The Total Synthesis of Coleophomones B, C, and D

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Supporting Information

Experimental Data for Compounds

General Procedures. All reactions were carried out under an argon atmosphere with dry solvents under anhydrous conditions, unless otherwise noted. Dry tetrahydrofuran (THF), toluene, benzene, diethyl ether (Et₂O), ethylene glycol dimethyl ether (DME), and methylene chloride (CH₂Cl₂) were obtained by passing commercially available pre-dried, oxygen-free formulations through activated alumina columns. Yields refer to chromatographically and spectroscopically (¹H NMR) homogeneous materials, unless otherwise stated. Reagents were purchased at the highest commercial quality and used without further purification, unless otherwise stated. Reactions were monitored by thin-layer chromatography (TLC) carried out on 0.25 mm E. Merck silica gel plates (60F-254) using UV light as visualizing agent and an ethanolic solution of phosphomolybdic acid and cerium sulfate, and heat as developing agents. E.

Merck silica gel (60, particle size 0.040–0.063 mm) was used for flash column chromatography. Preparative thin-layer chromatography (PTLC) separations were carried out on 0.25 or 0.50 mm E. Merck silica gel plates (60F-254). NMR spectra were recorded on Bruker DRX-600, DRX-500, AMX-500 or AMX-400 instruments and calibrated using residual undeuterated solvent as an internal reference. The following abbreviations were used to explain the multiplicities: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, quin = quintuplet, sext = sextet, sep = septet, br = broad, AB = AB quartet, app = apparent. IR spectra were recorded on a Perkin-Elmer 1600 series FT-IR spectrometer. Electrospray ionization (ESI) mass spectrometry (MS) experiments were performed on an API 100 Perkin Elmer SCIEX single quadrupole mass spectrometer at 4000V emitter voltage. High-resolution mass spectra (HRMS) were recorded on a VG ZAB-ZSE mass spectrometer using MALDI (matrix-assisted laser-desorption ionization).

Monoprenylated vinylogous ester 6b (Scheme 2):

A solution of 5-methyl-1,3-cyclohexadione (5.0 g, 39.68 mmol) in MeOH (50 mL) containing H₂SO₄ (98%, 0.5 mL) was heated to reflux for 12 h. The solution was then cooled to room temperature and neutralized (KOH pellets). The volume was reduced *in vacuo* to approximately 10 mL. The residual liquid was diluted with Et₂O (50 mL). The organic solution was then washed with brine and dried (anhydrous K₂CO₃). The solvent was then removed *in vacuo* to afford the corresponding vinylogous ester (4.72 g, 85%) as a pale yellow syrup.

$R_f = 0.27$ (silica gel, hexane/EtOAc 2:1); IR (film) $\nu_{\max} = 2964, 2955, 1648, 1607, 1458, 1440, 1381, 1224, 1140, 1008, 886, 858, 606 \text{ cm}^{-1}$; ^1H NMR (500 MHz, CDCl₃): $\delta = 5.30$ (s, 1 H), 3.64 (s, 3 H), 2.37 (m, 2 H), 2.16 (m, 1 H), 2.10 (dd, $J = 16.8, 10.3 \text{ Hz}$, 1 H), 1.98 (dd, $J = 16.5, 11.3 \text{ Hz}$, 1 H), 1.02 (d, $J = 6.6 \text{ Hz}$, 3 H) ppm; ^{13}C NMR (125 MHz, CDCl₃): $\delta = 199.5, 178.0, 101.8, 55.5, 44.9, 36.8, 28.7, 20.7 \text{ ppm}$; HRMS (MALDI): calcd for C₈H₁₂O₂ [MH]⁺: 141.0910, found: 141.0912.

A solution of the vinylogous ester prepared above (4.72 g, 33.73 mmol) in anhydrous THF (150 mL) was added slowly to a solution of LiHMDS (35.41 mL, 1 M in THF) in anhydrous THF (100 mL) at -78°C . The solution was then stirred for 1 h at the same temperature. A solution of

prenyl bromide (4.28 mL, 37.10 mmol) in anhydrous THF (10 mL) was added, also at $-78\text{ }^{\circ}\text{C}$, and the resulting solution warmed over a period of 3 h to $0\text{ }^{\circ}\text{C}$. The reaction was quenched with saturated aq. NH_4Cl (75 mL) and diluted with Et_2O (150 mL). The layers were separated and the organic layer phase was washed with brine (100 mL) and dried (MgSO_4). The solvent was removed *in vacuo* and the residue was purified by flash column chromatography (silica gel, EtOAc :hexane 1:3 $\rightarrow$ 1:2) to afford **6b** (5.96 g, 85%) as a pale yellow syrup.

The product is a mixture of *trans*:*cis* (4:1) diastereoisomers, which could be separated by very careful flash column chromatography. A similar procedure was applied in order to prepare **6a** (80% yield) using allyl bromide as the alkylating agent rather than prenyl bromide.

6b (major diastereoisomer): $R_f = 0.53$ (silica gel, hexane/ EtOAc 2:1); IR (film) $\nu_{\text{max}} = 2963$, 2913, 1650, 1613, 1442, 1381, 1222, 1160, 1008, 834 cm^{-1} ; ^1H NMR (500 MHz, CDCl_3): $\delta = 5.31$ (s, 1 H), 5.01 (tt, $J = 6.9$, 1.3 Hz, 1 H), 3.65 (s, 3 H), 2.46 (m, 2 H), 2.27 (m, 1 H), 2.10 (m, 2 H), 2.00 (m, 1 H), 1.65 (brs, 3 H), 1.61 (brs, 3 H), 1.03 (d, $J = 6.6$ Hz, 3 H) ppm; ^{13}C NMR (125 MHz, CDCl_3): $\delta = 201.1$, 176.0, 132.9, 121.3, 101.4, 55.5, 52.3, 35.0, 30.6, 26.7, 25.8, 19.7, 17.8 ppm; HRMS (MALDI): calcd for $\text{C}_{13}\text{H}_{20}\text{O}_2$ $[\text{MH}]^+$: 209.1536, found: 209.1536.

Bisprenylated-1,3-cyclohexadione **8b** (Scheme 2):

To solution of LDA at $-78\text{ }^{\circ}\text{C}$, prepared by treating a solution of diisopropylamine (3.12 mL, 23.79 mmol) in anhydrous THF (15 mL) with *n*-BuLi (9.90 mL, 1.6 M in hexane) for 20 min,

was added slowly (over 30 min) a solution of **6b** (3.0 g, 14.42 mmol) in anhydrous THF:HMPA (7:1, 18 mL). The resulting solution was stirred for 30 min at the same temperature. A solution of prenyl bromide (3.33 mL, 28.84 mmol) in anhydrous THF (5 mL) was then added and the temperature

was slowly raised to $20\text{ }^{\circ}\text{C}$ over a period of 12 h. The reaction was quenched with saturated aq. NH_4Cl (20 mL) and diluted with Et_2O (40 mL). The layers were separated and the organic phase was washed with brine (40 mL) and dried (MgSO_4). The solvent was removed *in vacuo* and the crude residue was purified by flash column chromatography (silica gel, EtOAc :hexane 1:5) to furnish the desired bisprenylated vinylogous ester (3.54 g, 89%) as a pale yellow syrup.

$R_f = 0.67$ (silica gel, hexane/ EtOAc 2:1); IR (film) $\nu_{\text{max}} = 2966$, 2912, 1650, 1614, 1442, 1383, 1221, 1172, 1007, 836 cm^{-1} ; ^1H NMR (600 MHz, CDCl_3): $\delta = 5.29$ (s, 1 H), 5.04 (tt, $J = 6.2$, 1.3 Hz, 1 H), 4.89 (tt, $J = 5.7$, 1.3 Hz, 1 H), 3.64 (s, 3 H), 2.52 (dd, $J = 14.4$, 5.2 Hz, 1 H), 2.40 (m, 1

H), 2.26 (m, 3 H), 2.06 (m, 2 H), 1.65 (brs, 3 H), 1.62 (brs, 3 H), 1.57 (brs, 3 H), 1.56 (brs, 3 H), 0.96 (d, $J = 6.5$ Hz, 3 H) ppm; ^{13}C NMR (150 MHz, CDCl_3): $\delta = 202.9, 175.1, 133.2, 132.8, 120.4, 119.3, 101.6, 55.4, 50.9, 34.1, 33.0, 31.6, 29.5, 26.0, 25.9, 17.8$ (2 C), 15.4 ppm; HRMS (MALDI): calcd for $\text{C}_{18}\text{H}_{28}\text{O}_2$ $[\text{MH}]^+$: 277.2162, found: 277.2158.

The same yield (89%) was obtained for the vinylogous ester synthesized by prenylation of **6a** using an identical procedure. The same protocol was also applied to the alkylation of **6b** with allylic bromide **20** (Scheme 4) and allylic bromide **34** (Scheme 6).

A solution of the bisprenylated vinylogous ester (3.54 g, 12.83 mmol), prepared above, in THF (100 mL) was treated with HCl (10 mL, 1 M) at 25 °C for 14 h. The reaction mixture was diluted with EtOAc/ H_2O (2:1, 100 mL). The layers were separated and the organic phase was washed with brine (75 mL) and dried (MgSO_4). The solvent was removed *in vacuo* to afford **8b** (3.19 g, 95%) as a pale yellow syrup. The keto- and enol-tautomers of **8b** can both be seen in the NMR spectra (keto:enol, 4:1). Identical procedures were used for the preparation of **8a** from its corresponding vinylogous ester and for the hydrolysis of monoalkylated vinylogous esters **6a** and **b** to afford the corresponding monoalkylated 1,3-cyclohexadiones **7a** and **b**, respectively.

8b: $R_f = 0.21$ (silica gel, hexane/EtOAc 2:1); IR (film) $\nu_{\text{max}} = 2968, 2913, 1606, 1560, 1443, 1407, 1382, 1306, 1227, 1194, 846\text{ cm}^{-1}$; ^1H NMR (500 MHz, CDCl_3 , keto form): $\delta = 5.00$ (tt, $J = 7.3, 1.5$ Hz, 1 H), 4.89 (tt, $J = 7.1, 1.3$ Hz, 1 H), 3.46 (dd, $J = 17.2, 1.1$ Hz, 1 H), 3.29 (dd, $J = 17.2, 1.4$ Hz, 1 H), 2.81 (dd, $J = 16.7, 5.5$ Hz, 1 H), 2.47 (m, 2 H), 2.40 – 2.20 (m, 4 H), 1.68 (d, $J = 1.1$ Hz, 3 H), 1.66 (d, $J = 1.1$ Hz, 3 H), 1.59 (brs, 6 H), 0.92 (d, $J = 7.0$ Hz, 3 H) ppm; ^{13}C NMR (125 MHz, CDCl_3 , keto form): $\delta = 207.4, 204.4, 134.9, 134.8, 118.4, 118.1, 56.9, 54.7, 44.8, 32.4, 31.5, 29.1, 26.1, 26.0, 17.9$ (2 C), 15.8 ppm; HRMS (MALDI): calcd for $\text{C}_{17}\text{H}_{26}\text{O}_2$ $[\text{MH}]^+$: 263.2005, found: 263.2008

The four-step procedure described above for the transformation of **5** into **8a** and **b**, was also applied to the preparation of **65a** and **b**, starting from **64** (Scheme 13).

