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TETRAHEDRON: *ASYMMETRY*

A short enantioselective synthesis of a component of cryptophycin A and arenastatin A

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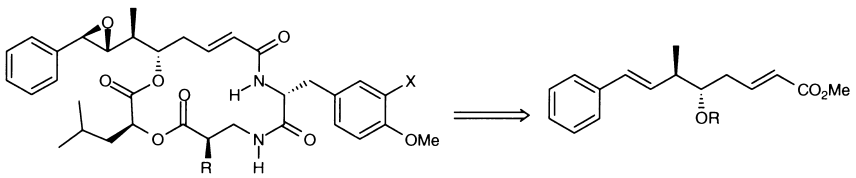
Abstract

Synthesis of **1**, a component of cryptophycin A **2** and arenastatin A **3**, was achieved by applying palladium-catalyzed reductive ring opening of optically active alkenyl oxirane **13** for the construction of the vicinal stereogenic centers.

1. Introduction

Methyl (5*S*,6*R*)-(*E*,*E*)-5-hydroxy-6-methyl-8-phenyl-2,7-octadienoate **1a**[1,2] is a synthetic component of depsipeptides, cryptophycins **2**[3,4] and arenastatins **3**.[5,6] Due to their important biological activities,[7–10] development of practical synthesis of **2** and **3** including their synthetic analogs is of current interest.[11–14] One of the problems in the synthesis of these compounds is the preparation of the hydroxy ester **1** by controlling both the absolute and the relative stereochemistry of the methyl group at C6 and the hydroxy group at C5.



Cryptophycin A **2** X=Cl; R=Me
Arenastatin A **3** X=H; R=H

1a: -R=H
1b: -R=TBS

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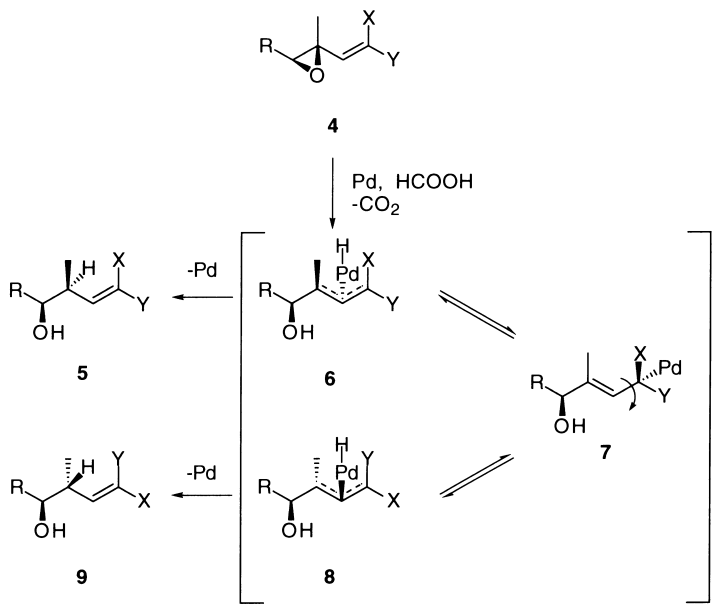
2. Results and discussion

