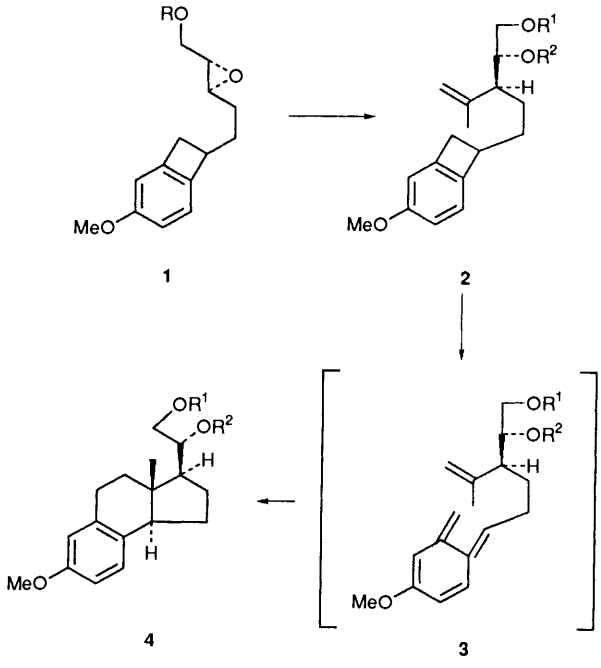
Concise and Practical Approach to Chiral Des-A B-trienic Corticosteroids

Hideo Nemoto, Atsushi Satoh and Keiichiro Fukumoto*
Pharmaceutical Institute, Tohoku University, Aobayama, Sendai 980, Japan

A concise and practical route to the enantiomerically pure des-A B-trienic steroid **14** was developed by thermolysis of the optically active alkenic benzocyclobutene **13** obtained by selective nucleophilic addition of isopropenyl group to the chiral epoxide **9** as a key step.

Much effort[1] has been devoted to the chemistry of corticosteroids because of their physiological and also their clinical importance.[2] Recent activity in this field has led to a number of efficient methods for introducing dihydroxyacetone[3] and oxygen[4] substituents at C-17 and C-11, respectively, of steroidal compounds; such functionalities are important for the physiological activity of this type of steroids. Recently, analogous compounds lacking the usual tetracyclic steroid structure (*e.g.*, 16,17-secosteroids or compounds without either ring D or A of the steroid nucleus) have attracted much attention because of their hormonal or antihormonal activities.[5] These facts have stimulated us to explore an effective methodology which could be applied to the chiral synthesis of both enantiomers of des-A B-trienic steroids[6] having dihydroxyethyl substituents at C-17 suitable for generating the dihydroxyacetone moiety of corticoids, so that the physiological activities of both enantiomers[7] of such compounds could be evaluated. Our synthetic strategy for the compound **4** is characterized by the one-step creation of the B, C and D rings in a stereoselective manner by an intramolecular [4 + 2] cycloaddition of the alkenic *o*-quinodimethane **3** generated *in situ* by regio- and stereo-selective epoxide-ring opening of the chiral epoxide **1** with an isopropenyl group to give compound **2**, and herein we describe our results (see Scheme 1).

The benzocyclobutenyl aldehyde **5**,[6a] easily prepared in large quantities from 1-cyano-4-methoxybenzocyclobutene,[8] was subjected to the Wadsworth–Emmons reaction under Masamune's modified procedure[9] to give the unsaturated ester **6** selectively (94%), which on reduction with diisobutylaluminium hydride (DIBAH) afforded the alcohol **7** (93%). Asymmetric epoxidation of the allyl alcohol **7** was effected by following the Sharpless procedure to give the chiral epoxy alcohol **8a** (91%) with a high degree (97% e.e) of enantiomeric excess.† Silylation (99%) of the epoxy alcohol **8a** followed by nucleophilic addition of the isopropenyl group to the resulting epoxy silyl ether **9** afforded the addition products **10** and **11** in the ratio 1 : 3 (89%) in moderate regio- and high stereo-selective manner.[10] The major product **11**, which was easily separated on silica gel column chromatography from the minor product **10**, was then deprotected to give the diol **12** (95%), which on protection afforded the acetonide **13** (84%). Finally the thermolysis of **13** furnished our aimed-for *trans*-fused des-A B-trienic steroid **14** (98%) {$[\alpha]_D^{20}$ -1.4×10^{-1} deg cm^2 g^{-1} (*c* 1.01, $CHCl_3$)} as a single product which was identical with the authentic enantiomer[6c] **14** in all aspects including ^{1}H NMR (500 MHz; $CDCl_3$) and IR ($CHCl_3$) spectra and optical rotation {opposite sign and almost the same degree; $[\alpha]_D^{20}$ +1.6 (*c* 0.92, $CHCl_3$)} (see Scheme 2).



