HETEROSTEROIDS VIA ORGANOIRON COMPLEXES: ENANTIOSELECTIVE SYNTHESIS OF THE 9-(4-KETO-1-METHYLCYCLOHEX-2-ENYL)-8-KETO-DES-AB-ERGOSTA-14,15-22,23-DIENE; AN EASY REARRANGEMENT OF THE TITLE COMPOUND INTO A 6-OXA B-NOR HETEROSTEROID STRUCTURE

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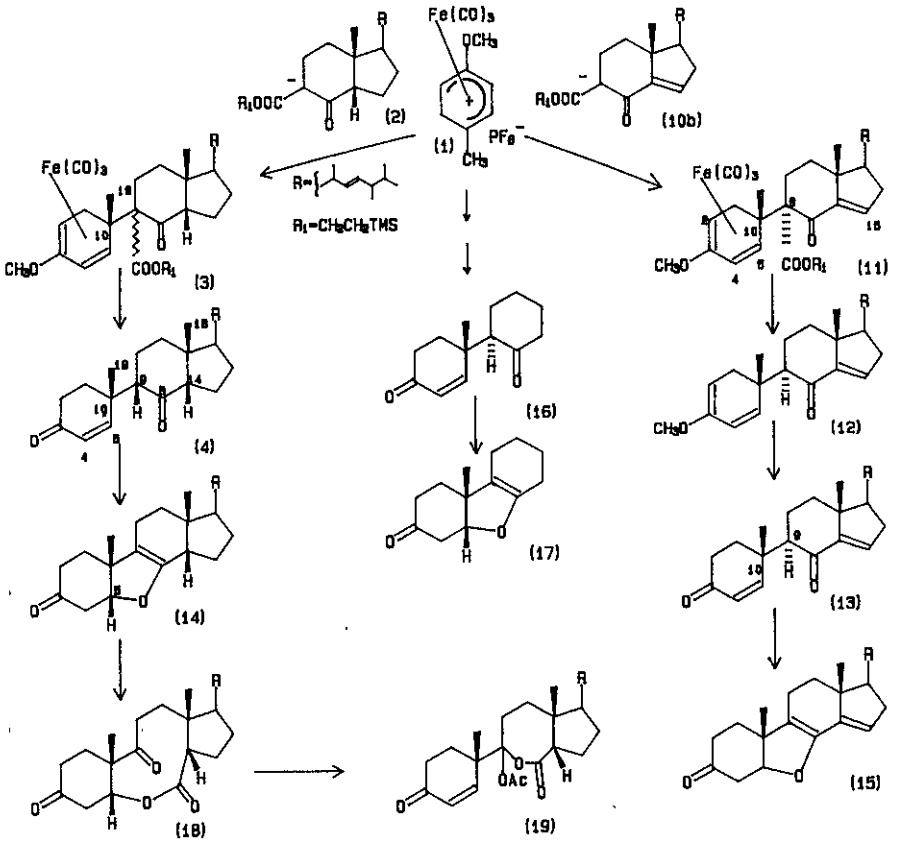
Abstract - The synthesis via organoiron complexes of the chiral 9-(4-keto-1-methylcyclohex-2-enyl)-8-keto-des-AB-ergosta-14,15-22,23-diene 13, as well as the rearrangement of 4, 13 to 6-oxa B-nor heterosteroids are described

We previously reported[1] that the junction reaction between the racemic iron tricarbonyl cyclohexadienyl cation 1 (scheme 1) and the chiral carbanion 2 occurred enantioselectively at C_{10} giving, as the main product, the complex 3 which shows the natural β steroid configuration of the C_{19} methyl.[2] By further elaboration 3 was converted into the enone 4, an useful heterosteroid intermediate.[1] Nevertheless, since the C_9 hydrogen of 4 results to be oriented in the β unnatural steroid configuration,[1] we have now planned to prepare an enone having the α configuration of this hydrogen, in order to get a suitable intermediate to be converted into natural steroids as well as heterosteroids.

Scheme 1



Dreiding models examination showed that, despite conformational flexibility showed by the corresponding hydrindane[4], the hydrindene moiety could only exist in the conformation reported in fig. 1 (scheme 2), i.e., with the C_9 axial hydrogen in the desired α natural orientation. Therefore, in order to prepare the complex 11, having the natural stereochemistry at C_9, we planned the synthesis of the hydrindene ketoester 10a by the junction reaction of the corresponding anion 10b with the cation 1 (scheme 2).

