

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 reported¹ 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 D₂ 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 C₉ and C₁₀ 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 C₁₀, 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 C₉ carbon during the decarboxylation stage. Furthermore, the β axial configuration resulting for the C₉ hydrogen from the X-Ray investigation of derivative (9)⁷ means that the hydrindane moiety exists in (6) and (7) in the conformation depicted in Figure 2, whereas with the alternative conformation (Figure 3) the C₉ hydrogen should be observed in the α axial configuration. Moreover, the epimer (6), with the natural steroid configuration of the C₁₉ angular methyl, is obtained in a predominant amount (4 : 1) with respect to

Scheme

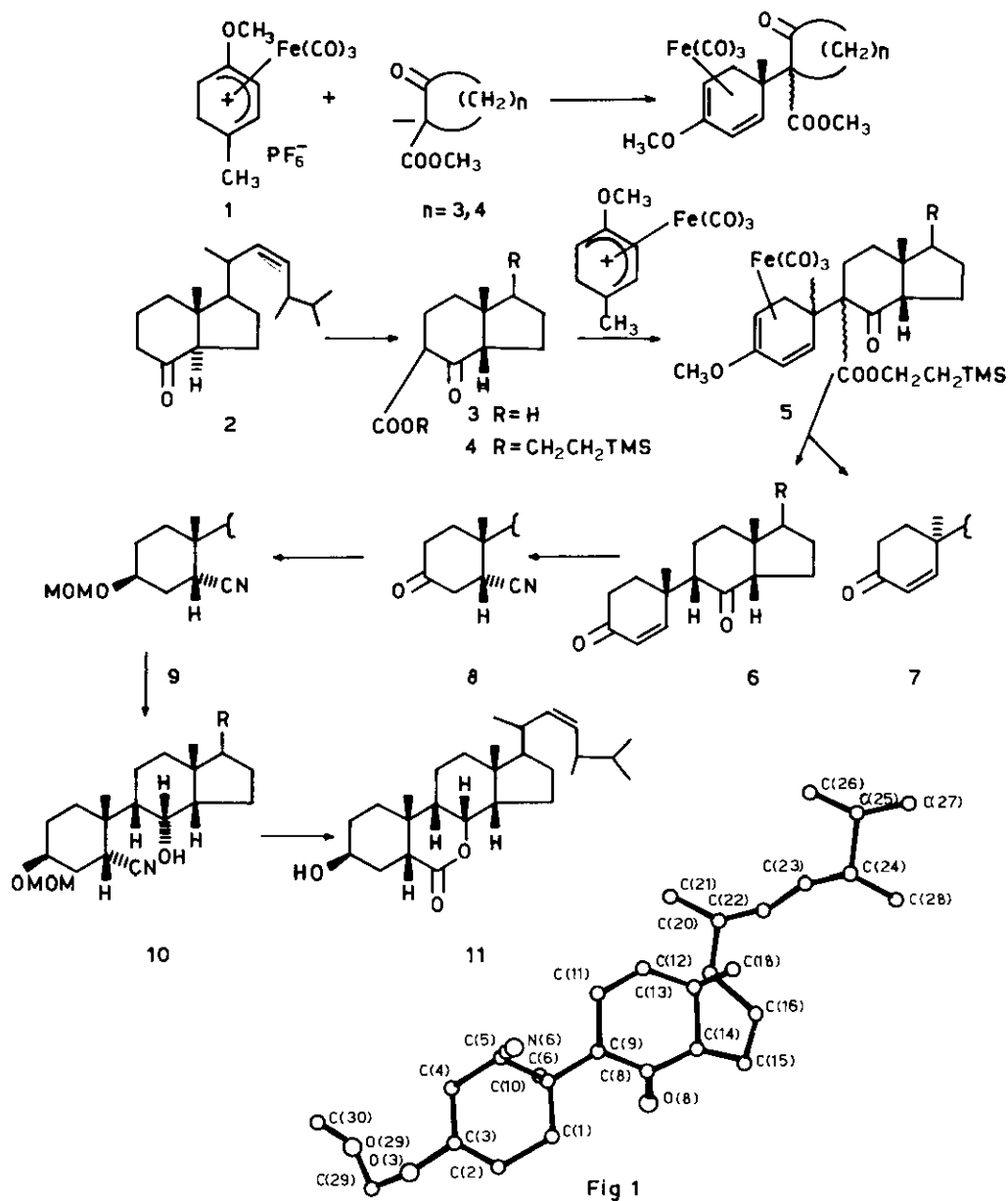
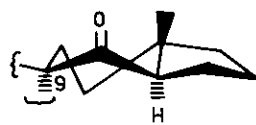
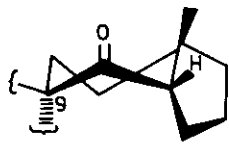
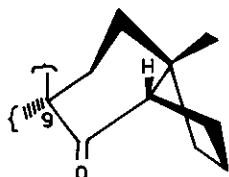


Fig 1



(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 C₃ 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 8- α -alcohol (10) only.

Compound (10) was hydrolysed first in acid conditions to remove the protective group at C₃ (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 C₉ 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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- Compound (6): low melting compound; $[\alpha]_D^{25} -7^\circ$ (CHCl₃); Mass 384 (M⁺); IR (CHCl₃) 1675, 1710 cm⁻¹; ¹H-NMR (CDCl₃) δ , 0.95 and 1.18 (6H, s, C₁₈ and C₁₉ protons), 5.20 (2H, m, C₂₂-C₂₃ olefinic protons), 5.80 (1H, d, C₄ olefinic proton, J₄₋₅ 10 Hz), 6.95 (1H, d, C₅ olefinic proton). Compound (7): low melting compound; $[\alpha]_D^{25} -10^\circ$ (CHCl₃); Mass 384 (M⁺); IR (CHCl₃) 1675, 1710 cm⁻¹; ¹H-NMR (CDCl₃) δ , 0.95 and 1.18 (6H, s, C₁₈ and C₁₉ protons), 5.20 (2H, m, C₂₂-C₂₃ olefinic protons), 5.82 (1H, d, C₄ olefinic proton, J₄₋₅ 10 Hz), 6.78 (1H, d, C₅ olefinic proton).
- 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 P2₁2₁2₁ with a = 7.005(1), b = 19.986(3), c = 20.293(3) Å; V = 2841.1(7) Å³, D_c = 1.07 gr cm⁻³, Z = 4. The intensity data were collected on a Synthex P2₁ four-circle automatic diffractometer, using graphite monochromated Cu-K α radiation: 1937 I_h 1 σ (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 SIR⁸ 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} ; 1H -NMR δ , 1.0 and 1.05 (C_{18} and C_{19} protons), 4.22 (1H, m, C_3 proton), 4.60 (1H, m, $J_{1/2} = 7\text{ Hz}$, 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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