Synthesis of Unit A of Cryptophycin via a [2,3]-Wittig Rearrangement

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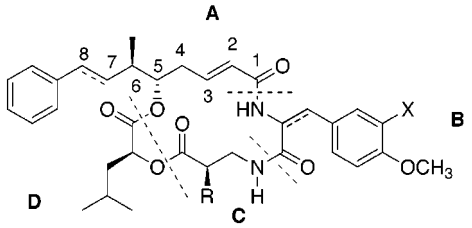
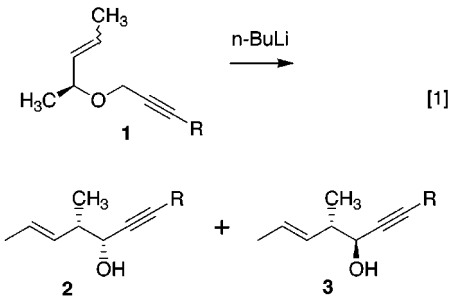
The synthesis of unit A of the cryptophycins from (*S*)-*trans*-3-penten-2-ol and from (*S*)-*trans*-4-hexen-3-ol has been completed. The key stereodetermining step is a [2,3]-Wittig rearrangement of a propargyl ether. Elaboration of the rearrangement product was accomplished by means of a selective hydroboration−oxidation of a terminal alkyne, Horner−Emmons homologation of the derived aldehyde, followed by selective ozonolytic cleavage and Wittig olefination. This synthesis provides easy access to the series of cryptophycin analogues that incorporate a modified aromatic ring in unit A.

The cryptophycins are a group of potent tumor-selective cytotoxins associated with the terrestrial blue-green algae *Nostoc* sp. GSV 224[1] and *Nostoc* sp. ATCC 53789.[2] Compounds related to the cryptophycins, the arenastatins, were also isolated from an Okinawan sponge. Arenastatin A was identical with cryptophycin 24, one of the minor isolates from GSV 224.[3] The first total synthesis of cryptophycin 1 was carried out at the University of Hawaii and served to determine the relative and absolute stereochemistry.[4] The retrosynthetic analysis of the cryptophycins is straightforward because the molecule is composed of four units. Unit A is an unsaturated δ-hydroxy acid, unit B is a chlorinated D-tyrosine derivative, whereas units C and D are (*R*)-(−)-2-methyl-β-alanine and (*S*)-(−)-leucic acid, respectively.



R = CH_3, X = Cl, C7-C8 β-epoxy, cryptophycin 1
R = CH_3, X = Cl, C7-C8 alkene, cryptophycin 3
R = H, X = H, C7-C8 β-epoxy, arenastatin A

The synthesis of unit A represents the greatest challenge. Our first cryptophycin synthesis described a strategy for the preparation of unit A based on the Sharpless asymmetric epoxidation.[5] Since then, several total syntheses and formal total syntheses of cryptophycin have been published.[6] We conceived an attractive strategy for the synthesis of unit A based on the anionic Wittig rearrangement, starting with a single enantiomer of a secondary allylic alcohol.



1 R = H, *E* **2**:**3** = 9:91
1 R =TMS, *Z* **2**:**3** = 99:1

Nakai and Mikami's thorough study of the [2,3]-Wittig rearrangement provided ample support for our plan.[7] The stereoselectivity of the rearrangement can be predicted on the basis of a five-membered cyclic transition state. For example, Wittig rearrangement of *E*-ether **1** (R= H) led in good yield and excellent selectivity to anti alcohol **3** (eq 1).[8] The *Z*-isomer of **1** (R = TMS) showed a preference for syn product **2**. In the homochiral series, transfer of asymmetry is reported to take place efficiently.

