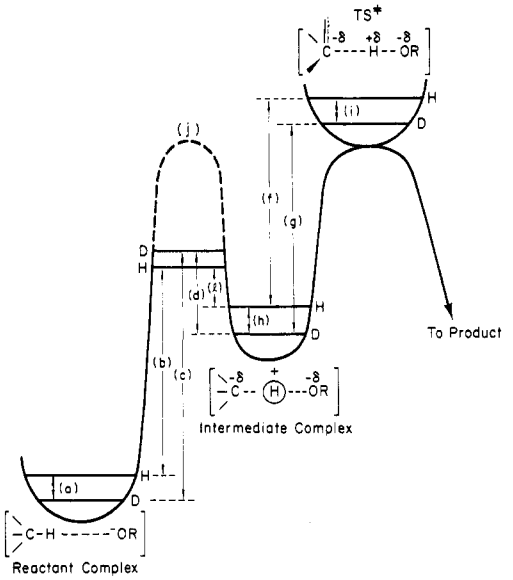

Figure 1. The activation quantities are as follows $a = [\Delta E_0]^H_D$, the ground-state zero-point energy difference for the corresponding C–H and C–D bonds to be ruptured in the TS‡ (=1.15 kcal/mol). $b = E_1^H$ = the energy requirement for reaching the level at which proton tunneling occurs. $c = E_1^D$ = the same energy term (as above) but involving deuteron tunneling. $d = E_{-1}^D$ = the energy required by the deuterated intermediate for tunneling of deuterium in the reverse direction. $e = E_{-1}^H$ = the same energy term (as above) for reverse proton tunneling. $f = E_2^H$ = the energy required by the protonated intermediate to reach the top of the barrier to its decomposition to products in the rate-determining step. $g = E_2^D$ = the corresponding energy term for the deuterated intermediate decomposition. $h = [\Delta E_0]^H_D$ (intermediate) = the zero point energy difference of H and D stretching vibrations in their respective intermediates. $i = [\Delta E_0]^H_D(TS^‡)$ = the zero-point energy difference for the corresponding C–H and C–D bonds in the TS‡ (=1.15 kcal/mol). $[\Delta E_a]^H_D$ (reaction) = $[\Delta E_0]^H_D$ (reactant) – $[\Delta E_0]^H_D(TS^‡)$; i.e., $[\Delta E_a]^H_D = a - i = 0$. j is the classical barrier to proton abstraction. The height of this barrier has been arbitrarily drawn to be approximately equal to that for decomposition of the intermediate to form product. This was done on the (perhaps unjustifiable) assumption that if the width of this barrier had been sufficient to preclude tunneling, the probabilities of the intermediate to proceed in either the forward or reverse direction were similar. The observed $k_H/k_D = 1.228$ was modeled by the internal return mechanism which assumes a significant isotope effect for the second step, i.e., $k_2^H \neq k_2^D$. The kinetic expression used is the following: Parameter values yielding the lowest sum

$$\ln\left[\frac{k^H_{calcd}}{k^D_{calcd}}\right] = \left[\frac{(E_1^D - E_{-1}^D) - (E_1^H - E_{-1}^H) + (E_2^D - E_2^H)}{RT}\right] + \ln\left[\frac{1 + (A_2/A_{-1})\exp[(E_{-1}^D - E_2^D)/RT]}{1 + (A_2/A_{-1})\exp[(E_{-1}^H - E_2^H)/RT]}\right]$$

of variances and percent differences of less than 0.21 on comparing k^H_{obsd}/k^D_{obsd} to k^H_{calcd}/k^D_{calcd} are as follows: (1) $E_2^D - E_2^H = 0.231$ kcal/mol; (2) $E_{-1}^H - E_2^H = -2.000$ kcal/mol; (3) $E_{-1}^D - E_{-1}^H = 2.000$ kcal/mol; (4) $E_1^D - E_1^H = 1.769$ kcal/mol; (5) $A_2/A_{-1} = 0.3$; (6) $E_{-1}^D - E_2^D = -0.231$ kcal/mol. These also result in values for (7) $\Delta H_1^D - \Delta H_1^H = (E_1^D - E_1^H) - (E_{-1}^D - E_{-1}^H) = -0.231$ kcal/mol. The fact that the $E_{-1}^D - E_2^D$ and the $\Delta H_1^D - \Delta H_1^H$ values are identical and opposite in magnitude to the $E_2^D - E_2^H$ value is a fortuitous circumstance that was realized after numerous computer iterations yielded the parameter values 1–5. Likewise, the equivalence of the $E_{-1}^H - E_2^H$ and the $E_{-1}^D - E_{-1}^H$ absolute values is purely the result of arriving at the "best" solution through many computer loops.

differs by less than 1% from that of the initial **3**.

