Enantioselective Total Synthesis of Marine Natural Products Untenone A and Plakevulin A

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Abstract: An enantioselective total synthesis of untenone A and plakevulin A has been achieved. Construction of a cyclopentene derivative, the key intermediate in this synthesis, was carried out by using a ruthenium-catalyzed ring-closing metathesis reaction of a divinyl compound, prepared from octadecanal in several steps including the Sharpless asymmetric epoxidation to generate a chiral quaternary carbon center.

Key words: natural product, total synthesis, DNA polymerase inhibitor, Sharpless asymmetric epoxidation, ring-closing metathesis

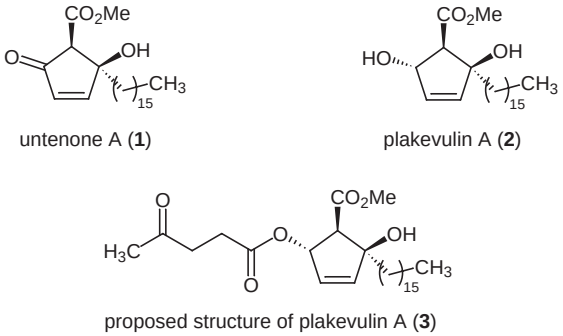
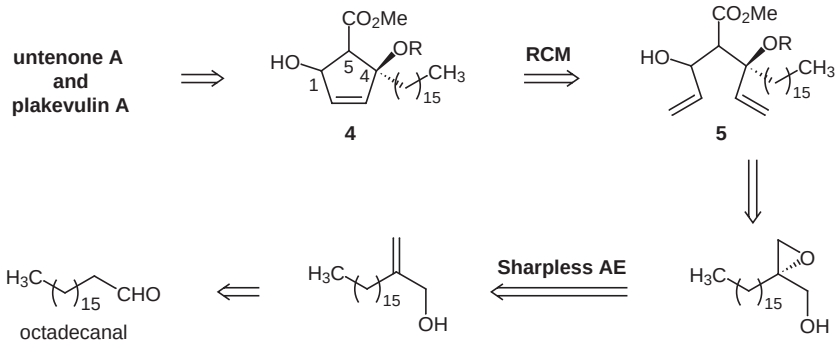


Figure 1 Structure of untenone A and plakevulin A

Untenone A (**1**), isolated from the Okinawan marine sponge, *Plakortis* sp., in 1993,[1] is known to exhibit an inhibitory activity against mammalian DNA polymerases α and β.[2] Owing to its interesting biological activity, several synthetic approaches toward **1** have been reported to date.[2,3] Plakevulin A (**2**) was also isolated from the Okinawan *Plakortis* sponge (SS-973) and inhibits DNA polymerases.[4] Although the levulinyl ester **3** was initially reported as the structure of plakevulin A, it has recently been revised to **2** by Kobayashi's group (Figure 1).[5] Herein, we describe the enantioselective syntheses of untenone A and plakevulin A by employing ring-closing metathesis as a key reaction.

The retrosynthetic analysis for untenone A and plakevulin A is outlined in Scheme 1, where construction of a cyclopentene skeleton of **1** and **2** would be envisaged via ring-closing metathesis[6] of a divinyl compound **5**, since RCM has been recognized to be a powerful synthetic tool for construction of cyloalkene ring systems. We also assumed that the stereochemistry at the C-1 and C-5 positions in **5** could be controlled at the later stage of this synthesis. Thus, the introduction of chirality at the tetra-substituted carbon center would be a crucial step in this synthesis. To generate the desired stereochemistry, we adopted a similar synthetic strategy to our previous work,[7] in which the Sharpless asymmetric epoxidation[8] of an allyl alcohol and subsequent regioselective ring-opening reaction of a chiral epoxide with a nucleophile were exploited as key reactions.

