# A Practical Route for Enantioselective Total Synthesis of (+)-11-Deoxy-19-norcorticosterone *via* Intramolecular Diels–Alder Addition to an *ortho*-Quinodimethane†

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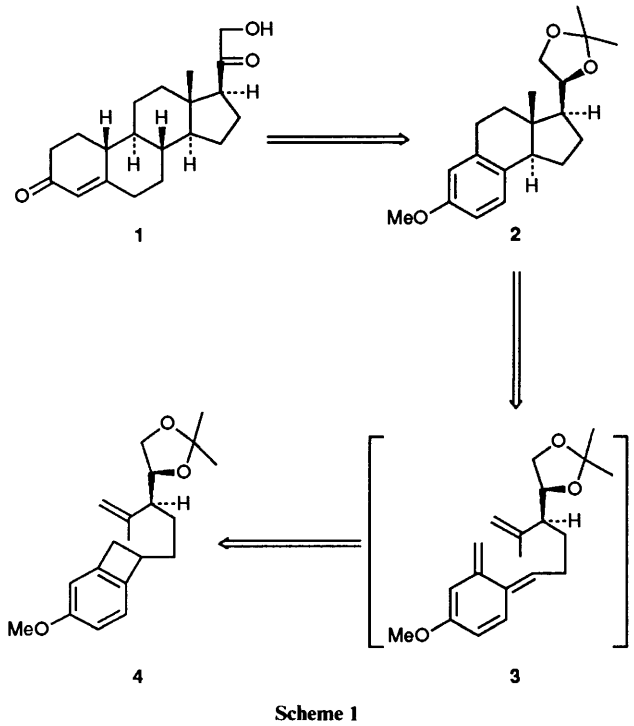
A convenient and practical route for enantioselective synthesis of the A-nor-B-trienic steroid **2** *via* an intramolecular [4 + 2] cycloaddition of the olefinic *ortho*-quinodimethane **3** generated *in situ* by thermolysis of the olefinic benzocyclobutene **4** is reported. This leads to the total synthesis of (+)-11-deoxy-19-norcorticosterone **1** by use of a usual chemical manipulation on intermediate **2**.

Because of the increasing interest[1,2] in its physiological significance, much attention has been focused on the chemistry[3] of (+)-11-deoxy-19-norcorticosterone **1** (a potent mineralcorticoid with sodium-retaining activity comparable to that of aldosterone) with a view to developing synthetic routes effective in providing significant amounts of this compound. However, a practical and flexible synthetic methodology, affording satisfactory yields and providing a wide variety of compounds of this type for biological studies, still remains to be developed. Hence, we have undertaken to try to develop an efficient and flexible route for the production of deoxycorticosterone derivatives. We describe herein an efficient, enantioselective, total synthesis of (+)-11-deoxy-19-norcorticosterone **1**. Our synthetic strategy for compound **1** is characterized by the one-step creation of the B, C and D rings (structure **2**) in a stereoselective manner (Scheme 1), namely the stereoselective introduction of the three successive chiral centres, C-13, C-14 and C-17 (steroid numbering), achieved by an intramolecular [4 + 2] cycloaddition of the olefinic *ortho*-quinodimethane **3** generated *in situ* by thermolysis of the olefinic benzocyclobutene **4** as a key step and then generation of the A-ring, followed by manipulation of the side-chain (**2** → **1**).

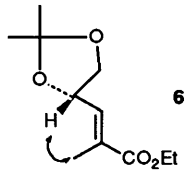
The synthesis of the benzocyclobutene **4** was straightforward (Scheme 2). (*R*)-Isopropylideneglyceraldehyde[4] **5**, easily obtainable in large quantity from D-mannitol, was subjected to Wittig reaction[5] with ethoxycarbonylethylidene(triphenyl)-phosphorane to give the unsaturated ester **6**‡ {$[\alpha]_D^{26}$ +8.8° (*c* 1.16 in $CHCl_3$)} selectively in 80% yield, which on reduction with diisobutylaluminium hydride (DIBAL) afforded the alcohol **7** {$[\alpha]_D^{22}$ +9.5° (*c* 0.91 in $CHCl_3$)} in 75% yield. Johnson–Claisen rearrangement of compound **7** with triethyl orthoacetate at 135 °C yielded the *erythro*-ester **9** and the *threo*-ester **12** in 16 and 18% yield, respectively. The selectivity for the *threo*-isomer over the *erythro* isomer was improved by subjecting the acetate **8** {$[\alpha]_D^{25}$ +20.4° (*c* 0.87 in $CHCl_3$)}, obtained in 80% yield by acetylation [$Ac_2O$, pyridine and 4-(dimethylamino)pyridine (DMAP)] of the alcohol **7**, to Ireland–Claisen rearrangement [lithium diisopropylamide (LDA), trimethylsilyl chloride (TMSCl), tetrahydrofuran (THF), −78 °C; then reflux] followed by direct reduction, with lithium aluminium hydride (LAH), of the resulting crude mixture of acids **10** and **13** to give the *erythro*-alcohol **11** and *threo*-alcohol **14**§ in 15 and 30% overall yield, respectively. The tosyl derivative **15** {$[\alpha]_D^{24}$ +24.2° (*c* 1.37 in $CHCl_3$)} obtained in 87% yield by tosylation [toluene-*p*-sulphonyl chloride (*p*-TsCl), pyridine] of the alcohol **14** was converted into the iodide **16** {$[\alpha]_D^{24}$ +63.0° (*c* 1.03 in $CHCl_3$)} in 99% yield by iodination (sodium iodide). Alkylation of 1-cyano-1,2-dihydro-4-methoxy-




Scheme 1

† Preliminary communication: H. Nemoto, A. Satoh, M. Ando and K. Fukumoto, *J. Chem. Soc., Chem Commun.*, 1990, 1001.

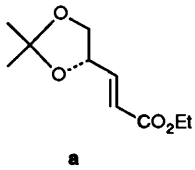
‡ The stereochemistry of compound **6** was determined on the basis of nuclear Overhauser effect (NOE) experiments, in which an 11.0% NOE between the methyl and methine protons was observed.



