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β-Lactam derivatives as enzyme inhibitors: halogenated β-lactams and related compounds

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Abstract Different modifications of the imine – acyl chloride reaction were used for the synthesis of 3-mono- and 3,3-dihalogenated 1,4-diaryl substituted β-lactams. Furthermore, these β-lactams were modified by halogen substitution either at the aryl at position 1 or at the aryl substituent at position 4, or at both positions. The influence of the halogen atoms on the reactivity of the β-lactam ring, visible by the carbonyl frequence in their IR spectra, was studied. A selection of compounds was tested as inhibitors of the serin protease porcine pancreatic elastase. No simple correlation between IR frequence and biological activity was found. Finally, the base induced rearrangement of *N*-benzyl β-lactams was used for the synthesis of 4,5-diaryl substituted pyrrolidinones.

Keywords β-Lactams; Halogenated; 1,4-Diaryl-substituted; Pyrrolidinone derivatives; Elastase inhibitors.

Introduction

The β-lactam structure known from penicillins and cephalosporins as highly active and clinically useful β-lactam antibiotics [1] has motivated synthesis and evaluation during the last few decades. Apart from clinical use as antibacterials, these compounds serve as synthons in the synthesis of other biological active heterocycles [2], and in many examples the biological activity can be interpreted as an interaction between the β-lactam and a serine containing enzyme (serine protease) like elastase [3]. Therefore, the search for clinical useful β-lactams is a growing field of interest. We have described a number of β-lactam peptides [4] and studied their properties as elastase inhibitors. In continuation of our research in this field, we describe herein the synthesis of other substituted β-lactams and their biological evaluation. Some of these compounds showed a weak activity as inhibitors of elastase, and some showed an activity against some tumor cell lines [5]. As α-halo-β-lactams have attracted attention [6] because of their interesting biological properties we have extended our studies in this direction.

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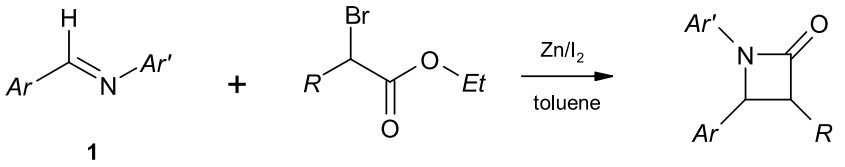
Results and discussion

All β-lactams were synthesized from the appropriate imines **1**, which were obtained by reaction between aldehyde and aromatic amine according to literature procedures. The ring formation was done depending on the substituents by different methods. Using a *Reformatsky*-like reaction [7] with 2-bromoalkanoates and zinc/iodine in toluene, we obtained the substituted β-lactams **2a**–**2g** with a fluoro substituent as part of the aromatic substituents *Ar* or *Ar′*.

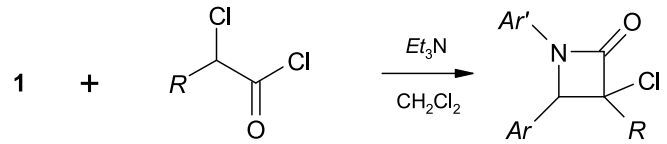


2a *R* = H *Ar* = *Ph Ar'* = *p*-F-*Ph*
2b *R* = *Me Ar* = *Ph Ar'* = *p*-F-*Ph*
2c *R* = H *Ar* = *p*-F-*Ph Ar'* = *p*-*Me*O-*Ph*
2d *R* = *Me Ar* = *p*-F-*Ph Ar'* = *p*-*Me*O-*Ph*
2e *R* = H *Ar* = *p*-F_3C-*Ph Ar'* = *p*-*Me*O-*Ph*
2f *R* = *Me Ar* = *p*-F_3C-*Ph Ar'* = *p*-*Me*O-*Ph*
2g *R* = H *Ar* = *p*-F_3C-*Ph Ar'* = *p*-F-*Ph*

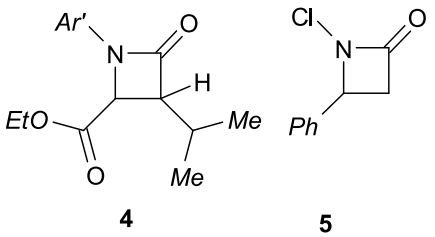
These compounds were obtained either as racemates (**2a**, **2c**, **2e**, and **2g**) or as racemates of the *trans* form (**2b**, **2d**, and **2f**), which was deduced from their ^{1}H NMR spectra and their chromatographic properties (exp. part). The ^{1}H NMR spectra of **2a**, **2c**, **2e**, and **2g** were characterized by AMX spectra of the protons 3-H, 3′-H, and 4-H with coupling constants of $J_{AX} =$ 2.5–2.6 Hz, $J_{AM} = 15.1$–15.2 Hz, and $J_{MX} = 5.6$–5.7 Hz. The signals of the protons 3-H and 4-H were found in the ^{1}H NMR spectra of **2b**, **2d**, and **2f** at $\delta = 3.63$ and 5.16 (5.13 and 5.20) ppm with $J_{3,4} = 5.8$–5.9 Hz, clearly indicating the *trans* configuration.

In HPLC experiments using a column with a nonchiral adsorbent the compounds showed one single peak, while using a column with a chiral adsorbent resulted in two separated peaks (1:1) from the racemates. All IR spectra showed a strong carbonyl band between $\bar{\nu} = 1730$ and 1760 cm^{-1}, whereby the highest values were found for **2e** and **2f**, compounds bearing in position 4 a *p*-(trifluoromethyl)phenyl substituent.

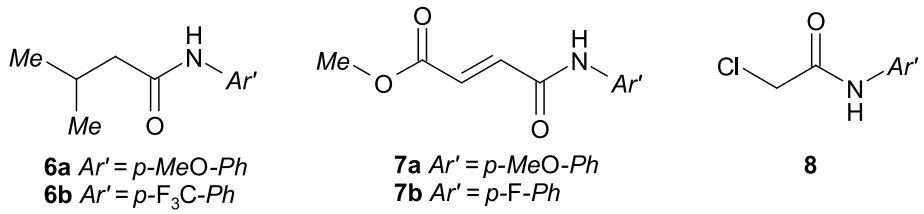
A second charge of β-lactams, 3-mono, and 3,3-dichloro derivatives **3a**–**3g**, and the ester derivative **4**, was prepared by a modification of the *Staudinger* reaction [8]. The imine and Et_3N were dissolved in CH_2Cl_2, and the acyl chloride was dropwise added. Using 3-methylbutyryl chloride or methyl (chlorocarbonyl)acrylate and some imines under similar reaction conditions (Et_3N) we could not isolate any β-lactam. Instead, an amidation had occurred form-



3a *R* = Cl *Ar* = *Ph Ar'* = *p*-*Me*O-*Ph*
3b *R* = H *Ar* = *p*-*Me*O-*Ph Ar'* = *p*-F-*Ph*
3c *R* = Cl *Ar* = *p*-*Me*O-*Ph Ar'* = *p*-F-*Ph*
3d *R* = Cl *Ar* = *Ph Ar'* = *p*-F-*Ph*
3e *R* = Cl *Ar* = *Ph Ar'* = *p*-F_3C-*Ph*
3f *R* = Cl *Ar* = *Ar'* = *p*-F_3C-*Ph*
3g *R* = H *Ar* = *p*-F_3C-*Ph Ar'* = *m*-O_2N-*Ph*



4 *Ar'* = *p*-*Me*O-*Ph**5**



6a *Ar'* = *p*-*Me*O-*Ph*
6b *Ar'* = *p*-F_3C-*Ph*

7a *Ar'* = *p*-*Me*O-*Ph*
7b *Ar'* = *p*-F-*Ph*

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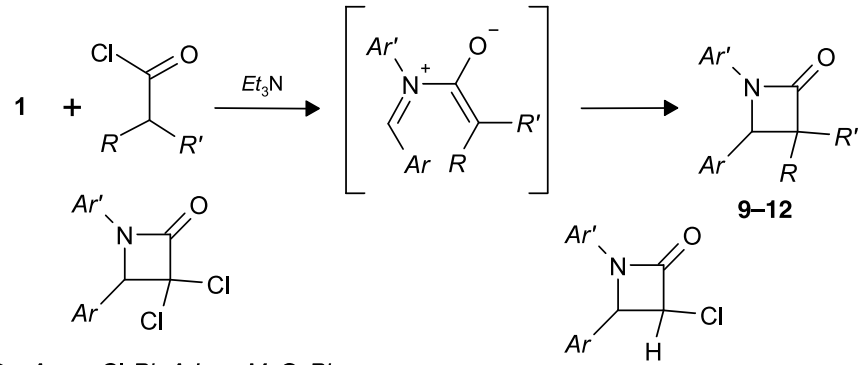
ing the amides **6a**, **6b** [9], **7a** [10], and **7b**. Each of the four compounds was prepared from the acyl chloride and two different imines (see Experimental) or may be prepared from the acyl chloride and the appropriate amine. Additionally, we prepared **8** by the same way, and the reactive *N*-chloro β-lactam **5** was obtained by direct chlorination of **18** at room temperature with 75% yield.

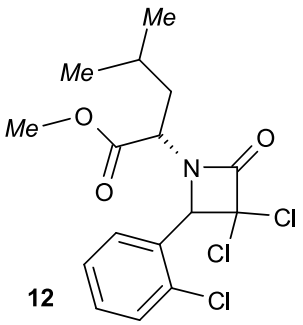
A third charge of halogenated β-lactams was prepared by addition of **1** to a solution of the acyl chloride in toluene, adding of Et_3N with heating, and refluxing the mixture for 3–4 h. This mode was described as a two step reaction with a zwitterionic intermediate [11] which cyclized to the lactam ring. We isolated the crystalline β-lactams **9a**–**12** usually in high yields. The 3,3-dichloro derivatives **9a**–**9l** and **12** were obtained as racemates whereas the 3-monochloro compounds **10a**–**10g** should be isolated as *trans*/*cis* mixtures. As demonstrated by the HPLC and ^{1}H NMR data, the isolated compounds were racemates of the favored *trans* diastereoisomers with $J_{3H,4H} = 1.9$–2.6 Hz. Furthermore, the IR spectra of the dichloro compounds showed the highest carbonyl absorption between $\bar{\nu} = 1770$ and $1796\,cm^{-1}$, whereas these bands in the spectra of the monochloro compounds were registered between $\bar{\nu} = 1759$ and $1777\,cm^{-1}$.

The lowest values of the carbonyl bands, $\bar{\nu} = 1731$–$1747\,cm^{-1}$, were found in the spectra of **11a**–**11e**, derivatives substituted at position 3 by an isopropyl group and at position 1 by a *p*-fluoro phenyl ring. The coupling constants $J_{3H,4H} = 2.0$–2.5 Hz clearly showed the *trans* orientation of the substituents at C-3 and C-4.

