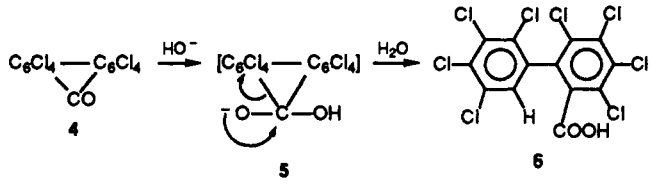
Table I. ESR Data on Radical-Anions (THF)

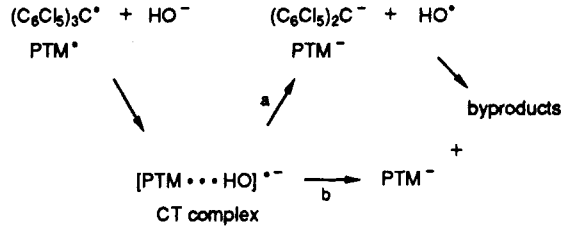
radical	linewidth, G	hyperfine coupling constants, G		
		α	bridgehead	ortho
PTM• (CCl_4)[a]	1.3	29.4	12.7[b]	10.7[b]
$^-$PTM-PTM•[c]	1.1	14.8[d]	5.5[d]	
$^-$O-PTM•	1.0	21.8	9.5[b]	7.9[b]
$^-$O-PTM•-P•TM-O$^-$	1.0	22.4	9.4[b]	8.0[b]

[a] Reference 12. [b] Data obtained from computer simulation. [c] Reference 22. [d] Hyperfine coupling constant halving.

Scheme IV



Scheme V



The ESR spectrum was taken from 0.5 to 25 h. The $^-$O-PTM• signal increased gradually up to 2 h, remaining constant thereafter (complete conversion of 1).

Perchlorodifuchsone (2). This diketone was obtained by hydrolysis of perchloro-α,α,α′,α′-tetraphenylbi-*p*-toluene-α,α′-diyliumhexachloroantimonate ($^+$PTM-PTM$^+$ $2SbCl_6^-$) in wet CH_2Cl_2.[21]

In an argon atmosphere, a drop (a great excess) of concentrated aqueous solution of $(n\text{-Bu})_4N^+$ HO^- was added to a solution of difuchsone **2** (0.007 g) in THF (1.5 mL) at room temperature. The ESR spectrum was also taken from 0.5 to 25 h, the ESR signal increasing gradually up to 2 h, and remaining constant thereafter (complete conversion of 2).

Reaction of Perchlorofluorenone (4) with $(n\text{-Bu})_4N^+$ HO^-. The perchlorofluorenone (4) was prepared from perchlorofluorene as described.[14] To a solution of 4 (0.152 g) in THF (35 mL) was added aqueous (40%) $(n\text{-Bu})_4N^+$ HO^- (3 mL) at room temperature in an argon atmosphere. The original deep-yellow solution became colorless immediately. After letting it stand (72 h), it was poured into diluted aqueous HCl, the mass was extracted with $CHCl_3$, and the organic layer washed with water, dried over anhydrous Na_2SO_4, and evaporated. The residue (0.154 g) was passed through silica gel in $CHCl_3$ containing a 2% of HCOOH, and by evaporation under vacuum and recrystallization of the residue (0.132 g), 2*H*-2′-carboxyoctachlorobiphenyl (**6**) was obtained (0.107 g; 77% yield): white solid; mp 191–193 °C; UV-vis (C_6H_{12}) 198 nm, 220 (sh), 285, 294 (ε 100000, 78000, 1265, 1270); IR (KBr) 3300–2700, 1720, 1535, 1435, 1415, 1375, 1345, 1335, 1265, 1232, 1180, 1120, 1078, 845, 655, 645, 620, 592, 525, 470 cm^{-1}. Anal. Calcd for $C_{13}H_2Cl_8O_2$: C, 32.9; H, 0.4; Cl, 59.9. Found: C, 33.2; H, 0.4; Cl, 60.0.

