Synthesis of Chiral Prostanoid Intermediates from Phenol

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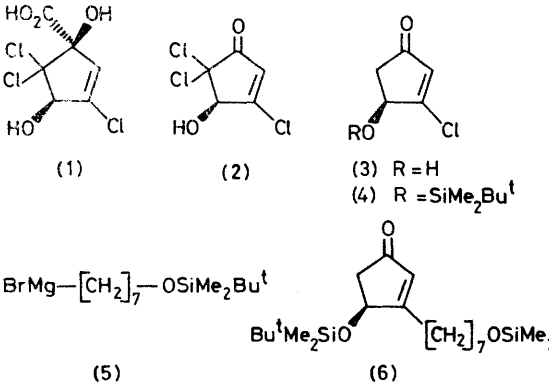
Summary The 2-substituted derivatives of (4*R*)-4-hydroxycyclopent-2-enone (**11**) and (**12**), important intermediates in prostaglandin synthesis, are prepared from (4*S*)-3-chloro-4-(dimethyl-t-butylsilyloxy)cyclopent-2-enone (**4**) which is available in five steps from phenol.

WE report an efficient general synthesis from phenol of chiral 2-substituted 4-hydroxycyclopent-2-enones, *e.g.* (**12**), which are important intermediates in prostanoid synthesis[1] since their ethers undergo stereospecific conjugate addition reactions to yield 2,3-disubstituted 4-hydroxycyclopentanones possessing the natural prostaglandin configuration. For example, (−)-PGE_1 (**13**) is produced from the (4*R*)-tetrahydropyranyl ether (**11**) either by reaction with the appropriate chiral *trans*-vinyl cuprate,[2] or by kinetic resolution of a racemic *cis*-divinyl cuprate[3] followed by correction of side chain stereochemistry.[4] The (4*R*)-4-hydroxycyclopent-2-enone (**12**) has been prepared by microbiological reduction of 2-(6-methoxycarbonylhexyl)-cyclopentane-1,3,4-trione,[2] synthesis from D-glyceraldehyde,[3] or resolution of its diastereoisomeric oximes.[5] Microbiological hydroxylation of 2-(6-carboxyhexyl)cyclopent-2-enone gave the (4*R*)-hydroxy acid corresponding to the ester (**12**) in only 34% enantiomeric excess.[6] The early incorporation of the potential 2-alkyl substituent in the existing routes to chiral intermediates of the type (**12**) impedes their use for the production of prostanoids modified in the α-chain.

The present route makes a variety of 2-substituted (4*R*)-4-hydroxycyclopent-2-enones readily available from a common chiral precursor. This key synthon, (4*S*)-3-chloro-4-(dimethyl-t-butylsilyloxy)cyclopent-2-enone (**4**), is prepared from phenol in five steps, chirality being introduced at the second step. Easy replacement of the vinylic chlorine in (**4**) by functionalised alkyl chains leads, after stereospecific transposition of the oxygen functions, to the required prostanoid intermediates. In conjunction with previous work,[2–4] this constitutes a new route to prostanoids in which *both* side chains are attached to a chiral cyclopentenone by conjugate addition reactions. The route is illustrated here by the synthesis of the established precursors (**11**) and (**12**) of (−)-PGE_1 (**13**).

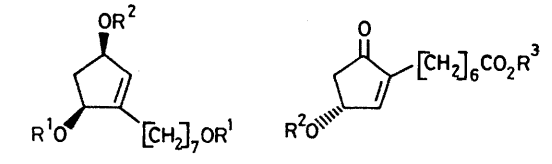
Ring contraction of phenol or 2,4,6-trichlorophenol with alkaline hypochlorite[7] yields the acid (**1**) in 50—60% yield as a racemate with the relative configuration shown.[8] Crystallisation of the diastereoisomeric brucine salts from methanol gave the desired (1*R*,4*R*)-enantiomer (**1**) as its (−)-brucine salt, m.p. 143—146 °C, $[\alpha]_D^{25}$ − 120° (*c* 0·247, $CHCl_3$), optically pure in 74% yield after one recrystallisation. Acidification gave the free (1*R*,4*R*)-acid (**1**), m.p. 188—190 °C, $[\alpha]_D^{22}$ − 207° (*c* 0·100, EtOH), $[\theta]_{219}^{25}$ − 75,500 (*c* 5·18 × 10^{-3}, EtOH). Oxidative decarboxylation with lead tetra-acetate[9] of the acid (**1**) afforded in 98% yield the (4*R*)-trichlorocyclopentenone (**2**), $[\theta]_{333}^{25}$ + 8410 (*c* 5·66 × 10^{-2}, EtOH). Partial dechlorination with chromous chloride (H_2O–acetone; 0 °C)† and protection of the hydroxy-function (Me_2Bu^tSiCl, hexamethylphosphoric triamide; 2 °C) in the resulting unstable (4*S*)-chlorocyclopentenone (**3**)‡ proceeded in 61% overall yield to give (4*S*)-3-chloro-4-(dimethyl-t-butylsilyloxy)cyclopent-2-enone (**4**) as a stable oil, $[\theta]_{333}^{25}$ + 6700 (*c* 9·14 × 10^{-2}, hexane), λ_{max}(hexane) 222 nm (ε 13,900), ν_{max}(film) 1730 cm^{-1} (CO), δ ($CDCl_3$) 6·22 (1H, d, *J* 1 Hz, 2-H), 4·84 (1H, ddd, *J* 6, 2·4, and 1 Hz, 4-H), 2·87 (1H, dd, *J* 18·3 and 6 Hz, 5α-H), and 2·43 (1H, dd, *J* 18·3 and 2·4 Hz, 5β-H). Significantly, the (4*R*)-enantiomer of this synthon (**4**) possesses the hydroxy-configuration corresponding to that of natural prostaglandins. Since it also is a useful prostanoid precursor,[10] the intrinsic loss of material normally involved in a resolution does not occur upon resolution of the racemic acid (**1**).



