Efficient Asymmetric Synthesis of the C_9−C_{21} Portion of the Aplysiatoxin and Oscillatoxin Marine Natural Products

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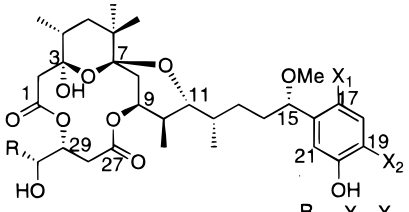
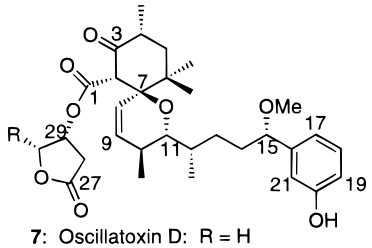
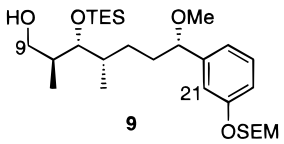
Metabolites of tropical marine bluegreen algae of the class oscillatoriaeceae, the toxic aplysiatoxin, oscillatoxin A, and their brominated variants (**1**−**6**) are significant tumor promotors,[2,3] whereas the nontoxic oscillatoxin D (**7**) and 30-methyloscillatoxin D (**8**) possess antileukemic activity.[4,5] Because of their biological activities and because they cannot be produced by fermentation of the algae that produce them, these natural products have been the goal of a number of synthetic studies.[3,5] As part of our synthetic efforts aimed at producing oscillatoxin D,[5a−c] we have perfected a short (10 steps from commercially available starting materials) and efficient (26% overall yield) preparation of a selectively protected C_9−C_{21} portion of the aplysiatoxins and oscillatoxins, compound **9**, which can serve as an advanced intermediate for the total synthesis of any one of the natural products **1**−**8**. In this note, we describe the full details of our synthesis of **9**, using a route which is an improvement over a similar route described in a preliminary report.[5b]



	R	X_1	X_2
1: Aplysiatoxin	CH_3	Br	H
2: Debromoaplysiatoxin	CH_3	H	H
3: 19-Bromoaplysiatoxin	CH_3	Br	Br
4: Oscillatoxin A	H	H	H
5: 17-Bromooscillatoxin A	H	Br	H
6: 17,19-Dibromooscillatoxin A	H	Br	Br



7: Oscillatoxin D: R = H
8: 30-Methyloscillatoxin D: R = CH_3



9

As indicated in Scheme 1, (*S*)-methyl 3-hydroxy-2-methylpropanoate was O-protected with the *para*-methoxybenzyl (PMB) group[6] and then reduced to the aldehyde **10**,[7] which was allowed to react with the Evans enolate **11**[8] to yield the aldol **12**. It is important to note that the phenylpropanolamine-derived oxazolidinone in **11** was best suited for this asymmetric aldol reaction, compared to other oxazolidinone chiral auxiliaries, because the aldol product **12** could be isolated as a single stereoisomer from the crude product mixture by crystallization. In earlier studies,[5b] using acetal derivatives of **12**, we demonstrated that the aldol product **12** did indeed possess the desired 11*S*,12*R* (aplysiatoxin−oscillatoxin numbering system) configuration at the newly introduced stereogenic carbon centers.

Protection of the 11-hydroxyl group of **12** as the triethylsilyl (TES) ether **13** and subsequent reductive removal of the oxazolidinone[9] yielded the alcohol **14**, which was smoothly converted to the iodide **15** using Corey's conditions.[10] The C_{13} iodide in **15** was cleanly displaced by the lithioenamine **16**, derived from the *N*-cyclohexylimine deriative of 3-(trimethylsilylethoxymethoxy)-acetophenone,[11] yielding (after aqueous hydrolysis of the imine group) the ketone **17**. Corey's asymmetric oxazaborolidine-catalyzed reduction[12] of the 15-keto group of **17** produced the alcohol **19** as a single stereoisomer, which we demonstrated earlier,[5b] using CD spectroscopy, to be the desired 15*S* epimer. O-Methylation of the 15-hydroxyl group of **19** yielded the triprotected product **20**, and oxidative cleavage of the PMB

