was 103 g (97%) of crude crystalline material from which 1 g was recrystallized from methanol–ether to give 0.9 g of pure product, $[\alpha]^{23}D$ −23.1° (c 5, methanol), mp 115 °C. Anal. Calcd for $C_5H_{12}NO_3Cl$: C, 35.41; H, 7.13; N, 8.26; Cl, 20.91. Found: C, 35.33; H, 7.39; N, 8.45; Cl, 20.70.

***allo*-Boc-D-threonine Methyl Ester (6).** Crude **5** (103 g, 0.61 mol) was dissolved in 1 l. of dry (Linde 4A) dimethyl sulfoxide and 170 ml (1.22 mol) of triethylamine was added with vigorous stirring. After the addition of 90 ml (0.67 mol) of *tert*-butyloxycarbonyl azide the mixture was stirred for 48 h at room temperature. The volume was reduced to 200 ml under vacuum before 1 l. of ice water was added. Following acidification to pH 2.5 with citric acid the solution was extracted with five 200-ml portions of ethyl acetate. The combined extracts were washed with $NaHCO_3$ solution. Evaporation of the solvent after drying over Na_2SO_4 gave 124 g (87%) of a pale yellow oil, $[\alpha]^{23}D$ +14.4° (c 5.0, ethanol). Anal. Calcd for $C_{10}H_{19}NO_5$: C, 51.49; H, 8.21; N, 6.00. Found: C, 50.80; H, 8.53; N, 5.80.

***allo*-Boc-*O*-tosyl-D-threonine Methyl Ester (7). 6** (124 g, 0.53 mol) was dissolved in 400 ml of pyridine (distilled and stored over 4A sieves) and cooled to 0 °C. Tosyl chloride (133 g, 0.70 mol, recrystallized from petroleum ether) was added in portions over 10 min to maintain a temperature of 0–5 °C. The solution stood at 5 °C for 30 h and was then poured onto 1 l. of crushed ice and stirred for 0.5 h. The oily precipitate was extracted into 1.5 l. of ether and washed with ice-cold 0.01 N HCl (5–6 l.) to an acid reaction and finally with water to neutrality. Evaporation of the ether after drying over Na_2SO_4 yielded 189 g (91%) of crude **7**. Although the racemic compound crystallized readily, **7** resisted and was purified by extraction into cyclohexane–petroleum ether (1:1) at 37 °C and precipitation in the cold. Final yield of purified product 147 g (71%); homogeneous by TLC and showing the same R_f as the crystalline racemate; $[\alpha]^{19}D$ +4.2° (c 8, ethanol). Anal. Calcd for $C_{17}H_{25}NO_7S$: C, 52.70; H, 6.50; N, 3.62; S, 8.28. Found: C, 53.48; H, 6.58; N, 3.53; S, 9.33.[8]

***threo*-Boc-*S*-acetyl-β-methyl-D-cysteine Methyl Ester (8).** **7** (90.8 g, 0.227 mol) was dissolved in 300 ml of DMF (purified by passage over a column of acidic Al_2O_3 Brockman activity I and stored over 4A sieves). The solution was divided equally among five 100-ml Kjeldahl flasks.

Potassium thiolacetate was prepared by the addition of a 10% excess of thiolacetic acid to a methanolic solution of KOH. The solvent was removed on a rotary evaporator and excess thiolacetic acid under high vacuum. A water solution of the salt had a pH of 5.5.

After cooling to 0 °C, the Kjeldahl flasks were cleared of oxygen by alternate application of vacuum and nitrogen; 7.8 g (0.07 mol) of potassium thiolacetate was added, and each flask was again flushed, and prior to sealing under vacuum equipped with a magnetic stirring bar. The reaction was allowed to proceed with stirring at room temperature for 36 h although a copious precipitate of potassium tosylate appeared within 0.5 h. The contents of the reaction vessels were combined and the DMF removed in vacuo. The residue was extracted with 250 ml of ethyl acetate and washed with three 150-ml portions of water. Upon evaporation of the ethyl acetate 53 g (75%) of an orange oil was obtained, $[\alpha]^{23}D$ −55.6° (c 5, ethanol). Examination of an analytical amount by amino acid analysis after hydrolysis and oxidation with performic acid revealed the presence of 90% of the expected amount of β-methylcysteic acid and 10% of threonine. The product was considered pure enough for the subsequent steps in the synthesis. For the purpose of characterization 3 g was subjected to 1250 transfers in a countercurrent distribution machine [solvent system chloroform–benzene–methanol–water (1:1:1.5:0.5)] to yield 2.2 g of a pale yellow oil, K = 0.105, 99% pure by amino acid analysis, $[\alpha]^{23}D$ −66.1° (c 5, ethanol). Anal. Calcd for $C_{12}H_{21}NO_5S$: C, 49.47; H, 7.26; N, 4.80; S, 11.01. Found: C, 49.38; H, 7.57; N, 4.74; S, 12.63.[8] **7** (100 mg), K = 0.092, was also isolated. A fraction comprising the intersection of the incompletely resolved thiol ester and tosylate accounted for another 500 mg. Amino acid analysis showed this fraction to be 70% thiol ester.

