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Total Synthesis of (−)-Denticulatins A and B: Marine Polypropionates from *Siphonaria denticulata*

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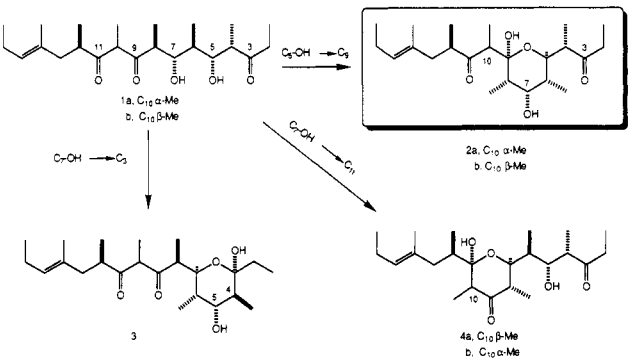
A synthesis of the marine polypropionates (−)-denticulatin A (**2a**) and B (**2b**) is described. The targets, which are β-hydroxy ketones wherein the hydroxyl group is also a tertiary hemiketal, are sensitive to acid dehydration. An open-chain form (**26**) of the denticulatins, having the 1,3-diol functionality protected as its *p*-methoxyacetophenylidene derivative, is prepared and is demonstrated to undergo only one of three possible modes of hemiketalization upon acid hydrolysis. The open-chain structure is constructed by an aldol condensation between ketone **5** and keto aldehyde **25**, which is synthesized by the 3-methyl-γ-butyrolactone strategy.

The genus *Siphonaria*, air-breathing mollusks of the subclass Pulmonata, produces numerable, structurally intriguing polypropionate metabolites.[1] In particular, denticulatin A (**2a**) and denticulatin B (**2b**) have been isolated from *Siphonaria denticulata*, which was collected in the intertidal zone of the coast of New South Wales, Australia.[2] Through a combination of IR, ^{1}H NMR, and ^{13}C NMR spectroscopy and a single-crystal X-ray analysis of denticulatin B, the structures were determined. The absolute stereochemistry was established by the isolation of (*R*)-ketone **5** upon exposure of denticulatin A or B to 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU). Interconversion of the denticulatins was achieved upon brief treatment with DBU through retrohemiketalization via the β-diketone enolate.

Although the denticulatins have been shown to arise via propionate biosynthesis,[3] the actual timing of the hemiketalization is an intriguing question. One possibility is that an open-chain C_9 monoketone undergoes cyclization followed by subsequent oxidation at C_3 and C_{11}. The prospect that the open-chain C_3, C_9, C_{11} trione **1** can be formed in Nature prior to any intermediates suffering cyclization is unlikely. However, the very challenge of generating trione **1** in the laboratory to assess its fate offered itself as a formidable challenge.

Three modes of hemiketalization are available to the two diasteromers of trione **1**. First, the C_7-OH may add to the C_3-carbonyl to give hemiketal **3** that would most likely have the hydroxyl group axial in accord with the anomeric effect. The C_4-methyl and the C_5-hydroxyl groups are axial

Scheme I



to the tetrahydropyran ring while the remaining alkyl substituents are equatorial. A second mode of cyclization has the C_7-OH adding to the C_{11}-carbonyl. In this instance, open-form **1a** affords **4a** that has all the carbon substituents about the ring equatorial except for the C_{10}-methyl group that is axial. On the other hand, open-form **1b** gives rise to **4b** that has all of the carbon substituents of the ring equatorial. Lastly, cyclization of the C_5-OH group with the C_9-carbonyl provides the denticulatins **2** having all the carbon substituents equatorial and the C_7-OH axial and hydrogen bonded to the anomeric hydroxyl. If the cyclization were to be thermodynamically controlled and mediated by steric interactions about the ring, the formation of pyranone **4b** and the denticulatins would be the expected products. The denticulatins have the advantage of hydrogen bonding between the axial hydroxyl groups.

Precedent for the proposed modes of cyclization was found in earlier work wherein the diol **6**, which is chiral by virtue of the stereochemistry of a single methyl group, underwent ozonolysis and cyclization to give only the anomeric acetals **7** and not those of structure **8**.[4] Acetals

(1) (a) Hochlowski, J. E.; Faulkner, D. J. *Tetrahedron Lett.* **1983**, *24*, 1917. (b) Hochlowski, J. E.; Faulkner, D. J. *J. Org. Chem.* **1984**, *49*, 3838. (c) Hochlowski, J. E.; Coll, J. C.; Faulkner, D. J.; Biskupiak, J. E.; Ireland, C. M.; Zheng, Q.; He, C.; Clardy, J. *J. Am. Chem. Soc.* **1984**, *106*, 6748. (d) Roll, D. M.; Biskupiak, J. E.; Mayne, C. L.; Ireland, C. M. *J. Am. Chem. Soc.* **1986**, *108*, 6680.

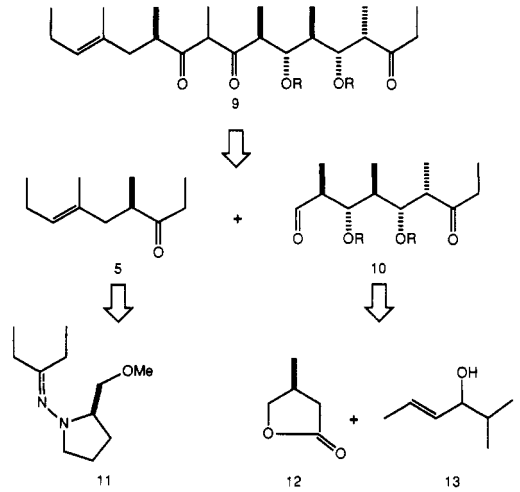
(2) Hochlowski, J. E.; Faulkner, D. J.; Matsumoto, G. K.; Clardy, J. *J. Am. Chem. Soc.* **1983**, *105*, 7413.

(3) Manker, D. C.; Garson, M. J.; Faulkner, D. J. *J. Chem. Soc., Chem. Commun.* **1988**, 1061.

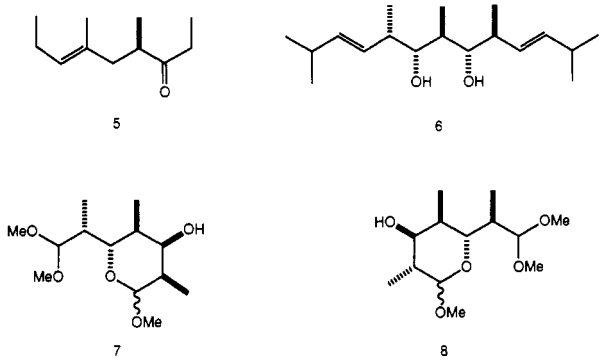
(4) Ziegler, F. E.; Cain, W. T.; Kneisley, A.; Stirchak, E. P.; Wester, R. T. *J. Am. Chem. Soc.* **1988**, *110*, 5442.

0022-3263/90/1955-2800$02.50/0

Scheme II

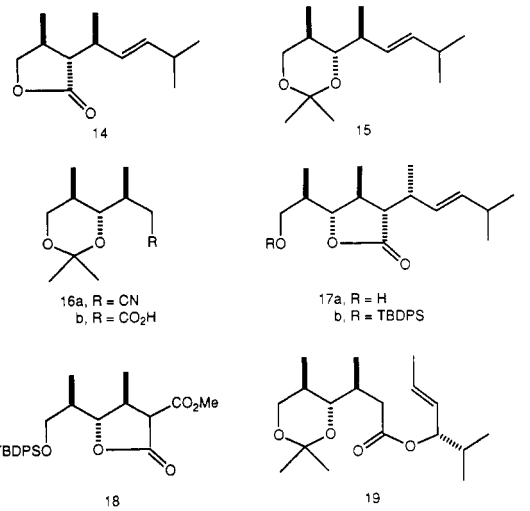


7 have all the carbon substituents about the heterocyclic ring equatorial.



