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NEW APPROACH TO THE SYNTHESIS OF 6-KETOSTEROIDS *via* ORGANOIRON COMPLEXES.[1]

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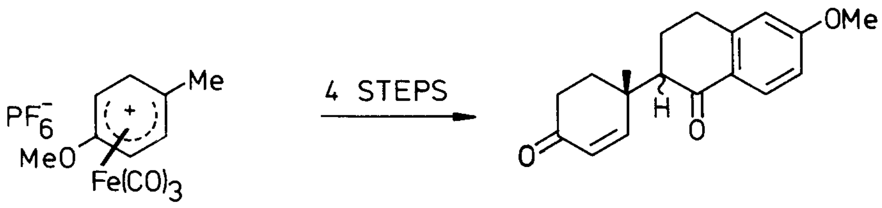
Abstract: New Methodology is described for the synthesis 6-ketosteroids, of potential value for the synthesis of β-ecdysone, *via* tricarbonyl (4-methoxy-1-methylcyclohexadienyl) iron hexafluorophosphate 1.

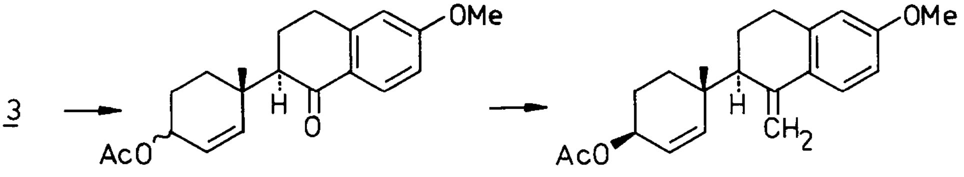
There has been much activity in recent years in steroid total synthesis, with the development of a number of elegant approaches via o-quinodimethane intermediates,[2] among others.[3] We recently described[4,5] the conversion of tricarbonyl(4-methoxy-1-methylcyclohexadienyl)iron hexafluorophosphate 1 in four steps to the 4,4 disubstituted cyclohexenones 2 and 3, and have also developed one method for the conversion of 2 to D-homoaromatic steroids.[5] We now describe our initial results on the conversion of enone 3, by a different route, to 6-keto-D-homoaromatic steroids.



1

2 β- H
3 α- H

Reduction of 3 ($NaBH_4$, MeOH, dioxan, 0°C) followed by acetylation (Ac_2O, pyridine) afforded the acetate 4[6] in 95% yield. The tetralone keto group was completely inert to normal Wittig reaction conditions, but methylenation was readily accomplished using the method described by *Takai et al.*[7] (Zn, $TiCl_4$, CH_2Br_2) to give the diene 5 in 60% yield.[6,8]



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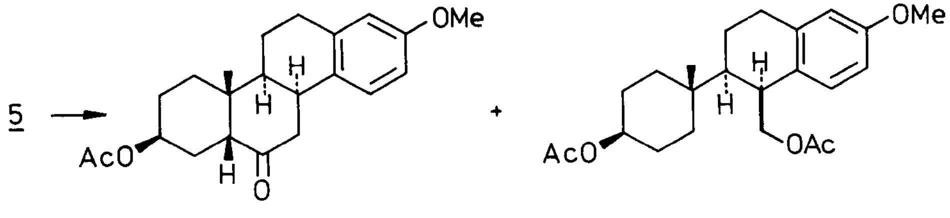
4 3β : 3α ≃2.5 :1

