4-Hydroxy-2-hydroxymethylcyclopent-2-en-1-one: a Versatile Intermediate for the Synthesis of Cyclopentanoid Natural Products

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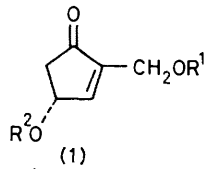
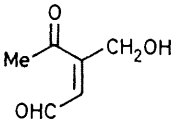
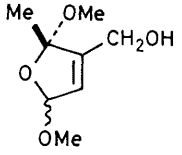
Summary The title compound has been prepared as the racemate, by way of 3-hydroxymethyl-2-methylfuran, and as the (4*R*)-isomer, starting with (−)-quinic acid

CYCLOPENTENONES of type (**1**) are expected to be versatile intermediates in the synthesis of bioactive cyclopentanoid natural products, such as prostaglandins,[1] pentenomycins,[2] methylenomycins,[3] and xanthocidin[4] We now describe syntheses of the parent compound (**1a**) in racemic and optically active form


(1)
a; $R^1 = R^2 = H$


(2)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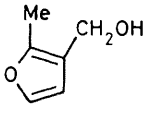
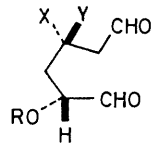
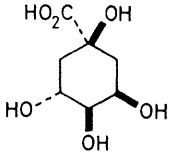
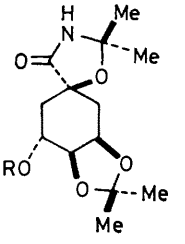

(4)

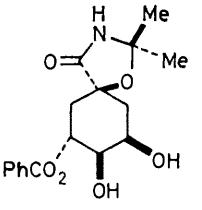

(5)

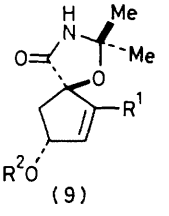

(6)

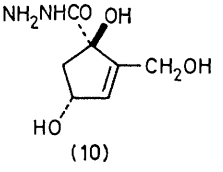
Our retrosynthetic analysis for the construction of the racemate of (**1a**) relied upon achieving the intramolecular aldol reaction of the species (**2**), this approach defined the racemate of the dihydrofuran (**3**) as a possible precursor Treatment of the readily prepared furan (**4**)[5] in methanol–ether with bromine followed by triethylamine, according to the procedure of Lee,[6] gave the racemate of the dihydrofuran (**3**)† (80%) as a 1 : 1 mixture of diastereoisomers The transformation of the mixture (**3**) into the racemate of the cyclopentenone (**1a**) was effected, by the method of Floyd,[7] in refluxing aqueous dioxan buffered at pH 6 2, following silica gel chromatography, the racemate of (**1a**)† was isolated (50%), m p 57—59 °C

The synthesis of optically active cyclopentenone (**1a**) rested upon effecting the intramolecular aldolisation and dehydration of a species of type (**5**, X,Y = masked CO group) Whilst there was ample precedent for such cyclisations, it was vital in the present context that no epimerisation of the chiral centre, destined to become position 4 of the product (**1a**), should occur ‡ (−)-Quinic acid (**6**) was selected as the chiral starting material from which to generate a species of type (**5**, X,Y = masked CO group)


(7)
a, R = H
b, R = PhCO


(8)


(9)
a; R^1 = CHO , R^2 = PhCO
b; R^1 = CH_2OH , R^2 = H


(10)

(−)-Quinic acid (**6**) was converted into the di-isopropylidene derivative (**7a**), m p 126—128 °C (lit[8] 122 °C), $[\alpha]_D$ −27° (EtOH) {lit[8] −27° (EtOH)}, by the method of Fischer[8] Benzoylation (PhCOCl, pyridine) of compound (**7a**) afforded the benzoate (**7b**)† (80%), m p 143—145 °C, $[\alpha]_D$ −35° (EtOH), which was transformed into the diol (**8**)† (81%), m p 164—167 °C, $[\alpha]_D$ −19° (EtOH), when heated in aqueous acetic acid Oxidation of the diol (**8**) with sodium periodate in aqueous tetrahydrofuran and evaporation gave a residue which was dried by repeated evaporation from benzene, treatment of the residue in

† This compound was identified by its spectral properties its composition was confirmed by elemental analysis and/or mass spectroscopy

‡ Trost and his co-workers have shown that no epimerisation occurs in the cyclisation of (**5** X = CO_2Me Y = H R = *p*-PhC_6H_4CO) to the corresponding cyclopentene carbaldehyde (B M Trost, J M Timko and J L Stanton *J Chem Soc , Chem Commun* , 1978, 436)

benzene with pyrrolidinium acetate at 60 °C gave the cyclopentene carbaldehyde (**9a**)† (60% after SiO_2 chromatography), m.p. 212 °C, $[\alpha]_D$ +87° (EtOH). Sequential reaction of the compound (**9a**) with sodium borohydride and sodium methoxide afforded the diol (**9b**)† (80% after SiO_2 chromatography), m.p. 157—158 °C, $[\alpha]_D$ −80° (EtOH).

The conversion of the oxazolidinone (**9b**) into the hydrazide (**10**)† (75% after SiO_2 chromatography), $[\alpha]_D$ −42° (EtOH), was effected in refluxing hydrazine hydrate. Treatment of the hydrazide (**10**) with nitrous acid at 0 °C followed by heating of the mixture at 60 °C gave the syrupy cyclopentenone (**1a**)† (50% after silica gel chromatography), $[\alpha]_D$ +50° (EtOH).

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[1] J. S. Bindra and R. Bindra, 'Prostaglandin Synthesis,' Academic Press, London, 1979.
[2] K. Umino, T. Furumai, N. Matsuzawa, Y. Awataguchi, Y. Ito, and T. Okuda, *J. Antibiot.*, 1973, **26**, 506; K. Hatano, T. Hasegawa, M. Izawa, M. Asai, and H. Kwasaki, *Japan, Kokai*, **75**, 70 597 (June 1975), *Chem. Abstr.*, 1976, **84**, 3287.
[3] T. Haneishi, N. Kitahara, V. Takiguchi, M. Arai, and S. Sugawara, *J. Antibiot.*, 1974, **27**, 386.
[4] K. Asahi, J. Nagatsu, and S. Suzuki, *J. Antibiot.*, 1966, **19**, 195; K. Asahi and S. Suzuki, *Agric. Biol. Chem.*, 1970, **34**, 325.
[5] H. E. Winberg, F. S. Fawcett, N. E. Mochel, and C. W. Theobald, *J. Am. Chem. Soc.*, 1960, **82**, 1428.
[6] T. Lee, *Tetrahedron Lett.*, 1979, 2297.
[7] M. B. Floyd, *J. Org. Chem.*, 1978, **43**, 1641.
[8] H. O. L. Fischer and G. Dangschat, *Ber.*, 1932, **65**, 1009.