This result is taken to signify that double bond development in the TS‡ has not proceeded more than halfway, i.e., much less than full sp^2 character has developed at C_α, corresponding to considerably less than complete C–Br bond breaking. In point, of fact, the $(k_H/k_D)_\alpha$ per deuterium found for **3** is even less than is reported[10b] for β-phenylethyl bromide **4**, one of the most typical E2 substrates. It can be regarded as evidence of a reactant-like structure of the TS‡. This is a somewhat surprising result, since the additional $COOCH_3$ group at C_α (compared to **4**) would be expected to encourage the development of sp^2 character. Evidently, the conjugation with a COOR group, such as it is, affords very little driving force in the development of an ElcB reaction TS‡. It is the inductive effect of this substituent which is influencing the course of elimination.

Acknowledgment. We are grateful for the support of this work by the National Science Foundation under Grant CHE 7911110.

Registry No. 2, 79722-34-2; **3**, 79722-35-3.

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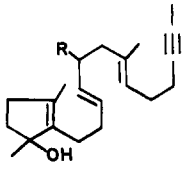
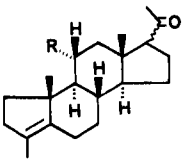
Corticoid Synthesis via Vinylic Fluoride Terminated Biomimetic Polyene Cyclizations[1]

Summary: Acid-catalyzed cyclization of substrate **8**, having a *pro-C(11)*-oxy group and a vinylic fluoride terminator, proceeds with significantly higher regio- and stereoselectively than in the case of the cyclization of the related substrate **3** with the methylacetylenic terminator to give a 58% yield of **5** which is convertible (seven steps) into hydrocortisone acetate.

Sir: By far the most important reaction in the biomimetic polyene cyclization approach to corticoids is the multiring closure step, i.e., the acid-catalyzed transformation of **2** into



1 (R = H)
2 (R = HO)
3 (R = Me_3SiO)



4 (R = H)
5 (R = AcO)

tetracyclic material, consisting mainly (after acetylation) of substance **5**. This latter material is readily converted (two steps) into 11α-hydroxyprogesterone, the key intermediate in the Upjohn method for producing hydrocortisone acetate.[2]

Recently it was disclosed[3] that the vinylic fluoride terminated cyclization **6** → **4** proceeded with exceptionally

(1) For a recent paper in the series on biomimetic polyene cyclizations see: Johnson, W. S.; Frei, B.; Gopalan, A. S. *J. Org. Chem.* **1981**, *46*, 1512–1513.
(2) (a) Johnson, W. S.; Escher, S.; Metcalf, B. W. *J. Am. Chem. Soc.* **1976**, *98*, 1039–1041. (b) Johnson, W. S.; Brinkmeyer, R. S.; Kapoor, V.M.; Yarnell, T. M. *Ibid.* **1977**, *99*, 8341–8343.
(3) Johnson, W. S.; Daub, G. W.; Lyle, T.A.; Niwa, M. *J. Am. Chem. Soc.* **1980**, *102*, 7800–7802.

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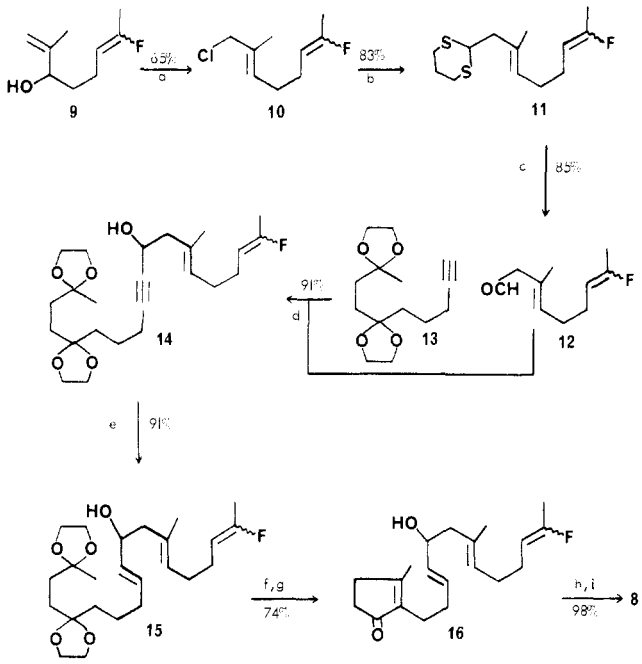
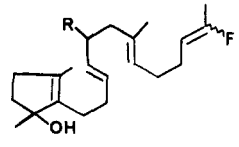
Scheme I



