A Novel Stereoselective Access to Des-*A B*-Aromatic Corticosteroids *via* Intramolecular Cycloaddition Reaction — Potential Intermediates for the Synthesis of Corticosteroids †

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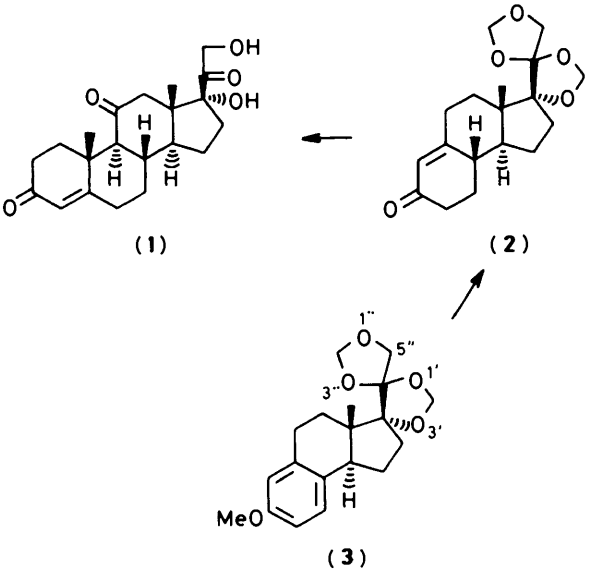
A short and stereoselective synthesis of protected des-*A B*-aromatic corticosteroids (**3**) and (**23**) *via trans*-2,3,3a,4,5,9b-hexahydro-3β-isopropenyl-7-methoxy-3aβ-methyl-1H-benz[*e*]inden-3α-ol (**13**) and its methoxymethyl ether derivative (**20**), which were prepared by thermolysis of 3-[2-(1,2-dihydro-4-methoxybenzocyclobuten-1-yl)ethyl]-2,4-dimethylpenta-1,4-dien-3-ol (**11**) and its methoxymethyl ether (**19**), respectively, is described.

Because of their clinical importance, the chemistry of corticosteroids has been well studied.[1] Recent activity in this field has resulted in efficient methods for introducing dihydroxyacetone[2] and oxygen substituents[3] at C-17 and C-11 of steroidal compounds, respectively; such functionalities are important for steroidal physiological activity. In the course of our studies[4] directed toward the total synthesis of steroids by means of intramolecular cycloaddition reactions, we have been interested in the total synthesis of des-*A B*-aromatic steroids because of the potential synthetic flexibilities in constructing the *A*-ring and in introducing functional groups at C-9 and C-11. We have succeeded[5] in achieving a stereoselective synthesis of des-*A B*-aromatic steroids having a *trans*-hydrindane(hexahydroindan) moiety, whose construction had been otherwise difficult and which had provided one of the main unresolved problems[3c-e,g,6] in the total synthesis of steroids. Once we were able to synthesize des-*A B*-aromatic steroids in a stereoselective manner, we planned a total synthesis of cortiocosteroids, and those for our target molecule cortisone (**1**), which we believed could be prepared from the tricyclic compound (**3**) *via* the bismethylenedioxy derivative (**2**) as shown in Scheme 1. Here we report a stereoselective and efficient synthesis of the des-*A B*-aromatic steroid (**3**) having a suitable substituent at C-17 position (steroid numbering) for generating the dihydroxyacetone moiety in cortisone (**1**).



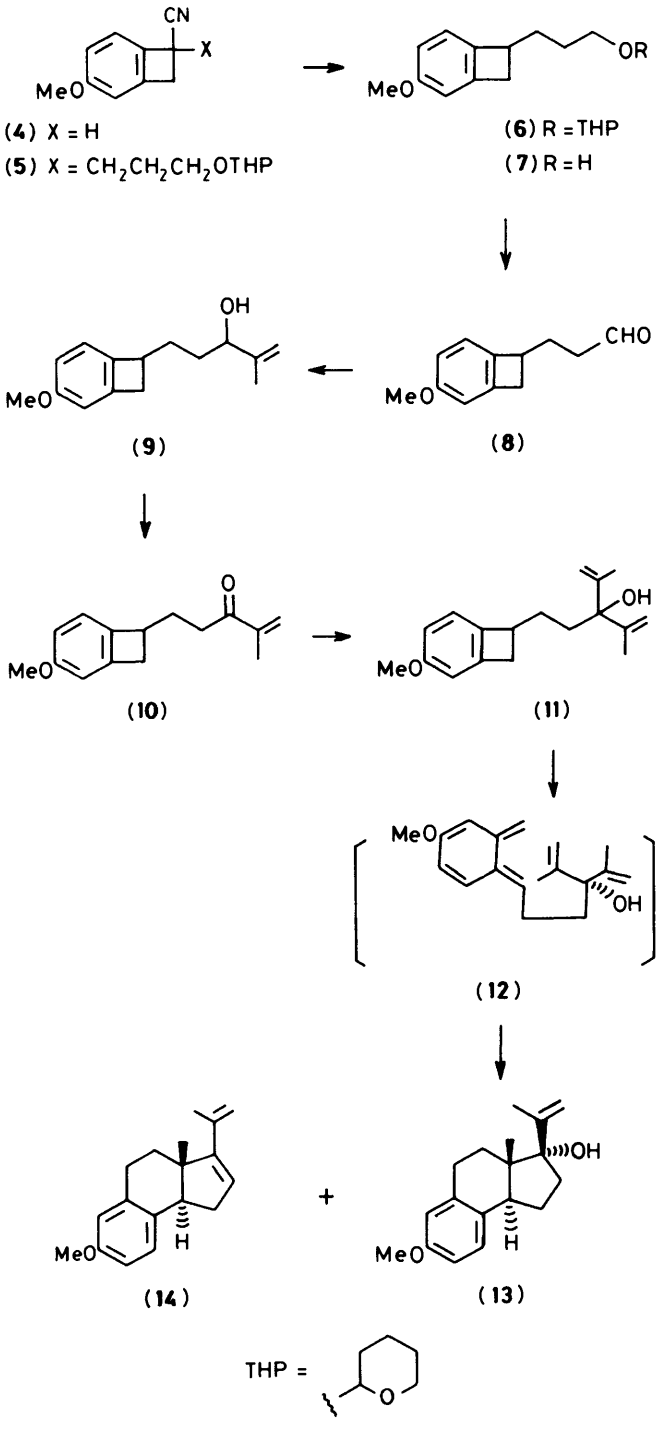
Scheme 1.

