Total Synthesis of the Cytotoxic *Threo, Trans, Erythro, Cis, Threo* Annonaceous Acetogenin Trilobin

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A synthesis of trilobin, a new stereochemical varient of the adjacent bis-tetrahydrofuran subgroup of the Annonaceous acetogenins, is described. The synthesis involves three stereochemically defining carbon−carbon bond-forming steps. The first of these introduces the C23−C24 stereocenters and the left side chain by means of an S_E2' addition of the nonracemic 11-carbon γ-oxygenated allylic indium reagent derived from the α-oxygenated allylic stannane **4** to a C24−C16 core aldehyde **3**. The second develops the C15−C16 stereocenters and a segment of the right chain through BF_3-promoted S_E2' addition of the nonracemic 6-carbon γ-oxygenated allylic stannane **11** to the C16−C34 aldehyde **10**. The third employs the addition of the dialkylzinc reagent **17** to the C10−C34 aldehyde **15** in the presence of a chiral bis-sulfonamide catalyst to establish the C10 stereocenter while adding the C1−C9 residue of the right chain. The C36 stereocenter and the butenolide are appended through condensation of the C1−C34 ester with the protected (*S*)-lactaldehyde **23**.

The recently described Annonaceous acetogenins trilobacin and trilobin are the first known members of adjacent bis-tetrahydrofuran Annonaceous acetogenins with a *threo, trans, erythro, cis, threo* backbone (Figure 1).[1] We have previously delineated methodology that could, in principle, be employed for the synthesis of any possible stereochemical arrangement of this backbone,[2] and have applied this methodology to total syntheses of the *threo, trans, threo, trans, threo* compounds (+)-asimicin,[3] (+)-asiminecin,[4] (+)-asiminocin,[4] and the *threo, trans, threo, trans, erythro* acetogenin (+)-(30*S*)-bullanin.[5] The high potency of trilobin and trilobacin against human lung cancer, breast cancer, and colon cancer cell lines (one million to nearly 10 billion times the cytotoxic potency of the reference compound, adriamycin),[1] coupled with their unusual backbone stereochemistry and limited availability,[6] stimulated our interest in undertaking a total synthesis of these natural products.

As a test of the methodology and strategy, we selected trilobin as our synthetic target. Our proposed route, outlined in Figure 2, parallels that followed in our recent synthesis of the nonadjacent bis-tetrahydrofuran squamostatin-D.[7] The stereocenters of intermediates **B** and **C** are formed through S_E2' additions of γ-oxygenated nonracemic allylic indium and tin reagents to aldehydes **A** and **B**. The C10 stereocenter of intermediate **D** is introduced by addition of a dialkylzinc reagent catalyzed by a nonracemic bis-sulfonamide. Introduction of the butenolide moiety, and the remaining stereocenter, is achieved through condensation of ester **D** with a protected lactic aldehyde.

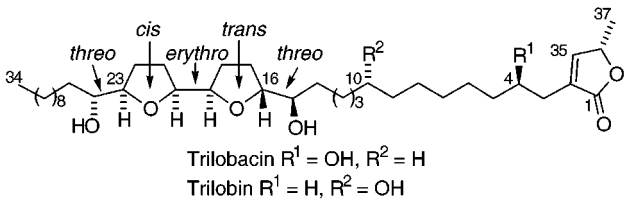

Figure 1. Proposed structures for trilobacin and trilobin.

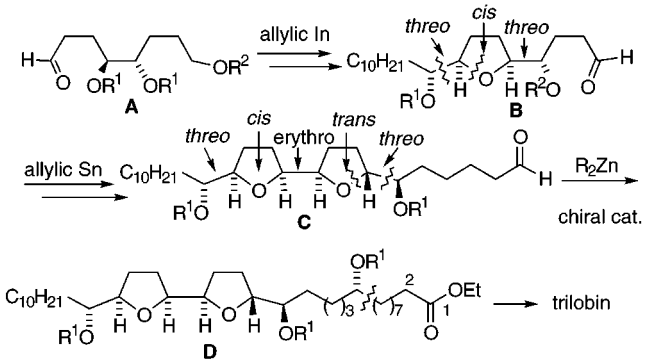

Figure 2. Proposed synthetic route to trilobin.

The starting material for this project, aldehyde **3** of >95% ee, was prepared as previously described[5,8] from alcohol **1** by a sequence involving (1) ortho ester Claisen rearrangement, (2) asymmetric dihydroxylation leading to hydroxy lactone **2** of >95% ee,[9] (3) formation of the

(1) (a) Zhao, G.-X.; Gu, Z.-M.; Zeng, L. Chao, J.-F.; Kozlowski, J. F.; Wood, K. V.; McLaughlin, J. L. *Tetrahedron* **1995**, *51*, 7149. (b) Reviews: Cavé, A.; Figadére, B.; Laureno, A.; Cortes, D. In *Progress in the Chemistry of Natural Products*; Herz, W., Kirby, G.-W., Moore, R. E., Steglich, W., Tamm, Ch., Eds.; Springer: New York, 1997; Vol. 70, pp 81−288. Zeng, L.; Ye, Q.; Oberlies, N. H.; Shi, G.; Gu, Z.-M.; He, K.; McLaughlin, J. L. *Nat. Prod. Rep.* **1996**, 275. (c) For leading references to recent synthetic efforts in this area, see Hoye, T. R.; Ye, Z. *J. Am. Chem. Soc.* **1996**, *118*, 1801. Yazbec, A.; Sinha, S. C.; Keinan, E. *J. Org. Chem.* **1998**, *63*, 5863.

(2) Marshall, J. A.; Hinkle, K. W. *J. Org. Chem.* **1996**, *61*, 4247.

(3) Marshall, J. A.; Hinkle, K. W. *J. Org. Chem.* **1997**, *62*, 5989.

(4) Marshall, J. A.; Chen, M.; *J. Org. Chem.* **1997**, *62*, 5996.

(5) Marshall, J. A.; Hinkle, K. W. *Tetrahedron Lett.* **1998**, *39*, 1303.

(6) Only 4 mg was obtained in pure form from 200 g of stem bark extract.[1a]

(7) Marshall, J. A.; Jiang, H. *J. Org. Chem.* **1998**, *63*, 7066.