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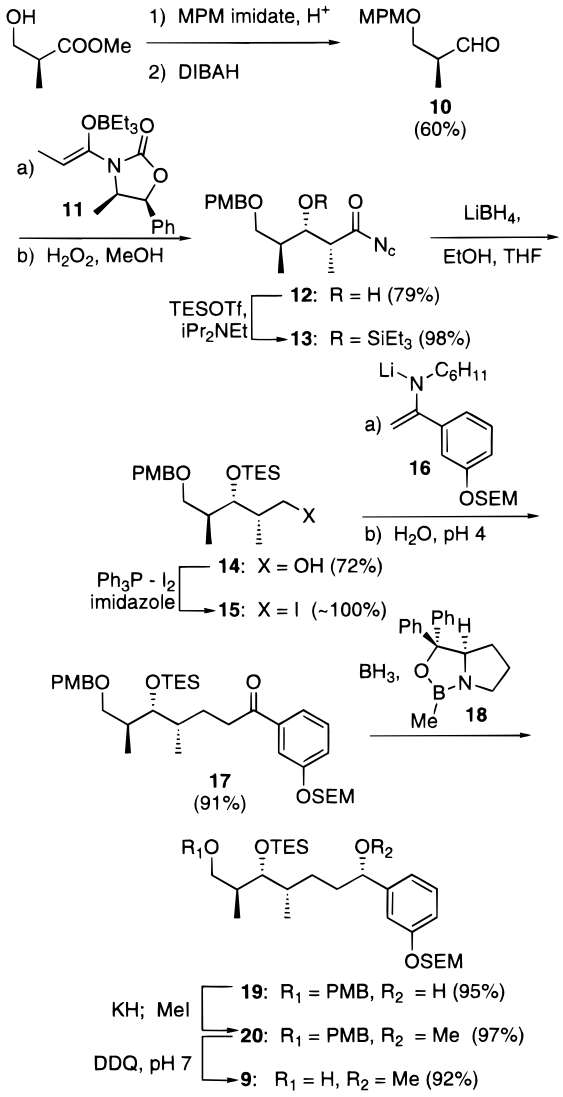
Scheme 1



ether group in **20**, under conditions which did not affect the benzylic ether group at C_{15}, produced the C_9-C_{21} building block, **9**, for the aplysiatoxin and oscillatoxin natural products.

In summary, a concise synthesis of an advanced intermediate for the preparation of an entire class of natural products, using methodology amenable for large scale preparation, is reported. The choice of protecting groups is worth noting; we have found, for instance, that the TES ether group at C_{11} can be cleanly removed without affecting the SEM ether group at C_{20}.[13] Synthetic studies using the intermediate **9** will be the objective of future research.

Experimental Section

General. Thin-layer chromatography (TLC) was performed using silica gel UV254 coated onto aluminum plates. Chromatography was performed using 230−240 mesh silica gel and predistilled solvents. NMR spectra were obtained from solutions in $CDCl_3$. Proton chemical shifts are reported in δ units relative to the signal for trace chloroform in the solvent (δ 7.24), and ^{13}C chemical shifts were also reported relative to deuteriochloroform (δ 77.00). Optical rotations were measured using dilute solutions in a 10-cm cell. Elemental analyses were conducted by Desert Analytics, Tucson, Arizona. High-resolution mass spectrometric analyses were conducted by the Midwest Center for Mass Spectrometry, Department of Chemistry, University of Nebraska−Lincoln. All solvents were predistilled using methods described by Perrin and Armarego[14] and stored over oven-dried 4A molecular sieves.

