Pergamon

Tetrahedron 54 (1998) 12561–12570

TETRAHEDRON

Total Synthesis and Structural Revision of Chromomoric Acid D-I Methyl Ester[1]

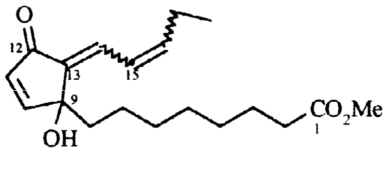
Zhi-Yu Liu* and Xin-Jie Chu

Shanghai Institute of Organic Chemistry, Chinese Academy of Sciences
354 Fenglin Lu, Shanghai 200032, CHINA

Received 13 February 1998; revised 18 May 1998; accepted 28 July 1998

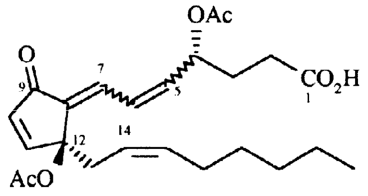
Abstract: A first total synthesis and structural revision of chromomoric acid D-I methyl ester 1 were described. Addition of organolithium reagent 13 to epoxy ketone 10 followed by regio- and stereospecific reductive ring opening afforded diol 16 which, after PDC oxidation and aldol condensation, gave rise to dienone 19. Sequential desilylation, oxidation, esterification and thermolysis provided precursor 24 which was then converted to 1, resulting in the revision of the originally postulated structures. © 1998 Elsevier Science Ltd. All rights reserved.

Chromomoric acid D I-IV (1-4) were isolated as their methyl esters from *Chromolacna morii* and their structures were elucidated originally by Bohlmann *et al.*[2] This group of natural products are metabolites of linolenic acid and their biological activity has not yet been determined. However, they bear structural resemblance to the marine prostanoids clavulones I-IV (5-8),[3] which are biosynthetically derived from arachidonic acid and exhibit remarkable antitumor and antiinflammatory activity. This distinct feature greatly aroused our interest in the possible biological activity of this family of new octadecanoids and a total synthesis would be highly significant as they exist only in minute amounts. Herein we report the first total synthesis and structural revision of chromomoric acid D-I methyl ester.[4]



Chromomoric acid D I-IV

I 13*E*, 15*Z* 1 III 13*Z*, 15*E* 3
II 13*E*, 15*E* 2 IV 13*Z*, 15*Z* 4



Clavulone I-IV

I 5*Z*, 7*E* 5 III 5*E*, 7*Z* 7
II 5*E*, 7*E* 6 IV 5*Z*, 7*Z* 8

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

Contrary to the previous synthesis of clavulones which was based upon the cyclopentenone chemistry,[5] our synthesis of chromomoric acid D methyl ester utilizes tricyclo[5.2.1.$0^{2,6}$]decadienone (9) as a starting

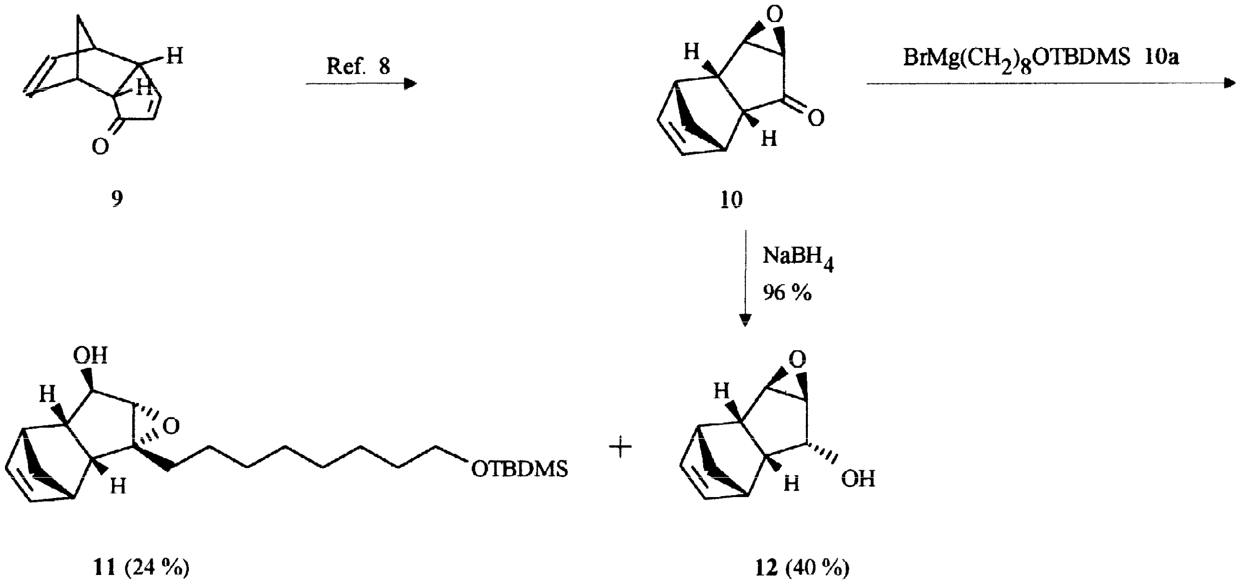
---

Dedicated to the memory of the late Professor Y. Wang

0040-4020/98/$ - see front matter © 1998 Elsevier Science Ltd. All rights reserved.
PII: S0040-4020(98)00735-2

material with a [4+2] thermal cycloreversion as the key strategy. As a consequence of the rigid molecule 9 with the endo configuration, the stereochemical course of the reactions at the enone function is well defined, which allows highly stereocontrolled synthesis of a variety of natural products.[6]

Epoxy ketone 10[7] was readily available from dienone 9 by epoxidation with alkaline hydrogen peroxide in quantitative yield.[8] The attachment of the eight-carbon side chain was initially made through the addition of Grignard reagent 10a. Treatment of epoxide 10 with Grignard reagent 10a prepared from the corresponding bromide at 40 °C for 3 hrs in THF afforded only 24% yield of the rearranged adduct 11 plus 40% yield of epoxy alcohol 12 resulting from the reduction of epoxy ketone 10. The stereochemistry of the *endo*-alcoholic group was confirmed by direct $NaBH_4$ reduction of epoxy ketone 10 (96 %).

