SUPPORTING INFORMATION

Exploiting the Reversibility of Olefin Metathesis. Syntheses of Macrocyclic Trisubstituted Alkenes and (*R*,*R*)-(−)-Pyrenophorin

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General. All reactions were carried out under Ar in pre-dried glassware using Schlenk techniques. The solvents were dried by distillation over the drying agents indicated and were stored and transferred under Ar: CH_2Cl_2 (P_4O_{10}), benzene (Na/K), THF (magnesium/ anthracene). Flash chromatography: Merck silica gel (230-400 mesh). NMR: Spectra were recorded on a Bruker DPX 300 spectrometer in the solvent indicated. Chemical shifts (δ) are given in ppm relative to TMS, coupling constants (*J*) in Hz. IR: Nicolet FT-7199, wavenumbers in cm^{-1}. MS: Finnigan MAT 8200 (70 eV); HR-MS: Finnigan MAT SSQ 7000 (70 eV). Elemental analyses: Dornis & Kolbe, Mülheim. Commercially available reagents (Aldrich, Fluka) were used as received.

Ester 5. ^{1}H-NMR (CD_2Cl_2, 300MHz) δ 5.90-5.70 (m, 1H), 5.05-4.85 (m, 2H), 4.80 (m, 1H), 4.73 (m, 1H), 4.16 (t, 2H, *J* = 6.8 Hz), 2.35-2.24 (m, 4H), 2.10-2.00 (m, 2H), 1.75 (s, 3H), 1.60-1.55 (m, 2H), 1.40-1.25 (m, 10H); ^{13}C-NMR (CD_2Cl_2, 75 MHz) δ 173.6, 142.2, 139.4, 113.9, 111.8, 62.3, 36.8, 34.3, 33.9, 29.4, 29.3, 29.2, 29.2, 29.0, 25.0, 22.3; IR (film): 3077, 2927, 2855, 1739, 1651, 1641, 1456, 1376, 1170, 994, 909, 892 cm^{-1}; MS (EI) *m/z* (rel. intensity) 252 ([M^+], 4), 237 (1), 223 (2), 182 (3), 165 (3), 149 (9), 123 (4), 110 (6), 95 (12), 81 (12), 68 (100), 55 (24), 41 (34); $C_{16}H_{28}O_2$ (252.40) *calcd.*: C, 76.14; H, 11.18; *found* C, 75.99; H 11.26.

Compound 6. ^{1}H-NMR ($CDCl_3$, 300MHz) δ 5.36-5.33 (m, 2H), 4.77 (s, 2H), 4.70 (s, 2H), 4.15 (t, 4H, *J* = 6.8 Hz), 2.33-2.23 (m, 8 H), 2.00-1.90 (m, 4H), 1.73 (s, 6H), 1.65-1.45 (m, 4H), 1.40-1.15 (m, 20 H); ^{13}C-NMR ($CDCl_3$, 75 MHz) δ 173.8, 141.7, 130.3, 129.8, 112.2, 62.4, 36.7, 34.3, 32.5, 29.7, 29.6, 29.5, 29.3, 29.3, 29.2, 29.1, 29.0, 27.2, 24.9, 22.4; IR (KBr): 3077, 2925, 2854, 1737, 1652, 1456, 1376, 1171, 969, 891, 724 cm^{-1}; MS (EI) *m/z* (rel. intrensity) 476 ([M^+], 5), 391 (6), 321 (8), 303 (17), 95 (8), 69 (100), 41 (33).

12-Methyl-1-oxa-2-oxo-cyclotetradec-11-ene (7). ^{1}H-NMR ($CDCl_3$, 300MHz) δ 5.23 (t, 1H, *J* = 7.7 Hz), 4.21 (t, 2H, *J* = 5.5 Hz), 2.40-2.28 (m, 4H), 2.06-1.99 (m, 2H), 1.63 (s, 3H), 1.61-1.52 (m, 2H), 1.40-1.10 (m, 10H); ^{13}C-NMR ($CDCl_3$, 75 MHz) δ 174.1, 131.5, 127.9, 61.9, 38.8, 34.9, 27.6, 27.0, 26.0, 25.9, 25.7, 24.1, 23.8, 15.3 ; IR (film) : 2930, 2858, 1733, 1456, 1383, 1336, 1250, 1174, 1134, 1084, 1039 cm^{-1}; MS (EI) *m/z* (rel. intensity) 224 ([M^+], 51), 209 (2), 195 (23), 177 (5), 167 (5), 154 (17), 136 (27), 109 (44), 95 (59), 81 (100), 68 (85), 55 (40), 41 (50); HR-MS *calcd.* 224.17763; *found* 224.17763.