(*S*)-3-(4′-Methoxyphenyl)methoxy-2-methylpropanal (10). To a stirring mixture of 17.03 g (123.29 mmol) of 4-methoxybenzyl alcohol in 150 mL of ether at room temperature under nitrogen was added 0.46 g of a 60% dispersion of sodium hydride in mineral oil (~11.63 mmol of NaH). The resulting suspension was allowed to stir until the solid had dissolved and gas evolution had ceased (approximately 1 h). Then, the mixture was cooled to 0 °C, and 12.36 mL (123.30 mmol) of trichloroacetonitrile was added over 15 min. The mixture was stirred at 0 °C for another 5 min and at room temperature for 20 min. It was then transferred to a separatory funnel, washed with saturated sodium bicarbonate and brine, dried ($MgSO_4$), and concentrated to yield the crude 4-methoxybenzyl trichloroacetimidate as a yellow oil. That oil was stirred in 150 mL of dichloromethane with 9.07 mL (82.20 mmol) of (*S*)-methyl 3-hydroxy-2-methylpropanoate and 0.90 g (3.59 mmol) of pyridinium *p*-toluenesulfonate at room temperature for 22 h (a white solid forms during the reaction). The reaction mixture was then washed with saturated sodium bicarbonate and brine, dried ($MgSO_4$), and concentrated under vacuum. The resulting semisolid mixture was triturated with 1:1 hexanes/dichloromethane, and the triturant solution was concentrated to an oil, which was distilled under 0.07 mmHg vacuum, with collection of pure **(*S*)-methyl 3-(4′-methoxyphenyl)methoxy-2-methylpropanoate** as the fraction distilling at 98−110 °C in a yield of 13.10 g (67%): ^1H NMR δ 7.24 (d, J = 8.7, 2H), 6.87 (d, J = 8.7, 2H), 4.45 (s, 3H), 3.80 (s, 3H), 3.69 (s, 3H), 3.63 (d of d, J = 9.2, 7.4, 1H), 3.45 (d of d, J = 9.2, 5.9, 1H), 2.77 (m, 1H), 1.17 (d, J = 7.1, 3H); ^{13}C NMR δ 159.2, 129.4, 129.2, 113.8, 72.8, 71.7, 71.5, 55.3, 51.7, 40.2, 14.0; $[\alpha]^{25}_D$ +9.67° (*c* 8.38, $CHCl_3$). Anal. Calcd for $C_{13}H_{18}O_4$: C, 65.52; H, 7.61. Found: C, 65.34; H, 7.45.

To a stirring solution of 3.00 g (12.58 mmol) of the ester in 125 mL of dry dichloromethane, at −78 °C under nitrogen was added diisobutylaluminum hydride (10.49 mL of a 1.5 M solution in toluene, 15.7 mmol) dropwise over 2 h. The solution was stirred for an additional hour at −78 °C and 3 mL of anhydrous methanol was added dropwise. The mixture was warmed to room temperature, diluted with 100 mL of ether, mixed carefully with 2 mL of water, and then stirred for 15 min. The milky suspension was then filtered through a 3-cm pad of Celite, and the filtrate was concentrated under vacuum to yield 2.69 g (>100%) of a clear liquid. NMR analysis of this crude product indicated that it was ~95% pure aldehyde **10**. Due to concerns about the tendency of this aldehyde to undergo self-condensation reactions and to epimerize during purification procedures, the crude material was carried on to the next step without further purification: ^1H NMR δ 9.71 (d, J = 1.5, 1H), 7.24 (d, J = 8.6, 2H), 6.88 (d, J = 8.6, 2H), 4.45 (s, 2H), 3.80 (s, 3H), 3.63 (m, 2H), 2.65 (m, 1H), 1.08 (d, J = 6.1, 3H); ^{13}C NMR δ 204.0, 159.2, 130.0, 129.2, 113.8, 73.0, 69.7, 55.2, 46.8, 10.7; $[\alpha]^{25}_D$ +29.4° (*c* 9.06, CH_2Cl_2).

(2′*R*,3′*S*,4′*S*,4*R*,5*S*)-3-(3′-Hydroxy-5′-[4″-methoxyphenyl]-methoxy-2′,4′-dimethylpentanoyl)-5-phenyl-4-methyl-2-oxazolidinone (12). To a 100-mL round-bottomed flask containing 4.7 mL of a 1.0 M solution of triethylborane in hexanes (3.9 mmol) at 0 °C under nitrogen was added dropwise 0.41 mL (3.9 mmol) of trifluoromethanesulfonic acid. The solution was warmed using a 40 °C oil bath, with stirring, for 30 min (gas evolution ceased at that time). The solution was then cooled to 0 °C, and 0.91 g (3.9 mmol) of (4*R*,5*S*)-4-methyl-5-phenyl-3-propionyloxazolidin-2-one in 45 mL dichloromethane was added, followed by 0.81 mL (4.1 mmol) of ethyldiisopropylamine. After 30 min, the reaction mixture was cooled to −78 °C, and 0.8 g (3.9 mmol) of the freshly prepared aldehyde **10** was slowly added. The reaction mixture was maintained at −78 °C for 3 h and then warmed to room temperature. Four hours later the reaction was

