

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 frequency in their IR spectra, was studied. A selection of compounds was tested as inhibitors of the serine protease porcine pancreatic elastase. No simple correlation between IR frequency 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

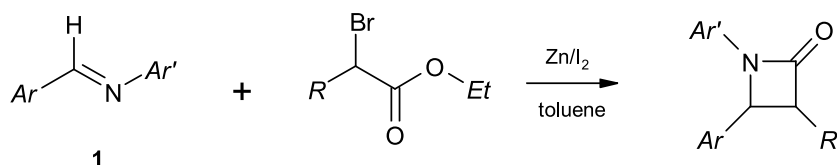
The β -lactam structure known from penicillins and cephalosporins as highly active and clinically useful β -lactam antibiotics [1] has motivated synthesis and evaluation during the last few decades. Apart from

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.

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'*.

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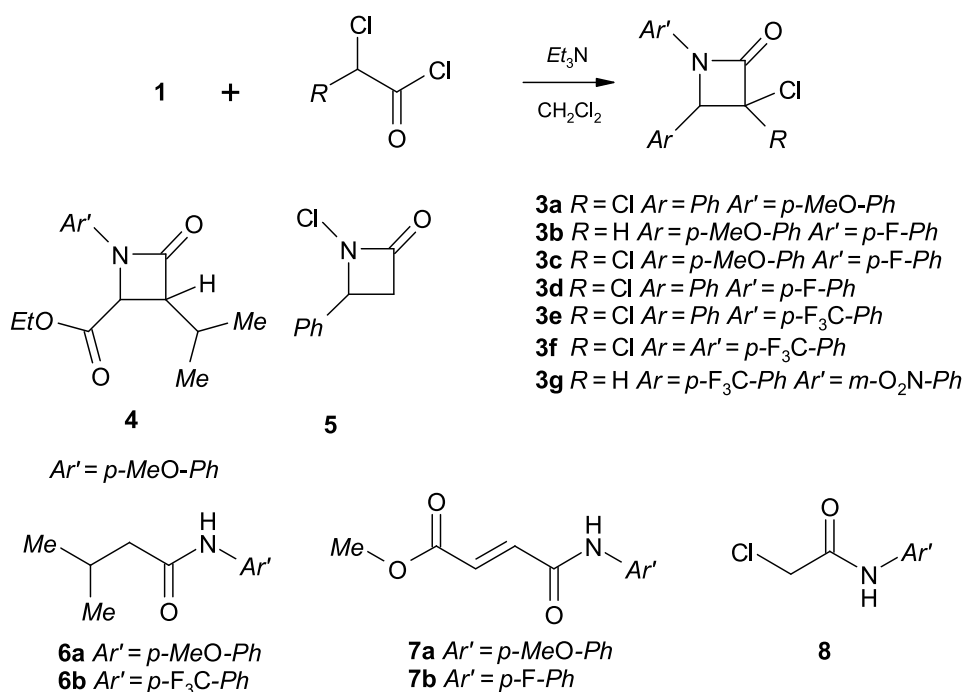
- 2a** $R = \text{H}$ $\text{Ar} = \text{Ph}$ $\text{Ar}' = p\text{-F-Ph}$
2b $R = \text{Me}$ $\text{Ar} = \text{Ph}$ $\text{Ar}' = p\text{-F-Ph}$
2c $R = \text{H}$ $\text{Ar} = p\text{-F-Ph}$ $\text{Ar}' = p\text{-MeO-Ph}$
2d $R = \text{Me}$ $\text{Ar} = p\text{-F-Ph}$ $\text{Ar}' = p\text{-MeO-Ph}$
2e $R = \text{H}$ $\text{Ar} = p\text{-F}_3\text{C-Ph}$ $\text{Ar}' = p\text{-MeO-Ph}$
2f $R = \text{Me}$ $\text{Ar} = p\text{-F}_3\text{C-Ph}$ $\text{Ar}' = p\text{-MeO-Ph}$
2g $R = \text{H}$ $\text{Ar} = p\text{-F}_3\text{C-Ph}$ $\text{Ar}' = p\text{-F-Ph}$

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 ^1H NMR spectra and their chromatographic properties (exp. part). The ^1H 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 $J_{\text{AX}} = 2.5\text{--}2.6\text{ Hz}$, $J_{\text{AM}} = 15.1\text{--}15.2\text{ Hz}$, and $J_{\text{MX}} = 5.6\text{--}5.7\text{ Hz}$. The signals of the protons 3-H and 4-H were found in the ^1H NMR spectra of **2b**, **2d**, and **2f** at $\delta = 3.63$ and 5.16 (5.13 and 5.20) ppm with $J_{3,4} = 5.8\text{--}5.9\text{ Hz}$, clearly indicating the *trans* configuration.

