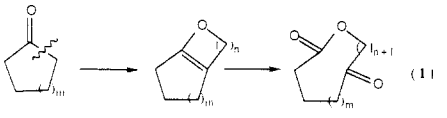
One-Pot, Four-Component Annulations: Flexible and Simple Syntheses of Unsaturated Macrolides and of Substituted Aromatics and Heteroaromatics†

Gary H. Posner,*[1a] Kevin S. Webb, Edward Asirvatham,[1b] Sang-sup Jew,[1c] and Alessandro Degl'Innocenti[1d]

Contribution from the Department of Chemistry, The Johns Hopkins University, Baltimore, Maryland 21218. *Received November 30, 1987*

Abstract: One-pot, four-component, sequential, Michael–Michael–Michael–ring closure and Michael–Michael–aldol–ring closure annulations initiated by tri-*n*-butyltinlithium have been developed as flexible and efficient new synthetic methods for preparation of substituted 9-, 10-, and 11-membered unsaturated macrolides having carbon–carbon double bonds of fixed geometry at specific positions in the lactone rings. 2,4-Disubstituted (*E*)-6-nonenolides (eq 3, 4), 8-monosubstituted (eq 5), 6,8-disubstituted (eq 6), and 8,9-disubstituted (eq 10) 5-nonenolides, 9,10-disubstituted (*E*)-6-decenolides (eq 8, 9), and a 7,8-disubstituted (*E*)-4-octenolide (eq 7) have been prepared by using this methodology. Intramolecular cyclizations of the vicinal substituents in these macrolides have produced regiospecifically polysubstituted naphthalenes, benzothiophenes, benzofurans, and quinolines in a conceptually new approach to these aromatic and heteroaromatic systems (eq 11–15).

Many macrolides have high physiological potency including antibiotic, antitumor, cytostatic, and platelet aggregation activities.[2] Great progress has been made in recent years toward stereocontrolled synthesis of homochiral polysubstituted macrolides involving cyclization (lactonization) of enantiomerically pure ω-hydroxy carboxylic acid derivatives.[2] Significant but much more limited progress has been made toward preparation of medium and large ring lactones via ring-expansion reactions. One of the most notable and useful developments in this area involves conversion of a cycloalkanone into a bicyclic vinylic ether, which is oxidatively cleaved to form a ring-enlarged keto lactone (eq 1).[3]



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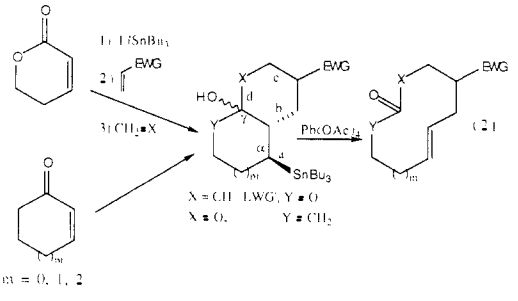
Several variations on this theme have been reported including scission of alkoxy radicals.[4] In most of these cases, a superfluous functional group (e.g., ketone, iodide) is produced during cleavage of the bicyclic system. *Regiospecific* conversion of such functional groups into one alkene structural unit is usually not possible because of the similar chemical environments α and α' to the functional group.[5] Because many regiospecifically unsaturated lactones are physiologically active natural products,[2] we have developed methodology to prepare unsaturated macrolides having a carbon–carbon double bond with specific geometry and at a specific position in the macrolide skeleton.

Because of our interest in one-pot multicomponent annulations,[6] we envisioned a flexible and efficient protocol linking together four components via four new bonds (a–d, eq 2) and forming



(2)

intermediate γ-hydroxy stannanes. On the basis of pioneering work in Japan,[7] oxidative fragmentation of such systems was expected to produce *both* ring enlargement and regiospecific formation of an alkenyl unit (eq 2). This approach involves four-atom ring expansions of common-sized α,β-unsaturated lactones and ketones leading to much less common, regiospecifically monosubstituted and disubstituted, 9-, 10-, and 11-membered unsaturated lactones. We report here details of new results using this convergent and convenient methodology.

Results and Discussion

MIMI-MIRC Annulations. Nucleophilic conjugate addition of tri-*n*-butyltinlithium[8] to pentenolide **1**, followed by reaction of the intermediate lactone enolate ion with slightly more than 2 equiv of methyl acrylate,[6c] produced Michael–Michael–Michael–ring closure (MIMI-MIRC) product lactol **2**, isolated chromatographically as a mixture of diastereomers in 76% yield; this hexannulation reaction represents a 2 + 2 + 2 atom cyclization and a convergent and efficient A + B + C + C[6d] sequential connection of four components in one reaction vessel. Oxidative fragmentation of γ-hydroxy stannane **2** by lead tetraacetate

† Dedicated to Professor E. J. Corey with admiration, respect, and best wishes on his 60th birthday.

(1) (a) 1987 Maryland Chemist of the Year Awardee. (b) 1987 Ralph H. Potts Memorial Fellowship Awardee. (c) Visiting Professor on leave from Seoul National University, Seoul, Korea. (d) Italian C.N.R. Postdoctoral Fellow on leave from Centro C.N.R. Sulla Chimica e la Struttura dei Composti Etrociclici, Dipartimento di Chimica Organica "Ugo Schiff," Florence, Italy.

(2) For reviews, see: (a) Paterson, I.; Mansuri, M. M. *Tetrahedron* **1985**, *41*, 3569. (b) *Macrolide Antibiotics. Chemistry, Biology and Practice*; Omura, S., Ed.; Academic: Orlando, FL, 1984. (c) Masamune, S. *Aldrichimica Acta* **1978**, *11*, 23. (d) Nicolaou, K. C. *Tetrahedron* **1977**, *33*, 683.

(3) (a) Borowitz, I. J.; Bandurco, V.; Heyman, M.; Rigby, R. D. G.; Ueng, S.-N. *J. Org. Chem.* **1973**, *38*, 1234 and references therein. (b) Mahajan, J. R.; Araujo, H. C. *Synthesis* **1976**, 111 and references therein. (c) Immer, H.; Bagli, J. F. *J. Org. Chem.* **1968**, *33*, 2457.

(4) (a) Dowd, P.; Choi, S.-C. *J. Am. Chem. Soc.* **1987**, *109*, 6548. (b) Beckwith, A. L. J.; O'Shea, D. M.; Gerba, S.; Westwood, S. W. *J. Chem. Soc., Chem. Commun.* **1987**, 666. (c) Suginome, H.; Yamada, S. *Tetrahedron Lett.* **1987**, *28*, 3963; *Tetrahedron* **1987**, *43*, 3386; *Chem. Lett.* **1988**, 245. (d) Beckwith, A. L. J.; Kazlauskas, R.; Syner-Lyons, M. R. *J. Org. Chem.* **1983**, *48*, 4718 and references therein. (e) Schreiber, S. L. *J. Am. Chem. Soc.* **1980**, *102*, 6163. See also (f) Stanchev, S.; Hesse, M. *Helv. Chim. Acta* **1987**, *70*, 1389 and references therein. (g) Milenkov, B.; Guggisberg, A.; Hesse, M. *Tetrahedron Lett.* **1987**, *28*, 315. (h) Schreiber, S. L.; Sammakia, T.; Hulin, B.; Schulte, G. *J. Am. Chem. Soc.* **1986**, *108*, 2106. (i) Freire, R.; Marrero, J. J.; Rodriguez, M. J.; Suarez, E. *Tetrahedron Lett.* **1986**, *27*, 383.

(5) For a useful exception, see: Schreiber, S. L.; Hulin, B.; Liew, W.-F. *Tetrahedron* **1986**, *42*, 2945.

(6) (a) Posner, G. H.; Asirvatham, E.; Webb, K. S.; Jew, S.-S. *Tetrahedron Lett.* **1987**, *28*, 5071. (b) Posner, G. H.; Asirvatham, E. *Ibid.* **1986**, *27*, 663. (c) Posner, G. H.; Lu, S.-B.; Asirvatham, E.; Silversmith, E. F.; Shulman, E. M. *J. Am. Chem. Soc.* **1986**, *108*, 511. (d) Posner, G. H. *Chem. Rev.* **1986**, *86*, 831.

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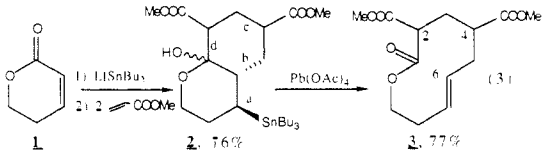
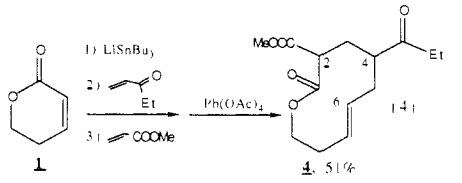
produced 2,4-dicarboxylated (*E*)-6-nonenolide **3** as a 2:5 mixture of carboxyl isomers in 77% yield (eq 3). Base-promoted



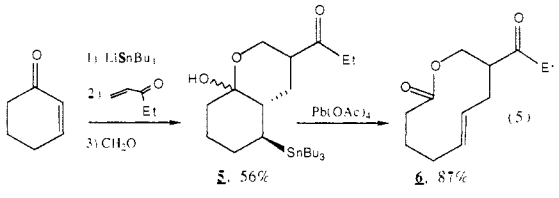
equilibration converted the chromatographically purified minor (trans) into the major (cis) isomer. That only the *E*-olefinic macrolide was produced is consistent with the expectation of a stereocontrolled concerted oxidative fragmentation[7] in which the apparently trans relationship[9] of bonds a and b in γ-hydroxy stannane intermediate **2** leads exclusively to *trans*-olefinic product **3**. Transannular cyclization of nonenolide **3** and a few of its derivatives is expected to produce some interesting and useful bicyclic synthons.

In a similar fashion but using sequentially four *different* components (A + B + C + D), pentenolide **1** underwent overall alkene inversion and ring expansion into keto ester (*E*)-nonenolide **4** in 51% yield (eq 4). Removal of very small aliquots from the



reaction vessel for TLC monitoring of the reaction's progress indicated when to add each successive component. Often a small amount of a MIMI-MIRC product was detected in which two molecules of ethyl vinyl ketone (component C) had condensed in an A + B + C + C fashion; the surprise was that, by operating in tetrahydrofuran as solvent at −78 °C for a short time, the formation of such undesired side products could be effectively minimized. Equations 3 and 4, therefore, represent rapid, convenient, flexible, and efficient conversions of a simple, readily available molecule into substantially more complex, richly functionalized unsaturated macrolides.

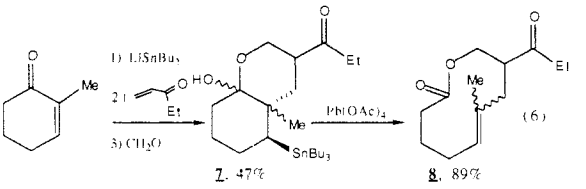
MIMI-ARC Annulations. Nucleophilic conjugate addition of tri-*n*-butyltinlithium to cyclohexenone, followed by reaction of the intermediate ketone enolate ion with a small excess of ethyl vinyl ketone and subsequently with a large excess formaldehyde, represents a one-pot, sequential, four-different-component (A + B + C + D) Michael–Michael–aldol–ring closure (MIMI-ARC) process which gave γ-hydroxy stannane **5** as a mixture of diastereomers in 56% yield (eq 5); oxidative cleavage with lead



tetraacetate gave 8-acylated (*E*)-5-nonenolide **6** exclusively in 87% yield. Nonenolide **6** has three isolated and distinct functional groups (alkene, ketone, and lactone), which can be manipulated independently. This four-atom ring expansion of cyclohexenone into macrolide **6** in 49% overall yield with use of only two reaction vessels represents the synthetic equivalent of an unprecedented homologous Baeyer–Villiger oxidation (i.e., ketone → lactone)[10]

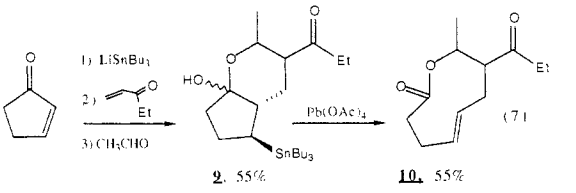
in which globally the original bond between the carbonyl carbon atom and the α-vinylic carbon atom in cyclohexenone is broken and a one oxygen atom and three carbon atom unit is inserted. The potential flexibility of this protocol is clear: by varying one or more of the four components in this MIMI-ARC annulation oxidation protocol, many different macrolides can be prepared, as illustrated by the following examples.

2-Methyl-2-cyclohexenone underwent this type of four-atom ketone → lactone ring enlargement to form methyl-substituted olefinic macrolide **8** as a separable mixture of double bond geometric isomers in 47% yield overall (eq 6). The *Z* configuration

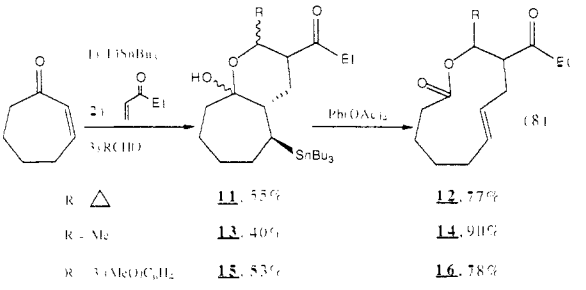


of the major olefinic isomer (**8**-*cis*, 37%) was assigned on the basis of the observed δ 1.78 chemical shift for its vinylic methyl group in the 400-MHz ^{1}H NMR spectrum; the minor (*E*)-nonenolide showed a δ 1.69 chemical shift for the vinylic methyl group.[11]

Cyclopentenone underwent this type of homologous Baeyer–Villiger oxidation to form 7,8-disubstituted (*E*)-4-octenolide **10** in 30% yield overall (eq 7), and cycloheptenone was transformed in this way into 9,10-disubstituted (*E*)-6-decenolides in 36–42% yields overall. Nucleophilic addition of tri-*n*-butyltinlithium to



cycloheptenone, followed by ethyl vinyl ketone and then by either cyclopropanecarboxaldehyde or acetaldehyde or 3-methoxybenzaldehyde, gave γ-hydroxy stannane lactols **11**, **13**, and **15**; these lactols were oxidatively cleaved by lead tetraacetate forming mixtures of *cis*- and *trans*-9,10-disubstituted-(*E*)-6-decenolides **12**, **14**, and **16** (eq 8). The lactols were found to be slightly



unstable to silica, and 10–20% higher overall yields were obtained by directly oxidizing the crude lactols (for example, see the Experimental Section for decenolide **12**). The alkene double bond stereochemistry was assigned based on 400-MHz ^{1}H NMR coupling constants (J = 15–18 Hz, *E*-alkene). Along with *E*-decenolide **14** there was formed 3% of the corresponding *Z*-decenolide (J = 2.8 Hz, vinylic CH).