First, we developed an efficient route to the known aldehyde (**8**).[5a] Thus, the tetrahydropyranyl ether[7] derived from 3-bromopropan-1-ol was condensed with the 1-cyano-4-methoxybenzocyclobutene (**4**)[8] in the presence of lithium diisopropylamide (LDA) in tetrahydrofuran (THF), affording the alkylated 1-cyanobenzocyclobutene (**5**) in 95% yield. Reductive decyanation of compound (**5**) with sodium in liquid ammonia, followed by cleavage of the tetrahydropyranyl group of the resulting compound (**6**) with 10% hydrochloric acid in methanol, gave the alcohol (**7**) in 96% overall yield from the alkylated compound (**5**). This alcohol (**7**) was then oxidized with pyridinium chlorochromate (PCC) in methylene dichloride to furnish the aldehyde (**8**) in 96% yield. Next, the isopropenylated alcohol (**9**), which was prepared from the aldehyde (**8**) by the known procedure,[5a] was oxidized with PCC in CH_2Cl_2 to give the enone (**10**) [*m/z* 230 (M^+)] in 94% yield. The enone (**10**) was then treated with isopropenyl-lithium[9] to give the di-isopropenyl alcohol (**11**) [*m/z* 272 (M^+)] in 92% yield. Thermolysis of the alcohol (**11**) was conducted in boiling *o*-dichlorobenzene to afford the tricyclic compound (**13**)‡ [*m/z* 272 (M^+)] along with the dehydrated compound (**14**) [*m/z* 254 (M^+)] in 60 and 30% yield, respectively (Scheme 2). The stereoselectivity in the thermolysis of the di-isopropenyl alcohol (**11**) can best be explained by the intervention of the most sterically favoured olefinic *o*-quinodimethane (**12**).

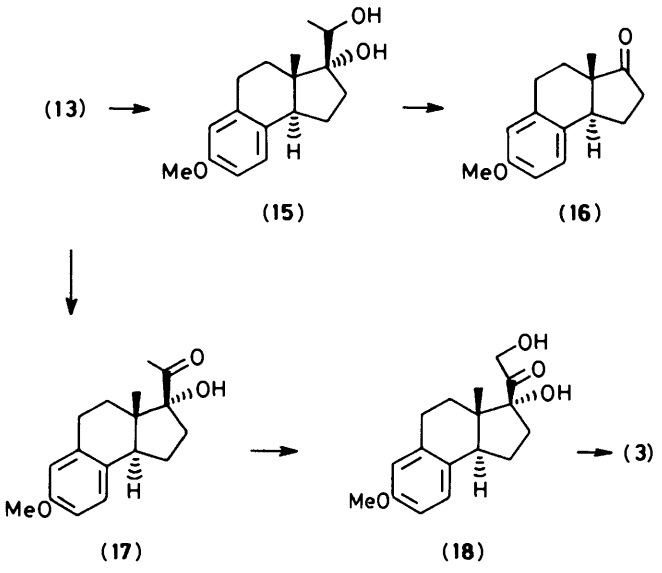
At this stage, the isopropenyl compound (**13**) was converted into the hexahydroindanone (**16**) *via* the diol (**15**) by treatment with ozone, followed by sodium borohydride and then oxidative cleavage with lead tetra-acetate. The hexahydroindanone (**16**) thus obtained was identical with an authentic sample,[5a] showing that the ring junction of the hexahydroindanone (**16**) was *trans*. The angular methyl group of the hexahydroindanone (**16**) resonated at δ 0.70 in its ^{1}H n.m.r. ($CDCl_3$) spectrum, suggesting that the angular methyl and hydroxy groups in compound (**13**) are *trans*; *i.e.* the angular methyl and isopropenyl group are *cis*. These assignments were confirmed later. Next, the isopropenyl compound (**13**) was subjected to ozonolysis in CH_2Cl_2–methanol to yield the hydroxy ketone (**17**) [*m/z* 274 (M^+)] in 76% yield. The dihydroxy ketone (**18**) [*m/z* 290 (M^+)], obtained in 47% yield by oxidation[10]

† A preliminary communication of part of this work appeared in *J. Chem. Soc., Chem. Commun.*, 1985, 1316.

‡ All compounds reported in this paper are racemic. For convenience, only one enantiomer is shown.



Scheme 2.

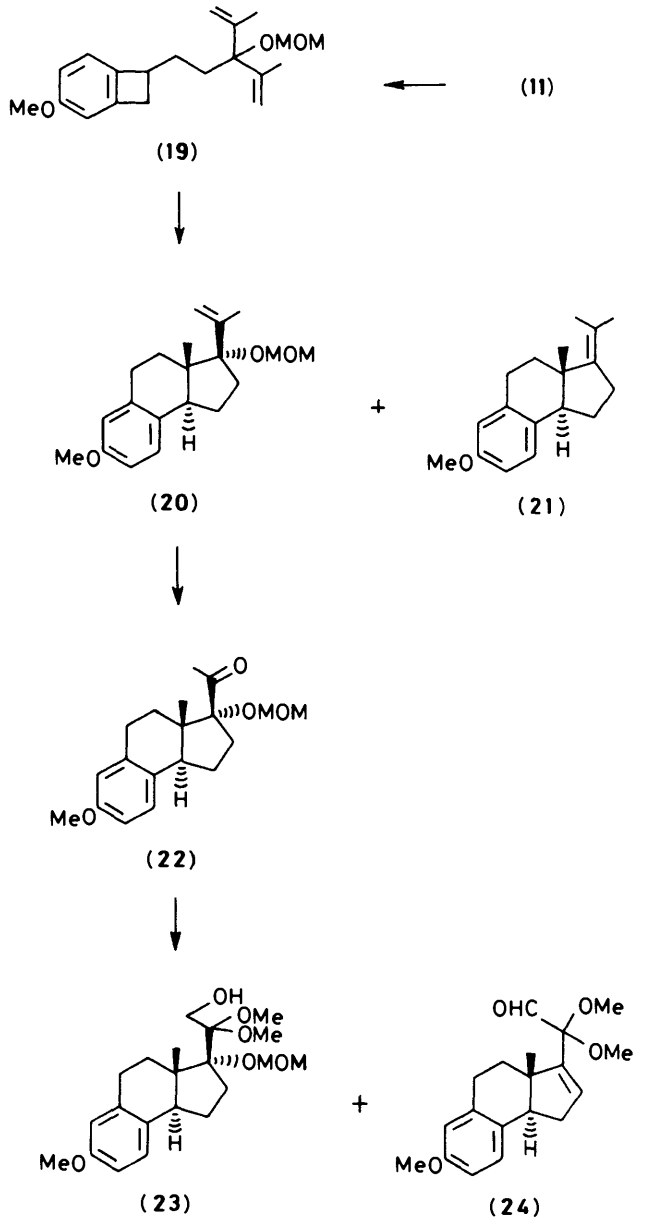


Scheme 3.

