Stereoselective Synthesis of C5−C20 and C21−C34 Subunits of the Core Structure of the Aplyronines. Applications of Enantioselective Additions of Chiral Allenylindium Reagents to Chiral Aldehydes

James A. Marshall* and Brian A. Johns†

Department of Chemistry, University of Virginia, Charlottesville, Virginia 22904

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The stereoselective synthesis of a C5−C20 and a C21−C34 subunit of the aplyronine family of polyketide marine macrolides has been achieved. These subunits contain all 15 stereocenters of the core structure. Six of the 15 stereocenters were introduced through enantioselective and diastereoselective additions of chiral allenylindium reagents to α-methyl-*β*-oxygenated propionaldehydes. The products of these additions were further transformed by reactions involving the terminal alkynyl substituent produced in the addition reactions. Unlike previous applications of this methodology, the present synthesis employs Pd(0)-catalyzed transmetalations of chiral allenylpalladium intermediates to generate the chiral allenylindium reagents in situ.

The aplyronines (A, B, and C, see Figure 1), a group of three closely related macrolides first isolated in 1993 from the sea hare *Aplysia kurodai* off the Pacific coast of Japan, show a high degree of activity toward a variety of tumor cell lines.[1] The mode of action is related to their inhibition of actin polymerization, analogous to that of cytochalasin B.[2] This novel mode of bioactivity and the extremely limited availability of the aplyronines (10^{-5}–10^{-7}% yield) make these polyketides attractive targets for total synthesis on a scale that could provide amounts of the natural products and analogues for evaluation as possible chemotherapeutic agents.

A total synthesis of aplyronine A was reported by the Yamada group in 1994 as a culmination of their work on the structure elucidation.[3,4] We viewed the aplyronine core structure as an attractive target to develop synthetic methodology relating to our recently disclosed synthesis of stereotriad subunits of polyketide natural products employing enantioenriched allenyindium reagents (eqs 1 and 2).[5]

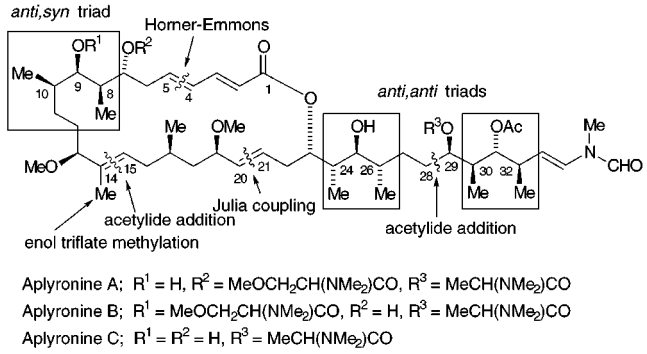
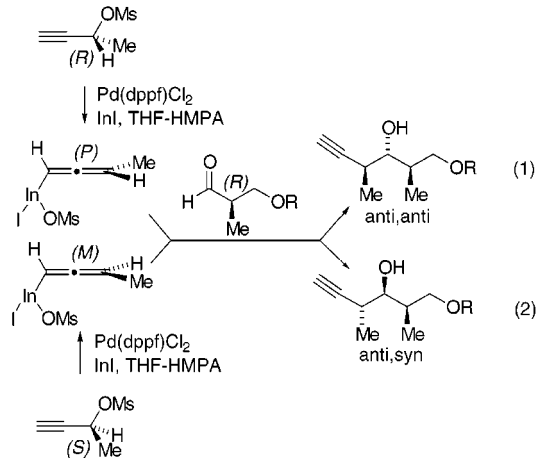


Figure 1. Aplyronines A, B, and C and principal synthetic constructs for the core unit.



Three such stereotriads can be discerned in the aplyronine core structure (Figure 1). Of particular interest to our synthetic plan was the development of chain elaboration and coupling strategies that utilize the

† Present address: Department of Medicinal Chemistry, Glaxo-Wellcome, Research and Development, 5 Moore Drive, Research Triangle Park, NC 27709.

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(2) (a) Saito, S.-y.; Watabe, S.; Ozaki, H.; Kigoshi, H.; Yamada, K.; Fusetani, N.; Kuraki, H. *J. Biochem.* **1996**, *120*, 552. (b) Suenaga, K.; Kamei, N.; Okugawa, Y.; Tukegi, M.; Akao, A.; Kigoshi, H.; Yamada, K. *Bioorg. Med. Chem. Lett.* **1997**, *7*, 269.

(3) (a) Kigoshi, H.; Ojika, M.; Ishigaki, T.; Suenaga, K.; Mutou, T.; Sakakura, A.; Ogawa, T.; Yamada, K. *J. Am. Chem. Soc.* **1994**, *116*, 7443. (b) Kigoshi, H.; Suenaga, K.; Mutou, T.; Ishigaki, T.; Atsumi, T.; Ishiwata, H.; Sakakura, A.; Ogawa, T.; Ojika, M.; Yamada, K. *J. Org. Chem.* **1996**, *61*, 5326.

(4) Other synthetic studies: Paterson, I.; Cowden, C.; Watson, C. *Synlett* **1996**, 209. Paterson, I.; Woodrow, M. D.; Cowden, C. J. *Tetrahedron Lett.* **1998**, *39*, 6041. Paterson, I.; Cowden, C. J.; Woodrow, M. D. *Tetrahedron Lett.* **1998**, *39*, 6037.

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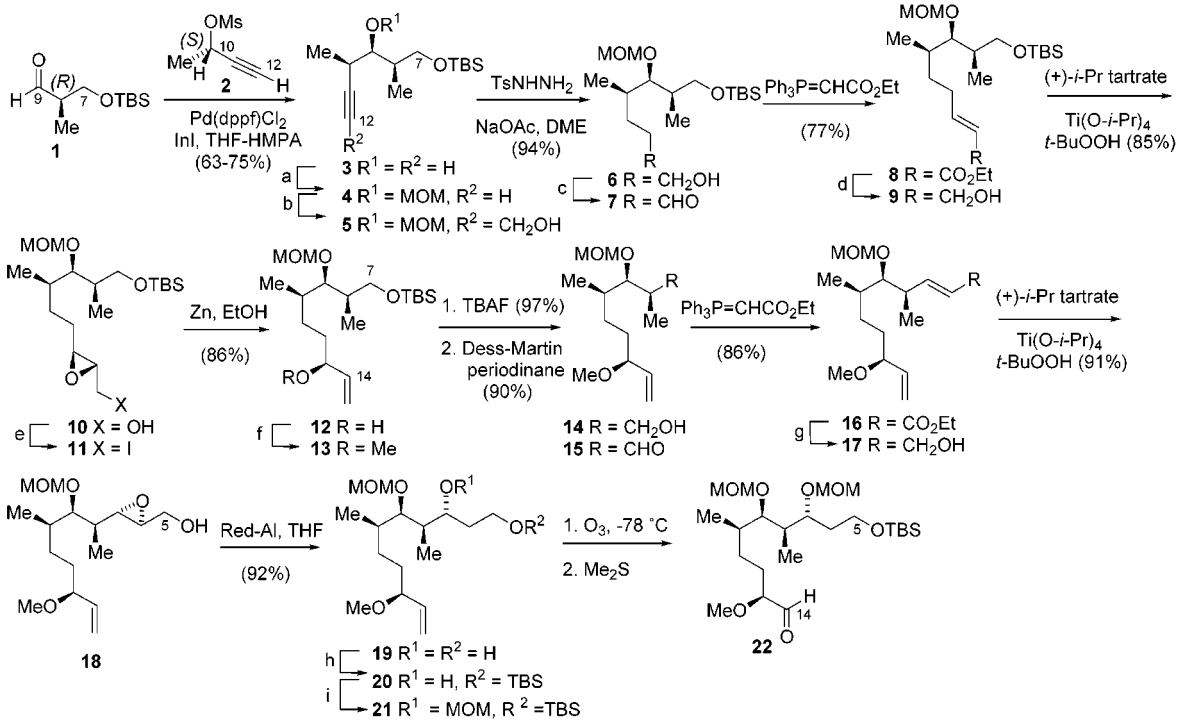
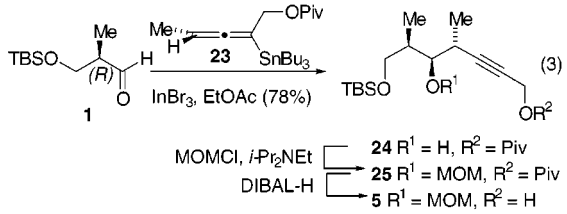
Scheme 1[a]



[a] Key: (a) MOMCl, Bu_4NI, *i*-Pr_2NEt (96%); (b) BuLi, $(CH_2O)_n$, THF (78%); (c) Dess−Martin (99%); (d) DIBAL-H, CH_2Cl_2 (93%); (e) I_2, Ph_3P, imid. (93%); (f) NaH, CH_3I, THF, 15-C-5 (99%); (g) DIBAL-H, CH_2Cl_2, −78 °C (98%); (h) TBSCl, imid., DMF (78%); (i) MOMCl, Bu_4NI, *i*-Pr_2NEt, CH_2Cl_2 (99%).

alkynyl moieties produced in the allenylmetal additions. The present report describes initial efforts along those-lines which have culminated in the synthesis of two major segments, C5−C20 and C21−C34, that incorporate all 15 stereocenters and the (*E*)-trisubstituted double bond of the aplyronine core.

The anti,syn stereotriad segment **3** of the C5−C20 subunit was prepared by addition of the allenylindium reagent generated in situ from the (*S*)-propargylic mesylate **2** to the (*R*)-aldehyde **1**[6] (Scheme 1**)**. This adduct was protected as the MOM ether **4**. Formylation of the lithiated alkyne led to the propargylic alcohol **5**. This intermediate could also be prepared from aldehyde **1** and the allenic stannane **23** along lines previously reported (eq 3).[7] Although the addition is quite efficient, the formation of objectionable tin byproducts makes the large-scale application of this methodology less attractive.



Hydrogenation of the alkyne grouping of alcohol **5** was best achieved with diimide.[8] Catalytic hydrogenation over Pd−C or Rh−Al_2O_3 was less successful because of partial hydrogenolysis of the propargylic OH. Oxidation of the saturated alcohol **6** to aldehyde **7** was effected with the Dess−Martin periodinane reagent.[9] Subsequent Horner−Emmons condensation led to the (*E*)-conjugated ester **8**, which was reduced to the allylic alcohol **9**. Sharpless epoxidation[10] directed by the (+)-isopropyl tartrate ligand afforded the epoxy alcohol **10** as a single diastereomer. Conversion to the iodide **11** was smoothly effected with I_2 in the presence of Ph_3P and imidazole.[11] This intermediate proved quite stable to storage and displayed excellent reactivity in the ensuing reductive elimination to allylic alcohol **12** with Zn in ethanol.[12] The configuration of alcohol **12** was confirmed through ^1H NMR analysis of the *(R)*- and *(S)*-*O*-methyl mandelic esters.[13] Methylation of the alcohol function led to the methyl ether **13** in high yield. This intermediate represents C7−C14 of the aplyronine core structure in which an eventual C14 aldehyde is masked as a terminal double bond.

