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The oligomerization and acylation of precocene I

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ABSTRACT

The oligomerization of precocene I with Brönsted and Lewis acids has been studied. In this way, the reaction of this chromene with HCl/MeOH gave two dimers, a trimer, a linear tetramer and a mixture of pentamers, whilst with $FeCl_3$/HOAc a dimer and six cyclic tetramers were obtained. The cyclization of linear tetramers occurs between C-4‴ and C-6 or, in lower yield, between C-4‴ and C-8. In the formation of linear tetramers the C-8 functionalization was not detected, which could indicate that it occurs during the cyclization process. Moreover, oxidative one-electron coupling reactions were also observed in the treatment of precocene I with $FeCl_3$/HOAc. On the other hand, the reaction of precocene I with $FeCl_3/Ac_2O$ produced 6-acylation leading to the natural chromene encecalin.

1. Introduction

The chromenes precocene I (**1**) and precocene II (**2**), isolated from *Ageratum houstonianum*, have been shown to induce precocious metamorphosis when applied to larval stages of insects.[1–3] Analogues of these antijuvenile hormones have been synthesized with the aim of obtaining compounds with better activity.[4–8] In this way, we have prepared dimers A (**4**), C (**6**) and D (**7**) by treatment of precocene II (**2**) with $SiO_2/AgNO_3$.[9,10] We also obtained the 3,3′-dimer of precocene II (**8**) in one step by treatment of **2** with dry ferric trichloride in acetic acid.[11] Whilst **4** and **7** were obtained by acid dimerization, the formation of dimers **6** and **8** occurred by oxidative one-electron coupling reactions. We also studied the reaction of precocene II (**2**) with $FeCl_3$ in Ac_2O leading to the trimer **9** and to the 3-acylated precocene II.[12] Later, other authors also obtained this trimer **9** by treatment of **2** with $AlCl_3$ in diethyl ether.[13]

Continuing with these studies we describe here the results obtained in the reactions of precocene I (**1**) with HCl/MeOH, Fe_3Cl/HOAc and Fe_3Cl/Ac_2O, comparing them with those obtained in the reactions of precocene II (**2**) with these acids.

2. Results and discussion

The reaction of precocene I (**1**) with HCl/MeOH afforded the dimers **3** and **10**, the trimer **11**, the tetramer **12** and a mixture of pentamers. The structure of the dimer **3** was given on the basis of the following considerations: In the mass spectrum the molecular ion was in accordance with the molecular formula $C_{24}H_{28}O_4$ showing also significant peaks at *m/z* 191 and 189, characteristic of the monomeric fragments produced by the cleavage of the 3′,4-bond. The ^{1}H NMR spectrum showed signals of four methyls, two methoxy groups, two H-3 at δ_H 1.79 (t, *J*=12.5 Hz) and 2.01 (dd, *J*=12.5, 6.0 Hz), H-4 at δ_H 3.52 (dd, *J*=12.5, 6.0 Hz), H-4′ at δ_H 6.00 (br s) and four aromatic hydrogens. These signals and the ^{13}C NMR spectrum (Table 2) were assigned using double resonance, COSY,

Table 1
^{13}C NMR data of **1**, **5** and **19**

Carbon	1	5	19
2	76.2	76.6	77.6
3	127.8	48.9	127.0
4	121.9	71.7	121.3
5	126.9	130.5	128.2
6	106.6	108.4	120.6
7	160.6	160.4	161.0
8	102.0	101.7	99.5
9	114.6	115.0	113.9
10	154.2	154.6	158.4
11	28.0	27.8[a]	28.3
12	28.0	24.8[a]	28.3
13	55.3	55.2	55.5
14			197.6
15			30.1

[a] These values can be interchanged.

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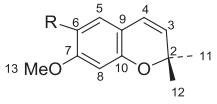
Table 2
^{13}C NMR data of dimers **3** and **10**

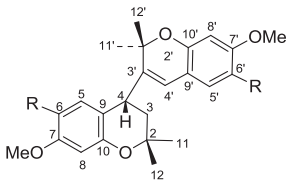
Carbon	3	10	Carbon	3	10
2	74.6	75.1	2′	78.1	76.2
3	45.4	41.7	3′	143.1	127.4
4	37.3	30.3	4′	120.9	121.9
5	130.1	130.0	5′	126.4	126.6
6	107.3	106.9	6′	106.6	125.1
7	159.4	158.9	7′	160.4	158.2
8	101.6	101.4	8′	101.6	99.3
9	116.0	117.1	9′	114.6	114.1
10	155.5	155.0	10′	153.8	152.3
11	29.2	29.8	11′	26.8[b]	27.9[c]
12	24.0	24.2	12′	27.2[b]	28.1[c]
13	55.1[a]	55.5	13′	55.2[a]	55.1

[a–c]These values can be interchanged.

HMQC and HMBC experiments. This compound possesses an analogous structure to that of **4**, which was obtained under the same conditions with precocene II (**2**).[14]



1 R = H
2 R = OMe



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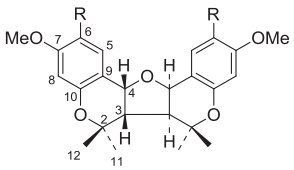
4 R = OMe



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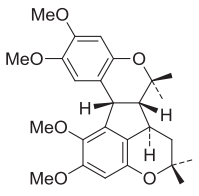
6 R = OMe



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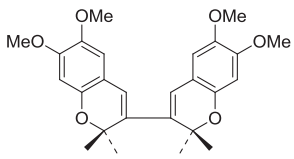

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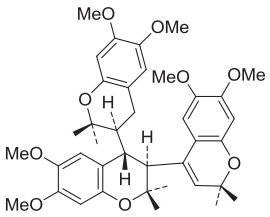

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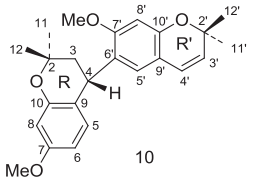
The second of the dimers (**10**) is isomeric with **3**, but its structure presents now the union of the two monomeric units between C-4 and C-6′. This dimer can be formed by protonation of the 3,4-double bond of precocene I (**1**) to form a carbocation at C-4, which attacks a second molecule of **1** at C-6′, with aromatic substitution. This compound had been prepared by treatment of precocene I with trichloroacetic acid-silica gel.[15,16] We have now unambiguously assigned its ^{1}H and ^{13}C NMR spectra using bidimensional NMR data.