In HPLC experiments using a column with a non-chiral 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 (chloro-carbonyl)acrylate and some imines under similar reaction conditions (Et_3N) we could not isolate any β -lactam. Instead, an amidation had occurred form-



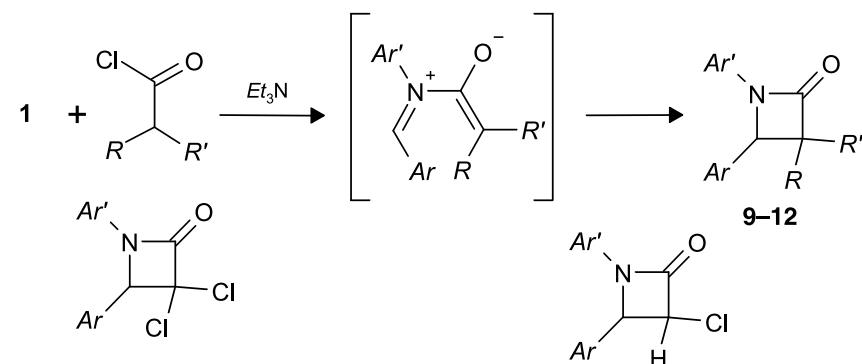
ing the amides **6a**, **6b** [9], **7a** [10], and **7b**. Each of the four compounds was prepared from the acyl chloride and two different imines (see Experimental) or may be prepared from the acyl chloride and the appropriate amine. Additionally, we prepared **8** by the same way, and the reactive *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 ^1H NMR data, the isolated compounds were racemates of the favored *trans* diastereoisomers with $J_{3\text{H},4\text{H}} = 1.9\text{--}2.6\text{ Hz}$. 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} .

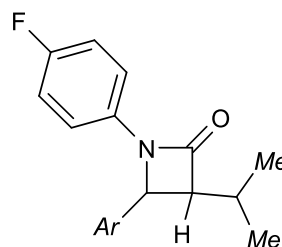
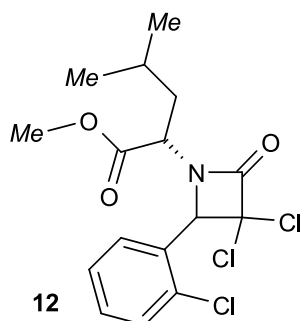
The lowest values of the carbonyl bands, $\bar{\nu} = 1731\text{--}1747\text{ cm}^{-1}$, were found in the spectra of **11a–11e**, derivatives substituted at position 3 by an isopropyl group and at position 1 by a *p*-fluoro phenyl ring. The coupling constants $J_{3\text{H},4\text{H}} = 2.0\text{--}2.5\text{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

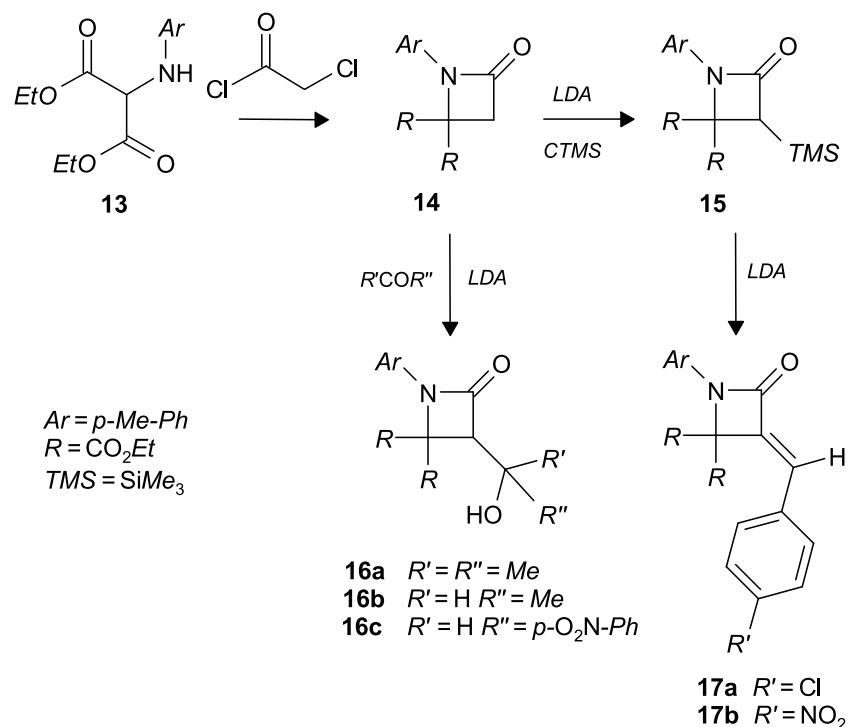


- 9a** $\text{Ar} = p\text{-Cl-Ph}$ $\text{Ar}' = p\text{-MeO-Ph}$
9b $\text{Ar} = p\text{-Cl-Ph}$ $\text{Ar}' = p\text{-F-Ph}$
9c $\text{Ar} = o\text{-Cl-Ph}$ $\text{Ar}' = p\text{-MeO-Ph}$
9d $\text{Ar} = \text{Ph}$ $\text{Ar}' = p\text{-F-Ph}$
9e $\text{Ar} = p\text{-Me}_2\text{N-Ph}$ $\text{Ar}' = p\text{-F-Ph}$
9f $\text{Ar} = o\text{-Cl-Ph}$ $\text{Ar}' = o\text{-F-Ph}$
9g $\text{Ar} = p\text{-Cl-Ph}$ $\text{Ar}' = o\text{-F-Ph}$
9h $\text{Ar} = p\text{-Cl-Ph}$ $\text{Ar}' = m\text{-F-Ph}$
9i $\text{Ar} = p\text{-F}_3\text{C-Ph}$ $\text{Ar}' = p\text{-MeO-Ph}$
9j $\text{Ar} = p\text{-MeO-Ph}$ $\text{Ar}' = p\text{-F-Ph}$
9k $\text{Ar} = p\text{-Cl-Ph}$ $\text{Ar}' = \text{CH}_2\text{CO}_2\text{CH}_2\text{Ph}$
9l $\text{Ar} = o,p\text{-F}_2\text{-Ph}$ $\text{Ar}' = p\text{-F-Ph}$

