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Synthesis of the C17-C23 Subunit of Ionomycin from C1-Functionalized 8-Oxabicyclo[3.2.1]oct-6-en-3-one. New Synthetic Methodology to Prepare Polyfunctionalized Heptane Building Blocks with Four Stereocenters

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Abstract:

The application of a new methodology to synthesize the C17-C23 subunit of Ionomycin is presented. This synthetic methodology is based on the preparation of heptane building blocks with four stereocenters and up to four different organic functionalities. 2,4-Dimethyl-1-methoxy-8-oxabicyclo[3.2.1]oct-6-en-3-one has been used as a key intermediate, which can easily be prepared by a [4+3] cycloaddition reaction between 2-methoxy-furan and the oxyallyl cation generated *in situ* from 2,4-dibromo-3-pentanone. This cycloadduct has an acetal functionality on C1 which allows the easy opening of the oxabicyclic system, affording versatile synthons.

Keywords: Antibiotics, bridgehead chemistry, cycloadditions, cycloheptenes.

Macrolide antibiotics are important synthetic targets due to both their biological activity (antimicrobial and in many cases antitumor) and their challenging complex chemical structure [1]. One of these antibiotic macrolides with important properties is Ionomycin. There have been in the past several approaches to the partial and total synthesis of Ionomycin, based on different synthetic methodologies [2], most of them based on poliketide chemistry. The *anti-syn* relative stereochemistry established between C19 and C20 and C17 and C19 respectively in the structure of Ionomicyn, is the array which cannot be obtained directly using the aldol methodology, routinely employed in the synthesis of these polypropionate fragments [2d].

In our research group we have developed a new synthetic methodology to prepare polyfunctionalized heptane building blocks with up to four stereocenters based on the use of C1 functionalized 2,4-dimethyl-8-oxabicyclo[3.2.1]oct-6-en-3-ones as key intermediates [3]. Application of this new methodology to the synthesis of the C17-C23 fragment of antibiotic Ionomycin, starting from cheap and commercially available precursors, and involving versatile intermediates, is presented here.

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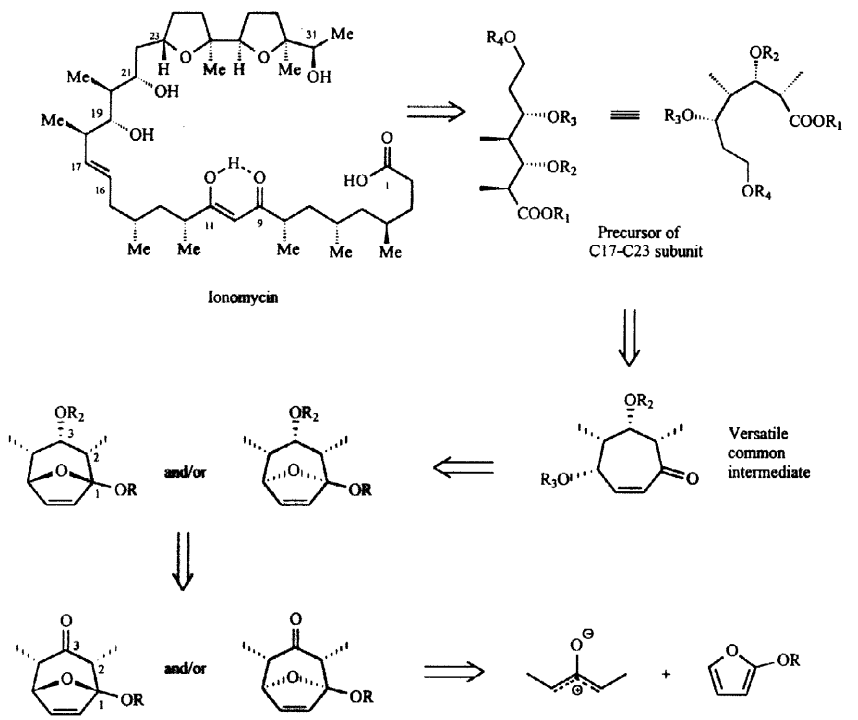
The C1-functionalized 2,4-dimethyl-8-oxabicyclo[3.2.1.]oct-6-en-3-ones, whose synthesis and applicability have been studied by us [3], are readily available by [4+3] cycloaddition reactions between C2-functionalized furans and the oxyallyl cation generated *in situ* from 2,4-dibromo-3-pentanone (Scheme 1). These cycloadducts have on C1 an acetal function which allows the easy opening of the oxygen-bridge and its further chemical derivatization.

Discrimination between the ketone group on C3 and the masked carbonyl group on C1 (as acetal) has been accomplished by a highly stereoselective reduction of the C3-carbonyl group to the corresponding alcohol (Scheme 1). A further hydrolysis of the cyclic acetal affords a versatile building block, which could be readily transformed into linear seven membered synthons, with four different organic functions and up to four stereocenters (Scheme 1). The key intermediate in the present synthetic approach is a C1-functionalized 8-oxabicyclo[3.2.1]oct-6-en-3-one obtained, as mentioned before, by [4+3] cycloaddition reactions. In the aforementioned reaction, under optimized experimental conditions, two diastereoisomers (depending on the relative positions of methyl groups on C2 and C4 as *cis*-diequatorial and/or *cis*-diaxial) are formed in almost quantitative yield. Both diastereoisomers are equally useful to prepare the target molecule (C17-C23 subunit of Ionomycin), and parallel synthetic pathways have been conducted with both diastereoisomers.

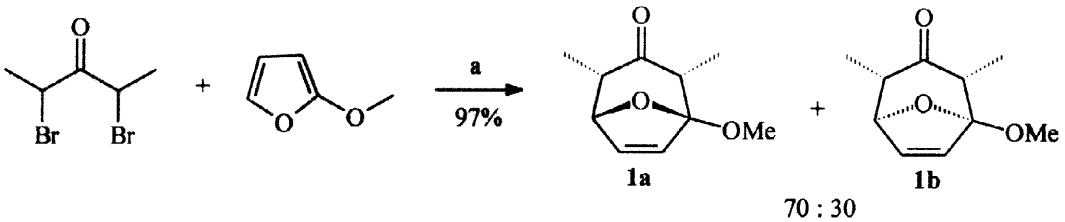


Scheme 1.- Retrosynthetic approach to the C17-C23 subunit of antibiotic Ionomycin.

The preparation of the aforementioned diastereoisomeric cycloadducts was carried out by the Hofmann's methodology [4], using the reducing system NaI/Cu in MeCN to generate, *in situ*, an oxyallyl cation from 2,4-dibromo-3-pentanone. This cation reacts according to a [4+3] cycloaddition reaction with 2-methoxy-furan affording in a 97% yield the diastereoisomers *cis*-diequatorial (**1a**) and *cis*-diaxial (**1b**) in a 70:30 ratio, respectively (Scheme 2). No *trans*

stereoisomers were detected which, on the other hand, are formed in a certain yield (10-20%) when Noyori's cycloaddition methodology is used ($Fe_2(CO)_9$, C_6H_6, 80°C) [5].

The products **1a** and **1b** were easily separated by column chromatography and they were completely characterized [3a, 3c].



Scheme 2.- Preparation of 2,4-Dimethyl-1-methoxy-8-oxabicyclo[3.2.1]oct-6-en-3-one. Reaction conditions: (a) Cu, NaI, CH_3CN, 60°C , followed by chromatographic separation.

Synthetic pathway to prepare a precursor of the C17-C23 subunit of Ionomycin from the *cis*-diequatorial cycloadduct 1a.

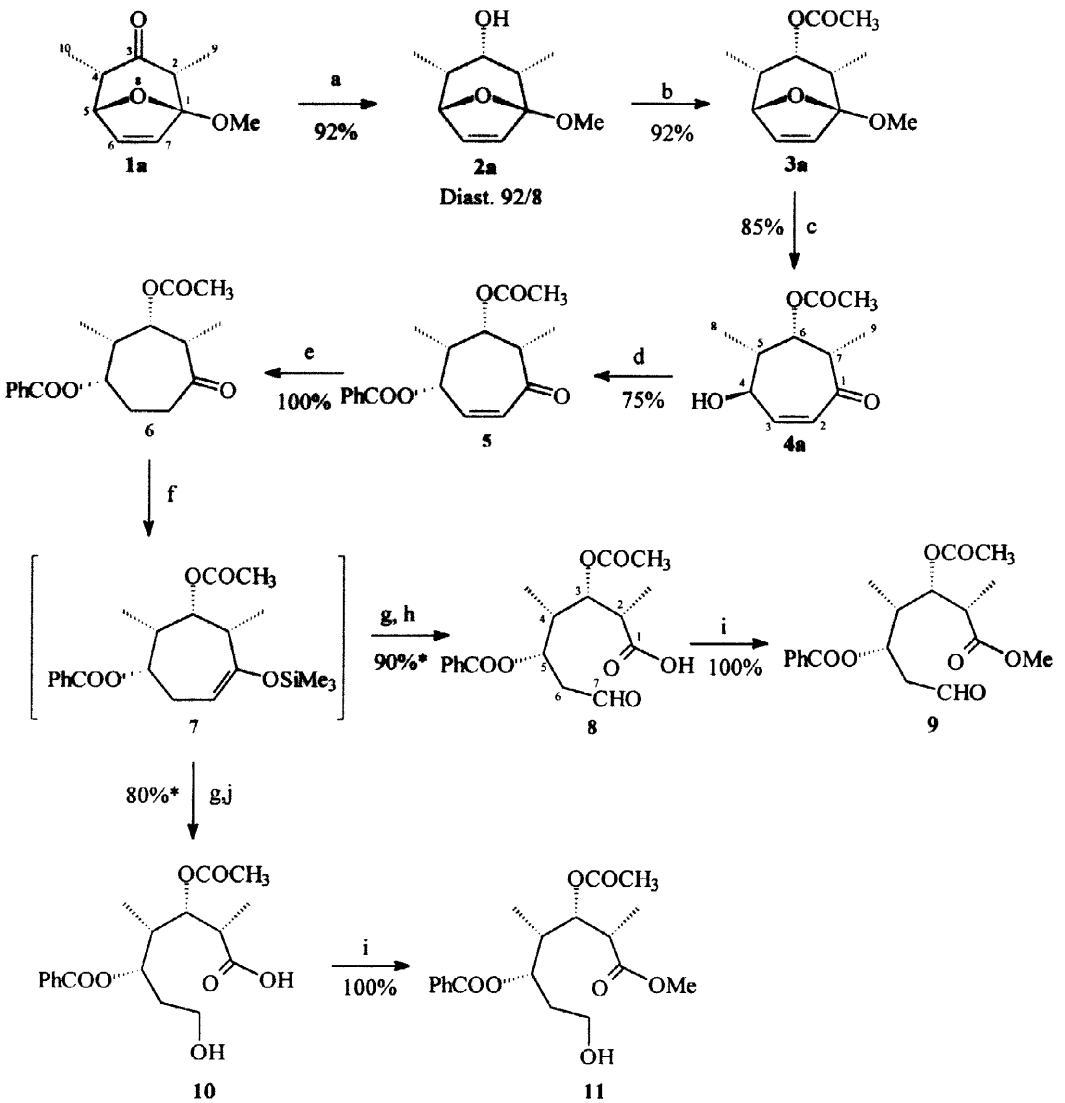
Once the major diasteroisomer **1a** was isolated and purified, in order to chemically discriminate its ketone group on C3 and the masked carbonyl group on C1, a reduction of the former was carried out by $NaBH_4$ in MeOH at 0°C (Scheme 3).