(8) Sinha, S. C.; Sinha, A.; Yazbec, A.; Keinan, E. *J. Org. Chem.* **1996**, *61*, 7640.

(9) Kolb, H. C.; VanNiewenkze, M. S.; Sharpless, K. B. *Chem. Rev.* **1994**, *94*, 2483. The ee of hydroxy lactone **2** was determined through ^{1}H NMR analysis of the *(R)*- and *(S)*-*O*-methyl mandelates as described in the Ph.D. Thesis of Kevin Hinkle, University of Virginia, 1998. Copies of these spectra are included in the Supporting Information.

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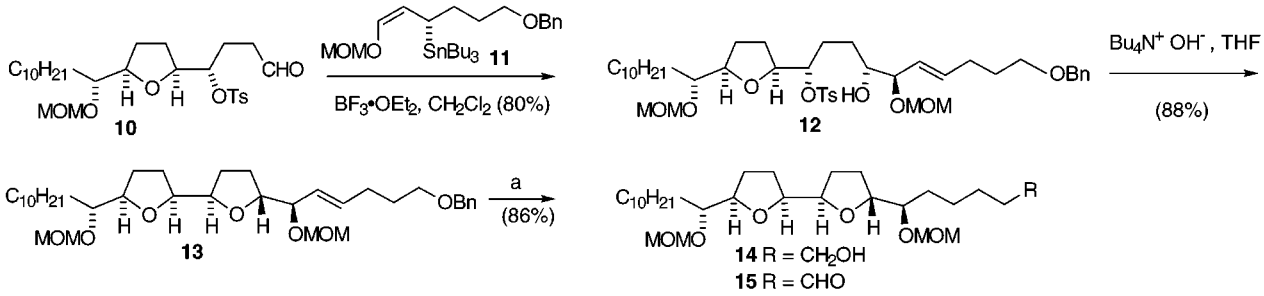
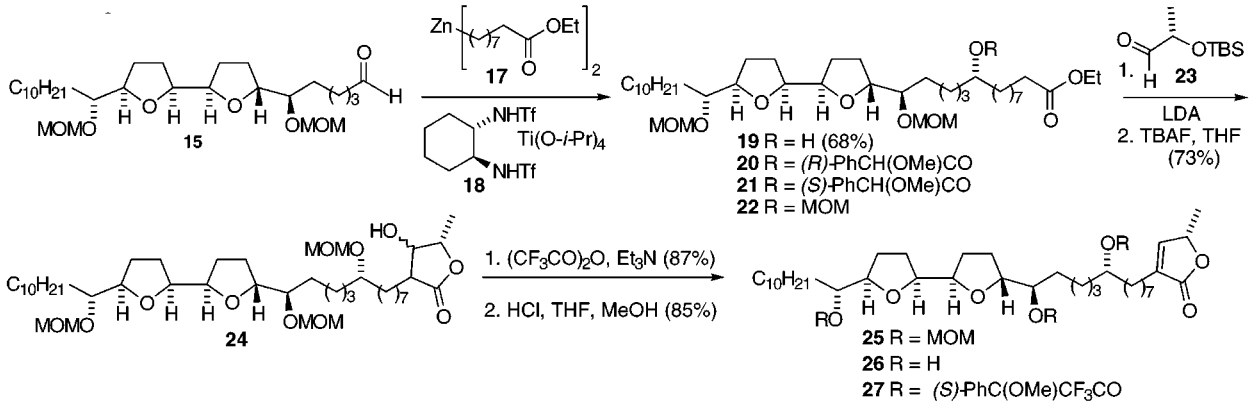
Scheme 1

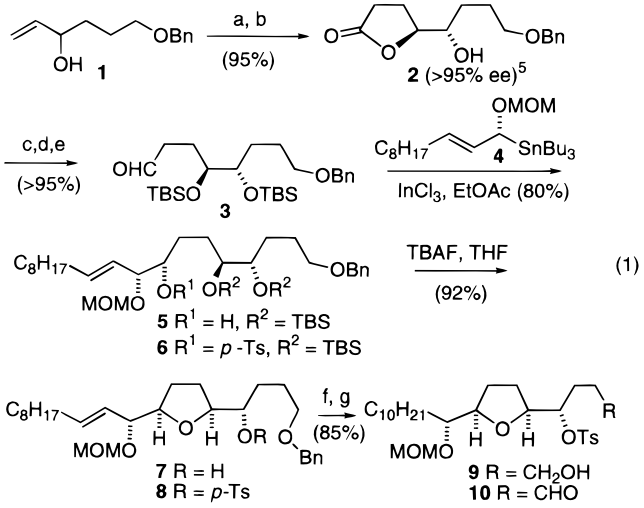


a) 1. H_2/Pd-C, EtOAc, (86%); 2. Dess-Martin periodinane (86%)

Scheme 2



Weinreb amide,[10] (4) diol protection as the bis-TBS ether, and (5) reduction of the Weinreb amide (eq 1). Addition



a) $(MeO)_3CMe$, $EtCO_2H$, heat (96%); b) AD-mix β (99%); c) MeONHMe•HCl, $AlMe_3$ (99%); d) TBSCl, Im (99%); e) DIBAL-H (99%) f) H_2/Pd-C, EtOAc-EtOH (90%); g) Dess-Martin periodinane (95%)

of the γ-alkoxy allylic indium reagent derived from the (*R*)-α-OMOM allylic stannane **4** and $InCl_3$[11,12] afforded the *anti* adduct **5** as a single diastereomer in 80% yield. The derived tosylate **6** cyclized to the *cis threo* tetrahydrofuran **7** upon exposure to TBAF in THF. The ^{1}H NMR spectrum of this cyclc product was devoid of spurious signals that would be expected to arise from diastereomeric byproducts, thereby confirming the high diastereo- and enantioselectivity of the stannane addition step leading to the precursor **6**. The tosylate derivative **8** was hydrogenated with concomitant hydrogenolysis of the benzyl ether over 5% Pd−C as the catalyst to afford the alcohol **9** in 90% yield. Oxidation to the aldehyde **10** was effected with the Dess−Martin periodinane reagent[13] in 95% yield (eq 1).