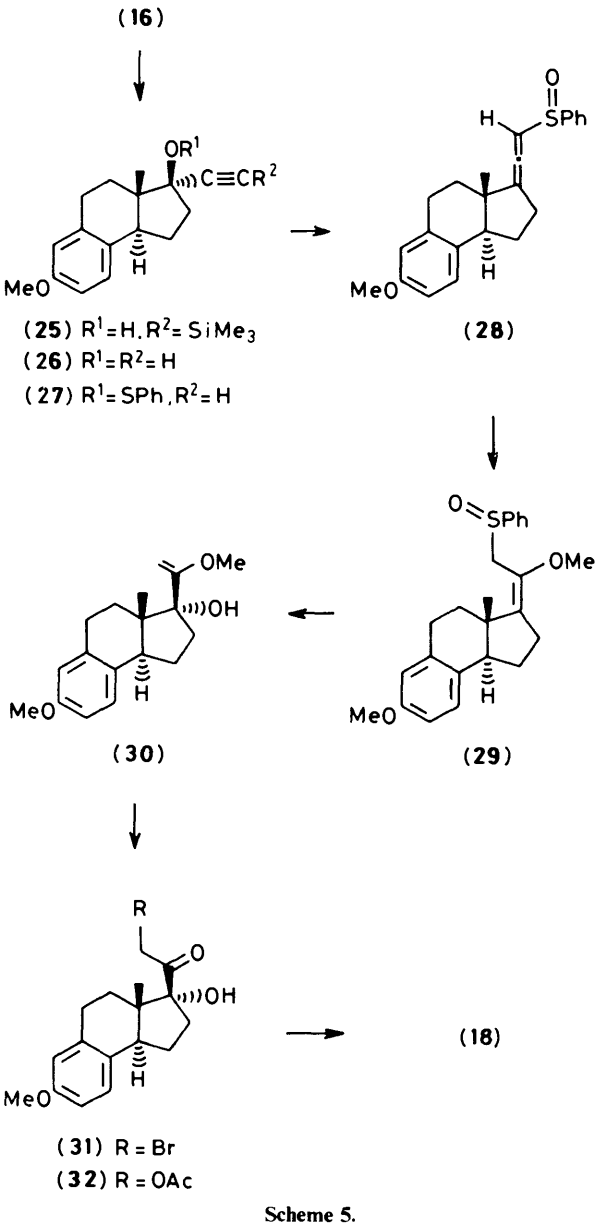
of the hydroxy ketone (**17**) with molybdenum pentaoxide–hexamethylphosphoramide (HMPA)–pyridine complex in the presence of LDA in THF, was protected with formalin in the presence of conc. hydrochloric acid in CH_2Cl_2 to furnish the initial target compound (**3**) [*m/z* 332 (M^+)] in 26% yield (Scheme 3).

Although we could develop a novel route to des-*A B*-aromatic steroid (**3**), the cycloaddition step, which was the key step in this synthesis, did not proceed in satisfactory yield. Therefore we undertook a synthesis of des-*A B*-aromatic steroid (**23**), which has a suitably protected dihydroxyacetone group at C-17, by a different route. Thus, the methoxymethyl ether (**19**) of the di-isopropenyl alcohol (**11**) [*m/z* 272 (M^+)], prepared by treatment of the compound (**11**) with methoxymethyl chloride (MOMCl) in the presence of Hünig's base (Pr^i_2EtN) and dimethylaminopyridine (DMAP) was subjected to thermolysis to give the tricyclic methoxymethyl ether (**20**) [*m/z* 316 (M^+)] and the retroene product (**21**) [*m/z* 256 (M^+)] in 82 and 16% yield respectively. Compound (**20**) thus obtained was identical with a sample prepared by the methoxymethylation of the isopropenyl compound (**13**). The ketone (**22**) [*m/z* 318 (M^+)], obtained by Lemieux–Johnson oxidation of the methoxymethyl ether (**20**) in 99% yield, was then oxidized[11] with iodosylbenzene in the presence of potassium hydroxide in methanol to afford the protected dihydroxyacetone derivative (**23**) [*m/z* 380 (M^+)] and the aldehyde (**24**) [*m/z* 316 (M^+)] in 17 and 14% yield, respectively (Scheme 4). In this synthesis, the cycloaddition process (**19**) ⟶ (**20**) proceeded in higher yield than that of the corresponding hydroxy compound (**11**) ⟶ (**13**), and the overall yield leading to the protected dihydroxyacetone derivative (**23**) was also better than that of the bismethylenedioxy derivative (**3**).

Although the ring junction of the cycloaddition product (**13**) was confirmed as being *trans* by comparing the derived tricyclic ketone (**16**), which was derived from the isopropenyl compound (**13**), with an authentic sample, the stereochemistry about C-17 was not determined unambiguously. We therefore undertook an alternative synthesis of the dihydroxy ketone (**18**) starting from the tricyclic ketone (**16**) by following Shephard's procedures.[2b] Thus, the tricyclic ketone (**16**) was treated with lithium trimethylsilylacetylide and the resulting acetylide (**25**) was deprotected with tetra-n-butylammonium fluoride in THF to give the alcohol (**26**) [*m/z* 256 (M^+)] in 87% overall yield from (**16**). The acetylenic alcohol (**26**) was then subjected to the sulphinate–sulphoxide rearrangement with benzenesulphenyl chloride in the presence of triethylamine in CH_2Cl_2 *via* the sulphinate (**27**) to afford the allene sulphoxide (**28**) in 56% overall yield from (**26**). The enol ether (**29**), obtained by the addition of methoxide ion to the allene sulphoxide (**28**), was subjected to a sulphoxide–sulphinate rearrangement in the presence of trimethyl phosphite as a thiophile to give the hydroxy enol ether (**30**), which was directly brominated with pyridinium perbromide in carbon tetrachloride to afford the hydroxy bromo ketone (**31**) in 52% overall yield based on the allene sulphoxide (**28**). Finally the hydroxy acetoxy ketone (**32**), prepared by the acetoxylation of the hydroxy bromo ketone



Scheme 4.



