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Synthetic Approach to 11α-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 11α-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 efforts[1] 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 11β-hydroxy-steroids, 11α-hydroxy-steroids[2] have received relatively little attention. We therefore planned to synthesize 11α-hydroxy-steroid, which could be converted to the corresponding 11-oxo- and 11β-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 reaction[4] 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-steps[5] as follows. Treatment of the aldehyde (5) with nitromethane in the presence of potassium fluoride and 18-crown-6 in isopropanol at 80 ℃ 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 ℃ 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 ℃ 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 analysis[8] 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 11α-hydroxy-steroids in an optically active form.

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

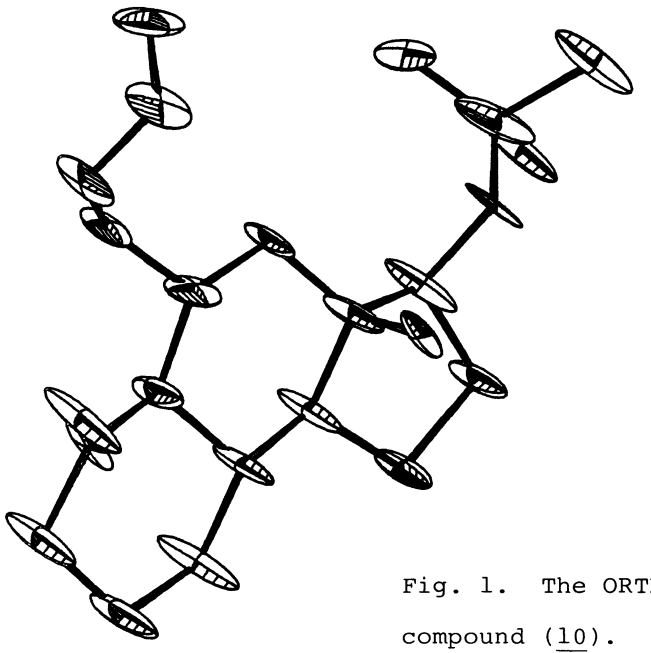
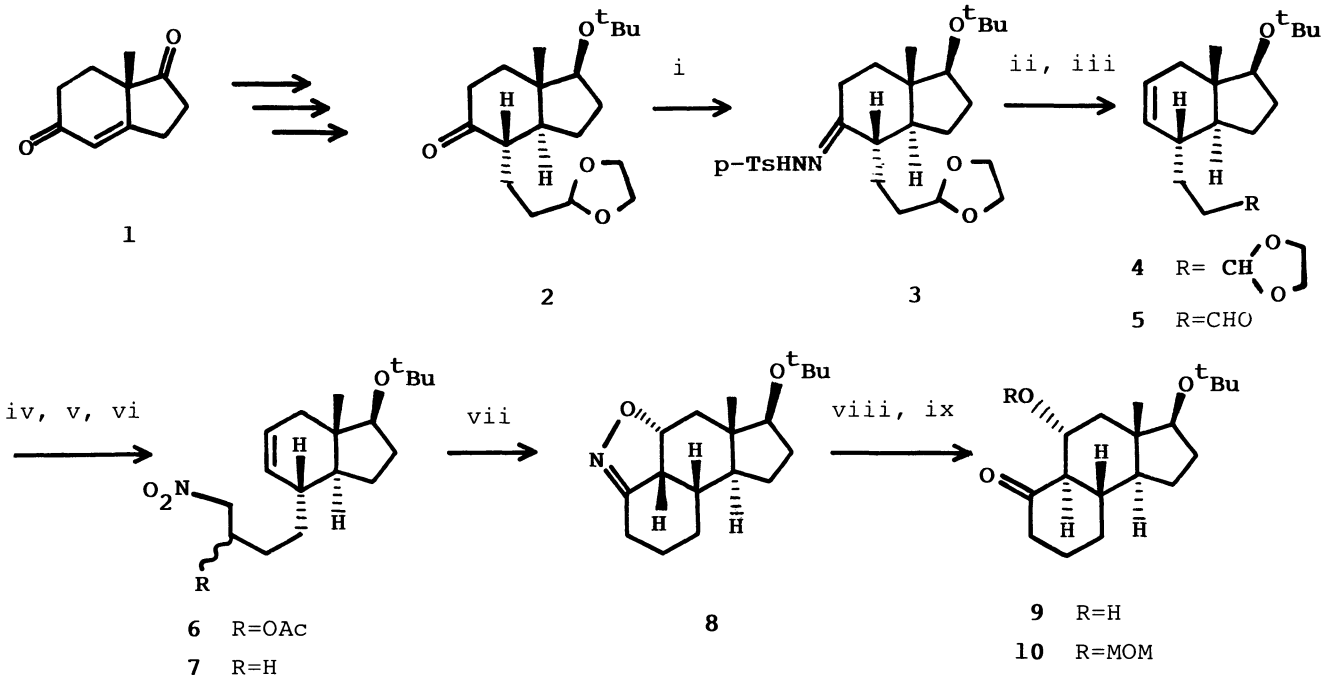
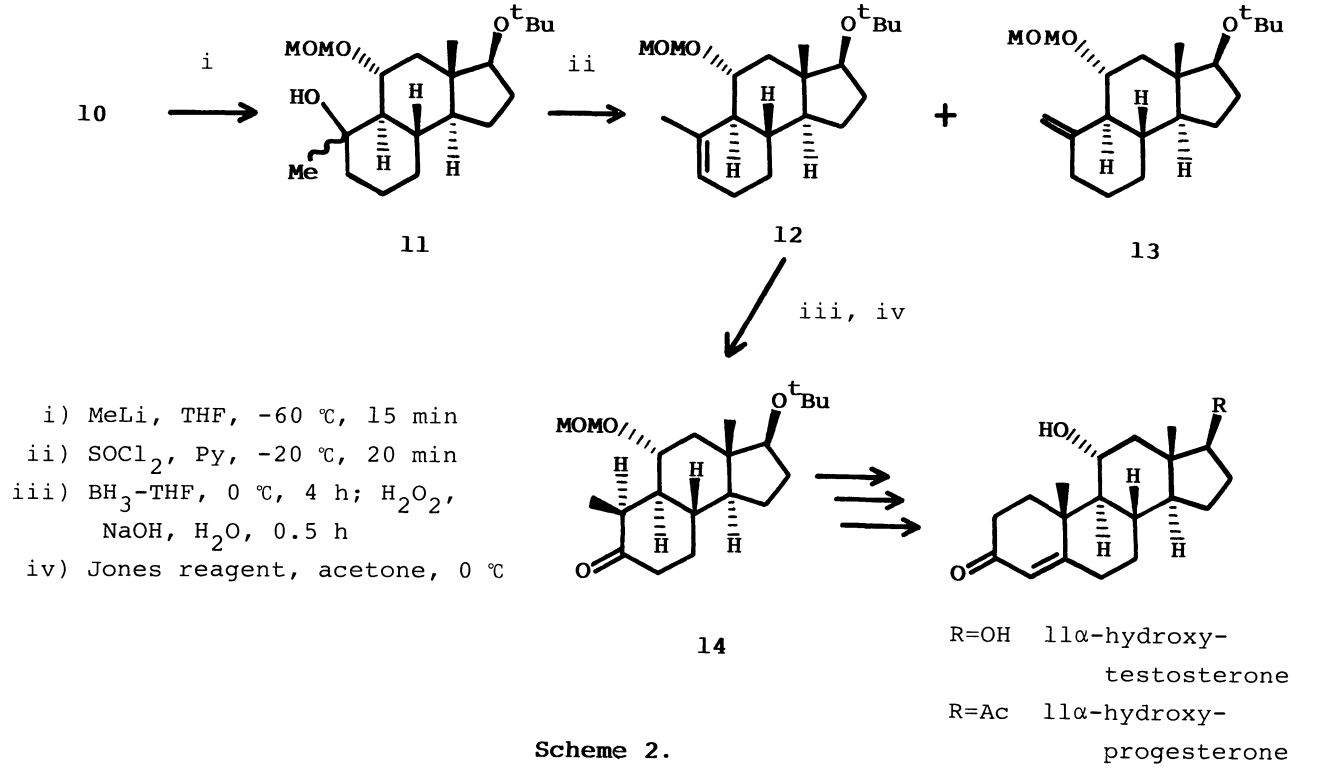


