(s, 1 H); MS, *m/e* (%) 650 (2.6), 649 (9), 377 (18), 342 (8), 334 (6), 333 (11), 319 (5), 318 (29), 317 (25), 130 (18), 129 (63); calcd for $C_{35}H_{38}O_{12}$: 650.2363; found: 650.2364.

Preparation of 2-Acetyl-3,4,10,11,12-pentaacetoxy-3-(*S),4(*R**),4a(*S**),5-tetrahydronaphthacene (12a-Deoxypillaromycinone Pentaacetate, 56).** A solution of 0.69 mg (0.00388 mmol) of NBS in 45 μL of acetic acid and 5 μL of water was added to 2.3 mg (0.00353 mmol) of pentaacetate **55** at 0 °C. After 40 min at 0 °C, the solvent was removed in a stream of nitrogen. Acetic anhydride (250 μL) was added to the residue, and after stirring 30 min at room temperature, 100 μL of pyridine was added also. After 1.5 h, the mixture was evaporated in vacuo and the residue purified by flash chromatography and elution with ethyl acetate to give 1.6 mg (80% yield) of crystalline **56**, mp 211–212 °C. IR ($CHCl_3$) 1770, 1745, 1670, 1600, 1366; NMR ($CDCl_3$) δ 2.02 (s, 3 H), 2.13 (s, 3 H), 2.38 (s, 6 H), 2.42 (s, 6 H), 2.77 (t, J = 15.6 Hz, H_5 axial), 3.08 ~ 3.20 (m, 2 H, H_5 equatorial and H_{4a}), 4.95 (dd, J = 11, 3 Hz, H_4), 6.32 (d, J = 3 Hz, H_3), 7.11 (d, J = 8 Hz, 1 H), 7.48 (t, J = 8 Hz, 1 H), 7.60 (s, 1 H), 7.64 (s, 1 H), 7.67 (d, J = 8 Hz, 1 H); NMR (C_6D_6) δ 2.56 (t, J = 14.5 Hz, 1 H), 2.87 (dd, J = 14.5, 5 Hz, 1 H), 3.11 (ddd, J = 14.5, 12, 5 Hz, 1 H), 5.01 (dd, J = 12, 3 Hz, 1 H), 6.60 (d, J = 3 Hz, 1 H); MS, *m/e* (%) 565 (3), 564 (11), 463 (13), 462 (53), 421 (8), 420 (33), 404 (6), 379 (18), 378 (100), 377 (7), 376 (15), 361 (9), 360 (8), 344 (8), 343 (25), 336 (6), 335 (10), 334 (9), 320 (14), 319 (63), 318 (60), 302 (7); calcd for $C_{30}H_{28}O_{11}$: 564.1631; found: 564.1633.

Acknowledgment. We thank the National Cancer Institute of the National Institutes of Health for their generous support of our programs. C.G.C. thanks the NSF for the award of a predoctoral fellowship and D. H. thanks CNRS-France and NATO for support during his stay in these laboratories.

Registry No. **12**, 86668-63-5; **14**, 86668-37-3; **15a**, 73794-51-1; **15b**, 81418-04-4; **16a**, 86668-38-4; **16b**, 86668-39-5; **17a**, 86668-40-8; **17b**, 86668-41-9; **20**, 86668-42-0; **26a**, 86668-43-1; **26b**, 86668-44-2; **27a**, 86668-45-3; **27b**, 86668-46-4; **29**, 65174-13-2; **33**, 81418-09-9; **34**, 81418-10-2; **35**, 86668-47-5; **36**, 86668-48-6; **37**, 86668-49-7; **37** sulfoxide, 86668-64-6; **37** β-keto sulfoxide, 86668-65-7; **38**, 86668-50-0; **39**, 86668-51-1; **40**, 86668-52-2; (*E*)-**44**, 86668-53-3; (*Z*)-**44**, 86708-55-6; **45**, 86668-54-4; **47**, 86668-55-5; **48**, 86668-56-6; **49**, 86668-57-7; **50**, 86668-58-8; **51**, 86668-59-9; **52**, 86668-60-2; **54**, 86668-61-3; **54** diol, 86668-66-8; **55**, 86668-62-4; **56**, 86688-41-7; juglone, 481-39-0; (*E*)-1-acetoxy-1,3-butadiene, 35694-20-3; di-*tert*-butylchlorosilane, 56310-18-0; di-*tert*-butyldichlorosilane, 18395-90-9; 1-acetoxy-2-[(4-methoxyphenyl)thio]cyclobutene, 65174-11-0; (1-methoxyethyl)diphenylphosphine oxide, 64304-77-4.

