Tetrahedron Letters,Vol.29,No.35,pp 4427-4430,1988 0040-4039/88 $3.00 + .00
Printed in Great Britain Pergamon Press plc

ENANTIOSELECTIVE PREPARATION OF KEY [ABC] INTERMEDIATES FOR STEROID SYNTHESIS THROUGH THE ASYMMETRIC MICHAEL ADDITION PROCESS INVOLVING CHIRAL IMINES.

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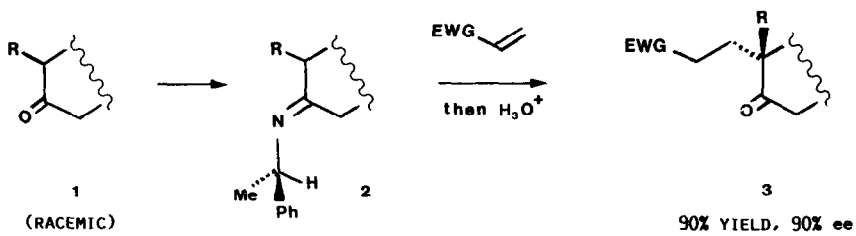
Summary : *(S)-Phenanthrone* ***7****, prepared from ketone* ***4*** *(80 % yield, 93 % ee), was transformed into compounds* ***8****,* ***9****,* ***13****,* ***15*** *and* ***16****, useful intermediates in steroid synthesis.*

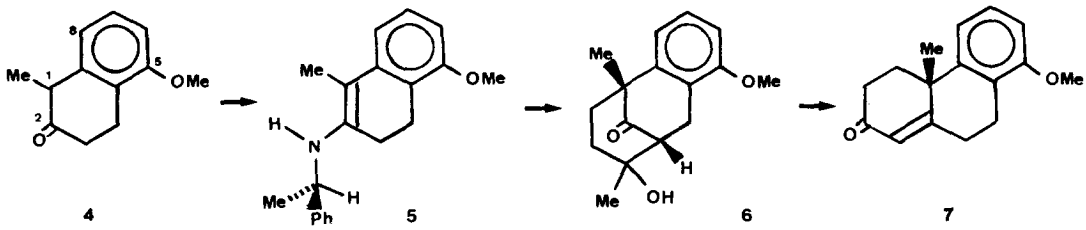
We have recently disclosed a very efficient asymmetric Michael process based on the "*deracemizing alkylation*" of 2-substituted cyclanones **1**, through the conjugate addition of their chiral imine derivatives **2** to electron-deficient alkenes [1]. Since the alkylation generally takes place exclusively at the *more* substituted α-position of the imine, this method is particularly well suited for the enantioselective synthesis of cyclanones **3** bearing an α-quaternary carbon center.



EWG = ELECTRON WITHDRAWING GROUP

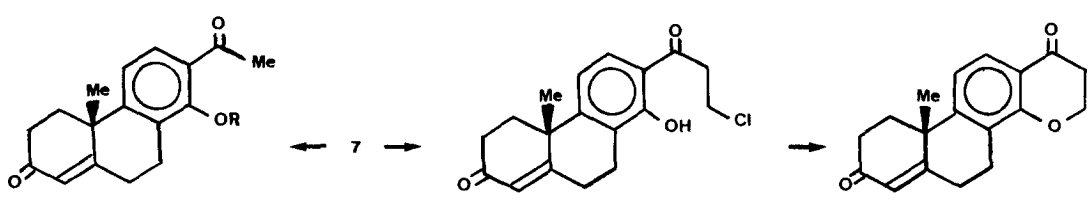
We have proposed a compact approach of the reactants, involving an "*aza ene synthesis-like*" transition state for this process, on the basis of both theoretical [2] and experimental [3] studies, and have illustrated this methodology by an enantioselective approach to ring-C aromatic steroids [4].

In the present paper, we report on the application of such a method to the asymmetric synthesis of phenanthrone **7**, and on the conversion of this compound into useful intermediates for steroid synthesis [5]. Thus, secondary enamine **5** [prepared form 1-methyl-5-methoxy-2-tetralone **4** and (*R*)-(+)-1-phenylethylamine by azeotropic removal of water, toluene, 18 h] and methylvinylketone (18 h at 20 °C then AcOH 20 %, 20 °C, 1 h) led to bridged ketol **6** which was then transformed into target (*S*)-phenanthrone **7** (MeONa in MeOH, 55 °C, 48 h, 80 % yield from **4**, 93 % ee) [6], in a highly regioselective manner, the alkylation process taking place exclusively at the C-1 center. In contrast, the related Michael addition reaction, starting from 1-methyl-8-methoxy-2-tetralone derivative, suffers from a considerable lack of regioselectivity, due to the *peri* interaction between C-1 and C-8 substituents [4].

