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Total Synthesis of Chromomoric Acid B and F Methyl Esters[1]

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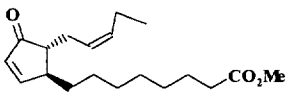
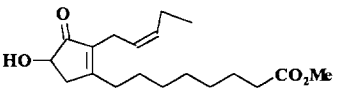
Abstract: A convenient total synthesis of chromomoric acid B methyl ester **1** and the first synthesis of chromomoric acid F methyl ester **2** have been described. A one-pot Michael addition-enolate trapping sequence afforded ketone **5** which after a few steps was converted to **1**. Retro Diels-Alder reaction of ester **7** afforded enone **9** which was then transformed to the target molecule **2** through hydrogenation and α-hydroxylation.

Chromomoric acid B **1**[2,3] and acid F[3] methyl esters **2**, two of the chromomoric acid family[4] which is the metabolite of linolenic acid, were isolated from *Chromolaena morii* and *Chromolaena chasleae*. Chromomoric acid B methyl ester **1** was also found in other species such as *Schistostepnium*,[5] *Montanoa*,[6] *Inulanthera calva*[7] and Japanese moss *Leucobryum scabrum*[8] and showed antibiotic and antihypertensive activities.[8,9] Chromomoric acid F methyl ester **2** exists only in minute amounts and, therefore, its biological activity was not determined. In continuation with our synthetic study on chromomoric acid family,[4,10] we reported herein a convenient stereospecific total synthesis of chromomoric acid B methyl ester **1** and the first synthesis of chromomoric acid F methyl esters **2**.



Chromomoric acid B
methyl ester **1**



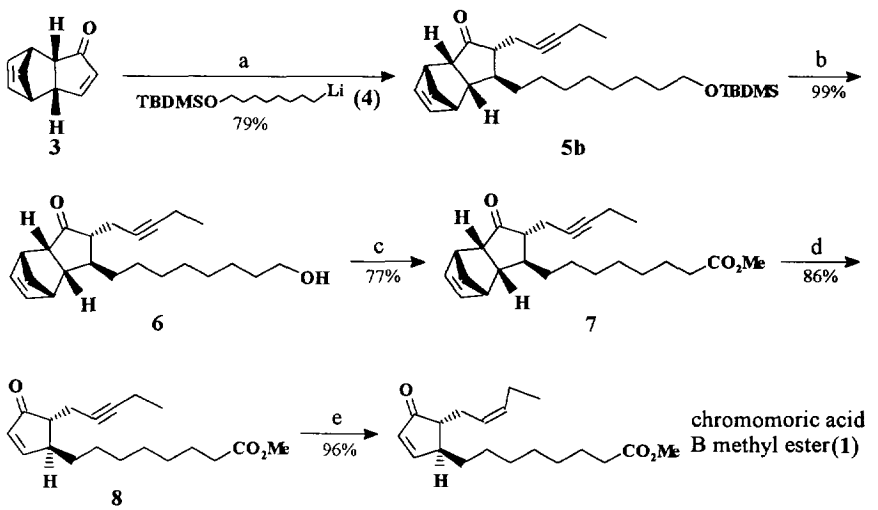
Chromomoric acid F
methyl ester **2**

Total Synthesis of Chromomoric Acid B Methyl Ester (1)

Synthesis of this naturally occurring octadecanoid **1** has been reported by Sakai[9] and Bohlmann's groups.[11] Our synthesis of chromomoric acid B methyl ester **1** is to use a rigid molecule **3** as the starting material to stereospecifically construct the skeleton of chromomoric acid B methyl ester which was then subjected to thermal retro Diels-Alder reaction to give the desired target molecule.

In situ trapping of the lithium enolate, generated by conjugate addition of lithium reagent **4** (1.1 equiv) to enone **3** [12] in the presence of a catalytic amount of CuI (9 mol%) at -78 °C for 1.5 h, with 1-iodo-2-pentyne (5 equiv) at -78 °C for 80 min and then at -78→0 °C over 5 h, provided 87% yield of *cis*-disubstituted ketone **5a**. Exposure of crude **5a** to 5% methanolic lithium hydroxide-THF (3:1) at 50~60 °C for 15 h readily