The protonation of the dimer **10** with formation of a 4′-carbocation and attack on the C-6″ of a third molecule of precocene I (**1**) forms the trimer **11**, which has the molecular formula $C_{36}H_{42}O_6$ (*m*/*z* 570.2975). Its ^{1}H NMR spectrum showed six methyls, three methoxy groups, H-3 at δ_H 1.67 (m) and 1.92 (dd), H-3′ at δ_H 1.67 (m) and 1.97 (dd), H-4 and H-4′ at δ_H 4.39 (br s) and 4.33 (br s), respectively, whilst H-3″ and H-4″ resonate at δ_H 5.40 and 6.09 as two doublets (*J*=10.0 Hz). Signals also appear in this spectrum of seven aromatic protons, H-5, H-6 and H-8 at δ_H 6.57 (d, *J*=8.0 Hz), 6.22 (dd, *J*=8.0, 2.0 Hz) and 6.24 (br s), respectively, whilst H-5″, H-8″, H-5′ and H-8′ resonate as singlets at δ_H 6.44, 6.26, 6.46 and 6.39, respectively. These signals and the ^{13}C NMR spectrum of **11** (Table 3) were assigned by a study of their COSY, HSQC and HMBC spectra. Indeed the resonances of the geminal methyl group at C-2 and the 3α,3β-hydrogens could be located by running a NOESY experiment. This compound had been identified by other authors as a component of an unresolved mixture, which had been obtained by treatment of precocene I with trichloroacetic acid–silica gel.[16]

To another product obtained in this reaction the structure **12** was given. The HRMS showed that it had a tetrameric structure ($C_{48}H_{56}O_8$, *m*/*z* 760.3936). Its ^{1}H NMR spectrum showed that it was not totally pure, probably contaminated by other stereoisomers. In this spectrum could be observed that **12** was a linear tetramer, which is formed by bonds between the C-4 of a chromane ring and C-6 of an aromatic ring of two different monomeric units, while a chromene ring remained unchanged as the end of the tetramer chain. The two hydrogens of this chromene ring, H-3‴ and H-4‴, appear as two doublets at δ_H 5.35 and 6.05 (*J*=10.0 Hz), and the corresponding carbons at δ_C 127.3 and 122.1, respectively. Thus, this tetramer **12** may be formed from the trimer **11** by reaction once more with another molecule of **1** as explained above for the formation of **11** from **10**.

We also obtained in low yield a mixture of linear pentamers, which was detected in the MS by a molecular ion at *m*/*z* 950 (100%) and fragments at *m*/*z* 760, 570, 380 and 191, which are formed by loss of a different number of precocene units. This mixture was also characterized in the ^{1}H NMR spectrum by signals of the ABX systems of the four chromane cycles and those due to the 3,4-double bond protons of the chromene ring.



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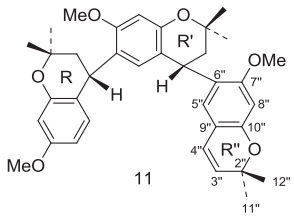

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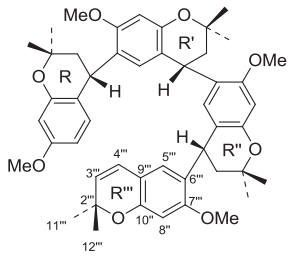

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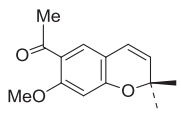

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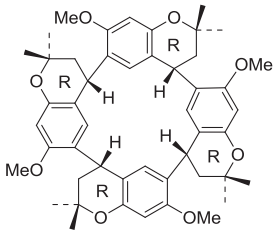
Continuing with these works we studied the reaction of precocene I (**1**) with $FeCl_3$ in HOAc, a Lewis acid with oxidative properties. In this way, the dimer **5** and six cyclic tetramers **13**–**18** were obtained. The molecular formula, $C_{24}H_{28}O_5$, and NMR data of **5** showed that it was a symmetrical dimer with a tetrahydrofuran ring. In the ^1H NMR spectrum, the aromatic signals (each 2H) at δ_H 6.36 (d, J=2.5 Hz), 6.54 (dd, J=8.5, 2.5 Hz) and 7.23 (d, J=8.5 Hz) were assigned to H-8, H-6 and H-5, respectively, whilst two doublets at δ_H 2.43 and 4.75 (each 2H, J=6.3 Hz) were due to H-3 and H-4. These last chemical shifts and coupling constants were similar to those depicted, δ_H 2.43 and 4.74 (J=7.0 Hz), for dimer C (**6**), obtained from precocene II (**2**) by treatment with $SiO_2/AgNO_3$, whose structure was determined by X-ray analysis.[9] In consequence both dimers **5** and **6**, formed by an oxidative one-electron coupling reaction,[12] must have a similar structure with the same stereochemistry in the tetrahydrofuran ring. The ^{13}C NMR spectrum (Table 1) and 2D NMR data were also in accordance with the structure **5** for this dimer. Thus for example, the *cis*-relationship between H-3 and H-4 was confirmed by the correlation observed in the NOESY spectrum between these hydrogens.



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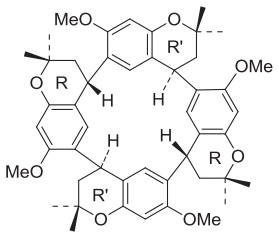

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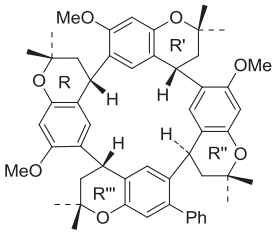

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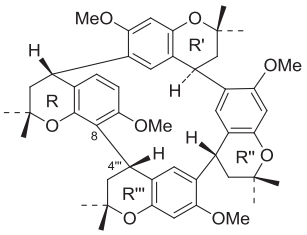

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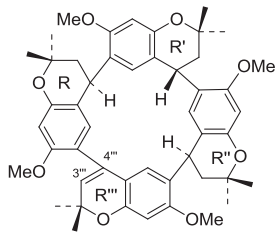
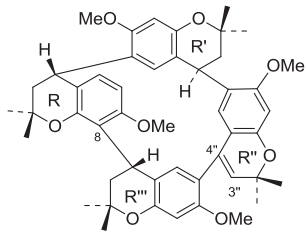


