JOURNAL OF PHYSICAL ORGANIC CHEMISTRY
J. Phys. Org. Chem. 2002; **15:** 590–598
Published online in Wiley InterScience (www.interscience.wiley.com). DOI: 10.1002/poc.493

Thermal and hyperbaric addition of *N,N*- and *N,O*-binucleophiles on cycloalkylidenic bromo esters†

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Received 16 November 2001; revised 30 January 2002; accepted 6 February 2002

ABSTRACT: The thermal and high-pressure (11 kbar) induced reaction between 2-bromo-2-(cycloalkylidene)acetates and *N,O*- and *N,N*-binucleophiles (such as ethylenediamines or aminoethanols) provides morpholin-2-ones and piperazin-2-ones. Thus, in contrast to simple primary amines, binucleophiles do not form spirocyclic derivatives. The expected Michael addition competes with a cascade reaction consisting of a migration of the double bond followed by the substitution of the newly established allylic halogen and a lactonization (lactamization), and eventually ended by a back-migration of the double bond. Copyright © 2002 John Wiley & Sons, Ltd.

KEYWORDS: high pressure; hetero-Michael addition; cascade reaction; migration

INTRODUCTION

The activation of organic reactions relies most of the time on two very general methods, heat and catalysis, and, occasionally, photochemistry. Ultrasound, microwaves or high pressure (the so-called 'extreme' conditions) can also, in special circumstances, offer a helpful alternative to the classical techniques.[1] The latter is particularly well suited to cases where bulky or fragile reagents/products are needed and can therefore become helpful in solving problems encountered along complex synthetic pathways.[2]

In this context, we have recently been interested in the applications of the high pressure-promoted hetero-Michael addition of amines to tri- or tetrasubstituted electron-deficient olefins. The effect of high pressure on the (hetero) Michael addition is very well known and has long been exploited. The large negative activation volume value associated with these reactions leads not only to their spectacular acceleration but also to a dramatic increase in their regio- and stereoselectivities.[3] α-Halo-α,β-unsaturated carbonyl compounds are good substrates for these reactions and, as such, constitute a class of simple building blocks in the synthesis of biologically important heterocycles and natural analogs of interest owing to their multifunctional reactivity.[4] The hetero-Michael addition provides efficiently and with good diastereoselectivities the corresponding β-amino esters, which are good templates for pseudo-peptide chemistry, for instance.[5] Interestingly, the presence of a leaving group at the α-position of the ester triggers a direct spiroaziridination.[6] The possibilities opened up by this reaction for the construction of other spiroheterocycles prompted us to investigate the use of binucleophiles.[7] In principle, these can undergo a conjugated addition of their amino group, leading to an intermediate α-halo-β-amino ester that could cyclize through an intramolecular nucleophilic substitution (Fig. 1).

In such a strategy, primary amines can become troublesome since they are likely to add and then

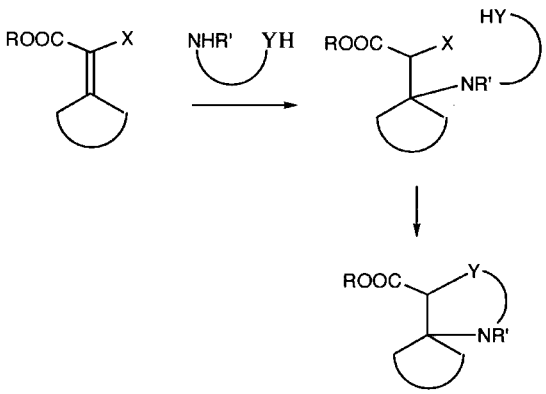

Figure 1

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†Presented at the 8th European Symposium on Organic Reactivity (ESOR-8), Cavtat (Dubrovnik), Croatia, September 2001.
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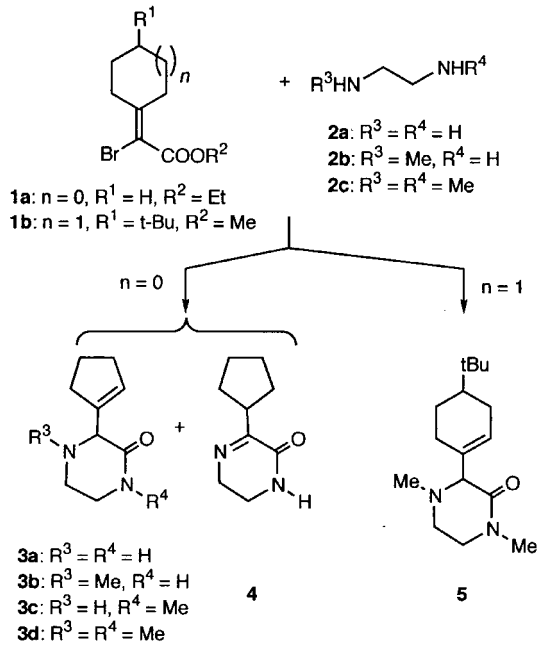
Contract/grant sponsor: Conseil Régional de Haute-Normandie.



Scheme 1

substitute the halogen, yielding the corresponding spiroaziridines, as previously established in various cases.[6] On the other hand, secondary amines are known to be poor nucleophiles in conjugated additions, at least under thermal conditions.[5a] We therefore examined both thermal and hyperbaric versions of this reaction and present our results here.

RESULTS AND DISCUSSION

We first considered ethylenediamine (**2a**), the simplest diamine, that was reacted with ethyl cyclopentylidenebromoacetate (**1a**), a substrate known to undergo the conjugate addition,[6b] in the presence of 1 equiv. of triethylamine (Scheme 1 and Table 1). At reflux of ethanol and at atmospheric pressure, no spiropiperazine was observed; instead, a mixture of cyclopentenylpiperazinone (**3a**) and cyclopentyldihydropirazinone (**4**) was recovered in mediocre yields (entry 1). The primary product is probably formed in a sequence of reactions in which the double bond first deconjugates to an endocyclic position, yielding an allylic bromine, rapidly substituted by the amine; the second amino group would then convert the ester intramolecularly into a lactam. The back-migration of the double bond into its original exocyclic position leads to a secondary enamine, tautomer of the cyclic imine (**4**). Under 11 kbar, in the same solvent but at room temperature and after 3.5 days, the same piperazinone (**3a**) is obtained in a better yield of 52% (entry 2), without any isomerization into **4**. Thus, the final migration of the double bond appears to be favored by a temperature increase or to be slowed by pressure. We next decided to examine the case of a primary/secondary diamine, resorting to *N*-methylethylenediamine (**2b**). The corresponding regioisomeric piperazinones (**3b,c**) were obtained in higher yields, under both thermal and hyperbaric conditions (entries 3 and 4). The selectivity of the addition was relatively high (>85%) and, expectedly, in favor of a quicker substitution of the allylic bromine by the secondary (more nucleophilic) amine. We finally moved to *N,N′*-dimethylethylenediamine (**2c**). At reflux of ethanol the same sequence of reactions takes place, providing **3d** in fair yield (entry 5). Similarly, the reaction between **2c** and the corresponding six-membered ring substrate methyl cyclohexylidenebromoacetate (**1b**) gave, in methanol, the *N,N*-dimethylpiperazinone **5** (entry 6).