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quenched by the addition of 25 mL of pH 7 buffer, and the aqueous layer was extracted with dichloromethane (2 × 25 mL). The combined organic extracts were concentrated, and the resulting yellow oil was dissolved in 35 mL of methanol, cooled in an ice−water bath, and mixed with 12 mL of 30% aqueous H_2O_2. This solution was warmed to room temperature over the course of 1 h, 60 mL of water was added, the methanol was removed under vacuum, and the aqueous suspension was extracted with dichloromethane. The combined organic extracts were washed with brine, dried over $MgSO_4$, and concentrated to afford a clear oil which slowly crystallized. The white solid was recrystallized from diethyl ether to yield 1.2 g (70%) of the pure product **12**. The mother liquor from the crystallization was concentrated and chromatographed (7:3 hexanes/ethyl acetate) to yield an additional 0.2 g (9%) of the pure product: ^{1}H NMR δ 7.40 (m, 5H), 7.28 (d, J = 8.7, 2H), 6.87 (d, J = 8.7, 2H), 5.62 (d, J = 7.1, 1H), 4.74 (p, J = 6.7, 1H), 4.45 (s, 2H), 3.90 (m, 2H), 3.80 (br, 1H), 3.79 (s, 3H), 3.57 (m, 2H), 1.97 (m, 1H), 1.22 (d, J = 6.8, 3H), 0.96 (d, J = 7.0, 3H), 0.90 (d, J = 6.6, 3H); ^{13}C NMR δ 175.93, 159.27, 152.82, 133.24, 129.82, 129.40, 128.71, 125.62, 113.81, 78.95, 75.58, 74.75, 73.19, 55.26, 55.21, 40.85, 35.90, 14.31, 13.55, 9.51; $[\alpha]^{25}_D$ +23.7° (*c* 9.87, CH_2Cl_2). Anal. Calcd for $C_{25}H_{31}NO_6$: C, 68.00; H, 7.08. Found: C, 69.13; H, 7.20.

(2′*R*,3′*S*,4′*S*,4*R*,5*S*)-3-(5′-[4″-Methoxyphenyl]methoxy-2′,4′-dimethyl-3′-triethylsilyloxypentanoyl)-5-phenyl-4-methyl-2-oxazolidinone (13). To 0.44 g (1.0 mmol) of the aldol product **12** in 20 mL of dichloromethane stirring at 0 °C under nitrogen was added 0.21 mL (1.4 mmol) of diisopropylethylamine and 0.24 mL (1.2 mmol) of triethylsilyl triflate. The reaction mixture was allowed to stir at 0 °C for 30 min, and then 10 mL of saturated sodium bicarbonate solution was added. The aqueous layer was extracted with diethyl ether, and the combined organic layers were washed with brine, dried over $MgSO_4$, and concentrated. Chromatography (8:2 hexanes/ethyl acetate) yielded 0.54 g (98%) of the product **13** as a thick colorless oil: ^{1}H NMR δ 7.42−7.16 (m, 7H), 6.80 (d, J = 8.8), 4.96 (d, J = 7.1, 2H), 4.50 (p, J = 6.8, 1H), 4.35 (d of d, J = 15.0, 11.4, 2H), 4.02−3.85 (m, 2H), 3.63 (s, 3H), 3.58 (d of d, J = 9.1, 5.9, 1H), 3.45 (d of d, J = 14.9, 7.0, 1H), 1.94 (m, 1H), 1.67 (br s, 1H), 1.21 (d, J = 6.3, 3H), 0.99 (d, J = 6.2, 3H), 0.94 (s, 9H), 0.80 (d, J = 6.5, 3H), 0.61 (q, J = 8.0, 6H); ^{13}C NMR δ 175.8, 159.0, 152.4, 133.3, 130.8, 129.3, 128.5, 125.6, 113.6, 78.5, 72.7, 71.7, 65.8, 55.1, 54.9, 41.9, 38.4, 15.5, 15.2, 14.7, 14.2, 7.1, 5.4; $[\alpha]^{25}_D$ −6.9° (*c* 1.52, $CHCl_3$). Anal. Calcd for $C_{31}H_{45}O_6NSi$: C, 67.46; H, 8.24. Found: C, 66.35; H, 7.22.

