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11,16 Oxetane lactones. Spectroscopic evidences and conformational analysis

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Abstract—Sesquiterpene lactones constitute a wide group of compounds with several biological activities, including allelopathic. The naturally occurring sesquiterpene lactones dehydrocostuslactone and cynaropicrin have been modified in three different ways: preparation of 11,13-oxetane lactones, addition of a second Michael acceptor and reduction of the α-methylene-γ-lactone in order to future structure–activity relationship (SAR) studies. We have obtained all oxetane lactones stereoisomers at C-11 and C-16 positions. This fact has allowed us to establish some correlations between experimental data, derived by NMR and X-ray analysis, and the configuration at C-11 and C-16, which could be a useful tool to establish the stereochemistry as well as to confirm the presence of an oxetane ring on similar compounds. Comparative conformational analyses as a key aspect in the biological behaviour of those compounds in future structure–activity relationship (SAR) studies are presented.
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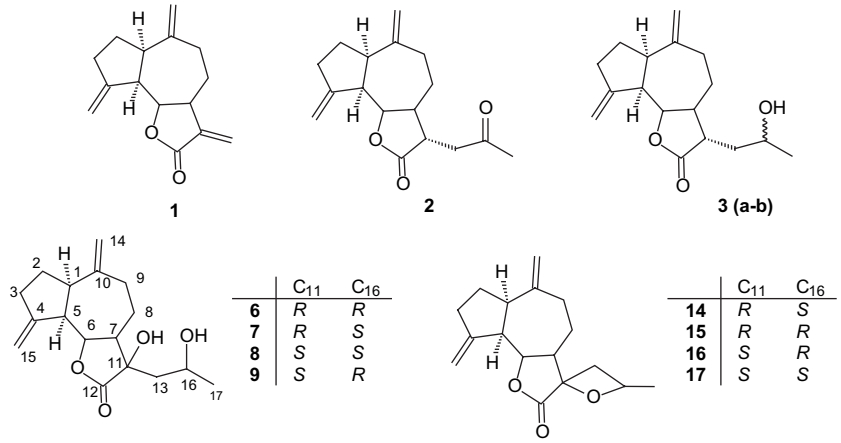
1. Introduction

Five natural oxetane lactones, clementein, clementein B, clementein C, subexpinnatin B and subexpinnatin C, were isolated from *Centaurea clementei* Boiss,[1] and *Centaurea canariensis* Brous. Var. *subexpinnata* Burchd (Fig. 1),[2] and some of them have been obtained later by hemi-synthetic methods.[3] Oxetane ring containing compounds have been reported to display a wide range of biological activities and this structural feature is regarded to be essential for their bioactivity.[4–6] However, despite the efforts, in many cases the biochemical behaviour of the oxetane ring remains unclear and more research on both conformational and electronic effects needs to be done. In this way, we have achieved



	C_{11}	C_{16}
6	*R*	*R*
7	*R*	*S*
8	*S*	*S*
9	*S*	*R*

	C_{11}	C_{16}
14	*R*	*S*
15	*R*	*R*
16	*S*	*R*
17	*S*	*S*

Figure 1. Natural oxetane lactones and synthetic intermediates.

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the preparation of four new oxetane lactones (compounds **14**–**17**) from (**1**) as starting material. The accomplished semi-synthesis also yielded six other derivatives (compounds **2**, **3**(**a**–**b**) and **6**–**9**), which present different stereochemistries and have been afforded for first time in this study (Fig. 1). The fact that we have obtained all oxetane lactones stereoisomers at C-11 and C-16 positions has allowed us to establish some correlations between experimental data, derived by NMR and X-ray analysis, and the configuration at C-11 and C-16, that could be a useful tool in proposing the stereochemistry as well as in confirming the presence of an oxetane ring on similar compounds. Moreover, we carried out a comparative conformational analysis as a key aspect in the biological behaviour of those compounds in future structure–activity relationship (SAR) studies.

Herein, we present the methodology, which has been accomplished to obtain the new oxetane lactones as well as the prior results derived from their spectroscopic and conformational analysis.

2. Results and discussion

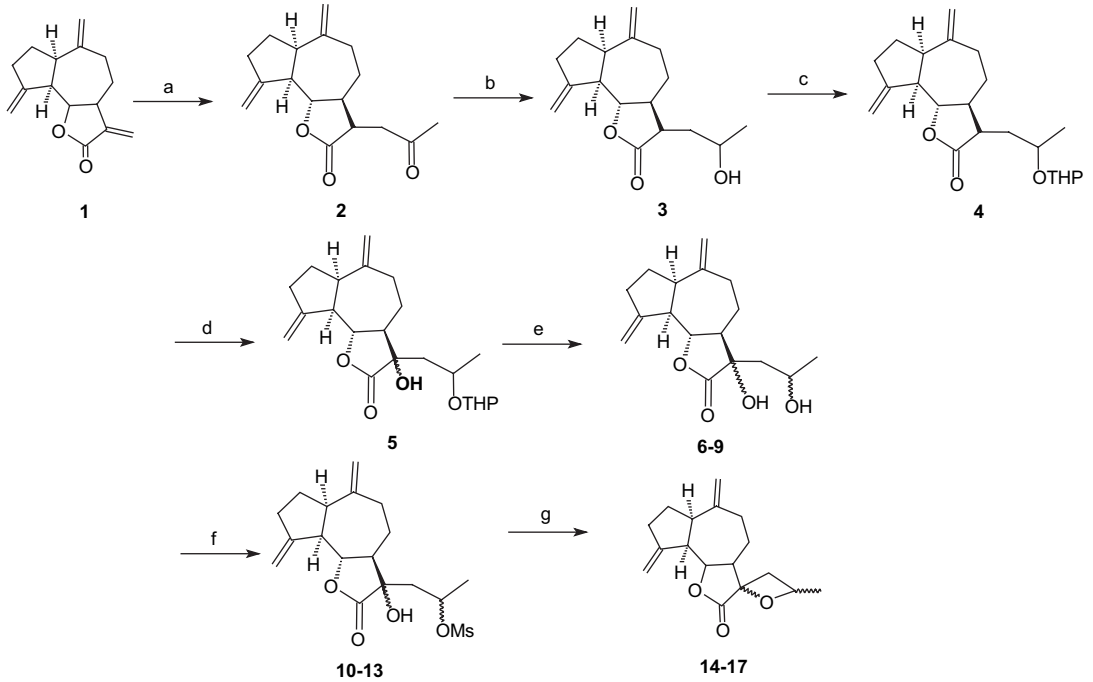
In order to perform the hemi-synthesis, we employed the previously reported methodology[7] for the formation of an oxetane ring at C-11 and C-13 positions from the corresponding α-methylene-γ-lactone using dehydrocostuslactone (**1**) as starting material. This natural product in one of the major constituents obtained from the root of the Chinese plant *Saussurea lappa* and, therefore, it is readily available in the amounts needed to accomplish the synthesis in seven steps as shown in Scheme 1.

The first step was the photoaddition of acetaldehyde to dehydrocostuslactone (**1**) providing the methylketone (**2**) (66% yield) (step a). Reduction of compound (**2**) with sodium borohydride at 0 °C afforded the 1:1 mixture of epimers at C-16, **3** (**a**–**b**) in 98% yield (step b). The new hydroxyl group formed is protected with DHP and *p*-toluenesulfonic acid as catalyst, yielding an epimeric mixture of diastereoisomers **4** (step c).

The α-hydroxylation of **4** to obtain the mixture of diastereoisomers **5** was carried out under the specific conditions as shown below. First, the enolate at C-11 of **4** is generated at −73 °C in THF by deprotonation with potassium hexamethyldisilazide (KHMDS) under a restricted dry argon atmosphere. Then, dry oxygen is bubbled through the solution for an hour in order to achieve the corresponding hydroperoxide ion. The latter treatment with triethylphosphite as 'in situ' reducing agent afforded the mixture **5** (step d). Both the 11*R* and the 11*S* configurations were obtained as it was deduced after step **5**.

