SYNTHESIS VIA ORGANOIRON COMPLEXES OF 9-(4-KETO-1-METHYLCYCLOHEX-2-ENYL)-8-KETO-DES-AB-ERGOST-22,23-ENE; A USEFUL CHIRAL INTERMEDIATE IN STEROID SYNTHESIS

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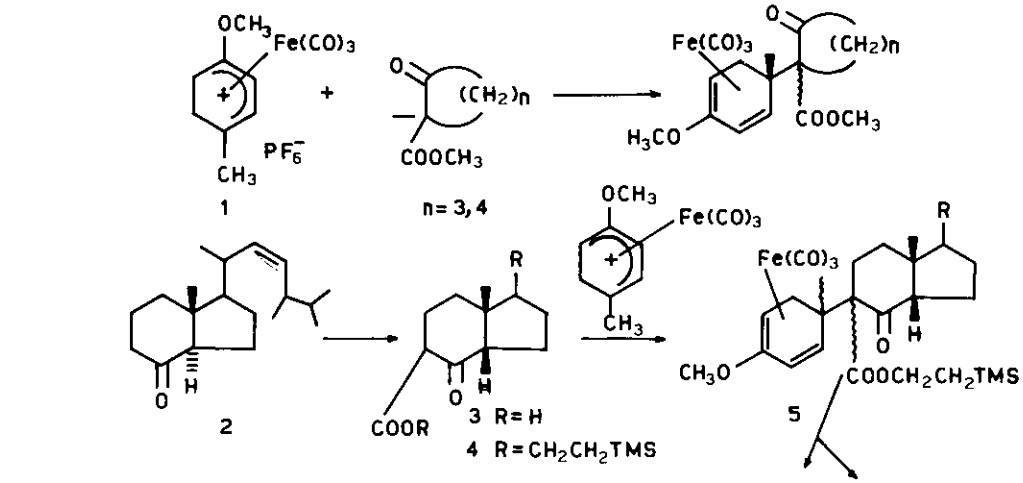
Abstract - *The synthesis via organoiron complexes of 9-(4-keto-1-methylcyclohex-2-enyl)-8-keto-des-AB-ergost-22,23-ene, a useful chiral intermediate in steroid synthesis, is described.*

It has been previously reported[1] that the reaction of the iron dienyl cation (1) (Scheme) with the anions of cyclic β-ketoesters affords the corresponding junction complexes suitable for the synthesis of polycyclic structures. In a further utilization of this method, we have now planned to prepare a chiral intermediate useful to be converted into optically active steroids.
With this aim, we have prepared by oxidation of vitamin D_2 the chiral ketone (2)[2] which, by carboxylation (magnesium methyl carbonate, 140°C, 5 h),[3] gives the ketoacid (3) (75% yield) having the more stable cis-hydrindane junction.
Compound (3) is converted into the silyl ester (4) (trimethylsilylethanol dicyclohexylcarbodiimide),[4] the anion of which (sodium hydride, tetrahydrofuran, r.t., 0.5 h) reacts with the cation (1) to give the junction complex (5) (70% yield) as a mixture of the four C_9 and C_{10} diastereoisomers.
After decarboxylation of (5) (tetrabutylammonium fluoride, tetrahydrofuran, r.t., 1 h),[4] elimination of the iron carbonyl group, and final hydrolysis of the thereby formed enol ether (trimethylamine N-oxide, benzene, 80°C, then oxalic acid, r.t., 2 h)[5] only two diketones,(6) (60% yield) and (7) (15% yield),[6] diastereoisomers at C_{10}, are obtained as well as some amount (10%) of a monoketone now under investigation. The formation of the two diastereoisomers (6) and (7) only from the elaboration of (5) is due to the equilibration occurring at the C_9 carbon during the decarboxylation stage. Furthermore, the β axial configuration resulting for the C_9 hydrogen from the X-Ray investigation of derivative (9)[7] means that the hydrindane mojety exists in (6) and (7) in the conformation depicted in Figure 2, whereas with the alternative conformation (Figure 3) the C_9 hydrogen should be observed in the α axial configuration. Moreover, the epimer (6), with the natural steroid configuration of the C_{19} angular methyl, is obtained in a predominant amount (4 : 1) with respect to