Scheme 2

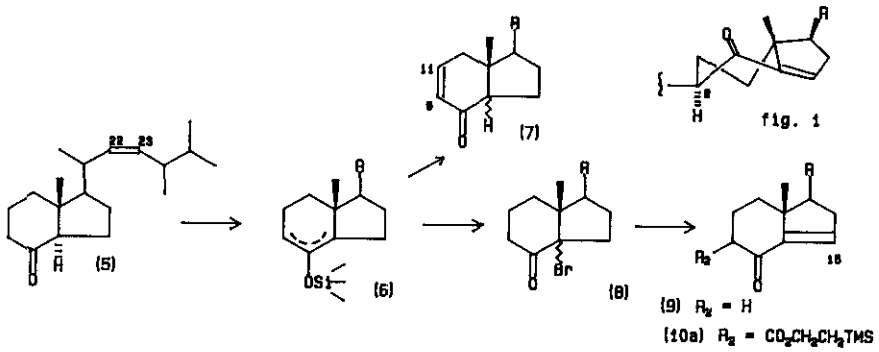


fig. 1

For the synthesis of 10a (scheme 2) the chiral ketone 5[1] was utilized as starting material. This ketone was converted (trimethylsilyl iodide, hexamethyldisilazane, carbon tetrachloride, -20°C)[3] into the silyl enol ether 6[4] (90%). Nevertheless, 6 was dehydrogenated by Pd salts ($Pd(OAc)_2$, CH_3CN, r.t.)[5] at the least substituted carbon atom to give 7. Alternatively, reaction of 6 with NBS (NBS, CCl_4, r.t.),[6] yielded the more substituted bromo-ketone 8 which was dehydrobrominated (γ-collidine, 170°C 2 h) to give the desired enone 9. The latter was further converted (lithium isopropylamide, carbon dioxide, -25°C, then trimethylsilylethanol and dicyclohexylcarbodiimide) into the β keto silyl ethyl ester 10a,[7] in order to remove the ester group under mild conditions. The following junction reaction between the corresponding carbanion 10b (NaH, THF, 0°C) and the iron tricarbonyl dienyl cation 1 (r.t., 0.5 h) yielded 11. Crude 11 was converted into 12 by decarboxylation (tetrabutylammonium fluoride, THF, r.t., 1 h),[7] followed by decomplexation of the iron carbonyl group (trimethylamine N-oxide, benzene, 80°C, 12 h).[8] Compound 12 was found to be stable and, on hydrolysis with oxalic acid (r.t., 1 h), gave the chiral dienone 13 (65%) as a main product, having the natural steroid configuration at C_9 as well as at C_{10}[9]. Therefore, 13 is a suitable intermediate to be converted by previously reported methods[11] into 6-oxa as well as 6-keto natural steroids.

Both the enones 4 and 13, are easily converted by enolization at C_9 into the unusual B nor-6 oxa heterosteroids 14 and 15 having the dihydrofuran moiety. The conversion (reported here) occurs quantitatively and regioselectively at C_9 in basic medium (sodium methoxide, methanol, 3 h, reflux), as well as, by chromatography, (on basic alumina) and it occurs also for similar enones. In fact, under the above conditions the diketone 16[12] rearranges into the corre-

sponding dihydrofuran compound 17. The X ray analysis[13] carried out on 14 confirmed its heterocyclic structure (fig. 2) and evidenced the stereochemistry β of the C_5 hydrogen resulting from a stereoselective α attack of the enolate to the enonic double bond.

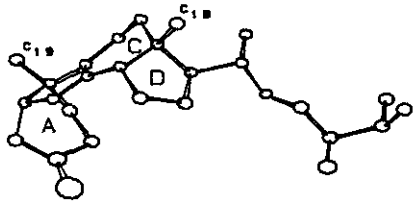


fig.2

The new compounds 14 and 15 appear to be stable under strong hydrolytic conditions (hydrochloric acid 10%, dioxane, 60°C). Compound 14, on treatment with m-chloroperbenzoic acid under controlled conditions (peracid 1 eq., $CHCl_3$, r.t., 4 h) reacted selectively at the activated enolic double bond to give, as the main product, the ketoester 18 formed by oxidative opening of the liable intermediate epoxidation product.[20] Compound18 was further converted on hydrolysis (acetone, sulphuric acid 2%, 12 h, r.t.), followed by acetylation, into a compound with the structure 19.

As a useful extention of this oxidative sequence, we plan to utilize specific enolethers as starting material to get a cyclohexane ring bearing a functionalized carbon chain.