***threo*-2-Amino-3-mercapto-D-butyric Acid (9).** Crude **8** (50 g, 0.172 mol) was exposed for 0.5 h to 100 ml of trifluoroacetic acid at room temperature. The acid was evaporated in vacuo and the product dissolved in 150 ml of 12 N HCl and heated to 65 °C for 5 h. Evaporation of the solution gave a yellow oil which solidified on lyophilization. The material was dissolved in 900 ml of ethanol and treated with 1 equiv of NH_4OH. Upon cooling 12.4 g of a white, crystalline product was obtained. A further 2 g remained in the mother liquor, overall yield 65%. The product (300 mg) was allowed to react with benzyl bromide in liquid ammonia to give in 80% yield (2*S*,3*R*)-2-amino-3-benzylthiolbutyric acid on precipitation from neutral aqueous solution and crystallization from ethanol. The compound was pure by amino acid analysis, $[\alpha]^{22}D$ −76.2° (c 1, 1 N HCl) [lit.[3] $[\alpha]^{25}D$ −72.0° (c 1, 1 N HCl)]. The disulfide desired for the preparation of derivatives was obtained by air oxidation of 7.0 g of **9** over a period of 4 days in 200 ml of aqueous ammonia at pH 8.6. After recrystallization from water–ethanol 5.6 g (80%) of a white hemihydrate was obtained. The product was homogeneous by amino acid analysis, $[\alpha]^{19}D$ −414° (c 1, 1 N HCl). Anal. Calcd for $C_8H_{17}N_2O_{5.5}S_2$: C, 34.77; H, 6.20; N, 10.14; S, 23.20. Found: C, 34.69; H, 6.10; N, 10.06; S, 22.64.[8]

Registry No.—**1**, 60538-15-0; **2**, 60538-16-1; **3**, 60538-17-2; **4**, 24830-94-2; **5**, 60538-18-3; **6**, 60538-19-4; **7**, 60538-20-7; **8**, 60538-21-8; **9**, 43083-49-4, D-threonine, 632-20-2; benzoyl chloride, 98-88-4; thionyl chloride, 7719-09-7; *tert*-butyloxycarbonyl azide, 1070-19-5; tosyl chloride, 98-59-9; potassium thiolacetate, 10387-40-3; β-methylcysteic acid, 60538-22-9; (2*S*,3*S*)-2-amino-3-benzylthiolbutyric acid, 60538-23-0.

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Prostaglandins and Congeners.[1] 11. Synthesis of *dl*-13-Hydroxyprostanoic Acids

