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STUDIES ON THE STEREOCHEMICAL COURSE OF INTRAMOLECULAR CYCLOADDITION REACTIONS OF OLEFINIC o-QUINODIMETHANES — STEREOSELECTIVE SYNTHESIS OF 8α,9α,14β-ESTRANES

TETSUJI KAMETANI*, MASAHIRO AIZAWA, and HIDEO NEMOTO

Pharmaceutical Institute, Tohoku University, Aobayama, Sendai 980, Japan

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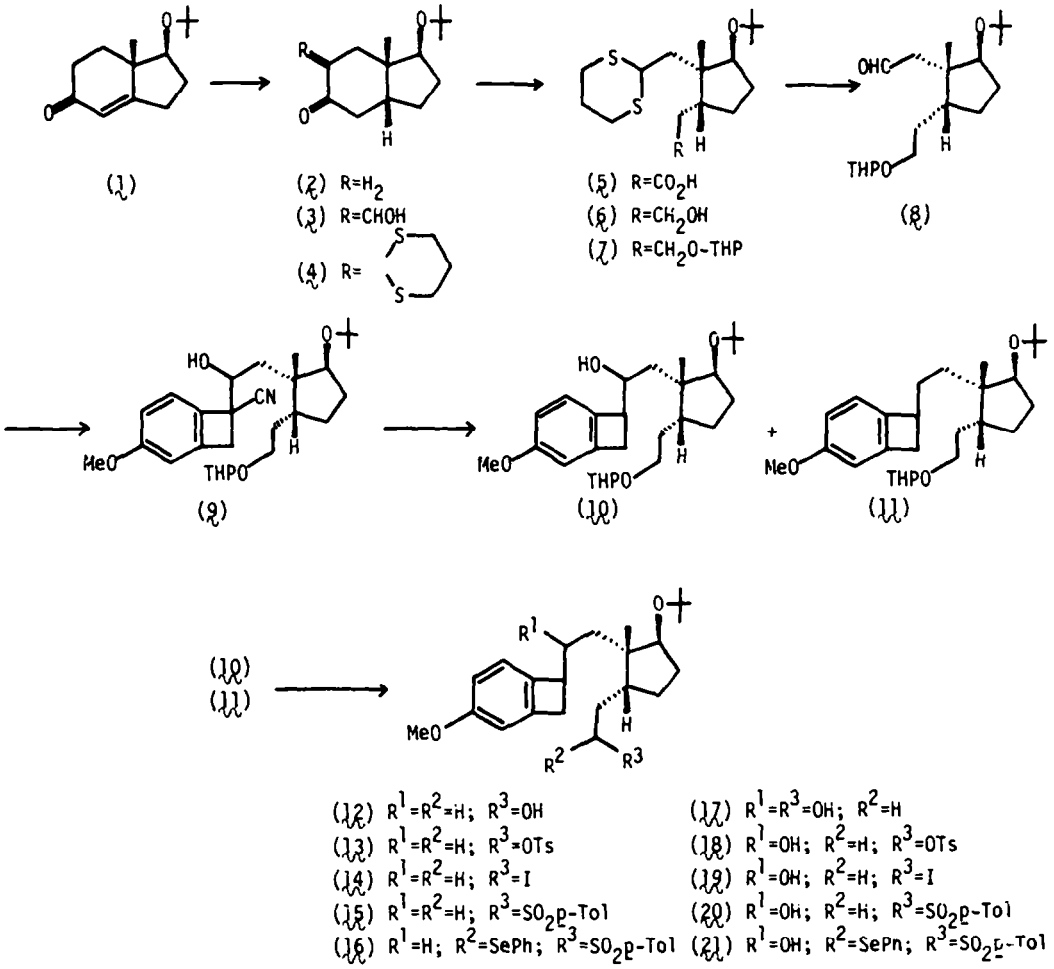
Abstract — The stereoselective synthesis of 3-O-methyl-7α-p-toluenesulphonyl-8α,9α,14β-estradiol(25) and its 11-oxo derivative (26) via thermolysis of 1β-tert-butoxy-2α-[2-(4-methoxybenzocyclobutenyl)ethyl]-2β-methyl-3α-[2-(p-toluenesulphonyl)ethenyl]cyclopentane (22) and its oxo derivative (24), which were derived from condensation product (9) of optically active aldehyde (8) and 1-cyano-4-methoxybenzocyclobutene through 10 and 11 to selenides 16 and 21, is described.

Recent advances in intramolecular cycloaddition of the olefinic o-quinodimethane has proven such reaction to be one of the most efficient methodology for the synthesis of steroids[1]. In connection with our interest[1b] in the synthetic development of cycloaddition starting from o-quinodimethanes based on benzocyclobutenes, we investigated a stereochemical course of the thermolysis of the olefinic benzocyclobutenes (22) and (24) giving rise to the estranes (25) and (26) respectively which could be important intermediates for the synthesis of various types of 7-substituted steroids, since the steroids which have substituents at C-7 position were shown to have biologically important activities[2].