(2*R*,3*S*,4*S*)-2,4-Dimethyl-5-[4′-methoxyphenyl]methoxy-3-triethylsilyloxypentanol (14). The silyl ether **13** (1.46 g, 2.69 mmol) and 0.17 mL (2.9 mmol) of absolute ethanol were stirred at 0 °C under nitrogen, and then 2.96 mL of a 1.1 M solution of $LiBH_4$ in THF (3.5 mmol) was added. The reaction mixture was allowed to stir at 0 °C until the starting material was consumed, according to TLC analysis (generally after 2 h). The reaction was then quenched with 1 M NaOH (15 mL), and the aqueous layer was extracted with diethyl ether (3 × 15 mL). The combined organic extracts were washed with 10 mL brine, dried over $MgSO_4$, and concentrated. Chromatography (8:2 hexanes/ethyl acetate) yielded 0.73 g (72%) of the alcohol **14** as a clear oil: ^{1}H NMR δ 7.23 (d, J = 8.8, 2H), 6.85 (d, J = 8.8, 2H), 4.40 (s, 2H), 3.78 (s, 3H), 3.70 (d of d, J = 6.2, 3.2, 1H), 3.58−3.42 (m, 3H), 3.26 (d of d, J = 9.0, 6.9, 1H), 1.90 (m, 3H), 0.95 (t, J = 7.4, 9H), 0.95 (d, J = 6.9, 3H), 0.83 (d, J = 6.9, 3H), 0.57 (q, J = 8.0, 6H); ^{13}C NMR δ 159.1, 130.6, 129.2, 113.7, 75.3, 72.7, 72.6, 66.2, 55.2, 38.9, 37.4, 15.1, 7.0, 5.3; $[\alpha]^{25}_D$ −3.4° (*c* 2.95, $CHCl_3$). Anal. Calcd for $C_{21}H_{38}O_4Si$: C, 65.91, H, 10.03. Found: C, 66.04; H, 10.19.

(2*R*,3*S*,4*S*)-2,4-Dimethyl-5-[4″-methoxyphenyl]methoxy-3-triethylsilyloxy-1-iodopentane (15). Triphenylphosphine (0.76 g, 2.85 mmol), imidazole (0.2 g, 2.85 mmol), diisopropylethylamine (0.4 mL, 2.85 mmol), 10 mL of benzene, 10 mL of diethyl ether, and 0.73 g (2.85 mmol) of iodine were stirred at room temperature for 30 min. To the resulting bronze mixture was added 0.73 g (2.0 mmol) of the alcohol **14** in 5 mL of ether. After 30 min, the reaction was quenched by the addition of saturated sodium bicarbonate. The aqueous layer was extracted with diethyl ether, and the combined organic layers were washed with brine, dried over MgSO4, and concentrated. The crude material was triturated with hexane, and the combined hexane triturants were concentrated to afford the iodide as a clear oil in a yield of 0.95 g (∼100%), which was pure according to ^{1}H NMR analysis. In some cases, the crude material was passed through a 2-cm pad of silica gel with 9:1 hexanes/ethyl acetate to yield a purer product. The iodide thus obtained was used in the next step without further purification: ^{1}H NMR δ 7.23 (d, J = 8.7, 2H), 6.85 (d, J = 8.7, 2H), 4.39 (d of d, J = 9.0, 4.6, 2H), 3.79 (s, 3H), 3.63 (d of d, J = 6.2, 3.2, 1H), 3.58−3.40 (m, 2H), 3.27−3.10 (m, 3H), 1.87 (m, 2H), 0.99−0.87 (m, 18H), 0.57 (q, J = 8.0, 6H); ^{13}C NMR δ 159.1, 130.6, 129.2, 113.7, 77.4, 72.7, 72.3, 55.2, 39.6, 38.1, 26.1, 25.8, 25.6, 18.4, 15.2, 14.9, 14.6, −3.7, −4.1; $[\alpha]^{25}_D$ +11.9° (*c* 4.33, $CHCl_3$); HRMS *m*/*z* 323.2043, $C_{18}H_{31}O_3Si$ (M − C_3H_6I) calcd 323.2042; low resolution FAB-MS (NBA−Na^+ matrix) *m*/*z* 515.2 (M^+ + Na).