In a similar fashion, cycloheptenone was converted in two stages without purification of the intermediate lactol(s) into iodobenzyl macrolide **17** in 38% overall yield (eq 9). Only the *E*-decenolide was detected.

The generality of the four-different-component MIMI-ARC annulations in which the fourth component is an arylacetaldehyde or a heteroarylacetaldehyde was established by preparation of a variety of arylmethyl-substituted macrolides; specifically, cyclo-

(9) For trans α,β-difunctionalization of α,β-enones, see: (a) Stork, G. *Pure Appl. Chem.* **1986**, *17*, 383. (b) Kretchmer, R. A.; Schafter, W. M. *J. Org. Chem.* **1973**, *38*, 95. (c) Grieco, P. A.; Finkelhor, R. *Ibid.* **1973**, *38*, 2100. (d) Boeckman, R. K., Jr. *Ibid.* **1973**, *38*, 4450. (e) Coates, R. M.; Sandefur, L. O. *Ibid.* **1974**, *39*, 275. (f) Patterson, J. W., Jr.; Fried, J. H. *Ibid.* **1974**, *39*, 2506. (g) Posner, G. H. *Ann. N. Y. Acad. Sci.* **1978**, *295*, 249. (h) Noyori, R.; Suzuki, M. *Angew. Chem., Int. Ed. Engl.* **1984**, *23*, 847. (i) Taylor, R. J. K. *Synthesis* **1985**, 364. (j) Chapdelaine, M. J.; Hulce, M. *Org. React.* (*N. Y.*), review in preparation.

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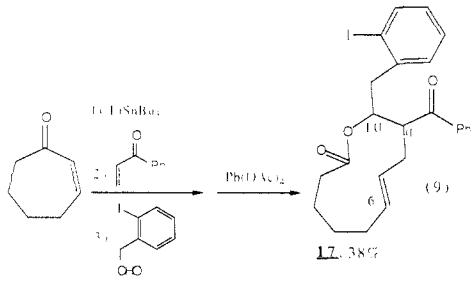
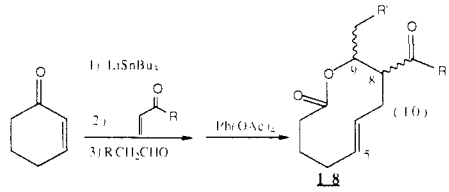
(11) Wharton, P. S. *J. Org. Chem.* **1961**, *26*, 4781.



hexenone underwent ring expansion into a series of 8-acyl-9-[(hetero)arylmethyl]-(*E*)-5-nonenolides (**18a–f**) in 34–54% yields overall (eq 10). The *E* configuration of the product macrolides

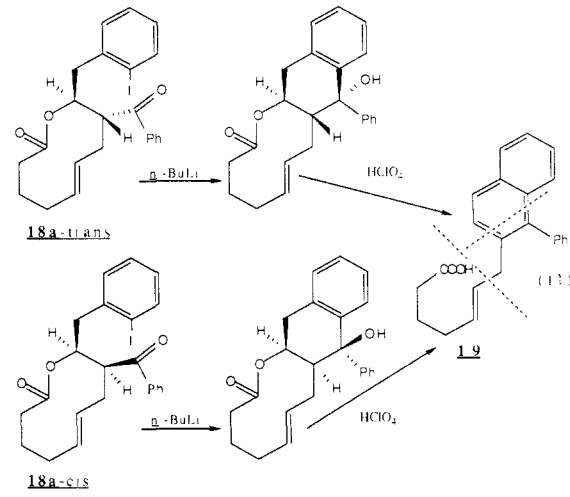


18	R¹	R	% Yield	trans : cis
a	2-IC_6H_4	Ph	34	1.0
b	2,3-$(MeO)_2C_6H_3$	Et	52	1.0
c		Ph	53	1.5
d	3-thienyl	Et	52	0.7
e		Ph	52	1.8
f	3-furyl	Et	50	0.7

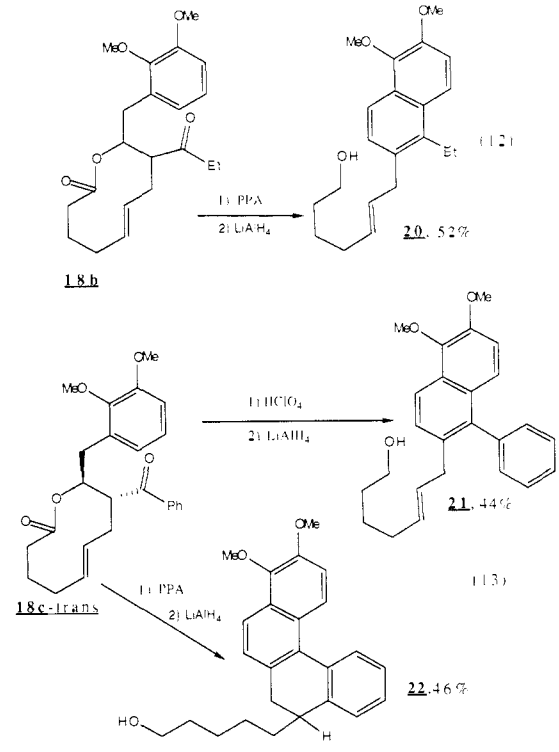
was assigned on the basis of the observed 14–16-Hz coupling constant for the vinylic hydrogen atoms in the 400-MHz ^{1}H NMR spectra. The stereochemistry of the vicinal substituents varied between 0.7 and 1.8 (trans–cis). Assignment of trans–cis stereochemistry to the vicinal substituents could not be done easily on the basis of ^{1}H NMR coupling constants in the macrolides themselves (often the magnitude of the coupling constants were similar), and therefore the intermediate lactols were separated (only two were detected) and were examined carefully, showing typical coupling constants for the cis (J = 2–4 Hz) and for the trans (J = 8–13 Hz) vicinal isomers; each lactol isomer was separately oxidatively cleaved to form the corresponding *cis*- or *trans*-9,10-disubstituted-(*E*)-5-nonenolide. Attempts to epimerize the acyl side chain produced only α-enones via β-elimination of the macrolide carboxylate group. Several of the transformations shown in eq 10 were performed on gram scale.

Aromatics and Heteroaromatics. To illustrate some of the considerable synthetic potential of this four-different-component MIMI-ARC fragmentation sequence, the 9,10-disubstituted decenolide in eq 9 and the 8,9-disubstituted nonenolides in eq 10 were converted, via intramolecular cyclization of the vicinal substituents, into the corresponding vicinally disubstituted naphthalenes, benzothiophenes, and benzofurans. For example, iodobenzyl macrolides **18a**-*trans* and **18a**-*cis* underwent iodine → lithium exchange[12] and in situ cyclization; acid-promoted aromatization gave only 2,3-disubstituted naphthalene **19** in quantitative yields (eq 11). The overall yield of naphthalene **19** from cyclohexenone with use of four reaction vessels was 27%. Similar results were obtained also starting with cycloheptenone. The dotted lines in the structure of naphthalene **19** are meant to indicate the original three structural units that have been combined in this convergent procedure. Often regiospecifically substituted naphthalenes are prepared by attachment of substituents onto a *preformed* naphthalene ring; eq 11 represents a complementary procedure, which constitutes a new, flexible, and simple synthesis of 2,3-disubstituted naphthalenes.

In a similar fashion, cyclohexenone was converted simply, conveniently, and on gram scale into dimethoxybenzyl macrolides **18b**-*trans* and **18b**-*cis*, which were then intramolecularly cyclized



with polyphosphoric acid (PPA) to give, after carboxyl reduction for easier purification, regiospecifically tetrasubstituted naphthalene **20** exclusively in 27% overall yield (eq 12). Likewise, an A + B + C + D MIMI-ARC cyclization–fragmentation sequence converted cyclohexenone into benzylmacrolide **18c**, which underwent aromatization in the presence of perchloric acid to form tetrasubstituted naphthalene **21**; polyphosphoric acid, however, promoted an intramolecular Friedel–Crafts cycloalkylation[13] to form trisubstituted tetracycle **22** (eq 13).

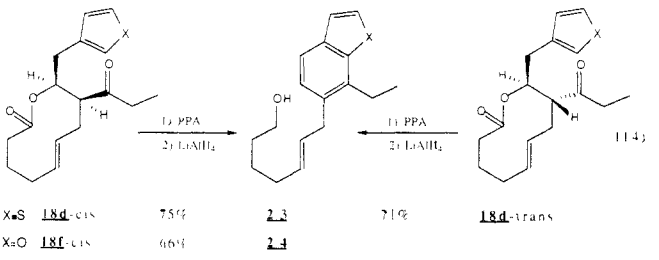


Finally polyphosphoric acid promoted intramolecular cyclization and then aromatization of thienylmethyl macrolides **18d** and of furylmethyl macrolide **18f** to form regiospecifically 5,6-disubstituted benzothiophene **23** and benzofuran **24** in 20–39% yields overall from cyclohexenone (eq 14). These transformations, along with our recently reported MIMI-ARC synthesis of regiospecifically disubstituted quinolines (e.g., eq 15),[6a] represent an efficient, new synthesis of such heteroaromatic compounds, which are key structural units in various physiologically active materials[14]

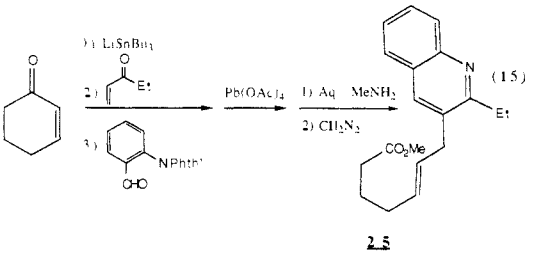
(12) (a) Gilman, H. J.; Morton, J. W. *Org. React.* (*N.Y.*) **1954**, *8*, 258. (b) Wakefield, B. J. *The Chemistry of Orgonolithium Compounds*; Pergamon: New York, 1974.

(13) Olah, G. *Friedel–Crafts and Related Reactions*; Interscience: New York, 1963–1965; Vol. 2, pp 785–977.

(14) (a) Harrison, I. T.; Lewis, B.; Nelson, P.; Rooks, W.; Roszkowski, A.; Tomolenis, A.; Fried, T. H. *J. Med. Chem.* **1970**, *13*, 203. (b) Chamberlain, K.; Carter, G. A.; *Pestic. Sci.* **1981**, *12*(5), 539; (c) Balzarini, J.; DeCiercq, E.; Dann, O. *Invest. New Drugs* **1983**, *1*(2), 103.



and which themselves are versatile synthons for many different transformations.[15]



Conclusion

A conceptually new protocol for ring expansion of *n*-sized alkenolides and cycloalkenones into *n* + 4 macrolides has been demonstrated based on one-pot, sequential, four-component annulations. 6-Nonenolides with specifically *E* geometry have been prepared with 2,4-disubstitution patterns (eq 3, 4), and (*E*)-6-decenolides have been prepared with 9,10-disubstitution patterns (eq 8, 9). 5-Nonenolides with specifically *E* geometry have been prepared with 8-monosubstitution (eq 5) and with 8,9-disubstituion patterns (eq 10), and a 7,8-disubstituted (*E*)-4-octenolide has been prepared (eq 7). Intramolecular cyclizations of the vicinal substituents in these macrolides have produced regiospecifically polysubstituted naphthalenes, benzothiophenes, benzofurans, and quinolines in a new approach to these aromatic and heteroaromatic systems. These results demonstrate clearly the substantial potential of one-pot, four-component annulations as a flexible and simple new synthetic method.

Experimental Section[16]

MIMI-MIRC Synthesis of Nonenolide 3. Tri-*n*-butyltinlithium was prepared at 0 °C in THF from lithium diisopropylamide (231 μL, 1.65 mmol of diisopropylamine and 1.08 mL of 1.52 M *n*-BuLi, hexane) and tri-*n*-butyltin hydride (457 μL, 1.65 mmol) and cooled to −78 °C. After 10 min, 130 μL (1.50 mmol) of pentenolide **1** in 2 mL of THF was added dropwise (5 min). After 10 min, 325 μL (3.60 mmol) of methyl acrylate was added, and the reaction mixture was allowed to stir at −70 °C for 16 h. The reaction mixture was quenched with aqueous NH_4Cl solution. The organic layer was separated, and the aqueous layer was extracted with Et_2O (3 × 10 mL). Combined organic layers were dried over $MgSO_4$. Solvent evaporation gave 975 mg of crude product, which was purified by column chromatography (eluting solvent, Et_2O–hexane, 1:9). Lactol **2a** was obtained in 40% yield (333.0 mg): IR ($CHCl_3$, cm^{-1}) 3460, 1735–1705; ^1H NMR ($CDCl_3$) δ 0.82 (t, *J* = 8.2 Hz, 6 H), 0.88 (t, *J* = 7.2 Hz, 9 H), 1.20–1.50 (m, 12 H), 1.60–2.10 (m, 8 H), 2.40–2.50 (m, 1 H), 2.55 (dd, *J* = 13.6, 4.0 Hz, 1 H), 3.55 (m, 1 H), 3.66 (s, 3 H), 3.72 (s, 3 H), 4.00 (m, 1 H), 4.60 (s, 1 H, OH); HRMS calcd for $C_{21}H_{37}O_6Sn$ (M − C_4H_9) *m/e* 505.1613, found *m/e* 505.1613. Lactol **2b** was obtained in 18.7% yield (158.0 mg): IR ($CHCl_3$, cm^{-1}) 3450, 1730–1710; ^1H NMR ($CDCl_3$) δ 0.85 (t, *J* = 8.2 Hz, 6 H), 0.88 (t, *J* = 7.2 Hz, 9 H), 1.22–1.50 (m, 12 H), 1.60–2.50 (m, 8 H), 2.75 (m, 1 H), 2.85 (dd, *J* = 13.6, 4.0 Hz, 1 H), 3.52–3.64 (m, 1 H), 3.69 (s, 3 H), 3.72 (s, 3 H), 3.99 (dt, *J* = 12.0, 2.8 Hz, 1 H), 4.60 (s, 1 H). Lactol **2c** was obtained in 17.8% yield (150.0 mg): IR ($CHCl_3$, cm^{-1}) 3560–3440, 1740–1710; ^1H NMR ($CDCl_3$) δ 0.85 (t, *J* = 8.2 Hz, 6 H), 0.88 (t, *J* = 7.2 Hz, 9 H), 1.20–1.55 (m, 12 H), 1.60–1.85 (m, 5 H), 2.90 (s, 1 H), 2.00–2.12 (m, 2 H), 2.48 (dt, *J* = 12.4, 3.3 Hz, 1 H), 2.17 (dd, *J* = 5.4, 2.6 Hz, 1 H), 3.08 (tt, *J* = 12.4, 4.4 Hz, 1 H), 3.60–3.70 (m, 1 H), 3.65 (s, 3 H), 3.68 (s, 3 H), 3.92 (m, 1 H); HRMS calcd for $C_{21}H_{37}O_6Sn$ (M − C_4H_9) *m/e* 505.1613, found *m/e* 505.1585. Lactol **2a** (200.0 mg, 0.36 mmol) was oxidatively cleaved by lead tetraacetate (198.0 mg, 0.45 mmol) in refluxing benzene (10 min) to afford 212.0 mg of a crude oil, which was purified by column chromatography (eluting solvent, Et_2O–hexane, 2:8). Lactone **3a**, 2,4-bis(methoxycarbonyl)-(*E*)-6-nonenolide, was obtained (52.0 mg) in 55% yield: IR ($CHCl_3$, cm^{-1}) 1755–1715; ^1H NMR ($CDCl_3$) δ 2.10–2.70 (m, 7 H), 3.20 (dd, *J* = 10.0, 1.2 Hz, 1 H), 3.68 (s, 3 H), 3.71 (s, 3 H), 4.06 (m, 1 H), 4.82 (m, 1 H), 5.21 (m, 1 H), 5.34 (m, 1 H). When the proton signals at 2.10–2.70 ppm were irradiated, the olefinic multiplet at 5.21 ppm collapsed into dd, *J* = 15.6, 2.4 Hz, and the olefinic multiplet at 5.34 ppm collapsed into a doublet (*J* = 15.6 Hz): HRMS calcd for $C_{13}H_{18}O_6$ *m/e* 270.1104, found *m/e* 270.1096. Lactone **3b** was obtained (22.0 mg) in 22% yield: IR ($CHCl_3$, cm^{-1}) 1750–1700 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.15–2.70 (m, 6 H), 2.95 (m, 1 H), 3.55 (m, 1 H), 3.70 (s, 3 H), 3.71 (s, 3 H), 3.97 (m, 1 H), 4.89 (dt, *J* = 10.8, 4.2 Hz, 1 H), 5.26–5.46 (m, 2 H). When the proton signals at 2.15–2.70 ppm were irradiated, the olefinic multiplets collapsed into doublets (*J* = 15.6 Hz): HRMS calcd for $C_{13}H_{18}O_6$ *m/e* 270.1104, found *m/e* 270.1105.

