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A Facile Synthesis of Natural Products Chaetomellic Acid A and 1,7(*Z*)-Nonadecadiene-2,3-dicarboxylic Acid[†,‡]

Anirban Kar and Narshinha P. Argade*[,§]

Division of Organic Chemistry (Synthesis), National Chemical Laboratory, Pune 411 008, India

argade@dalton.ncl.res.in

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Abstract: Synthesis of recently isolated bioactive natural products chaetomellic acid A anhydride (**1**) and a novel 1,7-(*Z*)-nonadecadiene-2,3-dicarboxylic acid (**2**) have been described. Chemoselective carbon−carbon S_N2' coupling reactions of appropriate Grignard reagents with dimethyl bromomethylfumarate (**7**) in diethyl ether in the presence of HMPA at room temperature furnished the corresponding diesters **8** and **15** in 60−62% yields. The formed diesters **8** and **15** on hydrolysis gave respectively the corresponding desired diacids **9** and **2** in quantitative yields. Acetic anhydride induced ring closure of diacids **9** and **2** respectively gave the chaetomellic acid A anhydride (**1**) and isochaetomellic acid B anhydride (**16**) with 38−39% overall yields in five steps.

Chaetomellic acid A anhydride (**1**) and chaetomellic acid B anhydride have been recently isolated[1] from *Chaetomella acutiseta*, and their dianionic forms are potent and highly specific inhibitors of ras farnesyl-protein transferase. At present a number of FPTase inhibitors are in human clinical trials by several companies,[2] and provision of new facile synthetic approaches to these natural products chaetomellic acid A anhydride (2-tetradecyl-3-methylmaleic anhydride) and chaetomellic acid B anhydride [(*Z*)-2-hexadec-7-enyl-3-methylmaleic anhydride] is a task of current interest.[3−10] Eight alternate syntheses of **1**, including three from our group,[7,8,10] and two syntheses of chaetomellic acid B[5,9] have been recently accomplished using elegant synthetic strategies.[3−10] Very recently the Watanabe's group from Kyoto University in Japan isolated[11] a novel compound 1,7(*Z*)-nonadecadiene-2,3-dicarboxylic acid (NDA, **2**) from cultures of a white-rot fungus *Ceriporiopsis subvermispora* as a corresponding diester **15**. The structural assignment of NDA (**2**) was done on the basis of ^{1}H NMR, ^{1}H−^{1}H COSY, ^{13}C NMR, HMQC and HMBC NMR, and GC-MS data of corresponding dimethyl ester **15**. Since chaetomellic acids are active in their dianionic form, we felt that synthesis of itaconic acid analogues **9** and **2** of these acids will be of interest and useful for biological evaluation studies point of view. The compounds containing such a exo-type or exocyclic carbon−carbon double bonds are generally synthesized by using Wittig reactions,[12] coupling reactions involving reduction of carbon−carbon triple bonds,[13] and S_N2' coupling reactions[14] of appropriate substrates and nucleophiles. Chemoselective Grignard reactions, with preservation of substrate functional groups such as ester,[15,16] carboxylic acid,[17] nitrile,[15] and epoxide,[18] are known in the literature, and recently we have demonstrated a chemoselective Grignard coupling reaction with an intact preservation of the cyclic anhydride moiety.[10] We have studied several Michael type addition reactions to the carbon−carbon double bond in maleic anhydrides and their derivatives, and they are potential starting materials for the synthesis of natural products[19] and heterocycles.[20] We planned a chemoselective S_N2' carbon−carbon coupling reaction[21] of an appropriate Grignard reagent with bromomethylmaleic anhydride (**4**) and dimethyl bromomethylfumarate (**7**) for an easy access to these natural products, and we herein report the synthesis of chaetomellic anhydrides **1** and **16** and novel itaconic acid analogues **2** and **9** (Schemes 1 and 2).

Reaction of citraconic anhydride (**3**) with NBS/benzoyl peroxide in carbon tetrachloride under reflux followed by Kugelrohr distillation of the obtained oily product gave bromomethylmaleic anhydride (**4**)[22] in 55% yield with 98% purity (by ^{1}H NMR). The reactions of Grignard reagent tertadecylmagnesium bromide with highly reactive monosubstituted bromoanhydride **4** in the presence/absence of HMPA with/without copper catalyst were not selective and yielded only 8−10% of the desired product chaetomellic acid A anhydride (**1**). To obtain the selectivity, we planned for preparation of relatively less reactive starting material dimethyl bromomethylfumarate (**7**),

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[‡] Dedicated to Dr. B. G. Hazra, OCS, NCL, Pune.