The synthesis of the olefinic benzocyclobutenes (22) and (24) was straightforward and as follows. The cis-indanone (2) prepared by catalytic hydrogenation (H_2, Pd-C, n-hexane) of 1[3] was converted into the keto thioketal (4) through 3 by successive treatment of 2 with ethyl formate in the presence of sodium hydride in benzene followed by propane-1,3-dithiol di-p-toluenesulphonate in the presence of potassium acetate in ethanol. The thioketal (7), which was derived from the keto thioketal (4) via the acid (5) and alcohol (6) by successive treatment with potassium hydroxide in t-butanol, lithium aluminium hydride in tetrahydrofuran, and dihydropyrane in the presence of catalytic amount of p-toluenesulphonic acid in dichloromethane, was hydrolysed with methyl iodide in the presence of sodium carbonate in aqueous acetonitrile to give the optically active aldehyde (8). Condensation of the aldehyde (8) and 1-cyano-4-methoxybenzocyclobutene[4] was effected by sodium amide in liquid ammonia to afford the hydroxy cyano compound (9) as a diastereoisomeric mixture which was reduced under Birch conditions by using sodium in liquid ammonia yielding a mixture of 10 and 11. The tosylate (13), which was obtained from 11 by hydrolysis with 5 % hydrochloric acid in methanol, followed by tosylation of the resulting alcohol (12) with p-toluenesulphonyl chloride in pyridine, was converted into the sulphone (15) via the iodide (14) by successive treatment of 13 with sodium iodide in acetone and sodium p-toluenesulphinate in dimethylformamide. Phenylselenenylation of 15 was carried out with diphenyl diselenide in the presence of lithium diisopropylamide in tetrahydrofuran to give the selenide (16), conversion of which into the olefin (22) was effected by treatment with 30 % hydrogen peroxide in the presence of pyridine in dichloromethane. E-

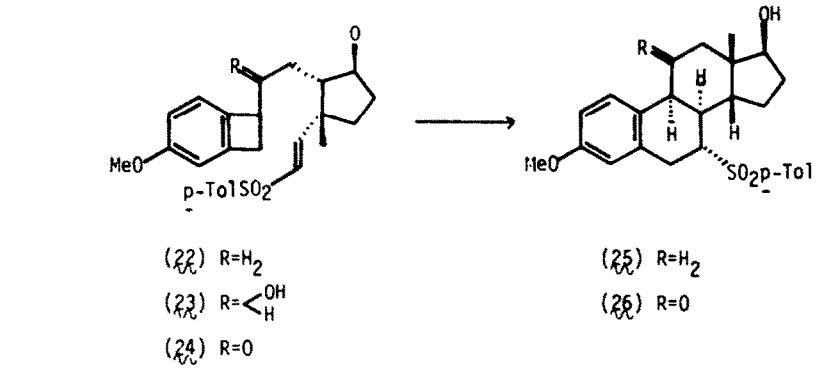
orientation of (22) was apparent from its NMR spectrum in which olefinic protons were observed at 6.0 and 6.25 ppm as a pair of doublets having J value of 14 Hz. The alcohol (10) was also converted into the olefin (23) through (17), (18), (19), (20) and (21) by using the same reaction sequences described for the compound (22) and the olefin (23) thus obtained was transformed into the ketone (24).

Chart 1



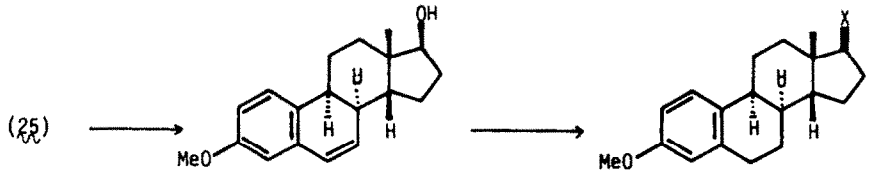
The thermolysis of (22) was conducted in boiling o-dichlorobenzene for 6 hr to give the cis-anti-cis fused estrane (25) as colorless prisms, in 61.6 % yield which was further converted into (29) to confirm its stereochemistry. Namely, the styrene (27) obtained by treatment of (25) with 1,8-diazabicyclo-[5.4.0]-7-undecene was hydrogenated on palladium-carbon to give (28) which on oxidation with Jones reagent, afforded 3-O-methyl-8α,9α,14β-estrone (29) which was found to be superimposable in the comparison of its IR ($CHCl_3$) spectrum with that of authentic sample[5].

Chart 2



(22) R=H2
(23) R=<OH H
(24) R=O

(25) R=H2
(26) R=O



(27)

(28) X=<OH H
(29) X=O

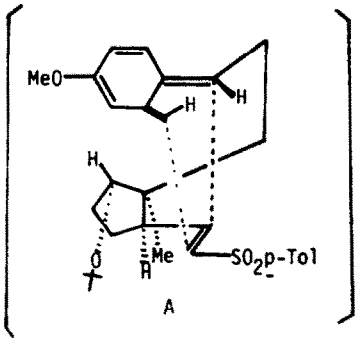


Figure 1

This stereoselectivity of the addition (22 → 25) reflects a transition state with the p-toluenesulphonyl group in the unusual exo orientation (A) releasing the steric repulsion between methyl and t-butoxy groups and o-quinodimethane group, as shown in figure 1. The thermolysis of 24 was also carried out under the same conditions for 22 to give 11-oxoestrane (26)[6]. Thus we could have demonstrated the remarkable effect of p-toluenesulphonyl group attached on olefinic carbon for the stereochemical course of cycloaddition of o-quinodimethanes derived from thermolysis of benzocyclobutenes.

