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STUDIES ON THE SYNTHESES OF HETEROCYCLIC AND NATURAL COMPOUNDS. PART 939.[1] AN EFFICIENT AND STEREOSELECTIVE SYNTHESIS OF DES-A-RING STEROIDS—— POTENTIAL INTERMEDIATES TO ESTRADIOL, CORTISONE AND PROGESTERONE

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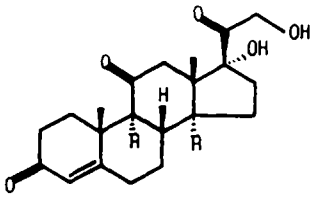
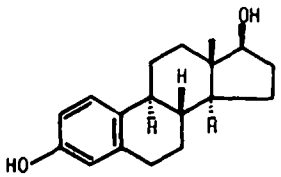
Abstract——A stereoselective synthesis of des-A-ring steroids 9 and 17 has been achieved by an intramolecular cycloaddition of 3-isopropenyl-5-(4-methoxybenzocyclobutenyl)pentan-2-one-2-ethylene ketal 7 and 1-(4-methoxybenzocyclobutenyl)-4-methylpent-4-en-3-ol 16, respectively.

Recently, a number of papers towards the synthesis of A-aromatic steroids,[2-10] such as estrone and estradiol, has been appeared, in which an intramolecular cycloaddition of o-quinodimethane derived from benzocyclobutenes or other precursors has been utilized as a key reaction. Although this type of reaction was already proved to proceed stereoselectively, many steps could be required in a conversion of A-aromatic steroids into the steroids having C_{19}-methyl under correct stereochemistry such as testosterone and progesterone. In order to synthesise steroids having C_{19}-methyl, the conversion of D-aromatic D-homosteroids, synthesised by the application of the above cycloaddition, has been investigated.[11] However, this approach has also taken several steps to introduce C_{18}-methyl group and a modification of functional groups at the C_{17}-position has attracted much less attention. It would be therefore very important to search an efficient method for construction steroidal ring system with an appropriate functional group at the C_{17}-position. For the purpose of this study, we undertook the stereoselective synthesis of steroidal B-C-D ring system with an appropriate functional group on D-ring and C_{18}-methyl group with correct stereochemistry by an intramolecular Diels-Alder reaction of benzocyclobutenes, because these tricyclic compounds may serve as important intermediates to cortisone 1 and estradiol 2.

