115. α-Methylidene- and α-Alkylidene-β-lactams from Nonproteinogenic Amino Acids

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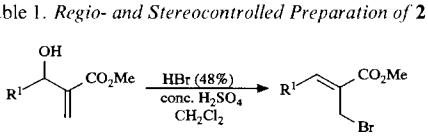
Treatment of methyl 2-(1-hydroxyalkyl)prop-2-enoates **1** with conc. HBr solution afforded methyl (*Z*)-2-(bromomethyl)alk-2-enoates **2**, which were transformed regioselectively into *N*-substituted methyl (*E*)-2-(aminomethyl)alk-2-enoates **3** (S_N2 reaction) and into *N*-substituted methyl 2-(1-aminoalkyl)prop-2-enoates **4** (S_N2' reaction). Regiocontrol of nucleophilic attack by amine was accomplished simply by choice of solvent, the S_N2 reaction occurring in MeCN and the S_N2' reaction in petroleum ether. Hydrolysis and lactamization afforded β-lactams **7** and **8**, containing an exocyclic alkylidene and methylidene group at C(3), respectively.

Introduction. – The discovery of the antibiotic activity of penicillin and cephalosporin has been a breakthrough in the treatment of bacterial infections. The systematic chemical modification of natural lead structures has been unprecedented and has provided a great number of clinically valuable β-lactam antibiotics, which have facilitated the development of modern medicine. However, problems of resistance and new therapeutical approaches require a continuous supply and development of new compounds. Comparatively little work has been done on β-lactams with exocyclic double bond at C(3) [1].

Results. – A variety of methyl 2-(1-hydroxyalkyl)prop-2-enoates [2] **1** was converted into allylic bromides **2** (*Table 1*) by simple treatment with conc. aq. HBr soln. [3]. The reaction had a considerable thermodynamic driving force and proceeded with clean allylic rearrangement, giving trisubstituted olefin **2**. The rearrangement was not only regioselective, but also stereoselective, providing (*Z*)-configurated olefin (see below). The controlled introduction of N-nucleophiles was accomplished by the choice of solvent. We found that S_N2 product **3** was formed with high regioselectivity in MeCN, except for

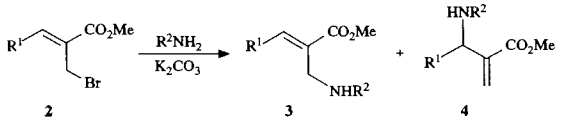
Table 1. *Regio- and Stereocontrolled Preparation of* **2**



1 **2**

	R^1	Yield **2** [%]
α	Ph	91
β	4-$O_2NC_6H_4$	65
γ	Et	78
δ	i-Pr	72
ε	4-(i-Pr)C_6H_4	70

Table 2. *Regiocontrol in Reactions of* **2** *with Amines*

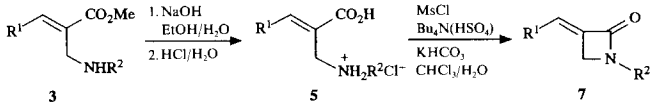


2 **3** **4**

	R^1	R^2	Solvent	Yield [%]	
				3	**4**
a	Ph	Ph	MeCN	76	[a])
			petroleum ether	64	13
b	Ph	4-$MeOC_6H_4$	MeCN	59	0
			petroleum ether	47	21
c	Ph	Pr	MeCN	60	0
			petroleum ether	0	37
d	Ph	i-Pr	MeCN	69	0
			petroleum ether	0	73
e	Ph	*t*-Bu	MeCN	62	0
			petroleum ether	0	70
f	4-$O_2NC_6H_4$	Pr	MeCN	30	48
			petroleum ether	–	–
g	4-$O_2NC_6H_4$	*t*-Bu	MeCN	67	0
			petroleum ether	–	–
h	Et	*t*-Bu	MeCN	42	31
			petroleum ether	0	44
i	i-Pr	*t*-Bu	MeCN	89	0
			petroleum ether	11	69
j	i-Pr	4-$MeOC_6H_4$	MeCN	–	–
			petroleum ether	60	10
k	4-(i-Pr)C_6H_4	*t*-Bu	MeCN	–	–
			petroleum ether	0	72

[a]) Obtained as a mixture with **3a**.

Table 3. N-*Substituted 2-(Aminomethyl)alk-2-enoic Acids and Corresponding β-Lactams*



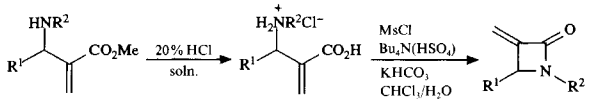
3 **5** **7**

	R^1	R^2	Yield [%] of **7**[a])		R^1	R^2	Yield [%] of **7**[a])
a	Ph	Ph	60[b])	**f**	4-$O_2NC_6H_4$	Pr	39
b	Ph	4-$MeOC_6H_4$	40[b])	**g**	4-$O_2NC_6H_4$	*t*-Bu	66
c	Ph	Pr	40	**h**	Et	*t*-Bu	40
d	Ph	i-Pr	46	**i**	i-Pr	*t*-Bu	19
e	Ph	*t*-Bu	73	**j**	i-Pr	4-$MeOC_6H_4$	10

[a]) Yield for the two-step transformation of **3** into **7**.

[b]) Yield for free amino acids: **5a** (without HCl; 99%), **5b** (without HCl; 99%); yield for cyclization **5** → **7**: **7a** (61%), **7b** (40%).