Thus, the requisite starting material was prepared as follows. Octadecanal **6** was converted into α,β-unsaturated aldehyde **7** by using the Eschenmoser salt in CH_2Cl_2,[9] which on reduction with sodium borohydride in the



Scheme 1 Retrosynthetic route for untenone A and plakevulin A

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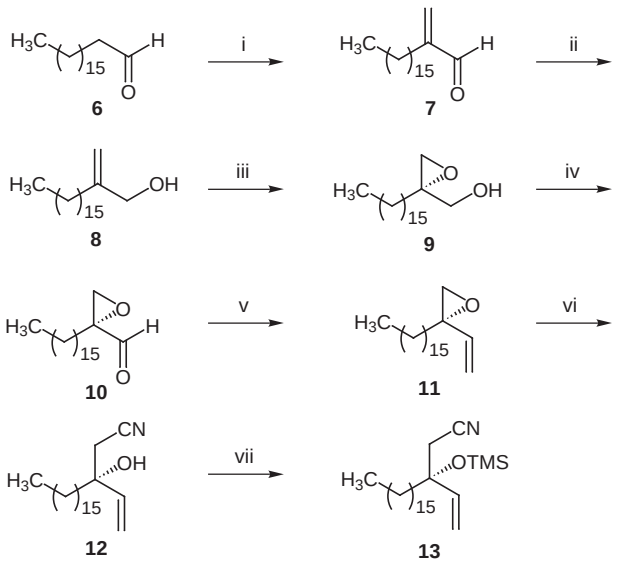
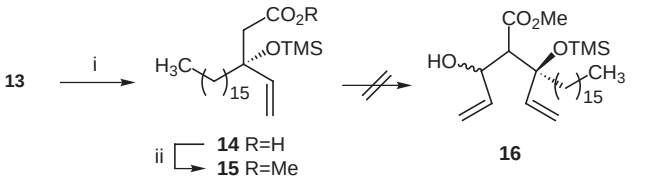
presence of cerium(III) chloride in methanol[10] afforded the allyl alcohol **8** in 80% yield from **6**. The Sharpless asymmetric epoxidation reaction of **8** with L-(+)-diisopropyl tartrate as a chiral source gave the corresponding epoxy alcohol **9** in 94% yield, whose optical purity was determined as 97% ee based on the HPLC analysis of its *p*-nitrobenzoate using the chiral stationary phase (CHIRALCEL OD, Daicel Chemical Industries). Treatment of **9** with Dess–Martin periodinane[11] in CH_2Cl_2 followed by Wittig methylenation of the resulting epoxy aldehyde **10** furnished the corresponding vinyl epoxide **11** in 75% yield in two steps. Regioselective cyanation reaction of epoxide **11** was accomplished by treatment with potassium cyanide and ammonium chloride to give the cyanide **12**[12] which, on protection of the *tert*-alcohol with TMSCl, provided the silyl ether **13** in quantitative yield (Scheme 2).



Scheme 2 *Reagents and conditions*: (i) $CH_2{=}N(CH_3)_2{}^+I^-$, CH_2Cl_2, r.t. (82%); (ii) $NaBH_4$, $CeCl_3{\cdot}7H_2O$, MeOH–$CHCl_3$ (20:1), 0 °C to r.t. (97%); (iii) Ti(O*i*-Pr)$_4$, L-DIPT, TBHP, $CHCl_3$, –20 °C (94%); (iv) Dess–Martin periodinane, CH_2Cl_2, r.t. (94%); (v) $CH_3PPh_3{}^-Br^+$, *n*-BuLi, THF, –78 °C to r.t. (80%); (vi) KCN, NH_4Cl, THF–MeOH–H_2O (5:4:1), 80 °C (98%); (vii) TMSCl, imidazole, DMF, r.t. (99%)

To prepare the divinyl compound **5**, a key compound for the ruthenium-catalyzed ring-closing metathesis reaction, hydrolysis of the cyanide **13** under alkaline reaction conditions followed by methylation of the resulting carboxylic acid **14** was carried out to give the methyl ester **15** in 62% in two steps. Although aldol reaction of **15** with acrolein under various reaction conditions was attempted to obtain the diene **16**, none of the desired product was generated (Scheme 3).

