A straightforward synthesis of 3-substituted azetidinic amino acids

Mangaleswaran Sivaprakasham,[a] François Couty,[a,*] Gwilherm Evano,[a] B. Srinivas,[b] R. Sridhar,[b] and K. Rama Rao[b]

[a] *Institut Lavoisier, UMR 8180, Université de Versailles, 45, avenue des Etats-Unis, 78035, Versailles Cedex, France*

[b] *Organic Chemistry Division-I, Indian Institute of Chemical Technology, Hyderabad-500 007, India*

E-Mail: couty@chimie.uvsq.fr

Dedicated to Professor A. Krief on the occasion of his 65th anniversary

Abstract

A series of enantiomerically pure *N*,*N*-disubstituted β-amino alcohols were chlorinated by treatment with thionyl chloride. This reaction afforded a mixture of regioisomeric β-amino chlorides that could be equilibrated to the more stable regioisomer by heating in DMF. The secondary chlorides thus obtained were engaged in an intramolecular anionic ring-closure to give access to fully protected enantio- and diastereoisomerically pure 2,3-*cis*-disubstituted azetidinic amino acid. One of the latter was deprotected for inclusion in a tripeptide sequence. This synthetic methodology was applied for *N*,*N*-disubstituted γ-amino alcohols, leading to 3- or 5-substituted proline derivatives but with a low 2,3- or 2,5- diastereoselectivity.

Keywords: Azetidines, amino-acids, amino-alcohols

Introduction

Conformationally constrained amino acids have been the subject of growing interests within past years in peptide chemistry. These modified amino acids can be used as tools for the modification of the secondary structure of peptides of biological relevance allowing a better knowledge of the shape of the catalytic site within the biomolecule and leading ultimately to the development of peptide-derived pharmaceutical drugs.[1] In this vast area of research, the asymmetric synthesis of novel α-amino acids, in which the constraint is brought by an heterocycle that holds the nitrogen is particularly rich, as illustrated by the synthesis of proline derivatives,[2] as well as pipecolic acid derivatives.[3] In contrast, the asymmetric synthesis of cyclic four-membered azetidinic amino acids is less documented. Yet, since the discovery by Fowden[4] nearly fifty years ago (1955) of L-

Azetidine-2-carboxylic acid 1, from the liliaceae Convallaria Majalis (lily-of-the-valley) (Fig.1), this non proteinogenic amino acid homologue of proline has been the subject report of impressive biological acivities,[5] and the modification of the structure of proteins brought by the replacement of proline by 1 has been investigated in detail.[6] In the last decade, the asymmetric synthesis of substituted derivatives of 1 has therefore been the subject of intense investigations.[7] This article follows a preliminary communication[8] reporting the asymmetric synthesis of 2,3-cis-substituted derivatives 2 of this amino acid through a stereoselective anionic intramolecular alkylation and there upon the attempts to generalise this synthetic methodology for the preparation of proline derivatives 3 and 4.

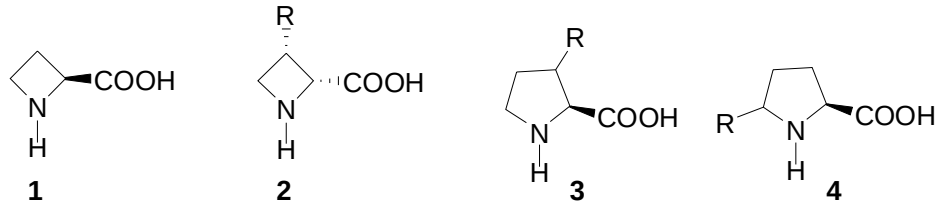
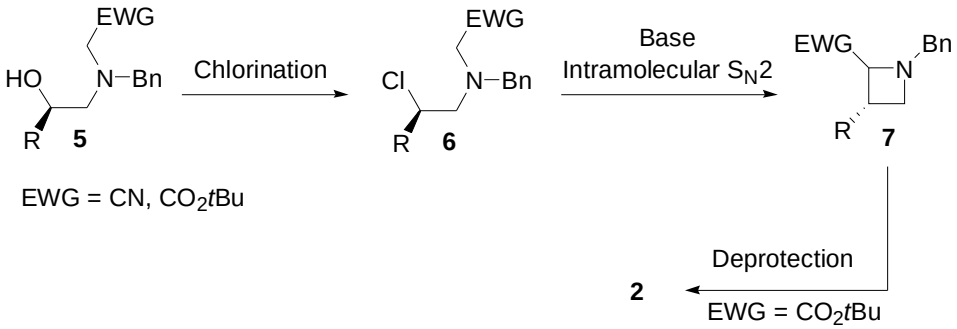


