Asymmetric Total Syntheses of (+)-Cheimonophyllon E
and (+)-Cheimonophyllal

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$(1R,6R,8S)-8-[(1R)- (22) and (1S,6S,8R)-8-[(1S)-1-[(2S)-2-Acetoxy-2-
phenylacetoxyl]-3-methylbutyl]-3-methyl-7-methylene-9-oxabicyclo[4.3.0]non-2-
ene (23). To a cooled (0 °C) stirred solution of rac-7 (231 mg, 0.979 mmol) in CH$_2$Cl$_2$ (5 mL)
were added (S)-O-acetylmandelic acid (476 mg, 2.45 mmol), Et$_3$N (0.34 mL, 2.4 mmol), 4-
DMAP (36.2 mg, 0.296 mmol), and WSC-HCl (469 mg, 2.45 mmol). The mixture was stirred for
1.5 h, diluted with Et$_2$O (25 mL), and washed with 0.05 M aqueous HCl (25 mL x 2), 0.05 M
aqueous NaOH (25 mL x 2), and H$_2$O (25 mL), successively. The organic layer was dried and
concentrated in vacuo. The residue was purified by column chromatography on silica gel
(EtOAc:hexane, 1:18) to provide 187 mg (46%) of 22 and 190 mg (47%) of 23. Compound 22
was obtained as a colorless oil: TLC \( R_f 0.60 \) (EtOAc:hexane, 1:4); \([\alpha]_D^{22} +115 \) (c 4.69, CHCl\(_3\)); IR 1760, 1750, 1670 cm\(^{-1}\); \(^1\)H NMR \( \delta 0.61 \) (d, 3 H, \( J = 6.6 \) Hz), 0.62 (d, 3 H, \( J = 6.6 \) Hz), 0.90 (m, 1 H), 1.13 (m, 1 H), 1.52-1.81 (m, 4 H), 1.66 (s, 3 H), 2.01 (m, 1 H), 2.19 (s, 3 H), 2.73 (m, 1 H), 4.51 (m, 1 H), 4.54 (m, 1 H), 5.00-5.05 (m, 3 H), 5.42 (s, 1 H), 5.95 (s, 1 H), 7.32-7.40 (m, 3 H), 7.42-7.50 (m, 2 H); \(^{13}\)C NMR \( \delta 20.8, 21.2, 23.2, 23.5, 23.8, 23.9, 26.1, 37.6, 40.7, 74.7, 76.2, 76.3, 80.4, 106.3, 121.4, 127.8 x 2, 128.7 x 2, 129.2, 134.1, 139.3, 150.2, 168.9, 170.3; HRMS calcd for \( C_{25}H_{32}O_5 \) (M\(^+\)) \( m/z \) 412.2250, found 412.2250. Compound 23 was obtained as white crystals, mp 63-65 °C; TLC \( R_f 0.64 \) (EtOAc:hexane, 1:4); \([\alpha]_D^{22} -36.3 \) (c 5.43, CHCl\(_3\)); IR (CHCl\(_3\)) 1740, 1670 cm\(^{-1}\); \(^1\)H NMR \( \delta 0.89 \) (d, 3 H, \( J = 6.6 \) Hz), 0.93 (d, 3 H, \( J = 6.6 \) Hz), 1.30 (m, 1 H), 1.55-1.78 (m, 5 H), 1.59 (s, 3 H), 1.85 (m, 1 H), 2.19 (s, 3 H), 2.33 (m, 1 H), 4.17 (m, 1 H), 4.22 (m, 1 H), 4.67 (t, 1 H, \( J = 2.2 \) Hz), 4.79 (t, 1 H, \( J = 2.2 \) Hz), 5.15 (ddd, 1 H, \( J = 10.3, 3.9, 3.1 \) Hz), 5.23 (s, 1 H), 5.88 (s, 1 H), 7.35-7.40 (m, 3 H), 7.45-7.55 (m, 2 H); \(^{13}\)C NMR \( \delta 20.7, 21.7, 22.5, 23.5, 23.6, 24.2, 25.6, 38.6, 40.0, 74.7, 75.4, 75.8, 80.4, 105.8, 121.5, 128.0 x 2, 128.7 x 2, 129.2 x 2, 133.8, 149.3, 168.5, 170.3; HRMS calcd for \( C_{25}H_{32}O_5 \) (M\(^+\)) \( m/z \) 412.2250, found 412.2251.

