JOC*Note*

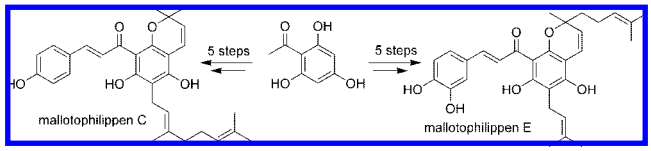
Concise Total Synthesis of Biologically Interesting Mallotophilippens C and E

Yong Rok Lee,* Xin Li, and Jung Hee Kim

School of Chemical Engineering and Technology, Yeungnam University, Gyeongsan 712-749, Korea

yrlee@yu.ac.kr

Received February 14, 2008



This paper describes a new and efficient synthetic approach for biologically interesting natural mallotophilippens C and E. The key strategies involved ethylenediamine diacetate-catalyzed benzopyran formation reactions and base-catalyzed aldol reactions.

Pyranochalcones are an abundant subclass of flavonoids that are distributed widely in nature.[1] Some pyranochalcones have been reported to exhibit antimutagenic, antimicrobial, antiulcer, and antitumor activities, and some plants containing these compounds have been used in traditional medicines in China and Europe.[2] This wide range of biological properties has stimulated interest in the synthesis of naturally occurring pyranochalcones. Among these, mallotophilippens C (**1**), D (**2**), and E (**3**) with the pyranochalcone moiety were isolated from *Mallotus philippinensis*, a deciduous tree distributed widely throughout tropical Asia, Australia, and the Philippines (Figure 1).[3] Kamara, a red powder consisting of the glandular hairs from this plant, has been used in traditional medicine as an anthelmintic and cathartic.[4] Mallotophilippens C (**1**), D (**2**), and E (**3**) have been shown to potently inhibit the production of nitric oxide (NO) induced by interferon-γ (IFN- γ) and LPS activated RAW 264.7 cells.[3] They also strongly inhibit inducible nitric oxide synthesis (iNOS), cyclooxygenase-2 (COX-2), interleukin-6 (IL-6), and interleukin-1β (IL-1 β) *m*RNA expression.[3] These effects are expected to be used for the development of new drugs to treat rheumatoid arthritis, which involves excessive NO production.

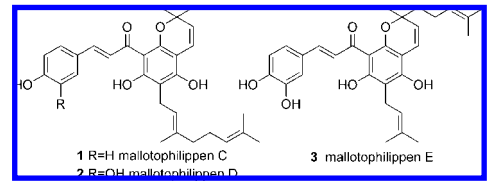


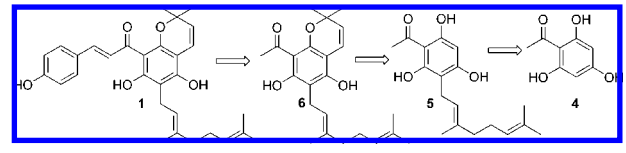
FIGURE 1. Natural products isolated from *Mallotus philippinensis*.

One synthetic approach to mallotophilippen C (**1**) was recently reported,[5] but this synthetic approach has a limitation due to the large number of reaction steps (11 steps). Therefore, there is still a demand for a more concise and efficient method that can provide biologically interesting mallotophilippen C (**1**). In particular, there are no synthetic approaches to mallotophilippen E (**3**) with the biologically interesting prenyl moiety reported thus far. Interestingly, natural mallotophilippen E (**3**) has a chiral carbon but is isolated as a racemate.[3]

Recently, we developed a new and useful methodology for preparing a variety of benzopyrans using ethylenediamine diacetate-catalyzed reactions of resorcinols to α,β-unsaturated aldehydes.[6] These reactions involve a formal [3+3]-cycloaddition via 6π-electrocyclization. Using this methodology as a key step, we also described a rapid route for the synthesis of biologically interesting pyranochalcone natural products.[7] As a part of an ongoing study into the synthetic efficacy of these methodologies, this study examined the synthesis of naturally occurring mallotophilippens C (**1**) and E (**3**). We report the very concise total synthesis of mallotophilippen C (**1**) and the first efficient total synthesis of mallotophilippen E (**3**).