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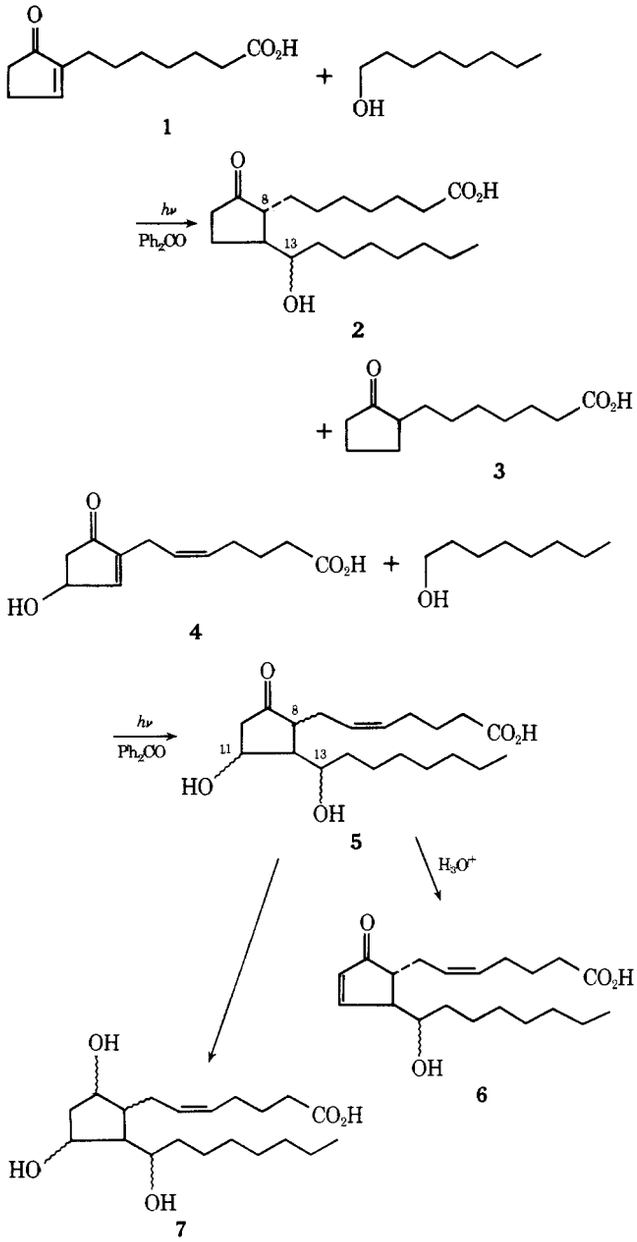
In an effort to prepare biologically more selective prostaglandin congeners, a program was initiated in our laboratory involving the synthesis of congeners in which the 15-hydroxy function was shifted to other positions in the β chain. In a previous report we have described the synthesis and biological properties of prostaglandin analogues wherein the 15-hydroxy group is moved to the C_{16}, C_{17}, and C_{20} position or is replaced by a hydroxymethyl group.[2] Another group has reported compounds wherein the hydroxy group is placed at C_{14}.[3] We now describe a convenient synthesis of prostaglandin congeners wherein the hydroxy function has been shifted to the C_{13} position. After this work was completed, two reports appeared concerning the synthesis of 13-hydroxyprostanoic acids which do not contain the 11-hydroxy substituent.[4] Our synthesis, which is different, is also applicable to the synthesis of 13-hydroxyprostaglandins which contain this biologically important 11-hydroxy group.

dl-9-Oxo-13-hydroxyprostanoic acid (**2**) is conveniently obtained by the benzophenone sensitized photoaddition of 1-octanol to the cyclopentenone **1**[5] using a 350-nm light source and a Pyrex reaction vessel.[6] Since 1-octanol also serves as the solvent, the product is isolated by sodium hydroxide extraction, which also serves to epimerize any 8-iso isomers to the corresponding 8-normal isomers, followed by silica gel chromatography. 13-Hydroxyprostaglandin **2** is obtained as two C_{13} epimers, separable by thin layer chromatography. The major side product of this reaction has been identified as the conjugate reduction product **3**.

In a similar manner photoaddition of 1-octanol to 4-hydroxycyclopentenone **4**[7] gives, after extraction with sodium bicarbonate solution and silica gel chromatography, *dl*-9-

oxo-11,13-dihydroxyprosta-(5Z)-enoic acid (5) as a mixture of isomers. Silica gel chromatography has allowed a partial



separation of isomers. That both 8-iso and 8-normal isomers were isolated is evidenced by epimerization experiments. However, the configuration at C_{11} is uncertain; it is likely that both the 11α and 11β isomers are formed.

On treatment with dilute hydrochloric acid in THF, **5** is converted to *dl*-9-oxo-13-hydroxyprosta-(5Z),10-dienoic acid (**6**). The course of this reaction was monitored by TLC; it was apparent that epimerization of the 8-iso isomers to the corresponding 8-normal isomers was competitive with PGA formation under these conditions; consequently the trans configuration for **6** can be assigned.

Reduction of **5** with lithium perhydro-9b-boraphenalylhydride gives *dl*-9,11,13-trihydroxyprosta-(5Z)-enoic acid (**7**).

