However, later reports by Schwartz, confirmed in our laboratory, have shown that complex I, which is charged and has fast leaving groups, is very active.[25] The anomolous activity of this complex may be attributed to the formation in vivo of II and III, which have superior activities and are less toxic than I. The hydroxo-bridged complexes have been shown to be substitutionally inert[4] and may not be easily sequestered to an ineffective and possibly toxic form in extracellular reactions. However, in intracellular reactions, the polynuclear complexes may undergo a slow equilibrium to the monomeric form. This may be promoted by ease of reaction of the monomer with DNA bases. This may provide the basis for a slow conversion of the polynuclear complexes to a monomeric aquated form that is responsible for the anticancer activity in intracellular reactions.[5e] Hence, it is tantamount to a slow release of the drug in its active form within the cell. Slow infusion or divided doses in the case of cisplatin produce less toxicity to the patient than the same dose given as a rapid push.[5e]

(25) P. Schwartz, S. J. Meischen, G. R. Gale, L. M. Atkins, A. B. Smith, and E. M. Walker, Jr., *Cancer Treat. Rep.*, **61**, 1519 (1977).

Acknowledgment. This work was supported in part by fellowship funds from Engelhard Corp. and International Nickel Co.

Registry No. 1, 81473-15-6; 1b, 82373-56-6; 11, 82398-34-3; 111, 82338-62-3; Pt(*trans*-dach)Cl_2, 38780-40-4; K_2PtCl_4, 10025-99-7.

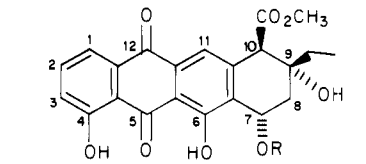
An Efficient Total Synthesis of (±)-Aklavinone[1]

Robert K. Boeckman, Jr.,* and F.-W. Sum

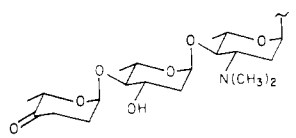
Contribution from the Department of Chemistry, University of Rochester, Rochester, New York 14627. *Received December 4, 1981*

Abstract: An 11-step total synthesis of (±)-aklavinone from 1,3-cyclohexadione is reported. The key steps include a Diels–Alder condensation of **3** and **4** and the stereoselective aldol condensation of **21** to **22**. The overall yield is ~13%.

Among the most promising of the new generation of anthracyclinone antitumor agents currently under clinical evaluation is aclacinomycin A (**1**).[2] Toxicity problems associated with



1, R =

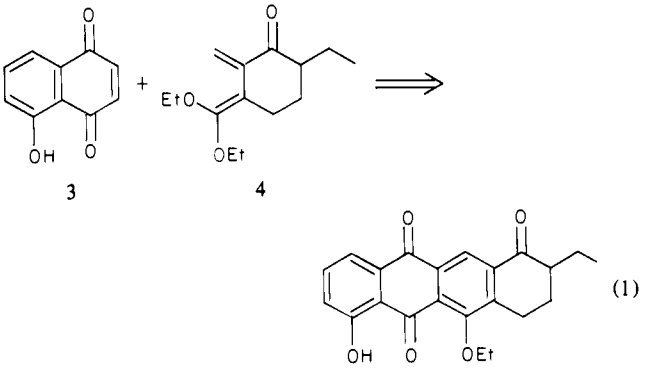


2, R = H

adriamycin appear to be reduced in the case of **1**.[2] Since microbiological methods permit transformation of the aglycon, (+)-aklavinone (**2**), to **1**,[3] there has been a significant effort directed torward the development of synthetic routes to **2**. Recently these efforts have culminated in four total syntheses of **2**.[4-6]

We also have been engaged in studies directed toward synthesis of **2** and report the results of our efforts, which have resulted in a short efficient total synthesis of **2**.

Our strategy for construction of the tetracyclic nucleus of **2** is based upon the combination of the two major synthons **3** and **4** by means of a Diels–Alder cycloaddition, as shown in eq 1.[7,8]



3 4

(1)

Preparation of cyclobutene **5**, the anticipated precursor of **4**, was initiated by a one-pot successive alkylation and acylation of the dianion of 1,3-cyclohexanedione, as indicated in Scheme I. The resulting mixture of enol pivalates is readily separated by preparative chromatography (20-g scale) and the minor isomer recycled to afford 72% of **6** after one recycle. Photolysis of **6** (1 equiv) and ketene diethyl acetal (6 equiv)[9] in ether at room

(1) Preliminary stages of this investigation were carried out at Wayne State University, Detroit, MI.

(2) (a) Oki, T.; Kitamura, I.; Yoshimoto, A.; Matsuzawa, Y.; Shibamoto, N.; Ogasawara, T.; Irui, T.; Takamatsu, A.; Takeuchi, T.; Masuda, T.; Hamada, S.; Suda, J.; Ishizuka, M.; Sawa, T.; Umezawa, H. *J. Antibiot.* **1979**, *32*, 791. (b) Oki, T.; Kitamura, I.; Matsuzawa, Y.; Shibamoto, N.; Ogasawara, Y.; Yoshimoto, A.; Irui, T.; Naganawa, H.; Takeuchi, T.; Umezawa, H. *Ibid.* **1979**, *32*, 801. (c) Taneka, H.; Yoshioka, T.; Shimauchi, Y.; Matsuzawa, Y.; Oki, T.; Irui, T. *J. Antibiot.* **1980**, *33*, 1323. (d) Yamaki, H.; Suzuki, H.; Mishimura, T.; Tanaka, N. *J. Antibiot.* **1978**, *31*, 1149. (e) Misumi, M.; Yamaki, H.; Akiyama, T.; Tanaka, N. *Ibid.* **1979**, *32*, 48.

(3) Oki, T.; Yoshimoto, A.; Matsuzawa, Y.; Takeuchi, T.; Umezawa, H. *J. Antibiot.* **1980**, *33*, 1331.

(4) (a) Kende, A. S.; Rizzi, J. P. *J. Am. Chem. Soc.* **1981**, *103*, 4247. (b) Pearlman, B. A.; McNamara, J. M.; Hasan, I.; Hatkeyama, S.; Sekizaki, H.; Kishi, Y. *Ibid.* **1981**, *103*, 4248.

(5) Confalone, P. N.; Pizzolato, G. *J. Am. Chem. Soc.* **1981**, *103*, 4251.

(6) (a) Model studies: Li, T.; Walsgrove, T. C. *Tetrahedron Lett.* **1981**, *22*, 3741. Total synthesis: Li, T.; Wu, Y. L. *J. Am. Chem. Soc.* **1981**, *103*, 7007. (b) Related Studies: Krohn, K. *Tetrahedron Lett.* **1981**, *22*, 3219.

(7) (a) Boeckman, R. K., Jr.; Delton, M. H.; Nagasaka, T. *J. Org. Chem.* **1977**, *42*, 2946. (b) Boeckman, R. K., Jr.; Delton, M. H.; Dolak, T. R.; Watanabe, T.; Glick, M. D. *J. Org. Chem.* **1979**, *44*, 4396.

(8) Boeckman, R. K., Jr.; Dolak, T. R.; Culos, K. O. *J. Am. Chem. Soc.* **1978**, *100*, 7098.

(9) McElvain, S. M.; Kundiger, D. "Organic Syntheses"; Wiley: New York, 1955; Collect. Vol. III, p 506.

