First Enantioselective Total Synthesis of (+)-Cortisone

Hideo Nemoto, Norikazu Matsuhashi, Mari Imaizumi, Mitsuo Nagai, and Keiichiro Fukumoto*

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

Received April 3, 1990

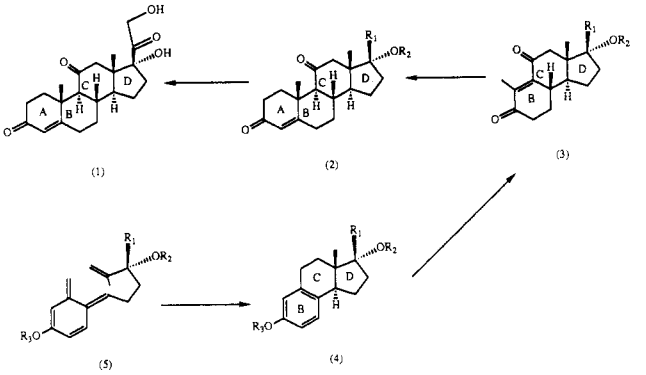
The intramolecular [4 + 2] cycloaddition of an olefinic *o*-quinodimethane, having an optically active oxathiane system as a stereodirecting group, leads enantioselectively to A-nor B-aromatic steroids. This reaction is the key in an enantioselective total synthesis of (+)-cortisone (1).

Herein, we report full details for an efficient enantioselective approach to C-17-substituted steroids via intramolecular [4 + 2] cycloaddition reaction as a key process. This leads to the first enantioselective total synthesis of (+)-cortisone.[1]

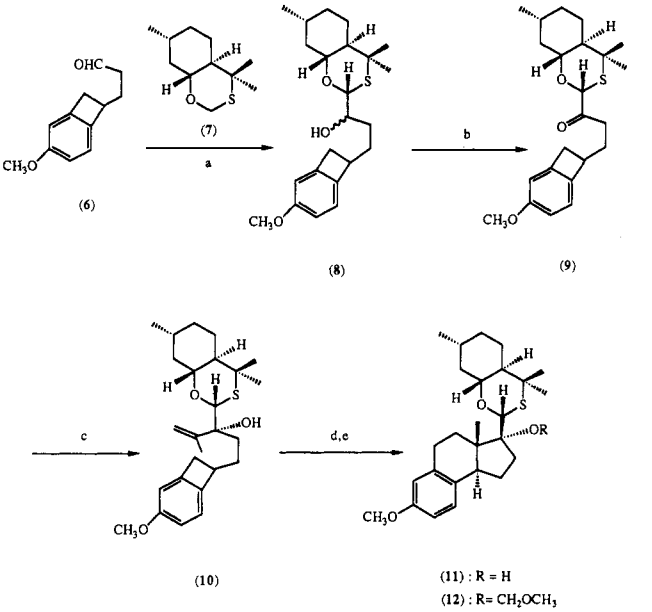
Corticosteroids that have an oxygen functionality at C-11 are important regulatory hormones.[2] Because of this physiological and also clinical importance, much effort has been devoted to solving the problems presented by this class of steroids,[3] especially developing efficient methods for introducing a hydroxyacetyl[4] and an oxygen substituent[5] at C-17 and C-11 positions, respectively; such functionalities are important for steroidal physiological activity.

These facts and the fact that analogous compounds lacking the usual tetracyclic steroid structure (e.g., 16,17-secosteroids or compounds without either ring D or A of the steroid nucleus) have recently attracted much attention because of their hormonal or antihormonal activities[6] have stimulated us to explore an effective methodology for the enantioselective total synthesis of (+)-cortisone (1) and of the steroid nucleus itself (Scheme I). Our synthetic plan for 1 is characterized by a one-step creation of the B, C, and D rings (4) in an enantioselective manner via a chirality transfer from C-17 to C-13 and C-14 positions (steroid numbering) by means of an intramolecular [4 + 2] cycloaddition reaction of the olefinic *o*-quinodimethane 5 as the key step. In turn, the chiral center at C-17 is introduced with the aid of substituent R_1, which has a chiral auxiliary so that its absolute configuration is the same as C-17 in (+)-cortisone (1). The total synthesis is

Scheme I



Scheme II[a]



[a] (a) 7, *n*-C_4H_9Li, THF, −78 °C, then 6, −78 °C, 30 min; (b) DMSO, $(CF_3CO)_2O$, CH_2Cl_2, −78 °C, −78 °C, 30 min, then $(C_2H_5)_3N$, −78 °C, 1 h, (c) $CH_2{=}C(CH_3)MgBr$, THF, −78 °C, 1 h; (d) *o*-dichlorobenzene, reflux, 6.5 h; (e) CH_3OCH_2Cl, DMAP, $(^iC_3H_7)_2NC_2H_5$, CH_2Cl_2, room temperature, 72 h.

(1) (a) Woodward, R. B.; Sondheimer, F.; Taub, D.; Heusler, K.; McLamore, W. M. *J. Am. Chem. Soc.* **1951**, *73*, 4057; (b) **1952**, *74*, 4223. (c) Sarett, L. H.; Arth, G. E.; Lukes, R. M.; Beyler, R. E.; Poos, G. I.; Johns, W. F.; Constantin, J. M. *Ibid.* **1952**, *74*, 4974. For a formal enantioselective total synthesis, see: Johnson, W. S.; Brinkmeyer, R. S.; Kapoor, V. M.; Yarnell, T. M. *J. Am. Chem. Soc.* **1977**, *99*, 8341. Johnson, W. S.; Frei, B.; Gopalan, A. S. *J. Org. Chem.* **1981**, *46*, 1512.

(2) Griggs, M. H.; Brotherton, J. *Steroid Biochemistry and Pharmacology*; Academic Press: New York, 1970.

(3) For classical syntheses of this class of steroids, see: (a) Akhen, A. A.; Titov, Y. A. *Total Steroid Synthesis*; Plenum Press: New York, 1970. (b) Blickenstaff, R. T.; Ghosh, A.-C.; Wolf, G. C. *Total Synthesis of Steroids*; Academic Press: New York, 1974. For the microbiological oxidation of deoxy precursors, see: (c) Johnson, R. A. *Oxidation in Organic Chemistry, Part C*; Trahanosky, W. S., Ed.; Academic Press: New York, 1978.

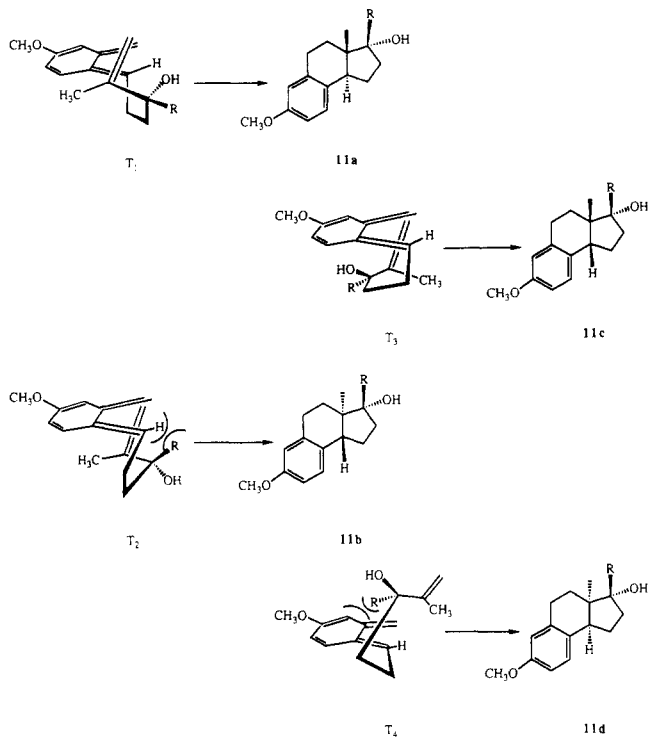
(4) (a) Baldwin, J. E.; Lever, O. W., Jr.; Tzodikov, N. R. *J. Org. Chem.* **1976**, *41*, 2312. (b) Van Rheenen, V.; Shephard, K. P. *Ibid.* **1979**, *44*, 1582. (c) Moriarty, R. M.; John, L. S.; Du, P. C. *J. Chem. Soc., Chem. Commun.* **1981**, 641. (d) Barton, D. H. R.; Motherwell, W. B.; Zard, S. Z. *Ibid.* **1981**, 774. (e) Nedelec, L.; Torelli, V.; Hardy, M. *Ibid.* **1981**, 775. (f) Barton, D. H. R.; Motherwell, W. B.; Zard, S. Z. *Ibid.* **1982**, 551. (g) Daniewsky, A. R.; Wojciechowska, W. *J. Org. Chem.* **1982**, *47*, 2993. (h) Van Leusen, D.; Van Leusen, A. M. *Tetrahedron Lett.* **1984**, *25*, 2581. (i) Tamura, Y.; Yakura, T.; Haruta, J.; Kita, Y. *Ibid.* **1985**, *26*, 3837. (j) Fetizon, M.; Goulaouic, P.; Hanna, I. *Ibid.* **1985**, *26*, 4925. (k) Nitta, I.; Fujimori, S.; Ueno, H. *Bull. Chem. Soc. Jpn.* **1985**, *58*, 978. (l) Nitta, I.; Fujimori, S.; Haruyama, T.; Inoue, S.; Ueno, H. *Ibid.* **1985**, *58*, 981. (m) Nitta, I.; Haruyama, T.; Fujimori, S.; Inoue, S.; Ueno, H. *Ibid.* **1985**, *58*, 1081. (n) Horiguchi, Y.; Nakamura, E.; Kuwajima, I. *J. Org. Chem.* **1986**, *51*, 4323; *J. Am. Chem. Soc.* **1989**, *111*, 6257.