Experimental Section

***dl*-9-Oxo-13-hydroxyprostanoic Acid (2).** A mixture of 18.4 g (0.0875 mol) of 2-(6-carboxyhexyl)cyclopent-2-en-1-one (**1**)[5] and 3.75 g of benzophenone was dissolved in 260 ml of 1-octanol. The solution was placed in a Pyrex tube and was flushed with nitrogen. The solution was then irradiated in a Rayonet reactor (Model MGR-100) using a 3500-Å light source for 4 days. The solution was then mixed with 150 ml of hexane and a solution of 8.0 g of NaOH in 300 ml of water. The mixture was stirred for 20 min. The aqueous layer was separated and the organic layer was washed with 100 ml of water. The combined aqueous solutions were then washed three times with ether. The aqueous solution was then acidified with HCl. The mixture was extracted with ether. The ether solution was washed with a saturated solution of NaCl and then dried over $MgSO_4$. The solvent was removed and the residue (26.5 g) was chromatographed on a dry column of silica gel eluting with benzene–ethyl acetate (2:1) containing 0.5% acetic acid to give a fraction containing 11.2 g (0.033 mol) of **2** as a mixture of two isomers: NMR δ_{Me_4Si} ($CDCl_3$) 6.73 (bs, 2 H, OH), 3.70 (m, 1 H, CHOH), 2.31 (t, 2 H, CH_2CO_2H), 2.45–1.10 (m's, 28 H, alkyl), 0.90 (m, 3 H, terminal CH_3); IR (neat) 3455 (OH), 1730 cm^{-1} (C=O); MS *m/e*, 340 (M^+), 322 ($M - H_2O$).

Anal. Calcd for $C_{20}H_{36}O_4$: C, 70.55; H, 10.66. Found: C, 70.42; H, 10.60.

The two isomers can be separated by thin layer chromatography on silica gel using a solvent mixture consisting of ethyl acetate–benzene (2:3), 1% acetic acid.

From a less polar fraction was obtained 1.7 g of the conjugate reduction product **3** identified by comparison with an authentic sample.[5]

***dl*-9-Oxo-11,13-dihydroxyprosta-(5Z)-enoic Acid (5).** A solution of 5.4 g (0.024 mol) of **4**[7] and 1.47 g of benzophenone in 100 ml of 1-octanol was placed in a Pyrex tube and irradiated (3500 Å) under nitrogen for 43 h. The solution was poured into a cold solution of 9.0 g of $NaHCO_3$ in 130 ml of water. To this was added 130 ml of hexane. The organic layer was separated and discarded. The aqueous layer was washed three times with ether and then acidified (HCl) at 0 °C. The mixture was extracted with ether. The ether solution was washed with water and saturated NaCl. The ether solution was dried ($MgSO_4$). The ether was removed to give 5.8 g of a yellow oil. This was chromatographed on a 5 ft × 3 in. dry column of silica gel eluting with ether containing 0.5% acetic acid. Fractions 18–31 contained 2.01 g of a lower R_f isomer mixture; fractions 35–37 contained 0.5 g of a higher R_f isomer(s). For the lower R_f isomer mixture: NMR δ_{Me_4Si} ($CDCl_3$) 6.00 (bs, 3 H, OH), 5.43 (m, 2 H, vinyl), 4.47 and 4.10–3.56 (m's, 2 H, CHOH), 3.00–1.10 (m's, 24 H, alkyl), 0.90 (m, 3 H, terminal CH_3); IR (neat) 3370 (OH), 1720 cm^{-1} (C=O); high-resolution MS, 336.2309 [calcd for $C_{20}H_{34}O_5$ ($M - H_2O$), 336.2300]. For the higher R_f isomer(s): NMR δ_{Me_4Si} ($CDCl_3$) 5.65 (bs, 3 H, OH), 5.45 (m, 2 H, vinyl), 4.64 (m, 1 H, CHOH), 3.87 (m, 1 H, CHOH), 2.92–1.00 (m's, 24 H, alkyl), 0.90 (m, 3 H, terminal CH_3); IR (neat) 3370 (OH), 1722cm^{-1} (C=O); high-resolution MS, 336.2306 [calcd for $C_{20}H_{34}O_5$ ($M - H_2O$), 336.2300].

That the higher R_f fraction is composed of one or more 8-iso isomers is evidenced by that fact that on treatment with dilute HCl in THF or brief treatment with K_2CO_3 in methanol–water, it is epimerized to a material with the same R_f as the more polar isomer mixture.

