# A Synthesis of (2*S*,6*S*)-2-Hydroxymethyl-6-methoxytetrahydropyran; a Useful Chiral Intermediate

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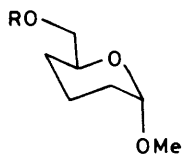
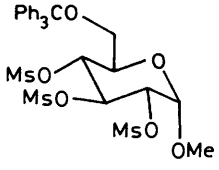
(2*S*,6*S*)-2-Hydroxymethyl-6-methoxytetrahydropyran (**2**) has been prepared in enantiomerically pure form in 13% yield from D-glucose.

As part of a project concerned with the enantiospecific synthesis of macrolide antibiotics using the 'chiron' approach,[1] we wished to study both the chain extension[2] and the resulting stereochemistry at the so-called off-template centres.[3] In order to carry out these studies, we needed a model compound that would contain the major features of the intermediates envisaged in the natural product syntheses. Specifically, we were interested in the extension of hexopyranosides at C-6 and the ensuing stereochemistry.[4] For this reason, we chose the differentially protected (**1**) as the model compound so that deprotection of the primary alcohol function and oxidation would allow both the addition of a methyl group and chain extension at C-6. Compound (**1**) contains the two features that we anticipated would provide the main stereochemical bias, namely the anomeric methoxy group and the $^4C_1$ conformation of the pyranoside ring. Although compound (**1**) contains only two chiral centres, after considering alternative approaches, we decided that synthesis from a carbohydrate precursor would provide the most convenient and practical synthesis of this model compound. We now present our concise synthesis of compound (**2**) which illustrates the convenience of the 'chiron' approach even when several of the chiral centres present in the starting material have to be destroyed.



(**1**) R = $CPh_3$
(**2**) R = H



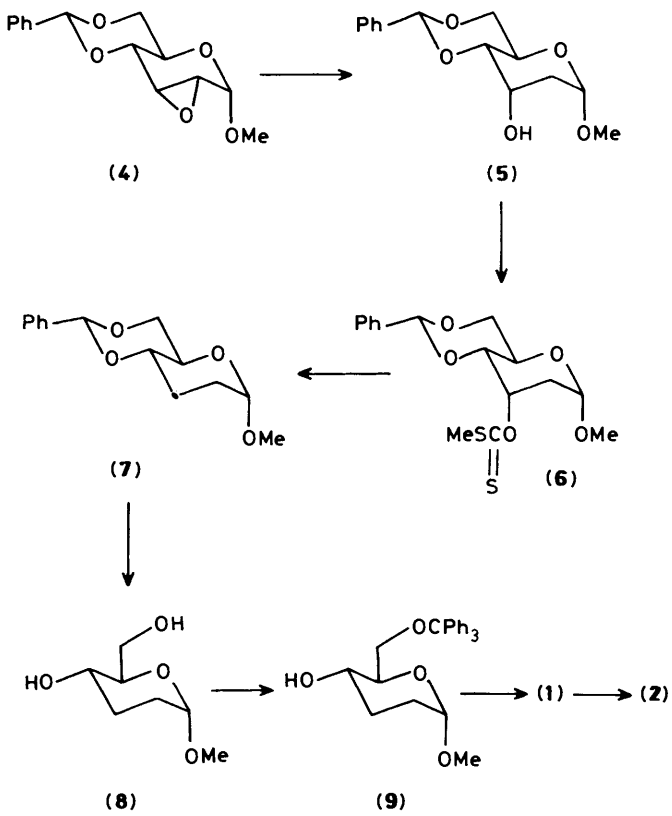
(**3**) Ms = $MeSO_2$

## Results

Preliminary experiments involving reduction of the trimesylate (**3**) using lithium aluminium hydride proved completely unsuccessful and so attention was focussed on the Barton deoxygenation procedure.[5] It has been reported[5] that this radical deoxygenation procedure fails in the case of diols and triols owing to the formation of thiocarbonates. In view of this, we decided to approach our problem in a stepwise manner. Treatment of the readily available epoxide (**4**)[6] with lithium aluminium hydride gave the 2-deoxy compound (**5**) as a white crystalline solid in 95% yield. Formation of the sodium salt of compound (**5**) followed by treatment with carbon disulphide and finally methyl iodide gave the dithiocarbonate ester (**6**) which, without purification, was treated with tributyltin hydride in refluxing toluene to give the 2,3-dideoxy compound (**7**) in 51% overall yield from the epoxide (**4**) without the need for chromatographic purification.

