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Comparison of the reaction pathways and intermediate products of a microwave-assisted and high-pressure-promoted cycloaddition of vinyl-moiety-containing dienophiles on 2*H*-pyran-2-ones

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ABSTRACT

A comparative study of the reaction pathway of the cycloaddition of various vinyl-containing dienophiles on a set of substituted 3-acylamino-2*H*-pyran-2-ones under microwave-assisted and high-pressure conditions is presented. In the course of the reaction both the intermediate products, i.e., the 2-oxabicyclo[2.2.2]oct-5-ene (the *exo*/*endo* selectivity depended upon the dienophile) and the alkoxycyclohexadiene systems, were isolated and comprehensively characterized; this included X-ray diffraction analyses. The role of the base (DABCO) as an organocatalyst was further elucidated.

1. Introduction

The Diels–Alder reaction, is one of the most important synthetic methods for forming new, C–C bonds, and still a topic of intense research activities.[1] Substituted 2*H*-pyran-2-ones and their fused analogues[2] represent a group of dienes with a great applicability for cycloadditions with a plethora of alkene and alkyne dienophiles, as clearly demonstrated by other research groups[3] and our previous work.[4] In the course of certain synthetic strategies, it might be advantageous to replace the C–O fragment of the 2*H*-pyran-2-one ring with a C=C fragment. This, of course, can be easily achieved with the application of suitable alkyne dienophiles. However, in the case where the substituents are not desired, a molecule of acetylene would be needed. Its reactivity for Diels–Alder reactions are notoriously low (as well as its undesirable property of being a gas at room conditions). Therefore, we envisaged a pathway[5] to circumvent these problems by using not an alkyne but an alkene as the dienophile; however, one possessing an appropriate group that would be straightforwardly eliminated after the cycloaddition step. Previously, we[5] and others[6] have shown that ethyl vinyl ether is such a dienophile; now we embarked on a search for more synthetic equivalents of acetylene, as this seems to be of wider interest.[7] We also decided to elucidate the reaction pathway and the differences caused by various reaction conditions (microwave heating vs high-pressure conditions) and to isolate, if possible, the appropriate intermediate products.

2. Results and discussion

The reaction of vinyl dienophiles **2**, as the appropriate synthetic equivalents of acetylene for Diels–Alder reactions with various electron-deficient 2*H*-pyran-2-ones **1**[8] (Scheme 1), most probably starts with the initial cycloaddition of the vinyl moiety of **2** on the 2*H*-pyran-2-one system **1**, yielding the CO_2-bridged 2-oxabicyclo[2.2.2]oct-5-ene derivative **3**. The activation volume of this step should be negative.[9] The next step is the elimination of a molecule of CO_2 via a retro-Diels–Alder reaction, which at the relatively high reaction temperature, proceeds spontaneously, yielding a cyclohexadiene system **4**. It is obvious that its aromatization into the final product **5** via the elimination of the corresponding small molecule (R^4OH, 2-pyrrolidone or 2-azepanone) is very facile. We have already demonstrated[5] the importance of an appropriate base (e.g., DABCO) as the organocatalyst for such a reaction to yield **5** under milder conditions. Though it is reasonable to propose that the reaction between **1** and **2** toward **5** proceeds via the two intermediate products **3** and **4**, as described above, under the previously[5] applied conditions we could not detect them. Therefore, our plan was to modify the reaction conditions in such a way as to make their isolation, or at least their detection, possible.

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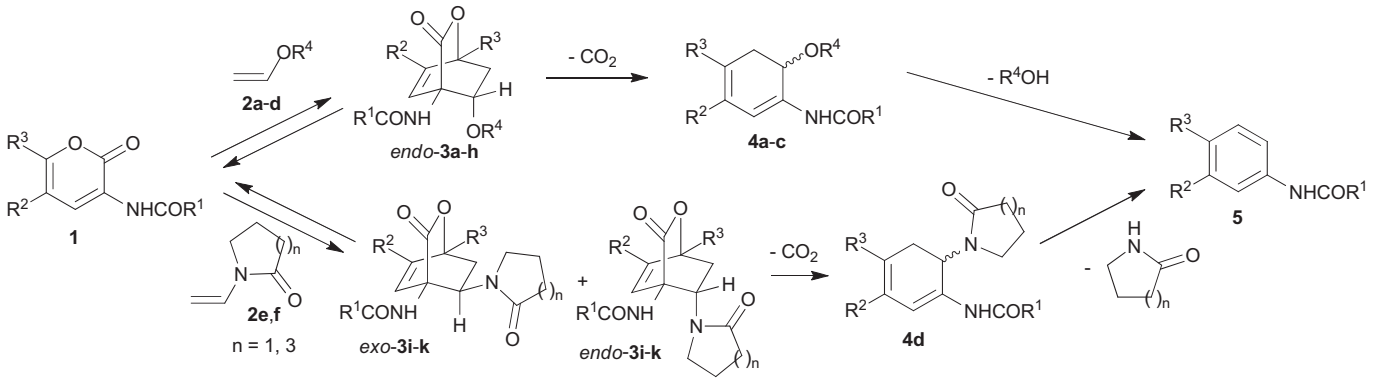


R^1 = Ph, Me, 2-chloro-3-pyridyl, 2-furyl, 3,4,5-$(MeO)_3$-C_6H_2, 4-NO_2-C_6H_4, 6-chloro-3-pyridyl, cyclobutyl, cyclopropyl;
R^2 = CO_2Me, CO_2Et, COMe, COPh; R^3 = Me, CH_2CO_2Et; R^4 = Et, COMe, COEt, cyclohexyl; n = 1, 3

Scheme 1. Reaction pathway between the 2*H*-pyran-2-ones **1** and the vinyl-moiety-containing dienophiles **2**.

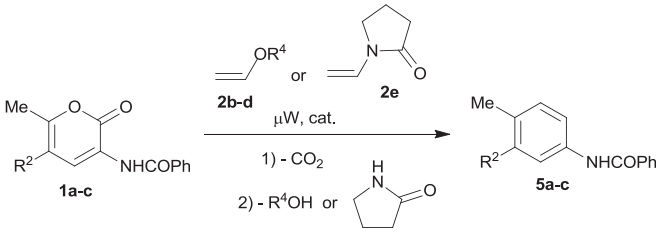
2.1. Comparison of the reactivity of various vinyl dienophiles 2 and reaction conditions

Our first goal was to find some suitable acetylene equivalents, besides ethyl vinyl ether, that would preferably be liquids at standard conditions and that would possess the appropriate groups for elimination after the cycloaddition and would be relatively easily available. In addition to ethyl vinyl ether (**2a**, R^4=Et), we selected vinyl acetate (**2b**, R^4=COMe), vinyl propionate (**2c**, R^4=COEt), cyclohexyl vinyl ether (**2d**, R^4=cyclohexyl), 1-vinyl-2-pyrrolidone (**2e**, *n*=1) and *N*-vinylcaprolactam (**2f**, *n*=3). The results presented in Table 1 show that all the novel acetylene equivalents **2b**–**e** were applicable for the synthesis of the aniline products **5** under microwave-assisted conditions[10] with the addition of catalytic amounts of DABCO as the base;[11] however, they were not superior to the ethyl vinyl ether (**2a**) as their reactivity was similar to **2a** (or even lower in the case of **2b**,**c**).

For example, in the case of the cycloaddition of 2*H*-pyran-2-one **1a** (0.5 mmol) and 1-vinyl-2-pyrrolidone (**2e**) (15 mmol, 30 equiv) after 1.5 h of microwave irradiation (at 120 °C), when no catalyst was applied, the starting **1a** disappeared completely; however, not only was the desired product **5a** formed (Table 1, entry 1), but also some traces of the intermediate of the type **4** were detected. By decreasing the amount of dienophile **2e** to 3 equiv (and the addition of acetonitrile as a solvent) under otherwise identical conditions to those described above, the ratio of **1a** to **5a** deteriorated to 1:0.15 (Table 1, entry 2) (again accompanied by traces of the intermediate **4**). With DABCO (15 mol %) under the same reaction conditions (3 equiv of **2e** and 1.5 mL of acetonitrile, 1.5 h at 120 °C) the ratio **1a** to **5a** improved toward **5a** to 1:2 (Table 1, entry 3) and none of the intermediates were detected. This clearly demonstrates the overall efficiency of DABCO as an organocatalyst for the preparation of the products **5**. On the other hand, an acid catalyst (Dowex) did not prove to be appropriate as no product was observed after 1.5 h of microwave irradiation (at 120 °C) (Table 1, entry 5).

The results with the vinyl acetate (**2b**), however, were different: after 2 h of microwave irradiation (at 120 °C) the ratio between the starting **1b** and the aromatic product **5b** was 1:0.1, regardless of the catalyst applied (Table 1, entries 7–10). Analogous behavior was found for the vinyl propionate (**2c**) (Table 1, entries 11–13). These results point to the possibility that in the case of the cycloaddition of **2b**,**c** the elimination from the corresponding intermediate **4** takes place more easily than is the case with the cycloaddition of **2a**,**e** (where the assistance of DABCO is observed). It seems that the elimination of acetic or propionic acid (after the cycloaddition of **2b**,**c**, respectively) takes place very rapidly (with a very low activation barrier) and is therefore not influenced by either the base or the acid. In contrast, the other two cases where ethanol or 2-pyrrolidone are eliminated (stemming from the cycloaddition of **2a**,**e**, respectively) are greatly accelerated by the catalytic amount of the base (DABCO) (see also below). Analogous results, supporting

Table 1
Optimization of reaction conditions and catalysts for the transformation between the 2*H*-pyran-2-ones **1a**–**c** (R^1=Ph; R^3=Me) (0.5 mmol) and the vinyl-moiety-containing dienophiles **2** yielding **5**