- 10a** $\text{Ar} = p\text{-Cl-Ph}$ $\text{Ar}' = p\text{-MeO-Ph}$
10b $\text{Ar} = p\text{-Cl-Ph}$ $\text{Ar}' = p\text{-F-Ph}$
10c $\text{Ar} = o\text{-Cl-Ph}$ $\text{Ar}' = p\text{-MeO-Ph}$
10d $\text{Ar} = o\text{-Cl-Ph}$ $\text{Ar}' = o\text{-F-Ph}$
10e $\text{Ar} = o,p\text{-Cl}_2\text{-Ph}$ $\text{Ar}' = p\text{-F-Ph}$
10f $\text{Ar} = p\text{-MeO-Ph}$ $\text{Ar}' = p\text{-F-Ph}$
10g $\text{Ar} = o,p\text{-F}_2\text{-Ph}$ $\text{Ar}' = p\text{-F-Ph}$



- 11a** $\text{Ar} = p\text{-Cl-Ph}$
11b $\text{Ar} = o\text{-Cl-Ph}$
11c $\text{Ar} = o,p\text{-Cl}_2\text{-Ph}$
11d $\text{Ar} = p\text{-Me}_2\text{N-Ph}$
11e $\text{Ar} = p\text{-MeO-Ph}$

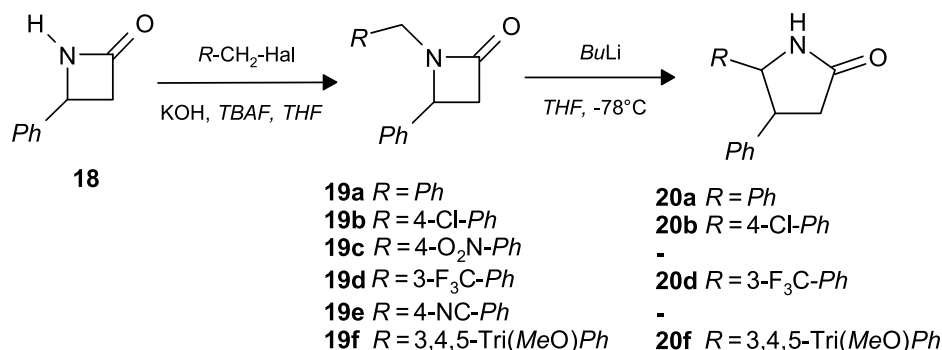


by reaction with chloroacetyl chloride yielding **14** [12] which was transformed into the 3-trimethylsilyl compound **15** by the reaction with *LDA* and *CTMS* at -78°C . The reaction of **14** with acetone or acetaldehyde in the presence of *LDA* yielded the 3-(α -hydroxy)ethyl derivatives **16a** and **16b**, whereas using similar conditions and 4-nitrobenzaldehyde the parent α -hydroxy compound **16c** became assessible. 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 ben-

zyl halogenides in *THF* in the presence of *KOH* and tetrabutylammonium bromide (*TBAF*). Treatment of these *N*-benzyl derivatives with *BuLi* 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 *BuLi*, 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 ^1H ; δ (ppm) rel. to *TMS* as internal standard; ^1H -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, $5\mu\text{m}$, and Chiralcel OJ-R, Flow = 1 ml/min, $\lambda_{\text{max}} = 220\text{ nm}$, $T = 20^\circ\text{C}$ (**2a–2g**), Flow 1 = $0.8\text{ cm}^3/\text{min}$, $\lambda_{\text{max}} = 220\text{ nm}$, $T = 30^\circ\text{C}$ (**5–12**), solvents $^b\text{MeCN}/\text{H}_2\text{O}$ 7/3, or $^c\text{MeCN}/\text{H}_2\text{O}$ 4/6, or $^d\text{MeCN}/\text{H}_2\text{O}$ 1/1. *PPE* (Porcine pancreatic elastase, $\approx 200\text{ U/mg}$) 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 $\text{HN}(\text{CHMe}_2)_2$ and *n-BuLi* (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-chlorobenzylidene)(4-methoxyphenyl)amine (**1m**); (2-chlorobenzylidene)(4-fluorophenyl)amine (**1n**); (2,4-dichlorobenzyl-

idene)(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 *EtOH*. The mixture was stirred at $3\text{--}18^\circ\text{C}$ until the precipitate was completed. The products were crystallized from *EtOH*.

(2-Chlorobenzylidene)(2-fluorophenyl)amine

(**1r**, $\text{C}_{13}\text{H}_9\text{ClFN}$)

From 11.11 g (0.1 mol) 2-fluoroaniline and 14.1 g (0.1 mol) 2-chlorobenzaldehyde in 60 cm^3 *EtOH*. 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} ; ^1H NMR (60 MHz): $\delta = 6.75\text{--}7.3$ (m, 7 *ar* H), $7.87\text{--}8.3$ (m, 1 *ar* H), 8.76 (s, H-C=) ppm.