The removal of the benzylidene protecting group from compound (**7**) was first investigated using hydrogenation but this proceeded in low yield. However, treatment of compound (**7**) with toluene-*p*-sulphonic acid in methanol gave the diol (**8**) in 72% yield after chromatography. Removal of the 5-hydroxy group now required selective protection of the primary hydroxy group on C-6. Treatment of diol (**8**) with trityl chloride in pyridine for 3 days at 50 °C gave compound (**9**) in 62% overall yield from the benzylidene derivative (**7**). Tributyltin hydride reduction of the dithiocarbonate ester of compound (**9**) as before gave the differentially protected (**1**) in 90% yield. Selective removal of the trityl group in compound (**1**) initially gave some problems which were eventually traced to the presence of small quantities of sulphur residues in compound (**1**) obtained from radical deoxygenation even after chromatography. Pre-treatment of compound (**1**) with W2 Raney nickel followed by the usual catalytic hydrogenation gave the required model compound (**2**) in 44% yield (Scheme).

This route provides a practical synthesis of a useful chiral intermediate (**2**); we were easily able to prepare the differentially protected (**1**) on a 10-g scale using this approach. The final removal of the trityl group gave somewhat disappointing yields



Scheme.

and it might be that the use of a silicon-based protecting group such as the diphenyl-t-butylsilyl group[7] would give higher yields of the final product. The potential for using compound (**2**) in the enantiospecific synthesis of 6-substituted valerolactone derivatives[8] by chain extension through the primary hydroxy group[2] followed by oxidation of the acetal to a lactone[9] is obvious.

## Experimental

I.r. spectra were recorded as Nujol mulls on a Perkin-Elmer 297 instrument using polystyrene as standard. $^1$H N.m.r. spectra were recorded at 250 MHz on a Bruker WM250 instrument in $CDCl_3$ solution with tetramethylsilane as internal standard. $^{13}$C N.m.r. spectra were recorded at 22.6 MHz on a Bruker HFX90 instrument in $CDCl_3$ solution with tetramethylsilane as internal standard. Mass spectra were recorded on an A.E.I. MS30 instrument using electron impact ionisation. M.p.s were measured on a Gallenkamp heated block apparatus and are uncorrected. Optical rotations were measured on a Perkin-Elmer 141 automatic polarimeter using a 10 cm cell. Analytical t.l.c. was carried out on Merck glass-backed plates pre-coated with silica gel 60 F-254 to a depth of 0.2 mm. T.l.c. plates were visualised using u.v. light or a 1:1 ethanol–concentrated sulphuric acid spray. Column chromatography was carried out using the technique of flash chromatography as described by Still *et al.*[10] Diethyl ether and tetrahydrofuran (THF) were distilled from lithium aluminium hydride prior to use. Toluene was dried over sodium wire.

*Methyl* 4,6-O-*Benzylidene*-2-*deoxy*-α-D-ribo-*hexopyranoside* (**5**).—Lithium aluminium hydride (4.5 g, 120 mmol) was added to a solution of methyl 2,3-anhydro-4,6-*O*-benzylidene-α-D-allopyranoside (**4**) (15.2 g, 58 mmol)[6] in ether (1 $dm^3$). The mixture was refluxed for 2 h, cooled, and quenched with water (20 ml). The mixture was filtered through Celite, dried, and evaporated under reduced pressure to give a white crystalline solid. Recrystallisation from diethyl ether gave the product (**5**) (14.7 g, 95%), m.p. 123—125 °C (lit.,[11] 116—117 °C); $[\alpha]_D^{23}$ +144.8° (*c* 1 in $CHCl_3$) [lit.,[11] $[\alpha]_D^{20}$ +150.9° (*c* 2.1 in $CHCl_3$)]; $\nu_{max.}$ 3 520 $cm^{-1}$ (OH); $\delta_H$ 2.01 and 2.22 (2 H, ABdd, *J* 1, 3, 4, 4, and 14.5 Hz, 2-$H_{ax}$ and 2-$H_{eq}$), 3.05 (1 H, d, *J* 6.5 Hz, OH), 3.41 (3 H, s, OMe), 3.61 (1 H, dd, *J* 3 and 10 Hz, 4-H), 3.77 (1 H, t, *J* 10 Hz, 6-$H_{ax}$), 4.16—4.36 (3 H, m, 3- and 5-H and 6-$H_{eq}$), 4.79 (1 H, d, *J* 4 Hz, 1-H), 5.62 (1 H, s, PhC*H*), and 7.34—7.56 (5 H, m, ArH); $\delta_C$ 35.4 (C-2), 55.3 (OMe), 58.1 (C-5), 64.9 (C-6), 69.3 (C-3), 79.6 (C-4), 98.6 (C-1), 102 (Ph*C*H), and 126.4—137.3 (ArC); *m/z* 265 ($M^+$, 100%) and 234 ($M^+$ − 31).