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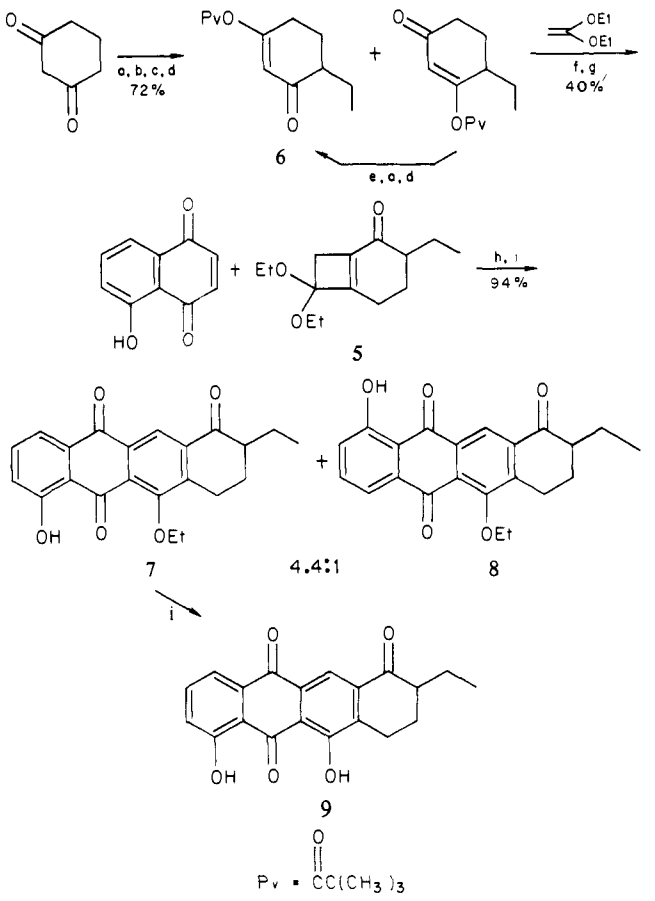
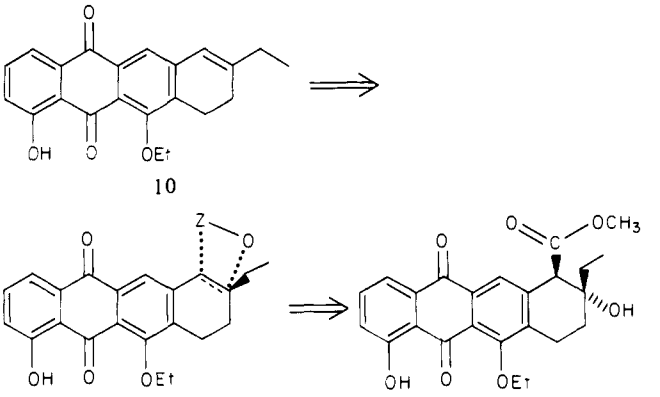
Scheme I[a]



[a] Reagents: (a) NaH (1.1 equiv)/THF/0 °C/0.5 h; (b) HMPA/*n*-BuLi (1.1 equiv)/0 °C/0.75 h; (c) CH_3CH_2I (1.1 equiv)/0 °C/0.67 h; (d) $[(CH_3)_3CCO]_2O$ (1.5 equiv)/−78 °C (1.5 h) → room temperature (12 h); (e) KOH/CH_3OH/room temperature; (f) *hν*(450 W Hg/corex filter)/ether/room temperature/40 h; (g) $LiOC_2H_5$/THF/room temperature/14 h; (h) mesitylene/175-180 °C/2 h; (i) $NaOCH_3$(cat)/O_2/CH_3OH/room temperature/0.5 h; (j) $AlCl_3$(excess)/PhH/room temperature/6 h.

temperature for 40 h (Corex filter/450-W medium-pressure Hanovia Hg lamp) afforded a mixture of cyclobutane photoadducts, which were directly treated with LiOEt in the THF (room temperature/14 h) to afford **5** in ~40% overall yield (two steps) after purification by chromatography.[10] The key Diels–Alder cycloaddition was conducted by heating **5** (1 equiv) and juglone (1 equiv)[11] in mesitylene at 175–180 °C (2 h), followed by an air oxidation to complete aromatization of the initial cycloadducts, which affords the readily separable (by crystallization) tetracyclic ketones **7** (mp 122–123 °C) and **8** (mp 158–159 °C) in 94% yield (4.4:1). The regiochemistry of the major adduct was confirmed by conversion to the known tetracyclic ketone **9**, which has been previously transformed to (±)-aklavinone by Confalone.[5,12]

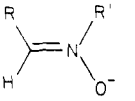
With a short efficient route to **7** secured, we turned our attention to introduction of the remaining functionality in ring A. We initially envisioned that the required interconversion could be effected by a cycloaddition process, as shown in eq 2, involving an olefin such as **10**. The required olefin **10** was readily prepared, as shown in Scheme II, by reduction of ketone **7** with $NaCNBH_3$ (excess) in THF methanol at pH 3 to afford a mixture of alcohols



(2)

11 and **12** in ~100% yield. Dehydration of **11** and **12** readily occurred upon heating the mixture of **11** and **12** in toluene in the presence of *p*-TsOH (cat) for 3 h to provide the desired olefin **10** in 74% overall yield from **7**. Dealkylation of **10** ($AlCl_3$/CH_2Cl_2/25 °C/5 h) afforded olefin **13**, which has been converted to (±)-decarbomethoxyaklavinone by Kende.[13]

The first method examined for introduction of the required one-carbon residue at C-10 and oxygen atom at C-9 into **10** was cycloaddition of a suitable nitrone to **10**, since LeBel has shown that oxidative cleavage of nitrone–olefin cycloadducts can afford hydroxy aldehydes and related products.[14] Further oxidation, methylation, and equilibration would then have afforded the desired β-hydroxy ester. However, reaction of **10** with a variety of nitrones such as **14–16** uniformly failed to afford a cycloadduct



14, R = Ph; R' = CH_3
15, R = COPh; R' = *t*-Bu
16, R = H; R' = *t*-Bu

with olefin **10**. The only product observed with *N-tert*-butylnitrone **16**,[15] among the most reactive of all nitrones known, was that of oxidative dimerization of **16**. Alternatively, we then attempted to induce cycloaddition of dichloroketene. A sequence involving Baeyer–Villiger oxidation of such an adduct and reductive silylation and ozonolysis in methanol, followed by equilibration, would then have afforded the desired system. Protection of the free phenolic hydroxyl (Ag_2O/CH_3I) afforded the methyl ether **17** in quantitative yield. Again, the olefin **17** proved resistant to addition of dichloroketene under all reaction conditions examined, including those developed recently by Hassner specifically for especially unreactive systems.[16]

Attempts were also made to introduce the required carbon by cleavage of epoxide **18**, which was readily prepared by epoxidation of **17** (MCPBA/CH_2Cl_2/25 °C/5 h). Epoxide **18** proved resistant to a variety of organometallic reagents. Where reaction with **18** did occur, spectral data of the products suggested that the quinone system had been attacked preferentially.

We then turned to examination of the reactivity of ketone **7** with Wittig reagents. The experience of Confalone suggested that kinetically the C-12 quinone carbonyl was most reactive.[17] Indeed, we have confirmed this reactivity sequence, although we had hoped that a more stabilized Wittig reagent might react reversibly with the C-12 carbonyl, permitting thermodynamic control, which

(10) Crude purification of the photolysis product by flash chromatography (SiO_2) prior to base treatment removes products derived from self-condensation of ketene diethyl acetal. After base treatment, purification was effected by prep 500 LC.

(11) Prepared in 40–50% yield by oxidation of purified 1,5-dihydroxynaphthalene (crystallization) with O_2/salcomine in DMF at room temperature (~2–3 h).

(12) We thank Drs. Confalone and Uskokovic of Hoffmann-La Roche for providing samples of **9** and **27** and spectral data for comparison.

(13) Kende, A. S.; Rizzi, J. P. *Tetrahedron Lett.* **1981**, *22*, 1779.

