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# Formation of 14-membered carbocycles by intramolecular Michael reaction of cyclic β-ketoesters on enones and ynones

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**Summary** – The intramolecular Michael addition of cyclic β-ketoesters on enones **31** and **32** and ynones **23**, **24**, **40** and **45** was used for 14-membered ring formation. High yields (65-90%) were obtained in all cases at a relatively high concentration (0.01 M) without slow addition techniques. These reactions were fast, simple and used particularly soft reaction conditions ($Cs_2CO_3$ in acetonitrile) allowing the presence of several functional groups.

**macrocyclization / 14-membered ring formation / intramolecular Michael addition / cesium carbonate**

## Introduction

The potential of medium and large rings has been underlined and tested by several researchers [1]. The chemical consequences of conformation and reactivity in cyclohexanes was pointed out by Barton [2] more than 40 years ago. Despite the more accurate picture of these macrocycle conformations, not many examples have been reported concerning their use as an element of stereochemical control for the introduction of substituents [3]. Likewise, transannular reactions have rarely been explored, in spite of the power of such an approach, particularly in reference to the transannular Diels-Alder reaction [1, 4].

One of the most important problems in these strategies is still the synthesis of the macrocyclic compounds. The intramolecular Michael reaction has been used in our laboratory for the synthesis of medium-sized rings and, after the success encountered for the synthesis of 9- and 10-membered rings [5], it was anticipated that the formation of large rings by this reaction could eventually lead to excellent yields (>80%) for macrocyclization, provided that the transannular interactions and the conformational mobility were reduced. Recently, the formation of a 14-membered ring by an intramolecular Michael reaction has been achieved with good yields using pseudo-high-dilution technique [6]. We have undertaken the synthesis of 14-membered rings by adapting our previous results on the intramolecular Michael addition of 5-membered β-ketoesters to enones and ynones for the formation of small and medium rings [7] in such a way that we could verify the relative facility of macrocyclization for our system. In this article, we report our results on 14-membered ring formation, whose precursors show variations in the geometry of the double bonds ($E$; $Z$), in the nature of the Michael acceptors (enones; ynones) and the hybridation state of one carbon ($sp^2$; $sp^3$).

## Results and discussion

The synthesis of the macrocyclization precursors sensibly uses the same approach as that used in our first study on intramolecular Michael reactions [7]. The conjugate addition of allyltrimethylsilane in the presence of titanium(IV) chloride [8] on conjugated ester **1** [9] provided olefins **2a** and **2b** in 85% yield as a *trans-cis* mixture in a 3.7:1 ratio (scheme 1). The *cis* and *trans* isomers were separated by preparative liquid chromatography under medium pressure. Hydroboration [10] of olefin **2a** followed by Swern oxidation [11] provided aldehyde **4** in 80% yield.

The Claisen reaction was used to lengthen the side chain by four carbons while inserting a double bond. To do so, aldehyde **4** was alkylated with prop-2-enylmagnesium bromide [12] and the resulting allyl alcohol was treated with ethylvinylether in the presence of mercuric acetate [13] providing enol ether **6**. This product was heated in decalin at 165°C and led to a mixture of aldehydes **7** with the $E$, and $Z$ double bonds in a 85:15 ratio. Fortunately, these isomers could be separated in a later step. This mixture of aldehydes was alkylated by the Grignard reagent prepared from 3-chloropropanol [14], adding three carbons to the side chain and providing diols **8** in 74% yield. The primary alcohol was selectively protected as a *t*-butyldiphenylsilyl ether. The two double bond isomers

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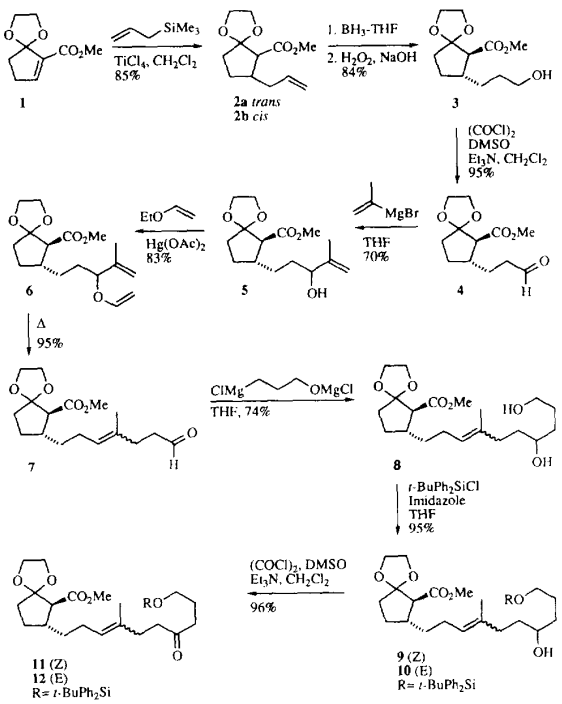
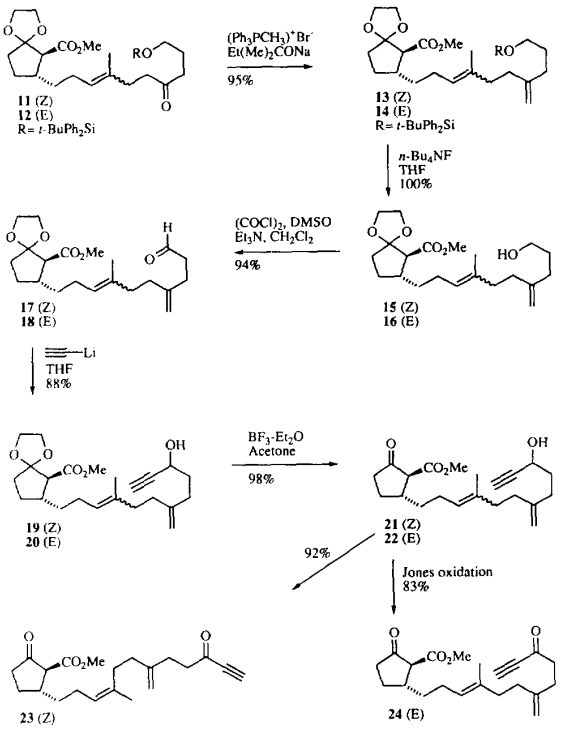


Scheme 1



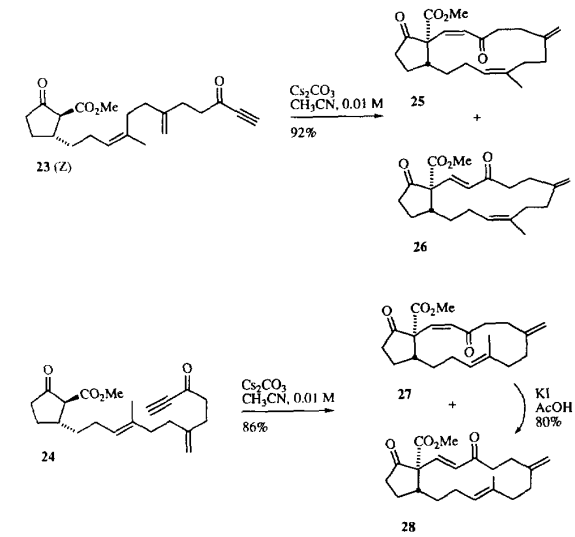
Scheme 2

were separated at this stage by medium pressure chromatography giving alcohols **9** and **10**.

Swern oxidation [11] of alcohols **9** and **10** provided the corresponding ketones **11** and **12**. Rather than protecting the ketone as a ketal, which might produce unfavorable steric interactions during the cyclization step, we kept the $sp^2$ center by converting the ketone to an *exo*-methylene group. This methylenation was accomplished on ketones **11** and **12** by the action of triphenylmethylphosphonium bromide in the presence of sodium *t*-pentanolate in benzene [15] to provide dienes **13** and **14** (scheme 2). The silyl group was cleaved by the action of fluoride ions in THF, giving alcohols **15** and **16** in quantitative yield.

The construction of the ynone function was then undertaken. Swern oxidation of alcohols **15** and **16** provided aldehydes **17** and **18**, which were alkylated by lithium acetylide [16] in THF at −78°C giving propargylic alcohols **19** and **20**. The ketals were cleaved by the action of boron trifluoride-diethyl etherate in acetone for 18 h at 20°C giving β-ketoesters **21** and **22**. Finally, Jones oxidation provided ynones **23** and **24**. These two precursors for the cyclizations were obtained with a global yield of 20% in 15 steps from **2a**.

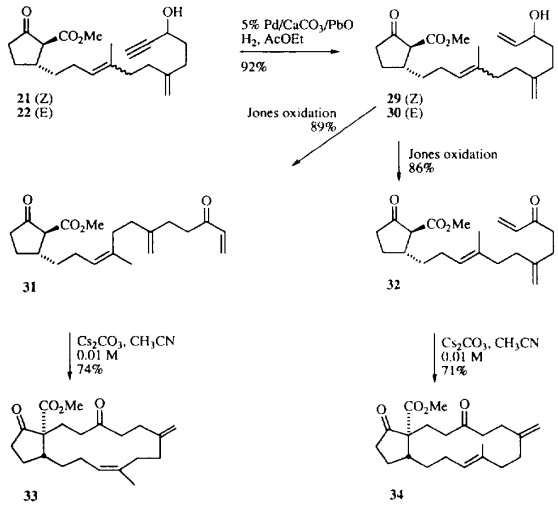
Our preliminary macrocyclization trials were carried out using the same reaction conditions as in our previous study for the formation of 5- to 8-membered rings by the intramolecular Michael reaction [7], which are cesium carbonate (0.2 equiv) in acetonitrile at 0.002 M concentration without slow addition. The formation of large rings was very fast and nearly quantitative and so we increased the concentration to 0.01 M. Using these reaction conditions, after 1 h at 20°C, the ynone **23** provided the 14-membered rings **25** and **26**, which easily separated by flash-chromatography, in 38 and 54% yield respectively (scheme 3). In the same way, the ynone **24**, after 30 min, provided the 14-membered rings **27** and **28** in 40 and 46% yield respectively. The *cis*-enone **27** was isomerized to the *trans*-enone **28** by the action of potassium iodide in acetic acid [17] for 18 h providing a mixture of **27** and **28** in a 5:95 ratio. On standing, the *trans*-enone **28** isomerized to the *cis*-enone **27** (al-



Scheme 3

though to a small extent) so that the ratio of 5:95 is probably the real thermodynamic equilibrium.

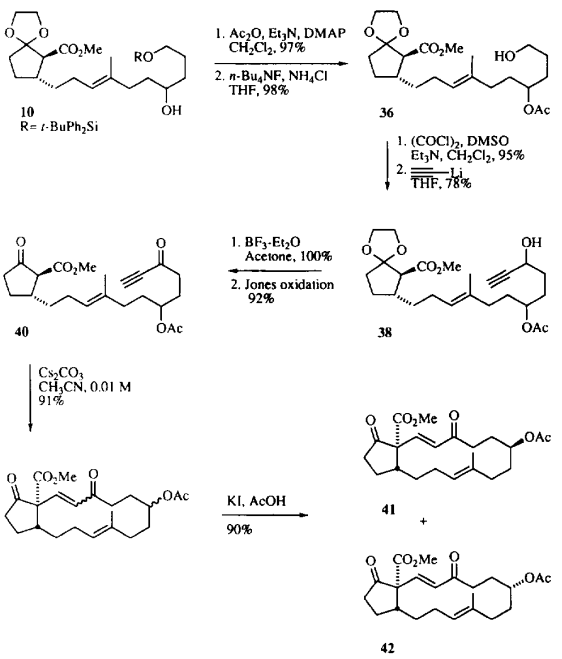
It has been observed in our laboratory [5] that there is a great difference between the cyclization by intramolecular Michael reaction of malonates on ynones and enones for the formation of 10-membered rings, the enones being much less effective than the ynones. We have therefore set out to verify this aspect of our cyclizations by obtaining the enone group from propargylic alcohols **21** and **22**. The catalytic hydrogenation of these alcohols over Lindlar catalyst under hydrogen atmosphere provided allylic alcohols **29** and **30** (scheme 4). Jones oxidation of the allylic alcohols gave enones **31** and **32**. When these enones were treated by cesium carbonate in acetonitrile at 0.01 M, the 14-membered rings **33** and **34** were obtained in 74 and 71% yield respectively.




**Scheme 4**

An X-ray diffraction analysis was accomplished on the large rings **28** and **34** (fig 1 and 2) [18], proving the *trans* relationship at the ring junction. Many literature examples [19] showed that the alkylation of cyclic $\beta$-ketoesters is strongly influenced by steric hindrance. The alkylation takes place on the least hindered side, so that the product of *trans*-junction for our macrocycles is easily rationalized on this basis. The proton at the $\beta$ position of the ester group is also characteristic of the ring junction. In our previous study [7] the proton of the *cis* ring junction was clearly distinct from all other protons, being deshielded by the ester group to 3.0-3.3 ppm. It is interesting to note that the X-ray diffraction of products **28** and **34** shows a conformation where the ring forms a square with the unsaturations located at the center of each side of the square, which reduces transannular interactions. We have thus obtained good macrocyclization yields with the enones (70-75%), and very good yields with the ynones (85-90%). In all cases studied, the *E* or *Z* geometry of the trisubstituted olefin did not have any influence on the cyclization.

