The Journal of
Organic
Chemistry

VOLUME 55, NUMBER 15 JULY 20, 1990

Communications

A Novel Synthetic Approach to Steroids via Intramolecular 1,3-Dipolar Cycloaddition. A Highly Stereocontrolled Synthesis of Testosterone

Masataka Ihara, Yuji Tokunaga, and Keiichiro Fukumoto*

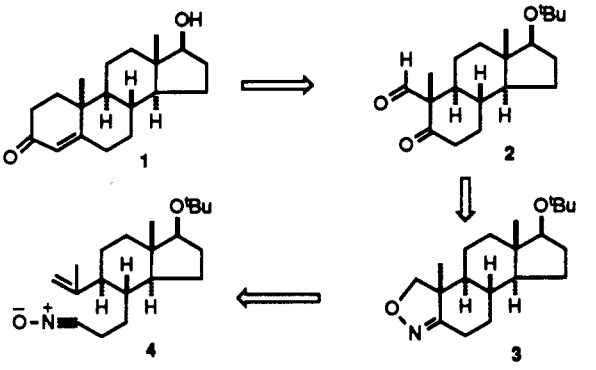
Pharmaceutical Institute, Tohoku University, Aobayama, Sendai 980, Japan

Received May 7, 1990

Summary: A new synthetic methodology for construction of the A/B ring system of steroids was developed consisting of a 1,3-dipolar cycloaddition, followed by incorporation of a three-carbon unit; a facile total synthesis of (+)-testosterone was achieved via this strategy.

Due to their important medicinal properties and unique architectural features, steroids have been the challenging goal of many synthetic programs.[1] Recently, we conducted studies of two different approaches to androgens through A/B ring construction, employing in one case an intramolecular Diels–Alder reaction[2] and in another an intramolecular double Michael reaction;[3] the stereochemical outcomes of these procedures were unsatisfactory. Therefore, a new approach, via an intramolecular 1,3-dipolar cycloaddition, was contemplated in order to overcome this problem. Specifically, a potential intermediate **2** of testosterone (**1**) would be synthesized by way of an isoxazoline derivative **3**, which would be created by the intramolecular cycloaddition of a nitrile oxide **4** (Scheme I). Preferential generation of the desired stereoisomer **3** was expected on the basis of conformational considerations in the transition state (vide infra). We report herein

Scheme I



a highly stereocontrolled synthesis of testosterone (**1**) according to the above novel strategy.

The precursor **12** of the nitrile oxide **4** was prepared via a straightforward sequence starting from the optically active indanone **5**.[5] The indanone **5** was alkylated using 3-(*tert*-butyldimethylsiloxy)-1-iodopropane[6] in the presence of sodium methylsulfinylmethanide in dimethyl sulfoxide.[7] Reduction of the enone **6**, $[\alpha]^{26}_{D}$ +30.03° ($CHCl_3$), obtained in 63% yield, with sodium borohydride in the presence of cobalt(II) dichloride[8] at −20 to 0 °C produced the desired ketone **8**, $[\alpha]^{26}_{D}$ +30.48° ($CHCl_3$), in 67% yield with no equilibration process.[2,3,7] The readily

(1) Taub, D. *The Total Synthesis of Natural Products*; Wiley-Interscience; New York, 1973; Vol. 2, pp 641–725; 1984; Vol. 6, pp 1–49. Kametani, T.; Nemoto, H. *Tetrahedron* **1981**, *37*, 1.

(2) Ihara, M.; Sudow, I.; Fukumoto, K.; Kametani, T. *J. Org. Chem.* **1985**, *50*, 144. *J. Chem. Soc., Perkin Trans. 1* **1986**, 117.

(3) Ihara, M.; Takahashi, T.; Shimizu, N.; Ishida, Y.; Sudow, I.; Fukumoto, K.; Kametani, T. *J. Chem. Soc., Chem. Commun.* **1987**, 1467; *J. Chem. Soc., Perkin Trans. 1* **1989**, 529.

(4) (a) Kozikowski, A. P. *Acc. Chem. Res.* **1984**, *17*, 410. (b) Shishido, K.; Tokunaga, Y.; Omachi, N.; Hiroya, K.; Fukumoto, K.; Kametani, T. *J. Chem. Soc., Chem. Commun.* **1989**, 1093. (c) Desimoni, G.; Tacconi, G.; Barco, A.; Pollini, G. P. *Natural Products Synthesis through Pericyclic Reactions*; American Chemical Society: Washington, DC, 1983; pp 89–117. (d) Curran, D. P. *Advances in Cycloaddition*; JAI press: London, 1988; Vol. 1, pp 129–189.