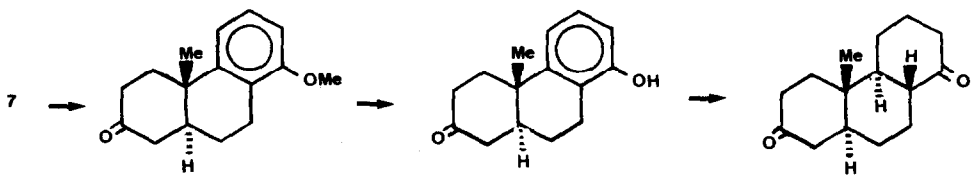


With the optically active key phenanthrone **7** in hand, we then proceeded with its transformation into potential intermediates for steroid synthesis. Taking advantage of the presence of an aromatic ring in this molecule, we first examined the introduction of an acyl side chain by using a Friedel-Crafts substitution reaction. *Ortho* and/or *para* substitutions relative to the activating methoxy group could *a priori* be expected for such a process ; however a reactant approaching the *para* position would obviously be hindered by the angular methyl group. Indeed, acylation of compound **7**, by using either acetyl chloride ($AlCl_3$, 1,2-dichloroethane, 20 °C, 15 h, followed by saponification of acetate **8a**) or 3-chloropropionyl chloride ($AlCl_3$, 1,2-dichloroethane, 48 h, 20 °C) is highly regioselective, giving only the *ortho* substituted phenol derivatives **8b** and **9** with 86 % and 60 % yields, respectively. Furthermore, it should be noted that, in both cases, cleavage of the aromatic methoxy group takes place during the acylation process. Spectral data on phenols **8b** and **9** (IR : chelated OH, ^1H NMR : coupling constants analysis of aromatic protons), as well as the easy transformation of compound **9** into tetracyclic derivative **10** (Na_2CO_3, $EtOH/H_2O$, 2 h, 20 °C, 88 % yield) support the proposed *ortho* substitution regiochemistry [7].

By introducing a side chain with the desired regiochemistry and the required future C-17 carbonyl functionality, this aromatic substitution process seems well suited for the subsequent construction of ring D of steroids [8].

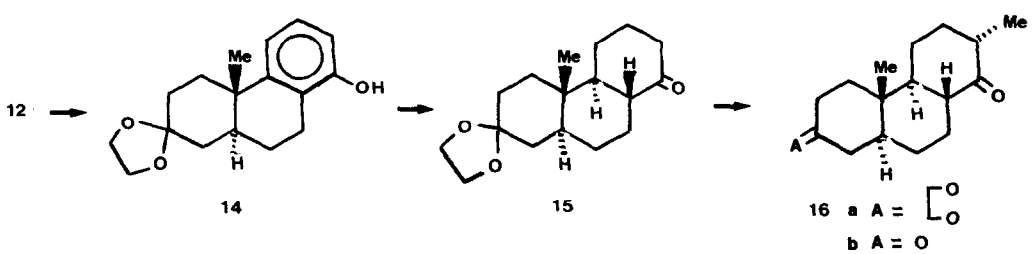


Phenanthrone **7** being a pivotal compound in the Cornforth-Robinson approach to steroids [5], we next examined its conversion into saturated key **[ABC]** intermediates **13**, **15** and **16**. For this purpose, enone **7** was first reduced into *trans* saturated ketone **11** (Li/NH_3, 80 % yield), the latter being then converted into the free phenol **12** (60 % HI in AcOH, reflux, 1 h, 72 % yield). Finally, the aromatic ring of phenanthrone **12** was catalytically hydrogenated (rhodium on carbon, 95 bars of hydrogen, 4 days, 85 °C, followed by Jones oxidation and epimerization in ethanolic KOH), leading to (*trans, anti, trans*) diketone **13** with a 70 % yield (the hydrogenation process, which takes place on the less hindered α-*face* of the molecule, secures the *anti* relationship,and the epimerization process leads to the thermodynamically more stable *trans* **[BC]** ring junction) [9].



Carbonyl monoprotection of tricyclic compound **13** was indirectly achieved as follows. Ketone **12** was ketalized (ethylene glycol, PTSA, benzene, azeotropic removal of water, 84 % yield), and ketal **14** transformed (W2 Raney-Ni, 100 bars of hydrogen, 110 °C, 19 h, followed by Swern oxidation and epimerization using KOH in EtOH) into saturated (*trans, anti, trans*) compound **15** with a 65 % yield [10].

