Catalytic, Asymmetric Synthesis of Siphonarienal

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This paper describes the synthesis of the marine natural product, siphonarienal. The key step of this synthesis is an aldol reaction that constructs most of the skeleton and sets all three stereocenters of the target in one step from commercially available starting materials. Deoxygenation and chain homologation steps complete the synthesis.

Introduction

Mollusks of the genus *Siphonaria* produce a number of polypropionate natural products.[1] The siphonarienes are one class of such compounds.[2] The members of this class all contain a 2*S*,4*S*,6*S*-trimethylnonane segment connected through an olefinic linker to a more polar, oxygen-containing group (Figure 1). This oxygen-containing group gives the class its diversity, and, presumably, its biological activity. Most of the members of this class are active against Gram-positive bacteria, yeast, and several human cancer cell lines.[2b,d]

Several groups have used chiral auxiliary methodology to synthesize the 2*S*,4*S*,6*S*-trimethylnonane segment. Both Enders and Masamune used iterative alkylations to construct the segment.[3] In a synthesis of siphonarienal, **1**, particularly relevant to the current study, Norté et al. used the diastereoselective aldol reaction of a β-ketoimide to assemble and set the stereochemistry of the trimethylnonyl unit (Scheme 1).[2c] Deoxygenation and homologation led to **1**. We report here a similar route to **1** that, however, starts with a catalytic, asymmetric reaction.

We recently reported a convenient procedure for the conversion of propionic anhydride to polypropionates by a ketene formation/dimerization/opening/aldol reaction sequence.[4] We realized that this sequence would give us ready access to an intermediate very similar to the intermediate in the Norté synthesis of siphonarienal (Scheme 2), and that a similar sequence of deoxygenation and homologation could afford the natural product.

Results and Discussion

The key aldol reaction requires (*S*)-2-methylpentanal, **3**, as an electrophile (Scheme 3). Although alternative syntheses exist,[5] we developed a facile preparation of **3** from **2**. As described earlier, in situ opening of **2** and

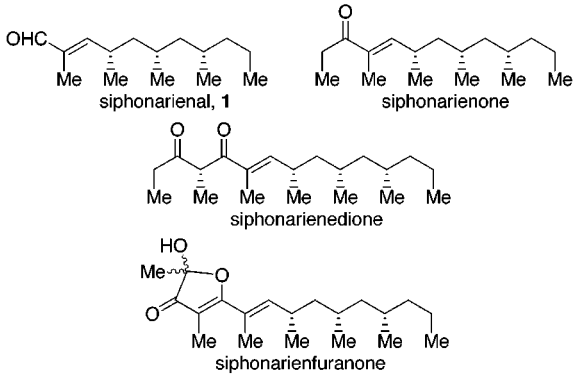
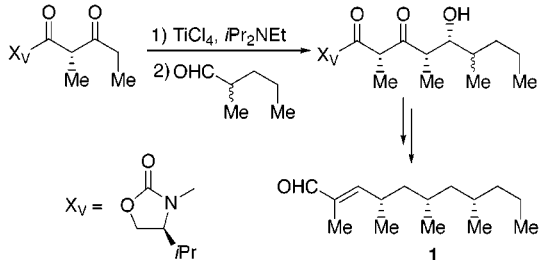
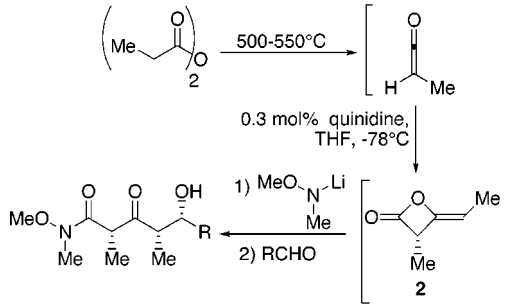


Figure 1. The siphonarienes.

Scheme 1



Scheme 2



reduction yielded β-hydroxyamide **4**.[6] We then converted **4** to **3** by xanthate formation,[7] free radical deoxygenation,[8] and amide reduction.[9]

As described in a previous publication, the key aldol reaction proceeds in high diastereoselectivity and moder-

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(3) (a) Abiko, A.; Masamune, S. *Tetrahedron Lett.* **1996**, *37*, 1081−1084. (b) Birkbeck, A. A.; Enders, D. *Tetrahedron Lett.* **1998**, *39*, 7823−7826.

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(7) Barton, D. H. R.; McCombie, S. W. *J. Chem. Soc., Perkin Trans. 1* **1975**, 1574−1585.

