Organic & Biomolecular Chemistry

PAPER

View Article Online
View Journal | View Issue

Cite this: *Org. Biomol. Chem.*, 2019, **17**, 692

Site-selectivity control in hetero-Diels–Alder reactions of methylidene derivatives of lawsone through modification of the reactive carbonyl group: an experimental and theoretical study†

Maria Tsanakopoulou, [a] Erifili Tsovaltzi,[a] Marina A. Tzani, [a] Periklis Selevos,[a] Elizabeth Malamidou-Xenikaki, *[a] Evangelos G. Bakalbassis[b] and Luis R. Domingo [c]

Received 25th September 2018,
Accepted 18th December 2018

DOI: 10.1039/c8ob02383b

rsc.li/obc

A new perspective on the reactivity of hydroxyquinones was revealed as an acetal derivative of lawsone was synthesized, isolated, and used in tandem Knoevenagel/hetero-Diels–Alder reactions catalyzed by *S*-proline. The intermediate alkylidene-1,3-diones that were formed *in situ* reacted with electron rich alkenes to predominantly afford pyrano-1,2-naphthoquinone (β-lapachone) derivatives along with the isomeric pyrano-1,4-naphthoquinone (α-lapachone) derivatives in high to excellent total yields. Interestingly, the highly reactive arylidene-1,3-dione derivatives were found to be stable and isolable. DFT calculations suggest that these hetero-Diels–Alder reactions have a high polar character, taking place through a *two-stage one-step* mechanism. An analysis of the conceptual DFT indices allows explaining the remarkable site-selectivity observed.

Introduction

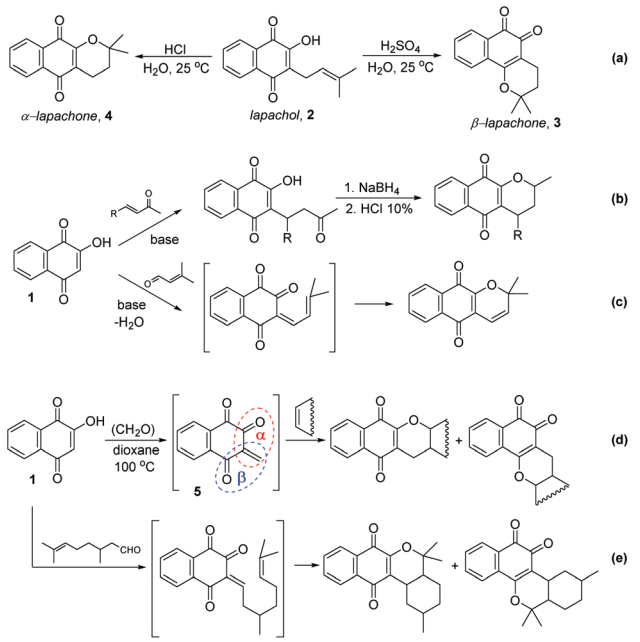
The synthesis of hydroxyquinone derivatives is of great importance in organic chemistry as these compounds consist of versatile synthetic intermediates.[1] A characteristic example of this class of compounds is lawsone (2-hydroxy-1,4-naphthoquinone, **1**) which was isolated from the henna plant (*Lawsonia inermis*) and has been extensively studied.[2] Lawsone (**1**) can be considered as the stable enol form of a β-diketone that can be either *O*-alkylated or *C*-alkylated. Lapachol [2-hydroxy-3-(3-methylbut-2-en-1-yl)naphthalene-1,4-dione, **2**] was obtained in low yield from the reaction of a lithium salt of lawsone with dimethylallyl bromide,[3a] whereas the palladium-catalysed allylation of lawsone with allyl alcohols and allyl esters[3b] offered an easy access to 3-allyl-2-hydroxy-1,4-naphthoquinones. Alternatively, *C*-alkylation was achieved *via* the Michael addition of lawsone (**1**) to nitroolefins under aqueous conditions (Scheme 1)[4] and to α,β-unsaturated carbonyl compounds as will be discussed below. Interestingly, functionalization of the 3-position with a phenyliodonium group enriched the chemistry of lawsone by providing the opportunity for the formation of new 3-aryl and 3-styryl substituted 2-hydroxynaphthoquinone derivatives.[5–9]

Continuing our studies on the reactivity of hydroxyquinones and their potential cyclized derivatives, pyranonaphthoquinones attracted our interest, especially as these compounds exhibit a range of important biological activities. More specifically, β-lapachone (**3**) is a naturally occurring pyrano-1,2-naphthoquinone, which was isolated from the lapacho tree (*Tabebuia avellanedae*)[10] and showed significant antineoplastic activity against various human cancer cells without affecting the non-cancerous cells.[2,11,12] After searching the literature, we realized that hydroxynaphthoquinones, which represent excellent starting materials for the synthesis of pyranonaphthoquinones, predominantly yielded the pyrano-1,4-naphthoquinone (α-lapachone, **4**) derivatives. β-Lapachone (**3**) exhibits more remarkable biological activities than its α-isomer **4** and, thus, we decided to investigate the potential reactivity of lawsone (**1**) toward the synthesis of β-lapachone derivatives.

Regarding the known syntheses of pyranonaphthoquinones, we will discuss herein the ones related to the present work. Sulfuric acid catalyzed cyclization of lapachol (**2**) afforded the angular β-lapachone (**3**) as the C-2 hydroxyl group attacked the protonated double bond, while the hydrochloric

[a]*Laboratory of Organic Chemistry, School of Chemistry, Faculty of Sciences, Aristotle University of Thessaloniki, 54124 Thessaloniki, Greece. E-mail: malamido@chem.auth.gr; Fax: (+30) 2310 997679; Tel: (+30) 2310 997874*
[b]*Laboratory of Applied Quantum Chemistry, School of Chemistry, Faculty of Sciences, Aristotle University of Thessaloniki, 54124 Thessaloniki, Greece*
[c]*Universidad de Valencia, Departamento de Química Orgánica, Dr Moliner 50, E-46100 Burjassot, Valencia, Spain*

†Electronic supplementary information (ESI) available: Detailed experimental procedures, copies of NMR spectra and computational data. See DOI: 10.1039/c8ob02383b



Scheme 1 Synthetic approaches to pyranonaphthoquinones starting from hydroxynaphthoquinones.

acid catalyzed reaction led to the synthesis of the linear α-lapachone (**4**) by an alternative attack of the C-4 quinonic oxygen (Scheme 1a).[13] However, this synthetic method is limited by the low yielding synthesis of lapachol (**2**).[3] Furthermore, the Michael addition of lawsone (**1**) to α,β-unsaturated carbonyl compounds followed by sodium borohydride reduction and acid-catalyzed cyclization led exclusively to α-lapachone derivatives (Scheme 1b).[14,15] Similar products were obtained from the base-catalyzed addition of lawsone to α,β-unsaturated aldehydes followed by electrocyclization (Scheme 1c).[16] These dehydro-α-lapachones could then be converted to α-lapachones by palladium-catalyzed hydrogenation.[16d,17] Regarding other examples of addition/cyclization cascade organocatalyzed reactions of hydroxynaphthoquinones with α,β-unsaturated carbonyl compounds, only the α-lapachone derivatives were initially obtained.[18] These products were then efficiently isomerized to the β-isomers in an extra synthetic step, which inevitably decreased the total yield of the synthesis.[18b] Interestingly, another pyranonaphthoquinone synthesis derived from the Knoevenagel condensation of lawsone (**1**) with aldehydes in refluxing dioxane that was followed by the Diels–Alder reaction with alkenes, enol ethers[19] or silyl enol ethers (Scheme 1d).[20] The reaction mixtures contained either exclusively α-lapachones[20] or both α- and β-lapachone derivatives[19] that were usually enriched in the α isomer (α : β ratio: 0.94–3.75). This attractive three-component one-pot protocol was mostly limited to Knoevenagel condensations with formaldehyde.[21] In the case of arylaldehydes in ethanol/water solvent, the rate, regioselectivity and yield of the reaction were improved.[22] Although the α : β ratio was found to be 3.1–4.7 for the reactions with formaldehyde in ethanol/water, this changed dramatically to 0.6–0.8 for the reactions with arylaldehydes. Accordingly, the Knoevenagel condensation of lawsone (**1**) with an aldehyde bearing a remote double bond, like citronellal, led to the tandem intramolecular hetero-Diels–Alder reaction of the alkylidene-1,3-dione intermediate and the synthesis of tetracyclic α- and β-pyranonaphthoquinones (Scheme 1e).[16b,23] However, the selectivity of these reactions was low and the ratio of α : β lapachone polycyclic derivatives ranged from 1.0 to 0.6.