We then verified another aspect of these cyclizations by eliminating one $sp^2$ center along the chain linking both reacting groups. In order to do so, we kept the $sp^3$ center of alcohol **10**. Acetylation of this alcohol followed by cleavage of the group gave the primary alcohol **36** (scheme 5). Swern oxidation of this alcohol provided aldehyde **37**, which was alkylated by lithium acetylide. Cleavage of the ketal and Jones oxidation of the propargylic alcohol was accomplished in the same way as before providing the desired ynone **40**. When this ynone was treated with cesium carbonate in acetonitrile at 0.01 M, it yielded a mixture of four products, two diastereoisomeric acetates and two isomeric enones (*E* and *Z*), in a combined yield of 91%. According to the NMR spectrum, the ratio of the *cis* and *trans* enones is 45:55. This mixture was treated with potassium iodide in acetic acid [17] in order to isomerize the *cis* enones to the *trans* enones. In this way, the two *trans* enones were isolated in 42 and 48% yield respectively, the former being contaminated by about 10% of the *cis* enones initially present in the mixture. The *trans* enones correspond to compounds **41** and **42**, but their exact stereochemistry at the acetate asymmetric center has not yet been established.




**Scheme 5**

Finally, we prepared compound **45** (scheme 6) from acetate **38** to verify the influence of an additional carbonyl group on the molecule, which is a group susceptible of being trapped by the intermediate allenic enolate generated during the cyclization. The acetate group of compound **38** was cleaved by the action of potassium methoxide in methanol giving diol **43** in a quantitative yield. Cleavage of the ketal followed by a Jones oxidation of diol **44** was carried out in the usual way giving ynone **45**. When this product was treated with cesium carbonate in acetonitrile at 0.01 M, it gave the

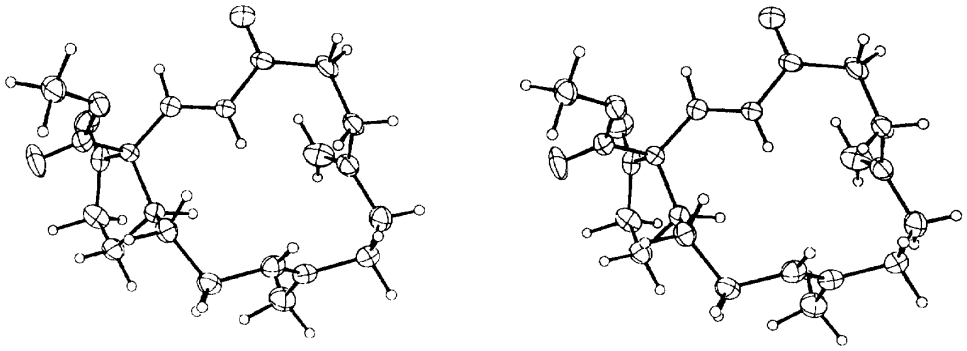


**Fig 1.** Stereoview of the ORTEP drawing of **28**.

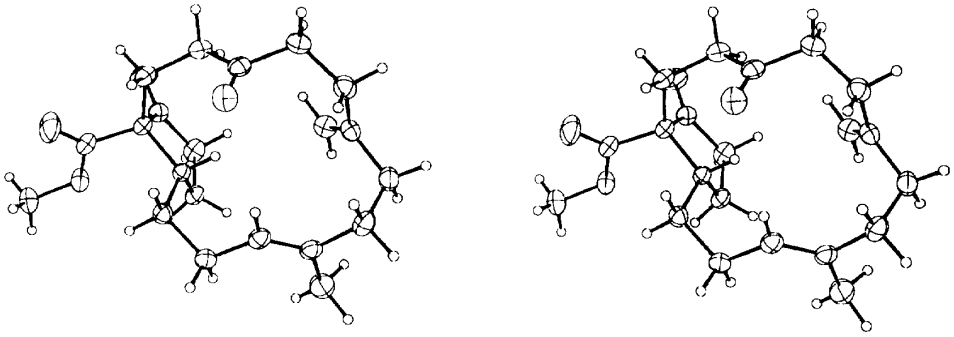
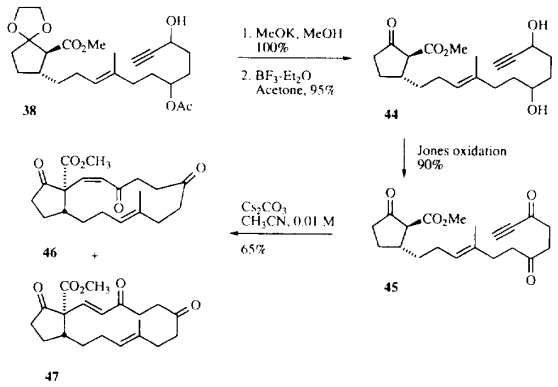


**Fig 2.** Stereoview of the ORTEP drawing of **34**.




**Scheme 6**

14-membered rings **46** and **47** in 27 and 38% yields respectively. The combined yield was increased from 65 to 77% by using a lower concentration (0.005 M).

The above results indicate that the intramolecular Michael reaction has a fast reaction rate and at a relatively high concentration it provides 14-membered rings with excellent yields. How do these results compare to other methods which have been used for the formation of large rings? The best way to answer this question is to rely on the values of effective molarity (EM). As mentioned by Mandolini [20], the fundamental quantity in cyclization reaction is the EM, determined as the $k_{intra}/k_{inter}$ ratio, which represents the concentration of reagents at which the cyclization ($K_{intra}$) and the polymerization ($K_{inter}$) take place at the same rate. The EM values reflect structural effects inherent to the formation of rings. In a review article, Mandolini compared the EM values for four different cyclization reactions covering the small, medium and large ring domains [21]. The EM values are relative, allowing the comparison of reactions. In that review article, the formation of lactones (displacement of a bromide by a carboxylate), *N*-tosylazacycloalkanes (displacement of a bromide by an *N*-tosylamide), and catecholpolymethylene ethers (displacement of a bromide by a phenoxide) gave EM values that tend to reach a plateau with a value of log EM of 1.5 in the large ring domain, which corresponds to a concentration of 0.03 M with 50% yield for the cyclization. The cyclization reaction using intramolecular alkylation of a malonate on a bromide shows EM values lower than the other reactions for the formation of medium and large rings because of the larger steric interaction of the malonate (a quaternary center) and also because the ring thus formed contains only carbon atoms while the other rings have one lactone, one nitrogen or two oxygens in the ring.

In our case, 65-90% yield was obtained at 0.01 M for the 14-membered rings, and so we can estimate that the EM values for the cyclizations are slightly above 0.01 M, *ie* between 0.01 and 0.03 M. On that basis, we can conclude that these cyclizations are not exceptional but rather normal. It should be pointed out, however, that in our case, an all-carbon ring formation can take place when a quaternary center is created during the cyclization. Examination of the results reported in the literature [22] concerning the formation of a carbocyclic

14-membered ring, where the concentration used is specified, indicates that our cyclizations compare favorably with the best direct methods (without slow addition) of cyclization. The absence of highly unfavorable transannular interactions in our macrocyclic compounds, as can be seen in the X-ray structures of two macrocycles, is almost certainly responsible for the success of these cyclizations.

## Conclusion

With our systems, the formation of 14-membered rings by intramolecular Michael reaction of 5-membered ring $\beta$-ketoesters on enones and ynones was highly effective. This intramolecular Michael reaction is characterized by a fast reaction rate, simplicity, generality, and by the fact that it creates a macrocyclic compound with many functionalities. The reaction conditions are particularly gentle, allowing the presence of several functional groups without the need for protecting groups. The large rings are more easily accessible and it becomes henceforth possible to use them ingeniously for the construction of complex molecules. The potential of large rings as a strategy in organic synthesis has rarely been exploited and the field of investigation is still intact.

## Experimental section

The IR spectra were taken on a Perkin-Elmer 681 spectrophotometer. The samples were prepared as solutions in chloroform. Proton spectra were recorded on a Bruker WP-250 instrument and the carbon 13 NMR were taken on a Bruker AC300F instrument. The following abbreviations were used : s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; b, broad; dd, doublet of doublets; dt, doublet of triplets, *etc.* Chemical shifts are reported in $\delta$ values relative to chloroform as internal standard. Mass spectra were obtained on a Micromass ZAB-2F instrument. Melting points were determined on a Buchi M-50 or on a Reichert apparatus and are uncorrected.

Thin-layer chromatography was performed using silica gel 60 F-250. For flash chromatography [23], Merck Kieselgel 60 (230-400 mesh) was used. For preparative liquid chromatography, a Water Prep LC/System 500A was used. All solvents used in chromatography were distilled. Unless otherwise noted, starting materials and reactants were obtained commercially and used as such or purified by standard means. All reactions were carried out under an argon atmosphere. Organic solutions were dried over magnesium sulfate and evaporated on a rotatory evaporator under reduced pressure.

### *Methyl 7-(prop-2-enyl)-1,4-dioxaspiro[4.4]nonane-6-carboxylate* **2**

To a solution of the conjugated ester **1** (8.62 g, 46.8 mmol) in dichloromethane (300 mL) at $-78°C$ was added titanium tetrachloride (10.66 g, 56.2 mmol). After 5 min stirring, allyltrimethylsilane (6.42 g, 56.2 mmol) was quickly added to the orange suspension. After the addition, the red solution was stirred for 30 min at $-78°C$. Water (150 mL) was then added and the reaction mixture was warmed to room temperature by removing the cooling bath. The reaction mixture, now colorless, was extracted with diethyl ether ($1 \times 400$ mL and $2 \times 100$ mL). The organic phases were washed with a saturated solution of sodium bicarbonate, dried, filtered and the solvent was evaporated under reduced pressure. The product was purified by flash chromatography using hexane/ethyl acetate (85:15) as eluent to afford a mixture of *trans/cis* isomers (3.7:1) **2a** and **2b** (8.98 g, 85%). To a solution of olefins **2a** and **2b** (8.98 g, 39.7 mmol, 3.7:1 mixture of *trans* and *cis*) in benzene (150 mL) was added *p*-toluenesulfonic acid monohydrate (151 mg, 0.79 mmol) and ethylene glycol (1 mL). After 5 h of reflux, the reaction mixture was cooled to 20°C and potassium carbonate was added to form a paste with ethylene glycol. The suspension was filtered on a bed of silica gel, rinsed with diethyl ether and the solvents were evaporated under reduced pressure. The products (7.3:1 mixture of *trans* and *cis*) are separated by preparative liquid chromatography using hexane/ethyl acetate (9:1) as eluent affording the olefins **2a** and **2b** as oils (8.17 g, 91% (1.03 g of the *cis* isomer, 6.67 g of the *trans* isomer and 0.47 g of a mixture)).

- trans *isomer* **2a**

IR ($CHCl_3$) : 1 730, 1 640 $cm^{-1}$.

$^1H$ NMR ($CDCl_3$, $\delta$ ppm) : 5.73 (1H, ddt, $J$ = 17.1, 10.1 and 7.1 Hz, $CH$=$CH_2$), 4.94-5.07 (2H, m, CH=C$H_2$), 3.80-4.07 (4H, m, OC$H_2$C$H_2$O), 3.69 (3H, s, OC$H_3$), 2.50-2.64 (2H, m, C$H$C$H$C$O_2CH_3$), 2.09-2.24 (2H, m, C$H_2$CH=C$H_2$), 1.84-2.00 (3H, m), 1.25-1.44 (1H, m).

$^{13}C$ NMR ($CDCl_3$, $\delta$ ppm) : 172.2, 136.3, 117.6, 116.1, 65.1, 64.3, 58.5, 51.7, 40.4, 39.3, 37.0, 28.4.

MS ($m/e$) : 226 ($M^+$), 211 ($M^+$-$CH_3$), 195 ($M^+$-$OCH_3$).

Exact mass ($M^+$) : calc : 226.1205, found : 226.1202.

- cis *isomer* **2b**

IR ($CHCl_3$) : 1 730, 1 640 $cm^{-1}$.

$^1H$ NMR ($CDCl_3$, $\delta$ ppm) : 5.75 (1H, ddt, $J$ = 17.1, 10.1 and 7.0 Hz, $CH$=$CH_2$), 4.92-5.05 (2H, m, CH=C$H_2$), 3.85-4.05 (4H, m, OC$H_2$C$H_2$O), 3.68 (3H, s, OC$H_3$), 2.84 (1H, d, $J$ = 6.8 Hz, C$H$C$O_2CH_3$), 2.05-2.45 (4H, m, C$H_2$CH=C$H_2$ and C$H_2$C), 1.71-1.99 (3H, m, C$H_2$C$H_2$C$H$).

$^{13}C$ NMR ($CDCl_3$, $\delta$ ppm) : 172.3, 136.8, 118.2, 115.6, 65.1, 64.1, 55.6, 51.2, 40.9, 35.9, 34.4, 27.2.

