7α,17-Dimethyl-4-hydroxy-3-methoxy-*B*/*C*-*trans*-morphinan-6-one (5b). Compound **4b** was hydrogenated in a similar manner to that reported for **4a**. Workup gave a foam which was chromatographed to give **5b** as a foam: NMR δ 6.68 (H-1 and H-2), 6.20 (br, 4-OH), 4.09 (s, 0.5, 1/2 doublet for H-5α), 3.87 (unsymmetrical s, 3.5, 1/2 doublet for H-5α, OCH_3), 2.32 (NCH_3), 1.02 (unsymmetrical d, 3, 7β-CH_3, J = 5 Hz); mass spectrum, m/e 315 (M^+, 80), 272 (55), 244 (100), 178 (76), 122 (53), 115 (31), 59 (0). Conversion to the HCl salt followed by two crystallizations from MeOH-EtOAc gave an analytical sample of **5b**·HCl, mp sinters 142-145 °C, melts 222-224 °C.

Anal. Calcd for $C_{19}H_{25}NO_3$·HCl: C, 64.86; H, 7.45; N, 3.98. Found: C, 64.47; H, 7.73; N, 4.21.

5,6-Didehydro-3,6-dimethoxy-7β,17-dimethyl-4-hydroxymorphinane (7). A solution of Me_2CuLi (12.5 mmol) was prepared in Et_2O (75 mL) as previously described. To this was added rapidly dropwise a solution of dihydrothebaine (**6**, 3.13 g, 10 mmol) in benzene (75 mL) and the reaction mixture was stirred for 1 h in the ice bath. The mixture was poured into saturated NH_4Cl solution, stirred for 30 min and then adjusted to pH 11 with NH_4OH. Extraction with $CHCl_3$ followed by processing in the usual fashion gave 3.76 g of a foam which was chromatographed (400 g, 10:1:1%). Fractions containing the major product, homogeneous by TLC, were combined and evaporated to give **7** (2.54 g, 77%) as a foam; NMR δ 6.60 (s, H-1 and H-2), 6.13 (br, 4-OH), 5.68 (s, 1, H-5), 3.83 (3-OCH_3), 3.58 (6-OCH_3), 2.40 (NCH_3), 1.18 (m, 3, 7β-CH_3).

Hydrolysis of 7 to 5a. Compound **7** (2.54 g, 7.7 mmol) in 1 N HCl (30 mL) was heated on the steam bath for 30 min. The cooled solution was made basic with NH_4OH and extracted with $CHCl_3$. Processing followed by evaporation gave a crystalline residue. Recrystallization from acetone gave **5a**·0.5C_3H_6O (1.29 g, 48%), mp 166-167 °C, identical with material prepared above.

Reaction of Dihydrocodeinone Enol Acetate (7) with Me_2CuLi. A solution of **8** (6.40 g, 18.75 mmol) in benzene (100 mL) was added rapidly dropwise to a solution of Me_2CuLi (40 mmol), prepared in Et_2O (200 mL), at 0 °C under argon. The mixture was stirred for 1 h at 0 °C and poured into saturated NH_4Cl solution and the pH was adjusted to 10 with NH_4OH. After the mixture was stirred for 30 min, processing of the combined organic phase and $CHCl_3$ extracts gave a foam which contained four major compounds as indicated by TLC. The foam was chromatographed (750 g, 15:1:0.75%) and fractions were pooled on the basis of TLC.

First eluted was 5,6-didehydro-7β,17-dimethyl-4-hydroxy-3-methoxymorphinane (**10**, 1.48 g, 26%): NMR δ 6.63 (2.5, H-1, H-2, and 1/2 doublet for H-5), 6.46 (1/2 unsymmetrical doublet for H-5), 6.00 (4-OH), 5.55 (pair of d, 1, H-6, $J_{5,6}$ = 10 Hz, $J_{6,7}$ = 3.5 Hz), 3.83 (OCH_3), 2.45 (NCH_3), 1.05 (unsymmetrical d, 7-CH_3, J = 7 Hz). This material was converted to the HCl salt which was crystallized from EtOAc to give **10**·HCl, mp >250 °C dec.

Anal. Calcd for $C_{19}H_{25}NO_2$·HCl: C, 67.94; H, 7.80; N, 4.17. Found: C, 67.70; H, 7.89; N, 4.07.

Next eluted was 7β,17-dimethyl-4-hydroxy-3-methoxymorphinan-6-one (**9**, 1.71 g, 28%); NMR δ 6.62 (H-1 and H-2), 4.10 (H-5α, J = 15 Hz), 3.82, 2.43, 1.21 (d, 7β-CH_3, J = 7 Hz). Two recrystallizations from EtOAc gave the hemi-EtOAc solvate of **9**, mp 163-165 °C, $[\alpha]_D$ -115° (c 1.0, $CHCl_3$).

Anal. Calcd for $C_{19}N_{25}NO_3$·0.5$C_4H_8O_2$: C, 70.17; H, 8.13; N, 3.90. Found: C, 70.44; H, 8.19; N, 3.87.

Continued elution gave **5a** (1.66 g, 27%) followed by **11** (0.65 g, 12%) which was identified by comparison with an authentic sample.

Acknowledgment. We are indebted to Drs. R. N. Schut and J. E. Villarreal for their continued interest and encouragement during the course of this work.

Registry No. 1, 115-37-7; 2, 74466-73-2; 3, 74466-74-3; 4a, 74466-75-4; 4b, 74497-87-3; 5a, 74497-88-4; 5b, 74497-89-5; 5b·HCl, 74497-90-8; 6, 57281-79-5; 7, 74466-76-5; 8, 466-90-0; 9, 74497-91-9; 10, 74466-77-6; 10·HCl, 74466-78-7; 11, 847-86-9.

Two New Germacranolides from *Melampodium leucanthum* and Their Reductive and Oxidative Rearrangements

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The isolation and structure elucidation of two new 4,5-dihydrogermacranolides, 9-acetoxymelnerin A and B, from *Melampodium leucanthum* Torr. and Gray (Compositae, Heliantheae) are reported. Reduction of the two germacranolides with sodium borohydride proceeds, besides saturation of the lactonic exocyclic methylene function, under 1(10) to 9,10 double bond rearrangment with the loss of the C-9 acetoxy group, a process which can be interpreted as a S_N' reaction. Pyridinium chlorochromate oxidation of the C-15 alcohol function of 9-acetoxymelnerin A provides the aldehyde as a minor product, the major product being a ketone formed by a C-4 to C-15 shift of C-5 of the ten-membered ring, resulting in an 11-membered-ring skeleton. The separation of the previously inseparable melnerin A and B mixture by reverse-phase high-pressure liquid chromatography is described, and the physical parameters of the pure compounds are reported.

