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Stereo- and regiochemistry in the (asymmetric) cycloaddition reaction of 5-chloro-2(1*H*)-pyrazinones with cyclic and monosubstituted alkenes and with a *N*-acryloyl substituted chiral auxiliary

Frederik J. R. Rombouts, David A. J. Vanraes, Jo Wynendaele, Patrick K. Loosen, Ingrid Luyten, Suzanne Toppet, Frans Compernolle* and Georges J. Hoornaert*

Department of Organic Chemistry, K.U. Leuven, Leuven B-3001, Belgium

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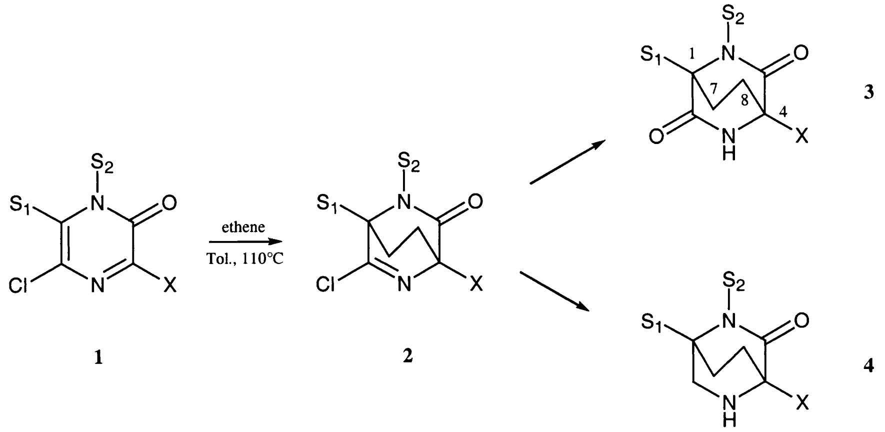
Abstract—The cycloaddition of 5-chloro-2(1*H*)-pyrazinones **1** with various dienophiles was used to generate the corresponding 2,5-diazabicyclo[2.2.2]octanes. Following reduction or hydrolysis of the bridged adducts, the regio- and stereochemical structure was determined by analysis of the coupling and NOE patterns in the ^{1}H NMR spectra. With symmetric dienophiles the *endo* adducts are formed exclusively. The regiochemistry for the reaction of **1** with methyl acrylate and ethyl vinyl ether, and the asymmetric induction found with the *N*-acryloyl substituted chiral auxiliary (4*S*)-4-isopropyl-1-methyltetrahydro-2*H*-imidazol-2-one, largely depend on the electron donating or attracting properties and size of the 3-substituents of **1**. © 2001 Elsevier Science Ltd. All rights reserved.

1. Introduction

As described previously,[1,2] 2(1*H*)-pyrazinones **1** easily undergo Diels–Alder addition with ethene to give adducts **2** which are converted to 2,5-diazabicyclo[2.2.2]octane-3,6-diones **3** or 2,5-diazabicyclo[2.2.2]-octan-3-ones **4**, respectively via hydrolysis or reduction of the imidoyl choride function (Scheme 1). Now we report the synthesis and structure assignment of 7- and/or 8-functionalised 2,5-diazabicyclo[2.2.2]octane-3(,6-di)ones, generated from the reaction of **1** and either symmetric cyclic olefins, i.e. cyclopentene and *N*-phenylmaleimide, or the monosubstituted alkenes methyl acrylate and ethyl vinyl ether. The scope of cycloadditions involving the pyrazinone azadiene system is extended further to include the asymmetric Diels–Alder reaction of **1** with a *N*-acryloyl substituted chiral auxiliary, (4*S*)-4-isopropyl-1-methyltetrahydro-2*H*-imidazol-2-one. In view of the large number and structural complexity of



Scheme 1. Diels–Alder reaction of pyrazinones **1** with ethene and further conversion of adducts **2**.

Keywords: pyrazinones; Diels–Alder reactions; bicyclic heterocyclic compounds; chiral auxiliary.

* Corresponding authors. +32-16-327409; fax: +32-16-327990; e-mail: georges.hoornaert@chem.kuleuven.ac.be

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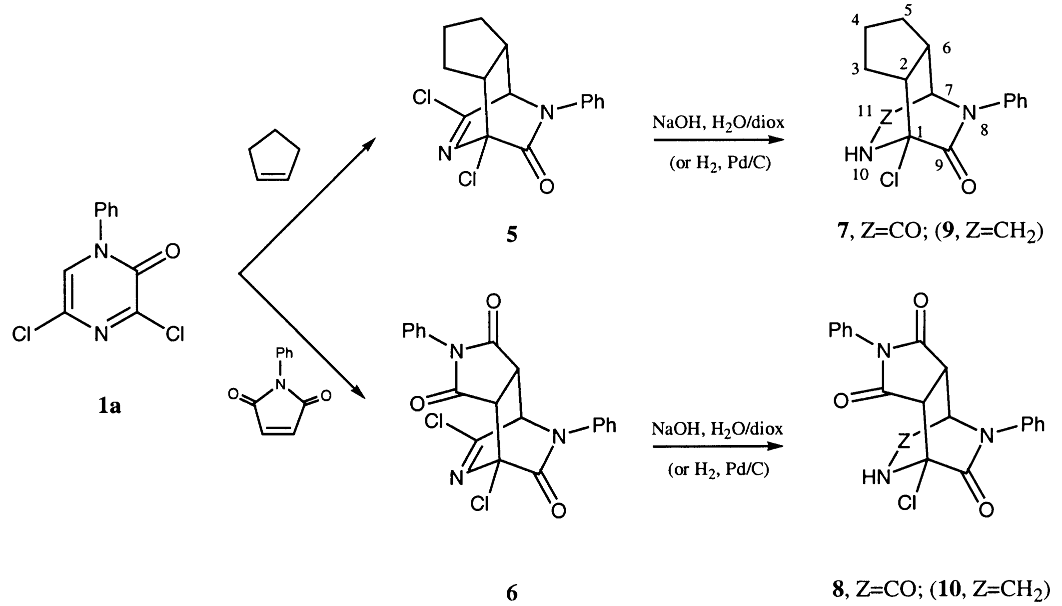


Scheme 2. Diels–Alder reactions of pyrazinone **1a** with the symmetric cyclic dienophiles cyclopentene and NMPA.

isomeric bridged adducts that may be formed, ^{1}H NMR analytical criteria have been developed to distinguish the various regio- and stereoisomers obtained after reduction or hydrolysis of the reactive imidoyl chloride function. The synthetic route described provides access to variously substituted diazabicyclo[2.2.2]octane derivatives. To our knowledge, only two groups of 7(,8)-substituted 2,5-diazabicyclo[2.2.2]octane-3,6-diones[3,4,5] and two 7,8-disubstituted compounds of type **2**[5,6] have been reported previously. The 2,5-diazabicyclo[2.2.2]octane unit is found also in a series of indolic secondary metabolites isolated from various fungi (paraherquamides,[7] brevianamides,[8] macfortines,[9] VM55599,[10] and sclerotamides[11]) some of which display potent anti-parasitic activity. The biosynthesis of these compounds is believed to involve an intramolecular [4+2] cycloaddition,[5,6,12] and some biomimetic synthetic pathways have been reported recently.[12,13]

2. Results and discussion

The reactivity and stereochemical aspects of these cycloadditions were investigated first by reaction of pyrazinone **la** with symmetric cyclic dienophiles, cyclopentene and *N*-phenylmaleimide (Scheme 2). The resulting adducts **5** and **6** were subjected to alkaline hydrolysis or catalytic reduction to afford the corresponding 2,5-diazabicyclo-[2.2.2]octane-3,6-diones **7**, **8** and 2,5-diazabicyclo[2.2.2]-octan-3-ones **9**, **10**, respectively. ^{1}H NMR analysis of compounds **7**–**10** revealed that adducts **5**, **6** had been formed via the *endo* transition state, as detailed below. Note that, irrespective of the actual mode of cycloaddition, the *endo*/*exo* notation in the present context also serves to define the orientation of atoms on the bridge positions, i.e. the ZNH (*endo*) or PhNCO (*exo*) side of the bridge.

For reduced 2,5-diazabicyclo[2.2.2]octane analogues of type **9** and **10**, the *endo*/*exo* stereochemistry can be derived from ^{1}H NMR spectral data using the following criteria:

1. For the *endo* but not for the *exo* compounds, a long range coupling is observed between proton H6 and the quasi-axial proton H11′ (Fig. 1a), in accordance with their W-shaped bond connectivity.
2. Diverging ^{3}J-values are found for the coupling between the bridgehead proton H7 and an *exo*-proton H6 (J=ca. 4 Hz) as compared to that between H7 and an *endo*-proton H6′ (J=ca. 2 Hz). Both kinds of coupling values can be determined from the spectra of the previously described reduced ethene adducts **4**. Notwithstanding the identical dihedral angles ϕ and ϕ' (Fig. 1b) defined by the atoms H6C6C7H7 and H6′C6C7H7, a different environment is created by the *N*-Ph and CH_2 groups, resulting in characteristically different J-values.[14]
3. When using DMSO-d_6 as a solvent, a long range coupling is observed in the spectra of the *endo* compounds between the NH proton and the *exo* proton H2, implying both the *endo* orientation for the non-H atom located at C2 and a pseudo-axial orientation for the NH proton (see Table 1).

The main ^{1}H NMR spectral data of **9** ($CDCl_3$) and **10** (DMSO-d_6) are summarised in Table 1. On the basis of the previous criteria and the relevant coupling constant values, compounds **9** and **10** can be characterised as the *endo* isomers: see the ^{4}J-coupling observed between H6 and H11′, a ^{3}J-value of ca. 4 Hz between H7 and H6, and

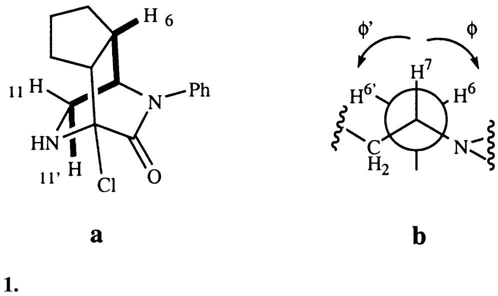


Figure 1.

Table 1. The chemical shifts (δ, ppm) and coupling constants (Hz) of protons in compounds **9** and **10**

		δ	$^2J_{11,11'}$	$^3J_{7,11}$	$^3J_{7,11'}$	$^3J_{7,6}$	$^3J_{2,6}$	$^3J_{10,11}$	$^3J_{10,11'}$	$^4J_{6,11'}$	$^4J_{2,10}$[a]
9[b]	H2	2.80					–[a]				–[a]
	H6	2.80				3.5	–[a]			1.0	
	H7	3.95		1.5	3.0	3.5					
	H10	2.35						–	–		–[a]
	H11	3.40	11.0	1.5				–			
	H11′	3.20	11.0		3.0				–	1.0	
10[c]	H2	3.70					10.0				3.0
	H6	3.90				4.0	10.0			2.0	
	H7	4.60		1.5	2.0	4.0					
	H10	4.25						3.0	10.0		3.0
	H11	3.35	11.0	1.5				3.0			
	H11′	3.05	11.0		2.0				10.0	2.0	

[a] Due to overlap of H2 and H6, the $^3J_{2,6}$ and $^4J_{2,10}$ values could not be determined.
[b] $CDCl_3$.
[c] DMSO-d_6 (40°C).

the long range (^4J) coupling between H2 and NH proton H10.