\((1R,6R,8S)-8-[(1R)-1-Hydroxy-3-methylbutyl]-3-methyl-7-methylene-9-oxabicyclo[4.3.0]non-2-ene \((+)-7\). The following reaction was carried out under Ar. To a cooled (−78 °C) stirred solution of 22 (230 mg, 0.558 mmol) in CH\(_2\)Cl\(_2\) (5 mL) was added Dibal-H (1.0 M solution in toluene, 3.1 mL, 3.1 mmol). The mixture was stirred at −78 °C for 1 h, quenched with H\(_2\)O (1 mL), diluted with CH\(_2\)Cl\(_2\) (20 mL) and 15 wt% aqueous potassium sodium tartrate (20 mL). After being stirred for 5 h, the mixture was extracted with CH\(_2\)Cl\(_2\) (50 mL \( \times 3 \)). The combined extracts were dried and concentrated in vacuo. The residue was purified by column chromatography on silica gel (EtOAc:hexane, 1:10) to provide 132 mg
(quat.) of (+)-7 as a colorless oil.

\((1S,6S,8R)-8-[(1S)-1-Hydroxy-3-methylbutyl]-3-methyl-7-methylene-9-oxabicyclo[4.3.0]non-2-ene (--)\). As described for the preparation of (+)-7 from 22, compound 23 (241 mg, 0.584 mmol) was treated with Dibal-H (1.0 M solution in toluene, 3.2 mL, 3.2 mmol) in \(\text{CH}_2\text{Cl}_2\) (5 mL) to provide 133 mg (96\%) of (--)\)-7 as a colorless oil.

\((1R,6R,8S)-8-[(1R)-1-[(2R)-2-Methoxy-2-phenyl-2-(trifluoromethyl)acetoxycarbonyl]-3-methylbutyl]-3-methyl-7-methylene-9-oxabicyclo[4.3.0]non-2-ene (24).\) To a cooled (0 °C) stirred solution of (+)-7 (12.9 mg, 54.6 \(\mu\)mol) in \(\text{CH}_2\text{Cl}_2\) (2 mL) were added (\(\text{R}\))-MTPA (26.0 mg, 0.111 mmol), 4-DMAP (14.0 mg, 0.115 mmol), and DCC (70.3 mg, 0.341 mmol). The mixture was stirred for 18 h, diluted with EtOAc (20 mL), and washed with saturated aqueous NaHCO\(_3\) (15 mL x 3). The organic layer was dried and concentrated in vacuo. The residue was purified by column chromatography on silica gel (EtOAc:hexane, 1:40) and finally PTLC (EtOAc:hexane, 1:16) to provide 4.0 mg (16\%) of 24, and 6.7 mg (52\%) of (+)-7 was recovered. Compound 24 was obtained as a colorless oil: TLC \(R_f\) 0.78 (EtOAc:hexane, 1:4); \(^1\)H NMR \(\delta\) 0.815, 0.827 (2d, each 3 H, \(J = 6.6\) Hz, CH\(\text{CH}_3\)), 1.208 (ddd, 1 H, \(J = 12.7, 9.8, 2.7\) Hz, H-2 of the side chain at C-8), 1.656 (s, 3 H, CH\(\text{CH}_3\)-3), 1.401 (m, 1 H, H-3 of the side chain at C-8), 1.72-1.90, 1.94-2.06 (2m, total 5 H, H-4, 4', 5, 5', and H-2' of the side chain at C-8), 2.713 (m, 1 H, H-6), 3.569 (d, 3 H, \(J = 1.0\) Hz, OCH\(_3\)), 4.569 (m, 1 H, H-1), 4.662 (m, 1 H, H-8), 5.040, 5.065 (2t, each 1 H, \(J = 2.2\) Hz, C=CH\(_2\)), 5.253 (dt, 1 H, \(J = 10.6, 2.7\) Hz, H-1 of the side chain at C-8), 5.354 (m, 1 H, H-2), 7.26-7.41, 7.56-7.64 (2m, total 5 H, Ph).