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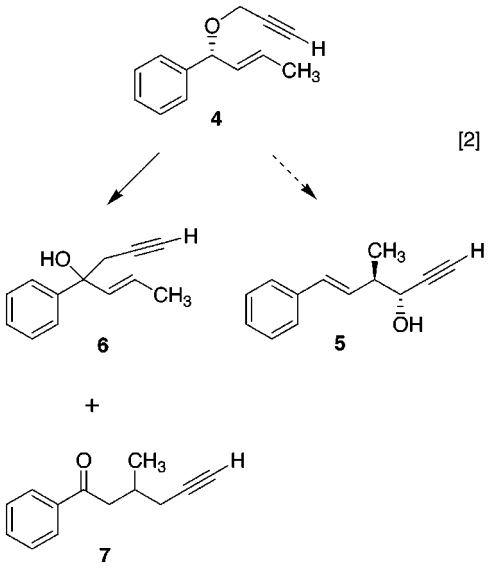
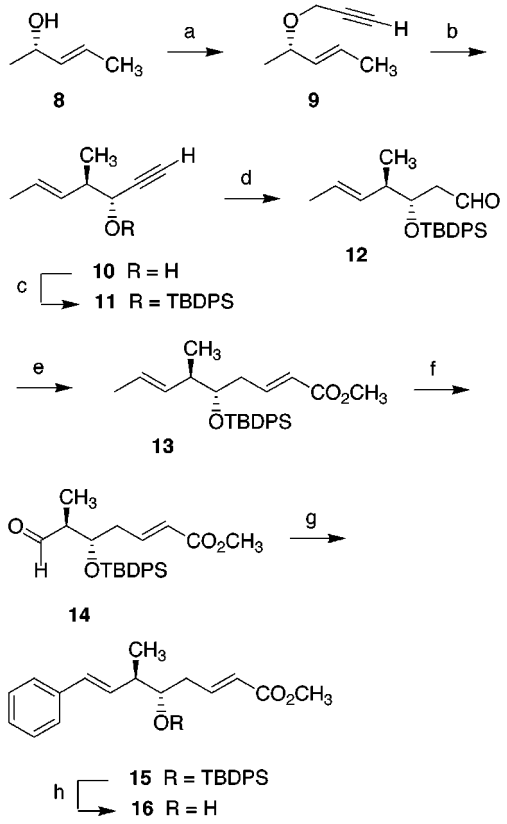
For example, (*Z*)-allyl propargyl ether **1** (R = TMS) of 98% ee rearranges to a 99/1 mixture of **2** and **3** in 64% yield with no loss in optical purity for the major product.[8a]



Our analysis of the problem led us to consider propargyl ether **4** as an attractive starting material (eq 2). On the basis of published work, rearrangement of the propargyl anion derived from **4** was expected to lead selectively to anti alcohol **5**.[7] In our first attempt to put this into practice, phenyl propenyl ketone was reduced with sodium borohydride in methanol, in the presence of cerous chloride,[9] and the resulting alcohol was then alkylated under phase-transfer conditions with propargyl bromide to produce (±)-**4** in excellent overall yield. Treatment of **4** with *n*-butyllithium failed to furnish any of the desired product **5**, but instead gave a mixture of tertiary alcohol **6** and phenone **7** (ca. 1/2.5). Alcohol **6** was apparently the product of a competing [1,2]-Wittig rearrangement of a *benzylic* carbanion. Rearrangement of the same carbanion through a vinylogous process can rationalize the formation of ketone **7**. An attempt was made to suppress benzylic deprotonation by employing the more hindered alkyllithium bases, phenyllithium or *tert*-butyllithium, but both bases also produced **6** and **7** as the major reaction products. The route was therefore modified.

The starting point for the successful synthesis of unit A was (*S*)-*trans*-3-penten-2-ol **8** (Scheme 1). This material was prepared in greater than 95% ee[10] by kinetic resolution of the racemate. Commercially available porcine pancreatic lipase was used to trans-esterify racemic **8** with trifluoroethyl laurate.[11] Volatile allylic alcohol **8** was distilled from the reaction mixture and was converted to propargyl ether **9** in 86% yield under phase-transfer conditions.[12] The Wittig rearrangement was accomplished by treatment of **9** with an excess of *n*-butyllithium in THF

Scheme 1[a]



[a] Key: (a) propargyl bromide, 50% aqueous NaOH, *n*-Bu_4NHSO_4 (cat.); 86%; (b) *n*-BuLi, THF, −90 °C to rt; 71%; (c) TBDPSCl, DMF, imidazole; 92%; (d) 2-methyl-2-butene, BH_3, THF, 0 °C; H_2O_2, aqueous KH_2PO_4/K_2HPO_4 (2.2 M), 0 °C; 83%; (e) trimethyl phosphonoacetate, tetramethylguanidine, THF, −78 °C; 92%; (f) O_3, CH_2Cl_2, pyridine, −78 °C; Zn, AcOH; 85%; (g) $PhCH{=}PPh_3$, THF, −78 °C to rt; PhSH, VAZO 88, PhMe, reflux; 82%; (h) aqueous HF, CH_3CN, rt; 93%.

at −90 °C, followed by slow warming to room temperature.[13] The butyllithium was delivered in hexane, which was evaporated under vacuum and replaced with THF.[14] The desired (3*R*,4*R*)-4-methylhept-5(*E*)-en-1-yn-3-ol **10** was isolated as a 9/1 mixture with a diastereoisomer in 71% yield. The ratio of products was estimated by integration of the propargylic methine signals in the ^1H NMR spectrum of the crude reaction product. Separation of the two diastereoisomers was accomplished by careful column chromatography on silica gel to furnish **10** (≥95% ee).

The next task was to functionalize the acetylenic terminus of **10**. Protection as the *tert*-butyldiphenylsilyl (TBDPS) ether was followed by selective monohydroboration of the terminal alkyne with disiamylborane, which was prepared in situ from 2-methyl-2-butene.[15] Aldehyde

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(14) This solvent change is essential for the stereoselectivity of the rearrangement.