Fig. 1. The ORTEP drawing of compound (10).



i) p-$TsNHNH_2$, benzene, reflux, 0.5 h ii) $^{n}BuLi$, THF, -78 ℃, 15 min iii) p-TsOH, acetone-H_2O (25:1 v/v), reflux, 1 h iv) $MeNO_2$, KF, 18-crown-6, $^{i}PrOH$, 80 ℃, 1 h v) Ac_2O, DMAP, THF, 0 ℃, 0.5 h vi) $NaBH_4$, EtOH, 0 ℃, 1 h vii) PhNCO, Et_3N, benzene, reflux, 15 h viii) Ra-Ni, AcOH, H_2, MeOH, r.t., 8 h ix) MOMCl, $^{i}Pr_2NEt$, THF, r.t., 8 h

Scheme 1.



i) MeLi, THF, -60 ℃, 15 min
ii) $SOCl_2$, Py, -20 ℃, 20 min
iii) BH_3-THF, 0 ℃, 4 h; H_2O_2, NaOH, H_2O, 0.5 h
iv) Jones reagent, acetone, 0 ℃

Scheme 2.

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7) 9: mp 94 ℃; $[\alpha]_D^{25}$ -30.6° (c 1.04, $CHCl_3$); IR ($CHCl_3$): 3550 and 1700 cm^{-1}; ^{1}H-NMR ($CDCl_3$): 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 ℃; Monoclinic, space group $P2_1$ with a=16.707 (16), b=6.924 (10), c=9.431 (10) Å; Dc=1.132 $g \cdot cm^{-3}$ for Z=2. Final R value was 0.142 for 1251 observed reflexions.

9) 14: oil; $[\alpha]_D^{25}$ -23.1° (c 0.92, $CHCl_3$); IR ($CHCl_3$): 1710 cm^{-1}; ^{1}H-NMR ($CDCl_3$): 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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