Formation of Macrocycles *via* Ring-Closing Olefin Metathesis

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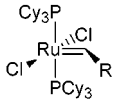
The enhanced metathesis activity of 1,3-dimesityl-4,5-dihydroimidazole-2-ylidene ruthenium carbene catalyst **3** significantly increases the feasibility of synthesizing macrocyclic compounds. Catalyst **3** exhibits sufficient activity in RCM to dimerize α,β-unsaturated ester substrates and afford the corresponding head-to-tail (*E*,*E*)-dimeric (and trimeric) macrocycles. The dimerization appears to be under thermodynamic control with the product mixture dependent not only on the electronic and steric nature of the substrate but also on concentration.

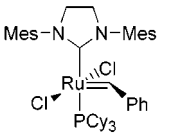
Introduction

Ring-closing olefin metathesis (RCM) is a highly efficient reaction for the synthesis of carbocyclic, heterocyclic and fused ring frameworks.[1,2] While most RCM reactions are performed using either $Cl_2(PCy_3)_2Ru{=}CHPh$ (**1**)[3] or $((CF_3)_2MeCO)_2(ArN)Mo{=}CH(t\text{-}Bu)$ (**2**)[4] as catalyst, the former complex has enjoyed wide application in organic synthesis due to its high functional group tolerance. The activity of **1** can be greatly enhanced via the substitution of a single phosphine ligand with 1,3-dimesityl-4,5-dihydroimidazol-2-ylidene, an N-heterocyclic carbene.[5] The resulting complex **3** exhibits metathesis activity that not only approaches **2**, but also maintains the high thermal stability and excellent functional group tolerance of **1**.[6] In particular, high yields and *trans*-selectivity of 14-membered lactones are obtainable through macrocyclic RCM using **3**. This excellent selectivity is apparently related to the ability of **3** to rapidly isomerize olefins through "secondary metathesis" and ultimately afford the thermodynamically favored ring-closed product.[6b]

As established by related studies in our group, complex **3** also displays significant activity toward previously metathesis-inactive substrates, including α,β-unsaturated carbonyl compounds.[6a] These abilities significantly increase the scope of macrocycle synthesis, especially those containing (*E*)-olefins or (*E*)-α,β-unsaturated esters. Herein, we report the synthesis of various macrocyclic lactones (14−26 membered) via RCM using catalyst **3**.



1



Mes= C_6H_2-2,4,6-$(CH_3)_3$

3

Results and Discussion

Knowing that **3** effectively catalyzes the metathesis of α,β-unsaturated esters, we focused efforts on the preparation of those macrocycles shown in Table 1. Attempted cyclization of substrate **4** with **1** afforded only the linear homo-dimeric compound **5**, not the ring-closed product (Table 1, entry 1).[7] When the more active catalyst **3** was employed, the expected seven-membered ring was again not observed, but instead the 14-membered dimeric ring-closed product **6** was obtained in 59% yield (entry 2).[8] Interestingly, this RCM product was not simply that of homo-dimer **5**, but rather its "head-to-tail dimer".[9] When the same reaction was performed at higher concentration (entries 3 and 4), the yield of dimer decreased, presumably due to competing oligomerization. Further evidence that product distribution is strongly dependent on con-

(1) For recent reviews in olefin metathesis, see: (a) Grubbs, R. H.; Chang, S. *Tetrahedron* **1998**, *54*, 4413−4450. (b) Wright, D. L. *Curr. Org. Chem.* **1999**, *3*, 211−240. (c) Fürstner, A. *Angew. Chem., Int. Ed.* **2000**, *39*, 3012−3043. (d) Trnka, T. M.; Grubbs, R. H. *Acc. Chem. Res.* **2001**, *34*, 18−29.