Scheme 5.

(**31**) with potassium acetate in the presence of potassium iodide in acetic acid, was hydrolysed with lithium hydroxide in aqueous methanol to furnish the dihydroxy ketone (**18**) in 40% overall yield from the hydroxy bromo ketone (**31**) (Scheme 5). The dihydroxy ketone (**18**) thus obtained was identical with the sample prepared previously from the isopropenyl compound (**13**) *via* the hydroxy ketone (**17**), showing that the stereochemistry about C-17 was that shown in Scheme 3.

Thus, we have achieved an efficient route to des-*A B*-aromatic steroids which could be potential intermediates in the synthesis of corticosteroids.

Experimental

General Methods.—All m.p.s were measured on a Yanaco micromelting apparatus and are uncorrected. I.r. spectra were recorded for $CHCl_3$ solutions on a Hitachi 260-10 spectrophotometer. ^1H N.m.r. spectra were measured for $CDCl_3$ solutions (unless otherwise indicated) on a JEOL-PMX-60 or a JEOL-PS-100 spectrometer. Chemical shifts are reported as δ values relative to internal tetramethylsilane (Me_4Si). Mass spectra were taken on a Hitachi M-52G or a JEOL-JMX-01SG-2 spectrometer.

1,2-*Dihydro*-4-*methoxy*-1-[3-(*tetrahydropyran*-2-*yloxy*)*propyl*]*benzocyclobutene*-1-*carbonitrile* (**5**).—To a stirred solution of LDA [prepared from n-butyl-lithium (1.56M solution in hexane; 2.2 ml) and di-isopropylamine (0.53 ml, 3.77 mmol)] in THF (10 ml) at −78 °C was added dropwise a solution of 1,2-dihydro-4-methoxybenzocyclobutene-1-carbonitrile (**4**)[8] (0.5 g, 3.1 mmol) in THF (10 ml). After 10 min, a solution of 3-bromopropyl tetrahydropyranyl ether (0.77 g, 3.5 mmol) in THF (5 ml) was added to the stirred solution, and the reaction mixture was stirred for a further 45 min at the same temperature before being treated with saturated aqueous ammonium chloride and extracted with ether. The extract was washed with saturated aqueous sodium chloride and dried (Na_2SO_4). Removal of the solvent left a residue, which was chromatographed on silica gel (10g) with n-hexane–ethyl acetate (4:1 v/v) as eluant to afford the *alkylated compound* (**5**) (0.89 g, 95%)

as an oil (Found: C, 71.65; H, 7.8; N, 4.45. $C_{18}H_{23}NO_3$ requires C, 71.75; H, 7.7; N, 4.65%); $\nu_{max.}$ 2 240 cm^{-1} (CN); δ 3.73 (3 H, s, OMe), 4.50 (1 H, br s, OCHO), and 6.67—7.23 (3 H, m, ArH); *m/z* 301 (M^+).

3-(1,2-*Dihydro*-4-*methoxybenzocyclobuten*-1-*yl*)*propan*-1-*ol* (**7**).—To a stirred solution of the alkyl derivative (**5**) (0.68 g, 2.26 mmol) in a mixture of absolute ethanol (0.22 ml), THF (5 ml), and liquid ammonia (33 ml) at −78 °C was added sodium (0.1 g, 4.5 mmol) and the solution was stirred for 30 min at the same temperature. After addition of an excess of crystalline ammonium chloride, followed by evaporation of the solvent, the residue was diluted with saturated aqueous ammonium chloride and extracted with ether. The extract was washed with saturated aqueous sodium chloride and dried (Na_2SO_4). Evaporation of the solvent afforded the pyranyl ether (**6**) as a reddish gum.

A mixture of this crude product (**6**), methanol (25 ml), and 10% hydrochloric acid (1.3 ml) was stirred for 4 h at room temperature. After evaporation of the solvent, water was added to the residue and the resulting solution was extracted with ether. The extract was washed with saturated aqueous sodium chloride and dried (Na_2SO_4). Removal of the solvent gave a yellow oil, which was chromatographed on silica gel (10 g) with n-hexane–ethyl acetate (4:1 v/v) as eluant to afford the *propanol* (**7**) (0.18 g, 42%) as an oil (Found: C, 74.6; H, 8.4. $C_{12}H_{16}O_2$ requires C, 74.95; H, 8.4%); $\nu_{max.}$ 3 500 cm^{-1} (OH); δ 3.78 (3 H, s, OMe) and 6.64—7.70 (3 H, m, ArH); *m/z* 192 (M^+).

3-(1,2-*Dihydro*-4-*methoxybenzocyclobuten*-1-*yl*)*propanal* (**8**).—A mixture of the alcohol (**7**) (10 g, 52 mmol), PCC (33.7 g, 268 mmol), Florisil (17 g), and methylene dichlororide (200 ml) was stirred for 2 h at room temperature and then filtered through Celite. The filtrate was washed successively with saturated aqueous sodium chloride, aqueous sodium hydrogen carbonate, and aqueous sodium chloride, and dried (Na_2SO_4). Removal of the solvent left a residue, which was chromatographed on silica gel (200 g) with n-hexane–ethyl acetate (9:1 v/v) as eluant to give the aldehyde (**8**), (8 g, 81%) as an oil, identical with an authentic sample [5a] on comparison of i.r. and n.m.r. spectra.

5-(1,2-*Dihydro*-4-*methoxybenzocyclobuten*-1-*yl*)-2-*methylpent*-1-*en*-3-*one* (**10**).—A mixture of the alcohol (**9**) [5a] (200 mg, 0.8 mmol), PCC (370 mg, 1.7 mmol), Florisil (150 mg), and methylene dichloride (5 ml) was stirred for 1 h at room temperature. The reaction mixture was diluted with ether (50 ml) and filtered through Celite. The filtrate was washed successively with saturated aqueous sodium hydrogen carbonate and aqueous sodium chloride, and dried (Na_2SO_4). Removal of the solvent left a residue, which was chromatographed on silica gel (5 g) with n-hexane–ethyl acetate (95:5 v/v) as eluant to give the *ketone* (**10**) (187 mg, 94%) as an oil (Found: C, 77.85; H, 7.95. $C_{15}H_{18}O_2$ requires C, 78.25; H, 7.9%); $\nu_{max.}$ 1 670 cm^{-1} (CO); δ 1.81 (3 H, s, 2-Me), 3.66 (3 H, s, OMe), 5.66 and 5.94 (each 1 H, br s, C=CH_2), and 6.58—7.00 (3 H, m, ArH); *m/z* 230 (M^+).