Figure 1

Results and Discussion

Synthesis of optically pure β-amino chlorides

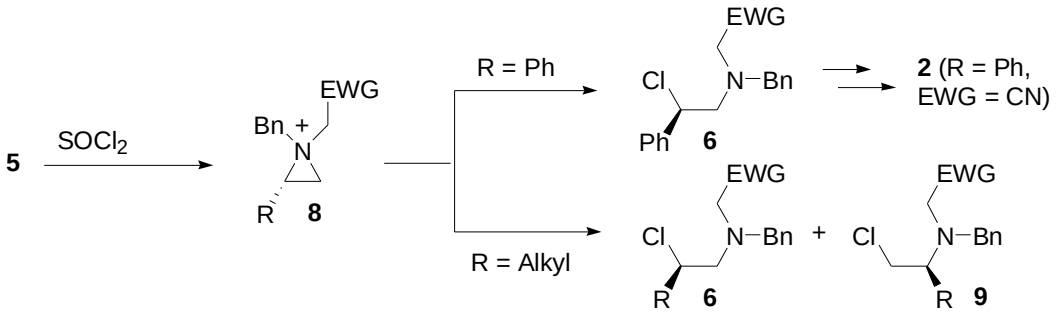
The synthetic scheme envisioned to access **2** is based on an anionic intramolecular alkylation of amino chloride **6**, which was prepared from the corresponding β-amino alcohol **5**, bearing an electron withdrawing group on the nitrogen atom, which was able to stabilize an adjacent carbanion (Scheme 1).



Scheme 1

This synthetic scheme has been previously validated when R = Ph and EWG = CN,[9] and the retention of configuration during the chlorination step was explained by a double inversion, involving an intermediate aziridinium ion **8** regioselectively opened by the chloride anion at the benzylic position. Due to the straightforwardness of this synthetic scheme, which leads to

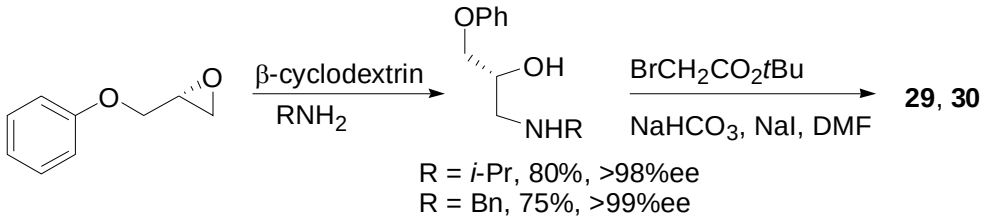
enantiomerically pure functionalized azetidines of high synthetic potential,[10] it was highly desirable to generalize this sequence when R is an alkyl group. However, in this case, the chlorination step leads to regioisomeric chlorides **6** and **9**, due to a low selectivity during the opening of the intermediate aziridinium ion by the chloride anion (Scheme 2). We report herein a solution to this problem of regioselectivity and its application to the synthesis of **2** with R being different from an aromatic ring, thus considerably enhancing the generality of this sythetic sequence.



Scheme 2

The β-amino alcohol substrates **10**-**20** were prepared in order to study the regioselectivity of the chlorination step (Table 1). These compounds were made either from commercially available enantiomerically pure β-amino alcohols (for **10**-**16**), from (*S*)-*O*-benzyl tyrosinol (for **17**),[11] or from (2*S*,3*R*)-*O*–benzyl threoninol (for **20**),[12] following a two-step sequence involving *N*-benzylation (PhCHO, 4Å Molecular sieves, then $NaBH_4$) and *N*-alkylation with either bromoacetonitrile (for **10**-**13**: K_2CO_3, CH_3CN) or *tert*-butyl bromoacetate (for **14**-**20**: $NaHCO_3$, NaI, DMF).