Our interest was drawn to the one-pot synthesis of lapachone derivatives through domino Knoevenagel/hetero-Diels–Alder (DKHDA) reactions. Considering the electrophilic character of the heterodiene participating in this hetero-Diels–Alder reaction, we reasoned that the site-selectivity would be driven by the C-1 carbonyl of lawsone (**1**). Therefore, this carbonyl has the potential to attract electrons and, thus, further increase the reactivity of the electron poor α-heterodiene compared to the remote β-heterodiene (depicted as **α** and **β**, respectively, in Scheme 1) that is also present in the molecule. We thus envisaged that the site-selectivity of the cycloaddition could be altered in favor of the desired β-lapachone derivatives by amending the effect of the carbonyl at C-1, which is also the most reactive one of lawsone (**1**). For this purpose, we decided to investigate the effect of the modification of this carbonyl to an acetal group, which would be bulkier and less electron withdrawing. Subsequently, we studied the site-selectivity of the cycloaddition reactions with electron rich dienophiles aiming at the selective formation of β-lapachone derivatives and herein we report our experimental results along with our DFT theoretical studies, which are in total agreement.

Results and discussion

Chemistry

Our plan of differentiating the reactivities of the two heterodiene moieties of the 3-methylidene derivatives of lawsone was based on information from the literature for several hetero-Diels–Alder reactions which are considered polar, asynchronous one-step processes.[24,25] Their feasibility has been related to the electrophilic and nucleophilic character of each one of the two reagents, and hence to the polar character of the transition state structure (TS).[26]

We carried out a preliminary theoretical study for the model compounds **6**, **7**, **8**, and **9** (Fig. 1) bearing only one heterodiene group. This study verified the significant effect of the carbonyl group acetalization on the ω value of model compound **7** compared to that of **6** (see later, Table 2). We found that acetalization of the carbonyl group reduces the electrophi-

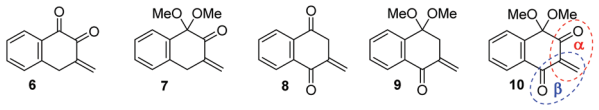
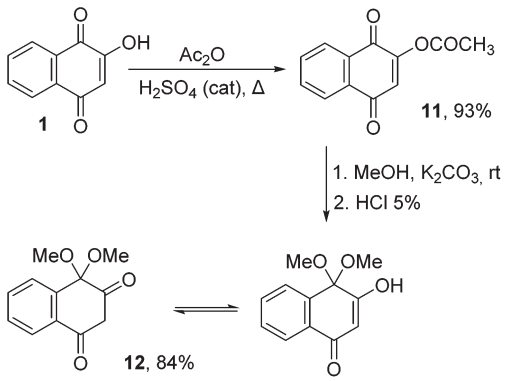


Fig. 1 Model compounds used for the theoretical study.

licity of the α-heterodiene functional group. On the other hand, a similar transformation of the model compound **8** toward acetal **9** resulted in a smaller decrease of the calculated ω value, signaling a favorable effect on the reactivity of the β-heterodiene functional group. An even greater effect resulted from the analogous acetalization of compound **5** affording **10**. Obviously, acetalization of the C=O group affects the electrophilicity of the α-heterodiene group to a greater extent than that of the β-heterodiene.

Based on the encouraging theoretical results above, we prepared the acetal of lawsone **12**, in very good total yield, through a two-step course (Scheme 2). The acetate **11**[27] was initially prepared upon treatment of lawsone with acetic anhydride and isolated by filtration in 93% yield. The most electrophilic carbonyl group of **11** was then selectively acetalized in a methanolic suspension of K_2CO_3. Efforts to form such acetal derivatives by directly applying the conventional acid catalyzed process were unsuccessful due to the activation of all three carbonyl groups in nucleophilic attacks through tautomerization. Acetal **12** was isolated by crystallization in 84% yield and it was found to exist in equilibrium with its keto form in $CDCl_3$ solution according to the NMR data that we recorded. In different ^{1}H NMR experiments, the keto/enol ratios varied from 1.9 : 1 to 2.2 : 1 or 3.4 : 1 depending probably on the concentration of the contextual $CDCl_3$ solution and perhaps on the quality of the solvent. Although acetal **12** is readily hydrolyzed upon standing, it can be kept unchanged for a long time in a freezer.



Scheme 2 Preparation of the starting acetal **12**.

We first tried the reaction of **12** with aldehyde **13b** applying conditions (Table 1, entry 1) similar to the ones described in the literature[23] for *in situ* reactions of lawsone with aldehydes. The alkylidene derivative **14b** was isolated in low yield (10%). In order to optimize the reaction conditions, a series of experiments presented in Table 1 were conducted. Reactions were performed in various solvents (CH_2Cl_2, C_6H_6, DME, and MeOH) and basic catalysts (K_2CO_3, pyrrolidine, DMAP, glycine, L-alanine, DL-piperidin-2-carboxylic acid, and *S*-proline), under reflux, microwave irradiation (MW) or at rt, but without significant improvement of the yield. Addition of anhydrous $MgSO_4$ proved to be essential as it resulted in a spectacular increase in the yield of product **14b** (entries 7 and 11). The effect of the ratio of the reactants was also investigated by using an excess of the aldehyde from 1 : 1 to 1 : 3 (Table 1, entries 11, 12, and 13). Interestingly, a twofold excess of the aldehyde gave 73% yield of the product **14b** (entry 12). The optimal reaction conditions were used for the preparation of all the arylidene-1,3-diones **14** and are outlined as follows: stirring of a solution of **12** and **13** (ratio 1 : 2) in CH_2Cl_2 at rt, in the presence of anhydrous $MgSO_4$ and an *S*-proline catalyst (20 mol%).

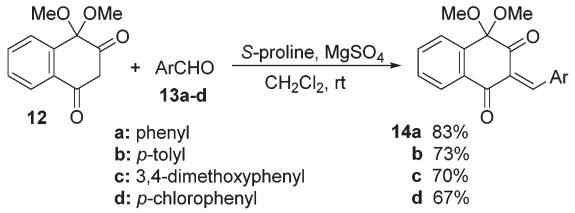
The arylidene compounds **14** were obtained in very good yields (Scheme 3) and isolated in pure state from the reaction mixture by column chromatography in the form of the *Z*-isomer, although indications exist for the formation of small amounts of the *E*-isomer. The isolation of one stereoisomer **14** in very good yield is rather indicative of the remarkable stereoselectivity of the above reaction. Arylidene-1,3-diones **14** are stable compounds and can be stored for a long time in the freezer.

We base the elucidation of the stereochemical structure of the new isolable compounds **14** on their $^3J_{CH}$ coupling constants between the C-1 and C-3 carbonyl carbons with the alkenyl hydrogen. As depicted in Fig. 2, the C-3 (δ = 194.2) and

Table 1 Optimization of conditions for the preparation of arylidene-1,3-dione **14b**

	Solvent	**12 : 13b**	Catalyst (dehydrating agent)	Temperature (°C)	Yield (%)
1	MeOH	1 : 1	Ethylenediamine·2HCl	Reflux	10
2	DME	1 : 1	Ethylenediamine·2HCl	80	—
3	C_6H_6	1 : 1	*S*-Proline	80	9
4	CH_2Cl_2	1 : 2	*S*-Proline	45	21
5	CH_2Cl_2	1 : 2	*S*-Proline	80 (MW)	—
6	CH_2Cl_2	1 : 2	[a]	25	0–20
7	CH_2Cl_2	1 : 1	*S*-Proline	25	10
8	CH_2Cl_2	1 : 2	*S*-Proline	25	30
9	MeOH	1 : 2	*S*-Proline	25	—
10	CH_2Cl_2	1 : 2	*S*-Proline (DCC)	25	—
11	CH_2Cl_2	1 : 1	*S*-Proline ($MgSO_4$)	25	52
12	CH_2Cl_2	1 : 2	*S*-Proline ($MgSO_4$)	25	73
13	CH_2Cl_2	1 : 3	*S*-Proline ($MgSO_4$)	25	76

[a] Various catalysts were tested: glycine, L-alanine, pyrrolidine, DMAP, K_2CO_3, DL-piperidine-2-carboxylic acid.



