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Total Synthesis and Structural Revision of Chromomoric Acid C-I and C-II Methyl Esters[1]

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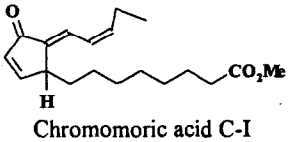
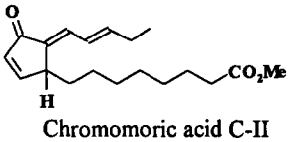
Abstract: Stereospecific total synthesis of chromomoric acid C-I and C-II methyl esters and delicate elucidation of their structures have been reported. A stereospecific five-step synthesis, starting from enone **5**, with one-pot three-component coupling and retro Diels-Alder reaction as the key reactions provided a target molecule which was proved to be chromomoric acid C-I methyl ester (**1**), but its physical data were identical with that of the natural product originally assigned to be chromomoric acid C-IV methyl ester (**4**). Structural elucidation with a lanthanide shift reagent showed the original assignment should be revised to **1**. Total synthesis and structural confirmation of chromomoric acid C-II methyl ester (**2**) was thereafter fulfilled.

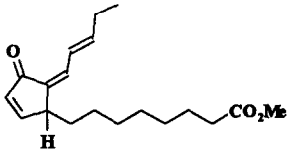
Chromomoric acid C I-IV methyl esters (**1-4**) are a group of optically active natural products isolated from *Chromolaena morii* and *Chromolaena chasleae* by Bohlmann *et al.*[2,3] This family of octadecanoids are metabolites of linolenic acid and bear structural resemblance to prostaglandins[4-6] which are biosynthetically derived from arachidonic acid and exhibit diverse pharmacological properties.[7] This distinct feature greatly arouses our interests in the possible biological activities of this group of new substances. However, they exist only in minute amounts and their stereochemistry has not yet been determined. Therefore, a total synthesis should be of high interest and significance. We detailed here the stereospecific total synthesis and the delicate structure elucidation of chromomoric acid C-I and C-II methyl esters (**1** and **2** respectively).[8]



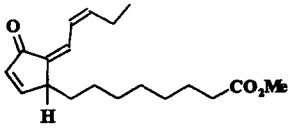
Chromomoric acid C-I
methyl ester (**1**)



Chromomoric acid C-II
methyl ester (**2**)



Chromomoric acid C-III
methyl ester (**3**)

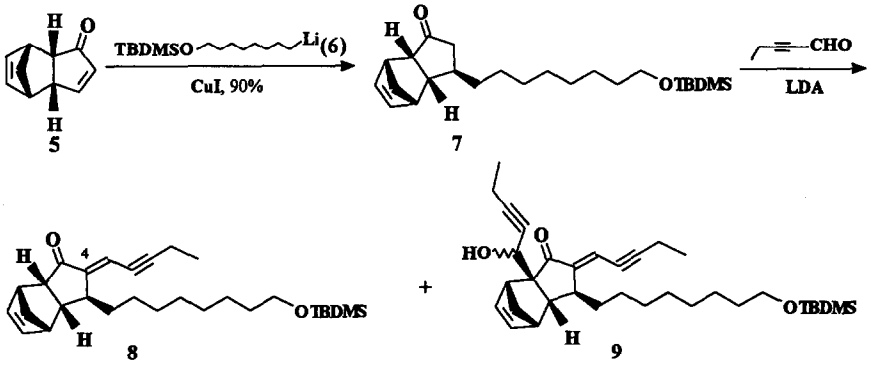


Chromomoric acid C-IV
methyl ester (**4**)

Up to now, only a synthesis of chromomoric acid C-II was reported with 4-trimethylsiloxycyclopentenone as the starting material, and the overall yield and stereoselectivity were very poor[9] probably due to the flexibility of the cyclopentenone and the lability of the crossed conjugated trienone substructure in **2**. In continuation of the study on synthesis of chromomoric acid family,[8,10] our approach to chromomoric acid C was to use rigid dienone **5** as the starting material for facile but highly stereoselective attachment of two side chains which possess the required functional groups, and then after some functional group transformation, to have the resulting intermediate subjected to thermal cycloreversion to release the labile exo-methylene cyclopentenone moiety of chromomoric acid C.

Total Synthesis of Chromomoric Acid C-I Methyl Ester (1)

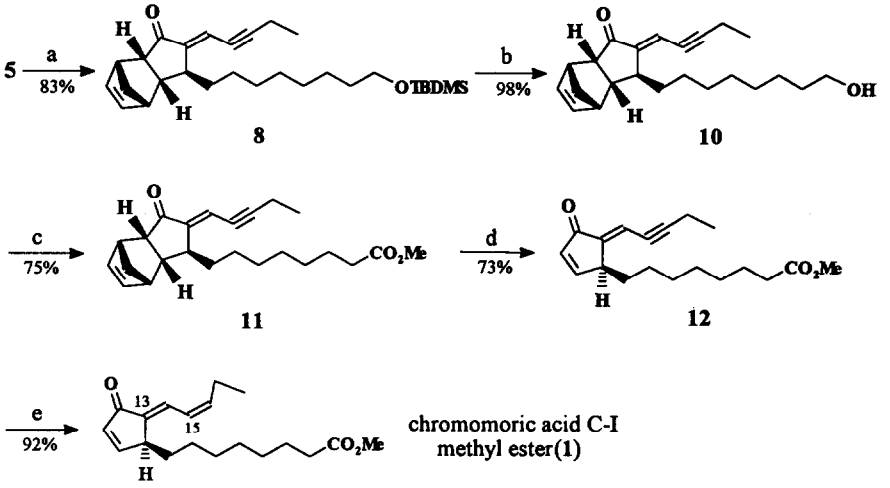
Our first challenge was to prepare well equipped skeleton **8**, the expected key intermediate to a chromomoric acid C methyl ester. Conjugate addition of the organocuprate reagent, derived from copper(I) iodide and the corresponding lithium reagent **6**, to enone **5**[11] at -40 °C smoothly afforded a high yield (90%) of adduct **7**. Stepwise attachment of the five-carbon upper side chain was initially made through aldol condensation of the lithium enolate generated from ketone **7** and LDA (1.1~2.0 equiv.) with 2-pentynal, giving rise to a mixture of desired enone **8** (58%) and unexpected double-aldol product **9** (11%) in ca. 5:1 ratio in addition to the recovered ketone **7** (9%). Preparation of enone **8** without the formation of double-aldol product **9** was achieved through one-pot Michael addition-aldol condensation sequence. Conjugate addition of enone **5** with the cuprate (1.2 equiv.) at -78 °C for 2 h followed by *in situ* trapping of the resulting enolate with 2-pentynal (3.5 equiv.) at -78 °C for 1 h and then warming the reaction mixture to 0 °C over 4 h, afforded a satisfactory yield (83%) of desired **8**; not detectable amount of **9** or olefinic isomer at C-4 was found.