Synthetic Approaches to Rhodomycinone and Olivin

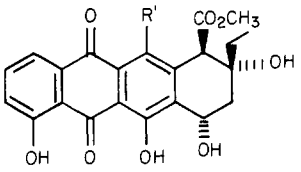
George A. Kraus* and Michael D. Hagen

Department of Chemistry, Iowa State University, Ames, Iowa 50011

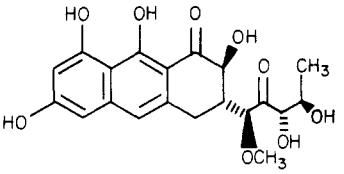
Received February 1, 1983

Intermediates for the synthesis of olivin and rhodomycinone were prepared by a sequence involving a Diels–Alder reaction followed by a Friedel–Crafts cyclization. In all cases optimal yields were obtained by regioselective methanolysis of anhydrides **9**, **10**, and **21** followed by treatment of the crude ester acids with trifluoroacetic anhydride. An added advantage of the latter reaction is that aromatization also occurs.

The important biological activity exhibited by compounds **1–3** has prompted considerable synthetic attention.[1] Several imaginative and successful approaches to **1** have been reported.[2] In contrast, comparatively few



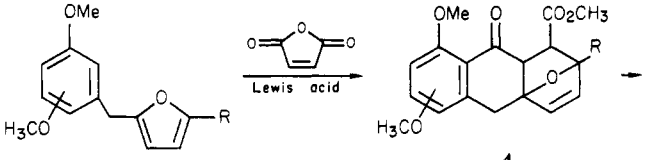
1 (aklavinone), R′ = H
2 (rhodomycinone), R′ = OH



3 (olivin)

approaches to the related molecules **2** and **3** have been published.[3] In this paper we will describe a direct and efficient approach to both **2** and **3**. The approach solves the regiochemical control problems associated with compound **3**.

Our strategy centered around a tandem Diels–Alder/Friedel–Crafts acylation sequence. Since certain Lewis acids catalyze both reactions,[4] we anticipated that the one-pot transformation depicted in eq 1 might occur.



2 or 3 (1)

Additionally, the stereochemistry developed in the Diels–Alder step would ultimately lead to the stereoselective introduction of functionality in the A ring. Furans **5** and **6** were prepared (eq 2) by the efficient reductive sequence developed by Hall and co-workers.[5] The acid-catalyzed reaction was attempted under a variety of conditions (**5**: $AlCl_3$, −78 °C, 0 °C, 25 °C; BF_3 Et_2O, −78 °C; AgO_3SCF_3, 0 °C). Extensive decomposition was invariably observed. We suspected that the oxabicyclo[2.2.1]heptene subunit formed in the Diels–Alder reaction was unstable to Lewis acids. This proved to be the case, since adducts

(1) For excellent reviews of biological properties and syntheses of anthracyclines, see: Remers, W. A. "The Chemistry of Antitumor Antibiotics"; Wiley-Interscience: Somerset, NJ, 1979; Vol. 1. Arcamone, F. *Top. Antibiot. Chem.* **1978**, *2*, 89.

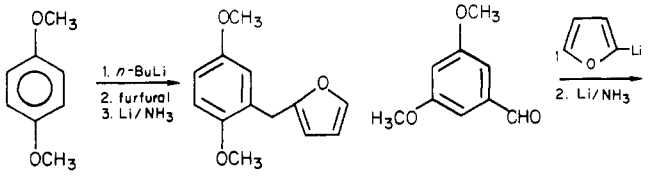
(2) Kende, A. S.; Rizzi, J. P. *J. Am. Chem. Soc.* **1981**, *103*, 4247. Pearlman, B. A.; McNamara, J. M.; Hasan, I.; Hatkeyama, S.; Sekizaki, H.; Kishi, Y. *Ibid.* **1981**, *103*, 4248. Confalone, P. N.; Pizzolat, G. J. *Ibid.* **1981**, *103*, 4251. Li, R.; Wu, Y. L. *Ibid.* **1981**, *103*, 7007. Boeckman, R. K., Jr.; Sum, F.-W. *Ibid.* **1982**, *104*, 4604.

(3) Hatch, R. P.: Shringarpure, J.; Weinreb, S. M. *J. Org. Chem.* **1978**, *43*, 4172. Franck, R. W.; John, T. V. *Ibid.* 1980, *45*, 1172. Thiem, J.; Wessel, H.-P. *Tetrahedron Lett.* **1980**, 3571; *Liebigs Ann. Chem.* **1981**, 2216. Dodd, J. H.; Garigipati, R. S.; Weinreb, S. M. *J. Org. Chem.* **1982**, *47*, 4045. Krohn, K. *Tetrahedron Lett.* **1981**, *22*, 3219 and references therein.

