

Article

Synthesis of Key Fragments of Amphidinolide Q — A Cytotoxic 12-membered Macrolide

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Abstract: β -Hydroxy aldehyde and alkyl ketone moieties were effectively synthesized as key intermediates of amphidinolide Q, a cytotoxic macrolide from the cultured dinoflagellate *Amphidinium* sp.. The asymmetric center of the former derivative was produced by Sharpless asymmetric epoxidation, followed by *E*-selective 1,4-addition to give the sp^2 methyl group. Derivatization of the L-ascorbic acid derivative by Evans asymmetric alkylation and Peterson olefination provided the latter intermediate. The coupling reaction of the segments was examined.

Keywords: amphidinolide Q; *Amphidinium* sp.; macrolide synthesis; cytotoxic marine natural product

1. Introduction

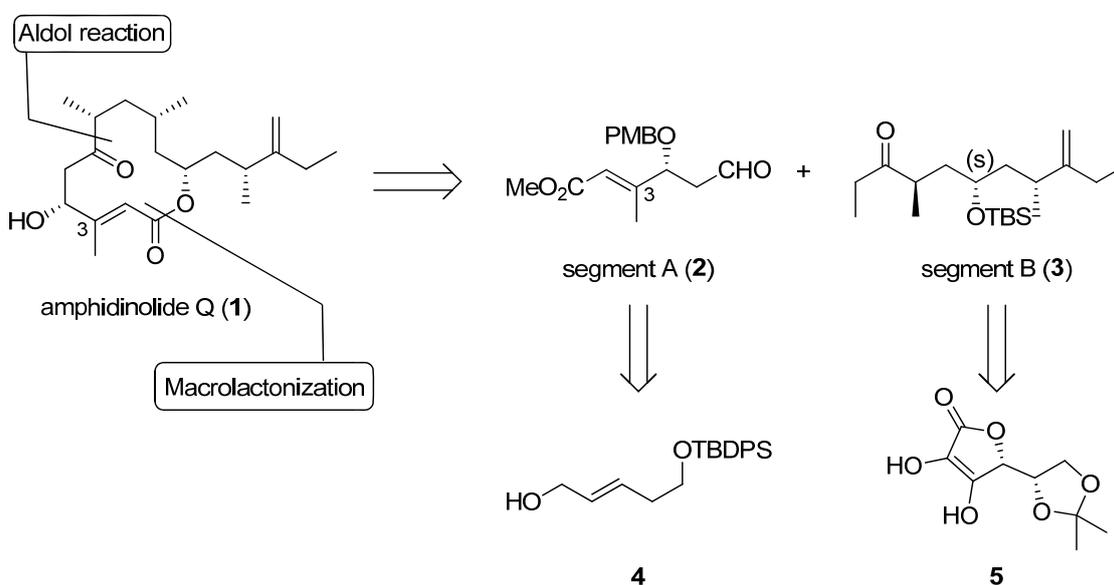
Amphidinolide Q (**1**, Scheme 1) is a member of the cytotoxic macrolide family isolated from the cultured dinoflagellate *Amphidinium* sp., and its absolute stereostructure was chemically determined by Kobayashi and co-workers [1,2]. This macrolide exhibits potent cytotoxicity against L1210 murine leukemia cells. Due to its low natural abundance, the detailed structure-activity relationship of **1** has not been established. Although **1** was synthesized by Kobayashi's group in 2009 [3], further increases in synthetic efficiency and examination of related substances based on new synthetic approaches are

required to explain the detailed mode of action of **1** by structure-activity relationship studies, and to develop new bioactive substances superior to the mother macrolide. We describe herein an efficient method for synthesis of segments **2** and **3**, which will be important intermediates for the construction of **1**.

2. Results and Discussion

As outlined in Scheme 1, retrosynthetic analysis showed that amphidinolide Q (**1**) could be obtained by successive coupling of **2** and **3**, with the former, carrying a stereogenic center and a tri-substituted olefin, being produced from the known allyl alcohol **4** through *E*-selective 1,4-addition of a methyl group at C3 and Sharpless asymmetric epoxidation. The alkyl ketone **3** carrying three stereogenic centers could be obtained from the ascorbic acid derivative **5** through Evans asymmetric alkylation.

Scheme 1. Amphidinolide Q (**1**) and retrosynthetic analysis.



2.1. Synthesis of segment A (**2**)

The synthesis of **2** commenced with the conversion of 1,3-propanediol (**6**) into alcohol **4** (Scheme 2) [4]. Incorporation of the asymmetric center at C4 and carbon chain elongation were carried out by Sharpless asymmetric epoxidation, followed by chlorination, alkylation [5], and final *p*-methoxybenzyl (PMB) protection of the newly produced OH group under acidic conditions to avoid unexpected removal of the *tert*-butyldiphenylsilyl (TBDPS) group. Further manipulation of **7** involved introduction of a methoxycarbonyl group at the terminal of the alkynyl carbon to give **8**, which upon *E*-selective alkylation using a PhS group as an auxiliary [6], afforded the α,β -unsaturated ester **9**. In this case, the two-step procedure involving preparation of the vinyl sulfide, followed by exchange with a methyl group must be used to afford the α,β -unsaturated ester **9** in good yield (Table 1). In the case of direct methylation (path A), the desired compound **9** was obtained in low yield, even when the reaction temperature was increased to 0 °C (entry 2). Although a number of reagent combinations to

control the properties of cuprates are known, the desired product was obtained in good yield in the case of entry 5.

Deprotection and oxidation processes ultimately gave the β -hydroxyl aldehyde **2** (segment A) in good overall yield.

Scheme 2. Synthesis of segment A (**2**).