### *Methyl (3-hydroxypropyl)1,4-dioxaspiro[4.4]nonane-6-carboxylate* **3**

To a solution of olefin **2a** (6,62 g, 29,3 mmol) in THF (90 mL) at $-78°C$ was slowly added the borane THF complex (43.8 mL of 1.0 M in THF, 43.8 mmol). The cooling bath was replaced by an ice-water bath and the mixture was stirred for 5 min at 0°C. The excess reactant was carefully destroyed by adding a small amount of water. An aqueous solution of sodium hydroxide (70.7 mL of a 3 N solution, 212 mmol) was slowly added at the beginning and then in one portion when the effervescence had ceased. Hydrogen peroxide (70.7 mL of a 30% solution, 626 mmol) was added and the mixture was vigorously stirred at room temperature for 1 to 2 h. A saturated sodium chloride aqueous solution (90 mL) was added and the reaction mixture was extracted with diethyl ether ($3 \times 90$ mL). The organic phase was dried, filtered and evaporated under reduced pressure. The product was purified by flash chromatography using diethyl ether as eluent affording the alcohol **3** (5.98 g, 84%).

IR ($CHCl_3$) : 3 620, 3 500, 1 730 $cm^{-1}$.

$^1H$ NMR ($CDCl_3$, $\delta$ ppm) : 3.82-4.07 (4H, m, OC$H_2$C$H_2$O), 3.71 (3H, s, OC$H_3$), 3.58-3.69 (2H, m, C$H_2$OH), 2.58 (1H, d, $J$ = 9.2 Hz, C$H$C$O_2CH_3$), 2.39-2.57 (1H, m, C$H$CHC$O_2CH_3$), 1.86-2.00 (3H, m), 1.16-1.70 (6H, m).

$^{13}C$ NMR ($CDCl_3$, $\delta$ ppm) : 172.5, 117.7, 65.1, 64.3, 62.7, 59.4, 51.7, 40.8, 37.1, 31.4, 30.7, 28.9.

MS ($m/e$) : 244 ($M^+$), 226 ($M^+$-$H_2O$), 213 ($M^+$-$OCH_3$).

Exact mass ($M^+$) : calc : 244.1311, found : 244.1308.

*Methyl 7-(2-formylethyl)-1,4-dioxaspiro[4.4]nonane-6-carboxylate* **4**

Dimethylsulfoxide (4.34 mL, 61.1 mmol) was slowly added to a solution of oxalyl chloride (2.43 mL, 27.9 mmol) in dichloromethane (90 mL) at −78°C. After 5 min of stirring, a solution of alcohol **3** (5.43 g, 22.6 mmol) in dichloromethane (20 mL) was slowly added. After 10 min of stirring at −78°C, triethylamine (17.6 mL, 126 mmol) was added, the reaction mixture was allowed to reach room temperature by removing the cooling bath and stirring was continued for 10 min at room temperature. After addition of water (120 mL), the reaction mixture was extracted with dichloromethane (3 × 100 mL). The organic phase was dried, filtered and evaporated under reduced pressure. The product was purified by flash chromatography using hexane/ethyl acetate (3:1) as eluent, affording the aldehyde **4** as an oil (5.12 g, 95%).

IR ($CHCl_3$) : 2 730, 1 730 $cm^{-1}$.

$^1H$ NMR ($CDCl_3$, $\delta$ ppm) : 9.75 (1H, t, $J$ = 1.6 Hz, C*H*O), 3.79-4.07 (4H, m, $OCH_2CH_2O$), 3.71 (3H, s, $OCH_3$), 2.59 (1H, d, $J$ = 9.2 Hz, $CHCO_2CH_3$), 2.30-2.58 (3H, m, $CHCHCO_2CH_3$ and $CH_2CHO$),1.58-1.99 (5H, m),1.20-1.41 (1 H, m).

$^{13}C$ NMR ($CDCl_3$, $\delta$ ppm) : 201.8, 172.1, 117.5, 65.1, 64.3, 59.2, 51.8, 42.1, 40.5, 37.0, 28.7, 27.2.

MS ($m/e$) : 214 ($M^+$-CO), 211 ($M^+$-$OCH_3$).

Exact mass ($M^+$-CO) : calc : 214.1213, found : 214.1213.

*Methyl 7-(3-hydroxy-4-methylpent-4-enyl)-1,4-dioxaspiro[4.4]nonane-6-carboxylate* **5**

Prop-2-enylmagnesium bromide (45 mL, 0.70 M in THF, 31 mmol) was quickly added to a solution of aldehyde **4** (5.01 g, 20.7 mmol) in diethyl ether (300 mL) at −78°C. After 5 min of stirring, the reaction mixture was poured into an aqueous solution of ammonium chloride (150 mL). The organic phase was separated and the aqueous phase was extracted with diethyl ether (2 × 50 mL). The organic phases were dried, filtered and the solvent was evaporated under reduced pressure. The product was purified by flash chromatography using dichloromethane/diethyl ether (9:1 to 7:3) as eluent, affording the allylic alcohol **5** as an oil (4.10 g, 70%, with 1.19 g of recovered aldehyde **4**).

IR ($CHCl_3$) : 3 600, 3 500, 1 730, 1 650 $cm^{-1}$.

$^1H$ NMR ($CDCl_3$, $\delta$ ppm) : 4.92 (1H, bs, $C=CH_AH_B$), 4.83 (1H, bs, $C=CH_AH_B$), 3.79-4.07 (5H, m, $OCH_2CH_2O$ and C*H*OH), 3.71 and 3.70 (3H, 2s, $OCH_3$), 2.58 and 2.57 (1H, 2d, $J$ = 9.1 and 9.0 Hz, $CHCO_2CH_3$), 2.38-2.58 (1H, m, $CHCHCO_2CH_3$), 1.86-2.00 (3H, m), 1.70 (3H, bs, $CH_3$), 1.20-1.63 (6H, m).

$^{13}C$ NMR ($CDCl_3$, $\delta$ ppm) : 172.5, 147.4, 147.2, 117.7, 111.3, 111.0, 75.8, 75.7, 65.1, 64.3, 59.4, 51.7, 40.9, 37.1, 32.8, 31.25, 31.18, 29.0, 28.8, 17.5, 17.3.

MS ($m/e$) : 284 ($M^+$), 267 ($M^+$-OH), 253 ($M^+$-$OCH_3$).

Exact mass ($M^+$) : calc : 284.1024, found : 284.1020.

*Methyl 7-[4-methyl-3-(vinyloxy)pent-4-enyl]-1,4-dioxaspiro[4.4]nonane-6-carboxylate* **6**

To a solution of allylic alcohol **5** (5.94 g, 20.9 mmol) in ethylvinylether (40 mL), was added mercuric acetate (6.67 g, 20.9 mmol). After stirring for 18 h at 20°C, the reaction mixture was poured into a 20% aqueous solution of potassium carbonate and stirred for 20 min. This mixture was extracted with dichloromethane (3 × 120 mL) and the organic phases were dried, filtered and the solvent was evaporated under reduced pressure. The product was purified by flash chromatography using dichloromethane/diethyl ether (95:5 to 7:3 containing 0.1% of triethylamine) as eluent, affording the enol ether **6** as an oil (5.36 g, 83%, with 378 mg of recovered allylic alcohol **5**).

IR ($CHCl_3$) : 1 730, 1 630, 1 615 $cm^{-1}$.

$^1H$ NMR ($CDCl_3$, $\delta$ ppm) : 6.26 (1H, dd, $J$ = 14.2 and 6.5 Hz, O-C*H*=$CH_2$), 4.92 and 4.89 (2H, 2 bs, C=C*H*$_2$), 4.28 and 4.27 (1H, 2dd, $J$ = 14.2 and 1.5 Hz, C=C*H*$_E$H$_Z$), 3.97 (1H, bd, $J$ = 6.5 Hz, C=CH$_E$*H*$_Z$), 3.78-4.08 (5H, m, $OCH_2CH_2O$ and C*H*OCH=$CH_2$), 3.71 and 3.70 (3H, 2s, $OCH_3$), 2.57 (1H, d, $J$ = 9.1 Hz, $CHCO_2CH_3$), 2.34-2.53 (1H, m, $CHCHCO_2CH_3$), 1.82-2.00 (3H, m), 1.64 (3H, bs, $CH_3$), 1.15-1.76 (5H, m).

$^{13}C$ NMR ($CDCl_3$, $\delta$ ppm) : 172.3, 150.38, 150.33, 143.9, 143.8, 117.6, 113.4, 113.3, 88.6, 83.5, 83.4, 65.1, 64.2, 64.0, 59.3, 51.6, 40.8, 40.7, 37.0, 31.3, 31.1, 28.84, 28.77, 16.8, 16.6.

MS ($m/e$) : 310 ($M^+$), 267 ($M^+$-OCH=$CH_2$).

Exact mass ($M^+$) : calc : 310.1780, found : 310.1776.

*Methyl 7-(4-methyl-7-oxohept-4-enyl)-1,4-dioxaspiro[4.4]nonane-6-carboxylate* **7**

A solution of the enol ether **6** (5.35 g, 17.2 mmol) in decalin (25 mL) was heated at 165°C (oil bath at 166-170°C) for 90 min. The mixture was cooled at 20°C, and then the product was purified by flash chromatography using hexane/ethyl acetate (100:0 to 7:3) as eluent to afford the aldehyde **7** as an oil (5.13 g, 95%, as a 85:15 mixture of *E*:*Z* isomers by GLC analysis).

IR ($CHCl_3$) : 2 730, 1 730 $cm^{-1}$.

$^1H$ NMR ($CDCl_3$, $\delta$ ppm) : 9.77 and 9.75 (1H, 2t, $J$ = 1.9 Hz, C*H*O, *Z* and *E*), 5,12 (1H, bt, $J$ = 6 Hz, C*H*=C), 3.80-4.05 (4H, m, $OCH_2CH_2O$), 3.70 (3H, s, $OCH_3$), 2.57 (1H, d, $J$ = 9.0 Hz, $CHCO_2CH_3$), 2.25-2.54 (5H, m), 1.85-2.05 (5H, m), 1.66 and 1.59 (3H, 2s, $CH_3$, *Z* and *E*), 1.18-1.57 (3H, m).

$^{13}C$ NMR ($CDCl_3$, $\delta$ ppm, *E* isomer) : 202.6, 172.5, 133.2, 125.1, 117.7, 65.1, 64.3, 59.4, 51.7, 42.1, 40.9, 37.1, 35.4, 31.8, 28.9, 26.1, 16.0.

MS ($m/e$) : 310 ($M^+$).

Exact mass ($M^+$) : calc : 310.1780, found : 310.1776.

*Methyl 7-(7,10-dihydroxy-4-methyldec-3-enyl)-1,4-dioxaspiro[4.4]nonane-6-carboxylate* **8**

The Grignard reagent (56 mL, 0.6 M in THF, 33 mmol), prepared according to the literature [14] from 1-chloroprop-3-anol, was measured with a syringe and added to a 250 mL flask containing THF (56 mL). This solution was cooled at −78°C and a solution of the aldehyde **7** (5.13 g, 16.5 mmol) in THF (18 mL) was added over 5 min. A small amount of THF (2 mL) was used to rinse the syringe. After 5 min of stirring, the reaction mixture was poured onto an aqueous solution of ammonium chloride (80 mL) and the aqueous phase was extracted with diethyl ether (3 × 150 mL). The organic phases were dried, filtered and the solvent was evaporated under reduced pressure. The product was purified by flash chromatography using hexane/ethyl acetate (65:35 to 0:100) as eluent to afford diol **8** as an oil (4.51 g, 74%, with 1.04 g of recovered aldehyde **7**).

IR ($CHCl_3$) : 3 620, 3 400, 1 730 $cm^{-1}$.

$^1H$ NMR ($CDCl_3$, $\delta$ ppm) : 5.15 (1H, bt, $J$ = 6 Hz, C*H*=C), 3.78-4.06 (4H, m, $OCH_2CH_2O$), 3.70 (3H, s, $OCH_3$),

3.55-3.75 (3H, m, C*H*OH and C$H_2$OH), 2.58 (1H, d, $J$ = 9.0 Hz, C*H*C$O_2$C$H_3$), 1.18-2.55 (19H, m), 1.68 and 1.59 (3H, bs, C$H_3$, $Z$ and $E$).

$^{13}$C NMR (C$Cl_3$, $\delta$ ppm, $E$ isomer) : 172.5, 135.0, 124.2, 124.1, 117.6, 71.2, 71.1, 65.0, 64.2, 62.6, 59.2, 51.6, 40.7, 36.9, 35.8, 35.35, 35.30, 34.3, 28.9, 28.7, 25.9, 15.8.

MS ($m/e$) : 370 ($M^+$), 352 ($M^+$-$H_2O$), 339 ($M^+$-$OCH_3$).

Exact mass ($M^+$) : calc : 370.2355, found : 370.2349.

• *Alcohols* **9** *and* **10**

To a solution of diol **8** (4.99 g, 13.5 mmol) in THF (130 mL) was added imidazole (2.15 g, 31.7 mmol) and *t*-butyldiphenylchlorosilane (3.96 g, 14.4 mmol). After 2 h of stirring at 20°C, the white suspension was poured on water (95 mL) and the aqueous phase was extracted with diethyl ether (3 × 150 mL). The organic phases were dried, filtered and the solvent was evaporated under reduced pressure. The product was purified by flash chromatography using hexane/ethyl acetate (85:15) as eluent, to afford the alcohols **9** and **10** as a mixture (7.73 g, 95%). The $Z$ and $E$ isomers were separated by medium pressure chromatography (pre-column 22 cm × 20 mm; column 100 cm × 30 mm; $SiO_2$ 240-400 mesh; 40 psi; 1 g per injection) by eluting with a mixture of hexane/*t*-butanol (94:6).

