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Enantioselective total synthesis of both diastereomers of preclavulone-A methyl ester

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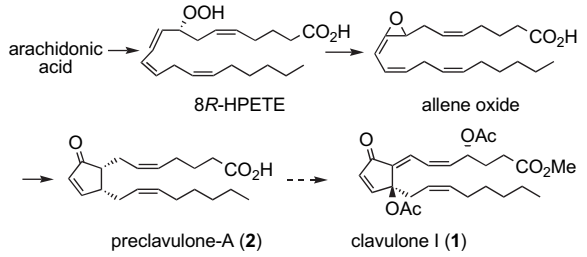
Abstract—The enantioselective total synthesis of preclavulone-A methyl ester and its diastereomer was achieved from enantiomerically pure **5** in a stereocontrolled manner. The absolute stereochemistry of naturally occurring preclavulone-A methyl esters was determined by comparison of the $[\alpha]_D$ value.

1. Introduction

Clavulones[1] (claviridenones[2]) and related marine prostanoids,[3] isolated from the Okinawan soft coral, *Clavularia viridis*, have received much attention owing to their structural features, significant biological activities, and unique biosynthesis. Corey et al. proposed a biosynthetic pathway of clavulones starting from oxidation of arachidonic acid by lipoxygenase (LOX) through (8*R*)-HPETE, allene oxide, and preclavulone-A (**2**) as shown in Scheme 1.[4]



Scheme 1. Biosynthetic pathway of calvulones proposed by Corey et al.

This biosynthesis was based on experimental results showing that **2** was obtained by treating labeled arachidonic acid as well as labeled (8*R*)-HPETE with the cell-free extract or acetone powder prepared from *C. viridis*, although the absolute configuration of **2** could not be determined due to its small amount. The trans diastereomer of preclavulone-A was also obtained in this biosynthetic experiment, but its absolute configuration was not determined.

Very recently, a trace amount of preclavulone-A methyl ester (**4**) and its diastereomer **3** was isolated from the methanol extract of *C. viridis* by our group (Fig. 1).[5] Interestingly, both compounds **4** and **3** were found to be an enantiomeric mixture (**4**: 8% ee, **3**: 46% ee) from the HPLC analysis using a chiral column. Preclavulone-A derivatives **3** and **4** were previously synthesized by Corey and Xiang (**4**: enantiomerically pure form)[6] and Traverso et al. (**3**: racemic form).[7] Although the determination of absolute stereochemistry of **4** was achieved by the comparison of $[\alpha]_D$ value reported by Corey et al., the absolute stereochemistry of trans isomer **3** could not be determined. Therefore, stereocontrolled synthesis of **3** as an enantiomerically pure form was required to establish the stereochemistry of the natural compounds and to clarify the detailed stereochemical course of the biosynthesis of clavulones. We have recently developed a novel stereocontrolled synthetic method for (±)-**3** and (±)-**4** in a highly stereoselective manner via the common intermediate **5**.[8] Now, both compounds **3** and **4** were prepared from an enantiomerically pure **5** and the predominant enantiomer of natural **3** and **4** was determined.

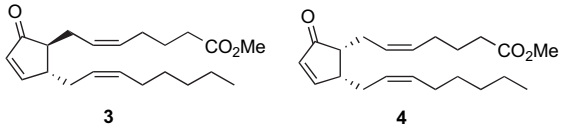


Figure 1.

2. Results and discussions

2.1. Retrosynthetic analysis

Our synthetic plan of compounds **3** and **4** each in enantiomerically pure form was the same as that for our previously

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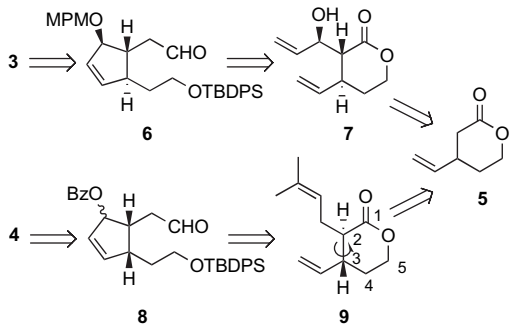
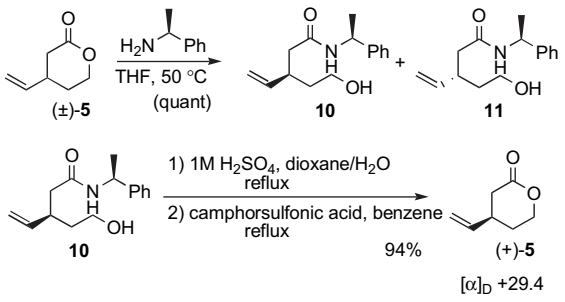


Figure 2. Retrosynthetic pathway of compounds **3** and **4**.

reported synthesis of racemic **3** and **4** as shown in Figure 2.[8] The α- and ω-chains of compounds **3** and **4** could be constructed from the corresponding aldehyde by Wittig reaction with high *Z*-selectivity. So, it was important to prepare compounds **6** and **8** in a highly stereocontrolled manner. For the construction of the cyclopentene ring of **6** and **8**, ring-closing olefin metathesis was employed. Compound **7** having a trans-relationship between the α- and β-substituents on the lactone was prepared from **5** through diastereoselective Mukaiyama aldol reaction using boron enolate. On the other hand, compound **9** could be prepared by the trans-selective α-alkylation of compound **5**. The 3-methyl-2-butenyl group was chosen as an alkylating agent because tri-substituted carbon–carbon double bond should not be reacted during the ring-closing olefin metathesis and is possible for the site-selective epoxidation. Introduction of vinyl group to carbonyl moiety and following ring-closing olefin metathesis could be obtained cis-disubstituted cyclopentene derivative **8**.

2.2. Synthesis of the common key intermediate 5

The preparation of optically pure compound **5** was essential for the enantioselective synthesis of **3** and **4**. Our main purpose in the synthesis of compounds **3** and **4** as enantiomerically pure form is for the determination of the absolute stereochemistry of natural **3** and **4**. So, both enantiomers of **5** could be applied for the synthesis of **3** and **4**. Additionally, racemic **5** was easily obtained by the 1,4-addition of vinylmagnesium chloride to 5,6-dihydro-2*H*-pyran-2-one.[9] Therefore, optical resolution of racemic **5** was selected for the preparation of enantiomerically pure **5** as shown in Scheme 2. Racemic **5** was reacted with (*S*)-1-phenylethylamine and

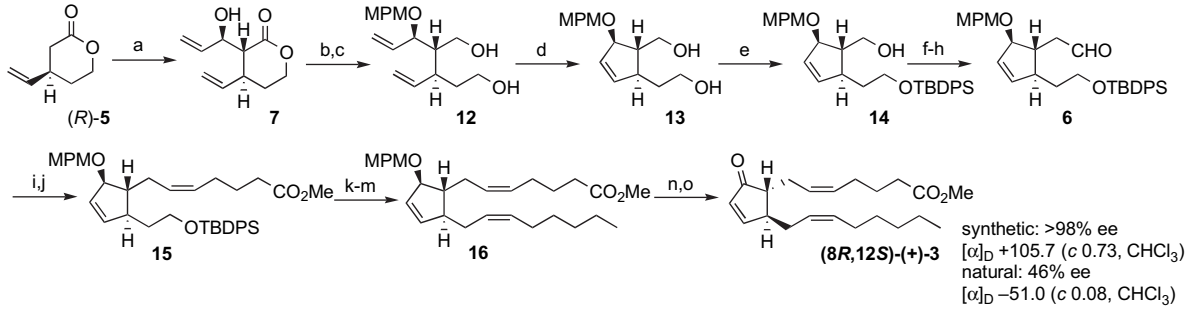


Scheme 2. Synthesis of enantiomerically pure **5**.

compounds **10** and **11** were obtained as a diastereomeric mixture (Scheme 2). After separation of each diastereomer by HPLC, compound **10** was converted to (+)-**5** ($[\alpha]_D$ +29.4) by acid hydrolysis and following lactonization using an acid catalyst in 91% yield. Compound (−)-**5** ($[\alpha]_D$ −29.2) was also prepared from compound **11** in the same manner. Absolute stereochemistry of compound **5** was determined by comparing optical rotation value of the literature after conversion of **5** to 4-ethyltetrahydropyran-2-one.[10]

2.3. Enantioselective and stereocontrolled total synthesis of 3

The total synthesis of (+)-**3** from (*R*)-(+)-**5** is shown in Scheme 3. The construction of **7** having two trans-related substituents on the lactone was achieved by Mukaiyama aldol reaction through boron enolate using dibutylboron triflate and diisopropylethylamine in a highly diastereoselective manner (80% yield, minor isomer could not be detected by crude ^{1}H NMR).[11] Although other metals (lithium, zinc, and magnesium) for the enolate were examined, the control of the stereochemistry of the newly formed chiral centers could not be achieved. After the conversion of compound **7** to **12** by protection of hydroxyl group and reduction of lactone moiety, the ring-closing olefin metathesis of **12** by the use of first generation Grubbs catalyst[12] proceeded to give compound **13** in 76% yield. One carbon elongation of the α-chain was achieved as follows. Mono-protection of the hydroxyl groups to obtain compound **14**, oxidation of another hydroxyl group, Wittig reaction by the use of methoxymethyltriphenylphosphonium chloride with butyllithium, and following acid hydrolysis of the resulting enol ether