Completion of the bis-tetrahydrofuran core was effected by addition of the (*S*)-γ-OMOM allylic stannane **11**[14] to aldehyde **10** with BF_3•OEt_2 in CH_2Cl_2 to afford the *syn* adduct **12** in 80% yield. Treatment of this adduct with Bu_4NOH in THF led to the bis-tetrahydrofuran **13** with the requisite *threo*, *trans*, *erythro*, *cis threo* core stereochemistry. Again, the ^{1}H NMR spectrum of this cyclic ether was free of signals that would arise from stereoisomeric byproducts. Hydrogenation − hydrogenolysis of **13** over 5% Pd−C gave the saturated alcohol **14** in 86% yield. Oxidation, as before, with the periodinane reagent[13] led to the aldehyde **15** in 86% yield (Scheme 1).

For introduction of the C1−C9 carbon chain of trilobin, the diorganozinc reagent **17** was required. This intermediate was prepared from unsaturated ester **16**[15] through boron−zinc exchange of the derived organoborane with Et_2Zn (eq 2).[16]

Addition of **17** to aldehyde **15** in the presence of the (*S*,*S*)-1,2-diaminocyclohexane-bis-triflamide **18** as a catalyst afforded adduct **19** in 68% yield (Scheme 2).[16] The

(10) Baska, A.; Lipton, M.; Weinreb, S. M. *Tetrahedron Lett.* **1977**, *17*, 4171.

(11) Stannane **4** was prepared from (*E*)-2-undecenal by the sequence (1) $LiSnBu_3$ then ADD (1,1′-(azodicarbonyl)dipiperidine); (2) (*S*)-BINAL-H; (3) MOMCl, *i*-Pr_2NEt.[2] For details see the Supporting Information.

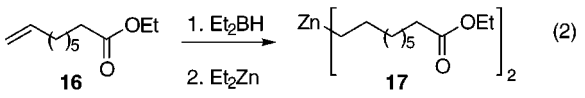
(12) Marshall, J. A.; Jiang, H. *Tetrahedron Lett.* **1998**, *39*, 1493.

(13) Dess, D. B.; Martin, J. C. *J. Org. Chem.* **1983**, *48*, 4156. Meyer, S. D.; Schreiber, S. L. J. *Org. Chem.* **1994**, *59*, 7549.

(14) The α-OMOM precursor of stannane **11** was prepared from (*E*)-6-(benzyloxy)-2-hexenal by the sequence of ref 10. Isomerization to the γ-isomer **11** was effected with BF_3•OEt_2 in CH_2Cl_2. For details, see the Supporting Information.

(15) Liu, S.-H. *J. Org. Chem.* **1977**, *42*, 3209.

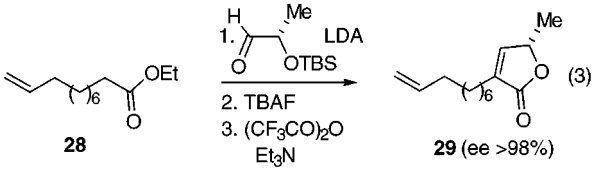
(16) Lutz, C.; Knochel, P. *J. Org. Chem.* **1997**, *62*, 7895.



ee of this adduct was judged to be >95% based on analysis of the ^{1}H NMR spectra of the *(R)*- and *(S)*-O-methyl mandelates **20** and **21**.[17] Protection of alcohol **19** as the MOM ether **22** followed by condensation with (*S*)-OTBS lactaldehyde **23**[18] yielded the hydroxy lactone **24** which was dehydrated by treatment with $(CF_3CO)_2O$ and Et_3N to afford butenolide **25** in 63% overall yield for the three steps.[19]

The final stage of the synthesis, deprotection of the MOM ethers of butenolide **25**, was effected in 85% yield with aqueous HCl in methanol−THF. The resulting product **26** was identified as (+)-trilobin through comparison of the ^{1}H and ^{13}C NMR spectra, and the ^{1}H NMR spectrum of the (*S*)-Mosher ester derivative **27**[20] with those of the natural product.[1a] The rotation was somewhat lower than that reported (+22.7 compared to +33.3[1a]). However, the latter was measured in methanol at a concentration of 0.15 mg/mL. We employed CH_2Cl_2 as the solvent for our measurement because of the limited solubility of the material in methanol and the intrinsic error associated with the determination of small rotational values of dilute samples.

A recent report indicated that racemization of the butenolide moiety of Annonaceous acetogenins was effected by treatment with Et_2NH, implying that these compounds are configurationally labile under even weakly basic conditions.[21] This report was of some concern to us as the elimination reaction leading to butenolide **25** employs Et_3N as the base and a previous synthesis of asiminocin and asiminecin involved a Sonogashira coupling of a vinylic iodide and a terminal acetylenic butenolide in which Et_2NH served as the solvent.[4] We therefore conducted a control experiment with butenolide **29** of >98% ee (prepared as detailed in eq 3) to evaluate



its stability toward amine bases. Upon stirring for 16 h in Et_2NH, the ee of **29** fell to 80% as measured by GC and optical rotation (Table 1). The same experiment with Et_3N as solvent led to negligible loss of ee. In refluxing Et_2NH, racemization of butenolide **29** was complete within 24 h. We also carried out the coupling of a terminal alkynyl butenolide with 1-bromopropene (~1.5:1 *E*:*Z*) under the Sonogashira conditions (2 h reaction time at room temperature).[22] The coupling products exhibited a 10% decrease in ee compared to the starting material. It would therefore appear that exposure to diethylamine, but not triethylamine, can indeed effect racemization of the 4-methylbutenolide moiety.

Table 1. Enantiomeric Stability of Butenolide 29 in Amine Solvents

solvent	*T*, °C	*t*, h	**29** ee, %[a]
Et_2NH	23	16	80
Et_3N	23	16	~98
Et_2NH	reflux	24	0

[a] Analysis by GC and optical rotation.

The present synthesis of trilobin confirms the assigned structure and demonstrates the applicability of chiral oxygenated allylic metal methodology to this subgroup of interesting natural products. Future studies will be directed toward other subgroups and analogues of the most cytotoxic members of the family.