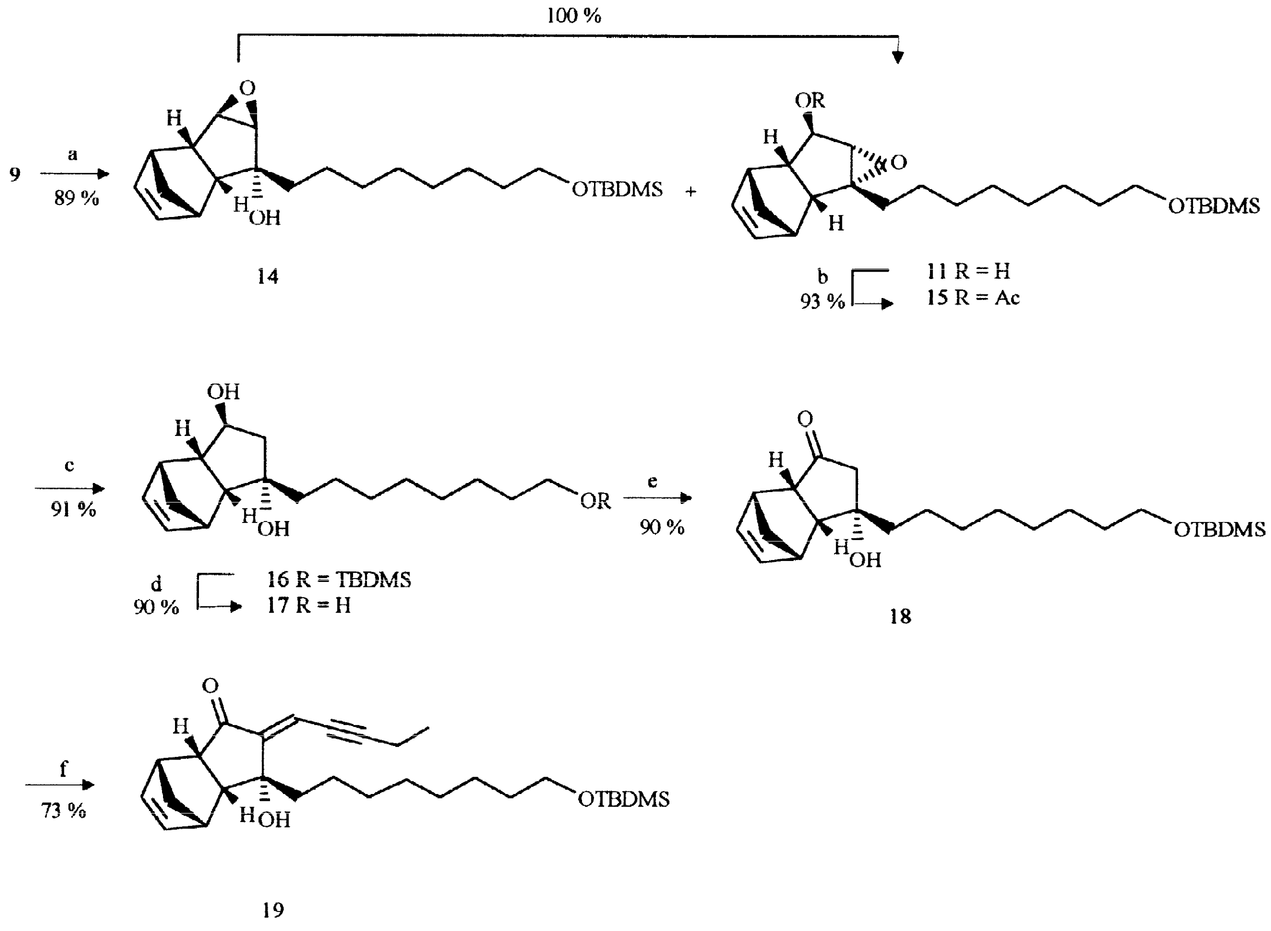


Scheme 1

However, addition of the corresponding organolithium reagent 13 to epoxy ketone 9 at 0 °C for 3.5 hrs stereospecifically produced ca. 1:3 mixture of epoxy alcohols 14 and 11. After this reaction mixture was stirred overnight (15 hrs) at room temp., tertiary alcohol 14 was completely converted via a Payne rearrangement[9] to secondary alcohol 11 in 89 % ioslated yield. Acetylation of 11 with acetic anhydride in pyridine afforded a less polar product 15 in which the δ of H-5 was shifted down to 4.42 ppm (d) from 3.77 ppm (d) in alcohol 11, indicating that 11 was a secondary alcohol. Upon treatment with $LiAlH_4$, epoxy alcohol 11 underwent stereospecific reductive ring opening to give diol 16 in 91% yield.

As the target molecule contains a ketone and a carboxylate group, we initially intended to make the modification of the eight-carbon side chain before attachment of the five-carbon chain. Exposure of diol 16 to tetrabutylammonium fluoride at 30 °C for 6 hrs afforded triol 17 (90% yield). Unfortunately, attempts to oxidize triol 17 to a keto acid or a keto aldehyde always led to complicated results. However, PDC oxidation of the secondary hydroxyl group in diol 16 afforded in high yield β-hydroxyl ketone 18 (90% yield), which is the key intermediate to all members of chromomoric acid D.

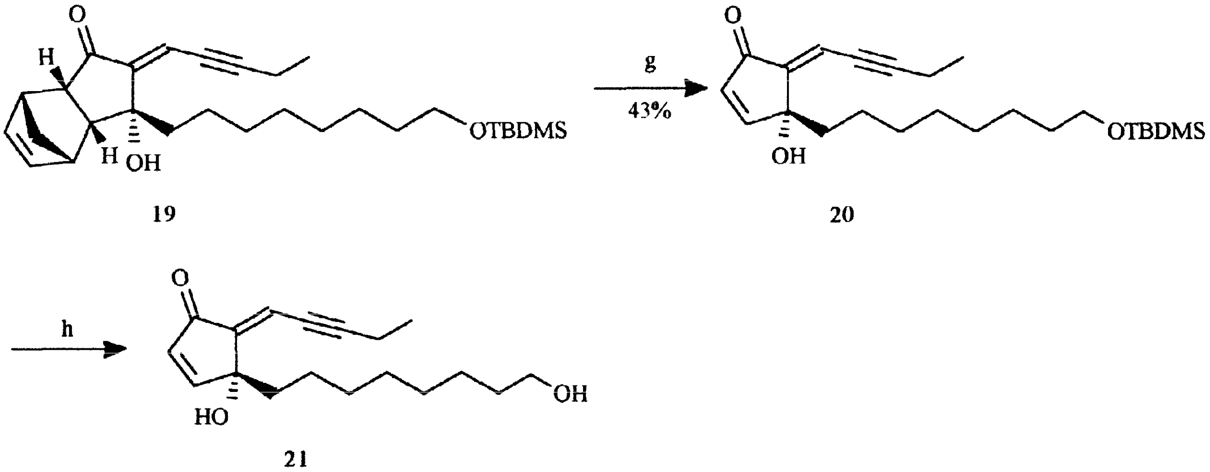
The most critically difficult step, construction of the whole skeleton of chromomoric acid D through crossed aldol condensation, was achieved after a great deal of experimentation. The lithium enolate, generated by dropwise addition of β-hydroxy enone 18 to 2.5 equiv. of LDA in THF over 25 min followed by a further 10 min stirring at -78 ^{0}C, was treated with 2.0 equiv of freshly distilled 2-pentynal at -78 ^{0}C for 5 min. The resulting reaction mixture was allowed to warm from -78 ^{0}C to -10 ^{0}C, and then stirred at -10~0 ^{0}C for 4 hrs to afford 73% of dienone 19 in isolated yield. The newly formed olefinic bond at C-4 was assigned to be *E* configuration without the 4,19-*Z* isomer by ^{1}H NMR analysis (Scheme 2).