(5) (a) Kametani, T.; Aizawa, M.; Nemoto, H. *J. Chem. Soc., Perkin Trans. I* **1980**, 2793. (b) Stork, G.; Logusch, E. W. *J. Am. Chem. Soc.* **1980**, *102*, 1218. (c) Stork, G.; Clark, G.; Shiner, C. S. *Ibid.* **1981**, *103*, 4948. (d) Stork, G.; Sherman, D. H. *Ibid.* **1982**, *104*, 3758. (e) Stork, G.; Winkler, J. D.; Shiner, C. S. *Ibid.* **1982**, *104*, 3767. (f) Snider, B. B.; Kirk, T. C. *Ibid.* **1983**, *105*, 2364. (g) Ziegler, F. E.; Wang, T.-F. *Ibid.* **1984**, *106*, 718. (h) Ziegler, F. E.; Lim, H. *J. Org. Chem.* **1984**, *49*, 3278.

(6) (a) Randall, L. O.; Selitto, J. J. *Endocrinology* **1958**, *62*, 693. (b) Boris, A.; Stevens, R. H. *Ibid.* **1966**, *78*, 549. (c) Znati, G.; Wolf, M. E. *J. Med. Chem.* **1973**, *16*, 90. (d) Morales-Alanis, H.; Brienne, M. J.; Jacques, J.; Bouton, M.-M.; Nedelec, L.; Torelli, V.; Tournemine, C. *Ibid.* **1985**, *28*, 1796.

0022-3263/90/1955-5625$02.50/0

Chart I



completed by the functionalization at the C-5, C-9, C-10, and C11 positions (**4** → **3**), A-ring formation (**3** → **2**), and introduction of the hydroxyacetyl group at C-17 (**2** → **1**).

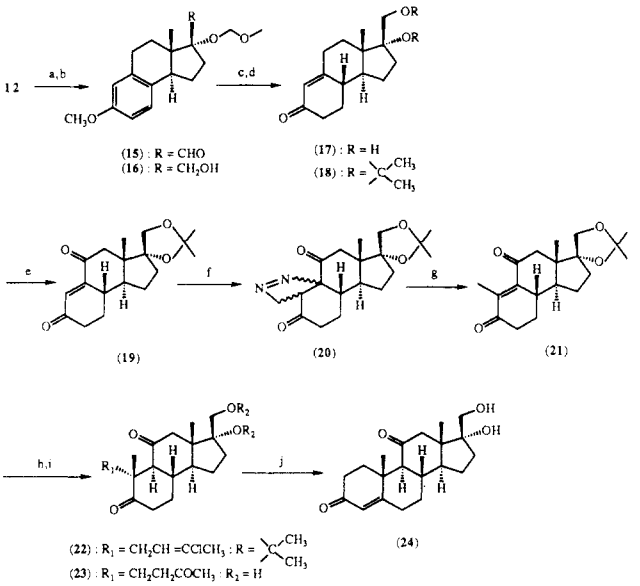
Results and Discussion

Intramolecular [4 + 2] Cycloaddition of Olefinic *o*-Quinodimethanes. Our recent studies[7] demonstrated that an A-nor B-aromatic steroid (**4**) could be formed in a highly stereoselective manner by an intramolecular [4 + 2] cycloaddition of an olefinic *o*-quinodimethane (**5**) bearing a sufficiently bulky substituent (R_1). On the basis of these observations, olefinic benzocyclobutene **10**, a source of the *o*-quinodimethane **5**, emerged as a suitable candidate for these steric demands and a high degree of an asymmetric induction at C-17 was expected (**9** → **10**).[8] The synthesis of this benzocyclobutene (**10**) was straightforward (Scheme II).

Reaction of the aldehyde **6**[7d] with lithiated oxathiane **7**[8] gave in 96% yield alcohol **8** as a stereoisomeric mixture of four diastereomers. Grignard reaction of the ketone **9**, obtained in 86% yield by Swern oxidation of alcohol **8**, afforded the isopropenyl alcohol **10** in 90% yield as a single stereoisomer with respect to alcoholic position but two diastereoisomers with respect to benzocyclobutenylic position.

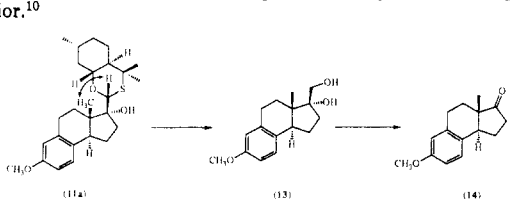
The thermal reaction of the olefinic benzocyclobutene **10** was conducted in boiling *o*-dichlorobenzene to give the tricyclic compound **11a**[9] in 100% yield with no detectable amount of any isomers (**11b**, **11c**, **11d**). From this result, it seems possible that the high stereoselectivity for the trans-syn[11] isomer **11a** rather than the trans-anti **11b**, cis-syn **11c**, and cis-anti **11d** isomers probably reflects the severe steric interactions present in the endo transition states T_3 and T_3 and the exo transition state T_2 relative to the exo transition state T_1 (Chart I). The corresponding MOM ether **12** was derived quantitatively from **11**.

Scheme III[a]



[a] (a) NCS, $AgNO_3$, CH_3CN–H_2O, room temperature, 30 min; (b) $NaBH_4$, CH_3OH, room temperature, 10 min; (c) Li, liquid NH_3, THF–C_2H_5OH, −78 °C, 1 h, then 10% HCl, CH_3OH, room temperature, 10 min; (d) $(CH_3O)_2C(CH_3)_2$, CSA, CH_2Cl_2, room temperature, 10 min; (e) SeO_2, CH_3CN, reflux, 30 min, then PCC, CH_2Cl_2, room temperature, 2 h; (f) CH_2N_2, $CHCl_3$, 0 °C, 1 h; (g) *o*-dichlorobenzene, reflux, 5 min; (h) Li, liquid NH_3, THF, −78 °C, 45 min, then $BrCH_2CH{=}CClCH_3$, THF, −78 °C, 30 min; (i) $Hg(OCOCF_3)_2$, CH_3NO_2, room temperature, 42 h, then 10% HCl, room temperature, 1 h; (j) 10% KOH, CH_3OH, room temperature, 90 min.

Construction of Basic Skeleton of (+)-Cortisone (1). Aldehyde **15**, obtained in 90% yield by oxidative hydrolysis of **12** with *N*-chlorosuccinimide and silver nitrate in aqueous acetonitrile, was reduced with sodium borohydride to the alcohol **16** in 98% yield. Birch reduction of this alcohol, followed by an acid-catalyzed isomerization of the



(7) (a) Nemoto, H.; Nagai, M.; Fukumoto, K.; Kametani, T. *Tetrahedron Lett.* **1985**, *26*, 4613. (b) Nemoto, H.; Nagai, M.; Moizumi, M.; Kohzuki, K.; Fukumoto, K.; Kametani, T. *Ibid.* **1988**, *29*, 4959. (c) Nemoto, H.; Nagai, M.; Fukumoto, K.; Kametani, T. *J. Chem. Soc., Perkin Trans. I* **1986**, 1621. (d) Nemoto, H.; Nagai, M.; Abe, Y.; Moizumi, M.; Fukumoto, K.; Kametani, T. *Ibid.* **1987**, 1727. (e) Nemoto, H.; Moizumi, M.; Nagai, M.; Fukumoto, K.; Kametani, T. *Ibid.* **1988**, 885. (f) Nemoto, H.; Fujita, S.; Nagai, M.; Fukumoto, K.; Kametani, T. *J. Am. Chem. Soc.* **1988**, *110*, 2931. (g) Nemoto, H.; Nagai, M.; Moizumi, M.; Kohzuki, K.; Fukumoto, K.; Kametani, T. *J. Chem. Soc., Perkin Trans. I* **1989**, 1639.

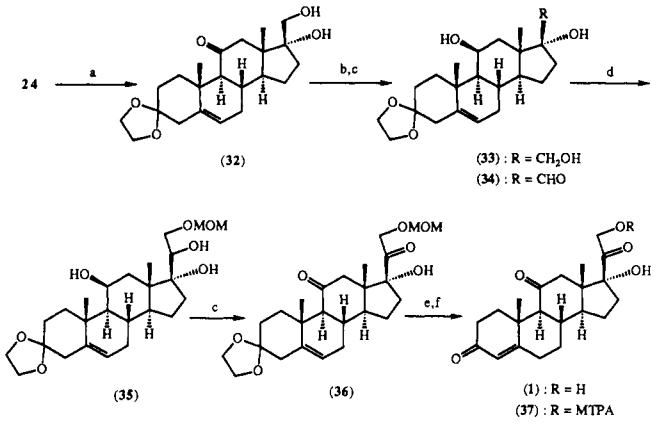
(8) Lynch, J. E.; Eliel, E. L. *J. Am. Chem. Soc.* **1984**, *106*, 2943 and references cited herein.

(9) The structure including the absolute configuration and the optical purity of **11a** were determined as follows. The syn relationship between the angular methyl and the oxathiane group was confirmed by the definite NOE enhancement (9.3%) observed for the oxathiane C-2′ hydrogen upon irradiation of the angular methyl group. Oxidative hydrolysis (NCS, $AgNO_3$, CH_3CN–H_2O, room temperature, 30 min) of the oxathiane ring followed by reduction ($NaBH_4$, CH_3OH, room temperature, 10 min) of the resulting aldehyde gave the diol **12**. Oxidative cleavage (HIO_4, THF–ether, room temperature, 5 min) of **12** afforded the ketone **13**, which was identical with an authentic sample[7b] in all aspects including optical behavior.[10]

(10) Bucourt, P. R.; Tessier, J.; Nomine, G. *Bull. Soc. Chim. Fr.* **1963**, 1923.

(11) For convenience, the trans-syn, trans-anti, cis-syn, and cis-anti representations of stereoisomers refer to the CD ring juncture and the relative arrangements of the angular methyl and large substituent, oxathiane group at C-17 position, respectively.