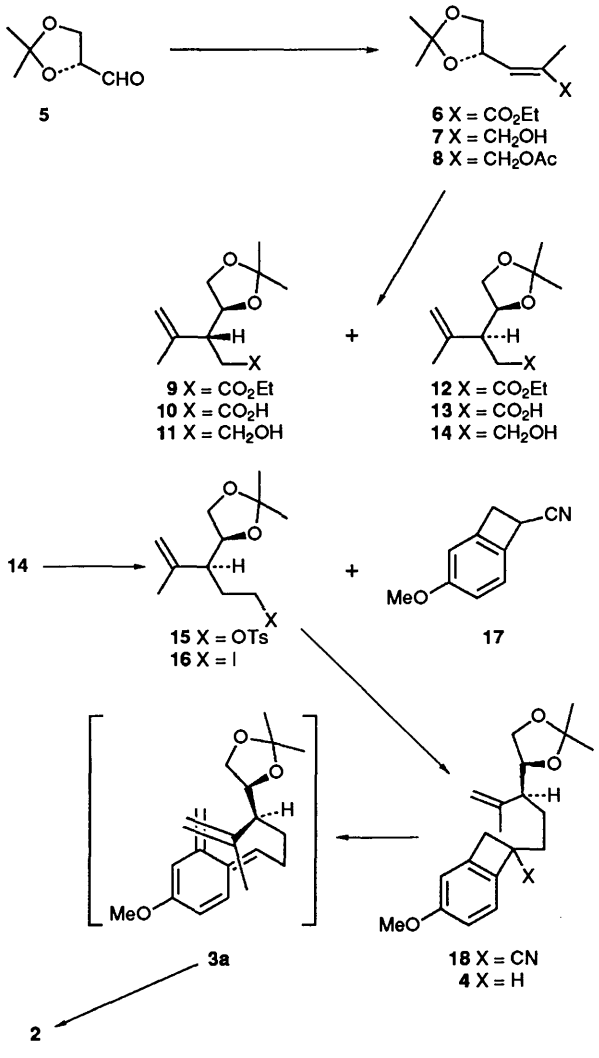

**6**

11.0% NOE

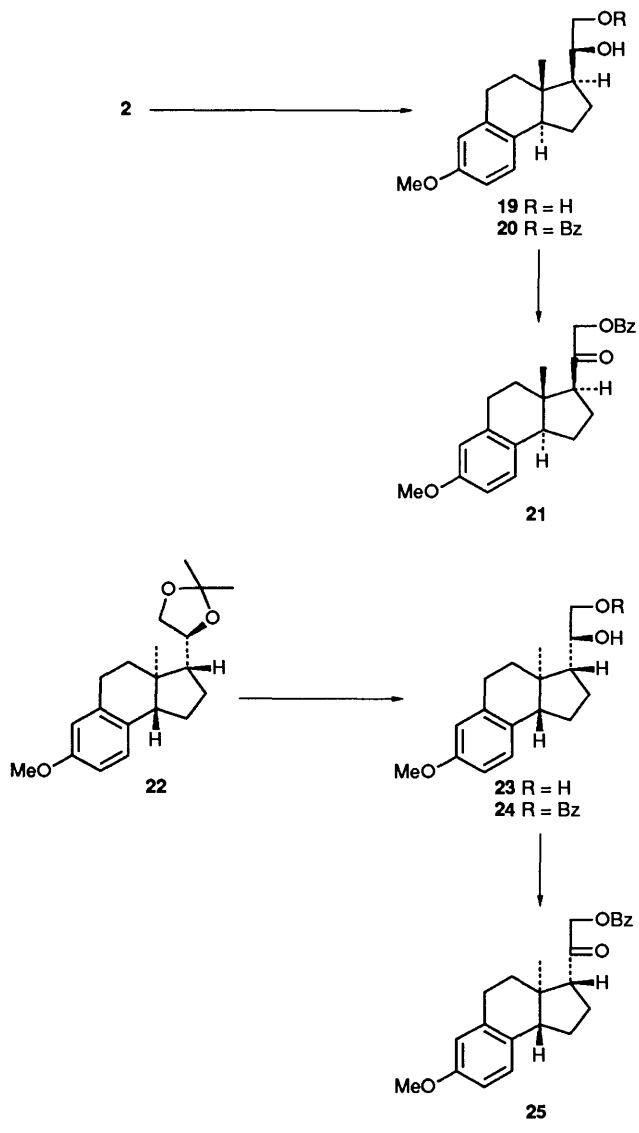
§ In our recent studies[6] the mixture of the *erythro*- **9** and *threo*-ester **12**, with *erythro*-ester **9** predominating, was obtained by 1,4-addition of isopropenylmagnesium bromide to the unsaturated ester **a**, and these products were converted into the corresponding alcohol **11** and **14**, respectively.




**a**




Scheme 2



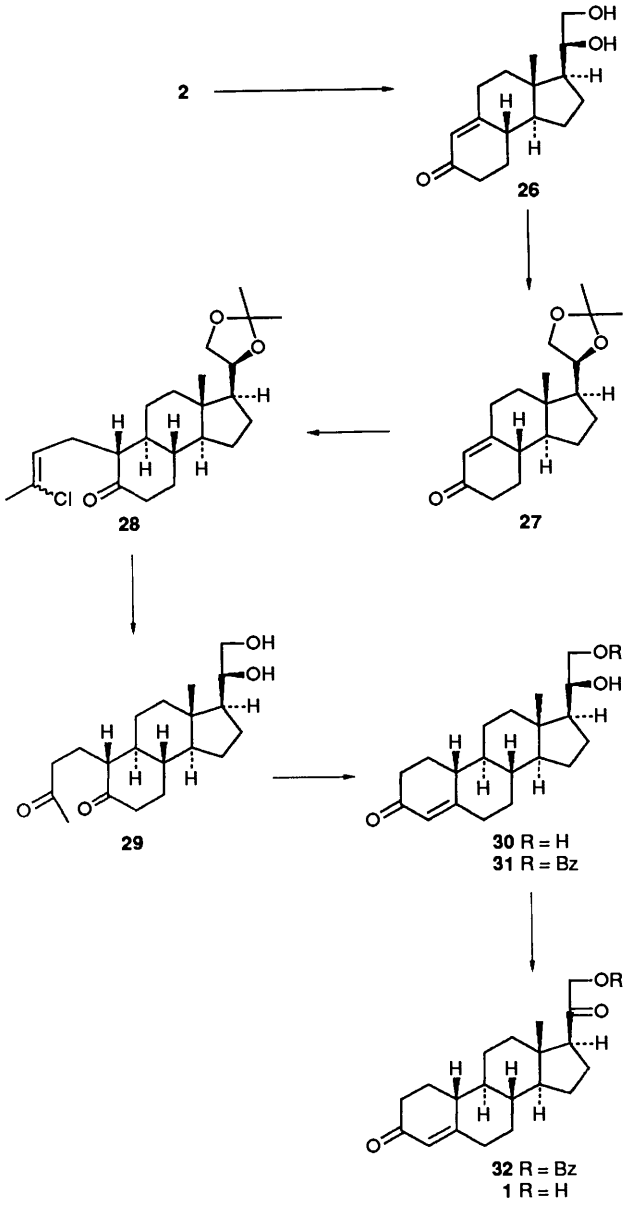

Scheme 3

benzocyclobutene **17**[7] with the iodide **16** in liquid ammonia in the presence of sodium amide (sodamide), followed by reductive decyanation of the resulting cyanide **18** by sodium in liquid ammonia, furnished the olefinic benzocyclobutene **4** {$[\alpha]_D^{23}$ +19.7° (*c* 1.03 in $CHCl_3$); 90% overall yield from **17**}. The generation of the *ortho*-quinodimethane **3** and cycloaddition of this intermediate **3** were effected by thermolysis of the benzocyclobutene **4** in boiling *o*-dichlorobenzene (ODB) to give stereoselectively the A-nor-B-trienic steroid **2** {$[\alpha]_D^{25}$ +15.6° (*c* 1.34 in $CHCl_3$)} in 98% isolated yield. The stereoselectivity[8] in this reaction can best be explained by the intervention of the most sterically favoured olefinic *ortho*-quinodimethane **3a**. The stereochemistry, including absolute configuration, of the product **2** was confirmed as follows (Scheme 3).