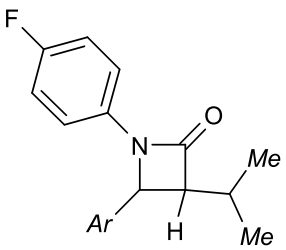
The β-lactam derivatives **16c**–**16b** and **17a**, **17b** were prepared from diethyl *p*-toluidinomalonate (**13**)



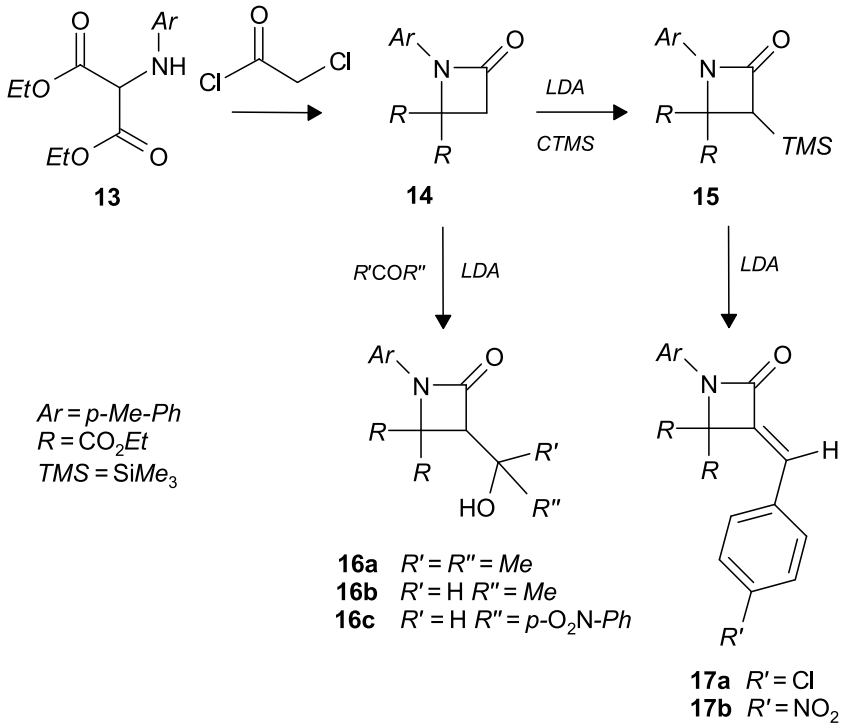
9a *Ar* = *p*-Cl-*Ph* *Ar′* = *p*-*Me*O-*Ph*
9b *Ar* = *p*-Cl-*Ph* *Ar′* = *p*-F-*Ph*
9c *Ar* = *o*-Cl-*Ph* *Ar′* = *p*-*Me*O-*Ph*
9d *Ar* = *Ph* *Ar′* = *p*-F-*Ph*
9e *Ar* = *p*-Me_2N-*Ph* *Ar′* = *p*-F-*Ph*
9f *Ar* = *o*-Cl-*Ph* *Ar′* = *o*-F-*Ph*
9g *Ar* = *p*-Cl-*Ph* *Ar′* = *o*-F-*Ph*
9h *Ar* = *p*-*Cl*-*Ph* *Ar′* = *m*-*F*-*Ph*
9i *Ar* = *p*-F_3C-*Ph* *Ar′* = *p*-*Me*O-*Ph*
9j *Ar* = *p*-*Me*O-*Ph* *Ar′* = *p*-F-*Ph*
9k *Ar* = *p*-Cl-*Ph* *Ar′* = $CH_2CO_2CH_2Ph$
9l *Ar* = *o*,*p*-F_2-*Ph* *Ar′* = *p*-F-*Ph*



10a *Ar* = *p*-Cl-*Ph* *Ar′* = *p*-*Me*O-*Ph*
10b *Ar* = *p*-Cl-*Ph* *Ar′* = *p*-F-*Ph*
10c *Ar* = *o*-Cl-*Ph* *Ar′* = *p*-*Me*O-*Ph*
10d *Ar* = *o*-Cl-*Ph* *Ar′* = *o*-F-*Ph*
10e *Ar* = *o*,*p*-Cl_2-*Ph* *Ar′* = *p*-F-*Ph*
10f *Ar* = *p*-*Me*O-*Ph* *Ar′* = *p*-F-*Ph*
10g *Ar* = *o*,*p*-F_2-*Ph* *Ar′* = *p*-F-*Ph*



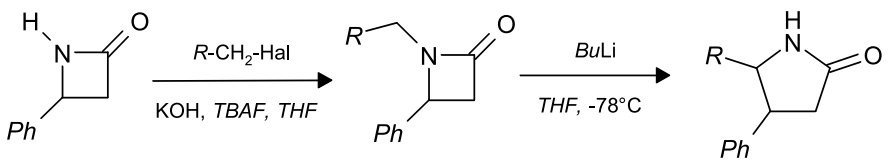
11a *Ar* = *p*-Cl-*Ph*
11b *Ar* = *o*-Cl-*Ph*
11c *Ar* = *o*,*p*-Cl_2-*Ph*
11d *Ar* = *p*-Me_2N-*Ph*
11e *Ar* = *p*-*Me*O-*Ph*



by reaction with chloroacetyl chloride yielding **14** [12] which was transformed into the 3-trimethylsilyl compound **15** by the reaction with *LDA* and *CTMS* at −78°C. The reaction of **14** with acetone or acetaldehyde in the presence of *LDA* yielded the 3-(α-hydroxy)ethyl derivatives **16a** and **16b**, whereas using similar conditions and 4-nitrobenzaldehyde the parent α-hydroxy compound **16c** became assesible. On the other hand, reactions of **15** with aromatic aldehydes resulted in the formation of the α,β-unsaturated lactams **17a** and **17b** [13].

An interesting observation was made when we tried to alkylate *N*-benzyl β-lactams at position 3. **19b**–**19f** were prepared by reaction of **18** with benzyl halogenides in *THF* in the presence of KOH and tetrabutylammonium bromide (*TBAF*). Treatment of these *N*-benzyl derivatives with *Bu*Li in *THF* at −78°C resulted in a deprotonation of the benzylic methylene group followed by a rearrangement ending up with the isolation of the pyrrolidinone derivatives **20a**–**20f** [14]. An analogous reaction was described for *N*-benzyl azetidines [15] and aza-β-lactams [16], and **20a** was first described by *Durst* [17] who discussed a diradical mechanism for this rearrangement.

The pyrrolidinones **20a** and **20f** were isolated as *trans* isomers, whereas compounds **20b** and **20d** were obtained as *cis*/*trans* mixtures. No product



was isolated from the reaction of **19c**, probably because the nitro group had reacted with *Bu*Li, and from the reaction of **19e** most of the starting material was reisolated. Furthermore, experiments to rearrange β-lactams with one or 2 aliphatic substituents in position 4 failed completely. No defined products were obtained.

Testing the biological activity of these compounds as inhibitors of elastase was done as we described earlier [18]. Compounds **3b**, **3e**, **3g**, **6b**, **7a**, **9b**, **10b**, and **10f** showed activities against *PPE* reaching maxima of about 10% of the activity of the standard inhibitor trifluoroacetyl-L-*val*-L-*tyr*-L-*val*. Therefore, no further experiments and elastase tests were done with these compounds.

Experimental

General

Mp PHMX 80/2778 (Küstner, Dresden) apparatus. IR Spectra: Perkin-Elmer FTIR 1600; in KBr, if not noted otherwise. NMR Spectra: Bruker DPX 200 (200 MHz), ARX 300 (300 MHz) for ^{1}H; δ (ppm) rel. to *TMS* as internal standard; ^{1}H-values from DPX 200 (200 MHz) spectra in $CDCl_3$, if not noted otherwise. Elementary analyses: Perkin-Elmer Analyzer 2400 CHN, Pharmazeutisches Institut der Universität Greifswald. All compounds gave satisfactory elemental analyses. Column chromatography (CC): Silica gel *60* (Merck 7734). HPLC with LaChrom apparatus series 7000 Merck Hitachi, LiChrospher 250–4, RP-18, 5 μm, and Chiralcel OJ–R, Flow = 1 ml/min, $\lambda_{max} = 220$ nm, $T = 20°C$ (**2a**–**2g**), Flow 1 = *0.8 cm^3/min, $\lambda_{max} = 220$ nm, $T = 30°C$ (**5**–**12**), solvents [b]*Me*CN/H_2O 7/3, or [c]*Me*CN/H_2O 4/6, or [d]*Me*CN/H_2O 1/1. *PPE* (Porcine pancreatic elastase, ≈200 U/mg) was purchased from Serva, *Suc*-(*Ala*)$_3$-pNA from Fluka. *THF* was stored with $CaCl_2$, refluxed with Na and benzophenone, and distilled *prior to* use. Other solvents were dried/purified according to literature procedures. *LDA* (lithium diisopropylamide) was freshly prepared by mixing of equivalent amounts of freshly distilled HN(CH*Me*$_2$)$_2$ and *n*-*Bu*Li (15% in hexane) at −78°C. *CTMS* = Chlorotrimethylsilane; *PE* = Petroleum ether.

Benzylidene(4-fluorophenyl)amine (**1a**); benzylidene(trifluoromethylphenyl)amine (**1b**); 4-fluorobenzylidene(4-methoxyphenyl)amine (**1c**); 4-fluorobenzylidene(3-nitrophenyl)-amine (**1d**); 4-trifluoromethylbenzylidene(4-trifluoromethylphenyl)amine (**1e**); 4-fluorophenyl(4-trifluoromethylbenzylidene)amine (**1f**); (4-methoxyphenyl)-4-trifluoromethylbenzylideneamine (**1g**); 4-fluorophenyl(4-methoxybenzylidene)-amine (**1h**); 4-(dimethylamino)benzylidene(4-fluorophenyl)-amine (**1i**); isopropylidene(4-methoxyphenyl)amine (**1j**); (4-chlorobenzylidene)(4-methoxyphenyl)amine (**1k**); (4-chlorobenzylidene)(4-fluorophenyl)amine (**1l**); (2-chloro-benzylidene)(4-methoxyphenyl)amine (**1m**); (2-chlorobenz-ylidene)(4-fluorophenyl)amine (**1n**); (2,4-dichlorobenzylidene)(4-fluorophenyl)amine (**1o**) [19]; ethyl (4-methoxyphenylimino)acetate (**1p**) [20]; benzyl (4-chlorobenzylideneamino)acetate (**1q**) [21]; diethyl 1-(4-methylphenyl)-2-oxoazetidine-4,4-dicarboxylate (**14**) [22]; *trans*-3-chloro-4-(2-chlorophenyl)-1-(4-methoxyphenyl)azetidin-2-one (**10c**); 3,3-dichloro-1-methoxyphenyl-4-phenylazetidin-2-one (**3a**) [23]; Ethyl 3-isopropyl-1-(4-methoxyphenyl)-4-oxoazetidin-2-carboxylate (**4**) [24] 3-chloro-4-(4-chlorophenyl)-1-(4-methoxyphenyl)azetidin-2-one (**10a**) [25]; (*RS*)-1-benzyl-4-phenylazetidin-2-one (**19a**) [26]; (*RS*)-4-phenylazetidin-2-one (**18**) [18].

Synthesis of imines. General procedure

If not otherwise noted, 0.25 mol of the aldehyde, and 0.25 mol of the amine were dissolved with slight warming in 200 cm^3 *Et*OH. The mixture was stirred at 3–18°C until the precipitate was completed. The products were crystallized from *Et*OH.

(2-Chlorobenzylidene)(2-fluorophenyl)amine

(**1r**, $C_{13}H_9ClFN$)

From 11.11 g (0.1 mol) 2-fluoroaniline and 14.1 g (0.1 mol) 2-chlorobenzaldehyde in 60 cm^3 *Et*OH. Yield 22.6 g (97%); colorless needles; mp 44°C; IR: $\bar{\nu} = 3062$ (CH), 1620 (C=N), 1239 (C–F), 1051 (C–Cl), 762 (*ar*) cm^{-1}; ^{1}H NMR (60 MHz): $\delta = 6.75$–7.3 (m, 7 *ar* H), 7.87–8.3 (m, 1 *ar* H), 8.76 (s, H–C=) ppm.

