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Stereoselective Synthesis of the C1−C13 Fragment of 2,3-Dihydrodorrigocin A

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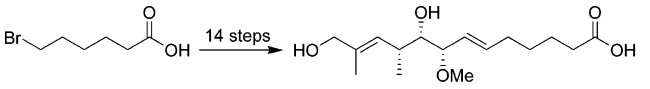


C1-C13 fragment of 2,3-dihydro-dorrigocin A

The first synthesis of the C1−C13 fragment of 2,3-dihydrodorrigocin A has been achieved from 6-bromohexanoic acid in 14 linear steps and an overall yield of 2%. The configurations of the stereogenic centers C8, C9, and C10 have been determined to be the same as for migrastatin.

Dorrigocins A and B along with migrastatins A and B represent a new class of natural products isolated from *Streptomyces platensis*[1] (Figure 1). In the context of our oncology program, we focused our attention on dorrigocin A, which presented the potential ability[2] to block the activation of the Ras pathway involved in the control of tumor cell growth, differentiation, migration, and survival.[3]

Njardarson et al.[4] have shown that migrastatin A was able to inhibit cell migration in 4T1 mouse breast tumor cells. More interestingly, the macrolactone core of migrastatin A was much more potent than the natural product itself. We hypothesized that the analogous core structure of dorrigocin may also provide interesting biological activities and set out to prepare derivative **1** (Scheme 1). As the configuration of the stereogenic centers of dorrigocins was unknown, we made the hypothesis that the C1−C13 fragment of dorrigocin would have the same stereochemistry as the migrastatin core.

We embarked on the synthesis of the 2,3-dihydrodorrigocin A fragment by a retrosynthetic analysis starting with the C11−C12 disconnection leading to the retron **2** (Scheme 1). Cleavage of the C9−C10 bond gave rise to the aldehyde **3**, which is now set for an aldol addition and the subsequent control of two stereogenic centers. The C6−C7 double bond represents the last disconnection affording the phenyltetrazole sulfone **4**, precursor for a Julia−Kocieñski[5] coupling. As depicted in Scheme 2, the

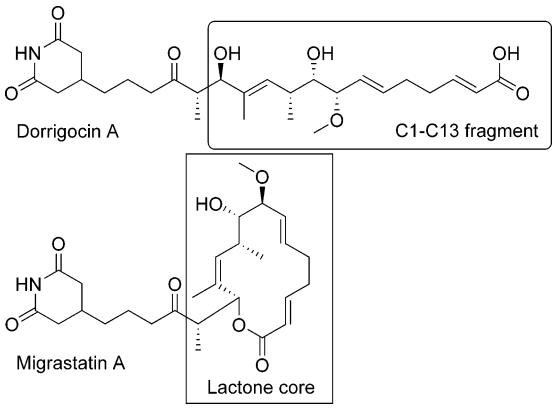
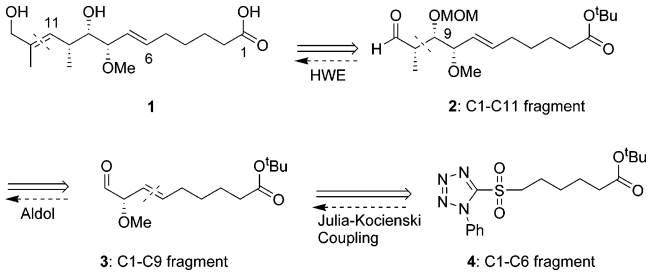


FIGURE 1. Structures of dorrigocin A and migrastatin A.

SCHEME 1. Retrosynthetic Analysis of the C1−C13 Fragment of 2,3-Dihydrodorrigocin A



sulfone **4**,[6] easily available in three steps from 6-bromohexanoic acid, is reacted with the aldehyde **5**[7] in the presence of KHMDS at low temperature to give the non-6-enoic acid *tert*-butyl ester derivative **6** as a 1:1 mixture of *E*/*Z* isomers. Upon heating and treatment with thiophenol and AIBN, the alkene **6** is converted into a 9:1 mixture of isomers amenable to produce, after cleavage of the TBDPS ether with TBAF and oxidation using the Dess−Martin reagent, the aldehyde **8**.

At this stage, the Evans asymmetric aldol reaction using the boron enol ether of **9** afforded the product **10** in good yield and with excellent syn/syn selectivity[8] (Scheme 3). After protection of the secondary alcohol of **10** as a methoxymethyl ether, the chiral auxiliary was reduced to give the alcohol **12** in moderate yield.