Table 4. N-*Substituted 2-(1-Aminoalkyl)prop-2-enoic Acids and Corresponding β-Lactams*



4 6 8

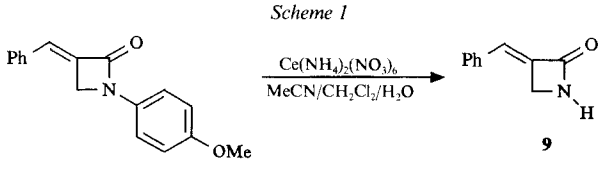
	R^1	R^2	Yield **6** [%]	Yield **8** [%]
c	Ph	Pr	75	43
d	Ph	i-Pr	83	65
e	Ph	*t*-Bu	95	80
h	Et	*t*-Bu	99	85
i	i-Pr	*t*-Bu	94	55
k	4-(i-Pr)C_6H_4	*t*-Bu	95[a])	75

[a]) Educt: hydrochloride of **4k**.

compounds **3f**/**4f** and **3h**/**4h**. In contrast, in petroleum ether, usually the S_N2' product **4** was favored (*Table 2*); however, for aromatic amines (aniline, 4-methoxyaniline), S_N2' selectivity in petroleum ether was lost. Saponification of esters **3** proceeded under alkaline conditions and afforded the amino-acid hydrochlorides **5** after acidic workup (*Table 3*). Derivatives **5a** and **5b** which contain two aryl groups could be obtained as free amino acids (without HCl; 99% yield each). Amino-acid hydrochlorides **5c–j** were accompanied by NaCl, which, however, did not affect the next step. As expected, the simple propenoates **4** were sensitive to alkali and had to be hydrolyzed with acid (→ **6**; *Table 4*).

The two types of amino acids **5** and **6** are new nonproteinogenic [4] representatives. They were lactamized to **7** and **8** under phase-transfer conditions (*Tables 3* and *4*), as described by *Watanabe* and *Mukaiyama* [5] for simple β-amino acids. Oxidative dearylation of **7b** by ceric ammonium nitrate [6] gave deprotected β-lactam **9** (*Scheme 1*).

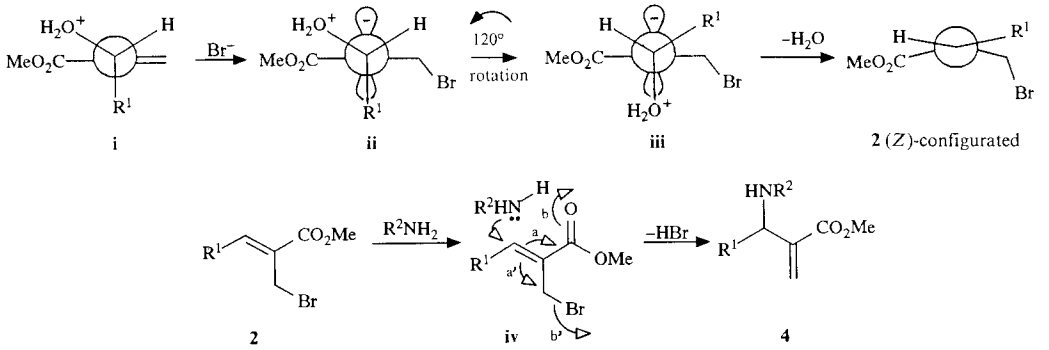
Scheme 1



7b **9**

Discussion. – The (*Z*)-selective formation of allylic bromide **2** from **1** is quite striking and can be explained as follows (*Scheme 2*). Protonation of alcohol **1** provides **i**, which is attacked by the Br^- ion in *Michael* fashion, giving zwitterion **ii**. Formation of the (*E*)-configurated olefin (not formed) would require a clockwise rotation of 60° around the central C–C bond. In this case, substituent R^1 would have to be pushed against the neighbouring COOMe group. However, molecular modelling suggests that the neighbouring CH_2Br group is sterically less demanding. Therefore, counterlockwise rotation by 120° is presumably preferred, giving **iii** and then olefin **2**. In support of this argument, we have found that replacement of COOMe by a CN group causes loss of (*Z*)-selection,

Scheme 2



e.g. 2-[(fur-2-yl)hydroxymethyl]prop-2-enenitrile gives a 3:1 mixture of the related (*Z*)- and (*E*)-configurated allylic bromides [7].

As regards regiocontrol of nucleophilic attack on **2** with amines, it will be seen that charge development in the *Menshutkin*-type transition state of the S_N2 reaction is more marked and is favored in polar MeCN. In contrast, S_N2' displacement offers the possibility for charge spreading (*cf.* a,b and a′,b′ and intramolecular H-bonding in **iv**, *Scheme 2*) and is facilitated in petroleum ether.

The yield for the cyclization to lactams **7** and **8** depends mainly on the bulk of substituent R^2 on the N-atom provided that R^1 is constant (R^1 = Ph; *cf.* **7c–e** and **8c–e**).

Conclusion. – Starting from methyl acrylate and aldehydes, a variety of nonproteinogenic β-amino acids was prepared for the first time. The compounds were transformed into β-lactams with an exocyclic double bond at C(3).

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Experimental Part

Methyl (Z)-2-(Bromomethyl)-3-phenylprop-2-enoate (**2α**). To a stirred soln. of **1α** (7.90 g, 41.1 mmol) in CH_2Cl_2 was added dropwise conc. HBr soln. (48%; 13.5 ml) and then conc. H_2SO_4 soln. (11.9 ml) at 0°. After stirring overnight at r.t., the mixture was carefully diluted with CH_2Cl_2 and H_2O. The aq. phase was extracted twice with CH_2Cl_2, the combined org. phase washed twice with H_2O, dried (Na_2SO_4), and evaporated, and the residual oil purified by flash chromatography (FC, silica gel, cyclohexane/Et_2O 5:1): 9.49 g (91%) of **2α**. Colorless oil. IR (film): 2951, 1718, 1626. ^{1}H-NMR (200 MHz, $CDCl_3$): 7.79 (*s*, 1 H); 7.54 (*m*, 2 H); 7.40 (*m*, 3 H); 4.36 (*s*, 2 H); 3.83 (*s*, 3 H). ^{13}C-NMR ($CDCl_3$): 166.37, 142.75, 134.24, 129.58, 128.84, 128.80, 52.27, 26.66.