*Methyl 7-[(3Z)-10-(*tert*-butyldiphenylsilyloxy)-7-hydroxy-4-methyldec-3-enyl]-1,4-dioxaspiro [4.4]nonane-6-carboxylate* **9**

IR (C$HCl_3$) : 3 600, 3 440, 1 730, 1 590 cm$^{-1}$.

$^1$H NMR (C$Cl_3$, $\delta$ ppm) : 7.64-7.72 (4H, m), 7.34-7.47 (6H, m), 5.11 (1H, bt, $J$ = 6 Hz, C*H*=C), 3.77-4.04 (4H, m, OC$H_2$C$H_2$O), 3.69 (2H, t, $J$ = 5.8 Hz, C$H_2$OSi), 3.69 (3H, s, OC$H_3$), 3.57 (1H, m, C*H*(OH)), 2.58 (1H, d, $J$ = 9.0 Hz, C*H*C$O_2$C$H_3$), 2.35-2.54 (1H, m, C*H*CHC$O_2$C$H_3$), 2.22 and 2.17 (1H, 2d, $J$ = 4.6 Hz, O*H*), 1.84-2.15 (6H, m), 1.68 (3H, bs, C$H_3$),1.18-1.73 (10H, m), 1.05 (9H, s, C(C$H_3$)$_3$).

*Methyl 7-[(3E)-10-(*tert*-butyldiphenylsilyloxy)-7-hydroxy-4-methyldec-3-enyl]-1,4-dioxaspiro [4.4]nonane-6-carboxylate* **10**

IR (C$HCl_3$) : 3 600, 3 420, 1 730, 1 590 cm$^{-1}$.

$^1$H NMR (C$Cl_3$, $\delta$ ppm) : 7.65-7.72 (4H, m), 7.34-7.43 (6H, m), 5.14 (1H, bt, $J$ = 6 Hz, C*H*=C), 3.80-4.05 (4H, m, OC$H_2$C$H_2$O), 3.70 (3H, s, OC$H_3$), 3.67 (2H, t, $J$ = 5.9 Hz, C$H_2$OSi), 3.60 (1H, m, C*H*(OH)), 2.58 (1H, d, $J$ = 9.0 Hz, C*H*C$O_2$C$H_3$), 2.35-2.53 (1H, m, C*H*CHC$O_2$C$H_3$), 2.13 and 2.11 (1H, 2d, $J$ = 4.5 Hz, O*H*), 1.86-2.13 (6H, m), 1.59 (3H, bs, C$H_3$), 1.18-1.73 (10H, m), 1.05 (9H, s, C(C$H_3$)$_3$).

$^{13}$C NMR (C$Cl_3$, $\delta$ ppm) : 172.5, 135.5, 135.2, 133.6, 129.5, 127.5, 124.2, 117.6, 71.2, 65.0, 64.2, 59.3, 51.6, 40.9, 37.0, 35.8, 35.5, 35.4, 34.1, 28.8, 28.7, 26.7, 26.0, 19.1, 15.8.

MS ($m/e$) : 608 ($M^+$), 590 ($M^+$-$H_2O$), 551 ($M^+$-C(C$H_3$)).

Exact mass ($M^+$) : calc : 608.3533, found : 608.3541.

*Methyl 7-[(3Z)-10-(*tert*-butyldiphenylsilyloxy)-4-methyl-7-oxodec-3-enyl]-1,4-dioxaspiro[4.4]nonane-6-carboxylate* **11**

• *General procedure 1*

To a solution of oxalyl chloride (246 mg, 1.94 mmol) in dichloromethane (20 mL) at −78°C was added dimethyl sulfoxide (331 mg, 4.24 mmol). After stirring for 10 min at −78°C, a solution of alcohol **9** (942 mg, 1.55 mmol) in dichloromethane (5 mL) was slowly added. After stirring for another 10 min at −78°C, triethylamine (893 mg, 8.82 mmol) was added and the reaction mixture was warmed up to 0°C by taking away the cooling bath. Water was then added (20 mL) and the mixture was extracted with dichloromethane (3×20 mL). The organic phases were dried, filtered and the solvent was evaporated under reduced pressure. The product was purified by flash chromatography using hexane/ethyl acetate (75:25) as eluent to afford the ketone **11** as an oil (905 mg, 96%).

IR (C$HCl_3$) : 1 730, 1 715, 1 590 cm$^{-1}$.

$^1$H NMR (C$Cl_3$, $\delta$ ppm) : 7.62-7.68 (4H, m), 7.33-7.47 (6H, m), 5.11 (1H, bt, $J$ = 6 Hz, C*H*=C), 3.75-4.07 (4H, m, OC$H_2$C$H_2$O), 3.69 (3H, s, OC$H_3$), 3.66 (2H, t, $J$ = 6.1 Hz, C$H_2$OSi), 2.35-2.58 (6H, m), 2.16-2.28 (2H, m), 1.74-2.01 (7H, m), 1.64 (3H, bs, C$H_3$), 1.20-1.54 (3H, m), 1.04 (9H, s, C(C$H_3$)$_3$).

*Methyl 7-[(3E)-10-(*tert*-butyldiphenylsilyloxy)-4-methyl-7-oxodec-3-enyl]-1,4-dioxaspiro[4.4]nonane-6-carboxylate* **12**

According to procedure 1, the oxidation of alcohol **10** (1.26 g, 2.06 mmol) provided ketone **12** as an oil (1.20 g, 96%).

IR (C$HCl_3$) : 1 730, 1 715, 1 590 cm$^{-1}$.

$^1$H NMR (C$Cl_3$, $\delta$ ppm) : 7.61-7.69 (4H, m), 7.33-7.47 (6H, m), 5.08 (1H, bt, $J$ = 6 Hz, C*H*=C), 3.80-4.06 (4H, m, OC$H_2$C$H_2$O), 3.70 (3H, s, OC$H_3$), 3.66 (2H, t, $J$ = 6.1 Hz, C$H_2$OSi), 2.36-2.60 (6H, m), 2.17-2.26 (2H, m), 1.76-2.00 (7H, m), 1.56 (3H, bs, C$H_3$), 1.16-1.55 (3H, m), 1.04 (9H, s, C(C$H_3$)$_3$).

$^{13}$C NMR (C$Cl_3$, $\delta$ ppm) : 210.5, 172.5, 135.5, 133.8, 133.7, 129.5, 127.6, 124.5, 117.7, 65.1, 64.2, 63.0, 59.3, 51.7, 41.5, 40.9, 39.0, 37.0, 35.5, 33.4, 28.8, 26.8, 26.6, 26.1, 19.1, 16.0.

MS ($m/e$) : 606 ($M^+$), 575 ($M^+$-$OCH_3$), 549 ($M^+$-C(C$H_3$)).

Exact mass ($M^+$) : calc : 606.3376, found : 606.3371.

*Methyl 7-[(3Z)-10-(*tert*-butyldiphenylsilyloxy)-4-methyl-7-methylidenedec-3-enyl]-1,4-dioxaspiro[4.4]nonane-6-carboxylate* **13**

To a solution of triphenylmethylphosphonium bromide (1.24 g, 3.46 mmol) in benzene (30 mL) was added sodium *t*-amylate (2.98 mL, 1,0 M in benzene, 2.98 mmol). A solution of the ketone **11** (905 mg, 1.49 mmol) in benzene (5 mL) was added to the yellow suspension of triphenylmethylenephosphorane. After 2 h of stirring at room temperature, an aqueous solution of ammonium chloride (20 mL) was added and the mixture was extracted with diethyl ether (3 × 20 mL). The organic phases were dried, filtered and the solvent was evaporated under reduced pressure. The product was purified by flash chromatography using hexane/ethyl acetate (8:2) as eluent to afford the diene **13** as an oil (846 mg, 94%).

IR (C$HCl_3$) : 1 730, 1 640, 1 590 cm$^{-1}$.

$^1$H NMR (C$Cl_3$, $\delta$ ppm) : 7.64-7.71 (4H, m), 7.34-7.47 (6H, m), 5.10 (1H, bt, $J$ = 6 Hz, C*H*=C), 4.68-4.74 (2H, m, C=C$H_2$), 3.78-4.04 (4H, m, OC$H_2$C$H_2$O), 3.69 (3H, s, OC$H_3$), 3.67 (2H, t, $J$ = 6.4 Hz, C$H_2$OSi), 2.56 (1H, d, $J$ = 9.0 Hz, C*H*C$O_2$C$H_3$), 2.35-2.55 (1H, m, C*H*CHC$O_2$C$H_3$), 1.83-2.13 (11H, m), 1.63-1.76 (2H, m), 1.66 (3H, bs, C$H_3$), 1.20-1.59 (3H, m), 1.05 (9H, s, C(C$H_3$)$_3$).

*Methyl 7-[(3E)-10-(tert-butyldiphenylsilyloxy)-4-methyl-7-methylidenedec-3-enyl]-1,4-dioxaspiro[4.4]nonane-6-carboxylate* **14**

According to the procedure used to obtain diene **13**, the methylenation of ketone **12** (1.20 g, 1.98 mmol) provided diene **14** as an oil (1.14 g, 95%).

IR ($CHCl_3$) : 1 730, 1 640, 1 590 $cm^{-1}$.

$^1H$ NMR ($CDCl_3$, $\delta$ ppm) : 7.64-7.71 (4H, m), 7.33-7.46 (6H, m), 5.09 (1H, bt, $J$ = 6 Hz, $CH$=C), 4.68 (2H, bs, C=$CH_2$), 3.79-4.06 (4H, m, $OCH_2CH_2O$), 3.70 (3H, s, $OCH_3$), 3.67 (2H, t, $J$ = 6.4 Hz, $CH_2OSi$), 2.58 (1H, d, $J$ = 8.9 Hz, $CHCO_2CH_3$), 1.35-1.55 (1H, m, $CHCHCO_2CH_3$), 1.80-2.12 (11H, m), 1.62-1.74 (2H, m), 1.58 (3H, bs, $CH_3$), 1,17-1.53 (3H, m), 1.05 (9H, s, $C(CH_3)_3$).

$^{13}C$ NMR ($CDCl_3$, $\delta$ ppm) : 172.3, 149.1, 135.3, 134.8, 133.8, 129.2, 127.3, 123.8, 117.5, 108.6, 64.9, 64.0, 63.3, 59.1, 51.4, 40.8, 37.8, 36.8, 35.4, 34.5, 32.0, 30.5, 28.7, 26.6, 25.9, 18.9, 15.7.

MS ($m/e$) : 604 ($M^+$).

Exact mass ($M^+$) : calc : 604.3584, found : 604.3569.

*Methyl 7-((3Z)-10-hydroxy-4-methyl-7-methylidenedec-3-enyl)-1,4-dioxaspiro[4.4]nonane-6-carboxylate* **15**

To a solution of diene **13** (778 mg, 1.29 mmol) in THF, was added tetrabutylammonium fluoride (1.54 mL of 1.0 M in THF, 1.54 mmol). After stirring for 3 h at 20°C, the solvent was evaporated under reduced pressure and the product was directly purified by flash chromatography using diethyl ether as eluent to afford the alcohol **15** as an oil (475 mg, 100%).

IR ($CHCl_3$) : 3 620, 3 530, 1 730, 1 640 $cm^{-1}$.

$^1H$ NMR ($CDCl_3$, $\delta$ ppm) : 5.10 (1H, bt, $J$ = 6 Hz, $CH$=C), 4.75 (2H, bs, C=$CH_2$), 3 78-4.06 (4H, m, $OCH_2CH_2O$), 3.72 (3H, s, $OCH_3$), 3.67 (2H, bt, $J$ = 6 Hz, $CH_2OH$), 2.58 (1H, d, $J$ = 9.0 Hz, $CHCO_2CH_3$), 2.35-2.55 (1H, m, $CHCHCO_2CH_3$), 1.80-2.20 (11H, m), 1.51-1.80 (3H, m), 1.67 (3H, bs, $CH_3$), 1.20-1.53 (3H, m).

*Methyl 7-((3E)-10-hydroxy-4-methyl-7-methylidenedec-3-enyl)-1,4-dioxaspiro[4.4]nonane-6-carboxylate* **16**

According to procedure used to obtain alcohol **15**, diene **14** (1.14 g, 1.88 mmol) provided alcohol **16** as an oil (687 mg, 100%).

IR ($CHCl_3$) : 3 620, 3 530, 1 730, 1 640 $cm^{-1}$.

$^1H$ NMR ($CDCl_3$, $\delta$ ppm) : 5.10 (1H, bt, $J$ = 6 Hz, $CH$=C), 4.73 (2H, bs, C=$CH_2$), 3.78-4.07 (4H, m, $OCH_2CH_2O$), 3.70 (3H, s, $OCH_3$), 3.60-3.70 (2H, m, $CH_2OH$), 2.58 (1H, d, $J$ = 9.0 Hz, $CHCO_2CH_3$), 2.35-2.55 (1H, m, $CHCHCO_2CH_3$), 1.80-2.18 (11H, m), 1.66-1.79 (2H, m), 1.58 (3H, bs, $CH_3$), 1.18-1.56 (4H, m).

