Total Synthesis of Optically Active 17β-t-Butoxy-3-methoxy-7α- or -7β-18-dimethyl-1,3,5(10)-estratriene

Zu-Yun Cai,* Yuan Ni, Jen-Kon Sun, Xin-Di Yu, and Yan-Qiu Wang

Shanghai Institute of Organic Chemistry, Academia Sincia, Shanghai 200032, China

In the preparation of 7-methyl-19-nor-steroids, a new method for the synthesis of key intermediates (**10**), which involves alkylation of the CD ring fragment (**4**) and subsequent hydrogenation, cyclization, and hydrogenation is described.

The introduction of a 7-methyl group into the steroid nucleus usually results in an enhancement of the basic hormonal activities of the molecules.[1,2] 7-Methyl steroids have been obtained by partial[3] and total synthesis.[4] In this paper, we report an enantioselective synthesis of the key intermediate (**10a**) for 7α-methyl-19-nor-steroids, which can be secured by Birch reduction from (**10a**) or (**9a**).

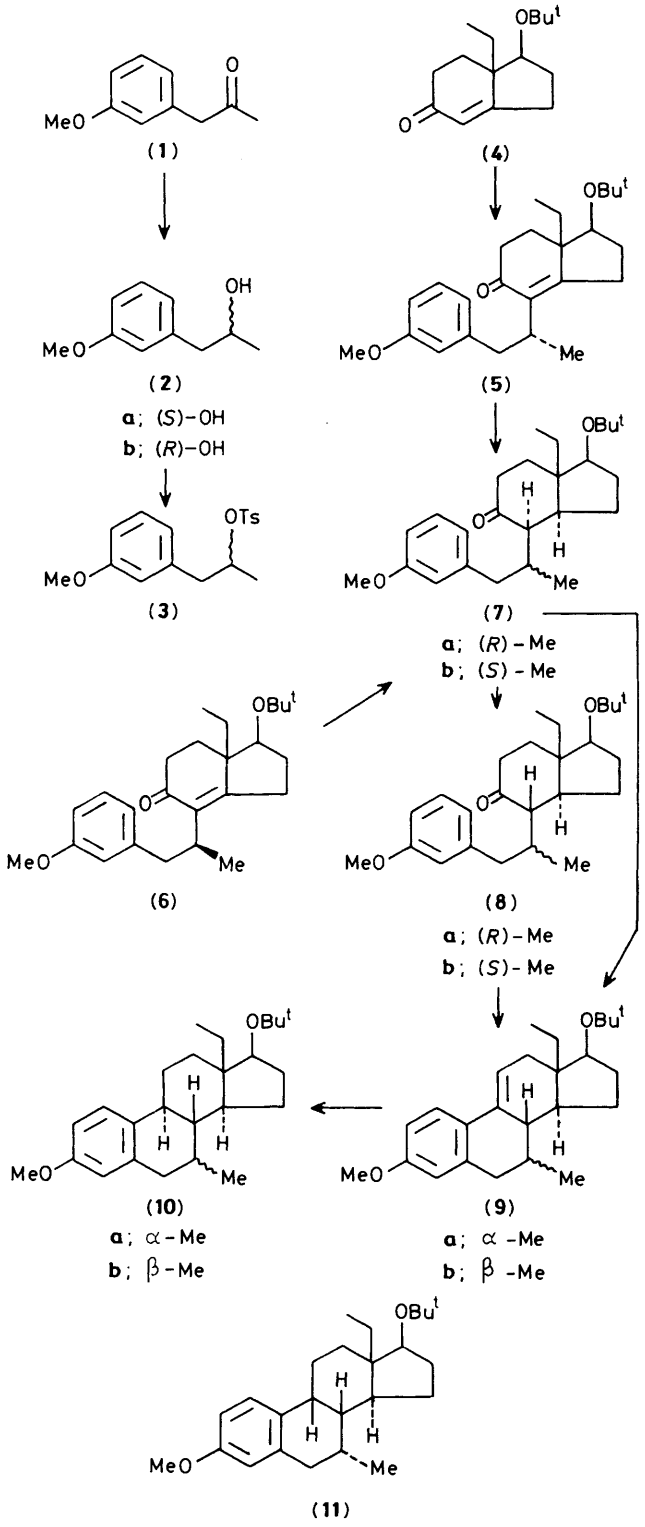
By *Saccharomyces cerevisiae* asymmetric reduction, the compound (**1**) obtained from eugenol[5] was transformed to (**2a**) {yield 96%; $[\alpha]_D^{12}$ +31.8° (*c* 1.53, $CHCl_3$); i.r.: 3350 cm^{-1}; ^1H n.m.r. (CCl_4): δ 1.1 [d, 3H, *J* 6 Hz, –CH(OH)Me]; *m/z*: 166 (M^+)}. The hydroxy group of (**2a**) was determined to be in the *S*-configuration by the Horeau method.[6] The optical purity† of (**2a**) was shown to be 98—99% enantiomeric excess (e.e.) by ^{19}F n.m.r. analysis of the (*R*)-(+)-methoxy(trifluoromethyl)phenylacetyl (MTPA) ester[7] of (**2a**).

