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A new access to racemic carbacephems

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Summary — A new approach to carbacephems is reported involving the formation of the six-membered ring by cyclization of *N*-acyliminium ions. With methylene iminium species the reaction appeared general, while with (methoxycarbonyl)methylene iminium intermediates the cyclization occurred only if the acceptor carbon-carbon double bond was sufficiently electron enriched.

carbacephem / iminium ion / Lewis acid / β-lactam / azetidinone / cyclization

Résumé — Une nouvelle approche des carbacéphèmes racémiques. *Une nouvelle approche des carbacéphèmes basée sur la formation du cycle pipéridine par cyclisation exocyclique d'un* N*-acyl iminium est rapportée. Avec les méthylène iminiums comme intermédiaires la réaction de cyclisation semble générale, alors qu'avec les (méthoxycarbonyl)méthylène iminiums la cyclisation n'est observée que si la double liaison réceptrice est suffisamment électroniquement enrichie.*

carbacéphème / ion iminium / acide de Lewis / β-lactame / azétidinone / cyclisation

Introduction

Structural modification of naturally occurring β-lactams without loss of their bioactivity appears to be a good way to compete against bacterial resistance. The structural modification of cephalosporins into carbacephems [1], recently put in concrete form by the commercialization of Lorabid®, corresponds to such an aim (fig 1) [2].

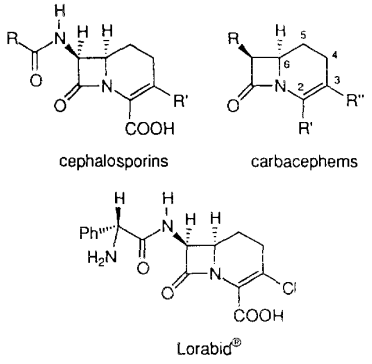


Fig 1

Different approaches have been employed to gain access to the carbacephem framework [3]. One of the strategies consists of the obtention of the β-lactam ring in the final step by either cycloaddition [4] or ring closure [5]. However, most methods studied involve the construction of the six-membered ring on the existing β-lactam ring. In these approaches, the formation of the *N-C* [6] or the *C-C* [7] bonds and a catalyzed Diels–Alder reaction [8] have been examined.

We wish to report our approach to the carbacephem skeleton in which the piperidine ring was formed by a C_2-C_3 bond ring closure using a highly reactive *N*-acyliminium intermediate (fig 2). Indeed, although the reactivity of *N*-acyliminium ions has been intensively studied [9], little is known about such an *exo*-cyclization in the β-lactam field.

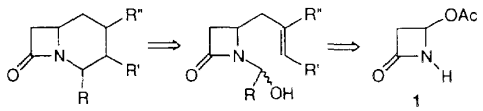


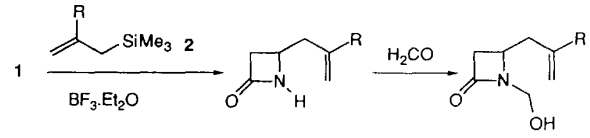
Fig 2

The lactams studied (table I) have been prepared starting from 4-acetoxyazetidin-2-one **1** [10]. Its reaction with allyltrimethylsilane **2a** in the presence of $BF_3.Et_2O$ was reported to give 4-allylazetidin-2-one **3a** [11]. This reaction was applied to the substituted allylsilanes **2b–e**. Allylazetidinones **3a–d** were obtained in satisfactory yields (table I). No product could be isolated in the case of the deactivated silane **2e**. The

* Correspondence and reprints

β-lactams **3a–d** were purified by liquid chromatography and characterized from their NMR and IR spectra. In these reactions we found that other Lewis acids, such as $SnCl_4$, $TiCl_4$ and $AlCl_3$, gave lower yields. The subsequent hydroxymethylation, which could be carried out in high yields by reaction of paraformaldehyde in the presence of potassium carbonate [12], led to the lactams **4a–d**, also characterized by standard spectroscopic methods.

Table I. Preparation of 4-allyl-1-(hydroxymethyl)azetidin-2-ones **4a–d**.



	3	*4*
a: R = H	50%	95%
b: R = Ph	83%	95%
c: R = CH_2COOMe	62%	72%
d: R = CH_2SPh	52%	95%
e: R = COOMe	0%	–

The β,γ-ethylenic ester **3c** was also transformed into the (*Z*)-α,β-ethylenic ester **3f** by reaction with 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) in methanol (80% yield, fig 3). The subsequent hydroxymethylation led to the β-lactam **4f**.

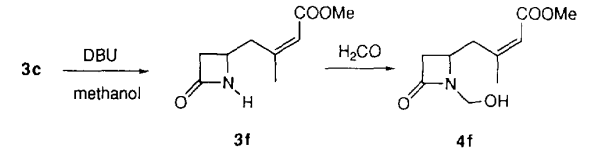


Fig 3. Preparation of lactam **4f**.

The formation carbacephem skeleton was then studied by reaction of lactams **4a–d, f** with $BF_3.Et_2O$ and $SnCl_4$ as Lewis acids (2.2 equiv). Our results are reported in table II.