[§] Fax: +91-20-5893153.

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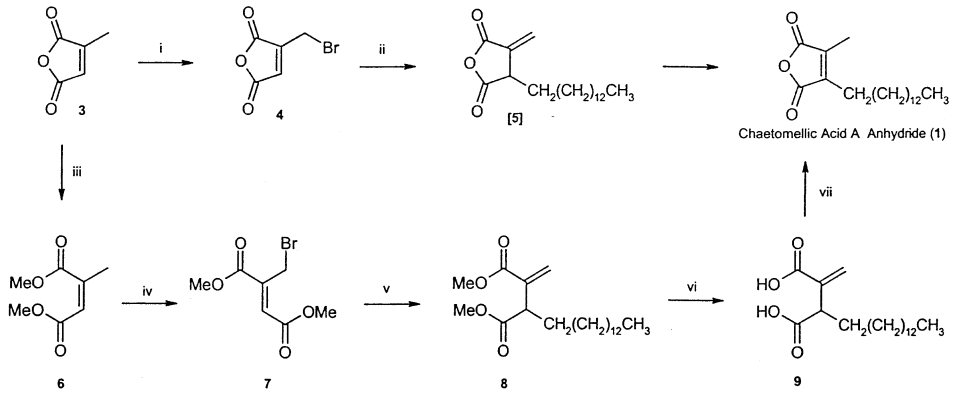
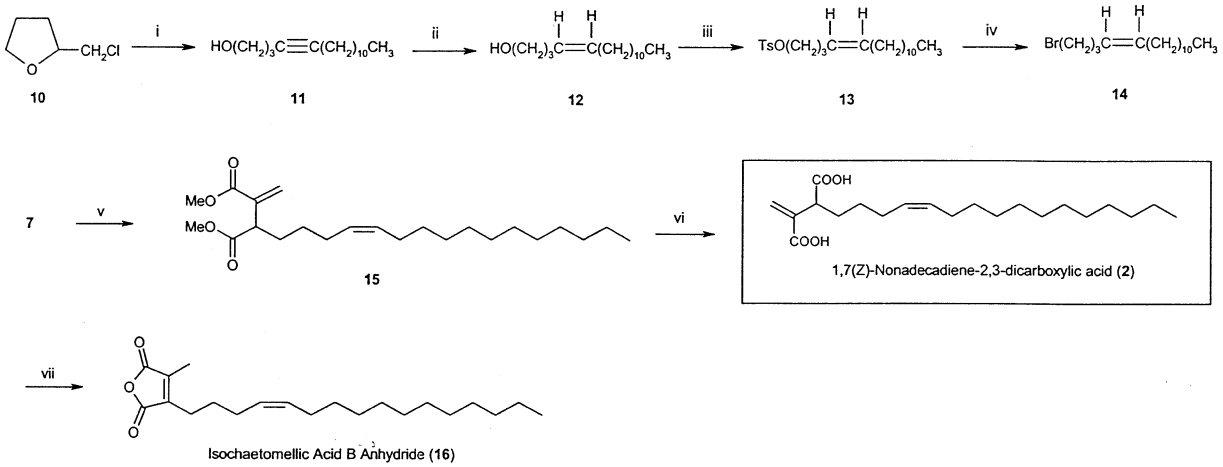
SCHEME 1[a]



[a] Key: (i) NBS, DBP, CCl_4, reflux, 8 h (55%); (ii) $C_{14}H_{29}MgBr$, Et_2O, rt, 8 h (8-10%); (iii) CH_3OH, H^+/H_2SO_4, reflux, 12 h (75%); (iv) NBS, AIBN, CCl_4, reflux, 12 h (85%); (v) $C_{14}H_{29}MgBr$, Et_2O, HMPA, rt, 8 h (60%); (vi) AcOH + HCl (7:3), reflux, 2 h (98%); (vii) Ac_2O, reflux, 2 h (~100%).