(4-Chlorobenzylidene)(2-fluorophenyl)amine

(**1s**, $\text{C}_{13}\text{H}_9\text{ClFN}$)

From 8.33 g (0.075 mol) 2-fluoroaniline and 10.6 g (0.075 mol) 4-chlorobenzaldehyde in 60 cm^3 *EtOH*. 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} ; ^1H NMR (300 MHz): $\delta = 7.08$ (t, 2 *ar* H), $7.16\text{--}7.22$ (m, 2 *ar* H), 7.45 (d, $J = 8.5\text{ Hz}$, 2 *ar* H), 7.38 (d, $J = 8.5\text{ Hz}$, 2 *ar* H), 8.40 (s, H-C=) ppm.

(4-Chlorobenzylidene)(3-fluorophenyl)amine

(**1t**, $\text{C}_{13}\text{H}_9\text{ClFN}$)

From 8.3 g (0.075 mol) 3-fluoroaniline and 10.5 g (0.075 mol) 4-chlorobenzaldehyde in 60 cm^3 *EtOH*. 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} ; ^1H NMR (60 MHz): $\delta = 6.48\text{--}7.60$ (m, 4 *ar* H), 7.7 (d, $J = 9\text{ Hz}$, 2 *ar* H), 7.58 (d, $J = 9\text{ Hz}$, 2 *ar* H), 8.11 (s, H-C=) ppm.

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

(**1u**, $\text{C}_{13}\text{H}_8\text{F}_3\text{N}$)

From 4.4 g (0.04 mol) 4-fluoroaniline and 5.7 g (0.04 mol) 2,4-difluorobenzaldehyde in 100 cm^3 of *EtOH*. 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} ; ^1H NMR (60 MHz): $\delta = 6.16\text{--}7.26$ (m, 7 *ar* H), 8.27 (s, H-C=) ppm.

(2,4-Difluorobenzylidene)(4-methoxyphenyl)amine
(**1v**, C₁₄H₁₁F₂NO)

From 9.2 g (0.075 mol) *p*-anisidine and 10.7 g (0.075 mol) 2,4-difluorobenzaldehyde in 100 cm³ EtOH 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): δ = 3.61 (s, OMe), 6.0–7.4 (m, 7 *ar* H), 8.44 (s, H–C=) ppm.

Ethyl-2-[(2-chlorobenzylidene)amino]-4-methylvalerate
(**1w**, C₁₄H₁₈ClNO₂)

5 g (0.0344 mol) L-Leu-OMe was added to 4.8 g (0.0344 mol) 2-chlorobenzaldehyde. The mixture was cooled to room temperature, dissolved in 250 cm³ CH₂Cl₂, dried (Na₂SO₄), 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): δ = 1.0–1.4 (m, 2Me), 1.7–2.32 (m, CH, CH₂), 3.95 (s, OMe), 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**, C₁₀H₁₀FNO₂)

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 MgSO₄ in 200 cm³ 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): δ = 1.38 (t, Me), 4.41 (q, CH₂) 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 cm³ toluene, equivalent amounts (0.05–0.1) of **1**, Zn (filings), and a crystal of I₂ 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 cm³), water (50 cm³), HCl (10%, 50 cm³), a solution of NaHSO₃ (20%, 50 cm³), and water. The organic layer was dried (Na₂SO₄), and evaporated *in vacuo*. The residue was crystallized from MeOH.

(*RS*)-1-(4-Fluorophenyl)-4-phenylazetidin-2-one
(**2a**, C₁₅H₁₂FNO)

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: δ = 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**, C₁₆H₁₄FNO)

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: δ = 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**, C₁₆H₁₄FNO₂)

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: δ = 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, OMe), 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, MeCN/H₂O 1/3.

trans-4-(4-Fluorophenyl)-1-(4-methoxyphenyl)-3-methylazetidin-2-one (**2d**, C₁₇H₁₆FNO₂)

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: δ = 0.85 (d, *J* = 7.6 Hz, Me), 3.63 (m, 3-H), 3.76 (s, OMe), 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**, C₁₇H₁₄F₃NO₂)

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: δ = 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, OMe), 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**, C₁₈H₁₆F₃NO₂)

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: δ = 0.85 (d, *J* = 7.6 Hz, Me), 3.63 (m, 3-H), 3.76 (s, OMe), 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**, C₁₆H₁₁F₄NO)

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: δ = 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 Et₃N (0.2–0.5 mol) in 100 cm³ CH₂Cl₂ was dropwise added to a solution of the acid chloride (0.2–0.5 mol) in 50 cm³ CH₂Cl₂ 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 NaHCO₃, dried (Na₂SO₄), and evaporated *in vacuo*. The residue was crystallized as noted.

trans-3-Chloro-1-(4-fluorophenyl)-4-(4-methoxyphenyl)-azetidin-2-one (**3b**, C₁₆H₁₃ClFNO₂)

From **1h** and ClCH₂COCl. Yield 1.3 g (19%); colorless needles; mp 132°C (Me₂CHOH); 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): δ = 3.81 (s, OMe), 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**, C₁₆H₁₂Cl₂FNO₂)

From **1h** and Cl₂CHCOCl. Yield 0.4 g (5%); colorless needles; mp 140–141°C (AcOEt/*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: δ = 3.83 (s, OMe), 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**, C₁₅H₁₀Cl₂FNO)

From **1a** and Cl₂CHCOCl. Yield 4.2 g (27%); colorless needles; mp 112°C (MeOH); 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): δ = 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, MeCN/H₂O 45/55.