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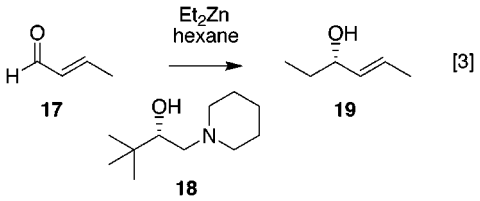
12 was produced in 83% yield. The TBDPS ether was chosen instead of the *tert*-butyldimethylsilyl, which was used in our first synthesis,[4] so as to render **11** and **12** less volatile. The hydroboration could also be accomplished with catecholborane. Oxidative workup of the intermediate vinyl borane was carried out with hydrogen peroxide in a phosphate solution buffered at pH 7. In the absence of buffer, mixtures of **12** and of the α,β-unsaturated aldehyde derived from elimination of the β-silyloxy group were formed. On larger scale, it was found that saturated aqueous sodium acetate could also be used during the oxidation of the borane. Carbon atoms 1 and 2 of unit A were introduced by means of a Horner−Emmons reaction that led stereospecifically to the *E* isomer of ester **13**.[16] Selective ozonolysis of the unconjugated alkene of **13** took place at −78 °C in dichloromethane containing a small amount of pyridine.[17] Reductive workup of the ozonide with zinc and acetic acid led to aldehyde **14** in 85% overall yield from **13**. Addition of Sudan 7B as an indicator made it possible to follow the progress of the ozonolysis by monitoring the disappearance of the red color of the dye.[18] The synthesis of unit A in protected form was completed by first exposing **14** to benzyltriphenylphosphonium ylide[19] and then treating the mixture of (*E*)- and (*Z*)-styryl isomers (ca. 4/1) with thiophenol and 1,1′-azobis(cyclohexanecarbonitrile) (VAZO 88) in refluxing toluene[20] to give *E* isomer **15** as the exclusive product. The overall yield for this process was 82% from **14**. Fluorodesilylation of **15** led to alcohol **16** in high yield. The physical data for **16** were identical with those reported for this compound in our first synthesis.[4]

The preparation of **8** by means of the enzymatic kinetic resolution was inconvenient to scale-up. This prompted us to develop an alternative starting material for the synthesis that was much easier to prepare on a multimolar scale, but at the cost of some erosion in optical purity. Since the double bond in **8** is ozonized in the penultimate step of the synthesis, *trans*-(*S*)-4-hexen-3-ol **19**[21] (eq 3) can serve equally well as the starting material for unit A. This material was prepared according



to Noyori's procedure,[22] from crotonaldehyde **17** and diethylzinc, in the presence of 1 mol % (*S*)-1-piperidino-3,3-dimethyl-2-butanol **18** (68.5% ee).[23] Under these conditions, **19** was formed in 64% yield from 2.41 mol of **17** in 83% ee. The addition reaction exhibits asymmetric amplification, but the effect of catalyst ee on product enantioselectivity also appears to be attenuated. For example, when **18** of 98% ee was used in the reaction, the ee of **19** improved to 86%, a difference of only 3%. The Noyori group has reported a higher ee (90%) for alcohol **19** in this reaction. Fortunately, the erosion in optical purity of **19** was of little consequence to the synthesis (vide infra). Unit A was prepared from **19** by following the same sequence of reactions as summarized in Scheme 1. Yields for the two syntheses of unit A, starting from **8** or from **19**, were identical within a few percent at each step. For reasons that are not clear, the diastereoselectivity of the [2,3]-Wittig rearrangement of the propargyl ether derived from **19** was ca. 10% lower than for **9**. This may reflect subtle differences in transition state energies for the rearrangement. This result, and also the failure of **4** to undergo successful Wittig rearrangement, underscores the sensitivity of this process to seemingly minor structural modification of the substrate, a factor that deserves consideration during the planning of a synthesis. Coupling of unit A, which was derived from **19**, with unit B led to chromatographically separable diastereomers. Unit B, which was easily prepared in high enantiomeric purity, thus served as a resolving agent for unit A.

In conclusion, a successful synthesis of cryptophycin unit A by means of a [2,3]-Wittig rearrangement has been completed. Introduction of the phenyl group at the end of the synthetic sequence has provided convenient access to a large number of cryptophycin analogues that incorporate modifications in the aromatic ring of unit A. The synthesis and the properties of those analogues will be discussed in future publications.