The alcohol **12** was then oxidized into the aldehyde **13** followed by a coupling reaction with the stabilized phosphorilidene **14** to generate the diester **15** with acceptable yield and excellent control of the double bond stereochemistry. For the next step which required the chemoselective reduction of an α,β-unsaturated ethyl ester in the presence of a *tert*-butyl ester, we first tried DIBAL at low temperature without success. However, lithium borohydride in the presence of 1 equiv of methanol[9] selectively reduced the ethyl ester to give the alcohol

(1) Hochlowski, J. E.; Whittern, D. N.; Hill, P.; McAlpine, J. B. *J. Antibiot.* **1994**, *47*, 870−874.
(2) Kadam, S.; McAlpine, J. B. *J. Antibiot.* **1994**, *47*, 875−880.
(3) Kloog, Y.; Cox, A. D. *Mol. Med. Today* **2000**, *6*, 398−402.
(4) Njardarson, J. T.; Gaul, C.; Shan, D.; Huang, X.-Y.; Danishefsky, S. J. *J. Am. Chem. Soc.* **2004**, *126*, 1038−1040.
(5) Blakemore, P. R.; Cole, J. C.; Kocieński, P. J.; Morley, A. *Synlett* **1998**, 26−28.
(6) See the Supporting Information for experimental details.
(7) Nicolaou, K. C.; Piscopio, A. D.; Bertinato, P.; Chakraborty, T. K.; Minowa, N.; Koide, K. *Chem. Eur. J.* **1995**, 318−33.
(8) No other diastereomers were detected on the crude ^{1}H NMR or during the purification by column chromatography.

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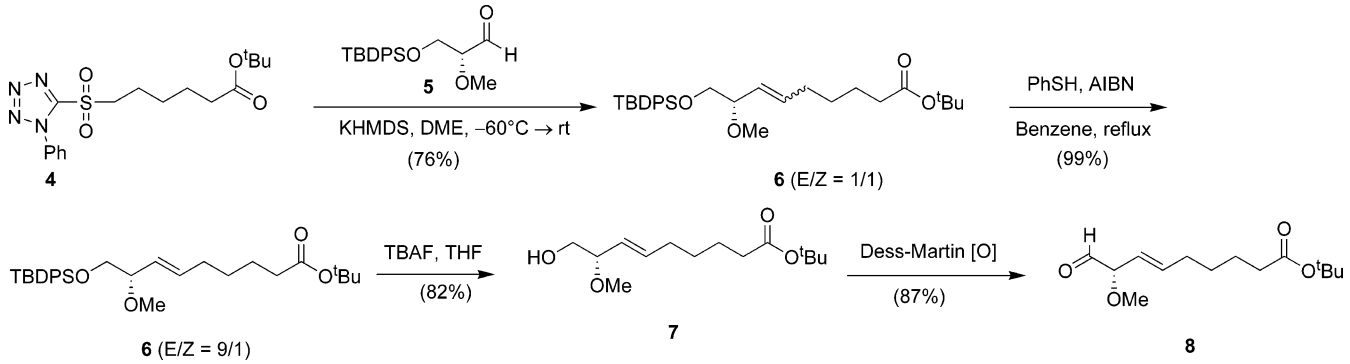
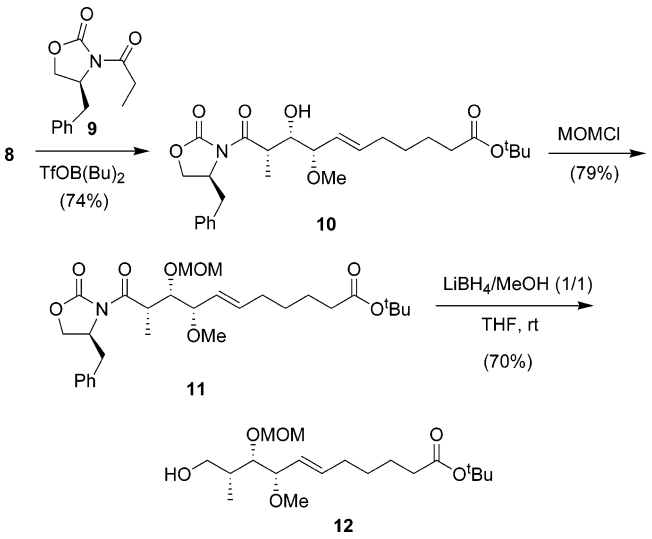
SCHEME 2. Synthesis of Aldehyde 8



SCHEME 3. Synthesis of *tert*-Butyl Ester 12



16 with moderate yield (Scheme 4). Finally, the MOM ether and the *tert*-butyl ester were cleaved under acidic conditions to give the C1−C13 fragment of dorrigocin A with moderate yield.