Fast reactions (15 min) were observed in methylene chloride. The structures of products **5–14** were deduced from their NMR, IR and mass spectra. Cyclization of β-lactam **4a** (entry a) led to compound **5** as a mixture of two diastereomers (75:25). Halogenated compounds **7** and **10** (entries c and d) formed during the reaction of lactam **4c** were obtained as single diastereomers of unknown stereochemistry and were only characterized by mass spectra (EI and CI). Their structures were confirmed by transformation into unsaturated esters **8** and **9** (50:50 ratios), after reaction of the reaction mixtures with DBU (90% yields). Cyclization of lactam **4d** in the presence of $BF_3.Et_2O$ (entry e) was more surprising. If the reaction was carried out in the absence of molecular sieves, the hydroxysulfide **11** was isolated as a single product (80% yield). Even in the presence of molecular sieves, the formation of the alcohol **11** could not be completely prevented. Compound **11** was isolated as a unique diastereomer of unknown stereochemistry,

Table II. Preparation of carbacephems.

Entry	*Substrate*	*Lewis acid*	*Products (yield, %)*
a	**4a**	$SnCl_4$	**5** (83)
b	**4b**	$BF_3.Et_2O$	**6** (30)
c	**4c**	$BF_3.Et_2O$	**7** (35) + **8** (15) + **9** (25)
d	**4c**	$SnCl_4$	**10** (40) + **8** (28) + **9** (12)
e	**4d**	$BF_3.Et_2O$	**11** (80) + **12** (0)
			11 (40)[a] **12** (40)[a]
f	**4d**	$SnCl_4$	**13** (60)
g	**4f**	$SnCl_4$	**14** (60)

[a] In the presence of molecular sieves.

while compound **12** was obtained as a mixture of two diastereomers (40:60). This result suggests that compound **11** was obtained under thermodynamic control, while the fluorides were formed under kinetic control. Cyclization of lactam **4d** with $SnCl_4$ (entry f) led to a single diastereomer **13**, while lactam **4f** (entry g) led to a mixture. Reaction of the carbacephems **13** and **14** with DBU led to the unsaturated compounds **15** and **16** (fig 4).

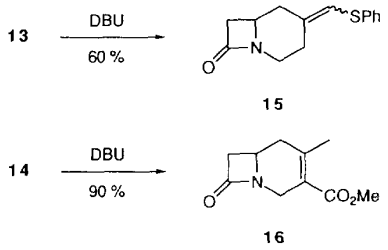


Fig 4

The next step of our work was to study the introduction of a carboxylic function onto C2 of the carbacephem framework (R′ = COOH, fig 1). The *N*-α-hydroxyesters **17a–c,f** were obtained in quantitative yields (50:50 mixture of the two diastereomers) by

reaction of allyl-β-lactams **3a–c,f** with the commercially available methyl 2-hydroxy-2-methoxyacetate in the presence of triethylamine in THF (fig 5).

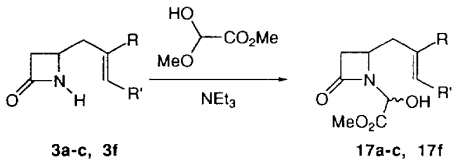


Fig 5

The subsequent cyclization was studied under the conditions used with the *N*-(hydroxymethyl)lactams **4**. With the lactams **17a–b,f** or their corresponding acetates, only tarry material was generally obtained. These results were unexpected, since, for example, the cyclization of the equivalent to compound **3a** in the γ-butyrolactam series was achieved in 73% yield [13] (fig 6).

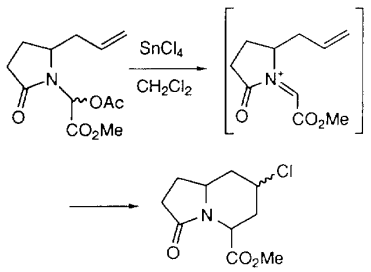


Fig 6

Only lactam **17c** led to a cyclized product by reaction with $BF_3.Et_2O$ (30% yield, fig 7). A single diastereomer was isolated as an oily compound. By comparison with the results reported for the β-lactam [7x] and γ-butyrolactam series [13] the ester function onto C2 should have an axial stereochemistry (*S* configuration). We expected to confirm this possibility by comparison of the coupling constants of the different hydrogens in the ^{1}H NMR spectrum with those calculated from the Karplus–Altona equation [14] after determination of the more stable conformations of the different diastereomers by molecular modelling (Pro Chemist Model 5.3 program). The results reported in the table III are in fact ambiguous and it is difficult to chose between the various diastereomers.

From these cyclization results, it appears that the formation of the six-membered ring by reaction of iminium ions formed from *N*-α-hydroxyesters is only

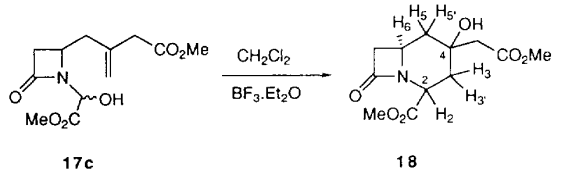


Fig 7

Table III. ^{1}H NMR coupling constants for compound **18** (6*R*).