(2) (a) Miller, S. J.; Blackwell, H. E.; Grubbs, R. H. *J. Am. Chem. Soc.* **1996**, *118*, 9606−9614. (b) Yang, Z.; He, Y.; Vourloumis, D.; Vallberg, H.; Nicolaou, K. C. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 166−168. (c) Meng, D. F.; Bertinato, P.; Balog, A.; Su, D. S.; Kamenecka, T.; Sorensen, E. J.; Danishefsky, S. J. *J. Am. Chem. Soc.* **1997**, *119*, 10073−10092. (d) Lee, D.; Sello, J. K.; Schreiber, S. L. *J. Am. Chem. Soc.* **1999**, *121*, 10648−10649. (e) Paquette, L. A.; Fabris, F.; Tae, J. S.; Gallucci, J. C.; Hofferberth, J. E. *J. Am. Chem. Soc.* **2000**, *122*, 3391−3398. (f) Smith, A. B.; Kozmin, S. A.; Adams, C. M.; Paone, D. V. *J. Am. Chem. Soc.* **2000**, *122*, 4984−4985. (g) Fürstner, A.; Thiel, O. R.; Kindler, N.; Bartkowska, B. *J. Org. Chem.* **2000**, *65*, 7990−7995. (h) Crimmins, M. T.; Emmitte, K. A. *J. Am. Chem. Soc.* **2001**, *123*, 1533−1534. (i) Cefalo, D. R.; Kiely, A. F.; Wuchrer, M.; Jamieson, J. Y.; Schrock, R. R.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2001**, *123*, 3139−3140.

(3) Schwab, P.; Grubbs, R. H.; Ziller, J. W. *J. Am. Chem. Soc.* **1996**, *118*, 100−110.

(4) Schrock, R. R.; Murdzeck, J. S.; Bazan, G. C.; Robbin, J.; Dimare, M.; O'Regan, M. *J. Am. Chem. Soc.* **1990**, *112*, 3875−3886.

(5) Scholl, M.; Ding, S.; Lee, C. W.; Grubbs, R. H. *Org. Lett.* **1999**, *1*, 953−956.

(6) (a) Chatterjee, A. K.; Morgan, J. P.; Scholl, M.; Grubbs, R. H. *J. Am. Chem. Soc.* **2000**, *122*, 3783−3784. (b) Lee, C. W.; Grubbs, R. H. *Org. Lett.* **2000**, *2*, 2145−2147. (c) Bielawski, C. W.; Grubbs, R. H. *Angew. Chem., Int. Ed.* **2000**, *39*, 2903−2906.

(7) It appears that the reaction between complex **1** and acrylates is slow and facilitates catalyst decomposition, see: Ulman, M.; Belderrain, T. R.; Grubbs, R. H. *Tetrahedron Lett.* **2000**, *41*, 4689−4693.

(8) The major RCM products of **4** and **7**, assigned as the monomeric ring-closed compounds in ref 6a, were later found to be dimeric or trimeric rings by additional characterization, see: Lefloch, Y.; Yvergnaux, F.; Toupet, L.; Gree, R. *Bull. Soc. Chim. Fr.* **1991**, 742−759. The dimeric product **6** was obtained by RCM using an analogue of complex **3**, see: Fürstner, A.; Thiel, O. R.; Ackermann, L.; Schanz, H. J.; Nolan, S. P. *J. Org. Chem.* **2000**, *65*, 2204−2207.

(9) For a previous example, "the head-to-tail" dimer of unfunctionalized olefin was obtained by RCM using **1** or **3**, see: ref. (2f).

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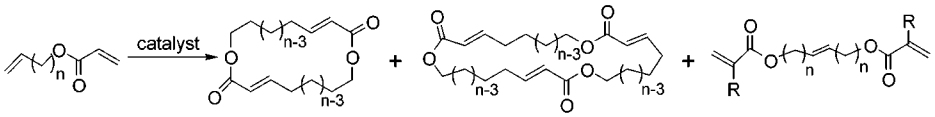
Table 1. Formation of Macrocycles *via* RCM[a]



4 (n=3)
7 (n=4)

6 (n=3)
8 (n=4)

9 (n=4)

R=H: **5** (n=3), **10** (n=4)
R=CH_3: **12** (n=4)

entry	substrates	conc (mM)	catalyst (mol %)	products[b] (% yield[c])
1	**4**	30	**1** (5.0)	**5** (62)
2	**4**	3	**3** (5.0)	**6** (59)
3	**4**	30	**3** (5.0)	**6** (39)
4	**4**	100	**3** (5.0)	**6** (17)
5	**7**	2	**3** (7.5)	**8** (38), **9** (38)
6	**7**	6	**3** (5.0)	**8** (20), **9** (54)
7	**7**	100	**3** (5.0)	**9** (73)
8	**7**	2[d]	**3** (5.0)	**10** (37)[e]
9	**11**[f]	3	**3** (5.0)	**12** (75)

