A NOVEL APPROACH TO OPTICALLY ACTIVE DES-A C-13 ETHYL STEROIDS

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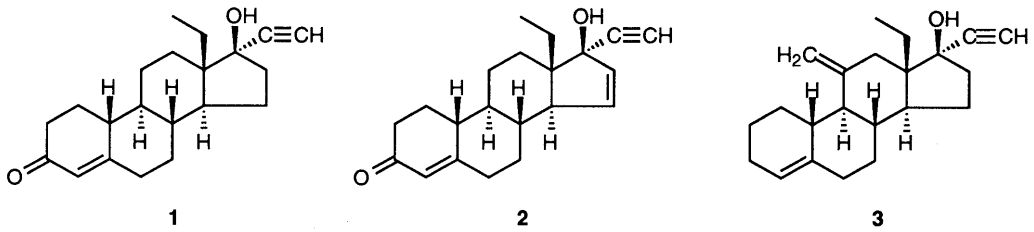
Optically active des-A C-13 ethyl steroids 17~20 have been synthesized by thermolysis of the optically active alkenic benzocyclobutene 14 as a key process.

KEYWORDS C-13 ethyl steroid; benzocyclobutene; asymmetric synthesis; Diels-Alder reaction

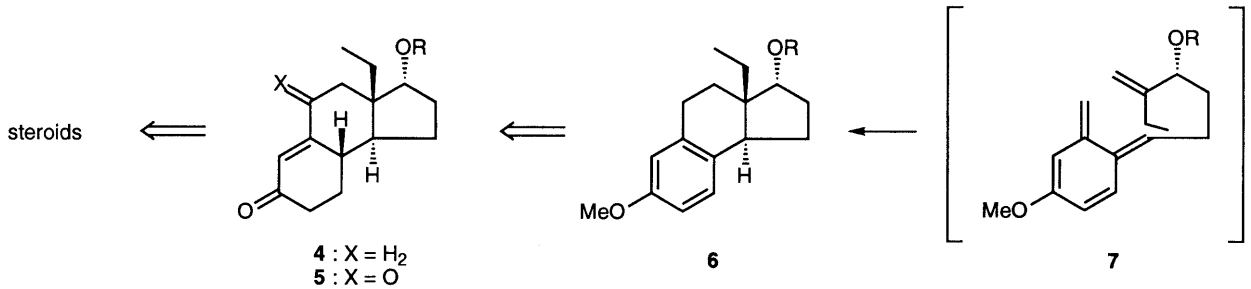
The steroids possessing an angular C-13 ethyl substituent such as norgestrel (**1**),[1] its C-15-dehydro analogue (**2**),[2] and desogestrel (**3**)[3] have recently attracted much attention as second and third generations of steroid oral contraceptives and have been produced commercially by total synthesis[4] because there are no naturally occurring steroid precursors having such a substituent at C-13 (Fig. **1**).



1 **2** **3**

Fig. 1

During our work[5] directed towards the des-A B-trienic steroids (potential synthons for a variety of physiologically important steroids), we have developed a novel approach, which relies on the stereoselective [4+2] cycloaddition reaction of alkenic *o*-quinodimethane **7** to give the C,D-*trans*-fused des-A B-trienic steroid **6**, to optically active des-A steroids **4** and **5**, and herein we describe the results (Chart **1**).



4 : X = H_2
5 : X = O

6 **7**

Chart 1

The synthesis of the optically active benzocyclobutene **14**, substrate for generating **7**, was straightforward (Chart **2**).[6] The benzocyclobutenyl aldehyde **8**,[7] easily obtainable in large quantities from 1-cyano-4-methoxybenzocyclobutene,[8] was subjected to the Wittig reaction to give the unsaturated ester **9** selectively (88%), which on reduction with diisobutylaluminum hydride (DIBAL) afforded the alcohol **10** (98%). Asymmetric epoxidation of the allyl alcohol **10** was effected by following the Sharpless procedure to give the chiral epoxy alcohol **11** (93%) with a high degree (93% e.e.) of enantiomeric excess.[9] Mesylation of **11**, followed by reductive epoxide ring opening of **12**, afforded the isopropenyl alcohol **13** (94% from **11**). Silylation of **13** with *tert*-butyldimethylsilyl

trifluoromethanesulfonate (TBSOTf) gave the silyl ether **14** (100%), which on thermolysis in boiling *o*-dichlorobenzene afforded the des-A B-trienic steroids **15** and **16** selectively. Birch reduction of this mixture of **15** and **16** followed by acid treatment afforded a 3 : 1 mixture of the enones **17** and **18**, easily separable on silica gel column chromatography (69% from **14**).[10]