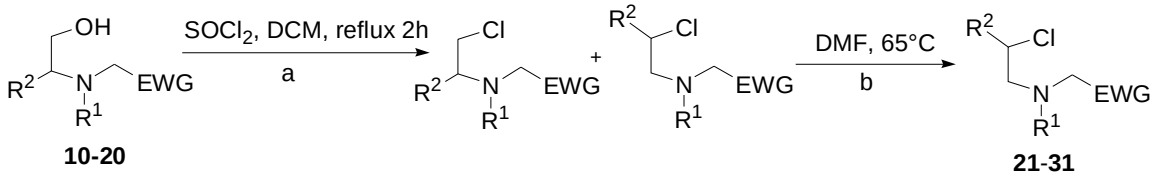
Amino alcohols **18** and **19** were prepared from the corresponding epoxides by reaction with either isopropylamine or benzylamine in the presence of β-cyclodextrin (β-CD) following our earlier described methodology.[14] The resulting amino alcohols were obtained with good yields and high ee's (Scheme 3) and were transformed into **29** and **30** through the above described alkylation procedure.

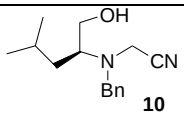
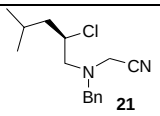
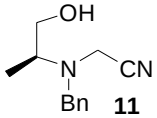
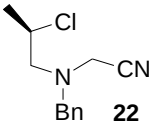
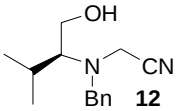
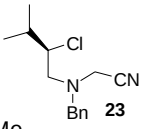
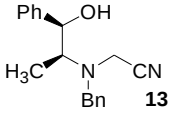
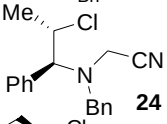
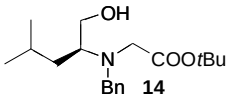
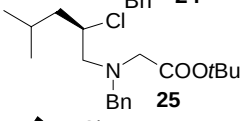
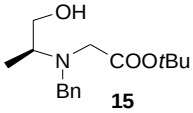
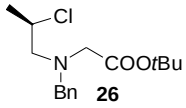
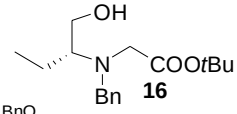
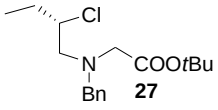
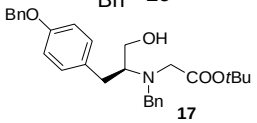
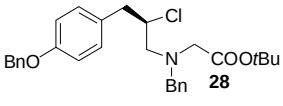
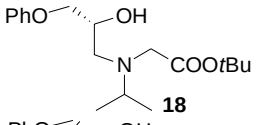
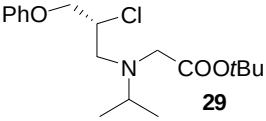
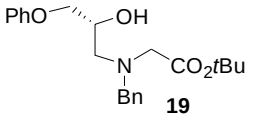
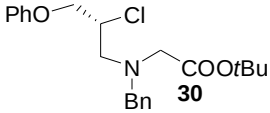
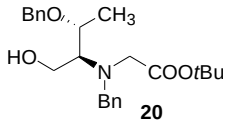
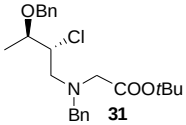


Scheme 3

All these β-amino alcohols were chlorinated by treatment with thionyl chloride in DCM to furnish a regioisomeric mixture of chlorides in good yields. Heating this mixture in DMF at 65°C for the time specified in Table 1 resulted in a complete equilibration to give the secondary chlorides **21**-**31**. These conditions were adjusted in order to minimize degradation and the secondary chlorides were obtained in high overall yields and >98% regioisomeric purity.