Epoxy iodide **11** was also used to explore an alternative strategy that involved use of a carbometalation reaction to prepare the vinylic iodide **28** for eventual coupling with a C16 boronate, along the lines of our recent discodermolide synthesis[14] (eq 4). However, this approach was abandoned because of our inability to effect the requisite

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(7) Marshall, J. A.; Palovich, M. R. *J. Org. Chem.* **1997**, *62*, 6001. Marshall, J. A.; Lu, Z.-H.; Johns, B. A. *J. Org. Chem.* **1998**, *63*, 817.
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(9) (a) Dess, D. B.; Martin, J. C. *J. Org. Chem.* **1983**, *48*, 4156. (b) Frigerio, M.; Santagostino, M.; Sputore, S. *J. Org. Chem.* **1999**, *64*, 4537. (c) Meyer, S. D.; Schreiber, S. L. *J. Org. Chem.* **1994**, *59*, 7549.
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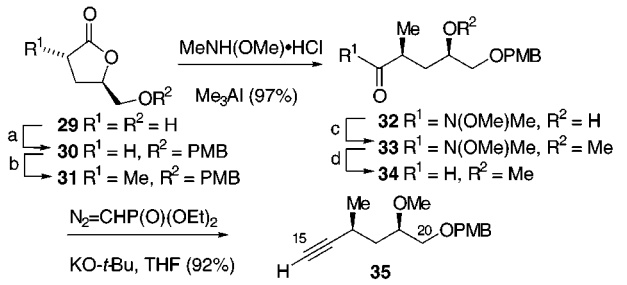
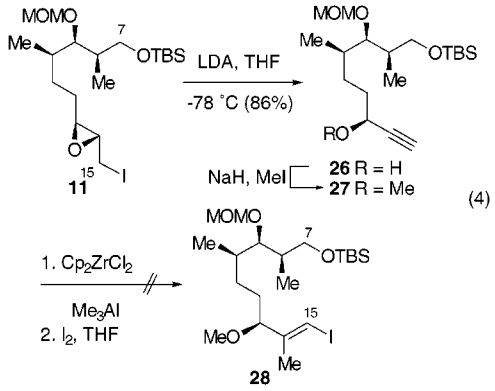
(14) Marshall, J. A.; Johns, B. A. *J. Org. Chem.* **1998**, *63*, 7885.

Scheme 2[a]



[a] Key: (a) $Cl_3CC(NH)O$-*p*-$CH_2C_6H_4OMe$, PPTS, CH_2Cl_2 (91%); (b) LDA, CH_3I, THF, −78 °C (67%) plus 16% of the cis diastereoisomer; (c) NaH, CH_3I, 15-C-5, THF (96%); (d) DIBAL-H, THF, −78 °C (99%).

carbometalation of propargylic ether **27**.[15]



(4)

Two-carbon homologation at C7 of intermediate **13** was effected through cleavage of the TBS ether followed by Dess−Martin periodinane oxidation[9] of the alcohol **14** and Wittig condensation with ethyl α-triphenylphosphorylidene acetate. The ester **16** was reduced with Red-Al and the resulting allylic alcohol **17** subjected to Sharpless asymmetric epoxidation with (+)-isopropyl tartrate ligand control.[10] A single epoxy alcohol, **18**, was thereby obtained. It has been our experience that the Sharpless epoxidation of allylic alcohols such as **17** are little influenced by the stereogenicity of the allylic center.[7,14] Reduction of epoxy alcohol **18** with Red-Al afforded the diol **19**, which was converted to the protected intermediate **21** through sequential reaction with TBSCl and MOMCl. The C5−C14 aldehyde **22** was produced upon ozonolysis of **21** and reductive workup with Me_2S.

The synthesis of a suitable C15−C20 segment started with the known γ-lactone **29**, derived in two steps from D-glutamic acid.[16] Protection of the alcohol as the PMB ether **30** followed by alkylation with MeI afforded the trans isomer **31** as the major component of an 80:20 separable mixture of diastereomers (Scheme 2). Careful control of conditions such as inverse addition of the lactone enolate and inverse quench of the reaction mixture was required to prevent dialkylation. The use of LDA proved superior to LiHMDS.[17] The assignment of stereochemistry to lactone **31** was confirmed through analysis of the coupling constants of the contiguous lactone ring protons at C17−C19.[18] The derived Weinreb amide **32**[19] was converted to the methyl ether **33** and then reduced to the aldehyde **34** with DIBAL-H. Reaction of aldehyde **34** with the Seyferth−Gilbert diazo phosphonate reagent[20] afforded the C15−C20 alkyne **35**. The use of Ph_3P and CBr_4 for this transformation resulted in extensive decomposition.[21]

Despite the strongly basic conditions employed for the methylation of alcohol **32**, none of the epimer (at C2) of the ether amide **33** was formed. The relative nonacidity of the α-proton of **32** and **33** can be attributed to conformational factors that disfavor the stereoelectronically favorable orientation for loss of that proton.[22]

Addition of the lithio acetylide **36** of alkyne **35** to aldehyde **22** afforded an inconsequential mixture of diastereomeric alcohols **37** (Scheme 3). Reduction of the alkyne with diimide and oxidation of the alcohol **38** with the Dess−Martin periodinane reagent[9] led to the ketone **39**. Treatment of ketone **39** with LiHMDS in 4:1 THF−HMPA to form the enolate, followed by addition of *N*-(5-chloro-2-pyridyl)triflimide,[23] gave the (*Z*)-vinyl triflate **40** as the sole product.[24] Vinyl triflate **40** was converted to the (*E*)-trisubstituted alkene **41** in near-quantitative yield through Suzuki Pd(dppf)-catalyzed coupling with a methylboronate reagent prepared in situ from B-methoxy-9-BBN and MeLi in THF and aqueous K_3PO_4−DMF,[14,25] thus completing construction of the C5−C20 subunit of the aplyronine core structure. The methylation of vinyl triflate **40** could not be effected with various methylcuprate reagents.

Synthesis of the anti,anti stereotriad segment **43** of the C21−C34 subunit was achieved through addition of the allenylindium reagent derived from the (*S*)-propargylic

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(17) A reviewer suggested that this alkylation step could be improved through application of a procedure described by Williams and Im for the alkylation of oxazinones in which potassium hexamethyldisilazide in toluene is added at −80 °C to a solution of the oxazinone and methyl iodide. Williams, R. M.; Im, M.-N. *J. Am. Chem. Soc.* **1991**, *113*, 9276. Unfortunately, circumstances did not permit the exploration of this methodology.

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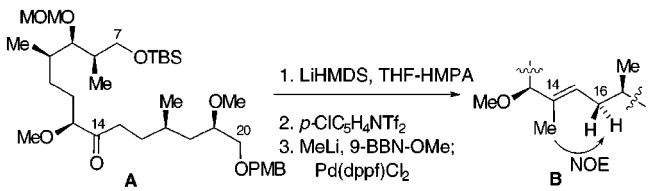
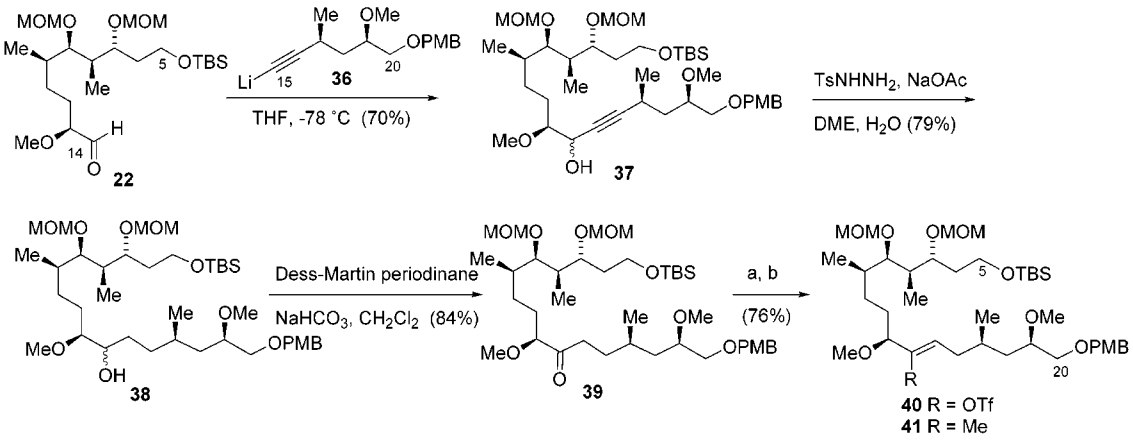
(25) Initial studies of this reaction were conducted with the C7−C20 prototype **A**. The stereochemistry of the derived olefin **B** was confirmed by the observation of an NOE between the C14 Me and the C16 methylene.

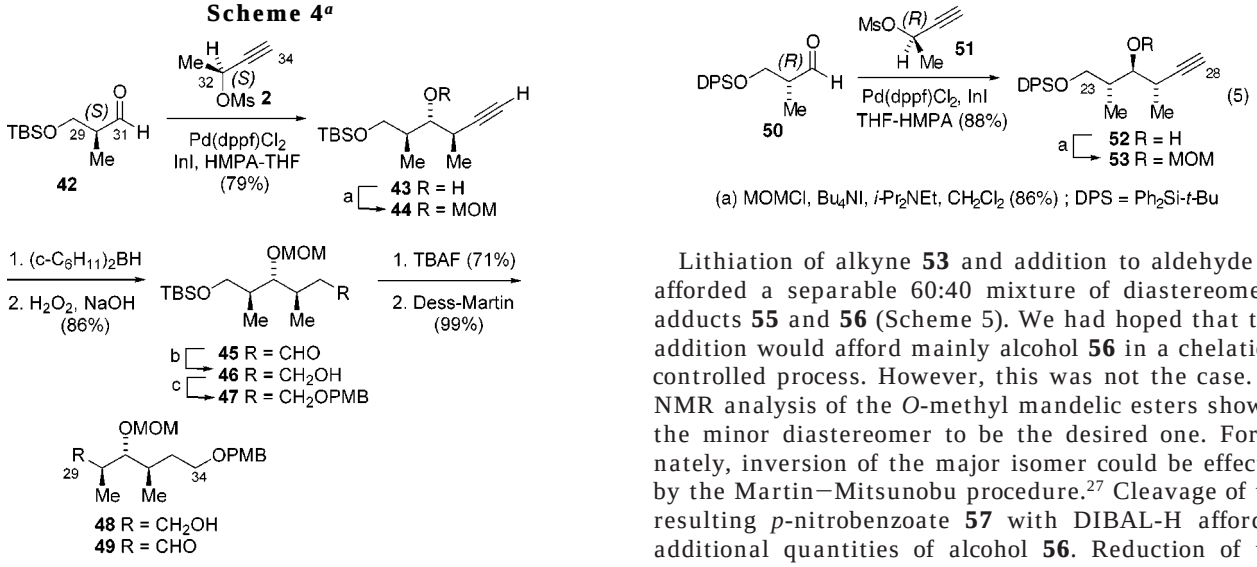


Scheme 3[a]



[a] Key: (a) LiHMDS, THF−HMPA, *N*-(5-Cl-2-pyridyl)triflimide; (b) MeLi, 9-BBN-OMe THF; $Pd(dppf)Cl_2$, K_3PO_4(aq), DMF.