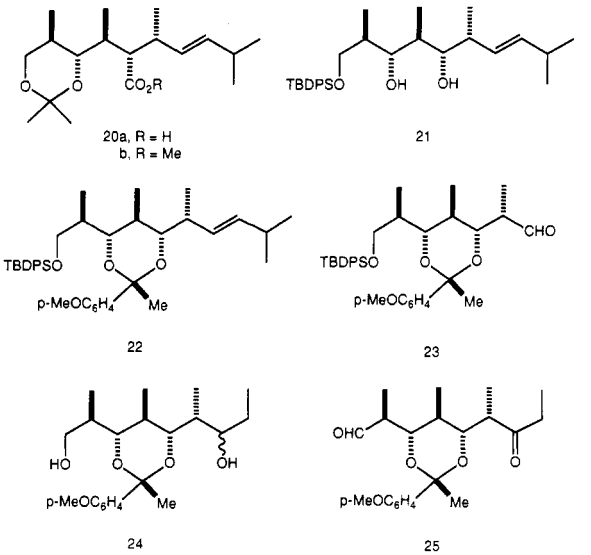
The retrosynthetic plan for the in situ generation of trione 1 (Scheme II) requires the preparation of a suitably protected diol precursor **9**. The protecting group, if labile to acid, would have to be removable under conditions where the acid-sensitive tertiary hydroxyl group, which is at once a hemiketal and β to a ketone, is stable. The dione **9** arises from an aldol condensation between the enolate of degradation ketone **5** and an appropriately protected keto aldehyde **10**. (*R*)-Ketone **5** is accessible through the Enders RAMP hydrazone alkylation procedure,[5] and the keto aldehyde **10** is available through our previously developed 3-methyl-γ-butyrolactone route for polypropionate synthesis.[4,6] The latter procedure requires the (*S*)-3-methyl-γ-butyrolactone (**12**) and the two enantiomers of (*E*)-allylic alcohol **13**.

The synthesis of the protected keto aldehyde **10**, namely, keto aldehyde **25**, is considered first. Lactone **14**, which was prepared by the Claisen rearrangement of the diethyl orthoester of (*S*)-lactone **12** and the (*R*)-allylic alcohol **13**, was converted into acetonide **15** by the following series of operations (Criegee sequence): (1) MeLi; (2) H_2O_2, H^+; (3) Ac_2O, Δ; (4) $LiAlH_4$; (5) 2,2-dimethoxypropane, H^+.[6] Following earlier protocol, the unsaturated acetonide **15** was transformed by sequential ozonolysis, reduction ($LiAlH_4$), tosylation, and cyanide displacement to the cyano acetonide **16a** in 62% yield. With the goal of preparing lactone **17b** that bears the absolute stereochemistry present in keto aldehyde **25**, a method involving palladium-mediated alkylation was explored because it had served our needs well on previous occasions.[5,6] Accordingly, the nitrile



16a was heated in refluxing methanolic HCl to afford an intermediate hydroxy lactone that was successively silylated (TBDPSCl) and carbomethoxylated ($NCCO_2Me$, LDA) to provide lactonic ester **18**. When the sodium salt of **18** was alkylated with the diethyl phosphate ester of (*S*)-alcohol **13** in the presence of $(Ph_3P)_4Pd$ as a catalyst and the product was subsequently subjected to decarbomethoxylation, lactone **17b** proved to be the major component of an 80:20 mixture of **17b** and its epimer at the site of alkylation. Although the stereoisomers were separable, efforts to enrich the mixture through base-catalyzed equilibrium proved futile.

An alternative to the palladium-catalyzed alkylation was found in the Ireland–Claisen rearrangement.[7] Nitrile **16a** was converted into its carboxylic acid **16b** with aqueous KOH/H_2O_2. The isolation of the acid required cautious workup to avoid acetonide hydrolysis and subsequent lactonization. Esterification of the carboxylic acid with (*S*)-alcohol **13** under Keck conditions[8] led to ester **19** in 74% yield. The absence of DMAP·HCl gave modest yields of ester and appreciable amounts of the *N*-acylurea of DCC. Treatment of the ester with LDA/THF followed by silylation with *tert*-butyldimethylsilyl chloride ostensibly formed the (*E*)-*O*-silylketene acetal, which underwent rearrangement in THF at reflux. Brief, dilute acid hydrolysis provided acid **20a**, whose derived methyl ester **20b**



(5) Enders, D.; Baus, U. *Justus Liebigs Ann. Chem.* **1983**, 1439.
(6) Ziegler, F. E.; Kneisley, A.; Thottathil, J. K.; Wester, R. T. *J. Am. Chem. Soc.* **1988**, *110*, 5434.
(7) Ireland, R. E.; Mueller, R. H.; Willard, A. K. *J. Am. Chem. Soc.* **1976**, *98*, 2868.
(8) Boden, E. P.; Keck, G. E. *J. Org. Chem.* **1985**, *50*, 2394.

(CH_2N_2) was shown by GLC to be a 97:3 ratio of epimers adjacent to the ester group. Prolonged acid hydrolysis of the acid **20a** gave rise to the hydroxy lactone **17a** in 84% overall yield. The minor amount of isomeric product was removed upon chromatography of the silyl ether **17b**.

The excision of the carbonyl carbon of lactone **17b** and its stereospecific replacement by a hydroxyl group were accomplished as had been reported for stereoisomers of **17b**.[4] The procedure is essentially the same as was described for the transformation of lactone **14** into the diol corresponding to acetonide **15**, except that DIBAL replaced $LiAlH_4$ in the Criegee sequence, a process that was achieved in 78% overall yield.

The juncture had been reached where the selection of an appropriate diol protecting group had to be chosen. While the acetonide group was too stable, the more reactive *p*-methoxyacetophenylidene derivative, developed by Lipshutz[9] for removal with $SnCl_4$, proved to have the desired acid lability, a property that had to be cautiously avoided during intervening operations. The protecting group was installed in 94% yield with α-*p*-dimethoxystyrene using pyridinium *p*-toluenesulfonate (PPTS) as a catalyst. A single diastereomer of **22** was produced whose stereochemistry was confirmed by ^1H NMR by the appearance of a 5% enhancement (NOE) of both ring methine protons adjacent to oxygen (δ 3.61 and 3.56) upon irradiation of the methyl singlet at δ 1.55.

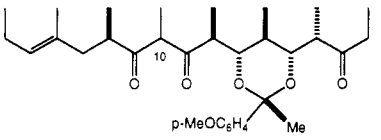
Ozonolysis of olefin **22** followed by dimethyl sulfide workup often gave appreciable amounts of the carboxylic acid along with the aldehyde **23**. Thus, reduction of the ozonolysis mixture with $LiAlH_4$ followed by Swern oxidation[10] proved to be more efficient. Realization of the keto aldehyde **25** was achieved in a straightforward manner. Addition of ethylmagnesium bromide to aldehyde **23** gave a mixture of alcohols that were desilylated with tetra-*n*-butylammonium fluoride to a mixture of diols **24**. A double Swern oxidation provided the keto aldehyde in 68% yield from aldehyde **23**.

The RAMP hydrazone of 3-pentanone was successfully alkylated with 1-bromo-2-methyl-2(*E*)-pentene (**24**) as described by Enders for 1-bromo-2-methyl-2(*E*)-butene.[5] The prescribed acid hydrolysis conditions that were reported to be successful with the latter alkylating agent gave a ketone with an enantiomeric excess (ee) of 20%. The method of Corey and Knapp,[11] which employs cupric acetate for the cleavage of dialkylhydrazones, afforded ketone **5** with an ee of 89%. While the ee of the lower homologue of ketone **5** had been determined by ^1H NMR using shift reagents, ketone **5** was not amenable to such an analysis owing to the density of the signals in the high-field region of the spectrum. As an alternative, the ketone was reduced with $LiAlH_4$ to a 1:1 mixture of alcohols that was derivatized as their Mosher esters. Analysis was accomplished by ^{19}F NMR.

The union of the fragments **5** and **25** was accomplished via an aldol condensation. Ketone **5** was treated with LDA and the resultant less substituted enolate was condensed with the keto aldehyde **25** to afford a 1.0:3.6:2.1 mixture of three aldol products A, B, and C, respectively, in 86% yield. Although the least polar isomer (A) could be separated from the other two, chromatographic separation proved unnecessary. Swern oxidation of the mixture provided after flash chromatography a 2.7:1 ratio of β-dicarbonyls **26a** and **26b**, respectively, in 81% yield.[12]

(9) Lipshutz, B.; Morey, M. C. *J. Org. Chem.* **1981**, *46*, 2419.
(10) Omura, K.; Swern, D. *Tetrahedron* **1978**, *34*, 1651.
(11) Corey, E. J.; Knapp, S. *Tetrahedron Lett.* **1976**, 3667.
(12) Smith, A. B., III; Levenberg, P. A. *Synthesis* **1981**, 567.

