View metadata, citation and similar papers at core.ac.uk

brought to you by CORE

provided by Biblioteca Digital do IPB

ChemPubSoc Europe

DOI: 10.1002/ejoc.201700944

European Journal of Organic Chemistry

Full Paper

Conjugate Addition

1,6-Conjugate Additions of Carbon Nucleophiles to 2-[(1*E*,3*E*)-4-Arylbuta-1,3-dien-1-yl]-4*H*-chromen-4-ones

Hélio M. T. Albuquerque,[a] Clementina M. M. Santos,[a,b] Mannix P. Balanay,[c] José A. S. Cavaleiro,[a] and Artur M. S. Silva*[a]

Abstract: The 1,6-conjugate addition of nitromethane to 2-[(1*E*,3*E*)-4-arylbuta-1,3-dien-1-yl]-4*H*-chromen-4-ones was accomplished and led mainly to the corresponding β-(nitromethyl)chromones. (*E*)-5′-(Nitromethyl)-3′-styryl-[1,1′-biphenyl]-2-ol and 3′-aryl-2′-nitro-5′-(nitromethyl)spiro[chromane-2,1′-cyclohexan]-4-one derivatives were also isolated as minor products from tandem processes, which result from the addition of a second molecule of nitromethane. The nucleophile scope was investigated with malononitrile, acetylacetone, ethyl cyanoacetate, and diethyl malonate, which gave the expected 1,6-addition products; in the last case, it was also possible to isolate a minor product formed through a 1,8-/1,6-addition sequence. Computational calculations provided a rationale for the experimental reactivity of carbon nucleophiles with 2-[(1*E*,3*E*)-4-arylbuta-1,3-dien-1-yl]-4*H*-chromen-4-ones. The further functionalization of some adducts allowed the preparation of new nitrogen-containing heterocyclic compounds, such as new styrylpyrrolidines and new pyrazole and bis(pyrazole) derivatives.

Introduction

Chromones (or 4*H*-chromen-4-ones) are a group of oxygen-containing heterocycles with a benzo-γ-pyrone ring and are widespread in nature. Several biological activities have been attributed to simple chromones and their analogues.[1] Anticancer,[1a] cytotoxic,[2] antioxidant,[3] anti-inflammatory,[1a,4] antifungal,[5] and antiviral[1a] activities are often reported. Chromone derivatives are also seen as interesting scaffolds for further functionalizations, most of which arise from chemical transformations[6] such as oxidation,[7] condensation,[8] Diels–Alder,[9] and conjugate addition reactions.[10]

The conjugate addition of carbon nucleophiles to electron-deficient alkenes is one of the most important methods available for carbon–carbon bond-forming reactions.[11] Moreover, the asymmetric catalysis of such reactions constitutes a powerful synthetic tool for the formation of carbon stereocenters, which are key structural features in the development of new bioactive compounds.[12] Commonly reported soft carbon nucleophiles such as nitroalkanes,[10a,13] malonates,[10c,14] malononitrile,[10c,13e,15] cyanoacetates,[16] or enamines[17] readily undergo conjugate additions with various substrates such as chalcones,[13d,15,16b,18] vinyl ketones,[16a] cinnamylideneacetophenones,[13d,13e] and 2-styrylchromones.[10a,10c,11b,17]

Although the 1,4-conjugate addition of carbon nucleophiles has been widely reported, studies involving the analogous 1,6-addition reactions are less commonly reported. One of the reasons for the underdevelopment in this area seems to be the presence of several electrophilic sites in extended conjugated systems and the inherent difficulties with the control of the regioselectivity.[11] However, there are cases involving extended conjugated π systems (such as cinnamylideneacetophenones) in which the regioselectivity could be controlled, and the 1,4-conjugate addition products were obtained exclusively.[13d,13e,19]

Previous work of our group involved the 1,6-conjugate addition of nitromethane to (*E*)-2-styrylchromones with 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) as an organocatalyst to form 2-(2-aryl-3-nitropropyl)chromones in moderate-to-good yields.[10a] Later, the 1,6-conjugate additions of ethyl malonate and malononitrile were also reported, and these reactions unexpectedly afforded the stereochemically complex pentasubstituted spirocyclohexanes.[10c] On the basis of this knowledge, herein, we intend to provide new insights into the reactivity of the extended 3,2:α,β:γ,δ-triunsaturated 2-[(1*E*,3*E*)-4-arylbuta-1,3-dien-1-yl]-4*H*-chromen-4-one systems in conjugate addition reactions with several carbon nucleophiles and further functionalizations of the addition products. The presence of a third unsaturated moiety extends the π system of 2-[(1*E*,3*E*)-4-arylbuta-1,3-dien-1-yl]-4*H*-chromen-4-ones relative to that of 2-styrylchromones and allows the δ position to become a new site for nucleophilic attack (possible 1,8-conjugate addition, Figure 1). This feature enables the synthesis of multisubstituted heterocyclic derivatives with new stereocenters as well as their further functionalization to give new nitrogen-containing heterocyclic compounds.

[a] *Department of Chemistry & QOPNA, University of Aveiro, Campus de Santiago, 3810-193 Aveiro, Portugal*
E-mail: artur.silva@ua.pt
https://sites.google.com/site/artursilvaua/silva-ams
[b] *School of Agriculture, Polytechnic Institute of Bragança, Campus de Santa Apolónia, 5300-253 Bragança, Portugal*
[c] *Department of Chemistry, Nazarbayev University, 53 Kabanbay Batyr Ave, Block 7, Astana 010000, Kazakhstan*

Supporting information and ORCID(s) from the author(s) for this article are available on the WWW under https://doi.org/10.1002/ejoc.201700944.

© 2017 Wiley-VCH Verlag GmbH & Co. KGaA, Weinheim

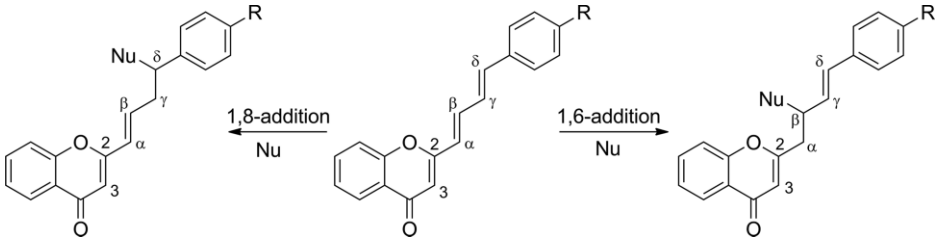


Figure 1. Possible sites of conjugate addition to 2-[(1*E*,3*E*)-4-arylbuta-1,3-dien-1-yl]-4*H*-chromen-4-ones. Nu = nucleophile.

Results and Discussion

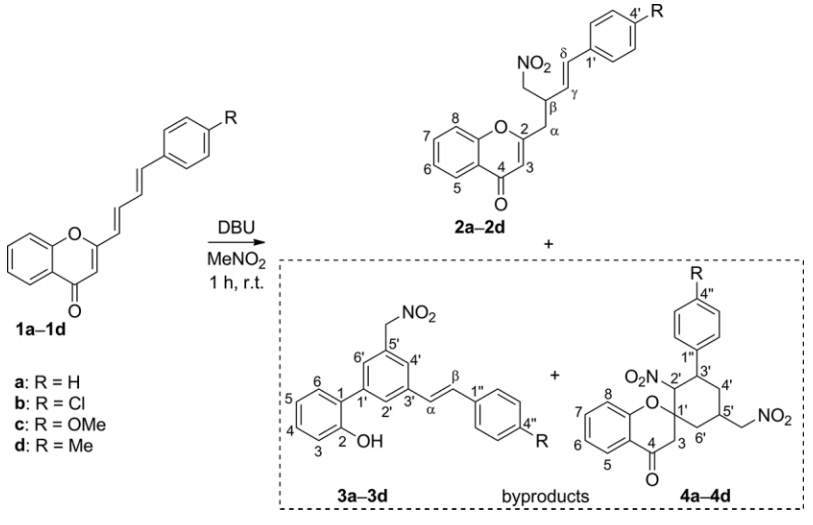
Nitromethane Conjugate Additions

On the basis of our previous results on the organocatalyzed (DBU) 1,6-conjugate addition of nitromethane to (*E*)-2-styrylchromones, our first approach involved the reaction of chromone **1c** as a model substrate with 20 and 60 mol-% of DBU under neat conditions at room temperature (Table 1, Entries 1 and 2). After 24 h, no reaction had occurred, and 85–95 % of the starting chromone was recovered. If the reaction was performed at higher temperatures of 65 and 100 °C, **2c** was obtained in ca. 40 % yield, and a lower yield was obtained in the presence of $Sc(OTf)_3$ (OTf = triflate) as a Lewis acid catalyst[9b] (Table 1, Entries 3–5). The amount of DBU was increased to 100 mol-%, and several reaction times were investigated (Table 1, Entries 6–10). The best results were obtained for a

Table 1. Screening of the conditions for the reaction of chromone **1c** with nitromethane.[a]

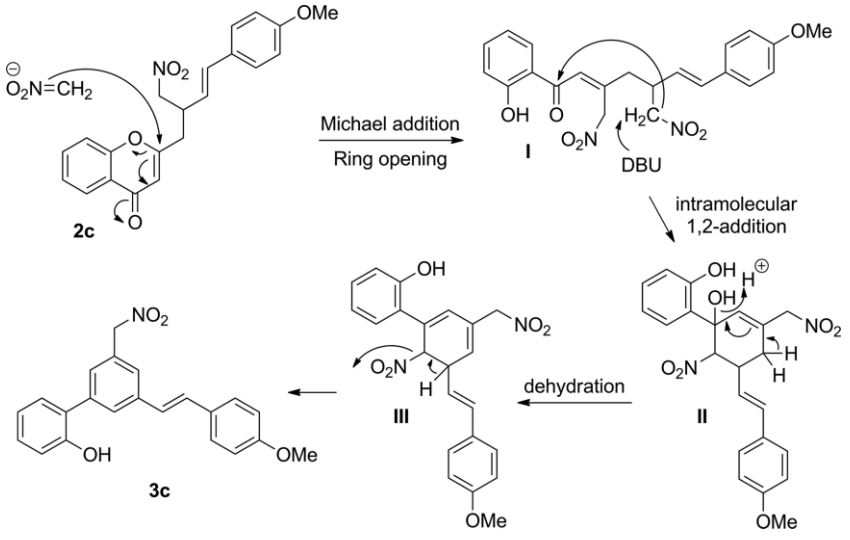
Entry	Base [mol-%]	Solvent	*T* [°C]	Time	Yield of **2c** [%][b]	Yield of **3c** [%][b]	Yield of **4c** [%][b]	Recovered **1c** [%][b]
1	DBU (20)	neat	r.t.	24 h	–	–	–	95
2	DBU (60)	neat	r.t.	24 h	–	–	–	85
3	DBU (20)	neat	65	24 h	41	–	–	–
4[c]	DBU (20)	neat	65	24 h	18	–	–	62
5	DBU (20)	neat	100	24 h	40	–	–	–
6	DBU (100)	neat	r.t.	15 min	25	–	–	37
7	DBU (100)	neat	r.t.	30 min	44	13	7	20
8	DBU (100)	neat	r.t.	1 h	52	18	12	–
9	DBU (100)	neat	r.t.	4 h	30	30	8	–
10	DBU (100)	neat	r.t.	24 h	12	22	7	–
11	TBD (100)	neat	r.t.	6 d	–	–	–	90
12	DBN (100)	neat	r.t.	2 h	30	–	–	traces
13	Cs_2CO_3 (100)	neat	r.t.	72 h	–	–	–	80
14[d,e]	Cs_2CO_3 (120)	MeCN	r.t.	96 h	–	–	–	90
15[e]	DBU (100)	MeCN	r.t.	24 h	–	–	–	95
16[e]	DBU (100)	DMF	r.t.	1 h	50	15	11	–
17[e]	DBU (20)	THF	reflux	24 h	10	–	–	67
18[e]	DBU (20)	EtOH	reflux	24 h	18	–	–	50
19[e]	DBU (150)	EtOH	reflux	5 h	20	–	–	–

[a] Reaction conditions: chromone **1c** (0.1 mmol) in nitromethane (0.4 mL). r.t. = room temperature; TBD = 1,5,7-triazabicyclo[4.4.0]dec-5-ene. [b] Isolated yields. [c] Addition of 30 mol-% of $Sc(OTf)_3$. [d] Addition of 50 mol-% of tetrabutylammonium bromide (TBAB). [e] Reaction performed with chromone **1c** (0.1 mmol) and nitromethane (0.4 mL) in solvent (0.5 mL).



Scheme 1. DBU-catalyzed conjugate addition reaction of nitromethane to chromones **1a**–**1d**.

© 2017 Wiley-VCH Verlag GmbH & Co. KGaA, Weinheim



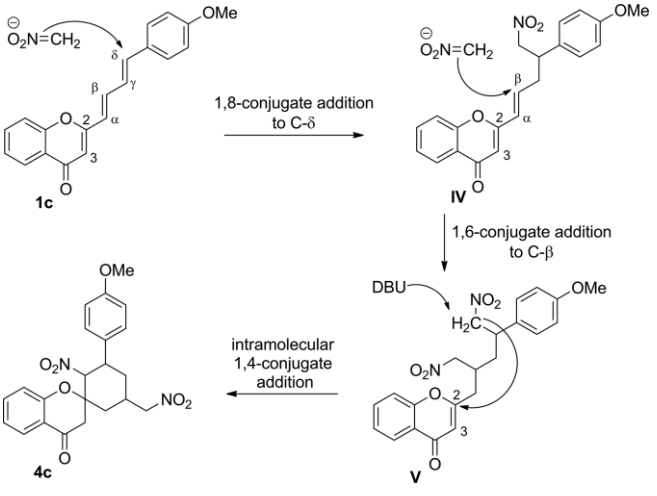
Scheme 2. Proposed mechanism for the formation of **3c**.

reaction time of 1 h, and derivative **2c** (1,6-addition product) was obtained as the major product in 52 % yield along with minor products **3c** and **4c** in 18 and 12 % yield, respectively (Scheme 1 and Table 1, Entry 8).

The efficiencies of other organic and inorganic bases were also evaluated (Table 1, Entries 11–13), but the reaction only occurred in the presence of 1,5-diazabicyclo[4.3.0]non-5-ene (DBN), and derivative **2c** was obtained in a lower yield (30 %) than that obtained with DBU. Several solvents were tested at different temperatures (Table 1, Entries 14–19), and similar results to those obtained under neat conditions were achieved in *N*,*N*-dimethylformamide (DMF), in which **2c** was obtained in 50 % yield together with **3c** and **4c** in 15 and 11 % yield, respectively (Table 1, Entries 5 and 16).

The ^{1}H NMR spectrum confirmed the structure of **3c** and showed three triplets (J = 1.6 Hz) at δ = 7.44, 7.58, and 7.68 ppm for 6′-H, 4′-H, and 2′-H, respectively (see Scheme 1 for atom numbering). Moreover, a singlet corresponding to 2-OH at δ = 5.44 ppm and another singlet corresponding to CH_2NO_2 at δ = 5.51 ppm were also observed. Two doublets at δ = 7.00 and 7.15 ppm were assigned to α-H and β-H, respectively, in a *trans* configuration ($^3J_{\alpha\text{-H},\beta\text{-H}}$ 16.3 Hz). The formation of derivative **3c** could be attributed to the Michael addition of a nitromethane anion to C-2 of **2c** along with chromone ring opening to give intermediate **I**. A DBU-catalyzed intramolecular 1,2-addition leads to intermediate **II**, which affords intermediate **III** upon dehydration, and the elimination of HNO_2 affords derivative **3c** (Scheme 2).