(4-Chlorobenzylidene)(2-fluorophenyl)amine

(**1s**, $C_{13}H_9ClFN$)

From 8.33 g (0.075 mol) 2-fluoroaniline and 10.6 g (0.075 mol) 4-chlorobenzaldehyde in 60 cm^3 *Et*OH. Yield 14.9 g (85%); light yellow needles; mp 47°C; IR: $\bar{\nu} = 3058$ (CH), 1626 (C=N), 1567 (*ar*), 1219 (C–F), 1092 (C–Cl), 827, 757 (*ar*) cm^{-1}; ^{1}H NMR (300 MHz): $\delta = 7.08$ (t, 2 *ar* H), 7.16–7.22 (m, 2 *ar* H), 7.45 (d, $J = 8.5$ Hz, 2 *ar* H), 7.38 (d, $J = 8.5$ Hz, 2 *ar* H), 8.40 (s, H–C=) ppm.

(4-Chlorobenzylidene)(3-fluorophenyl)amine

(**1t**, $C_{13}H_9ClFN$)

From 8.3 g (0.075 mol) 3-fluoroaniline and 10.5 g (0.075 mol) 4-chlorobenzaldehyde in 60 cm^3 *Et*OH. Yield 15.4 g (88%); colorless needles; mp 48°C; IR: $\bar{\nu} = 1630$ (C=N), 1586 (*ar*), 1259 (C–F), 1087 (C–Cl), 824, 779 (*ar*) cm^{-1}; ^{1}H NMR (60 MHz): $\delta = 6.48$–7.60 (m, 4 *ar* H), 7.7 (d, $J = 9$ Hz, 2 *ar* H), 7.58 (d, $J = 9$ Hz, 2 *ar* H), 8.11 (s, H–C=) ppm.

(2,4-Difluorobenzylidene)(4-fluorophenyl)amine

(**1u**, $C_{13}H_8F_3N$)

From 4.4 g (0.04 mol) 4-fluoroaniline and 5.7 g (0.04 mol) 2,4-difluorobenzaldehyde in 100 cm^3 of *Et*OH. When the reaction was completed, the solvent was evaporated, the residue was dissolved in 200 cm^3 Et_2O, the solution was dried (Na_2SO_4) and evaporated *in vacuo*. Yield 7.5 g (80%); brown viscous liquid; IR: $\bar{\nu} = 1624$ (C=N), 1589, 1502 (*ar*), 1238 (C–F), 832, 787 (*ar*) cm^{-1}; ^{1}H NMR (60 MHz): $\delta = 6.16$–7.26 (m, 7 *ar* H), 8.27 (s, H–C=) ppm.

(2,4-Difluorobenzylidene)(4-methoxyphenyl)amine (**1v**, $C_{14}H_{11}F_2NO$)
From 9.2 g (0.075 mol) *p*-anisidine and 10.7 g (0.075 mol) 2,4-difluorobenzaldehyde in 100 cm^3 *Et*OH as described for **1u**. Yield 13.1 g (66%); greenish viscous liquid; IR: $\bar{\nu} = 1622$ (C=N), 1578, 1504 (*ar*), 1247 (C–F), 828, 786 (*ar*) cm^{-1}; ^1H NMR (60 MHz): $\delta = 3.61$ (s, O*Me*), 6.0–7.4 (m, 7 *ar* H), 8.44 (s, H–C=) ppm.

Ethyl-2-[(2-chlorobenzylidene)amino]-4-methylvaleriate (**1w**, $C_{14}H_{18}ClNO_2$)
5 g (0.0344 mol) L-*Leu*-O*Me* was added to 4.8 g (0.0344 mol) 2-chlorobenzaldehyde. The mixture was cooled to room temperature, dissolved in 250 cm^3 CH_2Cl_2, dried (Na_2SO_4), and evaporated *in vacuo*. Yield 7.9 g (86%); light yellow viscous liquid; IR: $\bar{\nu} = 3067$, 2954 (CH), 1738 (CO), 1634 (C=N), 1592 (*ar*), 756 (*ar*) cm^{-1}; ^1H NMR (60 MHz): $\delta = 1.0$–1.4 (m, 2*Me*), 1.7–2.32 (m, CH, CH_2), 3.95 (s, O*Me*), 4.3 (t, $J = 6$ Hz, CH), 7.1–8.3 (m, 4 *ar* H), 8.8 (s, H–C=) ppm.

Ethyl-(4-fluorophenylimino)acetate (**1x**, $C_{10}H_{10}FNO_2$)
From 10.2 g (0.1 mol) ethyl glyoxylate (~20 g, 50% solution in toluene), 11.1 g (0.1 mol) 4-fluoroaniline, and 20 g $MgSO_4$ in 200 cm^3 toluene as described for **1u**. Yield 7.8 g (40%); orange solid used for the synthesis of **7b** without further purification; IR: $\bar{\nu} = 3381$ (NH), 2993 (CH), 1740 (CO), 1612 (C=N), 1513 (*ar*), 1275 (C–F), 820 (*ar*) cm^{-1}; ^1H NMR (300 MHz): $\delta = 1.38$ (t, *Me*), 4.41 (q, CH_2) 7.1 (t, 2 *ar* H), 7.32 (m, 2 *ar* H), 7.90 (s, H–C=) ppm.

Synthesis of β-lactams ***2****. General procedure*
In 50–100 cm^3 toluene, equivalent amounts (0.05–0.1) of **1**, Zn (filings), and a crystal of I_2 were refluxed, while ethyl 2-bromoalkanoate (0.05–0.1 mol) was dropwise added with stirring. Then, the mixture was refluxed for another 30 min, cooled to room temperature, and washed with conc. ammonia (50 cm^3), water (50 cm^3), HCl (10%, 50 cm^3), a solution of $NaHSO_3$ (20%, 50 cm^3), and water. The organic layer was dried (Na_2SO_4), and evaporated *in vacuo*. The residue was crystallized from *Me*OH.

(RS)-1-(4-Fluorophenyl)-4-phenylazetidin-2-one (**2a**, $C_{15}H_{12}FNO$)
From **1a** and ethyl 2-bromoacetate. Yield 10 g (30%); colorless crystals; mp 116°C; IR: $\bar{\nu} = 3060$, 2956 (CH), 1739 (CO), 1511(*ar*), 1456, 1383, 1361 (N–C), 1210, 1156 (C–F), 837, 814, 759, 701 (*ar*) cm^{-1}; ^1H NMR: $\delta = 2.91$–3.0 (dd, $J_{AX} = 2.6$, $J_{AM} = 15.2$ Hz, 3-H), 3.51–3.61 (dd, $J_{MX} = 5.7$, $J_{AM} = 15.2$ Hz, 3′-H), 4.96 (dd, $J_{AX} = 2.6$, $J_{MX} = 5.7$ Hz, 4-H), 6.88–6.97 (t, $J = 8.6$, $J = 8.8$ Hz, 2 *ar* H), 7.22–7.36 (m, 7 *ar* H) ppm; HPLC: $t_R = 4.88$ min, $k' = 1.77$, RP-18[b]; $t_R = 12.17$, 13.52 min, $k' = 5.76$, 6.51, Chiralcel OJ–R[c].

trans-1-(4-Fluorophenyl)-3-methyl-4-phenylazetidin-2-one (**2b**, $C_{16}H_{14}FNO$)
From **1a** and ethyl 2-bromopropionate. Yield 7.6 g (48%); colorless crystals; mp 123°C; IR: $\bar{\nu} = 3064$, 2978 (CH), 1735 (CO), 1515 (*ar*), 1453, 1391 (C–N), 1216 (C–F), 836, 818 (*ar*) cm^{-1}; ^1H NMR: $\delta = 0.86$ (d, $J = 7.6$ Hz, *Me*), 3.63 (m, $J = 7.6$, 5.9 Hz, 3-H), 5.16 (d, $J = 5.9$ Hz, 4-H), 6.90 (t, $J = 8.7$, 8.5 Hz, 2 *ar* H), 7.19–7.38 (m, 7 *ar* H) ppm; HPLC: $t_R = 5.96$ min, $k' = 2.39$, RP-18[b]; $t_R = 12.35$, 14.05 min, $k' = 5.86$, 6.80, Chiralcel OJ–R[c].

(RS)-4-(4-Fluorophenyl)-1-(4-methoxyphenyl)azetidin-2-one (**2c**, $C_{16}H_{14}FNO_2$)
From **1c** and ethyl 2-bromoacetate. Yield 7.3 g (31%); colorless crystals; mp 127°C; IR: $\bar{\nu} = 3063$, 2972 (CH), 1740 (CO), 1604, 1508 (*ar*), 1379 (C–N), 1298 (C–F), 802 (*ar*) cm^{-1}; ^1H NMR: $\delta = 2.85$–2.94 (dd, $J_{AX} = 2.6$, $J_{AM} = 15.1$ Hz, 3-H), 3.49–3.59 (dd, $J_{MX} = 5.6$, $J_{AM} = 15.1$ Hz, 3′-H), 3.74 (s, O*Me*), 4.94–4.98 (dd, $J_{AX} = 2.5$ Hz, $J_{MX} = 5.5$ Hz, 4-H), 6.76–6.80 (d, $J = 8.9$ Hz, 2 *ar* H), 7.02–7.10 [t(2d), $J = 8.6$ Hz, $J = 8.6$ Hz, 2 *ar* H], 7.18–7.23 (d, $J = 9.0$ Hz, 2 *ar* H), 7.31–7.38 (2 d, $J = 8.8$ Hz, 2 *ar* H) ppm; HPLC: $t_R = 4.39$ min, $k' = 1.49$, RP-18[b]; $t_R = 27.50$ min, $k' = 14.28$, Chiralcel OJ–R, *Me*CN/H_2O 1/3.

trans-4-(4-Fluorophenyl)-1-(4-methoxyphenyl)-3-methyl-azetidin-2-one (**2d**, $C_{17}H_{16}FNO_2$)
From **1c** and ethyl 2-bromopropionate. Yield 3.7 g (44%); colorless crystals; mp 125°C; IR: $\bar{\nu} = 3058$, 2973 (CH), 1731 (CO), 1518 (*ar*), 1389 (C–N), 1160 (C–F), 839, 804 (*ar*) cm^{-1}; ^1H NMR: $\delta = 0.85$ (d, $J = 7.6$ Hz, *Me*), 3.63 (m, 3-H), 3.76 (s, O*Me*), 5.13 (d, $J = 5.8$ Hz, 4-H), 6.77–6.82 (d, $J = 9.0$ Hz, 2 *ar* H), 7.05–7.09 (t (2d), $J = 8.6$ Hz, 2 *ar* H), 7.17–7.25 (m, 4 *ar* H) ppm; HPLC: $t_R = 5.24$ min, $k' = 1.98$, RP-18[b]; $t_R = 12.93$, 14.52 min, $k' = 6.18$, 7.07, Chiralcel OJ–R[c].

