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CYCLOPENTANOIDS FROM PHENOL. PART III.[1]

SYNTHESIS OF CHIRAL 4-HYDROXYCYCLOPENT-2-ENONES

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Summary Chiral 4-hydroxycyclopent-2-enones (1 and 2), of which the (R)-enantiomers are important intermediates in prostanoid synthesis, are readily prepared in optically pure form from phenol via reduction of the corresponding 3-chloro-4-t-butyldimethylsilyloxy-cyclopent-2-enones (5 and 3).

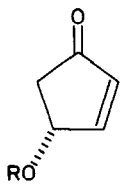
Derivatives of (R)-4-hydroxycyclopent-2-enone (1; R=H) are important intermediates in several efficient syntheses of prostanoids. Conjugate addition of the potential β-chain, followed by reaction of the resulting enolate with suitable electrophiles to introduce the eventual α-chain, leads to prostanoids in which the three substituents on the cyclopentanone ring have the same absolute configuration as in natural prostaglandins.[2] The enantiomeric (S)-4-hydroxycyclopent-2-enone (2; R=H) is a key chiral intermediate in a synthesis of the "eastern zone" of maytansine.[3]

(R)-4-Hydroxycyclopent-2-enone has been prepared previously in optically pure form as its acetate (1; R=Ac) only by chemical modification of the fungal metabolite terrein.[4] The same (R)-enantiomer (1; R=H) resulted in 85% optical purity by synthesis from the less common (2S,3S)- or (-)-enantiomer of tartaric acid,[5] and in up to 90% enantiomeric excess but low overall yield from combined microbiological and chemical transformation of 3,5-diacetoxycyclopent-1-ene.[6] The opposite (S)-4-hydroxycyclopent-2-enone (2; R=H) resulted in 86% optical purity from (2R,3R)- or (+)-tartaric acid,[5] and in low enantiomeric excess and overall yield from 3,5-diacetoxycyclopent-1-ene.[6]

We describe here convenient, efficient preparations of the optically pure (R)- and (S)-enantiomers (1) and (2) respectively of 4-hydroxycyclopent-2-enone, in both free (R=H) and derivatised (R=SiBu^{t}Me$_2$ or Ac) forms.

The conversion of phenol or 2,4,6-trichlorophenol in five steps into optically pure (S)-3-chloro-4-t-butyldimethylsilyloxycyclopent-2-enone (3), itself a versatile prostanoid synthon,[7] has recently been described.[7] In this conversion, chirality is introduced in the second step by resolution with brucine of the racemic ring contraction product (1R*,4R*)-3,5,5-trichloro-1,4-dihydroxycyclopent-2-ene-1-carboxylic acid.[1,8] The (1R,4R)-enantiomer (4) of this acid is then oxidatively decarboxylated, partially

dechlorinated, and derivatised to afford the (S)-cyclopentenone (3). The enantiomeric (R)-3-chloro-4-t-butyldimethylsilyloxycyclopent-2-enone (5) {an oil, λ_{max} (hexane) 221 nm (ε 14,100); $[\theta]_{225}^{25}$ + 83,800 (c 1.58 x 10^{-3}, hexane), $[\theta]_{333}^{25}$ - 6,770 (c 3.15 x 10^{-2}, hexane); i.r. and ^{1}H n.m.r. as reported[7] for the (S)-enantiomer (3)} is available optically pure in similar fashion from the opposite (1S,4S)-enantiomer (6) of the ring-contracted acid.[9] This (1S,4S)-acid (6) {m.p. 188-189°; $[\alpha]_D^{25}$ + 207° (c 0.11, EtOH); $[\theta]_{219}^{25}$ + 76,300 (c 4.93 x 10^{-3}, EtOH)} is derived from the more soluble brucine salt {m.p. 149-152°; $[\alpha]_D^{25}$ + 93° (c 0.265, $CHCl_3$)} which is obtained pure in 74% yield from the resolution by fractional recrystallisation from ethanol.



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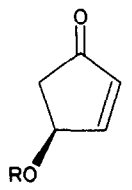

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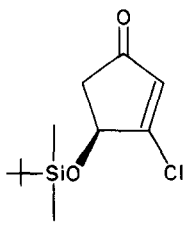

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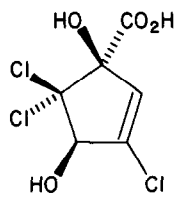

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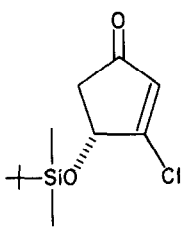

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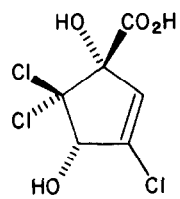

(6)

Both zinc-copper (in THF-H_2O)[10] and zinc-silver (in MeOH)[11] couples reduces 3-chloro-cyclohex-2-enones efficiently to cyclohex-2-enones. The reduction of racemic 3-chloro-4-t-butyldimethylsilyloxycyclopent-2-enone (3 + 5) with a zinc-copper couple in aqueous tetrahydrofuran was very slow (< 20% reduction in 24 h). However, the use of methanol as solvent (2 ml per 0.5 mmol substrate) and a large excess of couple (600 mg per 0.5 mmol substrate; 5 min, room temperature) gave an 82% yield of racemic 4-t-butyldimethylsilyl-oxycyclopent-2-enone (1 + 2; R=SiBu^{t}Me$_2$) {m.p. 25-27°; ^{1}H n.m.r. identical with enantiomer (1; R=SiBu^{t}Me$_2$)}. The product was purified by preparative layer chromatography on silica gel (CH_2Cl_2-MeOH, 20:1) and crystallisation from pentane (-78°). Similarly, reduction of the racemate (3 + 5) (0.5 mmol) in methanol (2 ml) with zinc-silver couple (700 mg; 5-10 min, room temperature) yielded the same product (1 + 2; R=SiBu^{t}Me$_2$) in 94% yield.