3-[2-(1,2-*Dihydro*-4-*methoxybenzocyclobuten*-1-*yl*)*ethyl*]-2,4-*dimethylpenta*-1,4-*dien*-3-*ol* (**11**).—To a stirred solution of isopropenyl bromide (3.9 g, 31 mmol) in THF (300 ml) at −78 °C was added dropwise a 1.6M solution of t-butyl-lithium (40 ml; 64 mmol) in n-hexane. After the mixture had been stirred for 1 h at the same temperature, a solution of the ketone (**10**) (5.56 g, 24 mmol) in THF (150 ml) was added to this solution and the mixture was stirred for a further 30 min before being treated with saturated aqueous sodium chloride and extracted with ether. The extract was washed with saturated aqueous sodium chloride and dried (Na_2SO_4). Removal of the solvent gave a residue, which was chromatographed on silica gel (100 g) with n-hexane–ethyl acetate (98:2 v/v) as eluant to afford the *alcohol* (**11**) (6.12 g, 92%) as an oil, $\nu_{max.}$ 3 590 cm^{-1} (OH); δ 1.63 (6 H, s, 2 × CMe), 3.70 (3 H, s, OMe), 4.97 and 5.08 (each 2 H, br s, 2 × C=CH_2), and 6.57—7.03 (3 H, m, ArH); *m/z* 272 (M^+) (Found: M^+, 272.1776. $C_{18}H_{24}O_2$ requires *M*, 272.1775).

Thermolysis of the Alcohol (**11**).—A solution of the alcohol (**11**) (112 mg, 0.4 mmol) in *o*-dichlorobenzene (5 ml) was refluxed for 40 h. The residue obtained after evaporation of the solvent was chromatographed on silica gel (5 g) with n-hexane–ethyl acetate (98:2 v/v) as eluant. From the first fraction, trans-3a,4,5,9b-*tetrahydro*-3-*isopropenyl*-7-*methoxy*-3-aβ-*methyl*-1H-*benz*[e]*indene* (**14**) (31.3 mg, 30%) was obtained as an oil, δ (CCl_4) 0.50 (3 H, s, CMe), 1.73 (3 H, s, CMe), 3.65 (3 H, s, OMe), 4.75 and 4.93 (each 1 H, each br s, C=CH_2), 5.66 (1 H, t, *J* 2 Hz, 2-H), and 6.30—6.90 (3 H, m, ArH); *m/z* 254 (M^+) (Found: M^+, 254.1686. $C_{18}H_{22}O$ requires *M*, 254.1670).

From the second fraction, trans-2,3,3a,4,5,9b-*hexahydro*-3β-*isopropenyl*-7-*methoxy*-3aβ-*methyl*-1H-*benz*[e]*inden*-3α-*ol* (**13**) (51.7 mg, 60%) was obtained as a glass, $\nu_{max.}$ 3 580 cm^{-1} (OH); δ 0.45 (3 H, s, 3a-Me), 1.78 (3 H, s, CMe), 3.64 (3 H, s, OMe), 4.94 and 5.01 (each 1 H, m, C=CH_2), and 6.50—7.00 (3 H, m, ArH); *m/z* 272 (M^+) (Found: M^+, 272.1757. $C_{18}H_{24}O_2$ requires *M*, 272.1775).

trans-2,3,3a,4,5,9b-*Hexahydro*-3β-(1-*hydroxyethyl*)-7-*methoxy*-3aβ-*methyl*-1H-*benz*[e]*inden*-3α-*ol* (**15**).—Ozone was bubbled into a solution of the isopropenyl compound (**13**) (135 mg, 50 mmol) in methanol–methylene dichloride (2:1 v/v; 13.5 ml) at −78 °C for 3 min, and then sodium borohydride (43.6 mg, 1.2 mmol) was added at the same temperature. After the mixture had been stirred for 45 min at room temperature, the solvent was evaporated off to leave a residue, which was dissolved in chloroform. The solution was washed with saturated aqueous sodium chloride and dried ($MgSO_4$). Removal of the solvent afforded a crude product, which was chromatographed on silica gel (5 g) with n-hexane–ethyl acetate (4:1 v/v) as eluant to give the *diol* (**15**) (58.6 mg, 43%) as needles, m.p. 161—162 °C (from Et_2O); $\nu_{max.}$ 3 550 cm^{-1}; δ 0.60 (3 H, s, 3a-Me), 3.69 (3 H, s, OMe), and 6.60—7.00 (3 H, m, ArH); *m/z* 276 (M^+) (Found: M^+, 276.1707. $C_{17}H_{24}O_3$ requires *M*, 276.1724).

trans-1,2,3a,4,5,9b-*Hexahydro*-7-*methoxy*-3aβ-*methylbenz*[e]*inden*-3-*one* (**16**).—A mixture of the diol (**15**) (30 mg, 0.1 mmol), pyridine (0.5 ml), lead tetra-acetate (164 mg, 0.34 mmol), and benzene (8 ml) was stirred for 2 h at room temperature. The reaction mixture was treated with water and extracted with ether. The extract was washed with saturated aqueous sodium chloride and dried ($MgSO_4$). The residue obtained on evaporation of the solvent was chromatographed on silica gel (1 g) with n-hexane–ethyl acetate (95:5 v/v) as eluant to give the ketone (**16**) (14.6 mg, 93%) as needles, m.p. 74—75 °C (from n-hexane), identical with an authentic sample [5a] (i.r., and n.m.r., and mixed m.p.).