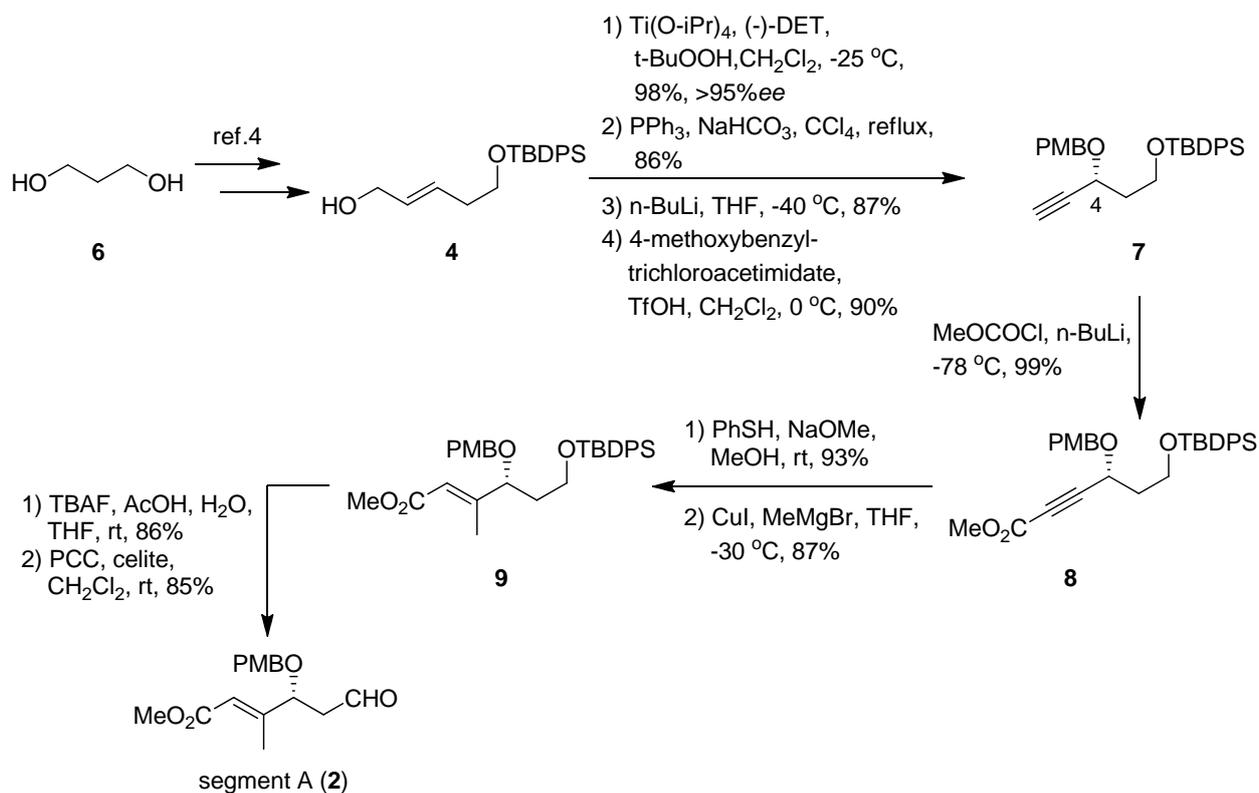


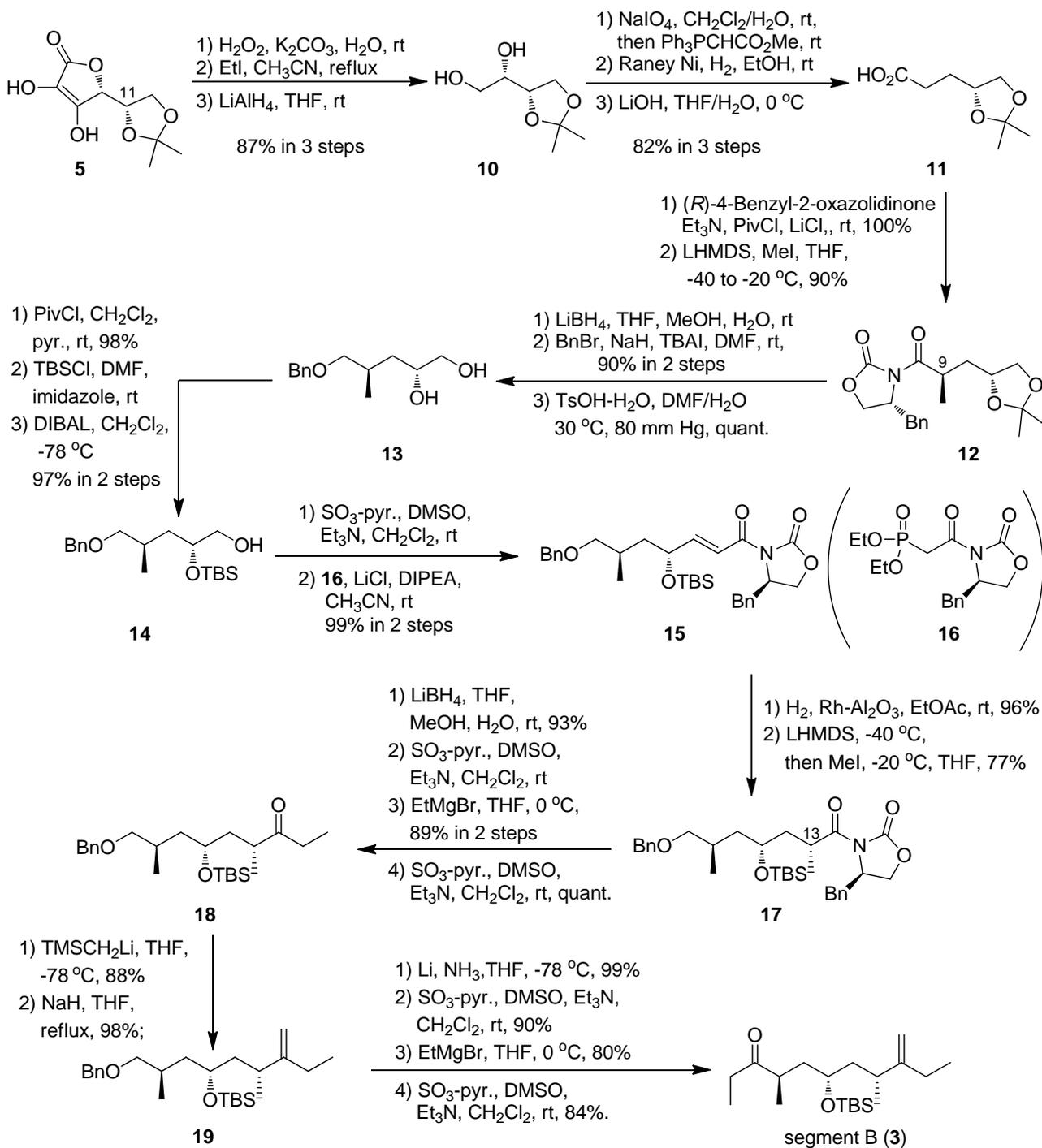
Table 1. 1,4-Addition of methyl group at C3 position of compound **6**.

entry	path	Cu reagent (20 eq.)	alkylating agent (39 eq.)	solvent	reaction temperature	yields	
						9	8
1	A	CuCN	MeLi	Et_2O	$-30\text{ }^\circ\text{C}$	18%	-
2		CuCN	MeLi	Et_2O	$0\text{ }^\circ\text{C}$	32%	-
3	B	CuCN	MeLi	Et_2O	$-30\text{ }^\circ\text{C}$	-	100%
4		CuI	MeLi	Et_2O	$-30\text{ }^\circ\text{C}$	-	71%
5		CuI	MeMgBr	THF	$-30\text{ }^\circ\text{C}$	87%	-
6		CuI	MeMgBr	THF	$-78\text{ }^\circ\text{C}$	33%	52%

2.2. Synthesis of segment B (3)

Synthesis of alkyl ketone **3** was initiated by transformation of the ascorbic acid derivative **5** into diol **10** by a known procedure [7] (Scheme 3).

Scheme 3. Synthesis of segment B (3).



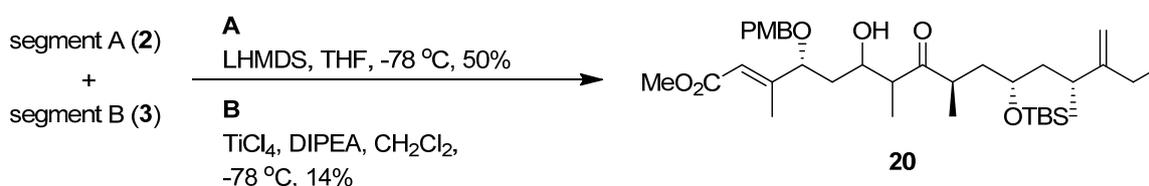
Compound **10** was subjected to oxidative cleavage of the vicinal diol, followed by immediate Wittig reaction, hydrogenation, and hydrolysis to give **11**. In particular, the second Wittig reaction was carried out using crude aldehyde to avoid undesired epimerization of the asymmetric center at C11.

Selective asymmetric induction at C9 by the Evans protocol effected the desired introduction of a methyl group to yield **12**. Removal of the chiral auxiliary by LiBH₄ and manipulation of protecting groups in five steps gave the alcohol **14** via **13**. After Parikh–Doering oxidation of **14**, the aldehyde generated was reacted with Horner–Wadsworth–Emmons reagent **16** [8] to yield **15**, which on hydrogenation followed by addition of a methyl group produced **17**. After removal of the auxiliary by LiBH₄, an ethyl ketone function was constructed (compound **18**), and the *exo*-methylene function was introduced by Peterson olefination, followed by basic treatment, whereas other methods, such as the Wittig and Petasis reactions did not produce the desired compound, probably due to the low reactivity of the ethylketone moiety. Synthesis of segment B (**3**) was accomplished by Birch reduction, followed by alkylation similar to that described the case of **18** and Parikh–Doering oxidation and Grignard reaction.

The synthetic strategies used for both segments may enable the synthesis of analogs. The stereogenic centers were introduced via asymmetric reactions, which can produce another enantiomer by exchanging the auxiliary group or catalyst, with the exception of the C11 center: in this case the opposite (*R*)-enantiomer would be produced using (*R*)-glyceraldehyde acetonide, derived from D-mannitol [9].

Aldol coupling of both segments was attempted, as shown in Scheme 4. Whereas Lewis acidic conditions such as method B [10] caused undesirable elimination of **2** and **20** [11] to give the corresponding $\alpha,\beta,\delta,\gamma$ -unsaturated ester, basic conditions (method A) provided **20**, equipped with the complete carbon framework, in moderate yield,. Detailed studies of the diastereomer distribution to improve the coupling yields are currently in progress in our laboratory.

Scheme 4. Coupling attempts between **2** and **3** [12].



3. Experimental

General

All reactions were carried out under an argon atmosphere unless otherwise noted. When necessary, solvents were dried prior to use. Dry THF, dry Et₂O and dry CH₂Cl₂ were purchased from Kanto Chemical Co., Inc. Optical rotations were measured on a JASCO P-2200 digital polarimeter with a sodium (D line) lamp. IR spectra were recorded on a Jasco Model A-202 spectrophotometer. ¹H-NMR spectra and ¹³C-NMR spectra were obtained on JEOL JNM-EX270, JNM-GX400, JNM-α400, JNM-AL400 and JNM-ECX400 spectrometers in deuterated solvent using tetramethylsilane as an internal standard. Deuteriochloroform was used as a solvent, unless otherwise stated. Optical purity was determined by HPLC using an OJ-H column. High-resolution mass spectra were obtained on a Waters LCT Premier XE (ESI) or JEOL JMS-700 (FAB). Preparative and analytical TLC were carried

out on silica gel plate (Kieselgel 60 F254, E. Merck AG., Germany) using UV light and/or 5% molybdophosphoric acid in ethanol for detection. Kanto silica 60N (spherical, neutral, 105–210 μm) was used for column chromatography.