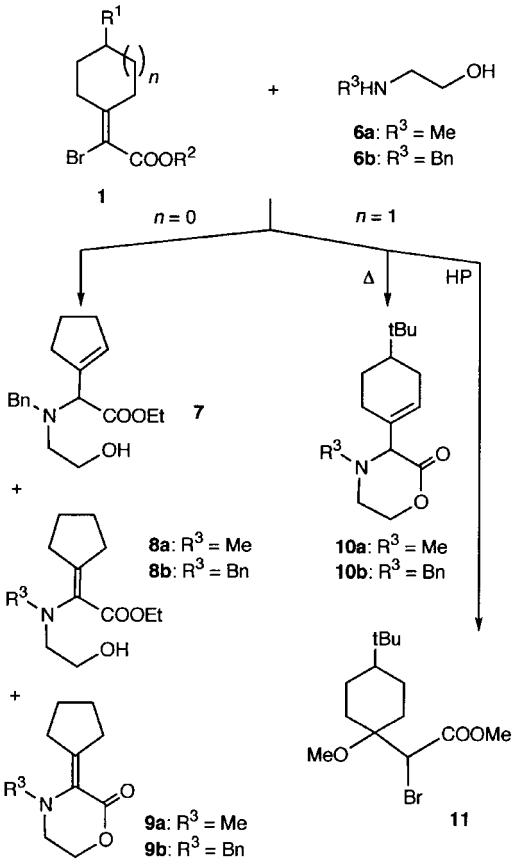
Thus, the high pressure-induced spiroaziridination of bromo esters **1**, observed previously with various primary amines in alcohols, appears to strongly depend on the structure of the amine, the nucleophilic and basic properties of the diamines entering in competition in this case.

We next considered aminoethanols **6** as possible binucleophiles, in an attempt to take advantage of an eventual concerted proton transfer from the hydroxyl proton during the hetero-Michael step (the importance of this proton transfer step was clearly emphasized in Ref. 5c). The reaction was first performed between ester **1a** and *N*-methylaminoethanol (**6a**) under similar thermal (refluxing ethanol, 1 equiv NEt_3) or hyperbaric (11 kbar, EtOH, room temperature) conditions. In both cases, the deconjugation–substitution–reconjugation sequence occurred, providing the cyclopentylidenic 1,3-

Table 1. Thermal and/or hyperbaric reaction between esters **1** and diamines **2** (chromatographic yields)

Entry	Ester	Amine	Conditions[a]	Products (yield, %)
1	**1a**	**2a**	EtOH, 80 °C, 1 bar, 24 h	**3a** (24) + **4** (18)
2	**1a**	**2a**	EtOH, RT, 11 kbar, 86 h	**3a** (56)
3	**1a**	**2b**	EtOH, 80 °C, 1 bar, 24 h	**3b** (54) + **3c** (9)
4	**1a**	**2b**	EtOH, RT, 11 kbar, 43 h	**3b** (62) + **3c** (9)
5	**1a**	**2c**	EtOH, 80 °C, 1 bar, 24 h	**3d** (53)
6	**1b**	**2c**	MeOH, 75 °C, 1 bar, 168 h	**5** (71)

[a] RT = room temperature.



Scheme 2

dihydro-[1,4]oxazinone (**9a**) in fair to good yields (Scheme 2 and Table 2, entries 1 and 2). In the high-pressure process, the final lactonization step was incomplete and about 10% amino alcohol **8a** was recovered (entry 2), in a comparable 70% overall yield. Replacing the *N*-methyl by an *N*-benzylaminoethanol (**6b**) changed only the base-catalyzed double bond migration step. Hence, entry 3 shows that under conditions identical with those of entry 1, a quasi-equimolar mixture of oxazinone **9b** and its unconjugated (and unlactonized) precursor **7b** is obtained. Actually, the products ratio is much less influenced by the nitrogen substituent under high pressure (entry 4). In the hyperbaric case, replacing triethylamine by a second equivalent of **5b** is also of little consequence (entry 5), while replacing methanol by a 9:1 mixture of methylene chloride (DCM) and tert-butyl alcohol (to combine a very fluid solvent and a non-nucleophilic proton donor) inhibits the reaction (entry 6). Interestingly, in this last case, *N*-benzyloxazolidine, probably resulting from the side-condensation of DCM and **6b** under high pressure, was isolated in 15% yield (with respect to **6b**).The critical influence of methanol on this reaction, which has been emphasized before,[5b,c,6] is once more obvious in this case.

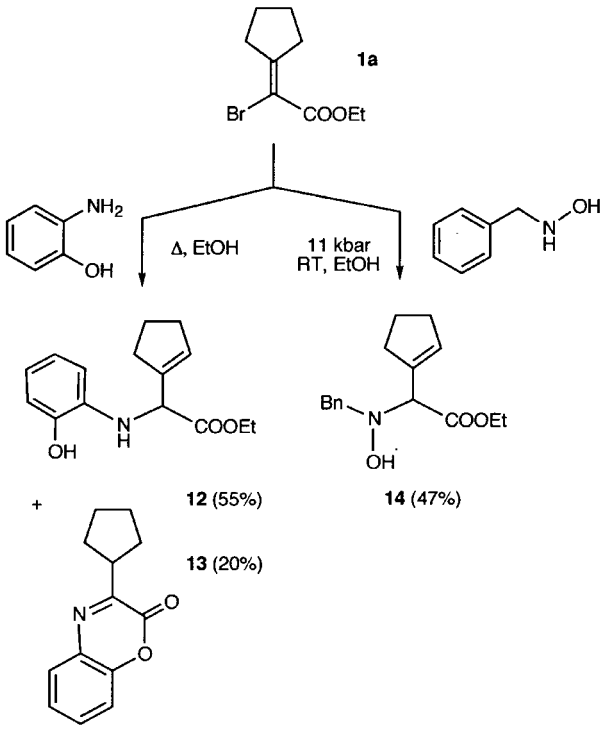
Finally, the sensitivity of this reaction to the ester structure was also evaluated, repeating the experiments of entries **1** and **2** on bromo ester **1b**. The thermal reaction (in methanol to avoid transesterification) gives access to the cyclohexenylic 1,3-dihydro-[1,4]oxazinone **10**, the six-membered ring stabilizing the endocyclic double bond (entry 7). By contrast, in the hyperbaric version **1b** undergoes a conjugate addition of methanol and provides the methyl ether **11** (entry 8), as already observed with other secondary amines.[6a] Replacing this solvent by DCM leads to **10** only in very low yields, almost 80% of the starting material being recovered after 48 h at 11 kbar (entry 9). This suggests that neither a concerted nor an intermolecular proton transfer from the hydroxyl group of the amino alcohol takes place efficiently.