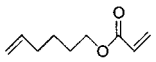
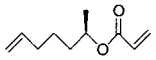
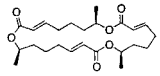
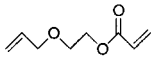
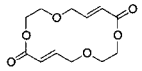
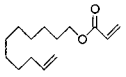
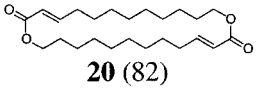
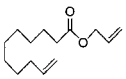
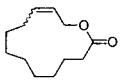
[a] Unless otherwise noted, reactions were performed in refluxing CH_2Cl_2 under an atmosphere of argon. [b] The spectroscopic data (^1H, ^{13}C, IR, HR-MS) of the products were in agreement with their previously reported values (see ref 8). [c] Isolated yields. [d] Reaction was performed in refluxing THF. [e] No starting material remained. [f] The compound **11** is methacrylate compound, $CH_2{=}C(CH_3)COO(CH_2)_4CH{=}CH_2$.

centration was obtained from a study of substrate **7** (a homologous isomer of **4**). As shown in Table 1 (entries 5−7), increasing initial concentration of substrate decreases yields of product **8**. However, a close analysis of the reaction mixtures reveals that the "head-to-tail" trimeric ring-closed product **9** (24-membered) was formed concomitantly with the loss of dimer. In fact, under more concentrated conditions, the sole isolated product (73%) was the cyclic trimer **9** (entry 7). Since olefin metathesis presumed to be under thermodynamic control, the dependence of product distribution on concentration is presumably a reflection of the relative stabilities of the various macrocycles (monomer, dimer, trimer, etc).[10] In all cases, only the thermodynamically favored *E* isomers were observed, as noted previously in the metathesis of other acrylic compounds.[6a]

Macrocycle formation appears to be dependent not only on activity of the catalyst, but also on solvent. THF sufficiently attenuates catalyst activity (presumably due to competitive solvent coordination). With THF as solvent, the only acyclic homo-dimer **10** was isolated (entry 8).[11] Likewise, only acyclic homo-dimer was obtained when an analogous substrate **11**, containing a relatively sterically hindered olefin (a methacrylate), was employed (entry 9). Additional studies show that substrate structure has a significant influence on product formation as well (Table 2). The steric difference (i.e., a methyl group) between **7** and **13** has a profound effect on the dimer−trimer distribution in the product mixture (entry 10 vs 11 in Table 2).

The observed product distributions are also presumably dependent on the relative thermodynamic stabilities of macrocycles. Heteroatom substitution (i.e., carbon for oxygen) in the substrate affects the observed products distribution (entry 5 vs entry 12). Despite the similar

Table 2. RCM of Various α,β-Unsaturated Ester Containing Substrates with 3[a]

10	 **7**	6	**8** (20), **9** (54)
11	 **13**	6	 **14** (81)
12	 **15**	3	 **16** (97)
13	 **17**	3	 **18** (65)
14	 **19**	3	 **20** (82)
15	 **21**	1	 **22** (78)[c]

[a] Reactions were performed in refluxing CH_2Cl_2 using catalyst **3** (5 mol %) under an atmosphere of argon. [b] Isolated yields. [c] Yield with using catalyst **1** (5 mol %). Only 26% yield is obtained under these conditions for catalyst **3**. E/Z = 3.6:1 on GC and NMR.[12]

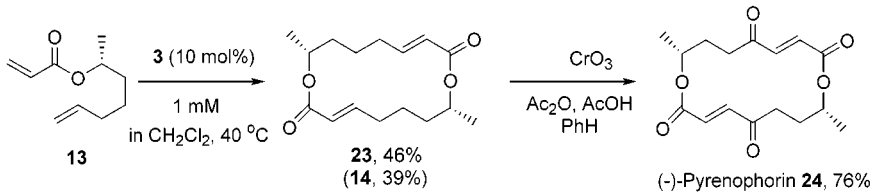
chain length in substrates **7** and **15**, the presence of oxygen atoms in the latter influences the product distribution presumably differences in bond angles in **15** stabilizes the ring-closed dimer even at similar concentrations. Conformational restriction must also play an important role in the RCM of α,β-unsaturated ester containing substrates (entry 13). The six-membered ring in **17** should enforce the proximity of olefins, thereby favoring the ring-closed monomeric compound. By comparing substrates **19** and **21**, it is clear that the presence of an α,β-unsaturated carbonyl in the substrate is critical for the formation of dimerized macrocycles (entry 14 vs 15).