SCHEME 2[a]



[a] Key: (i) $LiNH_2/NH_3$, $C_{11}H_{23}Br$, −78 °C to −33 °C to rt, 4 h (80%); (ii) H_2, Lindlar Pd, quinoline, hexane, rt, 30 min (99%); (iii) *p*-TsCl, TEA, DMAP, CH_2Cl_2, rt, 6 h (86%); (iv) LiBr, $NaHCO_3$, acetone, rt, 15 h (85%); (v) $CH_3(CH_2)_{10}CH{=}CH(CH_2)_3MgBr$, Et_2O, HMPA, rt, 8 h (62%); (vi) LiOH, THF + H_2O (2:1), rt, 18 h (98%); (vii) Ac_2O, reflux, 2 h (~100).

which is also a more appropriate precursor for the synthesis of natural dicarboxylic acid **2**. The reaction of citraconic anhydride (**3**) with methanol/H_2SO_4 under reflux gave the desired diester **6** in 75% yield.[23] The diester **6** on treatment with NBS/AIBN in refluxing carbon tetrachloride underwent smooth allylic bromination and isomerization of carbon−carbon double bond to yield the dimethyl bromomethylfumarate (**7**) in 85% yield.[24] An in situ isomerization of (*Z*)-isomer to (*E*)-isomer was confirmed[25] by obtaining the same product **7** from the corresponding dimethyl methylfumarate under the same set of reaction conditions. The unsymmetrical bromodiester **7** has five alternate sites available for nucleophilic reactions, viz. (i) two ester carbonyls for 1,2-additions, (ii) two sites for Michael addition, and (iii) allylic bromo atom for nucleophilic substitution reaction. The freshly prepared Grignard reagent from tetradecyl bromide, in the presence of HMPA reacted in a highly chemo- and regioselective fashion with bromodiester **7** and the exclusive Michael addition followed by elimination of allylic bromo atom gave the net S_N2' product **8** in 60% yield.[24] The diester **8** on refluxing with glacial acetic acid plus concentrated HCl (7:3) mixture gave the dicarboxylic acid **9** in 98% yield. The dicarboxylic acid **9** in refluxing acetic anhydride furnished the desired bioactive natural product chaetomellic acid A anhydride (**1**) in nearly 100% yield. In this reaction both the formation of cyclic anhydride **5** and *gem*-dialkyl-substituted exocyclic to tetrasubstituted endocyclic carbon−carbon double bond migration took place in one pot. In the present five-step synthesis the chaetomellic acid A anhydride (**1**) was obtained in 38% overall yield. The analytical and spectral data obtained for **1** were in complete agreement with the reported data.[1]

On successful completion of synthesis of **1** via **8**, we planned for the first synthesis of recently isolated novel dicarboxylic acid **2**. The reaction of tetrahydrofurfuryl chloride (**10**) with $LiNH_2/NH_3$, followed by treatment with undecyl bromide, gave the acetylene derivative **11** in 80% yield.[26] Catalytic hydrogenation of **11** with Lindlar catalyst gave the cis olefin **12** in 97% yield. Conversion

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(25) As a control experiment, we treated dimethyl maleate with NBS/AIBN in refluxing CCl_4 and obtained exclusively the corresponding dimethyl fumarate in quantitative yield, proving that our condition employed for allylic bromination of **6** is also sufficient for isomerization of carbon−carbon double bond in these systems.

of **12** to corresponding tosylate **13** (86%) followed by displacement of OTs with LiBr in acetone at room temperature gave the required (*Z*)-hexadeca-4-enyl bromide (**14**) in 85% yield. The overall yield of **14** in four steps was 57%. The freshly prepared Grignard reagent from **14**, in the presence of HMPA, chemo- and regioselectively coupled with bromodiester **7** to yield S_N2' product **15** with 62% yield. The diester **15** on LiOH-induced hydrolysis followed by acidification gave the desired novel natural product 1,7(*Z*)-nonadecadiene-2,3-dicarboxylic acid (**2**) in 98% yield. In the present four-step synthesis the natural product **2** was obtained with 39% overall yield. The analytical and spectral data obtained for the corresponding dimethyl ester **15** were in complete agreement with reported data.[11] The dicarboxylic acid **2** in refluxing acetic anhydride gave isochaetomellic acid B anhydride **16** in quantitative yield.