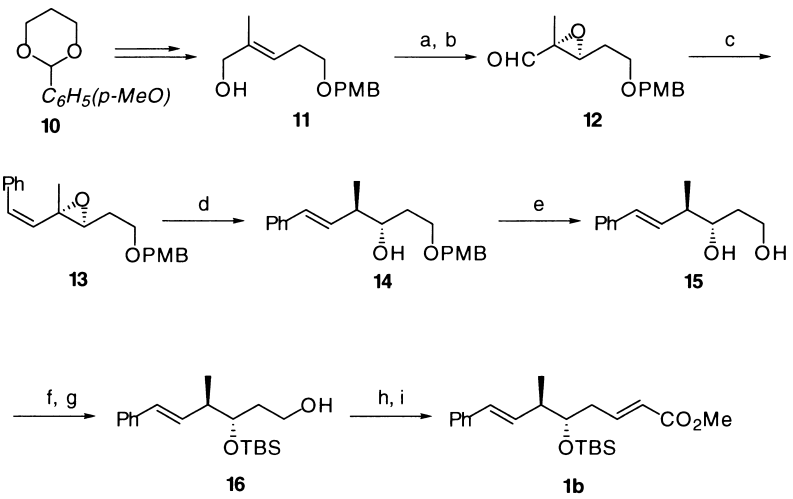
We have reported that the stereoselective synthesis of acyclic compounds which have a methyl and a hydroxy group at vicinal carbons can be carried out by a palladium-catalyzed reductive ring opening reaction of optically active alkenyl oxiranes using formic acid as a hydrogen source.[15] *syn*-Stereochemistry is constructed starting with *E*-alkenyloxiranes (*E*)-**4**, since the hydride derived from formic acid attacks via π-allylpalladium complex **6** from the palladium side as shown in Scheme 1. On the contrary, *anti*-stereochemistry of the methyl and the hydroxy groups can be expected to be generated if the π–σ–π interconversion takes place to form **8** prior to the hydride attack. In this paper we have established a facile preparation of **1** having *anti*-stereochemistry from the oxirane **13** by retention in the hydride attack via π–σ–π interconversion (**6**→**7**→**8** in Scheme 1).



Scheme 1.

2-*p*-Methoxyphenyl-1,3-dioxorane **10** was reduced with DIBAH, and subsequent Swern oxidation gave 3-*p*-methoxyphenyl-1-propanal,[16] which was converted to the allylic alcohol **11** by an Emmons–Horner type Wittig reaction and DIBAH reduction. The Sharpless asymmetric epoxidation of **11** with (+)-DET gave the chiral epoxy alcohol with 99% ee in 95% yield, subsequent Swern oxidation gave the aldehyde **12** in 80% yield. The Wittig reaction using $[Ph_3P(Ph)CH_2]Br$ under salt free conditions[17] gave the (*Z*)-alkenyloxirane **13** in 67% yield without observation of the (*E*)-isomer. The alkenyloxirane **13** was subjected to Pd-catalyzed transfer hydrogenolysis with HCOOH to give the homoallyl alcohol **14** selectively in 91% yield. Deprotection of the *p*-methoxy benzyl ether using $AlCl_3$ gave the diol **15,** from which the synthesis of **1b** has been reported.[1] Thus, the hydroxy groups of the diol **15** were protected as the TBS ethers in 94% yield. The silyl ether of the primary alcohol was deprotected selectively using AcOH at room temperature in 85% yield.[2] The alcohol **16** was oxidized to the corresponding aldehyde followed by the Emmons–Horner type Wittig reaction with trimethyl phosphonoacetate to give the ester **1b** in 72% overall yield (see Scheme 2), which was identified from the physical and spectral data reported in the literature.[1]

In conclusion, we have established a convenient route for the synthesis of the ester **1b**, a key intermediate for the synthesis of cryptophycins and arenastatins. The palladium-catalyzed reaction



(a) Ti(O*i*-Pr)$_4$, (+)-DET, TBHP, CH_2Cl_2, -25°C, 5 h, 95%; (b) $(COCl)_2$, DMSO, CH_2Cl_2, -78°C, 1.5 h; then Et_3N, r.t, 1.5 h, 80%; (c)[$Ph_3P(Ph)CH_2$]Br, NaN(TMS)$_2$, HMPA, THF, r.t, 8 h, 67%; (d) $Pd_2(dba)_3CHCl_3$, *n*-Bu_3P, HCOOH, Et_3N, Dioxane, r.t, 10 h, 91%; (e) $AlCl_3$, CH_2Cl_2, r.t, 30 min, 75%; (f) TBDMSCl, Imidazole, DMAP, DMF, r.t, 8 h, 94%; (g) AcOH: H_2O: THF (1:1:2), r.t, 72 h, 85% (h) $(COCl)_2$, DMSO, CH_2Cl_2, -78°C, 1 h; then Et_3N, r.t, 1 h; (i) Trimethyl phosphonoacetate, NaH, THF, r.t, 4 h, 2 steps 72%

Scheme 2.

described in this paper provides a useful method for construction of chiral building blocks which have *anti*-stereochemistry of methyl and hydroxy groups at the vicinal carbons.