Mild acid treatment of **5** (*p*-TsOH, ethyl acetate) provided the diols **6**, **7**, **8** and **9** and not the oxetane lactones as we expected (step e). Thus, it was necessary to include two more steps into the sequence. The above four diols were isolated in 20% yield each as crystalline compounds, allowing us to establish the structures of compounds **6** and **7** by X-ray analysis. The absolute configuration of compound **7** was also determined using Cu Kα radiation, establishing the absolute configuration of the entire series.

The introduction of the mesyl moiety as leaving group at C-16 to afford compounds **10**, **11**, **12** and **13** (90%) was accomplished by the reactions of diols with mesyl chloride in pyridine at 0 °C (step f). Basic treatment of mesylated compounds **10**, **11**, **12** and **13** with butyllithium in THF led to the ring closure with inversion in the configuration at C-16 yielding the oxetane lactones **14**, **15**, **16** and **17** (step g)



Scheme 1. (a) CH_3CHO, hν; (b) $NaBH_4$, MeOH, 0 °C; (c) DHP, *p*-Toluenesulfonic acid, THF; (d) KHMDS, THF, −73 °C; (e) *p*-Toluenesulfonic acid, AcOEt; (f) MesCl, py, 0 °C and (g) BuLi, THF.

Table 1

Compounds	δ H-5	δ H-6	δ H-7	δ H-13	δ H-13′	δ H-16	δ H-17	C-11	C-16
14	2.69	4.05	2.01	2.71	2.61	5.10	1.35	*R*	*S*
15	2.68	4.05	1.93	2.96	2.22	4.75	1.50	*R*	*R*
16	2.80	3.78	2.35	2.84	2.24	4.84	1.60	*S*	*R*
17	2.83	3.78	2.26	2.56	2.44	5.24	1.39	*S*	*S*
1	2.78	3.92	—	—	—	—	—	—	—

with an overall yield of 21%. Since compounds **15** and **16** were crystalline, we confirmed the proposed mechanism of the step g based on their X-ray analyses and, consequently, we established the stereochemistry of compounds **14** and **17**.

Once we obtained the four oxetane lactones their configurations at C-11 and C-16 were assigned, a depth analysis of their ^{1}H NMR and ^{13}C NMR spectra revealed some interesting relationships, especially for the NMR data corresponding to the nucleus found in the area close to the oxetane ring.

In Table 1, we present the ^{1}H NMR chemical shifts for H-5, H-6, H-7, H-13, H-13′, H-16 and H-17, as well as the assigned configuration at C-11 and C-16 for the compounds **14**, **15**, **16** and **17**.

A slight shift downfield is observed for H-6 signals when the configuration at C-11 is *R* (compounds **14** and **15**), which may be due to the paramagnetic effect that the oxygen nucleus of the oxetane rings induce over those signals. On the other hand, a similar effect occurs for the H-5 and H-7 signals in case of the (*S*)-configuration at C-11 (compounds **16** and **17**). With respect to the configuration at C-16, for oxetane lactones **15** and **16** (16*S*) a shift downfield is also observed for the H-17 signals and, it is worth noting that, in the latter compounds, the difference between the chemical shifts for H-13 and H-13′ is 0.68±0.08 ppm, being 0.11±0.01 ppm for the oxetane lactones **14** and **17** (16*R*). Furthermore, these results show how it may be possible to make the C-11 and C-16 configuration assignments in other oxetane lactones using their experimental data derived from ^{1}H NMR. In Table 1, the chemical shifts for H-5 and H-6 of dehydrocostuslactone (**1**) is also included, because comparing those with the respective signals of the lactones can be an interesting clue for C-11 configuration assignment, to determine whether we obtained one of the possible diastereoisomers.

Determining the presence of the oxetane ring moiety can be difficult, so a comparative NMR spectroscopic study between the oxetane lactones and the corresponding diols was undertaken to provide evidence, which may be useful to overcome the problem. The most significant results derived from this comparative analysis are shown in Table 2.

It is interesting to note the large downfield for the H-13 and H-13′ signals when the ring closure occurs. Following with the analysis of these signals, it is relevant the $J_{H13–H16}$ and $J_{H13'–H16}$ coupling constants, which are similar on the oxetane lactones whereas the differences among them are far longer on the corresponding diols. These results are consistent with the relative angle formed between protons H-13 and H-13′ with proton H-16 at the oxetane moiety. With respect to the ^{13}C NMR spectra, we emphasize the shift downfield for C-11 and C-16 signals as well as the contrary effect for C-13 as a result of the ring closure in compounds **14**, **15**, **16** and **17**.

Regardless, it is well established that conformational aspects are a keystone for the biological activity; little has been done about the conformational changes that the oxetane ring induces on the guaianolide backbone. Following this way, we have carried out a comparative structural study of the oxetane lactones **15** and **16** with the corresponding α-methylene-γ-lactone, dehydrocostuslactone (**1**). To perform that, we used the experimental data obtained from the X-ray analysis of the crystalline compounds **1**,[8] **15** and **16**, which are shown in Figure 2.

Comparing the resultant geometries reveals that the essential difference appears to be the conformation of the cycloheptane ring. Whereas in compound **1** the cycloheptane presents the theoretical lowest energy conformer (twist-chair), in both oxetane lactones (**15** and **16**) the heptane ring is in a chair conformation.[9] Those preferential conformations are in good agreement with the coupling constants $J_{H9β–H8β}$, $J_{H9β–H8α}$, $J_{H9α–H8β}$ and $J_{H9α–H8α}$ derived from ^{1}H NMR analysis of **15** and **16** (see Table 3).[10]

In Figure 2, the modification of the relative positions of C-2, C-9, C-10 and C-14 with respect to the guaianolide backbone, as a result of the different seven-membered ring conformations is shown. With regard to this matter, we have prepared other guaianolide-type sesquiterpene lactones, both natural and semi-synthetic (**18**, **19**,[11] **20**, **21** and **22**[12]) and revised other published results (**23**[13] and **24**[14]). Different behaviours have been observed in guaianolides with a methylene at C-10 (Fig. 3). Thus, **1**, **20** and **24** possess an α-methylene-γ-lactone moiety twist-chair conformation, whereas **6**,

Table 2

	6	**14**	**7**	**15**	**8**	**16**	**9**	**17**
δ H-13	1.89	2.71	1.73	2.84	1.94	2.96	1.76	2.56
δ H-13′	1.65	2.61	1.55	2.24	1.79	2.22	1.68	2.44
$J_{13–16}$	10.8	6.4	11.2	7.7	10.3	7.0	8.5	7.6
$J_{13'–16}$	2.7	7.8	2.2	6.5	3.0	7.3	2.7	7.5
δ C-11	75.7	81.7	76.4	82.9	76.4	82.3	76.4	82.8
δ C-13	41.4	32.5	37.8	32.4	43.1	32.4	43.3	32.3
δ C-16	64.9	75.3	65.7	75.3	64.7	75.3	64.7	75.2

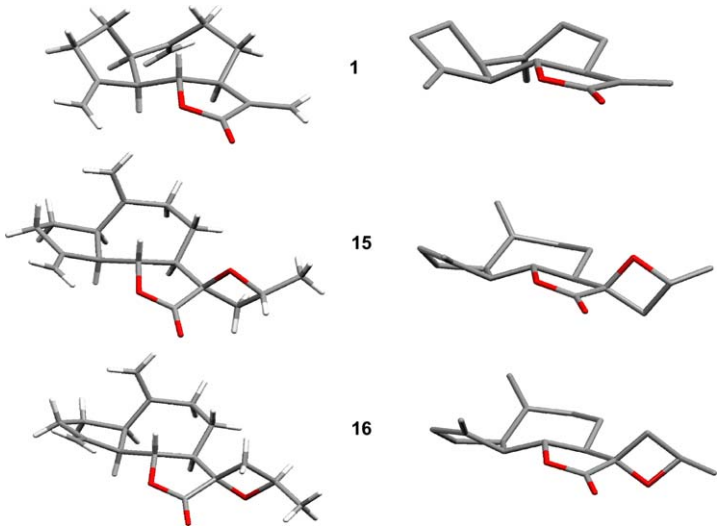


Figure 2. Conformations of **1**, **15** and **16** obtained by X-ray analysis.