Although the stereochemistry at C_{10} could not be determined at this juncture, it was assigned as a result of the ensuing cyclizations. Careful rechromatography afforded fractions enriched in the C_{10} α-isomer **26a** (4.6:1) and the β-isomer **26b** (5.3:1).



26a, C_{10} α-Me
b, C_{10} β-Me

The deprotection of the β-diketones **26** in the presence of strong acid, e.g., TFA, was successful, but the reaction mixture contained products of dehydration and none of the denticulatins. The use of 5% oxalic acid in 1:1 aqueous THF at room temperature afforded the denticulatins without products of dehydration as long as the reaction was run to ~50% conversion. Thus, a mixture of β-diketones **26a** and **26b** (4.6:1) gave denticulatins A and B (6:1) in 69% yield based on recovered starting material; a 1:4.7 mixture of the respective β-diketones gave denticulatins A and B (1:8) in 72% yield. In the former experiment, the recovered β-diketone had a ratio of **26a**:**26b** of 2.9:1; in the latter case, the ratio was 1:1.5. These data indicate an appreciable degree of stereospecificity, i.e., **26a** → **2a** and **26b** → **2b**. The β-diketones do not completely isomerize prior to hydrolysis and cyclization. No other modes of cyclization could be detected, even prior to 50% conversion. The identity of the denticulatins was confirmed by comparison of ^1H NMR spectra, ^{13}C NMR spectra,[2] high-resolution mass spectra (CI), and optical rotation.

Experimental Section

All reactions were conducted in flame-dried glassware under an atmosphere of N_2 with a magnetic stirring bar unless otherwise noted. Diethyl ether and THF were distilled from sodium benzophenone ketyl under N_2. Diisopropylamine, pyridine, triethylamine, hexane, methylene chloride, oxalyl chloride and dimethyl sulfoxide were distilled from CaH_2. All other reagents were used as received unless otherwise indicated. GLC: capillary, 25-m bonded Carbowax 20M, 0.25 μm (160 °C). HPLC: Du Pont Zorbax, 4.6 × 250 mm, 5 μm, 1.5 mL/min, 20% EtOAc/heptane. Workup means the organic extracts were dried over anhydrous $MgSO_4$, filtered, and concentrated in vacuo. Microanalyses were within 0.4%.

4(*S*)-[1(*S*),4-Dimethyl-2(*E*)-pentenyl]-2,2,5(*R*)-trimethyl-1,3-dioxane (15). A solution of pure 2(*R*),4(*S*),7-trimethyl-5(*E*)-octene-1,3(*S*)-diol[6] (13.98 g, 75.0 mmol) in 400 mL of 2,2-dimethoxypropane and 200 mg of *p*-TsOH·H_2O was stirred at room temperature for 24 h. The solution was diluted with 800 mL of Et_2O and washed with aqueous $NaHCO_3$. Workup afforded 16.94 g of acetonide **15** (99% yield) containing a minor amount of excess reagent. The acetonide was used without further purification. A small portion (115 mg) was chromatographed (10% Et_2O/hexanes) for analysis: IR ($CDCl_3$) 2961, 1604 cm^{-1}; ^1H NMR ($CDCl_3$, 250 MHz) δ 5.37 (m, 2 H), 3.65 (dd, 1 H, *J* = 11.4, 5.2 Hz), 3.48 (t, 1 H, *J* = 11.3 Hz), 3.35 (dd, 1 H, *J* = 10.1, 2.4 Hz), 2.28 (m, 2 H), 1.75 (m, 1 H), 1.41 (s, 3 H), 1.38 (s, 3 H), 1.02 (d, 3 H, *J* = 7.0 Hz), 0.98 (d, 3 H, *J* = 6.7 Hz), 0.97 (d, 3 H, *J* = 6.7 Hz), 0.69 (d, 3 H, *J* = 6.7 Hz); $[\alpha]^{19}_D$ −14.4° (*c* 0.25, $CDCl_3$); HRMS (CI, M + H) calcd for $C_{14}H_{26}O_2$(H), 227.2012; found, 227.2026.

4(*S*)-[1(*S*)-Methyl-2-cyanoethyl]-2,2,5(*R*)-trimethyl-1,3-dioxane (16a). A solution of crude acetonide **15** (19.18 g, 84.7 mmol) was subjected to sequential ozonolysis, $LiAlH_4$ reduction, tosylation, and cyanide displacement as previously described[6] to give 9.16 g (62%) of crude nitrile **16a** as a brown oil. A portion (2.5 g) was distilled (Kugelrohr, 100 °C, 20 Torr) to give 2.06 g of nitrile **16a** that contained a minor amount of isovaleronitrile: IR (CCl_4) 2968, 2248 cm^{-1}; ^1H NMR ($CDCl_3$, 250 MHz) δ 3.71 (dd,

1 H, J = 12.1, 4.8 Hz), 3.48 (dd, 1 H, J = 11.9, 11.0 Hz), 3.41 (dd, 1 H, J = 10.2, 2.5 Hz), 2.46 (dd, 1 H, J = 16.7, 4.6 Hz), 2.35 (d, 1 H, J = 9.2 Hz), 2.13 (m, 1 H), 1.74 (m, 1 H), 1.41 (s, 3 H), 1.36 (s, 3 H), 1.17 (d, 3 H, J = 7.5 Hz), 0.79 (d, 3 H, J = 7.1 Hz).

4(*S*)-[1(*S*)-Methyl-2-carboxyethyl]-2,2,5(*R*)-trimethyl-1,3-dioxane (16b). A mixture of nitrile **16a** (0.60 g, 3.04 mmol), 17 mL of 30% KOH solution, and 1.1 mL of 30% aqueous H_2O_2 was heated at 48 °C for 5 h and then at reflux for 78 h. The reaction mixture was cooled to room temperature, diluted with 20 mL of water, and extracted with $CHCl_3$ (3×). The basic, aqueous layer was neutralized to pH 7 with 25% HCl, taken to pH 4 with 10% aqueous oxalic acid, and then extracted with $CHCl_3$ (4×). Workup (Na_2SO_4) of the combined organics from the acidic extracts gave 0.51 g of acetonide acid **16b** (78% yield), which was used without further purification: IR (CCl_4) 3200–2800, 1708 cm^{-1}; ^{1}H NMR ($CDCl_3$, 250 MHz) δ 3.72 (dd, 1 H, J = 11.6, 5.1 Hz), 3.50 (t, 1 H, J = 11.1 Hz), 3.41 (dd, 1 H, J = 10.2, 1.5 Hz), 2.55 (m, 1 H), 2.26 (m, 2 H), 1.77 (m, 1 H), 1.41 (s, 3 H), 1.37 (s, 3 H), 1.07 (d, 3 H, J = 6.5 Hz), 0.78 (d, 3 H, J = 6.7 Hz).

(*S*)-2-Methyl-4(*E*)-hexen-3-ol Ester of Acetonide Acid 16b (19). (*S*)-2-Methyl-4(*E*)-hexen-3-ol[6,13] (0.15 g, 1.36 mmol) was dissolved in 1.0 mL of CH_2Cl_2, and to this solution was added dicyclohexylcarbodiimide (DCC, 0.19 g, 0.91 mmol), 4-(dimethylamino)pyridine (DMAP, 12.0 mg, 0.098 mmol), and DMAP·HCl (16.0 mg, 0.10 mmol). The mixture was brought to reflux (45 °C) and acetonide acid **16b** (0.17 g, 0.80 mmol) in 1.8 mL of CH_2Cl_2 was added dropwise via a syringe pump over a period of 15 h followed by a 1.0-mL rinse with CH_2Cl_2 of the syringe. After addition was complete, the yellow solution was heated at reflux for an additional 24 h. The reaction mixture was diluted with 25 mL of Et_2O and filtered through a Celite plug. Concentration in vacuo followed by flash chromatography (8% Et_2O/hexanes) provided 0.18 g of pure ester **19** (74%): IR (CCl_4) 2964, 1730 cm^{-1}; ^{1}H NMR ($CDCl_3$, 250 MHz) δ 5.71 (dqd, 1 H, J = 15.2, 6.4, 0.7 Hz), 5.39 (ddd, 1 H, J = 15.3, 7.8, 1.6 Hz), 5.00 (t, 1 H, J = 7.1 Hz), 3.68 (dd, 1 H, J = 11.5, 5.1 Hz), 3.47 (t, 1 H, J = 11.0 Hz), 3.37 (dd, 1 H, J = 10.2, 1.9 Hz), 2.48 (dd, 1 H, J = 14.5, 2.9 Hz), 2.25 (m, 1 H), 2.14 (dd, 1 H, J = 14.6, 9.8 Hz), 1.83 (m, 1 H), 1.70 (dd, 3 H, J = 6.6, 1.3 Hz), 1.69 (m, 1 H), 1.39 (s, 3 H), 1.35 (s, 3 H), 1.00 (d, 3 H, J = 6.5 Hz), 0.90 (d, 3 H, J = 6.8 Hz), 0.88 (d, 3 H, J = 6.8 Hz), 0.76 (d, 3 H, J = 6.6 Hz); $[\alpha]^{21}_D$ −32.7° (c 1.26, $CHCl_3$); HRMS (CI, M + H) calcd for $C_{18}H_{32}O_4$(H), 313.2380; found, 313.2363. Anal. Calcd for $C_{18}H_{32}O_4$: C, 69.20; H, 10.32. Found: C, 69.18; H, 10.34.