This study on amino alcohols was completed by varying the nucleophilicity/electrophilicity of the partners. First, 2-aminophenol, a known inhibitor of tyrosinase,[8] was heated in refluxing ethanol with **1a** and triethylamine. Despite its lower nucleophilicity, this aniline reacts as the aminoethanols **5** do, providing amino ester **12** along with the corresponding benzoxazinone **13** in 55 and 20% yield, respectively (Scheme 3). The very nucleophilic *N*-benzylhydroxylamine[9] was also reacted with **1a**. Under high pressure, the same reaction suite as above takes place and the double bond remains

Table 2. Thermal and/or hyperbaric reaction between esters **1** and aminoethanols **6** (chromatographic yields)

Entry	Ester	Amine (equiv.)	Conditions	Products (yield, %)
1	**1a**	**6a** (1)	EtOH, NEt_3, 80 °C, 1 bar, 24 h	**9a** (71)
2	**1a**	**6a** (1)	EtOH, NEt_3, RT, 11 kbar, 48 h	**8a** (12) + **9a** (57)
3	**1a**	**6b** (1)	EtOH, NEt_3, 80 °C, 1 bar, 24 h	**7** (25) + **9b** (30)
4	**1a**	**6b** (1)	EtOH, RT, NEt_3, 11 kbar, 72 h	**8b** (4) + **9b** (66)
5	**1a**	**6b** (2)	EtOH, RT, 11 kbar, 72 h	**8b** (11) + **9b** (53)
6	**1a**	**6b** (2)	CH_2Cl_2, *t*-BuOH, RT, 11 kbar, 96 h	**9b** (4)[a]
7	**1b**	**6a** (1)	MeOH, NEt_3, 75 °C, 1 bar, 56 h	**10a** (72)
8	**1b**	**6a** (1)	MeOH, NEt_3, RT, 11 kbar, 64 h	**11** (39)[b]
9	**1b**	**6a** (1)	CH_2Cl_2, NEt_3, RT, 11 kbar, 48 h	**10a** (13)[c]

[a] Together with 87% starting material **1a** and 15% *N*-benzyloxazolidine.
[b] Together with 21% starting material **1b**.
[c] Together with 78% starting material **1b**.

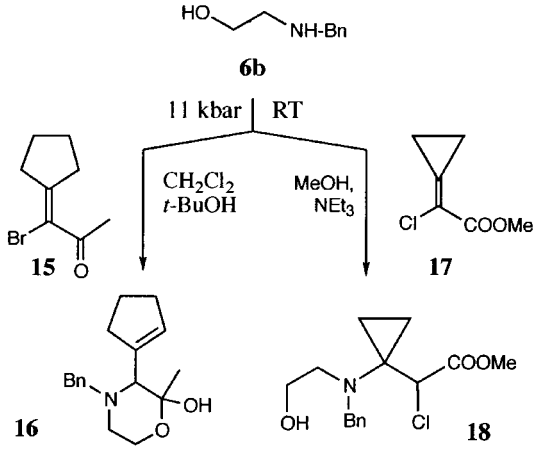


Scheme 3

intracyclic, yielding the α-hydroxyamino ester **14** (47%) (Scheme 3).

Increasing the electrophilicity of the substrate was another way of boosting the reactivity. We thus considered the α,β-unsaturated bromoketone **15**, prepared following the route described for **1**.[6] When reacted with *N*-benzylaminoethanol **6b** under high pressure (Scheme 4), this bromoketone undergoes the deconjugation–substitution described above. Surprisingly in this case, the intramolecular addition of the alcohol to the ketone leads to a perfectly stable hemiacetal, viz. cyclopentenylmethylmorpholinol (**16**), in 75% yield (and with a high diastereoselectivity of about 10:1). The strained 2-chloro-2-cyclopropylidene acetate **17**, a useful building block extensively studied by de Meijere and co-workers,[10] could also be considered as an activated substrate for a conjugated addition.[11] Reacting this compound with aminoethanol **6b** under our hyperbaric conditions finally provides the expected α-chloro-β-amino ester **18** that did not lactonize (Scheme 4). However, the yield was moderate (40%) and several unidentified side-products were also obtained.

In conclusion to this part, it appears that the amino alcohols behave similarly to diamines in this reaction, giving similar products under thermal and hyperbaric conditions. A deconjugation–substitution sequence, eventually followed by a back-migration of the double bond to an exocyclic position and by a final lactonization step, occurs in most cases. Only with the highly activated chlorocyclopropylidene acetate **17** could the hetero-



Scheme 4

Michael addition of benzylaminoethanol be observed, in low yield.

We finally decided to swap the order of the steps, according to the strategy depicted in Fig. 2. An α,β-dibromo ester could first undergo a nucleophilic substitution in the α-position, followed by a dehydrohalogenation to generate a double bond that could, in turn, behave as a substrate for a final intramolecular hetero-Michael addition.[12] This was achieved on dibromo esters **19**, both compounds being intermediates en route to bromo esters **1** (Scheme 5).

Both esters **19** were treated with *N*,*N*′-dimetylaminoethylenediamine (**2c**) or *N*-benzylaminoethanol (**6b**). The results are collected in Table 3. No thermal experiments were run in this case since the dehydrohalogenation is the only reaction to take place. It turns out that under high pressure, the bromine β-elimination is also the first event to occur, converting **19** in α-bromo-α,β-unsaturated esters **1**. After 1 h under 11 kbar, this is almost

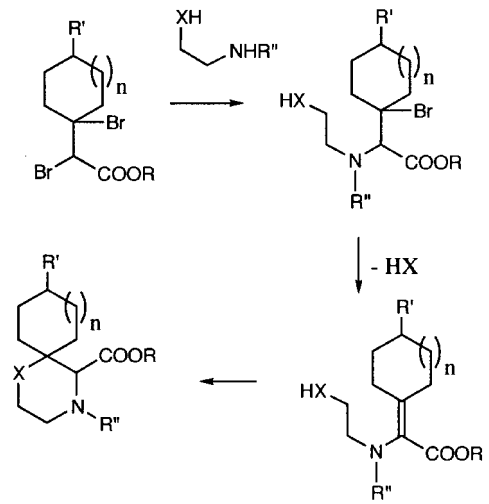
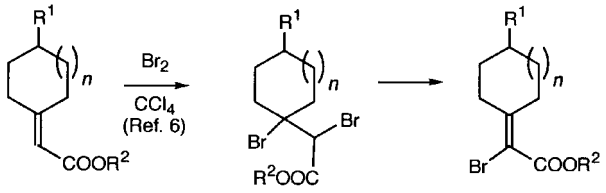