Table 3

Compound	$J_{H9\beta-H8\beta}$	$J_{H9\beta-H8\alpha}$	$J_{H9\alpha-H8\beta}$	$J_{H9\alpha-H8\alpha}$	Conformations
1	4.9	5.8	5.9	4.4	Twist-chair
15	7.0	6.8	10.1	4.0	Chair
16	7.3	7.5	11.3	4.0	Chair

7, **15**, **16**, **18**, **19** and **23** lacking that functionalization showed chair conformation in the seven-membered ring. Nevertheless, the influence of the functionalization of the other five-membered ring is also important (Fig. 4). Thus, **21** and **22** that have the α-methylene-γ-lactone and a carbonyl group at C-3 showed a chair conformation. So, the functionalization and hybridization of both five-membered rings of guaianolides do influence the conformation of the seven-membered group ring and, probably, their biological activities. So, any structure–activity relationship study of this type of compounds should consider this parameter.

3. Experimental

3.1. General

^{1}H NMR and ^{13}C NMR spectra were recorded at 399.952 and 100.577 MHz, respectively, on a Varian UNITY-400 spectrometer using $CDCl_3$ as solvent. The resonances of residual chloroform at δ_H 7.25 ppm in the ^{1}H spectra and of δ_C at 77.00 ppm in the ^{13}C spectra were used as internal references. Mass spectra were obtained by using a VG 1250 or a Kratos MS-80-RFA instrument at 70 eV. The infrared (IR) spectra were recorded on a PERKIN Elmer Spectrum BX. Column chromatography (CC) was performed on silica gel (35–75 mesh). For HPLC, LiChrosorb silica 60 was used in the normal-phase mode using differential LaChrom RI L-7490 refractometer and UV–vis LaChrom L-7420 detectors, with an HPLC MERCK HITACHI instrument. All solvents were of spectral grade or distilled from glass prior to use. The diffraction data were collected at low temperature

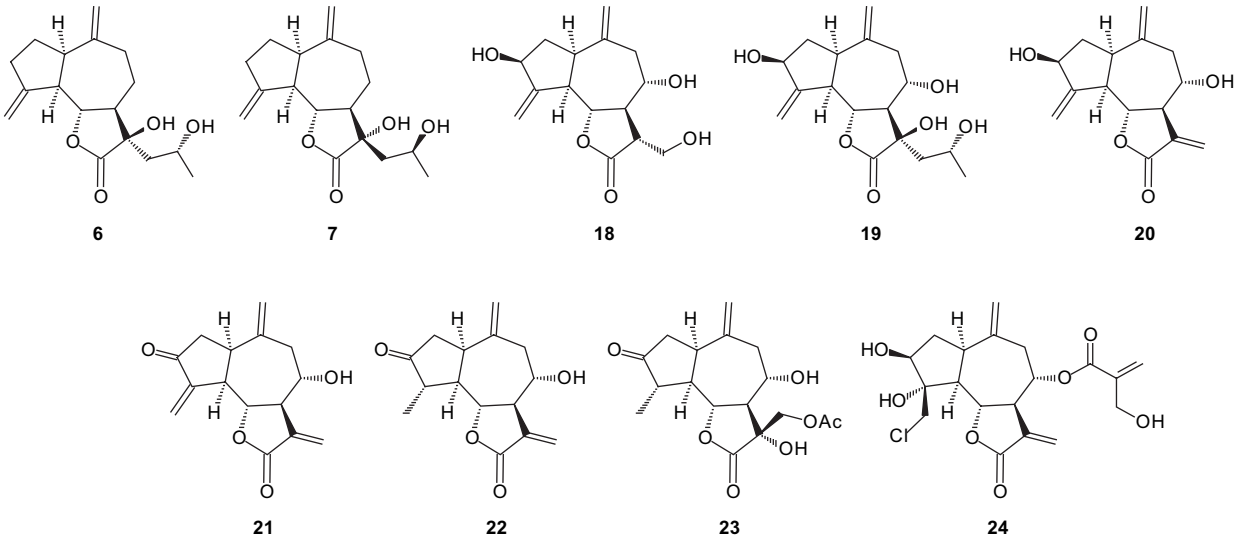


Figure 3. Natural and semi-synthetic guaianolides to be studied.

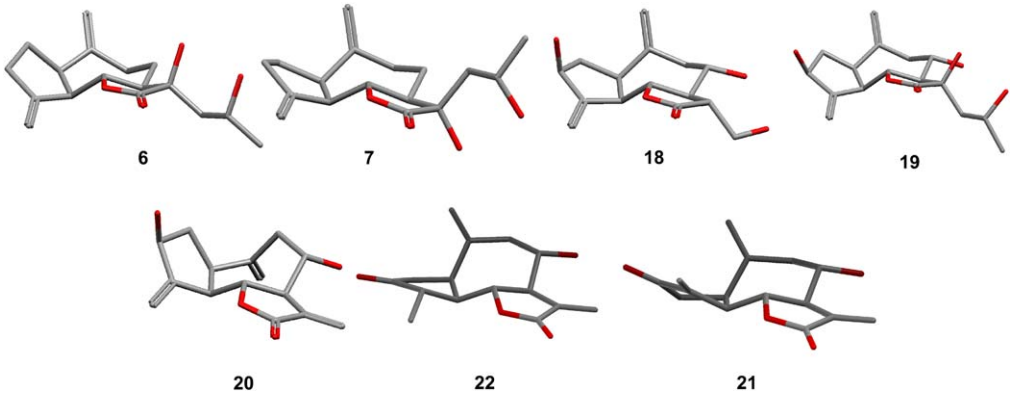


Figure 4. Conformations obtained for **6**, **7**, **18**, **19**, **20**, **22** and **21** by X-ray analysis.

on a KappaCCD diffractometer equipped with Mo Kα radiation and an Oxford Cryosteam sample chiller. Room-T Cu Kα was also collected for **7** in order to determine its absolute configuration.

3.2. Starting material

Dehydrocostuslactone (**1**) was obtained from crude costus-resin oil (*S. lappa*) by previous column chromatography (CC) separation and then purified by crystallization from hexane/ethyl acetate mixtures.

3.3. 13-Acetylmokkolactone (2)

Photochemical reactions were carried out in a modified Hanovia reactor equipped with a Pyrex jacket as filter and a 125 W Hg/medium pressure lamp. The filter solution contained $NiSO_4 \cdot 6H_2O$ (46 g) and $CoSO_4 \cdot 7H_2O$ (14 g) per 100 mL of water. Compound **1** (250 mg, 1.08 mmol) in freshly distilled acetaldehyde (100 mL) was irradiated for 1 h with stirring. The reaction was kept fresh by a water recirculation device. The reaction mixture was concentrated under reduced pressure with the addition of small amounts of cyclohexane. This procedure was repeated ten times. The reaction mixtures were purified by means of CC (Hexane–EtOAc 9:1) to afford 13-acetylmokkolactone **2** (7.17 mmol, 66%). Colourless oil. IR (neat, KBr) ν_{max}, 1719 (carbonyl group) cm^{-1}; EIMS *m/z* (rel int.) 274 $[M]^+$ (25), 232 $[M-C_2H_6O]^+$ (15). ^1H NMR, see Table 4. ^{13}C NMR, see Table 5; HREIMS (M^+) found 274.1571, $C_{17}H_{22}O_3$ requires 274.1568.

