Tetrahedron 64 (2008) 8938–8942

Contents lists available at ScienceDirect

Tetrahedron

journal homepage: www.elsevier.com/locate/tet

An efficient synthesis of embelin derivatives through domino Knoevenagel hetero Diels–Alder reactions under microwave irradiation

Sandra Jiménez-Alonso [a,b], Haydee Chávez [a,c], Ana Estévez-Braun [a,b,*], Ángel G. Ravelo [a,b,*], Gabriela Feresin [d], Alejandro Tapia [d]

[a] Instituto Universitario de Bio-Orgánica 'Antonio González', Universidad de La Laguna, Avda. Astrofísico Francisco Sánchez No 2, 38206, La Laguna, Tenerife, Spain
[b] Hospital Universitario de La Candelaria, 38010, Tenerife, Spain
[c] Facultad de Farmacia y Bioquímica, Universidad San Luis Gonzaga de Ica, Peru
[d] Instituto de Biotecnología-Instituto de Ciencias Básicas, Universidad Nacional de San Juan. Av. Libertador General San Martín 1109, CP 5400, San Juan, Argentina

ARTICLE INFO

Article history:
Received 15 April 2008
Received in revised form 13 June 2008
Accepted 16 June 2008
Available online 20 June 2008

Keywords:
Quinones
Multicomponent reactions
Knoevenagel heteroDiels–Alderreactions
MW irradiation

ABSTRACT

The synthesis of novel pyrano embelin derivatives has been achieved through domino Knoevenagel hetero Diels–Alder reactions of embelin (**1**) with paraformaldehyde and electron rich alkenes. This synthetic approach is highly efficient when microwave irradiation is used.

© 2008 Published by Elsevier Ltd.

1. Introduction

Quinonic compounds are ubiquitous in nature. They are implicated in numerous cellular functions and are involved in mechanisms of electron and hydrogen transfers. Quinones form a large class of antitumor agents approved for clinical use, and many other antitumor quinones are in different stages of clinical and preclinical development.[1] The efficiency of the quinonic compounds in inhibiting cancer cell growth is believed to stem from their participation in key cellular redox mechanisms with consequent generation of highly reactive oxygen species (ROS). The ROS turn out to modify and degrade nucleic acids and proteins within the cells.[2]

One of the most simple 1,4-benzoquinonic compound isolated from natural sources is embelin (**1**). Embelin (**1**) is isolated as the main secondary metabolite from species of the Myrsinaceae[3] and Oxalidaceae[4] families. Compound **1** shows a diversity of relevant biological activities such as chemopreventive effect against DENA/PB-induced hepatocarcinogenesis in Wistar rats,[5] anti-fertility effects,[6] and in vitro cytotoxic activity against B16 and XC cell lines.[7] In addition, recent studies have shown that embelin is a fairly potent, nonpeptidic, cell-permeable inhibitor of XIAP (X-linked inhibitor of apoptosis protein), and it represents a promising lead compound for designing an entirely new class of anticancer agents that target the BIR3 domain of XIAP.[8] These antecedents justify the interest in evolving newer synthetic methods for the construction of embelin derivatives.

We have recently published the preparation of several bis-pyrano-1,4-benzoquinones following a double domino Knoevenagel hetero Diels–Alder reaction.[9] We thought that embelin is a suitable substrate for a similar approach and, in one pot reaction in the presence of electron rich alkenes and paraformaldehydes, a variety of pyrano derivatives can be obtained.

2. Results and discussion

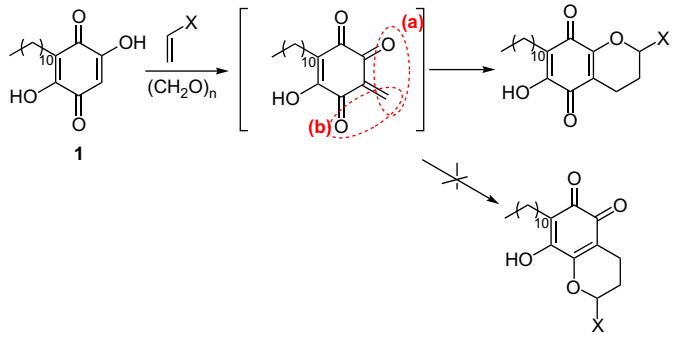
The domino Knoevenagel hetero Diels–Alder reaction (DKHDA) is a powerful weapon in organic synthesis, especially in the area of heterocycles and natural products.[10] The most widely used heterodienes are usually those where the olefinic bond is flanked between symmetrical 1,3-dicarbonyl compounds.[11] In the present work, we were interested in the mode of cycloaddition of a heterodiene obtained from unsymmetrical 2,5-dihydroxy-1,4-benzoquinone.