Phenolic aldehyde **32** (Scheme 6):

To a solution of benzylic alcohol **31**²⁴ (5.0 g, 25.77 mmol) in CH_2Cl_2 (150 mL) was added Et_3N (5.38 mL, 38.65 mmol), 4-DMAP (157 mg, 1.28 mmol), and 4-bromo benzoyl chloride (5.94 g, 27.05 mmol). The resulting solution was stirred for 20 min at 25 °C. The organic solution was

washed with saturated aq. NaHCO_3 (100 mL), dried (MgSO_4), and concentrated *in vacuo* to afford the corresponding *p*-bromobenzoate ketal (9.40 g, 97%) as a white solid.

R_f = 0.49 (silica gel, hexane/EtOAc 2:1); IR (film) ν_{max} = 1720, 1590, 1460, 1374, 1270, 1099, 1011, 755 cm^{-1} ; ^1H NMR (500 MHz, CDCl_3): δ = 7.89 (d, J = 8.4 Hz, 2 H), 7.58 (d, J = 8.8 Hz, 2 H), 7.19 (t, J = 8.1 Hz, 1 H), 7.00 (d, J = 7.3 Hz, 1 H), 6.84 (d, J = 8.4 Hz, 1 H), 5.23 (s, 2 H), 4.94 (s, 2 H), 1.55 (s, 6 H) ppm; ^{13}C NMR (125 MHz, CDCl_3): δ = 165.5, 151.5, 132.4, 131.8 (2 C), 131.1 (2 C), 128.6, 128.4, 128.1, 121.4, 118.5, 117.8, 99.1, 64.0, 59.1, 24.6 (2 C) ppm; HRMS (MALDI): calcd for $\text{C}_{18}\text{H}_{17}\text{O}_4\text{Br}$ $[\text{MH}]^+$: 399.0202, found: 399.0200.

To a mixture of the *p*-bromo benzoate ketal (9.40 g, 25.0 mmol), prepared above, in THF:H₂O (1.5:1, 350 mL) was added *p*-TSOH $\cdot$ H₂O (1.42 g, 7.5 mmol). The mixture was then heated for 10 h at 75 °C. The mixture was then diluted with EtOAc (150 mL) and the organic phase washed with saturated aq. NaHCO_3 (200 mL). The solution was dried (MgSO_4) and concentrated *in vacuo* to afford the corresponding hydroxy phenol (7.14 g, 85%) as white crystals.

M.p. = 145 °C (EtOAc); R_f = 0.15 (silica gel, hexane/EtOAc 2:1); IR (film) ν_{max} = 3100, 1703, 1589, 1467, 1396, 1276, 1117, 1011, 755 cm^{-1} ; ^1H NMR (500 MHz, CDCl_3): δ = 7.87 (d, J = 8.8 Hz, 2 H), 7.56 (d, J = 8.6 Hz, 2 H), 7.21 (t, J = 7.8 Hz, 1 H), 6.97 (d, J = 7.3 Hz, 1 H), 6.93 (d, J = 8.0 Hz, 1 H), 5.32 (s, 2 H), 5.03 (s, 2 H) ppm; ^{13}C NMR (125 MHz, CDCl_3): δ = 165.5, 156.9, 133.3, 131.8 (2 C), 131.1 (2 C), 129.2, 128.7, 128.4, 123.7, 122.1, 117.7, 65.0, 60.0 ppm; HRMS (MALDI): calcd for $\text{C}_{15}\text{H}_{13}\text{O}_4\text{Br}$ $[\text{MNa}]^+$: 358.9889, found: 358.9898.

A solution of the above prepared hydroxy phenol (7.14 g, 21.25 mmol) in EtOAc (250 mL) was treated with MnO_2 (18.48 g, 212.5 mmol). The reaction mixture was stirred for 1.5 h at 25 °C and then filtered through a pad of celite. The solvent was removed *in vacuo* and the crude residue was purified by flash column chromatography (silica gel, EtOAc:hexane 1:8 $\rightarrow$ 1:3) to afford phenolic aldehyde **32** (6.15 g, 87%) as white crystals.

32: M.p. 133 – 135 °C (EtOAc); R_f = 0.43 (silica gel, hexane/EtOAc 2:1); IR (film) ν_{max} = 1727, 1643, 1587, 1453, 1267, 1165, 1099, 1069, 1010, 842, 803, 752, 712 cm^{-1} ; ^1H NMR (500 MHz, CDCl_3): δ = 11.91 (s, 1 H), 10.38 (s, 1 H), 7.86 (d, J = 8.7 Hz, 2 H), 7.56 (d, J = 8.3 Hz, 2 H), 7.50 (dd, J = 7.8, 7.4 Hz, 1 H), 7.03 (d, J = 7.4 Hz, 1 H), 7.02 (d, J = 8.2 Hz, 1 H), 5.62 (s, 2 H) ppm; ^{13}C NMR (125 MHz, CDCl_3): δ = 194.8, 165.1, 163.4, 138.3, 137.2, 131.8 (2 C), 131.1 (2

C), 128.6, 128.2, 121.7, 119.4, 117.4, 63.4 ppm; HRMS (MALDI): calcd for $C_{15}H_{11}O_4Br$ $[MNa]^+$: 356.9733, found: 356.9743.

Acyl cyanide **41** (Scheme 8a):

To a solution of **32** (3.0 g, 8.98 mmol) in anhydrous acetone (100 mL) was added finely powdered K_2CO_3 (2.48 g, 17.96 mmol) followed by 3-bromo-2-methyl-propene (1.82 g, 13.47 mmol). The reaction mixture was heated to reflux for 2 h. It is important to note that the R_f value (silica gel, hexane/EtOAc 2:1) of the reaction product is identical to that of the starting material **32**. Filtration through a pad of celite followed by evaporation of the solvent *in vacuo* afforded the requisite alkylated benzaldehyde (3.17 g, 91%) as white crystals.

M.p. 86 – 87 °C (acetone); R_f = 0.43 (silica gel, hexane/EtOAc 2:1); IR (film) ν_{max} = 1720, 1684, 1584, 1473, 1393, 1274, 1172, 1121, 1071, 895, 770, 751 cm^{-1} ; 1H NMR (500 MHz, $CDCl_3$): δ = 10.72 (s, 1 H), 7.96 (d, J = 8.8 Hz, 2 H), 7.86 (d, J = 8.7 Hz, 2 H), 7.50 (t, J = 7.9 Hz, 1 H), 7.12 (d, J = 7.9 Hz, 1 H), 6.96 (d, J = 8.3 Hz, 1 H), 5.75 (s, 2 H), 5.11 (s, 1 H), 5.04 (s, 1 H), 4.55 (s, 2 H), 1.85 (s, 3 H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$): δ = 191.4, 165.3, 162.3, 139.8, 139.5, 135.1, 131.7 (2 C), 131.2 (2 C), 128.9, 128.1, 122.0, 119.0, 113.4, 112.2, 72.4, 64.9, 19.4 ppm; HRMS (MALDI): calcd for $C_{19}H_{17}O_4Br$ $[MNa]^+$: 411.0202, found: 411.0214.

A solution of Et_2AlCN (8.98 mL, 1 M in toluene) was added slowly to a solution of the alkylated benzaldehyde (3.17 g, 8.17 mmol), prepared above, in toluene (70 mL) at 0 °C. After 30 min stirring at the same temperature, the reaction solution was warmed to 25 °C and stirred for a further 30 min. Saturated aq. sodium potassium tartrate (50 mL) was added and the emulsion was stirred vigorously for 1 h. The layers were separated and the organic phase was dried with $MgSO_4$ and concentrated *in vacuo*. The crude residue was purified by flash column chromatography (silica gel, EtOAc:hexane 1:6 $\rightarrow$ 1:4) to provide the desired cyanohydrin (2.71 g, 82%) as a viscous syrup.

R_f = 0.28 (silica gel, hexane/EtOAc 2:1); IR (film) ν_{max} = 3430, 3086, 2975, 2937, 1720, 1589, 1473, 1450, 1397, 1377, 1268, 1101, 1011, 916, 756 cm^{-1} ; 1H NMR (500 MHz, $CDCl_3$): δ = 7.92 (d, J = 8.5 Hz, 2 H), 7.57 (d, J = 8.8 Hz, 2 H), 7.38 (dd, J = 8.5, 7.7 Hz, 1 H), 7.11 (dd, J = 7.7, 0.7 Hz, 1 H), 7.03 (d, J = 8.5 Hz, 1 H), 5.85 (d, J = 11.4 Hz, 1 H), 5.43 (AB system $\Delta\delta$ = 0.0374 ppm, J = 12.8 Hz, 2 H), 5.17 (s, 1 H), 5.09 (s, 1 H), 4.63 (AB system $\Delta\delta$ = 0.0476 ppm, J = 12.1

Hz, 2 H), 4.45 (d, J = 11.4 Hz, 1 H) 1.91 (s, 3 H) ppm; ^{13}C NMR (125 MHz, CDCl_3): δ = 165.5, 157.1, 139.4, 134.4, 131.9 (2 C), 131.3 (2 C), 131.0, 128.7, 128.2, 123.7, 123.6, 119.1, 114.3, 113.5, 72.9, 64.7, 57.9, 19.6 ppm; HRMS (MALDI): calcd for $\text{C}_{20}\text{H}_{18}\text{O}_4\text{NBr}$ $[\text{MNa}]^+$: 438.0311, found: 438.0305.

A solution of the cyanohydrin (2.17 g, 6.70 mmol), prepared above, in anhydrous CH_2Cl_2 (90 mL) was heated to reflux for 12 h in the presence of PCC (5.77 g, 26.80 mmol). A sufficient amount of celite was then added to absorb the reaction mixture accompanied by vigorous stirring. The resulting paste was transferred directly on to the top of a silica gel column and subsequent flash column chromatography (EtOAc:hexane 1:6 $\rightarrow$ 1:3) furnished acyl cyanide **41** (2.02 g, 73%) as white crystals.

41: M.p. 93 – 95 °C (EtOAc); R_f = 0.41 (silica gel, hexane/EtOAc 2:1); IR (film) ν_{max} = 3079, 2949, 1720, 1650, 1592, 1474, 1453, 1268, 1102, 1069, 1011, 980, 918, 754 cm^{-1} ; ^1H NMR (500 MHz, CDCl_3): δ = 7.92 (d, J = 8.7 Hz, 2 H), 7.59 (d, J = 8.7 Hz, 2 H), 7.56 (dd, J = 8.7, 7.8 Hz, 1 H), 7.16 (d, J = 7.8 Hz, 1 H), 7.04 (d, J = 8.7 Hz, 1 H), 5.46 (s, 2 H), 5.15 (s, 1 H), 5.08 (s, 1 H), 4.66 (s, 2 H), 1.90 (s, 3 H) ppm; ^{13}C NMR (125 MHz, CDCl_3): δ = 167.6, 165.2, 160.2, 139.4, 139.3, 135.9, 131.8 (2 C), 131.2 (2 C), 128.5, 128.4, 122.4, 121.1, 114.6, 114.4, 113.1, 73.5, 63.9, 19.5 ppm; HRMS (MALDI): calcd for $\text{C}_{20}\text{H}_{16}\text{O}_4\text{NBr}$ $[\text{MNa}]^+$: 436.0155, found: 436.0160.

