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Improved methodologies for synthesis of prenylated xanthones by microwave irradiation and combination of heterogeneous catalysis (K10 clay) with microwave irradiation

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ABSTRACT

Eleven prenylated xanthone derivatives (**4**–**9**, **11**–**15**) have been synthesized for the first time by the microwave irradiation method. Prenylation of the xanthone building blocks **1** and **2** with prenyl bromide in alkaline medium, using microwave irradiation, gave the oxyprenylated xanthones **4** and **6**, as major products in high yields, as well as diprenylated by-products (**5**, **7**, **8**, and **9**) in very low yields. Microwave irradiation of oxyprenylated xanthones **4** and **6** furnished three new Claisen rearranged products (**11**, **14**, and **15**), as well as the previously described dihydrofuranoxanthones (**12**, **13**). Furthermore, three new (**19**, **20**, **21**) and three previously described (**16**, **17**, **18**) dihydropyranoxanthones have also been prepared by a one-pot synthesis from xanthones **1**, **2**, and **3**, using Montmorillonite K10 clay as a heterogeneous catalyst and a combination of Montmorillonite K10 clay with microwave irradiation in various conditions. The presence of solvent and the type of the clay (commercial or dry) were found to have a strong influence on the product yields. This is the first report of using these methodologies for the synthesis of dihydropyranoxanthone derivatives. The structures of the prenylated xanthones obtained were established by IR, UV, HRMS, and NMR (^{1}H, ^{13}C, HSQC, and HMBC) techniques.

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1. Introduction

Prenylated xanthones, including furan and pyran derivatives, have been reported to mediate several interesting biological activities, concerning a large variety of targets with therapeutic value.[1,2] Although the oxygenation pattern of these derivatives can play an important role in their biological activity, the presence of the prenyl side chains seems also to be associated with the enhanced interaction with biological membranes and with target proteins when compared with their non-prenylated analogs.[3] For this reason, we have synthesized a series of prenylated xanthone derivatives to evaluate their effect on the in vitro growth of some human cancer cell lines. The synthesis of the prenylated xanthone derivatives is normally carried out by introduction of the prenyl side chain to the hydroxyxanthone nucleus, in a vigorous condition. In addition, the reactions usually involved toxic reagents.[4,5] Consequently, these processes are considered to be not only very demanding but also environmentally unfriendly. Taking this into account, we have looked for an alternative to obtain prenylated xanthones.

One of the considered methods was the microwave-assisted organic synthesis (MAOS), which has been demonstrated not only to dramatically accelerate many organic reactions, but also to improve yields and selectivity.[6,7] With this technique, many reaction parameters such as reaction temperature and time, variations in solvents, additives, and catalysts can be evaluated to optimize the desired chemistry.[8] As a result, pharmaceutical industry is starting to incorporate microwave (MW) methodologies in processes of discovery of pharmacologically active small-molecules.[8] On the other hand, much attention has been paid to clays, which can act as solid catalysts for a wide range of organic reactions and a subgroup of clays, Montmorillonite, is particularly useful. With this clay, the reaction proceeds not only under mild conditions but also with selectivity, good yields, and short reaction times. As this catalyst can be easily separated from the reaction mixture and can be regenerated, the purification procedures are usually simple.[9,10]

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Furthermore, the coupling of MW irradiation with the use of inorganic solid supports such as Montmorillonite K10 clay, either with solvent or under solvent-free conditions, can also provide a chemical process with inherent advantages such as enhanced reaction rates, high yields, ease of manipulation, and selectivity.[11]

Here we report the microwave-assisted synthesis of two oxyprenylated xanthones (**4** and **6**), along with four diprenylated by-products (**5**, **7**–**9**) from the simple hydroxylated xanthones (**1** and **2**) and prenyl bromide, as well as the synthesis of dihydrofuranoxanthones (**11**–**13**) and two new rearranged prenylxanthones (**14**, **15**) from the oxyprenylated xanthones **4** and **6** (Fig. 1). MW method was found to dramatically increase the yields of the two major oxyprenylated xanthones (**4**, **6**), while the yields of the diprenylated by-products were not improved. Furthermore, a one-pot synthesis of dihydropyranoxanthones (**16**–**21**) from the hydroxylated xanthones (**1**–**3**) using the Montmorillonite K10 clay with different conditions was also described. A combination of MW and Montmorillonite K10 clay with solvent was found to be the method of choice to prepare dihydropyranoxanthones since it dramatically increased the yields of products as well as shortening the reaction time (Fig. 1).

2. Results and discussion

2.1. Synthesis of prenylated xanthones

Oxyprenylated xanthones are not only an emerging group of biologically interesting natural products[3] but also important building blocks for the synthesis of furano- and pyranoxanthone derivatives.[12] Consequently, we have previously described the synthesis of oxyprenylated xanthones by prenylation of xanthones **1**, **2**, and **3** with prenyl bromide and K_2CO_3 in acetone[5] (Scheme 1).

