

Synthetic Approach to 11 α -Oxygenated Steroid. Stereoselective
Construction of a B,C,D-Ring System in an Optically Active Form

Tetsuji KAMETANI, Kohji FUKATSU, Masayoshi TSUBUKI,

Ken-ichi KAWAI, and Tohsio HONDA

Institute of Medicinal Chemistry, Hoshi University,

Ebara 2-4-41, Shinagawa-ku, Tokyo 142

Stereoselective synthesis of a B,C,D-ring system of
11 α -oxygenated steroid has been achieved by employing 1,3-dipolar
cycloaddition reaction as a key step.

Corticosteroids, having an oxygen functionality at the 11-position, have been known to play important roles as regulatory hormones in a human being, and have been the subject of extensive synthetic efforts¹⁾ due to their interesting biological properties. In connection with our work on the synthesis of physiologically active poly-hydroxy steroids, we became interested in searching a new method for their synthesis.

Whereas a considerable effort has been devoted towards, the synthesis of 11-oxo- or 11 β -hydroxy-steroids, 11 α -hydroxy-steroids²⁾ have received relatively little attention. We therefore planned to synthesize 11 α -hydroxy-steroid, which could be converted to the corresponding 11-oxo- and 11 β -hydroxy derivatives, because of the interest to examine its biological activity, and here report the stereoselective construction of its B,C,D-ring system in an optically active form.

Our synthesis involved 1,3-dipolar cycloaddition reaction of a nitrile oxide as a key step in order to introduce a desired hydroxy group. The acetal (2)³⁾ readily derived from the indanedione (1) was treated with *p*-toluenesulfonylhydrazide in refluxing benzene to afford the hydrazone (3), which was then subjected to a Shapiro reaction⁴⁾ using *n*-butyllithium as the base in dry tetrahydrofuran to give the olefin (4) in 71.9% yield from the ketone (2). Deacetalization of the olefin (4) with *p*-toluenesulfonic acid in aqueous acetone furnished the aldehyde (5) in 96% yield. Introduction of a nitromethyl moiety to the aldehyde (5) was carried out by three-steps⁵⁾ as follows. Treatment of the aldehyde (5) with nitromethane in the presence of potassium fluoride and 18-crown-6 in isopropanol at 80 °C gave the alcohol, whose acetylation with acetic anhydride in tetrahydrofuran in the presence of *N,N*-dimethylaminopyridine yielded the acetate (6). Sodium borohydride reduction of the acetate (6) in ethanol at 0 °C furnished the nitro compound (7) in 98% yield from the aldehyde (5). Heating of

the nitro compound (7) in refluxing benzene in the presence of phenyl isocyanate and triethylamine for 15 h brought about the desired 1,3-dipolar cycloaddition reaction cleanly to afford the isoxazoline derivative (8) in 92% yield. Since the conversion of an isoxazoline ring to a β -hydroxy-ketone was well studied, we adopted Kozikowski's procedure.⁶⁾ Thus, the compound (8) was treated with Raney-nickel in methanol containing a catalytic amount of acetic acid under an atmosphere of hydrogen at 0 °C to give the hydroxy-ketone (9) in 95% yield, whose structure was assumed to have a B/C-trans ring juncture based on the spectral data,⁷⁾ and was unambiguously determined by X-ray analysis⁸⁾ of its MOM ether (10), derived from the alcohol (9) on treatment with methoxymethyl chloride. This result indicated that the epimerization of B/C-cis-compound to thermodynamically more stable B/C-trans-isomer occurred during the above conversion as expected.

Finally the introduction of a methyl group to the carbonyl function of the ketone (10) on treatment with methyllithium gave the alcohol (11) as a mixture of diastereoisomers in 96% yield, whose dehydration with thionyl chloride and pyridine provided the endo- (12) and exo-olefins (13), in 63% and 16% yields, respectively. Hydroboration reaction of the major olefin (12), followed by Jones oxidation of the resulting alcohol afforded the ketone (14)⁹⁾ in 83% yield.

Thus, we could achieve the stereoselective construction of a B,C,D-ring system of 11 α -hydroxy-steroids in an optically active form.

Since this ketone (14) seems to be a potential intermediate for the synthesis of 11 α -oxygenated steroids, its conversion is now in progress.