5 **7** **8** **9**

With enone **8** in hand, the next steps involved the transformation of the silylated octanol side chain to the corresponding methyl carboxylate. Deprotection of silyl ester **8** with a 6:3:1 mixture of HOAc-H_2O-THF gave nearly quantitative yield of alcohol **10**. For oxidation of the hydroxy group in alcohol **10** to the

corresponding acid, PDC in DMF was chosen because of its mild and nearly neutral conditions.[12] Treatment of the resulting carboxylic acid with an excess of CH_2N_2 afforded ester **11**; the overall yield was 75% from alcohol **10**. The retro Diels-Alder reaction of dienone **11** proceeded at 254 ^{0}C and 200 mmHg under N_2 atmosphere to provide the key intermediate **12** in 73% yield, without any by-products resulted from thermal olefin migration. A carefully controlled hydrogenation of **12** in the presence of 5% wt Lindlar Pd-$CaCO_3$ catalyst in toluene at room temp. for 7 min provided in excellent yield (92%) the target molecule which was believed to be chromomoric acid C-I methyl ester (**1**).

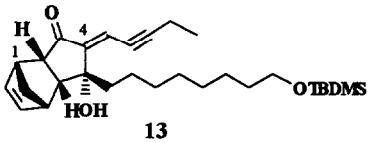


Reagents and Conditions: **a**). TBDMSO$(CH_2)_7CH_2LI$ (**6**) (2.4 equiv.), CuI (1.2 equiv.), Et_2O, -78 ^{0}C, 2h; then EtC≡CCHO (3.5 equiv.), -78 ^{0}C, 1h, -78~0 ^{0}C, 4h. **b**). HOAc-H_2O-THF (6:3:1), 0 ^{0}C then room temp., 3h. **c**). 1. PDC, DMF, 4Å molecular sieves, room temp., 10.5 h; 2. CH_2N_2, Et_2O, 0 ^{0}C, 40 min. **d**). 254 ^{0}C, 200 mmHg, 2~3 min. **e**). H_2, Pd-$CaCO_3$, toluene, room temp., 7 min.

Structure Elucidation of the Synthetic Molecule and Revision of Original Assignment

On the basis of our previous work,[10] we believed that our synthetic molecule was chromomoric acid C-I methyl ester (**1**) having a 13*E* configuration.[13] However, we were much surprised to find that the ^{1}H NMR spectrum (600 MHz) and all the other spectroscopic data (IR, MS, HRMS) of our synthetic molecule were completely identical with those of a natural product which had been originally postulated[2] to be chromomoric acid C-IV methyl ester (**4**). It was obvious that our synthetic compound and the natural product must be the same molecule and, therefore, some mistakes in its structural elucidation, either from Bohlmann and his co-workers or our group, has been caused. Consequently, the stereochemistry of the olefinic bond at C-13 in this natural product must be re-elucidated.

We have previously concluded that the exo-cyclic olefinic bond in aldol product **13** and synthetic target molecule **14** have the *E* configuration by analysis of relevant ^{1}H NMR data.[10] In addition, definite strong confirmation of the *E* configuration of the olefinic bond at C-4 in enone **15**, prepared by the same methodology, was derived from a series of n.O.e. experiments.[15] We therefore have some reasons to suggest that our synthetic molecule **1** (i.e. the natural product) was chromomoric acid C-I methyl ester with a 13*E* configuration and the originally postulated structure may be erroneously assigned by Bohlmann.[2] However, a direct and strong evidence for the stereochemistry of this olefinic bond at C-13 is needed.



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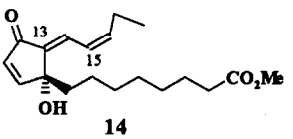

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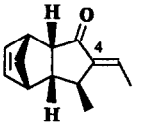
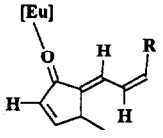
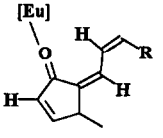


15

This stereochemical problem was once expected to be solved through n.O.e. difference but met with no success. On irradiation of the signal of H-14 (or H-15), n.O.e. could not be observed between H-9 and H-14 (or H-15) due to its conformationally mobile structure. However, it was successfully achieved with lanthanide shift reagent Eu(fod)$_3$.[16] An inspection of the molecular model revealed that in spite of the conformationally mobile structure of **1** or **4**, the conjugated moiety which includes all the sp^2 hybridized carbons and the atoms attached to these carbons is most probably in a plane and, the distances of various olefinic hydrogens, particularly H-14 and H-15, to the carbonyl oxygen in these two isomers (**1** and **4**) were different. Therefore, when Eu(fod)$_3$ is added to coordinate with the carbonyl group, these olefinic protons should behave in a considerably different manner.[17] In the 13E isomer **1**, a larger downfield shift of the signal of H-14 than that of H-15 should be observed because the distance between the coordinated Eu and H-14 is much closer than that between Eu and H-15; in contrast, with the 13Z isomer **4**, a larger downfield shift of the signal of H-15 than that of H-14 should result.



a 13**E** configuration



a 13**Z** configuration

In experimental, a series of ^{1}H NMR spectra with variable ratios of synthetic molecule **1** to Eu(fod)$_3$ were recorded and the the results were summarized in Table 1.

