Investigations into a Biomimetic Approach toward CP-225,917 and CP-263,114

Gary A. Sulikowski,* Fabio Agnelli, and R. Michael Corbett

Department of Chemistry, Texas A&M University, College Station, Texas 77842

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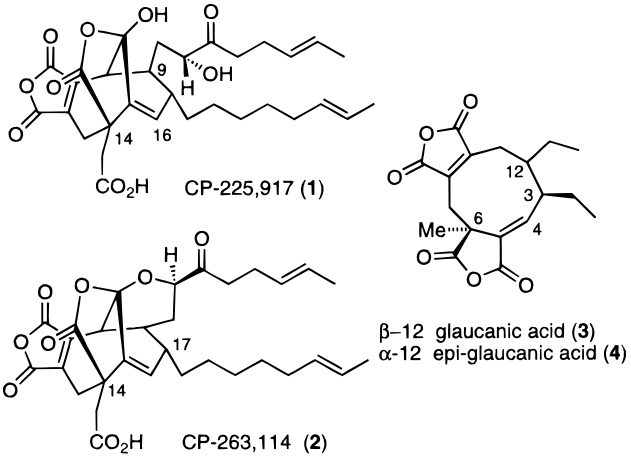
A biosynthesis of the structurally complex nonadride CP-225,917 (**1**) is outlined. A key step in this proposal is the dimerization of a C_{16} anhydride derived from the condensation of lauric acid and oxaloacetic acid. An important element of this step is a templating effect imposed by two thioester linkages, reminiscent of a polyketide or fatty acid synthase pathway. On the basis of this principle, the dimerization of two C_{11} anhydrides, templated by a 1,*n*-diol tether, leading to the core structure of CP-225,917 and CP-263,114 was investigated.

Introduction

Several years ago, workers at Pfizer reported the isolation and structure elucidation of two secondary metabolites produced by an unidentified fungus.[1] These natural products were found to inhibit the enzymes *ras*-farnesyl transferase and squalene synthase, suggesting that they may serve as lead structures for the development of anticancer and cholesterol-lowering agents. The compounds were assigned the company registry numbers CP-225,917 (**1**) and CP-263,114 (**2**) and classified as belonging to the nonadride group of natural products.[2] Among this small group of natural products, CP-225,-917 (**1**) and CP-263,114 (**2**) are the most unique and structurally complex members. Interestingly, very minor structural differences aside from the length of the alkyl side chains exist between these recently isolated metabolites and the prototypical nonadride glaucanic acid (**3**).[3] The major difference is the geometry of the carbon−carbon double bonds embedded within the common cyclononane ring substructure [C(15)−C(16) and C(4)−C(5) in the CP molecules and glaucanic acid, respectively]. This minor structural alteration leads to a major difference in perceived structural complexity. The novel structures and combined biological activities of **1** and **2** have attracted the attention of many synthetic groups[4] including Nicolaou and co-workers,[5] who reported the first total synthesis of these compounds earlier this year. Our group has been pursuing a biomimetic approach to CP-225,917 (**1**) and ultimately to CP-263,114 (**2**), as **1** can be converted into **2** upon treatment with acid. We outline in this paper our biosynthetic proposal and early experiments designed to test our hypothesis.

In contemplating a biosynthetic pathway leading to CP-225,917 (**1**), it was particularly instructive to examine



the biosynthesis of glaucanic acid (**3**) as outlined by Barton and Sutherland.[2] A key intermediate in their proposal was unsaturated anhydride **5** derived from the condensation of hexanoic acid and oxaloacetic acid. The head-to-head dimerization of this C_9 unit (**5**) was proposed to give glaucanic acid (**3**). The dimerization itself was proposed to occur by addition of conjugate base **5a** to **5** leading to a formal $6\pi + 4\pi$ cycloaddition affording *cis*,*cis*-cyclononadienolate **6**. Sutherland and co-workers demonstrated, both in vitro and in vivo, that unsaturated anhydride **5** indeed undergoes dimerization, leading to

