Synthetic Approach to Aklavinone Using 2-Oxo-2*H*-pyran-5-carboxylate (Coumalate) Intermediates[1]

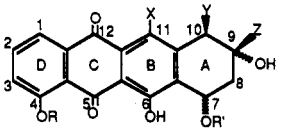
Michael E. Jung*[2] and Jeffrey A. Hagenah

Department of Chemistry and Biochemistry, University of California, Los Angeles, California 90024

Received December 22, 1986

A novel approach for the preparation of aklavinone **5** is described in which the key step is the cycloaddition of a substituted coumalate with a ketene acetal to produce a masked A ring with the C and D rings attached. The 4-(arylmethyl)coumalate **53** was prepared from naphthalene-1,5-diol (**6**) by a seven-step route involving as the key step the cyclocondensation of the methyl (arylmethyl)propiolate **52** with methyl 3-oxopentanoate **10**. Cycloaddition of **53** with dimethyl ketene acetal **12** produced the potential A-ring precursor **67**, which could not be cleanly reduced, thereby ending this scheme. The preparation of functionalized 4,6-dialkylpyrone-5-carboxylates and their use in the synthesis of bicyclic lactones and substituted benzoates via cycloaddition reactions are also described.

Several anthracycline antitumor agents, e.g. adriamycin (**1**) and daunorubicin (**2**), are extensively used today in cancer chemotherapy.[3] Their use in cancer treatment is limited by their severe cumulative cardiotoxicity.[3] In the past few years, several 11-deoxyanthracyclines have been isolated, e.g. aclacinomycin A (**3**) and marcellomycin (**4**),



1 R=Me; X=OH; Y=H; Z=$COCH_2OH$; R'=daunosamine
2 R=Me; X=OH; Y=H; Z=$COCH_3$; R'=daunosamine
3 R=H; X=H; Y=COOMe; Z=Et;
R'=rhodosamine--2-deoxyfucose--cinerulose A
4 R=H; X=H; Y=COOMe; Z=Et; (1-OH instead of H)
R'=rhodosamine--2-deoxyfucose--2-deoxyfucose
5 R=H; X=H; Y=COOMe; Z=Et; R'=H

which possess good tumor-inhibitory properties and, more importantly, exhibit much lower cardiotoxicity.[4] The synthesis of this group of compounds has been an active area of research for some time, and several syntheses of aklavinone **5**, the aglycon of aclacinomycin A, have recently been described.[5] We have in the recent past reported several approaches to **5** using the cycloaddition of bicyclic pyrones.[6] We now describe a new approach to **5** in which the key step involves a reverse electron demand [4 + 2] cycloaddition of a substituted 4-(naphthylmethyl)-6-ethylcoumalate and a ketene acetal to produce a bicyclic lactone as a potential precursor of the A ring of aklavinone. In addition we report in detail on the preparation of functionalized 4,6-dialkylpyrone-5-carboxylates and their cycloadditions to afford bicyclic lactones and substituted benzoates.[7]

Nearly all of the published syntheses of aklavinone **5** use two methods for the introduction of the stereochemistry in the A ring. For C9–C10, the aldol-retro-aldol process of Brockmann[8] has been often used in various procedures to give primarily the 9α-hydroxy 10β-ester. For C7–C9, the solvolysis of the mixture of 7-bromo compounds under aqueous acidic conditions gives predominately the desired 7α-alcohol. Although the syntheses using these routes are excellent, we decided to investigate a different approach in which the desired C9–C10 stereochemistry would be introduced by hydrogenation of an olefinic bicyclic lactone. Our proposed synthetic route is shown in Scheme I. The readily available, inexpensaive 1,5-naphthalenediol (**6**) would be converted into the protected CD-ring synthon **7** in five simple steps. Alkylation of the Grignard reagent derived from **7** with the protected propargyl bromide **8** would then afford, after deprotection, an acetylene that would be carbomethoxylated to give the substituted propiolate **9**. Condensation of **9** with the β-keto ester **10** should then give the desired 2-oxo-2*H*-pyran-5-carboxylate **11**. The key step in this approach is the thermal cycloaddition of ketene dimethyl acetal **12** with **11** to give the olefinic bicyclic lactone **13**. Hydrogenation of **13** should occur from the less hindered face to produce the saturated lactone **14**, in which the C9–C10 stereochemistry of aklavinone is established. Conversion of **14** into the acid **15** would involve deketalization, hydride reduction, protection, and mild basic hydrolysis of the lactone. The cyclization of the acid via internal Friedel–Crafts acylation is well precedented[9] and should produce the tetracyclic

(1) Taken from Ph.D. dissertation of J.A.H., UCLA, 1984.
(2) UCLA Gold Shield Faculty Awardee, 1986–1988.
(3) (a) Henry, D. W. *Cancer Chemotherapy*; Sartorelli, A. C., Ed.; American Chemical Society: Washington, DC, 1976; Chapter 2. (b) Arcamone, F. *Lloydia* **1977**, *40*, 45. (c) Kelly, T. R. *Annu. Rep. Med. Chem.* **1979**, *14*, 288. (d) *Anthracyclines: Current Status and New Developments*; Crooke, S. T., Reich, S. D., Eds.; Academic: New York, 1980. (e) Remers, W. A. *The Chemistry of Antitumor Antibiotics*; Wiley-Interscience: Somerset, NJ, 1979; Vol. 1, Chapter 2. (f) Brown, J. R. *Prog. Med. Chem.* **1978**, *15*, 165.
(4) (a) Oki, T.; Matsuzawa, Y.; Yoshimoto, A.; Numata, K.; Kitamura, I.; Hori, S.; Takamatsu, A.; Umezawa, H.; Ishizuka, M.; Naganawa, H.; Suda, H.; Hamada, M.; Takeuchi, T. *J. Antibiot.* **1975**, *28*, 830. (b) Nettleton, D. E., Jr.; Bradner, W. T.; Bush, R. A.; Coon, A. B.; Moseley, J. E.; Myllymaki, R. W.; O'Herron, F. A.; Schreiber, R. H.; Vulcano, A. L. *Ibid.* **1977**, *30*, 525. (c) Doyle, T. W.; Nettleton, D. E.; Grulich, R. E.; Balitz, D. M.; Johnson, D. L.; Vulcano, A. L. *J. Am. Chem. Soc.* **1979**, *101*, 4041. (d) Wiley, P. F.; Kelly, R. B.; Caron, E. L.; Wiley, V. H.; Johnson, J. H.; MacKellar, F. A.; Mizsak, S. A. *Ibid.* **1977**, *99*, 542. (e) Arcamone, F.; Cassinelli, G.; DiMatteo, F.; Forenza, S.; Ripamonti, M. C.; Rivola, G.; Vigevani, A.; Clardy, J.; McCabe, T. *Ibid.* **1980**, *102*, 1462. (f) Keller-Schierlein, W.; Rickle, W. *Antimicrob. Agents Chemother.* **1971**, 68. (g) Kitamura, I.; Shibamoto, N.; Oki, T.; Inui, T.; Naganawa, H.; Ishizuka, M.; Masuda, T.; Takeuchi, T. and Umezawa, H. *J. Antibiot.* **1977**, *30*, 616.
(5) (a) Kende, A. S.; Rizzi, J. P. *J. Am. Chem. Soc.* **1981**, *103*, 4247. (b) Pearlman, B. A.; McNamara, J. M.; Hasan, I.; Hatakeyama, S.; Sekizaki, H.; Kishi, Y. *Ibid.* **1981**, *103*, 4248. (c) Confalone, P. N.; Pizzolato, G. *Ibid.* **1981**, *103*, 4251. (d) Li, T.-t; Wu, Y. L. *Ibid.* **1981**, *103*, 7007. (e) Boeckman, R. K., Jr.; Sum, F.-W. *Ibid.* **1982**, *104*, 4604. (f) For more recent work, see *Tetrahedron Symposium-in-Print* No. 17: *Tetrahedron* **1984**, *40*, 4537–4793.
(6) (a) Jung, M. E.; Lowe, J. A. *J. Chem. Soc., Chem. Commun.* **1978**, 95. (b) Jung, M. E.; Brown, R. W. *Tetrahedron Lett.* **1981**, 3355. (c) Jung, M. E.; Blum, R. B. *J. Chem. Soc., Chem. Commun.* **1981**, 962. (d) Jung, M. E.; Node, M.; Pfluger, R. W.; Lyster, M. A.; Lowe, J. A., III. *J. Org. Chem.* **1982**, *47*, 1150. (e) Jung, M. E.; Hagenah, J. A. *Ibid.* **1983**, *48*, 5359. (f) Jung, M. E.; Brown, R. W.; Hagenah, J. A.; Strouse, C. E. *Tetrahedron Lett.* **1984**, *25*, 3659. (g) Jung, M. E.; Lowe, J. A., III; Lyster, M. A.; Node, M.; Pfuger, R. W.; Brown, R. W. *Tetrahedron* **1984**, *40*, 4751.
(7) Jung, M. E.; Hagenah, J. A. *Heterocycles* **1987**, *25*, 117.
(8) Brockmann, H. *Prog. Chem. Org. Nat. Prods.* **1963**, *21*, 121, 153; *Naturwissenshaften* **1960**, *47*, 135.
(9) (a) Yadav, J.; Corey, P.; Hsu, C.-T.; Perlman, K.; Sih, C. J. *Tetrahedron Lett.* **1981**, 811. (b) Parker, K. A.; Kallmerten, J. L. *Ibid.* **1979**, 1197. (c) Kende, A. S.; Rizzi, J.; Riemer, J. *Ibid.* **1979**, 1201.

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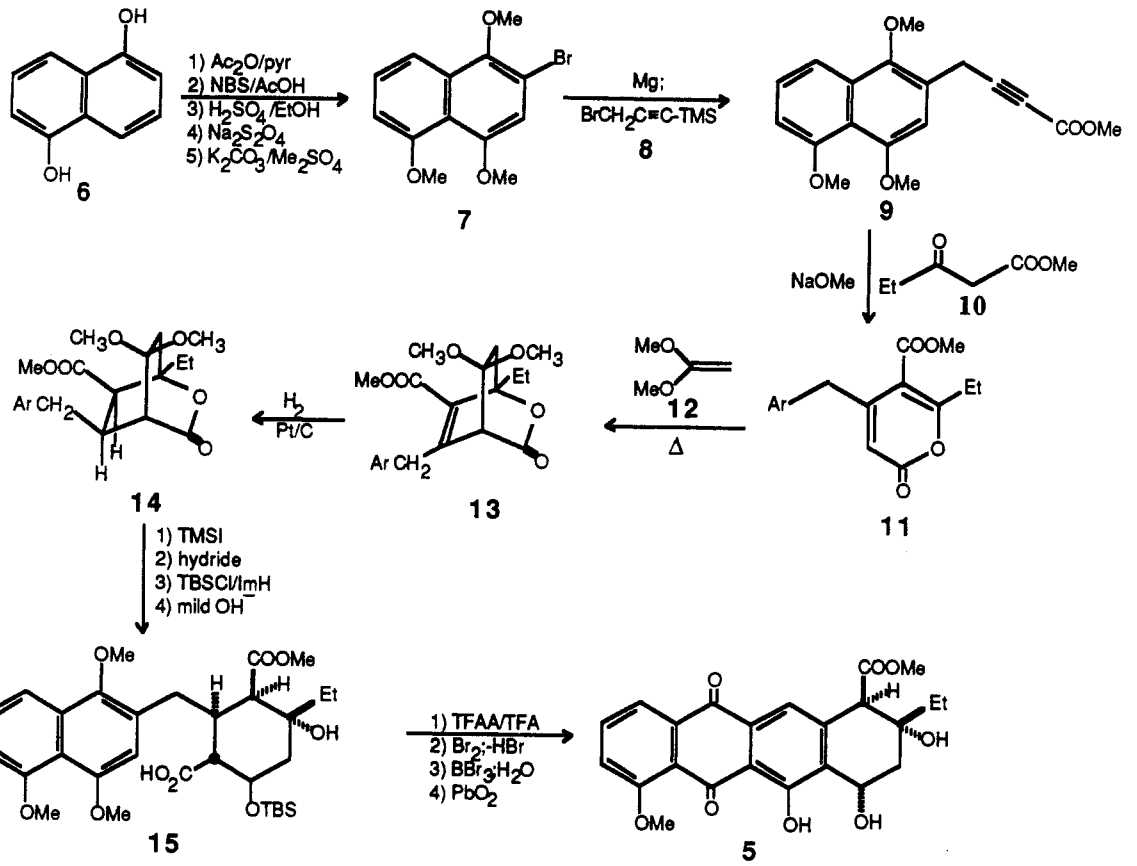
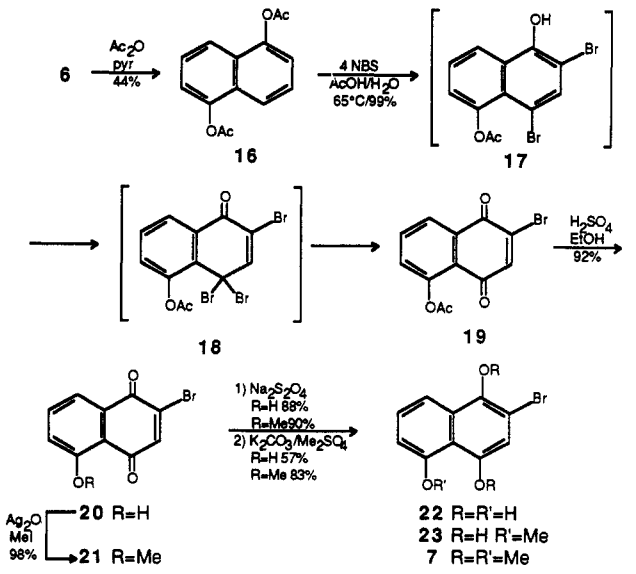
Scheme I



ketone, which on bromination–dehydrobromination, followed by demethylation–hydrolysis and final oxidation should give aklavinone **5**. While several of the final steps might be troublesome due to multiple reactive functionality, we decided to investigate this quite different approach to **5**.

Results and Discussion

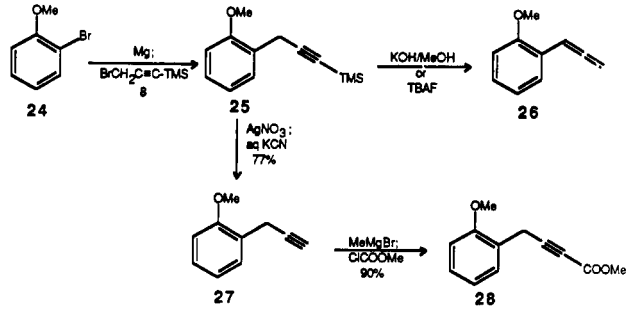
Preparation of 2-Bromo-1,4,5-trimethoxynaphthalene (7). Although **7** had not been prepared before, other similar CD-ring synthons were known.[10] Literature precedent suggested that **7** would be readily available by reduction and permethylation of 2-bromojuglone (**20**) or its methyl ether **21**. Although derivatives of this sort had been prepared before by Carter[11] and Rapoport,[10] the report of Grunwell[12] that treatment of 1,5-diacetoxynaphthalene (**16**) with 4 equiv of NBS in aqueous acetic acid produced 2-bromojuglone acetate (**19**) in 90% yield argued that this approach be used, especially for the production of large quantities of **7**. Thus, 1,5-naphthalenediol (**6**) was acetylated[13] to give **16**, which was brominated–oxidized by a slight variation of the Grunwell route[12] to furnish 2-bromojuglone acetate (**19**) in 99% yield. We have shown recently[6e] that this most likely proceeds via the intermediacy of 5-acetoxy-2,4-dibromonaphthol (**17**) and 5-acetoxy-2,4,4-tribromonaphthalen-1-one (**18**), which can be prepared and separately carried on to **19** under the reaction conditions.[6e] Acid hydrolysis of **19** afforded 2-bromojuglone (**20**)[14] in 92% yield. Sodium dithionate reduction of **20** gave an 88% yield of the triol **22**, which was permethylated to give **7** in 57% yield, thus ending a short five-step route to **7** from **6** in 18% overall yield. A longer, higher yielding procedure involved methylation of bromojuglone **20** to give **21** in 98% yield. This ether was then reduced with dithionate to give in 90% yield diol **23**, which was then dimethylated to give **7** in 83% yield. This six-step route produced **7** from **6** in nearly 30% overall yield.



