Synthesis of (±)-Methyl Tuberonate, a Potato Tuber-forming Substance, and Its Epimer

Hiromasa Kiyota, Daisuke Nakashima, and Takayuki Oritani

Laboratory of Applied Bioorganic Chemistry, Division of Life Science, Graduate School of Agricultural Science, Tohoku University, 1-1 Tsutsumidori-Amamiyamachi, Aoba-ku, Sendai 981-8555, Japan

Received June 23, 1999; Accepted August 26, 1999

Methyl esters of (±)-tuberonic acid and (±)-12-hydroxyjasmonic acid (trans-tuberonic acid), the aglycons of strong potato tuber-forming substances, were synthesized from norbornene via side-chain elongation and Baeyer-Villiger oxidation as key steps.

Key words: methyl tuberonate; methyl 12-hydroxyjasmonate; jasmonic acid; potato tuberization; total synthesis

Tuberonic acid (TA, 1, Fig. 1), tuberonic acid glucoside (TAG, 2), and its methyl ester (3) were isolated from the leaves of potato (Solanum tuberosum L.) as tuber-forming substances. In addition, epimers of this tuberonate, derivative 7 (from Perilla frutescens) and 8 (from Jerusalem artichoke, Helianthus tuberosus L.) were isolated. TA and TAG are biosynthesized from the plant hormone-like substance, epijasmonic acid (EpiJA, 5), in potato leaves, and EpiJA showed similar potato tuber-forming activity to that of TA. On the contrary, TA had no plant growth inhibitory activity like EpiJA. So far, only one study has reported the synthesis of TA derivatives. Kitahara et al. have recently synthesized both the enantiomers of 3 and its aglycon, methyl tuberonate (4, natural jasmonoids are usually synthesized as their methyl esters to avoid autoepimerization by their own acidity). As for the 12-hydroxyjasmonate (trans-tuberonic) series, Gerlach and Künzler and Kitahara et al. have reported the synthesis of acid derivative 6 as the synthetic intermediate of jasmine ketolactone (10). We describe here new syntheses of racemic methyl tuberonate (4) and methyl 12-hydroxyjasmonate (9).

Synthesis

As shown in Scheme 1, our synthesis of methyl tuberonate (4) started from norbornene. The conversion of norbornene to dichlorinated bicyclic compound 11 was accomplished by following the procedures of Fritz et al. and Seto and Yoshioka that were used for the synthesis of (±)-methyl epijasmonate. The hydroxy group of 11 was protected as a tetrahydropyranyl (THP) ether to give 12. We then tried subsequent elongation of the side chain. Treatment of 12 with 3 equivalents of butyllithium produced an acetylenic anion, which was trapped with methyl iodide to give propynyl compound 13. Transfer of the inner triple bond of 13 to the end of the side chain was done by the acetylene zipper reaction; however, the C-7 position was partially epimerized (14). Synthesis of anti-16 (15). The acetylene zipper reaction on this hydroxyl compound successfully afforded syn-16 in an 83% yield accompanied with a small amount of anti-16 (12%). The stereochemistry of these compounds was determined by a 1H-NMR analysis: the chemical shift of the 8-protons of syn-16 was more deshielded by the nearby hydroxy group (δ=2.51 and 2.54 ppm) than that of anti-16 (δ=2.14 ppm). The hydroxyl group of syn-16 was then protected with an ethoxethyl (EE) group to afford syn-17. Subsequent elongation of the side chain of syn-17 with THP-protected ethylene bromohydrin and deprotection of both the THP and EE groups gave syn-18 in a 79% yield. The primary hydroxyl group of syn-18 was selectively protected as a tert-butyldiphenylsilyl (TBDPS) ether (syn-19), and the secondary hydroxyl group was oxidized with Dess-
Synthesis of (±)-Methyl Tuberonate


a) DHP, TsOH, CH₂Cl₂ (93%). b) BuLi, MeI, THF (97%). c) Li₃H₂NC₂H₅, teri-BuOK, H₂NCH₂CH₂NH₂ (90%), 7-syn/7-anti = 54:36. d) TsOH, MeOH—H₂O (quant.), e) i. Li₃H₂NC₂H₅, teri-BuOK, H₂NCH₂CH₂NH₂; ii. Separation (83% of syn-16 and 12% of anti-16). f) Ethyl vinyl ether, PPTS, CHCl₃ (99%). g) i. BuLi, THF-HMPA, Br(CH₂)₂OTHP. b) TsOH, MeOH (79% of syn-18 and 21% of recovered syn-16). i) TBDDS, imidazole, DMF (83%). j) Dess-Martin periodinane (90%). k) MCPBA, NaHCO₃, K₂CO₃, CHCl₃ (63%); 74% of syn-20, 2-oxa/3-oxa = 1:1.