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4. 6: liquid mixture of C_8-C_{14} and C_8-C_9 unsaturated silyl ethers (82:18 ratio by nmr examination), mass 348(M^+); ir ($CHCl_3$) 1660 cm^{-1}. 7: liquid, mass 274 (M^+); ir ($CHCl_3$) 1675 cm^{-1}; ^{1}H-nmr ($CDCl_3$) δ, 5.20 (2H, m, C_{22}-C_{23} olefinic protons), 5.90 (1H, d, C_9-olefinic proton, J_{9-11} 10 Hz), 6.75 (1H, m, C_{11}-olefinic proton). 8: liquid, mass 355 (M^+); ir ($CHCl_3$) 1710 cm^{-1}. 9: liquid , mass 274 (M^+); ir ($CHCl_3$): 1675, 1610 cm^{-1}; ^{1}H-nmr ($CDCl_3$) δ, 5.20 (2H, m, C_{22}-C_{23}-olefinic protons), 6.40 (1H, m, C_{15}-olefi-

nic proton). 10a: liquid, mass 420 (M^+); ir ($CHCl_3$) 1725, 1675, 1610 cm^{-1}; ^1H-nmr ($CDCl_3$) δ, 4.35 (2H, t, O-C$\underline{H_2}$-CH_2-TMS), 5.25 (2H, m, C_{22}-C_{23}-olefinic proton), 6.35 (1H, m, C_{15}-olefinic proton). 11: liquid, mass 682 (M^+); ir ($CHCl_3$) 2050, 1970, 1670, 1660, 1615 cm^{-1}; ^1H-nmr ($CDCl_3$) δ, 3.60 (3H, s, O-C$\underline{H_3}$), 4.35 (2H, t, O-C$\underline{H_2}$-CH_2-TMS), 4.60 (1H, m, C_4-olefinic proton), 4.90 (1H, m, C_5-olefinic proton), 5.25 (2H, m, C_{22}-C_{23}-olefinic protons) 5.50 (1H, m, C_2-olefinic proton), 6.90 (1H, m, C_{15}-olefinic proton), 12: liquid, ir($CHCl_3$) 1665, 1610 cm^{-1}; ^1H-nmr ($CDCl_3$) δ, 0.85 and 1.15 (6H, 2s, C_{18} and C_{19}-protons), 3.55 (3H, s, OC$\underline{H_3}$), 4.50 and 4.80 (2H, two broad d, C_4 and C_5-protons), 5.2 (2H, m, C_{22} and C_{23}-protons), 5.50 (1H, m, C_2 proton), 6.90 (1H, m, C_{15}-proton). 13: microcrystals from hexane-diethyl ether), mp 114-117°C $[\alpha]_D$=-52°; mass 382 (M^+); ir ($CHCl_3$) 1670, 1615 cm^{-1}; ^1H-nmr ($CDCl_3$) δ, 5.20 (2H, m, C_{22}-C_{23}-olefinic protons), 5.8 (1H, d, C_4-olefinic proton) 6.35 (1H, m, C_{15}-olefinic proton),6.8 (1H, d, C_5-olefinic proton). 14: prisms from hexane, mp 85-88°C; mass 384 (M^+); ir ($CHCl_3$) 1710, 1670 cm^{-1}; ^1H-nmr ($CDCl_3$) δ, 0.88 and 1,25 (6H, 2s, C_{18} and C_{19}-protons), 2.63 and 2.66 (2H, m, C_4-geminal protons), 4.49 (1H, pseudo t, C_5-proton), 5.25 (2H, m, C_{22} and C_{23}-protons). 15: microcrystals from hexane-diethyl ether, mp 110-111°C; mass 382 (M^+): ir ($CHCl_3$) 1715, 1675, 1620 cm^{-1}; ^1H-nmr ($CDCl_3$) δ, 0.89 and 0.98 (6H, 2s, C_{18} and C_{19}-protons), 2,67 (2H, m, C_4-protons), 4.50 (1H, pseudo t, C_5-proton), 5.25 (2H, m, C_{22} and C_{23}-protons), 5.50 (1H, m, C_{15}-proton). 17: liquid, mass 206 (M^+); ir ($CHCl_3$) 1710, 1660 cm^{-1}. ^1H-nmr ($CDCl_3$) δ, 1.25 (3H, s, angular methyl), 2.65 (2H, m, C_4-protons), 4.48 (1H, pseudo t, C_5-proton). 18: liquid, mass 416 (M^+); ir ($CHCl_3$) 1720, 1710 cm^{-1}; ^1H-nmr ($CDCl_3$) δ, 0.97 and 1.25 (6H, 2s, C_{18} and C_{19}-protons), 2.60 (2H, m, C_4-protons), 3.40 (1H, m, C_{14}-proton), 4.10 (1H, pseudo t, C_5-proton), 5.20 (2H, m, C_{22} and C_{23} protons). 19: liquid, mass 458 (M^+); ir ($CHCl_3$) 1725, 1670 cm^{-1}; ^1H-nmr ($CDCl_3$) δ, 2.07 (3H, m, OCOC$\underline{H_3}$), 3.50 (1H, m, C_{14}-proton), 5.20 (2H, m, C_{22} and C_{23}-protons), 5.90 (1H, d, C_4-proton), 7.15 (1H, d, C_5-proton).