Scheme 1 shows the retrosynthetic strategy for mallotophilippen C (**1**). Mallotophilippen C (**1**) could be prepared from base-catalyzed aldol reactions of compound **6** to the corresponding benzaldehyde protected by a SEM group. The crucial intermediate **6** could be generated from geranylated phloroac-

SCHEME 1. Retrosynthetic Analysis of Mallotophilippen C (1)



(1) (a) Wagner, H.; Farkas, L. In *The Flavonoids*; Harorne, J. B., Mabry, T. J., Mabry, H., Eds.; Academic Press: New York, 1975; p 127. (b) Gripenberg, J. In *The Chemistry of Flavonoid Compounds*; Geissman, T. A., Ed.; MacMillan: New York, 1962; p 409. (c) Wollenweber, E. In *The Flavonoids*; Harborne, J. B., Ed.; Chapman & Hall: London, UK, 1994; p 259. (d) *The Handbook of Natural Products*; Harborne, J. B., Baxter, H., Eds.; John Wiley & Sons Ltd.; London, UK, 1999; Vol. 2, p 1.

(2) (a) Welton, A. F.; Tobias, L. D.; Fiedler-Nagy, C.; Anderson, W.; Hope, W.; Meyers, K.; Coffey, J. W. In *Plant Flavonoids in Biology and Medicine: Biochemical Pharmacological and Structure-Activity Relationships;* Cody, V.; Middleton, E., Jr.; Harborne, J. B. Eds.; Alan R. Liss, Inc: New York, 1986; p 231. (b) Miranda, C. L.; Stevens, J. F.; Helmrich, A.; Henderson, M. C.; Rodriguez, R. J.; Yang, Y.-H.; Deinzer, M. L.; Barnes, D. W.; Buhler, D. R. *Food Chem. Toxicol.* **1999**, *37*, 271. (c) Han, A.-R.; Kang, Y.-J.; Windono, T.; Lee, S. K.; Seo, E.-K. *J. Nat. Chem.* **2006**, *69*, 719.

(3) Daikonya, A.; Katsuki, S.; Kitanaka, S. *Chem. Pharm. Bull.* **2004**, *52*, 1326.

(4) (a) Daikonya, A.; Katsuki, S.; Wu, J.-B.; Kitanaka, S. *Chem. Pharm. Bull.* **2002**, *50*, 1566. (b) Gupta, S. S.; Verma, P.; Hishikar, K. *Indian J. Physiol. Pharmacol.* **1984**, *19*, 103.

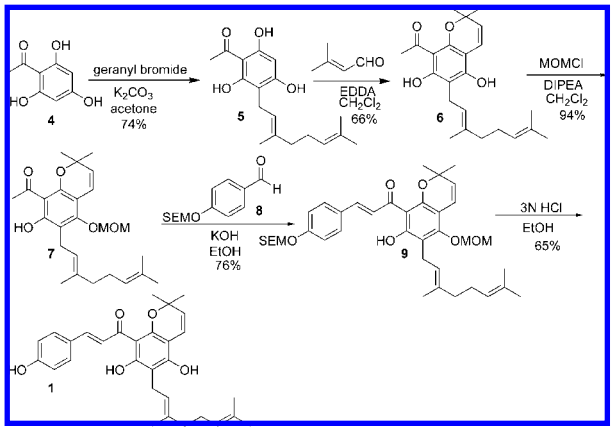
(5) Li, Y.; Luo, Y.; Hung, W.; Wang, J.; Lu, W. *Tetrahedron Lett.* **2006**, *47*, 4153.

(6) (a) Lee, Y. R.; Choi, J. H.; Yoon, S. H. *Tetrahedron Lett.* **2005**, *46*, 7539. (b) Lee, Y. R.; Kim, J. H. *Synlett* **2007**, 2232. (c) Wang, X.; Lee, Y. R. *Synthesis* **2007**, 3044. (d) Wang, X.; Lee, Y. R. *Tetrahedron Lett.* **2007**, *48*, 6275. (e) Lee, Y. R.; Lee, W. K.; Noh, S. K.; Lyoo, W. S. *Synthesis* **2006**, 853.

(7) (a) Lee, Y. R.; Xia, L. *Synthesis* **2007**, 3240. (b) Lee, Y. R.; Kim, D. H. *Synthesis* **2006**, 603.

10.1021/jo800367r CCC: $40.75 © 2008 American Chemical Society
Published on Web 04/29/2008

SCHEME 2. Synthesis of Mallotophilippen C (1)



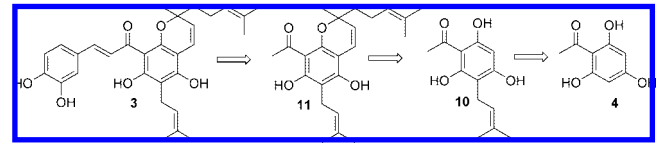
etophenone **5** via ethylenediamine diacetate-catalyzed benzopyran formation reactions. Compound **5** could be obtained from commercially available 2,4,6-trihydroxyacetophenone (**4**).