As it is illustrated in Scheme 1, there are two possible heterodienes from the intermediate, which will generate the corresponding

* Corresponding authors.
E-mail addresses: aestebra@ull.es (A. Estévez-Braun), agravelo@ull.es (Á.G. Ravelo).
URL: http://www.icic.es

0040-4020/$ – see front matter © 2008 Published by Elsevier Ltd.
doi:10.1016/j.tet.2008.06.057

ortho and *para*-pyranobenzoquinones. We found out that the reaction of embelin, paraformaldehyde, and alkenes is regioselective, since only 1,4-benzoquinone derivatives were obtained from the more electron-poor heterodiene (a). These reactions are inverse electron demand hetero Diels–Alder, and the dominating orbital interaction (corresponding to the lowest LUMO–HOMO energy separation) is the LUMO heterodiene–HOMO dienophile.[12]



Scheme 1.

The first reaction that we carried out was the reaction of embelin, paraformaldehyde, and ethyl vinyl ether in dioxane as solvent. After 24 h and reflux conditions, the corresponding adduct was obtained in only 8% yield. Microwave irradiation has been applied with success to cycloaddition reactions.[13] Under classical heating conditions, these reactions usually require long reaction times, high temperatures, and/or Lewis acid catalyst resulting in partial or total decomposition of sensitive compounds. These problems have been conveniently overcome by the use of microwave irradiation. The short reaction time associated with microwave activation avoids decomposition of reagents and products, and prevents polymerization of the diene or dienophiles. For all these reasons and with the aim of improving the yields, we explored the possibility of using microwaves.

First we optimized the synthesis of the pyrano-1,4-benzoquinone derivative (**3**) from embelin (**1**), paraformaldehyde (**2**), and ethyl vinyl ether as a model. Optimized results for this reaction are shown in Table 1. The reaction only works with large excess of paraformaldehyde. The ratio of reagents that produced the highest yields was 1 equiv of embelin/3 equiv of ethyl vinyl ether/8 equiv $(CH_2O)_n$. Different solvents were used, from good microwave absorbers like EtOH or MeOH to solvents more or less transparent to the microwave irradiation as toluene or dioxane. The power and temperature were also optimized for a Discover-CEM focused microwave. We also carried out the reaction without the solvent (neat media) (entry 8) but **3** was obtained in low yield. The best result was achieved with EtOH (entry 3).

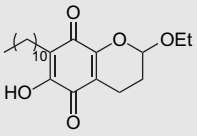
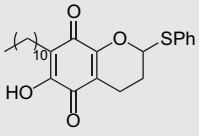
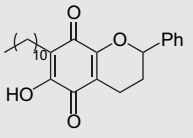
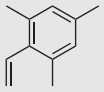
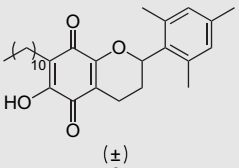
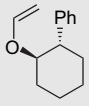
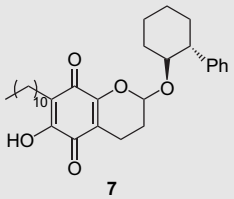
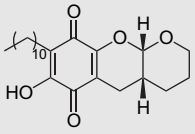
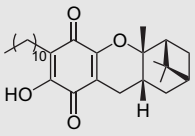
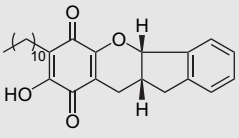
The optimized conditions described above were applied to prepare a set of dihydropyran–embelin derivatives using several dienophiles. The structures of the adducts (**3**–**10**) and the obtained yields are detailed in Table 2.

The reaction proceeds normally in good yields, and tolerates several types of electron-releasing groups in the alkene component.

Table 1
Optimized yields and conditions for compound **3**

Entry	Solvent	Power (W)	Temperature (°C)	Time (min)	Yield (%)
1	DCM	185	150	20	50
2	DCE	80	150	20	42
3	EtOH	110	150	20	99
4	Dioxane	150	150	20	8
5	Toluene	123	150	20	56
6	MeOH	90	150	20	58
7	MeCN	200	150	20	27
8	—	94	150	20	9

Table 2
Synthesized embelin adducts

Entry	Dienophile	Adduct	Yield (%)
1		 (±) **3**	100
2		 (±) **4**	89
3		 (±) **5**	81
4		 (±) **6**	83
5		 **7**	50
6		 (±) **8**	57
7		 **9**	76
8		 (±) **10**	74

In fact, the bicyclic pyrano-1,4-benzoquinones (**3**–**6**) were obtained in high yield from ethyl vinyl ether, phenyl vinyl sulfide, styrene, and 2,4,6-trimethylstyrene, respectively. The resulting adducts present substituents of different nature (oxygen, sulfur, and carbon-based substituents) at the contiguous carbon of the heterocyclic oxygen, which will allow to examine its influence in the biological activity when these compounds will be tested. A moderate yield (50%) was obtained with the

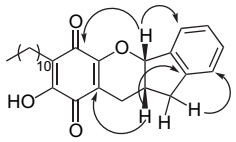


Figure 1. HMBC-key correlations for **10**.