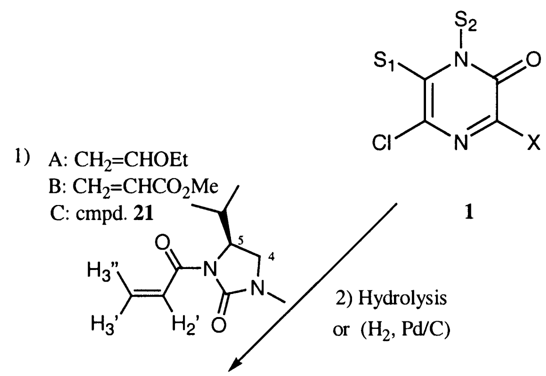
To validate the ^{1}H NMR criteria based on relevant coupling constant values in the spectra of the reduced adducts, unequivocal confirmation for our stereochemical assignments was sought from the 2D NOESY spectrum of compound **9**. This spectrum revealed a crosspeak for H6 and the *ortho* protons of the phenyl group, proving the *endo*nature of the product. A further remarkable feature is the existence of NOE crosspeaks for these aromatic protons with both the NH proton H10 and H11′, confirming their pseudo-axial orientations away from the cyclopentane ring. This in turn corresponds to the W-patterns that were inferred from the long-range couplings observed between protons H10 and H2, and between H11′ and H6, respectively.

Since neither hydrolysis nor reduction of the cycloadducts affects the stereochemistry imposed by the Diels–Alder reaction, the *endo* structure established for the reduced adducts **9** and **10** also applies to the hydrolysed compounds **7** and **8**. For the latter compounds the criteria (1) and (3) cannot be used since (1) no coupling can occur between H6 and (the non-existent) H11, and (3) the zig-zag pattern required for a long range coupling with H2 is precluded by the sp^2 character of the amide NH-group. However, the criterion (2) that involves the difference in ^3J-value for the vicinal coupling of protons H6 and H6′ with the bridgehead proton H7, still can be applied: as expected, this ^3J-value is about 4 Hz for both compounds.

In the reaction of 5-chloro-2(1*H*)-pyrazinones with the monosubstituted ethylenic dienophiles ethyl vinyl ether and methyl acrylate, stereoisomers as well as regioisomers can be formed. To facilitate the spectral analysis of the adducts, these were subjected to reduction or hydrolysis to form the isomeric amines (**11**–**13**, **17**)**a**–**d**, or bis-lactams (**14**–**16**, **18**–**20**)**a**–**d**, respectively. The total and relative yields of the four isomers produced in each reaction are summarised in the table attached to Scheme 3. This also includes the regio- and stereomeric product distribution (**19**, **20**)**a**–**d** observed for the reaction with the chiral dienophile **21** (see also below).

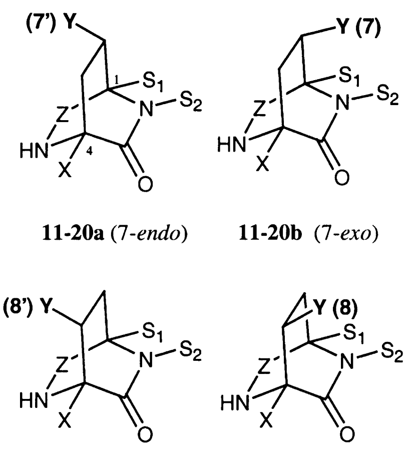
Analysis of the product ratios **11a**–**d** and **12a**–**d** reveals no appreciable regioselectivity for the reaction of 3,5-dichloropyrazinone **la** with either methyl acrylate or ethyl vinyl ether. The same holds true for the product isomers **13a**–**d** and **14a**–**d** derived from the pyrazinone analogues **lb** (6-Me instead of 6-H) and **1c** (3-H instead of 3-Cl). A better regioselectivity was observed, however, for the 3-phenyl analogue **1d**, which mainly afforded the 8-*endo*/*exo* isomers **15c**, **d** and **16c**, **d** in the reaction with the two dienophiles. Finally, the 8-regioisomers **17c**, **d** and **18c**, **d** were the only products isolated from the reaction of 3-methoxypyrazinone **1e** with methyl acrylate and of 3-cyanopyrazinone **1f** with ethyl vinyl ether. Calculations using the AM1 semi-empirical method indicate favoured LUMO diene–HOMO dienophile interactions in the case of the reactions with an electron rich dienophile (series **12**, **15**, **18**). In the reaction with an electron poor dienophile (series **11**, **16**, **17**) the normal electron demand reaction (HOMO diene–LUMO dienophile) is energetically favoured over the inverse reaction, especially for the electron rich 3-methoxypyrazinone **1e**. Since reaction of the latter yields the 8-*endo*/*exo* products **17c**, **d** only, this result implies a marked differentiation of the HOMO-diene orbital coefficients by the 3-OMe substituent, similar to the effect of the 3-cyano group (**18**) on the LUMO-diene. AM1 calculations of the pyrazinone orbital coefficients indeed marginally favoured the 8-regioisomers for both the normal and inverse reaction. However, from the rather small variation in relative magnitudes calculated for these coefficients it was not possible to explain consistently the changes in regioselectivity observed with the various 3-substituents.

Inspection of the data shown in Scheme 3 reveals higher yields for stereoisomers of type **a** and **d** as compared to **b** and **c**, respectively. While preferential formation of the 7-*endo* isomers **a** may be ascribed to secondary orbital interactions, that of the 8-*exo* products **d** probably reflects electrostatic repulsion between parallel dipoles in the transition state leading to the 8-*endo* isomers, i.e. C3═N4 of the pyrazinone and either the carbonyl group of methyl acrylate or the carbon–oxygen bond of ethyl vinyl ether. Analogous results have been described for the reaction of dimethyl maleate and fumarate with a cyclic 2-azadiene obtained



1

a) S_1 = H, S_2 = Ph, X = Cl
b) S_1 = Me, S_2 = Ph, X = Cl
c) S_1 = H, S_2 = Ph, X = H
d) S_1 = H, S_2 = Ph, X = Ph
e) S_1 = H, S_2 = Ar*, X = OMe
f) S_1 = H, S_2 = Ph, X = CN
g) S_1 = H, S_2 = Bn, X = Cl
h) S_1 = H, S_2 = Bn, X = Ph



11-20a (7-*endo*) **11-20b** (7-*exo*)

11-20c (8-*endo*) **11-20d** (8-*exo*)

	S_1	S_2	X		Z	rel. yield (%)				tot. yield (%)
						a	b	c	d	
11	H	Ph	Cl	B	CH_2	22	11	22	45	81
12	H	Ph	Cl	A	CH_2	22	22	15	41	81
13	Me	Ph	Cl	A	CH_2	19	16	7	58	78
14	H	Ph	H	B	CO	44	15	12	29	91
15	H	Ph	Ph	A	CO	7	6	26	61	95
16	H	Ph	Ph	B	CO	12	4	41	43	86
17	H	Ar*	OMe	B	CH_2	--	--	30	70	66
18	H	Ph	CN	A	CO	--	--	35	65	62
19	H	Bn	Cl	C	CO	74	5	--	21	62
20	H	Bn	Ph	C	CO	28	--	32	40	90

Scheme 3. Diels–Alder reactions of pyrazinones **1** with ethyl vinyl ether (A), methyl acrylate (B), and the chiral dienophile **21** (C). *Ar=*p*-MeO–Ph

via bis-silylation of glutarimides.[15] 1,4-Oxazin-2-ones also react in a similar way.[16]

The position of the Y substituent in the various regio- and stereoisomers of type **a**–**d** was assigned by ^1H NMR spectroscopy, based on the characteristic coupling constant values observed for the bridgehead proton H1 and the bridge protons H7 and H8 (see Section 4). In the spectra of the reduced adducts **11–13** and **17** except for isomers of type **b**, this assignment was confirmed by an additional $^4J_{6,7}$ long range coupling. To validate further the criteria used for these structure assignments, a detailed 1D and 2D NMR analysis was carried out for the bis-lactam isomers **14a–d**. These compounds contain two angular protons H1 and H4, both of which display the characteristic-coupling pattern of bridgehead and bridge protons. Following chromatographic purification of the regioisomers **14a** and **14c** (**14b** and **14d** were isolated as a mixture), the compounds were subjected to 1D homonuclear decoupling and 2D NOESY experiments (Table 2).

For each of the four isomers, H4 is determined by its NOE crosspeak with the NH proton whereas H1 shows a NOE crosspeak with the *ortho* protons of the *N*-phenyl group. In the spectrum of **14a**, H4 shows a NOE with both the *exo* and *endo* protons H8 and H8′. H8 in turn only displays a NOE with the *exo* proton H7, which further gives a crosspeak with the *ortho* protons of the *N*-phenyl group, indicating that the ester group is in the *endo* position 7′. In the spectrum of **14c**, H1 gives a NOE with both H7′ and H7, whereas H7 shows a crosspeak with the *N*-phenyl *ortho* protons and a strong crosspeak with H8, revealing the 8′ position for the ester group. In the mixture **14b, c** the isomers **14b** and **14c** were characterised by their typical NOE and coupling pattern (Table 2). In **14b**, H4 shows a NOE crosspeak with both methylene protons H8 and H8′ and in **14d**, H1 gives a NOE to both H7 and H7′. From Table 2 we can conclude that each coupling constant has a typical value ($^3J_{7,8'}\cong5$ Hz; $^3J_{7,8}\cong10$ Hz; $^3J_{7',8'}\cong10$ Hz; $^3J_{7',8}\cong5$ Hz; $^3J_{1,7}\cong4$ Hz; $^3J_{1,7'}\cong2$ Hz; $^3J_{4,8}\cong2$ Hz; $^3J_{4,8'}\cong4$ Hz; $_3J_{NH,4}\cong$ 5 Hz; $^4J_{NH,1}\cong2$ Hz), which leads to a characteristic coupling pattern for each isomer. The diverging values found for the coupling between each bridgehead proton H1 and H4 and the bridge protons H7, H7′ and H8, H8′, respectively, provide ample support for the second criterion established above. In this case a different environment is created not

Table 2. The chemical shifts (δ, ppm) and coupling constants (Hz) of protons in **14a–d** ($CDCl_3$)

14		δ	$^2J_{7,7'}/^2J_{8,8'}$	$^3J_{7,8'}/^3J_{7',8'}$	$^3J_{7,8}/^3J_{7',8}$	$^3J_{1,7}/^3J_{1,7'}$	$^3J_{4,8}/^3J_{4,8'}$	$^3J_{NH,4}$	$^4J_{NH,1}/^4J_{NH,8}$
a	H_1	4.72				3.0			2.0
	H_4	4.20					2.0; 4.0	5.0	
	H_7	3.48		5.0	10.0	3.0			
	H_8	2.38	14.0		10.0		2.0		0.5
	$H_{8'}$	2.66	14.0	5.0			4.0		
b	H_1	4.76				2.0			2.0
	H_4	4.21					2.0; 4.0	5.0	
	$H_{7'}$	3.24		10.0	10.0	2.0			
	H_8	2.69	14.0				2.0		0.5
	$H_{8'}$	2.43	14.0	10.0	10.0		4.0		
c	H_1	4.47				2.0; 4.0			2.0
	H_4	4.54					2.0	5.0	
	H_7	2.62	15.0		10.0	4.0			
	$H_{7'}$	2.54	15.0		5.0	2.0			
	H_8	3.26			10.0; 5.0		2.0		–
d	H_1	4.43				–			–
	H_4	4.43					–	–	
	H_7	2.80	14.0	5.0		4.0			
	$H_{7'}$	2.29	14.0	10.0		2.0			
	$H_{8'}$	3.36		10.0; 5.0			4.0		

only by the NPh group for the coupling between H1 and the bridge protons H7, H7′, but also by the NH group for the analogous coupling between H4 and H8, H8′.

Asymmetric Diels–Alder reactions using (4S)-3-acryloyl-4-isopropyl-1-methyl-2-imidazolidinone **21** as a chiral dienophile were carried out for 1-benzyl-3,5-dichloro-2(1H)-pyrazinone **1g** and the corresponding 3-phenyl analogue **1h**. The adduct mixtures were then hydrolysed by heating with phosphate buffer (THF/H_2O, pH=5) or by exposing at the air, to form the more stable bis-lactams **19** and **20**, respectively. The latter were submitted to column chromatography followed by HPLC to separate the regio- and stereoisomers present. Due to the incorporation of the chiral auxiliary, eight isomers can be formed that are denominated as the four diastereomeric pairs **a1**, **a2** (7-*endo*), **b1**, **b2** (7-*exo*), **c1**, **c2** (8-*endo*), and **d1**, **d2** (8-*exo*). Although not all of these isomers could be isolated in pure form, the quantitative composition of the adduct mixtures could be reconstituted from the weight of the fractions isolated by HPLC combined with ^{1}H NMR analysis. The regio- and stereomeric structures could be assigned by using the ^{1}H NMR criteria described above except for the stereochemical differences in the isomeric pairs (**a**–**d**)**1** and (**a**–**d**)**2** induced by the chiral auxiliary.