The compound (**4**)[8] was alkylated with the toluene-*p*-sulphonate of (**2a**) in the presence of NaH in dimethoxyethane (DME) to afford compound (**5**) {yield 72%; $[\alpha]_D^{27}$ −25° (*c* 1.06, $CHCl_3$); $\lambda_{max.}$ 255 nm (log ε 4.39); ^1H n.m.r. (CCl_4, 200 MHz): δ 1.16 (d, 3H, *J* 8 Hz, 7α-Me), 3.44 (t, 1H, *J* 8 Hz, 17-αH); *m/z*: 385 (M^+ +1)}. Hydrogenation of compound (**5**) (5% Pd/C, MeOH, 2 atm, room temp., 24 h), gave *trans*-perhydroindane (**7a**) with 8α-H {yield 47.4%; $[\alpha]_D^{10}$ +8.9° (*c* 0.99, $CHCl_3$); $\lambda_{max.}$ 280 nm (log ε 3.36), 273 (3.39)}. Compound (**7a**) was cyclized to tetracyclic major product (**9a**) {yield 71.6%; $[\alpha]_D^{9}$ +29.56° (*c* 0.56, EtOH); $\lambda_{max.}$ 266 nm; ^1H n.m.r. (CCl_4, 200 MHz): δ 6.15 (m, 1H, $w_{1/2}$ 12 Hz, 11-H)} and the minor product (**8a**) with 8β-H, $[\alpha]_D^{18}$ +20.2° (*c* 1.54, $CHCl_3$).

The *trans* junction of ring C and D in compound (**7a**) was established by c.d. spectroscopy, $\lambda_{max.}$ 293 nm (Δε +0.78).[4b] Treatment of (**8a**) with acid also gave (**9a**), confirming a β-H on C(8).

Hydrogenation of compound (**9a**) (10% Pd/C, $MeCO_2Et$, room temp., 38 h), afforded the 7α,18-dimethyl estradiol derivative (**10a**) {$[\alpha]_D^{21}$ +23.1° (*c* 0.53, $CHCl_3$); m.p. 151—154 °C; $\lambda_{max.}$ 279, 287 nm; c.d. (MeOH): $\lambda_{max.}$ 279 nm (Δε +0.23); ^1H n.m.r. ($CDCl_3$, 200 MHz): 1.00 (d, 3H, *J* 8 Hz,7-αMe); *m/z*: 370 (M^+)}, and the compound (**11**) with 9-βH, c.d. (MeOH): $\lambda_{max.}$ 276 nm (Δε −0.22). It is easy to envisage that in the presence of 7-αMe, hydrogen added from the α side would be hindered and eventually result in a mixture of compound (**10a**) and (**11**), although the compound (**10a**) is formed preferentially.

The 7β-methyl steroid was prepared by a similar reaction sequence as described above. Alkylation of compound (**4**) with racemic (**3**), obtained by reduction of compound (**1**) ($NaBH_4$) and subsequent toluene-*p*-sulphonation of (**2**), led to



† ^{19}F N.m.r. studies were performed on a Varian XL-200 MHz instrument, using CF_3CO_2H as internal standard. Chemical shifts of the (*R*)-(+)-MTPA esters of (**2a,b**) were 6.747, 6.776 p.p.m. respectively.

a mixture of (**5**) and (**6**) (g.c. 44:33).‡ The isolated pure compound (**6**) was converted into (**7b**), then (**9b**), and finally compound (**10b**) {$[\alpha]_D^{27}$ −65.5° (*c* 0.8, $CHCl_3$); m.p. 53—54 °C; $\lambda_{max.}$ 273, 284 nm; c.d. (MeOH): $\lambda_{max.}$ 274 nm ($\Delta\varepsilon$ −0.71), 225 (+0.86); ^1H n.m.r. ($CDCl_3$, 200 MHz): δ 0.81 (d, 3H, *J* 6 Hz, 7-βMe)}.

The preparation of (**10a**) and (**10b**) also provides a case for the comparison of coupling constants between axial and equatorial methyl groups. Our observations were consistent with those made by Danneels and Anteunis.[9]

Received, 3rd April 1985; Com. 457

‡ G.c. was carried out on a Varian 3700 instrument, H_2 flame detector. Column: FFAP, 25 m × 0.2 mm programmed from 160 to 240 °C, 15 °C/min, retention time 12.29 min for (**2a**) and 10.25 min for (**2b**).

References

1 G. W. Duncan, S. C. Lyster, and J. A. Campbell, *Proc. Soc. Exp. Biol. Med.*, 1964, **116**, 800.
2 R. Rosso, G. Porcile, and F. Brema, *Cancer Chemother. Rep. Part 1*, 1975, **59**, 890.
3 J. F. Grunwell, H. D. Benson, J. O'Neal Johnston, and V. Petrow, *Steroids*, 1976, **27**, 759.
4 (a) U. Eder, H. Gibian, G. Haffer, G. Neef, G. Sauer, and R. Wiechert, *Chem. Ber.*, 1976, **109**, 2948; (b) U. Eder, G. Haffer, G. Neef, G. Sauer, A. Seeger, and R. Wiechert, *ibid.*, 1977, **110**, 3161; (c) G. Sauer, K. Junghans, U. Eder, G. Haffer, G. Neef, R. Wiechert, G. Cleve, and G. A. Hoyer, *Liebigs Ann. Chem.*, 1982, 431; (d) U. Eder, *J. Steroid Biochem.*, 1979, **11**, 55.
5 H. Inoue, *Yakugaku Zasshi*, 1967, **87**, 1419.
6 A. Horeau and H. B. Kagan, *Tetrahedron*, 1964, **20**, 2431.
7 W. Oppolzer and C. Chapuis, *Tetrahedron Lett.*, 1983, **24**, 4665.
8 Z. G. Hajos and D. R. Parrish, *J. Org. Chem.*, 1974, **39**, 1615.
9 D. Danneels and M. Anteunis, *Org. Magn. Reson.*, 1974, **6**, 617.