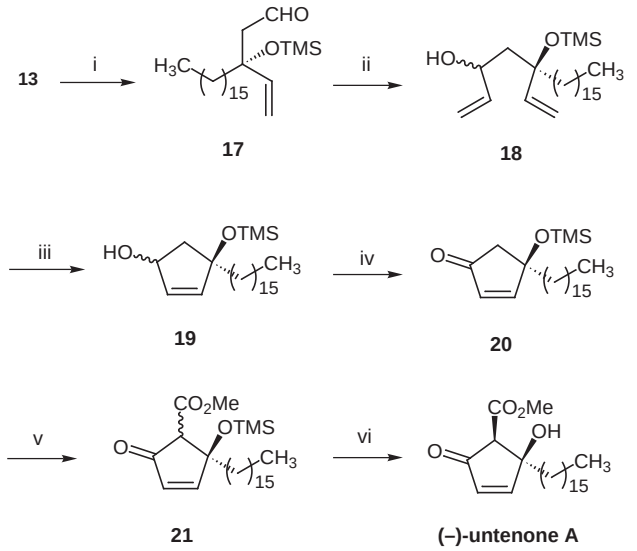
Therefore, we were obliged to change the synthetic route to untenone A through the reported key intermediate **20** as shown in Scheme 4. The cyanide **13** was treated with DIBALH in CH_2Cl_2 to give the aldehyde **17** in 94% yield, which on further treatment with vinylmagnesium bromide



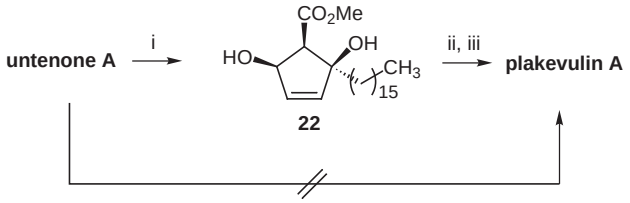
Scheme 3 *Reagents and conditions*: (i) 3 M aq NaOH, 30% H_2O_2, EtOH, 45 °C; (ii) catalytic amount of *p*-TsOH, MeOH, reflux (62% for two steps)

in THF provided an unseparable 1:1 diastereomeric mixture of the allyl alcohol **18**[13] in 82% yield. The ring-closing metathesis reaction of **18** was achieved by using 1 mol% of Grubbs' 2nd generation ruthenium catalyst {tricyclohexylphosphine[1,3-bis(2,4,6-trimethylphenyl)-4,5-dihydroimidazol-2-ylidene][benzylidene]ruthenium(IV) dichloride} in CH_2CH_2 at room temperature to afford the desired cyclopentene **19**[14] in quantitative yield. Oxidation of an allylic alcohol in **19** with manganese oxide gave the cyclopentenone **20**,[15] which is the known key intermediate for the synthesis of untenone A, in 99% yield. According to the reported reaction conditions,[3d] compound **20** was subjected to methoxycarbonylation with LDA and methyl cyanocarbonate in the presence of HMPA in THF to give β-ketoester **21** in 68% yield as a 5:1 diastereomeric mixture. Deprotection of the TMS group and epimerization at the C-5 position of **21** with Dowex 50W-8 and MS 4 Å in MeOH–THF (1:1) at room temperature furnished untenone A as a 10:1 diastereomeric mixture. After recrystallization of the mixture from hexane, pure untenone A[16] was obtained as a white solid, whose spectroscopic data including specific optical rotation and melting point {$[\alpha]_D{}^{26}$ –79.7 (*c* 1.0, $CHCl_3$), mp 63–65 °C; lit.[3d] $[\alpha]_D{}^{27}$ –73.3 (*c* 1.2, $CHCl_3$), mp 62–64 °C} were identical to those reported in the literature.