17



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The cyclic tetramer **13** showed the molecular ion and the base peak at m/z 760.3940 in accordance with the molecular formula $C_{48}H_{56}O_8$. The ^1H NMR spectrum showed that this was a compound of symmetrical structure, with four identical monomeric precocene I units. The aromatic hydrogens H-5 and H-8 appear at δ 6.28 and 6.10 as singlets, the two H-3 resonate at δ_H 1.65 (t, J=13.0 Hz) and 1.75 (dd, J=13.0, 5.5 Hz), respectively, whilst H-4 appears at δ_H 4.40 (dd, J=13.0, 5.5 Hz). Irradiation of H-4, in a double resonance experiment, transformed the H-3 signals into a pair of doublets and sharpened the H-5 singlet. These resonances indicated that all the bonds of the monomeric units are between C-4 and C-6, and have the same configuration at C-4. Its ^{13}C NMR spectrum (Table 4) was unambiguously assigned using 2D NMR data. The NOESY spectrum showed correlations of H-4 with H-5, H-3β with H-4, and H-3α with H-5 of another precocene unit. Therefore, we assigned to this compound the relative structure **13**. It can be formed from the linear tetramer **12** by an internal electrocyclic substitution at C-6.

Table 3
^{13}C NMR data of trimer **11**

Carbon	δ	Carbon	δ	Carbon	δ
2	74.9	2′	74.9	2″	76.1
3	42.1	3′	42.0	3″	127.2
4	30.4	4′	30.4	4″	122.1
5	129.8	5′	130.0	5″	126.4
6	106.8	6′	124.7	6″	125.1
7	158.6	7′	155.7	7″	157.9
8	101.2	8′	99.3	8″	99.2
9	117.0	9′	116.2	9″	113.9
10	154.8	10′	153.5	10″	152.1
11	29.8	11′	29.8	11″	27.7[a]
12	24.2	12′	24.2	12″	28.0[a]
13	55.9	13′	55.4	13″	55.3

Table 4
^{13}C NMR data of tetramers **13** and **14**

Carbon	**13**	Carbon	**14**	Carbon	**14**
2	75.1	2	75.3	2′	74.8
3	42.5	3	42.1	3′	37.4
4	30.0	4	30.3	4′	39.0
5	128.6	5	133.6	5′	126.7
6	124.2	6	121.8	6′	124.0
7	156.4	7	157.4	7′	156.6
8	99.2	8	101.6	8′	98.9
9	118.2	9	113.2	9′	117.3
10	152.9	10	154.7	10′	152.0
11	28.7	11	29.3	11′	31.3[a]
12	24.7	12	25.1	12′	30.3[a]
13	55.6	13	55.0	13′	55.4

[a] These values can be interchanged.

Another symmetrical structure was given to the tetramer **14**. Its ^1H and ^{13}C NMR spectra showed signals of two different types of monocyclic units (two different chemical shift for the methoxy groups, four for the methyls, etc.), indicating that the configuration at C-4 was identical for each of two pairs of the precocene unit. Two different pairs of signals corresponding to two C-4 methines could be also observed in the ^1H and ^{13}C NMR spectra at δ_H 4.38 (dd, J=10.2, 6.1 Hz), δ_C 30.3 and δ_H 3.72 (dd, J=13.0, 5.0 Hz), δ_C 39.0, the first pair of these resonances being very similar to those observed in the symmetrical tetramer **13** (Table 7). Consequently, we assigned to these two symmetrical H-4 protons a relative β-stereochemistry as in **13**, and to the other two H-4 an α-stereochemistry. Double resonance experiments showed that irradiation of H-4(β) sharpened H-5, whilst irradiation of H-4′(α) has no effect on H-5 or H-5′. The structure **14** was given to this tetramer considering that in the HMBC spectrum correlations of H-4 (δ_H 4.38) with C-6′ (δ_C 124.0) and of H-4′ (δ_H 3.72) with C-6 (δ_C 121.8) were observed, which indicated that the R and R′ monomeric units were joined in an alternative form. All the NMR signals were assigned using 1D and 2D NMR data.

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Table 5
^{13}C NMR data of tetramer **15**

Carbon	δ	Carbon	δ	Carbon	δ	Carbon	δ
2	75.7	2′	74.5	2″	74.9	2‴	75.4
3	42.2	3′	41.2	3″	37.3	3‴	38.4
4	28.3	4′	32.0	4″	39.0	4‴	28.8
5	129.0	5′	128.1	5″	126.4	5‴	134.0
6	124.9	6′	122.3	6″	124.3	6‴	121.0
7	156.8	7′	156.9	7″	156.2	7‴	156.6
8	98.9	8′	98.4	8″	100.0	8‴	99.8
9	118.8	9′	114.1	9″	117.3	9‴	116.8
10	152.2	10′	154.0	10″	151.7	10‴	153.2
11	30.4	11′	30.1	11″	30.3	11‴	23.8[a]
12	27.5	12′	27.2	12″	25.7	12‴	25.8[a]
13	55.3[b]	13′	54.7 [b]	13″	54.6	13‴	55.2[b]

[a,b]These values can be interchanged.

Table 6
^{13}C NMR data of tetramer **16**

Carbon	δ	Carbon	δ	Carbon	δ	Carbon	δ
2	77.6	2′	74.7	2″	74.6	2‴	76.1
3	41.2	3′	38.6	3″	41.3	3‴	37.6
4	35.7	4′	38.0	4″	32.3	4‴	28.6
5	126.2	5′	132.8	5″	128.5	5‴	126.2
6	103.7	6′	122.3	6″	122.1	6‴	124.7
7	157.4	7′	155.7	7″	158.1	7‴	156.3
8	124.3	8′	99.1	8″	102.6	8‴	98.8
9	118.2	9′	113.6	9″	117.3[a]	9‴	117.1[a]
10	154.7	10′	154.4	10″	152.0	10‴	152.6
11	29.0[b]	11′	30.5	11″	30.0	11‴	30.3
12	28.6[b]	12′	26.2	12″	23.3	12‴	26.7
13	55.8	13′	55.2[c]	13″	55.0	13‴	55.8[c]

[a–c]These values can be interchanged.