Scheme 1



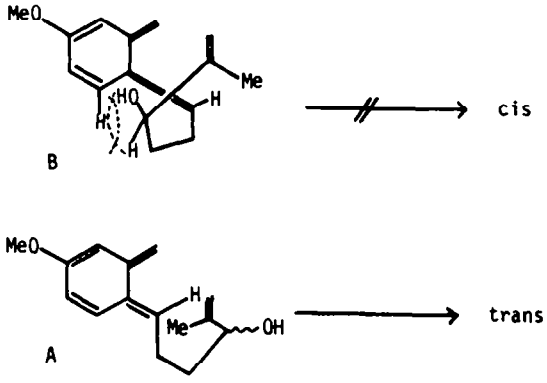
1



2

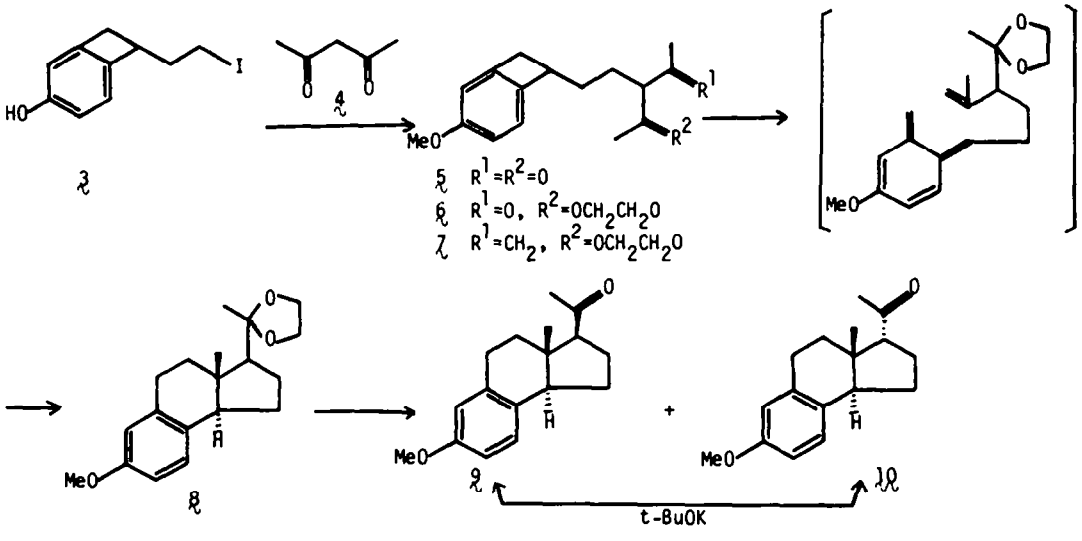
We firstly took an aim at progesterone-type compound which has acetyl group at the C_{17}-position. Thus, 2-(4-methoxybenzocyclobutenyl)ethyl iodide (3)[3] was treated with pentane-2,4-dione (4) in the presence of potassium carbonate in acetone to give the diketone (5) in 81.2 % yield. Ketal exchange reaction of (5) with 2-ethyl-2-methyl-1,3-dioxolane[12] in the presence of a catalytic amount of D-camphorsulfonic acid in methylene chloride afforded the mono-ketal compound (6) in 95 % yield. Wittig methylenation of (6) with triphenylmethylphosphonium bromide and n-butyllithium gave the olefin (7), m/e 302 (M^+), whose NMR spectrum exhibited olefinic protons as a singlet (2H) at 4.74 ppm. Heating a toluene solution of (7) in a sealed tube at 190 - 200° for 7 hr furnished the tricyclic compound[13] (8), m/e 302 (M^+), in 64 % yield. The stereochemistry of CD ring juncture was deduced to be trans from its NMR spectral data, which showed an angular methyl resonance as a singlet (3H) at 0.63 ppm.[14] This stereoselectivity is rationalised by assuming that the reaction proceeds via the intermediate A rather than B in the least sterically hindered manner as depicted in scheme 2.