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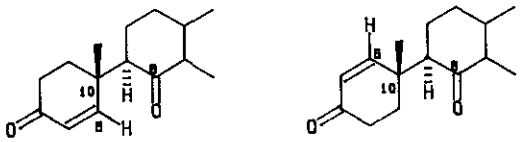
9. The natural stereochemistry of C_{19} methyl of 4 has been determined by X ray analysis,[1] the same expected natural stereochemistry of the C_{19} methyl of 13 has been confirmed as follows: previous X ray analysis reports evidence that in the junction compounds similar to 13 the C_{19} methyl and the C_9 hydrogen are disposed in a relative trans conformation.[1,10] Since the C_9 hydrogen of 13 is in the α axial position, the two possible C_{10} epimers to be formed in the junction reaction could stay in the trans conformations shown in figures A and B. Therefore the C_5 olefinic proton could be deshielded or not, respectively, by the keto group located at C_8. In fact, nmr spectra of some pairs of enones similar to 13, as well as epimers at C_9 and C_{10}, show that the C_5 hydrogen, according to its position, falls at 6.95±0.04 δ cis or 6.75±0.03 δ trans with respect to the keto group. Since the C_5 hydrogen of 13 appears at 6.93 δ, we conclude that the stereochemistry at C_{10} of the dienone 13 is as reported.



A B

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13. Suitable single crystals of 14 were grown at room temperature by slow concentration from an hexane solution.

Preliminary X-ray photographs showed that the crystals have orthorhombic symmetry, space group P 2_1 2_1 2_1; a=7.500(3), b=12.058(2), c=26.046(6)A°, V=2355.4(1.1) A°^{3}, D_c=1.08 gr.cm^{-3}, Z=4.

Unique intensity data with $\vartheta \leq 140^0$ were collected on a Syntex P 2_1 four circle automatic diffractometer, using variable ϑ-2ϑ scans and graphite-monochromated Cu-K_α radiation, $\mu(CuK_\alpha)$= 5.14 cm^{-1} of the 2524 independent measured reflections, 2284 were considered significant ($I \geq 1.5\sigma(I)$) and used for the structure elucidation.

The crystal structure was solved by multisolution direct methods, using

one-phase and two-phases structure semi-invariants to determine the starting set of phases, and negative quartets to discriminate the best set of refined phases.

The positions of hydrogen atoms were found on difference Fourier syntheses; full-matrix least-squares calculations with anisotropic thermal parameters for non-hydrogen atoms and isotropic B values for hydrogens riding on the corresponding carbon atoms, have converged to the residual R=0.049.

Calculations were performed with S.I.R.[14] and C.A.O.S.[15] packages on a Data General Eclipse MV/8000 II.

Positional parameters and the U_{eq} values, anisotropic thermal vibration parameters of the heavy atoms, the observed and calculated structure factors and the torsion angle tables have been deposited.

A general view of the molecular structure of 14 toghether with the numbering scheme is shown in Figure 2.

The conformation of the molecule is described by the torsion angle table, deposited.

They allow us to assign a distorted boat conformation to the cyclohexanone ring (A); a flattened envelope conformation to the dihydrofuran ring (B) with C_s-C(5) pseudosymmetry, ΔC_s=3.3°; an half-chair conformation to the cyclohexene ring (C) with the pseudo-binary axis passing through the middle points of C(8)-C(9) and C(12)-C(13) bonds, ΔC_2=6.8°; an envelope conformation to the cyclopentane ring (D) with C_s-C(13) pseudosymmetry, ΔC_s=0.2° [16].

The most characteristic feature of this steroid system concerns the junction of the rings. Indeed the junction is cis for either the (A) and (B) rings and the hydrindane (C/D) moiety so that the molecule shows an U-shape with the methyl groups at C(10) and C(13) and the hydrogen atoms at C(5) and C(14) protruding out of the convex face of the skeleton.

If the C(17)...C(25) distance (of 6.0 Å)is taken as a measure of the extention of the tail, this is not fully extended being 6.9 Å the distance for the fully extended side-chain [17,18]. This is by virtue of the anticlinal conformation about C(20)-C(22) and C(23)-C(24), which have rotational variability. The two terminal methyl groups denoted by C(26) and C(27) give rise to a gauche+ and gauche conformation respectively. The molecules

of 14 are held in the crystal by Van der Waals forces only; no short contacts are observed.

The molecules are oriented in the cell with the side-chains parallel to the b axis.[19]

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