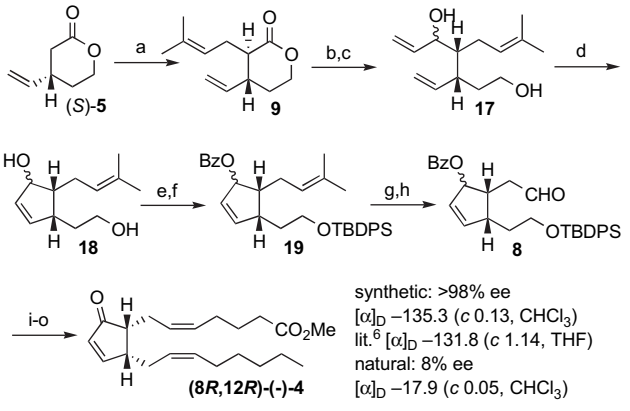


Scheme 3. Reagents and conditions: (a) Bu_2BOTf, $EtNiPr_2$, CH_2Cl_2, −78 °C, then acrolein, −78 °C to 0 °C, 80%; (b) *p*-methoxybenzyl trichloroacetimidate, camphorsulfonic acid, CH_2Cl_2, 0 °C to rt; (c) $LiAlH_4$, ether, rt, two steps 50%; (d) first Grubbs catalyst, toluene, 50 °C, 78%; (e) TBDPSCl, imidazole, DMF, rt, 53%; (f) Dess–Martin periodinane, CH_2Cl_2, rt, 95%; (g) $Ph_3P^+Cl^-CH_2OMe$, *n*-BuLi, THF, rt; (h) TsOH, acetone, rt, two steps, 50%; (i) $Ph_3P^+Br^-(CH_2)_4CO_2H$, NaHMDS, THF, rt, 78%; (j) CH_2N_2, ether, 0 °C, 90%; (k) TBAF, THF, rt, 99%; (l) Dess–Martin periodinane, CH_2Cl_2, rt, 89%; (m) $Ph_3P^+Br^-(CH_2)_5CH_3$, NaHMDS, THF, rt, 87%; (n) DDQ, CH_2Cl_2/H_2O, rt, 95%; and (o) Dess–Martin periodinane, CH_2Cl_2, rt, 98%.

gave compound **6**. Construction of the α- and ω-chains by Wittig reaction proceeded with high *Z*-selectivity (minor isomer could not be detected by ^{1}H NMR) to give compound **16**. Total synthesis of enantiomerically pure (8*R*,12*S*)-**3** (>98% ee, determined by HPLC using chiralcel OD-H) was achieved by deprotection of MPM group by treating with DDQ and following oxidation of resulting allylic alcohol moiety using Dess–Martin periodinane. Comparison of the optical rotation values of the synthetic and natural compounds indicated that the synthetic (8*R*,12*S*)-**3** was a minor enantiomer of natural **3** and a major enantiomer was (8*S*,12*R*)-**3**.

2.4. Enantioselective and stereocontrolled total synthesis of 4

Although the enantioselective total synthesis of **4** was achieved by Corey and Xiang,[6] an alternative total synthesis of **4** as an enantiomerically pure form was established by our developed synthetic route from (*S*)-(−)-**5** as shown in Scheme 4. Two chiral centers of **4** were constructed diastereoselectively through the α-alkylation of **5** by employing 1-bromo-3-methyl-2-butene. The reaction proceeded to give compound **9** as a single diastereomer in 94% yield. Compound **9** was converted to the precursor of the ring-closing olefin metathesis by half-reduction of the lactone moiety and following addition of vinylmagnesium chloride. The ring-closing metathesis of **17** was examined by the use of second generation Grubbs catalyst[13] and compound **18** was obtained as a diastereomeric mixture in 80% yield. If first generation of Grubbs catalyst was employed in this step, the reaction did not proceed. After the protection of two hydroxyl groups, the site-selective oxidative cleavage of the tri-substituted carbon–carbon double bond was achieved to give compound **8**. Stereoselective construction of both side chains was achieved in the same manner as mentioned for the synthesis of the trans isomer **3** through the Wittig reaction, and (8*R*,12*R*)-**4** was obtained as an enantiomerically pure form (>98% ee, determined by HPLC using chiralcel OD-H). Comparison of the optical rotation values of the synthetic and natural compounds indicated that (8*R*,12*R*)-**4** is a major enantiomer of the natural **4** and was in good accordance with the reported value of synthetic **4**.[6]



Scheme 4. Reagents and conditions: (a) LiHMDS, THF, −78 °C, then 1-bromo-3-methyl-2-butene, −78 °C to 0 °C, 94%; (b) DIBALH, ether, −78 °C to −20 °C, 98%; (c) vinylmagnesium chloride, THF, 0 °C to rt, 94%; (d) second Grubbs catalyst, CH_2Cl_2, rt, 80%; (e) TBDPSCl, triethylamine, DMAP, CH_2Cl_2, 0 °C, 98%; (f) benzoyl chloride, pyridine, DMAP, CH_2Cl_2, 0 °C, 78%; (g) *m*-CPBA, CH_2Cl_2, 0 °C, 80%; (h) HIO_4, H_2O, *t*-BuOH, rt, 99%; (i) $Ph_3P^+Br^-(CH_2)_4CO_2H$, NaHMDS, THF, −78 °C to rt, 76%; (j) CH_2N_2, ether, 0 °C, 90%; (k) TBAF, THF, rt, 98%; (l) Dess–Martin periodinane, CH_2Cl_2, rt, 99%; (m) $Ph_3P^+Br^-(CH_2)_5CH_3$, NaHMDS, THF, −78 °C to 0 °C, 98%; (n) NaOMe, MeOH, 50 °C, 88%; and (o) MnO_2, CH_2Cl_2, rt, 95%.

3. Conclusion

The enantioselective total syntheses of preclavulone-A methyl ester and its diastereomer were achieved from enantiomerically pure common intermediate **5** and the absolute stereochemistries of the predominant enantiomers of naturally occurring **3** and **4** were determined as shown in Figure 1. These results are an important information for the elucidation of the biosynthetic pathway of clavulones.

4. Experimental

4.1. General

All reactions were carried out under an argon atmosphere. Unless otherwise noted, materials were obtained from commercial suppliers and used without further purification. ^{1}H and ^{13}C NMR spectra were measured on a Bruker AV-300 and the chemical shifts are given in parts per million using $CHCl_3$ (7.26 ppm) in $CDCl_3$ for ^{1}H NMR and $CDCl_3$ (77.0 ppm) for ^{13}C NMR as an internal standard. IR spectra were taken with a Perkin–Elmer PARAGON 1000 FT-IR and only noteworthy absorptions were listed. Mass spectra were measured on a Micromass LCT.

4.1.1. 3-(2-Hydroxyethyl)-4-pentenoic acid (1-phenylethyl) amide (10, 11). To a solution of racemic **5** (6.9 g, 54.7 mmol) in THF (20 mL) was added (*S*)-phenylethylamine (9 mL, 71.1 mmol) at ambient temperature and the mixture was stirred at 50 °C for 2 days. The mixture was concentrated under vacuum and the resulting residue was purified by silica gel column chromatography (AcOEt) and the compounds **10** and **11** were obtained as a diastereomeric mixture (13.5 g, 54.6 mmol, 99%). The resulting diastereomeric mixture was separated by HPLC (AcOEt/IPA, 10:1). Compound **10**: colorless oil. $[\alpha]_D^{24}$ −66.0 (*c* 0.65, $CHCl_3$). IR (neat) ν cm^{-1}: 699, 915, 995, 1050, 1548, 1643, 2930, 3284. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 1.47 (3H, d, *J*=7.1 Hz), 1.63 (2H, q, *J*=6.4 Hz), 2.00 (1H, br s), 2.22 (1H, dd, *J*=7.3, 14.4 Hz), 2.28 (1H, dd, *J*=6.8, 14.4 Hz), 2.74 (1H, sext, *J*=7.2 Hz), 3.63 (2H, t, *J*=5.7 Hz), 5.04 (1H, dd, *J*=1.2, 10.2 Hz), 5.08 (1H, dd, *J*=1.2, 17.2 Hz), 5.13 (1H, quint, *J*=7.1 Hz), 5.68 (1H, ddd, *J*=8.3, 10.2, 17.2 Hz), 5.80 (1H, br d, *J*=7.2 Hz), 7.23–7.38 (5H, m). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 21.6, 37.1, 37.5, 42.0, 48.8, 60.5, 115.5, 126.2, 127.4, 128.7, 141.0, 143.0, 170.8. HREIMS calcd for $C_{15}H_{22}NO_2$: 248.1651 (M+H)$^+$, found: 248.1663. Compound **11**: colorless oil. $[\alpha]_D^{24}$ −96.0 (*c* 0.65, $CHCl_3$). IR (neat) ν cm^{-1}: 699, 916, 994, 1050, 1449, 1548, 1643, 2930, 3284. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 1.47 (3H, d, *J*=6.9 Hz), 1.62 (2H, q, *J*=6.4 Hz), 2.20 (1H, dd, *J*=7.5, 14.3 Hz), 2.29 (1H, dd, *J*=6.7, 14.3 Hz), 2.73 (1H, sext, *J*=7.3 Hz), 3.57–3.72 (2H, m), 5.01 (1H, d, *J*=10.2 Hz), 5.05 (1H, d, *J*=17.2 Hz), 5.11

(1H, quint, J=7.1 Hz), 5.65 (1H, ddd, J=8.4, 10.2, 17.2 Hz), 6.01 (1H, br s), 7.21–7.37 (5H, m). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 21.6, 36.9, 37.4, 41.9, 48.8, 60.2, 115.5, 126.2, 127.4, 128.6, 140.9, 142.9, 171.2.