Scheme 2



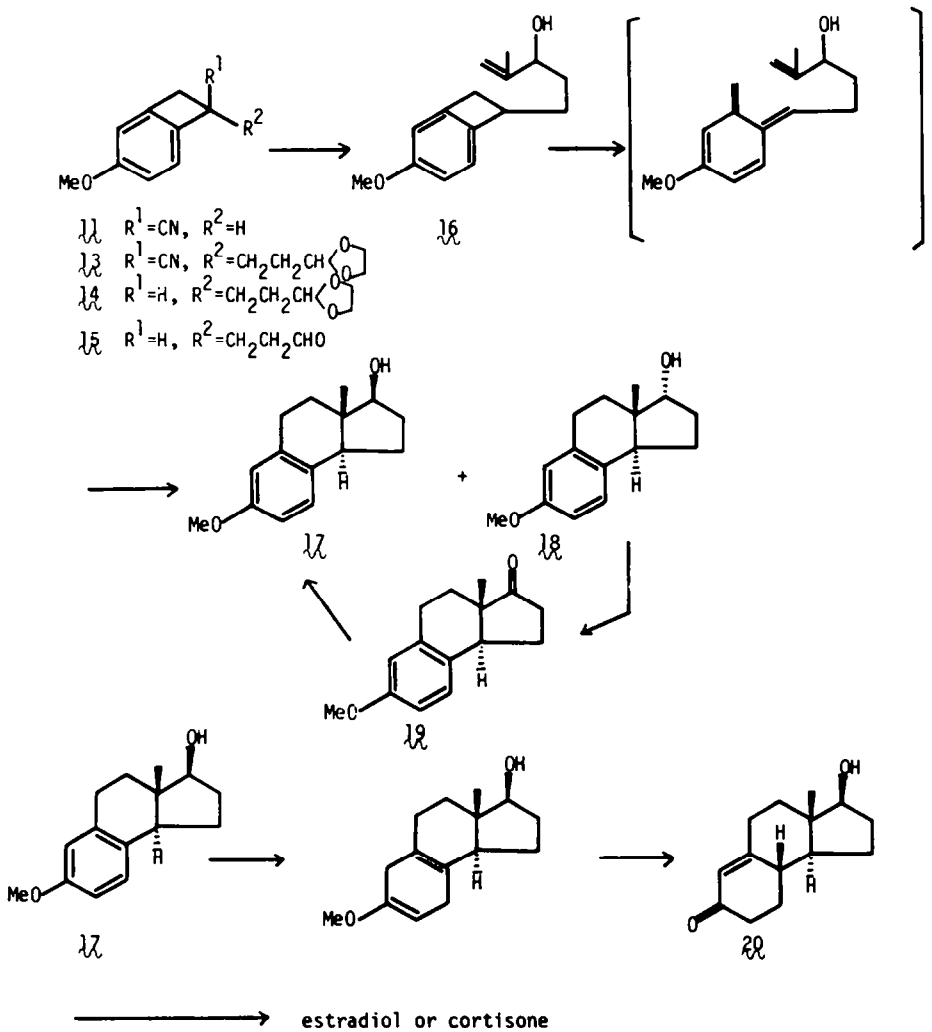
In order to determine the stereochemistry of the acetyl group at the C_{17}-position,[15] the ketal compound (8) was treated with 10 % aqueous hydrochloric acid in tetrahydrofuran to give the ketones (9) and (10) as an epimeric mixture in the ratio of 10 : 1 (an angular methyl resonance at 0.52 ppm for (9) and at 0.90 ppm for (10)). The major ketone was again treated with potassium t-butoxide to produce a mixture of (9) and (10) in the same ratio. As this equilibration was also observed in the case of pregnenolone-type compound,[11] the stereochemistry of the major compoud (9) was assigned to have β-acetyl group tentatively.

Scheme 3



Our attention focused next on the synthesis of estrone-type compound which bears hydroxyl group at the C_{17}-position. The requisite starting material for a thermolysis was synthesised as follows. Alkylation of the benzocyclobutene 11[16] with bromoacetal 12[17] in liquid ammonia in the presence of sodium amide gave the acetal 13 in 96.2 % yield, whose reductive decyanation with sodium in liquid ammonia furnished the decyanated acetal 14 in 74.2 % yield. The aldehyde 15, obtained by deacetalisation of 14 with 10 % aqueous hydrochloric acid in acetone was treated with isopropenylmagnesium bromide in tetrahydrofuran to afford the olefinic alcohol 16, m/e 232 (M^+), in 55.9 % yield from 14. This derivative exhibited an absorption at 3450 cm^{-1} in its IR spectrum due to the hydroxyl group and resonances due to the olefinic protons at 4.75 and 4.86 as an each singlet in its NMR spectrum. Thermolysis of this olefinic alcohol 16 at 180° for 6 hr via the o-quinodimethane afforded the cyclised compounds 17 and 18 with BC trans ring juncture stereoselectively in 85.5 % yield in the ratio of 1 : 1. The conversion of the unnatural-type of alcohol 18 to the natural-type of alcohol 17 was effected by oxidation of 18 with Jones reagent to the ketone 19 followed by sodium borohydride reduction in 64.7 % overall yield. The alcohol 17, identical with the authentic specimen[18] provided by Prof. J. Mathieu, was converted with lithium in liquid ammonia in the presence of ethanol to the tricyclic enone 20 in 58 % yield.

Scheme 4



Thus, the stereoselective synthesis of des-A-ring steroids having an appropriate functional group at the C_{17}-position and the C_{18}-methyl group with correct stereochemistry was achieved by an intramolecular cycloaddition of benzocyclobutenes, and this approach would be a useful route for the synthesis of steroids having C_{19}-methyl group .