Table 1. ^{1}H NMR Data Comparison of Our Synthetic Molecule in a Variety of **3**:Eu(fod)$_3$ Ratios*

Entry	3:Eu(fod)$_3$	Chemical Shift (δ, ppm)				
		H-10	H-11	**H-14**	**H-15**	H-16
1	1 : 0	7.54	6.37	7.26	6.22	6.00
2	1 : 0.14	7.61	6.55	7.55	6.30	6.03
		-0.07	-0.18	-0.29	-0.08	-0.03
3	1 : 0.28	7.78	6.98	8.18	6.50	6.11
		-0.24	-0.61	-0.92	-0.28	-0.11

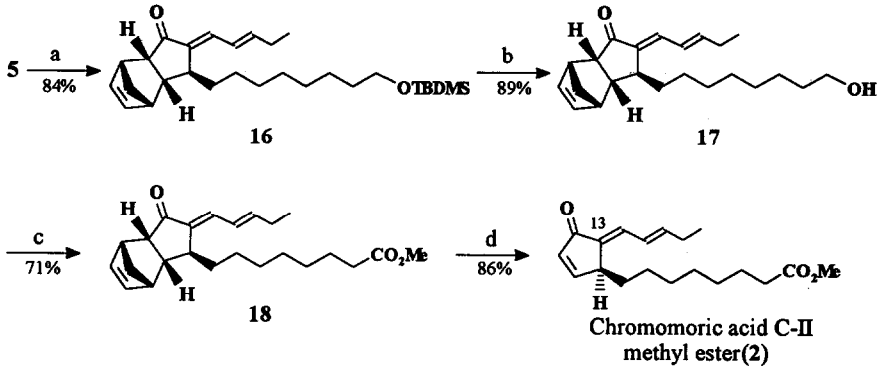
*a). **3**:Eu(fod)$_3$ was in mole ratios; b). the spectra was measured in $CDCl_3$ at 600 MHz.

It was noted from Table 1 that, upon addition of 0.14 mole equivalent of shift reagent Eu(fod)$_3$, the signals of all the olefinic protons shifted downfield in a various magnitude. They shifted in the order of H-14 (-0.29 ppm), H-11(-0.18 ppm), H-15(-0.08 ppm), H-10(-0.07 ppm) and finally, H-16(-0.03 ppm), indicating a larger shift of H-14 and H-11 than that of H-15. The spectrum with 0.28 mole equivalent of Eu(fod)$_3$ revealed the same order (see Table 1). On this basis, it was concluded that H-14 was at a distance much closer to the C-12 carbonyl than H-15, just as predicted from the 13*E* isomer and, our synthetic molecule (i.e., the natural one isolated by Bohlmann *et al*[2]) had the 13*E* configuration. The olefinic bond at C-15 in our synthetic molecule was generated through Pd-$CaCO_3$ catalyzed hydrogenation of a triple bond and should be in *Z* configuration, which was confirmed by the coupling constant of $J_{15,16}$=10.8 Hz. As a consequence, our synthetic molecule (i.e. the natural product[2]) was chromomoric acid C-I methyl ester (**1**) and the *originally postulated* structure, chromomoric acid C-IV methyl ester (**4**), should be revised to **1**.

Total Synthesis of Chromomoric Acid C-II Methyl Ester (2)

Our synthesis of chromomoric C-II methyl ester (**2**) followed the same strategy in the synthesis of chromomoric acid C-I methyl ester (**1**).

In situ trapping of the enolate, generated from conjugation addition of lithium reagent **6** (1.3 equiv.) in the presence of catalytic amount of CuI (9.8 mol%) to enone **5**, with freshly distilled *trans*-2-pentenal (4.9 equiv., -78 ^{0}C for 2 h, then warmed gradually to 0 ^{0}C over 5 h) gave rise to a 84% yield of the desired trienone **16**. Treatment of silyl ether **16** with a mixture of HOAc-H_2O-THF (6:3:1) at 0 ^{0}C for 1.5 h provided alcohol **17** in 89% yield. PDC oxidation of **17** followed by esterification with CH_2N_2 gave the precursor **18** in 71% overall yield from alcohol **17**. The final step, retro Diels-Alder reaction of ester **18**, was carried out by heating the neat sample in the tube and collecting the thermolysis product with a cold finger (cooled with liquid nitrogen) at 262~265 ^{0}C/220 mmHg for 2 min, affording a 86% yield of chromomoric acid C-II methyl ester (**2**). Its spectra (^{1}H NMR, IR, MS, HRMS) were in agreement with that reported by Bohlmann *et al.*[2]



Reagents and Conditions: **a**). TBDMSO$(CH_2)_7CH_2LI$ (**6**) (1.3 equiv.), cat. CuI (9.8 mol%), Et_2O, -78 °C, 1 h; then *trans*-EtCH=CHCHO (4.9 equiv.), -78 °C, 2 h, -78~0 °C, 5 h. **b**). HOAc-H_2O-THF (6:3:1), 0 °C, 1.5 h. **c**). 1. PDC, DMF, 4Å molecular sieves, room temp., 3 h; 2. CH_2N_2, Et_2O, 0 °C, 5 min. **d**). 262~265 °C, 220 mmHg, 2 min.