Scheme 4[a]



[a] Key: (a) MOMCl, Bu_4NI, *i*-Pr_2NEt, CH_2Cl_2 (96%); (b) DIBAL-H (84%); (c) NaH, *p*-$MeOC_6H_4CH_2Cl$, Bu_4NI, 15-C-5, THF (90%).

mesylate **2** to the (*S*)-aldehyde **42**[6] (Scheme 4). Hydroboration−oxidation of the derived alkyne **44** led to a separable 85:15 mixture of aldehyde **45** and alcohol **46**. Aldehyde **45** was reduced with DIBAL-H, and the combined alcohol product **46** was protected as the PMB ether **47**. The use of dicyclohexylborane *in DME* for this hydroboration[26] gave a significantly higher yield of the aldehyde/alcohol mixture than BH_3·THF or catecholborane. The formation of the alcohol byproduct **46** may result from in situ reduction of the intermediate aldehyde by borohydride species, $R_2B(H)OH^-$, produced during the basic oxidation procedure. However, in the case at hand, this side reaction is of no consequence. TBS ether cleavage of **47** and oxidation of the alcohol **48** gave the aldehyde **49** representing C29−C34 of the targeted subunit.

The preparation of the anti,anti stereotriad segment, C23−C28, of the C21−C34 subunit was achieved through addition of the allenylindium intermediate derived from the (*R*)-propargylic mesylate **51** to the (*R*)-aldehyde **50** (eq 5). After protection as the MOM ether **53,** this segment was ready for joining to the C29−C34 aldehyde **49**.

(a) MOMCl, Bu_4NI, *i*-Pr_2NEt, CH_2Cl_2 (86%) ; DPS = Ph_2Si-*t*-Bu

Lithiation of alkyne **53** and addition to aldehyde **49** afforded a separable 60:40 mixture of diastereomeric adducts **55** and **56** (Scheme 5). We had hoped that this addition would afford mainly alcohol **56** in a chelation-controlled process. However, this was not the case. ^1H NMR analysis of the *O*-methyl mandelic esters showed the minor diastereomer to be the desired one. Fortunately, inversion of the major isomer could be effected by the Martin−Mitsunobu procedure.[27] Cleavage of the resulting *p*-nitrobenzoate **57** with DIBAL-H afforded additional quantities of alcohol **56**. Reduction of the alkyne was again carried out with diimide to afford the tetrahydro intermediate **58**, protected as the MOM ether **59**.

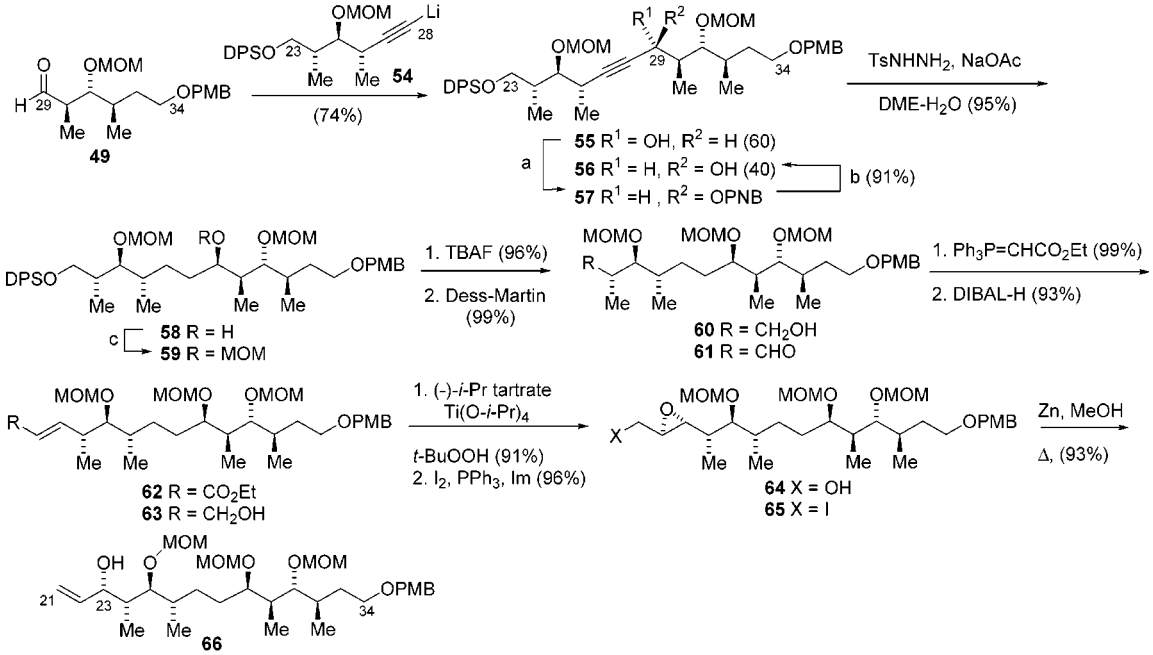
Addition of the remaining two carbons and the C23 stereocenter was achieved along the lines employed for the C5−C14 segment (Scheme 1, **15** → **19**). Thus, deprotection of the silyl ether of **59** and Dess−Martin oxidation[9] led to aldehyde **61**, which was homologated through Wittig condensation to the conjugated ester **62**. Reduction and Sharpless asymmetric epoxidation[10] afforded the epoxy alcohol **64**. Reductive elimination of the derived iodide **65** gave the allylic alcohol **66**, thereby completing the synthesis of the C21−C34 subunit.

The foregoing synthetic sequences underscore the use of readily prepared chiral allenylindium reagents to access anti,anti and anti,syn stereotriads through additions to β-oxygenated α-methyl aldehydes in which C−C bond formation is accompanied by the highly selective creation of two adjacent stereocenters and a terminal alkyne. This terminal alkyne can be manipulated in a variety of transformations to extend the carbon chain with introduction of additional stereocenters, as required. In the present application, the alkyne moiety also serves as a nucleophile for C−C bond formation and then provides requisite $(CH_2)_2$ links between stereocenters.

(26) Hoffmann, R. W.; Dresely, S. *Synthesis* **1988**, 103.

(27) Martin, S. F.; Dodge, J. A. *Tetrahedron Lett.* **1991**, *32*, 3017.

Scheme 5[a]



[a] Key: (a) *p*-$NO_2C_6H_4CO_2H$, *i*-$PrO_2CN{=}NCO_2$-*i*-Pr, Ph_3P (59%); (b) DIBAL-H (91%); (c) MOMCl, Bu_4NI, *i*-$PrNEt_2$, CH_2Cl_2 (99%).

Experimental Section

(2*R*,3*R*,4*R*)-1-(*tert*-Butyldimethylsilyloxy)-2,4-dimethyl-5-hexyn-3-ol (3). To a cold (0 °C) vigorously stirred solution of aldehyde (*R*)-**1** (2.00 g, 9.90 mmol) and mesylate (*S*)-**2** (1.61 g, 10.89 mmol) in THF (32 mL) was added $PdCl_2$(dppf)·CH_2Cl_2 (404 mg, 0.49 mmol) followed by powdered indium(I) iodide (2.86 g, 11.88 mmol). HMPA (8 mL) was then added by syringe pump at a rate of 1 mL/min. The resultant solution was stirred for 2 h. The mixture was quenched by the addition of H_2O followed by Et_2O. The organic layer was washed with brine. The aqueous layer was extracted with Et_2O, and the combined extracts were dried over Na_2SO_4. Filtration and concentration followed by flash chromatography (14:1 to 8:1 hexanes−EtOAc with 1% triethylamine) provided homopropargylic alcohol **3**[5] (1.59 g, 63%) as a clear oil: R_f 0.61 (4:1 hexanes−EtOAc); $[\alpha]_D$ +4.7 (*c* 3.4, $CHCl_3$); IR (film) 3503 (broad), 3311, 2112 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 2.72 (d, J = 4.5 Hz, 1 H), 2.66 (m, 1 H), 2.13 (d, J = 2.4 Hz, 1 H), 1.80 (m, 1 H), 1.19 (d, J = 6.9 Hz, 3 H), 0.96 (d, J = 7.2 Hz, 3 H), 0.89 (s, 9 H), 0.06 (s, 6 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 86.35, 76.12, 70.11, 67.16, 37.34, 30.41, 25.79, 18.12, 17.54, 10.26, −5.63.

(2*R*,3*R*,4*R*)-1-(*tert*-Butyldimethylsilyloxy)-2,4-dimethyl-3-(methoxymethoxy)-5-hexyne (4). To a cold (0 °C) solution of alcohol **3** (3.19 g, 12.5 mmol) in CH_2Cl_2 (80 mL) were added *N*,*N*-diisopropylethylamine (43.5 mL, 250 mmol), chloromethyl methyl ether (9.5 mL, 125 mmol) and tetrabutylammonium iodide (461 mg, 1.25 mmol). The reaction mixture was immediately allowed to warm to room temperature and protected from light. After 18 h, saturated aqueous $NaHCO_3$ was added followed by Et_2O. The organic layer was washed with brine, the aqueous layer was extracted with Et_2O, and the combined extracts were dried over Na_2SO_4. Filtration and concentration followed by flash chromatography (16:1 hexanes−EtOAc with 1% triethylamine) provided alkyne **4** (3.60 g, 96%) as a clear syrup: R_f 0.72 (4:1 hexanes−EtOAc); $[\alpha]^{20}_D$ −19.9 (*c* 2.0, $CHCl_3$); IR (film) 3308, 2114 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 4.77 (d, J = 6.9 Hz, 1H), 4.73 (d, J = 6.9 Hz, 1 H), 3.57 (dd, J = 9.9, 6.3 Hz, 1 H), 3.52 (dd, J = 9.9, 6.0 Hz, 1 H), 3.51 (dd, J = 5.4, 4.5 Hz, 1 H), 3.41 (s, 3H), 2.76 (m, 1 H), 2.07 (d, J = 2.4 Hz, 1 H), 1.93 (m, 1 H), 1.22 (d, J = 7.2 Hz, 3 H), 0.94 (d, J = 6.9 Hz, 3 H), 0.89 (s, 9 H), 0.04 (s, 6 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 98.27, 86.72, 81.99, 69.56, 65.53, 56.12, 38.50, 29.71, 25.87, 18.22, 18.06, 11.82, −5.47. Anal. Calcd for $C_{16}H_{32}O_3Si$: C, 63.95; H, 10.73. Found: C, 64.07; H, 10.84.

(2*R*,3*R*,4*R*)-1-(*tert*-Butyldimethylsilyloxy)-2,4-dimethyl-3-(methoxymethoxy)-5-heptyn-7-ol (5). To a cold (−78 °C) solution of alkyne **4** (3.52 g, 11.7 mmol) and 4 Å molecular sieves in THF (70 mL) was added BuLi (9.5 mL, 1.6 M in hexane, 15.2 mmol) dropwise. The solution was allowed to warm to −40 °C, stirred for 1 h, and recooled to −78 °C. Solid paraformaldehyde (704 mg, 23.5 mmol) was added in one portion, and the cloudy suspension was stirred for 5 min before being allowed to warm to room temperature. The solution was stirred for an additional 3 h. The mixture was quenched with saturated aqueous NH_4Cl, and Et_2O was added. The organic layer was washed with brine. The aqueous layer was extracted with Et_2O, and the combined extracts were dried over Na_2SO_4. Filtration and concentration followed by flash chromatography (4:1−3:1 hexanes−EtOAc with 1% triethylamine) provided alcohol **5** (3.02 g, 78%) as a clear oil:[7] R_f 0.31 (4:1 hexanes−EtOAc); $[\alpha]^{20}_D$ − 17.2 (*c* 1.9, $CHCl_3$); IR (film) 3438 (broad) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 4.76 (d, J = 6.6 Hz, 1 H), 4.72 (d, J = 6.6 Hz, 1 H), 4.24 (m, 2 H), 3.55−3.48 (m, 3 H), 3.41 (s, 3 H), 2.78 (m, 1 H), 1.97−1.85 (m, 2 H), 1.18 (d, J = 6.9 Hz, 3 H), 0.91 (d, J = 6.9 Hz, 3 H), 0.88 (s, 9 H), 0.04 (s, 6 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 98.30, 88.55, 82.07, 79.75, 65.50, 56.07, 51.36, 38.31, 29.90, 25.87, 18.22, 17.87, 11.51, −5.43. Anal. Calcd for $C_{17}H_{34}O_4Si$: C, 61.77; H, 10.37. Found: C, 61.80; H, 10.36.