effected the epimerization at C-4,[13] affording a 91% yield of spectroscopically pure *trans* isomer **5b** (79% overall yield from enone **3**). Ketone **5b** was smoothly transformed *via* a three-step sequence including (i) hydrolytic cleavage of the *t*-butyldimethylsilyl ether [HOAc:H_2O:THF (6:3:1), 30 °C, 4.5 h, 99% yield)], (ii) oxidation of the primary alcohol to carboxylic acid (PDC, DMF, 9 h, 84% yield), and (iii) esterification (CH_2N_2, Et_2O, 25 min, 92% yield) into the key intermediate **7** in 77% overall yield from **5b**. Direct thermolysis of neat substrate **7** at 270~275 °C/200 mmHg over 3 min in a thermolysis apparatus gave rise to a 86% yield of dehydrochromomoric acid B methyl ester **8**. Selective hydrogenation of the triple bond in ester **8** in the presence of 5% wt Lindlar Pd-$CaCO_3$ catalyst at room temp (25 °C) for 15 min provided an excellent yield (96%) of chromomoric acid B methyl ester **1**, which was completely identical in all respects (^{1}H NMR, IR, MS, HRMS) with the natural product.[2]



Reagents and Conditions: **a**). (i) TBDMSO$(CH_2)_7CH_2Li$ (**4**) (1.1 equiv), CuI (9 mol%), Et_2O, -78 °C, 1.5 h; then EtC≡CCH_2I (5 equiv), HMPA (10 equiv), -78 °C, 80 min, then -78~0 °C, 5 h; (ii). 5% LiOH/CH_3OH-THF (3:1), 50~60 °C, 15 h. **b**). HOAc-H_2O-THF (6:3:1), 30 °C, 4.5 h. **c**). (i) PDC, DMF, 4Å molecular sieves, 30 °C, 9 h; (ii) CH_2N_2, Et_2O, 0 °C, 25 min. **d**). 270~275 °C, 200 mmHg, 3 min. **e**). H_2, Pd-$CaCO_3$, toluene, 25 °C, 15 min.

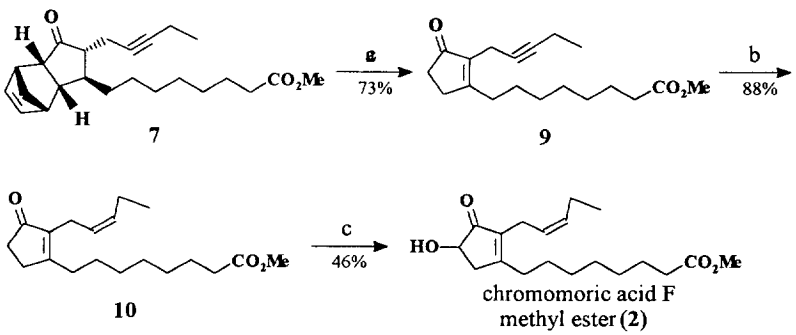
First Synthesis of Chromomoric Acid F Methyl Ester (2)

To complete the synthesis of chromomoric acid F ester, the most convenient route was to employ tricyclodecenone **7** or cyclopentenone **1** as the key intermediate. Our basic strategy included migration of the conjugated olefinic bond in **1** to the thermodynamically stable, tetrasubstituted olefinic bond required in chromomoric acid F methyl ester (**2**), followed by introduction of a hydroxy function adjacent to the carbonyl at C-12.

Thermolysis of ester **7** in refluxing Ph_2O (260 °C) gave **8** and **9** as a ca. 2:1 mixture which, upon treatment with 1.0 M solution of sodium methoxide in methanol at 50~55 °C for 2.5 h, readily gave enone **9**

(73% yield from **7**). Selective hydrogenation (H_2, Pd-$CaCO_3$, toluene, 30 °C, 10 min) of the triple bond in enone **9** furnished a 88% yield of dienone **10**, the pivotal intermediate to chromomoric acid F methyl ester **2**. Alternatively,[14] dienone **10** could be obtained from chromomoric acid B methyl ester **1** upon contact with a 1.0 M solution of sodium methoxide in methanol at 65 °C for 1.5 h in 85% yield.