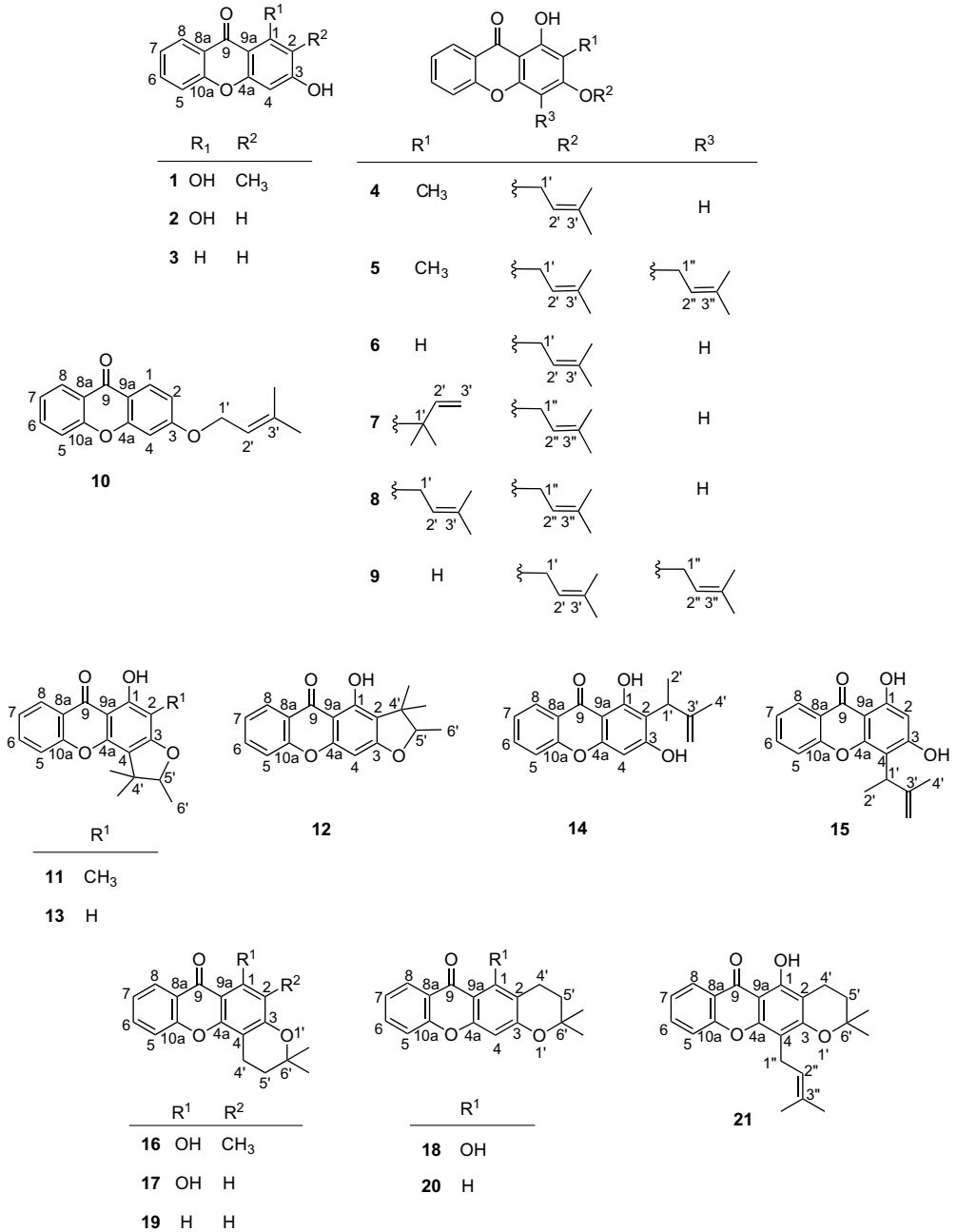
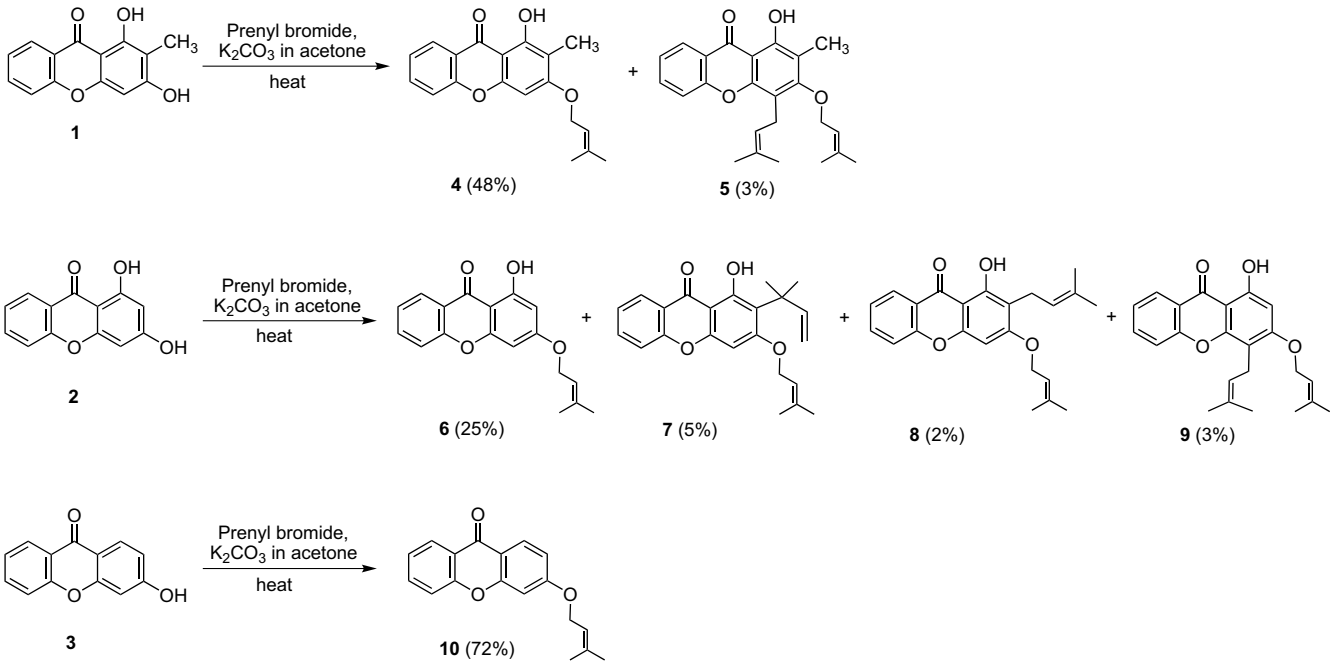


Figure 1. Structures of building blocks **1**–**3** and of prenylated derivatives **4**–**21** (the numbering used concerns the NMR assignments).



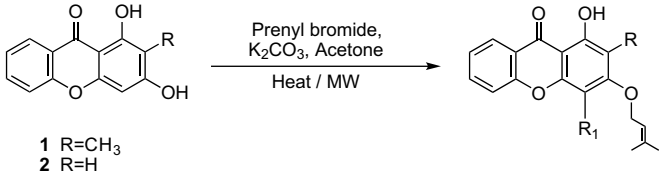
Scheme 1.

Using this method of prenylation, xanthone **1** gave the oxyprenylated xanthone **4** as a major product in 48% yield and a diprenylated by-product **5** (3%). However, xanthone **2** gave only 25% yield of the oxyprenylated xanthone **6** and three diprenylated by-products **7** (5%), **8** (2%), and **9** (3%). On the contrary, xanthone **3** gave 72% yield of the oxyprenylated xanthone **10**.

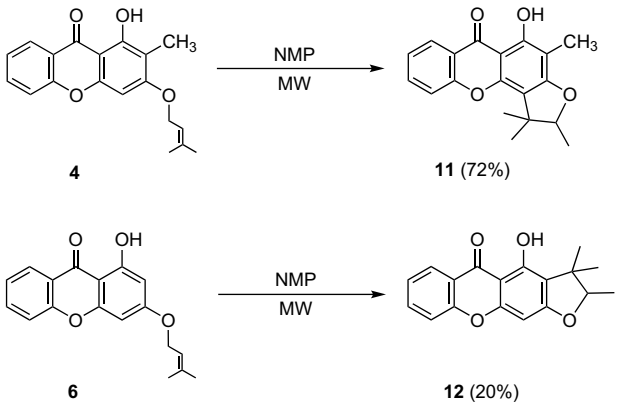
In order to improve the yields of the oxyprenylated xanthones **4** and **6**, we used the MW irradiation instead of conventional heating. With this method, the yields of oxyprenylated xanthones **4** and **6** were increased, respectively, to 83% and 53%. However, the yields of the diprenylated xanthone by-products **5**, **7**–**9** did not change significantly (Table 1). Furthermore, the reaction time was reduced from 8 h in the conventional heating to only 1 h in the MW method.

The oxyprenylated xanthones **4** and **6** were then used as precursors for the synthesis of the dihydrofuranoxanthones **11** and **12**, by MW irradiation. When *N*-methylpyrrolidone (NMP) was used as a solvent, xanthone **4** gave the angular dihydrofuranoxanthone **11** in 72% yield while xanthone **6** gave only 20% yield of the linear dihydrofuranoxanthone **12** (Scheme 2).

Table 1
Comparison of results obtained in the prenylation reaction of hydroxyxanthones **1**, **2** under MW and classical heating conditions



	Classical	MW
4 R=CH_3, R_1=H	48	83
5 R=CH_3, R_1=–CH_2–CH=$C(CH_3)_2$	3	5
6 R=H, R_1=H	25	53
7 R=–$C(CH_3)_2$–CH=CH_2, R_1=H	5	1
8 R=–CH_2–CH=$C(CH_3)_2$, R_1=H	2	1
9 R=H, R_1=–CH_2–CH=$C(CH_3)_2$	3	2



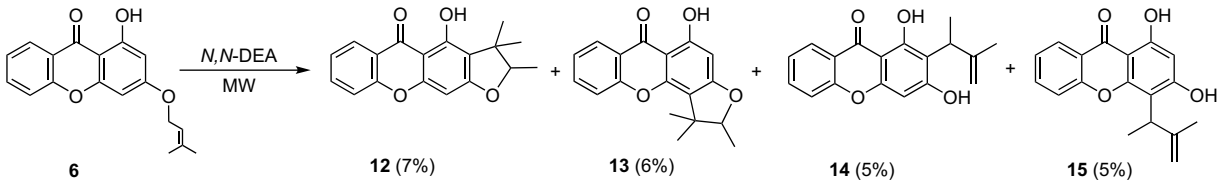
Scheme 2.