EXPERIMENTAL

General. IR spectra were obtained with a Hitachi 260-10 spectrophotometer, NMR spectra with a JEOL JNM-PMX-60 instrument (TMS as an internal reference), and mass spectra with Hitachi M-52G and JMS-01SG-2 spectrometers.

3-Acetoxy-5-(4-methoxybenzocyclobutenyl)penta-2-one 5. A mixture of the iodide 3 (1.2 g), K_2CO_3 (1.86 g), pentane-2,4-dione (1.54 g) and dry MeOH (17 ml) was refluxed for 16 hr in a current of N_2. After evaporation of the solvent, the residue was treated with water and extracted with ether. The ethereal layer was washed with saturated NaCl soln and dried (Na_2SO_4). Evaporation of the solvent afforded an oil which was subjected to silica gel column chromatography. Elution with n-hexane-$CHCl_3$ (6 : 4 v/v) gave the diketone 5 (0.81 g, 81.2 %) as needles, mp 83 - 86° (MeOH). (Found: C, 73.55, H, 7.73. $C_{16}H_{20}O_3$ requires C, 73.82; H, 7.74 %), IR $\nu_{max.}$ ($CHCl_3$) 1690 (C=O) cm^{-1}; NMR (CCl_4)δ 2.13 (6H, s, 2 x $COCH_3$), 3.72 (3H, s, OCH_3), 6.50 - 7.02 (3H, m, 3 x Ar-H); MS m/e 260 (M^+).

3-Acetoxy-5-(4-methoxybenzocyclobutenyl)pentan-2-one-2-ethylene ketal 6. A soln of the diketone 5 (2.12 g), 2-ethyl-2-methyl-1,3-dioxolane (9.35 g) and D-camphorsulfonic acid (8.29 g) in dry CH_2Cl_2 (400 ml) was stirred at ambient temp for 2 hr in a current of N_2. The mixture was basified with saturated $NaHCO_3$ and the organic layer separated was washed with water and dried (Na_2SO_4). Evaporation of the solvent gave an oil which was chromatographed on silica gel using n-hexane-AcOEt (85 : 15 v/v) as eluant to give the monoketal compound 6 (2.36 g, 95 %) as an oil. (Found: C, 70.76; H, 7.76. $C_{18}H_{24}O_4$ requires C, 71.02; H, 7.95 %). IR ν_{max} ($CHCl_3$) 1710 (C=O) cm^{-1}; NMR (CCl_4)δ 1.20 (3H, s, $-\overset{O}{\overset{\|}{C}}-CH_3$), 2.13 (3H, s, $COCH_3$), 3.70 (3H, s, OCH_3), 3.92 (4H, s, OCH_2CH_2O), 6.50 - 7.01 (3H, m, 3 x Ar-H), MS m/e 304 (M^+).

3-Isopropenyl-5-(4-methoxybenzocyclobutenyl)pentan-2-one-2-ethylene ketal 7. To a stirred soln of triphenylmethylphosphonium bromide (0.72 g) in dry THF (12 ml) was added n-BuLi (0.128 g) at room temp in a current of N_2. After the mixture had been stirred for further 3 hr, a soln of the ketal 6 (42 mg) in THF (10 ml) was added and then stirred at ambient temp for 5hr. The resulting mixture was treated with NH_4Cl and extracted with benzene. The extract was washed with water and dried (Na_2SO_4). Evaporation of the solvent gave an oil which was chromatographed on silica gel using n-hexane-AcOEt (95 : 5 v/v) as eluant to afford the olefin 7 (22 mg, 52 %) as an oil. IR $\nu_{max.}$ ($CHCl_3$) 895 cm^{-1} NMR (CCl_4)δ 1.16 (3H, s, $-\overset{O}{\overset{\|}{C}}-CH_3$), 1.69 (3H, s, C=C-$CH_3$), 3.69 (3H, s, OCH_3), 3.88 (4H, s, OCH_2CH_2O), 4.74 (2H, s, CH_2=C), MS m/e 302.1860 (M^+) (Calcd. for $C_{19}H_{26}O_3$ 302.1880).

