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Studies on the formation of 14-membered macrocycles by intramolecular Michael addition

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Summary – Intramolecular Michael addition of β-ketoesters on enones **1**, **2** and **3** with two conjugated unsaturations along the connecting chain led to cyclic monomers and dimers. These reactions work best with a *cis* alkene; they give poor yield of monomer with a *trans* alkene and no monomer with an alkyne.

macrocyclization / intramolecular Michael reaction / steroids

Introduction

As previously demonstrated, the transannular Diels-Alder cycloaddition represents a powerful approach towards the syntheses of several classes of natural products, such as diterpenes, triterpenes and steroids [1]. The tricyclic cores of all these compounds can be generated using this strategy with 14-membered trienic rings as precursors (scheme 1). The major possible drawback of this transannular approach lies in the construction of the large rings required. Indeed, our transannular Diels-Alder investigation study had revealed that some 14-membered trienic rings were difficult to obtain by direct intramolecular S_N2 displacement of an allylic chloride by a malonate anion (disconnection A, scheme 1). Although this direct S_N2 type macrocyclization procedure [2] was effective in most cases, an alternative approach (disconnection B, scheme 1) based on an intramolecular Michael addition [3] was investigated [4]. However, the macrocyclization of ynones to the macrocyclic enone precursors met with little success leading to moderate yields of isomeric enones (*cis* and *trans* mixtures). Thus, a third disconnection (C, scheme 1), also based on Michael addition macrocyclizations, was devised, taking advantage of recent interesting results in our laboratory [5]. This new path leads to completely controlled diene geometries and is the subject the present report.

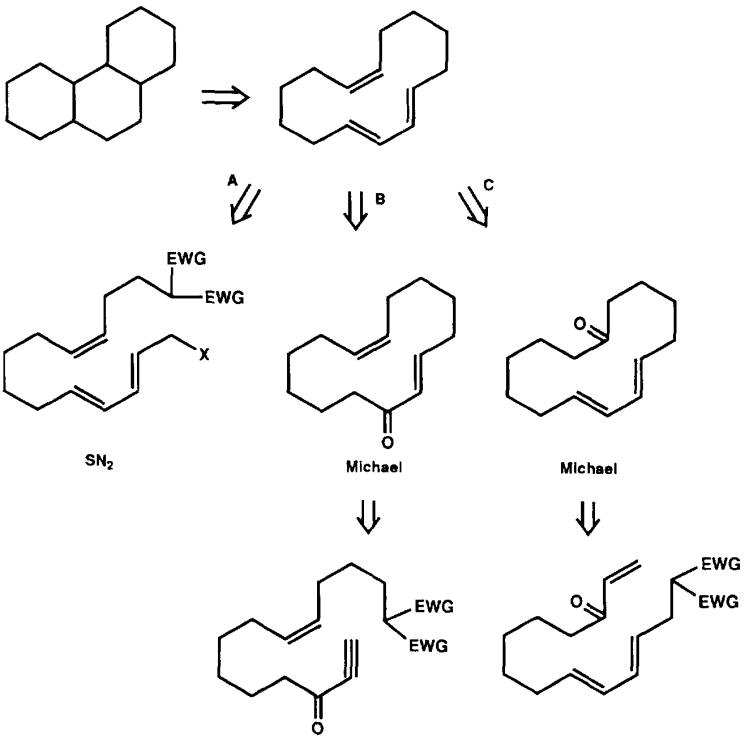
Chemistry

Three macrocyclization processes have been investigated (scheme 2) starting from the enones **1**, **2** and **3** differing only from their diene geometries : *trans*-acetylene (TA), *trans-cis* (TC) and *trans-trans* (TT), respectively. Each of these materials should give two bicycles with either *cis* or *trans* ring junctions when they are treated under Michael addition conditions. The syntheses of compounds **1**, **2** and **3** have been carried out according to schemes 3-6. The enone precursor **15** (scheme 3), common to the preparations of compounds **1**, **2** and **3**, was obtained from aldehyde **10** [6]. Vinyl Grignard addition to the aldehyde **10** gave the allylic secondary alcohol **11** in 53% yield. The alcohol **11** was protected as acetate **12** in 89% yield, and then the tetrahydropyranyl ether group was cleaved with pyridinium *para*-toluenesulfonate [7] in 76% yield. The alcohol **13** was transformed into the mesylate **14** by means of methanesulfonyl chloride and triethylamine. The mesylate **14** was then coupled, without purification, with sodium dimethyl malonate in the presence of potassium iodide to yield the substituted malonate **15** in 83% yield from **13**.

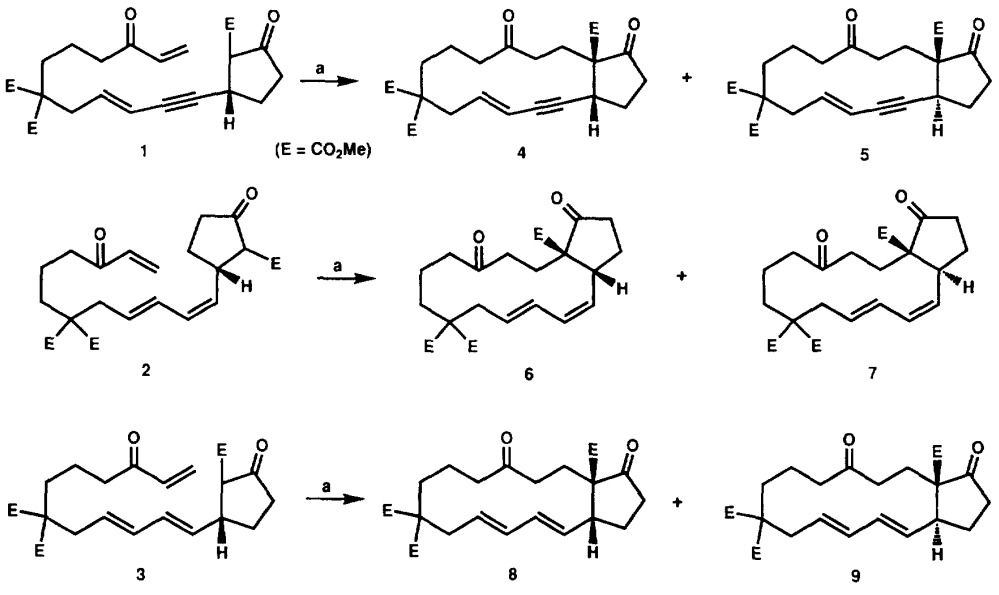
The Michael addition precursor 1 (scheme 4)

The enyne alcohol **16** [8] was protected as the silyl ether **17** in 96% yield. The acetylenic anion of **17** was added in a Michael fashion in the presence of dimethyl aluminium chloride to the enone **18** [9] to give the coupled product **19** (*trans* relationship) and its diastereomer (overall yield : 64%; 90% of **19**) which could not be separated or properly characterized. Thus, the remaining steps from **19** to **1** were performed on a mixture of diastereomers where the *trans* isomer (ester *versus* chain) was always the major one (~90%); for reasons

* Correspondence and reprints

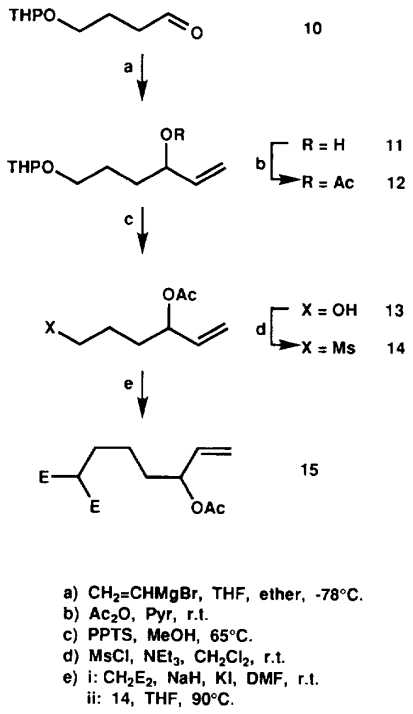


Scheme 1

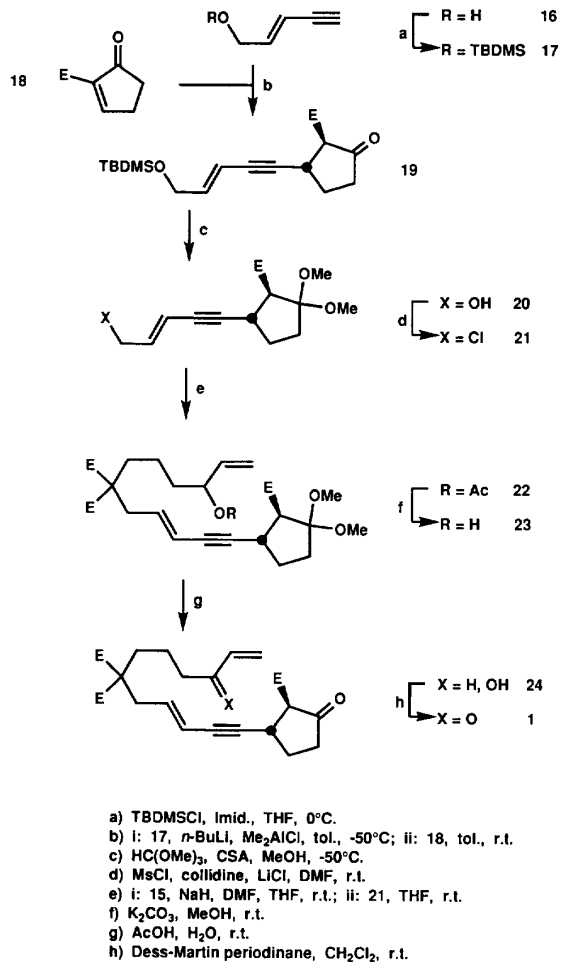


Scheme 2

of clarity, only this *trans* diastereomer will be considered in the forthcoming discussion. The ketoether **19** was protected as a dimethoxy ketal with concomitant cleavage of the silyl ether group by means of trimethyl orthoformate and camphor sulfonic acid in methanol in 77% yield. The alcohol **20** was transformed into chloride **21** using Meyers' conditions [10] in 83% yield. The allylic chlorine atom was subsequently displaced by the sodium anion of **15** to afford triester **22** in 67% yield. Both the acetate and the ketal were sequentially cleaved



Scheme 3



Scheme 4

under basic and acidic conditions respectively in 93 and 97% yield to the keto alcohol **24**. Oxidation of allylic alcohol **24** by means of Dess-Martin periodinane [11] gave precursor **1** in 92% yield.