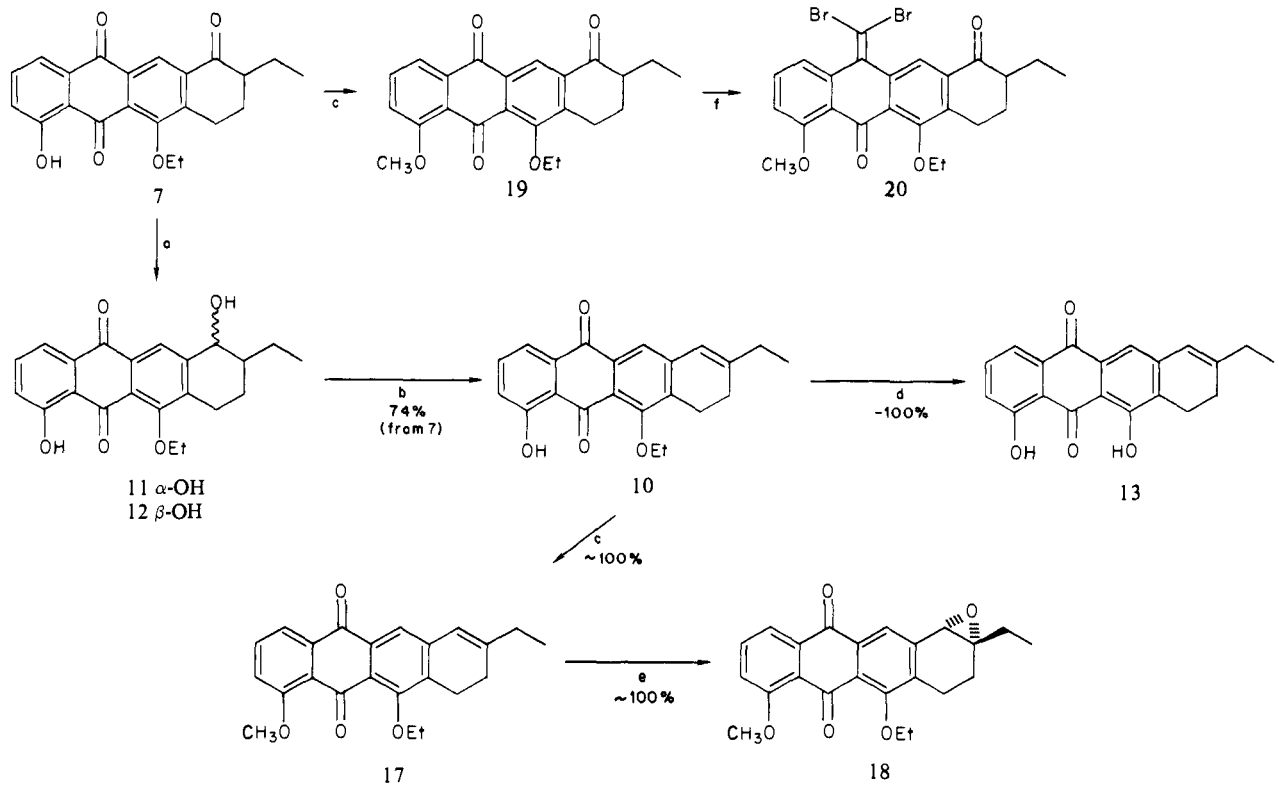
(14) LeBel, N. A.; Post, M. E.; Hwang, D. *J. Org. Chem.* **1979**, *44*, 1819.

(15) (a) Sims, J.; Houk, K. N. *J. Am. Chem. Soc.* **1973**, *95*, 5798. (b) Sims, J. Ph.D. Dissertation, Louisiana State University, Baton Rouge, LA 1973.

(16) (a) Krepski, L. R.; Hassner, A. *J. Org. Chem.* **1978**, *43*, 2879. (b) Hassner, A.; Krepski, L. R. *Ibid.* **1979**, *44*, 1376. (c) Bak, D. A.; Brady, W. T. *Ibid.* **1979**, *44*, 107.

(17) Private communication, P. N. Confalone.

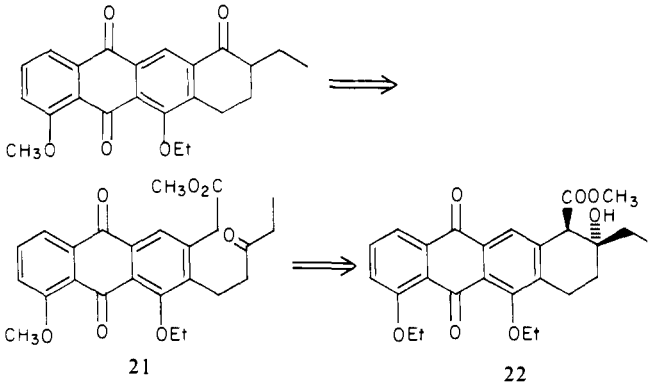
Scheme II[a]



[a] Reagents: (a) $NaCNBH_3$/HCl/MeOH–THF/60 h; (b) *p*-TsOH(cat)/$PhCH_3$/Δ/3 h; (c) $CH_3I/CH_2Cl_2/Ag_2O$/Δ/40 h; (d) $AlCl_3$ (excess)/CH_2Cl_2/5 h; (e) MCPBA/CH_2Cl_2/room temperature/5 h; (f) CBr_4/Ph_3P/PhH–$CHCl_3$/Δ/2 h.

should afford the desired adducts by reaction at C-10. Methylation of ketone **7** with Ag_2O/CH_3I affords the methyl ether **19** in quantitative yield. Treatment of **19** with CBr_4/Ph_3P in benzene/chloroform at reflux for 2 h provided a dibromo olefin in 86% yield. However, the structure of this substance was eventually established to be the undesired C-12 adduct **20** (Scheme II).

Since our attempts to functionalize the intact ring A in tetracyclic systems such as **7** and **10** had been frustrated, we altered our strategy. On the basis of the work of Krohn, it appeared that preparation of a seco derivative **21**, as shown in eq 3, would afford

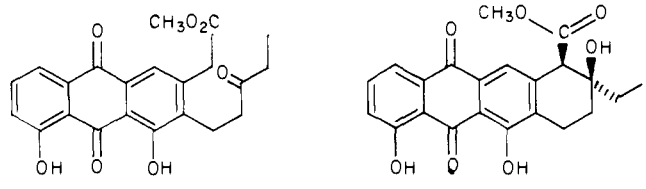


(3)

tetracyclic ester **22** possessing the required ring A functionality upon recyclization.[18] Kishi also adopted this general approach in his recently published total synthesis.[4b]

The successful application of this strategy for the efficient conversion of ketone **7** to (±)-aklavinone (**2**) is outlined in Scheme III. The route was initiated by conversion of **7** to methyl ether **19** as previously described, followed by treatment of methyl ether **19** with $Ac_2O/HClO_4$, which afforded the enol acetate **23** in approximately quantitative yield. The enol acetate **23** was directly ozonized at −78 °C in CH_2Cl_2 followed by successive treatment with dimethyl sulfide and aqueous base, affording keto acid **24** after acidification (~100%). The crude keto acid **24** was subjected to Arndt–Eistert homologation, providing the desired keto ester **21** in 63% overall yield from **7**.[19] The crucial cyclization was conducted with Triton B hydroxide in dry CH_3OH/CH_2Cl_2 (2:1) at −20 °C, affording a readily separable 4:1 mixture of the desired aldol **22** (mp 217–218 °C) and its stereoisomer **25** (mp 182–184 °C) in 95% yield. The undesired isomer could be equilibrated with Et_3N, affording a ~2:1 mixture of **22** and **25**, making the overall conversion to **22** quite efficient.

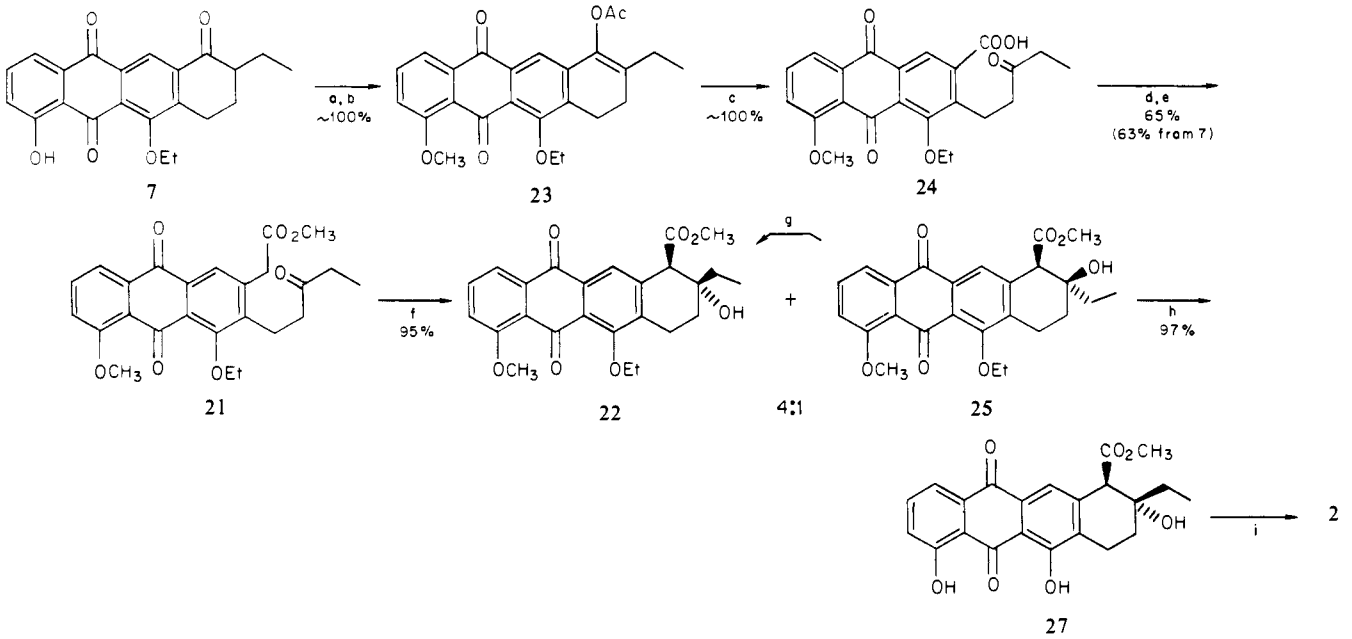
The stereoselectivity observed in this cyclization is superior to that observed by Kishi; however, the system studied by Kishi is complicated by the presence of an additional asymmetric center.[4b] Use of the Kishi cyclization conditions (K_2CO_3/CH_3OH/room temperature/2 h) for the conversion **21** → **22** + **25** afforded a mixture in which the undesired stereoisomer predominates (41:59 **22**/**25**). In aprotic media, the undesired isomer **25** is nearly the exclusive product. We have also observed that Triton B hydroxide in aprotic media behaves similarly. Use of low temperatures and short reaction times in addition to a protic reaction medium is crucial to obtaining maximum stereoselectivity in the desired sense. We have, furthermore, noted that extended reaction periods apparently result in equilibration of the carbomethoxyl group at C-10. For example, cyclization of **21** with Triton B hydroxide in CH_3OH/CH_2Cl_2 at −20 °C for 31 h affords a 1.5:1 ratio of **22** to **25**. Protection of the phenolic hydroxyl groups is also important, since cyclization of dealkylated keto ester **26**, prepared by