EXPERIMENTAL SECTION

General. All m.p.s were uncorrected. IR spectra were obtained with a Hitachi 215 spectrometer, NMR spectra with a JNM-PMX-60 instrument ($SiMe_4$ as an internal reference), mass spectra with Hitachi M-52G and JMS-01SG-2 spectrometers, and optical rotations with JEOL-DIP-4 spectrometer using $CHCl_3$ as solvent at 20°C.

(+)-(1S,3aR,7aS)-1-tert-Butoxy-3a,4,7,7a-tetrahydro-7a-methyl-5(6H)-indanone (2). A mixture

of (+)-(1S,3aR,7aS)-1-tert-butoxy-7,7a-dihydro-7a-methyl-5(6H)-indanone[3] (1) (10 g), 10 % Pd-C (1 g), and n-hexane (500 ml) was stirred for 2 hr in H_2 at room temp. After filtration of catalyst, the filtrate was evaporated to leave a syrup which was subjected to silica gel (200 g) column chromatography. Evaporation of the n-hexane-benzene (1 : 1 v/v) eluate, followed by crystallization from benzene-n-hexane, gave the indanone 2 (8.21 g, 81.4 %) as colorless prisms, m.p. 59.5 - 60.0°, $[\alpha]_D$ + 45.36° (c = 0.80). (Found: C, 74.79; H, 10.96. $C_{14}H_{24}O_2$ requires C, 74.95; H, 10.78 %); IR $\nu_{max.}$ ($CHCl_3$) 1715 cm^{-1}; NMR (CCl_4) δ 1.05 (3H, s, Me), 1.12 (9H, s, O-CMe_3); MS m/e 224 (M^+).

(+)-(1S,3aR,7aS)-1-tert-Butoxy-3a,4,7,7a-tetrahydro-[6,6-(propane-1,3-dithio)]-7a-methyl-5-indanone (4). To a soln of the indanone 2 (11.342 g) and NaH (60 % in oil)(2.657 g) in anhyd benzene (100 ml) was added a soln of ethyl formate (5.953 g) in anhyd benzene (50 ml) at room temp. After the soln was stirred at room temp for 3 hr, water (100 ml) was added. The resulting aqueous layer was acidified with 10 % H_2SO_4 and extracted with ether. The ethereal layer was washed with anhyd Na_2SO_4. After removal of the solvent, crude formyl derivative 3 (13.236 g) was obtained and used for the next reaction without further purification. Thus, a soln of crude 3 (13.236 g), propane-1,3-dithiol di-p-toluenesulphonate (26.22 g) and KOAc (25.74 g) in abs EtOH (150 ml) was refluxed for 18 hr. After removal of the solvent, water (50 ml) was added and extracted with ether. The organic layer was washed with satd NaCl aq soln and dried over anhyd Na_2SO_4. Evaporation of the solvent afforded the crude product which was chromatographed on silica gel (200 g) using benzene-n-hexane (1 : 1 v/v) for elution to give the keto thioketal 4 (12.975 g, 78.1 % from 2) as a colorless oil; $[\alpha]_D$ + 45.82° (c = 2.03). (Found: C, 61.87; H, 8.67. $C_{17}H_{28}O_2S_2$ requires C, 62.15; H, 8.59 %); IR $\nu_{max.}$ ($CHCl_3$) 1700 cm^{-1}; NMR (CCl_4) δ 1.08 (3H, s, Me), 1.11 (9H, s, O-CMe_3); MS m/e 328 (M^+).

(+)-(1R,2S,3S)-3-tert-Butoxy-2-methyl-2-[2,2-(propane-1,3-dithio)ethyl]cyclopent-1-ylacetic Acid (5). To a stirred soln of the keto thioketal 4 (28.323 g) in t-BuOH (250 ml) was added powdered KOH (14.71 g). The reaction mixture was heated at 60°C for 12 hr. After removal of the solvent, water (150 ml) was added and the aqueous layer was extracted with ether. The organic layer was washed with satd $NaCl_4$ aq soln and dried over anhyd Na_2SO_4. Evaporation of the solvent afforded crude product which was chromatographed on silica gel (500 g) using n-hexane-ether (7 : 3 v/v) for elution to give the acid 5 (27.196 g, 91 %) as a colorless oil, $[\alpha]_D$ + 51.76° (c = 1.19). (Found: C, 57.66; H, 8.48. $C_{17}H_{30}O_3S_2 \cdot 0.3H_2O$ requires C, 58.01; H, 8.76 %); IR $\nu_{max.}$ ($CHCl_3$) 1705 cm^{-1}; NMR (CCl_4) δ 1.03 (3H, s, Me), 1.14 (9H, s, O-CM_3), 11.67 (1H, br s, -CO_2H); MS m/e 346 (M^+).