Scheme 3 Preparation of the stable 2-arylidene-1,3-diones **14**.

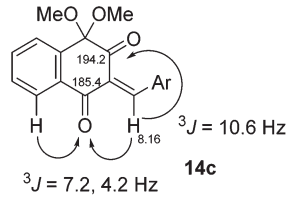


Fig. 2 $^{3}J_{CH}$ coupling constants of compound **14c**.

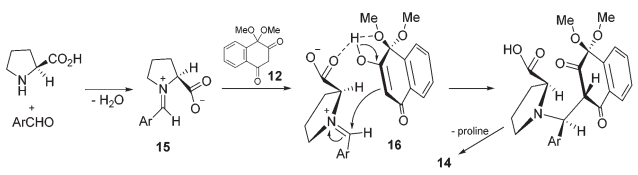
C-1 (δ = 185.4) carbonyls of **14c** appear as a doublet ($^{3}J_{CH}$ = 10.6 Hz) and a doublet of doublets ($^{3}J_{CH}$ = 7.2, 4.2 Hz), respectively. In accordance with the literature,[28,29] the greater ^{3}J value is assigned to the carbonyl carbon positioned trans to the alkenyl hydrogen, namely C-3.

The selective formation of the *Z*-isomer, which, incidentally, was calculated to be more stable by 0.4 kcal mol^{-1} than the *E*-isomer for **14b** (Table S3†), could be attributed to the catalytic activity of proline whose action as an effective organocatalyst in asymmetric aldol reactions[30] is well known. With regard to the mechanism, we assume that the reaction of *S*-proline with arylaldehyde **13** results in the asymmetric iminium ion **15** (Scheme 4) which is subsequently attacked by β-diketone **12**. A hydrogen bonded intermediate like **16** provides stereochemical selectivity. Analogous iminium ions have been reported to mediate in asymmetric Michael additions[18b] of lawsone to α-unsaturated aldehydes.

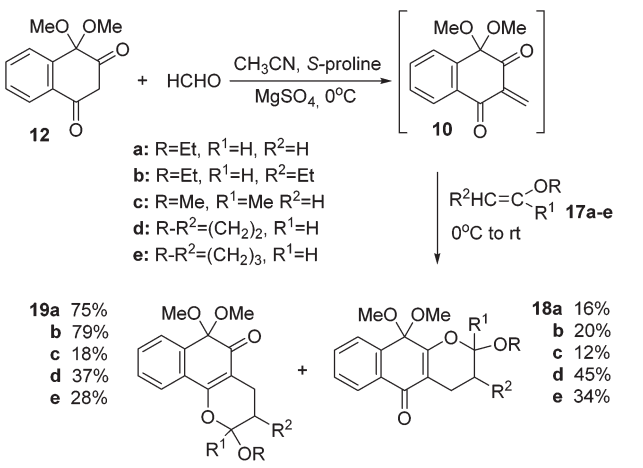
Considering the above good results we tried the reaction of acetal **12** with HCHO in order to prepare the methylidene derivative of lawsone **10**. In particular, the acetal **12** reacted with an aqueous solution (37%) of formaldehyde (3.6 equiv.) in CH_3CN, at 0 °C, in the presence of a catalytical amount of *S*-proline and anhydrous $MgSO_4$ as the dehydrating agent. After 1 day at rt, the isolation of product **10** was not possible due to its high reactivity. In order to trap the alkylidene derivative **10** as a Diels–Alder product, the reaction was repeated in the presence of a dienophile. After 30 min at 0 °C, an excess of ethoxyethene (**17a**) was added and the mixture was stirred at room temperature overnight. Products **18a** and **19a** were formed and then isolated by column chromatography in 16% and 75% yields, respectively (Scheme 5). Under these optimized conditions, the analogous reactions with some β- (**17b**) or α-substituted (**17c**) and cyclic enol ethers (**17d,e**) were performed and the products **18b,d,e** and **19b,d,e** were isolated in good to excellent yields. In the case of dihydropyran **17e** the total yield appears relatively reduced, possibly due to steric effects. The very low yield in the case of **17c** is due to the formation of by-products, as will be discussed below.

The distinction between isomers **18** and **19** was based on their ^{1}H NMR and ^{13}C NMR spectra. Specifically, the ^{13}C NMR peak for the more conjugated carbonyl carbon of the dihydrobenzo[*g*]chromenones **18** appeared upfield (δ_C between 183.8 and 183.4 ppm) relative to that of the dihydrobenzo[*h*]chromenones **19** (δ_C between 192.9 and 192.3 ppm). On the other hand, the aromatic hydrogens of the compounds exhibit characteristic patterns in the ^{1}H NMR spectrum. In the spectrum of **19** all aromatic hydrogens resonate between 7.42 and 7.87 ppm. The two doublets for the hydrogens adjacent to the junction give distinguishable peaks at 7.87–7.79 and 7.70–7.69 ppm, whereas the peaks of the other two hydrogens are very close and almost overlap each other at 7.49–7.47 and 7.46–7.42 ppm. In contrast, the ^{1}H NMR spectra of the isomers **18** show separate peaks for each of the four aromatic hydrogens, three of them at 7.72–7.68, 7.64–7.60 and 7.51–7.50 and one, corresponding to the hydrogen positioned *ortho* to the carbonyl group, at lower field values of 8.12–8.09 ppm.

The results of the above reactions fully verify the theoretical predictions. Indeed, the transformation of the carbonyl functional group into its corresponding acetal appears to contribute to the reversal of the site-selectivity of the DKHDA reactions of lawsone. The reactions of the unsubstituted and β-substituted open chain enol ethers **17a,b** with the *in situ* generated alkylidene-1,3-dione **10** exhibit excellent selectivity



Scheme 4 Proposed mechanism for the proline-catalyzed stereoselective synthesis of arylidene-1,3-diones **14**.



Scheme 5 Reactions of the *in situ* generated alkylidene-1,3-diones **10** with alkyl vinyl ethers **17**.

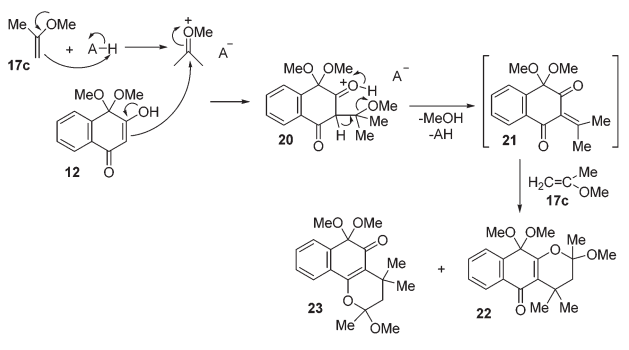
toward the cycloaddition product of the β-heterodiene group **19a,b**, the product α : β ratio ranging from 0.21 to 0.25. The site-selectivity decreases significantly in the case of cyclic ethers **17d,e** (α : β = 1.21). The calculated nucleophilicity indexes suggest that they, along with steric factors, play an important role. In analogous DKHDA reactions of lawsone with HCHO and 2-(methoxyvinyl)benzene or ethoxyethene mentioned in the literature,[19] the α : β ratio is 3.75 and 1.67, respectively. Furthermore, the isolation of product α, in 60% yield, is only referred from the corresponding reaction with 1-(vinyloxy)butane. With respect to the reaction of **17e**, products of the α (**18e**) and β (**19e**) series were formed in yields of 34% and 28%, respectively, while for the corresponding reaction of lawsone, the formation of the analogous β product, in yield 12%, was only reported.[31]