In our biochemical systematic study of the genus *Melampodium* (Compositae, Heliantheae) we have in the past reported results of our populational analysis for sesquiterpene lactones in *M. leucanthum*. Our previous investigations of this chemically diverse species have led to the isolation of melampolides,[1-4] germacranolide dilactones,[5,6] and *cis,cis*-germacranolides.[6] Now we wish to describe the isolation, structure elucidation, and chemistry of two new 4,5-dihydrogermacranolides which are structurally related to melnerins A and B, compounds which have previously

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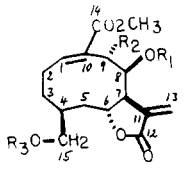
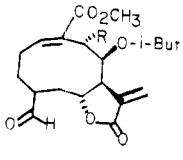
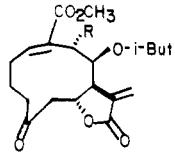
Chart I



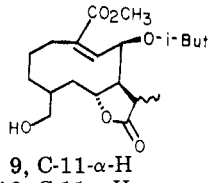
	R_1	R_2	R_3
1a	*i*-But	OAc	H
1b	*i*-But	OAc	Ac
1c	*i*-But	OAc	Me_3Si
1d	*i*-But	OAc	Me_3Si-d_9
2a	α-MeBut	OAc	H
2b	α-MeBut	OAc	Ac
2c	α-MeBut	OAc	Me_3Si
2d	α-MeBut	OAc	Me_3Si-d_9
3	*i*-But	H	H
4	α-MeBut	H	H



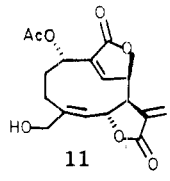
5, R = OAc
6, R = H



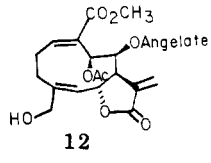
7, R = OAc
8, R = H



9, C-11-α-H
10, C-11-β-H



11



12

i-But = isobutyrate; α-MeBut = α-methylbutyrate

been isolated from *M. cinereum*[4] and due to separation problems were determined as a mixture. Melnerins A (3) and B (4) (see Chart I) were subsequently separated by reverse-phase high-pressure LC, and we report here the physical data of pure melnerins A and B.

Structural data of the two new compounds were obtained by chemical transformations and the application of ^1H NMR and mass spectal data. Chromate oxidations as well as $NaBH_4$ reductions led to interesting rearrangements which to our best knowledge are novel within the germacranolide series.

Results and Discussion

The areal parts of *M. leucanthum* from New Mexico provided two new sesquiterpene lactones which were separated by reverse-phase high-pressure LC.

9-Acetoxymelnerin A (1a; $C_{22}H_{30}O_9$), a colorless crystalline solid (mp 149–151 °C), exhibited a UV maximum at 213 nm and an IR absorbance at 3500 cm^{-1} (OH) overlapping several overlapping carbonyl peaks, including 1760 cm^{-1} (α,β-unsaturated γ-lactone) and 1745 cm^{-1} (acetate). Further absorptions indicated the presence of double bonds (1660 and 1640 cm^{-1}) and overlapping signals at various C–O stretching frequencies (1260, 1230, 1220, 1060, 1040 cm^{-1}). The ambient-temperature ^1H NMR spectrum of **1a** showed only broadened absorptions. At 60 °C the spectrum exhibited much sharper signals, allowing detailed decoupling experiments, the results of which are summarized in Table I. The NMR data suggested a sesquiterpene lactone and exhibited great similarities with the 4,5-dihydromelampolide melnerin A (3). Two doublets assigned to protons of a lactonic exocyclic methylene appeared at 5.48 (J = 2 Hz) and 6.18 ppm (J = 2 Hz), and a three-proton singlet characteristic of a carbomethoxyl methyl was present at 3.57 ppm. In addition, the most downfield signal at 6.89 ppm (1 H, dd, J = 8.9, 8.9 Hz) together with the carbomethoxy signal also indicated a melampolide skeleton for **1a**. The pressure of two side chains in **1a** was evident in the NMR spectrum; absorptions typical of acetate (1.89 ppm, 3 H, s) and isobutyrate (1.05 ppm, 3 H, d, J = 7 Hz; 1.08 ppm, 3 H, d, J = 7 Hz; 2.43 ppm, 1 H, heptet, J = 7 Hz) were observed. The mass spectrum of **1a** verified the above NMR assignments, showing strong peaks at m/e 43 ($CH_3C{\equiv}O^+$) and m/e 71 [$(CH_3)_2CHC{\equiv}O^+$]. The absence of a C-4 vinyl methyl near 2 ppm together with the presence of a broadened two-proton doublet at 3.30 ppm (J = 5.5 Hz) suggested that C-15 must be present as a CH_2OH group and that **1a** contained a saturated C-4, C-5 bond. Acetylation of **1a** produced a single product (**1b**) whose NMR spectrum showed two acetate absorptions and, in contrast to the broadened CH_2–OH resonance in **1a**, a sharper two-proton absorption at 3.71 ppm (2 H). This established the presence of an OH group at C-15 in **1a**.