The same protocol was applied for the following transformations: **27** $\rightarrow$ **28** (Scheme 5), **35** $\rightarrow$ **36** (Scheme 6), and **33** $\rightarrow$ **38** (Scheme 7).

General procedure for the coupling of acyl cyanides **28**, **38**, and **41** with 1,3-cyclohexadiones **5**, **7a**, **7b**, **8a**, and **8b** (Scheme 8a):

To a solution of acyl cyanide **41** (1.0 g, 2.42 mmol) in THF (25 mL) was added the appropriate 1,3-cyclohexadione **5** or **7a** or **7b** (2.90 mmol) followed by Et_3N (0.67 mL, 4.84 mmol). The resulting solution was stirred for 6–12 h (until complete consumption of the starting acyl cyanide **41** by TLC) at 25 °C. The solution was diluted with Et_2O (50 mL), washed with 1 M HCl (50 mL) and brine (50 mL) and dried (MgSO_4). The solvent was removed *in vacuo* and the residual crude syrup was purified by flash column chromatography (silica gel, EtOAc:hexane 1:6 $\rightarrow$ 1:2) furnishing pure tricarbonyls **42a**, **b**, and **c** (91–98%) as syrups.

42a: R_f = 0.40 (silica gel, hexane/EtOAc 2:1); IR (film) $\nu_{\max}$ = 2956, 1722, 1676, 1589, 1556, 1469, 1453, 1398, 1267, 1101, 1069, 1011, 882, 756 cm^{-1} ; ^1H NMR (600 MHz, CDCl_3): δ = 17.34 (s, 1 H), 7.81 (d, J = 8.8 Hz, 2 H), 7.53 (d, J = 7.7 Hz, 2 H), 7.34 (t, J = 7.7 Hz, 1 H), 7.08 (d, J = 7.7 Hz, 1 H), 6.87 (d, J = 7.7 Hz, 1 H), 5.36 (brs, 1 H), 5.16 (brs, 1 H), 4.94 (s, 1 H), 4.89 (s, 1 H), 4.37 (brs, 1 H), 4.34 (brs, 1 H), 2.64 (brs, 1 H), 2.45 – 2.00 (brm, 4 H), 1.70 (s, 3 H), 1.01 (brd, J = 5.5 Hz, 3H) ppm; ^{13}C NMR (150 MHz, CDCl_3): δ = 198.1 (br), 195.8, 193.2 (br), 165.2, 161.6 (br), 154.9 (br), 140.4, 132.8 (br), 131.6 (2 C), 131.2 (2 C), 130.1, 128.9, 128.8, 128.0, 121.5, 114.5, 112.1, 72.0, 64.6, 46.1 (br), 40.3, 26.4, 20.8, 19.2 ppm; HRMS (MALDI): calcd for $\text{C}_{26}\text{H}_{25}\text{O}_6\text{Br}$ [MNa^+]: 535.0727, found: 535.0719.

The same protocol was applied to the coupling of acyl cyanide **28** with cyclohexadione **5** or **7b** (Scheme 5) and for the coupling of acyl cyanide **38** with **7b** (Scheme 7). In the case of bisalkylated 1,3-cyclohexadiones **8a** or **8b**, addition of 1.0 equiv. of 4-DMAP and longer reaction times (72–96 h) proved to be necessary for the formation of ticarbonyles **44a**, and **b** (83–86%, Scheme 8B). 4-DMAP was also used for the coupling of **41** with **65a**, or **b** (Scheme 13). Compounds **42b**, **42c**, **44a**, and **44b** appear in the NMR spectra as complicated mixtures of at least four tautomeric atropisomers making their full spectral analysis difficult.

Preparation of $\Delta^{16,17}$ (Z)-macrocyclic compound **43** (Scheme 8):

To a degassed solution of **42b** or **42c** (0.082 mmol, bubbling for 15 min with Ar) in anhydrous CH_2Cl_2 (5 mL) was added the second generation Grubbs catalyst **A** (14.0 mg, 0.0164 mmol or 21.0 mg, 0.0247 mmol, respectively) in one portion. The resulting pink solution was heated to reflux, with light excluded from the reaction vessel, for 5 or 18 h, respectively. The solvent was removed *in vacuo* and the residue was purified by flash column chromatography (silica gel, EtOAc:hexane 1:8 $\rightarrow$ 1:2) to afford $\Delta^{16,17}$ (Z)-macrocycle **43** (25.8 mg, 60% or 12.9 mg, 30%, respectively) as a white crystalline solid. The structure of **43** was unambiguously assigned by x-ray analysis (Ref. 28).

43: M.p. 184 – 186 $^\circ\text{C}$ (EtOAc); R_f = 0.41 (silica gel, hexane/EtOAc 2:1); IR (film) $\nu_{\max}$ = 2961, 1721, 1668, 1589, 1456, 1412, 1266, 1115, 1103, 1068, 1011, 757, 735 cm^{-1} ; ^1H NMR (500 MHz, CDCl_3): δ = 16.57 (brs, 1 H), 7.83 (d, J = 8.3 Hz, 2 H), 7.49 (d, J = 9.1 Hz, 2 H), 7.39 (dd, J = 8.3, 7.3 Hz, 1 H), 7.15 (d, J = 7.3 Hz, 1 H), 6.92 (d, J = 8.3 Hz, 1 H), 5.61 (brs, 1 H), 5.60 (d,

$J = 12.9$ Hz, 1 H), 5.27 (d, $J = 12.9$ Hz, 1 H), 4.42 (brs, 1 H), 4.15 (brs, 1 H), 2.90 – 2.30 (brm, 4 H), 2.25 – 2.10 (brm, 2 H), 1.90 (s, 3 H), 1.09 (brs, 3H) ppm; ^{13}C NMR (125 MHz, CDCl_3): $\delta = 197.2$ (br), 195.0 (br), 191.9 (br), 171.1, 165.2, 135.4 (br), 131.4 (2 C), 131.2 (2 C), 128.9, 127.9, 127.6 (br), 122.4 (br), 115.5, 76.4, 64.8, 60.4, 54.4 (br), 24.4 (br), 21.0, 19.5 (br), 14.2 ppm. Most of the peaks in the NMR spectra are broadened because of the fast tautomeric atropisomerism, some were, therefore, difficult to assign regardless of the sample concentration. The same problem was faced when using different NMR solvents like C_6D_6 and $\text{THF-}d_8$, while the compound is not very soluble in CD_3CN and acetone- d_6 . As a result, we report 23 out of the expected 27 carbon signals; HRMS (MALDI): calcd for $\text{C}_{27}\text{H}_{25}\text{O}_6\text{Br}$ $[\text{MNa}]^+$: 547.0727, found: 547.0720.

Esterification of tricarbonyl compound **42a** to vinylogous esters **46** and **47** (Scheme 9):

To a solution of **42a** (0.57 g, 1.11 mmol) in Et_2O (20 mL), at 0 °C, was added slowly a pre-prepared solution of anhydrous CH_2N_2 in Et_2O (prepared using the Aldrich protocol) until the color of the solution remained constantly pale yellow. The formation of a white precipitate was observed. The solution was stirred for 30 min at the same temperature. The excess CH_2N_2 was removed by bubbling argon through the reaction mixture for 10 min at 25 °C. The white crystalline solid was isolated by filtration and proved to be vinylogous ester **47**. The mother liquor was concentrated *in vacuo* and the residue was purified by flash column chromatography (silica gel, $\text{CH}_2\text{Cl}_2 \rightarrow \text{CH}_2\text{Cl}_2:\text{EtOAc}$ 2:1) to afford the regioisomeric vinylogous ester **46** (0.28 g, 48%) as a syrup, plus some further quantities of crystalline **47** (0.28 g, 48%, total).

46 (mixture of two atropisomers in 1:1 ratio in CDCl_3): $R_f = 0.23$ (silica gel, hexane/ EtOAc 2:1); IR (film) $\nu_{\text{max}} = 2953, 1722, 1650, 1589, 1519, 1454, 1267, 1115, 1011, 757\text{ cm}^{-1}$; ^1H NMR (600

MHz, CDCl_3): $\delta = 7.91$ (d, $J = 8.8$ Hz, 2 H), 7.89 (d, $J = 7.7$ Hz, 2 H), 7.58 (d, $J = 8.8$ Hz, 2 H), 7.57 (d, $J = 8.8$ Hz, 2 H), 7.40 (dd, $J = 8.7, 7.7$ Hz, 1 H), 7.39 (t, $J = 7.7$ Hz, 1 H), 7.13 (d, $J = 7.7$ Hz, 1 H), 7.12 (d, $J = 7.7$ Hz, 1 H), 6.92 (t, $J = 8.8$ Hz, 2 H), 5.30 (d, $J = 13.1$ Hz, 1 H), 5.24 (d, $J = 13.1$ Hz, 1 H), 5.20 (d, $J = 12.1$ Hz, 1 H), 5.18 (d, $J = 12.1$ Hz, 1 H), 5.00 (s, 1 H), 4.99 (s, 1

H), 4.93 (s, 2 H), 4.43 (AB system, $\Delta\delta = 0.0274$ ppm, $J = 12.1$ Hz, 2 H), 4.41 (s, 2 H), 3.64 (s, 3 H), 3.63 (s, 3 H), 2.67 (m, 2 H), 2.43 (m, 2 H), 2.30 – 2.05 (m, 6 H), 1.73 (s, 6 H), 1.01 (d, $J = 6.6$ Hz, 3H) 1.00 (d, $J = 6.6$ Hz, 3H) ppm; ^{13}C NMR (150 MHz, CDCl_3): $\delta = 197.0, 196.9, 196.4,$

196.2, 174.9, 174.8, 165.4 (2 C), 154.9, 154.4, 140.0 (2 C), 135.6, 134.7, 131.8 (4 C), 131.2 (2 C), 131.2 (2 C), 131.0 (2 C), 128.7, 128.6, 128.4, 128.3, 122.1, 121.8, 121.3, 121.1, 118.8 (2 C), 112.5, 112.5, 112.1, 112.0, 72.1, 72.0, 64.7, 64.7, 57.5, 57.5, 48.7, 48.6, 48.0, 47.9, 25.4, 25.3, 20.9, 20.8, 19.2 (2 C) ppm; HRMS (MALDI): calcd for $C_{27}H_{27}O_6Br$ $[MNa]^+$: 549.0883, found: 549.0876.