To confirm the stereochemistry of the stereogenic centers, the Mosher esters[10] of the aldol adduct **10** were prepared following a literature precedent[9] (see the Supporting Information). As the chemical shift differences were unexpectedly negative and positive on both sides of carbon 9, this method was considered inconclusive as reported in some cases.[11] We then carried out a fragmentation study of **12** which was first converted into the dioxane **18** using acidic conditions (Scheme 5).

The small coupling constant between H9 and H10 (2.1 Hz) corresponds to a *cis* axial−equatorial relative stereochemistry which confirms the *syn* relationship between the C9−OH and C10-Me. Second, the treatment of **12** with RuO_4 and methyl orthoformate produced a mixture of anomers **19**α and **19**β. As the coupling constants between H8 and H9 (9.3 Hz for **19**α and 8.5 Hz for **19**β) are in the range expected for a *trans* diaxial relative stereochemistry, the MeO and MOM groups are confirmed to be *syn* in the compound **12**. In addition to confirming the stereochemistry of the three stereogenic centers of the C1−C13 fragment of dorrigocin A, the coupling constants and the chemical shifts of H8 and H9 were compared to the published data (Table 1) for dorrigocin A.[1] The excellent match led us to conclude that the configurations of the stereogenic centers of dorrigocin A and migrastatin are the same. Finally, our stereochemistry assignment has been corroborated by the work of Ju et al. who have recently shown that dorrigocin and migrastatin were shunt metabolites of isomigrastatin.[12]

TABLE 1. Chemical Shifts and Coupling Constants of H8 and H9

	dorrigocin A	compound **1**
H8	3.54 (dd, J = 4.1, 8.6 Hz)	3.49 (dd, J = 4.1, 8.6 Hz)
H9	3.21 (dd, J = 4.1, 6.9 Hz)	3.17 (dd, J = 4.2, 7.0 Hz)

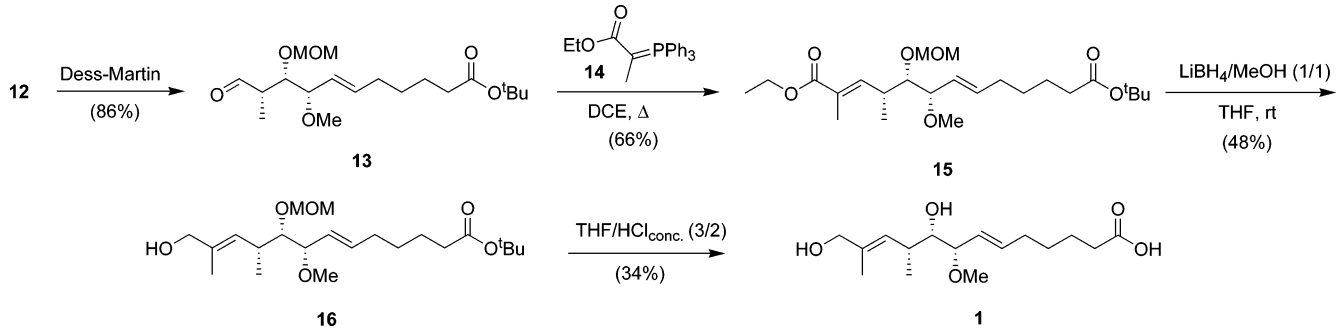
In conclusion, this synthetic effort has led to the production of an advance fragment of dorrigocin A, for which the configuration of the three contiguous stereogenic centers was assigned. This work contributes to shed light on a new family of natural products which have been of interest for synthetic chemists due to their complexity and their biological activity.

