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Tetrahedron
Tetrahedron 64 (2008) 4575–4584
www.elsevier.com/locate/tet

Synthesis of *trans*-4-aryl-3-(3-chloropropyl)azetidin-2-ones and their transformation into *trans*- and *cis*-2-arylpiperidine-3-carboxylates

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Received 7 February 2008; received in revised form 29 February 2008; accepted 3 March 2008
Available online 7 March 2008

Abstract

Treatment of arylmethylideneamines with 5-chloropentanoyl chloride in benzene in the presence of 2,6-lutidine afforded novel *trans*-4-aryl-3-(3-chloropropyl)azetidin-2-ones in good yields. The latter 3-(3-chloropropyl)-β-lactams were transformed selectively into *trans*-methyl 1-alkyl-2-arylpiperidine-3-carboxylates in high yields and purity upon subsequent treatment with hydrogen chloride in methanol and triethylamine in dichloromethane. These *trans*-1-alkyl-2-arylpiperidine-3-carboxylates were easily converted into either their cis-isomers upon treatment with hydrazine monohydrate in methanol, or into the corresponding piperidine-1,3-dicarboxylates by reaction with alkyl chloroformates in benzene. Finally, 3-(3-chloropropyl)-1-(4-methoxybenzyl)-4-phenylazetidin-2-one was transformed into the corresponding *trans*-1-*tert*-butoxycarbonyl-3-(4-methoxybenzylcarbamoyl)piperidine via a three-step sequence in a good overall yield.

1. Introduction

Since the introduction of the term 'β-lactam synthon method' in 1997,[1] azetidin-2-ones have acquired a prominent place in organic chemistry as synthons for further elaboration. Consequently, the constrained azetidin-2-one ring has been employed successfully in a large variety of different synthetic methodologies towards all kinds of nitrogen-containing target compounds.[2] Whereas several efforts have been devoted to the application of 1-(ω-haloalkyl)-β-lactams[3] and 4-(ω-haloalkyl)-β-lactams[4] in organic synthesis, the use of 3-(ω-haloalkyl)azetidin-2-ones has been evaluated only sporadically up to now, and no convenient and general procedure for their preparation is available. In a report, the alkylation of 1-(*tert*-butyldimethylsilyl)-4-phenylazetidin-2-one with 1-bromo-3-chloropropane has been described, affording the corresponding *trans*-1-(*tert*-butyldimethylsilyl)-3-(3-chloropropyl)-2-phenyl-β-lactam in 77% yield.[5] The latter *trans*-3-(3-chloropropyl)-2-phenylazetidin-2-one was transformed into *cis*-methyl 2-phenylpiperidine-3-carboxylate upon subsequent treatment with H_2SO_4 in methanol and NaI/$NaHCO_3$ in DMF.[5] Further elaboration of this piperidine-3-carboxylate furnished *cis*-3-(2-methoxybenzylamino)-2-phenylpiperidine (compound CP-99,994) as a potent substance P antagonist.[6] Analogously, the alkylation of a 1-silylated 4-carboxyazetidin-2-one with 1-iodo-3-chloropropane has been described. The resulting 3-(3-chloropropyl)-β-lactam served as a substrate for the synthesis of different 3-(3-guanidinopropyl)azetidin-2-ones as triptase inhibitors.[7] However, the β-lactams used for the above mentioned alkylation reactions are not readily available, hence there is an actual need for a more practical and general method for the preparation of 3-(3-halopropyl)-β-lactams.

In the present report, a convenient procedure for the synthesis of 4-aryl-3-(3-chloropropyl)-β-lactams is described based on the Staudinger reaction between arylmethylideneamines and 5-chloropentanoyl chloride in the presence of a base. The 3-(3-chloropropyl)azetidin-2-ones thus obtained were further converted into novel *trans*- and *cis*-methyl 2-arylpiperidine-3-carboxylates in high yields and purity. The final goal of this work comprised the transformation of the latter piperidine-3-carboxylates into the corresponding 3-carbamoylpiperidines as precursors for the synthesis of biologically relevant 3-aminopiperidines (CP-99,994 analogues)[6] via a Hofmann rearrangement protocol. The need for new

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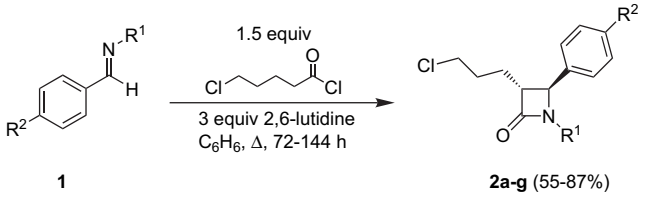
doi:10.1016/j.tet.2008.03.006

stereoselective routes to substituted piperidines has been underlined very recently in a review of synthetic approaches towards biologically relevant trans-3,4-disubstituted piperidines.[8] Furthermore, 2-arylpiperidine-3-carboxylic acid derivatives are of significant interest due to their potential use in the treatment of Alzheimer's disease,[9] while 2,4-diarylpiperidine-3-carboxylic acid derivatives have been reported as potential farnesyltransferase inhibitors.[10]

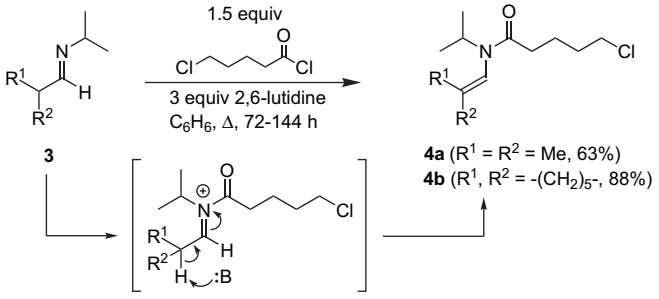
2. Results and discussion

The synthesis of 4-aryl-3-(3-chloropropyl)-β-lactams **2** was performed by means of a Staudinger reaction between the appropriate imines and ketenes. Thus, treatment of arylmethylideneamines **1** with 1.5 equiv of 5-chloropentanoyl chloride in benzene in the presence of 3 equiv of 2,6-lutidine afforded the corresponding novel 3-(3-chloropropyl)azetidin-2-ones **2a–g** in good yields after reflux for 72–144 h (Scheme 1, Table 1). The stereochemical outcome of the Staudinger reaction towards azetidin-2-ones **2** was shown to be trans based on the coupling constants between the protons at C3 and C4 in ^{1}H NMR (2.0 Hz, $CDCl_3$).[11] When triethylamine was used as a base instead of 2,6-lutidine, complex reaction mixtures were obtained in which the desired β-lactams **2** were present in very low yields (<10%). The required imines **1** were easily prepared via condensation of the corresponding benzaldehydes with different primary amines under reflux for 1 h in dichloromethane in the presence of $MgSO_4$ (yields 90–99%).[12]



Scheme 1.

In order to evaluate the synthesis of the analogous 4-alkyl-3-(3-chloropropyl)-β-lactams, aliphatic alkylideneamines **3** were used for the Staudinger reaction with 5-chloropentanoyl chloride, applying the same reaction conditions as described above. Surprisingly, 5-chloropentanamides **4a–b** were obtained instead as the sole reaction products in 63–88% yield (Scheme 2). Obviously, the presence of electron-donating alkyl groups has a distinct effect on the reactivity of the imines **3** as compared to arylmethylideneamines **1**. Nucleophilic addition of alkylideneamines **3** across the acid chloride carbonyl group and subsequent α-deprotonation with respect to the in situ formed iminium moiety can account for the formation of the observed 5-chloropentanamides **4** (Scheme 2).



Scheme 2.

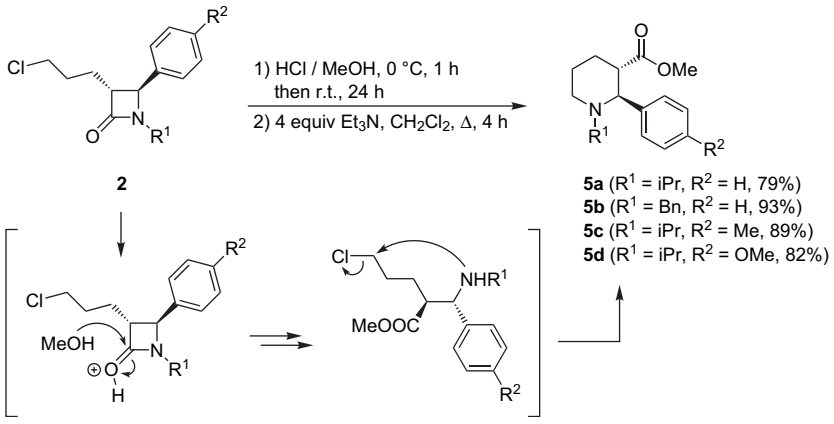
In the next phase, the aptitude of 4-aryl-3-(3-chloropropyl)-β-lactams **2** as substrates for ring expansion towards piperidine derivatives was investigated, as the combination of the constrained four-membered β-lactam ring and the electrophilic centre (halogenated carbon atom) at a remote position results in a potential useful substrate for various transformations.