2b: R^4 = COMe; **2c**: R^4 = COEt; **2d**: R^4 = cyclohexyl

Entry	**1** R^2		**2**	Catalyst	*t*/h[a]	Product	Ratio **1**:**5**[b]
1	CO_2Me	**1a**	**2e**[c]	—	1.5	**5a**	0:2.5[d]
2	CO_2Me	**1a**	**2e**[e]	—	1.5	**5a**	1:0.15[d]
3	CO_2Me	**1a**	**2e**[e]	DABCO[f]	1.5	**5a**	1:2
4	CO_2Me	**1a**	**2e**[e]	DABCO[f]	1	**5a**	1:0.8
5	CO_2Me	**1a**	**2e**[e]	Dowex[g]	1.5	**5a**	1:0
6	CO_2Me	**1a**	**2d**[e]	DABCO[f]	1	**5a**	1:2
7	CO_2Et	**1b**	**2b**[c]	—	2	**5b**	1:0.1
8	CO_2Et	**1b**	**2b**[c]	DABCO[f]	2	**5b**	1:0.1
9	CO_2Et	**1b**	**2b**[c]	DABCO[h]	2	**5b**	1:0.1
10	CO_2Et	**1b**	**2b**[c]	Dowex[g]	2	**5b**	1:0.1
11	CO_2Et	**1b**	**2c**[c]	—	2	**5b**	1:0.2
12	CO_2Et	**1b**	**2c**[c]	DABCO[h]	2	**5b**	1:0.2
13	CO_2Et	**1b**	**2c**[c]	Dowex[g]	2	**5b**	1:0.2
14	COMe	**1c**	**2c**[c]	—	2	**5c**	1:1
15	COMe	**1c**	**2c**[c]	DABCO[f]	2	**5c**	1:1
16	COMe	**1c**	**2c**[c]	Dowex[g]	2	**5c**	1:1
17	COMe	**1c**	**2e**[e]	DABCO[f]	1.5	**5c**	1:12
18	COMe	**1c**	**2e**[e]	DABCO[f]	1	**5c**	1:5

[a] Microwave irradiation in a closed vessel (10 mL) at 120 °C.
[b] Ratio estimated from ^{1}H NMR spectra of crude reaction mixtures; intermediates **4** are neglected.
[c] Dienophile **2** (15 mmol).
[d] With traces of intermediate of the type **4**.
[e] Dienophile **2** (1.5 mmol) and 1.5 mL of acetonitrile.
[f] Catalyst 8.4 mg (15 mol %).
[g] Dowex (40 mg) 50WX8-200 (strongly acidic).
[h] Catalyst 56 mg (100 mol %).

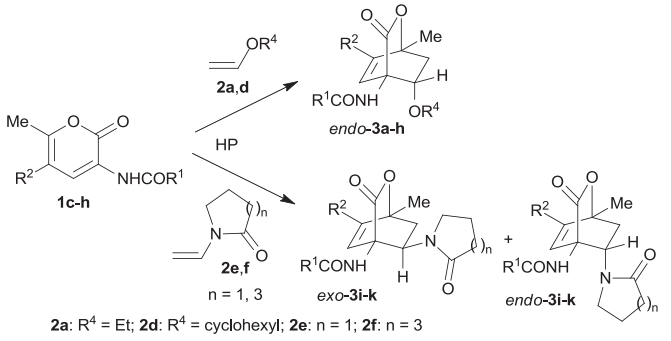
this proposition, were obtained in the case of the cycloaddition of acetyl derivative **1c** with **2c**,**e** (Table 1, entries 14–18).

When the reaction between **1a** (0.5 mmol) and **2a** (15 mmol) was conducted in different solvents (1 mL) in the presence of DABCO (8.4 mg, 15 mol %) after 0.5 h of μW irradiation at 120 °C (150 W) we observed a clear effect of the solvent properties: for acetonitrile, the ratio between the remaining **1a** and the product **5a** was 0.4:1, in methanol it was 0.5:1, in DMF 0.6:1, in EtOH 0.7:1, in toluene 1.7:1, in THF 2.5:1, whereas in hexane the ratio **1a**:**5a** was 3.3:1. On the basis of these results it is clear that acetonitrile is the most appropriate solvent for this transformation.

2.2. High-pressure synthesis of 2-oxabicyclo[2.2.2]oct-5-enes 3

It is well known that high-pressure conditions[12] favor the reaction steps with a negative activation volume; therefore, we wondered if it would be possible to accomplish a high-pressure synthesis of the CO_2-bridged intermediates **3**. Indeed, it turned out that a mixture of 2*H*-pyran-2-ones **1** and vinyl derivatives **2a**,**d**–**f** in dichloromethane–acetonitrile not being suitable for work under high-pressure—(or, alternatively without any solvent) after a sufficiently long reaction time (around 15 days) at 13–15 kbar at room temperature, exclusively affords the corresponding 2-oxabicyclo [2.2.2]oct-5-ene products **3a**–**k** (Table 2). The products **3** proved to be quite stable at ambient conditions; however, their crystallizations had to be executed carefully and at temperatures below approximately 50 °C. DABCO was avoided in these cases because it did not influence the cycloaddition step toward the products **3**. Namely, after 336 h at 13–15 kbar a mixture of **1h** and **2a** yielded **3f** (together with some unreacted **1h**; ratio **1h**:**3f** approx. 0.15:1) regardless of the addition of DABCO (15 mol %) (Table 2, entries 7 and 8). Additionally, we would like to stress that the compounds **3a**–**k** represent the first reported cases of the special class of 2-oxabicyclo [2.2.2]oct-5-ene derivatives containing a substituted amino group at the position 4 and concomitantly having an alkoxy group (or another amide group in the cases of **3i**–**k**) at the neighboring position 8. Thus, the compounds **3** might offer interesting synthons for highly substituted cyclohexenes (via the hydrolysis of the bridge lactone group).

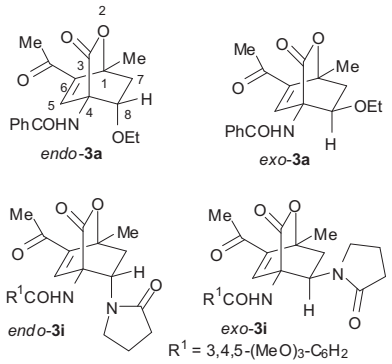
Table 2
Reaction conditions and yields for the high-pressure synthesis of **3** from **1c**–**h** (R^3=Me) (0.5 mmol)



2a: R^4 = Et; **2d**: R^4 = cyclohexyl; **2e**: n = 1; **2f**: n = 3

Entry	Starting compound **1**			**2**	Product[a]	*t*/h	Yield (%)[b]
	R^1	R^2					
1	Ph	COMe	**1c**	**2a**	*endo*-**3a**	312	69
2	Ph	COPh	**1d**	**2a**	*endo*-**3b**	312	69
3	Me	COMe	**1e**	**2a**	*endo*-**3c**	432	72
4	2-Chloro-3-pyridyl	COMe	**1f**	**2a**	*endo*-**3d**	360[c]	61
5	2-Furyl	COMe	**1g**	**2a**	*endo*-**3e**	360[c]	67
6	3,4,5-$(MeO)_3$–C_6H_2	COMe	**1h**	**2a**	*endo*-**3f**	360[c]	62
7	3,4,5-$(MeO)_3$–C_6H_2	COMe	**1h**	**2a**	*endo*-**3f**	336[c]	**1h**:**3f**=0.15:1[d]
8	3,4,5-$(MeO)_3$–C_6H_2	COMe	**1h**	**2a**	*endo*-**3f**	336[c,e]	**1h**:**3f**=0.15:1[d]
9	Ph	COMe	**1c**	**2d**	*endo*-**3g**	384[c]	52
10	Ph	COPh	**1d**	**2d**	*endo*-**3h**	384[c]	64
11	3,4,5-$(MeO)_3$–C_6H_2	COMe	**1h**	**2e**	*exo*-**3i**	384[c]	64
					endo-**3i**		0.5
12	Ph	COPh	**1d**	**2e**	*exo*-**3j**[f]	408[c]	61
13	Ph	COMe	**1c**	**2f**	**2k**[g] (*exo*+*endo*)	384[c]	63[h]
14	Ph	COMe	**1c**	**2f**	*exo*-**3k**	2544[c]	67

[a] High-pressure (13–15 kbar) at room temperature.
[b] Yield of isolated pure products.
[c] In CH_2Cl_2.
[d] Determined from ^{1}H NMR of the crude reaction mixture.
[e] With 8.4 mg (15 mol %) DABCO.
[f] With 5–8% of the *endo* isomer as determined from ^{1}H NMR of the crude reaction mixture.
[g] As a 1:1 mixture of *exo* and *endo* isomers.
[h] Combined yield of *endo*-**3k** and *exo*-**3k** before the separation of the isomers.



A structural determination of the products **3** with different NMR techniques was not sufficient to elucidate their structures; therefore, a single-crystal X-ray diffraction analysis was necessary to unequivocally establish the position and the stereo orientation of the group stemming from the dienophile (i.e., OR,[4] 2-oxo-1-pyrrolidinyl or 2-oxoazepan-1-yl moiety). In the case where the ethyl vinyl ether (**2a**) was applied as a dienophile (i.e., the synthesis of **3a**) and in the case of cyclohexyl vinyl ether (**2d**) as the dienophile (i.e., the synthesis of **3h**) (Table 2, entries 1 and 10) it was determined that the alkoxy group in the products is bound to the 8-C (neighboring the bridge carbon atom bearing the amide group) and is in the *endo* position. These data are in agreement with the few literature examples[6a] and semi-empirical calculations[13] that we performed and that show the *exo*-**3a** to be thermodynamically more stable than the *endo*-**3a** by approximately 2.12 or 1.25 kcal/mol, according to AM1 and PM3, respectively.[14] The obtained product (i.e., *endo*-**3a**) should therefore be the kinetically controlled product; this result also being in accordance with the Alder *endo* rule, which predicts the predominance of kinetically controlled products arising via an *endo* transition state.[14] In contrast, in the case of the major product (i.e., *exo*-**3i**) obtained from **1h** with dienophile **2e**, the group stemming from **2e** (i.e., 2-oxo-1-pyrrolidinyl moiety) is, according to the X-ray diffraction analysis,[15] positioned *exo* (though also on 8-C). Furthermore, besides the major *exo*-**3i** isomer, we could also isolate from the crude reaction mixture a minimal amount of the minor *endo*-**3i** isomer (~1 mg) and determine its crystal structure.[15] The semi-empirical calculations in this case (i.e., the addition between **1h** and **2e** yielding **3i**) prove that the major stereoisomer (i.e., *exo*-**3i**) is thermodynamically less stable (by approximately 1.02 or 1.66 kcal/mol, according to AM1 and PM3, respectively) and may therefore also represent a kinetic product (as in the previous cases). In the case of the reaction of 2*H*-pyran-2-one **1c** with the dienophile **2f**, however, an equimolar mixture of *exo*-**3k** and *endo*-**3k** adducts was obtained (Table 2, entry 13); we were able to separate both and characterize

them using X-ray diffraction (Fig. 1). The semi-empirical calculations in this case gave inconclusive results that point to a similar stability of both the *exo*-**3k** and *endo*-**3k**. However, after a significantly longer reaction time (approximately 6.5-times longer, Table 2, entry 14), we detected only the *exo*-**3k** adduct (suggesting its slightly greater thermodynamic stability), most probably pointing to the reversibility of the cycloaddition toward the products **3**.

