JOURNAL OF THE CHEMICAL SOCIETY

Chemical Communications

Number 15
1990

A Facile and Enantioselective Total Synthesis of (+)-19-Nordeoxycorticosterone

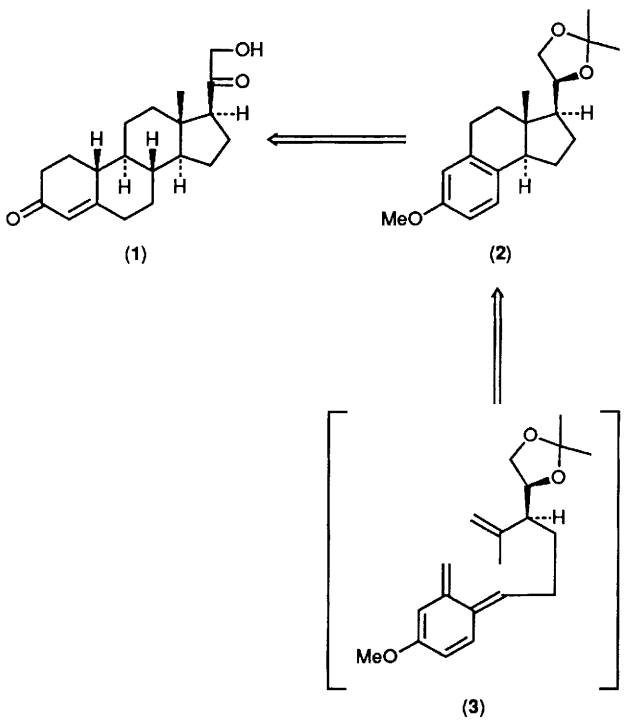
Hideo Nemoto, Atsushi Satoh, Masahiro Ando, and Keiichiro Fukumoto*

Pharmaceutical Institute, Tohoku University, Aobayama, Sendai 980, Japan

(+)-19-Nordeoxycorticosterone (**1**) has been synthesised by *A*-ring construction of the (+)-*A*-nor-*B*-trienic steroid (**2**) obtained enantioselectively from the alkenic benzocyclobutene (**12**).

Recently, much attention has been focussed on synthetic[1] and biological[2] studies of (+)-19-nordeoxycorticosterone (**1**), which is a potent mineral corticoid with sodium-retaining activity comparable to that of aldosterone, exploring effective synthetic routes to provide satisfactory amounts and evaluating its physiological significance. However, no facile and flexible synthetic methodology, promising satisfactory yields and providing a wide variety of this type of compound for biological studies, has been reported. We herein describe an efficient and flexible route for producing deoxycorticosterone derivatives leading to the enantioselective total synthesis of (+)-19-nordeoxycorticosterone (**1**). Our synthetic strategy for (**1**) is characterized by the one-step creation of *B*, *C*, and *D* rings (**2**) in a stereoselective manner (Scheme 1). Namely, stereoselective introduction of three successive chiral centres, C-13, C-14, and C-17 (steroid numbering), is achieved by an intramolecular [4 + 2] cycloaddition reaction of the alkenic *o*-quinodimethane (**3**) as the key step and then *A*-ring formation, followed by side chain manipulation (**2**)→(**1**).

The synthesis of the benzocyclobutene (**12**), a substrate for generating (**3**), and the transformation of (**2**) into (**1**) were straightforward and as follows (Scheme 2).† Glyceraldehyde acetonide (**4**),[3] easily obtainable in large quantities from D-mannitol, was subjected to the Wittig reaction[4] to give the unsaturated ester (**5**) selectively, which on reduction with di-isobutylaluminium hydride (DIBAL) afforded the alcohol (**6**) ($[\alpha]_D^{22}$ + 9.5°) [60% overall yield from (**4**)]. Ireland rearrangement[5] of the acetate (**7**) ($[\alpha]_D^{25}$ + 20.4°), obtained (in 80% yield) by acetylation of (**6**), followed by direct reduction of the resulting carboxylic acid afforded the desired *threo* alcohol (**8**)‡ ($[\alpha]_D^{25}$ + 36.7°) (30%) as the main product together with the *erythro* alcohol (15%) ($[\alpha]_D^{24}$ −3.6°). Tosylation of (**8**), followed by iodination of (**9**) afforded the iodide (**10**) ($[\alpha]_D^{24}$ +63.0°) [86.1% overall from (**8**)]. Alkylation of 1-cyano-4-methoxybenzocyclobutene[6] (**11**) with the iodide (**10**), followed by reductive decyanation furnished the alkenic benzocyclobutene (**12**) ($[\alpha]_D^{23}$ + 19.7°) (49%). The generation and cycloaddition reaction of the *o*-quinodimethane (**3**) were effected by the thermolysis of (**12**) at 190 °C to give stereoselectively[7] the tricyclic compound (**2**) ($[\alpha]_D^{25}$ +15.6°) (98%). Birch reduction of (**2**) followed by acid treatment