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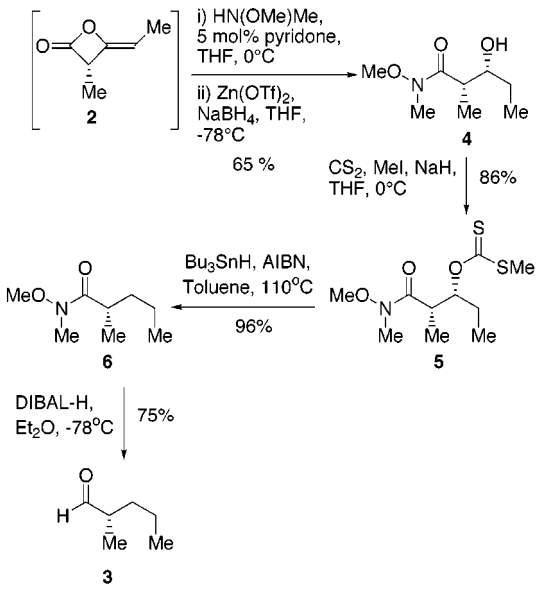
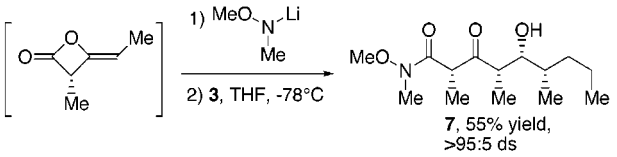
Scheme 3



Scheme 4



ate yield to afford aldol adduct **7** (Scheme 4).[4] The diastereoselectivity of this transformation was quite high, even though this was technically a case of mismatched double stereochemical induction. *Z*-Enolates were reported to favor the anti-Cram diastereomer,[10] and the observed all syn diastereomer results from Cram selective attack on the aldehyde. However, the small difference in size between the large and medium substituents on the chiral center of **3** obviously led to a very moderate facial bias, which was completely overridden by the high preference of the enolate.

In an effort to further increase the practicality of the synthesis, we explored the use of commercially available, racemic 2-methylpentanal (Scheme 5). According to the analysis above, the facial bias of the aldehyde was expected to favor undesired, *R*-(6) diastereomer **8** of the aldol adduct, but only by a moderate amount. In the event, reactions run in THF employing 1.1 equiv of racemic 2-methylpentanal afforded a 1.2:1 mixture of diastereomers, favoring **8**. Separation of this mixture on SiO_2 afforded a 25% yield of **7**. A simple screen of solvents for the reaction revealed that CH_2Cl_2 raised the overall yield and the proportion of the desired diastereomer such that we could isolate **7** in 35% yield. Again, the fact that all the starting materials, including the catalyst, are all commercially available mitigated the low yield of this reaction.

The synthesis of **1** next required deoxygenation. To have the same functional group at both carbons requiring deoxygenation, we first reduced **7** to *syn*-diol **9** (Scheme 6).[11] On the basis of the effectiveness of the Barton–

Scheme 5

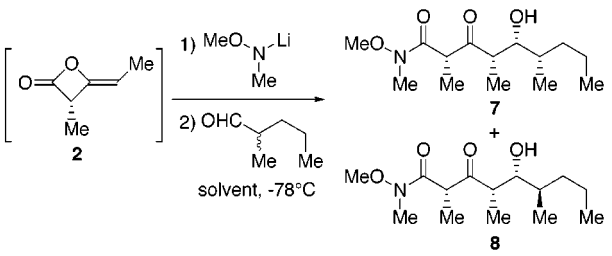
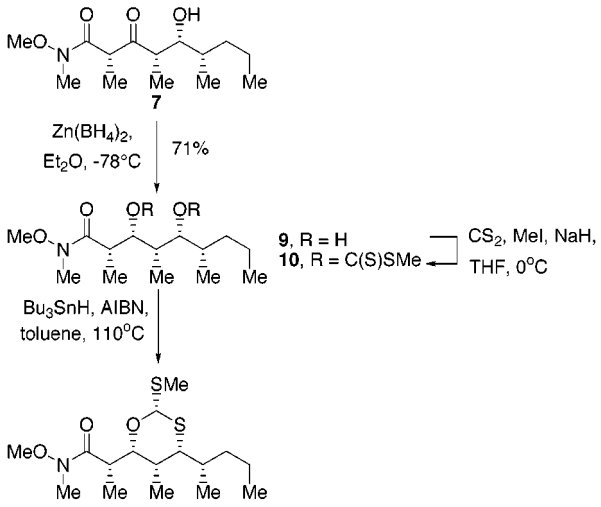


Table 1. Yields and Selectivities of Aldol Reaction

solvent	% yield of **7**	% yield of **8**
THF	25	30
Et_2O	31	29
CH_2Cl_2	35	36

Scheme 6



McCombie decarboxylation of **5**, we initially formed and attempted the deoxygenation of bis-xanthate **10**. However, treatment of this compound under standard conditions led to formation of a cyclic thioortho ester rather than the desired material. Formation of this compound likely occurred by trapping of the intermediate radical by the thiocarbonyl group of the adjacent xanthate. ^{1}H NOE experiments confirmed the all cis stereochemistry for this compound. Numerous other groups have reported the formation of such byproducts in cases where the geometry favors cyclization.[7] Use of a large excess of Bu_3-SnH (50 equiv) or an alternative hydrogen atom source such as $(Me_3Si)_3SiH$[12] did not lead to production of any of the desired compound. Therefore, we decided to test hydride reductions of sulfonates as an alternative deoxygenation strategy.

