philized from pH 5 (1 g) was added to 25 mL of anhydrous dioxane containing 2.5 mmol of 1 and 5 mmol of succinic anhydride. The suspension was shaken at 250 rpm and 20 °C. After 24 h, the enzyme was removed by filtration and the solvent evaporated. The crude residue was dissolved in 40 mL of AcOEt and extracted with 5% $NaHCO_3$. The aqueous solution was acidified to pH 4.5 and extracted with AcOEt. Anhydrification of the organic layer and evaporation of the solvent furnished crude **3d**, which was crystallized from benzene. Mp: 126–8 °C (lit.[13] mp 127 °C). [α]: +12.8° (*c* = 5 in EtOH). ^1H NMR: selected data δ 5.32 (1 H, d, H-1); 4.55 (1 H, ddd, H-2); 4.50 (1 H, dd) and 4.39 (1 H, dd), CH_2-3; 2.53 (4 H, s), succinyl moiety. Anal. Calcd for $C_{15}H_{16}Cl_2N_2O_8$: C, 42.57; H, 3.81; N, 6.62. Found: C, 42.81; H, 3.65; N, 6.42.

***threo*-(1*R*,2*R*)-1-(4-Methylsulfonyl)-2-(dichloroacetamido)-1,3-propanediol 3-Palmitate.** Thiamphenicol (880 mg) was dissolved in 75 mL of anhydrous acetone containing 3 molar equiv of TFE palmitate. Lipase G prelyophilized from pH 5 (500 mg) was added, and the suspension was shaken at 250 rpm and 45 °C for 48 h. Following the previously described workup, 3-*O*-palmitoylthiamphenicol was obtained in 83% yield after crystallization from aqueous acetone. Mp: 101–3 °C. [α]: −20.8° (*c* = 2.5 in AcOEt). ^1H NMR: δ 7.80 (2 H, d, *J* = 8.5 Hz) and 7.60 (2 H, d, *J* = 8.5 Hz), aromatic protons; 6.23 (1 H, s, CCl_2H); 5.07 (1 H, d, *J* = 2.8 Hz, H-1); 4.35 (1 H, ddd, J_1 = 2.8 Hz, J_2 = 5.3 Hz, J_3 = 8.2 Hz, H-2); 4.27 (1 H, dd, J_1 = 5.3 Hz, J_2 = 10.9 Hz) and 4.12 (1 H, dd, J_1 = 8.2 Hz, J_2 = 10.9 Hz), CH_2-3; 3.03 (3 H, s, CH_3SO_2); 2.20 (2 H, t), 1.20 (26 H, m), and 0.76 (3 H, t), aliphatic chain. Anal. Calcd for $C_{28}H_{45}Cl_2NO_6S$: C, 56.56; H, 7.63; N, 2.36. Found: C, 57.30; H, 7.81; N, 2.20.

(13) Hanroth, F. *Chem. Abstr.* **1966**, *64*, 17483d.

Acknowledgment. We thank the Consiglio Nazionale delle Ricerche, Progetto Finalizzato "Biotecnologie e Biostrumentazioni", and the Biotechnology Action Programme of the Commission of the European Communities for financial support of this work.

Registry No. 1, 56-75-7; 2, 15318-45-3; **3a**, 59005-99-1; **3b**, 530-43-8; **3c**, 14399-14-5; **3d**, 3544-94-3; TFE butanoate, 371-27-7; TFE laurate, 70253-78-0; TFE palmitate, 119596-14-4; TFE cinnamate, 23094-31-7; lipase, 9001-62-1; methyl acetate, 79-20-9; methyl propionate, 554-12-1; methyl butanoate, 623-42-7; methyl hexanoate, 106-70-7; methyl octanoate, 111-11-5; succinic anhydride, 108-30-5; *threo*-(1*R*,2*R*)-1-[4-(methylsulfonyl)phenyl]-2-(dichloroacetamido)-1,3-propanediol 3-palmitate, 21478-01-3.

Conversion of Sandaracopimaric Acid into an Androstane Analogue Steroid

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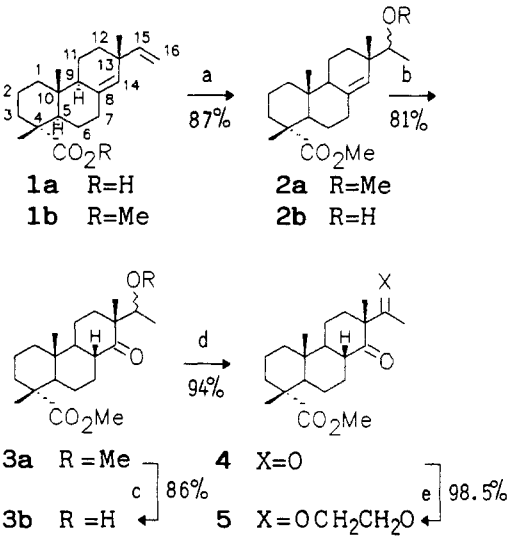
The conversion of the diterpenoid resin acid, sandaracopimaric acid **1a**, into a tetracyclic system of steroid is described. Key steps for the construction of the D ring are reductive nucleophilic acylation of ketone **5** and intramolecular aldol condensation of keto aldehyde **10**. Various unsuccessful attempted methods for achieving the one-carbon homologation of the C-14 carbonyl group of **5** are described.

The use of podocarpic, abietic, and dehydroabietic resin acids as starting materials for the synthesis of steroids has been investigated by several groups.[1] In recent years the conversion of tricyclic diterpenes with pimarane or isopimarane skeleton into such compounds has also been reported,[2] but hitherto none of these syntheses has resulted in the preparation of a steroidal structure possessing the trans-anti-trans arrangement of BCD rings of androstane steroids. In this paper, we describe the conversion of the readily available[3] sandaracopimaric acid **1a** into an androstane analogue steroid, utilizing a new approach for the construction of the D ring which involves as key steps reductive nucleophilic acylation of ketone **5** and intramolecular aldol condensation of keto aldehyde **10**, as illustrated by the reaction sequence shown in Schemes I–IV.

Scheme I[a]



[a] (a) (i) $Hg(OAc)_2$, MeOH; (ii) $NaBH_4$, NaOH, dioxane; (b) (i) BH_3, THF; (ii) H_2O_2, KOH, H_2O–dioxane; (iii) Jones reagent, acetone; (iv) NaOMe, MeOH; (c) NaI, TMSCl; (d) Jones reagent, acetone; (e) $HO(CH_2)_2OH$, PTSA, benzene.