(2*R*,3*R*,4*R*)-1-(*tert*-Butyldimethylsilyloxy)-2,4-dimethyl-3-(methoxymethoxy)heptan-7-ol (6). To a flask charged with propargylic alcohol **5** (2.97 g, 8.99 mmol) and 1,2-dimethoxyethane (240 mL) was added *p*-toluenesulfonyl hydrazide (41.8 g, 225 mmol) in one portion. The flask was fitted with a reflux condensor and warmed to reflux (bath temperature = 90 °C). A solution of NaOAc (19.9 g, 242 mmol) in H_2O (100 mL) was added by a syringe pump over 8 h. The reaction mixture was heated for an additional 1 h and cooled to room temperature, and Et_2O was added. The organic layer was washed with brine, the aqueous layer was extracted with Et_2O, and the combined extracts were dried over Na_2SO_4. Triethylamine (5 mL) was then added with stirring to the mixture resulting in a cloudy suspension that was stirred overnight. Filtration and concentration followed by flash chromatography (4:1 to 3:1 to 2:1 hexanes−EtOAc with 1% triethylamine) provided saturated alcohol **6** (2.82 g, 94%) as a syrup. On occasion, incomplete reduction was noted and the material was resubjected to the above conditions resulting in

complete reaction: R_f 0.67 (2:1 hexanes−EtOAc); $[\alpha]^{20}_D$ + 2.4 (*c* 2.6, $CHCl_3$); IR (film) 3407 (broad) cm $^{-1}$; ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.68 (d, J = 6.0 Hz, 1 H), 4.63 (d, J = 6.0 Hz, 1 H), 3.64 (m, 2 H), 3.48 (dd, J = 9.5, 7.5 Hz, 1 H), 3.44 (dd, J = 9.5, 6.0 Hz, 1 H), 3.41 (dd, J = 7.0, 2.5 Hz, 1 H), 3.39 (s, 3 H), 1.83 (m, 1 H), 1.74−1.59 (m, 3 H), 1.55−1.43 (m, 2 H), 1.21 (m, 1 H), 0.89 (d, J = 7.0 Hz, 3 H), 0.89 (s, 9 H), 0.85 (d, J = 7.0 Hz, 3 H), 0.04 (s, 6 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 98.42, 83.17, 65.90, 63.31, 55.92, 37.49, 35.65, 30.33, 28.77, 25.90, 18.22, 16.22, 10.81,−5.36, −5.43. Anal. Calcd for $C_{17}H_{38}O_4Si$: C, 61.03; H, 11:45. Found: C, 60.87; H, 11.50.

(4*R*,5*R*,6*R*)-7-(*tert*-Butyldimethylsilyloxy)-4,6-dimethyl-5-(methoxymethoxy)heptanal (7). To a solution of alcohol **6** (3.43 g, 10.25 mmol) in CH_2Cl_2 (70 mL) were added solid $NaHCO_3$ (8.61 g, 103 mmol) and the Dess−Martin periodinane reagent (5.22 g, 12.31 mmol).[9] The resultant solution was stirred for 1 h and then quenched by the simultaneous addition of saturated aqueous $Na_2S_2O_3$ and saturated aqueous $NaHCO_3$. Diethyl ether was added, and the biphasic mixture was stirred vigorously for 1 h, at which time both layers had cleared. The organic layer was washed with brine, the aqueous layer was extracted with Et_2O, and the combined extracts were dried over Na_2SO_4. Filtration and removal of solvent in vacuo provided aldehyde **7** (3.41 g, 99%) as a clear oil. This material was used immediately without further purification: R_f 0.55 (4:1 hexanes−EtOAc); ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.78 (t, J = 1.5 Hz, 1 H), 4.68 (d, J = 6.6 Hz, 1 H), 4.61 (d, J = 6.6 Hz, 1 H), 3.47−3.40 (m, 3 H), 3.39 (s, 3 H), 2.52 (m, 1 H), 2.39 (m, 1 H), 1.94 (m, 1 H), 1.83 (m, 1 H), 1.70 (m, 1 H), 1.47 (m, 1 H), 0.88 (d, J = 6.6 Hz, 3 H), 0.88 (s, 9 H), 0.83 (d, J = 6.9 Hz, 3 H), 0.03 (s, 6 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 202.84, 98.38, 82.75, 65.65, 55.99, 41.69, 37.53, 35.31, 25.86, 24.97, 18.19, 16.08, 10.74, −5.40, −5.46.

Ethyl (2*E*,6*R*,7*R*,8*R*)-1-(*tert*-Butyldimethylsilyloxy)-6,8-dimethyl-7-methoxymethoxy)-2-nonenoate (8). To a solution of aldehyde **7** (3.41 g, 10.25 mmol) in CH_2Cl_2 (110 mL) was added (carbethoxymethylene)triphenylphosphorane (7.15 g, 20.50 mmol) in one portion. The solution was heated to reflux for 15 h. The mixture was cooled to room temperature, concentrated in vacuo, and subjected to flash chromatography (8:1 hexanes−EtOAc) to provide α,β-unsaturated ester **8** (3.18 g, 77%) as a clear oil: R_f 0.59 (4:1 hexanes−EtOAc); IR (film) 1724, 1652 cm $^{-1}$; ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.96 (dt, J = 15.6, 6.9 Hz, 1 H), 5.82 (dt, J = 15.6, 1.5 Hz, 1 H), 4.66 (d, J = 6.6 Hz, 1 H), 4.60 (d, J = 6.6 Hz, 1 H), 4.16 (q, J = 7.2 Hz, 2 H), 3.47 (dd, J = 9.9, 7.8 Hz, 1 H), 3.42 (dd, J = 9.9, 6.0 Hz, 1 H), 3.39 (m, 1 H), 3.37 (s, 3 H), 2.30 (m, 1 H), 2.14 (m, 1 H), 1.88−1.62 (m, 3 H), 1.27 (m, 1 H), 1.27 (t, J = 7.2 Hz, 3 H), 0.88 (d, J = 6.9 Hz, 3 H), 0.88 (s, 9 H), 0.83 (d, J = 6.9 Hz, 3 H), 0.03 (s, 6 H); ^{13}C NMR (75 MHz $CDCl_3$) δ 166.71, 149.44, 121.17, 98.32, 82.91, 65.78, 60.07, 55.94, 37.51, 35.49, 31.08, 29.89, 25.87, 18.19, 16.06, 14.25, 10.87, −5.40. Anal. Calcd for $C_{21}H_{42}O_5Si$: C, 62.64; H, 10.51. Found: C, 62.77; H, 10.50.

(2*E*,6R,7*R*,8*R*)-7-(*tert*-Butyldimethylsilyloxy)-6,8-dimethyl-7-(methoxymethoxy)-2-hexen-1-ol (9). To a cold (−78 °C) solution of ester **8** (2.34 g, 5.81 mmol) in CH_2Cl_2 (40 mL) and hexanes (40 mL) was added DIBAL-H (14.5 mL, 1.0 M in hexane, 14.5 mmol) dropwise with a syringe pump. The reaction was stirred at −78 °C for 45 min and then poured into a vigorously stirred solution of saturated aqueous sodium potassium tartrate (Rochelle's salt) and Et_2O. The biphasic mixture was stirred vigorously for 1 h, at which time both layers had cleared. The organic layer was washed with brine. The aqueous layer was extracted with Et_2O, and the combined extracts were dried over Na_2SO_4. Filtration and concentration followed by flash chromatography (2:1 hexanes−EtOAc with 1% triethylamine) provided allylic alcohol **9** (1.94 g, 93%) as a clear oil: R_f 0.29 (4:1 hexanes−EtOAc); $[\alpha]^{20}_D$ +0.7 (*c* 2.5, $CHCl_3$); IR (film) 3390 (broad) cm $^{-1}$; ^{1}H NMR, (500 MHz, $CDCl_3$) δ 5.72−5.62 (m, 2 H), 4.66 (d, J = 6.5 Hz, 1 H), 4.62 (d, J = 6.5 Hz, 1 H), 4.07 (m, 2 H), 3.49−3.41 (m, 3 H), 3.38 (s, 3 H), 2.17 (m, 1 H), 2.00 (m, 1 H), 1.83 (m, 1 H), 1.72 (m, 1 H), 1.64 (m, 1 H), 1.46 (broad, 1 H), 1.21 (m, 1 H), 0.89 (d, J = 7.0 Hz, 3 H), 0.89 (s, 9 H), 0.85 (d, J = 7.0 Hz, 3 H), 0.04 (s, 6 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 133.47, 129.02, 98.11, 82.63, 66.00, 63.84, 55.87, 37.33, 35.39, 32.14, 29.85, 25.91, 18.24, 16.09, 11.11, −5.36, −5.42. Anal. Calcd for $C_{19}H_{40}O_4Si$: C, 63.28; H, 11.18. Found: C, 63.35; H, 11.29.

(2*S*,3*S*,6*R*,7*R*,8*R*)-9-(*tert*-Butyldimethylsilyloxy)-6,8-dimethyl-2,3-epoxy-7-(methoxymethoxy)nonanol (10). To a suspension of freshly activated powdered 4 Å molecular sieves (ca. 1 g) in CH_2Cl_2 (30 mL) was added L-(+)-diisopropyl tartrate (0.14 mL, 0.64 mmol). The mixture was cooled to −20 °C, and Ti(O-*i*-Pr)$_4$ (0.16 mL, 0.54 mmol) was added dropwise. After 10 min, *tert*-butyl hydroperoxide (2.14 mL, 5−6 M in decane, ca. 10.7 mmol) was added dropwise. The mixture was stirred at −20 °C for 30 min, and then allylic alcohol **9** (1.93 g, 5.36 mmol) in CH_2Cl_2 (precooled to −20 °C) was added dropwise. The mixture was stirred at −20 °C for 24 h, quenched with 5 mL of H_2O, diluted with EtOAc, and allowed to warm to room temperature. The heterogeneous mixture was filtered through a pad of Celite and the filtrate was washed with brine. The aqueous layer was extracted with EtOAc, and the combined extracts were dried over Na_2SO_4. Filtration and concentration followed by flash chromatography (2:1 to 1:1 hexanes−EtOAc with 1% triethylamine) provided epoxy alcohol **10** (1.88 g, ca. 85%) as a clear oil contaminated with ca. 10% DIPT. Further efforts to remove the impurity were not made as it was removed in the next step without incident: R_f 0.33 (2:1 hexanes−EtOAc); ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.68 (d, J = 6.5 Hz, 1 H), 4.62 (d, J = 6.5 Hz, 1 H), 3.89 (d, J = 12.5 Hz, 1 H); 3.62 (m, 1 H), 3.48 (dd, J = 9.5, 8.0 Hz, 1 H), 3.44 (dd, J = 9.5, 6.0 Hz, 1 H), 3.41 (dd, J = 7.0, 2.5 Hz, 1 H), 3.39 (s, 3 H), 2.96−2.92 (m, 2 H), 1.83 (m, 1 H), 1.80−1.64 (m, 4 H), 1.54 (m, 1 H), 1.24 (m, 1 H), 0.89 (d, J = 6.5 Hz, 3 H), 0.89 (s, 9 H), 0.85 (d, J = 6.5 Hz, 3 H), 0.04 (s, 6 H), ^{13}C NMR (125 MHz, $CDCl_3$) δ 98.33, 82.89, 65.84, 61.75, 58.22, 56.27, 55.95, 37.48, 35.64, 29.25, 28.92, 25.90, 18.23, 16.13, 10.87, −5.36, −5.43.