Four NMR signals remained to be assigned for **1a**. A multiplet at 3.08 ppm was attributed to H-7 in that irradiation at this position caused the collapse of the two lactonic methylene doublets. Two other signals which must correspond to H-6 and H-8 were also affected. A broad multiplet at 4.94 ppm (1 H) sharpened distinctly but still remained broad, and a doublet of doublets centered at 5.63 ppm (1 H, J = 2.2, 3.5 Hz) was transformed into a doublet (J = 3.5 Hz). The assignments of the above resonances were derived as follows. Irradiation of the doublet of doublets at 5.63 ppm affected a signal at 6.27 ppm (1 H), changing it from a broad doublet to a broad singlet. This latter signal was assigned to H-9 due to its allylic coupling with H-1 whose irradiation produced a sharpening of the H-9 doublet. Reciprocal decoupling experiments confirmed the assignments. On the basis of the above results, the signals at 4.94 and 5.63 ppm were assigned to H-6 and H-8, respectively. The chemical shift of H-6 relative to H-8 and H-9 is in agreement with the notion that the lactonic exocyclic methylene bond reduces by conjugation the amount of deshielding experienced by H-6, whereas protons at C-8 and C-9 are deshielded more strongly by saturated ester groups. In addition, the fact that the signals for H-6 and H-9 show a large degree of temperature dependence indicates that they are attached to centers of conformational flexibility. This is borne out by examination of molecular models. While the chemical shift of H-9 relative to H-8 is what one might predict, since H-9 is at an allylic position, this is in contrast to what has normally been observed in melampolides. Because of the conformation enforced in melampolides by the cis-1,10 double bond and the trans-4,5 double bond, H-8 usually appears downfield of H-9 by about 1 ppm due to deshielding by the C-14 carbonyl oxygen.[1] Recent X-ray investigations[4] of melnerin A (3) have indicated that 3 and therefore most likely **1a** possess in the crystal structure a conformation in which H-8 does not lie in the deshielding region of the C-14 carbonyl oxygen. While the predominant conformation in solution may not be that in the crystal, it is true that for melnerin A (3) H-8 produces a signal at 5.76 ppm in benzene-d_6, indicating at least that the solution conformations of the two compounds are similar. By use of 3 as a conformational analogue, the stereochemical results suggested for **1a** may therefore be deduced from the coupling constants for H-8 and H-9 by assuming that H-7 is α oriented.

The stereochemistry at C-4 in **1a** is tentatively based on the similarity of the chemical shifts of **1a** and 3. The C-6

Table I. ^{1}H NMR Parameters[a] of 9-Acetoxymelnerin A and Related Compounds

	1a[b]	2a[b,c]	1b[b,c]	7[b,c]	5	8[d]	6[d]	3	4	9	10
H-1	7.01 [6.89] dd (8.9, 8.9)	6.82 dd (8.9, 8.9)	6.79 dd (8.9, 8.9)	6.76 dd (7.4, 9.8)	6.99 [6.68] dd (5.2, 13.0)	6.91 dd (5.9, 11.0)	6.87 dd (5.3, 11.0)	6.88 [6.70] dd (4.4, 12.1)	6.87 [6.72] dd (4.4, 12.1)		
H-6	4.95 [4.94] br m	4.96 br m	4.82 br m	5.25 br m	6.61 [5.37] br m	5.23 br m	5.08 br m	5.08, [4.78] br dd (4.7, 10.5)	5.07 [4.80] ddd (1.6, 5.1, 11.0)	4.21 [4.92] dd (10, 8.3)	4.46 [4.26] m
H-7	3.20 [3.08] br m	2.89 br m	2.90 br m	2.87 br m	3.07 [2.72] br m	2.86 br m, ob	2.79 br m	2.86 [2.63] br m	2.85 [2.64] br m	2.15 [1.95] m (5.0, 10.9)	3.08 [2.62] m
H-8	5.51 [5.63] dd (2.2, 3.5)	5.70 dd (2.0, 3.5)	5.69 dd (2.1, 3.5)	5.69 dd (2.5, 3.5)	5.54 [5.69] dd (5.1, 3.2)	5.58 br m	5.50 br m	5.49 [5.70] ddd (2.6, 5.9, 10.5)	5.50 [5.73] ddd (2.8, 6.4, 11.0)	5.90 [5.80] dd (5.0, 8.8)	5.78 [5.0] br dd (6.5, 4.9)
H-9	6.15 [6.27] br d (3.5)	6.23 br d (3.5)	6.25 br d (3.5)	6.21 br d (3.5)	6.42 [6.13] br d (5.1)	ob	ob	2.91 [2.94] dd (5.9, 13.6)	2.93 [2.98] dd (5.9, 13.6)	6.61 [6.63] br d (8.8)	6.60 [6.70] br d (6.5, 1.0)
H-13a	5.72 [5.48] d (2.0)	5.32 d (2.0)	5.36 d (2.0)	5.26 d (2.1)	5.74 [5.10] d (1.6)	5.72 d (1.6)	5.71 d (1.5)	5.67 [5.10] d (1.6)	5.67 [5.12] d (1.6)		
H-13b	6.26 [6.18] d (2.0)	6.19 d (2.0)	6.18 d (2.2)	6.16 d (2.3)	6.35 [6.13] d (1.8)	6.34 d (2.1)	6.33 d (1.7)	6.28 [6.16] d (2.0)	6.28 [6.17] d (2.0)	1.38 [1.24] d (6.9)	1.35 [1.19] d (7.9)
H-15	3.47 [3.30] br d (5.5)	3.03 br d (5.7)	3.71 br d (6.0)		9.59 [8.90]		9.56	3.45 [2.84] d (5.7) [br m]	3.45 [2.86] d (5.7) [br m]	3.52 [3.10] m	3.51 [3.01] m (5.6, 11.2)
Ac	2.10 [1.89]	1.79	1.80, 1.77	1.82	2.15 [1.65]						
CO_2Me	3.77 [3.57]	3.48	3.49	3.45	3.86 [3.42]	3.81	3.83	3.82 [3.50]	3.82 [3.50]	3.78 [3.41]	3.80 [3.38]
H-2′	2.46 [2.43] hept (7.0)	2.0–2.5 m ob	2.38 m ob	2.38 hept (7.0)	2.43 [2.30] hept (7.0)	ob	ob	ob [2.42] hept (7.0)	ob	2.63 [2.27] m ob	2.60 [2.31] hept (6.9)
2′-Me	1.06 [1.05] d (7.0)	1.05 d (7.0)	1.04 d (7.0)	1.04 d (7.0)	1.09 [1.04] d (7.0)	1.10 d (7.0)	1.09 d (7.0)	1.10 [1.09] d (7.0)	1.12 [1.11] d (7.0)	1.20 [0.80] d (7.0)	2.20 [1.01] d (6.9)
2′-Me′	1.09 [1.08] d (7.0)		1.07 d (7.0)	1.04 d (7.0)	1.08 [1.04] d (7.0)	1.13 d (7.0)	1.11 d (7.0)	1.12 [1.11] d (7.0)		1.20 [1.00] d (7.0)	2.20 [1.02] d (6.9)
miscellaneous		3′-Me, 0.85 t (7.0)		H-5, 2.21, br d (11.9); H-5′, 2.87 dd (4.5, 11.9)				H-9′, 2.39 [2.62] dd (10.5, 13.6)	3′-Me, 0.87 [0.85] t (7.0); H-9′, 2.61 [ob] dd (10.4, 13.6)	H-11, 2.68 [2.28] m ob (10.9)	H-11, 2.80 [2.46] m (8.6)