Treatment of the methyl ester **1b** with mercuric acetate in methanol (Scheme I) followed by treatment with sodium borohydride afforded the methyl ether **2a** as a C-15[4] ep-

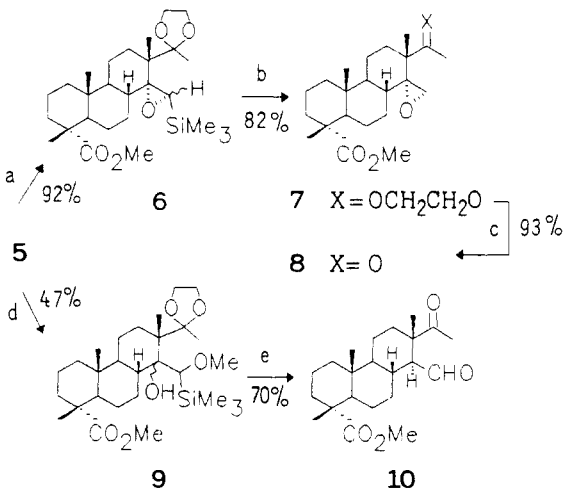
(1) (a) Wheeler, D. M. S.; Witt, P. R. *J. Org. Chem.* **1972**, *37*, 4211. (b) Bell, R. A.; Cravestock, M. B. *Can. J. Chem.* **1969**, *47*, 3661. (c) Huffman, J. W.; Arapakos, P. G. *J. Org. Chem.* **1965**, *30*, 1604. (d) Wirthlin, T.; Wehrli, H.; Jeger, O. *Helv. Chim. Acta* **1974**, *57*, 351 and 368. (e) Tahara, A.; Harigaya, Y.; Onda, M. *Chem. Pharm. Bull.* **1976**, *24*, 1497.

(2) (a) Wenkert, E.; Davis, L. L.; Mylari, B. L.; Solomon, M. F.; Da Silva, R. R., Shulman, S.; Warner, R. J.; Ceccherelli, P.; Curini, M.; Pellicciari, R. *J. Org. Chem.* **1982**, *47*, 3242. (b) De Pascual, J.; Gonzalez, F. B.; Mateos, A. F.; Conde, F. G.; Alarcón, M. E. R. *An. Quim.* **1983**, *79C*, 447. (c) Wenkert, E.; Curini, M.; Coccia, R.; Ceccherelli, P.; Halls, T. D. J.; Porter, B. *J. Org. Chem.* **1984**, *49*, 2054. (d) Delmond, B.; Arreguy, S. M.; Maillard, B. *Tetrahedron Lett.* **1987**, *28*, 2127. (e) Bermejo, F.; Bordell, M.; Fernandez, A. *Can. J. Chem.* **1988**, *66*, 2200.

(3) Edwards, O. E.; Nicolson, A.; Rodger, M. N. *Can. J. Chem.* **1960**, *38*, 663.

0022-3263/90/1955-2369$02.50/0

Scheme II[a]

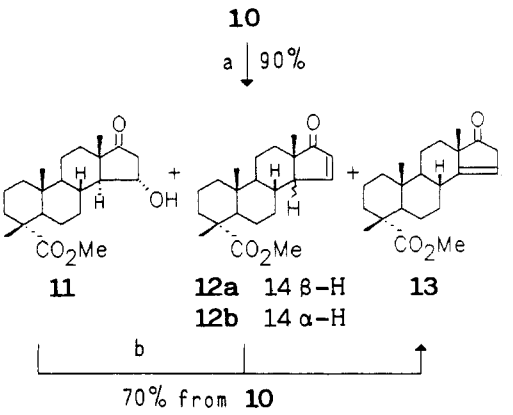


[a] (a) Me_3SiCH_2Cl, *s*-BuLi, TMEDA, THF; (b) $Bu_4NF \cdot 3H_2O$, THF; (c) PPTS, acetone–H_2O; (d) Me_3SiCH_2OMe, *s*-BuLi, THF; (e) 90% HCO_2H.

imeric mixture of diastereoisomers in 87% yield.[5] Regioselective hydroboration of **2a** with borane in tetrahydrofuran followed by alkaline hydrogen peroxide oxidation in dioxane[7] gave a mixture of isomeric alcohols which underwent Jones oxidation and subsequent epimerization at C-8 with sodium methoxide in methanol to afford ketone **3a** in 81% overall yield from **2a**. Cleavage of the hydroxy protecting group in **3a** employing a mixture of chlorotrimethylsilane/sodium iodide in acetonitrile[8] afforded hydroxy ketone **3b** in 86% isolated yield. Compound **3b** was readily converted to the known[9] diketone **4** in high yield upon oxidation with Jones reagent.[10] Chemoselective ketalization of the C-15 carbonyl group could be accomplished by treatment of **4** with 1,2-ethanediol and *p*-toluenesulfonic acid (PTSA) in refluxing benzene to give **5** in 98.5% yield.

The planned subsequent conversion of ketone **5** to keto aldehyde **10** (Scheme II) required reductive nucleophilic acylation and unmasking of C-14 and C-15 carbonyl groups, respectively. Not unexpectedly, the same steric factors that enabled the chemoselective ketalization of the C-15 carbonyl group of **4** now worked against us preventing the reaction of the C-14 carbonyl group of **5** with most of the classical nucleophilic reagents used in the one carbon homologation of ketones.[11a] Thus, the hindered ketone

Scheme III[a]



[a] (a) KOH, MeOH; (b) PTSA, benzene.

function in keto ketal **5** did not react with $Ph_3P{=}CH_2$, $Ph_3P{=}CHOCH_3$, $Ph_2PO{=}CHOCH_3$, $ClCHKCO_2Me$,[12] KCN, or tosylmethylisocyanide. However, more promising results were obtained by the use of trimethylsilyl carbanions,[11b,c] which appear to be considerably more nucleophilic than their phosphorane counterparts. Thus, treatment of keto ketal **5** with chloromethyl(trimethylsilyl)lithium in tetrahydrofuran at −78 °C afforded the α,β-epoxy trimethylsilane **6** in 92% yield.[13] However, it was very disappointing to find that even mild acid hydrolysis of the α,β-epoxy trimethylsilane **6** resulted only in complex reaction mixtures from which the desired aldehyde **10** could not be isolated.