However, when the reaction was performed in *N*,*N*-diethylaniline (*N*,*N*-DEA), both linear (**12**) and angular (**13**) dihydrofuranoxanthones were obtained, from the oxyprenylated xanthone **6**, together with the two new rearranged products **14** and **15** (Scheme 3).

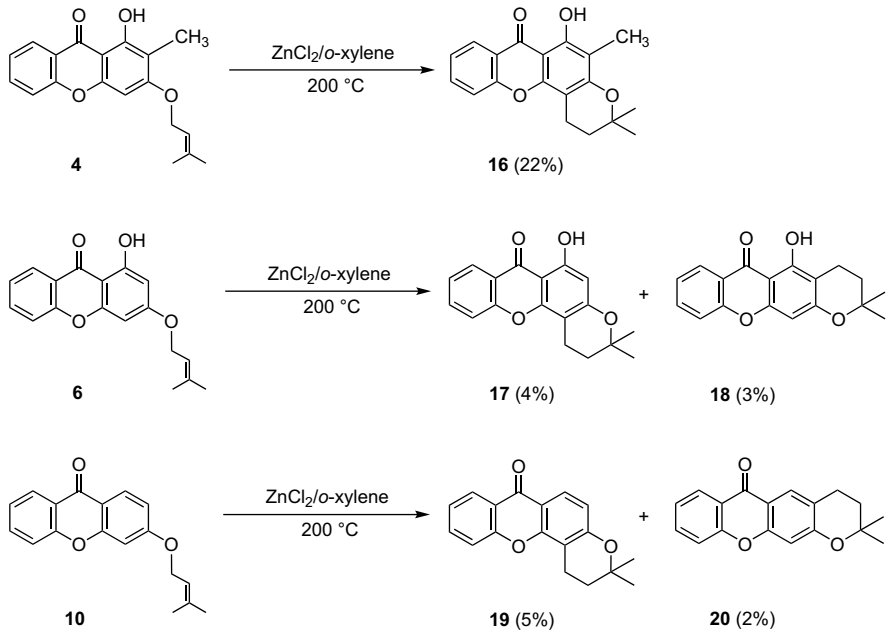
The dihydrofuranoxanthones **12** (17.5%) and **13** (8.8%) have been previously prepared by heating xanthone **6** in vacuum at 200 °C for 2 h.[12]

Recently, we have also used the oxyprenylated xanthones **4** and **6** as precursors for the synthesis of dihydropyranoxanthones. By heating these xanthones with $ZnCl_2$ in *o*-xylene at 200 °C for 21 h, xanthone **4** gave the angular dihydropyranoxanthone **16** in 22% yield, while xanthone **6** furnished both angular and linear dihydropyranoxanthones **17** and **18** in low yields.[5] By using the same reaction conditions, we have obtained dihydropyranoxanthones **19** and **20** from xanthone **10**, also in very low yields (Scheme 4).[13]

In order to improve the yields, we have designed a one-pot synthesis of these dihydropyranoxanthones by using Montmorillonite K10 clay to catalyze direct condensation of the xanthones **1**, **2**, and **3**, with prenyl bromide (Scheme 5) in different conditions, either at room temperature (Method A) or at 100 °C under conventional thermal heating (Method B) or with MW irradiation (Method C). As



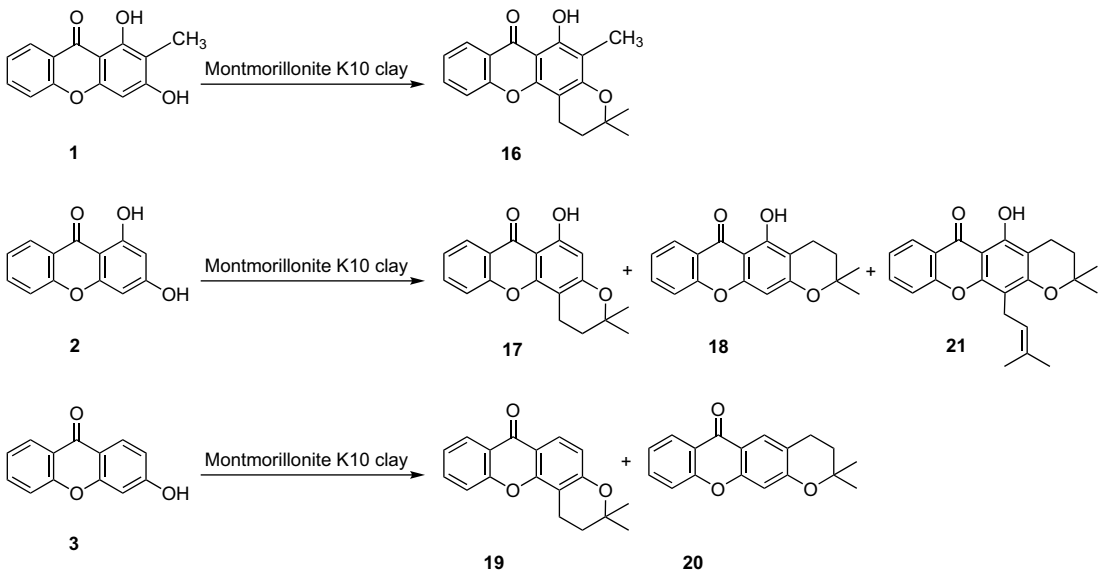
Scheme 3.



Scheme 4.

expected, xanthone **1** gave only the angular dihydropyranoxanthone **16**, while xanthone **3** gave dihydropyranoxanthones **19** and **20**. However, xanthone **2** gave, besides dihydropyranoxanthones **17** and **18**, the prenylated dihydropyranoxanthone **21**.

The yields of these dihydropyranoxanthones obtained by using Montmorillonite K10 clay in different conditions and those obtained by a classical synthesis through oxyprenylated xanthones intermediates are found in Table 2.



Scheme 5.

It can be observed from Table 2 that, the yield of the dihydropyranoxanthone **16** was increased, when Montmorillonite K10 clay was used as catalyst in all three methods. When the reaction is performed at room temperature with the commercial Montmorillonite K10 clay, the yield was increased about five folds when compared to that obtained by classical synthesis (51% vs 10.5%). However, the disadvantage of this method is its long reaction time (5 days). The yields of xanthones **17**, **18**, and **21** were found to be slightly improved but continued to be insignificant while those of xanthones **19** and **20** were found to decrease. When the Montmorillonite K10 clay was used in combination with conventional heating at 100 °C (Method B), xanthone **16** was obtained in 63% yield with a remarkably shorter reaction time (60 min). Interestingly, the yields of xanthones **17**, **18**, and **21** were also improved significantly when compared to those obtained by classical synthesis. However, when the commercial clay was replaced by dry clay, the yield of the linear dihydrofuranoxanthone **18** was increased from 12% to 18%. MW irradiation was also used instead of conventional heating and it can be carried out with or without solvent. The advantage of MW irradiation over conventional heating is its shorter reaction time (20 min). However, when this method is performed without solvent, the yield of xanthone **16** was only 53% while the yield of the xanthones **17**, **18**, and **21** were less than 2%. Surprisingly, when the solvent was used, the yields of all xanthones were dramatically increased, being 86% for xanthone **16**. Interestingly, when dry clay was used instead of the commercial clay, the yield of xanthone **18** was increased from 14% to 20%.