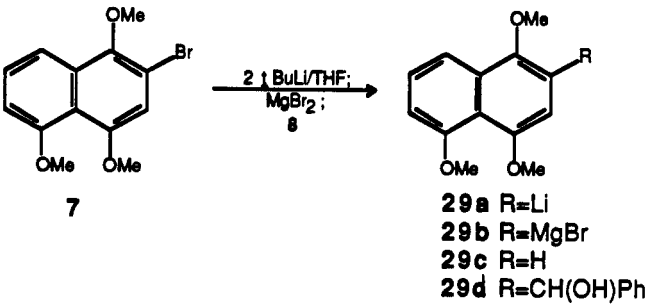
Attempted Preparation of 9. The procedure for the attachment of the propargyl chain **8** to **7** and carbomethoxylation to give **9** were first investigated in a model system. 2-Bromoanisole (**24**) was converted to its Grignard reagent and alkylated with the known (3-bromo-1-propynyl)trimethylsilane (**8**)[15] to give the coupled product

(10) Hannan, R. L.; Barber, R. B.; Rapoport, H. *J. Org. Chem.* **1979**, *44*, 2153.
(11) Carter, A. H.; Race, E.; Rowe, F. M. *J. Chem. Soc.* **1942**, *236*.
(12) Heinzman, S.; Grunwell, J. *Tetrahedron Lett.* **1980**, 4305.
(13) Leman, A. *Ann. Chim. (Paris)* **1938**, *9*, 357.
(14) Thomson, R. H. *J. Org. Chem.* **1948**, *13*, 371, 377.

25 in 96% yield. Deprotection of the silylacetylene of 25 with 10% potassium hydroxide in methanol[15] removed the silyl group but also isomerized the resulting acetylene 27 to the allene 26. This allene was also formed when 26 was treated with the less basic tetra-*n*-butylammonium fluoride (TBAF). However, treatment of 25 with silver nitrate followed by aqueous potassium cyanide afforded the desired acetylene 27 in 77% yield. The acetylene was then easily carbomethoxylated by quenching of its bromomagnesium salt with methyl chloroformate to give 28 in 98% yield.

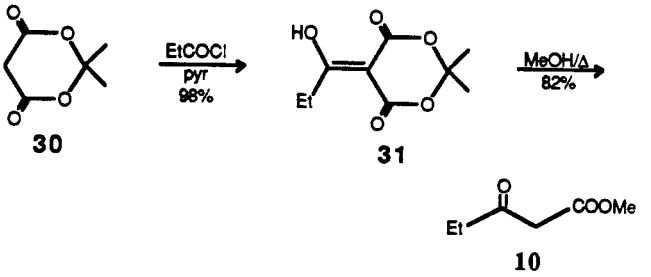


Having established the procedure in this model, we then attempted to extend it to 7. The formation of aryl Grignard reagents from heavily oxygenated aryl bromides is often difficult, and as expected, the reaction of 7 with magnesium proceeded slowly even at elevated temperatures. Therefore, this Grignard reagent was prepared by



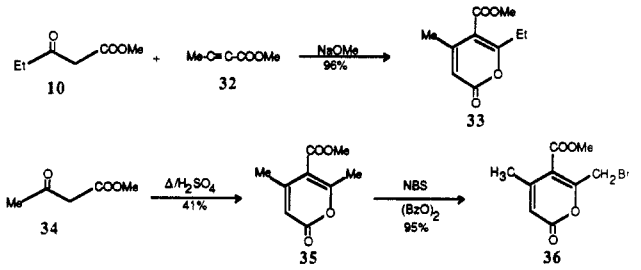
reaction of 7 with 2 equiv of *tert*-butyllithium at −78 °C followed by addition of the resulting lithiate **29a** to an excess of magnesium bromide. Reaction of this Grignard reagent **29b** with the propargyl bromide 8 in refluxing THF failed to give any alkylation, producing instead 1,4,5-trimethoxynaphthalene (**29c**). There are a few reports in the literature of successful condensations of anions such as **29a,b** with aldehydes, esters, and azides,[16] but no alkylations are reported. Studying the quenching of the Grignard reagent **29b** at various times with D_2O gave evidence that the protonation was occurring from either traces of water in the solvent or the solvent THF itself. While it is known that strongly basic anions such as *n*-butyllithium or tritylllithium will deprotonate THF,[17] it is surprising that **29b** is basic enough to do so at temperatures near and above 0 °C.[18] The use of other solvents such as diethyl ether or DME was equally unsuccessful. The lithiate **29a** was not alkylated by 8 to any great extent although it could be trapped with carbonyl derivatives, e.g. benzaldehyde, to give the diarylcarbinol **29d** in 82% yield. Our inability to prepare 9 from 7 caused us to change our synthetic scheme and investigate three parallel alternatives: (1) the reaction of the lithate **29a** with coumalates functionalized at C4 with electrophilic groups such as halomethyl or aldehyde; (2) the condensation of coumalates functionalized at C4 as nucleophiles with bromojuglone derivatives; (3) the use of dialkoxynaphthalenes as less oxidized CD-ring synthons. In order to attempt the first two alternatives we had to study the preparation of coumalates with functionality at C4.

Formation of Substituted Functionalized Coumalates. The literature reports several methods for the preparation of 4,6-disubstituted 2-oxo-2*H*-pyran-5-carboxylic esters.[19] Hantzsch observed in the late 1800s and Wiley and Smith in the 1950s that β-keto esters undergo an intermolecular condensation in the presence of concentrated sulfuric acid to produce 4,6-disubstituted 2-oxo-2*H*-pyran-5-carboxylic acids and esters.[20] This reaction is useful only for the preparation of 2-oxo-2*H*-pyran-5-carboxylates having the same substituents at C4 and C6. "Unsymmetrical" 4,6-disubstituted 2-oxo-2*H*-pyran-5-carboxylates have been synthesized most often by the reaction of β-keto ester enolate anions with acetylenic esters.[21] The initial Michael addition product readily cyclizes under the basic reaction conditions to give the desired 2-pyrone. β-Chloro α,β-unsaturated esters react in an analogous manner with β-keto ester enolate anions and have also found use in the preparation of 2-oxo-2*H*-pyran-5-carboxylates.[22] The use of these methods to introduce an ethyl substituent into our 2-pyrone intermediate **11** required the formation of methyl 3-oxopentanoate (**10**). This β-keto ester has been prepared by Weiler[23] by alkylation of the dianion of methyl acetoacetate with methyl iodide. While this reaction is useful for the synthesis of small amounts of **10**, the reaction becomes impractical on a large scale. Several methods have been developed for the synthesis of β-keto esters from malonic ester derivatives via acylation and subsequent decarboxylation.[24] The most recent of these, reported by Yonemitsu,[24] allows the facile preparation of **10**. Acylation of Meldrum's acid (**30**) with propionyl chloride in the presence of pyridine gave **31** in 98% yield as an orange solid. Refluxing this solid in methanol then produced methyl 3-oxopentanoate (**10**) in 82% yield. This synthesis is amenable to the multigram preparation of β-keto esters.



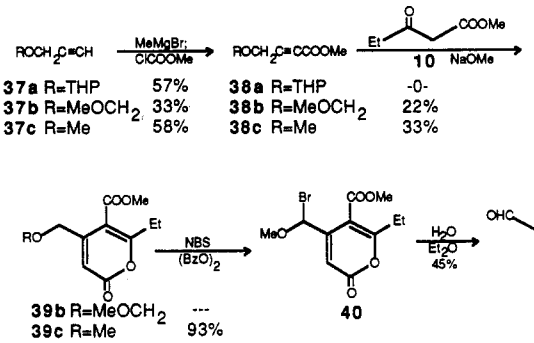
(15) Miller, R. B. *Synth. Commun.* **1972**, *2*, 267.
(16) (a) Trost, B. M.; Pearson, W. H. *Tetrahedron Lett.* **1983**, 269. (b) Kometani, T.; Takeuchi, Y.; Yoshii, E. *J. Org. Chem.* **1983**, *48*, 2311. (c) See also ref 9a.
(17) (a) Jung, M. E.; Blum, R. B. *Tetrahedron Lett.* **1977**, 3791. (b) Tomboulian, P.; Amick, D.; Beare, S.; Dumke, K.; Hart, D.; Hites, R.; Metzger, A.; Nowak, R. *J. Org. Chem.* **1973**, *38*, 322. (c) Bates, R. B.; Kroposki, L. M.; Potter, D. E. *Ibid.* **1972**, *37*, 560.
(18) Perhaps the combined electron-donating effects of the three methoxy substituents increase the basicity of **29b** enought to allow it to deprotonate THF at the temperatures (around 0 °C) required for alkylation.
(19) For a good review, see: Shusherina, N. P.; Dmitrieva, N. D.; Luk'yanets, E. A.; Levina, R. Y. *Russ. Chem. Rev.* **1967**, *36*, 175.
(20) Hantzsch, A. *Justus Liebigs Ann. Chem.* **1883**, *222*, 1. (b) Wiley, R. H.; Smith, N. R. *J. Am. Chem. Soc.* **1951**, *73*, 3531.
(21) (a) Ruhemann, S. *J. Chem. Soc.* **1899**, *75*, 245. (b) Ruhemann, S.; Cunnington, A. *Ibid.* **1899**, *75*, 778. (c) Walker, G. *J. Am. Chem. Soc.* **1954**, *76*, 309.
(22) Anschütz, R.; Bendix, P.; Kerp, W. *Justus Liebigs Ann. Chem.* **1890**, *259*, 148.
(23) Huckin, S. N.; Weiler, L. *J. Am. Chem. Soc.* **1974**, *96*, 1082.
(24) Oikawa, Y.; Sugano, K.; Yonemitsu, O. *J. Org. Chem.* **1978**, *43*, 2078 and references therein.

The condensation of **10** with methyl butynoate (**32**) in the presence of a catalytic amount of sodium methoxide affords methyl 6-ethyl-4-methyl-2-oxo-2*H*-pyran-5-carboxylate (**33**) in 96% yield. Allylic bromination of the



methyl group of **33** would allow the introduction of a reactive functional group in the desired position. However, allylic bromination can occur at either the C4 methyl group or the C6 methylene group of the ethyl side chain. To determine whether there is any preferential bromination of 4,6-dialkyl-2-oxo-2*H*-pyran-5-carboxylates, we examined the bromination of the 4,6-dimethyl-2-pyrone **35**, a compound readily prepared by dimerizative cyclization of methyl acetoacetate (**34**) with sulfuric acid.[22] In this compound, each of the allylic radical intermediates is primary, and therefore, any preferential bromination is due to stabilizing effects inherent in the 2-oxo-2*H*-pyran-5-carboxylate structure. Reaction of **35** with *N*-bromosuccinimide and a catalytic amount of benzoyl peroxide produced only the 6-(bromomethyl)-2-pyrone **36**, with none of the 4-bromomethyl isomer being produced. The observed specificity is expected since an intermediate radical at the C6 methyl group is stabilized by conjugation with both the C5 carbomethoxy group and the C2 carbonyl group, while a radical intermediate at the C4 methyl group is only stabilized by conjugation with the C2 carbonyl group. Since this reaction is completely regiospecific, further attempts to functionalize the methyl group of **32** via reactions that involve radical intermediates seemed unlikely. We therefore sought to introduce functionality into this methyl group before formation of the pyrone ring. A protected alcohol at this point was expected to be stable to the reaction conditions, yet easily transformable into a variety of reactive functional groups. Therefore, a synthetic approach that incorporates a protected alcohol at this position was examined.

Carbomethoxylation of the acetylenic anion of propargyl tetrahydropyranyl ether (**37a**)[25] with methyl chloroformate afforded the ester **38**.[26] However, all attempts to cyclize this acetylenic ester with methyl 3-oxopentanoate (**10**) under basic conditions were unsuccessful. As an alternative, the methoxymethyl protecting group was investigated. This protecting group is normally introduced by reaction of an alcohol with chloromethyl methyl ether under basic conditions. However, Fujita[27] has developed a method for the methoxymethylation of alcohols under mild acidic conditions, which avoids the use of this potent carcinogen. Addition of phosphorus pentoxide to a solution of propargyl alcohol and dimethoxymethane catalyzes an acetal exchange reaction that forms the methoxymethyl propargyl ether (**37b**)[28] in 39% yield. This acetylene can be carbomethoxylated to give the acetylenic ester **38b** in 33% yield. Condensation of **38b** with methyl 3-oxopentanoate (**10**) then affords the desired 2-pyrone **39b** in 22% yield. Deprotection of **39c** under mild acidic conditions is complicated by concurrent hydrolysis of the pyrone to give a mixture of rearranged products. The successful removal of alternative protecting groups seemed to be equally uncertain, due to preferential or concurrent reaction of the pyrone. Therefore, a method was needed that would allow the transformation of a protected alcohol into a reactive functional group, without involving deprotection. We had shown earlier that allylic bromination of 4,6-dialkyl-2-oxo-2*H*-pyran-5-carboxylates occurs regiospecifically at the C6 alkyl group. An alkoxy substituent on the alkyl group at C4, however, should stabilize an allylic radical and allow bromination to occur at this position. To examine this possibility, the methoxy pyrone **39c** was synthesized. Methyl propargyl ether (**37c**)[29] was carbomethoxylated (58%) to give **38c**,[26a] which was condensed with **10** to give pyrone **39c** in 33% yield. Bromination of **39c** with *N*-bromosuccinimide and benzoyl peroxide occurs exclusively at the C4 methoxymethyl group. The resulting bromide **40** is extremely sensitive to moisture, and stirring with aqueous diethyl ether rapidly produces aldehyde **41**.

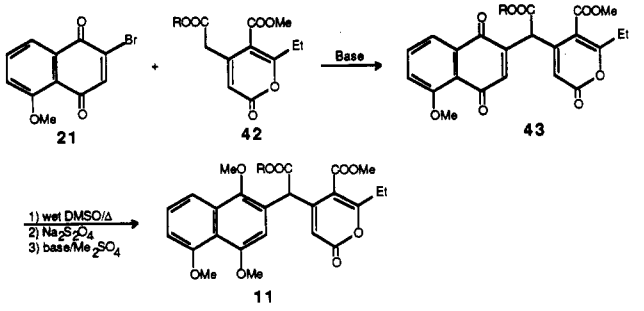


Aldehyde **41** is ideally functionalized for reaction with the anion of 2-bromo-1,4,5-trimethoxynaphthalene (**7**). As we have shown, lithiate **29a** reacts readily with benzaldehyde at −78 °C without complications to give a good yield of **29d**. However, reaction of the lithiate **29a** with **41** produced only a mixture of products that could not be identified. The aldehyde functionality of **41** is expected to be the most reactive functionality in the molecule toward nucleophilic addition; however, this molecule has numerous other reactive sites, perhaps accounting for the variety of products produced. With the failure of this step, all routes using trimethoxynaphthyl bromide (**7**) were abandoned.

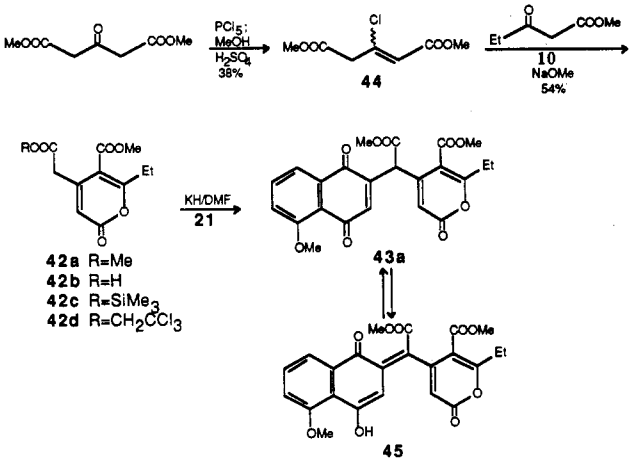
Preparation of 2-Oxo-2*H*-pyran-4-acetates and Their Reaction with 2-Bromojuglone Methyl Ether. An alternative to the preparation of compounds like **11** via a nucleophilic naphthalene derivative and an electrophilic pyrone is the opposite approach, namely using an electrophilic naphthalene unit, e.g. 2-bromojuglone methyl ether **21**, and a nucleophilic pyrone, e.g. the 4-(carbalkoxymethyl)coumalate **42**. The resulting condensation product **43** could theoretically be decarboalkoxylated (vinylogous β-diester), reduced, and methylated to give **11**. Condensations of active methylene compounds with bromonaphthoquinones are known[30] so that the formation of **43** from **21** and **42** has literature precedent. Therefore, we

(25) Henbest, H. B.; Jones, E. R. H.; Walls, I. M. S. *J. Chem. Soc.* **1950**, 3646.
(26) This compound has been reported in the literature but without any spectral or physical data: (a) Wlostowski, M.; Jaworski, T.; Jaworska, R. Polish Patent 96451; *Chem. Abstr.* **1979**, *90*, 151692m. (b) Keck, G. E.; Nickell, D. G. *J. Am. Chem. Soc.* **1980**, *102*, 3632.
(27) Fuji, K.; Nakano, S.; Fujita, E. *Synthesis* **1975**, 276.
(28) Atavin, A. S.; Trofimov, B. A.; Lavrov, V. I. *Zh. Org. Khim.* **1972**, *8*, 1569.
(29) Vincens, M.; Dussange, A.; Vidal, M. *Tetrahedron* **1977**, *33*, 2937.
(30) (a) Kallmayer, H. J. *Arch. Pharm. (Weinheim, Ger.)* **1973**, *306*, 257. (b) Buggle, K.; Donnelly, J. A.; Maher, L. *J. Chem. Soc., Perkin Trans. 1* **1973**, 1006.

investigated the preparation of 2-pyrones possessing an acetate unit at C4.