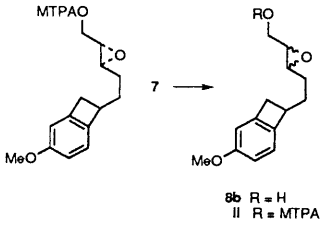
Scheme 1

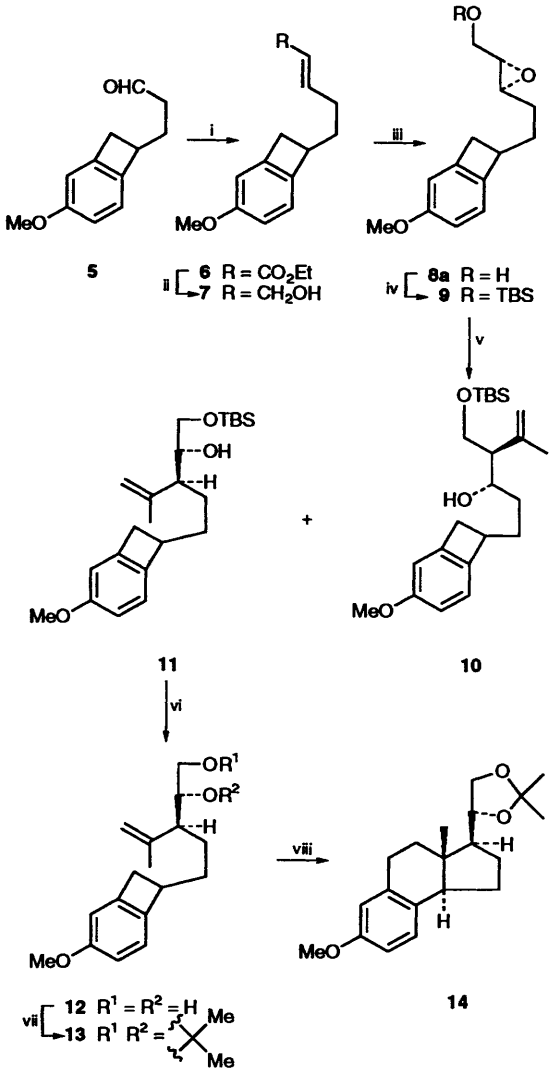
Thus, we have developed a short and practical route to chiral des-A B-trienic steroid having a suitable substituent at C-17 for generating the dihydroxyacetone moiety of corticosteroids. It should be noted that the methodology described above could be applied to the chiral synthesis of enantiomers by simply changing the chiral auxiliary in the epoxide-forming step.

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. NMR spectra were obtained on JEOL FX-90 and JNM GX-500 spectro-

† The enantiomeric excess of this epoxy alcohol **8a** was determined by comparison of the ^{1}H NMR (500 MHz) spectra of the 'methoxy(trifluoromethyl)phenylacetyl' (MTPA) esters **i** and **ii** derived [MTPA acid, dicyclohexylcarbodiimide (DCC), 4-(dimethylamino)pyridine (DMAP), CH_2Cl_2, room temp., 22 h] from the alcohol **8a** and the corresponding racemic epoxy alcohol **8b**, which was prepared by epoxidation [Bu^{t}OOH, $VO(acac)_2$ (acac = pentane-2,4-dionato), CH_2Cl_2, 0 °C, 30 min] of compound **7**, respectively.