In summary, we have demonstrated the ninth synthesis of bioactive natural product Chaetomellic acid A anhydride (**1**) with 38% overall yield in five-step and the first four-step synthesis of very recently isolated natural product 1,7(*Z*)-nonadecadiene-2,3-dicarboxylic acid (**2**) with 39% overall yield. In both above-mentioned coupling reactions with **7**, the chemo- and regioselective attack of the Grignard reagents on vinylic carbon in absence of copper catalyst is interesting and useful. It was also possible to couple the above Grignard reagents under similar reaction conditions without using HMPA to obtain **8** and **15** with 48 to 50% yields. We also feel that such type of migration of trisubstituted carbon−carbon double bond to *gem*-disubstituted carbon−carbon double bond with the loss of conjugation with one of the ester carbonyls is noteworthy. The present studies also provide a useful general approach for the synthesis of compounds containing such exo-type or exocyclic carbon−carbon double bonds[27] for stucture−activity relationship studies.

Experimental Section

Melting points are uncorrected. Column chromatographic separations were carried out on silica gel (60−120 mesh). Commercially available citraconic anhydride, methyl fumaric acid, undecyl bromide, tetradecyl bromide, magnesium turnings, HMPA, tertrahydrofurfuryl chloride, lithium ribbon, Lindlar catalyst, quinoline, *p*-toluenesulfonyl chloride, DMAP, lithium bromide, and acetic anhydride were used.

Dimethyl Methylmaleate (6). A solution of **3** (4.48 g, 40 mmol) in methanol (40 mL) and H_2SO_4 (0.5 mL) mixture was refluxed for 12 h under nitrogen. The reaction mixture was concentrated in vacuo. The residue was diluted with water and extracted with ethyl acetate (20 mL × 3). The combined organic layer was washed with water (20 mL) and brine and dried over Na_2SO_4. Concentration of organic layer in vacuo followed by silica gel column chromatographic purification of the crude product using petroleum ether/ethyl acetate (9:1) as eluent furnished pure diester **6**: 4.74 g (75% yield); thick oil; ^{1}H NMR ($CDCl_3$, 200 MHz) δ 2.04 (bs, 3H), 3.70 (s, 3H), 3.81 (s, 3H), 5.84 (bs, 1H); IR (Neat) ν_{max} 1736, 1726, 1655 cm^{-1}.

Dimethyl Methylfumarate. Repetition of above experimental procedure with methylfumaric acid (5.20 g, 40 mmol) yielded the dimethyl methylfumarate in same yield; thick oil; ^{1}H NMR ($CDCl_3$, 200 MHz) δ 2.24 (d, J = 2 Hz, 3H), 3.72 (s, 3H), 3.76 (s, 3H), 6.73 (q, J = 2 Hz, 1H); IR (Neat) ν_{max} 1734, 1724, 1645 cm^{-1}.

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Dimethyl Bromomethylfumarate (7).[24] A mixture of **6** (4.74 g, 30 mmol), *N*-bromosuccinimide (8.00 g, 45 mmol), and catalytic amount of AIBN (200 mg, 1.22 mmol) in carbon tetrachloride (150 mL) was gently refluxed for 12 h in a 250 mL round-bottom flask. The mixture was left overnight at room temperature and then filtered. The residue was washed with CCl_4 (25 mL × 2), and the combined organic layer was washed with water (50 mL × 2) and brine (50 mL) and then dried over Na_2SO_4 and concentrated in vacuo to furnish thick yellow oil, which was purified by chromatography on silica gel column using petroleum ether/ethyl acetate (9:1) to give the desired bromo diester **7**: 6.05 g (85% yield); thick oil; ^{1}H NMR ($CDCl_3$, 200 MHz) δ 3.83 (s, 3H), 3.88 (s, 3H), 4.72 (s, 2H), 6.83 (s, 1H); ^{1}H NMR (CCl_4, 200 MHz) δ 3.87 (s, 3H), 3.93 (s, 3H), 4.70 (s, 2H), 6.79 (s, 1H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 22.1, 51.7, 52.5, 127.9, 142.4, 164.5, 164.7; MS (*m*/*e*) 238, 236, 206, 204, 179, 177, 125, 98, 68, 59; IR (Neat) ν_{max} 1730, 1726, 1643 cm^{-1}. Anal. Calcd for $C_7H_9BrO_4$: C, 35.47; H, 3.83. Found: C, 35.59; H, 3.72.