In order to transform β-lactams **2** into piperidine derivatives, hydrochloric acid was bubbled through an ice-cooled methanolic solution of 3-(3-chloropropyl)azetidin-2-ones **2** for 1 h, followed by a resting period of 24 h at room temperature and a reflux period of 4 h in dichloromethane in the presence of 4 equiv of triethylamine. In this way, novel methyl 1-alkyl-2-arylpiperidine-3-carboxylates **5a–d** were obtained in high yields (82–93%) and purity (Scheme 3). The relative stereochemistry of the latter piperidines **5** could be assigned as trans based on a coupling constant of 9.9 Hz (^{1}H NMR, $CDCl_3$) between the protons at C2 and C3.[13] This reaction proceeds through initial nucleophilic ring opening of the protonated β-lactam by methanol,[14] followed by intramolecular nucleophilic displacement of chloride by the in situ formed free amine upon addition of base (Scheme 3). Apparently, isomerization takes place during the reaction, as normally cis-2,3-disubstituted piperidines would be expected. The ring opening of azetidin-2-ones by methanol comprises a valuable approach towards β-amino esters with plentiful applications.[15] It should be noted that the application of literature-based reaction conditions for the contemplated ring transformation of β-lactams **2** into piperidines **5** proved to be less or not successful at all. For example, the use of sulfuric acid in methanol[5] resulted in the desired piperidine-3-carboxylates **5** as major constituents besides several unidentified side-products, whereas the use of sodium cyanide in methanol[16] led only to the complete recovery of the starting material.

In order to expand the scope, the preparation of 1-(alkoxycarbonyl)piperidines **6** as the activated counterparts of 1-alkylpiperidines **5** was evaluated by means of two different approaches. The direct conversion of 1-alkylpiperidines **5** into 1-(alkoxycarbonyl)piperidines **6** could be realized upon treatment of piperidine-3-carboxylates **5a** and **5b** with a large excess (10 equiv) of methyl or ethyl chloroformate in benzene,

Table 1
Synthesis of *trans*-4-aryl-3-(3-chloropropyl)-β-lactams **2a–g**

Entry	R^1	R^2	Compound	Yield (%)
1	*i*-Pr	H	**2a**	75
2	Et	H	**2b**	60
3	Bn	H	**2c**	55
4	4-MeOC$_6$H$_4$CH$_2$	H	**2d**	70
5	*c*-Hex	H	**2e**	62
6	*i*-Pr	Me	**2f**	87
7	*i*-Pr	OMe	**2g**	66



Scheme 3.

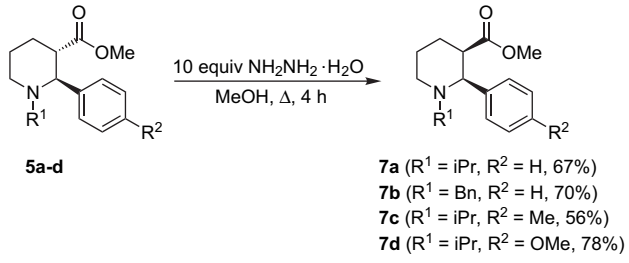
affording piperidine-1,3-dicarboxylates **6a** and **6b** after reflux for 10 h (Scheme 4, Table 2). On the other hand, *N*-Boc protected piperidine **6c** was prepared starting from β-lactam **2c** through a sequence of transformations, involving acid-mediated β-lactam ring opening by methanol, N-debenzylation by means of hydrogenolysis, base-mediated cyclization towards the free piperidine and finally *N*-Boc protection utilizing 1 equiv of Boc_2O in acetonitrile for 2 h at room temperature (Scheme 4, Table 2).

Due to the biological relevance of 3-carbamoylpiperidines,[10] several attempts were performed in order to convert the ester moiety of piperidine-3-carboxylates **5** into an N-unsubstituted amide by means of reaction with dimethylaluminium amides.[17] Furthermore, the latter 3-carbamoylpiperidines could then serve as precursors for the synthesis of the corresponding biologically relevant 3-aminopiperidines (CP-99,994 analogues)[6] via a Hofmann rearrangement protocol. Treatment of 1-isopropylpiperidine **5a** (or the corresponding hydrochloride salt) with 2 equiv of dimethylaluminium amide, derived from ammonia and trimethylaluminium, in dichloromethane at 40 °C for 16 h only resulted in the recovery of the starting material. When the dimethylaluminium reagent derived from 4-methoxybenzylamine was used, again no conversion was observed. Also treatment of piperidine-1,3-dicarboxylates **6** with 3–10 equiv of chloromethylaluminium amide in toluene at 50 °C for 12 h resulted in either recovery of the starting material or in complex reaction mixtures.

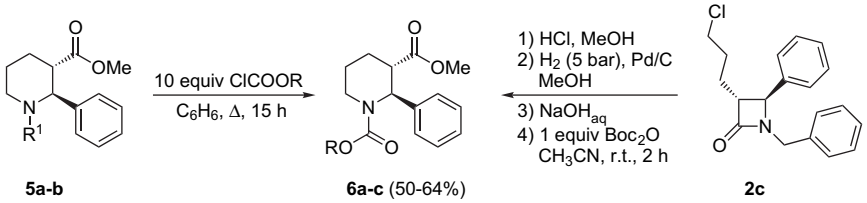
According to another strategy,[18] piperidine-3-carboxylates **5** were treated with 10 equiv of hydrazine monohydrate in refluxing methanol for 4 h. Although complete conversion of the starting compounds had taken place, this approach did not afford the anticipated hydrazides. Surprisingly, only cis-2,3-disubstituted piperidines **7a–d** were formed in good yields through isomerization of the starting trans-derivatives **5a–d** (Scheme 5). The relative stereochemistry of piperidines **7** could be assigned as cis based on coupling constants of 5.0–5.3 Hz (^{1}H NMR, $CDCl_3$) between the protons at C2 and C3.[13] According to the literature, *cis*-piperidines **7** adopt a chair conformation with an axial orientation for the alkoxycarbonyl group and an equatorial orientation for the aryl group.[19] The isomerization of *trans*-piperidines **5** to *cis*-piperidines **7** can be rationalized considering the basic properties of hydrazine,[20] as the hydroxide present in an aqueous solution of hydrazine can be responsible for the deprotonation of piperidines **5** in α-position with respect to the ester moiety. Protonation of the enolate thus formed should take place from the

Table 2
Synthesis of piperidine-1,3-dicarboxylates **6a–c**

Entry	Substrate	Compound	Yield (%)
1	**5a** (R^1=*i*-Pr)	**6a** (R=Me)	56
2	**5b** (R^1=Bn)	**6b** (R=Et)	50
3	**2c**	**6c** (R=*t*-Bu)	64



Scheme 5.



Scheme 4.

less hindered face, i.e., the opposite face with regard to the aryl group, affording *cis*-piperidines **7**.

As the ring opening of 3,3-disubstituted β-lactams by lithium amides has been reported before,[21] the direct conversion of 3-(3-chloropropyl)-β-lactams **2** into the corresponding 3-carbamoylpiperidines was evaluated upon treatment with 2 equiv of $LiNH_2$ in THF and reflux for 20 h. Again, the substrate was recovered completely. Apparently, in this case the β-lactam ring had to be activated by the introduction of an electron-withdrawing group at nitrogen in order to facilitate ring opening by amines.

Thus, 1-(4-methoxybenzyl)azetidin-2-one **2d** was converted into β-lactam **8** bearing a free NH moiety through debenzylation by means of 3.4 equiv of potassium peroxodisulfate in a 1/1 mixture of water/acetonitrile and refluxed for 1 h in the presence of 6.8 equiv of KH_2PO_4 (Scheme 6). Subsequently, treatment of β-lactam **8** with 2 equiv of di-*tert*-butyl dicarbonate (Boc_2O) in the presence of 1 equiv of Et_3N and a catalytic amount of DMAP afforded the corresponding *N*-Boc protected β-lactam **9** in 75% yield after 4 h at room temperature (Scheme 6). The latter activated azetidin-2-one **9** was then successfully subjected to several subsequent transformations, i.e., the nucleophilic ring opening of the β-lactam moiety by 4-methoxybenzylamine, N-deprotection by means of 20 equiv of trifluoroacetic acid, base-mediated cyclization towards the corresponding piperidine and finally *N*-Boc protection by means of Boc_2O, furnishing *trans*-1-*tert*-butoxycarbonyl-3-(4-methoxybenzylcarbamoyl)-piperidine **10** in good overall yield (Scheme 6). Attempted N-debenzylation of amide **10** using either ceric ammonium nitrate or potassium peroxodisulfate resulted in recovery of the starting material or in complex reaction mixtures.

In summary, novel *trans*-4-aryl-3-(3-chloropropyl)azetidin-2-ones have been prepared upon treatment of arylmethylideneamines with 5-chloropentanoyl chloride in benzene in the presence of 2,6-lutidine. These 3-(3-chloropropyl)azetidin-2-ones were transformed selectively into *trans*-methyl 1-alkyl-2-arylpiperidine-3-carboxylates in high yields and purity upon subsequent treatment with hydrogen chloride in methanol and triethylamine in dichloromethane. Furthermore, *trans*-1-alkyl-2-arylpiperidine-3-carboxylates were converted into their cis-isomers upon treatment with hydrazine monohydrate in methanol and into the corresponding *trans*-piperidine-1,3-dicarboxylates by reaction with alkyl chloroformates in benzene. Finally, 3-(3-chloropropyl)-1-(4-methoxybenzyl)-4-phenylazetidin-2-one was transformed into the corresponding 1-*tert*-butoxycarbonyl-3-(4-methoxybenzylcarbamoyl)piperidine via subsequent N-debenzylation, *N*-Boc protection, nucleophilic ring opening by 4-methoxybenzylamine, N-deprotection, base-mediated cyclization and *N*-Boc protection in a good overall yield.