The corresponding alcohol on C3 was obtained in a 92% yield and with high diastereoselectivity *endo* (**2a**) : *exo* (**2a'**) (98:2, respectively). The use of DIBAL-H® [6] or $(iPrO)_3Al$ / iPrOH did not improve the yield and/or diastereoselectivity. To work with DIBAL-H® at -78°C was thought to exert a kinetic control on the reduction reaction, however, lower yield and diastereoselectivity were obtained, probably due to a possible coordination of aluminium atom to the oxygen of the bridge, which hinders the *re* face of the ketone group on C3, making difficult the attack of hydride ion on that face.

The major diastereoisomer **2a** is the one having the C3-OH group with the *endo* configuration, so it comes from the attack of hydride ion on the *re* face (less hindered one) of the C3-ketone group. The *si* face is hindered by both the $\Delta^{6,7}$ double bond and the methyl groups on C2 and C4, while the *re* face is only flanked by the oxygen bridge (see Fig. 1). As a new stereocenter (at C3) is formed in this reduction reaction, the establishment of the relative stereochemistry of **2a** and **2a'** was carried out by a careful correlation of their ^1H- and ^{13}C-NMR spectra, as it will be discussed later on.

Next step in the synthetic pathway is the protection of the hydroxyl group on C3, in **2a**. For this purpose, **2a** was treated with one equivalent of MeLi, to abstract the hydroxylic hydrogen, followed by one equivalent of CH_3COCl, (other bases like NEt_3, NaH, ^tBuLi, LDA, etc., were used in this reaction, but because the -OH group is flanked by methyl groups C9 and C10 it is considerably hindered and the acid-base reaction did not take place to an appreciable extent). In this way, the corresponding acetate **3a** was obtained in 92% yield (Scheme 3).

One key step in the present synthetic methodology is the opening of the oxabicyclic system in **3a**. This transformation is carried out by hydrolysis in acidic medium of the acetal function on C1. The system CF_3COOH/H_2O was very effective affording cycloheptenone **4a** in a 85% yield.



Scheme 3.- Synthetic pathway to prepare compounds **8/9** and **10/11**, precursors of subunit C17-C23 of Ionomycin. Reaction conditions: **a)** $NaBH_4$, MeOH (chromatographic separation); **b)** 1) MeLi, 0°C, THF, 2) CH_3COCl, THF; **c)** CF_3COOH, H_2O, $CHCl_3$; **d)** PhCOOH, DEAD, Ph_3P, THF: **e)** H_2, Pd(10%)/C, THF; **f)** LDA, Me_3SiCl, HMPA, -78°C, THF; **g)** O_3, CH_2Cl_2/MeOH 1/1, -78°C; **h)** Me_2S, CH_2Cl_2/MeOH 1/1; **i)** CH_2N_2, Et_2O; **j)** $NaBH_4$, CH_2Cl_2/MeOH 1/1.
* Overall yield in steps (g, h, i) and/or (g, j, i).

The configuration at C4 in **4a** had to be inverted in order to get the right stereochemistry in the final product (C17-C23 subunit of Ionomicyn). This inversion of configuration was performed by the Mitsunobu methodology [7], which simultaneously protected the C4-alcohol as a benzoate. Under these conditions the benzoate **5** was isolated in 75% yield. On the other hand, the structure of **5** was confirmed by synthesizing it by following another synthetic pathway, starting from compound **1b** (Scheme 4).

Hydrogenation of cycloheptene **5** was accomplished in quantitative yield by using H_2 and Pd/C(10%), as a catalyst, in THF. This aprotic solvent was chosen to avoid hydrogenolysis [8] of the benzoate group, which is a good leaving group and moreover it is in an allylic position. In usual solvents for this kind of reaction the compound **5** underwent a certain degree of hydrogenolysis.

The silyl enol ether **7** was prepared under kinetic conditions at -78°C [9]. This product, because of its unstability, was directly ozonized without isolation. Reduction of the intermediate ozonide was carried out by using either SMe_2 or $NaBH_4$ as reducing agents [10]. When dimethyl sulphide was used, the molecule **8** was obtained in 90% overall yield from **6**. The building block prepared in this way is a linear structure of seven carbons, four consecutive stereocenters and four different organic functions, with a formyl and a carboxyl group at the ends of the carbon chain. This fact is quite important because it facilitates the synthetic work of a further derivatization and assembling of that building block to other fragments or subunits, in order to perform a convergent synthesis of Ionomycin. Acid **8** was easily transformed into its methyl ester **9** , in quantitative yield, by reaction with diazomethane. This reduction approach has the advantage that, in the case of a non-complete conversion, the starting material (ketone **6**) could be recycled, because it is not reduced. When $NaBH_4$ was used in the reductive ozonolysis, the final product was the hydroxy-acid **10**, formed in a 80% overall yield from ketone **6**. In this particular case the non-transformed starting material is also reduced and could not be recycled. Esterification of acid **10** with diazomethane afforded methyl ester **11** also in quantitative yield.

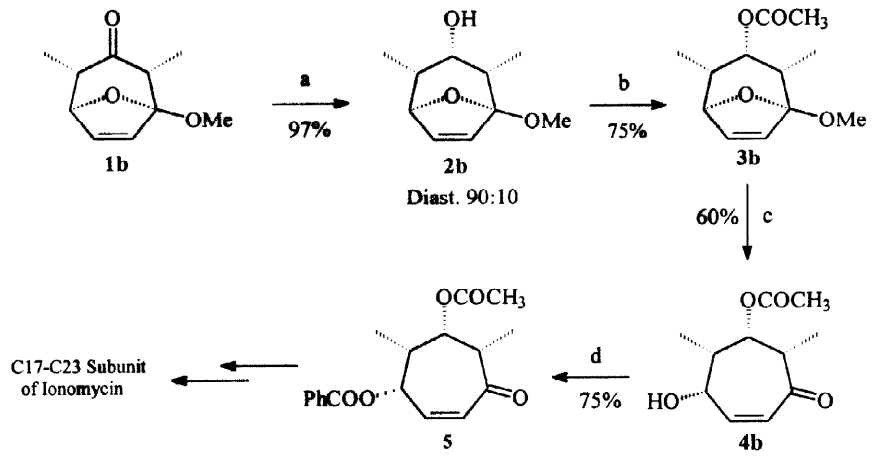
Synthetic pathway to prepare a precursor of the C17-C23 subunit of Ionomycin from the *cis*-diaxial cycloadduct 1b.

As was already mentioned, both diastereoisomers **1a** and/or **1b,** resulting from the [4+3] cycloaddition of 2-methoxy-furan and 2,4-dimethyl-2-oxy-allyl cation, could be used as precursors for the synthesis of subunit C17-C23 of Ionomycin. Starting from **1b** it is possible to follow a similar synthetic pathway as shown in Scheme 4. In both synthetic pathways, yields and diastereoselectivities are not very different. The main difference with the former pathway (Scheme 3) rests on the fact that in this second one it is not necessary to invert the configuration at C4 in **4b,** because this compound has the same stereochemistry in all four stereocenters than the target molecule. Thus, it is possible to transform **1b** into the common intermediate **5** in only four steps.

The reaction conditions are almost identical to the ones established in the pathway of Scheme 3, only a few new aspects deserve to be commented, especially regarding the stereochemistry involved in the reactions.

When reducing cycloadduct **1b** with $NaBH_4$ two separable diastereomeric alcohols were obtained, **2b** and **2b'**, in 97% yield and in 90:10 ratio, respectively, (Fig. 4). The major alcohol is the one resulting from the attack of hydride ion on the less hindered face, the *si* face, due to the 1-oxan-4-one ring in **1b** adopts a boat like conformation [3a, 3c].

The protection of the C3-hydroxyl group in **2b** was accomplished under the same conditions as in compound **2a**, obtaining product **3b** in 75% yield. Hydrolysis of the acetal function on C1 was carried out by using CF_3COOH/H_2O affording cycloheptenone **4b** in 60% yield.



Scheme 4.- Synthetic pathway to prepare the C17-C23 subunit of Ionomycin from the *cis*-diaxial cycloadduct **1b**. Reaction conditions: a) $NaBH_4$, MeOH, (chromatographic separation); **b)** 1)MeLi, 0°C, THF, 2) MeCOCl, THF; **c)** CF_3COOH, H_2O, $CHCl_3$; **d)** Et_3N, DMPA, PhCOOH, $CHCl_3$.

Cycloheptenone **4b,** which has the appropriate relative configuration in all four stereocenters, was treated with PhCOCl / Et_3N, DMAP to protect the free alcohol as a benzoate, which was accomplished in 75% yield. This benzoylation product had identical physical and spectroscopic properties to the substance **5.** Cycloheptenone **5** is, then, a common intermediate in both synthetic pathways.

Establishment of the relative stereochemistry of the diastereomeric cyclic intermediates 1a/1b, 2a/2a', 2b/2b' and 5.

The products **1a** and **1b** were purified by column chromatography and they were physicaly and spectroscopicaly characterized. Also their relative stereochemistry was unequivocally established by correlation of their ^{1}H- and ^{13}C-NMR spectra, and confirmed by X-Ray diffraction on single crystals [3a, 3c].