	$J_{H_2H_3}$ (Hz)	$J_{H_2H_{3'}}$ (Hz)	$J_{H_5H_6}$ (Hz)	$J_{H_{5'}H_6}$ (Hz)
Experimental values	0.0	7.3	10.7	4.5
Calculated values				
2*R*-4*R*	1.8	11.6	10.7	4.9
2*R*-4*S*	1.8	11.7	10.7	4.9
2*S*-4*S*	2.6	3.5	11.5	2.8
2*S*-4*R*	2.8	3.2	11.4	2.9

possible if the CC double bond is not too electron-poor. Better results should thus be expected if this CC double bond was electronically enriched. Compound **21** was prepared from the β-lactam **17c** (fig 8). After acetylation (Ac_2O, NEt_3, 95% yield) the lactam **19** was treated with ozone to give the β-ketoester **20** (60% yield), which was transformed into the desired trimethylsilyl enol ether **21** (70% yield; *E*/*Z* mixture 20:80).

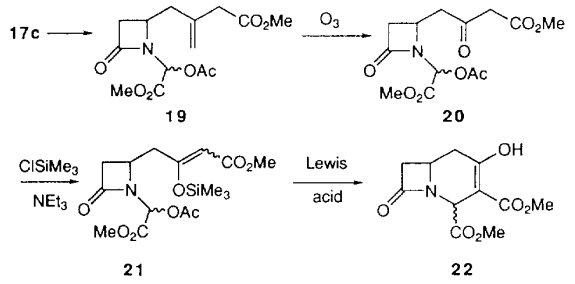


Fig 8

The subsequent cyclization was achieved with different Lewis acids (1 equiv). Yields of 44, 34 and 50% in carbacephem **22** (mixture 60:40 of the two diastereomers) were obtained with $SnCl_4$, $Et_2O.BF_3$ and $ZnCl_2$, respectively.

In conclusion, this study has shown that the formation of the six-membered ring of carbacephems is possible using the cyclization of *N*-acyliminium intermediates. However, introduction of the carboxylic function onto the C2 position because of the formation of the corresponding *N*-acyliminium ion (or its low reactivity) requires increasing the electronic density of the acceptor C=C double bond. Work is in progress to apply this strategy to the preparation of optically active carbacephems.

Experimental section

All NMR spectra were measured in $CDCl_3$ and chemical shifts are expressed in ppm relative to internal $CHCl_3$. In chemical ionization mass spectra were recorded in the presence of ammonia. All solvents were purified by known standard procedures; in particular CH_2Cl_2 was distilled over CaH_2. $BF_3.Et_2O$ and $SnCl_4$ were distilled over CaH_2 under argon.

4-Acetoxyazetidin-2-one **1** was prepared as reported previously [10]. Allyltrimethylsilane **2a** is commercially available. The other allylsilanes were prepared as previously reported: **2b** [15], **2c** [16], **2d** [17] and **2e** [18].

Molecular calculations were made using Pro Chemist Model 5.3 program with specific parameters for the nitrogen of the β-lactam ring.

General procedure for the preparation of lactams **3a–d**

To a solution of 4-acetoxyazetidin-2-one **1** [10] (0.9 g, 6.9 mmol) and allylsilane **2** (13.8 mmol) in CH_2Cl_2 (20 mL) under argon was added $BF_3.Et_2O$ (1.3 mL, 8.29 mmol). The mixture was stirred overnight at rt. Aqueous $NaHCO_3$ (10 mL of a 5% solution) was added and, after separation of the organic phase, the aqueous phase was extracted with CH_2Cl_2 (2 × 10 mL). The combined organic phases were dried ($MgSO_4$), concentrated and purified by liquid chromatography on silica gel (eluent: MeOH/CH_2Cl_2 1:99).

• *4-Allylazetidin-2-one* **3a**

Reported previously [11, 19].

^{1}H NMR (200 MHz) δ 2.40 (m, 2H), 2.60 (m, 1H), 3.10 (ddd, J = 2.0, 4.0, 14.0 Hz, 1H), 3.68 (m, 1H), 5.10–5.20 (m, 2H), 5.75 (m, 1H), 6.40 (bs, 1H).

• *4-(2-Phenylallyl)azetidin-2-one* **3b**

^{1}H NMR (250 MHz) δ 2.77 (ddd, part A of an ABCXY system, J = 14.4, 8.2, 0.7 Hz, 1H), 2.89 (ddd, part B of ABCXY system, J = 14.4, 4.6, 0.9 Hz, 1H), 2.60 (m, 1H), 3.10 (ddd, J = 12.5, 7.4, 4.9 Hz, 1H), 3.69 (m, 1H), 5.08 (d, J = 0.9 Hz, 1H), 5.40 (d, J = 0.9 Hz, 1H), 6.40 (bs, 1H), 7.40 (m, 5H).

^{13}C NMR δ 168.0, 144.7, 140.0, 128.5, 127.8, 125.9, 114.6, 46.7, 43.2, 41.3.

MS CI m/z (rel int): 205 (M^+ + 18, 61), 188 (M^+ + 1, 50, 145 (M^+ – 42, 100).

Anal calc for $C_{12}H_{13}NO$: C, 76.98; H, 7.00. Found: C, 77.00; H, 7.11.

• *4-(3-Methoxycarbonyl-2-methylallyl)azetidin-2-one* **3c**

^{1}H NMR (250 MHz) δ 2.38 (dd, part A of a ABCX system, J = 14.7, 8.2 Hz, 1H), 2.47 (dd, B part of ABCX system, J = 14.7, 5.6 Hz, 1H), 2.65 (m, 1H), 3.05(s, 2H), 3.15 (m, 1H), 3.70 (s, 3H), 3.79 (m, 1H), 4.90 (s, 1H), 5.05 (s, 1H), 6.05 (bs, 1H).