4.1.2. (4*R*)-4-Vinyltetrahydropyran-2-one ((+)-5). The mixture of **10** (1.07 g, 8.46 mmol) and H_2SO_4 (1 M in water, 10.2 mL, 10.2 mmol) in dioxane (10 mL) and water (10 mL) was heated under reflux for 1 h. After cooling at ambient temperature, the mixture was extracted with AcOEt three times and the resulting organic layer was washed with brine, dried over $MgSO_4$, and concentrated under vacuum. The mixture was diluted with benzene (10 mL) and camphorsulfonic acid (213 mg, 0.85 mmol) was added to the mixture. The mixture was refluxed with removal of water for 15 h. Then, saturated aqueous $NaHCO_3$ was added to the mixture and the mixture was extracted with AcOEt. The organic layer was washed with brine, dried over $MgSO_4$, and concentrated under vacuum. The residue was purified by silica gel column chromatography (hexane/AcOEt, 2:1) to afford the compound (+)-**5** as an enantiomerically pure form (1.54 g, 7.91 mmol, 94%). Colorless oil. $[\alpha]_D^{24}$ +29.4 (c 0.52, $CHCl_3$). IR (neat) ν cm^{-1}: 921, 996, 1737, 2977. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 1.56–1.73 (1H, m), 1.88–2.02 (1H, m), 2.28 (1H, dd, J=11.2, 18.8 Hz), 2.54–2.69 (2H, m), 4.22 (1H, ddd, J=3.9, 9.8, 11.4 Hz), 4.35 (1H, td, J=4.8, 11.4 Hz), 5.01 (1H, dd, J=1.0, 17.4 Hz), 5.02 (1H, dd, J=1.0, 10.1 Hz), 5.71 (1H, ddd, J=6.1, 10.1, 17.4 Hz). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 28.9, 35.5, 35.9, 68.7, 115.4, 140.0, 171.0.

4.1.3. (+)-4-Ethyltetrahydropyran-2-one. The mixture of (+)-**5** (20 mg, 0.16 mmol) and catalytic amount of 5% Pd/C in MeOH (2 mL) was stirred at ambient temperature under hydrogen atmosphere for 2 h. The reaction mixture was filtered and the filtrate was concentrated under vacuum and the resulting residue was purified by silica gel column chromatography (hexane/AcOEt, 3:1) to afford 4-ethyltetrahydropyran-2-one (9.1 mg, 0.071 mmol) in 44% yield. $[\alpha]_D^{24}$ +17.9 (c 0.52, $CHCl_3$). Colorless oil. $[\alpha]_D^{24}$ +27.8 (c 8.1, $CHCl_3$).[10] The spectral data was same as reported value.[10]

4.1.4. 3-(1-Hydroxy-2-propenyl)-4-vinyltetrahydropyran-2-one (7). To a solution of (*R*)-**5** (550 mg, 4.35 mmol) in CH_2Cl_2 (10 mL) was added dibutylboron trifluoromethanesulfonate (1 M in dichloromethane, 8.7 mL, 8.7 mmol) and diisopropylethylamine (1.86 mL, 10.9 mmol) was added at −78 °C. After being stirred for 2 h at the same temperature, acrolein (0.58 mL, 8.7 mmol) was added to the mixture and the resulting mixture was stirred at the same temperature for 1 h. After being stirred for further 2 h at 0 °C, phosphate buffer (pH 6.86, 10 mL), methanol (20 mL), and H_2O_2 (10 mL) were added to the mixture and the resulting mixture was stirred at ambient temperature for 16 h. The mixture was concentrated under reduced pressure and extracted with CH_2Cl_2. The organic layer was washed with brine and dried over $MgSO_4$. Filtration and concentration of the mixture under reduced pressure gave crude material, which was purified by silica gel column chromatography (hexane/AcOEt, 2:1) to afford **7** (630 mg, 3.46 mmol) in 80% yield. Colorless oil. $[\alpha]_D^{24}$ +43.1 (c 1.37, $CHCl_3$). IR (neat) ν cm^{-1}: 1122, 1727, 2918, 3432. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 1.68–1.82 (1H, m), 1.95–2.08 (1H, m), 2.51 (1H, dd, J=3.1, 9.4 Hz), 2.77 (1H, quint, J=7.6 Hz), 3.06 (1H, br s), 4.23–4.35 (2H, m), 4.35 (1H, br d, J=4.2 Hz), 5.13 (1H, d, J=10.3 Hz), 5.14 (1H, d, J=17.2 Hz), 5.15 (1H, d, J=10.3 Hz), 5.24 (1H, d, J=17.2 Hz), 5.74 (1H, ddd, J=8.1, 10.3, 17.2 Hz), 6.08 (1H, ddd, J=6.2, 10.3, 17.2 Hz). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 29.0, 37.7, 50.3, 67.0, 72.2, 116.0, 116.5, 138.8, 139.5, 172.3. Anal. Calcd for $C_{10}H_{14}O_3$: C, 65.92; H, 7.74. Found: C, 65.60; H, 8.03. HREIMS calcd for $C_{10}H_{15}O_3$: 183.1021 $(M+H)^+$, found: 183.1012.

4.1.5. 4-Hydroxymethyl-5-(4-methoxybenzyloxy)-3-vinyl-6-hepten-1-ol (12). To a solution of **7** (1.0 g, 5.48 mmol) in CH_2Cl_2 (5 mL) was added a solution of MPM imidate (10 mmol) in cyclohexane (5 mL) and camphorsulfonic acid (125.2 mg, 0.5 mmol) and the mixture was stirred at ambient temperature for 24 h. The resulting mixture was filtered through Celite and concentrated under vacuum. To the residue, which was diluted with ether (20 mL) was added $LiAlH_4$ (249.6 mg, 6.58 mmol) at ambient temperature. After being stirred for 2 h, saturated aqueous Rochelle salt was added to the mixture and stirred for 1 h. The mixture was extracted with AcOEt and the organic layer was washed with brine and dried over $MgSO_4$. Filtration and concentration of the mixture under reduced pressure gave crude material, which was purified by silica gel column chromatography (hexane/AcOEt, 1:1) to afford **12** (839.5 mg, 2.74 mmol) in 50% yield. Colorless oil. $[\alpha]_D^{24}$ −15.8 (c 1.06, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$) δ: 1.33–1.49 (2H, m), 1.81–1.96 (1H, m), 1.94 (1H, br s), 2.53–2.66 (1H, m), 3.49–3.75 (3H, m), 3.80 (3H, s), 3.94 (1H, dd, J=1.8, 11.8 Hz), 4.07–4.16 (1H, m), 4.18 (1H, d, J=11.0 Hz), 4.51 (1H, d, J=10.0 Hz), 4.96 (1H, dd, J=1.8, 17.0 Hz), 5.06 (1H, dd, J=1.8, 10.2 Hz), 5.28 (1H, d, J=17.0 Hz), 5.33 (1H, d, J=9.8 Hz), 5.60 (1H, dt, J=9.8, 17.0 Hz), 5.84 (1H, ddd, J=7.0, 10.2, 17.0 Hz), 6.86 (2H, d, J=8.5 Hz), 7.21 (2H, d, J=8.5 Hz). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 33.7, 39.1, 48.3, 55.2, 60.2, 61.3, 70.7, 82.1, 113.8, 116.7, 117.8, 129.5, 129.9, 137.4, 141.0, 159.3. HREIMS calcd for $C_{18}H_{26}O_4Na$: 329.1729 $(M+Na)^+$, found: 329.1749.

4.1.6. 2-[5-Hydroxymethyl-4-(4-methoxybenzyloxy)-2-cyclopentenyl]ethanol (13). To a solution of **12** (227 mg, 0.74 mmol) in toluene (7 mL) was added benzylidenebis(tricyclohexylphosphine)dichlororuthenium (60.9 mg, 0.07 mmol) at 50 °C. After being stirred for 1.5 h at the same temperature, water was added to the mixture and the mixture was extracted with AcOEt. The organic layer was washed with brine and dried over $MgSO_4$. Filtration and concentration of the mixture under reduced pressure gave crude material, which was purified by silica gel column chromatography (hexane/AcOEt, 1:1) to afford **13** (161.5 mg, 0.58 mmol) in 78% yield. Colorless oil. $[\alpha]_D^{24}$ −46.0 (c 1.51, $CHCl_3$). IR (neat) ν cm^{-1}: 1060, 1248, 1585, 1612, 2931, 3361. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 1.52–1.65 (2H, m), 1.80–1.93 (1H, m), 2.18–2.28 (1H, m), 2.52–2.62 (1H, m), 3.53 (1H, t, J=9.4 Hz), 3.68–3.78 (3H, m), 3.80 (3H, s), 4.26 (1H, br s), 4.49 (2H, s), 5.81 (1H, td, J=1.9, 5.6 Hz), 5.88 (1H, dd, J=1.5, 5.6 Hz), 6.87 (2H, d, J=8.6 Hz), 7.27 (2H, d, J=8.6 Hz). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 37.7, 45.1, 51.5, 55.3, 60.8, 65.4, 70.5, 86.6, 113.8, 129.1, 129.4, 130.4, 138.9, 159.2. HREIMS calcd for $C_{16}H_{23}O_4$: 279.1596 $(M+H)^+$, found: 279.1624.