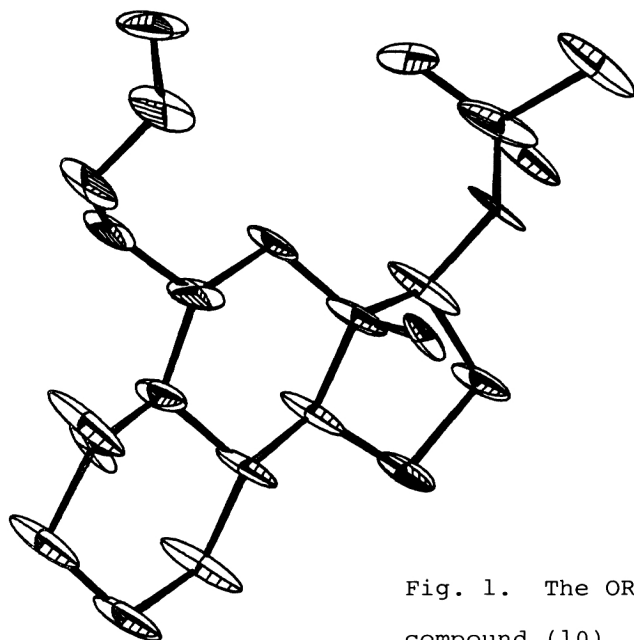
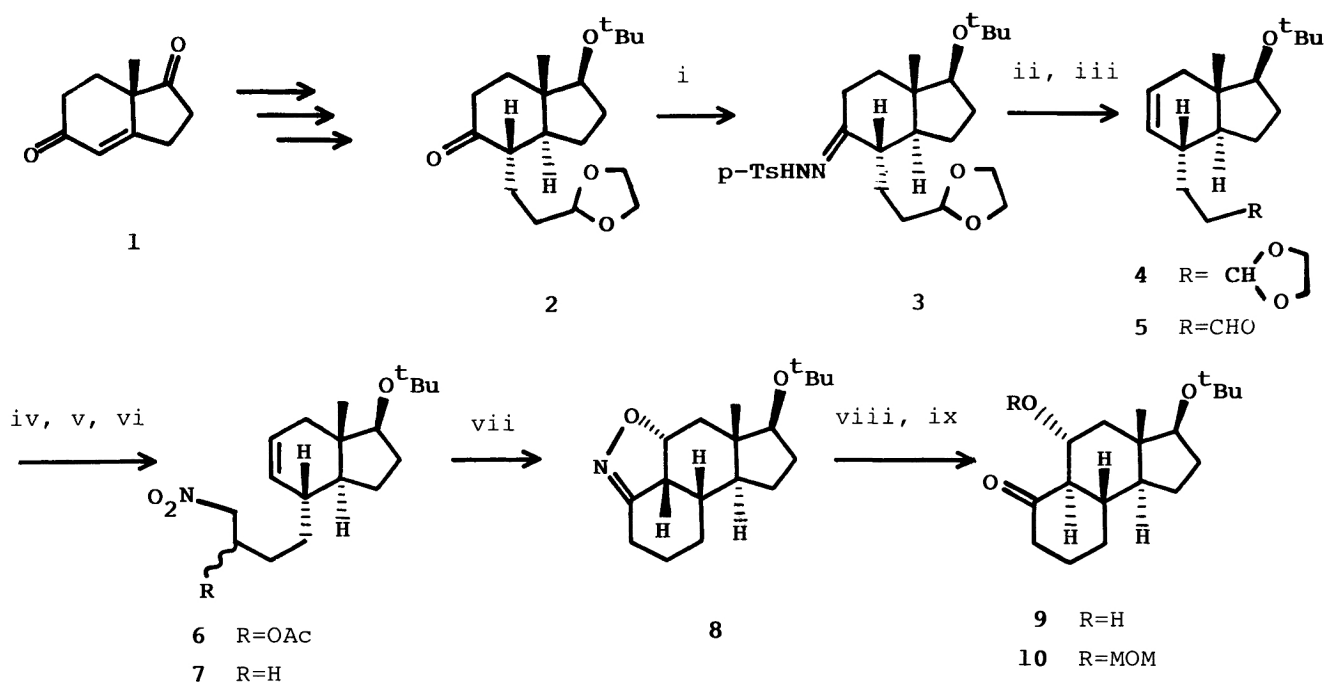
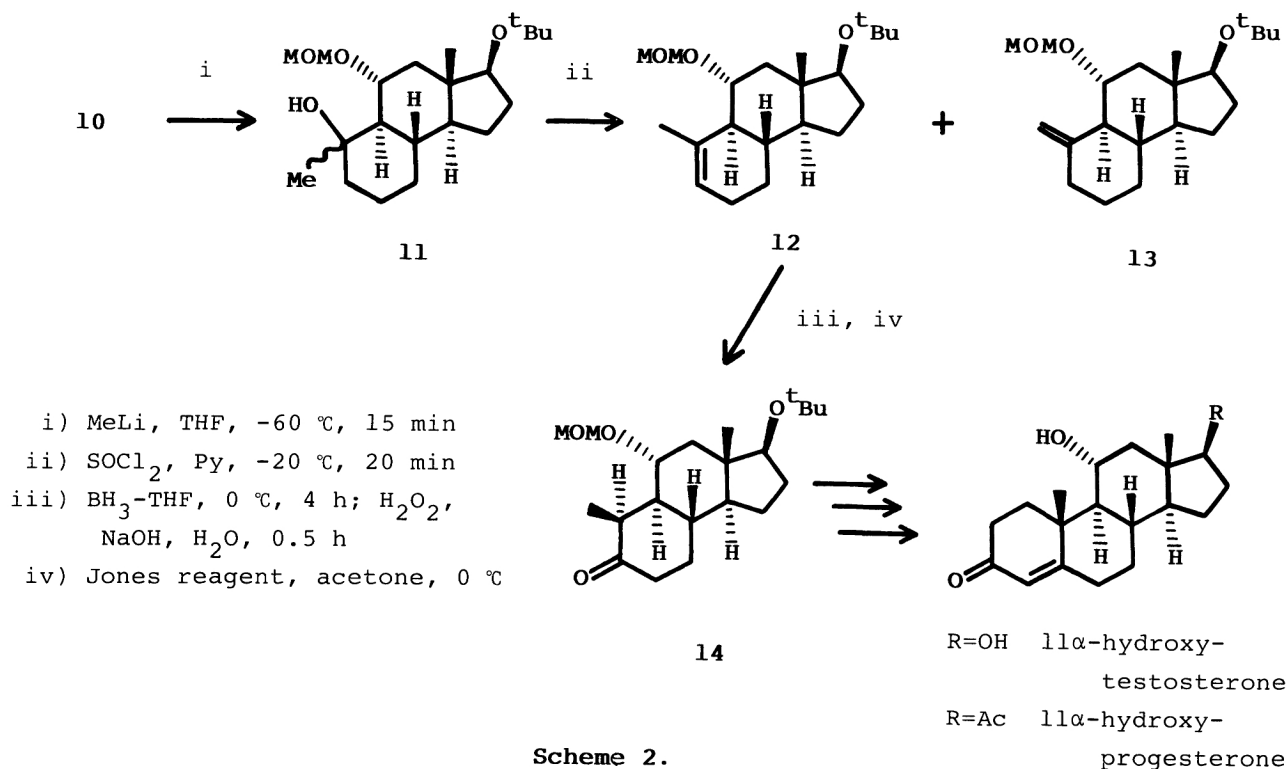