(RS)-1-(4-Methoxyphenyl)-4-[4-(trifluoromethyl)phenyl]-azetidin-2-one (**2e**, $C_{17}H_{14}F_3NO_2$)
From **1g** and ethyl 2-bromoacetate. Yield 3.8 g (33%); colorless needles; mp 135°C; IR: $\bar{\nu} = 3078$, 2961 (CH), 1760 (CO), 1621, 1511 (*ar*), 1376 (C–N), 1298 (C–F), 854, 824, 800 (*ar*) cm^{-1}; ^1H NMR: $\delta = 2.88$ (dd, $J_{AX} = 2.5$, $J_{AM} = 15.1$ Hz, 3-H), 3.56 (dd, $J_{MX} = 5.7$, $J_{AM} = 15.1$ Hz, 3′-H), 3.74 (s, O*Me*), 5.03 (dd, $J_{AX} = 2.5$, $J_{MX} = 5.6$ Hz, 4-H), 6.77–6.81 (d, $J = 9.0$ Hz, 2 *ar* H), 7.17–7.22 (d, $J = 9.2$ Hz, 2 *ar* H), 7.46 (d, $J = 8.2$ Hz, 2 *ar* H), 7.61 (d, $J = 8.6$ Hz, 2 *ar* H) ppm; HPLC: $t_R = 5.75$ min, $k' = 2.27$, RP-18[c]; $t_R = 12.61$, 13.50 min, $k' = 6.01$, 6.50, Chiralcel OJ–R[c].

trans-1-(4-Methoxyphenyl)-3-methyl-4-[4-(trifluoromethyl)-phenyl]azetidin-2-one (**2f**, $C_{18}H_{16}F_3NO_2$)
From **1g** and ethyl 2-bromopropionate. Yield 3.3 g (35%); colorless crystals; mp 107°C; IR: $\bar{\nu} = 3076$, 2961 (CH), 1760 (CO), 1621, 1511 (*ar*), 1376, 1333, (C–F), 1246 (C–O), 854, 824 (*ar*) cm^{-1}; ^1H NMR: $\delta = 0.85$ (d, $J = 7.6$ Hz, *Me*), 3.63 (m, 3-H), 3.76 (s, O*Me*), 5.20 (d, $J = 5.9$ Hz, 4-H), 6.78–6.83 (d, $J = 8.9$ Hz, 2 *ar* H), 7.2–7.24 (d, $J = 8.9$ Hz, 2 *ar* H), 7.33–7.37 (d, $J = 8.0$ Hz, 2 *ar* H), 7.61 (d, $J = 8.3$ Hz, 2 *ar* H) ppm; HPLC: $t_R = 6.93$ min, $k' = 2.94$, RP-18[b]; $t_R = 12.66$, 14.99 min, $k' = 6.03$, 7.33, Chiralcel OJ–R[c].

(RS)-1-(4-Fluorophenyl)-4-[4-(trifluoromethyl)phenyl]-azetidin-2-one (**2g**, $C_{16}H_{11}F_4NO$)
From **1f** and ethyl 2-bromoacetate. Yield 2.5 g (25%); colorless crystals; mp 176–177°C; IR: $\bar{\nu} = 3085$, 2971 (CH), 1749 (CO), 1513 (*ar*), 1384 (C–N), 1214, 1113 (C–F), 887, 815 (*ar*) cm^{-1}; ^1H NMR: $\delta = 2.90$–2.99 (dd, $J_{AX} = 2.6$, $J_{AM} = 15.2$ Hz, 3-H), 3.59 (dd, $J_{MX} = 5.7$, $J_{AM} = 15.2$ Hz, 3′-H), 5.03 (dd, $J_{AX} = 2.6$, $J_{MX} = 5.7$ Hz, 4-H), 6.91–7.0 [t(2d), $J = 9.0$, 8.4 Hz, 2 *ar* H], 7.20–7.26 (m, 2 *ar* H), 7.46 (d, $J = 8.2$ Hz, 2 *ar* H), 7.63 (d, $J = 8.2$ Hz, 2 *ar* H) ppm; HPLC: $t_R = 6.25$ min, $k' = 2.53$, RP-18[b]; $t_R = 22.33$, 23.67 min, $k' = 11.40$, 12.15, Chiralcel OJ–R[c].

*Synthesis of compounds **3**–**8**. General procedure*
A solution of **1** (0.2–0.5 mol), and Et_3N (0.2–0.5 mol) in 100 cm^3 CH_2Cl_2 was dropwise added to a solution of the acid chloride (0.2–0.5 mol) in 50 cm^3 CH_2Cl_2 over 2 h. Then, the mixture was refluxed for 30 min, cooled to room temperature and filtered. The filtrate was pored into a mixture (1/1) of 0.1 *N* HCl and crashed ice, the organic layer was separated, washed with a satd. solution of $NaHCO_3$, dried (Na_2SO_4), and evaporated *in vacuo*. The residue was crystallized as noted.

trans-3-Chloro-1-(4-fluorophenyl)-4-(4-methoxyphenyl)-azetidin-2-one (**3b**, $C_{16}H_{13}ClFNO_2$)
From **1h** and $ClCH_2COCl$. Yield 1.3 g (19%); colorless needles; mp 132°C (*Me*$_2$CHOH); IR: $\bar{\nu} = 3067$, 2964 (CH), 1759 (CO), 1508 (*ar*), 1382 (C–N), 1248 (C–F), 1028 (C–Cl), 834, 816 (*ar*) cm^{-1}; ^1H NMR (300 MHz): $\delta = 3.81$ (s, O*Me*), 4.59 (d, $J =$ 1.9 Hz, 3-H), 4.93 (d, $J = 1.9$ Hz, 4-H), 6.91–6.98 (m, 4 *ar* H), 7.23–7.29 (m, 4 *ar* H) ppm; HPLC: $t_0 = 1.83$ min, $k' = 2.27$, RP-18[b]; $t_0 = 1.81$ min, $k' = 12.79$, 14.67, Chiralcel OJ–R*[,c].

(RS)-3,3-Dichloro-1-(4-fluorophenyl)-4-(4-methoxyphenyl)-azetidin-2-one (**3c**, $C_{16}H_{12}Cl_2FNO_2$)
From **1h** and $Cl_2CHCOCl$. Yield 0.4 g (5%); colorless needles; mp 140–141°C (*Ac*O*Et*/*n*-hexane); IR: $\bar{\nu} = 3064$, 2946 (CH), 1769 (CO), 1511 (*ar*), 1388 (C–N), 1264 (C–F), 834, 818 (*ar*) cm^{-1}; ^1H NMR: $\delta = 3.83$ (s, O*Me*), 5.43 (s, 4-H), 6.93–7.02 (m, 4 *ar* H), 7.22–7.31 (m, 4 *ar* H) ppm; HPLC: $t_0 = 1.77$ min, $k' =$ 4.10, RP-18[b]; $t_0 = 2.25$ min, $k' = 8.59$, 15.26, Chiralcel OJ–R[d].

(RS)-3,3-Dichloro-1-(4-fluorophenyl)-4-phenylazetidin-2-one (**3d**, $C_{15}H_{10}Cl_2FNO$)
From **1a** and $Cl_2CHCOCl$. Yield 4.2 g (27%); colorless needles; mp 112°C (*Me*OH); IR: $\bar{\nu} = 3065$, 2922 (CH), 1782, 1741 (CO), 1509 (*ar*), 1387 (C–N), 1229 (C–F), 1051 (C–Cl), 832, 765, 700 (*ar*) cm^{-1}; ^1H NMR (300 MHz): $\delta = 5.49$ (s, 4-H), 7.0 (t, $J_1 = 8.4$, $J_2 = 8.8$ Hz, 2 *ar* H), 7.29 (m, 5 *ar* H), 7.42-7.45 (m, 2 *ar* H) ppm; HPLC: $t_0 = 1.83$ min, $k' = 3.53$, RP-18[b]; $t_0 = 1.73$ min, $k' = 14.08$, 21.35, Chiralcel OJ–R, *Me*CN/H_2O 45/55.

(RS)-3,3-Dichloro-4-phenyl-1-[4-(trifluoromethyl)phenyl]-azetidin-2-one (**3e**, $C_{16}H_{10}Cl_2F_3NO$)
From **1b** and $Cl_2CHCOCl$. Yield 1.7 g (69%); light brown crystals; mp 73–75°C (*Me*OH/*n*-hexane); IR: $\bar{\nu} = 3093$, 2934 (CH), 1792 (CO), 1522 (*ar*), 1386 (C–N), 1187 (C–F), 838, 824, 763, 700 (*ar*) cm^{-1}; ^1H NMR (300 MHz): $\delta = 5.55$ (s, 4-H), 7.32 (m, 2 *ar* H), 7.45 (m, 5 *ar* H), 7.56 (d, $J = 8.9$ Hz, 2 *ar* H) ppm; HPLC: $t_0 = 1.77$ min, $k' = 7.16$, RP-18[b]; $t_0 =$ 2.25 min, $k' = 9.07$, 11.25, Chiralcel OJ–R*[,d].

(RS)-3,3-Dichloro-1,4-bis[4-(trifluoromethyl)phenyl]-azetidin-2-one (**3f**, $C_{17}H_9Cl_2F_6NO$)
From **1e** and $Cl_2CHCOCl$. Yield 1.2 g (28%); colorless crystals; mp 113°C (*Ac*O*Et*/*n*-hexane); IR: $\bar{\nu} = 1789$ (CO), 1615, 1521 (*ar*), 1381 (C–N), 1327 (C–F), 1068 (C–Cl), 840 (*ar*) cm^{-1}; ^1H NMR (300 MHz): $\delta = 5.60$ (s, 4-H), 7.37 (d, $J = 8.5$ Hz, 2 *ar* H), 7.45 (d, $J = 7.9$ Hz, 2 *ar* H), 7.59 (d, $J = 8.5$ Hz, 2 *ar* H), 7.73 (d, $J = 8.2$ Hz, 2 *ar* H) ppm; HPLC: $t_0 = 1.77$ min, $k' = 10.23$, RP-18[b]; $t_0 = 2.25$ min, $k' = 11.59$, Chiralcel OJ–R*[,d].

trans-3-Chloro-4-(4-fluorophenyl)-1-(3-nitrophenyl)azetidin-2-one (**3g**, $C_{15}H_{10}ClFN_2O_3$)
From **1d** and $ClCH_2COCl$. Yield 0.6 g (9%); colorless crystals; mp 140°C (*Ac*O*Et*/*n*-hexane); IR: $\bar{\nu} = 3090$ (CH), 1775 (CO), 1530, 1512 (*ar*), 1376 (C–N), 1229 (C–F), 880 (C–Cl), 840, 736 (*ar*) cm^{-1}; ^1H NMR (300 MHz): $\delta = 4.67$ (d, $J = 2.1$ Hz, 3-H), 5.08 (d, $J = 2.1$ Hz, 4-H), 7.15 (t, $J =$ 8.5 Hz, 2 *ar* H), 7.39 (m, 2 *ar* H), 7.48 (t, $J = 8.1$ Hz, 1 *ar* H), 7.68 (dq, $J = 8.2$ Hz, 1 *ar* H), 7.95–8.0 (m, 2 *ar* H) ppm; HPLC: $t_0 = 1.82$ min, $k' = 1.79$, RP-18[d]; $t_0 = 2.33$ min, $k' = 5.11$, Chiralcel OJ–R*[,b].

(RS)-1-Chloro-4-phenylazetidin-2-one (**5**, C_9H_8ClNO)
1.6 g (10.8 mmol) of **18** was dissolved in a mixture of Et_2O and H_2O (100 cm^3, 1/1) and with stirring, chlorine was blown in for 1 h. Stirring was continued for 12 h, the organic layer was separated, dried (Na_2SO_4), and evaporated *in vacuo*. Yield 1.48 g (75%); colorless crystals; mp 67°C; IR: $\bar{\nu} = 3086$, 2959 (CH), 1791, 1772 (CO), 762, 701 (*ar*) cm^{-1}; ^1H NMR: $\delta = 3.05$ (dd, $J_{AM} = 2.6$, $J_{AX} = 13.6$ Hz, 3-H), 3.55 (dd, $J_{AM} = 5.5$, $J_{MX} = 13.6$ Hz, 3′-H), 4.81 (dd, $J_{AX} = 2.6$, $J_{MX} =$ 5.5 Hz, 4-H), 7.34 (m, 5 *ar* H) ppm; HPLC: $t_0 = 1.77$ min, $k' = 5.34$, RP-18[b]; $t_0 = 1.77$ min, $k' = 18.01$, 19.29, Chiralcel OJ–R[d].