$^{13}C$ NMR ($CDCl_3$, $\delta$ ppm) : 172.5, 149.1, 134.9, 124.1, 117.6, 109.0, 65.0, 64.2, 62.5, 59.3, 51.6, 40.8, 37.8, 36.9, 35.4, 34.5, 32.1, 30.6, 28.7, 25.9, 15.8.

MS ($m/e$) : 366 ($M^+$), 335 ($M^+$-$OCH_3$).

Exact mass ($M^+$) : calc : 366.2406, found : 366.2413.

*Methyl 7-[(3Z)-4-methyl-7-methylidene-10-oxodec-3-enyl]-1,4-dioxaspiro[4.4]nonane-6-carboxylate* **17**

According to procedure 1, the oxidation of alcohol **15** (475 mg, 1.30 mmol) provided aldehyde **17** as an oil (446 mg, 94%).

IR ($CHCl_3$) : 2 720, 1 730, 1 640 $cm^{-1}$.

$^1H$ NMR ($CDCl_3$, $\delta$ ppm) : 9.79 (1H, t, $J$ = 1.7 Hz, $CHO$), 5.10 (1H, bt, $J$ = 6 Hz, $CH$=C), 4.80 and 4.72 (2H, 2 bs, C=$CH_2$), 3.78-4.05 (4H, m, $OCH_2CH_2O$), 3.70 (3H, s, $OCH_3$), 2.54-2.63 (2H, m, $CH_2CHO$), 2.57 (1H, d, $J$ = 9.4 Hz, $CHCO_2CH_3$), 2.30-2.55 (3H, m, $CH_2CH_2CHO$ and $CHCHCO_2CH_3$), 1.82-2.17 (9H, m), 1.67 (3H, bs, $CH_3$), 1.17-1.58 (3H, m).

*Methyl 7-[(3E)-4-methyl-7-methylidene-10-oxodec-3-enyl]-1,4-dioxaspiro[4.4]nonane-6-carboxylate* **18**

According to procedure 1, oxidation of alcohol **16** (687 mg, 1.88 mmol) provided aldehyde **18** as an oil (622 mg, 91%).

IR ($CHCl_3$) : 2 720, 1 730, 1 640 $cm^{-1}$.

$^1H$ NMR ($CDCl_3$, $\delta$ ppm) : 9.78 (1H, t, $J$ = 1.7 Hz, $CHO$), 5.10 (1H, bt, $J$ = 6 Hz, $CH$=C), 4.77 and 4.70 (2H, 2 bs, C=$CH_2$), 3.80-4.06 (4H, $OCH_2CH_2O$), 3.70 (3H, s, $OCH_3$), 2.54-2.62 (3H, m, $CHCO_2CH_3$ and $CH_2CHO$), 2.30-2.54 (3H, m, $CHCHCO_2CH_3$ and $CH_2CH_2CHO$), 1.10 (4H, bs, =$CCH_2CH_2C$=), 1.80-2.04 (5H, m), 1.58 (3H, bs, $CH_3$), 1.18-1.56 (3H, m).

$^{13}C$ NMR ($CDCl_3$, $\delta$ ppm) : 202.1, 172.4, 147.5, 134.6, 124.3, 117.7, 109.6, 65.1, 64.2, 59.3, 51.6, 41.7, 40.8, 37.8, 37.0, 35.5, 34.8, 28.8, 28.0, 26.0, 15.8.

MS ($m/e$) : 364 ($M^+$), 336 ($M^+$-CO), 333 ($M^+$-$OCH_3$).

Exact mass ($M^+$) : calc : 364.2250, found : 364.2246.

*Methyl 7-[(3Z)-10-hydroxy-4-methyl-7-methylidenedodec-3-en-11-ynyl]-1,4-dioxaspiro[4.4]nonane-6-carboxylate* **19**

• *General procedure 2*

Acetylene was purified by passing sequentially through two cold traps at −78°C, one sulfuric acid trap and one trap filled with two equal portions of sodium hydroxide and anhydrous calcium sulfate. Gaseous acetylene (175 mL, 7.3 mmol) was measured with a 50 mL gas-tight syringe and dissolved in THF (25 mL) at −78°C. *n*-Butyllithium (2.22 mL of 1.65 M in hexane, 3.66 mmol) was added and the solution was stirred for 15 min at −78°C. A solution of the aldehyde **17** (446 mg, 1.2 mmol) in THF (3 mL) was rapidly added to the solution of the acetylide. After stirring for 5 min at −78°C, the reaction mixture was poured into an aqueous solution of ammonium chloride (20 mL) and extracted with diethyl ether (3 × 10 mL). The organic phase was dried, filtered and evaporated under reduced pressure. The product was purified by flash chromatography using dichloromethane/diethyl ether (9:1 to 7:3) as eluent to afford the propargylic alcohol **19** as an oil (397 mg, 83%, with 62 mg of recovered starting material).

IR ($CHCl_3$) : 3 600, 3 480, 3 310, 1 730, 1 640 $cm^{-1}$.

$^1H$ NMR ($CDCl_3$, $\delta$ ppm) : 5.10 (1H, bt, $J$ = 6 Hz, $CH$=C), 4.77 (2H, bs, C=$CH_2$), 4.41 (1H, bq, $J$ = 6 Hz, $CH$(OH)), 3.79-4.06 (4H, m, $OCH_2CH_2O$), 3.70 (3H, s, $OCH_3$), 2.58 (1H, d, $J$ = 9,0 Hz, $CHCO_2CH_3$), 2.49 (1H, d, $J$ = 2.1 Hz, C≡$CH$), 2.35-2.55 (1H, m, $CHCHCO_2CH_3$),1.81-2.30 (14H, m), 1.67 (3H, bs, $CH_3$), 1.22-1.53 (3H, m).

*Methyl 7-[(3E)-10-hydroxy-4-methyl-7-methylidenedodec-3-en-11-ynyl]-1,4-dioxaspiro[4.4]nonane-6-carboxylate* **20**

According to procedure 2, alkylation of aldehyde **18** (687 mg, 1.88 mmol) provided propargylic alcohol **20** as an oil (588 mg, 88%, with 55 mg of recovered starting material).

IR ($CHCl_3$) : 3 600, 3 480, 3 310, 1 730, 1 640 $cm^{-1}$.

$^1H$ NMR ($CDCl_3$, $\delta$ ppm) : 5.10 (1H, bt, $J$ = 6 Hz, $CH$=C), 4.75 (2H, bs, C=$CH_2$), 4.40 (1H, bq, $J$ = 6 Hz, $CH$(OH)),

3.79-4.06 (4H, m, $OCH_2CH_2O$), 3.71 (3H, s, $OCH_3$), 2.58 (1H, d, $J$ = 9.0 Hz, $CHCO_2CH_3$), 2.48 (1H, d, $J$ = 2.1 Hz, C≡C*H*), 2.35-2.55 (1H, m, $CHCHCO_2CH_3$), 1.80-2.27 (14H, m), 1.58 (3H, bs, $CH_3$), 1.20-1.55 (3H, m).

$^{13}$C NMR ($CDCl_3$, $\delta$ ppm) : 172.5, 148.4, 134.7, 124.1, 117.6, 109.3, 84.8, 72.8, 65.0, 64.2, 61.7, 59.2, 51.6, 40.7, 37.8, 36.9, 35.5, 35.3, 34.6, 31.1, 28.7, 25.9, 15.7.

MS ($m/e$) : 390 ($M^+$), 374 ($M^+$-$H_2O$), 359 ($M^+$-$OCH_3$).

Exact mass ($M^+$) : calc : 390.2406, found : 390.2413.

*Methyl 2-((3Z)-10-hydroxy-4-methyl-7-methylidene-dodec-3-en-11-ynyl)-5-oxocyclopentane-1-carboxylate* **21**

• *General procedure 3*

To a solution of propargylic alcohol **19** (451 mg, 1.16 mmol) in acetone (40 mL) was added boron trifluoride-diethyl etherate (41 mg, 0.29 mmol). After stirring for 14 h at room temperature, water (10 mL) was added and most of the acetone was evaporated under reduced pressure. The aqueous phase was extracted with dichloromethane (3 × 20 mL) and the organic phase was dried, filtered and evaporated under reduced pressure. The product was purified by flash chromatography using dichloromethane/diethyl ether (95:5 to 8:2) as eluent, to afford the $\beta$-ketoester **21** as an oil (393 mg, 98%).

IR ($CHCl_3$) : 3 600, 3 480, 3 300, 1 760, 1 730, 1 640 cm$^{-1}$.

$^1$H NMR ($CDCl_3$, $\delta$ ppm) : 5.12 (1H, bt, $J$ = 6 Hz, C*H*=C), 4.78 (2H, bs, C=C$H_2$), 4 41 (1H, qd, $J$ = 6.0 and 2.1 Hz, C*H*(OH)), 3.76 (3H, s, $OCH_3$), 2.86 (1H, d, $J$ = 11.2 Hz, $CHCO_2CH_3$), 2.50-2.68 (1H, m, $CHCHCO_2CH_3$), 2.49 (1H, d, $J$ = 2.1 Hz, C≡C*H*), 1.80-2.50 (14H, m), 1.69 (3H, bs, $CH_3$), 1.37-1.68 (3H, m).

*Methyl 2-((3E)-10-hydroxy-4-methyl-7-methylidene-dodec-3-en-11-ynyl)-5-oxocyclopentane-1-carboxylate* **22**

According to procedure 3, propargylic alcohol **20** (461 mg, 1.18 mmol) provided $\beta$-ketoester **22** as an oil (395 mg, 96%).

IR ($CHCl_3$) : 3 600, 3 500, 3 310, 1 760, 1 730, 1 640 cm$^{-1}$.

$^1$H NMR ($CDCl_3$, $\delta$ ppm) : 5.12 (1H, bt, $J$ = 6 Hz, C*H*=C), 4.76 (2H, bs, C=C$H_2$), 4 41 (1H, bq, $J$ = 6 Hz, C*H*(OH)), 3.75 (3H, s, $OCH_3$), 2.86 (1H, d, $J$ = 10.7 Hz, $CHCO_2CH_3$), 2.52-2.68 (1H, m, $CHCHCO_2CH_3$), 2.49 (1H, d, $J$ = 2.1 Hz, C≡C*H*), 2.00-2.50 (11H, m), 1.98 and 1.97 (1H, 2d, $J$ = 5.8 Hz, O*H*), 1.81-1.91 (2H, m), 1.61 (3H, bs, $CH_3$), 1.38-1.71 (3H, m).

$^{13}$C NMR ($CDCl_3$, $\delta$ ppm) : 211.9, 169.9, 148.3, 135.3, 123.6, 109.4, 84.8, 72.8, 61.6, 52.3, 40.9, 38.3, 37.8, 35.5, 34.8, 34.5, 31.1, 27.1, 25.4, 15.8.

MS ($m/e$) : 346 ($M^+$), 331 ($M^+$-$CH_3$), 318 ($M^+$-$H_2O$), 315 ($M^+$-$OCH_3$).

Exact mass ($M^+$) : calc 346.2144, found : 346.2142.

*Methyl 2-((3Z)-4-methyl-7-methylidene-10-oxododec-3-en-11-ynyl)-5-oxocyclopentane-1-carboxylate* **23**

• *General procedure 4*

To a solution of the $\beta$-ketoester **21** (196 mg, 0.565 mmol) in acetone (20 mL), was slowly added the Jones reagent at 10°C until persistence of the red color. Excess reagent was destroyed by adding isopropanol until a green color appeared. Water (10 mL) was added and most of the acetone was removed by evaporation under reduced pressure. The resulting green solution was extracted with dichloromethane (3 × 30 mL) and the organic phase was dried, filtered and evaporated under reduced pressure. The product was rapidly purified by flash chromatography using dichloromethane/diethyl ether (95:5) as eluent to afford ynone **23** as an oil (178 mg, 92%).

IR ($CHCl_3$) : 3 300, 2 100, 1 750, 1 725, 1 680, 1 640 cm$^{-1}$.

$^1$H NMR ($CDCl_3$, $\delta$ ppm) : 5.12 (1H, bt, $J$ = 6 Hz, C*H*=C), 4.80 and 4.73 (2H, 2 bs, C=C$H_2$), 3.75 (3H, s, $OCH_3$), 3.25 (1H, s, C≡C*H*), 2.85 (1H, d, $J$ = 11.1 Hz, $CHCO_2CH_3$), 2.71-2.81 (2H, m), 2.50-2.68 (1H, m, $CHCHCO_2CH_3$), 1.85-2.50 (11H, m), 1.68 (3H, s, $CH_3$), 1.35-1.70 (3H, m).

*Methyl 2-((3E)-4-methyl-7-methylidene-10-oxododec-3-en-11-ynyl)-5-oxocyclopentane-1-carboxylate* **24**

According to procedure 4, $\beta$-ketoester **22** (110 mg, 0.318 mmol) provided ynone **24** as an oil (91 mg, 83%).