(2*R*,3*R*,4*R*,7*S*,8*R*)-1-(*tert*-Butyldimethylsilyloxy)-2,4-dimethyl-7,8-epoxy-9-iodononane (11). To a solution of epoxy alcohol **10** (1.87 g, 4.97 mmol, ca. 90% pure) in benzene (100 mL) and ether (200 mL) were added imidazole (1.35 g, 19.88 mmol) and triphenylphosphine (1.96 g, 7.46 mmol). Iodine (1.83 g, 7.20 mmol) was added as a solution in Et_2O (30 mL) dropwise via a pressure equalizing funnel over 30 min with vigorous stirring. The resultant mixture was stirred an additional 1 h, concentrated to one-fourth volume, and filtered through a pad of silica gel (eluting with Et_2O). The filtrate was concentrated in vacuo, and the residue was purified by flash chromatography (12:1 hexanes−EtOAc with 1% triethylamine) to provide iodo epoxide **11** (2.25 g, 93%, 86% for two steps from allylic alcohol **10**) as a clear oil: R_f 0.73 (4:1 hexanes−EtOAc); $[\alpha]^{20}_D$ +6.6 (*c* 4.9, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.66 (d, J = 6.0 Hz, 1 H), 4.61 (d, J = 6.0 Hz, 1 H), 3.46 (dd, J = 10.0, 7.5 Hz, 1 H), 3.42 (dd, J = 10.0, 6.0 Hz, 1 H), 3.39 (m, 1 H), 3.39 (s, 3 H), 3.23 (dd, J = 9.5, 5.0 Hz, 1 H), 3.05−2.98 (m, 2H), 2.79 (td, J = 6.0, 1.5 Hz, 1 H), 1.82 (m, 1 H), 1.77−1.60 (m, 3 H), 1.52 (m, 1 H), 1.22 (m, 1 H), 0.87 (s, 9 H), 0.87 (d, J = 7.0 Hz, 3 H), 0.83 (d, J = 7.0 Hz, 3 H), 0.03 (s, 6 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 98.31, 82.84, 65.80, 62.82, 58.16, 55.97, 37.47, 35.61, 29.38, 28.79, 25.88, 18.19, 16.09, 10.83, 5.10, −5.37, −5.45.

(2*R*,3*R*,4*R*,7*S*)-1-(*tert*-Butyldimethylsilyloxy)-2,4-dimethyl-3-(methoxymethoxy)-8-nonen-7-ol (12). To a solution of iodo epoxide **11** (2.25 g, 4.63 mmol) in EtOH (115 mL) was added zinc dust (3.03 g, 46.35 mmol) in one portion. The suspension was immediately heated to reflux. Iodine crystals were added in several portions, and the progress of the reaction was monitored closely by TLC. Upon complete reaction (25 min), the mixture was cooled to room temperature and filtered through Celite. The filtrate was concentrated, and the residue was purified by flash chromatography (4:1 hexanes−EtOAc) to provide allylic alcohol **12** (1.43 g, 86%) as a clear oil: R_f 0.54 (4:1 hexanes−EtOAc); $[\alpha]^{20}_D$ +7.5 (*c* 1.7, $CHCl_3$); IR (film) 3429, 1036 cm $^{-1}$; ^{1}H NMR (500 MHz $CDCl_3$) δ 5.87 (ddd, J = 17.5, 10.5, 6.5 Hz, 1 H), 5.23 (d, J = 17.5 Hz, 1 H), 5.10 (d, J = 10.5 Hz, 1 H), 4.67 (d, J = 6.5 Hz, 1 H), 4.62 (d, J = 6.5 Hz, 1 H), 4.10 (m, 1 H), 3.48 (dd, J = 10.0, 7.5 Hz, 1 H), 3.43 (dd, J = 10.0, 6.0 Hz, 1 H), 3.41 (dd, J = 7.0, 2.5 Hz, 1 H), 3.38 (s,

3 H), 1.83 (m, 1 H), 1.72−1.60 (m, 4 H), 1.50 (m, 1 H), 1.14 (m, 1 H), 0.89 (s, 9 H), 0.89 (d, J = 7.0 Hz, 3 H), 0.84 (d, J = 6.5 Hz, 3 H), 0.04 (s, 6 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 141.18, 114.62, 98.34, 83.08, 73.62, 65.91, 55.94, 37.47, 35.88, 34.66, 28.25, 25.91, 18.23, 16.24, 10.88, −5.35, −5.42.

(*S*)-*O*-Methyl Mandelate of Alcohol 12. To a solution of alcohol **12** (14 mg, 0.03 mmol) in CH_2Cl_2 (2 mL) were added dicyclohexylcarbodiimide (12 mg, 0.06 mmol), (*S*)-(+)-α-(methoxy)phenylacetic acid (9.5 mg, 0.06 mmol), and a catalytic amount of DMAP. After 30 min, the mixture was concentrated in vacuo and purified by flash chromatography (4:1 hexanes−EtOAc) to provide the (*S*)-α-(methoxy)phenyl acetate [(*S*)-MPA] derivative of **12** (19 mg, 99%) as a clear oil: R_f 0.66 (4:1 hexanes−EtOAc); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.45−7.43 (m, 2 H), 7.37−7.31 (m 3 H), 5.63 (ddd, J = 17.5, 10.5, 6.0 Hz, 1 H), 5.27 (apparent q, J = 6.0 Hz, 1 H), 4.99 (d, J = 10.5 Hz, 1 H), 4.92 (d, J = 17.5 Hz, 1 H), 4.76 (s, 1 H), 4.64 (d, J = 6.5 Hz, 1 H), 4.59 (d, J = 6.5 Hz, 1 H), 3.47 (dd, J = 9.5, 8.0 Hz, 1 H), 3.42 (dd, J = 9.5, 6.0 Hz, 1 H), 3.41 (s, 3 H), 3.37 (s, 3 H), 3.37 (m, 1 H), 1.79 (m, 1 H), 1.74−1.53 (m, 4 H), 1.07 (m, 1 H), 0.89 (s, 9 H), 0.85 (d, J = 7.0 Hz, 3 H), 0.83 (d, J = 7.5 Hz, 3 H), 0.04 (s, 6 H).

(*R*)-*O*-Methyl Mandelate of Alcohol 12. Alcohol **12** (7.0 mg, 0.014 mmol), DCC (6 mg, 0.028 mmol), (*R*)-(−)-α-(methoxy)phenylacetic acid (5 mg, 0.028 mmol), and DMAP were combined for 5 min as previously described to provide the (*R*)-MPA derivative of **12** (9 mg, 99%) as a clear oil: R_f 0.66 (4:1 hexanes−EtOAc); ^{1}H NMR (500 MHz $CDCl_3$) δ 7.46−7.44 (m, 2 H), 7.37−7.30 (m, 3 H), 5.77 (ddd, J = 17.0, 10.5, 6.5 Hz, 1 H), 5.27 (apparent q, J = 6.5 Hz, 1 H), 5.22 (d, J = 17.0, 1 H), 5.15 (d, J = 10.5 Hz, 1 H), 4.75 (s, 1 H), 4.57 (d, J = 6.5 Hz, 1 H), 4.53 (d, J = 6.5 Hz, 1 H), 3.43 (dd, J = 10.0, 7.5 Hz, 1 H), 3.41 (s, 3 H), 3.38 (dd, J = 10.0, 6.5 Hz, 1 H), 3.37 (s, 3 H), 3.28 (dd, J = 7.0, 3.0 Hz, 1 H), 1.69 (m, 1H), 1.61 (m, 1 H), 1.53 (m, 1 H), 1.46 (m, 1 H), 1.33 (m, 1 H), 0.89 (s, 9 H), 0.84 (m, 1 H), 0.79 (d, J = 7.0 Hz, 3 H), 0.72 (d, J = 6.5, 3 H), 0.03 (s, 6 H).

(2*R*,3*R*,4*R*,7*S*)-1-(*tert*-Butyldimethylsilyloxy)-2,4-dimethyl-7-methoxy-3-(methoxymethoxy)-8-nonene (13). To a cold (0 °C) solution of alcohol **12** (1.35 g, 3.75 mmol) in THF (40 mL) was added NaH (135 mg, 5.62 mmol) in small portions. Iodomethane (1.15 mL, 18.7 mmol) was added dropwise followed by 15-crown-5 (0.07 mL, 0.38 mmol). The resultant mixture was allowed to warm to room temperature and stirred for 3 h. The solution was then cooled to 0 °C and quenched by the dropwise addition of saturated aqueous NH_4Cl (***Caution: vigorous evolution of H₂ may result***). The organic layer was washed with brine. The aqueous layer was extracted with Et_2O, and the combined extracts were dried over Na_2SO_4. Filtration and concentration followed by flash chromatography (14:1 hexanes−EtOAc with 1% triethylamine) provided methyl ether **13** (1.39 g, 99%) as a clear oil: R_f 0.88 (4:1 hexanes−EtOAc); $[\alpha]^{20}_D$ − 5.3 (*c* 1.7, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.64 (ddd, J = 17.5, 10.5, 7.0 Hz, 1 H), 5.19 (d, J = 10.5 Hz, 1 H), 5.18 (d, J = 17.5 Hz, 1 H), 4.65 (d, J = 6.5 Hz, 1 H), 4.61 (d, J = 6.5 Hz, 1 H), 3.48 (dd, J = 10.0, 7.5 Hz, 1 H), 3.47 (m, 1 H), 3.43 (dd, J = 10.0, 6.5 Hz, 1 H), 3.38 (s, 3 H), 3.38 (m, 1 H), 3.26 (s, 3 H), 1.83 (m, 1 H), 1.71−1.49 (m, 4 H), 1.08 (m, 1 H), 0.89 (s, 9 H), 0.88 (d, J = 6.5 Hz, 3 H), 0.85 (d, J = 7.0 Hz, 3 H), 0.03 (s, 6 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 138.82, 117.12, 98.18, 83.51, 83.05, 65.99, 56.09, 55.92, 37.44, 36.03, 33.07, 28.29, 25.91, 18.23, 16.12, 11.08, −5.37, −5.44. Anal. Calcd for $C_{20}H_{42}O_4Si$: C, 64.12; H, 11.30. Found: C, 64.29; H, 11.39.