Experimental Section

(9*E*)-(11*R*,12*S*,15*S*,16*S*)-19-(Benzyloxy)-15,16-bis[(*tert*-butyldimethylsilyl)oxy]-11-(methoxymethoxy)-9-nonadecen-12-ol (5). A solution of 0.92 g (4.16 mmol) of $InCl_3$ in 80 mL of EtOAc was sonicated for 15 min, and to it was added a solution of 2.00 g (4.04 mmol) of aldehyde **3**[5] in 1.0 mL of EtOAc. The mixture was cooled to −78 °C, and a solution of 3.04 g (6.04 mmol) of stannane **4** in 1.0 mL of EtOAc was added. The reaction mixture was allowed to warm to room temperature (3 h), quenched with $NaHCO_3$, and extracted with ether. The extracts were washed with brine, dried over $MgSO_4$, filtered, and concentrated under reduced pressure. Purification by column chromatography on silica gel (elution with 10% EtOAc in hexane) afforded 2.24 g (80%) of alcohol **5**. $[\alpha]_D$ −56.8 (*c* 1.26, $CHCl_3$); IR (film) 3493, 2925, 2846 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.33 (m, 5 H), 5.71 (dt, J = 8.8, 15.8 Hz, 1 H), 5.40 (dd J = 8.6, 15.8 Hz, 1 H), 4.73 (d, J = 6.5 Hz, 1 H), 4.55 (d, J = 6.5 Hz, 1 H), 4.50 (s, 2 H), 3.91 (m, 1 H), 3.69 (m, 1 H), 3.56 (m, 2 H), 3.47 (t, J = 6.9 Hz, 2 H), 3.37 (s, 3 H), 2.06 (m, 2 H), 1.21−1.83 (m, 20 H), 0.88 (m, 21 H), 0.04 (m, 12 H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 137.8, 128.2, 127.5, 127.3, 124.7, 93.3, 80.1, 75.4, 75.2, 73.5, 72.7, 70.7, 55.4, 32.4, 31.8, 29.5, 29.4, 29.2, 29.1, 27.1, 26.7, 26.0, 25.8, 22.6, 18.0, 14.1, −4.1, −4.2, −4.5, −4.6. Anal. Calcd for $C_{40}H_{76}O_6Si_2$: C, 67.74; H, 10.80. Found: C, 67.86; H, 10.79.

(9*E*)-(11*R*,12*R*,15*S*,16*S*)-19-(Benzyloxy)-11-(methoxymethoxy)-12,15-oxido-9-nonadecen-16-ol (7). To a solution of 2.10 g (2.82 mmol) of alcohol **5** in 2.0 mL of pyridine was added 3.20 g (16.8 mmol) of TsCl. The reaction mixture was stirred at room temperature for 12 h, quenched with water, and extracted with ether. The extracts were washed with brine, dried over $MgSO_4$, and concentrated under reduced pressure. To the residue was added 60.0 mL of THF followed by 17.0 mL (17.0 mmol) of TBAF (1.0 M in THF). The reaction mixture was heated at 45 °C for 12 h, quenched with water, and extracted with ether. The ether extracts were washed with brine, dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The crude product was purified by column chromatography on silica gel (elution with 20% EtOAc in hexane) to afford 1.20 g (92%) of alcohol **7**. $[\alpha]_D$ −62.2 (*c* 0.78, $CHCl_3$); IR (film) 3458, 2916, 2855 cm^{-1}; ^{1}H NMR ($CDCl_3$ 300 MHz) δ 7.33 (m, 5 H), 5.70 (dt, J = 6.9, 15.8 Hz, 1 H), 5.36 (dd, J = 8.5, 15.5 Hz, 1 H), 4.73 (d, J = 6.5 Hz, 1 H), 4.55 (d, J = 6.5 Hz, 1 H), 4.51 (s, 2 H), 4.04 (m, 1 H), 3.90 (m, 2 H), 3.52 (m, 2 H), 3.40 (m, 1 H), 3.38 (s, 3 H), 2.05 (m, 2 H), 1.18−

(17) Trost, B. M.; Belletire, J. L.; Godleski, S.; McDougal, P. G.; Balkovec, J. M.; Baldwin, J. J.; Christy, M. E.; Ponticello, G. S.; Varga, S. L.; Springer, J. D. *J. Org. Chem.* **1986**, *51*, 2370.

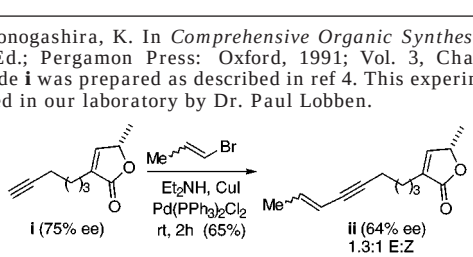
(18) Massad, S. K.; Hawkins, L. D.; Baker, D. C. *J. Org. Chem.* **1983**, *48*, 5180.

(19) Yao, Z.-J.; Wu, Y.-L. *Tetrahedron Lett.* **1994**, *35*, 157.

(20) Dale, J. A.; Dull, D. L.; Mosher, H. S. *J. Org. Chem.* **1969**, *34*, 2543.

(21) Duret, P.; Figadère, B.; Hocquemiller, R.; Cavé, A. *Tetrahedron Lett.* **1997**, *38*, 8849.

(22) Sonogashira, K. In *Comprehensive Organic Synthesis*; Trost, B. M., Ed.; Pergamon Press: Oxford, 1991; Vol. 3, Chapter 2.4. Butenolide **i** was prepared as described in ref 4. This experiment was performed in our laboratory by Dr. Paul Lobben.



1.97 (m, 20 H), 0.88 (t, J = 7.0 Hz, 3 H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 138.5, 136.6, 128.2, 127.5, 127.3, 126.4, 93.3, 82.6, 81.6, 79.4, 72.7, 70.2, 55.4, 32.2, 31.8, 31.1, 29.3, 29.2, 29.1, 29.0, 28.0, 27.8, 26.1, 22.6, 14.0. Anal. Calcd for $C_{28}H_{46}O_5$: C, 72.69; H, 10.02. Found: C, 72.67; H, 10.06.