IR ($CHCl_3$) : 3 300, 2 100, 1 755, 1 730, 1 680, 1 645 cm$^{-1}$.

$^1$H NMR ($CDCl_3$, $\delta$ ppm) : 5.12 (1H, bt, $J$ = 6 Hz, C*H*=C), 4.77 and 4.71 (2H, 2 bs, C=C$H_2$), 3.76 (3H, s, $OCH_3$), 3.24 (1H, s, C≡C*H*), 2.85 (1H, d, $J$ = 11.1 Hz, $CHCO_2CH_3$), 2.71-2,80 (2H, m), 2.50-2.67 (1H, m, $CHCHCO_2CH_3$), 1.84-2.50 (7H, m), 2.11 (4H, bs, =C-C$H_2$C$H_2$-C=),1.60 (3H, bs, $CH_3$),1.35-1.73 (3H, m).

$^{13}$C NMR ($CDCl_3$, $\delta$ ppm) : 211.7, 186.6, 169.8, 147.0, 135.1, 123.7, 109.6, 81.2, 78.7, 61.6, 52.2, 43.5, 40.9, 38.3, 37.7, 34.8, 34.7, 29.4, 27.1, 25.4, 15.8.

MS ($m/e$) : 344 ($M^+$), 329 ($M^+$-$CH_3$), 316 ($M^+$-CO), 303 ($M^+$-$OCH_3$).

Exact mass ($M^+$) : calc : 344.1987, found : 344.1985.

• *Large rings* **25** *and* **26**

• *General procedure 5*

To a solution of ynone **23** (127 mg, 0.37 mmol) in acetonitrile (37 mL) was added cesium carbonate (24 mg, 0.074 mmol). After stirring for 1 h at room temperature, the suspension was filtered on celite and the solvent was evaporated under reduced pressure. The products were purified by flash chromatography using hexane/ethyl acetate (9:1 to 8:2) as eluent to afford the large rings **25** and **26** as oils (48 mg of **25**, 68 mg of **26**, 38% and 54%).

*Methyl (2Z,10Z)-10-methyl-7-methylidene-4,17-dioxo-*trans*-bicyclo[12.3.0]heptadeca-2,10-diene-1-carboxylate* **25**

IR ($CHCl_3$) : 1 750, 1 730, 1 685, 1 640, 1 605 cm$^{-1}$.

$^1$H NMR ($CDCl_3$, $\delta$ ppm) : 6.91 (1H, d, $J$ = 12.1 Hz, C*H*=CH), 6.44 (1H, d, $J$ = 12.1 Hz, CH=C*H*C=O), 5.00 (1H, bt, $J$ = 8 Hz, C*H*=C), 4.90 and 4.82 (2H, 2 bs, C=C$H_2$), 3,76 (3H, s, $OCH_3$), 3.07 (1H, dt, $J$ = 19.1 and 10.0 Hz), 1.20-2.85 (16H, m), 1.67 (3H, bs, $CH_3$).

MS ($m/e$) : 344 ($M^+$), 326 ($M^+$-$H_2O$), 313 ($M^+$-$OCH_3$).

Exact mass ($M^+$) : calc : 344.1987, found : 344.1983.

*Methyl (2E,10Z)-10-methyl-7-methylidene-4,17-dioxo-*trans*-bicyclo[12.3.0]heptadeca-2,10-diene-1-carboxylate* **26**

IR ($CHCl_3$) : 1 750, 1 730, 1 690, 1 665, 1 640, 1 620 cm$^{-1}$.

$^1$H NMR ($CDCl_3$, $\delta$ ppm) : 6.94 (1H, d, $J$ = 16.8 Hz, C*H*=CHCO), 6.17 (1H, d, $J$ = 16.8 Hz, CH=C*H*CO),

5.04 (1H, bt, $J$ = 6.0 Hz, C$H$=C), 4.80 (2H, bs, C=C$H_2$), 3.76 (3H, s, OC$H_3$), 1.80-2.90 (15H, m), 1.68 (3H, bs, C$H_3$),1.47-1.65 (2H, m).

MS ($m/e$) : 344 ($M^+$), 326 ($M^+$-$H_2O$), 313 ($M^+$-$OCH_3$).

Exact mass ($M^+$) : calc : 344.1987, found : 344.1983.

• *Large rings* **27** *and* **28**

According to procedure 5, ynone **24** (50 mg, 0.146 mmol) provided the large rings. **27** as an oil and **28** as a solid (20 mg of **27**, 23 mg of **28**, 40% and 46%).

*Methyl (2Z,10E)-10-methyl-7-methylidene-4,17-dioxo-*trans*-bicyclo[12.3.0]heptadeca-2,10-diene-1-carboxylate* **27**

IR ($CHCl_3$) : 1 750, 1 730, 1 690, 1 645, 1 610 $cm^{-1}$.

$^1H$ NMR ($CDCl_3$, $\delta$ ppm) : 6.88 (1H, d, $J$ = 12.0 Hz, C$H$=CHCO), 6.34 (1H, d, $J$ = 12.0 Hz, CH=C$H$CO), 4.95 and 4.74 (2H, 2 bs, C=C$H_2$), 4.77 (1H, bt, $J$ = 6 Hz, C$H$=C), 3.75 (3H, s, OC$H_3$), 3.15 (1H, dt, $J$ = 18.9 and 10.0 Hz), 2.76 (1H, ddd, $J$ = 14.1, 8.6 and 3.3 Hz), 1.60-2.63 (13H, m), 1.54 (3H, bs, C$H_3$), 1.23-1.40 (2H, m).

$^{13}C$ NMR ($CDCl_3$, $\delta$ ppm) : 211.1, 200.1, 171.1, 144.9, 144.7, 134.4, 126.6, 124.8, 111.0, 66.0, 52.3, 46.3, 40.5, 37.9, 35.8, 33.1, 32.5, 30.6, 27.2, 24.4, 16.1.

MS ($m/e$) : 344 ($M^+$), 326 ($M^+$-$H_2O$), 313 ($M^+$-$OCH_3$).

Exact mass ($M^+$) : calc : 344.1987, found : 344.1983.

*Methyl (2E,10E)-10-methyl-7-methylidene-4,17-dioxo-*trans*-bicyclo[12.3.0]heptadeca-2,10-diene-1-carboxylate* **28**

MP : 97-98°C (crystallized from hexane/ethyl ether).

IR ($CHCl_3$) : 1 750, 1 730, 1 690, 1 645, 1 620 $cm^{-1}$.

$^1H$ NMR ($CDCl_3$, $\delta$ ppm) : 7.06 (1H, d, $J$ = 16.1 Hz, C$H$=CHCO), 6.34 (1H, d, $J$ = 16.1 Hz, CH=C$H$CO), 5.8 (1H, bt, $J$ = 7 Hz, C$H$=C), 4.82 and 4.58 (2H, 2 bs, C=C$H_2$), 3.70 (3H, s, OC$H_3$), 1.80-2.78 (15H, m), 1.62 (3H, bs, C$H_3$), 1.45-1.62 (2H, m).

$^{13}C$ NMR ($CDCl_3$, $\delta$ ppm) : 211.7, 200.0, 168.8, 146.5, 141.8, 136.0, 126.7, 124.3, 110.9, 65.1, 52.4, 43.5, 39.0, 38.2, 36.7, 34.5, 31.1, 29.5, 26.1, 24.2, 15.2.

MS ($m/e$) : 344 ($M^+$), 326 ($M^+$-$H_2O$), 313 ($M^+$-$OCH_3$).

Exact mass ($M^+$) : calc : 344.1987, found : 344.1984.

• *Large ring* **28** *obtained by enone isomerization of the large ring* **27**

To a solution of **27** (32.7 mg, 0.095 mmol) in acetic acid (0.5 mL) was added potassium iodide (31 mg, 0.19 mmol). After 60 h of stirring, water was added (3 mL) and the mixture was extracted with dichloromethane (3 × 5 mL). The organic phases were washed with an aqueous solution of saturated sodium bicarbonate to which a few crystals of sodium thiosulfate had been added. The organic phase was dried, filtered and the solvent was evaporated under reduced pressure. The product was purified as usual to afford the products as a 95:5 mixture of **28** and **27** (26.3 mg, 80%).

*Methyl 2-((3Z)-10-hydroxy-4-methyl-7-methylidene-dodeca-3,11-dienyl)-5-oxocyclopentane-1-carboxylate* **29**

The $\beta$-ketoester **21** (189 mg, 0.546 mmol) in solution in ethyl acetate (20 mL) was hydrogenated under a hydrogen pressure of one atmosphere with the Lindlar catalyst (10 mg of 5% palladium on calcium carbonate and lead oxide) for 2 h at room temperature. The suspension was filtered through silica gel and the solvent was evaporated under reduced pressure. The product was purified by flash chromatography using dichloromethane/diethyl ether (9:1) as eluent to afford the allylic alcohol **29** as an oil (174 mg, 92%).

IR ($CHCl_3$) : 3 600, 3 540, 1 750, 1 730, 1 655, 1 645 $cm^{-1}$.

$^1H$ NMR ($CDCl_3$, $\delta$ ppm) : 5.89 (1H, ddd, $J$ = 17.2, 10.4 and 6.2 Hz, C$H$=CH$_2$), 5.24 (1H, bd, $J$ = 17.2 Hz, CH=C$H_E$H$_Z$), 5.13 (1H, d, $J$ = 10.4 Hz, CH=CH$_E$$H_Z$), 5.13 (1H, bt, C$H$=C), 4.76 (2H, bs, C=C$H_2$), 4.14 (1H, m, C$H$(OH)), 3.75 (3H, s, OC$H_3$), 2.85 (1H, d, $J$ = 11.1 Hz, C$H$CO$_2$CH$_3$), 1.90-2.70 (12H, m), 1.69 (3H, bs, C$H_3$), 1.38-1.77 (4H, m).

*Methyl 2-((3E)-10-hydroxy-4-methyl-7-methylidene-dodeca-3,11-dienyl)-5-oxocyclopentane-1-carboxylate* **30**

According to the procedure used to obtain the allylic alcohol **29**, $\beta$-ketoester **22** (108 mg, 0.314 mmol) provided allylic alcohol **30** as an oil (100 mg, 92%).

IR ($CHCl_3$) : 3 600, 3 500, 1 755, 1 725, 1 640 $cm^{-1}$.

$^1H$ NMR ($CDCl_3$, $\delta$ ppm) : 5.88 (1H, ddd, $J$ = 17.2, 10.4 and 6.2 Hz, C$H$=CH$_2$), 5.24 (1H, dt, $J$ = 17.2 and 1.4 Hz, CH=C$H_E$H$_Z$), 5.13 (1H, dt, $J$ = 10.4 and 1.3 Hz, CH=CH$_E$$H_Z$), 5.11 (1H, bt, $J$ = 7 Hz, C$H$=C), 4.74 (2H, bs, C=C$H_2$), 4.13 (1H, m, C$H$(OH)), 3.76 (3H, s, OC$H_3$), 2.85 (1H, d, $J$ = 11.1 Hz, C$H$CO$_2$CH$_3$), 1.94-2.70 (13H, m),1.37-1.78 (4H, m), 1.60 (3H, bs, C$H_3$).

*Methyl 2-((3Z)-4-methyl-7-methylidene-10-oxododeca-3,11-dienyl)-5-oxocyclopentane-1-carboxylate* **31**

According to procedure 4, the oxidation of allylic alcohol **29** (165 mg, 0.474 mmol) provided enone **31** as an oil (146 mg, 89%).

IR ($CHCl_3$) : 1 750, 1 725, 1 700, 1 680, 1 645, 1 615 $cm^{-1}$.

$^1H$ NMR ($CDCl_3$, $\delta$ ppm) : 6.38 (1H, dd, $J$ = 17.7 and 10.1 Hz, C$H$=CH$_2$), 6.25 (1H, dd, $J$ = 17.7 and 1.5 Hz, CH=C$H_E$H$_Z$), 5.85 (1H, dd, $J$ = 10.1 and 1.5 Hz, CH=CH$_E$$H_Z$), 5.11 (1H, bt, $J$ = 7 Hz, C$H$=C), 4.78 and 4.72 (2H, 2 bs, C=C$H_2$), 3.75 (3H, s, OC$H_3$), 2.85 (1H, d, $J$ = 11.2 Hz, C$H$CO$_2$CH$_3$), 1.90-2.80 (14H, m), 1.69 (3H, bs, C$H_3$), 1.35-1.75 (3H, m).

*Methyl 2-((3E)-4-methyl-7-methylidene-10-oxododeca-3,11-dienyl)-5-oxocyclopentane-1-carboxylate* **32**

According to procedure 4, the oxidation of allylic alcohol **30** (57.5 mg, 0.165 mmol) provided enone **32** as an oil (49.5 mg, 86%).

IR ($CHCl_3$) : 1 755, 1 730, 1 700, 1 680, 1 645, 1 615 $cm^{-1}$.