Diol **9** readily afforded bis-methanesulfonate (bis-mesylate) **11** (Scheme 7). Our initial hope was to selectively reduce the mesylates in the presence of the amide with $LiBEt_3H$.[13] Our earlier work had confirmed that the amide was stable to this reagent at −78 °C. However, the reduction of secondary mesylates generally requires temperatures in excess of 0 °C. At this temperature, the amide apparently reduced first, and subsequent elimination of the *β*-mesylate and further reduction of the

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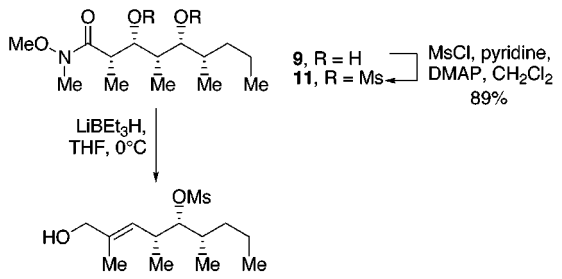
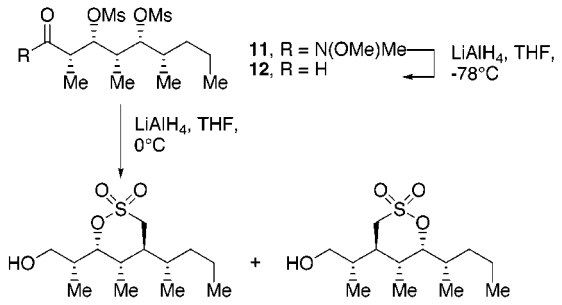
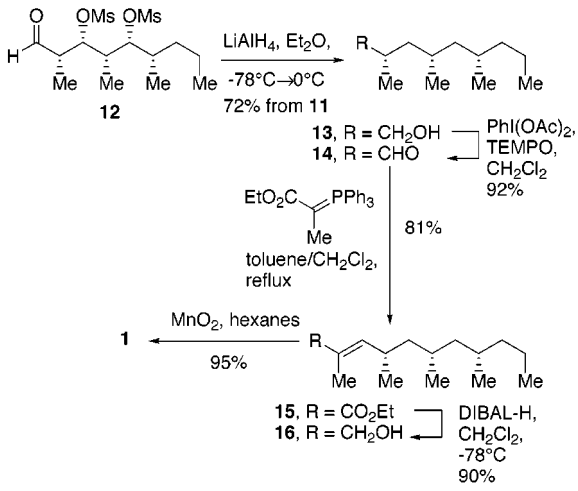
Scheme 7



Scheme 8



Scheme 9



aldehyde yielded an allylic alcohol. Reduction of **11** with $LiAlH_4$ at 0 °C yielded the same alcohol.

The higher reactivity of the amide than the sulfonates allowed us to reduce **11** to aldehyde bis-mesylate **12** with $LiAlH_4$ at −78 °C (Scheme 8). We hoped that exhaustive reduction of **12** would yield alcohol **13**, wherein the aldehyde was reduced to the alcohol and the mesylates displaced to yield the hydrocarbon. However, reduction of **12** with excess $LiAlH_4$ (8 equiv) in tetrahydrofuran (THF) yielded a mixture of regioisomeric, cyclic sulfonates. These products result from deprotonation of the methyl group of one mesylate followed by intramolecular displacement of the other.

Fortunately, the simple modification of running the reaction in ether resulted in formation of **13** to the almost complete exclusion of cyclic sulfonate products (Scheme 9). The remainder of the synthesis proceeded in a fashion similar to that of Norté's,[2c] with a few minor modifications. We found that oxidation of **13** to aldehyde **14** gave higher yields with the iodobenzene diacetate/TEMPO system[14] rather than under the Parikh−Doering conditions.[15] Wittig homologation to **15**, followed by reduction, effectively yielded allylic alcohol **16**. Finally, oxidation of **16** with MnO_2 in hexanes yielded siphonarienal.[16] We found that the use of hexanes for this oxidation gave higher yields than the use of CH_2Cl_2, reported by Norté. The properties of the synthetic material matched those reported for the natural product.

Conclusions

In summary, we completed an efficient synthesis of siphonarienal, proceeding in nine steps and 10.2% overall yield from propionic anhydride and 2-methylpentanal. The first reaction of the synthesis set all the asymmetric centers and constructed most of the carbon backbone of the target. This synthesis further demonstrated the utility of the methylketene dimer in the asymmetric synthesis of polypropionates. Further research into the synthesis of other siphonarienes employing aldehyde **14** continues.