The final stage of the synthesis was the hydroxylation of dienone **10** at the α position to the C-12 carbonyl function.[15] Kinetically controlled proton removal from **10** was effected with LDA (1.8 equiv, -40 °C, 15 min) and the resulting enolate were quenched with chlorotrimethylsilane (from -40 to 0 °C, 3.5 h) to give a ca. 70% yield of the crude silyldienol ether after a brief column chromatography. Selective peracid oxidation of this silyldienol ether with MCPBA (1.2 equiv) afforded, after treatment with a solution of tetrabutylammonium fluoride in THF (3.0 equiv) for 1.5 h at -20 °C, chromomoric acid F methyl ester **2** (46% overall yield from **10**), the spectra (^{1}H NMR, IR, and MS) of which were identical with those reported.[3]



Reagents and Conditions: **a**). (i) 250~260 °C, Ph_2O, 5 min; (ii) CH_3ONa, CH_3OH, 50~60 °C, 3.5 h. **b**). H_2, Pd-$CaCO_3$, toluene, 30 °C, 10 min. **c**). (i) LDA (1.8 equiv), Me_3SiCl (11 equiv), -40~0 °C, 3.5 h; (ii) MCPBA (1.2 equiv), $NaHCO_3$, CH_2Cl_2, -10 °C, 70 min; (iii) Bu_4NF (3 equiv), THF, -10 °C, 1 h.

In summary, a stereospecific total synthesis of chromomoric acid B methyl ester (**1**) has been achieved in high overall yield starting from enone **3** and the first synthesis of chromomoric acid F methyl ester (**2**) has been fulfilled with ester **7** or chromomoric acid B methyl ester (**1**) as the key precursor.

EXPERIMENTAL

General remarks. IR spectra were measured as neat films on a Shimadzu IR-440 or a Bio-Rad Digilab FTS-20 E infrared spectrometer. ^{1}H NMR spectra were determined with TMS as an internal standard in $CDCl_3$ (unless otherwise specified) at 300 MHz on a Bruker AM-300 spectrometer or at 600 MHz on a AMX-600 spectrometer; *J* values are given in Hz. Mass spectra were obtained on a HP5989A spectrometer. HRMS were recorded with a Finnigan MAT 8430 spectrometer. Flash column chromatography was conducted on silica gel H (10-40 μ) from Qingdao Haiyang Chemical Works, with petroleum ether (60~90 °C) and EtOAc as eluant in the ratio specified and all the eluants were purified by distillation.

***trans*-5-(8-*tert*-Butyldimethylsiloxyoctyl)-3-oxo-4-(2-pentynyl)tricyclo[5.2.1.$0^{2,6}$]dec-8-ene (5b).** A suspension of CuI (60 mg, 0.32 mmol) in dry Et_2O (8 mL) was treated with lithium reagent **4** (8.31 mL, 0.42 M, 3.49 mmol) at -78 °C with stirring and the resulted mixture was stirred at the same temp. for 80 min. Enone **3** (463 mg, 3.17 mmol) in dry Et_2O (4 mL) was then added dropwise at -78 °C over 25 min and the reaction was stirred at this temp. for 1.5 h when TLC showed the complete destruction of enone **3**. Freshly distilled 1-iodo-2-pentyne (3.10 g, 15.8 mmol) in dry HMPA (5.5 mL) was added through a syringe to the stirring mixture at -78 °C. After stirred at -78 °C for 80 min the reaction was allowed to warm from -78 °C to 0 °C over 5 h, quenched with saturated aqueous NH_4Cl (15 mL). The reaction mixture was extracted with EtOAc (4×20 mL) and the combined organic extracts were washed with brine (3×10 mL), dried over Na_2SO_4 and concentrated. The residual oil was subjected to flash chromatography (petroleum ether/EtOAc, 98/2), yielding **5a** (1.258 g, 87%) as a colorless oil. To the solution of *cis* disubstituted ketone **5a** in THF (5 mL) was added 5% MeOLi/MeOH (15 mL) and the reaction was heated at 50~60 °C for 15 h. The reaction mixture was concentrated *in vacuo* to remove the solvent and the residue was extracted with EtOAc (4×20 mL) after addition of water (10 mL). The combined organic extracts were washed with brine (5×10 mL), dried over anhydrous Na_2SO_4 and concentrated *in vacuo*. The residual oil was subjected to flash chromatography (petroleum ether/EtOAc, 95/5), affording the *trans* isomer **5b** (1.131 g, 91%). IR 3061.10(w, olefinic C-H), 2928.84(s), 2855.67(s), 1733.37(s, C=O), 1462.91(m), 1255.06(s), 1097.43(s), 835.41(s), 774.86(s) and 728.98(m); ^{1}H NMR δ 6.23(dd, 1H, H-8 or H-9, J=5.6 and 3.0 Hz), 6.11(dd, 1H, H-9 or H-8, J=5.6 and 2.9 Hz), 3.60(t, 2H, H-18, J=6.6 Hz), 3.18(m, 1H), 2.99(m, 1H), 2.95(m, 1H), 2.61(m, 1H), 2.42-2.26(m, 2H, H-19), 2.13(qt, 2H, H-22, J=7.4 and 2.3 Hz), 2.04 (m, 1H, H-4), 1.84(m, 1H, H-5), 1.58-1.52(m, 4H), 1.44-1.26(m, 12H), 1.31(t, 3H, CH_3, J=7.2 Hz), 0.90(s, 9H, ^{t}BuSi≡) and 0.05(s, 6H, Me_2Si<); MS m/z 457 (M^++1, 4.17%), 399(M^+-Bu^t, 13.33), 391(M^++1-C_5H_6, 30.83), 375(M^+-C_5H_6-Me, 7.65), 333(M^+-C_5H_6-Bu^t, base peak), 259(M^+-C_5H_6-$OSiMe_2Bu^t$, 4.17) and 66 (C_5H_6, 26.67). HRMS Found 456.3434, Calcd. for $C_{29}H_{48}O_2Si$ 456.3423.