chiral enol ether[14] (entry 5), because the corresponding adduct **7** turned out to be unstable under purification conditions. We were also interested in achieving pyrano-1,4-benzoquinones with structural complexity, since moderately complex structures are preferable lead compounds and they lead to specific binding events involving the complete ligand molecule. In this sense, tricyclic and tetracyclic adducts were obtained with cyclic alkenes such as 3,4-dihydro-2*H*-pyran (entry 6), (+)-α-pinene (entry 7), and indene (entry 8). These alkenes were selected because these motifs are present in numerous biological active compounds.[15] The structures of the synthesized compounds were rigorously characterized by NMR techniques. In particular the cis stereochemistry of the adducts **8** was determined by the coupling constant (^3J=2.1 Hz) and the corresponding cis stereochemistry of **9** was established on the basis of the NOE effect detected between the methyl group at δ 1.44 and the multiplet at δ 1.90–2.72. The cis stereochemistry of the hydrogens implied in the fused rings of **10** was also established by the value of the coupling constant (^3J=5.6 Hz), as well as by the NOE effect detected in the ROESY spectrum. The structure of **10** was also ratified on the basis of the HMBC correlations (see Fig. 1), which established the orientation of the five-membered ring, with the methylene opposite to the heterocycle oxygen.

3. Conclusions

In short, these findings clearly demonstrate that microwave irradiation provides an excellent way to induce the generation of *o*-quinonemethide intermediates from embelin (**1**) and paraformaldehyde. These reactive intermediates give regioselective hetero Diels–Alder cycloadditions in the presence of electron rich alkenes to yield pyrano-1,4-benzoquinone adducts in good yields. Biological assays of the synthesized embelin derivatives are in progress, and they will be reported elsewhere.

4. Experimental section

4.1. General procedures

All solvents and reagents were purified by Standard techniques reported[16] or used as supplied from commercial sources when appropriate. Reactions were monitored by TLC (on silica gel POLYGRAM® SIL G/UV$_{254}$ foils). Pre-coated TLC plates SIL G-100 UV$_{254}$ (Machery-Nagel) were used for preparative-TLC purification. ^{1}H NMR spectra were recorded in $CDCl_3$ or C_6D_6 at 300 and 400 MHz, using Bruker AMX300 and Bruker AMX400 instruments. For ^{1}H spectra, chemical shifts are given in parts per million (ppm) and are referenced to the residual solvent peak. The following abbreviations are used: s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; br, broad. Proton assignments and stereochemistry are supported by ^{1}H–^{1}H COSY and ROESY when necessary. Data are reported in the following manner: chemical shift (integration, multiplicity, coupling constant if appropriate). Coupling constants (J) are given in hertz (Hz) to the nearest 0.5 Hz. ^{13}C NMR spectra were recorded at 75 and 100 MHz using Bruker AMX300 and Bruker AMX400 instruments. Carbon spectra assignments are supported by DEPT-135 spectra, ^{13}C–^{1}H (HMQC) and ^{13}C–^{1}H (HMBC) correlations when necessary. Chemical shifts are quoted in parts per million and are referenced to the appropriate residual solvent peak. EIMS and EIHRMS were recorded at VG Micromass ZAB-2F. All compounds were named using ACD40 Name-Pro program, which is based on IUPAC rules. IR spectra were taken on a Bruker IFS28/55 spectrophotometer. The embelin (**1**) used in the reactions was obtained from *Oxalis erythrorhiza* following the procedure described in Ref. 4.

4.2. Microwave irradiation experiments

All microwave irradiation experiments were carried out in a Discover®-CEM monomode microwave apparatus, operating at a frequency of 2.45 GHz with continuous irradiation power from 0 to 300 W with utilization of the standard absorbance level of 300 W maximum power. The reactions were carried out in 10 mL glass tubes, sealed with aluminum/Teflon crimp tops, which can be exposed up to 250 °C and 20 bar internal pressure. Melting points were recorded using a Buchi B540 capillary apparatus and are uncorrected. Temperature was measured with an IR sensor on the outer surface of the process vial. After the irradiation period, the reaction vessel was cooled rapidly to ambient temperature by air jet cooling.

4.3. General procedure for the preparation of embelin adducts (3–10)

2,5-Dihydroxy-1,4-benzoquinone (20 mg, 0.068 mmol), 8 equiv of paraformaldehyde, and 3 equiv of the corresponding alkenes were suspended in 2 mL of EtOH in a 10 mL reaction glass containing a stirring magnet. The vial was sealed tightly with an aluminum/Teflon crimp top. After the irradiation period, the reaction vessel was cooled rapidly to ambient temperature by air jet cooling. The solvent was removed under reduced pressure then the residue was treated with a saturated solution of $Na_2S_2O_5$ and extracted with CH_2Cl_2. The combined organic extracts were washed with brine and dried over $MgSO_4$, filtered, and the solvent was removed under reduced pressure. The residue was purified by preparative-TLC chromatography.