3(*S*)-[1(*R*),4-Dimethyl-2(*E*)-pentenyl]-4(*S*)-methyl-5-(*S*)-[1(*R*)-methyl-2-hydroxyethyl]dihydro-2(3*H*)-furanone (17a). LDA (0.28 M solution) was formed in 10 mL of THF at −5°C by adding diisopropylamine (0.490 mL, 3.47 mmol) followed by dropwise addition of n-BuLi (2.17 mL of a 1.60 M solution in hexanes, 3.47 mmol). After 15 min, the solution was cooled to −78 °C and a solution of allylic ester **19** (0.834 g, 2.67 mmol) in 1.5 mL of THF was added, followed by 3 × 0.1 mL of THF rinses. After 2 h at −78 °C, *tert*-butyldimethylsilyl chloride (0.523 g, 3.47 mmol) was added to the yellow solution and stirring was continued for 30 min at −78 °C. The reaction mixture was allowed to warm slowly to room temperature over a period of 45 min. A reflux condenser was affixed and the solution was heated at reflux for 18 h and then cooled to room temperature. The solution was treated with 3.0 mL of 5% HCl, stirred for 30 min, diluted with Et_2O, and washed successively with H_2O, saturated $NaHCO_3$ solution, and brine. Workup yielded 1.154 g of crude acid **20a**. A small portion of the acid (13 mg) was purified by flash chromatography (35% EtOAc/hexanes) to give 10 mg (77%) of the acid: IR (CCl_4) 3200–2500, 1701 cm^{-1}; ^{1}H NMR ($CDCl_3$, 250 MHz) δ 5.38 (m, 2 H), 3.68 (dd, 1 H, J = 11.6, 4.9 Hz), 3.40 (m, 2 H), 2.58 (m, 1 H), 2.52 (m, 1 H), 2.24 (m, 1 H), 2.20 (m, 1 H), 1.83 (m, 1 H), 1.39 (s, 3 H), 1.38 (s, 3 H), 1.05 (d, 3 H, J = 7.1 Hz), 1.01 (d, 3 H, J = 6.7 Hz), 0.98 (d, 3 H, J = 6.8 Hz), 0.97 (d, 3 H, J = 6.8 Hz), 0.82 (d, 3 H, J = 6.7 Hz), $[\alpha]^{26}_D$ −32.3° (c 0.53, $CHCl_3$); HRMS (CI, M + H) calcd for $C_{18}H_{32}O_4$(H), 313.2380; found, 313.2374. The crude acid dissolved in 12 mL of THF was treated with 6 mL of 10% HCl and stirred at room temperature for 6.5 h. The mixture was diluted with Et_2O and washed as above. Workup yielded 0.81 g of crude lactone, which upon flash chromatography (35% EtOAc/hexanes) provided 0.57 g of pure hydroxy lactone **17a** (84% overall yield); IR (CCl_4) 3480, 2965, 1772 cm^{-1}; ^{1}H NMR ($CDCl_3$, 250 MHz) δ 5.48 (dd, 1 H, J = 15.6, 6.4 Hz), 5.31 (dd, 1 H, J = 15.5, 6.9 Hz), 3.87 (t, 1 H, J = 7.3 Hz) 3.68 (broad, 2 H), 2.75 (m, 1 H), 2.24 (m, 3 H), 1.87 (m, 1 H), 1.69 (broad, 1 H), 1.19 (d, 3 H, J = 6.2 Hz), 1.15 (d, 3 H, J = 7.0 Hz), 1.02 (d, 3 H, J = 7.0 Hz), 0.97 (d, 6 H, J = 6.7 Hz); $[\alpha]^{26}_D$ +49.0° (c 1.63, $CHCl_3$); HRMS (EI) calcd for $C_{15}H_{26}O_3$, 254.1883; found, 254.1879.

3(*S*)-[1(*R*),4-Dimethyl-2(*E*)-pentenyl]-4(*S*)-methyl-5-(*S*)-[1(*R*)-methyl-2-[(*tert*-butyldiphenylsilyl)oxy]ethyl]-dihydro-2(3*H*)-furanone (17b). Hydroxy lactone **17a** (0.57 g, 2.25 mmol), Et_3N (1.13 mL, 8.10 mmol), and DMAP (14 mg, 0.11 mmol) were dissolved in 22 mL of CH_2Cl_2. *tert*-Butyldiphenylsilyl chloride (1.05 mL, 4.05 mmol) was added via a syringe and the resultant solution was stirred at room temperature for 13 h. The contents were diluted with Et_2O and washed successively with 5% HCl, saturated $NaHCO_3$ solution, and water, followed by workup, which gave 1.66 g of crude silyl ether. Flash chromatography (5% EtOAc/hexanes) afforded 0.84 g of silyl ether **17b** (94% yield based on recovered starting material) and 0.11 g of unreacted hydroxy lactone **17a**. Careful chromatography (if desired) of the above product provided 0.83 g of the desired trans lactone **17b** and 17 mg of its cis isomer. Silyl ether lactone **17b**: IR ($CHCl_3$) 2964, 1758 cm^{-1}; ^{1}H NMR ($CDCl_3$, 250 MHz) δ 7.67 (m, 4 H), 7.42 (m, 6 H), 5.45 (dd, 1 H, J = 15.5, 6.5 Hz), 5.29 (dd, 1 H, 15.6, 6.8 Hz), 3.99 (t, 1 H, J = 7.1 Hz), 3.68 (d, 2 H, J = 5.3 Hz), 2.71 (m, 1 H), 2.24 (m, 1 H), 2.21 (m, 2 H), 1.93 (m, 1 H), 1.17 (d, 3 H, J = 6.2 Hz), 1.13 (d, 3 H, J = 7.0 Hz), 1.07 (s, 9 H), 0.99 (d, 3 H, J = 7.0 Hz), 0.93 (d, 6 H, J = 6.6 Hz); $[\alpha]^{21}_D$ +34.3° (c 1.06, $CHCl_3$); HRMS (CI, M + H) calcd for $C_{31}H_{44}O_3Si$(H), 493.3139; found, 493.3131. Anal. Calcd for $C_{31}H_{44}O_3Si$: C, 75.56; H, 8.85. Found: C, 75.40; H, 9.01. Cis silyl ether lactone: ^{1}H NMR ($CDCl_3$, 250 MHz) δ 7.67 (m, 4 H), 7.42 (m, 6 H), 5.45 (dd, 1 H, J = 15.5, 6.0 Hz), 5.32 (dd, 1 H, J = 15.6, 7.0 Hz), 4.01 (dd, 1 H, J = 8.3, 6.3 Hz), 3.68 (dd, 2 H, J = 5.5, 1.8 Hz), 2.63 (m, 1 H), 2.31 (m, 1 H), 2.23 (m, 2 H), 1.97 (m, 1 H), 1.13 (d, 3 H, J = 6.2 Hz), 1.11 (d, 3 H, J = 6.9 Hz), 1.07 (s, 9 H), 1.00 (d, 3 H, J = 7.0 Hz), 0.96 (d, 3 H, J = 6.7 Hz), 0.95 (d, 3 H, J = 6.7 Hz).