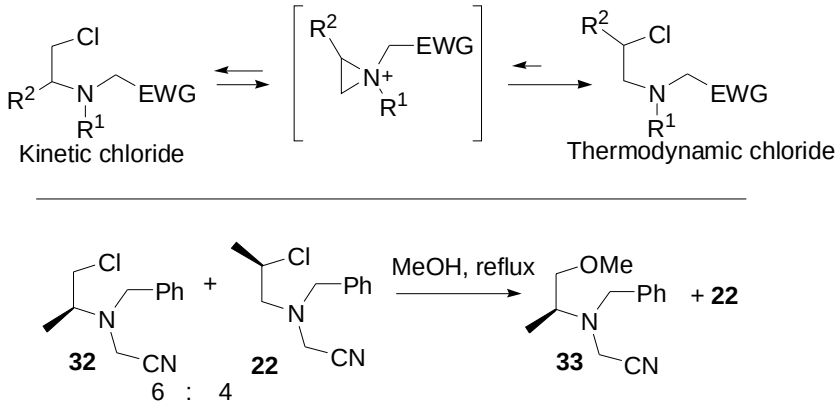
Table 1. Regioselective chlorination of β-amino alcohols



Entry	Substrate	Step a Yield (%), Regioisomeric ratio	Step b Yield (%), Time for equilibration	Product	Overall yield[a] (%)
1	 **10**	90 (1/1)	95 65h	 **21**	85
2	 **11**	93 (1/1)	95 60h	 **22**	88
3	 **12**	90 (1/1)	98 65h	 **23**	88
4	 **13**	90 (1/0)	95 65h	 **24**	85
5	 **14**	80 (1/1)	95 65h	 **25**	76
6	 **15**	90 (2/1)	95 60h	 **26**	85
7	 **16**	92 (1/1)	95 80h	 **27**	83
8	 **17**	93 (2/3)	95 65h	 **28**	88
9	 **18**	90 (2/1)	95 60h	 **29**	85
10	 **19**	83 (4/1)	77 60h	 **30**	64
11	 **20**	90 (3/1)	95 60h	 **31**	85

[a] Yield of pure isolated product.

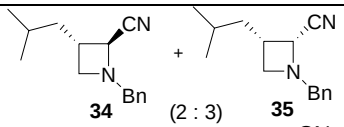
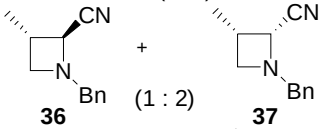
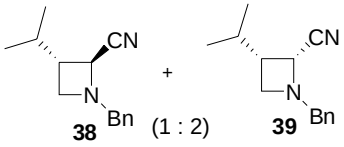
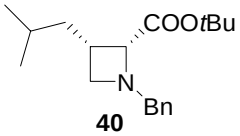
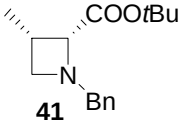
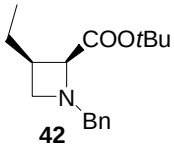
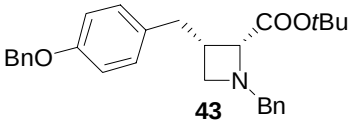
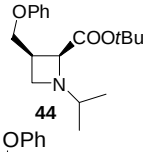
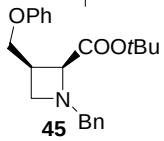
The high regioselectivity obtained of the chlorination step can be explained by the occurrence of an equilibration through an intermediate aziridinium ion (Scheme 4). Upon heating in DMF, both primary and secondary chlorides can produce an aziridinium ion through intramolecular alkylation. Chloride anion can then reattack this electrophilic intermediate to give either primary or secondary chloride. The accumulation of the secondary chloride in the reaction mixture can be explained by the fact that it is less prone to give back the aziridinium ion, due to the crowding of the electrophilic center. It should be noted that a very similar behaviour with azetidinium ions has been reported recently.[15] Long reaction times required for equilibration suggests that the opening at the less hindered position to give back the primary chloride is the more rapid process. Therefore, the primary chloride is the kinetic product, and the secondary chloride is the thermodynamic product and that these compounds are obtained without loss of the optical purity was demonstrated by the high optical purity of the azetidines derived from these products (vide supra). The kinetic opening by a nucleophile at the less hindered position can be easily evidenced: heating a 6/4 mixture of chlorides derived from **11** in MeOH gave a mixture of primary ether **33** and unreacted secondary chloride **22**; no trace of secondary ether could be detected in the reaction mixture.