2.2. Structure elucidation of prenylated xanthones

The structure of the new prenylated xanthones **11**, **14**, **15**, and **19**–**21** were established by IR, UV, HRMS, and NMR techniques. The spectroscopic data of compound **1**–**10**, **12**, **13**, **16**–**18** are in agreement with those found in the literature.[5,12,14,15] The previously unreported ^{13}C NMR of compounds **12** and **13** are also included in Table 4.

The ^{1}H and ^{13}C NMR spectra of the prenylated xanthones **11**–**15** and **19**–**21** (Tables 3 and 4, respectively) showed that all of them have retained a non-substituted aromatic ring of their xanthone precursors. Like the xanthones precursors, only the ^{1}H NMR spectra of the xanthones **11**–**15** and **21** showed a proton signal of the hydrogen bonded hydroxyl group at ca. 13 ppm (OH-1). The ^{1}H and ^{13}C NMR spectra of xanthones **11**, **12**, and **13** showed some common features: the presence of a 4′,4′,5′-trimethyldihydrofuran fused ring, which was evidenced by the two singlets of geminal methyl groups (δ_H ca. 1.3 and 1.5) on the quaternary carbon (δ_C ca. 43) and a doublet of another methyl group (δ_H 1.4, $J\sim7$ Hz) on the oxymethine carbon (δ_C ca. 90). The EIHRMS gave an accurate molecular mass of 310.1215 and a molecular formula of $C_{19}H_{18}O_4$ for xanthone **11**. As xanthone **11** was obtained by cyclization of the oxyprenylated xanthone **4**, the proton and carbon chemical shifts of the methyl group on C-2 (δ_H 2.12 s; δ_C 7.4) of xanthone **11** were similar to those of the methyl group of xanthone **4**. That the 4′,4′,5′-trimethyldihydrofuran fused ring was on C-3 and C-4 of the xanthone nucleus was supported by the correlations observed between the proton signals of the geminal methyl groups (δ_H 1.30 s and 1.58 s) and the carbon signal of C-4 (δ_C 111.8) in the HMBC spectrum (Fig. 2). In turn, the EIHRMS gave the molecular formula of $C_{18}H_{16}O_4$ for both xanthones **12** and **13**. The ^{1}H NMR spectra of these xanthones were similar to that of xanthone **11** except for the singlet of the aromatic proton at δ_H 6.35 s for xanthone **12** and at δ_H 6.33 s for xanthone **13** instead of the signal of the protons of the methyl group on C-2. The fact that xanthone **12** was a linear dihydrofuranoxanthone was substantiated by the correlations between the proton signals of the geminal methyl groups (δ_H 1.27 s and 1.51 s) and the carbon signal of C-2 (δ_C 116.8) in the HMBC spectrum. In the same way, the structure of xanthone **13** was established as an angular dihydrofuranoxanthone.

Table 2
Results obtained with different methods for synthesis of compounds **16**–**21**

Method	K10 clay	Reaction time	Final temp (°C)	Substrate	Product	Yield (%)	
						With K10 clay	Conventional heating[a]
A: K10 clay	Commercial	5 days	rt	**1**	**16**	51	10.5
				2	**17**	3	1
					18	9	0.5
					21	<2	—
				3	**19**	<2	3.6
					20	<2	1.4
B: K10 clay with conventional heating	Commercial	60 min	100	**1**	**16**	63	10.5
				2	**17**	7	1
					18	12	0.5
					21	6	—
	Dry	60 min	100	**1**	**16**	63	10.5
				2	**17**	8	1
					18	18	0.5
					21	7	—
C: K10 clay with MW (without solvent)	Commercial	20 min	110	**1**	**16**	53	10.5
			150	**2**	**17**	<2	1
					18	<2	0.5
					21	<2	—
			132	**3**	**19**	9	3.6
					20	3	1.4
C: K10 clay with MW (with solvent)	Commercial	20 min	105	**1**	**16**	86	10.5
			113	**2**	**17**	10	1
					18	14	0.5
					21	4	—
			115	**3**	**19**	25	3.6
					20	9	1.4
	Dry	20 min	110	**2**	**17**	10	1
					18	20	0.5
					21	5	—

[a] Yield of the products relative to the precursor xanthones **1**, **2**, and **3**.

Table 3
^{1}H NMR chemical shifts of prenylated xanthones **11**–**15** and **19**–**21**[a]

	11[b]	**12**[b]	**13**[c]	**14**[b]	**15**[b]	**19**[b]	**20**[b]	**21**[b]
H-1	13.36 [OH, s]	13.06 [OH, s]	13.09 [OH, s]	13.44 [OH, s]	12.89 [OH, s]	8.11 (d, *J*=8.9)	8.07 (s)	13.07 [OH, s]
H-2	—	—	6.33 (s)	—	6.30 (s)	6.83 (d, *J*=8.9)	—	—
H-3	—	—	—	7.06 [OH, br s]	7.04 [OH, br s]	—	—	—
H-4	—	6.35 (s)	—	6.38 (s)	—	—	6.82 (s)	—
H-5	7.42 (d, *J*=8.4)	7.42 (d, *J*=8.5)	7.43 (d, *J*=8.4)	7.42 (d, *J*=8.5)	7.48 (d, *J*=8.5)	7.49 (d, *J*=8.4)	7.45 (d, *J*=8.4)	7.44 (d, *J*=8.4)
H-6	7.69 (ddd, *J*=8.4, 7.1, 1.6)	7.70 (ddd, *J*=8.5, 7.2, 1.7)	7.70 (ddd, *J*=8.4, 7.0, 1.6)	7.71 (ddd, *J*=8.5, 7.1, 1.6)	7.73 (ddd, *J*=8.5, 7.1, 1.6)	7.69 (ddd, *J*=8.4, 7.0, 1.6)	7.68 (ddd, *J*=8.4, 7.0, 1.7)	7.69 (ddd, *J*=8.4, 7.1, 1.6)
H-7	7.36 (dd, *J*=8.1, 7.1)	7.37 (dd, *J*=8.0, 7.2)	7.37 (dd, *J*=8.0, 7.0)	7.37 (dd, *J*=8.0, 7.1)	7.40 (dd, *J*=8.0, 7.1)	7.37 (t, *J*=8.0, 7.0)	7.34 (t, *J*=8.0, 7.0)	7.34 (t, *J*=8.0, 7.1)
H-8	8.26 (dd, *J*=8.1, 1.6)	8.24 (dd, *J*=8.0, 1.7)	8.24 (dd, *J*=8.0, 1.6)	8.26 (dd, *J*=8.0, 1.6)	8.27 (dd, *J*=8.0, 1.6)	8.33 (dd, *J*=8.0, 1.6)	8.32 (dd, *J*=8.0, 1.7)	8.24 (dd, *J*=8.0, 1.6)
2-CH_3	2.12 (s)	—	—	—	—	—	—	—
H-1′	—	—	—	4.13 (q, *J*=7.0)	4.24 (q, *J*=6.9)	—	—	—
H-2′	—	—	—	1.43 (d, *J*=7.0)	1.49 (d, *J*=6.9)	—	—	—
3′-CH_3	—	—	—	1.79 (s)	1.79 (s)	—	—	—
H-4′	—	—	—	—	—	3.01 (t, *J*=6.8)	2.93 (t, *J*=6.8)	2.75 (t, *J*=6.9)
H-5′	4.53 (q, *J*=6.6)	4.53 (q, *J*=6.6)	3.29 (q, *J*=7.2)	5.31, 5.25 (2 s)	5.32, 5.26 (2 s)	1.92 (t, *J*=6.8)	1.89 (t, *J*=6.8)	1.86 (t, *J*=6.9)
H-6′	1.44 (d, *J*=6.6)	1.41 (d, *J*=6.6)	1.32 (d, *J*=7.2)	—	—	—	—	—
4′-CH_3	1.58, 1.30 (2 s)	1.51, 1.27 (2 s)	1.46, 1.44 (2 s)	—	—	—	—	—
6′-CH_3	—	—	—	—	—	1.41 (s)	1.40 (s)	1.39 (s)
H-1″	—	—	—	—	—	—	—	3.48 (d, *J*=7.4)
H-2″	—	—	—	—	—	—	—	5.24 (t, *J*=7.4)
3″-CH_3	—	—	—	—	—	—	—	1.67 (s)