In view of the above result, an alternative plan to transform **6** into the aldehyde **10** was devised, in which the formyl group at C-14 would be introduced via transposition of the epoxide moiety present in **7**/**8**. In the event, **6** was converted to the epoxide **7** by treatment with trihydrated tetra-*n*-butylammonium fluoride (TBAF) in tetrahydrofuran in 82% yield. The epoxide **7** was also obtained by reaction of **5** with 1.1 equiv of dimethyl sulfonium methylide in 50% yield (94% based on recovered **5**) following standard conditions.[14] Although we were not immediately able to define the stereochemistry of **7** unmabiguously, the indicated α-stereochemistry of the oxirane ring was ultimately established after its conversion to epoxy ketone **8** by treatment with pyridinium *p*-toluenesulfonate (PPTS) in aqueous acetone at room temperature. A crystalline sample of epoxy ketone **8** was eventually obtained of which

(4) The usual diterpene and steroid nomenclature and numbering is used for all tricyclic and tetracyclic compounds, respectively. Systematic *Chemical Abstracts* names are used for title compounds in the Experimental Section.

(5) Our initial approach to ketone **5** involved the known[6] solvomercuration–reduction of **1b** to alcohol **2b** and subsequent hydroboration–reduction of the C-8–C-14 double bond followed by oxidation of the resulting diol to diketone **4**. However, the low yield obtained in the hydroboration–oxidation step prompted us to investigate the alternative route discussed in the text.

(6) (a) Apsimon, J. W.; Krehm, H. *Can. J. Chem.* **1969**, *47*, 2865. (b) Herz, W.; Hall, A. L. *J. Org. Chem.* **1974**, *39*, 14.

(7) (a) Huffman, J. W.; Kamiya, T.; Wright, L. H.; Schmid, J. J.; Herz, W. *J. Org. Chem.* **1966**, *31*, 4128. (b) Burgstahler, A. W.; Marx, J. N. *J. Org. Chem.* **1969**, *34*, 1550.

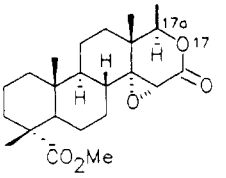
(8) Olah, G. A.; Narang, S. C.; Balaram Gupta, B. G.; Malhotra, R. *J. Org. Chem.* **1979**, *44*, 1247.

(9) Afonso, A. *J. Org. Chem.* **1970**, *35*, 1949.

(10) In the ^{1}H-NMR spectrum of **4** the C-8 proton displays a triplet of doublets (J = 11.6 and 4.2 Hz). These values indicate a β-orientation for the C-8 proton and hence a (8β,9α) trans ring junction of B/C rings.

(11) (a) For reviews, see: Martin, S. F. *Synthesis* **1979**, 633. (b) Magnus, P.; Burford, C.; Cooke, F.; Roy, G. *Tetrahedron* **1983**, *39*, 867. (c) Cooke, F.; Roy, G.; Magnus, P. *Organometallics* **1982**, *1*, 893.

(12) (a) We also investigated the intramolecular Darzens glycidic ester condensation[12b] as a means of effecting the one carbon elongation. The mixture of epimeric 15-alcohols **3b** was converted to the corresponding α-chloroesters **3c** (**3**, R = $COCH_2Cl$) ($ClCOCH_2Cl$, pyridine, dioxane, room temperature; 92%), which on treatment with *t*-BuOK in *t*-BuOMe afforded the epoxy lactone i, derived from the 15R isomer, as the only identifiable product (40% yield). Lactone i was very stable toward basic hydrolysis, and we were unsuccessful in finding conditions for its transformation into **10**. For experimental details of these reactions, see the supplementary material. (b) Newman, M. S.; Magerlein, B. J. *Org. React.* **1949**, *5*, 413.



i

(13) The α-orientation of the oxirane ring is tentatively assigned on the basis of its transformation into **8** (vide infra).

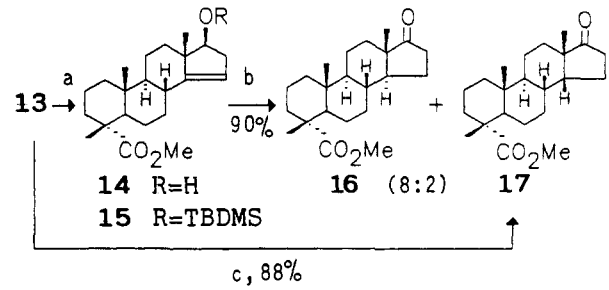
(14) Corey, E. J.; Chaykovsky, M. *J. Am. Chem. Soc.* **1965**, *87*, 1353.

X-ray diffraction analysis (see supplementary material) confirmed the α-stereochemistry of the oxirane ring in compounds **6**, **7**, and **8**. Both epoxy ketal **7** and epoxy ketone **8** were exposed to a variety of standard Lewis and protic acids (e.g., LiBr, BF_3, $HClO_4$, etc.) in an effort to achieve transposition of the 14α,14'-epoxide to the formyl moiety. However, either no reaction or extensive decomposition of the starting material was observed.[15]

On the other hand, addition of methoxymethyl(trimethylsilyl)lithium[11c] to keto ketal **5** also took place under analogous conditions to give a mixture of diastereoisomeric β-alcoxy silane adducts **9** in 47% yield. The percent conversion of this reaction was always low (less than 50%). The fact that, in absence of basic equilibration, unreacted **5** was recovered as a mixture of epimers at C-8 seems to indicate that α-deprotonation was a serious competitive reaction. Attempts to improve the reaction by using a large excess of methoxymethyl(trimethylsilyl)lithium or by prolonged reaction time resulted in lower yields of **9**. However, by repeated addition of reagent to the recovered starting material (three times), 69% conversion could be achieved. In contrast to the behavior of the α,β-epoxy trimethylsilane **6**, exposure of the mixture of β-hydroxy silanes **9** to 90% formic acid at room temperature smoothly afforded the desired homologous aldehyde. As expected, the latter step also effected deblocking of the ketal moiety to deliver keto aldehyde **10** directly. Evidence for the stereochemistry at C-14 in **10** was found for $J_{14,8}$ in the ^1H NMR spectrum. The C-14 proton appeared as a doublet of doublets at δ 2.61 ppm with coupling constants of 10.9 and 2.6 Hz. The first value indicates a diaxial arrangement of C-8 and C-14 protons, indicating the equatorial attachment of the C-14 formyl group.