Experimental Section

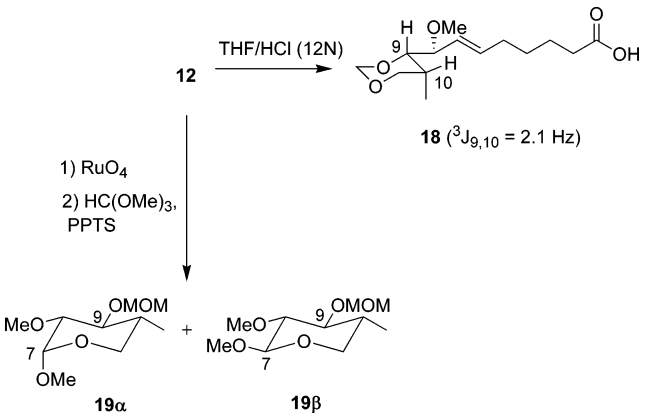
(*S*)-9-(*tert*-Butyldiphenylsilanyloxy)-8-methoxynon-6-enoic Acid *tert*-Butyl Ester 6. To a solution of sulfone **4** (14.0 g, 36.6 mmol) in anhydrous DME at −78 °C was added KHMDS (88.0 mL, 43.9 mmol, 0.5 M solution in toluene). The resulting orange solution was stirred for 0.5 h, after which time a solution of aldehyde **5** (8.00 g, 36.6 mmol) in DME (40 mL) was added via cannula. The reaction was stirred for 3.0 h during which time it was allowed to warm to rt. The reaction solution was then diluted with H_2O (100 mL) and extracted with ethyl acetate (3 × 100 mL). The combined organics were dried (Na_2SO_4) and concentrated under reduced pressure. The viscous, orange oil was purified on a column of silica gel (ethyl acetate/ hexane, 1:4, v/v), affording 13.8 g (76%) of alkene **6** as a colorless oil consisting of a 6:4 ratio of *E*/*Z* isomers. This mixture was dissolved in benzene (125 mL) and benzenethiol (1.5 mL) and AIBN (2.98 g, 18.1 mmol) were added whereupon it was refluxed for 20 h, during which time an additional 3 equiv of AIBN was added successively. Solvent was removed under reduced pressure, and the resulting viscous, yellow oil was purified by column chromatography (ethyl acetate/hexane, 1:4, v/v), affording 17.9 g (99%) of **6** as a colorless oil consisting of a 9:1 ratio of *E*/*Z* isomers: ^{1}H NMR ($CDCl_3$, 400 MHz) δ *E* isomer: 7.68 (m, 4H),

(9) Zhang, W.; Carter, R. G.; Yokochi, A. F. T. *J. Org. Chem*. **2004**, *69*, 2569−2572.
(10) Ohtani, I.; Kusumi, T.; Kashman, Y.; Kakisawa, H. *J. Am. Chem. Soc.* **1991**, *113*, 4092−4096.
(11) Seco, J. M.; Quiòoá, E.; Riguera, R. *Chem. Rev.* **2004**, *104*, 17−117.
(12) Ju, J.; Lim, S.-K.; Jiang, H.; Shen, B. *J. Am. Chem. Soc.* **2005**, *127*, 1622−1623.

SCHEME 4. Achievement of the Synthesis of the C1−C13 Fragment of 2,3-Dihydrodorrigocin A



SCHEME 5. Fragmentation Study of the *tert*-Butyl Ester 12



7.39 (m, 6H), 5.65 (dt, J = 15.5, 6.6 Hz, 1H), 5.28 (dd, J = 15.4, 7.5 Hz, 1H), 3.72 (m, 1H), 3.61 (m, 2H), 3.29 (s, 3H), 2.21 (t, J = 7.3 Hz, 2H), 2.05 (q, J = 7.2 Hz, 2H), 1.59 (dd, J = 7.7, 3.99 Hz), 1.43 (s, 9H), 1.40 (m, 2H), 1.04 (s, 9H); *Z* isomer: 5.60 (br dt, J = 11.1, 7.8 Hz, 1H), 5.215 (ddt, J = 11.0, 9.1, 1.6 Hz, 1H), 3.54 (dd, J = 10.6, 4.9 Hz, 1H), 3.30 (s, 3H), 2.04−2.01 (m, 1H), 1.96−1.85 (m, 1H), 1.35−1.31 (m, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 173.1, 135.6, 134.6, 133.8, 129.5, 128.0, 127.6, 83.1, 80.0, 66.7, 56.6, 35.4, 32.0, 28.6, 28.1, 26.8, 24.6, 19.2; HRMS calcd for $C_{30}H_{44}O_4Si$ (M + Na)$^+$ 519.2901, found 519.2910.