Acknowledgment. This research has been supported by the DGICYT (Ministerio de Educación y Ciencia, Spain) through Project PB87-0388. Thanks are due to Mrs. A. Diez for the ESR spectra, to Mr. A. Llebaria and Mr. J. Vidal for their experimental assistance, and to Drs. C. Rovira, J. Riera, and J. Castañer for their support. I.P. wishes to express her gratitude to the Spanish Ministry of Education and Science for a grant.

Synthesis of the 6-Benzoyl Derivative of 1-Deoxy-1-oxo-7-desacetylforskolin and an Unambiguous Assignment of the Absolute Stereochemistry of Forskolin

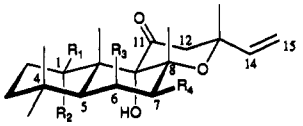
Leander J. Valdés III[1] and Masato Koreeda*

Department of Chemistry, The University of Michigan, Ann Arbor, Michigan 48109

Received June 6, 1990

Forskolin (1), isolated from the Indian mint *Coleus forskohlii*,[2] has attracted considerable interest due to its unique properties as an activator of adenylate cyclase to produce cyclic AMP in various eukaryotic systems.[3,4] In addition to its use as a tool in biochemical research, positive preclinical test results have led to scheduling of the clinical trial of forskolin as an antihypertensive agent.[5] The compound is also being studied as a possible bronchodilator, as an antithrombotic and antimetastatic agent, as a drug for the treatment for glaucoma, and as a cardiovascular agent.[3,6]

The absolute stereochemistry of forskolin was originally postulated as shown in 1 in 1977[1] by the application of the empirical Mills rule[7] to its 5-ene derivatives. This stereochemical proposal was subsequently corroborated through the statistical analysis of the X-ray data obtained for 7-desacetyl-7-bromoisobutyrylforskolin.[8,9] However, the calculated R_2 values[10] of the enantiomers (7.9 and 8.4%) used in this analysis might be deemed as being comparatively large for drawing an unequivocal conclusion. Therefore, in light of extreme biological significance of forskolin and its analogues, an independent, nonempirical validation of the absolute stereochemistry of forskolin was undertaken. We describe a novel, highly efficient method for the synthesis of a 6-benzoylated forskolin (5) involving the regioselective hydrolysis of the 6,7-cyclic orthoester intermediate 4 and an unambiguous assignment of the absolute stereochemistry of forskolin (1) by the use of the exciton chirality circular dichroism (CD) method[11] on the 6,7-dibenzoate derivative of forskolin (6).



1 R_1 = H; R_2 = R_3 = OH; R_4 = OAc
2 R_1, R_2 = O; R_3 = OH; R_4 = OAc
3 R_1, R_2 = O; R_3 = R_4 = OH
4 R_1, R_2 = O; R_3, R_4 = O-C(OCH$_3$)Ph (O)
5 R_1, R_2 = O; R_3 = OBz; R_4 = OH
6 R_1, R_2 = O; R_3 = R_4 = OBz

(1) Present address: School of Pharmacy, Northeast Louisiana University, Monroe, LA 71209.

(2) Bhat, S. V.; Bajwa, B. S.; Dornauer, H.; de Souza, N. J. *Tetrahedron Lett.* **1977**, 1669.

(3) For reviews, see: (a) Seamon, K. B.; Daly, J. W. *J. Cyclic Nucl. Res.* **1981**, *7*, 201. (b) *Adv. Cyclic Nucl. Res.* **1986**, *20*, 1. (c) Seamon, K. B. *Ann. Rep. Med. Chem.* **1984**, *19*, 293.

(4) de Souza, N. J.; Dohadwalla, A. N.; Reden, J. *Med. Res. Rev.* **1983**, *3*, 201.