47: M.p. 165 – 167 °C (Et₂O); R_f = 0.11 (silica gel, hexane/EtOAc 2:1); IR (film) ν_{max} = 1718, 1675, 1646, 1589, 1458, 1376, 1333, 1287, 1103, 1070, 1010, 757 cm^{-1} ; ¹H NMR (600 MHz,

CDCl₃): δ = 7.94 (d, J = 8.8 Hz, 2 H), 7.55 (d, J = 7.7 Hz, 2 H), 7.29 (dd, J = 8.8, 7.7 Hz, 1 H), 7.09 (d, J = 7.7 Hz, 1 H), 6.81 (d, J = 8.8 Hz, 1 H), 5.46 (s, 2 H), 4.98 (s, 1 H), 4.95 (s, 1 H), 4.36 (AB system, $\Delta\delta$ = 0.0274 ppm, J = 12.1 Hz, 2 H), 3.72 (s, 3 H), 2.66 (m, 1 H), 2.34 (dd, J = 14.3, 3.2 Hz, 1 H), 2.15 (m, 2 H), 2.00 (dd, J = 16.0, 12.6 Hz, 1 H), 1.76 (s, 3 H), 1.07 (d, J = 5.5 Hz,

3H) ppm; ¹³C NMR (150 MHz, CDCl₃): δ = 195.3, 194.7, 176.5, 165.5, 156.2, 140.8, 136.2, 131.5 (2 C), 131.3 (2 C), 130.6 (2 C), 129.3, 127.8, 122.2, 120.9, 112.8, 111.9, 72.4, 64.8, 56.9, 45.0, 34.5, 27.4, 21.0, 19.4 ppm; HRMS (MALDI): calcd for $C_{27}H_{27}O_6Br$ $[MNa]^+$: 549.0883, found: 549.0891.

Preparation of $\Delta^{16,17}$ (*E*)-macrocycle **49** (Scheme 9).

A solution of vinylogous ester **46** (0.15 g, 0.285 mmol) in anhydrous THF (2.0 mL), containing anhydrous HMPA (0.2 mL), was treated with LiHMDS (0.3 mL, 1 M in THF) at –78 °C for 1 h.

A solution of prenyl bromide (66 μ L, 0.57 mmol) in anhydrous THF (0.5 mL) was then added drop-wise to the solution, at the same temperature. The resulting solution was allowed to warm slowly to 0 °C over a period of 5 h. The solution was diluted with Et₂O (10 mL) and quenched with saturated aq. NH₄Cl (5 mL). The layers were separated and the organic phase was dried

(MgSO₄) and concentrated *in vacuo*. The residue was purified by flash column chromatography (silica gel, EtOAc:hexane 1:4) to afford **48** (0.107 g, 63%) as a syrup. Based on the ¹H-NMR spectrum, compound **48** was found to be a complicated mixture of four stereo- and atropisomers, as expected.

A degassed solution of **48** (0.10 g, 0.17 mmol, bubbling for 15 min with Ar) in anhydrous CH₂Cl₂ (10 mL) was treated with the second generation Grubbs catalyst A (29.0 mg, 0.034

mmol). The resulting pink solution was heated to reflux, with light excluded from the reaction vessel, for 20 h. The solvent was removed *in vacuo* and the residue was purified by flash column chromatography (silica gel, EtOAc:hexane 1:8 $\rightarrow$ 1:2) to afford $\Delta^{16,17}$ (*E*)-macrocycle **49** (27.4 mg, 30%) as a syrup along with recovered starting material **48** (35 mg, 35%). The (*E*)-geometry of the newly formed $\Delta^{16,17}$ macrocyclic double bond was unambiguously proved by extensive NOE experiments (see Scheme 9).

49: R_f = 0.30 (silica gel, hexane/EtOAc 2:1); IR (film) $\nu_{\max}$ = 2955, 1721, 1651, 1589, 1531, 1455, 1267, 1233, 1117, 1101, 1011, 849, 757 cm^{-1} ; ^1H NMR (500 MHz, CDCl_3): δ = 7.92 (d, J = 8.3 Hz, 2 H), 7.59 (d, J = 8.3 Hz, 2 H), 7.40 (dd, J = 8.3, 7.3 Hz, 1 H), 7.23 (d, J = 7.3 Hz, 1 H), 7.19 (d, J = 8.3 Hz, 1 H), 5.69 (brdd, J = 11.0, 2.7 Hz, 1 H), 5.48 (d, J = 12.9 Hz, 1 H), 5.29 (d, J = 12.9 Hz, 1 H), 4.51 (AB system, $\Delta\delta$ = 0.0384 ppm, J = 11.9 Hz, 2 H), 3.52 (s, 3 H), 2.65 – 2.57 (m, 2 H), 2.26 – 2.17 (m, 4 H), 1.37 (s, 3 H), 1.10 (d, J = 5.5 Hz, 3H) ppm; ^{13}C NMR (125 MHz, CDCl_3): δ = 201.7, 195.1, 173.7, 165.9, 155.0, 139.0, 135.8, 132.2 (2 C), 131.7 (2 C), 131.4, 130.0, 129.2, 128.7, 125.0, 123.1, 120.5, 120.3, 65.8, 57.8, 55.9, 47.8, 32.0, 28.7, 23.1, 19.5, 14.5 ppm. HRMS (MALDI): calcd for $\text{C}_{28}\text{H}_{27}\text{O}_6\text{Br}$ [MNa^+]: 561.0883, found: 561.0886.

Stereospecific olefin metathesis of regioisomeric vinylogous esters **50**, **51** and **52** (Scheme 10):

To a solution of tricarbonyl compound **44b** (0.80 g, 1.23 mmol) in Et_2O (20 mL), at 0 $^\circ\text{C}$, was added slowly a pre-prepared solution of anhydrous CH_2N_2 in Et_2O (prepared using the Aldrich protocol) until the color of the solution remained constantly yellow. The solution was stirred for a further 1 h at the same temperature. The excess CH_2N_2 was removed by bubbling argon through the reaction mixture for 15 min at 25 $^\circ\text{C}$. Formation of three more polar spots, compared to the starting material **44b**, was observed by TLC. Separation of the products corresponding to these spots by flash column chromatography (silica gel, EtOAc:hexane 1:6 $\rightarrow$ 1:4) afforded **50** (0.26 g, 32%), **51** (0.39 g, 48%) and **52** (0.13 g, 16%) as syrups. Regioisomer **51** was a mixture of $\Delta^{8,9}$ double bond geometrical isomers (ca. 1.3:1), each of which again consisted of a pair of atropisomers (ca. 1:1). As a result the NMR spectral data for **51** can not easily be reported.

50: R_f = 0.47 (silica gel, hexane/EtOAc 2:1); IR (film) $\nu_{\max}$ = 2966, 2914, 1721, 1672, 1650, 1590, 1455, 1377, 1268, 1115, 1069, 1011, 904, 848, 757 cm^{-1} ; ^1H NMR (600 MHz, CDCl_3): δ = 7.97 (d, J = 8.3 Hz, 2 H), 7.54 (d, J = 9.1 Hz, 2 H), 7.29 (t, J = 8.2, Hz, 1 H), 7.12 (d, J = 7.4 Hz,

1 H), 6.79 (d, $J = 8.2$ Hz, 1 H), 5.50 (AB system, $\Delta\delta = 0.0299$ ppm, $J = 13.1$ Hz, 2 H), 4.96 (s, 1 H), 4.93 (s, 1 H), 4.80 (brt, $J = 6.8$ Hz, 1 H), 4.69 (brt, $J = 6.8$ Hz, 1 H), 4.29 (s, 2 H), 3.76 (s, 3 H), 2.67 (dd, $J = 19.2, 5.5$ Hz, 1 H), 2.38 (m, 2 H), 2.23 (m, 1 H), 2.15 (dd, $J = 15.6, 6.4$ Hz, 1 H), 2.05 – 1.95 (m, 2 H), 1.75 (s, 3 H), 1.60 (s, 3 H), 1.58 (s, 3 H), 1.53 (s, 3 H), 1.52 (s, 3 H), 0.96 (d, $J = 7.3$ Hz, 3 H) ppm; ^{13}C NMR (125 MHz, CDCl_3): $\delta = 199.6, 195.7, 173.6, 165.6, 155.9, 140.9, 136.2, 133.4, 132.6, 131.5$ (2 C), 131.4 (2 C), 130.9, 130.3, 129.4, 127.8, 121.3, 121.1, 120.3, 119.0, 112.5, 111.4, 71.9, 64.9, 56.2, 50.5, 31.9, 31.5, 31.3, 28.7, 26.1, 25.9, 19.4, 17.9, 17.8, 15.7 ppm; HRMS (MALDI): calcd for $\text{C}_{37}\text{H}_{43}\text{O}_6\text{Br}$ $[\text{MH}]^+$: 663.2316, found: 663.2330.

52: $R_f = 0.62$ (silica gel, hexane/EtOAc 2:1); IR (film) $\nu_{\text{max}} = 2968, 2913, 1721, 1659, 1643, 1589, 1453, 1378, 1322, 1268, 1115, 1011, 910, 846, 757, 733$ cm^{-1} ; ^1H NMR (500 MHz,

CDCl_3): $\delta = 7.91$ (d, $J = 8.5$ Hz, 2 H), 7.51 (d, $J = 8.5$ Hz, 2 H), 7.30 (dd, $J = 8.4, 7.7$ Hz, 1 H), 7.13 (d, $J = 7.7$ Hz, 1 H), 6.79 (d, $J = 8.4$ Hz, 1 H), 5.52 (AB system, $\Delta\delta = 0.0895$ ppm, $J = 13.6$ Hz, 2 H), 5.14 (brt, $J = 6.5$ Hz, 1 H), 4.94 (brt, $J = 6.5$ Hz, 1 H), 4.93 (brs, 1 H), 4.92 (brs, 1 H), 4.45 (brs, 2 H), 3.86 (s, 3 H), 2.75 – 2.50 (m, 2 H), 2.40 – 2.20 (m, 3 H), 2.15 – 2.00 (m, 2 H), 1.72 (s, 3 H), 1.68 (s, 3 H), 1.65 (s, 3 H), 1.63 (s, 3 H), 1.60 (s, 3 H), 0.93 (d, $J = 6.6$ Hz, 3H) ppm; ^{13}C NMR (125 MHz, CDCl_3): $\delta = 207.6, 196.7, 194.9, 165.4, 156.2, 140.0, 136.7, 134.1, 132.9, 131.5$ (2 C), 131.3 (2 C), 130.9, 129.9, 129.3, 127.7, 122.8, 121.3, 120.1, 119.8, 112.5, 112.0, 72.0, 67.7, 65.1, 63.1, 55.0, 49.3, 42.3, 33.0, 26.0, 25.9, 19.1, 17.9, 17.8, 15.2 ppm; HRMS (MALDI): calcd for $\text{C}_{37}\text{H}_{43}\text{O}_6\text{Br}$ $[\text{MNa}]^+$: 685.2135, found: 685.2127.

The same protocol was used for the protection of tricarbonyl compounds **66a** and **b** (Scheme 13).

To a degassed solution of regioisomeric vinylogous esters **50** or **51** or **52** (0.10 g, 0.15 mmol, bubbling for 15 min with Ar) in anhydrous CH_2Cl_2 (10 mL) was treated with the second generation Grubbs catalyst **A** (12.8 mg, 0.015 mmol), added in a single portion. The resulting pink solution was heated to reflux, with light excluded from the reaction vessel, for 3 h or 3 h or 4.5 h, respectively. The solvent was removed *in vacuo* and the residue was purified by flash column chromatography (silica gel, EtOAc:hexane 1:8 $\rightarrow$ 1:3) to afford 11-membered $\Delta^{16,17}$ (Z)-

macrocycle **53** (73 mg, 80%) as a white crystalline solid, or $\Delta^{16,17}$ (*E*)-macrocycle **54** (78 mg, 86%) as syrup, or $\Delta^{16,17}$ (*Z*)-macrocycle **55** (61 mg, 67%) as a syrup. The structure of **53** was unambiguously assigned by x-ray analysis (Ref. 32) while the $\Delta^{16,17}$ double bond geometry of **55** was assigned by extensive NOE experiments (see Scheme 10).

