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Sulfinyl Moiety as an Internal Nucleophile. 1. Efficient Stereoselective Synthesis of Fragment A of Cryptophycin 3†

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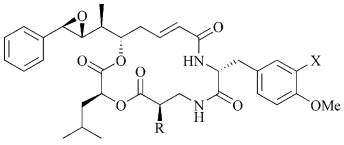
Abstract: A novel, efficient, and stereoselective synthesis of fragment A of cryptophycin 3 is disclosed. The key step involves the regio- and stereoselective transformation of an unsaturated ester to a bromohydrin via anchimeric assistance by the sulfinyl group.

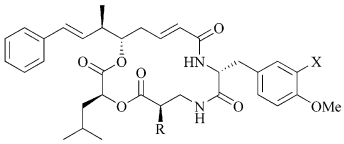
Cryptophycin 1 (**1**) is a macrocyclic depsipeptide isolated from the blue-green alga belonging to the *Nostocaceae*.[1] Its structure was established as **1** by Moore et al.,[2] who had isolated this and six other cryptophycins independently from *Nostoc sp*. GSV 224. Among these were cryptophycin 2 (**2**), cryptophycin 3 (**3**), and cryptophycin 4 (**4**).[3] At about the same time, Kitagawa isolated a depsipeptide from the marine sponge *Dysidea arenaria*[4] that he named arenastatin which was found to be identical to cryptophycin 24 (**5**). Moore and co-workers have shown cryptophycin 1 to be a potent tumor-selective cytotoxin.[3,5] Its exceptional antiproliferative effects are believed to be due to reversible high affinity binding to microtubules.[6]



1, R = Me, X = Cl (cryptophycin 1)

2, R = Me, X = H (cryptophycin 2)

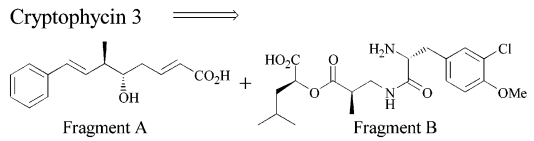
5, R = X = H (cryptophycin 24)



3, R = Me, X = Cl (cryptophycin 3)

4, R = Me, X = H (cryptophycin 4)

The first synthesis of arenastatin was reported by Kitagawa et al. in 1994,[7] and thereafter many syntheses[8] of cryptophycin 1 (**1**) and analogues were reported. The significant clinical potential of the cryptophycins and their relatively low natural abundance make them an attractive target for total synthesis. By retrosynthetic analysis, the structure of cryptophycins can be divided into two halves, a hydroxy acid (fragment A) and a peptidic subunit (fragment B). Herein we report a stereocontrolled synthesis of fragment A of cryptophycin 3.



The synthesis of fragment A commenced from alcohol **9**, which was prepared from the oxazolidinone **6**[9] (Scheme 1). Acylation of **6**[10] with methacraloyl chloride afforded the imide **7**. Titanium tetrachloride-promoted Michael addition[11] of thiophenol to oxazolidinone **7** afforded the sulfide **8** and its diastereomer in a ratio of 92:8 (HPLC) which were separated by column chromatography. Reduction of sulfide **8** with lithium aluminum hydride afforded alcohol **9**[12] and recovery of the chiral auxiliary **6**.

Swern oxidation[13] of alcohol **9** afforded the corresponding aldehyde which without purification was subjected to Wittig olefination using Still's phosphonate[14] to yield predominantly the cis ester **10** along with the trans ester in small quantity which were separated by column chromatography. The stereochemical integrity of the chiral center during the transformation of the alcohol **9** to the ester **10** was proven by a two-step transformation of the latter to a diastereomerically homogeneous mandelate ester **12**. The sulfide **10** upon oxidation with $NaIO_4$[15] afforded an equimolar, inseparable mixture of sulfoxides **13a** and **13b**. Treatment of the mixture of unsaturated sulfoxides **13a** and **13b** with *N*-bromosuccinimide (NBS) in toluene as the solvent in the presence of a stoichiometric quantity of water under an inert atmo-