*4.3.1. 2-Ethoxy-6-hydroxy-7-undecyl-3,4-dihydro-2H-chromene-5,8-dione (**3**)*

Following the procedure described above, 20 mg of embelin (0.068 mmol) in 2 mL of EtOH was treated with 8 equiv of paraformaldehyde (16.3 mg, 0.54 mmol) and 3 equiv of ethyl vinyl ether (0.019 mL, 0.20 mmol). The reaction mixture was irradiated for 20 min at a pre-selected temperature of 150 °C, with an irradiation power of 110 W. The crude was purified by preparative-TLC using Hex/EtOAc (4:1) to provide 25.7 mg (100%) of **3** as an amorphous yellow solid. Mp 82–84 °C. R_f (Hex/AcOEt 4:1): 0.46. ^{1}H NMR ($CDCl_3$): δ=0.86 (t, ^3J=6.4 Hz, 3H), 1.19 (t, ^3J=7.1 Hz, 3H), 1.23 (br s, 16H), 1.42 (t, ^3J=7.0 Hz, 2H), 1.78–1.82 (m, 1H), 2.00–2.04 (m, 1H), 2.38–2.48 (m, 4H), 3.70 (dq, ^2J=9.7 Hz, ^3J=7.8 Hz, 1H), 3.91 (dq, ^3J=9.1 Hz, ^3J=7.1 Hz, 1H), 5.42 (t, ^3J=2.3 Hz, 1H), 7.23 (s, 1H). ^{13}C NMR ($CDCl_3$): δ=13.2 (t), 14.0 (q), 14.9 (q), 22.4 (t), 22.6 (t), 24.9 (t), 28.0 (t), 29.2 (t), 29.3 (t), 29.52 (t), 29.55 (t), 29.58 (t), 29.6 (t), 31.8 (t), 65.0 (t), 98.8 (d), 114.6 (s), 118.4 (s), 151.05 (s), 152.6 (s), 181.8 (s), 182.4 (s). EIMS m/z (%) 378 (M^+, 100), 350 (M^+-CO, 39), 333 ($M^+-C_2H_5O$, 25), 306 ($M^+-C_4H_8O$, 8), 278 ($M^+-C_4H_8O-CO$, 25), 72 (C_4H_8O, 41). EIHRMS: 378.2424 (calcd for $C_{22}H_{34}O_5$ (M^+) 378.2406). Anal. Calcd for $C_{22}H_{34}O_5$: C, 69.81; H, 9.05. Found: C, 69.46; H, 9.36. IR ($CHCl_3$) ν_{max} (cm^{-1}): 2358, 1733, 1643, 1619, 1461, 1337, 1271, 1221, 1165, 1112, 1075, 979, 926, 830, 761.

*4.3.2. 6-Hydroxy-2-phenylsulfanyl-7-undecyl-3,4-dihydro-2H-chromene-5,8-dione (**4**)*

Following the procedure described above, 40 mg of embelin (0.136 mmol) in 2 mL of EtOH was treated with 8 equiv of paraformaldehyde (32.6 mg, 1.08 mmol) and 3 equiv of phenyl vinyl sulfide (0.053 mL, 0.41 mmol). The reaction mixture was irradiated for 20 min at a pre-selected temperature of 150 °C, with an

irradiation power of 95 W. The crude was purified by preparative-TLC using Hex/EtOAc (4:1) to provide 53.5 mg (89%) of **4** as an amorphous yellow solid. Mp 110–112 °C. R_f (Hex/AcOEt 4:1): 0.43. ^{1}H NMR (300 MHz, $CDCl_3$): δ=0.87 (t, ^3J=6.3 Hz, 3H), 1.24 (br s, 16H), 1.45 (t, ^3J=7.5 Hz, 2H), 2.19–2.26 (m, 3H), 2.40–2.45 (m, 2H), 2.54–2.60 (m, 2H), 5.81 (t, ^3J=3.7 Hz, 1H), 7.30–7.37 (m, 3H), 7.53 (dd, ^3J=5.8 Hz, ^4J=2.1 Hz, 2H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ=13.8 (t), 15.0 (q), 22.3 (t), 22.4 (t), 25.7 (t), 27.9 (t), 29.2 (t), 29.2 (t), 29.3 (t), 29.39 (t), 29.41 (t), 29.42 (t), 31.6 (t), 85.0 (d), 114.2 (s), 118.5 (s), 128.0 (s) 128.9 (s×2), 132.1 (s), 132.3 (s×2), 150.9 (s), 152.6 (s), 181.0 (s), 182.0 (s) ppm. EIMS *m*/*z* (%): 442 (M^+, 7), 414 (M^+−CO, 1), 333 (M^+−C_6H_5S, 100), 166 (47). EIHRMS: 442.2194 (calcd for $C_{26}H_{34}O_4S$ (M^+) 442.2178). Anal. Calcd for $C_{22}H_{34}O_4S$: C, 70.55; H, 7.74. Found: C, 70.03; H, 7.49. IR ($CHCl_3$) ν_{max} (cm^{-1}): 2853, 2360, 1619, 1465, 1352, 1268, 1158, 1118, 1057, 946, 751, 690.