Tosylate 8. A mixture of 0.20 g (0.43 mmol) of alcohol **7** and 0.30 g (1.57 mmol) of TsCl in 0.5 mL of pyridine was stirred at room temperature for 12 h. The reaction mixture was quenched with water and extracted with ether. The extracts were washed with brine, dried over $MgSO_4$, filtered, and concentrated under reduced pressure. Purification by column chromatography on silica gel (elution with 15% EtOAc in hexane) afforded 0.24 g (90%) of tosylate **8**. $[\alpha]_D$ −21.2 (*c* 0.66, $CHCl_3$); IR (film) 2925, 2855 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.80 (d, J = 8.5 Hz, 2 H), 7.30 (m, 7 H), 5.64 (dd, J = 7.3, 14.6 Hz, 1 H), 5.20 (dd, J = 6.9, 15.8 Hz, 1 H), 4.70 (d, J = 6.5 Hz, 1 H), 4.65 (m, 1 H), 4.54 (d, J = 6.5 Hz, 1 H), 4.44 (s, 2 H), 4.08 (m, 1 H), 3.87 (m, 2 H), 3.39 (t, J = 6.9 Hz, 2 H), 3.32 (s, 2 H), 2.42 (s, 3 H), 2.01 (m, 2 H), 1.20−1.95 (m, 20 H), 0.88 (t, J = 6.9 Hz, 3 H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 144.3, 138.4, 136.6, 134.6, 129.6, 128.3, 127.7, 127.4, 125.8, 93.3, 84.2, 81.9, 79.0, 72.7, 69.6, 55.1, 32.3, 31.8, 29.3, 29.2, 29.1, 29.0, 28.0, 27.4, 27.0, 25.4, 22.6, 21.5, 14.1.

Mono-THF Alcohol 9. A mixture of 0.087 g (0.14 mmol) of tosylate **8** and 0.085 g of 5% Pd−C in 1.0 mL of EtOAc−EtOH (3:1) was placed under a H_2 atmosphere. The reaction mixture was stirred for 12 h and filtered through Celite. The solvent was removed under reduced pressure, and the crude product was purified by column chromatography on silica gel (elution with 40% EtOAc in hexane) to afford 0.067 g (90%) of alcohol **9**. $[\alpha]_D$ +31.4 (*c* 0.65, $CHCl_3$); IR (film) 3449, 2933, 2855 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.70 (d, J = 8.5 Hz, 2 H), 7.31 (d, J = 8.5 Hz, 2 H), 4.77 (d, J = 6.5 Hz, 1 H), 4.64 (m, 1 H), 4.61 (d, J = 6.5 Hz, 1 H), 4.02 (m, 1 H), 3.85 (m, 1 H), 3.56 (t, J = 6.9 Hz, 2 H), 3.42 (m, 1 H), 3.36 (s, 3 H), 2.43 (s, 3 H), 1.17−1.94 (m, 26 H), 0.88 (t, J = 7.0 Hz, 3 H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 144.5, 134.5, 129.6, 127.6, 96.6, 83.9, 82.4, 79.6, 78.7, 62.1, 55.7, 31.9, 31.2, 29.8, 29.6, 29.3, 28.1, 27.7, 27.0, 25.3, 22.6, 21.6, 14.1.

Mono-THF Aldehyde 10. To a solution of 0.105 g (0.20 mmol) of alcohol **9** in 2.0 mL of CH_2Cl_2 was added 0.130 g (0.31 mmol) of Dess−Martin periodinane.[13] The reaction mixture was stirred for 60 min, quenched with $Na_2S_2O_3$, and extracted with ether. The ether extracts were washed with brine, dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The crude product was purified by column chromatography on silica gel (elution with 25% EtOAc in hexane) to afford 0.101 g (95%) of aldehyde **10**. $[\alpha]_D$ +17.1 (*c* 0.55, $CHCl_3$); IR (film) 2916, 2864, 1719 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 9.70 (s, 1 H), 7.80 (d, J = 8.5 Hz, 2 H), 7.33 (d, J = 8.5 Hz, 2 H), 4.75 (d, J = 6.9 Hz, 1 H), 4.67 (m, 1 H), 4.62 (d, J = 6.9 Hz, 1 H), 3.96 (m, 1 H), 3.84 (m, 1 H), 3.41 (m, 1 H), 3.36 (s, 3 H), 2.57 (t, J = 7.7 Hz, 2 H), 2.45 (s, 3 H), 1.13−2,14 (m, 24 H), 0.88 (t, J = 6.9 Hz, 3 H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 200.7, 144.6, 134.2, 129.7, 127.7, 96.6, 82.7, 82.3, 79.6, 78.9, 55.6, 39.4, 31.8, 31.0, 29.8, 29.6, 29.3, 27.5, 27.1, 25.3, 23.2, 22.6, 21.6, 14.1.

Alcohol 12. To a mixture of 0.28 g (0.53 mmol) of mono-THF aldehyde **10** and 0.29 g (0.58 mmol) of stannane **11**[14] in 3.0 mL of CH_2Cl_2 at −78 °C was slowly added 0.08 mL (0.60 mmol) of BF_3•OEt_2. The reaction mixture was stirred at −78 °C for 30 min, quenched with $NaHCO_3$, diluted with ether and allowed to warm to room temperature. The aqueous layer was extracted with ether and the combined ether extracts were washed with brine, dried over $MgSO_4$ and concentrated under reduced pressure. The crude product was purified by column chromatography on silica gel (elution with 30% EtOAc in hexane) to afford 0.31 g (80%) of alcohol **12**. $[\alpha]_D$ -11.2 (*c* 0.55, $CHCl_3$); IR (film) 3501, 2925, 2855 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.80 (d, J = 8.5 Hz, 2 H), 7.31 (m, 7 H), 5.70 (dt, J = 8.8, 15.7 Hz, 1 H), 5.24 (dd, J = 8.8, 15.8 Hz, 1 H), 4.77 (d, J = 6.9 Hz, 1 H), 4.69 (d, J = 6.9 Hz, 1 H), 4.66 (m, 1 H), 4.62 (d, J = 6.9 Hz, 1 H), 4.50 (m, 3 H), 4.00 (m, 1 H), 3.83 (m, 1 H), 3.73 (m, 1 H), 3.48 (t, J = 6.7 Hz, 2 H), 3.41 (m, 2 H), 3.36 (s, 6 H), 2.42 (s, 3 H), 2.17 (m, 2 H), 1.19−2.11 (m, 28 H), 0.88 (t, J = 6.9 Hz, 3 H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 144.2, 138.5, 136.8, 134.7, 129.5, 128.3, 127.6, 127.5, 127.4, 126.4, 96.7, 93.4, 84.6, 82.3, 80.4, 79.7, 78.7, 77.2, 73.3, 72.8, 69.5, 55.6, 55.5, 31.8, 31.0, 29.8, 29.6, 29.3, 29.1,29.0, 28.4, 27.5, 27.2, 25.3, 22.6, 21.5, 14.1.