$^1H$ NMR ($CDCl_3$, $\delta$ ppm) : 6.38 (1H, dd, $J$ = 17.7 and 10.1 Hz, C$H$=CH$_2$), 6.23 (1H, dd, $J$ = 17.7 and 1.6 Hz, CH=C$H_E$H$_Z$), 5.83 (1H, dd, $J$ = 10.1 and 1.6 Hz, CH=CH$_E$$H_Z$), 5.12 (1H, bt, $J$ = 7 Hz, C$H$=C), 4.75 and 4.70 (2H, 2 bs, C=C$H_2$), 3.75 (3H, s, OC$H_3$), 2.85 (1H, d, $J$ = 11.1 Hz, C$H$CO$_2$CH$_3$), 1.85-2.78 (14H, m), 1.60 (3H, bs, C$H_3$), 1.34-1.70 (3H, m).

*Methyl (10Z)-10-methyl-7-methylidene-4,17-dioxo-*trans*-bicyclo[12.3.0]heptadec-10-ene-1-carboxylate* **33**

According to procedure 5, enone **31** (140 mg, 0.405 mmol) provided the large ring **33** as an oil (104 mg, 74%).

IR ($CHCl_3$) : 1 750, 1 725, 1 715, 1 640 $cm^{-1}$.

$^1H$ NMR ($CDCl_3$, $\delta$ ppm) : 5.15 (1H, bt, $J$ = 7 Hz, C$H$=C), 4.72 (2H, bs, C=C$H_2$), 3.66 (3H, s, OC$H_3$), 2.83 (1H,

ddd, $J$ = 18.2, 8.7 and 3.3 Hz), 1.60-2.75 (18H, m), 1.69 (3H, s, $CH_3$), 1.13-1.40 (2H, m).

MS ($m/e$) : 346 ($M^+$), 328 ($M^+$-$H_2O$), 315 ($M^+$-$OCH_3$).

Exact mass ($M^+$) : calc : 346.2144, found : 346.2138.

*Methyl (10E)-10-methyl-7-methylidene-4,17-dioxo-*trans*-bicyclo[12.3.0]heptadec-10-ene-1-carboxylate* **34**

According to procedure 5, enone **32** (45.0 mg, 0.130 mmol) provided the large ring **34** as a white powder (32 mg 71%).

MP : 140-142°C (crystallized from hexane/diethyl ether).

IR ($CHCl_3$) : 1 750, 1 725, 1 715, 1 640 $cm^{-1}$.

$^1H$ NMR ($CDCl_3$, $\delta$ ppm) : 4.96 (1H, bdd, $J$ = 10.0 and 4.2 Hz, $CH$=C), 4.59 and 4.53 (2H, 2 bs, C=$CH_2$), 3.65 (3H, s, $OCH_3$), 1.50-2.82 (20H, m), 1.57 (3H, s, $CH_3$), 1.10-1.17 (1H, m).

MS ($m/e$) : 346 ($M^+$), 328 ($M^+$-$H_2O$), 315 ($M^+$-$OCH_3$).

Exact mass ($M^+$) : calc : 346.2144, found : 346.2138.

*Methyl 7-[(3E)-7-acetoxy-10-(*tert*-butyldiphenylsilyloxy)-4-methyldec-3-enyl]-1,4-dioxaspiro[4.4]nonane-6-carboxylate* **35**

To a solution of alcohol **10** (1.82 g, 2.99 mmol) in dichloromethane (20 mL) were added acetic anhydride (611 mg, 5.98 mmol), triethylamine (907 mg, 8.97 mmol) and 4-dimethylaminopyridine (18 mg, 0.15 mmol). After stirring for 3 h at room temperature, water was added (20 mL) and the organic phase was separated and the aqueous phase was extracted with dichloromethane (2 × 20 mL). The organic phases were dried, filtered and the solvent was evaporated under reduced pressure. The product was purified by flash chromatography using dichloromethane/diethyl ether (95:5) as eluent to afford the acetate **35** as an oil (1.89 g, 97%).

IR ($CHCl_3$) : 1 730, 1 590 $cm^{-1}$.

$^1H$ NMR ($CDCl_3$, $\delta$ ppm) : 7.63-7.70 (4H, m), 7.33-7.48 (6H, m), 5.07 (1H, bt, $J$ = 7 Hz, $CH$=C), 4.84 (1H, m, $CH$(OAc)), 3.80-4.07 (4H, m, $OCH_2CH_2O$), 3.70 (3H, s, $OCH_3$), 3.64 (2H, d, $J$ = 6.0 Hz, $CH_2OSi$), 2.58 (1 H, d, $J$ = 9.0 Hz, $CHCO_2CH_3$), 2.35-2.55 (1H, m, $CHCHCO_2CH_3$), 1.80-2.02 (7H, m), 2.01 (3H, s, $CH_3CO$), 1.22-1.75 (9H, m), 1.56 (3H, bs, $CH_3$), 1.04 (9H, s, $C(CH_3)_3$).

$^{13}C$ NMR ($CDCl_3$, $\delta$ ppm) : 172.4, 170.6, 135.4, 134.3, 133.8, 129.5, 127.5, 124.3, 117.7, 73.8, 65.0, 64.2, 63.5, 59.3, 51.6, 40.9, 37.0, 35.5, 35.2, 32.2, 30.2, 28.8, 28.2, 26.7, 26.1, 21.1, 19.1, 15.8.

MS ($m/e$) : 650 ($M^+$), 593 ($M^+$-$C(CH_3)_3$).

Exact mass ($M^+$) : calc : 650.3638, found : 650.3631.

*Methyl 7-((3E)-7-acetoxy-10-hydroxy-4-methyldec-3-enyl)-1,4-dioxaspiro[4.4]nonane-6-carboxylate* **36**

To a solution of acetate **35** (1.80 g, 2.77 mmol) in THF (20 mL), were added ammonium chloride (148 mg, 2.77 mmol) and tetrabutylammonium fluoride (6.93 mL, 1.0 M in THF, 6.93 mmol). After stirring for 3 h at room temperature, the solvent was evaporated under reduced pressure and the mixture was directly purified by flash chromatography using diethyl ether as eluent to afford the alcohol **36** as an oil (1.12 g, 98%).

IR ($CHCl_3$) : 3 620, 3 520, 1 730 $cm^{-1}$.

$^1H$ NMR ($CDCl_3$, $\delta$ ppm) : 5.08 (1H, bt, $J$ = 7 Hz, $CH$=C), 4.84 (1H, m, $CH$(OAc)), 3.77-4.09 (4H, m, $OCH_2CH_2O$), 3.70 (3H, s, $OCH_3$), 3.56-3.72 (2H, m, $CH_2OH$), 2.57 (1H, d, $J$ = 8.9 Hz, $CHCO_2CH_3$), 2.35-2.55 (1H, m, $CHCHCO_2CH_3$), 2.04 (3H, s, $CH_3CO$), 1.80-2.05 (7H, m), 1.57 (3H, bs, $CH_3$), 1.12-1.75 (10H, m).

$^{13}C$ NMR ($CDCl_3$, $\delta$ ppm) : 172.5, 170.8, 134.1, 124.3, 117.6, 73.6, 65.0, 64.1, 62.2, 59.2, 51.6, 40.8, 36.9, 35.3, 35.1, 32.2, 30.2, 28.7, 28.2, 25.9, 21.1, 15.7.

MS ($m/e$) : 412 ($M^+$), 381 ($M^+$-$OCH_3$).

Exact mass ($M^+$) : calc : 412.2461, found : 412.2415.

*Methyl 7-((3E)-7-acetoxy-4-methyl-10-oxodec-3-enyl)-1,4-dioxaspiro[4.4]nonane-6-carboxylate* **37**

According to procedure 1, the oxidation of alcohol **36** (1.125 g, 2.73 mmol) provided aldehyde **37** as an oil (1.060 g, 95%).

IR ($CHCl_3$) : 2 730, 1 720-1 740 $cm^{-1}$.

$^1H$ NMR ($CDCl_3$, $\delta$ ppm) : 9.76 (1H, t, $J$ = 1.4 Hz, $CHO$), 5.08 (1H, bt, $J$ = 7 Hz, $CH$=C), 4.80-4.91 (1H, m, $CH$(OAc)), 3.78-4.07 (4H, m, $OCH_2CH_2O$), 3.70 (3H, s, $OCH_3$), 2.57 (1H, d, $J$ = 8.9 Hz, $CHCO_2CH_3$), 2.48 (2H, td, $J$ = 7.5 and 1.4 Hz, $CH_2CHO$), 2.35-2.55 (1H, m, $CHCHCO_2CH_3$), 2.03 (3H, s, $CH_3CO$) 1.18-2.05 (14H, m), 1.56 (3H, bs, $CH_3$).

$^{13}C$ NMR ($CDCl_3$, $\delta$ ppm) : 201.3, 172.4, 170.6, 133.9, 124.6, 117.6, 72.9, 65.0, 64.2, 59.3, 51.6, 40.8, 39.8, 37.0, 35.4, 35.1, 32.2, 28.8, 26.2, 26.0, 21.0, 15.8.

MS ($m/e$) : 410 ($M^+$), 379 ($M^+$-$OCH_3$).

Exact mass ($M^+$) : calc : 410.2304, found : 410.2302.

*Methyl 7-((3E)-7-acetoxy-10-hydroxy-4-methyldodec-3-en-11-ynyl)-1,4-dioxaspiro[4.4]nonane-6-carboxylate* **38**

According to procedure 2, alkylation of aldehyde **37** (1.060 g, 2.58 mmol) provided propargylic alcohol **38** as an oil (873 mg, 78% with 183 mg of recovered starting material).

IR ($CHCl_3$) : 3 600, 3 480, 3 300, 1 720-1 740 $cm^{-1}$.

$^1H$ NMR ($CDCl_3$, $\delta$ ppm) : 5.09 (1H, bt, $J$ = 7 Hz, $CH$=C), 4.80-4.95 (1H, m, $CH$(OAc)), 4.33-4.47 (1H, m, $CH$(OH)), 3.78-4.07 (4H, m, $OCH_2CH_2O$), 3.70 (3H, s, $OCH_3$), 2.58 (1H, d, $J$ = 9.0 Hz, $CHCO_2CH_3$), 2.47 (1H, d, $J$ = 2.2 Hz, C≡$CH$), 2.35-2.55 (1H, m, $CHCHCO_2CH_3$), 2.04 (3H, s, $CH_3CO$), 1.20-2.20 (17H, m), 1.57 (3H, bs, $CH_3$).

$^{13}C$ NMR ($CDCl_3$, $\delta$ ppm) : 172.6, 170.8, 134.2, 124.5, 117.7, 84.6, 73.5, 72.9, 65.0, 64.2, 61.8, 61.6, 59.3, 51.7, 40.8, 37.0, 35.3, 35.2, 33.1, 32.2, 29.4, 29.2, 28.7, 26.0, 21.2, 15.8.

MS ($m/e$) : 436 ($M^+$), 405 ($M^+$-$OCH_3$).

Exact mass ($M^+$) : calc : 436.2461, found : 436.2459.

*Methyl 2-((3E)-7-acetoxy-10-hydroxy-4-methyldodec-3-en-11-ynyl)-5-oxocyclopentane-1-carboxylate* **39**

According to procedure 3 (but using 0.75 equiv of boron trifluoride diethyl etherate), propargylic alcohol **38** (268 mg, 0.614 mmol) provided β-ketoester **39** as an oil (243 mg, 100%).

IR ($CHCl_3$) : 3 600, 3 480, 3 300, 1 760, 1 730 $cm^{-1}$.

$^1H$ NMR ($CDCl_3$, $\delta$ ppm) : 5.10 (1H, bt, $J$ = 7 Hz, $CH$=C), 4.80-4.95 (1H, m, $CH$(OAc)), 4.33-4.45 (1H, m, $CH$(OH)), 3.75 (3H, s, $OCH_3$), 2.87 (1H, d, $J$ = 11.1 Hz), 1.35-2.67 (19H, m), 2.04 (3H, s, $CH_3CO$), 1.59 (3H, bs, $CH_3$).

$^{13}C$ NMR ($CDCl_3$, $\delta$ ppm) : 211.9, 170.8, 169.9, 134.6, 123.9, 84.6, 77.4, 77.0, 76.6, 73.3, 72.9, 61.6, 61.5, 52.3, 40.9,

38.3, 35.1, 34.7, 33.0, 32.1, 29.3, 29.2, 27.4, 27.1, 25.9, 25.4, 21.1, 15.8.

MS (*m/e*) : 392 ($M^+$), 360 ($M^+$-$CH_3OH$).

Exact mass ($M^+$) : calc : 392.2199, found : 392.2194.

*Methyl 2-((3E)-7-acetoxy-4-methyl-10-oxododec-3-en-11-ynyl)-5-oxocyclopentane-1-carboxylate* **40**

According to procedure 4, β-ketoester **39** (81.3 mg, 0.207 mmol) provided ynone **40** as an oil (74.7 mg, 92%).

IR ($CHCl_3$) : 3 300, 2 100, 1 755, 1 720-1 740, 1 670 $cm^{-1}$.

$^1H$ NMR ($CDCl_3$, δ ppm) : 5.10 (1H, bt, C*H*=C), 1.77-1.92 (1H, m, C*H*(OAc)), 3.75 (3H, s, $OCH_3$), 3.25 (1H, s, C≡C*H*), 2.85 (1H, d, *J* = 11.1 Hz, C*H*$CHCO_2CH_3$), 2.63 (2H, t, *J* = 7.4 Hz, $CH_2C$=O), 1.38-2.70 (15H, m), 2.04 (3H, s, $CH_3CO$), 1.59 (3H, s, $CH_3$).