Martin periodinane⁵⁵ to give bicyclic ketone syn-20 in a 90% yield.

The regioselectivity of the Baeyer-Villiger oxidation of syn-20 with m-chloroperbenzoic acid (MCPBA) was low (2-oxa/3-oxa = 1:1), because in the 7-syn-substituted norbornan-2-one system, the transition state of the energy of migration of the C-3 methylene carbon was lower than that of the C-1 bridgehead carbon.⁶⁶ We tried several reagents such as magnesium monopropaalate (MMPP), peracetic acid, performic acid, oxone⁶⁷, urea hydrogen peroxide and alkali hydrogen peroxide; however, the ratio did not exceed 1:1. However, in the case of its 7-epimer anti-20, the selectivity was good (2-oxa/3-oxa = 6:1) by using MCPBA. The resulting regioisomeric lactone mixture of syn-21 was inseparable, so the regioisomers were separated after methanalysis of the lactone rings. Hydrogenation of the triple bond of syn-22 gave syn-23 with a Z-double bond. Dess-Martin oxidation of the hydroxyl group afforded syn-24. Finally, the TBDPS group was removed with HF at -20°C according to Shibasaki’s procedure⁷⁷ to give (±)-methyl tuberonate (4). However, the α-position of the keto carbonyl group was slightly epimerized (ca. 86% de), due to the strong acidity of HF required to remove the highly acid-resistant TBDPS group. Therefore, we changed the protection to a trimethylsilyl (TMS) group. The TBDPS group of syn-23 was removed with tetrabutyrammonium fluoride (TBAF) to give diol syn-25 (76%). The primary hydroxy group of syn-25 was selectively protected with diethyl(trimethyl)silyl)amine⁷⁸ in acetone at -40°C to afford syn-26. This was then subjected to Dess-Martin oxidation, but the TMS group was deprotected under the conditions used. In this case, rapid and selective conversion was done with a tetrabutyrammonium peroxynitrite (TPAP)⁷⁹ catalyst to give syn-27. Finally, the TMS group was removed with pyridinium poly(hydrogen fluoride) (HF·pyridine) at -40°C without any epimerization of the 7-position to give pure (±)-methyl tuberonate (ca. 98% de, estimated by a ¹H-NMR analysis, Fig. 2) in a 92% yield from syn-25. The total yield was 10.5% in 15 steps from 12. The ¹H- and ¹³C-NMR data for 24 agree with those reported⁸⁰ and were characterized with ¹H- and ¹³C COSY experiments.

The synthesis of (±)-methyl 12-hydroxyjasmonate [(±)-methyl trans-tuberonate, 9] was accomplished in a manner similar to that described for 4 from anti-16 (9.3% from 12). The ¹H- and ¹³C-NMR data for 24 were in good accordance with those for its glucoside 8.⁸¹

In summary, diastereoselective syntheses of (±)-methyl tuberonate (4, ca. 98% de) and (±)-methyl 12-hydroxyjasmonate [(±)-methyl trans-tuberonate, 9] were achieved from norbornene via side-chain elongation and Baeyer-Villiger oxidation as key steps.
Scheme 2. Syntheses of Methyl Tuberone and Methyl 12-Hydroxyjasmonate.

a) MeONa, MeOH, separation (50%). b) H2, Pd-BaSO4, quinoline, MeOH (92%). c) Dess-Martin periodinate (90%). d) HF, H2O-CH3CN (quant.). e) TBAF, THF (76%). f) TMSNCS, acetone, −40°C. g) TPAP, NMO, MS4A, CH2Cl2. h) HF-Pyridine, THF, −40°C, 5 min (92% from syn-25). i) TBAF, THF (quant.).