(2*R*,3*R*,4*R*,7*S*)-2,4-Dimethyl-7-methoxy-3-(methoxymethoxy)-8-nonen-1-ol (14). To a cold (0 °C) solution of silyl ether **13** (1.39 g, 3.71 mmol) in THF (37 mL) was added TBAF (5.56 mL, 1.0 M in THF, 5.56 mmol) dropwise. The reaction mixture was allowed to warm to room temperature and stirred for 15 h. Saturated aqueous NH_4Cl was added followed by Et_2O. The organic layer was washed with brine. The aqueous layer was extracted with Et_2O, and the combined extracts were dried over Na_2SO_4. Filtration and concentration followed by flash chromatography (2:1 to 1:1 hexanes−EtOAc with 1% triethylamine) provided alcohol **14** (932 mg, 97%) as a clear oil: R_f 0.27 (2:1 hexanes−EtOAc); $[\alpha]^{20}_D$ −68.3 (*c* 3.6 $CHCl_3$); IR (film) 3453, 1038 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.63 (ddd, J = 18.0, 10.5, 7.5 Hz, 1 H), 5.22−5.14 (m, 2 H), 4.66 (s, 2 H), 3.51−3.46 (m, 3 H), 3.42 (s, 3 H), 3.39 (m, 1 H), 3.26 (s, 3 H), 3.00 (t, J = 6.6 Hz, 1 H), 1.94 (m, 1 H), 1.74−1.45 (m, 4 H), 1.02 (m, 1 H), 0.84 (d, J = 6.6 Hz, 3 H), 0.78 (d, J = 6.9 Hz, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 138.67, 117.25, 98.94, 83.70, 83.36, 65.09, 56.18, 56.10, 36.63, 35.96, 32.76, 28.30, 15.71, 9.86. Anal. Calcd for $C_{14}H_{28}O_4$: C, 64.58; H, 10.84. Found: C, 64.55; H, 10.77.

(2*S*,3*R*,4*R*,7*S*)-2,4-Dimethyl-7-methoxy-3-(methoxymethoxy)-8-nonenal (15). To a solution of alcohol **14** (932 mg, 3.58 mmol) in CH_2Cl_2 (36 mL) were added solid $NaHCO_3$ (3.00 g, 35.8 mmol) and the Dess−Martin periodinane reagent (1.82 g, 4.30 mmol).[9] The resultant solution was stirred for 1.25 h and then quenched by the simultaneous addition of saturated aqueous $Na_2S_2O_3$ and saturated aqueous $NaHCO_3$. Diethyl ether was added, and the biphasic mixture was stirred vigorously for 1 h at which time both layers had cleared. The organic layer was washed with brine, the aqueous layer was extracted with Et_2O, and the combined extracts were dried over Na_2SO_4. Filtration and removal of solvent in vacuo provided aldehyde **15** (831 mg, 90%) as a clear oil. This material was used immediately without further purification: R_f 0.69 (2:1 hexanes−EtOAc); ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.72 (d, J = 0.6 Hz, 1 H), 5.64 (ddd, J = 18.0, 10.5, 7.5 Hz, 1 H), 5.23−5.16 (m, 2 H), 4.63 (d, J = 6.9 Hz, 1 H), 4.57 (d, J = 6.9 Hz, 1 H), 3.80 (dd, J = 7.5, 3.0 Hz, 1 H), 3.48 (m, 1 H), 3.27 (s, 3 H), 3.26 (s, 3 H), 2.53 (qd, J = 7.2, 3.0 Hz, 1 H), 1.77−1.49 (m, 4 H), 1.13 (d, J = 7.2 Hz, 3 H), 1.12 (m, 1 H), 0.92 (d, J = 6.9 Hz, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 204.15, 138.55, 117.35, 97.68, 83.22, 81.82, 56.09, 55.80, 48.81, 35.99, 32.75, 28.04, 15.92, 7.57.

Ethyl (2*E*,4*R*,5*R*,6*R*,9*S*)-4,6-Dimethyl-9-methoxy-5-(methoxymethoxy)-2,10-undecadienoate (16). To a solution of aldehyde **15** (831 mg, 3.22 mmol) in CH_2Cl_2 (32 mL) was added (carbethoxymethylene)triphenylphosphorane (3.36 g 9.66 mmol) in one portion. The solution was heated to reflux for 20 h. The mixture was cooled to room temperature, concentrated in vacuo, and subjected to flash chromatography (8:1 to 4:1 hexanes−EtOAc with 1% triethylamine) to provide α,*β*-unsaturated ester **16** (909 mg, 86%) as a clear oil: R_f 0.37 (4:1 hexanes−EtOAc); $[\alpha]^{20}_D$ +25.3 (*c*, 2.5, $CHCl_3$); IR (film) 1718, 1652, 1035 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.95 (dd, J = 15.6, 7.8 Hz, 1 H), 5.80 (dd, J = 15.6, 1.2 Hz, 1 H), 5.61 (ddd, J = 16.8, 10.5, 7.8 Hz, 1 H), 5.18 (d, J = 10.5 Hz, 1 H), 5.15 (d, J = 16.8 Hz, 1 H), 4.61 (d, J = 6.9 Hz, 1 H), 4.58 (d, J = 6.9 Hz, 1 H), 4.17 (q, J = 7.2 Hz, 2 H), 3.43 (m, 1 H), 3.36 (s, 3 H), 3.24 (s, 3 H), 3.23 (m, 1 H), 2.59 (m, 1 H), 1.68−1.41 (m, 4 H), 1.27 (t, J = 7.2 Hz, 3 H), 1.07 (d, J = 6.9 Hz, 3 H), 1.07 (m, 1 H), 0.91 (d, J = 6.6 Hz, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 166.59, 152.08, 138.63, 120.51, 117.26, 97.94, 86.21, 83.30, 60.16, 56.04, 39.08, 35.84, 32.93, 27.09, 16.57, 14.71, 14.22. Anal. Calcd for $C_{18}H_{32}O_5$: C, 65.82; H, 9.82. Found: C, 65.88; H, 9.91.

(2*E*,4*R*,5*R*,6*R*,9*S*)-2,4-Dimethyl-9-methoxy-5-(methoxymethoxy)-2,10-undecadien-1-ol (17). To a cold (−78 °C) solution of ester **16** (909 mg, 2.77 mmol) in CH_2Cl_2 (35 mL) was added diisobutylaluminum hydride (6.92 mL, 1.0 M in hexane, 6.92 mmol) dropwise with a syringe pump. The reaction was stirred at −78 °C for 1.5 h and then poured into a vigorously stirred solution of saturated aqueous sodium potassium tartrate (Rochelle's salt) and Et_2O. The biphasic mixture was stirred vigorously for 1 h, at which time both layers had cleared. The organic layer was washed with brine. The aqueous layer was extracted with Et_2O, and the combined extracts were dried over Na_2SO_4. Filtration and concentration followed by flash chromatography (2:1 to 1:1 hexanes−EtOAc) provided allylic alcohol **17** (774 mg, 98%) as a clear oil: R_f 0.25 (2:1 hexanes−EtOAc); $[\alpha]^{20}_D$ +15.0 (*c* 2.5, $CHCl_3$); IR (film) 3446 (broad), 1039 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.75−5.57 (m, 3 H), 5.18 (d, J = 10.5 Hz, 1 H), 5.17 (d, J = 16.5 Hz, 1 H), 4.65 (d, J = 6.9 Hz, 1 H), 4.62 (d, J = 6.9 Hz, 1 H), 4.08 (apparent t, J = 5.4 Hz, 2 H), 3.44 (m, 1 H), 3.38 (s, 3 H), 3.25

(s, 3 H), 3.19 (dd, J = 5.7, 4.5 Hz, 1 H), 2.48 (m, 1 H), 2.02 (m, 1 H), 1.77−1.38 (m, 4 H), 1.04 (m, 1 H), 1.03 (d, J = 6.9 Hz, 3 H), 0.94 (d, J = 6.9 Hz, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 138.75, 135.69, 128.44, 117.02, 97.74, 87.08, 83.65, 63.66, 56.16, 55.91, 38.84, 35.56, 33.61, 27.69, 17.22, 16.11. Anal. Calcd for $C_{16}H_{30}O_4$: C, 67.10; H, 10.56. Found: C, 66.89; H, 10.59.

(2*S*,3*S*,4*S*,5*R*,6*R*,9*S*)-4,6-Dimethyl-2,3-epoxy-9-methoxy-5-(methoxymethoxy)-10-undecen-1-ol (18). To a suspension of freshly activated 4 Å molecular sieves (ca. 1 g) in CH_2Cl_2 (20 mL) was added L-(+)-diisopropyl tartrate (0.07 mL, 0.32 mmol). The mixture was cooled to −20 °C, and Ti(O-*i*-Pr)$_4$ (0.08 mL, 0.26 mmol) was added dropwise. After 10 min, *tert*-butyl hydroperoxide (1.05 mL, 5−6 M in decane, ca. 5.27 mmol) was added dropwise. The solution was stirred at −20 °C for 30 min, and then allylic alcohol **17** (754 mg, 2.64 mmol) in CH_2Cl_2 (precooled to −20 °C) was added dropwise. The resultant solution was stirred at −20 °C for 21 h, quenched with 5 mL of H_2O, diluted with EtOAc, and allowed to warm to room temperature. The heterogeneous mixture was filtered through a pad of Celite, and the filtrate was washed with brine. The aqueous layer was extracted with EtOAc, and the combined extracts were dried over Na_2SO_4. Filtration and concentration followed by flash chromatography (1:1 hexanes−EtOAc with 1% triethylamine) provided epoxy alcohol **18** (723 mg, 91%) as a clear oil: R_f 0.30 (1:1 hexanes−EtOAc); $[\alpha]^{20}_D$ −14.8 (*c* 2.3, $CHCl_3$); IR (film) 3446 (broad), 1036 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.65 (ddd, J = 16.5, 10.5, 8.1 Hz, 1 H), 5.20 (d, J = 10.5 Hz, 1 H), 5.19 (d, J = 16.5 Hz, 1 H), 4.72 (d, J = 6.6 Hz, 1 H), 4.67 (d, J = 6.6 Hz, 1 H), 3.86 (ddd, J = 12.3, 5.7, 3.3 Hz, 1 H), 3.70−3.63 (m, 1 H), 3.48 (m, 1 H), 3.41 (s, 3 H), 3.38 (dd, J = 6.6, 3.3 Hz, 1 H), 3.27 (s, 3 H), 2.99−2.94 (m, 2 H), 2.00 (broad, 1 H), 1.76−1.46 (m, 5 H), 1.08 (m, 1 H), 0.93 (d, J = 6.9 Hz, 3 H), 0.88 (d, J = 6.9 Hz, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 138.61, 117.16, 98.25, 84.65, 83.36, 61.82, 58.37, 58.27, 55.99, 37.51, 35.58, 32.85, 27.89, 16.11, 10.16. Anal. Calcd for $C_{16}H_{30}O_5$: C, 63.55; H, 10.00. Found: C, 63.45; H, 10.02.