Table 7
H-4 and C-4 chemical shifts of the cyclic tetramers **13**–**18**

Compound	Unit	H-4	C-4
13	**R**	4.40 (dd, *J*=12.8, 5.5 Hz, H-4β)	30.0
14	**R**	4.38 (dd, *J*=10.2, 6.1 Hz, H-4β)	30.3
	R′	3.72 (dd, *J*=13.0, 5.0 Hz, H-4α)	39.0
15	**R**	4.48 (dd, *J*=13.0, 6.5 Hz, H-4β)	28.3
	R′	4.26 (t, *J*=6.6 Hz, H-4β)	32.0
	R″	3.45 (dd, *J*=13.1, 4.4 Hz, H-4α)	39.0
	R‴	4.41 (dd, *J*=13.4, 4.2 Hz, H-4β)	28.8
16	**R**	4.19 (dd, *J*=5.3, 2.5 Hz, H-4β)	35.7
	R′	3.65 (dd, *J*=13.0, 6.7 Hz,, H-4α)	38.8
	R″	4.28 (t, *J*=6.9 Hz, H-4β)	32.3
	R‴	4.89 (dd, *J*=13.0, 4.3 Hz, H-4β)	28.6
17	**R**	3.72 (dd, *J*=13.0, 5.2 Hz, H-4α)	38.8
	R′	4.41 (dd, *J*=13.0, 5.7 Hz, H-4β)	31.8
	R″	3.70 (dd, *J*=13.0, 5.4 Hz, H-4α)	39.1
	R‴	—	127.3
18	**R**	4.22 (dd, *J*=4.3, 2.1 Hz, H-4β)	36.3
	R′	3.68 (dd, *J*=13.1, 6.2 Hz, H-4α)	38.0
	R″	—	128.8
	R‴	4.92 (dd, *J*=13.0, 4.2 Hz, H-4β)	28.8

Structure **15** was given to another tetramer on the basis of the following considerations: This compound was an asymmetrical stereoisomer of **13** with C-4,C-6 bonds joining the four precocene I units. Its ^{1}H NMR spectrum showed signals of four different ABX systems corresponding to the hydrogens at C-3 and C-4 of the four chromane rings. Double resonance, COSY and HSQC experiments permitted us to assign the chemical shifts of these hydrogens and of the corresponding carbons. The four X-hydrogens (H-4) resonate at δ_H 3.45 (dd, *J*=13.1, 4.4 Hz), 4.26 (t, *J*=6.6 Hz), 4.41 (dd, *J*=13.4, 4.2 Hz) and 4.48 (1H, dd, *J*=13.0, 6.5 Hz). It can be observed in Table 7 that the resonance of one of these at δ_H 3.45, and the corresponding carbon at δ_C 39.0, showed a greater difference with those of the other three X-hydrogens and carbons of the ABX systems. In consequence, only one of the monomeric units must have a different configuration at C-4. An arduous and rigorous study of the 2D NMR data permitted us to assign the ^{1}H and ^{13}C NMR signals of each monomeric unit as follows: a) The resonances of C-9, C-10 and C-6 (following precocene unit) were located by their correlation with the corresponding four H-4 in the HMBC spectrum. The C-10 values were determined considering that these carbons bear oxygen atoms, whilst C-9 and C-6 resonances were differentiated by comparison with those of compound **11**. b) The HMBC experiment was also used to assign the four H-8, observing their crosspeaks with the corresponding C-9 and C-10, whilst correlations of the H-8 protons with the four C-6 confirmed the assignments of these carbons. c) At this point, the order in which the monomers were joined was determined by examining the crosspeaks of the H-4 protons with each of the C-6 in the HMBC spectrum. d) The four H-5 protons were assigned on the basis of their connectivities with the corresponding C-10 carbons. Each of these four H-5 showed correlations with two different C-4, one with that of its monomeric unit and a second with that of its preceding unit, which confirmed the order in which the four precocenes were linked. e) The C-7 carbons were assigned by their connectivities with the related H-5 and H-8 protons. This cyclic tetramer **15**, as in **13**, must be formed from a linear tetramer, but now one of the steps of the oligomerization or of the cyclization may have taken place by a different face of the protonated chromene ring.

Another cyclic tetramer **16** was isomeric with **13**–**15**. Its NMR data were identical with those of a compound obtained in a reaction of precocene I (**1**) with HCl/MeOH.[17] After a meticulous study of the 2D NMR data, we have assigned the ^{1}H and ^{13}C NMR spectra of each monomeric unit and determined the relative stereochemistry of this compound, in a manner analogous to that indicated for **15**. This tetramer **16** must be formed from an asymmetrical linear tetramer, the cyclization now occurring between C-4‴ and C-8. The other three junctions are between the C-4 and C-6 carbons of two different monomers. Considering the proton and carbon chemical shift of H-4 and C-4 (Table 7) we can deduce the presence in the molecule of three H-4(β) and one H-4 (α), whilst the order in which the monomers were joined was determined by observing connectivities, in the HMBC experiment, of H-4/C-6′, H-4′/C-5″, H-4′/C-6″, H-4″/C-6‴, H-4‴/C-7, H-5′/C-4, H-5″/C-4′ and H-5‴/C-4″.

Two minor tetramers **17** and **18** were also obtained in the reaction of precocene I with $FeCl_3$/HOAc and possess a C-3, C-4 double bond in one of the monomeric units. The structure of **17** was given on the following basis: The presence in the ^{1}H NMR spectrum of four singlets at δ_H 6.25, 6.33, 6.39 and 6.42, assigned to the H-8, and another four singlets at δ_H 6.43, 6.53, 6.87 and 6.88, due to the H-5, indicated that the four monomeric units are bonded between the corresponding C-4 and C-6 of two different precocene units. Other signals observed in this spectrum were three ABX systems of the chromane rings, which were located using COSY and double resonance experiments. Its high resolution MS spectrum showed the molecular ion at *m*/*z* 758.3884 ($C_{48}H_{54}O_8$), which means two amu less than the tetramers **13**–**16**. These facts indicated that in the formation of **17** an oxidative one-electron coupling reaction takes place between the C-4 of a chromene ring and the aromatic C-6 of another monomer. Although the yield of **17** was very low, we could assign the main signals of its NMR spectra. The vinylic H-3‴ and C-3‴ appear at δ_H 5.71 (*s*) and δ_C 127.8, respectively, and H-3‴ showed a correlation with C-2‴ (δ_C 76.0) in the HMBC experiment. Two C-4 methines with similar resonances are observed at δ_H 3.70, δ_C 38.8 and δ_H 3.72, δ_C 39.1, typical of a 4α-H relative configuration at these centres (Table 7), which are different from those of a third methine at δ_H 4.41, δ_C 31.7, characteristic of a 4β-H configuration. Also in this table it can be observed that these resonance values are similar to those of the symmetrical tetramer **14**. These facts indicate that the

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structure **17** is analogous to that of **14**, but now with the presence of a 3,4-double bond in one of the monomeric units. We could confirm this assert observing correlations in the HMBC spectrum of H-3‴ (δ_H 5.71) with C-6 (δ_C 116.0), and of H-4″ (δ_H 3.72) with C-6‴ (δ_C 121.2) and C-7‴ (δ_C 158.0), which also indicated that the monomeric units were linked in the order showed in structure **17**.

