Communications

Chiral Synthesis of Androsterone through Intramolecular Diels-Alder Reaction

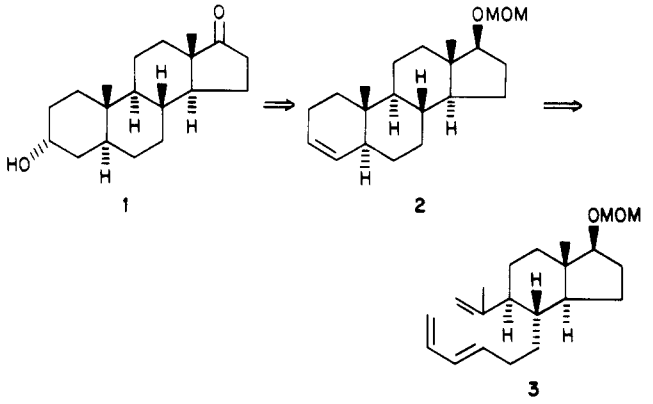
Summary: Steroidal A,B ring system **2** was stereoselectively constructed by the intramolecular Diels-Alder reaction of the (*E*)-triene **3**, a novel approach, which led to a chiral synthesis of androsterone (**1**).

Sir: Medicinally important steroids are very attractive targets in the development of a new regio- and stereocontrolled synthesis. Recently it has been demonstrated that an intramolecular Diels-Alder reaction is extremely useful for the construction of the steroid structure.[1] We have planned a novel assembly of a steroidal ring system by the intramolecular cycloaddition of the triene **3**. A,B ring formation by this methodology has not been reported[2] and it has been suggested by several studies that the stereochemical course in the cycloaddition of 1,3,9-decatriene derivatives leading to bicyclo[4.4.0]decenes is markedly varied by the substituents.[1c] From our preliminary inspection of the Dreiding molecular model (vide infra), a favored formation of the trans-fused adduct **2** from the (*E*)-triene **3** was expected. Here we report an enantioselective synthesis of androsterone (**1**) according to this strategy (Scheme I).

Condensation of the optically active indanone **4**[3] with 3-bromo-1,1-(ethylenedioxy)propane[4] in the presence of sodium hydride in dimethyl sulfoxide[5] gave the acetal **6**,[6] mp 116 °C; $[\alpha]^{20}_D$ + 31° ($CHCl_3$), in 60% yield together with the ether **5**[6] in 17% yield, separable by silica gel column chromatography (Scheme II). Catalytic hydrogenation of **6** with 3.5 atm of hydrogen in the presence of 10% palladium-charcoal in ethanol followed by treatment of the product with sodium methoxide in hot methanol for equilibration[3] afforded the ketone **7**,[6] mp 116-116.5 °C, $[\alpha]^{20}_D$ + 77° ($CHCl_3$), in 73% yield and its epimer in 6% yield. Wittig reaction of **7** using ethyltriphenylphosphonium bromide and *n*-butyllithium produced the olefin **8**[6] in 95% yield as a mixture of two isomers, which was subjected to the hydroboration reaction using borane-methyl sulfide complex followed by the oxidation with alkaline hydrogen peroxide. The oxidation of the resulting diastereomeric alcohols with chromium trioxide in pyridine and the subsequent basic epimerization gave the ketone **9**[6] in 86% yield from **8**. Transformation of **9** to the olefin **10**[6] was carried out by two steps, methylation with methyllithium (91% yield) and dehydration with phosphoryl chloride and pyridine (82% yield). Direct deprotection of the acetal group was troublesome and this was accomplished via the dithioacetal **11**. Namely, treatment of **10** with ethanedithiol in the presence of boron trifluoride etherate caused the acetal exchange accompanied by deblocking of the *tert*-butyl ether. After protection of the hydroxyl group of **11**[6] obtained in 91% yield with methoxymethyl ether (81% yield), refluxing the product with methyl iodide and sodium carbonate in aqueous acetonitrile[7] formed the aldehyde **12** in 59% yield.