(*R*)-*tert*-Butyl(3-(4-methoxybenzyloxy)pent-4-ynyloxy)diphenylsilane (**7**). To a suspension of $\text{Ti}(\text{OiPr})_4$ (4.28 mL, 14.6 mmol) and MS4A (4.9 g) in CH_2Cl_2 (100 mL) was added (-)-DET (3.32 mL, 19.5 mmol) at $-25\text{ }^\circ\text{C}$. To the mixture were added **4** (3.31 g, 9.73 mmol) and *t*-BuOOH (3.17 mL, 29.2 mmol); the solution was stirred overnight. The reaction was quenched by L-(+)-tartaric acid (12.4 g, 82.6 mmol) aqueous and iron (II) sulfate heptahydrate (12.2 g, 43.9 mmol). The mixture was extracted with Et_2O , and the organic extracts were dried (Na_2SO_4), and concentrated *in vacuo*. The crude product was purified by silica gel column chromatography using hexane-ethyl acetate (3:1) to give an alcohol (3.38 g, 98%, 95% *ee*) as a colorless oil: $[\alpha]_D^{23} +14.7$ (c 1.00, CHCl_3); IR (film) 3437, 3048, 1428, 1110, 936, 822 cm^{-1} ; $^1\text{H-NMR}$ (400 MHz) δ 1.06 (9H, s), 1.81 (2H, td, $J = 12.1, 6.0$ Hz), 2.98 (1H, td, $J = 4.7, 2.5$ Hz), 3.13 (1H, td, $J = 6.0, 2.5$ Hz), 3.63 (1H, m), 3.80 (2H, m), 3.91 (1H, m), 7.40 (6H, m), 7.66 (4H, m); $^{13}\text{C-NMR}$ (100 MHz) δ 19.2, 26.8, 34.8, 53.7, 58.5, 60.7, 61.6, 127.7, 129.7, 133.6, 135.5. ESI-MS: calcd for $\text{C}_{21}\text{H}_{29}\text{O}_3\text{Si}$ 357.1886 ($\text{M}+\text{H}$) $^+$, found, m/z 357.1897.

A stirred mixture of the alcohol (3.38 g, 9.49 mmol), PPh_3 (7.47 g, 28.5 mmol), and NaHCO_3 (0.80 g, 9.5 mmol) in CCl_4 (100 mL) was refluxed under argon atmosphere overnight. After completion of the reaction, CCl_4 was removed under reduced pressure, and the residue was purified by silica gel column chromatography (hexane-ethyl acetate 40:1) to furnish an epoxy chloride (3.04 g, 86%) as a colorless oil: $[\alpha]_D^{23} +12.9$ (c 1.00, CHCl_3); IR (film) 3049, 1428, 1111, 939, 822 cm^{-1} ; $^1\text{H-NMR}$ (400 MHz) δ 1.06 (9H, s), 1.81 (2H, td, $J = 11.2, 5.6$ Hz), 3.07 (2H, m), 3.56 (2H, m), 3.80 (2H, m), 7.41 (6H, m), 7.66 (4H, m); $^{13}\text{C-NMR}$ (100 MHz) δ 19.2, 26.8, 34.7, 44.7, 56.7, 57.3, 60.5, 127.7, 129.7, 133.5, 135.5. ESI-MS: calcd for $\text{C}_{21}\text{H}_{28}\text{O}_2\text{SiCl}$ 375.1547 ($\text{M}+\text{H}$) $^+$, found, m/z 375.1539.

To a stirred solution of the epoxy chloride (0.23 g, 0.63 mmol) in dry THF (7 mL) was added *n*-BuLi (2.4 mL, 1.6 M solution in *n*-hexane, 3.79 mmol) dropwise at $-40\text{ }^\circ\text{C}$ under argon atmosphere; and the mixture was stirred for an additional 2 h. The mixture was quenched with saturated aqueous NH_4Cl , and the mixture was extracted with ethyl acetate. The organic extracts were dried (Na_2SO_4), and concentrated *in vacuo*. The residue was purified by silica gel column chromatography (hexane-ethyl acetate 7:1) to give an alcohol (0.18 g, 87%) as a colorless oil: $[\alpha]_D^{23} +3.67$ (c 1.00, CHCl_3); IR (film) 3422, 3304, 3071, 1428, 1111, 823 cm^{-1} ; $^1\text{H-NMR}$ (400 MHz) δ 1.06 (9H, s), 1.92 (1H, tdd, $J = 14.0, 6.3, 3.6$ Hz), 2.05 (1H, tdd, $J = 14.0, 8.0, 4.3$ Hz), 2.48 (1H, d, $J = 5.8$ Hz), 3.34 (1H, d, $J = 5.8$ Hz), 3.85 (1H, ddd, $J = 12.0, 6.3, 4.3$ Hz), 4.07 (1H, ddd, $J = 12.0, 8.0, 3.6$ Hz), 4.71 (1H, m), 7.42 (6H, m), 7.69 (4H, m); $^{13}\text{C-NMR}$ (100 MHz) δ 19.0, 26.8, 38.5, 61.5, 61.7, 73.0, 84.4, 127.8, 129.9, 132.8, 135.6. ESI-MS: calcd for $\text{C}_{21}\text{H}_{27}\text{O}_2\text{Si}$ 339.1780 ($\text{M}+\text{H}$) $^+$, found, m/z 339.1775.

To a solution of the alcohol (0.10 g, 0.30 mmol) in anhydrous CH_2Cl_2 (7 mL) were added 4-methoxybenzyl trichloroacetimidate (0.493 g, 1.74 mmol) and TfOH (cat.) at $0\text{ }^\circ\text{C}$, and the mixture was stirred overnight. The reaction was quenched with saturated aqueous NH_4Cl , and extracted with ethyl acetate. The organic extracts were dried (Na_2SO_4), and concentrated *in vacuo*. The residue was purified by silica gel column chromatography (hexane-ethyl acetate 7:1) to give **7** (0.12 g, 90%) as a colorless oil: $[\alpha]_D^{23} +45.1$ (c 1.02, CHCl_3); IR (film) 3286, 1514, 1249, 1111, 823 cm^{-1} ; $^1\text{H-NMR}$ (400 MHz) δ 0.94 (9H, s), 1.91 (2H, m), 2.36 (1H, d, $J = 2.1$ Hz), 3.72 (5H, m), 4.34 (2H, m), 4.66 (1H,

d, $J = 11.2$ Hz), 6.77 (2H, m), 7.20 (2H, m), 7.31 (6H, m), 7.56 (4H, m); ^{13}C -NMR (100 MHz) δ 19.2, 26.8, 38.7, 55.2, 59.7, 65.0, 70.3, 73.8, 83.0, 113.8, 127.6, 129.6, 133.7, 135.5, 159.2. ESI-MS: calcd for $\text{C}_{29}\text{H}_{34}\text{O}_3\text{SiK}$ 497.1914 (M+K) $^+$, found, m/z 497.1911.

(*R*)-Methyl-6-(*tert*-Butyldiphenylsilyloxy)-4-(4-methoxybenzyloxy)hex-2-ynoate (**8**). To a solution of **7** (50.8 mg, 0.11 mmol) in THF (1.5 mL) was added dropwise *n*-BuLi (0.3 mL, 1.6 M solution in hexane, 0.48 mmol) at -78 °C, and the mixture was stirred at the same temperature for 1 h. Methyl chloroformate (0.09 mL, 1.11 mmol) was added dropwise to the mixture; the resulting mixture was stirred at 0 °C for 2.5 h. After being quenched with saturated aqueous NH_4Cl , the mixture extracted with ethyl acetate. The organic layer was dried (Na_2SO_4), and concentrated *in vacuo*. The residue was purified by silica gel column chromatography (hexane-ethyl acetate 9:1) to give **8** (56.4 mg, 99%) as a colorless oil: $[\alpha]_D^{23} +59.8$ (c 0.99, CHCl_3); IR (film) 3071, 2233, 1719, 1249, 1111 cm^{-1} ; ^1H -NMR (400 MHz) δ 1.00 (9H, s), 2.01 (2H, ddd, $J = 12.7, 7.6, 6.0$ Hz), 3.79 (8H, m), 4.43 (1H, d, $J = 11.2$ Hz), 4.55 (1H, d, $J = 7.6, 6.0$ Hz), 4.74 (1H, d, $J = 11.2$ Hz), 6.86 (2H, m), 7.26 (2H, m), 7.37 (6H, m), 7.60 (4H, m); ^{13}C -NMR (100 MHz) δ 19.1, 26.7, 38.0, 52.8, 55.2, 59.3, 64.7, 71.0, 86.9, 113.8, 127.7, 129.2, 129.6, 129.7, 133.5, 135.5, 153.7, 159.4. ESI-MS: calcd for $\text{C}_{31}\text{H}_{36}\text{O}_5\text{SiK}$ 555.1969 (M+K) $^+$, found, m/z 555.1970.