Stereochemical confirmation of the olefinic bond at C-13 in **2** was made with shift reagent $Eu(fod)_3$. A solution of chromomoric C-II methyl ester (**2**) (1.6 mg, 5.3×10^{-3} mmole) in C_6D_6 (0.5 mL) was treated with $Eu(fod)_3$ (0.6 mg, 5.8×10^{-4} mmole, **2**:$Eu(fod)_3$=1:0.11) and the resulting 600 MHz ^1H NMR spectrum showed unambiguous downfield shift of the olefinic protons in the order of H-14(-0.22 ppm), H-11(-0.18 ppm), H-10 (-0.07 ppm), H-15(-0.06 ppm) and H-16(-0.04 ppm), indicating that H-14 was at the distance closer to the C-12 carbonyl than H-15 and consequently, the olefinic bond at C-13 in **2** was in the *E* configuration

In summary, stereospecific total synthesis of chromomoric acid C-I and C-II methyl esters has been achieved in excellent overall yield starting from enone **5**. Moveover, with the aid of shift reagent $Eu(fod)_3$, the total synthesis resulted in the revision of originally postulated structure for natural product chromomoric acid C-I methyl ester.

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. ^1H NMR spectra were determined with TMS as an internal standard in $CDCl_3$ (unless otherwise specified) at 200 MHz on a Varian XL-200 spectrometer, 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 Finnigan 4021 or HP5989A spectrometers using the electron impact technique. HRMS were recorded with Finnigan MAT 8430 spectrometer. UV spectra was recorded on HP 8451 Diode array spectrophotometer. All reactions were monitored by thin-layer chromatography (TLC) and TLC-spots were visualized with an UV lamp, or after spraying with a 5% ethanolic phosphomolybdic acid solution followed by heating until the spots clearly visible. Flash column chromatography was conducted on silica gel H (10-40 μ) from Qingdao Haiyang Chemical Works, with petroleum ether (60~90 °C), EtOAc as eluant in the ratios

specified and all solvents used as eluant were purified by distillation. Dry ether, THF were distilled over sodium-benzophenone ketyl under N_2 atmosphere. Dry DMF were distilled under reduced pressure over CaH_2 and stored over 4Å molecular sieve. i-Pr_2NH was refluxed over NaH and distilled under N_2 atmosphere.

(8Z)-5-(8-*tert*-Butyldimethylsiloxyoctyl)-3-oxo-[5.2.1.0.^{2,6}]dec-8-ene (7). To a 250-mL three-necked flask charged with dry Et_2O(80 mL) and lithium (1.30 g, 188 mmol), was added about 2 mL of a solution of 8-*tert*-butyldimethylsiloxyoctyl bromide (14.2 g, 44.0 mmol) in dry Et_2O (30 mL) with stirring at room temp. 10 min later the solution was cooled to -5 ^{0}C and the rest of the bromide was added dropwise at ~-5 ^{0}C over 1.5 h. The gray mixture was stirred at this temp. for additional 2 h, affording a 0.38 M solution of Lithium reagent **6**. To a well-stirred suspension of CuI (2.09 g, 11.0 mmol) and dry Et_2O (20 mL) was added the lithium reagent **6** (58 mL, 22 mmol) at -60 ^{0}C and the mixture was stirred at -40~-30 ^{0}C for 3 h, affording a dark mixture. To this cuprate (~1.3 equiv.) at -40 ^{0}C, was added a solution of enone **5** (1.24 g, 8.46 mmol) in Et_2O (12 mL) over 1.5 h. The reaction was stirred at this temp for additional 4 h, then quenched with saturated aqueous NH_4Cl (20 mL), extracted with Et_2O (3×40 mL) and dried over anhydrous Na_2SO_4. Removal of the solvent followed by flash chromatography with petroleum ether and EtOAc (95/5) as the eluant gave **7** (2.98 g, 90%) as an oil. IR 3050 (w, olefinic C-H), 2920 (s), 2850 (s), 1735 (s, C=O), 1460 (m) and 1100 (s); ^{1}H NMR δ 6.14 (m, 2H), 3.60 (t, 2H, J=7 Hz), 3.17 (m, 1H), 3.03 (m, 1H), 2.94 (m, 1H), 2.63 (m, 1H), 2.29-2.16 (m, 1H), 2.01-1.87 (m, 1H), 1.74-1.20 (m, 17H), 0.89 (s, 9H) and 0.05 (s, 6H); MS m/z 391 (M^++1, 2.85%), 325 (M^+-C_5H_6+1, 50.35), 268 (M^+-C_5H_6-Bu^t+1, base peak) and 267 (M^+-C_5H_6-Bu^t, 82.80); HRMS Found 390.2945, Calcd. for $C_{24}H_{42}O_2Si$ 390.2954

Aldol condensation of ketone 7 with 2-pentynal. To a solution of dry THF (15 mL) and *i*-Pr_2NH (0.92 mL, 662 mg, 6.55 mmol) cooled to -10 ^{0}C, was added a solution of BuLi (1.60 M in Et_2O, 4.1 mL, 6.56 mmol) and the stirring was continued at -10~0 ^{0}C for additional 1.5 h. The resulted LDA solution was cooled to -78 ^{0}C and ketone **7** (1.501 g, 3.85 mmol) in dry THF (10 mL) was added slowly over 30 min. After the addition, the solution was stirred at this temp. for additional 2.5 h. Newly distilled 2-pentynal (1.6 mL, 1.429 g, 17.4 mmol, 4.5 equiv.) was added dropwise at -78 ^{0}C, stirring was kept at this temp. for 2.5 h. Then the reaction was allowed to warm slowly to 0 ^{0}C over 4 h. The reaction mixture was quenched with saturated aqueous NH_4Cl (20 mL) at 0 ^{0}C and extracted with EtOAc (3×30 mL). The combined organic extracts were washed with aqueous NH_4Cl (2×10 mL), brine (3×10 mL) and dried over anhydrous Na_2SO_4. Removal of the solvent followed by flash chromatography (petroleum ether/EtOAc, 90/10) afforded **7** (135 mg, 9%), enone **8** (922 mg, 58%) and double-aldol product **9** (206 mg, 11%) as yellow oils. For **9**: IR 3400 (br s, OH), 3050(w, olefinic C-H), 2250(m, C≡C), 1705 (s, C=O), 1600(s, C=C-C=O) and 1140 (s); ^{1}H NMR δ 6.25 (q, 1H, J=2.4 Hz), 6.16 (m, 1H), 5.98 (m, 1H), 4.36 (m, 1H), 3.62 (t, 2H, J=6.4 Hz), 3.40 (m, 1H), 2.99 (m, 1H), 2.44 (qd, 2H, J=7.5 and 2.4 Hz), 2.28-2.40 (m, 2H), 2.15 (qd, 2H, J=7.6 and 1.6 Hz), 1.74-1.28 (m, 17H), 1.21 (t, 3H, J=7.5 Hz), 1.08 (t, 3H, J=7.6 Hz), 0.90 (s, 9H, t-BuSi≡), 0.05 (s, 6H, Me_2Si<); MS m/z 536 (M^+, 7.43%), 483 (M^+-C_4H_5, 18.17), 470 (M^+-C_5H_6, base peak), 455 (M^+-C_5H_6-Me, 29.87), 417 (M^+-C_5H_6-C_4H_5, 57.42), 413 (M^+-C_5H_6-Bu^t, 34).