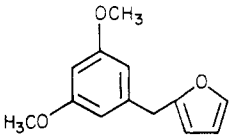
(4) Lewis acids known to catalyze Diels–Alder reactions and also Friedel–Crafts acylations: $AlCl_3$, BF_3·Et_2O, $SnCl_4$, $ZnCl_2$.

(5) Zilenovski, J. S. R.; Hall, S. S. *J. Org. Chem.* **1979**, *44*, 1159.

0022-3263/83/1948-3265$01.50/0



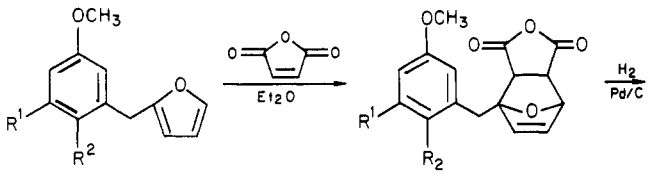
5



(2)

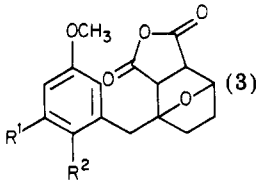
6

7 and 8 prepared by the reaction of 5 and 6 with maleic anhydride at ambient temperature (eq 3) decomposed



5, R^1 = H; R^2 = OCH_3
6, R^1 = OCH_3; R^2 = H

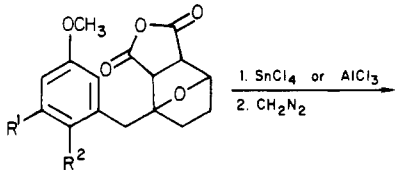
7, R^1 = H; R^2 = OCH_3
8, R^1 = OCH_3; R^2 = H



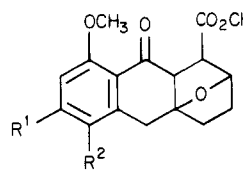
(3)

9, R^1 = H; R^2 = OCH_3
10, R^1 = OCH_3; R^2 = H

rapidly in the presence of Lewis acids. Although we had planned to introduce the C-7[6] hydroxyl group by way of the olefin, there is ample precedent for its introduction by means of benzylic oxidation methodologies.[2] Catalytic hydrogenation of 7 and 8 provided 9 and 10, respectively, in high yield. While 10 cyclized to 12 in 70% yield with tin tetrachloride, 9 was recovered unchanged upon reaction with tin tetrachloride, titanium tetrachloride, or aluminum chloride. A 35% yield of keto ester 11 (eq 4) was obtained



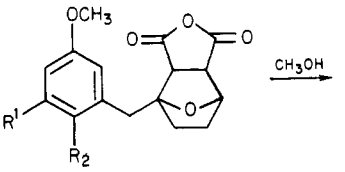
9, R^1 = H; R^2 = OCH_3
10, R^1 = OCH_3; R^2 = H



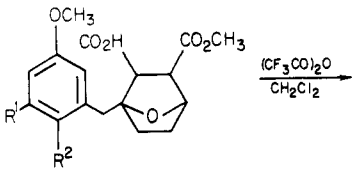
(4)

11, R^1 = H; R^2 = OCH_3
12, R^1 = OCH_3; R^2 = H

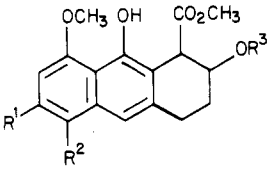
with aluminum chloride in a dichloromethane/nitromethane at 25 °C. The structure of 11 was supported by a change in the pattern of the aromatic protons from a multiplet to an AB quartet centered at δ 6.84. The ^{13}C NMR exhibited resonances at 171.6 and 196.5 ppm that are characteristic of an ester and aromatic ketone, respectively. Similar data supported the structure of 12. Both of the corresponding acids were only slightly soluble in most organic solvents. This characteristic necessitated the esterification with diazomethane and may be partly responsible for the modest yields. These yields were surprising, since many intramolecular Friedel–Crafts reactions proceed in high yield.[7] The possibility that a conformation favorable for cyclization was difficult to achieve could be tested by modifying anhydride 9 or 10. After the selective opening of the oxygen bridge of the oxabicyclo[2.2.1]heptane system could not be accomplished, we then examined the selective conversion of the anhydride to an ester acid. This proceeded rapidly and regioselectively in hot methanol. The reaction of methanol at the least hindered carbonyl of the anhydrides 9 and 10 produced 13 and 14, respectively (eq 5). The selectivity



9, R^1 = H, R^2 = OCH_3
10, R^1 = OCH_3; R^2 = H



13, R^1 = H; R^2 = OCH_3
14, R^1 = OCH_3; R^2 = H



(5)