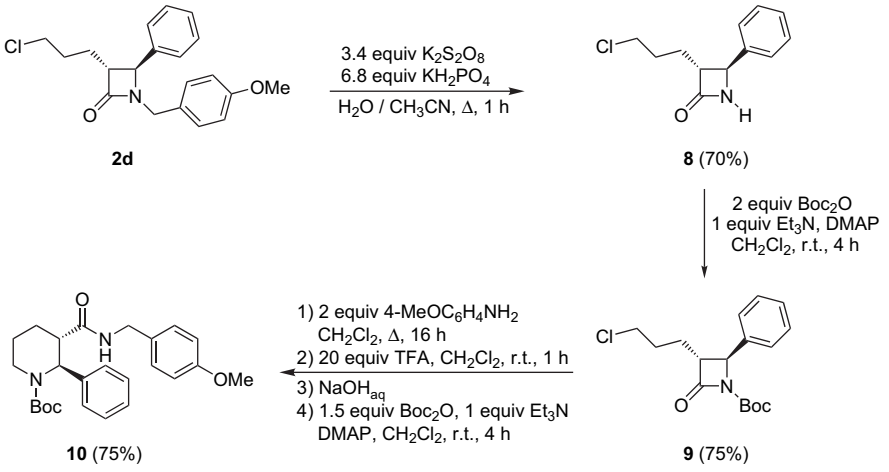
3. Experimental part

3.1. General

^1H NMR spectra were recorded at 270 MHz (JEOL JNM-EX 270) with $CDCl_3$ as solvent and tetramethylsilane as internal standard. ^{13}C NMR spectra were recorded at 68 MHz (JEOL JNM-EX 270) with $CDCl_3$ as solvent. Mass spectra were obtained with a mass spectrometer (VARIAN MAT 112, 70 eV) using a GC–MS coupling (RSL 200, 20 m glass capillary column, i.d. 0.53 mm, He carrier gas). IR spectra were measured with a PerkinElmer 1310 spectrophotometer or a Spectrum One FT-IR. Elemental analyses were performed with a PerkinElmer Series II CHNS/O Analyzer 2400. Dichloromethane was dried over calcium hydride, while diethyl ether and THF were dried by distillation over sodium benzophenone ketyl. Other solvents were used as received from the supplier.

3.2. Synthesis of trans-4-aryl-3-(3-chloropropyl)-β-lactams 2

General procedure: To a refluxing solution of imine **1** (10 mmol) and 2,6-lutidine (30 mmol) in benzene (50 mL) was added dropwise a solution of 5-chloropentanoyl chloride (15 mmol) in benzene (50 mL). The resulting solution was kept at reflux temperature for 72 h (or 144 h for β-lactams **2c** and **2d**). Subsequently, the precipitated 2,6-lutidine hydrochloride was filtered off and the filtrate was washed with hydrochloric acid (2×35 mL, 1 M). Drying (magnesium



Scheme 6.

sulfate) and evaporation of the solvent afforded 4-aryl-3-(3-chloropropyl)-β-lactam **2**, which was further purified by means of column chromatography on silica gel (hexane/EtOAc 3/2).

3.2.1. trans-3-(3-Chloropropyl)-1-isopropyl-4-phenylazetidin-2-one ***2a***

Light-yellow oil. Yield 75%. R_f 0.53 (hexane/EtOAc 3/2). ^{1}H NMR (270 MHz, $CDCl_3$): δ 1.01 and 1.26 (2×3H, 2×d, J=6.6 Hz, CH(CH_3)$_2$), 1.83–2.00 (4H, m, (CH_2)$_2$CH_2Cl), 2.89–2.93 (1H, m, CHCH$_2$), 3.52 (2H, t, J=5.0 Hz, CH$_2$Cl), 3.76 (1H, septet, J=6.6 Hz, CHMe$_2$), 4.22 (1H, d, J=2.0 Hz, NCH), 7.35–7.39 (5H, m, C_6H_5). ^{13}C NMR (68 MHz, $CDCl_3$): δ 20.4 and 21.2 (CH(*C*H$_3$)$_2$), 26.0 and 30.1 ((*C*H$_2$)$_2$CH$_2$Cl), 44.6 (CH$_2$Cl), 44.9 (*C*HMe$_2$), 58.8 (*C*HCH$_2$), 60.1 (NCH), 126.5, 128.4 and 128.9 (CH$_{arom}$), 139.4 (C_q), 169.8 (C=O). IR (NaCl): ν=1745 cm^{-1} (C=O). MS (70 eV): *m/z* (%): 265/7 (0.66, M$^+$), 230 (0.70, M$^+$–Cl), 180/2 (6), 117/9 (16), 88 (12), 86 (62), 84 (100), 73 (6), 57 (5), 55 (8), 51 (9), 49 (34), 47 (29). Anal. Calcd for $C_{15}H_{20}ClNO$: C 67.79, H 7.58, N 5.27. Found: C 67.62, H 7.79, N 5.13.

3.2.2. trans-3-(3-Chloropropyl)-1-ethyl-4-phenylazetidin-2-one ***2b***

Light-yellow oil. Yield 60%. R_f 0.28 (hexane/EtOAc 3/2). ^{1}H NMR (270 MHz, $CDCl_3$): δ 1.05 (3H, t, J=7.3 Hz, CH$_2$C*H*$_3$), 1.78–1.99 (4H, m, (C*H*$_2$)$_2$CH$_2$Cl), 2.85–3.01 (2H, m, C*H*CH$_2$ and (*H*CH)CH$_3$), 3.40–3.65 (3H, m, CH$_2$Cl and (HC*H*)CH$_3$), 4.13 (1H, d, J=2.0 Hz, NCH), 7.28–7.42 (5H, m, C_6H_5). ^{13}C NMR (68 MHz, $CDCl_3$): δ 12.6 (CH$_2$*C*H$_3$), 25.6 and 29.8 ((*C*H$_2$)$_2$CH$_2$Cl), 35.0 (*C*H$_2$CH$_3$), 44.3 (CH$_2$Cl), 59.2 (*C*HCH$_2$), 60.4 (NCH), 126.0, 128.2 and 128.7 (CH$_{arom}$), 137.8 (C_q), 169.5 (C=O). IR (NaCl): ν=1745 cm^{-1} (C=O). MS (70 eV): *m/z* (%): no M$^+$, 144 (10), 119 (9), 106 (33), 105 (38), 101 (12), 91 (11), 86 (42), 84 (55), 77 (41), 55 (22), 51 (51), 49 (100). Anal. Calcd for $C_{14}H_{18}ClNO$: C 66.79, H 7.21, N 5.56. Found: C 66.66, H 7.41, N 5.40.

3.2.3. trans-1-Benzyl-3-(3-chloropropyl)-4-phenylazetidin-2-one ***2c***

Light-yellow oil. Yield 55%. R_f 0.44 (hexane/EtOAc 3/2). ^{1}H NMR (270 MHz, $CDCl_3$): δ 1.75–1.98 (4H, m, (CH_2)$_2$CH$_2$Cl), 2.93–3.04 (1H, m, CHCH$_2$), 3.48 (2H, t, J=5.0 Hz, CH$_2$Cl), 3.64 (1H, d, J=14.9 Hz, (*H*CH)N), 4.02 (1H, d, J=2.0 Hz, NCH), 4.81 (1H, d, J=14.9 Hz, (HC*H*)N), 7.10–7.40 (10H, m, C_6H_5). ^{13}C NMR (68 MHz, $CDCl_3$): δ 25.9 and 30.0 ((*C*H$_2$)$_2$CH$_2$Cl), 44.3 (CH$_2$N), 44.5 (CH$_2$Cl), 59.8 (*C*HCH$_2$), 60.5 (NCH), 126.5, 127.7, 128.4, 128.5, 128.8 and 129.1 (CH$_{arom}$), 135.6 and 137.5 (2×C_q), 169.7 (C=O). IR (NaCl): ν=1750 cm^{-1} (C=O). MS (70 eV): *m/z* (%): 313/5 (0.3, M$^+$), 180/2 (100), 118 (10), 117 (69), 115 (10), 91 (27). Anal. Calcd for $C_{19}H_{20}ClNO$: C 72.72, H 6.42, N 4.46. Found: C 72.86, H 6.65, N 4.38.

3.2.4. trans-3-(3-Chloropropyl)-1-(4-methoxybenzyl)-4-phenylazetidin-2-one ***2d***

Light-yellow oil. Yield 70%. R_f 0.38 (hexane/EtOAc 3/2). ^{1}H NMR (270 MHz, $CDCl_3$): δ 1.82–1.97 (4H, m, (CH_2)$_2$CH$_2$Cl), 2.98–3.02 (1H, m, CHCH$_2$), 3.50 (2H, t, J=5.0 Hz, CH$_2$Cl), 3.68 (1H, d, J=14.9 Hz, (*H*CH)N), 3.79 (3H, s, OCH$_3$), 4.02 (1H, br s, NCH), 4.77 (1H, d, J=14.9 Hz, (HC*H*)N), 6.82 (2H, d, J=7.3 Hz, CH$_{ar}$), 7.04 (2H, d, J=7.3 Hz, CH$_{ar}$), 7.21–7.41 (5H, m, C_6H_5). ^{13}C NMR (68 MHz, $CDCl_3$): δ 25.9 and 30.1 ((*C*H$_2$)$_2$CH$_2$Cl), 43.8 (CH$_2$N), 44.5 (CH$_2$Cl), 55.3 (OCH$_3$), 59.7 (*C*HCH$_2$), 60.3 (NCH), 114.1, 126.5, 127.6, 128.5, 129.1 and 129.8 (CH$_{arom}$), 137.7 (C_q), 159.1 (C_q), 169.6 (C=O). IR (NaCl): ν=1748 cm^{-1} (C=O). MS (70 eV): *m/z* (%): 343/5 (8, M$^+$), 342/4 (30), 255 (10), 179/81 (100), 162 (36), 142 (18), 121 (63), 117 (53), 91 (13). Anal. Calcd for $C_{20}H_{22}ClNO_2$: C 69.86, H 6.45, N 4.07. Found: C 69.72, H 6.57, N 3.88.

