Rapid Enantioselective Access to Des-*AB*-trienic Corticosteroids *via* Intramolecular Cycloaddition

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

A short synthesis of an enantiomerically pure des-*AB*-trienic steroid **11** has been achieved by thermolysis of the optically active alkenic benzocyclobutene **9** obtained by selective nucleophilic addition of an isopropenyl group to the chiral epoxide **5** as a key step.

Because of their medicinal importance, corticosteroids have been much studied.[1] Recently, an efficient method for introducing dihydroxyacetone[2] and oxygen substituents[3] at C-17 and C-11, respectively, has given access to compounds with considerable physiological activity. This, together with the fact that analogous compounds lacking the usual tetracyclic steroid structure (*e.g.*, 16,17-secosteroids or compounds having neither ring *D* nor *A* of the steroid nucleus) have recently attracted much attention because of their hormonal or antihormonal activities,[4] has stimulated us to explore an effective methodology for the enantioselective synthesis of des-*AB*-trienic steroids having dihydroxyethyl substituents at C-17[5] suitable for generating the dihydroxyacetone moiety of corticosteroids. Our synthetic strategy for compound **11** 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 **10** generated *in situ* by thermolysis of the alkenic benzocyclobutene **9** which is effectively prepared by a regio- and stereo-selective epoxide ring-opening reaction of the chiral epoxide **5** with an isopropenyl group. Herein we describe our results.†

The benzocyclobutenyl aldehyde **1**,[5a] easily obtainable in large quantities from 1-cyano-4-methoxybenzocyclobutene,[6] was subjected to a Wadsworth–Emmons reaction under Masamune's modified procedure[7] to give the unsaturated ester **2** selectively (94%); this, on reduction with diisobutylaluminium hydride (DIBAH), afforded the alcohol **3** (93%). Asymmetric epoxidation of the allyl alcohol **3** was effected by following the Sharpless procedure to give the chiral epoxy alcohol **4** (91%) with a high degree (97% e.e.) of enantiomeric excess.‡ Silylation (99%) of the epoxy alcohol **4** followed by nucleophilic addition of the isopropenyl group to the resulting epoxy silyl ether **5** afforded the addition products **6** and **7** in the ratio of 1:3 (89%) in a moderate regio- and high stereo-selective manner.§ The major product **7**, which was easily separated by silica gel column chromatography from the minor product **6**, was then deprotected to give the diol **8** (95%); this on protection afforded the acetonide **9** (84%). Finally, thermolysis of **9** furnished the *trans*-fused des-*AB*-trienic steroid **11** (98%), the goal of our synthesis {$[\alpha]_D^{20}$ −1.4 (*c* 1.01, $CHCl_3$)} as a single product which was identical with the authentic enantiomer[5c] of **11** in all aspects including ^1H 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, $CHCl_3$)}.

† All new substances exhibited spectroscopic data [IR, ^1H NMR (500 MHz) and mass spectrometry] in accord with the assigned structure and provided acceptable combustion or high resolution mass spectral data.

‡ The enantiomeric excess of the epoxy alcohol **4** was determined by comparing the ^1H NMR (500 MHz) of the methoxy(trifluoromethyl)-phenylacetyl (MTPA) esters derived [MTPA acid, dicyclohexylcarbodiimide (DCC), 4-*N*,*N*-dimethylaminopyridine (DMAP), CH_2Cl_2, room temp., 22 h] from **4** and the corresponding racemic epoxy alcohol which was prepared by epoxidation [Bu^{t}OOH, $VO(acac)_2$ (acac = pentane-2,4-dionato), CH_2Cl_2, 0 °C, 30 min] of **3**.