Equilibration Experiment: Conversion of 3b to 3a. The minor diastereomer (**3b**) was dissolved in dry methanol under a nitrogen atmosphere. A catalytic amount of dilute sodium methoxide in methanol was added. After 1 h, diastereomer **3b** was epimerized to the major diastereomer **3a**. This epimerization was monitored by glass capillary GC and ^1H NMR spectroscopy. An attempted equilibrium experiment on **3a** showed no change.

MIMI-MIRC Synthesis of Nonenolide 4. To tri-*n*-butyltinlithium (3.60 mmol) in 8 mL of anhydrous THF at −78 °C under argon was added dropwise over 3 min pentenolide **1** (294.0 mg, 3.00 mmol) in 3 mL of THF. After 30 min, ethyl vinyl ketone (303.0 mg, 3.25 mmol) in 3 mL of THF was added dropwise over a 5-min period, and the solution stirred for 1 h at −78 °C followed by 12 h at −20 °C. Methyl acrylate (348.6 mg, 4.05 mmol) in 3 mL of THF was then added to the reaction mixture, and the whole mixture was stirred 10 h at −20 °C, warmed to 23 °C, and quenched with 5 mL of a saturated NH_4Cl solution. Usual workup afforded 2.083 g of a yellow oil. One gram of the crude material was purified by column chromatography (Et_2O–hexane, 1:9) to obtain 520.0 mg (64.5%) of a colorless oil: IR (neat, cm^{-1}) 3450, 3000–2820, 1705. ^1H NMR ($CDCl_3$) δ 0.83 (t, *J* = 8.1 Hz, 6 H) 0.89 (t, *J* = 7.3 Hz, 9 H), 1.04–2.15 (m, 21 H), 2.40–2.60 (m, 4 H), 2.70–3.0 (m, 2 H), 3.47–3.50 (m, 2 H), 3.72 (s, 3 H), 3.95–4.05 (m, 2 H), 4.57 (s, 1 H).

This MIMI-MIRC adduct (100 mg, 0.18 mmol) dissolved in 1 mL of dry benzene was added dropwise via a syringe to a refluxing suspension of lead tetraacetate (79.2 mg, 0.18 mmol) in 250 μL of benzene, under nitrogen. The reaction mixture was refluxed for 2 h, cooled, diluted with 2 mL of water, and extracted with ether (3 × 10 mL). The combined organic layers were washed successively with 5% $NaHCO_3$ (2 × 20 mL), 5% HCl (2 × 20 mL), water (2 × 20 mL), and brine. Drying over $MgSO_4$, filtration, and evaporation of the solvent afforded 112.0 mg of crude material, which upon purification by preparative TLC (EtOAc–hexane, 1:4, multiple developments) gave 31.0 mg (64.6%) of 2-(methoxycarbonyl)-4-propionyl-(*E*)-6-nonenolide (**4**): IR (CCl_4, cm^{-1}) 3000–2840, 1750, 1730, 1715; ^1H NMR ($CDCl_3$) δ 1.03–1.07 (m, 3 H), 2.03–2.63 (m, 9 H), 2.90–3.21 (m, 1 H), 3.50–4.09 (m, 4 H), 4.75–4.92 (m, 1 H), 5.10–5.62 (m, 2 H); HRMS calcd for $C_{14}H_{20}O_5$ *m/e* 268.1308, found *m/e* 268.1318.

The crude MIMI-MIRC adduct (400.0 mg, 0.72 mmol) dissolved in 5 mL of dry benzene was added dropwise to a refluxing solution of lead tetraacetate (317.0 mg, 0.71 mmol) in 1 mL of benzene. The reaction mixture was refluxed for 2 h and then cooled to 23 °C, diluted with 10 mL of water, and extracted with ether (3 × 30 mL). Usual workup afforded 427.0 mg of crude material, which was purified by preparative TLC (EtOAc–hexane, 1:5) to afford **4**: 78.0 mg (50.5%) of a colorless oil having physical properties identical with those described above.

MIMI-ARC Synthesis of Nonenolide 6. To tri-*n*-butyltinlithium (1.15 mmol) in 2 mL of anhydrous THF at −78 °C under argon was added

(15) (a) *Thiophene and Its Derivatives*; Gronowitz, S., Ed.; Wiley: New York, 1985–1986; Parts 1–3. (b) Gronowitz, S.; Hallberg, A.; Nikitidis, G. *Tetrahedron* **1987**, *43*, 4793.

(16) Melting points were determined by using a Syfron/Thermolyne Model MP-12615 melting point apparatus; melting points are uncorrected. IR spectra were recorded on a Perkin-Elmer 559B spectrometer and were calibrated by using the 1601-cm^{-1} polystyrene absorption as reference. ^1H NMR spectra were recorded by using a Varian XL-400 spectrometer operating at 400 MHZ. Chemical shifts are reported in parts per million (ppm) downfield from a tetramethylsilane (Me_4Si) internal standard, and the resonances are noted as being a singlet (s), a doublet (d), a triplet (t), or a multiplet (m). Mass spectra were performed by the mass spectrometry service laboratory at the University of Minnesota, Minneapolis, and by in-house services. Elemental analyses were performed by Atlantic Microlab, Atlanta, GA. The following solvents were distilled from sodium/benzophenone before use: diethyl ether and tetrahydrofuran. Pyridine and triethylamine were distilled from calcium hydride; dichloromethane and chloroform were distilled from phosphorus pentoxide. Methanol was distilled from magnesium. All other reagents and solvents were used as received.

dropwise over 5 min 2-cyclohexenone (97 μL, 1.00 mmol) in 2 mL of THF. After 10 min, ethyl vinyl ketone (124 μL, 1.25 mmol) in 2 mL of THF was added dropwise (5 min). The reaction mixture was stirred at −78 °C for 1 h and then diluted with 6 mL of THF. Gaseous formaldehyde, generated by pyrolysis of paraformaldehyde (ca. 1 g) at 155–160 °C, was added by means of a stream of dry argon, and then the reaction mixture was stirred at −50 °C for 2 h and stirred at −10 °C for 16 h. The reaction mixture was quenched, and usual workup gave 570.0 mg of a crude oil, which was purified by column chromatography (eluting solvent, Et_2O–hexane, 1:4). Lactols **5** were obtained (284.0 mg, 56%) as a colorless oil: IR (neat, cm^{-1}) 3400, 1700; ^1H NMR ($CDCl_3$) δ 0.81 (t, J = 8.0 Hz, 9 H), 0.90 (t, J = 7.6 Hz, 9 H), 1.05 (t, J = 7.2 Hz, 3 H), 1.25–1.90 (m, 23 H), 2.95–2.60 (m, 2 H), 2.60–2.70 (m, 1 H), 3.75 (dd, J = 11.2, 3.6 Hz, 1 H), 4.04 (t, J = 11.2 Hz, 1 H). To a suspension of lead tetraacetate (70.0 mg, 0.16 mmol) in 2 mL of refluxing benzene (80 °C), were added lactols **5** (66.0 mg, 0.13 mmol) in 2 mL of benzene and refluxed for 15 min. The reaction mixture was cooled to 23 °C and quenched with water. The usual workup gave a pale yellow oil, which was purified by column chromatography (eluting solvent, Et_2O–hexane, 1:4). 8-Propionyl-(*E*)-5-nonenolide (**6**) was obtained (24.0 mg, 87%) as a white solid: IR ($CHCl_3$, cm^{-1}) 1730–1700; ^1H NMR ($CDCl_3$) δ 1.04 (t, J = 7.2 Hz, 3 H), 1.70–3.00 (m, 11 H), 3.80–4.20 (m, 1 H), 5.05–5.70 (m, 3 H). When proton signals at 1.90–2.90 ppm were irradiated, the two olefinic multiplets collapsed into two doublets (J = 15.2 Hz). An analytical sample was recrystallized from hexane: mp 70–71 °C. Anal. Calcd for $C_{12}H_{18}O_3$: C, 68.57; H, 8.57. Found: C, 68.47; H, 8.68.

MIMI-ARC Synthesis of Nonenolide 8. To tri-*n*-butyltinlithium (0.58 mmol) in 2 mL of anhydrous THF at −78 °C under argon was added dropwise over 2 min 2-methyl-2-cyclohexenone (55.0 mg, 0.50 mmol) in 1 mL of THF. After 10 min, 62 μL (0.63 mmol) of ethyl vinyl ketone in 1 mL of THF was added dropwise (5 min). The reaction mixture was stirred at −78 °C for 30 min and then diluted with 4 mL of THF. Gaseous formaldehyde, generated by pyrolysis of paraformaldehyde (ca. 1 g) at 155–160 °C, was added by means of a stream of dry argon. The reaction mixture was stirred at −30 °C for 1 h and at −10 °C for 16 h. The reacton mixture was quenched with saturated NH_4Cl solution and warmed to 23 °C. Standard workup gave a pale yellow oil, which was purified by column chromatography (eluting solvent, Et_2O–hexane, 1:4). Lactols **7** were obtained (120.0 mg, 46.5%) as a colorless oil: IR ($CHCl_3$, cm^{-1}) 3580, 1700; ^1H NMR ($CDCl_3$) δ 0.82 (t, J = 8.0 Hz, 6 H), 0.88 (t, J = 7.6 Hz, 9 H), 1.02 (t, J = 7.2 Hz, 3 H), 1.14 (s, 3 H), 1.25–1.95 (m, 22 H), 2.35–2.55 (m, 2 H), 3.03 (m, 1 H), 3.72 (dd, J = 11.2, 5.6 Hz, 1 H), 4.16 (t, J = 11.2 Hz, 1 H). To a suspension of lead tetraacetate (115.0 mg, 0.26 mmol) in 2 mL of refluxing benzene (80 °C) were added lactols **7** (111.0 mg, 0.22 mmol) in 2 mL of benzene, and the mixture was refluxed for 15 min. Standard quench and workup gave a pale yellow oil, which was purified by column chromatography (eluting solvent, Et_2O–hexane, 1:4). 6-Methyl-8-propionyl-(*Z*)-5-nonenolide (**8-*Z***) was obtained (38.0 mg, 79%) as a white solid: IR ($CHCl_3$, cm^{-1}) 1735–1705; ^1H NMR ($CDCl_3$) δ 1.05 (t, J = 7.2 Hz, 3 H), 1.78 (s, 3 H), 1.85–2.60 (m, 10 H), 3.16 (tt, J = 11.6, 2.8 Hz, 1 H), 3.81 (dt, J = 11.6, 2.4 Hz, 1 H), 5.11 (t, J = 11.6 Hz, 1 H), 5.20 (m, 1 H). An analytical sample was recrystallized from hexane: mp 51–52 °C. Anal. Calcd for $C_{13}H_{20}O_3$: C, 69.64; H, 8.92. Found: C, 69.71; H, 9.02. A minor nonenolide (**8-*E***) was obtained (5.0 mg, 10%) as a colorless oil: IR ($CHCl_3$, cm^{-1}) 1740–1710; ^1H NMR ($CDCl_3$) δ 1.10 (t, J = 7.2 Hz, 3 H), 1.68 (s, 3 H), 1.85–2.90 (m, 11 H), 4.17 (dd, J = 11.6, 2.4 Hz, 1 H), 4.33 (dd, J = 11.6, 4.8 Hz, 1 H), 5.15 (m, 1 H).