***trans*-5-(8-Hydroxyoctyl)-3-oxo-4-(2-pentynyl)tricyclo[5.2.1.$0^{2,6}$]dec-8-ene (6).** To a solution of TBDMS-ether **5b** (809 mg, 1.77 mmol) was added a 6:3:1 mixture of HOAc-H_2O-THF (15 mL) at room temp (30 °C). After stirred at room temp. for 4.5 h, the reaction mixture was diluted with EtOAc (60 mL), water (15 mL) and neutralized with aqueous NaOH (5 M, 31 mL) followed by extraction with EtOAc (4×30 mL). The combined organic extracts were washed with brine (3×10 mL), dried over Na_2SO_4 and concentrated *in vacuo*. The crude colorless oil was purified by flash chromatography (petroleum ether/EtOAc, 80/20), affording alcohol **6** (605 mg, 99.5%) as an oil. IR 3440(br s, OH), 3059(w, olefinic C-H), 2972(s), 2931(s), 2854(s), 1730(s, C=O), 1456(s), 1432(m), 1337(s), 1320(m), 1058(s) and 730(s); ^{1}H NMR δ 6.23(dd, 1H, H-8 or H-9, J=5.6 and 3.0 Hz), 6.11(dd, 1H, H-9 or H-8, J=5.6 and 2.9 Hz), 3.64(t, 2H, H-18, J=6.6 Hz), 2.99-2.94(m, 2H), 2.62(ddd, 1H, H-6, J=9.4, 4.0 and 3.9 Hz), 2.44-2.27(m, 2H, H-19), 2.13(qt, 2H, H-22, J=7.7 and 2.2 Hz), 2.05(m, 1H, H-4), 1.84(m, 1H, H-5), 1.58-1.53(m, 4H), 1.40(s, 1H, OH), 1.44-1.26(m, 12H) and 1.10(t, 3H, J=6.9 Hz); MS m/z 342(M, 3.57%), 277(M^++1-C_5H_6, base peak), 259(M^++1-C_5H_6-H_2O, 3.16), 247 (M^+-C_5H_6-C_2H_5, 6.98), 189[M^+-C_5H_6-$(CH_2)_5OH$, 2.50], 175[M^+-C_5H_6-$(CH_2)_6OH$, 6.65],

161[M^+-C_5H_6-$(CH_2)_7OH$, 21.61], 147[M^+-C_5H_6-$(CH_2)_8OH$, 16.63] and 66(C_5H_6, 79.80); HRMS Found 342.2566, Calcd. for $C_{23}H_{34}O_2$ 342.2559.