The total synthesis of mallotophilippen C (**1**) was carried out by using the sequence shown in Scheme 2. With use of a known method, the treatment of 2,4,6-trihydroxyacetophenone (**4**) and geranyl bromide with anhydrous potassium carbonate in dry acetone under reflux for 24 h afforded the product **5** in 74% yield.[8] A reaction of compound **5** with 3-methyl-2-butenal in the presence of 20 mol % of ethylenediamine diacetate in methylene chloride for 5 h gave benzopyran **6** in 66% yield. In this reaction, the remarkable regioselectivity for cyclization may result from the presence of a bulky geranyl group. This similar selectivity was observed by Li's group in the case of a cyclization reaction of the geranylated polyhydroxychalcone to give flavanone natural products.[9] Compound **6** was next protected with 1.1 equiv of methoxymethyl chloride to give product **7** in 94% yield. The selective methoxymethylation of compound **6** was confirmed by an analysis of the ^{1}H NMR spectrum. The signal for the proton of one hydroxyl group in the benzopyran ring of compound **7** was observed as a singlet associated with a hydrogen bond to a carbonyl group at δ 13.72 ppm, and a methoxy signal of MOM ether was observed as a singlet at δ 3.53 ppm. Condensation of compound **7** with aldehyde **8** protected with a SEM group was next accomplished in an ethanolic KOH solution at room temperature for 48 h to afford the pyanochalcone **9** in 76% yield. Deprotection of compound **9** by a treatment with 3 N HCl in methanol at room temperature for 1 h gave mallotophilippen C (**1**) in 65% yield. The spectral data of the synthetic material **1** were in agreement with those reported in the literature.[3]

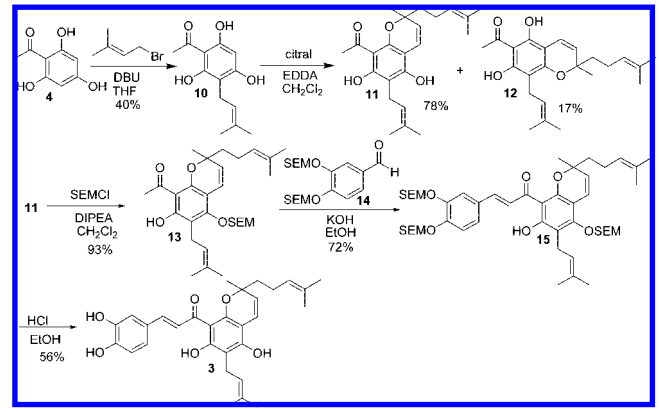
Scheme 3 shows the retrosynthetic approach for synthesizing the natural product, mallotophilippen E (**3**). Mallotophilippen E (**3**) could be prepared by base-catalyzed aldol reactions of benzopyran **11** to the corresponding benzaldehyde protected with SEM groups. The key intermediate **11** also could be generated from the prenylated phloroacetophenone (**10**) by using ethylenediamine diacetate-catalyzed benzopyran formation reactions. The prenylated phloroacetophenone **10** could be derived from commercially available 2,4,6-trihydroxyacetophenone (**4**).

The total synthesis of mallotophilippen C (**3**) was attempted starting from 2,4,6-trihydroxyacetophenone (**4**), as shown in Scheme 4. Prior work has shown that C-prenylation can be

SCHEME 3. Retrosynthetic Analysis of Mallotophilippen E (3)



SCHEME 4. Synthesis of Mallotophilippen E (3)



achieved with prenyl bromide in the presence of either potassium hydroxide[10] or potassium carbonate.[11] Under these conditions, the desired product **10** was obtained in 30−34% yield. Another base was used to increase the yield. A reaction of compound **4** with prenyl bromide in the presence of DBU in THF gave compound **10** in 40% yield. Treatment of compound **10** with citral in the presence of 20 mol % of ethylenediamine diacetate in methylene chloride at room temperature for 8 h provided the products **11** and **12** in 78% and 17% yield, respectively. Compound **10**, which contains a less bulky prenyl group, showed a reduced regioselectivity. These two compounds were readily separated by column chromatography and assigned by spectral analysis. Protection of compound **11** with 1.1 equiv of SEMCl provided compound **13** in 93% yield, which was condensed with the aldehyde **14** in ethanolic KOH solution at room temperature for 48 h to give pyranochalcone **15** in 72% yield. Attempts to deprotect compound **15** with TBAF or magnesium bromide diethyl etherate[12] did not give the desired product **3**. Fortunately, all the SEM groups were easily removed by treatment with HCl in methanol at room temperature for 1 h to yield compound **3** in 56% yield. The spectroscopic data of synthetic material **3** were in agreement with those reported in the literature

In summary, this paper described a concise and efficient synthetic route for biologically interesting natural products, mallotophilippens C and E, with a pyranochalcone moiety through a five-step process starting from 2,4,6-trihydroxyacetopheneone.