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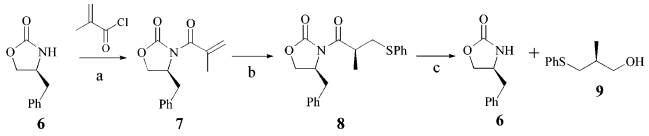
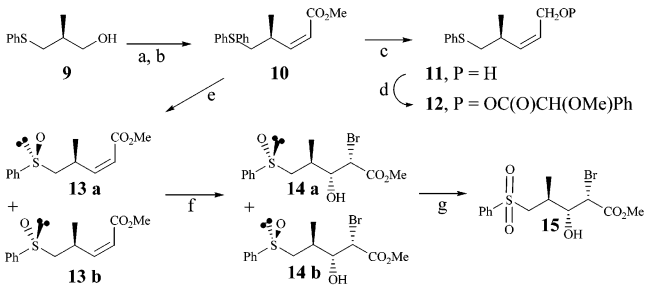
SCHEME 1[a]



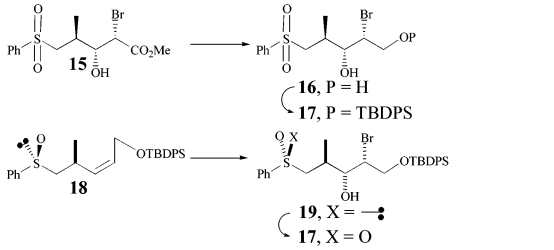
[a] Reaction conditions: (a) *n*-BuLi, THF, −78 °C, 90%; (b) $TiCl_4$, PhSH, CH_2Cl_2, −78 °C, 88%, 92:8 of **8** and its diastereomer; (c) $LiAlH_4$, THF, 0 °C, 80%.

SCHEME 2[a]



[a] Reaction conditions: (a) $(COCl)_2$, DMSO, $^iPrNEt_2$, CH_2Cl_2, −60 °C; (b) NaH, $(F_3CH_2O)_2P(O)CH_2CO_2Me$, THF, 0 °C, −78 °C, aldehyde, 71% for two steps, 8.5:1.5 of cis ester **10**:trans ester; (c) DIBAL, CH_2Cl_2, −78 °C, 75%; (d) DCC, DMAP, (*S*)-methoxymandelic acid, CH_2Cl_2, 0 °C to rt, 75%; (e) $NaIO_4$, MeOH, H_2O, 0 °C to rt, 95%; (f) NBS, toluene, H_2O, rt, 80%; (g) *m*-CPBA, CH_2Cl_2, 0 °C to rt, 80%.

SCHEME 3[a]



[a] Reaction conditions: (a) DIBAL, CH_2Cl_2, −78 °C, 80%; (b) TBDPS-Cl, imidazole, CH_2Cl_2, rt, 85%; (c) NBS, toluene, H_2O, rt, 75%; (d)) *m*-CPBA, CH_2Cl_2, 0 °C to rt, 80%.

sphere afforded the bromohydrins **14a** and **14b** as an inseparable mixture in high yield. Sulfoxides **14a** and **14b** yielded sulfone **15** (Scheme 2) upon treatment with *m*-CPBA, the ^1H NMR spectrum of which revealed only one set of signals, proving beyond doubt the isomeric character of **14a** and **14b** as a consequence of sulfur chirality.

The structure of bromohydrin **14** that has both the stereocenters required for elaboration to fragment A was unambiguously proven by transforming the sulfone **15** to the known silyl ether **17**, elaborated earlier from the allyl ether **18**[16] (Scheme 3).