***trans*-5-(7-Carbomethoxyheptyl)-3-oxo-4-(2-pentynyl)tricyclo[5.2.1.$0^{2,6}$]dec-8-ene (7).** To a solution of alcohol **6** (200 mg, 0.58 mmol) in dry DMF (20 mL) was added 4Å molecular sieves (820 mg). After 10 min of stirring, PDC (1.78 g, 4.73 mmol, 8.2 equiv.) was added and the reaction was stirred at room temp (30 °C) for 9 h, then quenched with water (30 ml) at 0 °C. The mixture was extracted with EtOAc (6× 40 mL) and the combined organic extracts were washed with brine (5×15 mL), dried over anhydrous Na_2SO_4. Removal of the solvent *in vacuo* followed by flash chromatography (petroleum ether/EtOAc/MeOH, 80/20/2) provided the corresponding acid as an oil (175 mg, 84.1%) which was directly used for the following reaction. The oil was dissolved in ether (4 mL) and treated with a solution of CH_2N_2-ether at 0 °C. 25 min later, the excess of CH_2N_2 was removed under reduced pressure and the residual oil was subjected to flash chromatography (petroleum ether/EtOAc, 90/10), giving ester **7** (115 mg, 92.2%, overall yield 77%) as an oil. IR 3060(w, olefinic C-H), 2931(s), 2855(s), 1735(br s, C=O and CO_2R), 1457(m), 1436(m), 1249(m), 1196(m), 1170(s) and 731(s); ^{1}H NMR δ 6.20(dd, 1H, H-8 or H-9, J=5.5 and 3.0 Hz), 6.08(dd, 1H, H-9 or H-8, J=5.5 and 2.8 Hz), 3.64(s, 3H, CH_3O), 3.15(br s, 1H), 2.97-2.92(m, 2H), 2.60-2.57(m, 2H),2.44-2.32(m,1H) 2.29(t, 2H, H-17, J=7.5 Hz), 2.10(qt, 2H, H-22, J=7.6 and 2.2 Hz), 2.02(m, 1H, H-4), 1.81(m, 1H, H-5), 1.61-1.53(m, 6H), 1.41-1.21(m, 8H) and 1.07(t, 3H, H-23, J=7.6 Hz); MS m/z 370(M^+, 5.00%), 305(M^++1-C_5H_6, base peak), 273(M^+-C_5H_6-OCH_3, 30.76), 275(M^+-C_5H_6-C_2H_5, 8.31), 231(M^+-C_5H_6-CH_2CO_2Me, 3.33), 217 [M^+-C_5H_6-$(CH_2)_2CO_2Me$, 2.91], 189[M^+-C_5H_6-$(CH_2)_4CO_2Me$, 2.50], 175[M^+-C_5H_6-$(CH_2)_5CO_2Me$, 6.65], 161[M^+-C_5H_6-$(CH_2)_6CO_2Me$, 18.29], 147[M^+-C_5H_6-$(CH_2)_7CO_2Me$, 14.96] and 66(C_5H_6, 60.34); HRMS Found 370.2508, Calcd. for $C_{24}H_{34}O_3$ 370.2508.

Methyl *trans*-8-[3-oxo-2-(2-pentynyl)-4-cyclopentenyl]octanoate (8). Into the tube of the thermolysis apparatus was placed substrate **7** (115 mg) and the apparatus was evacuated and filled with N_2, the pressure was then adjusted to 200 mmHg. The cold finger was cooled to -78 °C with dry ice-acetone and the tube was put into the heating bath (270~275 °C, previously set) to effect thermolysis and evaporation. After completion of the reaction (3 min) the heating bath was removed and the apparatus was allowed to attain room temp. The thermolysis product (with the unreacted substrate) on the cold finger was collected with EtOAc, concentrated *in vacuo*. The residual yellow oil was subjected to flash chromatography (petroleum ether/EtOAc, 90/10), affording substrate **7** (9 mg) and enone **8** (78 mg, 86%) as well as the thermodynamic stable isomer **9** (6.9 mg, 8%). For enone **8**: IR 2926(s), 2855(s), 1739(s, CO_2R), 1711(s, C=O), 1587(m, C=C), 1462(m), 1436(m), 1355(m), 1321(m), 1246(m), 1196(m), 1173(s) and 785(m); ^{1}H NMR δ 7.63(dd, 1H, H-10, J=5.7 and 2.4 Hz), 6.13(dd, 1H, H-11, J=5.7 and 1.9 Hz), 3.67(s, 3H, CH_3O), 2.83(m, 1H, H-9), 2.55(ddt, 1H, H-14, J=16.6, 4.7 and 2.4 Hz), 2.41(ddt, 1H, H-14', J=16.6, 7.4 and 2.4 Hz), 2.31(t, 2H, H-2, J=7.4 Hz), 2.10(qt, 2H, H-17, J=7.4 and 2.3 Hz), 2.05(ddd, 1H, H-13, J=7.4, 4.7 and 2.3 Hz), 1.65-1.53(m, 4H, H-3 and H-8), 1.44-1.26(m, 8H, H-4 through H-7) and 1.07(t, 3H, H-18, J=7.4 Hz); MS m/z 304(M^+, 13.33%), 289(M^+-CH_3, 4.17), 275(M^+-C_2H_5, 29.17), 273(M^+-OCH_3, 7.83), 231(M^+-CH_2CO_2Me, 2.92), 217[M^+-$(CH_2)_2CO_2Me$, 2.92], 203[M^+-$(CH_2)_3CO_2Me$, 5.00), 189[M^+-