anti-trans-1-Acetyl-4,5-(4-methoxybenzo)-8β-methylhydrindane ethylene ketal 8. A soln of the olefin 7 (194 mg) in toluene (19 ml) was heated at 190 - 200° for 7 hr in a sealed tube. After evaporation of the solvent, the residue was subjected to silica gel column chromatography. Elution with n-hexane-AcOEt (95 : 5 v/v) afforded the tricyclic compound 8 (125 mg, 64 %) as an oil. (Found: C, 75.29; H, 8.60. $C_{19}H_{26}O_3$ require C, 75.46; H, 8.67 %), NMR (CCl_4) δ 0.63 (3H, s, $-\overset{O}{\overset{\|}{C}}-CH_3$), 1.32 (3H, s, C_3-CH_3), 3.74 (3H, s, OCH_3), 3.92 (4H, s, OCH_2CH_2O); MS m/e 302 (M^+).

anti-trans-1β-Acetyl-4,5-(4-methoxybenzo)-8β-methylhydrindane 9. A soln of the ketal 8 (125 mg), 10 % HCl (2 ml) in THF (10 ml) was stirred at ambient temp for 4 hr. The soln was basified with $NaHCO_3$ and the organic layer separated was washed with water and dried (Na_2SO_4). Removal of the solvent gave the ketone 9 and 10, which was recrystallised from MeOH to afford 9 (69.5 mg, 65 %) as needles, mp 65 - 66°. (Found: C, 78.84; H, 8.39. $C_{17}H_{22}O_2$ requires C, 79.03; H, 8.58 %). IR $\nu_{max.}$ ($CHCl_3$) 1700 (C=O) cm^{-1}; NMR ($CDCl_3$) δ 0.52 (3H, s, C_8-CH_3), 2.19 (3H, s, $COCH_3$), 3.74 (3H, s, OCH_3), MS m/e 258 (M^+).

Equilibration of 9 using potassium t-butoxide. To a stirred soln of t-BuOK [prepared from K (5.1 mg) in t-BuOH (2ml)] was added a soln of the ketone 9 (17 mg) in dry t-BuOH (3 ml) and the mixture was refluxed for 16 hr in a current of N_2. After evaporation of the solvent, the residue was diluted with water and extracted with benzene. The benzene extract was washed with saturated NaCl soln and dried (Na_2SO_4). Removal

of the solvent and chromatography of the residue on silica gel using n-hexane-AcOEt (95 : 5 v/v) as eluant gave a mixture of 9 and 10 [10 : 1 (NMR)] (9.5 mg, 56 %) as needles, identical with the mixture of 9 and 10 obtained above [IR ($CHCl_3$) and NMR ($CDCl_3$) spectra].

1-(1-Cyano-4-methoxybenzocyclobutenyl)propanal ethylene acetal 12. To a stirred soln of $NaNH_2$ [prepared from Na (2.2 g)] in liquid NH_3 was added a soln of the benzocyclobutene 11 (14.4 g) in THF (50 ml). After the mixture had been stirred for 15 min, a soln of the bromoacetal 12 (16.4 g) in THF (50 ml) was added to the above soln and the resulting mixture was stirred for further 1 hr. After addition of an excess of NH_4Cl, the solvent was evaporated to give the residue, which was diluted with water and extracted with ether. The ethereal layer was washed with water and dried (Na_2SO_4). Removal of the solvent gave an oil which was subjected to silica gel column chromatography. Elution with n-hexane AcOEt (8 : 2 v/v) furnished the acetal 13 (22.5 g, 96.2 %) as an oil. (Found: C, 68.03; H, 6.78; N, 4.90. $C_{15}H_{17}NO_3 \cdot 0.25H_2O$ requires C, 68.29; H, 6.59; N, 5.30 %). IR $\nu_{max.}$ ($CHCl_3$) 2230 (CN) cm^{-1}; NMR (CCl_4) δ1.95 (4H, s, $-CH_2CH_2-C<^{O}_{O}$]), 3.13 (1H, d, J = 14 Hz, ArCH), 3.65 (1H, d, J = 14 Hz, ArCH), 3.80 (3H, s, OCH_3), 3.75 - 3.82 (4H, m, OCH_2CH_2O), 4.80 (1H, t, J = 4 Hz, $CH<^{O}_{O}$), MS m/e 259 (M^+).