Scheme 2

Reagents and Conditions: a) Li$(CH_2)_8$OTBDMS(13) (1.1equiv.), Et_2O, 0°C, 3.5h, then rt, 15h; b) Ac_2O, Py, rt, overnight, 93%; C)$LiAlH_4$, THF, 0-5°C, 5h; d) n-Bu_4NF, THF, 30°C, 6h; e) PDC, CH_2Cl_2, 4ÅMS, rt, 2.5h; f) LDA(2.5equiv.), EtC≡CCHO(2.0equiv.), THF, -78°C, 5 min; then -10~0°C, 4h.

With the well-equipped dienone 19 in hand, the next steps were to subject it to retro Diels-Alder reaction and modify the side chains. Thermolysis of 19 by heating in a tube under N_2 and collecting the thermolysis product with a cold finger (cooled with dry ice-acetone) at 255 ^{0}C and 55 mmHg afforded crossed conjugated dienone 20 (43% yield). However, desilylation of 20 was found to be extremely disappointing. Treatment of 20 with TBAF at room temp. afforded a very complicated mixture, whereas the reaction with HOAc-H_2O-THF gave a low yield of diol 21 (less than 20%) (Scheme 3).

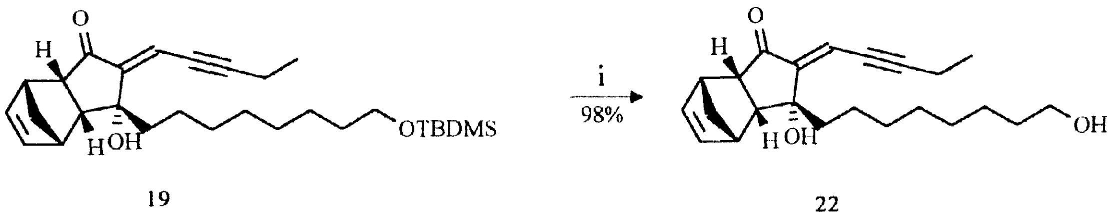


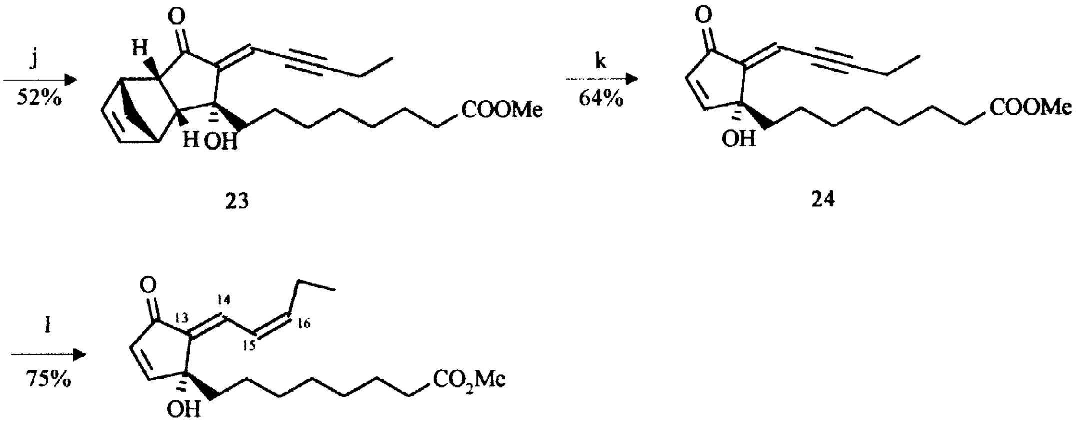
Scheme 3

Reagents and Conditions: g) 255°C, 55mmHg, 4min; h) HOAc-H_2O-THF(3:3:1), 0°C, 1.5h.

Since this approach to chromomoric acid D methyl ester 1 eventually foundered on the poor yield of the transformation of 20 to 21, we turned to the alteration in the synthetic sequence. Treatment of TBDMS ether 19 with weak acid , HOAc-H_2O-THF (6:3:1) at room temp. for 3 hrs gave alcohol 22 in quantitative yield. Mild oxidation of alcohol 22 with PDC in DMF to the corresponding carboxylic acid followed by esterification with an excess of CH_2N_2 provided ester 23 (52 % yield from 22). Retro Diels-Alder reaction of ester 23 at 240 ^{0}C and 70 mmHg afforded dienone 24 (64% yield), the precursor of chromomoric acid D-I methyl ester 1 (Scheme 4).

The last step, selective hydrogenation of the triple bond in 24 to the *cis* double bond, turned out to be very difficult. Hydrogenation with Pd-$CaCO_3$ in EtOAc -Py or other solvents such as EtOAc, EtOAc-quinoline or *n*-hexane gave very complicated mixtures. After considerable endeavour, this hydrogenation was eventually achieved when it was carried out in toluene with Pd-$CaCO_3$ as catalyst (15 ^{0}C, 9 min, 75% yield). The product afforded from this reaction system initially revealed, on its ^{1}H NMR (600 M Hz, with $CDCl_3$ as the solvent), the presence of only four olefinic protons in comparison with the ^{1}H NMR spectrum reported by Bohlmann, the absent fifth olefinic protons should appeared at δ 6.89 ppm. To our delight, however, with CD_3COCD_3 as the solvent in place of $CDCl_3$, the ^{1}H NMR analysis distinctly showed five olefinic protons, four of which corresponded well to those found in the ^{1}H NMR spectrum in $CDCl_3$ and could be absolutely assigned, on the basis of the multiplicity and coupling constant, to be H-10, H-11, H-15 and H-16; the fifth proton which was hidden in the signal of $CHCl_3$ (7.26 ppm) appeared now at 7.14 ppm! Further characterization of this compound by IR, MS, HRMS and UV led to the unambiguous elucidation of the target molecule 1 (Scheme 4).