3.2.5. trans-3-(3-Chloropropyl)-1-cyclohexyl-4-phenylazetidin-2-one ***2e***

Light-yellow oil. Yield 62%. R_f 0.53 (hexane/EtOAc 3/2). ^{1}H NMR (270 MHz, $CDCl_3$): δ 0.97–1.99 (14H, m, (CH_2)$_2$CH$_2$Cl and (CH$_2$)$_5$), 2.89–2.94 (1H, m, CHCH$_2$), 3.35–3.53 (1H, m, NCH), 3.51 (2H, t, J=5.0 Hz, CH$_2$Cl), 4.24 (1H, d, J=2.0 Hz, NCH), 7.28–7.39 (5H, m, C_6H_5). ^{13}C NMR (68 MHz, $CDCl_3$): δ 25.0, 25.15, 25.16, 30.7 and 31.4 (CH$_2$)$_5$), 26.0 and 30.0 ((*C*H$_2$)$_2$CH$_2$Cl), 44.6 (CH$_2$Cl), 52.6 (NCH), 58.8 (*C*HCH$_2$), 60.3 (NCH), 126.5, 128.4 and 128.9 (CH$_{arom}$), 139.4 (C_q), 170.1 (C=O). IR (NaCl): ν=1744 cm^{-1} (C=O). MS (70 eV): *m/z* (%): 305/7 (2, M$^+$), 180/2 (100), 122 (9), 117 (69), 115 (9), 91 (9), 73 (15). Anal. Calcd for $C_{18}H_{24}ClNO$: C 70.69, H 7.91, N 4.58. Found: C 70.77, H 8.17, N 4.74.

3.2.6. trans-3-(3-Chloropropyl)-1-isopropyl-4-(4-methylphenyl)azetidin-2-one ***2f***

Light-yellow oil. Yield 87%. R_f 0.45 (hexane/EtOAc 3/2). ^{1}H NMR (270 MHz, $CDCl_3$): δ 1.01 and 1.25 (2×3H, 2×d, J=6.6 Hz, CH(CH_3)$_2$), 1.81–1.99 (4H, m, (CH_2)$_2$CH$_2$Cl), 2.36 (3H, s, CH$_3$), 2.88–2.93 (1H, m, CHCH$_2$), 3.51 (2H, t, J=5.0 Hz, CH$_2$Cl), 3.76 (1H, septet, J=6.6 Hz, CHMe$_2$), 4.21 (1H, d, J=2.0 Hz, NCH), 7.18 and 7.25 (2×2H, 2×d, J=8.3 Hz, C_6H_4). ^{13}C NMR (68 MHz, $CDCl_3$): δ 20.4 and 21.17 (CH(*C*H$_3$)$_2$), 21.24 (CH$_3$), 25.9 and 30.1 ((*C*H$_2$)$_2$CH$_2$Cl), 44.6 (CH$_2$Cl), 44.8 (*C*HMe$_2$), 58.7 (*C*HCH$_2$), 60.1 (NCH), 126.5 and 129.6 (CH$_{arom}$), 136.2 and 138.3 (2×C_q), 170.0 (C=O). IR (NaCl): ν=1744 cm^{-1} (C=O). MS (70 eV): *m/z* (%): 279/81 (3, M$^+$), 193/5 (100), 146 (15), 130 (96), 91 (14). Anal. Calcd for $C_{16}H_{22}ClNO$: C 68.68, H 7.93, N 5.01. Found: C 68.53, H 7.82, N 4.87.

3.2.7. trans-3-(3-Chloropropyl)-1-isopropyl-4-(4-methoxyphenyl)azetidin-2-one ***2g***

Light-yellow oil. Yield 66%. R_f 0.33 (hexane/EtOAc 3/2). ^{1}H NMR (270 MHz, $CDCl_3$): δ 1.00 and 1.24 (2×3H, 2×d, J=6.6 Hz, CH(CH_3)$_2$), 1.82–2.00 (4H, m, (CH_2)$_2$CH$_2$Cl), 2.86–2.91 (1H, m, CHCH$_2$), 3.52 (2H, t, J=5.3 Hz, CH$_2$Cl), 3.75 (1H, septet, J=6.6 Hz, CHMe$_2$), 3.82 (3H, s, OCH$_3$), 4.18 (1H, d, J=2.0 Hz, NCH), 6.90 and 7.28 (2×2H, 2×d, J=8.6 Hz, C_6H_4). ^{13}C NMR (68 MHz, $CDCl_3$): δ 20.4 and 21.3 (CH(*C*H$_3$)$_2$), 25.9 and 30.1 ((*C*H$_2$)$_2$CH$_2$Cl), 44.6

(CH_2Cl), 44.7 ($CHMe_2$), 55.3 (OCH_3), 58.7 ($CHCH_2$), 59.7 (NCH), 114.3 and 127.7 (CH_{arom}), 131.2 (C_q), 159.7 (C_q), 169.9 (C=O). IR (NaCl): ν=1742 cm^{-1} (C=O). MS (70 eV): *m/z* (%): 295/7 (11, M^+), 218 (18), 210/2 (69), 176 (12), 162 (42), 147 (100), 134 (9), 117 (12), 115 (9), 91 (13). Anal. Calcd for $C_{16}H_{22}ClNO_2$: C 64.97, H 7.50, N 4.74. Found: C 65.06, H 7.68, N 4.89.

3.3. Synthesis of N-isopropyl-5-chloropentanamides **4**

5-Chloropentanamides **4** were obtained upon reaction of alkylideneamines **3** with 5-chloropentanoyl chloride applying the same reaction conditions as described for the synthesis of 3-(3-chloropropyl)-β-lactams **2**.

3.3.1. N-isopropyl-N-(2-Methylprop-1-enyl)-5-chloropentanamide **4a**

Light-yellow oil. Yield 63%. R_f 0.52 (hexane/EtOAc 3/2). ^{1}H NMR (270 MHz, $CDCl_3$): δ 1.04 (6H, d, J=6.6 Hz, $CH(CH_3)_2$), 1.59 and 1.80 (6H, 2×d, J=1.3 Hz, $C(CH_3)_2$), 1.70–1.84 (4H, m, $(CH_2)_2CH_2Cl$), 2.19 (2H, t, J=6.9 Hz, CH_2CO), 3.53 (2H, t, J=6.3 Hz, CH_2Cl), 4.82 (1H, septet, J=6.6 Hz, $CHMe_2$), 5.71 (1H, septet, J=1.3 Hz, C=CH). ^{13}C NMR (68 MHz, $CDCl_3$): δ 17.9 and 22.0 ($C(CH_3)_2$), 19.8 ($CH(CH_3)_2$), 22.5 and 32.2 ($(CH_2)_2CH_2Cl$), 33.3 (CH_2CO), 44.8 (CH_2Cl), 45.6 ($CHMe_2$), 119.28 (C=CH), 138.3 (C=CH), 172.1 (C=O). IR (NaCl): ν=1736, 1647 cm^{-1}. MS (70 eV): *m/z* (%): 231/3 (19, M^+), 216/8 (64, M^+-CH_3), 174/6 (10), 113 (57), 98 (100), 91 (15), 70 (10), 55 (37). Anal. Calcd for $C_{12}H_{22}ClNO$: C 62.19, H 9.57, N 6.04. Found: C 62.42, H 9.76, N 5.91.

3.3.2. N-Cyclohexylidenemethyl-N-isopropyl-5-chloropentanamide **4b**

Light-yellow oil. Yield 88%. R_f 0.49 (hexane/EtOAc 3/2). ^{1}H NMR (270 MHz, $CDCl_3$): δ 1.05 (6H, d, J=6.9 Hz, $CH(CH_3)_2$), 1.70–2.24 (16H, m, $(CH_2)_5$, $(CH_2)_2CH_2Cl$ and CH_2CO), 3.53 (2H, t, J=6.3 Hz, CH_2Cl), 4.82 (1H, septet, J=6.9 Hz, $CHMe_2$), 5.67 (1H, s, C=CH). ^{13}C NMR (68 MHz, $CDCl_3$): δ 19.9 ($CH(CH_3)_2$), 22.6, 26.4, 26.6, 28.0, 28.2, 32.3, 33.3 and 33.4 ($(CH_2)_5$, $(CH_2)_2CH_2Cl$ and CH_2CO), 44.8 (CH_2Cl), 45.3 ($CHMe_2$), 116.0 (C=CH), 145.1 (C=CH), 172.1 (C=O). IR (NaCl): ν=1735, 1646 cm^{-1}. MS (70 eV): *m/z* (%): no M^+, 270/2 (27), 236 (9, M^+-Cl), 227/9 (33), 179 (13), 152 (37), 151 (39), 137 (67), 119 (10), 118 (9), 111 (12), 110 (72), 95 (11), 93 (17), 91 (24), 82 (14), 67 (14), 55 (63). Anal. Calcd for $C_{15}H_{26}ClNO$: C 66.28, H 9.64, N 5.15. Found: C 66.37, H 9.80, N 5.02.

3.4. Synthesis of trans-methyl 1-alkyl-2-arylpiperidine-3-carboxylates **5a–d**

General procedure: Gaseous hydrochloric acid, generated by adding sulfuric acid dropwise to a mixture of sodium chloride and hydrochloric acid (CAUTION), was bubbled through a solution of 3-(3-chloropropyl)-β-lactam **2** (5 mmol) in methanol (15 mL) at 0 °C for 1 h, followed by a resting period of 24 h at room temperature in a closed vessel. Afterwards, methanol was removed in vacuo, followed by the addition of dichloromethane (25 mL) and triethylamine (20 mmol, 4 equiv). The resulting mixture was heated under reflux for 4 h, after which the solvent was removed in vacuo. Addition of diethyl ether, filtration of triethylamine hydrochloride, drying of the filtrate ($MgSO_4$), filtration of the drying agent and removal of the solvent in vacuo afforded the crude methyl 1-alkyl-2-arylpiperidine-3-carboxylate **5**, which was purified by means of column chromatography on silica gel (CH_2Cl_2/MeOH 95/5).