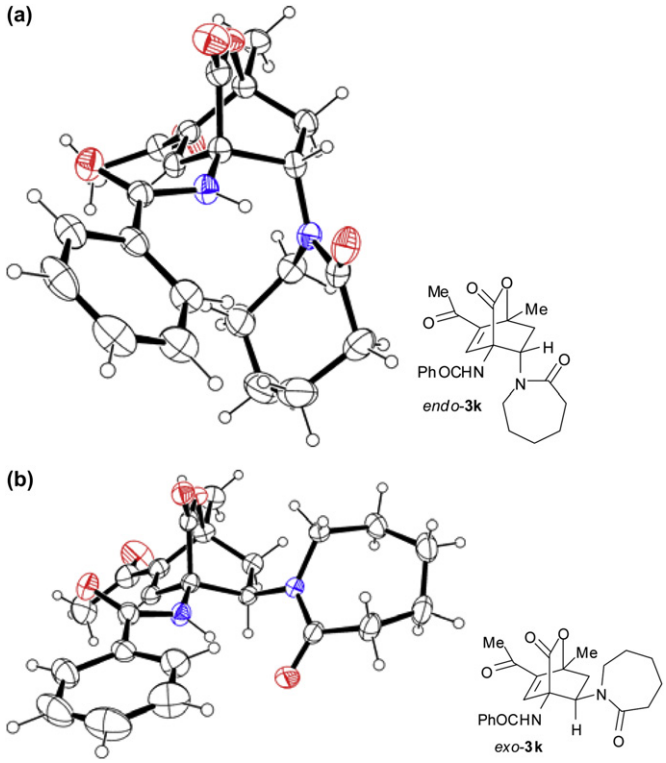


Fig. 1. Single-crystal X-ray diffraction analyses of *endo*-**3k** (a), and *exo*-**3k** (b). The atomic displacement parameters at 293 K are drawn at the 30% probability level.

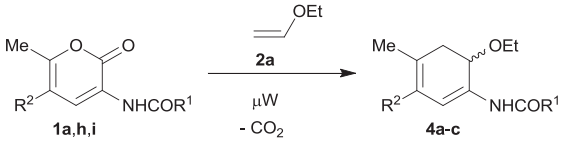
As far as we know, this is one of the rare cases[4f,6e,f] of different stereoselectivity that can be attributed to the change in the stereoelectronic requirements of the reagents **2a**,**d** versus **2e**,**f** in the cycloaddition step. Furthermore, from the examination of the ^{1}H NMR spectra it is possible to conclude that all the CO_2-bridged cycloadducts obtained with **2a** (i.e., **3a**–**f**) are of the same structural type as shown by the relatively narrow ranges of the chemical shifts (1.77–1.92 and 2.25–2.37 for *endo* and *exo* 7-H, respectively; and 3.92–4.09 for 8-H) and coupling constants ($J_{7endo\text{-H}-8\text{-H}}$=2.3–2.4, $J_{7exo\text{-H}-8\text{-H}}$=7.1–7.5 and $J_{7endo\text{-H}-7exo\text{-H}}$=13.7–13.9 Hz) obtained for this set of protons.

We were somewhat perplexed as to why in the ^{1}H NMR spectrum of *exo*-**3k** at 29 °C no signal for the 8-H appeared in the region δ 4–6 ppm, as was usual in the other cases (e.g., *exo*-**3i**,**j** dd for 8-H at 4.98 or 5.08 ppm, respectively). However, upon recording the ^{1}H NMR of *exo*-**3k** at a lower temperature (−11 to −51 °C), two multiplets appeared in this region (at 4.25–4.29 and 5.42–5.51) suggesting the existence of two slowly- or non-interconverting conformers of *exo*-**3k** (in the approximate ratio 1:0.75) at lower temperatures, which at room temperature can interconvert fast enough to cause the coalescence of these signals.

2.3. Synthesis of cyclohexadiene intermediates 4

Next, we wished to find the appropriate conditions for the preparation of the cyclohexadiene intermediates **4**. According to our preliminary studies with **2a**,[5] we found that under suitable microwave-assisted conditions without the addition of DABCO it was indeed possible to obtain various mixtures of the starting 2*H*-pyran-2-one **1**, the final aromatized product **5** as well as the desired cyclohexadiene **4** (Table 3). However, all our attempts to optimize the reaction conditions in such a way as to produce exclusively **4** were unsuccessful. To obtain more dihydro adduct **4** it was advantageous to use a large excess of dienophile (molar ratio of **1**:**2a** up to 1:20; cf. entries 2 and 5, Table 3). We also showed that, for example, 90 °C is not an appropriate temperature for the preparation of **4** and that it was better to use a higher temperature, i.e., 120 °C (cf. entries 3 and 4, Table 3). Furthermore, according to the literature data,[16] such systems have proved to be elusive to isolate (under the reaction conditions applied therein) as they are extremely sensitive to aromatization; we found that our products **4** spontaneously aromatize upon simply standing at ambient temperature under an inert atmosphere (or at −18 °C as well) in a few days (and therefore it was not possible to determine the melting points). It was also impossible to perform a chromatographic separation as the aromatization upon such a procedure was inevitable. However, we were able to grow a single crystal of **4a**, and its X-ray diffraction analysis[15] clearly showed the same position of the ethoxy group as in the case of the intermediates **3a**–**f**, further proving the proposed structural pattern and the regioselectivity of the reaction.

Table 3
Reaction conditions for the microwave-assisted synthesis of **4** with the cycloaddition of ethyl vinyl ether (**2a**) from **1a**,**h**,**i** (R^3=Me) (0.5 mmol) without DABCO



Entry	Starting compound **1**			Product[a]	*t*/h	Ratio **1**:**4**:**5**[b]
	R^1	R^2				
1	Ph	CO_2Me	**1a**[c]	**4a**	1	0.8:1:0
2	Ph	CO_2Me	**1a**[c]	**4a**	2	0.3:1:0.04
3	Ph	CO_2Me	**1a**[c]	**4a**	3	0.2:1:0.2
4	Ph	CO_2Me	**1a**[c]	**4a**	3[d]	2.5:1:0
5	Ph	CO_2Me	**1a**[e]	**4a**	2	0.3:1:0.2
6	3,4,5-$(MeO)_3$–C_6H_2	COMe	**1h**[c]	**4b**	1.5	0.03:1:0.4
7	4-NO_2–C_6H_4	COMe	**1i**[c]	**4c**	1.5	0:1:0.4

[a] Microwave irradiation in acetonitrile (1 mL) in a closed vessel (10 mL) at 120 °C.
[b] Ratio estimated from ^{1}H NMR spectra of crude reaction mixtures (intermediates **3** were not detected).
[c] Molar ratio **1a**:**2a**=1:20.
[d] At 90 °C.
[e] Molar ratio **1a**:**2a**=1:10.

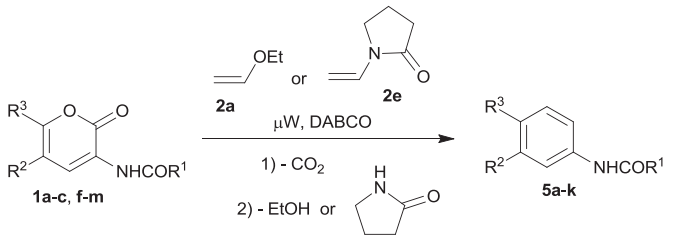
2.4. Further details on DABCO catalytic activity

Additional proof that DABCO indeed facilitates the elimination of ethanol from the cyclohexadiene intermediates **4** was provided by the transformation of the pure 2-oxabicyclo[2.2.2]oct-5-ene derivative **3f** into **4b** and **5f**. Without the addition of DABCO, after 0.5 h of microwave irradiation at 120 °C we obtained from **3f** a mixture of cyclohexadiene **4b** and the aromatized final product **5f** in the ratio 1:0.15 (all of the **3f** was consumed). On the other hand, with the addition of DABCO (40 mol %) under identical reaction conditions the conversion of the **3f** to the **5f** was complete. It is important to stress that the CO_2-bridged adduct **3f** in both cases decomposed completely, thus showing that our adducts **3** are less stable than the related systems previously mentioned in the literature.[6e,f,h,i]

2.5. Synthesis of aniline derivatives 5 from 1 and 2

The optimized, microwave-assisted conditions were further applied for the reaction between various 2*H*-pyran-2-ones **1** and two vinyl dienophiles **2a**,**e** with the addition of DABCO as the most successful catalyst. The syntheses were conducted with microwave irradiation at 120 °C for 2 h and provided the aniline derivatives **5a**–**k** in good yields (Table 4).

Table 4
Reaction conditions and yields for the microwave-assisted synthesis of **5** with vinyl dienophiles **2** starting from **1a**–**c**,**f**–**m** (1 mmol)



Entry	Starting compound **1**				**2**	Product[a]	Yield (%)[b]
	R^1	R^2					
1	Ph	CO_2Me	Me	**1a**	**2e**	**5a**[c]	74
2	Ph	CO_2Et	Me	**1b**	**2e**	**5b**[d]	71
3	Ph	COMe	Me	**1c**	**2e**	**5c**[c,e]	71
4	2-Chloro-3-pyridyl	COMe	Me	**1f**	**2a**	**5d**	60
5	2-Furyl	COMe	Me	**1g**	**2a**	**5e**	69
6	3,4,5-$(MeO)_3$–C_6H_2	COMe	Me	**1h**	**2a**	**5f**	70
7	4-NO_2–C_6H_4	COMe	Me	**1i**	**2a**	**5g**	69
8	6-Chloro-3-pyridyl	COMe	Me	**1j**	**2a**	**5h**	74
9	Ph	CO_2Et	CH_2CO_2Et	**1k**	**2e**	**5i**[c,f]	73
10	Cyclobutyl	COMe	Me	**1l**	**2a**	**5j**	63
11	Cyclopropyl	COMe	Me	**1m**	**2a**	**5k**	65

[a] Microwave irradiation in acetonitrile (1.5 mL) in a closed vessel (10 mL) with **2a** (10 mmol, 10 equiv) or **2e** (6 mmol, 6 equiv) at 120 °C for 2 h with 8.4 mg (7.5 mol %) DABCO.
[b] Yield of isolated products.
[c] See Ref. 5.
[d] Irradiation (2.5 h).
[e] See Ref. 16.
[f] At 150 °C.