The diol **19** {m.p. 117–118 °C; $[\alpha]_D^{24}$ +6.5° (*c* 1.05 in $CHCl_3$)} obtained in 82% yield by solvolysis (MeOH) in the presence of a catalytic amount of pyridinium toluene-*p*-sulphonate (PPTS) was subjected to selective benzoylation with benzoyl chloride in the presence of DMAP and pyridine to give the monobenzoate **20** {$[\alpha]_D^{25}$ +26.9°, (*c* 0.87 in $CHCl_3$)} in 92% yield, which on oxidation with pyridinium chlorochromate (PCC) afforded the keto benzoate **21** {m.p. 91–92 °C; $[\alpha]_D^{24}$ +90.8° (*c* 1.17 in $CHCl_3$)} in 97% yield. By following exactly the same procedure for compound **2** as described above, the acetonide **22**§,* was converted through the diol **23** {m.p. 120–121 °C; $[\alpha]_D^{24}$ −20.4° (*c* 0.59 in $CHCl_3$); 87% yield} and the monobenzoate **24** {$[\alpha]_D^{23}$ +5.6° (*c* 1.06 in $CHCl_3$); 82% yield} into the keto benzoate **25** {m.p. 91–92 °C; $[\alpha]_D^{23}$ −98.9° (*c* 0.55 in $CHCl_3$); 84% yield}. The spectral data, including $[\alpha]_D$-value, as well as the sign of the optical rotation of these two keto benzoates (**21** and **25**), were identical, showing keto benzoates **21** and **25** to be enantiomeric and the structure of compound **2**, including its absolute configuration, to be correct.

Conversion of the A-nor-B-trienic steroid **2** into (+)-11-deoxy-19-norcorticosterone **1** was as follows (Scheme 4). Birch reduction (lithium, liquid ammonia) of compound **2** followed by acid (10% HCl) treatment afforded the thermodynamically predominant product **26** {$[\alpha]_D^{25}$ −11.7° (*c* 1.33 in $CHCl_3$)} in 75% overall yield. The corresponding acetonide **27** {$[\alpha]_D^{23}$ +2.6° (*c* 1.33 in $CHCl_3$)} obtained in 94% yield by treatment of the diol **26** with 2,2-dimethoxypropane in the presence of camphorsulphonic acid (CSA) was subjected to reductive alkylation[9] (lithium, liquid ammonia) with 1-bromo-3-chloro-but-2-ene to give the ketone **28** {$[\alpha]_D^{24}$ +17.3° (*c* 1.26 in $CHCl_3$)} in 59% yield, which on hydrolysis with mercury(II) trifluoroacetate yielded the diketone **29** {$[\alpha]_D^{23}$ +8.1° (*c* 0.52 in $CHCl_3$)} in 73% yield. The diol **30** {$[\alpha]_D^{23}$ +35.6° (*c* 1.00 in

* In our recent studies,[6] the acetonide **22** was prepared from the *erythro*-alcohol **11** by following the same chemical manipulation described for compound **2** *via* intermediates **15**, **16**, **18** and **4**.




Scheme 4

$CHCl_3$)} obtained in 81% yield by cyclization of dione **29** in the presence of potassium hydroxide was selectively converted into the monobenzoate **31** {$[\alpha]_D^{25}$ +4.00° (*c* 0.32 in $CHCl_3$)} in 52% yield, which on oxidation with PCC yielded the keto benzoate **32** {m.p. 216–217 °C; $[\alpha]_D^{24}$ +74.9° (*c* 0.43 in $CHCl_3$)} in 76% yield. Finally, hydrolysis of keto ester **32** in the presence of potassium carbonate furnished (+)-11-deoxy-19-norcorticosterone **1** {m.p. 123–124 °C; $[\alpha]_D^{24}$ +97.0° (*c* 0.27 in $CHCl_3$); lit.,[3a,*] m.p. 124–125 °C; $[\alpha]_D^{24}$ +98.5° (*c* 0.13 in $CHCl_3$)} in 90% yield. The compound **1** thus synthesized was identical with an authentic sample in all aspects, including mixed m.p.[3a,*] and optical behaviour.

## Experimental

*General Methods.*—M.p.s were determined on a Yanagimoto MP-22 apparatus and are uncorrected. IR spectra were recorded on a Hitachi 260-10 spectrophotometer. $^1H$ NMR spectra were obtained on a JEOL PS-100, JEOL FX-90, or a JNM GX-500 spectrometer. Chemical shifts were recorded as $\delta$-values relative to internal $SiMe_4$, and *J*-values are given in Hz. Mass spectra were taken on a Hitachi M-52 or a JEOL-TMS-01SG-2 spectrometer. Optical rotations were measured with a JASCO-DIP-340 polarimeter. All reactions were carried out under dry nitrogen. Column chromatography was carried out with silica gel (Wako gel C-200). The phrase 'residue upon work-up' refers to the residue obtained when the organic layer was separated, dried over anhydrous $Na_2SO_4$, and the solvent was evaporated off under reduced pressure. All new compounds described in this section were homogenous on TLC.

(+)-*Ethyl* (2E,4S)-4,5-*Isopropylidenedioxy*-2-*methylpent*-2-*enoate* **6**.—To a stirred suspension of 1,2:5,6-di-*O*-isopropylidene-D-mannitol (596 mg, 2.27 mmol) in aq. 5% sodium hydrogen carbonate (6 $cm^3$) at 0 °C was added an aq. solution (2 $cm^3$) of $NaIO_4$ (584 mg, 2.73 mmol), and the mixture was stirred for 1 h at room temperature. To this stirred reaction mixture at 0 °C was added a solution of ethoxycarbonylethylidene(triphenyl)phosphorane (1.646 g, 4.54 mmol) in $CH_2Cl_2$ (2 $cm^3$), and the mixture was stirred for 3 h, then extracted with $CH_2Cl_2$, and the extract was washed with water. The residue upon work-up was chromatographed with hexane–ethyl acetate (19:1 v/v) to give the *ester* **6** (775 mg, 80%) as an oil (Found: C, 61.45; H, 8.35. $C_{11}H_{18}O_4$ requires C, 61.65; H, 8.45%); $[\alpha]_D^{26}$ +8.8° (*c* 1.16 in $CHCl_3$); $\nu_{max}$(neat)/$cm^{-1}$ 1715 (C=O); $\delta_H$(500 MHz; $CDCl_3$) 1.30 (3 H, t, *J* 7.3, $CO_2CH_2Me$), 1.41 and 1.45 (6 H, each s, $CMe_2$), 1.89 (3 H, d, *J* 1.5, MeC=C) and 6.69 (1 H, dd, *J* 8.7 and 1.5, CH=C); *m*/*z* 199 ($M^+$ − 15).