N-(4-Methoxyphenyl)-3-methylbutyramide (**6a**, $C_{12}H_{17}NO_2$)
a) From 8.1 g isovalerianyl chloride, 9.3 g (12.8 cm^3) Et_3N, and 10 g **1j**. b) From 3 g **1k** and 1.9 g isovalerianyl chloride. Yield a) 6.2 g (49%), b) 0.7 g (28%); colorless needles; mp 126°C (*Me*OH); IR: $\bar{\nu} = 3293$ (NH), 3049, 2954 (CH), 1655, 1601 (CO), 1530, 1513 (*ar*), 1369 (C–N), 823 (*ar*) cm^{-1}; ^1H NMR (300 MHz): $\delta = 1.01$ (d, $J = 6.5$ Hz, 2 *Me*), 2.17–2.23 (m, CH, CH_2), 3.78 (s, O*Me*), 6.85 (d, $J = 9.0$ Hz, 2 *ar* H), 7.06 (s, H–N), 7.41 (d, $J = 9.0$ Hz, 2 *ar* H) ppm; HPLC: $t_0 = 1.79$ min, $k' = 0.74$, RP-18[b]; $t_0 = 1.94$ min, $k' = 3.87$, Chiralcel OJ–R[b].

3-Methyl-N-(4-trifluoromethylphenyl)butyramide (**6b**, $C_{12}H_{14}F_3NO$)
a) From 2.5 g **1b** or b) from 3.2 g **1e**, 1.2 g isovalerianyl chloride, and 1.5 g Et_3N. Yield a) 1.3 g (53%); b) 0.6 g

(24%); colorless crystals; mp 123°C (*Et*OH/*n*-hexane) (Ref. [9] 115°C); IR: $\bar{\nu} = 3305$ (NH), 3040, 2952 (CH), 1669 (CO), 1526 (*ar*), 1335 (C–N), 1160 (C–F), 1068 (C–Cl), 839 (*ar*) cm^{-1}; ^1H NMR (300 MHz): $\delta = 1.02$ (d, $J = 6.6$ Hz, 2 *Me*), 2.17–2.27 (m, CH, CH_2), 7.30 (s, H–N), 7.56 (d, $J = 8.7$ Hz, 2 *ar* H), 7.66 (d, $J = 8.6$ Hz, 2 *ar* H) ppm; HPLC: $t_0 = 1.77$ min, $k' = 1.90$, RP-18[b]; $t_0 = 2.30$ min, $k' = 4.00$, Chiralcel OJ–R*[,c].

(E)-Methyl-3-(4-methoxyphenylcarbamoyl)acrylate (**7a**, $C_{12}H_{13}NO_4$) [10]
From 5 g **1p**, 3.2 g Et_3N, and 4.7 g methyl 3-(chlorocarbonyl)acrylate. Yield 0.7 g (12%); yellow needles; mp 169–170°C (*Me*OH); IR: $\bar{\nu} = 3353$ (NH), 3072, 2955 (CH), 1715, 1677, 1645 (CO), 1545, 1512 (*ar*), 1342 (C–N), 830 (*ar*) cm^{-1}; ^1H NMR (300 MHz): $\delta = 3.80$, 3.82 (2 s, 2 O*Me*), 6.87 (d, $J = 9$ Hz, 2 *ar* H), 6.92–7.10 (dd, $J = 15.3$ Hz, HC=CH), 7.51 (d, $J = 9.1$ Hz, 2 *ar* H), 7.61 (s, H–N) ppm; HPLC: $t_0 = 1.83$ min, $k' = 0.57$, RP-18[b]; $t_0 = 1.87$ min, $k' = 3.86$ (3.85), Chiralcel OJ–R[b].

(E)-Methyl-3-(4-fluorophenylcarbamoyl)acrylate (**7b**, $C_{11}H_{10}FNO_3$)
a) From 8 g **1a**, 4.5 g Et_3N, and 6.8 g methyl 3-(chlorocarbonyl)acrylate. b) From 5 g **1x**, 3.37 g Et_3N, and 4.95 g methyl 3-(chlorocarbonyl)acrylate. Yield a) 2.4 g (27%); b) 2.3 g (40%); colorless needles; mp 169–170°C (*Me*OH); IR: $\bar{\nu} = 3358$ (NH), 3066, 2955 (CH), 1710, 1679, 1649 (CO), 1551, 1510 (*ar*), 1339 (C–N), 1206 (C–F), 847 (*ar*) cm^{-1}; ^1H NMR (300 MHz): $\delta = 3.83$ (s, O*Me*), 6.93–7.11 (dd, $J = 15.3$ Hz, HC=CH), 7.0–7.7 (m, 4 *ar* H), 7.67 (s, H–N) ppm; HPLC: $t_0 = 1.83$ min, $k' = 0.62$ (0.68), RP-18[b]; $t_0 = 1.87$ min, $k' = 4.23$ (4.17), Chiralcel OJ–R[b].

2-Chloro-N-(4-methoxyphenyl)acetamide (**8**, $C_9H_{10}ClNO_2$)
From 3 g **1v** and 1.4 g $ClCH_2COCl$. Yield 0.4 g (17%); colorless crystals; mp 120–121°C (*Ac*O*Et*/*n*-hexane); IR: $\bar{\nu} = 3294$ (NH), 3073, 2957 (CH), 1665, 1630 (CO), 1512 (*ar*), 1345 (C–N), 1251 (C–F), 1030 (C–Cl), 830 (*ar*) cm^{-1}; ^1H NMR (300 MHz): $\delta = 3.80$ (s, O*Me*), 4.18 (s, CH_2), 6.89 (d, $J = 9.0$ Hz, 2 *ar* H), 7.44 (d, $J = 9.0$ Hz, 2 *ar* H), 8.14 (s, N–H) ppm; HPLC: $t_0 = 1.73$ min, $k' = 1.56$, RP-18[d]; $t_0 = 2.29$ min, $k' = 3.52$, Chiralcel OJ–R*[,b].

*Synthesis of β-lactams **9–12**. General procedure*
The acyl chloride was given at once to a solution of **1** in toluene (80 cm^3). Then, Et_3N (2.5 g, 0.024 mol, 3.4 cm^3) dissolved in toluene (80 cm^3) was dropwise added with heating. After refluxing for 3–4 h, the solution was cooled to room temperature, filtered, the filtrate was dried (Na_2SO_4), and evaporated *in vacuo*. The residue was crystallized or purified by CC.

(RS)-3,3-Dichloro-4-(4-chlorophenyl)-1-(4-methoxyphenyl)-azetidin-2-one (**9a**, $C_{16}H_{12}Cl_3NO_2$)
From 5 g **1k** and 3 g $Cl_2CHCOCl$. Yield 1.5 g (17%); colorless crystals; mp 135°C (*Ac*O*Et*/*n*-hexane); IR: $\bar{\nu} = 3087$, 2998 (CH), 1767 (CO), 1513 (*ar*), 1390 (C–N), 1092 (C–Cl), 825, 808 (*ar*) cm^{-1}; ^1H NMR (60 MHz): $\delta = 3.65$ (s, O*Me*), 5.3 (s, 4-H), 6.63 (d, $J = 9.0$ Hz, 2 *ar* H), 6.9–7.42 (m, 6 *ar* H) ppm; HPLC: $t_0 = 1.77$ min, $k' = 6.60$ RP-18, *Me*CN/H_2O 7/3); $t_0 = 2.21$ min, $k' = 15.17$, 16.67, Chiralcel OJ–R*[,d].

(RS)-3,3-Dichloro-4-(4-chlorophenyl)-1-(4-fluorophenyl)-azetidin-2-one (**9b**, $C_{15}H_9Cl_3FNO$)
From 3 g **1l** and 1.9 g $Cl_2CHCOCl$. Yield 2.8 g (63%); colorless needles; mp 118°C (*Et*OH); IR: $\bar{\nu} = 3088$ (CH), 1780 (CO), 1509 (*ar*), 1385 (C–N), 1228 (C–F), 1092 (C–Cl), 833, 820 (*ar*) cm^{-1}; ^1H NMR (300 MHz): $\delta = 5.46$ (s, 4-H), 6.99 (t, $J = 8.4$ Hz, 2 *ar* H), 7.24–7.29 (m, 4 *ar* H), 7.41 (d, $J = 8.5$ Hz, 2 *ar* H) ppm; HPLC: $t_0 = 1.77$ min, $k' = 3.76$, RP-18[b]; $t_0 = 2.26$ min, $k' = 9.20$, 11.48, Chiralcel OJ–R*[,d].

(RS)-3,3-Dichloro-4-(2-chlorophenyl)-1-(4-methoxyphenyl)-azetidin-2-one (**9c**, $C_{16}H_{12}Cl_3NO_2$)
From 3 g **1m** and 2.6 g $Cl_2CHCOCl$. The residue was dissolved in Me_2CHOH, and dropwise addition of *PE* yielded light yellow crystals. Yield 1.8 g (41%); colorless needles; mp 136.5°C (*Et*OH); IR: $\bar{\nu} = 1778$ (CO), 1513 (*ar*), 1388 (C–N), 1052 (C–Cl), 838, 754 (*ar*) cm^{-1}; ^1H NMR (300 MHz): $\delta = 3.78$ (s, O*Me*), 5.89 (s, 4-H), 6.8–7.6 (m, 8 *ar* H) ppm; HPLC: $t_0 = 1.77$ min, $k' = 5.54$, RP-18[b]; $t_0 = 2.21$ min, $k' = 13.65$, Chiralcel OJ–R*[,d].

(RS)-3,3-Dichloro-1-(4-fluorophenyl)-4-phenylazetidin-2-one (**9d**, $C_{15}H_{10}Cl_2FNO$)
From 3 g **1a** and 2.2 g $Cl_2CHCOCl$. Yield 2.5 g (53%); colorless needles; mp 134–136°C (*Et*OH); IR: $\bar{\nu} = 1784$ (CO), 1510 (*ar*), 1388 (C–N), 1231 (C–F), 832, 700 (*ar*) cm^{-1}; ^1H NMR (300 MHz): $\delta = 5.49$ (s, 4-H), 7.02 (t, $J_1 = 9.0$, $J_2 = 8.3$ Hz, 2 *ar* H), 7.29 (m, 5 *ar* H), 7.44 (m, 2 *ar* H) ppm; HPLC: $t_0 = 1.77$ min, $k' = 4.10$, RP-18[b]; $t_0 = 2.26$ min, $k' = 9.65$, 14.30, Chiralcel OJ–R*[,d].

(RS)-3,3-Dichloro-4-[4-(dimethylamino)phenyl]-1-(4-fluorophenyl)azetidin-2-one (**9e**, $C_{17}H_{15}Cl_2FN_2O$)
From 3 g **1i** and 1.9 g $Cl_2CHCOCl$. Yield 2.3 g (52%); colorless needles; mp 148–150°C (*Et*OH); IR: $\bar{\nu} = 1778$ (CO), 1510 (*ar*), 1386 (C–N), 1232 (C–F), 1054 (C–Cl), 834, 816 (*ar*) cm^{-1}; ^1H NMR (300 MHz): $\delta = 2.99$ (s, N*Me*$_2$), 5.38 (s, 4-H), 6.69 (d, $J = 8.9$ Hz, 2 *ar* H), 6.97 (t, $J_1 = 9.0$, $J_2 = 8.4$ Hz, 2 *ar* H), 7.15 (d, $J = 8.8$ Hz, 2 *ar* H), 7.31 (dd, $J_1 = 9.1$, $J_2 = 4.6$ Hz, 2 *ar* H) ppm; HPLC: $t_0 = 1.77$ min, $k' = 5.72$, RP-18[b]; $t_0 = 2.26$ min, $k' = 19.81$, 26.67, Chiralcel OJ–R*[,d].

