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Tetrahedron 63 (2007) 3066–3074
Tetrahedron

Double domino Knoevenagel hetero Diels–Alder strategy towards bis-pyrano-1,4-benzoquinones

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Received 28 November 2006; revised 12 January 2007; accepted 17 January 2007
Available online 20 January 2007

Abstract—Several bis-pyrano-l,4-benzoquinones have been synthesized by a double domino Knoevenagel hetero Diels–Alder reaction. The synthetic approach is highly efficient allowing the construction of complex polycyclic scaffolds with six new σ-bonds. These reactions performed more efficiently and more rapidly using microwave irradiation. The resulting bis-pyrano-1,4-benzoquinones are the first examples of a double domino Knoevenagel hetero Diels–Alder reaction. Our approach represents a novel contribution to the chemistry of 2,5-dihydroxy-l,4-benzoquinones and the first general method for the synthesis of bis-pyranobenzoquinones.

1. Introduction

Among the strategies that can lead to the discovery of new drugs, the identification and use of privileged structures have gained particular attention, in an attempt to shorten the time required to find new drugs.[1] Driven by our interest in antitumoral compounds,[2] we decided to explore the possibility of preparing new bis-pyranobenzoquinones. These systems present benzopyran and benzoquinone cores, both designated as privileged structures in medicinal chemistry.[1] Many antitumoral compounds contain a 1,4-benzoquinone core (e.g., isoasterriquinone,[3] irisquinone,[4] nakijiquinones,[5] geldanamycin[6]) or a benzopyran nucleus (e.g., tephrosin,[7] acronycine,[8] calanone,[9] seselin[10]), but there are no many examples containing both building blocks. Dactyloquinones[11] and hydnuferrugin[12] are the only natural compounds with a pyranobenzoquinone structural framework known so far. On the other hand, only one synthetic compound having a bis-pyrano-benzoquinone structure has been reported,[13] and it was obtained in low yield.

During the last years, the use of domino reactions has emerged as a powerful and efficient tool for the synthesis of structurally diverse compounds along with biologically active natural products and drugs.[14] One of the most successful applications, known as the domino Knoevenagel hetero Diels–Alder approach (DKHDA), involves a sequence of two in depth investigated and well recognized reactions.[15] It consists of a Knoevenagel condensation of an aldehyde with a 1,3-dicarbonyl compound with formation of a 1,3-oxabutadiene as an intermediate, which undergoes a hetero Diels–Alder reaction with either an enol ether or an alkene. Tietze et al. have exploited this particular way to construct fused heterocycles, usually in a stereoselective manner.[16] The DKHDA reaction can be performed as a two-, three- or four-component transformations, being the stereoselectivity more pronounced in the case of the two-component transformations. Solid-phase three-component DKHDA has been also achieved using a resin-linked 1,3-dicarbonyl compound.[17] The resulting dihydropyrans were obtained in 12–37% overall yield and the selectivity from 1:1 to 1:5 in favour of the cis-product depending on the applied aldehyde.

With this background, we report the synthesis of bis-pyrano-l,4-benzoquinones, having two well known privileged structures, through a direct and highly efficient approach based on DKHDA.

2. Results and discussion

Most of the examples of DKHDA use three 1,3-dicarbonyl compounds[18] (Fig. 1): *N*,*N*-dimethyl barbituric acid (**A**), Meldrum's acid (**B**) and dimedone (**C**). Besides these compounds, other useful 1,3-dicarbonyl compounds for the domino Knoevenagel hetero Diels–Alder reaction are

Keywords: Domino reactions; Cycloaddition; Privileged structures; Multicomponent reaction; Quinones.
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doi:10.1016/j.tet.2007.01.033

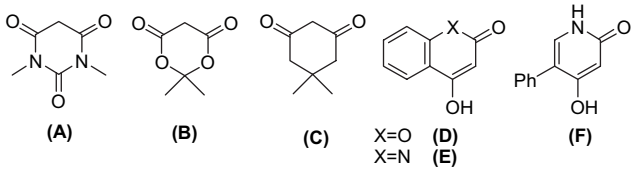
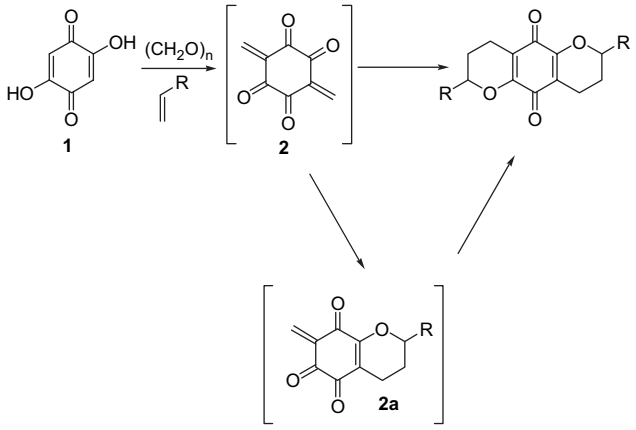


Figure 1. Typical carbonyl compounds in DKHDA.

4-hydroxy coumarins (**D**),[19] 4-hydroxyquinolinones (**E**)[20] and hydroxy pyridones (**F**).[21]

We use in our approach 2,5-dihydroxy-1,4-benzoquinone as an adequate and symmetric synthetic equivalent to 1,3-dicarbonyl compound. In this case, the Knoevenagel condensation of 2,5-dihydroxy-1,4-benzoquinone **1** and paraformaldehyde leads to a reactive intermediate **2** (Scheme 1), which undergoes a double hetero Diels–Alder reaction with diverse electron-rich alkenes as dienophiles, yielding the corresponding bis-pyrano-1,4-benzoquinone derivatives in one-pot reaction. The formation of the two pyran rings may occur simultaneously starting from the intermediate **2** or, alternatively, one of the two pyran rings is formed first to give a second intermediate **2a**, which then undergoes the second hetero Diels–Alder reaction.



Scheme 1. Plausible formation of bis-pyranobenzoquinones.

The hypothetical intermediates **2** and **2a** show similarities with *o*-quinone methides that constitute other examples of highly reactive and ephemeral intermediates.[22] These transient species are known to react with nucleophiles in 1,4-Michael-type fashion and with a range of dienophiles, to perform [4+2] cycloadditions. The synthesis of the natural compounds like xyloketal D[23] and (±)-alboatrin[24] is an illustrative application of hetero Diels–Alder cycloaddition through *o*-quinone methide derivatives.

The preparation of pyranobenzoquinones generally requires several steps and the generation of the quinonic moiety from oxidation of the corresponding 1,4-dihydroxy derivatives.[25] Our approach represents a novel contribution to the chemistry of 2,5-dihydroxy-1,4-benzoquinone and the first general method for the synthesis of bis-pyranobenzoquinones.

Initially, we examined the reaction of **1** and ethyl vinyl ether under different conditions. Some results are summarized in Table 1. Acceptable yields were obtained only when a large excess of paraformaldehyde and dienophile were employed; the best results were achieved with the following ratio **1**/(CH_2O)/ethyl vinyl ether (1/24/9). When the reaction was carried out with 1,4-dioxane under reflux (entry 1), the corresponding adduct was obtained in 28% yield. This result was improved using a sealed tube at 110 °C (entry 2). The use of a 37 wt % water solution of formaldehyde instead of paraformaldehyde decreased the yield (32%).