Dimethyl methylfumarate (4.74 g, 30 mmol) with same set of reaction conditions furnished **7** in 86% yield.

4-Hexadecyn-1-ol (11). Lithium (1.05 g, 150 mmol) in the presence of ferric nitrate (50 mg) was dissolved in freshly distilled ammonia (250 mL) at − 78 °C (disappearance of blue color). To this freshly prepared lithium amide solution was added tetrahydrofurfuryl chloride (6.03 g, 50 mmol) during 10 min time, and the reaction mixture was stirred for 3 h at − 33 °C. After all the tetrahydrofurfuryl chloride was consumed (by TLC), *n*-undecyl bromide (11.75 g, 50 mmol) in THF (10 mL) was added dropwise to the stirred and cooled reaction mixture at − 33 °C. It was then stirred for additional 0.5 h and allowed to reach room temperature. The residue was treated with saturated ammonium chloride solution and extracted with ether (50 mL × 5); the combined organic layer was washed with water (50 mL × 2) and brine (50 mL) and then dried over Na_2SO_4 and concentrated in vacuo to furnish thick oil, which was purified by chromatography on silica gel column using petroleum ether/ethyl acetate (8:2) to give pure **11**: 9.53 g (80% yield); thick oil; ^{1}H NMR ($CDCl_3$, 200 MHz) δ 0.87 (t, J = 8 Hz, 3H), 1.25 (bs, 16H), 1.43 (quintet, J = 6 Hz, 2H), 1.73 (quintet, J = 8 Hz, 2H), 1.89 (bs, 1H), 2.05−2.20 (m, 2H), 2.20−2.35 (m, 2H), 3.74 (t, J = 6 Hz, 2H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 14.0, 15.4, 18.7, 22.6, 28.9−29.6 (7 carbons), 31.6, 31.9, 61.9, 79.2, 81.0; MS (*m*/*e*) 238, 226, 209, 184, 153, 111, 97, 83, 67, 55; IR ($CHCl_3$) ν_{max} 3423, 2400, 1215 cm^{-1}. Anal. Calcd for $C_{16}H_{30}O$: C, 80.61; H, 12.68. Found: C, 80.57; H, 12.70.

4(*Z*)-Hexadecen-1-ol (12). To a solution of **11** (9.52 g, 40 mmol) in hexane (150 mL) were added Lindlar palladium catalyst (800 mg) and quinoline (2 mL). The reaction mixture was vigorously stirred at room temperature under slightly positive pressure until hydrogen absorption ceased (0.5 h). The mixture was filtered, and filtrate was concentrated in vacuo. The residue was chromatographed over silica gel using petroleum ether/ethyl acetate (8:2) to give **12**: 9.51 g (99% yield), thick oil; ^{1}H NMR ($CDCl_3$, 200 MHz) δ 0.88 (t, J = 6 Hz, 3H), 1.26 (bs, 18H), 1.51 (bs, 1H), 1.64 (quintet, J = 8 Hz, 2H), 2.04 (quintet, J = 6 Hz, 2H), 2.14 (quintet, J = 6 Hz, 2H), 3.67 (t, J = 6 Hz, 2H), 5.30−5.50 (m, 2H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 13.9, 22.6, 23.6, 27.2, 29.3−29.6 (7 carbons), 31.9, 32.7, 62.5, 128.8, 130.7; MS (*m*/*e*) 240, 222, 194, 152, 109, 96, 82, 68, 55; IR (neat) ν_{max} 3354, 1465 cm^{-1}. Anal. Calcd for $C_{16}H_{32}O$: C, 79.93; H, 13.41. Found: C, 79.91; H, 13.44.