Scheme IV[a]



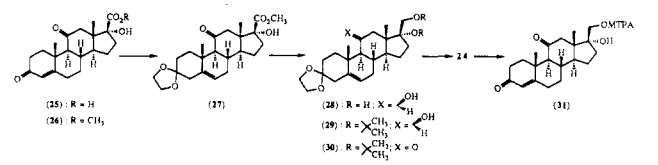
[a] (a) $HOCH_2CH_2OH$, CSA, benzene, reflux, 3 h; (b) $LiAlH_4$, THF, 0 °C, 30 min; (c) DMSO, $(COCl)_2$, −78 °C, 1 h, then $(C_2H_5)_3N$, −78 °C → 0 °C, 1 h; (d) $(^nC_4H_9)_3SnCH_2OCH_2OCH_3$, $^nC_4H_9Li$, THF, −78 °C, 30 min; (e) 10% HCl, CH_3OH, room temperature, 96 h; (f) MTPACl, DMAP, $(C_2H_5)_3N$, CH_2Cl_2, room temperature, 1 h.

resulting dihydrobenzene, afforded in 75% yield the thermodynamically favored stereoisomer **17** as a single product, which was then converted to the acetonide **18** quantitatively. Allylic oxidation of **18** with selenium dioxide, followed by oxidation of the resulting mixture of allylic alcohols and ene dione with PCC, gave ene dione **19** in 75% yield. 1,3-Dipolar cycloaddition of diazomethane to **19** proceeded in regioselective manner to give the adduct **20** in 89% yield as a stereoisomeric mixture of the α- and β-pyrazolines (ca. 3:1).[12] Thermolysis of **20** in boiling *o*-dichlorobenzene afforded in 73% yield the C-10-methylated compound **21**. Thus, the functionalization at the C-11 position and the introduction of 19-methyl were achieved in moderate yield. Stereoselective A-ring formation was carried out by Stork's procedure.[13] The ene dione **21** was reduced with lithium in liquid ammonia–THF and then alkylated by trapping of the in situ generated enolate anion with Wichterle's reagent to give in 64% yield alkylated dione **22**, which was then hydrolyzed with mercuric trifluoroacetate to triketone **23** in 42% yield. Base-catalyzed cyclization of **23** with potassium hydroxide furnished in 86% yield the tetracyclic compound **24**,[14] which has the basic skeleton of (+)-cortisone. (Scheme III).

(12) The stereochemistry for individual diastereomeric products of diazomethane addition was tentatively assigned on the basis of ^1H NMR spectrum.

(13) Stork, G.; Logusch, E. W. *J. Am. Chem. Soc.* **1980**, *102*, 1219.

(14) The structure of **24** including the stereochemistry at C-8, C-9, and C-10 positions, which were newly introduced, and the optical purity were confirmed by comparison with an authentic sample, which was prepared as follows. The ester **26** obtained by the esterification (CH_2N_2) of the known acid **25**[15] was converted ($HOCH_2CH_2OH$, CSA) into the monoacetal **27**. Reduction ($LiAlH_4$) of **27** followed by acetonide formation [$(CH_3O)_2C(CH_3)_2$, CSA] of the resulted triol **28** afforded the alcohol **29**, which was then oxidized (PDC) to give the ketone **30**. Acid treatment (10% HCl) of **30** furnished the diol **24**, which was identical with the sample obtained in Scheme III in all aspects including optical behavior and mixed melting point test. The corresponding mono MTPA esters **31** derived [MTPACl, DMAP, $(C_2H_5)_3N$] from the each diol **24** were identical in all aspects.



(15) Mason, H.; Myers, C.; Kendall, E. *J. Biol. Chem.* **1936**, *116*, 267.

Total Synthesis of (+)-Cortisone (1). The monoacetal **32** obtained in 54% yield by the acetalization of diol **24** was reduced with lithium aluminum hydride to give in 80% yield triol **33**, which was then selectively oxidized under the Swern conditions to afford aldehyde **34** in 83% yield. The reaction of the aldehyde with [(methoxymethoxy)methyl]lithium, generated in situ by the transmetalation of [(methoxymethoxy)methyl]tributylstannane with *n*-butyllithium,[16] gave in 83% yield MOM ether adduct **35**, which was then subjected to Swern oxidation to afford the diketone **36** in 72% yield. Finally, removal of the protecting groups of **36** by acid treatment furnished in 75% yield (+)-cortisone, which was also converted into the mono MTPA ester **37**. (Scheme IV). (+)-Cortisone and the corresponding MTPA ester thus synthesized were identical with authentic samples[17] in all aspects including optical behavior. Thus we have completed the first enantioselective total synthesis of (+)-cortisone.

Experimental Section

General Procedures. All reactions were carried out under dry nitrogen unless indicated. Column chromatography was carried out with silica gel (Wako gel C-200). All new compounds described in this Experimental Section were homogeneous on TLC. The phrase "residue upon workup" refers to the residue obtained when the organic layer was separated and dried over anhydrous magnesium sulfate, and the solvent was evaporated under reduced pressure.

(2′*R*,4a′*R*,7′*R*,8a′*R*)-3-(1,2-Dihydro-4-methoxybenzocyclobuten-1-yl)-1-(4a′,5′,6′,7′,8′,8a′-hexahydro-4′,4′,7′-trimethyl-4′*H*-[1,3]benzoxathian-2′-yl)propan-1-ol (8). To a stirred solution of 1,3-oxathiane **7**[8] (2.4 g, 11.8 mmol) in 35 mL of THF was added dropwise *n*-butyllithium (1.54 M solution in *n*-hexane, 7.2 mL, 11.0 mmol) at −78 °C. After stirring was continued for 3 min at −78 °C, the temperature was raised to 0 °C, and then the solution was cooled to −78 °C again. After stirring was continued for 10 min at −78 °C, a solution of aldehyde **6**[7d] (1.36 g, 7.15 mmol) in 40 mL of THF was added, and the reaction mixture was stirred for 30 min at the same temperature. Then, the reaction mixture was treated with 40 mL of saturated aqueous NH_4Cl solution and extracted with ether (100 mL × 3). The combined extracts were washed with water. The residue upon workup was chromatographed on silica gel (50 g) with *n*-hexane–ethyl acetate (95:5 v/v) to give alcohol **8** (2.7 g, 96%) as a colorless oil: IR ($CHCl_3$) 3550 (OH) cm^{-1}; ^1H NMR (90 MHz, $CDCl_3$) δ 0.95–1.04 (3 H, m, $C_{7'}$-CH_3), 1.27, 1.28, 1.42 [6 H, each s, $C_{4'}$-$(CH_3)_2$], 3.77 (3 H, m, OCH_3), 4.78, 4.99 (1 H, each d, J = 4.5 and 6.6 Hz, $C_{2'}$-H), 6.60–7.10 (3 H, m, Ar H); MS, m/z 390 (M^+); exact mass calcd for $C_{23}H_{34}O_3S$ 390.2227 (M^+), found 390.2229.

(2′*R*,4a′*R*,7′*R*,8a′*R*)-3-(1,2-Dihydro-4-methoxybenzocyclobuten-1-yl)-1-(4a′,5′,6′,7′,8′,8a′-hexahydro-4′,4′,7′-trimethyl-4′*H*-[1,3]benzoxathian-2′-yl)propan-1-one (9). To a stirred solution of DMSO (0.54 mL, 7.61 mmol) in 30 mL of CH_2Cl_2 was added dropwise a solution of trifluoroacetic anhydride (1.07 mL, 7.61 mmol) in 30 mL of CH_2Cl_2 at −78 °C. After the reaction mixture was stirred for 30 min at −78 °C, a solution of **8** (2.7 g, 6.92 mmol) in 75 mL of CH_2Cl_2 was added at the same temperature. After stirring was continued for 1 h at −78 °C, triethylamine (2.32 mL, 15.61 mmol) was added at the same temperature, and the reaction mixture was stirred for 1 h at 0 °C. The reaction mixture was then treated with 150 mL of 5% aqueous hydrochloric acid and extracted with CH_2Cl_2 (50 mL × 3). The combined extracts were washed with water. The residue upon workup was chromatographed on silica gel (50 g) with *n*-hexane–ethyl acetate (95:5 v/v) to give the ketone **9** (2.3 g, 86%) as a colorless oil: IR ($CHCl_3$) 1780 (C=O) cm^{-1}; ^1H NMR (90 MHz, $CDCl_3$) δ 0.95 (3 H, d, J = 5.1 Hz, $C_{7'}$-CH_3), 1.29, 1.46 [6 H, each s, $C_{4'}$-$(CH_3)_2$], 3.77 (3 H, s, OCH_3), 5.44 (1 H, d, J = 2.3

(16) Johnson, C. R.; Medich, J. R. *J. Org. Chem.* **1988**, *53*, 4131.

(17) Commercially available (+)-cortisone was purified by crystallization (C_2H_5OH) and used as an authentic sample.

Hz, $C_{2'}$-H), 5.60–7.05 (3 H, m, Ar H); MS m/z 388 (M^+); exact mass calcd for $C_{23}H_{22}O_3S$ 388.2070 (M^+), found 388.2091; $[\alpha]^{25}_D$ +41.55° (c 0.35, $CHCl_3$). Anal. Calcd for $C_{23}H_{22}O_3S$: C, 71.10; H, 8.31; S, 8.24. Found: C, 71.00; H, 8.41; S, 8.29.