[a] 4.0 molar equiv of $SOCl_2$ in CCl_4 added over 3.5 h, then 1.3 h at 24 °C. [b] 1.1 molar equiv of lithiodithiane, THF, 6.5 h, −78 to −15 °C. [c] 9 molar equiv of CH_3I, 4 molar equiv of $CaCO_3$, 4:1 CH_3CN-H_2O, 16 h, 23 °C. [d] 1.1 molar equiv of Li salt of 13, DME, 1.5 h, −20 to +10 °C. [e] 3.0 molar equiv of $NaAlH_2(OCH_2CH_2OCH_3)_2$, THF, 4 h, reflux. [f] To give the dione: 0.5 molar equiv of pyridinium *p*-toluenesulfonate, 19:1 acetone-H_2O, 6.5 h, reflux. [g] To give 16: 4:4:1 THF-CH_3OH-5% NaOH, 4 h, reflux. [h] To give Me_3Si ether of 16: 20:1:1 THF-pyridine-bis(trimethylsilyl)acetamide, 18 h, 21 °C. [i] To give 8: excess CH_3Li-LiBr, Et_2O, −78 °C (two treatments).

high regio- as well as stereoselectivity, giving a 78% yield of tetracyclic material 95% of which was the product **4** (mixture of interconvertible 17α and 17β epimers) having natural steroidal constitution. This result is to be compared with the considerably less selective methylacetylenic-terminated cyclization **1** → **4** which afforded tetracyclic material (77% yield), 26% of which consisted of regio- and stereoisomeric forms of the desired (naturally constituted) product **4**.

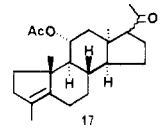
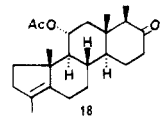
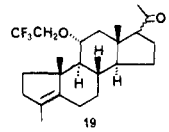
This favorable cyclization result obtained with **6** has prompted us to examine the cyclization of the related *pro-C(11)*-hydroxy substrate **7**, and the present paper discloses the results of such a study which includes the development of an improved cyclization procedure for **2** as well as **7** along with a detailed comparative product analysis.



6(R=H)
7(R=HO)
8(R=Me_3SiO)

The synthesis of the fluoro cyclization substrate was accomplished by the sequence shown in Scheme I which is similar to the method previously used for the preparation of **2**.[2a] Thus the known fluoro allylic alcohol **9**[3] (mixture of *E* and *Z* isomers), on treatment with thionyl chloride, gave the rearranged allylic chloride **10**[4b,5] which on reaction with the anion of dithiane was converted into the alkylation product **11**.[4d,5] Hydrolysis of **11** afforded the aldehyde **12**[5] which, on treatment with the anion of the known acetylenic diketal **13**,[2a] gave the adduct **14**.[4a,5] Stereoselective reduction of this propargylic alcohol to the *E* allylic alcohol **15**[5] followed by deketalization afforded the diketone[5] corresponding to **15** which, on cyclodehydration, was transformed into the enone **16**.[4a,5] Complete conversion of **15** into **7** required several treatments with methyllithium because of considerable competition from enolate formation which appeared to be catalyzed by the alkoxide ion at *pro-C(11)*. Thus when **16** was converted into its trimethylsilyl ether,[4a,5] two treatments with methyllithium gave tthe cyclopentenol **8** in quantitative yield. Under cyclization conditions this material first underwent very rapid desilylation (giving **7** in situ); hence, **8** was used directly and without purification in the studies described below.