(*R,E*)-Methyl 6-(*tert*-butyldiphenylsilyloxy)-4-(4-methoxybenzyloxy)-3-methylhex-2-enoate (**9**). To a solution of **8** (90.8 mg, 0.18 mmol) in MeOH was added PhSH (36 μL , 0.35 mmol) and NaOMe (0.18 mL, 0.02 mmol) at room temperature. After being stirred at the same temperature for 3 h, the reaction mixture was concentrated *in vacuo*. The residue was purified by silica gel column chromatography (hexane-ethyl acetate 9:1) to give a methyl ester (102.1 mg, 93%) as a colorless oil: $[\alpha]_D^{23} -91.3$ (c 1.0, CHCl_3); IR (film) 1705, 1513, 1248, 1110 cm^{-1} ; ^1H -NMR (400 MHz) δ 0.93 (9H, s), 1.63 (1H, m), 2.02 (1H, m), 3.46 (1H, m), 3.50 (1H, m), 3.77 (3H, s), 3.79 (3H, s), 3.96 (1H, dd, $J = 2.5, 9.9$ Hz), 4.04 (1H, d, $J = 10.8$ Hz), 4.46 (1H, d, $J = 10.8$ Hz), 6.35 (1H, s), 6.79 (2H, m), 7.07 (2H, m), 7.21 (3H, m), 7.34 (4H, m), 7.43 (4H, m), 7.53 (4H, m); ^{13}C -NMR (100 MHz) δ 19.1, 26.8, 39.8, 51.4, 55.3, 60.2, 70.7, 75.3, 113.8, 111.6, 113.7, 127.5, 129.2, 129.3, 129.5, 135.3, 135.5, 159.2, 160.5, 166.8. ESI-MS: calcd for $\text{C}_{37}\text{H}_{42}\text{O}_5\text{SiNa}$ 649.2420 (M+Na) $^+$, found, m/z 649.2440.

To a suspension of CuI (0.62 g, 3.2 mmol) in THF was added MeMgBr (6.7 mL, 0.95 M in THF, 6.3 mmol) at -78 °C; the solution was warmed to -30 °C and stirred for 1.5 h. The solution was cooled to -78 °C, and the methyl ester (0.10 g, 0.16 mmol) was added. The reaction mixture was stirred at -30 °C for 1 h, then quenched with saturated aqueous NH_4Cl and NH_4OH . The reaction mixture was extracted with ethyl acetate, and the organic layer was dried (Na_2SO_4) and concentrated *in vacuo*. The residue was purified by silica gel column chromatography (benzene-hexane 7:1) to give **9** (75 mg, 87%) as a colorless oil: $[\alpha]_D^{23} +64.0$ (c 0.50, CHCl_3); IR (film) 1720, 1428, 1249, 1111, 822 cm^{-1} ; ^1H -NMR (400 MHz) δ 0.96 (9H, s), 1.69 (2H, m), 2.05 (3H, d, $J = 1.0$ Hz), 3.64 (8H, m), 3.99 (1H, t, $J = 6.6$ Hz), 4.08 (1H, d, $J = 11.2$ Hz), 4.34 (1H, d, $J = 11.2$ Hz), 5.86 (1H, s), 6.77 (2H, m), 7.12 (2H, m), 7.31 (6H, m), 7.56 (4H, m); ^{13}C -NMR (100 MHz) δ 14.3, 19.2, 26.8, 37.2, 51.0, 55.2, 59.9, 70.6, 80.2, 113.8, 116.4, 127.6, 129.4, 129.6, 130.1, 133.7, 135.5, 158.9, 159.2, 167.0. ESI-MS: calcd for $\text{C}_{32}\text{H}_{40}\text{O}_5\text{SiNa}$ 555.2543 (M+Na) $^+$, found, m/z 555.2530.

(*R,E*)-Methyl 4-(4-methoxybenzyloxy)-3-methyl-6-oxohex-2-enoate (**segment A**, **2**). To a solution of **9** (0.33 g, 0.62 mmol) in THF (6 mL) was added reagent (TBAF-AcOH-H₂O= 1:1:5 0.1 M in THF, 0.3 mmol) at room temperature; the mixture was stirred at the same temperature overnight. After the addition of cold water, the mixture was extracted with Et₂O. The organic layer was dried (Na₂SO₄) and concentrated *in vacuo*. The residue was purified by silica gel column chromatography (hexane-ethyl acetate 1:1) to give an alcohol (0.16 g, 88%) as a colorless oil: $[\alpha]_D^{23} +68.7$ (*c* 0.99, CHCl₃); IR (film) 3429, 1718, 1654, 1613, 1513, 1156, 1035 cm⁻¹; ¹H-NMR (270 MHz) δ 1.84 (2H, m), 2.15 (3H, d, *J* = 1.3 Hz), 3.73 (5H, m), 3.81 (3H, s), 3.98 (1H, dd, *J* = 9.1, 3.8 Hz), 4.20 (1H, d, *J* = 11.2 Hz), 4.48 (1H, d, *J* = 11.2 Hz), 5.95 (1H, s), 6.89 (2H, m), 7.23 (2H, m); ¹³C-NMR (67.5 MHz) δ 14.4, 29.7, 36.3, 51.1, 55.2, 60.4, 70.6, 82.03, 113.9, 116.6, 128.3, 129.5, 129.6, 157.7, 159.4, 166.8. ESI-MS: calcd for C₁₆H₂₂O₅Na 317.1365 (M+Na)⁺, found, *m/z* 317.1363.

To a mixture of PCC (35 mg, 0.16 mmol) and Celite in CH₂Cl₂ (2 mL) was added the alcohol (31.7 mg, 0.11 mmol) at 0 °C; the mixture was stirred at room temperature for 30 min. After concentration of the reaction mixture, the residue was purified by silica gel column chromatography (Et₂O-hexane 2:1) to give **segment A** (26.7 mg, 85%) as a colorless oil: $[\alpha]_D^{23} +28.9$ (*c* 0.91, CHCl₃); IR (film) 1720, 1655, 1612, 1513, 1248, 1034 cm⁻¹; ¹H-NMR (270 MHz, C₆D₆) δ 1.90 (1H, ddd, *J* = 1.1, 3.6, 16.6 Hz), 2.14 (3H, m), 2.34 (1H, ddd, *J* = 2.5, 9.2, 16.6 Hz), 3.38 (3H, s), 3.53 (3H, s), 4.05 (1H, m), 4.07 (1H, d, *J* = 11.2 Hz), 4.32 (1H, d, *J* = 11.2 Hz), 6.09 (1H, m), 6.84 (2H, m), 7.18 (2H, m), 9.38 (1H, dd, *J* = 1.1, 2.5 Hz); ¹³C-NMR (67.5 MHz, C₆D₆) δ 14.3, 47.5, 50.7, 54.7, 70.7, 77.6, 78.2, 114.1, 117.4, 129.7, 130.0, 156.6, 166.3, 198.3. ESI-MS: calcd for 293.1389 (M+H)⁺, found, *m/z* 293.1402.

(*R*)-3-(2,2-Dimethyl-1,3-dioxolan-4-yl)propanoic acid (**11**). To a solution of NaIO₄ (3.78 g, 17.7 mmol) in CH₂Cl₂ (60 mL) and H₂O (30 mL) was added **10** (1.91 g, 11.8 mmol) at 0 °C; the mixture was stirred at room temperature for 1.5 h. After the addition of Ph₃PCHCO₂Me (7.89 g, 23.6 mmol) at 0 °C, the mixture was stirred at room temperature overnight. The organic layer was separated and the aqueous layer was extracted with CHCl₃ three times. The combined organic layers were washed with brine, dried (Na₂SO₄), and concentrated *in vacuo*. The residue was purified by silica gel column chromatography (hexane-ethyl acetate 3:1) to give an α,β -unsaturated ester (1.84 g, 84%, *E:Z* = 1:3) as a colorless oil.