53: M.p. 192 – 194 °C (hexane/EtOAc 3:1); R_f = 0.32 (silica gel, hexane/EtOAc 2:1); IR (film) $\nu_{\max}$ = 2917, 1721, 1682, 1651, 1621, 1590, 1469, 1378, 1321, 1268, 1236, 1173, 1115, 1068,

1011, 990, 910, 848, 757, 731 cm^{-1} ; ^1H NMR (500 MHz, CD_3CN): δ = 7.94 (d, J = 9.1 Hz, 2 H), 7.66 (d, J = 9.1 Hz, 2 H), 7.37 (t, J = 8.2 Hz, 1 H), 7.12 (d, J = 8.2 Hz, 1 H), 7.04 (d, J = 8.2 Hz, 1 H), 5.59 (dd, J = 11.9, 4.6 Hz, 1 H), 5.43 (d, J = 13.7 Hz, 1 H), 5.33 (d, J = 13.7 Hz, 1 H), 4.86 (brm, 1 H), 4.52 (d, J = 11.0 Hz, 1 H), 4.34 (d, J = 11.0 Hz, 1 H), 3.53 (s, 3 H), 2.73

(brd, J = 13.7 Hz, 1 H), 2.59 (m, 2 H), 2.45 (dd, J = 18.8, 11.4 Hz, 1 H), 2.19 (m, 1 H), 2.05 (m, 2 H), 1.82 (s, 3 H), 1.65 (s, 6 H), 0.96 (d, J = 6.5 Hz, 3 H) ppm; ^{13}C NMR (150 MHz, CDCl_3): δ = 195.8, 194.6, 170.3, 165.5, 156.5, 137.3, 132.8, 132.3, 131.6 (2 C), 131.3 (2 C), 131.0, 130.0, 129.3, 127.9, 127.1, 122.5, 120.3, 120.2, 111.5, 66.2, 64.7, 55.8, 51.2, 31.4, 30.9, 30.0, 29.5, 25.9, 25.5, 17.9, 14.9 ppm; HRMS (MALDI): calcd for $\text{C}_{33}\text{H}_{35}\text{O}_6\text{Br}$ [MH^+]: 607.1690, found: 607.1680.

54 (1:1 mixture of $\Delta^{8,9}$ geometrical isomers): R_f = 0.40 (silica gel, hexane/EtOAc 2:1); IR (film) $\nu_{\max}$ = 2958, 1772, 1720, 1686, 1642, 1589, 1511, 1458, 1376, 1301, 1268, 1174, 1115, 1069,

1035, 1010, 987, 929, 850, 758 cm^{-1} ; ^1H NMR (600 MHz, CDCl_3): δ = 7.94 (d, J = 7.7 Hz, 2 H), 7.93 (d, J = 7.7 Hz, 2 H), 7.58 (d, J = 7.7 Hz, 2 H), 7.57 (d, J = 8.7 Hz, 2 H), 7.42 (t, J = 7.7 Hz, 1 H), 7.41 (t, J = 7.7 Hz, 1 H), 7.26 (d, J = 7.7 Hz, 1 H), 7.25 (d, J = 7.7 Hz, 1 H), 7.12 (d, J = 8.7 Hz, 1 H), 7.06 (d, J = 7.7 Hz, 1 H), 5.49 (d, J = 13.1 Hz, 1 H), 5.48 (d, J = 13.2

Hz, 1 H), 5.42 (brt, J = 7.6 Hz, 1 H), 5.29 (d, J = 13.2 Hz, 1 H), 5.25 (d, J = 13.1 Hz, 1 H), 5.19 (dd, J = 8.8, 5.5 Hz, 1 H), 5.05 (brt, J = 7.1 Hz, 1 H), 4.88 (brd, J = 8.8 Hz, 1 H), 4.61 (d, J = 11.0 Hz, 1 H), 4.55 (d, J = 11.0 Hz, 1 H), 4.27 (d, J = 11.0 Hz, 1 H), 4.07 (d, J = 11.0 Hz, 1 H), 3.57 (s, 3 H), 3.55 (s, 3 H), 2.81 (dd, J = 17.6, 4.4 Hz, 1 H), 2.65 – 2.50 (m, 5 H), 2.35 – 2.20 (m, 5 H), 2.10 (m, 2 H), 1.74 (dd, J = 14.2, 5.4 Hz, 1 H), 1.67 (s, 3 H), 1.63 (s, 3 H), 1.61 (s, 3 H), 1.57 (s, 6 H), 1.51 (s, 3 H), 0.98 (d, J = 6.6 Hz, 3H), 0.94 (d, J = 6.6 Hz, 3H) ppm; ^{13}C NMR (150 MHz, CDCl_3): δ = 201.7, 199.2, 195.8, 195.4, 174.9, 173.9, 165.5, 165.4, 155.2, 155.0,

139.1, 139.0, 134.7, 134.1, 133.9, 132.8, 131.8 (2 C), 131.7 (2 C), 131.5, 131.3 (4 C), 128.8, 128.4, 128.3, 128.2, 127.6, 125.9, 125.4, 123.4, 123.1, 122.6, 121.4, 120.9, 120.7, 120.5, 119.8, 82.4, 80.1, 65.9, 65.6, 57.8, 57.6, 54.7, 54.4, 45.5, 45.3, 34.7, 32.6, 31.5, 30.8, 30.8, 29.5, 26.1, 26.0, 22.6, 18.0, 17.8, 17.5, 16.5, 16.0, 15.1, 14.1 ppm; HRMS (MALDI): calcd for $C_{33}H_{35}O_6Br$ $[MNa]^+$: 629.1509, found: 629.1513.

55: R_f = 0.55 (silica gel, hexane/EtOAc 2:1); IR (film) ν_{max} = 2956, 2931, 1721, 1671, 1634, 1584, 1466, 1450, 1318, 1267, 1116, 1103, 1011, 976, 848, 757, 735 cm^{-1} ; 1H NMR (500 MHz,

$CDCl_3$): δ = 8.01 (d, J = 9.1 Hz, 2 H), 7.58 (d, J = 8.2 Hz, 2 H), 7.38 (t, J = 8.2 Hz, 1 H), 7.20 (d, J = 7.4 Hz, 1 H), 7.01 (d, J = 8.2 Hz, 1 H), 5.81 (d, J = 14.6 Hz, 1 H), 5.80 (m, 1 H), 5.57 (d, J = 14.6 Hz, 1 H), 4.94 (brs, 1 H), 4.36 (AB system, $\Delta\delta$ = 0.0263 ppm, J = 9.9 Hz, 2 H), 3.83 (s, 3 H), 2.82 (brd, J = 11.9 Hz, 1 H), 2.54 (t, J = 11.9 Hz, 1 H), 2.40 (m, 1 H), 2.35 –

2.22 (m, 2 H), 2.14 (dd, J = 14.6, 9.1 Hz, 1 H), 2.05 (dd, J = 11.9, 5.5 Hz, 1 H), 1.95 (s, 3 H), 1.71 (s, 3 H), 1.66 (s, 3 H), 0.92 (d, J = 6.5 Hz, 3H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$): δ = 198.5, 197.5, 177.1, 165.5, 156.8, 138.6, 133.7, 132.6, 132.0, 131.6 (2 C), 131.4 (2 C), 131.3, 129.4, 128.2, 127.9, 122.1, 121.0, 119.8, 114.9, 68.2, 64.6, 60.6, 49.3, 41.6, 32.7, 32.3, 30.1, 26.0, 24.1, 18.0, 15.1 ppm; HRMS (MALDI): calcd for $C_{33}H_{35}O_6Br$ $[MNa]^+$: 629.1509, found: 629.1527.

Introduction of $\Delta^{11,12}$ double bond in macrocycles **53** and **54** (Scheme 11):

To a solution of macrocycle **53** or **54** (70 mg, 0.115 mmol) in anhydrous THF (4 mL) at $-78^\circ C$ was added slowly a solution of LiHMDS (150 μL , 1 M in THF). The resulting solution was allowed to warm to $-10^\circ C$ ($25^\circ C$ for **54**) over a period of 1 h. After re-cooling to $-78^\circ C$ ($-60^\circ C$ for **54**) a solution of PhSeCl (31 mg, 0.16 mmol) in anhydrous THF (1 mL) was added slowly. The solution was allowed to warm to $0^\circ C$ ($25^\circ C$ for **54**) over a period of 30 min. At this stage, formation of the less polar intermediate selenide, was observed by TLC. Once this conversion was complete, saturated aq. NH_4Cl (0.3 mL) and 31% aq. H_2O_2 (0.3 mL) were added and the mixture was stirred for 1 h at $25^\circ C$. The mixture was diluted with EtOAc (10 mL) and the layers were separated. The organic phase was washed with H_2O (5 mL) and brine (5 mL) and then dried ($MgSO_4$). The solvent was removed *in vacuo* to afford, after purification by flash column

chromatography (silica gel, EtOAc:hexane 1:6 $\rightarrow$ 1:3), **56** (43 mg, 61%) as a syrup, or **57** (37 mg, 51%) as a syrup accompanied by recovered **54** (10.5 mg, 15%).

56: R_f = 0.33 (silica gel, hexane/EtOAc 2:1); IR (film) $\nu_{\max}$ = 2971, 2914, 1717, 1650, 1619, 1590, 1532, 1464, 1397, 1376, 1326, 1269, 1116, 1104, 1011, 986, 757, 734 cm^{-1} ; ^1H NMR (500

MHz, CD_3CN): δ = 7.88 (d, J = 9.1 Hz, 2 H), 7.59 (d, J = 8.3 Hz, 2 H), 7.38 (t, J = 8.3 Hz, 1 H), 7.17 (d, J = 7.4 Hz, 1 H), 7.01 (d, J = 8.3 Hz, 1 H), 6.50 (brs, 1 H), 5.50 (d, J = 13.2 Hz, 1 H), 5.38 (brt, J = 8.3 Hz, 1 H), 5.30 (d, J = 13.2 Hz, 1 H), 4.44 (d, J = 9.2 Hz, 1 H), 4.43 (brt, J = 6.4 Hz, 1 H), 4.11 (brd, J = 9.2 Hz, 1 H), 3.85 (s, 3 H), 2.81 (brd, J = 13.7 Hz, 1 H), 2.50 (dd,

J = 12.8, 10.1 Hz, 1 H), 2.32 (m, 2 H), 2.02 (d, J = 1.8 Hz, 3 H), 1.81 (s, 3 H), 1.56 (s, 3 H), 1.47 (s, 3 H) ppm; ^{13}C NMR (125 MHz, CDCl_3): δ = 200.5 (br), 192.0, 171.5 (br), 165.5, 159.5, 157.4, 136.6, 135.0, 133.5, 131.5 (2 C), 131.3 (2 C), 131.2, 130.8, 129.3, 127.6, 125.5, 123.1 (br), 119.0 (br), 114.9 (br), 107.8, 106.9 (br), 69.5 (br), 65.3, 58.6, 57.9, 53.4, 39.9, 25.5, 23.3 (br), 20.3, 18.0 ppm; HRMS (MALDI): calcd for $\text{C}_{33}\text{H}_{33}\text{O}_6\text{Br}$ $[\text{MNa}]^+$: 627.1353, found: 627.1362.