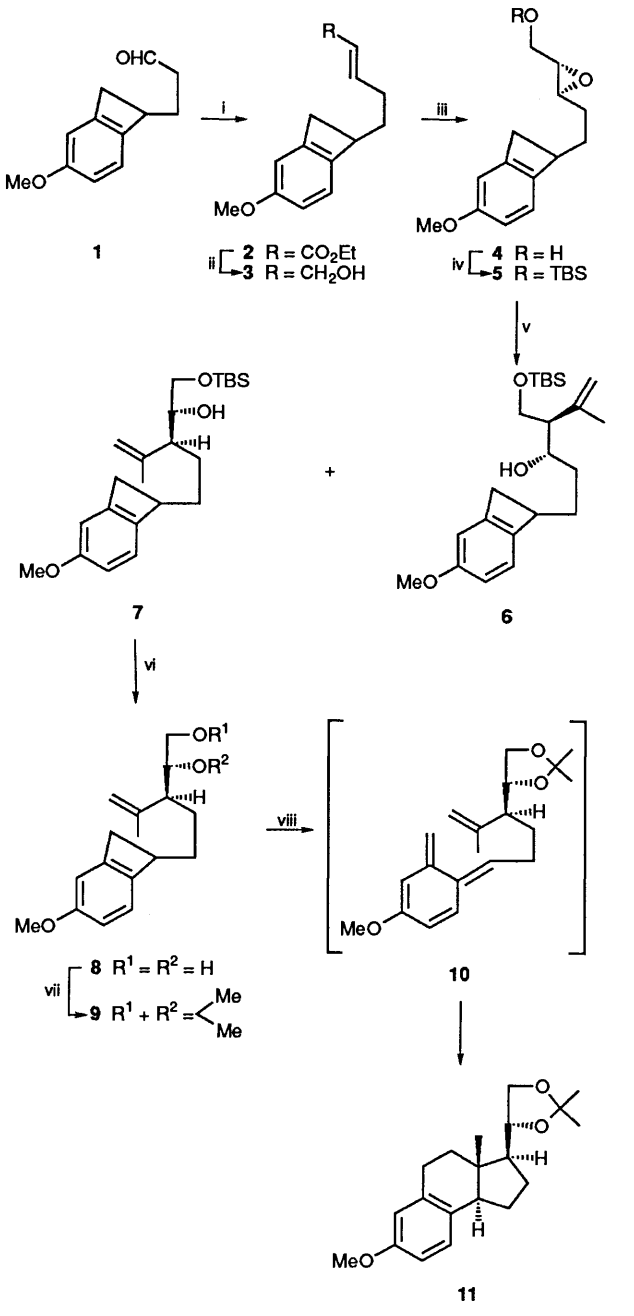
§ We could not detect any other stereoisomers corresponding to **6** and **7**. For recent studies on this type of nucleophilic addition of various types of reagents to glycidol and related 2,3-epoxy alcohols, see ref. 8.

Experimental

(2R,3S)-1-tert-*Butyldimethylsilyloxy*-3-[2′-(1,2-*dihydro*-4-*methoxybenzocyclobuten*-1-*yl*)*ethyl*]-4-*methylpent*-4-*en*-2-*ol* **7** *and* (2S,3S)-3-tert-*Butyldimethylsilyloxymethyl*-6-(1,2-*dihydro*-4-*methoxybenzocyclobuten*-1-*yl*)-2-*methylhex*-1-*en*-4-*ol* **6**.—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 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. The mixture was stirred for a further 10 min, after which a solution of the epoxide **5** (2.57 g, 7.39 mmol) in Et_2O (5 cm^3) was added to it at −21 °C. Stirring was continued for 20 h at the same temperature, after which the reaction mixture was treated with saturated aqueous NH_4Cl and extracted with Et_2O. The combined extracts were washed with saturated brine and worked up. The residue obtained by this process was chromatographed with hexane–Et_2O (49:1, v/v) to give the *alcohol* **7** (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* **6** (0.62 g, 21%) as an oil (Found: C, 70.7; H, 9.9. $C_{23}H_{38}O_3Si$ requires C, 70.72; H, 9.81%); 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^+).

(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* **11**.—A stirred solution of the benzocyclobutene **9** (1.14 g, 3.61 mmol) in ODB (360 cm^3) was refluxed for 13 h and then evaporated. The residue was chromatographed with hexane–AcOEt (17:3, v/v) to give the *des*-AB-*trienic steroid* **11** (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. $C_{20}H_{28}O_3$ requires C, 75.91; H, 8.92%); 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^+).



Scheme 1 *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, $Ti(OPr^i)_4$, (+)-L-diisopropyl 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 = camphorsulfonic acid, ODB = *o*-dichlorobenzene)

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