(+)-(1R,2S,3S)-1-tert-Butoxy-3-(2-hydroxyethyl)-2-methyl-2-[2,2-(propane-1,3-dithio)ethyl]cyclopentane (6). To a stirred suspension of LAH (850 mg) in anhyd THF (40 ml) was added at room temp a soln of the acid 5 (2.683 g) in anhyd THF (70 ml). After the solution was stirred for 6 hr at room temp, 10 % NaOH aq soln (30 ml) was added and the organic layer was separated. The aqueous layer was extracted with ether. The combined organic layer was washed with satd NaCl aq soln and dried over anhyd Na_2SO_4. After removal of the solvent, the resulting crude product was chromatographed on silica gel (80 g) using n-hexane-ether (4 : 1 v/v) for elution to give the thioacetal alcohol 6 (2.357 g, 91.6 %) as a colorless oil, $[\alpha]_D$ + 60.42° (c = 1.13).(Found: C, 61.13; H, 9.71. $C_{17}H_{32}O_2S_2$ requires C, 61.39; H, 9.70 %); IR $\nu_{max.}$ ($CHCl_3$) 3630 cm^{-1}; NMR (CCl_4) δ 0.98 (3H, s, Me), 1.13 (9H, s, O-CMe_3); MS m/e 332 (M^+).

(+)-(1R,2S,3S)-1-tert-Butoxy-2-methyl-2-(2,2-(propane-1,3-dithio)ethyl]cyclopentane (7). A soln of the thioacetal alcohol 6 (1.058 g) and 2,3-dihydropyrane (325 mg) in anhyd CH_2Cl_2 (30 ml) containing catalytic amount of p-toluenesulphonic acid was stirred for 3 hr at room temp. After addition of satd $NaHCO_3$ aq soln (30 ml), the organic phase was separated and the aqueous layer was extracted with CH_2Cl_2. The combined organic phase was washed with satd NaCl aq soln dried over anhyd Na_2SO_4, and evaporated to leave the crude product which was chromatographed on silica gel (30 g) using n-hexane-ether (9 : 1 v/v) as eluent to give the tetrahydropyranyl ether 7 (1.257 g, 94.8 %) as a colorless oil, $[\alpha]_D$ + 46.93° (c = 0.85). (Found: C, 63.21; H, 9.57. $C_{22}H_{40}O_3S_2$ requires C, 63.41; H, 9.68 %); NMR (CCl_4) δ 0.98 (3H, s, Me), 1.15 (9H, s, O-CMe_3), 4.47 (1H, br s, O-CH-O); MS m/e 416 (M^+).

(+)-[(1R,2R,3S)-1-tert-Butoxy-3-(2-tetrahydropyranyloxy)ethyl]-2-methylcyclopent-2-ylacetaldehyde (8). A soln of the tetrahydropyranyl ether 7 (835 mg), CH_3I (2.85 g), and Na_2CO_3 (1.06 g) in water (3 ml) and CH_3CN (15 ml) was stirred for 8 hr at 50°C. After evaporation of CH_3CN, water (30 ml) was added. The aqueous layer was extracted with ether. The organic layer was washed with satd NaCl aq soln, dried over anhyd Na_2SO_4, and evaporated to give the crude product which was chromatographed on silica gel (20 g) using n-hexane-ether (9 : 1 v/v) as eluent to afford the aldehyde 8 (497 mg, 76 %) as a colorless oil, $[\alpha]_D$ + 52.12° (c = 0.66). (Found: C, 68.79; H, 10.35 $C_{19}H_{34}O_4 \cdot 0.3H_2O$ requires C, 68.74; H, 10.51 %); IR $\nu_{max.}$ ($CHCl_3$) 1705 cm^{-1}; NMR (CCl_4) δ 1.08 (3H, s, Me), 1.10 (9H, s, O-CMe_3). 4.49 (1H, br s, O-CH-O), 9.80 (1H, t, J = 3 Hz, CHO); MS m/e 326 (M^+).

1-tert-Butoxy-2-[2-(1-cyano-4-methoxybenzocyclobutenyl)-2-hydroxyethyl]-3-(2-tetrahydropyranyloxy)ethyl-2-methylcyclopentane (9). To a suspension of NaH (60 % in oil) (61 mg) in anhyd DMF (4 ml) was added a soln of 1-cyano-4-methoxybenzocyclobutene[4] (162 mg) in anhyd DMF (6 ml) at room temp. After the soln was stirred for 10 min at room temp, a soln of the aldehyde 8 (166 mg) in anhyd DMF (6 ml) was added dropwise at room temp and stirring was continued for 1 hr at room temp. At this end, the reaction mixture was diluted with satd NH_4Cl aq soln and extracted with ether. The extract was washed with satd NaCl aq soln, dried over anhyd Na_2SO_4, and evaporated to give crude product which was chromatographed on silica gel (7 g) using benzene-EtOAc (95 : 5 v/v) as eluent to afford the hydroxy cyano compound 9 (190 mg, 77 %) as a colorless oil. (Found: C, 71.20; H, 8.76. $C_{29}H_{43}NO_5$ requires C, 71.72; H, 8.93 %); IR $\nu_{max.}$ ($CHCl_3$) 3660, 2225 cm^{-1}; NMR (CCl_4) δ 0.92 and 0.97 (3H, each s, Me), 1.22 (9H, s, O-CMe_3), 3.73 (3H, s, OMe), 6.52 - 7.14 (3H, m, ArH); MS m/e 485 (M^+).