(5) Bhat, S. V.; Dohadwalla, A. N.; Bajwa, B. S.; Dadkar, N. K.; Dornauer, H.; de Souza, N. J. *J. Med. Chem.* **1983**, *26*, 486.

(6) Khandelwal, Y.; Rajeshwari, K.; Rajagopalan, R.; Swamy, L.; Dohadwalla, A. N.; de Souza, N. J. *J. Med. Chem.* **1988**, *31*, 1872.

(7) Mills, J. A. *J. Chem. Soc.* **1952**, 4976.

(8) Paulus, E. F. *Z. Kristallog.* **1980**, *153*, 43.

(9) For the statistical analysis of X-ray data for the determination of the absolute stereochemistry, see: Hamilton, W. C. *Acta Crystallogr.* **1965**, *18*, 502.

(10) R_2 is defined as $[\Sigma w(F_o - F_c)^2/\Sigma wF_o^2]^{1/2}$.

(11) Harada, N.; Nakanishi, K. *Circular Dichroic Spectroscopy–Exciton Coupling in Organic Stereochemistry*; University Sci. Books: Mill Valley, CA, 1983.

0022-3263/91/1956-0844$02.50/0

Among the potential dibenzoate derivatives of 7-desacetylforskolin, the 6,7-dibenzoate should be ideally suited for the application of the exciton chirality CD method since the relative stereochemistry of the two benzoyloxy chromophores can be readily assessed due to the rigid, all-chair conformation of the forskolin ring system. A large number of hydroxy derivatives of 7-desacetylforskolin has been prepared in an effort to improve its pharmacological profile.[3,5,6,12,13] However, the esters of the 6-hydroxy group remain difficult to obtain in high yields because of its highly congested environment imposed by the three 1,3-diaxially juxtaposed methyl groups. At present, the base-catalyzed migration of the 7-acyl group of forskolin compounds appears to be the only viable means for the synthesis of 6-acylated forskolin analogues. For example, treatment of the 7-acetate with alumina (55%),[12] the 7-morpholinoacetate with LiN(TMS)$_2$ (31%),[13] the 7-aminoacetates with NaOMe at 0 °C (≈70%) or in piperidine at reflux (85%),[6] and the 7-acrylate with NaOH at room temperature (65%) or with n-Bu$_4$NF (85%)[6] resulted in acyl transfer onto the 6-hydroxyl group, providing the corresponding 6-monoester derivatives.

The direct introduction of the two benzoyl units onto the 6- and 7-hydroxyl groups of 1-deoxy-1-oxo-7-desacetylforskolin (**3**), obtained from the known 1-deoxy-1-oxoforskolin (**2**)[12] by mild alkaline hydrolysis, proved, as anticipated, to be difficult. The use of standard conditions (excess benzoyl chloride in pyridine at room temperature) resulted in the clean formation of the 7-monobenzoate. In contrast, treatment of **3** with excess benzoyl chloride or excess benzoic anhydride/4-(dimethylamino)pyridine (catalytic) in pyridine at higher temperatures or with a slight excess of benzoyl trifluoromethanesulfonate[14] at room temperature resulted in the formation of a complex mixture of products. However, on the basis of observations made by us[15] and others,[16] there appears to exist a general trend in the acid-catalyzed hydrolysis of cyclic orthoester derivatives of *cis*-cyclohexane-1,2-diols for the preferential formation of the axial monoesters.[17] Therefore, 6,7-diol **3** was first heated in trimethyl orthobenzoate in the presence of a catalytic amount of benzoic acid. The resulting cyclic orthoester **4** was immediately hydrolyzed under aqueous acidic conditions to afford monobenzoate **5** in 94% overall yield. The ^{1}H NMR analysis of this monobenzoate, ascertained through decoupling experiments, clearly indicated that the benzoate was introduced selectively onto the 6β-axial hydroxyl: $^3J_{5\alpha,6\alpha}$ = 2.6 Hz, $^3J_{6\alpha,7\alpha}$ = 4.4 Hz, and $^3J_{6\alpha,OH}$ = 3.0 Hz. Monobenzoate **5** was subsequently converted to 6,7-dibenzoate **6** with benzoyl chloride in pyridine.