With keto aldehyde **10** in hand, we next turned our attention to the closure of the five-membered ring. Heating **10** in refluxing methanol (Scheme III) in the presence of potassium hydroxide[16] resulted in formation of an approximately 1:2:1.8 mixture of cycloaldolization products **11**, **12a**, and **13**, respectively, in 90% combined yield after their chromatographic separation. The structures of **12a** and **13** are assigned unambiguously from their spectral data. Of special significance is the splitting pattern shown by the C14-H signal of **12a** (a ddd, with $J_{14,8}$ = 4.7, and $J_{14,15} = J_{14,16}$ = 2.3 Hz) from which an equatorial orientation of the C-14 hydrogen and hence a (13β,14β) cis ring junction of C/D rings is assigned. The stereochemistry of ketol **11** is assigned by comparison of its ^{13}C and ^1H NMR spectral data with those of **16** and **17** (vide infra). Apart from the expected shift at positions close to the 15-hydroxy function, the carbons of **11** exhibit chemical shifts similar to those of **16**; this is consistent with a trans CD ring junction and an α-orientation of the hydroxyl group, since inversion of the configuration at C-15 should cause an upfield shift on C-8 of at least 7 ppm, due to the γ-gauche interaction of the hydroxyl group with the axial hydrogen at C-8. As our goal at this stage was to optimize the yield of the β,γ-unsaturated ketone **13** (vide infra) it proved both more expeditious and efficient in practice to subject the crude mixture of **11**–**13** to acid treatment (PTSA in refluxing benzene) to provide, after column chromatography, the β,γ-unsaturated ketone **13** (42% yield) and an inseparable mixture of 14-epimeric α,β-unsaturated ketones **12a** and **12b** (43% yield). A 70% overall yield of **13** could be achieved after repeated treatment of the α,β-unsaturated ketones **12** with PTSA under the above-stated conditions.

Scheme IV[a]



[a] (a) (i) $NaBH_4$, MeOH; (ii) TBDMSCl, imidazole, DMF; (b) (i) H_2, EtOAc; (ii) Jones reagent, KF, acetone; (c) H_2, PtO_2, AcOH.

Since it was known[17] that catalytic hydrogenation of enone **13** would give **17**,[18] with a cis arrangement of CD rings, it was necessary to modify the functionalization at C-17 in order to obtain the desired stereoselectivity in the hydrogenation step. Thus, transformation of the enone **13** into target ketone **16** was carried out via a four-step sequence (Scheme IV) involving reduction of **13** with sodium borohydride, protection of the resulting alcohol **14** as the *tert*-butyldimethylsilyl ether,[19] and stereoselective hydrogenation of the C-14–C-15 double bond of **15**, followed by oxidation of the *tert*-butyldimethylsilyl ether moiety with the Jones reagent in presence of potassium fluoride.[20] The entire sequence, when carried out without purification of intermediates, gave a mixture of the known[9] ketone **16** and its C-14 epimer **17** in 90% overall yield from **13**. This mixture was separated by preparative HPLC to give **16** and **17** in the approximate ratio 8:2. These two isomers can be differentiated by their ^{13}C and ^1H NMR spectra. Of particular significance is the different shift of C-9 in both compounds; this carbon resonates 7.43 ppm upfield in the C/D cis isomer **17** compared with the C/D trans isomer **16** (49.05 and 56.48 ppm, respectively) due to the γ-effect exerted by the axially oriented C-15. The ^{13}C and ^1H chemical shifts of the angular methyl groups at C-13 are also consistent with the assigned stereochemistries.[21]

Experimental Section

^1H and ^{13}C NMR spectra were measured, respectively, at 200.13 and 50.32 MHz in $CDCl_3$ solution. Analytical TLC was carried out on Merck precoated 0.2-mm thick plates of silica gel 60 HF_{254}. Column chromatography refers to flash chromatography and was performed on Merck silica gel 60, 230–240 mesh. Melting points are uncorrected. All reactions involving moisture- or air-sensitive reactants were excuted under an atmosphere of dry argon using oven-dried glassware and freshly distilled and dried solvents. Unless stated otherwise, reaction mixtures were worked up by addition of water and extraction with ether, the ethereal extract being washed with water and brine and dried using anhydrous sodium sulfate. Evaporation was performed under reduced pressure.

Sandaracopimaric acid **1a** was isolated from gum sandarac resin

(15) (a) Reaction of **8** with $MgBr_2$ (from Mg and 1,2-dibromoethane, ether, room temperature, 24 h)[15b] afforded bromohydrin methyl 14β-(bromomethyl)-14α-hydroxy-15-oxoisopimaran-18-oate (ii) in almost quantitative yield (see supplementary material). (b) Rosenberger, M.; Jackson, W.; Saucy, G. *Helv. Chim. Acta* **1980**, *63*, 1665.

(16) Attempts to induce aldol condensation by acid (PTSA, benzene, reflux) gave no detectable cyclization products.

(17) For similar reductions, see: Sondheimer, F.; Burstein, S.; Mechoulam, R. *J. Am. Chem. Soc.* **1960**, *82*, 3209 and references cited therein.

(18) In fact, when **13** was hydrogenated in presence of platinum as catalyst, the undesired ketone **17** was formed exclusively (see the Experimental Section).

(19) Corey, E. J.; Venkateswarlu, A. *J. Am. Chem. Soc.* **1972**, *94*, 6190.

(20) Liu, H. J.; Han, I. S. *Synth. Commun.* **1985**, *15*, 759.