In the reduction reaction of Ketone group on C3 of **1a** (Scheme 3), the major diastereoisomer formed **2a**, is the one having the C3-OH group with the *endo* configuration, while the minor diastereoisomer **2a'** has an *exo* configuration for the C3-OH group. As a new stereocenter (at C3) is formed in this reduction reaction, the establishment of the relative stereochemistry of **2a** and **2a'** was carried out by a careful correlation of their ^{1}H- and ^{13}C-NMR spectra. The unequivocal assignment of signals was possible by 2D (COSY ^{1}H-^{1}H) experiments, so, the observation of a coupling between hydrogens H4 and H5 allowed us to clearly assign the signals of hydrogens H2, H4, H9 and H10 (see Table 1).

Based on the $J_{4,5}$ values (Table 1), it is possible to deduce that **2a** has a chair like conformation, and **2a'** a half-chair like conformation for the 1-oxan-4-ol ring. The small values of these coupling constants (1.5 and 3.6 Hz respectively) are coherent with dihedral angles H4-C4-C5-H5 close to 63° and 47°, respectively, according to the Karplus' equation [11]. On the other hand, comparing $J_{2,3}$ and $J_{3,4}$ coupling constants it is possible to appreciate that in **2a**

they have values (see Table 1) corresponding to dihedral angles H2-C2-C3-H3 and H3-C3-C4-H4 near 34° (*syn* relationship of H3 with both H2 and H4). However, in **2a'** those coupling constants have values as high as 8.8 Hz, which is coherent with dihedral angles close to 168° (*anti* relationship of H3 with both H2 and H4). Moreover, the major differences among ^{1}H-NMR chemical shifts (δ, ppm) of **2a** and **2a'** are observed for H2, H3, H4, H6 and H7 (see Table 1). Proton H3 in **2a'** appears to be highly shielded (Δδ=0.99 ppm) by the interaction with C9 and C10 methyl groups [3a, 3c, 12] and also by a possible effect of the anisotropy cone of double bond $\Delta^{6,7}$, (see Fig. 1)[13]. In **2a** a deshielding effect could be observed on both H6 and H7, with respect to **2a'**, probably due to an electrostatic field interaction [14] with the C3 hydroxylic oxygen, which adopts an *endo* configuration (Fig. 1).

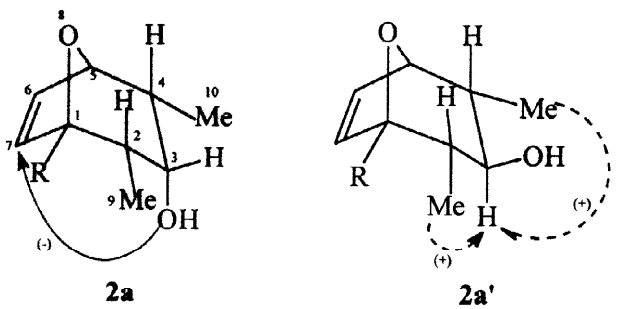


Figure 1.- Relative configuration of **2a** and **2a'**: shielding (+) and deshielding (-) effects.

In **2a** hydrogens H2 and H4 appear at lower field than in **2a'** (Table 1), which is due to the diamagnetic anisotropy effect of the -OH group on C-3 which is generally observed when all H2, H4 and C3-OH are in axial disposition [15]. This deshielding effect would be more intense than the down field shift effect possibly exerted by the equatorial C3-OH on H2 and H4 by electrostatic field effect in **2a'**.

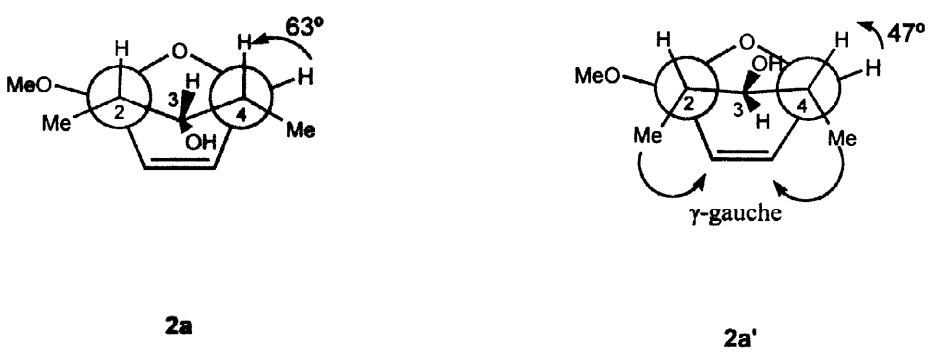
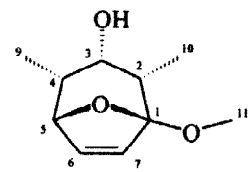


Figure 2.- Newman projection of **2a** and **2a'** where the different intensity of γ-shielding effects between (C6, C7) and (C9, C10) are observed.

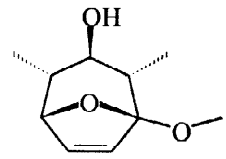
Regarding the correlation of ^{13}C-NMR data (see Table 2), the main differences in δ(ppm) between **2a** and **2a'** are observed on C2, C3, C4, C6 and C7 carbons. In **2a'**, C6 and C7 are up-

field shifted, with respect to the same carbons in **2a**, by a γ-gauche shielding effect [16, 17] exerted by methyl groups C9 and C10, which are in closer proximity in **2a'** than in **2a** (see Fig. 2).

Table 1.- Correlation of ^{1}H-NMR spectral data of **2a** and **2a'**.



2a



2a'

	2a			**2a'**			
	δ(ppm)	**m**	**J(Hz)**	**δ(ppm)**	**m**	**J(Hz)**	**Δδ(2a-2a')**
H2	2.20	dq	$J_{2,9}$=7.5 $J_{2,3}$=5.5	1.75	m	Not resolved	0.45
H3	3.77	dd	$J_{3,4}$=5.5 $J_{3,2}$=5.5	2.78	dd	$J_{3,4}$=8.8 $J_{3,2}$=8.8	0.99
H4	2.28	ddq	$J_{4,3}$=5.5 $J_{4,5}$=1.5 $J_{4,10}$=7.0	1.75	m	Not resolved	0.53
H5	4.57	dd	$J_{5,4}$=1.5 $J_{5,6}$=1.5	4.56	dd	$J_{5,4}$=3.6 $J_{5,6}$=1.8	0.01
H6	6.60	dd	$J_{6,7}$=6.0 $J_{6,5}$=1.5	6.30	dd	$J_{6,7}$=6.0 $J_{6,5}$=1.8	0.30
H7	6.31	d	$J_{7,6}$=6.0	6.09	d	$J_{7,6}$=6.0	0.22
H9	1.06	d	$J_{9,2}$=7.5	1.02	d	$J_{9,2}$=7.0	0.04
H10	0.99	d	$J_{10,4}$=7.0	0.97	d	$J_{10,4}$=7.0	0.02

The previous observation is also consistent with the fact that C9 and C10 appear at higher field in **2a'** than in **2a**. The differences observed in δ(ppm) of C2 and C4 could be interpreted on the basis of a deshielding β-effect[18] exerted by the -OH group. This down-field shift is of higher intensity when the -OH group is in an equatorial disposition than when it adopts an axial orientation. The aforementioned diamagnetic shift is of steric origin [19] and also explains the great difference observed in δ(C3) between both diastereoisomers due to an α-effect [18,19].

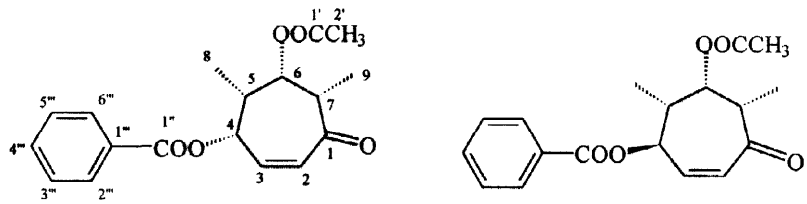
The internal coherence of all these effects and the NMR data correlations allows to assign to **2a** and **2a'** the structures and relative stereochemistry depicted in Fig.1.

Table 2.- Correlation of ^{13}C-NMR spectral data of **2a** and **2a'**.

Carbon	δ_{2a}(ppm)	$\delta_{2a'}$(ppm)	$\Delta\delta$ (2a-2a')
C1	111.38	112.10	-0.72
C2	42.09	44.69	-2.60
C3	72.77	78.89	-6.12
C4	38.92	40.89	-1.97
C5	82.03	80.85	1.18
C6	138.81	134.09	4.72
C7	134.94	131.13	3.81
C9	11.50	12.84	-1.34
C10	12.62	14.20	-1.58
C11	50.52	50.69	-0.17

Looking at Scheme 3, is is possible to appreciate how the configuration at C4 in cycloheptenone **4a** had to be inverted in order to get the right stereochemistry in the final product (subunit C17-C23 of Ionomicyn). This inversion of configuration was performed by the Mitsunobu methodology [7], which simultaneously protected the C4-alcohol as a benzoate.

In order to confirm the inversion of configuration at C-4, the epimer of **5** (Fig. 3), **5'** , was synthesized by benzoylation of alcohol **4a** using LDA/PhCOCl, with the purpose of comparing the physical and spectroscopic properties of both compounds.



5 **5'**

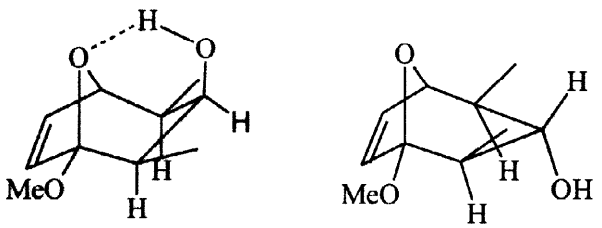
Figure 3.- Comparison of epimeric benzoates **5** and **5'**.

Looking at NMR spectra of **5 and 5'** is is possible to observe a few differences between the ^{1}H- and ^{13}C-NMR data of both epimers. Noticeable $\Delta\delta$ are seen in hydrogen H4 and carbon C4, affected by the change of configuration at C4, and in a lesser extent in their vicinal protons and carbons, respectively.

To rationalize the observed shielding and deshielding effects is quite difficult due to the high degree of conformational freedom of cycloheptenone ring in both compounds. In any case, a simple comparison of the aforementioned data induces to think that **5** and **5'** are not identical but diastereoisomers, and due to the type of reactions carried out on **4a**, to afford **5** and **5'**, is quite clear that both diastereoisomers should necessarily be epimers, because the configuration of stereocenters at C5, C6 and C7 is not modified. On the other hand, the structure of **5** is confirmed by synthesizing it by an other synthetic pathway, starting from compound **1b** (Scheme 4).

