## Synthesis of (*R*)-4-Hydroxy-2-(1,3-dithian-2-ylmethyl)cyclopent-2-en-1-one, a Chiral Prostaglandin E<sub>2</sub> Synthon, from D-Glucose

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The transformation of D-glucose to (R)-4-hydroxy-2-(1,3-dithian-2-ylmethyl)cyclopent-2-en-1-one (1), a potential chiral synthon for prostaglandin E<sub>2</sub> and its analogues, is described.

Several total syntheses of biologically active cyclopentanoid natural products, notably in the prostaglandin series,<sup>1</sup> rest on the conjugate addition of organometallic derivatives to 2-substituted 4-hydroxycyclopent-2-en-1-ones. Despite the existence of numerous synthetic approaches to substituted cyclopentenones,<sup>1,2</sup> the need for improvement and diversification still remains. Besides, the development of efficient stereocontrolled routes to such compounds from inexpensive chiral starting materials is currently an important area of research.<sup>3,4</sup> We report here the synthesis of an optically active functionalized cyclopentenone, (R)-4-hydroxy-2-(1,3dithian-2-ylmethyl)cyclopent-2-en-1-one (1), a potential chiral synthon for prostaglandin E<sub>2</sub> and its analogues, from D-glucose.

The synthesis of (1) rested upon achieving the intramolecular aldolisation-dehydration of the acyclic 4-ketoaldehyde (2) which could be envisaged as the product of acidic hydrolysis of the 3,4-unsaturated furanoside (10). The latter was obtained in an overall yield of about 55% from the readily available D-glucose derivative 1,2-O-isopropylidene- $\alpha$ -D-glucofuranose (3) as outlined in Scheme 1.



Compound (3) was directly converted<sup>5</sup> into the 5,6anhydro-compound (4) by using the diethyl azodicarboxylatetriphenylphosphine (DEAD-TPP) system (85% yield after chromatography). Treatment of (4) with 2-methoxypropene in the presence of a catalytic<sup>6</sup> amount of trifluoroacetic acid afforded the methoxyisopropyl ether (5) (100%) as an oil,  $[\alpha]_{\rm p}$  -46° (c 0.9, CHCl<sub>3</sub>). Reaction with 2-lithio-1,3-dithian<sup>7</sup> in dry tetrahydrofuran-hexamethylphosphoric triamide (THF-HMPT) transformed (5) into the dithioacetal alcohol (6) (93 %) as a thick syrup,  $[\alpha]_D - 8^\circ$  (c 0.93, CHCl<sub>3</sub>). Methylsulphonation of (6) and work-up under slightly acidic conditions gave (7) (90%), m.p. 138 °C (decomp.),  $[\alpha]_D + 3^\circ$  $(c 1, CHCl_3)$ , which was reduced with sodium borohydride in HMPT to the alcohol (8) (80 %), m.p. 88 °C,  $[\alpha]_{\rm D} - 7^{\circ}$  (c 1, CHCl<sub>3</sub>). Trifluoromethylsulphonation gave the trifluoromethanesulphonate (9) (97%), m.p. 75 °C,  $[\alpha]_{\rm p} - 9^{\circ}$  (c 9.5, CHCl<sub>3</sub>) which on exposure to 1,8-diazabicyclo[5.4.0]undec-7ene (DBU) in dry ether solution at room temperature led to the enol ether (10) (100%), m.p. 55 °C,  $[\alpha]_{\rm D} - 4^{\circ}$  (c 16.4, CHCl<sub>a</sub>).

Hydrolysis of (10) with 80% aqueous formic acid in THF (1:1) at room temperature (15 min) generated in 65% yield the 2-hydroxy-4-keto-aldehyde (2), or its hydrated equivalent,<sup>8</sup> characterized<sup>†</sup> only by mass spectrometry ( $M^{++}$  248). In view

<sup>&</sup>lt;sup>†</sup> Satisfactory <sup>1</sup>H n.m.r. and mass spectral data were obtained for all other compounds reported here by using purified and chromatographically homogeneous samples.



Scheme 1. Reagents and conditions: i, DEAD-TPP, PhH, reflux 2.5 h; ii,  $CH_2=C(OMe)Me$ ,  $CHCl_3$ ,  $CF_3CO_2H$  (trace); iii, 1,3-dithian, Bu<sup>n</sup>Li (1.2 equiv.), THF-HMPT (4:1), -78 to 0 °C; iv, MeSO\_2Cl, NEt\_3,  $CH_2Cl_2$ , 0 °C; v, MeOH,  $CHCl_3$ ,  $CF_3CO_2H$ ; vi, NaBH<sub>4</sub>, HMPT, 85 °C, overnight; vii, ( $CF_3SO_2$ )<sub>2</sub>O, pyridine,  $CH_2Cl_2$ , -10 °C; viii, DBU (1.1 equiv.), Et\_2O, room temp.

of its probable instability, compound (2) was cyclized, without purification, to the optically pure hydroxycyclopentenone dithioacetal (1) (35%),§ as an oil, by treatment with 0.1 M sodium hydroxide in ethanol,<sup>9</sup> under an inert atmosphere for 4 h.

The optical purity of (1),  $[\alpha]_D + 7^\circ$  (c 0.3, CHCl<sub>3</sub>) was determined by its transformation to the benzoate (1a) (with benzoyl chloride-pyridine),  $[\alpha]_D + 52^\circ$  (c 1.3, CHCl<sub>3</sub>) as well

§ No attempt was made to optimize the yield.

as to the (4S)-benzoyloxy-enantiomer (with DEAD-TPPbenzoic acid),<sup>10</sup>  $[\alpha]_D - 53^\circ$  (c 0.9, CHCl<sub>3</sub>) and measurements of their 400 MHz <sup>1</sup>H n.m.r. spectra using different concentrations of the chiral shift reagent tris-[3-(trifluoromethylhydroxymethylene)-(-)-camphorato]europium(III).

The chiral compound (1), which closely resembles a previously described<sup>11</sup> racemic synthetic intermediate, presents all the structural features required for its elaboration to prostaglandin  $E_2$ . Whereas the conversion of glucose into prostaglandin  $F_{2\alpha}$  has been previously achieved,<sup>12,13</sup> to our knowledge, the approach adopted here represents a second example<sup>8</sup> of the transformation of glucose to a functionalized cyclopentenone.

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