3.4. 13-(1′-Hydroxyethyl)-mokkolactone (3)

A 2 mL methanolic solution with 7.1 mmol of compound **2** was kept in a Dewar glass at 0 °C. While the solution was stirring, $NaBH_4$ (1.4 equiv) was added during the first 5 min of reaction. After 1 h, the reaction was stopped by addition of 2 mL of distilled water. Extraction with AcOEt yielded the mixture 1:1 of epimers at C-16, **3** (**a**–**b**) in 98% yield (6.96 mmol). Compound **3**: colourless oil. IR (neat, KBr) ν_{max} 3670 (hydroxyl group), 1750 (carbonyl group) cm^{-1}; EIMS *m/z* (rel int.) 276 $[M]^+$ (10), 258 $[M-H_2O]^+$ (10); HREIMS (M^+) found 276.1746, $C_{17}H_{24}O_3$ requires 274.1725. ^1H NMR (400 MHz, $CDCl_3$) δ 5.17 (1H, dd, *J*=2.2 and 2.2, H-15), 5.03 (1H, dd, *J*=2.3 and 2.3, H-15′), 4.86 (1H, s, H-14), 4.76 (1H, s, H-14′), 4.20a and 4.00b (1H, m, H-16), 4.00a and 3.95 (1H, dd, *J*=9.7 and 9.3, H-6), 2.84 (1H, m, H-1), 2.82 (1H, m, H-5), 2.51 (1H, m, H-3α), 2.47 (1H, ddd, *J*=12.6, 8.9 and 3.8, H-11β), 2.38 (1H, ddd, *J*=11.6, 8.5 and 4.4, H-9α), 2.11 (1H, m, H-8α), 2.10 (1H, m, H-7), 1.99 (1H, m, H-9β), 1.95 (1H, m, H-2α), 1.93 (1H, m, H-3β), 1.86 (1H, m, H-2β), 1.84 (1H, ddd, *J*=14.5, 9.0 and 3.7, H-13), 1.66 (1H, ddd, *J*=14.5, 8.9 and 3.1, H-13′), 1.34 (1H, m, H-8β), 1.22a and 1.20 (3H, d, *J*=6.2, H-17). ^{13}C NMR (100 MHz, $CDCl_3$) δ 180.1 and 179.4 (C-12), 151.6 and 151.5 (C-10), 149.8 and 149.6 (C-4), 112.1 and 111.9 (C-14), 109.3 and 109.1 (C-15), 86.4 and 85.9 (C-6), 67.1 and 64.8 (C-16), 51.9 and 51.8 (C-5), 48.4 and 47.4 (C-7), 47.1 and 46.4 (C-1), 43.4 and 43.3 (C-11), 38.3 and 38.2 (C-13), 38.2 and 37.5 (C-9), 32.6 and 32.5 (C-3), 32.3 and 32.2 (C-2), 30.1 and 29.7 (C-8) 24.2 and 23.8 (C-17).

3.5. 13-[1′-(2″-Tetrahydropyranyloxy)-ethyl]-mokkolactone (4)

To a solution of **3** (**a**–**b**) (6.96 mmol) in dry THF (50 mL), fresh distilled DHP (500 mL) and a few crystals of *p*-toluenesulfonic acid were added. After 3 h, anhydrous potassium carbonate was added and the mixture is kept during an hour. The salts were separated by filtration and the mixture was purified by means of CC (Hexane–Et_2O 9:1) to give the mixture of diastereoisomers **4**. Compound **4**: IR (neat, KBr) ν_{max}, 1746 (carbonyl group) cm^{-1}; EIMS *m/z* (rel int.) 360 $[M]^+$ (2), 85 $[C_5H_9O]^+$ (100); HREIMS (M^+) found 360.2354, $C_{22}H_{32}O_4$ requires 360.2301. ^1H NMR (400 MHz, $CDCl_3$) δ 5.18 (1H, s, H-15), 5.03 (1H, s, H-15′), 4.85 (1H, s, H-14), 4.75 (1H, s, H-14′), 4.49 (1H, m, H-2-THP), 4.20a and 4.13 (1H, ddq, *J*=9.8, 6.1 and 3.3, H-16), 3.91a and 3.90b (1H, dd, *J*=9.2 and 9.1, H-6), 3.43 (2H, m, H-6-THP), 2.84 (1H, m, H-1), 2.79 (1H, m, H-5), 2.47 (1H, m, H-3), 2.43 (1H, ddd, *J*=11.6, 8.5 and 4.4, H-9), 2.32 (1H, ddd, *J*=12.0, 8.6 and 3.5, H-11β), 2.11 (1H, m, H-7), 1.99 (1H, m, H-9′), 1.98 (1H, m, H-8), 1.95 (1H, m, H-2), 1.93 (1H, m, H-3′), 1.86 (1H, m, H-2′), 1.75 (1H, ddd, *J*=14.5, 9.8 and 3.5, H-13), 1.66 (1H, ddd, *J*=14.5, 8.6 and 3.3, H-13′), 1.63–1.45 (6H, m, H-3-THP, H-4-THP, H-5-THP), 1.28 (1H, m, H-8′), 1.26a and 1.13b (3H, d, *J*=6.2, H-17). ^{13}C NMR (100 MHz, $CDCl_3$) δ 179.6 and 179.0 (C-12), 150.8 and 149.9 (C-10), 147.6 and 146.6 (C-4), 111.5 and 111.3 (C-14), 108.8 and 108.1

Table 4. ^{1}H NMR data for compounds **2**, **6–9** and **14–17** (400 MHz in $CDCl_3$, signal of residual $CHCl_3$ centred at δ 7.25 ppm)

	2	**6**	**7**	**8**	**9**	**14**	**15**	**16**	**17**
1	2.81 m	2.84 ddd	2.86 m	2.86 ddd	2.84 m	2.85 ddd	2.85 ddd	2.88 m	2.86 m
2α	2.15 m	2.00 m	1.92 m	2.00 m	1.81 m	2.03 m	1.88 m	1.95 m	2.23 m
2β	1.84 m	1.86 m	1.81 m	1.86 m	1.75 m	1.88 m	1.82 m	1.82 m	2.00 m
3α	2.43 m	2.54 ddd	2.48 m	2.55 m	2.48 m	2.54 m	2.48 m	2.47 m	2.49 m
3β	1.93 m	1.79 m	1.95 m	1.73 m	1.95 m	2.20 m	2.13 m	2.42 m	2.22 m
5	2.82 m	2.69 ddd	2.85 m	2.69 ddd	2.87 m	2.69 m	2.68 m	2.80 m	2.83 m
6	3.92 dd	4.21 dd	3.86 dd	4.24 dd	3.96 dd	4.05 dd	4.05 dd	3.78 dd	3.78 dd
7	2.13 m	1.87 ddd	2.36 ddd	2.07 ddd	2.37 ddd	2.01 ddd	1.93 ddd	2.35 ddd	2.26 ddd
8α	1.95 m	2.45 m	2.08 m	1.87 m	1.97 m	2.45 m	2.45 m	2.45 m	1.95 m
8β	1.29 m	1.79 m	1.31 m	1.77 m	1.31 m	1.79 m	1.78 m	1.57 m	1.82 m
9α	2.41 m	2.47 ddd	2.52 m	2.47 m	2.51 m	2.48 ddd	2.54 ddd	2.58 ddd	2.46 ddd
9β	1.97 m	2.01 m	1.96 m	2.01 m	2.08 m	2.24 ddd	2.09 ddd	2.08 ddd	2.24 ddd
11	2.64 ddd								
13	2.88 dd	1.89 dd	1.73 dd	1.94 dd	1.76 dd	2.71 dd	2.96 dd	2.89 dd	2.56 dd
13′	2.65 dd	1.65 dd	1.55 dd	1.79 dd	1.68 dd	2.61 dd	2.22 dd	2.24 dd	2.44 dd
14	4.81 s	4.97 s	4.86 s	4.87 s	4.88 s	4.87 s	4.88 s	4.89 s	4.89 s
14′	4.72 s	4.86 s	4.75 s	4.79 s	4.79 s	4.79 s	4.79 s	4.77 s	4.77 s
15	5.15 d	5.18 d	5.18 d	5.18 d	5.16 d	5.17 d	5.17 d	5.14 d	5.16 d
15′	5.00 dd	5.03 dd	5.03 d	5.03 dd	5.06 dd	5.03 d	5.03 d	5.03 d	5.04 d
16	—	4.97 ddq	4.27 ddq	4.16 ddq	4.27 ddq	4.75 ddq	5.10 ddq	4.84 ddq	5.24 ddq
17	2.17 s	1.23 d	1.21 d	1.27 d	1.21 d	1.50 d	1.35 d	1.59 d	1.39 d