[a] Unless otherwise indicated spectra were run at 200 MHz at 60 °C in $CDCl_3$ with Me_4Si as an internal standard. Numbers in brackets indicate chemical shifts in C_6D_6. Values are recorded in parts per million relative to Me_4Si. Singlets are unmarked and multiplets are designated as follows: d, doublet; t, triplet; hept, heptet; m, multiplet whose center is given; br, broad; ob, obscured. Figures in parentheses are coupling constants or line separations in hertz. [b] Spectra obtained at 100 MHz at 60 °C. [c] Spectra determined in C_6D_6. [d] Spectra obtained at 27 °C.

orientation of the lactone is supported by CD results. As for melnerin A, 9-acetoxy-melnerin A exhibits a small positive CE at 249 nm ([θ] +9800) and a large negative band at 213 nm ([θ] −99 000). It is on the basis of the above arguments that the structure **1a** is proposed for 9-acetoxymelnerin A except for the sites of attachment of the two ester side chains at C-8 and C-9.

The placement of the side chains in **1a** is based on the following experimental results. Reduction of **1a** using sodium borohydride produced a complex mixture from which were isolated two components identified as the C-11 epimers **9** and **10**. The NMR spectra of compounds **9** and **10** indicated the loss of the acetoxy moiety and a shift of H-9 from 6.15 ppm in **1a** to 6.61 and 6.60 ppm in **9** and **10**, respectively. Detailed NMR decouplings suggested a double bond shift from the 1(10) to the 9,10 position in the medium rings with the loss of the acetoxy group at C-9. The transformation apparently results from an S_N' displacement of the C-9 acetate by attack of hydride at the C-1 position in addition to the reduction of the lactonic exocyclic methylene group. Differentiation between the C-11 epimers **9** and **10** was tentatively made on the basis of the chemical shifts of the protons at positions 6–8 and 11, as well as the comparison of observed coupling constants with those predicted by examination of Dreiding models. The solvent-shifts method[7] for the distinction between the C-11 α-H and the C-11 β-H failed in that the shift values in changing from $CDCl_3$ to C_6D_6 were nearly the same for the two epimers, which might be expected due to the conformational flexibility of the ten-membered ring.

It should be pointed out that **9** and **10** bear a resemblence to sesquiterpene dilactones of the type represented by melampodin B (**11**), which co-occurs with **1a** in *M. leucanthum* and is found in several other *Melampodium* species.

The above reductive S_N' reaction represents a modification which might simulate the biological formation of melampodin B-type dilactones from melampolides[8] or more likely from the more recently found *cis,cis*-germacranolides[6] represented by melcanthin A (**12**). We are presently persuing transformations on other melampolides[9] and *cis,cis*-germacranolides to demonstrate a possible generality of this rearrangement.

It has been demonstrated recently[4] that GC/MS analyses of trimethylsilylated sesquiterpene lactones can be a convenient tool for their separation and structure elucidation. In this manner it was discovered that crude crystalline samples of 9-acetoxymelnerin A contained small amounts of a second compound which differed in its molecular weight by 14 mass units and produced a base peak at *m/e* 85, which is characteristic of the α-methylbutyrate acylium ion ($C_2H_5CH(CH_3)C{\equiv}O^+$). Other mass spectral peaks occurred at *m/e* values which differed from **1a** by 14 mass units. The only differences in the mass spectral patterns of the two compounds were therefore attributed to a difference in the side chains, α-methylbutyrate vs. isobutyrate. The mass spectral data of **1a** and 9-acetoxymelnerin B (**2a**) as well as their Me_3Si and other derivatives are given in Table II along with tentative assignments. Separation of the mixture of **1a** and **2a** on reverse-phase high-pressure LC with methanol–water as eluant provided pure 9-acetoxymelnerin B which was used for physical measurements. The NMR data for **2a** which are summarized in Table I were obtained by detailed decoupling experiments as previously outlined for **1a**.

As expected, 9-acetoxymelnerin A (**1a**) resisted MnO_2 oxidation. Oxidation by pyridinum chlorochromate, however, resulted in the formation of a mixture of carbonyl derivatives. The structure of the expected aldehyde (**5**), which was formed as the minor product, was established by NMR and mass spectral analyses (Tables I and II) and gave IR absorptions (2880, 2730, and 1725 cm^{-1}) typical for aldehydes. The second, major oxidation product, a crystalline compound with the same molecular weight as the aldehyde **5**, exhibited an IR carbonyl absorption at 1715 cm^{-1} but no aldehydic proton signal in the NMR spectrum, suggesting a ketone function in the molecule. The NMR spectrum of the new compound showed signals similar to those of the starting alcohol **1a** except that the C-15 methylene absorption was missing in the ketone. Instead, two new resonances appeared, a broadened doublet at 2.21 ppm (1 H, J = 11.9 Hz) and a doublet of a doublet at 2.87 ppm (1 H, J = 4.5, 11.9 Hz). Decoupling experiments involving irradiations at the H-7 and H-6 signals established the attachment of the two new protons to C-5, with the adjacent carbon being a carbonyl group. This strongly suggested that the oxidation of **1a** involves a migration of C-5 from C-4 to C-15 to give ketone **7**.

The mechanism of oxidation of alcohols by PCC was proposed to most likely involve cationic intermediates.[12] Initial hydride abstraction from C-15 of alcohol **1a** by the chromate agent under formation of a cationic intermediate could be envisioned. Subsequent loss of a proton from the previous C-15 hydroxyl would provide the expected aldehyde **5**. Alternatively, migration of C-5 from C-4 to C-15 would give, after loss of a proton from C-15, the enol and finally ketone **7**. A ketone resulting from C-3 migration was not observed, suggesting a conformationally dictated transition state which might favor C-4 migration. Since in the case of melnerin A (**3**) PCC oxidation produced the aldehyde **6** as the main product and ketone **8** as the minor product, the ester group at C-9 in **1a** may also play a role in the oxidative ring expansion. This could occur either directly by transannular influences or indirectly by conformational changes possibly involving C-15 chromate ester intermediates.

Experimental Section[13]

Isolation and Separation of Melnerins A (3) and B (4). Stems and leaves (729 g) of *Melampodium cinereum* (collected in Jim Wells Co., TX, on Dec 27, 1974, Stuessy-Stuessy No. 3791,

(7) Narayanan, C. R.; Venkatasubramanian, N. K. *J. Org. Chem.* **1968**, *33*, 3156.