Experimental Section

^{1}H NMR and ^{13}C NMR spectra were recorded at 300 MHz ^{1}H or 75 MHz ^{13}C in deuteriochloroform ($CDCl_3$) with chloroform as an internal reference, unless noted otherwise. ^{1}H and ^{13}C chemical shift assignments are based on detailed analysis of two-dimensional NMR spectra when necessary. IR spectra were recorded neat. MS data are reported in the form of *m*/*z*. TLC was performed on EM Reagents precoated silica gel 60 F-254 analytical plates (0.25 mm). Normal-phase flash column chromatography was performed on Brinkmann silica gel (0.040−0.063 mm). Reversed-phase column chromatography was performed on YMC-GEL ODS-A (120A, I-63/210 mm) silica. Purity and homogeneity of all materials were determined chromatographically and from ^{1}H and ^{13}C NMR or combustion analysis. THF and ethyl ether were distilled from sodium−benzophenone ketyl. Methylene chloride was distilled from phosphorus pentoxide and hexane from calcium hydride. Other reagents were obtained commercially and used as received unless otherwise specified. All reactions were performed under a static nitrogen or argon atmosphere in flame-dried glassware. Elemental analyses were performed by Desert Analytics, Inc., Tucson, AZ.

Propargyl Ether 4. A mixture of 300 mg of 1-phenyl-2(*E*)-buten-1-ol (2.0 mmol), 69 mg of *n*-Bu_4NHSO_4 (0.2 mmol), and 2.5 g of 50% aqueous NaOH was stirred vigorously at 0 °C. To this mixture was added 0.68 mL of propargyl bromide (80% in toluene, 6.0 mmol), and the two-phase system was stirred

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overnight. Approximately 20 mL of water and ice was added, and the aqueous layer was neutralized with 6 N HCl. The product was extracted with hexanes (3 × 50 mL), and the combined organic layer was washed with brine, dried, and evaporated. The oily product that remained was passed through a short silica column to give 335 mg of pure propargyl ether (90% yield): colorless oil; IR ν_{max} 3294, 1062 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.25−7.38 (Ph-H; m), 5.76 (3-H; dq, 15.3 and 6.4), 5.79 (2-H; dd, 15.3 and 7.4), 4.97 (1-H; d, 7.4), 4.16/4.09 (CH_2CCH; d AB q, 2.2 and-15.7), 2.42 (CCH, br t, 2.2), 1.73 (4-H; d, 6.3); ^{13}C NMR ($CDCl_3$) δ (carbon position) 140.8 (Ph-1), 131.1 (2), 129.1 (3), 128.3 (Ph-3/5), 127.5 (Ph-4), 126.9 (Ph-2/6), 81.0 (1), 80.0 (CH_2CCH), 73.9 (CH_2CCH), 55.1 (CH_2CCH), 17.6 (4).

Alcohol 6 and Ketone 7. To a solution of 30 mg of propargyl ether **4** (0.16 mmol) in 5 mL of THF at −78 °C was slowly added 0.22 mL of *n*-BuLi (0.44 mmol, 2.0 M in hexane). The reaction was monitored by TLC. After 3 h, the temperature was raised to −20 °C and then to 0 °C over the course of 2 h. TLC indicated two products along with starting material. Another 0.50 mL of *n*-BuLi (1.00 mmol, 2.0 M in hexane) was added, and the reaction mixture was stirred for 1 h before quenching with saturated aqueous NH_4Cl. Extraction with ether (3 × 50 mL), drying, and solvent evaporation gave a mixture of **6** and **7**. Chromatographic separation produced 5 mg of **6** (ca. 15% yield) and 12 mg of **7** (ca. 41% yield). Compound **6**: colorless oil; ^1H NMR ($CDCl_3$) δ 7.20−7.48 (Ph-H; m), 5.81 (2-H; d, 15.8), 5.77 (3-H; dq, 15.8 and 6.5), 2.81 (CH_2CCH; d, 2.3), 2.04 (CCH, br t, 2.2), 1.75 (4-H; d, 6.5); ^{13}C NMR ($CDCl_3$) δ 139.6 (Ph-1), 135.8 (2), 127.8 (Ph-3/5), 127.2 (3), 125.7 (Ph-4), 125.5 (Ph-2/6), 80.4 (CH_2CCH), 75.1 (1), 72.5 (CH_2CCH), 33.3 (CH_2CCH), 17.7 (4). Compound **7**: Colorless oil; IR ν_{max} 3299, 1680 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.98 (2′-H/6′-H; dd, 8.1 and 1.6), 7.56 (4′-H; td, 7.8 and 1.6), 7.46 (3′-H/5′-H; td, 7.8 and 1.6), 3.20 (2-H; dd, 6.5 and −16.5), 2.85 (2-H′; dd, 7.6 and −16.5), 2.45 (3-H; m), 2.29 (CH_2CCH; m), 2.04 (CCH, br t, 2.2), 1.09 (3-Me; d, 7.1); ^{13}C NMR ($CDCl_3$) δ 199.3 (1), 132.8 (Ph-4), 128.5 (Ph-2/6), 128.0 (Ph-3/5), 82.4 (CH_2CCH), 70.0 (CH_2CCH), 44.2 (2), 28.8 (3), 25.7 (CH_2CCH), 19.7 (4).