$(CH_2)_4CO_2Me$, 7.08], 175[M^+-$(CH_2)_5CO_2Me$, 24.17], 161[M^+-$(CH_2)_6CO_2Me$, base peak] and 147[M^+-$(CH_2)_7CO_2Me$, 40.42]; HRMS Found 304.2044, Calcd. for $C_{19}H_{28}O_3$ 304.2038.

Methyl *trans*-8-[3-oxo-2-((Z)-2-pentenyl)-4-cyclopentenyl]octanoate (1). To a solution of enone **8** (6.9 mg) in dry toluene (1.0 mL) was added 5% wt Lindlar Pd-$CaCO_3$ catalyst (2.6 mg). The system was alternately evacuated and filled with H_2 for three times. The contents were then stirred in an atmosphere of H_2 at room temp (25 °C) for 15 min. After removal of toluene the residue was subjected to flash chromatography (petroleum ether/EtOAc, 95/5 to 90/10), yielding chromomoric acid B methyl ester (**1**) (6.7 mg, 96%) as a yellowish oil. IR 3008.0(m, olefinic C-H), 2928.0(s), 2855.4(s), 1740.0(s, CO_2R), 1709.4(s, *O*=*C*-C=C), 1588.6(m, O=C-*C*=*C*), 1463.0(m), 1436.4(m), 1352.8(m), 1245.3(m), 1196.1(m), 1172.9(s) and 724.6(m); ^{1}H NMR δ 7.59(dd, 1H, H-10, J=5.7 and 2.4 Hz), 6.12(dd, 1H, H-11, J=5.7 and 1.8 Hz), 5.45 (ddd, 1H, H-15, J=10.8, 7.2 and 5.6 Hz), 5.25(dt, 1H, H-16, J=10.8 and 7.4 Hz), 3.67(s, 3H, CH_3O), 2.57 (m, 1H, H-9), 2.47(ddd, 1H, H-14, J=14.6, 5.8 and 5.8 Hz), 2.30(t, 2H, H-2, J=7.4 Hz), 2.28(ddd, 1H, H-14', J=14.7, 7.4 and 7.4 Hz), 2.05(qd, 2H, H-17, J=7.4 and 7.4 Hz), 2.01(ddd, 1H, H-13, J=7.4, 5.7 and 2.0 Hz), 1.65-1.46(m, 4H, H-3 and H-8), 1.40-1.26(m, 8H, H-4 through H-7) and 0.96(t, 3H, H-18, J=7.5 Hz); MS m/z 307(M^++1, 13.33%), 306(M^+, 11.67), 275(M^+-OCH_3, 28.75), 238(M^++1-C_5H_9, 4d3.33), 219[M^+-$(CH_2)_2CO_2Me$, 10.83], 205[M^+-$(CH_2)_3CO_2Me$, 7.50), 191[M^+-$(CH_2)_4CO_2Me$, 6.76], 177[M^+-$(CH_2)_5CO_2Me$, 23.33], 163[M^+-$(CH_2)_6CO_2Me$, 59.75], 149[M^+-$(CH_2)_7CO_2Me$, 52.50], 95 ($C_6H_6O^+$+1, base peak) and 69[$(CH_2CH{=}CHC_2H_5)^+$, 36.25]; HRMS Found 306.2187, Calcd. for $C_{19}H_{30}O_3$ 306.2195