(+)-(2E,4S)-4,5-*Isopropylidenedioxy*-2-*methylpent*-2-*en*-1-*ol* **7**.—To a stirred solution of the ester **6** (558 mg, 2.60 mmol) in $CH_2Cl_2$ (13 $cm^3$) at −78°C was added a 1.0 mol $dm^{-3}$ solution of DIBAL in hexane (5.50 $cm^3$). The reaction mixture was stirred for 1 h at −78 °C, the temperature was raised to 0 °C, and the mixture was quenched with saturated aq. $NH_4Cl$, and extracted with $CH_2Cl_2$. The extract was filtered through Celite. The residue upon work-up was chromatographed with hexane–ethyl acetate (95:5 v/v) to give the *alcohol* **7** (335 mg, 75%) as an oil (Found: C, 62.7; H, 9.35. $C_9H_{16}O_3$ requires C, 62.75; H, 9.35%); $[\alpha]_D^{22}$ +9.5° (*c* 0.91 in $CHCl_3$); $\nu_{max}$(neat)/$cm^{-1}$ 3450 (OH); $\delta_H$(90 MHz; $CDCl_3$) 1.41 and 1.44 (6 H, each s, $CMe_2$), 1.65 (1 H, br s, OH), 1.76 (3 H, d, *J* 1.5, MeC=C), 4.05 (2 H, d, *J* 1.0, C=C$CH_2$O) and 5.48 (1 H, ddd, *J* 8.7, 1.5 and 1.0, CH=C); *m*/*z* 157 ($M^+$ − 15).

*Ethyl* (3R,4′S *and* 3S,4′S)-3-(2′,2′-*Dimethyl*-1′,3′-*dioxolan*-4′-*yl*)-4-*methylpent*-4-*enoate* **9** *and* **12**.—A mixture of the alcohol **7** (122 mg, 0.71 mmol), triethyl orthoacetate (1.3 $cm^3$, 7.09 mmol), and a catalytic amount of propionic acid was stirred for 10 min at 135 °C. The residue upon evaporation of volatile substances under reduced pressure was chromatographed with hexane–ethyl acetate (99:1 v/v) to give the 3R,4′S-*ester* **9** (29 mg, 16%) as an oil (Found: C, 64.3; H, 9.2%; $M^+$, 242.1498. $C_{13}H_{22}O_4$ requires C, 64.45; H, 9.15%; M, 242.1518); $[\alpha]_D^{25}$ +6.2° (*c* 0.55 in $CHCl_3$); $\nu_{max}$(neat)/$cm^{-1}$ 1735 (C=O); $\delta_H$(90 MHz; $CDCl_3$) 1.23 (3 H, t, *J* 7.2, $CO_2CH_2Me$), 1.34 and 1.40 (6 H, each s, $CMe_2$), 1.70 (3 H, br s, MeC=C), 4.10 (2 H, q, *J* 7.2, $CO_2CH_2Me$) and 4.81 (2 H, br s, $CH_2$=C).

The second fraction, from hexane–ethyl acetate (98:2 v/v) eluent, afforded the 3S,4′S-*ester* **12** (32 mg, 18%) as an oil (Found: C, 64.3; H, 9.15%; $M^+$, 242.1531); $[\alpha]_D^{25}$ +13.1° (*c* 0.70 in $CHCl_3$); $\nu_{max}$(neat)/$cm^{-1}$ 1735 (C=O); $\delta_H$(90 MHz; $CDCl_3$)

* (+)-11-Deoxy-19-norcorticosterone, which was donated by Dr T. Terasawa at Shionogi Research Laboratories, was recrystallized from acetone–diethyl ether and used for mixed m.p. and optical rotation measurements.

1.23 (3 H, t, *J* 7.2, $CO_2CH_2Me$), 1.35 and 1.41 (6 H, each s, $CMe_2$), 1.80 (3 H, s, MeC=C), 4.10 (2 H, q, *J* 7.2, $CO_2CH_2Me$) and 4.81 and 4.91 (2 H, each br s, $CH_2$=C).

(+)-(3S,4'S)-3-(2',2'-*Dimethyl*-1',3'-*dioxolan*-4'-*yl*)-4-*methylpent*-4-*enol* **14**.—To a stirred solution of the ester **12** (12.15 g, 50.1 mmol) in THF (50 $cm^3$) at 0 °C was added LAH (1.91 g, 50.3 mmol). After the mixture had been stirred for 1 h at room temperature, it was diluted with diethyl ether, quenched with 10% aq. NaOH and filtered through Celite. The residue upon evaporation of the filtrate was chromatographed with hexane–ethyl acetate (8:2 v/v) to give the *alcohol* **14** (7.73 g, 77%) as an oil (Found: C, 65.75; H, 10.0. $C_{11}H_{20}O_3$ requires C, 65.95; H, 10.05%); $[\alpha]_D^{24}$ +35.3° (*c* 1.34 in $CHCl_3$); $\nu_{max}$(neat)/$cm^{-1}$ 3420 (OH); $\delta_H$(90 MHz; $CDCl_3$) 1.36 and 1.44 (6 H, each s, $CMe_2$), 1.77 (3 H, br s, MeC=C), 4.83 and 4.92 (2 H, each br s, $CH_2$=C); *m/z* 200 ($M^+$).

(+)-(2E,4S)-4,5-*Isopropylidenedioxy*-2-*methylpent*-2-*enyl Acetate* **8**.—To a stirred solution of the alcohol **7** (149 mg, 0.87 mmol) and a catalytic amount of DMAP in pyridine (9 $cm^3$) at 0 °C was added acetic anhydride (0.16 $cm^3$, 1.7 mmol) and the mixture was stirred for 1 h at room temperature, diluted with water (15 $cm^3$) and extracted with diethyl ether. The extract was washed successively with water, 10% HCl, saturated aq. sodium hydrogen carbonate and saturated aq. NaCl. The residue upon work-up was chromatographed with hexane–ethyl acetate (4:1 v/v) to give the *acetate* **8** (148 mg, 80%) as an oil (Found: C, 61.7; H, 8.45. $C_{11}H_{18}O_4$ requires C, 61.65; H, 8.45%); $[\alpha]_D^{25}$ +20.4° (*c* 0.87 in $CHCl_3$); $\nu_{max}$(neat)/$cm^{-1}$ 1740 (C=O); $\delta_H$(90 MHz; $CDCl_3$) 1.36 and 1.42 (6 H, each s, $CMe_2$), 1.78 (3 H, d, *J* 1.5, MeC=C), 2.10 (3 H, s, $MeCO_2$), 4.48 (2 H, s, C=$CCH_2$) and 5.49 (1 H, dq, *J* 8.7 and 1.5, CH=C); *m/z* 199 ($M^+$ − 15).