Table 1. Reaction of **1** with ethyl vinyl ether under various conditions

Entry	**1**/CH_2O/OEt	Solvent	Conditions	Yield (%)
1	1/24/9	Dioxane	Reflux, 24 h	28
2	1/24/9	Dioxane	Sealed tube, 110 °C	88
3[a]	1/24/9	DCE	MW, 20 min, 200 °C	97
4[a]	1/16/9	DCE	MW, 20 min, 200 °C	88
5[a]	1/12/9	DCE	MW, 20 min, 200 °C	73
6[a]	1/24/9	—	MW, 20 min, 200 °C	52

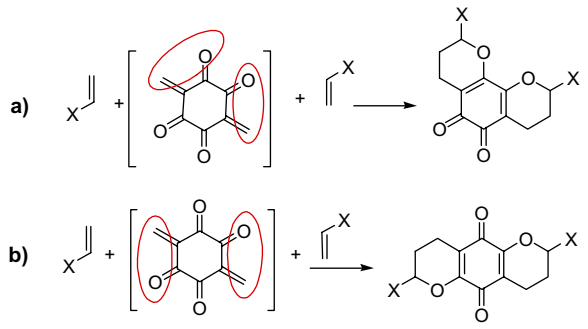
[a] The reactions were carried out in a CEM-Discover monomode microwaves apparatus.

We also used TAMA (*N*-methylanilinium trifluoroacetate) and 1,3,5-trioxane as an equivalent controlling aldol condensation of formaldehyde,[26] but we did not get good results. We also explored the possibility of microwave irradiation since it is known to accelerate a wide variety of transformations.[27] We were pleased to find that in the presence of microwaves, the domino Knoevenagel hetero Diels–Alder reaction proceeds remarkably fast and clean, specially when 1,2-dichloroethane is used as solvent. Ratio of reagents, power, temperature and time were optimized for a monomode CEM-Discover microwave. We also carried out the reaction without the solvent (neat media) (entry 6) but the yield did not improve.

To the best of our knowledge, this paper presents the first example of benzoquinone derivatives' formation through 3,6-dimethylene-cyclohexane-1,2,4,5-tetraone intermediate (**2**). In the mass spectra of the adducts, we found a peak at *m*/*z* 164 with the molecular formula $C_8H_4O_4$ (HRMS) attributable as a retro-Diels–Alder fragment of the intermediate **2**. This polyfunctional intermediate has two heterodiene systems that in the presence of appropriate dienophiles give the corresponding hetero Diels–Alder reactions. There are two possibilities. In one of them the two heterodienes in contiguous disposition react to afford angular bis-pyrano-1,2-benzoquinones. In the other case the two heterodienes in not contiguous disposition act to yield lineal bis-pyrano-1,4-benzoquinones (Scheme 2).

The process was regioselective since we have not found traces of the angular regioisomers bis-pyrano-1,2-benzoquinones. The adducts were obtained as a mixture of 1:1 diastereomers with different R_f and, surprisingly, with identical ^1H and ^{13}C NMR spectroscopic data. Similar behaviour has been detected in the synthesis of iptycene quinone adducts.[28] One of them is achiral because of the existence of a centre of symmetry, and the other one is chiral (±) and presents a C_2 symmetry (Fig. 2). These diastereomers are formed from the suprafacial approaches in the cycloaddition process.[29]

To further demonstrate the versatility of this methodology, several bis-pyrano-1,4-benzoquinone cores have been



Scheme 2. Heterodiene systems.

prepared under different conditions using a set of dienophiles. The structures of the adducts and the yields obtained are detailed in Table 2. The resulting bis-pyrano-1,4-benzoquinones obtained represent the first examples of a double domino Knoevenagel hetero Diels–Alder reaction.

Table 2 shows how the presence of microwaves greatly improves the rate of reaction and the yields. In all cases we obtained a 1:1 ratio of diastereomers.[30] We did not find variations in these ratios from heating to microwave irradiation. It is possible to increase the structural complexity of the adducts using cyclic dienophiles. For example, from

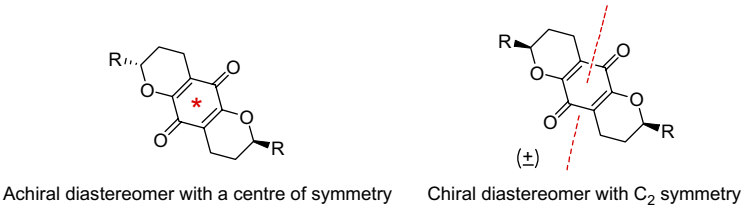
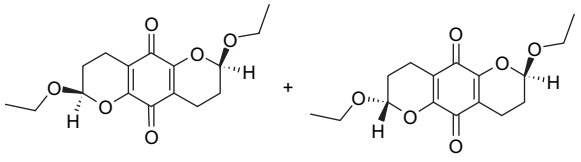
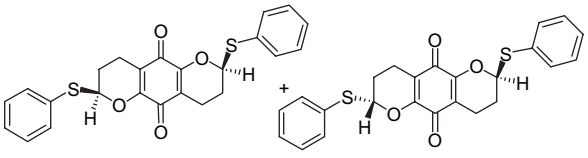
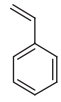
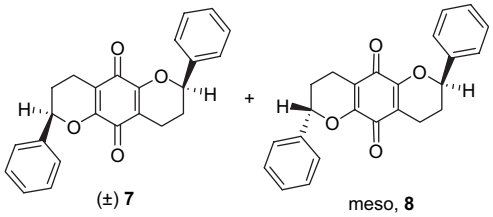
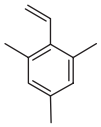
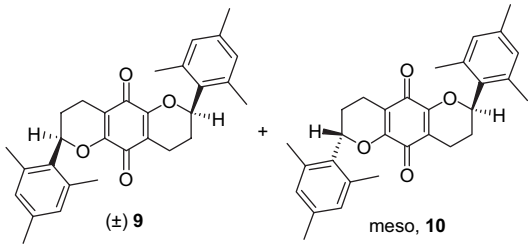


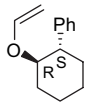
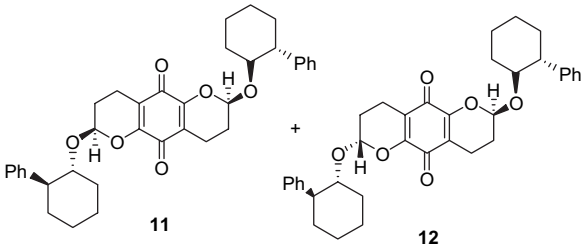
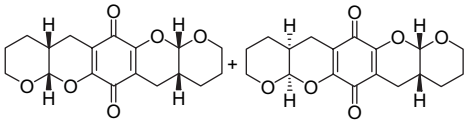
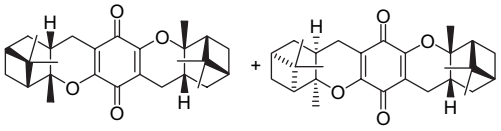
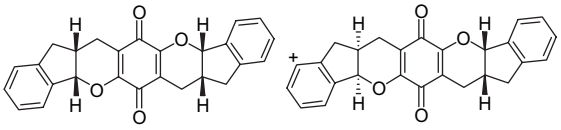
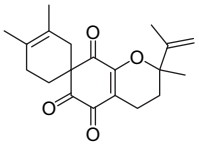
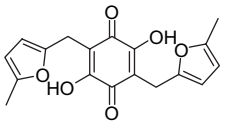
Figure 2. Diastereomers formed.

