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NOVEL STEREOSELECTIVE TOTAL SYNTHESIS OF 14α-HYDROXYESTRONE METHYL ETHER

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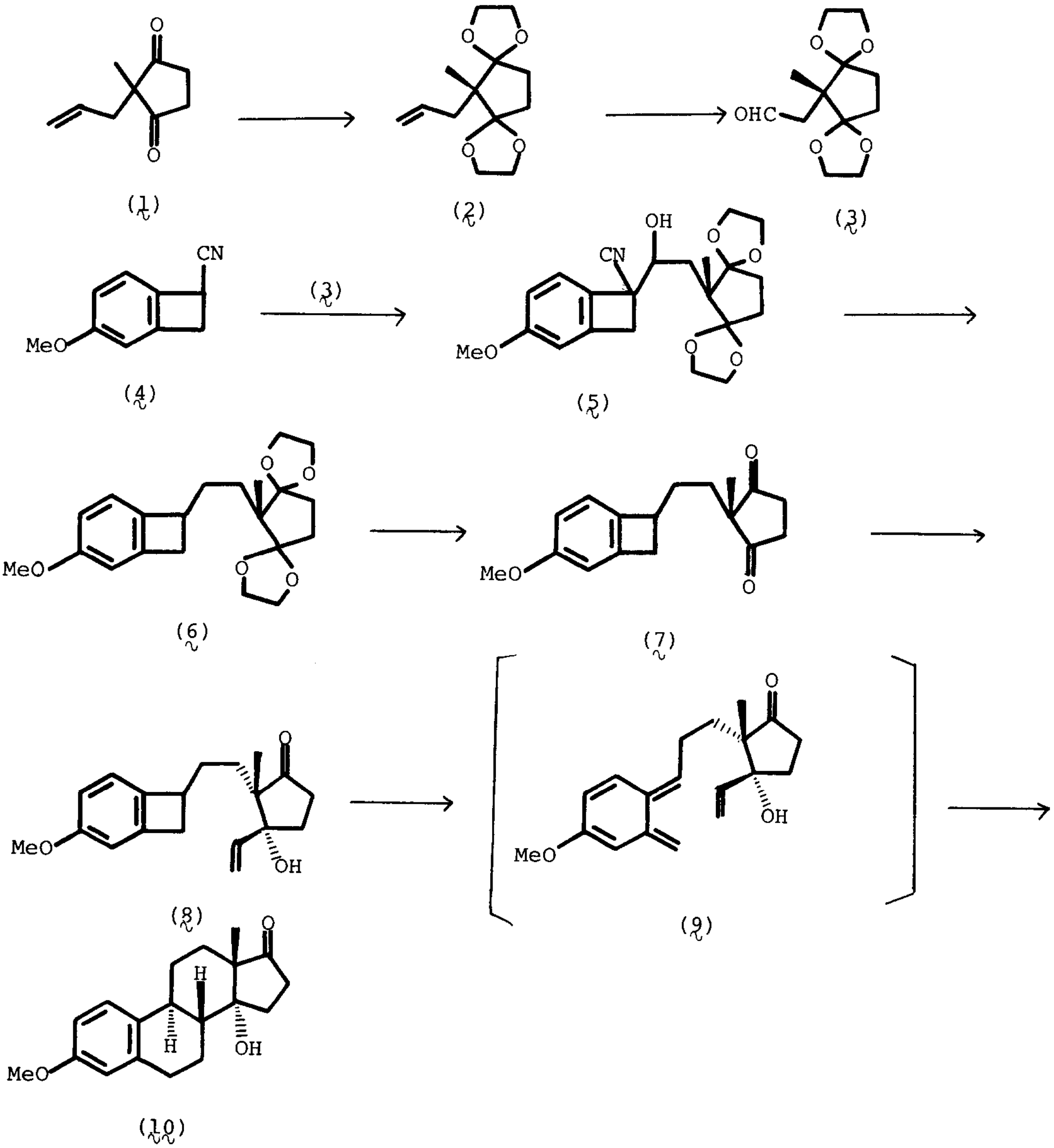
14α-Hydroxyestrone has been identified as a new estrogen metabolite[1-3] and its methyl ether could be an important intermediate for the synthesis of 14-dehydro-19-nortestosterone which shows a high androgenic activity.[4,5] This prompted us to develop a new stereoselective synthesis of 14α-hydroxyestrone methyl ether (**10**) by using a cycloaddition of electrocyclic reaction by way of *o*-quinodimethanes derived from benzocyclobutenes.[6] The aldehyde (**3**), which was synthesised from the cyclopentadione (**1**)[9] *via* the diketal (**2**) by ketalisation of **1** with ethylene glycol in the presence of catalytic amount of *p*-toluenesulphonic acid followed by ozonolysis of (**2**), was condensed with 1-cyano-4-methoxybenzocyclobutene (**4**)[10] in the presence of sodium amide in liq. ammonia to give the hydroxycyano-compound (**5**) as a diastereoisomeric mixture in 66.3 % yield [ir 3425 and 2225 cm^{-1}, m/e 401 (M^{+})]. Reaction of (**5**) with sodium in ammonia and ethanol afforded directly, in 68 % yield, the compound (**6**) [m/e 360 (M^{+})], which was hydrolysed with 10 % hydrochloric acid in tetrahydrofuran to give the diketone (**7**) [ir 1720 cm^{-1}, m/e 272 (M^{+})]. The key intermediate (**8**) [ir 1740 cm^{-1}, NMR (CCl$_4$) 0.9 (3H, s, Me), 3.73 (3H, s, OMe), 5.0 - 6.43 (3H, m, olefinic protons), 6.55 - 7.1 (3H, m, ArH), m/e 300 (M^{+})] was obtained, in 20 % yield, by the reaction of (**7**) with vinylmagnesium bromide in tetrahydrofuran.