3. Conclusions

We have demonstrated the utility of a variety of vinyl-substituted compounds as masked equivalents of acetylene in a base-catalyzed Diels–Alder reaction with electron-deficient 2*H*-pyran-2-ones yielding a set of anilines. Furthermore, by changing the reaction conditions from the microwave irradiation to high-pressure (13–15 kbar at ambient temperature) and alternatively omitting the catalyst (DABCO) we were able to isolate both the intermediate compounds **3** and **4** (2-oxabicyclo[2.2.2]oct-5-ene and cyclohexadiene, respectively) and to determine their structure. The regio- and stereoselectivity of the cycloaddition is thus unequivocally established; we additionally demonstrated that the size of the dienophile crucially influences the stereoselectivity of the Diels–Alder reaction. DABCO has no effect on the cycloaddition step, acting only in the last elimination step. The structures of the products having similar spectroscopic properties were unequivocally determined by the X-ray analyses. The results represent a further example of the utility of high-pressure for Diels–Alder reactions, where the primary Diels–Alder adducts are thermally not stable and can be prepared only via the reaction at high-pressure and at ambient temperature.

4. Experimental section

4.1. General

Melting points were determined on a micro hot stage apparatus and are uncorrected. ^{1}H NMR spectra were recorded at 29 °C and 300 MHz using Me_4Si as an internal standard. ^{13}C NMR spectra were recorded at 75.5 MHZ and are referenced against the central line of the solvent signal ($CDCl_3$ triplet at 77.0 ppm, DMSO-d_6 septet at δ 39.5 ppm). The coupling constants (J) are given in hertz. IR spectra were obtained as KBr pellets for all compounds. The starting compounds **1** were prepared according to the published procedures.[8] All other reagents and solvents were used as received from commercial suppliers.

Microwave reactions were conducted in air using a focused microwave unit (Discover by CEM Corporation, Matthews, NC). The machine consists of a continuous, focused microwave power-delivery system with an operator-selectable power output from 0 to 300 W. Reactions were performed in darkness in glass vessels (capacity 10 mL) sealed with a septum. The pressure was controlled by a load cell connected to the vessel via the septum. The temperature of the contents of the vessel was monitored using a calibrated infrared temperature controller mounted under the reaction vessel and measuring the temperature of the outer surface of the reaction vessel. The mixtures were stirred with a Teflon-coated magnetic stirring bar in the vessel. Temperature, pressure, and power profiles were recorded using commercially available software provided by the manufacturer of the microwave unit.

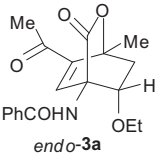
High-pressure reactions were conducted in Teflon ampoules (capacity 3.8 mL) immersed into a piston-cylinder type of pressure vessel (U101, Unipress Equipment, Warszawa, Poland) filled with white spirit and pressurized at 13–15 kbar (at room temperature).

Crystallographic data (excluding structure factors) for *endo*-**3k** and *exo*-**3k** have been deposited with the Cambridge Crystallographic Data Center as supplementary publication number CCDC 802653–802654. Copies of these data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK [fax: +44 0 1223 336033 or e-mail: deposit@ccdc.cam.ac.uk].

4.2. High-pressure synthesis of the products 3

A solution of the starting 2*H*-pyran-2-one **1** (0.5 mmol) and ethyl vinyl ether (**2a**) (721 mg, 10 mmol), cyclohexyl vinyl ether (**2d**) (1.26 g, 10 mmol), 1-vinyl-2-pyrrolidone (**2e**) (1.5 g, 13.5 mmol) or *N*-vinylcaprolactam (**2f**) (487 mg, 3.5 mmol) [and DABCO (8.4 mg, 15 mol %) in one case of the reaction between **1h** and **2a** (toward **3f**) (Table 2, entry 8)] in a Teflon ampoule (3.8 mL) was filled with CH_2Cl_2, immersed into a piston-cylinder type of pressure vessel filled with white spirit and pressurized at 13–15 kbar for the time specified (Table 2). (For the preparation of **3a**–**c** the reactions of **1** were preferentially conducted without CH_2Cl_2 solvent in **2a**.) Thereafter, the reaction mixture was evaporated to the half volume, *i*-Pr_2O (1.5 mL) was added and the mixture left overnight; the precipitated material was filtered off and washed with *i*-Pr_2O to give the products *endo*-**3a**–**h** and *exo*-**3i**,**j**. For other details of isolation, see individual examples below.

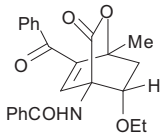
*4.2.1. N-[rel-(1R,4S,8R)-6-Acetyl-8-ethoxy-1-methyl-3-oxo-2-oxabicyclo [2.2.2]oct-5-ene-4-yl]benzamide (endo-**3a**).*



endo-**3a**

Yield: 119 mg (69%) as a white solid, mp 127–129 °C (MeOH); ν_{max} (KBr) 3344, 1774, 1680, 1640, 1531 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 1.19 (3H, t, *J* 7.1 Hz, OCH_2CH_3), 1.78 (1H, dd, *J* 13.9, 2.3 Hz, 7*endo*-H), 1.88 (3H, s, Me), 2.27 (1H, dd, *J* 13.9, 7.1 Hz, 7*exo*-H), 2.39 (3H, s, COMe), 3.53 (2H, 2× dq, *J* 9.4, 7.1 Hz, OCH_2CH_3), 4.02 (1H, dd, *J* 7.1, 2.3 Hz, 8-H), 6.92 (1H, s, NH), 7.43 (1H, s, 5-H), 7.55 (3H, m, Ph), 7.89 (2H, m, Ph); δ_C (75.5 MHz, $CDCl_3$) 15.2, 21.7, 27.5, 42.0, 65.1, 65.7, 75.2, 82.0, 127.3, 128.8, 132.2, 133.5, 141.4, 142.7, 167.4, 169.1, 194.6; *m*/*z* (ES^+) 366 (MNa^+), 344 (MH^+); *m*/*z* (EI) 299 (4, $[M-CO_2]^+$), 105 (100%); HRMS (ES^+): MH^+, found 344.1501. $C_{19}H_{22}NO_5$ requires 344.1498.

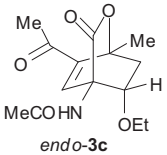
*4.2.2. N-[rel-(1R,4S,8R)-6-Benzoyl-8-ethoxy-1-methyl-3-oxo-2-oxabicyclo[2.2.2]oct-5-ene-4-yl]benzamide (endo-**3b**).*



endo-**3b**

Yield: 140 mg (69%) as a white solid, mp 140–142 °C (MeOH); [Found: C, 71.29; H, 5.97; N, 3.37. $C_{24}H_{23}NO_5$ requires C, 71.10; H, 5.72; N, 3.45%]; ν_{max} (KBr) 3431, 1756, 1672, 1656, 1519 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 1.19 (3H, t, *J* 7.0 Hz, OCH_2CH_3), 1.84 (3H, s, Me), 1.92 (1H, dd, *J* 13.7, 2.3 Hz, 7*endo*-H), 2.25 (1H, dd, *J* 13.7, 7.5 Hz, 7*exo*-H), 3.54 (2H, 2× dq, *J* 9.4, 7.0 Hz, OCH_2CH_3), 4.09 (1H, dd, *J* 7.5, 2.3 Hz, 8-H), 6.94 (1H, s), 6.95 (1H, s) (5-H, NH), 7.53 (6H, m), 7.86 (2H, m), 7.93 (2H, m) (2× Ph); δ_C (75.5 MHz, $CDCl_3$) 15.2, 20.8, 42.0, 65.1, 65.6, 75.0, 82.2, 127.4, 128.6, 128.8, 130.0, 132.0, 133.38, 133.43, 136.5, 139.8, 141.7, 167.3, 169.8, 191.5; *m*/*z* (FAB) 406 (MH^+), 105; *m*/*z* (EI) 361 (5, $[M-CO_2]^+$), 105 (100%).

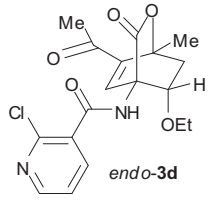
*4.2.3. N-[rel-(1R,4S,8R)-6-Acetyl-8-ethoxy-1-methyl-3-oxo-2-oxabicyclo[2.2.2]oct-5-ene-4-yl]acetamide (endo-**3c**).*



endo-**3c**

Yield: 101 mg (72%) as a white solid, mp 120–123 °C (EtOH); [Found: C, 59.75; H, 6.81; N, 4.98. $C_{14}H_{19}NO_5$ requires C, 59.78; H, 6.81; N, 4.98%]; ν_{max} (KBr) 3283, 1773, 1682, 1640, 1656, 1539 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 1.17 (3H, t, J 7.1 Hz, OCH_2CH_3), 1.77 (1H, dd, *J* 13.9, 2.3 Hz, 7*endo*-H), 1.87 (3H, s, Me), 2.19 (3H, s, Me), 2.36 (3H, s, COMe), 2.37 (1H, dd, *J* 13.9, 7.1 Hz, 7*exo*-H), 3.47 (2H, 2× dq, *J* 9.4, 7.1 Hz, OCH_2CH_3), 3.92 (1H, dd, *J* 7.1, 2.3 Hz, 8-H), 6.21 (1H, s, NH), 7.29 (1H, s, 5-H); δ_C (75.5 MHz, $CDCl_3$) 15.1, 21.6, 23.3, 27.3, 42.0, 64.7, 65.4, 74.7, 81.8, 141.3, 143.1, 168.6, 170.7, 194.5; *m*/*z* (ESI) 282 (MH^+), 192.