The ability to form α,β-unsaturated esters via olefin metathesis opens a number of avenues for preparing synthetically relevant large ring systems. For example,

(10) Efforts towards elucidating the factors that determine this distribution (e.g., the critical concentration, see: Chen, Z. R.; Claverie, J. P.; Grubbs, R. H.; Kornfield, J. A. *Macromolecules* **1995**, *28*, 2147−2154.) are currently in progress. The dependence of product distribution on concentration also applies to the RCM of normal olefins, see: Arisawa, M.; Kato, C.; Kaneko, H.; Nishida, A.; Nakagawa, M. *J. Chem. Soc., Perkin Trans. 1*, **2000**, 1873−1876.

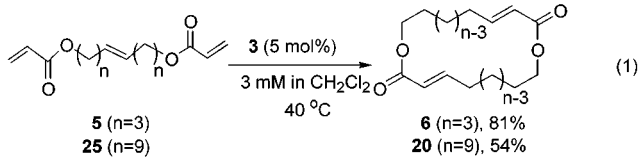
(11) Reduced activity of Ru based complexes in THF has been previously observed, see: Nguyen, S. T. Ph.D. Thesis, California Institute of Technology, Pasadena, CA, 1995.

Scheme 1

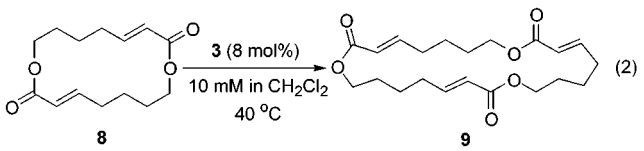


the macrocyclic compound **8** has been previously oxidized to norpyrenophorin,[13] a derivative of the anti-fungal, antibacterial natural product pyrenophorin.[14] Likewise, the macrocycle formation strategy described above was extended toward a concise total synthesis of (−)-pyrenophorin itself (Scheme 1).

As shown in Table 2, RCM of **13** at standard concentration (6 mM in CH_2Cl_2) afforded trimeric compound **14** (81%). Gratifyingly, the desired head-to-tail (*E*,*E*)-dimer **23** (46%) (along with trimer **14**, 39%) is obtained under more dilute conditions (1 mM). As previously reported,[14a] oxidation of **23** with CrO_3 affords (−)-pyrenophorin (**24**) in 76% yield.[15] In an effort to understand the pathways involved in macrocycle formation, isolated homo-dimeric compounds **5** and **25** were resubjected to catalyst **3** in order to isolate the respective cyclic dimers **6** or **20** (eq 1). The desired dimers were obtained in moderate to good yield, depending on ring size.



(1)



(2)

While formation of macrocyclic trimer may proceed analogously (i.e., from an acyclic trimer), an alternative pathway via dimer−trimer metathetical equilibration was independently established. As shown in eq 2, treatment of **8** with catalyst **3** (10 mM in CH_2Cl_2) afforded trimer **9** in 50% yield.[16] This observation demonstrates that byproducts of metathesis reactions are easily recycled. In summary, catalyst **3** exhibits sufficient activity in RCM to dimerize α,β-unsaturated ester substrates, affording the corresponding head-to-tail (*E*,*E*)-dimeric (and trimeric) macrocycles. The dimerization appears to be under thermodynamic control, with the product mixture dependent not only on the substrate (i.e., steric and electronic factors) but also on concentration. This dimerization process opens new vistas in the rapid synthesis of macrocyclic compounds, including natural products. Variation of substituent arrangement and reaction concentration provides the opportunity to easily produce a wide array of macrocycles with readily adjustable ring sizes.

Experimental Section

General. NMR spectra were recorded on GE-300 NMR. High-resolution mass spectra (EI or CI) were provided by the UCLA Mass Spectrometry Facility (University of California, Los Angeles). FTIR were obtained as thin films on NaCl plates. Analytical thin-layer chromatography (TLC) was performed using silica gel 60 F254 precoated plates (0.25 mm thickness) with a fluorescent indicator. Flash column chromatography was performed using silica gel 60 (230−400 mesh) from EM Science. All other chemicals were purchased from the Aldrich, Strem, or Nova Biochem Chemical Companies, and used as delivered unless noted otherwise. CH_2Cl_2 was purified by passage through a solvent column prior to use.[17]

General Procedure for Macrocyclic Formation via Ring-Closing Olefin Metathesis. To a solution of diene **7** (16 mg, 0.10 mmol) in CH_2Cl_2 (50 mL) was added Ru complex **3** (6.6 mg, 0.0050 mmol) in CH_2Cl_2 (2.0 mL) via cannula tarnsfer, and the reaction mixture was refluxed under argon for 11 h. The reaction mixture was then reduced in volume to 1 mL and purified directly on a silica gel column, eluting with 20% hexanes−ethyl acetate to give the cyclized products **8** (5.0 mg, 38%) and **9** (5.0 mg, 38%).