57: (mixture of $\Delta^{8,9}$ geometrical isomers in a 3:1 ratio): R_f = 0.29 (silica gel, hexane/EtOAc 2:1); IR (film) $\nu_{\max}$ = 2918, 1722, 1650, 1621, 1533, 1454, 1267, 1101, 1011, 758, 735 cm^{-1} ; ^1H NMR

(600 MHz, CDCl_3 , major (*E*)-isomer): δ = 7.95 (d, J = 9.1 Hz, 2 H), 7.59 (d, J = 8.3 Hz, 2 H), 7.38 (t, J = 7.9 Hz, 1 H), 7.23 (d, J = 7.9 Hz, 1 H), 7.17 (d, J = 8.3 Hz, 1 H), 6.30 (d, J = 1.3 Hz, 1 H), 5.56 (brd, J = 11.4 Hz, 1 H), 5.54 (d, J = 13.2 Hz, 1 H), 5.29 (d, J = 13.2 Hz, 1 H), 4.62 (brt, J = 6.5 Hz, 1 H), 4.50 (d, J = 11.9 Hz, 1 H), 4.43 (d, J = 11.9 Hz, 1 H), 3.51 (s, 3 H),

2.86 (dd, J = 14.5, 6.6 Hz, 1 H), 2.31 (m, 2 H), 2.16 (dd, J = 14.5, 7.1 Hz, 1 H), 1.95 (s, 3 H), 1.57 (s, 3 H), 1.54 (s, 3 H), 1.35 (s, 3 H) ppm; ^{13}C NMR (125 MHz, CDCl_3 , major (*E*)-isomer): δ = 199.2, 185.6, 173.1, 165.5, 155.8, 154.0, 139.0, 135.3, 134.3, 131.8 (2 C), 131.3 (2 C), 130.6, 129.2, 128.8, 128.3, 125.0, 122.4, 120.2, 119.8, 119.6, 118.6, 76.4, 65.4, 57.3, 57.1, 37.5, 34.5, 25.8, 19.8, 19.1, 18.0 ppm; HRMS (MALDI): calcd for $\text{C}_{33}\text{H}_{33}\text{O}_6\text{Br}$ $[\text{MNa}]^+$: 627.1353, found: 627.1361.

One-pot basic hydrolysis of the *p*-bromobenzoate and vinylogous methyl ester moieties of **56 and **57** (Scheme 11):**

To a solution of **56** or **57** (35 mg, 0.058 mmol) at 25 °C in absolute MeOH (4 mL) was added finely powdered K₂CO₃ (24 mg, 0.174 mmol). The mixture was stirred for 11 h (40 min for **57**) at the same temperature. Hydrolysis of the *p*-bromobenzoate and formation of the intermediate more polar benzylic alcohol was observed by TLC. In order to facilitate the hydrolysis of the vinylogous methyl ester moiety, five drops of H₂O were added and the mixture was stirred for a further 3 h (30 min for **57**) at 25 °C. The reaction mixture was then diluted with H₂O (6 mL) and washed twice with hexane/Et₂O (3:1, 5 mL) to remove organic impurities. The aqueous phase was acidified to pH = 1 with 1 M HCl and saturated with solid NaCl. The suspension was then extracted twice with EtOAc (5 mL). The organic phase was washed with brine (5 mL), dried (MgSO₄) and concentrated *in vacuo* to afford benzylic alcohol **58** (21 mg, 90%) as a yellow oil or benzylic alcohol **59** (23 mg, 96%) as an amorphous solid. The (*Z*) and (*E*) configuration at $\Delta^{16,17}$ double bond in **58** and **59**, respectively, were unambiguously confirmed by extensive NOE studies (see Scheme 11).

58: *R*_f = 0.44 (silica gel, hexane/EtOAc, 1:1); IR (film): ν_{max} = 3436, 2920, 1651, 1549, 1449, 1261, 1008, 914, 726 cm⁻¹; ¹H NMR (600 MHz, CDCl₃): δ = 15.71 (s, 1 H), 7.38 (t, *J* = 7.7 Hz,

1 H), 7.11 (d, *J* = 7.7 Hz, 1 H), 6.89 (d, *J* = 7.7 Hz, 1 H), 6.29 (s, 1 H), 5.28 (dd, *J* = 11.0, 6.6 Hz, 1 H), 4.56 (d, *J* = 12.1 Hz, 1 H), 4.51 (d, *J* = 12.1 Hz, 1 H), 4.50 (br dd, *J* = 6.5, 5.5 Hz, 1 H), 4.34 (d, *J* = 8.7 Hz, 1 H), 4.10 (d, *J* = 8.7 Hz, 1 H), 2.84 (dd, *J* = 14.8, 6.0 Hz, 1 H), 2.69 (dd, *J* = 14.3, 11.0 Hz, 1 H), 2.22 (m, 2 H), 2.08 (s, 3 H), 1.82 (s, 3 H), 1.55 (s, 3 H), 1.50 (s, 3 H);

¹³C NMR (150 MHz, CDCl₃): δ = 198.8, 181.0, 164.1, 156.4, 139.8, 136.0, 134.4, 131.9, 131.7, 131.4, 124.1, 123.6, 122.2, 117.8, 115.1, 113.1, 69.7, 64.2, 59.2, 39.0, 37.1, 25.7, 23.2, 20.1, 18.1; HRMS (MALDI) calcd for C₂₅H₂₇O₄ [MH-H₂O]⁺: 391.1904; found: 391.1905. MS (ESI) 409 (MH⁺), 431 (MNa⁺).

59: *R*_f = 0.32 (silica gel, hexane/EtOAc, 1:1); IR (film): ν_{max} = 3412, 2920, 1651, 1556, 1455, 1262, 997, 866, 736 cm⁻¹; ¹H NMR (500 MHz, CDCl₃): δ = 16.54 (s, 1 H), 7.29 (t, *J* = 8.2 Hz, 1

H), 7.12 (d, *J* = 8.2 Hz, 1 H), 7.09 (d, *J* = 7.4 Hz, 1 H), 6.38 (s, 1 H), 5.41 (br d, *J* = 12.0 Hz, 1 H), 4.66 (d, *J* = 12.3 Hz, 1 H), 4.56 (d, *J* = 11.4 Hz, 1 H), 4.55 (br dd, *J* = 7.4, 5.5 Hz, 1 H), 4.49 (d, *J* = 12.3 Hz, 1 H), 4.31 (d, *J* = 11.4 Hz, 1 H), 2.99 (dd, *J* = 14.2, 6.8 Hz, 1 H), 2.44 (t, *J* = 12.8 Hz, 1 H),

2.33 (br d, $J = 13.8$ Hz, 1 H), 2.25 (dd, $J = 14.6, 6.4$ Hz, 1 H), 2.11 (s, 3 H), 1.58 (br s, 3 H), 1.57 (br s, 3 H), 1.33 (s, 3 H); ^{13}C NMR (125 MHz, CDCl_3): $\delta = 200.0, 198.6, 183.0, 164.9, 153.5, 139.6, 135.7, 134.9, 132.2, 129.6, 128.1, 123.3, 122.9, 118.3, 118.0, 114.2, 76.3, 63.7, 58.8, 38.3, 34.4, 25.7, 20.1, 19.7, 18.0$; HRMS (MALDI) calcd for $\text{C}_{25}\text{H}_{27}\text{O}_4$ $[\text{MH}-\text{H}_2\text{O}]^+$: 391.1904; found: 391.1898. MS (ESI) 409 (MH^+), 431 (MNa^+).

Completion of the total synthesis of coleophomones B and C (Scheme 11):

To a solution of CrO_3 (29 mg, 0.29 mmol) in CH_2Cl_2 (2 mL) at 0 °C was added pyridine (47 mg, 0.58 mmol). The solution was allowed to warm to 25 °C and was stirred for 20 min prior to the addition of benzylic alcohol **58** (20 mg, 0.049 mmol) at the same temperature. Complete consumption of the starting material after 2 h was observed by TLC. The solvent was removed *in vacuo* and the residue was taken up in Et_2O (2 mL) and filtered through a short pad of celite. Once again, the solvent was removed *in vacuo*. The residue was taken up in 1 M aq. K_2CO_3 (5 mL) and washed with hexane/ Et_2O (7:3, 5 mL) to remove organic impurities. The aqueous phase was carefully acidified with 1 M HCl to pH = 1 and then extracted twice with EtOAc (5 mL). The layers were separated and the organic phase dried (MgSO_4) and concentrated *in vacuo* to afford coleophomone C (16 mg, 81%) as a yellow amorphous solid.

3 (coleophomone C): $R_f = 0.42$ (silica gel, hexane/ EtOAc 2:1); IR (film) $\nu_{\text{max}} = 2920, 1713, 1693, 1649, 1555, 1454, 1262, 1029, 790$ cm^{-1} ; ^1H NMR (500 MHz, CDCl_3): $\delta = 16.02$ (s, 1 H),

10.02 (s, 1 H), 7.67 (d, $J = 7.4$ Hz, 1 H), 7.53 (dd, $J = 8.3, 7.4$ Hz, 1 H), 7.20 (d, $J = 8.3$ Hz, 1 H), 6.34 (brs, 1 H), 5.28 (m, 1 H), 4.52 (brt, $J = 6.4$ Hz, 1 H), 4.40 (d, $J = 8.3$ Hz, 1 H), 4.14 (d, $J = 8.3$ Hz, 1 H), 2.84 (dd, $J = 13.7, 5.0$ Hz, 1 H), 2.68 (dd, $J = 13.7, 11.0$ Hz, 1 H), 2.23 (m, 2 H), 2.10 (brs, 3 H), 1.83 (brs, 3 H), 1.57 (brs, 3 H), 1.51 (brs, 3 H) ppm; ^{13}C NMR (150 MHz, CDCl_3): $\delta = 198.5, 196.7, 190.9, 181.7, 164.7, 156.1, 135.7, 134.6, 134.5, 134.2, 130.7, 123.9, 123.4, 122.3, 121.9, 117.8, 113.1, 70.6, 59.2, 39.1, 36.8, 25.7, 22.9, 20.2, 18.1$ ppm; HRMS (MALDI): calcd for $\text{C}_{25}\text{H}_{26}\text{O}_5$ $[\text{MNa}]^+$: 429.1672, found: 429.1671.

A solution of benzylic alcohol **59** (20 mg, 0.049 mmol) in Et_2O (3 mL) was treated with MnO_2 (85 mg, 0.98 mmol) and the resulting mixture was heated to reflux for 8 h. Filtration through a short pad of celite was followed by removal of the solvent *in vacuo* to afford coleophomone B (14.5 mg, 73%) as a yellow amorphous solid.