Experimental

All melting point (mp) and boiling point (bp) data are uncorrected. IR spectra were recorded as films by a Jasco IR-810 spectrometer. 1H- and 13C-NMR spectra were recorded with a Jeol JNM GSX-270 (270 MHz for 1H and 68.0 MHz for 13C), Varian Gemini 2000 (300 MHz for 1H), Jeol GSX-400 (400 MHz for 1H), Varian Unity Inova 500 (500 MHz for 1H) and Varian Unity Inova 600 (151 MHz for 13C) spectrometers in CDCl3 unless otherwise noted, using tetramethylsilane as an internal standard. Mass spectra were recorded with a Jeol JMS-HX-105 and Jeol JMS-700 spectrometers. Merck silica gel 60 (70–230 mesh) and Kanto silica gel 60N (spherical, neutral, 70–140 mesh) were used for column chromatography, while Merck silica gel 60 F254 was used for preparative TLC.

(1S*, 2S*, 4S*, 7R*)-7-(1-Propynyl)-2-(2RS)-tetrahydropyran-2-ylhydrobicyclo[2.2.1]heptane (13). To a solution of 12 (11.5 g, 39.5 mmol) in THF (100 ml) was added dropwise a solution of BuLi in hexane (1.56 M, 80.0 ml, 120 mmol) at −70°C under argon, and the mixture was stirred for 1 h at this temperature. To this mixture was added a solution of MeI (5.0 ml, 11.4 g, 80 mmol) in THF (20 ml), and the resulting mixture was allowed to warm to room temperature. The reaction mixture was poured into a sat. aq. NH4Cl soln. and extracted with Et2O. The organic layer was successively washed with H2O and brine, dried with MgSO4 and concentrated in vacuo. The residue was chromatographed on silica gel (hexane/EtOAc=100:1–30:1) to give 13 (8.82 g, 98%) as a pale yellow oil. This oil was further purified by distillation, bp 140–142°C at 1 torr. IR v max cm−1: 3050 (w, vinylic H), 1615 (m, C=O), 1130 (s), 1115 (s), 1080 (s), 1035 (s), 1020 (s), 875 (s, vinylic H), 650 (m, C=Cl). NMR δH (400 MHz): 1.05–1.15 (2H, m), 1.5–1.9 (10H, m), 2.2–2.6 (3H, m), 3.50 (1H, m), 3.75 (1H, m), 3.86 (1H, m), 4.61 (1H, m, O–CH=O), 6.3–6.5 (1H, m, 8-H). HREIMS m/z (M+H): calcld. for C17H23O2Cl2, 291.092; found, 291.092.
(2H, m), 2.35–2.5 (2H, m), 3.45–4.15 (3H, m), 4.65–
4.75 (1H, m, O–CH–O). EIMS m/z: 234 (M+), 219
(M+−H2O), 133 (M+−OHPP). HREIMS m/z (M+):
calced. for C13H23O6, 234.162; found, 234.160.

(1S*, 2S*, 4S*, 7R*)-7-[(2-Propynyl)bicyclo[2.2.1]heptan-2-ol (1S)]. A solution of 13 (20.7, 88.2 mmol) and p-toluenesulfonic acid (TsOH, 30 mg) in MeOH–H2O (1/3, 150 mL) was stirred at room temperature for 12 h. To the reaction mixture was added a sat. aq. NaHCO3
solv. before it was concentrated in vacuo. The residue was extracted with EtOAc (3 times), and the combined extract was washed with brine, dried with MgSO4 and concentrated in vacuo. The residue was chromatographed on silica gel (hexane/EtOAc=10:1) to give 15 (13.2 g, 88.2 mmol, quant.) as a colorless oil. This oil gradually crystallized upon standing, and was recrystallized from hexane at −40°C, mp 44−45°C. IR ν max cm−1: 3550 (s, O−H), 1080 (s), 1045 (m), 1020
(m). NMR δH (270 MHz): 1.06 (2H, m), 1.52 (2H, m), 1.81 (3H, d, J=2.7 Hz), 1.89 (2H, m), 2.29 (1H, m), 2.32 (2H, m), 2.80 (1H, d, J=12 Hz, OH), 3.69 (1H, m). EIMS m/z: 149 (M−H), 133 (M+H−H2O), 117
(M+−H−CH3). HREIMS m/z (M+−H): calcd. for C10H13O4: 144.099; found, 149.097; m/z (M+H−H2O): calced. for C10H13O3: 133.102; found, 133.102.