Compound **18** (*m*/*z* 758.3830, $C_{48}H_{54}O_8$), an isomer of **17**, was another tetramer with a 3,4-double bond in one of the precocene I units. It was obtained in a very small amount, insufficient to obtain a good ^{13}C NMR spectrum. We have observed, in its ^1H NMR spectrum, similar chemical shifts and coupling constants for the three H-4 of **18** and the corresponding hydrogens of the tetramer **16** (see Table 7), which pointed to a similar structure and molecular arrangement for the R, R′ and R‴ monomeric units of both tetramers, thus locating the 3,4-double bond in the R″ unit. Other signals of this spectrum were a H-3″ singlet at δ_H 5.75 of the 3″,4″-double bond, two coupled doublets centred at δ_H 6.83 and 6.36 (*J*=8.0 Hz) due to H-5 and H-6, respectively, six singlets of aromatic protons, three ABX systems of the chromane rings, four methoxy groups and eight methyl groups. Consequently, we have assigned the structure **18** to this tetramer.

The reaction of precocene I (**1**) with $FeCl_3/Ac_2O$ afforded an acylated derivative **19**, which is formed by a Friedel–Crafts acylation involving an acetyl cation. With a molecular formula $C_{14}H_{16}O_3$, its ^1H NMR showed signals of the chromene ring, of an acetyl group at δ_H 2.55 (*s*), which was located at C-6, and of two aromatic hydrogens at δ_H 6.37 (*s*) and 7.52 (*s*), which were assigned at H-8 and H-5, respectively. Therefore, we gave to this compound the structure **19** which was identical with that of the chromene encecalin, first isolated from *Encelia californica*.[18]

Several conclusions can be reached from this work on precocene I reactions, in comparison with those carried out with precocene II.

1. While the main result in the reactions of precocene II (**2**) with acids is the formation of dimers, in the case of precocene I (**1**) the creation of tetramers is favoured. This is due to the fact that in the precocene II reaction the oligomerization is blocked by the formation of dimer D (**7**), whose analogous compound is not produced in the reaction of precocene I (**1**) with acids. Thus, only a trimer of precocene II with the structure **9** had been obtained in low yield.[12,13]
2. The oligomerization of precocene I is produced between C-4 and C-6′, while the dimerization of precocene II preferably occurs between C-4 and C-3′.[9,14]
3. The cyclization of linear tetramers to produce the cyclic form occurs between C-4 and C-6′ or, in lower yield, between C-4 and C-8′. In the formation of linear tetramers the C-8 substitution was not observed, which could indicate that the functionalization of this carbon occurs during the cyclization process.
4. In the treatment of precocene I with $FeCl_3$/HOAc oxidative one-electron coupling reactions were observed in the formation of dimer **5** and tetramers **17** and **18**.
5. The reaction of precocene I (**1**) with $FeCl_3/Ac_2O$ gave the acylation of the aromatic ring at C-6 forming encecalin (**19**), whilst the same reaction with precocene II (**2**) afforded acylated derivatives in the chromene ring at C-3.[12]

3. Experimental

3.1. General experimental procedures

^1H NMR spectra were recorded in $CDCl_3$ solution at 500.13 MHz with a Bruker AMX-500 spectrometer, and the ^{13}C NMR at 125.03 MHz in a Bruker AMX-500, except those of **3** and **6**–**10**, which were recorded at 50 MHz in a Bruker AC-200. Mass spectra were taken at 70 eV (probe) in a Micromass Autospec. HPLC was performed using a Beckman System Gold 125P. Purification by HPLC was achieved using a silica gel column (Ultrasphere Si 5 μm, 10×250 mm). Dry column chromatography was made on silica gel Merck 0.2–0.065 mm. Precocene I was purchased from Aldrich.

3.2. Reaction of precocene I (1) with HCl/MeOH

Precocene I (**1**) (200 mg) was dissolved in HCl/MeOH 8 M (8 ml) and heated at reflux for 12 h. Usual work up afforded a mixture of products, which was chromatographed on silica gel eluting with petrol–EtOAc (5%) and HPLC (petrol–EtOAc 10%) to give **3** (6 mg), **10** (4 mg), **11** (24 mg), **12** (3 mg), and a mixture of pentamers.

*3.2.1. Dimer **3**.* ^1H NMR (500 MHz, $CDCl_3$): δ 1.26 and 1.42 (each 3H, s, H-11, H-12), 1.53 and 1.57 (each 3H, s, H-11′, H-12′), 1.79 (1H, t, *J*=12.5 Hz, H-3), 2.01 (1H, dd, *J*=12.5, 6.0 Hz, H-3), 3.52 (1H, dd, *J*=12.5, 6.0 Hz, H-4), 3.74 (6H, s, 2 OMe), 6.00 (1H, br s, H-4′), 6.34 (1H, d, *J*=2.6 Hz, H-8′), 6.36 (1H, dd, *J*=8.0, 2.6 Hz, H-6′), 6.37 (1H, d, *J*=2.6 Hz, H-8), 6.41 (1H, dd, *J*=8.0, 2.6 Hz, H-6), 6.73 (1H, d, *J*=8.0 Hz, H-5′), 7.00 (1H, d, *J*=8.0 Hz, H-5); ^{13}C NMR: see Table 2; EIMS *m*/*z* (rel int.): 380 $[M]^+$ (24), 365 (100), 309 (6), 191 (12), 175 (8), 155 (8); $[M]^+$ at 380.1973, $C_{24}H_{28}O_4$ requires 380.1987.