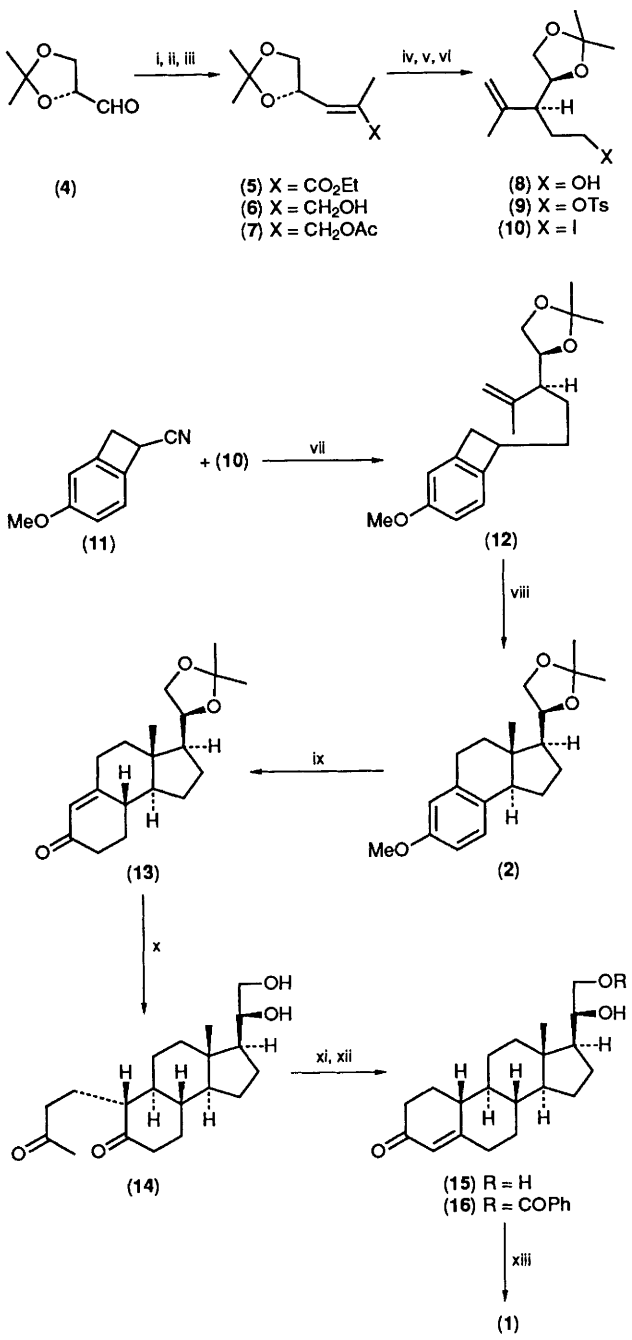


(1) (2) (3)

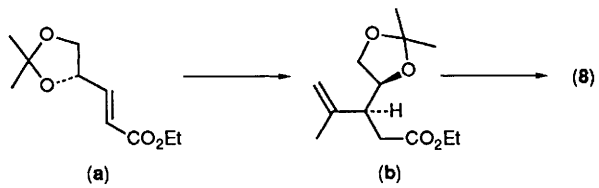
Scheme 1

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

‡ In our recent study, the *threo* alcohol (**8**) was obtained by reduction of the ester (**b**) which was derived as a minor product by 1,4-addition of isopropenylmagnesium bromide on the unsaturated ester (**a**). These results will be reported elsewhere.



Scheme 2. *Reagents and conditions:* i, $Ph_3P{=}CMeCO_2Et$, CH_2Cl_2, room temp., 3 h; ii, DIBAL, CH_2Cl_2 −78 °C, 1 h; iii, Ac_2O, dimethylaminopyridine, pyridine, room temp., 1 h; iv, TMSCl, LDA, THF, −78 °C; then reflux 3 h; $LiAlH_4$, THF, 0 °C, 5 h; v, TsCl, pyridine, room temp., 3 h; vi, NaI, acetone, room temp., 47 h; vii, $NaNH_2$, liq. NH_3, THF, −33 °C, 1 h; then Na, −78 °C, 30 min; viii, *o*-dichlorobenzene, 190 °C, 13 h; ix, Li, liq. NH_3, THF, EtOH, −78 °C, 45 min; 10% HCl, MeOH, room temp., 13 h; then $Me_2C(OMe)_2$, CSA, CH_2Cl_2, room temp., 1 h; x, Li, liq. NH_3, THF, −78 °C, 45 min; then $MeCCl{=}CHCH_2Br$, 30 min; $Hg(OCOCF_3)_2$, $MeNO_2$, room temp., 3 h; then 10% HCl, room temp., 1 h; xi, 10% KOH, MeOH, room temp., 2 h; xii, PhCOCl, pyridine, CH_2Cl_2, room temp., 1 h; xiii, PCC, Florisil, CH_2Cl_2, room temp., 5 h; K_2CO_3, MeOH, CH_2Cl_2, H_2O, room temp., 80 min. TMS = trimethylsilyl, LDA = lithium di-isopropylamide, THF = tetrahydrofuran, Ts = $MeC_6H_4SO_2$, PCC = pyridinium chlorochromate, CSA = camphorsulphonic acid.