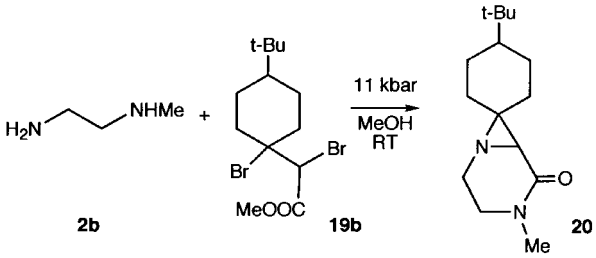
Figure 2



19a: n = 0, R^1 = H, R^2 = Et
19b: n = 1, R^1 = t-Bu, R^2 = Me

1

Scheme 5



2b **19b** **20**

Scheme 6

the only transformation observed with both the diamine and the amino alcohol (entries 1 and 3), while after 3 days the usual sequence is completed and the same condensation products as described above are obtained (entries 2 and 4). Working in methanol led, in the case of **18b**, to the competitive conjugate addition of the solvent (entries 5 and 7). The replacement of this alcohol by a DCM–t-BuOH mixture (9:1), as mentioned above, stopped the sequence at its very first step, providing ester **1b** in high yield (entry 6). It is worth pointing out the efficiency of the β-elimination, which does not seem to be inhibited by pressure. This was checked compressing esters **19a** at 11 kbar in ethanol with triethylamine and recovering **1a,b** in 41–71% yield after 1 h at room temperature.

We also decided to examine the action of a primary amine on such dibromo esters. Placing **19b** in methanol under 11 kbar in the presence of 1 equiv. of *N*-methylethylenediamine (**2b**) at room temperature provided the unexpected strained spiroaziridine **20** in low yield (28%) after 72 h (Scheme 6). The mechanism of this reaction has not been detailed; one can suspect, however, that **19b** converts into **1b** which, in turn, undergoes the hetero-Michael addition, followed by the spiroaziridination and the final lactamization. The more or less concerted aspect of this reaction is to be emphasized since this reaction does not take place when **2b** and **1a** are put under 11 kbar (Table 1, entry 4). On the other hand this sequence makes more sense, in our opinion, than a double nucleophilic substitution of the two bromines (one of which being on a tertiary carbon) by the primary amine.

This last reaction illustrates the well-known propensity of high pressures to favor highly compact structures and processes leading to the formation of a maximum number of bonds.

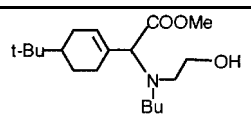
CONCLUSION

The spiroaziridination reaction between 2-bromo-2-(cycloalkylidene)acetates and primary amines cannot be extended to other spiroheterocycles resorting to simple neutral binucleophiles. Indeed, the *N,O*- and *N,N*-binucleophiles that we considered (ethylenediamines and aminoethanols) under thermal or hyperbaric (11 kbar) conditions provide in all cases morpholin-2-ones and piperazin-2-ones. The expected hetero-Michael addition apparently competes with a cascade beginning by a migration of the double bond followed by a substitution of the allylic halogen and a lactonization (lactamization), and eventually ended by a back-migration of the double bond. Enhancing the nucleophilicity of the amine or the electrophilicity of the substrate did not change the course of this reaction. No substantial difference between the thermal and hyperbaric versions of the reaction could be observed during this work, only the distribution of the products being slightly altered. A relatively large set of unusual and attractive α-amino

Table 3. Hyperbaric reaction (11 kbar, RT) between dibromo esters **19** and 1 equiv. of diamine **2c** or aminoethanol **6b** in the presence of 1 equiv. of NEt_3 (chromatographic yields)

Entry	Ester	Amine	Conditions	Products (yield,%)
1	**19a**	**2c**	EtOH, 1 h	**1a** (41) + **3d** (35)
2	**19a**	**2c**	EtOH, 67 h	**3d** (84)
3	**19a**	**6b**	EtOH, 1 h	**1a** (71) + **7** (5) + **9b** (5)
4	**19a**	**6b**	EtOH, 67 h	**8b** (11) + **9b** (60)
5	**19b**	**2c**	MeOH, 72 h	**5** (34) + **11** (46)
6	**19b**	**2c**	CH_2Cl_2, *t*-BuOH, 65 h	**1b** (94)
7	**19b**	**6b**	MeOH, 72 h	**10b** (6) + **11** (52)[a]

[a] Together with 10% of



esters, lactones and lactams has nevertheless been obtained through this approach. In addition, the control of the absolute configuration of the asymmetric center created by this sequence would be of special interest. Results in this direction will be published in due course.

EXPERIMENTAL

^{1}H and ^{13}C NMR spectra were measured on Bruker AM-200 and Avance 300 spectrometers; coupling constants (*J*) are given in Hz. MS analyses (EI, 70 eV) were performed on an ATI-Unicam Automass apparatus. High-resolution mass spectra (HRMS) were recorded with a Jeol JMS AX-500 spectrometer. IR spectra were measured on a Perkin-Elmer 16 PC FT-IR spectrometer. High-pressure reactions were performed in a Unipress piston-cylinder apparatus for pressures up to 14 kbar. The silica gel used for flash chromatography was obtained from SDS (230–400 mesh). Diethyl ether and THF were distilled from sodium–benzophenone. Methylene chroride, methanol and ethanol were dried over 3 Å molecular sieves and then distilled. Ethyl cyclopentylidenebromoacetate (**1a**), methyl 4-tert-butylcyclohexylidenebromoacetate (**1b**) and dibromo esters **19** were prepared as reported previously.[6] Methyl 2-chloro-2-(cyclopropylidene)acetate (**17**) was obtained from Professor Armin de Meijere (University of Göttingen, Germany). Cyclopentylidenepropanone was prepared following Villieras and Rambaud's convenient procedure.[13] Ketone **15** was prepared in 62% yield from cyclopentylidenepropanone in a similar fashion to **1a,b**.[6]

1-Bromo-1-cyclopentylidenepropanone (15). ^{1}H NMR ($CDCl_3$), δ ppm: 1.50–1.65 (m, 2H); 1.65–1.80 (m, 2H); 2.34 (s, 3H); 2.37 (t, J = 7.2 Hz, 2H); 2.61 (t, J = 7.2 Hz, 2H). ^{13}C NMR ($CDCl_3$), δ ppm: 25.58, 28.84, 36.96, 40.43, 30.98, 114.81, 164.55, 195.78. IR (v, cm^{-1}): 1589 (C═C); 1678 (C═O). MS (*m/z*): 204, 202 (58, M^+); 161, 159 (20), 123 (72), 79 (100). Anal. Calcd for $C_8H_{11}BrO$: C 47.32; H 5.46. Found: C 47.32; H 5.58%.