The results assembled in Table 3 are in line with the regiomeric and *endo*, *exo*-stereomeric product distributions mentioned above for **11** and **16** (Scheme 3). The asymmetric induction found for the various modes of cycloaddition can be explained on the basis of a preferential approach of the chiral dienophile **21** with its large isopropyl group turned away from the plane of the azadiene reaction partner. As can be seen from Fig. 2 such induction should be weak for the 7-*endo*/*exo* isomers, since the isopropyl group meets only with a small H-substituent when approaching from the opposite side. However, for the 8-*endo* and 8-*exo* reactions a higher asymmetric induction can be expected on the basis of the larger size of the chloro and especially the phenyl substituent. This expectation is verified by the experiment, as seen from the 8:1 ratio for the 8-*exo* products obtained from the 3,5-dichloropyrazinone **1g** and the fact that only one 8-*endo* and one 8-*exo* isomer was isolated from the reaction of the 3-phenyl analogue **1h**. For compounds $\mathbf{a_{1,2}}$ a low ratio 1:1 or 2:1 has been observed.

3. Conclusions

The cycloaddition of double bond systems to 5-chloro-2(1*H*)-pyrazinones followed by hydrolysis or reduction of the adducts offers an interesting method for the generation of variously substituted 2,5-diazabicyclo[2.2.2]octane derivatives. The regio- and stereochemical structure was assigned by analysis of the coupling and NOE patterns in the ^{1}H NMR spectra. The regioselective character of this addition can be enhanced by introduction of strongly electron donating or electron withdrawing substituents in 3-position of the pyrazinone. In preliminary experiments using (4*S*)-4-isopropyl-1-methyltetrahydro-2*H*-imidazol-2-one as a chiral dienophile, a much higher asymmetric

Table 3. Regio- and diastereomeric product distribution observed for the adducts **19** and **20** obtained from the Diels–Alder reaction of **1g** and **1h** with the chiral dienophile **21**

	$\mathbf{a_{1,2}}$ (7-*endo*)	$\mathbf{b_{1,2}}$ (7-*exo*)	$\mathbf{c_{1,2}}$ (8-*endo*)	$\mathbf{d_{1,2}}$ (8-*exo*)
Yield **19** (%)	46	3	–	13
Ratio $(a–d)_1/(a–d)_2$	1:1	Not determined	–	8:1
Yield **20** (%)	25	–	29	36
Ratio $(a–d)_1/(a–d)_2$	2:1	–	1 isomer detected	1 isomer detected

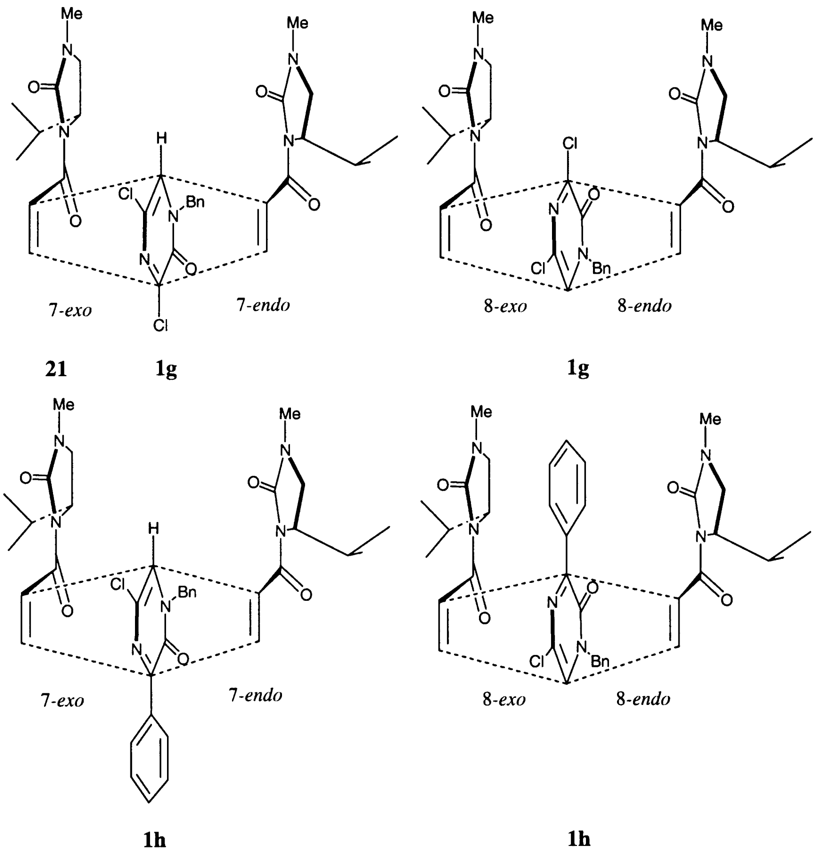


Figure 2. Model for the asymmetric induction for *endo* and *exo* Diels–Alder reactions of azadienes **1g** and **1h**. This model is based on a preferential approach of the chiral dienophile **21** with the large isopropyl group turned away from the azadiene. Also note the energetically favourable antiparallel orientation of the carbonyl groups.

induction was observed for the 8-substituted adducts as compared to the 7-regioisomers.

4. Experimental

Melting points were taken using a Reichert–Jung Thermovar apparatus and an Electrothermal IA 9000 digital melting point apparatus and are uncorrected. Infrared spectra were recorded on a Perkin–Elmer 297 grating IR spectrophotometer and a Perkin–Elmer 1720 Fourier transform spectrometer. Mass spectra were run using a Hewlett Packard MS-Engine 5989A apparatus for EI and CI spectra, and a Kratos MS50TC instrument for exact mass measurements performed in the EI mode at a resolution of 10,000. For the NMR spectra (δ, ppm) a Bruker WM-250, a Bruker AMX 400 (cmpds. **9**, **14**, **16b**, **19**, **20** and **21**) and a Bruker Avance 300 (cmpds **15**, **16a**, **c**, **d**) spectrometer were used. The 2D NOESY spectra in $CHCl_3$ were recorded with sweep widths of 5000 MHz in both dimensions, a mixing time of 1.5 s, 32 scans, 1024 datapoints in t_2 and 256 increments in t_1. Model calculations were carried out using the AM1 semi-empirical method of HyperChem™: Release 4.5, Hypercube. Analytical and preparative thin layer chromatography was carried out using Merck silica gel 60 PF-224, for column chromatography 70–230 mesh silica gel 60 (E.M. Merck) was used as the stationary phase. HPLC separations were carried out using a HIBAR column [Merck, cat. 151435] (cmpds **15** and **16**) or a Bio-Sil [BIORAD, Ref. 614-0183] (cmpds **19** and **20**).

4.1. Synthesis of 2(1*H*)-pyrazinones

The 2(1*H*)-pyrazinones **la**, **b** and **1e–g** were prepared as described previously.[1]

The 3-phenyl and 3-H substituted pyrazinones **1c**, **d** and **1h** were prepared via Pd-catalysed substitution of **1a** and **1g** according to procedures described previously.[17,18]

4.1.1. 5-Chloro-1-phenyl-2(1*H*)-pyrazinone 1c. Yield: 4%; yellow crystals, decomp. upon heating; IR (NaCl) cm^{-1}: 1672 (CO); ^1H NMR (DMSO): 8.10–7.57 (m, 7H, H3+H6+arom-H); ^{13}C NMR (DMSO): 154.1 (C_2), 148.6 (C_3), 138.3 (C_{ipso}), 129.1 (C_m), 129, 128.6 (C_6+C_p), 126.2 (C_o), 125.3 (C_5); *m*/*z*: 207 (M^+, 31), exact mass calcd for $C_{10}H_7N_2OCl$: 206.0247, found: 206.0271.

4.1.2. 5-Chloro-1,3-diphenyl-2(1*H*)-pyrazinone 1d. Yield: 83%; yellow crystals, mp 86–87°C; IR (KBr) cm^{-1}: 1664 (CO) ^1H NMR ($CDCl_3$): 8.42–7.56 (arom-H), 7.33 (s, 1H, H_6); ^{13}C NMR ($CDCl_3$): 154.0, 153.1 (C_2+C_3), 139.1, 134.7 (C_{ipso}), 130.9, 129.7, 129.5, 129.4, 128.1, 126.5, 125.9, 125.7 (arom-C+C_6); *m*/*z*: 282 (M^+, 7) exact mass calcd for $C_{16}H_{11}N_2OCl$: 282.0560, found: 282.0548.

4.1.3. 1-Benzyl-5-chloro-3-phenyl-2(1*H*)-pyrazinone 1h. Yield: 82%; see Ref. 1 for spectral and analytical data.

4.2. Addition of symmetric dienophiles

4.2.1. *endo*-1-Chloro-8-phenyl-8,10-diazatricyclo[5,2,2,0^{2,6}]-undecane-9,11-dione 7. A mixture of pyrazinone **1a** (400 mg, 1.6 mmol), 10 ml cyclopentene and 10 ml toluene was heated at 100°C in a sealed tube for four days. The solvent and dienophile were then removed under reduced pressure. The residue (compound **5**) was treated with a mixture of aqueous 1N NaOH/dioxane (30 ml) for 2 h. After 2 h the solvent was evaporated and the residue was dissolved in water. Following extraction of the aqueous layer with EtOAc, the organic layer was dried on magnesium sulphate, filtered and evaporated. The residue was purified on preparative plates (alumina, eluent=EtOAc) to afford 250 mg of compound **7**. Yield: 54%; white crystals, mp: 242–243°C; IR (KBr) cm^{-1}: 1700 (CO); ^{1}H NMR (DMSO-d$_6$): 9.7 (broad s, 1H, NH), 7.3 (m, 5H, Ar–H), 4.3 (d, J=4 Hz, 1H, H$_7$), 3.05 (dtd, J=10, 8, 4 Hz, 1H, H$_6$), 2.85 (dt, J=10, 7.5 Hz, 1H, H$_2$), 2.0–1.2 (m, 6H, H$_3$+H$_4$+H$_5$); ^{13}C NMR (DMSO-d$_6$): 168.5 (C$_{11}$), 165.1 (C$_9$), 139.1–123.7 (arom-C), 80.3 (C$_1$), 64.9 (C$_7$), 48.6 (C$_6$), 43.6 (C$_2$) 28.8, 27.4, 26.8 (C$_3$+C$_4$+C$_5$); *m/z*: 290 (M$^+$, 45), 254 (M$^+$−HCl, 8), 171 (M$^+$−PhNCO, 25), 143 (100); exact mass calcd for $C_{15}H_{15}N_2O_2Cl$: 290.0822; found: 290.0825.

4.2.2. *endo*-1-Chloro-4,8-diphenyl-4,8,10-triazatricyclo-[5,2,2,0^{2,6}]undecane-3,5,9,11-tetrone 8. A mixture of pyrazinone **1a** (400 mg, 1.6 mmol) and *N*-phenylmaleimide (1.1 g, 6.4 mmol) was heated at 100°C in 10 ml dry toluene for three days. The precipitate was isolated by filtration, and the crude adduct **6** was hydrolysed by stirring with a mixture of aqueous 1N NaOH/dioxane (30 ml) for 3 h. The residue was redissolved in water, the aqueous phase extracted several times with EtOAc, and the organic phase was dried on magnesium sulphate and evaporated. Crystallisation from toluene yielded 400 mg of compound **8**. Yield: 63%; white solid, mp: 330°C; IR (KBr) cm^{-1}: 1720–1710 (broad, CO); ^{1}H NMR (DMSO-d$_6$): 7.6–7.2 (m, 10H, arom-H), 4.73 (dd, 1H, H$_7$), 4.33 (dd, 1H, H$_6$), 3.99 (d, J=8.7 Hz, 1H, H$_2$), 2.5 (br. s, 1H, NH); ^{13}C NMR (DMSO-d$_6$): 171.7, 170.8 (C$_3$, C$_5$), 165.9 (C$_{11}$), 162.7 (C$_9$), 138.5–124.3 (arom-C), 76.8 (C$_1$), 62.0 (C$_7$), 49.2, 45.2 (C$_2$, C$_6$); *m/z*: 395 (M$^+$, 56), 248 (M$^+$−PhN(CO)$_2$, 100), 119 (PhNCO$^+$, 38), 101 (88); exact mass calcd for $C_{20}H_{14}N_3O_4Cl$: 395.0673; found: 395.0669.