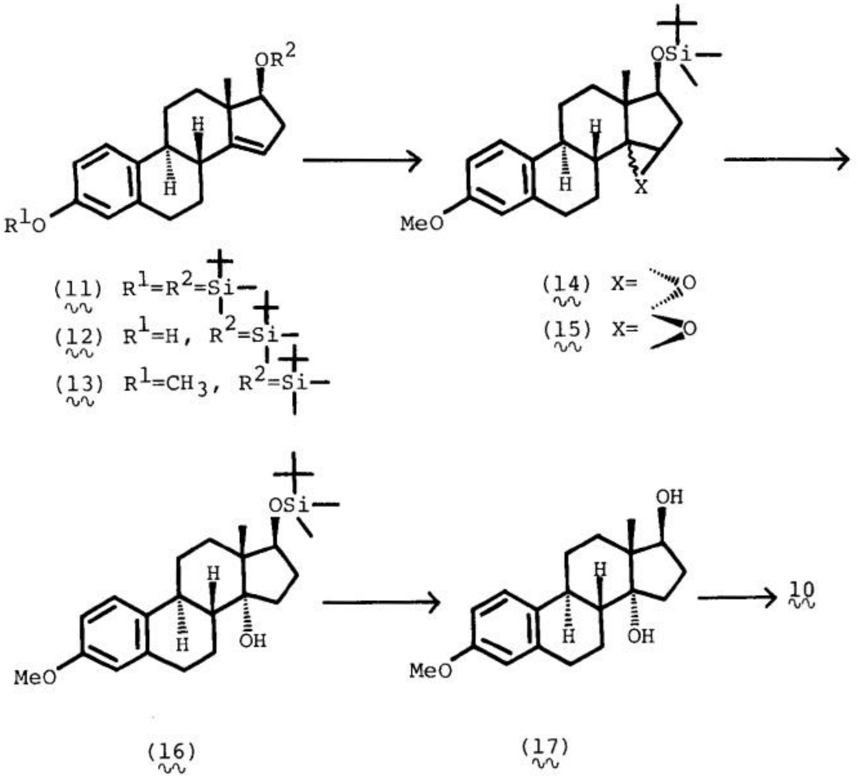
Heating the olefinic compound (**8**) in *o*-dichlorobenzene at 180°C for 4 h under a current of nitrogen gave [*via* the *o*-quinodimethane (**9**)], in 45 % yield, the compound (**10**), mp 195 - 196° [ir 1740 cm^{-1}, NMR (CDCl$_3$) 1.03 (3H, s, Me), 3.8 (3H, s, OMe) 6.76 (1H, d, *J* 3 Hz, ArH), 6.83 (1H, dd, J 3 and 8 Hz, ArH), and 7.33 (1H, d, *J* 8 Hz, ArH), m/e 300 (M^{+})].

Scheme 1



14α-Hydroxyestrone methyl ether (10) was synthesised alternatively starting from 14-dehydroestradiol disilyl ether (11)[11] in order to determine the stereochemistry of the compound (10) as follows. The methyl ether (13) [m/e 398 (M^+)], which was synthesised quantitatively by the selective hydrolysis of (11) with 10 % aqueous sodium hydroxide in methanol, followed by methylation of the resulting phenol (12) [m/e 384 (M^+)] with dimethyl sulphate in the presence of 40 % aqueous potassium hydroxide in acetone, was treated with m-chloroperbenzoic acid in dichloromethane to give, in 57.6 % yield, the epoxide (14)[12] [m/e 414 (M^+)]. The diol (17), [m/e 302 (M^+)], obtained, in 59 % yield, by the reduction of epoxide (14) with lithium aluminium hydride in ether followed by hydrolysis of the resulting silyl ether (16) [m/e 416 (M^+)] with 10 % hydrochloric acid in acetone, was finally oxidised with Jones' reagent to give, in 67 % yield, 14α-hydroxyestrone methyl ether (10), mp 176 - 177°, $[\alpha]_D$ + 152.5° (c = 0.008, $CHCl_3$) which was found to be identical with the sample obtained above in its ir ($CHCl_3$) and NMR (δ in $CDCl_3$) spectral comparisons

Scheme 2



Thus, a simple and stereoselective synthesis of 14α-hydroxyestrone methyl ether has been accomplished.

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References and Notes

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12 The *β*-epoxide (**15**) was also obtained in 13.5 % yield.

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