Reduction of chiral (R)-3-chloro-4-t-butyldimethylsilyloxycyclopent-2-enone (5) with zinc-silver couple gave (R)-4-t-butyldimethylsilyloxycyclopent-2-enone (1; R=SiBu^{t}Me$_2$) (94%) {needles, m.p. 30-31°, from pentane at -78°; $[\alpha]_D^{22}$ + 67° (c 1.17 x 10^{-1}, MeOH); $[\theta]_{217}^{25}$ + 77,800 (c 1.17 x 10^{-3}, MeOH), $[\theta]_{317}^{25}$ - 10,700 (c 1.17 x 10^{-2}, MeOH); ^{1}H n.m.r. ($CDCl_3$) δ 0.12 (6H, s, SiMe), 0.92 (9H, s, Bu^t), 2.23 (1H, dd, J 18.2 and 2.2 Hz, H-5α), 2.71 (1H, dd, J 18.2 and 5.9 Hz, H-5β), 4.98 (1H, dddd, J 5.9, 2.2, 2.2, and 1.3 Hz, H-4), 6.16 (1H, dd, J 5.6 and 1.3 Hz, H-2), 7.43 (1H, dd, J 5.6 and 2.2 Hz, H-3)}.

Hydrolysis (HOAc-H_2O-THF, 3:1:1; 25°, 48 h) of the silyl ether (1; R=SiBu^{t}Me$_2$) afforded (R)-4-hydroxycyclopent-2-enone (1; R=H) (91%) {an oil; $[\alpha]_D^{22}$ + 96° (c 1.18 x 10^{-1}, MeOH), $[\alpha]_D^{22}$ + 81° (c 1.035 x 10^{-1}, $CHCl_3$); $[\theta]_{215}^{25}$ + 68,000 (c 1.12 x 10^{-3}, MeOH), $[\theta]_{317}^{25}$ - 7990 (c 1.12 x 10^{-2}, MeOH); ^{1}H n.m.r. ($CDCl_3$) δ 2.25 (1H, dd, J 18.4 and 2.3 Hz, H-5α), 2.77 (1H, dd, J 18.4 and 5.9 Hz, H-5β), 3.5 (1H, bs, OH), 4.98 (1H, m, H-4), 6.20 (1H, dd, J 5.6 and 1.2 Hz, H-2), 7.59 (1H, dd, J 5.6 and 2.3 Hz, H-3), in agreement with literature spectra[5,6]}. Ogura et al[5] predicted $[\alpha]_D$ ca. + 81° ($CHCl_3$) for the optically pure alcohol (1; R=H). Acetylation (Ac_2O-NaOAc, THF, 65°, 16 h) of this (R)-4-hydroxycyclopent-2-enone (1; R=H) gave (R)-4-acetoxycyclopent-2-enone (1; R=Ac) (86%) {b.p. 45°/0.05 mm (bath temp.); $[\alpha]_D^{22}$ + 97° (c 1.03 x 10^{-1}, MeOH); $[\theta]_{208}^{25}$ + 80,000 (c 1.03 x 10^{-3}, MeOH), $[\theta]_{320}^{25}$ - 5965 (c 1.03 x 10^{-2}, MeOH); $[\phi]_{221}^{25}$ + 42,000° (c 1.03 x 10^{-3}, MeOH); $[\phi]_{348}^{25}$ - 1900° (c 1.03 x 10^{-2}, MeOH); ^{1}H n.m.r. as reported[4]}. The (R)-acetate (1; R=Ac) derived from terrein showed $[\alpha]_D^{20}$ + 95° (c 0.061, MeOH), $[\phi]_{220}^{27}$ + 40,000° and $[\phi]_{350}^{27}$ - 1900° (c 0.062, MeOH).[4]

The preparation of these (R)-4-substituted cyclopentenones (1; R=SiBu^{t}Me$_2$), (1; R=H), and (1; R=Ac) by Tanaka et al[6] were considered to contain 90% excess of (R)-enantiomer, but showed $[\alpha]_D^{20}$ (MeOH) values of + 53°, + 59°, and + 82° respectively, which may indicate lower optical or chemical purities.

Reduction of the enantiomeric (S)-3-chloro-4-t-butyldimethylsilyloxycyclopent-2-enone (3) with zinc-copper couple in methanol gave (S)-4-t-butyldimethylsilyloxycyclopent-2-enone (2; R=SiBu^{t}Me$_2$) (91%) {needles, m.p. 29-31°, from pentane at -78°; $[\alpha]_D^{22}$ - 66° (c 5.01 x 10^{-2}, MeOH); $[\theta]_{217}^{25}$ - 80,600 (c 1.00 x 10^{-3}, MeOH), $[\theta]_{317}^{25}$ + 10,100 (c 5.01 x 10^{-2}, MeOH); ^{1}H n.m.r. identical with the enantiomer (1; R=SiBu^{t}Me$_2$)}.

The present conversion of (1S,4S)-3,5,5-trichloro-1,4-dihydroxycyclopent-2-ene-1-carboxylic acid (6) into (R)-4-hydroxycyclopent-2-enone (1; R=H) and its t-butyldimethylsilyl ether (1; R=SiBu^{t}Me$_2$) complements our previous conversion[7] of the (1R,4R)-acid (4) into (S)-3-chloro-4-t-butyldimethylsilyloxycyclopent-2-enone (3). Both enantiomers of the acid resulting from alkaline chlorination of phenol now provide useful prostanoid intermediates.

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