(*RS*)-3,3-Dichloro-4-phenyl-1-[4-(trifluoromethyl)phenyl]-azetidin-2-one (**3e**, C₁₆H₁₀Cl₂F₃NO)

From **1b** and Cl₂CHCOCl. Yield 1.7 g (69%); light brown crystals; mp 73–75°C (MeOH/*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): δ = 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**, C₁₇H₉Cl₂F₆NO)

From **1e** and Cl₂CHCOCl. Yield 1.2 g (28%); colorless crystals; mp 113°C (AcOEt/*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): δ = 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**, C₁₅H₁₀ClFNO₃)

From **1d** and ClCH₂COCl. Yield 0.6 g (9%); colorless crystals; mp 140°C (AcOEt/*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): δ = 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**, C₉H₈ClNO)

1.6 g (10.8 mmol) of **18** was dissolved in a mixture of Et₂O and H₂O (100 cm³, 1/1) and with stirring, chlorine was blown in for 1 h. Stirring was continued for 12 h, the organic layer was separated, dried (Na₂SO₄), 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: δ = 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**, C₁₂H₁₇NO₂)

a) From 8.1 g isovalerianyl chloride, 9.3 g (12.8 cm³) Et₃N, 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 (MeOH); 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): δ = 1.01 (d, J = 6.5 Hz, 2 Me), 2.17–2.23 (m, CH, CH₂), 3.78 (s, OMe), 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**, C₁₂H₁₄F₃NO)

a) From 2.5 g **1b** or b) from 3.2 g **1e**, 1.2 g isovalerianyl chloride, and 1.5 g Et₃N. Yield a) 1.3 g (53%); b) 0.6 g

(24%); colorless crystals; mp 123°C (*EtOH*/*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): δ = 1.02 (d, J = 6.6 Hz, 2 *Me*), 2.17–2.27 (m, CH, CH₂), 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**, C₁₂H₁₃NO₄) [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 (*MeOH*); 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): δ = 3.80, 3.82 (2 s, 2 *OMe*), 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**, C₁₁H₁₀FNO₃)

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 (*MeOH*); 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): δ = 3.83 (s, *OMe*), 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**, C₉H₁₀ClNO₂)

From 3 g **1v** and 1.4 g ClCH₂COCl. Yield 0.4 g (17%); colorless crystals; mp 120–121°C (*AcOEt*/*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): δ = 3.80 (s, *OMe*), 4.18 (s, CH₂), 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 cm³). Then, *Et*₃N (2.5 g, 0.024 mol, 3.4 cm³) dissolved in toluene (80 cm³) was dropwise added with heating. After refluxing for 3–4 h, the solution was cooled to room temperature, filtered, the filtrate was dried (Na₂SO₄), 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**, C₁₆H₁₂Cl₃NO₂)

From 5 g **1k** and 3 g Cl₂CHCOCl. Yield 1.5 g (17%); colorless crystals; mp 135°C (*AcOEt*/*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): δ = 3.65 (s, *OMe*), 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, *MeCN*/*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**, C₁₅H₉Cl₃FNO)

From 3 g **1l** and 1.9 g Cl₂CHCOCl. Yield 2.8 g (63%); colorless needles; mp 118°C (*EtOH*); 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): δ = 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**, C₁₆H₁₂Cl₂NO₂)

From 3 g **1m** and 2.6 g Cl₂CHCOCl. 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 (*EtOH*); IR: $\bar{\nu}$ = 1778 (CO), 1513 (*ar*), 1388 (C–N), 1052 (C–Cl), 838, 754 (*ar*) cm^{-1} ; ^1H NMR (300 MHz): δ = 3.78 (s, *OMe*), 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**, C₁₅H₁₀Cl₂FNO)

From 3 g **1a** and 2.2 g Cl₂CHCOCl. Yield 2.5 g (53%); colorless needles; mp 134–136°C (*EtOH*); IR: $\bar{\nu}$ = 1784 (CO), 1510 (*ar*), 1388 (C–N), 1231 (C–F), 832, 700 (*ar*) cm^{-1} ; ^1H NMR (300 MHz): δ = 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**, C₁₇H₁₅Cl₂FN₂O)

From 3 g **1i** and 1.9 g Cl₂CHCOCl. Yield 2.3 g (52%); colorless needles; mp 148–150°C (*EtOH*); 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): δ = 2.99 (s, *NMe*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**, C₁₅H₉Cl₂FNO)

From 3 g **1r** and 1.8 g Cl₂CHCOCl. 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): δ = 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**, C₁₅H₉Cl₃FNO)

From 3 g **1s** and 1.9 g Cl₂CHCOCl. Yield 2.5 g (57%); colorless crystals; mp 119–121°C (*Me*₂CHOH/*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**, C₁₅H₉Cl₃FNO)

From 3 g **1t** and 1.9 g Cl₂CHCOCl. Yield 1.1 g (25%); colorless plates; 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-(trifluoromethyl)phenyl]azetidin-2-one (**9i**, C₁₇H₁₂Cl₂F₃NO₃)

From 2.5 g **1g** and 1.3 g Cl₂CHCOCl. Yield 1.2 g (34%); colorless crystals; mp 110–112°C (*Me*₂CHOH); 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, *OMe*), 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**, C₁₆H₁₂Cl₂FNO₂)

From 3 g **1h** and 1.9 g Cl₂CHCOCl. Yield 3.5 g (79%); colorless crystals; mp 145–147°C (*Me*₂CHOH/*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, *OMe*), 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**, C₁₈H₁₄Cl₃NO₃)

