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SIMPLE TOTAL SYNTHESIS OF 18-HYDROXYESTRONE

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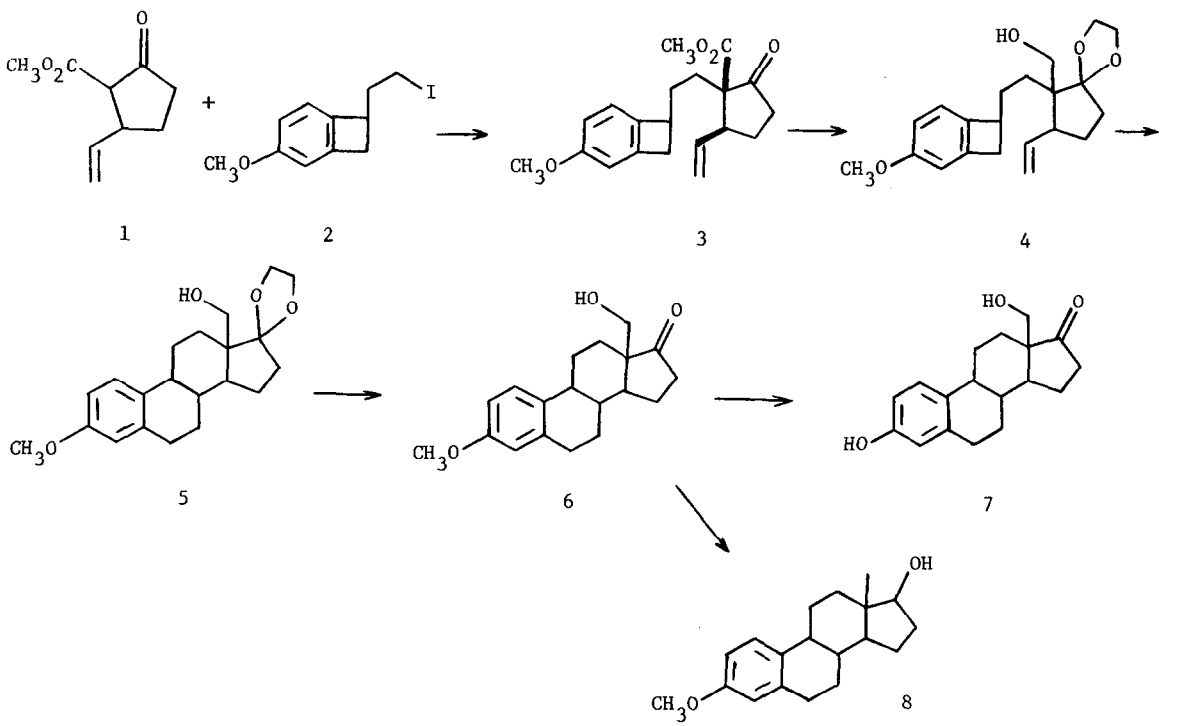
Summary: A simple total synthesis of 18-hydroxyestrone (7) was carried out by the cycloaddition of *o*-quinodimethane intermediate. 2-Methoxycarbonyl-3-vinylcyclopentanone (1) was used as the D ring component.

In a previous paper we have reported a facile synthesis of 2-methoxycarbonyl-3-vinylcyclopentanone (1) by the palladium catalyzed cyclization.[1] Using this compound as the D ring component, we have carried out a simple total synthesis of 18-hydroxyestrone (7), which was isolated from urine of pregnant women and identified by Marrian and coworkers.[2] Two partial syntheses[3,4] and one formal total synthesis[5] of 7 have been reported. However, these syntheses required multistep operation and the yields were low. Our synthesis is based on the well-known thermal cycloaddition of benzocyclobutene developed by Kametani[6] and Oppolzer[7] as shown by the following scheme.



1 2 3 4 5 6 7 8

The alkylation of 1 with the iodide 2[8] in refluxing acetone in the presence of K_2CO_3 for 36 h afforded 2-methoxycarbonyl-3-vinyl-2-[2-(3-methoxybicyclo[4.2.0]-octa-1,3,5-trien-7-yl)ethyl]cyclopentanone (3) in 62% yield. The alkylation is expected to proceed preferentially in trans manner to the vinyl group. Actually, the content of the cis isomer was less than 10%, and it was easily removed from the trans isomer by column chromatography (silica gel, hexane-benzene): NMR ($CDCl_3$) δ 3.54 (s, 3 H, CH_3), 3.63 (s, 3 H, OCH_3); IR (neat) 1752 and 1730 cm^{-1}.[9] The ketone group of 3 was protected as the acetal and the ester group was reduced to the alcohol 4 with $LiAlH_4$ in 73% yield: NMR ($CDCl_3$) δ 3.69 (s, 3 H, OCH_3), 3.86 (s, 4 H, OCH_2CH_2O); IR (neat) 3550, 1605, and 1590 cm^{-1}. The cycloaddition of 4 in refluxing *o*-dichlorobenzene produced the steroid skeleton 5 in 75% yield. Careful analysis by HPLC showed that the product was a single compound: NMR ($CDCl_3$) δ 3.72 (s, 3 H, OCH_3), 3.90 (s, 4 H, OCH_2CH_2O); IR ($CHCl_3$) 3570 cm^{-1}; mp 147-149°C. On the other hand, the cycloaddition of the ester 3 afforded in 75% yield two products which were the cis and trans isomers of the BC ring junction in a ratio of 1 : 4. Recrystallization of the mixture from CCl_4 produced the pure trans isomer, which was converted to 5 in 71% yield. Then the acetal group of 5 was removed (3N-HCl - acetone, room temp.) to give 6 in 89% yield: NMR ($CDCl_3$) δ 3.69-3.80 (m, 2 H, CH_2OH), 3.70 (s, 3 H, OCH_3); IR (nujol) 3430 and 1713 cm^{-1}; mp 183-185°C (recrystallized from benzene). Then 18-hydroxyestrone (7) was obtained from 6 by the treatment with BBr_3 in dichloromethane at -78°C (1 h) and 0°C (1 h) in 87% yield: NMR (pyridine) δ 4.0 (s, 2 H, CH_2OH);[4] IR (nujol) 3000-3650, 1715, and 1610 cm^{-1};[3] mp 205-208°C (dec.) (recrystallized from ethanol). The mass spectrum (M^+/286) was completely identical with the reported spectrum for the optically active one.[4] Also the structure of 6 was confirmed by converting it into 3-methoxyestra-1,3,5(10)-trien-17-ol (8) (mesylation, $LiAlH_4$), which was identified by its mp [132-133°C, recrystallization from hexane/methanol (lit,[10] 134-135°C)] and spectral data with those of an authentic sample.

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