Table S-1. Key features of previous total syntheses[21,22] of pyrenophorin **8**.[a]

Method[b]	Yield (%)[b]	Overall Steps[a]	Overall Yield (%)[a]	Rac / (–)[c]	Principal Investigator	Ref.
Dilactonization (Mitsunobu)	24	9	1	d/l + meso	Gerlach	19b
	23	11	<1	d/l + meso	Bakuzis	19c
	17	9	<<6	d/l + meso	Takei	19d
	20	10	<1	d/l + meso	Bates	19g
	50	9	<7	d/l + meso	Hirao	19i
	75	10	15	(–)	Seebach	14b
	45-55	8	20	(–)	Seebach	14c
	44	>10	<7	(–)	Kibayashi	14f
	47	8	?	d/l + meso	Fujisawa	19k
	44	12	3	(–)	Matsushita	14g
Dilactonization ($Me_2Sn=O$)	34	9	2	d/l + meso	Steliou	19f
Dilactonization (lipase catalyzed)	44	16	<2	(–)	Ohta	14i
Dilactonization [$(EtO)_2P(O)Cl$]	60	8	3	d/l + meso	Wakamatsu	19h
Stepwise esterification	60	14	1	d/l + meso	Colvin	19a
Olefination (Wittig)	83	9	4	d/l + meso	Le Floc'h	19j
Olefination (Horner)	52	>10	<6	(–)	Takano	14d
Olefination (sulfoxide)	56	11	14	(–)	Nokami	14h
1,3-dipolar cycloaddition	85	7	17	d/l + meso	Takei	19e
Stille coupling	38	7	12(23)	(–)	Baldwin	14e

[a] In some cases it is difficult to determine the precise number of steps as well as the overall yield of a given sequence for the following reasons: (i) eventually, some syntheses of **8** commence with substrates which themselves must be prepared by several steps; (ii) ambiguities arise where several reactions are carried out in "one pot" without isolating or rigorously purifying the intermediates; (iii) in some cases, the yield of individual steps are not reported. Therefore the numbers compiled in Table S-1 are only meant to provide a gross picture and refer to the sequence as traced back to *commercially* available starting materials. [b] Refers to the method and yield of the reaction which forms the macrocyclic ring. [c] It is worth mention that cyclo-dimerizations of racemic precursors necessarily lead to the formation of mixtures of *rac*-**8** and *meso*-**8** and are therefore inherently less productive than cyclizations of optically active substrates.

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[21] For syntheses of (–)-pyrenophorin see ref. 14. See the following for syntheses of rac-pyrenophorin: (a) Colvin, E. W.; Purcell, T. A.; Raphael, R. A. *J. Chem. Soc. Perkin Trans. 1* **1976**, 1718. (b) Gerlach, H.; Oertle, K.; Thalmann, A. *Helv. Chim. Acta* **1977**, *60*, 2860. (c) Bakuzis, P.; Bakuzis, M. L. F.; Weingartner, T. F. *Tetrahedron Lett*. **1978**, 2371. (d) Asaoka, M.; Yanagida, N.; Sugimura, N.; Takei, H. *Bull. Chem. Soc. Jpn.* **1980**, *53*, 1061. (e) Asaoka, M.; Mukuta, T.; Takei, H. *Tetrahedron Lett*. **1981**, *22*, 735. (f) Steliou, K.; Poupart, M-A. *J. Am. Chem. Soc*. **1983**, *105*, 7130. (g) Bates, G. S.; Ramaswamy, S. *Can. J. Chem*. **1983**, *61*, 2466. (h) Wakamatsu, T.; Yamada, S.; Ozaki, Y.; Ban, Y. *Tetrahedron Lett*. **1985**, *26*, 1989. (i) Hirao, T.; Fujihara, Y.; Kurokawa, K.; Ohshiro, Y.; Agawa, T. *J. Org. Chem*. **1986**, *51*, 2830. (j) Le Floc'h, Y.; Dumartin, H.; Grée, R. *Bull. Soc. Chim. Fr*. **1995**, *132*, 114. (k) Fujisawa, T.; Takeuchi, M.; Sato, T. *Chem. Lett*. **1982**, 1795.