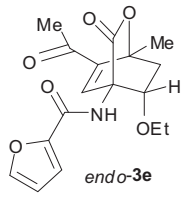
*4.2.4. N-[rel-(1R,4S,8R)-6-Acetyl-8-ethoxy-1-methyl-3-oxo-2-oxabicyclo[2.2.2]oct-5-en-4-yl]-2-chloronicotinamide (endo-**3d**).*



endo-**3d**

Yield: 115 mg (61%) as a white solid, mp 113–116 °C (CH_2Cl_2/EtOH); ν_{max} (KBr) 3503, 3243, 1766, 1678, 1613, 1585, 1542 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 1.20 (3H, t, *J* 7.0 Hz, OCH_2CH_3), 1.85 (1H, dd, *J* 13.8, 2.3 Hz, 7*endo*-H), 1.91 (3H, s, Me), 2.41 (3H, s, COMe), 2.44 (1H, dd, *J* 13.8, 7.8 Hz, 7*exo*-H), 3.53 (2H, 2× dq, *J* 9.3, 7.0 Hz, OCH_2CH_3), 4.05 (1H, m, 8-H), 7.36 (1H, d, *J* 0.9 Hz, 5-H), 7.43 (1H, dd, *J* 7.7, 4.8 Hz, 5′-H), 7.58 (1H, br s, NH), 8.36 (1H, dd, *J* 7.7, 2.1 Hz, 4′-H), 8.53 (1H, dd, *J* 4.8, 2.1 Hz, 6′-H); δ_C (75.5 MHz, $CDCl_3$) 15.1, 21.6, 27.5, 41.9, 65.2, 65.6, 75.0, 82.1, 123.0, 130.0, 140.7, 141.99, 142.01, 147.0, 151.5, 164.5, 167.8, 194.5; *m*/*z* (ESI) 401 (MNa^+), 379 (MH^+); HRMS (ESI): MH^+, found 379.1055. $C_{18}H_{20}ClN_2O_5$ requires 379.1061.

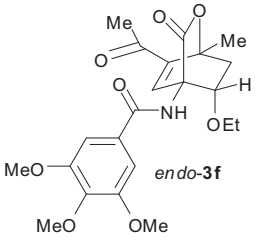
*4.2.5. N-[rel-(1R,4S,8R)-6-Acetyl-8-ethoxy-1-methyl-3-oxo-2-oxabicyclo[2.2.2]oct-5-en-4-yl]furan-2-carboxamide (endo-**3e**).*



endo-**3e**

Yield: 112 mg (67%) as a white solid, mp 137–140 °C (EtOH); [Found: C, 61.28; H, 5.80; N, 4.09. $C_{17}H_{19}NO_6$ requires C, 61.25; H, 5.75; N, 4.20%]; ν_{max} (KBr) 3383, 1764, 1678, 1620, 1597, 1509 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 1.20 (3H, t, *J* 7.1 Hz, OCH_2CH_3), 1.82 (1H, dd, *J* 14.0, 2.4 Hz, 7*endo*-H), 1.90 (3H, s, Me), 2.38 (3H, s, COMe), 2.42 (1H, dd, *J* 14.0, 7.8 Hz, 7*exo*-H), 3.53 (2H, m, OCH_2CH_3), 4.06 (1H, dd, *J* 7.8, 2.4 Hz, 8-H), 6.56 (1H, dd, *J* 3.3, 1.8 Hz, 4′-H), 7.04 (1H, br s, NH), 7.23 (1H, dd, *J* 3.4, 0.8 Hz, 3′-H), 7.40 (1H, s, 5-H), 7.52 (1H, dd, *J* 1.8, 0.8 Hz, 5′-H); δ_C (75.5 MHz, $CDCl_3$) 15.1, 21.7, 27.4, 42.1, 64.7, 65.6, 75.1, 81.9, 112.4, 115.5, 141.7, 142.4, 144.4, 147.2, 158.3, 168.4, 194.5; *m*/*z* (ESI) 356 (MNa^+), 334 (MH^+).

*4.2.6. N-[rel-(1R,4S,8R)-6-Acetyl-8-ethoxy-1-methyl-3-oxo-2-oxabicyclo[2.2.2]oct-5-en-4-yl]-3,4,5-trimethoxybenzamide (endo-**3f**).*

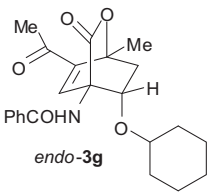


endo-**3f**

Yield: 135 mg (62%) as a white solid, mp 144–147 °C (CH_2Cl_2); [Found: C, 60.83; H, 6.25; N, 3.18. $C_{22}H_{27}NO_8$ requires C, 60.96; H, 6.28; N, 3.23%]; ν_{max} (KBr) 3384, 1753, 1684, 1668, 1618, 1588 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 1.18 (3H, t, *J* 7.0 Hz, OCH_2CH_3), 1.68 (1H, dd, *J* 13.8, 2.1 Hz, 7*endo*-H), 1.85 (3H, s, Me), 1.94 (1H, dd, *J* 13.8, 7.7 Hz, 7*exo*-H), 2.37 (3H, s, COMe), 3.51 (2H, 2× dq, *J* 9.5, 7.0 Hz, OCH_2CH_3), 3.92 (3H, s, 4′-OMe), 3.94 (6H, s, 3′-OMe, 6′-OMe), 3.97 (1H, m, 8-H), 7.00 (1H, br s, NH), 7.12 (2H, s, 2′-H, 6′-H), 7.34 (1H, br s, 5-H); δ_C (75.5 MHz, $CDCl_3$) 15.2, 21.4, 27.4, 41.8, 56.1, 60.9, 65.2, 65.8, 74.7, 82.3, 104.7, 128.2, 141.08,

141.40, 142.9, 153.3, 166.9, 170.2, 194.4; *m*/*z* (ES$^+$) 456 (MNa$^+$), 434 (MH$^+$).

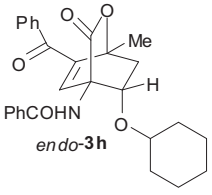
*4.2.7. N-[rel-(1R,4S,8R)-6-Acetyl-8-(cyclohexyloxy)-1-methyl-3-oxo-2-oxabicyclo[2.2.2]oct-5-en-4-yl]benzamide (endo-**3g**).*



endo-**3g**

Yield: 103 mg (52%) as a white solid, mp 130–133 °C (EtOH); [Found: C, 69.80; H, 7.07; N, 3.51. $C_{23}H_{27}NO_5$ requires C, 69.50; H, 6.85; N, 3.52%]; ν_{max} (KBr) 3378, 1755, 1675, 1616, 1580, 1518 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 1.25 (5H of cyclohexyl, m), 1.53 (1H of cyclohexyl, m), 1.70 (3H of cyclohexyl, m), 1.76 (1H, dd, *J* 13.8, 2.4 Hz, 7*endo*-H), 1.87 (3H, s, Me), 1.92 (1H of cyclohexyl, m), 2.33 (1H, dd, *J* 13.8, 7.8 Hz, 7*exo*-H), 2.39 (3H, s, Me), 3.34 (1H, m, 1′-H), 4.13 (1H, dd, *J* 7.8, 2.4 Hz, 8-H), 6.86 (1H, br s, NH), 7.42 (1H, s, 5-H), 7.53 (3H, m, Ph), 7.87 (2H, m, Ph); δ_C (75.5 MHz, $CDCl_3$) 21.6, 23.89, 23.96, 25.3, 27.4, 31.8, 33.2, 43.2, 65.1, 72.8, 78.1, 82.0, 127.3, 128.8, 132.0, 133.4, 141.1, 143.3, 167.3, 169.3, 194.5; *m*/*z* (ES$^+$) 398 (MH$^+$).

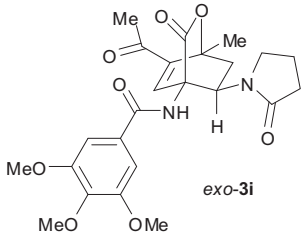
*4.2.8. N-[rel-(1R,4S,8R)-6-Benzoyl-8-(cyclohexyloxy)-1-methyl-3-oxo-2-oxabicyclo[2.2.2]oct-5-en-4-yl]benzamide (endo-**3h**).*



endo-**3h**

Yield: 148 mg (64%) as a white solid, mp 130–132 °C (EtOH); [Found: C, 73.11; H, 6.38; N, 3.00. $C_{28}H_{29}NO_5$ requires C, 73.18; H, 6.36; N, 3.05%]; ν_{max} (KBr) 3380, 1757, 1668, 1651, 1619, 1596, 1515 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 1.28 (5H of cyclohexyl, m), 1.53 (1H of cyclohexyl, m), 1.73 (3H of cyclohexyl, m), 1.86 (3H, s, Me), 1.93 (1H of cyclohexyl, m), 1.94 (1H, dd, *J* 13.8, 2.1 Hz, 7*endo*-H), 2.42 (1H, dd, *J* 13.8, 7.8 Hz, 7*exo*-H), 3.39 (1H, m, 1′-H), 4.23 (1H, m, 8-H), 6.82 (1H, br s, NH), 6.95 (1H, s, 5-H), 7.52 (6H, m), 7.83 (2H, m), 7.95 (2H, m) (2× Ph); δ_C (75.5 MHz, $CDCl_3$) 20.8, 23.79, 23.85, 25.4, 31.8, 33.2, 43.4, 65.1, 73.1, 77.6, 82.1, 127.3, 128.6, 128.7, 130.1, 131.9, 133.4, 133.5, 136.6, 139.8, 141.9, 167.3, 169.6, 191.4; *m*/*z* (ES$^+$) 460 (MH$^+$).