In the case of 2-methoxypropene (**17c**), product **19c** predominates again, but the selectivity of the reaction is noticeably reduced (α : β ratio: 0.66). Both the reduced yield and the lower selectivity of this reaction could be attributed to stereochemical factors. Regarding the low yields of the products, it should be noted that, in addition to products **18c** and **19c**, the unexpected products **22** and **23** were also isolated in yields of 11% and 27%, respectively (Scheme 6). These products could be derived from an analogous DKHDA process in which the Knoevenagel condensation product **21** is initially formed from the reaction of acetal **12** with acetone, deriving probably from the partial hydrolysis of enol ether **17c**, and is then subjected to a hetero-Diels–Alder reaction with **17c**. Nevertheless, when acetone was used instead of HCHO in the reaction of **12** with **17c**, under similar conditions, the products **22** and **23** were not detected. In Scheme 6, a possible route for the formation of these products is proposed, which involves protonation of the methoxy group of **17c**, perhaps by the *S*-proline or the acidic acetal **12**, and its subsequent nucleophilic attack by **12**. Elimination of methanol from the intermediate **20** results in the unstable heterodiene **21** from which the cycloaddition products **22** and **23** are finally formed upon the reaction with **17c**. Following this observation, the overall yield of the cycloaddition products coming from the α-heterodiene group rises up to 23% and that derived from the β-heterodiene group to 45% (overall α : β ratio: 0.51). In contrast, the analogous reaction of lawsone with 2-methoxy-1-propene is referred[19] to give only the α-lapachone derivative in 60% yield.

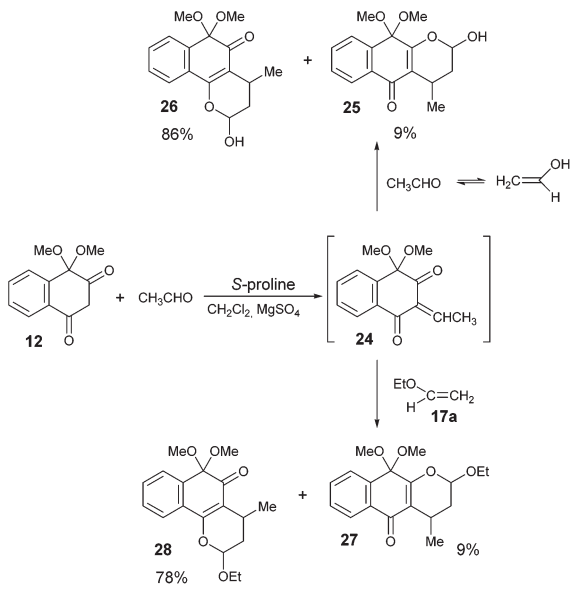
Both results recorded in Scheme 5 for the hetero-Diels–Alder reaction of compound **10** with ethoxyethene (**17a**) and that reported in the literature for the corresponding reaction of **5** are in excellent agreement with the theoretical study that we carried out (see the theoretical study below).

In our effort to synthesize heterodiene analogues of **14** from aliphatic aldehydes, we attempted the reaction of **12** with acetaldehyde under conditions similar to those applied earlier for formaldehyde. When the reaction with an excess of acetaldehyde was performed at rt in CH_2Cl_2 using *S*-proline as the catalyst and anhydrous $MgSO_4$ as the dehydrating agent, the products **25** and **26** were isolated as a non-separable mixture in 95% total yield and in a ~1 : 8.5 ratio as estimated by ^{1}H NMR (Scheme 7). In our attempt to separate the products **25** and **26** by silica column chromatography we observed their hydrolysis. The products apparently derived from the *in situ* generated Knoevenagel condensation product **24**, which then participated in a hetero-Diels–Alder reaction with the acetaldehyde enolate. The relative ratio **25** : **26** confirms, once again, the excellent site-selectivity of the cycloaddition. High selectivity was also shown by the same reaction when carried out in the presence of ethoxyethene **17a** from which the products **27** (yield 9%) and **28** (78%) were obtained.

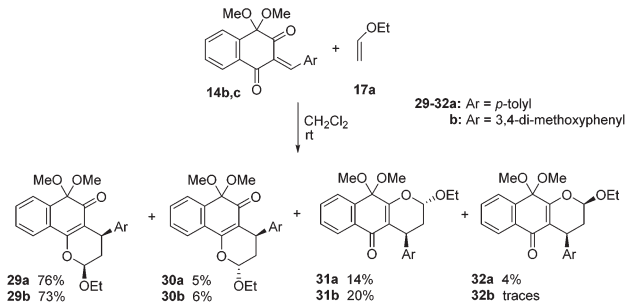
Equally remarkable site-selectivity, and at the same time excellent stereoselectivity, was also demonstrated by the hetero-Diels–Alder reactions of the stable heterodienes **14b,c** with ethoxyethene (**17a**), with which our research effort continued. These reactions took place under mild conditions (CH_2Cl_2, rt) and afforded the four cycloaddition products **29–32a,b** depicted in Scheme 8, in quantitative total yields. Both products **29**, **30** and **31**, **32** are pairs of diastereomers



Scheme 6 A plausible mechanistic scheme for the formation of products **22** and **23**.



Scheme 7 Reactions of the *in situ* generated ethylidene derivative of lawsone **24** with acetaldehyde and ethoxyethene.

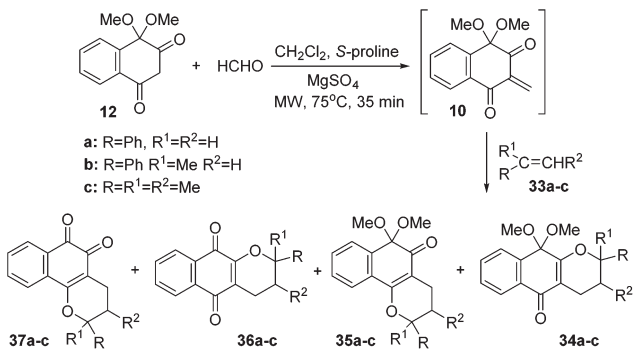


Scheme 8 Hetero-Diels–Alder reactions of the stable arylidene derivatives of lawsone **14** with ethoxyethene.

derived from the *endo* (**29**, **31**) or *exo* (**30**, **32**) cycloaddition mode of the dienophile to the β- and α-heterodiene group, respectively. The separation of the products was laborious and was accomplished by successive chromatography columns. The stereochemical structure elucidation of the products was based on NOESY experiments from which a *syn*-configuration for the 2-H and 4-H of the pyran ring was assumed in the case of cycloadduct **29a** and an *anti*-configuration for the same hydrogens in the case of **31a**.

Our findings suggest that both the yields and the site-selectivity of the hetero-Diels–Alder reactions studied are very good with the activated dienophiles. Furthermore, they are virtually unaffected by the alkylidene group substitution of the substrates, but both are significantly affected by the degree of substitution and the stereochemical hindrance of dienophiles.

We also investigated the analogous hetero-Diels–Alder reactions of the *in situ* formed alkylidene compound **10** with the less activated alkene dienophiles **33a–c** (Scheme 9). Due to the absence of a 2-alkoxy substituent on the pyran ring, the expected cycloadducts are supposed to be more stable than their analogs coming from the DKHDA reactions of **12** with aldehydes and enol ethers. The possibility of the pyran ring opening, which is observed in the latter products upon long standing at rt, and which is due to their acetal nature, is certainly eliminated.



Scheme 9 Reactions of the *in situ* generated arylidene-1,3-dione **10** with alkenes **33** under MW irradiation.