4.1.7. [5-[2-(*tert*-Butyldiphenylsilanyloxy)ethyl]-2-(4-methoxybenzyloxy)-3-cyclopentenyl]methanol (14). To a solution of **13** (155 mg, 0.558 mmol) in DMF (2 mL) were added imidazole (83.6 mg, 1.228 mmol) and TBDPSCl (0.16 mL, 0.614 mmol) at 0 °C. After being stirred for 1 h, water was added to the reaction mixture. The mixture was extracted with AcOEt and the organic layer was washed with brine and dried over $MgSO_4$. Filtration and concentration of the mixture under reduced pressure gave crude material, which was purified by silica gel column chromatography (hexane/AcOEt, 5:1) to afford **14** (150 mg, 0.29 mmol) in 53% yield. Colorless oil. $[\alpha]_D^{24}$ −48.8 (*c* 1.15, $CHCl_3$). IR (neat) ν cm^{-1}: 702, 1036, 1111, 1247, 1513, 1612, 2929, 3450. ^1H NMR (300 MHz, $CDCl_3$) δ: 1.05 (9H, s), 1.53–1.67 (2H, m), 1.67–1.81 (1H, m), 2.03–2.14 (1H, m), 2.49–2.60 (1H, m), 3.65 (2H, d, *J*=7.0 Hz), 3.70–3.80 (2H, m), 3.82 (3H, s), 4.35 (1H, br s), 4.50 (2H, s), 5.78 (1H, dt, *J*=1.9, 5.7 Hz), 5.83 (1H, d, *J*=5.7 Hz), 6.87 (2H, d, *J*=8.6 Hz), 7.27 (2H, d, *J*=8.6 Hz), 7.34–7.47 (6H, m), 7.67 (4H, dd, *J*=1.5, 7.5 Hz). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 19.2, 38.2, 44.3, 52.8, 55.3, 62.5, 65.3, 70.5, 86.8, 113.8, 127.7, 129.3, 129.4, 129.7, 130.8, 133.5, 133.6, 135.5, 138.3. HREIMS calcd for $C_{32}H_{40}O_4NaSi$: 539.2594 $(M+Na)^+$, found: 539.2580.

4.1.8. [5-[2-(*tert*-Butyldiphenylsilanyloxy)ethyl]-2-(4-methoxybenzyloxy)-3-cyclopentenyl]acetaldehyde (6). To a solution of **14** (265 mg, 0.512 mmol) in CH_2Cl_2 (5 mL) was added Dess–Martin periodinane (239 mg, 0.564 mmol) at ambient temperature. After being stirred for 30 min, the mixture was diluted with ether and washed with saturated aqueous $NaHCO_3$. The organic layer was washed with brine and dried over $MgSO_4$. Filtration and concentration of the mixture under reduced pressure gave crude material, which was purified by silica gel column chromatography (hexane/AcOEt, 5:1) to afford aldehyde (251 mg, 0.487 mmol) in 95% yield. A solution of *n*-butyllithium (1.58 M in hexane, 1.74 mL, 2.7 mmol) was added to a suspension of methoxymethyltriphenylphosphonium chloride (858 mg, 2.5 mmol) in THF (15 mL) at −40 °C and the mixture was stirred at the same temperature for 1 h. A solution of aldehyde (247 mg, 0.481 mmol) in THF (5 mL) was added to the reaction mixture at the same temperature and the mixture was stirred at ambient temperature for 2 h. Saturated aqueous ammonium chloride was added to the reaction mixture and the mixture was extracted with ether. The organic layer was washed with brine and dried over $MgSO_4$. Filtration and concentration of the mixture under reduced pressure gave crude material, which was used for next step without further purification. To a solution of crude material in acetone (5 mL) was added a catalytic amount of *p*-toluenesulfonic acid (20 mg) and the mixture was stirred at ambient temperature for 1 h. Water was added to the mixture and the resulting mixture was extracted with CH_2Cl_2. The organic layer was washed with brine and dried over $MgSO_4$. Filtration and concentration of the mixture under reduced pressure gave crude material, which was purified by silica gel column chromatography (hexane/AcOEt, 5:1) to afford **6** (127 mg, 0.24 mmol) in 50% yield. Colorless oil. $[\alpha]_D^{24}$ −20.4 (*c* 1.11, $CHCl_3$). IR (neat) ν cm^{-1}: 702, 1111, 1248, 1722. ^1H NMR (300 MHz, $CDCl_3$) δ: 1.04 (9H, s), 1.58–1.83 (2H, m), 2.21–2.33 (1H, m), 2.38–2.58 (3H, m), 3.73 (2H, t, *J*=6.3 Hz), 3.79 (3H, s), 4.21 (1H, d, *J*=3.0 Hz), 4.46 (2H, s), 5.79 (1H, td, *J*=1.8, 5.8 Hz), 5.87 (1H, br d, *J*=5.8 Hz), 6.86 (2H, d, *J*=8.7 Hz), 7.23 (2H, d, *J*=8.7 Hz), 7.33–7.47 (6H, m), 7.65 (4H, d, *J*=7.7 Hz), 9.73 (1H, t, *J*=2.6 Hz). Anal. Calcd for $C_{33}H_{40}O_4Si$: C, 74.68; H, 7.98. Found: C, 74.58; H, 7.70.

4.1.9. 7-[2-[2-(*tert*-Butyldiphenylsilanyloxy)ethyl]-5-(4-methoxybenzyloxy)-3-cyclopentenyl]-5-heptenoic acid methyl ester (15). To a suspension of 4-hydroxycarbonylbutyltriphenylphosphonium bromide (45.3 mg, 0.102 mmol) in THF (1.2 mL) was added a solution of NaHMDS (1 M in THF, 0.2 mL, 0.2 mmol) at 0 °C and the mixture was stirred at ambient temperature for 1 h. A solution of **6** (18 mg, 0.034 mmol) in THF (0.3 mL) was added to the mixture at 0 °C and the mixture was stirred at ambient temperature for 1 h. Saturated aqueous ammonium chloride was added to the reaction mixture and the resulting mixture was extracted with $CHCl_3$. The organic layer was washed with brine and dried over $MgSO_4$. Filtration and concentration of the mixture under reduced pressure gave crude material, which was purified by silica gel column chromatography (hexane/AcOEt, 2:1) to afford carboxylic acid (16 mg, 0.026 mmol) in 76% yield. Colorless oil. $[\alpha]_D^{24}$ −16.1 (*c* 0.58, $CHCl_3$). IR (neat) ν cm^{-1}: 702, 1247, 1587, 1707, 3069. ^1H NMR (300 MHz, $CDCl_3$) δ: 1.06 (9H, s), 1.60–1.82 (4H, m), 1.83–1.92 (1H, m), 2.00–2.21 (4H, m), 2.32 (2H, t, *J*=7.5 Hz), 2.35–2.45 (1H, m), 3.73 (2H, t, *J*=6.4 Hz), 3.80 (3H, s), 4.17 (1H, br s), 4.46 (2H, s), 5.30–5.54 (2H, m), 5.76 (1H, td, *J*=1.9, 5.7 Hz), 5.58 (1H, dd, *J*=1.3, 5.7 Hz), 6.86 (2H, d, *J*=8.7 Hz), 7.26 (2H, d, *J*=8.7 Hz), 7.34–7.47 (6H, m), 7.68 (4H, d, *J*=7.3 Hz). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 19.2, 24.5, 26.6, 26.8, 31.3, 33.4, 38.7, 46.9, 49.9, 55.2, 62.5, 70.4, 88.8, 113.6, 127.6, 128.9, 129.3, 129.5, 130.9, 133.9, 135.5, 138.6, 159.0, 179.5. Anal. Calcd for $C_{38}H_{48}O_5Si$: C, 74.47; H, 7.89. Found: C, 74.44; H, 7.82. To a solution of carboxylic acid (16 mg, 0.026 mmol) in ether (2 mL) was added a solution of diazomethane in ether at 0 °C and the mixture was stirred for 15 min at the same temperature. After concentration under the reduced pressure, crude material was purified by silica gel column chromatography (hexane/AcOEt, 3:1) to afford **15** (14.7 mg, 0.023 mmol) in 90% yield. Colorless oil. $[\alpha]_D^{24}$ −10.0 (*c* 1.62, $CHCl_3$). IR (neat) ν cm^{-1}: 702, 1111, 1247, 1737, 2930. ^1H NMR (300 MHz, $CDCl_3$) δ: 1.06 (9H, s), 1.59–1.79 (4H, m), 1.79–1.92 (1H, m), 1.96–2.21 (4H, m), 2.29 (2H, t, *J*=7.5 Hz), 2.35–2.44 (1H, m), 3.66 (3H, s), 3.73 (2H, t, *J*=6.5 Hz), 3.80 (3H, s), 4.17 (1H, br s), 4.45 (2H, s), 5.34–5.52 (2H, m), 5.76 (1H, td, *J*=1.9, 5.8 Hz), 5.87 (1H, dd, *J*=1.3, 5.8 Hz), 6.86 (2H, d, *J*=8.6 Hz), 7.25 (2H, d, *J*=8.6 Hz), 7.34–7.48 (6H, m), 7.67 (4H, d, *J*=7.4 Hz). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 19.2, 24.8, 26.5, 26.7, 26.8, 31.3, 33.4, 38.7, 46.9, 49.9, 51.4, 55.2, 62.5, 70.4, 88.8, 113.7, 127.6, 127.7, 128.8, 129.2, 129.3, 129.5, 129.7, 131.0, 133.9, 134.8, 135.5, 138.5, 159.0, 174.0. Anal. Calcd for $C_{39}H_{50}O_5Si$: C, 74.72; H, 8.04. Found: C, 74.53; H, 8.06.