Ethyl (1-bromocyclopentyl) bromoacetate (19a). ^{1}H NMR ($CDCl_3$), δ ppm: 1.26 (t, J = 7.2 Hz, 3H); 1.65–2.45 (m, 8H); 4.21 (q, J = 7.2 Hz, 2H); 4.81 (s, 1H). ^{13}C NMR ($CDCl_3$), δ ppm: 14.56, 23.61, 24.39, 39.21, 42.76, 53.04, 62.75, 75.28, 168.36. IR (KBr, cm^{-1}): 1747 (C═O). MS (*m/z*): 313 (2, $M^+ - 1$), 233 (80), 125 (98), 79 (100). Anal. Calcd for $C_9H_{14}Br_2O_2$: C 34.42; H 4.49. Found: C 34.32; H 4.54%.

General procedure for the reaction of esters 1a,b with the binucleophiles

A solution of an ester **1a,b** (1–1.5 mmol) and binucleophile (1.0–1.5 mmol) and, eventually, triethylamine (1.0–1.5 mmol) in methanol/ethanol (3–4 g) or in a 9:1 mixture of methylene chloride and *tert*-butanol was compressed to 11 kbar at room temperature or brought to reflux under atmospheric pressure for a suitable time (see Tables 1–3). After returning to atmospheric pressure, the solvent was evaporated. The residue was chromatographed (CH_2Cl_2–MeOH for 3–5 and pentane–Et_2O for 7–14) to yield the corresponding products. The following compounds were thus prepared.

2-Cyclopent-1-en-1-yl tetrahydropyrazin-2(1*H*)-one (3a). ^{1}H NMR ($CDCl_3$), δ ppm: 1.75–2.00 (m, 2H); 1.80 (br s, 1H); 2.30–2.45 (m, 4H); 2.85–3.15 (m, 2H); 3.20–3.40 (m, 2H); 4.14 (s, 1H); 5.70 (s, 1H); 6.84 (br s, 1H). ^{13}C NMR ($CDCl_3$), δ ppm: 23.70, 32.74, 32.90, 40.87, 43.43, 60.24, 130.02, 141.70, 171.41. IR (KBr, cm^{-1}): 1669 (br s, C═C, C═O), 3273 (NH). MS (*m/z*): 166 (37, M^+), 137 (21), 109 (40), 94 (67), 81 (100). Anal. Calcd for $C_9H_{14}N_2O$: C 65.03; H 8.49; N 16.85. Found: C 64.78; H 8.45; N 16.62%.

2-Cyclopent-1-en-1-yl-4-methyltetrahydropyrazin-2(1*H*)-one (3b) and 2-cyclopent-1-en-1-yl-1-methyltetrahydropyrazin-2(1*H*)-one (3c). ^{1}H NMR ($CDCl_3$), δ ppm: 1.75–1.95 (m, 2H); 2.19 (for 4-Me isomer), 2.91 (for 1-Me isomer) (2 s, 3H); 2.10–2.40 (m, 4H); 2.43 (td, J = 11.0, 4.0 Hz, 1H); 2.80–2.90 (m, 2H); 3.10–3.20 (m, 2H); 3.38 (s, 1H); 3.42 (td, J = 11.0, 4.0 Hz, 1H); 5.70 (for 4-Me isomer), 5.62 (for 1-Me isomer) (2 s, 1H); 6.72 (for 4-Me isomer), 6.82 (for 1-Me isomer) (br s, 1H). ^{13}C NMR ($CDCl_3$), δ ppm: 23.71, 31.71, 32.54, 43.91, 41.25, 51.04, 69.37, 132.45, 140.75, 170.82. IR (KBr, cm^{-1}): 1636 (C═C), 1668 (br s, C═O), 3195 (NH). MS (*m/z*): 180 (50, M^+), 109 (74), 94 (93), 44 (100). Anal. Calcd for $C_{10}H_{16}N_2O$: C 66.64; H 8.95; N 15.54. Found: C 66.45; H 8.86; N 15.29%.

2-Cyclopent-1-en-1-yl-1,4-dimethyltetrahydropyrazin-2(1*H*)-one (3d). ^{1}H NMR ($CDCl_3$), δ ppm: 1.70–1.95 (m, 2H); 2.17 (s, 3H); 2.10–2.40 (m, 4H); 2.45 (td, J = 11.0, 4.0 Hz, 1H); 2.89 (s, 3H); 2.85–2.95 (m, 1H); 3.07 (qd, J = 11.0, 3.4 Hz, 1H); 3.35 (s, 1H); 3.47 (td, J = 11.0, 4.4 Hz, 1H); 5.67 (br s, 1H). ^{13}C NMR ($CDCl_3$), δ ppm: 23.71, 31.96, 32.51, 34.84, 44.01, 48.50, 51.20, 69.65, 132.00, 141.09, 167.98. IR (KBr, cm^{-1}): 1650 (br s, C═C, C═O). MS (*m/z*): 194 (24, M^+), 165 (23), 94 (70), 42 (100). Anal. Calcd for $C_{11}H_{18}N_2O$: C 68.01; H 9.34; N 14.42. Found: C 67.90; H 9.28; N 14.42%.

3-Cyclopentyl-2*H*-oxazin-2-one (4). ^{1}H NMR ($CDCl_3$), δ ppm: 1.50–1.70 (m, 5H); 1.75–1.95 (m, 3H); 3.30–3.45 (m, mask., 1H); 3.36 (td, J = 6.2, 2.9 Hz, 2H); 3.71 (t, J = 6.2 Hz, 2H); 7.14 (br s, 1H). ^{13}C NMR ($CDCl_3$), δ ppm: 25.98, 30.72, 39.23, 47.95, 42.45, 43.91, 158.86, 169.20. IR (KBr, cm^{-1}): 1620 (C═N), 1685 (C═O), 3229 (NH). MS (*m/z*): 166 (15, M^+), 125 (60), 110 (38),

97 (100). Anal. Calcd for $C_9H_{14}N_2O$: C 65.03; H 8.49; N 16.85. Found: C 64.21; H 8.37; N 16.69%.