MIMI-ARC Synthesis of Octenolide 10. To tri-*n*-butyltinlithium (1.80 mmol) in 2 mL of anhydrous THF at −78 °C under argon was added dropwise over 5 min 2-cyclopentenone (123.1 mg, 1.50 mmol) in 2 mL of THF. After 15 min, ethyl vinyl ketone (186 μL, 1.87 mmol) in 3 mL of THF was added dropwise (5 min) and stirred at −78 °C for 3 h. Then, 840 μL of acetaldehyde (2.5 M THF solution (2.10 mmol)) was added dropwise (5 min), and the reaction mixture was stirred at −60 °C for 16 h. Standard quench and workup gave a pale yellow oil, which was purified by column chromatography (eluting solvent, Et_2O–hexane, 1:4). Lactol **9a** was obtained (151.0 mg, 20%) as a colorless oil: IR (neat, cm^{-1}) 3400, 1700; ^1H NMR ($CDCl_3$) δ 0.84 (t, J = 8.0 Hz, 6 H), 0.89 (t, J = 7.2 Hz, 9 H), 1.04 (t, J = 7.2 Hz, 3 H), 1.11 (d, J = 6.8 Hz, 3 H), 1.26–1.52 (m, 13 H), 1.57 (s, 1 H, OH), 1.62–2.10 (m, 5 H), 2.45–2.64 (m, 5 H), 4.15 (dq, J = 9.4, 3.6 Hz, 1 H). Lactol **9b** was obtained (260.0 mg, 35%) as a colorless oil: IR (neat, cm^{-1}) 3440, 1725; ^1H NMR ($CDCl_3$) δ 0.85 (t, J = 8.0 Hz, 6 H), 0.90 (t, J = 7.2 Hz, 9 H), 1.02 (dt, J = 7.2, 1.6 Hz, 3 H), 1.16 (dd, J = 6.4, 2.4 Hz, 3 H), 1.22–1.60 (m, 13 H), 1.62 (s, 1 H, OH), 1.74–1.96 (m, 2 H), 2.10–2.34 (m, 2 H), 2.50–2.62 (m, 4 H), 3.35 (m, 2 H), 3.85 (m, 1 H); HRMS calcd for $C_{20}H_{37}O_3Sn$ (M − C_4H_9) m/e 445.1766, found m/e 445.1751.

Lactol **9a** (116.0 mg, 0.23 mmol) was oxidatively cleaved with lead tetraacetate (123.0 mg, 0.27 mmol) in a refluxing benzene (10 min) to give 28 mg (58%) of *trans*-8-methyl-7-propionyl-(*E*)-4-octenolide (**10-*trans***) as a colorless oil after chromatographic purification (eluting solvent, ethyl acetate–hexane, 1:9): IR ($CHCl_3$, cm^{-1}) 1740–1700, 970; ^1H NMR ($CDCl_3$) δ 1.07 (t, J = 7.4 Hz, 3 H), 1.22 (d, J = 5.6 Hz, 3 H), 2.10–2.64 (m, 8 H), 2.78 (m, 1 H), 5.30 (dq, J = 10.8, 5.6 Hz, 1 H), 5.50–5.67 (m, 2 H). When the proton signals at 2.10–2.80 ppm were irradiated, the olefinic multiplets collapsed into doublets (J = 11.2 Hz). When the doublet at 1.22 ppm was irradiated, the multiplet at 5.30 ppm collapsed into a doublet (J = 10.8 Hz): HRMS calcd for $C_{12}H_{18}O_3$ m/e 210.1256, found m/e 210.1265.

Lactol **9b** (107.0 mg, 0.21 mmol) was oxidatively cleaved by lead tetraacetate (114.0 mg, 0.25 mmol) in refluxing benzene (10 min) to give 23.0 mg (52%) of *cis*-8-methyl-7-propionyl-(*E*)-4-octenolide (**10-*cis***) as a colorless oil: IR ($CHCl_3$, cm^{-1}) 1740–1700, 980; ^1H NMR ($CDCl_3$) δ 1.05 (t, J = 7.2 Hz, 3 H), 1.16 (d, J = 6.8 Hz, 3 H), 2.05–2.65 (m, 7 H), 2.95 (m, 1 H), 3.36 (ddd, J = 10.0, 4.8, 2.8 Hz, 1 H), 5.14–5.27 (m, 1 H), 5.40–5.58 (m, 2 H). When the proton signals at 2.10–2.65 ppm were irradiated, the olefinic multiplets collapsed into doublets (J = 16.0 Hz). When the doublet at 1.16 ppm was irradiated, the multiplet at 5.25 ppm collapsed into a doublet (J = 5.2 Hz): HRMS calcd for $C_{12}H_{18}O_3$ m/e 210.1256, found m/e 210.1261.

MIMI-ARC Synthesis of Decenolide 12. To tri-*n*-butyltinlithium (2.00 mmol) in 5 mL of anhydrous THF at −78 °C under argon was added dropwise over 2 min cycloheptenone (224.0 mg, 2.04 mmol) in 4 mL of THF. After it was stirred for 30 min, a solution of ethyl vinyl ketone (178.0 mg, 2.11 mmol) in 4 mL of THF was added via cannula. After 1.5 h, a solution of cyclopropanecarboxaldehyde (175.0 mg, 2.50 mmol) in 4 mL of THF was cannulated. The reaction mixture was stirred at −70 °C for 32 h. Standard quench and workup gave 1.1750 g of a pale yellow oil. The pale yellow oil was purified via short-path column chromatography, giving 611.0 mg (55.0%) of lactols **11**. To a suspension of lead tetraacetate (363.0 mg, 0.82 mmol) in a 8 mL of dry refluxing benzene was added a solution of lactols **11** (340.0 mg) in 10 mL of dry benzene. After the mixture was refluxed for 2 h and 40 min, standard quench and workup gave 343.0 mg of a pale yellow oil. The pale yellow oil was purified via short-path column chromatography (silica gel, 20 g; eluting solvent, Et_2O–hexane, 1:9) to give 124.0 mg (77%) of 10-cyclopropyl-9-propionyl-(*E*)-6-decenolide (**12**).

In a gram-scale reaction, to tri-*n*-butyltinlithium (6.36 mmol) in 15 mL of anhydrous THF at −78 °C under argon was added dropwise over 15 min 2-cycloheptenone (661.0 mg, 6.00 mmol) in 15 mL of anhydrous THF. After 1.5 h at −78 °C, ethyl vinyl ketone (550 mg, 6.54 mmol) in 15 mL of THF was cannulated during 8 min. After 1.5 h, a cooled solution (−78 °C) of cyclopropanecarboxaldehyde (559.0 mg, 7.98 mmol) in 15 mL of THF was cannulated during 12 min and stirred at −70 °C for 18 hours. Standard quench and workup gave 3.58 g of a pale yellow caramel.

To a suspension of lead tetraacetate (5.3200 g, 12.00 mmol) in 25 mL of refluxing benzene was added a solution of the pale yellow caramel (3.5800 g) in 60 mL of benzene. It was refluxed for 2 h and then cooled to 23 °C. Standard quench and workup gave 3.403 g of pale yellow oil. The pale yellow oil was separated via short path column chromatography (silica gel, 200 g, Et_2O–hexane, 1:9). **12-*trans*** (441.0 mg (yield 28%), colorless caramel): IR ($CHCl_3$, cm^{-1}) 2970, 2910, 2840, 1700, 1440, 1330, 1260, 1150, 1010, 970, 915; ^1H NMR ($CDCl_3$) δ 0.10–0.20 (m, 1 H), 0.35–0.44 (m, 1 H), 0.48–0.60 (m, 2 H), 0.75–1.00 (m, 1 H), 1.10 (t, J = 7.2 Hz, 3 H), 1.20–1.80 (m, 4 H), 1.85–2.70 (m, 8 H), 3.28–3.39 (m, 1 H), 4.30 (dd, J = 9.6, 4.4 Hz, 1 H), 5.35 (m, 2 H); HRMS calcd for $C_{16}H_{24}O_3$ m/e 264.1725, found m/e 264.1725. **12-*cis*** (390.0 mg (yield 25%) colorless semisolid): IR ($CHCl_3$, cm^{-1}) 2975, 2910, 2840, 1700, 1480, 1330, 1260, 1160, 1130, 1100, 1010, 970, 935; ^1H NMR ($CDCl_3$) δ 0.17–0.26 (m, 1 H), 0.32–0.44 (m, 2 H), 0.44–0.52 (m, 1 H), 0.87–1.00 (m, 1 H), 1.08 (t, J = 7.2 Hz, 3 H), 1.25–1.42 (m, 1 H), 1.45–1.68 (m, 2 H), 1.70–1.92 (m, 3 H), 2.16–2.40 (m, 4 H), 2.47–2.66 (m, 2 H), 3.02 (ddd, J = 9.6, 9.6, 4.0 Hz, 1 H), 4.46 (dd, J = 10.0, 10.0 Hz, 2 H), 5.25–5.32 (m, 2 H); HRMS calcd for $C_{16}H_{24}O_3$ m/e 264.1725, found m/e 264.1731.

MIMI-ARC Synthesis of Decenolide 14. To tri-*n*-butyltinlithium (0.90 mmol) in 2.5 mL of anhydrous THF at −78 °C under argon was added dropwise over 2 min 2-cycloheptenone (101.2 mg, 0.92 mmol) in 2 mL of anhydrous THF. After 25 min at −78 °C, ethyl vinyl ketone (95 μL, 0.95 mmol) in 2 mL of THF was added dropwise over 10 min. After 90 min, acetaldehyde (450 μL, 1.13 mmol) (2.5 M THF) was added, and the reaction mixture was then allowed to stir under argon at −60 °C for 32 h. Standard quench and workup gave a colorless oil (535.0 mg), which was purified by short-path column chromatography (silica gel, 35 g, eluting solvent, Et_2O–hexane, 1:9) to yield lactol **13a** (190.3 mg (39.8%) as a colorless oil): IR (neat, cm^{-1}) 3550–3380, 1710–1670, 1460, 1375, 1240, 1170; ^1H NMR ($CDCl_3$) δ 0.89 (m, 15 H), 1.01 (m, 3 H), 1.14 (m, 3 H), 1.23–1.75 (m, 18 H), 1.80–2.72 (m, 10 H), 3.81 (m, 1

H). **13b**: 24.9 mg (5.2%) as a colorless oil; IR (neat, cm^{-1}) 3460, 1720–1680, 1460, 1382, 1110–1075; ^1H NMR ($CDCl_3$) δ 0.89 (m, 15 H), 1.03 (t, J = 7.2 Hz, 3 H), 1.13 (d, J = 6.4 Hz, 3 H), 1.20–1.70 (m, 18 H), 1.82–2.70 (m, 10 H), 3.76 (m, 1 H).

To a suspension of lead tetraacetate (94.6 mg, 0.21 mmol) in dry refluxing bezene (2 mL) was added **13a** (89.7 mg, 0.17 mmol) in 2.6 mL of benzene. The mixture was refluxed under argon for 30 min and cooled to 23 °C, and standard workup gave 84.5 mg of a crude oil, which was purified by short-path column chromatography (silica gel, 5 g, eluting solvent Et_2O–hexane (3:10)) to yield 10-methyl-9-propionyl-(*E*)-6-decenolide (**14**) (36.2 mg (90.0%) as a colorless oil)): IR (neat, cm^{-1}) 1740–1700, 1450, 1380, 1340, 1260, 1190, 1165, 1030, 980, 935; ^1H NMR δ 1.05 (t, J = 6.0 Hz, 1.5 H), 1.07 (t, J = 6.4 Hz, 1.5 H), 1.11 (d, J = 6.0 Hz, 1.5 H), 1.17 (d, J = 6.8 Hz, 1.5 H), 1.25–2.63 (m, 12 H), 2.81 (m, $^1/_2$ H), 3.32 (m, $^1/_2$ H), 5.19 (m, 1 H), 5.34 (m, 2 H); proton decoupled spectrum ^1H NMR ($CDCl_3$) peak irradiated δ 2.00, 5.34 (d, J = 18.8 Hz); HRMS calcd for $C_{14}H_{22}O_3$ m/e 238.1569, found m/e 238.1566.

***Z*-Decenolide 14′.** To a suspension of lead tetraacetate (18.8 mg, 0.04 mmol) in dry refluxing benzene (0.6 mL) was added **13b** (16.0 mg, 0.03 mmol) in 1.6 mL of benzene. The mixture was refluxed under argon for 6.5 h and cooled to 23 °C, and standard workup gave 10.0 mg of a crude oil, which was purified by a 250 μm Prep TLC plate with eluting solvent 20% ethyl acetate–hexane to yield *Z*-decenolide **14′** (4.4 mg (62.0%) as a colorless oil): IR ($CHCl_3$, cm^{-1}) 1715–1680, 1455, 1380, 1335, 1190, 1165, 970; ^1H NMR δ 1.08 (t, J = 6.0 Hz, 3 H), 1.18 (d, J = 6.0 Hz, 3 H), 1.25–2.40 (m, 10 H), 2.51 (q, J = 6.4 Hz, 2 H), 3.33 (m, 1 H), 5.17 (m, 1 H), 5.37 (m, 2 H); proton decoupled spectra ^1H NMR ($CDCl_3$) peak irradiated δ 1.18, 5.17 (d, J = 4.0 Hz, 1 H), peak irradiated δ 2.00, 5.37 (d, J = 2.8 Hz, 1 H); HMRS calcd for $C_{14}H_{22}O_3$ m/e 238.1569, found m/e 238.1572.

MIMI-ARC Synthesis of Decenolide 16. To tri-*n*-butyltinlithium (1.80 mmol) in 10 mL of anhydrous THF at −78 °C under argon was added dropwise over 2 min 2-cycloheptenone (189.8 mg, 1.72 mmol) in 2.5 mL of anhydrous THF. After 25 min at −78 °C, ethyl vinyl ketone (190 μL, 1.97 mmol) in 2.5 mL of THF was added dropwise over 10 min. After 90 min, *m*-anisaldehyde (268 μL, 2.20 mmol) was added, and the reaction mixture was then allowed to stir under argon at −60 °C for 16 h. Standard quench and workup gave a crude caramel (1.2535 g), which was purified by short-path column chromatography (silica gel, 70 g, eluting solvent Et_2O–hexane (1:9)) to yield lactol **15a** (344.0 mg (32.0%) as a colorless caramel): IR (neat, cm^{-1}) 1710–1680, 1595, 1587, 1482, 1452, 1370, 1260, 1154, 1143, 957, 865, 788, 735, 702; ^1H NMR ($CDCl_3$) δ 0.75 (m, 6 H), 0.90 (m, 12 H), 1.20–1.53 (m, 15 H), 1.78–1.95 (m, 5 H), 2.15–2.65 (m, 6 H), 2.86–2.92 (m, 2 H), 3.80, (s, 3 H), 4.64 (m, 1 H), 6.82 (m, 2 H), 7.22 (d, J = 8.0 Hz, 1 H). **15b** (220.1 mg (20.5%) as a colorless caramel): IR (neat, cm^{-1}) 1705–1680, 1595, 1580, 1480, 1450, 1370, 1255, 1150, 955, 870, 784, 702; ^1H NMR ($CDCl_3$) δ 0.75 (m, 6 H), 0.90 (m, 12 H), 1.10–1.50 (m, 15 H), 1.52–2.05 (m, 5 H), 2.18–2.60 (m, 6 H), 2.84–2.91 (m, 2 H), 3.79 (s, 3 H), 4.77 (m, 1 H), 6.79 (dd, J = 8.0 Hz, 2.4 Hz, 1 H), 6.87 (m, 2 H), 7.22 (d, J = 8.0 Hz, 1 H).