(*S*)-*trans*-3-Penten-2-ol (8). A mixture of *trans*-3-penten-2-ol (933 mg, 11 mmol), trifluoroethyl laurate (4.14 g, 15 mmol), and 2.00 g of porcine pancreatic lipase was stirred in 25 mL of anhydrous diethyl ether for 80 h. The PPL was filtered off and washed with ether (3 × 20 mL). Evaporation of the ether produced a sticky oil that was distilled in a Kugelrohr apparatus in vacuo (20 °C water bath, 1−0.3 mmHg) to produce 383 mg (40% yield) of (*S*)-*trans*-3-penten-2-ol, which was condensed in a trap cooled with liquid N_2: colorless oil; $[\alpha]_D$ = −7.4 (*c* 12.3, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 5.57 (4-H; dq, 15.3 and 6.0), 5.47 (3-H; ddd, 15.3, 6.4 and 1.2), 4.19 (2-H; 1:4:6:4:1 pent, 6.4), 2.24 (OH; br s), 1.63 (5-H; d, 6.0), 1.19 (1-H; d, 6.4); ^{13}C NMR ($CDCl_3$) δ 135.5 (3), 125.5 (4), 68.7 (2), 23.3 (5), 17.5 (1).

(3*R*,4*R*)-4-Methylhept-5(*E*)-en-1-yn-3-ol (10). To a vigorously stirred mixture of neat (*S*)-*trans*-3-penten-2-ol **8** (628 mg, 7.3 mmol), *n*-Bu_4NHSO_4 (138 mg, 0.41 mmol), and 40% aqueous NaOH (5 mL) was slowly added propargyl chloride (767 mg, 10.3 mmol, 745 μL) at 0 °C. Vigorous stirring was continued overnight, and the mixture was neutralized with aqueous HCl at 0 °C. The product was extracted into pentane, the solvent was dried and evaporated, and the propargyl ether was purified on a short silica gel column (2% Et_2O/pentane) to give 778 mg (86% yield) of (*S*)-*trans*-2-(2-propynyloxy)-3-pentene **9**:[8a] colorless oil; $[\alpha]_D$ = −118.9 (*c* 2.0, $CHCl_3$); IR ν_{max} 3297 cm^{-1};^1H NMR ($CDCl_3$) δ 5.70 (4-H; dq, 18.5 and 6.5), 5.31 (3-H; ddd, 18.5, 7.2 and 1.4), 4.15 (CH_2CCH; dd, 2.1 and −15.6), 4.01 (CH_2CCH; dd, 2.1 and −15.6), 4.01 (2-H; m), 2.38 (CCH; t, 2.1), 1.73 (5-H; dd, 6.5 and 1.4), 1.25 (1H; d, 6.3); ^{13}C NMR ($CDCl_3$) δ 132.2 (3), 128.7 (4), 80.5 (*C*CH), 75.4 (C*C*H), 73.5 (2), 54.8 (*C*H_2CCH), 21.4 (1), 17.6 (5). An aliquot of *n*-butyllithium in hexane (2.5 M, 5.1 mL, 12.8 mmol) was evaporated in vacuo and the residue cooled to −90 °C. A solution of (*S*)-*trans*-2-(2-propynyloxy)-3-pentene **9** (454 mg, 3.66 mmol) in 10 mL of THF was slowly added. After the mixture was allowed to warm to room temperature overnight, the reaction was quenched with aqueous NH_4Cl. Extraction with Et_2O, drying, evaporation of the solvent, and purification of the residue on a silica gel column (5% EtOAc/hexane) gave 322 mg (71% yield) of (3*R*,4*R*)-4-methylhept-5(*E*)-en-1-yn-3-ol **10**:[8a,24] colorless oil; $[\alpha]_D$ = +32.9 (*c* 3.0, $CHCl_3$); IR ν_{max} 3405, 2119 cm^{-1};^1H NMR ($CDCl_3$) δ 5.61 (6-H; dq, 15.3 and 6.3), 5.38 (5-H; dd, 15.3 and 7.7), 4.13 (3-H; br s), 2.45 (1-H; d, 1.5), 2.38 (4-H; m), 2.20 (OH; br d, 3.3), 1.68 (7-H; d, 6.2), 1.09 (4-CH_3; d, 6.8); ^{13}C NMR ($CDCl_3$) δ 131.5 (5), 127.9 (6), 83.5 (2), 73.6 (1), 66.2 (3), 43.4 (4), 18.1 (7), 15.7 (4-Me).