The stereochemical assignments proposed for compound **15** were unambiguously established by correlation with the known optically active diketone **16b** [11]. Thus, methylation of ketone **15** (LDA/MeI, followed by epimerization with KOH in EtOH) produced with a 65 % yield the thermodynamically more stable (*equatorial* Me) derivative **16a**, which was then converted into diketone **16b** by acidic hydrolysis (94 % yield) [12].



To conclude, we have shown in this work that our general method aimed at the enantioselective elaboration of quaternary carbon centers is well suited for the preparation of chiral phenanthrone **7**, a key intermediate in steroid synthesis.

REFERENCES AND NOTES

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2. A. Sevin, J. Tortajada, M. Pfau, *J. Org. Chem.* 51, 2671 (1986).
3. J. d'Angelo, A. Guingant, C. Riche, A. Chiaroni, *Tetrahedron Lett.*, 29, 2667 (1988).
4. T. Volpe, G. Revial, M. Pfau, J. d'Angelo, *Tetrahedron Lett.*, 28, 2367 (1987).
5. Racemic phenanthrone **7** has been used in total synthesis of steroid : J.W. Cornforth, O. Kauder, J.E. Pike, R. Robinson, *J. Chem. Soc.*, 3348 (1955).
6. Tetralone **4** was prepared as follows. Birch reduction of 1,6-dimethoxynaphthalene (Na, NH_3, tBuOH) led with a 86 % yield to 5-methoxy-2-tetralone which was then methylated (pyrrolidine, benzene, azeotropic removal of water, then MeI in MeOH, 81 % yield). **5** : oil, IR (neat) 1625 cm^{-1} (any tautomeric imine form could be detected). **6** : m.p 157 °C. **7** (enantiomerically pure form, after recrystallization of the semicarbazone derivative) : m.p 46-47 °C, $[\alpha]_D^{25}$ + 278° (c = 1.04, EtOH), MS (m/e) 242 (M^+), IR (neat) 1680, 1630 cm^{-1}, ^1H NMR (200 MHz, $CDCl_3$) δ 1.56 (s, 3H) 3.81 (s, 3H) 5.90 (s, 1H) 6.68 (dd, J = 8.1 Hz, J = 0.7 Hz, 1H) 6.88 (dd, J = 8.0 Hz, J = 0.7 Hz, 1H) 7.20 (dd, J = 8.0 Hz, J = 8.1 Hz, 1H).
7. **8b** : oil, IR (neat) 1670, 1630 cm^{-1} ; ^1H NMR (90 MHz, CCl_4) δ 7.53 (d, J = 9 Hz, 1H) 6.73 (d, J = 9 Hz, 1H). **9** : oil, ^1H NMR (200 MHz, $CDCl_3$) δ 1.60 (s, 3H) 5.95 (s, 1H) 6.88 (d, J = 8.65 Hz, 1H) 7.63 (d, J = 8.65, 1H) 12.11 (s, 1H). **10** : oil, IR (neat) 1690, 1675, 1630 cm^{-1}.
8. Construction of ring D by using this mehtodology is now in progress.
9. **11** : m.p 120 °C, $[\alpha]_D^{25}$ + 104° (c = 1, EtOH). **12** : m.p 192-193 °C. **13** : m.p 55 °C, $[\alpha]_D^{25}$ + 21° (c = 2.1, EtOH).
10. **14** : m.p 68 °C. **15** : oil, $[\alpha]_D^{23}$ + 2° (c = 2.2, EtOH).
11. J.R. Billeter, K. Miescher, *Helv. Chim. Acta*, 33, 388 (1950).
12. **16a** : m.p 97 °C, $[\alpha]_D^{23}$ +8° (c = 2.3, EtOH). **16b** : m.p 85 °C, $[\alpha]_D^{20}$ + 33 ± 1° (c = 1.7, EtOH), MS (m/e) 248 (M^+), IR (CCl_4) 1715 cm^{-1}, ^1H NMR (250 MHz, C_6D_6) δ 0.49 (s, 3H) 1.04 (d, J = 15.4 Hz, 3H), ^{13}C NMR (C_6D_6) δ 10.7, 14.95, 25.4, 26.1,28.0, 35.4, 36.3, 38.1, 38.3, 44.5, 44.9, 45.4, 49.3, 54.8, 207.8, 211.1. [Lit [11] : m.p 87 °C, $[\alpha]_D^{20}$ + 35 ± 3° (c = 1.7, EtOH)].

(Received in France 3 June 1988)