Methyl (Z)-2-(Bromomethyl)-3-(4-nitrophenyl)prop-2-enoate (**2β**) was prepared from **1β** in 65% yield analogously to **2α**. M.p. 124°. IR (KBr): 1724, 1628, 1517, 1347. ^{1}H-NMR (200 MHz, $CDCl_3$): 8.33 (*m*, 2 H); 7.83 (*s*, 1 H); 7.73 (*m*, 2 H), 4.32 (*s*, 2 H); 3.92 (*s*, 3 H).

Methyl (Z)-2-(Bromomethyl)pent-2-enoate (**2γ**) was prepared from **1γ** in 78% yield analogously to **2α**. The residual oil was purified by distillation (b.p. 95°/1 Torr). IR (film): 1719, 1642. ^{1}H-NMR (200 MHz, $CDCl_3$): 6.97 (*t*, 1 H); 4.23 (*s*, 2 H); 3.80 (*s*, 3 H); 2.33 (*quint.*, 2 H); 1.14 (*t*, 3 H).

Methyl (Z)-2-(Bromomethyl)-4-methylpent-2-enoate (**2δ**) was prepared from **1δ** in 72% yield analogously to **2α**. The residual oil was purified by distillation (b.p. 105°/1 Torr). IR (film): 2964, 1719, 1643. ^{1}H-NMR (200 MHz, $CDCl_3$): 6.78 (*d*, 1 H); 4.24 (*s*, 2 H); 3.80 (*s*, 3 H); 2.78 (*m*, 1 H); 1.10 (*d*, 6 H).

Methyl (Z)-2-(Bromomethyl)-3-(4-isopropylphenyl)prop-2-enoate (**2ε**) was prepared from **1ε** in 70% yield analogously to **2α**. IR (film): 2961, 1718, 1624. ^{1}H-NMR (200 MHz, $CDCl_3$): 7.81 (*s*, 1 H); 7.54 (*m*, 2 H); 7.33 (*m*, 2 H); 4.43 (*s*, 2 H); 3.88 (*s*, 3 H); 2.95 (*sept.*, 1 H); 1.28 (*d*, 6 H).

General Procedure for the Synthesis of **3** *and* **4**. A soln. of **2** (1 mmol) in solvent was dropped into a mixture of amine (3 mmol) and powdered K_2CO_3 (3 mmol) in the same solvent at 0° (total amount of solvent, 5 ml). After stirring at r. t. for the given time, the inorg. salts were filtered off. The filter cake was washed with small portions of the same solvent, and the filtrate was evaporated. The residual oil was purified by FC (silica gel, cyclohexane/Et_2O mixtures). Variant *A*: abs. MeCN as solvent. Variant *B*: petroleum ether, b.p. 35–65°, as solvent.

Methyl (E)-3-Phenyl-2-[(phenylamino)methyl]prop-2-enoate (**3a**) *and Methyl 2-[α-(Phenylamino)benzyl]-prop-2-enoate* (**4a**). Variant *A*: after 4 h, 76% of **3a**. Variant *B*: after 20 h, 64% of **3a** and 13% of **4a**.

3a: IR (film): 3392, 1708, 1632, 1602, 1505. ^{1}H-NMR (200 MHz, $CDCl_3$): 7.89 (*s*, 1 H); 7.41 (*m*, 5 H); 7.14 (*m*, 2 H); 6.72 (*m*, 1 H); 6.53 (*m*, 2 H); 4.13 (br., 2 H + NH); 3.83 (*s*, 3 H). ^{13}C-NMR ($CDCl_3$): 167.98, 147.85, 142.65, 134.79, 129.56, 129.40, 129.17, 129.13, 128.65, 117.76, 113.37, 51.96, 41.00.

4a: IR (film): 3400, 1715, 1626, 1600, 1500. ^{1}H-NMR (200 MHz, $CDCl_3$): 7.34 (*m*, 5 H); 7.16 (*m*, 2 H); 6.72 (*m*, 1 H); 6.58 (*m*, 2 H); 6.39 (*t*, 1 H); 5.97 (*t*, 1 H); 5.42 (*s*, 1 H); 4.25 (br., NH); 3.70 (*s*, 3H).

Methyl (E)-2-{[(4-Methoxyphenyl)amino]methyl}-3-phenylprop-2-enoate (**3b**) *and Methyl 2-{α-[(4-Methoxyphenyl)amino]benzyl}prop-2-enoate* (**4b**). Variant *A*: After 1 h, 59% of **3b**. M.p. 78°. Variant *B*: After 24 h, 47% of **3b** and 21% of **4b**.

3b: IR (KBr): 3395, 1718, 1628, 1512. ^{1}H-NMR (200 MHz, $CDCl_3$): 7.88 (*s*, 1 H); 7.42 (*m*, 5 H); 6.74 (*m*, 2 H); 6.52 (*m*, 2 H); 4.09 (*s*, 2 H); 3.83 (*s*, 3 H); 3.79 (br., NH); 3.74 (*s*, 3 H).

4b: IR ($CHCl_3$): 3425, 1717, 1629, 1512. ^{1}H-NMR (200 MHz, $CDCl_3$): 7.28 (*m*, 5 H); 6.69 (*m*, 2 H); 6.48 (*m*, 2 H); 6.32 (*s*, 1 H); 5.90 (*s*, 1 H); 5.33 (*s*, 1 H); 4.01 (br., NH); 3.62 (*s*, 3 H); 3.58 (*s*, 3 H). ^{13}C-NMR ($CDCl_3$): 166.59, 152.27, 140.93, 140.84, 140.40, 128.62, 127.64, 127.49, 126.01, 114.68, 59.61, 55.49, 51.71.

Methyl (E)-3-Phenyl-2-[(propylamino)methyl]prop-2-enoate (**3c**) *and Methyl 2-[α-(Propylamino)benzyl]-prop-2-enoate* (**4c**). Variant *A*: after 30 min, 60% of **3c**. Variant *B*: after 24 h, 37% of **4c**.