The CD spectrum of dibenzoate **6** in 9:1 MeOH/dioxane showed a pair of Cotton effects with the opposite signs centered upon the UV absorption (227 nm) of the benzoate chromophore, indicating that these CD Cotton effects are the results of exciton splitting.[11] Therefore, the positive, longer wavelength Cotton effect ($\Delta\epsilon$ +15.18) at 239 nm clearly defines the positive chirality between the two electric transition dipoles of the benzoate chromophores

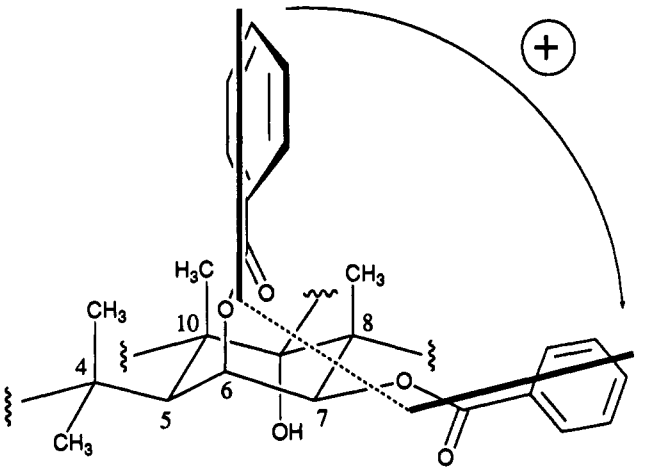


Figure 1.

assignable to the long axis $\pi \rightarrow \pi^*$ transitions[11] (see Figure 1), thus *unequivocally assigning the absolute stereochemistry of forskolin as given in 1*.

In summary, the independent, nonempirical assignment of the absolute stereochemistry described above has unambiguously confirmed the previously proposed absolute stereochemistry of forskolin, i.e., **1**.[2,8] In addition, in view of the availability of a wide range of both orthoester reagents and regioselectively hydroxy-protected forskolin derivatives, the one-pot, cyclic orthoester hydrolysis approach described above might serve as a general method for the synthesis of a wide variety of 6-acylated derivatives of forskolin.

Experimental Section

Forskolin (1). *Coleus forskohlii* was grown at the University of Michigan Matthaei Botanical Gardens. A voucher specimen has been deposited at the University Herbarium. Air-dried roots (430 g) of *C. forskohlii* were finely ground and extracted with ether (Soxhlet apparatus). After concentration in vacuo, the ether extract (27.5 g) was subjected to silica gel flash column chromatography (hexanes/EtOAc 7/3 followed by CH_2Cl_2/MeOH 50/1), yielding 1.03 g of pure forskolin (**1**), mp 229–232 °C. The ^{1}H and ^{13}C NMR and IR spectra, as well as the optical rotation of the forskolin thus isolated, were identical with those of the compound purchased from Calbiochem-Behring.[1]

8,13-Epoxy-7β-acetoxy-6β,9α-dihydroxylabd-14-ene-1,11-dione (1-Deoxy-1-oxoforskolin, 2) was prepared from forskolin (**1**) following the procedure described by Bhat et al.:[12] mp 200–202 °C (hexanes/EtOAc). The ^{1}H NMR and IR spectra of **2** were identical with previously reported data.[12]