Scheme 2 *Reagents and conditions:* i, $(EtO)_2P(O)CH_2CO_2Et$, LiCl, DBU, MeCN, room temp., 1 h; ii, DIBAH, CH_2Cl_2, −78 °C, 1 h; iii, Bu^tOOH, $Ti(OPr^i)_4$, (+)-diisopropyl L-tartrate, 4 Å molecular sieves, CH_2Cl_2, −30 °C, 14 h; iv, TBSCl, DMAP, imidazole, DMF, room temp., 2 h; v, isopropenylmagnesium bromide, CuI, THF–Et_2O, −21 °C, 20 h; vi, Bu_4NF, THF, room temp., 12 min; vii, 2,2-dimethoxypropane, CSA, CH_2Cl_2, room temp., 3 h; viii, ODB, 180 °C, 13 h (DBU = 1,8-diazabicyclo[5.4.0]undec-7-ene, DMF = dimethylformamide, THF = tetrahydrofuran, CSA = camphor-10-sulfonic acid, ODB = *o*-dichlorobenzene)

meters. Chemical shifts were recorded relative to internal $SiMe_4$, and *J* values are given in Hz. Mass spectra were taken on Hitachi M-52 G and JEOL-TMS-OISG-2 spectrometers. Optical rotations were measured with a JASCO-DIP-340 polarimeter, and are given in units of 10^{-1} deg cm^2 g^{-1}. 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 Experimental section were homogeneous on TLC.

(2E)-*Ethyl* 5-(1,2-*Dihydro*-4-*methoxybenzocyclobuten*-1-*yl*)-*pent*-2-*enoate* **6**.—To a stirred suspension of lithium chloride (1.7 g, 40.1 mmol) in MeCN (180 cm^3) was added ethyl (diethoxyphosphonyl)acetate (7.7 cm^3, 38.6 mmol), 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) (5.0 ml, 33.4 mmol) and a solution of the aldehyde **5** in MeCN (20 cm^3) at room temperature and the mixture was stirred for 1 h at the same temperature. The residue obtained upon evaporation of the solvent was treated with water and extracted with $CHCl_3$. The combined extracts were washed successively with 10% aq. HCl, saturated aq. $NaHCO_3$, and aq. NaCl. The residue obtained upon work-up was chromatographed with hexane–AcOEt (97:3 v/v) to give the *ester* **6** (6.78 g, 94%) as an oil (Found: C, 73.7; H, 7.8. $C_{16}H_{20}O_3$ requires C, 73.82; H, 7.74%); ν_{max}(neat)/cm^{-1} 1715 (C=O); δ_H(90 MHz; $CDCl_3$) 1.28 (3 H, t, *J* 7.2, CO_2CH_2Me), 3.76 (3 H, s, ArO*Me*), 4.18 (2 H, q, *J* 7.2, CO_2CH_2Me) and 5.85 (1 H, d, *J* 14.4, C=$CHCO_2$); *m*/*z* 160 (M^+).

(2E)-5-(1,2-*Dihydro*-4-*methoxybenzocyclobuten*-1-*yl*)*pent*-2-*en*-1-*ol* **7**.—To a stirred solution of the ester **6** (5.69 g, 2.18 mmol) in CH_2Cl_2 (50 cm^3) was added a 0.95 mol dm^{-3} solution of DIBAH in hexane (46 cm^3, 43.7 mmol) at −78 °C and the mixture was stirred for 45 min at the same temperature. Then, the reaction mixture was treated with saturated aq. NH_4Cl and extracted with CH_2Cl_2. The combined extracts were filtered through Celite. The residue obtained upon work-up was chromatographed with hexane–AcOEt (17:3 v/v) to give the *alcohol* **7** (4.44 g, 93%) as an oil (Found: C, 77.3; H, 8.35. $C_{14}H_{18}O_2$ requires C, 77.03; H, 8.31%); ν_{max}(neat)/cm^{-1} 3350 (OH); δ_H(90 MHz; $CDCl_3$) 3.77 (3 H, s, ArO*Me*), 4.10 (2 H, d, *J* 3.6, CH_2O), 5.66–5.77 (2 H, m, CH=CH) and 6.68–7.02 (3 H, m, ArH); *m*/*z* 218 (M^+).