(+)-(3R,4'S *and* 3S,4'S)-3-(2',2'-*Dimethyl*-1',3'-*dioxolan*-4'-*yl*)-4-*methylpent*-4-*en*-1-*ol* **11** *and* **14**.—A solution of the acetate **8** (24.4 mg, 0.114 mmol) in THF (0.5 $cm^3$) was added dropwise to a stirred solution of LDA in THF (1 $cm^3$) [prepared from a 1.56 mol $dm^{-3}$ solution of butyllithium in hexane (0.38 $cm^3$, 0.41 mmol) and diisopropylamine (0.08 $cm^3$, 0.653 mmol)] at −78 °C. After the mixture had been stirred for 5 min at −78 °C, it was treated with TMSCl (0.18 $cm^3$, 0.674 mmol) and stirred for 1 h at room temperature, and then refluxed for 3 h. The stirred mixture was treated with MeOH (2 $cm^3$) for 15 min and then with 5% aq. NaOH (4 $cm^3$), and washed with diethyl ether. The aq. layer was then acidified with 10% HCl and extracted with $CH_2Cl_2$. The extract was washed with saturated aq. NaCl.

To a stirred solution of the residue upon work-up in THF (2 $cm^3$) at 0 °C was added LAH (40 mg, 1 mmol). After being stirred for 5 h, the mixture was diluted with diethyl ether, quenched with 10% aq. NaOH, and filtered through Celite. The residue upon evaporation of the filtrate was chromatographed with hexane–ethyl acetate (9:1 v/v) to give the 3R,4'S-*alcohol* **11** (3.4 mg, 15%) as an oil (Found: C, 66.25; H, 10.25%; $M^+$ − 15, 185.1170. $C_{11}H_{28}O_3$ requires C, 66.0; H, 10.0%; *m/z* 185.1178); $[\alpha]_D^{24}$ −3.6° (*c* 0.11 in $CHCl_3$); $\nu_{max}$(neat)/$cm^{-1}$ 3490 (OH); $\delta_H$(90 MHz; $CDCl_3$) 1.30 and 1.35 (6 H, each s, $CMe_2$), 1.61 (3 H, s, MeC=C) and 4.74 (2 H, br s, $CH_2$=C).

The second fraction, from hexane–ethyl acetate (8:2 v/v) eluent, afforded the 3*S*,4'*S*-alcohol **14** (6.8 mg, 30%) which was identical in all aspects with the sample obtained previously by LAH reduction of the ester **12**.

(+)-(3S,4'S)-3-(2',2'-*Dimethyl*-1',2'-*dioxolan*-4'-*yl*)-4-*methylpent*-4-*enyl Toluene*-p-*sulphonate* **15**.—To a stirred solution of the alcohol **14** (5.02 g, 25.1 mmol) in pyridine (25 $cm^3$) at 0 °C was added *p*-TsCl (9.56 g, 50.15 mmol) and the mixture was stirred for 3 h. The mixture was diluted with water and extracted with $CH_2Cl_2$. The extract was washed successively with water, 10% HCl, saturated aq. sodium hydrogen carbonate and saturated aq. NaCl. The residue upon work-up was chromatographed with hexane–ethyl acetate (4:1 v/v) to give the *tosyl derivative* **15** (7.71 g, 87%) as an oil (Found: $M^+$, 354.1501. $C_{18}H_{26}O_4S$ requires M, 354.1501); $[\alpha]_D^{24}$ +24.2° (*c* 1.37 in $CHCl_3$); $\nu_{max}$(neat)/$cm^{-1}$ 1180 ($SO_2$); $\delta_H$(90 MHz; $CDCl_3$) 1.33 and 1.37 (6 H, each s, $CMe_2$), 2.46 (3 H, s, *Me*Ar), 4.63 and 4.84 (2 H, each br s, $CH_2$=C) and 7.29–7.80 (4 H, m, ArH).

(+)-(3S,4'S)-3-(2',2'-*Dimethyl*-1',3'-*dioxolan*-4'-*yl*)-4-*methylpent*-4-*enyl Iodide* **16**.—A mixture of the tosyl derivative **15** (4.86 g, 13.7 mmol), sodium iodide (10.28 g, 68.6 mmol) and acetone (20 $cm^3$) was stirred for 47 h. The mixture was then diluted with water and extracted with $CH_2Cl_2$. The extract was washed successively with water, saturated aq. $Na_2S_2O_3$, and saturated aq. NaCl. The residue upon work-up was chromatographed with hexane–ethyl acetate (7:3 v/v) to give the *iodide* **16** (4.21 g, 99%) as an oil (Found: $M^+$, 310.0437. $C_{11}H_{19}IO_2$ requires M, 310.0430); $[\alpha]_D^{24}$ +63.0° (*c* 1.03 in $CHCl_3$); $\delta_H$(90 MHz; $CDCl_3$) 1.09 and 1.17 (6 H, each s, $CMe_2$), 1.43 (3 H, br s, MeC=C), 2.61–3.14 (2 H, m, $CH_2I$) and 4.62 and 4.73 (2 H, each br s, $CH_2$=C).

(+)-(4S,1'S) 4-{1'-[2-(1,2-*Dihydro*-4-*methoxybenzocyclobuten*-1-*yl*)*ethyl*]-2'-*methylprop*-2'-*enyl*}-2,2-*dimethyl*-1,3-*dioxolane* **4**.—To a stirred suspension of sodamide [prepared from sodium (0.24 g, 10.4 mmol)] in liquid ammonia (60 $cm^3$) at − 33 °C was added a solution of 1,2-dihydro-4-methoxybenzocyclobutene-1-carbonitrile **17**[7] (1.56 g, 9.8 mmol) in THF (14 $cm^3$), and the mixture was stirred for 30 min at the same temperature before being treated at −33 °C with a solution of the iodide **16** (1.68 g, 5.4 mmol) in THF (7 $cm^3$). After the mixture had been stirred for 1 h at the same temperature, it was treated with EtOH (2 $cm^3$), cooled to −78 °C, treated with sodium (0.28 g, 12.2 mmol) and stirred for 30 min at −78 °C. The mixture was treated with MeOH and evaporated to leave a residue, which was treated with water and extracted with $CH_2Cl_2$. The extract was washed with saturated aq. NaCl. The residue upon work-up was chromatographed with hexane–ethyl acetate (98:2 v/v) to give the *olefinic benzocyclobutene* **4** (1.55 g, 90%) as an oil (Found: C, 75.6; H, 8.9%; $M^+$, 316.2040. $C_{20}H_{28}O_3$ requires C, 75.9; H, 8.95%; M, 316.203 9); $[\alpha]_D^{23}$ +19.7° (*c* 1.03 in $CHCl_3$); $\delta_H$(90 MHz; $CDCl_3$) 1.37 and 1.41 (6 H, each s, $CMe_2$), 1.60 (3 H, br s, MeC=C), 3.78 (3 H, s, *Me*OAr), 4.78 and 4.89 (2 H, each br s, $CH_2$=C) and 6.68–7.03 (3 H, m, ArH).