Methyl 8-[3-oxo-2-(2-pentynyl)-1-cyclopentenyl]octanoate (9). A solution of substrate **7** (110 mg) in diphenyl ether (5 mL) was heated at 250~260 °C for 5 min with vigorous stirring and then cooled with an ice-water bath. The yellowish solution was directly subjected to a short column flash chromatography to remove the solvent, yielding a ca. 2:1 mixture of enones **8** and **9** (82 mg, 91%). To a solution of this mixture (82 mg, 0.27 mmol) in dry MeOH (12 mL) was added a solution of CH_3ONa in CH_3OH (1 M, 0.63 mL, 0.63 mmol) and the reaction was stirred at 50~60 °C for 3.5 h. After cooled to room temp. the solvent was removed *in vacuo* below 30 °C and the residue was treated with EtOAc (40 mL) and water (10 ml). The organic layer was separated and the aqueous layer was extracted with EtOAc (3×20 mL). The combined organic extracts were washed with brine (5×10 mL), dried with anhydrous Na_2SO_4 and concentrated *in vacuo*. The residual oil was subjected to flash chromatography (petroleum ether/EtOAc, 90/10 to 80/20) to afford enone **9** (67mg, 81%; 73% yield from **7**) as a yellow oil. IR 2930(s), 2850(s), 1730(s, CO_2R), 1705 (s, C=O) and 1420(m); ^{1}H NMR δ 3.67(s, 3H, CH_3O), 3.05(br, 2H, H-14), 2.59~2.50(m, 4H, H-10 and H-11), 2.39(m, 2H, H-8), 2.31(t, 2H, H-2, J=7.4 Hz), 2.12(qt, 2H, H-17, J=7.5 and 2.3 Hz), 1.68~1.53(m, 4H, H-3 and H-7), 1.41~1.28(m, 6H, H-4 through H-6) and 1.08(t, 3H, H-18, J=7.4 Hz); MS m/z 304(M^+, 9.72%), 289(M^+-CH_3, 12.53), 275(M^+-C_2H_5, 25.36), 273(M^+-OCH_3, 7.24), 231(M^+-CH_2CO_2Me, 4.57), 217[M^+-$(CH_2)_2CO_2Me$, 7.89], 203[M^+-$(CH_2)_3CO_2Me$, 12.53), 175[M^+-$(CH_2)_5CO_2Me$, 35.41] and 147 [M^+-$(CH_2)_7CO_2Me$, base peak]; HRMS Found 304.2029, Calcd. for $C_{19}H_{28}O_3$ 304.2038.

Methyl 8-[3-oxo-2-((Z)-2-pentenyl)-1-cyclopentenyl]octanoate (10). To a solution of enone **9** (32 mg) in dry toluene (5.0 mL) was added 5% wt Lindlar Pd-$CaCO_3$ catalyst (11 mg) and the system was evacuated and filled with H_2 alternately. The content was then stirred under an atmosphere of H_2 at room temp (30 °C) for 25 min, concentrated *in vacuo* to remove toluene and subjected to flash chromatography (petroleum ether/EtOAc, 90/10), yielding dienone **10** (28 mg, 88%) as a yellow oil. IR 3020(w, olefinic C-H), 2920(s), 2860(s), 1740 (s, CO_2R), 1700(s, *O*=*C*-C=C), 1640(s, O=C-*C*=*C*) and 1435(m); ^{1}H NMR δ 5.34(dtt, 1H, H-15, J=10.7, 7.1 and 1.6 Hz), 5.21(dtt, 1H, H-16, J=10.8, 7.1 and 1.2 Hz), 3.62(s, 3H, CH_3O), 2.92(dm, 2H, H-14, J=6.9 Hz), 2.55(m, 2H, H-10), 2.49(t, 2H, H-11, J=7.6 Hz), 2.30(t, 2H, H-2, J=7.5 Hz), 2.28(m, 2H, H-8), 2.16 (qdd, 2H, H-17, J=7.5, 7.5 and 1.2 Hz), 1.62~1.55(m, 4H, H-3 and H-7), 1.39~1.29(m, 6H, H-4 through H-6) and 0.97(t, 3H, H-18, J=7.4 Hz); MS m/z 306(M^+, 21.67%), 277(M^+-Et, 5.83), 275(M^+-OMe, 19.17), 246(M^+-Et-OMe, 6.67), 219[M^+-$(CH_2)_2CO_2Me$, 41.67], 191[M^+-$(CH_2)_4CO_2Me$, 7.50], 177 [M^+-$(CH_2)_5CO_2Me$, base peak], 163[M^+-$(CH_2)_6CO_2Me$, 12.50], 149[M^+-$(CH_2)_7CO_2Me$, 99.17] and 135 [M^++1-$(CH_2)_7CO_2Me$-Me, 42.50]; HRMS Found 306.2184, Calcd. for $C_{19}H_{30}O_3$ 306.2195.