Compound 5. ^{1}H NMR (300 MHz, $CDCl_3$, ppm): δ 6.39 (2H, dd, J = 17.1, 1.8 Hz), 6.11 (2H, dd, J = 17.1, 10.5 Hz), 5.81 (2H, dd, J = 10.5, 1.8 Hz), 5.43 (2H, m), 4.14 (4H, t, J = 6.6 Hz), 2.08 (4H, m), 1.72 (4H, m). ^{13}C NMR (75 MHz, $CDCl_3$, ppm): δ 166.4, 130.8 ∼ 128.7 (m), 64.3, 29.2 ∼ 28.7 (m), 23.9. IR (cm^{-1}): 2955, 1725, 1637, 1409, 1296, 1271, 1190. R_f = 0.33 (10% hexanes−ethyl acetate). HRMS (FAB) calcd for $C_{14}H_{21}O_4$ $[M+H]^+$ 253.1440, found 253.1436.

Compound 6. ^{1}H NMR (300 MHz, $CDCl_3$, ppm): δ 7.02 (2H, dt, J = 15.6, 7.2 Hz), 5.65 (2H, dt, J = 15.6, 1.8 Hz), 4.27 (4H, t, J = 4.8 Hz), 2.37 (4H, m), 1.93 (4H, m). ^{13}C NMR (75 MHz, $CDCl_3$, ppm): δ 166.1, 150.9, 120.7, 65.0, 31.9, 28.4. IR (cm^{-1}): 2961, 1704, 1635. R_f = 0.46 (30% hexanes−ethyl acetate). HRMS (EI) calcd for $C_{12}H_{16}O_4$ $[M]^+$ 224.1049, found 224.1049.

Compound 8. ^{1}H NMR (300 MHz, $CDCl_3$, ppm): δ 6.96 (2H, dt, J = 15.9, 6.6 Hz), 5.88 (2H, dt, J = 15.9, 1.5 Hz), 4.16 (4H, t, J = 5.4 Hz), 2.30 (4H, m), 1.71 (8H, m). ^{13}C NMR (75 MHz, $CDCl_3$, ppm): δ 166.4, 149.0, 122.5, 64.2, 31.1, 27.3, 24.7. IR (cm^{-1}): 2935, 1718, 1654. R_f = 0.55 (30% hexanes−ethyl acetate). HRMS (CI, NH_3) calcd for $C_{14}H_{20}O_4$ $[M]^+$ 252.1362, found 252.1368.

Compound 9. ^{1}H NMR (300 MHz, $CDCl_3$, ppm): δ 6.96 (3H, dt, J = 15.9, 6.9 Hz), 5.84 (3H, dt, J = 15.9, 1.2 Hz), 4.17 (6H, t, J = 5.7 Hz), 2.24 (6H, m), 1.68 (6H, m), 1.56 (6H, m). ^{13}C NMR (75 MHz, $CDCl_3$, ppm): δ 166.7, 148.8, 121.8, 64.0, 32.1,

(12) The *E*/*Z* ratio of compound **22** was obtained on GC and NMR by comparison with the authentic sample prepared by reported method, see: Cameron, A. G.; Knight, D. W. *J. Chem. Soc., Perkin Trans. 1*, **1986**, 161−167.

(13) Bestmann, H. J.; Schobert, R. *Angew. Chem., Int. Ed. Engl.* **1985**, *24*, 791−792.

(14) (a) Mali, R. S.; Pohmakotr, M.; Weidmann, B.; Seebach, D. *Liebigs Ann. Chem.* **1981**, 2272−2284. (b) Kobayashi, Y.; Nakano, M.; Kumar, G. B.; Kishihara, K. *J. Org. Chem.* **1998**, *63*, 7505−7515. (c) Götzö, S. P.; Seebach, D.; Sanglier, J.-J. *Eur. J. Org. Chem.* **1999**, 2533−2544.