(4E,8Z)-5-(8-*tert*-Butyldimethylsiloxyoctyl)-3-oxo-4-(2-pentynylidene)tricyclo[5.2.1.0.^{2,6}]dec-8-ene (8). To a well-stirred suspension of CuI (535 mg, 2.81 mmol) in dry Et_2O (10 mL) under N_2 atmosphere, was added lithium reagent **6** (14.8 mL, 0.38 M, 5.62 mmol) at -68~ -70 ^{0}C and the stirring was continued at the same temp. for additional 1.5 h. Enone **5** (342 mg, 2.34 mmol) in dry Et_2O (5 mL) was added dropwise at -78 ^{0}C over 30 min and the mixture was stirred at this temp. for 1.5 h when TLC showed the complete destruction of enone **5**. Freshly distilled 2-pentynal (672 mg, 8.20 mmol) was added through a syringe at -78 ^{0}C. After stirring at this temp. for 1 h, the reaction was allowed to warm from -78 ^{0}C to 0 ^{0}C over 4 h, quenched with saturated aqueous NH_4Cl (15 mL) and the mixture was extracted with EtOAc (3×25 mL). The combined organic extracts were washed with brine (3×10 mL), dried over Na_2SO_4 and concentrated *in vacuo*. The residual brown oil was subjected to flash chromatography with petroleum ether and EtOAc as the eluant (98/2), yielding **8** (882 mg, 83%) as a yellow oil. IR 3060(w, olefinic C-H), 2200(m, C≡C), 1710(s, C=O), 1605(s, C=C-C=O) and 1100 (s); ^{1}H NMR δ 6.15 (q, 1H, H-19, J=2.4 Hz), 6.04 (m, 1H, H-8 or H-9), 5.96 (m, 1H, H-9 or H-8), 3.60 (t, 2H, H-18, J=7.0 Hz), 3.24 (m, 1H, H-5), 3.04 (m, 2H), 2.48-2.26 (m, 2H), 2.40 (qd, 2H, H-22, J=7.5 and 2.4 Hz), 1.46 (m, 2H), 1.42-1.24 (m, 14H), 1.20 (t, 3H, H-23, J=7.5 Hz), 0.89(s, 9H, t-BuSi≡), 0.07 (s, 6H, Me_2Si<); MS m/z 455 (M^++1, 2.74%), 389 (M^+-C_5H_6+1, 37.11), 373 (M^+-C_5H_6-Me, 18.40), 332 (M^+-C_5H_6-Bu^t+1, base peak), 331 (M^+-C_5H_6-Bu^t, 69.64); HRMS Found 454.3276, Calcd. for $C_{29}H_{46}O_2Si$ 454.3267

(4E,8Z)-5-(8-Hydroxyoctyl)-3-oxo-4-(2-pentynylidene)tricyclo[5.2.1.0.^{2,6}]dec-8-ene (10). A 6:3:1 mixture of HOAc-H_2O-THF (5 mL) was added dropwise to TBDMS-ether **8** (115 mg, 0.253 mmol) at 0 ^{0}C. The ice-bath was then removed and the reaction was stirred at room temp. for 3 h. The reaction mixture was diluted with EtOAc (50 mL), water (10 mL) and neutralized with saturated $NaHCO_3$ solution (48 mL), then extracted with EtOAc (3×30 mL). The combined organic extracts were washed with brine (4×15 mL), dried over Na_2SO_4 and concentrated *in vacuo*. The residual yellow oil was subjected to flash chromatography with petroleum ether and EtOAc as the eluant (70/30), affording alcohol **10** (84 mg, 98%) as a yellow oil. IR 3400 (s, OH), 3060 (w), 2200 (m, C≡C), 1705 (s, C=O), 1605 (s, C=C-C=O); ^{1}H NMR δ 6.15 (q, 1H, H-19, J=2.3 Hz), 6.04 (m, 1H, H-8 or H-9), 5.96 (m, 1H, H-9 or H-8), 3.64 (t, 2H, H-18, H=7.0 Hz), 3.25 (m, 1H, H-5), 3.08-2.95 (m, 2H), 2.62-2.50 (m, 2H), 2.42 (qd, 2H, H-22, J=7.0 and 2.3 Hz), 1.95 (br, 1H, OH), 1.52 (m, 2H), 1.42-1.25 (m, 14H), 1.20 (t, 3H, H-23, J=7.0 Hz); MS m/z 340 (M^+, 25.21%), 325 (M^+-CH_3, 5.97), 275 (M^+-C_5H_6+1, base peak), 274 (M^+-C_5H_6, 47.02), 257 (M^+-C_5H_6-H_2O+1, 20.70), 173 (M^+-C_5H_6-$C_6H_{12}OH$, 11.63), 159(M^+-C_5H_6-$C_7H_{14}OH$, 51.99), 145 (M^+-C_5H_6-$C_8H_{16}OH$, 20.24); HRMS Found 340.2417, Calcd. for $C_{23}H_{32}O_2$ 340.2402