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3. Experimental section

^{1}H NMR and ^{13}C NMR spectra were recorded on a JEOL JNM-EX270 in $CDCl_3$. IR spectra were recorded on a Perkin–Elmer 1640. Optical rotations were measured in $CHCl_3$ with a JASCO DIP-1000. Mass spectra were recorded on a JEOL JMS-SX102A. Anhydrous reactions were carried out under Ar using freshly dried solvents.

*3.1. (2*E*)-5-(*p*-Methoxybenzyl)oxy-2-methyl-2-penten-1-ol **11***

To a solution of **10** (2.01 g, 10.3 mmol) in Et_2O (40 ml) at 0°C was added DIBAH (0.95 M in hexane, 16.3 ml). The mixture was stirred for 1 h. The reaction mixture was quenched with Rochelle salt aqueous solution (0.5 M, 35 ml) at r.t., then the resulting mixture was stirred for 3 h. The reaction mixture was extracted with Et_2O. The extract was washed with brine, dried over $MgSO_4$, filtered, and concentrated in vacuo. The residue was chromatographed on silica gel (hexane:AcOEt=3:1) to give 3-(*p*-methoxybenzyl)oxy-1-propanol **17** (2.00 g, 99%). ^{1}H NMR δ 7.25 (d, 8.6, 2H), 6.87 (d, 8.4, 2H), 4.45 (s, 2H), 3.80 (s, 3H), 3.76 (dt, 5.6/5.8, 1H), 3.63 (dt, 5.6/5.8, 2H), 2.45 (broad, 1H), 1.89–1.80 (tt, 5.6/5.8, 2H); ^{13}C NMR δ 159.2, 130.1, 129.2, 113.8, 72.8, 69.0, 61.8, 55.2, 32.0; IR ν 3422, 2950, 2858, 1613, 1514, 1248, 1121, 1084, 1034, 873, 820 cm^{-1}; HREIMS m/z calcd for $C_{11}H_{16}O_3$: 196.1100, found: 196.1120.

To a solution of DMSO (2.50 ml) in CH_2Cl_2 (30 ml) were added $(COCl)_2$ (1.33 ml) and the alcohol **17** (1.98 g, 10.1 mmol) in CH_2Cl_2 (15 ml) sequentially at −78°C. After the mixture was stirred for 1 h, Et_3N (8.43 ml) was added and the mixture was stirred for 1 h at r.t. The reaction mixture was quenched with sat. NH_4Cl, and the aqueous layer was extracted with CH_2Cl_2. The extract was washed with brine, dried over $MgSO_4$, filtered, and concentrated in vacuo to give a crude aldehyde, which was used in the next step without purification.

To a suspension of [1-(ethoxycarbonyl)ethyl]triphenylphosphonium bromide (5.36 g) in THF (30 ml) was added *n*-BuLi (1.66 M in hexane, 6.8 ml) at 0°C. After the mixture was stirred for 10 min, the crude aldehyde obtained above in THF (15 ml) was added and the mixture was stirred for 2 h. The reaction mixture was quenched with H_2O, and the aqueous layer was extracted with CH_2Cl_2. The extract was washed with brine, dried over $MgSO_4$, filtered, and concentrated in vacuo. The residue was chromatographed on silica gel (hexane:AcOEt=9:1) to give ethyl *(2E)*-5-(*p*-methoxybenzyl)oxy-2-methyl-2-heptenoate **18** (2.08 g, 74% from **10**). ^{1}H NMR δ 7.26 (d, 8.58, 2H), 6.88 (d, 8.58, 2H), 6.77 (ddd, 1.3/5.9/8.6, 1H), 4.46 (s, 2H), 4.19 (q, 7.26, 2H), 3.81 (s, 3H), 3.53 (dd, 6.6/6.9, 2H), 2.48 (ddd, 0.99/6.9/11.9, 2H), 1.84 (d, 0.99, 1H), 1.29 (t, 7.3, 3H); ^{13}C NMR δ 168.0, 159.2, 138.3, 130.3, 129.4, 129.2, 113.8, 72.7, 68.3, 60.4, 55.3, 29.4, 14.3, 12.5; IR ν 2956, 2934, 2904, 2858, 1709, 1513, 1248, 1097, 1036, 821 cm^{-1}; HREIMS m/z calcd for $C_{16}H_{22}O_4$: 278.1996, found: 278.1519.