Selective preparation of the (*E*)-dienes, recently developed by Yamamoto,[8] utilizing allyldiphenylphosphine oxide and *n*-butyllithium in the presence of hexamethylphosphoric triamide was applied to the aldehyde **12** to afford the triene **3**[6] in 37% yield. Heating the triene **3** in the presence of a catalytic amount of methylene blue[9] in toluene at 220 °C for 100 h in a sealed tube produced quantitatively a mixture of two tetracyclic compounds, mp 70-71 °C, $[\alpha]^{20}_D$ +33° (EtOH), in a ratio of 4:1. Stereochemistry of the both products was easily deduced by the chemical shifts due to C-19 methyl hydrogens (Scheme III). The signal of the major component was observed at 0.78

Scheme I



(1) Reviews: (a) Kametani, T.; Nemoto, H. *Tetrahedron* **1981**, *37*, 1-16. (b) Oppolzer, W. *Angew. Chem., Int. Ed. Engl.* **1977**, *16*, 10-23. (c) Fallis, A. G. *Can. J. Chem.* **1984**, *62*, 183-234, and references therein.

(2) A conceptually close route was reported by Stork and his coworkers: Stork, G.; Clark, G., Shiner, C. S. *J. Am. Chem. Soc.* **1981**, *103*, 4948-4949.

(3) Hajos, Z. G.; Micheli, R. A.; Parrish, D. R.; Oliveto, E. P. *J. Org. Chem.* **1967**, *32*, 3008-3010.

(4) Büchi, G.; Wüest, H. *J. Org. Chem.* **1969**, *34*, 1122-1123.

(5) Hajos, Z. G.; Parrish, D. R.; Oliveto, E. P. *Tetrahedron* **1968**, *24*, 2039-2046.

(6) All new compounds have been characterized by elemental analyses and/or high resolution mass spectra. Their purity was established by TLC and/or HPLC using a Hitachi 635 instrument. Significant spectral data are recorded below. **6**: IR ($CHCl_3$) cm^{-1} 1640 (C=O); ^1H NMR ($CDCl_3$) δ 1.07 (3 H, s, Me), 1.17 (9 H, s, *t*-Bu), 4.81 [1 H, t, J = 4 Hz, C*H*($OCH_2)_2$]. **7**: IR ($CHCl_3$) cm^{-1} 1690 (C=O); ^1H NMR ($CDCl_3$) δ 1.04 (3 H, s, Me), 1.12 (9 H, s, *t*-Bu), 3.43 (1 H, t, J = 7 Hz, CHO-*t*-Bu), 4.82 [1 H, t, *J* = 4 Hz, C*H*($OCH_2)_2$]. **8**: ^1H NMR ($CDCl_3$) δ 0.73 and 0.85 (3 H, each s, Me), 1.11 (9 H, s, *t*-Bu), 4.78 [1 H, t, *J* = 4 Hz, C*H*($OCH_2)_2$], 5.01-5.35 (1 H, m, CH=). **9**: IR ($CHCl_3$) cm^{-1} 1700 (C=O); ^1H NMR ($CDCl_3$) δ 0.76 (3 H, s, Me), 1.11 (9 H, s, *t*-Bu), 2.14 (3 H, s, Ac), 3.34 (1 H, t, *J* = 8 Hz, CHO-*t*-Bu), 4.72 [1 H, t, *J* = 4.5 Hz, C*H*($OCH_2)_2$]. **10**: ^1H NMR ($CDCl_3$) δ 0.75 (3 H, s, Me), 1.11 (9 H, s, *t*-Bu), 1.65 (3 H, s, =CCH_3), 3.33 (1 H, t, *J* = 8 Hz, CHO-*t*-Bu), 4.68 [3 H, br s, C*H*($OCH_2)_2$ and =CH_2]. **11**: IR ($CHCl_3$) cm^{-1} 3430 (OH); ^1H NMR (CCl_4) δ 0.74 (3 H, s, Me), 1.69 (3 H, s, =CCH_3), 4.26 [1 H, t, *J* = 7 Hz, C*H*($SCH_2)_2$], 4.71 (2 H, s, =CH_2). **12**: IR ($CHCl_3$) cm^{-1} 1720 (C=O); ^1H NMR (CCl_4) δ 0.80 (3 H, s, Me), 1.69 (3 H, s, =CCH_3), 3.27 (3 H, s, OMe), 3.48 (1 H, t, *J* = 6 Hz, CHOMOM), 4.51 (2 H, s, OCH_2O), 4.72 (2 H, s, =CH_2), 9.62 (1 H, t, *J* = 1.5 Hz, CHO). **3**: ^1H NMR ($CDCl_3$) δ 0.82 (3 H, s, Me), 1.67 (3 H, s, =CCH_3), 3.34 (3 H, s, OMe), 3.52 (1 H, t, *J* = 8 Hz, CHOMOM), 4.61 (2 H, s, OCH_2O). **2** as a mixture of the cis isomer: ^1H NMR ($CDCl_3$) δ 0.78 and 0.98 (6 H, in a ratio of 9:1, each s, 2 × Me), 3.34 (3 H, s, OMe), 3.51 (1 H, t, *J* = 8 Hz, CHOMOM), 4.61 (2 H, s, OCH_2O), 5.19-5.68 (2 H, m, CH=CH). **13**: IR ($CHCl_3$) cm^{-1} 3420 (OH); ^1H NMR ($CDCl_3$) δ 0.74 (3 H, s, 18-Me), 0.77 (3 H, s, 19-Me), 3.62 (1 H, t, *J* = 8 Hz, CHOH), 5.20-5.60 (2 H, m, CH=CH).