Isomerization of chromomoric acid B methyl ester (1) to enone 10. A solution of chromomoric acid B methyl ester (**1**) (48 mg, 0.16 mmol) in dry MeOH (10 mL) was treated with a solution of CH_3ONa in CH_3OH (1 M, 0.48 ml, 0.48 mmol) and the reaction was stirred at 65 °C for 1.5 h. After cooling to room temp, the solution was diluted with EtOAc (50 mL) and brine (10 ml). The organic layer was separated and the aqueous layer was extracted with EtOAc (3×30 mL). The combined organic extracts were washed with brine (5×10 mL), dried with anhydrous Na_2SO_4 and concentrated *in vacuo*. The residual oil was subjected to flash chromatography (petroleum/EtOAc, 90/10 to 85/15) to afford **10** (41 mg, 85%) as a yellow oil.

Methyl 8-[4-hydroxy-3-oxo-2-((Z)-2-pentenyl)-1-cyclopentenyl]octanoate (2). A solution of LDA in THF was prepared from *i*-Pr_2NH (120 μL, ~88 mg, 0.88 mmol) in THF (10 mL) and BuLi (1.15 M in *n*-hexane, 0.78 mL, 0.90 mmol) at -10 °C under N_2 atmosphere. To the solution of enone **10** (15 mg, 0.049 mmol) in dry THF (4 mL) at -40 °C was added dropwise the LDA prepared above (1.0 mL, ~0.088 mmol) with a syringe over 5 min. After stirred for 15 min, the reaction was quenched with Me_3SiCl (65 μL, 56 mg, 0.52 mmol, 11 equiv.) at -40 °C and was then allowed to warm to 0 °C over 3.5 h. The reaction mixture was treated with saturated aqueous NaCl (2 mL) and extracted with Et_2O (4×10 mL). The organic extracts were washed with brine (5×4 mL) and dried (Na_2SO_4). Removal of the solvent followed by a short column chromatography afforded the crude silyldienol ether (12 mg, ~70%) which was directly used in the next reaction. To the solution of the above silyldienol ether (~0.032 mmol) in methylene chloride (4 mL) containing sodium bicarbonate (5.1 mg) at -10 °C, was added *m*-chloroperbenzoic acid (7.2 mg, 0.042 mmol). After 70 min, the reaction mixture was treated at -10 °C for 1 h with a solution of tetrabutylammonium fluoride in THF (1.0 M, 96 μL, 3 equiv.). The reaction was then quenched by the addition of a saturated solution of sodium sulfite (80 μL) and diluted with water (10 mL), extracted with methylene chloride (4×20 mL). The combined organic extracts were dried over anhydrous Na_2SO_4 and concentrated *in vacuo*. The residue was subjected to flash chromatography (petroleum ether/EtOAc, 90/10), affording chromomoric acid

F methyl ester **2** (7.2 mg, 46%). IR 3450(br s, OH), 2930(s), 2850(s), 1740(s, CO_2R), 1705(s, *O*=*C*-C=C), 1635(s, O=C-*C*=*C*) and 1425(m); ^{1}H NMR δ 5.12(dtt, 1H, H-15, J=10.4, 6.8 and 1.8 Hz), 5.35(dtt, 1H, H-16, J=10.4, 7.5 and 2.1 Hz), 4.15(dd, 1H, H-11, J=5.5 and 3.7 Hz), 3.65(s, 3H, CH_3O), 2.94~2.85(m, 2H, H-14), 2.80(dd, 1H, H-10, J=17.1 and 5.4 Hz), 2.26(dd, 1H, H-10', J=127.2 and 3.7 Hz), 2.41(m, 1H, H-8), 2.33(m, 1H, H-8'), 2.30(t, 2H, H-2, J=7.2 Hz), 2.15(qdd, 2H, H-17, J=7.5, 7.5 and 1.7 Hz), 1.61~1.45(m, 4H, H-3 and H-7), 1.38~1.15(m, 7H, H-4 through H-6, OH) and 0.97(t, 3H, H-18, J=7.2 Hz); MS m/z 322(M^+, 6.78%), 304(M^+-H_2O, 37.68), 291(M^+-OMe, 25.16), 275(M^+-H_2O-Et, 43.24) and 165(M^+-$C_7H_{14}CO_2Me$, base peak).

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