(+)-(4S,3'S,3a'S,9b'R)-trans-4-(2',3',3a',4',5',9b'-*Hexahydro*-7'-*methoxy*-3a'-*methyl*-1'H-*cyclopenta*[a]*naphthalen*-3'-*yl*)-2,2-*dimethyl*-1,3-*dioxolane* **2**.—A stirred solution of the olefinic benzocyclobutene **4** (532.6 mg, 1.68 mmol) in ODB (55 $cm^3$) was refluxed for 13 h. The residue upon evaporation of the solvent was chromatographed with hexane–ethyl acetate (99:1 v/v) to give the *tricyclic compound* **2** (525 mg, 98%) as an oil (Found: C, 75.9; H, 9.2%; $M^+$, 316.206 0. $C_{20}H_{28}O_3$ requires C, 75.9; H, 8.95%; M, 316.2039); $[\alpha]_D^{25}$ +15.6° (*c* 1.34 in $CHCl_3$); $\delta_H$(500 MHz; $CDCl_3$) 0.65 (3 H, s, MeC), 1.37 and 1.42 (6 H, each s, $Me_2C$), 3.78 (3 H, s, *Me*OAr) and 6.66–7.05 (3 H, m, ArH).

(+)-(1S,3'S,3a'S,9b'R)-trans-1-(2',3',3a',4',5',9b'-*Hexahydro*-7'-*methoxy*-3a'-*methyl*-1'H-*cyclopenta*[a]*naphthalen*-3-*yl*)*ethane*-1,2-*diol* **19**.—A stirred solution of the acetonide **2** (38.9 mg, 0.123 mmol) and a catalytic amount of PPTS in MeOH (4 $cm^3$) was refluxed for 2 h. The residue upon evaporation of the

solvent was chromatographed with hexane–ethyl acetate (3:1 v/v) to give the *diol* **19** (28 mg, 82%) as needles (from diethyl ether–hexane), m.p. 117–118 °C (Found: C, 73.75; H, 8.75%; $M^+$, 276.1697. $C_{17}H_{24}O_3$ requires C, 73.9; H, 8.75%; M, 276.1725); $[\alpha]_D^{24}$ +6.5° (*c* 1.05 in $CHCl_3$); $\nu_{max}(CHCl_3)/cm^{-1}$ 3450 (OH); $\delta_H$(500 MHz, $CDCl_3$) 0.67 (3 H, s, MeC), 3.80 (3 H, s, *Me*OAr) and 6.65–6.93 (3 H, m, ArH).

(−)-(1S,3′R,3a′R,9b′S)-trans-1-(2′,3′,3a′,4′,5′,9b′-*Hexahydro-7′-methoxy-3a′-methyl-1′H-cyclopenta*[a]*naphthalen-3′-yl*)*ethane*-1,2-*diol* **23**.—By following the same procedure described for compound **2**, the acetonide **22*** (134.2 mg, 0.424 mmol) afforded the *diol* **23** (117.2 mg, 87%) as needles (from diethyl ether–hexane), m.p. 120–121 °C (Found: C, 73.85; H, 8.75%; $M^+$, 276.1715); $[\alpha]_D^{24}$ −20.4° (*c* 0.59 in $CHCl_3$); $\nu_{max}(CHCl_3)/cm^{-1}$ 3450 (OH); $\delta_H$(500 MHz; $CDCl_3$) 0.58 (3 H, s, MeC), 3.78 (3 H, s, *Me*OAr) and 6.66–6.95 (3 H, m, ArH).

(+)-(2S,3′S,3a′S,9b′R)-trans-2-(2′,3′,3a′,4′,5′,9b′-*Hexahydro-7′-methoxy-3a′-methyl-1′H-cyclopenta*[a]*naphthalen-3′-yl*)-2-*hydroxyethyl Benzoate* **20**.—A solution of the diol **19** (91.5 mg, 0.33 mmol), pyridine (0.06 $cm^3$, 0.74 mmol), a catalytic amount of DMAP, and benzoyl chloride (0.04 $cm^3$, 0.34 mmol) in $CH_2Cl_2$ (1 $cm^3$) was stirred for 2 h. The mixture was diluted with water and extracted with $CH_2Cl_2$. The extract was washed successively with 10% HCl, saturated aq. sodium hydrogen carbonate, and saturated aq. NaCl. The residue upon work-up was chromatographed with hexane–ethyl acetate (19:1 v/v) to give the *benzoate* **20** (116 mg, 92%) as an oil (Found: $M^+$, 380.2011. $C_{24}H_{28}O_4$ requires M, 380.198 8); $[\alpha]_D^{25}$ +26.9° (*c* 0.87 in $CHCl_3$); $\nu_{max}$(neat)/$cm^{-1}$ 1720 (C=O); $\delta_H$(90 MHz; $CDCl_3$) 0.69 (3 H, s, MeC), 3.78 (3 H, s, *Me*OAr), 6.62–6.97 (3 H, m, ArH) and 7.36–8.18 (5 H, m, ArH); *m/z* 380 ($M^+$).

(+)-(2S,3′R,3a′R,9b′S)-trans-2-(2′,3′,3a′,4′,5′,9b′-*Hexahydro-7′-methoxy-3a′-methyl-1′H-cyclopenta*[a]*naphthalen-3′-yl*)-2-*hydroxyethyl Benzoate* **24**.—By following the same procedure described for compound **19**, the diol **23** (39 mg, 0.141 mmol) afforded the *benzoate* **24** (44.2 mg, 82%) as an oil (Found: $M^+$, 380.2000); $[\alpha]_D^{23}$ +5.6° (*c* 1.06 in $CHCl_3$); $\nu_{max}$(neat)/$cm^{-1}$ 1720 (C=O); $\delta_H$(90 MHz; $CDCl_3$) 0.70 (3 H, s, MeC), 3.78 (3 H, s, *Me*OAr), 6.15–6.99 (3 H, m, ArH) and 7.38–8.14 (5 H, m, ArH).