^{13}C NMR δ 171.4, 168.2, 138.4, 116.3, 51.9, 45.9, 43.2, 41.7, 41.6.

MS EI m/z (rel int): 183 (25), 110 (100), 73 (56).

Anal calc for $C_9H_{13}NO_3$: C, 59.00; H, 7.15. Found: C, 59.17; H, 7.38.

• *4-{2-[(Phenylthio)methyl]allyl}azetidin-2-one* **3d**

^{1}H NMR (200 MHz) δ 2.15 (m, 2H), 2.60 (m, 1H), 3.10 (m, 1H), 3.55 (s, 2H), 3.85 (m, 1H), 4.82 (s, 1H), 4.95 (s, 1H), 6.90 (bs, 1H), 7.30 (m, 5H).

^{13}C NMR δ 168.3, 140.5, 135.2, 129.5, 128.5, 126.2, 115.0, 46.0, 42.9, 40.3, 39.6.

MS CI m/z (rel int): 251 (18), 233 (23), 123 (100).

Anal calc for $C_{13}H_{15}NOS$: C, 66.92; H, 6.48. Found: C, 66.73; H, 6.29.

(Z)-4-[3-(Methoxycarbonyl)-2-methylallyl]azetidin-2-one **3f**

To the β-lactam **3c** (0.55 g, 3 mmol) in solution in MeOH (5 mL) was added dry DBU (0.92 mL, 6 mmol). After 4 h at rt, the methanol was removed and the residue was purified by chromatography over silica gel (elution MeOH/CH_2Cl_2 1:99) to give 0.44 g of lactam **3f** (80%).

^{1}H NMR (200 MHz) δ 1.90 (s, 3H), 2.10 (dd, J = 17.0, 6.3 Hz, 1H), 2.45 (m, 3H), 3.55 (m, 1H), 3.65 (s, 3H), 5.68 (s, 1H), 6.40 (bs, 1H).

^{13}C NMR δ 171.0, 166.1, 151.3, 118.9, 51.0, 46.8, 38.7, 34.2, 22.8.

MS EI m/z (rel int): 183 (6), 141 (7), 82 (51), 39 (100).

Anal calc for $C_9H_{13}NO_3$: C, 59.00; H, 7.15. Found: C, 59.28; H, 7.16.

4-Allyl-1-(hydroxymethyl)azetidin-2-ones **4a–d**

Compounds **4a–d** were obtained by a known procedure and have been described previously [12].

(Z)-1-(Hydroxymethyl)-4-[3-(methoxycarbonyl)-2-methylallyl]azetidin-2-one **4f**

^{1}H NMR (200 MHz) δ 1.89 (s, 3H), 2.35–2.70 (m, 3H), 3.00 (m, 1H), 3.70 (s, 3H), 4.00 (m, 1H), 4.60 (m, 1H), 4.80 (m, 1H), 5.70 (s, 1H), 5.80 (s, 1H).

^{13}C NMR δ 167.3, 166.5, 155.2, 118.1, 63.7, 51.1, 44.5, 36.7, 25.6, 19.0.

MS CI m/z (rel int): 231 (20), 213 (51), 200 (100), 183 (52), 154 (13).

General procedure for the reaction of lactams **4** *with Lewis acid*

To a solution of lactam **4** (0.4 mmol) in CH_2Cl_2 (5 mL) under argon was added $BF_3.Et_2O$ (102 μL, 0.88 mmol) or $SnCl_4$ (102 μL, 0.88 mmol). After 15 min at rt, a 10% aqueous solution of sodium bicarbonate (5 mL) was added and the organic phase was separated. After extraction of the aqueous phase with CH_2Cl_2 (3 × 5 mL), the combined organic phases were dried (Na_2SO_4) and concentrated. The residue was purified by liquid chromatography over silica gel (eluent CH_2Cl_2/McOH 99:1). In the cases of entries c, d, f and g (table II) the mixture of products obtained after chromatography was dissolved in MeOH (5 mL) and dry DBU (0.2 mL, 12 mmol) was added. After 2 h at rt, the solvent was removed under vacuum and the residue was purified by liquid chromatography over silica gel (eluent CH_2Cl_2/MeOH 99:1).

• *4-Chloro-1-azabicyclo[4.2.0]octan-8-one* **5**

Obtained as a 75:25 mixture of the two diastereoisomers.

^{1}H NMR (250 MHz, C_6D_6) δ 0.58 (m, 1H), 0.90 (m, 1H), 1.10 (m, 1H), 1.28 (m, 0.25H), 1.50 (dt, J = 5.3, 13.3 Hz, 0.75H), 1.68 (dt, J = 2.6, 10.6 Hz, 0.25H), 1.75 (m, 0.25H), 2.00 (dd, J = 1.0, 13.3 Hz, 0.75H), 2.28 (m, 0.25H), 2.46 (ddd, J = 1.0, 5.5, 15.9 Hz, 0.25H), 2.55 (ddd, J = 1.0, 5.1, 13.2 Hz, 0.75H), 2.70 (m, 1H), 3.15 (m, 1H), 3.40 (dd, J = 5.3, 13.2 Hz, 1H), 3.69 (m, 1H).