(RS)-3,3-Dichloro-4-(2-chlorophenyl)-1-(2-fluorophenyl)-azetidin-2-one (**9f**, $C_{15}H_9Cl_3FNO$)
From 3 g **1r** and 1.8 g $Cl_2CHCOCl$. Yield 0.6 g (14%); colorless solid; mp 113–114°C (Me_2CHOH); IR: $\bar{\nu} = 1785$ (CO), 1504 (*ar*), 1372 (C–N), 1238 (C–F), 1053 (C–Cl), 754 (ar) cm^{-1}; ^1H NMR (60 MHz): $\delta = 6.22$ (d, $J = 3.6$ Hz, 4-H), 6.99–7.09 (m, 2 *ar* H), 7.15–7.23 (m, 3 *ar* H), 7.30–7.36 (dt, 1 *ar* H), 7.49–7.52 (dd, 1 *ar* H), 8.02–8.08 (dt, 1 *ar* H)

ppm; HPLC: $t_0 = 1.77$ min, $k' = 6.02$, RP-18[b]; $t_0 = 2.26$ min, $k' = 8.37$, 8.60, Chiralcel OJ–R*[,d].

(RS)-3,3-Dichloro-4-(4-chlorophenyl)-1-(2-fluorophenyl)-azetidin-2-one (**9g**, $C_{15}H_9Cl_3FNO$)
From 3 g **1s** and 1.9 g $Cl_2CHCOCl$. Yield 2.5 g (57%); colorless crystals; mp 119–121°C (*Me*$_2$CHOH/*PE*); IR: $\bar{\nu} = 1780$ (CO), 1504 (*ar*), 1374 (C–N), 1240 (C–F), 1093 (C–Cl), 827, 817, 763 (*ar*) cm^{-1}; ^1H NMR (300 MHz): $\delta = 5.7$ (d, $J = 3.5$ Hz, 4-H), 6.9–8.0 (m, 8 *ar* H) ppm; HPLC: $t_0 = 1.77$ min, $k' = 5.96$, RP-18[b]; $t_0 = 2.05$ min, $k' = 11.26$, 11.43, Chiralcel OJ–R*[,d].

(RS)-3,3-Dichloro-4-(4-chlorophenyl)-1-(3-fluorophenyl)-azetidin-2-one (**9h**, $C_{15}H_9Cl_3FNO$)
From 3 g **1t** and 1.9 g $Cl_2CHCOCl$. Yield 1.1 g (25%); colorless plats; mp 97°C (*Et*OH); IR: $\bar{\nu} = 1782$ (CO), 1611, 1594 (*ar*), 1387 (C–N), 1256 (C–F), 1092 (C–Cl), 845, 827, 784, 772 (*ar*) cm^{-1}; ^1H NMR (300 MHz): $\delta = 5.47$ (s, 4-H), 6.8–7.5 (m, 8 *ar* H) ppm; HPLC: $t_0 = 2.05$ min, $k' = 7.37$, RP-18[b]; $t_0 = 2.26$ min, $k' = 12.14$, 12.58, Chiralcel OJ–R*[,d].

(RS)-3,3-Dichloro-1-(4-methoxyphenyl)4-[4-(trifluoro-methyl)phenyl]azetidin-2-one (**9i**, $C_{17}H_{12}Cl_2F_3NO_3$)
From 2.5 g **1g** and 1.3 g $Cl_2CHCOCl$. Yield 1.2 g (34%); colorless crystals; mp 110–112°C (*Me*$_2$CHOH); IR: $\bar{\nu} = 3010$, 2981 (CH), 1781 (CO), 1511 (*ar*), 1327 (C–N), 1256 (C–F), 1065 (C–Cl), 840, 807 (ar) cm^{-1}; ^1H NMR (300 MHz): $\delta = 3.78$ (s, O*Me*), 5.75 (s, 4-H), 6.15–7.5 (m, 8 *ar* H) ppm; HPLC: $t_0 = 1.75$ min, $k' = 11.63$, RP-18[b]; $t_0 = 2.25$ min, $k' = 8.57$, Chiralcel OJ–R*[,d].

(RS)-3,3-Dichloro-1-(4-fluorophenyl)-4-(4-methoxyphenyl)-azetidin-2-one (**9j**, $C_{16}H_{12}Cl_2FNO_2$)
From 3 g **1h** and 1.9 g $Cl_2CHCOCl$. Yield 3.5 g (79%); colorless crystals; mp 145–147°C (*Me*$_2$CHOH/*n*-hexane); IR: $\bar{\nu} = 3064$ (CH), 1769 (CO), 1512 (*ar*), 1388 (C–N), 1264 (C–F), 1028 (C–Cl), 834, 818 (*ar*) cm^{-1}; ^1H NMR (300 MHz): $\delta = 3.83$ (s, O*Me*), 5.43 (s, 4-H), 6.9–7.4 (m, 8 *ar* H) ppm; HPLC: $t_0 = 2.05$ min, $k' = 4.15$, RP-18[b]; $t_0 = 2.25$ min, $k' = 8.38$, 15.09, Chiralcel OJ–R*[,d].

(RS)-Benzyl 3,3-dichloro-4-(4-chlorophenyl)-2-oxoazetidin-1-yl]acetate (**9k**, $C_{18}H_{14}Cl_3NO_3$)
From 3 g **1q** and 1.5 g $Cl_2CHCOCl$. Yield 0.3 g (7%); brown solid; mp 95°C (*Me*$_2$CHOH); IR (KBr): $\bar{\nu} = 3068$, 2971 (CH), 1796, 1750 (CO), 1492 (*ar*), 1386 (C–N), 1089 (C–Cl), 828 (*ar*) cm^{-1}; ^1H NMR (60 MHz): $\delta = 3.5$, 4.4 (2 d, $J = 18$ Hz, CH_2), 5.02 (s, $CH_{2(benzyl)}$), 5.4 (s, 4-H), 6.9–7.4 (m, 9 *ar* H) ppm; HPLC: $t_0 = 1.77$ min, $k' = 4.72$, RP-18[b]; $t_0 = 2.21$ min, $k' = 6.32$, 9.11, Chiralcel OJ–R*, *Me*CN/H_2O 6/4.

(RS)-3,3-Dichloro-4-(2,4-difluorophenyl)-1-(4-fluorophenyl)-azetidin-2-one (**9l**, $C_{15}H_8Cl_2F_3NO$)
From 3 g **1u** and 1.9 g $Cl_2CHCOCl$. Yield 1.3 g (29%); colorless needles; mp 121–122.5°C (*Et*OH); IR: $\bar{\nu} = 3081$ (CH), 1737 (CO), 1626, 1593 (*ar*), 1391 (C–N), 1231 (C–F), 1054 (C–Cl), 835, 814, 784 (*ar*) cm^{-1}; ^1H NMR (60 MHz): $\delta = 5.72$ (s, 4-H), 6.5–7.6 (m, 7 *ar* H) ppm; HPLC: $t_0 = 1.77$ min, $k' = 3.63$, RP-18[b]; $t_0 = 2.27$ min, $k' = 6.55$, Chiralcel OJ–R*[,d].

trans-3-Chloro-4-(4-chlorophenyl)-1-(4-fluorophenyl)-azetidin-2-one (**10b**, $C_{15}H_{10}Cl_2FNO$)
From 3 g **1l** and 1.45 g $ClCH_2COCl$. Yield 1.2 g (30%); colorless crystals; mp 115°C (*Me*$_2$CHOH/*PE* 1/1); IR: $\bar{\nu} = 1769$ (CO), 1509 (*ar*),1380 (C–N), 1229 (C–F), 1091 (C–Cl), 831, 817 (*ar*) cm^{-1}; ^1H NMR (60 MHz): $\delta = 4.46$ (d, $J = 2.4$ Hz, 3-H), 4.82 (d, $J = 2.4$ Hz, 4-H), 6.63–7.38 (m, 8 *ar* H) ppm; HPLC: $t_0 = 1.77$ min, $k' = 3.77$, RP-18[b]; $t_0 = 2.26$ min, $k' =$ 9.21, 11.82, Chiralcel OJ–R*[,d].

trans-3-Chloro-4-(2-chlorophenyl)-1-(2-fluorophenyl)-azetidin-2-one (**10d**, $C_{15}H_{10}Cl_2FNO$)
From 3 g **1r** and 1.6 g $ClCH_2COCl$. Yield 1.1 g (35%); colorless needles; mp 114–116°C (*Me*$_2$CHOH); IR: $\bar{\nu} = 1777$, 1758 (CO), 1504 (*ar*), 1373 (C–N), 1230 (C–F), 1037 (C–Cl), 754 (*ar*) cm^{-1}; ^1H NMR (300 MHz): $\delta = 4.66$ (d, $J = 2.0$ Hz, 3-H), 5.76 (dd, $J_1 = 2.0$ Hz, $J_2 = 3.4$ Hz, 4-H), 6.99–7.30 (m, 6 *ar* H), 7.45 (d, $J = 7.6$ Hz, 1 *ar* H), 7.99 (dt, $J_1 = 1.9$ Hz, $J_2 = 7.8$ Hz, 1 *ar* H) ppm; HPLC: $t_0 = 1.77$ min, $k' = 3.72$, RP-18[b]; $t_0 = 2.49$ min, $k' = 14.63$, Chiralcel OJ–R*, *Me*CN/H_2O 4/6.

trans-3-Chloro-4-(2,4-dichlorophenyl)-1-(4-fluorophenyl)-azetidin-2-one (**10e**, $C_{15}H_9Cl_3FNO$)
From 3 g **1o** and 1.3 g $ClCH_2COCl$. Yield 0.3 g (13%); colorless solid; mp 83°C (*Me*$_2$CHOH/*PE*); IR: $\bar{\nu} = 1774$ (CO), 1509 (*ar*), 1378 (C–N), 1229 (C–F), 1047 (C–Cl), 832, 818, 743 (*ar*) cm^{-1}; ^1H NMR (60 MHz): $\delta = 4.40$ (d, $J = 2.6$ Hz, 3-H), 5.2 (d, $J = 2.6$ Hz, 4-H), 6.48–7.32 (m, 7 *ar* H) ppm; HPLC: $t_0 = 1.77$ min, $k' = 6.65$, RP-18[b]; $t_0 = 2.32$ min, $k' =$ 1.93, Chiralcel OJ–R*[,b].

trans-3-Chloro-1-(4-fluorophenyl)-4-(4-methoxyphenyl)-azetidin-2-one (**10f**, $C_{16}H_{13}ClFNO_2$)
From 3 g **1h** and 1.5 g $ClCH_2COCl$. Yield 1.8 g (45%); colorless crystals; mp 138–139°C (*Me*$_2$CHOH/*n*-hexane); IR: $\bar{\nu} =$ 2965 (CH), 1759 (CO), 1508 (*ar*), 1382 (C–N), 1248 (C–F), 1028 (C–Cl), 834, 816 (*ar*) cm^{-1}; ^1H NMR (300 MHz): $\delta = 3.78$ (s, O*Me*), 4.60 (d, $J = 1.9$ Hz, 3-H), 4.94 (d, $J =$ 1.9 Hz, 4-H), 6.9–7.3 (m, 8 *ar* H) ppm; HPLC: $t_0 = 2.05$ min, $k' = 2.55$, RP-18[b]; $t_0 = 2.27$ min, $k' = 4.51$, 5.13, Chiralcel OJ–R*[,d].

trans-3-Chloro-4-(2,4-difluorophenyl)-1-(4-fluorophenyl)-azetidin-2-one (**10g**, $C_{15}H_9ClF_3NO$)
From 3 g **1u** and 1.5 g $ClCH_2COCl$. Yield 1.6 g (40%); colorless crystals; mp 89–93°C (*Et*$_2$O); IR: $\bar{\nu} = 1771$ (CO), 1510 (*ar*), 1380 (C–N), 1221 (C–F), 835, 728 (*ar*) cm^{-1}; ^1H NMR (60 MHz): $\delta = 5.51$ (d, $J = 2.4$ Hz, 3-H), 5.38 (d, $J = 2.4$ Hz, 4-H), 6.6–7.8 (m, 7 *ar* H) ppm; HPLC: $t_0 = 1.77$ min, $k' = 2.50$, RP-18[b]; $t_0 = 2.27$ min, $k' = 3.70$, 4.08, Chiralcel OJ–R*[,d].