23

24

Chromomoric acid D- I
methyl ester 1

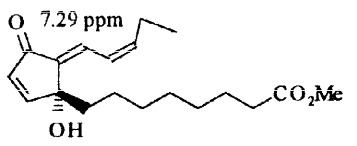
Scheme 4

Reagents and Conditions: i). HOAc-H_2O-THF (6:3:1), 0 ^{0}C then room temp., 3h. j). PDC, DMF, 4Åmolecular sieves, room temp., 5 h; then CH_2N_2, Et_2O, 0 ^{0}C, 10 min. k). 254 ^{0}C, 70 mmHg, 5 min. l). H_2, Pd-$CaCO_3$, toluene, room temp., 9 min.

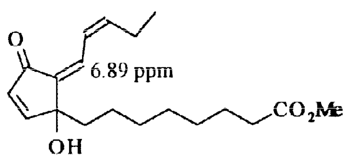
Structure Elucidation of the Synthetic Molecule and Revision of Original Assignment

The stereochemistry of the two olefinic bonds at C-13 and C-15 in our synthetic trienone **1** as elucidated by analysis of its ^{1}H NMR spectrum and in comparison with that of natural chromomoric acid D methyl ester reported by Bohlmann[2] and clavulones.[10] The configuration of the olefinic bond at C-15 was expected to be *cis* since hydrogenation with Lindlar catalyst always gives a *cis* double bond and this was confirmed by the coupling constant ($J_{15,16}$ 10.8 Hz) between H-15 and H-16. The configuration of the olefinic bond at C-13 was determined from the chemical shift values (δ) of the H-14 signals of our synthetic chromomoric acid D methyl ester and the natural substance reported by Bohlmann.[2]

Due to the anisotropy effect (shielding effect) of the C-12 carbonyl moiety, the signal of proton H-14 in in 13*E* configuration should appeared in a lower field than that of the corresponding 13*Z*-isomer. The signal of the olefinic proton H-14 in our synthetic chromomoric acid methyl ester was observed at δ 7.29 ppm, whereas in the natural compound[2] which was previously postulated to have the structure of chromomoric acid D-I methyl ester 1, the chemical shift of H-14 was at δ 6.89 ppm. In clavulone I, H-7 corresponding to H-14 in chromomoric acids was at 7.27 ppm, whereas in clavulone IV, the chemical shift of H-7 was at 7.02ppm.[10] Therefore it was concluded that our synthetic chromomoric acid D methyl ester should be assigned chromomoric acid D-I methyl ester 1 having 13*E* configuration and the natural product which was once postulated to be chromomoric acid D-I methyl ester 1 should be revised to be chromomoric acid D-IV methyl ester 4 having 13*Z* configuration.



Chromomoric acid D-I
methyl ester (1)



Chromomoric acid D-IV
methyl ester (4)

In summary, starting from dienone 9, the first total synthesis of chromomoric acid D-I methyl ester 1 was achieved in nine steps in 13 % overall yield . The synthesis described herein is highly regio- and stereoselective and is also allowed for the synthesis of chiral chromomoric acid D methyl esters in a straightforward way due to the availability of chiral enone 9.[11] Furthermore, through this total synthesis, the originally postulated structure[2] has been revised.

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 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 become clearly visible. Flash column chromatography was conducted on silica gel H (10-40 μ) from Qingdao Haiyang Chemical Works, with petroleum ether (60~90 ^{0}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.

3-(8-tert-Butyldimethylsiloxyoctyl)-endo-3,4-epoxytricyclo[5.2.1.0^{2,6}]dec-8-en-5-ol 11 and endo-4,5-epoxytricyclo[5.2.1.0^{2,6}]dec-8-en-3-ol 12

A Grignard solution of 8-tert-butyldimethylsiloxyoctylmagnesium bromide was prepared from 8-tert-butyldimethylsiloxyoctyl bromide (1.78 g, 5.5 mmol) and activiated magnesium (500 mg, 20.6 mmol) in THF (20 ml) at 40~50°C for 2h. To the Grignard reagent was added dropwise epoxy ketone 9 (488 mg, 3 mmol) in THF (5 ml) at 30~35°C over 15 min. After the reaction was stirred at 40°C for a further 3 hr, it was quenched with saturated NH_4Cl (20 ml). The resulting mixture was extracted with EtOAc (3X 40 ml) and the combined extracts were washed with aqueous NH_4Cl(15 ml), brine (3X 10 ml) and dried over Na_2SO_4. Removal of the solvent followed by flash chromatography (petroleum ether / EtOAc, 90/10 to 80/20) afforded epoxy alcohol 11 (298 mg, 24%) and 12 (199 mg, 40%) as a colorless oil and a white solid, respectively.

For 11: IR 3400(br s, OH), 2900(s), 2850(m), 1460(m), 1095(s) and 840(s)cm^{-1}; ^{1}HNMR: δ 6.18(dd, 1H, H-8 or H-9, *J*=5.4 and 2.8 Hz), 5.87(dd, 1H, H-9 or H-8, *J*=5.4 and 3.0 Hz), 3.77(d, 1H, H-5, *J*=2.5 Hz), 3.60(t, 2H, CH_2OR, *J*=6.8 Hz), 3.01(s, 1H, H-4), 3.00~2.73(m, 4H), 1.68~1.20(m, 16H), 1.70(br, 1H, OH), 0.90(s, 9H, Bu^t) and 0.05(s, 6H, Me_2Si); MS(m/z): 406(M^+, 1.14%), 349(M^+-Bu^t, 33.73), 325(M^+-C_5H_6-Me, 5.80), 283(M^+-C_5H_6-Bu^t, base peak), 265(M^+-C_5H_6-H_2O-Bu^t, 20.44) and 257(M^+-OTBDMS-H_2O, 9.87); Found: C, 70.99; H, 10.53; Calcd. For $C_{24}H_{42}O_3Si$: C, 70.88; H, 10.41%. For 12: m.p. 63~64°C(EtOH); IR 3400(s, OH), 2950(s), 2850(m), 1080(m); ^{1}HNMR: δ 6.23~5.93(m, 2H, H-8 and H-9), 4.22(m, 1H, H-3), 3.22(m, 2H, H-4 and H-5), 2.92(m, 4H), 1.54(s, 1H, OH) and 1.61~1.42(m, 2H); MS(m/z): 165(M^++1, 3.63%), 164(M^+, 10.96), 147(M^+-H_2O+1, 10.66) and 99(M^+-C_5H_6+1, 27.79).

Reduction of the epoxy ketone 9 to the epoxy alcohol 12

To a stirring suspension of $NaBH_4$(40 mg, 1.06 mmol) in THF(5 ml) was added epoxy ketone 9 (100 mg, 0.62 mmol) in THF(5 ml) at 0°C. After stirred at this temp. for 80 min., the reaction was quenched with saturated NH_4Cl (20 ml) and extracted with EtOAc(3X 20 ml). The combined extracts were washed with brine (3X 10 ml), dried over Na_2SO_4 and concentrated in vacuo. The residue was subjected to flash chromatography (petroleum ether / EtOAc, 80/20), affording 12 (97 mg, 96%) as a white solid.