(+)-(3′S,3a′S,9b′R)-trans-2-(2′,3′,3a′,4′,5′,9b′-*Hexahydro-7′-methoxy-3a′-methyl-1′H-cyclopenta*[a]*naphthalen-3′-yl*)-2-*oxoethyl Benzoate* **21**.—To a stirred suspension of PCC (55 mg, 0.26 mmol) and Florisil (50 mg) in $CH_2Cl_2$ (2 $cm^3$) was added the alcohol **20** (20.5 mg, 0.05 mmol). After being stirred for 2 h at room temperature, the mixture was diluted with diethyl ether and filtered through Celite. The residue upon evaporation of the filtrate was chromatographed with hexane–ethyl acetate (90:10 v/v) to give the *ketone* **21** (19.8 mg, 97%) as needles (from diethyl ether–hexane), m.p. 91–92 °C (Found: C, 75.95; H, 6.9%; $M^+$, 378.1799. $C_{24}H_{26}O_4$ requires C, 76.15; H, 6.75%; M, 378.1831; $[\alpha]_D^{24}$ +90.8° (*c* 1.17 in $CHCl_3$); $\nu_{max}(CHCl_3)/cm^{-1}$ 1720 (C=O); $\delta_H$(500 MHz; $CDCl_3$) 0.62 (3 H, s, MeC), 3.81 (3 H, s, *Me*OAr), 6.64–6.99 (3 H, m, ArH) and 7.46–8.18 (5 H, m, ArH).

(−)-(3′R,3a′R,9b′S)-trans-2-(2′,3′,3a′,4′,5′,9b′-*Hexahydro-7′-methoxy-3a′-methyl-1′H-cyclopenta*[a]*naphthalen-3′-yl*)-2-*oxoethyl Benzoate* **25**.—By following the same procedure described for compound **20**, the alcohol **24** (11.2 mg, 0.029 mmol) afforded the *ketone* **25** (9.4 mg, 84%) as needles (from diethyl ether–hexane), m.p. 91–92 °C (Found: C, 76.1; H, 6.95%; $M^+$, 378.1796); $[\alpha]_D^{23}$ −98.9° (*c* 0.55 in $CHCl_3$); $\nu_{max}(CHCl_3)/cm^{-1}$ 1720 (C=O); $\delta_H$(90 MHz; $CDCl_3$) 0.62 (3 H, s, MeC), 3.81 (3 H, s, *Me*OAr), 6.64–6.99 (3 H, m, ArH) and 7.46–8.18 (5 H, m, ArH); *m/z* 378 ($M^+$).

(−)-(1′S,3S,3aS,9aS,9bS)-anti-trans-3-(1′,2′-*Dihydroxyethyl*)-1,2,3,3a,4,5,8,9,9a,9b-*decahydro*-3a-*methylcyclopenta*[a]*naphthalen-7-one* **26**.—To a stirred solution of the acetonide **2** (525.4 mg, 1.63 mmol) in a mixture of THF (52 $cm^3$), EtOH (1 $cm^3$) and liquid ammonia (120 $cm^3$) at −78 °C was added lithium metal (560 mg, 80.7 mmol). After being stirred for 45 min at the same temperature, the mixture was treated with EtOH and evaporated to leave a residue, which was diluted with water and extracted with diethyl ether. The extract was washed with saturated aq. NaCl. The residue upon work-up was dissolved in MeOH (10 $cm^3$) containing 10% HCl (0.6 $cm^3$) and was stirred for 13 h at room temperature, neutralized with saturated aq. sodium hydrogen carbonate, and evaporated to give a residue, which was diluted with water and extracted with $CH_2Cl_2$. The extract was washed with saturated aq. NaCl. The residue upon work-up was chromatographed with hexane–ethyl acetate (1:1 v/v) to give the *enone* **26** (328.8 mg, 75%) as an oil (Found: $M^+$, 264.1759. $C_{16}H_{24}O_3$ requires M, 264.1725); $[\alpha]_D^{25}$ −11.7° (*c* 1.33 in $CHCl_3$); $\nu_{max}$(neat)/$cm^{-1}$ 3450 (OH) and 1660 (C=O); $\delta_H$(90 MHz; $CDCl_3$) 0.92 (3 H, s, MeC) and 5.87 (1 H, br s, C=CHC); *m/z* 264 ($M^+$).

(+)-(3S,3aS,4′S,9aS,9bS)-anti-trans-3-(2′,2′-*Dimethyl-1′,3′-dioxolan-4′-yl*)-1,2,3,3a,4,5,8,9,9a,9b-*decahydro*-3a-*methylcyclopenta*[a]*naphthalen-7-one* **27**.—A solution of the diol **26** (49 mg, 0.18 mmol), 2,2-dimethoxypropane (0.11 $cm^3$, 0.9 mmol), and a catalytic amount of *d*-camphor-10-sulphonic acid in $CH_2Cl_2$ (3 $cm^3$) was stirred for 1 h at room temperature. The mixture was washed successively with saturated aq. sodium hydrogen carbonate and saturated aq. NaCl. The residue upon work-up was chromatographed with hexane–ethyl acetate (9:1 v/v) to give the *acetonide* **27** (50.8 mg, 94%) as an oil (Found: C, 74.95; H, 9.25%; $M^+$, 304.2038. $C_{19}H_{28}O_3$ requires C, 74.45; H, 9.25%; M, 304.2039); $[\alpha]_D^{23}$ +2.6° (*c* 1.33 in $CHCl_3$); $\nu_{max}$(neat)/$cm^{-1}$ 1660 (C=O); $\delta_H$(90 MHz; $CDCl_3$) 0.92 (3 H, s, MeC), 1.36 and 1.40 (6 H, each s, $Me_2C$) and 5.88 (1 H, br s, C=CH); *m/z* 304 ($M^+$).

(+)-(3S,3aS,4′S,5aS,6S,9aR,9bS)-trans-anti-trans-6-(3-*Chlorobut-2-enyl*)-3-(2′,2′-*dimethyl-1′,3′-dioxolan-4′-yl*)-1,2,3,3a,-4,5,5a,6,8,9,9a,9b-*dodecahydro*-3a-*methylcyclopenta*[a]*naphthalen-7-one* **28**.—To a stirred solution of lithium (16.7 mg, 2.4 mmol) in liquid ammonia (6 $cm^3$) at −78 °C was added a solution of the enone **27** (48.8 mg, 0.16 mmol) in THF (2 $cm^3$). After being stirred for 30 min at −78 °C, the mixture was treated with 1-bromo-3-chlorobut-2-ene (0.22 $cm^3$, 1.728 mmol) and was stirred for 30 min at the same temperature. The residue upon evaporation of the solvent was diluted with water and extracted with diethyl ether. The extract was washed with saturated aq. NaCl. The residue upon work-up was chromatographed with hexane–ethyl acetate (97:3 v/v) to give the *vinyl chloride* **28** (37.3 mg, 59%) as an oil (Found: $M^+$, 394.228 2. $C_{23}H_{35}ClO_3$ requires M, 394.227 4); $[\alpha]_D^{24}$ +17.3° (*c* 1.26 in $CHCl_3$); $\nu_{max}$(neat)/$cm^{-1}$ 1710 (C=O); $\delta_H$(90 MHz; $CDCl_3$) 0.82 (3 H, s, MeC), 1.30 and 1.34 (6 H, each s, $Me_2C$), 2.05 (3 H, s, C=CClMe) and 5.53 (1 H, m, CH=CCl); *m/z* 394 ($M^+$).