(18) Krohn, K.; Radeloff, M. *Chem. Ber.* **1978**, *111*, 3823.

(19) Bachmann, W. E.; Sheehan, J. C. *J. Am. Chem. Soc.* **1940**, *62*, 2687.

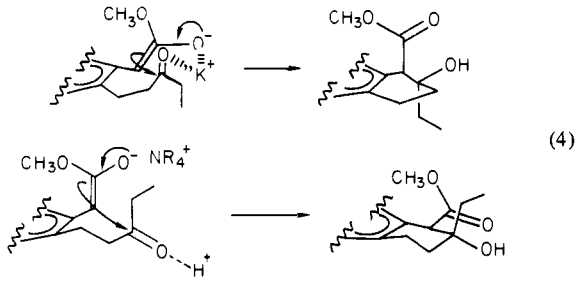
Scheme III[a]



[a] Reagents: (a) $CH_3I/Ag_2O/CH_2Cl_2/\Delta/40$ h; (b) $Ac_2O/HClO_4$(cat)$/CH_2Cl_2$/room temperature/3.5 h; (c) $O_3/CH_2Cl_2/-78$ °C/1 h; $CH_3SCH_3/-78$ °C → room temperature; aqueous NaOH extraction; (d) $SOCl_2$/Py (cat)$/CH_2Cl_2$/room temperature/4 h; CH_2N_2/Et_2O–THF/0 °C (0.5 h) → room temperature (0.5 h); (e) $Ag_2O/CH_3OH/\Delta/2$ h; (f) Triton B(OH^-)/anhydrous CH_3OH–CH_2Cl_2 (2:1)/−20 °C/2 h; (g) Et_3N/CH_2Cl_2/room temperature/12 h; (h) $AlCl_3$ (excess)$/CH_2Cl_2$/room temperature/40 h; (i) Br_2/CCl_4/AIBN/Δ/1 h; THF–H_2O (1:1).

treatment **21** with $AlCl_3$, with Triton B hydroxide in methanol at room temperature affords a product ratio of 45:55 (**27**/**28**) in which the undesired stereoisomer predominates.

Taken together, these results are consistent with the following mechanistic rationale. In aprotic media, cyclization proceeds by way of a transition state involving strong chelation to facilitate transfer of the metal ion in the poorly solvating medium (eq 4),



(4)

whereas in a protic medium, cyclization proceeds, under kinetic control, largely through a transition state that is nonchelating and is activated by carbonyl protonation by the protic medium—hence the importance of a protic medium and a nonchelating counterion ($PhCH_2N(CH_3)_3^+$). The products are clearly prone to equilibration, necessitating use of low temperatures and short reaction times to ensure minimal equilibration.

The final conversion of hydroxy ester **22** to (±)-aklavinone (**2**) was accomplished in a straightforward way. Dealkylation of **22** with excess $AlCl_3$ in CH_2Cl_2 afforded (±)-7-deoxyaklavinone (**27**) (mp 209–211 °C) in 97% yield which was identical in all respect with authentic samples (IR, NMR, MS).[12,20] (±)-7-Deoxyaklavinone (**27**) was transformed to (±)-aklavinone (**2**) (mp 211–213 °C) by the procedure of Kende involving homolytic bromination and solvolysis of the crude bromide in THF–H_2O (1:1).[4a] Thus, the above described route makes available (±)-aklavinone (**2**) in 11 steps in an overall yield of ~13% from readily available starting materials. It is of particular interest that the precursor to cyclization **21** is achiral, affording the possibility of an asymmetric synthesis of **2** by induction of chirality during cyclization. Efforts are currently being made to effect an enantioselective synthesis of **22** by inducing the cyclization of **21** → **22** by chiral catalysts.

(20) We thank Professor Kende for providing samples of **27** and **2** and spectral data for comparison.

Experimental Section

Melting points were determined on a Fisher-Johns hot stage melting point apparatus and are uncorrected. Infrared (IR) spectra were obtained on a Beckman Acculab 1R8 and are reported in wavenumbers (cm^{-1}) with polystyrene as standard. Nuclear magnetic resonance (NMR) spectra were recorded on Varian T60 (60 MHz), Varian EM390 (90 MHz), or Bruker WH-400 (400 MHz) spectrometers. Chemical shifts are reported in ppm (δ) downfield relative to tetramethylsilane (Me_4Si) as standard. Low-resolution mass spectra were obtained on a Du Pont 490-B spectrometer, and high-resolution spectra were obtained on a VG 7035 mass spectrometer. Elemental analyses were performed by Midwest Microlab, Indianapolis, IN.

All reactions were run under an inert atmosphere of Ar or N_2, and reactions requiring anhydrous conditions were performed in flame-dried or oven-dried (120 °C) apparatus. Vigorous stirring refers to mechanical overhead stirring. Solvents and anhydrous reagents were dried according to established procedures by distillation under argon from an appropriate drying agent: benzene, ether, THF (Na/benzophenone); DME (LAH); toluene, hexane, DMF (calcium hydride); piperidine, pyridine, triethylamine (barium oxide); $CH_2Cl_2(P_2O_5)$; methanol (magnesium).

Analytical TLC was performed on EM precoated silica gel plates (0.25 mm). Column chromatography was performed with E. Merck gel 60 (230–400 mesh), and preparative LC was performed with the Waters Prep 500 system on SiO_2.

3-Pivaloxy-6-ethyl-2-cyclohexen-1-one (6) and 3-Pivaloxy-4-ethyl-2-cyclohexen-1-one. To a suspension of washed NaH (10.56 g, 0.22 mol) in 1 L of anhydrous THF was added a solution of 1,3-cyclohexanedione (23.09 g, 0.2 mol) in 50 mL of anhydrous THF, and the mixture was stirred vigorously for 0.5 h. Anhydrous HMPA (350 mL) was then added and a clear light tan solution resulted. After this solution was cooled to 0 °C, 139 mL of a 1.58 M solution of *n*-butyllithium (0.22 mol) was added, and the resulting orange-tan suspension was stirred at 0 °C for 0.75 h. After this time period, the mixture was treated with 34.32 g (0.22 mol, 17.6 mL) of ethyl iodide (added rapidly), and stirring was continued for an additional 0.67 h at 0 °C. The mixture was then cooled to −78 °C and treated with 56 g (0.3 mol, 61 mL) of pivalic anhydride (added rapidly), and stirring was continued for 1.5 h at −78 °C followed by warming to room temperature over a period of 15 h.

The reaction mixture was poured into 600 mL of cold 10% $NaHCO_3$ solution and extracted with three 60-mL portions of a mixture of ether/hexane (1:1). The combined extracts were washed with water (2 × 500 mL) and saturated cupric sulfate solution (500 mL), dried over $MgSO_4$, and evaporated to afford 58.47 g of crude products.