*3.2.2. Dimer **10**.* ^1H NMR (500 MHz, $CDCl_3$): δ 1.32 (3H, s, H-12), 1.40 [6H, s, H-11 and (H-11′ or H-12′)], 1.41 (3H, s, H-12′ or H-11′), 1.85 (1H, m, H-3α), 1.93 (1H, dd, *J*=13.0, 6.0 Hz, H-3β), 3.73 (3H, s, OMe′), 3.76 (3H, br s, OMe), 4.40 (1H, br s, H-4), 5.39 (1H, d, *J*=10.0 Hz, H-3′), 6.13 (1H, br d, *J*=10.0 Hz, H-4′), 6.33 (1H, dd, *J*=8.0, 2.6 Hz, H-6), 6.36 (1H, d, *J*=2.6 Hz, H-8), 6.37 (1H, s, H-8′), 6.60 (1H, br s, H-5′), 6.68 (1H, d, *J*=8.0 Hz, H-5); ^{13}C NMR: see Table 2; EIMS *m*/*z* (rel int.): 380 $[M]^+$ (29), 365 (100), 293 (9), 278 (3), 263 (4), 175 (8), 155 (13); EIMS *m*/*z* (rel int.): $[M]^+$ at 380.1970, $C_{24}H_{28}O_4$ requires 380.1987.

*3.2.3. Trimer **11**.* ^1H NMR (500 MHz, $CDCl_3$): δ 1.29, 1.32, 1.34, 1.35, 1.37 and 1.38 (each 3H, s, 6 Me), 1.67 (2H, m, H-3, H-3′), 1.92 (1H, dd, *J*=13.6, 5.6 Hz, H-3), 1.97 (1H, dd, *J*=13.6, 5.7 Hz, H-3′), 3.66 (3H, s, OMe), 3.71 (3H, br s, OMe″), 3.77 (3H, br s, OMe′), 4.33 (1H, br s, H-4′), 4.39 (1H, br s, H-4), 5.40 (1H, d, *J*=10.0 Hz, H-3″), 6.09 (1H, br d, *J*=10.0 Hz, H-4″), 6.22 (1H, dd, *J*=8.0, 2.0 Hz, H-6), 6.24 (1H, br s, H-8), 6.26 (1H, s, H-8″), 6.39 (1H, s, H-8′), 6.44 (1H, br s, H-5″), 6.46 (1H, s, H-5′), 6.57 (1H, d, *J*=8.0 Hz, H-5); ^{13}C NMR: see Table 3; EIMS *m*/*z* (rel int.): 570 $[M]^+$ (64), 555 (100), 515 (6), 483 (18), 379 (10), 365 (14), 277 (7), 250 (8), 234 (18), 191 (11), 175 (6); $[M]^+$ at 570.2975, $C_{36}H_{42}O_6$ requires 570.2981.

*3.2.4. Linear tetramer **12**.* ^1H NMR (500 MHz, $CDCl_3$): δ 1.23, 1.24, 1.29, 1.31, 1.34, 1.37, 1.38 and 1.40 (each 3H, s, 8 Me), 1.70–1.93 (6H, m, 2H-3, 2H-3′, 2H-3″), 3.68 (3H, s, OMe), 3.74 (6H, br s, 2 OMe), 3.76 (3H, s, OMe), 4.38 (3H, br m, $W_{1/2}$=28 MHz, H-4, H-4′, H-4″), 5.35 (1H, d, *J*=10.0 Hz, H-3‴), 6.05 (1H, br d, *J*=10.0 Hz, H-4‴), 6.24 (1H, d, *J*=2.2 Hz, H-8), 6.26 (1H, dd, *J*=8.0, 2.2 Hz, H-6), 6.28, 6.30 and 6.32 (each 1H, s, H-8′, H-8″, H-8‴), 6.41, 6.44 and 6.47 (each 1H, br s, H-5′, H-5″, H-5‴), 6.57 (1H, d, *J*=8.0 Hz, H-5); ^{13}C NMR (125 MHz, $CDCl_3$): δ 23.9, 24.2, 24.7, 27.9, 28.3 and 29.6 (6 Me), 29.9 (2 Me), 30.2, 30.4 and 30.6 (C-4, C-4′, C-4″), 42.1, 42.3 and 42.5 (C-3, C-3′, C-3′), 54.9 and 55.3 (2 OMe), 55.4 (2 OMe), 74.6, 74.8 and 75.0 (C-2, C-2′, C-2″), 76.2 (C-2‴), 99.1, 99.8, 101.0 and 101.1 (C-8, C-8′, C-8″, C-8‴), 107.0 (C-6), 114.1 (C-9‴), 116.0 (C-9), 116.9 and 118.1 (C-9′, C-9″), 122.1 (C-4‴), 124.3, 125.8 and 126.4 (C-6′, C-6″, C-6‴), 127.2 (C-3‴), 126.6, 127.4, 128.9 (C-5′, C-5″, C-5‴), 130.0 (C-5), 152.0, 152.2, 153.3 and 154.9 (C-10, C-10′, C-10″, C-10‴), 156.2, 156.5, 158.0 and 158.7 (C-7, C-7′, C-7″, C-7‴); EIMS *m*/*z* (rel int.): 760 $[M]^+$ (100), 745 (47), 705 (9), 689 (13), 673 (16), 570 (19), 555 (25), 483 (7), 379

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(12), 365 (11), 345 (6), 329 (19), 293 (6), 191 (9), 175 (10); $[M]^+$ at 760.3936, $C_{48}H_{56}O_8$ requires 760.3975.

3.3. Reaction of precocene I (1) with iron (III) chloride-acetic acid

Precocene I (**1**) (150 mg) in acetic acid (2 ml) was treated with iron (III) chloride (300 mg) and left with stirring, under nitrogen, for 4 h at room temperature. Usual work up and chromatography in silica gel eluting with petrol–EtOAc (5%) and HPLC (petrol–EtOAc 10%) afforded dimer **5** (8 mg) and tetramers **13** (7 mg), **14** (3 mg), **15** (8 mg), **16** (6 mg), **17** (1.6 mg) and **18** (0.9 mg).