1-[(*tert*-Butyldiphenylsilyl)oxy]-2(*R*),4(*S*),6(*R*),9-tetramethyl-7(*E*)-decene-3(*R*),5(*S*)-diol (21). Lactone **17b** (2.72 g, 5.52 mmol) gave diol **21** (1.84 g, 78%) as previously described for its stereoisomer:[14] mp 83–84.5 °C; IR (CCl_4) 3461, 2961, 1549 cm^{-1}; ^{1}H NMR ($CDCl_3$, 250 MHz) δ 7.70 (m, 4 H), 7.44 (m, 6 H), 5.55 (dd, 1 H, J = 15.7, 5.9 Hz), 5.46 (dd, 1 H, J = 15.7, 5.5 Hz), 4.28 (broad, 2 H), 3.88 (dd, 1 H, J = 10.2, 4.1 Hz), 3.69 (dd, 1 H, J = 10.2, 4.7 Hz), 3.59 (m, 2 H), 2.40 (m, 1 H), 2.31 (m, 1 H), 2.03 (m, 1 H), 1.88 (m, 1 H), 1.13 (d, 3 H, J = 7.0 Hz), 1.08 (s, 9 H), 1.01 (d, 3 H, J = 6.8 Hz), 1.00 (d, 6 H, J = 6.8 Hz), 0.79 (d, 3 H, J = 6.8 Hz); $[\alpha]^{23}_D$ −18.7° (c 1.00, $CHCl_3$); HRMS (CI, M + H) calcd for $C_{30}H_{46}O_3Si$(H), 483.3296; found, 483.3283. Anal. Calcd for $C_{30}H_{46}O_3Si$: C, 74.64; H, 9.60. Found: C, 74.53; H, 9.63.

6(*S*)-[1(*R*),4-Dimethyl-2(*E*)-pentenyl]-4(*S*)-[1(*R*)-methyl-2-[(*tert*-butyldiphenylsilyl)oxy]ethyl]-2(*S*),5(*S*)-dimethyl-2-(*p*-methoxyphenyl)-1,3-dioxane (22). To diol **21** (0.301 g, 0.623 mmol) dissolved in 4 mL of CH_2Cl_2 under Ar were added sequentially 15 4-Å molecular sieves, α,p-dimethoxystyrene (0.4 mL, 2.4 mmol), and 5 mg of pyridinium tosylate (PPTS). The reaction appeared complete (TLC) after 1 h. The contents were diluted with 100 mL of Et_2O and washed successively with saturated $NaHCO_3$ solution, water, and brine. Workup yielded 0.79 g of crude ketal **22**, which upon flash chromatography (5% Et_2O/hexanes) provided 0.36 g (94%) of pure p-methoxyacetophenylidene ketal **22**: IR (CCl_4) 2961, 1616, 1551, 1513 cm^{-1}; ^{1}H NMR ($CDCl_3$, 250 MHz) δ 7.66 (m, 4 H), 7.45–7.23 (m, 8 H), 6.85 (d, 2 H), 5.55 (dd, 1 H, J = 15.6, 7.4 Hz), 5.40 (dd, 1 H, J = 15.5, 6.4 Hz), 3.92 (dd, 1 H, J = 10.2, 6.4 Hz), 3.82 (s, 3 H), 3.61 (dd, 1 H, J = 10.4, 1.9 Hz), 3.56 (dd, 1 H, J = 10.2, 2.7 Hz), 3.52 (dd, 1 H, J = 10.2, 6.9 Hz), 2.36 (m, 1 H), 2.28 (m, 1 H), 2.14 (m, 1 H), 1.87 (m, 1 H), 1.55 (s, 3 H), 1.08 (d, 3 H, J = 7.0 Hz), 1.04 (s, 9 H), 1.00 (d, 6 H, J = 6.7 Hz), 0.88 (d, 3 H, J = 6.9 Hz), 0.75 (d, 3 H, J = 6.5 Hz); $[\alpha]^{23}_D$ −47.1° (c 1.15, $CHCl_3$); HRMS (CI,

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M + H) calcd for $C_{39}H_{54}O_4Si(H)$, 615.3871; found, 615.3827. Anal. Calcd for $C_{39}H_{54}O_4Si$: C, 76.17; H, 8.85. Found: C, 76.26; H, 8.89.

6(*R*)-[1(*R*)-Methyl-2-[(*tert*-butyldiphenylsilyl)oxy]-ethyl]-4(*R*)-[1(*S*)-methyl-2-oxoethyl]-2(*R*),5(*R*)-dimethyl-2-(*p*-methoxyphenyl)-1,3-dioxane (23). Olefin **22** (0.34 g, 0.55 mmol) was dissolved in 12 mL of a 4:1 mixture of MeOH/EtOAc and cooled to −78 °C. Solid $NaHCO_3$ was added as a buffer, and ozone was bubbled through the solution until a blue color persisted for 4 min. The vessel was purged with N_2 and allowed to warm to room temperature. The crude mixture was filtered through a Celite plug and concentrated in vacuo. The residue was dissolved in 24 mL of Et_2O and cooled to 0 °C. $LiAlH_4$ (90 mg, 2.21 mmol) was added in four portions over a 5-min period, and the resultant mixture was stirred overnight at room temperature. Excess reagent was decomposed (90 μL of H_2O, 90 μL of 15% NaOH, 270 μL of H_2O) at 0 °C and workup gave 0.31 g of crude primary alcohol: ^1H NMR ($CDCl_3$, 250 MHz) δ 7.67 (m, 4 H), 7.42–7.24 (m, 8 H), 6.84 (d, 2 H), 3.93 (dd, 1 H, *J* = 10.2, 6.6 Hz), 3.89 (dd, 1 H, *J* = 10.2, 2.3 Hz), 3.82 (s, 3 H), 3.81–3.65 (m, 3 H), 3.50 (dd, 1 H, *J* = 10.3, 6.5 Hz), 2.18 (m, 2 H), 2.01 (m, 1 H), 1.96 (m, 1 H), 1.65 (s, 3 H), 1.07 (d, 3 H, *J* = 4.1 Hz), 1.04 (s, 9 H), 0.86 (d, 3 H, *J* = 7.0 Hz), 0.75 (d, 3 H, *J* = 6.6 Hz); HRMS (CI, M + H) calcd for $C_{35}H_{48}O_5Si(H)$, 577.3351; found, 577.3323. Oxalyl chloride (0.14 ml, 1.60 mmol) was dissolved in 8 mL of CH_2Cl_2 and cooled to −78 °C. DMSO (0.118 mL, 1.66 mmol) in 3 mL of CH_2Cl_2 was added via syringe, and the mixture was stirred for 5 min. Crude alcohol (0.31 g, 0.53 mmol) in 3 mL of CH_2Cl_2 was then added dropwise, followed by 3 × 0.1 mL rinses with CH_2Cl_2. The resultant solution was stirred for 20 min at −78 °C and then treated with Et_3N (0.372 mL, 2.67 mmol). The mixture was stirred an additional 20 min at −78 °C and then warmed to 0 °C for 10 min. The contents were diluted with 75 mL of Et_2O and washed with water followed by brine. Workup and flash chromatography (25% Et_2O/hexanes) afforded 0.24 g of pure aldehyde **23** (75% yield overall): IR (CCl_4) 2932, 1732, 1550, 1513 cm^{-1}; ^1H NMR ($CDCl_3$, 250 MHz) δ 9.75 (s, 1 H), 7.67 (m, 4 H), 7.45–7.21 (m, 8 H), 6.83 (d, 2 H), 4.27 (dd, 1 H, *J* = 10.3, 2.5 Hz), 3.93 (dd, 1 H, *J* = 10.3, 7.1 Hz), 3.81 (s, 3 H), 3.74 (dd, 1 H, *J* = 10.2, 1.5 Hz), 3.50 (dd, 1 H, *J* = 10.3, 6.2 Hz), 2.55 (m, 1 H), 2.21 (m, 1 H), 2.11 (m, 1 H), 1.62 (s, 3 H), 1.06 (d, 3 H, *J* = 7.7 Hz), 1.04 (s, 9 H), 1.03 (d, 3 H, *J* = 4.8 Hz), 0.81 (d, 3 H, *J* = 6.6 Hz); $[\alpha]^{22}_D$ −6.25° (*c* 0.96, $CHCl_3$); HRMS (CI, M + H) calcd for $C_{35}H_{46}O_5Si(H)$, 575.3194; found, 575.3206.