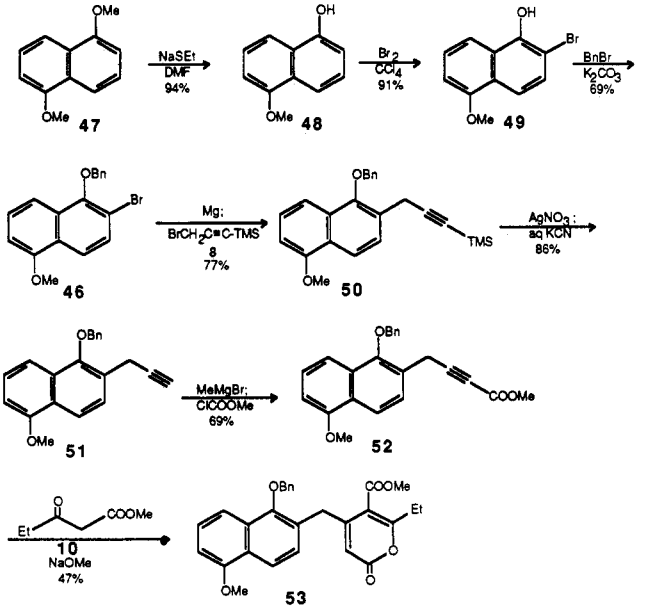


Dimethyl 3-chloro-2-pentenedioate (**44**) was prepared as a mixture of *E* and *Z* isomers from dimethyl acetonedicarboxylate by reaction with phosphorus pentachloride, followed by reesterification with acidic methanol.[31] Condensation of **44** with methyl 3-oxopentanoate (**10**) then gave the desired 2-pyrone **42a** in 54% yield.[32] Initial attempts to react **42a** with 2-bromojuglone methyl ether (**21**) using the conditions reported by Kallmayer,[30a] sodium methoxide in methanol at 25 °C, were unsuccessful. However, by using potassium hydride as a base, in *N,N*-dimethylformamide at −23 °C, the desired product **43a** was obtained in 52% yield. Spectroscopic data indicate that, in deuteriochloroform solution, **43a** exists as a 1:1 mixture with a tautomeric isomer, possibly **45**. The additional carbomethoxy group in **43a** is both a vinylogous diester and β-keto ester and therefore should be readily decarboxylated following hydrolysis to the carboxylic acid. However, selective hydrolysis of this ester seemed unlikely. Recently, a number of methods have been reported for the decarboalkoxylation of β-keto esters.[33] Crabbé[33a] has employed alumina to effect this transformation and Krapcho[33b] has reported similar results using aqueous dimethyl sulfoxide. The use of these methods, however, to decarbomethoxylate **43a** resulted in complete decomposition.



Replacement of this methyl ester with a protected carboxylate that can be selectively hydrolyzed would allow this decarboxylation to be accomplished in the presence of the other functional groups in the molecule. Reaction of **42a** with dilute sulfuric acid for 4.5 days[32] produced the carboxylic acid **42b** in 65% yield, along with 25% of unreacted **42a**. We chose two different easily removed protecting groups for the acid functionality of **42a**, namely the trimethylsilyl ester **42c** and the trichloroethyl ester **42d**, both prepared by known routes.[34] Attempts to form the anion of **42c** with potassium hydride in *N,N*-dimethylformamide resulted, however, in cleavage of the extremely labile trimethylsilyl group and subsequent decarboxylation of the resulting carboxylate anion to give **33**. The carboxylate anion of **42b** is unstable in DMF even at −78 °C and readily loses carbon dioxide to form **33**. Formation of the anion of **42d** was easily accomplished with potassium hydride. However, the steric hindrance of the bulky trichloroethyl group prevented the nucleophilic addition of the anion to 2-bromojuglone methyl ether (**21**). Only starting material was obtained, even after prolonged reaction times and temperatures. The majority of other ester-protecting groups appeared to be equally unsuitable, either for steric reasons or because the procedures for their removal were incompatible with the other functional groups in the molecule, and thus this route was abandoned.

Alkylation of 1,5-Dialkoxynaphthalenes. As the third alternative route to compounds such as **11**, we chose to investigate the use of 1,5-dialkoxynaphthalenes as less oxidized CD-ring synthons, analogous to **7**. For example, 1-(benzyloxy)-2-bromo-5-methoxynaphthalene (**46**) might be expected to resemble 2-bromoanisole (**24**) more in its reactivity than the trimethoxy bromide **7**. Although the use of **46** as the CD-ring component would necessitate an oxidation at C5 later in the synthesis, it seemed a useful system on which to test our coumalate cycloaddition chemistry. Therefore, we prepared **46** as follows. 1,5-Dimethoxynaphthalene (**47**) was monodemethylated in 94% yield by treatment with sodium thioethoxide in DMF at 100 °C.[10,35] The resulting phenol **48** was brominated selectively at C2 with bromine in carbon tetrachloride at room temperature to give in 91% yield the bromophenol **49**,[11] which was then converted into **46** by protection of the phenol as the benzyl ether (69%).



With **46** in hand, we applied the procedure developed earlier for 2-bromoanisole. Reaction of the Grignard

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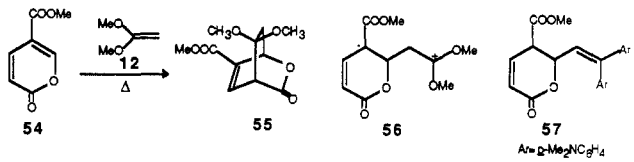
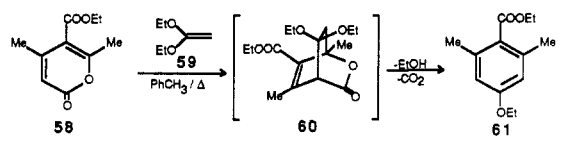
(34) (a) Kita, Y.; Haruta, J.; Segawa, J.; Tamura, Y. *Tetrahedron Lett.* **1979**, 4311. (b) Woodward, R. B.; Heusler, K.; Gosteli, J.; Oppolzer, W.; Ramage, R.; Ranganathan, S.; Vorbrüggen, H. *J. Am. Chem. Soc.* **1966**, *88*, 852.
(35) Rutolo, D.; Lee, S.; Sheldon, R.; Moore, H. W. *J. Org. Chem.* **1978**, *43*, 2304.

reagent of **46** with (3-bromo-1-propynyl)trimethylsilane (**8**) at 50 °C produces the propargylated product **50** in 77% yield, without formation of the protonated compound 5-methoxy-1-(phenylmethoxy)naphthalene. Therefore, removal of an electron-donating alkoxy substituent from this naphthalene system decreases the basicity of this anion and thus prevents proton abstraction from the solvent tetrahydrofuran. Desilylation of **50** was achieved under the conditions developed for the model compound, namely reaction with silver nitrate in aqueous ethanol, followed by stirring with a concentrated potassium cyanide solution, to afford the acetylene **51** in 96% yield. This acetylene was carbomethoxylated by formation of the acetylenic anion with methylmagnesium bromide, followed by quenching with methyl chloroformate to give **52** in 69% yield. Condensation of this acetylenic ester with methyl 3-oxopentanoate (**10**) in the presence of a catalytic amount of sodium methoxide then produced the desired 2-pyrone **53** in 47% yield. This pyrone differs from our original key intermediate **11** only by lacking an alkoxy substituent at the C4 position of the naphthalene. However, since several methods have been reported in the literature for the oxidation of anthranols to anthraquinones (using chromium trioxide,[36] thallium trinitrate,[9a] and molecular oxygen[5a]), introduction of this oxygen should be possible at a later stage of our synthesis. We therefore investigated the cycloaddition of various coumalates.

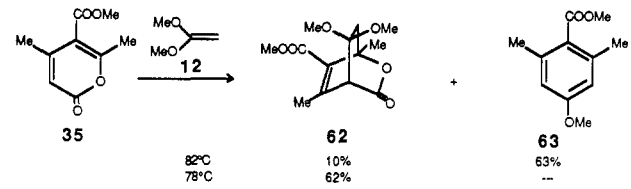
Cycloaddition Reactions of 2-Oxo-2*H*-pyran-5-carboxylates. In 1969, Behringer[37] reported that methyl 2-oxo-2*H*-pyran-5-carboxylate (methyl coumalate, **54**) undergoes a cycloaddition reaction with 1,1-dimethoxyethylene (**12**)[38] to give the bicyclic adduct **55**. Unlike the Diels–Alder reactions of 2-pyrones with electron-deficient dienophiles,[39] this reaction is unsuccessful with 2-pyrones lacking a C3 or C5 carbomethoxy substituent. This suggests that the reaction is not a concerted cycloaddition but rather a nucleophilic addition of the electron-rich dimethoxyethylene to the pyrone to give a zwitterionic intermediate **56**, followed by carbon–carbon bond formation to produce the observed product **55**. This nonsynchronous mechanism is supported by the isolation of **57** in 92% yield from the reaction of the corresponding diarylethylene with **54**.[37]



4,6-Disubstituted 2-oxo-2*H*-pyran-5-carboxylates such as **58** were also reported by Behringer[37] to undergo this cycloaddition reaction with 1,1-diethoxyethylene (**59**). However, the bicyclic intermediate **60** was unstable at the reaction temperature (refluxing toluene) and subsequent loss of carbon dioxide and methanol gave the aromatic product **61**. Boger recently reported similar reactions with

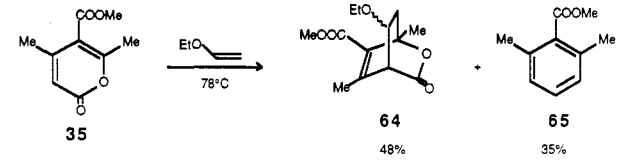


substituted 2-pyrone-3-carboxylates.[40] Since our 2-pyrone intermediate **53** has an alkyl substituent at the C6 position, the cycloaddition product with 1,1-dimethoxyethylene (**12**) is expected to have low thermal stability. To determine whether the isolation of such adducts is possible, we examined the reaction of methyl 4,6-dimethyl-2-oxo-2*H*-pyran-5-carboxylate (**35**) with 1,1-dimethoxyethylene (**12**) at various temperatures. Behringer[37] originally reported



that reaction of **58** with **59** in refluxing toluene for 15 h produced the aromatic product **61** in 73% yield. We found that the reaction of **35** with 2 equiv of 1,1-dimethoxyethylene (**12**) in refluxing benzene (82 °C) afforded the analogous aromatic product **63**[41] in 63% yield after purification. However, at this lower temperature, the desired bicyclic intermediate **62** was also isolated in 10% yield. Lowering the reaction temperature to 75 °C allowed the isolation of the desired adduct **62** in 62% yield. Proton NMR of the reaction mixture indicated that, at this temperature, none of the aromatic product is produced. At reaction temperatures below 75 °C, this cycloaddition reaction occurs very slowly. Therefore, formation of the desired bicyclic intermediate is limited to a narrow 5 °C temperature range.

As a possible alternative to the use of 1,1-dimethoxyethylene (**12**), we also examined the cycloaddition of **35** with ethyl vinyl ether, since Behringer had reported its reaction with methyl coumalate. The reaction of **35** with



ethyl vinyl ether was much slower than that with the ketene acetal due to the reduced nucleophilicity of the vinyl ether. After 6 days at 78 °C, the adduct **64** was isolated in 48% yield, along with 35% of the aromatic product **65**.[42] Unlike the crystalline 1,1-dimethoxyethylene adduct **62**, the oily adduct **64** is unstable at room temperature and slowly decomposes into methyl 2,6-dimethylbenzoate (**65**) after several days. Vinyl acetate was too weakly nucleophilic to react with **35** at all, with only starting material being recovered after 7 days of reflux.

The cycloaddition of the 4-(arylmethyl)coumalate **53** with **12**, the key step in our approach to aklavinone, proceeded well under the proper conditions. Heating a solution of **53** with excess **12** in benzene at 78 °C for 48 h furnished a mixture of the undesired aromatic ester **66** and the desired bicyclic lactone **67** in yields of 28% and 54%, respectively. The prolonged reaction time, due to steric hindrance imposed by the bulky naphthalene ring, allows the formation of a substantial amount of the aromatic product **66** at this temperature. But we were still able to obtain as the major product the desired compound **67**,

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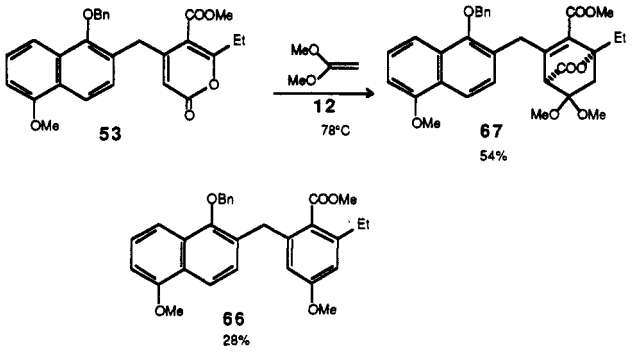
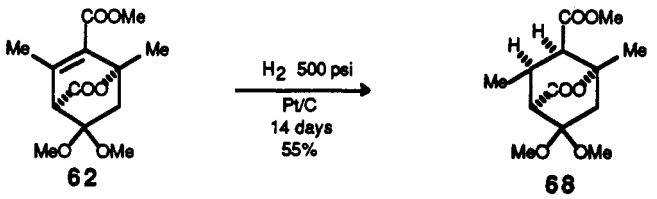
analogous to 13 in our original scheme. We then studied the various reactions of the bicyclic lactones, especially their catalytic hydrogenation.



Reactions of Substituted Coumalate Cycloadducts. Catalytic hydrogenation of unsubstituted bicyclic lactones similar to 67 have been reported in the literature before,[37,42] but one would expect the tetrasubstituted olefin of 67 to be more difficult to hydrogenate. We initially examined the hydrogenation of the more readily available model compound 62 to determine the conditions required for this type of reduction. After various catalysts (palladium on carbon, rhodium on alumina, platinum oxide) and pressures of hydrogen were examined, we achieved hydrogenation of 62 by using 500 psi of hydrogen over 5% platinum on carbon for 14 days to afford 68 in 55% yield. Com-

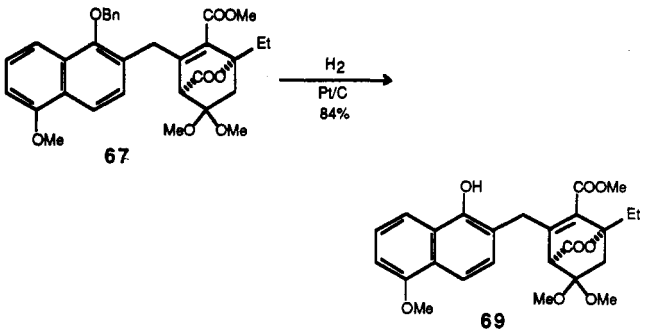


parison of these conditions with those required for hydrogenation of similar trisubstituted olefins (50 psi of hydrogen for 2 h)[37] indicates the extreme difficulty of hydrogenating olefins in 4,6-disubstituted coumalate cycloadducts. The thermal instability of these adducts prevents the use of higher reaction temperatures to increase the rate of hydrogenation. The 200-MHz ^{1}H NMR of the hydrogenated adduct 68 shows the C1 methyl group to be a sharp singlet and the C5 methyl group to be a sharp doublet, indicating that hydrogenation has occurred exclusively from one face of the olefin to give a single isomer. From ^{1}H NMR data, we cannot assign the stereochemistry of this adduct; however, hydrogenation has most probably occurred from the less hindered face of the olefin, namely syn to the lactone bridge, to give the stereochemistry shown in compound 68.

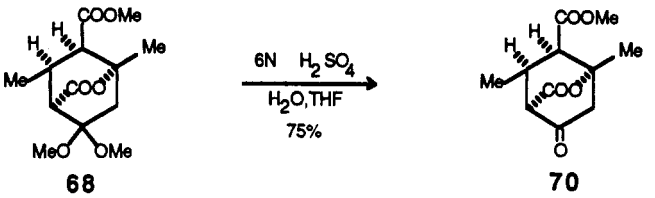
Attempts to hydrogenate the olefin of 67 under the conditions used for the model compound 62 were unsuccessful. As expected, the benzyl protecting group was removed under these conditions to give 69; however, even at pressures of 2500 psi of hydrogen, the olefin was unreactive.

Deketalization of 67 would reduce some of this steric crowding and possibly allow the olefin to be hydrogenated. The stereochemistry of the hydrogenation could not be predicted in this case. However, introduction of the correct stereochemistry at this stage of the synthesis is not crucial, since Kishi[5b] has shown that the asymmetric centers of aklavinone 5 can be epimerized to give the correct stereochemistry.