trans-2,3,3a,4,5,9b-*Hexahydro*-3α-*hydroxy*-7-*methoxy*-3aβ-*methyl*-1H-*benz*[e]*inden*-3β-*yl Methyl Ketone* (**17**).—Ozone was bubbled into a stirred solution of the isopropenyl compound (**13**) (500 mg, 1.8 mmol) in methylene dichloride–methanol (1:2 v/v; 25 ml) at −78 °C for 4.5 min, and then dimethyl sulphide (708 gm, 11.4 mmol) was added at the same temperature. After the mixture had been stirred for 30 min, evaporation of the solvent afforded a residue, which was dissolved in ether. The solution was washed with saturated aqueous sodium chloride solution and dried (Na_2SO_4). Evaporation of the solvent gave a crude product, which was chromatographed on silica gel (10 g) with n-hexane–ethyl acetate (9:1

v/v) as eluant to afford the *ketone* (**17**) as needles, m.p. 97—98 °C (from EtOH) (Found: C, 74.25; H, 8.4. $C_{17}H_{22}O_3$ requires C, 74.45; H, 8.1%); $\nu_{max.}$ 3 550 (OH) and 1 700 cm^{-1} (CO); δ 0.56 (3 H, s, 3a-Me), 2.27 (3 H, s, COMe), 3.69 (3 H, s, OMe), and 6.53—7.01 (3 H, m, ArH); *m/z* 274 (M^+).

trans-2,3,3a,4,5,9b-*Hexahydro*-3α-*hydroxy*-7-*methoxy*-3aβ-*methyl*-1H-*benz*[e]*inden*-3β-*yl Hydroxymethyl Ketone* (**18**).—To a solution of LDA [prepared from di-isopropylamine (56 mg, 0.55 mmol) and 1.3M-n-butyl-lithium (0.42 ml, 0.55 mmol)] in THF (4.5 ml) at −78 °C was added dropwise a solution of the ketone (**17**) (65.2 mg, 0.24 mmol) in THF (1.5 ml), and the mixture was stirred for 30 min at the same temperature. To this solution was added (hexamethylphosphoric triamide)(oxo)-diperoxy(pyridine)molybdenum complex (MoO_5·Py·HMPA) (237 mg, 0.55 mmol) and the mixture was stirred for a further 1 h at the same temperature, treated with water, and extracted with ether. The extract was washed successively with saturated aqueous sodium hydrogen carbonate, 5% hydrochloric acid, and saturated aqueous sodium chloride, and dried ($MgSO_4$). The residue obtained on evaporation of the solvent was chromatographed on silica gel (2 g) with n-hexane–ethyl acetate (4:1 v/v) as eluant to give the *keto diol* (**18**) (25.8 mg, 47%) as needles, m.p. 139—140 °C (from Et_2O); $\nu_{max.}$ 3 450 (OH) and 1 710 cm^{-1} (CO); δ 0.52 (3 H, s, 3a-Me), 3.75 (3 H, s, OMe), 4.53 (2 H, m, CH_2OH), and 6.55—7.00 (3 H, m, ArH); *m/z* 290 (M^+) (Found: M^+, 290.1515. $C_{17}H_{22}O_4$ requires *M*, 290.1516).

(3RS)-trans-2,3,3a,4,5,9b-*Hexahydro*-7-*methoxy*-3aβ-*methyl*-1H-*benz*[e]*indene*-3-*spiro*-3′-(1,3-*dioxolane*)-5′-*spiro*-4″-(1,3-*dioxolane*) (**3**).—Formalin (0.5 ml) and conc. hydrochloric acid (0.1 ml) were added to a solution of the keto diol (**18**) (35.3 mg, 0.12 mmol) in methylene dichloride (3 ml) at room temperature. The reaction mixture was stirred for 50 h at room temperature and then for 24 h at 40 °C. The two layers were separated and the aqueous phase was extracted with chloroform. The extract was combined with the original organic phase, and the resulting solution was washed with saturated aqueous sodium hydrogen carbonate and aqueous sodium chloride, and dried (Na_2SO_4). Removal of the solvent gave a crude product, which was chromatographed on silica gel (1 g) with n-hexane–ethyl acetate (95:5 v/v) as eluant to afford the *dispiro derivative* (**3**) (10.2 mg, 26%) as a glass, δ 0.60 (3 H, s, 3a-Me), 3.40 (3 H, s, OMe), 3.77 (2 H, br s, 5″-H_2), 4.73 (2 H, s, OCH_2O), 4.90 (2 H, s, OCH_2O), and 6.60—7.06 (3 H, m, ArH); *m/z* 332 (M^+) (Found: M^+, 332.1644. $C_{19}H_{24}O_5$ requires *M*, 332.1624).

1,2-*Dihydro*-1-(3-*isopropenyl*-3-*methoxymethoxy*-4-*methylpent*-4-*enyl*)-4-*methoxybenzocyclobutene* (**19**).—To a stirred solution of the alcohol (**11**) (51 mg, 0.187 mmol), Hünig's base (0.17 ml, 0.34 mmol) and a catalytic amount of DMAP in methylene dichloride (6 ml) at 0 °C was added methoxymethyl chloride (0.06 ml, 0.75 mmol), and the resulting mixture was stirred for 1 h at 0 °C and for 14 h at room temperature, diluted with methylene dichloride (50 ml), and washed successively with water and saturated aqueous sodium chloride. The organic layer was dried ($MgSO_4$) and evaporated to leave a residue, which was chromatographed on silica gel (2 g) with n-hexane–ether (4:1 v/v) as eluant to give the *methoxymethyl ether* (**19**) (56.9 mg, 96%) as an oil, δ 1.54 (6 H, s, 2 × CMe), 3.36 (3 H, s, CH_2OMe), 3.76 (3 H, s, ArO*Me*), 4.56 (2 H, s, OCH_2OMe), 5.03 and 5.16 (each 2 H, each s, 2 × $=CH_2$), and 6.50—7.00 (3 H, m, ArH); *m/z* 316 (M^+) (Found: M^+, 316.2018. $C_{20}H_{28}O_3$ requires *M*, 316.2037).

Thermolysis of the Methoxymethyl Ether (**19**).—A solution of the methoxymethyl ether (**19**) (1.1 g, 3.4 mmol) in *o*-dichlorobenzene (80 ml) was refluxed for 5 h. The residue obtained on evaporation of the solvent was chromatographed on silica gel (20 g) with n-hexane–ether (99:1 v/v) as eluant. From the first fraction, trans-2,3,3a,4,5,9b-*hexahydro*-3-*isopropylidene*-7-*methoxy*-3a-*methyl*-1H-*benz*[e]*indene* (**21**) (136 mg, 16%) was obtained as needles, m.p. 88—89 °C (from Et_2O) (Found: C, 79.45; H, 9.15. $C_{18}H_{24}O$ requires C, 79.55, H, 8.9%); δ 0.73 (3 H, s, 3a-Me), 1.60 and 1.73 (6 H, s, $=CMe_2$), 3.70 (3 H, s, OMe), and 6.50—7.00 (3 H, m, ArH); *m/z* 256 (M^+). From the second fraction, trans-2,3,3a,4,5,9b-*hexahydro*-3β-*isopropenyl*-7-*methoxy*-3α-*methoxymethoxy*-3aβ-*methyl*-1H-*benz*[e]*indene* (**20**) (877 mg, 82%) was obtained as needles, m.p. 99—100 °C (from EtOH); δ 0.43 (3 H, s, 3a-Me), 1.50 (3 H, s, =CMe), 3.30 (3 H, s, CH_2OMe), 3.70 (3 H, s, ArO*Me*), 4.39 and 4.47 (each 1 H, each d, *J* 8 Hz, OCH_2O), 5.00 (2 H, br s, $=CH_2$), and 6.50—6.93 (3 H, m, Ar*H*); *m/z* 316 (M^+) (Found: M^+, 316.2062. $C_{20}H_{28}O_3$ requires *M*, 316.2037).