[22] Formal total syntheses: (a) Trost, B. M.; Gowland, F. W. *J. Org. Chem*. **1979**, *44*, 3448. (b) Hase, T. A.; Ourila, A.; Holmberg, C. *J. Org. Chem*. **1981**, *46*, 3137. (c) Breuilles, P.; Uguen, D. *Tetrahedron Lett*. **1984**, *25*, 5759. (d) Lygo, B.; O'Connor, N. *Synlett* **1990**, 282. (e) Ngooi, T. K.; Scilimati, A.; Guo, Z-W.; Sih, C. J. *J. Org. Chem*. **1989**, *54*, 911. (f) Barco, A.; Benetti, S.; De Risi, C.; Pollini, G. P.; Zanirato, V. *Tetrahedron* **1995**, *51*, 7721. (g) Derguini, F.; Linstrumelle, G. *Tetrahedron Lett*. **1984**, *25*, 5763. (h) Labadie, J. W.; Stille, J. K. *Tetrahedron Lett*. **1983**, *24*, 4283. (i) Dumont, W.; Vermeyen, C.; Krief, A. *Tetrahedron Lett*. **1984**, *25*, 2883. (j) Solladié, G.; Gerber, C. *Synlett* **1992**, 449. (k) Yokota, S.; Nishida, M.; Mitsunobu, O. *Bull. Chem. Soc. Jpn*. **1983**, *56*, 1803. (l) Zimmer, R.; Collas, M.; Roth, M.; Reissig, H-U. *Liebigs Ann. Chem*. **1992**, 709. (m) Gu, J.-X.; Li; Z.-Y.; Lin, G.-Q. *Tetrahedron* **1993**, *49*, 5805.

(*R*)-Hept-6-en-2-ol (**10**). A solution of 3-butenylmagnesium bromide [prepared from 4-bromo-1-butene (4.24 g, 31.4 mmol) and Mg (820 mg, 34.6 mmol)] in THF (30 mL) is added over 30 min to a suspension of (*R*)-methyloxirane (1.4 mL, 19.9 mmol) and CuCl(COD) (592 mg, 2.84 mmol) in THF (25 mL) at -78 °C. The mixture is allowed to warm to ambient temperature overnight. The reaction is quenched by addition of aq. sat. NH_4Cl (30 ml) and the aqueous layer is extracted with Et_2O (3 x 30 mL). Drying of the combined organic phases over Na_2SO_4, evaporation of the solvent followed by flash chromatography of the crude product (pentane/Et_2O, 4 : 1) affords product **10** as a colourless oil (1.69 g, 75 %). ^{1}H-NMR (CD_2Cl_2, 300 MHz) δ 5.82 (1H, ddt, J = 17.0, 9.8, 6.7 Hz), 5.07 - 4.92 (2H, m), 3.82 - 3.69 (1H, m), 2.11 - 2.03 (2H, m), 1.49 - 1.34 (5H, m), 1.15 (3H, d, J = 6.1 Hz); ^{13}C-NMR (CD_2Cl_2, 75.5 MHz) δ 139.3, 114.6, 68.1, 39.2, 34.1, 25.5, 23.7; $[\alpha]^{20}_D$ = −10.8 (0.82, $CHCl_3$) [ref[23]: $[\alpha]^{26}_D$ of the (*S*)-enantiomer: +10.4 (0.79, $CHCl_3$)]; IR (neat) 3356, 3077, 2969, 2932, 2861, 1641, 1459, 1440, 1416, 1374, 1122, 996, 910 cm^{-1}; MS (EI) *m/z* (rel. intensity) 114 ([M^+], < 1), 96 (10), 81 (41), 71 (19), 54 (49), 45 (100).