The plausible mechanism for the formation of derivative **4c** involves the 1,8-conjugate addition of a nitromethane anion to C-δ of chromone **1c** to afford intermediate **IV**. Then, the 1,6-conjugate addition of another nitromethane anion to C-β of **IV** gives intermediate **V**, which undergoes a DBU-catalyzed intramolecular 1,4-conjugate addition to C-2 to form the spirotrisubstituted cyclohexane **4c** (Scheme 3). The ^{1}H NMR spectrum of **4c** showed aliphatic signals corresponding to five protons (2′-H, 3′-H, 4′-H, 5′-H, and 6′-H). In particular, the doublet assigned to 2′-H at δ = 4.81 ppm confirms the presence of a nitro group at the 2′-position. Moreover, the ^{13}C NMR spectrum revealed a signal assigned to C-1′ at δ = 78.5 ppm, which is typical of a spiro carbon atom (see Scheme 1 for atom numbering).



Scheme 3. Proposed mechanism for the formation of **4c**.

At this point, the reaction proceeded smoothly in neat conditions or in DMF with 100 mol-% of DBU, but we were not able to control the regioselectivity. To handle this drawback, we limited the available amount of nitromethane in the reaction mixture to 1 equiv.; derivative **2c** was isolated in 25 % yield, and 31 % of the starting material was recovered (Table 2, Entry 1).

Table 2. Influence of the amount of nitromethane in the reaction with chromone **1c**.[a]

Entry	$MeNO_2$ [equiv.]	Time [h]	Yield of **2c** [%][b]	Recovered **1c** [%][b]
1	1	1	25	31
2	1	8	6	25
3	3	4	13	21
4	5	2	45	traces

[a] Reaction conditions: chromone **1c** (0.1 mmol) in DMF (0.5 mL) with 100 mol-% of DBU. [b] Isolated yields.

© 2017 Wiley-VCH Verlag GmbH & Co. KGaA, Weinheim

A longer reaction time resulted in a lower yield of **2c** (Table 2, Entry 2). In both reactions, **3c** and **4c** were not detected; therefore, **2c** may undergo degradation as the reaction proceeds. Moreover, the recovery of a significant amount of the starting chromone suggests that more nitromethane is needed to obtain complete reactions. Two experiments were performed with 3 and 5 equiv. of nitromethane, and only **2c** was isolated in 13 and 45 % yield, respectively (Table 2, Entries 3 and 4).

The reaction proceeded more quickly and with less degradation with 5 equiv. of nitromethane. The global yield (**2c**) only reached 45 %, whereas the global yield (**2c** + **3c** + **4c**) reached 82 and 76 % in neat conditions or DMF with a large excess of nitromethane, respectively. With the optimized neat conditions in hand (Table 1, Entry 8) we explored the reactivities of chromones **1a**, **1b**, and **1d** (Scheme 1 and Table 3). Products **2a**–**2d** were obtained in yields of 38–52 %, along with **3a**–**3d** in 3–18 % and **4a**–**4d** in 6–12 % yields.

Table 3. Nitromethane conjugate addition reaction to chromones **1a**–**1d**.[a]

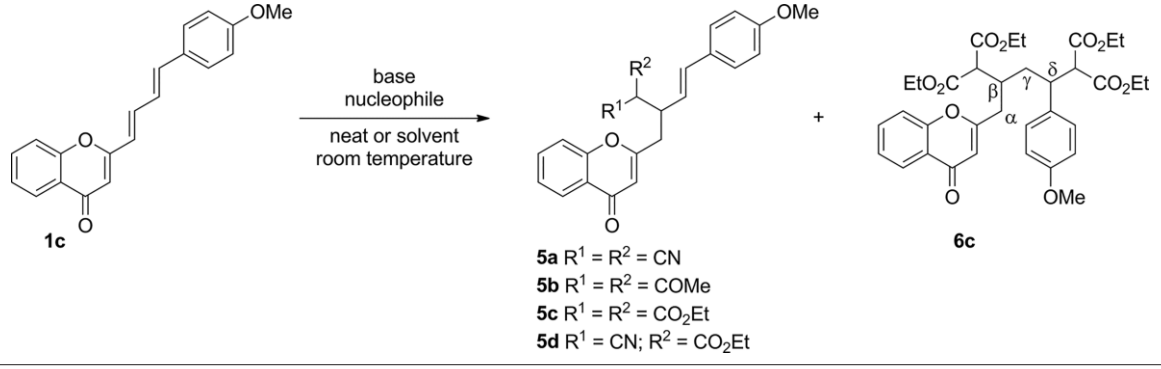
Entry	R	Yield of **2** [%][b]	Yield of **3** [%][b]	Yield of **4** [%][b]
1	H	40 (**2a**)	7 (**3a**)	6 (**4a**)
2	Cl	38 (**2b**)	15 (**3b**)	10 (**4b**)
3	OMe	52 (**2c**)	18 (**3c**)	12 (**4c**)
4	Me	40 (**2d**)	3 (**3d**)	8 (**4d**)

[a] Reactions conditions: chromones **1a**–**1d** (0.1 mmol) and DBU (0.1 mmol) in nitromethane (0.4 mL) at room temperature for 1 h. [b] Isolated yields.

Nucleophile Scope

Once we had determined the optimal reaction conditions for the conjugate addition of nitromethane to chromones **1**, the scope of the reaction was extended to other carbon nucleophiles (Table 4). The best reaction conditions for the addition of nitromethane to chromone **1c**, that is, 100 mol-% of DBU in DMF, did not work well for malononitrile and led to several unidentified byproducts (Table 4, Entries 1 and 2). If the amount of DBU was reduced to 50 mol-% and different amounts of malononitrile were used, the 1,6-conjugate addition product **5a** was obtained in low yields (23–28 %), and 26–37 % of the starting chromone was recovered (Table 4, Entries 3–5). Other organic bases were applied, but none of them improved the yield of **5a** (Table 4, Entries 6–8). For acetylacetone as the nucleophile under neat conditions, the respective 1,6-addition product **5b** was isolated in good yield (Table 4, Entry 9). The reaction of chromone **1c** with diethyl malonate under neat conditions or with DMF as the solvent led to the 1,6-addition product **5c** in yields of 51 and 60 %, respectively (Table 4, Entries 10 and 11). Interestingly, these reactions also afforded the double addition product **6c** as an inseparable mixture of two diastereomers in a 70:30 ratio (Figure 2A), as a result of the 1,8-conjugate addition at C-δ, followed by the 1,6-conjugate addition at C-β. Finally, if ethyl cyanoacetate was employed as the nucleophile in the reaction with chromone **1c**, an inseparable mixture of two diastereomers **5d** in a 68:32 ratio was obtained in good yield (Figure 2B; Table 4, Entry 12).

Table 4. Nucleophile scope in conjugate addition reactions with chromone **1c**.



Entry	Base [mol-%]	Nucleophile	Nucleophile [equiv.]	Solvent	Reaction time	Yield of **5** [%][d]	Yield of **6c** [%][d]	Recovered **1c** [%]
1[a]	DBU (100)	malononitrile	3	DMF	16 h	[e]		
2[a]	DBU (100)	malononitrile	6	DMF	16 h	[e]		
3[a]	DBU (50)	malononitrile	1	DMF	16 h	23 (**5a**)	–	33
4[a]	DBU (50)	malononitrile	3	DMF	16 h	28 (**5a**)	–	26
5[a]	DBU (50)	malononitrile	6	DMF	16 h	26 (**5a**)	–	37
6[a]	DBN (50)	malononitrile	3	DMF	24 h	21 (**5a**)	–	33
7[a]	TBD (50)	malononitrile	3	DMF	24 h	19 (**5a**)	–	28
8[a]	DABCO (50)	malononitrile	3	DMF	72 h	10 (**5a**)	–	37
9[b]	DBU (100)	acetylacetone	–	neat	48 h	60 (**5b**)	–	traces
10[b]	DBU (100)	diethyl malonate	–	neat	24 h	51 (**5c**)	18[f]	traces
11[c]	DBU (100)	diethyl malonate	–	DMF	24 h	60 (**5c**)	15[f]	traces
12[b]	DBU (100)	ethyl cyanoacetate	–	neat	24 h	70 (**5d**)[f]	–	traces

[a] Reaction conditions: chromone **1c** (0.1 mmol) in DMF (0.4 mL). [b] Reaction conditions: chromone **1c** (0.1 mmol) in nucleophile (0.5 mL). [c] Reaction conditions: chromone **1c** (0.1 mmol) in DMF (0.6 mL) with diethyl malonate (0.4 mL). [d] Isolated yields. [e] Unidentified degradation products. [f] Mixture of two diastereomers.

© 2017 Wiley-VCH Verlag GmbH & Co. KGaA, Weinheim

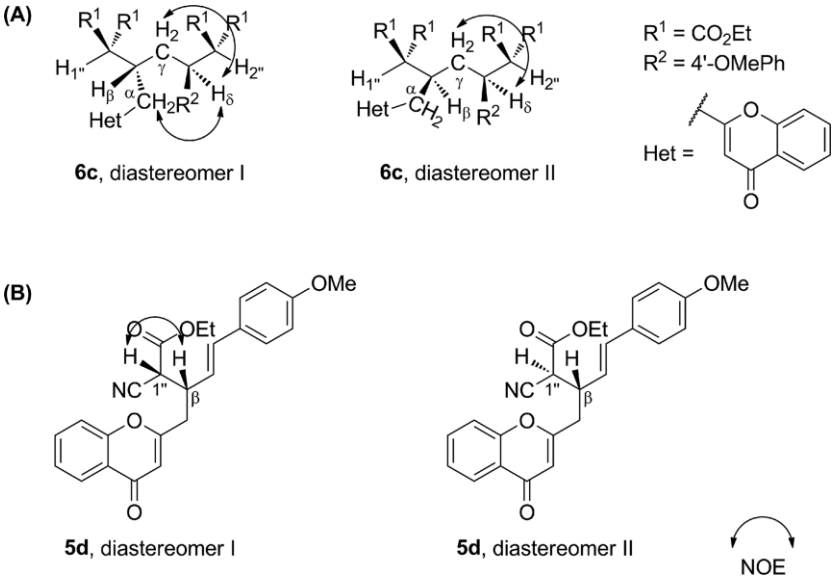


Figure 2. Relative stereochemistry of diastereomers I and II of (A) **6c** and (B) **5d**.

Computational Studies

To understand better the reactivity of carbon nucleophiles with chromones **1** in conjugate additions, computational calculations were performed. All of the ground-state structures were optimized with the M06-2X exchange-correlation (xc) functional and the 6-31G(d,p) basis set in vacuo without symmetry constraints. The energy and frequency calculations were performed with the 6-311+G(d,p) basis set and the same xc functional. The effects of the solvent and substituents (methoxy substituent) on the structure were also investigated for some compounds, and negligible effect on the energies was found. Thus, to decrease the computational cost, only the base structure shown in Figure 3 without any solvent effects was used to calculate the Gibbs free energies. All of the calculations were performed with the Gaussian 09 software.[20]

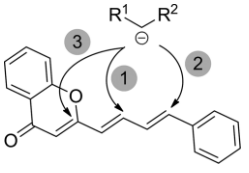


Figure 3. Possible nucleophilic addition sites of chromones **1**.

The three possible reactive sites of the chromone for nucleophilic addition are presented in Figure 3. The results suggest that sites 1 and 2 would be the most likely reaction pathways for the reaction, whereas site 3 resulted in an endergonic type of reaction with a high activation energy, which would be unfavorable. Thus, only sites 1 and 2 will be discussed further.

The Gibbs free energy diagram of the formation of **5b** and **5c** for the first reactive site is presented in Figure 4. The forma-

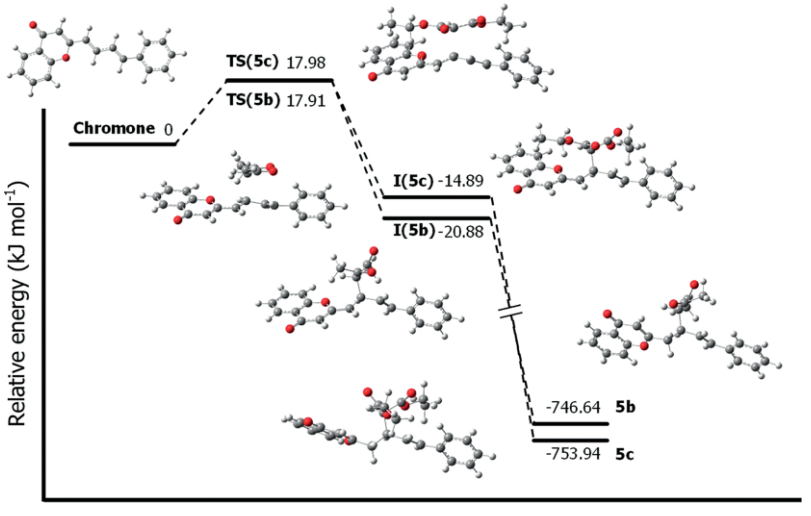


Figure 4. Gibbs free energy profile for the formation of **5b** and **5c** through reaction at site 1. TS and I represent the transition states and intermediate structures, respectively.

© 2017 Wiley-VCH Verlag GmbH & Co. KGaA, Weinheim

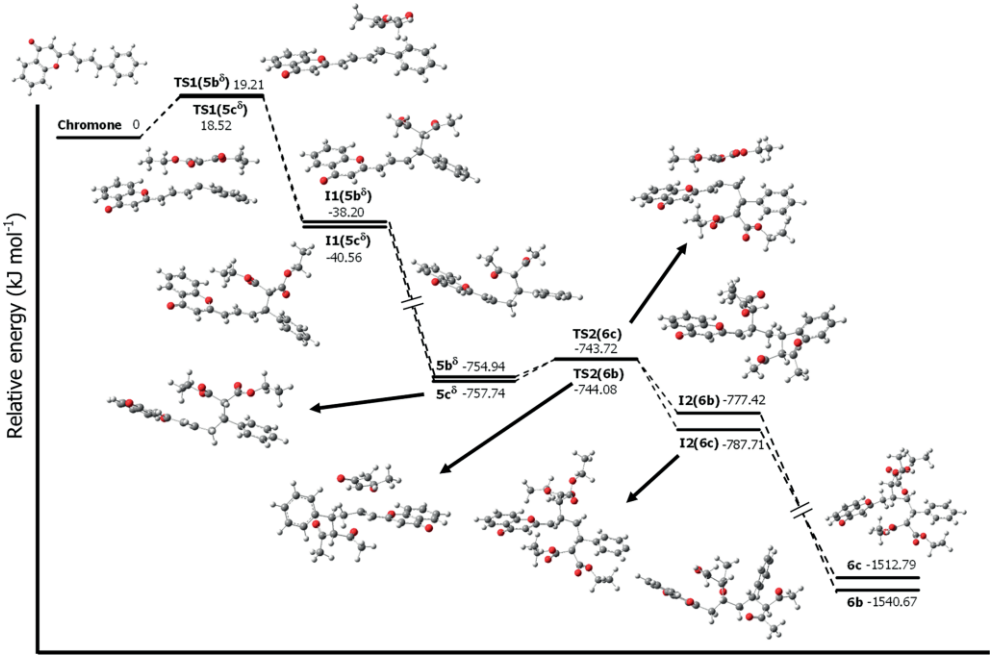


Figure 5. Gibbs free energy profile for the formation of **5b**$^{\delta}$, **5c**$^{\delta}$, **6b**, and **6c** through reaction at site 2. TS and I represent the transition states and intermediate structures, respectively.