The Michael addition precursor 2 (scheme 5)

The alkyne **20** was reduced to the *cis*-alkene **25** using dicyclohexylborane in 58% yield. The dienol **25** was transformed into the precursor **2** by the same five-step procedure used to prepare **1** from **20** and in 29% overall yield.

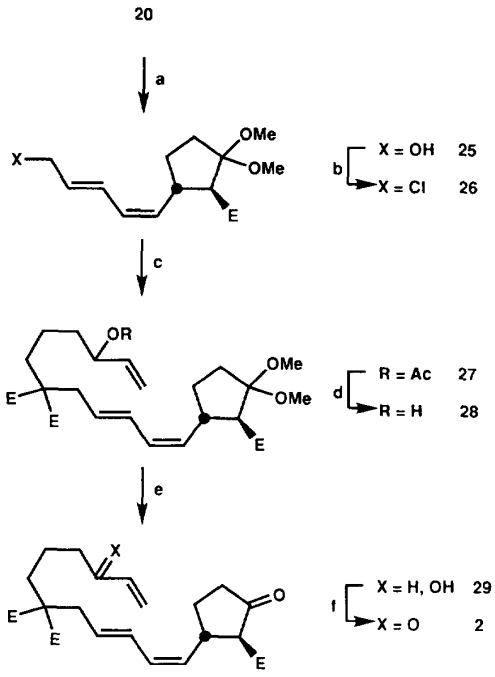
The Michael addition precursor 3 (scheme 6)

The allylic alcohol **25** was oxidized to aldehyde **30** by means of manganese dioxide in 86% yield. Isomerization of the *trans-cis*-diene **30** into the *trans-trans* isomer **31** was accomplished with iodine (90% yield). Reduction of aldehyde **31** with sodium borohydride provided alcohol **32** in 69% yield. Subsequent transformation of alcohol **32** into the precursor **3** was performed according to the same five-step procedure used to prepare **1** from alcohol **20** (29% overall yield).

Results and discussion

The three Michael addition precursors **1**, **2** and **3** were treated under similar conditions (scheme 2, table I) in order to obtain the corresponding macrocycles. Thus, slow addition of the TA precursor **1** to a cesium carbonate suspension in acetonitrile (final concentration of **1** : 2×10^{-3} M) at room temperature afforded a mixture of two cyclic dimers **37** (scheme 7) (yield : 25%; ratio : 90:10) whose stereochemistries (four chiral centers) could not be assessed. No cyclic monomers **4** and **5** were observed. Identical treatment of the TC precursor **2** afforded the cyclic monomer **7** with a *trans* ring junction as the sole product (yield : 90%) (structure confirmed by X-ray crystal analysis) [12]. The same conditions applied to the TT precursor **3** yielded 8% of cyclic monomer **8** (*cis* ring junction) (structure confirmed by X-ray crystal analysis)' [12] and 40% of 2 cyclic dimers **38** (scheme 7) (ratio 90:10) whose stereochemistries at the ring junctions are thought to be *trans* on the grounds that the ring junction proton NMR signals have values below 3.0 ppm [5]. Slow injection (10 h) of the precursor **3** to a well-stirred suspension of cesium carbonate led qualitatively to the same mixture, but the monomer **8** was the major product (30% yield) and the quantity of cyclic dimer **38** was, as expected, significantly diminished (27% yield).

Simple conclusions can be drawn from these data. Due to the size of the rings desired (14-membered) and the medium to high dilution conditions used for the macrocyclizations, we should theoretically approach



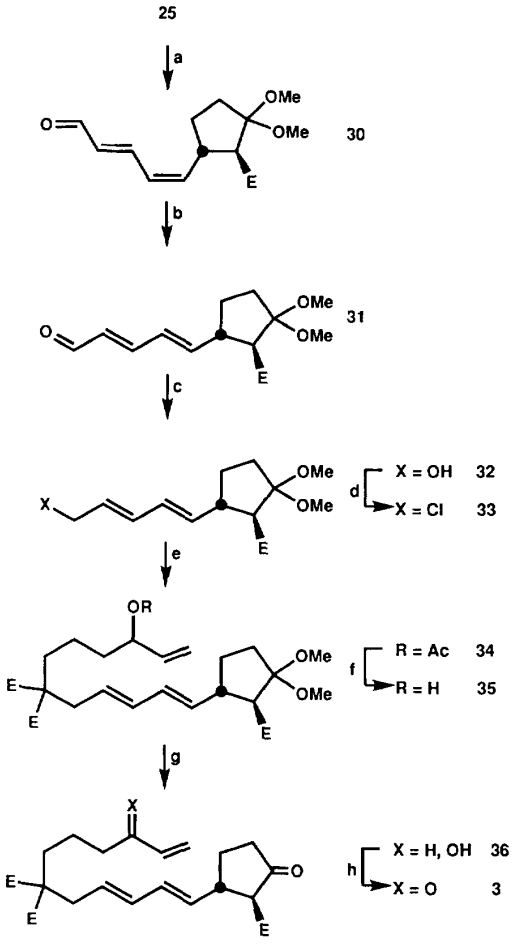
a) Dicyclohexylborane, THF, AcOH, 0°C.
b) MsCl, collidine, LiCl, DMF, r.t.
c) i: 15, NaH, DMF, THF, r.t.; ii: 26, THF, r.t.
d) K_2CO_3, MeOH, r.t.
e) AcOH, H_2O, r.t.
f) Dess-Martin periodinane, CH_2Cl_2, r.t.

Scheme 5

the case of intermolecular Michael addition and facilitate cyclic monomers over dimers and polymers. Intermolecular addition would give rise to *trans* adducts for obvious steric reasons. Consequently, this type of *trans* junction should also be observed in constraint-free macrocyclization processes.

A *trans* junction adduct is formed from the TC precursor **2** only. Moreover, this adduct **7** is formed in 90% yield with no trace of *cis* junction adduct **6** or dimer. As a result, the macrocyclization of **2** compares completely with an intermolecular process, devoid of any unfavorable constraint or steric factors. As regards the isomeric TT precursor **3**, the opposite ring junction stereochemistry is observed in the cyclic monomer **8** and a great deal of cyclic dimer is also formed. These data demonstrate how difficult the macrocyclization is in the present case in which only one double bond geometry has been modified compared with the previous case.

Simple Dreiding model manipulations of these rather conformationally restricted isomers **2** and **3** show that the TC isomer **2** can adopt a sterically free geometry corresponding roughly to a Michael addition transition state leading to **7**. Such is not the case for the TT isomer **3**, whose fully elongated *s-trans* diene moves the two reacting centers away from each other. Thus, the transition state from **3** to the *trans* junction product **9** displays strong transannular steric interactions and



a) MnO_2, CH_2Cl_2, r.t.
b) I_2, C_6H_6, r.t.
c) $NaBH_4$, MeOH, -20°C.
d) MsCl, collidine, LiCl, DMF, r.t.
e) i: 15, NaH, DMF, THF, r.t.; ii: 33, THF, r.t.
f) K_2CO_3, MeOH, r.t.
g) AcOH, H_2O, r.t.
h) Dess-Martin periodinane, CH_2Cl_2, r.t.

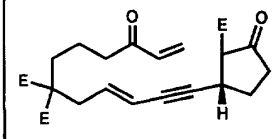
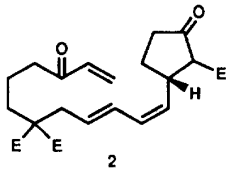
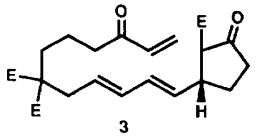
Scheme 6

cycle tensions. These disfavorable effects can be significantly reduced in the transition state leading to the *cis* junction adduct **8**. All the negative interactions found in the TT case are even enhanced in the TA precursor **1** macrocyclization, since only the cyclic dimer is produced.

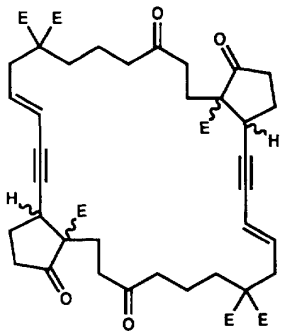
Conclusion

We have shown that the intramolecular Michael addition can be used to form 14-membered macrocycles, when the geometrical conformation allows it. In this regard, the macrocyclization of the *trans-cis* precursor **2** provides a high yield of the *trans* junction bicycle **7**. On the other hand, such a reaction performed on the *trans-trans* precursor **3** gives the *cis* junction macrocycle **8** along with the corresponding cyclic dimer, while the

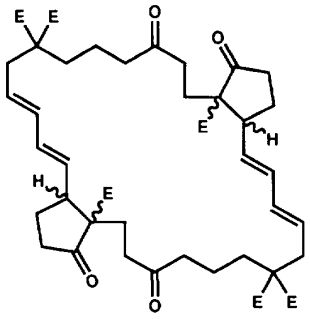
Table I

MICHAEL PRECURSOR	PRODUCTS			
	total yield	cyclic monomer *cis* fused	cyclic monomer *trans* fused	cyclic dimers
 (E=CO_2Me) 1	25%[1]	0%	0%	100%
		4	5	37
 2	90%[1]	0%	100%	0%
		6	7	
 3	48%[1]	17%	0%	83%
	57%[1]	53%	0%	47%
		8	9	38

[1] Injection over 1 h or less.
[2] Injection over 10 h.