15, R^1 = H; R^2 = OCH_3; R^3 = $OCCF_3$
16, R^1 = OCH_3; R^2 = H; R^3 = $OCCF_3$
17, R^1 = H; R^2 = OCH_3; R^3 = H
18, R^1 = OCH_3; R^2 = R^3 = H

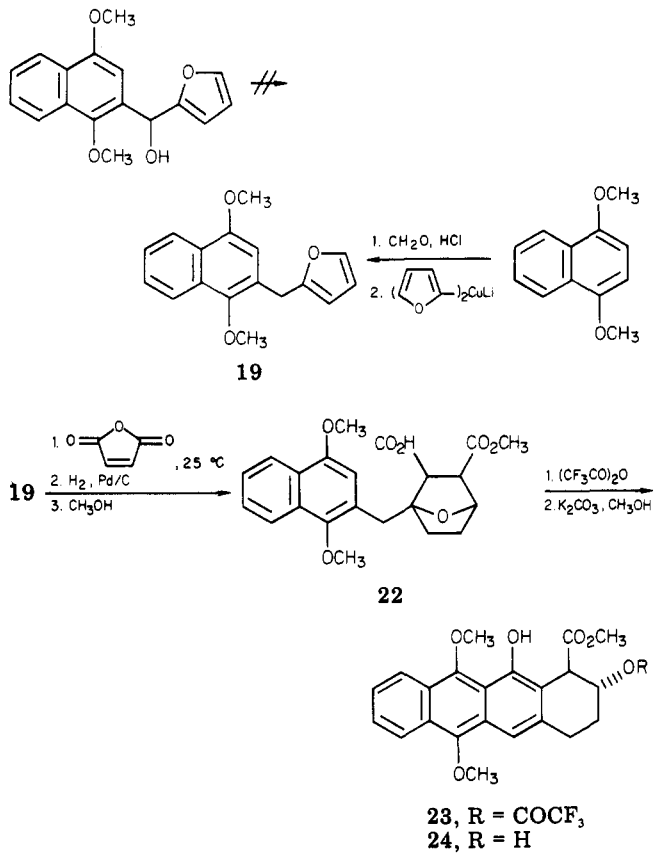
of the methanol addition has analogy in other systems.[8] The monoacids were treated with 2 equiv of trifluoroacetic anhydride in dichloromethane to afford the chromatographically unstable trifluoroacetates 15 and 16 which were hydrolyzed with potassium carbonate in methanol at 0 °C[9] to furnish the hydroxy esters 17 and 18. The 300-MHz proton NMR spectrum of 15 provided an excellent opportunity to examine the relative stereochemistry. The spectrum exhibited only one doublet for the benzylic methine proton at δ 4.60 with a coupling of 7 Hz. This is consistent with a trans relationship of the hydroxyl and ester groups.

The extension of our route to a tetracyclic system required furan 19. The use of Hall's reductive sequence failed in this case due to competitive reduction of the naphthalene. However, furan 19 could be obtained from 1,4-dimethoxynaphthalene[10] by the pathway shown in Scheme I. Chloromethylation followed by coupling[11] with

(6) Anthracycline numbering; see 1.

(7) Sethna, S. "Friedel–Crafts and Related Reactions"; Wiley Interscience: New York, 1964; Vol. 3, Chapter 35.
(8) McCrindle, R.; Overton, K. H.; Raphael, R. A. *J. Chem. Soc.* **1962**, 4798. Yuldashev, K. Y.; Tsukervanik, I. P. *Uzbeksk. Khim. Zh.* **1965**, *9*, 27.
(9) Lardon, A.; Reichstein, T. *Helv. Chim. Acta* **1954**, *37*, 388.
(10) Baker, B. R.; Carlson, G. H. *J. Am. Chem. Soc.* **1942**, *64*, 2657.

Scheme I



difurylcopper–lithium provided **19** in 48% yield. A Diels–Alder reaction at ambient temperature followed by catalytic hydrogenation, and methanol addition to the anhydride provided acid **22**. Acid **22** was treated with trifluoroacetic anhydride at 25 °C to afford an unstable trifluoroacetate that was hydrolyzed to the hydroxy ester **24**.

The five-step sequence provides esters **17**, **18**, and **24** in 33%, 52%, and 51% overall yields, respectively. The reactions are operationally convenient and clean. The four-step sequence involving hydrogenation, methanolysis, cyclization, and hydrolysis can be conducted without chromatographic purification. We expect that **18** will be a key intermediate for the synthesis of **3** and that **24** will be useful for the synthesis of **2** and other anthracyclines.