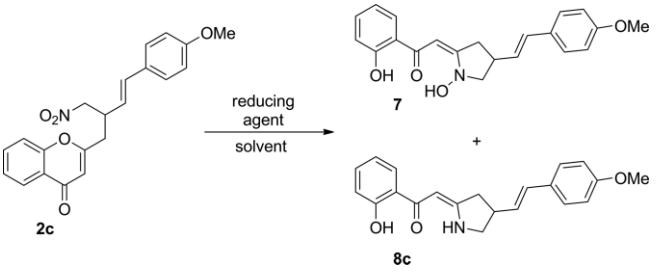
tion of the intermediate is the rate-determining step, as the protonation step was determined to be a barrierless reaction. Although **5c** is 7.3 kJ mol^{-1} more stable than **5b**, the energies of their corresponding intermediates are reversed. On the basis of the experimental yields (Table 4) for **5b** (60 %) and **5c** (51 %), the reaction is probably kinetically driven.

The further addition of the nucleophile will not yield stable products at this site. The formation of **6** starts with the nucleophilic addition at reactive site 2, followed by addition at site 1. The energy profile for the possible formation of **6b** and **6c** at site 2 is shown in Figure 5. The results show that the energy barrier for the transition state in the rate-determining step for site 1 was significantly lower than that for site 2; therefore, if the reaction is kinetically driven, then the reaction at site 1 would be the predominant pathway. The formation of **6** is basically a thermodynamically controlled process, and **6c** was considered to be the most stable structure, especially because the energy for the formation of the second intermediate [I2(**6c**)] is more than 10 kJ mol^{-1} lower than that for I2(**6b**).

Functionalization of the 1,6-Conjugate Addition Products

Nitromethane conjugate addition products are commonly used to prepare biologically relevant heterocycles such as spiro-γ-lactams,[21] pyrrolidines,[22] and diarylpyrrolines and their isostere *N*-oxides.[23] Thus, the reduction of the nitro groups of β-(nitromethyl)chromones **2a**–**2d** was considered for the preparation of primary amine derivatives. The reduction studies started with β-(nitromethyl)chromone **2c**, Sn (powder), and HCl (37 %) in a 1:1 ethanol/dichloromethane mixture by an adaptation of a previously reported method.[10a] After the complete disappearance of the starting material, hydroxylamine derivative **7** was obtained in 35 % yield (Table 5, Entry 1). The formation of this hydroxylamine derivative **7** can be explained by the incomplete reduction of the nitro group, which undergoes an intramolecular aza-Michael addition to the α,β-unsaturated system of the chromone moiety.[19,23]

Table 5. Reduction of the nitro group of β-(nitromethyl)chromone **2c**.[a]



Entry	Reducing agents [equiv.]	Time	Yield of **8c** [%][b]	Yield of **7** [%][b]
1[c]	Sn (5)/HCl (5)	6 h	–	35
2	Sn (10)/NH_4OAc (10)	24 h	–	–
3[d]	Sn (10)/NH_4OAc (10)	24 h	–	–
4	Zn (5)/NH_4OAc (5)	4 h	16	25
5	Zn (10)/NH_4OAc (10)	2 h	64	–
6	Zn (15)/NH_4OAc (15)	30 min	75	–

[a] Reaction conditions: **2c** (0.137 mmol) in MeOH/CH_2Cl_2 (1:1, 5 mL) at room temperature. [b] Isolated yields. [c] Reaction performed in EtOH/CH_2Cl_2 (1:1, 5 mL). [d] Activated Sn.

A different proton source and activated Sn were both inefficient for the reduction of the nitro group (Table 5, Entries 2 and 3). Next, Zn was considered as a reduction agent, as previously reported for nitrochalcones.[13d] The best reaction conditions were the use of 15 equiv. of Zn/NH_4OAc, which afforded the

© 2017 Wiley-VCH Verlag GmbH & Co. KGaA, Weinheim

styrylpyrrolidine derivative **8c** in 75 % yield (Table 5, Entry 6). These reaction conditions were extended to derivatives **2a**, **2b**, and **2d** (Table 6), and the styrylpyrrolidines **8a**–**8d** were obtained in good yields (66–75 %).

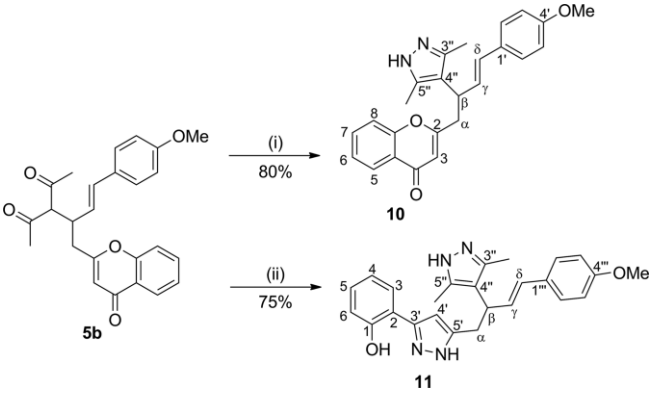
Table 6. Reduction of the nitro groups of β-(nitromethyl)chromones **2a**–**2d**.[a]

Entry	R	Yield of **8** [%][b]
1	H	71 (**8a**)
2	Cl	66 (**8b**)
3	OMe	75 (**8c**)
4	Me	66 (**8d**)

[a] Reaction conditions: β-(nitromethyl)chromones **2a**–**2d** (0.137 mmol) with Zn (powder, 2 mmol) and NH_4OAc in $MeOH/CH_2Cl_2$ (1:1, 5 mL), 30 min at room temperature. [b] Isolated yields.

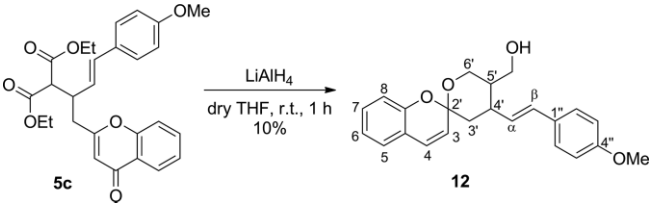
Styrylpyrrolidine derivatives **8a**–**8d** were formed through the aza-Michael addition of the primary amino group to the α,β-unsaturated system in intermediates **9a**–**9d** with chromone ring opening, as reported previously (Scheme 4).[10a] The ^1H NMR spectra of styrylpyrrolidines **8a**–**8d** showed two singlets at δ = 9.86–9.88 and 13.75–13.78 ppm, assigned to the N*H* and O*H* protons, respectively, owing to intramolecular hydrogen bonds with the carbonyl group. It was also possible to observe five aliphatic signals corresponding to protons 3′-H, 4′-H, and 5′-H (see Scheme 4 for atom numbering). Furthermore, the coupling constant between α-H and β-H ($^3J_{\alpha\text{-H},\beta\text{-H}}$ = 15.7–15.8 Hz) indicates the maintenance of the double bond in a *trans* configuration.

The presence of a dicarbonyl moiety in **5b** allows further functionalization through the 1,2-addition of aza-nucleophiles to prepare nitrogen heterocycles. The reaction of **5b** with 2 equiv. of hydrazine hydrate afforded the expected pyrazole derivative **10** [Scheme 5, (i)]. On the other hand, if hydrazine (5 equiv.) was employed, the bis(pyrazole) derivative **11** was obtained [Scheme 5, (ii)]. The formation of this compound implies that **10** reacts with hydrazine hydrate by a well-known pathway (i.e., a 1,4-Michael addition and heterocyclic ring opening, followed by intramolecular hydrazone formation).[24]



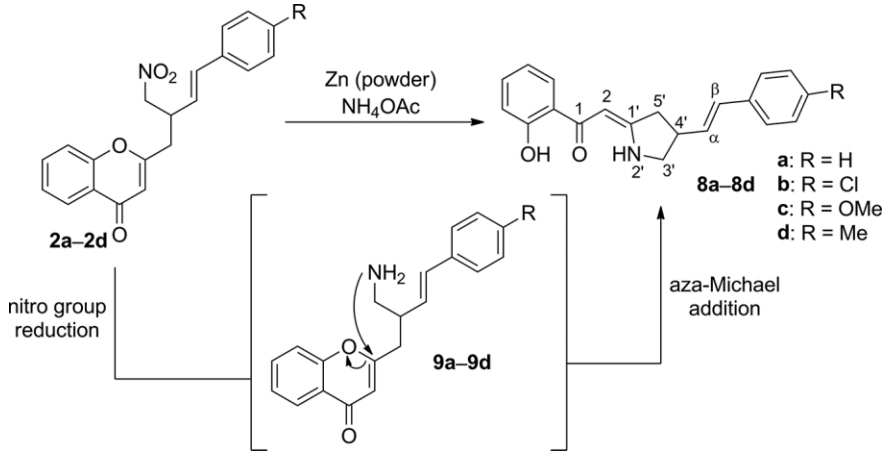
Scheme 5. Synthesis of pyrazole derivatives **10** and **11**. Reaction conditions: (i) $NH_2NH_2{\cdot}H_2O$ (50–60 %, 2 equiv.), EtOH, room temperature, 1 h. (ii) $NH_2NH_2{\cdot}H_2O$ (50–60 %, 5 equiv.), EtOH, room temperature, 1 h.

The functionalization of adduct **5c** was also attempted through the reduction of the malonate group to the corresponding primary alcohol with $LiAlH_4$. The reaction afforded several unidentified products; however, it was possible to isolate and fully characterize the spiro derivative **12** (Scheme 6).



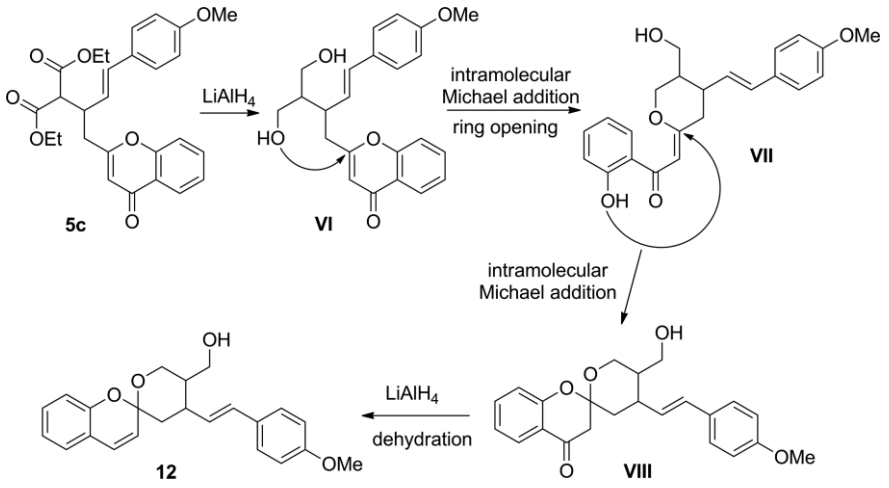
Scheme 6. Synthesis of spiro derivative **12**.

The ^1H NMR spectrum of derivative **12** showed aliphatic signals corresponding to protons 3′-H, 4′-H, 5′-H, 6′-H, and CH_2OH as well as two doublets at δ = 5.74 and 6.69 ppm for 3-H and 4-H ($^3J_{3\text{-H},4\text{-H}}$ = 9.6 Hz). Moreover, the ^{13}C NMR spectrum showed a signal at δ = 95.4 ppm, which corresponds to the spiro carbon atom C-2′ (see Scheme 6 for atom numbering). The proposed mechanism for the formation of derivative **12** proceeds through the reduction of the ester groups to primary alcohols in **VI**,



Scheme 4. Transformation of β-(nitromethyl)chromones **2a**–**2d** into the corresponding styrylpyrrolidine derivatives **8a**–**8d**.

© 2017 Wiley-VCH Verlag GmbH & Co. KGaA, Weinheim



Scheme 7. Proposed mechanism for the formation of **12**.

followed by an intramolecular Michael addition and chromone ring opening to give intermediate **VII**, which undergoes a second intramolecular Michael addition to yield **VIII**. Then, a carbonyl reduction and dehydration of this intermediate afford the spiro compound **12** (Scheme 7).

Conclusions

β-(Nitromethyl)chromones were the major products of the DBU-catalyzed 1,6-conjugate addition of nitromethane to 2-[(1*E*,3*E*)-4-arylbuta-1,3-dien-1-yl]-4*H*-chromen-4-ones. Stoichiometric amounts of DBU are required for the reaction to proceed smoothly, and it was possible to direct the regioselectivity of the reaction towards the 1,6-conjugate addition by limiting the amount of nitromethane. The formation of minor compounds such as nitromethyl(styryl)biphenols and spirocyclohexanes occurs because of the competition between 1,6- and 1,8-conjugate additions in this extended 3,2:α,β:γ,δ-triunsaturated system. The scope of the reaction was extended to other carbon nucleophiles, and the major products were obtained from the 1,6-conjugate addition of malononitrile, acetylacetone, diethyl malonate, and ethyl cyanoacetate to the starting chromones. For diethyl malonate, we also obtained a minor product resulting from consecutive 1,8- and 1,6-conjugate addition reactions. Computational calculations showed that the reaction is probably kinetically driven towards 1,6-addition, and the products from reaction at the δ position are formed through a thermodynamically controlled process. The reduction of the nitro groups of the β-(nitromethyl)chromones afforded primary amine derivatives, which underwent intramolecular aza-Michael additions to the α,β-unsaturated system of the chromone nucleus to afford styrylpyrrolidine derivatives. Further functionalization of the acetylacetone adduct through reaction with hydrazine hydrate gave a pyrazole or bis(pyrazole) derivative depending on the amount of nucleophile.

Experimental Section

The melting points were measured with a Büchi B-540 melting-point apparatus. The NMR spectra were recorded with a Bruker Avance 300 spectrometer (300.13 MHz for ^{1}H and 75.47 MHz for ^{13}C) or a Bruker Avance 500 spectrometer (500.13 MHz for ^{1}H and 125.77 MHz for ^{13}C). The chemical shifts (δ) are reported in ppm, and the coupling constants (*J*) are in Hz; the internal standard was tetramethylsilane (TMS). Unequivocal ^{13}C NMR assignments were made with the aid of 2D gradient heteronuclear single quantum coherence (gHSQC) and gradient HMBC (gHMBC, the delays for one-bond $J_{C,H}$ couplings were optimized for 145 and 7 Hz, respectively) experiments. Positive-ion ESI mass spectra were acquired with a QTOF 2 instrument [the sample (1 μL) in chloroform solution (ca. 10^{-5} M) was diluted in 0.1 % trifluoroacetic acid/methanol solution (200 μL); nitrogen was used as the nebulizer gas, and argon was used as the collision gas; the needle voltage was set to 3000 V, the ion source was set to 80 °C, and the desolvation temperature was set to 150 °C; the cone voltage was 35 V]. Other low- and high-resolution mass spectra (EI, 70 eV) were measured with VG Autospec Q and M spectrometers. Preparative thin-layer chromatography was performed with Merck silica gel (60 DGF254). All chemicals and solvents used were obtained from commercial sources and used as received or dried by standard procedures.

General Procedure for the Synthesis of 2a–2d, 3a–3d, and 4a–4d: DBU (0.1 mmol, 14.9 μL) was added to a mixture of the appropriate chromone **1a**–**1d** (0.1 mmol) in nitromethane (0.4 mL). The resulting mixture was stirred at room temperature for 1 h and then poured into water (5 mL), and the pH was adjusted to 4 with dilute HCl. The aqueous mixture was extracted with dichloromethane (3 × 5 mL), dried with anhydrous sodium sulfate, and concentrated under reduced pressure. The residue was purified by preparative TLC with dichloromethane as the eluent to afford derivatives **2a**–**2d** (higher R_f values), **3a**–**3d**, and **4a**–**4d** (lower R_f value).