(21) Hanson, R. J.; Siverns, M. *J. Chem. Soc., Perkin Trans. 1* **1975**, 1956 and references cited therein.

following the procedure of Edwards et al.[3] Its methyl ester (**1b**) was prepared by reaction of its lithium salt with dimethyl sulfate in DMF.[22]

[1R-(1α,4aβ,4bα,7α,10aα)]-1,2,3,4,4a,4b,5,6,7,9,10,10a-Dodecahydro-7-(1-methoxyethyl)-1,4a,7-trimethyl-1-phenanthrenecarboxylic Acid Methyl Ester (2a). To a solution of methyl sandaracopimarate (**1b**) (1.42 g, 4.5 mmol) in anhydrous methanol (20 mL) was added mercuric acetate (1.71 g, 5.4 mmol). After the mixture was stirred for 1 h at room temperature, dioxane (20 mL) and NaOH (35 mL of a 10% aqueous solution) were added, followed by a solution of $NaBH_4$ (200 mg, 5.3 mmol) in 10% aqueous NaOH solution (15 mL). The mixture was stirred for 30 min at room temperature. After being cooled in an ice bath, the reaction mixture was quenched by dropwise addition of 1 N HCl until no more effervesence could be detected. Usual workup gave a colorless oil, which was purified by chromatography (hexane–ethyl acetate, 9:1, as eluent) to give an 1:1 mixture of the C-15 epimers of **2a** (1.35 g, 87%) as an oil: IR (film) 1722 cm^{-1}; ^1H NMR δ 0.77 (s, 3 H, CH_3-10), 0.89 (s, 3 H, CH_3-13), 0.97 and 1.01 (each d, J = 6.3 Hz, 1.5 H each, CH_3-15), 1.16 (s, 3 H, CH_3-4), 2.84 (2 overlapped q, 1 H, J = 6.3 Hz, H-15), 3.26 and 3.27 (each s, 1.5 H each, OCH_3), 3.61 (s, 3 H, CO_2CH_3), 5.21 and 5.31 (each s, 0.5 H each, H-14). Anal. Calcd for $C_{22}H_{36}O_3$: C, 75.82; H, 10.41. Found: C, 75.97; H, 10.18.

[1*R*-(1α,4aβ,4bα,7α,8aβ,10aα)]-Tetradecahydro-7-(1-methoxyethyl)-1,4a,7-trimethyl-8-oxo-1-phenanthrenecarboxylic Acid Methyl Ester (3a). To a mixture of **2a** (1.55 g, 4.45 mmol) and $NaBH_4$ (250 mg, 6.6 mmol) in dry THF (15 mL) was added boron trifluoride etherate (1.2 mL) dropwise at 0 °C. After stirring for 6 h at room temperature the reaction was quenched with water and stirred until hydrogen evolution ceased. The THF was distilled off under reduced pressure, and the residue was dissolved in dioxane (15 mL). The mixture was cooled to 0 °C, and 5 mL of 2 M aqueous KOH solution was added slowly with vigorous stirring. Hydrogen peroxide (2 mL of 30% aqueous solution) was introduced dropwise to the stirred reaction mixture, which was allowed to reach room temperature and then stirred for 6 h. Usual workup gave a mixture of diastereomeric alcohols (1.64 g), which was dissolved in acetone (20 mL) and dropwise treated at 0 °C with 2.5 mL of 2 N Jones reagent.[23] The green precipitate was filtered off, and most of the acetone was distilled under reduced pressure. Water was added, and the mixture was worked up to give an oil (1.32 g), a mixture of epimeric ketones at C-8. A solution of this oil and sodium methoxide (300 mg) in anhydrous methanol (30 mL) was stirred at room temperature for 6 h. After aqueous workup, an oil was obtained that could be used without further purification for the next step or chromatographed (hexane–ethyl acetate, 8:2, as eluent) to give an 1:1 mixture of the C-15 epimers of **3a** (1.31 g, 81% for the four-step process): an amorphous solid of broad melting point; IR (KBr) 1725, 1705 cm^{-1}; ^1H NMR δ 0.92 and 0.94 (each s, 1.5 H each, CH_3-13), 0.96 (s, 3 H, CH_3-10), 1.00 and 1.01 (each d, J = 6.1 Hz, 1.5 H each, CH_3-15), 1.14 (s, 3 H, CH_3-4), 3.26 and 3.32 (each s, 1.5 H each, OCH_3), 3.50 and 3.64 (each q, J = 6.1 Hz, 0.5 H each, H-15), 3.61 (s, 3 H, CO_2CH_3). Anal. Calcd for $C_{22}H_{36}O_4$: C, 72.49; H, 9.95. Found: C, 72.37; H, 10.12.

[1*R*-(1α,4aβ,4bα,7α,8aβ,10aα)]-Tetradecahydro-7-(1-hydroxyethyl)-1,4a,7-trimethyl-8-oxo-1-phenanthrenecarboxylic Acid Methyl Ester (3b). To a stirred solution of **3a** (1.60 g, 4.39 mmol) and sodium iodide (0.66 g, 4.40 mmol) in dry acetonitrile (5 mL) was added chlorotrimethylsilane (0.55 mL, 4.39 mmol) at room temperature. The reaction mixture was stirred at the same temperature for 7 h and then quenched with water and extracted with ether. The ether layer was washed with sodium thiosulfate and brine and dried. Evaporation of the solvent afforded an oil, which after chromatography (hexane–ethyl acetate, 8:2, as eluent) gave a mixture of the C-15 epimers of **3b** (1.24 g, 81%) as an amorphous solid: IR (KBr 3520, 1715, 1690 cm^{-1}; ^1H NMR δ 0.97 (s, 3 H, CH_3-10), 1.02 and 1.06 (each d, J = 6.6 Hz, 1.5 each, CH_3-15), 1.08 and 1.15 (each s, 1.5 each, CH_3-13), 1.16 (s, 3 H, CH_3-4), 2.47 (m, 1 H, H-8), 3.63 (s, 3 H, CO_2CH_3), 3.87 and 4.0 (each q, J = 6.6 Hz, 0.5 Hz each, H-15). Anal. Calcd for $C_{21}H_{34}O_4$: C, 71.96; H, 9.77. Found: C, 72.12; H, 9.89.

[1*R*-(1α,4aβ,4bα,7α,8aβ,10aα)]-Tetradecahydro-7-acetyl-1,4a,7-trimethyl-8-oxo-1-phenanthrenecarboxylic Acid Methyl Ester (4). This compound was prepared by oxidation of **3b** (0.93 g, 2.65 mmol) with Jones reagent, as described for the synthesis of **3a**. Chromatography of the crude product (hexane–ethyl acetate, 8:2, as eluent) yielded **4** (0.865 g, 93.5%) as a white solid: mp 123–124 °C (from MeOH) (lit.[9] mp 122–123 °C); $[\alpha]_D$ −51° (*c* 0.6, $CHCl_3$); IR (KBr) 1720, 1690, 1685 cm^{-1}; ^1H NMR δ 0.97 (s, 3 H, CH_3-10), 1.16 (s, 3 H, CH_3-4), 1.34 (s, 3 H, CH_3-13), 1.93 (m, 1 H, H-7β), 2.1 (dd, J = 17.5 and 4.8 Hz, 1 H, H-12β), 2.13 (s, 3 H, CH_3-15), 2.43 (td, J = 11.6 and 4.2 Hz, 1 H, H-8), 3.63 (s, 3 H, CO_2CH_3); MS m/e (relative intensity) 348 (M^+, 6), 307 (13), 306 (72), 291 (1.5), 247 (1.5), 43 (100). Anal. Calcd: C, 72.38; H, 9.26. Found: C, 72.53; H, 9.46.