To a suspension of lead tetraacetate (277.1 mg, 0.63 mmol) in dry refluxing benzene (1.5 mL) was added lactol **15a** (311.5 mg, 0.51 mmol) in 1.5 mL of benzene. The mixture was refluxed under argon for 60 min and cooled to 23 °C, and standard workup gave 308.0 mg of a crude oil, which was purified by short-path column chromatography (silica gel, 20 g, eluting solvent, Et_2O–hexane (1:9)) to yield *trans*-10-(3-methoxyphenyl)-9-propionyl-(*E*)-6-decenolide (**16**-*trans*) (140.1 mg (83.7%) as a colorless oil): IR (neat, cm^{-1}) 1735–1702, 1602, 1592, 1492, 1442, 1252, 1160, 1022, 975, 932, 795, 708; ^1H NMR ($CDCl_3$) δ 0.72 (t, J = 7.2 Hz, 3 H), 1.34 (m, 2 H), 1.60–1.92 (m, 4 H), 2.05–2.48 (m, 6 H), 3.21 (ddd, J = 10.8 Hz, 10.0 Hz, 3.2 Hz, 1 H), 3.78 (s, 3 H), 5.41 (m, 2 H), 6.02 (d, J = 10.0 Hz, 1 H), 6.77 (m, 1 H), 6.83 (m, 1 H), 6.87 (dd, J = 7.6 Hz, 1.6 Hz, 1 H), 7.19 (dd, J = 8.0 Hz, 8.0 Hz, 1 H); proton decoupled spectrum ^1H NMR ($CDCl_3$) peak irradiated δ 2.05, 5.44 (d, J = 14.8 Hz); HRMS: calcd for $C_{20}H_{26}O_4$ m/e 330.1831, found m/e 330.1830.

To a suspension of lead tetraacetate (172.6 mg, 0.39 mmol) in dry refluxing benzene (1.5 mL) was added lactol **15b** (198.3 mg, 0.32 mmol) in 2.0 mL of benzene. The mixture was refluxed under argon for 60 min and cooled to 23 °C, and standard workup gave 195.7 mg of a crude oil, which was purified by short path column chromatography (silica gel, 7 g, eluting solvent, Et_2O–hexane (1:9)) to yield decenolide **16**-*cis* (75.7 mg (72.0%) as a colorless oil): IR (neat, cm^{-1}) 1720–1690, 1600, 1580, 1430, 1250, 1150, 975, 780, 700; ^1H NMR ($CDCl_3$) δ 0.87 (t, J = 7.6 Hz, 3 H), 1.44 (m, 2 H), 1.75 (m, 2 H), 1.88 (m, 2 H), 2.12 (q, J = 7.6 Hz, 2 H), 2.25 (m, 1 H), 2.35 (m, 1 H), 2.44 (m, 1 H), 2.64 (m, 1 H), 3.30 (ddd, J = 5.9, 3.2, 2.8 Hz, 1 H), 3.80 (s, 3 H), 5.42 (ddd, J = 15.6, 8.0, 7.2, 1 H), 5.66 (ddd, J = 15.6, 7.6, 7.2, 1 H), 6.08 (d, J = 2.8 Hz, 1 H), 6.82 (m, 3 H), 7.24 (d, J = 8.0 Hz, 1 H); proton decoupled spectrum ^1H NMR ($CDCl_3$) peak irradiated δ 1.76, 5.42 (d, J = 15.6 Hz, 1 H); HRMS calcd for $C_{20}H_{26}O_4$ m/e 330.1831, found m/e 330.1836.

MIMI-ARC Synthesis of Decenolide 17. To tri-*n*-butyltinlithium (7.81 mmol) in 16 mL of anhydrous THF at −78 °C under argon was added dropwise over 7 min 2-cycloheptenone (810.0 mg, 7.36 mmol) in 16 mL of anhydrous THF. After 1 h at −78 °C, phenyl vinyl ketone (1.058 g, 8.02 mmol) in 16 mL of THF was added via cannula (12 min). After 90 min, a solution (−78 °C) of 2-iodophenylacetaldehyde (2.375 g, 9.66 mmol) in 16 mL of THF was cannulated (10 min), and the reaction mixture turned to pale yellow. After being stirred for 24 h at −65 °C, the reaction was quenched and usual workup gave 7.0430 g of pale yellow caramel. This yellow caramel (7.4030 g) was dissolved in 100 mL of benzene and added to a suspension of lead tetraacetate (6.5200 g, 14.71 mmol) in 20 mL of refluxing benzene. The suspension was allowed to reflux under argon for 2 h, cooled to 23 °C, and worked up as usual to afford 7.0980 g of pale yellow caramel. The pale yellow caramel was separated via short-path column chromatography (silica gel 140 g, Et_2O–hexane 1:9), giving *trans*-10-(2-iodobenzyl)-9-benzoyl-(*E*)-6-decenolide (**17**-*trans*) (878.0 mg (yield 25%), colorless caramel): IR ($CHCl_3$, cm^{-1}) 3140, 3050, 2985, 2940, 2905, 2835, 1710, 1665, 1570, 1460, 1430, 1410, 1330, 1250, 1160, 1135, 1050, 965, 900, 850; ^1H NMR ($CDCl_3$) δ 1.25–1.37 (m, 1 H), 1.50–1.62 (m, 1 H), 1.73–1.93 (m, 4 H), 2.08–2.16 (m, 1 H), 2.16–2.25 (m, 1 H), 2.38–2.52 (m, 2 H), 2.91 ($^1/_2$ ABX, J = 14.4, 10.5 Hz, 1 H), 3.00 ($^1/_2$ ABX, J = 14.4, 3.7, 1 H), 3.90 (ddd, J = 14.0, 6.5, 3.1 Hz, 1 H), 5.30 (ddd, J = 14.7, 9.4, 4.1 Hz, 1 H), 5.45 (ddd, J = 14.7, 9.4, 4.1 Hz, 1 H), 5.67–5.75 (m, 1 H), 5.67–5.78 (m, 1 H), 6.80–6.87 (m, 2 H), 7.16–7.20 (m, 2 H), 7.50 (t, J = 8.0 Hz, 2 H), 7.61 (t, J = 7.2 Hz, 1 H), 7.73 (dd, J = 8.0, 2.4 Hz, 1 H), 8.04 (dd, J = 7.2, 1.6 Hz, 2 H); HRMS calcd for $C_{24}H_{25}IO_3$ m/e 488.0848, found m/e 488.0849. **17**-*cis* (479.0 mg (yield 13%), colorless caramel): IR ($CHCl_3$, cm^{-1}) 3042, 3020, 2950, 2920, 2840, 1710, 1665, 1590, 1470, 1430, 1250, 1165, 1009, 965, 920, 695, 660; ^1H NMR ($CDCl_3$) δ 1.53–1.67 (m, 2 H), 1.70–1.79 (m, 1 H), 2.04 (dd, J = 10.4, 5.2 Hz, 2 H), 2.10–2.22 (m, 2 H), 2.60–2.63 (m, 2 H), 2.71 (dd, J = 14.4, 10.8 Hz, 1 H), 3.13 (dd, J = 14.4, 10.8 Hz, 1 H), 4.45 (dd, J = 10.1, 4.6 Hz, 1 H), 5.31 (ddd, J = 14.4, 5.2, 3.1 Hz, 1 H), 5.45–5.57 (m, 2 H), 6.82 (ddd, J = 7.7, 7.7, 2.2 Hz, 1 H), 7.03 (dd, J = 7.6, 2.6 Hz, 1 H), 7.16 (t, J = 7.6 Hz, 1 H), 7.51 (t, J = 7.6 Hz, 2 H), 7.59 (t, J = 7.2 Hz, 1 H), 7.68 (d, J = 8.4 Hz, 1 H), 8.17 (d, J = 8.0 Hz, 2 H); HRMS calcd for $C_{24}H_{25}IO_3$ m/e 488.0848, found m/e 488.0853.

MIMI-ARC Synthesis of Nonenolides 18a. To tri-*n*-butyltinlithium (5.02 mmol) in 10 mL of anhydrous THF at −78 °C under argon was added dropwise over 10 min 2-cyclohexenone (455.0 mg, 4.74 mmol) in 10 mL of anhydrous THF. After 1 h, a solution (−78 °C) of phenyl vinyl ketone (682.0 mg, 5.17 mmol) in 10 mL of THF was added via cannula during 10 min. After 1 h, a solution (−78 °C) of (2-iodophenyl)acetaldehyde (1.530 g, 6.22 mmol) in 10 mL of THF was cannulated during 10 min, and the reaction mixture turned to pale yellow. It was stirred for 24 h at −65 °C; standard quench and workup gave 4.224 g of a pale yellow caramel. This caramel (2.3820 g) was dissolved in 65 mL of benzene and added to a suspension of lead tetraacetate (1.3850 g, 3.12 mmol) in 32 mL of refluxing benzene. It was refluxed for 2 h and cooled to 23 °C, and standard quench and workup gave 2.363 g of a pale yellow caramel. The pale yellow caramel (1.9790 g) was separated via short-path column chromatography (silica gel 60 g; eluting solvent, Et_2O–hexane (1:9)) to yield *trans*-9-(2-iodobenzyl)-8-benzoyl-(*E*)-5-nonenolide (**18a**-*trans*) (171.0 mg (yield 16%), colorless caramel): IR (neat, cm^{-1}) 3050, 2950, 2910, 2840, 1715, 1665, 1590, 1572, 1555, 1460, 1430, 1335, 1245, 1190–1155, 1130, 750, 705; ^1H NMR ($CDCl_3$) δ 1.52–2.00 (m, 2 H), 2.55 (m, 6 H), 2.83 ($^1/_2$ ABX, J = 16.0 Hz, 10.4 Hz, 1 H), 2.96 ($^1/_2$ ABX, J = 16.0, 4.0 Hz, 1 H), 3.83–3.90 (m, 1 H), 5.24–5.34 (m, 1 H), 5.55–5.63 (m, 1 H), 5.81 (ddd, J = 9.6, 9.6, 2.8 Hz, 1 H), 6.80–6.85 (m, 1 H), 7.18 (d, J = 4.4 Hz, 2 H), 7.53 (t, J = 8.0 Hz, 2 H), 7.62 (t, J = 8.0 Hz, 1 H), 7.74 (d, J = 7.6 Hz, 1 H), 8.03 (dd, J = 7.2, 1.6 Hz, 2 H); HRMS calcd for $C_{23}H_{23}IO_3$ m/e 474.0692, found m/e 474.0694. **18a**-*cis* (193.0 mg (yield 18%), colorless caramel): IR ($CHCl_3$, cm^{-1}), 2910, 2830, 1705, 1665, 1590, 1570, 1540, 1460, 1430, 1340, 1250, 1130, 1000; ^1H NMR ($CDCl_3$) δ 1.75–2.05 (m, 2 H), 2.10–2.47 (m, 4 H), 2.61–2.72 (m, 1 H), 2.80–2.93 (m, 1 H), 3.08 ($^1/_2$ ABX, J = 17.1, 10.6 Hz, 1 H), 3.14 ($^1/_2$ ABX, J = 16.3, 10.0 Hz, 1 H), 3.87–3.91 (m, 1 H), 5.41 (br s, 2 H), 5.87 (br s, 1 H), 6.85 (dt, J = 6.7, 2.1 Hz, 1 H), 7.07 (m, 1 H), 7.16 (dt, J = 6.4, 1.6 Hz, 1 H), 7.49 (t, J = 7.6 Hz, 2 H), 7.56–7.60 (m, 1 H), 7.72 (d, J = 8.0 Hz, 1 H), 8.11 (br s, 2 H); HRMS calcd for $C_{23}H_{23}IO_3$ m/e 474.0692, found m/e 474.0690.

MIMI-ARC Synthesis of Nonenolide 18e. To tri-*n*-butyltinlithium (1.80 mmol) in 10 mL of anhydrous THF at −78 °C under argon was added dropwise over 2 min 2-cyclohexenone (165.0 mg, 1.71 mmol) in

2 mL of THF. After 25 min at −78 °C, phenyl vinyl ketone (250.0 mg, 1.89 mmol) in 2 mL of THF was added dropwise during 10 min. After 90 min, 3-thienylacetaldehyde (261.0 mg, 2.07 mmol) in 2 mL of THF was added dropwise during 5 min to the −78 °C solution. Stirring was continued for 20 h at −65 °C. Saturated aqueous ammonium chloride was added, and the reaction mixture was allowed to warm slowly to room temperature. Standard workup gave a crude caramel (1.2767 g), which was dissolved in 6 mL of anhydrous benzene and added over 5 min to a suspension of lead tetraacetate (766.2 mg, 1.73 mmol) in dry refluxing benzene (5 mL). The suspension was allowed to reflux under argon for 2.5 h and then cooled to 23 °C. The reaction was worked up as usual to afford 1.3092 g of a crude light yellow oil. This crude oil was separated via short-path column chromatography (silica gel, 70 g, eluting solvent, Et_2O–hexane, 1:9) to yield *cis*-9-(3-thienylmethyl)-8-benzoyl-(*E*)-5-nonenolide (**18e-*cis***) (112.4 mg (18.5%), white crystals): mp 157.5–158.5 °C; IR ($CHCl_3$, cm^{-1}) 1745, 1695, 1375, 1200, 1155, 1005, 965, 935; ^1H NMR ($CDCl_3$) δ 1.78–2.58 (m, 10 H), 4.15 (ddd, J = 10.6, 10.0, 3.2 Hz, 1 H), 5.43 (m, 1 H), 5.69 (ddd, J = 14.8, 10.6, 3.2 Hz, 1 H), 6.57 (d, J = 10.0 Hz, 1 H), 7.03 (dd, J = 3.6, 1.2 Hz, 1 H), 7.10 (dd, J = 4.8, 2.8 Hz, 1 H), 7.17 (dd, J = 4.0, 1.2 Hz, 1 H), 7.39 (dd, J = 8.0, 7.2 Hz, 2 H), 7.51 (m, 1 H), 7.76 (d, J = 6.8 Hz, 2 H); proton decoupled spectrum ^1H NMR ($CDCl_3$) peak irradiated δ 2.00, 5.43 (d, J = 14.8 Hz, 1 H), peak irradiated δ 2.50, 4.15 (d, J = 10.0 Hz), 5.69 (d, J = 14.8 Hz, 1 H). **18e-*trans*** (204.1 mg (33.5%), white crystals): mp 129–130.0 °C; IR ($CHCl_3$, cm^{-1}) 1722, 1673, 1342, 1174, 997; ^1H NMR ($CDCl_3$) δ 1.55–2.45 (m, 8 H), 2.82 (dd, J = 14.8, 2.4 Hz, 1 H), 2.90 (dd, J = 15.0, 6.8 Hz, 1 H), 3.64 (ddd, J = 10.5, 9.6, 2.4 Hz, 1 H), 5.31 (m, 1 H), 5.52 (ddd, J = 14.8, 12.0, 3.2 Hz, 1 H), 5.81 (ddd, J = 9.6, 7.0, 2.4 Hz, 1 H), 6.78 (s, 1 H), 6.89 (d, J = 4.8 Hz, 1 H), 7.17 (dd, J = 4.8, 2.8 Hz, 1 H), 7.45 (dd, J = 8.0, 7.2 Hz, 2 H), 7.58 (dd, J = 7.6, 6.8 Hz, 1 H), 7.80 (d, J = 8.0 Hz, 2 H); proton decoupled spectrum ^1H NMR ($CDCl_3$) peak irradiated δ 2.28, 3.65 (d, J = 9.6 Hz, 1 H), 5.53 (d, J = 14.8 Hz, 1 H), peak irradiated δ 2.86, 5.81 (d, J = 9.6 Hz, 1 H). Anal. Calcd for $C_{21}H_{22}O_3S$: C, 71.16; H, 6.25; S, 9.04. Found: C, 71.40; H, 6.18; S, 9.41.