4.3.3. 6-Hydroxy-2-phenyl-7-undecyl-3,4-dihydro-2H-chromene-5,8-dione (**5**)

Following the procedure described above, 40 mg of embelin (0.136 mmol) in 2 mL of EtOH was treated with 8 equiv of paraformaldehyde (32.5 mg, 1.08 mmol) and 3 equiv of styrene (0.046 mL, 0.41 mmol). The reaction mixture was irradiated for 20 min at a pre-selected temperature of 150 °C, with an irradiation power of 67–70 W. The crude was purified by preparative-TLC using Hex/EtOAc (7:3) to provide 45.2 mg (81%) of **5** an amorphous yellow solid. Mp 91–93 °C. R_f (Hex/AcOEt 4:1): 0.43. ^{1}H NMR (300 MHz, $CDCl_3$): δ=0.87 (t, ^3J=6.3 Hz, 3H), 1.26 (br s, 16H), 1.45 (t, ^3J=7.5 Hz, 2H), 1.98–2.03 (m, 1H), 2.23–2.26 (m, 1H), 2.40–2.46 (m, 2H), 2.52–2.55 (m, 2H), 5.15 (dd, ^2J=9.4 Hz, ^3J=2.5 Hz, 1H), 7.30–7.37 (m, 5H), 7.41 (s, 1H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ=13.8 (q), 17.2 (t), 22.2 (t), 22.4 (t), 27.9 (t), 29.10 (t), 29.2 (t), 29.33 (t), 29.35 (t), 29.39 (t), 29.43 (t), 29.6 (t), 31.6 (t), 79.3 (d), 113.1 (s), 118.2 (s), 125.5 (s×2), 128.1 (s), 128.4 (s×2), 138.7 (s), 150.9 (s), 155.2 (s), 181.3 (s), 182.1 (s) ppm. EIMS *m*/*z* (%): 410 (M^+, 100), 382 (M^+−CO, 6), 306 ($C_{18}H_{26}O_4$, 23), 104 (C_8H_8, 48). EIHRMS: 410.2452 (calcd for $C_{26}H_{34}O_4$ (M^+) 410.2457). IR ($CHCl_3$) ν_{max} (cm^{-1}): 1652, 1616, 1496, 1455, 1405, 1351, 1268, 1210, 1121, 1061, 1035, 953, 757, 698.

4.3.4. 6-Hydroxy-2-(2,4,6-trimethyl-phenyl)-7-undecyl-3,4-dihydro-2H-chromene-5,8-dione (**6**)

Following the procedure described above, 20 mg of embelin (0.068 mmol) in 2 mL of EtOH was treated with 8 equiv of paraformaldehyde (16.3 mg, 0.54 mmol) and 3 equiv of 2,4,6-trimethylstyrene (0.032 mL, 0.20 mmol). The reaction mixture was irradiated for 20 min at a pre-selected temperature of 150 °C, with an irradiation power of 67–70 W. The crude was purified by preparative-TLC using Hex/EtOAc (4:1) to provide 25.4 mg (83%) of **6** as an amorphous orange solid. Mp 89–91 °C. R_f (Hex/AcOEt 4:1): 0.51. ^{1}H NMR (300 MHz, $CDCl_3$): δ=0.87 (t, ^3J=6.4 Hz, 3H), 1.25 (br s, 16H), 1.44 (t, ^3J=7.4 Hz, 2H), 2.05–2.09 (m, 2H), 2.20 (s, 3H), 2.22 (s, 6H), 2.21–2.30 (m, 3H), 2.74 (dd, J=17.6, 3.8 Hz, 1H), 5.38 (dd, J=11.5, 2.8 Hz, 1H), 6.84 (s, 2H), 7.29 (s, 1H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ=13.8 (q), 18.2 (t), 20.1 (q×2), 20.56 (t), 22.2 (t), 22.4 (t), 24.3 (t), 27.9 (t), 29.1 (t), 29.2 (t), 29.3 (t), 29.38 (t), 29.4 (t×2), 31.6 (t), 78.0 (d), 113.0 (s), 118.1 (s), 130.0 (d×2), 131.3 (s), 135.6 (s×2), 137.4 (s), 151.0 (s), 155.3 (s), 181.2 (s), 182.1 (s). EIMS *m*/*z* (%): 452 (M^+, 85), 424 (M^+−CO, 9), 308 ($C_{18}H_{28}O_4$, 18), 306 (M^+−$C_{11}H_{14}$, 3). EIHRMS: 452.2946 (calcd for $C_{29}H_{40}O_4$ (M^+) 452.2927). Anal. Calcd for $C_{29}H_{40}O_4$: C, 76.95; H, 8.91. Found: C, 76.85; H, 8.55. IR ($CHCl_3$) ν_{max} (cm^{-1}): 2360, 2338, 1731, 1654, 1575, 1463, 1355, 1283, 1237, 1129, 1009, 962, 858, 759, 670.