*Methyl* 4,6-O-*Benzylidene*-2,3-*dideoxy*-α-D-erythro-*hexopyranoside* (**7**).—A solution of compound (**5**) (14.7 g, 55 mmol) in THF (250 ml) was added to a suspension of sodium hydride (60% dispersion in oil, pre-washed with light petroleum; 6.6. g, 170 mmol) in THF (750 ml). After 15 min, carbon disulphide (12.5 g, 170 mmol) was added and the mixture stirred for 4 h at room temperature. Iodomethane (23.4 g, 170 mmol) was added and after 5 min, the reaction was quenched with water. The reaction mixture was diluted with brine and the product extracted with dichloromethane (3 × 100 ml). The combined organic extracts were dried, filtered through a pad of silica gel (t.l.c. grade), and concentrated under reduced pressure. The resulting oil was dissolved in toluene (1.5 $dm^3$) and tributyltin hydride (20.8 g, 72 mmol) was added along with a catalytic quantity of azoisobutyronitrile (AIBN). The reaction mixture was refluxed for 1.5 h and evaporated under reduced pressure. The oily residue was diluted with water and extracted with dichloromethane (3 × 100 ml). The combined organic extracts were filtered through Celite, washed with hydrochloric acid (100 ml, 1M), dried, and concentrated under reduced pressure to give an oil. Flash chromatography [light petroleum–ethyl acetate (gradient elution 10:1—3:2)] gave the title compound (**7**) (12.4 g, 90%), m.p. 84—87 °C (lit.,[12] 82—83 °C); $[\alpha]_D^{26}$ +118.6° (*c* 1 in $CHCl_3$); $\delta_H$ 1.94 (4 H, m, 2- and 3-$H_2$), 3.40 (3 H, s, OMe), 3.61 (1 H, m, 4-H), 3.74 (1 H, t, *J* 10 Hz, 6-$H_{ax}$), 3.85 (1 H, dt, *J* 10, 9.5, and 4 Hz, 5-H), 4.24 (1 H, dd, *J* 10 and 4 Hz, 6-$H_{eq}$), 4.71 (1 H, d, *J* 3.1 Hz, 1-H), 5.59 (1 H, s, PhC*H*), and 7.34—7.56 (5 H, m, ArH); $\delta_C$ 23.9 (C-3), 29.4 (C-2), 54.5 (OMe), 64.9 (C-5), 69.5 (C-6), 78.3 (C-4), 97.8 (C-1), 101.9 (Ph*C*H), 126.2, 128.2, 128.9, and 137.8 (ArC); *m/z* 250 ($M^+$) and 219 ($M^+$ − OMe).

*Methyl* 2,3-*Dideoxy*-6-O-*trityl*-α-D-erythro-*hexopyranoside* (**9**).—Toluene-*p*-sulphonic acid (1.75 g, 9.2 mmol) was added to a solution of compound (**7**) (11.6 g, 46 mmol) in methanol (1 $dm^3$). The reaction mixture was stirred at room temperature until t.l.c. [light petroleum–ethyl acetate (1:1)] showed that the reaction was complete, after which it was neutralised with solid sodium hydrogen carbonate and concentrated under reduced pressure. The product was dissolved in pyridine (300 ml) and trityl chloride (11.3 g, 41 mmol) was added. The solution was stirred for 3 days at 50 °C and then diluted with water and concentrated under reduced pressure. The residue was dissolved in dichloromethane, washed with brine, dried, and concentrated under reduced pressure. Flash chromatography [light petroleum–ethyl acetate (5:1)] yielded the *title compound* (**9**) (11.5 g, 62%), 129—132 °C (Found: C, 77.25; H, 6.8. $C_{26}H_{28}O_4$ requires C, 77.2; H, 6.98%); $[\alpha]_D^{25}$ +29° (*c* 0.62 in $CHCl_3$); $\nu_{max.}$ 3 395 (OH) $cm^{-1}$; $\delta_H$ 1.68—1.83 (4 H, m, 2- and 3-$H_2$), 2.75 (1 H, br s, OH), 3.27—3.63 (4 H, m, 4- and 5-H and 6-$H_2$), 3.32 (3 H, s, OMe), 4.62 (1 H, br s, 1-H), and 7.2—7.5 (15 H, m, ArH); $\delta_C$ 26.5 (C-3), 28.9 (C-2), 54.5 (OMe), 66.1, 69.4, and 71.0 (C-4, C-5, and C-6), 87.6 ($Ph_3C$), 97.1 (C-1), 127.2, 127.9, 128.4, and 143.7 (ArC); *m/z* 404 ($M^+$) and 373 ($M^+$ − OMe).