^{13}C NMR ($CDCl_3$) δ major diastereomer: 165.4, 55.4, 44.2, 42.3, 37.4, 33.5, 31.4; minor diastereomer: 165.3, 54.1, 46.6, 44.8, 44.2, 38.3, 37.4, 34.5.

MS EI m/z (rel int): major diastereomer: 161 (12), 159 (42), 131 (23), 124 (13), 96 (11), 82 (52), 55 (100); minor isomer: 161 (13), 159 (40), 131 (32), 124 (12), 55 (100).

Anal calc for $C_7H_{10}ClNO$: C, 52.67; H, 6.31. Found (mixture of the two diastereomers): C, 52.75; H, 6.50.

• *4-Phenyl-1-azabicyclo[4.2.0]oct-3-en-8-one* **6**

^{1}H NMR (250 MHz) δ 2.38 (m, 1H), 2.60 (dd, J = 1.3, 13.1 Hz, 1H), 2.80 (ddd, J = 1.1, 5.3, 15.9 Hz, 1H), 3.22 (ddd, J = 2.3, 4.7, 14.6 Hz, 1H), 3.49 (m, 1H), 3.60 (m, 1H), 4.20 (dt, J = 2.4, 18.6 Hz, 1H), 5.90 (m, 1H), 7.40 (m, 5H).

^{13}C NMR δ 167.0, 141.4, 134.5, 128.4, 127.6, 125.3, 119.6, 45.5, 43.8, 39.2, 32.5.

MS EI m/z (rel int): 199 (77), 170 (41), 156 (100), 141 (12), 129 (46), 115 (46).

Anal calc for $C_{13}H_{13}NO$: C, 78.36; H, 6.58. Found: C, 78.40; H, 6.63.

• *4-[(Methoxycarbonyl)methyl]-1-azabicyclo[4.2.0]oct-3-en-8-one* **9**

During the cyclization of the lactam **4c** (entry c, table I), a mixture of the three products **7**–**9** was obtained which could not be separated by liquid chromatography over silica gel (CH_2Cl_2/MeOH 99:1). By reaction of this mixture with DBU (1 equiv) in methanol, a 50:50 mixture of lactams **8** and **9** was obtained (80% yields).

^{1}H NMR (200 MHz) δ 2.10 (m, 1H), 2.39 (dd, J = 15.3, 5.1 Hz, 1H), 2.60 (dd, J = 1.1, 10.7 Hz, 1H), 3.10 (s, 2H), 3.20 (m, 1H), 3.48 (m, 2H), 3.70 (s, 3H), 4.15 (d, J = 15.3 Hz, 1H), 5.58 (m, 1H).

MS EI m/z (rel int): 195 (85), 136 (7), 122 (50), 94 (100).

Anal calc for $C_{10}H_{13}NO_3$: C, 61.53; H, 6.71. Found (mixture **8** and **9**): C, 61.77; H, 6.82.

• *4-Hydroxy-4-[(phenylthio)methyl]-1-azabicyclo[4.2.0]octan-8-one* **11**

^{1}H NMR (250 MHz, C_6D_6) δ 0.55 (dd, J = 11.2, 14.0 Hz, 1H), 0.85 (td, J = 6.8, 12.3 Hz, 1H), 1.22 (dd, J = 1.9, 12.3 Hz, 1H), 1.55 (dd, J = 0.8, 14.0 Hz, 1H), 2.09 (dd, J = 1.0, 14.0 Hz, 1H), 2.20 (bs, 1H), 2.60 (s, 2H), 2.70 (m, 2H), 3.15 (m, 1H), 3.46 (dd, J = 5.6, 14.2 Hz, 1H), 7.40 (m, 3H), 7.70 (m, 2H).

^{13}C NMR δ 166.1, 138.0, 129.6 (2C), 129.1 (2C), 126.6, 70.6, 48.3, 44.3, 43.9, 40.6, 34.8 (2C).

MS CI m/z (rel int): 283 (81), 266 (100), 265 (8), 246 (16), 158 (12).

Anal calc for $C_{14}H_{17}NO_2S$: C, 63.85; H, 6.51. Found: C, 63.99; H, 6.69.

• *4-Fluoro-4-[(phenylthio)methyl]-1-azabicyclo[4.2.0]octan-8-one* **12**

^{1}H NMR (200 MHz) δ 1.22 (dd, J = 11.3, 4.5 Hz, 1H), 1.50 (m, 1H), 1.70 (m, 1H), 1.90 (m, 1H), 2.40 (m, 1H), 2.60 (d, J = 11.3 Hz, 2H), 3.05 (m, 1H), 3.25 (s, 2H), 3.70 (m, 1H), 3.85 (dd, J = 4.5, 11.3 Hz, 1H), 7.3 (m, 3H), 7.4 (m, 2H).

^{13}C NMR δ 165.2, 136.9, 130.8, 129.9, 129.0, 126.7, 94.1, 44.2, 43.4, 39.5, 38.1, 34.5, 32.7, 32.4.

MS EI m/z (rel int): 265 (72), 245 (14), 156 (10), 142 (7), 136 (10), 123 (100).

Anal calc for $C_{14}H_{16}FNOS$: C, 63.37; H, 6.08. Found: C, 64.01; H, 6.20.

