Spiroaziridination of Cycloalkylidene Esters under High Pressure

Alexandre Rulev[b] and Jacques Maddaluno*[a]

Keywords: Amines / High pressure chemistry / Michael additions / Spiro compounds

The reaction between primary amines and 2-bromo-2-(cycloalkylidene)acetates in alcohol under high pressure provides the expected spiroaziridines in good yields and diastereomeric excesses. With bulky or aromatic amines, this reaction competes with the migration of the double bond, which, migrating from an exo to an endocyclic position, provides an intermediate allylic α-bromo ester, immediately converted into an α-amino ester. It was also possible to develop a tandem version, applying the same high pressure conditions to a 1,4-bis-cyclohexylidene acetate. The corresponding bis-spiroaziridine was obtained in good yield and moderate *de*. However, this reaction did not succeed with 2-chloro-2-(cyclopropylidene)acetate, which produced only glutaric acid derivatives in low yields.

Introduction

The biological potential of α- and β-amino acids and esters continually fuels the interest of organic chemists in synthetic methods that offer access to precursors of such functional patterns.[1] The possibilities opened by the regioselective ring-fission of aziridine-2-carboxylates to provide both α- and β-functionalized amino esters illustrate why this group of heterocycles is regarded as such a versatile tool in modern organic synthesis.[2] One classical route to aziridine-2-carboxylates consists of the hetero-Michael addition of primary amines to α,β-unsaturated-α-halo esters. This straightforward and general access is efficient and compatible with a large variety of functionalities.[3] However, one of its limitations is the sensitivity of the conjugate additions to steric factors.[4] This well known phenomenon was reported as early as 1967 for amine addition to unsaturated esters.[5] Consequently, it has been possible to prepare aziridines incorporating a tetrasubstituted carbon atom only in a restricted number of cases, using different methods (nitrene[6] or carbene[7] addition, addition of ammonia onto α,β-dibromo esters,[3d] photolysis of 2-(dialkylamino)cyclohex-2-enone,[8] or Payne-type[9] or iminium[10] rearrangements). To the best of our knowledge, only in two recent cases has the hetero-Michael addition successfully been applied to the synthesis of such highly substituted aziridines. Resorting to an activated substrate, methyl 2-chloro-2-cyclopropylideneacetate, De Meijere and colleagues obtained the expected azaspiropentanecarboxylate under thermal conditions, but only in relatively low yield.[11] We were able to show that, in the case of 2-bromo-2-(4′-*tert*-butylcyclohexylidene)acetate and benzylamine, high pressure activation could make this route viable.[12] High pressure is indeed known to help in overcoming steric problems[13] and to give access to tetrasubstituted centers bearing amino functions through direct addition of primary amines to β,β-disubstituted α,β-unsaturated esters.[14] Such a reaction is totally inefficient under atmospheric pressure.[5,12,14] Here we wish to present the developments we have made on our original results in an effort to define the scope and limitations of this method more accurately.

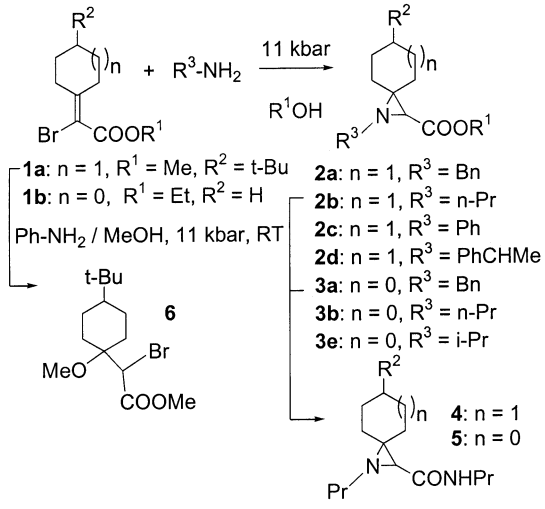
[a] Laboratoire des Fonctions Azotées et Oxygénées Complexes de l'IRCOF, UMR 6014 CNRS, Université de Rouen,
76821 Mont St Aignan, France
Fax: (internat.) +33 2 3552 2971
E-mail: jmaddalu@crihan.fr
[b] Permanent address: Favorsky Institute of Chemistry, Siberian Branch of Russian Academy of Sciences,
1 Favorsky St., 664033, Irkutsk, Russia

Results and Discussion

We first extended our reaction conditions to six common primary amines[15] and to the five-membered and six-membered ring haloacetates **1** (Scheme 1). The starting esters were prepared from the corresponding cycloalkanones by means of a Wittig−Horner/bromination/dehydrobromination sequence reported previously.[12] The hetero-Michael step was then performed, following the previously optimized experimental procedure (11 kbar, alcohol, room temperature) and the results from this are listed in Table 1. Ester **1a** was used in methanol and **1b** in ethanol, to avoid transesterification phenomena.

The results in Table 1 show that spiroaziridination took place for both five-membered and six-membered rings, provided that the primary amine used was sufficiently nucleophilic and not too bulky. Thus, entries 1, 2, 4, 5, and 6 represent fair to good yields in **2** and **3**. The presence of the *tert*-butyl group on the cyclohexylidene ester results in the formation of diastereomers, with selectivities in the 90% range being observed (entries 1−4). Use of a chiral amine such as (*S*)-α-methylbenzylamine (entry 4) produced spiroaziridine **2d** as a mixture of four different diastereomers, the ratio of which was potentially subject to influence both by the axial/equatorial selectivity of the addition and by induction by the chiral center of the amine. In reality, the NMR spectrum of the crude mixture of **2d** showed that the first type of selectivity had remained in the 90% range,

  1434−193X/01/0713−2569 $ 17.50+.50/0



Scheme 1

The reaction between **1b** and aniline (entry 7) provided the α-amino ester **9c**, probably because a migration of the double bond occurred first, and was immediately followed by a nucleophilic substitution of the allylic bromine by the aniline (Scheme 2). Depending on the exact experimental conditions, this latter compound tended to reconjugate through a second migration of the double bond back to its original position, affording the apparent *ipso*-substitution product: the enamino ester **10c**. We were indeed able to establish in one case that **9** is the kinetic product while **10** is the thermodynamic one: subjection of pure **9e** (R^3 = *i*Pr) to the conditions of the reaction (EtOH, 1 equiv. *i*PrNH$_2$, 11 kbar, room temp.) for 62 h produced a 3:1 mixture of **10e** and **9e**.

This reaction was also sensitive to the bulkiness of the carbon α to the nitrogen atom. For instance, use of isopropylamine instead of *n*-propylamine (entry 9) resulted in a mixture of the expected aziridine together with the two products originating from the double bond migration

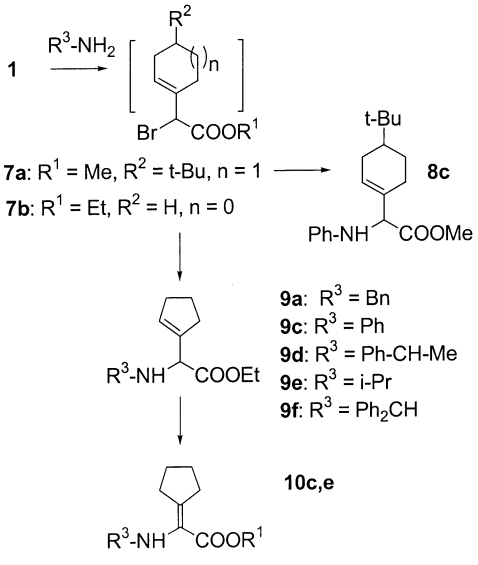
Table 1. Hetero-Michael addition of 2 equiv. of primary amines to cycloalkylidene acetates under high pressure (11 kbar)