MIMI-ARC Synthesis of Nonenolide 18f. To tri-*n*-butyltinlithium (1.80 mmol) in 10 mL of anhydrous THF at −78 °C under argon was added dropwise over 2 min 2-cyclohexenone (165.0 mg, 1.71 mmol) in 2 mL of THF. After 25 min at −78 °C, ethyl vinyl ketone (155.3 mg, 1.90 mmol) in 2 mL of THF was added dropwise during 10 min. After 90 min, 3-furylacetaldehyde (231.7 mg, 2.10 mmol) in 2 mL of THF was added dropwise during 5 min to the −78 °C solution. Stirring was continued for 18 h at −65 °C. Standard quench and workup gave a crude caramel (1.0568 g), which was dissolved in 6 mL of benzene and added over 5 min to a suspension of lead tetraacetate (741.4 mg, 1.67 mmol) in refluxing anhydrous benzene (5 mL). The suspension was allowed to reflux under argon for 2.5 h and then cooled to 23 °C. The reaction was worked up as usual to afford 1.0542 g of a crude light yellow oil. This crude oil was separated via short-path column chromatography (silica gel, 70 g, eluting solvent, Et_2O–hexane (1:9)) to yield *trans*-9-(3-furylmethyl)-8-propionyl-(*E*)-5-nonenolide (**18f-*trans***) (111.3 mg (22.3%), white crystals): mp 75–75.5 °C; IR ($CHCl_3$, cm^{-1}) 3130, 1725, 1705, 1505, 1443, 1438, 1350, 1255, 1145, 1070, 1025, 958, 880, 810; ^1H NMR ($CDCl_3$) δ 1.03 (t, J = 7.2 Hz, 3 H), 1.74 (m, 1 H), 1.93 (m, 2 H), 2.15 (m, 1 H), 2.31 (m, 4 H), 2.56 (m, 4 H), 2.81 (ddd, J = 12.2 Hz, 9.6 Hz, 2.6 Hz, 1 H), 5.28 (m, 1 H), 5.43 (m, 1 H), 5.52 (ddd, J = 9.6, 7.2, 3.2 Hz, 1 H), 6.27 (br s, 1 H), 7.17 (br s, 1 H), 7.33 (dd, J = 1.6 Hz, 1.6 Hz, 1 H); proton decoupled spectra ^1H NMR ($CDCl_3$) peak irradiated δ 1.93, 5.28 (d, J = 14.8 Hz, 1 H), peak irradiated δ 2.56, 5.52 (d, J = 9.6 Hz, 1 H). Anal. Calcd for $C_{17}H_{22}O_4$: C, 70.32; H, 7.64. Found: C, 70.10; H, 7.37. **18f-*cis*** (157.2 mg (31.5%), white crystals): mp 75.2–75.7 °C; IR ($CHCl_3$, cm^{-1}) 3145, 1723, 1709, 1503, 1450, 1438, 1365, 1212, 1146, 1073, 1020, 958, 875, 787; ^1H NMR ($CDCl_3$) δ 1.08 (t, J = 7.2 Hz, 3 H), 1.77 (m, 1 H), 1.92 (m, 2 H), 2.12 (m, 1 H), 2.29 (m, 3 H), 2.44 (m, 1 H), 2.57 (m, 2 H), 2.76 (m, 2 H), 3.00 (br s, 1 H), 5.22 (ddd, J = 7.4, 7.4, 2.4 Hz, 1 H), 5.30 (m, 1 H), 5.57 (m, 1 H), 6.27 (br s, 1 H), 7.22 (br s, 1 H), 7.34 (dd, J = 1.6, 1.6 Hz, 1 H); proton decoupled spectra ^1H NMR ($CDCl_3$) peak irradiated δ 1.92, 5.30 (d, J = 15.6 Hz, 1 H), peak irradiated δ 2.29, 5.57 (d, J = 15.6 Hz, 1 H), peak irradiated δ 2.76, 5.22 (d, J = 7.4 Hz, 1 H). Anal. Calcd for $C_{17}H_{22}O_4$: C, 70.32; H, 7.64. Found: C, 70.60; H, 7.64.

Naphthalene 19. To a cooled solution (−100 °C) of iodolactone **18a-*trans*** (154.0 mg, 0.32 mmol) in 8 mL of THF, was added (475 μL of 1.55 M (0.74 mmol)) *n*-BuLi (hexane) during 3 min under argon to give a yellow solution. After 20 min, 2 mL of saturated NH_4Cl solution was added, and the mixture was warmed to 23 °C and added to 100 mL of Et_2O. The organic solution was washed with 10 mL of brine, dried over anhydrous $MgSO_4$, and evaporated to give 113.8 mg (100%) of white crystals, mp 167–184 °C, having the spectral data described below. An analytical sample was purified via preparative TLC, followed by recrystallization from $CHCl_3$ to give 90.5 mg of colorless needles, mp 207–208 °C: IR ($CHCl_3$, cm^{-1}) 3566, 2905, 2837, 1710, 1430, 1338, 1165, 997; ^1H NMR ($CDCl_3$) δ 1.70–2.25 (m, 7 H), 2.27–2.44 (m, 2 H), 3.13 (ddd, J = 22.0, 17.6, 9.5 Hz, 2 H), 5.18–5.29 (m, 1 H), 5.40–5.49 (m, 1 H), 5.73 (ddd, J = 20.0, 17.1, 9.5 Hz, 1 H), 6.71 (d, J = 8.9 Hz, 1 H), 7.05 (t, J = 7.6 Hz, 1 H), 7.13 (d, J = 8.4 Hz, 1 H), 7.20 (t, J = 7.1 Hz, 1 H), 7.28 (d, J = 8.9 Hz, 1 H), 7.32 (t, J = 7.6 Hz, 2 H), 7.71 (d, J = 7.6 Hz, 2 H). Anal. Calcd for $C_{23}H_{24}O_3$: C, 79.28; H, 6.94. Found: C, 78.99; H, 6.99.

To a cooled mixture (0 °C) of the above-formed tertiary alcohols (77.2 mg, 0.22 mmol) in 20 mL of CH_3NO_2, was added 6.3 mL of 0.07 M $HClO_4$ (CH_3NO_2) under argon. After the mixture was stirred for 20 min at 0 °C, 50 mL of $CHCl_3$ was added, and the mixture was washed with 10 mL of H_2O, dried over anhydrous $MgSO_4$, and evaporated to give 77.1 mg (100%) of a pale yellow caramel **19**: IR ($CHCl_3$, cm^{-1}) 3500–3100, 3040, 2900, 2850, 2800–2200, 1692, 1585, 1488, 1435, 1205, 963, 815; ^1H NMR ($CDCl_3$) δ 1.63–1.70 (m, 2 H), 2.04 (ddd, J = 15.0, 8.0, 2.5 Hz, 2 H), 2.30 (t, J = 7.5 Hz, 2 H), 3.20 ($^1/_2$ AB, J = 9.4 Hz, 1 H), 3.21 ($^1/_2$ AB, J = 9.4 Hz, 1 H), 5.22 (dddt, J = 20.3, 9.4, 9.4, 2.3 Hz, 1 H), 5.49 (dddt, J = 20.3, 9.4, 9.4, 2.3 Hz, 1 H), 7.27–7.51 (m, 9 H), 7.83 (t, J = 8.8 Hz, 2 H); HRMS calcd for $C_{23}H_{22}O_2$ m/e 330.1620, found m/e 330.1625.

To a cooled solution (−100 °C) of iodo lactone **18a-*cis*** (68.5 mg, 0.144 mmol) in 3.5 mL of THF was added (219 μL of 1.55 M (0.34 mmol)) *n*-BuLi (hexane) during 13 min under argon to give a yellow solution. After 20 min, 1 mL of saturated NH_4Cl solution was added, and the mixture was warmed to 23 °C and added to 50 mL of Et_2O. The organic solution was washed with 5 mL of brine, dried over anhydrous $MgSO_4$, and evaporated to give 52.2 mg (100%) of white crystals, mp 154–186 °C, which was purified via short-path column chromatography, followed by recrystallization from Et_2O–$CHCl_3$ to give colorless needles (34.0 mg), mp 201–202 °C: IR ($CHCl_3$, cm^{-1}) 3526, 2942, 2900, 2825, 1710, 1480, 1425, 1323, 1165, 1108, 980, 910; ^1H NMR ($CDCl_3$) δ 1.78–2.08 (m, 4 H), 2.17–2.41 (m, 4 H), 3.13 ($^1/_2$ ABX, J = 17.1, 2.9 Hz, 1 H), 3.31 ($^1/_2$ ABX, J = 17.1, 4.0 Hz, 1 H), 3.55 (s, 1 H), 5.32 (ddd, J = 14.3, 8.6, 3.7 Hz, 1 H), 5.61 (ddd, J = 6.8, 4.0, 2.9 Hz, 1 H), 6.28 (ddd, J = 14.3, 10.6, 4.3 Hz, 1 H), 6.95 (d, J = 9.6 Hz, 1 H), 7.13 (t, J = 8.0 Hz, 2 H), 7.19 (d, J = 8.0 Hz, 1 H), 7.25–7.27 (m, 1 H), 7.34 (t, J = 7.2 Hz, 2 H), 7.41 (br s, 2 H). Anal. Calcd for $C_{23}H_{24}O_3$: C, 79.28; H, 6.94. Found: C, 79.41; H, 6.97.

To a cooled mixture (0 °C) of tertiary alcohols (22.5 mg, 0.06 mmol) in 5 mL of CH_3NO_2 was added 1.8 mL of a 0.07 M $HClO_4$(CH_3NO_2) under argon. After the mixture was stirred for 20 min at 0 °C, it was diluted with 40 mL of $CHCl_3$, washed with 4 mL of H_2O, dried over anhydrous $MgSO_4$, and evaporated to give 25.7 mg (100%) of pale yellow caramel, 7-[2-(1-phenyl)naphthyl]-(*E*)-5-heptenoic acid (**19**), having physical properties identical with those described above.

Naphthalene 20. A. 2,3-Dimethoxyphenyl Lactones 18. To tri-*n*-butyltinlithium (6.48 mmol) in 40 mL of anhydrous THF at −78 °C under argon was added dropwise over 5 min 2-cyclohexenone (594.3 mg, 6.18 mmol) in 8 mL of THF. After 25 min at −78 °C, ethyl vinyl ketone (577.9 mg, 6.66 mmol) in 8 mL of THF was added dropwise and was stirred for an additional 90 min. Finally, a solution (−78 °C) containing (2,3-dimethoxyphenyl)acetaldehyde (1.4200 g, 7.88 mmol) in 8 mL of THF was cannulated during 5 min, and the reaction mixture was allowed to stir for 16 h at −65 °C maintained by a flexicool cryostat. Standard quench and workup gave a crude caramel (4.6900 g), which was dissolved in 25 mL of benzene and added over 5 min to a suspension of lead tetraacetate (2.6945 g, 6.08 mmol) in refluxing benzene (20 mL). The suspension was allowed to reflux under argon for 2.5 h and then cooled to 23 °C. The reaction was worked up as usual to afford 5.1606 g of a pale yellow-orange oil. This crude oil was separated via short path column chromatography (silica gel, 100 g, eluting solvent, Et_2O–hexane, 1:9) to yield *cis*-9-(2,3-dimethoxybenzyl)-8-propionyl-(*E*)-5-nonenolide (**18b-*cis***) (601.5 mg (27.0%) as a colorless oil): IR ($CHCl_3$, cm^{-1}) 1723–1702, 1590, 1482, 1348, 1277, 1087, 1010, 977; ^1H NMR ($CDCl_3$) δ 1.11 (t, J = 7.2 Hz, 3 H), 1.70–2.59 (m, 10 H), 2.79 (d, J = 13.2 Hz, 1 H), 2.81 (d, J = 13.2 Hz, 1 H), 2.98 (br s, 1 H), 3.79 (s, 3 H), 3.84 (s, 3 H), 5.27 (m, 2 H), 5.57 (br s, 1 H), 6.78 (m, 2 H), 6.95 (dd, J = 8.0, 8.0 Hz, 1 H); proton decoupled spectrum ^1H NMR ($CDCl_3$) peak irradiated δ 1.89, 5.28 (d, J = 14.4 Hz, 1 H); HRMS calcd for $C_{21}H_{28}O_5$ m/e 360.1937, found m/e 360.1942. **18b-*trans*** (557.0 mg (25.0%), white crystals): mp 83.5–84 °C; IR ($CHCl_3$, cm^{-1}) 1727–1702, 1591, 1482, 1352, 1285–1250, 1141, 1084, 1002, 950; ^1H NMR ($CDCl_3$) δ 1.02 (t, J = 6.8 Hz, 3 H), 1.67–2.76 (m, 12 H) 2.87 (ddd, J = 7.6, 7.6, 3.2 Hz, 1 H) 3.83 (s, 6 H), 5.25 (m, 1 H), 5.45 (ddd, J = 15.6, 11.2, 3.2 Hz, 1 H), 5.57 (ddd, J = 7.6, 3.6, 1.2 Hz, 1 H), 6.72 (dd, J = 7.6, 1.6 Hz, 1 H), 6.75 (dd, J = 8.0, 1.6 Hz, 1 H), 6.90 (dd, J = 7.6, 7.6 Hz, 1 H); proton decoupled spectrum ^1H NMR ($CDCl_3$) peak irradiated δ 1.88, 5.25 (d, J = 15.6 Hz, 1 H), peak irradiated δ 2.10, 5.45 (d, J = 15.6 Hz,

1 H), peak irradiated δ 2.69, 5.57 (d, J = 7.6 Hz, 1 H). Anal. Calcd for $C_{21}H_{28}O_5$: C, 69.98; H, 7.83. Found: C, 70.01; H, 7.90.