• *4-Chloro-4-[(phenylthio)methyl]-1-azabicyclo[4.2.0]octan-8-one* **13**

^{1}H NMR (200 MHz) δ 0.7 (dd, J = 9.0, 13.6 Hz, 1H), 1.20 (m, 2H), 1.70 (m, 1H), 1.95 (dd, J = 1.1, 13.6 Hz, 1H), 2.60 (m, 2H), 2.90 (s, 2H), 3.05 (ddd, J = 2.2, 10.0, 13.6 Hz, 1H), 3.12 (m, 1H), 3.45 (dd, J = 5.1, 18.0 Hz, 1H), 6.90 (m, 3H). 7.30 (m, 2H).

^{13}C NMR δ 164.1, 137.6, 130.5, 129.3, 126.8, 72.2, 44.5, 43.8, 41.7, 36.0, 35.3.

MS CI m/z (rel int): 299 (55), 282 (100), 246 (15).

MS EI m/z (rel int): 284 (24), 283 (60), 282 (44), 281 (100), 246 (40), 245 (43), 172 (40), 136 (48), 123 (40), 110 (92), 94 (48).

Anal calc for $C_{14}H_{16}ClNOS$: C, 59.67; H, 5.72. Found: C, 60.01; H, 5.88.

• *4-[(Phenylthio)methylidene]-1-azabicyclo[4.2.0]octan-8-one* **15**

Prepared as reported for compound **16**. A 50:50 mixture of the E/Z isomers was obtained.

^{1}H NMR (250 MHz) δ 1.88 (m, 1H), 2.08 (m, 1H), 2.40 (m, 1H), 2.68 (m, 2H), 3.20 (m, 2H), 3.40 (m, 1H), 4.00 (m, 1H), 6.19 (s, 1H, A isomer), 6.21 (s, 1H, B isomer), 7.20–7.40 (m, 5H).

MS EI m/z (rel int): 246 (45), 245 (92), 136 (53), 108 (100), 94 (84).

Anal calc for $C_{14}H_{15}NOS$: C, 68.54; H, 6.16. Found: C, 68.59; H, 6.38.

• *3-(Methoxycarbonyl)-4-methyl-1-azabicyclo[4.2.0]oct-3-en-8-one* **16**

^{1}H NMR (250 MHz) δ 2.10 (bs, 3H), 2.22 (m, 1H), 2.48 (m, 1H), 2.55 (dd, J = 1.3, 14.7 Hz, 1H), 3.25 (ddd, J = 1.8, 4.3, 14.7 Hz, 1H), 3.45 (m, 1H), 3.65 (m, 1H), 3.73 (s, 3H), 4.3 (bdt, J = 17 Hz, 1H).

^{13}C NMR δ 166.5, 166.3, 145.1, 119.8, 51.5, 45.5, 42.3, 38.8, 37.2, 22.8.

MS CI m/z (rel int): 213 (100), 196 (60).

Anal calc for $C_{10}H_{13}NO_3$: C, 61.53; H, 6.71. Found: C, 61.88; H, 6.81.

General procedure for the preparation of lactams **17a–c,f**

To a solution of lactam **3** (1 mmol) in THF (5 mL) was added methyl 2-hydroxy-2-methoxyacetate (2 mmol, 0.24 g) triethylamine (1 mmol, 0.2 g) and 4 A molecular sieve (300 mg in powder). The mixture was stirred 1 h at rt, filtered and concentrated under vacuum. The residue was heated at 60 °C for 3 h under high vacuum (0.1 mmHg), and then purified by liquid chromatography over silica gel (elution: methanol/CH_2Cl_2 2:98). Lactams **17a–c,f** were obtained as 50:50 mixture of diastereomers. They did not give satisfactory elemental analysis, which were therefore carried out on their corresponding chloroacetates.

• *4-Allyl-1-[hydroxy(methoxycarbonyl)methyl]-azetidin-2-one* **17a**

^{1}H NMR (200 MHz) δ 2.25 (m, 1H), 2.50 (m, 2H), 2.68 (dd, J = 2.1, 14.8 Hz, 1H), 3.05 (dt, J = 4.2, 14.8 Hz, 1H), 3.80 (s, 1.5H, (1st diastereomer)), 3.90 (s, 1.5H, (2nd diastereomer)), 4.00 (m, 1H), 5.10 (m, 2H), 5.38 (d, J = 5 Hz, 0.5H, (1st diastereomer)), 5.42 (d, J = 5 Hz, 0.5H, (2nd diastereomer)), 5.70 (m, 1H).

^{13}C NMR (mixture of diastereomers) δ 169.2, 168.3, 167.0, 166.5, 132.5, 132.0, 117.9, 721.5, 71.0, 52.5, 50.6, 49.1, 41.4, 41.3, 37.3, 36.3.

MS CI m/z (rel int): 217 (9), 129 (100).

• *1-[Hydroxy(methoxycarbonyl)methyl]-4-(2-phenylallyl)azetidin-2-one* **17b**

^{1}H NMR (250 MHz) δ 2.65 (m, 1H), 2.72 (m, 1H), 2.80 (2d, J = 8 Hz, 1H (2 diastereoisomers), 2.96–3.20 (m, 2H), 3.80 (s, 3H), 3.95 (m, 1H), 5.13 (bs, 1H), 5.18 (bs, 1H), 5.37 (d, J = 8.0 Hz, 0.5H (1st diastereomer)), 5.39 (d, J = 8.0 Hz, 0.5 Hz (2nd diastereomer), 7.40 (m, 5H).