4(*Z*)-Hexadecene 1-Tosylate (13). *p*-Toluenesulfonyl chloride (11.47 g, 60 mmol) was added to a solution of **12** (7.20 g, 30 mmol), anhydrous triethylamine (9.09 g, 90 mmol), and DMAP (75 mg) in anhydrous dichloromethane (150 mL) with stirring and ice cooling. Stirring was continued for 6 h at room temperature. The reaction mixture was then poured into ice water and extracted with dichloromethane (50 mL × 3). The combined organic extracts were washed with water and brine, dried over Na_2SO_4 and concentrated in vacuo. The residue was chromatographed over silica gel using petroleum ether/ethyl acetate (9:1) to give **13**: 10.13 g (86% yield), thick oil; ^{1}H NMR ($CDCl_3$, 200 MHz) δ 0.88 (t, J = 6 Hz, 3H), 1.26 (bs, 18H), 1.69 (quintet, J = 8 Hz, 2H), 1.95 (quintet, J = 8 Hz, 2H), 2.06 (quintet, J =

8 Hz, 2H), 2.45 (s, 3H), 4.03 (t, J = 6 Hz, 2H), 5.15−5.45 (m, 2H), 7.35 (d, J = 8 Hz, 2H), 7.79 (d, J = 8 Hz, 2H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 13.9, 21.4, 22.5, 22.9, 27.0, 28.8−29.5 (8 carbons), 31.8, 69.9, 127.2, 127.7, 129.6, 131.5, 133.5, 144.4; MS (*m*/*e*) 222, 194, 173, 155, 124, 109, 91, 68; IR (neat) ν_{max} 1598, 1465, 1365, 1176 cm^{-1}. Anal. Calcd for $C_{23}H_{38}O_3S$: C, 70.00; H, 9.71. Found: C, 70.03; H, 9.67.

4(*Z*)-Hexadecene 1-Bromide (14). To a solution of **13** (9.85 g, 25 mmol) in dry acetone (150 mL) were added $NaHCO_3$ (21.0 g, 250 mmol) and anhydrous lithium bromide (15.23 g, 175 mmol). The reaction mixture was stirred for 15 h at room temperature and then diluted with ether (100 mL) and filtered through Celite. The organic solution was concentrated in vacuo, and the residue was diluted with ether (75 mL). The ether layer was washed with water, 5% $Na_2S_2O_3$ solution, saturated aquous $NaHCO_3$ solution, and brine, dried over Na_2SO_4, and concentrated in vacuo. The residue was chromatographed over silica gel using petroleum ether to give **14**: 6.44 g (85% yield); thick oil; ^{1}H NMR ($CDCl_3$, 200 MHz) δ 0.88 (t, J = 6 Hz, 3H), 1.26 (bs, 18H), 1.91 (quintet, J = 8 Hz, 2H), 2.05 (quintet, J = 6 Hz, 2H), 2.20 (quintet, J = 6 Hz, 2H), 3.41 (t, J = 8 Hz, 2H), 5.20−5.55 (m, 2H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 14.1, 22.7, 25.7, 27.3, 29.3−29.7 (7 carbons), 31.9, 32.7, 33.2, 127.3, 131.8; MS (*m*/*e*) 304, 302, 205, 181, 164, 162, 150, 148, 137, 111, 97, 83, 69; IR (Neat) ν_{max} 1465, 1224 cm^{-1}. Anal. Calcd for $C_{16}H_{31}Br$: C, 63.36; H, 10.30. Found: C, 63.39; H, 10.27.

Dimethyl 1-Heptadecene-2,3-dicarboxylate (8). A fresh solution of *n*-tetradecylmagnesium bromide in ether was prepared as follows. A solution of *n*-tetradecyl bromide (2.49 g, 9 mmol) in LAH-dried ether (10 mL) was added at room temperature to magnesium turnings (648 mg, 27 mmol) in ether (10 mL) under argon with constant stirring in three equal portions at an interval of 10 min. The reaction mixture was further stirred at room temperature for 4 h. TLC of the reaction mixture in *n*-pentane showed quantitative conversion of the halide in to the Grignard reagent. This freshly generated Grignard reagent was added dropwise to a solution of HMPA (2.69 g, 15 mmol) and **7** (711 mg, 3 mmol) in anhydrous ether (15 mL) at room temperature. The reaction mixture was further stirred at room temperature for 8 h. The reaction was quenched by the addition of a saturated ammonium chloride solution (20 mL) and ether (10 mL). The reaction mixture was extracted with ether (20 mL × 3), the combined ethereal extracts were washed with water and brine, dried with Na_2SO_4 and concentrated in vacuo. The residue was chromatographed over silica gel using petroleum ether/ethyl acetate (9.5:0.5) to give **8**: 637 mg (60% yield); thick oil; ^{1}H NMR ($CDCl_3$, 200 MHz) δ 0.86 (t, J = 6 Hz, 3H), 1.24 (bs, 24H), 1.50−2.00 (m, 2H), 3.49 (t, J = 8 Hz, 1H), 3.67 (s, 3H), 3.75 (s, 3H), 5.74 (s, 1H), 6.35 (s, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 14.0, 22.6, 27.4, 29.2−29.5 (9-carbons), 31.3, 31.8, 46.5, 51.8, 51.9, 126.3, 138.6, 166.6, 173.6; IR (Neat) ν_{max} 1738, 1728, 1630 cm^{-1}. Anal. Calcd for $C_{21}H_{38}O_4$: C, 71.14; H, 10.80. Found: C, 71.10; H, 10.73.