Table I. GC Product Distribution (in Percent) of Tetracyclic Material Produced from Cyclization of Substrates 3 and 8

	3		8	
	crude product	chromatographed product (47% yield)	crude product	chromatographed product (58% yield)
normal product 5 (17α and 17β epimers)	68.5	90	79.5	97
	12	0	3.3	0.7
	4.5	5.3	0	0
	2.2	0	6.8	0
unidentified products	13	4.4	10.5	2.1

Conditions for the cyclization of **3** and of **8** were developed by performing small-scale experiments with equilenin methyl ether added as an internal GC standard and analyzing the products on a 7.5-m OV-101 glass-capillary gas chromatograph. In this way the following points were demonstrated. (a) Formation of side products is suppressed at lower temperatures; however, at reaction temperatures below −15 °C the reaction is too slow to be practical. (b) High dilution is beneficial, suppressing formation of high molecular weight material probably resulting from dimerization involving the cyclopentenyl cation.[6] (c) Trifluoroethanol is an effective solvent and

(4) The product was purified by (a) chromatography on Florisil, (b) chromatography on silica gel, (c) distillation at reduced pressure through a short Vigreux column, and (d) distillation through a Kugelrohr apparatus by using a Büchi Kugelrohrofen or through a short-path apparatus (for high-boiling compounds and/or small amounts of material).

(5) (a) The NMR and IR spectra were consistent with the assigned structure. (b) A satisfactory combustion analysis was obtained for an appropriately purified specimen of this compound.

(6) Cf.: Deno, N. C.; Richey, H. G.; Friedman, N.; Hodge, J. D.; Houser, J. J.; Pittman, C. U. *J. Am. Chem. Soc.* **1963**, *85*, 2991-2995.

substitution of it by significant amounts of other solvents, e.g., 1,1-dichloroethane, generally resulted in increased complexity of the product mixture. (d) Trifluoroacetic acid was the best of several catalysts tried, and the optimum concentration at −15 °C was about 20%; higher concentrations favored formation of the trifluoroethyl ether **19** (see Table I) evidently produced by solvolysis of the *pro-C(11)* allylic hydroxyl group prior to cyclization. (e) Under the aforementioned preferred conditions the maximum yield was realized after a reaction time of about 24 h. Since the product composition remained unchanged when the mixture was kept at −15 °C for more than 1 week, it seemed that the desired dilution effect (see item b above) could be realized by adding daily increments of substrate over a period of 1 week.

From the information generated by the preliminary studies described above, preparative cyclizations were performed. Thus a solution of 209 mg of the silyl ether **8** in 5 mL of 1,1-dichloroethane was added in five equal portions over 23-h intervals to a stirred solution of 20% trifluoroacetic acid in trifluoroethanol at −15 °C. Each portion of substrate was added over a 10-min period and between additions the reaction mixture was allowed to stand in the freezer at −15 °C. After 51 h the solvents were removed at reduced pressure, and the residue was dissolved in 35 mL of methylene chloride and treated with 30 mL of 2 M methanolic KOH for 5 min at 23 °C. The crude product was acetylated (C_5H_5N, Ac_2O, 16 h, 22 °C), and the GC product analysis of the resulting mixture is shown in Table I. Purification[4b,d] gave 106 mg (58% yield) of material containing 97% of the desired products **5** (see Table I).

The same procedure was employed for the cyclization of the substrate **3** to give the product distribution shown in Table I. Purification[4a,d] afforded a 47% yield of material containing 90% of the desired products **5** (see Table I).

The product **5** was identified by GC (coinjection), NMR, and IR comparisions with authentic specimens[2a] of the interconvertible 17α and 17β epimers. Crystallization afforded the racemic 17β form [mp 108–110 °C lit.[2a] 108–110 °C) and the racemic 17α epimer,[5] mp 160–162 °C. Similarly, the more stable (17α) form of the 13α (C/D, cis) isomer **17** was compared with authentic material that had been converted, by ozonolysis followed by cyclodehydration of the resulting δ-diketone, into 11α-hydroxy-13α-progesterone, the structure of which was established by single-crystal X-ray diffraction analysis.[7] The D-homo structure **18**, which is a tentative assignment based on NMR and IR properties, is analogous to the presumed structure of a byproduct in the cyclization of **1**.[8] The constitution of the more stable, probably the 17β, form of the ether **19** has been established by ^{19}F NMR, IR, and mass spectral (M^+, m/e 398) analysis.

It is concluded from the results set forth in Table I that the vinylic fluoride terminated cyclization of substrate **8** is highly regio- and stereoselective, much more so than the methylacetylenic-terminated cyclization of **3**.

Acknowledgment. We are indebted to the National Institutes of Health and the National Science Foundation for support of this research. T.A.L. was the recipient of an NIH postdoctoral fellowship.