J (Hz): (**2**) 6,7=9.5; 6,5=9.3; 11,7=11.8; 11,13=6.3; 11,13′=5.7; 13,13′=16.8; 15,3=1.0; 15′,3=1.9; 15′,5=0.8. (**6**) 1,2β=14.7; 1,5=8.0; 1,2α=7.5; 3α,3β=11.3; 3α,2α=8.9; 3α,2β=1.86; 5,6=9.7; 5,15=2.2; 6,7=9.5; 7,8β=12.7; 7,8α=3.9; 9α,9β=12.9; 9α,8α=4.6; 9α,8β=9.6; 13,13′=14.5; 13,16=10.8; 13′,16=2.7; 16,17=6.2; 15,3=1.3; 15′,3=0.9. (**7**) 6,7=10.2; 6,5=8.7; 7,8β=12.4; 7,8α=3.0; 13,13′=14.7; 13,16=11.2; 13′,16=2.2; 16,17=6.1; 15,3=2.0; 15′,5=2.0. (**8**) 1,2β=15.0; 1,5=8.0; 1,2α=6.7; 5,6=9.6; 5,15=2.2; 6,7=9.8; 7,8β=13.0; 7,8α=3.7; 13,13′=15.0; 13,16=10.3; 13′,16=3.0; 16,17=6.2; 15,3=2.0; 15′,3=0.7. (**9**) 6,7=10.2; 6,5=8.9; 7,8β=12.6; 7,8α=3.3; 13,13′=14.7; 13,16=8.5; 13′,16=2.7; 16,17=6.2; 15,3=3.0; 15′,5=2.1; 15′,5=0.6. (**14**) 1,2β=14.6; 1,5=7.4; 1,2α=7.2; 6,7=9.5; 6,5=9.6; 7,8β=11.5; 7,8α=3.4; 9α,9β=13.2; 9α,8α=4.6; 9α,8β=10.6; 9β,8α=7.3; 9β,8β=7.6; 13,13′=11.7; 13,16=6.4; 13′,16=7.8; 16,17=6.1; 15,3=2.0; 15′,5=2.1. (**15**) 1,2β=15.0; 1,5=7.7; 1,2α=6.6; 5,6=9.6; 5,15′=1.5; 6,7=9.6; 7,8β=12.6; 7,8α=3.6; 9α,9β=13.0; 9α,8α=4.0; 9α,8β=10.1; 9β,8α=6.8; 9β,8β=7.0; 13,13′=11.5; 13,16=7.0; 13′,16=7.3; 16,17=6.0; 15,3=1.9. (**16**) 6,7=9.8; 6,5=9.0; 7,8β=12.6; 7,8α=3.6; 9α,9β=12.9; 9α,8α=4.0; 9α,8β=11.3; 9β,8α=7.5; 9β,8β=7.3; 13,13′=11.5; 13,16=7.7; 13′,16=6.5; 16,17=6.2; 15,3=2.3; 15′,5=1.7. (**17**) 6,7=8.9; 6,5=9.9; 7,8β=12.8; 7,8α=3.2; 9α,9β=12.8; 9α,8α=4.2; 9α,8β=11.1; 9β,8α=7.2; 9β,8β=6.9; 13,13′=11.4; 13,16=7.6; 13′,16=7.5; 16,17=6.1; 15,3=2.2; 15′,5=2.0.

(C-15), 84.8 (C-6), 72.5 (C-2-THP), 68.2 (C-16), 63.4 (C-6-THP), 51.7 (C-5), 47.2 (C-7), 46.8 (C-1), 42.9 and 42.7 (C-11), 37.4 and 37.3 (C-13), 36.4 and 36.1 (C-9), 32.1 (C-8), 32.0 (C-3), 31.1 and 29.8 (C-2), 25.1 (C-17), 22.2 (C-3-THP), 20.1 (C-5-THP), 19.5 (C-4-THP).

3.6. 11-Hydroxy-13-[1′-(2″-tetrahydropyranyloxy)-ethyl]-mokkolactone (5)

To a solution of **4** (100 mg) in dry THF (25 mL) at −73 °C a 0.4 M solution of KHMDS (8 mL) in dry THF was added under Ar. After 30 min of stirring at −73 °C a current of dry oxygen was bubbled for 1 h. At this point, treatment with triethylphosphite (50 μL) as a reducing agent took place. Then, the mixture was warmed to −20 °C and a buffer solution (pH=7) was added (20 mL). Extractive workup with Et_2O and CC separation (Hexane–EtOAc 9:1) gave the diastereoisomers **5**. This procedure was repeated with different amounts of the mixture **4**. Compound **5**: IR (neat, KBr) ν_{max}, 3540 (hydroxyl group), 1763 (carbonyl group) cm^{-1}; EIMS *m/z* (rel int.) 376 $[M]^+$ (2), 85 $[C_5H_9O]^+$ (100); HREIMS (M^+) found 376.2215, $C_{22}H_{32}O_5$ requires 376.2250. ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.17 (1H, d, *J*=2.4, H-15), 5.05 (1H, dd, *J*=2.8 and 0.8, H-15′), 4.86 (1H, s, H-14),

Table 5. ^{13}C NMR data for compounds **2**, **6–9** and **14–17** (400 MHz in $CDCl_3$, signal of residual $CHCl_3$ centred at δ 77.0 ppm)

	2	**6**	**7**	**8**	**9**	**14**	**15**	**16**	**17**
1	47.0	47.6	46.8	47.5	47.6	47.8	47.6	46.9	46.6
2	30.0	30.0	30.0	30.1	30.0	30.1	30.1	30.1	30.1
3	32.3	32.1	32.4	32.2	32.2	32.1	32.2	31.2	31.2
4	149.6	149.8	150.3	149.5	149.2	148.4	149.4	149.9	150.0
5	51.8	52.3	52.3	52.1	52.3	52.1	52.2	52.4	52.2
6	85.5	83.4	82.7	84.7	83.4	83.8	83.5	82.2	82.4
7	47.3	52.2	52.2	51.4	52.1	50.2	50.3	50.2	50.3
8	32.4	25.1	27.1	25.7	25.1	25.7	25.7	29.2	29.2
9	37.3	35.8	37.6	35.8	36.3	35.6	35.8	37.5	37.5
10	151.5	151.3	151.5	151.2	151.6	151.1	151.0	151.2	151.0
11	42.4	75.7	76.4	76.4	76.5	81.7	82.3	82.9	82.8
12	177.4	177.5	178.3	178.1	178.1	174.7	175.7	177.4	177.3
13	41.6	41.4	37.8	43.1	41.3	32.5	32.4	32.4	32.3
14	111.9	112.1	111.7	112.3	112.0	111.8	112.4	111.9	111.7
15	109.1	109.7	109.4	109.8	109.6	109.6	109.8	109.4	109.3
16	205.3	64.9	65.7	64.7	65.3	75.3	75.3	75.3	75.2
17	30.1	25.0	24.6	24.8	24.5	23.6	23.5	23.8	23.7

4.77 (1H, s, H-14′), 4.57 (1H, m, H-2-THP), 4.25 (1H, ddq, J=7.4, 6.2 and 4.1, H-16), 3.89 (1H, dd, J=10.2 and 8.2, H-6), 3.48 (2H, m, H-6-THP), 2.87 (1H, br dd, J=11.0 and 8.2, H-5), 2.84 (1H, ddd, J=11.0, 10.3 and 8.7, H-1), 2.50 (1H, m, H-3), 2.48 (1H, m, H-9), 2.37 (1H, ddd, J=12.3, 10.2 and 3.2, H-7), 1.98 (1H, m, H-9′), 1.96 (1H, m, H-8), 1.95 (1H, m, H-3′), 1.93 (1H, m, H-2), 1.93 (1H, dd, J=14.9 and 4.1, H-13), 1.82 (1H, dd, J=14.8 and 7.4, H-13′), 1.83 (1H, m, H-2′), 1.65–1.40 (6H, m, H-3-THP, H-4-THP, H-5-THP), 1.36 (1H, dddd, J=16.7, 12.4, 12.0 and 4.10, H-8), 1.21 (3H, d, J=6.2, H-17). ^{13}C NMR (100 MHz, $CDCl_3$) δ 180.0 (C-12), 150.3 (C-10), 148.0 (C-4), 111.5 (C-14), 109.3 (C-15), 83.9 (C-6), 76.2 (C-11), 72.4 (C-2-THP), 67.9 (C-16), 63.3 (C-6-THP), 52.0 (C-5), 47.6 (C-7), 47.2 (C-1), 38.3 (C-13), 37.9 (C-9), 33.0 (C-8), 32.8 (C-3), 31.1 (C-2), 26.0 (C-17), 22.8 (C-3-THP), 21.1 (C-5-THP), 19.7 (C-4-THP).