In order to accomplish the synthesis of plakevulin A, diastereoselective 1,2-reduction of α,β-unsaturated ketone would be required. Although we attempted a direct formation of **2** by using 1,2-reduction of untenone A under various reaction conditions such as tetramethylammonium triacetoxyborohydride in MeCN,[17] hydrogenation with a catalytic amount of $RuCl_2(PPh_3)_3$ and ethylene diamine in isopropanol,[18] none of the desired product was isolated. Finally, untenone A was treated with DIBALH in the presence of zinc bromide in THF to give the β-oriented allyl alcohol **22**[19] in 50% yield. The Mitsunobu reaction of **22**, followed by hydrolysis of the corresponding benzoate under alkaline conditions afforded plakevulin A (**2**)[20] in 66% yield in two steps (Scheme 5). Although the spectroscopic data of the synthesized compound were identical to those reported in the literature,[5] the specific optical rotation and melting point[21] {$[\alpha]_D{}^{22}$ +24.1 (*c* 0.6, $CHCl_3$), mp 74–75 °C} obtained here were different from the reported values {lit.[4] $[\alpha]_D{}^{25}$ +19 (*c* 2.0, $CHCl_3$)}, since the original data were reported for the mixture of **2** and levulinic acid in a ratio of 1:1.



Scheme 4 *Reagents and conditions*: (i) DIBALH, CH_2Cl_2, –40 °C (94%); (ii) vinylmagnesium bromide (1 M THF solution), THF, 0 °C (82%); (iii) Grubbs' 2nd generation Ru catalyst, CH_2Cl_2, r.t. (99%); (iv) MnO_2, CH_2Cl_2, r.t. (99%); (v) LDA, methyl cyanocarbonate, HMPA, THF, –70 °C to –42 °C (68%); (vi) Dowex 50W-8, MS 4 Å, MeOH–THF (1:1), r.t. (60%)



Scheme 5 *Reagents and conditions*: (i) DIBALH, $ZnBr_2$, THF, –50 °C (50%); (ii) 40% DEAD in toluene, PPh_3, *p*-bromobenzoic acid, THF, r.t. (72%); (iii) K_2CO_3, MeOH–THF (1:1), r.t., (92%)

In summary, we have succeeded in the enantioselective synthesis of untenone A and plakevulin A by employing the RCM reaction to construct the basic cyclopentene ring system and the Sharpless asymmetric epoxidation reaction to generate the chiral quaternary carbon center. This synthetic strategy would be applicable to the synthesis of its related derivatives in optically pure forms.

Acknowledgment

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(13) **Preparation and Spectroscopic Data of Compound 18.** To a stirred solution of aldehyde **17** (844 mg, 2.13 mmol) in THF (11.0 mL) was added a solution of vinylmagnesium bromide in THF (2.98 mL, 2.98 mmol) at –20 °C under argon, and the mixture was allowed to stir for 1 h. After quenching by addition of sat. aq NH_4Cl, the mixture was extracted with EtOAc. The organic layer was washed with brine, dried over Na_2SO_4, and concentrated in vacuo. The residue was purified by silica gel column chromatography (*n*-hexane–EtOAc, 40:1) to give **18** (737 mg, 82%) as a colorless oil. ^1H NMR ($CDCl_3$): δ = 0.14 and 0.17 (each 3 H, each s), 0.87 (3 H, t, *J* = 6.7 Hz), 1.19–1.33 (28 H, br m), 1.60–1.79 (4 H, m), 3.93 and 4.13 (each 0.5 H, each s), 4.32–4.48 (1 H, m), 5.01–5.30 (4 H, m), 5.73–6.00 (2 H, m). ^{13}C NMR ($CDCl_3$): δ = 2.47, 2.48, 14.0, 22.6, 24.0, 24.5, 29.3, 29.5, 29.5, 29.6, 30.0, 30.1, 31.9, 40.0, 42.2, 44.2, 45.5, 69.4, 69.7, 79.1, 80.8, 113.4, 113.5, 113.8, 114.0, 140.8, 141.0, 141.9, 143.6. IR (thin film): 3510, 2925, 2855, 1676, 1644, 1468, 1413, 1252, 1144, 1048, 922, 842, 755 cm^{-1}. HRMS:

m/*z* calcd for $C_{26}H_{52}O_2Si$: 424.3736; found: 424.3755. Anal. Calcd for $C_{26}H_{52}O_2Si$: C, 73.52; H, 12.34. Found: C, 73.50; H, 12.27.