(1S*, 2S*, 4S*, 7R*)-7-[(2-Propynyl)bicyclo[2.2.1]heptan-2-ol (syn-16) and its (7S*)-isomer (anti-16). 1,3-Di-
aminopropane (170 mL) was added to Li (3.9 g, 560 mg atom) under argon, and the mixture was stirred at 70°C for 4 h until its blue color had disappeared and a white suspension of lithium amide had been formed. The mixture was cooled to 0°C and to this was added tert-BuOK (21.3 g, 190 mmol) in one. The color of the solution then turned yellow. After the reaction mixture had been stirred for 30 min, to this was added 15 (13.2 g, 87.9 mmol) in one portion. The color of this mixture changed to dark red. The reaction mixture was stirred for 12 h and poured into an ice−H2O mixture, before being extracted with EtO (3 times). The organic layer was successively washed with dil. HCl (5 times), a sat. aq. NaHCO3 soln. and brine, dried with MgSO4 and concentrated in vacuo. The residue was chromatographed on silica gel (hexane/EtOAc=10:1) to give colorless oils of syn-16 (10.9 g, 83%) and its (7S*)-isomer anti-16 (1.56 g, 12%).

Syn-16: IR ν max cm−1: 3350 (s, O−H), 3210 (C=O), 1090 (s, C=O), 1055 (m), 1010 (m), 980
(m) 630 (m). NMR δH (300 MHz): 1.04 (1H, m), 1.08
(1H, m), 1.45−1.8 (3H, m), 1.77 (1H, dd, J=13.3, 7.0
Hz), 1.85 (2H, t, J=8.1 Hz), 1.96 (1H, t, J=2.7 Hz, C=CH), 2.14 (1H, m), 2.20 (1H, m), 2.51 (1H, dd, J=2.7, 0.8 Hz, 8-H), 2.54 (1H, dd, J=2.7, 1.1 Hz, 8-H), 3.86 (1H, ddd, J=7.3, 3.2, 1.0 Hz, 2-H). HREIMS m/z (M+−H): calcd. for C11H13O: 149.097; found, 149.093.

Anti-16: IR ν max cm−1: 3300 (s, C=H), 2120
(C=O), 1090 (s, C=O), 1055 (m), 1010 (m), 980
(m) 630 (m). NMR δH (270 MHz): 1.04 (1H, m), 1.06 (1H, m), 1.41 (1H, m), 1.51 (1H, br. s, OH), 1.60 (2H, m), 1.73 (1H, dd, J=13.2, 7.1 Hz), 1.95 (1H, dd, J=2.7, 2.4 Hz,
C=CH), 2.03 (1H, m), 2.11 (1H, m), 2.14 (2H, m, 8-H), 2.21 (1H, m), 3.79 (1H, dd, J=7.3, 2.2 Hz, 2-H). HREIMS m/z (M+−H): calcd. for C10H13O, 149.097; found, 149.095.

(1S*, 2S*, 4S*, 7R*)-2-[(1RS)-1-Ethoxyethyl]oxy-7-(2-propynyl)bicyclo[2.2.1]heptane (syn-17). To a solution of syn-16 (2.11 g, 14.0 mmol) and pyridinium p-toluenesulfonate (PPTS, 20 mg, 0.08 mmol) in dry CHCl3 (20 mL) was added ethyl vinyl ether (1.3 g, 18 mmol) at 0°C, and the mixture was stirred at room temperature for 12 h. After the reaction had been quenched by adding a sat. aq. NaHCO3 soln., the organic layer was separated, dried with MgSO4 and concentrated in vacuo. The residue was chromatographed on silica gel (hexane/ EtO=20:1) to give syn-17 (3.07 g, 99%) as a colorless oil. IR ν max cm−1: 3300 (m, C=H), 2110 (w, C=O), 1190 (m), 1115 (s), 1075 (s), 1060 (m), 990 (m), 620 (m). NMR δH (300 MHz): 1.0−1.25 (3H, m), 1.15−1.3 (3H, m), 1.5−1.9 (7H, m), 2.1−2.3 (2H, m), 2.4−2.5 (3H, m), 3.4−3.9 (3H, m), 4.6−4.8 (1H, m, O−CH−O). FABMS (NOBA + hexane + PEG) m/z: 177 (M+H−C2H5OH), 149 (M+−C2H5OH−C2H4OH), 133 (M+−C2H5O−C2H4OH). HRFABMS (NOBA + hexane + PEG) m/z (M+H− EEOH): calcd. for C14H22O5, 332.102; found, 332.10.1.1.