***dl*-9-Oxo-13-hydroxyprosta-(5Z),10-dienoic Acid (6).** A solution of 0.4 g (1.12 mmol) of **5** as a mixture of isomers in 15 ml of THF containing 8 ml of 1.5 N HCl was allowed to stand at room temperature under a nitrogen atmosphere for 2 days. The mixture was poured into water and extracted with ether. The ether solution was washed with a saturated solution of NaCl and dried over $MgSO_4$. The solvent was removed and the residue was chromatographed on three 200-mμ silica gel plates developing with ethyl acetate–benzene (1:1) containing 2% acetic acid. From the major band was isolated 0.325 g of **6** as a mixture of two C_{13} isomers: NMR δ_{Me_4Si} ($CDCl_3$) 7.72 and 7.60 (dd's, 1 H, vinyl β to C=O in each isomer, J = 2.2, 6.0 Hz), 7.67 (bs, 2 H, OH's), 6.24 (m, 1 H, vinyl α to carbonyl), 5.42 (m, 2 H, vinyl), 3.72 (m, 1 H, CHOH), 2.77 (m, 1 H, ring allylic proton), 2.55–1.90 (m's, 7 H, allylic, α to C=O), 1.90–1.10 (m, 16 H, alkyl), 0.90 (m, 3 H, terminal CH_3); IR (neat) 3330, 1707, 1585 cm^{-1}; UV (CH_3OH) 223 nm (ϵ 8100).

Anal. Calcd for $C_{20}H_{32}O_4$: C, 71.39; H, 9.59. Found: C, 71.00; H, 9.36.

***dl*-9,11,13-Trihydroxyprosta-(5Z)-enoic Acid (7).** To a solution of 0.5 g (1.41 mol) of **5** as a mixture of isomers in 20 ml of THF was added at −20 °C under nitrogen with stirring 7.3 ml of 0.5 M THF solution of lithium perhydro-9b-boraphenalylhydride (3.67 mmol). The solution was allowed to warm up to 5 °C over a 1-h period. To the solution was added a solution of 0.3 g of NaOH in 5 ml of water followed by 2 ml of 30% H_2O_2. After brief stirring, the mixture was poured into water. The water layer was washed with ether and then acidified with HCl. The mixture was extracted with ether. The ether solution was dried over $MgSO_4$. The ether was removed leaving 0.52 g of **7** as a mixture of isomers: NMR δ_{Me_4Si} ($CDCl_3$) 5.55 (m, 6 H, vinyl and OH's), 4.00–4.10 (m, 2 H, ring CHOH's), 3.94–3.50 (m, 1 H, chain CHOH), 2.55–1.10 (m's, 24 H, alkyl), 0.90 (m, 3 H, terminal CH_3); IR

(neat) 3340, 1710 cm^{-1}; MS *m/e* 338 (M − H_2O), 320 (M − $2H_2O$).

Anal. Calcd for $C_{20}H_{36}O_5$: C, 67.38; H, 10.18. Found: C, 67.64; H, 9.94.

Acknowledgment. I wish to thank Mr. L. Brancone and his staff for microanalyses, and Messrs. W. Fulmor and G. Morton and Dr. R. T. Hargreaves and staff for spectral data. I would also like to thank Dr. M. J. Weiss for many helpful discussions.

Registry No.—1, 5239-43-0; (13*R*)-**2**, 60676-39-3; (13*S*)-**2**, 60676-40-6; **4**, 54556-60-4; (8α)-**5**, 60733-21-3; (8β)-**5**, 60676-41-7; (13*R*)-**6**, 60676-42-8; (13*S*)-**6**, 60676-43-9; **7**, 60676-44-0; 1-octanol, 111-87-5.

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Influence of a 9α-Fluorine on the Epoxidation of an 11β-Hydroxy-Δ⁴-3-keto Steroid with Basic Hydrogen Peroxide

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Epoxidation of Δ⁴-3-keto steroids with hydrogen peroxide and base generally gives the β 4,5-epoxide as the major or exclusive product.[1] Various polar substituents including the 11β-hydroxyl group increase the proportion of α epoxide produced. We describe herein the effect of a 9α-fluorine on the epoxidation of an 11β-hydroxy steroid.

Reaction of enone **1a** with hydrogen peroxide and sodium hydroxide in methanol was complete in 4 h. From the resulting mixture of epoxides (ca. 2:1 ratio based on the intensity of the C-19 methyl signals in the NMR spectrum) the major isomer was isolated and characterized as the β epoxide **2a** by consideration of the molecular rotation difference (+4°) that attends the conversion of **1a** to **2a** (comparison values[2] for the cholestane and pregnan-20-one series are found in Table I).