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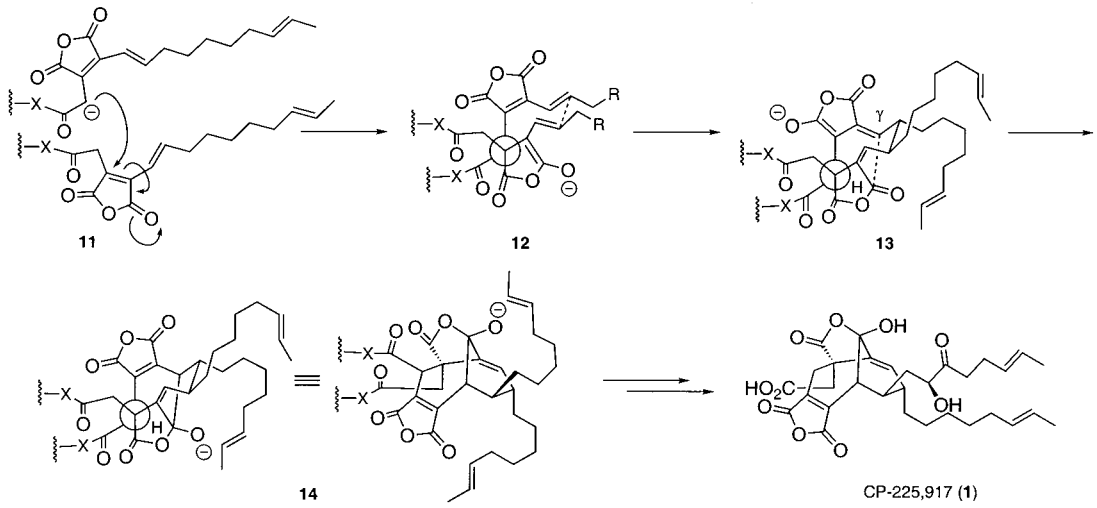
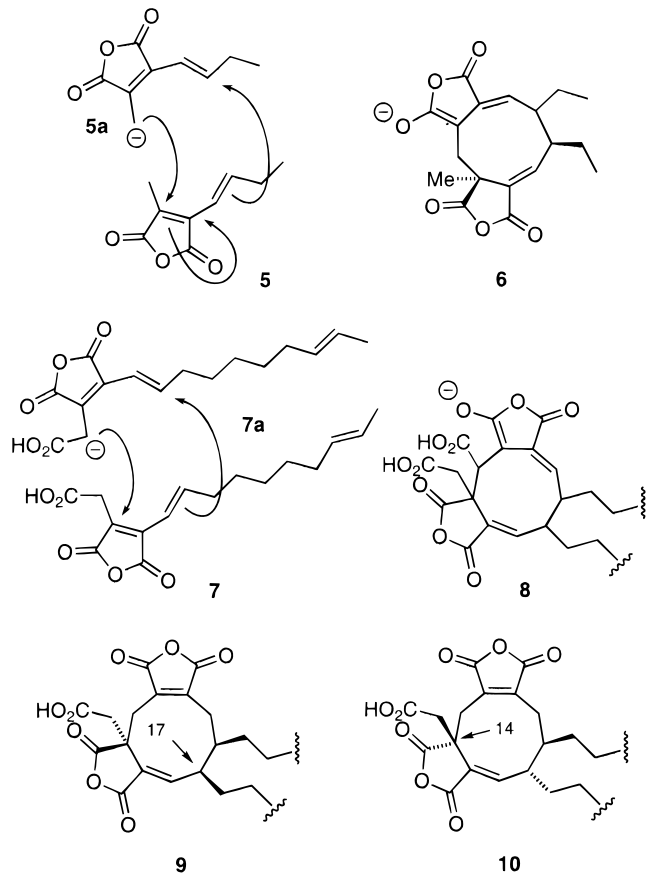


Figure 1. Proposed biosyntheses of CP-225,917 (**1**).

3.[6] In particular, the dimerization of **5** was conducted in DMF with triethylamine as base to give 12-*epi*-glaucanic acid (**4**) in 4% yield. As part of their interest in developing a biomimetic approach to CP-225,917 (**1**), Baldwin and co-workers have recently reinvestigated this reaction and confirmed the assigned structure of **3** as well as the isolation of two new dimerization products.[7] These results support a stepwise rather than concerted reaction pathway (i.e., $6\pi + 4\pi$ cycloaddition). Sutherland and co-workers also studied the biosynthesis of glaucanic acid in *Penicillium purpurogenum* using labeled intermediates. The in vivo results supported the dimerization of **5** to give glaucanic acid (**3**). The observation that 12-*epi*-glaucanic acid (**4**) is produced using triethylamine in DMF while whole cells gave glaucanic acid (**3**) suggests an exo and endo dimerization of **5** in vitro and in vivo, respectively.

Results and Discussion

In accord with Barton and Sutherland's proposed biogenesis of glaucanic acid, Kaneko and co-workers suggested CP-225,917 (**1**) to be derived from the condensation of oxaloacetic acid and lauric acid.[1b] However, ambiguity remained regarding the sequence of events leading to the complex core structure of CP-225,917 (**1**) from the simple condensation product of these two units. Continuing along the groundwork set by Barton and Sutherland, unsaturated anhydride **7** appeared to be a likely intermediate. Further analogy can be drawn by the dimerization of **7** in either an endo or exo orientation to give intermediate *cis*,*cis*-cyclononadienolate **8**. Protonation and decarboxylation of **8** would then deliver **9** and **10** from endo and exo addition modes, respectively. The flaw in this proposal is the cycloaddition products (**9** and **10**) possess the incorrect C(15)−C(16) double bond geometry en route to CP-225,917 (**1**). However, even assuming the possibility of a subsequent isomerization of the olefin geometry, neither intermediate is capable of delivering the correct relative stereochemistry between C(9), C(14), and C(17) (cf. **1** versus **9** and **10**). This led us to consider an alternative dimerization process as oultined in Figure 1.