[a] Values in parts per million (δ_H).
[b] Measured in $CDCl_3$ at 300.13 MHz.
[c] Measured in $CDCl_3$ at 500.13 MHz. *J* values (Hz) are shown in parenthesis. Assignments were confirmed by HSQC and HMBC experiments.

Table 4
^{13}C NMR chemical shifts of prenylated xanthones **11**–**15** and **19**–**21**[a]

	11[b]	**12**[b]	**13**[c]	**14**[b]	**15**[b]	**19**[b]	**20**[b]	**21**[b]
C-1	161.4	158.7	158.1	160.8	161.9	125.4	126.6	158.4
C-2	102.9	116.8	89.6	111.3	99.5	114.9	119.0	103.7
C-3	164.9	166.2	166.0	163.6	163.3	159.6	160.4	159.3
C-4	111.8	89.5	113.3	95.0	107.2	114.8	104.1	167.1
C-5	117.3	117.5	117.5	117.5	117.5	117.6	117.7	117.5
C-6	134.5	134.6	134.6	134.9	134.9	134.0	134.1	134.6
C-7	123.7	123.8	123.8	123.8	124.1	123.8	123.5	123.4
C-8	126.0	125.7	125.7	125.8	125.9	126.6	127.5	125.8
C-9	180.6	181.0	180.9	180.9	181.1	176.6	176.5	181.1
2-CH_3	7.4	—	—	—	—	—	—	—
C-4a	150.8	157.9	158.8	156.2	154.6	155.4	156.2	152.4
C-10a	155.6	155.9	155.9	156.0	155.9	156.1	156.3	156.1
C-8a	120.7	120.5	120.5	120.5	120.4	121.9	121.8	120.4
C-9a	103.6	103.0	104.1	103.5	104.0	108.6	115.2	102.6
C-1′	—	—	—	34.6	35.2	—	—	—
C-2′	—	—	—	16.7	17.2	—	—	—
C-3′	—	—	—	150.9	150.0	—	—	—
C-4′	44.0	43.3	92.6	—	—	16.8	15.3	16.4
3′-CH_3	—	—	—	22.7	22.7	—	—	—
C-5′	90.4	91.1	42.9	112.2	112.3	31.6	30.9	31.6
C-6′	14.3	14.3	14.2	—	—	75.7	76.2	76.2
4′-CH_3	25.9, 21.5	25.1, 20.6	28.5, 22.3	—	—	—	—	—
6′-CH_3	—	—	—	—	—	26.7	27.0	26.9
C-1″	—	—	—	—	—	—	—	21.6
C-2″	—	—	—	—	—	—	—	122.4
C-3″	—	—	—	—	—	—	—	131.2
3″-CH_3	—	—	—	—	—	—	—	25.8

[a] Values in parts per million (δ_C).
[b] Measured in $CDCl_3$ at 75.47 MHz.
[c] Measured in $CDCl_3$ at 125.77 MHz. Assignments were confirmed by HSQC and HMBC experiments.

On the other hand, the new prenylated xanthones **14** and **15** did not show characteristic proton and carbon signals of the 4′,4′,5′-trimethyldihydrofuran fused ring in their ^{1}H and ^{13}C NMR spectra. Besides the singlets of the aromatic protons at δ_H 6.38 s and 6.30 s, respectively, for xanthone **14** and xanthone **15**, the ^{1}H and ^{13}C NMR spectra showed the presence of the 3-methylbut-3-en-2-yl side chain as was evidenced by the signals of two vinyl protons at ca. δ_H 5.3 s, one allylic methyl group (δ_H 1.79 s; δ_C 22.7), one allylic methine proton (δ_H 4.13 q; δ_C 34.6 and δ_H 4.24 q; δ_C 35.2), and another methyl group (δ_H 1.43 d; δ_C 16.7 and δ_H 1.49 d; δ_C 17.2) on the methine carbon. That the prenyl side chain is on C-2 for the xanthone **14** was supported by the correlation between the methine proton of the side chain at δ_H 4.13 q (*J*=7.0 Hz) and the carbon signal at δ_C 160.8 (C-1) as well as between the signal of the methyl proton at δ_H 1.43 d (*J*=7.0 Hz) and the carbon signal at δ_C111.3 (C-2) in the HMBC spectrum. On the contrary, the signal of the methine proton of the side chain at δ_H 4.24 q (*J*=6.9 Hz) was correlated with the carbon signal at δ_C 154.6 (C-4a) in xanthone **15**, confirming that the prenyl side chain is on C-4.

Finally, the existence of a 6′,6′-dimethyldihydropyran fused ring in the prenylated xanthones **19**–**21** was based on an observation of the two geminal methyl groups (δ_H ca. 1.40 s, δ_C ca. 27) and the two methylene groups (δ_H ca. 1.9 and 2.9; δ_C ca. 16 and 30) as well as an oxygen bearing quaternary carbon (δ_C ca. 76) in the ^{1}H and ^{13}C NMR spectra. The EIHRMS gave a molecular formula $C_{18}H_{16}O_3$ for both xanthones **19** and **20**. However, the 6′,6′-dimethyldihydropyran fused ring on C-3 and C-4 in xanthone **19** was substantiated by the presence of the *ortho* coupled aromatic protons at δ_H 8.11 d (*J*=8.9 Hz, H-1) and 6.83 d (*J*=8.9 Hz, H-2), respectively. Furthermore, the HMBC spectrum showed a correlation between the proton signal of H-4′ (δ_H 3.0 t, *J*=6.8 Hz) and the carbon signal of C-4a (δ_C 155.4). Instead, the ^{1}H NMR spectra of xanthone **20** showed two singlets of H-1 (δ_H 8.07) and H-4 (δ_H 6.82) and thus the 6′,6′-dimethyldihydropyran fused ring must be on C-2 and C-3. This was confirmed by a correlation between the proton signal of H-4′ (δ_H

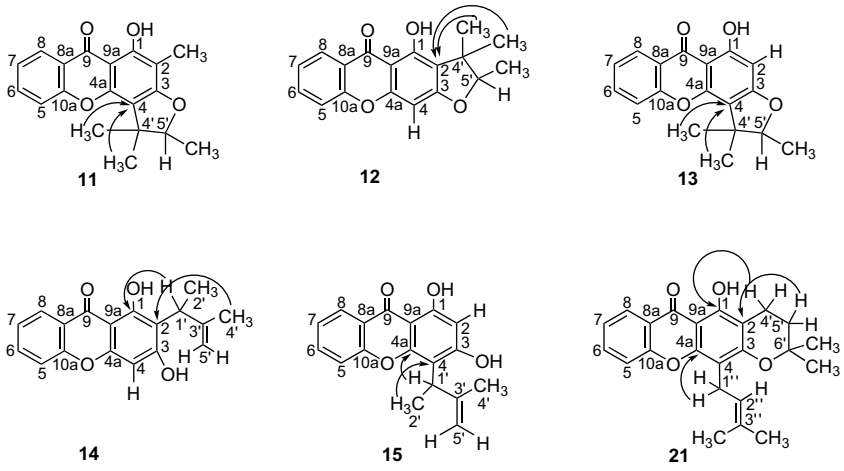


Figure 2. Main connectivities found in the HMBC of prenylated xanthones **11**–**15** and **21**.