(3*R*,4*R*,5*R*,6*R*,9*S*)-4,6-Dimethyl-9-methoxy-5-(methoxymethoxy)-10-undecene-1,3-diol (19). To a −10 °C solution of epoxy alcohol **18** (715 mg, 2.36 mmol) in THF (30 mL) was added Red-Al (3.55 mL, 65 wt % in toluene, 11.8 mmol) dropwise. The reaction mixture was stirred at −10 °C for 27 h and then quenched by the dropwise addition of saturated aqueous sodium potassium tartrate (Rochelle's salt) (***Caution: vigorous evolution of H_2 may result***). EtOAc was added, and the mixture was warmed to room temperature. The organic layer was washed with brine, the aqueous layer was extracted with EtOAc, and the combined extracts were dried over Na_2SO_4. Filtration and concentration followed by flash chromatography (1:5 hexanes−EtOAc to EtOAc) provided diol **19** (659 mg, 92%) as a clear oil: R_f 0.50 (1:3 hexanes−EtOAc); $[\alpha]^{20}_D$ −56.8 (*c* 2.3, $CHCl_3$); IR (film) 3425 (broad), 1035 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.60 (ddd, J = 17.1, 10.5, 7.5 Hz, 1 H), 5.19−5.13 (m, 2 H), 4.69−4.64 (m, 2 H), 4.39 (broad, 1 H), 3.81 (m, 2 H), 3.62 (m, 1 H), 3.54−3.36 (m, 2 H), 3.40 (s, 3 H), 3.23 (s, 3 H), 1.84 (m, 1 H), 1.66−1.22 (m, 6 H), 1.25 (broad, 1 H), 0.99 (m, 1 H), 0.79 (d, J = 6.6 Hz, 6 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 138.55, 117.24, 98.89, 83.62, 83.26, 73.88, 62.19, 56.05, 40.85, 35.98, 35.87, 32.65, 28.23, 15.63, 10.12. Anal. Calcd for $C_{16}H_{32}O_5$: C, 63.13; H, 10.60. Found: C, 62.88; H, 10.50.

(3*R*,4*R*,5*R*,6*R*,9*S*)-1-(*tert*-Butyldimethylsilyloxy)-4,6-dimethyl-9-methoxy-5-(methoxymethoxy)-10-undecen-3-ol (20). A 0 °C solution of diol **19** (659 mg, 2.17 mmol) in DMF (43 mL) was treated sequentially with imidazole (442 mg, 6.50 mmol) and *tert*-butylchlorodimethylsilane (357 mg, 2.38 mmol). The resultant solution was stirred at 0 °C for 14 h. The mixture was quenched by the addition of H_2O, followed by pentane. The organic layer was washed with brine, the aqueous layer was extracted with pentane, and the combined extracts were dried over Na_2SO_4. Filtration and concentration followed by flash chromatography (4:1 hexanes−EtOAc with 1% triethylamine) gave silyl ether **20** (706 mg, 78%) as a clear oil: R_f 0.43 (4:1 hexanes−EtOAc); $[\alpha]^{20}_D$ −10.9 (*c* 2.0, $CHCl_3$); IR (film) 3498 (broad), 1097 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.61 (ddd, J = 16.8, 10.5, 7.8 Hz, 1 H), 5.17 (dd, J = 10.5, 1.5 Hz, 1 H), 5.15 (dd, J = 16.8, 1.5 Hz, 1 H), 4.69 (d, J = 6.6 Hz, 1 H), 4.66 (d, J = 6.6 Hz, 1 H), 3.89−3.74 (m, 3 H), 3.60−3.53 (m, 2 H), 3.45 (m, 1 H), 3.38 (s, 3 H), 3.23 (s, 3 H), 1.81 (m, 1 H), 1.70−1.43 (m, 6 H), 1.03 (m, 1 H), 0.86 (s, 9 H), 0.80 (d, J = 6.9 Hz, 6 H), 0.04 (s, 3 H), 0.03 (s, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 138.71, 117.12, 98.73, 83.38, 83.24, 71.39, 61.64, 56.10, 56.02, 40.52, 36.61, 36.11, 32.76, 28.38, 25.83, 18.11, 15.76, 10.02, −5.49.

(*S*)-*O*-Methyl Mandelate of Alcohol 20. Alcohol **20** (17 mg, 0.04 mmol), DCC (84 mg, 0.41 mmol), (*S*)-(+)-α-(methoxy)-phenylacetic acid (67.5 mg, 0.41 mmol), and DMAP were combined for 15 min as previously described to provide the (*S*)-MPA derivative of alcohol **20** (23 mg, 99%) as a clear oil: R_f 0.40 (4:1 hexanes−EtOAc); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.50−7.20 (m, 5 H), 5.65 (ddd, J = 16.5, 10.8, 7.8 Hz, 1 H), 5.23−5.16 (m, 2 H), 4.91 (m, 1 H), 4.73 (s, 1 H), 4.53 (s, 2 H), 3.45−3.15 (m, 4H), 3.41 (s, 3 H), 3.35 (s, 3 H), 3.27 (s, 3 H), 2.03−1.01 (m, 8 H), 0.90 (d, J = 7.2 Hz, 3 H), 0.87 (d, J = 6.6 Hz, 3 H), 0.81 (s, 9 H), −0.12 (s, 3 H), −0.13 (s, 3 H).

(*R*)-*O*-Methyl Mandelate of Alcohol 20. Alcohol **20** (11.0 mg, 0.03 mmol), DCC (54 mg, 0.26 mmol), (*R*)-(−)-α-(methoxy)-phenylacetic acid (44 mg, 0.26 mmol), and DMAP were combined for 10 min as previously described to provide the (*R*)-MPA derivative of alcohol **20** (15 mg, 99%) as a clear oil: R_f 0.4 (4:1 hexanes−EtOAc); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.45−7.25 (m, 5 H), 5.62 (ddd, J = 16.8, 10.5, 7.8 Hz, 1 H), 5.23−5.15 (m, 2 H), 4.90 (td, J = 7.8, 3.0 Hz, 1 H), 4.70 (s, 1 H), 4.31 (d, J = 6.6 Hz, 1 H), 4.22 (d, J = 6.6 Hz, 1 H), 3.65−3.26 (m, 3 H), 3.40 (s, 3 H), 3.29 (s, 3 H), 3.26 (s, 3 H), 2.71 (dd, J = 6.6, 3.3 Hz, 1 H), 1.89−1.39 (m, 8 H), 0.87 (s, 9 H), 0.73 (d, J = 6.6 Hz, 3 H), 0.69 (d, J = 6.6 Hz, 3 H), 0.01 (s, 6 H).

(3*R*,4*R*,5*R*,6*R*,9*S*)-3,5-Bis(methoxymethoxy)-1-(*tert*-butyldimethylsilyloxy)-4,6-dimethyl-9-methoxy-10-undecene (21). To a cold (0 °C) solution of alcohol **20** (648 mg, 1.55 mmol) in CH_2Cl_2 (16 mL) were added *N*,*N*-diisopropylethylamine (10.8 mL, 62.0 mmol), chloromethyl methyl ether (2.35 mL, 31.0 mmol), and tetrabutylammonium iodide (58 mg, 0.16 mmol). The reaction mixture was immediately allowed to warm to room temperature and protected from light. After 42 h, saturated aqueous $NaHCO_3$ was added followed by Et_2O. The organic layer was washed with brine, the aqueous layer was extracted with Et_2O, and the combined extracts were dried over Na_2SO_4. Filtration and concentration followed by flash chromatography (8:1 hexanes−EtOAc with 1% triethylamine) provided bis-MOM ether **21** (714 mg, 99%) as a clear oil: R_f 0.65 (4:1 hexanes−EtOAc); $[\alpha]^{20}_D$ +9.3 (*c* 2.4, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.61 (d, J = 17.0, 11.0, 8.0 Hz, 1 H), 5.16 (d, J = 11.0 Hz, 1 H), 5.15 (d, J = 17.0 Hz, 1 H), 4.65−4.60 (m, 4 H), 3.70−3.61 (m, 3 H), 3.45 (m, 1 H), 3.35 (s, 3 H), 3.34 (s, 3 H), 3.28 (t, J = 5.0 Hz, 1 H), 3.23 (s, 3 H), 1.94 (m, 1 H), 1.68−1.47 (m, 6 H), 1.09 (m, 1 H), 0.90 (d, J = 7.0 Hz, 3 H), 0.89 (d, J = 6.5 Hz, 3 H), 0.86 (s, 9 H), 0.02 (s, 6 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 138.70, 117.16, 98.29, 96.57, 84.62, 83.36 76.93, 59.36, 56.00, 55.88, 55.63, 38.41, 35.99, 33.82, 33.03, 26.92, 25.86, 18.17, 16.41, 10.53, −5.40, −5.47. Anal. Calcd for $C_{24}H_{50}O_6Si$: C, 62.29; H, 10.89. Found: C, 62.28; H, 10.75.

(2*S*,5*R*,6*R*,7*R*,8*R*)-6,8-Bis(methoxymethoxy)-10-(*tert*-butyldimethylsilyloxy)-5,7-dimethyl-2-methoxydecanal (22). A solution of olefin **21** (417 mg, 0.90 mmol) in CH_2Cl_2 (15 mL) was cooled to −78 °C. An ozone/oxygen stream was bubbled through the reaction mixture at a rate of 2 L/min until a faint blue color persisted (ca. 2 min). The production of ozone was immediately stopped, and the reaction mixture was purged with O_2 until a clear solution resulted (ca. 3 min). Dimethyl sulfide (5 mL) was added, the mixture was stirred at −78 °C for 5 min, the bath was removed, and the solution was allowed to warm to room temperature. After 1 h, the solvent was removed in vacuo. The residue was taken up in Et_2O and washed successively with H_2O and brine. The aqueous layer was extracted once with Et_2O, and the combined extracts were dried over Na_2SO_4. Filtration and concentration provided aldehyde **22** (418 mg, 99%) as a clear oil. This

material was unstable to further handling and was used immediately without purification: R_f 0.3 (streaky, 4:1 hexanes−EtOAc); ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.65 (d, J = 2.1 Hz, 1 H), 4.67−4.64 (m, 4 H), 3.72−3.62 (m, 3 H), 3.54 (ddd, J = 7.2, 5.4, 2.4 Hz, 1 H), 3.43 (s, 3 H), 3.38 (s, 3 H), 3.37 (s, 3 H), 3.30 (t, J = 4.8 Hz, 1 H), 1.97 (m, 1 H), 1.85−1.50 (m, 6 H), 1.22 (m, 1 H), 0.93 (d, J = 6.0 Hz, 6 H), 0.88 (s, 9 H), 0.04 (s, 6 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 203.94, 98.46, 96.63, 86.05, 84.69, 76.79, 59.31, 55.96, 55.67, 38.63, 35.91, 33.80, 27.83, 26.46, 25.87, 18.20, 16.53, 10.53, −5.39.