(*E*)-2-[2-(Nitromethyl)-4-phenylbut-3-en-1-yl]-4*H*-chromen-4-one (2a): Yield 13.4 mg (40 %), colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.71–3.04 (m, 2 H, α-H), 3.58–3.70 (m, 1 H, β-H), 4.53 (dd, *J* = 12.4, 7.5 Hz, 1 H, NO_2CH_2), 4.58 (dd, *J* = 12.4, 6.7 Hz, 1 H, NO_2CH_2), 6.03 (dd, *J* = 15.8, 8.8 Hz, 1 H, γ-H), 6.23 (s, 1 H, 3-H), 6.55 (dd, *J* = 15.8, 0.8 Hz, 1 H, δ-H), 7.23–7.31 (m, 5 H, 2′-H, 3′-H, 4′-H, 5′-H, 6′-H), 7.40 (ddd, *J* = 8.0, 7.1, 1.0 Hz, 1 H, 6-H), 7.45 (dd, *J* = 8.6, 1.0 Hz, 1 H, 8-H), 7.67 (ddd, *J* = 8.6, 7.1, 1.7 Hz, 1 H, 7-H), 8.17 (dd, *J* = 8.0, 1.7 Hz, 1 H, 5-H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 37.2 (C-α), 39.8 (C-β), 78.7 (NO_2CH_2), 111.9 (C-3), 117.8 (C-8), 123.6 (C-4a), 125.0 (C-γ), 125.4 (C-6), 125.8 (C-5), 126.5 (C-2′, C-6′), 128.3 (C-4′), 128.7 (C-3′, C-5′), 133.9 (C-7), 134.6 (C-δ), 135.7 (C-1′), 156.3 (C-8a),

© 2017 Wiley-VCH Verlag GmbH & Co. KGaA, Weinheim

164.9 (C-2), 177.9 (C-4) ppm. ESI-HRMS: calcd. for $C_{20}H_{18}NO_4$ [M + H]$^+$ 336.1236; found 336.1226.

(*E*)-2-[4-(4-Chlorophenyl)-2-(nitromethyl)but-3-en-1-yl]-4*H*-chromen-4-one (2b): Yield 14.0 mg (38 %), colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.85 (dd, *J* = 14.5, 8.0 Hz, 1 H, α-H), 2.93 (dd, *J* = 14.5, 6.4 Hz, 1 H, α-H), 3.57–3.69 (m, 1 H, β-H), 4.49–4.62 (m, 2 H, NO_2CH_2), 6.01 (dd, *J* = 15.8, 8.8 Hz, 1 H, γ-H), 6.22 (s, 1 H, 3-H), 6.50 (d, *J* = 15.8 Hz, 1 H, δ-H), 7.20 (d, *J* = 8.5 Hz, 2 H, 2′-H, 6′-H), 7.26 (d, *J* = 8.5 Hz, 2 H, 3′-H, 5′-H), 7.41 (ddd, *J* = 8.0, 7.1, 1.1 Hz, 1 H, 6-H), 7.44 (dd, *J* = 8.7, 1.1 Hz, 1 H, 8-H), 7.68 (ddd, *J* = 8.7, 7.1, 1.7 Hz, 1 H, 7-H), 8.17 (dd, *J* = 8.0, 1.7 Hz, 1 H, 5-H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 37.1 (C-α), 39.9 (C-β), 78.6 (NO_2CH_2), 111.9 (C-3), 117.8 (C-8), 123.6 (C-4a), 125.5 (C-6), 125.7 (C-γ), 125.8 (C-5), 127.7 (C-2′, C-6′), 128.8 (C-3′, C-5′), 133.5 (C-δ), 133.9 (C-7), 134.0, 134.2 (C-1′, C-4′), 156.3 (C-8a), 164.7 (C-2), 177.9 (C-4) ppm. ESI-HRMS: calcd. for $C_{20}H_{17}{}^{35}ClNO_4$ [M + H]$^+$ 370.0846; found 370.0836; calcd. for $C_{20}H_{17}{}^{37}ClNO_4$ [M + H]$^+$ 372.0817; found 372.0803.

(*E*)-2-[4-(4-Methoxyphenyl)-2-(nitromethyl)but-3-en-1-yl]-4*H*-chromen-4-one (2c): Yield 19.0 mg (52 %), white solid, m.p. 139–141 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.84 (dd, *J* = 14.5, 8.0 Hz, 1 H, α-H), 2.92 (dd, *J* = 14.5, 6.5 Hz, 1 H, α-H), 3.58–3.70 (m, 1 H, β-H), 3.79 (s, 3 H, OCH_3), 4.51 (dd, *J* = 12.3, 7.5 Hz, 1 H, NO_2CH_2), 4.57 (dd, *J* = 12.3, 6.7 Hz, 1 H, NO_2CH_2), 5.87 (dd, *J* = 15.7, 8.8 Hz, 1 H, γ-H), 6.22 (s, 1 H, 3-H), 6.49 (d, *J* = 15.7 Hz, 1 H, δ-H), 6.82 (d, *J* = 8.7 Hz, 2 H, 3′-H, 5′-H), 7.22 (d, *J* = 8.7 Hz, 2 H, 2′-H, 6′-H), 7.40 (ddd, *J* = 8.0, 7.1, 1.1 Hz, 1 H, 6-H), 7.45 (dd, *J* = 8.7, 1.1 Hz, 1 H, 8-H), 7.67 (ddd, *J* = 8.7, 7.1, 1.6 Hz, 1 H, 7-H), 8.17 (dd, *J* = 8.0, 1.6 Hz, 1 H, 5-H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 37.3 (C-α), 39.9 (C-β), 55.3 (OCH_3), 78.9 (NO_2CH_2), 111.9 (C-3), 114.0 (C-3′, C-5′), 117.8 (C-8), 122.6 (C-γ), 123.7 (C-4a), 125.4 (C-6), 125.8 (C-5), 127.7 (C-2′, C-6′), 128.5 (C-1′), 133.9 (C-7), 134.0 (C-δ), 156.3 (C-8a), 159.7 (C-4′), 165.0 (C-2), 177.9 (C-4) ppm. ESI-HRMS: calcd. for $C_{21}H_{20}NO_5$ [M + H]$^+$ 366.1341; found 366.1330.

(*E*)-2-[4-(Methylphenyl)-2-(nitromethyl)but-3-en-1-yl]-4*H*-chromen-4-one (2d): Yield 14.0 mg (40 %), white solid, m.p. 103–104 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.31 (s, 3 H, CH_3), 2.84 (dd, *J* = 14.5, 8.0 Hz, 1 H, α-H), 2.92 (dd, *J* = 14.5, 6.6 Hz, 1 H, α-H), 3.56–3.68 (m, 1 H, β-H), 4.52 (dd, *J* = 12.3, 7.5 Hz, 1 H, NO_2CH_2), 4.57 (dd, *J* = 12.3, 6.7 Hz, 1 H, NO_2CH_2), 5.97 (dd, *J* = 15.8, 8.7 Hz, 1 H, γ-H), 6.23 (s, 1 H, 3-H), 6.52 (d, *J* = 15.8 Hz, 1 H, δ-H), 7.09 (d, *J* = 8.1 Hz, 2 H, 3′-H, 5′-H), 7.18 (d, *J* = 8.1 Hz, 2 H, 2′-H, 6′-H), 7.40 (ddd, *J* = 8.0, 7.1, 1.0 Hz, 1 H, 6-H), 7.45 (dd, *J* = 8.5, 1.0 Hz, 1 H, 8-H), 7.67 (ddd, *J* = 8.5, 7.1, 1.7 Hz, 1 H, 7-H), 8.17 (dd, *J* = 8.0, 1.7 Hz, 1 H, 5-H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 21.2 (CH_3), 37.3 (C-α), 39.9 (C-β), 78.8 (NO_2CH_2), 111.9 (C-3), 117.8 (C-8), 123.7 (C-4a), 123.9 (C-γ), 125.4 (C-6), 125.8 (C-5), 126.4 (C-2′, C-6′), 129.3 (C-3′, C-5′), 132.9 (C-1′), 133.9 (C-7), 134.5 (C-δ), 138.3 (C-4′), 156.3 (C-8a), 164.9 (C-2), 177.9 (C-4) ppm. ESI-HRMS: calcd. for $C_{21}H_{20}NO_4$ [M + H]$^+$ 350.1392; found 350.1385.

(*E*)-5′-(Nitromethyl)-3′-styryl-[1,1′-biphenyl]-2-ol (3a): Yield 2.3 mg (7 %), colorless oil. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 5.16 (s, 1 H, O*H*), 5.52 (s, 2 H, NO_2CH_2), 6.99 (dd, *J* = 8.6, 1.1 Hz, 1 H, 3-H), 7.04 (dt, *J* = 7.5, 1.1 Hz, 1 H, 5-H), 7.14 (AB, *J* = 16.3 Hz, 1 H, α-H), 7.20 (AB, *J* = 16.3 Hz, 1 H, β-H), 7.29–7.31 (m, 3 H, 4-H, 6-H, 4′′-H), 7.38 (t, *J* = 7.6 Hz, 2 H, 3′′-H, 5′′-H), 7.48 (t, *J* = 1.6 Hz, 1 H, 6′-H), 7.52–7.54 (m, 2 H, 2′′-H, 6′′-H), 7.61 (t, *J* = 1.6 Hz, 1 H, 4′-H), 7.72 (t, *J* = 1.6 Hz, 1 H, 2′-H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 79.9 (NO_2CH_2), 116.2 (C-3), 121.2 (C-5), 126.7 (C-2′′, C-6′′), 126.8 (C-1), 127.0 (C-α), 127.2 (C-4′), 128.2 (C-4′′), 128.6 (C-2′), 128.8 (C-3′′, C-5′′), 129.69, 129.70 (C-4, C-6′), 130.4 (C-6), 130.80 (C-β), 130.85 (C-5′), 136.7 (C-1′′), 138.8 (C-1′), 139.2 (C-3′), 152.4 (C-2) ppm. ESI-HRMS: calcd. for $C_{21}H_{16}NO_3$ [M – H]$^-$ 330.1130; found 330.1133.

(*E*)-3′-(4-Chlorostyryl)-5′-(nitromethyl)-[1,1′-biphenyl]-2-ol (3b): Yield 5.5 mg (15 %), colorless oil. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 5.14 (s, 1 H, O*H*), 5.52 (s, 2 H, NO_2CH_2), 6.99 (dd, *J* = 7.6, 1.2 Hz, 1 H, 3-H), 7.04 (dt, *J* = 7.5, 1.2 Hz, 1 H, 5-H), 7.10 (AB, *J* = 16.3 Hz, 1 H, α-H), 7.15 (AB, *J* = 16.3 Hz, 1 H, β-H), 7.29 (d, *J* = 7.5 Hz, 1 H, 6-H), 7.28–7.32 (m, 1 H, 4-H), 7.35 (d, *J* = 8.5 Hz, 2 H, 3′′-H, 5′′-H), 7.45 (d, *J* = 8.5 Hz, 2 H, 2′′-H, 6′′-H), 7.49 (t, *J* = 1.6 Hz, 1 H, 6′-H), 7.59 (t, *J* = 1.6 Hz, 1 H, 4′-H), 7.71 (t, *J* = 1.6 Hz, 1 H, 2′-H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 79.9 (NO_2CH_2), 116.2 (C-3), 121.2 (C-5), 126.9 (C-1), 127.1 (C-4′), 127.7 (C-α), 127.9 (C-2′′, C-6′′), 128.7 (C-2′), 129.0 (C-3′′, C-5′′), 129.44 (C-β), 129.7 (C-4), 129.9 (C-6′), 130.4 (C-6), 130.9 (C-5′), 133.8 (C-4′′), 135.2 (C-1′′), 138.8, 138.9 (C-1′, C-3′), 152.4 (C-2) ppm. ESI-HRMS: calcd. for $C_{21}H_{15}{}^{35}ClNO_3$ [M – H]$^-$ 364.0740; found 364.0748; calcd. for $C_{21}H_{15}{}^{37}ClNO_3$ [M – H]$^-$ 366.0711; found 366.0716.

(*E*)-3′-(4-Methoxystyryl)-5′-(nitromethyl)-[1,1′-biphenyl]-2-ol (3c): Yield 6.5 mg (18 %), yellowish oil. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 3.84 (s, 3 H, OCH_3), 5.14 (s, 1 H, O*H*), 5.51 (s, 2 H, NO_2CH_2), 6.92 (d, *J* = 8.7 Hz, 2 H, 3′′-H, 5′′-H), 6.99 (dd, *J* = 7.5, 1.0 Hz, 1 H, 3-H), 7.00 (d, *J* = 16.3 Hz, 1 H, α-H), 7.03 (dt, *J* = 7.5, 1.0 Hz, 1 H, 5-H), 7.15 (d, *J* = 16.3 Hz, 1 H, β-H), 7.28–7.31 (m, 1 H, 4-H), 7.29 (d, *J* = 7.5 Hz, 1 H, 6-H), 7.44 (t, *J* = 1.6 Hz, 1 H, 6′-H), 7.47 (d, *J* = 8.7 Hz, 2 H, 2′′-H, 6′′-H), 7.58 (t, *J* = 1.6 Hz, 1 H, 4′-H), 7.68 (t, *J* = 1.6 Hz, 1 H, 2′-H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 55.4 (OCH_3), 79.9 (NO_2CH_2), 114.3 (C-3′′, C-5′′), 116.1 (C-3), 121.1 (C-5), 124.8 (C-α), 126.9 (C-4′), 127.1 (C-1), 128.0 (C-2′′, C-6′′), 128.3 (C-2′), 129.2 (C-6′), 129.4 (C-1′′), 129.6 (C-4), 130.33, 130.35 (C-6, C-β), 130.8 (C-5′), 138.7 (C-1′), 139.6 (C-3′), 152.4 (C-2), 159.8 (C-4′′) ppm. ESI-HRMS: calcd. for $C_{22}H_{18}NO_4$ [M – H]$^-$ 360.1236; found 360.1236.

(*E*)-3′-(4-Methylstyryl)-5′-(nitromethyl)-[1,1′-biphenyl]-2-ol (3d): Yield 1.0 mg (3 %), colorless oil. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 2.37 (s, 3 H, CH_3), 5.14 (s, 1 H, O*H*), 5.51 (s, 2 H, NO_2CH_2), 6.99 (dd, *J* = 8.5, 1.2 Hz, 1 H, 3-H), 7.03 (dt, *J* = 7.5, 1.2 Hz, 1 H, 5-H), 7.09 (d, *J* = 16.3 Hz, 1 H, α-H), 7.17 (d, *J* = 16.3 Hz, 1 H, β-H), 7.19 (d, *J* = 8.0 Hz, 2 H, 3′′-H, 5′′-H), 7.29 (d, *J* = 7.5 Hz, 1 H, 6-H), 7.28–7.31 (m, 1 H, 4-H), 7.43 (d, *J* = 8.0 Hz, 2 H, 2′′-H, 6′′-H), 7.46 (t, *J* = 1.7 Hz, 1 H, 6′-H), 7.59 (t, *J* = 1.7 Hz, 1 H, 4′-H), 7.70 (t, *J* = 1.7 Hz, 1 H, 2′-H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 21.3 (CH_3), 79.9 (NO_2CH_2), 116.2 (C-3), 121.2 (C-5), 126.0 (C-α), 126.66 (C-2′′, C-6′′), 126.71 (C-1), 127.1 (C-4′), 128.5 (C-2′), 129.4 (C-6′), 129.5 (C-3′′, C-5′′), 129.7 (C-4), 130.3 (C-β), 130.7 (C-6), 130.8 (C-5′), 133.9 (C-1′′), 138.3 (C-4′′), 138.7 (C-1′), 139.4 (C-3′), 152.4 (C-2) ppm. ESI-HRMS: calcd. for $C_{22}H_{18}NO_3$ [M – H]$^-$ 344.1287; found 344.1278.