(8) Fischer, N. H.; Wiley, R. A.; Perry, D. L. *Rev. Latinoam. Quim.* **1976**, *7*, 87.

(9) We were recently informed by Professor Herz that base-catalyzed methanolysis of the melampolides orientalide[11a] and its analogues[11b] resulted in solvolytic displacement of the ester on C-9 in the manner previously observed with the acanthospermals.[10] Possible solvolysis of the ester group attached to C-9 by allylic arrangement was dismissed.[11b] Reduction of orientalide with $NaBH_4$ gave only the 11,13-dihydro derivative but no allylic rearrangement of the 1(10) double bond.[11a]

(10) Herz, W.; Kalyanaraman, P. S. *Phytochemistry* **1975**, *14*, 1664.

(11) (a) Barua, R. N.; Sharma, R. P.; Madhusudanan, K. P.; Thyagarayan, G.; Herz, W.; Murari, R. *Phytochemistry* **1979**, *18*, 991. (b) Barua, R. N.; Sharma, R. P.; Thyagarayan, G.; Herz, W.; Govindan, S. V. *Ibid.* **1980**, *19*, 323.

(12) Banerji, K. K. *Bull. Chem. Soc. Jpn.* **1978**, *51*, 2732.

(13) Melting points were performed in capillaries on a Thomas-Hoover apparatus and are uncorrected. Infrared spectra were taken on a Perkin-Elmer Model 621 spectrophotometer. Low-resolution mass spectra were obtained at 70 eV by using a Hewlett-Packard 5985 GC/MS instrument. High-resolution mass spectra were run at 70 eV on a Varian MAT 731 instrument. Some spectra of the Me_4Si derivatives were obtained on an interfaced LKB-9000 mass spectrometer. CD curves were measured on a Durram-JASCO J-20 CD/ORD spectrophotometer. ^1H NMR spectra were recorded on Varian HA-100 and Bruker WH200 spectrometers. High-pressure liquid chromatography separations were carried out on a Waters Chromatograph using a Model 440 absorbance detector (254 nm).

Table II. Mass Spectral Data[a] for 9-Acetoxymelnerin A and Related Compounds

m/e (relative intensity)									
1a	1c	1d	2a	2e	2c	3	4	M^-	assignment
	510 (1.5)	519 (1.0)	452 (0.9)	524 (1.7)	533 (1.5)	380 (0.2)	394 (0.6)	0	$M^+\cdot$
	495 (5.0)	501 (6.0)		509 (3.7)	515 (4.2)			15 or 18	$[M - CH_3$ or $CD_3]^+$
409 (5.9)	481 (2.0)	490 (2.0)	423 (4.6)	495 (5.3)	404 (3.6)	351 (2.6)	365 (3.8)	29	$[M - HC{\equiv}O\cdot]^+$
406 (5.9)			420 (3.8)			348 (4.2)	362 (4.3)	32	$[M - CH_3OH]^+\cdot$
396 (11.1)	468 (1.3)	477 (2.0)	410 (6.8)	482 (1.0)	491 (0.6)			42	$[M - H_2C{=}C{=}O]^+\cdot$
395 (48.9)	467 (2.0)	472 (2.0)	409 (29.5)	481 (1.2)	490 (1.1)			43	$[M - CH_3CO]^+$ [b]
378 (0.7)	450 (8.0)	459 (11.0)	392 (2.7)	464 (9.3)	473 (10.8)			60	$[M - HOAc]^+\cdot$
377 (7.4)			391 (6.5)					61	$[M - H_2O - CH_3C{\equiv}O\cdot]^+$
	440 (2.0)	449 (3.3)				320 (5.3)	334 (5.5)	70	$[M - (CH_3)_2C{=}C{=}O]^+\cdot$
367 (2.2)	439 (4.0)	448 (8.4)				319 (26.8)	333 (25.8)	71	$[M - (CH_3)_2C - C{\equiv}O\cdot]^+$
364 (20.7)	436 (1.5)	445 (1.6)	378 (9.1)	450 (5.8)	459 (4.9)			74	$[M - CH_3OH - H_2C{=}C{=}O]^+\cdot$
363 (84.4)	435 (2.2)	444 (2.0)	377 (51.6)	449 (3.9)	458 (3.6)			75	$[M - CH_3OH - CH_3C{\equiv}O\cdot]^+$ [c]
			368 (0.5)	440 (4.4)	449 (6.4)			84	$[M - C_2H_5C(CH_3){=}C{=}O]^+\cdot$
			367 (0.4)	439 (9.3)	448 (9.8)			85	$[M - C_2H_5CH(CH_3) - C{\equiv}O\cdot]^+$
350 (6.7)	422 (2.0)	431 (13.0)				292 (1.2)		88	[M – isobutyric acid]$^+\cdot$
349 (9.6)			363 (7.4)					89	$[M - HOAc - HC{\equiv}O\cdot]^+$
346 (8.9)	418 (9.3)	427 (13.4)	360 (6.7)	432 (10.6)	441 (13.4)			92	$[M - CH_3OH - HOAc]^+\cdot$
			350 (5.1)	422 (4.4)	431 (18.9)		292 (1.4)	102	[M – 2-methylbutyric acid]$^+\cdot$
336 (5.2)	408 (3.5)	417 (4.8)				278 (4.6)		102	$[M - CH_3OH - (CH_3)_2C{=}C{=}O]^+\cdot$
335 (11.9)	407 (10.9)	416 (15.2)				277 (0.6)		103	$[M - CH_3OH - (CH_3)_2CH - C{\equiv}O\cdot]^+$
			336 (4.5)	408 (5.3)	417 (4.7)		278 (6.4)	116	$[M - CH_3OH - C_2H_5C(CH_3){=}C{=}O]^+\cdot$
			335 (6.7)	407 (16.5)	416 (17.0)		277 (0.6)	117	$[M - CH_3OH - C_2H_5CH(CH_3) - C{\equiv}O\cdot]^+$
		112 (11.0)			112 (7.2)				$[H_2C{=}O - Si(CD_3)_3]^+$
	103 (9.0)			103 (9.1)					$[H_2C{=}O - Si(CH_3)_3]^+$
			85 (95.3)	85 (100)	85 (100)		85 (100)		$[C_2H_5CH(CH_3)C{\equiv}O]^+$
		82 (47.1)			82 (11.7)				$[Si(CD_3)_3]^+$
	73 (36.0)			73 (11.9)					$[Si(CH_3)_3]^+$
71 (100)	71 (80.0)	71 (82.5)				71 (100)			$[(CH_3)_2CH - C{\equiv}O]^+$
			57 (100)	57 (51.1)	57 (54.8)		57 (97.4)		$[C_2H_5 - CHCH_3]^+$
43 (50.4)	43 (100)	43 (100)	43 (19.0)	43 (16.0)	43 (16.8)	43 (35.7)			$[CH_3 - C{\equiv}O]^+$ or $[(CH_3)_2CH]^+$

