Convergent, Stereocontrolled Routes to Hydroxylated Tricyclic Systems: A New Annulation of 2-Cyclohexen-1-one

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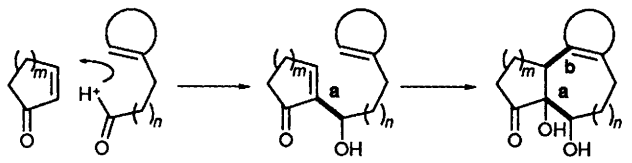
Tricyclic keto diols have been synthesised by a new, three-step annulation procedure in which hydroxyenones, prepared by the coupling of 2-cyclohexen-1-one with aldehydes, are diastereoselectively epoxidised and the *syn*-epoxides cyclised with tin(IV) chloride.

The stereocontrolled construction of polycarbocyclic systems has attracted immense and persistent interest,[1] chiefly owing to the vast array of differing classes of natural products.[2] In this Communication we report a new and versatile approach (Scheme 1) to the synthesis of tricyclic systems. The strategy, based upon annulations of cycloalkenones, is notable for being convergent, stereoselective, achievable under mild conditions, and for the introduction of hydroxy groups, often crucial to the conferment of biological activity.[3] The overall annulation (Scheme 1) is of an uncommon type[4] in which

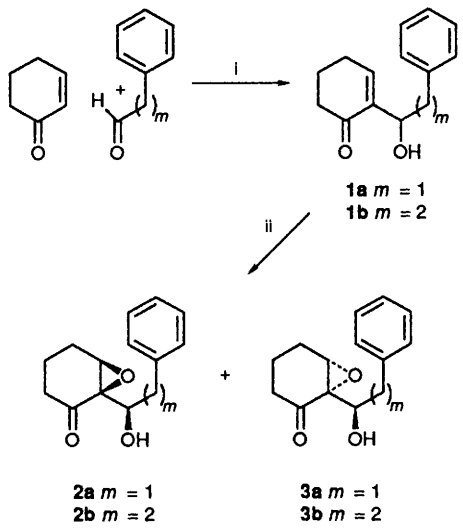


Scheme 1

carbon–carbon bond formation at C_α of an α,β-unsaturated carbonyl compound occurs prior to carbon–carbon bond formation at the β-position.

A variety of nucleophilic termini residing on the aldehydic fragment was envisaged; the modest π-nucleophile, an unactivated benzene ring, was initially selected in order to provide an effective test of the cyclisation step, and so that a comparison could be made with known epoxy–arene cyclisations.[5] Application of the new method to the ubiquitous perhydrophenanthrene nucleus was demonstrated in the three-step synthesis of keto diol **4** (Scheme 2). Coupling† of phenylacetaldehyde (1.5 equiv.) with 2-cyclohexen-1-one (1 equiv.) was effected with Et_2AlI‡ (1.2 equiv., 1 mol dm^{-3} in toluene) at −78 °C to give hydroxyenone **1a**,§ m.p. 59–62 °C in 58% yield. Treatment of **1a** with H_2O_2 (1.05 equiv., 35%) in methanolic NaOH (1.5 equiv.; 0.2 mol dm^{-3}) at 0 °C afforded quantitatively a 5 : 2 mixture of *syn* : *anti* epoxides **2a** and **3a**, respectively. Chromatography (silica gel; $CHCl_3$ eluant) afforded **2a** as an oil (69%) and **3a**,¶ m.p. 94–96 °C in 27% yield. Treatment of epoxide **2a** with $SnCl_4$ (5 mol equiv.; 20 °C, 24 h) afforded keto diol **4**, m.p. 160–162 °C, in 73% yield.

The synthetic challenge afforded by natural products incorporating a cyclohexane ring fused to a cycloheptane ring could be effectively met through a direct and efficient means of constructing that bicyclic substructure. In a relatively stringent test of the annulation methodology, keto diol **5** was selected as an appropriate target (Scheme 2). Coupling† of dihydrocinnamaldehyde (1.9 equiv.) with 2-cyclohexen-1-one