37



38

2 observed diastereoisomers out of 8 in each case

Scheme 7

trans-acetylene precursor **1** gave the carbocyclic dimer only.

Experimental section

Melting points were recorded on a Rinco M-50 apparatus and are uncorrected. MS data were determined at 70 eV on a VG Micromass ZAB-1F spectrometer. IR absorption spectra were measured on a Perkin Elmer 681 from neat compounds or chloroform solutions. Proton (^{1}H) NMR spectra were recorded on a Bruker WM-250. Chemical shifts are reported relative to TMS (δ 0.00) with residual $CHCl_3$ as internal standard (δ 7.26) or residual C_6D_6 (δ 7.21).

All reactions were conducted in oven-dried (120°C) or flame-dried glassware under an atmosphere of dry argon, unless otherwise stated.

• *6-[(Tetrahydropyran-2-yl)oxy] hex-1-en-3-ol* **11**

The aldehyde **10** (1.72 g, 10.0 mmol) in ether (30 mL) was added to a stirred solution of vinylmagnesium bromide (28 mL, 1 M in tetrahydrofuran, 28.0 mmol) in tetrahydrofuran (22 mL) at −78°C. The resulting mixture was stirred for a further 15 min, and then saturated aqueous ammonium chloride was added. Ether extraction, drying ($MgSO_4$) and removal of solvent afforded an oil which was purified by chromatography on silica gel (ethyl acetate/hexane, 1:4) to give the title compound (1.76 g, 88%).

IR ($CHCl_3$) : 3 620, 3 440 cm^{-1}.

^{1}H NMR ($CDCl_3$, δ ppm) : 5.87 (1H, ddd, J = 6, 10 and 16 Hz, C*H*=CH_2), 5.23 (1H, dd, J = 17.5 and 1.5 Hz, CH=C*H*H), 5.09 (1H, dd, J = 11 and 1.5 Hz, CH=CH*H*), 4.59 (1H, dd, J = 3 and 4 Hz, OC*H*O THP), 4.15 (1H, m, C*H*OH), 3.9-3.75 (2H, m, CH_2O), 3.55-3.4

(2H, m, CH_2O), 2.39 (1H, br, OH), 1.5-1.85 (10H, m, $OCH_2(CH_2)_3$ THP and $THPOCH_2(CH_2)_2$).

MS (m/e) : 115 (M^+-THP), 99 (M^+-THPO).

• *3-Acetoxy-6-[(tetrahydropyran-2-yl)oxy]hex-1-ene* **12**

A solution of the alcohol **11** (1.30 g, 6.50 mmol) and acetic anhydride (1.55 mL, 16.20 mmol) in pyridine (13 mL) was stirred at room temperature for 12 h, and then diluted into ether. The resulting mixture was washed several times with cold aqueous citric acid (1 N), and then with saturated aqueous sodium bicarbonate. Drying ($MgSO_4$) and removal of solvent under reduced pressure yielded the title compound (1.25 g, 79%).

IR ($CHCl_3$) : 1 740 cm^{-1}.

^1H NMR ($CDCl_3$, δ ppm) : 5.78 (1H, ddd, J = 6.5, 10 and 17 Hz, CH=CH_2), 5.1-5.25 (3H, m, $AcOCHCH$=CH_2), 4.57 (1H, t, J = 3 Hz, $OCHO$ THP), 3.7-3.85 (2H, m, CH_2O), 3.4-3.55 (2H, m, CH_2O), 2.06 (1H, br, Ac), 1.45-1.85 (10H, m, $OCH_2(CH_2)_3$ THP and $THPOCH_2(CH_2)_2$).

MS (m/e : 182 (M^+-AcOH).

Exact mass calc : 182.1307 (M^+-AcOH); found : 182.1305.

• *4-Acetoxyhex-5-en-1-ol* **13**

A solution of the ether **12** (1.82 g, 4.94 mmol) and pyridinium p-toluenesulfonate (125 mg, 0.5 mmol) in ethanol (30 mL) was stirred at 65°C for 2 h. The solvent was removed under reduced pressure and the residue purified by chromatography on silica gel (ethyl acetate/hexane, 1:3) to give the title compound (721 mg, 92%).

IR ($CHCl_3$) : 3 630, 3 500, 1 740 cm^{-1}.

^1H NMR ($CDCl_3$, δ ppm) : 5.78 (1H, ddd, J = 6.5, 10 and 17 Hz, CH=CH_2), 5.1-5.25 (3H, m, $AcOCHCH$=CH_2), 3.65 (2H, t, J = 6.5 Hz, CH_2OH), 2.07 (1H, s, Ac), 1.45-1.8 (5H, m, $HOCH_2(CH_2)_2$.

MS (m/e) : 98 (M^+-AcOH).

Exact mass calc : 98.0732 (M^+-AcOH); found : 98.0730.

• *Dimethyl 5-acetoxyhept-6-ene-1,1-dicarboxylate* **15**

To a stirred solution of the alcohol **13** (710 mg, 4.50 mmol) and triethylamine (0.88 mL, 6.30 mmol) in dichloromethane (15 mL) at 0°C was added methanesulfonyl chloride (420 μL, 5.4 mmol). The reaction mixture was stirred for 3 h, and then poured over ice and extracted with dichloromethane. Drying ($MgSO_4$) and removal of the solvent gave the crude mesylate **14** (106 g, 100%) which was used directly in the next step. To a suspension of sodium hydride (60% in oil, 0.54 g, 13.5 mmol) in anhydrous tetrahydrofuran (20 mL) and N,N-dimethylformamide (10 mL) at 0°C was added dimethylmalonate (1.58 mL, 13.5 mmol). The mixture was stirred at room temperature for 0.5 h, then added to a solution of the mesylate **14** and potassium iodide (0.75 g, 4.6 mmol) in anhydrous N,N-dimethylformamide (10 mL). The mixture was stirred at 90°C for 12 h, and then poured over saturated aqueous ammonium chloride and extracted with ether. The organic solution was dried ($MgSO_4$) and the solvent was removed under reduced pressure. The crude product was purified by flash chromatography (ethyl acetate/hexane, 1:4) to afford the title compound as an oil (1.01 g, 83%).

IR ($CHCl_3$) : 1 730, 1 647 cm^{-1}.

^1H NMR ($CDCl_3$, δ ppm) : 5.73 (1H, ddd, J = 6.5, 10.5 and 17.5 Hz, CH=CH_2), 5.1-5.35 (3H, m, $AcOCHCH$=CH_2), 3.73 (6H, s, CO_2Me), 3.35 (1H, t, J = 7.5 Hz, $CH(CO_2Me)_2$), 2.05 (3H, s, Ac), 1.91 (2H, q, J = 8 Hz, $CH_2CH(CO_2Me)_2$), 1.64 (2H, m, CH_2CHOAc), 1.36 (2H, m, $CH_2CH_2CH_2$).

^{13}C NMR ($CDCl_3$, δ ppm) : 170.0, 169.4, 136.0, 116.7, 74.7, 52.2, 51.3, 33.4, 28.3, 22.7, 21.0.

MS (m/e) : 273 (MH^+), 230 (MH^+-Ac), 213 (M^+-AcOH).

• *5-[(tert-Butyldimethylsilyl)oxy]pent-3-en-1-yne* **17**

t-Butyldimethylsilyl chloride (8.31 g, 55 mmol) in dry tetrahydrofuran (200 mL) was added dropwise at 0°C to a mixture of the alcohol **16** (4.10 g, 50 mmol) and imidazole (7.5 g, 110 mmol) in dry tetrahydrofuran (300 mL) and the resulting mixture was stirred overnight at room temperature. Usual work-up, evaporation of the solvent and silica-gel flash chromatography (hexane) gave the title compound (9.40 g, 96%).

IR (CH_2Cl_2) : 3 310, 2 120, 1 140 cm^{-1}.

^1H NMR ($CDCl_3$, δ ppm) : 6.31 (1H, tt, J = 4 and 16 Hz, CH_2CH=CH), 5.75 (1H, dd, J = 2.5 and 16 Hz, CH=CHC≡CH), 4.23 (2H, J = 2.5 and 4 Hz, CH_2O), 2.87 (1H, d, J = 2.5 Hz, C≡CH), 0.91 (9H, s, t-Bu Si), 0.07 (6H, s, Me_2Si).

MS (m/e) : 196 (M^+), 139 (M^+-t-Bu).

Exact mass calc : 196.1283; found : 196.1282.

• *Methyl 2-{(3E)-5-[(t-butyldimethylsilyl)oxy]pent-3-en-1-ynyl}-5-oxocyclopentane-1-carboxylate* **19**

To a cold (−50°C) stirred solution of the enyne **17** (1.80 g, 9.17 mmol) in dry toluene (10 mL) was added n-butyllithium (5.8 mL, 1.6 M in hexane) and the mixture was stirred for 20 min. A solution of dimethylaluminium chloride (850 μL, 9.15 mmol) in toluene (6.4 mL) was then added and the resulting mixture stirred for 30 min. The temperature was allowed to rise to 0°C and a solution of the enoate **18** (950 mg, 6.78 mmol) in toluene (1.8 mL) was added over a period of 2 h. The reaction mixture was stirred at room temperature for an additional 12 h. Saturated aqueous potassium dihydrogen phosphate was added and the water layer was separated and extracted with ether. The combined organic extract was successively washed with dilute sulfuric acid (10%), saturated aqueous sodium bicarbonate, water and dried ($MgSO_4$). The crude oil obtained after evaporation of solvent was purified by flash chromatography (toluene/acetone, 50:1) to give the title compound as an oil (1.46 g, 64%).

IR ($CHCl_3$) : 1 759, 1 730 cm^{-1}.