Table 2. Bis-pyranobenzoquinone derivatives

Entry	Dienophile	Adducts (1:1)	Yield (%)[a] Δ	Yield (%)[b] MW
1		 (±) **3** + meso, **4**	88	97
2		 (±) **5** + meso,**6**	17	98
3		 (±) **7** + meso, **8**	12	54
4		 (±) **9** + meso, **10**	30	83

(*continued*)

Table 2. (*continued*)

Entry	Dienophile	Adducts (1:1)	Yield (%)[a] Δ	Yield (%)[b] MW
5		 **11** + **12**	7	22
6		 (±) **13** + meso, **14**	25	74
7		 **15** + **16**	23	40
8		 (±) **17** + meso,**18**	76	80
9		 (±) **19**	7	56
10		 **20**	73	75

[a] Heating using a sealed tube at 110 °C and 1,4-dioxane as solvent.
[b] Heating using a CEM-Discover microwave and DCE as solvent.

3,4-dihydro-2*H*-pyran, (1*R*)-(+)-α-pinene and indene (entries 6–8), molecules with five or seven rings are achieved. Consequently, the synthetic efficiency of this approach also gives access to structurally diverse and complex molecules, which are essential for lead generation.[31] The cis-fusion of the pyran rings in diastereomers **13** and **14** was determined by the coupling constant (^3J=2.3 Hz), as well as by the NOE effect detected in the ROESY spectrum. The structure of **17** and **18** was confirmed on the basis of the HMBC correlations, which established the orientation of the five-membered ring, with the methylene opposite to the heterocycle oxygen. Low yields were obtained with the chiral enol ether[32] (entry 5) (22%) and with the hindered (1*R*)-(+)-α-pinene (entry 7) (40%). The latter is similar to the yield obtained by Baldwin et al. when (1*R*)-(+)-α-pinene reacted with an *o*-quinone methide intermediate generated in situ.[24] As for the former, the adducts turned out to be unstable under purification conditions. The structures of **4** and **15** were confirmed by X-ray crystal analysis (Fig. 3).

When the reaction was carried out in the presence of 2,3-dimethyl-1,3-butadiene (entry 9), it yielded an unexpected and complex derivative, which presents three carbonyl groups, a dihydropyran ring and a spiro moiety. The structure of

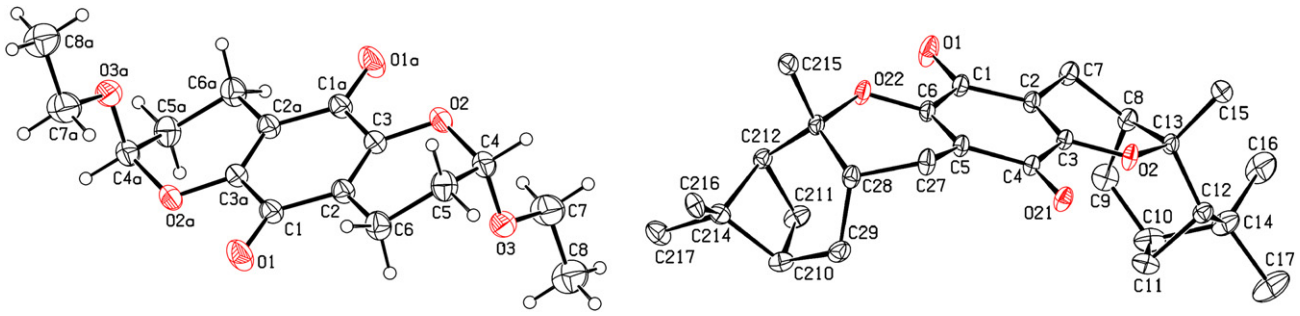


Figure 3. X-ray crystal structures of **4** and **15**.

19 was unequivocally determined by 2D NMR studies. The formation of this compound is plausible considering that two different pericyclic reactions have occurred. The spiro moiety results from a normal demand Diels–Alder reaction between 2,3-dimethyl-butadiene as homodiene and one of the methylene groups of the intermediate **2**. The pyran ring is formed by the expected hetero Diels–Alder reaction between one of the double bonds of 2,3-dimethyl-1,3-butadiene and the remaining heterodiene.

We also found that the reaction with 2-methyl-furan did not give the expected bis-pyrano derivative, rather, the compound showed in entry 10 was obtained as a result of a 1,4-conjugate addition. Pettus and Lindsey have recently reported the formation of various interesting and unexpected 1,4-conjugated addition adducts from the reaction of *o*-quinone methides with electron-rich oxazoles.[33] These two unexpected results reveal how our approach allows a rapid assembly of molecular diversity.

3. Conclusions

In short, the domino Knoevenagel hetero Diels–Alder reaction can be used as a simple and efficient approach towards the synthesis of bis-pyrano-1,4-benzoquinones. The reaction allows the rapid construction of complex polycyclic scaffolds with six new σ-bonds (four C–C σ-bonds and two O–C σ-bonds). These reactions performed more efficiently and more rapidly using microwave irradiation. The strategy can be easily extended to other aldehydes with a suitable double bond to achieve the corresponding intramolecular version. These two-component DKHDA reactions and the antitumoral assays of the bis-pyrano-1,4-benzoquinones are in progress and will be reported elsewhere.

4. Experimental

4.1. General methods

All solvents and reagents were purified by standard techniques reported in Ref. 34 or used as supplied from commercial sources as appropriate. Reactions were monitored by TLC (on silica gel POLYGRAM® SIL G/UV_{254} foils). Purification by column flash chromatography used Merck Kiesel 60-H (0.063–0.2 mm) as adsorbent and different mixtures of hexanes/ethylacetate as eluent. 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 NMR spectra, chemical shifts are given in parts per million (ppm) and 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 where necessary. Data are reported in the following manner: chemical shift (multiplicity, coupling constant if appropriate, integration). 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 spectral assignments are supported by DEPT-135 spectra, ^{13}C–^{1}H (HMQC) and ^{13}C–^{1}H (HMBC) correlations where necessary. Chemical shifts are quoted in parts per million and referenced to the appropriate residual solvent peak. MS and HRMS were recorded at VG Micromass ZAB-2F. All compounds were named using ACD40 Name-Pro program, which is based on IUPAC rules. Melting points were recorded using a Buchi B540 capillary apparatus and are uncorrected. IR spectra were taken on a Bruker IFS28/55 spectrophotometer.

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 aluminium/Teflon crimp tops, which can be exposed up to 250 °C and 20 bar internal pressure. 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. Analytical HPLC method

In order to corroborate the ratio of the diastereomers resulting from some DKHDA reactions, several samples were analyzed by HPLC employing a Jasco system (Tokyo, Japan) equipped with a PU-980 pump, a photodiode array detector model MD-2010 Plus, a Rheodyne (California, US) 7725i manual injector and a Supelco Discovery column C-18 reverse phase (250×4.6 mm I.D.), packed with 5 μm particles. The mobile phase was a mixture of 65:35 (v/v) CH_3CN/H_2O, eluted isocratically at a flow rate of 1 mL/min at room

temperature and detection conducted at 220 nm. The ratio of CH_3CN/H_2O was altered to 70:30 when necessary to optimize separation of some of the mixtures. The mobile phase ingredients were of HPLC grade, and prior to use were filtered through a 0.45 μm nylon filter and degassed. Under these analytical conditions elution times of the different diastereomers ranged from 3–4 min to a maximum of 14–18 min for other mixtures. It was determined that the proportion of the diastereomers formed was 1:1 in all cases.