Similar reasoning was applied to establish the relative stereochemistry in diastereoisomers **2b** and **2b'** (Scheme 4), by means of a correlation study of their ^{1}H and ^{13}C-NMR data. After this study it is possible to conclude that **2b**, the major isomer, adopts a boat-like conformation, having methyl groups H_3C9 and H_3C10 in a *quasi*-equatorial disposition (see Fig. 4). The values of $J_{2,3} = J_{3,4} = 6.9$Hz correspond to dihedral angles H2-C2-C3-H3 and H4-C4-C3-H3 close to 23° which are coherent with a configuration at C3 as shown in Fig. 4 for **2b**, where the C3-OH group is able to form a hydrogen bond with the oxygen atom of the bridge.

In **2b'** the values of coupling constants $J_{2,3}=J_{3,4}= 1.5$ Hz indicate dihedral angles H2-C2-C3-H3 and H3-C3-C4-H4 of 115°. According to this data, and by observation of Dreiding models, the dihedral angle H4-C4-C5-H5 is estimated as 75°. Thus, it was possible to deduce that molecule **2b'** adopts a half-boat like conformation for the 1-oxan-4-ol ring for a configuration at C3 as depicted in Figures 4 and 5. (Experimentally we observed a coupling constant $J_{4,5}\approx 0$ Hz, which calculated by Karplus' equation for a dihedral angle H4-C4-C5-H5 of 75° was estimated as 0.28 Hz, value which was not detected even by a high resolution 500 MHz NMR spectrometer).



2b **2b'**

Figure 4.- Structure of alcohols **2b** and **2b'**.

All these spectroscopic considerations made on the basis of NMR data correlations are consistent with a relative stereochemistry for **2b** and **2b'** as shown in Figure 4.

We can conclude that a new synthetic methodology to prepare, in a stereoselective manner, linear and cyclic polyfunctionalized heptane building blocks with up to four stereocenters has been developed. This methodology is based on three key steps: a) [4+3] cycloaddition reaction of 2-functionalized furans with 1,3-dimethyl-2-oxyallyl cation, b) reduction of the ketone on C3 to chemically discriminate it from the masked carbonyl group on C1, c) hydrolysis of the cyclic acetal on C1 for an easy opening of the oxygen bridge. By this methodology it is possible to synthesize versatile building blocks, useful as precursors of subunits of macrolide antibiotics like Ionomycin. We have also demonstrated the synthetic usefulness of both diastereomeric cycloadducts, **1a** and **1b**, designing parallel synthetic pathways to reach the same target molecule. An active research effort is been carried out in our laboratory to extend this methodology to the synthetic approach to other biologically active molecules.

EXPERIMENTAL SECTION

General Procedures. Unless otherwise noted, all reactions were conducted under an atmosphere of dry nitrogen or argon in oven-dried glassware. Raw materials were obtained

from commercial suppliers and used without further purification. All solvents were purified before use: ether, tetrahydrofuran, hexane and pentane were distilled under nitrogen from sodium / benzophenone. Methylene chloride and acetonitrile were distilled under nitrogen from CaH_2. Infrared spectra were recorded on a FT-IR NICOLET 510 spectrophotometer as thin films or as solutions. NMR spectra were taken in deuterated chloroform on spectrometers at 200 MHz (GEMINI-200), 300 MHz (UNITY-300) and/or 500 MHz (UNITY-500) for ^{1}H-NMR, and at 50 MHz and 75.43 MHz for ^{13}C-NMR. For ^{1}H-NMR tetramethylsilane was used as internal standard. ^{13}C-NMR spectra were referenced to the 77.0 ppm resonance of chloroform. Mass spectra were measured on a HEWLETT-PACKARD 5890 mass spectrometer using electron impact and/or chemical ionization. Melting points were measured on a GALLENKAMP equipment. GC analyses were performed on HP-8790 gas chromatograph equipped with a HEWLETT-PACKARD-crosslinked MePhe-Silicone capillary column (l=25 m, ϕ=0.2 mm, w= 0.25μm) using Helium as gas carrier and a FID detector (T=250°C, P_{H2}=4.2 psi, P_{air}=2.1 psi). GC analyses were carried out under different temperature/time conditions as follows: [Code; initial temperature(°C); initial time(min); rate(°C/min); final temperature(°C); final time(min)]. Elemental analyses are obtained with a FISONS Na-1500 apparatus, analyzing combustion gases by chromatography and using a thermal conductivity detector.

*Preparation of **1a** and **1b** by [4+3] cycloaddition reaction.*

a) Previous treatments: activation of copper powder.

In a 250 mL round bottomed flask, containing commercial copper powder (10g), a solution of iodine in acetone (2% w/v) (100 mL) was added. The suspension was stirred for 15 min. and filtered through a Büchner funnel. The solid was washed with 60 mL of a 1:1 mixture of 35% (w/w) aqueous HCl and acetone, and afterwards with distilled water (100 mL) and with acetone (50 mL). A copper powder, with metallic brightness, was obtained , which was dried at high vacuum for 30 min. and stored under inert atmosphere (Ar), in the darkness, inside a desiccator.

b) Activation of NaI.

Sodium iodide used in cycloaddition reactions should be activated (dehydrated) before use. This activation was carried out by grinding it followed by dehydration in an oven at 150°C under vacuum for 24 hour. It is necessary to cool it down to room temperature in a desiccator prior to use.

*c) Procedure for [4+3] Cycloaddition reaction of 2-methoxy-furan with 2,4-dimethyl-2-oxyallyl cation under Hoffmann's Conditions: **1a**, **1b**.*

A two-necked flask, fitted with a magnetic stirring bar and a Dimroth condenser, under nitrogen, was charged with 2-methoxyfuran (4.2 mL, 46 mmol) , freshly activated copper powder (10.17 g, 160 mmol), oven-dried (24 hours at 150°C) sodium iodide (45.38 g, 303 mmol) and dry acetonitrile as solvent (27 mL). To the resulting suspension, 2,4-dibromo-3-pentanone (6.6 mL, 48 mmol), (freshly passed through a small column of activated neutral alumina), was added dropwise, at room temperature. The reaction was maintained at 50°C and

controlled by TLC and GC. After 5 hours of reaction time, the reaction mixture was concentrated to dryness under vacuum at 0°C. The crude oily mixture was dissolved in cold methylene chloride (100 mL), and ice water was added (100 mL) and stirring was maintained for 15 min. If copper salts precipitated, they were separated by filtration through a Büchner funnel. The organic phase (CH_2Cl_2) was decanted and kept at 0°C meanwhile the aqueous phase was extracted with cold methylene chloride (6 x 20 mL). All the organic extracts were combined together and washed with cold aqueous (25% w/w) ammonia (2 x 50 mL), followed by cold distilled water (2 x 50 mL), until no blue colour of $Cu(NH_3)_4^{2+}$ was observed. The resulting organic solution was dried over anhydrous $MgSO_4$, filtered through neutral alumina and concentrated to dryness under vacuum without heating, obtaining (8.12 g , 97% yield) of a thick colourless oil, formed by a 70:30 diastereoisomeric mixture of cycloadducts **1a** and **1b**, respectively. The mixture was separated by flash column chromatography on silica gel (previously activated at 150°C overnight), using mixtures of hexane-ethyl acetate of increasing polarity. Diasteroisomer **1a** was eluted first and afterwards **1b**.

1a: white solid. **m.p.** 60-61°C (EtOEt). ν_{max} (film) 3105 (H-Csp^2), 3005, 2960, 2920, 2860 (H-Csp^3), 1710 (C=O), 1615 (C=C), 1460, 1450 (C-C, deform.), 1390, 1380, 1360, 1340, 1310, 1280 (C-H, deform.), 1200, 1170, 1130, 1110 (C-O), 1010, 990, 910, 830, 820, 770, 660. δ_H (500 MHz, $CDCl_3$) 0.84 (3H, d, J=7.0 Hz, H10), 0.91 (3H, d, J=7.0 Hz, H9), 2.60 (1H, q, J=7.0 Hz, H2), 2.62 (1H, dq, J_1=4.8 Hz, J_2=7.0 Hz, H4), 3.28 (3H, s, OMe), 4.73 (1H, dd, J_1= 4.8 Hz, J_2=1.9 Hz, H5), 6.06 (1H, d, J=6.1 Hz, H7), 6.28 (1H, dd, J_1=6.1 Hz, J_2=1.9 Hz, H6). δ_C (50 MHz, $CDCl_3$) 8.64 (C10), 10.18 (C9), 48.01 (C4), 51.14 (OMe), 54.68 (C2), 79.00 (C5), 112.16 (C1), 132.42 (C7), 136.10 (C6), 208.11 (C3). **GC** [Ti=50°C, ti=1min., r=10°C/min., Tf=250°C, tf=15min.]: retention time=13.4 min. **MS** [DIP-CI, CH_4, 70eV, 150°C, m/z(%)]: 211 (10, M+C_2H_5), 183 (100, M+H), 182 (9, M), 167 (2, M-CH_3), 151 (5, M-CH_3O), 127 (2, M-C_4H_7 or C_3H_4O), 125 (2, M-C_4H_9 or C_3H_5O), 95 (7, M-$C_5H_{11}O$ or $C_4H_7O_2$). **EA**, calculated for $C_{10}H_{14}O_3$: C(65.92%), H(7.74%). Found: C(65.67%), H(7.49%).

1b: white solid. **m.p.** 61-62°C (EtOEt). ν_{max}(film) 3100 (H-Csp^2), 3000, 2970, 2895, 2850 (H-Csp^3), 1730, 1715 (C=O), 1615 (C=C), 1470 (C-C, deform.), 1340, 1310, 1300, 1280 (C-H, deform.), 1200, 1130, 1100 (C-O), 970, 910, 820, 740. δ_H (500 MHz, $CDCl_3$) 1.27 (3H, d, J=7.5 Hz, H9), 1.36 (3H, d, J=7.5 Hz, H10), 2.23 (1H, q, J=7.5 Hz, H4), 2.54 (1H, q, J=7.5 Hz, H2), 3.42 (3H, s, OMe), 4.67 (1H, d, J=1.4 Hz, H5), 6.09 (1H, d, J=6.2 Hz, H7), 6.33 (1H, dd, J_1=6.2 Hz, J_2=1.4 Hz, H6). δ_C (50 MHz, $CDCl_3$) 13.14 (C9), 17.83 (C10), 47.82 (C4), 51.39 (OMe), 54.05 (C2), 79.72 (C5), 110.27 (C1), 133.39 (C7), 137.01 (C6), 213.74 (C3). **GC** [Ti=50°C, ti=1min., r=10°C/min., Tf=250°C, tf=15min.]: retention time=13.1 min. **MS** [DIP-CI, NH_3, 70eV, 150°C, m/z(%)] 182 (3, M), 167 (8, M-CH_3), 153 (6, M-CHO), 125 (37, M-C_4H_9 or C_3H_5O), 111 (100, M- C_5H_{11} or C_4H_7O), 95 (37, $C_5H_{11}O$, $C_4H_7O_2$), 83 (22, $C_5H_7O_2$),

67 (38, C_4H_4O). **EA**, calculated for $C_{10}H_{14}O_3$: C(65.92%), H(7.74%). Found: C(65.82%), H(7.61%).