(1S*, 2S*, 4S*, 7R*)-7-[(5-Hydroxy-2-pentynyl)bicyclo[2.2.1]heptan-2-ol (anti-17). In the same manner as that described for syn-17, anti-17 (5.08 g,
33.8 mmol) was converted to anti-17 (6.20 g, 83%). IR ν max cm−1: 3310 (m, C=H), 2120 (w, C=O), 1120 (s), 1080 (s, C=O). NMR δH (300 MHz): 0.95−1.1 (2H, m), 1.18 and 1.19 (total 3H, each t, J=7.0 Hz, CH2CH2), 1.24−1.3 (3H, m), 1.4−1.9 (6H, m), 2.10 (m, 2H), 2.3−2.5 (2H, m), 3.45 (1H, m, 3-H), 3.55−3.7 (2H, m, CH2O), 4.68 (1H, m, O−CH−O). EIMS m/z: 222 (M+), 207 (M+−CH3), 193 (M+−C2H5), 177 (M+−C2H3O), 149 (M+−C2H5O−C2H4OH), 133 (M+−C2H5O−C2H3O). HREIMS m/z (M+): calcd. for C14H22O5, 222.162; found, 222.163.

Synthesis of (+)-Methyl Tuberonate 2113

A mixture of the above-mentioned oil and a catalytic amount of TsOH in MeOH (40 mL) was stirred for 12 h
at room temperature. To this reaction mixture was added a sat. aq. NaHCO₃ soln., and the resulting mixture was concentrated in vacuo. The residue was extracted with EtOAc. The organic layers were combined and washed with brine, dried with MgSO₄ and concentrated in vacuo. The residue was chromatographed on silica gel (hexane/EtOAc = 5:1) to give syn-18 (1.78 g, 9.16 mmol; 79%); quantitative yield taking into account recovered syn-16) and recovered syn-16 (0.36 g, 21%) as a colorless oil. IR ν max cm⁻¹: 3350 (s, O—H), 1080 (m), 1040 (s, C—O), 1000 (w), 980 (w). NMR δH (270 MHz): 1.05 (2H, m), 1.5—1.6 (2H, m), 1.68 (1H, m), 1.76 (1H, dd, J = 13.2, 7.1 Hz), 1.79 (1H, t, J = 7.9 Hz), 2.00 (2H, br, s, OH), 2.15 (2H, m), 2.46 (2H, m), 3.69 (2H, t, J = 6.0 Hz, CH₂OH), 3.84 (1H, dd, J = 7.1, 3.3, 1.0 Hz, 2-H). EIMS m/z: 194 (M⁺), 176 (M⁺ — H₂O). HREIMS m/z (M⁺): calcld. for C₁₆H₁₅O₂, 194.131; found, 194.128. 

(18S, 2S*, 4S*, 7S*)-7-(5-Hydroxy-2-pentenyl) bicyclo[2.2.1]heptan-2-ol (anti-18). In the same manner as that described for syn-18, anti-17 (2.2 g, 10.0 mmol) was converted to anti-18 [0.599 g, 3.08 mmol, 31%; 40% taking into account recovered anti-16 (0.350 g, 2.33 mmole)]. IR ν max cm⁻¹: 3350 (s, O—H), 1080 (m), 1040 (s, C—O), 1000 (m), 920 (w), 850 (w). NMR δH (270 MHz): 1.05 (2H, m), 1.42 (2H, m), 1.48 (1H, br, OH), 1.57 (2H, m), 1.72 (1H, dd, J = 13.2, 7.1 Hz), 1.80 (1H, br, s, OH), 2.00 (1H, br, d, J = 3.4 Hz), 2.10 (2H, m), 2.17 (1H, m) 2.44 (2H, tdd, J = 6.1, 2.4, 2.2 Hz), 3.69 (2H, t, J = 5.9 Hz, CH₂OH), 3.78 (1H, dd, J = 7.1, 2.2 Hz, 2-H). EIMS m/z: 194 (M⁺), 176 (M⁺ — H₂O). HREIMS m/z (M⁺): calcld. for C₁₆H₁₅O₂, 194.131; found, 194.130.