(4*S*,5*R*,6*S*)-7-(4′-Methoxyphenylmethoxy)-4,6-dimethyl-5-(triethylsilyloxy)-1-(3″-(2‴-trimethylsilylethoxymethoxy)phenyl)-1-heptanone (17). To a stirring solution of 0.641 g (4.71 mmol) of 3-hydroxyacetophenone and 1.22 mL (7.0 mmol) of diisopropylethylamine in 10 mL of dichloromethane at 0 °C under nitrogen was added 1.0 mL (5.65 mmol) of 2-trimethylsilylethoxymethyl chloride dropwise over 5 min. The solution was then diluted with 25 mL of ether; washed successively with water, saturated sodium bicarbonate, and brine; dried ($MgSO_4$); and concentrated. Chromatography (9:1 hexanes/ethyl acetate) yielded 0.985 g (79%) of **3-(2′-trimethylsilylethoxymethoxy) acetophenone**: ^{1}H NMR δ 7.59 (m, 2H), 7.38 (t, J = 7.8, 1H), 7.24 (m, 1H), 5.26 (s, 2H), 3.76 (d of d, J = 8.3, 8.3, 2H), 2.59 (s, 3H), 0.96 (d of d, J = 8.3, 8.3, 2H), −0.01 (s, 9H); ^{13}C NMR δ 197.76, 157.57, 138.48, 129.56, 121.72, 121.02, 115.64, 92.84, 66.39, 26.70, 17.98, −1.46. Anal. Calcd for $C_{14}H_{22}O_3Si$: C, 63.12; H, 8.33. Found: C, 63.09; H, 8.43.

A mixture of 2.0 g (7.51 mmol) of this acetophenone and 3.43 mL (30 mmol) of cyclohexylamine, 5 g of activated 4A molecular sieves, and 15 mL of benzene were refluxed under a benzene-filled Dean−Stark trap for 12 h, cooled, filtered, and concentrated to yield 2.36 g (91%) of a yellow oil that, according to NMR analysis, was >95% pure ***N*-1-(3′-[2″-trimethylsilylethoxymethoxy]phenyl)ethylidinecyclohexylamine.** In practice, this imine was used in the next step without further purification. However, distillation provided a purer product with minimal loss of material: bp 185° (2 mmHg); ^{1}H NMR δ 7.41 (m, 1H), 7.37 (d of d of d, J = 7.7, 1.6, 1.1, 1H), 7.26 (d of d, J = 7.7, 8.1, 1H), 7.04 (d of d of d, J = 8.1, 2.5, 1.1, 1H), 5.24 (s, 2H), 3.76, (d of d, J = 9.6, 7.1, 2H), 3.47 (m, 1H), 2.22 (s, 3H), 1.83, (m, 2H), 1.70 (m, 3H), 1.60 (m, 2H), 1.36 (m, 3H), 0.96 (d of d, J = 9.6, 7.1, 2H), 0.00 (s, 9H); ^{13}C NMR δ 162.10, 157.33, 143.50, 129.09, 120.14, 116.71, 114.77, 92.0, 66.15, 59.85, 33.51, 25.78, 24.85, 18.01, 15.36, −1.42. Anal. Calcd for $C_{20}H_{33}NO_2Si$: C, 69.11; H, 9.57. Found: C, 69.48; H, 9.66.