^1H NMR ($CDCl_3$, δ ppm) : 6.16 (1H, dt, J = 16 and 4 Hz, CH=$CHCH_2$), 5.73 (1H, dq, J = 16 and 2 Hz, CH=CHC≡C), 4.21 (2H, dd, J = 4 and 2 Hz, CH_2OSi), 3.79 (3H, s, CO_2Me), 3.54 (1H, m, CHC≡C), 3.27 (1H, d, J = 10 Hz, $CHCO_2Me$), 2.2-2.6 (3H, m, CH_2), 1.85-2.05 (1H, m, CH_2), 0.91 (9H, s, Sit-Bu), 0.06 (6H, s, $SiMe_2$).

^{13}C NMR ($CDCl_3$, δ ppm) : 209.3, 168.2, 142.5, 108.3, 88.9, 81.0, 62.8, 61.2, 52.7, 37.6, 32.1, 28.2, 25.8, 18.4, −5.4.

MS (m/e) : 336 (M^+), 321 (M^+-Me), 305 (M^+-MeO), 279 (M^+-t-Bu).

Exact mass calc : 279.1053 (M^+-t-Bu); found : 279.1048.

• *Methyl 2-[(3E)-5-hydroxypent-3-en-1-ynyl]-5,5-dimethoxycyclopentane-1-carboxylate* **20**

A solution of trimethyl orthoformate (1.4 mL, 12.8 mmol), the ketoester **19** (1.46 g, 4.34 mmol) and camphorsulfonic acid (33 mg) in dry methanol (20 mL) was stirred for 5 h at 50°C. After cooling to room temperature, the mixture was poured over saturated aqueous sodium bicarbonate and extracted several times with dichloromethane. The combined

organic extract was dried ($MgSO_4$) and the crude oil obtained after solvent evaporation was purified by flash chromatography (hexane/ethyl acetate, 3:2) to give the title compound as an oil (893 mg, 77%).

IR ($CHCl_3$) : 3 611, 1 734, 1 457, 1 436 cm^{-1}.

^1H NMR ($CDCl_3$, δ ppm) : 6.17 (1H, dt, J = 16 and 5 Hz, CH=C*H*CH_2), 5.70 (1H, dq, J = 16 and 2 Hz, CH=C*H*C≡C), 4.17 (2H, dd, J = 5.5 and 2 Hz, CH_2OH), 3.73 (3H, s, CO_2Me), 3.38 (1H, m, C*H*C≡C), 3.29 (3H, s, CO*Me*), 3.18 (3H, s, CO*Me*), 3.04 (1H, d, J = 8.5 Hz, C*H*CO_2Me), 1.6-2.2 (4H, m, $(CH_2)_2$).

^{13}C NMR ($CDCl_3$, δ ppm) : 171.6, 141.0, 111.0, 110.7, 91.8, 79.1, 63.0, 57.9, 52.1, 50.1, 49.0, 36.0, 33.1, 30.4.

MS (m/e) : 268 (M^+), 251 (M^+-OH), 237 (M^+-MeO).

Exact mass calc : 268.1311 (M^+); found : 268.1306.

General procedure for the preparation of allylic chlorides

• *Methyl 2-[(3E)-5-chloropent-3-en-1-ynyl]-5,5-dimethoxycyclopentane-1-carboxylate* **21**

To a mixture of 2,4,6-collidine (135 μL, 102 mmol), methanesulfonyl chloride (75 μL, 970 μmol), lithium chloride (40 mg, 940 μmol) and dry *N,N*-dimethylformamide (3 mL) was added a solution of the alcohol **20** (217 mg, 810 mmol) in *N,N*-dimethylformamide (1.5 mL). The mixture was stirred for 2 h at 0°C, and then warmed to room temperature and stirred for another 1.25 h. Cold water was added to the mixture which was extracted three times with ether. The combined organic extract was washed twice with saturated aqueous cupric nitrate, and then with water, dried ($MgSO_4$) and concentrated. Flash chromatography (hexane/ethyl acetate, 4:1) of the residual material gave the title compound as an oil (192 mg, 83%).

IR ($CHCl_3$) : 2 219, 1 734, 1 458, 1 437 cm^{-1}.

^1H NMR ($CDCl_3$, δ ppm) : 6.11 (1H, dt, J = 15.5 and 7 Hz, CH=C*H*CH_2), 5.73 (1H, ddt, J = 15.5 and 1 Hz, CH=C*H*C≡C), 4.05 (2H, dd, J = 7 and 1 Hz, CH_2Cl), 3.73 (3H, s, CO_2Me), 3.39 (1H, m, C*H*C≡C), 3.29 (3H, s, CO*Me*), 3.18 (3H, s, CO*Me*), 3.04 (1H, d, J = 8.5 Hz, C*H*CO_2Me), 1.6-2.2 (4H, m, $(CH_2)_2$).

^{13}C NMR ($CDCl_3$, δ ppm) : 171.5, 136.9, 114.3, 111.0, 93.4, 78.4, 57.8, 52.1, 50.1, 49.0, 44.2, 36.0, 33.0, 30.3.

MS (m/e) : 286 (M^+), 271 (M^+-Me), 258, 255 (M^+-MeO), 251 (M^+-Cl).

Exact mass calc : 286.0972 (M^+); found : 286.0968.

• *Methyl 2-[(1Z,3E)-5-chloropenta-1,3-dienyl]-5,5-dimethoxycyclopentane-1-carboxylate* **26**

Yield : 56%.

IR ($CHCl_3$) : 1 733, 1 458, 1 437 cm^{-1}.

^1H NMR ($CDCl_3$, δ ppm) : 6.63 (1H, ddq, J = 15, 11 and 1 Hz, C*H*=$CHCH_2$), 5.94 (1H, t, J = 11 Hz, CHCH=C*H*), 5.75 (1H, dt, J = 15 and 7.5 Hz, CH=C*H*CH_2), 5.32 (1H, t, J = 10 Hz, CHC*H*=CH), 4.11 (2H, d, J = 7.5 Hz, CH_2Cl), 3.67 (3H, s, CO_2Me), 3.54 (1H, m, C*H*CH=CH), 3.25 (3H, s, CO*Me*), 3.19 (3H, s, CO*Me*), 2.70 (1H, d, J = 8.5 Hz, C*H*CO_2Me), 1.8-2.1 (3H, m, CH_2), 1.35-1.6 (1H, m, C*H*H).

^{13}C NMR ($CDCl_3$, δ ppm) : 171.9, 135.8, 129.5, 128.9, 127.9, 11 1.5, 58.0, 51.8, 50.0, 48.8, 45.2, 40.8, 36.3, 30.3.

MS (m/e) : 257 (M^+-MeO), 253 (M^+-Cl).

Exact mass calc : 257.0944 (M^+-MeO); found : 257.0941.

• *Methyl 2-[(1E,3E)-5-chloropenta-1,3-dienyl]-5,5-dimethoxycyclopentane-1-carboxylate* **33**

Yield : 65%.

IR ($CHCl_3$) : 1 733, 1 458, 1 436 cm^{-1}.

^1H NMR ($CDCl_3$, δ ppm) : 6.22 (1H, ddt, J = 15, 10.5 and 1 Hz, C*H*=$CHCH_2$), 6.06 (1H, dd, J = 15 and 10.5 Hz, CHCH=C*H*), 5.72 (1H, dt, J = 14.5, 7.5 Hz, CH=C*H*CH_2), 5.65 (1H, dd, J = 15 and 8 Hz, CHC*H*=CH), 4.09 (2H, dd, J = 7.5 and 1 Hz, CH_2Cl), 3.70 (3H, s, CO_2Me), 3.27 (3H, s, CO*Me*), 3.19 (3H, s, CO*Me*), 3.14 (1H, m, C*H*CH=CH), 2.75 (1H, d, J = 9 Hz, C*H*CO_2Me), 1.8-2.05 (3H, m, CH_2), 1.4-1.6 (1H, m, C*H*H).

^{13}C NMR (C_6D_6, δ ppm) : 171.4, 138.2, 134.2, 129.3, 127.5, 111.9, 57.8, 51.5, 49.7, 48.7, 45.7, 45.1, 36.6, 30.0.

MS (m/e) : 257 (M^+-MeO), 253 (M^+-Cl).

Exact mass calc : 257.0945 (M^+-MeO); found : 257.0941; 253.1440 (M^+-Cl); found : 253.1440.

General procedure for the preparation of disubstituted malonates

• *Methyl 5,5-dimethoxy-2-[(3E)-10-acetoxy-6,6-bis(methoxycarbonyl)dodeca-3,11-dien-1-ynyl] cyclopentane-1-carboxylate* **22**

To a stirred suspension of sodium hydride (16 mg, 60% dispersion in mineral oil, 387 μmol) in *N,N*-dimethylformamide (1.2 mL) at 0°C was added a solution of the malonate **15** (112 mg, 390 μmol) in tetrahydrofuran (3 mL). After the mixture had been stirred for 15 min, the chloride **21** (117 mg, 430 μmol) dissolved in tetrahydrofuran (2 mL) was introduced and the resulting mixture was stirred at 0°C for 20 min and then at room temperature for 6 h. Saturated aqueous ammonium chloride was added and the resulting mixture extracted three times with ether and hexane (1:1). The combined organic phase was dried ($MgSO_4$) and concentrated. Flash chromatography of the crude oil (hexane/ethyl acetate, 4:1 and then 3:2) gave the unreacted chloride **21** (30 mg, 27%) and then the title compound **22** (137 mg, 67%).

IR ($CHCl_3$) : 1 733, 1 458, 1 437 cm^{-1}.

^1H NMR ($CDCl_3$, δ ppm) : 5.6-5.9 (2H, m, CH=C*H*CH_2 and C*H*=CH_2), 5.48 (1H, br d, J = 15.5 Hz, CH=C*H*C≡C), 5.1-5.3 (3H, m, CH_2=CHC*H*OAc), 3.73 (3H, s, CO_2Me), 3.71 (6H, s, CO_2Me), 3.36 (1H, m, C*H*C≡C), 3.29 (3H, s, CO*Me*), 3.17 (3H, s, CO*Me*), 3.02 (1H, d, J = 8.5 Hz, C*H*CO_2Me), 2.64 (2H, d, J = 7.5 Hz, CH=CHC*H*$_2$), 2.05 (3H, s, *Ac*), 1.5-2.15 (8H, m, CH_2), 1.19 (2H, m, CH_2).