The dimerization of **7** leading to the core structures of the CP molecules is a carefully orchestrated process in that as well as establishing three new stereocenters [C(9), C(14), and C(17)] the topology of the process also dictates the geometry of the two double bonds within the newly formed nine-membered cyclononadienolate (cf. **13**). In analogy to polyketide and fatty acid biosyntheses, we speculate **7** is covalently attached, perhaps through thioester bonds, to an enzyme-active site during the

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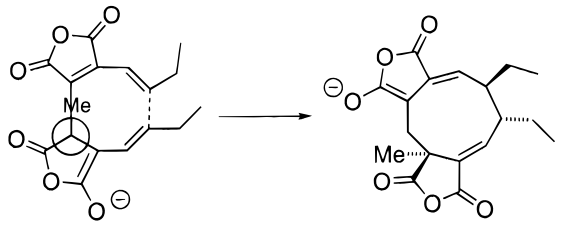
dimerization process (cf. **11**).[8] Significantly, this covalent attachment serves to govern the topology of the dimerization process leading to the formation of *trans,trans*-cyclononadienolate **13**. We envision the dimerization to occur by a stepwise mechanism starting with a Michael addition between two anhydride units (**11** to **12**) in an exo topology resulting in the formation of the C(13)−C(14) carbon−carbon bond to give dienolate **12**. Intermediate **12** undergoes a second intramolecular Michael addition; this key step determines the relative stereochemistry of C(9), C(14), and C(17) stereocenters as well as the endocyclic C(15)−C(16) olefin geometry. We hypothesize conformational restrictions imposed by the thioester linkages enforce a staggered conformation about the newly formed C(13)−C(14) bond. In this conformation, the second Michael addition can occur only by addition of an *s-cis*-dienolate to an *s-trans* Michael acceptor to give *trans,trans*-cyclononadienolate **13**, which further incorporates the C(9), C(14), and C(17) relative stereochemistry assigned to the CP molecules. *In contrast, the cyclization of* ***5*** *plus* ***5a*** *to cis,cis-cyclononadienolate* ***6*** *en route to glaucanic acid occurs by way of an eclipsed conformation (cf.* ***5*** *+* ***5a*** *→* ***6****).* The next step in the biosynthesis of CP-225,917 (**1**) is transannular Dieckmann condensation between the γ carbon of the extended dienolate and the neighboring anhydride carbonyl, resulting in the production of **14** and completion of the assembly of the core structure. Final steps of the proposed biosynthesis include hydrolysis, decarboxylation, and oxidation leading to CP-225,917 (**1**).

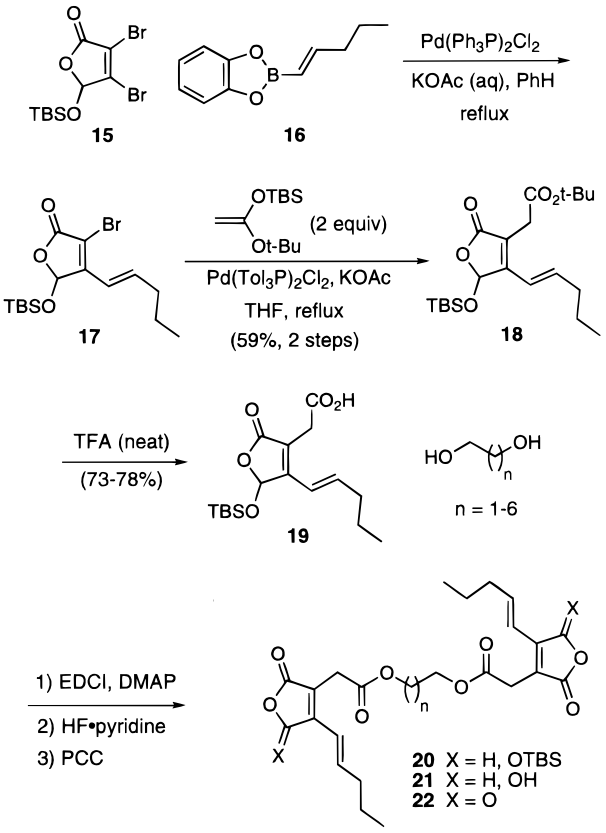


5 + 5a **6**

The biosynthetic pathway outlined in Figure 1 suggested the possibility of effecting a biomimetic synthesis of CP-225,917 (**1**). The identification of an appropriate template to guide the dimerization process proved critical to the synthetic design since several dimerization pathways are possible. As a first approximation, we examined six templates, in the form of an array of 1,*n*-diols, differing only in carbon chain length (**22**) (Scheme 1). Furthermore, provided an appropriate analytical method could be developed, we planned to simultaneously evaluate the dimerization of all six compounds as a single mixture under high dilution conditions.