[1*R*-(1α,4aβ,4bα,7α,8aβ,10aα)]-Tetradecahydro-7-(1,1-(ethylenedioxy)ethyl)-1,4a,7-trimethyl-8-oxo-1-phenanthrenecarboxylic Acid Methyl Ester (5). To a solution of diketone **4** (865 mg, 2.5 mmol) in dry benzene (60 mL) were added ethylene glycol (4 mL) and PTSA (30 mg). The mixture was refluxed overnight under a Dean–Stark trap. The benzene layer was washed with 5% aqueous $NaHCO_3$ solution and brine, dried, and concentrated to give a yellowish solid that was purified by chromatography (hexane–ethyl acetate, 6:4, as eluent) to afford **5** (960 mg, 98.5%) as a white crystalline solid: mp 100–101.5 °C (from hexane); IR (KBr) 1720, 1710 cm^{-1}; ^1H NMR δ 0.96 (s, 3 H, CH_3-10), 1.15 (s, 3 H, CH_3-4), 1.22 (s, 3 H, CH_3-13), 1.40 (s, 3 H, CH_3-15), 2.38 (td, J = 11.6 and 4 Hz, 1 H, H-8), 3.62 (s, 3 H, CO_2CH_3), 3.9 (m, 4 H, 2 OCH_2); MS m/e (relative intensity) 307 (0.5), 306 (3), 87 (100). Anal. Calcd: C, 70.38; H, 9.24. Found: C, 70.53; H, 9.22.

[1*R*,8*R*-(1α,4aβ,4bα,7α,8α,8aβ,10aα)]-Tetradecahydro-8,8-(epoxymethano)-7-(1,1-(ethylenedioxy)ethyl)-1,4a,7-trimethyl-1-phenanthrenecarboxylic Acid Methyl Ester (7). (a) Reaction of 5 with Chloromethyl(trimethylsilyl)lithium. *s*-BuLi (1.2 M in cyclohexane, 0.750 mL, 0.90 mmol) was added dropwise to a stirred solution of (chloromethyl)trimethylsilane (0.125 mL, 0.90 mmol) in anhydrous THF (1 mL) at −78 °C. After 10 min TMEDA (0.134 mL, 0.90 mmol) was added, and the solution was stirred for 30 min at the same temperature. A solution of **5** (120 mg, 0.30 mmol) in THF (1 mL) was added slowly to the above solution at −78 °C, and the mixture was stirred at this temperature for 5 h and then at room temperature for a further hour. The mixture was quenched by the addition of saturated aqueous NH_4Cl (0.5 mL) and subjected to aqueous workup to give an oil. Chromatography (hexane–ethyl acetate, 9:1, as eluent) gave the α,β-epoxy trimethylsilane **6** (123 mg, 92%).

(b) Reaction of 6 with TBAF. A solution of the above α,β-epoxy silane **6** (50 mg, 0.11 mmol) and tetra-*n*-butylammonium fluoride (TBAF) trihydrate (136 mg, 0.43 mmol), in THF (1 mL), was stirred at room temperature for 48 h. Usual workup afforded an oil, which after chromatography (hexane–ethyl acetate, 9:1, as eluent) gave epoxy ketal **7** (36 mg, 82%) as a solid: mp 133–135 °C (from hexane); IR (KBr) 1725 cm^{-1}; ^1H NMR δ 0.91 (s, 3 H, CH_3-10), 1.04 (s, 3 H, CH_3-13), 1.16 (s, 3 H, CH_3-4), 1.30 (s, 3 H, CH_3-15), 2.05 (td, J = 11.5 and 4.4 Hz, 1 H, H-8), 2.67 and 3.17 (each d, J = 4.5 Hz, 1 H each, OCH_2-14), 3.61 (s, 3 H, CO_2CH_3), 3.7–4 (m, 4 H, 2 OCH_2); MS m/e (relative intensity) 391 (0.5), 302 (2), 87 (100). Anal. Calcd for $C_{24}H_{38}O_5$: C, 70.90; H, 9.42. Found: C, 70.79; H, 9.36.

[1*R*,8*R*-(1α,4aβ,4bα,7α,8α,8aβ,10aα)]-Tetradecahydro-7-acetyl-8,8-(epoxymethano)-1,4a,7-trimethyl-1-phenanthrenecarboxylic Acid Methyl Ester (8). A mixture of **7** (150 mg, 0.37 mmol), PPTS (50 mg, 0.2 mmol), and water (3 drops) in acetone (7.5 mL) was stirred for 24 h at room temperature and then worked up. Purification by chromatography (hexane–ethyl acetate), 8:2, as eluent) afforded **8** (124 mg, 93%) as a solid: mp 117–119 °C (from hexane); $[\alpha]_D$ −60° (*c* 2.9, $CHCl_3$); IR (KBr) 3050, 1735, 1705 cm^{-1}; ^1H NMR δ 0.91 (s, 3 H, CH_3-10), 1.17 (s, 6 H, 2 CH_3), 2.18 (s, 3 H, CH_3-15), 2.28 and 2.67 (each d, J = 3.7 Hz, 1 H each, OCH_2-14), 3.62 (s, 3 H, CO_2CH_3); MS m/e (relative intensity) 363 (M^+ + 1, 1), 362 (M^+, 0.5), 347 (1), 319 (10), 121 (100); HRMS calcd for $C_{22}H_{34}O_4$ 362.2457, found 362.2468. Anal. Calcd: C, 72.89; H, 9.45. Found: C, 72.82; H, 9.38.

(22) Abad, A.; Arnó, M.; Domingo, L. R.; Zaragozá, R. J. *Tetrahedron* **1985**, *41*, 4937.

(23) Bowden, K.; Heilbron, I. M.; Jones, E. R. H.; Weedon, B. C. L. *J. Chem. Soc.* **1946**, 39.