(2′*R*,4a′*R*,7′*R*,8a′*R*,3*R*)-5-(1,2-Dihydro-4-methoxybenzocyclobuten-1-yl)-3-(4a′,5′,6′,7′,8′,8a′-hexahydro-4′,4′,7′-trimethyl-4′*H*-[1,3]benzoxathian-2′-yl)-2-methylprop-1-en-3-ol (10). To a stirred solution of ketone **9** (2.3 g, 5.93 mmol) in 60 mL of THF was added a solution of isopropenylmagnesium bromide [prepared from 2-bromopropene (1.32 mL, 14.8 mmol) and magnesium (504 mg, 20.8 mmol) in 80 mL of THF] at −78 °C. After stirring was continued for 1 h at the same temperature, the reaction mixture was treated with 100 mL of saturated aqueous NH_4Cl solution and extracted with ether (100 mL × 3). The combined extracts were washed with water and saturated aqueous NaCl solution. The residue upon workup was chromatographed on silica gel (60 g) with n-hexane–ethyl acetate (95:5 v/v) to give alcohol **10** (2.3 g, 90%) as a colorless oil: IR ($CHCl_3$) 3550 (OH) cm^{-1}; ^1H NMR (90 MHz, $CDCl_3$) δ 0.98 (3 H, d, J = 5.9 Hz, $C_{7'}$-CH_3), 1.29, 1.42 [6 H, each s, $C_{4'}$-$(CH_3)_2$], 1.77 (3 H, br s, =CHCH_3), 4.95 (1 H, br s, cis CH=CCH_3), 5.06 (1 H, br s, trans CH=CCH_3), 4.99 (1 H, s, $C_{2'}$-H), 3.76 (3 H, s, OCH_3), 6.65–7.05 (3 H, m, Ar H); MS m/z 430 (M^+); exact mass calcd for $C_{26}H_{38}O_3S$ 430.2540 (M^+), found 430.2517; $[\alpha]^{25}_D$ −934.72° (c 1.10, $CHCl_3$).

(2′*R*,4a′*R*,7′*R*,8a′*R*,1*R*,3a*R*,7a*S*)-1-(4a′,5′,6′,7′,8′,8a′-Hexahydro-4′,4′,7′-trimethyl-4′*H*-[1,3]benzoxathian-1′-yl)-1-hydroxy-4,5-(4-methoxybenzo)-7a-methylhydrindan (11). A solution of alcohol **10** (150 mg, 0.35 mmol) in 15 mL of o-dichlorobenzene was refluxed for 6.5 h under stirring. Removal of the solvent gave the crude product, which was chromatographed on silica gel (1 g) with n-hexane–ethyl acetate–benzene (60:1:4 v/v) to give hydrindan **11** (150 mg, 100%) as colorless needles: mp 135–136 °C (Et_2O–n-hexane); IR ($CHCl_3$) 3550 (OH) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 0.67 (3 H, s), 0.93 (3 H, d, J = 10.0 Hz), 1.26, 1.45 (6 H, each s), 2.59 (1 H, br s), 2.88 (2 H, s), 3.45 (1 H, dt, J = 5.0 and 11.0 Hz), 3.80 (3 H, s), 5.20 (1 H, s), 6.68–6.93 (3 H, m); ^{13}C NMR (125.65 MHz, $CDCl_3$) δ 15.00, 22.19, 23.09, 23.61, 24.45, 27.50, 29.59, 29.86, 31.57, 34.57, 34.80, 41.84, 42.87, 45.41, 48.48, 50.67, 55.26, 84.07, 84.31, 96.22, 111.00, 113.55, 126.93, 133.01, 137.57, 157.52; MS m/z 430 (M^+); exact mass calcd for $C_{26}H_{38}O_3S$ 430.2540 (M^+), found 430.2533; $[\alpha]^{25}_D$ +3.42° (c 0.7, $CHCl_3$). Anal. Calcd for $C_{26}H_{38}O_3S$: C, 72.51; H, 8.90; S, 7.43. Found: C, 72.53; H, 8.76; S, 7.48.

(2′*R*,4a′*R*,7′*R*,8a′*R*,1*R*,3a*R*,7a*S*)-1-(4a′,5′,6′,7′,8′,8a′-Hexahydro-4′,4′,7′-trimethyl-4′*H*-[1,3]benzoxathian-1′-yl)-4,5-(4-methoxybenzo)-1-[(methoxymethyl)oxy]-7a-methylhydrindan (12). To a stirred solution of alcohol **11** (389 mg, 0.91 mmol), (dimethylamino)pyridine (165 mg, 1.36 mmol), and diisopropylethylamine (4.0 mL, 22.62 mmol) in 39 mL of CH_2Cl_2 was added dropwise methoxymethyl chloride (0.32 mL, 4.52 mmol) at room temperature. After stirring was continued for 72 h at the same temperature, the reaction mixture was treated with 50 mL of water and extracted with CH_2Cl_2 (50 mL × 3). The combined extracts were washed with 10% aqueous hydrochloric acid (50 mL × 3) and saturated aqueous $NaHCO_3$ solution (50 mL × 3). The residue upon workup was chromatographed on silica gel (5 g) with n-hexane–ethyl acetate (97:3 v/v) to give methoxymethyl ether **12** (390 mg, 91%) as colorless needles: mp 120–121 °C (Et_2O); ^1H NMR (90 MHz, $CDCl_3$) δ 0.70 (3 H, s, C_{7a}-CH_3), 0.95 (3 H, d, J = 6.2 Hz, $C_{7'}$-CH_3), 1.26 (3 H, s, $C_{4'}$-CH_3), 1.41 (3 H, s, $C_{4'}$-CH_3), 3.38 (3 H, s, CH_2OCH_3), 3.77 (3 H, s, $ArOCH_3$), 5.10 (1 H, s, $C_{2'}$-H), 4.81, 5.16 (2 H, each d, J = 8.1 Hz, OCH_2O), 6.60–7.00 (3 H, m, Ar H); MS m/z 474 (M^+); $[\alpha]^{24}_D$ +49.23° (c 1.052, $CHCl_3$). Anal. Calcd for $C_{28}H_{42}O_4S$: C, 70.84; H, 8.92; S, 6.74. Found: C, 70.60; H, 9.05; S, 6.49.

(1*R*,3a*R*,7a*S*)-1-Hydroxy-1-(hydroxymethyl)-4,5-(4-methoxybenzo)-7a-methylhydrindan (13). To a stirred solution of hydrindan **11** (62 mg, 0.14 mmol) in 0.6 mL of acetonitrile was added dropwise a solution of N-chlorosuccinimide (40 mg, 0.3 mmol) and silver nitrate (51 mg, 0.3 mmol) in 7 mL of acetonitrile–H_2O (4:1 v/v) at room temperature. After stirring was continued for 30 min at the same temperature, the reaction mixture was treated with 2 mL of saturated aqueous Na_2SO_3, Na_2CO_3, and NaCl solutions successively and then extracted with CH_2Cl_2 (20 mL × 3). The combined extracts were washed with water. The residue upon workup was dissolved in 2 mL of methanol–THF (3:1 v/v) and treated with sodium borohydride (10.7 mg, 0.29 mmol) at 0 °C under stirring. After stirring was continued for 10 min at the same temperature, the reaction mixture was evaporated to leave the residue, which was treated with 20 mL of water and extracted with ethyl acetate (20 mL × 3). The combined extracts were washed with saturated aqueous NaCl solution. The residue upon workup was chromatographed on silica gel (500 mg) with n-hexane–ethyl acetate (2:1 v/v) to give diol **13** (7.4 mg, 37% from **11**) as colorless needles: mp 87–88 °C (n-hexane); IR ($CHCl_3$) 3550, 3450 (OH) cm^{-1}; ^1H NMR (90 MHz, $CDCl_3$) δ 0.62 (3 H, s, C_{7a}-CH_3), 3.77 (3 H, s, OCH_3), 3.60, 3.83 (2 H, each d, J = 5.7 Hz, OCH_2O), 6.60–7.03 (3 H, m, Ar H); MS m/z 262 (M^+); exact mass calcd for $C_{16}H_{22}O_3$ 262.1568 (M^+), found 262.1591; $[\alpha]^{25}_D$ −0.43° (c 0.74, $CHCl_3$).

(3a*R*,7a*S*)-4,5-(4-Methoxybenzo)-7a-methylhydrindan-1-one (14). To a stirred solution of diol **13** (7.4 mg, 0.028 mmol) in 0.6 mL of THF–ether (2:1 v/v) was added HIO_4·$2H_2O$ (32.2 mg, 0.14 mmol) at room temperature; the reaction mixture was treated with 5 mL of water and extracted with ether (5 mL × 4). The combined extracts were washed with saturated aqueous $NaHCO_3$ and NaCl solutions. The residue upon workup was chromatographed on silica gel (500 mg) with n-hexane–ethyl acetate (95:5 v/v) to give ketone (3.9 mg, 60%) as a colorless powder: $[\alpha]^{25}_D$ +99.45° (c 0.39, methanol) [lit.[10] $[\alpha]^{25}_D$ +99° (c 1.1, methanol)]. The spectral data of this sample were identical with those of an authentic sample.[7b]

(1*R*,3a*R*,7a*R*)-4,5-(4-Methoxybenzo)-1-[(methoxymethyl)oxy]-7a-methylhydrindancarbaldehyde (15). To a stirred solution of methoxymethyl ether **12** (2.2 g, 4.64 mmol) in 20 mL of acetonitrile was added dropwise a solution of N-chlorosuccinimide (1.24 g, 9.28 mmol) and silver nitrate (1.6 g, 9.47 mmol) in 100 mL of acetonitrile–water (4:1 v/v) at room temperature. After stirring was continued for 30 min at the same temperature, the reaction mixture was treated with saturated aqueous Na_2SO_3, Na_2CO_3, and NaCl solutions, successively, and extracted with CH_2Cl_2 (100 mL × 3). The combined extracts were washed with saturated aqueous Na_2CO_3 solution. The residue upon workup was chromatographed on silica gel (40 g) with n-hexane–ethyl acetate (95:5 v/v) to give aldehyde **15** (1.27 g, 90%) as colorless prisms: mp 81.5–82.5 °C (n-hexane); IR ($CHCl_3$) 1700 (C=O) cm^{-1}; ^1H NMR (90 MHz, $CDCl_3$) δ 0.55 (3 H, s, C_{7a}-CH_3), 3.43 (3 H, s, CH_2OCH_3), 3.79 (3 H, s, $ArOCH_3$), 4.60, 4.80 (2 H, each d, J = 7.0 Hz, OCH_2O), 6.60–7.00 (3 H, m, Ar H), 9.66 (1 H, s, CHO); MS m/z 304 (M^+); exact mass calcd for $C_{18}H_{24}O_4$ 304.1673 (M^+), found 304.1698; $[\alpha]^{25}_D$ +23.59° (c 0.85, $CHCl_3$). Anal. Calcd for $C_{18}H_{24}O_4$: C, 71.01; H, 7.95. Found: C, 70.86; H, 8.03.