The observed regio- and stereoselectivity in the reaction of sulfoxide **13a** and **13b** with NBS can be explained by invoking sulfoxonium intermediates **A** and **B**, respectively, formed by the nucleophilic attack of the sulfinyl group on the olefin complexed to the bromonium ion[17]

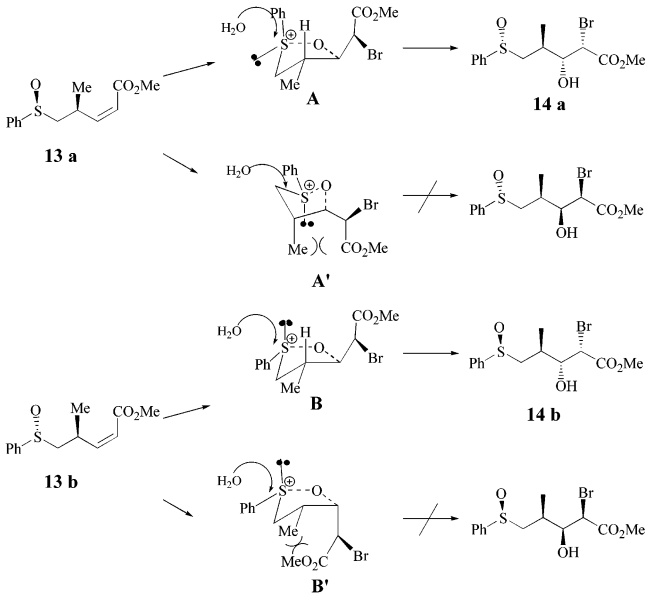
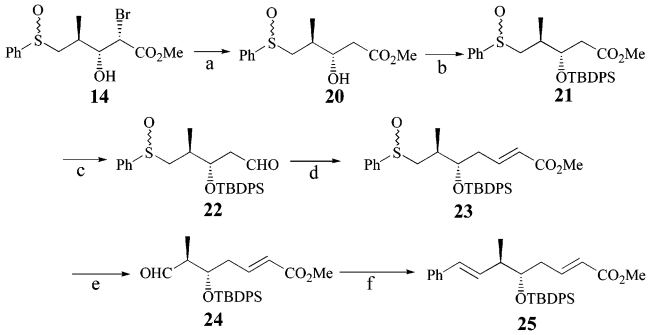


FIGURE 1.

SCHEME 4[a]



[a] Reaction conditions: (a) *n*-Bu_3SnH, AIBN, PhH, 80 °C, 82%; (b) TBDPS-Cl, imidazole, CH_2Cl_2, rt, 70%; (c) DIBAL, CH_2Cl_2, −78 °C, 85%; (d) Ph_3PCHCO_2Me, PhH, rt, 85%; (e) TFAA, Et_3N, CH_3CN, then aq sat. $NaHCO_3$; (f) (i) Ph_3PCH_2PhBr, *n*-BuLi, THF, 0 °C, aldehyde; (ii) PhSH, AIBN, PhH, 80 °C, 60% for three steps.

and subsequent hydrolysis of these by attack of water at sulfur[18] to yield bromohydrins **14a** and **14b**. The alternate intermediates **A′** and **B′** would be disfavored for steric reasons ($A^{1,3}$ strain,[19] Figure 1). The allyl substituent alone therefore influences the asymmetric induction, and the sulfoxide configuration has no influence on the stereochemical outcome.

The 5-exo nucleophilic attack by the sulfinyl group is probably due to the inductive electron-withdrawing nature of the carbomethoxy group which would destabilize any partial positive charge developing at C2.[20] The cis olefin geometry predicates *syn* disposition of the bromine and hydroxy groups due to the overall trans addition of the electrophile and nucleophile across the face of the olefin.

The bromohydrin **14** was transformed to fragment A as depicted in Scheme 4. Thus debromination of **14** with tributyltin hydride afforded sulfoxide **20** which revealed

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the presence of methylene protons adjacent to the carbomethoxy group as understood from an examination of its ^{1}H NMR and ^{13}C NMR spectra, thereby also proving the regioselectivity of bromohydrin formation.