*Reduction of the ketone group on C3 in **1a** and **1b**: preparation of alcohols **2a** / **2a'**, and **2b** / **2b'**, respectively.*

In a 25 mL flask fitted with a septum, magnetic stirring, nitrogen atmosphere and an ice-water bath, $NaBH_4$ (964 mg, 25.5 mmol) was suspended in dry methanol (8 mL). To this suspension, a solution of cycloadduct **1a** (or **1b**) (1.16 g, 6.4 mmol) in dry methanol (2 mL) was added *via* syringe. The reaction mixture was maintained at 0°C for 2 hours (monitored by GC), then concentrated to dryness. The resulting crude oil was redissolved in chloroform, filtered *via* cannula to remove inorganic byproducts and concentrated to dryness, affording alcohols **2a** and **2a'** (1.04 g, 92% yield from **1a**), with a diastereoselectivity *endo/exo* (**2a**:**2a'**) of 92/8. In a similar way, alcohols **2b** and **2b'** (1.14 g, 97% yield) were obtained from **1b**, with a diastereoselectivy 90/10 (*exo*:*endo*, **2b**:**2b'**). All the aforementioned diastereomeric alcohols were easily separated by flash column chromatography, using silica gel as stationary phase and mixtures of hexane/AcOEt of increasing polarity as eluents.

2a: white solid. **m.p.** 44-45°C ($CHCl_3$). ν_{max}(KBr) 3498 (O-H), 3079 (H-Csp^2), 2967, 2930, 2878 (H-Csp^3), 1601 (C=C), 1458, 1407 (C-C, deform.), 1377, 1346 (C-H, deform.), 1190, 1163, 1122, 1080, 1040, 1014, 989 (C-O), 966, 880, 853, 807, 762, 740. δ_H (200 MHz, $CDCl_3$) 0.99 (3H, d, J=7.0 Hz, H10), 1.06 (3H, d, J=7.5 Hz, H9), 2.20 (1H, dq, J_1=5.5 Hz, J_2=7.5 Hz, H2), 2.28 (1H, ddq, J_1=5.5 Hz, J_2=1.5 Hz, J_3=7.0 Hz, H4), 3.34 (3H, s, OMe), 3.77 (1H, dd, J_1=5.5 Hz, J_2=5.5 Hz, H3), 4.57 (1H, dd, J_1=1.5 Hz, J_2=1.5 Hz, H5), 6.31 (1H, d, J=6.2 Hz, H7), 6.60 (1H, dd, J_1=6.2 Hz, J_2=1.5 Hz, H6. δ_C (75 MHz, $CDCl_3$) 11.50 (C9), 12.62 (C10), 38.92 (C4), 42.09 (C2), 50.52 (OMe), 72.77 (C3), 82.03 (C5), 111.38 (C1), 134.94 (C7), 138.81 (C6). **MS** [DIP-CI, CH_4, 70eV, 150°C, m/z(%)] 213 (1, M+C_2H_5), 185 (100, M+H), 183 (18, M-H), 169 (22, M-CH_3), 167 (79, M-OH), 153 (24, M-CH_3O), 139 (15, M-C_2H_5O), 107 (7, M-$C_3H_9O_2$), 95 (19, M-$C_4H_9O_2$). **GC** [Ti =50°C, ti =1min., r =10°C/min., Tf =250°C, tf=15min.]: retention time =14.3 min. **EA**, calculated for $C_{10}H_{16}O_3$: C(65.18%), H(8.76%). Found: C(65.12%), H(8.65%).

2a': white solid. **m.p.** 94-96°C ($CHCl_3$). ν_{max}(film) 3417, 3081, 2964, 2935, 2877, 2838, 1599, 1457, 1374, 1341, 1300, 1256, 1221, 1189, 1164, 1117, 1088, 1034, 1007, 994, 976, 959, 895. δ_H (200 MHz, $CDCl_3$) 0.97 (3H, d, J=7.0 Hz , H10), 1.02 (3H, d, J=7.0 Hz, H9), 1.75 (2H, m, H2, H4), 2.78 (1H, dd, J_1=8.8 Hz, J_2=8.8 Hz, H3), 3.36 (3H, s, OMe), 4.56 (1H, dd, J_1=3.6 Hz, J_2=1.8 Hz, H5), 6.09 (1H, d, J=6.0 Hz, H7), 6.30 (1H, dd, J_1=6.0 Hz, J_2=1.8 Hz, H6). δ_C (75 MHz, $CDCl_3$) 12.84 (C9), 14.20 (C10), 40.89 (C4), 44.69 (C2), 50.69 (OMe), 78.89 (C3), 80.85 (C5), 112.10 (C1), 131.13 (C7), 134.09 (C6). **MS** [DIP-CI, NH_3, 70eV, 150°C, m/z(%)] 219 (2, M+N_2H_5), 202 (100,M+NH3), 185 (42, M+H), 184 (7, M), 167 (15,

M-OH), 166 (1, M-H_2O), 153 (2, M-OMe), 152 (M-MeOH). **EA**, calculated for $C_{10}H_{16}O_3$: C(65.18%), H(8.76%). Found: C(65.40%), H(8.64%).

2b: white solid. **m.p.** 49.5-51.5°C (hexane). ν_{max}(KBr) 3473, 3077, 2940, 2838, 1605, 1466, 1379, 1325, 1286, 1223, 1178, 1134, 1103, 1084, 1007, 984, 964, 931. δ_H (300 MHz, $CDCl_3$) 1.10 (3H, d, J=6.9 Hz, H9), 1.16 (3H, d, J=7.5 Hz, H10), 1.80 (1H, dq, J_1=7.5 Hz, J_2=6.9 Hz, H4), 2.09 (1H, dq, J_1=6.9 Hz, J_2=6.9 Hz, H2), 3.37 (3H, s, OMe), 4.01 (1H, m, H3), 4.62 (1H, d, J=1.8 Hz, H5), 5.97 (1H, d, J=6.0 Hz, H7), 6.24 (1H, dd, J_1=6.0 Hz, J_2=1.8 Hz, H6). δ_C (75 MHz, $CDCl_3$) 8.49 (C10), 13.65 (C9), 34.37 (C4), 39.96 (C2), 50.87 (OMe), 68.35 (C3), 81.75 (C5), 111.27 (C1), 131.61 (C7), 134.53 (C6). **MS** [DIP-CI, NH_3, 70eV, 150°C, m/z(%)] 219 (M+N_2H_7), 202 (100, M+NH_4), 185 (27, M+H), 184 (2, M), 169 (1, M-CH_3), 167 (8, M-OH), 153 (2, M-CH_3O), 152 (1, M-CH_4O), 151 (1, M-CH_5O), 136 (9, M-CH_4O_2), 134 (1, M-CH_6O_2). **EA**, calculated for $C_{10}H_{16}O_3$: C(65.18%), H(8.76%). Found: C(65.23%), H(8.71%).

2b': colourless thick oil. ν_{max}(film) 3477, 3077, 2936, 2836, 1653, 1468, 1402, 1377, 1325, 1294, 1227, 1177, 1130, 1105, 1082, 1059, 1041, 987, 966, 937, 883. δ_H (200 MHz, $CDCl_3$) 1.18 (3H, d, J=7.4 Hz, H9), 1.25 (3H, d, J=7.4 Hz, H10), 1.70 (1H, q, J=7.4 Hz, H4), 1.94 (1H, q, J=7.4 Hz, H2), 3.37 (3H, s, OMe), 3.50 (1H, s, H3), 4.63 (1H, s, H5), 6.20 (1H, d, J=6.0 Hz, H7), 6.53 (1H, dd, J_1=6.0 Hz, J_2=2.0 Hz, H6). δ_C (75 MHz, $CDCl_3$) 14.97 (C10), 19.68 (C9), 40.34 (C4), 44.05 (C2), 50.69 (OMe), 79.12 (C3), 82.95 (C5), 110.79 (C1), 134.45 (C7), 138.15 (C6). **MS** [DIP-CI, NH_3, 70eV, 150°C, m/z(%)] 219 (2, M+N2H7), 202 (72, M+NH4), 185 (100, M+H), 184 (1, M), 167 (17, M-OH), 166(1, M-H_2O), 153 (1, M-CH_3O), 152 (1, M-CH_4O). **EA**, calculated for $C_{10}H_{16}O_3$: C(65.18%), H(8.76%). Found: C(65.20%), H(8.80%).

*Acetylation of hydroxyl group on C3 in **2a** (and **2b**): preparation of acetates **3a** (and **3b**).*

In a 50 mL round bottomed flask fitted with septum, magnetic stirring bar, inert atmosphere (Argon) and an ice-water cooling bath, alcohol **2a** (or **2b**) (1 g, 5.43 mmol), dissolved in of anhydrous THF (16 mL), was placed. When the solution reached 0°C, (3.6 mL, 5.7 mmol) of MeLi (1.6 M in hexane) were added. After 15 min., freshly distilled CH_3COCl (448 µl, 5.7 mmol) was added at once. The reaction mixture was kept under these condition for 1.5 hours and then concentrated to dryness. The resulting oily crude was dissolved in diethyl ether (5 mL) and filtered *via* cannula, in order to remove solid LiCl. The ethereal filtrate was concentrated to dryness under vacuum, obtaining a yellowish oil which was purified by flash column chromatography on activated silica gel. The acetylation product **3a** (or **3b**) was eluted with mixtures of hexane/AcOEt 9/1, and the non-reacted initial alcohol **2a** (or **2b**) with hexane/AcOEt 7/3. This last fraction of starting material could be recycled and reacted again. In this way, 1.13 g (92% yield) of **3a** or 0.92 g (75% yield) of **3b** were obtained from **2a** or **2b**, respectively.