Purification was effected by chromatography (~20-g runs) on SiO_2 with a Waters Prep 500 system, in ether/hexane (1:2), affording 26 g of enol ester **6** (58%) and 9.86 g (22%) of the regioisomeric enol pivalate. The regioisomeric material could be recycled by hydrolysis (KOH/methanol, 25 °C) and reacylation with pivalic anhydride in pyridine (25 °C) to afford an additional 5.9 g (14%) of **6** after one recycle. The overall yield of **6** was 31.9 g (72%).

Enol pivalate **6**: IR ($CHCl_3$) 1755, 1680 cm^{-1}; NMR (60 MHz/$CDCl_3$) δ 5.83 (t, J = 1 Hz, 1), 2.75–1.40 (m, 7), 1.33 (s, 9), 0.97 (t, J = 7 Hz, 3); high-resolution mass spectrum: calcd for $C_{13}H_{20}O_3$, 224.1412; found, 224.1413.

Regioisomeric enol pivalate: IR ($CHCl_3$) 1755, 1680 cm^{-1}; NMR (60 MHz/$CDCl_3$) δ 5.83 (t, J = 1 Hz, 1), 3.0–1.60 (m, 7), 1.30 (s, 9), 0.90 (t, J = Hz, 3); high-resolution mass spectrum: calcd for $C_{13}H_{20}O_3$, 224.1412; found, 224.1412.

3-Ethyl-7,7-diethoxybicyclo[4.2.0]-1(6)-octen-2-one (5). A solution of ketene diethyl acetal (29.0 g, 0.25 mol) and enol pivalate **6** (11.2 g, 0.05 mol) in 250 mL of anhydrous ether was degassed with an argon flow for 0.5 h and irradiated in a base-washed (KOH/CH_3OH) photolysis apparatus with a 450-W medium-pressure mercury arc lamp through a Corex sleeve by using a quartz immersion well for 37 h at room temperature. Vigorous magnetic stirring was maintained throughout the irradiation period.

The mixture was concentrated on the rotary evaporator. Preliminary purification was effected by flash chromatography on SiO_2 in ether/hexane (1:1). Further purification was effected by chromatography on SiO_2 in ether/hexane (1:8) by using the Waters Prep 500 system (flow rate 0.2 L/min), which provided 7.7 g of a mixture of cyclobutane photoadducts.

This mixture of adducts (7.7 g, 22.5 mmol) was dissolved in 50 mL of anhydrous THF and added to a suspension of *freshly prepared* dry LiOEt (2.34 g, 45 mmol) in anhydrous THF (300 mL) at room temperature under Ar. The resulting mixture was stirred at room temperature for 14 h and then shaken with a mixture of half-saturated aqueous NH_4Cl (400 mL) and ether (600 mL). The aqueous phase was further extracted with ether (4 × 125 mL), and the combined organic phases were washed with 100 mL of saturated NaCl solution, dried over $MgSO_4$, and concentrated.

The resulting crude elimination product was purified by chromatography on SiO_2 in ether/hexane (1:6) by using the Prep 500 system, affording the oily bicyclic enone **5** (4.75 g) in ~40% yield from enol pivalate **6**: IR ($CHCl_3$) 1675 cm^{-1}; NMR (60 MHz/$CDCl_3$) δ 3.73 (q, J = 8 Hz, 4), 2.86 (m, 2), 2.70–1.40 (m, 7), 1.33 (t, J = 7 Hz, 6), 1.01 (t, J = 7 Hz, 3); high-resolution mass spectrum: calcd for $C_{14}H_{22}O_3$, 238.1569; found, 238.1568.

9,10-Dihydro-11-ethoxy-8-ethyl-1-hydroxy-5,7,12(8*H*)-naphthacenetrione (7) and 7,8-Dihydro-6-ethoxy-9-ethyl-10-hydroxy-5,10,12(9*H*)-naphthacenetrione (8). A solution of cyclobutenone **5** (2.975 g, 12.5 mmol) and juglone (2.175 g, 12.5 mmol) in 50 mL of dry mesitylene was degassed with a stream of argon for 0.5 h and then heated at 172–175 °C (preheated oil bath) for 1.5 h (TLC indicated starting materials consumed), during which time the solution remained deep orange. The mesitylene was removed under high vacuum on a rotary evaporator, and the residue was dissolved in 200 mL of anhydrous CH_3OH. Solid $NaOCH_3$ (743 mg, 13.5 mmol) was added, and a stream of air was introduced with stirring for 1 h. The base was quenched by addition of 5% aqueous HCl until acidic (pH ≤5), the solvents were removed, and the residue was taken up in a mixture of 150 mL of ether and 40 mL of CH_2Cl_2. The aqueous phase was extracted with ether (2 × 75 mL), and the combined organic phases were washed with brine, dried over $MgSO_4$, and evaporated to afford 4.32 g (95% yield) of a crystalline mixture of **7** and **8** (4.4:1).

Fractional crystallization of this mixture from ether/hexane/CH_2Cl_2 afforded pure ketone **7** (mp 128–130 °C): IR ($CHCl_3$) 1695, 1673, 1638, 1588 cm^{-1}; NMR (60 MHz/$CDCl_3$) δ 12.90 (s, 1), 8.60 (s, 1), 8.0–7.0 (m, 3), 4.15 (q, J = 6.7 Hz, 2), 3.47–2.83 (m, 2), 2.70–1.73 (m, 5), 1.53 (t, J = 6.7 Hz, 3), 1.03 (t, J = 6.5 Hz, 1). Anal. Calcd for $C_{22}H_{20}O_5$: C, 72.51; H, 5.53. Found: C, 72.71; H, 5.61.

Ketone **8** (mp 158–159 °C) was also obtained: IR ($CHCl_3$) 1690, 1670, 1640, 1580 cm^{-1}; NMR (60 MHz/$CDCl_3$) δ 12.67 (s, 1), 8.61 (s, 1). 7.75–7.00 (m, 3), 4.10 (q, J = 7 Hz, 2), 3.53–1.75 (m, 7), 1.55 (t, J = 7 Hz, 3), 1.03 (t, J = 7 Hz, 3). Anal. Calcd for $C_{22}H_{20}O_5$: C, 72.51; H, 5.53. Found: C, 72.43; H, 5.56.

9,10-Dihydro-7-acetoxy-11-ethoxy-8-ethyl-1-methoxy-5,12-naphthacenedione (23). A solution of methyl ether **19** (756 mg, 2.0 mmol) in 20 mL of CH_2Cl_2 was treated with 2.0 mL of acetic anhydride (2.16 g, 21.6 mmol) and 0.2 mL of 70% perchloric acid, and the reaction mixture was stirred at room temperature under N_2 for 3.5 h. The mixture was diluted with 20 mL of CH_2Cl_2 and washed with 20 mL of half-saturated aqueous $NaHCO_3$ solution. The aqueous phase was extracted with CH_2Cl_2 (5 mL) 5 times. The combined organic solutions were dried over $MgSO_4$ and evaporated to afford 947 mg of crude **23** (~100%), sufficiently pure for further reactions: IR ($CHCl_3$) 1745, 1665, 1583 cm^{-1}; NMR (400 MHz/$CDCl_3$) δ 7.82 (d, J = 8.5 Hz, 1), 7.67 (s, 1), 7.63 (t, J = 8.5 Hz, 1), 7.30 (d, J = 8.5 Hz, 1), 4.07 (q, J = 7 Hz, 2), 4.01 (s, 3), 3.05 (t, J = 7.8 Hz, 2), 2.44 (t, J = 7.8 Hz, 2), 2.41 (s, 3), 2.21 (q, J = 7.5 Hz, 2), 1.51 (t, J = 7 Hz, 3), 1.09 (t, J = 7 Hz, 3); high-resolution mass spectrum: calcd for $C_{25}H_{24}O_6$, 420.1572; found, 420.1572.