4.3.5. 6-Hydroxy-2-(2-phenyl-cyclohexyloxy)-7-undecyl-3,4-dihydro-2H-chromene-5,8-dione (**7**)

Following the procedure described above, 40 mg of embelin (0.136 mmol) in 2 mL of EtOH was treated with 8 equiv of paraformaldehyde (32.6 mg, 1.08 mmol) and 3 equiv of (1*R*,2*S*)-(−)-*trans*-2-phenyl-1-cyclohexyl vinyl ether[14] (82.4 mg, 0.41 mmol). The reaction mixture was irradiated for 20 min at a pre-selected temperature of 150 °C, with an irradiation power of 90 W. The crude was purified by preparative-TLC using Hex/EtOAc (7:3) to provide 34.3 mg (50%) of **7** as an amorphous yellow solid. Mp 88–90 °C. $[\alpha]_D^{25}$ −6 (*c* 0.3, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$): δ=0.88 (t, ^3J=7.0 Hz, 3H), 1.18–1.22 (m, 16H), 1.36–1.59 (m, 6H), 1.74–1.93 (m, 6H), 2.02–2.13 (m, 2H), 2.39–2.49 (m, 4H), 3.90–3.95 (m, 1H), 5.43 (t, ^3J=2.6 Hz, 1H), 7.21–7.36 (m, 5H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$) δ: 13.0 (q), 13.8 (t), 14.7 (t), 22.2 (t), 22.4 (t), 23.0 (t), 23.8 (t), 24.6 (t), 24.7 (t), 25.8 (t), 27.8 (t), 29.0 (t), 29.1 (t), 29.3 (t), 29.4 (t), 31.6 (t), 33.06 (d), 34.2 (t), 62.9 (d), 74.19 (d), 98.6 (d), 114.4 (s), 118.2 (s), 126.5 (d), 127.6 (d×2), 128.5 (d×2), 151.7 (s), 155.3 (s), 181.6 (s), 182.2 (s) ppm. EIMS *m*/*z* (%): 508 (M^+, 5), 378 (100), 350 (M^+−$C_{12}H_{16}$, 40), 308 (M^+−$C_{14}H_{18}O$, 14). EIHRMS: 508.3204 (calcd for $C_{32}H_{44}O_5$ (M^+) 508.3206). IR ($CHCl_3$) ν_{max} (cm^{-1}): 1727, 1654, 1619, 1494, 1448, 1337, 1271, 1221, 1164, 1111, 1044, 926, 829, 757, 699.

4.3.6. 7-Hydroxy-8-undecyl-3,4,4a,10a-tetrahydro-2H-5H-pyrano[2,3-b]chromene-6,9-dione (**8**)

Following the procedure described above, 30 mg of embelin (0.1 mmol) in 2 mL of EtOH was treated with 8 equiv of paraformaldehyde (24.5 mg, 0.8 mmol) and 3 equiv of 3,4-dihydro-2*H*-pyran (0.028 mL, 0.31 mmol). The reaction mixture was irradiated for 20 min at a pre-selected temperature of 150 °C, with an irradiation power of 85 W. The crude was purified by preparative-TLC using Hex/EtOAc (4:1) to provide 22.8 mg (57%) of **8**. Mp 75–77 °C. R_f (Hex/AcOEt 4:1): 0.14. ^{1}H NMR (300 MHz, $CDCl_3$): δ=0.87 (t,^3J=6.2 Hz, 3H), 1.24 (br s, 16H), 1.44 (t, ^3J=5.3 Hz, 2H), 1.62–1.70 (m, 5H), 2.17–2.22 (m, 1H), 2.38–2.44 (m, 4H), 3.74–3.79 (m, 1H), 3.93–3.99 (m, 1H), 5.59 (d, ^3J=2.13 Hz, 1H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ=13.8 (q), 22.2 (t), 22.4 (t), 23.3 (t), 23.5 (t), 27.9 (t), 29.1 (t), 29.2 (tx2), 29.32 (t), 29.35 (t), 29.38 (t), 29.4 (t), 30.3 (d), 31.6 (t), 65.0 (d), 111.5 (s), 115.0 (s), 118.3 (s), 150.8 (s), 153.0 (s), 181.0 (s), 182.3 (s). EIMS *m*/*z* (%): 390 (M^+, 100), 362 (M^+−CO, 6), 308 ($C_{18}H_{28}O_4$, 10), 306 (M^+−C_5H_8O, 4), 84 (C_5H_8O, 51). EIHRMS: 390.2405 (calcd for $C_{23}H_{34}O_5$ (M^+) 390.2406). Anal. Calcd for $C_{23}H_{34}O_5$: C, 70.74; H, 8.78. Found: C, 70.96; H, 8.78. IR ($CHCl_3$) ν_{max} (cm^{-1}): 2854, 2360, 1655, 1620, 1464, 1340, 1284, 1255, 1192, 1148, 1122, 1079, 1030, 916, 853, 758.