To a solution of **18** (2.05 g, 7.39 mmol) in Et_2O (30 ml) at 0°C was added DIBAH (0.95 M in hexane, 19.4 ml). After the mixture was stirred for 1 h, the reaction mixture was quenched with Rochelle salt aqueous solution (0.5 M, 40 ml) at r.t. After the mixture was stirred for 3 h the solution was extracted with Et_2O, washed with brine, dried over $MgSO_4$, filtered, and concentrated in vacuo. The residue was chromatographed on silica gel (hexane:AcOEt=5:1) to give **11** (1.69 g, 97%). ^{1}H NMR δ 7.25 (d, 8.6, 2H), 6.86 (d, 8.3, 2H), 5.41 (t, 6.9, 1H), 4.43 (s, 2H), 3.96 (s, 2H), 3.79 (s, 3H), 3.45 (t, 6.9, 2H), 2.34 (dt, 6.9, 2H), 2.03 (broad, 1H), 1.65 (s, 3H); ^{13}C NMR δ 159.0, 136.7, 130.4, 129.2, 121.8, 113.7, 72.4, 69.3, 68.4, 55.2, 28.2, 13.7; IR ν 3405, 2934, 2910, 2858, 1612, 1513, 1248, 1091, 1035, 820 cm^{-1}; HREIMS m/z calcd for $C_{14}H_{20}O_3$: 236.1413, found: 236.1379.

*3.2. (2*S*,3*S*)-2,3-Epoxy-5-(*p*-methoxybenzyl)oxy-2-methyl-1-pentanal **12***

To a mixture of 4Å–MS in CH_2Cl_2 (18 ml) at −25°C was added $Ti(O^iPr)_4$ (0.211 ml), L-(+)-DET (0.145 ml) and **11** (1.68 g, 7.10 mmol). After the mixture was stirred for 30 min, TBHP was added and the mixture was stirred for 4.5 h. The resulting mixture was quenched by a small amount of Me_2S and excess sat. NaF aqueous solution. After being stirred for 12 h, the solvent was filtered and extracted with CH_2Cl_2, washed with brine, dried over $MgSO_4$, filtered, and concentrated in vacuo. The residue was chromatographed on silica gel (hexane:AcOEt=7:3) to give (2*S*,3*S*)-2,3-epoxy-5-(*p*-methoxybenzyl)oxy-2-methyl-1-pentanol **19** (1.69 g, 95%). ^{1}H NMR δ 7.26 (d, 8.6, 2H), 6.88 (d, 8.6, 2H), 4.46 (s, 2H), 3.80 (s, 3H), 3.68–3.55 (m, 4H), 3.18–3.14 (dd, 5.3/6.9, 1H), 1.91–1.82 (m, 2H), 1.28 (s, 3H); ^{13}C NMR δ 159.0, 130.3, 129.2, 113.8, 72.7, 67.1, 65.3, 60.8, 57.9, 55.2, 29.0, 14.3; IR ν 3447, 2932, 2860, 2360, 2342, 1612, 1513, 1248, 1094, 1034, 820 cm^{-1}; $[\alpha]_D^{25}$=−44 (c 1.34, $CHCl_3$); HREIMS m/z calcd for $C_{14}H_{20}O_4$: 252.1362, found: 252.1384. The enantiomeric excess of **19** (99% e.e.) was calculated from the ^{19}F NMR of its (+)-MTPA ester.