4.4. General procedure by heating (procedure A)

2,5-Dihydroxy-1,4-benzoquinone, dissolved in dioxane (20 mL/mmol), was treated with 24 equiv of paraformaldehyde and 9 equiv of the corresponding alkenes. The reaction mixture was heated in a sealed tube at 110 °C for 24 h. 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 vacuum. The residue was purified by silica gel column chromatography.

4.5. General procedure by MW irradiation (procedure B)

2,5-Dihydroxy-1,4-benzoquinone (50 mg, 0.36 mmol), 24 equiv of paraformaldehyde and 9 equiv of the corresponding alkenes were suspended in 2 mL of 1,2-dichloroethane in a 10 mL reaction glass containing a stirring magnet. The vial was sealed tightly with an aluminium/Teflon crimp top. After the irradiation period, the reaction vessel was cooled rapidly to ambient temperature by air jet cooling. The solvent is removed under reduced pressure, then the residue is 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 vacuum. The residue was purified by TLC-preparative chromatography.

4.6. Characterization data

4.6.1. 2,7-Diethoxy-3,4,8,9-tetrahydro-2*H*,7*H*-pyrano[2,3-*g*]chromene-5,10-dione (3, 4). Following the procedure A described above, 150 mg of 2,5-dihydroxy-1,4-benzoquinone (1 mmol) was treated with 24 equiv of paraformaldehyde (720 mg, 24 mmol) and 9 equiv of ethyl vinyl ether (0.86 mL). The crude was purified by flash chromatography on silica gel with 8.5:1.5 Hex/AcOEt to obtain 273 mg (88%) of **3** and **4** (1:1). Following the procedure B described above, the reaction mixture was irradiated for 20 min at a pre-selected temperature of 200 °C, with an irradiation power of 225 W. The crude was purified by preparative-TLC using Hex/EtOAc (7:3) to provide 107 mg (97%) of **3** and **4** (1:1). Compound **3**: amorphous white solid, compound **4**: crystalline yellow solid. Mp=182–183 °C. R_f (hexanes/AcOEt; 4:1) **3**=0.64; **4**=0.56. HPLC (C-18 reverse phase, 65%, acetonitrile/H_2O, 1.0 mL/min) **3**=9.39, **4**=8.37. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 1.20 (t, ^3J=6.90 Hz, 6H), 1.77 (m, 2H), 2.03 (m, 2H), 2.45 (m, 4H), 3.68 (dq, ^2J=9.6 Hz, ^3J=7.0 Hz, 2H), 3.90 (dq, ^2J=9.6 Hz, ^3J=7.0 Hz, 2H), 5.40 (t, ^3J=1.1 Hz, 2H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$) δ: 13.5 (t), 15.5 (q), 25.1 (t), 64.8 (t), 98.3 (d), 117.1 (s), 150.8 (s), 181.3 (s) ppm. MS (70 eV, EI) *m*/*z* (%): 308 (M^+, 11), 263 ($M^+-C_2H_5O$, 18), 236 ($M^+-C_4H_8O$, 28), 164 ($C_8H_4O_4$, 18), 72 (C_4H_8O, 53). HRMS calculated for $C_{16}H_{20}O_6$: (M^+) 308.1259, found: 308.1237. IR ($CHCl_3$) ν_{max} (cm^{-1}): 2360, 1658, 1605, 1253, 948.

4.6.2. 2,7-Bis-phenylsulfanyl-3,4,8,9-tetrahydro-2*H*,7*H*-pyrano[2,3-*g*]chromene-5,10-dione (5, 6). Following the procedure A described above, 100 mg of 2,5-dihydroxy-1,4-benzoquinone (0.7 mmol) was treated with 24 equiv of paraformaldehyde (504 mg, 16.8 mmol) and 9 equiv of phenyl vinyl sulfide (0.78 mL). The crude was purified by flash chromatography on silica gel with 7:3 Hex/AcOEt to obtain 50 mg (17%) of **5** and **6** (1:1). Following the procedure B described above, the reaction mixture was irradiated for 20 min at a pre-selected temperature of 200 °C, with an irradiation power of 150 W. The crude was purified by preparative-TLC using Hex/EtOAc (7:3) to provide 155 mg (98%) of **5** and **6** (1:1). Compounds **5** and **6**: amorphous yellow solids. R_f (hexanes/AcOEt; 7:3) **5**=0.59; **6**=0.42. HPLC (C-18 reverse phase, 70%, acetonitrile/H_2O, 1.0 mL/min) **5**=3.99, **6**=3.81. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 2.24 (m, 4H), 2.55 (m, 4H), 5.82 (t, ^3J=3.6 Hz, 2H), 7.30 (m, 6H), 7.55 (dd, ^4J=2.0 Hz, ^3J=7.9 Hz, 4H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$) δ: 15.6 (t), 26.1 (t), 85.0 (d), 117.1 (s), 128.2 (d), 129.2 (d×2), 132.6 (d×2), 151.3 (s), 180.4 (s) ppm. MS (70 eV, EI) *m*/*z* (%): 438 (M^++2, 23), 436 (M^+, 9), 408 (M^+-CO, 42), 327 ($M^+-C_6H_5S$, 90), 218 ($M^+-2\times C_6H_5S$, 26), 164 (4), 136 (100). HRMS calculated for $C_{24}H_{20}O_4S_2$ (M^+): 436.0803, found: 436.0817. IR ($CHCl_3$) ν_{max} (cm^{-1}): 2926, 1657, 1608, 1439, 1364, 1253, 1209, 1096, 1026, 939, 864, 809, 748, 690.

4.6.3. 2,7-Diphenyl-3,4,8,9-tetrahydro-2*H*,7*H*-pyrano[2,3-*g*]chromene-5,10-dione (7, 8). Following the procedure A described above, 150 mg of 2,5-dihydroxy-l,4-benzoquinone (1.0 mmol) was treated with 24 equiv of paraformaldehyde (720 mg, 24 mmol) and 9 equiv of styrene (1.0 mL). The crude was purified by flash chromatography on silica gel with 9:1 Hex/AcOEt to obtain 43.2 mg (12%) of **7** and **8** (1:1). Following the procedure B described above, the reaction mixture was irradiated for 15 min at a pre-selected temperature of 200 °C, with an irradiation power of 140 W. The crude was purified by preparative-TLC using Hex/EtOAc (7:3) to provide 70.8 mg (54%) of **7** and **8** (1:1). Compounds **7** and **8**: amorphous orange solids. R_f (hexanes/AcOEt; 7:3) **7**=0.3; **8**=0.2. HPLC (C-18 reverse phase, 65%, acetonitrile/H_2O, 1.0 mL/min) **7**=18.13, **8**=12.0. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 1.98 (m, 2H), 2.30 (m, 2H), 2.55 (m, 4H), 5.22 (dd, ^3J=9.6 Hz, ^3J=2.7 Hz, 2H), 7.35 (m, 10H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$) δ: 17.8 (t), 28.0 (t), 79.6 (d), 112.6 (s), 125.5 (d×2), 128.2 (d), 128.6 (d×2), 139.2 (s), 158.2 (s), 178.4 (s) ppm. MS (70 eV, EI) *m*/*z* (%): 372 (M^+, 2), 344 (M^+-CO, 54), 268 ($M^+-C_8H_8$, 14), 240 ($M^+-C_8H_8-CO$, 50), 164 (19), 104 (100). HRMS calculated for $C_{24}H_{20}O_4$: (M^+) 372.1362, found: 372.1357. IR ($CHCl_3$) ν_{max} (cm^{-1}): 2928, 1646, 1600, 1409, 1287, 1209, 1115, 1970, 976, 921, 753, 699.