Experimental Section

Compound 5. A mixture of **4** (1.009 g, 6.0 mmol), geranyl bromide (1.303 g, 6.0 mmol), and K_2CO_3 (1.659 g, 12.0 mmol) in dry acetone (50 mL) was refluxed for 24 h. Evaporation of acetone, addition of 2 N HCl solution (30 mL), extraction with EtOAc (3

(8) Huang, C.; Zhang, Z.; Li, Y. *J. Nat. Prod.* **1998**, *61*, 1283.
(9) Wang, Y.; Tan, W.; Li, W. Z.; Li, Y. *J. Nat. Prod.* **2001**, *64*, 196.
(10) Diller, R. A.; Riepl, H. M.; Rose, O.; Frias, C.; Henze, G.; Prokop, A. *Chem. Biodiversity* **2005**, *2*, 1331.
(11) Yang, Y.-G.; Zhang, Y.; Cao, X.-P. *Huaxue Xuebao* **2005**, *63*, 1901.
(12) Vakalopoulos, A.; Hoffmann, H. M. R. *Org. Lett.* **2001**, *3*, 2185.

× 50 mL), and removal of the solvent followed by flash column chromatography on silica gel with hexane/EtOAc (7:1) gave **5** (1.351 g, 74%) as a solid: mp 113−114 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 11.67 (1H, s), 9.70 (1H, s), 5.94 (1H, s), 5.20 (1H, t, J = 7.0 Hz), 5.02 (1H, t, J = 6.8 Hz), 3.27 (2H, d, J = 7.0 Hz), 2.61 (3H, s), 2.20−1.84 (4H, m), 1.75 (3H, s), 1.62 (3H, s), 1.54 (3H, s); ^{13}C NMR (75 MHz, $CDCl_3$) δ 203.7, 161.3, 140.1, 132.2, 123.5, 121.4, 105.4, 105.2, 95.3, 39.7, 32.8, 26.2, 25.7, 21.5, 17.7, 16.2; IR (KBr) 3407, 2920, 1628, 1597, 1559, 1453, 1402, 1372, 1289 cm^{-1}; EIMS m/z (%) 304 (M^+, 38), 289 (3), 261 (9), 235 (25), 219 (22), 181 (100); HRMS m/z (M^+) calcd for $C_{18}H_{24}O_4$ 304.1675, found 304.1677.

Compound 6. To a solution of **5** (0.850 g, 2.79 mmol) and 3-methyl-2-butenal (0.469 g, 5.58 mmol) in CH_2Cl_2 (20 mL) was added ethylenediamine diacetate (0.101 g, 0.58 mmol). The reaction mixture was stirred at room temperature for 5 h. Evaporation of solvent and purification by column chromatography on silica gel with hexane/EtOAc (20:1) gave **6** (0.683 g, 66%) as a solid: mp 63−65 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 14.1 (1H, s), 6.52 (1H, d, J = 9.9 Hz), 6.38 (1H, s), 5.40 (1H, d, J = 9.9 Hz), 5.24 (1H, t, J = 7.0 Hz), 5.01 (1H, t, J = 6.8 Hz), 3.37 (2H, d, J = 7.0 Hz), 2.68 (3H, s), 2.15 (3H, s), 2.21−2.02 (4H, m), 1.79 (3H, s), 1.64 (3H, s), 1.58 (3H, s), 1.46 (6H, s); ^{13}C NMR (75 MHz, $CDCl_3$) δ 203.4, 162.9, 157.6, 155.3, 140.3, 132.3, 124.8, 123.5, 121.7, 116.6, 105.7, 105.2, 102.0, 77.7, 39.7, 33.2, 30.9, 27.9, 26.1, 25.7, 21.5, 17.7, 16.1; IR (KBr) 3297, 2971, 2924, 1645, 1607, 1564, 1466, 1427, 1381, 1317, 1256, 1200, 1175, 1132, 1094 cm^{-1}; EIMS m/z (%) 370 (M^+, 58), 356 (13), 355 (52), 301 (35), 285 (24), 247 (42), 246 (15), 232 (15), 231 (100), 219 (10), 213 (16), 115 (14); HRMS m/z (M^+) calcd for $C_{23}H_{30}O_4$ 370.2144, found 370.2145.