Reduction of Hydroxy Cyano Compound (9). Na (209 mg) was added to a soln of the hydroxy cyano compound 9 (1.1 g) in anhyd NH_3 (100 ml) and anhyd THF (10 ml) at - 78°C. Stirring was continued for 30 min at - 78°C and then NH_4Cl (120 mg) was added to the reaction mixture. After evaporation of NH_3, the residue was diluted with water (30 ml) and extracted with ether. The organic layer was washed with satd NaCl aq soln, dried over anhyd Na_2SO_4, and evaporated to leave a yellow oil which was chromatographed on silica gel (30 g). Evaporation of the n-hexane-benzene-EtOAc (20 : 9 : 1 v/v) eluate afforded the compound 11 (138 mg, 13.7 %) as a colorless oil. (Found: C, 75.29; H, 9.99. $C_{28}H_{44}O_4$ requires C, 75.63; H, 9.97 %); NMR (CCl_4) δ 0.88 (3H, s, Me), 1.10 (9H, s, O-CMe_3), 3.69 (3H, s, OMe), 4.49 (1H, br s, O-CH-O), 6.50 - 7.02 (3H, m, ArH); MS m/e 444 (M^+). Evaporation of the n-hexane-benzene-EtOAc (20 : 8 : 2 v/v) as eluate gave the compound 10 (720 mg, 69 %) as a colorless oil. (Found: C, 71.91; H, 9.93. $C_{28}H_{43}O_5 \cdot 0.3H_2O$ requires C, 72.16; H, 9.43 %); NMR (CCl_4) δ 0.96 (3H, s, Me), 1.15 (9H, s, O-CMe_3), 3.68 (3H, s, OMe), 4.47 (1H, br s, O-CH-O), 6.43 - 7.07 (3H, m, ArH); MS m/e 460 (M^+).

1-tert-Butoxy-3-(2-hydroxyethyl)-2-[2-(4-methoxybenzocyclobutenyl)ethyl]-2-methylcyclopentane (12) and 1-tert-Butoxy-3-(2-hydroxyetnyl)-2-[2-hydroxy-2-(4-methoxybenzocyclobutenyl)ethyl]-2-methylcyclopentane (17). A soln of the tetrahydropyranyl ether 11 (533 mg) in MeOH (12 ml) containing 3 drops of 5 % HCl was stirred for 3 hr at room temp. After addition of satd $NaHCO_3$ soln (30 ml), the resulting mixture was extracted with ether. The extract was washed with satd NaCl aq soln, dried over anhyd Na_2SO_4, and evaporated to leave the crude product which was chromatographed on silica gel (15 g) using n-hexane-benzene-EtOAc (3 : 2 : 1 v/v) as eluent to give the alcohol 12 (406 mg 93.9 %) as a colorless oil. (Found: C, 75.73; H, 10.33. $C_{23}H_{36}O_3 \cdot 0.3H_2O$ requires C, 75.49; H, 10.08 %), IR $\nu_{max.}$ ($CHCl_3$) 3610 cm^{-1}; NMR (CCl_4) δ 0.87 (3H, s, Me), 1.10 (9H, s, O-CMe_3), 3.67 (3H, s, OMe), 6.47 - 7.07 (3H, m, ArH); MS m/e 360 (M^+). By following the same procedure for 12, the alcohol 17 was obtained from 10 in 95.1 % yield as a colorless oil. (Found: C, 72.06; H, 9.36. $C_{23}H_{36}O_4 \cdot 0.3H_2O$ requires C, 72.32; H, 9.66 %); IR $\nu_{max.}$ ($CHCl_3$) 3600 cm^{-1}; NMR (CCl_4) δ 0.94 and 0.97 (3H, each s, Me), 1.19 (9H, s, O-CMe_3), 3.72 (3H, s, OMe), 6.49 - 7.13 (3H, m, ArH); MS m/e 376 (M^+).

1-tert-Butoxy-2-[2-(4-methoxybenzocyclobutenyl)-ethyl]-2-methyl-3-[2-(p-toluenesulphonyloxy)-ethyl]cyclopentane (13) and 1-tert-Butoxy-2-[2-hydroxy-2-(4-methoxybenzocyclobutenyl)ethyl]-2-methyl-3-[2-(p-toluenesulphonyloxy)ethyl]cyclopentane (18). A mixture of the alcohol 12

(530 mg), p-toluenesulphonyl chloride (421 mg), and pyridine (20 ml) was stirred for 4 hr at 0°C and then the reaction mixture was diluted with water (80 ml) and extracted with ether. The organic layer was washed with 10 % HCl and satd NaCl aq soln and dried over anhyd Na_2SO_4. After evaporation of the solvent, the residue was chromatographed on silica gel (15 g) using n-hexane-benzene-EtOAc (19 : 10 : 1 v/v) as eluent to give the tosylate 13 (604 mg, 79.8 %) as a colorless oil. (Found: C, 79.71; H, 8.36. $C_{30}H_{42}O_5S$ requires C, 70.00; H, 8.23 %); NMR (CCl_4) δ 0.83 (3H, s, Me), 2.46 (3H, s, ArMe), 3.72 (3H, s, OMe), 6.49 - 7.08 (3H, m, ArH), 7.28 (2H, d, J = 8 Hz, ArH), 7.77 (2H, d, J = 8 Hz, ArH); MS m/e 514 (M^+). By using the same procedure for 13, the tosylate 18 was prepared from 17 in 91.8 % yield as a colorless oil. (Found: C, 67.67; H, 7.44. $C_{30}H_{42}O_6S$ requires C, 67.88; H, 7.98 %); IR $\nu_{max.}$ ($CHCl_3$) 3680 cm^{-1}; NMR (CCl_4) δ 0.89 (3H, s, Me), 1.13 (9H, s, O-CMe_3), 2.43 (3H, s, ArMe), 3.70 (3H, s, OMe), 6.44 - 7.02 (3H, m, ArH), 7.27 (2H, d, J = 8 Hz, ArH), 7.72 (2H, d, J = 8 Hz, ArH); MS m/e 456 (M^+ - 74).