Experimental Section

Unless otherwise noted, materials were obtained from commercial suppliers and were used without purification. Diethyl ether and THF were distilled from $LiAlH_4$ prior to usage. Dichloromethane was distilled from P_2O_5. Melting points were determined on a Fisher-Johns melting point apparatus and are uncorrected. Infrared spectra were determined on a Beckmn IR-4250 spectrometer. Nuclear magnetic resonance spectra were determined on a Varian EM-360 60-MHz instrument. Carbon-13 NMR spectra were determined on a JOEL fx-90Q Fourier transform instrument. Both proton and carbon chemical shifts are expressed in parts per million downfield from internal tetramethylsilane. High-resolution mass spectra were recorded on an AEI MS-902 high-resolution mass spectrometer.

2-[(2,5-Dimethoxyphenyl)methyl]furan (5). To a solution of 1,4-dimethoxybenzene (2.00 g, 14.6 mmol) in 10 mL of ether at 0 °C was added *n*-butyllithium (7.1 mL, 14.9 mmol). The solution was allowed to warm to room temperature and was stirred for 24 h. The solution was then cooled to −78 °C, and distilled furfural (1.20 mL, 14.5 mmol) in 10 mL tetrahydrofuran was added. The resulting yellow solution was stirred at −78 °C for 15 min. Approximately 50 mL of liquid ammonia was then added followed by small pieces of lithium wire (55 mm, 32 mmol). The reaction mixture was stirred 60 min, solid ammonium chloride was added, and the ammonia was allowed to evaporate overnight. The residue was partitioned between ether and brine. The organic layer was dried over sodium sulfate, filtered, and concentrated in vacuo. Chromatography (60 g of silica gel) with 1:2 methylene chloride/hexane provided 2.15 g (68%) of furan **5**: NMR ($CDCl_3$) δ 3.74 s, 6 H), 3.91 (s, 2 H), 5.91 (d, J = 3 Hz, 1 H), 6.14–6.28 (m, 1 H), 6.58–6.80 (m, 3 H), 7.20 (d, J = 2 Hz, 1 H); IR (film) 1505, 1220, 1042, 900, 720 cm^{-1}; mass spectrum, $C_{13}H_{14}O_3$ requires m/e 218.0943, measured m/e 218.0938.

2-[(3,5-Dimethoxyphenyl)methyl]furan (6). To a solution of furan (1.60 mL, 22.0 mmol) in 25 mL of ether was added *n*-butyllithium (10.1 mL, 22.0 mmol). The solution was stirred for 1.5 h at room temperature. After the solution had been cooled to −78 °C, a solution of 3,5-dimethoxybenzaldehyde (3.60 g, 21.7 mmol) in 25 mL of THF was added, and the solution was stirred at −50 °C for 30 min. Approximately 100 mL of ammonia was then distilled into the flask, and pieces of lithium wire (0.433 g, 61.8 mmol) were added. The reaction was stirred for 1 h and then quenched by the addition of 8 g of solid ammonium chloride. The ammonia was allowed to evaporate overnight. The residue was partitioned between ether and brine. The organic layer was dried over sodium sulfate, filtered, and concentrated in vacuo. The chromatography (silica gel, 85 g) in 1:1 hexane/methylene chloride afforded 3.53 g (75%) of a colorless oil: NMR ($CDCl_3$) δ 3.77 (s, 6 H), 3.87 (br s, 2 H), 5.95–6.35 (m, 2 H), 6.37 (br s, 2 H), 7.32 (d, J = 2 Hz, 1 H); IR 1505, 1215, 909 cm^{-1}; ^{13}C NMR ($CDCl_3$) δ 34.64, 55.17, 98.51, 106.31, 106.80, 110.27, 140.44, 141.47, 154.15, 160.87; mass spectrum, $C_{13}H_{14}O_3$ requires m/e 218.0943, measured m/e 218.0940.

2-(Chloromethyl)-1,4-dimethoxynaphthalene. Gaseous HCl was passed through a solution of 37% aqueous formaldehyde (3.0 mL) and concentrated HCl (1.4 mL) in 6 mL of dioxane for 15 min. The rate of HCl was controlled so that the internal temperature of the solution was maintained between 55 and 60 °C. A solution of 1,4-dimethoxynaphthalene (4.00 g, 21.2 mmol) in 12 mL of dioxane was added over 20 min. After the addition was complete, the gaseous HCl addition was stopped, and the reaction mixture was cooled to room temperature and was poured into 30 mL ice and 10 mL of ether. The aqueous layer was extracted twice with ether. The organic layer was washed with water, dried over sodium sulfate, filtered, and concentrated in vacuo. Filtration chromatography with 9:1 hexane/methylene chloride afforded a 64% yield of 2-(chloromethyl)-1,4-dimethoxynaphthalene: mp 64–65 °C; NMR ($CDCl_3$) δ 3.96 (s, 6 H), 4.83 (s, 2 H), 6.75 (s, 1 H), 7.35–8.42 (m, 4 H); IR (film) 1630, 1600, 1462, 1372, 1271, 1225, 1092 cm^{-1}.