When the reactions were carried out at rt, that is under conditions analogous to those applied for the reactions of the enol ethers **17**, the observed overall yields of products **34** and **35** were low in the case of dienophiles **33a** (22%) and **33c** (13%) and moderate for **33b** (48%). This is to some extent due to steric factors, particularly in the case of **33c**, and simultaneously seems consistent with the relatively higher values of the calculated electrophilicity indexes, ω,[32] in combination with the lower values of the nucleophilicity indexes, N,[33] as compared to that of the enol ethers **17** (see below Table 2). Because of the difficulty of quantitatively separating products **34** and **35**, their relative proportions were evaluated from the ^{1}H NMR spectra of their crude mixtures as isolated by column chromatography. The estimated α : β (**34** : **35**) ratios were 1 : 1.48, 1 : 1.1 and 1 : 0.95 in the cases of dienophiles **33a**, **33b** and **33c**, respectively, reflecting the dependence of the site-selectivity on steric hindrances of dienophiles.

In an attempt to increase the yield and possibly improve the relative proportion of the products, the DKHDA reaction of **10** with HCHO and styrene **33a** was carried out under analogous conditions but in different solvents (CH_2Cl_2 and dioxane) or by using different energy sources. More specifically, thermal (reflux in ethanol solution), ultrasound (sonication in dioxane solution) or microwave irradiation (irradiation of the reactants in a microwave oven, in CH_2Cl_2, at 65 °C, 70 °C or 75 °C) was applied. The best result was obtained in the latter case where both consumption of all starting acetal **12** and the highest overall yields were observed.

These optimal conditions were also applied to the reactions of **10** with the alkenes **33b** and **33c**. The yield of the reactions increased, but in addition to the desired products **34** and **35**, their hydrolysis products **36** and **37** were also detected (Scheme 9). More specifically, under the intense reaction conditions that were applied, the products **36** and **37** could have derived either from the hydrolysis of the products **34** and **35** or from the hydrolysis of the intermediate **10** to **5** and a cycloaddition reaction with alkenes **33** or hydrolysis of the acetal **12** to lawsone **1** and a reaction with formaldehyde and then with alkenes **33**. Due to the almost identical R_f of the products **34**, **35** and **36**, the separation of the mixture by silica column chromatography was inefficient. Even though we did not purify the products in this instance, we could easily estimate the ratio of the products **34** and **35** by relative integration of the peaks of the methoxy groups in the ^{1}H NMR spectra of the crude mixtures. The α : β ratios found for the products **34a** : **35a**, **34b** : **35b**, and **34c** : **35c** were 1 : 1.75, 1 : 1.29, and 1 : 1.19, respectively, indicating again the site-selectivity for the β-cycloadducts, albeit significantly reduced. As reported in the literature,[21] the same reactions of lawsone (**1**) carried out *via* the intermediate **5** by heating in ethanol/water 1 : 1 gave almost quantitative overall yields, but the α : β ratio of the products ranged between 1 : 0.33 and 1 : 0.25. We then repeated the MW reaction and the crude mixture was hydrolyzed with TFA. The final mixtures of the hydrolyzed products **36** and **37** were purified by column chromatography in order to verify the formation of the cycloaddition products and to determine the

reaction yields (58% for **10**/**33a**, 71% for **10**/**33b**, and 28% for **10**/**33c**) that greatly increased compared to those of the reactions at rt. It is remarkable that even the less activated alkene dienophiles **33a–c** showed again site-selectivity in the DKHDA reaction with acetal **12**, validating once again that the latter constitutes an excellent tool for the synthesis of β-lapachone derivatives.

Theoretical study

Analysis of the conceptual DFT indices at the ground state of the reagents

Numerous studies devoted to polar and ionic organic reactions have shown that the analysis of the reactivity indices defined within Conceptual DFT (CDFT)[34] is a powerful tool to predict and understand the reactivity in polar reactions. The global indices, namely, the electronic chemical potential, μ, chemical hardness, η, electrophilicity, ω, and nucleophilicity, N, of the reagents involved in these hetero-Diels–Alder reactions are given in Table 2.

The electronic chemical potentials[35] μ of the ethylene derivatives **17a–d** and **33a–c**, between −3.43 (**33a**) and −2.18 (**17b**) eV, are higher than those of heterodienes, between −5.04 (**5**) and −4.06 (**7**) eV (see Table 2). These values suggest that along these polar hetero-Diels–Alder reactions, the Global Electron Density Transfer[36] (GEDT) will flux from the ethylenes towards the heterodienes.

The feasibility of a polar Diels–Alder reaction has been related to the polar character of the reaction measured through the analysis of the GEDT at the corresponding TSs.[26,36] This behavior can be anticipated analyzing the global electrophilicity[32] ω and nucleophilicity[33] N indices at the GS of the reagents. Compound **5** possessing three carbonyl groups is the most electrophilic species of this series of heterodienes, ω = 3.31 eV, being classified as a strong electrophile.[34] Acetalization of one carbonyl group in compound **10** (Fig. 1) decreases its electrophilicity to 2.44 eV, being also classified as a strong electrophile participating in polar Diels–Alder reactions. Similarly, dicarbonyl compounds **6** and **8** present high electrophilicity indices, ω = 2.80 eV and 2.35 eV, respectively. Finally, acetalization of one of the two carbonyl groups of compounds **6** and **8** markedly decreases their electrophilicity ω index to 1.80 eV (**7**) and 1.91 eV (**9**). Note that although the acetalization of one carbonyl group notably reduces the electrophilicity of the precursor compound, the acetal **10** possessing two carbonyl groups participates in polar hetero-Diels–Alder reactions.

On the other hand, ethylene derivatives **17a–d** and **33a–c** have nucleophilicity N indices ranging from 2.98 (**33c**) eV to 3.56 (**17d**) eV. Thus, while ethylene **33c** is located on the borderline of a moderate nucleophile, the other ethylene derivatives are classified as strong nucleophiles.[34]

Consequently, it is expected that the hetero-Diels–Alder reactions of heterodienes **5**, **10**, **6** and **8** with the electron-rich ethylenes **17a–d** and **33a–c** will have a highly polar character, and very low activation energy (see later).

Polar Diels–Alder reactions involving non-symmetrical substituted reagents present complete regioselectivity. The more favorable regioisomeric reaction path is that associated with a two-center interaction between the most electrophilic center of the electrophile and the most nucleophilic center of the nucleophile. Analysis of the Parr functions[37] permits characterizing these relevant centers, allowing us to explain the complete regioselectivity experimentally observed. The most electrophilic P_k^+ Parr function of **10**, and the most nucleophilic P_k^- Parr function of vinyl ether **17a** are given in Fig. 3. While at heterodiene **10** the terminal ethylene C1 carbon, P_k^+ = 0.57, presents the highest electrophilic Parr value, the non-substituted C5 carbon of vinyl ether **17a**, P_k^- = 0.62, presents the highest nucleophilic Parr value.

Consequently, it is expected that the more favorable regioisomeric reaction path will be that associated with the nucleophilic attack of the C5 carbon of vinyl ether **17a** on the C1 carbon of heterodiene **10**, in complete agreement with the experimental outcomes.

Interestingly, the electrophilic P_k^+ Parr functions at the β carbonyl group, 0.14 at the carbon and 0.13 at the oxygen, are

Table 2 The electronic chemical potential, μ, chemical hardness, η, electrophilicity, ω, and nucleophilicity, N, indices of the reagents involved in the hetero-Diels–Alder reactions

	μ	η	ω	N
5	−5.04	3.83	3.31	2.16
6	−4.64	3.84	2.80	2.56
14b	−4.44	3.83	2.57	2.77
10	−4.53	4.21	2.44	2.48
8	−4.62	4.54	2.35	2.23
9	−4.28	4.80	1.91	2.44
7	−4.06	4.56	1.80	2.78
33a	−3.43	5.20	1.13	3.09
33b	−3.31	5.42	1.01	3.10
33c	−2.55	7.17	0.45	2.98
17a	−2.41	7.22	0.40	3.10
17c	−2.32	7.26	0.37	3.17
17e	−2.25	6.93	0.37	3.40
17d	−2.20	6.71	0.36	3.56
17b	−2.18	7.02	0.34	3.43

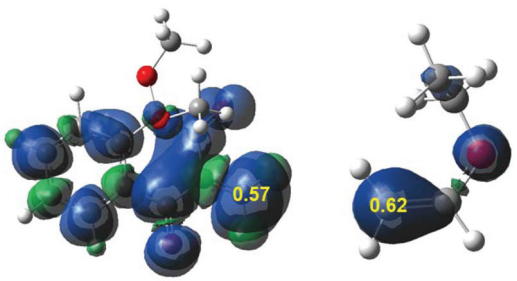


Fig. 3 3D representations of the Mulliken atomic spin density of the radical anion $\mathbf{10}^{\bullet-}$ and the radical cation $\mathbf{17a}^{\bullet+}$, together with the most electrophilic P_k^+ Parr function of **10**, and the most nucleophilic P_k^- Parr function of vinyl ether **17a**.

slightly larger than those at the α carbonyl group, 0.09 at the carbon and 0.04 at the oxygen. Consequently, a larger electron density is accumulated at the β carbonyl group through the GEDT taking place along this polar process. Therefore, along the second stage of the reaction, a more favorable electronic interaction takes place between the electron deficient C6 carbon of the ethylene framework and the β carbonyl oxygen, allowing us to explain the origin of the site-selectivity, *i.e. pseudocyclic* selectivity,[38] found in the hetero-Diels–Alder reaction of **10**.