(2S,3S)-5-(1,2-*Dihydro*-4-*methoxybenzocyclobuten*-1-*yl*)-2,3-*epoxypentan*-1-*ol* **8a**.—To a stirred suspension of 4 Å molecular sieves (0.65 g) in CH_2Cl_2 (20 cm^3) was added a 1.0 mol dm^{-3} solution of diisopropyl L-tartrate in CH_2Cl_2 (2.2 cm^3, 2.20 mmol) and titanium tetraisopropoxide (0.45 cm^3, 1.50 mmol) at −20 °C. After being stirred for 10 min at the same temperature, the reaction mixture was treated with a 3.5 mol dm^{-3} solution of Bu^tOOH in CH_2Cl_2 (10.0 cm^3, 35.0 mmol) and stirred for 10 min at the same temperature. To this reaction mixture was added a solution of the allyl alcohol **7** (3.16 g, 14.5 mmol) in CH_2Cl_2 (8 cm^3) at −30 °C and the mixture was stirred for 14 h at the same temperature. The reaction mixture was then diluted with water (15 cm^3), saturated with NaCl, and treated with 30% aq. NaOH (1.5 cm^3). After the mixture had been stirred for 10 min at room temperature, the organic layer was filtered through Celite. The residue obtained upon work-up was chromatographed with hexane–AcOEt (4:1 v/v) to give the *chiral epoxide* **8a** (3.08 g, 91%) as an oil (Found: C, 71.7; H, 7.85. $C_{14}H_{18}O_3$ requires C, 71.77; H, 7.74%); ν_{max}(neat)/cm^{-1} 3430 (OH); δ_H(90 MHz; $CDCl_3$) 3.77 (3 H, s, ArO*Me*) and 6.68–7.02 (3 H, m, ArH); *m*/*z* 234 (M^+).

5-(1,2-*Dihydro*-4-*methoxybenzocyclobuten*-1-*yl*)-2,3-*epoxypentan*-1-*ol* **8b**.—To a stirred solution of the allyl alcohol **7** (23.7 mg, 0.108 mmol) in CH_2Cl_2 (1 cm^3) was added a catalytic amount of vanadyl acetylacetonate and a 3.2 mol dm^{-3} solution of Bu^tOOH in CH_2Cl_2 (0.05 cm^3, 0.16 mmol) at 0 °C and the mixture was stirred for 4 h at room temperature. The reaction mixture was then filtered through a short plug of silica gel. The residue obtained upon evaporation of the filtrate was chromatographed with hexane–AcOEt (17:3 v/v) to give the *epoxide* **8b** (21.7 mg, 85%) as an oil (Found: M^+, 234.1258. $C_{14}H_{18}O_3$ requires M, 234.1256); ν_{max}(neat)/cm^{-1} 3430 (OH); δ_H(90 MHz; $CDCl_3$) 3.77 (3 H, s, ArO*Me*) and 6.68–7.02 (3 H, m, ArH); *m*/*z* 234 (M^+).

Preparation and Analysis of Mosher's Esters.—(1'S)-5-(1,2-*Dihydro*-4-*methoxybenzocyclobuten*-1-*yl*)-2,3-*epoxypentyl* 2',2',2'-*trifluoro*-1'-*methoxy*-1'-*phenylpropionate* **ii**. To a stirred solution of the alcohol **8b** (25.9 mg, 0.11 mmol), 2,2,2-trifluoro-