Entry	Ester	R^3	Time (h)	Solvent	Product	Yield (*de*)%	Side products
1	1a	Bn	96	MeOH	2a	83 (91)	–
2	1a	*n*Pr	36	MeOH	**2b**	70 (91)	4 (17%)
3	1a	Ph	65	MeOH[a]		9 (?)[b]	6 (44%) + 8c (25%)
4	1a	PhCHMe	40	MeOH	2d	78 (?)[c]	–
5	1b	Bn	48	EtOH	3a	57 (–)[d]	9a (12%)
6	1b	*n*Pr	48	EtOH	3b	78 (–)[d]	5 (8%)
7	1b	Ph	65	EtOH[a]	–	0	9c (22%) + 10c (50%)
8	1b	PhCHMe	40	EtOH	–	0	9d (56%)[e]
9	1b	*i*Pr	65	EtOH	3e	16 (–)[d]	9e (19%) + 10e (48%)
10	1b	Ph_2CH	48	EtOH	–	0	9f (10%)[e]

[a] Reaction run in the presence of 1 equiv. of aniline + 1 equiv. of NEt_3. – [b] *de* not determined (only one isomer was recovered after flash chromatography). – [c] Only one pair of diastereoisomers was detected in the crude reaction mixture by NMR. – [d] Only one asymmetric center created. – [e] Together with starting material **1b** (30% for entry 8, 69% for entry 10).

while the asymmetric induction was extremely low. This disappointing result is not too surprising in view of related experiments dealing with the addition of chiral amines to crotonates.[5b] The nucleophilic character of some of the amines used in excess in these reactions tends partly to transform the aziridino esters **2b** and **3b** into the corresponding amides **4** and **5**, as previously emphasized by de Meijere[11] and ourselves.[12]

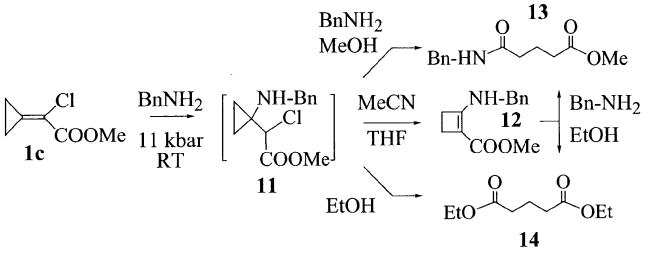
Conversely, a decrease in the amine nucleophilicity is also of consequence: use of aniline instead of an alkylamine results, in the case of **1a**, in the addition of methanol, providing the β-methoxy-α-bromo ester **6** (Scheme 1 and Table 1) in fair yield and good diastereoisomeric excess (90% from NMR spectroscopic data). In contrast, the side product **8c**, also detected in this reaction, the origin of which is discussed below, did not exhibit any diastereomeric excess, as reported in our previous paper.[12] Interestingly, under comparable experimental conditions, ethanol hardly added to **1a**, producing the corresponding β-ethoxyester in only 12% yield.[16]



Scheme 2

within the ring as described above (Scheme 2). With less nucleophilic or more cumbersome amines (such as aniline, α-methylbenzylamine, or diphenylmethylamine, entries 7, 8, and 10), the aziridination no longer took place, the two deconjugation/substitution products **9** and **10** being recovered in various ratios, together with significant amounts of starting material **1b**.

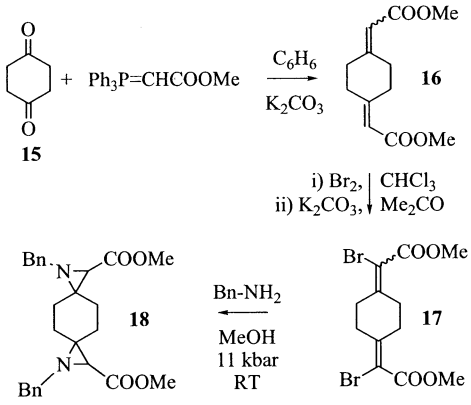
To extend our investigations further, we also considered the case of methyl 2-chloro-2-(cyclopropylidene)acetate **1c**, the activated substrate previously studied by de Meijere and colleagues.[11] No aziridination could be observed when the above conditions were applied to this substrate; treatment of **1c** with 2 equiv. benzylamine in methanol provided only the unexpected *N*-benzylglutaramide methyl ester **13**, in 15% yield (Scheme 3). To avoid possible opening of the aziridine by the nucleophiles present in the medium, we repeated the reaction in ethanol (vide supra), with only one equivalent of benzylamine. Only diethyl glutarate **14** was recovered this time, in 19% yield. We interpret these rather puzzling results in terms of the sequence depicted in Scheme 3. It is known that the putative intermediate spiroaziridine resulting from the cyclization of chloro ester **11** rearranges in basic methanolic solution into cyclobutenamino ester **12**. This stable product has indeed already been obtained by addition of benzylamine to **1c** and has been fully characterized.[11]



Scheme 3

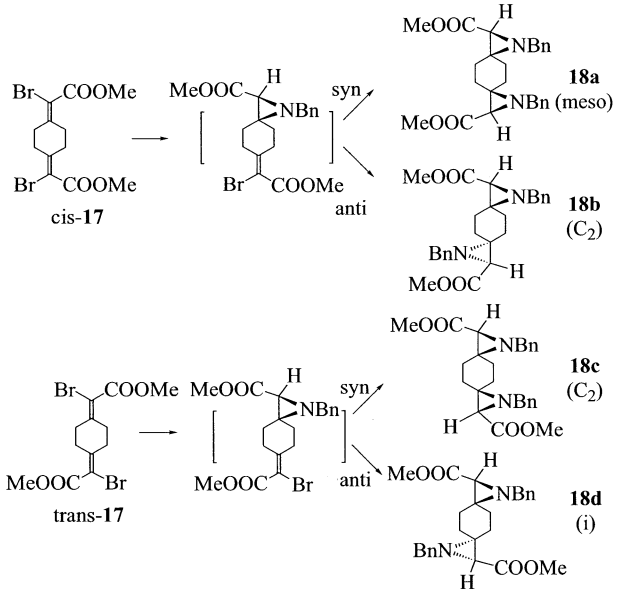
Actually, **12** can be obtained in about 75% yield under our conditions, provided that only one equivalent of amine is used, in a nonalcoholic solvent such as a 50:50 mixture of acetonitrile and THF.[17] We assume that, depending on the conditions, the tautomeric imino ester form of **12** can eventually undergo an addition of either benzylamine or ethanol to give an intermediate imidate or amidine that would hydrolyze upon workup into the corresponding amide or ester appendage.

Finally, we also explored the possibilities opened by a tandem version of this reaction, using dibromodiester **17**. This latter was prepared by means of a double Wittig reaction between cyclohexanedione **15** and (methoxycarbonylmethylene)triphenylphosphorane (Scheme 4).[18] As described, the expected diester **16** was obtained (as a 50:50 inseparable mixture of *cis* and *trans* isomers), together with the corresponding mono ester. Pure **16** was then brominated in chloroform and the crude tetrabromodiester subjected to base-induced dehydrobromation, using the conditions previously optimized for **1a**.[12] Again, a 50:50 mixture of *cis* and *trans* isomers of **17** was obtained, but this time careful flash chromatography on silica gel allowed us to isolate very pure samples of each isomer.



Scheme 4

These were separately subjected to compression in the presence of benzylamine in methanol at 11 kbar. As shown in Scheme 5, double aziridination took place in fair to good isolated yields (48% for the *cis* isomer, 63% for the *trans* one), the products **18** being obtained as a 50:50 mixture of two major diastereoisomers plus two minor ones. Interestingly, it appeared on the basis of simple TLC observation that the major diastereomers obtained from the diester *cis*-**17** corresponded to the minor diastereomers obtained from the diester *trans*-**17** and vice versa. The ratio between the major diastereomers and the minor ones was about 5:1, as determined from ^{1}H NMR integration.