(5) Micheli, R. A.; Hajos, Z. G.; Cohen, N.; Parrish, D. R.; Portland, L. A.; Sciamanna, W.; Scott, M. A.; Wehrli, P. A. *J. Org. Chem.* **1975**, *40*, 675.

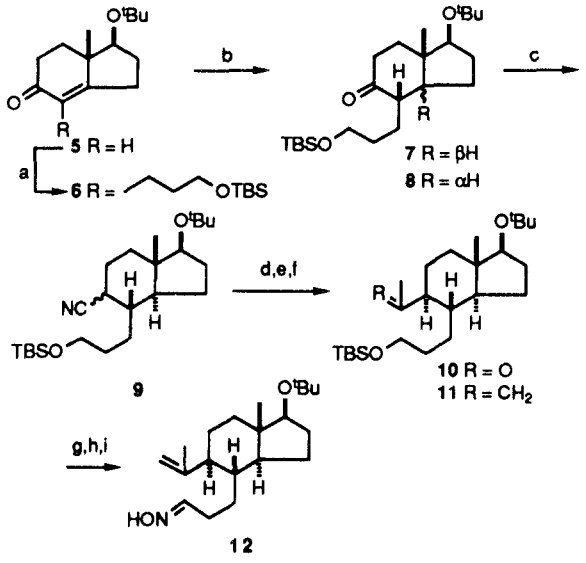
(6) Neary, A. P.; Parsons, P. J. *J. Chem. Soc., Chem. Commun.* **1989**, 1090.

(7) Hajos, Z. G.; Micheli, R. A.; Parrish, D. R.; Oliveto, E. P. *J. Org. Chem.* **1967**, *32*, 3008.

(8) Sasaki, T.; Arai, Y.; Ikekawa, T.; Chihara, G.; Fukuoka, F. *Chem. Pharm. Bull.* **1971**, *19*, 821.

0022-3263/90/1955-4497$02.50/0

Scheme II[a]

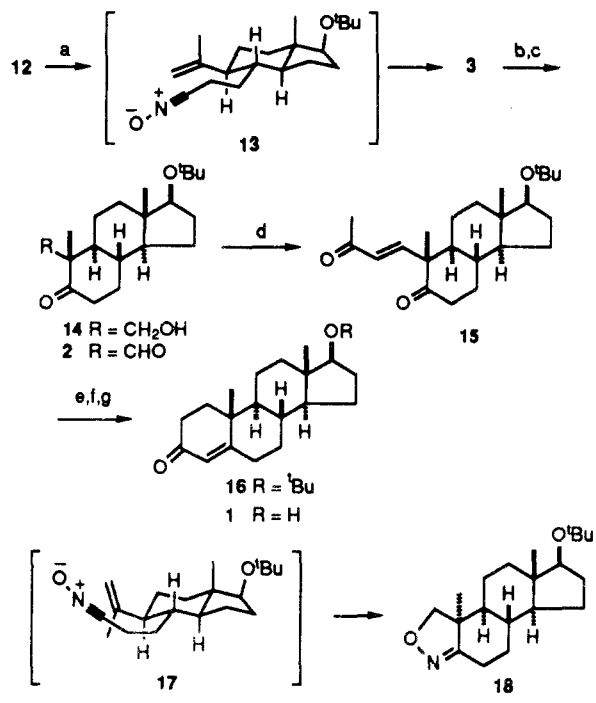


[a] Steps: (a) $NaCH_2SOMe$; $TBSO(CH_2)_3I$; (b) $NaBH_4$–$CoCl_2 \cdot 6H_2O$; (c) TosMIC, ^tBuOK, ^tBuOH; (d) MeLi then silica gel; (e) MeLi; (f) $POCl_3$, pyridine; (g) $^nBu_4NF$; (h) SO_3–pyridine, DMSO, Et_3N; (i) $H_2NOH \cdot HCl$, AcONa.