3.7. Diols 6, 7, 8 and 9

The mixture **4** was dissolved in EtOAc (25 mL) with a few crystal of *p*-toluenesulfonic acid. After 24 h potassium carbonate was added and the mixture stirred for several minutes. The salts were removed by filtration and the purification was accomplished by CC (Hexane–EtOAc 8:2) to yield diols (11*R*,16*R*) 11-hydroxy-13-(1′-hydroxyethyl)-mokkolactone (**6**) (1.39 mmol, 20%), (11*R*,16*S*) 11-hydroxy-13-(1′-hydroxyethyl)-mokkolactone (**7**) (1.53 mmol, 22%), (11*S*,16*S*) 11-hydroxy-13-(1′-hydroxyethyl)-mokkolactone (**8**) (1.32 mmol, 19%) and (11*S*,16*R*) 11-hydroxy-13-(1′-hydroxyethyl)-mokkolactone (**9**) (1.39 mmol, 20%). Compound **5**: colourless crystal. IR (neat, KBr) ν_{max}, 3490 (hydroxyl group), 1765 (carbonyl group) cm^{-1}; EIMS *m*/*z* (rel int.) 292 [M]$^+$ (9), 274 [M−H_2O]$^+$ (38); HREIMS (M$^+$) found 292.1620, $C_{17}H_{24}O_4$ requires 292.1675.^{1}H NMR, see Table 1. ^{13}C NMR, see Table 2. Compound **6**: colourless crystal. IR (neat, KBr) ν_{max}, 3450 (hydroxyl group), 1770 (carbonyl group) cm^{-1}; EIMS *m*/*z* (rel int.) 292 [M]$^+$ (7), 274 [M−H_2O]$^+$ (14); HREIMS (M$^+$) found 292.1677, $C_{17}H_{24}O_4$ requires 292.1675.^{1}H NMR, see Table 4. ^{13}C NMR, see Table 5. Compound **7**: colourless crystal. IR (neat, KBr) ν_{max}, 3460 (hydroxyl group), 1772 (carbonyl group) cm^{-1}; EIMS *m*/*z* (rel int.) 292 [M]$^+$ (3), 274 [M−H_2O]$^+$ (4); HREIMS (M$^+$) found 292.1703, $C_{17}H_{24}O_4$ requires 292.1675. ^{1}H NMR, see Table 4. ^{13}C NMR, see Table 5. Compound **8**: colourless crystal. IR (neat, KBr) ν_{max}, 3460 (hydroxyl group), 1772 (carbonyl group) cm^{-1}; EIMS *m*/*z* (rel int.) 292 [M]$^+$ (3), 274 [M−H_2O]$^+$ (4); HREIMS (M$^+$) found 292.1703, $C_{17}H_{24}O_4$ requires 292.1675. ^{1}H NMR, see Table 4. ^{13}C NMR, see Table 5.

3.8. Reaction of mesylation

Diols **6**–**9**, separately, were dissolved in pyridine (15 mL) and 1.5 equiv of mesyl chloride was added at 0 °C with stirring. After 24 h the reaction was stopped by addition of 2 mL of distilled water. The reaction mixture was extracted with AcOEt (5×), and the combined organic phases were washed with aq saturated $CuSO_4$ (3×). The organic phase was dried over anhydrous sodium sulfate, the solvent evaporated under vacuum, and the crude product of the reaction purified by CC (Hexane–EtOAc 8:2), yielding the corresponding mesylated compounds (11*R*,16*R*) 11-hydroxy-13-(1′-(methylsulfonyloxy)-ethyl)-mokkolactone (**10**) (1.36 mmol, 98%), (11*R*,16*S*) 11-hydroxy-13-(1′-(methylsulfonyloxy)-ethyl)-mokkolactone (**11**) (1.49 mmol, 98%), 11-hydroxy-13-(1′-(methylsulfonyloxy)-ethyl)-mokkolactone (**12**) (1.29 mmol, 98%) and (11*S*,16*R*) 11-hydroxy-13-(1′-(methylsulfonyloxy)-ethyl)-mokkolactone (**13**) (1.36 mmol, 98%). Compound **10**: colourless oil. IR (neat, KBr) ν_{max}, 3440 (hydroxyl group), 1770 (carbonyl group) cm^{-1}; EIMS *m*/*z* (rel int.) 370 [M]$^+$ (10), 275 [M−OMs]$^+$ (12); HREIMS (M$^+$) found 370.4410, $C_{18}H_{26}O_6S$ requires 370.1450. ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.45 (1H, ddq, J=9.8, 6.2 and 3.2, H-16), 5.17 (1H, d, J=1.2, H-15), 5.05 (1H, d, J=2.0, H-15′), 4.88 (1H, s, H-14), 4.79 (1H, s, H-14′), 4.21 (1H, dd, J=10.0 and 9.7, H-6), 3.02 (3H, s, H-Ms), 2.88 (1H, ddd, J=14.3, 8.1 and 7.3, H-1), 2.80 (1H, dd, J=9.7 and 8.1, H-5), 2.50 (1H, ddd, J=11.3, 8.9 and 4.5, H-3), 2.46 (1H, ddd, J=12.7, 9.3 and 4.2, H-9), 2.45 (1H, m, H-8), 2.33 (1H, dd, J=14.5 and 9.8, H-13), 2.01 (1H, ddd, J=12.7, 10.1 and 4.8, H-9′), 2.01 (1H, m, H-2), 1.85 (1H, ddd, J=12.7, 10.0 and 3.9, H-7), 1.86 (1H, m, H-2′), 1.79 (1H, m, H-8′), 1.86 (1H, dd, J=14.5 and 3.2, H-13′), 1.78 (1H, ddd, J=11.3, 5.1 and 2.0, H-3′), 1.52 (3H, d, J=6.2, H-17). ^{13}C NMR (100 MHz, $CDCl_3$) δ 177.5 (C-12), 151.3 (C-10), 149.8 (C-4), 112.1 (C-14), 109.7 (C-15), 83.4 (C-6), 75.7 (C-11), 63.0 (C-16), 52.3 (C-5), 52.2 (C-7), 47.6 (C-1), 41.6 (C-13), 38.2 (C-Ms), 35.8 (C-9), 32.1 (C-3), 30.0 (C-2), 25.1 (C-8), 23.2 (C-17). Compound **11**: colourless oil. IR (neat, KBr) ν_{max}, 3434 (hydroxyl group), 1774 (carbonyl group) cm^{-1}; EIMS *m*/*z* (rel int.) 370 [M]$^+$ (7), 275 [M−OMs]$^+$ (15); HREIMS (M$^+$) found 370.4411, $C_{18}H_{26}O_6S$ requires 370.1450. ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.18 (1H, d, J=1.2, H-15), 5.10 (1H, ddq, J=9.7, 6.1 and 3.3, H-16), 5.03 (1H, d, J=2.0, H-15′), 4.86 (1H, s, H-14), 4.76 (1H, s, H-14′), 3.87 (1H, dd, J=10.1 and 8.9, H-6), 3.02 (3H, s, H-Ms), 2.84 (1H, m, H-1), 2.83 (1H, m, H-5), 2.52 (1H, ddd, J=15.3, 8.5 and 4.5, H-3), 2.48 (1H, m, H-9), 2.28 (1H, ddd, J=12.7, 10.1 and 3.9, H-7), 2.15 (1H, dd, J=14.7 and 9.7, H-13), 2.00 (1H, m, H-8), 1.99 (1H, m, H-9′), 1.93 (1H, m, H-2), 1.92 (1H, m, H-3′), 1.86 (1H, dd, J=14.7 and 3.3, H-13′), 1.83 (1H, m, H-2′), 1.46 (3H, d, J=6.1, H-17), 1.35 (1H, m, H-8′). ^{13}C NMR (100 MHz, $CDCl_3$) δ 178.3 (C-12), 151.4 (C-10), 150.3 (C-4), 111.8 (C-14), 109.4 (C-15), 83.4 (C-6), 76.4 (C-11), 63.1 (C-16), 52.3 (C-5), 52.2 (C-7), 46.8 (C-1), 42.1 (C-13), 38.1 (C-Ms), 37.8 (C-9), 32.1 (C-3), 30.1 (C-2), 27.2 (C-8), 22.8 (C-17). Compound **12**: colourless oil. IR (neat, KBr) ν_{max}, 3456 (hydroxyl group), 1768 (carbonyl group) cm^{-1}; EIMS *m*/*z* (rel int.) 370 [M]$^+$ (10), 275 [M−OMs]$^+$ (18); HREIMS (M$^+$) found 370.4409, $C_{18}H_{26}O_6S$ requires 370.1450. ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.18 (1H, d, J=1.2, H-15), 5.12 (1H, ddq, J=9.9, 6.2 and 3.5, H-16), 5.03 (1H, d, J=2.0, H-15′), 4.88 (1H, s, H-14), 4.80 (1H, s, H-14′), 4.26 (1H, dd, J=10.1 and 9.6, H-6), 3.02 (3H, s, H-Ms), 2.84 (1H, ddd, J=14.3, 8.1 and 7.3, H-1), 2.68 (1H, dd, J=9.7 and 8.1, H-5), 2.51 (1H, m, H-3), 2.48 (1H, m, H-9), 2.23 (1H, dd, J=14.8 and 9.9, H-13), 2.03 (1H, ddd, J=12.7, 10.1 and 3.9, H-7), 2.01 (1H, m, H-9′), 1.99 (1H, m, H-2), 1.85 (1H, m, H-8), 1.84 (1H, m, H-2′), 1.83 (1H, dd, J=14.8 and 3.5, H-13′), 1.73 (1H, m, H-8′), 1.72 (1H, m, H-3′), 1.45 (3H, d, J=6.2, H-17). ^{13}C NMR (100 MHz, $CDCl_3$) δ 178.1 (C-12), 151.2 (C-10), 149.5 (C-4), 112.8 (C-14),