Scheme 5

These results can be explained by considering the stereochemical consequences of the tandem aspect of the reaction. Up to four (racemic) stereoisomers can indeed be expected from this bis-addition, the attack of the nitrogen on the exocyclic double bond taking place either in a *syn* or

in an *anti* fashion with respect to the first one (Scheme 5). Assuming that i) the first addition has no or little influence on the second one (the newly formed aziridine being in a remote "para" position with respect to the remaining double bond), ii) the proton source in the protonation step immediately following the addition is the methanol and that it adds mainly *anti* to the incoming amine (Figure 1), as established in a closely related example,[19] and iii) the intramolecular nucleophilic substitution closing the aziridine ring is almost perfectly of the S_N2 type, as generally accepted (Figure 1), one may then predict that the two major isomers result from the *syn* and *anti* second additions (producing **18a** and **18b**, in which the ester groups are *syn*, when starting from *cis*-**17**, and **18c** and **18d**, in which they are *trans*, when starting from *trans*-**17**). In the framework of these hypothesis, the two minor diastereomers may, in both cases, derive from a small amount of *syn* protonation, possibly occurring through competitive intramolecular proton transfer from the newly formed secondary amine. Competition between *syn* and *anti* proton transfers following the addition of a neutral nucleophile has been implicated in at least one case, with thiophenol and an α,β-unsaturated amides, by Miyata and colleagues.[20]

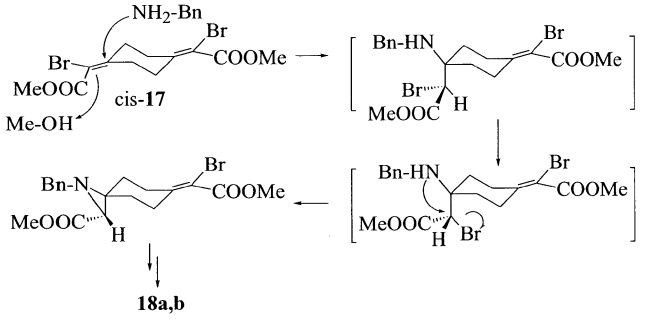


Figure 1. Proposed detailed mechanism for the *anti* protonation and spiroaziridination following the hetero-Michael addition reaction.

Conclusion

The results presented in this paper indicate that the spiroaziridination reaction we have previously described for cyclohexylidene α-bromo esters can be extended to cyclopentylidene and bis-spirocyclohexylidene ones, but not to cyclopropylidene bromo esters. Most conventional nucleophilic primary amines are also within the scope of this reaction. However, with poorly nucleophilic or bulky amines, the system undergoes a competitive double bond isomerization reaction, which yields α,β- or β,γ-unsaturated α-amino esters (depending on the cycloalkyl ring size). This "side" reaction offers an interesting means of access to unusual compounds that may be considered as nonproteogenic amino acids. Further developments in this area are currently in progress and will be reported in due time.

Experimental Section

^1H and ^{13}C NMR spectra were measured in deuterochloroform on Bruker AM 200 and 300 FT spectrometers, coupling constants (*J*) are given in Hz. Low resolution MS and GC/MS analyses (EI, 70 eV) were performed on an ATI-Unicam Automass instrument. 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 from the SDS company (230−400 mesh).

THF was distilled from sodium/benzophenone. Dichloromethane, methanol, and ethanol were dried over 3-Å molecular sieves and then distilled.

Methyl 2-bromo-2-(4-*tert*-butylcyclohexylidene)acetate (**1a**) was prepared as reported previously.[12] The ethyl cyclopentylideneacetate was obtained from cyclopentanone by means of a Wittig−Horner reaction.[21] The ester **1b** was prepared from ethyl cyclopentylideneacetate in similar fashion to **1a**, in 72% yield.

Ethyl 2-Bromo-2-cyclopentylideneacetate (1b): Oil. IR (KBr): $\tilde{\nu}$ = 1615 (C=C), 1708 (C=O) cm^{-1}. − ^1H NMR ($CDCl_3$): δ = 1.25 (t, *J* = 7.1 Hz, 3 H, CH_3); 1.60−1.70 (m, 2 H), 1.70−1.80 (m, 2 H, 3-CH_2, 4-CH_2); 2.47 (t, *J* = 7.2 Hz, 2 H), 2.71 (t, *J* = 7.1 Hz, 2 H, 2-CH_2, 5-CH_2); 4.18 (q, *J* = 7.1 Hz, 2 H, CH_2O). − ^{13}C NMR ($CDCl_3$): δ = 14.61 (CH_3); 25.58, 28.41 (C3, C4); 36.19, 40.07 (C2, C5); 62.08 (CH_2O); 105.83 (=CBr); 163.46 (C1); 165.96 (C=O). − MS: *m*/*z* (%) = 234, 232 (80) [M^+]; 206, 204 (60), 79 (100). − $C_9H_{13}BrO_2$ (233.1): calcd. C 46.36; H 5.62; found C 46.34; H 5.54.

General Procedure for the Treatment of Esters 1a and 1b with Amines: A solution of the ester **1a** or **1b** (1 mmol) and amine (2.0−2.5 mmol) in the corresponding alcohol (3−4 g) was allowed to stand under 11 kbar pressure at room temp. for a suitable time (see Table 1). After reversion to atmospheric pressure, the solvent was evaporated. The residue was chromatographed (pentane/Et_2O) to yield the corresponding reaction products. The following compounds were prepared in this manner.

Spiroaziridine 2a: Oil. All spectroscopic data in agreement with the literature (ref.[12]).

Spiroaziridine 2b: Oil. IR (KBr): $\tilde{\nu}$ = 1724, 1750 (C=O) cm^{-1}. − ^1H NMR ($CDCl_3$): major isomer: δ = 0.83 (s, 9 H, *t*-C_4H_9); 0.92 (t, *J* = 7.5 Hz, 3 H, $CH_3CH_2CH_2N$); 1.00−1.90 [m, 11 H, CH and CH_2 (cyclohex.) and $CH_3CH_2CH_2N$]; 1.97 (s, 1 H, CHN); 2.47 (AB system, 2 H, NCH_2); 3.71 (s, 3 H, OCH_3); minor isomer: δ = 0.80 (s, 9 H, *t*-C_4H_9); 0.87 (t, *J* = 7.0 Hz, 3 H, $CH_3CH_2CH_2N$); 1.00−1.80 (m, 11 H, CH and CH_2 (cyclohex.) and $CH_3CH_2CH_2N$); 1.91 (s, 1 H, CHN); 2.09 (qd, *J* = 9.0, 6.4 Hz, 1 H, NCH_2); 2.81 (qd, *J* = 9.4, 5.4 Hz, 1 H, NCH_2); 3.65 (s, 3 H, OCH_3). − ^{13}C NMR ($CDCl_3$): major isomer: δ = 12.15 (CH_3); 23.55 (CH_2CH_3); 26.38 (C3); 27.38 (C5); 27.93 [$C(CH_3)_3$]; 29.39 (C6); 32.19 [$C(CH_3)_3$]; 32.70 (C2); 48.17 (C4); 48.93 (CHN); 51.06 (C1); 52.20 (OCH_3); 53.97 (NCH_2); 171.48 (C=O); minor isomer: δ = 12.25 (CH_3); 23.61 (CH_2CH_3); 25.98 (C3); 26.44 (C5); 27.89 [$C(CH_3)_3$]; 28.55 (C6); 32.56 [$C(CH_3)_3$]; 32.85 (C2); 47.89 (C4); 49.28 (CHN); 49.73 (C1); 52.24 (OCH_3); 54.49 (NCH_2); 171.37 (C=O). − MS: *m*/*z* (%) = 267 (7) [M^+], 252 (25), 208 (60), 166 (50), 57 (100). − $C_{16}H_{29}NO_2$ (267.4): calcd. C 71.87; H 10.93; N 5.24; found C 71.87; H 11.02; N 5.12.

Spiroaziridine 2c: Oil. IR (KBr): $\tilde{\nu}$ = 1726, 1752 (C=O) cm^{-1}. − ^1H NMR ($CDCl_3$): δ = 0.79 (s, 9 H, *t*-C_4H_9); 1.00−1.90 [m, 9 H,

CH_2 and CH (cyclohex.)]; 2.68 (s, 1 H, CHN); 3.76 (s, 3 H, OCH_3); 6.75−7.20 (m, 5 H, C_6H_5). − ^{13}C NMR ($CDCl_3$): δ = 26.73 (C3); 27.38 (C5); 28.28 [C(*CH_3*)$_3$]; 32.31 [*C*(CH_3)$_3$]; 33.24 (C6); 35.72 (C2); 48.24 (C4); 48.58 (CHN); 52.93 (OCH_3); 53.27 (C1); 120.93, 123.26, 129.41, 149.06 (C_6H_5); 171.48 (C=O). − MS: *m*/*z* (%) = 301 (2) [M^+], 300 (6), 242 (100), 158 (20), 104 (45), 77 (78), 57 (99). − $C_{19}H_{27}NO_2$ (301.4): calcd. C 75.71; H 9.03; N 4.65; found C 75.73; H 10.02; N 4.28.