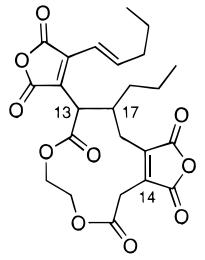
The preparation of intermediate carboxylic acid **19** started with Suzuki cross-coupling of vinyl boronate **16** and mucobromic acid derivative **15** to give dienoate **17**.[9] A second cross-coupling reaction, this time with the silylketene acetal derived from *tert*-butyl acetate, gave **18**, which on acid hydrolysis afforded carboxylic acid **19**.[10] EDCI condensation of **19** with an equimolar mixture of

Scheme 1



1,*n*-diols afforded a collection of bis-esters (**20**) with each diol linker approximately equally represented, as later determined by integration of an HPLC trace of bisanhydrides **22**. Desilylation and oxidation of **20** provided a mixture of six bis-anhydrides (**22**), which were characterized by NMR, low-resolution mass spectrometry, and HPLC analysis. We examined the cyclization of these compounds under several sets of reaction conditions. Below we describe the results of two of these experiments.

A solution of bis-anhydrides **22** and a catalytic amount of DBU in anhydrous acetonitrile was heated at 70 °C for 2 days and monitored by HPLC (Figure 2). The six starting bis-anhydrides (**22**) were easily distinguished by



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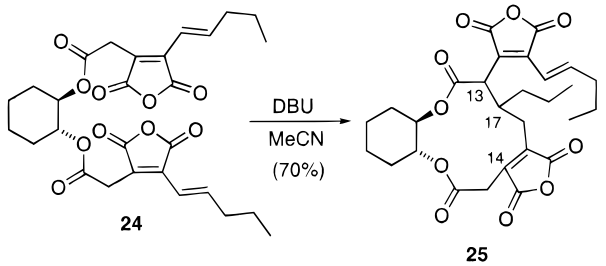

24 **25**

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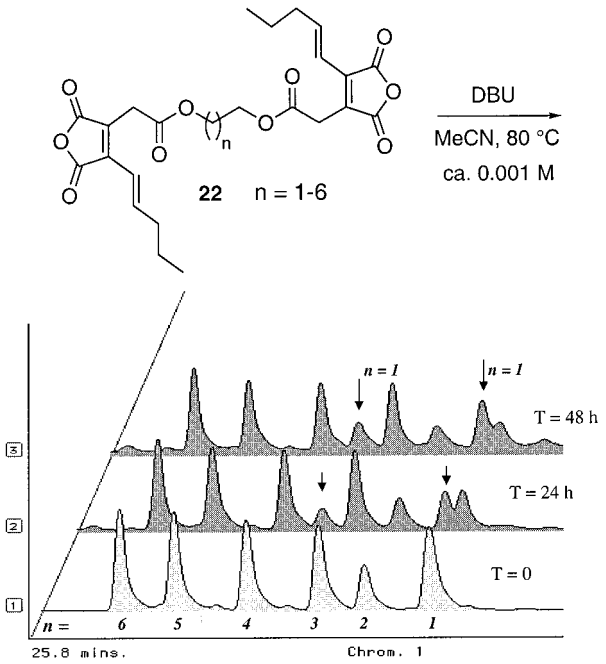
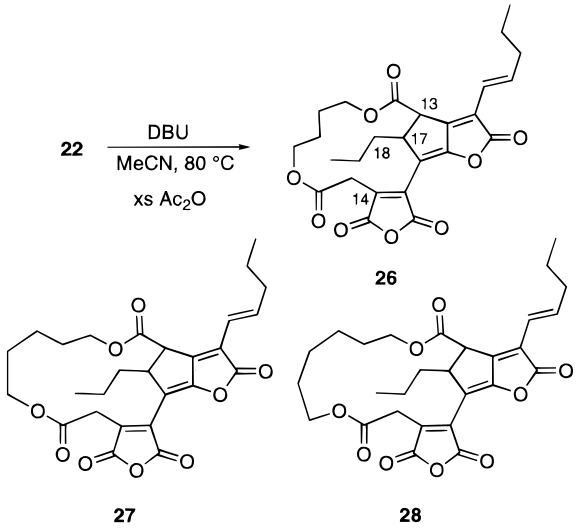


Figure 2. HPLC chromatogram of DBU-catalyzed reaction of bis-anhydrides **22**.

HPLC and characterized by low-resolution mass spectrometry (Figure 2). As the reaction progressed, two new products formed and were determined by low-resolution mass spectrometry to correspond to products bearing a two-carbon tether. These products were isolated by preparative HPLC, characterized by NMR analysis, and assigned the structure **23**, differing in relative configuration at the two newly formed stereocenters [C(13) and C(17)]. *For characterization purposes, the cyclization was repeated this time using* ***22*** *(*$n = 2$*) as a single substrate to give* ***23a*** *and* ***23b*** *in 4 and 20% yield, respectively (relative stereochemistry not assigned).* In a separate experiment, cyclization of C_2-symmetric bis-anhydride **24** (also a 1,2-diol) gave a single stereoisomer (unassigned) (**25**) in 70% yield. Thus, under the reaction conditions employed we observed exclusive carbon−carbon bond formation between C(13) and C(17) rather than the desired C(13)−C(14) positions.