trans-4-(4-Chlorophenyl)-1-(4-fluorophenyl)-3-isopropyl-azetidin-2-one (**11a**, $C_{18}H_{17}ClNO$)
From 3 g **1l** and 1.6 g isovalerianyl chloride as **9c**. Yield 0.6 g (15%); colorless needles; mp 136°C (*Et*OH); IR: $\bar{\nu} = 2961$ (CH), 1740 (CO), 1510 (*ar*), 1385 (C–N), 1226 (C–F), 1092 (C–Cl), 835, 817 (*ar*) cm^{-1}; ^1H NMR (300 MHz): $\delta = 1.06$, 1.14 (2 d, each $J = 6.7$ Hz, *Me*), 2.20 (m, CH), 2.88 (dd, $J_1 = 2.4$ Hz, $J_2 = 8.4$ Hz, 3-H), 4.66 (d, $J = 2.4$ Hz, 4-H), 6.9–7.4 (m, 8 *ar* H) ppm; HPLC: $t_0 = 1.77$ min, $k' = 6.47$, RP-18[b]; $t_0 = 2.26$ min, $k' = 9.95$, 10.55, Chiralcel OJ–R*[,d].

trans-4-(2-Chlorophenyl)-1-(4-fluorophenyl)-3-isopropyl-azetidin-2-one (**11b**, $C_{18}H_{17}ClFNO$)
From 3 g **1n** and 1.6 g isovalerianyl chloride. Yield 1.0 g (25%); colorless needles; mp 136–138°C (Me_2CHOH); IR: $\bar{\nu} = 3069$, 2959 (CH), 1747 (CO), 1508 (*ar*), 1388 (C–N), 1224 (C–F), 1033 (C–Cl), 830, 757 (*ar*) cm^{-1}; ^1H NMR (60 MHz): $\delta = 1.11$, 1.15 (2d, each $J = 6$ Hz, *Me*), 2.3 (m, CH), 3.0 (dd, $J_1 = 2.0$, $J_2 = 6.4$ Hz, 3-H), 5.15 (d, $J = 2.0$ Hz, 4-H), 6.51–7.42 (m, 8 *ar* H) ppm; HPLC: $t_0 = 1.77$ min, $k' = 7.11$, RP-18[b]; $t_0 = 2.26$ min, $k' = 8.15$, 8.45, Chiralcel, OJ–R*[,d].

trans-4-(2,4-Dichlorophenyl)-1-(4-fluorophenyl)-3-isopropylazetidin-2-one (**11c**, $C_{18}H_{16}Cl_2FNO$)
From 3 g **1o** and 1.4 g isovalerianyl chloride. Yield 0.1 g (2.5%); colorless needles; mp 128°C (Me_2CHOH); IR: $\bar{\nu} = 3063$, 2960 (CH) 1740 (CO), 1509 (*ar*), 1381 (C–N), 1231 (C–F), 1045 (C–Cl), 831, 816, 755 (*ar*) cm^{-1}; ^1H NMR (300 MHz): $\delta = 0.90$, 1.00 (2d, each $J = 6.0$ Hz, *Me*), 1.63 (m, CH), 2.8 (dd, $J_1 = 2.0$, $J_2 = 7.0$ Hz, 3-H), 4.9 (d, $J = 2.0$ Hz, 4-H), 6.5-7.4 (m, 7 *ar* H) ppm; HPLC: $t_0 = 1.77$ min, $k' = 11.98$, 12.11, RP-18[b]; $t_0 = 2.49$ min, $k' = 11.09$, 11.49, 12.50, Chiralcel OJ–R*[,d].

trans-4-[4-(Dimethylamino)phenyl]-1-(4-fluorophenyl)-3-isopropylazetidin-2-one (**11d**, $C_{20}H_{23}FN_2O$)
From 3 g **1i** and 1.5 g isovalerianyl chloride. Yield 1.7 g (42%); colorless needles; mp 134°C (*Et*OH); IR: $\bar{\nu} = 3077$, 2961 (CH), 1731 (CO), 1614, 1508 (*ar*), 1386 (C–N), 1212 (C–F), 1068 (C–Cl), 834, 810 (*ar*) cm^{-1}; ^1H NMR (300 MHz): $\delta = 1.05$, 1.75 (2d, each $J = 6.7$ Hz, *Me*), 2.15 (m, CH), 2.9 (dd, $J_1 = 2.3$, $J_2 = 8.4$ Hz, 3-H), 2.94 (s, NMe_2), 4.61 (d, $J = 2.3$ Hz, 4-H), 6.6–7.3 (m, 8 *ar* H) ppm; HPLC: $t_0 = 2.05$ min, $k' = 7.20$, RP-18[b]; $t_0 = 2.26$ min, $k' = 6.13$, 6.71, Chiralcel OJ–R*[,d].

trans-1-(4-Fluorophenyl)-3-isopropyl-4-(4-methoxyphenyl)-azetidin-2-one (**11e**, $C_{19}H_{20}FNO_2$)
From 3 g **1h** and 1.6 g isovalerianyl chloride. Yield 1.1 g (27%); colorless crystals; mp 114–115°C (Me_2CHOH/*n*-hexane); IR: $\bar{\nu} = 3065$, 2958 (CH), 1736 (CO), 1510 (*ar*), 1386 (C–N), 1248 (C–F), 832, 818 (*ar*) cm^{-1}; ^1H NMR (300 MHz): $\delta = 1.08$, 1.14 (2 d, each $J = 6.7$ Hz, *Me*), 2.17 (m, CH), 2.89 (dd, $J_1 = 2.5$ Hz, $J_2 = 8.4$ Hz, 3-H), 3.80 (s, O*Me*), 4.65 (d, $J = 2.4$, 4-H), 6.8–7.3 (m, 8 *ar* H) ppm; HPLC: $t_0 = 2.05$ min, $k' = 3.96$, RP-18[b]; $t_0 = 2.27$ min, $k' = 4.29$, 4.56, Chiralcel OJ–R*[,d].

(RS)-Methyl 2-[3,3-dichloro-2-(2-chlorophenyl)-4-oxoazetidin-1-yl]-4-methylpentanoate (**12**, $C_{16}H_{18}Cl_3NO_3$)
From 2.7 g **1w** and 1.5 g $Cl_2CHCOCl$. Yield 0.4 g (11%); lightly colored crystals; mp 85°C (Me_2CHOH); IR: $\bar{\nu} = 3073$, 2958 (CH), 1788, 1778, 1745 (CO), 1331 (C–N), 1039 (C–Cl), 760 (*ar*) cm^{-1}; ^1H NMR (300 MHz): $\delta = 0.85$, 0.95 (2d, each $J = 6.2$ Hz, *Me*), 1.59–1.78 (m, CH, $CH_{2(Leu)}$), 3.78 (s, O*Me*), 4.25 (m, α-$H_{(Leu)}$), 5.81 (s, 4-H), 7.2–7.5 (m, 4 *ar* H) ppm; HPLC: $t_0 = 1.77$ min, $k' = 6.13$, RP-18[b]; $t_0 = 2.25$ min, $k' = 4.35$, 4.83, Chiralcel OJ–R*[,d].

(RS)-Diethyl 1-(4-methylphenyl)-2-oxo-3-(trimethylsilyl)-azetidine-4,4-dicarboxylate (**15**, $C_{19}H_{27}NO_5Si$)
From 0.01 mol **14**, 0.02 mol *LDA*, and 0.05 mol *CTMS*, 1 h, −78°C, as described in Ref. [27]. Yield 98%; light yellow liquid; IR: $\bar{\nu} = 2980$, 2950, 2920 (CH), 1750 (CO) cm^{-1}; ^1H NMR (80 MHz): $\delta = 0.14$ (s, 3 *Me*), 1.24 (2 t, 2 *Me*), 2.28 (s, *Me*), 3.48 (s, 3-H), 4.26 (2 q, $2CH_2$), 7.2 (q, 4 *ar* H) ppm.

Diethyl 3-(α-hydroxyisopropyl)-1-(4-methylphenyl)-2-oxoazetidine-4,4-dicarboxylate (**16a**, $C_{19}H_{25}NO_6$)
From 0.005 mol **14**, 0.02 mol acetone, and 0.01 mol *LDA* as **16c**. Yield 0.3 g (8%); colorless crystals; mp 198–200°C (Acetone); IR: $\bar{\nu} = 3420$ (OH), 2980, 2930 (CH), 1740 (CO) cm^{-1}; ^1H NMR (80 MHz, $CDCl_3$/*DMSO*-d_6: 1/3): $\delta = 1.24$ (t, 2 *Me*), 1.30 (s, 2 *Me*), 2.24 (s, *Me*), 3.38 (s, O–H), 3.49 (s, 4-H), 4.16 (q, $2CH_2$), 7.26 (q, 4 *ar* H) ppm.

Diethyl 3-(α-hydroxyethyl)-1-(4-methylphenyl)-2-oxoazetidine-4,4-dicarboxylate (**16b**, $C_{18}H_{23}NO_6$)
From 0.005 mol **14**, 0.05 mol acetaldehyde, and 0.01 mol *LDA*. Yield 0.4 g (12%); colorless crystals; mp 196–198°C (*Me*OH/Et_2O: 1/1); IR: $\bar{\nu} = 3430$ (OH), 3160, 2980, 2920, 2860 (CH), 1750, 1745 (CO) cm^{-1}; ^1H NMR (80 MHz, $CDCl_3$/*DMSO*-d_6, 1/1): $\delta = 1.24$ (m, 2 *Me*), 2,27 (s, *Me*), 3.36 (s, O–H), 3.3–4.2 (m, 3-H, *Me*), 4.34 (q, $2CH_2$), 6.42 (s, α-H), 7.24 (q, 4 *ar* H) ppm.

Diethyl 3-(α-hydroxy-4-nitrobenzyl)-1-(4-methylphenyl)-2-oxoazetidine-4,4-dicarboxylate (**16c**, $C_{23}H_{24}N_2O_8$)
From 0.005 mol **14** and 0.0075 mol 4-nitrobenzaldehyde with 0.01 mol *LDA* as described in Ref. [28] 1 h, −78°C. Yield 0.9 g (39%); colorless crystals; mp 154°C (dec., *Et*OH); IR: $\bar{\nu} = 3430$ (OH), 3080, 3040, 2980, 2920 (CH), 1740 (CO), 1510, 1340 (NO_2) cm^{-1}; ^1H NMR (80 MHz, $CDCl_3$/*DMSO*-d_6, 1/1): $\delta = 1{,}12$ (t, 2 *Me*), 2.27 (s, *Me*), 3.24–4.28 (m, $2CH_2$, 3-H, O–H), 5.42 (s, α-H), 7.3 (q, 4 *ar* H), 8.0 (q, 4 *ar* H) ppm.

(E)-Diethyl 3-(4-chlorobenzylidene)-1-(4-methylphenyl)-2-oxoazetidine-4,4-dicarboxylate (**17a**, $C_{23}H_{22}ClNO_5$)
From 0.0005 mol **15**, 0.01 mol *LDA*, and 0.0075 mol *p*-chlorobenzaldehyde, −78°C, 1 h, as described in Ref. [28]. Yield 1.4 g (56%); colorless crystals; mp 105–106°C (*Et*OH); IR: $\bar{\nu} = 3060$, 3040, 2980, 2940, 2890 (CH), 1750, 1730 (CO), 1680 (C=C) cm^{-1}; ^1H NMR (80 MHz): $\delta = 1.24$ (t, 2 *Me*), 2.31 (s, *Me*), 4.3 (q, $2CH_2$), 6.66 (s, α-H), 6.95–8.06 (m, 8 *ar* H) ppm.