[1*R*-(1α,4aβ,4bα,7α,8β,8aβ,10aα)]-Tetradecahydro-7-acetyl-8-formyl-1,4a,7-trimethyl-1-phenanthrenecarboxylic Acid Methyl Ester (10). A solution of (methoxymethyl)trimethylsilane (0.248 mL, 1.64 mmol) in anhydrous THF (4 mL) was cooled at −78 °C and stirred while *sec*-butyllithium (1 mL, 1.5 mmol, 1.5 M in cyclohexane) was added dropwise. The mixture was allowed to warm to −30 °C and held at this temperature for 30 min. The solution was cooled again to −78 °C, and a solution of **5** (420 mg, 1.06 mmol) in THF (1 mL) was added. After 30 min at −78 °C the mixture was treated with methanol (2 mL) and then allowed to warm to room temperature. After 30 min it was quenched by addition of saturated NH_4Cl solution (1 mL) and worked up to give an oil. Chromatography (hexane–ethyl acetate, 8:2, as eluent) gave **9** (245 mg, 47%) and unreacted **5** (140 mg, 33%).

The above adduct was dissolved in 90% formic acid (20 mL) at 0 °C, and the solution was stirred at this temperature for 1.5 h and then at room temperature for an additional 1.5 h. Workup using benzene to extract gave a colorless oil, purified by chromatography (hexane–ethyl acetate, 8:2, as eluent) to give **10** (123 mg, 70%) as a solid: mp 143–145 °C (from MeOH); $[\alpha]_D$ +5.3° (*c* 0.2, $CHCl_3$); IR (KBr) 1730, 1720, 1710, cm^{-1}; ^1H NMR δ 0.92 (s, 3 H, CH_3-10), 1.18 (s, 3 H, CH_3-4), 1.19 (s, 3 H, CH_3-13), 2.14 (s, 3 H, CH_3-15), 2.61 (dd, *J* = 10.9 and 2.6 Hz, 1 H, H-14), 3.63 (s, 3 H, CO_2CH_3), 9.75 (d, *J* = 2.6 Hz, CHO); MS *m/e* (relative intensity) 362 (M^+, 1), 334 (12), 319 (36), 303 (4), 276 (32), 43 (100); HRMS calcd for $C_{22}H_{34}O_4$ 362.2457, found 362.2474. Anal. Calcd: C, 72.89; H, 9.45. Found: C, 73.11; H, 9.40.

Intramolecular Aldol Reaction of Keto Aldehyde 10. To a solution of **10** (234 mg, 0.64 mmol) in methanol (4 mL) was added 2% methanolic sodium hydroxide solution (4 mL). The stirred mixture was refluxed for 15 min, cooled, and worked up. Purification by chromatography (gradient elution: 20–40% ether hexane) afforded, in order of elution: (1) **(4α,5α)-4-methyl-17-oxoandrost-14-ene-4-carboxylic acid methyl ester (13)** (78 mg, 35%) as a solid: mp 114–115 °C (from hexane) (lit.[9] 102-103 °C);[24] $[\alpha]_D$ +120° (*c* 0.2, $CHCl_3$); IR (KBr) 1740, 1720 cm^{-1}; ^1H NMR δ 0.92 (s, 3 H, CH_3-10), 1.05 (s, 3 H, CH_3-13), 1.16 (s, 3 H, CH_3-4), 2.15 (m, 1 H, H-8), 2.76 (dt, *J* = 23 and 2.3 Hz, 1 H, H-16), 2.95 (ddd, *J* = 23, 3.7, and 1.7 Hz, 1 H, H′-16), 3.62 (s, 3 H, CO_2CH_3), 5.44 (q, *J* = 1.8 Hz, 1 H, H-15); MS *m/e* (relative intensity) 345 (M^+ + 1, 11.5), 344 (M^+, 46), 329 (2.5), 317 (23), 316 (100); HRMS calcd for $C_{22}H_{32}O_3$ 344.2351, found 344.2329. Anal. Calcd: C, 76.70; H, 9.36. Found: C, 76.61; H, 9.45. (2) **(4α,5α,14β)-4-methyl-17-oxoandrost-15-ene-4-carboxylic acid methyl ester (12a)** (83 mg, 37%) as a solid: mp 115–116 °C (from hexane); UV (MeOH) λ_{max} 229 nm (log ε 3.84); IR (KBr) 1730, 1725 cm^{-1}; ^1H NMR δ 0.83 (s, 3 H, CH_3-10), 1.04 (s, 3 H, CH_3-13), 1.14 (s, 3 H, CH_3-4), 2.51 (ddd, *J* = 4.7, 2.3, and 2.3 Hz, 1 H, H-14), 3.63 (s, 3 H, CO_2CH_3), 6.15 (dd, *J* = 5.9 and 2.3 Hz, 1 H, H-15), 7.72 (dd, *J* = 5.9 and 2.3 Hz, 1 H, H-16); MS *m/e* (relative intensity) 345 (M^+ + 1, 20), 344 (M^+, 83), 329 (25), 285 (74), 96 (100); HRMS calcd for $C_{22}H_{32}O_3$ 344.2351, found 344.2332. Anal. Calcd: C, 76.70; H, 9.36. Found: C, 76.81; H, 9.56. (3) **(4α,5α,15*S*)-15-hydroxy-4-methyl-17-oxoandrostane-4-carboxylic acid methyl ester (11)** (42 mg, 18%; and therefore 90% total yield) as a semisolid: IR (film) 3600–3200, 1720–1740 cm^{-1}; ^1H NMR δ 0.85 (s, 3 H, CH_3-10), 0.90 (s, 3 H, CH_3-13), 1.16 (s, 3 H, CH_3-4), 2.08 (dd overlapped with m, *J* = 19.3 and 6.5 Hz, 2 H, H-16 overlapped with H-14), 2.94 (dd, *J* = 19.3 and 8.1 Hz, H′-16), 3.61 (s, 3 H, CO_2CH_3), 4.32 (m, 1 H, H-15); MS *m/e* (relative intensity) 363 (M^+ + 1, 10), 362 (M^+, 45.5), 345 (13), 344 (53), 304 (13), 187 (100); HRMS calcd for $C_{22}H_{34}O_4$ 362.2457, found 362.2478.