\((1S,6S,8R)-8-[(1S)-1-[(2R)-2-Methoxy-2-phenyl-2-(trifluoromethyl)acetoxycarbonyl]-3-methylbutyl]-3-methyl-7-methylene-9-oxabicyclo[4.3.0]non-2-ene (25).\) As described for the preparation of 24, compound (--)\)-7 (14.6 mg, 61.8 \(\mu\)mol) was treated with
(R)-MTPA (23.4 mg, 0.100 mmol), 4-DMAP (18.9 mg, 0.155 mmol), and DCC (78.9 mg, 0.382 mmol) in CH₂Cl₂ (2 mL) to provide 4.7 mg (17%) of 25, and 7.0 mg (48%) of (−)-7 was recovered. Compound 25 was obtained as a colorless oil: TLC Rf 0.80 (EtOAc:hexane, 1:4); ¹H NMR δ 0.853, 0.858 (2d, each 3 H, J = 6.6 Hz, CH(CH₃)₂), 1.289 (ddd, 1 H, J = 13.9, 9.4, 3.3 Hz, H-2 of the side chain at C-8), 1.561 (s, 3 H, CH₃-3), 1.561 (m, 1 H, H-3 of the side chain at C-8), 1.50-1.78, 1.82-2.00 (2m, total 5 H, H-4, 4', 5, 5', and H-2' of the side chain at C-8), 2.490 (m, 1 H, H-6), 3.490 (d, 3 H, J = 1.0 Hz, OCH₃), 4.254 (m, 1 H, H-1), 4.413 (m, 1 H, H-8), 4.895, 4.914 (2t, each 1 H, J = 2.2 Hz, C=CH₂), 5.201 (br d, 1 H, J = 2.9 Hz, H-2), 5.223 (dt, 1 H, J = 9.8, 3.3 Hz, H-1 of the side chain at C-8), 7.28-7.36, 7.48-7.56 (2m, total 5 H, Ph).

(1S,2R,3R,6R,8S)-8-[(1R)-1-[(2S)-2-Acetoxy-2-phenylacetoxo]-3-methylbutyl]-2,3-dihydroxy-3-methyl-7-methylene-9-oxabicyclo[4.3.0]nonane (26). To a cooled (0 °C) stirred solution of 22 (20.4 mg, 49.5 µmol) in t-BuOH and H₂O (1:1, v/v, 1.7 mL) were added AD-mix-β (0.139 g) and MsNH₂ (9.4 mg, 0.099 mmol). The mixture was stirred at 0 °C for 22 h, quenched with Na₂SO₃ (76.9 mg, 0.610 mmol), diluted with EtOAc (20 mL), and washed with saturated brine (10 mL x 3). The organic layer was dried and concentrated in vacuo. The residue was purified by column chromatography on silica gel (EtOAc:hexane, 1:1) to provide 21.2 mg (96%) of 26 as a colorless oil: TLC Rf 0.19 (EtOAc:hexane, 1:1); [α]D²² +132 (c 1.03, CHCl₃); IR 3460, 1750, 1670 cm⁻¹; ¹H NMR δ 0.61 (d, 3 H, J = 6.6 Hz), 0.65 (d, 3 H, J = 6.6 Hz), 0.90-1.28 (m, 2 H), 1.22 (s, 3 H), 1.36-1.82 (m, 4 H), 2.10 (m, 1 H), 2.20 (s, 3 H), 2.22 (br, 2 H), 2.86 (m, 1 H), 3.13 (d, 1 H, J = 8.1 Hz), 4.20 (dd, 1 H, J = 8.1, 7.8 Hz), 4.52 (m, 1 H), 4.98 (s, 1 H), 5.02 (dt, 1 H, J = 8.1, 3.2 Hz), 5.08 (s, 1 H), 5.90 (s, 1 H) 7.34-7.40 (m, 3 H), 7.44-7.52 (m, 2 H); ¹³C NMR δ 18.3, 20.7, 21.1, 23.3, 23.8, 26.9, 31.6, 37.3, 41.9, 72.2, 74.6, 74.7, 75.8, 80.6, 83.2, 105.9, 127.6 x 2, 128.6 x 2, 129.2, 133.6, 147.4, 168.8,
170.4; HRMS calcd for C$_{25}$H$_{32}$O$_{6}$ (M$^+–$H$_2$O) m/z 428.2199, found 428.2203.