(1*R*,3a*R*,7a*S*)-1-(Hydroxymethyl)-4,5-(4-methoxybenzo)-1-[(methoxymethyl)oxy]-7a-methylhydrindan (16). To a stirred solution of aldehyde **15** (105 mg, 0.35 mmol) in 5 mL of methanol–THF (4:1 v/v) was added portionwise sodium borohydride (26.4 mg, 0.69 mmol) at 0 °C. After stirring was continued for 10 min at the same temperature, the reaction mixture was treated with 20 mL of water and extracted with ethyl acetate (30 mL × 3). The combined extracts were washed with a saturated aqueous NaCl solution. The residue upon workup was chromatographed on silica gel (3 g) with n-hexane–ethyl acetate (4:1 v/v) to give alcohol **16** (103.3 mg, 98%) as colorless prisms: mp 65–66 °C (n-hexane); IR ($CHCl_3$) 3500 (OH) cm^{-1}; ^1H NMR (90 MHz, $CDCl_3$) δ 0.67 (3 H, s, C_{7a}-CH_3), 3.45 (3 H, s, OCH_2OCH_3), 3.77 (3 H, s, $ArOCH_3$), 4.66, 4.89 (2 H, each d, J = 7.4 Hz, OCH_2O), 6.70–7.30 (3 H, m, Ar H); MS m/z 306 (M^+); $[\alpha]^{24}_D$ −61.26° (c 0.95, $CHCl_3$). Anal. Calcd for $C_{18}H_{26}O_4$: C, 70.55; H, 8.56. Found: C, 70.42; H, 8.57.

(3*R*,3a*S*,9a*S*,9b*S*)-2,3,3a,4,5,9,9a,9b-Octahydro-3-hydroxy-3-(hydroxymethyl)-3a-methyl-1*H*-benz[*e*]inden-7-(8*H*)-one (17). To a stirred solution of alcohol **16** (227.6 mg, 0.74 mmol) in a mixture of 13 mL of THF, 50 mL of liquid ammonia, and 1.3 mL of ethanol was added lithium (59 mg, 18.5 mmol) at −78 °C. After stirring was continued for 1 h at the same temperature, the solvent was concentrated. The residue was diluted with 50 mL of water and extracted with ethyl acetate (100 mL × 3). The combined extracts were washed with saturated aqueous NaCl solution. The residue upon workup was dissolved in a mixture of 26 mL of methanol and 1.3 mL of 10% hydrochloric acid. The reaction mixture was stirred for 10 h at room tem-

perature and then refluxed for 1 h. Evaporation of the solvent afforded the residue, which was diluted with 50 mL of water and extracted with ethyl acetate (90 mL × 4). The combined extracts were washed with saturated aqueous NaCl solution. The residue upon workup was chromatographed on silica gel (500 mg) with Et_2O to give diol **17** (139 mg, 75%) as a colorless oil: IR ($CHCl_3$) 3550, 3450 (OH), 1663 (C=O) cm^{-1}; ^1H NMR (90 MHz, $CDCl_3$) δ 0.95 (3 H, s, C_{3a}-CH_3), 3.58, 3.85 (2 H, each d, J = 2.5 Hz, CH_2O), 5.90 (1 H, br s, C_6-H); MS m/z 250 (M^+); exact mass calcd for $C_{15}H_{22}O_3$ 250.1568 (M^+), found 250.1545; $[\alpha]^{25}_D$ −35.16° (c 1.53, $CHCl_3$). Anal. Calcd for $C_{15}H_{22}O_3$: C, 71.95; H, 8.86. Found: C, 71.72; H, 8.77.

(3*R*,3a*S*,9a*S*,9b*S*)-2,3,3a,4,5,9,9a,9b-Octahydro-3-hydroxy-3-(hydroxymethyl)-3a-methyl-1*H*-benz[*e*]inden-7-(8*H*)-one 3,1′-*O*-Isopropylidene Acetal (18). A solution of diol **17** (290 mg, 1.16 mmol), 2,2-dimethoxypropane (2.14 mL, 17.4 mmol), and catalytic amount of D-camphor-10-sulfonic acid (CSA) in 29 mL of CH_2Cl_2 was stirred for 10 min at 0 °C. Then, the reaction mixture was diluted with 40 mL of methylene chloride and washed with saturated aqueous $NaHCO_3$ solution. The residue upon workup was chromatographed on silica gel (5 g) with n-hexane–ethyl acetate (4:1 v/v) to give acetonide **18** (325 mg, 97%) as a colorless powder: IR ($CHCl_3$) 1658 (C=O) cm^{-1}; ^1H NMR (90 MHz, $CDCl_3$) δ 0.83 (3 H, s, C_{3a}-CH_3), 1.32, 1.43 [6 H, each s, $C(CH_3)_2$], 3.85, 4.02 (2 H, each d, J = 8.5 Hz, CH_2O), 5.88 (1 H, br s, C_6-H); MS m/z 290 (M^+); exact mass calcd for $C_{18}H_{26}O_3$ 290.1881 (M^+), found 290.1891; $[\alpha]^{24}_D$ −52.67° (c 0.93, $CHCl_3$). Anal. Calcd for $C_{18}H_{26}O_3$: C, 74.43; H, 9.03. Found: C, 74.27; H, 9.13.

(3*R*,3a*S*,9a*S*,9b*S*)-2,3,3a,9,9a,9b-Hexahydro-3-hydroxy-3-(hydroxymethyl)-3a-methyl-1*H*-benz[*e*]indene-5,7-(4*H*,8*H*)-dione 3,1′-*O*-Isopropylidene Acetal (19). A mixture of enone **18** (60 mg, 0.21 mmol) and selenium dioxide (34.4 mg, 0.31 mmol) in 6 mL of acetonitrile was refluxed for 30 min under stirring. Then, the reaction mixture was diluted with 50 mL of CH_2Cl_2 and washed with aqueous 10% KOH solution. The residue upon workup was dissolved in 10 mL of CH_2Cl_2, pyridinium chlorochromate (PCC) (230 mg, 1.07 mmol) was added, and stirring was continued for 2 h at the same temperature, and the reaction mixture was diluted with 50 mL of CH_2Cl_2 and treated with aqueous 10% sodium hydroxide solution. The organic layer was washed with aqueous 10% hydrochloric acid and water. The residue upon workup was chromatographed on silica gel (500 mg) with n-hexane–ethyl acetate (1:1 v/v) to give dione **19** (47 mg, 75%) as a colorless oil: IR ($CHCl_3$) 1680, 1670 (C=O) cm^{-1}; ^1H NMR (90 MHz, $CDCl_3$) δ 0.84 (3 H, d, J = 1.1 Hz, C_{3a}-CH_3), 1.32, 1.43 [6 H, each s, $C(CH_3)_2$], 3.86, 3.96 (2 H, each d, J = 9.0 Hz, J = 10 Hz), 6.50 (1 H, d, J = 2.9 Hz, C_6-H); MS m/z 304 (M^+); exact mass calcd for $C_{18}H_{24}O_4$ 304.1675 (M^+), found 304.1707; $[\alpha]^{22}_D$ +14.41° (c 1.36, $CHCl_3$). Anal. Calcd for $C_{18}H_{24}O_4$: C, 71.01; H, 7.95. Found: C, 71.05; H, 8.21.

Reaction of the Enedione 19 with Diazomethane. A solution of enedione **19** (16 mg, 0.05 mmol) in 1.6 mL of chloroform was treated with an excess amount of an ethereal solution of diazomethane for 1 h at 0 °C. The residue upon evaporation of the solvent was chromatographed on silica gel (500 mg) with n-hexane–ethyl acetate (4:1 v/v) to give α-pyrazoline **20** (11.7 mg, 64%) as a colorless oil: IR ($CHCl_3$) 1715 (C=O) cm^{-1}; ^1H NMR (90 MHz, $CDCl_3$) δ 0.84 (3 H, s, C_{3a}-CH_3), 1.34, 1.46 [6 H, each s, $C(CH_3)_2$], 3.90, 3.97 (2 H, each d, J = 8.8 Hz, OCH_2O), 4.30 (1 H, dd, J = 8.6 and 18.0 Hz, HHCN=N), 5.15 (1 H, dd, J = 2.1 and 18.0 Hz, HHCN=N); MS m/z 318 (M^+ − 28); exact mass calcd for $C_{19}H_{26}O_4$ 318.1831 (M^+ − 28), found 318.1814; $[\alpha]^{25}_D$ −162.65° (c 0.71, $CHCl_3$). From the second fraction, n-hexane–ethyl acetate (2:1 v/v), β-pyrazoline **20** (4.8 mg, 25%) was obtained as a colorless oil: IR ($CHCl_3$) 1715 (C=O) cm^{-1}; ^1H NMR (90 MHz, $CDCl_3$) δ 1.00 (3 H, s, C_{3a}-CH_3), 1.30, 1.44 [6 H, each s, $C(CH_3)_2$], 3.89, 3.95 (2 H, each d, J = 10 Hz, OCH_2O), 4.43 (1 H, dd, J = 18.8 and 7.6 Hz, HHCN=N), 5.01 (1 H, dd, J = 18.8 and 3.1 Hz, HHCN=N); MS m/z 346 (M^+); exact mass calcd for $C_{19}H_{26}O_4N_2$ 346.1893 (M^+), found 346.1894; $[\alpha]^{25}_D$ +104.58° (c 0.71, $CHCl_3$).