B. Cyclization. Polyphosphoric acid (510.0 mg) was stirred under argon along with 30 mL of anhydrous toluene. To this was added 2,3-dimethoxyphenyl lactone **18b-*cis*** (157.1 mg, 0.43 mmol) in 30 mL of toluene, and the heterogeneous mixture was allowed to stir vigorously under argon at 23 °C for 24 h. The organic layer was decanted from the black tarry compound and diluted with 75 mL of diethyl ether. The organic layer (toluene + Et_2O) was washed with 2 × 25 mL of distilled water and 1 × 25 mL of brine and dried over $MgSO_4$. Solvent removal afforded 102.4 mg of a light yellow oil, which was dissolved in 10 mL of anhydrous diethyl ether and stirred under argon, followed by the addition of 570 μL (0.57 mmol) of lithium aluminum hydride (1 M in Et_2O) dropwise at 23 °C. After 20 min the reaction was quenched at 0 °C with 1 mL of distilled water followed by the addition of 5 mL of 10% H_2SO_4 and 50 mL of diethyl ether. The ether layer was separated, and the aqueous layer was washed with 1 × 25 mL of diethyl ether. The organic layers were combined and washed with 1 × 15 mL of saturated $NaHCO_3$ and 1 × 15 mL of brine, dried over anhydrous $MgSO_4$, and after solvent removal afforded 93.1 mg of a crude light yellow oil. The oil was separated via a 1500 μm Prep TLC plate with eluting solvent 1:4 ethyl acetate–hexane, to yield 7-(1-ethyl-5,6-dimethoxynaphth-2-yl)-(*E*)-5-heptenol (**20**) (60.3 mg (42.1%) as a colorless oil): IR ($CHCl_3$, cm^{-1}) 3540–3240, 1620, 1600, 1390, 1280, 1025, 978, 835; ^1H NMR ($CDCl_3$) δ 1.27 (m, 4 H), 1.44 (m, 2 H), 1.56 (m, 2 H), 2.04 (m, 2 H), 3.07 (q, J = 7.6 Hz, 2 H), 3.49 (d, J = 6.0 Hz, 2 H), 3.62 (m, 2 H), 3.98 (s, 3 H), 3.99 (s, 3 H), 5.44 (ddd, J = 15.2, 6.8, 6.8 Hz, 1 H), 5.62 (ddd, J = 15.2, 7.2, 6.4 Hz, 1 H), 7.29 (d, J = 8.8 Hz, 2 H), 7.80 (d, J = 9.2 Hz, 1 H), 7.95 (d, J = 8.8 Hz, 1 H); proton decoupled spectra ^1H NMR ($CDCl_3$) peak irradiated δ 3.49, 5.62 (d, J = 15.2 Hz, 1 H); HMRS calcd for $C_{21}H_{28}O_3$ m/e 328.2038, found m/e 328.2036.

Polyphosphoric acid (285.0 mg) was stirred under argon along with 30 mL of anhydrous toluene. To this was added 2,3-dimethoxyphenyl lactone **18b-*trans*** (130.0 mg, 0.36 mmol) in 15 mL of anhydrous toluene, and the heterogeneous mixture was allowed to stir vigorously for 26 h, after which time the reaction was worked up as above to yield 98.2 mg of a light yellow oil. This oil was dissolved in 10 mL of diethyl ether and stirred under argon, followed by the addition of 450 μL (0.45 mmol) of lithium aluminum hydride (1 M in Et_2O) dropwise at 23 °C. After 20 min, the reaction was quenched and after usual workup afforded 80.6 mg of a light yellow oil. The oil was separated via a 1000 μm Prep TLC plate with eluting solvent 1:4 ethyl acetate–hexane to yield 7-(1-ethyl-5,6-dimethoxynaphth-2-yl)-(*E*)-5-heptenol (**20**) (74.3 mg, 63.0%), having properties identical with those described above. The overall yield of naphthalene **20** from 2-cyclohexenone therefore is (27.0)(0.421)% + (25.0)(0.63)% = 27.1%.

Naphthalene 21. A. 2,3-Dimethoxyphenyl Lactones 18c. To tri-*n*-butyltinlithium (7.16 mmol) in 45 mL of anhydrous THF at −78 °C under argon was added dropwise over 2 min 2-cyclohexenone (664.0 mg, 6.90 mmol) in 8 mL of THF. After 25 min at −78 °C, phenyl vinyl ketone (966.9 mg, 7.32 mmol) in 8 mL of THF was added dropwise during 10 min. After 90 min (2,3-dimethoxyphenyl)acetaldehyde (1.569 g, 8.70 mmol) in 8 mL of THF was added dropwise during 5 min to the −78 °C solution. Stirring was continued for 20 h at −65 °C. Standard quench and workup gave a crude caramel (5.6277 g), which was dissolved in 20 mL of benzene and added over 5 min to a suspension of lead tetraacetate (2.8745 g, 6.50 mmol) in refluxing benzene (20 mL). The suspension was allowed to reflux under argon for 2.5 h and then cooled to 23 °C. The reaction was worked up as usual to afford 6.0619 g of a crude light yellow oil. This crude oil was separated via short-path column chromatography (silica gel, 100 g, eluting solvent, Et_2O–hexane (1:5) to yield *cis*-9-(2,3-dimethoxybenzyl)-8-benzoyl-(*E*)-5-nonenolide (**18c-*cis***) (541.3 mg (19.2%), as a colorless oil): IR ($CHCl_3$, cm^{-1}) 1712, 1677, 1584, 1482, 1267, 1142, 1076, 1007, 977, 914, 702; ^1H NMR ($CDCl_3$) δ 1.74–2.42 (m, 8 H), 2.62 (ddd, J = 14.8, 8.8, 6.0 Hz, 1 H), 2.83 ($^1/_2$ AB, J = 11.2 Hz), 2.88 ($^1/_2$ AB, J = 11.2 Hz), 3.48 (br s, 3 H), 3.78 (s, 3 H), 5.41 (br s, 2 H), 5.82 (br s, 1 H), 6.63 (dd, J = 6.4, 1.2 Hz, 1 H), 6.74 (dd, J = 7.2, 1.2 Hz, 1 H), 6.86 (dd, J = 8.0, 7.6 Hz, 1 H), 7.48 (dd, J = 7.6, 7.2 Hz, 2 H), 7.57 (dd, J = 7.6, 7.2 Hz, 1 H), 8.08 (br s, 2 H); proton decoupled spectrum ^1H NMR ($CDCl_3$) peak irradiated δ 1.95, 5.39 (d, J = 16.0 Hz, 1 H); HRMS calcd for $C_{25}H_{28}O_5$ m/e 408.1937, found m/e 408.1940. **18c-*trans*** (896.5 mg (31.8%), white crystals): mp 147.5–148 °C; IR ($CHCl_3$, cm^{-1}) 1724, 1673, 1587, 1482, 1347, 1283–1175, 1140, 1084, 1004, 950; ^1H NMR ($CDCl_3$) δ 1.66–2.50 (m, 8 H), 2.80 (m, 3 H), 3.75 (s, 3 H), 3.79 (s, 3 H), 5.28 (m, 1 H), 5.57 (ddd, J = 14.6, 11.8, 2.8 Hz, 1 H), 5.80 (ddd, J = 9.6, 9.6, 3.2 Hz, 1 H), 6.72 (d, J = 8.0 Hz, 1 H), 6.75 (dd, J = 8.0, 1.6 Hz, 1 H), 6.89 (dd, J = 8.0, 8.0 Hz, 1 H), 7.50 (dd, J = 7.6, 7.6 Hz, 2 H), 7.60 (dd, J = 8.0, 6.8 Hz, 1 H), 8.00 (d, J = 8.0 Hz, 2 H); proton decoupled spectrum ^1H NMR ($CDCl_3$) peak irradiated δ 1.92, 5.29 (d, J = 14.6 Hz, 1 H), peak irradiated δ 2.80, 5.80 (d, J = 9.6 Hz, 1 H). Anal. Calcd for $C_{25}H_{28}O_5$: C, 73.51; H, 6.91. Found: C, 73.41; H, 6.88.

B. Cyclization. To **18c-*trans*** (120.0 mg, 0.29 mmol) of in 30 mL of anhydrous nitromethane was added 80 μL of (70–72%) perchloric acid, and the homogeneous solution was allowed to stir for 24 hours at 23 °C under argon. The reaction was quenched with 10 mL of distilled water followed by the addition of 50 mL of diethyl ether. The organic layer was separated and washed with 1 × 15 mL of distilled water and 1 × 15 mL of brine, and dried over anhydrous $MgSO_4$, and solvent removal afforded 125.2 mg of a crude orange-red oil. To this oil was added 10 mL of anhydrous diethyl ether and 370 μL (0.37 mmol) of lithium aluminum hydride (dropwise addition (1 M in Et_2O)). The reaction was allowed to stir under argon at 23 °C for 20 min, after which time it was quenched, and usual workup afforded 108.7 mg of a yellow-orange oil. The oil was separated via a 1500 μm Prep TLC plate with eluting solvent 1:4 ethyl acetate–hexane to yield 7-(2-(1-phenyl-5,6-dimethoxy)-naphthyl)-(*E*)-5-heptenol (**21**), 48.6 mg (44.0%) as a colorless oil: IR ($CHCl_3$, cm^{-1}) 3610, 1607, 1583, 1470, 1375, 1260, 1040, 985, 965, 810, 698; ^1H NMR ($CDCl_3$) δ 1.26 (br s, 1 H), 1.39 (m, 2 H), 1.55 (m, 2 H), 1.98 (m, 2 H), 3.18 (d, J = 6.4 Hz, 2 H), 3.62 (t, J = 6.4 Hz, 2 H), 3.95 (s, 3 H), 4.01 (s, 3 H), 5.28 (ddd, J = 15.2, 6.4, 6.4 Hz, 1 H), 5.47 (ddd, J = 15.2, 6.4, 6.4 Hz, 1 H), 7.11 (s, 2 H), 7.24 (s, 1 H), 7.45 (m, 5 H), 8.11 (d, J = 8.4 Hz, 1 H); proton decoupled spectra ^1H NMR ($CDCl_3$) peak irradiated δ 3.18, 5.47 (d, J = 15.2 Hz, 1 H); HRMS calcd for $C_{25}H_{28}O_3$ m/e 376.2038, found m/e 376.2043.

Tetracycle 22. Polyphosphoric acid (1.08 g) was stirred under argon along with 30 mL of anhydrous toluene. To this was added 2,3-dimethoxyphenyl lactone **18c-*trans*** (131.0 mg, 0.32 mmol) in 20 mL of toluene, and the heterogeneous mixture was allowed to stir vigorously under argon at 23 °C for 24 h. Usual workup afforded 92.1 mg of a light yellow oil, which was dissolved in 10 mL of anhydrous diethyl ether and stirred under argon, followed by the addition of 400 μL (0.40 mmol) of lithium aluminum hydride (1 M in Et_2O) dropwise at 23 °C. After 20 min the reaction was quenched, and workup afforded 91.5 mg of a light yellow oil. The oil was separated via a 1500 μm Prep TLC plate with eluting solvent 1:4 ethyl acetate–hexane to yield tetracycle **22**, 55.7 mg (46.1%) as a colorless oil: IR ($CHCl_3$, cm^{-1}) 3620, 1620, 1597, 1485, 1385, 1275, 1055, 998, 820, 710; ^1H NMR ($CDCl_3$) δ 1.21–1.52 (m, 9 H), 2.79 (m, 2 H), 3.09 (m, 1 H), 3.57 (m, 2 H), 4.02 (s, 3 H), 4.03 (s, 3 H), 7.28–7.39 (m, 5 H), 7.90 (d, J = 7.6 Hz, 1 H), 8.05 (d, J = 8.4 Hz, 1 H), 8.29 (d, J = 9.6 Hz, 1 H); proton decoupled spectra ^1H NMR ($CDCl_3$) peak irradiated δ 2.79, 3.09 (dd, J = 7.2, 4.2 Hz, 1 H); HRMS calcd for $C_{25}H_{28}O_3$ m/e 376.2038, found m/e 376.2043.