Scheme 4

The regioselectivity issue being solved, we next focused on the nucleophilic ring closure in order to form the azetidine ring. Therefore, chlorides **21**-**24** bearing a cyanomethyl moiety on the nitrogen were treated with LiHMDS at -78°C, following our previously described conditions.[9] Cyclization occured in high yield with **21** and **22**, but not with **23**, in which the electrophilic center is more sterically crowded and decomposition was observed with ephedrin-derived chloride **24**. However, the 2,3-diastereoselectivity in the produced azetidines **34**-**39** was low in all cases, and the diasteroisomers were not easily separable. We therefore switched to the chlorides **25**-**31** bearing a large *tert*-butyl ester, in the hope of increasing the diasteroselectivity. As a matter of fact, the enolates derived from these esters proved to be less reactive than their aminonitrile homologues and it was crucial to use HMPA (hexamethylphosphoramide) as an additive (10% volume with THF) to induce the cyclization with these substrates. Nonetheless, under these conditions, cyclized compounds **40**-**45** were obtained in good yields and we were pleased to note that it occurred with total 2,3-*cis* diastereoselectivity. Results of these experiments are summarized in Table 2.

Table 2. Intramolecular alkylation of chlorides **21**-**30**

Entry	Substrate	Conditions	Products	Yield[a] (%)
1	**21**	LiHMDS, THF, -78 to -10°C	 **34** (2 : 3) **35**	95
2	**22**	LiHMDS, THF, -78 to -0°C	 **36** (1 : 2) **37**	60
3	**23**	LiHMDS, THF, -78 to -0°C	 **38** (1 : 2) **39**	25
4	**24**	LiHMDS, THF/HMPA -78 to 0°C	___	b)
5	**25**	LiHMDS, THF/HMPA -78 to 0°C	 **40**	73
6	**26**	LiHMDS, THF/HMPA -78 to 0°C	 **41**	80
7	**27**	LiHMDS, THF/HMPA -78 to -20°C	 **42**	85
8	**28**	LiHMDS, THF/HMPA -78 to -40°C	 **43**	50[c)]
9	**29**	LiHMDS, THF/HMPA -78 to 0°C	 **44**	50
10	**30**	LiHMDS, THF/HMPA -78 to 0°C	 **45**	75
11	**31**	LiHMDS, THF/HMPA -78 to 0°C	___	d)

[a] Yield of pure isolated product.
[b] decomposition of starting material
[c] A 20% yield of elimination product was produced with this substrate.
[d] The starting material was recovered.

Particularly noteworthy in these experiments is the high 2,3-*cis*-diastereoselectivity observed in the course of the cyclization. The 2,3-relative configuration in the produced azetidines was determined by NOE experiments performed with **41** and **44** (NOE enhancements are shown in Figure 2)**.**

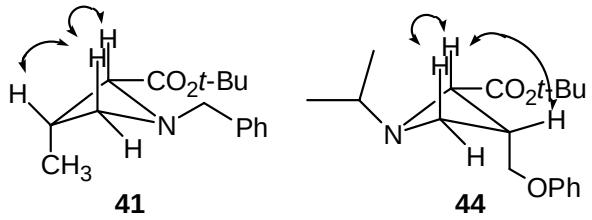
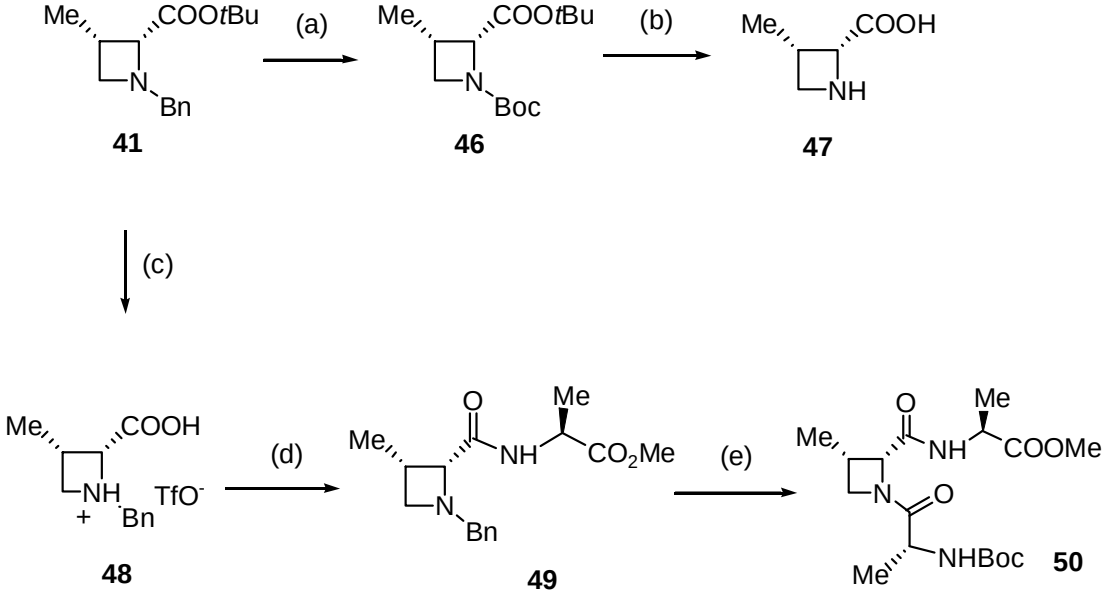