4.1.10. 7-[2-(4-Methoxybenzyloxy)-5-(2-octenyl)cyclopent-3-enyl]-5-heptenoic acid methyl ester (16). To a solution of **15** (74.6 mg, 0.119 mmol) in THF (2 mL) was added a solution of tetrabutylammonium fluoride (1 M in THF, 0.14 mL, 0.14 mmol) at ambient temperature. After being stirred for 2 h at the same temperature, the mixture was poured onto water and the mixture was extracted with

AcOEt. The organic layer was washed with brine and dried over $MgSO_4$. Filtration and concentration of the mixture under reduced pressure gave crude material, which was purified by silica gel column chromatography (hexane/AcOEt, 2:1) to afford the alcohol (45.7 mg, 0.118 mmol) in 99% yield. Colorless oil. $[\alpha]_D^{24}$ −29.2 (*c* 1.17, $CHCl_3$). IR (neat) ν cm^{-1}: 1057, 1247, 1513, 1736, 2930, 3441. ^1H NMR (300 MHz, $CDCl_3$) δ: 1.61–1.78 (4H, m), 1.94–2.16 (5H, m), 2.30 (2H, t, *J*=7.5 Hz), 2.29–2.42 (1H, m), 3.65 (3H, s), 3.62–3.72 (2H, m), 3.78 (3H, s), 4.15 (1H, br s), 4.45 (1H, d, *J*=11.4 Hz), 4.47 (1H, d, *J*=11.4 Hz), 5.35–5.51 (2H, m), 5.81 (1H, td, *J*=1.9, 5.7 Hz), 5.90 (1H, dd, *J*=2.0, 5.7 Hz), 6.85 (2H, *J*=8.7 Hz), 7.24 (2H, *J*=8.7 Hz). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 24.7, 26.6, 31.8, 33.4, 37.8, 47.3, 49.0, 51.5, 55.2, 60.8, 70.5, 88.8, 113.7, 128.6, 129.3, 129.6, 130.1, 130.6, 138.6, 159.1, 174.1. Anal. Calcd for $C_{23}H_{32}O_5$: C, 71.11; H, 8.30. Found: C, 70.73; H, 8.26. To a solution of alcohol (39 mg, 0.10 mmol) in CH_2Cl_2 (2 mL) was added Dess–Martin periodinane (55.1 mg, 0.13 mmol) at ambient temperature. After being stirred for 30 min, the mixture was diluted with ether and washed with saturated aqueous $NaHCO_3$. The organic layer was washed with brine and dried over $MgSO_4$. Filtration and concentration of the mixture under reduced pressure gave crude material, which was purified by silica gel column chromatography (hexane/AcOEt, 3:1) to afford aldehyde (34.4 mg, 0.089 mmol) in 89% yield. To a suspension of hexyltriphenylphosphonium bromide (119.2 mg, 0.279 mmol) in THF (2 mL) was added a solution of NaHMDS (1 M in THF, 0.28 mL, 0.28 mmol) at 0 °C and the mixture was stirred at ambient temperature for 1 h. A solution of aldehyde (36 mg, 0.093 mmol) in THF (1 mL) was added to the mixture at 0 °C and the mixture was stirred at ambient temperature for 2 h. Saturated aqueous ammonium chloride was added to the reaction mixture and the resulting mixture was extracted with $CHCl_3$. The organic layer was washed with brine and dried over $MgSO_4$. Filtration and concentration of the mixture under reduced pressure gave crude material, which was purified by silica gel column chromatography (hexane/AcOEt, 7:1) to afford **16** (36.8 mg, 0.081 mmol) in 87% yield. Colorless oil. $[\alpha]_D^{24}$ +5.6 (*c* 1.55, $CHCl_3$). IR (neat) ν cm^{-1}: 1247, 1513, 1613, 1739, 2926. ^1H NMR (300 MHz, $CDCl_3$) δ: 0.88 (3H, t, *J*=6.8 Hz), 1.19–1.39 (6H, m), 1.68 (2H, quint, *J*=7.4 Hz), 1.84–1.92 (1H, m), 1.97–2.26 (9H, m), 2.31 (2H, t, *J*=7.5 Hz), 3.66 (3H, s), 3.80 (3H, s), 4.18 (1H, br s), 4.47 (2H, s), 5.32–5.52 (4H, m), 5.77 (1H, td, *J*=1.6, 5.7 Hz), 5.86 (1H, d, *J*=5.7 Hz), 6.86 (2H, d, *J*=8.6 Hz), 7.27 (2H, d, *J*=8.6 Hz). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 14.1, 22.6, 24.8, 26.7, 27.3, 29.4, 31.3, 31.5, 33.4, 33.5, 49.5, 50.3, 51.5, 55.3, 70.5, 89.0, 113.7, 127.5, 128.8, 129.3, 129.6, 129.7, 131.0, 131.2, 138.3, 159.0. HREIMS calcd for $C_{29}H_{42}O_4Na$: 477.2981 $(M+Na)^+$, found: 477.2955. Anal. Calcd for $C_{29}H_{42}O_4$: C, 76.61; H, 9.31. Found: C, 76.78; H, 9.19.

4.1.11. *trans*-Preclavulone-A methyl ester (3). To a solution of **16** (32 mg, 0.07 mmol) in CH_2Cl_2 (2 mL) was added 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (58.5 mg, 0.21 mmol) at ambient temperature. After being stirred for 1 h, water was added to the reaction mixture and the resulting mixture was extracted with AcOEt. The organic layer was washed with brine and dried over $MgSO_4$. Filtration and concentration of the mixture under reduced pressure gave crude material, which was purified by silica gel column chromatography (hexane/AcOEt, 5:1) to afford an alcohol (22.2 mg, 0.067 mmol) in 95% yield. Colorless oil. $[\alpha]_D^{24}$ −20.3 (*c* 0.51, $CHCl_3$). IR (neat) ν cm^{-1}: 1260, 1731, 2924, 3446. ^1H NMR (300 MHz, $CDCl_3$) δ: 0.88 (3H, t, *J*=6.8 Hz), 1.17–1.39 (6H, m), 1.60–1.70 (2H, m), 1.70 (2H, quint, *J*=7.4 Hz), 2.01 (2H, q, *J*=6.8 Hz), 2.10 (2H, q, *J*=7.2 Hz), 2.15–2.34 (5H, m), 2.33 (2H, t, *J*=7.4 Hz), 3.67 (3H, s), 4.43 (1H, d, *J*=1.9 Hz), 5.28–5.57 (4H, m), 5.72 (1H, td, *J*=1.9, 5.7 Hz), 5.80 (1H, td, *J*=1.5, 5.7 Hz). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 14.1, 22.6, 24.8, 26.7, 27.3, 29.3, 30.6, 31.5, 32.8, 33.4, 50.2, 51.5, 53.7, 82.7, 127.1, 128.7, 130.0, 131.5, 132.4, 137.3, 166.9. HREIMS calcd for $C_{21}H_{33}O_2$: 317.2481 $(M-H_2O+H)^+$, found: 317.2471. To a solution of the alcohol (22.0 mg, 0.066 mmol) in CH_2Cl_2 (1 mL) was added Dess–Martin periodinane (42.4 mg, 0.1 mmol) at ambient temperature. After being stirred for 30 min, the mixture was diluted with ether and washed with saturated aqueous $NaHCO_3$. The organic layer was washed with brine and dried over $MgSO_4$. Filtration and concentration of the mixture under reduced pressure gave crude material, which was purified by silica gel column chromatography (hexane/AcOEt, 7:1) to afford **3**[5] (21.5 mg, 0.0647 mmol) in 98% yield. Colorless oil. $[\alpha]_D^{24}$ +105.4 (*c* 0.74, $CHCl_3$).

4.1.12. (3*R*,4*R*)-3-(3-Methyl-2-butenyl)-4-vinyltetrahydropyran-2-one (9). To a solution of (*S*)-**5** (1.07 g, 8.46 mmol) in THF (20 mL) was added a solution of LiHMDS (1 M in THF, 10.2 mL, 10.2 mmol) at −78 °C and the mixture was stirred at the same temperature for 1 h. 1-Bromo-3-methyl-2-butene (1.51 g, 10.2 mmol) was added to the reaction mixture at the same temperature and the resulting mixture was stirred for 3 h. Then, saturated aqueous ammonium chloride was added to the reaction mixture and the resulting mixture was extracted with AcOEt. The organic layer was washed with brine and dried over $MgSO_4$. Filtration and concentration of the mixture under reduced pressure gave crude material, which was purified by silica gel column chromatography (hexane/AcOEt, 10:1) to afford **9** (1.54 g, 7.91 mmol) in 94% yield. Colorless oil. $[\alpha]_D^{24}$ −24.0 (*c* 2.25, $CHCl_3$). IR (neat) ν cm^{-1}: 1190, 1732, 2922. ^1H NMR (300 MHz, $CDCl_3$) δ: 1.61 (3H, s), 1.70 (3H, s), 1.70–1.82 (1H, m), 1.88–1.97 (1H, m), 2.26–2.58 (4H, m), 4.24 (1H, ddd, *J*=3.7, 9.1, 11.2 Hz), 4.35 (1H, ddd, *J*=4.4, 5.3, 11.2 Hz), 5.05–5.15 (3H, m), 5.70 (1H, ddd, *J*=6.4, 10.5, 16.8 Hz). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 18.6, 26.4, 28.3, 29.7, 40.3, 46.2, 68.0, 116.6, 121.0, 134.9, 140.4, 173.7.

