), 4.77 (s, 1H, H-5), 7.31-7.38 (m, 5H, H_{Ar}); ^{13}C NMR (400 MHz) ppm 27.8, 28.9 (C-2, C-3), 33.8 (C-8), 55.8 (CH_3O), 67.3 (C-9), 72.4 (C-Bn), 74.0 (C-7), 99.1 (C-5), 110.0 (C-4a and C-8a).

Anal. Calcd for $C_{16}H_{20}O_3S_2$ (324.46): C, 59.23; H, 6.21. Found C, 59.49; H 6.26.

(2*S*,6*R*)-2-Methoxy-6-[(benzyloxy)methyl]-3,6-dihydro-2H-pyran (7). A solution of dihydropyran 6 (0.5 g; 1.5 mmol) in glacial acetic acid (10 mL) was added in one portion to a stirred suspension of Raney-Ni (W2) (5.5 g, wet) in the same solvent (10 mL) at 0° C and under argon stream. The suspension was stirred for 2 min (TLC monitoring). Then the solid was filtered off and washed with glacial acetic acid, water, and AcOEt. The filtrate was neutralized with saturated aq Na_2CO_3 and extracted with AcOEt. The combined organic layers were washed with water until neutral, dried (Na_2SO_4), and concentrated under reduced pressure to afford a crude residue. Chromatography of the latter on silica gel (CH_2Cl_2) gave pure **7** (0.26 g, 70% yield). ^1H NMR (200 MHz) δ 2.05-2.35 (m, 2H, H-5), 3.48 (s, 3H, OCH_3), 3.50-3.65 (m, 2H, H-7), 4.10-4.31 (m, 1H, H-6), 4.57 (d, 1H, $J_{Ha,Hb}$ = 12.0 Hz, Ha_{Bn}), 4.63 (d, 1H, $J_{Hb,Ha}$ = 12.0 Hz, Hb_{Bn}), 5.02 (d, 1H, $J_{6,5}$ = 6.5 Hz, H-2), 5.66 (dd, 1H, $J_{5,6}$ = 6.5 Hz, $J_{5,4}$ = 9.1 Hz, H-3), 5.92-6.15 (m, 1H, H-4), 7.15-7.32 (m, 5H, H_{Ar}).

Anal. Calcd for $C_{14}H_{18}O_3$ (234.30): C, 71.77; H, 7.74. Found: C, 71.56; H, 7.80.

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