^{13}C NMR (mixture of diastereomers) δ 169.9, 168.7, 167.3, 166.9, 144.1, 139.8, 128.4, 127.7, 125.8, 125.7, 71.8, 71.4, 53.2, 53.1, 50.9, 50.5, 49.3, 42.9, 39.8, 39.7.

^{1}H NMR of the chloroacetate (250 MHz) δ 2.70 (m, 2H), 3.05 (m, 2H), 3.78 (s, 1.5H, (1st diastereomer)), 3.81 (s, 1.5H (2nd diastereomer)), 3.90 (m, 1H), 4.12 (s, 2H), 5.13 (d,

J = 7.0 Hz, 1H), 5.38 (d, J = 7.0 Hz, 1H), 6.19 (s, 0.5H (1st diastereomer)), 6.40 (s, 0.5H, (2nd diastereomer)), 7.40 (m, 5H).

Anal calc for $C_{17}H_{16}ClNO_5$ (chloroacetates): C, 58.38; H, 4.61. Found: C, 58.59; H, 4.78.

- *1-[Hydroxy(methoxycarbonyl)methyl]-4-{[(3-methoxycarbonyl)methyl]allyl}azetidin-2-one* **17c**

^{1}H NMR (200 MHz) δ 2.20–2.62 (m, 2H), 2.71 (dd, J = 1.0, 14.8 Hz, 1H), 3.10 (s, 1H (1st diastereomer)), 3.13 (s, 1H (2nd diastereomer)), 3.20 (dd, J = 6.3, 14.8 Hz, 1H), 3.70 (s, 3H), 3.88 (s, 1.5H, 1st diastereomer)), 3.91 (s, 1.5H, 2nd diastereomer)), 4.99 (d, J = 7.0 Hz, 1H), 5.06 (d, J = 7 Hz, 1H), 5.34 (d, J = 6.4 Hz, 0.5H (1st diastereomer)), 5.36 (d, J = 6.4 Hz, 0.5 H (2nd diastereomer)).

Anal calc for $C_{14}H_{17}ClNO_7$ (chloroacetates): C, 48.50; H, 4.94. Found: C, 48.81; H, 5.13.

- *(Z)-1-[Hydroxy(methoxycarbonyl)methyl]-4-[3-(methoxycarbonyl)-2-methylallyl]azetidin-2-one* **17f**

^{1}H NMR (200 MHz) δ 1.90 (s, 3H), 2.18 (d, J = 9.9 Hz, 1H), 2.65 (m, 2H), 2.90 (m, 2H), 3.70 (s, 3H), 3.80 (s, 3H), 4.20 (m, 1H), 4.40 (d, J = 9.9 Hz, 0.5 H (1st diastereomer)), 4.90 (d, J = 9.9 Hz, 0.5H, (2nd diastereomer)), 5.70 (m, 1H).

^{13}C NMR (mixture of diastereomers) δ 171.6, 171.3, 169.0, 164.8, 164.3, 151.6, 151.1, 119.4, 119.1, 53.7, 53.0, 51.7, 51.4, 47.0, 39.0, 37.7, 34.4, 34.1, 29.8.

Anal calc for $C_{14}H_{17}ClNO_7$ (chloroacetates): C, 48.50; H, 4.94. Found: C, 48.90; H, 5.32.

4-Hydroxy-2-(methoxycarbonyl)-4-[(methoxycarbonyl)-methyl]bicyclo[4.2.0]octan-8-one **18**

The cyclization was conducted by using the conditions reported for the preparation of compounds **5**–**14**, with a reaction time of 6 h.

^{1}H NMR (250 MHz, C_6D_6) δ 0.45 (dd, J = 10.7, 11.6 Hz, 1H), 0.97 (dd, J = 7.2, 13.6 Hz, 1H), 1.55 (ddd, J = 1.4, 4.4, 11.6 Hz, 1H), 1.88 (d, J = 15.9 Hz, 1H (part A of an AB system)), 1.95 (d, J = 15.9 Hz, 1H (part B of an AB system)), 2.08 (dd, J = 1.9, 14.4 Hz, 1H), 2.20 (dt, J = 1.5, 13.6 Hz, 1H), 2.70 (dd, J = 4.7, 14.4 Hz, 1H), 3.19 (s, 3H), 3.35 (s, 3H), 3.68 (m, 1H), 3.73 (s, 1H), 4.48 (d, J = 7.2 Hz, 1H).

^{13}C NMR ($CDCl_3$) δ 172.1, 171.3, 165.4, 69.0, 51.9, 51.2, 48.1, 45.2, 44.7, 43.1, 40.3, 36.6.

MS CI m/z (rel int): 289 (45), 272 (94), 256 (100), 212 (12).

Anal calc for $C_{12}H_{17}NO_6$: C, 53.13; H, 6.32. Found: C, 53.18; H, 6.51.

1-[Acetoxy(methoxycarbonyl)methyl]-4-{2-[(methoxycarbonyl)methyl]allyl}azetidin-2-one **19**

To a solution of lactam **17c** (1 mmol) in THF (5 mL) was added methyl 2-hydroxy-2-methoxyacetate (2 mmol, 0.24 g), triethylamine (1 mmol, 0.2 g) and 300 mg of 4 Å molecular sieves in powder. After 1 h, triethylamine (1 mmol, 0.2 g) and acetic anhydride (2 mmol) were added and the mixture was stirred 1 h at rt. After filtration, the solution was concentrated under vacuum. The residue was heated at 60 °C for 3 h under high vacuum (0.1 mmHg) and purified by liquid chromatography over silica gel (elution methanol/CH_2Cl_2 2:98) to give lactam **19** as a 50:50 mixture of the two 1′-diastereomers (100% yield).