4.2.3. *endo*-l-Chloro-8-phenyl-8,10-diazatricyclo[5.2.2.0^{2,6}]-undecane-9-one 9. A solution of compound **5** (see preparation of **7**) and 200 mg DABCO in 30 ml dry THF was shaken with 100 mg Pd/C 10% in a Parr hydrogenation apparatus for 12 h. After filtration of the catalyst and removal of the solvent, the residue was separated on preparative plates (silica gel, eluent=100% EtOAc) yielding 290 mg of compound **9**. Yield: 66%; white solid, mp: 136–137°C; IR (KBr) cm^{-1}: 3305 (NH), 1685 (NCO); ^{1}H NMR (CDCl$_3$):7.4–7.1 (m, 5H, arom-H), 3.9 (ddd, J=4,2, 1.5 Hz, 1H, H$_7$), 3.35 (dd, J=11, 1.5 Hz, 1H, H$_{11'}$), 3.15 (ddd, J=11.2, 1.5 Hz, 1H, H$_{11}$), 2.75 (m, 2H, H$_2$+H$_6$), 2.40 (broad s, 1H, NH), 2.2–1.4 (m, 6H, H$_3$+H$_4$+H$_5$); ^{13}C NMR (CDCl$_3$): 167.8 (C$_9$), 139.9–123.5 (arom-C), 84.7 (C$_1$), 58.2 (C$_7$), 48.7 (C$_6$), 44.1 (C$_{11}$), 43.3 (C$_2$), 28.5, 27.29, 26.5 (C$_3$+C$_4$+C$_5$); *m/z*: 276 (M$^+$, 32), 248 (M$^+$−CO, 45), 119 (PhNCO$^+$, 100); exact mass calcd. for $C_{15}H_{17}N_2OCl$: 276.1029; found: 276.1033.

4.2.4. *endo*-1-Chloro-4,8-diphenyl-4,8,10-triazatricyclo-[5,2,2,0^{2,6}]undecane-3,5,9-trione 10. A solution of adduct **6** (see preparation of **8**) and 200 mg DABCO in 30 ml dry THF was shaken with 100 mg Pd/C 10% in a Parr hydrogenation apparatus for 14 h. After filtration of the catalyst and evaporation of the solvent, recrystallisation from toluene gave 350 mg of compound **10**. Yield: 57%; white solid, mp: 268–269°C; IR (KBr) cm^{-1}: 3300 (NH), 1720 (N(CO)$_2$), 1685 (NCO); ^{1}H NMR: (see Table 1); ^{13}C NMR (DMSO-d$_6$): 174.0 and 172.6 (N(CO)$_2$), 163.8 (C$_9$), 139.7–124.5 (arom-C), 82.1 (C$_4$), 55.2 (C$_7$), 50.0 (C$_{11}$), 46.3 (C$_6$), 45.7 (C$_2$); *m/z*:381 (M$^+$, 35), 353 (M$^+$−CO, 100), 119 (PhNCO$^+$, 31), 91 (31); exact mass calcd for $C_{20}H_{16}N_3O_3Cl$: 381.0880; found: 381.0871.

4.3. Addition of asymmetric dienophiles

4.3.1. Methyl 4-chloro-3-oxo-2-phenyl-2,5-diazabicyclo[2.2.2]octane-7(8)-carboxylate 11. A solution of pyrazinone **la** (200 mg, 0.8 mmol) and methyl acrylate 2 ml in dry toluene 10 ml was heated at 80°C for five days. The solvent and excess methyl acrylate were removed under reduced pressure. Without delay, the residue then was dissolved in dry THF. Pd/C 10% and 100 mg DABCO were added and the mixture was shaken in a Parr hydrogenation apparatus for 5 h under a hydrogen pressure of 4 atm. After filtration of the catalyst, the solvent was evaporated. The residue was purified on preparative plates (silica gel, eluent=100% EtOAc) to afford **11** as two fractions consisting of a mixture of **11a**, **c** and **11b**, **d**, respectively (190 mg, total yield=81%).

Fraction 1: **11a**+**11c**. Yield: 36%; oil; IR (NaCl) cm^{-1}: 1730 (COOR), 1695 (NCO). ^{1}H NMR (CDCl$_3$) **11a**: 7.4–7.2 (m, 5H, arom-H), 4.46 (m, 1H, H$_1$), 3.75 (s, 3H, CH$_3$), 3.32 (m, 2H, H$_6$), 3.29 (m, 1H, H$_7$), 3.03 (dd, J=11, 6 Hz, 1H, H$_{8'}$), 2.60 (dd, J=14, 11.5 Hz, 1H, H$_8$); **11c**: 7.4–7.2 (m, 5H, arom-H), 4.2 (m, 1H, H$_1$), 3.8 (s, 3H, CH$_3$), 3.42 (m, 2H, H$_6$), 3.37 (m, 1H, H$_8$), 2.42 (dddd, J=11, 4, 2, 1 Hz, 1H, H$_7$), 2.26 (ddd, J=13.5, 5, 2 Hz, 1H, H$_{7'}$). ^{1}H NMR (C$_6$D$_6$) **11a**: 4.0 (m, 1H, H$_1$), 3.2 (s, 3H, CH$_3$), 2.94 (dd, J=11, 1.5 Hz, 1H, H$_{6'}$), 2.90 (dd, J=14, 6 Hz, 1H, H$_{8'}$), 2.57 (dddd, J=11.5, 6, 4, 2 Hz, 1H, H$_7$), 2.45 (ddd, J=11, 3.5, 2 Hz, 1H, H$_6$), 2.26 (dd, J=14, 11.5 Hz, 1H, H$_8$); **11c**: 3.25 (m, 1H, H$_1$), 3.08 (dd, J=11, 5 Hz, 1H, H$_8$), 2.85 (dd, J=11, 1.5 Hz, 1H, H$_{6'}$), 2.67 (dt, J=11, 3 Hz, 1H, H$_6$), 1.74 (ddd, J=13.5, 2 Hz, 1H, H$_{7'}$), 1.60 (dddd, J=13.5, 11, 4, 3 Hz, 1H, H$_7$). ^{13}C NMR (CDCl$_3$) **11a**: 171 (CO–ester), 166 (C$_3$), 139.6–123.6 (arom-C), 80.1 (C$_4$), 56.7 (C$_7$), 52.4 (CH$_3$), 45.6 (C$_6$), 43.7 (C$_1$), 37.5 (C$_8$); **11c**: 171 (CO–ester), 166 (C$_3$), 139.6–123.6 (arom-C), 81.8 (C$_4$), 54.9 (C$_8$), 52.4 (CH$_3$), 45.6 (C$_6$), 43.7 (C$_1$), 37.5 (C$_8$); *m/z* 294 (M$^+$, 55), 173 (M$^+$−PhNCO−2H, 72), 119 (PhNCO$^+$, 100); exact mass calcd for $C_{14}H_{15}N_2O_3Cl$: 294.0769; found: 294.0769.

Fraction 2: **11b**+**11d**. Yield: 45%; oil; IR (NaCl)

cm^{-1}:1730 (COOR), 1695 (NCO). ^1H NMR ($CDCl_3$) **11b**: 7.4–7.2 (m, 5H, arom-H), 4.6 (m, 1H, H_1), 3.6 (s, 3H, CH_3), 3.4 (m, 1H, H_6), 3.08 (m, 1H, $H_{7'}$), 2.94 (dd, 1H, H_8), 2.72 (dd, 1H, $H_{8'}$); **11d**: 7.4–7.2 (m, 5H, arom-H), 4.2 (m, 1H, H_1), 3.75 (s, 3H, CH_3), 3.6 (dd, J=10, 6.5 Hz, 1H, $H_{8'}$), 3.4 (ddd, 1H, H_6), 3.25 (dd, J=10, 1.5 Hz, 1H, $H_{6'}$), 2.3 (m, 2H, H_7+$H_{7'}$); ^1H NMR (C_6D_6) **11b**: 7.4–6.9 (m, 5H, arom-H), 4.0 (m, 1H, H_1), 3.4 (s, 3H, CH_3), 3.22 (dd, J=10, 1.5 Hz, 1H, $H_{6'}$), 2.9 (dd, J=14, 5 Hz, 1H, H_8), 2.45 (m, 1H, $H_{8'}$), 2.3 (ddd, J=11, 5, 2 Hz, 1H, $H_{7'}$) (H_6 is hidden under the spectrum of **11d**); **11d**: 7.4–6.9 (m, 5H, arom-H), 3.43 (dd, J=10, 5.5 Hz, 1H, $H_{8'}$), 3.4 (s, 3H, CH_3), 3.3 (m, 1H, H_1), 2.58 (ddd, J=10, 3, 3 Hz, 1H, H_6), 2.47 (dd, J=10, 1.5 Hz, 1H, $H_{6'}$), 1.85 (dddd, J=13, 6, 4, 3 Hz, 1H, H_7), 1.42 (ddd, J=13, 10, 2 Hz, 1H, $H_{7'}$). ^{13}C NMR ($CDCl_3$) **11b**: 171.6 (CO–ester), 165.0 (C_3), 140.0–124.1 (arom-C), 79.9 (C_4), 58.0 (C_7), 52.2 (CH_3), 48.8 (C_6), 43.3 (C_1), 37.3 (C_8); **11d**: 171.6 (CO–ester), 165.0 (C_3), 140.0–124.2 (arom-C), 81.6 (C_4), 54.6 (C_8), 52.3 (CH_3), 51.9 (C_1), 48.8 (C_6), 31.6 (C_7); *m/z*: 294 (M^+, 24), 173 (M^+−PhNCO–2H, 55), 119 ($PhNCO^+$, 100); exact mass calcd for $C_{14}H_{15}N_2O_3Cl$: 294.0971; found: 294.0783.

4.3.2. 4-Chloro-7(8)-ethoxy-2-phenyl-2,5-diazabicyclo-[2.2.2]octane-3-one 12.

A solution of 2(1*H*)-pyrazinone **1a** (200 mg, 0.8 mmol) and 1 ml ethyl vinyl ether in 2 ml dry toluene was heated at 110°C in a sealed tube overnight. The solvent and dienophile were then removed under reduced pressure. A solution of the residue and 100 mg DABCO in dry THF was shaken with 50 mg Pd/C 10% under a hydrogen pressure of 4 atm for 4 h. Following removal of the catalyst by filtration and evaporation of the solvent, the residue was purified on preparative plates (silica gel, eluent=100% EtOAc). Three fractions were isolated with a combined yield of 81% (190 mg).

Fraction 1: **12a**. Yield:18%; white solid, mp: 128–129°C; IR (KBr) cm^{-1}: 3320 (NH), 1690 (NCO); ^1H NMR ($CDCl_3$):7.4–7.2 (m, 5H, arom-H), 4.15 (ddd, J=3.5, 3.5, 1.25 Hz, 1H, H_1), 4.0 (dddd, J=9, 3.5, 4, 1.5 Hz, 1H, H_7), 3.7 (dd, J=11, 1.5 Hz, 1H, $H_{6'}$), 3.55 (dq, J=7, 2.5 Hz, 1H, CH_2CH_3), 3.5 (dq, J=7, 2.5 Hz, 1H, CH_2CH_3), 3.2 (ddd, J=11, 3.5, 1.5 Hz, 1H, H_6), 2.7 (dd, J=14, 9 Hz, 1H, H_8), 2.6 (broad s, 1H, NH), 2.4 (dd, J=14, 4 Hz, 1H, $H_{8'}$), 1.2 (t, J=7 Hz, 3H, CH_3); ^{13}C NMR ($CDCl_3$): 167.3 (C_3), 140.0–123.8 (arom-C), 80.4 (C_4), 73.5 (C_7), 64.8 (CH_2CH_3), 57.7 (C_1), 43.1, 43.0 (C_6+C_8), 15.2 (CH_3); *m/z*: 280 (M^+, 2), 159 (M^+−PhNCO–2H, 30), 119 ($PhNCO^+$, 100), 77 (60); exact mass calcd for $C_{14}H_{17}N_2O_2Cl$: 280.0979; found: 280.0983.