4.6.4. 2,7-Bis-(3,4,5-trimethyl-phenyl)-3,4,8,9-tetrahydro-2*H*,7*H*-pyrano[2,3-*g*]chromene-5,10-dione (9, 10). Following the procedure A described above, 50 mg of 2,5-dihydroxy-l,4-benzoquinone (0.36 mmol) was treated with

24 equiv of paraformaldehyde (240 mg, 8 mmol) and 9 equiv of 2,4,6-trimethylstyrene (0.48 mL). The crude was purified by flash chromatography on silica gel with 4:1 Hex/AcOEt to obtain 48 mg (30%) of **9** and **10** (1:1). Following the procedure B described above, the reaction mixture was irradiated for 20 min at a pre-selected temperature of 200 °C, with an irradiation power of 225 W. The crude was purified by preparative-TLC using Hex/EtOAc (7:3) to provide 136.1 mg (83%) of **9** and **10** (1:1). Compounds **9** and **10**: amorphous yellow solids. R_f (hexanes/AcOEt; 8.5:1.5) **9**=0.6; **10**=0.4. HPLC (C-18 reverse phase, 70%, acetonitrile/H_2O, 1.0 mL/min) **9**=16.0, **10**=13.0. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 2.08 (m, 2H), 2.14 (s, 6H), 2.26 (s, 12H), 2.42 (m, 2H), 2.65 (dd, ^2J=17.9 Hz, ^3J=4.5 Hz, 4H), 5.38 (dd, ^3J=11.6 Hz, ^3J=2.8 Hz, 2H), 6.90 (s, 4H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$) δ: 18.7 (t), 20.4 (q×2), 20.8 (q), 24.7 (t), 77.8 (d), 115.6 (s), 131.8 (d×2), 132.0 (s), 135.9 (s), 137.5 (s), 153.8 (s), 180.9 (s) ppm. MS (70 eV, EI) *m/z* (%): 458 (M^++2, 15), 456 (M^+, 10), 428 ($M^+-C_6H_3(CH_3)_3$, 5), 310 ($M^+-2\times C_6H_3(CH_3)_3$, 15), 282 (310−CO, 12), 164 (1), 146 (100). HRMS calculated for $C_{30}H_{32}O_4$: (M^+) 456.2301, found: 456.2302. IR ($CHCl_3$) ν_{max} (cm^{-1}): 2928, 2361, 1734, 1653, 1603, 1449, 1356, 1258, 1150, 1069, 947, 848, 753.

4.6.5. 2,7-Bis-(2-phenyl-cyclohexyloxy)-3,4,8,9-tetrahydro-2*H*,7*H*-pyrano[2,3-*g*]chromene-5,10-dione (11, 12). Following the procedure A described above, 150 mg of 2,5-dihydroxy-l,4-benzoquinone (1.0 mmol) was treated with 16 equiv of paraformaldehyde (480 mg, 16 mmol) and 9 equiv of (1*R*,2*S*)-(−)-*trans*-2-phenyl-l-cyclohexyl vinyl ether[32] (181.9 mg). The crude was purified by Sephadex column with 2:1:1 Hex/MeOH/$CHCl_3$ to obtain 41.2 mg (7%) of **11** and **12** (1:1). Following the procedure B described above, the reaction mixture was irradiated for 15 min at a pre-selected temperature of 200 °C, with an irradiation power of 160 W. The crude was purified by preparative-TLC using Hex/EtOAc (7:3) to provide 26.3 mg (22%) of **11** and **12** (1:1). Compounds **11** and **12**: amorphous yellow solids. R_f (hexanes/AcOEt; 4:1) **11**=0.7; **12**=0.6. Compound **11**: $[\alpha]_D^{20}$ −120 (*c* 0.11, $CHCl_3$). Compound **12**: $[\alpha]_D^{20}$ −6 (*c* 0.15, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$) δ: 0.84 (m, 2H), 1.20–1.50 (m, 8H), 1.50–2.00 (m, 10H), 2.25 (m, 4H), 2.40 (m, 2H), 3.77 (m, 2H), 4.67 (t, ^3J=2.35 Hz, 2H), 7.13–7.28 (m, 10H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$) δ: 13.3 (t), 23.0 (t), 23.8 (t), 24.6 (t), 32.4 (t), 34.2 (t), 51.3 (d), 83.8 (d), 99.5 (d), 116.7 (s), 126.4 (d), 127.8 (d×2), 128.8 (d×2), 130.9 (s), 143.9 (s), 181.4 (s) ppm. MS (70 eV, EI) *m/z* (%): 570 (M^++2, 16), 568 (M^+, 12), 540 (M^+−CO, 13), 412 ($M^+-2\times C_6H_5$, 6), 410 ($M^+-2\times C_6H_5-2H$, 20), 382 (412−CH_2O, 100). HRMS calculated for $C_{36}H_{40}O_6$: (M^+) 568.2807, found: 568.2825. IR ($CHCl_3$) ν_{max} (cm^{-1}): 2931, 2856, 1658, 1610, 1448, 1253, 1179, 1105, 1038, 937, 755, 700.

4.6.6. 3,4,4a,10,11,11a,12,14a-Octahydro-2*H*,5*H*,7a*H*,9*H*-l,7,8,14-tetraoxa-pentacene-6,13-dione (13, 14). Following the procedure A described above, 150 mg of 2,5-dihydroxy-l,4-benzoquinone (1.0 mmol) was treated with 24 equiv of paraformaldehyde (720 mg, 24 mmol) and 9 equiv of 3,4-dihydro-2*H*-pyran (0.82 mL). The crude was chromatographed on silica gel with 9:1 to 7:3 Hex/AcOEt to obtain 81.6 mg (25%) of **13** and **14** (1:1). Following the procedure B described above, the reaction mixture was irradiated for 15 min at a pre-selected temperature of 200 °C, with an irradiation power of 130 W. The crude was purified by preparative-TLC using Hex/EtOAc (7:3) to provide 87.7 mg (74%) of **13** and **14** (1:1). Compounds **13** and **14**: amorphous orange solids. R_f (CH_2Cl_2/AcOEt; 9:1) **13**=0.6; **14**=0.4. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 1.47 (m, 2H), 1.67 (m, 6H), 2.20 (m, 2H), 2.45 (m, 4H), 3.74 (m, 2H), 3.95 (m, 2H), 5.36 (d, ^3J=2.3 Hz, 2H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$) δ: 2.7 (t), 23.6 (t), 23.8 (t), 30.6 (d), 62.7 (t), 98.3 (d), 114.2 (s), 151.5 (s), 180.6 (s) ppm. MS (70 eV, EI) *m/z* (%): 334 (M^++2, 6), 332 (M^+, 18), 314 (M^+-H_2O, 20), 304 (M^+−CO, 18), 248 ($M^+-C_8H_5O$, 100), 230 (248−CO, 5), 164 (5). HRMS calculated for $C_{18}H_{20}O_6$: (M^+) 332.1260, found: 332.1254. IR ($CHCl_3$) ν_{max} (cm^{-1}): 2936, 1653, 1602, 1339, 1280, 1248, 1151, 1068, 977, 940, 914, 846.