3c: IR ($CHCl_3$): 1703, 1632. ^{1}H-NMR (200 MHz, $CDCl_3$): 7.81 (*s*, 1 H); 7.49 (*m*, 2 H); 7.38 (*m*, 3 H); 3.83 (*s*, 3 H); 3.58 (*s*, 2 H); 2.58 (*t*, 2 H); 1.70 (br., NH); 1.50 (*sext.*, 2 H); 0.92 (*t*, 3 H).

4c: IR (film): 1719, 1627. ^{1}H-NMR (200 MHz, $CDCl_3$): 7.29 (*m*, 5 H); 6.34 (*m*, 1 H); 5.96 (*t*, 1 H); 4.67 (*s*, 1 H); 3.67 (*s*, 3 H); 2.50 (*m*, 2 H); 1.51 (*m*, 2 H + NH); 0.91 (*t*, 3 H).

Methyl (E)-2-[(Isopropylamino)methyl]-3-phenylprop-2-enoate (**3d**) *and Methyl 2-[α-(Isopropylamino)benzyl]prop-2-enoate* (**4d**). Variant *A*: after 30 min, 69% of **3d**. Variant *B*: after 4 d, 73% of **4d**.

3d: IR ($CHCl_3$): 1703, 1632. ^{1}H-NMR (200 MHz, $CDCl_3$): 7.81 (*s*, 1 H); 7.52 (*m*, 2 H); 7.39 (*m*, 3 H); 3.83 (*s*, 3 H); 3.59 (*s*, 2 H); 2.83 (*sept.*, 1 H); 1.76 (br., NH); 1.05 (*d*, 6 H).

4d: IR (film): 1720, 1627. ^{1}H-NMR (200 MHz, $CDCl_3$): 7.29 (*m*, 5 H); 6.32 (*m*, 1 H); 5.92 (*t*, 1 H); 4.79 (*s*, 1 H); 3.67 (*s*, 3 H); 2.72 (*sept.*, 1 H); 1.52 (br., NH); 1.07 (*d*, 3 H); 1.04 (*d*, 3 H).

Methyl (E)-2-{[(tert-Butyl)amino]methyl}-3-phenylprop-2-enoate (**3e**) *and Methyl 2-{α-[(tert-Butyl)amino]benzyl}prop-2-enoate* (**4e**). Variant *A*: after 1 h, 62% of **3e**. Variant *B*: after 24 h, 70% of **4e**.

3e: IR ($CHCl_3$): 1700, 1630. ^{1}H-NMR (200 MHz, $CDCl_3$): 7.79 (*s*, 1 H); 7.58 (*m*, 2 H); 7.38 (*m*, 3 H); 3.83 (*s*, 3 H); 3.53 (*s*, 2 H); 1.51 (br., NH); 1.16 (*s*, 9 H).

4e: IR (film): 1723, 1629. ^{1}H-NMR (200 MHz, $CDCl_3$): 7.27 (*m*, 5 H); 6.34 (*m*, 1 H); 6.22 (*m*, 1 H); 4.88 (*s*, 1 H); 3.67 (*s*, 3 H); 1.22 (br., NH); 1.07 (*s*, 9 H).

Methyl (E)-3-(4-Nitrophenyl)-2-[(propylamino)methyl]prop-2-enoate (**3f**) *and Methyl 2-[4-Nitro-α-(propylamino)benzyl]prop-2-enoate* (**4f**). Variant *A*: after 1.5 h, 30% of **3f** and 48% of **4f**.

3f: M.p. 62°. IR (KBr): 1722, 1634, 1595, 1516, 1344. ^{1}H-NMR (90 MHz, $CDCl_3$): 8.26 (*m*, 2 H); 7.80 (*s*, 1 H); 7.73 (*m*, 2 H); 3.87 (*s*, 3 H); 3.51 (*s*, 2 H); 2.61 (*t*, 2 H); 1.72 (br., NH); 1.53 (*m*, 2 H); 0.96 (*t*, 3 H).

4f: IR ($CHCl_3$): 1712, 1624, 1520, 1345. ^{1}H-NMR (90 MHz, $CDCl_3$): 8.19 (*m*, 2 H); 7.61 (*m*, 2 H); 6.42 (*s*, 1 H); 6.03 (*m*, 1 H); 4.76 (*s*, 1 H); 3.72 (*s*, 3 H); 2.52 (*m*, 2 H); 1.78 (br., NH); 1.54 (*m*, 2 H); 0.94 (*t*, 3 H).

Methyl (E)-2-{[(tert-Butyl)amino]methyl}-3-(4-nitrophenyl)prop-2-enoate (**3g**). Variant *A*: after 24 h, 67%. IR (KBr): 1724, 1635, 1595, 1515, 1345. ^{1}H-NMR (200 MHz, $CDCl_3$): 8.25 (*m*, 2 H); 7.83 (*m*, 2 H); 7.79 (*s*, 1 H); 3.85 (*s*, 3 H); 3.47 (*s*, 2 H); 1.68 (br., NH); 1.17 (*s*, 9 H).

Methyl (E)-2-{[(tert-Butyl)amino]methyl}pent-2-enoate (**3h**) *and Methyl 2-{1-[(tert-Butyl)amino]-propyl}prop-2-enoate* (**4h**). Variant *A*: after 4.5 h, 42% of **3h** and 31% of **4h**. Variant *B*: after 28 h at reflux, 44% of **4h**.

3h: IR (film): 1713, 1650. ^{1}H-NMR (200 MHz, $CDCl_3$): 6.85 (*t*, 1 H); 3.74 (*s*, 3 H); 3.37 (*s*, 2 H); 2.29 (*quint.*, 2 H); 2.04 (br., NH); 1.16 (*s*, 9 H); 1.08 (*t*, 3 H).

4h: IR (film): 1718, 1628. ^{1}H-NMR (200 MHz, $CDCl_3$): 6.20 (*d*, 1 H); 5.90 (*m*, 1 H); 3.76 (*s*, 3 H); 3.54 (*t*, 1 H); 1.58 (*m*, 1 H); 1.41 (*m*, 1 H); 1.23 (br., NH); 1.03 (*s*, 9 H); 0.87 (*t*, 3 H). ^{13}C-NMR ($CDCl_3$): 167.52, 146.33, 124.70, 54.80, 51.43, 50.92, 30.73, 30.07, 11.06.