(15) During the preparation of this manuscript, a similar synthesis of pyrenophorin was recently reported, see: Fürstner, A.; Thiel, O. R.; Ackermann, L. *Org. Lett.* **2001**, *3*, 449−451. Previous work has suggested that catalyst identity is important; however, we believe that the key issue for pyrenophorin synthesis by using catalyst **3** is the use of RCM under high dilute substrate concentrations.

(16) Dimer **8** (<50%) was also observed.

(17) The solvent columns are composed of activated alumina (A-2) and supported copper redox catalyst (Q-5 reactant). See: Pangborn, A. B.; Giardello, M. A.; Grubbs, R. H.; Rosen, R. K.; Timmers, F. J. *Organometallics* **1996**, *15*, 1518−1520.

28.6, 25.1. IR (cm^{-1}): 2945, 1719, 1655. R_f = 0.46 (30% hexanes−ethyl acetate). HRMS (CI, NH_3) calcd for $C_{21}H_{30}O_6$ $[M]^+$ 378.2042, found 378.2044.

Compound 10. ^1H NMR (300 MHz, $CDCl_3$, ppm): δ 6.41 (2H, dd, J = 17.4, 1.8 Hz), 6.12 (2H, dd, J = 17.4, 10.5 Hz), 5.82 (2H, dd, J = 10.5, 1.8 Hz), 5.41 (2H, m), 4.15 (4H, t, J = 6.6 Hz), 2.10 (4H, m), 1.70 ∼ 1.40 (8H, m). ^{13}C NMR of major (trans) component (75 MHz, $CDCl_3$, ppm): δ 166.6, 130.7, 130.5, 128.8, 64.8, 32.3, 28.3, 26.1. IR (cm^{-1}): 2998, 2361, 1726, 1637, 1408, 1296, 1273, 1191. R_f = 0.29 (10% hexanes−ethyl acetate). HRMS (EI) calcd for $C_{16}H_{23}O_4$ $[M-H]^+$ 279.1596, found 279.1606.

Compound 12. ^1H NMR (300 MHz, $CDCl_3$, ppm): δ 6.09 (2H, m), 5.54 (2H, t, J = 1.5 Hz), 5.40 (2H, m), 4.14 (4H, t, J = 6.6 Hz), 2.10 (4H, m), 1.94 (s, 6H), 1.70 ∼ 1.40 (8H, m). ^{13}C NMR of major (trans) component (75 MHz, $CDCl_3$, ppm): δ 167.8, 136.7, 130.5, 125.4, 64.9, 32.3, 28.3, 26.1, 18.6. IR (cm^{-1}): 2931, 1720, 1639, 1453, 1322, 1297, 1164. R_f = 0.46 (10% hexanes−ethyl acetate). HRMS (EI) calcd for $C_{18}H_{29}O_4$ $[M+H]^+$ 309.2066, found 309.2069.

Preparation of (*R*)-6-Hepten-2-ol. To a mixture of (*R*)-propylene oxide[18] (0.30 mL, 4.3 mmol) and CuCN (19 mg, 0.21 mmol) in THF (8 mL) was added the 3-butenylmagnesium bromide[18] (0.49 M in THF, 13 mL, 6.4 mmol) for 1h. The resulting mixture was stirred below −30 °C for 1h, warmed to 0 °C over 1h, and then poured into a NH_4Cl saturated solution with stirring. The solution was extracted with diethyl ether, washed with brine solution, dried over $MgSO_4$, and concentrated to give a residue, which was purified by chromatography (20% hexanes−ethyl acetate) to afford (*R*)-6-hepten-2-ol (0.40 g, 3.5 mmol) as a colorless liquid.

(*R*)-6-Hepten-2-ol. ^1H NMR (300 MHz, $CDCl_3$, ppm): δ 5.81 (1H, m), 4.98 (2H, m), 3.80 (1H, m), 2.06 (2H, m), 1.45 (4H, m), 1.19 (3H, d, J = 6.0 Hz). ^{13}C NMR (75 MHz, $CDCl_3$, ppm): δ 138.9, 114.8, 68.3, 39.1, 34.0, 25.4, 23.9. IR (cm^{-1}): 3351, 2969, 2932, 2862, 1642, 1459, 1375, 1321, 1122, 996, 910. R_f = 0.59 (30% hexanes−ethyl acetate), $[\alpha]_D^{26}$ = −12.9° (c= 6.9 in $CHCl_3$) (reported value of (*S*)-6-hepten-2-ol:[19] $[\alpha]_D^{26}$ = +10.4° (c = 0.79 in $CHCl_3$)), HRMS (EI) calcd for $C_7H_{15}O$ $[M+H]^+$ 115.1123, found 115.1127.