1-tert-Butoxy-3-(2-iodoethyl)-2-[2-(4-methoxybenzocyclobutenyl)ethy]-2-methylcyclopentane (14) and 1-tert-Butoxy-2-[2-hydroxy-3-(2-iodoethyl)-2-(4-methoxybenzocyclobutenyl)ethyl]-2-methylcyclopentane (19). A mixture of the tosylate 13 (580 mg), NaI (677 mg), and acetone (15 ml) was refluxed for 1.5 hr. After removal of the solvent, water (50 ml) was added and the resulting mixture was extracted with ether. The organic layer was washed with 5 % $Na_2S_2O_3$ aq soln and satd NaCl aq soln and dried over anhyd Na_2SO_4. The crude product obtained by evaporation of the solvent was chromatographed on silica gel (18 g) using n-hexane-benzene-EtOAc (9 : 5 : 1 v/v) as eluent to give the iodide 14 (496 mg, 93.5 %) as a colorless oil. (Found: C, 58.65; H, 7.59. $C_{23}H_{35}O_5I$ requires C, 58.72; H, 7.50 %); NMR (CCl_4) δ 0.90 (3H, s, Me), 1.10 (9H, s, O-CMe_3), 3.75 (3H, s, OMe), 6.58 - 7.22 (3H, m, ArH); MS m/e 470 (M^+). From the same reaction procedure for 14, the iodide 19 was obtained from 18 in 90.4 % yield as a colorless oil. (Found: C, 56.72; H, 6.70. $C_{23}H_{35}O_3I$ requires, C, 56.79; H, 7.25 %); IR $\nu_{max.}$ ($CHCl_3$) 3675 cm^{-1}; NMR (CCl_4) δ 0.97 (3H, s, Me), 1.13 (9H, s, O-CMe_3), 3.68 (3H, s, OMe), 6.48 - 7.07 (3H, m, ArH); MS m/e 486 (M^+).

1-tert-Butoxy-2-[2-(4-methoxybenzocyclobutenyl)ethyl]-2-methyl-3-[2-(p-toluenesulphonyl)-ethyl]cyclopentane (15) and 1-tert-Butoxy-2-[2-hydroxy-2-(4-methoxybenzocyclobutenyl)ethyl]-2-methyl-3-[2-(p-toluenesulphonyl)ethyl]cyclopentane (20). A mixture of the iodide 14 (572 mg), sodium p-toluenesulphinate (700 mg), and anhyd DMF (10 ml) was stirred for 2 hr at 80°C. After evaporation of the solvent, the residue was diluted with water (50 ml) and extracted with ether. The organic layer was washed with satd NaCl aq soln, dried over anhyd Na_2SO_4, and evaporated to leave the crude product which was chromatographed on silica gel (20 g) using n-hexane-benzene-EtOAc (9 : 5 : 1 v/v) as eluent to give the sulphone 15 (570 mg, 94 %) as a colorless oil. (Found: C, 71.25; H, 8.53. $C_{30}H_{42}O_4S \cdot 0.3H_2O$ requires C, 71.47; H, 8.52 %); NMR (CCl_4) δ 0.85 (3H, s, Me), 1.08 (9H, s, O-CMe_3), 2.43 (3H, s, ArMe), 3.71 (3H, s, OMe), 6.52 - 6.98 (3H, m, ArH), 7.27 (2H, d, J = 8 Hz, ArH), 7.83 (2H, d, J = 8 Hz, ArH); MS m/e 498 (M^+). The sulphone 20 was also obtained from 19 in 93.1 % yield as a colorless oil. (Found: C, 69.79; H, 8.31. $C_{30}H_{42}O_5S$ requires C, 70.00; H, 8.23 %); IR $\nu_{max.}$ ($CHCl_3$) 3680 cm^{-1}; NMR (CCl_4) δ 0.92 and 0.93 (3H, each s, Me), 1.12 (9H, s, O-CMe_3), 2.43 (3H, s, ArMe), 3.70 (3H, s, OMe), 6.47 - 7.01 (3H, m, ArH), 7.27 (2H, d, J = 8 Hz, ArH), 7.70 (2H, d, J = 8 Hz, ArH); MS m/e 441 (M^+ - 74).