4.1.13. 4-(3-Methyl-2-butenyl)-3-vinyl-6-heptene-1,5-diol (17). To a solution of **9** (1.26 g, 6.41 mmol) in THF (20 mL) was added a solution of DIBAL (0.93 M in hexane, 8.15 mL, 7.58 mmol) at −78 °C. After being stirred at −20 °C for 4 h, saturated aqueous potassium sodium tartrate was added to the reaction mixture and the mixture was stirred at ambient temperature for 1 h. The mixture was extracted with AcOEt and the organic layer was washed with brine and dried over $MgSO_4$. Filtration and concentration of the mixture under reduced pressure gave crude material, which was purified by silica gel column chromatography (hexane/AcOEt, 5:1) to afford lactol (1.32 g, 6.73 mmol) in 98% yield. Colorless oil. ^1H NMR (300 MHz, $CDCl_3$)

δ: 1.20–2.41 (6H, m), 1.59 (3H, s), {1.67 (s), 1.68 (s), 3H}, {2.84 (dd, *J*=1.0, 3.2 Hz), 3.35 (d, *J*=6.2 Hz), 1H}, 3.45–3.62 (1H, m), 3.92–4.13 (1H, m), 4.49 (0.4H, dd, *J*=6.0, 8.2 Hz), 4.97–5.23 (3.6H, m), {5.58 (ddd, *J*=8.7, 10.0, 17.1 Hz), 5.64 (ddd, *J*=8.5, 10.2, 17.2 Hz), 1H}. To a solution of lactol (1.26 g, 6.41 mmol) in THF (20 mL) was added a solution of vinylmagnesium chloride (1.38 M in THF, 18.6 mL, 25.7 mmol) at 0 °C. After being stirred for 1 h, saturated aqueous ammonium chloride was added to the reaction mixture and the resulting mixture was extracted with AcOEt. The organic layer was washed with brine and dried over $MgSO_4$. Filtration and concentration of the mixture under reduced pressure gave crude material, which was purified by silica gel column chromatography (hexane/AcOEt, 1:1) to afford **17** (1.36 g, 6.06 mmol) in 94% yield. Compound **17a**: colorless oil. IR (neat) ν cm^{-1}: 916, 994, 1044, 1436, 2915, 3345. ^1H NMR (300 MHz, $CDCl_3$) δ: 1.55–1.83 (3H, m), 1.60 (3H, s), 1.68 (3H, s), 2.01–2.20 (2H, m), 2.46 (1H, sept, *J*=4.7 Hz), 3.60 (1H, ddd, *J*=6.2, 7.2, 10.7 Hz), 3.68 (1H, td, *J*=6.1, 10.7 Hz), 4.23 (1H, t, *J*=5.4 Hz), 5.06 (1H, dd, *J*=2.0, 17.2 Hz), 5.07 (1H, dd, *J*=2.0, 10.3 Hz), 5.14 (1H, d, *J*=10.3 Hz), 5.15–5.22 (1H, m), 5.22 (1H, d, *J*=17.2 Hz), 5.73 (1H, ddd, *J*=9.4, 10.3, 17.2 Hz), 5.90 (1H, ddd, *J*=6.0, 10.3, 17.2 Hz). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 18.0, 25.5, 25.9, 35.5, 41.6, 48.1, 61.2, 75.2, 115.4, 116.4, 124.0, 132.3, 139.8, 140.6. Anal. Calcd for $C_{14}H_{24}O_2$: C, 74.95; H, 10.78. Found: C, 74.72; H, 10.56. Compound **17b**: colorless oil. IR (neat) ν cm^{-1}: 918, 995, 1440, 2926, 3346. ^1H NMR (300 MHz, $CDCl_3$) δ: 1.50–1.72 (3H, m), 1.61 (3H, s), 1.69 (3H, s), 1.86 (1H, br s), 1.99–2.21 (2H, m), 2.55–2.67 (1H, m), 3.54–3.71 (2H, m), 4.13 (1H, br t, *J*=7.1 Hz), 5.06–5.15 (3H, m), 5.18 (1H, td, *J*=1.5, 10.5 Hz), 5.26 (1H, td, *J*=1.6, 17.2 Hz), 5.76–5.87 (1H, m), 5.91 (1H, ddd, *J*=5.3, 10.5, 17.2 Hz). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 17.9, 25.2, 25.8, 35.9, 40.4, 48.5, 61.1, 74.6, 115.0, 116.7, 123.6, 132.8, 140.6, 141.4. Anal. Calcd for $C_{14}H_{24}O_2$: C, 74.95; H, 10.78. Found: C, 74.72; H, 10.56.

4.1.14. 4-(2-Hydroxyethyl)-5-(3-methyl-2-butenyl)-2-cyclopenten-1-ol (18). To a solution of **17** (1.21 g, 5.39 mmol) in CH_2Cl_2 (50 mL) was added second generation of Grubbs catalyst (229 mg, 0.27 mmol) and the mixture was stirred at ambient temperature for 1.5 h. Water was added to the mixture and the resulting mixture was extracted with AcOEt. The organic layer was washed with brine and dried over $MgSO_4$. Filtration and concentration of the mixture under reduced pressure gave crude material, which was purified by silica gel column chromatography (hexane/AcOEt, 1:1) to afford **18** as a diastereomeric mixture (846 mg, 4.31 mmol) in 80% yield. Compound **18a**: colorless oil. $[\alpha]_D^{24}$ −31.3 (*c* 0.46, $CHCl_3$). IR (neat) ν cm^{-1}: 1117, 1275, 2918, 3418. ^1H NMR (300 MHz, $CDCl_3$) δ: 1.45–1.59 (1H, m), 1.67 (3H, s), 1.72 (3H, s), 1.78–1.91 (3H, m), 2.08–2.23 (2H, m), 2.25–2.40 (1H, m), 2.63–2.73 (1H, m), 3.61–3.79 (2H, m), 4.53 (1H, dd, *J*=2.8, 5.6 Hz), 5.19–5.24 (1H, m), 5.99 (1H, ddd, *J*=1.5, 2.5, 5.8 Hz), 6.16 (1H, dd, *J*=2.8, 5.8 Hz). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 18.0, 24.1, 25.8, 35.0, 43.1, 45.7, 61.2, 76.5, 123.1, 132.4, 132.6, 140.4. Compound **18b**: colorless oil. $[\alpha]_D^{24}$ −191.4 (*c* 0.47, $CHCl_3$). IR (neat) ν cm^{-1}: 1117, 1275, 2918, 3418. ^1H NMR (300 MHz, $CDCl_3$) δ: 1.25–1.43 (2H, m), 1.64 (3H, s), 1.72 (3H, s), 1.77–1.88 (1H, m), 1.97–2.28 (3H, m), 2.83–2.93 (1H, m), 3.59–3.76 (2H, m), 4.51 (1H, br d, *J*=4.8 Hz), 5.18–5.26 (1H, m), 5.80 (1H, td, *J*=1.6, 5.8 Hz), 6.00 (1H, ddd, *J*=1.3, 2.4, 5.8 Hz). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 18.0, 25.8, 26.9, 33.8, 42.8, 51.8, 61.9, 81.8, 123.1, 133.0, 133.6, 137.7.