Dimethyl 1,7(*Z*)-Nonadecadiene-2,3-dicarboxylate (15). Repetition of above procedure using (*Z*)-hexadeca-4-enylmagnesium bromide [prepared from **14** (2.73 g, 9 mmol) and magnesium (648 mg, 27 mmol)] and **7** (711 mg, 3 mmol) gave the corresponding diester **15**: 707 mg (62% yield); thick oil; ^{1}H NMR ($CDCl_3$, 200 MHz) δ 0.88 (t, J = 6 Hz, 3H), 1.26 (bs, 18H), 1.35 (quintet, J = 6 Hz, 2H), 1.66 (m, 1H), 1.80−2.15 (m, 5H), 3.51 (t, J = 8 Hz, 1H), 3.68 (s, 3H), 3.77 (s, 3H), 5.34 (m, 2H), 5.76 (s, 1H), 6.37 (s, 1H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 14.0, 22.6, 26.8, 27.2, 27.5, 29.3, 29.6 (6 carbons), 30.8, 31.9, 46.4, 51.9, 52.0, 126.6, 128.8, 130.6, 138.4, 166.6, 173.6; MS (*m*/*e*) 380, 348, 320, 289, 261, 236, 193, 158, 140, 126, 107, 93, 79, 67; IR (Neat) ν_{max} 1740, 1726, 1630, 1458, 1437 cm^{-1}. Anal. Calcd for $C_{23}H_{40}O_4$: C, 72.59; H, 10.59. Found: C, 72.67; H, 10.53.

1-Heptadecene-2,3-dicarboxylic Acid (9). Concentrated hydrochloric acid (3 mL) was added to a solution of **8** (531 mg, 1.50 mmol) in acetic acid (7 mL), and the reaction mixture was refluxed for 2 h. The reaction mixture was then cooled and concentrated in vacuo, and the residue was diluted with ethyl acetate (30 mL). The ethyl acetate layer was washed with water and brine, dried over Na_2SO_4, and concentrated in vacuo. The residue was chromatographed over silica gel using petroleum ether/ethyl acetate (6:4) to give **9**: 479 mg (98% yield); mp 98−99 °C (benzene); ^{1}H NMR ($CDCl_3$, 200 MHz) δ 0.88 (t, J = 8 Hz, 3H), 1.26 (bs, 24H), 1.60−1.85 (m, 1H), 1.85−2.10 (m, 1H), 3.40 (t, J = 8 Hz, 1H), 5.84 (s, 1H), 6.55 (s, 1H), 7.35−8.30 (bs, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 14.0, 22.6, 27.4, 29.3−29.6 (9 carbons), 30.7, 31.9, 46.6, 129.4, 137.7, 171.6, 179.3; IR (Nujol) ν_{max} 1703, 1693, 1628 cm^{-1}. Anal. Calcd for $C_{19}H_{34}O_4$: C, 69.90; H, 10.50. Found: C, 69.93; H, 10.37.