The ester (1.02 g, 5.48 mmol) was dissolved in EtOH (55 mL) in the presence of Raney Ni W-4. The mixture was stirred at room temperature under hydrogen atmosphere overnight. After filtration, the filtrate was concentrated at 110 °C to afford the corresponding ester as a crude oil. To a solution of the ester in THF (17 mL) was added 1.5 M LiOH aqueous (17 mL) at 0 °C. The mixture was stirred at 0 °C for 3 h. The mixture was acidified to pH 4 with 10% aqueous citric acid and extracted with ethyl acetate three times. The combined organic layers were washed with brine, dried (Na₂SO₄), and concentrated *in vacuo* to give **11** (0.935 g, 98%) as a colorless oil: $[\alpha]_D^{23} +1.2$ (*c* 1.00, CHCl₃); IR (film) 2987, 1712, 1215, 1154, 1073 cm⁻¹; ¹H-NMR (270 MHz) δ 1.35 (3H, s), 1.42 (3H, s), 1.89 (2H, m), 2.51 (2H, m), 3.57 (1H, dd, *J* = 6.5, 7.8 Hz), 4.06 (1H, dd, *J* = 5.9, 7.8 Hz), 4.14 (1H, m); ¹³C-NMR (67.5 MHz) δ 25.6, 26.9, 28.5, 30.2, 68.9, 74.7, 109.1, 178.9. ESI-MS: calcd for C₈H₁₅O₄ 175.0970 (M+H)⁺, found, *m/z* 175.0968.

(*R*)-4-Benzyl-3-((*R*)-3-((*R*)-2,2-dimethyl-1,3-dioxolan-4-yl)-2-methylpropanoyl)oxazolidin-2-one (**12**). To a solution of **11** (6.10 g, 35.0 mmol) in THF (325 mL) were added Et₃N (15.0 mL, 0.190 mol) and PivCl (6.40 mL, 52.5 mmol) at 0 °C. After 2 h, LiCl (7.42 g, 175 mmol) and (*R*)-4-benzyl-2-oxazolidinone (9.30 g, 52.5 mmol) were added to the reaction mixture, and then the mixture was stirred at room temperature overnight. The reaction was quenched by the addition of saturated aqueous NH₄Cl at 0 °C, then the resulting slurry was extracted with ethyl acetate three times. The combined organic layers were washed with brine, dried (Na₂SO₄), and concentrated *in vacuo*. The residue was purified by silica gel column chromatography (hexane-ethyl acetate 3:1) to give an amide (10.8 g, 92%) as a colorless oil: $[\alpha]_D^{24}$ -42.4 (*c* 1.01, CHCl₃); IR (film) 2984, 1782, 1690, 1382, 1212, 1054 cm⁻¹; ¹H-NMR (400 MHz) δ 1.35 (3H, s), 1.42 (3H, s), 1.96 (2H, m), 2.78 (1H, dd, *J* = 9.8, 13.2 Hz), 3.07 (2H, t, *J* = 7.8 Hz), 3.30 (1H, dd, *J* = 3.4, 13.2 Hz), 3.60 (1H, dd, *J* = 6.8, 7.8 Hz), 4.08 (1H, dd, *J* = 5.9, 7.8 Hz), 4.64 (3H, m), 4.67 (1H, m), 7.27 (5H, m); ¹³C-NMR (100 MHz) δ 25.7, 27.0, 28.2, 32.0, 37.9, 55.1, 66.2, 69.2, 74.9, 108.9, 127.2, 128.8, 129.3, 135.1, 153.3, 172.5, 180.1. ESI-MS: calcd for C₁₈H₂₃NO₅Na (M+Na)⁺, found, *m/z* 356.1489.

To a solution of LHMDS (73.0 mL, 1.0 M solution in THF, 73.0 mmol) was added the amide (12.2 g, 36.5 mmol) in THF (400 mL) at -40 °C. After 1.5 h, MeI (22.7 mL, 0.365 mol) was added to the reaction mixture. The mixture was stirred at -20 °C for 4 h. The reaction was quenched by the addition of saturated aqueous NH₄Cl at 0 °C, then the resulting slurry was extracted with ethyl acetate three times. The combined organic layers were washed with brine, dried (Na₂SO₄), and concentrated *in vacuo*. The residue was purified by silica gel column chromatography (hexane-ethyl acetate 3:1) to give **12** (10.8 g, 85%) as a white needles: m.p. 93–93.5 °C (ethyl acetate); $[\alpha]_D^{24}$ -65.4 (*c* 1.00, CHCl₃); IR (film) 2983, 1780, 1697, 1381, 1213, 1159, 1085, 1053 cm⁻¹; ¹H-NMR (400 MHz) δ 1.26 (3H, d, *J* = 7.3 Hz), 1.30 (3H, s), 1.36 (3H, s), 1.66 (1H, ddd, *J* = 4.4, 5.4, 13.7 Hz), 2.05 (1H, ddd, *J* = 8.8, 8.3, 13.7 Hz), 2.79 (1H, dd, *J* = 9.8, 13.2 Hz), 3.26 (1H, dd, *J* = 3.4, 13.2 Hz), 3.50 (1H, dd, *J* = 7.3, 7.8 Hz), 4.01 (1H, m), 4.03 (1H, dd, *J* = 5.4, 7.8 Hz), 4.17 (3H, m), 4.67 (1H, m), 7.28 (5H, m); ¹³C-NMR (100 MHz) δ 18.2, 25.7, 26.9, 34.7, 38.0, 38.1, 55.4, 66.0, 69.5, 74.2, 108.9, 127.2, 128.8, 129.3, 153.2, 176.9, 180.1. ESI-MS: calcd for C₁₉H₂₆NO₅Na (M+Na)⁺ 348.1811, found, *m/z* 348.1805.

(2*R*,4*R*)-5-(Benzyloxy)-4-methylpentane-1,2-diol (**13**). To a solution of **12** (7.44 g, 21.4 mmol) in THF-MeOH-H₂O (4:4:1), (220 mL) was added LiBH₄ (2.1 g, 86 mmol) at 0 °C. The mixture was stirred at room temperature for 2.5 h. The reaction was quenched by the addition of saturated aqueous NH₄Cl at 0 °C, then the resulting slurry was extracted with Et₂O three times. The combined organic layers were washed with brine, dried (Na₂SO₄), and concentrated *in vacuo*. The residue was purified by silica gel chromatography (hexane-ethyl acetate (1:1)) to give an alcohol. To a solution of the alcohol in DMF (220 mL) was added BnBr (8 mL, 64.3 mmol), TBAI (3.2 g, 8.57 mmol) and NaH (3.1 g, 64.3 mmol) at 0 °C. The mixture was stirred at room temperature overnight. The reaction was quenched by the addition of saturated aqueous NH₄Cl at 0 °C, then the resulting slurry was extracted with Et₂O three times. The combined organic layers were washed with brine, dried (Na₂SO₄), and concentrated *in vacuo*. The residue was purified by silica gel column chromatography (hexane-ethyl acetate 10:1) to give an acetonide (5.09 g, 90%) as a colorless oil: $[\alpha]_D^{24}$ -11.5 (*c* 1.03, CHCl₃); IR (film) 2984, 1454, 1368, 1213, 1098, 1061 cm⁻¹; ¹H-NMR (400 MHz) δ 0.91 (3H, d, *J* = 6.8 Hz), 1.29 (7H, m), 1.71 (1H,

ddd, $J = 5.8, 8.3, 13.7$ Hz), 1.89 (1H, m), 3.24 (2H, m), 3.42 (1H, t, $J = 7.8$ Hz), 3.97 (1H, dd, $J = 7.8, 5.8$ Hz), 4.12 (1H, tt, $J = 7.8, 5.8$ Hz), 4.43 (2H, s), 7.26 (5H, m); ^{13}C -NMR (100 MHz) δ 17.1, 25.8, 27.1, 30.7, 37.8, 69.9, 72.9, 74.2, 108.5, 127.4, 127.5, 128.3, 138.6. ESI-MS: calcd for $\text{C}_{16}\text{H}_{25}\text{O}_3$ 265.1804 ($\text{M}+\text{H}$)⁺, found, m/z 265.1803.

To a solution of the acetonide (0.73 g, 2.8 mmol) in DMF (30 mL) were added $\text{TsOH}\cdot\text{H}_2\text{O}$ (1.6 g, 8.3 mmol) and H_2O (10 mL) at 0 °C; the mixture was stirred at 30 °C under 80 mmHg for 3 h. After the addition of saturated aqueous NH_4Cl , the mixture was extracted with Et_2O . The organic layer was dried (Na_2SO_4), and concentrated *in vacuo*. The residue was purified by silica gel column chromatography (hexane-ethyl acetate 1:1) to give **13** (0.66 g, quant.) as a colorless oil: $[\alpha]_{\text{D}}^{24} +16.0$ (c 0.99, CHCl_3); IR (film) 3375, 1454, 1363, 1074 cm^{-1} ; ^1H -NMR (400 MHz) δ 0.87 (3H, d, $J = 6.8$ Hz), 1.39 (2H, m), 1.93 (2H, m), 3.22 (1H, m), 3.37 (2H, m), 3.52 (2H, m), 3.70 (1H, m), 4.47 (2H, s), 7.24 (5H, m); ^{13}C -NMR (100 MHz) δ 18.2, 31.8, 39.6, 67.4, 71.0, 73.3, 76.6, 127.7, 127.8, 128.5, 137.6. ESI-MS: calcd for $\text{C}_{13}\text{H}_{20}\text{O}_3\text{Na}$ 247.1310 ($\text{M}+\text{Na}$)⁺, found, m/z 247.1309.