*3.3.1. Dimer **5**.* ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.36 and 1.43 (each 6H, H-11, H-12), 2.43 (2H, d, 6.3 Hz, H-3), 3.77 (H, s, 2 OMe), 4.75 (2H, d, J=6.3 Hz, H-4); 6.36 (2H, d, J=2.5 Hz, H-8), 6.54 (2H, dd, J=8.5, 2.5 Hz, H-6), 7.23 (2H, d, J=8.5 Hz, H-5); ^{13}C NMR: see Table 1; EIMS m/z (rel int.): 396 $[M]^+$ (46), 381 (6), 343 (13), 336 (14), 308, 274 (23), 245 (66), 229 (15), 206 (25), 191 (90), 175 (88); $[M]^+$ at 396.1935, $C_{24}H_{28}O_5$ requires 396.1936.

*3.3.2. Symmetrical tetramer **13**.* ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.26 (12H, s, 4H-11), 1.28 (12H, s, 4H-12), 1.65 (4H, t, J=12.8 Hz, 4H-3α), 1.75 (4H, dd, J=12.8, 5.5 Hz, 4H-3β), 3.74 (12H, s, 4OMe), 4.40 (4H, dd, J=12.8, 5.5 Hz, 4H-4), 6.10 (4H, s, 4H-5), 6.28 (4H, s, 4H-8); ^{13}C NMR: see Table 4; EIMS m/z (rel int.): 760 $[M]^+$ (100), 745 (38), 743 (96), 704 (13), 689 (11), 555 (11), 530 (20), 515 (8), 430 (9), 380 (10), 344 (8), 175 (7); $[M]^+$ at 760.3940, $C_{48}H_{56}O_8$ requires 760.3975.

*3.3.3. Symmetrical tetramer **14**.* ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.25, 1.30, 1.32 and 1.43 (each 6H, s, 2 Me), 1.38 (2H, dd, J=13.5 and 10.2 Hz, 2H-3), 1.67 (2H, dd, J=13.0, 5.0 Hz, 2H-3′), 2.11 (2H, dd, J=13.5, 6.1 Hz, 2H-3), 2.57 (2H, t, J=13.0 Hz, 2H-3′), 3.40 (6H, s, 2 OMe), 3.72 (2H, dd, J=13.0, 5.0 Hz, 2H-4′), 3.82 (6H, s, 2 OMe′), 4.38 (2H, dd, 10.2, 6.1 Hz, 2H-4), 6.22 (2H, s, 2H-8), 6.39 (2H, s, 2H-8′), 6.33 (2H, s, H-5′), 6.86 (2H, s, H-5); ^{13}C NMR: see Table 4; EIMS m/z (rel int.): 760 $[M]^+$ (100), 745 (10), 743 (17), 704 (15), 689 (10), 380 (7), 352 (6), 325 (8); $[M]^+$ at 760.3947, $C_{48}H_{56}O_8$ requires 760.3975.

*3.3.4. Tetramer **15**.* ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.00 and 1.26 (C-11′, C-12′), 1.28 and 1.43 (C-11‴, C-12‴), 1.32 and 1.40 (C-11, C-12), 1.38 and 1.39 (C-11″, C-12″), 1.59 (1H, dd, J=13.1, 4.4 Hz, H-3″), 1.62 (1H, dd, J=13.6, 6.6 Hz, H-3′), 1.65 (1H, t, J=13.0 Hz, H-3), 1.68 (1H, dd, J=13.4, 4.2 Hz, H-3‴), 1.95 (1H, dd, J=13.0, 6.5 Hz, H-3), 2.02 (1H, dd, J=13.6, 6.6 Hz, H-3′), 2.07 (1H, t, J=13.4 Hz, H-3‴), 2.54 (1H, t, J=13.1 Hz, H-3″), 3.37 (3H, s, OMe′), 3.45 (1H, dd, J=13.1, 4.4 Hz, H-4″), 3.75, 3.76 and 3.77 (each 3H, s, OMe, OMe″, OMe‴), 4.26 (1H, t, J=6.6 Hz, H-4′), 4.41 (1H, dd, J=13.4, 4.2 Hz, H-4‴), 4.48 (1H, dd, J=13.0, 6.5 Hz, H-4), 5.82 (1H, s, H-5″), 6.04 (2H, s, H-5, H-5‴), 6.10 (1H, s, H-8‴), 6.32 (1H, s, H-8″), 6.34 and 6.35 (each 1H, s, H-8, H-8′), 6.67 (1H, s, H-5′); ^{13}C NMR: see Table 5; EIMS m/z (rel int.): 760 $[M]^+$ (100), 745 (29), 743 (15), 705 (18), 689 (5), 649 (7), 380 (10), 352 (8), 325 (8), 297 (5); $[M]^+$ at 760.3997, $C_{48}H_{56}O_8$ requires 760.3975.

*3.3.5. Tetramer **16**.* ^{1}H NMR (500 MHz, $CDCl_3$): δ 0.75 and 1.10 (each 3H, s, H-11‴, H-12‴) 1.08 and 1.25 (each 3H, s, H-11‴, H-12‴), 1.18 and 1.38 (each 3H, s, H-11″, H-12″), 1.43 and 1.44 (each 3H, s, H-11, H-12), 1.60 (1H, dd, J=13.0, 6.7 Hz, H-3′), 1.61 (1H, dd, J=13.0, 5.3 Hz, H-3), 1.72 (1H, dd, J=13.8, 6.9 Hz, H-3″), 1.80 (1H, dd, J=13.0, 5.5 Hz, H-3‴), 2.12 (1H, dd, J=13.8, 6.9 Hz, H-3″), 2.34 (1H, dd, J=13.0, 2.5 Hz, H-3), 2.38 (1H, t, J=13.0 Hz, H-3′), 2.44 (1H, t, J=13.0 Hz, H-3‴), 3.26 (3H, s, OMe), 3.42 (3H, s, OMe″), 3.65 (1H, dd, J=13.0, 6.7 Hz, H-4′), 3.82 (6H, s, OMe′, OMe‴), 4.19 (1H, dd, J=5.3, 2.5 Hz, H-4), 4.28 (1H, t, J=6.9 Hz, H-4″), 4.89 (1H, dd, J=13.0, 4.3 Hz, H-4‴), s, H-8′), 6.41 (1H, s, H-8‴), 6.75 (1H, d, J=8.3 Hz, H-5), 6.83 (1H, s, H-5″); ^{13}C NMR: see Table 6; EIMS m/z (rel int.): 760 $[M]^+$ (100), 745 (15), 743 (22), 704 (28), 689 (79), 380 (4), 352 (4); $[M]^+$ at 760.3959, $C_{48}H_{56}O_8$ requires 760.3975.