1,7(*Z*)-Nonadecadiene-2,3-dicarboxylic Acid (2). Aquous lithium hydroxide solution (230 mg in 2 mL water) was added to a solution of **15** (570 mg, 1.50 mmol) in tetrahydrofuran (4 mL), and the reaction mixture was stirred for 18 h at room temperature. The reaction mixture was then concentrated in vacuo, and the residue was diluted with ethyl acetate (50 mL) and acidified to pH 2 with 2 N hydrochloric acid. The organic layer was separated and the aquous layer was further extracted with ethyl acetate (10 mL × 3). The combined organic layer was washed with water and brine, dried over Na_2SO_4, and concentrated in vacuo. The residue was chromatographed over silica gel using petroleum ether/ethyl acetate (6:4) to give **2**: 520 mg (98% yield); thick oil; ^{1}H NMR ($CDCl_3$, 200 MHz) δ 0.88 (t, J = 6 Hz, 3H), 1.26 (bs, 18H), 1.40 (quintet, J = 6 Hz, 2H), 1.65−1.85 (m, 1H), 1.85−2.20 (m, 5H), 3.43 (t, J = 8 Hz, 1H), 5.36 (m, 2H), 5.85 (s, 1H), 6.55 (s, 1H), 8.72 (bs, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 14.0, 22.6, 26.8, 27.3, 27.5, 29.2, 29.3 (6 carbons), 29.8, 31.9, 46.8, 128.7, 129.6, 130.8, 137.5, 171.5, 179.2; MS (*m*/*e*) 352, 334, 316, 306, 295, 277, 261, 239, 221, 193, 179, 151, 126, 112, 97, 81, 67; IR (neat) ν_{max} 2683, 1713, 1699, 1628 cm^{-1}. Anal. Calcd for $C_{21}H_{36}O_4$: C, 71.55; H, 10.29. Found: C, 71.47; H, 10.37.

2-Tetradecyl-3-methylmaleic Anhydride (Chaetomellic Acid A Anhydride, 1). A solution of **9** (326 mg, 1 mmol) in acetic anhydride (5 mL) was refluxed for 2 h, and the reaction mixture was allowed to reach room temperature, concentrated under vacuo at 50 °C, and diluted with ethyl acetate (20 mL). The organic layer was washed with water and brine, dried with Na_2SO_4, and concentrated in vacuo. The residue was chromatographed over silica gel using petroleum ether/ethyl acetate (9.5:0.5) to give **1**: 308 mg (∼100% yield); thick oil; ^{1}H NMR ($CDCl_3$, 200 MHz) δ 0.88 (t, J = 7 Hz, 3H), 1.15−1.45 (bs, 22H), 1.46−1.69 (m, 2H), 2.07 (s, 3H), 2.45 (t, J = 7 Hz, 2H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 9.6, 14.3, 22.9, 24.6, 27.7, 29.0−31.0 (9 carbons), 32.1, 140.6, 144.9, 166.0, 166.4; MS (*m*/*e*) 308, 290, 191, 150, 126, 91, 81, 69; IR (neat) ν_{max} 1770, 1680 cm^{-1}. Anal. Calcd for $C_{19}H_{32}O_3$: C, 73.98; H, 10.46. Found: C, 73.73; H, 10.39.

(*Z*)-2-Hexadeca-4-enyl-3-methylmaleic Anhydride (Isochaetomellic Acid B Anhydride, 16). It was prepared similarly from **2** (352 mg, 1 mmol) and acetic anhydride (5 mL) as described above to obtain the corresponding anhydride **16**: 333 mg (∼100% yield); thick oil; ^{1}H NMR ($CDCl_3$, 200 MHz) δ 0.88 (t, J = 6 Hz, 3H), 1.26 (bs, 18H), 1.65 (quintet, J = 8 Hz, 2H), 1.90−2.25 (m, 4H), 2.08 (s, 3H), 2.47 (t, J = 8 Hz, 2H), 5.20−5.55 (m, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 9.4, 14.0, 22.6, 26.9, 27.3, 27.5, 29.3, 29.5 (5 carbons), 29.6, 31.9, 127.7, 131.8, 140.5, 144.5, 165.8, 166.2; MS (*m*/*e*) 334, 289, 278, 266, 223, 205, 165, 149, 126, 97, 83, 69, 57; IR (Neat) ν_{max} 1767, 1740, 1460, 1271 cm^{-1}. Anal. Calcd for $C_{21}H_{34}O_3$: C, 75.41; H, 10.25. Found: C, 75.35; H, 10.33.

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Supporting Information Available: ^{1}H NMR and ^{13}C NMR spectra of **1**, **2**, **8**, **9**, **15**, **16**. Mass spectra of **1**, **2**, **15**, **16**. Experimental procedure and data for **4**. This material is available free of charge via the Internet at http://pubs.acs.org.

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