Methyl (E)-2-{[(tert-Butyl)amino]methyl}-4-methylpent-2-enoate (**3i**) *and Methyl 2-{1-[(tert-Butyl)-amino]-2-methylpropyl}prop-2-enoate* (**4i**). Variant *A*: after 1 h, 89% of **3i**. Variant *B*: after 24 h, 11% of **3i** and 69% of **4i**.

3i: IR (film): 1714, 1649. ^{1}H-NMR (200 MHz, $CDCl_3$): 6.65 (*d*, 1 H); 3.74 (*s*, 3 H); 3.37 (*s*, 2 H); 2.73 (*m*, 1 H); 1.55 (br., NH); 1.14 (*s*, 9 H); 1.06 (*d*, 6 H).

4i: IR (film): 1719, 1627. ^{1}H-NMR (200 MHz, $CDCl_3$): 6.24 (*d*, 1 H); 5.85 (*m*, 1 H); 3.76 (*s*, 3 H); 3.45 (*d*, 1 H); 1.70 (*m*, 1 H); 1.14 (br., NH); 1.02 (*s*, 9 H); 0.88 (*d*, 3 H); 0.83 (*d*, 3 H).

Methyl (E)-2-{[(4-Methoxyphenyl)amino]methyl}-4-methylpent-2-enoate (**3j**) *and Methyl 2-{1-[(4-Methoxyphenyl)amino]-2-methylpropyl}prop-2-enoate* (**4j**). Variant *B*: after 2.5 h at reflux, 60% of **3j** and 10% of **4j**.

3j: IR (film): 3387, 1713, 1647, 1514. ^{1}H-NMR (200 MHz, $CDCl_3$): 6.78 (*m*, 2 H); 6.70 (*d*, 1 H); 6.63 (*m*, 2 H); 3.92 (*s*, 2 H); 3.84 (br., NH); 3.75 (*s*, 3 H); 3.74 (*s*, 3 H); 2.78 (*m*, 1 H); 1.02 (*d*, 6 H).

4j: IR (film): 3409, 1713, 1624, 1514. ^{1}H-NMR (200 MHz, $CDCl_3$): 6.74 (*m*, 2 H); 6.51 (*m*, 2 H); 6.20 (*d*, 1 H); 5.64 (*s*, 1 H); 3.93 (*d*, 1 H); 3.85 (br., NH); 3.76 (*s*, 3 H); 3.72 (*s*, 3 H); 2.02 (*m*, 1 H); 1.00 (*d*, 3 H); 0.96 (*d*, 3 H).

Methyl 2-{α[(tert-Butyl)amino]-4-isopropylbenzyl}prop-2-enoate (**4k**). Variant *B*: after 24 h, 72%. IR (film): 1724, 1629, 1509. ^{1}H-NMR (200 MHz, $CDCl_3$): 7.24 (*m*, 2 H); 7.12 (*m*, 2 H); 6.33 (*m*, 1 H); 6.27 (*m*, 1 H); 4.85 (*s*, 1 H); 3.67 (*s*, 3 H); 2.86 (*sept.*, 1 H); 1.22 (*d*, 6 H); 1.15 (br., NH); 1.07 (*s*, 9 H).

(E)-3-Phenyl-2-[(propylamino)methyl]prop-2-enoic Acid Hydrochloride (**5c**) *and (E)-3-Benzylidene-1-propylazetidin-2-one* (**7c**). NaOH (300 mg, 7.5 mmol) was dissolved in EtOH (3 ml) and H_2O (2 ml) and cooled to 0°. To the stirred soln. was added a soln. of **3c** (350 mg, 1.5 mmol) in EtOH (3 ml). The resulting mixture was stirred for 15 min at 0° and then 2 h 45 min at r.t. The alcohol was distilled off under reduced pressure and the residue diluted with H_2O and washed twice with Et_2O. The aq. phase was acidified under ice cooling with conc. HCl soln. (→ pH 1) and evaporated. The mixture **5c**/NaCl thus obtained was dried under high vacuum. Assuming that the hydrolysis to **5c** was quantitative, the cyclization to **7c** was performed as described for **8c** (see below). The residual oil was purified by FC (silica gel, cyclohexane/Et_2O 3:1): 121 mg (40%) of **7c.**

5c: IR (KBr): 2969, 1690, 1638. ^{1}H-NMR (200 MHz, D_2O): 8.21 (*s*, 1 H); 7.50 (*m*, 5 H); 4.13 (*s*, 2 H); 2.94 (*t*, 2 H); 1.58 (*sext.*, 2 H); 0.88 (*t*, 3 H).

7c: Colorless solid. M.p. 53°. IR (KBr): 1739. ^{1}H-NMR (200 MHz, $CDCl_3$): 7.34 (*m*, 5 H); 6.93 (*t*, 1 H); 4.12 (*s*, 1 H); 4.10 (*s*, 1 H); 3.36 (*t*, 2 H); 1.64 (*sext.*, 2 H); 0.97 (*t*, 3 H).

(E)-2-[(Isopropylamino)methyl]-3-phenylprop-2-enoic Acid Hydrochloride (**5d**) *and (E)-3-Benzylidene-1-isopropylazetidin-2-one* (**7d**) were prepared from **3d** analogously to **5c** and **7c**.

5d: IR (KBr): 2943, 1695, 1637. ^{1}H-NMR (200 MHz, D_2O): 8.22 (*s*, 1 H); 7.53 (*m*, 5 H); 4.14 (*s*, 2 H); 3.45 (*sept.*, 1 H); 1.26 (*d*, 6 H).