Bis-THF Olefin 13. To a solution of 0.29 g (0.37 mmol) of alcohol **12** in 10.0 mL of THF was added 1.50 mL (1.50 mmol) of Bu_4NOH (1.0 M in MeOH). The reaction mixture was heated at 45 °C for 60 min, allowed to cool to room temperature, quenched with water, and extracted with ether. The ether extracts were washed with brine, dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The crude product was purified by column chromatography on silica gel (elution with 20% EtOAc in hexane) to afford 0.20 g (88%) of bis-THF olefin **13**. $[\alpha]_D$ −9.4 (*c* 0.67, $CHCl_3$); IR (film) 2925, 2846 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.37 (m, 5 H), 5.70 (dt, J = 8.8, 15.7 Hz, 1 H), 5.31 (dd, J = 8.8, 15.7 Hz, 1 H), 4.85 (d, J = 6.9 Hz, 1 H), 4.69 (d, J = 6.9 Hz, 1 H), 4.66 (d, J = 6.9 Hz, 1 H), 4.57 (d, J = 6.9 Hz, 1 H), 4.49 (s, 2 H), 4.00 (m, 1 H), 3.88 (m, 2 H), 3.80 (m, 2 H), 3.46 (d, J = 6.8 Hz, 2 H), 3.45 (m, 1 H), 3.39 (s, 3 H), 3.37 (s, 3 H), 2.16 (m, 2 H), 1.20−2.10 (m, 28 H), 0.88 (t, J = 6.9 Hz, 3 H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 138.5, 135.2, 128.3, 127.5, 127.4, 126.8, 96.6, 93.3, 82.4, 81.7, 81.6, 81.4, 81.3, 80.0, 78.8, 72.8, 69.5, 55.6, 55.1, 31.8, 31.3, 29.7, 29.5, 29.3, 29.1, 28.9, 28.8, 28.6, 28.1. 27.5, 25.3, 22.6, 14.0. Anal. Calcd for $C_{36}H_{60}O_7$: C, 71.49; H, 10.00. Found: C, 71.43; H, 9.96.

Bis-THF Alcohol 14. A mixture of 0.30 g (0.50 mmol) of olefin **13** and 0.30 g of 5% Pd−C in 3.0 mL of EtOAc was placed under a H_2 atmosphere. The reaction mixture was stirred for 40 h and filtered through Celite. The solvent was removed under reduced pressure, and the crude product was purified by column chromatography on silica gel (elution with 50% EtOAc in hexane) to afford 0.22 g (86%) of alcohol **14**. $[\alpha]_D$ +40.8 (*c* 0.53, $CHCl_3$); IR (film) 3440, 2925, 2855 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 4.84 (d, J = 6.9 Hz, 1 H), 4.82 (d, J = 6.9 Hz, 1 H), 4.68 (d, J = 1.9 Hz, 1 H), 4.66 (d, J = 1.9 Hz, 1 H), 3.98 (m, 1 H), 3.88 (m, 1 H), 3.81 (m, 2 H), 3.64 (t, J = 6.8 Hz, 2 H), 3.46 (m, 2 H), 3.39 (s, 6 H), 1.16−2.10 (m, 34 H), 0.88 (t, J = 6.9 Hz, 3 H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 96.7, 96.6, 82.5, 81.7, 81.5, 81.1, 80.0, 79.6, 62.8, 55.7, 55.6, 32.6, 31.9, 31.3, 31.1, 29.8, 29.6, 29.3, 29.1, 28.4, 28.3, 27.5, 25.8, 25.3, 25.1, 22.6, 14.1.

Bis-THF Aldehyde 15. To a solution of 0.147 g (0.28 mmol) of alcohol **14** in 2.0 mL of CH_2Cl_2 was added 0.160 g (0.37 mmol) of Dess−Martin periodinane.[13] The reaction mixture was stirred for 60 min, quenched with $Na_2S_2O_3$, and extracted with ether. The ether extracts were washed with brine, dried over $MgSO_4$, filtered, and concentrated under reduced pressure. Purification by column chromatography on silica gel (elution with 20% EtOAc in hexane) afforded 0.126 g (86%) of aldehyde **15**. $[\alpha]_D$ +46.9 (*c* 0.63, $CHCl_3$); IR (film) 2916, 2846, 1728 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 9.77 (t, J = 1.9 Hz, 1 H), 4.84 (d, J = 6.9 Hz, 1 H), 4.81 (d, J = 6.9 Hz, 1 H), 4.66 (d, J = 6.9 Hz, 2 H), 3.98 (m, 1 H), 3.88 (m, 1 H), 3.81 (m, 2 H), 3.46 (m, 2 H), 3.39 (s, 3 H), 3.38 (s, 3 H), 2.44 (dt, J = 1.9, 7.3 Hz, 2 H), 1.20−2.10 (m, 32 H), 0.88 (t, J = 6.9 Hz, 3 H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 202.3, 96.7, 96.5, 82.4, 81.8, 81.6, 81.1, 79.9, 79.3, 55.6, 43.7, 31.8, 31.3, 30.8, 29.7, 29.5, 29.2, 28.9, 28.4, 28.2, 27.4, 25.2, 25.0, 22.6, 22.1, 14.0. Anal. Calcd for $C_{29}H_{54}O_7$: C, 67.67; H, 10.57. Found: C, 67.89; H, 10.51.