(1S*, 2S*, 4S*, 7R*)-7-(5-[(tert-Butyldiphenylsilyl)oxy]-2-pentenyl)bicyclo[2.2.1]heptan-2-ol (syn-19). To a solution of syn-18 (7.84 mg, 40.4 mmol) and imidazole (3.4 g, 50 mmol) in dry DMF (40 ml) was added TBDPSI (12 ml, 45 mmol) at 0°C. The mixture was stirred at this temperature for 2 h and at room temperature for 12 h. The reaction mixture was poured into H₂O and extracted twice with Et₂O. The organic layer was washed with brine, dried with MgSO₄ and concentrated in vacuo. The residue was chromatographed on silica gel (hexane/EtOAc = 10:1) to give syn-19 (14.5 g, 33.5 mmol, 83%) as a colorless oil. IR ν max cm⁻¹: 3350 (m, O—H), 3070 (w, Ar—H), 3050 (w, Ar—H), 1420 (m, Si—Ph), 1100 (m, Si—O), 740 (m), 700 (s). NMR δH (270 MHz): 1.02 (2H, m), 1.05 (9H, s, tert-But), 1.35 (2H, m), 1.51 (2H, m), 1.70 (1H, dd, J = 13.1, 7.2 Hz), 1.95 (1H, m, OH), 2.11 (4H, m), 2.43 (2H, tdd, J = 7.0, 2.4, 2.0 Hz), 3.74 (2H, t, J = 7.1 Hz, CH₂OSi), 3.75 (1H, m, 2-H), 7.35—7.45 (6H, m, arom. H). Anal. Found: C, 77.46; H, 8.10%. Calcld. for C₂₈H₃₆O₃Si: C, 77.73; H, 8.39%.

(1S*, 2S*, 4S*, 7S*)-7-(5-[(tert-Butyldiphenylsilyl)oxy]-2-pentenyl)bicyclo[2.2.1]heptan-2-ol (anti-19). In the same manner as described for syn-19, anti-18 (270 mg, 1.5 mmol) was converted to anti-19 (610 mg, 96%) as a colorless oil. IR ν max cm⁻¹: 3350 (m, O—H), 3070 (w, Ar—H), 3050 (w, Ar—H), 1420 (m, Si—Ph), 1100 (m, Si—O), 740 (m), 700 (s). NMR δH (270 MHz): 1.02 (2H, m), 1.05 (9H, s, tert-But), 1.35 (2H, m), 1.51 (2H, m), 1.70 (1H, dd, J = 13.1, 7.2 Hz), 1.95 (1H, m, OH), 2.11 (4H, m), 2.43 (2H, tdd, J = 7.0, 2.4, 2.0 Hz), 3.74 (2H, t, J = 7.1 Hz, CH₂OSi), 3.75 (1H, m, 2-H), 7.35—7.45 (6H, m, arom. H), 7.65—7.75 (4H, m, arom. H). Anal. Found: C, 77.46; H, 8.10%. Calcld. for C₂₈H₃₆O₃Si: C, 77.73; H, 8.39%.

(1S*, 4S*, 7R*)-7-(5-[(tert-Butyldiphenylsilyl)oxy]-2-pentenyl)bicyclo[2.2.1]heptan-2-one (syn-20). To a solution of syn-19 (1.0 g, 2.3 mmol) in CH₂Cl₂ (10 ml) was added Dess-Martin periodinane (1.3 g, 2.9 mmol) at room temperature. After the reaction mixture had been stirred for 2 h, it was filtered through a Celite pad. The filtrate was concentrated in vacuo. The residue was chromato-}

...
Methyl (1S*, 2R*, 3S*)-2-[(2Z)-5-[(tert-Butylidiphenylsilyl)oxy]-2-pentenyl]-3-hydroxycyclopentanecacetate (anti-23). In the same manner as that described for syn-23, anti-22 (43 mg, 0.090 mmol) gave anti-23 (40 mg, 92%). IR ν max cm⁻¹: 3500 (s, O=H), 3070 (w, C–H), 3010 (w, C–H), 2915 (m, C–H), 1635 (s, CHO), 1540 (m, C=O), 1250 (m, C–O), 1240 (m, C–C), 1170 (m, C–O), 1130 (m, C–H), 1070 (m, C–O), 1030 (m, C–H). FABMS (NOBA + NaCl) m/z: 503 (M⁺ + Na), 481 (M⁺ + H), 424 (M⁺ + H – tert- Bu). HR FABMS (NOBA + NaCl) m/z (M⁺ + Na): calcd. for C₅₂H₅₀O₂SiNa, 503.259; found, 503.260.