Figure 2. NOE enhancements in **41** and **44**.

The optical purity of the azetidine **41** and *ent*-**41** (prepared from *ent*-**15**) was determined by NMR using (*S*)-α-(trifluoromethyl)benzyl alcohol as chiral solvent[16] and was found to be greater than 95%, demonstrating that no loss of the optical purity occurred during the equilibration process.

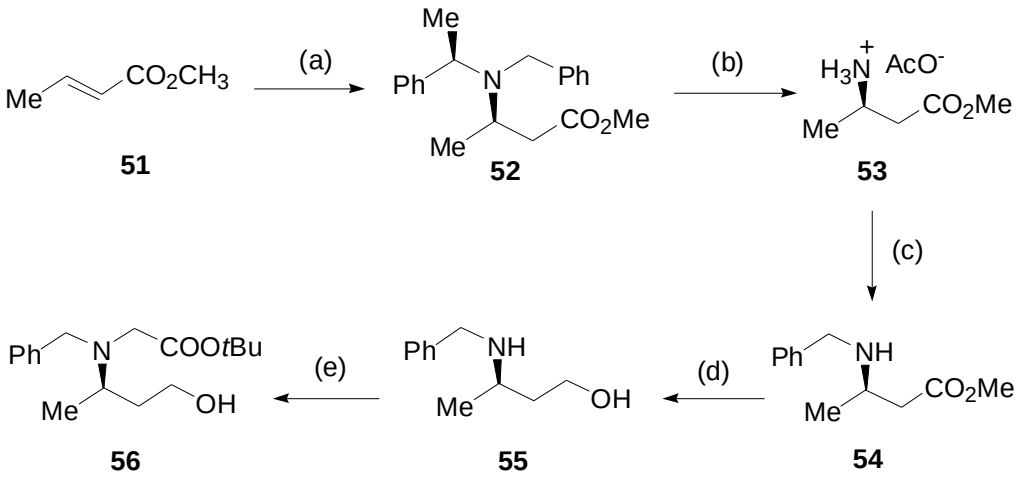
The rationalization of the observed *cis*-2,3 diastereoselectivity is not simple. The first question to be answered is whether the reaction is kinetically controlled or if further enolisation of the produced azetidine induces a thermodynamic control. In order to address this point, we have treated azetidine **41** under the conditions of the cyclization (LiHMDS in THF/HMPA) followed by quenching at 0°C with methanol-d_4. Since the starting product was recovered unchanged and did not show any incorporation of deuterium, we could conclude that it is not enolized in the reaction mixture. This observation is however not sufficient to conclude that a kinetic control is operating, since we cannot rule out an enolization of a 2,3-*trans* azetidine into the observed 2,3-*cis* isomer. If a kinetic control is assumed, then a clear cut explanation of the selectivity through the examination of the possible transition states is precluded by at least three important questions that we have not been able to answer so far: (i) what is the stereochemistry (*Z* or *E*) of the reactive enolate? (ii) what is the conformation of the azetidine ring in the transition state? and (iii) can the ester enolate support a *pseudo* axial position on the azetidine ring in the transition state? All the possibilities brought by these questions suggest at least eight possible transition states that we examined with the aid of molecular model: from this study, a preferred transition state did not emerge. Furthermore, in this first insight into the mechanism, the possible role of HMPA was neglected. It is therefore clear that further experimentation coupled with molecular modeling will be necessary to rationalize this disatereoselectivity. From a more pratical viewpoint, it should be noted that although the stereoselectivity is very good, the ease of this intramolecular alkylation depends on the steric crowding of the electrophilic center: compounds **24** and **31**, both bearing a substituent alpha to the reacting center, failed to give any azetidine. Furthemore, compound **28** gave substantial amount of elimination product, due to a benzylic position alpha to the reacting center. Thus, this series of experiments delineates well the scope of this reaction.