1-methoxy-1-phenylpropionic acid [(*S*)-α-methoxy-α-(trifluoromethyl)phenylacetic acid; Mosher's acid] (32.0 mg, 0.136 mmol) and a catalytic amount of DMAP in CH_2Cl_2 (11 cm^3) was added DCC (65.0 mg, 0.315 mmol) at 0 °C and the mixture was stirred for 22 h at the same temperature. The reaction mixture was diluted with Et_2O and washed successively with 10% aq. HCl, saturated aq. $NaHCO_3$, and aq. NaCl. The residue obtained upon work-up was chromatographed with hexane–AcOEt (19:1 v/v) to give the *ester* **ii** (41.6 mg, 96%) as an oil (Found: M^+, 450.1686. $C_{24}H_{25}F_3O_5$ requires M, 450.1654); ν_{max}(neat)/cm^{-1} 1750 (C=O); δ_H(500 MHz; $CDCl_3$) 3.56 (3 H, s, OMe), 3.77 (3 H, s, ArO*Me*), 4.22–4.26 (1 H, m, OCOCH*H*), 4.54, 4.55, 4.57 and 4.58 (1 H, each dd, *J* 3.7 and 11.9, OCOC*H*H), 6.68 (1 H, s, ArH), 6.73 (1 H, d, *J* 7.9, ArH), 6.95 (1 H, d, *J* 7.9, ArH) and 7.36–7.53 (5 H, m, ArH); *m/z* 450 (M^+).

By following the same procedure described above, the chiral epoxy alcohol **8a** was converted into the ester **i** (complete reaction by TLC). The residue obtained upon work-up was passed through a short plug of silica gel with hexane–AcOEt (20:1 v/v). ^1H NMR analysis in $CDCl_3$ at 500 MHz focused on HC*H*OMTPA. These protons were typically observed as two pairs of diastereoisomeric double doublets due to another chiral centre at C-1 of benzocyclobutenyl group at δ 4.54–4.58. The downfield pair at δ 4.58 and the upfield pair at δ 4.54 were compared by integration to determine the enantiomeric excess, which was shown to be 97%.

(2S,3S)-1-(tert-*Butyldimethylsiloxy*)-5-(1,2-*dihydro*-4-*methoxybenzocyclobuten*-1-*yl*)-2,3-*epoxypentane* **9**.—To a stirred solution of the alcohol **8a** (51.8 mg, 0.22 mmol), imidazole (30.9 mg, 0.454 mmol), and a catalytic amount of DMAP in dimethylformamide (DMF) (1 cm^3) was added *tert*-butyldimethylsilyl chloride TBDMSCl (53.3 mg, 0.354 mmol) at room temperature and the mixture was stirred for 2 h at the same temperature. The reaction mixture was diluted with Et_2O and washed successively with 10% aq. HCl, saturated aq. $NaHCO_3$, and aq. NaCl. The residue obtained upon work-up was chromatographed with hexane–AcOEt (19:1 v/v) to give the *silyl ether* **9** (77.5 mg, 99%) as an oil (Found: C, 69.1; H, 9.2. $C_{20}H_{32}O_3Si$ requires C, 68.92; H, 9.25%); δ_H(90 MHz; $CDCl_3$) 0.08 (6 H, s, $SiMe_2$), 0.90 (9 H, s, $SiCMe_3$), 3.78 (3 H, s, ArO*Me*) and 6.68–7.02 (3 H, m, ArH); *m/z* 348 (M^+).

