Synthesis of (*R*)-4-Hydroxy-2-(1,3-dithian-2-ylmethyl)-cyclopent-2-en-1-one, a Chiral Prostaglandin E_2 Synthon, from D-Glucose

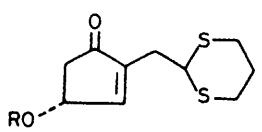
Saïd Achab and Bhupesh C. Das*

Institut de Chimie des Substances Naturelles, C.N.R.S., 91190 Gif-sur-Yvette, France

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_2 and its analogues, is described.

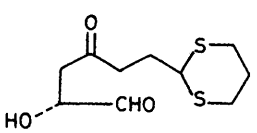
Several total syntheses of biologically active cyclopentanoid natural products, notably in the prostaglandin series,[1] rest on the conjugate addition of organometallic derivatives to 2-substituted 4-hydroxycyclopent-2-en-1-ones. Despite the existence of numerous synthetic approaches to substituted cyclopentenones,[1,2] 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.[3,4] We report here the synthesis of an optically active functionalized cyclopentenone, (*R*)-4-hydroxy-2-(1,3-dithian-2-ylmethyl)cyclopent-2-en-1-one (**1**), a potential chiral synthon for prostaglandin E_2 and its analogues, from D-glucose.

The synthesis of (**1**) rested upon achieving the intramolecular aldolisation–dehydration of the acyclic 4-keto-aldehyde (**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-α-D-glucofuranose (**3**) as outlined in Scheme 1.



(**1**) R = H

(**1a**) R = COPh

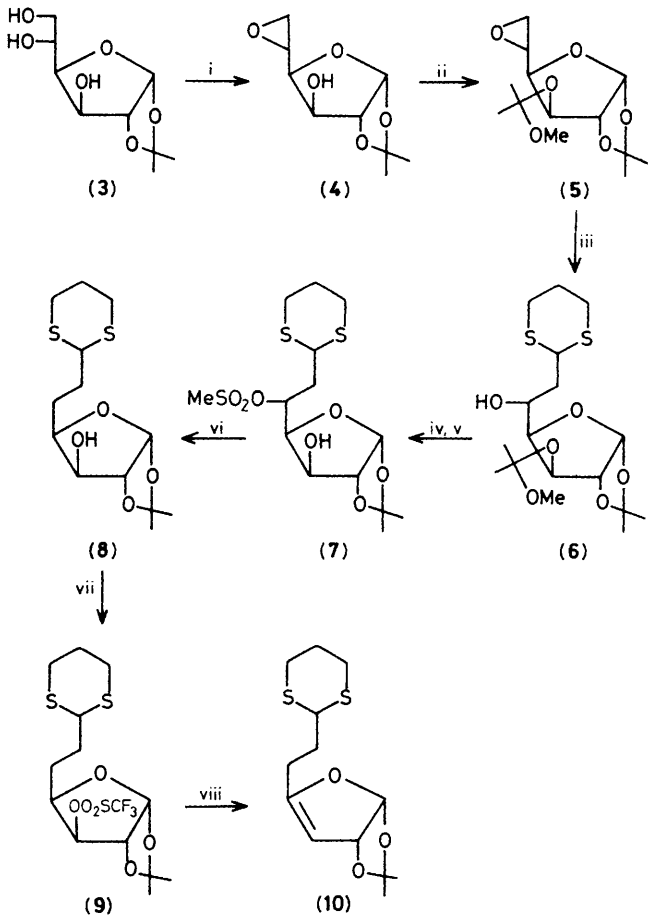


(**2**)

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

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,[8] characterized† only by mass spectrometry ($M^{\cdot+}$ 248). In view

† Satisfactory ^1H 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^{n}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, $NaBH_4$, HMPT, 85 °C, overnight; vii, $(CF_3SO_2)_2O$, 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,[9] under an inert atmosphere for 4 h.

The optical purity of (**1**), $[\alpha]_D$ + 7° (*c* 0.3, $CHCl_3$) was determined by its transformation to the benzoate (**1a**) (with benzoyl chloride–pyridine), $[\alpha]_D$ + 52° (*c* 1.3, $CHCl_3$) as well as to the (4*S*)-benzoyloxy-enantiomer (with DEAD–TPP–benzoic acid),[10] $[\alpha]_D$ −53° (*c* 0.9, $CHCl_3$) and measurements of their 400 MHz ^{1}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[11] 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,[12,13] to our knowledge, the approach adopted here represents a second example[8] of the transformation of glucose to a functionalized cyclopentenone.

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§ No attempt was made to optimize the yield.

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