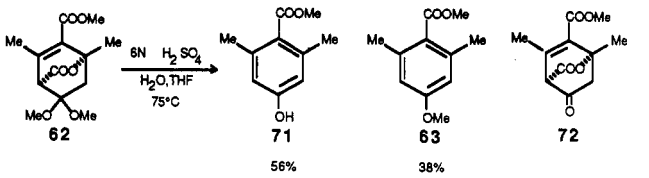
Attempts to hydrolyze the dimethyl ketal of the model compound 62, however, were unsuccessful using a variety of acidic catalysts (*p*-toluenesulfonic acid, hydrochloric



acid, sulfuric acid) in aqueous tetrahydrofuran. Starting material was recovered, quantitatively, after stirring 62 with 6 N sulfuric acid at room temperature for 7 days. Under similar conditions, the hydrogenated adduct 68 was deketalized in 2 h to give 70 in 75% yield. Thus, the strain introduced into this [2.2.2] bicyclic system by the olefin prevents the formation, at room temperature, of the planar carbocation required for hydrolysis of the ketal.



When hydrolysis of 62 is attempted at higher temperatures (75 °C), a 1.5:1 mixture of methyl 2,6-dimethyl-4-hydroxybenzoate (71) and methyl 2,6-dimethyl-4-methoxybenzoate (63) is obtained. The methoxybenzoate 63 is formed, as shown earlier, by the thermal loss of carbon dioxide and methanol. The hydroxybenzoate 71, however, is most likely formed by hydrolysis to the desired ketone 72 followed by rapid loss of carbon dioxide to give the observed phenol. Therefore, at the temperature at which 73 is formed, it is converted into 71 and cannot be isolated.

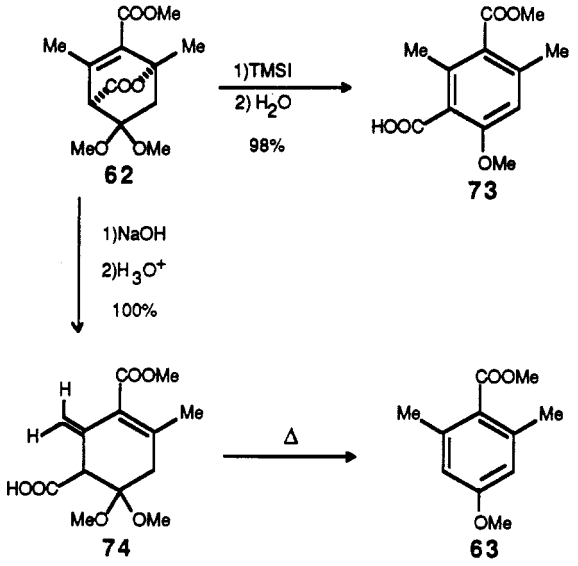


We had shown earlier that dimethyl ketals are readily cleaved with trimethylsilyl iodide (Me_3SiI) at room temperature to give the corresponding ketones.[43] Reaction of 62 with Me_3SiI at room temperature, however, produced the benzoic acid 73 in 98% yield, presumably by preferential reaction with the lactone. While this reaction is not useful for our synthesis of akalvinone 5, it does provide a facile method for the formation of pentasubstituted aromatic compounds, which are only accessible with difficulty by other methods. It is also possible that by using 1,1-dimethoxyalkenes in place of 12 in the initial cycloaddition followed by treatment with Me_3SiI, one could produce hexasubstituted aromatics, compounds of some interest as synthetic targets today.

Cleavage of the [2.2.2] bicyclic system of 62 by hydrolysis of the lactone should permit the dimethyl ketal to be hydrolyzed at room temperature, due to the lack of ring strain. Reaction of 62 with base, however, resulted in the unexpected formation of an *exo*-methylene compound. Proton abstraction from the acidic γ-position of the α,β-unsaturated ester is rapid at room temperature with so-

(43) Jung, M. E.; Andrus, W. A.; Ornstein, P. L. *Tetrahedron Lett.* 1977, 4175.

dium hydroxide in methanol and affords the carboxylic acid **74** in quantitative yield, following neutralization. This carboxylic acid is unstable, and attempted distillation results in the quantitative formation of methyl 2,6-dimethyl-4-methoxybenzoate (**63**) via loss of carbon dioxide and methanol and isomerization.



In addition to hydrogenation, there are several synthetic methods reported in the literature for the 1,4-reduction of α,β-unsaturated esters. In 1975, Semmelhack[44] reported the use of sodium bis(2-methoxyethoxy)aluminum hydride and cuprous bromide for the 1,4-reduction of conjugated ketones and esters. More recently, Yamashita[45] has shown that sodium hydrotelluride reduces α,β-unsaturated carbonyl compounds under mild conditions. Reaction of **62** with these reagents under the conditions described in the literature, however, resulted only in recovery of unreacted starting material. At longer reaction times or higher reaction temperatures, the starting material was destroyed. Therefore, these reagents appear to be ineffective for the reduction of sterically hindered α,β-unsaturated carbonyl compounds that have a potentially good leaving group β to the carbonyl group.

Our inability to reduce this sterically hindered olefin compelled us to abandon this synthetic approach to aklavinone **5**. Although this novel synthetic route was unsuccessful, a variety of useful synthetic information has been determined during the course of study. The mechanism for the bromination–oxidation of 1,5-diacetoxynaphthalene (**6**) has been elaborated,[6e] and the synthesis and reactivity of 2-oxo-2*H*-pyran-5-carboxylates have been examined. In addition, the isolation of 4,6-disubstituted 2-oxo-2*H*-pyran-5-carboxylate cycloadducts has been achieved, and their stability and reactivity have been determined.

Experimental Section

Proton nuclear magnetic resonance spectra (^{1}H NMR) were recorded on a Varian T-60 (60-MHz) or Bruker WP-200 (200-MHz) spectrometer and are so indicated. Carbon nuclear magnetic resonance spectra (^{13}C NMR) were recorded on a Varian CFT-20 (20-MHz) spectrometer. Spectra were recorded in the indicated solvent. Chemical shifts are reported in parts per million downfield from the internal standard, tetramethylsilane. Resonance patterns are reported with the notations s (singlet), d (doublet), t (triplet), q (quartet), and m (multiplet). In addition, the notation b is used to indicate a broad signal. Coupling constants (J) are reported in hertz (Hz). Infrared spectra (IR) were recorded on a Perkin-Elmer 710B infared spectrophotometer as a liquid film (neat), a Nujol mull, or a solution in the indicated solvent. Polystyrene was used as a standard, and the spectra are reported in reciprocal centimeters (cm^{-1}). Ultraviolet spectra (UV) were reported on a Varian Cary 219 spectrophotometer in the indicated solvent, and the spectra are recorded in nanometers (nm). Mass spectra (MS) were recorded on an AEI MS-9 spectrometer and are reported in m/e units for the most abundant peaks. Elemental analyses were performed by Spang Microanalytical Laboratory, Eagle Harbor, MI, or MicroAnal Organic Microanalysis, Tucson, AZ. Melting points were determined on a Büchi melting point apparatus and are uncorrected. E. Merck 60 (70–230-mesh) silica gel was used for column chromatography. Thin-layer chromatographic (TLC) analysis were performed with precoated Eastman Chromagram 13181 silica gel sheets. Visualization was accomplished by UV light or iodine vapor. Preparative high-pressure liquid chromatography (HPLC) was performed on a Waters PrepLC/System 500 using PrepPAK-500 silica gel columns and ethyl acetate/hexane mixtures as eluent. Diethyl ether (ether) and tetrahydrofuran (THF) were distilled from sodium benzophenone ketyl in a recirculating still prior to use. Carbon tetrachloride, chloroform, dichloromethane, hexane, pentane, and pyridine were distilled from calcium hydride, and ethanol and methanol from the corresponding magnesium alkoxide; acetone was distilled from calcium sulfate, benzene from sodium, and *N,N*-dimethylformamide (DMF) from barium oxide prior to use. All reagents were purified according to standard methods before use unless otherwise indicated. All reactions were performed under an inert atmosphere of nitrogen or argon.

1,5-Diacetoxynaphthalene (16). Practical-grade 1,5-naphthalenediol (**6**; 5.00 g, 31.2 mmol) was dissolved in pyridine (25 mL, 306 mmol) and acetic anhydride (25 mL, 265 mmol). The solution was heated at 100 °C for 8 h, and then the remaining acetic anhydride was quenched by careful addition of water. After cooling to room temperature, the solution was poured into 500 mL of water and then filtered to collect the light brown solid. The crude product was dried in vacuo and then recrystallized from benzene to give 3.37 g (44%) of **16** as white needles: mp 158–159 °C (lit.[13] mp 161 °C); ^{1}H NMR (60 MHz) ($CDCl_3$) δ 7.78 (2 H, dd, J = 2.0, 9.0 Hz), 7.18–7.65 (4 H, m), 2.40 (6 H, s); IR ($CDCl_3$) 3000, 1755, 1610, 1405, 1370, 1185, 1160, 1010, 950 cm^{-1}; MS (70 eV) m/e (% intensity) 244 (8.9) (M^+), 202 (15.2), 161 (10.8), 160 (100.0), 131 (11.8), 43 (16.9).

5-Acetoxy-2-bromo-1,4-naphthalenedione (19). A solution of **16** (2.4 g, 10.0 mmol) dissolved in 100 mL of warm acetic acid was added dropwise to a solution of *N*-bromosuccinimide (7.2 g, 40.0 mmol) in 200 mL of acetic acid and 100 mL of water, maintained at 65 °C. Stirring was continued at 65 °C for 45 min following the addition, and then 200 mL of water was added. The cooled solution was extracted with chloroform (4 × 50 mL), and the combined extracts were washed with water (4 × 200 mL) and brine (1 × 200 mL), dried over anhydrous sodium sulfate (Na_2SO_4), and then concentrated in vacuo to give 2.92 g (99%) of **19** as a yellow solid. Recrystallization from ethanol gave yellow needles: mp 153–154 °C (lit.[11] mp 158 °C); ^{1}H NMR (60 MHz) δ 8.13 (1 H, dd, J = 1.5, 8.0 Hz), 7.72 (1 H, t, J = 8.0 Hz), 7.38 (1 H, dd, J = 1.5, 8.0 Hz), 7.36 (1 H, s), 2.42 (3 H, s); IR ($CHCl_3$) 1772, 1684, 1682, 1600, 1370, 1330, 1270, 1190, 1098 cm^{-1}; MS (70 eV) m/e (% intensity) 296 (1.7) (M^+), 294 (0.8) (M^+), 254 (70.9), 252 (67.5), 173 (35.5), 145 (10.6), 63 (12.9), 43 (100.0).

2-Bromo-5-hydroxy-1,4-naphthalenedione (20). A suspension of **19** (2.8 g, 9.50 mmol) in 100 mL of ethanol and 30 mL of 3 N sulfuric acid was gently refluxed for 90 min. The solution was concentrated in vacuo to remove the ethanol and the residue extracted with chloroform (3 × 50 mL). The combined extracts were washed with water (2 × 100 mL) and brine (1 × 100 mL), dried over Na_2SO_4, and then concentrated in vacuo to give 2.21 g (92%) of **20** as a brown–orange solid. Recrystallization from ligroine (60–90 °C) gave bright orange needles: mp 135–136 °C (lit.[14] mp 136 °C); ^{1}H NMR (60 MHz) ($CDCl_3$) δ 11.84 (1 H, s), 7.23–7.86 (4 H, m); IR ($CHCl_3$) 1683, 1644, 1590, 1460, 1365, 1308, 1255, 1176, 1097, 905, 815 cm^{-1}; MS (70 eV) m/e (% intensity) 254 (100.0) (M^+), 252 (98.1) (M^+), 173 (90.3), 145 (44.1), 89 (35.5), 63 (54.0), 62 (22.2), 53 (29.1).

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2-Bromo-1,4,5-trihydroxynaphthalene (22). A suspension of **20** (1.28 g, 5.06 mmol) in 50 mL of diethyl ether (ether) was shaken in a separatory funnel with a freshly prepared solution of sodium dithionate (5.00 g, 28.7 mmol) in 50 mL of water. After the mixture was shaken for 10 min, the organic layer was separated, washed with brine (1 × 25 mL), dried over Na_2SO_4, and then concentrated in vacuo to give 1.14 g (88%) of **22** as a gray solid: mp 96–99 °C dec; ^1H NMR (60 MHz) (CD_3SOCD_3) δ 7.62 (1 H, dd, J = 1.5, 8.0 Hz), 7.33 (1 H, t, J = 8.0 Hz), 6.88 (1 H, dd, J = 1.5, 8.0 Hz), 6.87 (1 H, s), 3.38 (3 H, bs); IR (Nujol mull) 3400–2900, 1615, 1290, 1208, 1180, 1055, 955, 820, 755 cm^{-1}.

2-Bromo-5-methoxy-1,4-naphthalenedione (21). To a mixture of **20** (1.00 g, 3.95 mmol) and silver oxide (1.01 g, 43.5 mmol) in 30 mL of dichloromethane was added dropwise iodomethane (1.23 g, 8.69 mmol). The suspension was stirred at room temperature for 20 h, then filtered through Celite, and concentrated in vacuo to give 1.03 g (98%) of **21** as an orange solid. Recrystallization from ethanol gave yellow–orange needles: mp 131–133 °C (lit.[11] mp 134 °C); ^1H NMR (60 MHz) ($CDCl_3$) δ 7.24–7.84 (4 H, m), 4.02 (3 H, s); IR ($CHCl_3$) 2975, 1680, 1650, 1595, 1475, 1458, 1293, 1245, 1120, 1042, 908, 813 cm^{-1}; MS (70 eV) m/e (% intensity) 268 (100.0) (M^+), 266 (98.0) (M^+), 187 (35.9), 159 (24.9), 157 (43.5), 131 (27.4), 129 (40.9), 116 (37.9), 101 (31.2), 76 (33.0), 75 (28.0), 74 (25.2), 63 (23.2), 62 (31.6), 53 (23.7).

2-Bromo-5-methoxy-1,4-naphthalenediol (23). A suspension of **21** (1.03 g, 3.86 mmol) in 50 mL of ether was shaken in a separatory funnel with a freshly prepared solution of sodium dithionate (5.00 g, 28.7 mmol) in 50 mL of water. After the mixture was shaken for 10 min, the organic layer was separated, washed with brine (1 × 25 mL), dried over Na_2SO_4, and then concentrated in vacuo to give 0.93 g (90%) of **23** as a tan solid: mp 101–103 °C dec; ^1H NMR (60 MHz) ($CDCl_3$) δ 9.07 (1 H, bs), 7.88 (1 H, dd, J = 1.5, 8.0 Hz), 7.42 (1 H, t, J = 8.0 Hz), 6.99 (1 H, s), 6.82 (1 H, dd, J = 1.5, 8.0), 5.50 (1 H, bs), 4.02 (3 H, s); IR ($CDCl_3$) 3495, 3450–3275, 2955, 1630, 1610, 1465, 1445, 1415, 1305, 1275, 1218, 1078, 815 cm^{-1}.

2-Bromo-1,4,5-trimethoxynaphthalene (7) from 23. A solution of **23** (0.93 g, 3.47 mmol) dissolved in 10 mL of acetone was added to a suspension of powdered potassium carbonate (4.87 g, 38.6 mmol) in 40 mL of acetone. Dimethyl sulfate (2.92 g, 23.2 mmol) was then added in one portion and the mixture refluxed for 24 h. After cooling to room temperature, the mixture was filtered through Celite and concentrated in vacuo. The residue was dissolved in 50 mL of ether, and triethylamine (2.34 g, 23.2 mmol) was added. After being stirred for 20 min at room temperature, the solution was washed with 1 N hydrochloric acid (2 × 20 mL), water (1 × 25 mL), and brine (1 × 25 mL), dried over Na_2SO_4, and concentrated in vacuo to give 0.95 g (92%) of **7** as a dark red solid. Recrystallization from ligroine (60–90 °C) gave pale yellow prisms, mp 115–117 °C.

2-Bromo-1,4,5-trimethoxynaphthalene (7) from 22. By the procedure above, **22** (0.50 g, 1.98 mmol) was reacted with dimethyl sulfate (1.23 g, 8.90 mmol) and potassium carbonate (3.37 g, 26.7 mmol) in 40 mL of acetone to give 0.36 g (57%) of **7** as a dark red solid. Recrystallization from ligroine (60–90 °C) gave pale yellow prisms: mp 115–117 °C; ^1H NMR (200 MHz) ($CDCl_3$) δ 7.68 (1 H, dd, J = 1.0, 8.2 Hz), 7.43 (1 H, t, J = 8.2 Hz), 6.91 (1 H, s), 6.89 (1 H, d, J = 8.2 Hz), 3.95 (3 H, s), 3.93 (3 H, s), 3.92 (3 H, s); ^{13}C NMR (20 MHz) ($CDCl_3$) δ 157.62, 153.92, 146.79, 131.81, 127.55, 117.74, 114.71, 112.61, 109.97, 107.05, 61.15, 56.89, 56.47; IR ($CHCl_3$) 2970, 2930, 2910, 2820, 1615, 1605, 1465, 1385, 1330, 1270, 1155, 1135, 1090, 1055, 1005, 815 cm^{-1}; MS (70 eV) m/e (% intensity) 298 (67.6) (M^+), 296 (70.5) (M^+), 284 (11.6), 283 (94.1), 282 (13.0), 281 (100.0), 45 (27.8); high-resolution mass spectrum (70 eV) m/e 298.0022 (calcd for $C_{13}H_{13}{}^{81}BrO_3$ 298.0028), 296.0058 (calcd for $C_{13}H_{13}{}^{79}BrO_3$) 296.0048. Anal. Calcd for $C_{13}H_{13}BrO_3$: C, 52.55; H, 4.41. Found: C, 52.21; H, 4.39.