3-[4-(*tert*-Butyl)cyclohex-1-en-1-yl]-1,4-dimethyltetrahydropyrazin-2(1*H*)-one (5) (1:1 mixture of the two diastereomers). ^{1}H NMR ($CDCl_3$), δ ppm: 0.73, 0.74 (2 s, 9H); 0.90–1.30 (m, 2H); 1.60–2.05 (m, 5H); 2.08, 2.10 (2 s, 3H); 2.30–2.45 (m, 1H); 2.75–2.83 (m, 1H); 2.83, 2.84 (2 s, 3H); 2.90–3.00 (m, 2H); 3.45 (td, J = 11.6, 4.5 Hz, 1H); 5.55–5.65 (m, 1H). ^{13}C NMR ($CDCl_3$), δ ppm: 24.32, 24.41, 25.70, 27.06, 27.23, 27.28, 27.54, 27.58, 32.50, 32.59, 34.83, 43.85, 44.01, 44.24, 44.42, 48.60, 48.66, 51.44, 51.54, 75.66, 76.28, 129.17, 129.28, 134.81, 135.14, 168.40, 168.64. IR (KBr, cm^{-1}): 1654 (br s, C=C, C=O). MS (*m/z*): 264 (17, M^+), 128 (65), 99 (100), 57 (93). Anal. Calcd for $C_{16}H_{28}N_2O$: C 72.68; H 10.67; N 10.59. Found: C 72.77; H 10.92; N 10.50%.

Ethyl 2-cyclopent-1-en-1-yl-2-[(hydroxyethyl)(benzyl)amino]acetate (7). ^{1}H NMR ($CDCl_3$), δ ppm: 1.27 (t, J = 7.3 Hz, 3H); 1.86 (quint, J = 7.3 Hz, 2H); 2.10–3.05 (m, 6H); 3.40–3.60 (m, 2H); 3.67 (d, A part of an AB system, J = 14.2 Hz, 1H); 3.89 (d, B part of an AB system, J = 14.2 Hz, 1H); 4.05 (s, 1H); 4.19 (q, J = 7.3 Hz, 2H); 5.61 (s, 1H); 7.20–7.35 (m, 5H). ^{13}C NMR ($CDCl_3$), δ ppm: 14.76, 23.75, 32.89, 34.73, 52.85, 55.74, 59.51, 60.88, 64.42, 127.63, 129.02, 131.23, 139.79, 128.91, 139.71, 172.65. IR (KBr, cm^{-1}): 1636 (C=C), 1733 (C=O), 3448 (OH). MS (*m/z*): 303 (4, M^+), 272 (60), 230 (98), 120 (55), 91 (100). Anal. Calcd for $C_{18}H_{25}NO_3$: C 71.26; H 8.31; N 4.62. Found: C 71.43; H 8.38; N 4.28%.

Ethyl 2-cyclopentylidene-2-[(2-hydroxyethyl)(methyl)amino]acetate (8a). ^{1}H NMR ($CDCl_3$), δ ppm: 1.25 (t, J = 7.1 Hz, 3H); 1.55–1.70. (m, 4H); 2.44 (t, J = 6.2 Hz, 2H); 2.50 (s, 3H); 2.60 (t, J = 6.2 Hz, 2H); 2.89 (t, J = 5.2 Hz, 2H); 2.92 (br s, 1H); 3.45–3.55 (m, 2H); 4.15 (q, J = 7.1 Hz, 2H). ^{13}C NMR ($CDCl_3$), δ ppm: 14.80, 25.89, 27.37, 33.19, 33.56, 40.01, 57.54, 59.51, 60.39, 132.85, 158.74, 167.09. IR (KBr, cm^{-1}): 1634 (C=C), 1704 (C=O), 3451 (OH). MS (*m/z*): 227 (13, M^+), 196 (90), 81 (80), 42 (100). Anal. Calcd for $C_{12}H_{21}NO_3$: C 63.41; H 9.31; N 6.16. Found: C 63.45; H 9.28; N 6.44%.

Ethyl 2-cyclopentylidene-2-[(2-hydroxyethyl)(benzyl)amino]acetate (8b). ^{1}H NMR ($CDCl_3$), δ ppm: 1.26 (t, J = 7.2 Hz, 3H); 1.40–1.65. (m, 4H); 2.32 (t, J = 7.0 Hz, 2H); 2.56 (t, J = 7.0 Hz, 2H); 2.91 (br s, 1H); 2.96 (t, J = 5.0 Hz, 2H); 3.44 (br s, 2H); 3.92 (s, 2H); 4.16 (q, J = 7.2 Hz, 2H); 7.15–7.30 (m, 5H). ^{13}C NMR ($CDCl_3$), δ ppm: 14.82, 25.93, 27.24, 33.25, 34.15, 55.41, 58.15, 60.36, 60.63, 127.51, 128.66, 129.41, 139.81, 131.14, 159.95, 167.54. IR (KBr, cm^{-1}): 1631 (C=C), 1701 (C=O), 3446 (OH). MS (*m/z*): 303 (4, M^+), 272 (70), 230 (65), 205 (80), 91 (100). Anal. Calcd for $C_{18}H_{25}NO_3$: C 71.26; H 8.31; N 4.62. Found: C 71.46; H 8.49; N 4.77%.

4-Methyl-3-cyclopentylidenemorpholin-2-one (9a). ^{1}H NMR ($CDCl_3$), δ ppm: 1.55–1.75. (m, 4H); 2.30–2.40 (m, 2H); 2.55 (s, 3H); 2.55–2.75 (m, 2H); 3.00–3.10 (m, 2H); 4.20–4.25 (m, 2H). ^{13}C NMR ($CDCl_3$), δ ppm: 26.28, 26.78, 33.23, 33.99, 42.35, 51.57, 64.75, 129.33, 149.24, 165.05. IR (KBr, cm^{-1}): 1615 (C=C), 1729 (C=O). MS (*m/z*): 181 (45, M^+), 108 (100), 94 (60), 42 (70). Anal. Calcd for $C_{10}H_{15}NO_2$: C 66.27; H 8.34; N 7.73. Found: C 66.19; H 8.29; N 7.56%.

4-Benzyl-3-cyclopentylidenemorpholin-2-one (9b). ^{1}H NMR ($CDCl_3$), δ ppm: 1.60–1.80 (m, 4H); 2.42 (br t, J = 6.5 Hz, 2H); 2.60 (br t, J = 6.5 Hz, 2H); 2.83 (br t, J = 4.8 Hz, 2H); 3.96 (s, 2H); 4.12 (br t, J = 4.8 Hz, 2H); 7.20–7.40 (m, 5H). ^{13}C NMR ($CDCl_3$), δ ppm: 26.29, 26.89, 33.42, 33.77, 47.78, 58.97, 64.65, 127.87, 128.50, 129.00, 138.27, 129.05, 150.91, 165.26. IR (KBr, cm^{-1}): 1616 (C=C), 1732 (C=O). MS (*m/z*): 257 (36, M^+), 166 (50), 91 (100). Anal. Calcd for $C_{16}H_{19}NO_2$: C 74.68; H 7.44; N 5.44. Found: C 74.52; H 7.51; N 5.22%.