Study of the polar hetero-Diels–Alder reaction of compounds 5 and 10 with ethyl vinyl ether 17a

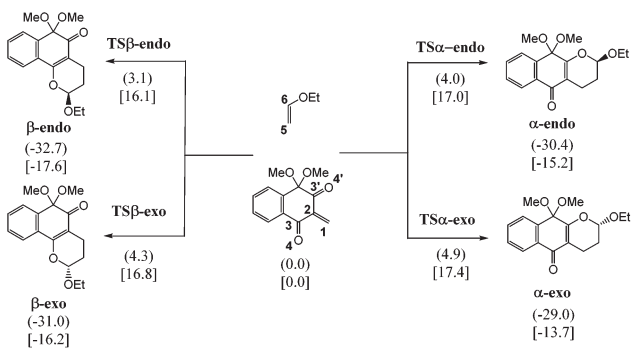
Due to the presence of two heterodiene frameworks at **5**, and the asymmetry of the reagents involved in this hetero-Diels–Alder reaction, eight competitive reaction paths are possible. They are related to a pair of regioisomeric reaction paths and a pair of *endo*/*exo* stereoisomeric reaction paths, for the participation of each of the two heterodiene frameworks. Due to the total regioselectivity found in polar Diels–Alder reactions, predicted by the analysis of the Parr functions, only the *endo* and *exo* stereoisomeric reaction paths associated with the formation of the C1(O4)–C5(C6) or C1(O4′)–C5(C6) single bonds were considered (see Scheme 10).

The activation enthalpies in DCM associated with the four competitive reaction paths dealing with the hetero-Diels–Alder reaction of **10** with **17a** are: 4.0 (**TSα-*endo***), 4.9 (**TSα-*exo***), 3.1 (**TSβ-*endo***) and 4.3 (**TSβ-*exo***) kcal mol^{-1}, the reaction being strongly exothermic by 29–33 kcal mol^{-1} (see Table S1†). Some appealing conclusions can be drawn from these energy values: (i) this hetero-Diels–Alder reaction presents a very low activation enthalpy due to the highly polar character of the reaction; (ii) this activation enthalpy is slightly lower than that associated with the hetero-Diels–Alder reaction involving compound **5** (see Fig. S2†); (iii) the *endo* approach modes are less energetic than the *exo* ones; (iv) the most favorable reaction path corresponds to the formation of the cycloadduct **β-*endo***, in complete agreement with the experimental outcomes; (v) as expected, the activation enthalpies associated with the *meta* TSs, ranging from 18.2 to 22.0 kcal mol^{-1} (Fig. S1†), are considerably higher than those associated with the *ortho* ones, in complete agreement with the analysis of the Parr functions; and finally, (vi) these hetero-Diels–Alder reactions are strongly exothermic by *ca.* 33 kcal mol^{-1}.

Inclusion of the entropies to the enthalpies increases the activation Gibbs free energies by *ca.* 13 kcal mol^{-1}, and decreases the exergonic character of these hetero-Diels–Alder reactions by 15 kcal mol^{-1} because of the unfavorable activation entropies associated with these bimolecular processes (see Table S1†). In spite of this, the selectivities are not modified, the **β-endo** reaction path being the most favorable one.

Highly polar Diels–Alder reactions involving non-symmetric reagents take place through highly asynchronous TSs associated with two-center interactions. Consequently, three stereoisomeric TSs associated with the two *gauche* and the *anti* approach modes of the C5 carbon of ethylene **17a** and the C6 carbon of heterodiene **10** are feasible. The two pairs of isomeric TSs given in Scheme 10 correspond to the *gauche* conformational approach modes of the C5–C6 double bond of the vinyl ether **17a** to the C1–C2 double bond of the heterodiene **10**. Additionally, two *anti* approach modes are feasible yielding two zwitterionic intermediates, which must rotate around the new C1–C5 single bond in order to achieve the formation of the corresponding cycloadducts (see Fig. S5, Scheme S1 and Table S1†). Although the activation enthalpies associated with the *anti* attacks are only 0.1 (**TS1α**) and 0.2 (**TS1β**) kcal mol^{-1} higher than that associated with **TSβ-*endo***, these energy differences rise to 1.3 (**TS1α**) and 1.4 (**TS2β**) kcal mol^{-1} at the TSs associated with the ring-closing step (see Table S1†). In this polar Diels–Alder reaction the *anti* reaction paths are somewhat competitive with the *gauche* ones.

The geometries of the four *gauche* TSs are shown in Fig. 4. Despite the different geometries derived for the corresponding



Scheme 10 Competitive stereoisomeric reaction paths associated with the polar hetero-Diels–Alder reaction of **10** with **17a**. Relative enthalpies in kcal mol^{-1} are given in parentheses, while relative Gibbs free energies in kcal mol^{-1} are given in brackets. Thermodynamic data were computed at 298.15 K in DCM.

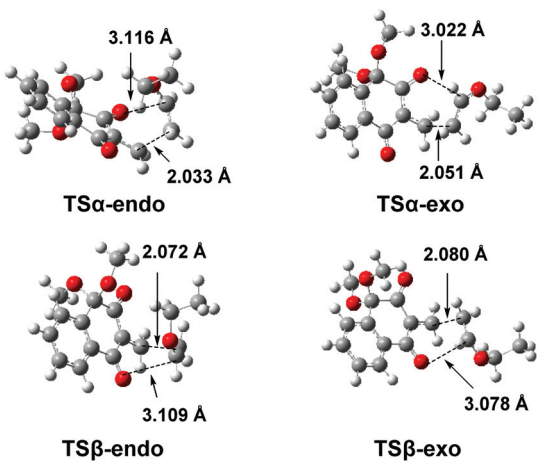


Fig. 4 Geometries of the four *gauche* TSs associated with the hetero-Diels–Alder reaction of **10** with **17a**.

reactant pairs, coming from the approach of the α- and β-heterodienes, the lengths of the C–C and C–O bonds forming at the TSs are of the same order of magnitude for all modes, ranging from 2.03 to 2.08 Å for the C1–C5 and from 3.02 to 3.12 Å for the O4(4′)–C6 single bonds. These lengths indicate that these TSs correspond to the highly asynchronous single bond formation processes. Analysis of the intrinsic reaction coordinates (IRCs) of the TSs indicates that these polar hetero-Diels–Alder reactions are associated with a non-concerted *two-stage one-step* mechanism,[39] in which the C6–O4 single bond formation begins when the first C1–C5 single bond is practically formed. Reactions **5**/**17a** show similar results (Fig. S2†).