1-(4-Methoxybenzocyclobutenyl)propanal ethylene acetal 14. To a stirred soln of the acetal 13 (14.6 g) in liquid NH_3-THF (98.2 v/v)(1 l)was added Na metal (3.10 g) in small portions and the mixture was stirred at -33° for 2.5 hr. After addition of an excess of NH_4Cl, the solvent was evaporated to give the residue, whose ethereal extract was washed with water and dried (Na_2SO_4). Evaporation of the solvent afforded an oil which was subjected to silica gel column chromatography. Elution with n-hexane-AcOEt (8 : 2 v/v) gave the acetal 14 (9.76 g, 74.2 %) as an oil. (Found: C, 69.21; H, 7.76. $C_{14}H_{18}O_3 \cdot 0.5H_2O$ requires C, 69.11; H, 7.87 %). IR $\nu_{max.}$ ($CHCl_3$) 1125 cm^{-1}; NMR ($CDCl_3$) δ 3.60 (3H, s, OCH_3), 3.70 - 3.81 (4H, m, OCH_2CH_2O), 4.75 (1H, t, J = 4 Hz, $CH<^{O}_{O}$), 6.50 - 6.95 (3H, m, 3 x Ar-H), MS m/e 234 (M^+).

1-(4-Methoxybenzocyclobutenyl)propanal 15. A solution of the acetal 14 (120 mg) and 10 % HCl 1.1 ml) in Me_2CO (2.2 ml) was stirred at ambient temp for 7min, basified with saturated $NaHCO_3$ and extracted with ether. The ethereal layer was washed with water, dried (Na_2SO_4) and evaporated to give the residue which was chromatographed on silica gel using n-hexane-AcOEt (85 : 15 v/v) as eluent to afford the aldehyde 15 (69 mg, 70.8 %) as an oil. IR $\nu_{max.}$ ($CHCl_3$) 1720 (C=O) cm^{-1}; NMR ($CDCl_3$) δ 3.75 (3H, s, OCH_3), 6.55 - 7.00 (3H, m, 3 x ArH), 9.75 (1H, t, J = 3 Hz, CHO); MS m/e 190.1001 (M^+) (Calcd. for $C_{12}H_{14}O_2$ 190.0994).

1-(4-Methoxybenzocyclobutenyl)-4-methyl-4-penten-3-ol 16. To a stirred soln of isopropenylmagnesium bromide [prepared from isopropenyl bromide (363 mg) and Mg (100 mg)] in THF (6 ml) was added a soln of the aldehyde 15 (380 mg) in THF (2 ml) at room temp. After stirring for 1 hr at room temp, the mixture was treated with saturated NH_4Cl soln and extracted with ether. The ethereal extract was washed with water, (Na_2SO_4) and evaporated to give an oil which was subjected to silica gel column chromatography. Elution with n-hexane-$CHCl_3$ (92.5 : 7.5 v/v) afforded the alcohol 16 (302 mg, 79 %) as an oil. (Found: 74.69; H, 8.20. $C_{15}H_{20}O_2 \cdot 0.5H_2O$ requires C, 74.65; H, 8.77 %). IR $\nu_{max.}$ ($CHCl_3$) 3450 (OH) cm^{-1}; NMR ($CDCl_3$)δ 1.70 (3H, s, C-CH_3), 3.70 (3H, s, OCH_3), 4.75 (1H, s, C=C<H), 4.86 (1H, s, C=C<H), 6.49 - 6.95 (3H, m, 3 x Ar-H): MS m/e 232 (M^+).