3-[4-(*tert*-Butyl)cyclohex-1-en-1-yl]-4-methylmorpholin-2-one (10a) (1:1 mixture of the two diastereomers). ^{1}H NMR ($CDCl_3$), δ ppm: 0.79, 0.80 (2 s, 9H); 1.00–1.30. (m, 2H); 1.80–2.20 (m, 5H); 2.15, 2.18 (2 s, 3H); 2.50–2.65 (m, 1H); 2.80–2.85 (m, 1H); 3.20, 3.21 (2 s, 1H); 4.33 (ddd, J = 10.7, 3.2, 1.8 Hz, 1H); 4.53 (td, J = 11.4, 3.2 Hz, 1H); 5.75–5.85 (m, 1H). ^{13}C NMR ($CDCl_3$), δ ppm: 24.28, 24.38, 25.63, 27.31, 27.35, 27.37, 27.56, 27.60, 32.58, 32.63, 43.48, 43.66, 44.21, 44.31, 51.50, 51.42, 68.62, 75.18, 75.85, 130.43, 130.46, 133.61, 133.86, 169.29, 169.56. IR (KBr, cm^{-1}): 1682 (C=C), 1723 (C=O). MS (*m/z*): 251 (2, M^+), 226 (8), 207 (64), 178 (50), 122 (100), 94 (70). Anal. Calcd for $C_{15}H_{25}NO_2$: C 71.67; H 10.02; N 5.57. Found: C 71.58; H 10.04; N 5.44%.

3-[4-(*tert*-Butyl)cyclohex-1-en-1-yl]-4-benzylmorpholin-2-one (10b) (1:1 mixture of the two diastereomers)

^{1}H NMR ($CDCl_3$), δ ppm: 0.78, 0.79 (2 s, 9H); 1.00–1.30 (m, 2H); 1.70–2.20 (m, 5H); 2.38 (qd, J = 12.0, 3.4 Hz, 1H); 2.75–2.85 (m, 1H); 2.97 (d, A part of an AB system, J = 13.6 Hz, 1H); 3.53, 3.54 (2 s, 1H); 3.92 (dd, B part of an AB system, J = 18.7, 13.6 Hz, 1H); 4.15–4.25 (m, 1H); 4.31 (td, J = 11.0, 3.0 Hz, 1H); 5.78–5.87 (m, 1H); 7.15–7.35 (m, 5H). ^{13}C NMR ($CDCl_3$), δ ppm: 24.62, 26.20, 27.67, 28.13, 27.84, 27.87, 32.86, 32.92, 44.50, 44.56, 47.63, 58.88, 59.16, 69.26, 73.90, 74.50, 128.02, 128.04, 129.35, 129.44, 131.40, 131.44, 138.41, 138.48, 129.17, 133.98, 134.27, 169.71, 169.97. IR (KBr, cm^{-1}): 1678

(C═C), 1744 (C═O). MS (*m/z*): 327 (5, M^+), 283 (54), 192 (97), 149 (86), 91 (99), 57 (100). Anal. Calcd for $C_{21}H_{29}NO_2$: C 77.03; H 8.93; N 4.28. Found: C 76.87; H 9.02; N 4.38%.

Ethyl 2-cyclopent-1-en-1-yl-2-(2-hydroxyanilino)acetate (12)

^{1}H NMR ($CDCl_3$), δ ppm: 1.26 (t, J = 7.1 Hz, 3H); 1.89 (quint, J = 7.3 Hz, 2H); 2.25–2.50 (m, 4H); 4.22 (q, J = 7.1 Hz, 2H); 4.68 (s, 1H); 5.79 (s, 1H); 6.50–6.80 (m, 4H). ^{13}C NMR ($CDCl_3$), δ ppm: 14.58, 23.57, 32.85, 33.05, 58.74, 62.04, 113.46, 115.15, 119.20, 121.37, 135.78, 145.06, 129.68, 140.04, 173.47. IR (KBr, cm^{-1}): 1647 (C═C), 1738 (C═O), 3413 (OH, NH). MS (*m/z*): 261 (13, M^+), 188 (100), 109 (25). Anal. Calcd for $C_{15}H_{19}NO_3$: C 68.94; H 7.33; N 5.36. Found: C 68.86; H 7.19; N 5.19%.

3-Cyclopentyl-2*H*-1,4-benzoxazin-2-one (13)

^{1}H NMR ($CDCl_3$), δ ppm: 1.55–2.20 (m, 8H); 3.54 (quint, J = 8.0 Hz, 1H); 7.20–7.75 (m, 4H). ^{13}C NMR ($CDCl_3$), δ ppm: 26.21, 31.02, 43.51, 116.62, 125.64, 129.23, 130.62, 131.57, 146.67, 153.43, 161.14. IR (KBr, cm^{-1}): 1743 (br s, C═N, C═O). MS (*m/z*): 215 (32, M^+), 146 (100). Anal. Calcd for $C_{13}H_{13}NO_2$: C 72.54; H 6.09; N 6.51. Found: C 72.38; H 6.05; N 6.32%.

Ethyl 2-cyclopent-1-en-1-yl-2-(*N*-hydroxy-*N*-benzylamino)acetate (14)

^{1}H NMR ($CDCl_3$), δ ppm: 1.20 (t, J = 7.2 Hz, 3H); 1.70–1.90 (m, 2H); 2.25–2.45 (m, 4H); 3.53 (d, A part of an AB system, J = 13.8 Hz, 1H); 3.93 (d, B part of an AB system, J = 13.8 Hz, 1H); 4.12 (qd, J = 7.2, 2.1 Hz, 2H); 4.14 (s, 1H); 5.45 (br s, 1H); 5.82 (s, 1H); 7.15–7.35 (m, 5H). ^{13}C NMR ($CDCl_3$), δ ppm: 14.58, 23.53, 32.71, 32.81, 60.84, 61.34, 72.48, 127.68, 129.76, 132.97, 138.42, 128.62, 137.92, 170.94). IR (KBr, cm^{-1}): 1649 (C═C), 1725 (C═O), 3443 (OH). MS (*m/z*): 275 (8, M^+), 202 (100), 186 (67), 91 (76). Anal. Calcd for $C_{16}H_{21}NO_3$: C 69.79; H 7.69; N 5.09. Found: C 70.05; H 7.85; N 5.28%.