Methyl (1S*, 2R*, 2S*, 3S*)-2-[(2Z)-5-[(tert-Butylidiphenylsilyl)oxy]-2-pentenyl]-3-oxycyclopentanecacetate (syn-24). To a solution of syn-23 (40 mg, 0.083 mmol) in CH₂Cl₂ (5 ml) was added Dess-Martin periodinane (45 mg, 2.9 mmol) at room temperature, and this mixture was stirred for 2 h. The reaction mixture was filtered through a Celite pad, and the filtrate was concentrated in vacuo. The residue was purified by preparative TLC (hexane/EtOAc=4:1) to give syn-24 (35 mg, 88%) as a colorless oil. IR ν max cm⁻¹: 3070 (w, Ar-H), 3050 (w, Ar-H), 2915 (m, C–H), 1735 (s, C=O), 1585 (w, C=C), 1425 (m, Si=Ph), 1110 (m, C–O). NMR δH (270 MHz): 1.05 (9H, t, J=6.6 Hz, CH₂O–Si), 0.86 (1.4H, d, J=12.0 Hz, 4-H of 3-oxa-isomer), 2.45 (2H, d, J=12.0 Hz, 4-H of 3-oxa-isomer), 4.25 (2H, t, J=7.1 Hz, CH₂OH), 4.02 (1H, m), 3.73–7.45 (6H, m, arom. H), 7.65–7.75 (4H, m, arom. H). HR FABMS (NOBA + NaCl) m/z (M⁺ + Na): calcd. for C₅₂H₅₀O₂SiNa, 503.244; found, 503.244.

Methyl (1S*, 2R*, 3S*)-2-[(2Z)-5-[(tert-Butylidiphenylsilyl)oxy]-2-pentenyl]-3-hydroxycyclopentanecacetate (anti-22). In the same manner as that described for syn-22, anti-21 (480 mg, 1.1 mmol) gave anti-22 (450 mg, 86%).
Methyl (1S, 2S)-2-[(2Z)-5-[(tert-Butyldiphenylsilyl)oxyl-2-pentenyl]-3-oxocyclopentanecarboxylate (anti-24). In the same manner as that described for syn-23, anti-23 (38 mg, 0.079 mmol) gave anti-24 (35 mg, 0.073 mmol, 92%) as a colorless oil. IR ν max cm⁻¹: 3070 (w, Ar-H), 3050 (w, Ar-H), 3020 (w, vinylic H), 1740 (s, C=O), 1425 (m, Si-Ph), 1110 (s). NMR δH (270 MHz): 1.04 (9H, s, tert-Bu), 1.75-2.45 (11H, m), 2.71 (1H, m), 3.66 (2H, t, J=7.6 Hz), 3.67 (3H, s, OMe), 5.39-5.51 (2H, m, CH=CH), 7.35-7.45 (6H, m, arom H), 7.65-7.75 (4H, m, arom H).

Methyl (1S*, 2S*)-2-[(2Z)-5-[(trimethylsilyloxy)-2-pentenyl]cyclopentanecarboxylate (syn-26). To a solution of syn-25 (25.7 mg, 0.106 mmol) in dry acetone (2 ml) was added diethyl(trimethylsilylamine) (0.44 ml, 0.34 g, 2.3 mmol) at -45°C under argon. The progress of the reaction was monitored by TLC (silica gel, hexane-EtOAc=4:1). After the reaction mixture had been stirred for 10 h at this temperature, TLC showed a mono-TMS ether (Rf=0.50), no starting material and no bis-TMS ether. The solution was then diluted with 4 ml of dry ether that had been previously cooled to -45°C. The resulting mixture was successively washed with a sat. aq. NaHCO₃ soln. and brine, dried with MgSO₄ and concentrated in vacuo to give syn-26 as a colorless oil (32.7 mg, 98%). This crude oil was found to be practically pure by its ¹H-NMR spectrum, so this was used in the next step without further purification. Part of the sample was analyzed. IR ν max cm⁻¹: 3470 (s, O=H), 3010 (w, vinylic H), 3010 (w, vinylic H), 1735 (s, C=O), 1435 (m, Si-CH₃), 1250 (s, Si-CH₃), 1090 (s, Si-O), 840 (s, Si-CH₃). NMR δH (500 MHz): 0.12 [9H, s, (CH₃)₃Si], 1.60 (1H, m), 1.69 (1H, m), 1.75-1.95 (5H, m), 2.12 (1H, m), 2.37-2.51 (4H, m), 2.61 (1H, m), 3.56 (1H, dt, J=4.4, 9.5 Hz, CH₂OSi), 3.66 (3H, s, OMe), 3.68 (1H, dt, J=4.4, 9.8 Hz, CH₂OSi), 4.10 (1H, m, 3-H), 5.34 (1H, br, dt, J=4.9, 11.0 Hz, CH=), 5.50 (1H, br, dt, J=5.1, 11.0 Hz, CH=). FABMS (NOBA+PEG+CHCl₃) m/z: 315 (M⁺+H), 226 [M⁺+2H-(CH₃)₂SiOH], 207 [M⁺+H-(CH₃)₂SiOH-H₂O], 154, 136, 133, 73. HRFBAMS (NOBA+PEG+CHCl₃) m/z (M⁺+H): calcd. for C₁₈H₃₀O₃SiNa, 315.199; found, 315.200.