Benzothiophene 23. A. Thiophene Lactones 18d. To tri-*n*-butyltinlithium (3.80 mmol) in 21 mL of anhydrous THF at −78 °C under argon was added dropwise over 5 min 2-cyclohexenone (346.1 mg, 3.60 mmol) in 4 mL of THF. After 25 min, ethyl vinyl ketone (348.2 mg, 4.01 mmol) in 4 mL of THF was added dropwise and was stirred for an additional 90 min. Finally, a solution (−78 °C) of 3-thienylacetaldehyde (580.0 mg, 4.60 mmol) in 4 mL of THF was cannulated (5 min), and the reaction mixture turned to pale yellow. The solution was allowed to stir for 19 h at −65 °C maintained by a flexicool cryostat. Standard quench and workup gave a crude yellow caramel (2.2944 g). To a suspension of lead tetraacetate (778.1 mg, 1.76 mmol) in dry refluxing benzene (6.6 mL) was added 1.1291 g of the pale yellow caramel in 8.0 mL of benzene. The suspension was allowed to reflux under argon for 2 h and then cooled to 23 °C. The reaction was worked up as usual to afford 1.1710 g of a pale yellow-orange oil. This crude oil was separated via short-path column chromatography (silica gel, 70 g, eluting solvent, Et_2O–hexane, 1:9) to yield *trans*-9-(2,3-dimethoxybenzyl)-8-propionyl-(*E*)-5-nonenolide (**18d-*trans***) (113.3 mg (20.9%), white crystals): mp 99.0–99.5 °C; IR ($CHCl_3$, cm^{-1}) 1735–1710, 1365–1345, 1145, 995–980; ^1H NMR ($CDCl_3$) δ 1.02 (t, J = 7.6 Hz, 3 H), 1.56–2.55 (m, 10 H), 2.80 (m, 3 H), 5.29 (m, 1 H), 5.43 (ddd, J = 15.2, 11.4, 2.4 Hz, 1 H), 5.58 (ddd, J = 6.0, 3.9, 2.8 Hz, 1 H), 6.93 (m, 2 H), 7.22 (dd, J = 1.6, 1.6 Hz, 1 H); proton decoupled spectrum ^1H NMR ($CDCl_3$) peak irradiated δ 2.76, 5.58 (d, J = 6.0 Hz, 1 H), peak irradiated δ 2.27, 5.44 (d, J = 15.2 Hz, 1 H), peak irradiated δ 1.94, 5.28 (d, J = 15.2 Hz, 1 H). Anal. Calcd for $C_{17}H_{22}O_3S$: C, 66.64; H, 7.24; S, 10.50. Found: C, 66.84; H, 7.48; S, 10.90. **18d-*cis*** (170.0 mg (31.3%), white crystals): mp 79.2–80.0 °C; IR ($CHCl_3$, cm^{-1}) 1723–1702, 1422, 1341, 1147, 977, 842; ^1H NMR ($CDCl_3$) δ 1.09 (t, J = 7.2 Hz, 3 H), 1.73–2.62 (m, 11 H), 2.96 (d, J = 7.6 Hz, 2 H), 5.30 (m, 2 H), 5.57 (m, 1 H), 6.93 (d, J = 5.2 Hz, 1 H), 6.98 (d, J = 2.0 Hz, 1 H), 7.24 (dd, J = 3.2 Hz, 3.2 Hz, 1 H); proton decoupled spectra ^1H NMR ($CDCl_3$) peak irradiated δ 1.92, 5.30 (d, J = 15.2 Hz, 1 H). Anal. Calcd for $C_{17}H_{22}O_3S$: C, 66.64; H, 7.24; S, 10.50. Found: C, 66.76; H, 7.39; S, 10.52.

B. Cyclization. Polyphosphoric acid (347.4 mg) was stirred under argon along with 15 mL of anhydrous toluene. To this was added thienyl lactone **18d-*trans*** (62.6 mg, 0.20 mmol) in 10 mL of toluene, and the

heterogeneous mixture was allowed to stir vigorously under argon at 23 °C for 19 h. Usual workup afforded 52.7 mg of a light yellow oil, which was dissolved in 10 mL of diethyl ether and stirred under argon, followed by the addition of 250 μL (0.25 mmol) of lithium aluminum hydride (1 M in Et_2O) dropwise at 23 °C. After 20 min the reaction was quenched, and workup afforded 44.2 mg of a crude light yellow oil. The oil was separated via a 500 μm Prep TLC plate with eluting solvent 1:4 ethyl acetate–hexane, to yield 6-(7-hydroxy-(*E*)-2-heptenyl)-7-ethylbenzothiophene (**23**), 40.0 mg (71.4%), as a colorless oil: IR ($CHCl_3$, cm^{-1}) 3600–3252, 1588, 1378, 973, 825, 710, 642; ^{1}NMR ($CDCl_3$) δ 1.26 (t, J = 7.2 Hz, 1 H), 1.30 (t, J = 8.0 Hz, 3 H), 1.43 (m, 2 H), 1.59 (m, 2 H), 2.05 (m, 2 H), 2.94 (q, J = 7.6 Hz, 2 H), 3.47 (d, J = 5.6 Hz, 2 H), 3.63 (m, 2 H), 5.45 (ddd, J = 15.2, 6.8, 6.8 Hz, 1 H), 5.62 (ddd, J = 15.2, 7.2, 6.8 Hz, 1 H), 7.19 (d, J = 8.0 Hz, 1 H), 7.30 (d, J = 5.2 Hz, 1 H), 7.36 (d, J = 5.6 Hz, 1 H), 7.61 (d, J = 7.6 Hz, 1 H); proton decoupled spectra ^{1}H NMR ($CDCl_3$) peak irradiated δ 2.05, 5.45 (d, J = 15.2 Hz, 1 H), peak irradiated δ 3.47, 5.62 (d, J = 15.2 Hz, 1 H); HRMS calcd for $C_{17}H_{22}OS$ m/e 274.1391, found m/e 274.1393.

Polyphosphoric acid (729.8 mg) was stirred under argon along with 20 mL of anhydrous toluene. To this was added thienyl lactone **18d**-*cis* (109.5 mg, 0.35 mmol) in 10 mL of anhydrous toluene, and the heterogeneous mixture was allowed to stir vigorously for 4.5 h, after which time the reaction was worked up to yield 82.3 mg of a light yellow oil. This oil was dissolved in 15 mL of diethyl ether and stirred under argon, followed by the addition of 450 μL (0.45 mmol) of lithium aluminum hydride (1 M in Et_2O) dropwise at 23 °C. After 20 min the reaction was quenched, and usual workup afforded 77.8 mg of a yellow oil. The oil was separated via a 1000 μm Prep TLC plate with eluting solvent 1:4 ethyl acetate–hexane to yield benzothiophene **23** (73.7 mg, 75.2%), having properties identical with those described above. The overall yield of benzothiophene **23** from 2-cyclohexenone therefore is (20.9)(0.714)% + (31.3)(0.752)% = 38.5%.

Benzofuran 24. Cyclization of Furan Lactone 18f. Polyphosphoric acid (26.0 mg) was stirred under argon along with 5 mL of anhydrous toluene. To this was added furyl lactone **18f**-*cis* (20.6 mg, 0.07 mmol) in 5 mL of anhydrous toluene, and the heterogeneous mixture was allowed to stir vigorously under argon at 2 °C for 23 h, after which time the reaction was worked up as above to yield 16.9 mg of a light yellow oil. This oil was dissolved in 5 mL of diethyl ether and stirred under argon, followed by the addition of 150 μL (0.15 mmol) of lithium aluminum hydride (1 M in Et_2O) dropwise at 23 °C. After 20 min the reaction was quenched, and usual workup afforded 16.1 mg of a yellow oil. The oil was separated via a 250 μm Prep TLC plate with eluting solvent 1:4 ethyl acetate–hexane, to yield 6-(7-hydroxy-(*E*)-2-heptenyl)-5-ethylbenzofuran (**24**) (12.0 mg, 65.6%) as a colorless oil: IR ($CHCl_3$, cm^{-1}) 3610, 1535, 1418, 1315, 1265, 1130, 1033, 972, 870, 818; ^{1}H NMR ($CDCl_3$) δ 1.26 (t, J = 7.6 Hz, 4 H), 1.43 (m, 2 H), 1.57 (m, 2 H), 2.04 (m, 2 H), 2.93 (q, J = 7.2 Hz, 2 H), 3.45 (d, J = 6.0 Hz, 2 H), 3.63 (t, J = 6.4 Hz, 2 H), 5.43 (ddd, J = 15.2, 6.8, 6.4 Hz, 1 H), 5.60 (m, 1 H), 6.71 (d, J = 2.0 Hz, 1 H), 7.04 (d, J = 8.0 Hz, 1 H), 7.35 (d, J = 8.0 Hz, 1 H), 7.58 (d, J = 2.4 Hz, 1 H); proton decoupled spectra ^{1}H NMR ($CDCl_3$) peak irradiated δ 2.04, 5.43 (d, J = 15.2 Hz, 1 H), peak irradiated δ 3.45, 5.60 (d, J = 15.2 Hz, 1 H); HRMS calcd for $C_{17}H_{22}O_2$ m/e 258.1620, found m/e 258.1625.

Methyl 7-(2-Ethyl-3-quinolyl)-(*E*)-5-heptenoate (25). To tri-*n*-butyltinlithium (1.80 mmol) in 10 mL of anhydrous THF at −78 °C under argon was added dropwise over 2 min 2-cyclohexenone (161.0 mg, 1.67 mmol) in 2 mL of anhydrous THF. After 25 min at −78 °C, ethyl vinyl ketone (159.8 mg, 1.90 mmol) in 2 mL of THF was added dropwise over 10 min. After 90 min, a solution (23 °C) of phthalimide-protected *o*-aminobenzaldehyde (517.7 mg, 2.06 mmol) in 3 mL of THF and 0.5 mL of DMF was cannulated during 5 min, and the reaction mixture was allowed to stir under argon at −65 °C for 16 h. Standard quench and workup gave a crude yellow caramel (1.2519 g), which was dissolved in 5 mL of anhydrous benzene and added over 5 min to a suspension of lead tetraacetate (668.0 mg, 1.50 mmol) in dry refluxing benzene (4 mL). The suspension was allowed to reflux under argon for 3.5 h and then cooled to 23 °C. The reaction was worked up as usual to afford 1.2207 g of a light yellow oil.

The 1.2207 g of the yellow oil was then dissolved in 6 mL of benzene and stirred at 23 °C. Next 5 mL of 40% aqueous methylamine was added dropwise, and the mixture was vigorously stirred for 72 h. After removal of water under reduced pressure, 10 mL of benzene was added, and any remaining water was removed azeotopically, producing a mixture of light yellow crystals and a light brown oil, which was dissolved in 20 mL of chloroform and cooled to 0 °C. To the 0 °C chloroform solution was added 16.3 mmol of diazomethane in 250 mL of diethyl ether. After 30 min all 250 mL of the diazomethane solution was added, and the reaction mixture was allowed to stir at 0 °C for an additional 20 min, after which time the reaction was quenched with glacial acetic acid and dried over anhydrous $MgSO_4$, and solvent removal afforded 1.6525 g of a yellow-brown solution. This crude oil was separated via short-path column chromatography (silica gel, 70 g, eluting solvent, Et_2O–hexane, 1:9) to yield methyl 7-(2-ethyl-3-quinolyl)-(*E*)-5-heptenoate (**25**) (134.8 mg, (27.1%), colorless oil): IR (neat, cm^{-1}) 1740–1720, 1612, 1250–1140, 965; ^{1}H NMR ($CDCl_3$) δ 1.37 (t, J = 7.6 Hz, 3 H), 1.73 (m, 2 H), 2.11 (m, 2 H), 2.32 (t, J = 8.0 Hz, 2 H), 2.99 (q, J = 7.2 Hz, 2 H), 3.51 (d, J = 6.4 Hz, 2 H), 3.66 (s, 3 H), 5.47 (ddd, J = 15.6, 7.2, 6.4 Hz, 1 H), 5.67 (ddd, J = 15.6, 7.2, 6.8 Hz, 1 H), 7.44 (dd, J = 7.2, 7.2 Hz, 1 H), 7.62 (dd, J = 6.8, 6.8 Hz, 1 H), 7.73 (d, J = 8.0 Hz, 1 H), 7.84 (s, 1 H), 8.02 (d, J = 8.4 Hz, 1 H); proton decoupled spectra ^{1}H NMR ($CDCl_3$) peak irradiated δ 2.11, 5.47 (d, J = 15.6 Hz, 1 H), peak irradiated δ 3.51, 5.67 (d, J = 15.6 Hz, 1 H); HRMS calcd for $C_{19}H_{23}O_2N$ m/e 297.1729, found m/e 297.1734.

Acknowledgment. Acknowledgement is made to the donors of the Petroleum Research Fund, administered by the American Chemical Society, and to the NSF (Grant CHE-86-07974) for support of this research.

Registry No. 1, 3393-45-1; **2**, 114633-63-5; **3a**, 114633-65-7; **3b**, 114714-89-5; **4**, 114633-66-8; **4** (MIMI–MIRC adduct), 114633-64-6; **5**, 114633-67-9; **6**, 114633-68-0; **7**, 114633-69-1; (*E*)-**8**, 114633-70-4; (*Z*)-**8**, 114633-71-5; **9**, 114633-72-6; *cis*-**10**, 114633-73-7; *trans*-**10**, 114714-90-8; **11**, 114633-74-8; *cis*-**12**, 114633-75-9; *trans*-**12**, 114714-91-9; **13**, 114633-76-0; *cis*-**14**, 114633-77-1; *trans*-**14**, 114714-92-0; **14′**, 114715-00-3; **15**, 114633-78-2; *cis*-**16**, 114633-79-3; *trans*-**16**, 114714-93-1; *cis*-**17**, 114633-80-6; *trans*-**17**, 114714-94-2; **17** (MIMI–ARC adduct), 114633-94-2; *trans*-**18a**, 114633-81-7; *cis*-**18a**, 114714-95-3; **18a** (MIMI–ARC adduct), 114633-96-4; *trans*-**18b**, 114633-82-8; *cis*-**18b**, 114714-96-4; *trans*-**18c**, 114633-83-9; *cis*-**18c**, 114714-97-5; *trans*-**18d**, 114633-84-0; *cis*-**18d**, 114714-98-6; *trans*-**18e**, 114716-17-5; *cis*-**18e**, 114633-85-1; **18e** (MIMI–ARC adduct), 114633-97-5; *trans*-**18f**, 114633-86-2; *cis*-**18f**, 114714-99-7; **18f** (MIMI–ARC adduct), 114633-98-6; **19**, 114633-87-3; **20**, 114633-88-4; **21**, 114633-89-5; **22**, 114633-90-8; **23**, 114633-91-9; **24**, 114633-92-0; **25**, 114633-93-1; $LiSnBu_3$, 4226-01-1; H_2C=CHCOOMe, 96-33-3; H_2C=CHCOEt, 1629-58-9; CH_2O, 50-00-0; CH_3CHO, 75-07-0; 3-(MeO)C_6H_4CHO, 591-31-1; H_2C=CHCOPh, 768-03-6; *o*-$OHCCH_2C_6H_4I$, 109347-41-3; 2,3-$(MeO)_2C_6H_3CH_2CHO$, 5707-56-2; *o*-$OHCC_6H_4NPhthl$, 114634-02-5; 2-cyclohexenone, 930-68-7; 2-methyl-2-cyclohexenone, 1121-18-2; 2-cyclopentenone, 930-30-3; cycloheptenone, 1121-66-0; cyclopropanecarboxaldehyde, 1489-69-6; 3-thienylacetaldehyde, 114633-95-3; 3-furylacetaldehyde, 99948-48-8; 9-hydroxy-9-phenyl-3,4,5,8,8a,9,14,14a-octahydro-2*H*-naphth[2,3-*b*]oxecin-2-one (isomer 1), 114633-99-7; 9-hydroxy-9-phenyl-3,4,5,8,8a,9,14,14a-octahydro-2*H*-naphth[2,3-*b*]oxecin-2-one (isomer 2), 114715-01-4; 2-(*o*-phthalimidophenyl)-3-propionyl-5-tributylstannyl-8a-hydroxy-2*H*-octahydrobenzopyran, 114634-00-3; 8-propionyl-9-(*o*-phthalimidophenyl)-5-decenolide, 114634-01-4.