3a: white solid. **m.p.** 40-42 °C (hexane). ν_{max}(film) 3453 (C=O, overtone), 3081 (=C-H), 2969, 2940, 2882, 2838 (C-H), 1734 (C=O), 1601 (C=C), 1456, 1381, 1341, 1300, 1246, 1190, 1165, 1124, 1082, 1041, 1018, 995, 978, 937, 904, 885, 872. δ_H (200 MHz, $CDCl_3$) 0.78 (3H, d, J=7.2 Hz, H9 or H10), 0.85 (3H, d, J=7.2 Hz, H9 or H10), 2.02 (3H, s, OOCMe), 2.26 (1H, dq, J_1=5.8 Hz, J_2=7.2 Hz, H2), 2.38 (2H, ddq, J_1=5.3 Hz, J_1=2.0 Hz, J_3=7.2 Hz, H4), 3.34 (3H, s, H11), 4.54 (1H, dd, J_1=2.0 Hz, J_2=2.0 Hz, H5), 5.32 (1H, ddd, J_1=5.8 Hz, J_2=5.3 Hz, J_3=2.0 Hz, H3), 6.15 (1H, d, J=6.0 Hz, H7), 6.41 (1H, dd, J_1=6.0 Hz, J_2=2.0 Hz, H6). δ_C (50 MHz, $CDCl_3$) 11.24 (C9), 12.39 (C10), 21.07 (C2'), 37.85 (C4), 40.92 (C2), 51.08 (OMe), 73.11 (C3), 82.12 (C5), 111.86 (C1), 133.31 and 137.17 (C6 and C7), 171.43 (C1'). **MS** [DIP-CI, NH_3, 70eV, 150°C, m/z(%)] 261 (9, M+N_2H_7), 244 (100, M+NH_4), 227 (76, M+H), 226 (2, M), 183 (1, M-$COCH_3$), 167 (12, M-$OCOCH_3$). **EA**, calculated for $C_{12}H_{18}O_4$: C(63.69%), H(8.02%). Found: C(63.58%), H(7.85%). **TLC:** Rf=0.59 (SiO_2, Hexane/AcOEt 1/1).

3b: white solid. **m.p.** 64.4-65.4°C (hexane). ν_{max}(KBr) 2942, 1744, 1564, 1452, 1373, 1325, 1240, 1173, 1138, 1082, 1040, 993, 964, 931. δ_H (200 MHz, $CDCl_3$) 1.13 (3H, d, J=7.2 Hz, H9 or H10), 1.19 (3H, d, J=7.2 Hz, H9 or H10), 1.97 (1H, dq, J_1=1.2 Hz, , J_2=7.2 Hz, H2 or H4), 2.11 (3H, s, H2'), 2.23 (1H, br q, J=7.2 Hz, H2 or H4), 3.40 (3H, s, OMe), 4.64 (1H, m, H5), 5.03 (1H, dd, J_1=7.2 Hz, J_2=7.2 Hz, H3), 6.05 (1H, d, J=6.0 Hz, H_7), 6.32 (1H, dd, J_1=6.0 Hz, J_2=2.2 Hz, H6). δ_C (50 MHz, $CDCl_3$) 9.9 (C9), 15.0 (C10), 21.5 (C2'), 32.6 (C_4), 38.0 (C_2), 51.3 (OMe), 71.8 (C3), 82. 2 (C5), 111.5 (C1), 133.3 and 135.2 (C6 and C7), 170.6 (C1'). **MS** [DIP-CI, NH_3, 70eV, 150°C, m/z(%)] 244 (100, M+NH_4), 227 (53, M+H), 226 (1, M), 211 (2, M-CH_3), 183 (1, M-$COCH_3$), 167 (11, M-$OCOCH_3$). **EA**, calculated for $C_{12}H_{18}O_4$. C(63.69%), H(8.02%). Found: C(63.48%), H(8.21%).

*Hydrolysis of the acetal function on C1 in **3a** and/or **3b**: preparation of cycloheptenones **4a** and/or **4b**, respectively.*

In a 25 mL flask, fitted with septum, magnetic stirring, nitrogen atmosphere and ice-water cooling bath, compound **3a** (or **3b**) (500 mg, 2.21 mmol) dissolved in $CHCl_3$ (7 mL) was placed. At 0°C, CF_3COOH (1.26 mL, 11 mmol) and H_2O (0.2 mL, 11mmol) were added by syringe in one go. Once the addition was finished, (5 min), the cooling bath was removed and the reaction mixture was kept at room temperature for 30 min. (until the starting material was transformed, as observed by TLC). The reaction mixture was then quickly concentrated to dryness under high vacuum (without heating), obtaining a colourless oil, which was submitted to a careful flash column chromatography on activated silica gel (using a jacketed column cooled by circulating ice-water). The product of interest was eluted with a mixture of hexane/AcOEt 1:1. By this procedure, compounds **4a** (400 mg, 85% yield) or **4b** (280 mg, 60% yield), were obtained.

4a:white solid. **m.p.** 109-110°C (hexane). ν_{max}(KBr) 3413 (OH), 2981 (C-H), 1746, 1665 (C=O), 1641 (C=C), 1452, 1383, 1229, 1159, 1115, 1072, 1026, 962, 916. δ_H (200 MHz,

$CDCl_3$) 1.11 (3H, d, J=6.8 Hz, H8), 1.21 (3H, d, J=7.0 Hz, H9), 2.05 (3H, s, H2'), 2.35 (1H, ddq, J_1=6.8 Hz, J_2=1.8 Hz, J_3=10.0 Hz, H5), 2.96 (1H, dq, J_1=1.8 Hz, J_2=7.0 Hz, H7), 4.27 (1H, ddd, J_1=10.0 Hz, J_2=2.2 Hz, J_3=2.2 Hz, H4), 5.35 (1H, dd, J_1=1.8 Hz, J_2=1.8 Hz, H6), 5.98 (1H, dd, J_1=13.2 Hz, J_2=2.2 Hz, H2 or H3), 6.42 (1H, dd, J_1=13.2 Hz, J_2=2.2 Hz, H2 or H3). δ_C (50 MHz, $CDCl_3$) 14.70 (C9), 18.30 (C8), 21.12 (C2'), 44.89 (C5), 51.80 (C7), 72.29 (C6), 78.26 (C4), 129.67 (C2), 145.76 (C3), 171.25 (C1'), 201.22 (C1). **MS** [DIP-CI, NH_3, 70eV, 150°C, m/z(%)] 247 (3, $M+N_2H_7$), 230 (100, $M+NH_4$), 213 (4, M+H).**EA**, calculated for $C_{11}H_{16}O_4$: C(62.25%), H(7.60). Found: C(62.31%), H(7.49%).

4b:white solid. **m.p.** 91-93°C (hexane). ν_{max}(KBr) 3405, 2993, 2973, 2936, 1744, 1655, 1456, 1385, 1312, 1240, 1165, 1082, 1057, 1022, 974, 904, 822. δ_H (200 MHz, $CDCl_3$) 0.98 (3H, d, J=7.0 Hz, H9), 1.14 (3H, d, J=6.8 Hz, H8), 2.05 (3H, s, H2'), 2.68 (1H, dq, J_1=6.0 Hz, J_2=6.8 Hz, H5), 2.86 (1H, dq, J_1=2.5 Hz, J_2=7.0 Hz, H7), 4.75 (1H, ddd, J_1=4.0 Hz, J_2=4.0 Hz, J_3=2.2 Hz, H4), 5.39 (1H, dd, J_1=6.0 Hz, J_2=2.5 Hz, H6), 6.11 (1H, dd, J_1=12.4 Hz, J_2=2.2 Hz, H2), 6.58 (1H, dd, J_1=12.4 Hz, J_2=4.0 Hz, H3). δ_C (50 MHz, $CDCl_3$) 10.20 (C9), 13.47 (C8), 20.55 (C2'), 41.98 (C5), 49.07 (C7), 70.54 (C6), 74.20 (C4), 131.04 (C2), 148.95 (C3), 170.83 (C1'), 199.99 (C1). **MS** [DIP-CI, NH_3, 70eV, 150°C, m/z(%)] 247 (1, $M+N_2H_7$), 230 (100, $M+NH_4$), 213 (3, M+H), 170 (1, $M-C_2H_2O$), 152 (1, $M-C_2H_4O_2$), 135 (1, $M-C_2H_5O_3$). **EA**, calculated for $C_{11}H_{16}O_4$: C(62.25%), H(7.60). Found: C(62.30%), H(7.56%).

*Mitsunobu reaction of cycloheptenone **4a**: obtention of benzoate **5**.*

In a 50 mL flask, fitted with a septum, magnetic stirring, nitrogen atmosphere and an an ice-water cooling bath, secondary alcohol **4a** (427 mg, 1.89 mmol) was placed, dissolved in anhydrous THF (9.2 mL). In other flask, a solution of Ph_3P (2.23 g, 8.5 mmol) and PhCOOH (1.04 g, 8.5 mmol) in anhydrous THF (20 mL) was prepared, and transferred by cannula to the first 50 mL flask, at 0°C. Once the mixture was homogenized by stirring, diethyl azodicarboxylate (DEAD) (1.34 mL, 8.5 mmol), dissolved in anhydrous THF (15 mL) was added dropwise during a period of 10 min. Afterwards, the cooling bath was removed and the reaction mixture allowed to reach room temperature, and maintained under these conditions for 25 hours (monitored by TLC). THF was distilled off by vacuum, diethyl ether (50 mL) was added and the crude mixture kept at room temperature for 12 hours, observing the precipitation of a solid, which was separated by filtration *via* cannula. The solid was washed several times with ether, until no extraction of product was observed by TLC. The ethereal solution was washed with an aqueous saturated solution of $NaHCO_3$ (2 x 10 mL), dried over anhydrous $MgSO_4$, filtered and concentrated to dryness under vacuum, obtaining 3.62 g of a viscous yellowish oil. This crude oil was submitted to flash column chromatography on activated silica gel, eluting with mixtures of hexane/AcOEt of increasing polarity. With hexane/AcOEt 8/2, 500 mg of product were isolated but traces of DEAD were present. This fraction was again chromatographed on silica gel, eluting with mixtures of hexane/acetone of increasing polarity. In the fraction of hexane/Acetone 97/3, 450 mg (75% yield) of pure product **5** were eluted.