2: coleophomone B

2 (coleophomone B): R_f = 0.40 (silica gel, hexane/EtOAc 1:1); IR (film) $\nu_{\max}$ = 2926, 2855, 1701, 1660, 1558, 1457, 1261, 1113, 912, 866, 822, 736, 703 cm^{-1} ; ^1H NMR (600 MHz, CDCl_3): δ = 16.41 (s, 1 H), 9.95 (s, 1 H), 7.59 (d, J = 7.7 Hz, 1 H), 7.48 (t, J = 7.7 Hz, 1 H), 7.44 (d, J = 7.7 Hz, 1 H), 6.36 (brs, 1 H), 5.43 (brd, J = 11.0 Hz, 1 H), 4.56 (d, J = 12.0 Hz, 1 H), 4.56 (brm, 1 H), 4.40 (d, J = 12.0 Hz, 1 H), 2.91 (dd, J = 15.2, 3.3 Hz, 1 H), 2.37 (dd, J = 13.2, 12.1 Hz, 1 H), 2.28 (dd, J = 13.2, 3.3 Hz, 1 H), 2.25 (dd, J = 15.3, 7.7 Hz, 1 H), 2.08 (brs, 3 H), 1.59 (brs, 3 H), 1.54 (brs, 3 H), 1.32 (brs, 3 H) ppm; ^{13}C NMR (150 MHz, CDCl_3): δ = 197.9, 196.9, 190.4, 182.2, 164.7, 153.8, 135.9, 135.0, 134.4, 133.4, 129.5, 129.1, 126.0, 125.0, 122.5, 118.5, 113.3, 76.8, 58.5, 38.4, 34.3, 25.7, 20.2, 19.8, 18.1 ppm; HRMS (MALDI): calcd for $\text{C}_{25}\text{H}_{26}\text{O}_5$ $[\text{MNa}]^+$: 429.1672, found: 429.1673.

Abortive attempts to synthesize coleophomone A. Preparation of spirocycle **62** (Scheme 12):

To a solution of CrO_3 (26 mg, 0.26 mmol) in CH_2Cl_2 (2 mL) at 0 °C was added pyridine (42 mg, 0.52 mmol). The solution was allowed to warm to 25 °C and stirred for 20 min. The solution was re-cooled to 0 °C, prior to the addition of benzaldehyde↔spirocycle **60** (17 mg, 0.037 mmol). The starting material was shown to have been completely consumed after 5 min by TLC. The solvent was removed *in vacuo* and the residue was taken up in Et_2O (2 mL) and filtered through a short pad of celite. The organic solution was dried (MgSO_4) and concentrated *in vacuo* to afford a crude residue that was purified by flash column chromatography (silica gel, EtOAc:hexane 1:2) to furnish pure **62** (7 mg, 39%) as a pale yellow oil.

62 (mixture of stereoisomers at C12 in a 2.5:1 ratio); R_f = 0.45 (silica gel, hexane/EtOAc 3:1); ^1H NMR (500 MHz, CDCl_3): δ = 7.75 (t, J = 8.2 Hz, 1 H, minor), 7.71 (t, J = 8.2 Hz, 1 H, major), 7.59 (d, J = 7.3 Hz, 1 H, minor), 7.55 (d, J = 7.3 Hz, 1 H, major), 7.24 (d, J = 8.2 Hz, 1 H, major), 7.22 (d, J = 8.2 Hz, 1 H, minor), 5.21 (brs, 1 H, major), 5.20 (brs, 1 H, minor), 5.05 (brs, 1 H, major plus 1 H, minor), 5.03 (brt, J = 6.4 Hz, 1 H, major plus 1 H, minor), 4.88 (brt, J = 6.4 Hz, 1 H, minor), 4.85 (brt, J = 6.4 Hz, 1 H, major), 4.64 (s, 2 H, major), 4.62 (s, 2 H, minor), 2.96 (m, 1 H, major plus 1 H, minor), 2.76 (m, 1 H, minor), 2.64 (m, 3 H, major plus 2 H, minor), 2.45 (m, 2 H, major plus 2 H, minor), 2.25 (dd, J = 14.6, 8.2 Hz, 1 H, major plus 1 H,

minor), 1.86 (brs, 3 H, major), 1.85 (brs, 3 H, minor), 1.70 (brs, 3 H, major plus 3 H, minor), 1.67 (brs, 3 H, major), 1.66 (brs, 3 H, minor), 1.62 (brs, 3 H, major plus 3 H, minor), 1.61 (brs, 3 H, major plus 3 H, minor), 1.12 (d, $J = 6.4$ Hz, 3 H, major), 1.09 (d, $J = 6.4$ Hz, 3 H, minor) ppm; ^{13}C NMR (125 MHz, CDCl_3 , major): $\delta = 204.7, 202.3, 190.8, 189.9, 157.2, 145.5, 139.0, 137.4, 134.7, 134.2, 119.4, 118.7, 118.1, 116.4, 115.7, 113.6, 85.1, 72.6, 55.1, 43.7, 30.3, 30.1, 29.7, 28.6, 26.1, 26.0, 19.2, 17.9, 15.7$ ppm. HRMS (MALDI): calcd for $\text{C}_{29}\text{H}_{34}\text{O}_5$ $[\text{MNa}]^+$: 485.2298, found: 485.2303.

Olefin metathesis of **67a**, **68a**, and **69a**. Preparation of spirocycles **70**, **72**, and **74** (Scheme 13):

To a degassed solution of regioisomeric vinylogous esters **67a** or **68a** or **69a** (50 mg, 0.078 mmol, bubbling for 15 min with Ar) in anhydrous CH_2Cl_2 (5 mL) was added the second generation Grubbs catalyst **A** (13 mg, 0.015 mmol) in one portion. The resulting pink solution was heated to reflux, with light excluded from the reaction vessel, until complete consumption of the starting material was observed by TLC (4 h for **67a**, 8 h for **68a** and 3 h for **69a**). The solvent was removed *in vacuo* and the residue was purified by flash column chromatography (silica gel, EtOAc:hexane 1:9 $\rightarrow$ 1:2) to afford spirocycle **70** (30 mg, 67%), an 1:5.6 inseparable mixture of macrocycle **71** and spirocycle **72** (34 mg, 75% total yield), and a 1:2.4 inseparable mixture of macrocycle **73** and spirocycle **74** (32 mg, 71% total yield), respectively. When the mixture of **71** and **72**, or the mixture of **73** and **74**, were treated again with catalyst **A** for 48 h, only spirocycles **72** (1.1:1 mixture of geometrical isomers at $\Delta^{8,9}$) and **74** were isolated as syrups in 50 and 41% overall yields, starting from **68a** and **69a**, respectively.

70: $R_f = 0.49$ (silica gel, hexane/EtOAc 2:1); IR (film) $\nu_{\text{max}} = 2918, 1722, 1660, 1644, 1589, 1454, 1267, 1102, 1011, 757$ cm^{-1} ; ^1H NMR (500 MHz, CDCl_3): $\delta = 7.95$ (d, $J = 9.1$ Hz, 2 H), 7.55 (d, $J = 9.1$ Hz, 2 H), 7.34 (t, $J = 8.2$ Hz, 1 H), 7.17 (d, $J = 7.4$ Hz, 1 H), 6.84 (d, $J = 8.2$ Hz, 1 H), 5.55 (s, 2 H), 5.24 (brs, 1 H), 4.98 (brs, 1 H), 4.97 (brs, 1 H), 4.39 (s, 2 H), 3.83 (s, 3 H), 2.85 (brd, $J = 13.7$ Hz, 2 H), 2.30 (m, 3 H), 2.17 (d, $J = 15.5$ Hz, 1 H), 1.85 (m, 2 H), 1.78 (s, 3 H), 1.74 (brs, 3 H) ppm; ^{13}C NMR (125 MHz, CDCl_3): $\delta = 197.0, 195.7, 183.2, 165.5, 156.4, 140.2, 137.8, 137.4, 131.8, 131.5$ (2 C), 131.4 (2 C), 131.3, 129.7, 129.4, 127.8, 121.7, 121.2, 113.6, 111.7, 72.5,

72.0, 65.1, 63.1, 48.8, 34.6, 33.7, 19.7, 19.3, 16.4 ppm; HRMS (MALDI): calcd for $C_{31}H_{31}O_6Br$ $[MNa]^+$: 601.1196, found: 601.1190.

74: R_f = 0.23 (silica gel, hexane/EtOAc 2:1); IR (film) ν_{max} = 2919, 1719, 1684, 1647, 1589, 1467, 1373, 1267, 1103, 1070, 1011, 984, 757 cm^{-1} ; 1H NMR (500 MHz, $CDCl_3$): δ = 7.94 (d, J = 9.1 Hz, 2 H), 7.54 (d, J = 8.3 Hz, 2 H), 7.28 (dd, J = 8.3, 7.3 Hz, 1 H), 7.10 (d, J = 7.3 Hz, 1 H), 6.81 (d, J = 8.3 Hz, 1 H), 5.48 (s, 2 H), 5.07 (d, J = 1.8 Hz, 1 H), 4.99 (brs, 1 H), 4.95 (brs, 1 H), 4.35 (s, 2 H), 3.76 (s, 3 H), 2.70 – 2.60 (m, 4 H), 2.09 (brd, J = 13.7 Hz, 1 H), 1.94 (m, 3 H), 1.77 (s, 3 H), 1.63 (brs, 3 H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$): δ = 198.4, 195.7, 175.5, 165.5, 156.0, 140.7, 137.2, 136.2, 131.5 (2 C), 131.4 (2 C), 130.8, 130.5, 129.4, 127.8, 121.3, 121.2, 121.1, 112.7, 111.9, 72.4, 64.9, 56.4, 50.3, 45.2, 41.1, 31.8, 23.5, 19.4, 16.3 ppm; HRMS (MALDI): calcd for $C_{31}H_{31}O_6Br$ $[MNa]^+$: 601.1196, found: 601.1184.

Total synthesis of coleophomone D (Scheme 14):

To a solution of LDA at $-78^\circ C$, prepared by 20 min treatment of a solution of diisopropylamine (0.554 mL, 4.22 mmol) in anhydrous THF (10 mL) with *n*-BuLi (1.76 mL, 1.6 M in hexane), was slowly added a solution of **75** (0.39 g, 1.41 mmol) in THF:HMPA (25:1, 10.4 mL) and the resulting solution was slowly warmed to $0^\circ C$ over a 2 h period. The solution was re-cooled to $-78^\circ C$ and a solution of PhSeCl (0.404 g, 2.11 mmol) in anhydrous THF (2 mL) was added. The resulting solution was warmed to $20^\circ C$ over a period of 30 min. At this stage, complete conversion of **75** to the intermediate selenide was observed by TLC. The solution was diluted with Et₂O (20 mL) and quenched with saturated aq. NH_4Cl (10 mL). The layers were separated and the organic phase was washed with brine (10 mL). The organic phase was then treated for 1 h at $45^\circ C$ with 31% aq. H_2O_2 (1.0 mL). The organics were then washed with H_2O (10 mL) and brine (10 mL), dried ($MgSO_4$), and concentrated *in vacuo* to afford, after purification by flash column chromatography (silica gel, EtOAc:hexane 1:9), vinylogous ester **76** (0.30 g, 78%) as a syrup.