(2*R*,4*R*)-5-(Benzyloxy)-2-(tert-butyltrimethylsilyloxy)-4-methylpentan-1-ol (**14**). To a solution of **13** (3.39 g, 15.1 mmol) in CH_2Cl_2 (75 mL) and pyridine (75 mL) was added PivCl (2.8 mL, 22.7 mmol) at 0 °C; the mixture was stirred at room temperature for 1.5 h. The reaction was quenched with saturated aqueous NH_4Cl , and the mixture was extracted with Et_2O . The organic layer was dried (Na_2SO_4), and concentrated *in vacuo*. The residue was purified by silica gel column chromatography (hexane-ethyl acetate 4:1) to give an alcohol (4.57 g, 98%) as a colorless oil: $[\alpha]_{\text{D}}^{24} +10.7$ (c 1.01, CHCl_3); IR (film) 3442, 1730, 1455, 1285, 1164, 1097 cm^{-1} ; ^1H -NMR (400 MHz) δ 0.88 (3H, d, $J = 7.3$ Hz), 1.15 (9H, s), 1.33 (1H, ddd, $J = 14.4, 6.8, 2.9$ Hz), 1.46 (1H, m), 1.95 (1H, m), 2.98 (1H, br), 3.22 (1H, dd, $J = 9.8, 6.3$ Hz), 3.32 (1H, dd, $J = 9.8, 5.4$ Hz), 3.84 (1H, m), 3.96 (2H, m), 4.46 (2H, s), 7.26 (5H, m); ^{13}C -NMR (100 MHz) δ 17.7, 27.2, 31.2, 38.8, 39.0, 68.8, 73.1, 76.2, 127.7, 128.3, 128.4, 138.0, 178.6. ESI-MS: calcd for $\text{C}_{18}\text{H}_{28}\text{O}_4\text{Na}$ 331.1885 ($\text{M}+\text{Na}$)⁺, found, m/z 331.1880.

To a solution of the alcohol (4.57 g, 14.8 mmol) in DMF (150 mL) were added imidazole (3.03 g, 44.5 mmol) and TBSCl (6.7 g, 44.5 mmol) at 0 °C; the mixture was stirred at room temperature overnight. After the addition of saturated aqueous NH_4Cl , the mixture was extracted with Et_2O . The organic layer dried (Na_2SO_4), and concentrated *in vacuo*. The residue was purified by silica gel column chromatography (hexane-ethyl acetate 7:1) to give a silyl ether (6.31 g, quant.) as a colorless oil: $[\alpha]_{\text{D}}^{24} +10.6$ (c 1.02, CHCl_3); IR (film) 1733, 1160, 836 cm^{-1} ; ^1H -NMR (400 MHz) δ 0.09 (6H, s), 0.88 (9H, s), 0.94 (3H, m), 1.20 (9H, s), 1.28 (1H, m), 1.63 (1H, ddd, $J = 4.5, 7.9, 13.7$ Hz), 1.97 (1H, m), 3.27 (1H, dd, $J = 6.1, 9.2$ Hz), 3.33 (1H, dd, $J = 6.1, 9.2$ Hz), 3.97 (3H, m), 4.50 (2H, s), 7.34 (5H, m); ^{13}C -NMR (100 MHz) δ -4.7, -4.4, 17.1, 18.0, 25.5, 25.8, 27.1, 27.2, 29.5, 38.7, 38.8, 68.1, 68.4, 76.2, 127.3, 127.4, 128.3, 138.7, 178.5. ESI-MS: calcd for $\text{C}_{24}\text{H}_{42}\text{O}_4\text{SiNa}$ 445.2750 ($\text{M}+\text{Na}$)⁺, found, m/z 445.2747.

To a solution of the silyl ether (11.7 mg, 27.7 μmol) in CH_2Cl_2 (0.3 mL) was added DIBAL-H (0.08 mL, 1.03 M in *n*-hexane, 83.1 μmol) at -78 °C. After being stirred for 1 h then the reaction was quenched by potassium-sodium tartrate aqueous. The mixture was extracted with CHCl_3 , dried (Na_2SO_4), and concentrated *in vacuo*. The crude product was purified by silica gel column chromatography using hexane-ethyl acetate (5:1) to give **14** (9.1 mg, 97%) as a colorless oil: $[\alpha]_{\text{D}}^{24} -2.3$ (c 0.97, CHCl_3); IR (film) 3437, 2857, 836 cm^{-1} ; ^1H -NMR (400 MHz) δ 0.08 (6H, s), 0.90 (9H, s),

0.95 (3H, m), 1.29 (2H, m), 1.66 (1H, m), 1.90 (1H, m), 3.29 (2H, m), 3.45 (1H, dd, $J = 4.9, 11.0$ Hz), 3.58 (1H, dd, $J = 4.9, 11.0$ Hz), 3.88 (1H, m), 4.49 (2H, s), 7.33 (5H, m); $^{13}\text{C-NMR}$ (100 MHz) δ -4.5, -4.4, 17.7, 18.1, 25.8, 29.6, 38.2, 66.6, 70.8, 73.0, 76.1, 127.4, 127.5, 128.3, 138.5. ESI-MS: calcd for $\text{C}_{19}\text{H}_{34}\text{O}_3\text{SiNa}$ 361.2175 ($\text{M}+\text{Na}$) $^+$, found, m/z 361.2168.

(*R*)-4-Benzyl-3-((4*R*,6*R*,*E*)-7-(benzyloxy)-6-methyl-4-(*tert*-butyldimethylsilyloxy)hept-2-enoyl)oxazolidin-2-one (**15**). To a solution of **14** (4.39 g, 13 mmol) in CH_2Cl_2 (65 mL) and DMSO (65 mL) were added Et_3N (5.4 mL, 39 mmol) and SO_3 -pyridine (6.2 g, 39 mmol) complex at 0 °C. After 2 h, the reaction was quenched with saturated aqueous NH_4Cl , and the mixture was partitioned between Et_2O and H_2O . The organic layer was dried (Na_2SO_4), and concentrated *in vacuo*. The residue was purified by silica gel column chromatography (hexane-ethyl acetate 6:1) to give an aldehyde (4.3 g, 99%) as a colorless oil.

To a suspension of LiCl (0.09 g, 2.2 mmol) in anhydrous CH_3CN (8 mL) were added **16** (0.29 g, 0.81 mmol), DIPEA (0.3 mL, 1.65 mmol), and the aldehyde (0.18 g, 0.55 mmol) at room temperature; the mixture was stirred at room temperature for overnight. The reaction was quenched with saturated aqueous NH_4Cl , and the mixture was partitioned between Et_2O and H_2O . The organic layer was dried (Na_2SO_4), and concentrated *in vacuo*. The residue was purified by silica gel column chromatography (hexane-ethyl acetate 6:1) to give **15** (0.33 g, quant.) as a colorless oil: $[\alpha]_D^{24}$ -23.1 (c 1.02, CHCl_3); IR (film) 1782, 1683, 1639, 1352, 1207, 1100, 836 cm^{-1} ; $^1\text{H-NMR}$ (400 MHz) δ 0.07 (6H, s), 0.93 (9H, s), 0.99 (3H, d, $J = 6.8$ Hz), 1.35 (1H, ddd, $J = 4.9, 8.8, 13.7$ Hz), 1.75 (1H, ddd, $J = 4.9, 8.8, 13.7$ Hz), 2.02 (1H, m), 2.81 (1H, dd, $J = 9.8, 13.7$ Hz), 3.32 (3H, m), 4.19 (2H, m), 4.50 (3H, m), 4.73 (1H, ddd, $J = 3.4, 6.8, 12.7$ Hz), 7.37 (12H, m); $^{13}\text{C-NMR}$ (100 MHz) δ -5.0, -4.3, 17.3, 18.1, 25.8, 29.7, 37.9, 41.6, 55.3, 66.1, 70.2, 72.9, 76.0, 77.3, 118.7, 127.3, 127.4, 127.5, 128.3, 128.9, 129.5, 135.3, 138.6, 153.2, 153.6, 165.0. ESI-MS: calcd for $\text{C}_{31}\text{H}_{43}\text{NO}_5\text{SiNa}$ 560.2808 ($\text{M}+\text{Na}$) $^+$, found, m/z 560.2808.