Compound 7. Methoxymethyl chloride (0.121 g, 1.50 mmol) was added to a solution of **6** (0.505 g, 1.36 mmol) and diisopropylethylamine (0.879 g, 6.80 mmol) in dry CH_2Cl_2 (10 mL). The reaction mixture was stirred at room temperature for 10 h and then water (20 mL) was added. The reaction mixture was extracted with CH_2Cl_2 (3 × 30 mL).The combined organic extracts were washed with saturated NH_4Cl solution (20 mL) and evaporated in vacuo. Flash chromatography on silica gel with hexane/EtOAc (20:1) afforded **7** (0.530 g, 94%) as an oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ 13.72 (1H, s), 6.48 (1H, d, J = 9.9 Hz), 5.44 (1H, d, J = 9.9 Hz), 5.18 (1H, t, J = 7.0 Hz), 5.02 (1H, t, J = 6.8 Hz), 4.96 (2H, s), 3.51 (3H, s), 3.27 (2H, d, J = 6.2 Hz), 2.65 (3H, s), 2.01−1.95 (4H, m), 1.73 (3H, s), 1.69 (3H, s), 1.53 (3H, s), 1.45 (6H, s); ^{13}C NMR (75 MHz, $CDCl_3$) δ 204.6, 163.8, 158.5, 155.2, 135.6, 131.7, 126.2, 124.8, 123.1, 118.3, 115.5, 108.8, 107.1, 100.5, 58.3, 40.1, 34.0, 28.1, 27.0, 26.1, 22.9, 18.1, 16.6; IR (neat) 2930, 1616, 1424, 1364, 1287, 1161, 1134, 1049 cm^{-1}; EIMS m/z (%) 414 (M^+, 66), 399 (22), 370 (17), 369 (58), 367 (11), 313 (10), 291 (17), 285 (25), 271 (26), 259 (12), 247 (54), 246 (15), 245 (12), 232 (15), 231 (100), 217 (14), 213 (13), 69 (14); HRMS m/z (M^+) calcd for $C_{25}H_{34}O_5$ 414.2406, found 414.2408.

Compound 9. To a solution of **7** (0.450 g, 1.09 mmol) in ethanol (10 mL) was added KOH (0.306 g, 5.45 mmol) and aldehyde **8** (0.331 g, 1.31 mmol). The reaction mixture was stirred at room temperature for 48 h. Evaporation of ethanol, addition of 2 N HCl (30 mL), extraction with EtOAc (3 × 50 mL), washing with brine (30 mL), and removal of the solvent followed by flash column chromatography on silica gel with hexane/EtOAc (20:1) gave **9** (0.538 g, 76%) as an oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ 13.96 (1H, s), 7.97 (1H, d, J = 15.6 Hz), 7.76 (1H, d, J = 15.6 Hz), 7.53 (2H, d, J = 8.8 Hz), 7.06 (2H, d, J = 8.8 Hz), 6.52 (1H, d, J = 9.9 Hz), 5.50 (1H, d, J = 9.9 Hz), 5.49 (2H, s), 5.25 (2H, s), 5.20 (1H, t, J = 7.0 Hz), 5.04 (1H, t, J = 6.8 Hz), 3.74 (2H, dd, J = 8.4, 8.3 Hz), 3.57 (3H, s), 3.31 (2H, d, J = 6.3 Hz), 2.06−1.97 (4H, m), 1.75 (3H, s), 1.62 (3H, s), 1.55 (3H, s) 1.52 (6H, s), 0.94 (2H, dd, J = 8.4, 8.3 Hz), −0.03 (9H, s); ^{13}C NMR (75 MHz, $CDCl_3$) δ 194.0, 164.0, 159.4, 158.4, 154.6, 142.8, 135.5, 132.2, 131.6, 130.3, 129.6, 126.0, 124.8, 123.3, 118.5, 117.0, 116.7, 115.8, 109.3, 107.4, 100.6, 94.6, 94.5, 78.0, 58.3, 56.7, 56.6, 40.1, 28.2, 27.1, 26.1, 23.1, 18.1, 16.7; IR (neat) 3447, 2957, 1632, 1589, 1549, 1510, 1418, 1341, 1235, 1144, 1090 cm^{-1}; EIMS m/z (%) 648 (M^+, 2), 414 (23), 370 (16), 369 (20), 355 (11), 285 (13), 271 (10), 247 (32), 231 (55), 219 (12), 183 (55), 129 (13), 115 (100), 91 (10); HRMS m/z (M^+) calcd for $C_{38}H_{52}O_7Si$ 648.3482, found 648.3486.