Treatment of the debrominated alcohol **20** with *tert*-butyldiphenylsilyl chloride afforded the silyl ether **21** as an epimeric mixture of sulfoxides. Reduction of the carbomethoxy group with DIBAL afforded the aldehyde **22** which was taken ahead to the next step without further purification. Two-carbon homologation by subjecting the aldehyde to treatment with methyl(triphenylphosphoranylidene)acetate in benzene afforded the trans ester **23** exclusively. Pummerer reaction[21] followed by an aq sodium bicarbonate workup of the resulting intermediate yielded the aldehyde **24**. Without further purification, Wittig reaction of aldehyde **24** with the unstable ylide generated from benzylphosphonium bromide afforded a mixture of cis and trans isomers. The above mixture without separation was subjected to treatment with thiophenol[22] to effect isomerization of the cis to the trans isomer to yield dienoate **25**. It is instructive to note that attempted elaboration of the dienoate **25** by Julia olefination of the sulfone derived from the sulfoxide **23** failed. Attempted condensation of the sulfone anion generated using a variety of bases and employing different protocols, with benzaldehyde only returned unreacted starting material. The dienoate **25** was found to be possess physical characteristics similar to the product elaborated by Tius and co-workers.[2]

In conclusion, we have developed a novel, efficient, and stereoselective route to fragment A of cryptophycin 3 employing the sulfinyl moiety as an intramolecular nucleophile to functionalize an unsaturated ester in a key step of the reaction sequence. The sulfinyl moiety has been exploited to reveal an aldehyde group for further elaboration.

Experimental Section

NBS was freshly recrystallized from hot water before use. NMR spectra were recorded on a 200, 300, or 400 MHz spectrometer. ^{1}H NMR and ^{13}C NMR samples were internally referenced to TMS (0.00 ppm). Column chromatography was performed with 60−120 mesh silica gel.

2-Methyl-3-phenylsulfanyl-(2*S*)-propan-1-ol 9. To the stirred suspension of LAH (0.42 g, 11.3 mmol) in dry THF (5 mL), cooled at 0 °C, was added the solution of sulfide **8** (5.32 g, 15 mmol) in dry THF (15 mL) over a period of 5 min and stirred at the same temperature for another 2 h. The reaction mixture was diluted with ether, and excess LAH was quenched by adding small pieces of ice and allowed to attain rt when a gel separated out. The gel was filtered and washed with hot EtOAc (2 × 25 mL). The combined filtrates were evaporated under reduced pressure, and the resulting crude product was purified by column chromatography using 8% EtOAc/petroleum ether (v/v) as the eluent to afford alcohol **9** (2.2 g) in 80% yield. Viscous liquid. ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.02 (d, J = 7.3 Hz, 3H), 1.90 (m, 1H), 2.80 (dd, J = 13.4, 7.3 Hz, 1H), 3.05 (dd, J = 13.4, 7.3 Hz, 1H), 3.50 (br s, 2H), 7.30 (m, 5H). $[\alpha]_D$ + 14.6 (*c* 1, CH_2Cl_2). Rotation for the enantiomer: (($[\alpha]_D$ −17 (*c* 1, CH_2Cl_2)).[12] Anal. Calcd for $C_{10}H_{14}OS$: C, 65.90; H, 7.70; Found: C, 65.70; H, 7.52.