The polar character of this hetero-Diels–Alder reaction was analyzed by computing the GEDT values at the corresponding TSs. These values at the *endo* TSs, 0.40*e* at **TSβ-*endo*** and 0.42 at **TSα-*endo***, point to the highly polar character of this hetero-Diels–Alder reaction. This finding is in complete agreement with the very low computed activation enthalpies.[26]

Calculations of other specific polar hetero-Diels–Alder reactions

The most favourable **14b**/**17a** β-type reaction paths were only studied, in line with the above results. It was shown that they exhibit the same characteristics as those of the **10**/**17a** reaction, being polar Diels–Alder ones, presenting a highly asynchronous mechanism. Moreover, the significant increase of the energies for these TSs (15.6 kcal mol^{-1} and 16.8 kcal mol^{-1}, for the **TSβ-*endo*** and the **TSβ-*exo***, respectively; see also Table S3†) compared to those of the **10**/**17a** reaction could be attributed to the significant steric hindrance introduced by the tolyl group of **14b**. It is worth noting here that the **14b**/**17a** reactions studied are medium exothermic processes; the cycloadducts **29a** and **30a** are located −24.1 and −21.1 kcal mol^{-1} below the reagents.

Calculations also showed that the **α-*endo*** and **β-*endo*** isomers from the reactions **10**/**33a** and **10**/**33c** afforded higher corresponding activation energy values (shown in Fig. S3 and S4,† respectively), than those of reaction **10**/**17a**, which could be associated with the lower reaction yields derived. Moreover, the low preference for the *endo* cycloadducts of the β-heterodiene group, exhibiting the lowest activation energies calculated – signifying also its higher electrophilicity with respect to that of the α-heterodiene group – is in line with the site-selectivity of the above reactions.

Conclusions

In this work, we developed a new and efficient method for the synthesis of the 1,1-dimethoxy acetal of lawsone under basic conditions. The alkylidene and arylidene derivatives of this protected lawsone were prepared through Knoevenagel condensation and they possessed two distinct heterodiene (α and β) parts that exhibited reduced overall electrophilicity relative to their unprotected analogs. This led to stabilization of the aryl substituted alkylidene derivatives, thus enabling their isolation and increasing the site-selectivity of their hetero-Diels–Alder reactions under mild conditions. The cycloadducts that derived from the β-heterodiene part resemble the β-lapachone structure and are the ones that were predominant in most of the reactions. Beyond this, a reversal of the site-selectivity was also observed in relation to that of the analogous hetero-Diels–Alder reactions of the corresponding unprotected derivatives, where the cycloaddition products of the α-heterodiene moiety predominated. The yields and the selectivity of the reactions studied were not significantly influenced by the substituents of the heterodiene groups. They were, however, affected by the type of substitution of the individual dienophiles and mainly by the steric hindrance they introduce.

The reactivity of the new dihydrobenzochromenone acetals was found to be reduced due to the selective protection of their most reactive carbonyl group. An application of this highly selective methodology in the synthesis of new functionalized quinone derivatives is currently in progress.

DFT calculations were in good agreement with the reactivity and site-selectivity of the reactions, revealing their polar nature and the operation of an asynchronous *two-stage one-step* mechanism. At the same time, our calculations precluded the operation of an alternative stepwise mechanism through a successive Michael addition/cyclization.

Experimental

Computational details

Details on the computational method used are given in a recent paper.[25] The B3LYP/6-31G(d) level of theory,[40,41] was used throughout for the study of the stationary points found in the potential energy surfaces (PES), since it was shown to be suitable for the analysis of the geometric and electronic properties of Diels–Alder reactions.[42] The determination of the appropriate TSs connecting reactants and products has been confirmed by IRC calculations,[43] and intrinsic reaction paths (IRPs) were traced from the various TSs to ensure that no further intermediates exist. Solvent effects of DCM were considered using the polarisable continuum model (PCM) developed by Tomasi's group.[44] Thermodynamic data were computed at 298.15 K in DCM. The GEDT[36] at the TSs were analyzed using the Natural Bond Order (NBO) method.[45] CDFT global reactivity indices and Parr functions were computed using the equations given in ref. 34. All calculations were carried out using the Gaussian09 programs suite.[46]

General information

All enol ethers and alkenes were commercially available. Melting points were measured with a Koffler hot stage and are uncorrected. ^{1}H and ^{13}C NMR spectra were recorded on a Bruker AM 300 (300 MHz for ^{1}H NMR; 75 MHz for ^{13}C NMR) or an Agilent Varian 500 (500 MHz for ^{1}H NMR; 125 MHz for ^{13}C NMR), in $CDCl_3$ and quoted relative to tetramethylsilane as an internal reference. Mass spectral data were obtained on a

High Performance Liquid Chromatograph/Mass Spectrometer (LC-MS) equipped with an ESI interface. Analyses were performed with a PerkinElmer 2400-II analyzer. The reactions under MW irradiation were performed in closed vessels in a Biotage Initiator 2.0 with an external sensor for measuring reaction mixture temperatures. Column chromatography was performed on silica gel (Merck 60, 70–230 Mesh) and analytical TLC was carried out on precoated silica gel plates (F254, 0.25 mm). Petroleum ether (PE) refers to the fraction 40–60 °C.

Preparation of 4,4-dimethoxynaphthalene-1,3-dione (12)

A catalytic amount of conc. H_2SO_4 (two drops) was added to a hot suspension of lawsone (1000 mg, 5.7 mmol) in acetic anhydride (1.4 mL, 14.4 mmol) and the mixture was heated in an oil bath for 15 min. Upon addition of water, acetyl lawsone **11** precipitated[26] and was collected by filtration. It was thoroughly washed with water and then dried under vacuum. The crude ester **11** (1186 mg, 5.49 mmol) was dissolved in methanol (30 mL) and K_2CO_3 (2273 mg, 16.47 mmol) was added. After stirring for 30 min at rt, potassium carbonate was removed by filtration and the filtrate was concentrated in a rotary evaporator. The resulting mixture was carefully neutralized with a dilute hydrochloric acid solution and then was extracted with CH_2Cl_2 (3 × 20 mL) and washed with brine. The organic layer was dried (Na_2SO_4) and concentrated to afford the acetal **12** in 78% total yield (983 mg, 4.47 mmol).

Preparation of arylidene-4,4-dimethoxynaphthalene-1,3-diones 14a–d

General procedure. In a solution of the acetal **12** (40 mg, 0.18 mmol) in CH_2Cl_2 (3 mL) the appropriate aldehyde **13** (0.36 mmol), anhydrous $MgSO_4$ (65 mg, 0.54 mmol) and a catalytic amount of *S*-proline (4 mg, 0.036 mmol) were added and the mixture was stirred for 2 days at rt. $MgSO_4$ was removed by filtration and the filtrate was concentrated and subjected to column chromatography (silica gel, PE/ethyl acetate 5 : 1) to afford the unreacted aldehyde and products **14** in order of elution. The arylidene-1,3-diones **14** were crystallized upon trituration with mixtures of PE/Et_2O.

General procedure for the reactions of acetal 12 with formaldehyde and vinyl ethers 17

Synthesis of the 4-aryl-dihydrobenzochromenones 18, 19, 22 and 23. A solution of the acetal **12** (60 mg, 0.27 mmol) in CH_3CN (6 mL) was placed in an ice bath. Aqueous formaldehyde 37% (0.05 mL), anhydrous $MgSO_4$ (97.5 mg, 0.814 mmol) and a catalytic amount of *S*-proline (6 mg, 0.054 mmol) were added and the mixture was stirred for 30 min. An excess of the appropriate vinyl ether **17** was added and the mixture was kept at rt overnight. $MgSO_4$ was removed by filtration and the filtrate was subjected to column chromatography (silica gel, PE/ethyl acetate 7 : 1) to afford the dihydrobenzochromenones **18**, **19**, **22** and **23**.

Conflicts of interest

There are no conflicts to declare.