4.3.7. Adduct obtained from the reaction of 2,5-dihydroxybenzoquinone with (+)-α-pinene (**9**)

Following the procedure described above, 30 mg of embelin (0.10 mmol) in 2 mL of EtOH was treated with 8 equiv of paraformaldehyde (24.5 mg, 0.82 mmol) and 3 equiv of (1*R*)-(+)-α-pinene (0.3 mmol, 0.04 mL). The reaction mixture was irradiated for 20 min at a pre-selected temperature of 150 °C, with an irradiation power of 80 W. The crude was purified by preparative-TLC using Hex/EtOAc (4:1) to provide 34.9 mg (76%) of **9** as an amorphous yellow solid. Mp 78–80 °C. $[\alpha]_D^{25}$ −250 (*c* 0.2, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$): δ=0.70 (d, ^3J=10.6 Hz, 2H), 0.86 (t, ^3J=6.3 Hz, 3H), 1.08 (s, 3H), 1.23 (br s, 14H), 1.30 (s, 3H), 1.44 (s, 3H), 1.90–2.72 (m, 14H). ^{13}C NMR (75 MHz, $CDCl_3$): δ=13.8 (q), 19.2 (t), 22.2 (q), 22.3 (q), 22.4 (t), 27.8 (t), 28.2 (q), 28.7 (t), 29.10 (t), 29.15 (t), 29.3 (t×2), 29.4 (t×3), 31.0 (q), 31.6 (t), 34.7 (t), 39.7 (s), 40.4 (q), 54.4 (q), 87.7 (s), 110.3 (s), 117.6 (s), 151.0 (s), 155.8 (s), 181.2 (s), 182.2 (s). EIMS *m*/*z* (%): 422 (M^+, 80), 427 (M^+−Me, 8), 399 (427−Me, 9), 308 ($C_{18}H_{28}O4$, 100). EIHRMS: 442.3068 (calcd for $C_{28}H_{42}O_4$ (M^+) 442.3083). Anal. Calcd for $C_{28}H_{42}O_4$: C, 75.48; H, 9.56. Found: C, 75.10; H, 9.35; O, 15.55. IR ($CHCl_3$) ν_{max} (cm^{-1}): 2362, 1728, 1657, 1617, 1461, 1359, 1338, 1301, 1282, 1224, 1151, 1128, 1089, 1010, 962, 864, 833, 759, 722, 663, 631.

*4.3.8. 8-Hydroxy-7-undecyl-4b,10,10a,11-tetrahydro-indeno-[1,2-b]chromene-6,9-dione (**10**)*

Following the procedure described above, 20 mg of embelin (0.068 mmol) in 2 mL of EtOH was treated with 8 equiv of paraformaldehyde (16.3 mg, 0.54 mmol) and 3 equiv of indene (0.023 mL, 0.2 mmol). The reaction mixture was irradiated for 20 min at a pre-selected temperature of 150 °C, with an irradiation power of 70–76 W. The crude was purified by preparative-TLC using Hex/EtOAc (7:3) to provide 21.2 mg (74%) of **11** as an amorphous orange solid. Mp 97–99 °C. R_f (Hex/EtOAc 4:1): 0.44. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 0.87 (t, ^3J=6.3 Hz, 3H), 1.24 (br s, 16H), 1.42 (t, ^3J=6.9 Hz, 2H), 2.21 (dd, ^2J=17.8 Hz, ^3J=5.3 Hz, 1H), 2.38–2.43 (m, 2H), 2.70–2.88 (m, 3H), 3.09 (dd, ^2J=14.5 Hz, ^3J=5.0 Hz, 1H), 5.63 (d, ^3J=5.0 Hz, 1H), 7.22–7.33 (m, 3H), 7.52 (d, ^3J=6.8 Hz, 1H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ=13.9 (q), 18.8 (t), 22.3 (t), 22.5 (t), 29.1 (t), 29.2 (t), 29.3 (t), 29.4 (t×3), 29.6 (t), 31.7 (t), 34.9 (d), 36.2 (t), 81.2 (d), 111.2 (s), 117.9 (s), 124.9 (d), 125.4 (d), 126.9 (d), 129.2 (d), 140.6 (s), 141.4 (s), 151.0 (s), 154.8 (s), 181.3 (s), 182.2 (s). EIMS *m*/*z* (%): 422 (M^+, 51), 394 (M^+−CO, 2), 308 ($C_{18}H_{28}O_4$, 18), 168 ($C_8H_8O_3$, 19), 84 (C_5H_8O, 51), 116 (C_9H_8, 100). HREIMS: 442.2455 (calcd for $C_{27}H_{34}O_4$ (M^+) 442.2457). Anal. Calcd for $C_{27}H_{34}O_4$: C, 76.74; H, 8.11. Found: C, 76.85; H, 8.55. IR ($CHCl_3$) ν_{max} (cm^{-1}): 2853, 2361, 1652, 1619, 1462, 1352, 1299, 1252, 1222, 1191, 1122, 1070, 1021, 954, 879, 835, 754.

Acknowledgements

This work has been funded by the Spanish MCYT (SAF2006-06720) and by ICIC. S.J.-A. thanks the MCYT for a predoctoral fellowship. We thank Dr. García-Tellado for granting access to the microwave apparatus.