(14) **Preparation and Spectroscopic Data of Compound 19.**
To a stirred solution of compound **18** (100 mg, 0.24 mmol) in CH_2Cl_2 (23.5 mL) was added Grubbs' 2nd generation ruthenium catalyst (2.00 mg, 2.36 μmol) at r.t., and the mixture was allowed to stir for 45 min. After removal of the solvent, the residue was purified by silica gel column chromatography (*n*-hexane–EtOAc, 7:1) to give **19** (92.9 mg, 99%) as a white solid; mp 31.5–33 °C. ^{1}H NMR ($CDCl_3$): δ = 0.06 and 0.12 (each 4.5 H, each t, *J* = 3.3 Hz), 0.87 (3 H, t, *J* = 6.7 Hz), 1.19–1.65 (30 H, br m), 1.72–1.73 and 1.78 (each 0.5 H, each m), 2.32 (0.5 H, dd, *J* = 7.09, 14.2 Hz), 2.45 (0.5 H, dd, *J* = 7.0, 13.6 Hz), 4.61 (0.5 H, m), 4.96 (0.5 H, m), 5.83–5.91 (2 H, m). ^{13}C NMR ($CDCl_3$): δ = 2.1, 2.4, 14.1, 22.7, 24.3, 24.4, 29.3, 29.7, 30.0, 30.0, 31.9, 42.4, 43.4, 48.8, 49.6, 75.3, 76.1, 86.1, 87.3, 134.1,135.1, 140.3, 140.3. IR (thin film): 3320, 2920, 2855, 1468, 1360, 1250, 1105, 1050, 960, 880, 840, 755 cm^{-1}. HRMS: *m*/*z* calcd for $C_{24}H_{48}O_2Si$: 396.3424; found: 396.3410. Anal. Calcd for $C_{24}H_{48}O_2Si$: C, 72.66; H, 12.20. Found: C, 72.76; H, 12.03.

(15) **Preparation of Compound 20.**
A mixed suspension of compound **19** (386 mg, 0.97 mmol) and MnO_2 (3.86 g, 44.4 mmol) in CH_2Cl_2 was stirred for 11.5 h at r.t. After filtration of the mixture through a Celite pad, the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography (*n*-hexane–EtOAc, 40:1) to give **20** (379 mg, 99%) as a white solid; mp 32.5–34.0 °C. $[\alpha]_D^{25}$ –14.9 (*c* 1.00, $CHCl_3$). ^{1}H NMR ($CDCl_3$): δ = 0.10 (9 H, s), 0.87 (3 H, t, *J* = 6.6 Hz), 1.18–1.35 (28 H, br m), 1.58–1.74 (2 H, m), 2.48 (2 H, s), 6.09 (1 H, d, *J* = 5.6 Hz), 7.43 (1 H, d, *J* = 5.8 Hz). ^{13}C NMR ($CDCl_3$): δ = 2.14, 14.1, 22.7, 24.3, 29.4, 29.5, 29.5, 29.7, 29.8, 31.9, 41.9, 49.6, 81.3, 132.8, 166.8, 206.9. IR (thin film): 2924, 2854, 1726, 1464, 1252, 1200, 1078, 840 cm^{-1}. HRMS: *m*/*z* calcd for $C_{24}H_{46}O_2Si$: 394.3267; found: 394.3253. Anal. Calcd for $C_{24}H_{46}O_2Si$: C, 73.03; H, 11.75. Found: C, 72.90; H, 11.86.