8,13-Epoxy-6β,7β,9α-trihydroxylabd-14-ene-1,11-dione (7-Desacetyl-1-deoxy-1-oxoforskolin, 3). To 40 mg of 1-deoxy-1-oxoforskolin (**2**) in 8 mL of MeOH was added 140 mg of K_2CO_3 at 0 °C. After 3 h at room temperature, the reaction mixture was partitioned between 15-mL volumes of EtOAc and water. The organic layer was washed with 15 mL of water and dried in vacuo, yielding 35 mg of 7-desacetyl derivative **3** (97% yield): mp 162–164 °C (hexanes/EtOAc); $[\alpha]^{27}_D$ −11.5° (*c* 0.830, $CHCl_3$); ^{1}H NMR (360 MHz, $CDCl_3$) δ 1.08, 1.42, 1.50, 1.62, and 1.88 (all s, 3 H), 1.58 (ddd, 1 H, J = 13.8, 13.8, 4.2 Hz, 3α-H), 1.76 (ddd, 1 H, J = 13.8, 5.6, 3.5 Hz, 3β-H), 2.12 (dd, 1 H, J = 2.7, 1.2 Hz, 5-H), 2.20 (ddd, 1 H, J = 13.8, 4.2, 3.5 Hz, 2β-H), 2.29 (dd, 1 H, J = 1.3, 1.2 Hz, 6-OH), 2.38 (d, 1 H, J = 3.0 Hz, 7-OH), 2.39 (d, 1 H, J = 15.3 Hz, 12α-H), 3.22 (ddd, 1 H, J = 13.8, 13.8, 5.6 Hz, 2α-H), 3.45 (d, 1 H, J = 15.3 Hz, 12β-H), 4.09 (dd, 1 H, J = 4.1, 3.0 Hz, 7-H), 4.11 (s, 1 H, 9-OH), 4.42 (ddd, 1 H, J = 4.1, 2.7, 1.3 Hz, 6-H), 5.00 (dd, 1 H, J = 10.6, 0.5 Hz, 15-H), 5.21 (dd, 1 H, J = 17.4, 0.5 Hz, 15-H), 6.07 (dd, 1 H, J = 17.4, 10.6 Hz, 14-H); ^{13}C NMR (90.56 MHz, $CDCl_3$) δ 18.1 (q), 22.6 (q), 24.0 (q), 30.1 (q), 31.8 (q), 34.3 (s, 4-C), 35.6 (t, 2-C), 44.1 (t, 3-C), 49.4 (t, 12-C), 49.9 (d, 5-C), 56.4 (s, 10-C), 71.7 (d, 6-C), 74.6 (d, 7-C), 77.2 (s, 13-C), 81.1 and 82.8 (both s, 8- and 9-C), 110.3 (t, 15-C), 146.3 (d, 14-C),

(12) Bhat, S. V.; Bajwa, B. S.; Dornauer, H.; de Souza, N. J. *J. Chem. Soc., Perkin Trans. 1* **1982**, 767.
(13) Kosley, R. W., Jr.; Cherill, R. J. *J. Org. Chem.* **1989**, *54*, 2972.
(14) (a) Koreeda, M.; Brown, L. *J. Chem. Soc., Chem. Commun.* **1983**, 1113. (b) Brown, L.; Koreeda, M. *J. Org. Chem.* **1984**, *49*, 3875.
(15) Koreeda, M.; Akhtar, M. N.; Boyd, D. R.; Neill, J. D.; Gibson, D. T.; Jerina, D. M. *J. Org. Chem.* **1978**, *43*, 1023.
(16) King, J. F.; Allbutt, A. D. *Can. J. Chem.* **1970**, *48*, 1754.
(17) For insightful mechanistic discussions on this reaction, see: Deslongchamps, P. *Steric Effects in Organic Chemistry*; Pergamon Press: Oxford, 1983; pp 82–85.

205.1 (s, 11-C), 215.6 (s, 1-C); IR (KBr) 3510, 3460, 1725, 1701, 1690, 988, 919; MS (CI; NH_3; 40 eV) m/z 384 (M^+ + 18, 0.92), 368 (M^+ + 2, 12), 367 (M^+ + 1, 100), 349 (14), 331 (46), 288 (55), 271 (8), 156 (7), 94 (6). Anal. Calcd for $C_{20}H_{30}O_6$: C, 65.55; H, 8.25. Found: C, 65.65; H, 8.20.