(7) Fetizon, M.; Jurion, M. *J. Chem. Soc., Chem. Commun.* **1972**, 382-383. Takano, S.; Hatakeyama, S.; Ogasawara, K. *J. Chem. Soc., Chem. Commun.* **1977**, 68.

(8) Ukai, J.; Ikeda, Y.; Ikeda, N.; Yamamoto, H. *Tetrahedron Lett.* **1983**, *24*, 4029-4032.

(9) The reaction proceeded slowly without methylene blue. Taber, D. F.; Saleh, S. A. *J. Am. Chem. Soc.* **1980**, *102*, 5085-5088.

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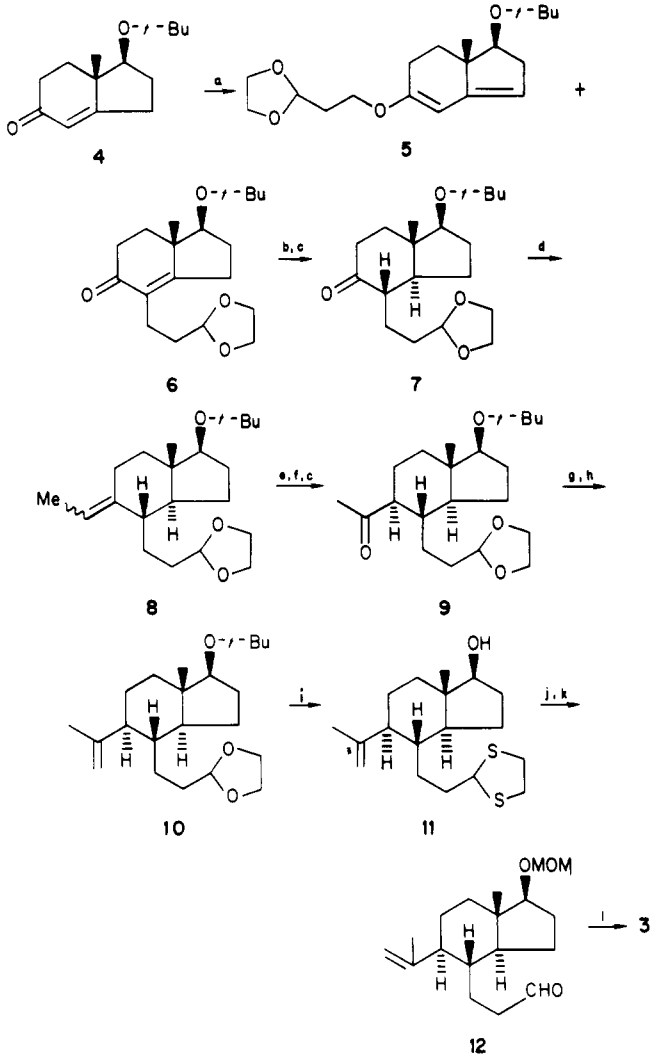
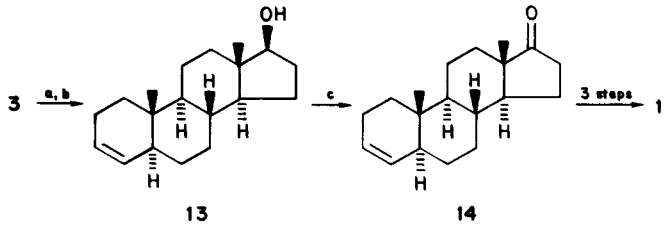
Scheme II[a]



[a] Methods: (a) NaH, $BrCH_2CH_2CH(OCH_2)_2$, Me_2SO. (b) H_2 (3.5 atm), Pd-C. (c) NaOMe. (d) $Ph_3P^+CH_2CH_3 \cdot Br^-$, *n*-BuLi. (e) $BH_3 \cdot Me_2S$; H_2O_2, NaOH. (f) CrO_3, pyridine. (g) MeLi. (h) $POCl_3$, pyridine. (i) $HSCH_2CH_2SH$, $BF_3 \cdot Et_2O$. (j) MOMCl, *i*-Pr_2NEt. (k) MeI, H_2O, CH_3CN, Na_2CO_3. (l) $Ph_2P(=O)CH_2CH=CH_2$, *n*-BuLi, HMPA.