2′-Nitro-5′-(nitromethyl)-3′-phenylspiro[chromane-2,1′-cyclohexan]-4-one (4a): Yield 2.4 mg (6 %), colorless oil. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.38 (dd, 1 H, 6′-H, *J* = 14.5, 12.6 Hz), 1.50–1.58 (m, 1 H, 4′-H), 2.19 (dq, *J* = 13.6, 3.5 Hz, 1 H, 4′-H), 2.53 (dt, *J* = 14.5, 3.5 Hz, 1 H, 6′-H), 2.70–2.79 (m, 1 H, 5′-H), 2.73 (d, *J* = 16.7 Hz, 1 H, 3-H), 3.15 (d, 1 H, 3-H, *J* = 16.7 Hz), 4.12 (dt, 1 H, 3′-H, *J* = 12.2, 3.5 Hz), 4.19 (dd, 1 H, NO_2CH_2, *J* = 12.5, 7.4 Hz), 4.24 (dd, 1 H, NO_2CH_2, *J* = 12.5, 6.0 Hz), 4.81 (d, 1 H, 2′-H, *J* = 12.2 Hz), 7.11 (ddd, 1 H, 6-H, *J* = 7.8, 7.1, 1.0 Hz), 7.18 (dd, 1 H, 8-H, *J* = 8.2, 1.0 Hz), 7.28–7.30 (m, 3 H, 2′′,4′′,6′′-H), 7.33–7.36 (m, 2 H, 3′′-H, 5′′-H), 7.60 (ddd, *J* = 8.2, 7.1, 1.7 Hz, 1 H, 7-H), 7.88 (dd, *J* = 7.8, 1.7 Hz, 1 H, 5-H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 31.0 (C-5′), 35.0 (C-6′), 36.2 (C-4′), 41.2 (C-3′), 44.8 (C-3), 78.5 (C-1′), 79.2 (NO_2CH_2), 93.8 (C-2′), 118.4 (C-8), 119.9 (C-4a), 122.5 (C-6), 126.8 (C-5), 127.2 (C-2′′, C-6′′), 128.2 (C-4′′), 129.2 (C-3′′, C-5′′), 137.1 (C-7), 138.7 (C-1′′), 157.2 (C-8a), 189.5 (C-4) ppm. ESI-HRMS: calcd. for $C_{21}H_{21}N_2O_6$ [M + H]$^+$ 397.1400; found 397.1412.

3′-(4-Chlorophenyl)-2′-nitro-5′-(nitromethyl)spiro[chromane-2,1′-cyclohexan]-4-one (4b): Yield 4.3 mg (10 %), colorless oil. ^{1}H

© 2017 Wiley-VCH Verlag GmbH & Co. KGaA, Weinheim

NMR (300 MHz, $CDCl_3$): δ = 1.37 (dd, *J* = 14.4, 12.7 Hz, 1 H, 6′-H), 1.45–1.59 (m, 1 H, 4′-H), 2.17 (dq, *J* = 14.6, 3.5 Hz, 1 H, 4′-H), 2.53 (dt, *J* = 14.4, 3.5 Hz, 1 H, 6′-H), 2.66–2.80 (m, 1 H, 5′-H), 2.72 (d, *J* = 16.7 Hz, 1 H, 3-H), 3.14 (d, *J* = 16.7 Hz, 1 H, 3-H), 4.11 (dt, *J* = 12.1, 3.5 Hz, 1 H, 3′-H), 4.21 (dd, *J* = 12.7, 7.7 Hz, 1 H, NO_2CH_2), 4.25 (dd, *J* = 12.7, 6.2 Hz, 1 H, NO_2CH_2), 4.75 (d, *J* = 12.1 Hz, 1 H, 2′-H), 7.12 (ddd, *J* = 7.9, 7.3, 1.0 Hz, 1 H, 6-H), 7.16 (dd, *J* = 8.7, 1.0 Hz, 1 H, 8-H), 7.23 (d, *J* = 8.5 Hz, 2 H, 2″-H, 6″-H), 7.33 (d, *J* = 8.5 Hz, 2 H, 3″-H, 5″-H), 7.60 (ddd, *J* = 8.7, 7.3, 1.8 Hz, 1 H, 7-H), 7.88 (dd, *J* = 7.9, 1.8 Hz, 1 H, 5-H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 30.9 (C-5′), 35.0 (C-6′), 36.0 (C-4′), 40.7 (C-3′), 44.7 (C-3), 78.4 (C-1′), 79.1 (NO_2CH_2), 93.7 (C-2′), 118.3 (C-8), 119.9 (C-4a), 122.6 (C-6), 126.9 (C-5), 128.6 (C-2″, C-6″), 129.4 (C-3″, C-5″), 134.1 (C-4″), 137.10, 137.15 (C-7, C-1″), 157.1 (C-8a), 189.3 (C-4) ppm. ESI-HRMS: calcd. for $C_{21}H_{18}{}^{35}ClN_2O_6$ [M – H]$^-$ 429.0853; found 429.0860; calcd. for $C_{21}H_{18}{}^{37}ClN_2O_6$ [M – H]$^-$ 431.0824; found 431.0830.

3′-(4-Methoxyphenyl)-2′-nitro-5′-(nitromethyl)spiro[chromane-2,1′-cyclohexan]-4-one (4c): Yield 5.1 mg (12 %), colorless oil. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.35 (dd, *J* = 14.4, 12.6 Hz, 1 H, 6′-H), 1.48–1.56 (m, 1 H, 4′-H), 2.16 (dq, *J* = 13.8, 3.6 Hz, 1 H, 4′-H), 2.52 (dt, *J* = 14.4, 3.6 Hz, 1 H, 6′-H), 2.70–2.77 (m, 1 H, 5′-H), 2.71 (d, *J* = 16.7 Hz, 1 H, 3-H), 3.13 (d, *J* = 16.7 Hz, 1 H, 3-H), 3.79 (s, 3 H, OCH_3), 4.06 (dt, *J* = 12.2, 3.6 Hz, 1 H, 3′-H), 4.19 (dd, *J* = 12.5, 7.4 Hz, 1 H, NO_2CH_2), 4.24 (dd, *J* = 12.5, 6.0 Hz, 1 H, NO_2CH_2) 4.73 (d, *J* = 12.2 Hz, 1 H, 2′-H), 6.87 (d, *J* = 8.7 Hz, 2 H, 3″-H, 5″-H), 7.11 (ddd, *J* = 7.9, 7.2, 1.0 Hz, 1 H, 6-H), 7.17 (dd, *J* = 8.4, 1.0 Hz, 1 H, 8-H), 7.21 (d, *J* = 8.7 Hz, 2 H, 2″-H,6″-H), 7.59 (ddd, *J* = 8.4, 7.2, 1.7 Hz, 1 H, 7-H), 7.88 (dd, *J* = 7.9, 1.7 Hz, 1 H, 5-H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 31.0 (C-5′), 35.0 (C-6′), 36.2 (C-4′), 40.4 (C-3′), 44.8 (C-3), 55.3 (OCH_3), 78.5 (C-1′), 79.2 (NO_2CH_2), 94.2 (C-2′), 114.5 (C-3″, C-5″), 118.4 (C-8), 119.9 (C-4a), 122.5 (C-6), 126.8 (C-5), 128.3 (C-2″, C-6″), 130.6 (C-1″), 137.0 (C-7), 157.3 (C-8a), 159.3 (C-4″), 189.5 (C-4) ppm. ESI-HRMS: calcd. for $C_{22}H_{21}N_2O_7$ [M – H]$^-$ 425.1349; found 425.1356.

3′-(4-Methylphenyl)2′-nitro-5′-(nitromethyl)spiro[chromane-2,1′-cyclohexan]-4-one (4d): Yield 3.3 mg (8 %), colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.36 (dd, *J* = 14.3, 12.6 Hz, 1 H, 6′-H), 1.44–1.60 (m, 1 H, 4′-H), 2.16 (dq, *J* = 13.6, 3.7 Hz, 1 H, 4′-H), 2.32 (s, 3 H, CH_3), 2.52 (dt, *J* = 14.3, 3.7 Hz, 1 H, 6′-H), 2.66–2.80 (m, 1 H, 5′-H), 2.72 (d, *J* = 16.7 Hz, 1 H, 3-H), 3.14 (d, *J* = 16.7 Hz, 1 H, 3-H), 4.08 (dt, *J* = 12.3, 3.7 Hz, 1 H, 3′-H), 4.18 (dd, *J* = 12.3, 7.1 Hz, 1 H, NO_2CH_2), 4.24 (dd, *J* = 12.3, 6.1 Hz, 1 H, NO_2CH_2), 4.78 (d, *J* = 12.3 Hz, 1 H, 2′-H), 7.11 (ddd, *J* = 8.0, 7.2, 1.1 Hz, 1 H, 6-H), 7.13–7.16 (m, 1 H, 8-H), 7.14 (AA′BB′, *J* = 8.5 Hz, 2 H, 3″-H, 5″-H), 7.18 (AA′BB′, *J* = 8.5 Hz, 2 H, 2″-H, 6″-H), 7.59 (ddd, *J* = 8.8, 7.2, 1.7 Hz, 1 H, 7-H), 7.88 (dd, *J* = 8.0, 1.7 Hz, 1 H, 5-H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 21.0 (CH_3), 31.0 (C-5′), 35.0 (C-6′), 36.2 (C-4′), 40.8 (C-3′), 44.8 (C-3), 78.5 (C-1′), 79.2 (NO_2CH_2), 94.0 (C-2′), 118.4 (C-8), 119.9 (C-4a), 122.5 (C-6), 126.8 (C-5), 127.0 (C-2″, C-6″), 129.8 (C-3″, C-5″), 135.6 (C-1″), 137.0 (C-7), 137.9 (C-4″), 157.3 (C-8a), 189.5 (C-4) ppm. ESI-HRMS: calcd. for $C_{22}H_{21}N_2O_6$ [M – H]$^-$ 409.1400; found 409.1402.

(*E*)-2-[4-(4-Methoxyphenyl)-1-(4-oxo-4*H*-chromen-2-yl)but-3-en-2-yl]malononitrile (5a): DBU (0.05 mmol, 7.5 μL) was added to a solution of chromone **1c** (0.1 mmol, 30 mg) and malononitrile (0.3 mmol, 19.8 mg) in dry DMF (0.4 mL). The reaction mixture was stirred at room temperature for 16 h and then poured into water (5 mL), and the pH was adjusted to 4 with dilute HCl. The aqueous mixture was extracted with dichloromethane (3 × 5 mL), dried with anhydrous sodium sulfate, and concentrated under reduced pressure. The crude residue was purified by preparative TLC with hexane/ethyl acetate (9:7) as the eluent. Yield 10.4 mg (28 %), brown oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 3.02 (dd, *J* = 14.6, 8.3 Hz, 1 H, α-H), 3.12 (dd, *J* = 14.6, 6.5 Hz, 1 H, α-H), 3.38–3.48 (m, 1 H, β-H), 3.80 (s, 3 H, OCH_3), 3.97 [d, *J* = 4.9 Hz, 1 H, $CH(CN)_2$], 5.96 (dd, *J* = 15.6, 9.1 Hz, 1 H, γ-H), 6.27 (s, 1 H, 3-H), 6.67 (d, *J* = 15.6 Hz, 1 H, δ-H), 6.85 (d, *J* = 8.7 Hz, 2 H, 3′-H, 5′-H), 7.29 (d, *J* = 8.7 Hz, 2 H, 2′-H, 6′-H), 7.41 (ddd, *J* = 7.9, 7.1, 0.9 Hz, 1 H, 6-H), 7.45 (d, *J* = 8.3 Hz, 1 H, 8-H), 7.69 (ddd, *J* = 8.3, 7.1, 1.7 Hz, 1 H, 7-H), 8.16 (dd, *J* = 7.9, 1.7 Hz, 1 H, 5-H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 28.6 [$CH(CN)_2$], 37.2 (C-α), 42.6 (C-β), 55.4 (OCH_3), 111.0, 111.3 [$CH(CN)_2$], 112.3 (C-3), 114.2 (C-3′, C-5′), 117.8 (C-8), 119.8 (C-γ), 123.6 (C-4a), 125.6 (C-6), 125.9 (C-5), 127.6 (C-1′), 128.2 (C-2′, C-6′), 134.1 (C-7), 136.8 (C-δ), 156.3 (C-8a), 160.2 (C-4′), 163.4 (C-2), 177.7 (C-4) ppm. ESI-MS: *m/z* (%) = 371 (100) [M + H]$^+$, 372 (25) [M + 2H]$^+$. ESI-HRMS: calcd. for $C_{23}H_{19}N_2O_3$ [M + H]$^+$ 371.1390; found 371.1374.

(*E*)-3-[4-(4-Methoxyphenyl)-1-(4-oxo-4*H*-chromen-2-yl)but-3-en-2-yl]pentane-2,4-dione (5b): DBU (0.1 mmol, 14.9 μL) was added to a solution of chromone **1c** (0.1 mmol, 30 mg) in acetylacetone (0.5 mL). The resulting mixture was stirred at room temperature for 48 h and then poured into water (5 mL), and the pH was adjusted to 4 with dilute HCl. The aqueous mixture was extracted with dichloromethane (3 × 5 mL), dried with anhydrous sodium sulfate, and concentrated under reduced pressure. The crude residue was purified by preparative TLC with hexane/ethyl acetate (9:7) as the eluent. Yield 24.3 mg (60 %), colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.14 (s, 3 H, 4″-CH_3), 2.27 (s, 3 H, 2″-CH_3), 2.63 (dd, *J* = 14.2, 9.5 Hz, 1 H, α-H), 2.82 (dd, *J* = 14.2, 4.3 Hz, 1 H, α-H), 3.58 (dq, *J* = 9.5, 4.3 Hz, 1 H, β-H), 3.77 (s, 3 H, OCH_3), 3.90 (d, *J* = 9.5 Hz, 1 H, 3″-H), 5.83 (dd, *J* = 15.8, 9.5 Hz, 1 H, γ-H), 6.15 (s, 1 H, 3-H), 6.36 (d, *J* = 15.8 Hz, 1 H, δ-H), 6.78 (d, *J* = 8.7 Hz, 2 H, 3′-H, 5′-H), 7.15 (d, *J* = 8.7 Hz, 2 H, 2′-H, 6′-H), 7.38 (ddd, *J* = 8.0, 7.1, 1.0 Hz, 1 H, 6-H), 7.43 (dd, *J* = 8.5, 1.0 Hz, 1 H, 8-H), 7.65 (ddd, *J* = 8.5, 7.1, 1.7 Hz, 1 H, 7-H), 8.15 (dd, *J* = 8.0, 1.7 Hz, 1 H, 5-H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 29.6 (4″-CH_3), 30.3 (2″-CH_3), 38.2 (C-α), 41.2 (C-β), 55.3 (OCH_3), 73.1 (C-3″), 111.8 (C-3), 114.0 (C-3′, C-5′), 117.8 (C-8), 123.7 (C-4a), 124.4 (C-γ), 125.2 (C-6), 125.8 (C-5), 127.6 (C-2′, C-6′), 128.8 (C-1′), 133.2 (C-δ), 133.7 (C-7), 156.4 (C-8a), 159.5 (C-4′), 166.2 (C-2), 178.0 (C-4), 202.6, 202.7 (C-2″, C-4″) ppm. ESI-MS: *m/z* (%) = 405 (100) [M + H]$^+$, 406 (28) [M + 2H]$^+$. ESI-HRMS: calcd. for $C_{25}H_{25}O_5$ [M + H]$^+$ 405.1697; found 405.1682.

Diethyl (*E*)-2-[4-(4-Methoxyphenyl)-1-(4-oxo-4*H*-chromen-2-yl)but-3-en-2-yl]malonate (5c): DBU (0.1 mmol, 14.9 μL) was added to a mixture of chromone **1c** (0.1 mmol, 30 mg) and diethyl malonate (0.4 mL) in dry DMF (0.6 mL). The solution was stirred at room temperature for 24 h and then poured into water (5 mL), and the pH was adjusted to 4 with dilute HCl. The aqueous mixture was extracted with dichloromethane (3 × 5 mL), dried with anhydrous sodium sulfate, and concentrated under reduced pressure. The crude residue was purified by preparative TLC with hexane/ethyl acetate (9:7) as the eluent to afford the desired product **5c** (higher R_f value) and compound **6c** (colorless oil, lower R_f value) as an inseparable mixture of two diastereomers.