8,13-Epoxy-6β-(benzoyloxy)-7β,9α-dihydroxylabd-14-ene-1,11-dione (6-Benzoyl-7-desacetyl-1-deoxy-1-oxoforskolin, 5). Trimethyl orthobenzoate (1.6 mL), 3 mg of benzoic acid and 48 mg of **3** were stirred at 105–110 °C for 3 h. Excess trimethyl orthobenzoate and methyl benzoate formed during the reaction were removed under vacuum (80 °C). The yellow-orange oily residue thus obtained (i.e., **4**) was immediately dissolved in 1.5 mL of THF and 0.5 mL of water treated with 6 drops of glacial acetic acid and 2 drops of concentrated HCl. After 22 h at room temperature, the reaction mixture was added to 10 mL of water and extracted three times with 15-mL portions of EtOAc. The combined organic layers were washed with water (2 × 10 mL) and were evaporated to dryness in vacuo, yielding 58 mg of 6-monobenzoate **5** (94% yield): mp 243–245 °C (hexanes/EtOAc); $[\alpha]^{25}_D$ +36.6° (*c* 0.791, $CHCl_3$); ^1H NMR (360 MHz, $CDCl_3$) δ 1.16, 1.18, 1.42, 1.66, 2.04 (all s, 3 H), 1.62 (m, 1 H, 3β-H), 1.76 (ddd, 1 H, *J* = 13.7, 5.5, 3.9 Hz, 3α-H), 2.12 (d, 1 H, *J* = 3.0 Hz, 7-OH), 2.25 (ddd, 1 H, *J* = 13.7, 3.9, 3.9 Hz, 2β-H), 2.42 (d, 1 H, *J* = 15.2 Hz, 12α-H), 2.52 (d, 1 H, *J* = 2.6 Hz, 5-H), 3.13 (ddd, 1 H, *J* = 13.7, 13.7, 5.5 Hz, 2α-H), 3.51 (d, 1 H, *J* = 15.2 Hz, 12β-H), 4.09 (s, 1 H, 9-OH), 4.36 (dd, 1 H, *J* = 4.4, 3.0 Hz, 7-H), 5.02 (dd, 1 H, *J* = 10.7, 0.7 Hz, 15-H), 5.22 (dd, 1 H, *J* = 17.2, 0.7 Hz, 15-H), 6.07 (dd, 1 H, *J* = 17.2, 10.7 Hz, 14-H), 6.14 (dd, 1 H, *J* = 4.4, 2.6 Hz, 6-H), 7.49 (dd, 2 H, *J* = 7.7, 7.7 Hz, Ar-H), 7.61 (tt, 1 H, *J* = 7.7, 1.4 Hz, Ar-H), 8.03 (dd, 2 H, *J* = 7.7, 1.4 Hz, Ar-H); ^{13}C NMR (90.56 MHz, $CDCl_3$) δ 18.1 (q), 21.9 (q), 23.5 (q), 30.1 (q), 31.8 (q), 34.0 (s, 4-C), 35.4 (t, 2-C), 43.5 (t, 3-C), 49.1 (d, 5-C), 49.6 (t, 12-C), 56.5 (s, 10-C), 72.3 (d, 6-C), 74.1 (d, 7-C), 77.3 (s, 13-C), 81.0 and 82.8 (both s, 8- and 9-C), 110.5 (t, 15-C), 128.7, 129.7, and 129.9 (all d, Ar-C), 133.3 (s, Ar-C), 146.0 (d, 14-C), 166.6 (s, ArCOO), 205.3 (s, 11-C), 214.0 (s, 1-C); IR (KBr) 3512, 1723, 1684, 1641, 994, 925 cm^{-1}; MS (CI; NH_3; 40 eV) m/z 488 (M^+ + 18, 16), 472 (M^+ + 2, 29), 471 (M^+ + 1, 100), 470 (M^+, 35), 453 (18), 436 (18), 435 (60), 393 (14), 392 (63), 348 (20), 331 (25), 285 (11), 226 (10), 156 (18), 139 (18), 139 (22), 105 (16), 94 (26). Anal. Calcd for $C_{27}H_{34}O_7$: C, 68.92; H, 7.28. Found: C, 68.83; H, 7.19.