(E)-Diethyl 3-(4-nitrobenzylidene)-1-(4-methylphenyl)-2-oxoazetidine-4,4-dicarboxylate (**17b**, $C_{23}H_{22}N_2O_7$)
From 0.005 mol **15**, 0.01 mol *LDA*, and 0.0075 mol *p*-nitrobenzaldehyde, −78°C, 45 min, as **17a**. Yield 1.53 g (70%); yellow crystals; mp 142–144°C (*Et*OH); IR: $\bar{\nu} = 3100$, 3060, 3040, 2980, 2940, 2850 (CH), 1750, 1730 (CO) cm^{-1}; ^1H NMR (80 MHz): $\delta = 1.26$ (t, 2 *Me*), 2.34 (s, *Me*), 4.36 (q, $2CH_2$), 6.88 (s, α-H), 7.34 (q, 4 *ar* H), 8.22 (m, 4 *ar* H) ppm.

Synthesis of N-benzyl-β-lactams **19**. *General procedure*
Compund **18** (1.47 g, 10 mmol) was dissolved in 100 cm^3 *THF*. Then 620 mg (11 mmol) KOH (pulv.), 320 mg (1 mmol) *TBABr*, and 15 mmol of the benzyl halogenide were added. The mixture was stirred for 8 h at room temperature, filtered, and the filtrate was evaporated. The residue was dissolved in CH_2Cl_2, twice washed with water, dried (Na_2SO_4), and evaporated *in vacuo*. Work-up as noted.

(RS)-1-(4-Chlorobenzyl)-4-phenylazetidin-2-one
(**19b**, $C_{16}H_{14}ClNO$)
From **18** and 4.8 g (15 mmol) 4-chlorobenzyl chloride, CC ($CHCl_3$). Yield 1.8 g (67%); light yellow viscous liquid; $n_D^{20} = 1.5850$; IR: $\bar{\nu} = 3070$, 3040, 2960, 2920 (CH), 1750 (CO), 1600, 1490 (*ar*) cm^{-1}; ^1H NMR (80 MHz): $\delta = 2.83$ (dd, $J = 2.8$ Hz, 14.5 Hz, 3-H_{trans}), 3.38 (dd, $J = 5.0$ Hz, 14.5 Hz, 3-H_{cis}) 3.73 (d, $J = 15.0$ Hz, 1H, CH_2), 4.35 (dd, $J = 2.8$ Hz, 5.0 Hz, 4-H), 4.73 (d, $J = 15.0$ Hz, 1H, CH_2), 6.97–7.55 (m, 9 *ar* H) ppm.

(RS)-1-(4-Nitrobenzyl)-4-phenylazetidin-2-one
(**19c**, $C_{16}H_{14}N_2O_3$)
From **18** and 3.2 g (15 mmol) 4-nitrobenzyl bromide, CC ($CHCl_3$). Yield 1.9 g (67%); yellowish viscous solid; mp 71–72°C; IR: $\bar{\nu} = 3070$, 3030, 2980, 2920 (CH), 1750 (CO), 1600 (*ar*), 1515, 1345 (NO_2) cm^{-1}; ^1H NMR (80 MHz): $\delta = 2.98$ (dd, $J = 2.5$ Hz, 15.0 Hz, 3-H_{trans}), 3.53 (dd, $J = 5.0$ Hz, 15.0 Hz, 3-H_{cis}), 4.02 (d, $J = 15.5$ Hz, 1H, CH_2), 4.55 (dd, $J = 2.5$ Hz, 5.0 Hz, 4-H), 4.83 (d, $J = 15.5$ Hz, 1H, CH_2), 7.10–8.22 (m, 9 *ar* H) ppm.

(RS)-1-[3-(Trifluoromethyl)benzyl]-4-phenylazetidin-2-one
(**19d**, $C_{17}H_{14}F_3NO$)
From **18** and 2.9 g (15 mmol) 3-(trifluoromethyl)benzyl chloride. CC ($CHCl_3$). Yield 2.5 g (83%); colorless liquid; $n_D^{20} = 1.5276$; IR: $\bar{\nu} = 3060$, 3040, 2960, 2920 (CH), 1750 (CO), 1495 (*ar*) cm^{-1}; ^1H NMR (80 MHz): $\delta = 2.97$ (dd, $J = 2.5$ Hz, 14.5 Hz, 3-H_{trans}), 3.50 (dd, $J = 5.0$ Hz, 14.5 Hz, 3-H_{cis}), 4.02 (d, $J = 15.0$ Hz, 1 H, CH_2), 4.53 (dd, $J = 2.5$ Hz, 5.0 Hz, 4-H), 4.88 (d, $J = 15$ Hz, 1H, CH_2), 7.20-7.90 (m, 9 *ar* H) ppm.

(RS)-1-(4-Cyanobenzyl)-4-phenylazetidin-2-one
(**19e**, $C_{17}H_{14}N_2O$)
From **18** and 2.9 g (15 mmol) 4-cyanobenzyl bromide, CC ($CHCl_3$). Yield 1.4 g (55%); colorless crystals; mp 63–65°C; IR: $\bar{\nu} = 3060$, 3040, 2960, 2920 (CH), 2220 (CN), 1750 (CO), 1610, 1495 (*ar*) cm^{-1}; ^1H NMR (80 MHz): $\delta = 2.95$ (dd, $J = 2.5$ Hz, 15.0 Hz, 3-H_{trans}), 3.50 (dd, $J = 5.0$, 15.0 Hz, 3-H_{cis}) 3.98 (d, $J = 16.0$ Hz, 1H, CH_2), 4.53 (dd, $J = 2.5$, 5.0 Hz, 4-H), 4.83 (d, $J = 16.0$ Hz, 1H, CH_2), 7.33–7.73 (m, 9 *ar* H) ppm.

(RS)-1-(3,4,5-Trimethoxybenzyl)-4-phenylazetidin-2-one
(**19f**, $C_{19}H_{21}NO_4$)
From **18** and 3.3 g (15 mmol) 3,4,5-trimethoxybenzyl chloride, CC ($CHCl_3$). Yield 1.7 g (52%); colorless liquid; $n_D^{20} = 1.5086$; IR: $\bar{\nu} = 3080$, 3000 (CH), 2940 (O*Me*), 2840 (CH), 1745 (CO), 1590, 1500 (*ar*) cm^{-1}; ^1H NMR (80 MHz): $\delta = 2.90$ (dd, $J = 2.5$ Hz, 14.5 Hz, 3-H_{trans}), 3.43 (dd, $J = 5.0$, 14.5 Hz, 3-H_{cis}), 3.82 (s, 2 O*Me*), 3.82 (d, $J = 15.0$ Hz, 1H, CH_2), 3.88 (s, O*Me*), 4.48 (dd, $J = 2.5$, 5.0 Hz, 4-H), 4.73 (d, $J = -15.0$ Hz, 1H, CH_2), 6.42 (s, 2 *ar* H), 7.20–7.63 (m, 5 *ar* H) ppm.

trans-4,5-Diphenylpyrrolidin-2-one (**20a**, $C_{16}H_{15}NO$)
A solution of 2.4 g (10 mmol) **19a** was dropwise added to a solution of 1.3 g (20 mmol) *Bu*Li in 10 cm^3 *THF* at −78°C, the mixture was stirred for 1 h, and then pored into 100 cm^3 of a satd. solution of NaCl. The organic layer was separated, dried (Na_2SO_4), and evaporated *in vacuo*. Yield 2.0 g (85%); colorless crystals; mp 204–205°C (*Me*$_2$CHOH); IR: $\bar{\nu} = 3200$, 3080 (NH), 3030, 2920, 2890 (CH), 1685 (CO), 1600, 1490 (*ar*) cm^{-1}; ^1H NMR (*DMSO*-d_6, 80 MHz): $\delta = 2.38$ (dd, $J = 10.0$, 16.0 Hz, 3-H), 2.64 (dd, $J = 8.5$, 16.0 Hz, 3-H), 3.29 (ddd, $J = 8.5$, 10.0, 7.5 Hz, 4-H), 4.61 (d, $J = 7.5$ Hz, 5-H), 7.00–7.43 (m, 10 *ar* H), 8.10 (m, N–H) ppm.

cis/trans-5-(4-Chlorophenyl)-4-phenylpyrrolidin-2-one
(**20b**, $C_{16}H_{14}ClNO$)
From 2.7 g (10 mmol) **19b** as described for **20a**, CC ($CHCl_3$). Yield 1.2 g (43%); light yellow waxy solid; mp 124–125°C; IR: $\bar{\nu} = 3185$, 3080 (NH), 3020, 2870 (CH), 1690 (CO), 1595, 1495 (*ar*) cm^{-1}; ^1H NMR (80 MHz) *trans*: $\delta = 2.54$ (dd, $J = 10.0$ Hz, 16.75 Hz, 3-H), 2.84 (dd, $J = 8.0$ Hz, 16.75 Hz, 3-H), 3.30 (ddd, $J = 10.0$ Hz, 8.0 Hz, 8.0 Hz, 4-H), 4.68 (d, $J = 8.0$ Hz, 5-H), 6.69–7.45 (m, 9 *ar* H), 7.56 (m, N–H); *cis*: $\delta = 3.99$ (ddd, $J = 8.0$ Hz, 4-H), 4.99 (d, $J = 8.0$ Hz, 5-H) ppm; ratio of isomers *trans*:*cis* = 9:1.

cis/trans-5-[3-(Trifluoromethyl)phenyl]-4-phenylpyrrolidin-2-one (**20d**, $C_{17}H_{14}F_3NO$)
From 3.1 g (10 mmol) **19d** as described for **20a**, CC ($CHCl_3$). Yield 1.5 g (50%); yellow waxy solid; mp 104–105°C; IR: $\bar{\nu} = 3180$, 3080 (NH), 2970, 2890 (CH), 1685 (CO), 1595, 1490 (*ar*) cm^{-1}; ^1H NMR (80 MHz) *trans*: $\delta = 2.60$ (dd, $J = 10.0$ Hz, 17.0 Hz, 3-H), 2.88 (dd, $J = 8.25$ Hz, 17.0 Hz, 3-H), 3.36 (ddd, $J = 10.0$ Hz, 8.25 Hz, 7.5 Hz, 4-H), 4.80 (d, $J = 7.5$ Hz, 5-H), 6.71–7.64 (m, 9 *ar* H), 7.69 (m, N–H); *cis*: $\delta = 4.05$ (ddd, $J = 7.5$ Hz, 4-H), 5.13 (d, $J = 7.5$ Hz, 5-H) ppm; ratio of isomers *trans*:*cis* = 8:2.

trans-5-(3,4,5-Trimethoxyphenyl)-4-phenylpyrrolidin-2-one
(**20f**, $C_{19}H_{21}NO_4$)
From 3.3 g (10 mmol) **19f** as described for **20a**, CC ($CHCl_3$), then extraction of the column with *Et*OH, and evaporation of

*Et*OH. Yield 1.44 g (44%); colorless crystals; mp 171–172°C; IR: $\bar{\nu} = 3320$ (NH), 3020, 2930 (CH), 2830 (O*Me*), 1690 (CO), 1595, 1505 (*ar*) cm^{-1}; ^1H NMR (80 MHz): $\delta = 2.63$ (dd, $J = 10.0$, 17.0 Hz, 3-H), 2.90 (dd, $J = 8.5$, 17.0 Hz, 3-H), 3.38 (ddd, $J = 10.0$, 8.5, 7.8 Hz, 4-H), 3.74 (s, 2 O*Me*), 3.80 (s, O*Me*), 4.63 (d, $J = 7.8$ Hz, 5-H), 6.36 (s, 2 *ar* H), 6.90 (m, N–H), 7.06–7.55 (m, 5 *ar* H) ppm.

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