Registry No. 3, 58404-34-5; (±)-**5** (α isomer), 65166-73-6; (±)-**5** (β isomer), 58404-30-1; **7**, 79827-51-3; **8**, 79827-52-4; (*E*)-(+−)-**9**, 79827-53-5; (*Z*)-(+−)-**9**, 79827-54-6; **10**, 79827-55-7; **11**, 79827-56-8; **12**, 79827-57-9; **13**, 43001-29-2; (±)-**14**, 79839-10-4; (±)-**15**, 79827-58-0; (±)-**15** diketone derivative, 79827-59-1; (±)-**16**, 79827-60-4; (±)-**16** TMS ether, 79839-07-9; (±)-**17** (α-isomer), 79896-00-7; (±)-**17** (β-isomer), 79896-38-1; (±)-**18**, 79839-08-0; (±)-**19** (α isomer), 79839-09-1; (±)-**19** (β-isomer), 79896-39-2.

(7) Johnson, W. S.; Kapoor, V. M.; Schubert, U., unpublished studies.
(8) See footnote 4 of ref 3.

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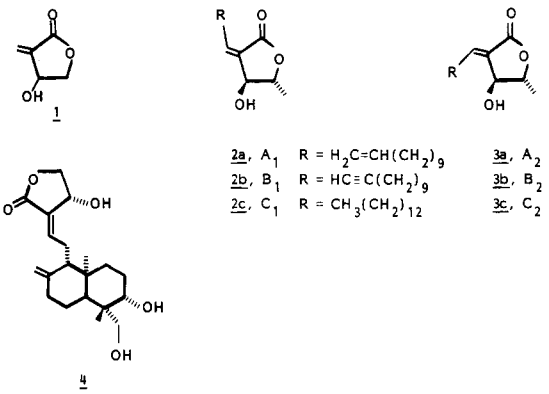
Stereochemistry of Deconjugative Alkylation of Ester Dienolates. Stereospecific Total Synthesis of the Litsenolides

Summary: Deconjugative protonations, alkylations, and aldol condensations of the dienolates from (*Z*)-2-alkenoates give the corresponding (*E*)-3-enoate products, whereas dienolates from (*E*)-2-enoates give mainly the (*Z*)-3-enoate products. These generalizations are exploited in stereospecific total syntheses of litsenolides A_2, B_2, and C_2.

Sir: The 3-alkylidene-4-hydroxy-2(3*H*)furanone (AHF) system is a common structural feature of polyoxygenated natural products, as exemplified by the compounds tulipalin B (**1**),[1] the litsenolides (**2**, **3**),[2] the mahubalactones,[3] the obtusilactones,[4] and andrographolide (**4**).[5] Despite the relative simplicity of the AHF moiety, no general synthesis of the AHF structure exists which offers control of substituent stereochemistry.[6]



Our interest in devising a stereospecific route to the AHF system, with particular focus on the litsenolides, has led us to examine the stereochemistry of the deconjugative alkylation of the dienolate ions derived from pure geometric isomers of 2-alkenoate esters. Prior to this research it has been well established that such alkylations occurred

(1) Tschesche, R.; Kämmerer, F.-J.; Wulff, G. *Chem. Ber.* **1969**, *102*, 2057.
(2) Takeda, K.; Sakwawi, K.; Ishü, H. *Tetrahedron* **1972**, *28*, 3757.
(3) Martinez, J. C. V.; Yoshida, M.; Gottlieb, O. R. *Tetrahedron Lett.* **1979**, 1021.
(4) Niwa, M.; Iguchi, M.; Yamamura, S. *Chem. Lett.* **1975**, 655.
(5) Cava, M. P.; Chan, W. R.; Stein, R. P.; Willis, C. R. *Tetrahedron* **1965**, *21*, 2617 and references cited therein. The structure of andrographolide has recently been rigorously established by means of X-ray crystallographic analysis (Smith, A. B., III; Toder, B. H.; Carroll, P., private communication).
(6) The total synthesis of several Lauraceae lactones, including epilitsenolides C_1 and C_2, has been described recently by Rollinson, S. W.; Amos, R. A.; Katzenellenbogen, J. A. *J. Am. Chem. Soc.* **1981**, *103*, 4114. References to earlier studies in this field are given in that paper; see also Corbet, J.-P.; Benezra, C. *J. Org. Chem.* **1981**, *46*, 1441. Wollenberg, R. H. *Tetrahedron Lett.* **1980**, 3139.

0022-3263/82/1947-0163$01.25/0