(4α,5α,14β)-4-Methyl-17-oxoandrostane-4-carboxylic Acid Methyl Ester (17). A mixture of ketone **13** (34 mg, 0.1 mmol) and PtO_2 (5 mg) in AcOH (1 mL) was shaken at room temperature under H_2 atmosphere overnight. The mixture was filtered through Celite, and the solvent was evaporated. The residual oil was dissolved in acetone (3 mL) and was treated at 0 °C with a few drops of the Jones reagent.[23] The mixture was poured into water and was extracted with ether. The organic phase was washed with dilute $NaHCO_3$ solution and brine. After drying and concentration the residue was chromatographed (hexane–ethyl acetate, 8:2, as eluent) to give **17** (30 mg, 88%) as a solid: mp 136–138 °C (from hexane); $[\alpha]_D$ +72° (*c* 0.2, $CHCl_3$), IR (KBr) 1745, 1715 cm^{-1}; ^1H NMR δ 0.86 (s, 3 H, CH_3-10), 1.03 (s, 3 H, CH_3-13), 1.16 (s, 3 H, CH_3-4), 2.1 (m, 1 H, H-16), 2.45 (m, 1 H, H′-16), 3.63 (s, 3 H, CO_2CH_3); MS *m/e* (relative intensity) 347 (M^+ + 1, 13), 346 (M^+, 57), 331 (2), 314 (9), 387 (54), 189 (100); HRMS calcd for $C_{22}H_{34}O_3$ 346.2508, found 346.2516. Anal. Calcd: C, 76.26; H, 9.89. Found: C, 76.42; H, 9.71.

(4α,5α)-4-Methyl-17-oxoandrostane-4-carboxylic Acid Methyl Ester (16). To an ice-cooled solution of ketone **13** (55.5 mg, 0.16 mmol) in dry methanol (3 mL) was added $NaBH_4$ (8.1 mg, 0.21 mmol) in one portion. The mixture was stirred for 2 h at 0 °C. After it was acidified with 2 M hydrochloric acid, the mixture was worked up to give alcohol **14** (55 mg) as a solid.[25]

To a stirred solution of the above alcohol in DMF (1 mL) were added *tert*-butyldimethylsilyl chloride (84 mg, 0.55 mmol) and imidazole (108 mg, 1.6 mmol). After 2 h of stirring at 30 °C the mixture was diluted with ether, washed with cold dilute hydrochloric acid, water, diluted aqueous $NaHCO_3$, and then with brine, and dried. Evaporation of the solvent yielded an oil, which was chromatographed (hexane–ethyl acetate, 9:1, as eluent) to give pure **15**[25] (69.7 mg, 95%) as a solid, which was hydrogenated over PtO_2 (10 mg) in ethyl acetate (2.5 mL) at room temperature for 24 h. After removal of the catalyst by filtration through a pad of silica gel the filtrate was concentrated in vacuo. To a solution of the residual solid in acetone (2.5 mL) at 0 °C were added potassium fluoride (17.5 mg, 0.30 mmol) and 2 N Jones reagent[23] (0.30 mL). The reaction mixture was stirred at room temperature for 2 h. Workup gave a solid that was purified by chromatography (hexane–ethyl acetate, 9:1, as eluent) to give an epimeric mixture of **16** and **17** (50.1 mg, 90% from **13**). Both isomers were separated by preparative HPLC on a μ-Porasil column, with hexane–ethyl acetate (95:5) as eluent, to give pure 14α*H* isomer **16** (39 mg, 79%) as a solid [mp 154–155 °C (from hexane) (lit.[9] 140–142 °C); $[\alpha]_D$ +61° (*c* 2, $CHCl_3$) [lit.[9] +42.9° (dioxane)]; IR (KBr) 1745, 1715 cm^{-1}; ^1H NMR δ 0.82 (s, 3 H, CH_3-13), 0.89 (s, 3 H, CH_3-10), 1.16 (s, 3 H, CH_3-4), 2.0 (ddd, *J* = 18.7, 9, and 1–2 Hz, 1 H, H-16), 2.40 (ddd, *J* = 18.7, 8.7, and 1–2 Hz, H′-16), 3.62 (s, 3 H, CO_2CH_3); MS *m/e* (relative intensity) 347 (M^+ + 1, 15), 346 (M^+, 60), 332 (3), 331 (6), 329 (3), 328 (10), 314 (4), 302 (4), 288 (14), 287 (54), 286 (14), 189 (54), 41 (100); HRMS calcd for $C_{22}H_{34}O_3$ 346.2508, found 346.2514. Anal. Calcd: C, 76.26; H, 9.89. Found: C, 76.38; H, 9.70] and 14β*H* isomer **17** (10.2 mg, 21%), in all observed respects identical with that above.

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Registry No. **1a**, 471-74-9; **1b**, 1686-54-0; **2a** (isomer 1), 125330-40-7; **2a** (isomer 2), 125330-41-8; **3a** (isomer 1), 125330-42-9; **3a** (isomer 2), 125330-44-1; **3b** (isomer 1), 125330-43-0; **3b** (isomer 2), 125330-45-2; **3c**, 125330-46-3; **4**, 23527-21-1; **5**, 125330-47-4; **6**, 125330-48-5; **7**, 125330-49-6; **8**, 125330-51-0; **9** (isomer 1), 125330-51-0; **9** (isomer 2), 125357-09-7; **10**, 125330-52-1; **11**, 125330-53-2; **12a**, 125330-54-3; **12b**, 125591-03-9; **13**, 23527-18-6; **14**, 125330-55-4; **15**, 125330-56-5; **16**, 23527-16-4; **17**, 125410-75-5; i, 125330-57-6; ii, 125330-58-7; $HO(CH_2)_2OH$, 107-21-1; Me_3SiCH_2Cl, 2344-80-1; Me_3SiCH_2OMe, 14704-14-4; chloroacetyl chloride, 79-04-9.

Supplementary Material Available: Procedures for the syntheses of **3c** and epoxy lactone i (see ref 12); physical and spectral properties of **3c**, **14**, **15**, lactone i, and ketobromohydrin ii (see ref 15); tables of ^{13}C NMR data for the compounds described herein (Tables I, II, and III); a crystallographic section, tables of atomic coordinates and temperature factors (Table IV), anisotropic temperature factors (Table V), bond angles (Table VI), bond lengths (Table VII), and torsion angles (Table VIII); and a perspective drawing (Figure 1) for epoxide **8** (9 pages). Ordering information is given on any current masthead page.

(24) The ^1H NMR chemical shifts of this compound were identical with that reported previously.[9]

(25) See the supplementary material for physical and spectral properties.