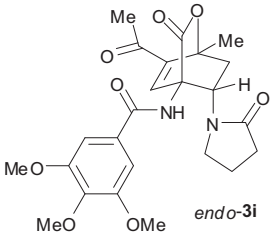
*4.2.9. N-[rel-(1R,4S,8S)-6-Acetyl-8-(2-oxo-1-pyrrolidinyl)-1-methyl-3-oxo-2-oxabicyclo[2.2.2]oct-5-en-4-yl]-3,4,5-trimethoxybenzamide (exo-**3i**).*



exo-**3i**

Yield: 151 mg (64%) as a white solid, mp 148–151 °C (CH_2Cl_2); [Found: C, 60.96; H, 6.17; N, 5.93. $C_{24}H_{28}N_2O_8$ requires C, 61.01; H, 5.97; N, 5.93%]; ν_{max} (KBr) 3309, 1768, 1681, 1665, 1624, 1587 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 1.96 (3H, s, Me), 2.01 (2H of pyrrolidinyl, m), 2.26 (2H of pyrrolidinyl, m), 2.36 (3H, s, Me), 2.39 (2H of pyrrolidinyl, m), 3.41 (2H, m, 7-CH_2), 3.91 (3H, s, 4′-OMe), 3.93 (6H, s, 3′-OMe, 6′-OMe), 4.98 (1H, dd, *J* 9.2, 6.8 Hz, 8-H), 7.12 (2H, s, 2′-H, 6′-H), 7.48 (1H, s, 5-H), 7.77 (1H, br s, NH); δ_C (75.5 MHz, $CDCl_3$) 18.7, 21.7, 27.4, 31.2, 35.4, 45.0, 50.7, 56.3, 60.8, 63.7, 82.5, 104.6, 128.0, 141.5, 143.3, 143.6, 153.2, 166.4, 169.2, 177.6, 194.0; *m*/*z* (ES$^+$) 495 (MNa$^+$), 473 (MH$^+$).

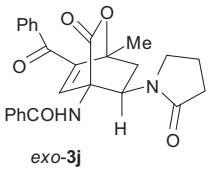
*4.2.10. N-[rel-(1R,4S,8R)-6-Acetyl-8-(2-oxo-1-pyrrolidinyl)-1-methyl-3-oxo-2-oxabicyclo[2.2.2]oct-5-en-4-yl]-3,4,5-trimethoxybenzamide (endo-**3i**).*



endo-**3i**

The mother liquor, obtained after the separation of the *exo*-**3i**, was left at room temperature for several days (~10 days) and crystals of the *endo*-**3i** were collected. Yield: 1 mg (0.5%) as a white solid, mp 144–146 °C (CH_2Cl_2); δ_H (300 MHz, $CDCl_3$) 1.93 (3H, s, Me), 2.42 (3H, s, Me), 2.50 (2H of pyrrolidinyl, m), 3.22 (2H of pyrrolidinyl, m), 3.52 (2H of pyrrolidinyl, m), 3.90 (3H, s, 4′-OMe), 3.94 (6H, s, 3′-OMe, 6′-OMe), 4.42 (2H, m), 4.98 (1H, m) (7-CH_2, 8-H), 7.11 (2H, s, 2′-H, 6′-H), 7.67 (1H, s, 5-H), 7.76 (1H, br s, NH); *m*/*z* (ES$^+$) 473 (MH$^+$); HRMS (ES$^+$): MH$^+$, found 473.1934. $C_{24}H_{29}N_2O_8$ requires 473.1924.

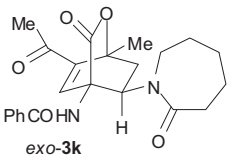
*4.2.11. N-[rel-(1R,4S,8S)-6-Benzoyl-1-methyl-3-oxo-8-(2-oxopyrrolidin-1-yl)-2-oxabicyclo[2.2.2]oct-5-en-4-yl]benzamide (exo-**3j**).*



exo-**3j**

Yield: 135 mg (61%) as a white solid, mp 134–136 °C (*i*-Pr_2O); [Found: C, 70.09; H, 5.62; N, 6.41. $C_{26}H_{24}N_2O_5$ requires C, 70.26; H, 5.44; N, 6.30%]; ν_{max} (KBr) 3357, 1739, 1692, 1663, 1609, 1593 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 1.92 (3H, s, Me), 2.01 (2H of pyrrolidinyl, m), 2.44 (4H of pyrrolidinyl, m), 3.42 (2H, m, 7-CH_2), 5.08 (1H, dd, *J* 10.5, 5.7 Hz, 8-H), 7.08 (1H, s, 5-H), 7.52 (6H, m, 2× Ph), 7.71 (1H, br s, NH), 7.84 (4H, m, 2× Ph); δ_C (75.5 MHz, $CDCl_3$) 18.7, 20.9, 31.1, 35.6, 45.1, 51.1, 63.5, 82.9, 127.1, 128.6, 128.7, 129.9, 132.1, 133.0, 133.8, 136.1, 141.3, 142.7, 166.8, 170.0, 177.1, 191.3; *m*/*z* (ES$^+$) 445 (MH$^+$).

*4.2.12. N-[rel-(1R,4S,8S)-6-Acetyl-1-methyl-3-oxo-8-(2-oxoazepan-1-yl)-2-oxabicyclo[2.2.2]oct-5-en-4-yl]benzamide (exo-**3k**).*

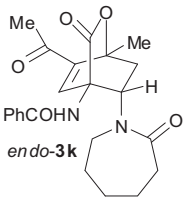


exo-**3k**

For preparing the *exo*- and *endo*-**3k**, the crude reaction mixture (after the shorter reaction time of 384 h, Table 2, entry 13) was separated by HPLC chromatography with MeCN as the mobile

phase (column: Alltech Associates, Deerfield, IL, preparative Econosil Silica 10U column, length 250 mm, I. D. 10 mm, Cat. No. 6233) yielding *exo*-**3k** and *endo*-**3k**. Alternatively, after a longer reaction time of 2544 h (Table 2, entry 14), pure *exo*-**3k** precipitated from the crude reaction mixture. Yield: 20 mg (10%) as a white solid, mp 152–154 °C (acetonitrile); ν_{max} (KBr) 3415, 3327, 3090, 2930, 1773, 1672, 1622, 1524, 1489 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 1.62 (7H, m, 3× CH_2 of oxoazepan and 7*exo*-H), 1.92 (3H, s, Me), 2.25 (1H, dd, *J* 13.0, 10.9 Hz, 7*endo*-H), 2.34 (3H, s, Me), 2.50 (2H of oxoazepan, m), 3.31 (2H of oxoazepan, m), 7.52 (4H, m, Ph, 5-H), 7.68 (1H, br s, NH), 7.86 (2H, m, Ph) (signal for 8-H is hidden in the region of 4–6 ppm); δ_C (75.5 MHz, $CDCl_3$) 21.8, 23.2, 27.4, 29.1, 29.4, 29.6, 35.2, 37.6, 63.3, 82.5, 127.1, 128.8, 132.3, 133.0, 143.6, 144.5, 166.9, 169.5, 177.9 br, 194.4 (1 signal hidden); *m*/*z* (ES^+) 411 (MH^+); HRMS (ES^+): MH^+, found 411.1932. $C_{23}H_{27}N_2O_5$ requires 411.1920. Crystal data for *exo*-**3k**: $C_{23}H_{26}N_2O_5$, *M*=410.46, monoclinic, space group $P2_1/n$ (No. 14), *a*=9.5607(2) Å, *b*=9.6009 (3) Å, *c*=23.1333(6) Å, *β*=92.953(2)°, *V*=2120.62(10) $Å^3$, *Z*=4, *T*=293(2) K, D_c=1.286 g cm^{-1}, μ(Mo Kα)=0.091 mm^{-1}, *F*(000)=872, crystal size=0.70×0.25×0.25 mm, 10,287 reflections collected, 5405 unique (R_{int}=0.0384). The final R_1=0.0526, wR_2=0.1333, and for all data R_1=0.0902, wR_2=0.1544.

*4.2.13. N-[rel-(1R,4S,8R)-6-Acetyl-1-methyl-3-oxo-8-(2-oxoazepan-1-yl)-2-oxabicyclo[2.2.2]oct-5-en-4-yl]benzamide (endo-**3k**).*



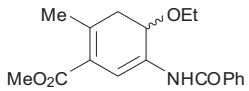
endo-**3k**

Yield: 31 mg (15%) as a white solid, mp 135–138 °C (acetonitrile); ν_{max} (KBr) 3417, 3310, 3069, 2931, 1767, 1674, 1620, 1533, 1489 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 1.46 (1H of oxoazepan, m), 1.66 (5H of oxoazepan, m), 1.87 (1H, dd, *J* 14.7, 3.9 Hz, 7*endo*-H), 1.92 (3H, s, Me), 2.43 (3H, s, Me), 2.52 (1H, dd, *J* 14.7, 9.9 Hz, 7*exo*-H), 2.57 (2H of oxoazepan, m), 3.11 (2H of oxoazepan, m), 5.45 (1H, dd, *J* 9.9, 3.9 Hz, 8-H), 7.51 (3H, m, Ph), 7.62 (1H, s, 5-H), 7.86 (2H, m, Ph), 8.03 (1H, br s, NH); δ_C (75.5 MHz, $CDCl_3$) 21.5, 23.0, 27.8, 28.6, 29.3, 36.4, 37.1, 44.9, 50.3, 66.1, 81.5, 127.2, 128.7, 132.1, 132.9, 140.7, 141.9, 167.9, 168.7, 179.6, 195.1; *m*/*z* (ES^+) 411 (MH^+); HRMS (ES^+): MH^+, found 411.1917. $C_{23}H_{27}N_2O_5$ requires 411.1920. Crystal data for *endo*-**3k**: $C_{23}H_{26}N_2O_5$, *M*=410.46, monoclinic, space group $P2_1/n$ (No. 14), *a*=13.0782(5) Å, *b*=11.9897(4) Å, *c*=13.2223(4) Å, *β*=91.191(2)°, *V*=2072.86(12) $Å^3$, *Z*=4, *T*=293 (2) K, D_c=1.315 g cm^{-1}, μ(MoKα)=0.093 mm^{-1}, *F*(000)=872, crystal size=0.35×0.18×0.13 mm, 9281 reflections collected, 5299 unique (R_{int}=0.0474). The final R_1=0.0653, wR_2=0.1380, and for all data R_1=0.1389, wR_2=0.1763.

4.3. Microwave-assisted synthesis of the products 4

A mixture of the starting 2*H*-pyran-2-one **1** (0.5 mmol) and ethyl vinyl ether (**2a**) (721 mg, 10 mmol) in MeCN (1 mL) in a sealed vial (10 mL) was irradiated (for **4a** the power was set to 180 W and for **4b**,**c** to 150 W) in the focused microwave equipment for 2 h (for **4a**) or 1.5 h (for **4b**,**c**). The final temperature was set to 120 °C and the ramp time to 5 min. Thereafter, the reaction mixture was cooled. The precipitated products **4a**–**c** were filtered off and washed with EtOH/H_2O (1:1). (See Table 3).