3.4.1. trans-Methyl 1-isopropyl-2-phenylpiperidine-3-carboxylate **5a**

Light-yellow oil. Yield 79%. R_f 0.20 (CH_2Cl_2/MeOH 95/5). ^{1}H NMR (270 MHz, $CDCl_3$): δ 0.94 and 0.97 (2×3H, 2×d, J=6.3 Hz, $CH(CH_3)_2$), 1.13–1.72 (4H, m, $(CH_2)_2CH_2N$), 2.53 (1H, septet, J=6.3 Hz, $CH(CH_3)_2$), 2.66–2.72 (1H, m, CHCOOMe), 3.20–3.40 (2H, m, CH_2N), 3.73 (3H, s, OCH_3), 3.85 (1H, d, J=9.9 Hz, NCH), 7.25–7.38 (5H, m, C_6H_5). ^{13}C NMR (68 MHz, $CDCl_3$): δ 21.3 and 23.9 ($CH(CH_3)_2$), 27.2 and 30.2 ($(CH_2)_2CH_2N$), 44.3 (CH_2N), 45.6 ($CHMe_2$), 51.8 (OCH_3), 52.3 (CHCOOMe), 62.2 (NCH), 127.5, 127.7 and 128.7 (CH_{arom}), 141.1 (C_q), 175.1 (C=O). IR (NaCl): ν=1738 cm^{-1} (C=O). MS (70 eV): *m/z* (%): 261 (12, M^+), 246 (92), 218 (12), 214 (10), 184 (13), 148 (100), 146 (11), 132 (30), 121 (11), 107 (24), 106 (11), 105 (13), 91 (23), 86 (15), 84 (22), 55 (10). Anal. Calcd for $C_{16}H_{23}NO_2$: C 73.53, H 8.87, N 5.36. Found: C 73.67, H 9.03, N 5.10.

3.4.2. trans-Methyl 1-benzyl-2-phenylpiperidine-3-carboxylate **5b**

Light-yellow oil. Yield 93%. R_f 0.83 (CH_2Cl_2/MeOH 95/5). ^{1}H NMR (270 MHz, $CDCl_3$): δ 1.22–1.35 and 1.49–1.65 (4H, 2×m, $(CH_2)_2CH_2N$), 2.65–2.73 (1H, m, CHCOOMe), 3.32–3.37 (2H, m, CH_2N), 3.42 and 3.63 (2×1H, 2×d, J=13.0 Hz, $N(HCH)C_6H_5$), 3.72 (3H, s, OCH_3), 3.74 (1H, d, J=8.0 Hz, NCH), 7.16–7.40 (10H, m, 2×C_6H_5). ^{13}C NMR (68 MHz, $CDCl_3$): δ 27.2 and 30.3 ($(CH_2)_2CH_2N$), 44.2 (CH_2N), 50.7 ($NCH_2C_6H_5$), 51.7 (OCH_3), 52.4 (CHCOOMe), 63.9 (NCH), 127.6, 127.8, 128.2, and 128.8 (CH_{arom}), 139.7 and 140.5 (2×C_q), 175.0 (C=O). IR (NaCl): ν=1736 cm^{-1} (C=O). MS (70 eV): *m/z* (%): 309 (16, M^+), 262 (11), 247 (100), 239 (19), 235 (11), 232 (12), 218 (40), 214 (12), 194 (21), 184 (19), 174 (13), 146 (11), 138 (16), 132 (20), 115 (13), 111 (15), 106 (15), 104 (15), 97 (38), 91 (64), 82 (18), 79 (14), 77 (13), 65 (16), 57 (78), 55 (18). Anal. Calcd for $C_{20}H_{23}NO_2$: C 77.64, H 7.49, N 4.53. Found: C 77.79, H 7.72, N 4.61.

3.4.3. trans-Methyl 1-isopropyl-2-(4-methylphenyl)-piperidine-3-carboxylate **5c**

Light-yellow oil. Yield 89%. R_f 0.53 (CH_2Cl_2/MeOH 95/5). ^{1}H NMR (270 MHz, $CDCl_3$): δ 0.91 and 0.94 (2×3H, 2×d, J=6.3 Hz, $CH(CH_3)_2$), 1.21–1.69 (4H, m, $(CH_2)_2CH_2N$), 2.34 (3H, s, CCH_3), 2.50 (1H, septet, J=6.3 Hz, $CH(CH_3)_2$), 2.60–2.66 (1H, m, CHCOOMe), 3.33–3.40 (2H, m, CH_2N),

3.73 (3H, s, OCH_3), 3.78 (1H, d, J=9.9 Hz, NCH), 7.12 and 7.15 (2×2H, 2×d, J=8.0 Hz, C_6H_4). ^{13}C NMR (68 MHz, $CDCl_3$): δ 21.4 (CCH_3), 21.7 and 24.3 ($CH(CH_3)_2$), 27.5 and 30.6 (($CH_2)_2CH_2N$), 44.5 (CH_2N), 45.6 ($CHMe_2$), 51.8 (OCH_3), 53.0 ($CHCOOMe$), 62.1 (NCH), 127.6 and 129.6 (CH_{arom}), 137.3 and 138.5 (2×C_q), 175.4 (C=O). IR (NaCl): ν=1736 cm^{-1} (C=O). MS (70 eV): *m/z* (%): 275 (7, M^+), 260 (37), 162 (34), 119 (14), 115 (13), 103 (15), 91 (10), 86 (66), 84 (100), 83 (13), 73 (18), 59 (75), 56 (18), 55 (21), 51 (16), 49 (47). Anal. Calcd for $C_{17}H_{25}NO_2$: C 74.14, H 9.15, N 5.09. Found: C 73.98, H 9.37, N 4.91.

3.4.4. *trans*-Methyl 1-isopropyl-2-(4-methoxyphenyl)-piperidine-3-carboxylate **5d**

Light-yellow oil. Yield 82%. R_f 0.36 (CH_2Cl_2/MeOH 95/5). ^1H NMR (270 MHz, $CDCl_3$): δ 0.88 and 0.92 (2×3H, 2×d, J=6.3 Hz, $CH(CH_3)_2$), 1.22–1.64 (4H, m, $(CH_2)_2CH_2N$), 2.50 (1H, septet, J=6.3 Hz, $CH(CH_3)_2$), 2.45–2.60 (1H, m, $CHCOOMe$), 3.35–3.42 (2H, m, CH_2N), 3.72 (3H, s, OCH_3), 3.75 (1H, d, J=9.9 Hz, NCH), 3.79 (3H, s, OCH_3), 6.87 and 7.13 (2×2H, 2×d, J=8.6 Hz, C_6H_4). ^{13}C NMR (68 MHz, $CDCl_3$): δ 21.6 and 24.2 ($CH(CH_3)_2$), 27.2 and 30.4 (($CH_2)_2CH_2N$), 44.3 (CH_2N), 45.2 ($CHMe_2$), 51.5 (OCH_3), 53.1 ($CHCOOMe$), 55.2 (OCH_3), 61.6 (NCH), 123.9 and 128.3 (CH_{arom}), 133.8 (C_q), 158.9 (C_q), 175.2 (C=O). IR (NaCl): ν=1732 cm^{-1} (C=O). MS (70 eV): *m/z* (%): 291 (7, M^+), 276 (20), 211 (10), 204 (29), 178 (100), 176 (17), 162 (25), 151 (14), 136 (33), 134 (17), 124 (13), 121 (21), 84 (17). Anal. Calcd for $C_{17}H_{25}NO_3$: C 70.07, H 8.65, N 4.81. Found: C 70.21, H 8.82, N 4.95.

3.5. Synthesis of piperidine-1,3-dicarboxylates **6a–c**

Two different approaches were used for the synthesis of piperidine-1,3-dicarboxylates **6**.

3.5.1. Synthesis of piperidine-1,3-dicarboxylates **6a–b**

General procedure: To a refluxing solution of 2-phenyl-3-piperidinecarboxylate **5** (3.2 mmol) in benzene (10 mL) was added slowly a solution of alkyl chloroformate (32.4 mmol) in benzene (5 mL). This mixture was refluxed overnight (15 h) and the solvent was evaporated in vacuo, affording the corresponding 2-phenylpiperidine-l,3-dicarboxylate **6**. Piperidine **6** was purified by means of column chromatography on silica gel (hexane/EtOAc 3/2) or by recrystallization from methanol.

3.5.1.1. *trans*-Methyl 1-methoxycarbonyl-2-phenylpiperidine-3-carboxylate **6a**

Light-yellow oil. Yield 56%. R_f 0.58 (hexane/EtOAc 3/2). ^1H NMR (270 MHz, $CDCl_3$): δ 1.51–1.62 and 1.64–1.79 (4H, 2×m, $(CH_2)_2CH_2N$), 3.45 (2H, t, J=6.3 Hz, CH_2N), 3.50–3.59 (1H, m, $CHCOOMe$), 3.73 (6H, s, 2×OCH_3), 5.32 (1H, d, J=11.0 Hz, NCH), 7.30–7.39 (5H, m, C_6H_5). ^{13}C NMR (68 MHz, $CDCl_3$): δ 27.8 and 30.2 (($CH_2)_2CH_2N$), 44.1 (CH_2N), 48.1 ($CHCOOMe$), 51.7 and 52.1 (2×OCH_3), 61.8 (NCH), 128.0, 128.6 and 128.7 (CH_{arom}), 138.0 (C_q), 157.3 (C=O), 174.2 (C=O). IR (NaCl): ν=1735, 1694 cm^{-1} (2×C=O). MS (70 eV): *m/z* (%): no M^+, 205 (100), 164 (39), 121 (26), 91 (9). Anal. Calcd for $C_{15}H_{19}NO_4$: C 64.97, H 6.91, N 5.05. Found: C 65.12, H 7.15, N 4.92.