4.6.7. Adducts obtained from the reaction of 2,5-dihydroxy-l,4-benzoquinone and (1*R*)-(+)-α-pinene (15, 16). Following the procedure A described above, 50 mg of 2,5-dihydroxy-l,4-benzoquinone (0.36 mmol) was treated with 24 equiv of paraformaldehyde (240 mg) and 9 equiv of (1*R*)-(+)-α-pinene (0.45 mL). The crude was chromatographed on silica gel using Hex/AcOEt (9:1) to obtain 55.8 mg (23%) of **15** and **16** (1:1). Following the procedure B, the reaction mixture was irradiated for 15 min at a pre-selected temperature of 200 °C, with an irradiation power of 130 W. The crude was purified by preparative-TLC using Hex/EtOAc (7:3) to provide 59.8 mg (40%) of **15** and **16** (1:1). Compound **15**: crystalline yellow solid. Mp=230–232 °C. Compound **16**: amorphous yellow solid. R_f (hexanes/AcOEt; 4:1) **15**=0.4; **16**=0.3. Compound **15**: $[\alpha]_D^{20}$ +266 (*c* 0.1, $CHCl_3$). Compound **16**: $[\alpha]_D^{20}$ +326 (*c* 0.1, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$) δ: 0.7–1.0 (m, 6H), 1.25 (s, 6H), 1.37 (s, 6H), 1.8–2.8 (m, 12H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$) δ: 19.8 (t), 22.7 (q), 28.5 (q×2), 29.0 (t), 29.7 (d), 35.0 (t), 39.5 (s), 40.7 (d), 54.4 (d), 86.7 (s), 112.7 (s), 154.3 (s), 180.9 (s) ppm. MS (70 eV, EI) *m/z* (%): 438 (M^++2, 100), 436 (M^+, 33), 408 (M^+−CO, 54), 300 ($M^+-C_{10}H_{16}$, 15), 164 (3), 136 ($M^+-2\times C_{10}H_{16}$, 17). HRMS calculated for $C_{28}O_4H_{36}$: (M^+) 436.2614, found: 436.2631. IR ($CHCl_3$) ν_{max} (cm^{-1}): 2921, 1655, 1608, 1445, 1376, 1339, 1295, 1278, 1225, 1125, 1087, 1011, 965, 754.

4.6.8. 4b,7,7a,8,12b,15,15a,16-Octahydro-indeno[l,2-*b*]indeno[2′,l′:5,6] pyrano[2,3-*g*]chromene-6,14-dione (17, 18). Following the procedure A described above, 50 mg of 2,5-dihydroxy-1,4-benzoquinone (0.36 mmol) was treated with 24 equiv of paraformaldehyde (240 mg, 8.9 mmol) and 9 equiv of indene (0.37 mL). The crude was chromatographed on silica gel with 8.5:1.5 Hex/AcOEt to obtain 108 mg (76%) of **17** and **18** (1:1). Following the procedure B, the reaction mixture was irradiated for 20 min at a pre-selected temperature of 200 °C, with an irradiation power of 220 W. The crude was purified by preparative-TLC using Hex/EtOAc (7:3) to provide 110 mg (80%) of **17** and **18** (1:1). Compounds **17** and **18**: amorphous yellow solids. R_f (hexanes/AcOEt; 4:1) **17**=0.5; **18**=0.4. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 2.15 (dd, ^2J=17.8 Hz, ^3J=5.5 Hz, 2H), 2.75 (m, 4H), 3.08 (dd, ^2J=16.6 Hz, ^3J=7.3 Hz, 2H), 5.60 (d, ^3J=4.9 Hz, 2H), 7.25 (m, 6H), 7.49 (d, ^3J=6.8 Hz, 2H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$) δ: 19.3 (t), 35.2 (d),

36.5 (t), 81.92 (d), 113.7 (s), 124.9 (d), 125.6 (d), 127.0 (d), 129.2 (d), 141.2 (s), 141.5 (s), 153.3 (s), 180.8 (s) ppm. MS (70 eV, EI) *m/z* (%): 396 (M^+, 1), 368 (M^+-CO, 6), 280 ($M^+-C_9H_8$, 9), 252 ($M^+-C_9H_8-2CO$, 8), 164 (2), 106 ($M^+-2C_9H_8-2CO$, 100), 115 (M^+-281, 50). HRMS calculated for $C_{26}H_{20}O_4$: (M^+) 396.1362, found: 96.1368. IR ($CHCl_3$) ν_{max} (cm^{-1}): 2944, 1732, 1655, 1613, 1461, 1372, 1242, 1110, 1071, 1023, 951, 884, 751.

4.6.9. Adduct obtained from the reaction of 2,5-dihydroxy-l,4-benzoquinone with paraformaldehyde and 2,3-dimethyl-buta-l,3-diene (±) (19). Following the procedure A described above, 100 mg of 2,5-dihydroxy-l,4-benzoquinone (0.7 mmol) was treated with 24 equiv of paraformaldehyde (480 mg, 16 mmol) and 9 equiv of 2,3-dimethyl-l,3-butadiene (0.7 mL). The crude was chromatographed on silica gel with 9:1 Hex/AcOEt to obtain 14.1 mg (7%) of **19**. Following the procedure B, the reaction mixture was irradiated for 20 min at a pre-selected temperature of 200 °C, with an irradiation power of 220 W. The crude was purified by preparative-TLC using Hex/EtOAc (4:1) to provide 65 mg (56%) of **19**. R_f (hexanes/AcOEt; 4:l)=0.25. ^1H NMR (300 MHz, $CDCl_3$) δ: 1.49 (s, 3H), 1.51 (s, 3H), 1.61 (s, 3H), 1.68 (s, 3H), 1.90–2.10 (m, 3H) 2.10–2.80 (m, 4H), 4.75 (br s, 1H), 4.81 (br s, 1H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$) δ: 16.3 (t), 18.1 (q), 18.8 (q), 18.7 (q), 26.3 (q), 28.6 (t), 29.7 (t), 30.6 (t), 31.1 (t), 65.5 (s), 84.1 (s), 112.0 (t), 122.4 (s), 123.5 (s), 124.8 (s), 144.1 (s), 158.7 (s), 183.0 (s), 189.8 (s), 192.8 (s) ppm. MS (70 eV, EI) *m/z* (%): 328 (M^+, 44), 313 (M^+-CH_3, 5), 286 ($M^+-C_3H_6$, 73), 246 ($M^+-C_6H_{10}$, 100), 218 (246−CO, 89), 203 (246−CO, 33). HRMS calculated for $C_{20}H_{24}O_4$: (M^+) 328.1667 found: 328.1675. IR ($CHCl_3$) ν_{max} (cm^{-1}): 2927, 2360, 1668, 1599, 1388, 1278, 1133, 755.

4.6.10. 2,5-Dihydroxy-3,6-bis-(5-methyl-furan-2-yl-methyl)-[l,4]benzoquinone (20). Following the procedure A described above, 150 mg of 2,5-dihydroxy-l,4-benzoquinone (1.0 mmol) was treated with 24 equiv of paraformaldehyde (720 mg, 24 mmol) and 9 equiv of 2-methylfuran (0.82 mL). The crude was chromatographed on silica gel with 4:1 Hex/AcOEt to obtain 238 mg (73%) of **20**. Following the procedure B, the reaction mixture was irradiated for 20 min at a pre-selected temperature of 200 °C, with an irradiation power of 225 W. The crude was purified by preparative-TLC using Hex/EtOAc (7:3) to provide 88.6 mg (75%) of **20**. Amorphous orange solid R_f (hexanes/AcOEt; 4:l)=0.33. ^1H NMR (300 MHz, $CDCl_3$) δ: 2.18 (s, 6H), 3.70 (s, 4H), 5.70 (d, ^3J=2.6 Hz, 2H), 5.88 (d, ^3J=2.6 Hz, 2H), 6.69 (m, 2H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$) δ: 13.3 (q), 21.2 (t), 105.9 (d), 106.8 (d), 112.0 (s), 149.0 (s), 150.8 (s) ppm. MS (70 eV, EI) *m/z* (%): 328 (M^+, 100), 286 ($M^+-C_3H_6$, 3), 246 ($M^+-C_5H_6O$, 92), 164 ($M^+-2\times C_5H_6O$, 4). HRMS calculated for $C_{18}H_{16}O_6$: (M^+) 328.0947, found: 328.0959. IR ($CHCl_3$) ν_{max} (cm^{-1}): 3312, 1614, 1322, 1296, 1207, 1034, 771, 693.