4(*S*)-[1(*R*)-Methyl-2-hydroxybutyl]-6(*R*)-[1(*R*)-methyl-2-hydroxyethyl]-2(*R*),5(*R*)-dimethyl-2-(*p*-methoxyphenyl)-1,3-dioxanes (24). To aldehyde **23** (45 mg, 0.078 mmol) dissolved in 3 mL of Et_2O at 0 °C was added dropwise ethylmagnesium bromide (0.30 mL; 3.3 M in Et_2O, 1.0 mmol). The resulting mixture was stirred at 0 °C for 45 min and then at room temperature for 30 min. Excess reagent was quenched with 0.5 mL of MeOH at 0 °C. The contents were diluted with 50 mL of Et_2O and washed with 30 mL of saturated NH_4Cl solution. The aqueous layer was reextracted with Et_2O. The combined organic layers were again washed with saturated NH_4Cl solution and then brine, followed by workup, which gave 50 mg of crude secondary alcohols in a ~2.4:1 ratio: ^1H NMR ($CDCl_3$, 250 MHz, partial) δ 3.98–3.66 (m, 4 H), 3.82, 3.81 (s, 3 H), 3.51 (m, 1 H), 1.70, 1.69 (s, 3 H), 1.06, 1.05 (s, 9 H). The crude alcohols (50 mg, 0.08 mmol) were dissolved in 3 mL of THF and were treated with *tert*-butylammonium fluoride (TBAF, 0.16 mL; 1.0 M solution, 0.16 mmol). After 15 h of stirring at room temperature, the contents were diluted with Et_2O and washed with water. The aqueous layer was reextracted with Et_2O and then with EtOAc. Workup and flash chromatography (20% EtOAc/hexanes) gave 26 mg (92% yield overall) of an inseparable mixture of diastereomeric diols **24**: IR (CCl_4) 3549, 2966, 1616, 1515 cm^{-1}; ^1H NMR for the major diastereomer ($CDCl_3$, 250 MHz, partial) δ 7.37 (d, 2 H), 6.85 (d, 2 H), 3.97 (dd, 1 H, *J* = 10.3, 2.2 Hz), 3.91 (dd, 1 H, *J* = 11.5, 3.8 Hz), 3.80 (s, 3 H), 3.58 (broad, 2 H), 3.25 (broad, 1 H), 2.32 (broad, 2 H), 1.98 (m, 2 H), 1.87 (m, 1 H), 1.74 (s, 3 H), 1.64 (m, 1 H), 1.49 (m, 1 H), 1.22 (d, 3 H, *J* = 7.1 Hz), 0.99 (t, 3 H, *J* = 7.5 Hz), 0.99 (d, 3 H, *J* = 7.1 Hz), 0.84 (d, 3 H, *J* = 6.6 Hz); $[\alpha]^{22}_D$ −26.1° (*c* 0.97, $CHCl_3$); HRMS (CI, M + H) calcd for $C_{21}H_{34}O_5(H)$, 367.2485; found, 367.2471.

4(*R*)-[1(*S*)-Methyl-2-oxobutyl]-6(*S*)-[1(*S*)-methyl-2-oxoethyl]-2(*R*),5(*R*)-dimethyl-2-(*p*-methoxyphenyl)-1,3-dioxane (25). Oxalyl chloride (0.08 mL, 0.90 mmol) was dissolved in 2.0 mL of CH_2Cl_2 and was cooled to −78 °C. DMSO (0.13 mL, 1.80 mmol) in 0.5 mL of CH_2Cl_2 was added, and the mixture was stirred for 3 min. Diols **24** (100 mg, 0.27 mmol) in 1.5 mL of CH_2Cl_2 were added dropwise, followed by 3 × 0.1 mL rinses with CH_2Cl_2. The resultant solution was stirred for 30 min at −78 °C, and was then treated with Et_3N (0.38 mL, 2.73 mmol). Stirring was continued an additional 15 min at −78 °C and then warmed to 0 °C for 10 min. Saturated NH_4Cl solution was added, and the contents were diluted with a 1:1 mixture of Et_2O/EtOAc. The layers were separated and the organics were washed with brine, whereupon workup and flash chromatography (20% EtOAc/hexanes) afforded 74 mg of pure keto aldehyde **25** (74%) as a crystalline white solid: mp 93–95 °C; IR ($CHCl_3$) 2981, 1718, 1701, 1614, 1514 cm^{-1}; ^1H NMR ($CDCl_3$, 250 MHz) δ 9.77 (d, 1 H, *J* = 2.9 Hz), 7.34 (d, 2 H), 6.85 (d, 2 H), 4.26 (dd, 1 H, *J* = 10.1, 3.2 Hz), 3.95 (dd, 1 H, *J* = 10.5, 2.1 Hz), 3.80 (s, 3 H), 2.68 (m, 2 H), 2.56 (q, 2 H, *J* = 7.3 Hz), 1.83 (m, 1 H), 1.65 (s, 3 H), 1.31 (d, 3 H, *J* = 7.0 Hz), 1.16 (d, 3 H, *J* = 7.1 Hz), 1.09 (t, 3 H, *J* = 7.2 Hz), 0.88 (d, 3 H, *J* = 6.6 Hz); ^{13}C NMR ($CDCl_3$, 250 MHz) δ 212.4, 204.3, 159.0, 137.8, 125.6 (2 C), 113.2 (2 C), 98.5, 77.3, 76.5, 55.2, 47.8, 47.4, 33.9, 33.4, 20.7, 11.7, 11.6, 8.8, 7.8; $[\alpha]^{22}_D$ −25.1° (*c* 1.25, $CHCl_3$); HRMS (CI, M + H) calcd for $C_{21}H_{30}O_5(H)$, 363.2172; found, 363.2164.

2-Methyl-2(*E*)-pentenyl Bromide.[15] 2-Methyl-2(*E*)-pentenol[16] (2.35 g, 23.5 mmol) gave 3.60 g of crude bromide. Kugelrohr distillation (55 °C, 20 Torr) provided 3.27 g (85%) of pure bromide: IR (CCl_4) 2971, 1661 (weak) cm^{-1}; ^1H NMR ($CDCl_3$, 250 MHz) δ 5.61 (t, 1 H), 3.99 (s, 2 H), 2.05 (quintet, 2 H), 1.76 (s, 3 H), 0.98 (t, 3 H).

Alkylation of the RAMP Hydrazone of 3-Pentanone. A 0.18 M solution of LDA was prepared in 29 mL of Et_2O at −5 °C under Ar by adding diisopropylamine (0.85 mL, 6.10 mmol) followed by dropwise addition of *n*-BuLi (3.81 mL; 1.60 M (hexanes), 6.10 mmol). After 25 min, 3-pentanone RAMP hydrazone[5] (1.15 g, 5.80 mmol) in 19 mL of Et_2O at 0 °C was added to the stirred solution via cannula over a period of 5 min under Ar. After 6 h at 0 °C, during which time 28 mL of Et_2O was added to facilitate dilution of the thickened slurry, the flask was cooled to −110 °C (pentane/liquid N_2 bath) for 15 min, and 2-methyl-2(*E*)-pentenyl bromide (1.23 g, 7.54 mmol) was added neat via a syringe with subsequent dissolution of the precipitate. The resultant mixture was kept at −110 °C for 30 min and then was allowed to warm slowly to room temperature overnight. After 19 h, the contents were diluted with 200 mL of Et_2O and were washed with 50 mL of H_2O. The aqueous layer was reextracted with Et_2O (2×), and workup of the combined organics provided 1.58 g (97%) of crude alkylated RAMP hydrazone that required no further purification: IR ($CHCl_3$) 2931, 2874, 1625, 1461 cm^{-1}; ^1H NMR ($CDCl_3$, 250 MHz) δ 5.12 (t, 1 H, *J* =7.1 Hz), 3.62 (sext, 1 H), 3.38 (d, 1 H, *J* = 5.8 Hz), 3.35 (s, 3 H), 3.23–2.99 (m, 2 H), 3.16 (d, 1 H, *J* = 5.4 Hz), 2.42 (q, 1 H, *J* = 9.0 Hz), 2.19–1.92 (m, 6 H), 1.83 (m, 2 H), 1.63 (m, 2 H), 1.61 (s, 3 H), 1.10 (t, 3 H, *J* = 7.9 Hz), 1.00 (d, 3 H, *J* = 7.5 Hz), 0.95 (t, 3 H, *J* = 7.7 Hz); $[\alpha]^{21}_D$ −200° (*c* 0.05, $CHCl_3$); HRMS (CI, M + H) calcd for $C_{17}H_{32}N_2O(H)$, 281.2595; found, 281.2592.