109.7 (C-15), 84.4 (C-6), 76.4 (C-11), 62.9 (C-16), 52.1 (C-5), 51.0 (C-7), 47.8 (C-1), 42.6 (C-13), 38.2 (C-Ms), 35.7 (C-9), 32.1 (C-3), 30.1 (C-2), 25.2 (C-8), 23.6 (C-17). Compound **13**: colourless oil. IR (neat, KBr) ν_{max}, 3448 (hydroxyl group), 1763 (carbonyl group) cm^{-1}; EIMS *m/z* (rel int.) 370 $[M]^+$ (8), 275 $[M-OMs]^+$ (9); HREIMS (M^+) found 370.4406, $C_{18}H_{26}O_6S$ requires 370.1450. ^1H NMR (400 MHz, $CDCl_3$) δ 5.26 (1H, ddq, *J*=8.4, 6.2 and 3.2, H-16), 5.16 (1H, d, *J*=2.0), 5.04 (H-15′, d, *J*=2.1, H-15), 4.88 (1H, s, H-14), 4.80 (1H, s, H-14′), 3.95 (1H, dd, *J*=10.3 and 8.9, H-6), 3.02 (3H, s, H-Ms), 2.84 (1H, m, H-1), 2.83 (1H, m, H-5), 2.51 (1H, m, H-9), 2.49 (1H, m, H-3), 2.33 (1H, ddd, *J*=12.7, 10.1 and 3.9, H-7), 2.30 (1H, dd, *J*=14.7 and 8.4, H-13), 2.04 (1H, m, H-9′), 2.02 (1H, m, H-8), 1.95 (1H, m, H-3′), 1.82 (1H, m, H-2), 1.77 (1H, m, H-2′), 1.74 (1H, dd, *J*=14.7 and 3.2, H-13′), 1.48 (3H, d, *J*=6.2, H-17), 1.35 (1H, m, H-8′). ^{13}C NMR (100 MHz, $CDCl_3$) δ 178.1 (C-12), 151.4 (C-10), 149.8 (C-4), 112.6 (C-14), 109.4 (C-15), 84.4 (C-6), 76.6 (C-11), 63.0 (C-16), 52.3 (C-5), 51.2 (C-7), 47.8 (C-1), 40.1 (C-13), 38.2 (C-Ms), 36.3 (C-9), 32.1 (C-3), 30.2 (C-2), 25.8 (C-8), 23.2 (C-17).

3.9. Oxetane lactones 14, 15, 16 and 17

The mesylated compounds **10**, **11**, **12** and **13**, separately, were dissolved in dry THF (20 mL). While the solution was stirring, BuLi (1.5 equiv) was added dropwise at 0 °C. After 12 min the mixture was warmed up to 55 °C and maintained for 2 h. The reaction was quenched by addition of 2 mL of distilled water and was extracted with AcOEt (5×). The organic phase was dried over anhydrous sodium sulfate, the solvent evaporated under vacuum, and the crude product of the reaction purified by CC (Hexane–EtOAc 9:1), yielding the oxetane lactones (11*R*,16*S*) 11,16-epoxy-13-ethylmokkolactone (**14**) (0.27 mmol, 20%), (11*R*,16*R*) 11,16-epoxy-13-ethylmokkolactone (**15**) (0.31 mmol, 21%), (11*S*,16*R*) 11,16-epoxy-13-ethylmokkolactone (**16**) (0.24 mmol, 19%) and (11*S*,16*S*) 11,16-epoxy-13-ethylmokkolactone (**17**) (0.29 mmol, 22%). Compound **14**: colourless crystal. IR (neat, KBr) ν_{max}, 1782 (carbonyl group) cm^{-1}; EIMS *m/z* (rel int.) 274 $[M]^+$ (15), 248 $[M-44]^+$ (36); HREIMS (M^+) found 274.1619, $C_{17}H_{22}O_3$ requires 274.1569. ^1H NMR, see Table 4. ^{13}C NMR, see Table 5. Compound **15**: colourless crystal. IR (neat, KBr) ν_{max}, 1766 (carbonyl group) cm^{-1}; EIMS *m/z* (rel int.) 274 $[M]^+$ (12), 248 $[M-44]^+$ (39); HREIMS (M^+) found 274.1656, $C_{17}H_{22}O_3$ requires 274.1569. ^1H NMR, see Table 4. ^{13}C NMR, see Table 5. Compound **16**: colourless crystal. IR (neat, KBr) ν_{max}, 1766 (carbonyl group) cm^{-1}; EIMS *m/z* (rel int.) 274 $[M]^+$ (11), 248 $[M-44]^+$ (38); HREIMS (M^+) found 274.1586, $C_{17}H_{22}O_3$ requires 274.1569. ^1H NMR, see Table 4. ^{13}C NMR, see Table 5. Compound **17**: colourless crystal. IR (neat, KBr) ν_{max}, 1766 (carbonyl group) cm^{-1}; EIMS *m/z* (rel int.) 274 $[M]^+$ (9), 248 $[M-44]^+$ (42); ^1H NMR, see Table 4. ^{13}C NMR see Table 5.