Assuming the above experiment provided thermodynamic products, we decided to evaluate the cyclization of the mixture of bis-anhydrides (**22**) in the presence of a trapping agent in the hope of intercepting a kinetically produced intermediate. To this end, a solution of **22**, DBU, and acetonitrile was again heated at 70 °C in the presence of an excess of acetic anhydride. In addition to the production of the previously observed compounds ($n = 2$; **23a** and **23b**), three new products were isolated. These new products, isolated by preparative HPLC and characterized by ^{1}H NMR and low-resolution mass spectrometry, showed strong yellow fluorescence and corresponded to dehydration products of $n = 3-5$ according to mass spectral analysis. To fully characterize these cyclization products, reactions were repeated using single-component substrates ($n = 3-5$, **22**); the resulting products were assigned the structures **26** (25% yield), **27** (26% yield), and **28** (29% yield) and proved to be spectroscopically identical to those isolated in the combinatorial format. Compound **26** was subjected to extensive NMR analysis including various decoupling experiments and ^{1}H,^{1}H−COSY analysis. The C(13) and C(17) protons overlap in the ^{1}H NMR spectrum of **26**, which complicates spectral analysis. However, C(18) is strongly coupled to C(17), supporting the assigned connectivity, although we were unable to assign the C(17) and C(13) relative stereochemistry of **26**−**28**. The ^{1}H and ^{13}C NMR spectra as well as UV−vis spectra of compounds **27** and **28** closely resemble **26**, and the structural assignments for these compounds were made on the basis of analogy with **26**.



In our studies, all products identified are produced by initial addition of the C13 enolate to the C17 Michael acceptor. No products corresponding to initial (desired) formation of the C13−C14 carbon−carbon bond were detected. In the case of the two-carbon tether only **23** was isolated. However, we found expanding to larger tethers ($n = 3-5$) allowed a second cyclization (in the presence of acetic anhydride acting as a dehydrating agent) to occur between carbons C16 and C30. This led to the identification of the yellow fluorescent compounds **26**−**28** (Chart 1).

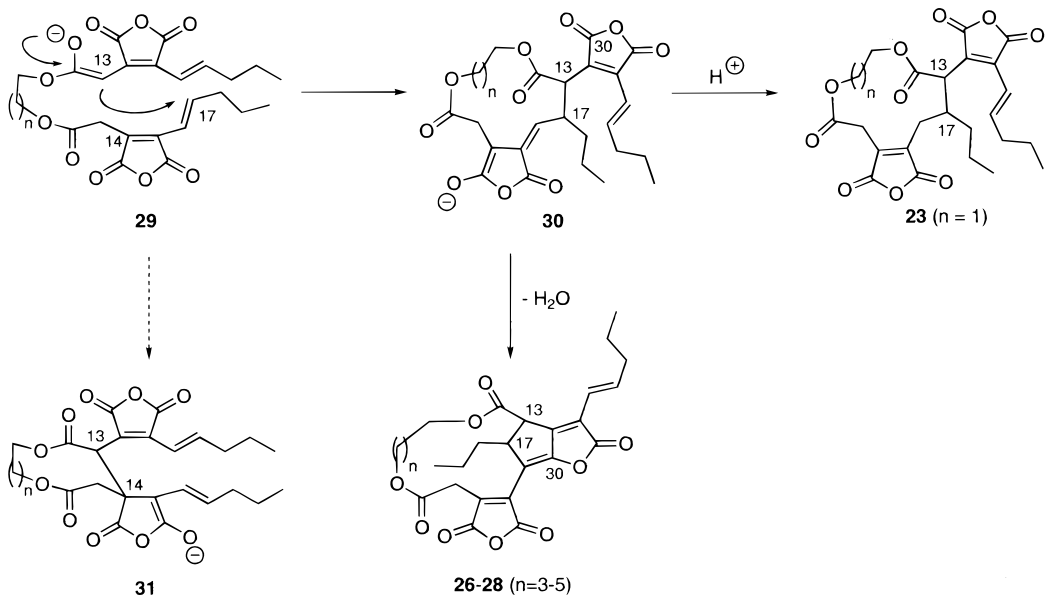
Conclusion

In conclusion, we have proposed a biosynthesis of CP-225,917 (**1**) and allude to the importance of pre-organization of the monomeric units by way of a covalent tether. Our initial studies showed cyclization to only occur by way of C(13) to C(17) Michael addition rather than the desired C(13) to C(14) addition. We are currently examining new substrates in order to effect the desired cyclization and lend experimental credence to our proposed biosynthesis.

Experimental Section

General Methods. All reactions were carried out under a nitrogen or argon atmosphere using flame-dried glassware, unless otherwise noted. Tetrahydrofuran was distilled from sodium/benzophenone; dichloromethane was distilled from calcium hydride. Triethylamine was distilled from calcium hydride and stored over sodium hydroxide. Reactions were monitored by thin-layer chromatography (TLC). Visualization was accomplished with UV light and aqueous ceric ammonium molybdate solution or anisaldehyde stain followed by charring on a hot-plate. Flash chromatography was performed with the indicated solvents using silica gel 60 (particle size 0.040−0.063 mm). Yields refer to chromatographically and spectroscopically pure compounds unless otherwise stated. Melting points are

Chart 1



uncorrected unless otherwise noted. High-resolution mass spectra were obtained at Texas A&M University Mass Spectrometry Service Center on a VG Analytical 70S high-resolution, double-focusing, sectored (EB) mass spectrometer.