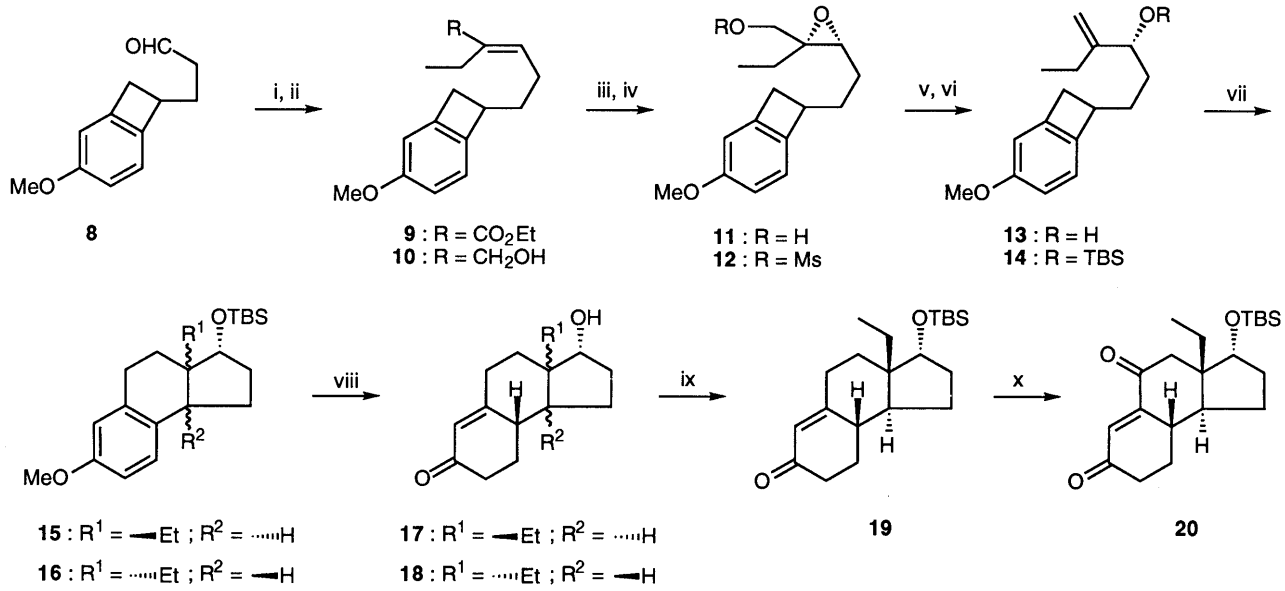


Chart 2. *Reagents and conditions* : i, $Ph_3P{=}CEtCO_2Et$, benzene, 50 °C, 24 h; ii, DIBAL, THF, -33 °C, 1 h; iii, Bu^tOOH, $Ti(OPr^i)_4$, (-)-D-diisopropyl tartrate, 4 Å molecular sieves, CH_2Cl_2, -70 °C, 13 h; iv, $MeSO_2Cl$, Et_3N, CH_2Cl_2, 0 °C, 1 h; v, Zn, NaI, DMF, 100 °C, 1 h; vi, TBSOTf, 2,6-lutidine, CH_2Cl_2, 0 °C, 1 h; vii, *o*-dichlorobenzene, reflux, 8 h; viii, Li, liq. NH_3, EtOH, -78 °C, 1 h, then 10% HCl, MeOH, room temp., 10 h→reflux 1 h; ix, TBSCl, imidazole, DMAP, room temp., 3.5 h; x, SeO_2, MeCN, reflux, 2 h, then PCC, CH_2Cl_2, room temp., 1 h.

Finally, oxidation of the silyl ether **19** (95%) derived from **17** furnished the aimed diketone **20** as colorless needles {mp 101 - 102 °; $[\alpha]_D^{22}$ + 26.6 ° ($CHCl_3$)} (43%).

Thus, we could disclose a novel route to optically active des-A C-13 ethyl steroids, potential synthons for a variety of physiologically important steroids.

REFERENCES AND NOTES

1) H. Smith, G. A. Hughes, G. H. Douglas, G. R. Wendt, G. C. Buzby, Jr., R. A. Edgren, J. Fisher, T. Foell, T. Gadsby, T. Hartley, D. Herbst, A. B. A. Jansen, K. Ledig. B. J. McLoughlin, J. McMenamin, T. W. Pattison, R. R. Phillips, J. Siddall, J. Siuda, L. L. Smith, J. Tokolics, D. H. P. Watson, *J. Chem. Soc.*, **1964**, 4472.

2) H. Hofmeister, K. Annen, H. Laurent, K. Petzold, R. Wiechert, *Arzneim.-Forsch.*, **36**, 781 (1986).

3) A. J. van den Broek, C. van Bockhoven, P. M. J. Hobbelen, J. Leemhuis, *Recl. Trav. Chim. Pays-Bas*, **94**, 35 (1975).

4) See references 1-3 and C. Djerassi, *Proc. R. Soc., Lond. B*, **195**, 175 (1976); R. T. Bickenstaff, A. C. Ghosh, G. C. Wolf, *Total Synthesis of Steroids*, Academic Press, New York, 1974.