Spiroaziridine 2d: Solid, M.p. = 81 °C. − IR (KBr): ṽ = 1726, 1747 (C=O) cm^{-1}. − ^1H NMR ($CDCl_3$, mixture of the two major diastereomers): δ = 0.65, 0.73 (2 s, 9 H, *t*-C_4H_9); 1.24, 1.27 (2 d, *J* = 6.4 Hz, 3 H, *CH_3*CH); 1.00−1.80 (m, 9 H, CH_2 and CH (cyclohex.)]; 1.88, 2.02 (2 s, 1 H, CHN); 3.20−3.35 (m, 1 H, *CH*CH_3); 3.58, 3.71 (2 s, 3 H, OCH_3); 7.05−7.35 (m, 5 H, C_6H_5). − ^{13}C NMR ($CDCl_3$): first isomer: δ = 24.94 (*CH_3*CH); 26.59 (C3); 27.67 (C5); 28.14 [C(*CH_3*)$_3$]; 32.52 [*C*(CH_3)$_3$]; 30.04 (C6); 32.90 (C2); 48.18 (C4); 48.56 (CHN); 52.55 (OCH_3); 52.67 (C1); 62.09 (*CH*CH_3); 126.90, 127.29, 128.82, 145.55 (C_6H_5); 171.73 (C=O); second isomer: δ = 25.21 (*CH_3*CH); 26.69 (C3); 27.75 (C5); 28.20 [C(*CH_3*)$_3$]; 32.77 [*C*(CH_3)$_3$]; 29.63 (C6); 32.99 (C2); 48.08 (C4); 48.48 (CHN); 52.37 (OCH_3); 52.88 (C1); 60.86 (*CH*CH_3); 127.05, 127.46, 128.95, 145.15 (C_6H_5); 171.35 (C=O). − MS: *m*/*z* (%) = 329 (3) [M^+], 270 (15), 224 (98), 180 (32), 105 (99), 81 (88), 57 (100). − $C_{21}H_{31}NO_2$ (329.5): calcd. C 76.55; H 9.48; N 4.25; found C 76.58; H 9.72; N 4.52.

Spiroaziridine 3a: Oil. IR (KBr): ṽ = 1717, 1744 (C=O) cm^{-1}. − ^1H NMR ($CDCl_3$): δ = 1.19 (t, *J* = 7.2 Hz, 3 H, *CH_3*CH_2O); 1.50−1.90 (m, 8 H, CH_2 (cyclopent.)]; 2.14 (s, 1 H, CHN); 3.63 (s, 2 H, $PhCH_2$); 4.05−4.20 (m, 2 H, (CH_2O); 7.05−7.35 (m, 5 H, C_6H_5). − ^{13}C NMR ($CDCl_3$): δ = 14.93 (CH_3); 25.20, 26.18 (C3, C4); 27.52, 32.78 (C2, C5); 49.83 (CHN); 56.16 (C1); 57.95 (NCH_2); 61.25 (CH_2O); 127.26, 127.80, 128.80, 139.54 (C_6H_5); 171.00 (C=O). − MS: *m*/*z* (%) = 259 (4) [M^+], 168 (68), 140 (34); 91 (100). − $C_{16}H_{21}NO_2$ (259.3): calcd. C 74.10; H 8.16; N 5.40; found C 74.27; H 8.22; N 5.24.

Spiroaziridine 3b: Oil. IR (KBr): ṽ = 1717, 1747 (C=O) cm^{-1}. − ^1H NMR ($CDCl_3$): δ = 0.87 (t, *J* = 7.5 Hz, 3 H, *CH_3*CH_2CH_2N); 1.23 (t, *J* = 7.2 Hz, 3 H, *CH_3*CH_2O); 1.45−1.85 [m, 10 H, CH_2 (cyclopent.) and $CH_3CH_2CH_2N$]; 1.99 (s, 1 H, CHN); 2.15, 2.45 (AB system, 2 H, NCH_2); 4.11, 4.15 (2 q, *J* = 7.2 Hz, 2 H, CH_2O). − ^{13}C NMR ($CDCl_3$): δ = 12.15 (*CH_3*CH_2CH_2N); 14.79 (*CH_3*CH_2O); 23.41 ($CH_3CH_2CH_2N$); 25.03, 25.96 (C3, C4); 26.93, 32.56 (C2, C5); 49.64 (CHN); 55.41 (C1); 56.41 (NCH_2); 61.04 (OCH_2); 171.25 (C=O). − MS: *m*/*z* (%) = 211 (15) [M^+], 138 (71), 95 (100). − $C_{12}H_{21}NO_2$ (211.3): calcd. C 68.21; H 10.02; N 6.63; found C 67.65; H 10.08; N 6.65.

Spiroaziridine 3e: Oil. IR (KBr): ṽ = 1719, 1746 (C=O) cm^{-1}. − ^1H NMR ($CDCl_3$): δ = 1.04 (d, *J* = 6.4 Hz, 3 H, *CH_3*CH); 1.08 (d, *J* = 6.4 Hz, 3 H, *CH_3*CH); 1.20 (t, *J* = 7.2 Hz, 3 H, *CH_3*CH_2O); 1.50−1.85 [m, 8 H, CH_2 (cyclopent.)]; 1.98 (s, 1 H, CHN); 1.90−2.00 (m, 1 H, *CH*CH_3); 4.12, 4.15 (2 q, *J* = 7.2 Hz, 2 H, CH_2O). − ^{13}C NMR ($CDCl_3$): δ = 15.02 (*CH_3*CH_2O); 22.70, 22.78 (*CH_3*CH); 25.24, 26.23 (C3, C4); 26.77, 33.18 (C2, C5); 48.79 (CHN); 54.53 (*CH*CH_3); 56.66 (C1); 61.24 (CH_2O); 171.47 (C=O). − MS: *m*/*z* (%) = 211 (13) [M^+], 210 (12); 168 (11); 149 (75); 71 (63); 57 (67); 43 (100). − $C_{12}H_{21}NO_2$ (211.3): calcd. C 68.21; H 10.02; N 6.63; found C 67.85; H 10.09; N 6.71.

Spiroaziridine 4: Oil. IR (KBr): ṽ = 1670 (br.s, C=C, C=O), 3382 (NH) cm^{-1}. − ^1H NMR ($CDCl_3$): mixture of two diastereomers: δ = 1.07 (major isomer), 1.09 (minor isomer) (2 s, 9 H, *t*-C_4H_9); 1.11 (t, *J* = 7.5 Hz, 3 H, *CH_3*CH_2CH_2N); 1.13 (t, *J* = 7.5 Hz, 3 H, *CH_3*CH_2CH_2N); 1.20−1.95 [m, 13 H, CH_2 and CH (cyclohex.) and $CH_3CH_2CH_2N$]; 2.13 (minor isomer), 2.17 (major isomer) (2 s, 1 H, CHN); 2.70 (AB system, 2 H, CH_2N); 3.42 (quint, *J* = 6.7 Hz, 2 H, CH_2NCO). − ^{13}C NMR ($CDCl_3$): major isomer: δ = 11.79 (CH_3); 12.31 (CH_3); 23.44 (*CH_2*CH_3); 23.96 (*CH_2*CH_3); 26.34 (C3); 27.26 (C5); 27.89 [C(*CH_3*)$_3$]; 29.96 (C6); 32.85 (C2); 32.87 [*C*(CH_3)$_3$]; 40.81 (CH_2N), 48.47 (C4); 50.12 (C1); 51.51 (CHN); 53.09 (NCH_2); 170.13 (C=O); minor isomer: 11.79 (CH_3); 12.38 (CH_3); 23.42 (*CH_2*CH_3); 23.96 (*CH_2*CH_3); 25.96 (C3); 27.26 (C5); 27.80 [C(*CH_3*)$_3$]; 28.87 (C6); 32.46 [*C*(CH_3)$_3$]; 32.85 (C2); 40.81 (CH_2N), 47.81 (C4); 49.20 (C1); 51.18 (CHN); 53.75 (NCH_2); 170.07 (C=O). − MS: *m*/*z* (%) = 294 (7) [M^+], 208 (100), 166 (23). − $C_{18}H_{34}N_2O$ (294.5): calcd. C 73.42; H 11.64; N 9.51; found C 73.12; H 11.61; N 9.17.