Fig. 1. The ORTEP drawing of compound (10).



Scheme 1.



Scheme 2.

References

- 1) R. T. Blickenstaff, A. -C. Ghosh, and G. C. Wolf, "Total Synthesis of Steroids," Academic Press, New York (1974); S. Djuric, T. Sarkar, and P. Magnus, J. Am. Chem. Soc., 102, 6885 (1980); G. Stork and E. W. Logush, *ibid.*, 102, 1218, 1219 (1980); G. Stork, G. Clark, and C. S. Shiner, *ibid.*, 103, 4948 (1981); G. Stork and D. H. Sherman, *ibid.*, 104, 3758 (1982); B. B. Snider and T. C. Kirk, *ibid.*, 105, 2364 (1983); F. E. Ziegler and T. F. Wang, *ibid.*, 106, 718 (1984); F. E. Ziegler and H. Lim, J. Org. Chem., 49, 3278 (1984); S. E. Denmark and J. P. Germanas, Tetrahedron, 25, 1231 (1984); H. Nemoto, M. Nagai, K. Fukumoto, and T. Kametani, J. Chem. Soc., Perkin Trans. 1, 1986, 1621.
- 2) W. S. Johnson, R. S. Brinkmeyer, V. M. Kapoor, and T. M. Yarnell, J. Am. Chem. Soc., 99, 8343 (1977); H. Yamashita, S. Kurata, and Y. Kurosawa, Nippon Noigei Kagaku Kaishi, 50, 61 (1976).
- 3) M. Ihara, I. Sudow, K. Fukumoto, and T. Kametani, J. Chem. Soc., Perkin Trans. 1, 1986, 117.
- 4) R. H. Shapiro, M. F. Lipton, K. J. Kolonko, R. L. Buswell, and L. A. Capuano, Tetrahedron Lett., 1975, 1811.
- 5) R. H. Wollenberg and S. J. Miller, Tetrahedron Lett., 1978, 3219.
- 6) A. P. Kozikowski, K. Hiraga, J. P. Springer, B. C. Wang, and Z. -B. Xu, J. Am. Chem. Soc., 106, 1845 (1984).
- 7) 9: mp 94 °C; $[\alpha]_D^{25}$ -30.6° (c 1.04, CHCl₃); IR (CHCl₃): 3550 and 1700 cm⁻¹; ¹H-NMR (CDCl₃): δ 0.75 (s, 3H), 1.13 (s, 9H), 3.46 (t, 1H, J=9 Hz), 4.18 (1H, m); m/z 294 (M⁺).
- 8) 10: mp 124 °C; Monoclinic, space group P2₁ with a=16.707 (16), b=6.924 (10), c=9.431 (10) Å; D_c=1.132 g·cm⁻³ for Z=2. Final R value was 0.142 for 1251 observed reflexions.
- 9) 14: oil; $[\alpha]_D^{25}$ -23.1° (c 0.92, CHCl₃); IR (CHCl₃): 1710 cm⁻¹; ¹H-NMR (CDCl₃): δ 0.79 (s, 3H), 1.13 (s, 9H), 1.25 (d, 3H, J=4 Hz), 3.36 (s, 3H), 4.60 (br s, 2H); m/z 352 (M⁺).

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