3-(2-Benzeneselenylethyl)-1-tert-butoxy-2-[2-(4-methoxybenzocyclobutenyl)ethyl]-2-methyl-3-[2-(p-toluenesulphonyl)ethyl]cyclopentane (16) and 3-(2-Benzeneselenylethyl)-1-tert-butoxy-2-[2-hydroxy-2-(4-methoxybenzocyclobutenyl)-ethyl]-2-methyl-3-[2-(p-toluenesulphonyl)ethyl]-cyclopentane (21). To a soln of the sulphone 15 (555 mg) in anhyd THF (12 ml) was added n-BuLi (1.6 mol soln in n-hexane) (1.07 ml) at - 78°C. After stirring for 10 min at the same temp, a soln of diphenyl diselenide (417 mg) in anhyd THF (8 ml) was added and stirring was continued for 1 hr at the same temp. At this end, the reaction mixture was diluted with satd NH_4Cl aq soln and extracted with ether. The ethereal layer was washed with satd NaCl aq soln, dried over anhyd Na_2SO_4, and evaporated to leave the crude product which was chromatographed on silica gel (20 g) using n-hexane-benzene-EtOAc (9 : 5 : 1 v/v) as eluent to give the selenide 16 (389 mg,

53.4 %) as a colorless oil. NMR (CCl_4) δ 0.75 (3H, s, Me), 1.12 (9H, s, O-CMe_3), 2.45 (3H, s, ArMe), 3.83 (3H, s, OMe), 6.52 - 7.03 (3H, m, ArH), 7.08 - 7.62 (7H, m, SeArH and ArH), 7.75 (2H, d, J = 8 Hz, ArH); MS m/e 654 and 652 (M^+). The selenide 21 was also obtained from sulphone 20 in 59.2 % yield as a colorless oil. IR $\nu_{max.}$ ($CHCl_3$) 3680 cm^{-1}; NMR (CCl_4) δ 0.83 (3H, s, Me), 1.14 (9H, s, O-CMe_3), 2.45 (3H, s, ArMe), 3.71 (3H, s, OMe), 6.52 - 6.97 (3H, m, ArH), 7.03 - 7.55 (7H, m, SeArH and ArH), 7.73 (2H, d, J = 8 Hz, ArH); MS m/e 670.2195 (M^+) (Calcd. for $C_{36}H_{46}O_5SSe^{80}$ 670.2230).

1-tert-Butoxy-2[2-(4-methoxybenzocyclobutenyl)-ethyl]-2-methyl-3[2-(p-toluenesulphonyl)ethenyl]-cyclopentane (22) and 1-tert-Butoxy-2-[2-hydroxy-2-(4-methoxybenzocyclobutenyl)ethyl]-2-methyl-3-[2-(p-toluenesulphonyl) ethenyl]cyclopentane (23). To soln of the selenide 16 (193 mg) and pyridine (28 mg) in CH_2Cl_2 (10 ml) was added 30 % H_2O_2 (165 mg) at 0°C and stirred for 20 min. After addition of water (10 ml), the resulting mixture was extracted with CH_2Cl_2. The organic layer was washed with satd NaCl aq soln, dried over anhyd Na_2SO_4, evaporated to leave the crude product which was chromatographed on silica gel (7 g) using n-hexane-benzene-EtOAc (9 : 5 : 1 v/v) as eluent to give the olefin 22 (126 mg, 86.1 %) as a colorless oil. (Found: C, 72.41; H, 8.31. $C_{30}H_{40}O_4S$ requires C, 72.54; H, 8.12 %); NMR (CCl_4) δ 0.89 (3H, s, Me), 1.10 (9H, s, O-CMe_3), 2.38 (3H, s, ArMe), 3.69 (3H, s, OMe) 6.00 (1H, d, J = 14 Hz, olefinic H), 6.25 (1H, d, J = 14 Hz, olefinic H), 6.48 - 7.07 (3H, m, ArH), 7.18 (2H, d, J = 8 Hz, ArH), 7.65 (2H, d, J = 8 Hz, ArH); MS m/e 496 (M^+). By following the same procedure for 22, the olefin 23 was also obtained from 21 in 90.1 % yield as a colorless oil. NMR (CCl_4) δ 0.93 and 0.99 (3H, each s, Me), 1.10 (9H, s, O-CMe_3), 2.35 (3H, s, ArMe), 3.67 (3H, s, OMe), 5.95 (1H, d, J = 14 Hz, olefinic H), 6.22 (1H, d, J = 14 Hz, olefinic H), 6.42 - 7.02 (3H, m, ArH), 7.17 (2H, d, J = 8 Hz, ArH), 7.68 (2H, d, J = 8 Hz, ArH); MS m/e 512.2565 (M^+) (Calcd. for $C_{30}H_{40}O_5S$ 512.2595).

1-tert-Butoxy-2-[2-(4-methoxybenzocyclobutenyl)-2-oxo-ethyl]-2-methyl-3-[2-(p-toluenesulphonyl)-cyclopentane (24). To a soln of the olefin 23 (115 mg) in acetone (8 ml) was added Jones reagent (4 drops) at 0°C.