Spiroaziridine 5: Oil. IR (KBr): ṽ = 1668 (br. s, C=O), 3382 (NH) cm^{-1}. − ^1H NMR ($CDCl_3$): δ = 0.84 (t, *J* = 7.5 Hz, 3 H, *CH_3*CH_2CH_2N); 0.88 (t, *J* = 7.2 Hz, 3 H, *CH_3*CH_2CH_2N); 1.40−1.75 [m, 12 H, CH_2 (cyclopent.) and $CH_3CH_2CH_2N$]; 1.93 (s, 1 H, CHN); 2.10 (dt, *J* = 11.7, 7.5 Hz, 1 H, NCH_2); 2.45 (dt, *J* = 11.7, 7.5 Hz, 1 H, NCH_2); 3.00−3.20 (m, 2 H, CH_2NCO); 6.63 (br.s, 1 H, NH). − ^{13}C NMR ($CDCl_3$): δ = 11.81, 12.30 (*CH_3*CH_2CH_2N); 23.60 ($CH_3CH_2CH_2N$); 25.20, 26.20 (C3, C4); 27.53, 32.48 (C2, C5); 40.76 (NCH_2); 51.44 (CHN); 54.70 (CN); 55.35 (*CH_2*NCO); 170.62 (C=O). − MS: *m*/*z* (%) = 224 (22) [M^+], 138 (100), 96 (60). − $C_{13}H_{24}N_2O$ (224.3): calcd. C 69.60; H 10.78; N 12.49; found C 68.02; H 10.68; N 12.20.

Methyl Anilino(4-*tert*-butylcyclohex-1-en-1-yl)acetate (8c): Oil. IR (KBr): ṽ = 1738 (C=O), 3405 (NH) cm^{-1}. − ^1H NMR ($CDCl_3$): δ = 0.77, 0.78 (2 s, 9 H, *t*-C_4H_9); 1.00−2.20 [m, 7 H, CH_2 and CH (cyclohex.)]; 3.68 (s, 3 H, OCH_3); 4.37 (s, 1 H, CHN); 4.47 (br. s., 1 H, NH); 5.82 (s, 1 H, =CH); 6.45−6.65 (m, 3 H, C_6H_5); 7.00−7.15 (m, 2 H, C_6H_5). − ^{13}C NMR ($CDCl_3$): δ = 24.52, 24.66 (C5); 26.90 (C6); 27.48, 27.55 (C3); 27.82 [(*CH_3*)$_3$C]; 32.84 [*C*(CH_3)$_3$]; 44.30, 44.55 (C4); 53.11, 53.16 (OCH_3); 62.81 (CHN); 113.98, 114.04, 118.48, 129.84, 147.18 (C_6H_5); 126.61, 128.02 (C2); 134.19, 134.50 (C1); 173.33, 173.38 (C=O). − MS: *m*/*z* (%) = 301 (6) [M^+], 300 (25); 242 (59); 158 (37); 93 (84); 77 (100). − $C_{19}H_{27}NO_2$ (301.4): calcd. C 75.71; H 9.03; N 4.65; found C 74.55; H 9.62; N 4.82.

Ethyl Benzylamino(cyclopent-1-en-1-yl)acetate (9a): Oil. IR (KBr): ṽ = 1732 (C=O), 3338 (NH) cm^{-1}. − ^1H NMR ($CDCl_3$): δ = 1.20 (t, *J* = 7.2 Hz, 3 H, CH_3); 1.75−1.85 (m, 2 H, 4-CH_2); 1.90 (br. s., 1 H, NH); 2.20−2.35 (m, 4 H, 3-CH_2 and 5-CH_2); 3.65 (AB system, 2 H, $PhCH_2$); 3.92 (s, 1 H, CHN); 4.12 (q, *J* = 7.2 Hz, 2 H, CH_2O); 5.62 (s, 1 H, =CH); 7.10−7.30 (m, 5 H, C_6H_5). − ^{13}C NMR ($CDCl_3$): δ = 14.97 (CH_3); 23.80 (C4); 32.92, 33.03 (C3, C5); 52.26 (CH_2N); 61.56 (CH_2O); 62.19 (CHN); 127.73, 129.04, 129.45, 141.15 (C_6H_5); 129.02 (=CH); 140.38 (C1); 173.69 (C=O). − MS: *m*/*z* (%) = 259 (0.2) [M^+], 186 (94); 91 (100). − $C_{16}H_{21}NO_2$ (259.3): calcd. C 74.10; H 8.16; N 5.40; found C 74.84; H 8.86; N 5.56.

Ethyl Cyclopent-1-en-1-yl(propylamino)acetate (9b): This compound was not obtained under the above hyperbaric conditions, which provided only spiroaziridines **3b** and **5** (see Table 1). It was, however, prepared under thermal conditions comparable to those described in ref. 12. Oil. IR (KBr): ṽ = 1648 (C=C), 1736 (C=O), 3334 (NH) cm^{-1}. − ^1H NMR ($CDCl_3$): δ = 0.85 (t, *J* = 7.5 Hz, 3 H, *CH_3*CH_2CH_2N); 1.20 (t, *J* = 7.2 Hz, 3 H, *CH_3*CH_2O); 1.35−1.50 (m, 2 H, $CH_3CH_2CH_2N$); 1.70 (br. s., 1 H, NH); 1.75−1.90 (m, 2 H, 4-CH_2); 2.20−2.35 (m, 4 H, 3-CH_2 and 5-CH_2); 2.35−2.50 (m, 2 H, CH_2N); 3.88 (s, 1 H, CHN); 4.12 (q, *J* = 7.2 Hz, 2 H, CH_2O); 5.61 (s, 1 H, =CH). − ^{13}C NMR ($CDCl_3$):

δ = 12.38 ($CH_3CH_2CH_2N$); 14.91 (CH_3CH_2O); 23.76 (C4); 23.88 ($CH_3CH_2CH_2N$); 32.82, 32.95 (C3, C5); 50.44 (CH_2N); 63.12 (CHN); 61.44 (CH_2O); 129.06 (C2); 141.26 (C1); 173.85 (C=O). − MS: *m*/*z* (%) = 211 (6) [M^+], 167 (27); 149 (100); 97 (72); 71 (99). − $C_{12}H_{21}NO_2$ (211.3): calcd. C 68.21; H 10.02; N 6.63; found C 68.15; H 10.88; N 6.73.

Ethyl Anilino(cyclopent-1-en-1-yl)acetate (9c): Oil. IR (KBr): ṽ = 1733 (C=O), 3398 (NH) cm^{-1}. − ^1H NMR ($CDCl_3$): δ = 1.19 (t, *J* = 7.2 Hz, 3 H, CH_3CH_2O); 1.75−1.90 (m, 2 H, 4-CH_2); 2.20−2.35 (m, 4 H, 3-CH_2 and 5-CH_2); 4.14 (q, *J* = 7.2 Hz, 2 H, CH_2O); 4.43 (br. s, 1 H, NH); 4.62 (s, 1 H, CHN); 5.73 (s, 1 H, =CH); 6.50−6.70 (m, 3 H, C_6H_5); 7.05−7.15 (m, 2 H, C_6H_5). − ^{13}C NMR ($CDCl_3$): δ = 14.86 (CH_3); 23.84 (C4); 33.04, 33.11 (C3, C5); 58.37 (CHN); 62.08 (CH_2O); 114.10, 118.73, 129.87, 147.21 (C_6H_5); 129.97 (C2); 140.47 (C1); 172.54 (C=O). − MS: *m*/*z* (%) = 245 (9) [M^+], 244 (9); 172 (100); 77 (44). − $C_{15}H_{19}NO_2$ (245.3): calcd. C 73.44; H 7.87; N 5.71; found C 73.21; H 7.98; N 5.79.