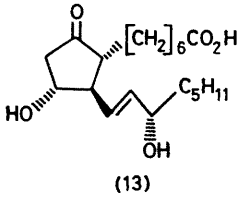
(1) (2) (3) R = H (4) R = $SiMe_2Bu^t$ (5) (6)

The synthon (**4**) underwent rapid conjugate addition–elimination with the Grignard reagent (**5**) in the presence of cuprous iodide (tetrahydrofuran; −10 °C; 10 min) to form the (4*S*)-cyclopentenone (**6**) in 89% yield, $[\theta]_{326}^{25}$ + 8540 (*c* 1·665 × 10^{-2}, hexane), ν_{max}(film) 1720 cm^{-1} (CO), δ($CDCl_3$) 5·90 (1H, dt, *J ca.* 1 and 1 Hz, 2-H), 4·76 (1H, m, 4-H), and 3·60 (2H, t, *J* 6 Hz, $CH_2OSiMe_2Bu^t$).

Stereospecific transposition of the ring oxygen functions in the (4*S*)-cyclopentenone (**6**) was initiated by reduction with lithium tri-s-butylborohydride (tetrahydrofuran; −78 °C) in 82% yield to the (1*R*,4*S*)-cyclopentenol (**7**), ν_{max}(film) 3600—3100 cm^{-1} (OH), δ($CDCl_3$) 5·54 (1H, m, 2-H), 4·52 (2H, m, 1-H and 4-H), and 2·68 (1H, dt, *J* 14 and 7 Hz, 5α-H). The stereohomogeneity of the product (**7**) was established from its ^{13}C n.m.r. spectrum, and the 1,4-*cis* relationship of its ring oxygen functions follows from analysis of the 5α-H resonance which is equally coupled to 1-H and 4-H.[11] Tetrahydropyranylation in 75% yield of



(7) R^1 = $SiMe_2Bu^t$, R^2 = H
(8) R^1 = $SiMe_2Bu^t$, R^2 = thp
(9) R^1 = H, R^2 = thp
(10) R^2 = thp, R^3 = H
(11) R^2 = thp, R^3 = Me
(12) R^2 = H, R^3 = Me



(13)

thp = tetrahydropyran-2-yl.

† We are indebted to Dr. R. M. Christie for preliminary work on this reaction.

‡ Identity established by t.l.c. comparison with the fully characterised racemate, and used without purification.

the newly formed hydroxy group of (**7**), followed by fluoride cleavage[12] of both silyl ethers (tetrahydrofuran, 0 °C) in the product (**8**) gave the (1*S*,4*R*)-cyclopentenol (**9**)§ as a 1 : 1 mixture of diastereoisomers in 93% yield, ν_{max}(film) 3700—2500 cm^{-1} (OH), $\delta(CDCl_3)$ 5·63 (1H, m, 3-H), 4·85—4·25 (3H, m, 1-H, 4-H, and –OCHO–), and 2·71 and 2·63 (each 0·5 H, dt, *J* 14 and 7 Hz, 5α-H in diastereoisomers). Treatment of (**9**) with Jones reagent (−20 °C; 3 h) completed the transposition of ring functionality and oxidised the side chain alcohol to the (4*R*)-keto-acid (**10**), which was methylated with diazomethane. The resulting (4*R*)-tetrahydropyranyl ether (**11**), obtained in 83% yield from the cyclopentenol (**9**), ν_{max}(film) 1735 (CO_2Me) and 1710 cm^{-1} (CO), $\delta(CDCl_3)$ 7·20 (1H, m, 3-H) and 3·66 (3H, s, CO_2Me), exhibited a negative Cotton effect at long wavelength, $[\theta]^{25}_{323}$ − 11,300 (*c* 4·47 × 10^{-2}, MeOH), thus confirming the reversal of configuration at C-4 relative to the (4*S*)-cyclopentenone (**6**).

Hydrolysis of the tetrahydropyranyl ether of (**11**) (HOAc, H_2O, tetrahydrofuran) removed the source of diastereoisomerism and gave (4*R*)-4-hydroxy-2-(6-methoxycarbonylhexyl)cyclopent-2-enone (**12**) in 88% yield, m.p. 57—59 °C (lit.,[3] m.p. 60—60·5 °C), ν_{max}(KBr) 3350 (OH), 1735 (CO_2Me), and 1710 cm^{-1} (CO), $\delta(CDCl_3)$ 7·12 (1H, dt, *J* 3 and 1·5 Hz, 3-H), 4·94 (1H, m, 4-H), 3·66 (3H, s, CO_2Me), 2·80 (1H, dd, *J* 18·5 and 6 Hz, 5β-H), and 2·28 (1H, dd, *J* 18·5 and 2 Hz, 5α-H), u.v. and ^{13}C n.m.r. data in agreement with published data.[2,3] Comparison of the c.d., $[\theta]^{25}_{320}$ − 9860 (*c* 4·14 × 10^{-2}, MeOH), of (**12**) with literature data ($[\theta]_{321}$ −9150,[3] and −9900[2]) confirms the optical integrity of the synthesis.

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§ I.U.P.A.C. Nomenclature requires a change of numbering in the cyclopentenol (**9**) compared to the cyclopentenol (**7**), the 1-position being that substituted by the free hydroxy-group in each case.

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