Methyl 4-Methyl-5-phenylsulfanyl-(*Z*,4*S*)-2-pentenoate 10. To the stirred solution of oxalyl chloride (1.40 g, 11.0 mmol) in dry dichloromethane (8 mL) cooled at −78 °C was added the solution of DMSO (1.09 g, 14 mmol) in dry dichloromethane (7 mL), and the mixture was stirred at the same temperature for another 15 min. The solution of the alcohol **9** (1.82 g, 10 mmol) in dry dichloromethane (10 mL) was added dropwise to the above mixture, and stirring was continued at the same temperature for 45 min. Hunig's base (6.50 g, 50 mmol) was then added and the reaction mixture allowed to warm to −10 °C. Water (50 mL) was added, and the two layers were separated. The aqueous layer was extracted with dichloromethane (2 × 25 mL). The combined organic layers were washed with water and brine and dried over Na_2SO_4. The solvent was evaporated under reduced pressure keeping the water bath temperature around 20 °C to afford the crude aldehyde which was taken ahead to the next step without further purification. To a stirred suspension of NaH (0.36 g, 50% in Nujol, 8 mmol) in dry THF (10 mL) cooled at 0 °C was added the solution of methyl (2,2,2-trifluoroethylphosphono)acetate (2.4 g, 7.5 mmol) in dry THF (5 mL) dropwise and stirred for 30 min. The reaction mixture was then cooled to −78 °C, and the solution of the aldehyde in dry THF (5 mL) was added and stirred at the same temperature for another 1 h. The reaction was quenched by the addition of a saturated aq NH_4Cl solution (10 mL). The reaction mixture was diluted with EtOAc (25 mL), and the organic layer was separated. The aqueous layer was extracted with EtOAc (25 mL), and the combined organic layers were washed with water and brine and dried over Na_2SO_4. The solvent was removed under reduced pressure to afford the crude product as a mixture of the cis and the trans esters. Separation of the esters by column chromatography using 3% EtOAc/petroleum ether (v/v) as the eluent afforded cis ester **10** (1.68 g) in 71% yield. Liquid. ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.98 (d, J = 6.8 Hz, 3H), 2.92 (d, J = 4.5 Hz, 2H), 3.68 (s, 3H), 3.80 (m, 1H), 5.78 (d, J = 10.0 Hz, 1H), 6.20 (t, J = 10.0 Hz, 1H), 7.12−7.26 (m, 5H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 19.6, 32.6, 40.5, 51.0, 119.4, 125.9, 128.8, 129.4, 136.7, 152.9, 166.3. $[\alpha]_D$ +65 (*c* 2.5 EtOAc). HRMS−FAB (*m*/*z*) $[M]^+$ calcd for $C_{13}H_{16}O_2S$ 236.0871, found 236.0872.

Methyl 4-Methyl-5-phenylsulfinyl-(*Z*,4*S*)-2-pentenoate 13. To the stirred solution of the ester **10** (2.36 g, 10 mmol) in MeOH (100 mL) cooled at 0 °C was added dropwise a solution of $NaIO_4$ (2.35 g, 11 mmol) in water (50 mL), and the reaction mixture was stirred overnight gradually allowing it to warm to rt. The precipitated solid was filtered, and the methanol in the filtrate was evaporated under reduced pressure. The aqueous layer was then extracted with EtOAc (2 × 100 mL). The combined organic layer was washed with brine and dried over Na_2SO_4. The solvent was evaporated under reduced pressure to afford the crude product which was then purified by column chromatography using 4:6 EtOAc:petroleum ether as the eluent to afford the sulfoxides **13a** and **13b** as an inseparable mixture (2.39 g) in 95% yield. Solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.20 (d, J = 7.2 Hz, 3H), 1.24 (d, J = 7.2 Hz, 3H), 2.70 (m, 2H), 2.86 (m, 2H), 3.68 (s, 3H), 3.69 (s, 3H), 4.0 (m, 1H), 4.05 (m, 1H), 5.95 (d, J = 9.2 Hz, 2H), 6.60 (t, J = 9.2 Hz, 2H), 7.48 (m, 6H), 7.60 (m, 4H). ^{13}C NMR (50 MHz, $CDCl_3$) δ 20.0, 20.1, 29.0, 29.4, 51.2, 64.8, 119.5, 119.8, 124.0, 124.1, 128.1, 129.2, 131.0, 151.0, 166.1. HRMS−FAB (*m*/*z*) $[M + H]^+$ calcd for $C_{13}H_{17}O_3S$ 253.0898, found 253.0900