Scheme 3

(HCl) and protection of the diol group afforded the thermodynamically predominant compound (**13**) ($[\alpha]_D^{23}$ +2.6°) [37.5% overall yield from (**2**)], which on reductive alkylation[8] using 1-bromo-3-chlorobut-2-ene and successive hydrolysis yielded the diketone (**14**) ($[\alpha]_D^{23}$ +8.1°) (43%). The diol (**15**) ($[\alpha]_D^{23}$ +35.6°), obtained in 81% yield by cyclization of (**14**), was selectively converted into the monobenzoate (**16**) ($[\alpha]_D^{25}$ +40.8°) (52%). Finally, oxidation of (**16**) followed by hydrolysis furnished 19-nordeoxycorticosterone (**1**) ($[\alpha]_D^{24}$ +97.0°, m.p. 124—125 °C) [68.4% overall yield from (**16**)], which was identical with the authentic sample[1a]§ in all aspects including ^1H NMR (500 MHz, $CDCl_3$) and IR (NaCl) spectra, optical rotation, and mixed melting point test.

We thank Dr. T. Terasawa at Shionogi Research Laboratories for the generous gift of an authentic sample of 19-nordeoxycorticosterone.

Received, 28th March 1990; Com. 0/01366H

References

1 (a) T. Terasawa and T. Okada, *Tetrahedron*, 1986, **42**, 537; (b) J. Fajkoš and J. Joska, *Coll. Czech. Chem. Commun.*, 1985, **50**, 973; (c) D. N. Kirk and B. L. Yeok, *J. Chem. Soc., Perkin Trans. 1*, 1983, 2945; (d) C.-Y. Byon and M. Gut, *J. Org. Chem.*, 1980, **45**, 4404, and references cited therein.

2 G. T. Griffing, M. Holbrook, J. C. Melby, and A. H. Brodie, *Clin. Physiol. Biochem.*, 1988, **6**, 171; M. Ohta, S. Fjii, T. Ohnishi, and M. Okamoto, *J. Steroid Biochem.*, 1988, **29**, 699; J. C. Melby, M. Holbrook, G. T. Griffing, and J. O. Johnston, *Hypertension*, 1987, **10**, 484; J. Gorsline and D. J. Morris, *J. Steroid Biochem.*, 1985, **23**, 535; M. L. Casey, A. Guerami, L. Milewich, C. E. Gomez-Sanchez, and P. C. MacDonald, *J. Clin. Invest.*, 1985, **75**, 1335. For reviews see: R. D. Perrone, H. H. Bengele, and E. A. Alexander, *Am. J. Physiol.*, 1986, **250**, E1; C. E. Gomez-Sanchez, E. P. Gomez-Sanchez, and O. B. Holland, 'Serono Symp.,' Raven Press, 1985, vol. 27, p. 177; H. Sekihara, *Jikken Igaku*, 1988, **6**, 651.

3 S. Takano, A. Kurotaki, M. Takahashi, and K. Ogasawara, *Synthesis*, 1986, 403.

4 T. Ibuka, N. Akimoto, M. Tanaka, S. Nishii, and Y. Yamamoto, *J. Org. Chem.*, 1989, **54**, 4055.

5 R. E. Ireland and R. H. Mueller, *J. Am. Chem. Soc.*, 1972, **94**, 5897.

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

7 For recent detailed discussion of the stereoselectivity in the intramolecular [4 + 2] cycloaddition reaction of alkenic *o*-quinodimethanes see: H. Nemoto, M. Nagai, M. Moizumi, K. Kohzuki, K. Fukumoto, and T. Kametani, *J. Chem. Soc., Perkin Trans. 1*, 1989, 1639; H. Nemoto, S. Fujita, M. Nagai, K. Fukumoto, and T. Kametani, *J. Am. Chem. Soc.*, 1988, **110**, 2931 and references cited therein.

8 G. Stork and E. W. Logusch, *J. Am. Chem. Soc.*, 1980, **102**, 1219.

§ 19-Nordeoxycorticosterone, which was donated by Dr. T. Terasawa of Shionogi Research Laboratories, was recrystallised from acetone–hexane and was used as an authentic sample (m.p. 124—125°, $[\alpha]_D^{27}$ +98.5°).