Fraction 2: **12c**. Yield: 12%; oil; IR (NaCl) cm^{-1}: 3325 (NH), 1700 (NCO); ^1H NMR ($CDCl_3$): 7.4–7.2 (m, 5H, arom-H), 4.2 (dddd, J=4, 3.25, 2.5, 2.5 Hz, 1H, H_1), 3.9 (dd, J=9, 2.5 , 1H, H_8), 3.8 (dq, J=7, 2.5 Hz, 1H, CH_2CH_3), 3.37 (dd, J=11, 2.5 Hz, 1H, $H_{6'}$), 3.32 (ddd, J=11, 4, 1 Hz, 1H, H_6), 2.9 (broad s, 1H, NH), 2.6 (dddd, J=14, 9, 3.25, 1 Hz, 1H, H_7), 1.9 (ddd, J 14, 2.5, 2.5 Hz, 1H, $H_{7'}$), 1.3 (t, J=7 Hz, 3H, CH_3); ^{13}C NMR ($CDCl_3$): 165.7 (CO), 139.6–123.5 (arom-C), 85.2 (C_4), 76.5 (C_8), 67.4 (CH_2CH_3), 54.5 (C_1), 48.0 (C_6), 36.7 (C_7), 15.4 (CH_3); *m/z*: 280 (M^+, 12), 208 (41), 159 (M^+− PhNCO–2H, 21), 119 ($PhNCO^+$, 100), 77 (36); exact mass calcd for $C_{14}H_{17}N_2O_2Cl$: 280.0977; found: 280.0973.

Fraction 3: **12b**+**12d**. Yield: 51%; IR (NaCl) cm^{-1}: 3295 (NH), 1695 (NCO). ^1H NMR ($CDCl_3$) **12b**: 7.4–7.2 (m, 5H, arom-H), 4.2 (m, 1H, H_1), 3.85 (ddd, J=8.5, 2.5, 2.5 Hz, 1H, $H_{7'}$), 3.75 (dq, J=7, 2.5 Hz, 1H, CH_2CH_3), 3.43 (dq, J=7, 2.5 Hz, 1H, CH_2CH_3), 3.10 (m, 2H, H_6), 2.82 (dd, J=14, 8.5 Hz, 1H, $H_{8'}$), 2.7 (broad s, 1H, NH), 2.25 (dd, J=14, 2.5 Hz, 1H, H_8), 1.2 (t, 3H, CH_3); **12d**: 7.4–7.2 (m, 5H, arom-H), 4.2 (m, 1H, H_1), 4.0 (dd, J=8, 2.5 Hz, 1H, $H_{8'}$), 3.73 (qd, J=7, 2.5 Hz, 1H, CH_2CH_3), 3.6 (dq, J=7, 2.5 Hz, 1H, CH_2CH_3), 3.30 (m, 2H, H_6), 2.7 (broad s, 1H, NH), 2.34 (ddd, J=14, 8, 2 Hz, 1H, $H_{7'}$), 2.08 (dddd, J=14, 3.5, 3, 2.5 Hz, 1H, H_7). ^{13}C NMR ($CDCl_3$) **12b**: 166.7 (C_3), 140.6–125.0 (arom-C), 79.9 (C_4), 74.6 (C_7), 63.6 (CH_2CH_3), 58.6 (C_1), 45.1, 44.6 (C_6+C_8), 15.0 (CH_3); **12d**: 165.2 (CO), 140.1–124.0 (arom-C), 84.1 (C_4), 81.2 (C_8), 66.2 (CH_2CH_3), 54.8 (C_1), 48.8 (C_6), 36.3 (C_7)115.2 (CH_3); *m/z*: 280 (M^+, 12), 208 (17), 159 (M^+−PhNCO–2H, 29), 119 ($PhNCO^+$, 100), 77 (45); exact mass calcd for $C_{14}H_{17}N_2O_2Cl$: 280.0979; found: 280.0983.

4.3.3. 4-Chloro-7(8)-ethoxy-1-methyl-2-phenyl-2,5-diazabicyclo[2.2.2]octane-3-one 13.

Compounds **13** were prepared using the method described for **12** (183 mg, total yield=78%).

Fraction 1: **13a**+**13c**. Yield:20%; oil; IR (NaCl) cm^{-1}: 1690 (NCO). ^1H NMR ($CDCl_3$) **13a**: 7.5–7.0 (m, 5H, arom-H), 3.7 (dq, J=9, 7 Hz, 1H, CH_2CH_3), 3.65 (m, 1H, H_7), 3.6 (d, J=11 Hz, 1H, $H_{6'}$), 3.45 (dq, J=9, 7 Hz, 1H, CH_2CH_3), 2.95 (dd, J=11, 2 Hz, 1H, H_6), 2.73 (dd, J=13.5, 9 Hz, 1H, H_8), 2.43 (dd, J=13, 3.5 Hz, 1H, $H_{8'}$), 1.2 (t, 3H, CH_2CH_3), 0.97 (s, 3H, CH_3); **13c**: 7.5–7.0 (m, 5H, arom-H), 3.95 (dd, J=10, 3 Hz, 1H, H_8), 3.90 (d, J=12 Hz, 1H, $H_{6'}$), 3.65 (m, 1H, H_6), 2.5 (m, 1H, H_7), 1.8 (dd, J=13, 2 Hz, 1H, $H_{7'}$), 1.27 (t, 3H, CH_2CH_3), 1.05 (s, 3H, CH_3). ^{13}C NMR ($CDCl_3$) **13a**: 168.5 (C_3), 136.9–128.3 (arom-C), 80.4 (C_4), 78.1 (C_7), 65.2 (CH_2CH_3), 61.0 (C_1), 50.0 (C_6), 43.1 (C_8), 18.5 (CH_3), 15.2 (CH_2CH_3); **13c**: 169.5 (C_3), 136.4–128.6 (arom-C), 84.8 (C_4), 80.1 (C_8), 67.2 (CH_2CH_3), 58.9 (C_6), 55.9 (C_1), 43.2 (C_7), 22.0 (CH_3), 15.4 (CH_2CH_3); *m/z*: 294 (M^+, 20), 258 (M^+−HCl, 47), 229 (258-Et, 44), 213 (258-OEt, 69), 173 (M^+−PhNCO–2H, 69), 133 (100); exact mass calcd for $C_{15}H_{19}N_2O_2Cl$: 294.1135; found: 294.1154.

Fraction 2: **13b**+**13d**. Yield: 58%; oil; IR (NaCl) cm^{-1}: 3290 (NH), 1690 (NCO). ^1H NMR ($CDCl_3$) **13b**: 7.4–7.1 (m, 5H, arom-H), 3.7 (hidden dd, 1H, H_6), 3.55 (dd, J=8, 2 Hz, 1H, $H_{7'}$), 3.4 (m, 2H, CH_2CH_3), 3.05 (d, J=8 Hz, 1H, $H_{6'}$), 2.8 (dd, J=14, 8 Hz, 1H, $H_{8'}$), 2.6 (broad s, 1H, NH), 2.3 (dd, J=14, 2 Hz, 1H, H_8), 1.28 (t, 3H, CH_2CH_3), 1.0 (s, 3H, CH_3); **13d**: 7.4–7.1 (m, 5H, arom-H), 4.0 (dd, J=8, 2 Hz, 1H, $H_{8'}$), 3.77 (dq, J=10, 7 Hz, 1H, CH_2CH_3), 3.68 (dq, J=10, 7 Hz, 1H, CH_2CH_3), 3.15 (dd, J=10, 3 Hz, 1H, H_6), 2.98 (d, J=10 Hz, 1H, $H_{6'}$), 2.6 (broad s, 1H, NH), 2.32 (dd, J=13.5, 8 Hz, 1H, $H_{7'}$), 1.95 (ddd, J=13.5, 3, 2 Hz, 1H, H_7), 1.2 (t, 3H, CH_2CH_3), 1.0 (s, 3H, CH_3). ^{13}C NMR ($CDCl_3$) **13b**: 167.9 (C_3), 137.3–127.9 (arom-C), 80.1 (C_4), 78.5 (C_7), 63.8 (CH_2CH_3), 60.7 (C_1), 52.2 (C_6), 44.1(C_8), 18.7 (CH_3), 15.2 (CH_2CH_3); **13d**: 166.2 (C_3), 137.3–127.9 (arom-C), 84.3 (C_4), 80.6 (C_8), 65.9 (CH_2CH_3), 57.3 (C_1), 55.4 (C_6), 43.7 (C_7), 21.6 (CH_3), 15.2 (CH_2CH_3); *m/z*: 294 (M^+, 34), 258 (M^+−HCl, 20), 222 (100), 213 (258-OEt, 33), 133 (62); exact mass calcd for $C_{15}H_{19}N_2O_2Cl$: 294.1133; found:. 294.1140.

4.3.4. Methyl 3,6-dioxo-2-phenyl-2,5-diazabicyclo[2.2.2]-octane-7(8)-carboxylate 14. The same reaction conditions were used as described for compounds **11** (reaction time=5 days). The products underwent spontaneous hydrolysis when exposed to the air and were purified on preparative plates (silica gel, eluent=50% EtOAc/CH_2Cl_2). Yield: 91%; oil; IR (NaCl) cm^{-1}: 1735 (CO–ester), 1704 (NCO). ^1H NMR ($CDCl_3$) **14a**: 7.2–7.5 (m, 5H, arom-H), 7.2 (broad s, 1H, NH), 4.72 (dd, J=3, 2 Hz, 1H, H_1), 4.2 (m, 1H, H_4), 3.77 (CH_3), 3.48 (ddd, J=10, 5, 3 Hz, 1H, H_7), 2.66 (ddd, J=14, 5, 4 Hz, 1H, $H_{8'}$), 2.38 (ddd, J=14, 10, 2 Hz, 1H, H_8); **14b**: 7.2–7.5 (m, 5H, arom-H), 7.1 (broad s, 1H, NH), 4.76 (t, J=2 Hz, 1H, H_1), 4.2 (m, 1H, H_4), 3.56 (CH_3), 3.24 (hidden ddd, 1H, $H_{7'}$), 2.67 (hidden ddd, 1H, H_8), 2.43 (ddd, J=15, 11, 4 Hz, 1H, $H_{8'}$); **14c**: 7.2–7.5 (m, 5H, arom-H), 6.9 (broad s, 1H, NH), 4.54 (dd, J=5, 2 Hz, 1H, H_4), 4.47 (m, 1H, H_1), 3.78 (CH_3), 3.26 (hidden ddd, 1H, H_8), 2.62 (ddd, J=15, 10, 4 Hz, 1H, H_7), 2.54 (ddd, J=15, 5, 2 Hz, 1H, $H_{7'}$); **14d**: 7.2–7.5 (m, 5H, arom-H), 7.2 (broad s, 1H, NH), 4.42 (m, 2H, H_1+H_4), 3.79 (CH_3), 3.36 (ddd, J=10, 5, 4 Hz, 1H, $H_{8'}$); 2.80 (ddd, J=14, 5, 4 Hz, 1H, H_7), 2.29 (ddd, J=14, 10, 2 Hz, 1H, $H_{7'}$). ^{13}C NMR **14a**: 170.5, 168.8, 168.2 (CO), 123.7–138.8 (arom-H), 63.9, 55.0 (C_1, C_4), 52.9 (CH_3), 42.7 (C_7), 28.34 (C_8); **14b**: 171.1, 170.7, 167.1 (CO), 123.7–138.8 (arom-H), 64.6, 57.6 (C_1, C_4), 52.6 (CH_3), 41.21 (C_7), 28.29 (C_8); **14c**: 170.9, 170.2, 168.0 (CO), 123.7–138.8 (arom-H), 62.3, 57.6 (C_1,C_4), 52.9 (CH_3), 41.24 (C_8), 28.1 (C_7); **14d**: 171.2, 170.8, 166.0 (CO), 123.7–138.8 (arom-H), 62.1, 57.4 (C_1,C_4), 52.9 (CH_3), 43.4 (C_8), 27.5 (C_7), *m/z*: 274 (M^+, 100), 229 (M^+−NCO–H_2, 13), 215 (M^+−CO_2Me, 11); exact mass calcd for $C_{14}H_{14}N_2O_4$: 274.0954; found: 274.0952.