2.93 t, J=6.8 Hz) and the carbon signal at δ_C 126.6 (C-1) in the HMBC spectrum. The molecular formula $C_{23}H_{24}O_4$ (accurate mass 364.1675), obtained from EIHRMS, for the new xanthone **21** indicated the existence of two prenyl substituents. That the 6′,6-dimethyldihydropyran fused ring was on C-2 and C-3, like in xanthone **20**, was supported by the correlations between the proton signal of H-4′ (δ_H 2.75 t, J=6.9 Hz) and the carbon signal at δ_C 158.4 (C-1) as well as between the proton signal at δ_H1.89 t (H-5′) and the carbon at δ_C103.7 (C-2) in the HMBC spectra. Thus, another prenyl side chain must be on C-4. The nature of the prenyl side chain on C-4 was established as 3-methylbut-2-enyl by the characteristic proton and carbon chemical shifts from the ^{1}H and ^{13}C NMR spectra (Tables 3 and 4, respectively). The HMBC spectrum showed that the signal of the methylene protons at δ_H 3.48 (H-1″) gave cross peaks with both carbon signals at δ_C 152.4 (C-4a) and δ_C 159.3 (C-3).

3. Conclusions

Microwave-assisted organic synthesis (MAOS) was successfully applied in the synthesis of oxyprenylated xanthones (**4** and **6**) from the hydroxyxanthone precursors (**1** and **2**) with the two folds increase of yields and remarkable shorter reaction times, when compared to the conventional heating conditions. Besides, the yields of diprenylated by-products did not suffer a significant alteration. Furthermore, we have applied the MW irradiation methodology to prepare dihydrofuranoxanthone derivatives from the oxyprenylated xanthones precursors (**4** and **6**). When NMP was used as a solvent, the oxyprenylated xanthone **4** furnished the angular dihydrofuranoxanthone **11** with a very good yield (72%) while the oxyprenylated xanthone **6** gave the linear dihydrofuranoxanthone **12**, but with slightly higher yield than the previously described in the classical method. However, when the reaction was performed in *N*,*N*-DEA, the oxyprenylated xanthone **6** gave both linear (**12**) and angular (**13**) dihydrofuranoxanthones, together with the previously unreported prenylated derivatives **14** and **15**, all in low yield. On the other hand, a combination of a MW irradiation with the Montmorillonite K10 clay was used in the one-pot synthesis of dihydropyranoxanthone derivatives directly from the hydroxyxanthone precursors without prior preparation of the oxyprenylated xanthone intermediates. One of the advantages of this methodology is the possibility to vary the conditions such as the type of clay, the absence or presence of solvent and the temperature. Besides being environmentally friendly, this methodology has proved to give a much higher yield (five to eight folds) of the angular dihydropyranoxanthone **16** from the hydroxyxanthone precursor **1**, when compared to the classical method in which zinc chloride and high temperature heating are used. As this is the first report on the application of the combined MW irradiation and Montmorillonite K10 clay for the synthesis of prenylated xanthones, it can open a new avenue for the environmentally friendly method to obtain other classes of bioactive compounds.

4. Experimental part

4.1. General methods

Purifications of compounds were performed by flash chromatography using Merck silica gel 60 (0.040–0.063 mm) and preparative thin layer chromatography (TLC) using Merck silica gel 60 (GF_{254}) plates. Reactions were monitored by TLC. MW reactions were performed using glassware setup for atmospheric-pressure reactions and also 12 mL and/or 50 mL closed glass reactors (internal reaction temperature measurement with a fiber-optic probe sensor) and were carried out using an Ethos MicroSYNTH 1600 Microwave Labstation from Milestone. Melting points were obtained in a Köfler microscope and are uncorrected. IR spectra were measured on an ATI Mattson Genesis series FTIR (software: WinFirst v. 2.10) spectrophotometer in KBr microplates (cm^{-1}). UV spectra were taken in ethanol[16] and were recorded on a Varian CARY 100 spectrophotometer: λ_{max} in nm (software: Cary Win UV v. 3.0). ^{1}H and ^{13}C NMR spectra were taken in $CDCl_3$ at room temperature, on Bruker Avance 300 and 500 instruments. Chemical shifts are expressed in δ (ppm) values relative to tetramethylsilane (TMS) as an internal reference. ^{1}H NMR spectra were measured at 300.13 MHz and/or 500.13 MHz and assignment abbreviations are the following: singlet (s), doublet (d), triplet (t), quartet (q), multiplet (m), doublet of doublets (dd), and double doublet of doublets (ddd). ^{13}C NMR spectra were measured at 75.47 MHz and/or 125.77 MHz. ^{13}C NMR assignments were made by 2D HSQC and HMBC experiments (long-range C, H coupling constants were optimized to 7 and 1 Hz). HRMS spectra were recorded as EI (electronic impact) mode on a VG Autospec M spectrometer (m/z) at CACTI—University of Vigo. Prenyl bromide 95% and Montmorillonite K10 clay were purchased from Sigma Aldrich.

4.2. General procedure for the synthesis of prenylated xanthones 4–9 under MW irradiation

A mixture of xanthones **1** or **2** (2.00 mmol), prenyl bromide (4.00 mmol), K_2CO_3 (4.20 mmol) in acetone (90 mL), in a two-necked glassware apparatus, provided with magnetic stirring bar, fiber-optic temperature control, and reflux condenser, was heated

for 3×20 min according to the following microwave program: Power: 200 W; temperature: 62 °C; ramp time: 5 min; hold time: 15 min; final temperature 59 °C. After cooling, the solid was filtered and the solvent removed under reduced pressure and afforded the crude product that was purified by flash chromatography (SiO_2; hexane/EtOAc 99:1 or CH_2Cl_2/petroleum ether/Et_2O 1:96:3). The isolation of the components of the mixture was then carried out by preparative TLC (SiO_2; hexane/EtOAc 9:1 or CH_2Cl_2/petroleum ether/Et_2O 5:90:5 and hexane/EtOAc 8:2). Prenylated xanthones **4**, **5** were crystallized from EtOH and prenylated xanthones **6**–**9** were crystallized from CH_2Cl_2/petroleum ether (60–80). Compounds **4**–**9** were shown to possess spectroscopic and analytical data according to those previously reported.[5] Compounds (yields): **4** (83%), **5** (5%), **6** (53%), **7** (1%), **8** (1%), **9** (2%).

4.3. General procedure for Claisen rearrangement of monoprenylated xanthones 4 and 6 in NMP under MW irradiation

A solution of monoprenylated xanthones **4** or **6** (0.35 mmol), in NMP (15 mL), was transferred to a two-necked glassware apparatus, provided with magnetic stirring bar, fiber-optic temperature control, and reflux condenser and heated for 2×30 min according to the following microwave program: step 1: 5 min, ramp to 202 °C, 800 W maximum power; step 2: 25 min, hold at 202 °C, 300 W maximum power. After completion of the reaction, the mixture was poured onto crushed ice, acidified (5 N HCl) and extracted successively with Et_2O and CH_2Cl_2. The organic layers were washed with water and dried. The crude products were purified by preparative TLC (SiO_2; hexane/EtOAc 25:1 or 95:5). Compounds **11** and **12** were crystallized from CH_2Cl_2/petroleum ether (60–80) and were identified by their spectroscopic and analytical data.