7d: Yield 46%. M.p. 53°. IR (KBr): 1726. ^{1}H-NMR (200 MHz, $CDCl_3$): 7.34 (*m*, 5 H); 6.92 (*t*, 1 H); 4.09 (*s*, 1 H); 4.08 (*sept.*, 1 H); 4.07 (*s*, 1 H); 1.26 (*d*, 6 H).

(E)-2-{[(tert-Butyl)amino]methyl}-3-phenylprop-2-enoic Acid Hydrochloride (**5e**) *and (E)-3-Benzylidene-1-(tert-butyl)azetidin-2-one* (**7e**) were prepared from **3e** analogously to **5c** and **7c**.

5e: IR (KBr): 2979, 1693, 1636. ^{1}H-NMR (200 MHz, D_2O): 8.23 (*s*, 1 H); 7.54 (*m*, 5 H); 4.12 (*s*, 2 H); 1.33 (*s*, 9 H).

7e: Yield 73%. M.p. 86°. IR (KBr): 1724. ^{1}H-NMR (200 MHz, $CDCl_3$): 7.34 (*m*, 5 H); 6.90 (*t*, 1 H); 4.06 (*s*, 1 H); 4.05 (*s*, 1 H); 1.41 (*s*, 9 H).

(E)-3-(4-Nitrophenyl)-2-[(propylamino)methyl]prop-2-enoic Acid Hydrochloride (**5f**) *and (E)-3-(4-Nitrobenzylidene)-1-propylazetidin-2-one* (**7f**) were prepared from **3f** analogously to **5c** and **7c**.

5f: IR (KBr): 2968, 1698, 1635, 1522, 1349. ^{1}H-NMR (200 MHz, D_2O): 8.38 (*m*, 2 H); 8.26 (*s*, 1 H); 7.65 (*m*, 2 H); 4.13 (*s*, 2 H); 2.98 (*t*, 2 H); 1.62 (*sext.*, 2 H); 0.91 (*t*, 3 H).

7f: Yield 39%. M.p. 107°. IR (KBr): 1741, 1518, 1344. ^{1}H-NMR (200 MHz, $CDCl_3$): 8.23 (*m*, 2H); 7.48 (*m*, 2 H); 6.99 (*s*, 1 H); 4.18 (*s*, 1 H); 4.17 (*s*, 1 H); 3.40 (*t*, 2 H); 1.67 (*sext.*, 2 H); 0.99 (*t*, 3 H).

(E)-2-{[(tert-Butyl)amino]methyl}-3-(4-nitrophenyl)prop-2-enoic Acid Hydrochloride (**5g**) *and (E)-1-(tert-Butyl)-3-(4-nitrobenzylidene)azetidin-2-one* (**7g**) were prepared from **3g** analogously to **5c** and 7c.

5g: IR (KBr): 2980, 1704, 1638, 1522, 1348. ^{1}H-NMR (200 MHz, D_2O): 8.35 (*m*, 2 H); 8.21 (*s*, 1 H); 7.66 (*m*, 2 H); 4.04 (*s*, 2 H); 1.30 (*s*, 9 H).

7g: Yield 66%. M.p. 166°. IR (KBr): 1729, 1520, 1342. ^{1}H-NMR (200 MHz, $CDCl_3$): 8.22 (*m*, 2 H); 7.47 (*m*, 2 H); 6.96 (*s*, 1 H); 4.12 (*s*, 1 H); 4.11 (*s*, 1 H); 1.43 (*s*, 9 H).

(E)-2-{[(tert-Butyl)amino]methyl}pent-2-enoic Acid Hydrochloride (**5h**) *and (E)-1-(tert-Butyl)-3-propylideneazetidin-2-one* (**7h**) were prepared from **3h** analogously to **5c** and **7c**.

5h: IR (KBr): 2977, 1698, 1650. ^{1}H-NMR (200 MHz, D_2O): 7.27 (*t*, 1 H); 3.90 (*s*, 2 H); 2.37 (*quint.*, 2 H); 1.43 (*s*, 9 H); 1.08 (*t*, 3 H).

7h: Yield 40%. IR (film): 2970, 1742. ^{1}H-NMR (200 MHz, $CDCl_3$): 6.08 (*tt*, 1 H); 3.71 (*m*, 2 H); 2.10 (*quint.*, 2 H); 1.36 (*s*, 9 H); 1.05 (*t*, 3 H).

(E)-2-{[(tert-Butyl)amino]methyl}-4-methylpent-2-enoic Acid Hydrochloride (**5i**) *and (E)-1-(tert-Butyl)-3-isobutylideneazetidin-2-one* (**7i**) were prepared from **3i** analogously to **5c** and **7c**.

5i: IR (KBr): 2970, 1697, 1645. ^{1}H-NMR (200 MHz, D_2O): 7.12 (*d*, 1 H); 3.94 (*s*, 2 H); 2.86 (*m*, 1 H); 1.46 (*s*, 9 H); 1.10 (*d*, 6 H).

7i: Yield 19%. IR (film): 2966, 1746. ^{1}H-NMR (200 MHz, $CDCl_3$): 6.00 (*dt*, 1 H); 3.74 (*m*, 2 H); 2.40 (*m*, 1 H); 1.36 (*s*, 9 H); 1.05 (*d*, 6 H).

(E)-2-{[(4-Methoxyphenyl)amino]methyl}-4-methylpent-2-enoic Acid Hydrochloride (**5j**) *and (E)-3-Isobutylidene-1-(4-methoxyphenyl)azetidin-2-one* (**7j**) were prepared from **3j** analogously to **5c** and **7c**.

5j: IR (KBr): 2962, 1696, 1648, 1514. ^{1}H-NMR (200 MHz, D_2O): 7.40 (*m*, 2 H); 7.14 (*m*, 2 H); 7.00 (*d*, 1 H); 4.34 (*s*, 2 H); 3.88 (*s*, 3 H); 2.41 (*m*, 1 H); 0.77 (*d*, 6 H).