Ethyl Cyclopent-1-en-1-yl(α-methylbenzylamino)acetate (9d): Oil. IR (KBr): first isomer: ṽ = 1650 (C=C), 1732 (C=O), 3331 (NH); second isomer: *n* = 1651 (C=C), 1734 (C=O), 3336 (NH) cm^{-1}. − ^1H NMR ($CDCl_3$): first diastereomer: δ = 1.19 (t, *J* = 7.2 Hz, 3 H, (CH_3CH_2O); 1.27 (d, *J* = 6.4 Hz, 3 H, CH_3CH); 1.70−1.85 (m, 2 H, 4-CH_2); 1.88 (br. s., 1 H, NH); 2.10−2.35 (m, 4 H, 3-CH_2 and 5-CH_2); 3.64 (q, *J* = 6.4 Hz, 1 H, CH_3CH); 3.65 (s, 1 H, CHN); 4.12 (dq, J = 7.2, 1.9 Hz, 2 H, CH_2O); 5.52 (s, 1 H, =CH); 7.10−7.30 (m, 5 H, C_6H_5); second diastereomer: δ = 1.13 (t, *J* = 7.2 Hz, 3 H, CH_3CH_2O); 1.29 (d, *J* = 6.8 Hz, 3 H, CH_3CH); 1.70−1.90 (m, 2 H, 4-CH_2); 2.01 (br. s., 1 H, NH); 2.10−2.35 (m, 4 H, 3-CH_2 and 5-CH_2); 3.63 (q, *J* = 6.8 Hz, 1 H, CH_3CH); 3.83 (s, 1 H, CHN); 4.03 (dq, J = 7.2, 1.9 Hz, 2 H, CH_2O); 5.51 (s, 1 H, =CH); 7.10−7.30 (m, 5 H, C_6H_5). − ^{13}C NMR ($CDCl_3$): first isomer: δ = 14.97 (CH_3CH_2O); 23.67 (C4); 33.02, 33.39 (C3, C5); 25.66 (CH_3CH); 57.04 (CH_3CH); 60.63 (CHN); 61.37 (CH_2O); 127.55, 127.70, 129.05, 145.59 (C_6H_5); 128.19 (C2); 141.66 (C1); 174.47 (C=O); second isomer: δ = 14.81 (CH_3CH_2O); 23.78 (C4); 32.22, 32.95 (C3, C5); 24.51 (CH_3CH); 55.74 (CH_3CH); 60.19 (CHN); 61.47 (CH_2O); 127.52, 127.68, 129.03, 145.57 (C_6H_5); 130.10 (C2); 140.98 (C1); 173.38 (C=O). − MS: *m*/*z* (%) = 273 (3) [M^+], 258 (8); 201 (80); 97 (100). − $C_{17}H_{23}NO_2$ (273.4): calcd. C 74.69; H 8.48; N 5.12; found C 74.92; H 8.73; N 5.32.

Ethyl Cyclopent-1-en-1-yl(isopropylamino)acetate (9e): Oil. IR (KBr): ṽ = 1651 (C=C), 1735 (C=O), 3330 (NH) cm^{-1}. − ^1H NMR ($CDCl_3$): δ = 0.98 (d, *J* = 6.0 Hz, 6 H, CH_3CH); 1.20 (t, *J* = 7.2 Hz, 3 H, CH_3CH_2O); 1.75−1.90 (m, 3 H, 4-CH_2 and NH); 2.15−2.35 (m, 4 H, 3-CH_2 and 5-CH_2); 2.66 (quint, *J* = 6.0 Hz, 1 H, CH_3CH); 4.01 (s, 1 H, CHN); 4.12 (q, *J* = 7.2 Hz, 2 H, CH_2O); 5.61 (s, 1 H, =CH). − ^{13}C NMR ($CDCl_3$): δ = 14.91 (CH_3CH_2O); 23.09, 23.77 (CH_3CH); 23.72 (C4); 32.73, 32.98 (C3, C5); 46.95 (CH_3CH); 60.46 (CHN); 61.48 (CH_2O); 129.12 (C2); 141.28 (C1); 174.08 (C=O). − MS: *m*/*z* (%) = 211 (8) [M^+], 167 (18); 149 (69); 94 (48); 57(100). − $C_{12}H_{21}NO_2$ (211.3): calcd. C 68.21; H 10.02; N 6.63; found C 67.92; H 10.01; N 6.62.

Ethyl Cyclopent-1-en-1-yl[(diphenylmethyl)amino]acetate (9f): Oil. IR (KBr): ṽ = 1732 (C=O), 3332 (NH) cm^{-1}. − ^1H NMR ($CDCl_3$): δ = 1.18 (t, *J* = 7.2 Hz, 3 H, CH_3CH_2O); 1.75−1.90 (m, 2 H, 4-CH_2); 2.20−2.35 (m, 5 H, 3-CH_2, 5-CH_2 and NH); 3.83 (s, 1 H, CHN); 4.12 (q, *J* = 7.2 Hz, 2 H, CH_2O); 4.70 (s, 1 H, $CHPh_2$); 5.54 (s, 1 H, =CH); 7.10−7.50 (m, 10 H, C_6H_5). − ^{13}C NMR ($CDCl_3$): δ = 14.96 (CH_3); 23.79 (C4); 33.05 (C3, C5); 60.64 (CHN); 61.50 (CH_2O); 65.38 ($CHPh_2$); 127.80, 128.14, 129.14, 143.72, 144.46 (C_6H_5); 128.18 (C2); 141.31 (C1); 173.92 (C=O). − MS: *m*/*z* (%) = 335 (0.3) [M^+], 262 (32); 167 (100). − $C_{22}H_{25}NO_2$ (335.4): calcd. C 78.77; H 7.51; N 4.18; found C 78.69; H 7.75; N 4.46.

Ethyl Anilino(cyclopentylidene)acetate (10c): Oil. IR (KBr): ṽ = 1644 (C=C), 1703 (C=O), 3379 (NH) cm^{-1}. − ^1H NMR ($CDCl_3$): δ = 1.16 (t, *J* = 7.2 Hz, 3 H, CH_3CH_2O); 1.50−1.60 (m, 2 H), 1.65−1.75 (m, 2 H, 3-CH_2 and 4-CH_2); 2.30 (t, *J* = 7.2 Hz, 2 H), 2.78 (t, *J* = 7.2 Hz, 2 H, 2-CH_2 and 5-CH_2); 4.10 (q, *J* = 7.2 Hz, 2 H, CH_2O); 5.17 (br. s, 1 H, NH); 6.45−6.70 (m, 3 H, C_6H_5); 7.00−7.15 (m, 2 H, C_6H_5). − ^{13}C NMR ($CDCl_3$): δ = 14.89 (CH_3); 26.11, 27.72 (C3, C4); 33.56, 34.62 (C2, C5); 61.17 (CH_2O); 114.89, 119.21, 129.60, 145.88 (C_6H_5); 122.41 (C1); 157.29 (=C-N); 166.68 (C=O). − MS: *m*/*z* (%) = 245 (35) [M^+], 244 (37); 215 (14); 198 (12); 170 (100); 104 (58); 77 (98). − $C_{15}H_{19}NO_2$ (245.3): calcd. C 73.44; H 7.87; N 5.71; found C 73.33; H 7.82; N 5.83.