(3*R*,3a*S*,9a*S*,9b*S*)-2,3,3a,9,9a,9b-Hexahydro-3-hydroxy-3-(hydroxymethyl)-3a,6-dimethyl-1*H*-benz[*e*]indene-5,7-(4*H*,8*H*)-dione 3,1′-*O*-Isopropylidene Acetal (21). A solution of a diastereoisomeric mixture of pyrazoline **20** (24 mg, 0.07 mmol) in 24 mL of o-dichlorobenzene was refluxed for 5 min under stirring. The residue upon evaporation of the solvent was chromatographed on silica gel (500 mg) with n-hexane–ethyl acetate (85:15 v/v) to give methylated enedione **21** (16.2 mg, 73%) as a colorless oil: IR ($CHCl_3$) 1680 (C=O) cm^{-1}; ^1H NMR (90 MHz, $CDCl_3$) δ 0.81 (3 H, d, J = 0.9 Hz, C_{3a}-CH_3), 1.32–1.43 [6 H, each s, $C(CH_3)_2$], 1.90 (3 H, d, J = 2.4 Hz, C_6-CH_3), 3.83, 3.97 (2 H, each d, J = 4.5 Hz, CH_2O); MS m/z 318 (M^+); exact mass calcd for $C_{19}H_{26}O_4$ 318.1831 (M^+), found 318.1837; $[\alpha]^{25}_D$ −15.78° (c 0.57, $CHCl_3$).

(3*R*,3a*S*,6*S*,9a*S*,9b*S*)-2,3,3a,9,9a,9b-Hexahydro-3-hydroxy-3-(hydroxymethyl)-6-(3-chloro-2-buten-1-yl)-3a,6-dimethyl-1*H*-benz[*e*]indene-5,7(4*H*,8*H*)-dione 3,1′-*O*-Isopropylidene Acetal (22). A solution of enedione **21** (45.2 mg, 0.142 mmol) in 2 mL of dry THF was added dropwise to a stirred solution of lithium (17 mg, 2.45 mmol) in 4 mL of dry, distilled ammonia at −78 °C over 30 min. After stirring for 45 min at the same temperature, a solution of 4-bromo-2-chloro-2-butene (511 mg, 2.60 mmol) in 1 mL of dry THF was rapidly added to the above solution, and the reaction mixture was stirred for 30 min at −78 °C. To this end ammonia was evaporated. After quenching with water, the residue was extracted with ether. The organic layers were washed with brine and dried (Na_2SO_4). Concentration of the solvent afforded the crude product, which was chromatographed on silica gel with n-hexane–ethyl acetate (19:1 v/v) as eluant to give alkylated compound **22** (39.7 mg, 64%) as a colorless oil: IR ($CHCl_3$) 1655 (C=C), 1700 (C=O) cm^{-1}; ^1H NMR (90 MHz, $CDCl_3$) δ 0.70 (3 H, s, CH_3), 1.25 (3 H, s, CH_3), 1.32, 1.43 (3 H, each s, CH_3), 1.97 (3 H, s, CH=ClCH$_3$), 3.85, 3.97 (1 H, each d, each J = 9 Hz, CH_2OC), 5.28–5.60 (1 H, m, CH=CClCH$_3$); MS m/z 408 (M^+), 410 (M^+ + 2); exact mass calcd for $C_{23}H_{33}O_4Cl$ 408.2066 (M^+) and 410.2036 (M^+ + 2), found 408.2068 and 410.2058; $[\alpha]^{20}_D$ −25.27° (c 1.29, $CHCl_3$).

(3*R*,3a*S*,6*S*,9a*S*,9b*S*)-2,3,3a,9,9a,9b-Hexahydro-3-hydroxy-3-(hydroxymethyl)-6-(3-oxobut-1-yl)-3a,6-dimethyl-1*H*-benz[*e*]indene-5,7(4*H*,8*H*)-dione (23). A mixture of mercuric trifluoroacetate (207 mg, 0.486 mmol), vinyl chloride **22** (39.7 mg, 0.097 mmol), and 5 mL of nitromethane was stirred for 42 h at room temperature. Two milliliters of 10% HCl were then added to the solution, and the mixture was stirred at the same temperature for 1 h. The reaction mixture was extracted with chloroform. The combined extracts were washed with brine and dried ($MgSO_4$) and evaporated in vacuo. The residue upon workup was chromatographed on silica gel with n-hexane–ethyl acetate (1:1 v/v) to give triketone **23** (14.4 mg, 42%) as a colorless oil: IR ($CHCl_3$) 1708 (C=O); ^1H NMR (90 MHz, $CDCl_3$) δ 0.85 (3 H, s, CH_3), 1.37 (3 H, s, CH_3), 2.15 (3 H, s, CH_3), 3.55, 3.75 (1 H, each d, J = 11 Hz, CH_2OH); MS m/z 350 (M^+); exact mass calcd for $C_{20}H_{30}O_5$ 350.2092, found 350.2093; $[\alpha]^{20}_D$ +12.72° (c 0.66, $CHCl_3$).

17α-Hydroxy-17β-(hydroxymethyl)androst-4-ene-3,11-dione (24). A mixture of triketone **23** (6.6 mg, 0.019 mmol), 0.1 mL of 10% KOH, and 1 mL of methanol was stirred for 90 min at room temperature and then diluted with 1 mL of water. Methanol was evaporated in vacuo. The residue was extracted with chloroform. The combined extracts were washed with brine and dried (Na_2SO_4) and evaporated in vacuo. The residue upon workup was chromatographed on silica gel with n-hexane–ethyl acetate (1:1 v/v) to give diol **24** (5.4 mg, 86%) as colorless needles: mp 177–178 °C [n-hexane–ethyl acetate (1:1 v/v)]; $[\alpha]^{24}_D$ +107.33° (c 0.3, $CHCl_3$). The IR, ^1H NMR, and MS data were identical with those of authentic sample.

Methyl 17α-Hydroxy-3,11-dioxoandrost-4-ene-17β-carboxylate (26). To a stirred solution of carboxylic acid **25**[15] (2.30 g, 6.6 mmol) in 200 mL of chloroform was added 20 mL of ethereal solution of diazomethane at 0 °C, and the mixture was stirred for 1 h at the same temperature. After removal of the solvent, the residue was chromatographed on silica gel (20 g) with n-hexane–ethyl acetate (1:1 v/v) to give methyl ester **26** (1.87 g, 78%) as colorless prisms: mp 230–231 °C (ethyl acetate); IR ($CHCl_3$) 1715, 1710, 1660 (C=O) cm^{-1}; ^1H NMR (90 MHz, $CDCl_3$) δ 0.70 (3 H, s, CH_3), 1.40 (3 H, s, CH_3), 3.00 (1 H, br s, OH), 3.80 (3 H, s, OCH_3), 5.75 (1 H, br s, CH=CO); MS m/z 360 (M^+); exact mass calcd for $C_{21}H_{28}O_5$ 360.1937 (M^+), found 360.1951; $[\alpha]^{25}_D$ +187.06° (c 1.02, $CHCl_3$).

Methyl 17α-Hydroxy-3,11-dioxoandrost-5-ene-17β-carboxylate 3-(Ethylene acetal) (27). To a stirred solution of

enone **26** (1.0 g, 2.77 mmol) in 35 mL of benzene was added a catalytic amount of CSA and ethylene glycol (500 mg, 8.0 mmol) at the room temperature. The reaction mixture was refluxed in a flask fitted with a Dean–Stark trap for 12 h. The reaction mixture was diluted with 40 mL of benzene, and the benzene solution was washed with saturated aqueous $NaHCO_3$ and NaCl solutions. The residue upon workup was chromatographed on silica gel (15 g) with *n*-hexane–ethyl acetate (3:2 v/v) to give acetal **27** (11 g, 98%) as colorless plates: mp 202 °C [*n*-hexane–ethyl acetate (2:3 v/v)]; IR ($CHCl_3$) 1730, 1720 (C=O) cm^{-1}; ^1H NMR (90 MHz, $CDCl_3$) δ 0.65 (3 H, s, CH_3), 1.20 (3 H, s, CH_3), 3.75 (3 H, s, OCH_3), 3.90–4.00 (4 H, m, OCH_2CH_2O), 5.30–5.45 (1 H, m, CH=C); MS *m/z* 404 (M^+); exact mass calcd for $C_{23}H_{32}O_6$ 404.2199 (M^+), found 404.2195; $[\alpha]^{25}_D$ −17.84° (*c* 1.36, $CHCl_3$).

11β,17α-Dihydroxy-17β-(hydroxymethyl)androst-5-en-3-one Ethylene Acetal (28). To a stirred solution of acetal **27** (200 mg, 0.49 mmol) in 15 mL of THF was added lithium aluminum hydride (1.0 M solution in THF, 0.594 mL, 0.594 mmol) at 0 °C. After being stirred for 15 min at 0 °C, the reaction mixture was diluted with 100 mL of ether and then quenched with water. The mixture was filtered through Celite. The filtrate was dried (Na_2SO_4). The residue upon workup was chromatographed on silica gel (2 g) with *n*-hexane–ethyl acetate (3:7 v/v) to afford triol **28** (158 mg, 84%) as a colorless oil, which was then directed to the next reaction.

11β-Hydroxy-spiro-(2′,2′-dimethyl-1′,3′-dioxolane)-4′,17-androst-5-en-3-one 3-(Ethylene acetal) (29). To a stirred solution of triol **28** (64 mg, 0.16 mmol) and 2,2-dimethoxypropane (64 mg, 0.61 mmol) in 3 mL of CH_2Cl_2 was added a catalytic amount of CSA at room temperature, and stirring was continued for 1 h at the same temperature. The reaction mixture was then diluted with 30 mL of CH_2Cl_2 and washed with saturated aqueous $NaHCO_3$ solution. The residue upon workup was chromatographed on silica gel (1 g) with *n*-hexane–ethyl acetate (3:2 v/v) to give acetonide **29** (70 mg, 98%) as colorless needles: mp 188–189 °C (*n*-hexane); IR ($CHCl_3$) 3500–3400 (OH) cm^{-1}; ^1H NMR (60 MHz, $CDCl_3$) δ 0.94 (3 H, s, CH_3), 1.33 [6 H, s, $C(CH_3)_2$], 1.43 (3 H, s, CH_3), 3.86 (2 H, br s, CH_2O), 3.97 (4 H, s, OCH_2CH_2O), 5.10–5.40 (1 H, m, CH=C); MS *m/z* 418 (M^+); exact mass calcd for $C_{25}H_{38}O_5$ 418.2719 (M^+), found 418.2709; $[\alpha]^{25}_D$ −56.84° (*c* 0.38, $CHCl_3$).