4.7. X-ray crystallographic data

4.7.1. Crystal structure analysis. Intensity data were collected at 293 K on an Enraf–Nonius Kappa CCD diffractometer with graphite monochromated Mo Kα radiation (λ=0.71070 Å). Data reduction and cell parameter refinement were carried out with the programs COLLECT[35] and DENZO.[36] The two structures were solved by direct methods using SIR97.[37] Refinement was performed with SHELXL-97[38] using full-matrix least squares with anisotropical thermal parameter for all non-H atoms. The hydrogen atoms were placed at calculated positions. Molecular graphics were computed with PLATON.[39]

4.7.2. Crystal data for 4. $C_{16}H_{20}O_6$, MW=308.3, triclinic, space group *P*-1, *a*=6.150(9), *b*=8.499(8), *c*=8.993(11) Å, *V*=394.5(8) Å^3, *Z*=l, ρ_c=1.30 gm cm^{-3}, *F*(000)=164.0, μ (Mo Kα)=0.10 mm^{-1}, *R*=0.0573, *wR*=0.1597 and *S*=1.06 for 1594 observed reflections of 1694 unique (94.1%), θ_{max}=27.4°, $I>2\sigma(I)$ criterion and 101 parameters. Maximum and minimal residuals in the final difference map: 0.24 and 0.18 e/Å^3.

4.7.3. Crystal data for 15. $C_{28}H_{36}O_4$, MW=436.6, monoclinic, space group $P2_1$ *a*=9.157(5), *b*=10.386(9), *c*=12.903(7) Å, *V*=1218.2(14) Å^3, *Z*=2, ρ_c=1.19 gm cm^{-3}, *F*(000)=472.0, μ (Mo Kα)=0.08 mm^{-1}, *R*=0.0446, *wR*=0.0471 and *S*=1.02 for 2788 observed reflections of 2917 unique (95.6%), θ_{max}=27.5°, $I>2\sigma(I)$ criterion and 290 parameters. Maximum and minimal residuals in the final difference map: 0.23 and 0.16 e/Å^3.

4.7.4. Crystallographic data. Data (excluding the structure factor tables) have been deposited with the Cambridge Crystallographic Data Center, deposition numbers 298212 and 298213. Copies of the data can be obtained free of charge, on application to the CCDC Director: 12 Union Road, Cambridge, CB2, 1EZ, UK [fax: +44 (0)1223 306033 or e-mail: deposit@ccdc.cam.ac.uk].

Acknowledgements

This work has been funded by the Spanish MCYT (SAF2003-04200-C02-02) and by ICIC. S.J.-A. thanks the MCYT for a predoctoral fellowship. We thank Dr. J.J. Marrero for insightful discussions and suggestions, and to Dr. García-Tellado for granting access to the microwave apparatus.

References and notes

1. (a) Costantino, L.; Barlocco, D. *Curr. Med. Chem.* **2006**, *13*, 65; (b) Li, J.; Liu, K.; Sakya, S. *Mini-Rev. Med. Chem.* **2005**, *5*, 1133; (c) DeSimone, R. W.; Currie, K. S.; Mitchell, S. A.; Darrow, J. W.; Pippin, D. A. *Comb. Chem. High Throughput Screen* **2004**, *7*, 473; (d) Li, J.; Liu, K. *Mini-Rev. Med. Chem.* **2004**, *4*, 207.
2. (a) Pérez-Sacau, E.; Estévez-Braun, A.; Ravelo, A. G.; Ferro, E.; Tokuda, H.; Mukainaka, T.; Nishino, H. *Bioorg. Med. Chem.* **2003**, *11*, 483; (b) Ravelo, A. G.; Estévez-Braun, A.; Chávez-Orellana, H.; Pérez-Sacau, E.; Mesa-Siverio, D. *Curr. Top. Med. Chem.* **2004**, *4*, 241; (c) Pérez-Sacau, E.; Soto-Delgado, J.; Estévez-Braun, A.; Ravelo, A. G. *Tetrahedron* **2005**, *61*, 437; (d) Mesa-Siverio, D.; Estévez-Braun, A.; Ravelo, A. G.; Murguía, J. R.; Rodríguez-Afonso, A. *Eur. J. Org. Chem.* **2003**, 4243; (e) Muñoz-Martínez, F.; Lu, P.; Cortés Selva, F.; Pérez Victoria, J. M.; Jiménez, I. A.; Ravelo, A. G.; Gamarro, F.; Castanys, S. *Cancer Res.* **2004**, *64*,