separable cis indanone **7**, a major product of Birch-type reduction of **6**, generated by carrying out the reaction with lithium in the presence of *tert*-butyl alcohol in liquid ammonia, was obtained in less than 5% yield. Reaction of the ketone **8** with tosylmethyl isocyanide in *tert*-butyl alcohol in the presence of potassium *tert*-butoxide[9] gave the nitrile **9** as an epimeric (54:46) mixture in 97% yield. Treatment of the epimeric mixture with methyllithium in hexane at 0–18 °C, followed by column chromatography, afforded the methyl ketone **10**, $[\alpha]^{26}_D$ +21.23° ($CHCl_3$) as a single stereoisomer in 84% yield. The ^1H NMR spectrum showed two different methyl groups at 0.76 and 2.13 ppm as singlets. The selective formation of **10** could be achieved through an equilibration occurring during the purification process via silica gel chromatography. The methyl ketone **10** was further treated with methyllithium in hexane at 0–18 °C. The olefin **11**, $[\alpha]^{27}_D$ +13.25° ($CHCl_3$), obtained in 63% overall yield from **10** (89% yield based on the recovered **10**), was transformed into the *E* and *Z* mixture (1:1) of the oximes **12**, in three steps, deprotection with tetrabutylammonium fluoride (99% yield), oxidation with dimethyl sulfoxide and pyridine–sulfur trioxide complex,[10] and condensation with hydroxylamine (94% overall yield for two steps) (Scheme II).

A dichloromethane solution of the oxime **12** was allowed to react with 6% aqueous sodium hypochlorite at room temperature to furnish, in 87% yield, the single isoxazoline **3**, $[\alpha]^{26}_D$ +25.01° ($CHCl_3$), mp 187.5–188 °C, whose two methyl groups at angular positions were observed at 0.75 and 1.18 ppm via ^1H NMR spectroscopy. Although the stereochemistry was not readily apparent from spectroscopic examination, it was anticipated that the formation

Scheme III[a]



[a] Steps: (a) NaClO; (b) H_2 (1 atm), Raney Ni, $B(OMe)_3$; (c) SO_3–pyridine, DMSO, Et_3N; (d) $MeCOCH{=}PPh_3$; (e) H_2 (3 atm), Pd–C; (f) KOH; (g) CF_3CO_2H.

of **3** via a chairlike transition state **13** would be more favorable than that of isomer **18** via a boatlike transition state **17**.[2,4b,11] Reductive hydrolysis of the isoxazoline **3**, utilizing Raney nickel in the presence of trimethyl borate under a hydrogen atmosphere in aqueous methanol,[12] afforded the hydroxyl ketone **14**, $[\alpha]^{26}_D$ +35.60° ($CHCl_3$), in 97% yield. Oxidation of the carbinol group of **14** with dimethyl sulfoxide and pyridine–sulfur trioxide complex,[10] followed by reaction of the formyl ketone **2**, $[\alpha]^{25}_D$ –22.05° ($CHCl_3$), obtained in 97% yield, with a stabilized ylid in hot xylene, provided the (*E*)-enone, $[\alpha]^{25}_D$ +41.19° ($CHCl_3$), in 89% yield. The enone **15** was converted into testosterone *tert*-butyl ether (**16**), mp 168.5–169.5 °C, $[\alpha]^{25}_D$ +100.52° ($CHCl_3$) [lit.[13] mp 165–166 °C, $[\alpha]_D$ +103° ($CHCl_3$)], in 88% overall yield in two steps: catalytic hydrogenation in the presence of 10% palladium on activated carbon, followed by treatment with potassium hydroxide in 90% aqueous methanol. Deprotection of **16** using trifluoroacetic acid[13] produced in 86% yield testosterone (**1**), mp 154–155.5 °C, $[\alpha]^{25}_D$ +107.26° (EtOH) [lit.[14] mp 154–154.5 °C, $[\alpha]_D$ +109° (EtOH)], which was identical with the authentic specimen in all respects.

Thus, total synthesis of testosterone (**1**) was accomplished in a highly stereoselective manner. The construction of the A/B ring system of steroids, employing the 1,3-dipolar cycloaddition of a nitrile oxide followed by incorporation of a three carbon unit, provides an effective route into the synthesis of medicinally important steroids.

(9) Oldenziel, O. H.; van Leusen, A. M. *Synth. Commun.* **1972**, *2*, 281. Bull, J. R.; Tuinman, A. *Tetrahedron* **1975**, *31*, 2151. Bull, J. R.; Floor, J.; Tuinman, A. *Tetrahedron* **1975**, *31*, 2157.
(10) Parikh, J. R.; Doering, W. von E. *J. Am. Chem. Soc.* **1967**, *89*, 5505.
(11) Murthy, K. S. K.; Hassner, A. *Tetrahedron Lett.* **1987**, *28*, 97.
(12) Curran, D. P. *J. Am. Chem. Soc.* **1982**, *104*, 4024.
(13) Beyerman, H. C.; Heiszwolf, G. J. *J. Chem. Soc.* **1963**, 755.
(14) David, K.; Dingemanse, E.; Freud, J.; Laqueur, E. *Z. Phys. Chem.* **1935**, *233*, 281.