Mallotophilippen C (1). To a solution of **9** (0.405 g, 0.62 mmol) in ethanol (10 mL) was added HCl (5 drops) and the reaction mixture was stirred at room temperature for 1 h. The reaction mixture was diluted with saturated $NaHCO_3$ solution (30 mL) and extracted with EtOAc (3 × 30 mL). Removal of solvent and purification by column chromatography on silica gel with hexane/EtOAc (10:1) gave **1** (0.191 g, 65%) as an oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ 14.6, (1H, s), 8.00 (1H, d, J = 15.6 Hz), 7.73 (1H, d, J = 15.6 Hz), 7.48 (2H, d, J = 8.6 Hz), 6.85 (2H, d, J = 8.6 Hz), 6.57 (1H, d, J = 9.9 Hz), 6.41 (1H, s), 5.61 (1H, s), 5.45 (1H, d, J = 9.9 Hz), 5.28 (1H, t, J = 7.0 Hz), 5.03 (1H, t, J = 6.8 Hz), 3.41 (2H, d, J = 7.1 Hz), 2.17−2.09 (4H, m), 1.80 (3H, s), 1.67 (3H, s), 1.58 (3H, s), 1.51 (6H, s); ^{13}C NMR (75 MHz, $CDCl_3$) δ 193.0, 163.8, 157.7, 157.5, 154.7, 142.1, 140.3, 132.4, 130.2, 128.6, 125.5, 124.8, 123.5, 121.8, 116.8, 116.2, 106.2, 105.5, 102.4, 77.8, 39.8, 28.0, 26.3, 25.7, 21.7, 17.6, 16.1; IR (neat) 3450, 2975, 1605, 1537, 1452, 1350, 1263, 1166 cm^{-1}; EIMS m/z (%) 474 (M^+, 91), 460 (22), 459 (69), 405 (20), 391 (14), 389 (15), 352 (26), 351 (96), 339 (18), 335 (18), 323 (12), 286 (10), 285 (52), 269 (16), 243 (12), 232 (14), 232 (82), 230 (14), 229 (12), 216 (14), 215 (100), 189 (15), 183 (18), 149 (14), 147 (16), 135 (11), 115 (35), 69 (29); HRMS m/z (M^+) calcd for $C_{30}H_{34}O_5$ 474.2406, found 474.2405.

Compound 10. A mixture of **4** (2.018 g, 12.0 mmol), prenyl bromide (1.788 g, 12.0 mmol), and DBU (1.827 g, 12.0 mmol) in dry THF (50 mL) was stirred at room temperature for 12 h. Addition of 2 N HCl solution (50 mL), extraction with EtOAc (3 × 50 mL), washing with brine (50 mL), and removal of the solvent followed by flash column chromatography on silica gel with hexane/EtOAc (5:1) gave **10** (1.134 g, 40%) as a solid: mp 166−167 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.82 (1H, s), 5.22 (1H, t, J = 7.0 Hz), 3.33 (2H, d, J = 7.1 Hz), 2.64 (3H, s), 1.80 (3H, s), 1.75 (3H, s); ^{13}C NMR (75 MHz, $CDCl_3$) δ 203. 6, 163.5, 162.1, 160.5, 132.4, 122.9, 106.5, 104.9, 94.7, 32.8, 25.9, 21.4, 17.9; IR (KBr) 3418, 1634, 1402, 1370, 1285, 1235, 1150, 1073 cm^{-1}; EIMS m/z (%) 236 (M^+, 60), 221 (29), 193 (29), 181 (100), 165 (40), 153 (17), 69 (24); HRMS m/z (M^+) calcd for $C_{13}H_{16}O_4$ 236.1049, found 236.1050.