Addition of the lithium reagent to the epoxy ketone 9 to give epoxy alcohol 11

A solution of 8-tert-butyldimethylsiloxyoctyl lithium was prepared from 8-tert-butyldimethylsiloxyoctyl bromide (18.9 g, 57.6 mmol) and lithium (1.58 g, 230 mmol) in dry Et_2O (120 ml) at -5~0°C for 3 h. To a solution of epoxy ketone 9 (5.85g, 36.1 mmol) in dry ether (45 ml) was added dropwise a solution of the above lithium reagent (0.39 M, 110 ml, 43 mmol) over 50 min. at -10°C. The reaction mixture was stirred at -10~0°C for 2.5 h and then at room temp. overnight (15 h). The resulting yellow solution was then quenched by aqueous NH_4Cl (50 ml) and extracted with EtOAc(4X 40 ml). The combined extracts were washed with aqueous NH_4Cl (3X 20 ml) and brine (3X 20 ml), dried over Na_2SO_4 and concentrated in vacuo. The residue was subjected to flash chromatography (petroleum ether / EtOAc, 90/10 to 70/30) to afford epoxy alcohol 11 (13.0 g, 89%) as a colourless oil.

Acetylation of the epoxy alcohol 11

A mixture of epoxy alcohol 11 (50 mg, 0.12 mmol), acetic anhydride (1.5 ml) and Pyridine (1 ml) was stirred at room temp overnight, diluted with EtOAc (40 ml) and then washed with saturated $CuSO_4$ (5X 10 ml), brine (3X 10 ml) and dried over Na_2SO_4. Removal of the solvent followed by flash chromatography (petroleum ether / EtOAc, 95/5) gave 15 (52 mg, 93%) as an oil. IR 2980(s), 2850(s), 1735(m), 1095(m) and 850(m); ^{1}HNMR: δ 6.10(m, 1H), 5.89(m, 1H), 4.42(d, 1H, H-5, J=2.6 Hz), 3.61(t, 2H, CH_2OR, J=6.8 Hz), 3.02(s, 1H, H-4), 2.95~2.73(m, 4H), 2.00(s, 3H, $COCH_3$), 1.64~1.22(m, 17H), 0.89(s, 9H, Bu^t) and 0.05(s, 6H, Me_2Si); MS(m/z): 448(M^+, 11.56%), 391(M^+-Bu^t, 29.87), 382(M^+-C_5H_6, 62.41), 325(M^+-C_5H_6-Bu^t, base peak).

3-(8-tert-Butyldimethylsiloxyoctyl)-tricyclo[5.2.1.0^{2,6}]dec-8-ene-3,5 diol 16

To a sulution of epoxy alcohol 11 (6.50 mg, 16.0 mmol) in dry THF (200 ml) was added $LiAlH_4$ (5.05 g, 14.9 mmol) at 0°C and the suspension was stirred at 5~0°C for 5 hr. The reaction mixture was then treated dropwise successively at 0°C with water (5 ml), aqueous 15% NaOH (5 ml) and water (15 ml). The resulting mixture was filtred and the granular precipitate was thoroughly washed with EtOAc. The filtrate was concentrated in vacuo and the residue was subjected to flash chromatography (petroleum ether / EtOAc, 70/30), affording 11 (650 mg) and diol 16 (5.35 g, 91%). m.p. 80.0~81.0°C(hexane); IR 3400~3270(br s, OH), 2950(s), 2850(m), 1460(m), 1240(m), 1120(m), 1090(m) 835(m), and 745(m); ^{1}HNMR: δ 6.34(dd, 1H, H-8 or H-9, J=5.6 and 2.5 Hz), 6.11(dd, 1H, H-9 or H-8, J=5.6 and 3.0 Hz), 3.73(m, 1H, H-5), 3.60(t, 2H, CH_2OR, J=6.6 Hz), 2.96(m, 1H), 2.86(m, 1H), 2.73(m, 1H), 2.65(m, 1H), 1.85(dd, 1H, H-4, J=13.6 and 6.2Hz), 1.72(dd, 1H, H-4', J=13.6 and 4.7Hz), 1.67~1.62(m, 2H), 1.56~1.30(m, 16H, including two OH at 1.54), 0.90(s, 9H, Bu^t) and 0.05(s, 6H, Me_2Si); MS(m/z): 391(M^+-H_2O+1, 38.37), 373(M^+-$2H_2O$+1, 42.52), 351(M^+-Bu^t, 19.74), 333(M^+-H_2O-Bu^t, base peak), 325(M^+-C_5H_6-H_2O+1, 21.68), 307(M^+-C_5H_6-$2H_2O$+1, 6.73) and 165(M^+-$(CH_2)_8$OTBDMS, 61.63); Found: C, 70.41; H, 10.75; Calcd. For $C_{24}H_{44}O_3Si$: C, 70.53; H, 10.85%.

3-(8-Hydroxyoctyl)-tricyclo[5.2.1.0^{2,6}]dec-8-ene-3,5 diol 17

To a solution of diol 16 (60 mg, 0.15 mmol) in THF (5 ml) was added Bu_4NF (0.75 ml 1M in THF, 0.75 mmol). After the reaction was stirred at 30°C for 6h, it was diluted with H_2O (5ml) and extracted with EtOAc (3X 20 ml). The combined organic extracts were washed with brine (3X 10 ml), dried over anhydrous Na_2SO_4 and concentrated in vacuo. The crude product was purified through flash chromatography (petroleum ether / EtOAc,50/50) to give triol 17 (40 mg, 90%) as a white solid. m.p. 116.5~117.0°C(EtOH); IR 3400~3100(br s, OH), 2900(s), 2850(m), 1460(m), and 1095(s); ^{1}HNMR: δ 6.32(m, 1H), 6.15(m, 1H), 3.75(m, 1H, H-5), 3.62(t, 2H, $C\underline{H_2}OH$, J=6.5 Hz), 2.92(m, 1H), 2.89(m, 1H), 2.65~2.82(m, 2H), 1.80(m, 2H) and 1.57~1.27(m, 19H, including three OH); MS(m/z): 276(M^+-H_2O, 6.45), 259(M^+-$2H_2O$+1, 11.22), 211(M^+-C_5H_6-H_2O+1, 1.55), 193(M^+-C_5H_6-$2H_2O$+1, 3.30), 165(M^+-$(CH_2)_8OH$, 56.35), 147(M^+-$(CH_2)_8OH$-H_2O, 2.40) and 66($C_5H_6^+$, base peak); Found: C, 73.25; H, 10.32; Calcd. For $C_{18}H_{30}O_3$: C, 73.43; H, 10.27%.