(3*R*,4*R*)-3-[(*tert*-Butyldiphenylsilyl)oxy]-4-methylhept-5(*E*)-en-1-yne (11). To a stirred solution of (3*R*,4*R*)-4-methylhept-5(*E*)-en-1-yn-3-ol **10** (600 mg, 4.8 mmol) and imidazole (823 mg, 12 mmol) in 10 mL of dry DMF was added *tert*-butyldiphenylsilyl chloride (2.02 g, 7.3 mmol). After the mixture was stirred overnight, 50 mL of 10% aqueous NaOH was added to destroy the excess *tert*-butyldiphenylsilyl chloride. The product was extracted into ether, and the extract was first washed successively with water and 0.5 N HCl and then dried and evaporated. Purification of the residue by chromatography on silica gel with hexane gave 1.60 g (92% yield) of (3*R*,4*R*)-3-[(*tert*-butyldiphenylsilyl)oxy]-4-methylhept-5(*E*)-en-1-yne **11**: colorless oil; $[\alpha]_D$ = +21.6 (*c* 3.0, $CHCl_3$); EI MS *m*/*z* (rel intensity) 362 (1, M^+), 305 (100, $[M - C_4H_9]^+$), 293 (19, $[M - MeHC{=}CHCHMe]^+$); HREIMS (M^+) calcd for $C_{24}H_{30}OSi$ 362.2066, found 362.2065; IR ν_{max} 3307, 2116, 1427 cm^{-1};^1H NMR ($CDCl_3$) δ 7.72/7.38 (Ph-H; m), 5.32 (6-H; m), 5.25 (5-H; dd, 16.2 and 7.3), 4.29 (3-H; dd, 5.2 and 2.0), 2.38 (4-H; m), 2.33 (1-H; d, 2.0), 1.64 (7-H; d, 5.3), 1.11 (4-Me; d, 6.9), 1.06 (CMe_3); ^{13}C NMR ($CDCl_3$) δ 136.1/135.9/133.6 /129.7/129.6/127.5/127.3 (Ph), 132.4 (5), 126.1 (6), 83.3 (2), 73.5 (1), 68.0 (3), 43.6 (4), 26.9 (CMe_3), 19.4 (CMe_3), 18.0 (7), 14.7 (4-Me). Anal. Calcd for $C_{24}H_{30}OSi$: C, 79.50; H 8.34. Found: C, 79.16; H, 8.40.

(3*S*,4*R*)-3-[(*tert*-Butyldiphenylsilyl)oxy]-4-methylhept-5(*E*)-enal (12). 2-Methylbutene (1.0 mL 2 M in THF, 2.0 mmol) was added to 1.0 mL of BH_3−THF solution (1 M, 1.0 mmol) at −25 °C, and the mixture was stirred in an ice bath for 2 h. The reaction mixture was cooled to −50 °C and a solution of **11** (315 mg, 0.9 mmol) in 1 mL of THF was added all at once. The cooling bath was removed, and the reaction mixture was allowed to warm to room temperature over 1 h. The reaction was quenched with 2.2 M aqueous KH_2PO_4/K_2HPO_4 (4.8 mL) and 30% H_2O_2 (0.8 mL) at 0 °C. One hour later, the THF was evaporated, and the residue was extracted into ether (3 × 40 mL). The combined ether extract was washed with brine, dried, and evaporated. The residue was purified on silica gel (1% EtOAc/hexane) to give 362 mg of aldehyde **12** (83% yield): colorless oil; $[\alpha]_D$ = +26.0 (*c* 0.30, $CHCl_3$); IR ν_{max} 1725 cm^{-1}; ^1H NMR ($CDCl_3$) δ 9.52 (1-H; t, 2.4), 7.69/7.40 (Ph-H), 5.28 (6-H; m), 5.22 (5-H; dd, 16.2 and 6.2), 4.19 (3-H; m), 2.42 (2-H; m), 2.29 (4-H; m), 1.60 (7-H; d, 5.4), 1.07 (CMe_3), 1.02 (4-Me; d, 6.9);^{13}C NMR ($CDCl_3$) δ 202.0 (1), 136.1/133.6/133.3 /130.2/129.7/127.7/127.6 (Ph), 132.3 (5), 126.2 (6), 72.8 (3), 47.6 (2), 42.2 (4), 27.1 (CMe_3), 19.6 (CMe_3), 18.3 (7), 14.9 (4-Me).