^{13}C NMR ($CDCl_3$, δ ppm) : 171.5, 171.2, 170.2, 136.5, 136.1, 116.9, 113.7, 110.9, 90.6, 79.2, 74.2, 57.8, 57.4, 52.4, 52.0, 50.0, 48.9, 36.2, 36.0 33.9, 33.0, 32.2, 30.3, 21.1, 19.5.

MS (m/e) : 522 (M^+), 491 (M^+-MeO).

Exact mass calc : 522.2465 (M^+); found : 522.2462.

• *Methyl 2-[(1Z,3E)-10-acetoxy-6,6-bis(methoxycarbonyl)-5,5-dimethoxydodeca-1,3,11-trienyl] cyclopentane-1-carboxylate* **27**

Yield : 66%; recovered starting chloride : 17%.

IR ($CHCl_3$) : 1 732, 1 458, 1 436 cm^{-1}.

^1H NMR ($CDCl_3$, δ ppm) : 6.40 (1H, dd, J = 15 and 11 Hz, C*H*=$CHCH_2$), 5.88 (1H, t, J = 11 Hz, CHCH=C*H*), 5.73 (1H, m, C*H*=CH_2), 5.45 (1H, dt, J = 15 and 7.5 Hz, CH=C*H*CH_2), 5.1-5.3 (4H, m, CHC*H*=CH and CH_2=CHC*H*OAc), 3.71 (3H, s, CO_2Me), 3.70 (3H, s, CO_2Me), 3.67 (3H, s, CO_2Me), 3.51 (1H, m,

C*H*CH=CH), 3.26 (3H, s, CO*Me*), 3.19 (3H, s, CO*Me*), 2.69 (1H, d, J = 8.5 Hz, C*H*CO_2Me), 2.66 (2H, d, J = 8 Hz, CH=CHC*H*$_2$), 2.04 (3H, s, *Ac*), 1.8-2.05 (SH, m, C*H*$_2$), 1.35-1.75 (3H, m, C*H*$_2$), 1.15-1.3 (2H, m, C*H*$_2$).

^{13}C NMR ($CDCl_3$, δ ppm) : 171.9, 171.5, 170.2, 136.1, 133.1, 129.5, 128.8, 128.1, 116.8, 111.5, 74.2, 58.0, 57.8, 52.3, 51.7, 50.0, 48.8, 40.8, 36.2, 34.0, 32.3, 30.3, 21.1, 19.6.

MS (m/e) : 492 (M^+-MeOH), 459, 433 (M^+-MeOH-CO_2Me).

Exact mass calc : 492.2359 (M^+-MeOH); found : 492.2350.

• *Methyl-2-[(1*E*,3*E*)-10-acetoxy-6,6-bis(methoxycarbonyl)-5,5-dimethoxydodeca-1,3,11-trienyl]cyclopentane-1-carboxylate* **34**

Yield : 59%; recovered starting chloride : 34%.

IR ($CHCl_3$) : 1 731 , 1 458, 1 436 cm^{-1}.

^{1}H NMR ($CDCl_3$, δ ppm) : 5.85-6.00 (2H, m, CH=C*H*CH*H*=CH), 5.70 (1H, ddd, J = 17.5, 10.5 and 6.5 Hz, C*H*=CH$_2$), 5.25-5.55 (2H, m, *H*C=CHCH=C*H*), 5.1-5.25 (3H, m, C*H*$_2$=CHC*H*OAc), 3.66 (9H, s, CO_2*Me*), 3.23 (3H, s, CO*Me*), 3.15 (3H, s, CO*Me*), 3.06 (1H, m, C*H*CH=CH), 2.70 (1H, d, J = 9 Hz, C*H*CO_2Me), 2.58 (2H, d, J = 7.5 Hz, CH=CHC*H*$_2$), 2.01 (3H, s, *Ac*), 1.75-2.0 (5H, m, C*H*$_2$), 1.35-1.7 (3H, m, C*H*$_2$), 1.1-1.25 (2H, m, C*H*$_2$).

^{13}C NMR ($CDCl_3$, δ ppm) : 172.0, 171.5, 170.1, 136.1, 134.9, 133.8, 129.7, 126.0, 116.8, 111.4, 74.2, 57.7, 57.5, 52.3, 51.8, 49.9, 48.7, 45.1, 36.2, 36.0, 34.0, 32.1, 29.6, 21.1, 19.5.

MS (m/e) : 524 (M^+), 492 (M^+-MeOH).

Exact mass calc : 524.2621 (M^+); found : 524.2616.

General procedure for the cleavage of acetates

• *Methyl 2-[(3*E*)-10-hydroxy-6,6-bis(methoxycarbonyl)-5,5-dimethoxydodeca-3,11-dien-1-ynyl]cyclopentane-1-carboxylate* **23**

Potassium carbonate (20 mg, 145 μmol) was added to a solution of the acetate **22** (137 mg, 262 μmol) in methanol (5.5 mL) and the resulting suspension was stirred for 3.5 h at room temperature. Saturated aqueous ammonium chloride was added and the mixture was extracted three times with dichloromethane. The combined organic extract was dried ($MgSO_4$) and concentrated. The residue was purified by flash chromatography on silica gel (toluene/ethyl acetate, 3:1) to give the title compound as an oil (117 mg, 93%).

IR ($CHCl_3$) : 3 608, 1 732, 1 458, 1 437 cm^{-1}.

^{1}H NMR ($CDCl_3$, δ ppm) : 5.75-5.9 (2H, m, CH=C*H*CH$_2$ and C*H*=CH$_2$), 5.46 (1H, br d, J = 15.5 Hz, CH=C*H*C≡C), 5.18 (1H, dt, J = 17 and 1.5 Hz, CH=C*H*H), 5.07 (1H, dt, J = 10.5 and 1 Hz, CH=CH*H*), 4.06 (1H, q, J = 6.5 Hz, C*H*OH), 3.70 (3H, s, CO_2*Me*), 3.69 (6H, s, CO_2*Me*), 3.33 (1H, m, C*H*C≡C), 3.26 (3H, s, CO*Me*), 3.15 (3H, s, CO*Me*), 3.00 (1H, d, J = 8.5 Hz, C*H*CO_2Me), 2.63 (2H, dd, J = 7.5 and 1 Hz, CH=CHC*H*$_2$), 1.6-2.1 (6H, m, C*H*$_2$), 1.45-1.55 (2H, m, C*H*$_2$), 1.1-1.35 (2H, m, C*H*$_2$).

^{13}C NMR ($CDCl_3$, δ ppm) : 171.5, 171.4, 140.9, 136.6, 114.8, 113.7, 110.9, 90.5, 79.3, 72.5, 57.8, 57.5, 52.4, 52.0, 50.0, 48.9, 36.7, 36.1, 36.0, 33.0, 32.2, 30.3, 19.8.

MS (m/e) : 480 (M^+), 465 (M^+-Me), 449 (M^+-MeO).

Exact mass calc : 480.2359 (M^+); found : 480.2352.

• *Methyl 2-[(1*Z*,3*E*)-10-hydroxy-6,6-bis(methoxycarbonyl)-5,5-dimethoxydodeca-1,3,11-trienyl]cyclopentane-1-carboxylate* **28**

Yield : 94%.

IR ($CHCl_3$) : 3 601, 1 732, 1 457, 1 437 cm^{-1}.

^{1}H NMR ($CDCl_3$, δ ppm) : 6.38 (1H, dd, J = 15 and 11 Hz, C*H*=CHCH$_2$), 5.83 (1H, t, J = 11 Hz, CHCH=C*H*), 5.79 (1H, m, C*H*=CH$_2$), 5.38 (1H, m, J = 15 and 7.5 Hz, CH=C*H*CH$_2$), 5.16 (1H, br d, J = 17 Hz, CH=C*H*H), 5.11 (1H, t, J = 10.5 Hz, CHC*H*=CH), 5.02 (1H, dt, J = 10.5 and 1 Hz, CH=CH*H*), 4.05 (1H, m, J = 6 Hz, C*H*OH), 3.66 (6H, s, CO_2*Me*), 3.61 (3H, s, CO_2*Me*), 3.47 (1H, m, C*H*CH=CH), 3.21 (3H, s, CO*Me*), 3.14 (3H, s, CO*Me*), 2.64 (3H, d, J = 8.5 Hz, C*H*CO_2Me and CH=CHC*H*$_2$), 1.7-2.0 (5H, m, C*H*$_2$), 1.1-1.55 (5H, m, C*H*$_2$).

^{13}C NMR ($CDCl_3$, δ ppm) : 172.0, 171.5, 141.1, 132.8, 129.5, 128.9, 128.1, 114.2, 111.4, 72.4, 71.9, 57.9, 57.6, 52.3, 51.8, 49.9, 48.7, 40.8, 36.9, 36.7, 36.3, 35.7, 32.0, 31.8, 30.3, 19.8, 19.4.

MS (m/e) : 482 (M^+), 451 (M^+-MeO).

Exact mass calc : 451.2332 (M^+-MeO); found : 451.2324.

• *Methyl 2-[(1*E*,3*E*)-10-hydroxy-6,6-bis(methoxycarbonyl)-5,5-dimethoxydodeca-1,3,11-trienyl]cyclopentane-1-carboxylate* **35**

Yield : 91%.

IR ($CHCl_3$) : 3 608, 1 731, 1 458, 1 436 cm^{-1}.