(*R*)-Acrylic acid 1-methyl-hex-5-enyl ester (**11**). A solution of acrylic acid chloride (0.89 mL, 11 mmol) in CH_2Cl_2 (25 mL) is added slowly at 0 °C to a solution of alcohol **10** (1.14 g, 10 mmol) and triethylamine (4.2 mL, 30 mmol) in CH_2Cl_2 (25 mL). After stirring at r. t. for 14 h the organic layer is washed with aq. HCl (1M, 3 x 25 mL) and brine (25 mL). Drying of the organic phases over Na_2SO_4, evaporation of the solvent and flash chromatography of the crude material (hexanes/ethyl acetate, 30:1) affords ester **11** as a colourless oil (1.37 g, 82 %). ^{1}H-NMR ($CDCl_3$, 300 MHz) δ 6.35 (1H, dd, J = 17.3, 1.6 Hz), 6.07 (1H, dd, J = 17.3, 10.4 Hz), 5.83 - 5.68 (2H, m), 5.03 - 4.89 (3H, m), 2.08 - 1.98 (2H, m), 1.68 - 1.32 (4H, m), 1.21 (3H, d, J = 6.3 Hz); ^{13}C-NMR ($CDCl_3$, 75.5 MHz) δ 165.8, 138.4, 130.1, 129.0, 114.7, 71.0, 35.3, 33.4, 24.6, 19.9; $[\alpha]^{20}_D$ = −8.6 (1.35, CH_2Cl_2); IR (neat) 3078, 2978, 2937, 2864, 1723, 1639, 1620, 1406, 1381, 1296, 1272, 1199, 1128, 1047, 986, 912, 810 cm^{-1}; MS (EI) *m/z* (rel. intensity) 168 ([M^+], < 1), 125 (1), 111 (2), 96 (16), 81 (32), 67 (12), 55 (100), 41 (20), 27 (26). HR-MS (CI) ($C_{10}H_{16}O_2$ + H) *calcd.* 169.1229; *found* 169.1228. $C_{10}H_{16}O_2$ (168.24) *calcd*. C 71.39, H 9.59; *found* C 71.48, H 9.64.

(3*E*,8*R*,11*E*,16*R*)-8,16-Dimethyl-1,9-dioxa-cyclohexadeca-3,11-diene-2,10-dione (**12**). Ruthenium complex **4** (42 mg, 0.05 mmol, 5 mol-%) is added to a refluxing solution of diene **11** (168 mg, 1 mmol) in CH_2Cl_2 (500 mL). The reaction is quenched after 50 min by addition of ethylvinyl ether (2 mL). Evaporation of the solvent and flash chromatography (hexanes/ ethyl acetate, 30:1→20:1) affords diolide **12** as a colourless oil (52.4 mg, 37 %). ^{1}H-NMR (CD_2Cl_2, 300 MHz) δ 6.93 (2H, ddd, J = 15.6, 7.7, 5.7 Hz), 5.81 (2H, dt, J = 15.6, 1.6 Hz), 5.01 - 4.91 (2H, m), 2.35 - 2.09 (4H, m), 1.78 - 1.48 (8H, m), 1.22 (6H, d, J = 6.4 Hz); ^{13}C-NMR (CD_2Cl_2, 75.5 MHz) δ 166.0, 148.6, 122.9, 70.4, 33.4, 31.0, 22.3, 19.1; $[\alpha]^{20}_D$ = −56.2 (0.68, CH_2Cl_2) [ref.[3c]: $[\alpha]^{21}_D$ = −32.5 (0.53, benzene)]; IR (neat) 2975, 2936, 2870, 1716, 1655, 1455, 1355, 1268, 1211, 1172, 1134, 1084, 983, 869, 842 cm^{-1}; MS (EI) *m/z* (rel. intensity) 280 ([M^+], 4), 262 (13), 140 (65), 122 (100), 95 (75), 81 (72), 68 (34), 55 (30), 43

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[23] Takahata, H.; Yotsui, Y.; Momose, T. *Tetrahedron*, **1998**, *54*, 13505.