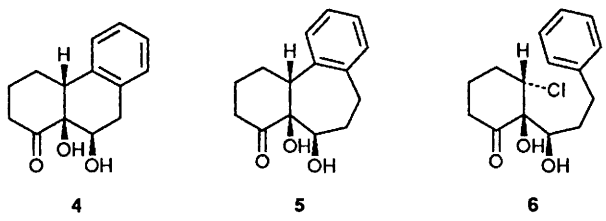


1a *m* = 1
1b *m* = 2

2a *m* = 1
2b *m* = 2

3a *m* = 1
3b *m* = 2

Scheme 2 *Reagents*: i, Et_2AlI; ii, H_2O_2, NaOH



4 **5** **6**

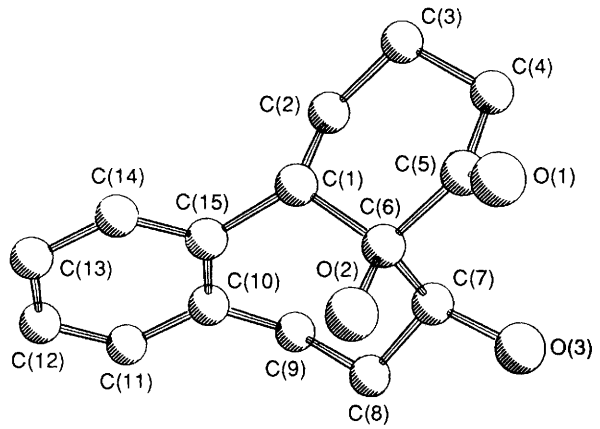


Fig. 1 Crystal structure of **5**

(1 equiv.) was effected with Et_2AlI‡ (1.25 equiv.; 1 mol dm^{-3} in toluene) at −15 °C to give hydroxyenone **1b**,§ as an oil in 79% yield. Epoxidation of **1b** with H_2O_2 (1.05 equiv., 35%) in methanolic NaOH (2 equiv.; 0.27 mol dm^{-3}) afforded in 97% yield an 11 : 2 mixture of epoxides **2b** and **3b** respectively, which were separated by chromatography (silica gel; $CHCl_3$ eluant) to give **2b**, m.p. 42–50 °C, in 61% yield and **3b** as an oil in 10% yield. Treatment of **2b** with $SnCl_4$ (5 mol equiv.; 20 °C, 24 h) afforded, after chromatography on silica gel, the keto diol **5**,‖ m.p. 183–184 °C, in 33% yield and the chlorinated keto diol **6**, m.p. 103–105 °C, in 46% yield. The keto diol **6** was converted into the epoxide **2b** in 87% yield by aqueous NaOH

† In the preparation of **1a**, phenylacetaldehyde (in $CHCl_3$) and Et_2AlI (1 mol dm^{-3} in toluene) were added at the same rate from separate syringes over 40 min to a solution of 2-cyclohexen-1-one in $CHCl_3$ kept at −78 °C. After a further 30 min at −78 °C, the solution was diluted with diethyl ether, and 1 mol dm^{-3} HCl then added to pH 4. Extraction with diethyl ether and column chromatography (silica gel; eluant diethyl ether: 40–60 °C petroleum ether; 1 : 1) afforded **1a**. In the preparation of **1b**, the solution of Et_2AlI was added at −15 °C to a mixture of the carbonyl compounds dissolved in $CHCl_3$. After 30 min at −15 °C the mixture was worked up as for **1a**, prior to column chromatography (silica gel; eluant $CHCl_3$: EtOAc, 10 : 1).

‡ Et_2AlI has been shown to couple 2-cyclohexen-1-one with a few aliphatic aldehydes: I. Kuwajima, T. Tanaka and K. Assumi, *Chem. Lett.*, 1979, 779.

§ All new compounds reported in this Communication have been fully characterised by elemental, ^1H NMR, and ^{13}C NMR analyses. All configurations depicted refer to racemic materials.

¶ *Crystal data* for **3a**: $C_{14}H_{16}O_3$, M = 232.28, monoclinic, $P2_1/c$, a = 8.964(13), b = 6.458(7), c = 21.66(7) Å, β = 93.92(20)°, U = 1251(4) $Å^3$, Z = 4, D_c = 1.233 g cm^{-3}, $F(000)$ = 495.9, μ(Mo-Kα) = 0.80 cm^{-1}. 957 Independent reflections with $|F| > 3\sigma|F|$ were used in the analysis. Final R = 0.056 (unit weights). Conformational disorder exists in part of the cyclohexyl ring.

