Tetrahedron Letters,Vol.26,No.25,pp 2981-2984,1985 0040-4039/85 $3.00 + .00
Printed in Great Britain

A CONVERGENT ORGANOIRON APPROACH TO STEROID SYNTHESIS

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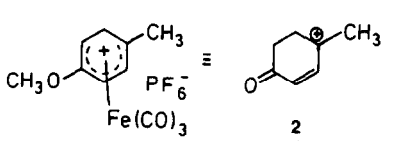
Abstract. The reaction of tricarbonyl (4-methoxy-1-methylcyclohexadienyl)iron hexafluorophosphate (**1**) with the keto ester nucleophile **5** to give complexes **6** and **7**, and conversion of **6** in eight steps, via the enone **8a**, to a D-homosteroid **11** is described.

The synthesis of steroids remains an active area of research,[1] particularly useful for the testing of new synthetic methodology and strategy. We have previously described[2] approaches to D-homoaromatic steroids which can function as precursors for the natural products.[3] Those experiments were based on the ability of the dienyliron complex **1** to react with stabilized enolate nucleophiles at C(1), thus behaving as a



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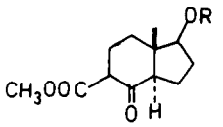

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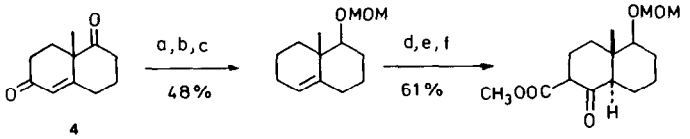
synthetic equivalent of the 4-methylcyclohexenone γ-cation (**2**). However, this approach has the disadvantage that a lengthy sequence is required to convert the aromatic D ring to the correct five-membered ring. Therefore, we have examined a convergent A + CD + B strategy which utilizes a CD fragment more closely resembling the proper steroid subunit, described herein.

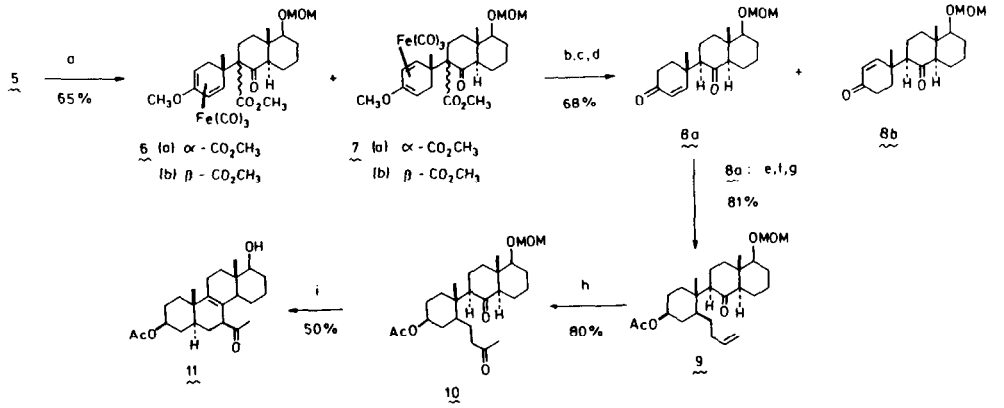
Ideally, the required ACD intermediate could be obtained by coupling a trans hydrindanone nucleophile such as **3** with complex **1**, but this is expected to be problematic owing to the tendency of molecules such as **3** to form a mixture of cis and trans ring junction isomers.[4] Consequently, we elected to use the configurationally stable trans-decalone keto ester **5**, prepared in six steps from the Wieland Miescher ketone (**4**) as shown in Scheme 1.[5]



Scheme 1

Reagents: (a) $NaBH_4$, $CeCl_3 \cdot 6H_2O$, MeOH, 0°C, 15 min. (b) $LiAlH_4$, $AlCl_3$ (1:1.5), Et_2O, 0°C, 5h. (c) $MeOCH_2Cl$, Pr^i_2NEt, CH_2Cl_2, reflux, 8h. (d) 3 BH_3 - THF, 0°C, 2h; then 2N NaOH, 30% H_2O_2, 20°C, 1h. (e) PCC, CH_2Cl_2, 20°C, 2h. (f) $(MeO)_2CO$, NaH, PhH, 60°C, 3h.