Methyl 2-Bromo-3-hydroxy-4-methyl-5-phenylsulfinyl-(2*S*,3*R*,4*S*)-pentanoate 14. To the stirred solution of the unsaturated sulfoxide **13** (1.76 g, 7 mmol) in toluene (28 mL) was added water (0.18 mL, 10 mmol) followed by NBS (1.37 g, 7.7 mmol) at rt. The reaction mixture was stirred at rt for 3 h when TLC examination revealed the completion of the reaction. The reaction mixture was diluted with EtOAc and washed successively with saturated aq $NaHCO_3$, water, and brine and dried over Na_2SO_4. The solvent was removed under reduced pressure to afford the crude product which was purified by column chromatography using 4.5:5.5 EtOAc:petroleum ether as the eluent to yield bromohydrin **14** (2.0 g) in 80% yield. Viscous oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.12 (d, J = 8.8 Hz, 3H), 1.20 (d, J = 8.8 Hz, 3H), 2.37 (m, 2H), 2.65−3.1 (m, 4H), 3.80 (m, 5H), 3.82 (s, 3H), 4.45 (d, J = 8.8 Hz, 2H), 7.50 (m, 6H), 7.62 (m, 4H). ^{13}C NMR (50 MHz, $CDCl_3$) δ 16.6, 17.2, 33.8,

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34.1, 50.7, 51.2, 53.3, 60.3, 61.4, 74.1, 74.3, 124.0, 124.1, 128.3, 131.1, 143.9, 177.5. HRMS−FAB (*m*/*z*) [M + H]$^+$ calcd for $C_{13}H_{18}O_4SBr$ 349.0109, found 349.0130.

Methyl 2-Bromo-3-hydroxy-4-methyl-5-phenylsulfonyl-(2*S*,3*R*,4*S*)-pentanoate 15. To the stirred solution of the sulfoxide **14** (0.174 g, 0.5 mmol) in dichloromethane (2 mL) cooled at 0 °C was added *m*-CPBA (70%, 0.15 g, 0.6 mmol), and the reaction was stirred overnight. The reaction mixture was diluted with EtOAc (10 mL) and washed successively with saturated aq sodium sulfite, saturated aq sodium bicarbonate, water, and brine and dried over Na_2SO_4. The solvent was removed under reduced pressure to afford the crude product which was purified by column chromatography using 3:7 EtOAc: petroleum ether to afford sulfone **15** (0.146 g) in 80% yield. Viscous oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.20 (d, J = 6.6 Hz, 3H), 2.35 (m, 1H), 2.95 (dd, J = 14.1, 8.1 Hz, 1H), 3.55 (dd, J = 14.1, 2.8 Hz, 1H), 3.70 (dd, J = 8.1, 3.7 Hz, 1H), 3.82 (s, 3H), 4.30 (d, J = 3.7 Hz, 1H), 7.55−7.74 (m, 3H), 7.85−7.88 (m, 2H). ^{13}C NMR (50 MHz, $CDCl_3$) δ 16.5, 33.1, 49.5, 53.4, 57.7, 73.4, 127.8, 129.3, 133.7, 139.8, 169.4. $[\alpha]_D$ −9.0 (*c* 1, EtOAc). Anal. Calcd for $C_{13}H_{18}O_5BrS$: C, 42.75; H, 4.69; S, 8.78. Found: C, 42.72; H, 4.62; S, 8.80.

Methyl 3-Hydroxy-4-methyl-5-phenylsulfinyl-(3*S*,4*S*)-pentanoate 20. To the stirred solution of the sulfoxide**14** (1.40 g, 4.0 mmol) in dry benzene (16 mL) maintained at 80 °C was added AIBN (65 mg, 0.4 mmol) followed by tributyltin hydride (1,28 g, 4.4 mmol), and reaction was stirred at the same temperature under a nitrogen atmosphere for 3 h when TLC examination revealed completion of the reaction. The solvent was removed under reduced pressure and the residue purified by column chromatography using 4.5:5.5 EtOAc:petroleum ether as the eluent to yield the debrominated product **20** (0.88 g) in 82% yield. Viscous oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.13 (d, J = 7.8 Hz, 3H), 1.25 (d, J = 7.8 Hz, 3H), 2.20 (m, 2H), 2.40−3.05 (m, 8H), 3.72 (s, 6H), 3.94 (m, 2H), 7.45−7.58 (m, 6H), 7.62−7.70 (m, 4H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 16.5, 17.3, 34.5, 35.3, 38.9, 39.3, 51.8, 61.2, 61.5, 71.3, 123.9, 124.0, 129.2, 129.3, 131.0, 143.7, 144.3, 172.7, 173.0. *ms* [EI] 271.