Diethyl (*E*)-2-[4-(4-Methoxyphenyl)-1-(4-oxo-4*H*-chromen-2-yl)but-3-en-2-yl]malonate (5c): Yield 27.9 mg (60 %), colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.21, 1.27 (2 × t, *J* = 7.1 Hz, 6 H, $CO_2CH_2CH_3$), 2.82 (dd, *J* = 14.3, 8.7 Hz, 1 H, α-H), 3.02 (dd, *J* = 14.3, 4.8 Hz, 1 H, α-H), 3.44–3.54 (m, 1 H, β-H), 3.56 (d, *J* = 7.9 Hz, 1 H, 1″-H), 3.77 (s, 3 H, OCH_3), 4.16, 4.22 (2 × dq, *J* = 7.1, 0.8 Hz, 4 H, $CO_2CH_2CH_3$), 6.00 (dd, *J* = 15.7, 9.0 Hz, 1 H, γ-H), 6.19 (s, 1 H, 3-H), 6.38 (d, *J* = 15.7 Hz, 1 H, δ-H), 6.78 (d, *J* = 8.8 Hz, 2 H, 3′-H, 5′-H), 7.18 (d, *J* = 8.8 Hz, 2 H, 2′-H, 6′-H), 7.37 (ddd, *J* = 8.0, 7.1, 1.1 Hz, 1 H, 6-H), 7.43 (dd, *J* = 8.3, 1.1 Hz, 1 H, 8-H), 7.64 (ddd, *J* = 8.3, 7.1, 1.7 Hz, 1 H, 7-H), 8.15 (dd, *J* = 8.0, 1.7 Hz, 1 H, 5-H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 14.1 ($CO_2CH_2CH_3$), 37.9 (C-α), 41.4 (C-β), 55.3 (OCH_3), 56.1 (C-1″), 61.62, 61.75 ($CO_2CH_2CH_3$), 111.6 (C-3), 113.9

© 2017 Wiley-VCH Verlag GmbH & Co. KGaA, Weinheim

(C-3′, C-5′), 117.9 (C-8), 123.7 (C-4a), 124.8 (C-γ), 125.1 (C-6), 125.7 (C-5), 127.5 (C-2′, C-6′), 129.2 (C-1′), 132.9 (C-δ), 133.6 (C-7), 156.4 (C-8a), 159.3 (C-4′), 166.6 (C-2), 167.7, 167.9 ($CO_2CH_2CH_3$), 178.1 (C-4) ppm. ESI-MS: *m/z* (%) = 465 (100) $[M + H]^+$, 466 (30) $[M + 2H]^+$. ESI-HRMS: calcd. for $C_{27}H_{29}O_7$ $[M + H]^+$ 465.1908; found 465.1891.

Tetraethyl *rel*-(2*S*,4*R*)-2-(4-Methoxyphenyl)-4-[(4-oxo-4*H*-chromen-2-yl)methyl]pentane-1,1,5,5-tetracarboxylate (6c, Diastereomer I): ^1H NMR (300 MHz, $CDCl_3$): δ = 0.95, 1.13, 1.25, 1.26 (4 × t, *J* = 7.1 Hz, 12 H, $CO_2CH_2CH_3$), 1.89–1.97 (m, 2 H, γ-H), 2.31–2.38 (m, 1 H, β-H), 2.73 (dd, *J* = 14.9, 8.6 Hz, 1 H, α-H), 3.01 (dd, *J* = 14.9, 4.5 Hz, 1 H, α-H), 3.34 (d, *J* = 5.3 Hz, 1 H, 1″-H), 3.47–3.54 (m, 1 H, δ-H), 3.55 (d, *J* = 10.6 Hz, 1 H, 2″-H), 3.79 (s, 3 H, OCH_3), 3.87 (q, *J* = 7.1 Hz, 2 H, $CO_2CH_2CH_3$), 4.07–4.29 (m, 6 H, $CO_2CH_2CH_3$), 6.17 (s, 1 H, 3-H), 6.84 (d, *J* = 8.7 Hz, 2 H, 3′-H, 5′-H), 7.15 (d, *J* = 8.7 Hz, 2 H, 2′-H, 6′-H), 7.35–7.41 (m, 2 H, 6-H, 8-H), 7.64 (ddd, *J* = 8.4, 7.3, 1.8 Hz, 1 H, 7-H), 8.17 (dd, *J* = 7.8, 1.8 Hz, 1 H, 5-H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 13.71, 13.77, 13.90, 14.09 ($CO_2CH_2CH_3$), 34.3 (C-β), 35.1, 35.2 (C-α, C-γ), 42.6 (C-δ), 54.0 (C-1″), 55.2 (OCH_3), 59.1 (C-2″), 61.2, 61.45, 61.46, 61.7 ($CO_2CH_2CH_3$), 111.7 (C-3), 113.9 (C-3′, C-5′), 118.0 (C-8), 123.7 (C-4a), 125.1 (C-6), 125.6 (C-5), 129.7 (C-2′, C-6′), 131.0 (C-1′), 133.5 (C-7), 156.4 (C-8a), 158.8 (C-4′), 167.0 (C-2), 167.6, 168.0, 168.14, 168.16 ($CO_2CH_2CH_3$), 178.0 (C-4) ppm. ESI-MS: *m/z* (%) = 625 (100) $[M + H]^+$, 626 (37) $[M + 2H]^+$. ESI-HRMS: calcd. for $C_{34}H_{41}O_{11}$ $[M + H]^+$ 625.2643; found 625.2628.

Tetraethyl *rel*-(2*S*,4*S*)-2-(4-Methoxyphenyl)-4-[(4-oxo-4*H*-chromen-2-yl)methyl]pentane-1,1,5,5-tetracarboxylate (6c, Diastereomer II): ^1H NMR (300 MHz, $CDCl_3$): δ = 0.90 (t, *J* = 7.1 Hz, 3 H, $CO_2CH_2CH_3$), 1.23–1.30 (m, 6 H, $CO_2CH_2CH_3$), 1.34 (t, *J* = 7.1 Hz, 3 H, $CO_2CH_2CH_3$), 1.66–1.74 (m, 2 H, γ-H), 2.31–2.38 (m, 1 H, β-H), 2.57 (dd, *J* = 14.4, 10.5 Hz, 1 H, α-H), 2.83 (dd, *J* = 14.4, 3.7 Hz, 1 H, α-H), 3.28–3.37 (m, 1 H, δ-H), 3.45 (d, *J* = 10.9 Hz, 1 H, 2″-H), 3.62 (s, 3 H, OCH_3), 3.74 (d, *J* = 3.9 Hz, 1 H, 1″-H), 3.74–4.30 (m, 8 H, $CO_2CH_2CH_3$), 6.04 (s, 1 H, 3-H), 6.50 (d, *J* = 8.6 Hz, 2 H, 3′-H, 5′-H), 6.91 (d, *J* = 8.6 Hz, 2 H, 2′-H, 6′-H), 7.12–7.14 (m, 1 H, 8-H), 7.35–7.41 (m, 1 H, 6-H), 7.58–7.64 (m, 1 H, 7-H), 8.15–8.18 (m, 1 H, 5-H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 13.71, 13.77, 13.90, 14.09 ($CO_2CH_2CH_3$), 34.1 (C-β), 35.3 (C-γ), 36.6 (C-α), 42.8 (C-δ), 52.5 (C-1″), 55.0 (OCH_3), 58.6 (C-2″), 61.1, 61.52, 61.58, 61.62 ($CO_2CH_2CH_3$), 111.6 (C-3), 113.7 (C-3′, C-5′), 117.9 (C-8), 123.5 (C-4a), 124.9 (C-6), 125.5 (C-5), 129.1 (C-2′, C-6′), 131.1 (C-1′), 133.3 (C-7), 156.3 (C-8a), 158.5 (C-4′), 167.1 (C-2), 167.5, 168.14, 168.16, 168.7 ($CO_2CH_2CH_3$), 178.0 (C-4) ppm. ESI-MS: *m/z* (%) = 625 (100) $[M + H]^+$, 626 (37) $[M + 2H]^+$. ESI-HRMS: calcd. for $C_{34}H_{41}O_{11}$ $[M + H]^+$ 625.2643; found 625.2628.

Ethyl (*E*)-2-Cyano-5-(4-methoxyphenyl)-3-[(4-oxo-4*H*-chromen-2-yl)methyl]pent-4-enoate (5d): DBU (0.1 mmol, 14.9 μL) was added to a solution of chromone **1c** (0.1 mmol, 30 mg) in ethyl cyanoacetate (0.5 mL). The reaction mixture was stirred at room temperature for 24 h and then poured into water (5 mL), and the pH was adjusted to 4 with dilute HCl. The aqueous mixture was extracted with dichloromethane (3 × 5 mL), dried with anhydrous sodium sulfate, and concentrated under reduced pressure. The crude residue was purified by preparative TLC with hexane/ethyl acetate (9:7) as the eluent. The desired product **5d** was obtained as an inseparable mixture of two diastereomers: yield 29.2 mg (70 %).

Ethyl *rel*-(2*R*,3*S*)-(*E*)-2-Cyano-5-(4-methoxyphenyl)-3-[(4-oxo-4*H*-chromen-2-yl)methyl]pent-4-enoate (5d, Diastereomer I): ^1H NMR (500 MHz, $CDCl_3$): δ = 1.23 (t, *J* = 7.1 Hz, 3 H, $CO_2CH_2CH_3$), 2.99 (d, *J* = 7.7 Hz, 2 H, α-H), 3.48–3.54 (m, 1 H, β-H), 3.74 (d, *J* = 4.2 Hz, 1 H, 1″-H), 3.80 (s, 3 H, OCH_3), 4.23 (q, *J* = 7.1 Hz, 2 H, $CO_2CH_2CH_3$), 6.00 (dd, *J* = 15.7, 9.4 Hz, 1 H, γ-H), 6.27 (s, 1 H, 3-H), 6.50 (d, *J* = 15.7 Hz, 1 H, δ-H), 6.83 (d, *J* = 8.8 Hz, 2 H, 3′-H, 5′-H), 7.26 (d, *J* = 8.8 Hz, 2 H, 2′-H, 6′-H), 7.37–7.42 (m, 1 H, 6-H), 7.46 (d, *J* = 8.0 Hz, 1 H, 8-H), 7.67 (ddd, *J* = 8.0, 7.0, 1.5 Hz, 1 H, 7-H), 8.17 (dd, *J* = 8.1, 1.5 Hz, 1 H, 5-H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 14.1 ($CO_2CH_2CH_3$), 38.2 (C-α), 41.94 (C-β), 42.8 (C-1″), 55.3 (OCH_3), 63.2 ($CO_2CH_2CH_3$), 111.9 (C-3), 114.07 (C-3′, C-5′), 114.6 (*C*N), 117.88 (C-8), 121.7 (C-γ), 123.69 (C-4a), 125.4 (C-6), 125.83 (C-5), 127.9 (C-2′, C-6′), 128.4 (C-1′), 133.9 (C-7), 134.9 (C-δ), 156.39 (C-8a), 159.8 (C-4′), 164.6 ($CO_2CH_2CH_3$), 164.72 (C-2), 177.88 (C-4) ppm. ESI-MS: *m/z* (%) = 418 (100) $[M + H]^+$, 419 (25) $[M + 2H]^+$. ESI-HRMS: calcd. for $C_{25}H_{24}NO_5$ $[M + H]^+$ 418.1649; found 418.1633.

Ethyl *rel*-(2*S*,3*S*)-(*E*)-2-Cyano-5-(4-methoxyphenyl)-3-[(4-oxo-4*H*-chromen-2-yl)methyl]pent-4-enoate (5d, Diastereomer II): ^1H NMR (500 MHz, $CDCl_3$): δ = 1.28 (t, *J* = 7.2 Hz, 3 H, $CO_2CH_2CH_3$), 2.92 (dd, *J* = 14.4, 9.2 Hz, 1 H, α-H), 3.09 (dd, *J* = 14.4, 5.4 Hz, 1 H, α-H), 3.48–3.54 (m, 1 H, β-H), 3.70 (d, *J* = 5.5 Hz, 1 H, 1″-H), 3.79 (s, 3 H, OCH_3), 4.19–4.23 (m, 2 H, $CO_2CH_2CH_3$), 5.95 (dd, *J* = 15.7, 9.1 Hz, 1 H, γ-H), 6.24 (s, 1 H, 3-H), 6.50 (d, *J* = 15.7 Hz, 1 H, δ-H), 6.81 (d, *J* = 8.7 Hz, 2 H, 3′-H, 5′-H), 7.22 (d, *J* = 8.7 Hz, 2 H, 2′-H, 6′-H), 7.37–7.42 (m, 1 H, 6-H), 7.44 (d, *J* = 7.8 Hz, 1 H, 8-H), 7.64–7.67 (m, 1 H, 7-H), 8.15 (dd, *J* = 8.6, 1.4 Hz, 1 H, 5-H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 14.0 ($CO_2CH_2CH_3$), 37.1 (C-α), 41.86 (C-β), 43.0 (C-1″), 55.3 (OCH_3), 63.3 ($CO_2CH_2CH_3$), 112.0 (C-3), 114.08 (C-3′, C-5′), 115.0 (*C*N), 117.86 (C-8), 122.8 (C-γ), 123.66 (C-4a), 125.3 (C-6), 125.77 (C-5), 127.8 (C-2′, C-6′), 128.3 (C-1′), 133.8 (C-7), 134.3 (C-δ), 156.36 (C-8a), 159.8 (C-4′), 164.71 (C-2), 165.0 ($CO_2CH_2CH_3$), 177.92 (C-4) ppm. ESI-MS: *m/z* (%) = 418 (100) $[M + H]^+$, 419 (25) $[M + 2H]^+$. ESI-HRMS: calcd. for $C_{25}H_{24}NO_5$ $[M + H]^+$ 418.1649; found 418.1633.

General Procedure for the Synthesis of (*Z*)-1-(2-Hydroxyphenyl)-2-[(*E*)-4-styrylpyrrolidin-2-yliden]ethan-1-ones 8a–8d: Zinc (powder, 2.055 mmol, 134 mg) and NH_4OAc (2.055 mmol, 158 mg) were added to a solution of the appropriate β-(nitromethyl)chromone **2a**–**2d** (0.137 mmol) in MeOH/CH_2Cl_2 (1:1, 5 mL). The slurry was stirred at room temperature for 30 min. The solid was removed by filtration, and the solvent was evaporated under reduced pressure. The crude product was purified by preparative TLC with dichloromethane as eluent to give **8a**–**8d** in good yields.