*4.3.1. 5-Hydroxy-1,1,2,4-tetramethyl-1,2-dihydrofuro[2,3-c]-xanthen-6-one (**11**)*

Yield 72%; yellow solid; mp 194–196 °C (CH_2Cl_2/petroleum ether); UV (EtOH) λ_{max} (ε): 316, 259, 237, 214 (15,367, 20,445, 31,634, 27,394); (EtOH+NaOH): 404, 295, 281, 220 (5522, 16,463, 16,163, 37,818); (EtOH+$AlCl_3$): 330, 264, 236, 221 (20,248, 25,502, 36,680, 37,839); IR (KBr) ν_{max}: 2959, 2918, 2898, 2865, 1643, 1620, 1594, 1475, 1432, 1311, 1221, 1142, 1101, 762 cm^{-1}; ^1H NMR data, see Table 3; ^{13}C NMR data, see Table 4; EIMS *m*/*z* (%): 310 (13, $M^{+\bullet}$), 295 (100), 280 (20), 267 (17); EIHRMS *m*/*z*: calcd for $C_{19}H_{18}O_4$: 310.1205, found: 310.1215.

*4.3.2. 4-Hydroxy-2,3,3-trimethyl-2,3-dihydrofuro[3,2-b]xanthen-5-one (**12**)*

Yield 20%; yellow solid; mp 151–154 °C (CH_2Cl_2/petroleum ether); UV (EtOH) λ_{max} (ε): 313, 240, 222 (7933, 15,185, 12,215); (EtOH+NaOH): 390, 276, 217 (2267, 7881, 25,607); (EtOH+$AlCl_3$): 314, 240, 222 (9274, 17,822, 16,230); IR (KBr) ν_{max}: 3430, 2966, 2922, 2885, 1655, 1611, 1569, 1474, 1447, 1305, 1145, 821, 749 cm^{-1}; ^1H NMR data, see Table 3; ^{13}C NMR data, see Table 4; EIMS *m*/*z* (%): 296 (32, $M^{+\cdot}$), 281 (100), 266 (9), 253 (7), 88 (42); EIHRMS *m*/*z*: calcd for $C_{18}H_{16}O_4$: 296.1049, found: 296.1049.

4.4. General procedure for Claisen rearrangement of monoprenylated xanthone 6 in *N*,*N*-DEA under MW irradiation

A solution of the monoprenylated xanthone **6** (100 mg; 0.34 mmol), in *N*,*N*-DEA (4 mL), under nitrogen atmosphere, was irradiated for 3×15 min at 750 W and 225 °C. After completion of the reaction, the reaction mixture was diluted with water, acidified (5 N HCl), and extracted successively with petroleum ether, Et_2O, and CH_2Cl_2. The organic layers were washed with water and dried. The crude product was purified by flash chromatography (SiO_2; hexane/EtOAc 95:5) and by preparative TLC (SiO_2; petroleum ether/Et_2O 95:5). Compounds **12**–**15** were identified by their spectroscopic and analytical data. Compound (yield): **12** (7%) was characterized as described above.

*4.4.1. 5-Hydroxy-1,1,2-trimethyl-1,2-dihydrofuro[2,3-c]xanthen-6-one (**13**)*

Yield 6%; yellow solid; mp 89–91 °C (CH_2Cl_2/petroleum ether); UV (EtOH) λ_{max} (ε): 313, 240, 223 (5763, 11,407, 9807); (EtOH+NaOH): 385, 274, 216 (1585, 6356, 45,659); (EtOH+$AlCl_3$): 329, 240, 223 (5437, 8785, 11,230); IR (KBr) ν_{max}: 3422, 2961, 2921, 2855, 1658, 1611, 1455, 1315, 1155, 1104, 832, 746 cm^{-1}; ^1H NMR data, see Table 3; ^{13}C NMR data, see Table 4; EIMS *m*/*z* (%): 296 (46, $M^{+\bullet}$), 281 (100), 253 (12), 237 (8), 84 (7); EIHRMS *m*/*z*: calcd for $C_{18}H_{16}O_4$: 296.1049, found: 296.1049.

*4.4.2. 1,3-Dihydroxy-2-(3-methylbut-3-en-2-yl)-9H-xanthen-9-one (**14**)*

Yield 5%; yellow solid; mp 192–195 °C (acetone); UV (EtOH) λ_{max} (ε): 312, 238, 217 (4756, 9985, 7985); (EtOH+NaOH): 373, 276, 215 (5526, 5437, 45,926); (EtOH+$AlCl_3$): 323, 238, 221 (4178, 8578, 9052); IR (KBr) ν_{max}: 3435, 2963, 2921, 1644, 1609, 1444, 1316, 1257, 1143, 1073, 749 cm^{-1}; ^1H NMR data, see Table 3; ^{13}C NMR data, see Table 4; EIMS *m*/*z* (%): 296 (17, $M^{+\bullet}$), 281 (100), 253 (13), 97 (15), 83 (18), 69 (29); EIHRMS *m*/*z*: calcd for $C_{18}H_{16}O_4$: 296.1049, found: 296.1046.

*4.4.3. 1,3-Dihydroxy-4-(3-methylbut-3-en-2-yl)-9H-xanthen-9-one (**15**)*

Yield 5%; yellow solid; mp 193 °C (decomp.); UV (EtOH) λ_{max} (ε): 312, 259, 236, 213 (13,234, 22,997, 30,178, 24,510); (EtOH+NaOH): 368, 285, 215 (12,582, 19,763, 94,896); (EtOH+$AlCl_3$): 416, 332, 274, 219 (4184, 16,409, 22,315, 30,772); IR (KBr) ν_{max}: 3401, 2960, 2922, 2853, 1646, 1607, 1422, 1222, 1143, 755 cm^{-1}; ^1H NMR data, see Table 3; ^{13}C NMR data, see Table 4; EIMS *m*/*z* (%): 296 (52, $M^{+\bullet}$), 281 (100), 253 (34), 225 (17), 213 (21), 149 (32), 69 (22); EIHRMS *m*/*z*: calcd for $C_{18}H_{16}O_4$: 296.1049; found: 296.1051.

4.5. General procedure for the synthesis of dihydropyranoxanthones 16–21 with Montmorillonite K10 clay

A slurry of the K10 clay (20 equiv by weight) in $CHCl_3$ (ca. 50 mL) was treated with the xanthones **1**, **2** or **3** (0.50 mmol), followed by the addition of prenyl bromide (1 mmol). The mixture was maintained under stirring at room temperature for 5 days. The reaction mixture was filtered under vacuum, washed with CH_2Cl_2, Me_2CO, and MeOH and the filtrate concentrated under vacuum. The recovered clay was reactivated by washing with MeOH. The crude product was purified by flash chromatography (SiO_2; petroleum ether/EtOAc) and by preparative TLC (SiO_2; petroleum ether/EtOAc or CH_2Cl_2). The products were identified by their spectroscopic and analytical data. Compounds (yields): **16**[5] (51%), **17**[5] (3%), **18**[5] (9%).

*4.5.1. 3,3-Dimethyl-2,3-dihydropyrano[2,3-c]xanthen-7(1H)-one (**19**)*

Yield <2%; white solid; mp 158–160 °C (Me_2CO); IR (KBr) ν_{max}: 2962, 2924, 2854, 1648, 1611, 1463, 1431, 1345, 1265, 1228, 1159, 1114, 1061, 748 cm^{-1}; ^1H NMR data, see Table 3; ^{13}C NMR data, see Table 4; EIMS *m*/*z* (%): 280 (31, $M^{+\bullet}$), 265 (11), 225 (100); EIHRMS *m*/*z*: calcd for $C_{18}H_{16}O_3$: 280.1100, found: 280.1111.