Methyl 3-*tert*-Butyldiphenysilyloxy-4-methyl-5-phenylsulfinyl-(3*S*,4*S*)-pentanoate 21. To the solution of the alcohol **20** (0.78 g, 2.9 mmol) in dry dichloromethane (3.5 mL) was added imidazole (0.47 g, 7.0 mmol) followed by TBDP-Cl (0.88 g, 3.2 mmol) and the mixture stirred at rt for 24 h. The reaction mixture was diluted with ether (50 mL), washed with water and brine, and dried over Na_2SO_4. The solvent was removed under reduced pressure to afford the crude product which was purified by column chromatography using 1:3 EtOAc:petroleum ether as the eluent to yield the silyl ether **21** (1.02 g) in 70% yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.02 (s, 18H), 1.06 (d, J = 8.0 Hz, 3H), 1.14 (d, J = 8.0 Hz, 3H), 2.04−2.26 (m, 2H), 2.25−2.88 (m, 8H), 3.40 (s, 6H), 4.08−4.20 (m, 2H), 7.25−7.72 (m, 30H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 15.6, 16.1, 19.3, 19.4, 27.0, 27.9, 34.2, 34.7, 38.6, 39.3, 51.4, 60.9, 61.0, 73.0, 73.4, 123.9, 124.1, 127.4, 127.5, 127.6, 129.2, 129.6, 129.7, 130.9, 131.0, 132.9, 133.0, 133.7, 133.8, 135.8, 135.9, 136.0, 144.2, 144.5, 171.2. HRMS−FAB (*m*/*z*) [M + H]$^+$ calcd for $C_{29}H_{37}O_4SiS$ 509.2181, found 509.2181.

Methyl 5-*tert*-Butyldiphenylsilyloxy-6-methyl-7-phenylsulfinyl-(*E*,5*S*,6*S*)-2-heptenoate 23. To the solution of the silyl ether **21** (0.912 g, 1.8 mmol) in dry dichloromethane (4.0 mL) cooled at −78 °C was added DIBAL (2.0 M/toluene, 0.9 mL, 1.8 mmol), and the mixture was stirred at the same temperature for 30 min. Ether (10 mL) followed by a few drops of water was added and the reaction mixture allowed to warm to rt. The gel was filtered and washed with hot EtOAc (2 × 10 mL). The combined filtrates were dried over Na_2SO_4, and the solvent was removed under reduced pressure to afford the crude aldehyde **22** (0.73 g) in 85% yield which was used in the next step without further purification. ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.98 (s, 18H), 1.0 (d, J = 6.6 Hz, 3H), 1.05 (d, J = 6.6 Hz, 3H), 1.98−2.02 (m, 4H), 2.20−2.85 (m, 6H), 4.02−4.20 (m, 2H), 7.20−7.70 (m, 30H), 9.30 (m, 2H).

To the solution of the above aldehyde in dry benzene (6.0 mL) was added methyl (triphenylphosphoranylidene)acetate (0.62 g, 1.84 mmol) and stirred at rt for 30 min. The solvent was removed under reduced pressure to afford a residue which was purified by column chromatography using 3:7 EtOAc:petroleum ether as the eluent to yield the unsaturated ester **23** (0.70 g) in an overall yield of 72% for two steps. Viscous oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.04 (s, 9H), 1.08 (d, J = 8.1 Hz, 3H), 1.15 (d, J = 8.1 Hz, 3H), 2.18−2.28 (m, 6H), 2.32−2.95 (m, 4H), 3.62−3.72 (m, 8H), 5.46 (d, J = 16.2 Hz, 1H), 5.60 (d, J = 16.2 Hz, 1H), 6.46 (m, 1H), 6.60 (m, 1H), 7.27−7.60 (m, 30H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 16.2, 17.0, 19.4, 27.0, 33.3, 33.8, 36.8, 36.9, 51.3, 60.6, 60.9, 75.6, 75.9, 123.5, 123.9, 124.1, 127.5, 127.6, 127.7, 129.2, 129.8, 129.9, 130.9, 131.2, 133.0, 133.5, 135.8, 135.9, 144.2, 144.3, 166.2, 166.3. HRMS−FAB (*m*/*z*) [M + H]$^+$ calcd for $C_{31}H_{39}O_4SiS$ 535.2338, found 535.2331.