(*R*)-4-Benzyl-3-((2*R*,4*R*,6*R*)-7-(benzyloxy)-2,6-dimethyl-4-(*tert*-butyldimethylsilyloxy)heptanoyl)oxazolidin-2-one (**17**). To a solution of **15** (6.21 g, 11.6 mmol) in ethyl acetate (120 mL) was added $\text{Rh-Al}_2\text{O}_3$ (cat.) at room temperature under hydrogen atmosphere; the mixture was stirred for 2 h. The reaction mixture was filtered and concentrated *in vacuo*. The residue was purified by silica gel column chromatography (hexane-ethyl acetate 6:1) to give an amide (5.99 g, 96%) as a colorless oil: $[\alpha]_D^{24}$ -23.6 (c 0.99, CHCl_3); IR (film) 1784, 1701, 1210, 835 cm^{-1} ; $^1\text{H-NMR}$ (400 MHz) δ 0.07 (6H, d, $J = 4.9$ Hz), 0.90 (9H, s), 0.97 (3H, d, $J = 6.5$ Hz), 1.26 (1H, ddd, $J = 5.4, 8.1, 13.7$ Hz), 1.62 (1H, ddd, $J = 5.4, 7.2, 13.7$ Hz), 1.88 (3H, m), 2.76 (1H, dd, $J = 9.6, 13.7$ Hz), 2.92 (1H, ddd, $J = 5.4, 9.6, 17.3$ Hz), 3.05 (1H, ddd, $J = 5.4, 9.6, 17.3$ Hz), 3.31 (3H, m), 3.89 (1H, tt, $J = 5.4, 11.7$ Hz), 4.17 (2H, m), 4.50 (2H, s), 4.66 (1H, ddd, $J = 3.4, 7.2, 13.0$ Hz), 7.34 (10H, m); $^{13}\text{C-NMR}$ (100 MHz) δ -4.5, -4.4, 17.6, 18.0, 25.9, 29.8, 31.5, 31.7, 37.9, 41.3, 55.1, 66.1, 69.2, 72.8, 76.1, 127.4, 127.5, 128.2, 128.3, 128.9, 129.4, 135.3, 153.4, 173.4. ESI-MS: calcd for $\text{C}_{31}\text{H}_{45}\text{NO}_5\text{SiNa}$ 562.2965 ($\text{M}+\text{Na}$) $^+$, found, m/z 562.2962.

To a solution of LHMDS (47 mL, 1.0 M in THF, 47 mmol) in THF (100 mL) was added the amide (5.07 g, 9.4 mmol) at -40 °C. After being stirred at same temperature for 2 h, MeI (12 mL, 0.19 mol) was added and the resultant mixture stirred at -20 °C for 0.5 h. After the addition of saturated aqueous

NH₄Cl, the mixture was extracted with ethyl acetate. The organic layer was dried (Na₂SO₄), and concentrated *in vacuo*. The residue was purified by silica gel column chromatography (hexane-ethyl acetate 9:1) to give **17** (4.03 g, 77%) as a colorless oil: $[\alpha]_D^{24}$ -41.5 (*c* 1.00, CHCl₃); IR (film) 1783, 1697, 1455, 1386, 1209, 836 cm⁻¹; ¹H-NMR (400 MHz) δ 0.05 (6H, d, *J* = 14.6 Hz), 0.90 (9H, s), 1.02 (3H, d, *J* = 6.1 Hz), 1.32 (4H, m), 1.58 (2H, m), 1.98 (1H, ddd, *J* = 6.7, 13.2, 19.7 Hz), 2.11 (1H, m), 2.80 (1H, dd, *J* = 10.1, 13.2 Hz), 3.34 (3H, m), 3.84 (2H, m), 4.18 (2H, m), 4.55 (2H, s), 4.67 (1H, m), 7.33 (10H, m); ¹³C-NMR (100 MHz) δ -4.7, -4.3, 17.9, 18.0, 18.6, 25.8, 29.9, 34.3, 37.9, 40.7, 41.6, 55.3, 65.9, 68.7, 72.9, 76.0, 127.3, 127.5, 128.2, 128.9, 129.4, 135.3, 138.8, 152.8, 176.8. ESI-MS: calcd for C₃₂H₄₈NO₅Si 554.3302 (M+H)⁺, found, *m/z* 554.3292.

(4*R*,6*R*,8*R*)-9-(Benzyloxy)-4,8-dimethyl-6-(tert-butyl dimethylsilyloxy)nonan-3-one (**18**). To a solution of **17** (4.7 g, 8.49 mmol) in THF-MeOH-H₂O (4:4:1, 90 mL) was added LiBH₄ (0.82 g, 34 mmol) at 0 °C; the mixture was stirred at room temperature for 1 h. After the addition of saturated aqueous NH₄Cl, the mixture was extracted with Et₂O. The organic layer was dried (Na₂SO₄), and concentrated *in vacuo*. The residue was purified by silica gel column chromatography (hexane-ethyl acetate 5:1) to give an alcohol (3.02 g, 93%) as a yellow oil: $[\alpha]_D^{24}$ +9.1 (*c* 1.00, CHCl₃); IR (film) 1459, 1255, 1049, 835 cm⁻¹; ¹H-NMR (400 MHz) δ 0.08 (6H, d, *J* = 3.6 Hz), 0.87 (3H, d, *J* = 7.2 Hz), 0.90 (9H, s), 0.95 (3H, d, *J* = 7.2 Hz), 1.38 (1H, ddd, *J* = 6.3, 7.2, 13.7 Hz), 1.55 (4H, m), 1.86 (2H, m), 3.26 (2H, m), 3.33 (1H, m), 3.44 (1H, m), 3.98 (1H, tt, *J* = 4.5, 11.4 Hz), 4.49 (2H, s), 7.33 (5H, m); ¹³C-NMR (100 MHz) δ -4.6, -4.4, 17.8, 18.0, 18.3, 25.8, 30.0, 31.8, 40.6, 42.6, 69.3, 73.0, 76.2, 127.4, 127.5, 128.3, 138.6. ESI-MS: calcd for C₂₂H₄₁O₃Si 381.2825 (M+H)⁺, found, *m/z* 381.2821.

To a solution of the alcohol (2.5 mg, 6.6 μ mol) in CH₂Cl₂ (0.05 mL) and DMSO (0.05 mL) were added Et₃N (3 μ L, 19.7 μ mol) and SO₃-pyridine (3 mg, 19.7 μ mol) complex at 0 °C. After 1.5 h, the reaction was quenched with saturated aqueous NH₄Cl, and the mixture was partitioned between Et₂O and H₂O. The organic layer was dried (Na₂SO₄), and concentrated *in vacuo*. The residue was purified by PLC (hexane-ethyl acetate 3:1) to give an aldehyde as a colorless oil.

To a solution of the aldehyde in THF (0.1 mL) was added EtMgBr (0.02 mL, 1.0 M in THF, 19.7 μ mol) at 0 °C; the mixture was stirred at the same temperature for 15 min. The reaction mixture was quenched with saturated aqueous NH₄Cl, and extracted with CH₂Cl₂. The organic layer was dried (Na₂SO₄), and concentrated *in vacuo*. The residue was purified by PLC (hexane-ethyl acetate (5:1)) to give an alcohol as a colorless oil.

To a solution of the alcohol in CH₂Cl₂ (0.05 mL) and DMSO (0.05 mL) were added Et₃N (3 μ L, 19.7 μ mol) and SO₃-pyridine (3 mg, 19.7 μ mol) complex at 0 °C. After 4 h, the reaction was quenched with saturated aqueous NH₄Cl, and the mixture was partitioned between Et₂O and H₂O. The organic layer was dried (Na₂SO₄), and concentrated *in vacuo*. The residue was purified by PLC (hexane-ethyl acetate (5:1) to give **18** (2.5 mg 89% in 3 steps) as a colorless oil: $[\alpha]_D^{24}$ +1.1 (*c* 0.98, CHCl₃); IR (film) 1714, 1459, 1255, 1099, 835 cm⁻¹; ¹H-NMR (400 MHz) δ 0.02 (6H, d, *J* = 6.7 Hz), 0.87 (9H, s), 0.95 (3H, d, *J* = 7.2 Hz), 1.05 (6H, m), 1.22 (1H, m), 1.35 (1H, m), 1.57 (1H, m), 1.93 (1H, m), 2.46 (2H, m), 2.66 (qt, 1H, *J* = 7.2, 13.7 Hz), 3.26 (1H, dd, *J* = 6.1, 8.8 Hz), 3.33 (1H, dd, *J* = 6.1, 8.8 Hz), 3.75 (1H, tt, *J* = 5.8, 12.1 Hz), 4.50 (2H, s), 7.33 (5H, m); ¹³C-NMR (100 MHz) δ -4.34, -4.30, 7.8, 17.5, 17.7, 18.1, 25.9, 29.8, 34.2, 40.6, 41.4, 42.3, 68.8, 75.9, 127.4, 127.5, 128.3, 138.8, 214.7. ESI-MS: calcd for C₂₄H₄₃O₃Si 407.2981 (M+H)⁺, found, *m/z* 407.2982.