(2R,3S)-1-(tert-*Butyldimethylsiloxy*)-3-[2'-(1,2-*dihydro*-4-*methoxybenzocyclobuten*-1-*yl*)*ethyl*]-4-*methylpent*-4-*en*-2-*ol* **11** *and* (3S,4R)-4-(tert-*Butyldimethylsiloxymethyl*)-1-(1,2-*dihydro*-4-*methoxybenzocyclobuten*-1-*yl*)-5-*methylhex*-5-*en*-3-*ol* **10**.—To a stirred suspension of CuI (0.257 g, 1.345 mmol) in Et_2O (5 cm^3) was added a solution of isopropenylmagnesium bromide in tetrahydrofuran (THF)–Et_2O (4:1) (25 cm^3) [prepared from Mg (1.15 g, 47.3 mmol) and isopropenyl bromide (3.1 cm^3, 32.5 mmol)] at −21 °C and the mixture was stirred for 10 min before a solution of the epoxide **9** (2.57 g, 7.39 mmol) in Et_2O (5 cm^3) was added at −21 °C. After being stirred for 20 h at the same temperature, the reaction mixture was treated with saturated aq. NH_4Cl and extracted with Et_2O. The combined extracts were washed with saturated aq. NaCl. The residue obtained upon work-up was chromatographed with hexane–Et_2O (49:1 v/v) to give the *alcohol* **11** (2.1 g, 68%) as an oil (Found: C, 70.4; H, 9.85. $C_{23}H_{38}O_3Si$ requires C, 70.72; H, 9.81%); ν_{max}(neat)/cm^{-1} 3500 (OH); δ_H(500 MHz; $CDCl_3$) 0.07 (6 H, s, $SiMe_2$), 0.89 (9 H, s, $SiCMe_3$), 1.55 (3 H, br s, C=CMe), 3.77 (3 H, s, ArO*Me*), 4.72 and 4.78 (2 H, each br s, $C=CH_2$) and 6.67–7.02 (3 H, m, ArH); *m/z* 390 (M^+).

The second fraction afforded the *alcohol* **10** (0.62 g, 21%) as an oil (Found: C, 70.7; H, 9.9%); ν_{max}(neat)/cm^{-1} 3480 (OH); δ_H(500 MHz; $CDCl_3$) 0.09 (6 H, s, $SiMe_2$), 0.90 (9 H, s, $SiCMe_3$), 1.70 (3 H, br s, C=CMe), 3.77 (3 H, s, ArO*Me*), 4.76 and 4.86 (2 H, each br s, $C=CH_2$) and 6.67–7.71 (3 H, m, ArH); *m/z* 390 (M^+).

(2R,3S)-3-[2'-(1,2-*Dihydro*-4-*methoxybenzocyclobuten*-1-*yl*)-*ethyl*]-4-*methylpent*-4-*ene*-1,2-*diol* **12**.—To a stirred solution of the silyl ether **11** (5.15 mg, 1.32 mmol) in THF (20 cm^3) was added a 1.0 mol dm^{-3} solution of Bu_4NF in THF (2.0 cm^3, 2.0 mmol) at room temperature and the mixture was stirred for 10 min at the same temperature. The reaction mixture was diluted with CH_2Cl_2 and washed with saturated aq. NaCl. The residue obtained upon work-up was chromatographed with hexane–AcOEt (3:1 v/v) to give the *diol* **12** (346 mg, 95%) as an oil (Found: C, 73.7; H, 8.9. $C_{17}H_{24}O_3$ requires C, 73.88; H, 8.75%); ν_{max}(neat)/cm^{-1} 3400 (OH); δ_H(90 MHz; $CDCl_3$) 1.62 (3 H, br s, C=CMe), 3.76 (3 H, s, ArO*Me*), 4.77 and 4.83 (2 H, each br s, $C=CH_2$) and 6.68–7.03 (3 H, m, ArH); *m/z* 276 (M^+).

(4R,1'S)-4-{1'-[2-(1,2-*Dihydro*-4-*methoxybenzocyclobuten*-1-*yl*)*ethyl*]-2'-*methylprop*-2'-*enyl*}-2,2-*dimethyl*-1,3-*dioxolane* **13**.—To a stirred solution of the diol **12** (1.18 g, 4.29 mmol) in CH_2Cl_2 (9 cm^3) was added a catalytic amount of camphor-10-sulfonic acid (CSA) and 2,2-dimethoxypropane (2.6 cm^3, 21.2 mmol) at room temperature and the mixture was stirred for 3 h, diluted with CH_2Cl_2, and washed successively with saturated aq. $NaHCO_3$ and aq. NaCl. The residue obtained upon work-up was chromatographed with hexane–AcOEt (19:1 v/v) to give the *acetonide* **13** (1.14 g, 84%) as an oil (Found: C, 75.7; H, 9.0. $C_{20}H_{28}O_3$ requires C, 75.91; H, 8.92%); δ_H(90 MHz; $CDCl_3$) 1.38 and 1.42 (each 3 H, each s, CMe_2), 1.63 (3 H, br s, C=CMe), 3.78 (3 H, s, OMe), 4.76 (2 H, br s, $C=CH_2$) and 6.68–7.03 (3 H, m, ArH); *m/z* 316 (M^+).