Alcohol 19. To 0.30 g (1.62 mmol) of ethyl 8-nonenoate **16**[15] was slowly added 0.20 mL (0.76 mmol) of Et_2BH (3.8 M in ether) at −10 °C. The reaction mixture was allowed to warm to room temperature and stirred for 2 h. Solvent and other volatiles were removed under reduced pressure (0.05 mmHg, 30 min) to afford the hydroboration product. To this organoborane was added 0.25 mL (2.34 mmol) of Et_2Zn at 0 °C. The reaction mixture was stirred for 30 min, and the excess Et_2Zn and Et_3B were removed under vacuum (0.05 mmHg, 3 h). The resulting dialkylzinc was diluted with 0.5 mL of ether. A mixture of 0.007 g (0.01 mmol) of (1*S*,2*S*)-1,2-bis-(trifluoromethanesulfonamido)cyclohexane **18** and 0.08 mL (0.28 mmol) of Ti(O-i-Pr)$_4$ in 0.5 mL of ether was stirred at room temperature for 10 min and cooled to −60 °C. To it was added

the dialkylzinc solution, and the mixture was warmed to −20 °C. After 20 min, a solution of 0.040 g (0.08 mmol) of aldehyde **15** in 0.5 mL of ether was added. The reaction mixture was stirred at −20 °C for 16 h, quenched with 1.0 M HCl, and extracted with ether. The extracts were washed with brine, dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The crude product was purified by column chromatography on silica gel (elution with 30% EtOAc in hexane) to afford 0.037 g (68%) of alcohol **19**. $[\alpha]_D$ +33.7 (*c* 0.3 $CHCl_3$); IR (film) 3458, 2916, 2855 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 4.84 (d, J = 6.9 Hz, 1 H), 4.81 (d, J = 6.9 Hz, 1 H), 4.66 (d, J = 6.9 Hz, 2 H), 4.11 (q, J = 7.3 Hz, 2 H), 3.98 (m, 1 H), 3.87 (m, 1 H), 3.80 (m, 2 H), 3.57 (m, 1 H), 3.44 (m, 2 H), 3.38 (s, 6 H), 2.28 (t, J = 7.7 Hz, 2 H), 1.13−2.10 (m, 51 H), 0.88 (t, J = 6.9 Hz, 3 H); ^{13}C NMR ($CDCl_3$, 300 MHz) δ 173.8, 96.6, 82.4, 81.8, 81.7, 81.5, 81.1, 80.0, 79.6, 79.5, 71.8, 60.1, 55.6, 37.4, 37.3, 36.6, 36.5, 34.3, 31.8, 31.3, 31.2, 31.1, 29.7, 29.5, 29.3, 29.2, 29.1, 29.0, 28.4, 28.3, 27.5, 25.7, 25.6, 25.5, 25.3, 24.9, 22.6, 14.2, 14.0. Anal. Calcd for $C_{40}H_{76}O_9$: C, 68.53; H, 10.93. Found: C, 68.29; H, 10.86.

Mandelates 20, 21. To a mixture of 5.0 mg (0.007 mmol) of alcohol **19** and 3.0 mg (0.018 mmol) of (*R*)-α-methoxyphenylacetic acid in 0.5 mL of CH_2Cl_2 was added 3.7 mg (0.018 mmol) of DCC followed by 1.0 mg of DMAP. The reaction mixture was stirred for 30 min, and the solvent was removed under reduced pressure. To the residue was added ether, and the mixture was filtered through Celite. Solvent was removed under reduced pressure, and the crude product was purified by column chromatography on silica gel (elution with 20% EtOAc in hexane) to afford 5.7 mg (95%) of **(*R*)-mandelate 20**: ^1H NMR ($CDCl_3$, 300 MHz) δ 4.88 (m, 1 H), 4.85 (d, J = 6.9 Hz, 1 H), 4.78 (d, J = 6.5 Hz, 1 H), 4.67 (d, J = 6.5 Hz, 1 H), *4.62 (d, J = 6.9 Hz, 1 H)*, 4.13 (q, J = 7.2 Hz, 2 H), 3.90 (m, 2 H), 3.80 (m, 2 H), 3.30−3.50 (m, 2 H), 3.41 (s, 3 H), 3.39 (s, 3 H), *3.36 (s, 3 H)*, 2.28 (t, J = 7.6 Hz, 2 H), 1.00−2.09 (m, 51 H), 0.88 (t, J = 6.9 Hz, 3 H). **(*S*)-Mandelate 21**: ^1H NMR ($CDCl_3$, 300 MHz) δ 4.89 (m, 1 H), 4.85 (d, J = 6.9 Hz, 1 H), 4.81 (d, J = 6.5 Hz, 1 H), 4.67 (d, J = 6.9 Hz, 1 H), *4.65 (d, J = 6.5 Hz, 1 H)*, 4.13 (q, J = 7.2 Hz, 2 H), 3.96 (m, 1 H), 3.88 (m, 1 H), 3.80 (m, 2 H), 3.35−3.50 (m, 2 H), 3.41 (s, 3 H), 3.39 (s, 3 H), *3.38 (s, 3 H)*, 2.27 (t, J = 7.6 Hz, 2 H), 1.00−2.10 (m, 51 H), 0.88 (t, J = 6.9 Hz, 3 H). Note: The italic data are diagnostic for each diastereomer.

Bis-THF Ester 22. To a mixture of 0.034 g (0.05 mmol) of alcohol **19** and 0.30 mL (1.72 mmol) of i-Pr_2NEt in 1.0 mL of CH_2Cl_2 at 0 °C was added 0.10 mL (1.24 mmol) of MOMCl. The reaction mixture was stirred for 12 h, quenched with water, and extracted with ether. The ether extracts were washed with brine, dried over $MgSO_4$, filtered, and concentrated under reduced pressure. Purification by column chromatography on silica gel (elution with 20% EtOAc in hexane) afforded 0.032 g (90%) of bis-THF ester **22**. IR (film) 2942, 2855, 1728 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 4.84 (d, J = 6.9 Hz, 1 H), 4.81 (d, J = 6.8 Hz, 1 H), 4.66 (d, J = 6.9 Hz, 2 H), 4.63 (s, 2 H), 4.11 (q, J = 7.3 Hz, 2 H), 3.97 (m, 1 H), 3.86 (m, 3 H), 3.79 (m, 2 H), 3.50 (m, 1 H), 3.45 (m, 2 H), 3,39 (s, 6 H), 3.36 (s, 3 H), 2.28 (t, J = 7.6 Hz, 2 H), 1.13−2.09 (m, 51 H), 0.88 (t, J = 6.9 Hz, 3 H).