Methyl 5-*tert*-Butyldiphenylsilyloxy-6-methyl-8-phenyl-(2*E*,5*S*,6*R*,7*E*)-2,7-octadienoate 25. To the solution of the ester **23** (0.15 g, 0.28 mmol) in dry acetonitrile (2.8 mL) was added Et_3N (0.23 g, 2.24 mmol) followed by TFAA (0.35 g, 1.68 mmol) at rt, and the mixture was stirred for 30 min. A solution of $NaHCO_3$ (0.24 g, mmol) in water (3 mL) was added at 0° C, and stirring was continued, gradually allowing it to attain rt. The reaction mixture was diluted with ether (10 mL) and the aqueous layer separated. The aqueous layer was extracted with ether (2 × 10 mL), and the combined organic layers were washed with brine and dried over Na_2SO_4. The solvent was removed under reduced, keeping the water bath temperature around 20 °C to afford the crude aldehyde **24** (0.14 g) which was taken ahead to the next step without further purification. To the suspension of benzyltriphenylphosphonium bromide (0.4 g, 0.8 mmol) in dry THF (3.2 mL) was added n-BuLi (1.6 M/hexanes, 0.35 mL, 0.56 mmol) at 0 °C and the mixture stirred for 15 min. The solution of the aldehyde in dry THF (1.2 mL) was then added and stirring continued for 30 min at 0 °C. The reaction was quenched with a saturated aqueous solution of NH_4Cl. The organic layer was separated and the aqueous layer was extracted with ether (2 × 10 mL). The combined organic layers were washed with water and brine and dried over Na_2SO_4. The solvent was removed under reduced pressure to afford the crude product which was purified by column chromatography using 1:9 EtOAc:petroleum ether as the eluent to yield the dienoate **25** and the cis isomer. This mixture was dissolved in benzene (0.5 mL), thiophenol (5 mg) was added, and the mixture was heated at 80 °C. AIBN (2 mg) was added and the mixture heated at reflux for 3 h. Evaporation of the solvent afforded the crude product which was purified by column chromatography using 1:9 EtOAc:petroleum ether as the eluent to yield dienoate **25** (70 mg) in 60% overall yield for three steps. Viscous oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.88 (s, 9H), 1.12 (d, J = 5.9 Hz, 3H), 2.35 (m, 2H), 2.42 (m, 1H), 3.68 (s, 3H), 3.82 (m, 1H), 5.66 (d, J = 11.8 Hz, 1H), 6.15 (dd, J = 11.8, 5.9 Hz, 1H), 6.25 (d, J = 11.8 Hz, 1H), 6.77 (dt, J = Hz, 1H), 7.12−7.50 (m, 11H), 7.68−7.71 (m, 4H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 16.2, 19.5, 27.1, 37.2, 42.2, 51.3, 76.3, 122.9, 126.1, 127.1, 127.5, 127.6, 128.5, 129.7, 129.8, 130.7, 131.8, 133.7, 134.1, 136.0, 137.6, 145.9, 166.7. $[\alpha]_D$ + 74 (*c* 1, $CHCl_3$) (($[\alpha]_D$ + 76 (*c* 0.4, $CHCl_3$)).[2a] HRMS−FAB (*m*/*z*) [M − H]$^+$ calcd for $C_{32}H_{37}O_3Si$ 497.2512, found 497.2508.

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Supporting Information Available: Experimental details for the preparation of compounds **7**, **8**, **11**, and **12** (including analytical data) and copies of ^{1}H and ^{13}C NMR data of all the reported compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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