5

Our plan was to effect carbonyl insertion[9] into the diene of 5, via organoborane formation, a method recently employed for ring C construction in a synthesis of estrone methyl ether.[10] Hydroboration of 5 (thexylborane, THF, 0°C) followed by carbonylation (KCN, TFAA, then H_2O_2, OH^-) and reacetylation (Ac_2O, pyridine) gave a mixture of two products. The desired 6-keto-D-homoaromatic steroid 6[6] was obtained as the minor product (15%), the major product being the undesired 7, probably formed by hydrolytic breakdown of the intermediate organoborane.[11] The spectral data of 6 are in accord with the structure and stereochemistry shown, which follows from the expected initial attack of thexylborane at the less hindered α-face of the exocyclic methylene group of 5, followed by intramolecular hydroboration of the 4,5-double bond (steroid numbering) by a α-attack. Dreiding models indicate this to be the preferred stereochemistry for the reaction. The methyl singlet at δ1.31 in the n.m.r. spectrum of 6 is consistent with the *cis*-BC ring structure shown (*trans*-BC compounds give δ 1.0-1.1 for this group).[12] The appearance of the CHOAc signal at δ5.1 p.p.m. suggests a *cis*-AB ring junction. This proton is usually observed at δ4.6-4.8 for both *cis*- and *trans*-AB compounds,[13] and the observed deshielding (0.3 p.p.m.) due to the 6-keto group is only possible with a *cis*-AB ring junction.



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6

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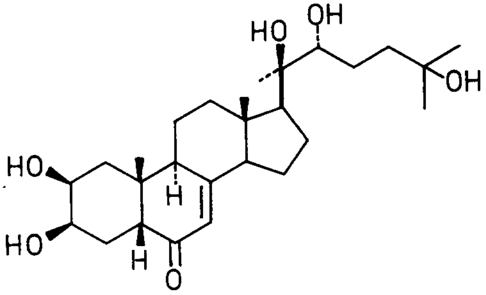

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Compounds similar to 6 have been proposed[12] as potential intermediates for the synthesis of β-ecdysone 8, an insect moulting hormone. We are continuing to investigate improved methods for carbonyl insertion to give 6, and these will be reported elsewhere.

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3. See ref. 10, and: F.E. Ziegler and T.-F Wang, Tetrahedron Lett., 1981, 22, 1179; P.A. Bartlett and W.S. Johnson, J. Am. Chem. Soc., 1973, 95, 7501; W.S. Johnson, G.W. Daub, T.A. Lyle and M. Niwa, ibid., 1980, 102, 7800; W.S. Johnson, C.E. Ward, S.G. Boots, M.B. Gravestock, R.L. Markezich, B.E. McCarry, D.A. Okorie and R.J. Parry, ibid., 1981, 103, 88.
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6. All new compounds were obtained as racemic mixtures and gave satisfactory combustion analyses. Spectral data are as follows: 4 (β-OAc) ν_{max} ($CHCl_3$) 1728, 1678, 1605 cm^{-1}; δ($CDCl_3$) 7.87 (1H, d, 9 Hz), 6.72 (1H, dd, 9, 3 Hz), 6.60 (1H, m), 5.92 (1H, d, 10 Hz), 5.55 (1H, d, 10 Hz), 5.15 (1H, m), 3.78 (3H, s) 2.85 (2H, m), 2.5-1.5 (7H), 2.02 (3H, s), 1.30 (3H, s). M^+328. 5: ν_{max} ($CHCl_3$) 1728, 1615 cm^{-1}; δ($CDCl_3$) 7.26 (1H, d, 9 Hz), 6.17 (1H, dd, 9, 3 Hz), 6.1 (1H, m), 5.56 (2H, ABq), 5.3 (1H, br s), 5.15 (1H, m) 4.91 (1H, br.s), 3.77 (3H, s), 2.0 (3H, s), 1.0 (3H, s), 2.8-1.2 (9H); M 326. 6: ν_{max} ($CHCl_3$) 1732, 1715 sh, 1617 cm^{-1}; δ ($CDCl_3$, 200 MHz) 7.0 (1H, d, J 9 Hz), 6.72 (1H, dd, 9, 3 Hz), 6.65 (1H, m), 5.10 (1H, m) 3.80 (3H, s), 3.5 (1H, m), 2.06 (3H, s), 1.31 (3H, s), 3.0-1.2 (15 H). M 356.
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