Spiro-(2′,2′-dimethyl-1′,3′-dioxolane)-4′,17-androst-5-ene-3,11-dione 3-(Ethylene acetal) (30). To a stirred suspension of pyridinium dichromate (PDC) (65 mg, 0.17 mmol) and Florisil (60 mg) in 5 mL of CH_2Cl_2 was added a solution of acetonide **29** (36 mg, 0.09 mmol) in 2 mL of CH_2Cl_2 at room temperature, and the mixture was stirred for 5 h at the same temperature. The mixture was diluted with 30 mL of ether and filtered through Celite. The filtrate was washed with water. The residue upon workup was chromatographed on silica gel (1 g) with *n*-hexane–ethyl acetate (7:3 v/v) to give ketone **30** (34 mg, 95%) as colorless needles: mp 161–162 °C (*n*-hexane); IR ($CHCl_3$) 1700 (C=O) cm^{-1}; ^1H NMR (90 MHz, $CDCl_3$) δ 0.65 (3 H, s, CH_3), 1.23, 1.27 [6 H, each s, $C(CH_3)_2$], 1.42 (3 H, s, CH_3), 3.83 (2 H, br s, CH_2O), 3.90 (4 H, s, OCH_2CH_2O), 5.20–5.40 (1 H, m, CH=C); MS *m/z* 416 (M^+); exact mass calcd for $C_{25}H_{36}O_5$ 416.2563 (M^+), found 416.2567; $[\alpha]^{25}_D$ −60.52° (*c* 0.38, $CHCl_3$).

17α-Hydroxy-17β-(hydroxymethyl)androst-4-ene-3,11-dione (24). A solution of ketone **30** (259 mg, 0.62 mmol) in 0.7 mL of aqueous 10% hydrochloric acid and 5 mL of methanol was stirred for 2 h at room temperature. The mixture was basified with $NaHCO_3$, and the solvent was then evaporated. The residue was diluted with 7 mL of water and extracted with chloroform (20 mL × 3). The combined extracts were washed with saturated aqueous NaCl solution. The residue upon workup was chromatographed on silica gel (1 g) with *n*-hexane–ethyl acetate (1:5 v/v) to give diol **24** (202 mg, 98%) as colorless needles: mp 177–178 °C [*n*-hexane–ethyl acetate (1:1 v/v)]; IR ($CHCl_3$) 1705, 1665 (C=O) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 0.74 (3 H, s, CH_3), 1.40 (3 H, s, CH_3), 3.55 (1 H, d, *J* = 11.0 Hz, $HOCH_2$), 3.70 (1 H, d, *J* = 11.0 Hz, $HOCH_2$), 5.70 (1 H, s, CH=C); MS *m/z* 332 (M^+); exact mass calcd for $C_{20}H_{28}O_4$ 332.1987 (M^+), found 332.1974; $[\alpha]^{25}_D$ +104.85° (*c* 0.515, $CHCl_3$).

17α-Hydroxy-17β-[[(*S*)-α-methoxy-α-(trifluoromethyl)-phenylacetoxy]methyl]androst-4-ene-3,11-dione (31). To a stirred solution of diol **24** (4.3 mg, 0.013 mmol), triethylamine (9.5 mg, 0.091 mmol), and a catalytic amount of (dimethylmino)-pyridine in 1 mL of CH_2Cl_2 was added dropwise (*S*)-α-methoxy-α-(trifluoromethyl)phenylacetyl chloride (9.8 mg, 0.039 mmol) at room temperature. After stirring was continued for 1 h at the same temperature, the reaction mixture was diluted with 10 mL of CH_2Cl_2 and washed with aqueous 10% hydrochloric acid, saturated aqueous $NaHCO_3$, and NaCl solutions. The residue upon workup was chromatographed on silica gel (100 mg) with *n*-hexane–ethyl acetate (1:1 v/v) to give mono MTPA ester **31** (7.2 mg, 99%) as a colorless powder: IR ($CHCl_3$) 3550 (OH), 1760, 1710, 1670 (C=O) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 0.71 (3 H, s, CH_3), 1.40 (3 H, s, CH_3), 3.53 (3 H, s, OCH_3), 4.27, 4.36 (2 H, each d, *J* = 11.0 Hz, CH_2O), 5.73 (1 H, br s, CH=CO), 7.40–7.43 (3 H, m, ArH), 7.45–7.55 (2 H, m, Ar H); MS *m/z* 548 (M^+); exact mass calcd for $C_{30}H_{35}O_6F_3$ 548.2365, found 548.2345. This was identical in all aspects with the sample, that was prepared from the diol **24** obtained in Scheme III.

17α-Hydroxy-17β-(hydroxymethyl)androst-5-ene-3,11-dione 3-(Ethylene acetal) (32). To a stirred solution of enone **24** (40 mg, 0.12 mmol) in 5 mL of benzene was added a catalytic amount of CSA and ethylene glycol (47 mg, 0.75 mmol) at room temperature. The reaction mixture was then refluxed in a flask fitted with a Dean–Stark trap for 3 h. The reaction mixture was diluted with 20 mL of benzene and washed with saturated aqueous $NaHCO_3$ and NaCl solutions. The residue upon workup was chromatographed on silica gel (0.5 g) with *n*-hexane–ethyl acetate (2:3 v/v) to give acetal **32** (24 mg, 54%) as colorless needles: mp 127–128 °C (ether); IR ($CHCl_3$) 3700–3300 (OH), 1705 (C=O) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 0.37 (3 H, s, CH_3), 1.23 (3 H, s, CH_3), 2.12 (1 H, br s), 2.30 (1 H, dd, *J* = 2.5 and 14 Hz), 2.34 (1 H, dt, *J* = 4.0 and 14.0 Hz), 2.43 (1 H, d, *J* = 15.0 Hz), 3.29 (1 H, d, *J* = 11.0 Hz, $HOCH_2$), 3.45 (1 H, d, *J* = 11.0 Hz, $HOCH_2$), 3.62–3.70 (4 H, m, OCH_2CH_2O), 5.07 (1 H, br s, CH=C); MS *m/z* 376 (M^+); exact mass calcd for $C_{22}H_{32}O_5$ 376.2250 (M^+), found 376.2249; $[\alpha]^{25}_D$ −3.68° (*c* 0.76, $CHCl_3$).

11β,17α-Dihydroxy-17β-(hydroxymethyl)androst-5-en-3-one 3-(Ethylene acetal) (33). To a stirred solution of acetal **32** (6.0 mg, 0.016 mmol) in 4 mL of THF was added lithium aluminum hydride (1.0 M solution in THF, 0.019 mL, 0.019 mmol) at 0 °C. After being stirred for 30 min at 0 °C, the reaction mixture was diluted with 30 mL of ether and then quenched with water. The mixture was filtered through Celite. The residue upon workup was chromatographed on silica gel (400 mg) with *n*-hexane–ethyl acetate (3:7 v/v) to afford triol **33** (4.8 mg, 80%) as a colorless oil: IR ($CHCl_3$) 3650–3300 (OH) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 0.98 (3 H, s, CH_3), 1.28 (3 H, s, CH_3), 3.54 (1 H, d, *J* = 10.0 Hz, $HOCH_2$), 3.75 (1 H, d, *J* = 10.0 Hz, $HOCH_2$), 3.88–3.96 (4 H, m, OCH_2CH_2O), 4.44 (1 H, s, HOCH), 5.22 (1 H, s, CH=C); MS *m/z* 378 (M^+); exact mass calcd for $C_{22}H_{34}O_5$ 378.2406 (M^+), found 378.2408; $[\alpha]^{25}_D$ −26.56° (*c* 0.625, $CHCl_3$).

11β,17α-Dihydroxy-17β-formylandrost-5-en-3-one 3-(Ethylene acetal) (34). To a stirred solution of dimethyl sulfoxide (DMSO) (20 mg, 0.25 mmol) in 1 mL of CH_2Cl_2 was added oxalyl chloride (30 mg, 0.24 mmol) at −78 °C. After the mixture was stirred for 10 min at −78 °C, triol **33** (68 mg, 0.18 mmol) was added to the mixture at the same temperature. After stirring was continued for 1 h at −78 °C, triethylamine (101 mg, 1 mmol) was added at the same temperature, and the reaction mixture was stirred for 1 h at 0 °C. The reaction mixture was then poured into 2 mL of aqueous 5% hydrochloric acid and extracted with chloroform (10 mL × 3). The combined extracts were washed with saturated aqueous NaCl solution. The residue upon workup was chromatographed on silica gel (1 g) with *n*-hexane–ethyl acetate (4:1 v/v) to give aldehyde **34** (56 mg, 83%) as colorless needles: mp 174–175 °C (ether); IR ($CHCl_3$) 3600–3400 (OH), 1715 (C=O) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 1.22 (3 H, s, CH_3), 1.29 (3 H, s, CH_3), 3.84–4.02 (4 H, m, OCH_2CH_2O), 4.48 (1 H, br s, HOCH), 5.25 (1 H, dt, *J* = 2.0 and 4.0 Hz, CH=C), 9.80 (1 H, s, CHO); MS *m/z* 378 (M^+); exact mass calcd for $C_{22}H_{32}O_5$ 376.2250 (M^+), found 376.2238; $[\alpha]^{25}_D$ −80.34° (*c* 0.59, $CHCl_3$).