Data for crystallographic analyses were measured $3.5 < 2\theta < 40°$ on a Nicolet R3 4-circle diffractometer using Mo-Kα radiation and ω-scans. Structures were solved by direct methods and refined by least-squares analysis using the SHELXTL package. Atomic coordinates, bond lengths and angles, and thermal parameters have been deposited at the Cambridge Crystallographic Data Centre. See Instructions for Authors in Issue No. 1.

‖ *Crystal data* for **5**: $C_{15}H_{18}O_3$, M = 246.30, monoclinic, $P2_1/c$, a = 12.760(11), b = 7.672(8), c = 13.199(8) Å, β = 91.93(6)°, U = 1291.3(19) $Å^3$, Z = 4, D_c = 1.267 g cm^{-3}, $F(000)$ = 527.9, μ(Mo-Kα) = 0.81 cm^{-1}. 975 Independent reflections with $|F| > 3\sigma|F|$ were used in the analysis. Final R = 0.048, weighted R_w = 0.052.

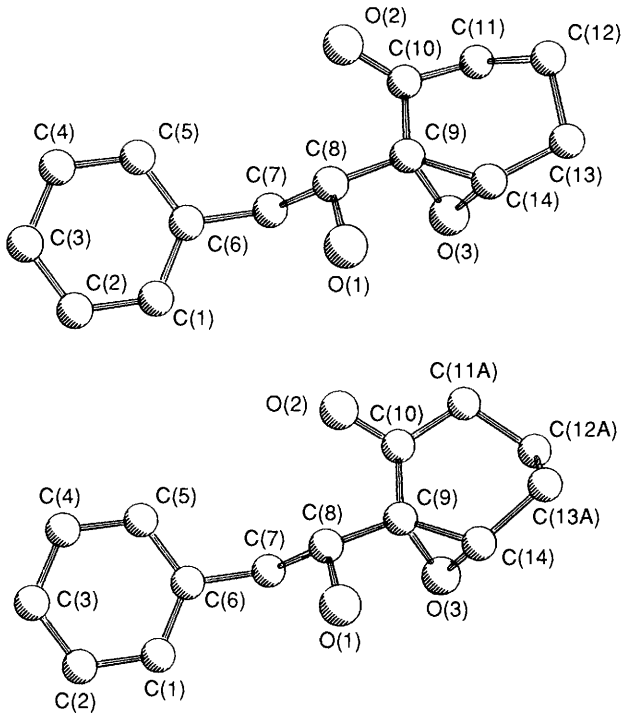


Fig. 2 Crystal structure of **3a**, showing the two conformations of the cyclohexyl ring

(0.075 mol dm^{-3}), thus allowing an improved yield of **5** to be obtained by recycling of the undesired **6**.

The high *syn*-diastereoselection observed during the alkaline epoxidations of hydroxyenones **1a** and **1b** has not been previously reported. Although *syn*-stereoselective epoxidations of cycloalkenols have been reported with peracids,[6,7] hydrogen bonding involving the hydrogen atom of the alcohol was postulated.[6,8] The t-butyldimethylsilyl derivative of **1b** (t-butyldimethylchlorosilane, 1.5 equiv., and imidazole, 3 equiv., at 25 °C for 18 h; yield 90%) afforded an 87% yield of a 5 : 2 mixture of *syn* : *anti* protected epoxides, implying that in the epoxidations of hydroxyenones of the type **1a** and **1b** effected with alkaline hydrogen peroxide the diastereoselection is not principally due to hydrogen bonding of the hydrogen atom of the hydroxy group of the hydroxyenone, and hence that a transition state model[6,8] proposed for the *syn*-epoxidation of cyclohexenes and unsaturated steroids bearing a free allylic hydroxy group is not sufficient to account for the origin of the diastereofacial selectivity reported in this Communication.

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4 The formation of a medium-sized ring by an annulation in which carbon–carbon bond formation at the β-position of an α,β-unsaturated cyclic ketone precedes carbon–carbon bond formation at the α-position is rare; the formation of a seven-membered ring by annulation of a cycloalkenone in which the above order of bond formation is reversed, as in Scheme 1, has apparently not been reported. For reviews of annulations see: G. H. Posner, *Chem. Rev.*, 1986, **86**, 831; M. Ramiah, *Synthesis*, 1984, 529; M. E. Jung, *Tetrahedron*, 1976, **32**, 3.
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