(8*S*,9*S*,10*S*)-11-(4-Benzyl-2-oxooxazolidin-3-yl)-9-hydroxy-8-methoxy-10-methyl-11-oxoundec-6-enoic Acid *tert*-Butyl Ester 10:

(*S*)-9-Hydroxy-8-methoxynon-6-enoic Acid *tert*-Butyl Ester 7. To a solution of *tert*-butyldiphenylsilyl ether **6** (10.7 g, 21.5 mmol) in CH_2Cl_2 (250 mL) was added TBAF (32.3 mL, 32.3 mmol; 1.0 M solution in THF). After 3 h, it was washed with H_2O (2 × 100 mL), dried with Na_2SO_4, and concentrated under reduced pressure to give a pale yellow oil which was purified on a column of silica gel (ethyl acetate/hexane, 4:5, v/v), affording 4.5 g (82%) of the alcohol **7**: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 5.59 (dt, J = 15.5, 6.7 Hz, 1H), 5.14 (dd, br, J = 15.5, 8.0 Hz, 1H), 3.51 (m, 1H), 3.38 (d, 6.3 Hz, 2H), 3.16 (s, 3H), 2.82 (s, br, 1H), 2.07 (t, J = 7.5, 2H), 1.94 (q, J = 7.0 Hz, 2H), 1.44 (m, 2H), 1.30 (s, 9H), 1.29 (m, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 172.6, 135.3, 126.7, 82.8, 79.6, 65.1, 55.8, 34.9, 31.6, 28.1, 27.8, 24.2; HRMS calcd for $C_{14}H_{24}O_4$ (M + Na)$^+$ 281.1723, found 281.1719.

(*S*)-8-Methoxy-9-oxonon-6-enoic Acid *tert*-Butyl Ester 8. To a solution of alcohol **7** (1.48 g, 5.73 mmol) in CH_2Cl_2 (60 mL) at room temperature was added Dess−Martin periodinane (2.92 g, 6.88 mmol). The reaction was stirred for 4 h, at which time it was diluted with H_2O (50 mL) and extracted with ethyl acetate (3 × 50 mL). The dried organics (Na_2SO_4) were concentrated under reduced pressure, affording 1.28 g (87%) of aldehyde **8** as a colorless oil: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 9.50 (d, J = 1.5 Hz, 1H), 5.88 (dt, J = 15.5, 6.6 Hz, 1H), 5.32 (dd, br, J = 15.6, 7.2 Hz, 1H), 4.05 (d, J = 7.2 Hz, 1H), 3.42 (s, 3H), 2.22 (t, J = 7.3 Hz, 2H), 2.13 (q, J = 7.4 Hz, 2H), 1.61 (m, 2H), 1.44 (s, 9H), 1.44 (m, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 199.3, 172.8, 138.0, 122.3, 86.8, 79.9, 56.8, 35.1, 32.1, 28.1, 28.0, 24.4.

To a solution of (*S*)-(+)-4-benzyl-3-propionyl-2-oxazolidinone (0.83 g, 3.56 mmol) in CH_2Cl_2 (50 mL) at 0 °C were added dibutyl borontriflate (3.92 mL, 3.92 mmol; 1.0 M solution in CH_2Cl_2) and Hunig's base (0.55 g, 4.27 mmol). The solution was stirred at 0 °C for 30 min and then cooled to −78 °C, at which time a solution of aldehyde **8** (0.92 g, 3.56 mmol) in CH_2Cl_2 was added dropwise over 5 min. The reaction was allowed to warm to rt over 18 h. The solution was quenched with 0.5 mL of H_2O_2 and 2.0 mL of MeOH and was stirred at rt for an additional 0.5 h. The resulting solution was absorbed directly onto silica gel (2 g) under reduced pressure and purified by column chromatography (ethyl acetate/hexane, 2:3, v/v) to give 1.3 g (74%) of oxazolidinone **10** as a colorless oil: $[\alpha]^{20}_D$ = +44.8 (*c* 1.25, CH_2Cl_2); IR (KBr, cm^{-1}) ν_{max} = 2974, 2935, 1778, 1726, 1697, 1453, 1386, 1366, 1208, 1151, 1098, 979; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.34−7.26 (m, 3H), 7.22−7.20 (m, 2H), 5.75 (dt, J = 15.5, 6.7 Hz, 1H), 5.32 (dd, J = 15.5, 9.0 Hz, 1H), 4.65 (m, 1H), 4.19, (m, 2H), 3.90 (m, 2H), 3.45 (dd, J = 8.9, 6.8 Hz, 1H), 3.32 (dd, J = 7.3, 3.2 Hz, 1H), 3.28 (s, 3H), 2.79 (d, J = 3.1 Hz, 1H), 2.74 (dd, J = 9.8, 8.4 Hz, 1H), 2.22 (t, J = 7.5 Hz, 2H), 2.11 (q, J = 6.7 Hz, 2H), 1.6 (m, 2H), 1.43 (m, 2H), 1.43 (s, 9H), 1.24 (d, J = 6.0 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 175.3, 172.8, 152.9, 136.8, 135.4, 129.4, 128.8, 127.1, 126.5, 84.7, 79.7, 73.4, 66.0, 55.8, 55.4, 39.8, 37.6, 35.1, 31.8, 28.2, 28.0, 24.4, 11.1; HRMS for $C_{27}H_{39}NO_7$ (M + Na)$^+$ 512.2619, found 512.2608.