Silyl Ether 15. A solution of mucobromic acid (25 g, 97 mmol) and *tert*-butyldimethylsilyl chloride (16 g, 107 mmol) in dimethylformamide (120 mL) was cooled to 0 °C. Diisopropylethylamine (20 mL, 118 mmol) was added to the solution over 10 min dropwise. After complete addition, ice−water (150 mL) was added over 5 min and the solid collected by vacuum filtration, washed with cold water (400 mL), and air-dried. The solid was then redissolved in diethyl ether (200 mL), dried over magnesium sulfate, filtered, and concentrated in vacuo to provide 33 g (92%) of silyl ether **15** as a white free-flowing solid: mp 93−94 °C; IR ($CHCl_3$) 1783 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) 5.98 (s, 1H), 0.96 (s, 9H), 0.24 (s, 3H), 0.20 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) 164.2, 146.2, 117.4, 98.8, 25.3, 18.0,−4.5, −5.3; HRMS (FAB) *m/z* 372.9294 [$(M + H)^+$, calcd for $C_{10}H_{16}O_3SiBr_2$ 372.9294].

Vinyl Bromide 17. A solution of silyl ether **15** (20 g, 53.6 mmol) was dissolved in benzene (250 mL) and warmed to reflux. Vinyl boronate **16** (12.1 g, 64.3 mmol), aqueous potassium acetate (50 mL, 2 M), and palladium-bis(triphenylphosphine) dichloride were added, and reflux was continued for 20 h. The reaction mixture was cooled to room temperature and filtered through Celite. The organic layer was washed with saturated aqueous sodium bicarbonate (2 × 30 mL), cooled to 0 °C, and washed briefly with 0.5 N aqueous sodium hydroxide solution (2 × 30 mL), 0.5 N aqueous HCl (30 mL) and brine (30 mL). The organic layer was dried over magnesium sulfate, filtered and concentrated in vacuo. The residue was purified by vacuum distillation (150 °C, 0.6 mmHg) to give 13.9 g (72%) of vinyl bromide **17** as a yellow oil: IR ($CHCl_3$) 1767 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) 6.48 (dt, J = 16.1, 7.1 Hz, 1H), 6.27 (d, J = 16.1 Hz, 1H), 6.15 (s, 1H), 2.20 (m, 2H), 1.48 (app septet, J = 7.8 Hz, 2H), 0.92 (t, J = 7.8 Hz, 3H), 0.87 (s, 9H), 0.19 (s, 3H), 0.15 (s, 3H);^{13}C NMR (75 MHz, $CDCl_3$) 166.2, 156.4, 145.6, 120.1, 108.4, 97.5, 35.8, 25.3, 21.5, 17.6, 13.5, −4.2, −5.1; HRMS (FAB) *m/z* 361.0829 [$(M + H)^+$, calcd for $C_{15}H_{25}O_3SiBr$ 361.0834].

***tert*-Butylacetate 18.** A solution of vinyl bromide **17** (13.9 g, 38.5 mmol) and 1-(*tert*-butoxy)-1-(*tert*-butyldimethylsilyloxy)ethylene (22.1 mL, 77 mmol) was dissolved in tetrahydrofuran (220 mL), and the mixture was warmed to reflux. Palladium bis(tri-*o*-tolylphoshine)dichloride (908 mg, 1.2 mmol) and potassium acetate (7.5 g, 77 mmol) were added, and reflux continued for 24 h. After the mixture was cooled to room temperature, saturated aqueous ammonium chloride (100 mL) was added, and the biphasic mixture was stirred for 20 min at room temperature. The layers were separated, and the aqueous layer was extracted with diethyl ether (3 × 75 mL). The combined organic layers were washed with water (100 mL) and brine (100 mL), dried over magnesium sulfate, filtered, and concentrated in vacuo. The residue was purified by flash chromatography (gradient elution: 1% EtOAc/hexanes to 4% EtOAc/hexanes). Fractions containing impurities were rechromatographed (gradient elution: 1% EtOAc/hexanes to 2% EtOAc/hexanes). Combination of the corresponding fractions gave 11.3 g (75%) of *tert*-butyl ester **18** as an oily solid: IR ($CHCl_3$) 1760, 1731 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) 6.30 (dt, J = 15.9, 6.8 Hz, 1H), 6.21 (d, J = 16.1 Hz, 1H), 6.14 (s, 1H), 3.27 (d, J = 16.4 Hz, 1H), 3.19 (d, J = 16.6 Hz, 1H), 2.18 (m, 2H), 1.44 (app septet, J = 7.3 Hz, 2H), 0.90 (t, J = 7.3 Hz, 3H), 0.86 (s, 9H), 0.18 (s, 3H), 0.14 (s, 3H);^{13}C NMR (75 MHz, $CDCl_3$) 171.2, 168.0, 156.1, 143.2, 120.3, 119.8, 96.9, 81.5, 35.8, 30.4, 27.9, 25.5, 21.8, 17.7, 13.6, −4.0, −5.0; HRMS (FAB) *m/z* 397.2404 [$(M + H)^+$, calcd for $C_{21}H_{37}O_5Si$ 397.2410].