In order to demonstrate that these azetidinic amino acids are suitable for peptide chemistry, amino ester **41** was included in a tripeptide, as shown in Scheme 5. Thus, cleavage of the *t*butyl ester in **41** with TFA was followed by coupling with (*L*)-Ala-OMe to give **49**. *N*-Debenzylation of **49** was then followed by coupling with (*L*)-*N*-Boc-Ala, to furnish tripeptide **50** with modest yield. The use of the BOP reagent proved to be necessary for this step to attain a reasonable yield (Scheme 5). This tripeptide was shown to exist as a mixture of two rotamers by ^{1}H NMR. Alternatively, *N*-Benzyl protecting group in **41** was changed in good yield to a Boc group to give **46**. The latter was fully depotected with TFA, to give amino acid **47** after ion-exchange chromatography. This unreported amino acid can be viewed as a conformationally restricted analogue of valine.



Scheme 5. (a) H_2, $(Boc)_2O$, $Pd(OH)_2$ cat., EtOH, r.t., 2h (89%). (b) TFA in DCM, r.t. 12h, then DOWEX (95%). (c) TFA in DCM, r.t., 12h (95%). (d) BOP reagent, (*L*)-Ala-OMe, HCl, Et_3N, MeCN, r.t., 16h, (65%). (e) (i) H_2, $Pd(OH)_2$ cat., MeOH/ AcOH, r.t., 3h, (95%). (ii) BOP reagent, *N*-Boc-(*L*)-Ala, Et_3N, MeCN, r.t., 16h, (50%).

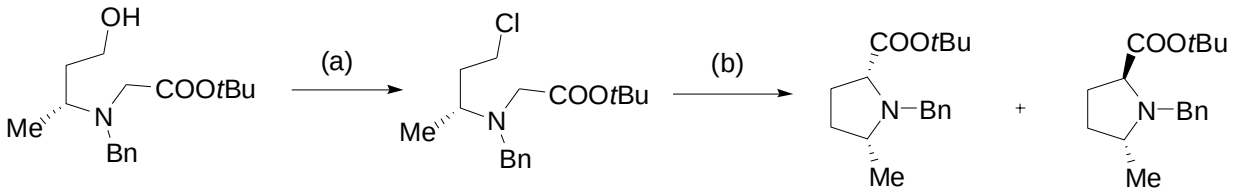
After success in synthesizing the enantio- and diasteromerically pure 3-substituted azetidinic amino acids, we planned to extrapolate the same strategy for the synthesis of substituted proline derivatives. In this regard, the desired enantiomerically pure γ-amino alcohol **56**, homologue to **15** was synthesized from **53**[17] through a three steps sequence involving *N*-benzylation, reduction of the ester moiety and alkylation with *tert*-butylbromoacetate, as depicted in Scheme 6.



51 **52** **53** **54** **55** **56**

Scheme 6. (a) (*R*)-Lithium *N*-benzyl-*N*-1-phenylethylamide, -78°C, 15mn, (80%). (b) H_2, $Pd(OH)_2$ cat., MeOH/AcOH/H_2O, (84%). (c) (i) Benzaldehyde, 4Å MS, DCM, 3h. (ii) $NaBH_4$, EtOH, r.t., 12h, (60% overall). (d) $LiAlH_4$, THF, reflux, 12h, (97%). (e) *tert*-Butylbromoacetate, $NaHCO_3$, NaI, DMF, (57%).