1,4-Dimethoxy-2-(2-furylmethyl)naphthalene (19). To a solution of furan (1.75 mL, 24.0 mmol) in 10 mL of ether at 0 °C was added *n*-butyllithium (10.60 mL, 23.1 mL). The solution was stirred at room temperature for 1 h. THF (5 mL) was added to dissolve the 2-furyllithium. The solution was transferred by a cannula to a suspension of cuprous bromide–dimethyl sulfide complex (2.40 g, 11.7 mmol) in 15 mL of THF at −40 °C. The dark solution was stirred for 30 min at −40 °C. A solution of 2-(chloromethyl)-1,4-dimethoxynaphthalene (2.00 g, 6.78 mmol) in 10 mL of ether was then added, and the reaction was allowed to warm slowly to room temperature overnight. (The flask was protected from light.) The reaction mixture was poured into ammonium chloride and extracted twice with ether. The organic layer was dried over sodium sulfate, filtered, and concentrated in vacuo. The crude product was chromatographed on silica gel with 1:4 methylene chloride/hexane to afford **19**: 1.35 g (75%); NMR ($CDCl_3$) δ 3.89 (s, 6 H), 4.15 (s, 2 H), 6.00 (d, J = 3 Hz, 1 H), 6.20–6.34 (m, 1 H), 6.64 (s, 1 H), 7.30–8.32 (m, 5 H); IR 1630, 1595, 1460, 1368, 1220, 1088, 900, 725 cm^{-1}; ^{13}C NMR ($CDCl_3$) δ 28.61, 55.54, 62.23, 105.54, 106.26, 110.29, 121.87, 122.32, 125.11, 125.77, 126.55, 128.63, 141.38, 147.10, 151.85, 154.51.

General Procedure for the Diels–Alder Reaction. Equimolar quantities of maleic anhydride and the furan were dissolved in sufficient anhydrous ether to afford a 1 M solution. This solution was stirred in a flask covered with aluminum foil for 20–24

(11) Posner, G. H. *Org. React.* **1975**, *22*, 253.
(12) Snyder, C. D.; Rapoport, H. *J. Am. Chem. Soc.* **1972**, *94*, 227.

h. The solid was filtered, washed with a 1:4 ether/hexane solution and dried in vacuo. The filtrated was concentrated. The combined yields are given below.

7: 95% yield; NMR ($CDCl_3$) δ 3.09–3.32 (m, 2 H), 3.72 (s, 3 H), 3.78 (s, 3 H), 5.27 (br s, 1 H), 6.28 (br s, 2 H), 6.63–7.02 (m, 3 H); IR ($CDCl_3$) 1785, 1504, 1232, 905 cm^{-1}.

8: 88% yield; NMR ($CDCl_3$) δ 3.20 (d, J = 2 Hz, 2 H), 3.34 (d, J = 4 Hz, 2 H), 3.74 (s, 6 H). 5.35 (d, J = 2 Hz, 1 H), 6.30–6.63 (m, 5 H); IR (Nujol) 1785, 905 cm^{-1}.

20: 70% yield; NMR ($CDCl_2$) δ 3.32 (s, 2 H), 3.94 (s, 6 H), 5.29 (br s, 1 H), 6.30 (br s, 2 H), 6.88 (s, 1 H), 7.30–8.38 (m, 4 H). IR (Nujol) 1785, 905 cm^{-1}.

General Procedure. Reduction of Diels–Alder Adducts. To a suspension of 10% Pd/C (whose weight was 10% the weight of the adduct) in acetone under a hydrogen atmosphere was added a 0.3 M solution of the adduct in acetone. The suspension was stirred 5–6 h, filtered through Celite, and concentrated in vacuo.

9: 92% yield; mp 160–162 °C; NMR ($CDCl_3$) δ 1.30–1.78 (m, 4 H), 3.19 (s, 3 H), 3.33 (s, 1 H), 3.72 (s, 3 H), 3.74 (s, 3 H), 4.77–4.92 (m, 1 H), 6.71 (br s, 2 H), 6.90–7.02 (m, 1 H); IR (film) 1875, 1845, 1786, 1504 cm^{-1}; ^{13}C NMR ($CDCl_3$) 29.46, 29.65, 30.89, 52.15, 52.87, 55.67, 55.99, 79.47, 89.74, 111.59, 112.83, 117.77, 125.57, 151.91, 153.47, 170.05, 171.55.