Compound 13. ^1H NMR (300 MHz, $CDCl_3$, ppm): δ 6.39 (1H, dd, J = 17.4, 1.5 Hz), 6.10 (1H, dd, J = 17.4, 10.5 Hz), 5.80 (2H, m), 4.98 (2H, m), 2.06 (2H, q, J = 7.2 Hz), 1.70 ∼ 1.38 (4H, m), 1.25 (3H, d, J = 6.3 Hz)). ^{13}C NMR (75 MHz, $CDCl_3$, ppm): δ 166.0, 138.6, 130.5, 129.2, 115.0, 71.4, 35.7, 33.8, 25.0, 20.4. IR (cm^{-1}): 2979, 2938, 1724, 1640, 1406, 1381, 1296, 1272, and 1199. R_f = 0.50 (10% hexanes−ethyl acetate), HRMS (EI) calcd for $C_{10}H_{17}O_2$ $[M+H]^+$ 169.1229, found 169.1233.

Compound 14. ^1H NMR (300 MHz, $CDCl_3$, ppm): δ 6.93 (3H, dt, J = 15.6, 8.1 Hz), 5.79 (3H, dt, J = 15.6, 1.5 Hz), 4.97 (3H, m), 2.32 ∼ 2.03 (6H, m), 1.68 ∼ 1.42 (12H, m), 1.24 (9H, d, J = 6.0 Hz). ^{13}C NMR (75 MHz, $CDCl_3$, ppm): δ 166.4, 148.8, 121.9, 70.5, 36.3, 32.5, 24.6, 20.7. IR (cm^{-1}): 2975, 2937, 1716, 1655, 1461, 1358, 1269, 1202, 1175. R_f = 0.53 (30% hexanes−ethyl acetate). HRMS (CI, NH_3) calcd for $C_{24}H_{37}O_6$ $[M+H]^+$ 421.2590, found 421.2603.

Compound 16. ^1H NMR (300 MHz, $CDCl_3$, ppm): δ 7.00 (2H, dt, J = 15.6, 4.2 Hz), 6.37 (2H, dt, J = 15.6, 2.1 Hz), 4.30 (4H, m), 4.22 (4H, m), 3.73 (4H, m). ^{13}C NMR (75 MHz, $CDCl_3$, ppm): δ 165.8, 145.3, 121.9, 70.3, 70.1, 64.1. IR (cm^{-1}): 2918, 1722, 1462, 1383, 1315, 1279, 1188. R_f = 0.19 (30% hexanes−ethyl acetate). HRMS (EI) calcd for $C_{12}H_{17}O_6$ $[M+H]^+$ 257.1025, found 257.1029.

Compound 18. ^1H NMR (300 MHz, $CDCl_3$, ppm): δ 6.45 (1H, ddd, J = 11.1, 2.7, 0.6 Hz), 6.03 (1H, ddd, J = 11.1, 2.7, 0.9 Hz), 4.32 (1H, m), 4.02 (1H,dquint, J = 11.1, 2.4 Hz), 3.83 (1H, ddd, J = 8.7, 7.8, 2.4 Hz), 3.45 (1H, ddd, J = 12.0, 11.1, 2.4 Hz), 2.72 (1H, m), 2.37 (1H, m), 2.23 (1H, m), 2.04 (1H, m), 1.78 (1H, m), 1.45 (1H, m). ^{13}C NMR (75 MHz, $CDCl_3$, ppm): δ 169.5, 139.0, 125.2, 77.0, 73.7, 67.9, 31.7, 28.2, 20.8. IR (cm^{-1}): 2957, 1723, 1691. R_f = 0.15 (30% hexanes−ethyl acetate). HRMS (EI) calcd for $C_9H_{12}O_3$ $[M]^+$ 168.0786, found 168.0787.

Compound 20. ^1H NMR (300 MHz, $CDCl_3$, ppm): δ 6.95 (2H, dt, J = 15.6, 6.9 Hz), 5.81 (2H, dt, J = 15.6, 1.2 Hz), 4.15 (4H, t, J = 6.0 Hz), 2.19 (4H, m), 1.52 ∼ 1.25 (28H, m). ^{13}C NMR (75 MHz, $CDCl_3$, ppm): δ 166.9, 149.4, 121.6, 64.4, 32.3, 29.3, 29.2, 29.0, 28.9, 28.0, 26.3. IR (cm^{-1}): 2922, 1717, 1643. R_f = 0.33 (10% hexanes−ethyl acetate). HRMS (EI) calcd for $C_{24}H_{40}O_4$ $[M]^+$ 392.2927, found 392.2915.