3.5.1.2. *trans*-Methyl 1-ethoxycarbonyl-2-phenylpiperidine-3-carboxylate **6b**

Colourless crystals. Mp 97.5–98.1 °C. Yield 50%. Recrystallized from methanol. ^1H NMR (270 MHz, $CDCl_3$): δ 1.21–1.78 (4H, m, $(CH_2)_2CH_2N$), 1.76 (3H, t, J=6.0 Hz, OCH_2CH_3), 3.44 (2H, t, J=6.3 Hz, CH_2N), 3.45–3.58 (1H, m, $CHCOOMe$), 3.65 (3H, s, OCH_3), 4.12 (2H, m, OCH_2CH_3), 5.16 (1H, d, J=11.0 Hz, NCH), 7.21–7.42 (5H, m, C_6H_5). ^{13}C NMR (68 MHz, $CDCl_3$): δ 14.5 (OCH_2CH_3), 27.7 and 30.1 (($CH_2)_2CH_2N$), 44.0 (CH_2N), 46.5 ($CHCOOMe$), 49.3 (OCH_2CH_3), 51.8 (OCH_3), 62.9 (NCH), 127.9, 128.6 and 128.9 (CH_{arom}), 138.0 (C_q), 156.2 (C=O), 174.0 (C=O). IR (NaCl): ν=1732, 1682 cm^{-1} (2×C=O). MS (70 eV): *m/z* (%): no M^+, 219 (12), 194 (13), 132 (14), 131 (24), 121 (14), 119 (21), 115 (24), 114 (12), 106 (16), 91 (29), 88 (13), 87 (21), 86 (67), 84 (100), 83 (10), 82 (10), 74 (9), 73 (9), 59 (15), 55 (36), 51 (10), 49 (29). Anal. Calcd for $C_{16}H_{21}NO_4$: C 65.96, H 7.27, N 4.81. Found: C 65.78, H 7.40, N 4.95.

3.5.2. Synthesis of 2-phenylpiperidine-1,3-dicarboxylate **6c**

trans-1-Benzyl-3-(3-chloropropyl)-4-phenylazetidin-2-one **2c** (2.00 g, 6.4 mmol) was hydrolyzed by means of gaseous hydrochloric acid in methanol according to the procedure described for the synthesis of 2-arylpiperidine-3-carboxylates **5**. After evaporation of methanol and residual hydrochloric acid, ethyl acetate (30 mL) was added from which the obtained ammonium salt precipitated. After filtration and additional drying under reduced pressure, the intermediate hydrochloride salt was used in a catalytic hydrogenolysis protocol. Thus, 10 weight% of palladium on carbon (10%) was added to a 10% solution of the substrate in absolute methanol, and the resulting mixture was stirred for 15 h in a Parr apparatus under pressure (5 bar of hydrogen gas). After filtration over Celite® and evaporation of the solvent, sodium hydroxide (30 mL, 1 M) was added. The aqueous phase was extracted with dichloromethane (3×30 mL), and the combined organic layers were dried (magnesium sulfate). The residue obtained after filtration and evaporation of the solvent was dissolved in acetonitrile (20 mL). Addition of di-*tert*-butyl dicarbonate (1.39 g, 6.4 mmol), stirring of the reaction mixture for 2 h at room temperature and removal of the solvent in vacuo furnished 2-phenylpiperidine-1,3-dicarboxylate **6c**, which was purified by means of column chromatography on silica gel (hexane/EtOAc 3/2) and recrystallization from ethanol.

3.5.2.1. *trans*-Methyl 1-*tert*-butoxycarbonyl-2-phenylpiperidine-3-carboxylate **6c**

Colourless crystals. Mp 111.4–111.7 °C. Yield 64%. Column chromatography, R_f 0.65 (hexane/EtOAc 3/2) and recrystallization from ethanol. ^1H NMR (270 MHz, $CDCl_3$): δ 1.24–1.43 and 1.61–1.91 (4H, 2×m, $(CH_2)_2CH_2N$), 1.43 (9H, s, $C(CH_3)_3$), 2.82–2.84 (1H, m, $CHCOOMe$), 3.52 (2H, m, CH_2N), 3.55 (3H, s, OCH_3), 4.93–4.95 (1H, m, NCH), 7.20–7.35 (5H, m, C_6H_5). ^{13}C NMR (68 MHz, $CDCl_3$):

δ 27.6 and 30.3 ((*C*H$_2$)$_2$CH$_2$N), 28.3 (C(*C*H$_3$)$_3$), 44.3 (CH$_2$N), 50.6 (*C*HCOOMe), 51.8 (OCH$_3$), 55.1 (NCH), 79.6 (*C*(CH$_3$)$_3$), 126.0, 127.5 and 128.6 (CH$_{arom}$), 140.8 (C$_q$), 155.4 (C=O), 174.6 (C=O). IR (NaCl): ν=1737, 1690 cm^{-1} (2×C=O). MS (70 eV): *m/z* (%): no M$^+$, 304 (28, M$^+$−OMe), 276 (12), 256 (44), 239 (100), 121 (98). Anal. Calcd for C$_{16}$H$_{21}$NO$_4$: C 67.69, H 7.89, N 4.39. Found: C 67.53, H 8.13, N 4.17.

3.6. Synthesis of cis-methyl 1-alkyl-2-arylpiperidine-3-carboxylates *7a–d*

The synthesis of *cis*-methyl 1-isopropyl-2-phenylpiperidine-3-carboxylate **7a** is described as a representative example. To a stirred solution of *trans*-methyl 1-isopropyl-2-phenylpiperidine-3-carboxylate **5a** (1.00 g, 3.8 mmol) in methanol (5 mL) at room temperature, hydrazine monohydrate (1.92 g, 38.4 mmol) was added and the resulting mixture was kept at reflux temperature for 4 h. Subsequently, methanol was evaporated in vacuo and the residue was dissolved in dichloromethane (15 mL) and dried (magnesium sulfate). After filtration and evaporation of the solvent, the crude *cis*-methyl 1-*iso*propyl-2-phenylpiperidine-3-carboxylate **7a** was obtained, which was purified by column chromatography on silica gel (CH$_2$Cl$_2$/MeOH 95/5).

3.6.1. cis-Methyl 1-isopropyl-2-phenylpiperidine-3-carboxylate *7a*

Light-yellow oil. Yield 67%. R_f 0.26 (CH$_2$Cl$_2$/MeOH 95/5). ^{1}H NMR (270 MHz, CDCl$_3$): δ 0.81 and 0.97 (2×3H, 2×d, *J*=6.6 Hz, CH(C*H*$_3$)$_2$), 1.57−1.73 and 1.97−2.19 (4H, 2×m, (C*H*$_2$)$_2$CH$_2$N), 2.39−2.48 (1H, m, (*H*CH)N), 2.85−3.03 (3H, m, C*H*(CH$_3$)$_2$, (HC*H*)N, C*H*COOMe), 3.32 (3H, s, OCH$_3$), 3.97 (1H, d, *J*=5.0 Hz, NCH), 7.19−7.34 (5H, m, C$_6$H$_5$). ^{13}C NMR (68 MHz, CDCl$_3$): δ 15.2 and 20.9 (CH(*C*H$_3$)$_2$), 22.6 and 24.4 ((*C*H$_2$)$_2$CH$_2$N), 42.6 (CH$_2$N), 46.6 (*C*HCOOMe), 49.7 (*C*HMe$_2$), 50.8 (OCH$_3$), 64.5 (NCH), 127.0, 128.0 and 128.6 (CH$_{arom}$), 141.5 (C$_q$), 173.7 (C=O). IR (NaCl): ν=1740 cm^{-1} (C=O). MS (70 eV): *m/z* (%): 261 (15, M$^+$), 246 (100), 218 (12), 214 (8), 184 (15), 174 (11), 132 (17), 106 (11), 91 (12), 86 (13), 84 (19), 49 (13). Anal. Calcd for C$_{16}$H$_{23}$NO$_2$: C 73.53, H 8.87, N 5.36. Found: C 73.75, H 9.08, N 5.22.

3.6.2. cis-Methyl 1-benzyl-2-phenylpiperidine-3-carboxylate *7b*

Light-yellow oil. Yield 70%. R_f 0.80 (CH$_2$Cl$_2$/MeOH 95/5). ^{1}H NMR (270 MHz, CDCl$_3$): δ 1.50−1.77 and 2.01−2.17 (4H, 2×m, (C*H*$_2$)$_2$CH$_2$N), 2.17−2.20 (1H, m, (*H*CH)N), 2.91−2.97 (1H, m, C*H*COOMe), 2.95−3.02 (1H, m, (HC*H*)N), 3.10 and 3.72 (2×1H, 2×d, *J*=13.9 Hz, N(*H*C*H*)C$_6$H$_5$), 3.34 (3H, s, OCH$_3$), 3.74 (1H, d, *J*=5.0 Hz, NCH), 7.18−7.39 (10H, m, 2×C$_6$H$_5$). ^{13}C NMR (68 MHz, CDCl$_3$): δ 22.1 and 25.1 ((*C*H$_2$)$_2$CH$_2$N), 46.5 (*C*HCOOMe), 50.5 (CH$_2$N), 50.8 (OCH$_3$), 59.3 (N*C*H$_2$C$_6$H$_5$), 66.8 (NCH), 126.6, 127.2, 128.0, 128.36 and 128.43 (CH$_{arom}$), 139.1 and 140.6 (2×C$_q$), 173.4 (C=O). IR (NaCl): ν=1738 cm^{-1} (C=O). MS (70 eV): *m/z* (%): 309 (32, M$^+$), 308 (28), 232 (43), 222 (34), 218 (100), 194 (43), 149 (15), 105 (13), 91 (47), 57 (9). Anal. Calcd for C$_{20}$H$_{23}$NO$_2$: C 77.64, H 7.49, N 4.53. Found: C 77.83, H 7.67, N 4.36.