7j: Yield 10%. M.p. 71°. IR (KBr): 1735, 1718, 1521. ^{1}H-NMR (200 MHz, $CDCl_3$): 7.33 (*m*, 2 H); 6.88 (*m*, 2 H); 6.19 (*dt*, 1 H); 4.13 (*m*, 2 H); 3.79 (*s*, 3 H); 2.49 (*m*, 1 H); 1.12 (*d*, 6 H).

(E)-3-Phenyl-2-[(phenylamino)methyl]prop-2-enoic Acid (**5a**; without HCl) *and (E)-3-Benzylidene-1-phenylazetidin-2-one* (**7a**). Amino acid methyl ester **3a** was treated with NaOH in EtOH/H_2O and worked up similarly to **5c**/**7c**. On acidification with conc. HCl soln., the free amino acid **5a** precipitated. It was dissolved with Et_2O, the aq. layer extracted twice with Et_2O, and the combined org. phase dried ($MgSO_4$) and evaporated to yield 99% of **5a**. Yellow solid. M.p. 151°.

IR (KBr): 3404, 3053, 1669, 1602. ^{1}H-NMR (200 MHz, $CDCl_3$): 8.02 (*s*, 1 H); 7.60 (br., CO_2H, NH); 7.42 (*m*, 5 H); 7.15 (*m*, 2 H); 6.76 (*m*, 1 H); 6.57 (*m*, 2 H); 4.16 (*s*, 2 H).

The cyclization to **7a** was performed according to the preparation of **8c**. Yield 61%. M.p. 158°. IR (KBr): 1732, 1596, 1500, 1381. ^{1}H-NMR (200 MHz, $CDCl_3$). 7.40 (*m*, 9 H); 7.10 (*m*, 2 H); 4.47 (*s*, 1 H); 4.46 (*s*, 1 H).

(E)-2-{[(4-Methoxyphenyl)amino]methyl}-3-phenylprop-2-enoic Acid (**5b**; without HCl) *and (E)-3-Benzylidene-1-(4-methoxyphenyl)azetidin-2-one* (**7b**) were prepared from **3b** analogously to **5a** and **7a**.

5b: Yield 99%. M.p. 147°. IR (KBr): 3386, 2935, 1673, 1514. ^{1}H-NMR (200 MHz, $CDCl_3$): 8.19 (br., CO_2H, NH); 7.97 (*s*, 1 H); 7.38 (*s*, 5 H); 6.70 (*m*, 4 H); 4.13 (*s*, 2 H); 3.73 (*s*, 3 H).

7b: Yield 40%. M.p. 152°. IR (KBr): 1729, 1515. ^{1}H-NMR (200 MHz, $CDCl_3$): 7.37 (*m*, 7 H); 7.05 (*t*, 1 H); 6.90 (*m*, 2 H); 4.42 (*s*, 1 H); 4.41 (*s*, 1 H); 3.79 (*s*, 3 H).

2-[α-(Propylamino)benzyl]prop-2-enoic Acid Hydrochloride (**6c**). For 2 h, 417 mg (1.79 mmol) of **4c** and 20% HCl soln. (12.5 ml) were refluxed. The mixture was washed twice with Et_2O, the aq. phase evaporated, and the resulting precipitate dried under high vacuum. Yield 75%. M.p. 177°. IR (KBr): 2966, 1708, 1631. ^{1}H-NMR (200 MHz, D_2O): 7.56 (*s*, 5 H); 6.72 (*s*, 1 H); 6.24 (*s*, 1 H); 5.36 (*s*, 1 H); 3.03 (*m*, 2 H); 1.77 (*m*, 2 H); 0.98 (*t*, 3 H).

2-[α-(Isopropylamino)benzyl]prop-2-enoic Acid Hydrochloride (**6d**) was prepared from **4d** in 83% yield analogously to **6c**. M.p. 139°. IR (KBr): 2927, 1704, 1634. ^{1}H-NMR (200 MHz, D_2O): 7.53 (*s*, 5 H); 6.70 (*s*, 1 H); 6.21 (*s*, 1 H); 5.45 (*s*, 1 H); 3.41 (*sept.*, 1 H); 1.42 (*d*, 3 H); 1.35 (*d*, 3 H).

2-{α-[(tert-Butyl)amino]benzyl}prop-2-enoic Acid Hydrochloride (**6e**) was prepared from **4e** in 95% yield analogously to **6c**. M.p. 133°. IR (KBr): 2980, 1708, 1633. ^{1}H-NMR (200 MHz, CD_3OD): 7.65 (*m*, 2 H); 7.45 (*m*, 3 H); 6.57 (*s*, 1 H); 6.35 (*s*, 1 H); 5.54 (*s*, 1 H); 1.38 (*s*, 9 H).

2-{1-[(tert-Butyl)amino]propyl}prop-2-enoic Acid Hydrochloride (**6h**) was prepared from **4h** in 99% yield analogously to **6c**. M.p. 200°. IR (KBr): 2976, 1699, 1626. ^{1}H-NMR (200 MHz, D_2O): 6.63 (*s*, 1 H); 6.20 (*s*, 1 H); 4.13 (*m*, 1 H); 1.99 (*m*, 2 H); 1.42 (*s*, 9 H); 0.88 (*t*, 3 H).

2-{1-[(tert-Butyl)amino]-2-methylpropyl}prop-2-enoic Acid Hydrochloride (**6i**) was prepared from **4i** in 94% yield analogously to **6c**. M.p. 178°. IR (KBr): 2970, 1692, 1618. ^{1}H-NMR (200 MHz, D_2O): 6.66 (*s*, 1 H); 6.15 (*s*, 1 H); 4.24 (*d*, 1 H); 2.27 (*m*, 1 H); 1.42 (*s*, 9 H); 1.02 (*d*, 3 H); 0.93 (*d*, 3 H).