(8*S*,9*S*,10*R*)-11-Hydroxy-8-methoxy-9-methoxymethoxy-10-methylundec-6-enoic Acid *tert*-Butyl Ester 12:

(8*S*,9*S*,10*S*)-11-(4-Benzyl-2-oxooxazolidin-3-yl)-8-methoxy-9-methoxymethoxy-10-methyl-11-oxoundec-6-enoic Acid *tert*-Butyl Ester 11. To a solution of the secondary alcohol **10** (3.76 g, 7.64 mmol) in anhydrous DCE (100 mL) at room temperature were added DMAP (0.28 g, 2.29 mmol), Hunig's base (1.48 g, 11.5 mmol), and chloromethylmethyl ether (1.23 g, 15.3 mmol). The reaction was stirred at 60 °C for 20 h. The reaction solution was diluted with H_2O (100 mL), extracted with CH_2Cl_2 (3 × 100 mL), dried with Na_2SO_4, and concentrated under reduced pressure to give a colorless oil that was purified on a column of silica gel (ethyl acetate/hexane, 1:1, v/v), affording 3.2 g (79%) of **11** as a colorless oil: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.28 (m, 5H), 5.19 (dt, J = 15.5, 6.7 Hz, 1H), 5.43 (dd, br, J = 15.5, 8.7 Hz, 1H), 4.71 (dd, J = 49.6, 6.9 Hz, 2H), 4.55 (m, 1H), 4.16 (m, 2H), 3.92 (m, 2H), 3.59 (dd, J = 8.6, 6.2 Hz, 1H), 3.33 (dd, J = 7.4, 3.4 Hz, 1H), 3.34 (s, 3H), 3.18 (s, 3H), 2.73 (dd, J = 13.3, 10.0 Hz, 1H), 2.10 (t, J = 7.6 Hz, 2H), 2.10 (q, J = 7.1 Hz, 2H), 1.59 (m, 2H), 1.42 (s, 9H), 1.42 (m, 2H), 1.21 (d, J = 6.7 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 174.8, 173.0, 153.1, 136.0, 135.6, 129.4, 128.9, 127.2, 126.5, 98.1, 84.8, 80.6, 79.9, 66.1, 56.2, 56.1, 39.7, 37.8, 35.3, 31.9, 28.4, 28.0, 24.5, 11.4; HRMS calcd for $C_{14}H_{24}O_4$ (MH)$^+$ 534.3061, found 534.3050.

To a solution of the oxazolidinone **11** (3.10 g, 5.81 mmol) in anhydrous THF (60 mL) at room temperature was added MeOH (464 mg, 14.5 mmol) followed by lithium borohydride (7.25 mL, 14.5 mmol; 2.0 M solution in toluene). The reaction was stirred for 1.5 h whereupon it was quenched with silica gel (2 g). Solvent removal in vacuo followed by purification on a column of silica gel (hexane/ethyl acetate, 1:1, v/v) afforded 1.46 g (70%) of alcohol

12 as a colorless oil: $[\alpha]^{20}_D = -2.8$ (*c* 5.0, CH_2Cl_2); IR (KBr, cm^{-1}) ν_{max} = 3418, 2930, 1754, 1455, 1367, 1151, 1032; ^1H NMR ($CDCl_3$, 400 MHz) δ 5.68 (dt, J = 15.4, 6.8 Hz, 1H), 5.27 (dd, br, J = 15.6, 8.2 Hz, 1H), 4.74 (dd, J = 32.2, 6.7 Hz, 2H), 3.63 (dd, J = 7.46, 3.08 Hz, 1H), 3.48 (t, J = 6.8 Hz, 2H), 3.39 (s, 3H), 3.22 (s, 3H), 3.16 (t, J = 6.8 Hz, 1H), 2.18 (t, J = 7.3 Hz, 2H), 2.16 (q, J = 7.0 Hz, 2H), 1.83 (m, 1H), 1.55 (m, 2H), 1.40 (s, 9H), 1.39 (m, 2H), 0.78 (d, J = 6.9 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 173.0, 135.6, 126.7, 98.8, 84.8, 80.5, 80.0, 64.6, 56.0, 55.8, 36.5, 35.2, 31.9, 28.4, 28.0, 24.5, 10.2; HRMS calcd for $C_{19}H_{36}O_6$ $(M + Na)^+$ 383.2404, found 383.2403.