(*Z*)-1-(2-Hydroxyphenyl)-2-[(*E*)-4-styrylpyrrolidin-2-yliden]-ethan-1-one (8a): Yield 29.7 mg (71 %), yellow solid, m.p. 128–130 °C. ^1H NMR (300 MHz, $CDCl_3$): δ = 2.73 (dd, *J* = 16.8, 7.8 Hz, 1 H, 5′-H), 3.00 (dd, *J* = 16.8, 7.8 Hz, 1 H, 5′-H), 3.26 (sext, *J* = 7.8 Hz, 1 H, 4′-H), 3.54 (dd, *J* = 10.9, 7.8 Hz, 1 H, 3′-H), 3.89 (ddd, *J* = 10.9, 7.8, 1.2 Hz, 1 H, 3′-H), 5.84 (s, 1 H, 2-H), 6.20 (dd, *J* = 15.8, 7.8 Hz, 1 H, α-H), 6.52 (d, *J* = 15.8 Hz, 1 H, β-H), 6.80 (ddd, *J* = 8.1, 7.2, 1.2 Hz, 1 H, 5‴-H), 6.92 (dd, *J* = 8.3, 1.2 Hz, 1 H, 3‴-H), 7.22–7.27 (m, 1 H, 4″-H), 7.30–7.38 (m, 5 H, 2″-H, 3″-H, 5″-H, 6″-H, 4‴-H), 7.64 (dd, *J* = 8.1, 1.7 Hz, 1 H, 6‴-H), 9.88 (br s, 1 H, N*H*), 13.76 (s, 1 H, O*H*) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 39.3 (C-4′), 40.0 (C-5′), 53.4 (C-3′), 85.5 (C-2), 118.15, 118.17 (C-3‴, C-5‴), 120.3 (C-1‴), 126.2 (C-2″, C-6″), 127.73, 127.77 (C-4″, C-6‴), 128.7 (C-3″, C-5″), 129.2 (C-α), 131.7 (C-β), 133.5 (C-4‴), 136.5 (C-1″), 162.4 (C-2‴), 168.7 (C-1′), 191.2 (C-1) ppm. ESI-HRMS: calcd. for $C_{20}H_{20}NO_2$ $[M + H]^+$ 306.1494; found 306.1490.

(*Z*)-2-[(*E*)-(4-Chlorostyryl)pyrrolidin-2-ylidene]-1-(2-hydroxyphenyl)ethan-1-one (8b): Yield 30.7 mg (66 %), yellow solid, m.p. 147–148 °C. ^1H NMR (300 MHz, $CDCl_3$): δ = 2.70 (dd, *J* = 16.8, 7.7 Hz, 1 H, 5′-H), 2.98 (dd, *J* = 16.8, 7.7 Hz, 1 H, 5′-H), 3.23 (sext, *J* = 7.7 Hz, 1 H, 4′-H), 3.52 (dd, *J* = 10.9, 7.7 Hz, 1 H, 3′-H), 3.87 (dd, *J* = 10.9, 7.7 Hz, 1 H, 3′-H), 5.83 (s, 1 H, 2-H), 6.16 (dd, *J* = 15.8, 7.7 Hz, 1 H, α-H), 6.46 (dd, *J* = 15.8, 0.9 Hz, 1 H, β-H), 6.80 (ddd, *J* = 8.2, 7.2, 1.2 Hz, 1 H, 5‴-H), 6.92 (dd, *J* = 8.5, 1.2 Hz, 1 H, 3‴-H), 7.32 (ddd, *J* = 8.5, 7.2, 1.7 Hz, 1 H, 4‴-H), 7.63 (dd, *J* = 8.2, 1.7 Hz, 1 H, 6‴-H), 9.86 (br s, 1 H, N*H*), 13.75 (s, 1 H, O*H*) ppm; the signals of 2″-H, 3″-

© 2017 Wiley-VCH Verlag GmbH & Co. KGaA, Weinheim

H, 5″-H, and 6″-H were overlapped with the solvent signal. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 39.2 (C-4′), 39.9 (C-5′), 53.3 (C-3′), 85.6 (C-2), 118.17, 118.18 (C-3‴, C-5‴), 120.3 (C-1‴), 127.4 (C-2″, C-6″), 127.7 (C-6‴), 128.8 (C-3″, C-5″), 129.9 (C-α), 130.5 (C-β), 133.4 (C-4″), 133.5 (C-4‴), 135.0 (C-1″), 162.4 (C-2‴), 168.5 (C-1′), 191.2 (C-1) ppm. ESI-HRMS: calcd. for $C_{20}H_{19}{}^{35}ClNO_2$ $[M + H]^+$ 340.1104; found 340.1095; calcd. for $C_{20}H_{19}{}^{37}ClNO_2$ $[M + H]^+$ 342.1075; found 342.1062.

(*Z*)-1-(2-Hydroxyphenyl)-2-[(*E*)-(4-methoxystyryl)pyrrolidin-2-yliden]ethan-1-one (8c): Yield 34.5 mg (75 %), yellow solid, m.p. 161–163 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.71 (dd, *J* = 16.8, 7.8 Hz, 1 H, 5′-H), 2.98 (dd, *J* = 16.8, 7.8 Hz, 1 H, 5′-H), 3.23 (sext, *J* = 7.8 Hz, 1 H, 4′-H), 3.53 (dd, *J* = 10.9, 7.8 Hz, 1 H, 3′-H), 3.81 (s, 3 H, O*CH*$_3$), 3.87 (ddd, *J* = 10.9, 7.8, 1.1 Hz, 1 H, 3′-H), 5.83 (s, 1 H, 2-H), 6.05 (dd, *J* = 15.7, 7.8 Hz, 1 H, α-H), 6.46 (d, *J* = 15.7 Hz, 1 H, β-H), 6.80 (ddd, *J* = 8.1, 7.2, 1.2 Hz, 1 H, 5‴-H), 6.86 (d, *J* = 8.7 Hz, 2 H, 3″-H, 5″-H), 6.92 (dd, *J* = 8.3, 1.2 Hz, 1 H, 3‴-H), 7.30 (d, *J* = 8.7 Hz, 2 H, 2″-H, 6″-H), 7.32 (ddd, *J* = 8.3, 7.2, 1.6 Hz, 1 H, 4‴-H), 7.63 (dd, *J* = 8.1, 1.6 Hz, 1 H, 6‴-H), 9.87 (b. s, 1 H, N*H*), 13.78 (s, 1 H, O*H*) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 39.4 (C-4′), 40.1 (C-5′), 53.6 (C-3′), 55.3 (OCH_3), 85.5 (C-2), 114.1 (C-3″, C-5″), 118.13, 118.16 (C-3‴, C-5‴), 120.3 (C-1‴), 127.0 (C-α), 127.4 (C-2″, C-6″), 127.7 (C-6‴), 129.3 (C-1″), 131.1 (C-β), 133.5 (C-4‴), 159.3 (C-4″), 162.4 (C-2‴), 168.8 (C-1′), 191.1 (C-1) ppm. ESI-HRMS: calcd. for $C_{21}H_{22}NO_3$ $[M + H]^+$ 336.1600; found 336.1598.

(*Z*)-1-(2-Hydroxyphenyl)-2-[(*E*)-(4-methylstyryl)pyrrolidin-2-yliden]ethan-1-one (8d): Yield 28.9 mg (66 %), yellow solid, m.p. 161–162 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.34 (s, 3 H, *CH*$_3$), 2.72 (dd, *J* = 16.8, 7.9 Hz, 1 H, 5′-H), 2.99 (dd, *J* = 16.8, 7.9 Hz, 1 H, 5′-H), 3.25 (sext, *J* = 7.9 Hz, 1 H, 4′-H), 3.53 (dd, *J* = 11.0, 7.9 Hz, 1 H, 3′-H), 3.88 (ddd, *J* = 11.0, 7.9, 0.9 Hz, 1 H, 3′-H), 5.83 (s, 1 H, 2-H), 6.14 (dd, *J* = 15.7, 7.9 Hz, 1 H, α-H), 6.49 (d, *J* = 15.7 Hz, 1 H, β-H), 6.78 (ddd, *J* = 8.0, 7.2, 1.2 Hz, 1 H, 5‴-H), 6.92 (dd, *J* = 8.4, 1.2 Hz, 1 H, 3‴-H), 7.13 (d, *J* = 8.0 Hz, 2 H, 3″-H, 5″-H), 7.26 (d, *J* = 8.0 Hz, 1 H, 2″-H, 6″-H), 7.32 (ddd, *J* = 8.4, 7.2, 1.7 Hz, 1 H, 4‴-H), 7.63 (dd, *J* = 8.0, 1.7 Hz, 1 H, 6‴-H), 9.88 (br s, 1 H, N*H*), 13.77 (br s, 1 H, O*H*) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 21.2 (CH_3), 39.3 (C-4′), 40.1 (C-5′), 53.5 (C-3′), 85.5 (C-2), 118.13, 118.17 (C-3‴, C-5‴), 120.3 (C-1‴), 126.1 (C-2″, C-6″), 127.7 (C-6‴), 128.1 (C-α), 129.4 (C-3″, C-5″), 131.6 (C-β), 133.5 (C-4‴), 133.7 (C-1″), 137.6 (C-4″), 162.4 (C-2‴), 168.8 (C-1′), 191.2 (C-1) ppm. ESI-HRMS: calcd. for $C_{21}H_{22}NO_2$ $[M + H]^+$ 320.1651; found 320.1642.

(*Z*)-1-(2-Hydroxyphenyl)-2-[(*E*)-(4-methoxystyryl)pyrrolidin-2-yliden]ethan-1-one (8c) and (*E*)-5-[2-(2-Hydroxyphenyl)-2-oxoethyl]-3-(4-methoxystyryl)-3,4-dihydro-2*H*-pyrrole 1-Oxide (7): Compounds **8c** and **7** (**I** and **II**) were obtained if zinc (powder, 5 equiv.) and NH_4OAc (5 equiv.) or Sn (5 equiv.) and HCl (5 equiv.) were employed in the reduction of the nitro group of **2c**. Yield 25–35 %, yellow solid. ^{1}H NMR (500 MHz, $CDCl_3$): **I**: δ = 2.79 (dd, *J* = 16.9, 7.1 Hz, 1 H, 5′-H), 3.07 (dd, *J* = 16.9, 8.5 Hz, 1 H, 5′-H), 3.37–3.43 (m, 1 H, 4′-H), 3.81 (s, 3 H, O*CH*$_3$), 3.89 (dd, *J* = 12.4, 7.2 Hz, 1 H, 3′-H), 4.10–4.17 (m, 1 H, 3′-H), 5.45 (s, 1 H, 2-H), 6.03 (dd, *J* = 15.7, 8.4 Hz, 1 H, α-H), 6.45 (d, *J* = 15.7 Hz, 1 H, β-H), 6.80 (ddd, *J* = 8.1, 7.2, 1.2 Hz, 1 H, 5‴-H), 6.87 (d, *J* = 8.8 Hz, 2 H, 3″-H,5″-H), 6.91 (dd, *J* = 8.3, 1.2 Hz, 1 H, 3‴-H), 7.25–7.32 (m, 1 H, 4‴-H), 7.30 (d, *J* = 8.8 Hz, 2 H, 2″-H, 6″-H), 7.57 (dd, *J* = 8.1, 1.6 Hz, 1 H, 6‴-H), 11.90 (s, 1 H, 2′-O*H*), 15.73 (br s, 1 H, N-O*H*) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): **I**: δ = 36.8 (C-4′), 40.2 (C-5′), 55.3 (OCH_3), 61.9 (C-3′), 84.1 (C-2), 114.13 (C-3″, C-5″), 118.4 (C-3‴), 118.7 (C-5‴), 119.9 (C-1‴), 125.7 (C-α), 127.54 (C-2″, C-6″), 128.0 (C-6‴), 128.8 (C-1″), 131.8 (C-β), 133.1 (C-4‴), 155.2 (C-1′), 159.5 (C-4″), 160.6 (C-2‴), 180.7 (C-1) ppm. ^{1}H NMR (500 MHz, $CDCl_3$): **II**: δ = 2.71–2.76 (m, 1 H, 5′-H), 3.08–3.13 (m, 1 H, 5′-H), 3.37–3.43 (m, 1 H, 4′-H), 3.82 (s, 3 H, OCH_3), 3.95–4.00 (m, 1 H, 3′-H), 4.23–4.27 (m, 1 H, 3′-H), 4.25 (s, 2 H, 2-H), 6.02 (dd, *J* = 15.7, 8.9 Hz, 1 H, α-H), 6.42 (d, *J* = 15.7 Hz, 1 H, β-H), 6.85 (d, *J* = 8.7 Hz, 2 H, 3″-H, 5″-H), 6.96 (ddd, *J* = 8.1, 7.2, 1.1 Hz, 1 H, 5‴-H), 7.00 (dd, *J* = 8.5, 1.1 Hz, 1 H, 3‴-H), 7.26 (d, *J* = 8.7 Hz, 2 H, 2″-H, 6″-H), 7.52 (ddd, *J* = 8.5, 7.2, 1.6 Hz, 1 H, 4‴-H), 7.91 (dd, *J* = 8.1, 1.6 Hz, 1 H, 6‴-H), 11.83 (s, 1 H, 2′-O*H*) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): **II**: δ = 34.9 (C-4′), 37.0 (C-2), 38.6 (C-5′), 55.3 (OCH_3), 67.2 (C-3′), 114.08 (C-3″, C-5″), 118.6 (C-3‴), 118.9 (C-1‴), 119.6 (C-5‴), 126.6 (C-α), 127.48 (C-2″, C-6″), 128.9 (C-1″), 130.4 (C-6‴), 131.3 (C-β), 137.3 (C-4‴), 140.5 (C-1′), 159.4 (C-4″), 162.6 (C-2‴), 200.1 (C-1) ppm. ESI-HRMS: calcd. for $C_{21}H_{22}NO_4$ $[M + H]^+$ 352.1549; found 352.1547.

(*E*)-2-[2-(3,5-Dimethyl-1*H*-pyrazol-4-yl)-4-(4-methoxyphenyl)but-3-en-1-yl]-4*H*-chromen-4-one (10): Hydrazine hydrate (50–60 %, 0.270 mmol, 8.4 µL) was added to a solution of derivative **5b** (0.135 mmol, 54.8 mg) in ethanol (4 mL). The mixture was stirred for 1 h at room temperature. The solvent was evaporated to dryness, and the residue was purified by preparative TLC with dichloromethane/ethyl acetate (1:2) as the eluent. Yield 43.2 mg (80 %), white solid, m.p. 93–96 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.21 (s, 6 H, 3″-C*H*$_3$, 5″-C*H*$_3$), 2.98 (dd, *J* = 14.1. 9.4 Hz, 1 H, H-α), 3.17 (dd, *J* = 14.1, 6.8 Hz, 1 H, α-H), 3.80 (s, 3 H, 4′-O*CH*$_3$), 3.99–4.06 (m, 1 H, β-H), 6.10 (s, 1 H, 3-H), 6.22–6.36 (m, 2 H, γ-H, δ-H), 6.83 (d, *J* = 8.7 Hz, 2 H, 3′-H, 5′-H), 7.26 (d, *J* = 8.7 Hz, 2 H, 2′-H, 6′-H), 7.39–7.42 (m, 2 H, 6-H, 8-H), 7.64 (ddd, *J* = 8.6. 7.1, 1.6 Hz, 1 H, 7-H), 8.15 (dd, *J* = 7.9, 1.6 Hz, 1 H, 5-H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 11.7 (3″-*C*H$_3$, 5″-*C*H$_3$), 36.2 (C-β), 39.5 (C-α), 55.3 (OCH_3), 111.1 (C-3), 114.0 (C-3′, C-5′), 114.7 (C-4″), 117.7 (C-8), 123.6 (C-4a), 125.1 (C-6), 125.8 (C-5), 127.3 (C-2′,6′), 128.2, 129.5 (C-γ, C-δ), 129.6 (C-1′), 133.6 (C-7), 142.2 (C-3″, C-5″), 156.3 (C-8a), 159.1 (C-4′), 167.4 (C-2), 178.1 (C-4) ppm. ESI-HRMS: calcd. for $C_{25}H_{25}N_2O_3$ $[M + H]^+$ 401.1865; found 401.1855.