4(*R*),6-Dimethyl-6(*E*)-nonen-3-one (5). To a stirred suspension of cupric acetate (1.64 g, 8.20 mmol) in 82 mL of H_2O at 0 °C was added dropwise the alkylated RAMP hydrazone (1.15 g, 4.10 mmol) in 82 mL of THF. The resultant blue-green mixture was allowed to warm to room temperature over a period of 17 h. The orange slurry was concentrated in vacuo, diluted with saturated NH_4Cl solution, and extracted with CH_2Cl_2 (3×). Workup (Na_2SO_4) and distillation (Kugelrohr, 50–55 °C, 0.5 Torr) afforded 0.39 g (56%) of ketone **5** as a yellow oil: IR ($CHCl_3$) 2967, 1708 cm^{-1}; ^1H NMR ($CDCl_3$, 250 MHz) δ 5.13 (t, 1 H, *J* = 7.5 Hz), 2.72 (sext, 1 H), 2.46 (q, 2 H, *J* = 7.6 Hz), 2.32 (dd, 1 H, *J* = 13.8, 7.3 Hz), 1.98 (m, 3 H), 1.60 (s, 3 H), 1.04 (t, 3 H, *J* = 7.5 Hz), 1.02 (d, 3 H, *J* = 7.5 Hz), 0.94 (t, 3 H, *J* = 7.7 Hz); $[\alpha]^{22}_D$ −23.9° (*c* 1.12, $CHCl_3$); HRMS (EI) calcd for $C_{11}H_{20}O$, 168.1515; found, 168.1508.

(15) This procedure is based on the report of Vig [Vig, O. P.; Sharma, S. D.; Handa, V. K. *Indian J. Chem.* **1978**, *16B*, 114] except that pentane was used as a solvent to minimize S_N2' bromide formation.

(16) Evans, M. B.; Higgins, G. M. C.; Saville, B.; Watson, A. A. *J. Chem. Soc.* **1962**, 5045.

6(*R*)-[1(*S*)-Methyl-2-oxobutyl]-4(*S*)-[1(*S*),3(*S*),5(*R*),7-tetramethyl-2,4-dioxo-7(*E*)-decenyl]-2(*S*),5(*S*)-dimethyl-2-(*p*-methoxyphenyl)-1,3-dioxane (26a) and 6(*R*)-[1(*S*)-Methyl-2-oxobutyl]-4(*S*)-[1(*S*),3(*R*),5(*R*),7-tetramethyl-2,4-dioxo-7(*E*)-decenyl]-2(*S*),5(*S*)-dimethyl-2-(*p*-methoxyphenyl)-1,3-dioxane (26b). To a solution of ketone **5** (33.0 mg, 0.19 mmol) dissolved in 0.5 mL of THF and cooled to -78 °C was added dropwise 1.14 mL of LDA in THF (0.17 M, 0.19 mmol). Stirring was continued for 1 h, and then keto aldehyde **25** (44.0 mg, 0.12 mmol) in 1.0 mL of THF was added via syringe. The resultant solution was stirred for 20 min at -78 °C, whereupon the reaction mixture was quenched with 10 mL of saturated NH_4Cl solution and allowed to warm to room temperature. The aqueous layers were extracted with 30 mL of a 1:1 mixture of Et_2O/EtOAc. The organic phase was washed with NH_4Cl and the combined aqueous layers were reextracted with Et_2O. Workup and flash chromatography (20% EtOAc/hexanes) gave 50 mg (86% yield) of β-hydroxy ketones in a ratio of 1.0:3.6:2.1 as determined by HPLC analysis. Rechromatography separated the minor component from the other two. Least polar, minor diastereomer (R_f = 0.29): ^1H NMR ($CDCl_3$, 250 MHz) δ 7.32 (d, 2 H), 6.82 (d, 2 H), 5.17 (t, 1 H, J = 7.1 Hz), 4.28 (dd, 1 H, J = 10.4, 3.1 Hz), 4.13 (d, 1 H, J = 9.6 Hz), 3.79 (s, 3 H), 3.76 (m, 1 H), 3.19 (broad, 1 H), 2.82 (complex m, 3 H), 2.58 (q, 2 H, J = 7.3 Hz), 2.33 (dd, 1 H, J = 14.2, 6.5 Hz), 2.01 (m, 3 H), 1.83 (m, 2 H), 1.64 (s, 3 H), 1.62 (s, 3 H), 1.25 (d, 3 H, J = 7.3 Hz), 1.22 (d, 3 H, J = 7.3 Hz), 1.11 (t, 3 H, J = 7.5 Hz), 1.09 (d, 3 H, J = 7.1 Hz), 1.02 (d, 3 H, J = 7.3 Hz), 0.97 (t, 3 H, J = 7.5 Hz), 0.86 (d, 3 H, J = 6.7 Hz). Major diastereomer (R_f = 0.22): IR (CCl_4) 3527, 2968, 1718, 1707, 1615, 1514 cm^{-1}; ^1H NMR ($CDCl_3$, 250 MHz, partial) δ 7.35 (d, 2 H), 6.84 (d, 2 H), 5.12 (t, 1 H, J = 7.5 Hz), 4.19 (dd, 1 H, J = 10.6, 3.3 Hz), 4.06 (m, 1 H), 3.83 (dd, 1 H), 3.81 (s, 3 H), 3.07 (broad, 1 H), 2.82 (m, 3 H), 2.57 (q, 2 H, J = 7.5 Hz), 2.37 (dd, 1 H); HRMS (CI, M + H) calcd for $C_{32}H_{50}O_6$(H), 531.3687; found, 531.3661. Other diastereomer (R_f = 0.21): ^1H NMR ($CDCl_3$, 250 MHz, partial) δ 7.30 (d, 2 H), 6.82 (d, 2 H), 5.15 (t, 1 H, J = 7.3 Hz), 4.28 (dd, 1 H, J = 10.4, 2.9 Hz), 4.10 (m, 1 H), 3.88 (dd, 1 H), 3.79 (s, 3 H), 3.09 (broad, 1 H), 2.72 (m, 3 H), 2.58 (q, 2 H, J = 7.5 Hz), 2.32 (dd, 1 H).