(3-Bromo-1-propynyl)trimethylsilane (8). This was prepared from the corresponding alcohol by the procedure of Miller,[15] giving **8** in 72% yield as a colorless liquid: bp 83–85 °C (33 mm) [lit.[16] bp 71–73 °C (26 mm)]; ^1H NMR (60 MHz) ($CDCl_3$) δ 3.84 (2 H, s), 0.14 (9 H, s); IR (neat) 3000–2890, 2160, 1415, 1250, 1205, 1045, 845 cm^{-1}. The necessary alcohol, (3-hydroxy-1-propynyl)trimethylsilane, was prepared as follows. To a suspension of magnesium turnings (40.11 g, 1.65 mol) in 1.0 L of ether was added bromoethane (196.15 g, 1.80 mol) in 100 mL of ether at such a rate as to maintain a gentle reflux. The resulting mixture was stirred at room temperature for 3 h, and then, after the mixture was cooled to 0 °C, propargyl alcohol (42.05 g, 0.75 mol) was added dropwise. Following the addition, the solution was stirred room temperature for 4 h. Chlorotrimethylsilane (179.06 g, 1.65 mol) was then added and this mixture stirred for an additional 3 h. The resulting trimethylsilyl alcohol was then hydrolyzed by addition of 1.5 N hydrochloric acid (1.0 L) and stirring for 40 min. The organic layer was then separated and the aqueous layer extracted with ether (2 × 100 mL). The combined organic layers were washed with brine (1 × 100 mL), dried over Na_2SO_4, and concentrated in vacuo. The resulting liquid was distilled to give 63.48 g (66%) of the alcohol as a colorless liquid: bp 79–82 °C (20 mm) [lit.[46] bp 65 °C (10 mm)]; ^1H NMR (60 MHz) ($CDCl_3$) δ 4.21 (2 H, s), 2.93 (1 H, bs), 0.20 (9 H, s); IR (neat) 3480–3120, 2930, 2140, 1250, 1035, 975, 845, 760 cm^{-1}.

[3-(2-Methoxyphenyl)-1-propynyl]trimethylsilane (25). A 1.0-mL portion of a solution of 2-bromoanisole (**24**; 1.46 g, 7.80 mmol) in 10 mL of tetrahydrofuran (THF) was added to a mixture of magnesium turnings (0.23 g, 9.37 mmol) in 2.0 mL of THF. When the Grignard reaction began, 40 mL of THF was added to the reaction mixture and the remaining solution of **24** added dropwise. Following the addition, the solution was stirred for 2 h at room temperature. (3-Bromo-1-propynyl)trimethylsilane (**8**; 2.24 g, 11.7 mmol) was then added dropwise and the solution refluxed for 12 h. After cooling to room temperature, the mixture was poured into 1.0 N hydrochloric acid (100 mL) and this solution extracted with ether (3 × 50 mL). The combined organic extracts were washed with water (1 × 25 mL) and brine (1 × 50 mL), dried over Na_2SO_4, and concentrated in vacuo. Purification by Kugelrohr distillation [185–190 °C oven temperature (60 mm)] gave 1.63 g (96%) of **25** as a colorless liquid: ^1H NMR (60 MHz) ($CDCl_3$) δ 6.63–7.60 (4 H, m), 3.73 (3 H, s), 3.58 (2 H, s), 0.19 (9 H, s); IR (neat) 2940, 2875, 2820, 2160, 1605, 1490, 1465, 1440, 1245, 1105, 1015, 845, 755 cm^{-1}; MS (70 eV) m/e (% intensity) 218 (83.7) (M^+), 203 (100.0), 173 (34.0), 145 (30.8), 129 (29.7), 75 (25.3), 73 (85.6), 43 (22.3).

1-Methoxy-2-(1,2-propadienyl)benzene (26). A solution of **25** (1.00 g, 4.58 mmol) dissolved in 50 mL of 10% potassium hydroxide in methanol was stirred for 6 h at room temperature. The solution was then concentrated in vacuo and the residue dissolved in 50 mL of ether. The ether solution was washed with water (2 × 25 mL) and brine (1 × 25 mL), dried over Na_2SO_4, and concentrated in vacuo. Kugelrohr distillation [58–64 °C oven temperature (0.31 mm)] gave 0.60 g (90%) of **26** as a colorless liquid [lit.[47] bp 62.5–63 °C (0.40 mm)]; ^1H NMR (60 MHz) ($CDCl_3$) δ 6.65–7.50 (4 H, m), 6.52 (1 H, t, J = 7.0 Hz), 5.06 (2 H, d, J = 7.0 Hz), 3.78 (3 H, s); IR (neat) 3050–2875, 2820, 1940, 1593, 1490, 1460, 1285, 1245, 1105, 1015, 850, 745 cm^{-1}.

1-Methoxy-2-(2-propynyl)benzene (27). To a vigorously stirred solution of **25** (0.50 g, 2.29 mmol) in 10 mL of ethanol was added dropwise a solution of silver nitrate (0.58 g, 3.43 mmol) dissolved in 3 mL of water and 7 mL of ethanol. During the addition, a gumlike oil separated from the solution. Stirring was continued at room temperature for an additional 30 min, and then a solution of potassium cyanide (1.49 g, 22.9 mmol) in 3 mL of water was added. This mixture was stirred until the oil dissolved, and then the solution was diluted with 75 mL of ether. The organic layer was washed with water (1 × 25 mL) and brine (1 × 25 mL), dried over Na_2SO_4, and concentrated in vacuo. Kugelrohr distillation [110–115 °C oven temperature (0.74 mm)] gave 0.26 g (77%) of **27** as a colorless liquid [lit.[48] bp 103–108 °C (20 mm)]: ^1H NMR (60 MHz) ($CDCl_3$) δ 6.70–7.61 (4 H, m), 3.80 (3 H, s), 3.54 (2 H, d, J = 3.0 Hz), 2.10 (1 H, t, J = 3.0 Hz); IR (neat) 3240, 2970–2860, 2790, 1485, 1455, 1245, 1105, 1030, 755 cm^{-1}; MS (70 eV) m/e (% intensity) 146 (100.0) (M^+), 145 (21.5), 131 (85.0), 115 (42.5), 103 (35.4), 77 (58.1), 63 (23.4), 51 (29.4).

Methyl 4-(2-Methoxyphenyl)-2-butynoate (28). To a solution of **27** (0.50 g, 3.42 mmol) in 25 mL of THF was added dropwise via syringe 2.8 M methylmagnesium bromide (1.47 mL,

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4.11 mmol) in ether. The solution was heated at 65 °C for 2 h and then cooled to room temperature. Methyl chloroformate (1.29 g, 13.7 mmol) was then added rapidly with vigorous stirring and the solution reheated to 65 °C for 18 h. After cooling to room temperature, the solution was diluted with 75 mL of ether, then washed with 1.0 N hydrochloric acid (1 × 25 mL), water (1 × 25 mL), and brine (1 × 25 mL), dried over Na_2SO_4, and concentrated in vacuo. Purification of the residue by Kugelrohr distillation [178–183°C oven temperature (0.55 mm)] gave 0.63 g (90%) of **28** as a pale yellow oil: ^{1}H NMR (60 MHz) ($CDCl_3$) δ 6.73–7.50 (4 H, m), 3.81 (3 H, s), 3.74 (3 H, s), 3.69 (2 H, s); IR (neat) 2960–2890, 2240, 1715, 1390, 1360, 1339, 1260, 1105, 1065, 1025, 755 cm^{-1}; MS (70 eV) *m/e* (% intensity) 204 (81.5) (M^+), 189 (37.3), 145 (100.0), 144 (35.4), 115 (95.6), 102 (47.1), 91 (59.0), 89 (35.4), 77 (46.4), 63 (42.6), 51 (47.5).

1,4,5-Trimethoxynaphthalene (29c) via 29a and 29b. To a solution of **7** (1.00 g, 3.37 mmol) in 50 mL of THF at −78 °C was added, dropwise, a 1.9 M *tert*-butyllithium solution (3.72 mL, 7.08 mmol) in pentane. This solution was stirred at −78 °C for 15 min to give the lithiate **29a** and then transferred, via a cannula, to a solution of magnesium bromide, prepared by stirring a suspension of magnesium turnings (0.13 g, 5.05 mmol) and 1,2-dibromoethane (1.04 g, 5.05 mmol) in 20 mL of THF, at −78 °C. The resulting Grignard reagent **29b** was warmed to room temperature and a solution of **8** (0.96 g, 5.05 mmol) in 10 mL of THF added slowly. This solution was refluxed for 12 h, then cooled to room temperature, and poured into 1.0 N hydrochloric acid (50 mL). This mixture was extracted with ether (3 × 50 mL), and the combined organic layers were washed with water (1 × 25 mL) and brine (1 × 25 mL), dried over Na_2SO_4, and concentrated in vacuo to give an oily brown solid. Recrystallization of the solid from ligroine (60–90 °C) gave 0.63 g (78%) of **29c** as tan prisms: mp 116–117.5 °C (lit.[49] mp 116–118 °C); ^{1}H NMR (200 MHz) ($CDCl_3$) δ 7.76 (1 H, dd, *J* = 1.2, 8.6 Hz), 7.37 (1 H, t, *J* = 8.6 Hz), 6.90 (1 H, dd, *J* = 1.2, 8.6 Hz), 6.78 (1 H, d, *J* = 8.4 Hz), 6.72 (1 H, d, *J* = 8.4 Hz), 3.97–3.92 (9 H, 3 overlapping s); ^{13}C NMR (20 MHz) ($CDCl_3$) δ 156.83, 150.97, 149.70, 128.83, 125.92, 114.74, 107.23, 107.04, 104.25, 57.50, 56.53, 55.82 (one carbon not resolved); IR ($CHCl_3$) 2990, 2940, 2820, 1600, 1470, 1410, 1390, 1275, 1085, 1060 cm^{-1}; MS (70 eV) *m/e* (% intensity) 218 (100.0) (M^+), 203 (79.0), 115 (11.9), 45 (13.2).

2-(Hydroxyphenylmethyl)-1,4,5-trimethoxynaphthalene (29d). To a solution of **7** (0.50 g, 1.68 mmol) in 25 mL of THF at −78 °C was added dropwise a 1.9 M *tert*-butyllithium solution (1.86 g, 3.53 mmol) in pentane. This solution was stirred at −78 °C for 15 min, and then benzaldehyde (0.18 g, 1.68 mmol) was added slowly. Stirring was continued at −78 °C for 1 h, and then the solution was quenched with 5 mL of a saturated ammonium chloride solution. This mixture was diluted with 75 mL of ether, and this solution was washed with water (1 × 25 mL) and brine (1 × 25 mL), dried over Na_2SO_4, and concentrated in vacuo to give a tan solid. Purification by silica gel chromatography using 33% ethyl acetate/hexane as eluent gave 0.45 g (82%) of **29d** (R_f 0.36) as white prisms: mp 151.5–152.5 °C; ^{1}H NMR (60 MHz) ($CDCl_3$) δ 7.30–7.80 (7 H, m), 7.90 (1 H, dd, *J* = 2.0, 7.0 Hz), 7.89 (1 H, s), 6.38 (1 H, s), 3.99 (3 H, s), 3.91 (3 H, s), 3.77 (3 H, s), 2.91 (1 H, bs); IR ($CDCl_3$) 3550, 2910, 2820, 1605, 1590, 1455, 1385, 1265, 1130, 1080 cm^{-1}; MS (70 eV) *m/e* (% intensity) 324 (56.5) (M^+), 281 (11.5), 105 (100.0), 77 (16.7).

5-(1-Hydroxypropylidene)-2,2-dimethyl-1,3-dioxane-4,6-dione (31). The procedure of Yonemitsu[24] gave **31** in 98% yield as an orange solid: mp 54–55 °C (lit.[24] mp 55 °C); ^{1}H NMR (60 MHz) ($CDCl_3$) δ 15.17 (1 H, bs), 3.15 (2 H, q, *J* = 7.5 Hz), 1.74 (6 H, s), 1.23 (3 H, t, *J* = 7.5 Hz); IR ($CDCl_3$) 2975, 1735, 1660, 1570, 1420–1385, 1335, 1275, 1165, 1035, 950, 915 cm^{-1}.

Methyl 3-Oxopentanoate (10) from Methyl Acetoacetate (34). The procedure of Weiler[23] gave **10** in 51% yield as an orange–brown liquid, bp 38–42 °C (1.0 mm) [lit.[50] bp 88–93 °C (17 mm)].

Methyl 3-Oxopentanoate (10) from 31. The procedure of Yonemitsu[24] gave **10** in 81% yield as a colorless liquid: bp 128–129 °C (118 mm) [lit.[50] bp 88–93 °C (17 mm)]; ^{1}H NMR (60 MHz) ($CDCl_3$) δ 3.74 (3 H, s), 3.48 (2 H, s), 2.60 (2 H, q, *J* = 7.5 Hz), 1.07 (3 H, t, *J* = 7.5 Hz); IR (neat) 3000–2875, 1750, 1720, 1445, 1325, 1255, 1165 cm^{-1}.

Methyl 6-Ethyl-4-methyl-2-oxo-2*H*-pyran-5-carboxylate (33). A mixture of methyl butynoate (**32**; 0.75 g, 7.65 mmol), methyl 3-oxopentanoate (**10**; 1.00 g, 7.65 mmol), and sodium methoxide (0.14 g, 2.52 mmol) was heated slowly to 100 °C and then maintained at that temperature for 3 h. After cooling to room temperature, the mixture was poured into 1.0 N sulfuric acid (25 mL) and this solution extracted with ether (3 × 25 mL). The combined organic extracts were washed with brine (1 × 25 mL), dried over Na_2SO_4, and concentrated in vacuo. Purification by Kugelrohr distillation [150–160 °C oven temperature (5.0 mm)] gave 1.44 g (96%) of **33** as a colorless liquid: ^{1}H NMR (60 MHz) ($CDCl_3$) δ 6.14 (1 H, m), 3.94 (3 H, s), 2.71 (2 H, q, *J* = 7.5 Hz), 2.25 (3 H, d, *J* = 1.5 Hz), 1.28 (3 H, t, *J* = 7.5 Hz); ^{13}C NMR (20 MHz) ($CDCl_3$) δ 168.55, 166.00, 160.72, 154.34, 112.50, 111.93, 52.39, 26.56, 20.97, 11.97; IR (neat) 2940, 1750–1710, 1645, 1555, 1445, 1405, 1285, 1085, 885 cm^{-1}; MS (70 eV) *m/e* (% intensity) 196 (65.9) (M^+), 168 (62.1), 167 (94.6), 165 (56.1), 164 (46.2), 153 (46.2), 139 (51.6), 109 (49.5), 57 (100.0), 53 (32.6), 52 (30.7).

Methyl 4,6-Dimethyl-2-oxo-2*H*-pyran-5-carboxylate (35). To concentrated sulfuric acid (93.18 g, 0.95 mol), cooled to 10 °C, was added methyl acetoacetate (**34**; 58.06 g, 0.50 mol) at such a rate as to maintain the temperature of the mixture between 10 and 15 °C. This solution was allowed to stand at room temperature for 4 days with occasional stirring and then was poured onto 100 g of ice. The resulting slurry was extracted with ether (6 × 50 mL). The combined ether extracts were washed with dilute sodium bicarbonate solution (3 × 50 mL) and brine (1 × 50 mL), dried over Na_2SO_4, and then concentrated in vacuo to give a white solid. Purification by distillation gave 37.35 g (41%) of **35** as a colorless liquid, bp 125–126 °C (1.0 mm) [lit.[22] bp 167 °C (14 mm)], which solidified on standing to a white solid: mp 65–67 °C [lit.[22] mp 60–63 °C); ^{1}H NMR (60 MHz) ($CDCl_3$) δ 6.02 (1 H, m), 3.89 (3 H, s), 2.40 (3 H, s), 2.23 (3 H, d, *J* = 1.0 Hz); IR ($CHCl_3$) 3010–2910, 1760–1715, 1555, 1435, 1405, 1330–1270, 1095, 880 cm^{-1}; MS (70 eV) *m/e* (% intensity) 182 (51.9) (M^+), 154 (76.2), 151 (39.2), 139 (42.5), 123 (36.0), 122 (46.9), 109 (23.3), 53 (26.3), 43 (100.0).