4.3.5. 7(8)-Ethoxy-2,4-diphenyl-2,5-diazabicyclo[2.2.2]-octane-3,6-dione 15. The same reaction conditions were used as described for compounds **12** (reaction time=21 days). The products underwent spontaneous hydrolysis when exposed to the air and were purified on preparative plates (silica gel, eluent=50% EtOAc/CH_2Cl_2). Total yield: 95% (256 mg). Further separation on preparative HPLC (silica gel, eluent=40% EtOAc/CH_2Cl_2) yielded four fractions.

Fraction 1: **15a**. Yield: 6.5%; oil, IR (NaCl) cm^{-1}:3244 (NH), 1702 (NCO); ^1H NMR ($CDCl_3$): 7.5–7.2 (m, 10H, arom-H), 6.49 (s, 1H, NH), 4.71 (dd, 1H, J=4, 2 Hz, H_1), 4.41 (ddd, 1H, J=8.5, 4, 3 Hz, H_7), 3.76, 3.59 (2×dq, 2H, J=8, 7 Hz, CH_2CH_3), 2.98 (dd, 1H, J=13.5, 8.5 Hz, H_8), 2.44 (dd, 1H, J=13.5, 3 Hz, $H_{8'}$), 1.25 (t, 3H, CH_3); ^{13}C NMR: 168.8 (C_3, C_6), 139.2 (NC_{ipso}), 134.7 (C_4C_{ipso}), 129.2, 128.8, 127.3, 126.8, 124.1 (arom-C), 74.3, 64.1 (C_1, C_7), 65.7 (C_8), 65.3 (C_4), 37.9 (CH_2CH_3), 15.2 (CH_3); *m/z*: 336 (M^+, 27), 264 (M^+−CH_2CHCO_2Me, 100), 215 (M^+−PhNCO–H_2, 72), 172 (M^+−PhNCO–EtOH, 56), 133 (M^+−PhNCO–CH_2CH_2OEt, 50); exact mass calcd for $C_{20}H_{20}N_2O_3$: 336.1474; found: 336.1471.

Fraction 2: **15c**. Yield: 25%; white solid, mp: 223°C; IR (NaCl) cm^{-1}: 3224 (NH), 1699 (NCO). ^1H NMR ($CDCl_3$): 7.5–7.2 (m, 10H, arom-H), 6.71 (s, 1H, NH), 4.55 (m, 1H, H_1), 4.49 (dd, 1H, J=8, 2 Hz, H_8), 3.57, 3.36 (2×dq, 2H, J=9, 7 Hz, CH_2CH_3), 2.84 (ddd, 1H, J=14, 8, 4 Hz, H_7), 2.18 (dt, 1H, J=14, 2 Hz, $H_{7'}$), 1.08 (t, 1H, J=7 Hz, CH_3); ^{13}C NMR: 170.9, 167.6 (C_3, C_6), 138.9 (NC_{ipso}), 133.2 (C_4C_{ipso}), 129.1, 128.5, 128.4 127.5, 126.6, 123.6 (arom-C), 75.2, 61.4 (C_1, C_8), 69.7 (C_4), 65.3 (C_7), 34.6 (CH_2CH_3), 15.1 (CH_3); *m/z*: 336 (M^+, 77), 264 (M^+−CH_2CH_2OEt, 100), 215 (M^+−PhNCO–H_2, 34), 20 (M^+−PhNCO–EtOH, 83), 133 (M^+−PhNCO–CH_2CH_2OEt, 56); exact mass calcd for $C_{20}H_{20}N_2O_3$: 336.14739; found: 336.1471.

Fraction 3: **15b**. Yield: 5.5%; oil, IR (NaCl) cm^{-1}: 3242 (NH), 1704 (NCO); ^1H NMR ($CDCl_3$): 7.5–7.3 (m, 10H, arom-H), 6.42 (s, 1H, NH), 4.66 (t, 1H, J=2 Hz, H_1), 4.27 (dt, 1H, J=9, 3 Hz, $H_{7'}$), 3.51 (m, 2H, CH_2CH_3), 2.94 (dd, 1H, J=14, 9 Hz, $H_{8'}$), 2.44 (dd, 1H, J=14, 3 Hz, H_8), 1.17 (t, 3H, J=7 Hz, CH_3); ^{13}C NMR: 170.0, 168.2 (C_3, C_6), 139.9 (NC_{ipso}), 134.6 (C_4C_{ipso}), 129.2, 129.0, 128.8, 127.1, 126.8, 125.1 (arom-C), 74.3, 66.0 (C_1, C_7), 64.7 (C_8), 63.7 (C_4), 38.5 (CH_2CH_3), 15.1 (CH_3); *m/z*: 336 (M^+, 7), 264 (M^+−CH_2CH_2OEt, 100), 46 (M^+−PhNCO–CH_2CH_2OEt, 46); exact mass calcd for $C_{20}H_{20}N_2O_3$: 336.1474; found: 336.1472.

Fraction 4: **15d**. Yield: 58%; white solid, mp: 173°C, IR (NaCl) cm^{-1}: 3242 (NH), 1708 (NCO). ^1H NMR ($CDCl_3$): 7.7–7.2 (m, arom-H), 6.36 (s, H, NH), 4.49 (m, 1H, H_1), 4.41 (dd, 1H, J=2, 8 Hz, $H_{8'}$), 3.62, 3.45 (2×dq, 2H, J=9, 7 Hz, CH_2CH_3), 2.51 (ddd, 1H, J=14, 8, 2 Hz, $H_{7'}$), 2.32 (ddd, 1H, J=14, 4, 2 Hz, H_7), 1.18 (t, 3H, J=7 Hz, CH_3); ^{13}C NMR: 170.9, 166.8 (C_3, C_6), 139.5 (NC_{ipso}), 134.0 (C_4C_{ipso}), 129.1, 128.8, 128.4, 128.3, 126.6, 124.6 (arom-C), 77.8, 61.6 (C_1, C_8), 66.0 (C_4), 65.1 (C_7), 32.6 (CH_2CH_3), 15.1 (CH_3); *m/z*: 336 (M^+, 6), 264 (M^+−CH_2CH_2OEt, 100), 133 (M^+−PhNCO–CH_2CH_2OEt, 48); exact mass calcd for $C_{20}H_{20}N_2O_3$: 336.1474; found: 336.1469.

4.3.6. Methyl 3,6-dioxo-2,4-diphenyl-2,5-diazabicyclo-[2.2.2]octane-7(8)-carboxylate 16. The same reaction conditions were used as described for compounds **11** (reaction time=6 days). The products underwent spontaneous hydrolysis when exposed to the air. The isomeric distribution was determined by NMR analysis of the mixture obtained following purification on preparative plates (silica gel, eluent=50% EtOAc/CH_2Cl_2). Total yield: 241 mg, 86%. Further separation using preparative HPLC (silica gel, eluent=40% EtOAc / CH_2Cl_2) yielded three fractions.

Fraction 1: **16a**. Yield: 10%; oil, IR (NaCl) cm^{-1}: 3244.1 (NH), 1738 (CO–ester), 1705 (NCO). ^1H NMR ($CDCl_3$): 7.6–7.3 (m, 10H, arom-H), 6.27 (s, 1H, NH), 4.86 (m, 1H, H_1), 3.64 (dt, J=10, 5, 3.5 Hz, H_7), 3.80 (s, 3H, CH_3), 3.10 (dd, J=13, 5 Hz, 1H, $H_{8'}$), 2.82 (dd, J=13, 10 Hz, 1H, H_8). ^{13}C NMR: 170.4, 168.7, 168.0 (CO), 138.8 (NC_{ipso}), 134.5 (C_4C_{ipso}), 124.0, 126.9, 127.4, 128.8, 129.3, 129.4 (arom-C), 63.8 (C_4), 63.7 (C_1), 53.1 (CH_3), 43.2 (C_7), 32.2 (C_8), *m/z*: 350 (M^+, 29), 229 (M^+−PhNCO–H_2, 100), 190 (M^+−MeAcr–Ph, 25), 172 (M^+−PhNCO–CO_2Me, 80), 144 (M^+−PhNCO–MeAcr–H, 22); exact mass calcd. for $C_{20}H_{18}N_2O_4$: 350.1267; found: 350.1260.

Fraction 2: **16b**+**16c**. Yield: 39%; oil, IR (NaCl) cm^{-1}:

3230 (NH), 1738 (CO–ester), 1704 (NCO). **16b**: ^{1}H NMR ($CDCl_3$) 7.45–7.2 (arom-H), 6.67 (s, 1H, NH), 4.84 (m, 1H, H_1), 3.54 (s, 3H, CH_3), 3.32 (ddd, J=10.5, 4.5, 2 Hz, 1H, $H_{7'}$), 3.10 (dd, J=13.5, 4 Hz, 1H, H_8), 2.66 (dd, J=13.5, 10.5 Hz, 1H, $H_{8'}$); ^{13}C NMR 171.0, 170.3, 168.4 (CO), 139.1 (NC_{ipso}), 134.4 (C_4C_{ipso}), 129.1, 129.0, 128.9, 128.5, 127.3, 124.3 (arom-H), 63.9 (C_4), 64.3 (C_1), 52.5 (CH_3), 41.5 (C_7), 29.5 (C_8), **16c**: 7.22–7.44 (arom-H), 7.00 (s, 1H, NH), 4.63 (m, 1H, H_1), 3.74 (dd, J=10, 4.5 Hz, 1H, H_8), 3.52 (s, 3H, CH_3), 2.89 (ddd, J=14, 10.5, 4 Hz, 1H, H_7), 2.38 (ddd, J=14, 4.5, 2 Hz, 1H, $H_{7'}$), ^{13}C NMR 171.0, 170.4, 167.2 (CO), 138.9 (NC_{ipso}), 133.2 (C_4C_{ipso}), 129.2, 128.8, 128.7, 126.8, 126.5, 123.8 (arom-H), 66.7 (C_4), 62.0 (C_1), 52.4 (CH_3), 44.4 (C_8), 31.3 (C_7) *m*/*z*: 350 (M^+), 229 (M^+−PhNCO–H_2, 31), 203 (M^+−MeAcr–Ph, 43), 172 (M^+−PhNCO–CO_2Me, 28), 144 (M^+−PhNCO–MeAcr–H, 76); exact mass calcd for $C_{20}H_{18}N_2O_4$: 350.1267; found: 350.1267.

Fraction 3: **16d**. Yield: 37%; oil, IR (NaCl) cm^{-1}: 3230 (NH), 1734 (CO–ester), 1704 (NCO). ^{1}H NMR ($CDCl_3$) 7.7–7.4 (m, 10H, arom-H), 6.34 (s, 1H, NH), 4.54 (m, 1H, H_1), 3.70 (dd, J=9, 6.5 Hz, 1H, $H_{8'}$), 3.66 (CH_3), 2.56 (m, 2H, H_7+$H_{7'}$); ^{13}C NMR: 172.0, 170.6, 166.3 (CO), 139.2 (NC_{ipso}), 133.7 (C_4C_{ipso}), 129.2, 128.7, 127.8, 126.9, 124.9 (arom-C), 64.6 (C_4), 61.4 (C_1), 52.6 (CH_3), 48.5 (C_8), 30.2 (C_7) *m*/*z*: 350 (M^+, 100), 264 (M^+−MeAcr, 13), 231 (M^+−PhNCO, 55), 172 (M^+−PhNCO–MeAcr, 11), 144 (M^+−PhNCO–MeAcr–H, 87); exact mass calcd. for $C_{20}H_{18}N_2O_4$: 350.1267; found: 350.1264.