3-(8-tert-Butyldimethylsiloxyoctyl)-3-hydroxy-tricyclo[5.2.1.0^{2,6}]dec-8-en-5-one 18

To a solution of diol **16** (4.0 g, 9.8 mmol) in dry THF (180 ml) was added 4Å molecular sieves (1.0 g) with stirring. PDC (7.8 g, 20.7 mmol, 2.1equiv) was added 10 mins later and the contents were stirred at room temp (27°C) for 2.5h. The resulting mixture was poured into petroleum ether (400 ml) and filtred. The filtrate was concentrated in vacuo and the residue was subjected to flash chromatography (petroleum ether / EtOAc, 90/10 to 80/20) affording **18** (3.59 g, 90%) as a white solid. m.p. 69.5~70.5°C(EtOH); IR 3450(br s, OH), 2900(s), 2850(s), 1715(s, C=O), 1460(m), and 1090(s); ^{1}HNMR: δ 6.38(m, 1H), 6.06(m, 1H), 3.61(t, 2H, CH_2OR, J=6.8 Hz), 3.24(m, 1H), 3.16(m, 1H), 2.99(m, 1H), 2.25(s, 2H, H-4), 1.62~1.20(m, 16H), 1.52(s, 1H, OH), 0.89(s, 9H, Bu^t) and 0.05(s, 6H, Me_2Si); MS(m/z): 349(M^+-Bu^t, 40.81), 323(M^+-C_5H_6-H_2O+1, 5.06), 283(M^+-Bu^t-C_5H_6, base peak) and 265(M^+-Bu^t-C_5H_6-H_2O, 18.48); Found: C, 70.96; H, 10.32; Calcd. For $C_{18}H_{30}O_3$: C, 70.88; H, 10.41%.

4*E*-3-(8-tert-Butyldimethylsiloxyoctyl)-3-hydroxy-4-(pent-2-ynylidene)tricyclo[5.2.1.0^{2,6}]dec-8-en-5-one 19

A solution of dry THF (10 ml) and *i*-Pr_2NH (302 mg, 2.98 ml) was cooled to -40 °C, then treated with a solution of BuLi (1.20 ml 2.50M in *n*-hexane, 3.00mmol) and the stirring was continued at this temp. For 1h. The resulting LDA-solution was cooled to -78 °C and β-hydroxy ketone **18** (485 mg, 1.19 mmol) in dry THF (4 ml) was added dropwise over 25 min. After the solution was stirred at this temp. for a further 15 min, newly distilled 2-pentynal (0.22 ml, 193 mg, 235 mmol) in THF (1 ml) was added. After the reaction was stirred at -78°C for 5 min, it was allowed to warm to -10°C and stirred at -10~0°C for 4h and then at room temp. for 2h. The resulting mixture was quenched with saturated aqueous NH_4Cl (6 ml) at 0°C and extracted with EtOAc (3X 20 ml). The combined organic extracts were washed with aqueous NH_4Cl (3X 8 ml), brine (3X 10 ml) and dried over anhydrous Na_2SO_4. Removal of the solvent followed by flash chromatography (petroleum ether / EtOAc, 95/5 to 85/15) afforded, in addition to recovered 18(86 mg), dienone 19 (337 mg, 73%) as a yellow oil. IR 3500(br s, OH), 2950(s), 2850(m), 2195(w, C≡C), 1700(s, C=O), and 1605(s, C=C-C=O), 1460(m) and 1090(m); ^{1}HNMR: δ 6.22(t, 1H, H-19, J=2.4Hz), 6.15(m, 1H, H-8 or H-9), 5.87(m, 1H, H-9 or H-8), 3.59(t, 2H, H-18, J=6.8 Hz), 3.24(m, 2H), 3.00(m, 1H), 2.85(m, 1H), 2.47(qd, 2H, H-22, J=7.2 and 2.4 Hz), 1.83~1.13(m, 20H, including OH at 1.67), 0.86(s, 9H, Bu^t) and 0.05(s, 6H, Me_2Si); MS(m/z): 470(M^+, 4.45%), 453(M^+-H_2O+1, 2.31), 405(M^+-C_5H_6+1, 4.81), 387(M^+-C_5H_6-H_2O+1, 8.47), 347(M^+-Bu^t-C_5H_6, base peak) and 161(M^+- C_5H_6-$(CH_2)_8OR$, 71.77); HRMS Found: 470.3238 Calcd. for $C_{29}H_{46}O_3Si$: 470.3216.

3-(8-tert-Butyldimethylsiloxyoctyl)-3-hydroxy-2-(pent-2-ynylidene)cyclopent-4-en-1-one 20

Into the tube of a thermdysis apparatus was placed dienone 19 (219 mg) and the apparatus was evacuated and filled with N_2, the pressure was then adjusted to 55 mmHg. The cooled finger was cold to -78°C with dry ice-acetone. The tube was then put into the heating bath (255°C, previously set) and heated for 4 min. The thermolysis product 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 to 80/20), affording substrate 19 (24 mg) and dienone 20 (72 mg, 43%). IR 3400 (br s, OH), 2950(s), 2850(s), 2200(w, C≡C), 1700(s, C=O), 1630(s, C=C-C=O) and 1110(m); ^{1}HNMR: δ 7.33(d, 1H, H-10, J=6.0 Hz), 6.41(t, 1H, H-14, J=2.4 Hz), 6.33(d, 1H, H-11, J=6.0 Hz), 3.54(t, 2H, H-1, J=6.7 Hz), 2.55(brd, 1H, OH), 2.45(qd, 2H, H-17, J=7.2 and 2.4 Hz), 1.98(m, 2H), 1.64~0.96(m, 15H), 0.85(s, 9H, Bu^t) and 0.05(s, 6H, Me_2Si); MS(m/z): 405(M^++1, 14.12), 387(M^+-H_2O+1, 16.70), 348(M^+-Bu^t+1, base peak) and 161(M^+-$(CH_2)_8$OTBDMS, 19.84).