The Tricyclic Methoxymethyl Ether (**20**) *from the Alcohol* (**13**).—To a stirred solution of the alcohol (**13**) (14.5 mg, 0.05 mmol) and Hünig's base (0.01 ml, 0.1 mmol) in methylene dichloride (1 ml) at 0 °C was added methoxymethyl chloride (0.015 ml, 0.2 mmol), and the mixture was stirred for 1 h at 0 °C and for 14 h at room temperature before being diluted with methylene dichloride and washed successively with water and saturated aqueous sodium chloride. The organic layer was dried ($MgSO_4$), and evaporated to leave a residue, which was chromatographed on silica gel (1 g) with n-hexane–ether (99:1 v/v) as eluant to give the methoxymethyl ether (**20**) (15.7 mg, 99%) as needles. This was identical with the sample obtained from the thermolysis of compound (**19**) (i.r., n.m.r., and mixed m.p.).

trans-2,3,3a,4,5,9b-*Hexahydro*-7-*methoxy*-3α-*methoxymethoxy*-3aβ-*methyl*-1H-*benz*[e]*inden*-3β-*yl Methyl Ketone* (**22**).—To a stirred solution of the tricyclic methoxymethyl ether (**20**) (37.8 mg, 0.12 mmol) and a catalytic amount of osmium tetraoxide in dioxane–water (2:1 v/v; 6 ml) was added sodium metaperiodate (1.4 g, 6.6 mmol) portionwise during 40 min, and the mixture was stirred for 24 h at 35 °C. Evaporation of the mixture afforded a residue, which was dissolved with ethyl acetate. The solution was washed successively with saturated aqueous sodium thiosulphate and aqueous sodium chloride solution, and dried ($MgSO_4$). Evaporation of the solvent left a residue, which was chromatographed on silica gel (2 g) with n-hexane–ethyl acetate (95:5 v/v) as eluant to give the *ketone* (**22**) (37.6 mg, 99%) as needles, m.p. 44—45 °C (from EtOH); $\nu_{max.}$ 1 700 cm^{-1} (CO); δ 0.40 (3 H, s, 3a-Me), 2.13 (3 H, s, COMe), 3.40 (3 H, s, OCH_2OMe), 3.73 (3 H, s, ArO*Me*), 4.60 (2 H, s, OCH_2O), and 6.50—7.00 (3 H, m, ArH) (Found: M^+, 318.1800. $C_{19}H_{26}O_4$ requires *M*, 318.1830).

2-(trans-2,3,3a,4,5,9b-*Hexahydro*-7-*methoxy*-3α-*methoxymethoxy*-3aβ-*methyl*-1H-*benz*[e]*inden*-3β-*yl*)-2,2-*dimethoxyethanol* (**23**).—A mixture of the ketone (**22**) (78.7 mg, 0.25 mmol), iodosylbenzene (186 mg, 0.85 mmol), potassium hydroxide (35.6 mg, 0.63 mmol), and methanol (5 ml) was stirred for 48 h at room temperature. The solvent was evaporated off to leave a residue, which was treated with water and extracted with ethyl acetate. The extract was washed with saturated aqueous sodium chloride and dried (Na_2SO_4). The residue obtained on evaporation of the solvent was chromatographed on neutral alumina (1 g) with n-hexane–ethyl acetate (9:1 v/v) as eluant to give the *aldehyde* (**24**) (10.6 mg, 14%) as an oil, $\nu_{max.}$ 1 740 cm^{-1} (CO); δ (CCl_4) 0.57 (3 H, s, 3a-Me), 3.20 and 3.50 [6 H, each s, $C(OMe)_2$], 3.67 (3 H, s, ArO*Me*), 6.43—6.90 (3 H, m, ArH), 6.93 (1 H, m, 2-H), and 9.03 (1 H, br s, CHO) (Found: M^+, 316.1675. $C_{19}H_{24}O_4$ requires *M*, 316. 1673).

From the second fraction, eluted with n-hexane–ethyl acetate (4:1 v/v), the *protected dihydroxyacetone derivative* (**23**) (16 mg,

17%) was obtained as an oil, $\nu_{max.}$ 3 500 cm^{-1} (OH); δ(CCl_4) 0.56 (3 H, s, 3a-Me), 3.33 (3 H, s, CH_2OMe), 3.37 and 3.40 [6 H, each s, $C(OMe)_2$], 3.70 (3 H, s, ArO*Me*), 3.80 (2 H, br s, CH_2OH), 4.53 and 5.03 (2 H, each d, *J* 8 Hz, OCH_2O), and 6.50—7.00 (3 H, m, ArH) [Found: M^+ − MeOH, 348.1950. $C_{20}H_{28}O_5$ (*M* − MeOH) requires *m/z*, 348.1937].

trans-3α-*Ethynyl*-2,3,3a,4,5,9b-*hexahydro*-7-*methoxy*-3aβ-*methyl*-1H-*benz*[e]*inden*-3β-*ol* (**26**).—To a stirred solution of ethynyltrimethylsilane (1.8 g, 18.6 mmol) in THF (50 ml) at −78 °C was added n-butyl-lithium (1.56M solution in hexane; 11 ml), and the mixture was stirred for 1 h at the same temperature. After addition of a solution of the ketone (**16**) (1.78 g, 7.7 mmol) in THF (80 ml), the resulting reaction mixture was stirred for 2.5 h at the same temperature, then treated with saturated aqueous ammonium chloride and extracted with ethyl acetate. The extract was washed successively with saturated aqueous sodium hydrogen carbonate and aqueous sodium chloride solution, and dried ($MgSO_4$). Evaporation of the solvent left the adduct (**25**) as a powder, which was used for the next reaction without further purification.