anti-trans-1β-Hydroxy-4,5-(4-methoxybenzo)-8β-methylhydrindane 17 and anti-trans-1α-Hydroxy-4,5-(4-methoxybenzo)-8β-methylhydrindane 18. A soln of the alcohol 16 (2.0 g) in toluene (75 ml) in a sealed tube was heated at 180° for 6 hr. After evaporation of the solvent, the residue was subjected to silica gel column chromatography. Elution with n-hexane-AcOEt (9 : 1 v/v) afforded the 1β-hydroxy compound 17 (850 mg, 42.5 %), mp 73 - 75°(MeOH). (Found: C, 76.07; H, 9.18. $C_{15}H_{20}O_2 \cdot 0.25H_2O$ requires C, 76.07; H, 8.73 %). IR $\nu_{max.}$ ($CHCl_3$) 3600 (OH) cm^{-1}; NMR ($CDCl_3$) δ 0.63 (3H, s, C_8-CH_3), 3.75 (3H, s, OCH_3); MS m/e 232 (M^+), whose spectral data were superimosable with those of the authentic sample provided by Dr. J. Mathieu. Elution with n-hexane-AcOEt (85 : 15 v/v) afforded the 1α-hydroxy compound 18 (860 mg, 43 %) as an oil. IR $\nu_{max.}$ ($CHCl_3$) 3600 (OH) cm^{-1}; NMR ($CDCl_3$)δ 0.56 (3H, s, C_8-CH_3), 3.69 (3H, s, OCH_3), 6.42 - 7.00 (3H, m, 3 x Ar-H); MS m/e 232 (M^+).

anti-trans-1-Keto-4,5-(4-methoxybenzo)-8β-methylhydrindane 19. To a stirred soln of the alcohol 18 (960 mg) in Me_2CO (30 ml) was added 8N CrO_3 in H_2SO_4 (Jones reagent) (1.28 ml) at 0° and the stirring was continued for 15 min. The mixture was diluted with water and extracted with AcOEt. The extract was washed with water and dried (Na_2SO_4). Removal of the solvent gave the ketone 19 (760 mg, 79.2 %), mp 111 - 113° (n-hexane). IR $\nu_{max.}$ ($CHCl_3$) 1740 (C=O)cm^{-1}; NMR ($CDCl_3$) δ0.70 (3H, s, C_8-CH_3), 3.75 (3H, s, OCH_3), 6.50 - 7.10 (3H, m, 3 x Ar-H); MS m/e 230 (M^+).

Reduction of the ketone 19 with sodium borohydride. To a stirred soln of the ketone 19 (6 mg) in EtOH (3 ml) was added $NaBH_4$ (4.9 mg) at room temp, and the stirring was continued for 1 hr. The mixture was diluted with water and extracted with CH_2Cl_2. The extract was washed with water, dried (Na_2SO_4) and evaporated to give the 1β alcohol 17 (4.9 mg, 81.7 %), identical with the authentic sample obtained above.

anti-trans-1β-Hydroxy-8β-methyl-4,5-(4'-keto-1',2',3',4'-tetrahydro)hydrindane 20. To a stirred soln of the alcohol 17 (100 mg) in liquid NH_3-THF (2 : 1 v/v) (45 ml) was added dry EtOH (15 ml) and Li metal (20 mg). After stirring for 2 hr, the solvent was evaporated and the residue was extracted with CH_2Cl_2. The extract was washed with water, dried (Na_2SO_4) and evaporated to give the residue which was dissolved in MeOH (9 ml) and 10 % HCl (1 ml). The resulting mixture was stirred at room temp for 12 hr and diluted with water. The aqueous layer was extracted with $CHCl_3$ and the extract was washed with saturated $NaHCO_3$ soln and water, and dried (Na_2SO_4). Evaporation of the solvent afforded the residue which was chromatographed on silica gel using n-hexane-AcOEt (8 : 2 v/v) as eluant to give the enone (20) (55 mg, 58%) as needles, mp 101 - 102° (ether-n-hexane). (Found: C, 76.07; H, 9.18. $C_{14}H_{20}O_2$ requires C, 76.32; H, 9.15 %). IR $\nu_{max.}$ ($CHCl_3$) 1665 (C=O) cm^{-1}; NMR ($CDCl_3$) δ0.87 (3H, s, C_8-CH_3), 5.78 (1H, s, olefinic proton); MS m/e 220 (M^+).

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