(4E,8Z)-5-(7-Carbomethoxyheptyl)-3-oxo-4-(2-pentynylidene)tricyclo[5.2.1.0.^{2,6}]dec-8-ene(11). To a solution of alcohol **10** (50 mg, 0.15 mmol) in dry DMF (4 mL) was added 4Å molecular sieves (331 mg) with stirring. 10 min later, PDC (468 mg, 1.24 mmol, 8.3 equiv.) was added and the contents were stirred at room temp. for 10.5 h. After water (15 ml) and EtOAc (80 mL) were added to the stirring mixture, the organic layer was separated and the aqueous layer was extracted with EtOAc (5×30 mL). The combined organic extracts were washed with brine (5×10 mL), dried over anhydrous Na_2SO_4. Removal of the solvent *in vacuo* followed by flash chromatography (petroleum ether/EtOAc, 95/5 then petroleum ether/EtOAc/MeOH, 70/30/2) provided a yellow oil (41 mg, 78.8%). The oil was dissolved in ether (5 mL) and treated with a

solution of CH_2N_2-ether at 0 °C. The reaction was stirred at this temp. for 40 min and the excess of CH_2N_2 was removed under reduced pressure. The residual yellow oil was subjected to flash chromatography (petroleum ether/EtOAc, 90/10), giving ester **11** (40 mg, 95.2%, 75% overall yield) as a yellow oil. IR 3050 (w), 2200 (m, C≡C), 1740 (s, CO_2R), 1710(s) and 1605(s, C=C-C=O); ^{1}H NMR δ 6.15 (q, 1H, H-19, J=2.4 Hz), 6.03 (m, 1H, H-8 or H-9), 5.98(m, 1H, H-9 or H-8), 3.68 (s, 3H, CH_3O), 3.25 (m, 1H, H-5), 3.10-2.94 (m, 2H), 2.64-2.50 (m, 2H), 2.42 (qd, 2H, H-22, J=7.5 and 2.4 Hz), 2.32 (t, 2H, H-2, J=7.5 Hz), 1.84-1.26 (m, 14H), 1.19 (t, 3H, H-23, J=7.5 Hz); MS m/z 368 (M^+, 42.70%), 353 (M^+-CH_3, 6.67), 303 (M^+-C_5H_6+1, base peak), 287 (M^+-C_5H_6-Me, 9.98), 271 (M^+-C_5H_6-MeO, 71.59), 243 (M^+-C_5H_6-CO_2Me, 10.44), 159 (M^+-C_5H_6-$C_6H_{12}CO_2Me$, 45.71), 145 (M^+-C_5H_6-$C_7H_{14}CO_2Me$, 11.73); HRMS Found 368.2318, Calcd. for $C_{24}H_{32}O_3$ 368.2351; HPLC [Column, μBONDASPHERE 5μ CN-100A, 3.9×150 mm; Solvent, MeOH/H_2O (8:2); Flow rate, 0.70 mL/min; Pressure, 2500.0; Detected at 254 nm] RT 3.11 min (single peak), 99.49%; UV λ_{max} (EtOH) 298 nm, $\varepsilon_{max}1.85\times10^4$.

Methyl 8-[(2E)-3-oxo-2-(2-pentynylidene)-4-cyclopentenyl]octanoate (12). Into the tube of a thermolysis apparatus was placed substrate **11** (29.8 mg) and the apparatus was evacuated and filled with N_2, the pressure was adjusted to 200 mmHg. The cold finger was cooled to -78 °C with dry ice-acetone. The tube was then put into the heating bath (254 °C, previously set) and heated in order to effect thermolysis and evaporation. After completion of the reaction (2~3 min) the heating bath was removed and the apparatus was allowed to attain room temp. The thermolysis product (with a little of unreacted substrate) on the cold finger was collected with EtOAc, concentrated *in vacuo*. The residual yellow oil was subjected to flash chromatography (PE/EA, 90/10 to 80/20), affording substrate **11** (3.5 mg) and compound **12** (15.7 mg, 72.7%). IR 2200 (m, C≡C), 1740 (s, CO_2R), 1695 (s) and 1625 (s, C=C-C=O); ^{1}H NMR δ 600 MHz, 7.58 (ddd, 1H, H-10, J=6.0, 2.4 and 0.7 Hz), 6.46 (m, 1H, H-14), 6.34(dd, 1H, H-11 J=6.0 and 1.9 Hz), 3.67 (s, 3H, CH_3O), 3.55 (m, 1H, H-9), 2.45 (qd, 2H, H-17, J=7.5 and 2.4 Hz), 2.30 (t, 2H, H-2, J=7.5 Hz), 1.61 (m, 2H), 1.30 (m, 10H), 1.22 (t, 3H, H-18, J=7.5 Hz); MS m/z 303 (M^++1, base peak), 302 (M^+, 56.13), 287 (M^+-CH_3, 8.11), 271 (M^+-OCH_3, 33.34), 160 (M^++1-$C_6H_{12}CO_2Me$, 79.56), 146 (M^++1-$C_7H_{14}CO_2Me$, 19.41); HRMS Found 302.1891, Calcd. for $C_{19}H_{26}O_3$ 302.1882; HPLC [Column, μBONDASPHERE 5μ CN-100A, 3.9×150 mm; Solvent, MeOH/H_2O (8:2); Flow rate, 0.70 mL/min; Pressure, 2500.0; Detected at 254 nm] RT 3.00 min (single peak), 98.34%; UV λ_{max} (EtOH) 296 nm, ε_{max} 2.78×10^4.