4-Ethoxy-3-(3-oxopentyl)-5-methoxyanthraquinone-2-carboxylic Acid (24). A solution of enol acetate **23** (756 mg, 1.8 mmol) in 50 mL of anhydrous CH_2Cl_2 was ozonized with a Welsbach ozonizer (flow rate 0.4 L/min) for 1 h at −78 °C. The solution had become dark greenish blue at the end of this period. Excess ozone was purged by bubbling oxygen through the solution for ~0.25 h at −78 °C. The solution became yellow during this period. Excess dimethyl sulfide (2 mL) was then added and the mixture allowed to warm to room temperature. After about 1 h, the resulting suspension was extracted with aqueous 2 N NaOH solution (4 × 30 mL). The combined aqueous phases were acidified to pH 1 with concentrated HCl and extracted with ethyl acetate (6 × 30 mL). The combined ethyl acetate solutions were dried over $MgSO_4$ and evaporated to afford the desired keto acid **24** (740 mg, ~100%), which was pure enough for further use: IR ($CHCl_3$) 1710, 1678, 1487 cm^{-1}; NMR (400 MHz/$CDCl_3$) δ 8.48 (s, 1), 7.87 (d, J = 8 Hz, 1), 7.68 (t, J = 8 Hz, 1), 7.34 (d, J = 8 Hz, 1), 4.12 (q, J = 7 Hz, 2), 4.03 (s, 3), 3.27 (t, J = 8 Hz, 2), 2.90 (t, J = 8 Hz, 2), 2.47 (q, J = 7 Hz, 2), 1.52 (t, J = 7 Hz, 3), 1.08 (t, J = 7 Hz, 3); high-resolution mass spectrum: calcd for $C_{23}H_{22}O_7$, 410.1365; found, 410.1364.

Methyl (4-Ethoxy-3-(3-oxopentyl)-5-methoxy-2-anthraquinonyl)-acetate (21). Keto acid **23** (285 mg, 0.7 mmol), as obtained from the previous preparation, was dissolved in 2 mL of anhydrous CH_2Cl_2 under nitrogen and cooled to ~10 °C in ice water. A catalytic amount of pyridine (~0.001 mL) was added, followed by 0.08 mL of thionyl chloride (130 mg, 1.10 mmol). The resulting mixture was stirred at room temperature for 4 h. The reaction mixture was then evaporated to dryness, 1.0 mL of toluene added, and the mixture again evaporated to dryness.

The residue thus obtained that taken up in anhydrous THF (2 mL) was added to a cold (0 °C), dry (Na_2SO_4) solution of ethereal diazomethane (10 mL) whose concentration was ~0.7 mmol of diazomethane/mL of ether. The resulting mixture was stirred at 0 °C for 0.5 h and then at room temperature for 20 min. After evaporation of the solvents and excess diazomethane, the residue was dissolved in anhydrous methanol (10 mL), 100 mg of silver oxide (Ag_2O) was introduced, and the resulting suspension was heated at reflux for 1 h. At this time, an additional 100-mg portion of silver oxide was added, and reflux continued for 1 h. The cooled mixture was filtered free of solids through Celite and the filter cake washed thoroughly with CH_2Cl_2. The combined filtrates were evaporated to afford 308 mg of crude products. Purification was effected by chromatography on SiO_2 in hexane/ether/CH_2Cl_2 (1:1:2), affording 200 mg of the desired keto ester **21** (63% overall from ketone **7**): IR ($CHCl_3$) 1730 (br), 1670, 1585 cm^{-1}; NMR (400 MHz/$CDCl_3$) δ 7.85 (s, 1), 7.82 (d, J = 8.5 Hz, 1), 7.65 (t, J = 8.5 Hz, 1), 7.20 (d, J = 8.5 Hz, 1), 4.12 (q, J = 7 Hz, 2), 4.02 (s, 3), 3.87 (s, 2), 3.73 (s, 3), 2.98 (t, J = 8 Hz, 2), 2.77 (t, J = 8 Hz, 2), 2.43 (q, J = 7 Hz, 2), 1.52 (t, J = 7 Hz, 3), 1.07 (t, J = 7 Hz, 3); high-resolution mass spectrum: calcd for $C_{25}H_{26}O_7$, 438.1678; found; 438.1679.

9,10-Dihydro-1,11-dihydroxy-8-ethyl-5,7,12(8*H*)-naphthacenetrione (9). To a suspension of anhydrous $AlCl_3$ (100 mg, excess) in 15 mL of anhydrous benzene was added a solution of ketone **7** (26 mg, 0.071 mmol) in benzene (1 mL) at room temperature under argon. After the solution was stirred 14 h at room temperature, the dark purple mixture was poured into a cold mixture of 5% HCl and saturated brine (10 mL) and extracted with ether until the extract was only pale yellow. The combined extracts were dried over $MgSO_4$, evaporated, and crystallized (CH_2Cl_2/ether/hexane) to afford 23 mg of ketone **9** (mp 204–205 °C): NMR (300 MHz/$CDCl_3$) δ 12.45 (s, 1), 11.95 (s, 1), 8.37 (s, 1), 7.84 (d, J = 7.5 Hz, 1), 7.70 (t, J = 7.5 Hz, 1), 7.29 (d, J = 7.5 Hz, 1), 3.24–3.17 (m, 1), 2.94–2.85 (m, 1), 2.51–2.44 (m, 1), 2.38–2.29 (m, 1), 2.03–1.88 (m, 2), 1.59 (quintet, J = 7.4 Hz, 1), 1.03 (t, J= 7.4 Hz, 3). This substance was identical with an authentic sample by TLC and all spectroscopic criteria.

9,10-Dihydro-11-ethoxy-8-ethyl-1-methoxy-5,7,12(8*H*)-naphthacenetrione (19). To a stirred suspension of ketone **7** (728 mg, 2.0 mmol) and silver oxide (Ag_2O) (1.392 g, 6 mmol) in 25 mL of CH_2Cl_2 at room temperature under argon was added 0.75 mL of methyl iodide (1.72 g, 10 mmol). The mixture was heated at reflux for 40 h. After the mixture was cooled, anhydrous $MgSO_4$ (excess) was added and stirring continued for 1 h. Filtration of the solids and concentration afforded as a solid residue 750 mg (99%) of essentially pure **19** (TLC

exhibited a single spot on SiO_2 in hexane/ether/CH_2Cl_2 (1:1:1)). Further purification was not necessary; however, ketone **19** was purified for analysis by recrystallization from ether/hexane to mp 134–135 °C: IR ($CHCl_3$) 1690, 1680, 1590 cm^{-1}; NMR (60 MHz/$CDCl_3$) δ 8.80 (s, 1), 7.93–7.27 (m, 3), 4.08 (q, J = 7 Hz, 2), 4.07 (s, 3), 3.40–1.60 (m, 7), 1.53 (t, J = 7 Hz, 3), 1.00 (t, J = 7 Hz, 3). Anal. Calcd for $C_{23}H_{22}O_5$: C, 73.00; H, 5.86. Found: C, 72.81; H, 5.74.

10(*R*,*S*)-Carbomethoxy-6-ethoxy-9(*R*,*S*)-ethyl-9(*R*,*S*)-hydroxy-4-methoxy-7,8,9,10-tetrahydro-5,12-naphthacenedione (22) and 10(*R*,*S*)-Carbomethoxy-6-ethoxy-9(*S*,*R*)-ethyl-9(*S*,*R*)-hydroxy-4-methoxy-7,8,9,10-tetrahydro-5,12-naphthacenedione (25). A solution of keto ester **21** (3 mg, 0.0068 mmol) in 0.3 mL of methanol/CH_2Cl_2 (2:1) was cooled to −20 °C in dry ice/CCl_4 under nitrogen. To this solution was added 0.02 mL of a 40% Triton B hydroxide solution in methanol. The orange-brown mixture was stirred at −20 °C for 2 h. The reaction mixture was treated with 0.5 mL of 2 N HCl solution to quench the base present and after an additional 5 min at −20 °C was poured into a mixture of methylene chloride (5 mL) and saturated brine (1 mL). The aqueous phase was separated and extracted with 3 mL of methylene chloride. The combined organic phases were washed with saturated brine (1 mL), dried over $MgSO_4$, and evaporated to afford ~3 mg (~100%) of crude products, which showed two components by TLC on SiO_2 (hexane/ether/CH_2Cl_2 (1:1:2)) of R_f ~0.2 and 0.3. Analysis of the mixture by NMR (400 MHz) indicated the ratio of **22** to **25** was ~4:1.

The mixture was readily separable by chromatography on SiO_2 in hexane/ether/CH_2Cl_2 (1:1:2) to afford the pure components **25** (0.57 mg), mp 182–184 °C (R_f 0.3), and **22** (2.28 mg), mp 217–218 °C (R_f 0.2). Total yield of both components was 95%.