Compounds 11 and 12. To a solution of **10** (0.795 g, 3.36 mmol) and citral (1.023 g, 6.72 mmol) in CH_2Cl_2 (20 mL) was added ethylenediamine diacetate (0.121 g, 0.67 mmol). The reaction mixture was stirred at room temperature for 8 h. Evaporation of solvent and purification by column chromatography on silica gel with hexane/EtOAc (20:1) gave **11** (0.971 g, 78%) and **12** (0.212 g, 17%). **11**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 14.1 (1H, s), 6.56 (1H, d, J = 9.9 Hz), 6.30 (1H, s), 5.37 (1H, d, J = 9.9 Hz), 5.24 (1H, t, J = 7.1 Hz), 5.07 (1H, t. J = 7.1 Hz), 3.36 (2H, d, J = 7.2 Hz), 2.64 (3H, s), 2.17−2.03 (2H, m), 1.85−1.80 (2H, m), 1.81 (3H, s), 1.76 (3H, s), 1.64 (3H, s), 1.55 (3H, s), 1.41 (3H, s); ^{13}C NMR (75 MHz, $CDCl_3$) δ 203.3, 162.9, 157.4, 155.5, 136.5, 132.1, 123.7, 123.4, 121.7, 117.0, 80.5, 41.5, 33.3, 26.5, 25.9, 25.6, 23.1, 21.5, 17.9, 17.6; IR (neat) 3349, 2930, 1615, 1429, 1372, 1294 cm^{-1}; EIMS m/z (%) 370 (M^+, 34), 355 (13), 315 (12), 303 (29), 288 (20), 287 (100), 285 (10), 247 (11), 235 (12), 232 (11), 231 (68), 219 (14), 213 (10); HRMS m/z (M^+) calcd for $C_{23}H_{30}O_4$ 370.2144, found 370.2146. **12**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 13.55 (1H, s), 6.66 (1H, d, J = 9.9 Hz), 5.39 (1H, d, J = 9.9 Hz), 5.17 (1H, t, J = 7.1 Hz), 5.06 (1H, t. J = 7.1 Hz), 3.31 (2H, d, J = 7.2 Hz), 2.63 (3H, s), 2.10−2.0 (2H, m), 1.82 (3H, s), 1.81−1.70 (2H, m), 1.75 (3H, s), 1.63 (3H, s), 1.55 (3H, s), 1.36 (3H, s); ^{13}C NMR (75 MHz, $CDCl_3$) δ 203.5, 159.3, 158.5, 157.4, 135.8, 131.8, 124.2, 123.8, 122.9, 121.5, 116.6, 105.0, 102.1, 80.3, 41.5, 33.0, 26.8, 25.8, 25.6, 22.6, 21.2, 17.8, 17.6; IR (neat) 2974, 1615, 1429, 1370, 1294 cm^{-1}; EIMS m/z (%) 370 (M^+, 45), 369 (10), 355 (22), 331 (10), 318 (21), 315 (21), 304 (13), 303 (62), 301 (13), 289 (10),

288 (22), 287 (100), 285 (21), 273 (11), 259 (10), 247 (23), 235 (26), 233 (12), 232 (11), 231 (62), 219 (21), 81 (13); HRMS *m/z* (M^+) calcd for $C_{23}H_{30}O_4$ 370.2144, found 370.2145.

Compound 13. 2-(Trimethylsilyl)ethoxymethyl chloride (0.233 g, 1.40 mmol) was added to a solution of **11** (0.470 g, 1.27 mmol) and diisopropylethylamine (0.821 g, 6.35 mmol) in dry CH_2Cl_2 (10 mL). The reaction mixture was stirred at room temperature for 12 h and then water (20 mL) was added. The reaction mixture was extracted with CH_2Cl_2 (3 × 30 mL) and the combined organic extracts were washed with saturated NH_4Cl solution (30 mL) and water (20 mL), then evaporated in vacuo. Flash chromatography on silica gel with hexane/EtOAc (30:1) afforded **13** (0.591 g, 93%) as an oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ 13.72 (1H, s), 6.55 (1H, d, J = 10.0 Hz), 5.40 (1H, d, J = 10.0 Hz), 5.18 (1H, t, J = 6.6 Hz), 5.05 (1H, t. J = 6.6 Hz), 5.00 (2H, s), 3.80 (2H, dd, J = 7.7, 7.5 Hz), 3.26 (2H, d, J = 6.5 Hz), 2.64 (3H, s), 2.17−2.04 (2H, m), 1.86−1.70 (2H, m), 1.73 (3H, s), 1.66 (3H, s), 1.61 (3H, s), 1.52 (3H, s), 1.40 (3H, s), 0.95 (2H, dd, J = 7.7, 7.5 Hz), −0.02 (9H, s); ^{13}C NMR (75 MHz, $CDCl_3$) δ 203.7, 163.3, 157.9, 154.9, 131.8, 131.1, 124.1, 123.5, 122.9, 118.4, 114.8, 108.0, 106.4, 98.2, 80.0, 67.6, 53.3, 41.2, 33.4, 26.1, 25.6, 25.5, 23.0, 22.4, 18.0, 17.7, 17.4, −1.63; IR (neat) 3567, 2971, 1616, 1422, 1283, 1055 cm^{-1}; EIMS *m/z* (%) 500 (M^+, 4), 427 (17), 360 (26), 359 (100), 213 (11), 73 (20); HRMS *m/z* (M^+) calcd for $C_{29}H_{44}O_5Si$ 500.2958, found 500.2961.