From 3 g **1q** and 1.5 g Cl₂CHCOCl. Yield 0.3 g (7%); brown solid; mp 95°C (*Me*₂CHOH); 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, CH₂), 5.02 (s, CH₂(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**, C₁₅H₈Cl₂F₃NO)

From 3 g **1u** and 1.9 g Cl₂CHCOCl. 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**, C₁₅H₁₀Cl₂FNO)

From 3 g **1l** and 1.45 g ClCH₂COCl. Yield 1.2 g (30%); colorless crystals; mp 115°C (*Me*₂CHOH/*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**, C₁₅H₁₀Cl₂FNO)

From 3 g **1r** and 1.6 g ClCH₂COCl. Yield 1.1 g (35%); colorless needles; mp 114–116°C (*Me*₂CHOH); 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**, C₁₅H₉Cl₃FNO)

From 3 g **1o** and 1.3 g ClCH₂COCl. Yield 0.3 g (13%); colorless solid; mp 83°C (*Me*₂CHOH/*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**, C₁₆H₁₃ClFNO₂)

From 3 g **1h** and 1.5 g ClCH₂COCl. Yield 1.8 g (45%); colorless crystals; mp 138–139°C (*Me*₂CHOH/*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, *OMe*), 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**, C₁₅H₉ClF₃NO)

From 3 g **1u** and 1.5 g ClCH₂COCl. Yield 1.6 g (40%); colorless crystals; mp 89–93°C (*Et*₂O); 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-isopropylazetidin-2-one (**11a**, C₁₈H₁₇ClNO)

From 3 g **11** and 1.6 g isovalerianyl chloride as **9c**. Yield 0.6 g (15%); colorless needles; mp 136°C (EtOH); 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): δ = 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-isopropylazetidin-2-one (**11b**, C₁₈H₁₇ClFNO)

From 3 g **11** and 1.6 g isovalerianyl chloride. Yield 1.0 g (25%); colorless needles; mp 136–138°C (Me₂CHOH); 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): δ = 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**, C₁₈H₁₆Cl₂FNO)

From 3 g **10** and 1.4 g isovalerianyl chloride. Yield 0.1 g (2.5%); colorless needles; mp 128°C (Me₂CHOH); 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): δ = 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**, C₂₀H₂₃FN₂O)

From 3 g **11** and 1.5 g isovalerianyl chloride. Yield 1.7 g (42%); colorless needles; mp 134°C (EtOH); 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): δ = 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, NMe₂), 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**, C₁₉H₂₀FNO₂)

From 3 g **11** and 1.6 g isovalerianyl chloride. Yield 1.1 g (27%); colorless crystals; mp 114–115°C (Me₂CHOH/*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): δ = 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, OMe), 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**, C₁₆H₁₈Cl₃NO₃)

From 2.7 g **1w** and 1.5 g Cl₂CHCOCl. Yield 0.4 g (11%); lightly colored crystals; mp 85°C (Me₂CHOH); IR: $\bar{\nu}$ = 3073, 2958 (CH), 1788, 1778, 1745 (CO), 1331 (C–N), 1039 (C–Cl), 760 (ar) cm⁻¹; ¹H NMR (300 MHz): δ = 0.85, 0.95 (2d, each J = 6.2 Hz, Me), 1.59–1.78 (m, CH, CH₂(Leu)), 3.78 (s, OMe), 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**, C₁₉H₂₇NO₅Si)

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): δ = 0.14 (s, 3 Me), 1.24 (2 t, 2 Me), 2.28 (s, Me), 3.48 (s, 3-H), 4.26 (2 q, 2CH₂), 7.2 (q, 4 ar H) ppm.

Diethyl 3-(α -hydroxyisopropyl)-1-(4-methylphenyl)-2-oxoazetidine-4,4-dicarboxylate (**16a**, C₁₉H₂₅NO₆)

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, CDCl₃/DMSO-d₆, 1/3): δ = 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, 2CH₂), 7.26 (q, 4 ar H) ppm.

Diethyl 3-(α -hydroxyethyl)-1-(4-methylphenyl)-2-oxoazetidine-4,4-dicarboxylate (**16b**, C₁₈H₂₃NO₆)

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 (MeOH/Et₂O: 1/1); IR: $\bar{\nu}$ = 3430 (OH), 3160, 2980, 2920, 2860 (CH), 1750, 1745 (CO) cm⁻¹; ¹H NMR (80 MHz, CDCl₃/DMSO-d₆, 1/1): δ = 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, 2CH₂), 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**, C₂₃H₂₄N₂O₈)

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., EtOH); IR: $\bar{\nu}$ = 3430 (OH), 3080, 3040, 2980, 2920 (CH), 1740 (CO), 1510, 1340 (NO₂) cm⁻¹; ¹H NMR (80 MHz, CDCl₃/DMSO-d₆, 1/1): δ = 1.12 (t, 2 Me), 2.27 (s, Me), 3.24–4.28 (m, 2CH₂, 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**, C₂₃H₂₂ClNO₅)

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 (EtOH); IR: $\bar{\nu}$ = 3060, 3040, 2980, 2940, 2890 (CH), 1750, 1730 (CO), 1680 (C=C) cm⁻¹; ¹H NMR (80 MHz): δ = 1.24 (t, 2 Me), 2.31 (s, Me), 4.3 (q, 2CH₂), 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**, C₂₃H₂₂N₂O₇)

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 $142\text{--}144^{\circ}\text{C}$ (*EtOH*); 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, 2CH₂), 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

Compound **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 CH₂Cl₂, twice washed with water, dried (Na₂SO₄), and evaporated *in vacuo*. Work-up as noted.