To 5 mL of a 1.0 M solution of LDA in hexane (4.9 mmol) and 0.1 mL (4.9 mmol) of hexamethylphosphoric triamide stirring at 0 °C under nitrogen was added 0.15 g (4.9 mmol) of the imine in 2.5 mL of THF. The resulting bright yellow solution was stirred at 0 °C for 10 min, then cooled to −78 °C, and stirred for an additional 30 min. The neat iodide **15** (0.12 g, 2.4 mmol) was then added dropwise. The mixture was allowed to warm to room temperature over the course of 3 h, and then maintained at room temperature for an additional 7 h. Then, pH 4 buffer (15 mL) was added, and the mixture was stirred for 2 h. The aqueous phase was then extracted with ether, and the combined organic phases were washed with brine, dried ($MgSO_4$), and concentrated. Chromatography (20:1 hexanes/ethyl acetate) yielded 1.38 g (91%) of the ketone **17** as a slightly yellow oil: ^{1}H NMR δ 7.55 (m, 2H), 7.34 (t, J = 7.8, 1H), 7.23 (m, 3H), 6.83 (d, J = 8.8, 2H), 5.24 (s, 2H), 4.39 (d of d, J = 10.0, 7.7, 2H), 3.77 (s, 3H), 3.73 (d of d, J = 12.2, 5.6, 2H), 3.50 (m, 1H), 3.25 (d of d, J = 6.0, 4.9, 1H), 3.01−2.82 (m. 2H), 1.91 (m, 1H), 1.79 (m, 1H), 1.62 (m, 3H), 0.96−0.86 (m, 18), 0.56 (q, J = 5.3, 6H), −0.3 (s, 9H); ^{13}C NMR δ 200.0, 159.0, 157.6, 138.5, 130.9, 129.5, 129.1, 121.4, 120.8, 115.5, 113.7, 92.9, 77.9, 72.7, 66.4, 55.2, 37.8, 36.9, 35.8, 29.7, 29.2, 18.0, 15.0, 13.7, 7.1, 5.5, −1.4; $[\alpha]^{25}_D$ −11.2° (*c* 1.91, $CHCl_3$). Anal. Calcd for $C_{35}H_{58}O_6Si_2$: C, 66.61; H, 9.28. Found: C, 67.42; H, 9.15.

(1*S*,4*S*,5*R*,6*S*)-7-(4′-Methoxyphenylmethxoxy)-4,6-dimethyl-5-(triethylsilyloxy)-1-(3′′-(2′′′-trimethylsilylethoxymethoxy)phenyl)-1-heptanol (19). To a stirring solution of 10 mL of THF, 0.29 mL (1.5 mmol) of a 1.0 M solution of borane in THF, and 0.012 g (0.15 mmol) of the (*R*)-oxaboro-

lidine **18** (prepared from (*R*)-(+)-2-(diphenylhydroxymethyl) pyrrolidine and methyl boronic acid)[12] at 0 °C under nitrogen was added 1.18 g (2.9 mmol) of the ketone **17** dropwise as a solution in 0.5 mL of THF. The mixture was maintained at 0 °C for 1 h, at which time TLC analysis indicated that the reaction was incomplete. Another 0.29 mL of 1.0 M borane solution (1.5 mmol) was added, and the reaction mixture was allowed to stir at 0 °C for an additional 30 min. The reaction (now complete, according to TLC analysis) was then quenched by the addition of 3 mL of methanol, followed by 15 mL of saturated sodium bicarbonate. The aqueous phase was extracted with diethyl ether, and the combined organic phases were washed with brine, dried ($MgSO_4$), and concentrated. Chromatography (20:1 hexanes/ethyl acetate) afforded 0.17 g (95%) of the alcohol **19** as a clear oil: ^{1}H NMR δ 7.22 (m, 3H), 6.94 (m, 3H), 6.84 (d, J = 8.8, 2H), 5.19 (s, 2H), 4.58 (d of d, J = 7.3, 5.6, 1H), 4.37 (d of d, J = 10.0, 7.7, 2H), 3.76 (s, 3H), 3.73 (d of d, J = 12.2, 5.6, 2H), 3.45 (m, 1H), 3.40 (m, 1H), 3.21 (d of d, J = 6.5, 5.0, 1H), 2.02−1.48 (m, 5H), 1.23−1.17 (m, 3H), 0.96−0.79 (m, 17H), 0.49 (q, J = 5.0, 6H), −0.02 (s, 9H); ^{13}C NMR δ 158.9, 157.6, 146.6, 130.8, 129.4, 129.2, 119.1, 114.9, 113.6, 92.9, 77.9, 74.9, 74.5, 72.6, 66.2, 55.2, 37.6, 37.3, 36.6, 35.9, 35.8, 30.7, 18.0, 15.2, 13.8, 7.1, 6.0, 5.4, 4.8, −0.93, −1.4; $[\alpha]^{25}_D$ −13.2° (*c* 2.74, $CHCl_3$). Anal. Calcd for $C_{35}H_{60}O_6Si_2$: C, 66.39; H, 9.57. Found: C, 67.03; H, 9.67.