[a] Spectra for 1a, 1c, 1d, 3, and 4 were obtained on a Hewlett-Packard 5895 GC/MS at 70 eV, while those for 2a, 2e, and 2c were determined on an interfaced LKB 9000 mass spectrometer at 20 eV. [b] Or $[M - (CH_3)_2CH]^+$. [c] Or $[M - CH_3OH - (CH_3)_2CH]^+$.

voucher at Ohio State University Herbarium, Columbus, OH) were extracted and worked up as previously described[2] to yield 12.7 g of crude syrup. Trituration of the syrup in 25 mL of isopropyl alcohol produced, after filtration and washing, 2.08 g of precipitate which was recrystallized from isopropyl alcohol to provide a crystalline mixture of melnerins A and B, mp 192–194 °C.

Injections (200 μL) of a 60 mg/mL stock solution of the mixture in methanol were loaded onto a Waters μ-Bondapack C-18 reverse-phase column (7.8 mm i.d. × 30 cm, 10-μm particle size). The eluant was methanol–water, 1:1 by volume, at a flow rate of 4.0 mL/min and a pressure of 1600 psi. The retention time for **3** was 11.5 min and for **4** was 17.6 min. The effluent collected was concentrated in vacuo for the removal of methanol. The residual water was extracted with CH_2Cl_2. The combined extracts were dried over Na_2SO_4 and evaporated in vacuo to yield the pure compounds.

Melnerin A (3): $C_{20}H_{28}O_7$; mp 202–204 °C; UV λ_{max} (MeOH) 212 nm (ϵ 6.9 × 10^4); CD $[\theta]_{212}$ −90 400, $[\theta]_{243}$ +10 400; IR ($CHCl_3$) ν_{max} 3620 and 3500 (OH), 1755 (γ-lactone), 1725 (ester), 1710 (ester), 1660 and 1640 cm^{-1} (double bonds).

Anal. Calcd for $C_{20}H_{28}O_7$: M_r = 380.1835. Found: M_r (mass spectrum) = 380.1808.

Melnerin B (4): $C_{21}H_{30}O_7$; mp 162–164 °C; UV λ_{max} (MeOH) 212 nm (ϵ 2.5 × 10^4); CD $[\theta]_{211}$ −82 400, $\theta]_{253}$ +9460; IR ($CHCl_3$) ν_{max} 3620 and 3510 (OH), 1760 (γ-lactone), 1725 (ester), 1710 (ester), 1660 and 1640 cm^{-1} (double bonds).

Anal. Calcd for $C_{21}H_{30}O_7$: M_r = 394.1994. Found: M_r (mass spectrum) = 394.1994.

Isolation of 9-Acetoxymelnerins A (1a) and B (2a). Dried leaves and stems (1162 g) of *Melampodium leucanthum* (collected in Chaves Co., NM, on June 21, 1974; Stuessy and Meacham No. 3538, voucher deposited at the Ohio State University Herbarium at Columbus, OH) were extracted with cold $CHCl_3$ and worked up as previously described,[2] yielding 67.2 g of crude syrup. Five grams of this syrup was chromatographed over 300 g of silica gel (EM Reagents, 70–230 mesh) by using *n*-propyl acetate as eluant and taking 50-mL fractions. The progress of the reaction was monitored by TLC. Fractions 60–90 were combined and evaporated to provide 1.65 g of oil which was further chromatographed over 50 g of neutral alumina with ethyl acetate as eluant. Fractions 10–15 of this column yielded 170 mg of a mixture of crystalline **1a** and **2a**, mp 123–128 °C. More crude syrup was chromatographed as additional material was sought for further investigations.

Preparation of Me_3Si Derivatives and Their GC/MS Analysis. Samples were silylated by heating 2–3 mg of compound with an excess of *N,O*-bis(trimethylsilyl)trifluoroacetamide (BSTFA) until dissolution was achieved. A 2.5-μL sample of the solution was injected onto a 6 ft × 4 mm (i.d.) silanized glass column packed with 1% SE-30 on Gas Chrom Q (100–120 mesh), and the mass spectra of the GC fractions were obtained on an interfaced LKB-9000 mass spectrometer at 20 eV. The GC trace showed two major peaks in an approximate ratio of 4:1, the major component corresponding to **1a**.

High-Pressure LC Separation of 1a and 2a. Injections of 100 μL of a 50 mg/mL solution of the mixture of **1a** and **2a** in methanol were loaded onto the same column described above. The eluant was methanol–water (1:1) at a flow rate of 2 mL/min and a column pressure of 1400 psi. The retention times were 36 min for **1a** and 48 min for **2a**. Workup was the same as described above.

9α-Acetoxymelnerin A (1a): $C_{22}H_{30}O_9$; mp 149–151 °C; UV λ_{max} (MeOH) 213 nm (ϵ 1.5 × 10^4); CD $[\theta]_{213}$ −99 000; $[\theta]_{249}$ +9800; IR (film) ν_{max} 3500 (OH), 1760 (γ-lactone), 1745 (acetate), 1730 (ester), 1660 and 1640 cm^{-1} (double bonds); mass spectrum (CI), *m/e* 439 (M + 1).

Anal. Calcd for $C_{21}H_{29}O_8$ (M − CHO): M_r = 409.1863. Found: M_r (mass spectrum) = 409.1867. Calcd for $C_{21}H_{26}O_8$ (M − CH_3OH): M_r = 406.1627. Found: M_r (mass spectrum) = 406.1636.

9α-Acetoxymelnerin B (2a): $C_{23}H_{32}O_9$; mp 136–138 °C; UV λ_{max} 213 nm (ϵ 3.4 × 10^4); CD $[\theta]_{213}$ −122 500, $[\theta]_{248}$ +14 600; IR (film) 3500 (OH), 1750 (γ-lactone), 1740 (acetate), 1660 and 1645 cm^{-1} (double bonds); mass spectrum, *m/e* 452.