(+)-(1′S,3S,3aS,5aS,6R,9aR,9bS)-trans-anti-trans-3-(1′,2′-*Dihydroxyethyl*)-1,2,3,3a,4,5,5a,6,8,9,9a,9b-*dodecahydro*-3a-*methyl*-6-(3-*oxobutyl*)*cyclopenta*[a]*naphthalen-7-one* **29**.—A solution of the vinyl chloride **28** (8 mg, 0.02 mmol) and mercury(II) trifluoroacetate (34.3 mg, 0.08 mmol) in nitrometh-

* As footnote on p. 1310.

ane (1 $cm^3$) was stirred for 3 h. The mixture was then treated with 10% HCl (0.5 $cm^3$), stirred for 1 h and extracted with $CHCl_3$. The extract was washed with saturated aq. NaCl. The residue upon work-up was chromatographed with hexane–ethyl acetate (1:1 v/v) to give the *diketone* **29** (5 mg, 73%) as an oil (Found: $M^+$, 336.2309. $C_{20}H_{32}O_4$ requires M, 336.2301); $[\alpha]_D^{23}$ +8.1° (*c* 0.52 in $CHCl_3$); $\nu_{max}$(neat)/$cm^{-1}$ 3420 (OH) and 1710 (C=O); $\delta_H$(90 MHz; $CDCl_3$) 0.83 (3 H, s, MeC) and 2.10 (3 H, s, MeC=O); *m/z* 336 ($M^+$).

(+)-(20S)-20,21-*Dihydroxy*-19-*norpregn*-4-*en*-3-*one* **30**.—A solution of the diketone **29** (5 mg, 0.015 mmol) and 10% aq. KOH (0.1 $cm^3$) in MeOH (1 $cm^3$) was stirred for 2 h. The mixture was diluted with water and extracted with $CHCl_3$. The extract was washed with saturated aq. NaCl. The residue upon work-up was chromatographed with hexane–ethyl acetate (1:1 v/v) to give the *enone* **30** (3.8 mg, 81%) as an oil (Found: $M^+$, 318.2184. $C_{20}H_{30}O_3$ requires M, 318.2195); $[\alpha]_D^{23}$ +35.6° (*c* 1.00 in $CHCl_3$); $\nu_{max}$(neat)/$cm^{-1}$ 3450 (OH) and 1660 (C=O); $\delta_H$(90 MHz; $CDCl_3$) 0.78 (3 H, s, MeC) and 5.82 (1 H, br s, C=CHC=O); *m/z* 318 ($M^+$).

(+)-(20S)-20,21-*Dihydroxy*-19-*norpregn*-4-*en*-5-*one* 21-*Benzoate* **31**.—To a stirred solution of the diol **30** (19 mg, 0.06 mmol), pyridine (0.04 $cm^3$, 0.5 mmol) and a catalytic amount of DMAP in $CH_2Cl_2$ (1 $cm^3$) was added benzoyl chloride (0.008 $cm^3$, 0.065 mmol) and the mixture was stirred for 1 h, diluted with water and extracted with $CH_2Cl_2$. The extract was washed successively with 10% HCl, saturated aq. sodium hydrogen carbonate, and saturated aq. NaCl. The residue upon work-up was chromatographed with hexane–ethyl acetate (1:1 v/v) to give the *benzoate* **31** (13.1 mg, 52%) as an oil (Found: $M^+$, 422.2457. $C_{27}H_{34}O_4$ requires M, 422.2457); $[\alpha]_D^{25}$ +40.0° (*c* 0.32 in $CHCl_3$); $\nu_{max}$(neat)/$cm^{-1}$ 3400 (OH), 1710 and 1660 (C=O); $\delta_H$(90 MHz; $CDCl_3$) 0.86 (3 H, s, MeC), 5.81 (1 H, br s, C=CHC=O) and 7.38–8.10 (5 H, m, ArH); *m/z* 422 ($M^+$).

(+)-11-*Deoxy*-19-*corticosterone Benzoate* **32**.—To a stirred suspension of PCC (19.8 mg, 0.09 mmol) and Florisil (20.6 mg) in $CH_2Cl_2$ (2 $cm^3$) was added the alcohol **31** (4.2 mg, 0.01 mmol). After being stirred for 5 h, the mixture was diluted with diethyl ether and filtered through Celite. The residue upon evaporation of the filtrate was chromatographed with hexane–ethyl acetate (1:1 v/v) to give the *ketone* **32** (3.1 mg, 76%) as needles (from acetone–diethyl ether), m.p. 216–217 °C (Found: $M^+$, 420.2291. $C_{27}H_{32}O_4$ requires M, 420.2301); $[\alpha]_D^{24}$ +74.9° (*c* 0.43 in $CHCl_3$); $\nu_{max}$($CHCl_3$)/$cm^{-1}$ 1710 and 1660 (C=O); $\delta_H$(90 MHz; $CDCl_3$) 0.78 (3 H, s, MeC), 4.72 and 5.00 (2 H, each d, *J* 16.3, $CH_2OBz$), 5.86 (1 H, br s, C=CHCO) and 7.38–8.16 (5 H, m, ArH); *m/z* 420 ($M^+$).

(+)-11-*Deoxy*-19-*norcorticosterone* **1**.—A mixture of the benzoate **32** (4 mg, 0.01 mmol), $K_2CO_3$ (7.5 mg) and MeOH–$CH_2Cl_2$–water (20:10:1 v/v) (1.5 $cm^3$) was stirred for 80 min, diluted with water and extracted with $CHCl_3$. The extract was washed with saturated aq. NaCl. The residue upon work-up was chromatographed with hexane–ethyl acetate (1:1 v/v) to give the alcohol **1** (2.7 mg, 90%) as needles (from acetone–hexane), m.p. 123–124 °C; $[\alpha]_D^{24}$ +97.0° (*c* 0.27 in $CHCl_3$) {lit., [3a,*] m.p. 124–125 °C; $[\alpha]_D^{24}$ +98.5° (*c* 0.13 in $CHCl_3$)}.

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* As footnote on p. 1311.

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