76: R_f = 0.60 (silica gel, hexane/EtOAc 2:1); IR (film) ν_{max} = 2971, 2914, 1658, 1631, 1582, 1444, 1387, 1218, 1147, 848 cm^{-1} ; 1H NMR (500 MHz, $CDCl_3$): δ = 6.00 (brd, J = 2.2 Hz, 1 H), 5.41 (d, J = 2.2 Hz, 1 H), 4.69 (brt, J = 7.0 Hz, 2 H), 3.72 (s, 3 H), 2.69 (dd, J

= 14.3, 7.0 Hz, 2 H), 2.26 (dd, J = 14.6, 7.0 Hz, 2 H), 1.90 (d, J = 1.1 Hz, 3 H), 1.57 (brs, 12 H); ^{13}C NMR (125 MHz, CDCl_3): δ = 204.2, 171.7, 155.3, 133.6, 120.6, 118.5, 99.8, 57.2, 55.4, 38.0, 25.7, 19.1, 18.0 ppm. HRMS (MALDI): calcd for $\text{C}_{18}\text{H}_{26}\text{O}_2$ $[\text{MH}]^+$: 275.2005, found: 275.2006.

To a solution of vinylogous ester **76**, prepared above, (0.20 g, 0.73 mmol) in $\text{MeOH}:\text{H}_2\text{O}$ (2:1, 9 mL) was added $\text{LiOH}\cdot\text{H}_2\text{O}$ (0.153 g, 3.65 mmol). The resulting mixture was heated for 12 h at 80 °C. The solution was cooled to room temperature, neutralized with 1 M HCl, diluted with H_2O (10 mL), and extracted twice with EtOAc (10 mL). The layers were separated and the organic phase was washed with brine, dried (MgSO_4), concentrated *in vacuo* and purified by flash column chromatography (silica gel, EtOAc:hexane 1:2) to afford 1,3-cyclohexedione **77** (0.173 g, 91%) as a syrup.

77: R_f = 0.12 (silica gel, hexane/EtOAc 2:1); IR (film) ν_{max} = 2916, 2618, 1650, 1556, 1445, 1385, 1313, 1222, 877, 734, 614 cm^{-1} ; ^1H NMR (600 MHz, CDCl_3 , keto:enol = 1.4:1): δ = 6.26

(s, 1 H, keto), 6.10 (brs, 1 H, enol), 5.70 (d, J = 1.7 Hz, 1 H, enol), 4.77 (brt, J = 7.0 Hz, 2 H, keto), 4.67 (brt, J = 7.0 Hz, 2 H, enol), 3.26 (s, 2 H, keto), 2.76 (dd, J = 14.5, 8.3 Hz, 2 H, keto plus 2 H, enol), 2.32 (dd, J = 14.5, 7.9 Hz, 2 H, enol), 2.25 (dd, J = 14.9, 6.6 Hz, 2 H, keto), 2.03 (d, J = 0.9 Hz, 3 H, keto),

1.90 (d, J = 1.3 Hz, 3 H, enol), 1.62 (s, 6 H, keto), 1.58 (s, 6 H, keto plus 6 H, enol) 1.57 (s, 6 H, enol); ^{13}C NMR (150 MHz, CDCl_3): δ = 207.1, 193.8, 186.9, 185.6, 158.8, 135.8, 134.0 (2 C), 129.8, 127.3, 119.7, 119.6, 117.8, (2 C), 105.5, 58.1, 53.7, 52.5, 36.3 (2 C), 35.4, 25.8, 25.6 (2 C), 19.8, 18.6, 18.0 (2 C), 17.8 ppm. HRMS (MALDI): calcd for $\text{C}_{17}\text{H}_{24}\text{O}_2$ $[\text{MNa}]^+$: 283.1668, found: 283.1665.

To a solution of aldehyde **79**³⁸ (0.73 g, 3.50 mmol) in anhydrous toluene (25 mL) at 0 °C was added slowly a solution of Et_2AlCN (3.5 mL, 1 M in toluene) and the resulting solution was stirred for 2 h at the same temperature. The mixture was then diluted with EtOAc (30 mL) and treated with saturated aq. sodium potassium tartrate (30 mL) for 30 min with vigorous stirring. The layers were separated and the organic phase was dried (MgSO_4), concentrated *in vacuo*, and purified with flash chromatography (silica gel, EtOAc:hexane 1:4 $\rightarrow$ 1:2) to afford the desired cyanohydrin **81** (0.485 g, 59%) as a syrup, accompanied by the regioisomeric migrated acetate **80** (0.123 g, 15%).

81: R_f = 0.18 (silica gel, hexane/EtOAc 2:1); ^1H NMR (500 MHz, CDCl_3): δ = 7.40 (dd, J = 8.4, 7.7 Hz, 1 H), 7.29 (brd, J = 7.7 Hz, 1 H), 6.98 (brd, J = 8.4 Hz, 1 H), 5.85 (d, J = 5.9 Hz, 1 H), 5.36 (d, J = 12.3 Hz, 1 H), 5.28 (d, J = 12.3 Hz, 1 H), 4.49 (d, J = 5.9 Hz, 1 H), 3.86 (s, 3 H), 2.05 (s, 3 H) ppm; ^{13}C NMR (125 MHz, CDCl_3): δ = 172.2, 159.2, 136.9, 131.2, 122.1, 120.3, 119.5, 112.8, 61.4, 57.8, 56.4, 21.4 ppm. HRMS (MALDI): calcd for $\text{C}_{12}\text{H}_{13}\text{O}_4\text{N}$

$[\text{MNa}]^+$: 258.0737, found: 258.0737.

A solution of cyanohydrin **81**, prepared above, (0.44 g, 1.87 mmol) in anhydrous CH_2Cl_2 (25 mL) was heated to reflux for 4 h in the presence of PCC (1.61 g, 7.48 mmol). A sufficient amount of celite was then added to absorb the reaction mixture accompanied by vigorous stirring. The resulting paste was transferred directly on to the top of a silica gel column and subsequent flash column chromatography (EtOAc:hexane 1:3 $\rightarrow$ 1:2) afforded acyl cyanide **82** (0.22 g, 51%) as white crystals.

82: M.p. 104 – 105 $^\circ\text{C}$ (CDCl_3); R_f = 0.33 (silica gel, hexane/EtOAc 2:1); IR (film) ν_{max} = 1724, 1672, 1588, 1472, 1281, 1247, 1013, 740 cm^{-1} ; ^1H NMR (500 MHz, CDCl_3): δ = 7.86 (brd, J = 7.7 Hz, 1 H), 7.61 (t, J = 8.1 Hz, 1 H), 7.32 (brd, J = 8.1 Hz, 1 H), 5.45 (s, 2 H), 3.92 (s, 3 H), 2.03 (s, 3 H) ppm; ^{13}C NMR (125 MHz, CDCl_3): δ = 170.7, 168.0, 159.0, 133.5, 130.6, 126.3, 125.4, 118.4, 113.3, 56.5, 56.4, 20.7 ppm. HRMS (MALDI): calcd for $\text{C}_{12}\text{H}_{11}\text{O}_4\text{N}$ $[\text{MNa}]^+$: 256.0580, found: 256.0582.

To a solution of acyl cyanide **82** (0.12 g, 0.52 mmol) in THF (7 mL) was added 1,3-cyclohexedione **77** (0.135 g, 0.52 mmol) followed by Et_3N (72 μL , 0.52 mmol). The resulting solution was stirred for 72 h at 25 $^\circ\text{C}$. The solution was diluted with Et_2O (10 mL), washed with 1 M HCl (5 mL) and brine (10 mL) and then dried (MgSO_4). The solvent was removed *in vacuo* and the residue was purified by flash column chromatography (silica gel, EtOAc:hexane 1:4 $\rightarrow$ 1:3) to provide the pure coupled product (0.193 g, 80%) as a yellow syrup. ^1H NMR spectrum of this tricarbonyl compound revealed a complicated mixture of enol and keto tautomers.

The coupled product (0.193 g, 0.41 mmol), prepared above, was dissolved in MeOH (15 mL) and was stirred with finely powdered K_2CO_3 (0.172 g, 1.25 mmol) for 24 h at 25 $^\circ\text{C}$. The mixture was diluted with H_2O (20 mL) and the aqueous phase was washed twice with 10 mL hexane/ Et_2O (7:3) to remove organic impurities. The aqueous phase was then acidified to pH = 1 with 1 M HCl, saturated with solid NaCl, and extracted twice with EtOAc (15 mL). Finally, the

organic phase was washed with brine, dried (MgSO₄) and concentrated *in vacuo* to afford benzylic alcohol **83** (0.165 g, 94%) as a yellow syrup.

83 (mixture of two keto atropisomers in 3:2 ratio in CDCl₃): R_f = 0.31 (silica gel, hexane:EtOAc, 2:1); IR (film): $\nu_{\max}$ = 2967, 2922, 1776, 1732, 1651, 1614, 1589, 1484, 1270, 1079, 728 cm⁻¹; ¹H NMR (600 MHz, CDCl₃): δ = 8.47 (d, J = 7.7 Hz, 1 H, minor), 8.07 (d, J = 7.7 Hz, 1 H, major), 7.41 (t, J = 7.7 Hz, 1 H, minor), 7.35 (t, J = 7.7 Hz, 1 H, major), 7.04 (d, J = 7.7 Hz, 1 H, minor), 7.02 (d, J = 7.7 Hz, 1 H, major), 6.29 (s, 1 H, minor), 6.27 (s, 1 H, major), 5.61 (s, 2 H, major), 5.58 (s, 2 H, minor), 4.85 (br t, J = 6.6 Hz, 2 H, major), 4.82 (br t, J = 6.6 Hz, 2 H, minor), 3.90 (s, 3 H, minor), 3.90 (s, 3 H, major), 2.83 (m, 2 H, minor and 2 H, major), 2.32 (dd, J = 14.3, 6.6 Hz, 2 H, major), 2.24 (dd, J = 14.3, 6.6 Hz, 2 H, minor), 1.97 (s, 3 H, minor), 1.95 (s, 3 H, major), 1.55 (s, 6 H, major and 6 H, minor), 1.49 (s, 6 H, major and 6 H, minor); ¹³C NMR (150 MHz, CDCl₃): δ = 202.2 (minor), 200.3 (major), 186.7 (minor), 185.6 (major), 177.2 (major), 176.9 (minor), 157.3 (minor), 156.0 (major), 153.4 (2C), 134.3, 134.2, 134.1, 133.8, 131.1, 130.5, 130.1, 129.8, 121.5, 120.5, 118.9 (2C), 118.8 (2C), 114.7 (minor), 114.6 (major), 113.9 (minor), 113.8 (major), 75.8 (major), 75.5 (minor), 57.5 (minor), 56.9 (major), 55.5 (major and minor), 36.5 (2 C minor), 36.3 (2 C major), 25.7 (2 C major and 2 C minor), 19.5 (minor), 19.2 (major), 18.1 (major), 17.9 (minor); HRMS (MALDI) calcd for C₂₆H₃₀O₄Na [MNa - H₂O]⁺: 429.2042; found: 429.2097; MS (ESI) 407 (MH⁺ - H₂O), 429 (MNa⁺ - H₂O).

A solution of benzylic alcohol **83** (0.15 g, 0.35 mmol) in Et₂O (15 mL) was treated with MnO₂ (0.308 g, 3.50 mmol) and the resulting mixture was refluxed for 4 h. Filtration through a short pad of celite followed by solvent evaporation *in vacuo* afforded coleophomone D (0.122 g, 83%) as a yellow amorphous solid. Coleophomone D exists as a complex and dynamic mixture of isomers (see Scheme 1). The spectral data we obtained for the synthetically derived sample is in full accord with the data reported³ for the naturally occurring sample.

Reference numbers used in this experimental section refer to the same reference numbers used in the main body of the manuscript.