Methyl (5*S*,6*R*)-5-[(*tert*-Butyldiphenylsilyl)oxy]-6-methylnona-2(*E*),7(*E*)-dienoate (13). To a stirred solution of aldehyde **12** (315 mg, 0.83 mmol) and trimethyl phosphonoacetate (182 mg, 1.0 mmol) in 3 mL of THF was added tetramethylguanidine (124 μL, 1.0 mmol) at −78 °C. After 30 min, the cooling bath was removed, and the mixture was stirred for another 4 h. The mixture was neutralized with 1 N aqueous HCl, and the product was extracted into ether (3 × 35 mL). Evaporation of the dried ether extract produced a residue that was purified on silica gel (5% EtOAc/hexane) to give 332 g of **13** (92% yield): colorless oil; $[\alpha]_D$ = +41.6 (*c* 3.0, $CHCl_3$); FAB MS *m*/*z* (rel intensity) 435 (10, $[M - H]^+$), 379 (59, $[M - C_4H_9]^+$), 367 (28, $[M - MeHC{=}CHCHMe]^+$), 359 (40, $[M - C_6H_5]^+$); HRFABMS ($[M - H]^+$) calcd for $C_{27}H_{35}O_3Si$

(24) Alcohol **10** was volatile, and we were unable to get mass spectrometric data using the direct probe method; therefore, complete characterization was performed on the derived *tert*-butyldiphenylsilyl ether **11**.

435.2355, found 435.2344; IR ν_{max} 1729 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.68/7.38 (Ph-H), 6.75 (3-H; dt, 15.6 and 7.4), 5.62 (2-H; d, 15.6), 5.34 (8-H, m), 5.29 (7-H, m), 3.70 (5-H, m), 3.68 (OMe, s), 2.28 (4-H, m), 2.20 (6-H, m), 1.62 (9-H; d, 5.3), 1.08 (CMe_3), 0.99 (6-Me; d, 6.9); ^{13}C NMR ($CDCl_3$) δ 166.7 (1), 146.4 (3), 136.0/134.2/133.8/129.62 /129.56/127.5/127.4 (Ph), 132.5 (7), 125.8 (8), 122.6 (2), 76.2 (5), 51.3 (OCH_3), 41.7 (6), 36.8 (4), 27.0 (CMe_3), 19.4 (CMe_3), 18.1 (9), 14.7 (6-Me). Anal. Calcd for $C_{27}H_{36}O_3Si$: C, 74.27; H, 8.31. Found: C, 74.31; H, 8.15.

Methyl (5*S*,6*R*)-5-[(*tert*-Butyldiphenylsilyl)oxy]-6-methyl-8-phenyl-octa-2(*E*),7(*E*)-dienoate (15). Ozone was passed through a solution of methyl ester **13** (436 mg, 1.0 mmol) and 97 μL of pyridine in 15 mL of CH_2Cl_2 at −78 °C, and the progress of the ozonolysis was monitored by TLC. After the methyl ester had been consumed, approximately 500 mg of zinc dust and 1 mL of glacial acetic acid were added. The reaction was slowly warmed to 25 °C. The mixture was filtered, and the filtrate was washed successively with saturated aqueous $CuSO_4$ and $NaHCO_3$. The solvent was evaporated, and the crude methyl (*5S,6R*)-5-[(*tert*-butyldiphenylsilyl)oxy]-6-methyl-7-oxohept-2(*E*)-enoate (**14**) (360 mg, 85% yield) was used in the next step with no further purification. To a stirred solution of aldehyde **14** (360 mg, 0.85 mmol) in 15 mL of THF at −78 °C was added 8.8 mL of a cold (−78 °C) solution of the ylide (0.88 mmol) prepared from benzyltriphenylphosphonium chloride (388 mg, 1.0 mmol) in 9.5 mL of THF and *n*-butyllithium (0.45 mL, 2.5 M in hexane). After 15 min, the cold bath was removed, and stirring was continued for 2 h. The reaction was quenched with saturated aqueous NH_4Cl, and the THF was evaporated. The residue was extracted with hexane twice and the combined extract was washed with brine, dried, and evaporated. The residual oil, a 5:1 mixture of the *E* and *Z* isomers, was dissolved in 10 mL of toluene containing thiophenol (0.02 M) and VAZO 88 (0.006 M), and the mixture was refluxed for 5 h. After the mixture was cooled to room temperature, hexane (15 mL) was added, and the organic solution was washed successively with 10% aqueous NaOH and brine, dried ($MgSO_4$), and evaporated. Chromatography of the residue on silica gel (2% EtOAc/hexane) gave 347 mg (82% yield) of **15**: colorless oil; $[\alpha]_D = +76$ (*c* 0.40, $CHCl_3$); FABMS *m/z* (rel intensity) 497 (5.9, $[M - H]^+$), 441 (36, $[M - C_4H_9]^+$); HRFABMS ($[M - H]^+$) calcd for $C_{32}H_{37}O_3Si$ 497.2512, found 497.2504; IR ν_{max} 1725, 1428 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.71/7.68 (SiPh, 2′-H, 6′-H/2″-H, 6″-H; d; 6.5), 7.45/7.43 (SiPh, 4′-H/4″-H; t; 7.4), 7.39/7.38 (SiPh, 3′-H, 5′-H/3″-H, 5″-H; dd; 7.4, 6.5), 7.29/7.21 ($Ph-H_5$; m), 6.77 (3-H; dt; 15.6 and 7.5), 6.25 (8-H, d, 16.0), 6.14 (7-H, dd, 16.0 and 7.8), 5.66 (2-H, dt, 15.6 and 1.4), 3.82 (5-H, ddd, 6.8, 5.5, and 3.5), 3.68 (CO_2CH_3, s), 2.42 (6-H, m), 2.35 (4-H, m), 2.30 (4-H′, m), 1.12 (6-CH_3, d, 7.1), 1.08 (CMe_3, s); ^{13}C NMR (125 MHz, $CDCl_3$) δ 166.7 (1), 145.9 (3), 137.6 (9), 136.0 (SiPh, 2′, 6′/2″, 6″), 134.1/133.7 (SiPh, 1′/1″), 131.8 (8), 130.6 (7), 129.8/129.7 (SiPh, 4′/4″), 128.5 (11/13), 127.6/127.5 (3′, 5′/ 3″, 5″), 127.1 (12), 126.1 (10/14), 122.9 (2), 76.3 (5), 51.3 (OCH_3), 42.2 (6), 37.2 (4), 27.1 (CMe_3), 19.5 (CMe_3), 16.2 (6-CH_3). Anal. Calcd for $C_{32}H_{38}O_3Si$: C, 77.06; H, 7.68. Found: C, 77.45; H, 7.36.