Methyl 8-[(2E)-3-oxo-2-((Z)-2-pentenylidene)-4-cyclopentenyl]octanoate (1). To a solution of compound **12** (6.3 mg) in toluene (1 mL) was added 5% wt Lindlar Pd-$CaCO_3$ catalyst (2.0 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 for 7 min. After removal of toluene the residue was subjected to flash chromatography (PE/EA, 95/5 to 90/10), yielding chromomoric acid C-I methyl ester (**1**) (5.8 mg, 92%) as a yellow oil. IR 3070 (w), 2926.0 (s), 2854.6 (s), 1739.8 (s, CO_2R), 1695.4 (s, C=O), 1629.8 (s, C=C-C=O), 1462.0 (m), 1437.0 (m) and 1205.5 (s); ^{1}H NMR δ 600 MHz, 7.54 (ddd, 1H, H-10, J=6.0, 2.6 and 0.8 Hz), 7.26 (dm, 1H, H-14, J=12.3 Hz), 6.37 (dd, 1H, H-11, J=6.0 and 1.8 Hz), 6.22 (ddt, 1H, H-15, J=12.4, 10.8 and 1.5 Hz), 6.00 (dtd, 1H, H-16, J=10.8, 7.7 and 1.0 Hz), 3.66 (s, 3H, CH_3O), 3.55 (m, 1H, H-9), 2.38 (qdd, 2H, H-17, J=7.7, 7.7 and 1.5 Hz), 2.29 (t, 2H, H-2, J=7.5 Hz), 1.66-1.53 (m, 4H, H-8 and H-3), 1.28-1.25 (m, 8H, H-

4 through H-7) and 1.05 (t, 3H, H-18, J=7.3 Hz); MS m/z 305 (M^++1, base peak), 275 (M^+-Et, 83.31), 273 (M^+-OMe, 36.81) and 162 (M^+-$C_6H_{12}CO_2Me$+1, 27.72); HRMS Found 304.2055, Calcd. for $C_{19}H_{28}O_3$ 304.2038; UV λ_{1max} (EtOH) 232 nm, $\varepsilon_{1max}7.14\times10^3$; λ_{2max} (EtOH) 306 nm, ε_{2max} 1.05×10^4.

(4E,8Z)-5-(8-*tert*-Butyldimethylsiloxyoctyl)-3-oxo-4-((E)-2-pentenylidene)tricyclo[5.2.1.0.^{2,6}]dec-8-ene (16). To a well-stirred suspension of CuI (25 mg, 0.13 mmol) in dry Et_2O (8 mL) was added lithium reagent **6** (0.56 M, 2.4 mL, 1.34 mmol, 1.3 equiv.) with a syringe under N_2 atmosphere at -78 ^{0}C and the reaction mixture was stirred at the same temp. for additional 50 min. A solution of enone **5** (152 mg, 1.04 mmol) in dry Et_2O (3 mL) was added dropwise at -78 ^{0}C over 15 min. After one-hour stirring, *trans*-2-pentenal (0.50 mL, ~428 mg, 5.10 mmol, 4.9 equiv.) was added in one portion, and 2 h later the reaction was allowed to warm from -78 ^{0}C to 0 ^{0}C over 5 h, quenched with saturated aqueous NH_4Cl (10 mL). The mixture was extracted with EtOAc (3×25 mL), and the combined organic extracts were washed with brine (3× 10 mL), dried and concentrated *in vacuo*. The residue was subjected to flash chromatography (petroleum ether/EtOAc, 98/2→96/4) to yield trienone **16** (398 mg, 84%) as a yellow oil. IR 2920 (s), 2850 (s), 1710 (s, C=O), 1630 (s) and 1605 (s, C=C-C=O), 1460 (m), 1250 (m), 1200 (m), 1100 (s), 840 (s) and 780 (s); ^{1}H NMR δ 6.70 (dd, 1H, H-19, J=10.9 and 2.0 Hz), 6.22~5.99 (m, 2H, H-20 and H-21), 5.97~5.92 (m, 2H, H-8 and H-9), 3.66 (t, 2H, H-18, J=6.6 Hz), 3.23 (m, 1H, H-5), 3.01~2.96 (m, 2H), 2.55~2.50 (m, 2H), 2.21 (qd, 2H, H-22, J=7.3 and 7.3 Hz), 1.51~1.47 (m, 4H, H-3 and H-8), 1.42-1.26 (m, 12H, H-3 through H-7, H-10), 1.05 (t, 3H, H-23, J=7.3 Hz), 0.90 (s, 9H, ^{t}BuSi≡), 0.06 (s, 6H, Me_2Si<); MS m/z 391 (M^++1-C_5H_6, 17.36), 375 (M^+-C_5H_6-Me, 32.78), 333 (M^+-C_5H_6-Bu^t, base peak); HRMS Found 456.3411, Calcd. for $C_{29}H_{48}O_2Si$ 456.3423.

(4E,8Z)-5-(8-Hydroxyoctyl)-3-oxo-4-((E)-2-pentenylidene)tricyclo[5.2.1.0.^{2,6}]dec-8-ene (17). A 6:3:1 mixture of HOAc-H_2O-THF (9 mL) was added dropwise to TBDMS-ether **16** (214 mg, 0.47 mmol) at 0 ^{0}C. The ice-bath was then removed and the reaction was stirred at room temp. for 1.5 h. The reaction mixture was diluted with EtOAc (60 mL), water (15 mL) and neutralized with saturated $NaHCO_3$ solution (40 mL), then extracted with EtOAc (3×50 mL). The combined organic extracts were washed with brine (4×20 mL), dried over Na_2SO_4 and concentrated *in vacuo*. The residual yellow oil was subjected to flash chromatography (petroleum ether/EtOAc, 90/10), affording alcohol **17** (142 mg, 89%) as a yellow oil. IR 3300~3450 (br s, OH), 2900 (s), 2850 (s), 1695 (s, C=O), 1620 (s) and 1595 (s, C=C-C=O), 1450 (s), 1210 (s); ^{1}H NMR δ 6.67 (dd, 1H, H-19, J=10.8 and 1.9 Hz), 6.22~6.02 (m, 2H, H-20 and H-21), 5.99~5.92 (m, 2H, H-8 and H-9), 3.64 (t, 2H, H-18, J=6.6 Hz), 3.24 (m, 1H, H-5), 3.01~2.96 (m, 2H), 2.55~2.48 (m, 2H), 2.21 (qd, 2H, H-22, J=7.2 and 7.2 Hz), 1.88 (br.s, 1H, OH), 1.59~1.52 (m, 4H, H-3 and H-8), 1.48~1.25 (m, 12H, H-3 through H-7, H-10), 1.05 (t, 3H, H-23, J=7.4 Hz); MS m/z 342 (M^+, 9.92%), 313 (M^+-Et, 14.04), 277 (M^++1-C_5H_6, 71.90), 276 (M^+-C_5H_6, 49.59), 259 (M^++1-C_5H_6-H_2O, 4.96), 247 (M^+-C_5H_6-Et, base peak).