3-(8-Hydroxyoctyl)-3-hydroxy-2-(pent-2-ynylidene) cyclopent-4-en-1-one 21

To TBDMS-ether 20 (35 mg) was added dropwise a 3:1:1 mixture of HOAc-H_2O-THF (3 ml) and the reaction was stirred at 0°C for 1.5h. The resulting mixture was diluted with EtOAc (20 ml) and water (5 ml) and neutralized with saturated $NaHCO_3$ solution (20 ml), then extracted with EtOAc (3X 30 ml). The combined organic extracts was washed with brine (3X 10 ml), dried over Na_2SO_4 and concentrated in vacuo. The residue was subjected to flash chromatography (petroleum ether / EtOAc, 70/30) affording diol 21 (4.9 mg, 19.5%) as a yellowish oil. IR 3400(br s, OH), 2920(s), 2850(s), 2195(m, C≡C), 1700(s, C=O), 1630(s, C=C-C=O) and 1050(m); ^{1}HNMR: δ 7.31(d, 1H, H-10, J=6.0 Hz), 6.42(t, 1H, H-14, J=2.4 Hz), 6.31(d, 1H, H-11, J=6.0 Hz), 3.57(t, 2H, H-1, J=7.0 Hz), 2.47(qd, 2H, H-17, J=7.1 and 2.4 Hz), 2.15(brd, 1H, OH), 1.96(m, 2H) and 1.70~0.93(m, 15H); MS(m/z): 290(M$^+$, 5.12%), 272(M$^+$-H_2O, 34.96), 254(M$^+$-$2H_2O$, 17.42) and 161[M$^+$-$(CH_2)_8OH$, base peak].

4*E*-3-(8-Hydroxyoctyl)-3-hydroxy-4-(pent-2-ynylidene)-tricyclo[5.2.1.0^{2,6}]dec-8-en-5-one 22

A 6:3:1 mixture of HOAc-H_2O-THF (6 ml) was added dropwise to TBDMS-ether 19 (160 mg) at 0°C and the reaction was then stirred at room temp. for 3h. The resulting mixture was diluted with Et_2O (80 ml), water (10 ml) and neutralized with saturated $NaHCO_3$ solution (58 ml), then extracted with EtOAc (3X 30 ml). The combined organic extracts was washed with brine (4X 15 ml), dried over anhydrous Na_2SO_4 and concentrated in vacuo. The residual yellow oil was subjected to flash chromatography (petroleum ether / EtOAc, 80/20) to give alcohol 22 (119 mg, 98%) as a yellow oil. IR 3450(br s, OH), 2900(s), 2850(s), 2200(m, C≡C), 1700(s, C=O), 1610(s, C=C-C=O) 1460(m) and 1200(m); ^{1}HNMR: δ 6.24(t, 1H, H-19, J=2.4 Hz), 6.17(m, 1H, H-8 or H-9), 5.88(m, 1H, H-9 or H-8), 3.61(t, 2H, H-18, J=6.8 Hz), 3.23(m, 2H), 3.02(m, 1H), 2.83(m, 1H), 2.46(qd, 2H, H-22, J=7.2 and 2.4 Hz), 1.78(m, 2H), 1.70~1.12(m, 17H, including two OH); MS(m/z): 291(M$^+$-C_5H_6+1, 30.28), 272(M$^+$-C_5H_6-H_2O, base peak), 254(M$^+$-C_5H_6-$2H_2O$, 3.46) and 161[M$^+$- C_5H_6-$(CH_2)_8OH$, 52.34].

4*E*-3-(7-Methoxycarbonylheptyl)-3-hydroxy-4-(pent-2-ynylidene)-tricyclo[5.2.1.0^{2,6}]dec-8-en-5-one 23

To a solution of alcohol 22 (107 mg, 0.30 mmol) in dry DMF (10 ml) was added 4Å molecular sieves (90 mg) with stirring. PDC (500 mg, 1.33 mmol, 4 equiv) was then added and the mixture was stirred at room temp for 5h. Water (20 ml) and Et_2O (70 ml) were then added to the stirring mixture, the organic layer was separated and the aqueous layer was extracted with Et_2O (5X 30 ml). The combined organic extracts was washed with brine (4X 10 ml), dried over anhydrous Na_2SO_4. Removal of the solvent followed by flash chromatography (petroleum ether / EtOAc / MeOH, 50/50/2) provided a yellow oil (57 mg). The oil was dissolved in Et_2O (1.5 ml) and treated with an excess of CH_2N_2-ether solution at 0°C. The excess of CH_2N_2 was removed under reduced pressure. The residue was subjected to flash chromatography (petroleum ether / EtOAc, 75/25) to yield ester 23 (58 mg, 52%) as a yellow oil. IR 3450(s, OH), 2900(s), 2850(s), 2200(w, C≡C), 1740(s, CO_2R), 1700(s, C=O), 1610(s, C=C-C=O) 1460(m) and 1200(m); ^{1}HNMR: δ 6.15(t, 1H, H-19, J=2.4 Hz), 6.08(m, 1H, H-8 or H-9), 5.80(m, 1H, H-9 or H-8), 3.59(s, 3H, OMe), 3.15(m, 2H), 2.93(m, 1H), 2.75(m, 1H), 2.37(qd, 2H, H-22, J=7.0 and 2.4 Hz), 2.22(t, 2H, H-2, J=7.2 Hz), 1.78~1.18(m, 14H), 1.16(s, 1H, OH) and 1.08(t, 3H, H-23, J=7.0Hz); MS(m/z): 384(M$^+$, 5.08%), 318(M$^+$-C_5H_6, 9.22), 287(M$^+$-C_5H_6-OCH_3, 7.51), 286(M$^+$-C_5H_6-CH_3OH) and 161[M$^+$- C_5H_6-$(CH_2)_7CO_2CH_3$, base peak]; HRMS Found: 384.2252 Calcd. for $C_{24}H_{32}O_4$: 384.2298.

3-(7-Methoxycarbonylheptyl)-3-hydroxy-2-(pent-2-ynylidene)-cyclopent-4-en-1-one,(15-Dehydro chromomoric acid methyl ester) 24

Into the tube of a thermolysis apparatus was placed substrate 23 (44 mg) and the apparatus was evacuated and filled with N_2, the pressure was then adjusted to 70 mmHg. The cooled finger was cooled to -78°C with dry ice-acetone. The tube was then put into the heating bath (240°C, previously set) and heat for 5 min. The thermolysis product on the cold finger was collected with EtOAc, concentrated in vacuo. The residual yellow oil was subjected to flash chromatography (petroleum ether / EtOAc, 70/30), providing substrate 23 (4 mg) and dienone 24 (21 mg, 64%). IR 3400 (s, OH), 2900(s), 2850(s), 2200(m, C≡C), 1740(s, CO_2R), 1700(s, C=O) and 1630(s, C=C-C=O); ^{1}HNMR: δ 7.31(d, 1H, H-10, J=6.0 Hz), 6.39(t, 1H, H-14, J=2.2 Hz), 6.32(d, 1H, H-11, J=6.0 Hz), 3.59(s, 3H, OMe), 2.42(qd, 2H, H-17, J=7.0 and 2.2 Hz), 2.23(t, 2H, H-2, J=7.0 Hz) and 1.66~1.05(m, 16H); MS(m/z): 318(M$^+$, 44.81%), 301(M$^+$-H_2O+1, 35.57), 286(M$^+$-CH_3OH, 42.77) and 161[M$^+$-$(CH_2)_7CO_2Me$, base peak].