3.10. 11,13-Dihydro-13-hydroxy-deacylcynaropicrin (18) and deacylcynaropicrin (20)

Cynaropicrin was isolated from *Cynara scolimus*.[15] Cynaropicrin (400 mg, 1.15 mmol) was mixed with aq 10% K_2CO_3 (200 mL) and stirred for 24 h at 50 °C. After acidification with diluted HCl, the mixture was extracted with ethyl acetate. The organic solution was washed with water, dried and the solvent evaporated. The reaction mixture was chromatographed on silica gel using hexane/AcOEt (3:2) as eluent yielding 94 mg of **18** (60%, 0.69 mmol) and 182 mg of **20** (29%, 0.34 mmol). Compound **18**: colourless crystal. IR (neat, KBr) ν_{max}, 3548 (hydroxyl group), 1772 (carbonyl group) cm^{-1}; EIMS *m/z* (rel int.) 280.1310 $[M]^+$ (18), 272.1519 $[M-18]^+$ (21); ^1H NMR (400 MHz, $CDCl_3$) δ 5.19 (1H, br s, H-15), 5.17 (1H, br s, H-15′), 4.92 (1H, s, H-14), 4.85 (1H, s, H-14′), 4.34 (1H, br dd, *J*=8.1 and 7.4, H-3), 3.96 (1H, dd, *J*=9.8 and 9.7, H-6), 3.95 (1H, dd, *J*=11.0 and 3.7, H-13), 3.54 (1H, dd, *J*=11.0 and 8.2, H-13′), 3.53 (1H, ddd, *J*=9.0, 7.6 and 5.0, H-8), 2.73 (1H, ddd, *J*=9.1, 9.0 and 8.4, H-1), 2.64 (1H, dd, *J*=9.8 and 9.1, H-5), 2.60 (1H, ddd, *J*=11.0, 9.7 and 7.6, H-7), 2.57 (1H, dd, *J*=12.2 and 5.0, H-9), 2.12 (1H, ddd, *J*=11.0, 8.2 and 3.7, H-11), 2.11 (1H, ddd, *J*=13.1, 8.4 and 7.4, H-2), 2.08 (1H, dd, *J*=12.2 and 7.6, H-9′), 1.58 (1H, ddd, *J*=13.1, 9.0 and 8.1, H-2′). ^{13}C NMR (100 MHz, $CDCl_3$) δ 73.8 (C-8), 73.2 (C-3), 62.1 (C-13), 54.7 (C-11), 50.3 (C-5), 50.1 (C-7), 44.1 (C-1), 43.7 (C-9), 39.0 (C-2), 175.6 (C-12), 153.2 (C-10), 143.6 (C-4), 116.1 (C-14), 111.6 (C-15), 79.6 (C-6). Compound **20**: colourless crystal. IR (neat, KBr) ν_{max}, 3427 (hydroxyl group), 1754 (carbonyl group) cm^{-1}; EIMS *m/z* (rel int.) 262.1198 $[M]^+$ (30), 244.1096 $[M-18]^+$; ^1H NMR (400 MHz, $CDCl_3$) δ 6.25 (1H, dd, *J*=3.3 and 0.7, H-13), 6.13 (1H, dd, *J*=3.1 and 0.8, H-13′), 5.47(1H, dd, *J*=1.9 and 1.6, H-15), 5.31 (1H, dd, *J*=1.7 and 1.4, H-15′), 4.97 (1H, dd, *J*=0.6 and 0.4, H-14), 4.94 (1H, dd, *J*=0.6 and 0.4, H-14′), 4.54 (1H, br dd, *J*=7.4 and 2.1, H-3), 4.14 (1H, dd, *J*=10.6 and 9.1, H-6), 3.96 (1H, br ddd, *J*=9.1, 5.0 and 4.0, H-8), 3.10 (1H, br ddd, *J*=10.0, 9.1, 3.3 and 3.1, H-7), 2.96 (1H, br ddd, *J*=11.0, 9.4 and 8.0, H-1), 2.79 (1H, br dd, *J*=10.5 and 9.7, H-5), 2.69 (1H, dd, *J*=14.1 and 5.1, H-9β), 2.28 (1H, dd, *J*=14.1 and 3.9, H-9α), 2.22 (1H, ddd, *J*=13.2, 7.6 and 7.4, H-2β), 1.72 (1H, ddd, *J*=13.2, 11.0 and 7.6, H-2α). ^{13}C NMR (100 MHz, $CDCl_3$) δ 183.5 (C-12), 152.4 (C-10), 142.7 (C-4), 138.1 (C-11), 123.2 (C-13), 117.4 (C-14), 113.1 (C-15), 78.8 (C-6), 73.7 (C-3), 70.9 (C-8), 51.2 (C-7), 50.9 (C-5), 45.1 (C-1), 41.3 (C-9), 39.2 (C-2).

3.11. 8α-Hydroxy-dehydrozaluzanin C (21)

Compound **20** (100 mg, 0.38 mmol) was dissolved in dried CH_2Cl_2 (20 mL). SeO_2 (45 mg, 0.40 mmol) was added over the stirred solution, and allowed to react for 24 h. Filtering the reaction mixture through silica gel stopped the reaction, the solvent was then evaporated under vacuum. The crude product was purified by CC using hexane/ethyl acetate mixtures as eluent, yielding 78 mg of **21** (79%, 30 mmol). Compound **21**: colourless crystal. IR (neat, KBr) ν_{max}, 3430 (hydroxyl group), 1762 (carbonyl group) cm^{-1}; EIMS *m/z* (rel int.) 260.1098 $[M]^+$ (21), 242.1069 $[M-18]^+$; ^1H NMR (400 MHz, $CDCl_3$) δ 6.36 (1H, dd, *J*=3.4 and 0.9, H-13), 6.30 (1H, dd, *J*=3.0 and 0.9, H-13′), 6.26 (1H, d, *J*=2.5, H-15), 5.87 (1H, d, *J*=2.2, H-15′), 5.03 (1H, s, H-14), 4.83, (1H, s, H-14′), 3.98 (1H, dd, *J*=9.5 and 9.2, H-6), 3.96 (1H, br ddd, *J*=9.1, 5.0 and 4.0, H-8), 3.25 (1H, ddd, *J*=9.5, 8.6 and 2.5, H-5α), 3.11 (1H, br ddd, *J*=8.2, 8.6 and 5.2, H-1α), 3.06 (1H, dddd, *J*=9.3,

9.2, 3.4 and 3.0, H-7), 2.79 (1H, dd, J=13.1 and 5.6, H-9β), 2.60 (1H, dd, J=13.2 and 8.2, H-2β), 2.49 (1H, dd, J=18.5 and 5.2, H-2α), 2.30 (1H, dd, J=3.1 and 7.0, H-9α). ^{13}C NMR (100 MHz, $CDCl_3$) δ 204.2 (C-3), 169.5 (C-12), 143.1 (C-11), 136.5 (C-10), 130.1 (C-4), 125.9 (C-13), 123.5 (C-15), 117.1 (C-14), 80.0 (C-6), 73.2 (C-8), 49.6 (C-7), 49.3 (C-5), 46.5 (C-9), 43.7 (C-2), 40.6 (C-1).

CCDC 602144-602148 and CCDC 605928-605933 contain the supplementary crystallographic data for this paper. These data can be obtained free of charge at www.ccdc.cam.ac.uk/conts/retrieving.html [or from the Cambridge Crystallographic Data Centre (CCDC), 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44(0)1223 336033; email: deposit@ccdc.cam.ac.uk].

4. Conclusions

The achievement of the four oxetane lactones using dehydrocostuslactone as starting material has provided some correlations, which can be useful tools in future researches with this type of molecules. Thus, a deep analysis of the NMR and X-ray derived data of the obtained oxetane lactones has allowed us to find some relationships that can be helpful in order to detect the presence of the oxetane ring as well as to establish its stereochemistry on similar compounds.

Furthermore, the results of the conformational analysis may also be important findings due to the key aspect that the molecular conformations play on the biological activity. We have found that guaianolides having the α-methylene-γ-lactone moiety and non-bulky substituents prefer a twist-chair conformation at the cycloheptane ring, whereas a chair conformation occurs when the lack of the α-methylene-γ-lactone group takes place.

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