^{1}H NMR (200 MHz) δ 2.15 (s, 3H), 2.30 (m, 1H), 2.70 (m, 2H), 3.05 (s, 1H (1st diastereomer)), 3,10 (s, 1H (2nd diastereomer)), 3.25 (m, 1H), 3.70 (s, 3H), 3.78 (s, 1.5H (1st diastereomer)), 3.80 (s, 1.5H, (2nd diastereomer)), 4.00 (m, 1H), 4.91 (d, J = 5.0 Hz, 1H), 4.99 (d, J = 5.0 Hz, 1H), 6.20 (s, 0.5H (1st diastereomer)), 6.30 (s, 0.5H, (2nd diastereomer)).

^{13}C NMR (mixture of diastereomers) δ 171.1, 171.0, 169.3, 169.2, 165.4, 164.8, 137.7, 137.6, 116.3, 116.1, 71.7, 71.6, 53.1, 52.9, 50.4, 50.1, 43.4, 43.3, 41.8, 41.7, 39.7, 38.9, 20.4, 20.2.

Anal calc for $C_{14}H_{19}NO_7$: C, 53.67; H, 6.11. Found: C, 53.81; H, 6.29.

1-[Acetoxy(methoxycarbonyl)methyl]-4-[3-(methoxycarbonyl)-2-oxopropyl]azetidin-2-one **20**

Through a solution of lactam **17c** (1 mmol) in CH_2Cl_2 (20 mL) cooled at −78 °C was bubbled an oxygen/ozone mixture until a persistent blue color appeared. After 30 min at −78 °C argon was bubbled into the solution to remove excess ozone and PPh_3 (1.5 mmol, 0.395 g) was added. The flask was warmed to rt and the solvent removed under vacuum. The residue was then purified by liquid chromatography over silica gel (eluent: CH_2Cl_2) to give lactam **20** (60% yield) as a mixture of the two 1′-diastereomers.

^{1}H NMR (200 MHz) δ 2.15 (s, 3H), 2.70 (dd, J = 2.1, 14.8 Hz, 1H), 2.95 (dd, J = 8.6, 17.0 Hz, 1H), 3.25 (m, 2H), 3.45 (d, J = 12.3 Hz, 1H (A part of an AB system)), 3.54 (d, J = 12.3 Hz, 1H (B part of an AB system)), 3.75 (s, 3H), 3.90 (s, 3H), 4.20 (m, 1H), 6.20 (s, 0.5H (1st diastereomer)), 6.40 (s, 0.5H (2nd diastereomer)).

^{13}C NMR (mixture of diastereomers) δ 200.2, 199.8, 169.4, 169.2, 167.0, 165.8, 165.5, 164.8, 71.9, 71.6, 53.3, 52.8, 49.5, 47.4, 47.2, 46.4, 46.2, 43.4, 43.2, 20.3, 20.2.

Anal calc for $C_{13}H_{17}NO_8$: C, 49.53; H, 5.43. Found: C, 49.66; H, 5.81.

1-[(Acetoxy(methoxycarbonyl)methyl]-4-{3-(methoxycarbonyl)-2-[(trimethylsilyl)oxy]allyl}azetidin-2-one **21**

To a solution of lactam **20** (1 mmol) in THF (5 mL) was added triethylamine (3 mmol, 0.3 g) and chlorotrimethylsilane (2 mmol, 0.265 mL), and the mixture was stirred 2 h at rt. After filtration over dry Celite under argon, the filtrate was carefully concentrated under vacuum to give a residue (85% yield in crude product) which was immediately used for the subsequent cyclization.

^{1}H NMR (200 MHz) δ 0.20 (s, 1.8H (*E* isomer)), 0.28 (s, 7.2H (*Z* isomer)), 2.15 (s, 3H), 2.70–3.20 (m, 9H), 3.70 (s, 3H), 3.80 (s, 0.6H (*E* isomer)), 3.88 (s, 2.4H (*Z* isomer)), 4.00 (m, 1H), 5.12 (s, 0.2H (*E* isomer)), 5.20 (s, 0.8H (*Z* isomer)), 6.40–6.42 (2s, 1H).

2,3-(Dimethoxycarbonyl)-4-hydroxy-1-azabicyclo[4.2.0]oct-3-en-8-one **22**

The cyclization was carried out as reported for lactams **4**.

^{1}H NMR (250 MHz) δ 2.45 (ddd, J = 1.3, 8.7, 18.0 Hz, 1H), 2.70 (m, 2H), 3.37 (dd, J = 4.7, 14.8 Hz, 1H), 3.75 (s, 3H), 3.76 (s, 3H), 3.78 (m, 1H), 5.10 (d, J = 1.3 Hz, 1H), 11.8 (bs, 1H).

^{13}C NMR δ 171.3, 170.8, 169.9, 164.2, 95.08, 52.0, 51.4, 49.9, 46.4, 42.4, 32.5.

Anal calc for $C_{11}H_{13}NO_6$: C, 51.77; H, 5.13. Found: C, 51.91; H, 5.15.

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