3-(7-Methoxylcarbonylheptyl)-3-hydroxy-2-(2-pent-2-enylidene)-cyclopent-4-en-1-one, (Chromomoric Acid methyl ester) 1

To a solution of compound **24** (5.0 mg) in dry toluene (1.0 mL) placed in a 5-mL flask was added 5%wt Lindlar Pd-$CaCO_3$ catalyst (2.0 mg). The System was alternately evacuated and filled with H_2, the operation was repeated for three times. The content was then stirred in an atmosphere of H_2 for 9 min. After removal of toluene in vacuo, the residue was subjected to flash chromatography (petroleum ether / EtOAc, 95/5 to 92/8 to 90/10), affording 24 (1 mg) and C.A.D.-I methyl ester (1) (3.0 mg, 75%) as a yellow oil. IR 3400 (br, OH), 3040(m, olefinic C-H), 1740(s, CO_2R), 1700(s) and 1635(s, C=C-C=O); ^{1}HNMR: δ 600 MHz, in $CDCl_3$, 7.31(dd, 1H, H-10, *J*=6.0 and 0.8 Hz), 7.29(dm, 1H, H-14, *J*=12.4Hz), 6.65(ddt, 1H, H-15, *J*=12.4, 10.8 and 1.5 Hz), 6.36(d, 1H, H-11, *J*=6.0 Hz), 6.08(dtd, 1H, H-16, *J*=10.8, 7.7 and 1.0 Hz), 3.66(s, 3H, CH_3O), 2.39(m, 2H, H-17), 2.28(t, 2H, H-2, *J*=7.6 Hz) 1.98(m, 2H), 1.59(t, 2H, *J*=7.0 Hz), 1.23~1.32(m, 9H) and 1.06(t, 3H, *J*=7.6 Hz); 600 MHz, in CD_3COCD_3, 7.44(dd, 1H, H-10, *J*=6.0 and 0.8 Hz), 7.14(ddd, 1H, H-14, *J*=12.4, 1.1 and 0.8 Hz), 6.75(ddt, 1H, H-15, *J*=12.4, 10.8 and 1.5 Hz), 6.29(d, 1H, H-11, *J*=6.0 Hz), 6.03(dtd, 1H, H-16, *J*=10.8, 7.7 and 1.1 Hz), 3.61(s, 3H, CH_3O), 2.37(m, 2H, H-17), 2.27(t, 2H, H-2, *J*=7.5 Hz) 1.96(m, 2H), 1.55(t, 2H, *J*=7.3 Hz), 1.32~1.22(m, 9H) and 1.05(t, 3H, *J*=7.6 Hz); MS(m/z): 320(M^+, 11.25%), 302(M^+-H_2O, 1.97), 291(M^+-Et, 6.41), 289(M^+-CH_3O, 7.48), 289(M^+-CH_3OH, 5.88), 273(M^+-H_2O-Et, 4.13), 259(M^+-Et-CH_3OH, 4.05), 163[M^+-$(CH_2)_7CO_2$ CH_3, base peak] and 55($C_4H_7^+$, 60.75); HRMS Found: 320.2008 Calcd. for $C_{19}H_{28}O_4$: 320.1987; UV λ_{1max}(EtOH) 236 nm, ε_{1max} 1.83×10^4; λ_{2max}(EtOH) 302 nm, ε_{2max} 1.20×10^4.

References and notes:

1. Part XVI on Natural Products Synthesis by Retro Diels-Alder Reaction. For part XV, see Liu, Z.-Y.; Zhao, L.-Y.; Xie, Y.-N.; Wu, Y.; Wang, L.-L.; Zheng, H., submitted for publication.
2. Bohlmann, F.; Borthakur, N.; King, R.M.; Robison, H., *Phytochemistry,* 1982, *21,* 125. For nomenclature of chromomonic acid family, see Ref. 4.
3. a. Kikuchi, H.; Tsukitani, Y.; Iguchi, K.; Yamada.Y., *Tetrahedron Lett.,* 1982, *23,* 5171. b. Kobayashi, M.; Yasuzawa, T.; Yoshihara, M.; Akutsu, H., Kyogoku, Y.; Kitagawa, I., *Tetrahedron Lett.;* 1982, *23,* 5331.
4. For preliminary communication, see Liu, Z.-Y.; Chu, X.-J., *Tetrahedron Lett.,* 1993, *34,* 349.
5. a. Corey, E.J.; Mehrotra, M.M., *J. Am. Chem. Soc.,* 1984, *106,* 3384. b. Nagaoka, H.; Miyakoshi, T.; Yamada, Y., *Tetrahedron Lett.,* 1984, *25,* 3621. c. Kruger, G.; Harde, C.; Bohlmann, F., *Tetrahedron Lett.,* 1985, *26,* 6027. d. Nagaoka, H.; Miyaoka, H.; Miyakoshi, T.; Yamada, Y., *J. Am. Chem. Soc.,* 1986, *108,* 5019-5021. e. Suzuki, M.; Morita, Y.; Yanagisawa, A.; Baker, B.J.; Scheuer, P.J.; Noyori, R., *J. Org. Chem.,* 1988, *53,* 286.
6. a. Liu, Z.-Y.; He, L.; Zheng, H., *Synlett,* 1993, 191. b. Liu, Z.-Y.; Dong, H.; Chu, X.-J., *Tetrahedron,* 1994, *50,* 12337. c. Chu, X.-J.; Dong, H.; Liu, Z.-Y., *Tetrahedron,* 1995, *51,* 173. d. Liu, Z.-Y.; Yang, J. Y.; Zhang, J.J.; Tao, X.L., *Chinese Chem. Lett.,* 1993, *4,* 947 (Engl.). e. Liu, Z.-Y.; Ma, J.-Y., *Chinese J. Chem.,* 1995, *13,* 190 (Engl.).
7. All the compounds in this paper are racemic.
8. Chapman, O.L.; Hess, T.C., *J. Org. Chem.,* 1979, *44,* 962.
9. Payne, G. B., *J. Org. Chem.,* 1962, 27, 3819.
10. Kitagawa, I.; Kobayashi, M.; Yasuzawa, T.; Son, B. N.; Yoshihara, M.; Kyoguku, Y., Tetrahedron, 1985, 41, 995.
11. a. Zhang, L.; Yang, J.-Y.; Liu, Z.-Y., *Chinese Chem. Lett.,* 1992, *3,* 787.
    b. Liu, Z.-Y.; He, L.; Zheng, H., *Tetrahedron Asymmetry,* 1993, *4,* 2277.