Ethyl Cyclopentylidene(isopropylamino)acetamide (10e): Oil. IR (KBr): ṽ = 1640 (C=C), 1690 (C=O), 3340 (NH) cm^{-1}. − ^1H NMR ($CDCl_3$): δ = 0.99 (d, *J* = 6.4 Hz, 6 H, CH_3CH); 1.25 (t, *J* = 7.2 Hz, 3 H, CH_3CH_2O); 1.55−1.70 (m, 4 H, 3-CH_2 and 4-CH_2); 2.25−2.35 (m, 2 H), 2.55−2.65 (m, 2 H, 2-CH_2 and 5-CH_2); 2.68 (br. s., 1 H, NH); 3.12 (quint, *J* = 6.4 Hz, 1 H, CH_3CH); 4.15 (q, *J* = 7.2 Hz, 2 H, CH_2O). − ^{13}C NMR ($CDCl_3$): δ = 15.00 (CH_3CH_2O); 24.18 (CH_3CH); 26.59, 27.83 (C3, C4); 33.48, 33.66 (C2, C5); 48.06 (CH_3CH); 61.07 (CH_2O); 128.76 (C1); 143.90 (=C−N); 167.33 (C=O). − MS: *m*/*z* (%) = 211 (28) [M^+], 168 (15); 119 (10); 86 (98); 84 (94); 49 (98); 48 (100). − $C_{12}H_{21}NO_2$ (211.3): calcd. C 68.21; H 10.02; N 6.63; found C 67.96; H 9.92; N 6.49.

Isomerization of Cyclopent-1-en-1-yl(isopropylamino)acetate 9e into Ethyl Cyclopentylidene(isopropylamino)acetate (10e): A solution of ester **9e** (8 mg), isopropylamine (9 mg), and triethylamine (20 mg) in ethanol (1 mL) was allowed to stand at 11 kbar at room temperature for 62 h. After a return to atmospheric pressure, the solvent and amines were evaporated to yield a mixture (1:3) of the initial substrate **9e** and its conjugated isomer **10e**, according to ^1H NMR.

Preparation of Dibromo Diester 17: A solution of Br_2 (1.6 g, 10 mmol) in $CHCl_3$ (15 mL) was added at 0 °C, over a period of 0.5 h, to a solution of diester **16** (1.1 g, 5 mmol) in $CHCl_3$ (10 mL). When the addition was complete, the solution was allowed to warm slowly to room temperature, and stirred at room temp. for 4 h. After evaporation of the solvent, the residue was dissolved in acetone (50 mL) and the solution was refluxed at the presence of K_2CO_3 (1.4 g) for 8 h. After filtration and evaporation of the solvent, the two isomers of diester **17** were isolated by flash chromatography (pentane/Et_2O, 7:1) in 76% overall yield. Both are solids (M.p. *cis* isomer: 117−118 °C, *trans* isomer: 130−131 °C) − IR (KBr): *cis* isomer: ṽ = 1594 (C=C), 1704 (C=O) cm^{-1}; *trans* isomer: ṽ = 1590 (C=C), 1705 (C=O) cm^{-1}. − ^1H NMR ($CDCl_3$): *cis* isomer: δ = 2.62 [s, 4 H, CH_2 (cyclohex.)]; 2.79 [s, 4 H, CH_2 (cyclohex.)], 3.74 (s, 6 H, OCH_3); *trans* isomer: δ = 2.52 [t, *J* = 6.5 Hz, 4 H, CH_2 (cyclohex.)], 2.86 [t, *J* = 6.5 Hz, 4 H, CH_2 (cyclohex.)]; 3.75 (s, 6 H, OCH_3). − ^{13}C NMR ($CDCl_3$): *cis* isomer: δ = 30.69 (C2, C3); 33.39 (C5, C6); 53.52 (OCH_3); 108.57 (=CBr); 153.41 (C1, C4); 164.58 (C=O); *trans* isomer: δ = 29.38 (C3, C6); 33.81 (C2, C5); 53.26 (OCH_3); 108.60 (=CBr); 153.07 (C1, C4); 164.28 (C=O). − MS: *m*/*z* (%) = 382 (15) [M^+]; 350 (28), 322 (52) 272, 271 (89), 191 (77), 103 (76), 59 (100). − $C_{12}H_{14}Br_2O_4$ (382.0): calcd. C 37.73; H 3.69; − found C 37.97; H 3.73.

Reaction between Diester 17 and Benzylamine: A solution of *trans* diester **17** (191 mg, 0.5 mmol) and benzylamine (219 mg, 2 mmol) in a mixture of MeOH/CH_2Cl_2 (1:1, 4 g) was pressurized at 11 kbar at room temperature for 70 h. After a return to atmospheric pres-

sure, the solvent was removed and the residue was chromatographed (pentane/Et_2O, 1:3) to give a mixture of two major (1:1) and two minor (1:1) diastereomers **18** (137 mg). Overall yield 63%.

Dispiro Compound 18: Solid. IR (KBr): major isomers: $\tilde{\nu}$ = 1743 (C=O) cm^{-1}; minor isomers: *n* = 1744 (C=O) cm^{-1}. – ^1H NMR ($CDCl_3$): major isomers: δ = 1.50–1.90 [m, 8 H, CH_2 (cyclohex.)]; 2.13, 2.14 (2 s, 2 H, CHN); 3.63, 3.64 (2 s, 6 H, OCH_3) 3.60–3.90 (AB system, 4 H, CH_2Ph); 7.10–7.35 (m, 10 H, C_6H_5); minor isomers: δ = 1.50–1.95 [m, 8 H, CH_2 (cyclohex.)]; 2.12, 2.14 (2 s, 2 H, CHN); 3.61, 3.65 (2 s, 6 H, OCH_3) 3.60–3.90 (AB-system, 4 H, CH_2Ph); 7.10–7.35 (m, 10 H, C_6H_5). – ^{13}C NMR ($CDCl_3$): major isomers: δ = 27.71, 28.24 (C5, C6); 30.34, 30.46 (C2, C3); 48.56, 48.63 (CHN); 49.95, 50.23 (C1, C4); 52.47 (OCH_3); 55.93 ($PhCH_2$); 127.40, 127.77, 127.83, 128.82, 139.01, 139.07 (C_6H_5); 170.62, 170.72 (C=O); minor isomers: δ = 27.05, 27.49 (C5, C6); 31.05, 31.14 (C2, C3); 48.41, 48.53 (CHN); 50.05, 50.32 (C1, C4); 52.44 (OCH_3); 55.93 ($PhCH_2$); 127.38, 127.83, 127.90, 128.79, 128.81, 139.02, 139.07 (C_6H_5); 170.74, 170.79 (C=O). – MS: *m/z* (%) = 435 (2) $[M + 1]^+$, 434 (2) $[M^+]$, 375 (3), 330 (4), 257 (13), 178 (25), 91 (100). – $C_{26}H_{30}N_2O_4$ (434.5): calcd. C 71.87; H 6.96; N 6.45; found C 71.74; H 7.14; N 6.39.

The same reaction conditions using *cis* diester **17** (191 mg, 0.5 mmol) and benzylamine produced a mixture of four diastereomers **18** (105 mg) in 48% overall yield.

Reaction between Methyl 2-Chloro-2-(cyclopropylidene)acetate 1c and Benzylamine. – a) Reaction in Methanol: A solution of ester **1c** (219 mg, 1.5 mmol) and benzylamine (321 mg, 3 mmol) in methanol (3.5 mL) was pressurized at 11 kbar at room temperature for 48 h. After a return to atmospheric pressure, the solvent was removed in vacuo and the residue was chromatographed on silica gel (CH_2Cl_2/MeOH, 95:5) to give **13** (55 mg, 15%) as the only isolable product.