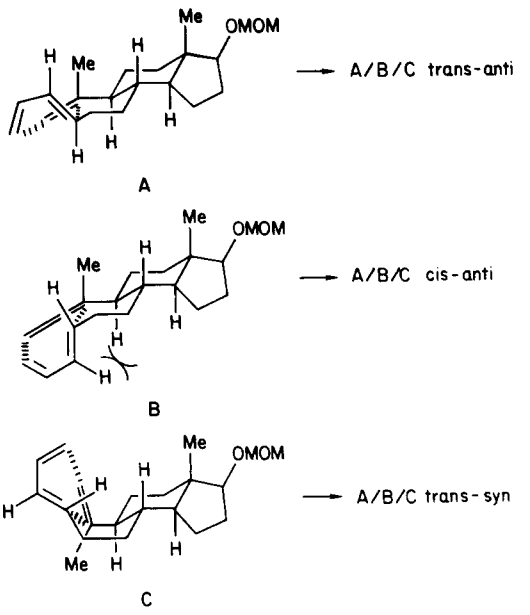
Scheme III[a]



[a] Methods: (a) 220 °C, toluene, methylene blue. (b) Concentrated HCl, MeOH. (c) CrO_3, pyridine.

ppm, while that of the minor one resonated at 0.98 ppm; this fact indicated that the major product was A/B trans isomer **2** and the minor was A/B cis. After conversion into the corresponding alcohols by the action of concentrated hydrochloric acid in methanol, the two stereoisomers were separated by HPLC on TSK gel ODS-120T eluting with acetonitrile–water (4:1 v/v): retention times, cis 11.6 and trans 16.0 min. All physical properties of the major product **13**,[6] mp 151–152 °C (lit.[10] mp 152–153 °C), $[\alpha]^{20}_D$ +49° ($CHCl_3$) [lit.[10] $[\alpha]_D$ +50° ($CHCl_3$)] were identical with

Scheme IV



those of the authentic sample prepared from testosterone.[10]

The preferred formation of the trans-fused product as expected can be understood by noting that in the transition state (B) leading to the cis fusion there is a severe nonbonded interaction between the vinylic hydrogen and the axial hydrogen (Scheme IV). Furthermore the transient C leading to the unnatural isomer has the thermodynamically unstable boat form. On the other hand, the intermediate to the desired product can adopt a more favorable conformation (A).

Oxidation of the alcohol **13** with chromium trioxide in pyridine furnished in 52% yield the ketone **14**, which had been converted into androsterone (**1**) by the usual method.[11] Thus a stereoselective synthesis of the steroid has been achieved.

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Registry No. **1**, 53-41-8; **2**, 93757-05-2; **2** A/B *cis*, 93757-06-3; **3**, 93757-07-4; **4**, 41878-38-0; **5**, 93757-08-5; **6**, 93781-69-2; **7**, 93757-09-6; **7** C-4 epimer, 93757-10-9; (*E*)-**8**, 93757-11-0; (*Z*)-**8**, 93757-12-1; **9**, 93781-79-4; **9** MeLi adduct, 93781-80-7; **10**, 93757-13-2; **11**, 93757-14-3; **11** methoxymethyl ether, 93757-15-4; **12**, 93757-16-5; **13**, 6173-23-5; **13** A/B *cis*, 6198-17-0; **14**, 14935-81-0; $BrCH_2CH_2CH(OCH_2)_2$, 18742-02-4; $Ph_3P^+CH_2CH_3 \cdot Br^-$, 1530-32-1; $HSCH_2CH_2SH$, 540-63-6; MOMCl, 107-30-2; $Ph_2P(=O)CH_2CH=CH_2$, 4141-48-4; MeLi, 917-54-4.

(10) Bowers, A.; Cross, A. D.; Edwards, J. A.; Carpio, H.; Caizada, M. C.; Denot, E. *J. Med. Chem.* **1963**, *6*, 156–161.
(11) Caglioti, L.; Cainelli, G.; Maina, G.; Selva, A. *Tetrahedron* **1964**, *20*, 957–961.

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