4-Benzyl-3-cyclopent-1-en-1-yl-2-methylmorpholin-2-ol (16). ^{1}H NMR ($CDCl_3$), δ ppm: major isomer: 1.20 (s, 3H); 1.60–1.95 (m, 2H); 2.08 (td, J = 12.0, 4.1 Hz, 1H); 2.17–2.35 (m, 3H); 2.40–2.50 (m, 1H); 2.55 (dd, J = 12.0, 2.4 Hz, 1H); 2.80 (dd, A part of an AB system, J = 13.5 Hz, 1H); 3.03 (s, 1H); 3.46 (dd, J = 12.0, 3.0 Hz, 1H); 3.80 (dd, B part of an AB system, J = 13.5 Hz, 1H); 3.86 (td, J = 12.0, 3.0 Hz, 1H); 4.50 (br s, 1H); 5.77 (s, 1H); 7.15–7.30 (m, 5H); minor isomer: 1.18 (s, 3H); 1.60–1.95 (m, 2H); 2.17–2.35 (m, mask., 3H); 2.40–2.50 (m, 1H); 2.70 (dd, J = 12.0, 4.1 Hz, 1H); 2.80 (dd, A part of an AB system, J = 13.5 Hz, 1H); 3.19 (s, 1H); 3.59 (dd, J = 12.0, 3.8 Hz, 1H); 3.80 (dd, B part of an AB system, J = 13.5 Hz, 1H); 3.98 (td, J = 12.0, 4.1 Hz, 1H); 4.50 (br s, 1H); 5.67 (s, 1H); 7.15–7.30 (m, 5H). ^{13}C NMR ($CDCl_3$), δ ppm: major isomer: 24.50, 25.27, 32.32, 32.69, 52.84, 59.42, 60.23, 96.15, 127.82, 129.36, 134.16, 139.28, 129.05, 141.68; minor isomer: 24.90, 24.93, 32.32, 32.65, 52.84, 59.99, 60.40, 95.99, 127.94, 129.48, 134.55, 138.78, 129.05, 141.68. IR (KBr, cm^{-1}): 1641 (C═C), 3463 (OH). MS (*m/z*): 273 (6, M^+), 255 (6), 182 (20), 91 (100). Anal. Calcd for $C_{17}H_{23}NO_2$: C 74.69; H 8.48; N 5.12. Found: C 74.73; H 8.74; N 5.22%.

Methyl 2-cyclopropyl-2-[(2-hydroxyethyl)(benzyl)amino]chloroacetate (18). ^{1}H NMR ($CDCl_3$), δ ppm: 0.70–1.20. (m, 4H); 1.97 (br s, 1H); 2.80 (br t, 2H), 3.24 (m, 2H); 3.71 (s, 3H); 3.77 (d, A part of an AB system, J = 14.0 Hz, 1H); 3.88 (d, B part of an AB system, J = 14.0 Hz, 1H); 4.60 (s, 1H); 7.10–7.30 (m, 5H). ^{13}C NMR ($CDCl_3$), δ ppm: 15.35, 17.30, 48.21, 53.61, 55.25, 58.76, 60.09, 61.54, 127.96, 128.77, 129.19, 140.52, 169.87. IR (KBr, cm^{-1}): 1752 (C═O), 3432 (OH). MS (*m/z*): 261 (7, $M^+ - HCl$), 229 (14), 91 (100). Anal. Calcd for $C_{15}H_{20}ClNO_3$: C 60.50; H 6.77; N 4.70. Found: C 61.29; H 7.07; N 5.55%.

Spirolactam 20 (10:1 mixture of the two diastereomers). ^{1}H NMR ($CDCl_3$), δ ppm: 0.80 (s, 9H); 0.90–1.50 (m, 6H); 1.65–1.90 (m, 3H); 2.21, 2.23 (2 s, 1H); 2.89, 2.90 (2 s, 3H); 2.80–3.00 (m, 2H); 3.10–3.35 (m, 1H); 3.69 (td, J = 12.0, 4.5 Hz, 1H). ^{13}C NMR ($CDCl_3$), δ ppm: major isomer: 26.50, 26.60, 27.50, 28.08, 32.79, 34.20, 38.33, 42.03, 49.44, 43.37, 48.03, 48.11, 167.66; minor isomer: 25.75, 25.85, 27.50, 29.73, 32.88, 34.20, 37.97, 42.78, 49.54, 42.96, 47.55, 47.72, 167.78. IR (KBr, cm^{-1}): 1654 (br s, C═O). MS (*m/z*): 250 (55, M^+), 235 (97), 193 (65), 165 (71), 86 (99), 57 (100). Anal. Calcd for $C_{15}H_{26}N_{28}O$: C 71.96; H 10.47; N 11.19. Found: C 71.03; H 10.67; N 11.27%.

Methyl 2-[4-(*tert*-butyl)cyclohex-1-en-1-yl]-2-[(hydroxyethyl)(benzyl)amino]acetate (21) (1:1 mixture of two diastereomers). ^{1}H NMR ($CDCl_3$), δ ppm: 0.77, 0.78 (2 s, 9H); 1.00–2.30 (m, 8H); 2.70–2.95 (m, 2H); 3.30–3.60 (m, 4H); 3.64, 3.65 (2 s, 2H); 3.80–3.90 (m, 2H); 5.50 (br s, 1H); 7.10–7.30 (m, 5H). ^{13}C NMR ($CDCl_3$), δ ppm: 24.54, 24.81, 27.64, 27.67, 29.51, 30.07, 27.78, 27.84, 32.86, 44.30, 44.48, 52.02, 52.03, 52.84, 53.44, 55.93, 56.16, 59.75, 60.03, 69.09, 70.64, 127.86, 128.62, 128.80, 129.17, 129.36, 140.11, 140.35, 129.88, 133.78, 133.85, 173.58, 173.74. IR (KBr, cm^{-1}): 1737 (C═O), 3443 (OH). MS (*m/z*): 359 (1, M^+), 328 (39), 300 (90), 192 (100), 149 (78), 91 (71), 57 (80). Anal. Calcd for $C_{22}H_{33}NO_3$: C 73.50; H 9.25; N 3.90. Found: C 73.55; H 9.35; N 3.98%.

3-Benzyloxazolidine. ^{1}H NMR ($CDCl_3$), δ ppm: 2.91 (t, $J = 6.8$ Hz, 2H); 3.64 (s, 2H); 3.74 (t, $J = 6.8$ Hz, 2H); 4.24 (s, 3H) 7.15–7.35 (m, 5H). ^{13}C NMR ($CDCl_3$), δ ppm: 52.39, 58.46, 63.69, 86.95, 127.70, 128.85, 129.20, 139.24. IR (KBr, cm^{-1}): 1006, 1057, 1674 (saturated ring). MS (*m/z*): 163 (20, M^+), 162 (53), 91 (100). Anal. Calcd for $C_{10}H_{13}NO$: C 73.59; H 8.03; N 8.58. Found: C 73.38; H 7.88; N 8.47%.

Acknowledgements

A.Y.R. is grateful to the CNRS for a research associate position (August–December 1999). Our high-pressure research program and equipment are supported by grants from the Conseil Régional de Haute-Normandie (France). We also warmly thank Professor Armin de Meijere (University of Göttingen, Germany) for providing a sample of methyl 2-chloro-2-(cyclopropylidene)-acetate (**17**).

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