The intermediate **1** has not previously been used in reaction with keto esters as complex as **5**, so we considered that the success of this reaction would be of considerable interest in paving the way for future synthetic design. Treatment of the sodium enolate of **5** with the dienyl salt **1** (THF, 0°C) gave 60 - 65% yield of a mixture of four diastereomeric complexes, two of which were major and in approximately equimolar proportion. When the potassium enolate of **5** was used one pair of diastereomers predominated in the mixture (ratio **6**:**7** = 75:25). This pair was assigned the structure **6**, the minor pair being **7**, on the basis of the following



Scheme 2

Reagents: (a) NaH or $KOBu^t$, THF, 60°C, 2h; cool to 0°C and add complex 1, 0.5h. (b) Me_3NO, PhH, 25°C, sonicate, 4h. (c) oxalic acid, MeOH, H_2O, 25°C, 1h. (d) Me_4NOAc, HMPA, 100°C, 16h. (e) $CH_2{=}CHCH_2CH_2MgBr$, CuBr, THF, -40°C, 1h. (f) $NaBH_4$, MeOH, 0°C, 10 min. (g) Ac_2O, py, 25°C, 16h. (h) $PdCl_2$, CuCl, O_2, DMF, 25°C, 24h. (i) p-TsOH, CH_2Cl_2, reflux, 24h.

observations. The major isomer **6a** crystallized from the reaction mixture and was obtained pure (m.p. 145 -147°C). This compound was readily converted to the single enone intermediate **8a** by demetallation, enol ether hydrolysis and decarboxylation (Scheme 2). The liquors from crystallization were converted to a mixture of two diastereomeric enones **8a** and **8b**. Since epimerisation is possible at pro- C(9) (Steroid numbering) the cyclohexenone substituent is now equatorial, so the stereochemistry at this center is fixed and these compounds are epimeric only at C(10). Examination of the NMR spectra of **8a** and **8b** confirmed the stereochemical

assignments, since the enone β -hydrogen in **8a** (δ = 7.0 ppm, J = 10.3 Hz) is found at considerably lower field than that for **8b** (δ = 6.8 ppm, J = 10.3 Hz) the α -hydrogens being at similar chemical shift (5.84 ppm for **8a**, 5.88 ppm for **8b**). This is exactly the pattern observed for several analogous compounds we have previously prepared and characterized by X-ray crystallography.[2,6]

In this way, enone **8a** having the desired stereochemistry was obtained as the predominant product. This represents the first observation of diastereoselectivity during the addition of keto ester enolates to dienyl-$Fe(CO)_3$ complexes.[7] The enone **8a** was converted to D-homo-steroid derivative **11** by a five step sequence (Scheme 2). Reaction of **8a** with 4-butenylcuprate, followed by selective ketone reduction and acetylation gave **9** which was converted to diketone **10** by Wacker oxidation.[8] Acid-catalyzed cyclization of **10** under anhydrous conditions afforded the 7-acetyl-D-homosteroid **11**, having unconjugated ketone (ν_{max} 1705 cm^{-1}). While the position of the double bond in **11** is uncertain we have assigned the Δ^8 structure based on the following considerations. The 8,9-double bond is endocyclic to both the B and C rings and is therefore in its thermodynamically preferred arrangement.[9] Throughout the entire series of compounds **5** - **11** the position of the C/D angular methyl in the NMR spectrum remains constant at ca δ 0.7 - 0.8 p.p.m. and appears not to be affected by a neighboring C=C double bond (see conversion of **4** to **5**). On the other hand, the A/B angular methyl experiences a large upfield shift on going from **10** (δ 1.02) to **11** (δ 0.84), suggesting neighboring functionality in the latter.[10]

This approach promises a highly convergent synthesis of steroids having a variety of 7-substituents, since the acetyl group may be converted to , e.g., acetoxy using Baeyer-Villiger reaction or acetylamino using Beckmann rearrangement. We are currently examining these aspects, as well as the use of keto ester **3** in a similar reaction sequence.