3.6.3. cis-Methyl 1-isopropyl-2-(4-methylphenyl)-piperidine-3-carboxylate *7c*

Light-yellow oil. Yield 56%. R_f 0.18 (CH$_2$Cl$_2$/MeOH 95/5). ^{1}H NMR (270 MHz, CDCl$_3$): δ 0.82 and 0.97 (2×3H, 2×d, *J*=6.6 Hz, CH(C*H*$_3$)$_2$), 1.56−1.70 and 1.97−2.17 (4H, 2×m, (C*H*$_2$)$_2$CH$_2$N), 2.31 (3H, s, CCH$_3$), 2.41−2.50 (1H, m, (*H*CH)N), 2.84−3.02 (3H, m, C*H*(CH$_3$)$_2$, (HC*H*)N, C*H*COOMe), 3.67 (3H, s, OCH$_3$), 3.97 (1H, d, *J*=5.3 Hz, NCH), 7.07 and 7.20 (2×2H, 2×d, *J*=8.0 Hz, C$_6$H$_4$). ^{13}C NMR (68 MHz, CDCl$_3$): δ 15.6 and 21.1 (CH(*C*H$_3$)$_2$), 20.9 (C*C*H$_3$), 22.8 and 24.2 ((*C*H$_2$)$_2$CH$_2$N), 42.6 (CH$_2$N), 46.6 (*C*HCOOMe), 49.8 (*C*HMe$_2$), 50.9 (OCH$_3$), 64.0 (NCH), 128.6 and 128.7 (CH$_{arom}$), 136.5 and 138.3 (2×C$_q$), 173.9 (C=O). IR (NaCl): ν=1739 cm^{-1} (C=O). MS (70 eV): *m/z* (%): 275 (23, M$^+$), 260 (100), 232 (14), 228 (15), 188 (11), 184 (15), 160 (11), 146 (14). Anal. Calcd for C$_{17}$H$_{25}$NO$_2$: C 74.14, H 9.15, N 5.09. Found: C 74.36, H 9.30, N 4.87.

3.6.4. cis-Methyl 1-isopropyl-2-(4-methoxyphenyl)-piperidine-3-carboxylate *7d*

Light-yellow oil. Yield 78%. R_f 0.28 (CH$_2$Cl$_2$/MeOH 95/5). ^{1}H NMR (270 MHz, CDCl$_3$): δ 0.82 and 0.96 (2×3H, 2×d, *J*=6.3 Hz, CH(C*H*$_3$)$_2$), 1.54−1.75 and 1.95−2.16 (4H, 2×m, (C*H*$_2$)$_2$CH$_2$N), 2.41−2.50 (1H, m, (*H*CH)N), 2.83−3.01 (3H, m, C*H*(CH$_3$)$_2$, (HC*H*)N, C*H*COOMe), 3.37 (3H, s, OCH$_3$), 3.78 (3H, s, OCH$_3$), 3.98 (1H, d, *J*=5.0 Hz, NCH), 6.80 and 7.24 (2×2H, 2×d, *J*=8.6 Hz, C$_6$H$_4$). ^{13}C NMR (68 MHz, CDCl$_3$): δ 15.7 and 20.8 (CH(*C*H$_3$)$_2$), 22.8 and 24.0 ((*C*H$_2$)$_2$CH$_2$N), 42.5 (CH$_2$N), 46.7 (*C*HCOOMe), 49.8 (*C*HMe$_2$), 50.9 (OCH$_3$), 55.1 (OCH$_3$), 63.5 (NCH), 113.3 and 129.8 (CH$_{arom}$), 133.3 (C$_q$), 158.5 (C$_q$), 173.8 (C=O). IR (NaCl): ν=1736 cm^{-1} (C=O). MS (70 eV): *m/z* (%): 291 (38, M$^+$), 276 (100), 248 (25), 244 (31), 204 (29), 190 (11), 184 (14), 176 (37), 162 (35), 148 (10), 134 (16), 121 (25), 115 (9), 91 (11). Anal. Calcd for C$_{17}$H$_{25}$NO$_3$: C 70.07, H 8.65, N 4.81. Found: C 70.29, H 8.91, N 4.66.

3.6.5. trans-3-(3-Chloropropyl)-4-phenylazetidin-2-one *8*

A solution of potassium hydrogenphosphate (13.16 g, 75.6 mmol) and potassium peroxodisulfate (40.84 g, 151.1 mmol) in water (240 mL) was added in four portions to a solution of *trans*-3-(3-chloropropyl)-1-(4-methoxybenzyl)-4-phenylazetidin-2-one **2d** (7.63 g, 22.2 mmol) in water/acetonitrile (1/2, 715 mL). The solution was kept at reflux for 1 h, and was subsequently concentrated at reduced pressure and extracted with ethyl acetate (3×150 mL). The organic layers were washed with saturated sodium bicarbonate (500 mL) and brine (500 mL), and the aqueous layers were extracted with ethyl acetate (200 mL). Drying of the combined organic layers (magnesium sulfate), filtration and evaporation of the solvent yielded crude *trans*-3-(3-chloropropyl)-4-phenylazetidin-2-one **8**, which was purified by column chromatography on silica gel (hexane/EtOAc 3/2).

Light-yellow oil. Yield 70%. R_f 0.28 (hexane/EtOAc 3/2). ^{1}H NMR (270 MHz, $CDCl_3$): δ 1.86–2.05 (4H, m, $(CH_2)_2CH_2Cl$), 2.98–3.04 (1H, m, $CHCH_2$), 3.55 (2H, t, J=6.0 Hz, CH_2Cl), 4.40 (1H, d, J=2.3 Hz, NCH), 6.63 (1H, br s, NH), 7.27–7.41 (5H, m, C_6H_5). ^{13}C NMR (68 MHz, $CDCl_3$): δ 26.0 and 30.0 ($(CH_2)_2CH_2Cl$), 44.6 (CH_2Cl), 57.5 ($CHCH_2$), 60.8 (NCH), 125.6, 128.2 and 128.9 (CH_{arom}), 139.8 (C_q), 171.1 (C=O). IR (NaCl): ν=1751 cm^{-1} (C=O). MS (70 eV): *m/z* (%): 223/5 (9, M^+), 182 (27), 180 (83), 160 (13), 132 (13), 129 (10), 117 (100), 116 (12), 115 (34), 106 (63), 105 (18), 104 (30), 91 (27), 77 (21), 55 (24), 51 (11). Anal. Calcd for $C_{12}H_{14}ClNO$: C 64.43, H 6.31, N 6.26. Found: C 64.30, H 6.54, N 6.38.

3.6.6. trans-1-tert-Butoxycarbonyl-3-(3-chloropropyl)-4-phenylazetidin-2-one **9**

To a solution of *trans*-3-(3-chloropropyl)-4-phenylazetidin-2-one **8** (4.96 g, 22.2 mmol) in dichloromethane (200 mL) was added di-*tert*-butyl dicarbonate (9.69 g, 44.4 mmol), triethylamine (2.25 g, 22.2 mmol) and 4-(*N*,*N*-dimethylamino)pyridine (1 mmol). The resulting reaction mixture was then stirred for 4 h at room temperature. Afterwards, diethyl ether (150 mL) was added and the resulting solution was successively washed with brine (150 mL), saturated ammonium chloride (75 mL) and again brine (150 mL). The organic layer was dried (magnesium sulfate), the drying agent removed by filtration and the solvent was removed in vacuo. Further purification was performed by means of column chromatography on silica gel (hexane/EtOAc 3/2).

Light-yellow oil. Yield 75%. R_f 0.62 (hexane/EtOAc 3/2). ^{1}H NMR (270 MHz, $CDCl_3$): δ 1.36 (9H, s, $C(CH_3)_3$), 1.91–2.05 (4H, m, $(CH_2)_2CH_2Cl$), 3.05–3.06 (1H, m, $CHCH_2$), 3.53 (2H, t, J=5.9 Hz, CH_2Cl), 4.60 (1H, d, J=3.0 Hz, NCH), 7.32–7.40 (5H, m, C_6H_5). ^{13}C NMR (68 MHz, $CDCl_3$): δ 25.8 and 29.9 ($(CH_2)_2CH_2Cl$), 27.8 ($C(CH_3)_3$), 44.3 (CH_2Cl), 58.8 ($CHCH_2$), 60.7 (NCH), 83.2 ($C(CH_3)_3$), 125.8, 128.5 and 128.9 (CH_{arom}), 137.9 (C_q), 147.4 (C=O), 167.6 (C=O). IR (NaCl): ν=1805, 1721 cm^{-1} (2×C=O). MS (70 eV): *m/z* (%): no M^+, 182 (39), 180 (100), 132 (39), 118 (12), 117 (76), 115 (14), 91 (13), 77 (9), 57 (30). Anal. Calcd for $C_{17}H_{22}ClNO_3$: C 63.06, H 6.85, N 4.33. Found: C 63.24, H 7.07, N 4.49.

3.6.7. trans-tert-Butyl 3-{[(4-methoxybenzyl)amino]-carbonyl}-2-phenylpiperidine-1-carboxylate **10**

The conversion of *trans*-1-(*tert*-butoxycarbonyl)-3-(3-chloropropyl)-4-phenylazetidin-2-one **9** into *trans-tert*-butyl 3-{[(4-methoxybenzyl)amino]carbonyl}-2-phenylpiperidine-1-carboxylate **10** was performed in one pot through a sequence of different reaction steps.

