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# A FORMAL, STEREOCONTROLLED SYNTHESIS OF (±) ESTRONE EMPLOYING THE TRIMETHYLSILYLCYANOHYDRIN COPE REARRANGEMENT

Frederick E. Ziegler and Tein-Fu Wang

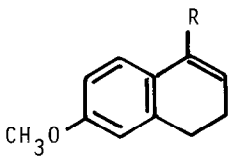
Sterling Chemistry Laboratory, Yale University, New Haven, CT 06511

*Summary:* *A new synthetic approach to estrone is discussed which employs control of stereochemistry via the Cope rearrangement.*

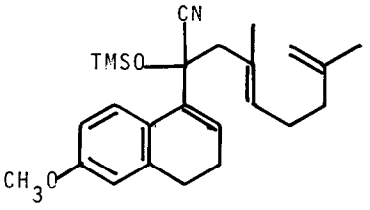
Steroids, by virtue of their polycyclic structures and well defined stereochemistries, have provided a means for the development of new synthetic strategies and the study of the stereochemical course of chemical reactions. Among the steroids, estrogens have served this role most admirably.[1] We have recently reported[2] a Cope rearrangement which provides δ,ε unsaturated esters. In order to explore the stereochemical course of this rearrangement, we have chosen estrone as a synthetic target and, in so doing, have also developed a polyene approach to the steroid nucleus which introduces an 11β-hydroxyl function rendering the two methods applicable to the synthesis of steroids.

The cyanohydrin of 6-methoxy-1-tetralone, prepared via the TMSCN method,[3] was dehydrated as described by Nagata[4] to provide unsaturated nitrile 1a (77%). Reduction of the nitrile (DIBAL, -78°C → 0°C, ether-hexane) afforded the unsaturated aldehyde[5] (85%) which was readily converted (TMSCN, $ZnI_2$ cat., $CH_2Cl_2$, 41°C, 24 h) to its trimethylsilylcyanohydrin 1c. The lithium anion of nitrile 1c (n-BuLi, THF, -78°C) was alkylated (-78°C → 25°C, 18 h) with 1-chloro-2,6-dimethyl-2(E),6-heptadiene[6] giving rise to the aryltriene 2 as a yellow liquid (58%).

Upon heating (160°C, 50 h, $N_2$) a solution of 2 in dimethylaniline, Cope rearrangement to the cinnamonitriles 3 was effected. The Cope rearrangement of the pro-homo-D-ring was not anticipated at such a low temperature.[7] Exposure of 3 to KF in refluxing methanol afforded (67% from 2) a pair of diastereomeric esters 4a and 5a in an 80/20 ratio, respectively. The major isomer was tentatively assigned the cis stereochemistry since equilibration ($NaOCH_3/HOCH_3$, reflux, 19 h) provided 4a/5a in a 17/83 ratio. Each isomer displayed 22 signals in its $^{13}C$ spectrum, attesting to its stereoisomeric purity. The stereochemistry at



1a, R=CN
b, R=CHO
c, R=CH(OTMS)CN



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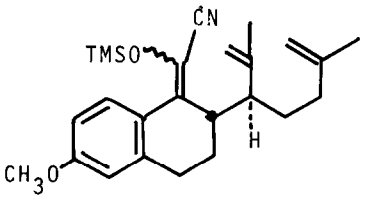
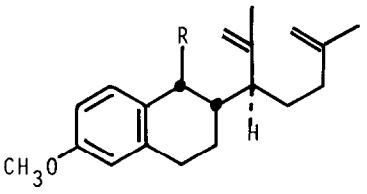
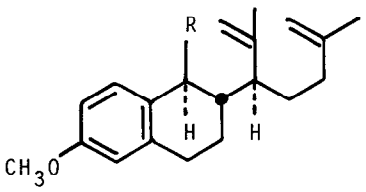


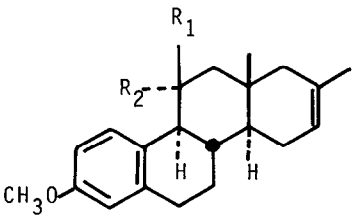
3



4a, R=$CO_2CH_3$
b, R=$CH_2OH$
c, R=CHO



5a, R=$CO_2CH_3$
b, R=$CH_2OH$
c, R=CHO



6a, $R_1$=OH, $R_2$=H
b, $R_1$=H, $R_2$=OH
c, $R_1$=OMs, $R_2$=H
d, $R_1$=H, $R_2$=OMs
e, $R_1$,$R_2$=O
f, $R_1$=$R_2$=H

pro-$C_8$ and pro-$C_{14}$ (steroid numbering) was tentatively assigned as depicted, arising from a chair-like transition state.

The individual esters were reduced ($LiAlH_4$, ether) to their respective alcohols (4b/5b) and subsequently oxidized (PCC, NaOAc, $CH_2Cl_2$)[8] to their aldehydes 4c and 5c. Exposure of either aldehyde to $NaOCH_3/HOCH_3$ resulted in a 92/8 (5c/4c) equilibrium mixture. Both aldehydes, upon irradiation of the aldehyde proton, revealed the pro-$C_9$ proton as a doublet (J = 3 Hz) which precluded definitive assignment of their stereochemistries on the basis of coupling constants. The stereochemical relationship between pro-$C_8$ and pro-$C_9$ was answered in the ensuing transformation.

Aldehyde 5c was readily cyclized ($SnCl_4/CH_3NO_2$, 0°C, 3 min)[9] to the tetracyclic alcohol 6a in 50% yield. No other identifiable products could be isolated. The relative stereochemistry at $C_8$, $C_9$, and $C_{11}$ of 6a was readily apparent upon examination of its 270 MHz nmr spectrum. The $C_9$ proton appeared at $\delta$ 2.55 (dd, $J_{8,9}$ = 11 Hz, $J_{9,11}$ = 3 Hz) requiring a trans-B,C juncture while the $C_{11}$ proton at $\delta$ 4.69 (q, J = 3 Hz) necessitated an axial hydroxyl group. Confirmation of the stereochemistry of the remaining centers was achieved by removal of the $C_{11}$ hydroxyl function.

Attempted mesylation (MsCl, $Et_3N$, $CH_2Cl_2$, 0°C)[9] of 6a produced a mixture of olefins ($\Delta^{9,10}$, $\Delta^{10,11}$?) presumably arising from facile trans diaxial elimination of the expected mesylate. However, oxidation (PDC, $CH_2Cl_2$, 25°C, 10 h) of axial alcohol 6a provided ketone 6e, mp 161-163°C (60%) ($C_9$-H, $\delta$ 3.68, d, J = 11 Hz) which was subsequently reduced ($Li/NH_3$/THF) to provide the equatorial alcohol 6b [$C_{11}$-H, 4.14 (td, J = 11 and 3 Hz)]. Mesylation of 6b proceeded without incident, producing 6d which was reduced ($Li/NH_3$/THF) to the crystalline tetracyclic 6f, mp 96.5-97.5°C (lit.[1g] 96-97°C) whose 270 MHz nmr spectrum was identical with an authentic sample.

The synthesis of 6f confirms the chair-like transition state of the Cope rearrangement and provides a formal total synthesis of estrone, since 6f has previously been converted to estrone by Valenta and co-workers.[1g] Moreover, 6f provides a potential intermediate for syntheses of corticoid steroids.[11]

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