Experimental Section

General Information. Commercial reagents were used directly as received or purified prior to use as described in the literature.[17] Toluene, hexanes, and methylene chloride where purified by distillation over CaH_2 under nitrogen. All reactions were conducted in flame dried, round-bottomed flasks under an atmosphere of dry nitrogen. Tetrahydrofuran and diethyl ether were purified by filtration through activated alumina as described by Grubbs.[18] Zinc borohydride was prepared as described in the literature.[19]

Purification of products by chromatography was performed by forced-flow chromatography on SiliCycle 60 Å, 230−400 mesh silica gel.[20] Thin-layer chromatography (TLC) was accomplished using SiliCycle 0.25 mm thickness, 60 Å pore size silica gel plates. Visualization of the developed TLC was accomplished using fluorescence quenching or anisaldehyde stain.

Mass spectra were obtained from the UC Riverside Mass Spec Facility. Elemental analyses were performed by Robertson Microlit Laboratories.

Formation methylketene Dimer (2) from Propionic Anhydride. The still pot of the pyrolysis apparatus (Figure 2) was charged with 250 mL of propionic anhydride. The variable DC source was adjusted so the nickel−chromium wire glowed red (~40 V), and the propionic anhydride solution was brought to reflux (**Caution:** To avoid the possibility of fire or explosion, it is essential that the system by maintained under a positive pressure of nitrogen during the entire process). The outlet from the pyrolysis device was passed through a −78 °C solution of 10.0 mg (0.031 mmol) of quinidine in 20 mL THF or CH_2Cl_2. The reaction was conducted for the appropriate amount of time to yield 10 mmol of methylketene dimer per hour. This unpurified reaction mixture can be used directly in the following reaction, or **2** could be isolated from CH_2Cl_2 by removal of the solvent under reduced pressure. The yield and optical purity was confirmed by conversion of the dimer into the β-hydroxyamide as described earlier.[6]

[2*S*,3*R*]-3-Hydroxy-*N*-methoxy-*N*,2-dimethylpentanamide (4). To a solution of **2** (0.2100 g, 1.88 mmol) in anhydrous THF (5 mL) was added *N*,*O*-dimethylhydroxylamine (0.1140 g, 1.88 mmol) and 2-hydroxypyridine (8.9 mg, 0.094 mmol) at −78 °C. The mixture was raised to 0 °C and

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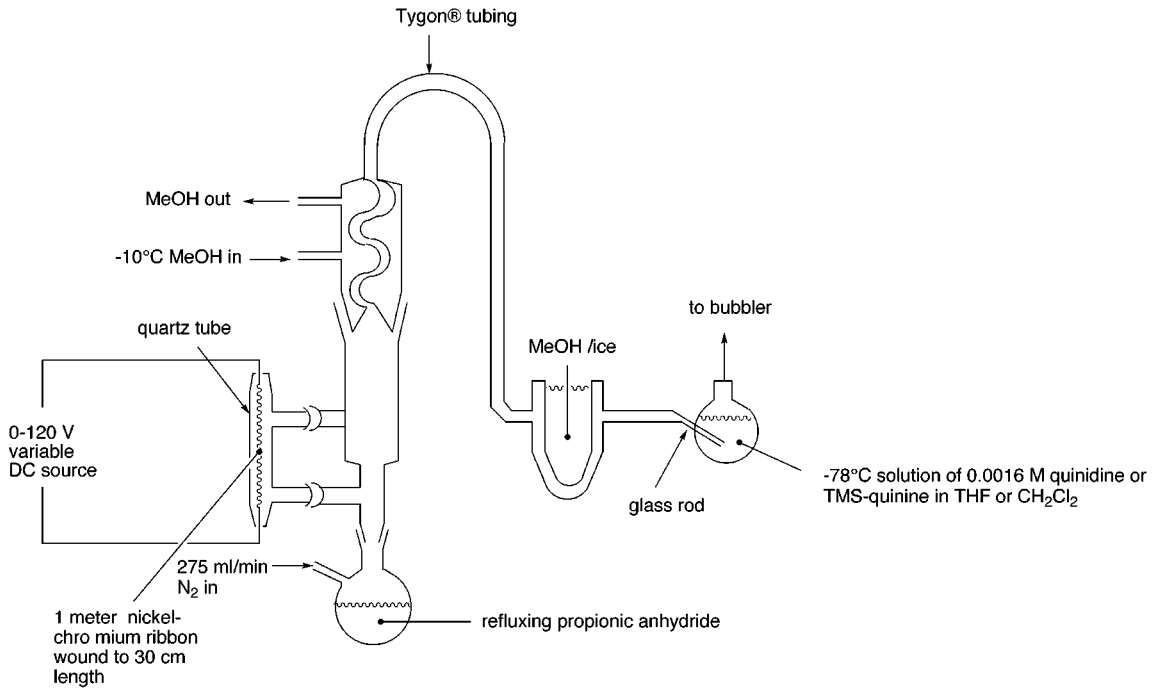

Figure 2. Pyrolysis device.