2-{α-[(tert-Butyl)amino]-4-isopropylbenzyl}prop-2-enoic Acid Hydrochloride (**6k**) was prepared from the hydrochloride of **4k** (obtained from **4k** and 10% HCl in acetone) in 95% yield analogously to **6c**. M.p. 170°. IR (KBr): 2964, 1712, 1632. ^{1}H-NMR (200 MHz, D_2O): 7.55 (*m*, 2 H); 7.41 (*m*, 2 H); 6.63 (*s*, 1 H); 6.27 (*s*, 1 H); 5.53 (*s*, 1 H); 2.97 (*sept.*, 1 H); 1.41 (*s*, 9 H); 1.24 (*d*, 6 H).

3-Methylidene-4-phenyl-1-propylazetidin-2-one (**8c**). To a mixture of **6c** (330 mg, 1.29 mmol), $KHCO_3$ (517 mg, 5.16 mmol), and $Bu_4N(HSO_4)$ (66 mg, 0.19 mmol) was added H_2O (1.9 ml) and a soln. of MsCl (0.2 ml, 2.59 mmol) in $CHCl_3$ (6.5 ml). After 24 h vigorous stirring, the mixture was partitioned between Et_2O and H_2O. The aq. layer

was extracted twice with Et_2O, the combined org. phase washed twice with sat. brine, dried ($MgSO_4$), and evaporated, and the resulting oil purified by FC (silica gel, cyclohexane/Et_2O 2:1): 112 mg (43%) of **8c**. Colorless oil. IR (film): 1752. ^{1}H-NMR (200 MHz, $CDCl_3$): 7.36 (*m*, 5 H); 5.70 (*t*, 1 H); 5.02 (*m*, 1 H); 4.98 (*m*, 1 H); 3.47 (*m*, 1 H); 2.97 (*m*, 1 H); 1.51 (*m*, 2 H); 0.88 (*t*, 3 H). ^{13}C-NMR ($CDCl_3$): 164.16, 150.95, 136.80, 128.90, 128.77, 127.26, 108.87, 63.28, 42.27, 21.23, 11.56.

1-Isopropyl-3-methylidene-4-phenylazetidin-2-one (**8d**) was prepared from **6d** in 65% yield analogously to **8c**. IR ($CHCl_3$): 1737. ^{1}H-NMR (200 MHz, $CDCl_3$): 7.36 (*m*, 5 H); 5.63 (*t*, 1 H); 5.01 (*m*, 1 H); 4.92 (*m*, 1 H); 3.88 (*sept.*, 1 H); 1.28 (*d*, 3 H); 1.03 (*d*, 3 H). ^{13}C-NMR ($CDCl_3$): 163.61, 151.01, 138.25, 128.74, 128.62, 127.34, 108.40, 62.01, 44.98, 21.39, 20.39.

*1-(*tert*-Butyl)-3-methylidene-4-phenylazetidin-2-one* (**8e**) was prepared from **6e** in 80% yield analogously to **8c**. M.p. 146°. IR (KBr): 1737. ^{1}H-NMR (200 MHz, $CDCl_3$): 7.36 (*m*, 5 H); 5.64 (*t*, 1 H); 5.00 (*m*, 1 H); 4.89 (*m*, 1 H); 1.29 (*s*, 9 H).

*1-(*tert*-Butyl)-4-ethyl-3-methylideneazetidin-2-one* (**8h**) was prepared from **6h** in 85% yield analogously to **8c**. IR (film): 1741. ^{1}H-NMR (200 MHz, $CDCl_3$): 5.59 (*t*, 1 H); 5.05 (*t*, 1 H); 4.13 (*m*, 1 H); 1.94 (*m*, 1 H); 1.67 (*m*, 1 H); 1.39 (*s*, 9 H); 0.97 (*t*, 3 H).

*1-(*tert*-Butyl)-4-isopropyl-3-methylideneazetidin-2-one* (**8i**) was prepared from **6i** in 55% yield analogously to **8c**. IR (film): 1741. ^{1}H-NMR (200 MHz, $CDCl_3$): 5.62 (*m*, 1 H); 5.04 (*m*, 1 H); 4.15 (*m*, 1 H); 2.18 (*m*, 1 H); 1.39 (*s*, 9 H); 1.04 (*d*, 3 H); 0.91 (*d*, 3 H). ^{13}C-NMR ($CDCl_3$): 163.61, 146.57, 108.08, 64.77, 54.26, 29.61, 28.26, 19.54, 14.46.

*1-(*tert*-Butyl)-4-(4-isopropylphenyl)-3-methylideneazetidin-2-one* (**8k**) was prepared from **6k** in 75% yield analogously to **8c**. IR (film): 1746. ^{1}H-NMR (200 MHz, $CDCl_3$): 7.29 (*m*, 2 H); 7.19 (*m*, 2 H); 5.62 (*t*, 1 H); 4.98 (*m*, 1 H); 4.90 (*m*, 1 H); 2.91 (*sept.*, 1 H); 1.28 (*s*, 9 H); 1.25 (*d*, 6 H).

*(*E*)-3-Benzylideneazetidin-2-one* (**9**). A soln. of **7b** (260 mg, 0.98 mmol) in MeCN (20 ml) and CH_2Cl_2 (4 ml) was cooled to 0° and treated with a soln. of $Ce(NH_4)_2(NO_3)_6$ (1.74 g, 3.17 mmol) in H_2O (15 ml) during 5 min. The mixture was stirred at 0° for 30 min, then diluted with H_2O (75 ml), and extracted 3 times with AcOEt. The org. extracts were washed with 5% $NaHCO_3$, and the aq. layer was reextracted with AcOEt. The combined org. soln. was washed with 10% Na_2SO_3 (until the aq. layer remained colorless), 5% $NaHCO_3$, and sat. NaCl soln., dried (Na_2SO_4), and evaporated, and the dark solid purified by FC (silica gel, CH_2Cl_2): 23 mg (15%) of **9**. Pale yellow solid. M.p. 159°. IR (KBr): 3148, 1762. ^{1}H-NMR (200 MHz, $CDCl_3$): 7.35 (*m*, 5 H); 7.01 (*s*, 1 H); 6.62 (br., NH); 4.20 (*s*, 1 H); 4.19 (*s*, 1 H).

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