Alcohol 24. To a solution of 0.037 mL (0.20 mmol) of diisopropylamine in 0.5 mL of THF at 0 °C was added 0.07 mL (0.18 mmol) of BuLi (2.5 M in hexane). The reaction mixture was stirred at 0 °C for 10 min and cooled to −78 °C. To it was added a solution of 0.029 g (0.04 mmol) of ester **22** in 0.5 mL of THF. After 60 min, a solution of 0.015 g (0.08 mmol) of aldehyde **23**[18] in 0.5 mL of THF was added. The reaction mixture was stirred for 1 h, quenched with NH_4Cl, and diluted with ether. The aqueous layer was extracted with ether, and the combined extracts were washed with brine, dried over $MgSO_4$, and concentrated under reduced pressure. To the residue was added 1.0 mL of THF followed by 0.2 mL (0.20 mmol) of TBAF (1.0 M in THF). The reaction mixture was stirred for 30 min, quenched with water, and extracted with ether. The extracts were washed with brine, dried over $MgSO_4$, and concentrated under reduced pressure. Purification by column chromatography on silica gel (elution with 50% EtOAc in hexane) afforded 0.022 g (73%) of alcohol **24**. IR (film) 3432, 2925, 2855 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 4.84 (J = 6.9 Hz, 1 H), 4.81 (d, J = 6.9 Hz, 1 H), 4.66 (d, J = 6.9 Hz, 2 H), 4.63 (s, 2 H), 4.20 (m, 1 H), 3.97 (m, 1 H), 3.86 (m, 1 H), 3.79 (m, 2 H), 3.52 (m, 1 H), 3.44 (m, 2 H), 3.39 (s, 6 H), 3.36 (s, 3 H), 2.56 (m, 1 H), 1.42 (d, J = 7.0 Hz, 3 H), 1.14−2.09 (m, 48 H), 0.88 (t, J = 6.9 Hz, 3 H).

MOM-Protected Trilobin 25. To a mixture of 0.02 g (0.026 mmol) of alcohol **24** and 0.035 mL (2.60 mmol) of Et_3N in 1.0 mL of CH_2Cl_2 at 0 °C was added 0.02 mL (0.14 mmol) of $(CF_3CO)_2O$. The reaction mixture was stirred at room temperature for 20 h, quenched with $NaHCO_3$, and extracted with ether. The extracts were washed with brine, dried over $MgSO_4$, and concentrated under reduced pressure. The crude product was purified by column chromatography on silica gel (elution with 20% EtOAc in hexane) to afford 0.017 g (87%) of butenolide **25**. ^1H NMR ($CDCl_3$, 300 MHz) δ 6.98 (s, 1 H), 4.84 (d, J = 6.9 Hz, 1 H), 4,81 (d, J = 6.9 Hz, 1 H), 4.66 (d, J = 6.9 Hz, 2 H), 4.63 (s, 2 H), 3.98 (m, 1 H), 3.88 (m, 1 H), 3.80 (m, 2 H), 3.52 (m, 1 H), 3.45 (m, 2 H), 3.39 (s, 6 H), 3.36 (s, 3 H), 2.26 (t, J = 8.1 Hz, 2 H), 1.42 (d, J = 7.0 Hz, 3 H), 1.19−2.09 (m, 46 H), 0.88 (t, J = 6.9 Hz, 3 H).

Trilobin (26). A solution of 0.013 g (0.02 mmol) of MOM-protected trilobin **25** in 1.5 mL of 6 N HCl−THF−MeOH (1:2:2) was stirred at room temperature for 12 h. The reaction was quenched with water and extracted with ether. The extracts were dried over $MgSO_4$, filtered, and concentrated under reduced pressure. Purification by column chromatography on silica gel (elution with 80% EtOAc in hexane) afforded 0.009 g (85%) of trilobin (**26**). $[\alpha]_D$ +22.7 (*c* 0.15, CH_2Cl_2); lit.[1a] $[\alpha]_D$ +33.3 (*c* 0.015, MeOH); ^1H NMR ($CDCl_3$, 300 MHz) δ 6.99 (s, 1 H), 5.00 (m, 1 H), 4.07 (m, 1 H), 3.96 (m, 1 H), 3.83 (m, 2 H), 3.59 (m, 1 H), 3.38 (m, 2 H), 2.27 (t, J = 7.4 Hz, 2 H), 1.42 (d, J = 7.0 Hz, 3 H), 1.12−2.16 (m, 46 H), 0.88 (t, J = 6.9 Hz, 3 H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 173.8, 148.9, 134.3, 83.2, 82.6, 81.6, 81.0, 74.5, 73.8, 71.9, 37.4, 34.3, 33.5, 31.9, 29.7, 29.6, 29.5, 29.3, 29.2, 29.1, 28.9, 28.2, 28.1, 27.4, 27.1, 25.8, 25.7, 25.6, 25.2, 22.7, 19.2, 14.1. **Tri-(*S*)-Mosher Ester**: ^1H NMR ($CDCl_3$, 300 MHz) δ 6.98 (s, 1 H), 5.05 (m, 3 H), 5.00 (m, 1 H), 3.96 (m, 1 H), 3.92 (m, 1 H), 3.71 (m, 1 H), 3.63 (m, 1 H), 2.26 (t, J = 7.4 Hz, 2 H), 1.40 (d, J = 7.0 Hz, 3 H), 1.20−2.00 (m, 46 H), 0.88 (t, J = 7.0 Hz, 3 H).

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Supporting Information Available: Experimental procedures for the synthesis of stannanes **4** and **11**; ^1H NMR spectra for all key intermediates. This material is available free of charge via the Internet at http://pubs.acs.org.

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