(*RS*)-1-(4-Chlorobenzyl)-4-phenylazetidin-2-one

(**19b**, C₁₆H₁₄ClNO)

From **18** and 4.8 g (15 mmol) 4-chlorobenzyl chloride, CC (CHCl₃). Yield 1.8 g (67%); light yellow viscous liquid; $n_{\text{D}}^{20} = 1.5850$; IR: $\bar{\nu} = 3070, 3040, 2960, 2920$ (CH), 1750 (CO), $1600, 1490$ (*ar*) cm^{-1} ; ^1H NMR (80 MHz): $\delta = 2.83$ (dd, $J = 2.8\text{ Hz}, 14.5\text{ Hz}, 3\text{-H}_{\text{trans}}$), 3.38 (dd, $J = 5.0\text{ Hz}, 14.5\text{ Hz}, 3\text{-H}_{\text{cis}}$), 3.73 (d, $J = 15.0\text{ Hz}, 1\text{H}, \text{CH}_2$), 4.35 (dd, $J = 2.8\text{ Hz}, 5.0\text{ Hz}, 4\text{-H}$), 4.73 (d, $J = 15.0\text{ Hz}, 1\text{H}, \text{CH}_2$), $6.97\text{--}7.55$ (m, 9 *ar* H) ppm.

(*RS*)-1-(4-Nitrobenzyl)-4-phenylazetidin-2-one

(**19c**, C₁₆H₁₄N₂O₃)

From **18** and 3.2 g (15 mmol) 4-nitrobenzyl bromide, CC (CHCl₃). Yield 1.9 g (67%); yellowish viscous solid; mp $71\text{--}72^{\circ}\text{C}$; IR: $\bar{\nu} = 3070, 3030, 2980, 2920$ (CH), 1750 (CO), 1600 (*ar*), $1515, 1345$ (NO₂) cm^{-1} ; ^1H NMR (80 MHz): $\delta = 2.98$ (dd, $J = 2.5\text{ Hz}, 15.0\text{ Hz}, 3\text{-H}_{\text{trans}}$), 3.53 (dd, $J = 5.0\text{ Hz}, 15.0\text{ Hz}, 3\text{-H}_{\text{cis}}$), 4.02 (d, $J = 15.5\text{ Hz}, 1\text{H}, \text{CH}_2$), 4.55 (dd, $J = 2.5\text{ Hz}, 5.0\text{ Hz}, 4\text{-H}$), 4.83 (d, $J = 15.5\text{ Hz}, 1\text{H}, \text{CH}_2$), $7.10\text{--}8.22$ (m, 9 *ar* H) ppm.

(*RS*)-1-[3-(Trifluoromethyl)benzyl]-4-phenylazetidin-2-one

(**19d**, C₁₇H₁₄F₃NO)

From **18** and 2.9 g (15 mmol) 3-(trifluoromethyl)benzyl chloride, CC (CHCl₃). Yield 2.5 g (83%); colorless liquid; $n_{\text{D}}^{20} = 1.5276$; IR: $\bar{\nu} = 3060, 3040, 2960, 2920$ (CH), 1750 (CO), 1495 (*ar*) cm^{-1} ; ^1H NMR (80 MHz): $\delta = 2.97$ (dd, $J = 2.5\text{ Hz}, 14.5\text{ Hz}, 3\text{-H}_{\text{trans}}$), 3.50 (dd, $J = 5.0\text{ Hz}, 14.5\text{ Hz}, 3\text{-H}_{\text{cis}}$), 4.02 (d, $J = 15.0\text{ Hz}, 1\text{H}, \text{CH}_2$), 4.53 (dd, $J = 2.5\text{ Hz}, 5.0\text{ Hz}, 4\text{-H}$), 4.88 (d, $J = 15\text{ Hz}, 1\text{H}, \text{CH}_2$), $7.20\text{--}7.90$ (m, 9 *ar* H) ppm.

(*RS*)-1-(4-Cyanobenzyl)-4-phenylazetidin-2-one

(**19e**, C₁₇H₁₄N₂O)

From **18** and 2.9 g (15 mmol) 4-cyanobenzyl bromide, CC (CHCl₃). Yield 1.4 g (55%); colorless crystals; mp $63\text{--}65^{\circ}\text{C}$; 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,

$J = 2.5\text{ Hz}, 15.0\text{ Hz}, 3\text{-H}_{\text{trans}}$), 3.50 (dd, $J = 5.0, 15.0\text{ Hz}, 3\text{-H}_{\text{cis}}$), 3.98 (d, $J = 16.0\text{ Hz}, 1\text{H}, \text{CH}_2$), 4.53 (dd, $J = 2.5, 5.0\text{ Hz}, 4\text{-H}$), 4.83 (d, $J = 16.0\text{ Hz}, 1\text{H}, \text{CH}_2$), $7.33\text{--}7.73$ (m, 9 *ar* H) ppm.