(4E,8Z)-5-(7-Carbomethoxyheptyl)-3-oxo-4-((E)-2-pentenylidene)tricyclo[5.2.1.0.^{2,6}]dec-8-ene(18) To a solution of alcohol **17** (42 mg, 0.12 mmol) in dry DMF (5 mL) was added 4Å molecular sieves (180 mg)

with stirring. 15 min later, PDC (360 mg, 0.95 mmol, 8 equiv.) was added and the reaction was stirred at room temp. for 3 h. After water (10 ml) and EtOAc (80 mL) were added to the stirring mixture, the organic layer was separated and the aqueous layer was extracted with EtOAc (4×15 mL). The combined organic extracts were washed with brine (4×8 mL), dried over anhydrous Na_2SO_4. Removal of the solvent *in vacuo* followed by flash chromatography (petroleum ether/EtOAc, 90/10 then petroleum ether/EtOAc/MeOH, 85/15/2) provided a yellowish oil (31 mg, 73%) which was directly used in the next reaction. The oil was dissolved in ether (4 mL) and treated with a solution of CH_2N_2-ether at 0 °C. The reaction was stirred at this temp. for 5 min and the excess of CH_2N_2 was removed under reduced pressure. The residual yellow oil was subjected to flash chromatography (petroleum ether/EtOAc, 95/5 to 90/10), giving ester **18** (31 mg, 97%, overall yield 71%) as a yellow oil. IR 2920 (s), 2850 (s), 1740 (s, CO_2R), 1625 (m) and 1600 (s, C=C-C=O), 1460 (s), 840 (s) and 740 (m); ^{1}H NMR δ 6.67 (dd, 1H, H-19, J=10.9 and 2.0 Hz), 6.20~6.07 (m, 2H, H-20 and H-21), 5.99~5.93 (m, 2H, H-8 and H-9), 3.67 (s, 3H, OMe), 3.24 (m, 1H, H-5), 3.00~2.96 (m, 2H), 2.54~2.50 (m, 2H), 2.30 (t, 2H, H-2, J=7.4 Hz), 2.21 (qd, 2H, H-22, J=7.4 and 6.3 Hz), 2.02 (m, 2H), 1.58~1.42 (m, 4H), 1.34~1.16 (m, 10H), 1.05 (t, 3H, H-23, J=7.5 Hz); MS m/z 370 (M^+, 15.70%), 341 (M^+-Et, 15.70), 304 (M^+-C_5H_6, 59.50), 275 (M^+-C_5H_6-Et, base peak), 273 (M^+-C_5H_6-MeO, 30.99), 175 (M^+-C_5H_6-$C_5H_{10}CO_2Me$, 7.43), 161 (M^+-$C_6H_{12}CO_2Me$-C_5H_6, 9.16) and 147 (M^+-C_5H_6-$C_7H_{14}CO_2Me$, 15.70); HRMS Found 370.2519, Calcd. for $C_{24}H_{34}O_3$ 370.2508

Methyl 8-[(2E)-3-oxo-2-((E)-2-pentenylidene)-4-cyclopentenyl]octanoate (2). Into the tube of the thermolysis apparatus was placed substrate **18** (9.1 mg) and the apparatus was evacuated and filled with N_2, the pressure was adjusted to 220 mmHg. The cold finger was cooled with liquid nitrogen. The tube was then put into the heating bath (262~265 °C, previously set) and heated in order to effect thermolysis and evaporation. After completion of the reaction (2 min) the heating bath was removed and the apparatus was allowed to attain room temp. The thermolysis product (with a little of unreacted substrate) on the cold finger was collected with EtOAc, concentrated *in vacuo*. The residual yellow oil was subjected to flash chromatography (PE/EA, 90/10 to 85/15), affording substrate **18** (2.1 mg) and chromomoric acid C-II methyl ester **2** (4.9 mg, 86%). IR 2930 (s), 2856 (s), 1739.8 (s, CO_2R), 1695.4 (s) and 1633.7 (s, C=C-C=O), 1462.0 (m), 1437.0 (m), 1201.6 (s) and 976.0 (m); ^{1}H NMR (C_6D_6) δ 7.22 (d, 1H, H-14, J=11.6 Hz), 6.86 (ddd, 1H, H-10, J=6.0, 2.6 and 0.8 Hz), 6.25 (dd, 1H, H-11, J=6.0 and 1.8 Hz), 6.20 (ddt, 1H, H-15, J=11.7, 15.0 and 1.5 Hz), 5.82 (dt, 1H, H-16, J=15.1and 7.5 Hz), 3.36 (s, 3H, CH_3O), 3.14 (m, 1H, H-9), 2.10 (t, 2H, H-2, J=7.4 Hz), 1.89 (qd, 2H, H-17, J=7.5 and 7.5 Hz), 1.67~1.48 (m, 4H, H-3 and H-8), 1.40~1.00 (m, 8H, H-4 through H-7), 0.82 (t, 3H, H-18, J=7.5 Hz); MS m/z 304 (M^+, 40.34%), 275 (M^+-Et, base peak), 273 (M^+-OMe, 18.31), 175 (M^+-$C_5H_{10}CO_2Me$, 8.10), 161 (M^+-$C_6H_{12}CO_2Me$, 27.52), 147 (M^+-$C_7H_{14}CO_2Me$, 20.51); HRMS Found 304.2021, Calcd. for $C_{19}H_{28}O_3$ 304.2038.

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