10: 80% yield; recrystallized from acetone/hexane; mp 137–139 °C; NMR ($CDCl_3$) δ 1.25–1.85 (m, 4 H), 3.20 (s, 2 H), 3.73 (s, 6 H), 4.92 (br d, J = 4 Hz, 1 H), 6.20–6.64 (m, 3 H); IR (film) 1785, 1600 cm^{-1}; ^{13}C NMR ($CDCl_3$) δ 34.64, 55.17, 98.51, 106.31, 106.80, 110.27, 140.44, 141.47, 154.15, 160.87; mass spectrum, $C_{17}H_{18}O_6$ requires m/e 318.1103, measured m/e 318.1110.

21: 80% yield; mp 163–164 °C; NMR ($CDCl_3$) δ 1.3–1.75 (m, 4 H), 3.27 (s, 2 H), 3.52 (d, J = 5 Hz, 2 H), 3.88 (s, 3 H), 3.97 (s, 3 H), 4.97 (br s, 1 H), 7.00 (s, 1 H), 7.38–8.34 (m, 4 H); IR (film) 1870, 1840, 1785, 1600, 1372, 1225, 1090, 905, 727 cm^{-1}; ^{13}C NMR ($CDCl_3$) 29.52, 30.37, 31.08, 52.02, 53.13, 55.73, 62.10, 79.73, 89.87, 106.65, 121.93, 122.39, 124.21, 125.31, 126.03, 126.55, 128.30, 147.81, 151.65, 170.23, 171.49.

General Procedure. Methanolysis of the Anhydride. A solution of the anhydride (0.5 M in anhydrous methanol) was refluxed for 4 h. After the solution had cooled to room temperature, it was diluted with four volumes of ether. The ether solution was extracted with sodium bicarbonate solution. The bicarbonate solution was washed twice with methylenechloride, acidified with 6 N HCl, and extracted three times with methylene chloride. The methylene chloride solution was dried over sodium sulfate, filtered and concentrated in vacuo. In each case the crude acid was sufficiently pure to be used in the next reaction.

13: 95% yield; mp 141–143 °C; NMR ($CDCl_3$) δ 1.32–1.72 (m, 4 H), 2.89–3.39 (m, 4 H), 3.64 (s, 3 H), 3.72 (s, 6 H), 5.05 (br s, 1 H), 6.68–7.03 (m, 3 H); 9.87 (br, s, 1 H); IR (film) 3360–2930 (br), 1742, 1716, 1500, 1213, 909 cm^{-1}.

14: 96% yield; mp 127–128 °C; NMR ($CDCl_3$) δ 1.32–1.82 (m, 4 H), 2.93–3.40 (m, 4 H), 3.68 (s, 3 H), 3.77 (s, 6 H), 5.10 (br s, 1 H), 6.28–6.58 (m, 3 H), 9.12 (br s, 1 H); IR (film) 3460–2420 (br), 1745, 1715, 1600, 1210, 1160, 910 cm^{-1}.

22: 93% yield; mp 161–164 °C; NMR ($CDCl_3$) δ 1.22–1.76 (m, 4 H), 2.85–3.52 (m, 4 H), 3.68 (s, 3 H), 3.79 (s, 3 H), 3.93 (s, 3 H), 5.06 (br s, 1 H), 6.93 (s, 1 H), 7.32–8.35 (m, 4 H); IR ($CDCl_3$) 3540–2430 (br), 1744, 1712, 1372, 1268, 908 cm^{-1}; ^{13}C NMR ($CDCl_3$) δ 29.78, 30.30, 31.41, 51.44, 52.48, 55.54, 56.77, 61.58, 76.47, 87.99, 106.32, 106.65, 121.48, 121.87, 124.53, 125.25, 125.96, 127.72, 147.03, 150.87, 171.49, 173.89.

General Procedure. Cyclization with Trifluoroacetic Anhydride. To a 0.1 M solution of the acid in methylene chloride at 0 °C was added 2 equiv of trifluoroacetic anhydride. Acid **13** was stirred at 0 °C 1 h and at room temperature 20 h. Acid **14** was stirred at 0 °C for 5 h. Acid **22** was stirred at 0 °C for 20 min and at room temperature for 15 h. In all cases the solution was then concentrated in vacuo, diluted with carbon tetrachloride, and concentrated in vacuo. The crude trifluoroacetates were immediately hydrolyzed to the corresponding alcohol.

15: NMR ($CDCl_3$) δ 1.80–2.48 (m, 2 H), 2.90–3.32 (m, 4 H), 3.72 (s, 3 H), 3.90 (s, 3 H), 3.95 (s, 3 H), 4.57 (d, J = 7 Hz, 1 H), 5.26–5.68 (m, 1 H), 6.56 (s, 2 H), 7.56 (br s, 1 H), 9.82 (br s, 1 H); IR (film) 3365, 1790, 1741, 1640, 1620, 1379, 1255, 1220, 1165, 1068, 910 cm^{-1}.