5) For our recent studies in this field, see H. Nemoto, M. Ando, K. Fukumoto, *Tetrahedron Lett.*, **31**, 6205 (1990); H. Nemoto, N. Matsuhashi, M. Imaizumi, M. Nagai, K. Fukumoto, *J. Org. Chem.*, **55**, 5625 (1990); H. Nemoto, A. Satoh, M. Ando, K. Fukumoto, *J. Chem. Soc., Chem. Commun.*, **1990**, 1001; *J. Chem. Soc., Perkin Trans. 1*, **1991**, 1309; H. Nemoto, N. Matsuhashi, K. Fukumoto, *J. Chem. Soc., Chem. Commun.*, **1991**, 705; H. Nemoto, N, Matsuhashi, A, Satoh, K. Fukumoto, *J.*

Chem. Soc., Perkin Trans. 1, **1992**, 495; H. Nemoto, A. Satoh, K. Fukumoto, *J. Chem. Soc., Perkin Trans. 1,* **1993**, 2237 and references cited therein.

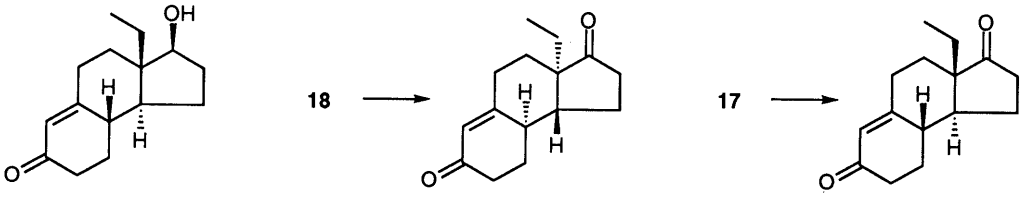
6) All new substances exhibited spectroscopic data [IR, ^{1}H NMR and mass spectrometry] in accord with the assigned structure and provided acceptable combustion or high resolution mass spectral data. ^{1}H NMR (300 MHz) data for representative compounds are as follows: **compound 14**: δ 0.00 (6H, s), 0.88 (9H, s), 1.05 (3H, t, *J* = 7.3 Hz), 3.77 (3H, s), 4.77 (1H, br s), 4.94 (1H, br s) 6.68 (1H, s), 6.72 (1H, d, *J* = 7.9 Hz), 6.96 (1H, d, *J* = 7.9 Hz). **compound 17**: δ 0.87 (3H, t, *J* = 7.3 Hz), 1.47 (1H, br s), 4.06 (1H, d, *J* = 6.1 Hz), 5.88 (1H, br s). **compound 18**: δ 1.08 (3H, t, *J* = 7.3 Hz), 3.79 (1H, dd, *J* = 7.9, 8.5 Hz), 5.88 (1H, br s). **compound 20**: δ 0.03 (3H, s), 0.06 (3H, s), 0.88 (9H, s), 1.14 - 1.28 (2H, m), 2.40 (1H, ddd, *J* = 4.9, 15.3, 17.1 Hz), 2.55 - 2.65 (1H, m), 2.62 (1H, d, *J* = 16.5 Hz), 2.63 (1H, d, *J* = 16.5 Hz), 4.00 (1H, d, *J* = 5.5 Hz), 6.48 (1H, d, *J* = 1.8 Hz).

7) H. Nemoto, M. Nagai, Y. Abe, M. Moizumi, K. Fukumoto, T. Kametani, *J. Chem. Soc., Perkin Trans. 1,* **1987**, 1727.

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

9) The enantiomeric excess of the epoxy alcohol **11** was determined by comparing the ^{1}H NMR (500 MHz) of the methoxy-(trifluoromethyl)phenylacetate (MTPA) derived [MTPA acid, DCC, DMAP, CH_2Cl_2, room temp., 12 h] from **11** and the corresponding racemic epoxy alcohol which was prepared by epoxidation [Bu^{t}O$_2$H, VO(acac)$_2$ (acac=pentane-2,4-dianoto), CH_2Cl_2, 0 °C, 30 min] of **10**.

10) The structure including absolute stereochemistry of **18** {$[\alpha]_D^{21}$ + 53.6 ° (MeOH)} was determined unambiguously by direct comparison with its enantiomer **i**[11] {$[\alpha]_D$ - 59 ° (MeOH)} with opposite sign of optical rotations. In turn, the diketones **ii** {$[\alpha]_D^{19}$ - 2.8 ° ($CHCl_3$)} derived by pyridinium chlorochromate (PCC) oxidation of **18** and **iii** {$[\alpha]_D^{22}$ + 2.4 ° ($CHCl_3$)} derived by PCC oxidation of **17** were identical in all aspects, with opposite sign of optical rotations showing these diketones to be enantiomers.



i **ii** **iii**

11) J. Warnant, B. Goffinet, *Fr.*, **1971**, 1, 062, 963 [*Chem. Abstr.*, **75**, 141053e (1971)].

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