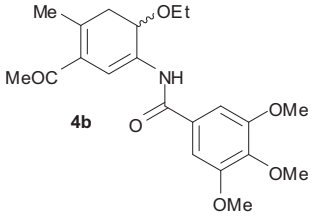
*4.3.1. rac-Methyl 5-(benzoylamino)-4-ethoxy-2-methylcyclohexa-1,5-diene-1-carboxylate (**4a**).*



4a

Yield (together with a minor amount of **1a**): 52 mg (ca. 50 mg (32%) of pure **4a**) as an off-white solid; [Found: C, 68.31; H, 6.47; N, 4.70. $C_{18}H_{21}NO_4$ requires: C, 68.55; H, 6.71; N, 4.44%]; ν_{max} (KBr) 3377, 1732, 1699, 1669, 1597, 1528 cm^{-1}; δ_H (300 MHz, $CDCl_3$)[17] 1.29 (3H, t, *J* 7.0 Hz, CH_2CH_3), 2.24 (3H, s, Me), 2.57 (2H, m, 3-CH_2), 3.47 (1H, dq, *J* 9.1, 7.0 Hz), 3.75 (1H, dq, *J* 9.1, 7.0 Hz) (CH_2CH_3), 3.77 (3H, s, CO_2Me), 4.34 (1H, ddd, *J* 12.7, 7.7, 1.4 Hz, 4-H), 7.34 (1H, d, *J* 1.5 Hz, 6-H), 7.51 (3H, m, Ph), 7.80 (2H, m, Ph), 8.30 (1H, br s, NH); δ_C (75.5 MHz, DMSO-d_6)[17] 15.6, 21.5, 38.2, 51.4, 64.2, 73.0, 107.9, 123.3, 126.7, 128.6, 130.9, 131.6, 134.7, 141.6, 165.3, 166.6; *m*/*z* (ESI) 338 (MNa^+), 238.

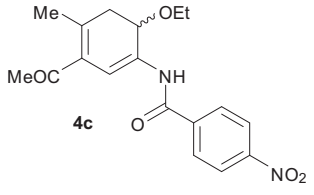
*4.3.2. rac-N-(3-Acetyl-6-ethoxy-4-methylcyclohexa-1,3-dien-1-yl)-3,4,5-trimethoxybenzamide (**4b**).*



4b

Yield (together with a minor amount of **5f**): 86 mg (ca. 75 mg (39%) of pure **4b**) as an off-white solid; ν_{max} (KBr) 3402, 2936, 1678, 1586, 1531, 1499 cm^{-1}; δ_H (300 MHz, $CDCl_3$)[17] 1.31 (3H, t, *J* 7.0 Hz, CH_2CH_3), 2.12 (3H, s, Me), 2.35 (3H, s, COMe), 2.55 (2H, m, 5-CH_2), 3.47 (1H, dq, *J* 9.0, 7.0 Hz), 3.79 (1H, dq, *J* 9.1, 7.0 Hz) (CH_2CH_3), 3.93 (9H, br s, 3× OMe), 4.33 (1H, ddd, *J* 14.0, 7.6, 1.6 Hz, 6-H), 7.04 (2H, s, 2′-H, 6′-H), 7.30 (1H, d, *J* 1.6 Hz, 2-H), 8.42 (1H, br s, NH); δ_C (75.5 MHz, $CDCl_3$)[17] 15.7, 21.5, 29.6, 37.8, 56.2, 60.9, 64.5, 73.4, 104.1, 106.8, 130.0, 131.4, 132.3, 137.4, 141.3, 153.3, 164.9, 200.4; *m*/*z* (ESI) 412 (MNa^+), 344; HRMS (ESI): MNa^+, found 412.1730. $C_{21}H_{27}NNaO_6$ requires 412.1736.

*4.3.3. rac-N-(3-Acetyl-6-ethoxy-4-methylcyclohexa-1,3-dien-1-yl)-4-nitrobenzamide (**4c**).*



4c

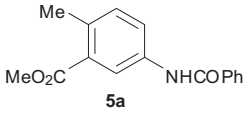
Yield (together with a minor amount of **5g**): 67 mg (ca. 55 mg (39%) of pure **4c**) as an off-white solid; ν_{max} (KBr) 3396, 1682, 1599, 1526 cm^{-1}; δ_H (300 MHz, $CDCl_3$)[17] 1.31 (3H, t, *J* 7.0 Hz, CH_2CH_3), 2.13 (3H, s, Me), 2.36 (3H, s, COMe), 2.55 (2H, m, 5-CH_2), 3.48 (1H, dq, *J* 9.2, 7.0 Hz), 3.79 (1H, dq, *J* 9.2, 7.0 Hz) (CH_2CH_3), 4.33 (1H, ddd, *J* 13.8, 7.5 Hz, 1.6 Hz, 6-H), 7.34 (1H, d, *J* 1.5 Hz, 2-H), 7.96 and 8.34 (2H each, AA′XX′, *J* 9.0 Hz, $C_6H_4NO_2$), 8.48 (1H, br s, NH); δ_C (75.5 MHz, $CDCl_3$)[17] 15.6, 21.6, 29.7, 37.8, 64.6, 73.0, 108.0, 124.0, 127.9, 131.0, 132.1, 138.2,

140.2, 149.7, 163.1, 200.3; *m*/*z* (ESI) 367 (MNa^+), 257; HRMS (ESI): MNa^+, found 367.1269. $C_{18}H_{20}N_2NaO_5$ requires 367.1270.

4.4. Microwave-assisted synthesis of the products 5

A mixture of the starting 2*H*-pyran-2-one **1** (1 mmol) and the corresponding vinyl dienophile **2a** (721 mg, 10 mmol) or **2e** (667 mg, 6 mmol) in MeCN (1.5 mL) and DABCO (8.4 mg, 0.075 mmol) in a sealed vial (10 mL), was irradiated in the focused microwave equipment for 2 h (Table 4). The final temperature was set to 120 °C, the power to 120 W (for **5d**,**g**,**j**,**k**), 150 W (for **5b**,**e**,**f**,**h**,**i**) or 180 W (for **5a**,**c**) and the ramp time to 5 min. Thereafter, the reaction mixture was cooled, volatile components were removed in vacuo, the remaining solid was treated with a mixture of $EtOH/H_2O$ (1:1), and cooled. The precipitated products **5a**–**k** were filtered off and washed with $EtOH/H_2O$ (1:1). (See Table 4).

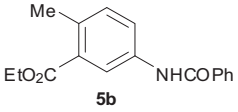
4.4.1. Methyl 5-(benzoylamino)-2-methylbenzoate (*5a*)[5].



5a

Yield: 199 mg (74%) as a pale yellow solid, lit.[5] mp 126–127 °C ($EtOH/H_2O$); mp 126–127 °C (EtOH).

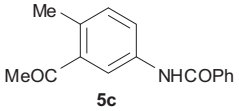
4.4.2. Ethyl 5-(benzoylamino)2-methylbenzoate (*5b*)[5].



5b

Yield: 202 mg (71%) as a pale yellow solid, lit.[5] mp 119–120.5 °C ($EtOH/H_2O$); mp 119–120.5 °C ($EtOH/H_2O$); [Found: C, 72.02; H, 5.98; N, 4.99. $C_{17}H_{17}NO_3$ requires C, 72.07; H, 6.05; N, 4.94%]; ν_{max} (KBr) 3296, 1726, 1648, 1583, 1530, 1448, 1404 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 1.38 (3H, t, *J* 7.1 Hz, CH_2CH_3), 2.57 (3H, s, Me), 4.35 (2H, q, *J* 7.1 Hz, CH_2CH_3), 7.23 (1H, d, *J* 8.1 Hz, 3-H), 7.50 (3H, m, Ph), 7.87 (3H, m, Ph, 4-H), 7.96 (1H, br s, NH), 8.02 (1H, d, *J* 2.4 Hz, 6-H); δ_C (75.5 MHz, $CDCl_3$) 14.2, 21.1, 60.9, 122.2, 124.0, 127.0, 128.7, 130.2, 131.8, 132.2, 134.6, 135.7, 136.1, 165.9, 167.2; *m*/*z* (EI) 283 (46, M^+), 105 (100%).

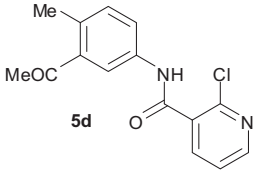
4.4.3. N-(3-Acetyl-4-methylphenyl)benzamide (*5c*)[5,18].



5c

Yield: 179 mg (71%) as a pale yellow solid, lit.[18] mp 137–138 °C ($EtOH/H_2O$); mp 131–132 °C (EtOH).

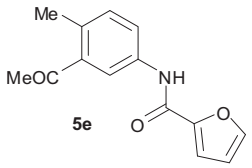
4.4.4. N-(3-Acetyl-4-methylphenyl)-2-chloronicotinamide (*5d*).



5d

Yield: 174 mg (60%) as a brown solid, mp 101–103 °C (EtOH); [Found: C, 62.28; H, 4.39; N, 9.96. $C_{15}H_{13}ClN_2O_2$ requires C, 62.40; H, 4.54; N, 9.70%]; ν_{max} (KBr) 3296, 1690, 1656, 1577, 1524, 1402 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 2.52 (3H, s, Me), 2.62 (3H, s, Me), 7.27 (1H, d, *J* 8.2 Hz, 5-H), 7.42 (1H, dd, *J* 7.6, 4.8 Hz, 5′-H), 7.56 (1H, dd, *J* 8.2, 2.1 Hz, 6-H), 8.11 (1H, d, *J* 2.1 Hz, 2-H), 8.22 (1H, dd, *J* 7.7, 1.8 Hz, 4′-H or 6′-H), 8.23 (1H, br s, NH), 8.53 (1H, dd, *J* 4.7, 1.8 Hz, 6′-H or 4′-H); δ_C (75.5 MHz, $CDCl_3$) 20.9, 29.6, 121.0, 122.9, 123.1, 131.3, 132.6, 134.9, 135.0, 138.3, 139.6, 147.0, 151.2, 162.9, 201.4; *m*/*z* (ES^+) 311 (MNa^+), 289 (MH^+); HRMS (ES^+): MH^+, found 289.0750. $C_{15}H_{14}ClN_2O_2$ requires 289.0744.