Acetic Acid 19. To a solution of *tert*-butyl ester **18** (1.6 g) dissolved in dichloromethane (12 mL) was added trifluoroacetic acid (4 mL). The gradually yellowing reaction was stirred at room temperature for 1 h and concentrated in vacuo, and benzene (10 mL) was evaporated from the residue three times to remove residual TFA. The residue was purified by flash chromatography (gradient elution: 4% EtOAc/hexanes to 20% EtOAc/hexanes) to yield 1.05 g (78%) of carboxylic acid **19** as an oil: IR ($CHCl_3$) 3020, 2860, 1760, 1718 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) 9.00 (br s, 1H), 6.38 (dt, J = 16.1, 6.8 Hz, 1H), 6.21 (d, 16.4, 1H), 6.19 (s, 1H), 3.41 (d, 16.8 Hz, 1H), 3.34 (d, 16.8 Hz, 1H), 2.21 (m, 2H), 1.46 (m, 2H), 0.92 (t, J = 7.3 Hz, 3H), 0.88 (s, 9H), 0.20 (s, 3H), 0.15 (s, 3H);^{13}C NMR (75 MHz, $CDCl_3$) 174.5, 171.4, 157.1, 144.4, 119.4, 118.9, 97.2, 35.8, 28.7, 25.5, 21.8, 17.8, 13.6, −4.0, −4.9; HRMS (FAB) *m/z* 363.1606 [$(M + Na)^+$, calcd for $C_{17}H_{28}O_5SiNa$ 363.1604].

DBU Cyclization of 22 (*n* = 2). A solution of **22** (n = 2; 50 mg, 0.105 mmol) in acetonitrile (5 mL) was slowly added to a solution of DBU (1.5 mg, 0.010 mmol) in acetonitrile (20 mL) at 70 °C and stirred under nitrogen for 2 days. The reaction mixture was concentrated and the residue filtrated through a silica gel pad, eluting with methylene chloride. The eluate was concentrated and separated by semipreparative HPLC (gradient elution 15% to 25% ethyl acetate−hexanes over 165 min, 4 mL/min). The first to elute was **23a** (2 mg, 4%): t_R 121 min; IR ($CHCl_3$) 2971, 1778, 1639 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.41 (dt, J = 16.2, 7.1 Hz, 1H), 6.09 (dt, J = 16.2, 1.6 Hz, 1H), 4.75 (m, 1H), 4.52 (m, 1H), 4.27 (m, 1H), 4.14 (m, 1H), 4.08 (d, J = 8.2 Hz, 1H), 3.60 (td, J = 12.3,

5.8 Hz, 2H), 3.04 (dd, J = 14.6, 10.3 Hz, 1H), 2.82 (m, 1H), 2.60 (dd, J = 14.6, J = 4.8 Hz, 1H), 2.28 (q, J = 8.4 Hz, 2H), 1.58−1.42 (complex m, 4H), 1.40−1.07 (complex m, 2H), 1.00−0.83 (complex m, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) 168.6, 166.0, 165.4, 164.9, 163.1, 151.6, 144.7, 140.0, 137.9, 132.4, 116.2, 62.4, 60.7, 43.0, 37.9, 36.6, 33.8, 29.5, 27.3, 21.2, 20.6, 13.7, 13.6; LRMS(FAB) m/z 497.1 [(M + Na)$^+$].

The second isomer to elute was **23b** (10 mg, 20%): t_R 149.9 min; IR ($CHCl_3$) 2930, 1772, 1634 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.41 (dt, J = 16.2, 7.1 Hz, 1H), 6.48 (dt, J = 16.2, 1.3 Hz, 1H), 4.84 (td, J = 11.6, 1.8 Hz, 1H), 4.78 (td, J = 11.6, 1.8 Hz, 1H), 4.03 (d, J = 12.6 Hz, 1H), 3.8 (d, J = 12.6 Hz, 1H), 3.65 (d, J = 15.7 Hz, 1H), 3.57 (d, J = 11.4 Hz, 2H), 3.36 (d, J = 15.7 Hz, 1H), 3.26 (m, 1H), 2.82 (d, J = 14.8 Hz, 1H), 2.40 (dd, J = 15.7, 7.3 Hz, 1H), 2.25 (q, J = 8.4 Hz, 2H), 1.58−1.45 (complex m, 4H), 1.35−1.20 (complex m, 2H), 1.00−0.78 (complex m, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) 169.3, 166.3, 165.0, 164.9, 163.4, 152.2, 145.9, 139.0, 135.0, 131.2, 117.1, 62.5, 61.4, 46.7, 36.6, 35.5, 34.8, 29.8, 29.3, 21.3, 18.9, 13.7, 13.6; LRMS(FAB) m/z 497.2 [(M + Na)$^+$].