4.1.15. Benzoic acid 4-[2-(*tert*-butyldiphenylsilanyloxy)-ethyl]-5-(3-methyl-2-butenyl)-2-cyclopentenyl ester (19). To a solution of **18** (647 mg, 3.29 mmol) in DMF (10 mL) were added triethylamine (367 mg, 0.5 mL, 3.63 mmol), *tert*-butyldiphenylchlorosilane (998 mg, 0.85 mL, 3.63 mmol), and 4-dimethylaminopyridine (22.2 mg, 0.18 mmol) at 0 °C and the mixture was stirred at same temperature for 1 h. Water was added to the reaction mixture and the resulting mixture was extracted with AcOEt. The organic layer was washed with brine and dried over $MgSO_4$. Filtration and concentration of the mixture under reduced pressure gave crude material, which was purified by silica gel column chromatography (hexane/AcOEt, 15:1) to afford silyl ether as a diastereomeric mixture (1.4 g, 3.22 mmol) in 98% yield. *a Isomer*: colorless oil. $[\alpha]_D^{24}$ −39.1 (*c* 2.88, $CHCl_3$). IR (neat) ν cm^{-1}: 1111, 1427, 2930, 3331. ^1H NMR (300 MHz, $CDCl_3$) δ: 1.06 (9H, s), 1.23–1.39 (1H, m), 1.68 (3H, s), 1.73 (3H, s), 1.87–2.00 (1H, m), 2.04–2.37 (3H, m), 2.63–2.73 (1H, m), 3.64–3.82 (2H, m), 4.50 (1H, dd, *J*=2.6, 5.4 Hz), 5.21–5.28 (1H, m), 5.93 (1H, ddd, *J*=1.3, 2.5, 5.7 Hz), 6.13 (1H, dd, *J*=2.8, 5.8 Hz), 7.35–7.48 (6H, m), 7.64–7.72 (4H, m). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 18.0, 19.2, 24.0, 25.8, 26.9, 36.0, 42.6, 45.9, 62.6, 123.2, 127.6, 129.6, 132.1, 132.2, 133.9, 135.6, 141.3. HREIMS calcd for $C_{28}H_{38}O_2NaSi$: 457.2539 $(M+Na)^+$, found: 457.2532. *b Isomer*: colorless oil. $[\alpha]_D^{24}$ −102.2 (*c* 4.34, $CHCl_3$). IR (neat) ν cm^{-1}: 1111, 1472, 2929, 3331. ^1H NMR (300 MHz, $CDCl_3$) δ: 1.06 (9H, s), 1.22–1.36 (1H, m), 1.65 (3H, s), 1.73 (3H s), 1.80–2.25 (4H, m), 2.86–2.97 (1H, m), 3.60–3.76 (2H, m), 4.47 (1H, br s), 5.17–5.23 (1H, m), 5.73 (1H, td, *J*=1.6, 5.8 Hz), 5.92 (1H, ddd, *J*=1.3, 2.5, 5.8 Hz), 7.35–7.48 (6H, m), 7.67 (4H, d, *J*=7.6 Hz). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 18.0, 19.2, 25.8, 26.8, 26.9, 33.6, 42.7, 51.8, 62.8, 81.9, 123.3, 127.6, 129.6, 132.7, 133.1, 133.9, 135.5, 138.2. HREIMS calcd for $C_{28}H_{38}O_2NaSi$: 457.2539 $(M+Na)^+$, found: 457.2565. To a solution of silyl ether (1.38 g, 3.17 mmol) in CH_2Cl_2 (15 mL) were added pyridine (377 mg, 0.38 mL, 4.76 mmol), benzoyl chloride (669 mg, 0.55 mL, 4.76 mmol), and 4-dimethylaminopyridine (38.7 mg, 0.32 mmol) at 0 °C. After being stirred at the same temperature for 2 h, methanol and saturated sodium hydrogen carbonate were added to the reaction mixture. The resulting mixture was extracted with AcOEt and the organic layer was washed with brine and dried over $MgSO_4$. Filtration and concentration of the mixture under reduced pressure gave crude material, which was purified by silica gel column chromatography (hexane/AcOEt, 15:1) to afford **19** as a diastereomeric mixture (1.34 g, 2.49 mmol) in 78% yield. Compound **19a**: colorless oil. $[\alpha]_D^{24}$ −177.5 (*c* 2.51, $CHCl_3$). IR (neat) ν cm^{-1}: 702, 1110, 1271, 1601, 1715, 2929. ^1H NMR (300 MHz, $CDCl_3$) δ: 1.07 (9H, s), 1.30–1.46 (1H, m), 1.61 (3H, s), 1.63 (3H, s), 1.85–1.98 (1H, m), 2.15 (2H, t, *J*=7.4 Hz), 2.38–2.49 (1H, m), 2.99–3.10 (1H, m), 3.65–3.81 (2H, m), 5.15 (1H, t, *J*=6.3 Hz), 5.64 (1H, br d, *J*=5.7 Hz), 5.86 (1H, br d, *J*=5.8 Hz), 6.06 (1H, td, *J*=1.0, 5.8 Hz), 7.36–7.48 (8H, m), 7.53 (1H, t, *J*=7.4 Hz),

7.68 (4H, t, J=7.4 Hz), 8.03 (2H,d, J=7.1 Hz). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 17.9, 19.2, 25.7, 26.7, 26.9, 33.4, 42.4, 47.5, 62.8, 84.6, 122.7, 127.6, 128.2, 129.4, 129.5, 129.6, 132.6, 132.7, 133.9, 135.5, 140.6, 166.5. Anal. Calcd for $C_{32}H_{42}O_3Si$: C, 78.02; H, 7.86. Found: C, 77.94; H, 7.90. HREIMS calcd for $C_{32}H_{42}O_3NaSi$: 561.2801 $(M+Na)^+$, found: 561.2800. Compound **19b**: colorless oil. $[\alpha]_D^{24}$ +72.5 (c 0.23, $CHCl_3$). IR (neat) ν cm^{-1}: 707, 1109, 1271, 1604, 1715, 2929. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 1.06 (9H, s), 1.41–1.58 (1H, m), 1.47 (3H, s), 1.66 (3H, s), 1.98–2.40 (4H, m), 2.76–2.86 (1H, m), 3.68–3.84 (2H, m), 5.11–5.18 (1H, m), 5.68 (1H, dd, J=2.6, 5.6 Hz), 6.02 (1H, ddd, J=1.0, 2.4, 5.8 Hz), 6.25 (1H, dd, J=2.8, 5.8 Hz), 7.31–7.46 (8H, m), 7.52 (1H, t, J=7.4 Hz), 7.64–7.72 (4H, m), 7.98 (2H, d, J=7.2 Hz). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 17.9, 19.2, 24.1, 25.8, 26.9, 35.4, 42.8, 45.4, 62.5, 77.2, 122.4, 127.6, 128.3, 129.1, 129.5, 129.6, 132.4, 132.7, 134.0, 135.5, 143.6. Anal. Calcd for $C_{32}H_{42}O_3Si$: C, 78.02; H, 7.86. Found: C, 77.94; H, 7.90. HREIMS calcd for $C_{32}H_{42}O_3NaSi$: 561.2801 $(M+Na)^+$, found: 561.2813.

4.1.16. Benzoic acid 4-[2-(*tert*-butyldiphenylsilanyloxy)-ethyl]-5-(2-oxoethyl)-2-cyclopentenyl ester (8). To a solution of **19** (651 mg, 1.21 mmol) in CH_2Cl_2 (10 mL) was added *m*-chloroperbenzoic acid (230 mg, 1.33 mmol) at 0 °C. After being stirred at the same temperature for 30 min, saturated aqueous sodium thiosulfate and saturated aqueous sodium hydrogen carbonate. The resulting mixture was extracted with ether and the organic layer was washed with brine and dried over $MgSO_4$. Filtration and concentration of the mixture under reduced pressure gave crude material, which was purified by silica gel column chromatography (hexane/AcOEt, 15:1) to give epoxide as a diastereomeric mixture (529 mg, 0.954 mmol) in 80% yield. Colorless oil. IR (neat) ν cm^{-1}: 702, 1110, 1271, 1714. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 1.06 (9H, s), 1.16–1.32 (6H, m), 1.34–2.13 (4H, m), {2.48–2.67 (m), 2.77–2.86 (m), 2H}, {2.80–2.94 (m), 3.02–3.16 (m), 1H}, 3.64–3.87 (2H, m), 5.66–5.82 (1H, m), {5.83–5.90 (m), 6.02–6.12 (m), 6.27 (ddd, J=2.8, 5.7, 8.2 Hz), 2H}, 7.31–7.48 (8H, m), 7.50–7.59 (1H, m), 7.62–7.71 (4H, m), 7.93–8.07 (2H, m). Anal. Calcd for $C_{32}H_{42}O_4Si$: C, 75.77; H, 7.63. Found: C, 75.53; H, 7.56. To a solution of epoxide (504 mg, 0.909 mmol) in aqueous *t*-BuOH (5 mL) was added sodium periodate (228 mg, 1.0 mmol). After being stirred at ambient temperature for 2 h, saturated aqueous sodium hydrogen carbonate was added to the reaction mixture. The resulting mixture was extracted with AcOEt and the organic layer was washed with brine and dried over $MgSO_4$. Filtration and concentration of the mixture under reduced pressure gave crude material, which was purified by silica gel column chromatography (hexane/AcOEt, 10:1) to give **8** as a diastereomeric mixture (466 mg, 0.906 mmol) in 99% yield. Colorless oil. IR (neat) ν cm^{-1}: 1109, 1270, 1715, 1731, 2932. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 1.08 (9H, s), 1.25–1.53 (1H, m), 1.65–1.88 (1H, m), {2.52–2.77 (m), 2.87–2.98 (m), 3.11–3.22 (m), 4H}, 3.62–3.83 (2H, m), {5.67 (dd, J=1.3, 6.0 Hz), 5.80 (dd, J=2.5, 5.8 Hz), 1H}, {5.86 (dt, J=1.8, 5.9 Hz), 6.01 (dd, J=1.7, 5.9 Hz), 1H}, {6.08 (dd, J=2.3, 5.9 Hz), 6.23 (dd, J=2.0, 5.9 Hz), 1H}, 7.33–7.48 (8H, m), 7.52–7.59 (1H, m), 7.63–7.71 (4H, m), 7.92–8.06 (2H, m), 9.80 (1H, br s). HREIMS calcd for $C_{32}H_{36}O_4NaSi$: 535.2281 $(M+Na)^+$, found: 535.2300.