To a solution of this crude product (**25**) in THF (20 ml) was added tetra-n-butylammonium fluoride (2.18 g, 8.3 mmol). After the mixture had been stirred for 1.5 h at room temperature, it was diluted with water (40 ml) and extracted with ether. The extract was washed with saturated aqueous sodium chloride and dried (Na_2SO_4). The residue obtained on evaporation of the solvent was chromatographed on silica gel (30 g) with n-hexane–ethyl acetate (9:1 v/v) as eluant to give the *acetylene* (**26**) (1.72 g, 87%) as needles, m.p. 129—130 °C (from EtOH) (Found: C, 78.95; H, 7.9. $C_{17}H_{20}O_2$ requires C, 79.65; H, 7.85); $\nu_{max.}$ 3 600 (OH) and 3 300 cm^{-1} (CO); δ 0.70 (3 H, s, 3a-Me), 2.43 (1 H, s, C≡CH), 3.73 (3 H, s, OMe), and 6.40—6.96 (3 H, m, ArH); *m/z* 256 (M^+).

trans-2,3,3a,4,5,9b-*Hexahydro*-7-*methoxy*-3aβ-*methyl*-3-(2-*phenylsulphinylvinylidene*)-1H-*benz*[e]*indene* (**28**).—To a stirred solution of the acetylene (**26**) (206 mg, 0.8 mmol) and triethylamine (1.35 ml, 0.96 mmol) in methylene dichloride (15 ml) at −78° was added dropwise a solution of benzenesulphinyl chloride (159 mg, 1.2 mmol) in methylene dichloride (5 ml), and the mixture was stirred for 30 min at −78 °C and then for 30 min at −40 °C, then diluted with chloroform (50 ml) and water (50 ml). The organic layer was washed with saturated aqueous sodium chloride and dried ($MgSO_4$). The residue obtained on evaporation of the solvent was chromatographed on silica gel (5 g) with n-hexane–ethyl acetate (4:1 v/v) as eluant to give the *allene sulphoxide* (**28**) (160 mg, 56%) as an oil, $\nu_{max.}$ 1 950 (C=C=C) and 1 090 cm^{-1} (SO); δ 0.75 (3 H, s, 3a-Me), 3.73 (3 H, s, OMe), 6.03 (1 H, br s, C=C=CH), 6.50—7.00 (3 H, m, ArH), and 7.50 (5 H, br s, Ph); *m/z* 239 ($M^+ - SOC_6H_5$) [Found: $M^+ - SOC_6H_5$, 239.1372, $C_{17}H_{19}OS$ (*M* − SOC_6H_5) requires *m/z*, 239.1435].

Bromomethyl trans-2,3,3a,4,5,9b-*Hexahydro*-3α-*hydroxy*-7-*methoxy*-3aβ-*methyl*-1H-*benz*[e]*inden*-3β-*yl Ketone* (**31**).—A solution of the allene sulphoxide (**28**) (127 mg, 0.35 mmol) and sodium methoxide (170 mg, 3.14 mmol) in methanol (10 ml) was stirred for 5 h at room temperature. The residue obtained on evaporation of the solvent was diluted with chloroform and water. The organic layer was washed with saturated aqueous sodium chloride and dried ($MgSO_4$). Evaporation of the solvent afforded the crude enol ether (**29**). A solution of this crude enol ether (**29**) and trimethyl phosphite (0.053 ml, 0.45 mmol) in methanol (10 ml) was refluxed for 2 h. After evaporation of the solvent, the residue was dissolved in chloroform (50 ml) and the solution was washed with saturated aqueous ammonium chloride and dried ($MgSO_4$). To a solution of the crude hydroxy enol ether (**30**), obtained on removal of the solvent, in carbon tetrachloride (5 ml) at 0 °C was added a solution of pyridinium perbromide (167 mg, 0.7 mmol) in carbon tetrachloride (5 ml). After the mixture had been stirred for 1 h at 0 °C it was diluted with chloroform (50 ml), washed successively with saturated aqueous sodium chloride, 10% hydrochloric acid, and saturated aqueous sodium hydrogen carbonate, and dried ($MgSO_4$). The residue obtained on removal of the solvent was chromatographed on silica gel (1 g) with n-hexane–ethyl acetate (9:1 v/v) as eluant to give the *bromide* (**31**) (64.3 mg, 52%) as a glass, $\nu_{max.}$ 3 500 (OH) and 1 720 cm^{-1} (CO); δ 0.52 (3 H, s, 3a-Me), 3.76 (3 H, s, OMe), 4.18 and 4.26 (each 1 H, each d, *J* 8 Hz, CH_2Br), and 6.50—7.00 (3 H, m, ArH); *m/z* 354 ($M^+ + 2$) and 352 (M^+) (Found: $M^+ + 2$, 354.0671; M^+, 352.0689. $C_{17}H_{21}BrO_3$ requires *M* + 2, 354.0636; *M*, 352.0673).

trans-2,3,3a,4,5,9b-*Hexahydro*-3α-*hydroxy*-7-*methoxy*-3aβ-*methyl*-1H-*benz*[e]*inden*-3β-*yl Hydroxymethyl Ketone* (**18**) *from the Bromide* (**31**).—A mixture of the bromide (**31**) (96.4 mg, 0.27 mmol), potassium acetate (66.9 mg, 0.68 mmol), potassium iodide (45.3 mg, 0.27 mmol), acetic acid (0.02 ml), and acetone (7 ml) was refluxed for 2 h. After evaporation of the solvent, the residue was extracted with chloroform. The extract was washed successively with saturated aqueous sodium thiosulphate and aqueous sodium chloride, and dried ($MgSO_4$). A mixture of the residue obtained on evaporation of the solvent, lithium hydroxide monohydrate (52.5 mg, 1.25 mmol), water (3 ml), and methanol (9 ml) was stirred for 1 h at room temperature. After evaporation of the solvent, the residue was extracted with chloroform (50 ml). The extract was washed with saturated aqueous sodium chloride and dried ($MgSO_4$). Evaporation of the solvent left a residue, which was chromatographed on silica gel (1 g) with n-hexane–ethyl acetate (5:1 v/v) as eluant to furnish the dihydroxyacetone (**18**) as needles. This compound was identical with the sample obtained on oxidation of the hydroxy ketone (**17**) (i.r., n.m.r., and mixed m.p.).

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