Methyl 6-(Bromomethyl)-4-methyl-2-oxo-2*H*-pyran-5-carboxylate (36). To a solution of **35** (1.00 g, 5.49 mmol) in 25 mL of carbon tetrachloride was added *N*-bromosuccinimide (0.98 g, 5.49 mmol) and benzoyl peroxide (0.01 g, 0.06 mmol). The solution was refluxed for 3 h, then cooled to room temperature, and filtered through Celite. The filtrate was concentrated in vacuo and the residue purified by Kugelrohr distillation [150–155 °C oven temperature (0.015 mm)] to give 1.36 g (95%) of **36** as a pale yellow oil: ^{1}H NMR (60 MHz) ($CDCl_3$) δ 6.19 (1 H, m), 4.40 (2 H, s), 3.96 (3 H, s), 2.26 (3 H, d, *J* = 1.0 Hz); IR (neat) 3080–2940, 1770–1710, 1665, 1550, 1440, 1395, 1380, 1290, 1085, 930 cm^{-1}; MS (70 eV) *m/e* (% intensity) 262 (8.0) (M^+), 260 (7.2) (M^+), 182 (29.4), 181 (38.8), 167 (46.0), 154 (40.0), 153 (29.0), 139 (35.1), 123 (26.6), 122 (29.9), 80 (22.1), 53 (26.2), 52 (25.8), 51 (26.9), 44 (21.9), 43 (100.0).

Methyl 4-[(Tetrahydro-2*H*-pyran-2-yl)oxy]-2-butynoate (38a). To a suspension of magnesium turnings (4.98 g, 205 mmol) in 100 mL of THF was added dropwise bromoethane (21.38 g, 196 mmol). After the addition, the solution was stirred at room temperature for 2 h and then cooled to 0 °C. A solution of **37a**[25] (25.0 g, 178 mmol) in 50 mL of THF was then added dropwise and this solution stirred an additional 1 h at room temperature. After cooling to 0 °C, the solution was transferred, dropwise via a cannula, to an ice-cooled solution of methyl chloroformate (20.22 g, 214 mmol) in 100 mL of THF. This solution was stirred at room temperature for 2 h and then diluted with water (200 mL) and this mixture extracted with ether (3 × 100 mL). The combined organic extracts were washed with water (1 × 50 mL) and brine (1 × 50 mL), dried over Na_2SO_4, and concentrated in vacuo. The residue was purified by distillation to give 20.29 g (57%) of **38a** as a colorless liquid: bp 145–148 °C (32 mm);[26] ^{1}H NMR (60 MHz) ($CDCl_3$) δ 4.77 (1 H, m), 4.33 (2 H, s), 3.45–3.95 (2 H, m), 3.74 (3 H, s), 1.40–1.84 (6 H, m); IR (neat) 2940–2805, 2220, 1720, 1435, 1255, 1125, 1030 cm^{-1}.

3-(Methoxymethoxy)-1-propyne (37b). To a suspension of phosphorus pentoxide (69.64 g, 0.49 mol) in 250 mL of dimeth-

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oxymethane (215.0 g, 2.83 mol) and 250 mL of chloroform was added propargyl alcohol (25.0 g, 0.45 mol). The mixture was stirred for 2 h and then poured into 250 mL of saturated sodium bicarbonate solution. The aqueous layer was separated and extracted with chloroform (3 × 50 mL). The combined organic extracts were washed with brine (1 × 50 mL), dried over Na_2SO_4, and concentrated in vacuo. Distillation of the residue gave 16.52 g (37%) of **37b** as a colorless liquid: bp 43–46 °C (55 mm) [lit.[28] bp 54 °C (80 mm)]; ^1H NMR (60 MHz) ($CDCl_3$) δ 4.64 (2 H, s), 4.17 (2 H, d, J = 2.3 Hz), 3.32 (3 H, s), 2.40 (1 H, t, J = 2.3 Hz); IR (neat) 3260, 3000–2800, 2100, 1442, 1370, 1210, 1150, 1100, 1040, 995, 935, 920, 860 cm^{-1}.

Methyl 4-(Methoxymethoxy)-2-butynoate (38b). To an ice-cooled solution of **37b** (17.00 g, 0.17 mol) in 300 mL of THF was added dropwise 3 M methylmagnesium bromide (62.30 mL, 0.18 mol) in ether. This solution was stirred for 1 h at room temperature and then, after cooling to 0 °C, was transferred, dropwise via a cannula, to an ice-cooled solution of methyl chloroformate (19.26 g, 0.20 mol) in 100 mL of THF. After being stirred at room temperature for 2 h, this solution was poured into water (300 mL) and this mixture extracted with ether (3 × 100 mL). The combined organic extracts were washed with brine (1 × 50 mL), dried over Na_2SO_4, and concentrated in vacuo. Distillation of the residue gave 8.92 g (33%) of **38b** as a colorless liquid: bp 155–157 °C (69 mm); ^1H NMR (60 MHz) ($CDCl_3$) δ 4.67 (2 H, s), 4.30 (2 H, s), 3.73 (3 H, s), 3.36 (3 H, s); IR (neat) 3000–2800, 2230, 1720, 1435, 1260, 1150, 1045 cm^{-1}; MS (16 eV) m/e (% intensity) 158 (1.8) (M^+), 127 (21.2), 113 (47.3), 99 (21.5), 98 (61.1), 75 (21.2), 68 (47.1), 59 (32.0), 45 (100.0).

Methyl 6-Ethyl-4-[(methoxymethoxy)methyl]-2-oxo-2*H*-pyran-5-carboxylate (39b). A mixture of **38b** (2.50 g, 15.8 mmol), **10** (2.06 g, 15.8 mmol), and sodium methoxide (0.28 g, 5.21 mmol) was heated slowly to 100 °C and then maintained at that temperature for 3 h. After cooling to room temperature, the mixture was poured into 1.0 N sulfuric acid (50 mL) and this solution extracted with ether (3 × 50 mL). The combined organic extracts were washed with brine (1 × 50 mL), dried over Na_2SO_4, and concentrated in vacuo. Purification by silica gel chromatography using 20% ethyl acetate/hexane as eluent gave an oily residue (R_f 0.33) that was further purified by Kugelrohr distillation [160–170 °C oven temperature (0.075 mm)] to give 0.89 g (22%) of **39b** as a colorless oil: ^1H NMR (200 MHz) ($CDCl_3$) δ 6.31 (1 H, t, J = 1.5 Hz), 4.60 (2 H, s), 4.42 (2 H, d, J = 1.5 Hz), 3.78 (3 H, s), 3.30 (3 H, s), 2.60 (2 H, q, J = 7.3 Hz), 1.20 (3 H, t, J = 7.3 Hz); ^{13}C NMR (20 MHz) ($CDCl_3$) δ 170.03, 165.49, 160.75, 154.16, 109.49, 96.34, 66.01, 55.73, 52.45, 26.66, 12.01 (one carbon not resolved); IR (neat) 3000–2860, 1750–1720, 1440, 1280, 1155, 1080, 1055 cm^{-1}.

Methyl 4-Methoxy-2-butynoate (38c). To an ice-cooled solution of **37c**[29] (10.0 g, 0.14 mol) in 200 mL of THF was added dropwise 3 M methylmagnesium bromide (52.32 mL, 0.16 mol) in ether. This solution was stirred for 1 h at room temperature and then, after cooling to 0 °C, was transferred, dropwise via a cannula, to an ice-cooled solution of methyl chloroformate (16.18 g, 0.17 mol) in 100 mL of THF. After being stirred at room temperature for 5 h, this solution was poured into water (300 mL) and this mixture extracted with ether (3 × 100 mL). The combined organic extracts were washed with brine (1 × 50 mL), dried over Na_2SO_4, and concentrated in vacuo. Distillation of the residue gave 10.58 g (58%) of **38c** as a colorless liquid, bp 41–43 °C (0.54 mm).[26a] (*Caution*! Attempted distillation of an impure sample of this compound at higher pressure resulted in an explosion.) ^1H NMR (60 MHz) ($CDCl_3$) δ 4.19 (2 H, s), 3.73 (3 H, s), 3.38 (3 H, s); IR (neat) 2975–2780, 2240, 1715, 1445, 1255, 1100, 1070, 945, 915 cm^{-1}.

Methyl 6-Ethyl-4-(methoxymethyl)-2-oxo-2*H*-pyran-5-carboxylate (39c). A mixture of **38c** (4.92 g, 38.4 mmol), **10** (5.00 g, 38.4 mmol), and sodium methoxide (0.69 g, 12.7 mmol) was heated slowly to 100 °C and then maintained at that temperature for 3.5 h. After cooling to room temperature, the mixture was poured into 1.0 N sulfuric acid (50 mL) and this solution extracted with ether (3 × 50 mL). The combined organic extracts were washed with brine (1 × 50 mL), dried over Na_2SO_4, and concentrated in vacuo. Purification by silica gel chromatography using 22% ethyl acetate/hexane as eluent gave an oily residue (R_f 0.29) that was distilled to give 2.86 g (33%) of **39c** as a pale yellow oil: bp 105–106 °C (0.055 mm); ^1H NMR (200 MHz) ($CDCl_3$) δ 6.31 (1 H, m), 4.36 (2 H, d, J = 1.2 Hz), 3.87 (3 H, s), 3.40 (3 H, s), 2.71 (2 H, q, J = 7.6 Hz), 1.28 (3 H, t, J = 7.6 Hz); ^{13}C NMR (20 MHz) ($CDCl_3$) δ 169.84, 165.59, 160.81, 154.31, 109.54, 71.25, 58.90, 52.43, 26.55, 11.98 (one carbon not resolved); IR (neat) 3000–2800, 1760–1720, 1550, 1440, 1280, 1075 cm^{-1}; MS (70 eV) m/e (% intensity) 226 (46.2) (M^+), 198 (47.3), 195 (28.7), 194 (46.7), 170 (60.8), 169 (21.5), 167 (21.5), 166 (39.2), 151 (29.2), 59 (26.7), 57 (100.0), 45 (41.6), 43 (24.8), 41 (20.3).

Methyl 4-(Bromomethoxymethyl)-6-ethyl-2-oxo-2*H*-pyran-5-carboxylate (40). To a solution of **39c** (1.00 g, 4.42 mmol) in 50 mL of carbon tetrachloride were added *N*-bromosuccinimide (0.79 g, 4.42 mmol) and benzoyl peroxide (0.01 g, 0.04 mmol). The mixture was heated at reflux for 45 min, then cooled to room temperature, and filtered through Celite. The filtrate was then concentrated in vacuo to give 1.25 g (93%) of **40** as a moisture-sensitive yellow oil: ^1H NMR (60 MHz) ($CDCl_3$) δ 6.91 (1 H, d, J = 1.0 Hz), 6.52 (1 H, d, J = 1.0 Hz), 3.85 (3 H, s), 3.62 (3 H, s), 2.69 (2 H, q, J = 7.0 Hz), 1.14 (3 H, t, J = 7.0 Hz); IR (neat) 2940, 1770–1700, 1550, 1445, 1285, 1080, 990 cm^{-1}.

Methyl 6-Ethyl-4-formyl-2-oxo-2*H*-pyran-5-carboxylate (41). To a solution of **40** (1.25 g, 4.10 mmol) in 25 mL of ether was added 1.0 mL of water. The solution was stirred at room temperature for 30 min, then washed with dilute sodium bicarbonate solution (1 × 10 mL) and brine (1 × 10 mL), dried over Na_2SO_4, and concentrated in vacuo. The residue was purified by silica gel chromatography using 33% ethyl acetate/hexane as eluent to give an oily residue (R_f 0.27). Kugelrohr distillation [110–120 °C oven temperature (0.026 mm)] of the residue gave 0.39 g (45%) of **41** as a colorless oil that solidified on standing to a white solid: mp 59–60.5 °C; ^1H NMR (200 MHz) ($CDCl_3$) δ 9.91 (1 H, s), 6.51 (1 H, s), 3.90 (3 H, s), 2.82 (2 H, q, J = 7.5 Hz), 1.31 (3 H, t, J = 7.5 Hz); ^{13}C NMR (20 MHz) ($CDCl_3$) δ 183.75, 172.27, 164.60, 160.06, 148.54, 115.82, 107.32, 52.94, 26.41, 11.87; IR ($CDCl_3$) 2950, 1770–1710, 1550, 1445, 1280, 1255, 1225, 1085, 865 cm^{-1}; MS (70 eV) m/e (% intensity) 210 (12.9) (M^+), 182 (24.4), 179 (22.5), 150 (28.2), 122 (24.6), 93 (27.3), 57 (100.0).

Dimethyl 3-Chloro-2-pentenedioate (44). The procedure of Bryson[31] gave **44** in 38% yield as a colorless liquid, bp 70–75 °C (0.063 mm) [lit.[31] bp 50–60 °C (0.02 mm)]. The product was a 6:1 mixture of *E* and *Z* isomers: ^1H NMR (60 MHz) ($CDCl_3$) (major isomer) δ 6.37 (1 H, s), 4.18 (2 H, s), 3.78 (6 H, s), (minor isomer) 6.31 (1 H, s), 4.18 (2 H, s), 3.78 (6 H, s); IR (neat) 2945, 1760–1720, 1640, 1440, 1325, 1205, 1170, 1020 cm^{-1}; MS (70 eV) m/e (% intensity) 192 (1.0) (M^+), 161 (50.8), 160 (53.4), 132 (37.4), 129 (38.4), 113 (34.4), 67 (29.8), 59 (100.0).

Methyl 6-Ethyl-5-(methoxycarbonyl)-2-oxo-2*H*-pyran-4-acetate (42a). A 50% sodium hydride dispersion (4.19 g, 87.3 mmol) in oil was washed with pentane (3 × 25 mL) and the resulting solid mixed with 500 mL of benzene. To this suspension was added dropwise **10** (11.36 g, 87.3 mmol). The mixture was heated at reflux for 30 min and then cooled to 50 °C. A solution of **44** (16.81 g, 87.3 mmol) in 50 mL of benzene was then added slowly over a 15-min period. The resulting solution was refluxed for 2 h and then cooled to room temperature and 50 mL of 0.5 N sulfuric acid added. The layers were separated, and the aqueous layer was extracted with benzene (3 × 50 mL). The combined organic layers were washed with water (1 × 50 mL) and brine (1 × 50 mL), dried over magnesium sulfate, and then concentrated in vacuo. The product was purified by distillation to give 11.98 g (54%) of **42a** as a colorless liquid: bp 138–144 °C (0.06 mm); ^1H NMR (200 MHz) ($CDCl_3$) δ 6.08 (1 H, s), 3.83 (3 H, s), 3.71 (3 H, s), 3.67 (2 H, s), 2.78 (2 H, q, J = 7.6 Hz), 1.30 (3 H, t, J = 7.6 Hz); ^{13}C NMR (20 MHz) ($CDCl_3$) δ 170.94, 169.46, 165.60, 160.24, 149.98, 114.34, 111.01, 52.35, 52.07, 39.97, 26.96, 11.97; IR (neat) 2930, 1760–1710, 1435, 1275, 1195, 1170, 1075 cm^{-1}; MS (70 eV) m/e (% intensity) 254 (24.9) (M^+), 224 (25.2), 223 (54.6), 222 (83.8), 194 (51.0), 193 (55.9), 167 (44.8), 166 (47.4), 59 (31.4), 57 (100.0).

Methyl 6-Ethyl-4-[(methoxycarbonyl)(5-methoxy-2-naphthalene-1,4-dionyl)methyl]-2-oxo-2*H*-pyran-5-carboxylate (43a). A 24.9% potassium hydride dispersion (0.30 g, 1.87 mmol) in oil was washed with hexane (3 × 10 mL) and the resulting solid mixed with 8.0 mL of *N*,*N*-dimethylformamide (DMF). This suspension was cooled to −23 °C, and a solution of **42a** (0.48 g, 1.87 mmol) in 2.0 mL of DMF was added dropwise.

This mixture was stirred at −23 °C for 20 min and then added dropwise, via a syringe, to a solution of **21** (0.50 g, 1.87 mmol) in 10 mL of DMF at −23 °C. The resulting dark blue solution was stirred an additional 30 min at −23 °C and then quenched with 10 mL of 1 N hydrochloric acid. This orange solution was diluted with 75 mL of dichloromethane, and the layers separated. The organic layer was washed with water (3 × 20 mL) and brine (1 × 25 mL), dried over Na_2SO_4, and then concentrated in vacuo. The residue was purified by silica gel chromatography using 50% ethyl acetate/hexane as eluent to give 0.43 g (52%) of **43a** (R_f 0.30) as an orange solid, mp 92–97 °C dec. ^1H NMR and IR show that in solution ($CDCl_3$) **43a** exists with the tautomeric **45** in an approximately 1:1 ratio.

43a: ^1H NMR (200 MHz) ($CDCl_3$) δ 7.69–7.85 (2 H, m), 7.30–7.39 (1 H, m), 6.68 (1 H, d, J = 1.3 Hz), 6.01 (1 H, d, J = 1.3 Hz), 5.79 (1 H, d, J = 1.3 Hz), 4.00 (3 H, s), 3.80 (3 H, s), 3.72 (3 H, s), 2.73 (2 H, q, J = 7.9 Hz), 1.32 (3 H, t, J = 7.9 Hz).