*Methyl* 2,3,4-*Trideoxy*-6-O-*trityl*-α-D-glycero-*hexopyranoside* (**1**).—Sodium hydride (60% dispersion in oil; 2.5 g, 60 mmol) was added to a solution of compound (**9**) (11.3 g, 28 mmol) in THF (250 ml) under nitrogen. After 15 min, carbon disulphide (4.6 g, 60 mmol) was added and the mixture heated under reflux for 3 days. Iodomethane (9.12 g, 64 mmol) was added and the solution stirred for 10 min before quenching with water. The reaction mixture was poured into brine and extracted with dichloromethane (3 × 100 ml). The combined organic extracts were treated with activated charcoal, filtered, dried, and concentrated under reduced pressure. The residue was dissolved in toluene (200 ml) and tributyltin hydride (11.64 g, 40 mmol) and a catalytic quantity of AIBN were added. The mixture was heated under reflux for 24 h and then concentrated under reduced pressure to give an oil. Flash chromatography [light petroleum–ethyl acetate (6:1)] yielded the *title compound* (**1**) (9.8 g, 90%) as an oil (Found: $M^+$, 388.2033. $C_{26}H_{28}O_3$ requires $M^+$, 388.2038); $[\alpha]_D^{32}$ +20.7° (*c* 0.78 in $CHCl_3$); $\delta_H$ 1.25—1.67 (6 H, m, 2-, 3-, and 4-$H_2$), 2.96 and 3.18 (2 H, ABdd, *J* 9.1 and 6.8 Hz, 6-$H_2$), 3.42 (3 H, s, OMe), 3.93 (1 H, m, 5-H), 4.75 (1 H, br s, 1-H), and 7.2—7.5 (15 H, m, ArH); $\delta_C$ 17.9 (C-4), 28.1 (C-3), 29.7 (C-2), 54.4 (OMe), 67.4 and 68.1 (C-5 and C-6), 86.4 ($Ph_3C$), 98.3 (C-1), 126.4, 127.8, 128.8, and 144.3 (ArC).

(2S,6S)-2-*Hydroxymethyl*-6-*methoxytetrahydropyran* (**2**).—W2 Raney nickel (5 g) was added to a solution of compound (**1**) (9.7 g, 25 mmol) in methanol (150 ml). The mixture was stirred for 2 h and then filtered through Celite and concentrated under reduced pressure. The residue was dissolved in methanol (250 ml) and palladium on charcoal (1 g, 10%) added. The mixture was hydrogenated at atmospheric pressure until the reaction was complete by t.l.c. [light petroleum–ethyl acetate (1:1)]. The mixture was then filtered through Celite and concentrated

under reduced pressure. Flash chromatography [light petroleum–ethyl acetate (5:1—3:1)] gave the *title compound* (**2**) (1.62 g, 44%) as an oil (Found: $M^+$, 130.0996. $C_7H_{14}O_2$ requires $M^+$, 130.0994); $[\alpha]_D^{30}$ +126.1° (*c* 1.44 in $CHCl_3$); $\nu_{max.}$ 3 440 (OH) $cm^{-1}$; $\delta_H$ 1.28—1.93 (6 H, m, 3-, 4-, and 5-$H_2$), 2.70 (1 H, br s, OH), 3.37 (3 H, s, OMe), 3.42 (1 H, dd, *J* 11.5 and 6.5 Hz, $CH_2$), 3.85 (1 H, m, 2-H), 3.93 (1 H, dd, *J* 11.5 and 3.4 Hz, $CH_2$), and 4.75 (1 H, br s, 6-H); $\delta_C$ 17.7 (C-3), 26.9 (C-4), 29.7 (C-5), 54.4 (OMe), 65.9 and 69.6 (C-2 and $CH_2OH$), and 98.4 (C-6).

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