The reaction mixture was stirred for 10 min, diluted with water (12 ml) and extracted with ether. The organic layer was washed with satd NaCl aq soln, dried over anhyd Na_2SO_4, and evaporated to give the crude product which was chromatographed on silica gel (10 g) using n-hexane-benzene-EtOAc (9 : 5 : 1 v/v) as eluent to afford the keto olefin 24 (110 mg, 96 %) as a colorless oil. IR $\nu_{max.}$ ($CHCl_3$) 1710 cm^{-1}; NMR (CCl_4) δ 0.93 and 0.98 (3H, each s, Me), 1.10 (9H, s, O-CMe_3), 2.37 (3H, s, ArMe), 3.70 (3H, s, OMe), 6.02 (1H, d, J = 14 Hz, olefinic H), 6.27 (1H, d, J = 14 Hz, olefinic H), 6.47 - 7.06 (3H, m, ArH), 7.17 (2H, d, J = 8 Hz, ArH), 7.63 (2H, d, J = 8 Hz, ArH); MS m/e 510.2476 (M^+) (Calcd. for $C_{30}H_{38}O_5S$ 510.2440).

3-O-Methyl-7 -p-toluenesulphonyl-8α,9α,14β-estradiol (25) and 3-O-Methyl-11-oxo-7-p-toluenesulphonyl-8α,9α,14β-estradiol (26). A soln of the olefin 22 (135 mg) in o-dichlorobenzene (10 ml) was stirred for 6 hr at 195°C in a current of N_2. After evaporation of the solvent, the residue was subjected to chromatography on silica gel (5 g). Evaporation of n-hexane-benzene-EtOAc (17 : 10 : 3 v/v) as eluate left a colorless oil which on crystallization from EtOH afforded the compound 25 (73.8 mg, 61.6 %) as colorless prisms, m.p. 146 - 147°C, $[\alpha]_D$ + 18.47° (c = 0.31). (Found: C, 70.42; H, 7.54. $C_{26}H_{32}O_4S$ requires C, 70.87; H, 7.32 %); IR $\nu_{max.}$ ($CHCl_3$) 3610 cm^{-1}; NMR ($CDCl_3$) δ 1.00 (3H, s, Me), 2.38 (3H, s, ArMe), 3.73 (3H, s, OMe), 6.37 - 7.88 (7H, m, ArH); MS m/e 440 (M^+). The compound 26 was also obtained from the keto olefin 24 in 36.7 % yield as a colorless oil by following the same procudure for 25 described above. The compound 26, $[\alpha]_D$ + 76.25° (c = 0.16); IR $\nu_{max.}$ ($CHCl_3$) 3610 and 1710 cm^{-1}; NMR ($CDCl_3$) δ 0.85 (3H, s, Me), 2.41 (3H, s, ArMe), 3.69 (3H, s, OMe), 6.33 - 7.17 (3H, m, ArH), 7.28 (2H, d, J = 8 Hz, ArH), 7.72 (2H, d, J = 8 Hz, ArH); MS m/e 454.1775 (M^+) (Calcd. for $C_{26}H_{30}O_5S$ 454.1812).

3-O-Methyl-$\Delta^{6(7)}$-8α,9α,14β-estradiol (27). A soln of the sulphone 25 (27 mg) in DBU (7 ml) was stirred for 12 hr at 130°C and the reaction mixture was diluted with water (10 ml) and then extracted with EtOAc. The organic layer was washed with satd NaCl aq soln, dried over anhyd Na_2SO_4, and evaporated to leave the crude product which was chromatographed on silica gel (5 g). Evaporation of benzene-n-hexane-EtOAc (80 : 17 : 3 v/v) eluate afforded the styrene 27 (14 mg, 58.6 %) as a colorless oil. $[\alpha]_D$ + 100.0° (c = 0.14); NMR ($CDCl_3$) δ 1.09 (3H, s, Me), 3.77

(3H, s, OMe), 5.57 - 6.47 (2H, m, olefinic H), 3-O-Methyl-8α,9α,14β-estradiol (28). A mixture of 27 (12 mg), 10 % Pd-C (15 mg), and acetone (6 ml) was stirred in H_2 at room temp. After filtration of the catalyst, the filtrate was evaporated to leave the crude product which was chromatographed on silica gel (5 g) using benzene-n-hexane-EtOAc (16 : 20 : 1 v/v) as eluent to give 28 (11.9 mg, 98.5 %) as a colorless oil. $[\alpha]_D$ - 12.2° (c = 0.164); NMR ($CDCl_3$) δ 1.10 (3H, s, Me), 3.75 (3H, s, OMe), 6.60 - 7.17 (3H, m, ArH); MS m/e 286 (M^+). 3-O-Methyl-8α,9α,14β-estrone (29). To a solution of 28 (6.4 mg) in acetone (2 ml) was added Jones reagent (1 drop) at 0°C and stirred for 10 min. After dilution with water (10 ml), the reaction mixture was extracted with EtOAc. The organic layer was washed with satd NaCl aq soln, dried over anhyd Na_2SO_4, and evaporated to leave the drude product which was chromatographed on silica gel (3 g). Evaporation of benzene-n-hexane-EtOAc (20 : 20 : 1 v/v) eluate afforded a colorless oil which was crystallized from MeOH to give the compound (29) as colorless prisms, m.p. 104 - 105°. IR $\nu_{max.}$ ($CHCl_3$) 1725 cm^{-1}; NMR ($CDCl_3$) δ 1.12 (3H, s, Me), 3.72 (3H, s, OMe), 6.50 - 7.37 (3H, m, ArH); MS m/e 284 (M^+).

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6. Although the stereochemistry of this compound could not be determined, we have tentatively assigned its stereochemistry as shown in Chart 2.