stirred at the same temperature for 4 h. The reaction was cooled to −78 °C, and zinc triflate (818 mg, 2.25 mmol) in THF (2.5 mL) was added. After 0.5 h, sodium borohydride (213 mg, 5.63 mmol) was added. The mixture was stirred at −78 °C for 2 h and then raised to 0 °C for 0.25 h. The reaction was quenched with 1.0 M HCl (20 mL) and extracted with CH_2Cl_2 (50 mL). The aqueous layer was washed with CH_2Cl_2 (3 × 10 mL). The combined organic extracts were dried (Na_2SO_4), concentrated in vacuo, and purified (SiO_2, 15% EtOAc in hexanes) to afford **4** (0.2145 g, 65%). The analytical data for this compound exactly matched that reported by Cane et al. for the same compound. [21]

[2*S*,3*R*]-3-(Methylsulfanylthiocarboxyoxy)-*N*-methoxy-*N*,2-dimethylpentanamide (5). To a solution of **4** (0.2715 g, 1.55 mmol) in THF (30 mL) were added carbon disulfide (6.75 mL, 112 mmol) and iodomethane (6.70 mL, 108 mmol) at 0 °C. The mixture was stirred at the same temperature for 0.25 h, and then sodium hydride (60% suspension in mineral oil, 136.3 mg, 3.4 mmol) was added. After 20 min at 0 °C, the reaction was quenched by slow addition to 60 g of crushed ice (**Caution:** hydrogen gas evolution). The mixture was raised to room temperature and separated, and the aqueous layer was washed with CH_2Cl_2 (4 × 15 mL). The combined organic extracts were dried (Na_2SO_4), concentrated in vacuo, and purified (SiO_2, 5% EtOAc in hexanes) to afford **5** (0.3535 g, 86%). $[\alpha]^{23}_D = 23.5$ (*c* 0.59, $CHCl_3$); IR (neat film1660 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 5.95 (td, 1 H, $J = 7.2$, 4.8 Hz), 3.67 (s, 3 H), 3.29 (m, 1 H), 3.15 (s, 3 H), 1.82−1.67 (m, 2 H), 1.16 (d, 3 H, 7.0 Hz), 0.90 (t, 3 H, $J = 7.4$ Hz); ^{13}C NMR (100.7 MHz, $CDCl_3$) 216.0, 174.3, 85.6, 61.4, 38.6, 32.2, 24.9, 18.7, 13.4, 9.6. Anal. Calcd for $C_{10}H_{19}NO_3S_2$: C, 45.26; H, 7.22; N, 5.28. Found: C, 45.08; H, 7.19; N, 5.26.

[2*S*]-*N*-Methoxy-*N*,2-dimethylpentanamide (6). A solution of **5** (2.9538 g, 11.1 mmol), tributyltin hydride (15.2 mL, 56.6 mmol), and AIBN (0.1091 g, 0.664 mmol) in toluene (100 mL) was heated to reflux for 1 h. The mixture was cooled, concentrated in vacuo, and purified (SiO_2, 100% hexanes to remove tin byproducts, followed by 10% EtOAc in hexanes to elute product) to afford **5** (1.6918 g, 96%). $[\alpha]^{23}_D = 16.9$ (*c* 0.8, $CHCl_3$); IR (neat film) 1665 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 3.66 (s, 3 H), 3.16 (s, 3 H), 2.86 (m, 1 H), 1.68−1.56 (m, 1 H), 1.37−12.3 (m, 3H), 1.08 (d, 3 H, 6.8 Hz), 0.87 (t, 3 H, $J = 7.0$ Hz); ^{13}C NMR (100.7 MHz, $CDCl_3$) 178.2, 61.4, 36.0, 34.8, 32.3, 20.7, 17.4, 14.0. Anal. Calcd for $C_8H_{17}NO_2$: C, 60.35; H, 10.76; N, 8.80. Found: C, 60.58; H, 10.72; N, 8.78.

[2*S*]-2-Methylpentanal (3). To a solution of **6** (0.5097 g, 3.201 mmol) in Et_2O (21 mL) at −78 °C was added dropwise DIBALH (0.86 mL, 4.8 mmol). After 1 h, the excess DIBALH was quenched by the addition of EtOAc (1.5 mL), and the mixture was stirred an additional 0.25 h at −78 °C. The reaction mixture was then poured into a mixture of tartaric acid (0.5 M aqueous solution, 40 mL) and Et_2O (15 mL). The layers were separated, the aqueous layer washed with Et_2O (3 × 15 mL). The combined organic extracts were dried (Na_2SO_4) and then carefully concentrated in vacuo, using a rotovap bath temperature of 0 °C. Kugel-Rohr distillation (58−62 °C, 100 Torr) afforded **3** (0.2404 g, 75%). The ^1H NMR, ^{13}C NMR, and IR spectra, and optical rotation of this sample matched those reported in the literature for **3**.[22]