(*RS*)-1-(3,4,5-Trimethoxybenzyl)-4-phenylazetidin-2-one

(**19f**, C₁₉H₂₁NO₄)

From **18** and 3.3 g (15 mmol) 3,4,5-trimethoxybenzyl chloride, CC (CHCl₃). Yield 1.7 g (52%); colorless liquid; $n_{\text{D}}^{20} = 1.5086$; IR: $\bar{\nu} = 3080, 3000$ (CH), 2940 (OMe), 2840 (CH), 1745 (CO), $1590, 1500$ (*ar*) cm^{-1} ; ^1H NMR (80 MHz): $\delta = 2.90$ (dd, $J = 2.5\text{ Hz}, 14.5\text{ Hz}, 3\text{-H}_{\text{trans}}$), 3.43 (dd, $J = 5.0, 14.5\text{ Hz}, 3\text{-H}_{\text{cis}}$), 3.82 (s, 2 OMe), 3.82 (d, $J = 15.0\text{ Hz}, 1\text{H}, \text{CH}_2$), 3.88 (s, OMe), 4.48 (dd, $J = 2.5, 5.0\text{ Hz}, 4\text{-H}$), 4.73 (d, $J = 15.0\text{ Hz}, 1\text{H}, \text{CH}_2$), 6.42 (s, 2 *ar* H), $7.20\text{--}7.63$ (m, 5 *ar* H) ppm.

trans-4,5-Diphenylpyrrolidin-2-one (**20a**, C₁₆H₁₅NO)

A solution of 2.4 g (10 mmol) **19a** was dropwise added to a solution of 1.3 g (20 mmol) *BuLi* in 10 cm^3 *THF* at -78°C , the mixture was stirred for 1 h, and then poured into 100 cm^3 of a satd. solution of NaCl. The organic layer was separated, dried (Na₂SO₄), and evaporated *in vacuo*. Yield 2.0 g (85%); colorless crystals; mp $204\text{--}205^{\circ}\text{C}$ (*Me*₂CHOH); IR: $\bar{\nu} = 3200, 3080$ (NH), $3030, 2920, 2890$ (CH), 1685 (CO), $1600, 1490$ (*ar*) cm^{-1} ; ^1H NMR (*DMSO*-d₆, 80 MHz): $\delta = 2.38$ (dd, $J = 10.0, 16.0\text{ Hz}, 3\text{-H}$), 2.64 (dd, $J = 8.5, 16.0\text{ Hz}, 3\text{-H}$), 3.29 (ddd, $J = 8.5, 10.0, 7.5\text{ Hz}, 4\text{-H}$), 4.61 (d, $J = 7.5\text{ Hz}, 5\text{-H}$), $7.00\text{--}7.43$ (m, 10 *ar* H), 8.10 (m, N-H) ppm.

cis/trans-5-(4-Chlorophenyl)-4-phenylpyrrolidin-2-one

(**20b**, C₁₆H₁₄ClNO)

From 2.7 g (10 mmol) **19b** as described for **20a**, CC (CHCl₃). Yield 1.2 g (43%); light yellow waxy solid; mp $124\text{--}125^{\circ}\text{C}$; 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, $J = 10.0\text{ Hz}, 16.75\text{ Hz}, 3\text{-H}$), 2.84 (dd, $J = 8.0\text{ Hz}, 16.75\text{ Hz}, 3\text{-H}$), 3.30 (ddd, $J = 10.0\text{ Hz}, 8.0\text{ Hz}, 8.0\text{ Hz}, 4\text{-H}$), 4.68 (d, $J = 8.0\text{ Hz}, 5\text{-H}$), $6.69\text{--}7.45$ (m, 9 *ar* H), 7.56 (m, N-H); *cis*: $\delta = 3.99$ (ddd, $J = 8.0\text{ Hz}, 4\text{-H}$), 4.99 (d, $J = 8.0\text{ Hz}, 5\text{-H}$) ppm; ratio of isomers *trans*:*cis* = 9:1.

cis/trans-5-[3-(Trifluoromethyl)phenyl]-4-phenylpyrrolidin-2-one

(**20d**, C₁₇H₁₄F₃NO)

From 3.1 g (10 mmol) **19d** as described for **20a**, CC (CHCl₃). Yield 1.5 g (50%); yellow waxy solid; mp $104\text{--}105^{\circ}\text{C}$; 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, $J = 10.0\text{ Hz}, 17.0\text{ Hz}, 3\text{-H}$), 2.88 (dd, $J = 8.25\text{ Hz}, 17.0\text{ Hz}, 3\text{-H}$), 3.36 (ddd, $J = 10.0\text{ Hz}, 8.25\text{ Hz}, 7.5\text{ Hz}, 4\text{-H}$), 4.80 (d, $J = 7.5\text{ Hz}, 5\text{-H}$), $6.71\text{--}7.64$ (m, 9 *ar* H), 7.69 (m, N-H); *cis*: $\delta = 4.05$ (ddd, $J = 7.5\text{ Hz}, 4\text{-H}$), 5.13 (d, $J = 7.5\text{ Hz}, 5\text{-H}$) ppm; ratio of isomers *trans*:*cis* = 8:2.

trans-5-(3,4,5-Trimethoxyphenyl)-4-phenylpyrrolidin-2-one

(**20f**, C₁₉H₂₁NO₄)

From 3.3 g (10 mmol) **19f** as described for **20a**, CC (CHCl₃), then extraction of the column with *EtOH*, and evaporation of

EtOH. Yield 1.44 g (44%); colorless crystals; mp 171–172°C; IR: $\bar{\nu}$ = 3320 (NH), 3020, 2930 (CH), 2830 (OMe), 1690 (CO), 1595, 1505 (ar) cm^{-1} ; ^1H NMR (80 MHz): δ = 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 OMe), 3.80 (s, OMe), 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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