References and notes

1. Ravelo, A. G.; Estévez-Braun, A.; Chávez-Orellana, H.; Pérez-Sacau, E.; Mesa-Siverio, D. *Curr. Top. Med. Chem.* **2004**, *4*, 241–265.
2. (a) Waris, G.; Ahsan, H. *J. Carcinog.* **2006**, *5*, 14; (b) Shiah, S. G.; Chuang, S. E.; Chau, Y. P.; Shen, S. C.; Kuo, M. L. *Cancer Res.* **1999**, *59*, 391–398.
3. (a) Haq, K.; Ali, M.; Siddiqui, A. W. *Pharmazie* **2005**, *60*, 69–71; (b) Raja, S.; Unnikrishnan, K. P.; Ravindran, P. N.; Balachandran, I. *Indian J. Pharm. Sci.* **2005**, *67*, 734–736.
4. Ferensin, G. E.; Tapia, A.; Sortino, M.; Zacchino, S.; Rojas de Arias, A.; Inchausti, A.; Yaluff, G.; Rodríguez, J.; Theoduloz, C.; Schmeda-Hirschmann, G. *J. Ethnopharmacol.* **2003**, *88*, 241–247.
5. Sreepriya, M.; Bali, G. *Fitoterapia* **2005**, *76*, 549–555.
6. Wango, E. O. *Acta Biol. Hung.* **2005**, *56*, 1–9.
7. Podolak, I.; Galanty, A.; Janeczko, Z. *Fitoterapia* **2005**, *76*, 333–335.
8. (a) Nikolovska-Coleska, Z.; Xu, L.; Hu, Z.; Tomita, Y.; Li, P.; Roller, P. P.; Wang, R.; Fang, X.; Guo, R.; Zhang, M.; Lippman, M. E.; Yang, D.; Wang, S. *J. Med. Chem.* **2004**, *47*, 2430–2440; (b) Chen, J.; Nikolovska-Coleska, Z.; Wang, G.; Qiu, S.; Wang, S. *Bioorg. Med. Chem. Lett.* **2006**, *16*, 5805–5808.
9. Jiménez-Alonso, S.; Estévez-Braun, A.; Ravelo, A. G.; Zarate, R.; López, M. *Tetrahedron* **2007**, *63*, 3066–3074.
10. (a) Tietze, L. F.; Brumby, T.; Pretor, M.; Remberg, G. *J. Org. Chem.* **1988**, *53*, 810; (b) Tietze, L. F.; Siegbert, B.; Brumby, T.; Pretor, M.; Remberg, G. *Angew. Chem., Int. Ed. Engl.* **1990**, *29*, 665; (c) Tietze, L. F.; Bratz, M.; Machinek, R.; Kiedrowski, G. *J. Org. Chem.* **1987**, *52*, 1638–1640; (d) *Multicomponent Reactions*; Zhu, J., Bienaymé, H., Eds.; Wiley-VCH: Weinheim, 2005; Chapter 5, pp 121-168.
11. (a) Simon, C.; Constantieux, T.; Rodríguez, J. *Eur. J. Org. Chem.* **2004**, 4957–4980; (b) Tietze, L. F. *J. Heterocycl. Chem.* **1990**, *27*, 47–69 and references cited therein.
12. (a) Wang, H.; Wang, Y.; Han, K. L.; Peng, X. J. *J. Org. Chem.* **2005**, *70*, 4910–4917; (b) Boger, D. L.; Weinreb, S. N. *Hetero Diels–Alder Methodology in Organic Synthesis*; Academic: New York, NY, 1987; (c) Carruthers, W. *Cycloaddition Reactions in Organic Synthesis*; Pergamon: Oxford, 1990; (d) Fringelli, F.; Taticchi, A. *The Diels–Alder reaction: Selected Practical Methods*; John Wiley and Sons: West Sussex, 2002.
13. (a) Kappe, C. O.; Stadler, A. *Methods and Principles in Medicinal Chemistry: Microwaves in Organic and Medicinal Chemistry*; Wiley-VCH: Weinheim, Germany, 2005; Vol. 25; (b) Kappe, C. O. *Angew. Chem., Int. Ed.* **2004**, *43*, 6250–6284; (c) De la Hoz, D.; Diaz-Ortiz, A.; Moreno, A. *Curr. Org. Chem.* **2004**, *8*, 903–918; (d) Nüchter, M.; Ondruschka, B.; Bonrath, W.; Gum, A. *Green Chem.* **2004**, *6*, 128–141; (e) Loupy, A. *Microwaves in Organic Synthesis*; Wiley-VCH: Weinheim, Germany, 2002; (f) Lidstrom, P.; Tierney, J.; Wathey, B.; Westman, J. *Tetrahedron* **2001**, *57*, 9225–9283; (g) Varma, R. S. *Green Chem.* **1999**, *1*, 43–55; (h) Perreux, L.; Loupy, A. *Tetrahedron* **2001**, *57*, 9199–9346.
14. The chiral enol ether was synthesized as described in the following references: (a) Denmark, S. E.; Schnute, M. E. *J. Org. Chem.* **1991**, *56*, 6738–6739; (b) Clark, R. C.; Pfeiffer, S. S.; Boger, D. L. *J. Am. Chem. Soc.* **2006**, *128*, 2587–2593.
15. Dewick, P. M. *Medicinal Natural Products: A Biosynthetic Approach*, 2nd ed.; Wiley: New York, NY, 2002.
16. Perrin, D. D.; Amarego, W. L. F. *Purification of Laboratory Chemicals*, 3rd ed.; Pergamon: Oxford, 1988.