(*S*)-(*E*)-4-Hexen-3-ol (19). Diethylzinc (1.0 M in hexane, 2.85 L, 2.85 mol) was combined with (*S*)-1-piperidino-3,3-dimethyl-2-butanol **18** (4.47 g, 24.1 mol, 68.5% ee), and the mixture was stirred for 20 min at room temperature. The reaction mixture was cooled to −60 °C, 200 mL (2.32 mol) of *trans*-crotonaldehyde **17** was added, and the mixture was allowed to warm to 0 °C and stir for 6 h. The reaction was quenched by carefully adding 1.5 L of saturated aqueous NH_4Cl and stirring the biphasic mixture for 30 min. The mixture was filtered, the organic phase was washed with 1 M aqueous HCl (980 mL), and the combined aqueous extract was extracted with 980 mL of hexane. The combined organic phase was washed with 980 mL of brine, dried ($MgSO_4$), and carefully concentrated in vacuo. Distillation at atmospheric pressure (135° C) produced 155.3 g (64% yield) of **19** as a colorless oil: $[\alpha]_D = +12.4$ (*c* 2.12, EtOH), 83% ee; IR ($CHCl_3$) ν_{max} 3607 cm^{-1}; ^1H NMR ($CDCl_3$) δ 5.64 (4-H, ddq, 15.3, 6.4, 0.8), 5.45 (5-H, ddq, 15.3, 7.0, 1.5), 3.94 (3-H, ddd, 6.7, 6.7, 6.7), 1.67 (2-H, dd, 6.4, 1.5), 1.65−1.40 (6-H, m), 0.88 (1-H, t, 7.4); ^{13}C NMR ($CDCl_3$) δ 134.0, 126.9, 74.5, 30.1, 17.7, 9.7; FDMS *m/z* 100 (M^+).

Methyl (5*S*,6*R*)-5-Hydroxy-6-methyl-8-phenylocta-2(*E*),7(*E*)-dienoate (16). To a stirred solution of silyl ether **15** (250 mg, 0.5 mmol) in 15 mL of acetonitrile was added 5 mL of 49% aqueous hydrofluoric acid. The clear solution was stirred overnight, saturated aqueous $NaHCO_3$ was slowly added to neutralize the excess acid, and the acetonitrile was evaporated under reduced pressure. The product was extracted with ether (2 × 80 mL), and the organic layers were combined, dried, and concentrated. The residue was purified by flash column chromatography to give 242 mg of **16** (93% yield): colorless oil; $[\alpha]_D = +55.2$ (*c* 0.31, $CHCl_3$); IR ν_{max} 3456, 1722 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.39/7.23 ($Ph-H_5$; m), 7.05 (3-H; dt; 15.6 and 7.4), 6.48 (8-H, d, 15.9), 6.13 (7-H, dd, 15.9 and 8.8), 5.93 (2-H, dt, 15.6 and 1.5), 3.74 (CO_2CH_3, s), 3.64 (5-H, m), 2.49 (4-H, m), 2.42 (6-H, m), 2.38 (4-H′, m), 1.15 (6-CH_3, d, 6.8); ^{13}C NMR ($CDCl_3$) δ 166.6 (1), 145.6 (3), 137.0 (9), 132.0 (8), 130.9 (7), 128.5 (11/13), 127.4 (12), 126.2 (10/14), 123.3 (2), 73.9 (5), 51.4 (OCH_3), 43.3 (6), 37.4 (4), 16.8 (6-CH_3).

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Supporting Information Available: Copies of ^1H and ^{13}C NMR spectra, IR spectra, and mass spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

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