Compound 22. ^1H NMR (300 MHz, $CDCl_3$, ppm): δ 5.83 ∼ 5.61 (2H, m), 4.52 and 4.50 (2H, d, J = 6.9 Hz and d, J = 7.5 Hz), 2.36 ∼ 2.10 (2H, m), 2.02 (2H, m), 1.70 ∼ 1.20 (12H, m). ^{13}C NMR (75 MHz, $CDCl_3$, ppm) δ 140.2, 139.3, 125.5, 123.3, 63.6, 35.1, 31.4.31.0, 26.5, 25.9 ∼ 25.4 (m), 24.7, 24.6, 24.1. R_f = 0.50 (10% hexanes−ethyl acetate). m/z: 196 (12%, M^+), 167 (7), 153 (10), 136 (16), 125 (19), 121 (19), 112 (40), 99 (11), 98 (56), 95 (57), 91 (72), 67 (84), 55 (100). HRMS (EI) calcd for $C_{12}H_{20}O_2$ $[M]^+$ 196.1463, found 196.1459.

Compound 23. ^1H NMR (300 MHz, $CDCl_3$, ppm): δ 6.94 (2H, dt, J = 15.9, 7.2 Hz), 5.85 (2H, dt, J = 15.9, 1.5 Hz), 5.01 (2H, m), 2.21 (4H, m), 1.80 ∼ 1.50 (8H, m), 1.25 (6H, d, J = 6.3 Hz). ^{13}C NMR (75 MHz, $CDCl_3$, ppm): δ 166.0, 148.4, 122.8, 70.5, 33.4, 31.0, 22.2, 19.4. IR (cm^{-1}): 2976, 2937, 1715, 1652, 1454, 1354, 1268, 1195, 1172, 1133. R_f = 0.61 (30% hexanes−ethyl acetate). HRMS (CI, NH_3) calcd for $C_{16}H_{25}O_4$ $[M+H]^+$ 281.1753, found 281.1746.

(−)-Pyrenophorin 24. ^1H NMR (300 MHz, $CDCl_3$, ppm): δ 6.95 (2H, d, J = 15.6 Hz), 6.49 (2H, d, J = 15.6 Hz), 5.04 (2H, m), 2.72 ∼ 2.48 (4H, m), 2.09 (4H, m), 1.29 (6H, d, J = 6.3 Hz). ^{13}C NMR (75 MHz, $CDCl_3$, ppm): δ 199.8, 165.1, 139.8, 131.6, 72.5, 37.7, 32.4, 20.0. IR (cm^{-1}): 3066, 2974, 2929, 1720, 1690, 1654, 1637. R_f = 0.30 (30% hexanes−ethyl acetate), $[\alpha]_D^{26}$ = −48.1° (c= 0.32 in $CHCl_3$) (reported value:[20] $[\alpha]_D^{20}$ = −47.6° (c= 0.17 in $CHCl_3$)), mp 168 ∼ 169 °C (reported value:[20] 170 ∼ 171 °C), HRMS (EI) calcd for $C_{16}H_{21}O_6$ $[M+H]^+$ 309.1338, found 309.1336.

Compound 25. ^1H NMR (300 MHz, $CDCl_3$, ppm): δ 6.40 (2H, dd, J = 17.4, 1.5 Hz), 6.12 (2H, dd, J = 17.4, 10.2 Hz), 5.81 (2H, dd, J = 10.2, 1.5 Hz), 5.36 (2H, m), 4.14 (4H, t, J = 6.9 Hz), 1.90 (4H, m), 1.70 (4H, m), 1.30 (m, 12H). ^{13}C NMR (75 MHz, $CDCl_3$, ppm): δ 166.5, 130.7 ∼ 128.9 (m), 65.0, 33.0, 29.8 ∼ 26.3 (m), 23.9. IR (cm^{-1}): 2922, 2854, 1726, 1636.R_f = 0.33 (10% hexanes−ethyl acetate), HRMS (EI) calcd for $C_{26}H_{44}O_4$ $[M]^+$ 421.3318, found 421.3307.

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Supporting Information Available: ^1H and ^{13}C NMR spectra of compounds **5**−**25** (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

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