Scheme



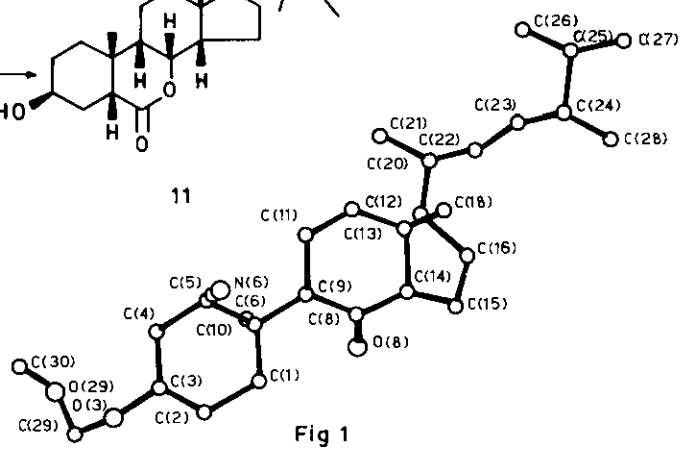


Fig 1

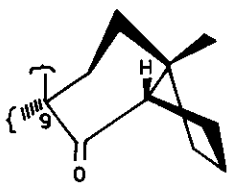


Fig 2

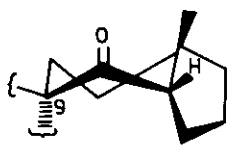


Fig 3

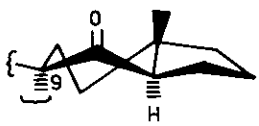


Fig 4

(7). This result evidences a remarkable asymmetric induction by the chiral β-ketoester (4) during the junction reaction with (1).

For a synthetic application we converted (6) into the steroid lactone (11) exhibiting the unusual all cis-configuration at the asymmetric centres of the steroid nucleus. Compound (6) was hydrocyanated (*diethylaluminium cyanide, toluene, r.t., 4 h*)[10] to give mainly the axial epimer (8) (75% yield).

By selective reduction at C_3 and protection of the OH group (sodium borohydride, methanol, 0°C, *then chlorodimethylether, diisopropylethylamine, methylene chloride, reflux, 18 h*)[11] compound (8) was converted into (9) (78% yield); the latter, by reduction with diisobutylaluminium hydride (tetrahydrofuran, -78°C, then r.t.) gave the 6-α-alcohol (10) only.

Compound (10) was hydrolysed first in acid conditions to remove the protective group at C_3 (tetrahydrofuran, water, 6M hydrochloric acid, 2 h, 60°C), then in basic conditions (40% potassium hydroxide, water, ethylene glycol, 80°C, 12 h) to give the steroid lactone (12) (41% yield) by acidification.[13] A similar junction reaction of the cation (1) with a β-ketoester having a trans--hydrandane junction causes necessarily the formation of a complex with the α-configuration of the C_9 hydrogen (Figure 4, work in progress). Therefore, we can consider this method as a general one for the stereoselective synthesis of optically active steroids as well as etherosteroids.

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6. Compound (6): low melting compound; $[\alpha]_D$ -7° ($CHCl_3$); Mass 384 (M^+); IR ($CHCl_3$) 1675, 1710 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ, *0.95 and 1.18 (6H, s, C_{18} and C_{19} protons)*, 5.20 (2H, *m, C_{22}-C_{23}* olefinic protons), 5.80 (1H, d, C_4 olefinic proton, J_{4-5} 10 Hz), 6.95 (1H, d, C_5 olefinic proton). Compound (7): low melting compound; $[\alpha]_D$ -10° ($CHCl_3$); Mass 384 (M^+); IR ($CHCl_3$) 1675, 1710 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ, *0.95 and 1.18* (6H, s, C_{18} and C_{19} protons), 5.20 (2H, m, C_{22}-C_{23} olefinic protons), 5.82 (1H, d, C_4 olefinic proton, J_{4-5} 10 Hz), 6.78 (1H, d, C_5 olefinic proton).
7. X-Ray analysis of compound (9). Suitable single crystal of (9) was grown at room temperature by slow evaporation from a hexane-ethyl acetate solution; mp 90-92°C. They are orthorhombic, space group $P2_12_12_1$ with a = 7.005(1), b = 19.986(3), c = 20.293(3) A°; V = 2841.1(7) A°^{3}, D_c = 1.07 gr cm^{-3}, Z = 4. The intensity data were collected on a Synthex $P2_1$ four-circle automatic diffractometer, using graphite monochromated Cu-K_α radiation: 1937 $I \geq 1\sigma$ (I) were considered observed and used in the refinement. The structure was solved by direct methods. The refinement by the block-diagonal least-squares method is in progress; the correct disagree-

ment index is R = 0.129. Calculations were performed with SIR[8] on the IBM 3033 computer of C.N.U.C.E. - Pisa, and with C.A.D.S.[9] package on the HP 1000 minicomputer of the C.N.R. Research Area of Rome.

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12. The only possible attack to the C_8 keton is from the β face, the α face resulting hindered as from the Dreiding Model examination.
13. Compound (12): uncrystallizable compound; $[\alpha]_D$ (as 3 β -acetate) -72° ($CHCl_3$); Mass 416 (M^+); IR ($CHCl_3$) 1720 cm^{-1}; ^{1}H-NMR δ , 1.0 and 1.05 (C_{18} and C_{19} protons), 4.22 (1H, m, C_3 proton), 4.60 (1H, m, $J_{1/2}$ = 7 Hz, C_8 proton), 5.20 (2H, m, C_{22}-C_{23} olefinic protons).
14. The conformation reported in Figure 4 is the only possible one for the 7-carbon ring of a trans-hydrindanic system.

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