C5−C20 Alkyne Adduct 37. To a cold (−78 °C) suspension of alkyne **35** (946 mg, 3.61 mmol) and 4 Å molecular sieves (ca. 1 g) in THF (15 mL) was added BuLi (1.29 mL, 2.5 M in hexanes, 3.24 mmol) dropwise. The resultant solution was stirred at −78 °C for 5 min and then warmed to −35 °C. After 1 h, the mixture was recooled to −78 °C, and a cold (−78 °C) solution of freshly prepared aldehyde **22** (418 mg, 0.90 mmol) was added by cannula. The resultant solution was placed in a −35 °C bath and stirred for 2 h. Water (5 mL) was added followed by Et_2O, and the mixture was warmed to room temperature. The organic layer was washed with brine. The aqueous layer was extracted with Et_2O, and the combined extracts were dried over Na_2SO_4. Filtration and concentration followed by flash chromatography (6:1 to 4:1 to 2:1 to 1:1 hexanes−EtOAc with 1% triethylamine) provided an inseparable mixture of C14 epimers **37** (458 mg, 70%) as a viscous oil. Excess starting alkyne **35** (657 mg, 93% recovery) eluted first and was recovered. For **37**: R_f 0.20 (2:1 hexanes−EtOAc). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.26 (d, J = 8.7 Hz, 2 H), 6.87 (d, J = 8.7 Hz, 2 H), 4.67−4.60 (m, 3 H), 4.47 (m, 3 H), 4.28−4.22 (m, 1 H), 3.80 (s, 3 H), 3.73−3.56 (m, 4 H), 3.51−3.36 (m, 2 H), 3.48, 3.43, 3.41, 3.37, 3.36 (all s, major and minor signals, 12 H), 3.30 (m, 1 H), 3.19 (m, 1 H), 2.79−2.57 (m, 2 H), 1.99 (m, 1 H), 1.81−1.42 (m, 8 H), 1.17 (d, J = 6.9 Hz, 3 H), 1.17 (m 1 H), 0.93 (d, J = 6.0 Hz, 6 H), 0.88 (s, 9 H), 0.04 (s, 6 H). Anal. Calcd for $C_{39}H_{70}O_{10}Si$: C, 64.43; H, 9.70. Found: C, 64.71; H, 9.61.

C5−C20 Alcohol 38. To a flask charged with propargylic alcohol **37** (726 mg, 1.00 mmol) and 1,2-dimethoxyethane (40 mL) was added *p*-toluenesulfonyl hydrazide (9.31 g, 50.0 mmol) in one portion. The flask was fitted with a reflux condensor and warmed to reflux (bath temperature = 90 °C). A solution of NaOAc (4.51 g, 55.0 mmol) in H_2O (15 mL) was added by a syringe pump over 4 h. The reaction mixture was then cooled to room temperature, and Et_2O was added. The organic layer was washed with brine, the aqueous layer was extracted with Et_2O, and the combined extracts were dried over Na_2SO_4. Triethylamine (10 mL) was added with stirring to the mixture, resulting in a cloudy suspension that was stirred overnight. Filtration and concentration followed by flash chromatography (4:1 to 2:1 to 1:1) hexanes−EtOAc with 1% triethylamine) provided saturated alcohol **38** (576 mg, 79%) as a viscous oil consisting of a mixture of C14 epimers. On some occasions, incomplete reduction was noted and the material was resubjected to the above conditions resulting in complete reaction: R_f 0.69 (1:1 hexanes−EtOAc); IR (film) 3486 (broad) cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) mixture of C14 epimers δ 7.26 (d, J = 8.7 Hz, 2 H), 6.87 (d, J = 8.7 Hz, 2 H), 4.70−4.62 (m, 4 H), 4.49−4.46 (m, 2 H), 3.80 (s, 3 H), 3.74−3.62 (m, 3 H), 3.47−3.27 (m, 18 H), 1.99 (m, 1 H), 1.74−1.30 (m, 13 H), 1.13 (m, 1 H), 0.96−0.92 (m, 9 H), 0.89 (s, 9 H), 0.04 (s, 6 H). Anal. Calcd for $C_{39}H_{74}O_{10}Si$: C, 64.07; H, 10.20. Found: C, 63.79; H. 10.19.

Ketone 39. To a solution of alcohol **38** (324 mg, 0.44 mmol) in CH_2Cl_2 (10 mL) were added solid $NaHCO_3$ (375 mg) and the Dess−Martin periodinane (245 mg, 0.58 mmol).[9] The resultant solution was stirred for 2 h and then quenched by the simultaneous addition of saturated aqueous $Na_2S_2O_3$ and saturated aqueous $NaHCO_3$. Et_2O was added, and the biphasic mixture was stirred vigorously for 20 min, at which time both layers had cleared. The organic layer was washed with brine. The aqueous layer was extracted with Et_2O, and the combined extracts were dried over Na_2SO_4. Filtration and concentration followed by flash chromatography (2:1 hexanes−EtOAc, column deactivated with 1% triethylamine in the slurry, but not in the eluent) provided ketone **39** (273 mg, 84%) as a clear syrup: R_f 0.50 (2:1 hexanes−EtOAc); $[\alpha]_D$ −0.6 (*c* 1.4, $CHCl_3$); IR (film) 1716 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.26 (d, J = 8.7 Hz, 2 H), 6.88 (d, J = 8.7 Hz, 2 H), 4.69−4.62 (m, 4 H), 4.48 (s, 2 H), 3.80 (s, 3 H), 3.73−3.61 (m, 3 H), 3.53 (m, 1 H), 3.43−3.37 (m, 3 H), 3.40 (s, 3 H), 3.38 (s, 3 H), 3.37 (s, 3 H), 3.32 (s, 3 H), 3.31 (m, 1 H), 2.53−2.46 (m, 2 H), 1.94 (m, 1 H), 1.69−1.30 (m, 11 H), 1.14 (m, 1 H), 0.93−0.89 (m, 9 H), 0.89 (s, 9 H), 0.04 (s, 6 H), ^{13}C NMR (75 MHz, $CDCl_3$) δ 213.32, 159.10, 130.39, 129.21, 113.72, 98.44, 96.68, 87.83, 84.67, 78.26, 77.00, 72.99, 71.81, 59.39, 58.14, 57.42, 55.96, 55.72, 55.23, 38.89, 38.66, 36.04, 34.81, 33.95, 30.06, 29.85, 29.17, 27.20, 25.92, 19.99, 18.22, 16.60, 10.58, −5.35.

Vinyl Triflate 40. To a cold (−78 °C) solution of lithium hexamethyldisilazide (0.74 mL, 1.0 M in THF, 0.74 mmol) and 4 Å molecular sieves (ca. 400 mg) in THF (2.8 mL) and HMPA (0.7 mL) was added ketone **39 (**270 mg, 0.37 mmol) (azeotroped three times with benzene prior to use and precooled to −78 °C) in 2 mL of THF/HMPA (4:1). After 3 min, 2-[(*N*,*N*-bistrifluoromethylsulfonyl)amino]-5-chloropyridine (435 mg, 1.11 mmol)[23] in THF (2 mL, precooled to −78 °C) was added by a cannula. The resultant solution was stirred at −78 °C for 30 min and then at 0 °C for 30 min. Saturated aqueous $NaHCO_3$ was added along with Et_2O, and the mixture was warmed to room temperature. The organic layer was washed with brine. The aqueous layer was extracted with Et_2O, and the combined extracts were dried over Na_2SO_4. Filtration and concentration followed by flash chromatography (rapid purification on a short column of silica gel, 2:1 hexanes−EtOAc with 1% triethylamine) provided (*Z*)-vinyl triflate **40** (ca. 318 mg) as a clear oil. This material was used immediately without further purification: R_f 0.68 (2:1 hexanes−EtOAc); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.24 (d, J = 8.7 Hz, 2 H), 6.87 (d, J = 8.7 Hz, 2 H), 5.51 (dd, J = 8.1, 6.6 Hz, 1 H), 4.68−4.60 (m, 4 H), 4.47 (s, 2 H), 3.79 (s, 3 H), 3.72−3.61 (m, 3 H), 3.56 (m, 1 H), 3.47−3.28 (m, 4 H), 3.39 (s, 3 H), 3.36 (s, 6 H), 3.29 (s, 3 H), 2.28 (m, 1 H), 2.06 (m, 1 H), 1.95 (m, 1 H), 1.22−1.80 (m, 9 H), 0.94−0.88 (m, 10 H), 0.88 (s, 9 H), 0.03 (s, 6 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 159.11, 147.12, 130.27, 129.19, 122.63, 113.68, 98.42, 96.59, 84.65, 81.67, 77.96, 76.91, 72.95, 71.49, 59.32, 57.29, 56.76, 55.86, 55.63, 55.18, 38.64, 35.94, 33.93, 32.28, 30.85, 29.41, 27.28, 25.86, 20.03, 18.16, 16.47, 10.51, −5.41.

Trisubstituted Olefin 41. To a cold (−78 °C) solution of *B*-methoxy-9-borabicyclo[3.3.1]nonane (1.85 mL, 1.0 M in hexane, 1.85 mmol) in THF (10 mL) was added methyllithium (1.32 mL, 1.4 M in Et_2O, 1.84 mmol) dropwise. After 5 min at −78 °C, the bath was removed and the solution allowed to warm to room temperature. The mixture was stirred for 1 h, aqueous 3 M K_3PO_4 (0.62 mL, 1.85 mmol) was added, the solution turned cloudy, and a precipitate formed. After 1 min, a solution of vinyl triflate **40** (ca. 318 mg, 0.37 mmol) in DMF (10 mL) was added by cannula, resulting in a clear solution. Solid $PdCl_2$(dppf) was then added, and the resultant dark solution was stirred overnight. The reaction was quenched by the addition of H_2O followed by Et_2O. The organic layer was washed with brine, the aqueous layer was extracted with Et_2O, and the combined extracts were dried over Na_2SO_4. Filtration and concentration (0.05 mmHg for 1 h to remove DMF) followed by flash chromatography (6:1 and 4:1 hexanes−EtOAc with 1% triethylamine) provided olefin **41** (204 mg, 76% for two steps from ketone **39**) as a clear oil: R_f 0.63 (2:1 hexanes−EtOAc); $[\alpha]^{20}_D$ +10.3 (*c* 2.6, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.24 (d, J = 8.7 Hz, 2 H), 6.85 (d, J = 8.7 Hz, 2 H), 5.31 (t, J = 7.5 Hz, 1 H), 4.67−4.59 (m, 4 H), 4.46 (s, 2 H), 3.78 (s, 3 H), 3.71−3.61 (m, 3 H), 3.45−3.33 (m, 4 H), 3.39 (s, 3 H), 3.35 (s, 3 H), 3.34 (s, 3 H), 3.29 (t, J = 4.8 Hz, 1 H), 3.12 (s, 3 H), 2.12 (m, 1 H), 1.98−1.79 (m, 2 H), 1.73−1.38 (m, 9 H), 1.48 (s, 3 H), 0.96 (m, 1 H), 0.92−0.87 (m, 9 H), 0.87 (s, 9 H), 0.03 (s, 6 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 159.07, 135.05, 130.32, 129.11, 127.44, 113.63, 98.21, 96.59, 88.14, 84.45, 78.47, 77.16, 72.91, 71.94, 59.39, 57.29, 55.78, 55.61, 55.54, 55.13, 38.68, 38.45, 36.16, 34.60, 33.97, 31.30, 30.18, 27.82, 25.84, 20.13,

18.14, 16.36, 10.51, 10.35, −5.42, −5.47. Anal. Calcd for $C_{40}H_{74}O_9Si$: C, 66.07; H, 10.26. Found: C, 66.30; H, 10.27.

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Supporting Information Available: Experimental procedures for **30**−**35**, **44**−**49**, **52**−**66**, and *O*-methylmandelates of **55** and **66**; ^{1}H and ^{13}C NMR spectra of **3**, **7**, **10**, **11**, **12**, **15**, **20**, **22**, **31**, **34**, **39**, **40**, **55**, **56**, **57**, and **61**; ^{1}H NMR spectra of the *(R)*- and *(S)*-*O*-methyl mandelates of **12**, **20**, **55**, and **66**. This information is available free of charge via the Internet at http://pubs.acs.org.

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