[2*S*,4*S*,5*R*,6*S*]-5-Hydroxy-*N*-methoxy-3-oxo-*N*,2,4,6-tetramethylnonanamide (7). To a solution of *N*,*O*-dimethylhydroxylamine (65.0 mg, 1.07 mmol) in hexane (6 mL) was added dropwise BuLi (2.5 M solution in hexanes, 0.428 mL, 1.07 mmol) at −78 °C. The mixture was stirred at the same temperature for 0.5 h. A solution of the methylketene dimer (120 mg, 1.07 mmol) in anhydrous CH_2Cl_2 (20 mL) was cannulated into this mixture at −78 °C, followed after 3 min by the addition of 2-methylpentanal (0.185 mL, 1.50 mmol). The solution was stirred at −78 °C for 0.5 h and then quenched with 1.0 M HCl (1.5 mL). The mixture was raised to room temperature, washed with brine, dried (Na_2SO_4), and concentrated in vacuo. The residue was purified by chromatography on silica gel (21:4 hexanes−EtOAc) to yield aldol adducts **7** (0.1020 g, 35%) and **8** (0.1049 g, 36%). Data for **7**. $[\alpha]^{23}_D = -22.7$ (*c* 0.15, $CHCl_3$); IR (neat film) 3470, 1710, 1660 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 3.95 (q, 1 H, $J = 7.06$ Hz), 3.68 (s, 3 H), 3.60 (dd, 1 H, $J = 7.6$, 3.4 Hz), 3.18 (s, 3 H), 2.88 (qd, 1 H, 7.2, 2.4 Hz), 1.57−1.43 (m, 1 H), 1.31 (d, 3 H, $J = 7.2$ Hz), 1.28−1.17 (m, 2 H), 1.09 (d, 3 H, $J = 7.1$ Hz), 1.06−0.97 (m, 2 H), 0.92 (d, 3 H, $J = 6.6$ Hz), 0.86 (t, 3 H, $J = 7.3$ Hz); ^{13}C NMR (100.7 MHz, $CDCl_3$) δ 211.2, 171.4, 74.6, 61.3, 48.9,

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46.1, 35.1, 34.8, 32.5, 19.5, 15.1, 14.2, 13.0, 10.4. Anal. Calcd for $C_{14}H_{27}NO_4$: C, 61.51; H, 9.95; N, 5.12. Found: C, 61.44; H, 9.92; N, 5.08. Data for **8**. $[\alpha]_D$ −10.3 (*c* 0.11, $CHCl_3$); IR (film) 3500, 1710, 1660 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 3.96 (q, J = 7.1 Hz, 1 H), 3.71 (s, 3 H), 3.59 (m, 1 H), 3.22 (s, 3 H), 2.90 (m, 1 H), 1.35 (d, J = 7.1 Hz, 3 H), 1.11 (d, J = 7.1 Hz, 3 H), 0.91 (t, J = 7.3 Hz, 3 H), 0.80 (d, J = 6.7 Hz, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 211.8, 171.5, 74.54, 61.32, 48.88, 45.83, 34.99, 34.88, 32.53, 19.75, 15.29, 14.37, 14.14, 13.04. Anal. Calcd for $C_{14}H_{27}NO_4$: C, 61.51; H, 9.95; N, 5.12. Found: C, 61.71; H, 9.94; N, 5.09.

[2*S*,4*S*,3*R*,5*R*,6*S*]-3,5-Dihydroxy-*N*-methoxy-*N*,2,4,6-tetramethylnonanamide (9). Zinc borohydride (0.16 M solution in ether, 70 mL, 11 mmol) was added to a solution of **7** (1.98 g, 7.25 mmol) in anhydrous diethyl ether (200 mL) at −78 °C. After 0.5 h, the reaction was quenched by addition of a saturated, aqueous NH_4Cl solution (60 mL). The mixture was warmed to room temperature, washed with brine, and the solvents were removed in vacuo. The residue was then subjected to six cycles of dilution and evaporation with MeOH/formic acid (10 mL of MeOH and 20 μL formic acid for each cycle). The mixture was purified by chromatography (3:1 hexanes:EtOAc) to afford **9** (1.42 g, 71%). $[\alpha]_D$ +3.3 (*c* 0.27, $CHCl_3$); IR (film) 3420, 1640 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 3.95 (dd, J = 7.0, 3.5 Hz, 1 H), 3.73 (s, 3 H), 3.43 (dd, J = 8.7, 2.4 Hz, 1 H), 3.19 (s, 3 H), 3.17 (m, 1 H), 1.79 (m, 1 H), 1.25 (d, J = 7.2 Hz, 3 H), 0.97 (d, J = 6.6 Hz, 3 H), 0.96 (d, J = 7.0 Hz, 3 H), 0.89 (t, J = 7.1 Hz, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 177.0, 80.23, 77.05, 61.58, 38.13, 36.27, 35.70, 34.70, 31.98, 19.45, 15.44, 14.22, 13.74, 5.99. Anal. Calcd for $C_{12}H_{19}NO_4$: C, 61.06; H, 10.61; N, 5.09. Found: C, 60.91; H, 10.55; N, 5.06.