(16) **Preparation and Spectroscopic Data of (–)-Untenone A (1).**
To a mixed solution of compound **21** (195 mg, 0.43 mmol) in MeOH–THF (5:1, 6 mL) were added Dowex 50W-X8 (1.95 g) and MS 4 Å (975 mg) at r.t. and the resulting mixture was allowed to stir for 5 h. After filtration through a Celite pad, the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography (*n*-hexane–EtOAc, 6:1) to give (–)-untenone A (**1**, 102 mg, 62%) as a white solid; mp 63–65 °C. $[\alpha]_D^{26}$ –79.7 (*c* 1.00, $CHCl_3$). ^{1}H NMR ($CDCl_3$): δ = 0.88 (3 H, t, *J* = 6.5 Hz), 1.22–1.33 (28 H, m), 1.64–1.88 (2 H, m), 3.47 (1 H, s), 3.61 (1 H, s), 3.80 (3 H, s), 6.11 (1 H, d, *J* = 5.6 Hz), 7.52 (1 H, d, *J* = 5.6 Hz). ^{13}C NMR ($CDCl_3$): δ = 14.1, 22.7, 23.8, 29.3, 29.4, 29.5, 29.6, 29.7, 31.9, 40.3, 52.9, 60.8, 79.9, 132.3, 167.0, 169.0, 199.9. IR (thin film): 3480, 2918, 2850, 1742, 1736, 1708, 1468, 1436, 1320, 1218, 1156, 770 cm^{-1}. HRMS: *m*/*z* calcd for $C_{23}H_{40}O_4$: 380.2926; found: 380.2924. Anal. Calcd for $C_{23}H_{40}O_4$: C, 72.59; H, 10.59. Found: C, 72.60; H, 10.74.

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(19) **Preparation and Spectroscopic Data of Compound 22.**
To a mixed solution of (–)-untenone A(**1**) (30.0 mg, 0.08 mmol) and $ZnBr_2$ (17.8 mg, 0.08 mmol) in THF (1.0 mL) was added 0.97 M DIBALH in hexane (0.21 mL, 0.20 mmol) at –50 °C under argon, and the resulting mixture was allowed to stir for 2 h. After quenching by addition of sat. NH_4Cl aq, the mixture was filtrated through a Celite pad, and then the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography (*n*-hexane–EtOAc, 4:1) to give compound **22** (15.1 mg, 50%) as colorless needles; mp 70–71 °C. $[\alpha]_D^{22}$ –54.6 (*c* 0.90, $CHCl_3$). ^{1}H NMR ($CDCl_3$): δ = 0.88 (3 H, t, *J* = 6.6 Hz), 1.22–1.33 (28 H, br m), 1.60–1.78 (2 H, m), 2.99 (1 H, d, *J* = 6.1 Hz), 3.04 (1 H, d, *J* = 8.2 Hz), 3.50 (1 H, s), 3.80 (3 H, s), 4.82 (2 H, ddd, *J* = 2.4, 5.8, 8.2 Hz), 6.04 (1 H, d, *J* = 5.8 Hz), 6.09 (1 H, dd, *J* = 2.4, 5.8 Hz). ^{13}C NMR ($CDCl_3$): δ = 14.1, 22.7, 24.4, 29.3, 29.5, 29.6, 29.6, 29.7, 29.9, 31.9, 39.3, 52.0, 55.0, 75.8, 83.9, 134.7, 140.0, 172.9. IR (thin film): 3527, 3462, 2916, 2848, 1720, 1464, 1396, 1366, 1240, 1176, 1096, 1049, 1030, 970, 924, 800, 781 cm^{-1}. HRMS: *m*/*z* calcd for $C_{23}H_{42}O_4$: 382.3083; found: 382.3085. Anal. Calcd for $C_{23}H_{42}O_4$: C, 72.21; H, 11.07. Found: C, 72.70; H, 11.20.