To a solution of DMSO (1.65 ml) in CH_2Cl_2 (20 ml) were added sequentially $(COCl)_2$ (0.872 ml) and the alcohol **19** (1.67 g, 6.64 mmol) in CH_2Cl_2 (12 ml) at −78°C. After the mixture was stirred for 1 h, Et_3N (5.55 ml) was added and the mixture was stirred for 1 h at r.t. The reaction mixture was quenched with sat. NH_4Cl, and the aqueous layer was extracted with CH_2Cl_2. The extract was washed with brine, dried over $MgSO_4$, filtered, and concentrated in vacuo. The residue was chromatographed on silica gel

(hexane:AcOEt=5:1) to give **12** (1.32 g, 80%). ^{1}H NMR δ 8.85 (s, 1H), 7.23 (d, 8.9, 2H), 6.88 (d, 8.6, 2H), 4.46 (s, 2H), 3.80 (s, 3H), 3.63 (t, 5.9, 2H), 3.30 (t, 5.9, 1H), 1.97–1.87 (m, 2H), 1.40 (s, 3H); ^{13}C NMR δ 199.7, 179.1, 130.2, 129.2, 113.9, 72.9, 66.5, 62.1, 57.9, 55.3, 28.8, 10.1; IR ν 2934, 2859, 1728, 1612, 1514, 1248, 1095, 1034, 821 cm^{-1}; $[\alpha]_D^{28}$=37 (c 1.04, $CHCl_3$).

3.3. (1Z)-(3S,4S)-3,4-Epoxy-6-(p-methoxybenzyl)oxy-3-methyl-1-phenyl-1-heptene **13**

To a solution of $[Ph_3P(Ph)CH_2]Br$ (3.38 g) in THF (12 ml) was added $NaN(TMS)_2$ (1.0 M in THF, 6.24 ml). After the mixture was stirred for 1 h, HMPA (8 ml) was added dropwise at 0°C and the resulting mixture was stirred for 1 h. The aldehyde **12** (1.30 g, 5.19 mmol) in THF was added at −100°C and the mixture was stirred for 10 h at r.t. The reaction mixture was quenched with sat. NH_4Cl, and the aqueous layer was extracted with Et_2O. The extract was washed with brine, dried over $MgSO_4$, filtered, and concentrated in vacuo. The residue was chromatographed on silica gel (hexane:AcOEt=9:1) to give **13** (1.12 g, 67%). ^{1}H NMR δ 7.37–7.18 (m, 7H), 6.86 (d, 8.6, 2H), 6.44 (d, 11.9, 1H), 5.86 (d, 11.9, 1H), 4.42 (s, 2H), 3.80 (s, 3H), 3.53 (dd, 6.3/6.9, 2H), 2.89 (dd, 4.3/7.3, 1H), 2.04–1.93 (m, 1H), 1.80–1.70 (m, 1H), 1.46 (s, 3H); ^{13}C NMR δ 159.3, 132.3, 130.5, 129.2, 128.8, 128.2, 128.0, 127.4, 113.9, 96.2, 72.7, 67.2, 62.6, 58.9, 55.3, 29.4, 17.6; IR ν 2961, 2932, 2858, 1612, 1512, 1248, 1095, 1034, 696 cm^{-1}; $[\alpha]_D^{27}$=84.2 (c 0.67, $CHCl_3$).

3.4. (1E)-(3R,4S)-4-Hydroxy-6-(p-methoxybenzyl)oxy-3-methyl-1-phenyl-1-heptene **14**

To a mixture of $Pd_2(dba)_3CHCl_3$ (0.178 g) and *n*-Bu_3P (0.0855 ml) in dioxane (6 ml) was added a mixture of HCOOH (0.661 ml) and Et_3N (0.957 ml) in dioxane (3 ml) at r.t. The mixture was stirred for 15 min. The oxirane **13** (1.11 g, 3.43 mmol) in dioxane (6 ml) was added and the mixture was stirred for 10 h. The reaction mixture was quenched with H_2O and the aqueous layer was extracted with Et_2O and the combined extract was washed with sat. NH_4Cl and brine, dried over $MgSO_4$, filtered, and concentrated in vacuo. The residue was chromatographed on silica gel (hexane:AcOEt=9:1) to give **14** (1.02 g, 91%). ^{1}H NMR δ 7.37–7.15 (m, 7H), 6.87 (d, 8.6, 2H), 6.41 (d, 15.8, 1H), 6.21 (dd, 7.9/15.8, 1H), 4.44 (s, 2H), 3.79 (s, 3H), 3.77–3.58 (m, 3H), 2.87 (broad, 1H), 2.42–2.35 (m, 1H), 1.79–1.70 (m, 2H), 1.13 (d, 6.9, 3H); ^{13}C NMR δ 159.3, 137.4, 132.1, 130.7, 130.1, 129.3, 128.5, 127.1, 126.1, 113.8, 74.7, 73.0, 69.0, 55.3, 43.5, 33.8, 16.4; IR ν 3462, 3003, 2960, 2932, 2867, 1612, 1513, 1248, 1089, 1035, 752, 694 cm^{-1}; $[\alpha]_D^{34}$=49.2 (c 0.67, $CHCl_3$)