(4R,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* **14**.—A stirred solution of the benzocyclobutene **13** (1.14 g, 3.61 mmol) in *o*-dichlorobenzene (ODB) (360 cm^3) was refluxed for 13 h. The residue obtained upon evaporation of the solvent was chromatographed with hexane–AcOEt (17:3 v/v) to give the *des-A B-trienic steroid* **14** (1.13 g, 98%) as prisms, m.p. 78–79 °C (from hexane); $[\alpha]_D^{20}$ − 1.4 (*c* 1.01, $CHCl_3$) (Found: C, 76.0; H, 9.0%); δ_H(500 MHz; $CDCl_3$) 0.57 (3 H, s, CMe), 1.38 and 1.40 (6 H, each s, CMe_2), 3.76 (3 H, s, ArO*Me*) and 6.67–6.93 (3 H, m, ArH); *m/z* 316 (M^+).

References

1 A. A. Akhrem and Y. A. Titov, *Total Steroid Synthesis*, Plenum Press, New York, 1970; *Terpenoids and Steroids*, The Chemical Society, London, vol. 1–12; R. T. Blickenstaff, A. C. Ghosh and G. C. Wolf, *Total Synthesis of Steroids*, Academic Press, New York, 1974.

2 For example, see: J. Elks and G. H. Phillipps, *Medicinal Chemistry, The Role of Organic Chemistry in Drug Research*, eds. S. M. Roberts and B. J. Price, Academic Press, London, 1985, p. 167.

3 J. E. Baldwin, O. W. Lever, Jr. and N. R. Tzodikov, *J. Org. Chem.*, 1976, **41**, 2312; V. Van Rheenen and K. P. Shephard, *J. Org. Chem.*, 1979, **44**, 1582; R. M. Moriarty, L. S. John and P. C. Du, *J. Chem. Soc., Chem. Commun.*, 1981, 641; D. H. R. Barton, W. B. Motherwell and S. Z. Zard, *J. Chem. Soc., Chem. Commun.*, 1981, 774; L. Nédélec, V. Torelli and M. Hardy, *J. Chem. Soc., Chem. Commun.*, 1981, 775; D. H. R. Barton, W. B. Motherwell and S. Z. Zard, *J. Chem. Soc., Chem. Commun.*, 1982, 551; A. R. Daniewski and W. Wojciechowska, *J. Org. Chem.*, 1982, **47**, 2993; D. Van Leusen and A. M. Van Leusen, *Tetrahedron Lett.*, 1984, **25**, 2581; Y. Tamura, T. Yakura, J. Haruta and Y. Kita, *Tetrahedron Lett.*, 1985, **26**, 3837; M. Fetizon, P. Goulaouic and I. Hanna, *Tetrahedron Lett.*, 1985, **26**, 4925; I. Nitta, S. Fujimori and H. Ueno, *Bull. Chem. Soc. Jpn.*, 1985, **58**, 978; I. Nitta, S. Fujimori, T. Haruyama, S. Inoue and H. Ueno, *Bull. Chem. Soc. Jpn.*, 1985, **58**, 981; I. Nitta, T. Haruyama, S. Fujimori, S. Inoue and H. Ueno, *Bull. Chem. Soc. Jpn.*, 1985, **58**, 1081; Y. Horiguchi, E. Nakamura and I. Kuwajima, *J. Org. Chem.*, 1986, **51**, 4323; *J. Am. Chem. Soc.*, 1989, **111**, 6257.