5: white solid. **m.p.** 93-95°C. ν_{max}(KBr) 3075 (=C-H), 2985, 2941 (C-H), 1719 (C=O), 1677 (C=C), 1603, 1584, 1491, 1453, 1374, 1233, 1179, 1111, 1071, 1025, 984, 911. δ_H (200 MHz, $CDCl_3$) 0.99 (3H, d, J=7.0 Hz, H9), 1.20 (3H, d, J=6.6 Hz, H8), 2.05 (3H, s, H2'), 3.02 (2H, m, H5, H7), 5.47 (1H, dd, J_1=7.7 Hz, J_2=2.5 Hz, H6), 6.15 (1H, m, H4), 6.22 (1H, dd, J_1=12.2 Hz, J_2=2.6 Hz, H2), 6.60 (1H, ddd, J_1=12.2 Hz, J_2=3.6 Hz, J_3=1.1 Hz, H3), 7.48 (2H, tt, J_1=7.0 Hz, J_2=1.5 Hz, H3''', H5'''), 7.60 (1H, dt, J_1=1.5 Hz, J_2=7.0 Hz, H4'''), 8.08 (2H, dt, J_1=1.5 Hz, J_2=7.0 Hz, H2''', H6'''). δ_C (50 MHz, $CDCl_3$) 10.31 (C9), 13.51 (C8), 20.43 (C2'), 39.70 (C5), 48.98 (C7), 72.88 (C6), 72.98 (C4), 128.50 (C3''',C5'''), 129.42 (C1'''), 129.62 (C2''', C6'''), 132.50 (C2), 133.46 (C4'''), 144.26 (C3), 165.40 (C1''), 170.65 (C1'), 198.97 (C1). **MS** [DIP-CI, NH_3, 70eV, 150°C, m/z(%)] 334 (100, M+NH_4), 317 (5, M+H), 257 (1, M-$OCOCH_3$), 195 (1, M-OCOPh), 105 (1, PhCO). **EA**, calculated for $C_{18}H_{20}O_5$: C(68.33%), H(6.37%). Found: C(68.20%), H(6.46%).

*Benzoylation of alcohol **4b**: preparation of benzoate **5**.*

In a round bottomed 50 mL flask, fitted with a septum, magnetic stirring and nitrogen atmosphere, cycloheptenone **4b** (170 mg, 0.8 mmol) and a catalytic amount of *p*-dimethylamino-pyridine (DMAP) were placed, dissolved in dry chloroform (3 mL). The solution was cooled down to 0°C and Et_3N (334 µl, 2.4 mmol) and PhCOCl (186 µl, 1.6 mmol) were added. After 5 min. the cooling bath was removed and the reaction mixture stirred, at room temperature, for 1.5 hours, and then concentrated to dryness under high vacuum. The resulting crude oil was dissolved in chloroform (25 mL), washed successively with cold HCl 0.5 M (2 x 5 mL)(to remove the remaining NEt_3 and DMAP), with aqueous saturated $NaHCO_3$ (2 x 5 mL)(to remove traces of PhCOOH and PhCOCl) and finally with distilled water (5 mL). The organic solution was dried over anhydrous $MgSO_4$, filtered and concentrated to dryness, obtaining an orange oil which was purified by careful flash column chromatography on silica gel (using a jacketed column cooled by circulating ice-water), eluting with hexane/ AcOEt 8:2, benzoate **5** (190 mg, 75% yield). The physical and spectroscopic properties of the benzoylation product of **4b**, obtained by this procedure, are identical to those of the before-described compound **5**.

*Benzoylation of alcohol **4a**: preparation of benzoate **5'**.*

In an oven-dried round-bottomed 10 mL flask, fitted with a septum, magnetic stirring and argon atmosphere, cycloheptenone **4a** (85 mg, 0.4 mmol), dissolved in anhydrous THF (2 mL), was placed. The solution was cooled to -78°C and LDA, 2.0 M in hexane, (0.25 mL, 0.4 mmol) was added by syringe. After 15 min. freshly purified PhCOCl (70 mg, 0.5 mmol) was added and the mixture stirred for 5 min. Then, the cooling bath was removed and the reaction mixture stirred at room temperature for 1.5 hours. Following similar work-up and purification procedures as for the previous benzoylation reaction (of **4b**), 76 mg (60 % yield) of benzoate **5'** were obtained.

5': thick colourless oil. ν_{max}(film) 3070, 2980, 2940, 1720, 1680, 1604, 1585, 1490, 1455, 1240, 1180,1110, 1100. δ_H (200 MHz, $CDCl_3$) 1.13 (3H, d, J=6.8 Hz, H9), 1.16 (3H, d, J=7.0 Hz, H8), 2.11 (3H, s, OOCMe), 3.03 (2H, dq, J_1=1.5 Hz, J_2= 6.8 Hz, H5, H7), 5.43 (1H, dd, J_1=1.5 Hz, J_2=2.5 Hz, H6), 5.74 (1H, ddd, J_1=2.5 Hz, J_2=2.8 Hz, J_3=10.0 Hz, H4), 6.07 (1H, dd, J_1=13.2 Hz, J_2=2.5 Hz, H2), 6.33 (1H, dd, J_1=13.2 Hz, J_2=2.8 Hz, H3), 7.48 (2H, dtt, J_1=1.4 Hz, J_2=2.1 Hz, J_3= 7.0 Hz, H3''', H5'''), 7.62 (1H, tt, J_1=2.1 Hz, J_2=7.2 Hz, H4'''), 8.07 (2H, ddt, J_1=1.4 Hz, J_2=2.1, J_3=7.0 Hz, Hz, H2''', H6'''). δ_C (50 MHz, $CDCl_3$) 14.24 (C9), 17.58 (C8), 20.74 (C2'), 42.18 (C5), 51.35 (C7), 74.13 (C6), 77.16 (C4), 128.50 (C3''',C5'''), 129.73 (C1'''), 129.63 (C2''', C6'''), 130.41 (C2), 133.40 (C4'''), 140.60 (C3), 165.53 (C1''), 170.58 (C1'), 200.01 (C1). **MS** [DIP-CI, NH_3, 70eV, 150°C, m/z(%)] 334 (100, M+NH_4), 317 (10, M+H), 257 (5, M-$OCOCH_3$), 195 (10, M-OCOPh). **EA**, calculated for $C_{18}H_{20}O_5$: C(68.33%), H(6.37%). Found: C(68.30%), H(6.32%).

Hydrogenation of cycloheptenone 5: preparation of cycloheptanone 6.

In a 100 mL round-bottomed flask, Pd(10%)/C (25 mg), suspended in anhydrous THF (5 mL), was placed and the system was purged with hydrogen twice. Then, cycloheptenone **5** (420 mg, 1.33 mmol), dissolved in THF (15 mL), was added by cannula. The system was again purged twice by two vacuum/hydrogen cycles and vigorously stirred under hydrogen atmosphere at room temperature overnight. The solvent was removed under vacuum and the resulting oil dissolved in ethyl acetate (2 mL) and filtered through neutral alumina. Ethyl acetate was distilled off under vacuum obtaining 423 mg (100% yield) of **6**, as a viscous yellowish oil.

6: viscous yellowish oil. **m.p.** 107-109°C (AcOEt). ν_{max}(film) 2979, 2941 (C-H), 1740, 1717 (C=O), 1453, 1372, 1316, 1275, 1241 (C-O), 1177, 1156, 1113, 1071, 1042, 1027, 996, 967, 928. δ_H (200 MHz, $CDCl_3$) 1.06, 1.13 (6H, d, J=7.4 Hz, J=7.0 Hz, H8 y H9), 2.11 (3H, s, H2''), 2.15, 2.37 (4H, m, H4, 2H6, H7), 2.79 (1H, ddd, J_1=18.8 Hz, J_2=13.1 Hz, J_3=4.2 Hz, H7), 3.17 (1H, dq. J_1=2.0 Hz, J_2=7.0 Hz, H2), 5.31 (1H, d, J=2.0 Hz, H3), 5.47 (1H, dd, J_1=6.2 Hz, J_2=3.0 Hz, H5), 7.44 (2H, tt, J_1=7.0 Hz, J_2=1.5 Hz, H3''', H5'''), 7.57 (1H, dt, J_1=1.5 Hz, J_2=7.0 Hz, H4'''), 8.06 (2H, dt, J_1=1.5 Hz, J_2=7.0 Hz, H2''', H6'''). δ_C (50 MHz, $CDCl_3$) 14.37 (C9), 15.93 (C8), 20.80 (C2'), 26.16 (C6), 37.09 (C7), 43.31 (C4), 48.63 (C2), 73.84 (C3), 76.36 (C5), 128.38 (C3''', C5'''), 129.57 (C2''', C6'''), 129.89 (C1'''), 133.21 (C4'''), 165.71 (C1''), 170.63 (C1'), 209.55 (C1). **MS** [DIP-CI, NH_3, 70eV, 150°C, m/z(%)] 336 (100, M+NH_4), 319 (3, M+H), 276 (1, M-$OCOCH_3$), 213 (1, M-COPh), 105 (2, PhCO). **EA**, calculated for $C_{18}H_{22}O_5$: C(67.91%), H(6.97%). Found: C(67.85%), H(7.12%).

Preparation of silyl enol ether 7 of cycloheptanone 6.

In a 25 mL flask, previously flamed and purged with argon, 205 mg (0.65 mmol) of **6** were placed, dissolved in anhydrous THF (8 mL). This solution was cooled down to -78°C and LDA (2.0 M in hexane)(355µl, 0.71 mmol) was added. The reaction mixture was stirred under these conditions for 30 min. Afterwards, HMPA (123 µl, 0.97 mmol) and freshly distilled Me_3SiCl

(>99% purity)(124 μl, 0.71mmol) was added. The reaction mixture was maintained at -78°C for 2.5 hours. The dry-ice/acetone cooling bath was removed and the mixture allowed to reach room temperature for 1 hour. Solvent was distilled off to dryness and the residual oil dissolved in anhydrous ethyl acetate (2 mL). The solution was filtered by cannula, in order to remove solid byproducts, and then concentrated to dryness under high vacuum (without heating), obtaining an oily silyl enol ether **7**, which was directly used in next synthetic step without isolation or further purification.

*Ozonolysis of silyl enol ether 7: preparation of acids **8** and **10**.*

a.- Use of Me_2S as reducing agent of intermediate ozonide.