4.3.7. Methyl 4-methoxy-2-(4-methoxyphenyl)-3-oxo-2,5-diazabicyclo[2.2.2]octane-8-carboxylate 17.

The same reaction conditions were used as described for compounds **11** (reaction time=4 days, total yield: 168 mg, 66%).

Fraction 1: **17c**. Yield: 20%; oil; IR (NaCl) cm^{-1}: 3300 (NH), 1735 (CO–ester), 1695 (NCO); ^{1}H NMR ($CDCl_3$): 7.3, 6.9 (m, 4H, arom-H), 4.0 (m, 1H, H_1), 3.8, 3.75 (s+s, 6H, CH_3OAr, CH_3OC), 3.6 (s, 3H, CH_3OCO), 3.4 (m, 2H, H_6), 3.2 (dd, J=11.5, 5.5 Hz, 1H, H_8), 2.35 (m, 1H, H_7), 2.1 (ddd, J=13.5, 5.5 Hz; 1H, $H_{7'}$). ^{13}C NMR ($CDCl_3$) 173.8 (CO–ester), 169.2 (C_3), 156.8, 132.4, 125.1, 114.4 (arom-C), 86.5 (C_4), 55.5, 55.3 (CH_3OAr, CH_3OC), 52.7, 52.1 (CH_3OCO, C_8), 47.2 (C_6), 45.6 (C_1), 30.5 (C_7); *m*/*z*: 320 (M^+, 9), 292 (M^+−CO, 49), 169 (M^+−ArNCO–2H, 13), 149 ($ArNCO^+$, 100); exact mass calcd for $C_{16}H_{20}N_2O_5$: 320.1372; found: 320.1365.

Fraction 2: **17d**. Yield: 46%; oil; IR (NaCl) cm^{-1}: 3300 (NH), 1735 (CO–ester), 1690 (NCO). ^{1}H NMR ($CDCl_3$) 7.35, 6.9 (m, 4H, arom-H), 4.0 (m, 1H, H_1), 3.8, 3.75 (s+s, 6H, CH_3OAr, CH_3OC), 3.6 (s, 3H, CH_3OCO), 3.35 (dd, J=10, 5 Hz, 1H, H_8), 3.35 (m, 1H, H_6), 3.2 (dd, J 11.5, 1.5Rz, 1H, $H_{6'}$), 2.35 (m, 1H, H_7), 2.15 (ddd, J=13, 10, 2 Hz, 1H, $H_{7'}$). ^{13}C NMR ($CDCl_3$) 172.3 (CO–ester), 167.9 (C_3), 158.0, 133.1, 126.0, 114.4 (arom-C), 85.8 (C_4), 55.4, 54.6 (CH_3OAr, CH_3OC), 52.3, 51.1 (CH_3OCO, C_8), 47.6 (C_6), 47.0 (C_1), 30.8 (C_7); *m*/*z*: 320 (M^+, 11), 292 (M^+−CO, 82), 149 ($ArNCO^+$, 100); exact mass calcd for $C_{16}H_{20}N_2O_5$: 320.1372; found: 320.1366.

4.3.8. 4-Cyano-7(8)-ethoxy-2-phenyl-2,5-diazabicyclo-[2.2.2]octane-3-one 18.

The same method was used as described for compound **12**. Hydrolysis was carried out by stirring in a mixture of dioxane/0.1N NaOH (yield: 141 mg, 62%).

Fraction 1: **18c**. Yield: 22%; white solid; mp: 168°C; IR (NaCl) cm^{-1}: 1670 (broad, NCO). ^{1}H NMR (DMSO-d_6) 10.2 (broad s, 1H, NH), 7.4–7.2 (m, 5H, arom-H), 4.51 (dd, J=8.5, 2 Hz, 1H, H_8), 4.5 (m, 1H, H_1), 3.7 (q, 2H, $CH_2$$CH_3$), 2.9 (ddd, J=14, 8.5, 4 Hz, 1H, H_7), 1.8 (ddd, J=14, 2, 2 Hz, 1H, $H_{7'}$), 1.2 (t, 3H, CH_3). ^{13}C NMR (DMSO-d_6) 168.4 (C_6), 161.8 (C_3), 138.0–123.8 (arom-C), 113.4 (CN), 75.4 (C_4), 65.5 ($CH_2$$CH_3$), 62.7 en 61.2 ($C_1$+$C_8$), 33.2 ($C_7$), 15.1 ($CH_3$); *m*/*z*: 285 ($M^+$, 14), 213 ($M^+$−EtOCHC$H_2$, 100), 165 (20), 133 (47); exact mass calcd for $C_{15}H_{15}N_3O_3$: 285.1113; found: 285.1107.

Fraction 2: **18d**. Yield: 40%; white solid; mp: 77°C; IR (NaCl) cm^{-1}: 1670 (broad, NCO). ^{1}H NMR ($CDCl_3$) 8.25 (broad s, 1H, NH), 7.5–7.3 (m, 5H, arom-H), 4.4 (dd, J=8, 2 Hz, 1H, $H_{8'}$), 3.8 (qd, 2H, $CH_2$$CH_3$), 2.54 (ddd, J=14, 8, 2 Hz, 1H, $H_{7'}$), 2.2 (ddd, J=14, 4, 2 Hz, 1H, H_7), 1.25 (t, 3H, CH_3). ^{13}C NMR ($CDCl_3$) 169.2 (C_6), 160.7 (C_3), 138.1–124.2 (arom-C), 113.4 (CN), 78.1 (C_4), 67.2 ($CH_2$$CH_3$), 61.0, 60.9 ($C_1$+$C_8$), 33.0 ($C_7$), 15.1 ($CH_3$); *m*/*z*: 285 ($M^+$, 14), 213 ($M^+$−EtOCHC$H_2$, 100), 165 (22), 133 (51); exact mass calcd for $C_{15}H_{15}N_3O_3$: 285.1113; found: 285.1108.

4.3.9. 5-Benzyl-1-chloro-7/8-[(5-isopropyl-3-methyl-2-oxo-1-imidazolidinyl)carbonyl]-2,5-diazabicyclo[2.2.2]octane-3,5-dione 19.

A mixture of 0.1 mol of 2-imidazolidinone **21** and 1.2 equiv. of pyrazinone **1g** was dissolved in dry toluene. The reaction mixture was heated at reflux temperature during six days. Following removal of the solvent, the residue was heated with a phosphate buffer (THF/H_2O, pH=5) at reflux temperature until completion of the hydrolysis (control via MS) After evaporation of the solvent the residue was redissolved in water and extracted three times with EtOAc. The organic phase was dried ($MgSO_4$), filtered and evaporated. The crude product was purified by column chromatography (silica gel, eluent=3% MeOH/97% EtOAc), followed by further separation using HPLC. Total yield: 62%. Each fraction showed similar IR and mass spectra. IR (NaCl) cm^{-1}: 3400.1 (NH), 1709 (CO-aux.), 1648 (CON); *m*/*z*: 432 (M^+, 26); 397 (M^+−Cl, 32); 341 (M^+−C_7H_7, 36); 305 (M^+−HCl–C_7H_7, 19); 227 (M^+−$C_8H_{13}N_2O_2$–HCl, 10); 91 ($C_7H_7^+$, 100); exact mass calcd for $C_{21}H_{25}N_4O_4Cl$: 432.1564; found:432.1562.

Fraction 1: **19a$_1$**+**19a$_2$**. Yield: 46%. ^{1}H NMR ($CDCl_3$) **19a$_1$** 7.3–7.2 (m, 5H, arom-H), 6.95 (s, 1H, NH), 5.04 (d, 1H, J=15 Hz, CH_2Ph), 4.55 (ddd, 1H, J=11, 5, 3 Hz, H_7), 4.55 (d, 1H, J=15 Hz, CH_2Ph), 4.30 (dd, 1H, J=3, 2 Hz, H_1), 4.27 (m, 1H, H_5-aux.), 3.39 (dd, 1H, J=10, 9 Hz, H_4-aux.), 3.14 (dd, 1H, J=13, 5 Hz, $H_{8'}$), 3.12 (dd, 1H, J=9, 5 Hz, H_4-aux.), 2.88 (s, 3H, N–CH_3), 2.40 (dd, 1H, J=13, 11 Hz, H_8), 2.29 (m, 1H, CH(*i*-Pr)), 0.85, 0.75 (2×d, 6H, J=7 Hz, CH_3(*i*-Pr)), **19a$_2$** 7.62 (s, 1H, NH); 7.3–7.2 (m, 5H, arom-H), 4.97 (d, 1H, J=15 Hz, CH_2Ph), 4.57 (ddd, 1H, J=11, 5, 3 Hz, H_7), 4.34 (d, 1H, J=15 Hz, CH_2Ph), 4.23 (m, 1H, H_5-aux.), 4.12 (dd, 1H, J=3, 2 Hz, H_1), 3.37 (dd, 1H, *J*=10, 9 Hz, H$_4$-aux.), 3.10 (dd, 1H, *J*=10, 3 Hz, H$_4$-aux.), 2.98 (dd, 1H, *J*=13, 5 Hz, H$_{8'}$), 2.84 (s, 3H, N–CH$_3$), 2.57 (dd, 1H, *J*=13, 11 Hz, H$_8$), 2.36 (m, 1H, CH(*i*-Pr)), 0.85, 0.74 (2×d, 6H, *J*=7 Hz, CH$_3$(*i*-Pr)). ^{13}C NMR (CDCl$_3$) **19a**$_1$ 168.3, 166.7, 165.9 (CO), 154.5 (C$_2$-aux.), 135.5 (C$_{ipso}$), 128.8, 128.1, 128 (arom-C), 75.4 (C$_4$), 62.4 (C$_1$), 55.6 (C$_5$-aux.), 49.5 (CH$_2$Bn), 44.3 (C$_4$-aux.), 42.9 (C$_7$), 37.9 (C$_8$), 30.4 (N–CH$_3$), 28.4 (CH(*i*-Pr)), 17.8, 14.2 (CH$_3$(*i*-Pr)), **19a**$_2$ 168.6, 167.7, 165.9 (CO), 154.5 (C$_2$-aux.), 135.3 (C$_{ipso}$), 128.7, 128.1 (arom-C), 75.3 (C$_4$), 60.9 (C$_1$), 55.6 (C$_5$-aux.), 49.2 (CH$_2$Bn), 43.9 (C$_4$-aux.), 42.7 (C$_7$), 37.9 (C$_8$), 30.3 (N–CH$_3$), 28 (CH(*i*-Pr)), 17.8, 14.1 (CH$_3$(*i*-Pr)).

Fraction 2: **19b**$_1$. Yield: 3%, ^{1}H NMR (CDCl$_3$) 7.3–7.2 (m, 5H, arom-H); 6.39 (s, 1H, NH), 5.27 (d, 1H, *J*=15 Hz, C*H*$_2$Ph), 4.37 (ddd, 1H, *J*=6, 5, 1 Hz, H$_{7'}$), 4.28 (m, 1H, H$_5$-aux.), 4.27 (dd, 1H, *J*=2, 1 Hz, H$_1$), 4.05 (d, 1H, *J*=15 Hz, CH$_2$Ph), 3.40 (dd, 1H, *J*=10, 9 Hz, H$_4$-aux.), 3.17 (dd, 1H, *J*=10, 2.5 Hz, H$_4$-aux.), 2.98 (dd, 1H, *J*=13, 5 Hz, H$_8$), 2.87 (s, 3H, N–CH$_3$), 2.62 (dd, 1H, *J*=13, 6 Hz, H$_{8'}$), 2.35 (m, 1H, (CH(*i*-Pr)), 0.93, 0.79 (2×d, 6H, ^{3}*J*=7 Hz, CH$_3$(*i*-Pr)).