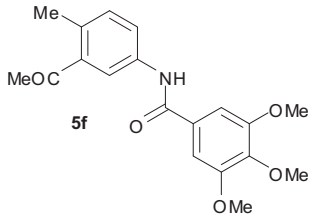
4.4.5. N-(3-Acetyl-4-methylphenyl)furan-2-carboxamide (*5e*).



5e

Yield: 167 mg (69%) as a brown solid, mp 63–65 °C (EtOH); ν_{max} (KBr) 3446, 1656, 1621, 1598, 1537, 1477 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 2.50 (3H, s, Me), 2.60 (3H, s, Me), 6.57 (1H, dd, *J* 3.4, 1.8 Hz, 4′-H), 7.23 (1H, d, *J* 8.4 Hz, 5-H), 7.25 (1H, dd, *J* 3.4, 0.8 Hz, 3′-H), 7.52 (1H, dd, *J* 1.8, 0.8 Hz, 5′-H), 7.55 (1H, dd, *J* 8.4, 2.4 Hz, 6-H), 8.16 (2H, d, *J* 2.4 Hz, 2-H, NH); δ_C (75.5 MHz, DMSO-d_6) 20.4, 29.4, 112.2, 114.9, 121.4, 123.3, 131.9, 132.4, 136.4, 137.5, 145.8, 147.4, 156.3, 201.1; *m*/*z* (ES^+) 266 (MNa^+), 244 (MH^+); HRMS (ES^+): MH^+, found 244.0978. $C_{14}H_{14}NO_3$ requires 244.0974.

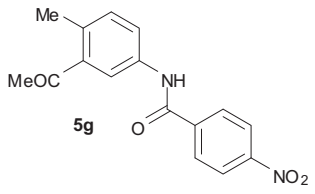
4.4.6. N-(3-Acetyl-4-methylphenyl)-3,4,5-trimethoxybenzamide (*5f*).



5f

Yield: 240 mg (70%) as a white solid, mp 158–161 °C (EtOH); [Found: C, 66.70; H, 6.14; N, 4.14. $C_{19}H_{21}NO_5$ requires C, 66.46; H, 6.16; N, 4.08%]; ν_{max} (KBr) 3262, 1684, 1644, 1581, 1515, 1499 cm^{-1}; δ_H (300 MHz, DMSO-d_6) 2.41 (3H, s, Me), 2.55 (3H, s, Me), 3.74 (3H, s, 4′-OMe), 3.88 (6H, s, 3′-OMe, 5′-OMe), 7.29 (1H, d, *J* 8.3 Hz, 5-H), 7.30 (2H, br s, 2′-H, 6′-H), 7.81 (1H, dd, *J* 8.3, 2.4 Hz, 6-H), 8.17 (1H, d, *J* 2.4 Hz, 2-H), 10.22 (1H, s, NH); δ_C (75.5 MHz, DMSO-d_6) 20.4, 29.4, 56.1, 60.1, 105.3, 121.5, 123.6, 129.7, 131.9, 132.2, 136.9, 137.5, 140.4, 152.6, 164.9, 201.1; *m*/*z* (ES^+) 366 (MNa^+), 344 (MH^+).

4.4.7. N-(3-Acetyl-4-methylphenyl)-4-nitrobenzamide (*5g*).

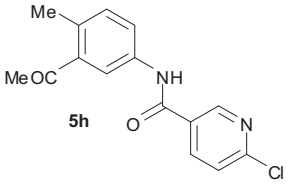


5g

Yield: 206 mg (69%) as a brown solid, mp 190–192 °C ($EtOH/H_2O$); [Found: C, 64.18; H, 4.71; N, 9.42. $C_{16}H_{14}N_2O_4$ requires C,

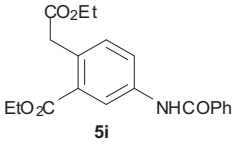
64.42; H, 4.73; N, 9.39%]; ν_{max} (KBr) 3341, 1664, 1601, 1531, 1522, 1343 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 2.52 (3H, s, Me), 2.61 (3H, s, Me), 7.28 (1H, d, *J* 8.2 Hz, 5-H), 7.57 (1H, dd, *J* 8.2, 2.3 Hz, 6-H), 7.88 (1H, br s, NH), 8.05 and 8.36 (2H each, AA′XX′, *J* 8.7 Hz, $C_6H_4NO_2$), 8.09 (1H, d, *J* 2.2 Hz, 2-H); δ_C (75.5 MHz, $CDCl_3$) 21.0, 29.6, 121.2, 123.2, 124.0, 128.3, 132.7, 135.06, 135.08, 138.4, 140.2, 149.8, 163.8, 201.4; *m*/*z* (ES^+) 321 (MNa^+), 299 (MH^+).

*4.4.8. N-(3-Acetyl-4-methylphenyl)-6-chloronicotinamide (**5h**).*



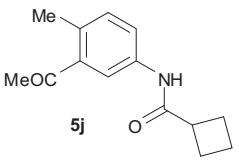
Yield: 213 mg (74%) as an orange solid, mp 141–144 °C (EtOH/H_2O); [Found: C, 62.34; H, 4.53; N, 9.40. $C_{15}H_{13}ClN_2O_2$ requires C, 62.40; H, 4.54; N, 9.70%]; ν_{max} (KBr) 3356, 1701, 1672, 1589, 1532, 1497 cm^{-1}; δ_H (300 MHz, DMSO-d_6) 2.42 (3H, s, Me), 2.56 (3H, s, Me), 7.29 (1H, d, *J* 8.2 Hz, 5-H), 7.71 (1H, d, *J* 8.4 Hz, 5′-H), 7.84 (1H, dd, *J* 8.2, 2.2 Hz, 6-H), 8.19 (1H, d, *J* 2.2 Hz, 2-H), 8.37 (1H, dd, *J* 8.4, 2.2 Hz, 4′-H), 8.97 (1H, dd, *J* 2.2 Hz, 2′-H), 10.56 (1H, s, NH); δ_C (75.5 MHz, DMSO-d_6) 20.4, 29.4, 121.3, 123.3, 124.1, 129.6, 132.0, 132.7, 136.5, 137.5, 138.9, 149.2, 152.8, 162.8, 200.9; *m*/*z* (ES^+) 311 (MNa^+), 289 (MH^+).

*4.4.9. Ethyl 5-(benzoylamino)-2-[(ethoxycarbonyl)methyl]benzoate (**5i**)[5].*



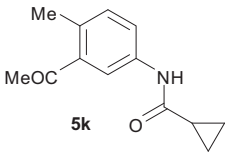
Yield: 259 mg (73%) as a pale yellow solid, lit.[5] mp 170.5–171.5 °C (MeOH); mp 170.5–171.5 °C (MeOH); [Found: C, 67.36; H, 6.21; N, 4.00. $C_{20}H_{21}NO_5$ requires C, 67.59; H, 5.96; N, 3.94%]; ν_{max} (KBr) 3298, 1736, 1714, 1651, 1588, 1523, 1420 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 1.25 (3H, t, *J* 7.1 Hz, CH_2CH_3), 1.37 (3H, t, *J* 7.1 Hz, CH_2CH_3), 3.99 (2H, s, CH_2), 4.15 (2H, q, *J* 7.1 Hz, CH_2CH_3), 4.32 (2H, q, *J* 7.1 Hz, CH_2CH_3), 7.24 (1H, d, *J* 8.9 Hz, 3-H), 7.53 (3H, m, Ph), 7.88 (2H, m, Ph), 7.95 (1H, dd, *J* 8.9, 2.4 Hz, 4-H), 7.98 (1H, br s, NH), 8.10 (1H, d, *J* 2.4 Hz, 6-H); δ_C (75.5 MHz, $CDCl_3$) 14.2, 40.2, 60.8, 61.1, 122.4, 123.8, 127.1, 128.8, 130.5, 131.7, 132.0, 132.9, 134.6, 137.2, 165.7, 166.6, 171.7 (1 signal hidden); *m*/*z* (EI) 355 (7, M^+), 105 (100%).

*4.4.10. N-(3-Acetyl-4-methylphenyl)cyclobutanecarboxamide (**5j**).*



Yield: 146 mg (63%) as a pale yellow solid, mp 67–70 °C (EtOH); [Found: C, 72.44; H, 7.43; N, 5.97. $C_{14}H_{17}NO_2$ requires C, 72.70; H, 7.41; N, 6.06%]; ν_{max} (KBr) 3266, 1686, 1657, 1610, 1524, 1493 cm^{-1}; δ_H (300 MHz, DMSO-d_6) 1.89 (2H, m, 3-CH_2), 2.19 (4H, m, 2-CH_2, 4-CH_2), 2.37 (3H, s, Me), 2.51 (3H, s, Me), 3.22 (1H, m, 1′-H), 7.20 (1H, d, *J* 8.3 Hz, 5-H), 7.66 (1H, dd, *J* 8.3, 2.3 Hz, 6-H), 8.06 (1H, d, *J* 2.3 Hz, 2-H), 9.81 (1H, s, NH); δ_C (75.5 MHz, DMSO-d_6) 17.7, 20.4, 24.6, 29.3, 39.6, 120.0, 122.0, 131.4, 131.9, 137.2, 137.4, 173.0, 201.0; *m*/*z* (ES^+) 254 (MNa^+), 232 (MH^+).

*4.4.11. N-(3-Acetyl-4-methylphenyl)cyclopropanecarboxamide (**5k**).*



Yield: 140 mg (65%) as a pale yellow solid, mp 85–88 °C (EtOH); ν_{max} (KBr) 3279, 1682, 1651, 1528, 1437, 1409 cm^{-1}; δ_H (300 MHz, DMSO-d_6) 0.81 (4H, m, 2× CH_2), 1.77 (1H, m, 1′-H), 2.37 (3H, s, Me), 2.51 (3H, s, Me), 7.20 (1H, d, *J* 8.3 Hz, 5-H), 7.62 (1H, dd, *J* 8.3, 2.2 Hz, 6-H), 8.05 (1H, d, *J* 2.2 Hz, 2-H), 10.28 (1H, s, NH); δ_C (75.5 MHz, DMSO-d_6) 7.1, 14.5, 20.3, 29.3, 119.8, 121.9, 131.3, 131.9, 137.2, 137.5, 171.7, 201.1; *m*/*z* (ES^+) 240 (MNa^+), 218 (MH^+); HRMS (ES^+): MH^+, found 218.1179. $C_{13}H_{16}NO_2$ requires 218.1181.

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Supplementary data

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.tet.2011.03.034.

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