Hydroxy ester **25**: IR ($CHCl_3$) 1712 (br), 1665, 1581 cm^{-1}; NMR (400 MHz/$CDCl_3$) δ 7.83 (d, J = 8.5 Hz, 1), 7.76 (s, 1), 7.65 (t, J = 8.5 Hz, 1), 7.30 (d, J = 8.5 Hz, 1), 4.20 (dq, J_1 = 14 Hz, J_2 = 7 Hz, 1), 4.06 (dq, J_1 = 14 Hz, J_2 = 7 Hz, 1), 4.02 (s, 3), 3.92 (s, 1), 3.86 (s, 3), 3.13 (dt, J_1 = 18 Hz, J_2 = 7 Hz, 1), 3.07 (s, 1), 2.90 (dt, J_1 = 18 Hz, J_2 = 7 Hz, 1), 2.26 (dt, J_1 = 14 Hz, J_2 = 7 Hz, 1), 1.77 (dt, J_1 = 14 Hz, J_2 = 7 Hz, 1), 1.58 (dq, J_1 = 14 Hz, J_2 = 7.5 Hz, 2), 1.52 (t, J = 7 Hz, 3), 0.99 (t, J = 7.5 Hz, 3); high-resolution mass spectrum: calcd for $C_{25}H_{26}O_7$, 438.1678; found, 438.1674.

Hydroxy ester **22**: IR ($CHCl_3$) 1725, 1665, 1580 cm^{-1}; NMR (400 MHz/$CDCl_3$) δ 7.83 (d, J = 8.3 Hz, 1), 7.82 (s, 1), 7.64 (t, J = 8.3 Hz, 1), 7.30 (d, J = 8.3 Hz, 1), 4.14 (m, 2), 4.02 (s, 3), 3.96 (s, 1), 3.71 (s, 3), 3.12 (dd, J_1 = 16.7 Hz, J_2 = 2.3 Hz, 1), 2.93 (m, 1), 2.29 (m, 1), 1.90 (dd, J_1 = 13 Hz, J_2 = 7 Hz, 1), 1.58 (dq, J_1 = 14 Hz, J_2 = 7.5 Hz, 1), 1.60 (dq, J_1 = 14 Hz, J_2 = 7.5 Hz, 1), 1.52 (t, J = 7 Hz, 3), 1.07 (t, J = 7.5 Hz, 3); high-resolution mass spectrum: calcd for $C_{25}H_{26}O_7$, 438.1678; found, 438.1677.

(±)-7-Deoxyaklavinone (27). To a suspension of $AlCl_3$ (20 mg, excess) in 0.5 mL of anhydrous CH_2Cl_2 was added a solution of keto ester **11** (3 mg, 0.0068 mmol) in 0.5 mL of anhydrous CH_2Cl_2. The resulting mixture was stirred at room temperature for 40 h under nitrogen. The reaction mixture was poured into cold 5% HCl/saturated brine (1 mL (1:1)) and the phases were separated. The aqueous phase was extracted with CH_2Cl_2 (6 × 2 mL), and the combined organic phases were combined, dried over $MgSO_4$, and evaporated to afford 3 mg of essentially pure **27** (one spot/TLC (SiO_2) in hexane/ether/CH_2Cl_2 (1:1:2)). Chromatography on SiO_2 in the same solvent system afforded 2.65 mg (97%) of pure (±)-7-deoxyaklavinone (**27**) (mp 209–211 °C), identical in all respects (IR, NMR, TLC) with an authentic sample: IR ($CHCl_3$) 1722, 1676, 1620, 1595 cm^{-1}; NMR (400 MHz/$CDCl_3$) δ 12.51 (s, 1), 12.12 (s, 1), 7.84 (d, J = 8 Hz, 1), 7.68 (t, J = 8 Hz, 1), 7.66 (s, 1), 7.31 (d, J = 8 Hz, 1), 3.95 (s, 1), 3.75 (s, 3), 3.08 (dd, J_1 = 16 Hz, J_2 = 7 Hz, 1), 2.33 (m, 1), 1.94 (dd, J_1 = 16 Hz, J_2 = 7 Hz, 1), 1.73 (dq, J_1 = 13 Hz, J_2 = 7.5 Hz, 1), 1.60 (dq, J_1 = 16 Hz, J_2 = 7.4 Hz, 1), 1.09 (t, J = 7.5 Hz, 3).

Equilibration of Keto Ester 25. A solution of keto ester **25** (3 mg, 0.0068 mmol) in 1 mL of anhydrous CH_2Cl_2 under nitrogen was treated with 0.1 mL of triethylamine (anhydrous) and the mixture was stirred at room temperature for 12 h. The solution was diluted with 4 mL of CH_2Cl_2 and washed with 2 N HCl (2 × 1 mL), dried over $MgSO_4$, and evaporated. Analysis of the residue (3 mg, ~100%) by NMR (400 MHz) and TLC (SiO_2, hexane/ether/CH_2Cl_2 (1:1:2)) revealed a mixture of **22** and **25** in a ratio of ~2:1. This permits recycling the undesired material **25** very efficiently and raising the yield of **22** to 89% after one equilibration.

(±)-Aklavinone (2). A solution of (±)-7-deoxyaklavinone (**27**) (6 mg, 0.015 mmol) in 25 mL of CCl_4, containing a catalytic amount of AIBN (one crystal), was heated to reflux, and a solution of bromine (4.8 mg, 0.03 mmol) in 25 mL of CCl_4 was added dropwise over ~1 h. At that time, TLC indicated all the starting material had been consumed. The solvent and any excess bromine were evaporated, and the residue was taken up in 2 mL of THF/H_2O (1:1) and stirred for 1 h at room temperature. The mixture was diluted with 5 mL of CH_2Cl_2 and poured into 2 mL of saturated $NaHCO_3$ solution. After separation of the phases, the aqueous phase was extracted with CH_2Cl_2 (3 × 2 mL). The combined organic phases were washed with saturated brine, dried over $MgSO_4$, and evaporated to afford 6 mg of crude products, which by TLC analysis was largely a single substance (R_f 0.4 on SiO_2 in hexane/ether/CH_2Cl_2 (1:1:2)). NMR (400 MHz) analysis suggested the ratio of (±)-aklavinone (**2**)/(±)-7-epiaklavinone was ~10:1.

Chromatography of the crude product mixture on SiO_2 in hexane/ether/CH_2Cl_2 (1:1:2) afforded 5.25 mg (85%) of the major component, (±)-aklavinone (**2**) (mp 209–211 °C), which was identical in all respects with an authentic sample (IR/NMR/TLC).

9,10-Dihydro-11-ethoxy-8-ethyl-10-hydroxy-5,12-naphthacenedione (10). The crude mixture of alcohols **11** and **12** (480 mg, ~1.25 mmol) was dissolved in toluene (60 mL), and 50 mg of *p*-TsOH–H_2O was added. The mixture was heated at reflux under a Dean–Stark trap for azeotropic removal of water for 3 h. Analysis by TLC showed complete consumption of the starting materials. The solvents were evaporated, and the residue was dissolved in chloroform (100 mL). The solution was washed with 15 mL of 15% $NaHCO_3$ solution and the aqueous wash solution extracted with an additional 20 mL of chloroform. The combined organic phases were dried over $MgSO_4$ and evaporated to afford 454 mg of crude olefin **10**.

Purification was effected by column chromatography on SiO_2 with hexane/ether/chloroform (4:1:2) as eluent, which afforded 322 mg of pure olefin **10** (74%): IR ($CHCl_3$) 1660, 1625, 1575 cm^{-1}; NMR (60 MHz/$CDCl_3$) δ 13.03 (s, 1), 7.82 (s, 1), 7.78–7.21 (m, 3), 6.43 (s, 1), 4.07 (q, J = 7 Hz, 2), 3.71–1.76 (m, 6), 1.53 (t, J = 7 Hz, 3), 1.17 (t, J = 7 Hz, 3); high-resolution mass spectrum: calcd for $C_{22}H_{20}O_4$, 348.13616; found, 348.13594.