4.1.17. *cis*-Preclavulone-A methyl ester (4). To a solution of hydroxycarbonylbutyltriphenylphosphonium bromide (1.17 g, 2.63 mmol) in THF (20 mL) was added a solution of NaHMDS (1 M in THF, 4.82 mL, 4.82 mmol) at 0 °C and the mixture was stirred at ambient temperature for 1 h. A solution of **8** in THF (5 mL) was added to the reaction mixture at 0 °C and the resulting mixture was stirred at ambient temperature for 2 h. Saturated aqueous NH_4Cl was added to the reaction mixture and the resulting mixture was extracted with AcOEt. The organic layer was washed with brine and dried over $MgSO_4$. Filtration and concentration of the mixture under reduced pressure gave crude material, which was purified by silica gel column chromatography (hexane/AcOEt, 5:1) to give carboxylic acid as a diastereomeric mixture (397 mg, 0.66 mmol) in 76% yield. Colorless oil. IR (neat) ν cm^{-1}: 707, 1111, 1272, 1713, 2930, 3069. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 1.06 (9H, s), 1.33–1.70 (3H, m), 1.79–2.48 (9H, m), {2.76–2.87 (m), 2.98–3.10 (m), 1H}, 3.63–3.85 (2H, m), 5.38–5.51 (2H, m), 5.64–5.71 (1H, m), {5.85 (dt, J=1.7, 5.8 Hz), 5.98–6.06 (m), 6.24 (dd, J=2.8, 5.8 Hz), 2H}, 7.30–7.47 (8H, m), {7.47 (1H, t, J=7.4 Hz), 7.97 (d, J=6.9 Hz), 8.00 (d, J=7.1 Hz), 7H}. Anal. Calcd for $C_{39}H_{44}O_5Si$: C, 74.72; H, 7.59. Found: C, 74.60; H, 7.56. A solution of carboxylic acid (304 mg, 0.51 mmol) in ether (20 mL) was treated with a solution of diazomethane to give methyl ester (280 mg, 0.458 mmol). Colorless oil. IR (neat) ν cm^{-1}: 702, 1109, 1270, 1713, 2931. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 1.06 (9H, s), 1.44–1.75 (3H, m), 1.82–2.50 (8H, m), {2.77–2.88 (m), 2.99–3.11 (m), 1H}, 3.64 (3H, s), 3.65–3.85 (2H, m), 5.32–5.50 (2H, m), {5.64 (br d, J=4.5 Hz), 5.68 (dd, J=2.5, 5.5 Hz), 1H}, {5.85 (td, J=1.7, 5.8 Hz), 6.02 (dd, J=1.5, 5.5 Hz), 1H}, {6.06 (dd, J=1.7, 5.8 Hz), 6.25 (dd, J=2.8, 5.8 Hz), 1H}, 7.32–7.48 (8H, m), 7.54 (1H, t, J=7.4 Hz), 7.63–7.70 (4H, m), {7.96 (d, J=8.6 Hz), 8.02 (d, J=7.5 Hz), 2H}. Anal. Calcd for $C_{40}H_{46}O_5Si$: C, 74.72; H, 7.59. Found: C, 74.79; H, 7.76. To a solution of methyl ester (25 mg, 0.04 mmol) in THF (0.5 mL) was added a solution of TBAF (1 M in THF, 0.05 mL, 0.05 mmol) at ambient temperature. After being stirred at the same temperature for 2 h, water was added to the mixture and the resulting mixture was extracted with AcOEt. The organic layer was washed with brine and dried over $MgSO_4$. Filtration and concentration of the mixture under reduced pressure gave crude material, which was purified by silica gel column chromatography (hexane/AcOEt, 2:1) to give alcohol as a diastereomeric mixture (16 mg, 0.04 mmol) in 98% yield. Colorless oil. IR (neat) ν cm^{-1}: 713, 1069, 1272, 1714, 1737, 2947, 3456. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 1.36–1.74 (4H, m), 1.82–2.13 (3H, m), 2.14–2.55 (5H, m), {2.72–2.82 (m), 2.96–3.07 (m), 1H}, {3.62 (s), 3.65 (s), 3H}, 3.58–3.85 (2H, m), 5.29–5.53 (2H, m), 5.66–5.74 (1H, m), {5.88–5.94 (m), 6.06–6.12 (m), 1H}, {6.15 (ddd, J=0.8, 2.3, 5.8 Hz), 6.36 (dd, J=2.8, 5.8 Hz), 1H}, 7.38–7.47 (2H, m), 7.55 (1H, t, J=7.4 Hz), 7.95–8.06 (2H, m). Anal. Calcd for $C_{22}H_{28}O_5$: C, 70.94; H, 7.58. Found: C, 70.91; H, 7.56. To a solution of alcohol (14.3 mg, 0.038 mmol) was added Dess–Martin periodinane (19.3 mg, 0.046 mmol) at ambient temperature and the mixture was stirred at the same temperature for 30 min. The mixture was diluted with ether and poured onto saturated aqueous sodium hydrogen carbonate. The mixture was extracted with AcOEt and the organic layer

was washed with brine and dried over $MgSO_4$. Filtration and concentration of the mixture under reduced pressure gave crude material, which was purified by silica gel column chromatography (hexane/AcOEt, 5:1) to give aldehyde as a diastereomeric mixture (14.0 mg, 0.038 mmol) in 99% yield. Colorless oil. IR (neat) ν cm^{-1}: 712, 1110, 1270, 1452, 1713, 1731, 1738, 2949. ^1H NMR (300 MHz, $CDCl_3$) δ: 1.50–1.74 (3H, m), 1.88–2.63 (7H, m), 2.66–2.87 (1H, m), {3.13–3.24 (m), 3.39–3.52 (m), 1H}, {3.62 (s), 3.65 (s), 3H}, 5.30–5.49 (2H, m), {5.66 (dd, J=1.0, 5.2 Hz), 5.68 (dd, J=1.6, 5.8 Hz), 1H}, {5.93 (dt, J=1.9, 5.8 Hz), 6.05–6.15 (m), 6.32 (dd, J=2.8, 5.8 Hz), 2H}, 7.39–7.49 (2H, m), 7.52–7.60 (1H, m), 7.95–8.06 (2H, m), {9.84 (s), 9.87 (s), 1H}. Anal. Calcd for $C_{22}H_{26}O_5$: C, 71.33; H, 7.07. Found: C, 71.02; H, 7.06. A solution of NaHMDS (1 M in THF, 1.5 mL, 1.5 mmol) was added to the suspension of hexyltriphenylphosphonium bromide (641 mg, 1.5 mmol) in THF (10 mL) at 0 °C and the mixture was stirred at ambient temperature for 1 h. Then, a solution of aldehyde (183.5 mg, 0.495 mmol) in THF (5 mL) was added to the reaction mixture at 0 °C and the mixture was stirred at ambient temperature for 2 h. Saturated aqueous ammonium chloride was added to the mixture and the mixture was extracted with AcOEt. The organic layer was washed with brine and dried over $MgSO_4$. Filtration and concentration of the mixture under reduced pressure gave crude material, which was purified by silica gel column chromatography (hexane/AcOEt, 5:1) to give benzoic acid 5-(6-methoxycarbonyl-2-hexenyl)-4-(2-octenyl)-2-cyclopentenyl ester as a diastereomeric mixture (212 mg, 0.483 mmol) in 98% yield. Colorless oil. IR (neat) ν cm^{-1}: 711, 1110, 1270, 1451, 1715, 1738, 2953. ^1H NMR (300 MHz, $CDCl_3$) δ: 0.82–0.93 (3H, m), 1.15–1.38 (6H, m), 1.49–1.74 (2H, m), 1.92–2.53 (11H, m), {2.61–2.72 (m), 2.86–2.98 (m), 1H}, {3.62 (s), 3.65 (s), 3H}, 5.28–5.54 (4H, m), {5.70 (dd, J=1.1, 5.6 Hz), 5.72 (dd, J=2.6, 5.4 Hz), 1H}, {5.89 (td, J=1.8, 5.8 Hz), 6.05 (dd, J=1.3, 5.7 Hz), 1H}, {6.08 (ddd, J=1.0, 2.3, 5.8 Hz), 6.29 (dd, J=2.8, 5.7 Hz), 1H}, 7.43 (2H, t, J=7.5 Hz), 7.56 (1H, t, J=7.4 Hz), 8.03 (2H, d, J=7.0 Hz). Anal. Calcd for $C_{28}H_{38}O_4$: C, 76.68; H, 8.73. Found: C, 76.65; H, 8.67. To a solution of benzoic acid 5-(6-methoxycarbonyl-2-hexenyl)-4-(2-octenyl)-2-cyclopentenyl ester (32 mg, 0.07 mmol) in MeOH (2 mL) was added NaOMe (58.5 mg, 0.21 mmol) at ambient temperature and the mixture was stirred at 50 °C for 10 h. Water was added to the mixture and the mixture was extracted with AcOEt. The organic layer was washed with brine and dried over $MgSO_4$. Filtration and concentration of the mixture under reduced pressure gave crude material, which was purified by silica gel column chromatography (hexane/AcOEt, 5:1) to give alcohol as a diastereomeric mixture (21.2 mg, 0.062 mmol) in 88% yield. Colorless oil. IR (neat) ν cm^{-1}: 702, 1109, 1270, 1715, 1736, 2930, 3404. ^1H NMR (300 MHz, $CDCl_3$) δ: 0.88 (3H, t, J=6.6 Hz), 1.11–1.79 (10H, m), 1.79–2.40 (10H, m), {2.54–2.65 (m), 2.75–2.86 (m), 1H}, 3.67 (3H, s), 4.47–4.52 (1H, m), 5.25–5.60 (4H, m), {5.78 (dt, J=1.5, 5.7 Hz), 5.97 (ddd, J=1.3, 2.4, 5.8 Hz), 1H}, {5.95 (br d, J=5.7 Hz), 6.12 (dd, J=2.7, 5.8 Hz), 1H}. To a solution of alcohol (32 mg, 0.096 mmol) in CH_2Cl_2 (2 mL) was added MnO_2 (83.5 mg, 0.96 mmol) at ambient temperature and the mixture was stirred at the same temperature for 2 days. The mixture was filtered and the filtrate was concentrated under vacuum. The residue was purified by silica gel column chromatography (hexane/AcOEt, 5:1) to give **4**[5] (30 mg, 0.091 mmol) in 95% yield. Colorless oil. $[\alpha]_D^{24}$ −165.8 (*c* 0.13, $CHCl_3$), $[\alpha]_D^{24}$ −135.3 (*c* 0.13, THF).

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