21-(Methoxymethoxy)-11β,17α,20-trihydroxypregn-5-en-3-one 3-(Ethylene acetal) (35). To a solution of [(methoxymethoxy)methyl]tributylstannane[16] (448 mg, 1.23 mmol) in 1 mL of THF was added *n*-butyllithium (1.63 M solution in *n*-hexane, 0.54 mL, 0.88 mmol) at −78 °C over a period of 2 min. After the mixture was stirred for 4 min, aldehyde **34** (37 mg, 0.098 mmol)

in 1 mL of THF was added to the mixture at -78 °C, and the reaction mixture was stirred for 30 min at the same temperature. After being quenched with saturated aqueous NH_4Cl solution, the mixture was extracted with ether (10 mL × 3). The combined extracts were washed with saturated aqueous NaCl solution. The residue upon workup was chromatographed on silica gel (1 g) with *n*-hexane–ethyl acetate (1:3 v/v) to yield methoxymethyl ether **35** (37 mg, 83%) as a colorless oil: IR ($CHCl_3$) 3650–3400 (OH) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 1.05 (3 H, s, CH_3), 1.29 (3 H, s, CH_3), 3.38 (3 H, s, OCH_3), 3.65 (1 H, dd, J = 7.0 and 10.0 Hz, C_{21}-H_2), 3.76 (1 H, dd, J = 2.0 and 10.0 Hz, C_{21}-H_2), 3.90–4.00 (4 H, m, OCH_2CH_2O), 4.47 (1 H, br s, HOCH), 4.67 (2 H, s, OCH_2O), 5.29 (1 H, br s, CH=C); MS m/z 452 (M^+); exact mass calcd for $C_{25}H_{40}O_7$ 452.2774 (M^+), found 452.2782; $[\alpha]^{25}_D$ -38.20° (*c* 0.445, $CHCl_3$).

17α-Hydroxy-21-(methoxymethoxy)pregn-5-ene-3,11,20-trione 3-(Ethylene acetal) (36). To a stirred solution of DMSO (12 mg, 0.16 mmol) in 1 mL of CH_2Cl_2 was added oxalyl chloride (20 mg, 0.16 mmol) at -78 °C. After the mixture was stirred for 10 min at -78 °C, methoxymethyl ether **35** (21 mg, 0.046 mmol) was added to the mixture at the same temperature. After stirring was continued for 1 h at -78 °C, triethylamine (101 mg, 1 mmol) was added at the same temperature, and the reaction mixture was stirred for 1 h at 0 °C. The reaction mixture was then poured into 2 mL of 5% hydrochloric acid and extracted with chloroform (10 mL × 3). The combined extracts were washed with saturated aqueous NaCl solution. The residue upon workup was chromatographed on silica gel (500 mg) with *n*-hexane–ethyl acetate (1:1 v/v) to give diketone **36** (15 mg, 72%) as colorless needles: mp 181–182 °C (ether); IR ($CHCl_3$) 1725, 1705 (C=O) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 0.53 (3 H, s, CH_3), 1.21 (3 H, s, CH_3), 2.31 (1 H, dt, J = 8.0 and 11.0 Hz), 2.57 (1 H, dd, J = 2.0 and 15.0 Hz), 2.62 (1 H, dt, J = 3.0 and 14.0 Hz), 2.72–2.80 (2 H, m), 3.39 (3 H, s, OCH_3), 3.90–4.98 (4 H, m, OCH_2CH_2O), 4.28 (1 H, d, J = 17.0 Hz, OCH_2CO), 4.53 (1 H, d, J = 17.0 Hz, OCH_2CO), 4.66 (2 H, br s, OCH_2O), 5.35 (1 H, br s, CH=C); MS m/z 448 (M^+); exact mass calcd for $C_{25}H_{36}O_7$ 448.2461 (M^+), found 448.2474; $[\alpha]^{25}_D$ +284° (*c* 0.915, $CHCl_3$).

(+)-Cortisone (1). A solution of diketone **36** (60 mg, 0.13 mmol) in 0.5 mL of aqueous 10% hydrochloric acid solution and 5 mL of methanol was stirred at room temperature for 96 h. The mixture was basified with $NaHCO_3$ and the solvent was then evaporated. The residue was diluted with 5 mL of water and extracted with chloroform (10 mL × 3). The combined extracts were washed with saturated aqueous NaCl solution. The residue upon workup was chromatographed on silica gel (500 mg) with *n*-hexane–ethyl acetate (2:3 v/v) to afford cortisone (1) (36 mg, 75%) as colorless needles: mp 213–215 °C (ethanol) [authentic sample[17] mp 214–216 °C (ethanol)]; IR ($CHCl_3$) 3550–3300 (OH), 1710, 1670 (C=O) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 0.67 (3 H, s, CH_3), 1.40 (3 H, s, CH_3), 3.00 (1 H, br s), 4.27 (1 H, dd, J = 3.0 and 17.0 Hz, OCH_2CO), 4.65 (1 H, dd, J = 4.0 and 17.0 Hz, OCH_2CO), 5.71 (1 H, s, CH=CO); MS m/z 360 (M^+); $[\alpha]^{25}_D$ +190.38° (*c* 0.104, EtOH) [authentic sample[17] $[\alpha]^{25}_D$ +196.80° (*c* 0.188, EtOH)]. The spectra of this sample are superimposable upon those of the authentic sample.[17]

Cortisone 21-(*S*)-α-Methoxy-α-(trifluoromethyl)phenylacetate (37). To a stirred solution of cortisone (1) (5.2 mg, 0.011 mmol), triethylamine (7.8 mg, 0.077 mmol), and a catalytic amount of (dimethylamino)pyridine in 1 mL of CH_2Cl_2 was added dropwise (*S*)-α-methoxy-α-(trifluoromethyl)phenylacetyl chloride (8.4 mg, 0.033 mmol) at room temperature. After stirring was continued for 1 h at the same temperature, the reaction mixture was diluted with 10 mL of CH_2Cl_2 and washed with aqueous 10% hydrochloric acid, saturated aqueous $NaHCO_3$, and NaCl solutions. The residue upon workup was chromatographed on silica gel (100 mg) with *n*-hexane–ethyl acetate (1:2 v/v) to give mono MTPA ester **37** (8.1 mg, 99%) as a colorless powder: IR ($CHCl_3$) 3550 (OH), 1760, 1740, 1710, 1670 (C=O) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 0.73 (3 H, s, CH_3), 1.42 (3 H, s, CH_3), 3.64 (3 H, s, OCH_3), 4.97, 5.10 (2 H, each d, J = 11.0 Hz, CH_2O), 5.75 (1 H, br s, CH=C), 7.41–7.45 (3 H, m, ArH), 7.62–7.66 (2 H, m, Ar H); MS m/z 576 (M^+); exact mass calcd for $C_{31}H_{35}O_7F_3$ 576.2336 (M^+), found 576.2349. This derivative was identical in all aspects with the sample that was prepared from authentic cortisone.[17]

Registry No. **1**, 53-06-5; **6**, 113627-43-3; **7**, 79618-03-4; **8** (isomer 1), 128802-39-1; **8** (isomer 2), 128898-72-6; **8** (isomer 3), 128898-73-7; **8** (isomer 4), 128898-74-8; **9** (isomer 1), 128802-40-4; **9** (isomer 2), 128898-75-9; **10** (isomer 1), 128802-41-5; **10** (isomer 2), 128898-76-0; **11**, 128802-42-6; **12**, 128802-43-7; **13**, 128802-44-8; **14**, 887-47-8; **15**, 128802-45-9; **16**, 128802-46-0; **17**, 128802-47-1; **18**, 128802-48-2; **19**, 128802-49-3; α-**20**, 128802-50-6; β-**20**, 128802-51-7; **21**, 128802-52-8; **22**, 128802-53-9; **23**, 128802-54-0; **24**, 128802-55-1; **25**, 3597-44-2; **26**, 3941-62-6; **27**, 3941-63-7; **28**, 128802-56-2; **29**, 128802-57-3; **30**, 128802-58-4; **31**, 128802-59-5; **32**, 128802-60-8; **34**, 128802-61-9; **35**, 128822-25-3; **36**, 128802-62-0; **37**, 128802-63-1; MTPACE, 39637-99-5; CH_2=$C(CH_3)MgBN$, 13291-18-4; CH_3OCH_2Cl, 107-30-2; $(CH_3O)_2C(CH_3)_2$, 77-76-9; CH_2N_2, 334-88-3; $BrCH_2CH$=$C(Cl)CH_3$, 51430-83-2; $HOCH_2CH_2OH$, 107-21-1; $(C_4H_9)_3SnCH_2OCH_2OCH_3$, 100045-83-8.

Supplementary Material Available: NMR spectra for 19 compounds (19 pages). Ordering information is given on any current masthead page.

Synthesis of the Ziegler Key Intermediate and Related Precursors for the Synthesis of Forskolin and Erigerol

María I. Colombo, Juan Zinczuk, José A. Bacigaluppo, Carmen Somoza, and Edmundo A. Rúveda*

Instituto de Química Orgánica de Síntesis (CONICET-UNR), Facultad de Ciencias Bioquímicas y Farmacéuticas, Casilla de Correo 991, 2000 Rosario, Argentina

Received March 19, 1990

The Ziegler key intermediate **2**, previously used in three total syntheses of forskolin (**1**), has been synthesized from enone **5a**. Starting from **5a**, two sequences to **2** have been developed (Schemes I and II). The key step in both sequences is the early and stereoselective introduction of the C-6, C-7 oxygen functional groups present in the natural product. This constitutes a new formal total synthesis of forskolin. The preparation of the key intermediate **18**, a diastereomer of **2**, potentially useful for the synthesis of analogues of **1** and for the synthesis of the highly oxygenated labdane diterpene erigerol (**3**), starting also from **5a**, is described.

Forskolin (**1**), the highly oxygenated labdane diterpene isolated from the roots of the Indian herb *Coleous forskolii*,[1] has generated an enormous amount of synthetic interest[2-6] because of its unique structural features and its

0022-3263/90/1955-5631$02.50/0