Anal. Calcd for $C_{22}H_{31}O_8$ (M − CHO): M_r = 423.2019. Found: M_r (mass spectrum) = 423.2017. Calcd for $C_{21}H_{29}O_8$ (M − $CH_3C{\equiv}O\cdot$): M_r = 409.1863. Found: M_r (mass spectrum) 409.1864.

Acetate 1b. An 86-mg sample of **1a** was acetylated with Ac_2O–py at room temperature for 1.5 h. Chromatography of the crude gum on preparative layer silica gel with 15% PE/85% Et_2O as eluant yielded 39 mg of pure **1b**: $C_{24}H_{32}O_{10}$; oil; IR (film) ν_{max} 1750 (γ-lactone), 1740 (acetate), 1730 (ester), 1710 (ester), 1660 and 1640 cm^{-1} (double bonds); mass spectrum, *m/e* 480 (M^+), 420 (M − HOAc), 410 (M − $(CH_3)_2C{=}C{=}O$), 409 (M − $(CH_3)_2CHC{\equiv}O\cdot$), 392 (M − isobutyric acid), 367 (M − ketene − $(CH_3)_2CH{\equiv}O\cdot$), 335 (M − CH_3OH − ketene − $(CH_3)_2CHC{\equiv}O\cdot$), 71 ($(CH_3)_2CHC{\equiv}O^+$), 43 ($CH_3C{\equiv}O^+$, base peak).

Anal. Calcd for $C_{24}H_{32}O_{10}$: M_r = 480.1995. Found: M_r (mass spectrum) = 480.1970.

$NaBH_4$ Reduction of 1a. To a stirred solution of 100 mg of **1a** in 25 mL of methanol at 0 °C was added 200 mg of $NaBH_4$. The mixture was allowed to react for 10 min after which the solvent was evaporated and the residue treated with 5% HCl, extracted with CH_2Cl_2, dried, and evaporated. Preparative-layer chromatography (twice with petroleum ether/EtOAc, 1:1) of the residual oil gave several bands of which **9** (14 mg) and **10** (4.6 mg) showed R_f values of 0.21 and 0.11, respectively.

Compound 9: $C_{20}H_{30}O_7$; oil; CD $[\theta]_{246}$ −2100, $[\theta]_{222}$ +30 900; IR (film) ν_{max} 3450 (OH), 1775 (saturated γ-lactone), 1725 (ester) 1650 cm^{-1} (double bond); mass spectrum, *m/e* 382 (M^+), 364 (M − H_2O), 350 (M − CH_3OH), 311 (M − $(CH_3)_2CHC{\equiv}O\cdot$), 295 (M − $(CH_3)_2CHCO_2\cdot$), 294 (M − isobutyric acid), 276 (M − H_2O − isobutyric acid), 262 (M − CH_3OH − isobutyric acid), 71 [$(CH_3)_2CHC{\equiv}O^+$, base peak], 43 ($C_3H_7^+$).

Anal. Calcd for $C_{20}H_{30}O_7$: M_r = 382.1991. Found: M_r (mass spectrum) = 382.1988.

Compound **10**: $C_{20}H_{30}O_7$; oil; CD $[\theta]_{248}$ −1020, $[\theta]_{218}$ +15 300; IR (film) ν_{max} 3450 (OH), 1775 (saturated γ-lactone), 1740, 1720 (ester), 1650 cm^{-1} (double bond); mass spectrum, *m/e* 382 (M^+), 364 (M − H_2O), 350 (M − CH_3OH), 332 (M − H_2O − CH_3OH), 312 (M − $(CH_3)_2C{=}C{=}O$), 311 (M − $(CH_3)_2CHC{\equiv}O\cdot$), 295 (M − $(CH_3)_2CHCO_2\cdot$), 294 (M − isobutyric acid), 276 (M − H_2O − isobutyric acid), 262 (M − CH_3OH − isobutyric acid), 71 [$(CH_3)_2CHC{\equiv}O^+$, base peak], 43 ($C_3H_7^+$).

Anal. Calcd for $C_{20}H_{30}O_7$: M_r = 382.1991. Found: M_r (mass spectrum) = 382.1963.

Reaction of 1a with Pyridinium Chlorochromate (PCC). Lactone **1a** (150 mg) dissolved in 2 mL of CH_2Cl_2 was added to a suspension of 150 mg of PCC in 5 mL of CH_2Cl_2. The mixture was stirred at room temperature and the reaction monitored by TLC. After 1.5 h three spots appeared, having R_f values (Et_2O, silica gel) of 0.57, 0.39, and 0.31, corresponding to the aldehyde **5**, ketone **7**, and starting material (**1a**). Neither additional reaction time nor additional PCC changed the appearance of the TLC notably. After 24 h the reaction mixture was filtered through a short column of Florisil. The effluent was combined with subsequent ether washings and evaporated. Preparative TLC provided 16 mg of **5**, 37 mg of **7**, and 44 mg of starting material (**1a**). The aldehyde **5** contained trace amounts of the corresponding acid.

Aldehyde 5: $C_{22}H_{28}O_9$; oil; UV λ_{max} (MeOH) 202 (ϵ 2.4 × 10^4); CD $[\theta]_{210}$ −2400, $[\theta]_{240}$ +2200, $[\theta]_{305}$ −270; IR (film) ν_{max} 2880 and 2730 (aldehyde), 1760 (γ-lactone), 1745 (acetate), 1725 (aldehyde), 1710 (ester), 1660 and 1640 cm^{-1} (double bonds); mass spectrum, *m/e* 436 (M^+), 394 (M − ketene), 377 (M − $CH_3CO_2\cdot$), 376 (M − HOAc), 306 (M − ketene − isobutyric acid), 71 [$(CH_3)_2CHC{\equiv}O^+$, base peak], 43 ($CH_3C{\equiv}O^+$).

Anal. Calcd for $C_{20}H_{24}O_7$ (M − AcOH): M_r = 376.1522. Found: M_r (mass spectrum) 376.1511.