^{1}H NMR ($CDCl_3$, δ ppm) : 5.95 (2H, m, CH=C*H*CH*H*=CH), 5.80 (1H, ddd, J = 17, 10.5 and 6 Hz, C*H*=CH$_2$), 5.3-5.55 (2H, m, *H*C=CHCH=C*H*), 5.17 (1H, dt, J = 17 and 1.5 Hz, CH=C*H*H), 5.06 (1H, dt, J = 10.5 and 1 Hz, CH=CH*H*), 4.06 (1H, q, J = 6 Hz, C*H*OH), 3.67 (9H, s, CO_2*Me*), 3.23 (s, 3H, CO*Me*), 3.15 (3H, s, CO*Me*), 2.95-3.15 (1H, m, *H*CCH=CH), 2.70 (1H, d, J = 9 Hz, C*H*CO_2Me), 2.60 (2H, d, J = 7.5 Hz, CH=CHC*H*$_2$), 1.75-2.0 (6H, m, C*H*$_2$ and O*H*), 1.1-1.6 (5H, m, C*H*$_2$).

^{13}C NMR ($CDCl_3$, δ ppm) : 172.1, 171.6, 140.9, 134.8, 133.8, 129.8, 126.1, 114.7, 111.4, 72.5, 57.8, 57.5, 52.3, 51.8, 49.9, 48.7, 45.1, 36.8, 36.2, 35.9, 32.2, 29.7, 19.8.

MS (m/e) : 482 (M^+), 450 (M^+-MeOH), 432 (M^+-MeOH-H_2O).

Exact mass calc : 450.2253 (M^+-MeOH) : found : 450.2248.

General procedure for the cleavage of dimethyl ketals

• *Methyl 2-[(3*E*)-10-hydroxy-6,6-bis(methoxycarbonyl)dodeca-3,11-dien-1-ynyl]-5-oxocyclopentane-1-carboxylate* **24**

A solution of the ketal **23** (117 mg, 244 μmol) in water (1 mL) and acetic acid (4 mL) was stirred at room temperature for 4 h. Ether was added and the resulting solution was washed three times with saturated aqueous sodium bicarbonate, dried ($MgSO_4$) and concentrated. Filtration of the crude oil over silica gel (hexane/ethyl acetate, 1:1) afforded the title compound as an oil (103 mg, 97%).

IR ($CHCl_3$) : 3 601, 1 757, 1 732, 1 458, 1 437 cm^{-1}.

^{1}H NMR ($CDCl_3$, δ ppm) : 5.75-5.95 (2H, m, CH=C*H*CH$_2$, and C*H*=CH$_2$), 5.48 (1H, ddd, J = 16 Hz, CH=C*H*C≡C), 5.19 (1H, dt, J = 17 and 1.5 Hz, CH=C*H*H), 5.08 (1H, dt, J = 10.5 and 1 Hz, CH=CH*H*), 4.08 (1H, q, J = 6.5 Hz, C*H*OH), 3.77 (3H, s, CO_2*Me*), 3.70 (s, 6H, CO_2*Me*), 3.49 (1H, m, C*H*C≡C), 3.22 (1H, d, J = 10 Hz, C*H*CO_2Me), 2.65 (2H, dd, J = 7.5 and 1 Hz, CH=CHC*H*$_2$), 2.2-2.55 (3H, m, C*H*$_2$), 1.8-2.0 (3H, m, C*H*$_2$), 1.45-1.55 (2H, m, C*H*$_2$), 1.1-1.35 (2H, m, C*H*$_2$).

^{13}C NMR ($CDCl_3$, δ ppm) : 209.1, 171.3, 168.1, 140.9, 137.7, 114.8, 113.1, 88.4, 80.7, 72.5, 61.0, 57.5, 52.7, 52.5, 37.5, 36.7, 36.2, 32.3, 31.9, 28.1, 19.8.

MS (m/e) : 434 (M^+), 416 (M^+-H_2O).

Exact mass calc : 434.1941 (M^+); found : 434.1929.

• *Methyl 2-[(1Z,3E)-10-hydroxy-6,6-bis(methoxycarbonyl)dodeca-1,3,11-trienyl]-5-oxocyclopentane-1-carboxylate* **29**

Yield : 96%.

IR ($CHCl_3$) : 3 608, 1 753, 1 728, 1 457, 1 437 cm^{-1}.

^{1}H NMR ($CDCl_3$, δ ppm) : 6.40 (1H, dd, J = 15 and 11 Hz, C*H*=CHCH$_2$), 5.98 (1H, t, J = 11 Hz, CHCH=C*H*), 5.80 (1H, dddd, J = 17, 10, 6 and 2 Hz, C*H*=CH$_2$), 5.48 (1H, dt, J = 15 and 8 Hz, CH=C*H*CH$_2$), 5.1-5.25 (2H, m, CHC*H*=CH and CH=C*H*H), 5.04 (1H, dt, J = 10.5 and 1.5 Hz, CH=CH*H*), 4.06 (1H, m, C*H*OH), 3.68 (9H, s, CO_2Me), 3.60 (1H, m, C*H*CH=CH), 2.93 (1H, d, J = 11.5 Hz, C*H*CO$_2$Me), 2.68 (2H, d, J = 7.5 Hz, CH=CHC*H*$_2$), 1.1-2.5 (10H, m, C*H*$_2$).

^{13}C NMR ($CDCl_3$, δ ppm) : 210.5, 171.5, 169.1, 141.1, 130.5, 129.5, 128.9, 114.3, 72.4, 72.0, 61.5, 57.6, 52.4, 39.7, 38.0, 37.0, 36.7, 35.8, 32.1, 32.0, 28.0, 19.8, 19.5.

MS (m/e) : 437 (MH^+), 419 (MH^+-H_2O), 405 (M^+-MeO).

Exact mass calc : 437.2175 (MH^+); found : 437.2165.

• *Methyl 2-[(1E,3E)-10-hydroxy-6,6-bis(methoxycarbonyl)dodeca-1,3,11-trienyl]-5-oxocyclopentane-1-carboxylate* **36**

Yield : 94%.

IR ($CHCl_3$) : 3 608, 1 753, 1 729, 1 458, 1 437 cm^{-1}.

^{1}H NMR ($CDCl_3$, δ ppm) : 5.95-6.15 (2H, m, CH=C*H*C*H*=CH), 5.82 (1H, ddd, J = 17, 10 and 6 Hz, C*H*=CH$_2$), 5.35-5.6 (2H, m, C*H*=CHCH=C*H*), 5.19 (1H, dt, J = 17 and 1 Hz, CH=C*H*H), 5.08 (1H, dt, J = 10 and 1 Hz, CH=CH*H*), 4.08 (1H, br q, J = 6 Hz, C*H*OH), 3.74 (3H, s, CO_2Me), 3.69 (6H, s, CO_2Me), 3.20 (1H, m, C*H*CH=CH), 2.97 (1H, d, J = 11.5 Hz, C*H*CO$_2$Me), 2.64 (2H, d, J = 7.5 Hz, CH=CHC*H*$_2$), 2.15-2.5 (3H, m, C*H*$_2$), 1.15-1.95 (8H, m, C*H*$_2$ and O*H*).

^{13}C NMR ($CDCl_3$, δ ppm) : 210.6, 171.6, 168.9, 140.9, 133.3, 132.4, 130.9, 127.4, 114.7, 72.5, 61.1, 57.7, 52.5, 52.4, 43.8, 38.1, 36.7, 36.0, 32.2, 27.5, 19.8.

MS (m/e) : 436 (M^+), 418 (M^+-H_2O), 404 (M^+-MeOH).

Exact mass calc : 436.2097; found : 436.2092.

General procedure for the oxidation of allylic alcohols

• *Methyl 2-[(3E)-6,6-bis(methoxycarbonyl)-10-oxododeca-3,11-dien-1-ynyl]-5-oxocyclopentane-1-carboxylate* **1**

Dess-Martin periodinane (39 mg, 91 μmol) was added to a solution of the alcohol **24** (29 mg, 66 μmol) in dichloromethane (3 mL) and the mixture was stirred at room temperature for 20 min. Ether was added and the mixture was washed with a solution of sodium thiosulfate pentahydrate (140 mg, 564 mmol) in saturated aqueous sodium bicarbonate then with water. The organic layer was dried ($MgSO_4$), condensed and filtered over silica gel (hexane/ethyl acetate, 1:1) to afford the title compound as an oil (26 mg, 92%).

IR ($CHCl_3$) : 1 752, 1 731, 1 704, 1 681, 1 616, 1 458, 1 437 cm^{-1}.

^{1}H NMR ($CDCl_3$, δ ppm) : 6.33 (1H, dd, J = 17.5 and 10.5 Hz, C*H*=CH$_2$), 6.19 (1H, dd, J = 17.5 and 1.5 Hz, CH=C*H*H), 5.89 (1H, dt, J = 15.5, 7.5 Hz, CH=C*H*CH$_2$), 5.82 (1H, dd, J = 10.5, 1.5 Hz, CH=CH*H*), 5.50 (1H, m, J = 15.5 and 1.5 Hz, CH=C*H*C≡C), 3.78 (3H, s, CO_2Me), 3.72 (6H, s, CO_2Me), 3.50 (1H, m, C*H*C≡C), 3.23 (1H, d, J = 10 Hz, C*H*CO$_2$CH$_3$), 2.69 (2H, dd, J = 7.5 Hz and 1.5 Hz, CH=CHC*H*$_2$), 2.59 (2H, t, J = 7 Hz, C*H*$_2$C=O), 2.2-2.55 (3H, m, C*H*$_2$), 1.8-2.0 (3H, m, C*H*$_2$), 1.4-1.55 (2H, m, C*H*$_2$).

^{13}C NMR ($CDCl_3$, δ ppm) : 209,1, 199,6, 171.1, 168.1, 137.6, 136.4, 128.1, 113.2, 88.4, 80.7, 61.0, 57.5, 52.7, 52.5, 39.2, 37.5, 36.1, 32.0, 28.1, 18.2.

MS (m/e) : 433 (MH^+), 401 (M^+-MeO).