Methyl (1S*, 2R*, 3S*)-3-Hydroxy-2-[(2Z)-5-[(trimethylsilyloxy)-2-pentenyl]cyclopentanecarboxylate (syn-27). A solution of crude syn-26 derived from 10.6 mg (43.7 μmol) of syn-25, TPAP (2 mg, 6 μmol), N-methylmorpholine N-oxide (NMO, 17 mg, 150 μmol) and 4 Å molecular sieves (MS4 Å, 60 mg) in CH₂Cl₂ (1 ml) was stirred for 30 min at 30°C. The reaction mixture was filtered through a silica gel pad, and the resulting filtrate was concentrated in vacuo. As the 2-position was highly prone to isomerization, syn-27 was used in the final step without further purification.

Methyl (1S*, 2R*, 3S*)-2-[(2Z)-5-[(trimethylsilyloxy)-2-pentenyl]cyclopentanecarboxylate (Methyl Tuberonate, Methyl 12-Hydroxyepipiasmonate, 4). To a solution of above-mentioned crude syn-27 in THF (1 ml) was added pyridinium poly(hydrogen fluoride) (0.1 ml) at -45°C, and this mixture was stirred for 5 min. The reaction mixture was diluted with Et₂O, successively washed three times with a sat. aq. NaHCO₃ soln. and brine, dried with MgSO₄ and concentrated in vacuo. The residue was purified by flash chromatography on neutral silica gel
(hexane/EtOAc=1:1) to give methyl tuberone (4, 9.7 mg, 92%) as a colorless oil with an orange-like odor. IR ν max cm⁻¹: 3450 (s, O–H), 3000 (w, C=O), 2950 (m), 2880 (m), 1735 (s, C=O), 1435 (m), 1405 (m), 1380 (w), 1340 (w), 1330 (w), 1260 (w), 1195 (m), 1160 (m), 1050 (m), 980 (w). NMR δH (500 MHz). IH positions were shown by jasmonate numbering: Fig. 1): 1.82 (1H, ddt, J=13.4, 7.8, 5.6 Hz, H-4), 2.02–2.07 (1H, m, H-4), 2.08–2.12 (1H, m, H-8), 2.16 (1H, dd, J=15.8, 9.9 Hz, H-2), 2.20–2.29 (2H, m, H-5), 2.33 (2H, pseudo quintet, H-11), 2.37–2.43 (2H, m, H-7 and H-8), 2.44 (1H, dd, J=15.8, 5.6 Hz, H-2), 2.85 (1H, pseudo septet, H-3), 3.67 (2H, t, J=6.3 Hz, H-12), 3.70 (3H, s, OMe), 5.47 (1H, ddt, J=10.8, 7.3, 1.5 Hz, H-10), 5.55 (1H, ddt, J=10.8, 6.6, 1.5 Hz, H-9). δC (151 MHz). 13C positions were shown by jasmonate numbering: Fig. 1): 23.2 (C-8), 25.7 (C-4), 30.9 (C-11), 33.9 (C-2), 35.4 (C-5), 35.8 (C-3), 51.8 (OMe), 52.5 (C-7), 62.0 (C-12), 127.5 (C-10), 129.5 (C-9), 172.9 (C-1), 219.1 (C-6). EIMS m/z: 240 (M⁺), 222 (M⁺ – H₂O), 210, 192, 167, 156, 149. HREIMS m/z (M⁺): calcd. for C₁₃H₉O₅, 240.136; found, 240.137.

Acknowledgment

Financial support by grant-aid from Japanese Ministry of Education, Science, Culture and Sport is acknowledged.

References