Ketone 7: $C_{22}H_{28}O_9$; mp 146–148 °C; UV λ_{max} (MeOH) 205 (ϵ 1.7 × 10^4); CD $[\theta]_{217}$ −32 468, $[\theta]_{238}$ +8040, $[\theta]_{300}$ −1917; IR (film) ν_{max} 1760 (γ-lactone), 1715 (ketone), 1710 (ester), 1660 and 1645 cm^{-1} (double bonds); mass spectrum, *m/e* 436 (M^+), 393 (M − $CH_3C{\equiv}O\cdot$), 376 (M − HOAc), 362 (M − ketene − CH_3OH), 330 (M − $C_4H_{10}O_3$), 309 [M − C_3H_4O − $(CH_3)_2CHC{\equiv}O\cdot$] 277 [M − CH_3OH − C_3H_4O − $(CH_3)_2CHC{\equiv}O\cdot$], 71 [$(CH_3)_2CHC{\equiv}O^+$, base peak], 43 ($CH_3C{\equiv}O^+$).

Anal. Calcd for $C_{20}H_{24}O_7$ (M − AcOH): M_r = 376.1522. Found: M_r (mass spectrum) 376.1519.

Oxidation 6: Melnerin A (3) with PCC. Lactone **3** (200 mg) in 5 mL of CH_2Cl_2 was added to a suspension of 170 mg of PCC in 5 mL of CH_2Cl_2. The mixture was stirred at room temperature for 1 h after which the workup proceeded as outlined above for

1a. Purification by preparative TLC yielded 100 mg of aldehyde 6 and 7.7 mg of ketone 8.

Aldehyde 6: $C_{20}H_{26}O_7$; oil; IR (film) ν_{max} 2860 and 2715 (aldehyde C-H), 1765 (γ-lactone), 1720 (aldehyde), 1670 and 1650 cm^{-1} (double bonds); mass spectrum, *m/e* 378 (M^+), 349 (M - CHO), 346 (M - CH_3OH), 335 [M - $(CH_3)_2CH$], 332 (M - C_2H_4O), 308 [M - $(CH_3)_2C{=}C{=}O$], 276 [M - CH_3OH - $(CH_3)_2C{=}C{=}O$], 258 (M - CH_3OH - isobutyric acid), 71 [$(CH_3)_2CHC{\equiv}O^+$, base peak], 43 ($CH_3C{\equiv}O^+$).

Ketone 8: $C_{20}H_{26}O_7$; oil; IR (film) ν_{max} 1750 (γ-lactone), 1735 (ester), 1720 (ketone), 1650 cm^{-1} (double bond); mass spectrum, *m/e* 378 (M^+), 346 (M - CH_3OH), 332 (M - 46), 321 (M - 57), 294 (M - 84), 276 [M - CH_3OH - $(CH_3)_2C{=}C{=}O$], 258 (M - CH_3OH - isobutyric acid), 71 [$(CH_3)_2CHC{\equiv}O^+$, base peak], 43 ($CH_3C{\equiv}O^+$).

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Registry No. **1a**, 74562-62-2; **1b**, 74562-63-3; **1c**, 74562-64-4; **1d**, 74562-65-5; **2a**, 74562-66-6; **2c**, 74577-77-8; **2d**, 74562-67-7; **3**, 67927-54-2; **4**, 67927-56-4; **5**, 74562-68-8; **6**, 74562-69-9; **7**, 74577-78-9; **8**, 74577-79-0; **9**, 74562-70-2; **10**, 74562-71-3.

Inhibitors of Sterol Biosynthesis. Synthesis of 9α-Fluoro-3β-hydroxy-5α-cholest-8(14)-en-15-one and Related Compounds[1]

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9α-Fluoro-3β-hydroxy-5α-cholest-8(14)-en-15-one has been prepared in 90% yield by treatment of 3β,9α-dihydroxy-5α-cholest-8(14)-en-15-one with HF-pyridine. These two compounds are potent inhibitors of sterol biosynthesis in animal cells in culture and the former compound has significant hypocholesterolemic action in animals. The latter compound was prepared in 78% yield by treatment of the $\Delta^{8,14}$-ethyl enol ether derivative of 3β-(benzoyloxy)-5α-cholest-8(14)-en-15-one with perchloryl fluoride and in 86% yield by hydrolysis of 3β-(benzoyloxy)-9α-hydroxy-5α-cholest-8(14)-en-15-one. The latter 9α-hydroxy ester was prepared by oxidation of the $\Delta^{8(14)}$-ethyl enol ether of 3β-(benzoyloxy)-5α-cholest-8(14)-en-15-one with either perchloryl fluoride or with *m*-chloroperbenzoic acid or by oxidation of 3β-(benzoyloxy)-5α-cholesta-8,14-diene with Jones reagent. 9α-Fluoro-5α-cholest-8(14)-ene-3,15-dione and 9α-hydroxy-5α-cholest-8(14)-ene-3,15-dione were prepared in high yield by oxidation of the corresponding 3β-hydroxysterols with pyridinium chlorochromate.

3β-Hydroxy-5α-cholest-8(14)-en-15-one (1) (Scheme I) is a potent inhibitor of sterol biosynthesis in L cells and in primary cultures of fetal mouse liver cells.[2,3] Moreover, this compound and a number of its derivatives have been shown to have significant hypocholesterolemic activity upon oral or subcutaneous administration to animals.[4-7]

Stimulated by these findings we sought the preparation of the 9α-fluoro derivative of 1. Our initial efforts toward this goal concentrated on the attempted 9α-fluorination of an enol ether of the α,β-unsaturated $\Delta^{8(14)}$-15-one derivative. Electrophilic fluorination by perchloryl fluoride to form a carbon-fluorine bond has found extensive use.[8,9] While treatment of enamines of Δ^4-3-ketosteroids with perchloryl fluoride has been reported to give products of mono- and difluorination at carbon atom 4,[10-13] the application of the same reaction to enol ethers and enol ethers of Δ^4-3-ketosteroids has been reported to give 6-fluorinated derivatives.[13-15] Accordingly, we sought to adopt the fluorination of the enol ethers of the Δ^4-3-ketosteroids to the case of the enol ether of $\Delta^{8(14)}$-15-ketosteroids. The ethyl enol ether (3) of 3β-(benzoyloxy)-5α-cholest-8(14)-en-15-one (2) and the enol ether (4) of 3β-hydroxy-5α-cholest-8(14)-en-15-one (1) were prepared in high yields by treatment of 2 and 1 with triethyl orthoformate and an acid catalyst, an adaptation of procedures described previously for the preparation of enol ethers of Δ^4-3-ketosteroids.[16,17] Treatment of 3 and 4 with perchloryl fluoride at -35 to -40 °C did not give the desired 9α-fluoro-$\Delta^{8(14)}$-15-ones as significant products but gave as the major products the corresponding 9α-hydroxy-$\Delta^{8(14)}$-15-one com-

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