(1*S*,4*S*,5*R*,6*S*)-7-(4′-Methoxyphenylmethoxy-1-methoxy)-4,6-dimethyl-5-(triethylsilyloxy)-1-(3″-(2‴-trimethylsilylethoxymethoxy)phenyl) heptane (20). To a hexane-washed suspension of potassium hydride (from 0.1 g of a 35% mineral oil dispersion, 0.7 mmol) in 5 mL THF stirring at 0 °C under nitrogen, was added 0.24 g (0.35 mmol) of the alcohol **19** in 1 mL of THF. The suspension was allowed to warm to room temperature over 1 h and then recooled to 0 °C. Then, methyl iodide (0.1 mL, 0.7 mmol) was added, and the reaction was maintained at 0 °C for 2 h, after which the reaction was quenched by the careful addition of ice. The mixture was then added to a separatory funnel containing ether and water. The layers were separated, and the aqueous layer was extracted with ether. The combined organic extracts were washed with brine, dried ($MgSO_4$), and concentrated. Chromatography (9:1 hexanes/ethyl acetate) afforded 0.24 g (97%) of the methyl ether **20** as a colorless oil: ^{1}H NMR δ 7.23 (m, 3H), 6.89 (m, 5H), 5.20 (s, 2H), 4.36 (d of d, J = 9.4, 7.7, 2H), 3.99 (t, J = 4.4, 1H), 3.77 (s, 3H), 3.75 (d of d, J = 11.2, 6.0, 1H), 3.46 (d of d, J = 5.9, 2.6, 1H), 3.37 (d of d, J = 4.7, 2.0, 1H), 3.21 (m, 1H), 3.19 (s, 3H), 1.83 (m, 2H), 1.58 (m, 2H), 1.24 (m, 2H) 0.96−0.83 (m, 14H), 0.78 (d, J = 4.5, 3H), 0.47 (q, J = 5.4, 6H), −0.02 (s, 9H); $[\alpha]^{25}_D$ −27.6° (*c* 2.17, $CHCl_3$). Anal. Calcd for $C_{30}H_{62}O_6Si$: C, 67.03; H, 9.67. Found: C, 68.68; H, 10.15.

(2*S*,3*R*,4*S*,7*S*)-7-Methoxy-2,4-dimethyl-3-(triethylsilyloxy)-7-(3′-(2″-trimethylsilylethoxymethoxy)phenyl)-1-heptanol (9). To 0.9 g (1.4 mmol) of the ether **20** stirring in 10 mL of dichloromethane and 4 mL of pH 7 buffer at room temperature was added 0.44 g (1.69 mmol)of 2,3-dichloro-5,6-dicayanobenzoquinone. After 30 min, the dark green mixture was added to a separatory funnel containing diethyl ether and saturated sodium bicarbonate solution. The layers were separated, and the aqueous layer was extracted with ether. The combined organic layers were washed with brine, dried (MgSO4), and concentrated. Chromatography (80:20 hexanes/ethyl acetate) afforded 0.68 g (92%) of the alcohol **9** as a thick clear oil: ^{1}H NMR δ 7.23 (d of d, J = 5.6, 5.1, 1H), 6.90 (m, 3H), 5.20 (s, 2H), 3.98 (t, J = 5.6, 1H), 3.73 (d of d, J = 8.3, 7.7, 2H), 3.56 (m, 2H), 3.44 (d of d, J = 5.9, 4.0, 1H), 3.19 (s, 3H), 1.78 (m, 2H), 1.54 (m, 2H), 1.31 (m, 2H), 0.96−0.81 (m, 17H), 0.55 (q, J = 8.2, 6H), −0.02 (s, 9H); ^{13}C NMR δ 157.7, 144.1, 129.3, 119.9, 115.1, 114.4, 92.9, 84.1, 81.4, 66.2, 56.7, 37.6, 36.4, 29.6, 18.0, 15.9, 14.7, 6.9, 5.2, −1.5; $[\alpha]^{25}_D$ −28.7° (*c* 1.63, $CHCl_3$).

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Supporting Information Available: ^{1}H and ^{13}C NMR spectra of compounds **9**, **10**, **12**−**14**, **17**, and **19** and the ^{1}H NMR spectra of compounds **15** and **20** (16 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

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