Oxalyl chloride (0.05 mL, 0.52 mmol) was dissolved in 1.0 mL of CH_2Cl_2 and cooled to -78 °C. DMSO (0.07 mL, 1.01 mmol) in 0.5 mL of CH_2Cl_2 was added, and the mixture was stirred for 3 min. The β-hydroxy ketones (48 mg, 0.09 mmol) (vide supra) in 1.5 mL of CH_2Cl_2 were added dropwise via a syringe. The resulting solution was stirred for 45 min at -78 °C, after which Et_3N (0.24 mL, 1.72 mmol) was added. The mixture was stirred an additional 20 min at -78 °C and then warmed to 0 °C for 10 min. The contents were diluted with saturated NH_4Cl solution, allowed to warm to room temperature, and extracted with CH_2Cl_2. The combined organic layers were washed with brine. Workup (Na_2SO_4) and flash chromatography (20% EtOAc/hexanes) provided 39 mg (81%) of pure β-diketones **26a** and **26b** (2.7:1.0) as determined by HPLC. Partial separation could be achieved by careful flash chromatography (10% EtOAc/hexanes) to provide enriched samples of both diastereomers. Trione **26a** (6.6:1.0): IR (CCl_4) 2979, 1722, 1706, 1700, 1696, 1616, 1514 cm^{-1}; ^1H NMR ($CDCl_3$, 250 MHz) δ 7.28 (d, 2 H), 6.83 (d, 2 H), 5.07 (t, 1 H, J = 7.2 Hz), 4.25 (dd, 1 H, J = 10.2, 3.0 Hz), 3.95 (q, 1 H, J = 7.0 Hz), 3.92 (dd, 1 H, J = 10.2, 5.0 Hz), 3.79 (s, 3 H), 2.90 (m, 1 H), 2.74 (m, 2 H), 2.55 (q, 2 H, J = 7.2 Hz), 2.19 (dd, 1 H, J = 13.4, 6.5 Hz), 1.96 (m, 2 H), 1.79 (m, 2 H), 1.62 (s, 3 H), 1.60 (s, 3 H), 1.26 (d, 3 H, J = 7.0 Hz), 1.20 (d, 3 H, J = 7.2 Hz), 1.17 (d, 3 H, J = 7.8 Hz), 1.08 (t, 3 H, J = 7.2 Hz), 0.95 (d, 3 H, J = 6.8 Hz), 0.90 (t, 3 H, J = 7.5 Hz), 0.90 (d, 3 H, J = 6.6 Hz); HRMS (CI, M + H) calcd for $C_{32}H_{48}O_6$(H), 529.3531; found, 529.3528. Trione **26b** (1.0:5.3): ^1H NMR ($CDCl_3$, 250 MHz) δ 7.35 (d, 2 H), 6.84 (d, 2 H), 5.14 (t, 1 H, J = 7.2 Hz), 4.24 (dd, 1 H, J = 10.3, 2.9 Hz), 4.13 (q, 1 H, J = 7.0 Hz), 3.85 (dd, 1 H, J = 10.3, 3.3 Hz), 3.80 (s, 3 H), 2.91 (m, 1 H), 2.80 (m, 1 H), 2.71 (m, 1 H), 2.55 (q, 2 H, J = 7.3 Hz), 2.32 (dd, 1 H, J = 12.8, 5.1 Hz), 2.05 (m, 3 H), 1.88 (dd, 1 H, J = 9.3, 4.2 Hz), 1.67 (s, 3 H), 1.64 (s, 3 H), 1.27 (d, 3 H, J = 7.1 Hz), 1.15 (d, 3 H, J = 7.1 Hz), 1.11 (d, 3 H, J = 7.1 Hz), 1.07 (t, 3 H, J = 7.1 Hz), 0.94 (t, 3 H, J = 7.2 Hz), 0.90 (d, 3 H, J = 5.3 Hz), 0.88 (d, 3 H, J = 6.7 Hz).

Denticulatin A (2a). Enriched β-diketone **26a** (28 mg, 0.05 mmol, 4.6:1.0 ratio) was dissolved in 0.6 mL of THF, and 0.6 mL of a 10% aqueous solution of oxalic acid was added. The mixture was stirred for 39 h at room temperature, at which time saturated aqueous $NaHCO_3$ was added and the mixture was extracted with EtOAc. The organic layer was washed with brine, and workup afforded 28 mg of a mixture of **2a**, **2b**, and unhydrolyzed starting material **26** (50% conversion; ^1H NMR integration). Flash chromatography (15% EtOAc/hexanes) gave 6.8 mg (69% yield based on recovered starting material) of pure denticulatins A (**2a**) and B (**2b**) (6:1) and 15 mg of unreacted β-diketone ketals **26a** and **26b** (2.9:1.0): IR (CCl_4) 3521, 3314, 2966, 1718, 1700, 1684 cm^{-1}; ^1H NMR ($CDCl_3$, 250 MHz) δ 6.10 (s, 1 H), 5.15 (t, 1 H, J = 7.0 Hz), 4.40 (dd, 1 H, J = 10.8, 2.8 Hz), 3.63 (dt, 1 H, J = 8.9, 2.5, 2.5 Hz), 3.38 (d, 1 H, J = 9.0 Hz), 2.96 (m, 1 H), 2.77 (q, 1 H, J = 7.3 Hz), 2.52 (complex m, 3 H), 2.21 (dd, 1 H, J = 13.7, 3.6 Hz), 2.00 (m, 2 H), 1.81 (m, 1 H), 1.75 (dd, 1 H, J = 13.3, 9.2 Hz), 1.67 (m, 1 H), 1.59 (s, 3 H), 1.21 (d, 3 H, J = 7.3 Hz), 1.11 (d, 3 H, J = 7.1 Hz), 1.05 (d, 3 H, J = 7.1 Hz), 1.04 (t, 3 H, J = 7.3 Hz), 0.97 (d, 3 H, J = 7.0 Hz), 0.95 (t, 3 H, J = 7.5 Hz), 0.94 (d, 3 H, J = 6.8 Hz); ^{13}C NMR (C_6D_6, 250 MHz) δ 219.4, 210.3, 132.3, 130.0, 103.5, 76.0, 70.2, 51.1, 47.8, 43.4, 43.1, 39.3, 38.3, 33.2, 22.1, 16.4, 16.1, 14.9, 14.0, 12.4, 8.6, 8.4; $[\alpha]^{21}_D$ -43.1° (c 0.33, $CHCl_3$) (lit.[2] $[\alpha]_D$ -30.7° (c 1.49, $CHCl_3$)[17]); HRMS (CI, M + H) calcd for $C_{23}H_{40}O_5$(H), 397.2955; found, 397.2968.

Denticulatin B (2b). Enriched β-diketone **26b** (15 mg, 0.028 mmol, 4.7:1.0) was dissolved in 0.5 mL of THF, and 0.5 mL of a 10% aqueous solution of oxalic acid was added. The mixture was stirred for 45 h at room temperature, at which time the reaction mixture was worked up (vide supra) to provide 12 mg of a mixture **2a**, **2b**, and unhydrolyzed starting material **26** (50% conversion; ^1H NMR integration). Flash chromatography (15% EtOAc/hexanes) gave 4.8 mg (72% yield based on recovered starting material) of pure denticulatins A (**2a**) and B (**2b**) (1:8) as a solid and 6.0 mg of unreacted β-diketone ketals **26a** and **26b** (1.0:1.5): IR ($CHCl_3$) 3437, 2972, 1712, 1695 cm^{-1}; ^1H NMR ($CDCl_3$, 250 MHz) δ 5.34 (s, 1 H), 5.19 (t, 1 H, J = 7.0 Hz), 4.42 (dd, 1 H, J = 10.7, 3.0 Hz), 3.57 (dt, 1 H, J = 8.6, 2.5, 2.5 Hz), 3.09 (d, 1 H, J = 8.8 Hz), 2.95 (q, 1 H, J = 7.0 Hz), 2.69 (m, 1 H), 2.52 (complex m, 3 H), 2.32 (dd, 1 H, J = 13.8, 3.2 Hz), 2.02 (m, 2 H), 1.73 (dd, 1 H, J = 13.7, 10.5 Hz), 1.69 (m, 1 H), 1.66 (m, 1 H), 1.62 (s, 3 H), 1.22 (d, 3 H, J = 7.0 Hz), 1.17 (d, 3 H, J = 7.1 Hz), 1.06 (t, 3 H, J = 7.1 Hz), 1.03 (d, 3 H, J = 6.8 Hz), 0.97 (d, 3 H, J = 7.1 Hz), 0.95 (t, 3 H, J = 7.0 Hz), 0.94 (d, 3 H, J = 6.9 Hz); ^{13}C NMR (C_6D_6, 250 MHz) δ 218.7, 209.7, 132.6, 130.0, 102.7, 77.0, 69.9, 52.7, 47.6, 43.9, 43.2, 42.3, 38.4, 33.1, 22.1, 16.1, 15.7, 15.2, 14.9, 13.8, 12.9, 8.6, 8.2; $[\alpha]^{21}_D$ -32.0° (c 0.44, $CHCl_3$) (lit.[2] $[\alpha]_D$ -26.4° (c 0.39, $CHCl_3$)[18]); HRMS (CI, M + H) calcd for $C_{23}H_{40}O_5$(H), 397.2955; found, 397.2931.

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Supplementary Material Available: ^1H NMR spectra for **15**, **16a**, **16b**, **20a**, **17a**, **17b**, **17b** (cis), **23**, **24**, **25**, 2-methyl-2-(*E*)-pentenyl bromide, RAMP hydrazone of **5**, **5**, **26a**, **26b**, **2a**, and **2b**; ^{13}C NMR spectra of **25**, **2a**, and **2b** (29 pages). Ordering information is given on any current masthead page.

(17) On the basis of the reported rotation, the mixture should have a calculated specific rotation of -31°.

(18) On the basis of the reported rotation, the mixture should have a calculated specific rotation of -26°.