(24). HR-MS (CI) ($C_{16}H_{24}O_4$ + H) *calcd.* 281.1753; *found* 281.1756. The analytical data are in full agreement with those reported in the literature.[16b]

(–)-Pyrenophorin (**8**). Chromium trioxide (150 mg, 1.5 mmol) is added in small portions to a mixture of acetic anhyride (0.6 mL) and acetic acid (1.2 mL). The mixture was cooled to 0 °C and diluted with benzene (1 mL). After stirring at 0 °C for 30 min, a solution of substrate **12** (42.0 mg, 0.15 mmol) in benzene (1 mL) was added. After stirring at 0 °C for 30 min, the reaction is quenched with chilled water (1 mL) and neutralised with aq. NaOH (1M, 5 mL). The aqueous phase is extracted with ethyl acetate (3 x 10 mL), the combined organic layers are washed with sat. aq. $NaHCO_3$ (10 mL), dried (Na_2SO_4), and evaporated. Flash chromatography (hexanes/ethyl acetate, 4:1) of the residue affords the title compound **8** as colourless crystals (25.0 mg, 54 %). ^{1}H-NMR (CD_2Cl_2, 300 MHz) δ 6.92 (2H, d, J = 16.0 Hz), 6.46 (2H, d, J = 16.0 Hz), 5.06 - 4.95 (2H, m), 2.71 - 2.49 (4H, m), 2.12 - 2.05 (4H, m), 1.27 (6H, d, J = 6.3 Hz); ^{13}C-NMR (CD_2Cl_2, 75.5 MHz) δ 200.1, 165.3, 140.0, 131.6, 72.5, 37.5, 32.4, 19.7; $[\alpha]^{20}_D$ = –53.3 (0.33, acetone) [ref.[16b]: $[\alpha]_D$ = –54.5 (0.48, acetone)]; IR (neat) 3066, 2980, 2917, 2873, 1716, 1692, 1632, 1448, 1352, 1295, 1184, 1125, 1054, 1003, 896, 744, 573 cm^{-1}; MS (EI) *m/z* (rel. intensity) 308 ([M^+], 7), 264 (4), 195 (4), 171 (2), 155 (39), 138 (100), 109 (15), 99 (34), 82 (42), 68 (9), 55 (41). HR-MS (EI) ($C_{16}H_{20}O_6$) *calcd*. 308.1260; *found* 308.1260. The analytical data are in full agreement with those reported in the literature.[16b]

(3*E*,8*R*,11*E*,16*R*,19*E*,24*R*)-8,16,24-Trimethyl-1,9,17-trioxa-cyclotetracosa-3,11,19-triene-2,10,18-trione (**13**).[16c] Ruthenium complex **2** (20.5 mg, 0.025 mmol) is added to a refluxing solution of diene **11** (84 mg, 0.5 mmol) in CH_2Cl_2 (50 mL). The solution is refluxed for 15 h. Evaporation of the solvent and flash chromatography (hexanes/ethyl acetate, 20:1) affords product **13** as a colourless oil (56.6 mg, 81 %). ^{1}H-NMR (CD_2Cl_2, 300 MHz) δ 6.89 (3H, ddd, J = 15.6, 7.9, 5.9 Hz), 5.78 (3H, dt, J = 15.6, 1.3 Hz), 4.99 - 4.88 (3H, m), 2.31 - 2.04 (6H, m), 1.77 - 1.42 (12H, m), 1.22 (9H, d, J = 6.3 Hz); ^{13}C-NMR (CD_2Cl_2, 75.5 MHz) δ 166.4, 148.8, 122.1, 70.5, 36.2, 32.4, 24.6, 20.4; IR (neat) 2976, 2935, 2865, 1716, 1653, 1458, 1379, 1358, 1310, 1270, 1203, 1176, 1131, 1091, 1064, 1016, 990 cm^{-1}; MS (EI) *m/z* (rel. intensity) 420 ([M^+], 3), 402 (2), 280 (4), 262 (8), 140 (35), 122 (100), 95 (56), 81 (58), 68 (22), 55 (24), 43 (12).