16: NMR ($CDCl_3$) δ 1.56–1.92 (m, 2 H), 3.23 (br s, 2 H), 3.58 (s, 3 H), 3.82 (s, 6 H), 4.17–4.85 (m, 2 H), 6.38 (br s, 2 H), 9.42 (s, 1 H); IR (film) 3400, 1786, 1737, 1630, 1600, 1210, 1155, 906 cm^{-1}.

23: NMR ($CDCl_3$) δ 1.4–1.8 (m, 2 H), 3.0–3.45 (m, 2 H), 3.76 (s, 3 H); 4.06 (s, 6 H), 4.72 (d, J = 7 Hz, 1 H), 5.27–5.84 (m, 1 H), 7.32–8.40 (m, 5 H), 10.23 (s, 1 H); IR ($CDCl_3$) 3320, 1790, 1740, 1372, 1172, 907 cm^{-1}.

Friedel–Crafts Cyclization to 11. To a solution of anhydride **9** (0.102 g, 0.32 mmol) in 3 mL of methylene chloride at 0 °C was added aluminum chloride (0.124 g, 0.93 mmol). The suspension was stirred at 0 °C for 2 h and at room temperature for 3 h. The suspension was cooled to 0 °C. Nitromethane (0.5 mL) was added followed by 6 N hydrochloric acid. After the mixture was partitioned between ether and water, the organic layer was dried over sodium sulfate, filtered, and concentrated in vacuo. The crude residue was then dissolved in methylene chloride and treated with diazomethane. The solvent was concentrated in vacuo and chromatographed to afford **11**: 0.036 g (35%) NMR ($CDCl_3$) δ 1.58–1.96 (m, 4 H), 2.83–3.42 (m, 4 H), 3.57 (s, 3 H), 3.76 (s, 3 H), 3.79 (s, 3 H), 4.58 (d, J = 4 Hz, 1 H), 6.84 (AB q, 2 H); ^{13}C NMR ($CDCl_3$) 26.08, 30.76, 34.66, 51.96, 55.99, 56.45, 57.36, 79.14, 83.39, 111.01, 115.75, 123.43, 129.80, 150.15, 153.47, 171.62, 196.52; IR (film) 1734, 1679, 1481, 1264, 1905, 727 cm^{-1}.

Friedel–Crafts Cyclization to 12. To a solution of anhydride **10** (0.496 g, 1.56 mmol) in 15 mL of methylene chloride at 0 °C was added tin tetrachloride (0.40 mL, 3.4 mmol). The solution was stirred at room temperature for 5 h. After the addition of water, the aqueous layer was extracted three times with methylene chloride. The organic layer was dried over sodium sulfate, filtered, and concentrated in vacuo. The crude acid proved to be insoluble. The acid was suspended in methylene and treated with diazomethane. The solvent was concentrated in vacuo and recrystallized to afford 0.361 g (70%) of ester **12**. The ester has a melting point of 205–207 °C: NMR ($CDCl_3$) δ 1.66–1.88 (m, 4 H),, 2.97 (d, J = 3.5 Hz, 1 H), 3.22 (br s, 2 H), 3.56 (s, 3 H), 3.83 (s, 6 H), 4.59 (d, J = 4 Hz, 1 H), 6.38 (br s, 2 H); IR (film) 1737, 1668, 1630, 1265, 909 cm^{-1}.

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Registry No. **2**, 21288-60-8; **3**, 6680-06-4; **5**, 86802-80-4; **6**, 86802-81-5; **7**, 86802-82-6; **8**, 86802-83-7; **9**, 86802-84-8; **10**, 86802-85-9; **11**, 86802-86-0; **12**, 86834-23-3; **13**, 86802-87-1; **14**, 86802-88-2; *trans*-**15**, 86802-89-3; *trans*-**16**, 86802-90-6; *trans*-**17**, 86802-91-7; *trans*-**18**, 86802-92-8; **19**, 86802-93-9; **20**, 86802-94-0; **21**, 86802-95-1; **22**, 86802-96-2; *trans*-**23**, 86802-97-3; *trans*-**24**, 86802-99-5; 1,4-dimethoxybenzene, 150-78-7; furfural, 98-01-1; furan, 110-00-9; 3,5-dimethoxybenzaldehyde, 7311-34-4; 2-(chloromethyl)-1,4-dimethoxynaphthalene, 86802-98-4; 1,4-dimethoxynaphthalene, 10075-62-4; maleic anhydride, 108-31-6.