Notes and references

1 (*a*) R. H. Thomson, *Naturally Occurring Quinones IV. Recent Advances*, Blackie A&P, London, 1997.
2 A. K. Jordão, M. D. Vargas, A. C. Pinto, F. de C. da Silva and V. F. Ferreira, *RSC Adv.*, 2015, **5**, 67909–67943; and references cited therein.
3 (*a*) J. S. Sun, A. H. Geiser and B. Frydman, *Tetrahedron Lett.*, 1998, **39**, 8221–8224; (*b*) G. Kazantzi, E. Malamidou-Xenikaki and S. Spyroudis, *Synlett*, 2007, 427–430.
4 K. D. Barange, V. Kavala, B. R. Raju, C.-W. Kuo, C. Tseng and Y.-C. Tu, *Tetrahedron Lett.*, 2009, **50**, 5116–5119.
5 E. Malamidou-Xenikaki and S. Spyroudis, *Synlett*, 2008, 2725–2740.
6 G. Kazantzi, E. Malamidou-Xenikaki and S. Spyroudis, *Synlett*, 2006, 2597–2600.
7 S. Koulouri, E. Malamidou-Xenikaki, S. Spyroudis and M. Tsanakopoulou, *J. Org. Chem.*, 2005, **70**, 8780–8784.
8 E. Glinis, E. Malamidou-Xenikaki, H. Skouros, S. Spyroudis and M. Tsanakopoulou, *Tetrahedron*, 2010, **66**, 5786–5792.
9 E. Malamidou-Xenikaki, M. Tsanakopoulou, M. Chatzistefanou and D. Hadjipavlou-Litina, *Tetrahedron*, 2015, **71**, 5650–5661.
10 A. R. Burnett and R. H. Thomson, *J. Chem. Soc. C*, 1967, 2100–2104.
11 Y. Li, X. Sun, J. T. LaMont, A. B. Pardee and C. J. Li, *Proc. Natl. Acad. Sci. U. S. A.*, 2003, **100**, 2674–2678.
12 N. E. Mealy and B. Lupone, *Drugs Future*, 2006, **31**, 627–639.
13 (*a*) S. C. Hooker, *J. Am. Chem. Soc.*, 1936, **58**, 1181; (*b*) K. Schaffner-Sabba, K. H. Schmidt-Ruppin, N. Wehrli, A. R. Schurch and J. W. Wasley, *J. Med. Chem.*, 1984, **27**, 990; and references cited therein.
14 C. Salas, R. A. Tapia, K. Ciudad, V. Armstrong, M. Orellana, U. Kemmerling, J. Ferreira, J. D. Maya and A. Morello, *Bioorg. Med. Chem.*, 2008, **16**, 668–674.
15 R. Cassis, R. Tapia and J. A. Valderrama, *J. Heterocycl. Chem.*, 1984, **21**, 865–868.
16 (*a*) V. F. Ferreira, A. V. Pinto and L. C. M. Coutada, *An. Acad. Bras. Cienc.*, 1980, **52**, 477–479; (*b*) A. B. de Oliveira, D. T. Ferreira and D. S. Raslan, *Tetrahedron Lett.*, 1988, **29**, 155–158; (*c*) Y. R. Lee, J. H. Choi, D. T. L. Trinh and N. W. Kim, *Synthesis*, 2005, 3026; (*d*) Y. R. Lee and W. K. Lee, *Synth. Commun.*, 2004, **34**, 4537.
17 R. Inagaki, M. Ninomiya, K. Tanaka and M. Koketsu, *ChemMedChem*, 2015, **10**, 1413–1423.
18 (*a*) Y. Gao, Q. Ren, S.-M. Ang and J. Wang, *Org. Biomol. Chem.*, 2011, **9**, 3691–3697; (*b*) M. Rueping, E. Sugiono and E. Merino, *Angew. Chem., Int. Ed.*, 2008, **47**, 3046–3049.
19 V. Nair and P. M. Treesa, *Tetrahedron Lett.*, 2001, **42**, 4549.
20 D.-Q. Peng, Y. Liu, Z.-F. Lu, Y.-M. Shen and J.-H. Xu, *Synthesis*, 2008, 1182–1192.

21 V. F. Ferreira, S. B. Ferreira and F. de C. da Silva, *Org. Biomol. Chem.*, 2010, **8**, 4793–4802.
22 F. de C. da Silva, S. B. Ferreira, C. R. Kaiser, A. C. Pinto and V. F. Ferreira, *J. Braz. Chem. Soc.*, 2009, **20**, 1478–1482.
23 S. Jiménez-Alonso, H. C. Orellana, A. Estévez-Braun, A. G. Ravelo, E. Pérez-Sacau and F. Machín, *J. Med. Chem.*, 2008, **51**, 6761–6772.
24 L. R. Domingo, M. T. Piche and P. Arroyo, *Eur. J. Org. Chem.*, 2006, 2570–2580.
25 E. Malamidou-Xenikaki, S. Spyroudis, E. Tsovaltzi and E. G. Bakalbassis, *J. Org. Chem.*, 2016, **81**, 2383–2398.
26 L. R. Domingo and J. A. Sáez, *Org. Biomol. Chem.*, 2009, 3576–3583.
27 (*a*) L. A. Cort and P. A. B. Rodriguez, *J. Chem. Soc. C*, 1967, 949–952; (*b*) R. B. Smith, C. Canton, N. S. Lawrence, C. Livingstone and J. Davis, *New J. Chem.*, 2006, **30**, 1718–1724.
28 J. L. Marshall, *Carbon-Carbon and Carbon-Proton NMR Couplings; Application to Organic Stereochemistry and Conformational Analysis*, Chemie, Deerfield Beach, Florida, USA, 1983, pp. 33–42.
29 B. Neochoritis, N. Eleftheriadis, C. Tsoleridis and J. Stephanidou-Stephanatou, *Tetrahedron*, 2010, **66**, 709–714.
30 C. List, R. A. Lerner and C. F. Barbas, *J. Am. Chem. Soc.*, 2000, **122**, 2395–2396.
31 S. B. Ferreira, K. Salomão, F. de C. da Silva, A. V. Pinto, C. R. Kaiser, A. C. Pinto, A. V. Pinto, V. F. Ferreira and S. L. de Castro, *Eur. J. Med. Chem.*, 2011, **46**, 3071–3077.
32 R. G. Parr, L. von Szentpaly and S. Liu, *J. Am. Chem. Soc.*, 1999, **121**, 1922–1924.
33 L. R. Domingo, E. Chamorro and P. Pérez, *J. Org. Chem.*, 2008, **73**, 4615–4624.
34 L. R. Domingo, M. Ríos-Gutiérrez and P. Pérez, *Molecules*, 2016, **21**, 748.
35 R. G. Parr and R. G. Pearson, *J. Am. Chem. Soc.*, 1983, **105**, 7512–7516.
36 L. R. Domingo, *RSC Adv.*, 2014, **4**, 32415–32428.
37 L. R. Domingo, P. Pérez and J. A. Sáez, *RSC Adv.*, 2013, **3**, 1486–1494.
38 L. R. Domingo, M. Ríos-Gutiérrez and P. Pérez, *Molecules*, 2018, **23**, 1913.
39 L. R. Domingo, J. A. Saéz, R. J. Zaragozá and M. Arnó, *J. Org. Chem.*, 2008, **73**, 8791–8799.
40 (*a*) A. D. Becke, *J. Chem. Phys.*, 1993, **98**, 5648–5652; (*b*) C. Lee, W. Yang and R. G. Parr, *Phys. Rev. B: Condens. Matter Mater. Phys.*, 1988, **37**, 785–789.
41 W. J. Hehre, L. Radom, P. v. R. Schleyer and J. A. Pople, *Ab initio Molecular Orbital Theory*, Wiley, New York, 1986.
42 D. H. Ess, G. O. Jones and K. N. Houk, *Adv. Synth. Catal.*, 2006, **348**, 2337–2361.
43 K. Fukui, *J. Phys. Chem.*, 1970, **74**, 4161–4163.
44 J. Tomasi and M. Persico, *Chem. Rev.*, 1994, **94**, 2027–2094.
45 (*a*) A. E. Reed, R. B. Weinstock and F. Weinhold, *J. Chem. Phys.*, 1985, **83**, 735–746; (*b*) A. E. Reed, L. A. Curtiss and F. Weinhold, *Chem. Rev.*, 1988, **88**, 899–926.
46 M. J. T. Frisch, *et al.*, *Gaussian 09, Revision B.01*, Gaussian, Inc., Wallingford, CT, 2010.