(8*S*,9*S*,10*R*)-8-Methoxy-9-methoxymethoxy-10,12-dimethyltrideca-6,11-dienedioic Acid 13-*tert*-Butyl Ester 1-Ethyl Ester 15:

(8*S*,9*S*,10*R*)-8-Methoxy-9-methoxymethoxy-10-methyl-11-oxoundec-6-enoic Acid *tert*-Butyl Ester 13. To a solution of alcohol **12** (1.46 g, 4.05 mmol) in CH_2Cl_2 (50 mL) was added DMP (2.03 g, 4.80 mmol). After 1 h, the solvent was removed in vacuo. Purification of the oily white solid by silica gel chromatography (1:1 hexane/ethyl acetate) gave 1.25 g (86%) of aldehyde **13** as a colorless oil: ^1H NMR ($CDCl_3$, 400 MHz) δ 9.74 (s, 1H), 6.70 (dd, J = 10.7, 1.4 Hz, 1H), 5.68 (dt, J = 15.5, 6.8 Hz, 1H), 5.32 (dd, br, J = 15.6, 8.2 Hz, 1H), 4.70 (dd, J = 32.0, 6.9 Hz, 2H), 3.91 (t, J = 4.57, 1H), 3.58 (dd, J = 8.3, 5.07, 1H), 3.31 (s, 3H), 3.18 (s, 3H), 2.57 (m, 1H), 2.18 (t, J = 7.5, 2H), 2.08 (q, J = 7.5, 2H), 1.55 (m, 2H), 1.41 (s, 9H), 1.40 (m, 2H), 1.04 (d, J = 6.9 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 202.8, 172.9, 136.1, 126.5, 97.6, 82.6, 80.6, 80.0, 56.2, 55.9, 48.2, 35.3, 32.0, 28.4, 28.1, 24.5, 8.72; HRMS calcd for $C_{19}H_{34}O_6$ $(M + Na)^+$ 381.2247, found 381.2240; HRMS calcd for $C_{19}H_{34}O_6$ $(M + Na)^+$ 381.2247, found 381.2240.

To a solution of aldehyde **13** (0.44 g, 0.994 mmol) in 1,2-dichloroethane (10 mL) at room temperature was added carbethoxyethylidene triphenylphosphorane (1.08 g, 2.98 mmol). The resulting yellow solution was heated to 60 °C for 18 h, at which time TLC showed only partial conversion to the diester **15**. More carbethoxyethylidenetriphenylphosphorane (1.08 g, 2.98 mmol) was added, and reaction was stirred for an additional 18 h at 60 °C whereupon it was concentrated under reduced pressure and by flash chromatography (ethyl acetate/hexane, 1:4, v/v) to afford 0.29 g (66%) of diester **15** as a colorless oil: $[\alpha]^{20}_D = +5.4$ (*c* 1.0, CH_2Cl_2); IR (KBr, cm^{-1}) ν_{max} = 2974, 2935, 1730,1706, 1649, 1453, 1367, 1252, 1151, 1026; ^1H NMR ($CDCl_3$, 400 MHz) δ 6.70 (dd, J = 10.7, 1.4 Hz, 1H), 5.68 (dt, J = 15.5, 6.8 Hz, 1H), 5.32 (dd, br, J = 15.6, 8.2 Hz, 1H), 4.70 (dd, J = 32.0, 6.9 Hz, 2H), 4.18 (q, J = 7.11 Hz, 2H), 3.48 (dd, J = 8.18, 4.86 Hz, 1H), 3.98 (s, 3H), 3.33 (t, J = 6.3 Hz, 1H), 3.19 (s, 3H), 2.85 (m, 1H), 2.20 (t, J = 7.3 Hz, 2H), 2.08 (q, J = 7.2 Hz, 2H), 1.82 (d, J = 2.3 Hz), 1.57 (m, 2H), 1.42 (s, 9H), 1.41 (m, 2H), 1.25 (t, J = 7.1 Hz, 3H), 1.03 (d, J = 6.8 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 173.0, 168.3, 144.4, 135.2, 127.5, 127.0, 98.3, 83.7, 80.0, 60.5, 56.3, 35.3, 35.0, 32.0, 28.5, 28.1, 24.6, 15.0, 14.3, 12.5; HRMS calcd for $C_{24}H_{42}O_7$ $(M + Na)^+$ 465.2823, found 465.2822.