((2*R*,4*S*,6*R*)-1-(Benzyloxy)-2,6-dimethyl-7-methylenonon-4-yloxy)(*tert*-butyl)dimethylsilane (**19**). To a solution of ethyl ketone **18** (60.0 mg, 0.12 mmol) in THF (1 mL) was added (trimethylsilylmethyl) lithium (0.5 mL, 1.0 M in pentane, 0.5 mmol) at -78 °C; the mixture was stirred at the same temperature for 20 min. The reaction mixture was quenched with saturated aqueous NH_4Cl , and extracted with ethyl acetate. The organic layer was dried (Na_2SO_4), and concentrated *in vacuo*. The residue was purified by PLC (hexane-ethyl acetate 9:1) to give an alcohol as a colorless oil.

To a solution of the alcohol in THF (2 mL) was added NaH (60% dispersion in mineral oil, 50 mg, 0.1 mmol) at room temperature; the mixture was stirred at reflux temperature overnight. The reaction was quenched with saturated aqueous NH_4Cl , and the mixture was extracted with ethyl acetate. The organic layer was dried (Na_2SO_4) and concentrated *in vacuo*. The residue was purified by PLC (hexane-ethyl acetate 9:1) to give **19** as a colorless oil (48 mg, 86% in 2 steps): $[\alpha]_D^{24} +17.8$ (*c* 1.01, CHCl_3); IR (film) 2958, 1642, 1460, 1254, 1097, 835 cm^{-1} ; $^1\text{H-NMR}$ (400 MHz) δ 0.05 (6H, s), 0.89 (9H, s), 0.95 (3H, d, $J = 6.5$ Hz), 1.02 (6H, m), 1.24 (1H, m), 1.46 (2H, m), 1.61 (1H, m), 1.99 (3H, m), 2.19 (1H, m), 3.23 (1H, dd, $J = 6.5, 9.1$ Hz), 3.34 (1H, dd, $J = 6.5, 9.1$ Hz), 3.77 (1H, m), 4.50 (2H, s), 4.72 (2H, dd, $J = 1.5, 11.9$ Hz), 7.33 (5H, m); $^{13}\text{C-NMR}$ (100 MHz) δ $-4.2, -4.1, 12.4, 17.4, 18.1, 20.3, 26.0, 26.2, 29.7, 36.8, 41.3, 44.2, 69.0, 72.8, 76.3, 106.4, 127.4, 127.5, 128.3, 138.8, 156.3$. ESI-MS: calcd for $\text{C}_{25}\text{H}_{45}\text{O}_2\text{Si}$ 405.3189 ($\text{M}+\text{H}$) $^+$, found, m/z 405.3181.

(4*R*,6*S*,8*R*)-6-(*tert*-Butyldimethylsilyloxy)-4,8-dimethyl-9-methyleneundecan-3-one (segment B, **3**). To a solution of lithium (12.4 mg, 1.9 mmol) in liquid NH_3 (10 mL) was added **19** (46.4 mg, 0.11 mmol) in dry THF (3 mL) at -78 °C. The reaction mixture was stirred for 15 min at the same temperature; and quenched with solid NH_4Cl . The mixture was extracted with ethyl acetate, and the organic layer was dried (Na_2SO_4), and concentrated *in vacuo*. The residue was purified by silica gel column chromatography (hexane-ethyl acetate 5:1) to give an alcohol (35.6 mg, 99%) as a colorless oil: $[\alpha]_D^{24} +36.4$ (*c* 0.98, CHCl_3); IR (film) 3346, 2959, 1643, 1461, 1254, 1046, 835 cm^{-1} ; $^1\text{H-NMR}$ (400 MHz) δ 0.06 (6H, d, $J = 1.6$ Hz), 0.89 (9H, s), 0.93 (3H, d, $J = 6.3$ Hz), 1.02 (6H, m), 1.27 (1H, ddd, $J = 3.7, 8.5, 13.9$ Hz), 1.46 (2H, m), 1.59 (1H, m), 1.81 (1H, ttd, $J = 2.2, 6.3, 13.0$ Hz), 2.00 (2H, m), 2.16 (1H, qt, $J = 6.3, 7.0$ Hz), 3.45 (2H, dd, $J = 4.5, 6.3$ Hz), 3.76 (1H, m), 4.72 (2H, ddd, $J = 1.6, 2.9, 11.9$ Hz); $^{13}\text{C-NMR}$ (100 MHz) δ $-4.2, -4.0, 12.4, 17.0, 18.1, 20.1, 25.8, 25.9, 26.3, 32.3, 36.9, 40.8, 44.4, 68.8, 69.3, 106.4, 156.3$. ESI-MS: calcd for $\text{C}_{18}\text{H}_{39}\text{O}_2\text{Si}$ 315.2719 ($\text{M}+\text{H}$) $^+$, found, m/z 315.2717.

To a solution of the alcohol (0.35 g, 1.10 mmol) in CH_2Cl_2 (6 mL) and DMSO (6 mL) were added Et_3N (0.5 mL, 3.29 mmol) and SO_3 -pyridine (0.52 g, 3.29 mmol) complex at 0 °C. After 1 h, the reaction was quenched with saturated aqueous NH_4Cl , and the mixture was partitioned between Et_2O and H_2O . The organic layer was dried (Na_2SO_4), and concentrated *in vacuo*. The residue was purified by silica gel column chromatography (hexane-ethyl acetate 7:1) to give an aldehyde as a colorless oil.

To a solution of the aldehyde in THF (10 mL) was added EtMgBr (3 mL, 1.0 M in THF, 2.95 mmol) at 0 °C; the mixture was stirred at the same temperature for 30 min. The reaction was quenched with saturated aqueous NH_4Cl , and the mixture was extracted with CH_2Cl_2 . The organic layer was dried (Na_2SO_4), and concentrated *in vacuo*. The residue was purified by silica gel column chromatography (hexane-ethyl acetate (9:1)) to give an alcohol as a colorless oil.

To a solution of the alcohol in CH₂Cl₂ (4 mL) and DMSO (4 mL) were added Et₃N (0.32 mL, 2.34 mmol) and SO₃-pyridine (0.4 g, 2.34 mmol) complex at 0 °C. After 40 min, the reaction was quenched with saturated aqueous NH₄Cl, and the mixture was partitioned between Et₂O and H₂O. The organic layer was dried (Na₂SO₄), and concentrated *in vacuo*. The residue was purified by silica gel column chromatography (hexane-ethyl acetate 11:1) to give **segment B** (0.22 g 60% in 3 steps) as a colorless oil.: [α]_D²⁴ +11.7 (*c* 0.99, CHCl₃); IR (film) 2960, 1716, 1643, 1461, 1255, 1101, 835 cm⁻¹; ¹H-NMR (400 MHz) δ 0.06 (6H, d, *J* = 3.8 Hz), 0.89 (9H, s), 1.02 (12H, m), 1.38 (2H, m), 1.55 (1H, ddd, *J* = 6.7, 7.0, 13.5 Hz), 1.74 (1H, ddd, *J* = 5.2, 7.0, 13.5 Hz), 1.97 (2H, m), 2.16 (1H, dd, *J* = 7.0, 14.0 Hz), 2.47 (2H, q, *J* = 7.0 Hz), 2.73 (1H, qt, *J* = 7.0, 14.0 Hz), 3.66 (1H, m), 4.70 (2H, m); ¹³C-NMR (100 MHz) δ -4.3, -4.1, 7.9, 12.3, 16.4, 18.1, 20.3, 25.9, 26.2, 34.2, 36.8, 40.1, 41.8, 44.0, 68.7, 77.3, 106.6, 156.0, 215.2. ESI-MS: calcd for C₂₀H₃₉O₂Si 339.2719 (M+H)⁺, found, *m/z* 339.2689.

4. Conclusions

In conclusion, this study reports the efficient synthesis of promising segments **2** and **3** for the construction of amphidinolide Q (**1**). Both routes provided good yields and availability for analog synthesis.

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11. At least two diastereomers were observed. Detailed structural elucidations are under way.
12. Experimental procedure and spectroscopic data will be reported elsewhere.

Sample Availability: Available from the authors.

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