*4.5.2. 2,2-Dimethyl-3,4-dihydropyrano[3,2-b]xanthen-6(2H)-one (**20**)*

Yield <2%; white solid; mp 135–138 °C (Me_2CO); IR (KBr) ν_{max}: 2964, 2921, 2852, 1655, 1615, 1460, 1311, 1272, 1154, 1115, 755 cm^{-1};

^{1}H NMR data, see Table 3; ^{13}C NMR data, see Table 4; EIMS *m*/*z* (%): 280 (32, $M^{+\bullet}$), 265 (19), 225 (100); EIHRMS *m*/*z*: calcd for $C_{18}H_{16}O_3$: 280.1100, found: 280.1103.

*4.5.3. 5-Hydroxy-2,2-dimethyl-12-(3-methylbut-2-enyl)-3,4-dihydropyrano[3,2-b]xanthen-6(2H)-one (**21**)*

Yield <2% as a yellow solid; mp 96–99 °C (Me_2CO); UV (EtOH) λ_{max} (ε): 317, 261, 237, 217 (11,403, 17,541, 23,333, 23,716); (EtOH+NaOH): 410, 280, 214 (3479, 13,534, 60,000); (EtOH+$AlCl_3$): 332, 265, 222 (10,674, 14,572, 24,681); IR (KBr) ν_{max}: 3441, 2967, 2920, 2855, 1646, 1611, 1580, 1473, 1434, 1224, 1159, 1109, 1037, 748 cm^{-1}; ^{1}H NMR data, see Table 3; ^{13}C NMR data, see Table 4; EIMS *m*/*z* (%): 364 (25, $M^{+\bullet}$), 309 (21), 293 (49), 265 (29), 253 (100); EIHRMS *m*/*z*: calcd for $C_{23}H_{24}O_4$: 364.1675, found: 364.1675.

4.6. General procedure for the synthesis of dihydropyranoxanthones 16–18 and 21 with Montmorillonite K10 clay and conventional heating

A slurry of the K10 clay (20 equiv by weight) in $CHCl_3$ (ca. 20 mL) was treated with the xanthones **1** or **2** (0.40 mmol), followed by the addition of prenyl bromide (0.80 mmol), in a sealed tube. The mixture was maintained under stirring at 100 °C in an oil bath for 60 min. The reaction mixture was filtered under vacuum, washed with CH_2Cl_2, Me_2CO, and MeOH, and the filtrate concentrated under vacuum. The recovered clay was reactivated by washing with MeOH. The crude product was purified by column chromatography (SiO_2; hexane/EtOAc) and by preparative TLC (SiO_2; hexane/EtOAc). The products were identified by their spectroscopic and analytical data. Compounds (yields): **16**[5] (63%), **17**[5] (7%), **18**[5] (12%). Compound (yield): **21** (6%) was characterized as described above.

4.7. General procedure for the synthesis of dihydropyranoxanthones 16–18 and 21 with dry Montmorillonite K10 clay and conventional heating

Montmorillonite K10 clay (2 g) was measured into a vial and heated in an oven at approximately 110 °C for 2 h. The activated clay was transferred to a desiccator and allowed to cool to room temperature. To the clay was added $CHCl_3$ (ca. 20 mL), xanthones **1** or **2** (0.40 mmol), followed by the addition of prenyl bromide (0.80 mmol), in a sealed tube. The mixture was maintained under stirring at 100 °C in an oil bath for 60 min. The reaction mixture was filtered under vacuum, washed with CH_2Cl_2, Me_2CO, and MeOH, and the filtrate concentrated under vacuum. The recovered clay was reactivated by washing with MeOH. The crude product was purified by column chromatography (SiO_2; hexane/EtOAc) and by preparative TLC (SiO_2; hexane/EtOAc). The products were identified by their spectroscopic and analytical data. Compounds (yields): **16**[5] (63%), **17**[5] (8%), **18**[5] (18%). Compound (yield): **21** (7%) was characterized as described above.

4.8. General procedure for the synthesis of dihydropyranoxanthones 16–21 with Montmorillonite K10 clay and MW irradiation without solvent

Xanthones **1**, **2** or **3** (0.140 mmol) were mixed and grounded with K10 clay (20 equiv by weight) in a mortar. The mixture was transferred to a 12 mL closed microwave reactor and prenyl bromide (1.15 mmol) was added. The mixture under stirring was irradiated at 150 W for 20 min and final temperatures range were 110–150 °C. The reaction mixture was filtered under vacuum, washed with CH_2Cl_2, Me_2CO, and MeOH, and the filtrate concentrated under vacuum. The recovered clay was reactivated by washing with MeOH. The crude product was purified by flash chromatography (SiO_2; petroleum ether/EtOAc) and by preparative TLC (SiO_2; petroleum ether/EtOAc or CH_2Cl_2). The products were identified by their spectroscopic and analytical data. Compounds (yields): **16**[5] (53%), **17**[5] (<2%), **18**[5] (<2%). Compounds (yields): **19** (9%), **20** (3%), **21** (<2%) were characterized as described above.

4.9. General procedure for the synthesis of dihydropyranoxanthones 16–21 with commercial Montmorillonite K10 clay and MW irradiation with solvent

A slurry of the K10 clay (20 equiv by weight) in $CHCl_3$ (ca. 8 mL) was treated with the xanthones **1**, **2** or **3** (0.140 mmol), followed by the addition of prenyl bromide (1.15 mmol), in a 12 mL closed microwave reactor. The mixture under stirring was irradiated at 150 W for 20 min and final temperatures range were 105–115 °C. The reaction mixture was filtered under vacuum, washed with CH_2Cl_2, Me_2CO, and MeOH, and the filtrate concentrated under vacuum. The recovered clay was reactivated by washing with MeOH. The crude product was purified by flash chromatography (SiO_2; petroleum ether/EtOAc) and by preparative TLC (SiO_2; petroleum ether/EtOAc or CH_2Cl_2). The products were identified by their spectroscopic and analytical data. Compounds (yields): **16**[5] (86%), **17**[5] (10%), **18**[5] (14%). Compounds (yields): **19** (25%), **20** (9%), **21** (4%) were characterized as described above.

4.10. General procedure for the synthesis of dihydropyranoxanthones 17, 18, and 21 with dry Montmorillonite K10 clay and MW irradiation with solvent

Montmorillonite K10 clay (2 g) was measured into a vial and heated in an oven at approximately 110 °C for 2 h. The activated clay was transferred to a desiccator and allowed to cool to room temperature. To the clay was added $CHCl_3$ (ca. 11 mL), xanthone **2** (0.43 mmol), followed by the addition of prenyl bromide (0.86 mmol), in a 50 mL closed microwave reactor. The mixture under stirring was irradiated at 250 W for 20 min and the final temperature was 110 °C. The reaction mixture was filtered under vacuum, washed with CH_2Cl_2, Me_2CO, and MeOH, and the filtrate concentrated under vacuum. The recovered clay was reactivated by washing with MeOH. The crude product was purified by flash chromatography (SiO_2; petroleum ether/EtOAc) and by preparative TLC (SiO_2; petroleum ether/EtOAc). The products were identified by their spectroscopic and analytical data. Compounds (yields): **17**[5] (10%), **18**[5] (20%). Compound (yield): **21** (5%) was characterized as described above.

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