$^{13}C$ NMR ($CDCl_3$, δ ppm) : 211.8, 186.1, 170.6, 169.9, 134.5, 124.1, 81.1, 78.8, 72.6, 61.7, 52.3, 41.3, 41.0, 38.4, 35.1, 34.8, 32.2, 27.7, 27.2, 26.6, 25.5, 21.0, 15.8.

MS (*m/e*) : 390 ($M^+$), 358 ($M^+$-$CH_3OH$).

Exact mass ($M^+$) : calc : 390.2042, found : 390.2036.

• *Large rings* **41** *and* **42**

According to procedure 5, ynone **40** (74.7 mg, 0.192 mmol) provided four large rings which were purified by flash chromatography using dichloromethane/diethyl ether (9:1) as eluent. No effort was made at this step to separate the products (68.0 mg, 91% as a 45:55 mixture of *cis* and *trans* enones according to the $^1H$ NMR spectra). To a solution of this mixture of products (64.3 mg, 0.165 mmol) in acetic acid (1 mL) was added potassium iodide (54.7 mg, 0.33 mmol). After stirring for 14 h, water (5 mL) was added and the mixture was extracted with dichloromethane (3 × 5 mL). The organic phases were washed with an aqueous solution of saturated sodium bicarbonate containing a few dissolved crystals of sodium thiosulfate. The organic phase was separated, dried, filtered and the solvent was evaporated under reduced pressure. The two *trans*-enones were separated by flash chromatography using hexane/ethyl acetate (65:35) as eluent to afford **41** and **42** as oils (26.9 mg of **41** (contaminated with ~10% of *cis* enones), 30.8 mg of **42**, 42% and 48%).

*Methyl (2E,7R*,10E,14S*)-7-acetoxy-10-methyl-4,17-dioxo-*trans*-bicyclo[12.3.0]heptadeca-2,10-diene-1-carboxylate* **41**

IR ($CHCl_3$) : 1 750, 1 725-1 740, 1 690, 1 670, 1 620 $cm^{-1}$.

$^1H$ NMR ($CDCl_3$, δ ppm) : 7.18 (1H, d, *J* = 16.3 Hz, C*H*=CHCO), 6.31 (1H, d, *J* = 16.3 Hz, CH=C*H*CO), 5.07 (1H, bt, *J* = 7 Hz, C*H*=C), 4.89 (1H, m, C*H*(OAc)), 3.73 (3H, s, $OCH_3$), 1.20-2.74 (17H, m), 2.04 (3H, s, $CH_3CO$), 1.56 (3H, s, $CH_3$).

$^{13}C$ NMR ($CDCl_3$, δ ppm) : 213.2, 200.1, 170.9, 169.0, 144.6, 135.3, 130.2, 125.3, 71.1, 65.4, 52.4, 49.5, 39.2, 37.8, 35.2, 31.1, 30.7, 30.5, 26.6, 24.6, 21.2, 15.5.

MS (*m/e*) : 390 ($M^+$), 331 ($M^+$-$CH_3CO_2$), 330 ($M^+$-$CH_3CO_2H$).

Exact mass ($M^+$) : calc : 390.2042, found : 390.2037.

*Methyl (2E,7S*,10E,14R*)-7-Acetoxy-10-methyl-4,17-dioxo-*trans*-bicyclo[12.3.0]heptadeca-2,10-diene-1-carboxylate* **42**

IR ($CHCl_3$) : 1 755, 1 730, 1 695, 1 670, 1 620 $cm^{-1}$.

$^1H$ NMR ($CDCl_3$, δ ppm) : 7.23 (1H, d, *J* = 16.4 Hz, C*H*=CHCO), 6.17 (1H, d, *J* = 16.4 Hz, CH=C*H*CO), 5.27 (1H, bt, *J* = 7 Hz, C*H*=C), 4.66 (1H, m, C*H*(OAc)), 3.75 (3H, s, $OCH_3$), 1.20-2.80 (17H, m), 2.04 (3H, s, $CH_3CO$), 1.63 (3H, bs, $CH_3$).

$^{13}C$ NMR ($CDCl_3$, δ ppm) : 212.1, 199.2, 170.5, 168.8, 144.1, 135.1, 127.9, 124.5, 71.4, 65.2, 52.6, 48.4, 39.0, 37.9, 34.9, 31.1, 30.9, 28.9, 26.5, 24.0, 21.1, 15.1.

MS (*m/e*) : 390 ($M^+$), 331 ($M^+$-$CH_3CO_2$), 330 ($M^+$-$CH_3CO_2H$).

Exact mass ($M^+$) : calc : 390.2042, found :390.2042.

*Methyl 7-((3E)-7,10-dihydroxy-4-methyldodec-3-en-11-ynyl)-1,4-dioxaspiro[4.4]nonane-6-carboxylate* **43**

A solution of potassium methoxide in methanol (5 mL, 1.08 M, 5.4 mmol) was added to the propargylic alcohol **38** (570 mg, 1.31 mmol). After stirring for 1 h at room temperature, an aqueous solution of ammonium chloride (5 mL) was added and the mixture was extracted with dichloromethane (3 × 20 mL). The organic phases were dried, filtered and the solvent was evaporated under reduced pressure. The product was purified by flash chromatography using diethyl ether/acetone (100:0 to 0:100) as eluent to afford diol **43** as an oil (514 mg, 100%).

IR ($CHCl_3$) : 3 600, 3 400, 3 300, 1 730 $cm^{-1}$.

$^1H$ NMR ($CDCl_3$, δ ppm) : 5.15 (1H, bt, *J* = 7 Hz, C*H*=C), 4.44 (1H, m, C*H*(OH)), 3.78-4.05 (4H, m, $OCH_2CH_2O$), 3.70 (3H, s, $OCH_3$), 3.60-3.72 (1H, m, C*H*(OH)), 2.57 (1H, d, *J* = 9.4 Hz, C*H*$CO_2CH_3$), 2.45 (1H, d, *J* = 2.1 Hz, C≡CH), 2.35-2.55 (1H, m, C*H*$CHCO_2CH_3$), 1.20-2.15 (18H, m), 1.58 (3H, s, $CH_3$).

$^{13}C$ NMR ($CDCl_3$, δ ppm) : 172.5, 134.9, 124.4, 124.3, 117.6, 84.9, 72.6, 72.5, 71.2, 71.0, 70.9, 65.0, 64.2, 61.8, 61.6, 59.2, 51.7, 40.6, 37.0, 35.7, 35.3, 35.1, 33.8, 32.7, 32.4, 28.7, 25.8, 15.7.

MS (*m/e*) : 394 ($M^+$), 376 ($M^+$-$H_2O$), 362 ($M^+$-$CH_3OH$).

Exact mass ($M^+$) : calc : 394 2355, found : 394.2351.

*Methyl 2-((3E)-7,10-dihydroxy-4-methyldodec-3-en-11-ynyl)-5-oxocyclopentane-1-carboxylate* **44**

According to procedure 3 (but using 0.50 equiv of boron trifluoride diethyletherate), diol **43** (514 mg, 1.31 mmol) provided β-ketoester **45**. The product was purified by flash chromatography using diethyl ether/acetone (100:0 to 0:100) as eluent (436 mg, 95%, oil).

IR ($CHCl_3$) : 3 600, 3 400, 3 300, 1 755, 1 730 $cm^{-1}$.

$^1H$ NMR ($CDCl_3$, δ ppm) : 5.17 (1H, bt, *J* = 7 Hz, C*H*=C), 4.45 (1H, m, C*H*(OH)), 3.76 (3H, s, $OCH_3$), 3.58-3.72 (2H, m, C*H*(OH)), 2.85 (1H, d, *J* = 11.1 Hz, C*H*$CO_2CH_3$), 2.50-2.70 (1H, m, C*H*$CHCO_2CH_3$), 2.46 (1H, d, *J* = 2.1 Hz, C≡C*H*), 1.40-2.50 (18H, m), 1.61 (3H, bs, $CH_3$).

$^{13}C$ NMR ($CDCl_3$, δ ppm) : 211.8, 169.9, 135.6, 123.8, 84.8, 72.7, 72.6, 71.4, 71.1, 61.8, 61.6, 52.4, 40.9, 38.3, 35.7, 35.4, 35.1, 34.8, 33.8, 32.7, 32.4, 27.1, 25.4, 15.8.

MS (*m/e*) : 318 ($M^+$-$CH_3OH$), 300 ($M^+$-$CH_3OH$-$H_2O$).

Exact mass ($M^+$-$CH_3OH$) : calc : 318.1831, found : 318.1827.

*Methyl 2-((3E)-4-methyl-7,10-dioxododec-3-en-11-ynyl)-5-oxocyclopentane-1-carboxylate* **45**

According to procedure 4, β-ketoester **44** (118 mg, 0.337 mmol) provided ynone **45**. The product was quickly chromatographed by eluting with diethyl ether (106 mg, 90%, oil).

IR ($CHCl_3$) : 3 300, 2 100, 1 755, 1 720-1 730, 1 670 $cm^{-1}$.

$^1$H NMR ($CDCl_3$, $\delta$ ppm) : 5.10 (1H, bt, $J$ = 7 Hz, C$H$=C), 3.75 (3H, s, OC$H_3$), 3.24 (1H, s, C≡C$H$), 1.90-3.00 (15H, m), 1.59 (3H, s, C$H_3$), 1.30-1.75 (3H, m).

$^{13}$C NMR ($CDCl_3$, $\delta$ ppm) : 211.7, 207.8, 185.4, 169.9, 134.2, 124.1, 81.1, 78.8, 61.7, 52.4, 41.1, 41.0, 38.9, 38.4, 35.6, 34.8, 33.2, 27.2, 25.5, 16.0.

MS ($m/e$) : 346 ($M^+$), 331 ($M^+$-$CH_3$), 328 ($M^+$-$H_2O$), 314 ($M^+$-$CH_3OH$).

Exact mass ($M^+$) : calc : 346.1780, found : 346.1789.

• *Large rings* **46** *and* **47**

According to procedure 5, ynone **45** (88 mg, 0.255 mmol) provided macrocycles **46** and **47** as oils (23.4 mg of **46**, 33.8 mg of **47**, 27% and 38%).

*Methyl (2Z,10E)-10-methyl-4,7,17-trioxo*-trans-*bicyclo[12.3.0]heptadeca-2,10-diene-1-carboxylate* **46**

IR ($CHCl_3$) : 1 750, 1 730, 1 715, 1 680, 1 605 cm$^{-1}$.

$^1$H NMR ($CDCl_3$, $\delta$ ppm) : 6.83 (1H, d, $J$ = 11.9 Hz, C$H$=CHCO), 6.52 (1H, d, $J$ = 11.9 Hz, CH=C$H$CO), 4.95 (1H, bt, $J$ = 7 Hz, C$H$=C), 3.74 (3H, s, OC$H_3$), 2.88-3.16 (3H, m), 2.37-2.75 (5H, m), 1.83-2.32 (6H, m), 1.57-1.79 (1H, m), 1.54 (3H, bs, C$H_3$), 1.15-1.46 (2H, m).

$^{13}$C NMR ($CDCl_3$, $\delta$ ppm) : 211.1, 207.7, 200.5, 171.1, 144.4, 133.7, 127.6, 126.3, 66.2, 52.4, 44.4, 40.3, 39.3, 38.3, 36.3, 33.1, 32.1, 26.9, 24.4, 15.7.

MS ($m/e$) : 346 ($M^+$), 328 ($M^+$-$H_2O$), 315 ($M^+$-$OCH_3$).

Exact mass ($M^+$) : calc : 346.1780, found : 346.1776.

*Methyl (2E,10E)-10-methyl-4,7,17-trioxo*-trans-*bicyclo[12.3.0]heptadeca-2,10-diene-1-carboxylate* **47**

IR ($CHCl_3$) : 1 750, 1 730, 1 715, 1 670, 1 690, 1 620 cm$^{-1}$.

$^1$H NMR ($CDCl_3$, $\delta$ ppm) : 7.07 (1H, d, $J$ = 16.1 Hz, C$H$=CHCO), 6.10 (1H, d, $J$ = 16.1 Hz, CH=C$H$CO), 5.07 (1H, bt, $J$ = 7 Hz, C$H$=C), 3.70 (3H, s, OC$H_3$), 2.86-3.00 (1H, m), 2.18-2.84 (11H, m), 2.04-2.15 (2H, m), 1.70-1.95 (1H, m), 1.64 (3H, bs, C$H_3$), 1.38-1.58 (2H, m).

$^{13}$C NMR ($CDCl_3$, $\delta$ ppm) : 211.8, 208.2, 198.8, 168.9, 143.1, 135.3, 127.2, 123.9, 65.3, 52.4, 44.9, 39.4, 38.7, 38.4, 34.9, 33.0, 31.1, 26.1, 24.1, 16.5.

MS ($m/e$) : 346 ($M^+$), 328 ($M^+$-$H_2O$), 315 ($M^+$-$OCH_3$).

Exact mass ($M^+$) : calc : 346.1780, found : 346.1776.

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