Total Synthesis of Oestra-1,3,5(10)-trien-17-one†

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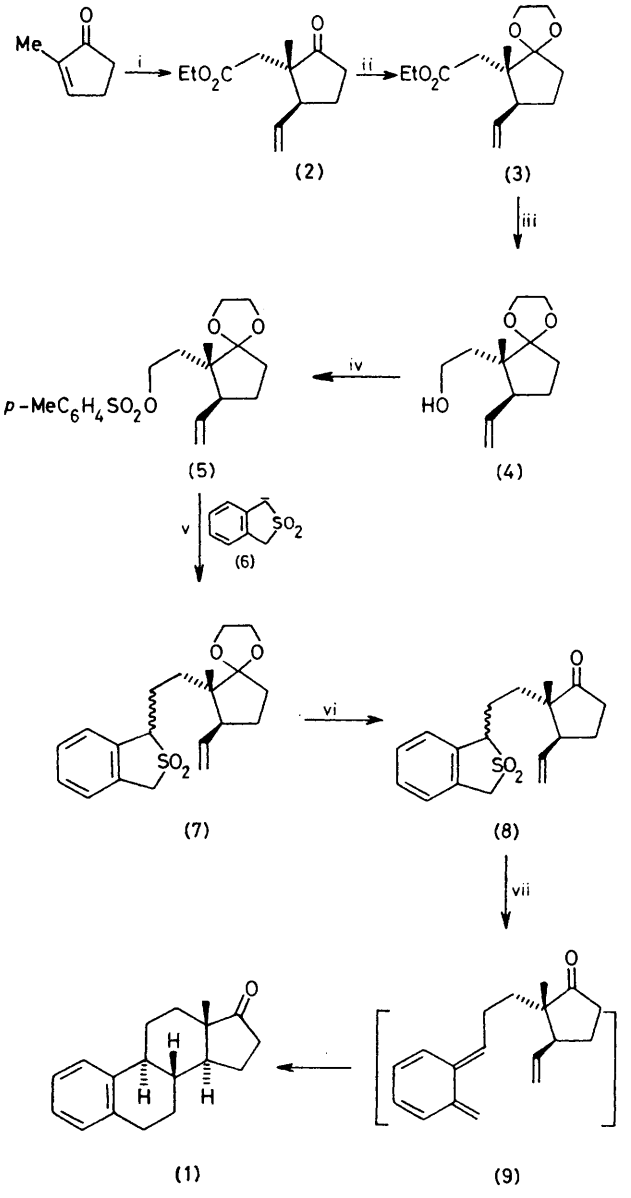
Summary A highly efficient and stereoselective synthesis of oestra-1,3,5(10)-trien-17-one (**1**) from the sulphones (**8**) *via* intramolecular capture of *o*-quinodimethanes generated by cheletropic elimination of SO_2 is reported.

STEROID hormones are of continuing interest in biological, clinical, and chemical research owing to their physiological role and challenging structures.[1] Recent, elegant syntheses of these systems include those of Vollhardt,[2] Oppolzer,[3] and Kametani[4] based on the intramolecular capture of *o*-quinodimethanes[5] generated from benzocyclobutenes by thermolysis. The benzocyclobutene precursors, however, are usually synthesized by multistep procedures in low-overall yields. Vollhardt's cobalt-catalysed synthesis of benzocyclobutenes[6] from acetylenes, which was modified to produce polycycles,[7] including steroids,[2] directly from acetylenic precursors under high dilution conditions, constitutes a considerable improvement. We now report the construction of steroidal structures by intramolecular capture of *o*-quinodimethanes generated by cheletropic elimination[8] of sulphur dioxide, originally observed by Cava over twenty years ago.[9]

† This work was reported in July 1979 at the Cambridge (England) 6th International Symposium on Synthesis in Organic Chemistry. Professor Oppolzer informed us of similar work in his laboratories.



SCHEME. i, CH_2=CHMgBr–CuI, $BrCH_2CO_2Et$ (see P. G. Gasman and J. M. Pascone, *J. Amer. Chem. Soc.*, 1973, **95**, 7801, and refs 2 and 3a); ii, $HOCH_2CH_2OH$, *p*-$MeC_6H_4SO_3H$, refluxing benzene; iii, $LiAlH_4$, Et_2O, 0 °C; iv, *p*-$MeC_6H_4SO_2Cl$, pyridine, 25 °C; v, (**5**):(**6**) 1:2, 25 °C, 15 h; vi, HOAc–tetrahydrofuran–H_2O 3:2:2, 50 °C, 24 h; vii, 210 °C, 8 h.

Our synthesis of steroids is demonstrated by the construction of oestratrienone (**1**) as shown in the Scheme. The ester (**2**) was obtained in one step from 2-methylcyclopent-2-enone and was converted into the acetal (**3**)‡ in 91% yield. Reduction of (**3**) to the alcohol (**4**), followed by tosylation afforded the crystalline tosylate (**5**), m.p. 86—87 °C (diethyl ether–hexane), in 60% overall yield from (**3**).

The tosylate (**5**) was then coupled with the anion (**6**) to give (**7**). The anion (**6**) can be obtained from the corresponding sulphone (2 equiv.) using KH (2 equiv.) in dimethoxyethane at 0—25 °C for 5 min to give a clear yellow solution. The diastereoisomeric mixture (**7**) (1:1 by ^{1}H n.m.r. spectroscopy) was obtained in 77% yield from (**5**) [87% yield based on the sulphone of (**6**)] and was deacetalised to give quantitatively a diastereoisomeric mixture of the ketone (**8**) (1:1 by ^{1}H n.m.r. spectroscopy). The isomers of (**8**) were separated chromatographically [silica, diethyl ether–petroleum, 1:1; R_f 0·14 (oil) and 0·18; m.p. 138—139 °C, diethyl ether–hexane; stereostructures not assigned].

Finally, thermolysis of either isomer of (**8**) or of a mixture of the two in di-n-butylphthalate led, after chromatography, to the isolation of oestra-1,3,5(10)-trien-17-one (**1**) in 85% yield, presumably *via* the intermediate (**9**). ^{1}H N.m.r. analysis (360 MHz) of the steroidal product revealed the presence of *ca.* 5% of what is assumed to be the *cis-anti-trans* C-9 epimer of (**1**). The recrystallized oestratrienone (**1**) (diethyl ether–hexane) was isomerically pure (±), m.p. 109—110 °C (lit.[2b] 107—109 °C) and was spectroscopically and chromatographically identical to an authentic sample.

The remarkable stereoselectivity of this reaction was expected on the basis of previous *o*-quinodimethane-based syntheses[2-4] and to our knowledge, this route is one of the simplest and shortest stereoselective syntheses of these important hormones. Furthermore, the readily available starting materials and reagents employed and the high overall yield [51% from (**4**)] make this route highly efficient and economically attractive. This method is now being used in the construction of the female hormone oestrone.

We thank Merck, Sharp, and Dohme, U.S.A., Chemie Grunenthal, W. Germany, and the University of Pennsylvania for financial support, and Dr. F. Li, Syntex Research Laboratories, U.S.A., for a generous gift of oestra-1,3,5(10)-trien-17-one.

(*Received*, 13*th August* 1979; *Com.* 866.)

‡ Satisfactory spectral data were obtained for all new compounds.

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