7130; (f) Cortés-Selva, F.; Campillo, M.; Reyes, C. P.; Jiménez, I. A.; Castanys, S.; Bazzocchi, I. L.; Pardo, L.; Gamarro, F.; Ravelo, A. G. *J. Med. Chem.* **2004**, *47*, 576; (g) Ravelo, A. G.; Estévez-Braun, A.; Mesa-Siverio, D.; Pérez-Sacau, E.; Lacal, J. C.; Ramírez-Molina, A. Patent no. P0200503263, 2006; (h) Cortes-Selva, F.; Jimenez, I. A.; Munoz-Martinez, F.; Campillo, M.; Bazzocchi, I. L.; Pardo, L.; Ravelo, A. G.; Castanys, S.; Gamarro, F. *Curr. Pharm. Des.* **2005**, *11*, 3125.
3. Alvi, K. A.; Pu, H. *J. Antibiot.* **1999**, *52*, 215.
4. (a) Han, R. *Stem. Cells* **1994**, *12*, 53; (b) Wang, X.-W. *Drugs Future* **1999**, *24*, 613.
5. (a) Stahl, P.; Kissan, L.; Mazitschek, R.; Giannis, A.; Waldmann, H. *Angew. Chem., Int. Ed.* **2002**, *41*, 1174; (b) Stahl, P.; Kissau, L.; Mazitschek, R.; Huwe, A.; Furet, P.; Giannis, A.; Waldmann, H. *J. Am. Chem. Soc.* **2001**, *123*, 11586.
6. Bunton, V. G.; Steele, G.; Lewis, A. D. *Cancer Chemother. Pharmacol.* **1998**, *41*, 417.
7. Li, L.; Wang, H. K.; Chang, J. J.; McPhail, A. T.; McPhail, D. R.; Terada, H.; Konoshima, T.; Kokumai, M. *J. Nat. Prod.* **1993**, *56*, 690.
8. Kawaii, S.; Tomono, Y.; Katase, E.; Ogawa, K.; Takemura, Y.; Ju-ichi, M.; Ito, C.; Furukawa, H. *J. Nat. Prod.* **1999**, *62*, 587.
9. Cao, S. G.; Wu, X. H.; Sim, K. Y.; Tan, B. H.; Vittal, J. J.; Pereira, J. T.; Goh, S. H. *Helv. Chim. Acta* **1998**, *81*, 1404.
10. Pillai, S. P.; Menon, S. R.; Mitscher, L. A.; Pillai, C. A.; Shankel, D. M. *J. Nat. Prod.* **1999**, *62*, 1358.
11. Mitome, H.; Nagasawa, T.; Miyaoka, H.; Yamada, H.; Van Soest, R. W. M. *J. Nat. Prod.* **2001**, *64*, 1506.
12. Gripenberg, J. *Acta Chem. Scand.* **1981**, *B35*, 513.
13. Nicolaides, D. M.; Gautam, D. M.; Litinas, K. E.; Papamehael, T. *J. Chem. Soc., Perkin Trans. 1* **2002**, 1455.
14. (a) Tietze, L. F. *Chem. Rev.* **1996**, *96*, 115 and references cited therein; (b) Tietze, L. F.; Modi, A. *Med. Res. Rev.* **2000**, *20*, 304; (c) Tietze, L. F.; Rackelmann, N. *Pure Appl. Chem.* **2004**, *76*, 1967; (d) Bhar, S.; Ramana, M. M. *J. Org. Chem.* **2004**, *69*, 8935; (e) Bunte, J. O.; Rinne, S.; Mattay, J. *Synthesis* **2004**, *4*, 619; (f) Tietze, L. F.; Beifuss, U. *Angew. Chem., Int. Ed. Engl.* **1993**, *32*, 131; (g) Ho, T. L. *Tandem Organic Reactions*; Wiley: New York, NY, 1992.
15. (a) Jones, G. *Org. React.* **1967**, *75*, 204; (b) Tietze, L. F.; Beifub, U. *Comprehensive Organic Synthesis*; Trost, B. M., Ed.; Pergamon: New York, NY, 1991; Vol. 2; (c) Boger, D. L.; Weinreb, S. M. *Hetero Diels–Alder Methodology in Organic Synthesis*; Academic: San Diego, CA, 1987.
16. (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*, 1640; (d) Zhu, J.; Bienaymé, H. *Multicomponent Reactions*; Wiley-VCH: Weinheim, 2005; Chapter 5, pp 121–168.
17. Tietze, L. F.; Hippe, T.; Steinmetz, A.; Töpken, E. *Eur. J. Org. Chem.* **2001**, 1631.
18. (a) Simon, C.; Constantieux, T.; Rodríguez, J. *Eur. J. Org. Chem.* **2004**, 4957; (b) Zhu, J.; Bienaymé, H. *Multicomponent Reactions*; Wiley-VCH: Weinheim, Germany, 2005; Chapter 5; (c) Tietze, L. F. *J. Heterocycl. Chem.* **1990**, *27*, 47 and references cited therein.
19. (a) Appendino, G.; Cravotto, G.; Minassi, A. *Eur. J. Org. Chem.* **2001**, 3711; (b) Shanmugsundaram, M.; Manikandan, S.; Raghunathan, R. *Tetrahedron* **2002**, *58*, 997.
20. Shanmugsundaram, M.; Manikandan, S.; Raghunathan, R. *Tetrahedron* **2002**, *58*, 8957.
21. Snider, B. B.; Lu, Q. *J. Org. Chem.* **1996**, *61*, 2839.
22. (a) For a recent review, see: Van De Water, R. W.; Pettus, T. R. *Tetrahedron* **2002**, *58*, 5367; (b) Barrero, A. F.; Quílez del Moral, J. F.; Herrador, M.; Arteaga, P.; Cortés, M.; Benites, J.; Rosellón, A. *Tetrahedron* **2006**, *62*, 6012; (c) Zhou, G.; Zheng, D.; Da, S.; Xie, Z.; Li, Y. *Tetrahedron* **2006**, *47*, 3349.
23. (a) Pettigrew, J. D.; Bexrud, J. A.; Freeman, R. P.; Wilson, P. D. *Heterocycles* **2004**, *62*, 445; (b) Pettigrew, J. D.; Freeman, R. P.; Wilson, P. D. *Can. J. Chem.* **2004**, *82*, 1640.
24. Rodriguez, R.; Adlington, R. M.; Moses, J. E.; Cowley, A.; Baldwin, J. E. *Org. Lett.* **2004**, *6*, 3617.
25. (a) Valderrama, J. A.; Pessoa-Mahana, D.; Tapia, R. A.; Rojas de Arias, A.; Nakayama, H.; Torres, S.; Miret, J.; Ferreira, M. E. *Tetrahedron* **2001**, *57*, 8653; (b) Zuloaga, F.; Tapia, R.; Quintanar, C. *J. Chem. Soc., Perkin Trans. 2* **1995**, 939; (c) Brimble, M. A.; Nairn, M. N.; Prabahara, H. *Tetrahedron* **2000**, *56*, 1937; (d) Spyroudis, S. *Molecules* **2000**, *5*, 1291.
26. Gras, J. L. *Tetrahedron Lett.* **1978**, *24*, 2211.
27. (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; (c) Hoz, A. D.; Diaz-Ortiz, A.; Moreno, A. *Curr. Org. Chem.* **2004**, *8*, 903; (d) Nüchter, M.; Ondruschka, B.; Bonrath, W.; Gum, A. *Green Chem.* **2004**, *6*, 128; (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; (g) Varma, R. S. *Green Chem.* **1999**, *43*, 1; (h) Loupy, A.; Perreux, L. *Tetrahedron* **2001**, *57*, 9199.
28. Xiao, Z. Z.; Chen, C. F. *J. Org. Chem.* **2005**, *70*, 917.
29. (a) Wang, H.; Wang, Y.; Han, K. L.; Peng, X. J. *J. Org. Chem.* **2005**, *70*, 4910; (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*; Wiley: West Sussex, 2002.
30. In order to corroborate the proportion of diastereomers resulting from each DKHDA, the samples were analyzed by HPLC using the conditions described in Section 4.
31. (a) Fergus, S.; Bender, A.; Spring, D. *Curr. Opin. Chem. Biol.* **2005**, *9*, 304; (b) Burke, M. D.; Schreiber, S. L. *Angew Chem., Int. Ed.* **2004**, *43*, 46; (c) Schreiber, S. L. *Science* **2000**, *287*, 1964.
32. The chiral enol ether was synthesized as described in the following references: (a) Denmark, S. E.; Schute, M. E. *J. Org. Chem.* **1991**, *56*, 6738; (b) Clark, R. C.; Pfeiffer, S. S.; Boger, D. L. *J. Am. Chem. Soc.* **2006**, *128*, 258.
33. Lindsey, C.; Pettus, T. *Tetrahedron Lett.* **2006**, *47*, 201.
34. Perrin, D. D.; Amarego, W. L. F. *Purification of Laboratory Chemicals*, 3rd ed.; Pergamon: Oxford, 1988.
35. Nonius, R. V. *Nonius Kappa CCD Server Software*; Delft, The Netherlands, 1998.
36. Otwinowsky, Z.; Minor, W. *Methods in Enzimology, Macromolecular Crystallography Part A*; Carter, C. E., Sweet, R. M., Eds.; Academic: New York, NY, 1997.
37. Sheldrick, G. M. *SHELXL-97: Program for the Refinement of Crystal Structures*; University of Göttingen: Germany, 1997.
38. Altomare, A.; Burla, M. C.; Camalli, M.; Cascarano, G.; Giacovazzo, C.; Guagliardi, A. R. *J. Appl. Crystallogr.* **1999**, *32*, 115.
39. Spek, A. L. *PLATON*; University of Utrecht: The Netherlands, 2003.