1,7(*R*,*S*)-Dihydroxy-11-ethoxy-8(*S*,*R*)-ethyl-7,8,9,10-tetrahydro-5,12-naphthacenedione (11) and 1,7(*S*,*R*)-Dihydroxy-11-ethoxy-8(*S*,*R*)-ethyl-7,8,9,10-tetrahydro-5,12-naphthacenedione (12). To a solution of ketone **7** (457 mg, 1.25 mmol) in 28 mL of THF/methanol (3:1) was added 1 mL of 2 N HCl in methanol along with a small amount of methyl orange as indicator. Over the period of 7 h, portions of solid $NaBH_3CN$ (~42 mg) were added (a total of 378 mg) at intervals of 0.5 h for the first 2 h and every hour after that. After each addition, sufficient 2 N HCl in methanol was added to regenerate the indicator color (orange-red). The mixture was permitted to stir for 12 h at room temperature, and portionwise addition of $NaBH_3CN$ and 2 N HCl in methanol was begun again. A total of 495 mg of $NaBH_3CN$ was added in nine additional portions (55 mg) over ~12 h (~once every 1.25 h). At this point, TLC analysis indicated complete consumption of starting material. The mixture was diluted with 10 mL of water and 20 mL of saturated brine, and the mixture was concentrated under reduced pressure. The residue was extracted with chloroform (5 × 10 mL). The combined organic extracts were dried over $MgSO_4$ and evaporated to afford 480 mg of a mixture of alcohols, which were used directly without further purification: IR ($CHCl_3$) 3050, 1670, 1636, 1587 cm^{-1}; NMR (60 MHz/$CDCl_3$) δ 12.93 (s, 1), 8.12 (s, 1), 7.80–7.28 (m, 3), 4.80 (s, 1), 4.05 (q, J = 7 Hz, 2), 3.13–0.90 (m, 7), 1.52 (t, J = 7 Hz, 3), 1.08 (t, J = 7 Hz, 3).

9,10-Dihydro-11-ethoxy-8-ethyl-1-methoxy-5,12-naphthacenedione (17). To a suspension of 580 mg of silver oxide (Ag_2O) in 10 mL of CH_2Cl_2 was added olefin **10** (170 mg, 0.49 mmol) and 0.19 mL of methyl iodide (430 mg, 2.5 mmol). The mixture was heated at reflux with stirring for 40 h. The mixture was filtered through Celite and evaporated to afford 173 mg of essentially pure title methyl ether **17** (~100%): NMR (60 MHz/$CDCl_3$) δ 8.00–7.10 (m, 3), 7.63 (s, 1), 6.33 (s, 1), 4.10 (q, J = 7 Hz, 2), 4.03 (s, 3), 3.73–1.73 (m, 6), 1.50 (t, J = 7 Hz, 3), 1.13 (t, J = 7 Hz, 3).

7,8-Epoxy-11-ethoxy-8-ethyl-1-methoxy-7,8,9,10-tetrahydro-5,12-naphthacenedione (18). A mixture of methyl ether **17** (60 mg, 0.16 mmol) and *m*-chloroperbenzoic acid (85%, 49 mg, 0.24 mmol) was dissolved in 4 mL of methylene chloride and stirred at room temperature for 5 h. The reaction mixture was diluted with 10 mL of ether and washed successively with 5 mL of 10% aqueous sodium carbonate solution and saturated brine, dried over Na_2SO_4, and evaporated to afford 60 mg of crude epoxide in essentially pure form (~100%): NMR (60 MHz/$CDCl_3$) δ 8.08 (s, 1), 7.91–7.23 (m, 3), 4.04 (q, J = 7 Hz, 2), 4.03 (s, 3), 3.80 (s, 1), 3.43–1.70 (m, 6), 1.50 (t, J = 7 Hz, 3), 1.07 (t, J = 7 Hz, 3); high-resolution mass spectrum: calcd for $C_{23}H_{22}O_5$, 378.1467; found, 378.1462.

9,10-Dihydro-1,11-dihydroxy-8-ethyl-5,12-naphthacenedione (13). A solution of methyl ether **10** (6 mg, 0.017 mmol) was dissolved in 0.5 mL of CH_2Cl_2 and treated with 20 mg of anhydrous $AlCl_3$. After the solution was stirred for 5 h at room temperature, the mixture was diluted with 10 mL of CH_2Cl_2 and 5 mL of 2 N aqueous HCl. The organic phase was dried over $MgSO_4$ and evaporated to afford 6 mg of the olefin **13**

(~100%): NMR (90 MHz/$CDCl_3$) δ 12.26 (s, 1), 12.08 (s, 1), 7.70 (s, 1), 7.85-7.40 (m, 3), 6.25 (s, 1), 3.20-1.33 (m, 6), 1.17 (t, J = 7 Hz, 3); high-resolution mass spectrum: calcd for $C_{20}H_{16}O_4$, 320.1048; found, 320.1042.

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Registry No. (±)-**2**, 78821-97-3; **3**, 481-39-0; (±)-**4**, 82247-48-1; (±)-**5**, 82247-49-2; (±)-**6**, 82247-50-5; (±)-**6**, regioisomer, 82247-51-6; (±)-**7**, 82247-52-7; (±)-**8**, 82265-50-7; (±)-**9**, 82247-53-8; **10**, 82247-54-9; *trans*-(±)-**11**, 82265-51-8; *cis*-(±)-**12**, 82247-55-0; **13**, 80926-96-1; **17**, 82247-56-1; (±)-**18**, 82247-57-2; (±)-**19**, 82247-58-3; (±)-**20**, 82247-59-4; **21**, 82247-60-7; *trans*-(±)-**22**, 82247-61-8; **23**, 82265-52-9; **24**, 82247-62-9; *cis*-(±)-**25**, 82247-63-0; (±)-**27**, 78821-96-2; 1,3-cyclohexanedione, 504-02-9; triethylamine, 121-44-8; 1,5-dihydroxynaphthane, 83-56-7.

Resolution of Conglomerates with the Assistance of Tailor-made Impurities. Generality and Mechanistic Aspects of the "Rule of Reversal". A New Method for Assignment of Absolute Configuration

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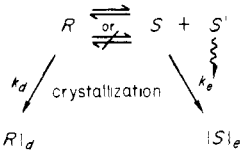
Abstract: A new general and efficient method for kinetic resolution of racemic conglomerates by crystallization in the presence of "tailor-made" additives is described. The process is explained in terms of stereoselective adsorption of the resolved additive at the surface of the growing crystals of the enantiomer of the same absolute configuration, resulting in a drastic decrease in their rate of growth and thus allowing preferential crystallization of the opposite enantiomer ("rule of reversal"). Some empirical resolutions reported in the literature are rationalized through this mechanism, and appropriate additives for the resolution of new systems are designed and successfully applied. The crystallization of the conglomerates (*R*,*S*)-glutamic acid hydrochloride (Glu·HCl), (*R*,*S*)-threonine (Thr), (*R*,*S*)-(*p*-hydroxyphenyl)glycine *p*-toluenesulfonate (pHpgpTs), and (*R*,*S*)-asparagine hydrate (Asn·H_2O) in the presence of other amino acids, used as additives, has been studied in particular. It is demonstrated that the additives are occluded in the bulk of the homochiral crystal in typical amounts of 0.5-1.5%, while they are not found in the bulk of the crystals of the antipode. The possible role of the additives in nucleation and dissolution of the affected crystals is considered. A new method for the assignment of absolute configuration of chiral molecules is proposed.

In recent years there has been an impressive advance in the analytical techniques for separation of enantiomers, mainly in the field of gas and liquid chromatography.[1] However these techniques are not suitable yet for large-scale applications, and thus industrial resolution of racemic mixtures is still mainly performed "Pasteur-like" through fractional crystallization of conglomerates or diastereoisomers.[2] Although these methods have been in use for more than 100 years, we feel that they are still in more of a state-of-the-art category as compared to well-established science. In the precipitation of a conglomerate, the only parameter that has thus far been exploited for achieving separation of the two enantiomorphs is the delay imposed on crystallization by the nucleation step. When seed crystals are supplied, this delay is eliminated, and kinetic resolution may be accomplished. This method is therefore not applicable to systems in which there is a low barrier to spontaneous nucleation or to systems where the two enantiomorphous crystals twin easily. In these cases the two enantiomers crystallize simultaneously, even in the presence of nuclei of one type only.

We present a general approach to the kinetic resolution of conglomerates by the introduction of selective inhibitors that delay the growth of one of the enantiomorphs. This novel approach can be furthermore efficiently coupled with the existing technologies, resulting in improved resolutions.

Scheme I[a]



[a] S' = impurity stereochemically similar to S. In the absence of S', $k_d = k_l$; in the presence of S', $k_d \gg k_l$.

The Rule of Reversal. In a previous study on generation and amplification of optical activity in closed symmetrical systems, we have encountered an interesting phenomenon of asymmetric induction on the crystallization of nonchiral photopolymerizable dienes in chiral crystals.[3] The inducing agents were the enantiomerically pure topochemical dimers, trimers, and oligomers of these same dienes (see Table I). In all the experiments performed, the enantiomorphic crystal with an absolute configuration opposite to that of the one in which the additive was generated crystallized in excess. We established that the additive, which is stereo-

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