(*E*)-2-{5-[2-(3,5-Dimethyl-1*H*-pyrazol-4-yl)-4-(4-methoxyphenyl)but-3-en-1-yl]-1*H*-pyrazol-3-yl}phenol (11): Hydrazine hydrate (50–60 %, 0.677 mmol, 0.02 mL) was added to a solution of derivative **5b** (0.135 mmol, 54.8 mg) in ethanol (4 mL). The mixture was stirred for 1 h at room temperature. The solvent was evaporated to dryness, and the residue was purified by preparative TLC with dichloromethane/ethyl acetate (1:1) as the eluent. Yield 42.1 mg (75 %), white solid, m.p. 229–231 °C. ^{1}H NMR [500 MHz, $CDCl_3$ + trifluoroacetic acid (TFA)]: δ = 2.49 (s, 6 H, 3‴-C*H*$_3$, 5‴-C*H*$_3$), 3.31 (dd, *J* = 14.8, 7.1 Hz, 1 H, α-H), 3.60 (dd, *J* = 14.8, 8.6 Hz, 1 H, α-H), 3.86 (s, 3 H, O*CH*$_3$), 3.92–4.00 (m, 1 H, β-H), 6.16 (dd, *J* = 15.9, 6.8 Hz, 1 H, γ-H), 6.35 (d, *J* = 15.9 Hz, 1 H, δ-H), 6.75 (s, 1 H, 4′-H), 6.89 (d, *J* = 8.8 Hz, 2 H, 3‴-H, 5‴-H), 7.03–7.11 (m, 2 H, 4-H, 6-H), 7.25 (d, *J* = 8.8 Hz, 2 H, 2‴-H, 6‴-H), 7.45 (ddd, *J* = 8.3, 7.8, 1.5 Hz, 1 H, 5-H), 7.62 (dd, *J* = 7.9, 1.5 Hz, 1 H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$ + TFA): δ = 10.3 (3‴-*C*H$_3$, 5‴-*C*H$_3$), 30.0 (C-α), 37.8 (C-β), 55.7 (4‴-OCH_3), 103.6 (C-4′), 111.3 (C-2), 114.5 (C-3‴, C-5‴), 117.2 (C-6), 119.2 (C-4″), 121.6 (C-4), 123.8 (C-γ), 127.7 (C-2‴, C-6‴), 128.3 (C-3), 128.7 (C-1‴), 132.6 (C-δ), 133.7 (C-5), 143.8 (C-3″, C-5″), 145.8 (C-3′), 146.0 (C-5′), 154.1 (C-1), 159.1 (C-4‴) ppm. ESI-HRMS: calcd. for $C_{25}H_{27}N_4O_2$ $[M + H]^+$ 415.2134; found 415.2132.

(*E*)-{4′-(4-Methoxystyryl)-3′,4′,5′,6′-tetrahydrospiro[chromene-2,2′-pyran]-5′-yl}methanol (12): $LiAlH_4$ [2.4 M in tetrahydrofuran (THF), 0.501 mmol, 0.25 mL] was added dropwise to a stirred solution of derivative **5c** (0.083 mmol, 38.8 mg) in dry THF (3 mL) under a nitrogen atmosphere. After 1 h, the mixture was poured into water (10 mL), and the pH was adjusted to 6–7 with dilute HCl. The aqueous mixture was extracted with dichloromethane (3 × 10 mL), dried with anhydrous sodium sulfate, and concentrated under reduced pressure. The crude residue was purified by preparative TLC

© 2017 Wiley-VCH Verlag GmbH & Co. KGaA, Weinheim

with hexane/ethyl acetate (9:7) as the eluent. Yield 3 mg (10 %), colorless oil. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.75 (dd, *J* = 13.5, 12.3 Hz, 1 H, 3′-H), 1.81–1.88 (m, 1 H, 5′-H), 2.22 (dd, *J* = 13.5, 4.1 Hz, 1 H, 3′-H), 2.89–2.97 (m, 1 H, 4′-H), 3.57–3.60 (m, 1 H, CH_2OH), 3.78–3.83 (m, 2 H, 6′-H, CH_2OH), 3.81 (s, 3 H, OCH_3), 3.90 (t, *J* = 11.4 Hz, 1 H, 6′-H), 5.74 (d, *J* = 9.6 Hz, 1 H, 3-H), 5.91 (dd, *J* = 15.8, 9.1 Hz, 1 H, α-H), 6.51 (d, *J* = 15.8 Hz, 1 H, β-H), 6.69 (d, *J* = 9.6 Hz, 1 H, 4-H), 6.86 (d, *J* = 8.7 Hz, 2 H, 3′′-H, 5′′-H), 6.97 (dt, *J* = 7.4, 1.1 Hz, 1 H, 6-H), 7.03 (d, *J* = 8.0 Hz, 1 H, 8-H), 7.15 (dd, *J* = 7.4, 1.6 Hz, 1 H, 5-H), 7.23 (ddd, *J* = 8.0, 7.4, 1.6 Hz, 1 H, 7-H), 7.31 (d, *J* = 8.7 Hz, 2 H, 2′′-H, 6′′-H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 36.9 (C-4′), 41.4 (C-3′), 42.2 (C-5′), 55.3 (OCH_3), 63.1 (CH_2OH), 63.6 (C-6′), 95.4 (C-2′), 114.0 (C-3′′,5′′), 116.5 (C-8), 121.0 (C-4a), 121.6 (C-6), 124.7 (C-3), 126.5 (C-4), 127.1 (C-5), 127.3 (C-2′′, C-6′′), 129.3 (C-7), 129.68 (C-α), 129.74 (C-1′′), 130.8 (C-β), 151.2 (C-8a), 159.1 (C-4′′) ppm. ESI-HRMS: calcd. for $C_{23}H_{25}O_4$ [M + H]$^+$ 365.1753; found 365.1742.

Acknowledgments

Thanks are due to the University of Aveiro and Fundação para a Ciência e a Tecnologia (FCT)/Ministerio de Educación y Ciencia (MEC) for the financial support of the QOPNA research unit (FCT UID/QUI/00062/2013) through national funds and, where applicable, cofinanced by Fundo Europeu de Desenvolvimento Regional (FEDER) within the PT2020 Partnership Agreement, and to the Portuguese NMR Network as well as the Instituto Politécnico de Bragança. H. M. T. A. is grateful to Fundação para a Ciência e a Tecnologia (FCT) for his PhD grant (SFRH/BD/86277/2012).

Keywords: Oxygen heterocycles · Conjugate addition · Nitrogen heterocycles · Density functional calculations

[1] a) A. Gaspar, M. J. Matos, J. Garrido, E. Uriarte, F. Borges, *Chem. Rev.* **2014**, *114*, 4960–4992; b) R. S. Keri, S. Budagumpi, R. K. Pai, R. G. Balakrishna, *Eur. J. Med. Chem.* **2014**, *78*, 340–374.
[2] W. F. Zhu, C. Chen, C. Y. Sun, S. Xu, C. J. Wu, F. Lei, H. Xia, Q. D. Tu, P. W. Zheng, *Eur. J. Med. Chem.* **2015**, *93*, 64–73.
[3] a) P. Yadav, B. Parshad, P. Manchanda, S. K. Sharma, *Curr. Top. Med. Chem.* **2014**, *14*, 2552–2575; b) C. Proença, H. M. T. Albuquerque, D. Ribeiro, M. Freitas, C. M. M. Santos, A. M. S. Silva, E. Fernandes, *Eur. J. Med. Chem.* **2016**, *115*, 381–392.
[4] Shaveta, A. Singh, M. Kaur, S. Sharma, R. Bhatti, P. Singh, *Eur. J. Med. Chem.* **2014**, *77*, 185–192.
[5] O. Prakash, R. Kumar, V. Parkash, *Eur. J. Med. Chem.* **2008**, *43*, 435–440.
[6] a) M. A. Ibrahim, T. E. Ali, Y. A. Alnamer, Y. A. Gabr, *ARKIVOC* **2010**, *i*, 98–135; b) C. M. M. Santos, A. M. S. Silva, *Eur. J. Org. Chem.* **2017**, 3115–3133.
[7] R. Bernini, E. Mincione, A. Coratti, G. Fabrizi, G. Battistuzzi, *Tetrahedron* **2004**, *60*, 967–971.
[8] a) K. Y. Lee, D. H. Nam, C. S. Moon, S. H. Seo, J. Y. Lee, Y. S. Lee, *Eur. J. Med. Chem.* **2006**, *41*, 991–996; b) C. I. C. Esteves, C. M. M. Santos, C. M. Brito, A. M. S. Silva, J. A. S. Cavaleiro, *Synlett* **2011**, 1403–1406.
[9] a) H. M. T. Albuquerque, C. M. M. Santos, J. A. S. Cavaleiro, A. M. S. Silva, *Eur. J. Org. Chem.* **2015**, 4732–4743; b) H. M. T. Albuquerque, C. M. M. Santos, C. F. R. A. C. Lima, L. M. N. B. F. Santos, J. A. S. Cavaleiro, A. M. S. Silva, *Eur. J. Org. Chem.* **2017**, 87–101.
[10] a) E. M. P. Silva, A. M. S. Silva, J. A. S. Cavaleiro, *Synlett* **2011**, 2740–2744; b) O. Talhi, L. Brodziak-Jarosz, J. Panning, B. Orlikova, C. Zwergel, T. Tzanova, S. Philippot, D. C. G. A. Pinto, F. A. A. Paz, C. Gerhäuser, T. P. Dick, C. Jacob, M. Diederich, D. Bagrel, G. Kirsch, A. M. S. Silva, *Eur. J. Org. Chem.* **2016**, 965–975; c) E. M. P. Silva, K. Grenda, I. N. Cardoso, A. M. S. Silva, *Synlett* **2013**, *24*, 2375–2382; d) J. L. C. Sousa, O. Talhi, D. H. A. Rocha, D. C. G. A. Pinto, F. A. Almeida Paz, K. Bachari, G. Kirsch, A. M. S. Silva, *Synlett* **2015**, *26*, 2724–2729.
[11] a) A. G. Csákÿ, G. de la Herrán, M. C. Murcia, *Chem. Soc. Rev.* **2010**, *39*, 4080–4102; b) E. M. P. Silva, A. M. S. Silva, *Synthesis* **2012**, *44*, 3109–3128.
[12] a) K. Nakashima, M. Kawada, S.-i. Hirashima, A. Kosugi, M. Kato, A. Yoshida, Y. Koseki, T. Miura, *Tetrahedron: Asymmetry* **2016**, *27*, 888–895; b) M. Giardinetti, J. Marrot, X. Moreau, V. Coeffard, C. Greck, *J. Org. Chem.* **2016**, *81*, 6855–6861; c) C. E. Grünenfelder, J. K. Kisunzu, H. Wennemers, *Angew. Chem. Int. Ed.* **2016**, *55*, 8571–8574; *Angew. Chem.* **2016**, *128*, 8713.
[13] a) R. Ballini, G. Bosica, D. Fiorini, *Tetrahedron Lett.* **2001**, *42*, 8471–8473; b) K. Mei, M. Jin, S. Zhang, P. Li, W. Liu, X. Chen, F. Xue, W. Duan, W. Wang, *Org. Lett.* **2009**, *11*, 2864–2867; c) B. Vakulya, S. Varga, T. Soós, *J. Org. Chem.* **2008**, *73*, 3475–3480; d) F. Cardona, J. Rocha, A. M. S. Silva, S. Guieu, *Dyes Pigm.* **2014**, *111*, 16–20; e) C. G. Oliva, A. M. S. Silva, D. I. S. P. Resende, F. A. A. Paz, J. A. S. Cavaleiro, *Eur. J. Org. Chem.* **2010**, 3449–3458; f) S. Liu, Q. Wang, L. Ye, Z. Shi, Z. Zhao, X. Yang, K. Ding, X. Li, *Tetrahedron* **2016**, *72*, 5115–5120.
[14] K. Lippur, S. Kaabel, I. Järving, K. Rissanen, T. Kanger, *J. Org. Chem.* **2015**, *80*, 6336–6341.
[15] N. D. Punyapreddiwar, S. P. Zodape, A. V. Wankhade, U. R. Pratap, *J. Mol. Catal. B* **2016**, *133*, 124–126.
[16] a) T.-Y. Liu, R. Li, Q. Chai, J. Long, B.-J. Li, Y. Wu, L.-S. Ding, Y.-C. Chen, *Chem. Eur. J.* **2007**, *13*, 319–327; b) C.-l. Gu, L. Liu, Y. Sui, J.-L. Zhao, D. Wang, Y.-J. Chen, *Tetrahedron: Asymmetry* **2007**, *18*, 455–463.
[17] J. L. C. Sousa, A. M. S. Silva, *Synlett* **2017**, *28*, 316–322.
[18] H. M. T. Albuquerque, C. M. M. Santos, J. A. S. Cavaleiro, A. M. S. Silva, *Curr. Org. Chem.* **2014**, *18*, 2750–2775.
[19] D. Resende, S. Guieu, C. G. Oliva, A. M. S. Silva, *Synlett* **2015**, *26*, 846–850.
[20] M. J. Frisch, G. W. Trucks, H. B. Schlegel, G. E. Scuseria, M. A. Robb, J. R. Cheeseman, G. Scalmani, V. Barone, B. Mennucci, G. A. Petersson, H. Nakatsuji, M. Caricato, X. Li, H. P. Hratchian, A. F. Izmaylov, J. Bloino, G. Zheng, J. L. Sonnenberg, M. Hada, M. Ehara, K. Toyota, R. Fukuda, J. Hasegawa, M. Ishida, T. Nakajima, Y. Honda, O. Kitao, H. Nakai, T. Vreven, J. A. Montgomery Jr., J. E. Peralta, F. Ogliaro, M. Bearpark, J. J. Heyd, E. Brothers, K. N. Kudin, V. N. Staroverov, R. Kobayashi, J. Normand, K. Raghavachari, A. Rendell, J. C. Burant, S. S. Iyengar, J. Tomasi, M. Cossi, N. Rega, J. M. Millam, M. Klene, J. E. Knox, J. B. Cross, V. Bakken, C. Adamo, J. Jaramillo, R. Gomperts, R. E. Stratmann, O. Yazyev, A. J. Austin, R. Cammi, C. Pomelli, J. W. Ochterski, R. L. Martin, K. Morokuma, V. G. Zakrzewski, G. A. Voth, P. Salvador, J. J. Dannenberg, S. Dapprich, A. D. Daniels, Ö. Farkas, J. B. Foresman, J. V. Ortiz, J. Cioslowski, D. J. Fox, *Gaussian 09, Revision E.01*, Gaussian, Inc., Wallingford CT, **2015**.
[21] a) Y. Matsuda, A. Koizumi, R. Haraguchi, S.-i. Fukuzawa, *J. Org. Chem.* **2016**, *81*, 7939–7944; b) S. Hajra, S. M. Aziz, R. Maji, *RSC Adv.* **2013**, *3*, 10185–10188.
[22] S. Guo, Y. Xie, X. Hu, H. Huang, *Org. Lett.* **2011**, *13*, 5596–5599.
[23] H. Kawai, Z. Yuan, T. Kitayama, E. Tokunaga, N. Shibata, *Angew. Chem. Int. Ed.* **2013**, *52*, 5575–5579; *Angew. Chem.* **2013**, *125*, 5685.
[24] a) D. C. G. A. Pinto, A. M. S. Silva, J. A. S. Cavaleiro, *Heterocycles* **1997**, *3*, 433–436; b) D. C. G. A. Pinto, A. M. S. Silva, J. A. S. Cavaleiro, *J. Heterocycl. Chem.* **2000**, *37*, 1629–1634; c) D. C. G. A. Pinto, A. M. S. Silva, J. S. Cavaleiro, C. Foces-Foces, A. L. Llamas-Saiz, N. Jagerovic, J. Elguero, *Tetrahedron* **1999**, *55*, 10187–10200; d) J. P. A. Ferreira, V. L. M. Silva, J. Elguero, A. M. S. Silva, *Tetrahedron Lett.* **2013**, *54*, 5391–5394.

Received: July 6, 2017

© 2017 Wiley-VCH Verlag GmbH & Co. KGaA, Weinheim