(8*S*,9*S*,10*R*)-9,13-Dihydroxy-8-methoxy-10,12-dimethyltrideca-6,11-dienoic Acid 1:

(8*S*,9*S*,10*R*)-13-Hydroxy-8-methoxy-9-methoxymethoxy-10,12-dimethyltrideca-6,11-dienoic Acid *tert*-Butyl Ester 16. To a solution of the diester **15** (0.076 g, 0.172 mmol) in THF (2.5 mL) at room temperature was added MeOH (0.017 mL, 0.430 mmol) followed by $LiBH_4$ (0.22 mL, 0.430 mmol, 2.0 M solution in toluene). The reaction was stirred for 6 h, whereupon it was quenched with silica gel (0.5 g). Purification of the resulting slurry by column chromatography (ethyl acetate/hexane, 2:3, v/v) provided 0.033 g (48%) of alcohol **16** as a colorless oil: ^1H NMR ($CDCl_3$, 400 MHz) δ 5.60 (dt, J = 15.4, 6.7 Hz, 1H), 5.27 (dd, br, J = 15.8, 7.9 Hz, 1H), 4.58 (d, J = 6.8 Hz, 1H), 4.65 (d, J = 6.8 Hz, 1H), 3.89 (s, 3H), 3.46 (dd, J = 8.2, 2.4 Hz, 1H), 3.33 (s, 3H), 3.18 (t, J = 5.3 Hz, 1H), 3.13 (s, 3H), 2.69 (m, 1H), 2.33 (s, br, 1H), 2.14 (t, J = 7.3 Hz, 2H), 2.02 (q, J = 7.0 Hz, 2H), 1.59 (d, J = 0.9 Hz, 3H), 1.51 (m, 2H), 1.35 (s, 9H), 1.34 (m, 2H), 0.90 (d, J = 6.8 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 172.8, 134.6, 134.1, 128.8, 127.7, 98.2, 84.8, 83.4, 79.8, 68.4, 56.0, 55.8, 35.1, 33.6, 31.8, 28.4, 27.9, 24.4, 15.6, 13.6; HRMS calcd for $C_{22}H_{40}O_6$ $(M + Na)^+$ 423.2717, found 423.2713.

To a 5:2 solution of THF/[HCl] (0.5 mL) at room temperature was added the ester **16**, and the mixture was stirred for 20 h whereupon it was quenched with saturated aqueous $NaHCO_3$ (2.0 mL), washed with ethyl acetate (2 × 4.0 mL), and reacidified with 1 N HCl to pH = 4. The aqueous layer was then extracted with ethyl acetate (2 × 4.0 mL), dried with Na_2SO_4, and concentrated under reduce pressure. The resulting oil was further purified by flash chromatography (acetone/hexane, 1:1, v/v) to give 3.4 mg (34%) of the title compound **1** as a colorless oil: $[\alpha]^{20}_D = +1.3$ (*c* 5.0, CH_2Cl_2); IR (KBr, cm^{-1}) ν_{max} = 2932, 1731, 1454, 1371, 1241, 1155, 1109; ^1H NMR (CD_3OD), 400 MHz) δ 5.71 (dt, J = 15.4, 6.7 Hz, 1H), 5.45 (dd, br, J = 15.5, 8.6 Hz, 1H), 5.29 (dq, J = 10.0, 1.3 Hz, 1H), 3.92 (s, br, 2H), 3.49 (dd, J = 8.6, 4.1 Hz, 1H), 3.19 (s, 3H), 3.17 (dd, J = 7.0, 4.2 Hz, 1H), 2.71 (m, 1H), 2.29 (t, J = 7.3 Hz, 2H), 2.12 (q, J = 7.0 Hz, 2H), 1.67 (d, J = 1.3 Hz, 3H), 1.62 (m, 2H), 1.45 (m, 2H), 0.97 (d, J = 6.7 Hz, 3H); ^{13}C NMR (CD_3OD, 100 MHz) δ 177.6, 138.4, 136.8, 130.0, 129.5, 84.7, 79.2, 68.9, 66.3, 35.8, 34.8, 33.1, 29.8, 25.6, 16.3, 14.0; HRMS calcd for $C_{16}H_{28}O_5$ $(M + Na)^+$ 323.1829, found 323.1827.

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Supporting Information Available: Experimental procedures, HRMS, and ^1H and ^{13}C NMR spectra for **4**, **6**−**8**, **10**−**14**, and **16**−**19**. This material is available free of charge via the Internet at http://pubs.acs.org.

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