In a two necked 50 mL round-bottomed flask fitted with magnetic stirring, a capillary ozone diffuser and a gas outlet, connected to a silicone bubbler, silyl enol ether **7** (250 mg, 0.65 mmol) was placed, dissolved in a 1:1 mixture of anhydrous CH_2Cl_2/MeOH (8 mL). Ozone was bubbled in the solution by the capillary diffuser , at -78°C, until the solution turned blue (and the blue colour was stable, which happened in 5 to 10 min.). Afterwards, the system was purged with nitrogen to remove the excess of ozone dissolved in the liquid. The blue colour disappeared and the cooling bath was removed, allowing the reaction mixture to reach room temperature. Then, Me_2S (92 μl, 1.26 mmol) was added and the mixture stirred for 15 min., and finally concentrated to dryness, obtaining a yellow oil. This crude oil was dissolved in chloroform (20 mL) and washed with a saturated aqueous solution of $NaHCO_3$ (3 x 5 mL). In the organic phase remained the non-reacted ketone **6**. The aqueous phase was acidified with 1 M HCl up to pH=3 and extracted with chloroform (5 x 5 mL). The organic extracts were combined together, dried over anhydrous $MgSO_4$, filtered and concentrated to dryness, resulting in 245 mg (90% yield) of acid **8**.

8: colourless oil. ν_{max}(film) 3300, 3066, 2979, 2940, 1719, 1603, 1584, 1493, 1452, 1420, 1375, 1315, 1275, 1232, 1178, 1113, 1070, 1026, 978. δ_H (200 MHz, $CDCl_3$) 1.11 (3H, d, J=7.5 Hz, H9), 1.33 (3H, d, J=7.0 Hz, H8), 2.16 (3H, s, H2''), 2.60 (1H, ddd, J_1=7.5 Hz, J_2=7.5 Hz, J_3=3.8 Hz, H4), 2.78 (1H, m, H6), 2.84 (1H, m, H6), 2.97 (1H, dq, J_1=7.2 Hz, J_2=7.0 Hz, H2), 5.18 (1H, dd, J_1=7.2 Hz, J_2=5.8 Hz, H3), 5.74 (1H, dt, J_1=3.8 Hz, J_2=8.0 Hz, H5), 7.48 (2H, d, J=7.0 Hz, H3''', H5'''), 7.60 (1H, t, J=7.0 Hz, H4'''), 8.20 (2H, d, J=7.0 Hz, H2''', H6'''), 9.78 (1H, s, H7). δ_C (50 MHz, $CDCl_3$) 11.46 (C9), 13.34 (C8), 20.80 (C2''), 37.47 (C4), 41.43 (C2), 43.94 (C6), 68.85 (C5), 75.32 (C3), 128.41 (C3''', C5'''), 129.55 (C2''', C6'''), 129.33 (C1'''), 133.27 (C4'''), 165.56 (C1'), 170.44 (C1''), 178.21 (C1), 199.08 (C7). **MS** [DIP-CI, NH_3, 70eV, 150°C, m/z(%)] 369 (1, M+NH_4), 333 (1, M-OH), 305(2, M-COOH), 321(1, M-CHO), 291 (2, M-$OCOCH_3$), 245 (100, M-COPh), 229 (1, M-PhCOO). **EA**, calculated for $C_{18}H_{22}O_7$: C(61.71%), H(6.33%). Found C(61.65%), H(6.28%).

b.- Use of $NaBH_4$ as a reducing agent for the ozonide intermediate.

In this procedure 215 mg (0.55 mmol) of silyl enol ether **7** were used, and the ozonization process was carried out under the same conditions than the reaction described before. Once the ozonide was formed, the reaction mixture was allowed to reach room temperature, and $NaBH_4$

(41.6 mg, 1.1 mmol) was added, maintaining stirring under these conditions for 2.5 hours. Then, 20 μl (1.1 mmol) of distilled H_2O were added to quench the excess of sodium borohydride. The reaction mixture was concentrated to dryness, obtaining a yellowish thick oil which was dissolved in chloroform (5 mL) and the resulting solution filtered through neutral alumina to remove inorganic byproducts. Concentration to dryness afforded 155 mg (80% yield) of **10** as a yellowish oil.

10: yellowish oil. ν_{max}(film) 3377, 2894, 1717, 1452, 1279, 982. δ_H (200 MHz, $CDCl_3$) 1.08 (3H, d, J=7.0 Hz, H9), 1.22 (3H, d, J=7.0 Hz, H8), 1.8-1.9 (2H, m, H6), 2.62 (3H, s, H2'), 2.4 (1H, m, H4), 2.9 (1H, m, H2), 3.5-3.7 (2H, m, H7), 5.17 (1H, dd, J_1=7.5 Hz, J_2=6.0 Hz, H3), 5.44 (1H, m, H5), 7.45 (2H, d, J=7.6 Hz, H3''', H5'''), 7.56 (1H, d, J=7.4 Hz, H4'''), 8.03 (2H, d, J=7.2 Hz, H2''', H6'''. δ_C (50 MHz, $CDCl_3$) 11.70 (C9), 13.43 (C8), 20.89 (C2'), 32.71 (C6), 38.20 (C4), 41.80 (C2), 58.70 (C7), 71.35 (C5), 75.65 (C3), 128.38 (C3''', C5'''), 129.65 (C2''', C6'''), 129.79 (C1'''), 133.23 (C4'''), 166.59 (C1''), 170.41 (C1'), 175.38 (C1). **MS** [DIP-CI, NH_3, 70eV, 150°C, m/z(%)] 370 (10, M+NH_4), 369 (100, M+NH_3), 353 (3, M+H), 231 (15, M-OCOPh), 105 (1, PhCO). **EA**, calculated for $C_{18}H_{24}O_7$: C(61.35%), H(6.86 %). Found : C(61.41%), H(6.92%).

*Esterification of acids **8** or **10** with diazomethane: preparation of methyl esters **9** or **11**, respectively.*

In a 50 mL flask 100mg of acids **8** or **10** were placed, and 25 mL of a freshly prepared ethereal yellowish solution of diazomethane [20] was added. The mixture was stirred for 30 min. in the darkness at room temperature. Then, concentrated to dryness, affording 104 mg of the corresponding methyl esters **9** or **11**, in quantitative yield.

9: colourless oil. ν_{max}(film) 3080, 2981, 2952, 2849, 1742, 1694, 1603, 1584, 1452, 1437, 1373, 1315, 1275, 1233, 1200, 1177, 1113, 1071, 1027, 986. δ_H (200 MHz, $CDCl_3$) 1.06 (3H, d, J=7.0 Hz, H9), 1.29 (3H, d, J=7.0 Hz, H8), 2.12 (3H, s, H2'), 2.6-3.0 (4H, m, 2H6, H4, H2), 3.68 (3H, s, H10), 5.15 (1H, dd, J_1=6.6 Hz, J_2=4.0 Hz, H3), 5.72 (1H, dt, J_1=8.0 Hz, J_2=4.0 Hz, H5), 7.46 (2H, d, J=7.5 Hz, H3''', H5'''), 7.56 (1H, d, J=7.5 Hz, H4'''), 8.06 (2H, d, J=7.5 Hz, H2''', H6'''), 9.76 (1H, dd, J_1=2.2 Hz, J_2=1.4 Hz, H7). δ_C (50 MHz, $CDCl_3$) 11.48 (C9), 13.39 (C8), 20.76 (C2'), 37.32 (C4), 41.74 (C2), 44.11 (C6), 51.81 (C10), 68.92 (C5), 75.60 (C3), 128.40 (C3''', C5'''), 129.54 (C2''', C6'''), 129.62 (C1'''), 133.23 (C4'''), 165.56 (C1''), 170.20 (C1'), 173.22 (C1), 199.01 (C7). **MS** [DIP-CI, NH_3, 70eV, 150°C, m/z(%)] 382 (1, M+NH_4), 332 (1, M-MeOH), 322 (1, M-$OCOCH_3$), 260 (100, M-COPh), 244 (1, M-PhCOO), 200 (4, M-$C_9H_8O_3$), 182 (4, M- $C_9H_{10}O_4$). **EA**, calculated for $C_{19}H_{24}O_7$: C(62.63%), H(6.64%) . Found: C(62.70%), H(6.65%).

11: colourless oil. ν_{max}(film) 3514, 3075, 2952, 1719, 1601, 1584, 1453, 1436, 1374, 1316, 1279, 1177, 1115, 1071, 1046, 1027, 976, 930. δ_H (200 MHz, $CDCl_3$) 1.05 (3H, d, J=7.0 Hz,

H9), 1.21 (3H, d, J=7.0 Hz, H8), 1.77 (1H, dddd, J_1=15.0 Hz, J_2=11.0 Hz, J_3=4.0 Hz, J_4=4.0 Hz, H6), 1.95 (1H, dddd, J_1=15.0 Hz, J_2=10.0 Hz, J_3=5.5Hz, J_4=2.0 Hz, H6), 2.08 (3H, s, H2'), 2.39 (1H, ddq, J_1=4.0 Hz, J_2=7.0 Hz, J_3=7.0 Hz, H4), 2.88 (1H, dq, J_1=6.0 Hz, J_2=7.0 Hz, H2), 3.52 (1H, ddd, J_1=11.0 Hz, J_2=10.0 Hz, J_3=4.0 Hz, H7), 3.64 (3H, s, H10), 3.67 (1H, ddd, J_1=11.5 Hz, J_2=5.5 Hz, J_3=4.0 Hz, H7), 5.14 (1H, dd, J_1=7.0 Hz, J_2=6.0 Hz, H3), 5.38 (1H, ddd, J_1=11.0 Hz, J_2=4.0 Hz, J_3=2.0 Hz, H5), 7.46 (2H, d, J=7.5 Hz, H3''', H5'''), 7.56 (1H, d, J=7.5 Hz, H4'''), 8.06 (2H, d, J=7.5 Hz, H2''', H6'''). δ_C (50 MHz, $CDCl_3$) 11.66 (C9), 13.44 (C8), 20.95 (C2'), 32.72 (C6), 38.07 (C4), 41.72 (C2), 51.82 (C10), 58.57 (C7), 71.25 (C5), 75.63 (C3), 128.41 (C3''', C5'''), 129.60 (C2''', C6'''), 129.77 (C1'''), 133.20 (C4'''), 166.60 (C1''), 170.39 (C1'), 173.31 (C1). **MS** [DIP-CI, NH_3, 70eV, 150°C, m/z(%)] 384 (17, M+NH_4), 383 (100, M+NH_3), 367 (7, M+H), 245 (10, M-OCOPh), 105 (1, PhCO). **EA**, calculated for $C_{19}H_{26}O_7$: C(62.28%), H(7.15%). Found : C(62.30%), H(6.92%).

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