45: ^1H NMR (200 MHz) ($CDCl_3$) δ 8.59 (1 H, s), 7.69–7.85 (2 H, m), 7.30–7.39 (1 H, s), 6.05 (1 H, s), 5.39 (1 H, s), 4.00 (3 H, s), 3.86 (3 H, s), 3.79 (3 H, s), 2.78 (2 H, q, J = 7.6 Hz), 1.30 (3 H, t, J = 7.6 Hz); IR ($CDCl_3$) 3550–3380, 3010, 2940, 1770–1710, 1685–1665, 1595, 1440, 1330–1200, 1085 cm^{-1}; MS (70 eV) m/e (% intensity) 440 (30.3) (M^+), 439 (40.6), 438 (100.0), 409 (37.1), 408 (96.3), 381 (60.1), 380 (42.4), 379 (46.1), 353 (30.6), 325 (38.7), 321 (67.6), 76 (31.6), 59 (30.0), 57 (93.5), 44 (32.6).

6-Ethyl-5-(methoxycarbonyl)-2-oxo-2*H*-pyran-4-acetic Acid (42b). A solution of **42a** (4.00 g, 157 mmol) in 10 mL of water and 10 mL of concentrated sulfuric acid was stirred at room temperature for 4.5 days and then was diluted with 50 mL of ether. The layers were separated, and the aqueous layer was extracted with ether (3 × 25 mL). The combined organic extracts were then washed with saturated sodium bicarbonate (2 × 25 mL). The ether layer was washed with brine (1 × 25 mL), dried over Na_2SO_4, and concentrated in vacuo to give 1.00 g (25%) of unreacted **42a**. The combined bicarbonate layers were cooled to 0 °C and acidified to pH 1 by slow addition of concentrated hydrochloric acid. The acidified mixture was extracted with ether (4 × 50 mL), and the combined organic extracts were washed with water (1 × 25 mL) and brine (1 × 50 mL), dried over Na_2SO_4, and then concentrated in vacuo to give 2.46 g (65%) of **42b** as a white solid: mp 93–96 °C; ^1H NMR (60 MHz) ($CDCl_3$) δ 10.50 (1 H, bs), 6.14 (1 H, m), 3.85 (3 H, s), 3.69 (2 H, s), 2.81 (2 H, q, J = 7.0 Hz), 1.19 (3 H, t, J = 7.0 Hz), 1.19 (3 H, t, J = 7.0 Hz); IR ($CDCl_3$) 3400–2800, 1770–1690, 1550, 1445, 1405, 1280, 1080 cm^{-1}; MS (70 eV) m/e (% intensity) 240 (2.5) (M^+), 196 (40.6), 168 (42.5), 167 (54.8), 165 (34.3), 164 (31.5), 153 (37.7), 139 (33.8), 109 (30.5), 57 (88.0), 44 (100.0).

Trimethylsilyl 6-Ethyl-5-(methoxycarbonyl)-2-oxo-2*H*-pyran-4-acetate (42c). To a solution of **42b** (0.50 g, 2.08 mmol) in 3.0 mL of dichloromethane added dropwise (*E*)-[(1-methoxy-1-propenyl)oxy]trimethylsilane[34a] (0.50 g, 3.12 mmol). The solution was stirred at room temperature for 60 min and then concentrated in vacuo. Purification by Kugelrohr distillation [150–160 °C oven temperature (0.10 mm)] gave 0.55 g (84%) of **42c** as a colorless oil: ^1H NMR (60 MHz) ($CDCl_3$) δ 6.08 (1 H, m), 3.86 (3 H, s), 3.71 (2 H, s), 2.79 (2 H, q, J = 8.0 Hz), 1.17 (3 H, t, J = 8.0 Hz), 0.31 (9 H, s); IR (neat) 2950, 1770–1710, 1550, 1445, 1280, 1255, 1200, 1080, 855 cm^{-1}.

2,2,2-Trichloroethyl 6-Ethyl-5-(methoxycarbonyl)-2-oxo-2*H*-pyran-4-acetate (42d). To a solution of **42b** (0.50 g, 2.08 mmol) in 20 mL of dichloromethane were added pyridine (0.17 g, 2.08 mmol), dicyclohexylcarbodiimide (0.43 g, 2.08 mmol), and 2,2,2-trichloroethanol (0.31 g, 2.08 mmol). This mixture was stirred at room temperature for 48 h and then was diluted with 50 mL of dichloromethane. The resulting solution was washed with 1.0 N hydrochloric acid (1 × 25 mL), water (1 × 25 mL), and brine (1 × 25 mL), then dried over Na_2SO_4, and concentrated in vacuo to give an oil residue. Purification by silica gel chromatography using 33% ethyl acetate/hexane as eluent gave 0.63 g (81%) of **42d** (R_f 0.56) as a white solid: mp 65–68 °C; ^1H NMR (60 MHz) ($CDCl_3$) δ 6.14 (1 H, m), 4.74 (2 H, s), 3.82 (3 H, s), 2.80 (2 H, q, J = 7.0 Hz), 1.14 (3 H, t, J = 7.0 Hz); IR ($CHCl_3$) 3040–2930, 1770–1710, 1635, 1550, 1445, 1410, 1280, 1160, 1080, 870, 825 cm^{-1}; MS (70 eV) m/e (% intensity) 374 (1.6) (M^+), 372 (4.0) (M^+), 370 (4.5) (M^+), 224 (46.3), 223 (74.2), 195 (37.1), 194 (100.0), 193 (67.4), 191 (46.1), 190 (47.3), 179 (52.7), 166 (35.1), 57 (61.4).

1,5-Dimethoxynaphthalene (47). The procedure of Naylor and Gardner[51] gave **47** in 50% yield as a dark brown solid. Recrystallization from ethanol gave pale yellow prisms: mp 180–181 °C (lit.[52] mp 183–184 °C); ^1H NMR (60 MHz) ($CDCl_3$) δ 7.94 (2 H, dd, J = 1.5, 8.0 Hz), 7.44 (2 H, t, J = 8.0 Hz), 6.90 (2 H, dd, J = 1.5, 8.0 Hz), 4.02 (3 H, s); IR ($CHCl_3$) 1600, 1515, 1410, 1270, 1090, 1070 cm^{-1}; MS (70 eV) m/e (% intensity) 188 (100.0) (M^+), 173 (54.4), 115 (41.6).

5-Methoxy-1-naphthalenol (48). The procedure of Rapoport[10] gave **48** in 94% yield as a tan solid. Recrystallization using the procedure above gave long white needles: mp 139–140 °C (lit.[14] mp 140 °C); ^1H NMR (60 MHz) ($CDCl_3$) δ 7.18–7.98 (4 H, m), 6.82 (2 H, m), 5.23 (1 H, s), 3.99 (3 H, s); IR ($CHCl_3$) 3575, 3400–3190, 1605, 1520, 1415, 1275, 1045, 905 cm^{-1}; MS (70 eV) m/e (% intensity) 174 (100.0) (M^+), 159 (75.9), 131 (51.8), 115 (16.1), 103 (12.0), 77 (12.4).

2-Bromo-5-methoxy-1-naphthalenol (49). To a solution of **48** (5.00 g, 28.7 mmol) dissolved in 250 mL of carbon tetrachloride was added, dropwise, a solution of bromine (4.58 g, 28.7 mmol) in 50 mL of carbon tetrachloride. Following the addition, the solution was stirred at room temperature for 24 h and then filtered with suction through a pad of silica gel. Concentration of the filtrate in vacuo gave a white solid that was recrystallized from ligroine (60–90 °C) to give 6.59 g (91%) of **49** as white needles: mp 94–95 °C (lit.[11] mp 95 °C); ^1H NMR (60 MHz) ($CDCl_3$) δ 7.43–8.10 (4 H, m), 7.00 (1 H, dd, J = 1.5, 8.0 Hz), 6.10 (1 H, s), 4.13 (3 H, s); IR ($CDCl_3$) 3500, 1595, 1415, 1270, 1055 cm^{-1}; MS (70 eV) m/e (% intensity) 254 (100.0) (M^+), 252 (95.5) (M^+), 211 (31.1), 209 (30.7), 102 (20.1), 101 (16.0).

2-Bromo-5-methoxy-1-(phenylmethoxy)naphthalene (46). To a solution of **49** (5.00 g, 1.98 mmol) dissolved in 50 mL of acetone were added powdered potassium carbonate (2.75 g, 1.98 mmol) and benzyl bromide (3.38 g, 1.98 mmol). The solution was stirred at room temperature for 36 h, then filtered through Celite, and concentrated in vacuo. The residue was redissolved in 100 mL of ether, and this solution was washed with 1 N sodium hydroxide (1 × 25 mL), 1 N hydrochloric acid (1 × 25 mL), water (1 × 25 mL), and brine (1 × 25 mL), dried over Na_2SO_4, and concentrated in vacuo to give a dark red solid. Purification by high-pressure liquid chromatography using 11% ethyl acetate/hexane as eluent gave 4.69 g (69%) of **46** (R_f 0.49) as a pale yellow solid: mp 117–118 °C; ^1H NMR (60 MHz) ($CDCl_3$) δ 7.37–8.13 (9 H, m), 6.81 (1 H, dd, J = 1.0, 8.0 Hz), 5.20 (2 H, s), 4.02 (3 H, s); ^{13}C NMR (20 MHz) ($CDCl_3$) δ 155.66, 151.52, 136.95, 130.46, 129.09, 128.46, 128.07, 127.02, 119.78, 114.15, 104.47, 75.44, 55.41 (three carbons not resolved); IR ($CHCl_3$) 1600, 1475, 1420, 1395, 1280, 1090 cm^{-1}; MS (70 eV) m/e (% intensity) 344 (4.5) (M^+), 342 (4.3) (M^+), 263 (35.2), 253 (14.4), 251 (13.8), 92 (12.3), 91 (100.0). Anal. Calcd for $C_{18}H_{15}BrO_2$: C, 62.99; H, 4.41. Found: C, 62.95; H, 4.41.

5-Methoxy-1-(phenylmethoxy)-2-[3-(trimethylsilyl)-2-propynyl]naphthalene (50). To a suspension of magnesium turnings (0.88 g, 36.4 mmol) in 20 mL of THF was added 1,2-dibromoethane (1.05 g, 5.60 mmol). When the reaction subsided, a solution of **46** (9.61 g, 28.0 mmol) in 100 mL of THF was added slowly and this solution then warmed to 50°C and stirred for 3 h. To the resulting Grignard reagent was added a solution of **8** (8.03 g, 42.0 mmol) in 50 mL of THF. Stirring was continued for 12 h at 50 °C, and then the solution was cooled to room temperature and poured into 100 mL of 1.0 N hydrochloric acid. This mixture was extracted with ether (3 × 100 mL), and the combined organic layers were washed with water (1 × 100 mL) and brine (1 × 50 mL), dried over Na_2SO_4, and concentrated in vacuo to give a dark oil. Purification by high-pressure liquid chromatography using 11% ethyl acetate/hexane as eluent gave 8.06 g (77%) of **50** (R_f 0.46) as a pale yellow oil: ^1H NMR (200 MHz) ($CDCl_3$) δ 8.07 (1 H, d, J = 8.5 Hz), 7.70 (1 H, d, J = 8.5 Hz), 7.40–7.62 (7 H, m), 6.81 (1 H, d, J = 7.9 Hz), 5.06 (2 H, s), 4.00 (3 H, s), 3.80 (2 H, s), 0.16 (9 H, s); IR (neat) 2940, 2160, 1595, 1505, 1410, 1395, 1365, 1260, 1060, 840, 755 cm^{-1}; MS (70 eV) m/e

(51) Naylor, C. A., Jr.; Gardner, S. H. *J. Am. Chem. Soc.* **1931**, *53*, 4109.

(52) Bentley, W. H.; Robinson, R.; Weizmann, C. *J. Chem. Soc.* **1907**, *91*, 104.

(% intensity) 374 (34.7) (M^+), 301 (21.4), 283 (55.4), 253 (14.7), 209 (16.1), 173 (15.8), 91 (100.0), 73 (58.1), 45 (14.6); high-resolution mass spectrum (70 eV) m/e 374.1717 (calcd for $C_{24}H_{26}O_2Si$ 374.1703).

5-Methoxy-1-(phenylmethoxy)-2-(2-propynyl)naphthalene (51). To a solution of **50** (7.50 g, 20.0 mmol) in 75 mL of ethanol was added, dropwise with vigorous stirring, a solution of silver nitrate (5.10 g, 30.0 mmol) dissolved in 20 mL of water. Stirring was continued at room temperature for an additional 30 min, and then a solution of potassium cyanide (13.02 g, 200 mmol) in 20 mL of water was added. This solution was stirred for 1 h and then diluted with 200 mL of ether. The organic layer was washed with water (2 × 50 mL) and brine (1 × 50 mL), dried over Na_2SO_4, and concentrated in vacuo. Purification of the residue by high-pressure liquid chromatography using 11% ethyl acetate/hexane as eluent gave 5.20 g (86%) of **51** as a colorless oil that solidified on standing to a white solid: mp 67–68 °C; ^1H NMR (200 MHz) ($CDCl_3$) δ 8.06 (1 H, d, J = 8.6 Hz), 7.70 (1 H, d, J = 8.6 Hz), 7.35–7.61 (7 H, m), 6.80 (1 H, d, J = 7.9 Hz), 5.05 (2 H, s), 3.99 (3 H, s), 3.74 (2 H, d, J = 2.4 Hz), 2.13 (1 H, t, J = 2.4 Hz); IR (neat) 3270, 3060–2800, 2105, 1600, 1500, 1450, 1410, 1395, 1365, 1255, 1060, 795, 750 cm^{-1}; MS (70 eV) m/e (% intensity) 302 (24.5) (M^+), 283 (12.1), 212 (15.6), 211 (100.0), 196 (14.7), 168 (22.6), 139 (14.0), 91 (74.0), 65 (14.1); high-resolution mass spectrum (70 eV) m/e 302.1287 (calcd for $C_{21}H_{18}O_2$ 302.1307).

Methyl 4-[5-Methoxy-1-(phenylmethoxy)-2-naphthyl]-2-butynoate (52). To a solution of **51** (7.07 g, 23.4 mmol) in 100 mL of THF at room temperature was added dropwise a solution of 3.0 M methylmagnesium bromide (11.70 mL, 35.1 mmol) in ether. This solution was heated to reflux for 2 h, then cooled to 0 °C, and transferred, via a cannula, to an ice-cooled solution of methyl chloroformate (6.63 g, 70.2 mmol) in 100 mL of THF. The resulting solution was stirred at room temperature for 12 h and then diluted with ether (250 mL). This mixture was washed with 1 N hydrochloric acid (1 × 50 mL), water (2 × 50 mL), and brine (1 × 75 mL), dried over Na_2SO_4, and then concentrated in vacuo. The residue was purified by high-pressure liquid chromatography using 17% ethyl acetate/hexane as eluent to give 5.85 g (69%) of **52** as colorless oil: ^1H NMR (200 MHz) ($CDCl_3$) δ 8.07 (1 H, d, J = 8.6 Hz), 7.70 (1 H, d, J = 8.6 Hz), 7.38–7.52 (7 H, m), 6.83 (1 H, d, J = 7.3 Hz), 5.06 (2 H, s), 4.00 (3 H, s), 3.82 (2 H, s), 3.75 (3 H, s); IR (neat) 3060–2810, 2140, 1710, 1600, 1510, 1420, 1400, 1370, 1265, 1065, 760 cm^{-1}; MS (70 eV) m/e (% intensity) 360 (18.7) (M^+), 269 (37.4), 237 (18.2), 211 (7.4), 91 (100.0); high-resolution mass spectrum (70 eV) m/e 360.1385 (calcd for $C_{23}H_{20}O_4$) 360.1362.

Methyl 6-Ethyl-4-[[5-methoxy-1-(phenylmethoxy)-2-naphthyl]methyl]-2-oxo-2*H*-pyran-5-carboxylate (53). A mixture of **52** (5.85 g, 16.2 mmol), **10** (2.53 g, 19.3 mmol), and sodium methoxide (0.29 g, 5.35 mmol) was heated at 105 °C for 3.5 h and then diluted with 0.5 N sulfuric acid. This mixture was extracted with ether (3 × 75 mL), and the combined organic extracts were washed with brine (1 × 50 mL), dried over Na_2SO_4, and then concentrated in vacuo. The resulting oil was purified by high-pressure liquid chromatography using 14% ethyl acetate/hexane as eluent to give 3.50 g (47%) of **53** (R_f 0.18) as a colorless oil: ^1H NMR (200 MHz) ($CDCl_3$) δ 8.03 (1 H, d, J = 9.2 Hz), 7.69 (1 H, d, J = 8.6 Hz), 7.36–7.46 (6 H, m), 7.12 (1 H, d, J = 8.6 Hz), 6.84 (1 H, d, J = 7.3 Hz), 5.74 (1 H, s), 4.99 (2 H, s), 4.00 (3 H, s), 3.95 (2 H, s), 3.69 (3 H, s), 2.60 (2 H, q, J = 7.3 Hz), 1.25 (3 H, t, J = 7.3 Hz); ^{13}C NMR (20 MHz) ($CDCl_3$) δ 167.80, 165.94, 160.96, 156.52, 152.71, 129.33, 128.64, 128.19, 127.97, 126.99, 126.73, 126.56, 125.37, 118.94, 114.44, 112.28, 112.09, 104.32, 76.49, 55.60, 52.47, 33.84, 26.38, 11.95 (two carbons not resolved); IR ($CHCl_3$) 2980–2875, 1740–1705, 1600, 1440, 1415, 1395, 1370, 1265, 1070 cm^{-1}; MS (70 eV) m/e (% intensity) 458 (26.2) (M^+), 426 (16.4), 367 (15.6), 335 (12.7), 307 (13.4), 283 (36.2), 251 (15.3), 91 (100.0), 57 (24.6); high-resolution mass spectrum (70 eV) m/e 458.1730 (calcd for $C_{28}H_{26}O_6$ 458.1729).