Exact mass calc : 432.1784; found : 432.1792.

• *Methyl 2-[(1Z,3E)-6,6-bis(methoxycarbonyl)-10-oxododeca-1,3,11-trienyl]-5-oxocyclopentane-1-carboxylate* **2**

Yield : 88%.

IR ($CHCl_3$) : 1 753, 1 730, 1 705, 1 681, 1 615, 1 458, 1 437 cm^{-1}.

^{1}H NMR ($CDCl_3$, δ ppm) : 6.40 (1H, dd, J = 15 and 11 Hz, C*H*=CHCH$_2$), 6.31 (1H, dd, J = 17.5 and 10.5 Hz, C*H*=CH$_2$), 6.17 (1H, dd, J = 17.5 and 1.5 Hz, CH=C*H*H), 6.00 (1H, t, J = 11 Hz, CHCH=C*H*), 5.80 (1H, dd, J = 10.5 and 1.5 Hz, CH=CH*H*), 5.54 (1H, m, J = 15 and 7.5 Hz, CH=C*H*CH$_2$), 5.21 (1H, t, J = 10 Hz, CHC*H*=CH), 3.71 (3H, s, CO_2Me), 3.70 (3H, s, CO_2Me), 3.69 (3H, s, CO_2Me), 3.62 (1H, m, C*H*CH=CH), 2.93 (1H, d, J = 11.5 Hz, C*H*CO$_2$Me), 2.71 (2H, d, J = 7.5 Hz, CH=CHC*H*$_2$), 2.60 (2H, m, J = 7 Hz, C*H*$_2$C=O), 2.1-2.55 (3H, m, C*H*$_2$), 1.8-1.9 (2H, m, C*H*$_2$), 1.45-1.7 (3H, m, C*H*$_2$).

^{13}C NMR ($CDCl_3$, δ ppm) : 210.6, 199.7, 171.3, 168.8, 136.4, 130.5, 129.4, 129.0, 128.0, 61.5, 57.7, 52.4, 39.7, 39.2, 38.1, 36.0, 31.9, 28.0, 18.2.

MS (m/e) : 434 (M^+), 416 (M^+-H_2O), 402 (M^+-MeOH).

Exact mass calc : 434.1941 (M^+); found : 434.1938.

• *Methyl 2-[(1E,3E)-6,6-bis(methoxycarbonyl)-10-oxododeca-1,3,11-trienyl]-5-oxocyclopentane-1-carboxylate* **3**

Yield : 89%.

IR ($CHCl_3$) : 1 751, 1 729, 1 704, 1 681, 1 616, 1 458, 1 437 cm^{-1}.

^{1}H NMR ($CDCl_3$, δ ppm) : 6.33 (1H, dd, J = 17.5 and 10.5 Hz, C*H*=CH$_2$), 6.19 (1H, dd, J = 17.5 and 1.5 Hz, CH=C*H*H), 6.0-6.15 (2H, m, CH=C*H*C*H*=CH), 5.82 (1H, dd, J = 10.5, 1.5 Hz, CH=CH*H*), 5.4-5.65 (2H, m, C*H*=CHCH=C*H*), 3.75 (3H, s, CO_2Me), 3.71 (6H, s, CO_2Me), 3.15-3.3 (1H, m, C*H*CH=CH), 2.98 (1H, d, J = 11.5 Hz, C*H*CO$_2$Me), 2.68 (2H, d, J = 7.5 Hz, CH=CHC*H*$_2$), 2.59 (2H, t, J = 7 Hz, C*H*$_2$CO), 2.15-2.55 (3H, m, C*H*$_2$), 1.8-1.9 (2H, m, C*H*$_2$), 1.45-1.75 (3H, m, C*H*$_2$).

^{13}C NMR ($CDCl_3$, δ ppm) : 210.7, 199.8, 171.5, 169.0, 136.4, 133.5, 132.5, 131.0, 128.2, 127.3, 61.1, 57.8, 52.5, 43.9, 39.3, 38.1, 35.9, 32.0, 27.5, 18.3.

MS (m/e) : 434 (M^+), 419 (M^+-Me), 403 (M^+-MeO).

Exact mass calc : 434.1941 (M^+); found : 434.1938.

• *Methyl 2-[(1Z,3E)-5-hydroxypenta-1,3-dienyl]-5,5-dimethoxycyclopentane-1-carboxylate* **25**

To a solution of cyclohexene (950 μL, 9.38 mmol) in dry tetrahydrofuran (2 mL) was added borane-methyl sulfide complex (450 μL, 4.74 mmol) at 0°C. The reaction mixture was stirred at room temperature for 5 min, and then the enyne **20** (501 mg, 1.87 mmol) in tetrahydrofuran (5 mL),

was introduced at 0°C. After the reaction mixture had been stirred for 45 min, acetic acid (350 μL, 6.11 mmol) was added and the mixture was stirred for an additional 20 min. The solution was poured onto cold aqueous sodium bicarbonate and extracted with ether. The organic layer was washed twice with saturated aqueous sodium bicarbonate, dried ($MgSO_4$) and condensed. Purification of the crude oil by flash chromatography (hexane/ethyl acetate, 3:2) afforded the title compound as an oil (292 mg, 58%).

IR ($CHCl_3$) : 3 610, 1 732, 1 458, 1 436 cm^{-1}.

^1H NMR ($CDCl_3$, δ ppm) : 6.61 (1H, ddq, J = 15, 11 and 1.5 Hz, C*H*=CHCH$_2$), 5.97 (1H, t, J = 11 Hz, CHCH=C*H*, 5.82 (1H, dt, J = 15 and 6 Hz, HC=C*H*CH$_2$), 5.28 (1H, t, J = 10.5 Hz, CHC*H*=CH), 4.20 (2H, d, J = 5 Hz, C*H*$_2$OH), 3.68 (3H, s, CO_2Me), 3.58 (1H, m, C*H*CH=CH), 3.28 (3H, s, CO*Me*), 3.20 (3H, s, CO*Me*), 2.72 (1H, d, J = 8.5 Hz, C*H*CO_2CH_3), 1.85-2.05 (3H, m, C*H*$_2$), 1.35-1.55 (2H, m, C*H*H and O*H*).

^{13}C NMR ($CDCl_3$, δ ppm) : 172.1, 134.0, 133.0, 128.6, 126.4, 111.6, 63.3, 58.0, 51.8, 50.0, 48.8, 40.8, 36.3, 30.3.

MS (m/e) : 253 (M^+-OH), 238 (M^+-MeOH).

Exact mass calc : 238.1205 (M^+-MeOH); found : 238.1198.

• *Methyl 2,2-dimethoxy-5-[(1Z,3E)-5-oxopenta-1,3-dienyl]cyclopentane-1-carboxylate* **30**

A solution of the diene **25** (398 mg, 1.47 mmol) in dichloromethane (15 mL) was treated with manganese dioxide (2.41 g, 27.70 mmol) and the resulting suspension was stirred for 30 min at room temperature. The mixture was filtered on celite and the solvent was evaporated to give the title compound.

IR ($CHCl_3$) : 1 732, 1 679, 1 635, 1 458, 1 436 cm^{-1}.

^1H NMR (C_6D_6, δ ppm) : 9.45 (1H, d, J = 8Hz, O=C*H*), 7.32 (1H, ddd, J = 15, 11.5 and 1 Hz, O=CHCH=C*H*), 5.95 (1H, dd, J = 15 and 8 Hz, O=CHC*H*=CH), 5.75 (1H, t, J = 11 Hz, CHCH=C*H*), 5.32 (1H, t, J = 10.5 Hz, CHC*H*=CH), 3.70 (1H, m, C*H*CH=CH), 3.35 (3H, s, CO_2Me), 3.17 (3H, s, CO*Me*), 2.98 (3H,s, CO*Me*), 2.74 (1H, d, J = 8.5 Hz, C*H*CO_2Me), 1.55-1.95 (3H, m, C*H*$_2$), 1.35 (1H, m, C*H*H).

^{13}C NMR (C_6D_6, δ ppm) : 192.6, 171.1, 145.4, 143.5, 133.3, 111.8, 58.0, 51.5, 49.8, 48.7, 41.4, 36.6, 30.4.

MS (m/e) : 268 (M^+), 239 (M^+-CHO), 236 (M^+-MeOH).

Exact mass calc : 268.1311 (M^+); found : 268.1304.

• *Methyl 2,2-dimethoxy-5-[(1E,3E)-5-oxopenta-1,3-dienyl]cyclopentane-1-carboxylate* **31**

To a solution of the aldehyde **30** (65.4 mg, 2.44 μmol) in deuterated benzene (1.2 mL) in an NMR tube, was added a tiny crystal of iodine. The resulting pink solution was heated at 45°C and its composition was periodically checked by ^1H NMR. When the amount of desired dienal reached the threshold of 90% (remaining starting material = 10%), the solution was concentrated and filtration of the residue on silica gel (hexane/ethyl acetate, 3:2) afforded the title compound contaminated with unreacted starting material (57 mg, total yield : 87%; ratio **31**/**30** = 11).

^1H NMR (C_6D_6, δ ppm) : 9.37 (1H, d, J = 8 Hz, O=C*H*), 6.37 (1H, dd, J = 15.5 and 10.5 Hz, O=CHCH=CH), 5.91 (1H, dd, J = 15 and 10.5 Hz, CHCH=C*H*), 5.85 (1H, dd, J = 15.5 and 8 Hz, O=CHC*H*=CH), 5.64 (1H, dd, J = 15 and 8 Hz, CHC*H*=CH), 3.44 (3H, s, CO_2Me), 3.24 (1H, m, C*H*CH=CH), 3.19 (3H, s, CO*Me*), 2.99 (3H, s, CO*Me*), 2.82 (1H, d, J = 8.5 Hz, C*H*CO_2Me), 1.55-1.95 (3H, m, C*H*$_2$), 1.40 (1H, m, C*H*H).