[2*S*,4*S*,3*R*,5*R*,6*S*]-3,5-Dimethanesulfonyl-*N*-methoxy-*N*,2,4,6-tetramethylnonanamide (11). To a solution of **9** (0.25 g, 0.91 mmol) in CH_2Cl_2 (5 mL) were added pyridine (5 mL) and (dimethylamino)pyridine (5 mg, 0.04 mmol), followed by methanesulfonyl chloride (0.35 mL, 0.52 g, 4.5 mmol). After stirring at room temperature for 2 h, the reaction was quenched with dionized water (7.5 mL) and diluted with CH_2Cl_2 (20 mL). The organic layer was separated, washed with brine, and dried (Na_2SO_4), and the solvents were removed in vacuo. The residue was purified by chromatography (4:1 hexanes:EtOAc) to afford **11** (0.35 g, 89%) as a syrup. $[\alpha]_D$ +7.6 (*c* 0.21, $CHCl_3$); IR (film) 1655 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 5.02 (dd, J = 8.4, 2.8 Hz, 1 H), 4.74 (dd, J = 8.4, 2.8 Hz, 1 H), 3.74 (s, 3 H), 3.35 (m, 1 H), 3.20 (s, 3 H), 3.15 (s, 3 H), 3.07 (s, 3 H), 1.31 (d, J = 7.2 Hz, 3 H), 1.26 (s, 3 H), 1.14 (d, J = 6.8 Hz, 3 H), 0.94 (t, J = 6.2 Hz, 3 H), 0.93 (d, J = 6.4 Hz, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 174.0, 87.93, 82.92, 61.66, 38.88, 38.74, 38.03, 37.82, 36.74, 34.31, 32.14, 20.09, 14.55, 14.10, 12.93, 10.99. Anal. Calcd for $C_{16}H_{33}NO_8S_2$: C, 44.53; H, 7.71; N, 3.25. Found: C, 44.38; H, 7.67; N, 3.22.

[2*S*,4*S*,6*S*]-2,4,6-Trimethyl-1-nonanol (13). Lithium aluminum hydride (1.0 M solution in diethyl ether, 2.0 mL, 2.0 mmol) was diluted with anhydrous diethyl ether (20 mL) at −78 °C. To this solution was added, via cannula, a solution of **11** (0.180 g, 0.417 mmol) in diethyl ether (30 mL, cooled to −78 °C). After stirring at −78 °C for 0.5 h, the reaction was quenched by addition of HCl (1.0 M, exactly 4.5 mL). The mixture was raised to room temperature, washed with brine, dried ($MgSO_4$), and solvents were removed in vacuo. To the residue was added anhydrous ether (30 mL), the mixture cooled to −78 °C, and $LiAlH_4$ (1.0 M solution in ether, 3.5 mL, 3.5 mmol) was added. The mixture was stirred at −78 °C for 10 min, and then raised to 0 °C. After keeping at 0 °C for 6 h, the reaction was quenched with HCl (1.0 M, 12 mL), washed with brine, and dried ($MgSO_4$), and the solvents were removed in vacuo. The residue was purified by flash chromatography on silica gel (60:1 hexanes:EtOAc) to afford **13** (56.5 mg, 72%) as a colorless oil. $[\alpha]_D$ +3.5 (*c* 0.20, $CHCl_3$); IR (film) 3335 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 3.54 (dd, J = 10.5, 5.0 Hz, 1 H), 3.37 (dd, J = 10.5, 6.9 Hz, 1 H), 1.73 (m, 1 H), 0.93 (d, J = 6.7 Hz, 3 H), 0.89 (t, J = 7.4 Hz, 3 H), 0.87 (d, J = 6.5 Hz, 3 H), 0.84 (d, J = 6.6 Hz, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 68.26, 45.13, 41.24, 38.79, 33.06, 29.71, 27.48, 20.90, 20.42, 19.93, 17.53, 14.42. Anal. Calcd for $C_{12}H_{26}O$: C, 77.35; H, 14.06. Found: C, 77.20; H, 14.01.

[2*S*,4*S*,6*S*]-2,4,6-Trimethyl-1-nonanal (14). Iodobenzene diacetate (121 mg, 0.380 mmol) was added to a solution of **13** (35.0 mg, 0.19 mmol) and 2,2,6,6-tetramethyl-1-piperidinooxy (10.0 mg, 64 μmol) in anhydrous CH_2Cl_2 (1.0 mL). After 0.5 h, the mixture was diluted with CH_2Cl_2 (5 mL), washed with saturated $Na_2S_2O_3$, saturated $NaHCO_3$, and saturated brine, and then dried (Na_2SO_4), and the solvents were removed in vacuo. The residue was purified by flash chromatography on silica gel (pure hexanes) to afford **14** (32 mg, 92%) as a colorless oil. $[\alpha]_D$ +5.6 (*c* 0.43, $CHCl_3$); IR (film) 1730 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 9.59 (d, J = 2.6 Hz, 1 H), 2.45 (m, 1 H), 1.09 (d, J = 6.9 Hz, 3 H), 0.89 (d, J = 6.5 Hz, 3 H), 0.88 (t, J = 6.9 Hz, 3 H), 0.85 (d, J = 6.6 Hz, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 205.5, 45.08, 44.08, 38.89, 38.39, 29.66, 27.86, 20.39, 20.23, 19.94, 14.37 (2 C). Exact mass: *m*/*z* 185.1903 (Calcd $C_{12}H_{25}O$ 185.1905).