3.5. (1E)-(3R,4S)-3-Methyl-1-phenyl-1-heptene-4,6-diol **15**

To a solution of the alcohol **14** (496 mg, 1.52 mmol) in CH_2Cl_2 (8 ml) was added $AlCl_3$ (223 mg) at r.t. After stirring for 30 min $AlCl_3$ (81.2 mg) was added and the mixture was stirred for 30 min. The reaction mixture was quenched with sat. $NaHCO_3$ and Rochelle salt aqueous solution (0.5 M, 10 ml). After stirred for 10 h, the solution was extracted with CH_2Cl_2, washed with brine, dried over $MgSO_4$, filtered and concentrated in vacuo. The residue was chromatographed on silica gel (hexane:AcOEt=4:1) to give the alcohol **15** (235 mg, 75%). ^{1}H NMR δ 7.35–7.14 (m, 5H), 6.43 (d, 16.2, 1H), 6.09 (dd, 8.6/15.8, 1H), 3.87–3.76 (m, 2H), 3.75–3.66 (m, 1H), 2.50–2.29 (broad, 1H, m, 2H), 1.80–1.59 (m, 1H), 1.08 (d, 6.6, 3H); ^{13}C NMR δ 137.0, 131.8, 131.5, 128.6, 127.4, 126.2, 75.5, 61.8, 44.1, 35.5, 16.5; IR ν 3356, 2961, 2878, 1493, 1448, 1053, 970, 750, 694 cm^{-1}; $[\alpha]_D^{26}$=57.0 (c 1.47, $CHCl_3$).

3.6. (1E)-(3R,4S)-4-(tert-Butyldimethylsilyl)oxy-3-methyl-1-phenyl-1-hepten-6-ol **16**

To a solution of the alcohol **15** (230 mg, 1.12 mmol) and imidazole (455 mg, 6.69 mmol) in DMF (5 ml) was added TBDMSCl (504 mg) and DMAP (cat.) at r.t. After the mixture was stirred for 10 h, the reaction mixture was quenched with H_2O, and the aqueous layer was extracted with Et_2O. The extract was washed with brine, dried over $MgSO_4$, filtered and concentrated in vacuo. The residue was chromatographed on silica gel (hexane:AcOEt=9:1) to give (1*E*)-(3*R*,4*S*)-4,6-bis(*tert*-butyldimethylsilyl)oxy-3-methyl-1-phenyl-1-heptene **20** (455 mg, 94%). ^{1}H NMR δ 7.35–7.15 (m, 5H), 6.35 (d, 16.17, 1H), 6.17 (dd, 7.6/15.8, 1H), 3.86–3.80 (dt, 4.0/5.9, 1H), 3.70–3.60 (m, 2H), 2.50–2.43 (m, 1H), 1.67–1.60 (dd, 6.6/12.9, 2H), 1.10 (d, 6.9, 3H), 0.91 (s, 9H), 0.89 (s, 9H), 0.07 (s, 6H), 0.03 (s, 6H); ^{13}C NMR δ 137.8, 132.8, 130.0, 128.4, 126.8, 126.0, 72.6, 60.1, 42.7, 36.7, 25.9, 18.3, 18.1, 15.5, −4.5, −5.3; IR ν 2955, 2942, 2928, 2856, 1472, 1466, 1256, 1098, 836, 775, 692 cm^{-1}; $[\alpha]_D^{32}$=48.2 (c 1.04, $CHCl_3$); HREIMS m/z calcd for $C_{25}H_{46}O_2Si_2$: 435.3116, found: 435.3082.