*3.3.6. Tetramer **17**.* ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.27, 1.29, 1.38, 1.42, 1.44 and 1.49 (each 3H, s, 6Me), 1.32 (6H, s, 2Me), 1.37 (1H, t, J=13.0, H-3′), 1.61 (1H, dd, J=13.0, 5.4 Hz, H-3), 1.70 (1H, dd, J=13.0, 5.2 Hz, H-3″), 2.04 (1H, dd, J=13.0, 5.7 Hz, H-3′), 2.67 (1H, t, J=13.0 Hz, H-3‴), 2.76 (1H, t, J=13.0 Hz, H-3), 3.43 (3H, s, OMe′), 3.47 (3H, s, OMe‴), 3.70 (1H, dd, J=1 Hz, dd, J=13.0, 5.4 Hz, H-4), 3.72 (1H, dd, J=13.0, 5.2 Hz, H-4″), 3.75 (3H, s, OMe″), 3.80 (3H, s, OMe), 4.41 (1H, dd, J=13.0, 5.7 Hz, H-4′), 5.71 (1H, s, H-3‴), 6.25 (1H s, H-8′), 6.33 (1H, s, H-8‴), 6.39 (1H, s, H-8″), 6.42 (1H, s, H-8), 6.43 (1H, s, H-5), 6.53 (1H, s, H-5″), 6.87 (1H, s, H-5‴), 6.88 (1H, s, H-5′); ^{13}C NMR (125 MHz, $CDCl_3$): δ 22.6, 24.8, 25.2, 28.8, 30.3 and 31.8 (6 Me), 27.2 (2 Me), 31.7 (C-4′), 32.0 (C-3), 37.3 (C-3″), 38.8 (C-4), 39.1 (C-4″), 41.9 (C-3′), 55.2 and 55.3 (OMe′, OMe‴), 55.4 and 55.7 (OMe, OMe″), 74.8 and 75.0 (C-2, C-2″), 75.6 (C-2′), 76.0 (C-2‴), 99.2 (C-8″), 100.3 (C-8), 101.3 (C-8‴), 102.0 (C-8′), 112.7 (C-9′), 115.2 (C-9‴), 116.0 (C-6), 116.2 (C-9″), 116.5 (C-9), 121.2 (C-6‴), 121.5 (C-6′), 123.6 (C-6″), 126.6 (C-5″), 127.3 (C-4‴), 127.8 (C-3‴), 129.8 (C-5), 130.5 (C-5‴), 133.0 (C-5′), 151.8 (C-10″), 152.4 (C-10), 153.7 and 153.8 (C-10′, C-10‴), 156.3 (C-7″), 156.8 (C-7), 157.0 (C-7′), 158.0 (C-7‴); EIMS m/z (rel int.): 758 $[M]^+$ (34), 743 (100), 687 (5), 371 (8), 364 (5), 344 (12), 316 (5); $[M]^+$ at 758.3884, $C_{48}H_{54}O_8$ requires 758.3819.

*3.3.7. Tetramer **18**.* ^{1}H NMR (500 MHz, $CDCl_3$): δ 0.63, 1.08, 1.11, 1.34, 1.39, 1.45, 1.46 and 1.47 (each 3H, s, Me), 1.59 (1H, dd, J=13.1, 6.2 Hz, H-3′), 1.64 (1H, dd, J=13.0, 4.2 Hz, H-3‴), 1.71 (1H, dd, J=13.0, 4.3 Hz, H-3), 2.38 (1H, dd, J=13.0, 2.1 Hz, H-3), 2.51(1H, t, J=13.0 Hz, H-3‴), 2.60 (1H, t, J=13.1 Hz, H-3′), 3.42 (6H, s, 2 OMe), 3.68 (1H, dd, J=13.1, 6.2 Hz, H-4′), 3.77 and 3.82 (each 3H, s, OMe), 4.22 (1H, dd, J=4.3, 2.1 Hz, H-4), 4.92 (1H, dd, J=13.0, 4.2 Hz, H-4‴), 5.75 (1H, s, H-3″), 6.15 (1H, s, H-5‴), 6.25 (1H, s, H-8″), 6.34 (1H, s, H-8′), 6.35 (1H, d, J=8.0 Hz, H-6), 6.39 (1H, s, H-5′), 6.48 (1H, s, H-8‴), 6.83 (1H, d, J=8.0 Hz, H-5), 6.95 (1H, s, H-5″); ^{13}C NMR (125 MHz, $CDCl_3$), due to the small amount obtained only some signals could be observed and tentatively assigned: δ 28.8 (C-4‴), 36.3 (C-4), 37.5 and 37.6 (C-3, C-3‴), 38.0 (C-4′), 41.8 (C-3′), 55.2, 55.5, 55.7 and 56.0 (4 OMe), 99.6, 100.7 and 101.4 (C-8′, C-8″, C-8‴), 105.4 (C-6), 126.1 (C-5), 126.2, 128.6 and 130.0 (C-5′, C-5″, C-5‴), 128.9 (C-4″); EIMS m/z (rel int.): 758 $[M]^+$ (34), 743 (100), 687 (5), 371 (4), 364 (2), 344 (7), 316 (4); $[M]^+$ at 758.3830, $C_{48}H_{54}O_8$ requires 758.3819.

3.4. Reaction of precocene I (1) with iron (III) chloride-acetic anhydride

To a solution of precocene I (**1**) (170 mg) in Ac_2O (0.84 ml), Fe_3Cl (84 mg) was added and kept with stirring under nitrogen for 1 h at room temperature. Usual work up and chromatography afforded encecalin (**19**) (24 mg).

*3.4.1. Encecalin (**19**).* ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.43 (6H, s, H-11, H-12), 2.55 (3H, s, –CO–Me), 3.87 (3H, s, OMe), 5.51 (1H, d, J=9.8 Hz, H-3), 6.29 (1H, d, J=9.8 Hz, H-4), 6.37 (1H, s, H-8), 7.52 (1H, s, H-5); ^{13}C NMR: see Table 1; EIMS m/z (rel int.): 232 $[M]^+$ (46), 217 (100), 174 (4), 144 (3); $[M]^+$ at 232.0959, $C_{14}H_{16}O_3$ requires 232.0947.

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