Epoxidation of **1b** under identical conditions proved to be both slower and more stereoselective. After 4 days a 49% yield of a single epoxide and 25% of unreacted **1b** were obtained. The molecular rotation difference (−19.8°) suggested that this epoxide was the β isomer **2b.** Because of the uncertain influence of the 1,3-diaxial interaction (F-C-4) in **2b** on conformation and optical rotation, we decided to provide further evidence for the stereochemistry of **2b.**

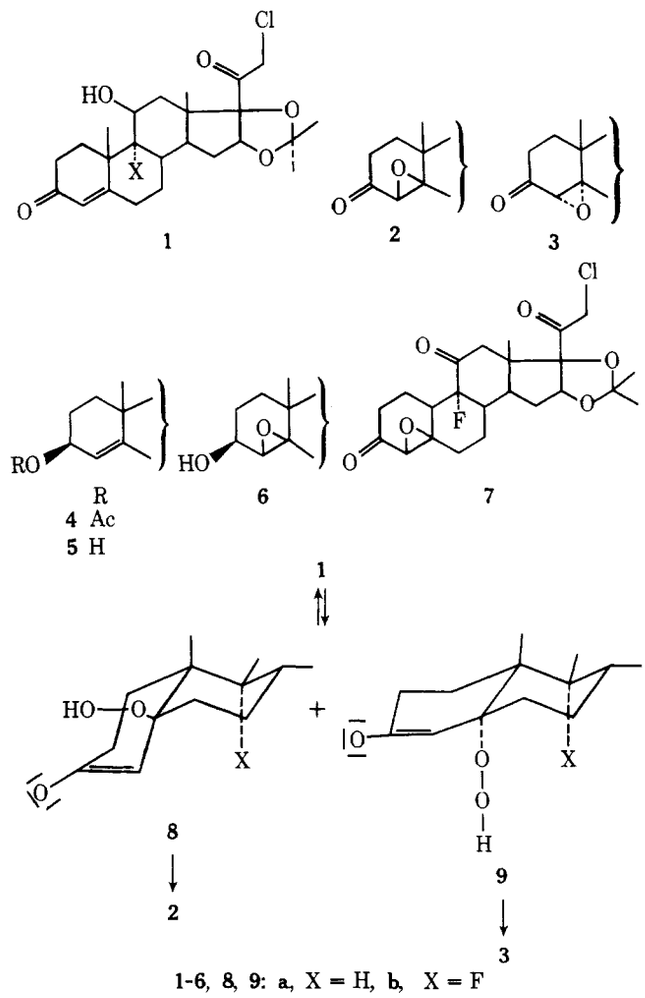
Epoxidation of allylic alcohols with peracid, which occurs on the side cis to the hydroxyl group,[3] provides the basis for the preparation of epoxy ketones of known stereochemistry provided that the requisite allylic alcohol is available.[4] Reduction of **1b** with sodium borohydride gave a single allylic alcohol **5b** after purification via its acetate **4b.** β stereochemistry is assigned to **5b** based on comparison of the molecular rotation differences in Table I with those for **4b** (−298.5°) and **5b** (−230°).[5] The NMR spectrum of **5b** is also consistent with this conclusion as the vinylic hydrogen lacks the characteristic (6–10 Hz) coupling expected for the α epimer which contains a pseudoequatorial 3β hydrogen.[6]

Table I. Molecular Rotation Differences

	Δ[M]D cholestane[a]	Δ[M]D pregnan-20-one[a]
4α,5α-Epoxid-3-one	−510.8	−546.1
4β,5β-Epoxid-3-one	+174	+108
3β-OH-Δ⁴-Ene	−152.9	−199.6
3β-OAc-Δ⁴-Ene	−299.9	−291.4
3α-OH-Δ⁴-Ene	+106.1	
3α-OAc-Δ⁴-Ene	+418.1	

[a] Based on conversion of the Δ⁴-3-one to the functionality indicated. Values of optical rotation from ref 2 were used to calculate these molecular rotation differences.

Epoxidation of **5b** with *m*-chloroperbenzoic acid followed by Jones oxidation of the crude product gave a single epoxy triketone (**7b**) via epoxy alcohol **6b** in 70% yield. Oxidation of



2b with Jones reagent gave the same epoxide **7b.** This sequence establishes the stereochemistry of **2b** as β and validates the use of molecular rotation differences in spite of the diaxial interaction present in **2b.**

The effect of the 9α-fluorine in **1b** on both the rate and stereochemistry of epoxidation is attributable to the steric and field effects present in transition states leading from intermediates **8** and **9** to epoxides **2** and **3,** respectively. Henbest[1] has suggested that (when X = H) more strain is released in the transition state leading from **8a** to **2a** than in that from **9a** to