8,13-Epoxy-6β,7β-bis(benzoyloxy)-9α-hydroxylabd-14-ene-1,11-dione (6,7-Dibenzoyl-7-desacetyl-1-deoxy-1-oxoforskolin, 6). To 15 mg of **5** and 6 mg of 4-(dimethylamino)-pyridine in 1 mL of pyridine was added 65 mg of benzoic anhydride at room temperature. After being stirred at room temperature overnight, the solution was treated with 1 mL of methanol. The resulting mixture was dried in vacuo and partitioned between 15-mL portions of EtOAc and 10% aqueous HCl. The organic layer was washed with 15-mL volumes of 10% aqueous $NaHCO_3$ and water and was taken to dryness in vacuo. Preparative HPLC (hexanes/EtOAc, 10/1) of the product yielded 15 mg of dibenzoate **6** (82% yield): mp 118–120 °C (hexanes/EtOAc); $[\alpha]^{24}_D$ +61.9° (*c* 0.832, $CHCl_3$); ^1H NMR (360 MHz, $CDCl_3$) δ 1.15, 1.20, 1.32, 1.81, 2.12 (all s, 3 H), 1.67 (ddd, 1 H, *J* = 13.7, 13.6, 4.1 Hz, 3β-H), 1.78 (ddd, 1 H, *J* = 13.7, 5.4, 4.6 Hz, 3α-H), 2.30 (ddd, 1 H, *J* = 13.9, 4.6, 4.1 Hz, 2β-H), 2.41 (d, 1 H, *J* = 14.6 Hz, 12α-H) 2.71 (d, 1 H, *J* = 2.6 Hz, 5-H), 3.08 (ddd, 1 H, *J* = 13.9, 13.6, 5.4 Hz, 2α-H), 3.56 (d, 1 H, *J* = 14.6 Hz, 12β-H), 4.03 (s, 1 H, 9-OH), 4.95 (dd, 1 H, *J* = 17.1, 1.0 Hz, 15-H), 5.26 (dd, 1 H, *J* = 10.6, 1.0 Hz, 15-H), 5.79 (d, 1 H, *J* = 4.5 Hz, 7-H), 5.89 (dd, 1 H, *J* = 17.1, 10.6 Hz, 14-H), 6.22 (dd, 1 H, *J* = 4.5, 2.6 Hz, 6-H), 7.31 (dd, 2 H, *J* = 8.1, 8.1 Hz, Ar-H), 7.48 (dd, 2 H, *J* = 7.8, 7.8 Hz, Ar-H), 7.50 (tt, 1 H, *J* = 8.1, 1.2 Hz, Ar-H), 7.62 (tt, 1 H, *J* = 7.8, 1.2 Hz, Ar-H), 7.85 (dd, 2 H, *J* = 8.1, 1.2 Hz, Ar-H), 7.90 (dd, 2 H, *J* = 7.8, 1.2 Hz, Ar-H); ^{13}C NMR (90.56 MHz, $CDCl_3$) δ 18.1 (q), 22.4 (q), 23.7 (q), 30.3 (q), 31.7 (q), 33.9 (s, 4-C), 35.3 (t, 2-C), 42.7 (t, 3-C), 48.4 (d, 5-C), 49.8 (t, 12-C), 56.3 (s, 10-C), 70.7 (d, 6-C), 74.7 (d, 7-C), 77.7 (s, 13-C), 81.2 and 82.1 (both s, 8- and 9-C), 110.5 (t, 15-C), 128.2, 128.7, 129.5, 129.6, 129.7, and 130.0 (all d, Ar-C), 132.8 and 133.3 (both s, Ar-C), 145.4 (d, 14-C), 165.7 and 166.3 (both s, ArCOO), 206.0 (s, 11-C), 212.6 (s, 1-C); IR (KBr) 3508, 1725, 1643, 987, 924 cm^{-1}; MS (CI; NH_3; 40 eV) m/z 593 (M^+ + 19, 13), 592 (M^+ + 18, 39), 576 (M^+ + 2, 32), 575 (M^+ + 1, 100), 557 (29), 529 (12), 497 (14), 496 (49), 436 (13), 435 (36), 313 (6), 285 (5), 245 (6). Anal. Calcd for $C_{34}H_{38}O_8$: C, 71.06; H, 6.66. Found: C, 70.94; H, 6.57. CD (MeOH/dioxane, 9/1): $\Delta\epsilon_{239}$ +15.18, $\Delta\epsilon_{227}$ 0, $\Delta\epsilon_{221}$ −2.43.