**Mixture of (1R,2S,3S,6S,8R)-8-[(1S)-1-[(2S)-2-Acetoxy-2-phenylacetoxy]-3-methylbutil]-2,3-dihydroxy-3-methyl-7-methylene-9-oxabicyclo[4.3.0]nonane (27) and its (1R,2R,3R,6S,8R)-isomer (28).** As described for the preparation of 26, compound 23 (21.3 mg, 51.6 µmol) was treated with AD-mix-β (0.144 g) and MsNH$_2$ (9.9 mg, 0.10 mmol) in t-BuOH and H$_2$O (1:1, v/v, 1.8 mL) to provide 9.6 mg (40%) of an inseparable mixture (1.2:1) of 27 and 28, and 13.0 mg (60%) of 23 was recovered. The diastereomeric mixture of 27 and 28 was obtained as a colorless oil: TLC $R_f$ 0.46 (EtOAc:hexane, 1:1); IR 3580, 1740, 1670 cm$^{-1}$; $^1$H NMR signals attributable to 27 $\delta$ 0.90 (d, 3 H, $J$ = 6.2 Hz), 0.94 (d, 3 H, $J$ = 6.2 Hz), 1.15 (s, 3 H), 1.20-1.84 (m, 7 H), 1.99 (br, 2 H), 2.19 (s, 3 H), 2.19 (m, 1 H), 2.92 (d, 1 H, $J$ = 8.2 Hz), 3.63 (dd, 1 H, $J$ = 8.2, 7.8 Hz), 4.25 (m, 1 H), 4.74 (s, 1 H), 4.77 (s, 1 H), 5.18 (dt, 1 H, $J$ = 10.0, 3.2 Hz), 5.86 (s, 1 H), 7.39-7.45 (m, 3 H), 7.47-7.56 (m, 2 H), signals attributable to 28 $\delta$ 0.88 (d, 3 H, $J$ = 6.3 Hz), 0.94 (d, 3 H, $J$ = 6.3 Hz), 1.15 (s, 3 H), 1.20-1.86 (m, 9 H), 2.21 (s, 3 H), 2.34 (m, 1 H), 3.34 (d, 1 H, $J$ = 3.8 Hz), 3.80 (dd, 1 H, $J$ = 5.6, 3.8 Hz), 4.44 (m, 1 H), 4.63 (t, 1 H, $J$ = 2.0 Hz), 4.86 (t, 1 H, $J$ = 2.0 Hz), 5.10-5.22 (m, 1 H), 5.86 (s, 1 H), 7.39-7.45 (m, 3 H), 7.47-7.56 (m, 2 H); HRMS calcd for C$_{25}$H$_{32}$O$_{6}$ (M$^+–$H$_2$O) m/z 428.2199, found 428.2191.
$^{13}$C NMR spectrum of 13
$^{13}$C NMR spectrum of 18
'H NMR spectrum of 21

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