DBU−Acetic Anhydride Cyclization of 22 (n = 3, 4, or 5). General Procedure. A solution of **22** (50 mg, 0.100, 0.097, and 0.094 mmol for n = 3, 4, and 5, respectively) in acetonitrile (5 mL) was slowly added to a solution of DBU (1.5 mg, 0.010 mmol) and acetic anhydride (177 mg, 2.00 mmol) in acetonitrile (20 mL) at 70 °C and stirred under nitrogen for 2 days. The reaction mixture was concentrated and the residue filtered through a silica gel pad, eluting with methylene chloride. The elute was concentrated and the residue subjected to flash chromatography (20% ethyl acetate−hexanes).

26: 12 mg (25%); IR ($CHCl_3$) 3026, 1779, 1745, 1634 cm^{-1}; UV−vis λ_{max} (MeOH) 208, 332 nm; ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.81 (dt, J = 16.2, 7.1 Hz, 1H), 6.24 (dt, J = 16.2, 1.3 Hz, 1H), 4.46 (m, 1H), 4.35 (m, 1H), 3.98 (t, J = 9.2 Hz, 2H), 3.94 (d, J = 15.8 Hz, 1H), 3.73 (m, 2H), 3.44 (d, J = 15.8 Hz, 1H), 2.20 (q, J = 7.3 Hz, 2H), 1.78 (m, 1H), 1.62 (m, 1H), 1.59−1.42 (complex m, 4H), 1.41−1.21 (complex m, 6H), 0.98−0.89 (complex m, 6H); ^{13}C NMR (125.7 MHz, $CDCl_3$) δ 169.8, 168.3, 166.6, 161.8, 154.9, 149.8, 143.2, 136.1, 134.4, 122.0, 117.5, 111.3, 65.3, 64.6, 51.6, 47.9, 37.0, 30.2, 25.7, 25.3, 21.8, 19.9, 13.8, 13.6; IR (cm^{-1}) 3026, 1779, 1745, 1525, 1423, 1228; LRMS(FAB) m/z 507.3 [(M + Na)$^+$].

27: 13 mg (26%); IR ($CHCl_3$) 2960, 1772, 1737, 1276 cm^{-1}; UV−vis λ_{max} (MeOH) 203, 318 nm; ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.81 (dt, J = 16.3, 7.1 Hz, 1H), 6.25 (dt, J = 16.3, 1.4 Hz, 1H), 4.43 (td, J = 9.5, 3.8 Hz, 1H), 4.2 (d, J = 17.2 Hz, 1H), 3.86 (m, 1H), 3.81 (d, J = 9.5 Hz, 1H), 3.76 (s, 1H), 3.62 (d, J = 17.2 Hz, 1H) 2.1 (q, J = 7.1 Hz, 2H), 1.64−1.21 (complex m, 14H), 1.00−0.79 (complex m, 6H); ^{13}C NMR (125.7 MHz, $CDCl_3$) δ 169.6, 168.2, 166.6, 165.3, 162.3, 155.6, 150.5, 143.5, 135.1, 134.2, 122.1, 117.5, 112.6, 64.6, 64.2, 51.7, 48.4, 37.9, 36.0, 30.4, 27.3, 26.7, 21.8, 21.0, 20.4, 13.9, 13.6; LRMS(FAB) m/z 521.4 [(M + Na)$^+$].

28: 15 mg (29%); IR ($CHCl_3$) 2966, 1772, 1731, 1281 cm^{-1}; UV−vis λ_{max} (MeOH) 206, 312 nm; ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.81 (dt, J = 16.2, 7.1 Hz, 1H), 6.24 (dt, J = 16.2, 1.3 Hz, 1H), 4.36 (m, 1H), 4.05 (m, 3H), 4.08 (d, J = 12.3 Hz, 1H), 3.72 (d, J = 16.7 Hz, 1H), 2.20 (q, J = 7.4 Hz, 2H), 1.61−1.18 (complex m, 16H), 1.00−0.81 (complex m, 6H); ^{13}C NMR (125.7 MHz, $CDCl_3$) δ 169.4, 168.5, 166.5, 165.1, 162.9, 156.0, 150.8, 143.5, 135.5, 134.4, 121.6, 117.5, 113.1, 66.8, 66.2, 52.2, 48.2, 38.1, 36.0, 31.2, 28.6, 28.2, 27.6, 26.6, 21.9, 20.3, 13.8, 13.6; LRMS(FAB) m/z 535.3 [(M + Na)$^+$].

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Supporting Information Available: Preparation of **20**−**22**, **32**, **33**, **24**, and **25**. ^{1}H and ^{13}C NMR spectra of **15**, **17**−**19**, **23**−**28**, and **32**−**33**. This material is available free of charge via the Internet at http://pubs.acs.org.

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