Acknowledgment. The National Institutes of Health (CA 25185) are gratefully acknowledged for financial support of this work. We thank Professor Christer Nordman for helpful discussions on the interpretation of the results from the statistical analysis of the X-ray data in connection with the determination of absolute stereochemistry.

Registry No. 1, 66575-29-9; 2, 81873-10-1; 3, 111511-64-9; 4, 130497-79-9; 5, 130497-80-2; 6, 130497-81-3.

Pyrolysis of β-Chlorine-Containing Esters, Vinyl Ether, and Alkene[1]

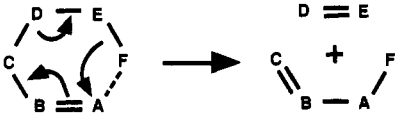
William J. Bailey† and Anatoli Onopchenko*,‡

Department of Chemistry, University of Maryland, College Park, Maryland 20742

Received April 16, 1990

Introduction

The synthetic utility of the pyrolysis reaction of acetates has been recognized for many years. This reaction proceeds via a cyclic, quasi-six-membered transition state, in which atoms A and C are oxygens, and the reaction is generally believed to be concerted. Several comprehensive review articles have been published.[2,3]



Over the years we, and others, were interested in finding out what other atoms would allow the six-membered cyclic process to operate. This led to pyrolysis of lactones,[4] esters in general,[5,6] vinyl ethers,[7] ketones,[8] olefins,[9] allyl sulfides,[10] β-hydroxy olefins,[11] β-hydroxy esters,[12] β-hydroxy ketones,[13] allylamines,[14] and carbamates.[15] In all of the compounds pyrolyzed, atoms A, B, C, D, or E were either carbon, sulfur, oxygen, or nitrogen. Atom F has always been the hydrogen atom.

White et al.[16] proposed a mechanism for the Claisen rearrangement involving a quasi-radical bond formation and bond cleavage in the transition state. It was reasoned that if the cyclic pyrolysis mechanism involved some radical character, either through an uncoupling of the electrons in the allylic bond or some $n\rightarrow\pi^*$ or $\pi\rightarrow\pi^*$ transition, then other atoms, including halogens should be capable of migration (atom F).

Yano and Bailey tested the above hypothesis by pyrolyzing 2,2,2-trichloroethyl vinyl ether and 2,2,2-trifluoroethyl vinyl ether to vinylidene chloride and vinylidene fluoride, respectively.[17] The pyrolysis of 2-chloroethyl vinyl ether was also briefly investigated, following the course of reaction by the amount of ethylene produced (33–80%).[17] The lowest yield of ethylene (33%), the statistical amount expected from a cyclic process, was obtained at low temperatures (<530 °C), but no mechanistic studies were carried out. We became interested in the pyrolysis of halogen-containing compounds to determine

† Deceased, December 17, 1989.

‡ Present address: Chevron Research and Technology Company, Richmond, CA 94802.

0022-3263/91/1956-0846$02.50/0