4 T. Kametani, M. Aizawa and H. Nemoto, *J. Chem. Soc., Perkin Trans. 1*, 1980, 2793; G. Stork and E. W. Logusch, *J. Am. Chem. Soc.*, 1980, **102**, 1218; G. Stork, G. Clark and C. S. Shiner, *J. Am. Chem. Soc.*, 1981, **103**, 4948; G. Stork and D. H. Sherman, *J. Am. Chem. Soc.*, 1982, **104**, 3758; G. Stork, J. D. Winkler and C. S. Shiner, *J. Am. Chem. Soc.*, 1982, **104**, 3767; B. B. Snider and T. C. Kirk, *J. Am. Chem. Soc.*, 1983, **105**, 2364; F. E. Ziegler and T.-F. Wang, *J. Am. Chem. Soc.*, 1984, **106**, 718; F. E. Ziegler and H. Lim, *J. Org. Chem.*, 1984, **49**, 3278.

5 L. O. Randall and J. J. Selitto, *Endocrinology*, 1958, **62**, 693; A. Boris and R. H. Stevens, *Endocrinology*, 1966, **78**, 549; G. Znati and M. E. Wolf, *J. Med. Chem.*, 1973, **16**, 90; H. Morales-Alanis, M. J. Brienne, J. Jacques, M.-M. Bouton, L. Nédélec, V. Torelli and C. Tournemine, *J. Med. Chem.*, 1985, **28**, 1796.

6 For our recent studies in this field, see: (*a*) H. Nemoto, N. Nagai, Y. Abe, M. Moizumi, K. Fukumoto and T. Kametani, *J. Chem. Soc., Chem. Commun.*, 1985, 1316; *J. Chem. Soc., Perkin Trans. 1*, 1987, 1727; (*b*) H. Nemoto, M. Moizumi, M. Nagai, K. Fukumoto and T. Kametani, *J. Chem. Soc., Perkin Trans. 1*, 1988, 885; (*c*) H. Nemoto, M. Ando and K. Fukumoto, *Tetrahedron Lett.*, 1990, **31**, 6205; (*d*) H. Nemoto, N. Matsuhashi, M. Imaizumi, M. Nagai and K. Fukumoto, *J. Org. Chem.*, 1990, **55**, 5625; (*e*) H. Nemoto, A. Satoh, M. Ando and K. Fukumoto, *J. Chem. Soc., Chem. Commun.*, 1990, 1001; *J. Chem. Soc., Perkin Trans. 1*, 1991, 1309.

7 For the enantiospecific biological effects, see: E. Juaristi, *Introduction to Stereochemistry and Conformational Analysis*, Wiley, New York, 1991, p. 106 and references cited therein.

8 T. Kametani, H. Matsumoto, H. Nemoto and K. Fukumoto, *J. Am. Chem. Soc.*, 1978, **100**, 6218.

9 M. A. Blanchette, W. Choy, J. T. Davis, A. P. Essenfeld, S. Masamune, W. R. Roush and T. Sakai, *Tetrahedron Lett.*, 1984, **25**, 2183.

10 For recent studies on this type of nucleophilic addition of various types of reagents to glycidol and related 2,3-epoxy alcohols, see: T. Suzuki, H. Saimoto, H. Tomioka, K. Oshima and H. Nozaki, *Tetrahedron Lett.*, 1982, **23**, 3597; A. Pfaltz and A. Mattenberger, *Angew. Chem., Int. Ed. Eng.*, 1982, **21**, 71; M. A. Tius and A. H. Fauq, *J. Org. Chem.*, 1983, **48**, 4131; J. M. Chong, D. R. Cyr and E. K. Mar, *Tetrahedron Lett.*, 1987, **28**, 5009; T. Skrydstrup, M. Bénéchie and F. Khuong-Huu, *Tetrahedron Lett.*, 1990, **31**, 7145; G. A. Molander and K. L. Bobbitt, *J. Org. Chem.*, 1992, **57**, 5031. For review, see: R. M. Hanson, *Chem. Rev.*, 1991, **91**, 437.

Paper 3/07349A
Received 13*th December* 1993
Accepted 4*th January* 1994