Fraction 3: **19d**$_1$+**19d**$_2$. Yield: 13%. ^{1}H NMR (CDCl$_3$) **19d**$_1$ 7.3 (m, 5H, arom-H), 6.40 (s, 1H, NH), 5.29 (dd, 1H, *J*=11, 5 Hz, H$_{8'}$), 4.89, 4.53 (2×d, 2H, *J*=15 Hz, CH$_2$Ph), 4.34 (m, 1H, H$_5$-aux.), 3.87 (m, 1H, H$_1$), 3.35 (dd, 1H, *J*=10, 9 Hz, H$_4$-aux.), 3.17 (dd, 1H, *J*=9, 5 Hz, H$_4$-aux.), 2.87 (s, 3H, N–CH$_3$), 2.47 (m, 1H, CH(*i*-Pr)), 2.30 (ddd, 1H, *J*=13, 11, 2 Hz, H$_{7'}$), 2.00 (ddd, 1H, *J*=13, 5, 4 Hz, H$_7$), 0.91, 0.83 (2×d, 6H, *J*=7 Hz, CH$_3$(*i*-Pr)). **19d**$_2$ 7.3 (m, 5H, arom-H), 6.34 (s, 1H, NH), 5.09 (dd, 1H, *J*=11, 5 Hz, H$_{8'}$), 4.99, 4.39 (2×d, 2H, *J*=15 Hz, CH$_2$Ph), 4.34 (m, 1H, H$_5$-aux.), 3.89 (m, 1H, H$_1$), 3.45 (dd, 1H, *J*=10, 9 Hz, H$_4$-aux.), 3.11 (dd, 1H, *J*=9, 3 Hz, H$_4$-aux.), 2.87 (s, 3H, N–Me), 2.45 (ddd, 1H, *J*=13, 11, 2 Hz, H$_{7'}$), 2.36 (m, 1H, CH(*i*-Pr)), 1.88 (ddd, 1H, *J*=13, 5, 4 Hz, H$_7$), 0.90, 0.72 (2×d, 6H, *J*=7 Hz, CH$_3$(*i*-Pr)); ^{13}C NMR (CDCl$_3$): sample too diluted.

4.3.10. 5-Benzyl-7/8-[(5-isopropyl-3-methyl-2-oxo-1-imidazolidinyl)carbonyl]-1-phenyl-2,5-diazabicyclo[2.2.2]-octane-3,6-dione 20. The same reaction conditions were used as described for compounds **12**. The product isomers **20** were separated using column chromatography (silica gel, eluent=3% MeOH/97% EtOAc), followed by further separation using HPLC. Total yield: 90%. Each fraction showed similar IR and mass spectra. IR (NaCl) cm^{-1}:3291 (NH); 1698 (CO-aux., CON); *m*/*z*: 474 (M$^+$, 63); 383 (M$^+$−C$_7$H$_7$, 11); 339 (M$^+$−C$_7$H$_7$NCO–2H, 100); 241 (M$^+$−C$_7$H$_{14}$N$_2$O–C$_7$H$_7$, 38); 172 (M$^+$−C$_8$H$_{13}$N$_2$O$_2$–C$_7$H$_7$NCO, 72); 91 (C$_7$H$_7^+$, 94); exact mass calcd for C$_{27}$H$_{30}$N$_4$O$_4$: 474.2267; found: 474.2262.

Fraction 1: **20d**$_1$. Yield: 36%, ^{1}H NMR (CDCl$_3$) 7.5–7.25 (m, 10H, arom-H), 6.15 (s, 1H, NH), 5.12 (d, 1H, *J*=15 Hz, CH$_2$Ph), 5.09 (dd, 1H, *J*=11, 5 Hz, H$_{8'}$), 4.36 (d, 1H, *J*=15 Hz, CH$_2$Ph), 0.66 (d, 3H, *J*=7 Hz, CH$_3$(*i*-Pr)), 4.12 (m, 1H, H$_5$-aux.), 3.98 (m, 1H, H$_1$), 3.15 (dd, 1H, *J*=10, 9 Hz, H$_4$-aux.), 2.98 (dd, 1H, *J*=10, 3 Hz, H$_4$-aux.), 2.71 (s, 3H, N–CH$_3$), 2.51 (ddd, 1H, *J*=13.5, 11, 4 Hz, H$_{7'}$), 2.28 (m, 1H, CH(*i*-Pr)), 1.90 (ddd, 1H, *J*=13.5, 5, 4 Hz, H$_7$), 0.85, 0.66 (2×d, 6H, *J*=7 Hz, CH$_3$(*i*-Pr)). ^{13}C NMR (CDCl$_3$) 171.2, 168.5 (CO), 154.1 (C$_2$-aux.), 134.6, 136.4 (C$_{ipso}$), 127.8–128.7 (arom-C), 63.7 (C$_4$), 58.3 (C$_1$), 55.4 (C$_5$-aux.), 48.9 (C$_4$-aux.), 48.2 (C$_8$), 44.0 (CH$_2$Bn), 30.8 (C$_7$), 30.2 (N–CH$_3$), 28.4 (CH(*i*-Pr)), 17.9, 14.7 (CH$_3$(*i*-Pr).

Fraction 2: **20a**$_1$+**20a**$_2$. Yield: 25%; ^{1}H NMR (CDCl$_3$) **20a**$_1$ 7.5–7.25 (m, 10H, arom-H), 6.31 (s, 1H, NH), 4.99 (d, 1H, *J*=15 Hz, CH$_2$Ph), 4.68 (ddd, 1H, *J*=10, 5, 3 Hz, H$_7$), 4.36 (d, 1H, *J*=15 Hz, CH$_2$Ph), 4.21 (m, 2H, H$_1$+H$_5$-aux.), 3.35 (dd, 1H, *J*=9.5, 8, H$_4$-aux.), 3.13 (dd, 1H, *J*=8, 6 Hz, H$_4$-aux.), 2.95 (dd, 1H, *J*=13, 5 Hz, H$_{8'}$), 2.86 (s, 3H, N–Me), 2.70 (dd, 1H, *J*=13, 10 Hz, H$_8$), 2.38 (m, 1H, CH(*i*-Pr)), 0.85, 0.76 (2×d, 6H, *J*=7 Hz, CH$_3$(*i*-Pr)). **20a**$_2$ 7.4–7.25 (m, 10H, arom-H), 6.38 (s, 1H, NH), 4.77 (d, 1H, *J*=15 Hz, CH$_2$Ph), 4.67 (m, 1H, H$_7$), 4.40 (m, 1H, H$_1$), 4.36 (d, 1H, *J*=15 Hz, CH$_2$Ph), 4.28 (m, 1H, H$_5$-aux.), 3.39 (dd, 1H, *J*=10, 9 Hz, H$_4$-aux.), 3.14 (dd, 1H, *J*=10, 3 Hz, H$_4$-aux.), 3.10 (dd, 1H, *J*=13, 6.5 Hz, H$_{8'}$), 2.88 (s, 3H, N–Me), 2.50 (dd, 1H, *J*=13, 10 Hz, H$_8$), 2.29 (m, 1H, CH(*i*-Pr)), 0.84, 0.79 (2×d, 6H, *J*=7 Hz, CH$_3$(*i*-Pr)). ^{13}C NMR (CDCl$_3$) **20a**$_1$ 170.7, 169.7 169.1, (CO), 154.6 (C$_2$-aux.), 136.1, 135.2 (C$_{ipso}$), 127.2–128.9 (arom-C); 63.4 (C$_4$), 61.3 (C$_1$), 55.7 (C$_5$-aux.), 48.7 (C$_4$-aux.), 44.1 (CH$_2$Bn); 42.9 (C$_7$), 33.7 (C$_8$), 30.4 (N–CH$_3$), 28.2 (CH(*i*-Pr)); 17.9, 14.3 (2×d, 3H, *J*=7 Hz, CH$_3$(*i*-Pr)). **20a**$_2$ sample too diluted.

Fraction 3: **20c**$_1$. Yield: 29%, ^{1}H NMR (CDCl$_3$): 7.4–7.25 (m, 10H, arom-H); 6.68 (s, 1H, NH), 5.05 (dd, 1H, *J*=11, 5 Hz, H$_8$), 4.89 (m, 1H, H$_5$-aux.), 4.70, 4.50 (d, 2H, *J*=15 Hz, CH$_2$Ph), 4.02 (m, 1H, H$_1$), 3.10 (dd, 1H, *J*=10, 9 Hz, H$_4$-aux.), 2.95 (dd, 1H, *J*=10, 3 Hz, H$_4$-aux.), 2.80 (s, 3H, N–CH$_3$), 2.64 (ddd, 1H, *J*=13.5, 11, 4 Hz, H$_7$), 2.17 (m, 1H, CH(*i*-Pr)), 1.95 (ddd, 1H, *J*=13.5, 5, 4.5 Hz, H$_{7'}$), 0.74, 0.64 (2×d, 6H, *J*=7 Hz, CH$_3$(*i*-Pr)); ^{13}C NMR (CDCl$_3$): sample too diluted.

4.3.11. (4*S*)-3-Acryloyl-4-isopropyl-1-methyl-2-imidazolidinone 21. To *N*-methylvalinamine (0.1 mol)—prepared by reduction of *N*-methylvalinamide[19]—was added 1.1 equiv. of diphenyl carbonate and 1.1 equiv. of K$_2$CO$_3$. The reaction mixture was stirred for 6 h at 110°C. After cooling to rt, the reaction products were dissolved in 100 ml of MeOH and the solution was heated at reflux temperature during 1 h. Following removal of the solvent, the mixture was extracted three times with EtOAc. The combined organic layers were washed two times with NaOH (2 M) and once with HCl (1 M). The organic layers were dried (MgSO$_4$) and the solvent was removed under reduced pressure. The crude (5*S*)-5-isopropyl-3-methyl-2-imidazolidinone was purified by column chromatography (silica gel, EtOAc).

To a solution of 0.1 mol of **21** in dry THF was added 1.1 equiv. of *n*-BuLi (1.6 M in hexane) at −30°C. After 15 min 1.1 equiv. of freshly distilled acryloyl chloride was added dropwise. The mixture was stirred at rt for 19 h. Following addition of water, the mixture was extracted three times with CH$_2$Cl$_2$ and the combined organic layers were dried on MgSO$_4$. After filtration and removal of the solvent, the crude product was purified by column chromatography (silica gel, eluent=10% EtOAc/90% CH$_2$Cl$_2$). Overall yield: 13%; oil; IR (NaCl; cm^{-1}): 1731 (CO-2);

1689 (CO-1′); 1620 (C═C). ^{1}H NMR ($CDCl_3$) 7.65 (dd, 1H, J=17, 11 Hz, $H_{2'}$), 6.45 (dd, 1H, J=17, 2.5 Hz, $H_{3'}$), 5.75 (dd, 1H, J=11, 2.5 Hz, $H_{3''}$), 4.48 (ddd, 1H, J=10, 4, 3 Hz, H_5), 3.42 (dd, 1H, J=10, 9 Hz, H_4), 3.16 (dd, 1H, J=9, 3 Hz, H_4), 2.44 (m, 1H, CH(*i*-Pr)), 2.87 (s, 3H, N–CH_3), 0.93, 0.81 (2×d, 6H, J=7 Hz, CH_3(*i*-Pr)). ^{13}C NMR ($CDCl_3$): 161.8 ($C_{1'}$), 156.9 (C_2), 147.4 ($C_{3'}$), 126.5 ($C_{2'}$), 54.2 (C_5), 45.3 (C_4), 35.1 (N–Me), 26.6 (CH(*i*-Pr)), 19.9, 19.0 (CH_3(*i*-Pr)); *m*/*z*: 196 (M^+, 9), 181 (M^+−Me, 10); 153 (M^+−*i*-Pr, 14); 55 ($C_2H_3CO^+$, 100); 43 (*i*-Pr^+, 28); exact mass calcd. for $C_{10}H_{16}N_2O_2$ (M^+): 196.1212; found: 196.1212.

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