Methyl 5-(Benzylamino)-5-oxopentanoate (13): Oil. IR (KBr): $\tilde{\nu}$ = 1649 (C=O), 1737 (C=O), 3295 (NH) cm^{-1}. – ^1H NMR ($CDCl_3$): δ = 1.88 (m, 2 H, 3-CH_2); 2.18 (m, 2 H, 4-CH_2); 2.28 (m, 2 H, 2-CH_2); 3.56 (s, 3 H, OCH_3); 4.30 (s, 1 H, CH_2Ph); 4.33 (s, 1 H, CH_2Ph); 6.14 (br. s, 1 H, NH); 7.10–7.30 (m, 5 H, C_6H_5). – ^{13}C NMR ($CDCl_3$): δ = 21.45, 33.66, 35.91 (CH_2); 52.16 (OCH_3); 128.02, 128.32, 129.24, 138.92 (C_6H_5); 172.67, 174.26 (C=O). – MS: *m/z* (%) = 235 (28) $[M^+]$, 204 (25); 175 (45); 106 (100); 91 (99). – $C_{13}H_{17}NO_3$ (235.3): calcd. C 66.36; H 7.28; N 5.95; found C 66.35; H 7.52; N 6.09.

b) Reaction in Ethanol: The same procedure was followed, but using ethanol as solvent. Similar workup and chromatography on silica gel (pentane/Et_2O, 3:1) gave **11-Et** (37 mg, 19%) and diethyl pentanedioate **14** (35 mg, 19%). The isolated Michael adduct **11-Et** was unstable at room temp. and when stored in a solution of $CDCl_3$ it underwent decomposition in a few days. The spectral characterization data for compound **11** were identical with those described earlier.[22]

Ethyl 2-[1-(Benzylamino)cyclopropyl]-2-chloroacetate (11-Et): IR (KBr): $\tilde{\nu}$ = 1750 (C=O), 3340 (NH) cm^{-1}. – ^1H NMR ($CDCl_3$): δ = 0.70–1.00 [m, 4 H, CH_2 (cycloprop.)]; 1.25 (t, *J* = 7.2 Hz, 3 H, CH_3CH_2O); 3.81 (d, *J* = 12.8 Hz, "A" part of an AB system, 1 H, CH_2Ph); 3.92 (d, *J* = 12.8 Hz, "B" part of an AB system, 1 H, CH_2Ph); 4.19 (q, *J* = 7.2 Hz, 2 H, CH_2O); 4.34 (s, 1 H, CHCl); 7.10–7.30 (m, 5 H, C_6H_5). – ^{13}C NMR ($CDCl_3$): δ = 14.73 (CH_3); 15.26, 15.44 (CH_2); 42.53 (C_{quat}); 50.92 (CH_2N); 62.92 (OCH_2); 63.58 (CHCl); 127.82, 128.82, 129.04, 140.34 (C_6H_5); 169.04 (C=O). – MS: *m/z* (%) = 232 (28) $[M^+ - Cl]$; 186 (44); 91 (100).

c) Reaction in Acetonitrile/THF: the same reaction was performed in a 1:1 acetonitrile/THF mixture under the conditions described above. After return to atmospheric pressure, the solvents were evaporated under reduce pressure to yield, according to ^1H NMR, the enamino ester **12** described earlier.[11]

Acknowledgments

A. R. is grateful to the CNRS for a research associate position (Aug. – Dec. 1999). We also wish to thank Prof. Armin de Meijere (University of Göttingen, Germany) for samples of methyl 2-chloro-2-(cyclopropylidene)acetate, Dr. Jean-Yves Valnot and Dr. Isabelle Chataigner (IRCOF), and Prof. Jean d'Angelo (Univ. Paris XI) for their productive comments.

[1] See for instance: [1a] D. C. Cole, *Tetrahedron* **1994**, *50*, 9517–9582; G. Cardillo, C. Tomasini, *Chem. Soc. Rev.* **1996**, 117–128. – [1b] E. Juaristi, *Enantioselective Synthesis of* β-*Amino Acids*, Wiley VCH, New York, **1997**. – [1c] N. N. Romanova, A. G. Gravis, G. M. Shaidullina, I. F. Leshcheva, Y. G. Bundel′, *Mendeleev Commun.* **1997**, 235–236.

[2] D. Tanner, *Angew. Chem. Int. Ed. Eng.* **1994**, *33*, 599–619.

[3] See for instance: [3a] G. Bouteville, Y. Gelas-Mialhe, R. Vessiere, *Bull. Soc. Chim. Fr.* **1971**, 3264–3270. – [3b] L. Wartski, C. Wakselman, A. Sierra-Escudero, *Bull. Soc. Chim. Fr.* **1972**, 1478–1482. – [3c] Y. Gelas-Mialhe, R. Hierle, R. Vessiere, *J. Heterocycl. Chem.* **1974**, *11*, 347–349. – [3d] Y. Gelas-Mialhe, E. Touraud, R. Vessiere, *Can. J. Chem.* **1982**, *60*, 2830–2851. – [3e] J. Expert, Y. Gelas-Mialhe, R. Vessiere, *J. Heterocycl. Chem.* **1985**, *22*, 1285–1289.

[4] S. Martin, *Tetrahedron* **1980**, *36*, 419–460.

[5] [5a] M. Pfau, *Bull. Soc. Chim. Fr.* **1967**, 1117–1125. – [5b] J. d′Angelo, J. Maddaluno, *J. Am. Chem. Soc.* **1986**, *108*, 8112–8114.

[6] M. Carducci, S. Fioravanti, M. A. Loreto, L. Pellacani, P. A. Terdella, *Tetrahedron Lett.* **1996**, *37*, 3777–3778

[7] [7a] M. N. Rao, A. G. Holkar, N. R. Ayyangar, *Tetrahedron Lett.* **1989**, *30*, 4717–4720. – [7b] M. N. Rao, A. G. Holkar, N. R. Ayyangar, *Tetrahedron Lett.* **1990**, *31*, 3343–3346. – [7c] J. M. Mohan, B. S. Uphade, V. R. Choudhary, T. Ravindranathan, A. Sudalai, *Chem. Commun.* **1997**, 1429–1430.

[8] [8a] J. Cossy, J. P. Pete, *Tetrahedron Lett.* **1980**, *21*, 2947–2948. – [8b] C. Meyer, J. P. Pete, O. Piva, *Recl. Trav. Chim. Pays-Bas* **1995**, *114*, 492–497.

[9] J. Moulines, P. Charpentier, J. P. Bats, A. Nuhrich, A. M. Lamidey, *Tetrahedron Lett.* **1992**, *33*, 487–490.

[10] E. Vedejs, S. Dax, G. R. Martinez, C. K. McClure, *J. Org. Chem.* **1987**, *52*, 3470–3472.

[11] M. Tamm, M. Thutewohl, C. B. Ricker, M. T. Bes, A. de Meijere, *Eur. J. Org. Chem.* **1999**, 2017–2024.

[12] A. Y. Rulev, J. Maddaluno, G. Plé, J. C. Plaquevent, L. Duhamel, *J. Chem. Soc., Perkin Trans. 1* **1998**, 1397–1401.

[13] W. G. Dauben, J. M. Gerdes, *Tetrahedron Lett.* **1983**, *24*, 3841–3844.

[14] J. Maddaluno, Ph.D. thesis, Univ. Paris VI, **1986**.

[15] Recent results by Reiser's group have, however, shown that secondary amines can also behave as nucleophiles in conjugated additions, provided that the hyperbaric reaction is performed at 60 °C: O. Reiser, Poster # 39 at the European High Pressure Research Group meeting, Kloster Banz (Germany), Aug. 30th – Sept. 2nd **2000**.

[16] A. Y. Rulev, J. Maddaluno, unpublished data. The addition of methanol to β-monosubstituted α,β-unsaturated esters takes place at atmospheric pressure, as described by F. Dumas et al. (ref.[19]).

[17] A solvent mixture compatible with the hetero-Michael addition of amines (ref.[14]).

[18] M. R. Bryce, H. M. Coates, J. Cooper, L. C. Murphy, *J. Org. Chem.* **1984**, *49*, 3399−3401.
[19] F. Dumas, B. Mezrhab, J. d′Angelo, *J. Org. Chem.* **1996**, *61*, 2293−2304.
[20] O. Miyata, T. Shinada, I. Ninomiya, T. Naito, *Tetrahedron Lett.* **1991**, *32*, 3519−3522.
[21] J. Volinsky, K. L. Erickson, *J. Org. Chem.* **1965**, *30*, 2208−2211.
[22] H. Urata, H. Maekawa, S. Takahashi, T. Fuchikami, *J. Org. Chem.* **1991**, *56*, 4320−4322.

Received November 6, 2000
[O00563]