Ethyl [4*S*,6*S*,8*S*]-2,4,6,8-Tetramethyl-undec-2-eneoate (15). To a solution of **14** (25.0 mg, 0.14 mmol) in toluene−CH_2Cl_2 (1.2 mL, 5:1 v/v) was added ethoxycarbonylethylidenetriphenylphosphorane (75.0 mg, 0.20 mmol). The mixture was maintained at 80 °C for 3 h, and then the solvents were removed in vacuo. The residue was purified by flash chromatography on silica gel (250:1 hexanes:EtOAc) to afford **15** (29.5 mg, 81%) as a colorless oil. $[\alpha]_D$ +19.8 (*c* 0.43, $CHCl_3$); IR (film) 1715 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 6.51 (dd, J = 10.2, 1.4 Hz, 1 H), 4.19 (m, 2 H), 2.62 (m, 1 H), 1.86 (d, J = 1.4 Hz, 3 H), 1.30 (t, J = 7.2 Hz, 3 H), 0.99 (d, J = 6.6 Hz, 3 H), 0.88 (d, J = 7.2 Hz, 3 H), 0.83 (d, J = 5.5 Hz, 3 H), 0.81 (d, J = 6.5 Hz, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.4, 148.2, 126.2, 60.34, 45.56, 44.30, 39.29, 30.86, 29.70, 29.59, 28.08, 20.62, 20.43, 19.97, 14.39, 14.27, 12.47. Anal. Calcd for $C_{17}H_{32}O_2$: C, 76.06; H, 12.02. Found: C, 75.90; H, 11.98.

[4*S*,6*S*,8*S*]-2,4,6,8-Tetramethyl-2-undecen-1-ol (16). To a −78 °C solution of **15** (20.0 mg, 74.6 μmol) in CH_2Cl_2 (1.0 mL) was added DIBAL-H (50 μL, 0.28 mmol) dropwise. After stirring at −78 °C for 1 h, the reaction was quenched by addition of EtOAc (1.0 mL). The temperature was raised to 0 °C and HCl (1.0 M, 1.0 mL) added. The mixture was extracted with CH_2Cl_2 (5 mL), washed with brine, and dried (Na_2SO_4), and the solvents were removed in vacuo. The residue was purified by flash chromatography on silica gel (60:1 hexanes:EtOAc) to afford **16** (15 mg, 90%). $[\alpha]_D$ +8.8 (*c* 0.25, $CHCl_3$); IR (film) 3300 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 5.13 (dd, J = 9.6, 1.2 Hz, 1 H), 4.00 (s, 2 H), 2.50 (m, 1 H), 1.69 (d, J = 1.2 Hz, 3 H), 0.93 (d, J = 6.6 Hz, 3 H), 0.88 (t, J = 7.0 Hz, 3 H), 0.83 (d, J = 6.1 Hz, 3 H), 0.81 (d, J = 6.4 Hz, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 133.2, 133.1, 69.20, 45.66, 44.92, 39.36, 29.70, 29.61, 27.86, 21.70, 20.54, 20.05, 20.00, 14.41, 13.84. Anal. Calcd for $C_{15}H_{30}O$: C, 79.58; H, 13.36. Found: C, 79.42; H, 13.32.

Siphonarienal (1). To a solution of **16** (8.50 mg, 37.6 μmol) in dry hexanes (1.0 mL) was added activated MnO_2 (130 mg, 1.27 mmol). After stirring at room temperature for 3 h, the mixture was passed through a short column packed with silica gel and eluted with 50:1 hexanes:EtOAc. The solvents were removed in vacuo to afford siphonarienal, **1** (8.0 mg, 95%), as an oil. $[\alpha]_D$ +7.3 (*c* 0.15, $CHCl_3$); IR (film) 1670 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 9.40 (s, 1 H), 6.22 (dd, J = 10.1, 1.2 Hz, 1 H), 2.84 (m, 1 H), 1.78 (d, J = 1.2 Hz, 3 H), 1.05 (d, J = 6.7 Hz, 3 H), 0.88 (t, J = 7.0 Hz, 3 H), 0.84 (d, J = 6.5 Hz, 3 H), 0.81 (d, J = 6.6 Hz, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 195.6, 160.8, 138.0, 45.56, 44.19, 39.22, 31.23, 29.61, 28.21, 20.53, 20.32, 20.02, 19.98, 14.38, 9.37; Exact mass (DEI): *m*/*z* 224.2133 (Calcd $C_{15}H_{28}O$ 224.2140).

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Supporting Information Available: ^{13}C NMR spectra of **1** and **14**. This material is available free of charge via the Internet at http://www.pubs.acs.org.

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