To a solution of *trans*-1-(*tert*-butoxycarbonyl)-3-(3-chloropropyl)-4-phenylazetidin-2-one **9** (5.40 g, 16.7 mmol) in dichloromethane (30 mL) was added 4-methoxybenzylamine (4.57 g, 33.4 mmol), after which the resulting reaction mixture was kept under gentle reflux overnight (16 h). Subsequently, the solvent was removed in vacuo and the residue was dissolved in dichloromethane (60 mL), to which trifluoroacetic acid (31.60 g, 277.1 mmol) was added. This solution was stirred at room temperature for 1 h and was subsequently cooled to 0 °C, followed by the addition of a sodium hydroxide solution (2 M) until pH 10. The organic layer was removed and the remaining aqueous layer was extracted with dichloromethane (2×30 mL). The combined organic layers were dried (magnesium sulfate), and after filtration and evaporation the crude reaction product was obtained. The latter was dissolved in dichloromethane (50 mL), to which di-*tert*-butyl dicarbonate (5.47 g, 25.0 mmol), triethylamine (1.69 g, 16.7 mmol) and one crystal of DMAP were added subsequently. The resulting solution was stirred for 4 h at room temperature, and workup proceeded as described before for the synthesis of β-lactam **9**, affording piperidine **10** in 75% yield after purification by column chromatography on silica gel (hexane/EtOAc 3/2).

Light-yellow oil. Yield 75%. R_f 0.28 (hexane/EtOAc 3/2). ^{1}H NMR (270 MHz, $CDCl_3$): δ 1.42 (9H, s, $C(CH_3)_3$), 1.64–2.05 (4H, m, $(CH_2)_2CH_2N$), 2.40–2.44 (1H, m, $CHCON$), 3.55 (2H, t, J=5.9 Hz, CH_2N), 3.77 (3H, s, OCH_3), 4.05 (1H, d×d, J=14.5, 4.6 Hz, N(HCH)Ar), 4.19 (1H, d×d, J=14.5, 5.9 Hz, N(HCH)Ar), 4.88 (1H, d, J=8.1 Hz, NCH), 5.30–5.40 (1H, br s, NH), 6.95–7.30 (9H, m, CH_{arom}). ^{13}C NMR (68 MHz, $CDCl_3$): δ 28.2 and 30.4 ($(CH_2)_2CH_2N$), 28.4 ($C(CH_3)_3$), 42.7 (CH_2NH), 44.6 (CH_2N), 52.0 ($CHCON$), 55.3 (OCH_3), 55.7 (NCH), 79.3 ($C(CH_3)_3$), 113.9, 125.8, 127.2, 128.6 and 128.8 (CH_{arom}), 129.4 and 141.6 (2×C_q), 155.8 (C_q), 158.8 (C=O), 173.1 (C=O). IR (NaCl): ν=1682, 1647 cm^{-1} (2×C=O). MS (70 eV): *m/z* (%): no M^+, 124 (100), 96 (9), 84 (11). Anal. Calcd for $C_{25}H_{32}N_2O_4$: C 70.73, H 7.60, N 6.60. Found: C 70.58, H 7.84, N 6.77.

Acknowledgements

The authors are indebted to the 'Fund for Scientific Research—Flanders (Belgium)' (F.W.O.—Vlaanderen) and to Ghent University (GOA) for financial support.

References and notes

1. Ojima, I.; Delaloge, F. *Chem. Soc. Rev.* **1997**, 377.
2. (a) Ojima, I. *Acc. Chem. Res.* **1995**, *28*, 383; (b) Fisher, J. F.; Meroueh, S. O.; Mobashery, S. *Chem. Rev.* **2005**, *105*, 395; (c) Alcaide, B.; Almendros, P. *Synlett* **2002**, 381; (d) Singh, G. S. *Tetrahedron* **2003**, *59*, 7631; (e) France, S.; Weatherwax, A.; Taggi, A. E.; Lectka, T. *Acc. Chem. Res.* **2004**, *37*, 592; (f) Alcaide, B.; Almendros, P.; Aragoncillo, C. *Chem. Rev.* **2007**, *107*, 4437.
3. (a) Begley, M. J.; Crombie, L.; Haigh, D.; Jones, R. C. F.; Osborne, S.; Webster, R. A. B. *J. Chem. Soc., Perkin Trans. 1* **1993**, 2027; (b) Crombie, L.; Jones, R. C. F.; Osborne, S.; Mat-Zin, A. R. *J. Chem. Soc., Chem. Commun.* **1983**, 959; (c) Van Brabandt, W.; Vanwalleghem, M.; D'hooghe, M.; De Kimpe, N. *J. Org. Chem.* **2006**, *71*, 7083.
4. (a) Leemans, E.; D'hooghe, M.; Dejaegher, Y.; Törnroos, K. W.; De Kimpe, N. *J. Org. Chem.* **2008**, *73*, 1422; (b) Van Brabandt, W.; Van Landeghem, R.; De Kimpe, N. *Org. Lett.* **2006**, *8*, 1105; (c) Van Brabandt, W.; Dejaegher, Y.; Van Landeghem, R.; De Kimpe, N. *Org. Lett.* **2006**, *8*,

1101; (d) Lee, E.; Kim, S. K.; Kim, J. Y.; Lim, J. *Tetrahedron Lett*. **2000**, *41*, 5915.
5. Desai, M. C.; Lefkowitz, S. L.; Thadeio, P. F.; Longo, K. P.; Snider, R. M. *J. Med. Chem*. **1992**, *35*, 4911.
6. (a) Harrison, T.; Williams, B. J.; Swain, C. J.; Ball, R. G. *Bioorg. Med. Chem. Lett*. **1994**, *4*, 2545; (b) Calvez, O.; Langlois, N. *Tetrahedron Lett*. **1999**, *40*, 7099; (c) Chandrasekhar, S.; Mohanty, P. K. *Tetrahedron Lett.* **1999**, *40*, 5071; (d) Rupniak, N. M. J. *Neurotransmissions* **1999**, *15*, 3.
7. Sutton, J. C.; Bolton, S. A.; Hartl, K. S.; Huang, M.-H.; Jacobs, G.; Meng, W.; Ogletree, M. L.; Pi, Z.; Schumacher, W. A.; Seiler, S. M.; Slusarchyk, W. A.; Treuner, U.; Zahler, R.; Zhao, G.; Bisacchi, G. S. *Bioorg. Med. Chem. Lett.* **2002**, *12*, 3229.
8. De Risi, C.; Fanton, G.; Pollini, G. P.; Trapella, C.; Valente, F.; Zanirato, V. *Tetrahedron: Asymmetry* **2008**, *19*, 131.
9. Hannam, J. C.; Kulagowski, J. J.; Madin, A.; Ridgill, M. P.; Seward, E. M. PCT Int. Appl. 2006, WO 2006043064 A1; *Chem. Abstr*. **2006**, *144*, 432693.
10. Tanaka, R.; Rubio, A.; Harn, N. K.; Gernert, D.; Grese, T. A.; Eishima, J.; Hara, M.; Yoda, N.; Ohashi, R.; Kuwabara, T.; Soga, S.; Akinaga, S.; Nara, S.; Kanda, Y. *Bioorg. Med. Chem*. **2007**, *15*, 1363.
11. (a) Barrow, K. D.; Spotswood, T. M. *Tetrahedron Lett*. **1965**, *6*, 3325; (b) Decazes, J.; Luche, J. L.; Kagan, H. B. *Tetrahedron Lett*. **1970**, *11*, 3365.
12. Van Driessche, B.; Van Brabandt, W.; D'hooghe, M.; Dejaegher, Y.; De Kimpe, N. *Tetrahedron* **2006**, *62*, 6882.
13. Pedersen, C. M.; Bols, M. *Tetrahedron* **2005**, *61*, 115.
14. Gyonfalvi, S.; Szakonyi, Z.; Fülöp, F. *Tetrahedron: Asymmetry* **2003**, *14*, 3965.
15. For a few recent examples, see: (a) Alcaide, B.; Almendros, P.; Cabrero, G.; Ruiz, M. P. *J. Org. Chem*. **2007**, *72*, 7980; (b) De Vitis, L.; Troisi, L.; Granito, C.; Pindinelli, E.; Ronzini, L. *Eur. J. Org. Chem*. **2007**, 356; (c) Mishra, R. K.; Coates, C. M.; Revell, K. D.; Turos, E. *Org. Lett*. **2007**, *9*, 575.
16. Cavagna, F.; Linkies, A.; Pietsch, H.; Reuschling, D. *Angew. Chem*. **1980**, *92*, 126.
17. (a) Basha, A.; Lipton, M.; Weinreb, S. M. *Tetrahedron Lett*. **1977**, *18*, 4171; (b) Levin, J. I.; Turos, E.; Weinreb, S. M. *Synth. Commun*. **1982**, *12*, 989.
18. Jean, L.; Baglin, I.; Rouden, J.; Maddaluno, J.; Lasne, M.-C. *Tetrahedron Lett*. **2001**, *42*, 5645.
19. Lapuyade, G.; Schlewer, G.; Wermuth, C. G. *Bull. Soc. Chim. Fr*. **1986**, 663.
20. Schmidt, E. W. *Hydrazine and its Derivatives: Preparation, Properties, Applications*; Wiley-Interscience: New York, NY, 1984.
21. Allen, M. P.; Blake, J. F.; Bryce, D. K.; Haggan, M. E.; Liras, S.; McLean, S.; Segelstein, B. E. *Bioorg. Med. Chem. Lett*. **2000**, *10*, 523.