To a solution of **20** (450 mg, 1.04 mmol) in THF (2 ml) and H_2O (1 ml) was added AcOH (1 ml) at r.t. After the mixture was stirred for 3 days the reaction mixture was quenched with $NaHCO_3$, and the aqueous layer was extracted with Et_2O. The extract was washed with brine, dried over $MgSO_4$, filtered and concentrated in vacuo. The residue was chromatographed on silica gel (hexane:AcOEt=9:1) to give **16** (281 mg, 85%). ^{1}H NMR δ 7.36–7.17 (m, 5H), 6.39 (d, 16.2, 1H), 6.13 (dd, 7.9/16.2, 1H), 3.91–3.86 (dd, 5.6/10.9, 1H), 3.79–3.70 (m, 2H), 2.59–2.51 (m, 1H), 1.76–1.70 (m, 2H), 1.10 (d, 6.6, 3H), 0.91 (s, 9H), 0.01 (d, 0.66, 6H); ^{13}C NMR δ 132.6, 130.0, 128.5, 127.0, 126.0, 74.6, 60.5, 42.7, 35.0, 25.9, 18.0, 14.8, −4.5, −4.6; IR ν 3410, 2957, 2943, 2929, 2856, 1733, 1472, 1257, 1094, 1058, 1031, 836, 758, 693 cm^{-1}; $[\alpha]_D^{21}$=150.8 (c 0.17, $CHCl_3$)

3.7. (5S,6R)-(E,E)-5-(tert-Butyldimethylsilyl)oxy-6-methyl-8-phenyl-octa-2,7-dienoate **1b**

To a solution of DMSO (0.206 ml) in CH_2Cl_2 (2 ml) were added sequentially $(COCl)_2$ (0.109 ml) and the alcohol **16** (265 mg, 0.829 mmol) in CH_2Cl_2 (2 ml) at −78°C. After the mixture was stirred for 1 h, Et_3N (0.693 ml) was added and the mixture was stirred for 1 h at r.t. The reaction mixture was quenched with sat. NH_4Cl, and the aqueous layer was extracted with CH_2Cl_2. The extract was washed with brine, dried over $MgSO_4$, filtered, and concentrated in vacuo to give a crude aldehyde, which was used in the next step without purification.

To a solution of NaH (66.3 mg) in THF (2 ml) was added trimethyl phosphonoacetate (0.268 ml) at 0°C. After the mixture was stirred for 10 min, the crude aldehyde obtained above in THF (2 ml) was added and the mixture was stirred for 4 h at r.t. The reaction mixture was quenched with H_2O, and the aqueous layer was extracted with Et_2O. The extract was washed with brine, dried over $MgSO_4$, filtered, and concentrated in vacuo. The residue was chromatographed on silica gel (hexane:AcOEt=9:1) to give **1b** (222 mg, 2 steps 72%). ^{1}H NMR δ 7.36–7.17 (m, 5H), 7.01–6.90 (m, 1H), 6.37 (d, 15.8, 1H), 6.20–6.11 (m, 1H), 5.84 (d, 15.8, 1H), 3.78–3.73 (m, 1H), 3.72 (s, 3H), 2.48–2.40 (m, 1H), 2.38–2.33 (m, 2H), 1.10 (d, 6.6, 3H), 0.90 (s, 9H), 0.05 (d, 0.25, 6H); ^{13}C NMR δ 166.8, 146.4, 137.6, 131.9, 130.5, 128.5, 127.0, 126.0, 122.9, 75.0, 51.4, 42.8, 37.6, 25.9, 18.1, 16.2, −4.4, −4.5; IR ν 2954, 2929, 2856, 1727, 1658, 1436, 1322, 1258, 1169, 1097, 970, 837, 775, 748, 693 cm^{-1}; $[\alpha]_D^{27}$=66.1 (c 0.80, $CHCl_3$); HRFABMS m/z calcd for $C_{22}H_{34}O_3Si$: 374.2278, found: 374.2253.

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