1,1-Dimethoxyethylene (12). The procedure of Corey[38] gave **12** in 42% yield as a colorless liquid: bp 80–90 °C (lit.[53] bp 89–91 °C); ^1H NMR (60 MHz) ($CDCl_3$) δ 3.59 (6 H, s), 3.07 (2 H, s).

Methyl 8,8-Dimethoxy-1,5-dimethyl-3-oxo-2-oxabicyclo[2.2.2]oct-5-ene-6-carboxylate (62). A solution of **35** (4.41 g, 24.2 mmol) and **12** (6.40 g, 72.6 mmol) in 50 mL of benzene was heated at 78 °C for 24 h, then cooled to room temperature, and concentrated in vacuo. Purification of the oily residue by high-pressure liquid chromatography using 20% ethyl acetate/hexane as eluent gave 4.06 g (62%) of **62** (R_f 0.34) as a white solid: mp 68–70 °C; ^1H NMR (200 MHz) ($CDCl_3$) δ 3.79 (3 H, s), 3.76 (1 H, s), 3.29 (3 H, s), 3.20 (3 H, s), 2.14 (3 H, s), 2.08 (1 H, d, J = 13.4 Hz), 2.01 (1 H, d, J = 13.4 Hz), 1.73 (3 H, s); ^{13}C NMR (20 MHz) ($CDCl_3$) δ 170.01, 164.92, 146.66, 131.93, 103.75, 82.71, 56.54, 51.64, 49.18, 44.72, 21.62, 19.72 (one carbon not resolved); IR (neat) 2930, 1762, 1720, 1435, 1345, 1240, 1110, 1060, 950, 755 cm^{-1}; MS (70 eV) m/e (% intensity) 239 (0.4) ($M^+ - OCH_3$), 226 (0.2) ($M^+ - CO_2$), 194 (63.7) ($M^+ - CH_3OH - CO_2$), 164 (11.2), 163 (100.0), 162 (22.3), 135 (13.6), 91 (13.9), 88 (17.3), 44 (45.0), 43 (15.8).

Methyl 2,6-Dimethyl-4-methoxybenzoate (63). A solution of **35** (2.00 g, 11.0 mmol) and **12** (1.06 g, 12.8 mmol) in 25 mL of benzene was heated at reflux for 24 h and then concentrated in vacuo to give an oily residue. Purification by silica gel chromatography using 14% ethyl acetate/hexane as eluent gave 1.35 g (63%) of **63** (R_f 0.52) as white prisms, mp 57–59 °C (lit.[41] mp 56.5 °C), and 0.30 g (10%) of **62** (R_f 0.24) as a white solid, mp 67–70 °C: ^1H NMR (60 MHz) ($CDCl_3$) δ 6.49 (2 H, s), 3.82 (3 H, s), 3.75 (3 H, s), 2.19 (6 H, s); IR ($CDCl_3$) 2950, 1720, 1610, 1445, 1325, 1275, 1200, 1160, 1110, 1065, 870 cm^{-1}; MS (70 eV) m/e (% intensity) 194 (56.9) (M^+), 164 (12.0), 163 (100.0), 162 (27.9), 135 (16.7), 91 (14.0).

Methyl 1,5-Dimethyl-8-ethoxy-3-oxo-2-oxabicyclo[2.2.2]-oct-5-ene-6-carboxylate (64) and Methyl 2,6-Dimethylbenzoate (65). A mixture of **35** (1.00 g, 5.49 mmol) and ethyl vinyl ether (3.96 g, 54.9 mmol) was heated at 78 °C in a sealed tube for 6 days. The mixture was then concentrated in vacuo to give an oily residue that was purified by high-pressure liquid chromatography using 25% ethyl acetate/hexane as eluent to give 0.32 g (35%) of methyl 2,6-dimethylbenzoate (**65**; R_f 0.55) as a colorless oil and 0.67 g (48%) of **64** (R_f 0.51) as a colorless oil. On standing for 2 days at room temperature, **64** was converted quantitatively into **65**, which was purified by Kugelrohr distillation [105–110 °C oven temperature (10 mm)] to give a colorless oil [lit.[54] bp 109 °C (19 mm)].

64: ^1H NMR (60 MHz) ($CDCl_3$) δ 5.62 (1 H, m), 3.93 (1 H, m), 3.80 (3 H, s), 3.48 (2 H, q, J = 7.0 Hz), 2.43 (1 H, m), 2.36 (1 H, m), 2.31 (3 H, s), 1.92 (3 H, s), 1.16 (3 H, t, J = 7.0 Hz).

65: ^1H NMR (60 MHz) ($CDCl_3$) δ 6.99–7.18 (3 H, m), 3.87 (3 H, s), 2.29 (6 H, s); IR (neat) 2930, 1730, 1435, 1275, 1115, 1075, 770 cm^{-1}. MS (70 eV) m/e (% intensity) 164 (64.1) (M^+), 133 (98.5), 132 (100.0), 105 (55.0), 104 (26.5), 103 (14.0), 79 (14.1), 78 (10.6), 77 (23.5), 51 (11.4).

Methyl 2-Ethyl-4-methoxy-6-[[5-methoxy-1-(phenylmethoxy)-2-naphthyl]methyl]benzoate (66) and Methyl 8,8-Dimethoxy-1-ethyl-5-[[5-methoxy-1-(phenylmethoxy)-2-naphthyl]methyl]-3-oxo-2-oxabicyclo[2.2.2]oct-5-ene-6-carboxylate (67). A solution of **53** (2.96 g, 6.45 mmol) and **12** (2.84 g, 32.2 mmol) in 30 mL of benzene was heated at 78 °C for 48 h, then cooled to room temperature, and concentrated in vacuo. The resulting oil was purified by high-pressure liquid chromatography using 17% ethyl acetate/hexane as eluent to give 0.85 g (28%) of **66** (R_f 0.36) as a colorless oil and 1.90 g (54%) of **67** (R_f 0.13) as a white solid, mp 59–61 °C.

67: ^1H NMR (200 MHz) ($CDCl_3$) δ 8.02 (1 H, d, J = 8.6 Hz), 7.71 (1 H, d, J = 8.6 Hz), 7.35–7.56 (6 H, m), 7.25 (1 H, d J = 8.6 Hz), 6.79 (1 H, d, J = 7.3 Hz), 5.09 (1 H, d, J = 11.3), 4.94 (1 H, d, J = 11.3 Hz), 3.95 (3 H, s), 3.92 (1 H, s), 3.78 (2 H, s), 3.75 (3 H, s), 3.14 (3 H, s), 3.02 (3 H, s), 1.92–2.29 (4 H, m), 0.99 (3 H, t, J = 7.3 Hz); ^{13}C NMR (20 MHz) ($CDCl_3$) δ 169.84, 165.69, 156.03, 152.52, 147.25, 137.34, 132.74, 129.33, 128.58, 128.10, 127.76, 126.71, 126.31, 125.60, 119.17, 114.39, 104.15, 85.32, 76.21, 55.57, 53.26, 51.93, 49.11, 43.83, 31.97, 27.09, 7.63 (five carbons not resolved); IR ($CDCl_3$) 2930, 1760, 1720, 1600, 1505, 1450, 1415, 1370, 1340, 1260, 1110, 1060 cm^{-1}; MS (70 eV) m/e (% intensity) 470 (3.3) ($M^+ - CH_3OH - CO_2$), 439 (17.0), 438 (51.3), 348 (30.1), 347 (100.0), 91 (45.2), 44 (18.1). Anal. Calcd for $C_{32}H_{34}O_8$: C,

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70.31; H, 6.27. Found: C, 70.21; H, 6.37.

66: ^{1}H NMR (60 MHz) ($CDCl_3$) δ 7.22–8.18 (9 H, m), 6.58–6.92 (3 H, m), 5.03 (2 H, s), 4.28 (2 H, s), 4.00 (3 H, s), 3.80 (3 H, s), 3.66 (3 H, s), 2.67 (2 H, q, J = 7.5 Hz), 1.23 (3 H, t, J = 7.5 Hz); IR (neat) 2940, 1720, 1600, 1505, 1455, 1415, 1395, 1365, 1260, 1155, 1060, 795, 760, 696 cm^{-1}; MS (70 eV) m/e (% intensity) 470 (8.6) (M^+), 439 (24.8), 438 (74.2), 379 (10.0), 348 (45.9), 347 (100.0), 319 (11.6), 91 (36.1); high-resolution mass spectrum (70 eV) m/e 470.2095 (calcd for $C_{30}H_{30}O_5$ 470.2093).

Methyl 8,8-Dimethoxy-1,5-dimethyl-3-oxo-2-oxabicyclo-[2.2.2]octane-6-carboxylate (68). A solution of **62** (1.00 g, 3.70 mmol) and 5% platinum on carbon (0.60 g, 0.15 mmol) in 30 mL of ethanol was maintained under an atmosphere of hydrogen (500 psi) for 14 days. The solution was then filtered through Celite and concentrated in vacuo. Purification of the residue by silica gel chromatography using 33% ethyl acetate/hexane as eluent gave an oil (R_f 0.46) that was further purified by Kugelrohr distillation [135–140 °C oven temperature (0.09 mm)] to give 0.55 g (55%) of **68** as a colorless oil: ^{1}H NMR (200 MHz) ($CDCl_3$) δ 3.71 (3 H, s), 3.23 (6 H, s), 2.95–3.06 (2 H, m), 2.63 (1 H, m), 1.93 (2 H, m), 1.44 (3 H, s), 1.14 (3 H, d, J = 7.6 Hz); IR (neat) 2990–2880, 1765, 1740, 1465, 1435, 1355, 1285, 1265, 1235, 1200, 1165, 1135, 1115, 1070, 1050, 955 cm^{-1}; MS (70 eV) m/e (% intensity) 272 (7.1) (M^+), 137 (60.7), 131 (100.0), 115 (31.1), 88 (76.7), 69 (31.2), 44 (33.3), 43 (63.6), 42 (29.5), 41 (34.3).

Methyl 8,8-Dimethoxy-1-ethyl-5-[(1-hydroxy-5-methoxy-2-naphthyl)methyl]-3-oxo-2-oxabicyclo[2.2.2]oct-5-ene-6-carboxylate (69). A solution of **67** (1.15 g, 2.10mmol) and 5% platinum on carbon (0.60 g, 0.15 mmol) in 30 mL of ethanol was maintained under an atmosphere of hydrogen (500 psi) for 14 days. The solution was then filtered through Celite and concentrated in vacuo to give 0.81 g (84%) of **69** as an amber solid: mp 70–72 °C dec; ^{1}H NMR (60 MHz) ($CDCl_3$) δ 8.12 (1 H, s), 7.82–8.00 (2 H, m), 7.23–7.56 (2 H, m), 6.85 (1 H, d, J = 7.5 Hz), 4.04 (1 H, s), 4.02 (3 H, s), 3.98 (2 H, s), 3.87 (3 H, s), 3.30 (3 H, s), 3.18 (3 H, s), 2.04–2.32 (4 H, m), 1.02 (3 H, t, J = 7.0 Hz); IR ($CDCl_3$) 3400–3200, 2930, 1760, 1690, 1595, 1505, 1440, 1405, 1335, 1265, 1060, 785 cm^{-1}; MS (70 eV) m/e (% intensity) 380 (13.0) ($M^+ - CH_3OH - CO_2$), 349 (40.9), 348 (100.0), 333 (17.7), 319 (15.2), 44 (41.8).

Methyl 1,5-Dimethyl-3,8-dioxo-2-oxabicyclo[2.2.2]octane-6-carboxylate (70). To a solution of **68** (0.10 g, 0.37 mmol) in 5 mL of THF at room temperature was added 1 mL of 6 N hydrochloric acid. This solution was stirred at room temperature for 2 h and then diluted with chloroform (50 mL). The layers were separated, and the aqueous layer was extracted with chloroform (3 × 10 mL). The combined organic layers were washed with water (1 × 20 mL) and brine (1 × 20 mL), dried over Na_2SO_4, and concentrated in vacuo to give an oil. Purification by Kugelrohr distillation [120–125 °C oven temperature (0.06 mm)] gave 0.06 g (75%) of **70** as a colorless oil that solidified on standing to a white solid: mp 105–109 °C; ^{1}H NMR (200 MHz) ($CDCl_3$) δ 3.75 (3 H, s), 3.20–3.44 (4 H, s), 2.91 (1 H, m), 1.57 (3 H, s), 1.00 (3 H, d, J = 7.3 Hz); IR ($CHCl_3$) 3005–2900, 1780–1710, 1440, 1390, 1370, 1320, 1220, 1165, 1055, 975 cm^{-1}; MS (70 eV) m/e (% intensity) 226 (10.0) (M^+), 141 (15.4), 69 (100.0), 44 (15.6), 43 (29.4), 41 (19.5).

Methyl 2,6-Dimethyl-4-hydroxybenzoate (71). A solution of **62** (0.50 g, 1.85 mmol) in 5 mL of THF and 1 mL of 6 N sulfuric acid was heated to 75 °C for 24 h. After cooling to room temperature, the solution was extracted with chloroform (3 × 25 mL) and the combined organic layers were washed with brine (1 × 25 mL), dried over Na_2SO_4, and concentrated in vacuo. Purification of the residue by silica gel chromatography using 33% ethyl acetate/hexane as eluent gave 0.14 g (38%) of **63** (R_f 0.56) as a white solid, mp 57–59 °C (lit.[41] mp 56.5 °C), and 0.19 g (56%) of **71** (R_f 0.39) as a white solid, mp 105–107 °C: ^{1}H NMR (60 MHz) ($CDCl_3$) δ 8.00 (1 H, bs), 6.60 (2 H, s), 3.94 (3 H, s), 2.34 (6 H, s); IR ($CHCl_3$) 3450–3150, 1725, 1600, 1445, 1325, 1280, 1160, 1100 cm^{-1}; MS (70 eV) m/e (% intensity) 180 (41.8) (M^+), 150 (10.1), 149 (100.0), 148 (26.2), 121 (14.4), 91 (13.2), 77 (12.8).

2,4-Dimethyl-6-methoxy-3-(methoxycarbonyl)benzoic Acid (73). To a solution of **62** (0.10 g, 0.37 mmol) in 5 mL of carbon tetrachloride at room temperature was added dropwise iodotrimethylsilane (0.07 g, 0.37 mmol). The solution was stirred at room temperature for 30 min and then was diluted with chloroform (50 mL). This mixture was washed with a saturated sodium thiosulfate solution (1 × 10 mL), water (1 × 10 mL), and brine (1 × 25 mL), dried over Na_2SO_4, and then concentrated in vacuo to give 0.09 g (98%) of **73** as a white solid: mp 139–140.5 °C; ^{1}H NMR (60 MHz) ($CDCl_3$) δ 9.49 (1 H, bs), 6.72 (1 H, s), 3.94 (3 H, s), 3.91 (3 H, s), 2.38 (6 H, s); IR ($CHCl_3$) 3300–2900, 1740–1710, 1610, 1330, 1270, 1115 cm^{-1}; MS (70 eV) m/e (% intensity) 238 (86.7) (M^+), 207 (100.0), 191 (40.5), 163 (31.3), 162 (22.1).

6,6-Dimethoxy-3-(methoxycarbonyl)-4-methyl-2-methylenecyclohexanecarboxylic Acid (74). To a solution of **62** (0.15 g, 0.56 mmol) in 5 mL of THF at room temperature was added a 0.98 M solution of sodium hydroxide (0.57 mL, 0.56 mmol) in methanol. The solution was stirred at room temperature for 1 h and then acidified with 5 mL of 1 N hydrochloric acid. This mixture was extracted with ether (3 × 25 mL), and the combined organic layers were washed with water (1 × 20 mL) and brine (1 × 25 mL), dried over Na_2SO_4, and concentrated in vacuo to give 0.15 g (100%) of **74** as a yellow oil. Kugelrohr distillation [120–125 °C oven temperature (0.02 mm)] converted **74** into 0.11 g of **63** which solidified to give a white solid, mp 57–59 °C.

74: ^{1}H NMR (60 MHz) ($CDCl_3$) δ 10.17 (1 H, bs), 5.16 (1 H, m), 5.09 (1 H, m), 3.90 (1 H, s), 3.83 (3 H, s), 3.34 (3 H, s), 3.20 (3 H, s), 2.55–2.70 (2 H, m), 1.82 (3 H, s); IR ($CHCl_3$) 3300–2800, 1745–1710, 1445, 1395, 1390, 1255, 1120, 1070 cm^{-1}.

Acknowledgment. We thank the National Institutes of Health (Grants CA-21968 and GM 31349) for financial support.