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NEW METHODOLOGY FOR STEROID TOTAL SYNTHESIS via ORGANOIRON COMPLEXES[1]

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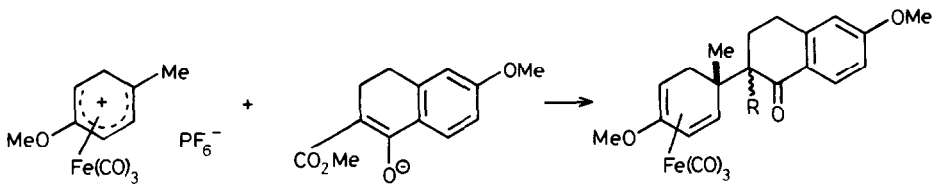
Abstract: The application of tricarbonyl(4-methoxy-1-methylcyclohexadienyl) iron hexafluorophosphate (1) as a steroidal ring A precursor is demonstrated.

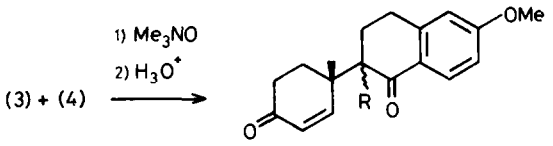
Steroid total synthesis is currently the subject of intensive investigation in a number of laboratories, many of the approaches relying on the generation of a suitable o-quinodimethane which undergoes intramolecular cycloaddition to generate the B and C rings.[2] We recently described[3] the reaction between the dienyl complex (1) and the tetralone carboxylic ester enolate (2) which gave, in almost quantitative yield, an equimolar mixture of diastereoisomers (3) and (4) resulting from regiospecific attack at the methylated terminus of (1). We report herein the initial results of our study on the conversion of (3) and (4) to steroid precursors. Of the many possible routes at our disposal, we in fact chose the least elegant, since this involves an aldol condensation for ring B closure which we considered to be potentially the least troublesome method.



(1) (2) (3) R = α-CO_2Me (4) R = β-CO_2Me

Whilst the products (3) and (4) are readily separated by crystallisation, the mixture was used for the immediate steps, since it was anticipated that either isomer would regenerate a mixture at the later decarbomethoxylation stage. Removal of iron (10 equiv. anhyd. Me_3NO, benzene, 55°, 3.5 h), followed by enol ether hydrolysis (oxalic acid, MeOH, H_2O, 20°C, 40 min.) gave the mixture of diastereoisomeric enones (5) and (6) in 93% overall yield.[4] Decarbometh-

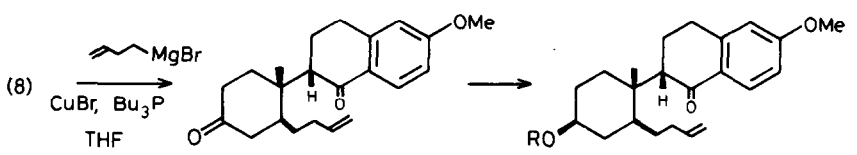
oxylation proceeded smoothly ($Me_4N^+OAc^-$, HMPA, 95°C, 6 h)[5] giving, in 87% yield, a mixture of diastereoisomers which was separated chromatographically to give the faster running component (7), m.p. 75-77°, followed by (8), m.p.



(5) R = α - CO_2Me
(6) R = β - CO_2Me
(7) R = α - H
(8) R = β - H

115-117°C, ν_{max} ($CHCl_3$) 1675, 1603 cm^{-1} (both isomers). Stereochemical assignments will be discussed elsewhere.

The epimer (8) underwent satisfactory cuprate addition (4-butenylmagnesium bromide, CuBr, Bu_3P, THF, -40°C, 5 h) to give (9), obtained chromatographically pure in 65-70% yield as a colourless oil, ν_{max} ($CHCl_3$) 3080, 1712, 1676, 1640, 1603 cm^{-1}. Under these conditions, the epimer (7), which has the correct steroid relative stereochemistry, underwent intramolecular reaction of the intermediate enolate with the tetralone carbonyl group. Inspection of models indicates that (7) is more likely than (8) to undergo this reaction, well-known for simpler examples.[6] Whilst there are a number of obvious ways in which this problem can be overcome, we have instead diverted the intermediate (7) to other studies. The stereochemistry of (9) follows from literature precedent for cuprate addition at the less hindered face of

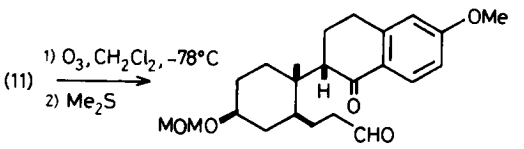


(9)

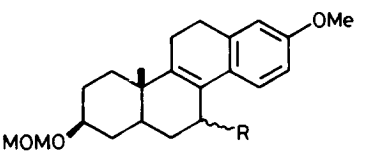
(10) R = H
(11) R = CH_2OMe

the enone.[7] Since (9) deteriorated considerably on storing for more than 48 h, it was immediately converted to alcohol (10) ($NaBH_4$, MeOH, 0°C, 0.5 h, 96%) which was protected as its methoxymethyl ether (11) ($ClCH_2OCH_3$, Pr^i_2NEt, CH_2Cl_2, reflux, 7 h). Ozonolysis of (11) gave the aldehyde (12), together with a minor amount of material from epimerisation alpha- to the tetralone carbonyl group, in 71% yield as a colourless oil, ν_{max} (CCl_4) 2705, 1725, 1670, 1603 cm^{-1}. The pure aldehyde underwent intramolecular aldol reaction (NaOMe, MeOH, reflux) to give an equimolar mixture of epimers (13) and (14)

(62%) ν_{max} (CCl_4) 1665, 1603 cm^{-1}, separable by chromatography. Decarbonylation of the mixture of aldehydes proceeded with difficulty ($(Ph_3P)_3RhCl$, toluene, reflux, 16 h) to give (15). Cyclisation of (12) under aprotic conditions ($KOBu^t$, THF, reflux) afforded an approximately equimolar mixture of the unconjugated aldehyde (16), ν_{max} 1722, 1602 cm^{-1}, and the mixture of

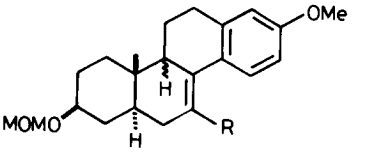


(12)



(16) R = CHO

(17) R = H



(13) α -H, R = CHO

(14) β -H, R = CHO

(15) R = H

(13) and (14). The product (16) was decarbonylated smoothly ($(Ph_3P)_3RhCl$, toluene, reflux, 3 h, 78%) to give (17), now a recognisable steroid intermediate.[8] Since stereochemical integrity is lost in all of these cyclisations, the use of the wrong diastereoisomer (8) is compensated.

This approach to steroid total synthesis is interesting in view of the recent asymmetric synthesis of the immediate precursor to complex (1).[9] We anticipate that alternative methods of ring B formation, currently under scrutiny in our laboratory, will lead to a number of functionalised analogues, and use of other nucleophiles in reaction with (1) will make available a large variety of rings C and D analogues.

Together with our other recent work,[10] the above results demonstrate the considerable potential of these organoiron derivatives for target-oriented organic synthesis.

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References and Notes

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