^{13}C NMR (C_6D_6, δ ppm) : 192.3, 171.2, 150.7, 146.5, 131.4, 128.6, 111.8, 57.4, 51.5, 49.8, 48.7, 45.6, 36.2, 29.5.

• *Methyl 2-[(1E,3E)-5-hydroxypenta-1,3-dienyl]-5,5-dimethoxycyclopentane-1-carboxylate* **32**

To a stirred solution of the aldehyde **31** (57 mg, 213 μmol) in dry methanol was added sodium borohydride (10 mg, 264 μmol) at −35°C. The temperature was allowed to rise to −20°C, water was then added and the mixture was extracted several times with dichloromethane. The combined organic phase was dried ($MgSO_4$) and condensed. Purification of the crude product by flash chromatography (toluene/ethyl acetate, 3:1) provided the title compound as an oil (40 mg, 69%).

IR ($CHCl_3$) : 3 611, 1 733, 1 458, 1 436 cm^{-1}.

^1H NMR ($CDCl_3$, δ ppm) : 6.18 (1H, ddt, J = 15, 10.5 and 1.5 Hz, C*H*=CHCH$_2$), 6.07 (1H, dd, J = 15 and 10.5 Hz, CHCH=C*H*), 5.76 (1H, dt, J = 14.5 and 6 Hz, CH=C*H*CH$_2$), 5.59 (1H, dd, J = 14.5 and 8 Hz, CHC*H*=CH), 4.16 (2H, t, J = 5.5 Hz, C*H*$_2$OH), 3.70 (3H, s, CO_2Me), 3.27 (3H, s, CO*Me*), 3.19 (3H, s, CO*Me*), 3.13 (1H, m, C*H*CH=CH), 2.75 (1H, d, J = 9 Hz, C*H*CO_2Me), 1.8-2.05 (3H, m, C*H*$_2$), 1.50 (1H, m, C*H*H), 1.31 (1H, br t, J = 5.5 Hz, O*H*).

^{13}C NMR ($CDCl_3$, δ ppm) : 172.1, 136.1, 131.2, 131.0, 129.5, 111.5, 63.3, 57.6, 51.8, 50.0, 48.8, 45.2, 36.2, 29.7.

MS (m/e) : 270 (M^+), 253 (M^+-OH), 239 (M^+-MeO).

Exact mass calc : 239.1283 (M^+-MeO); found : 239.1281.

• *Hexamethyl (10E,27E)-4,17,21,34-tetraoxo-tricyclo[29.3.0.0^{14,18}]tetratriaconta-10,27-dien-12,29-diyne-1,8,8,18,25,25-hexacarboxylate* **37**

A solution of the enone **1** (36 mg, 83 μmol) in acetonitrile (3 mL) was added over a period of 1 h to a stirred suspension of cesium carbonate (70 mg, 215 μmol) in acetonitrile (37 mL) at room temperature The resulting mixture was stirred for another 10 min, and then filtered over celite. Removal of the solvent under reduced pressure gave a residue which was purified by chromatography on silica gel (hexane/ethyl acetate, 3:2) to yield the title compound (7 mg, 20%) as a mixture of two inseparable isomers (90:10).

^1H NMR ($CDCl_3$, δ ppm) (major isomer) : 5.83 (2H, m, C*H*=CHC≡C), 5.53 (2H, ddd, J = 16, 3, 1.5 Hz, CH=C*H*C≡C), 3.74 (6H, s, CO_2Me), 3.73 (18H, s, CO_2Me), 3.71 (6H, s, CO_2Me), 3.70 (6H, s, CO_2Me), 3.02 (2H, br, C*H*C≡C), 2.85 (2H, ddd, J = 17.5, 10.5, 5 Hz, C*H*$_2$), 2.73 (4H, d, J = 7.5 Hz, C*H*$_2$), 2.55-2.7 (4H, m, C*H*$_2$), 2.49 (4H, t, J = 7 Hz, C*H*$_2$), 2.1-2.35 (8H, m, C*H*$_2$), 1.9-2.05 (2H, m, C*H*$_2$), 1.75-1.85 (4H, m, C*H*$_2$), 1.3-1.6 (4H, m, C*H*$_2$).

MS (m/e) : 864 (M^+), 833 (M^+-MeO), 805 (M^+-CO_2Me).

Exact mass calc : 864.3568 (M^+); found : 864.3483.

• *Trimethyl (10E,12Z)-4,17-dioxo-*trans*-bicyclo[12.3.0]heptadeca-10,12-diene-1,8,8-tricarboxylate* **7**

Cesium carbonate (22 mg, 67 μmol) was added to a solution of the enone **2** (55 mg, 125 μmol) in dry acetonitrile (60 mL). The mixture was stirred for 40 min at room temperature and then filtered on celite and condensed.

Purification of the crude product by flash chromatography (dichloromethane/acetone, 40:1) provided the title compound as a white solid (49 mg, 90%).

Mp : 210-212°C (hexane/ethyl acetate).

IR ($CHCl_3$) : 1 750, 1 732, 1 711, 1 458, 1 437 cm^{-1}.

^1H NMR ($CDCl_3$, δ ppm) : 6.39 (1H, dd, J = 15 and 11 Hz, C*H*=CHCH$_2$), 6.12 (1H, t, J = 11 Hz, CHCH=C*H*), 5.47 (1H, ddd, J = 15, 11.5 and 4.5 Hz, CH=C*H*CH$_2$), 5.23 (1H, t, J = 10.5 Hz, CHC*H*=CH), 3.71 (3H, s, CO_2Me), 3.69 (3H, s, CO_2Me), 3.67 (3H, s, CO_2Me), 3.26 (1H, q, J = 9.5 Hz, C*H*CH=CH), 2.88 (1H, dd, J = 14 and

4.5 Hz, CH_2), 2.4-2.75 (4H, m, CH_2), 1.8-2.35 (8H, m, CH_2), 1.25-1.75 (3H, m, CH_2).

^{13}C NMR ($CDCl_3$, δ ppm) : 213.6, 209.4, 171.1, 171.0, 169.9, 130.4, 129.6, 129.4, 129.0, 62.9, 56.4, 52.7, 52.1, 43.0, 42.9, 37.8, 35.5, 34.6, 30.6, 26.2, 24.4, 20.0.

MS (m/e) : 434 (M^+), 416 (M^+-H_2O), 402 (M^+-MeOH).

Exact mass calc : 434.1941 (M^+); found : 434.1938.

• *Trimethyl (10*E*,2*E*)-4,17-dioxo-*cis*-bicyclo [12.3.0]heptadeca-10-12-diene-1,8,8-tricarboxylate* **8** *and (10*E*,12*E*,27*E*,29*E*)-hexamethyl 4,17,21,34-tetraoxotricyclo[29.3.0.$0^{14,18}$]tetratriaconta-10,12-27,29-tetraene-1,8,8,18,25,25-hexacarboxylate* **38**

To a stirred supension of cesium carbonate (32.6 mg, 104 μmol) in dry acetonitrile (90 mL) was added a solution of the enone **3** (45.1 mg, 104 μmol) in acetonitrile (10 mL) over a period of 10 h. The mixture was stirred for another 1 h, and then filtered on celite and condensed. Flash chromatography (ethyl acetate/hexane, 1:1) of the crude material provided the macrocycle monomer **8** (13.5 mg, 30%, mp 135-137°C) and the macrocyclic dimer **38** (12.4 mg, 27%) mixture of two diastereomers, 90:10).

■ *Macrocycle* **8**

IR ($CHCl_3$) : 1 750, 1 728, 1 454, 1 437 cm^{-1}.

^1H NMR ($CDCl_3$, δ ppm) : 6.0-6.2 (2H, m, CH=C*H*CH=CH), 5.5-5.8 (2H, m, *H*C=CHCH=C*H*), 3.76 (3H, s, CO_2Me), 3.73 (3H, s, CO_2Me), 3.72 (3H, s, CO_2Me), 3.59 (1H, dt, J = 10 and 6.5 Hz, C*H*CH=CH), 2.75 (1H, dd, J = 5.5 and 14 Hz, CH_2), 2.3-2.65 (6H, m, CH_2), 1.65-2.2 (7H, m, CH_2), 1.35-1.55 (2H, m, CH_2).

^{13}C NMR ($CDCl_3$, δ ppm) : 212.6, 209.0, 171.6, 171.5, 170.6, 134.3, 130.7, 130.1, 127.9, 63.1, 56.9, 52.7, 45.7, 42.1, 38.2, 36.9, 31.2, 23.4, 22.5, 19.7.

MS (m/e) : 434 (M^+), 416 (M^+-H_2O), 402 (M^+-MeOH).

Exact mass calc : 434.1941 (M^+); found : 434.1933.

■ *Macrocycle* **38**

IR ($CHCl_3$) : 1 743, 1 730, 1 457, 1 436 cm^{-1}.

^1H NMR ($CDCl_3$, δ ppm) (major isomer) : 5.9-6.2 (4H, m, C=C*H*C*H*=CH), 5.4-5.6 (4H, m, C*H*=CHCH=C*H*), 3.71 (12H, s, CO_2Me), 3.70 (12H, s, CO_2Me), 3.67 (6H, s, CO_2Me), 3.66 (6H, s, CO_2Me), 2.5-2.85 (12H, m, C*H* and CH_2), 1.75-2.5 (18H, m, 2H, CH_2), 1.3-1.6 (4H, m, 2H, CH_2).

^{13}C NMR ($CDCl_3$, δ ppm) : 215.2, 214.9, 208.8, 171.5, 169.9, 133.5, 133.0, 132.7, 130.1, 129.9, 127.5, 61.9, 57.7, 57.5, 52.5, 52.0, 50.3, 49.8, 42.4, 42.0, 38.2, 37.5, 35.2, 31.1, 30.9, 26.4, 17.6.

MS (m/e) : 868 (M^+), 850 (M^+-H_2O).

Exact mass calc : 868.3881 (M^+); found : 868.3896.

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