(20) **Preparation and Spectroscopic Data of *p*-Bromobenzoate of 22 and (+)-Plakevulin A (2).**
To a solution of compound **22** (37.0 mg, 0.10 mmol) in THF (2.0 mL) were added PPh_3 (107 mg, 0.41 mmol), 40% DEAD in toluene solution (0.16 mL, 0.42 mmol) and *p*-bromobenzoic acid (70.1 mg, 0.35 mmol) at r.t. under argon, and the resulting mixture was allowed to stir for 6 h. After quenching by addition of sat. $NaHCO_3$ aq, the mixture was extracted with EtOAc. The organic layer was washed with brine, dried over Na_2SO_4, and concentrated in vacuo. The residue was purified by silica gel column chromatography (*n*-hexane–EtOAc, 5:1) to give *p*-bromobenzoate (39.4 mg, 72%) as a white solid; mp 59–62 °C. $[\alpha]_D^{20}$ +89.9 (*c* 0.60, $CHCl_3$). ^{1}H NMR ($CDCl_3$): δ = 0.88 (3 H, t, *J* = 6.6 Hz), 1.16–1.46 (28 H, br m), 1.82–1.88 (2 H, m), 2.32 (1 H, s), 3.11 (1 H, d, *J* = 4.3 Hz), 3.79 (3 H, s), 5.99–6.06 (2 H, m), 6.27 (1 H, m), 7.58 (2 H, dd, *J* = 1.8, 6.8 Hz), 7.87 (2 H, dd, *J* = 1.8, 6.8 Hz). ^{13}C NMR ($CDCl_3$): δ = 14.1, 22.7, 24.2, 29.3, 29.6, 29.6, 29.7, 29.9, 31.9, 40.8, 52.3, 57.9, 81.2, 85.4, 128.3, 128.7, 131.2, 131.3, 131.7, 140.2, 165.4, 171.7. IR (thin film): 3486, 2924, 2852, 1724, 1590, 1268, 1172, 1114, 1100, 1012, 758 cm^{-1}. HRMS: *m*/*z* [M + 1] calcd for $C_{30}H_{46}O_5Br$: 565.2528; found: 565.2534. Anal. Calcd for $C_{30}H_{45}O_5Br$: C, 63.71; H, 8.02. Found: C, 63.81; H, 8.03.
To a mixed solution of the *p*-bromobenzoate of **22** (45.0 mg, 0.08 mmol) in MeOH–THF (1:1, 1.0 mL) was added K_2CO_3 at r.t., and the mixture was allowed to stir for 1.5 h. After quenching by addition of sat. NH_4Cl aq, the resulting mixture was extracted with EtOAc. The organic layer was washed with brine, dried over Na_2SO_4, and concentrated in vacuo. The residue was purified by silica gel column chromatography (*n*-hexane–EtOAc, 2:1) to give (+)-plakevulin A (**2**, 28.0 mg, 92%) as colorless needles; mp 74–75 °C. $[\alpha]_D^{22}$ +24.1 (*c* 0.60, $CHCl_3$). ^{1}H NMR ($CDCl_3$): δ = 0.88 (3 H, t, *J* = 6.7 Hz), 1.19–1.38 (28 H, br m), 1.75–1.86 (2 H, m), 2.02 (1 H, d, *J* = 14.7 Hz), 2.45 (1 H, s), 2.83 (1 H, d, *J* = 5.3 Hz), 3.79 (3 H, s), 5.30–5.38 (1 H, m), 5.84 (1 H, dd, *J* = 1.6, 5.7 Hz), 5.94 (1 H, dd, *J* = 1.8, 5.7 Hz). ^{13}C NMR ($CDCl_3$): δ = 14.1, 22.7, 24.5, 29.4, 29.6, 29.7, 29.9, 31.9, 40.6, 52.1, 60.5, 78.2, 84.9, 135.7, 137.0, 172.6. IR (thin film): 3430, 2916, 2848, 1728, 1464, 1436, 1380, 1366, 1265, 1198, 1085, 994, 862, 786, 722 cm^{-1}. HRMS: *m*/*z* [M + 1] calcd for $C_{23}H_{43}O_4$: 383.3161; found: 383.3138. Anal. Calcd for $C_{23}H_{42}O_4$: C, 72.21; H, 11.07. Found: C, 71.96; H, 10.95.

(21) The melting point of optically active **2** has not been reported in the literature.