Acknowledgements.

Financial support for this research was provided by the National Institutes of Health (GM 30373). High field NMR equipment was obtained with the aid of grants from the National Science Foundation (CHE 80-24633) and National Institutes of Health (RR-01689). We are grateful to Dr. Robert Lattimer of the BF Goodrich Company and Professor H. Andrist, Cleveland State University for provision of mass spectra.

References and Notes.

1. For recent examples, see: Stork, G.; Clark, G.; Weller, T. Tetrahedron Lett., 1984, 25, 5367, and references cited therein. Cooper, G. F.; Van Horn, A. R. ibid., 1981, 22, 1479; Grieco, P. A.; Takigawa, T.; Schillinger, W. J. J. Org. Chem., 1980, 45, 2247; Djuri, S.; Sarker, T.; Magnus, P. J. Am. Chem. Soc., 1980, 102, 6885, and reference cited therein.

2. Pearson, A. J.; Heywood, G. C.; Chandler, M. J. Chem. Soc. Perkin Trans. 1, 1982, 2631.

3. Kametani, T.; Tsubuki, M.; Nemoto, H. Tetrahedron Lett., 1980, 21, 4855; Kametani, T.; Suzuki; Nemoto, H. J. Chem. Soc. Perkin Trans. 1, 1980, 2805.

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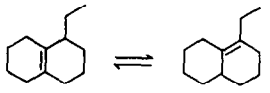
5. All new compounds were fully characterised by NMR and IR spectroscopy, and molecular compositions were established by high resolution mass spectrometry and/or combustion analysis where appropriate. 200 MHz ^{1}H NMR data for intermediate **8a** and final compound **11** are: **8a**: δ 7.0 (1H, d, J = 10.3 Hz), 5.84 (1H, d, J = 10.3 Hz), 4.72 and 4.58 (1H, d, each, J_{AB} = 7 Hz, diastereotopic OCH_2O), 3.38 (3H, s), 3.38 (1H, m, observed), 1.25 (3H, s), 0.77 (3H, s). **11**: δ4.67 (1H, m), 3.63 (1H, m), 2.18 (3H, s), 2.02 (3H, s), 1.8 - 0.9 (20H, m), 0.84 (3H, s), 0.74 (3H, s). IR: ν_{max} 3600, 3400 (br.), 1730, 1705 cm^{-1}.

6. Pearson, A. J.; Raithby, P. R. J. Chem. Soc. Perkin Trans. 1, 1980, 395; Pearson, A. J.; Mincione, E.; Chandler, M.; Raithby, P. R. ibid., 1980, 2774.

7. Approach of the bulky electrophile along the equatorial vector on the enolate of 5 is expected to give **6a** and **7a** as the major pair of products. The preference for **6a** is not understood at present, but may result from a destablizing non-bonded interaction involving the 6-methylene group of 1 during the approach which would lead to **7a**. We shall examine the effect of countercation more fully in the near future to gain a better understanding of this reaction.

8. Tsuji, J.; Shimizu, I.; Yamamoto, K. Tetrahedron Lett., 1976, 2975.

9. A preference for compound **A** over compound **B** (below) during acid-catalyzed equilibration has previously been noted, see: Aumiller, J. C.; Whittle, J. A. J. Org. Chem., 1976, 41, 2959.



A (83%) B (17%)

10. It is noteworthy that the A/B angular CH_3 signal for **10** is at the chemical shift expected for a saturated steroid (δ 1.0-1.1). See: Bhacca, N. S.; Williams, D. H. Applications of NMR Spectroscopy in Organic Chemistry. Holden-Day, San Francisco, 1964, pp. 78-80.

(Received in USA 12 March 1985)