Compound 15. To a solution of **13** (0.390 g, 0.78 mmol) in ethanol (10 mL) was added KOH (0.219 g, 3.90 mmol) and aldehyde **14** (0.373 g, 0.94 mmol). The reaction mixture was stirred at room temperature for 48 h. Evaporation of ethanol, addition of 2 N HCl (30 mL), extraction with EtOAc (3 × 50 mL), washing with brine (30 mL), and removal of the solvent followed by flash column chromatography on silica gel with hexane/EtOAc (30:1) gave **15** (0.495 g, 72%) as an oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ 14.08 (1H, s), 7.95 (1H, d, J = 15.5 Hz), 7.74 (1H, d, J = 15.5 Hz), 7.45 (1H, s), 7.30−7.20 (2H, m), 6.57 (1H, d, J = 10.0 Hz), 5.45 (1H, d, J = 10.0 Hz), 5.31 (2H, s), 5.30 (2H, s), 5.20 (1H, t, J = 6.6 Hz), 5.03 (3H, m), 3.85−3.75 (6H, m), 3.30 (2H, d, J = 6.0 Hz), 2.14−2.10 (2H, m), 1.89−1.70 (2H, m), 1.75 (3H, s), 1.67 (3H, s), 1.59 (3H, s), 1.51 (3H, s), 1.43 (3H, s), 0.98−0.91 (6H, m), 0.00 (27H, s); ^{13}C NMR (75 MHz, $CDCl_3$) δ 193.2, 165.5, 159.4, 155.9, 150.7, 148.9, 144.1, 133.3, 132.7, 130.8, 127.1, 125.7, 124.9, 124.6, 124.2, 119.7, 117.0, 116.5, 116.3, 109.8, 107.8, 99.4, 94.5, 81.0, 68.7, 67.4, 67.3, 41.9, 27.1, 26.3, 26.2, 23.5, 23.3, 18.7, 18.6, 18.5, 18.4, 18.1, −1.0; IR (neat) 2955, 1632, 1589, 1553, 1508, 1416, 1381, 1341, 1254, 1094 cm^{-1}; EIMS *m/z* (%) 881 (M^+, 23), 798 (21), 667 (11), 343 (24), 215 (14), 103 (11), 75 (10), 73 (100), 69 (10); HRMS *m/z* (M^+) calcd for $C_{48}H_{76}O_9Si_3$ 880.4797, found 880.4800.

Mallotophilippen E (3). To a solution of **15** (0.320 g, 0.36 mmol) in ethanol (10 mL) was added HCl (5 drops) and the reaction mixture was stirred at room temperature for 1 h. The reaction mixture was diluted with saturated $NaHCO_3$ solution (30 mL) and extracted with EtOAc (3 × 30 mL). Removal of solvent at reduced pressure left an oily residue, which was then purified by column chromatography on silica gel with hexane/EtOAc (20:1) to give **3** (0.099 g, 56%) as an oil: ^{1}H NMR (300 MHz, benzene-d_6) δ 15.4 (1H, s), 8.23 (1H, d, J = 15.5 Hz), 8.00 (1H, d, J = 15.6 Hz), 7.05−6.96 (2H, m), 6.87 (1H, d, J = 10.0 Hz), 6.62 (1H, br s), 6.30 (1H, br s), 5.16 (1H, d, J = 10.0 Hz), 5.18−5.11 (2H, m), 3.47 (2H, d, J = 7.1 Hz), 2.28−2.14 (2H, m), 1.87−1.67 (2H, m), 1.61 (3H, s), 1.49 (3H, s), 1.45 (6H, s), 1.31 (3H, s); ^{13}C NMR (75 MHz, benzene-d_6) δ 193.9, 165.2, 158.3, 155.9, 147.3, 145.0, 143.5, 136.2, 132.5, 129.7, 126.5, 124.8, 124.2, 123.2, 122.8, 118.2, 116.2, 115.5, 107.2, 106.6, 102.8, 80.9, 42.0, 26.8, 26.1, 25.9, 23.8, 22.4, 18.0, 17.9; IR (neat) 23389, 2973, 1597, 1520, 1447, 1354, 1283, 1152 cm^{-1}; EIMS *m/z* (%) 490 (M^+, 53), 475 (13), 435 (10), 408 (26), 407 (100), 271 (15), 215 (41); HRMS *m/z* (M^+) calcd for $C_{30}H_{34}O_6$ 490.2355, found 490.2353.

Acknowledgment. This work was supported by grant No. RTI04-01-04 from the Regional Technology Innovation Program of the Ministry of Commerce, Industry, and Energy (MOCIE).

Supporting Information Available: Copies of ^{1}H NMR and ^{13}C NMR for all product. This material is available free of charge via the Internet at http://pubs.acs.org.

JO800367R