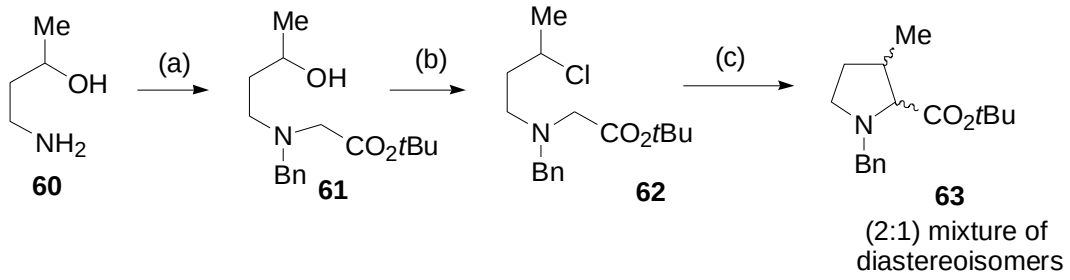
The synthesized chiral amino alcohol **56** was then transformed into the primary chloride **57** which was subjected to cyclization under set conditions and the reaction gave the desired proline derivatives **58** and **59** with very good yield but with poor diasteroselectivity (Scheme 7). The relative stereochemistries in these proline derivatives was assigned by comparison of the ^1H NMR spectra with the closely related *cis* and *trans* 5-heptyl analogues.[18] It is interesting to note here that the chlorination step leading to **57** occurred with high regioselectivity, suggesting that equilibration through an intermediate azetidinium ions is not operative under these conditions.



56 **57** **58** (3 : 2) **59**

Scheme 7. (a) $SOCl_2$, DCM, reflux, 1.5h, (78%). (b) LiHMDS, THF/HMPA, -90 to 0°C, (98%).

Having failed to get a good diasteroselectivity for the synthesis of 5-substituted proline derivatives we then focussed our attention towards 3-subsituted proline derivatives. Starting from commercially available racemic alcohol **60**, a similar sequence of *N*-benzylation and *N*-alkylation gave **61** which was chlorinated regioselectively to give the chloride **62.** Finally**,** this compound, subjected to intramolecular cyclization using LiHMDS, furnished mixture of diasteroisomers **63** with high yield but poor diasteroselectivity (Scheme 8).



Scheme 8. (a) (i) Benzaldehyde, 4Å MS, DCM, 3h. (ii) $NaBH_4$, EtOH, r. t., 12h, (iii) *tert*-Butylbromoacetate, $NaHCO_3$, NaI, DMF, (63 % overall). (b) $SOCl_2$, DCM, reflux, 1.5h, (93%). (c) LiHMDS, THF/HMPA, -90 to 0°C, (98%).

In conclusion, we have shown that diastereo- and enantiomerically pure *cis*-2,3-substituted azetidines can be prepared in a straighforward way from β-amino alcohols. We have also demonstrated that such azetidinic amino acids can be fully deprotected or included using conventional chemistry in a peptidic sequence. Finally, the extension of this synthetic sequence to synthesize proline derivatives has been studied and though the yield was very good, the crucial cyclization step occured with a low diasteroselectivity. Applications of these azetidinic amino acids will be reported in due course of time.

Acknowledgements

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Experimental Section

General Procedures. ^1H and ^{13}C spectra ($CDCl_3$ solution unless otherwise stated) were recorded on a Brüker AC 200 or 300 spectrometer at 200, 300 (^1H), 50.3 and 75.5 (^{13}C) MHz; chemical shifts are reported in ppm from TMS. Optical rotations were determined with a Perkin Elmer 141 instrument. All reactions were carried out under argon. Column chromatography was performed on silica gel 230-400 mesh by using various mixtures of petroleum ether (PE), ethyl acetate (AcOEt) and diethyl ether (Et_2O). TLCs were run on Merck Kieselgel $60F_{254}$. Melting points were uncorrected. THF was distilled from sodium/benzophenone ketyl. Dichloromethane was distilled from calcium hydride. The mention of "usual workup" means: (i) decantation of the organic layer; (ii) extraction of the aqueous layer with ether; (iii) washing the combined organic layers with brine and drying of the combined organic phases over $MgSO_4$ and (iv) solvent evaporation under reduced pressure. Compositions of stereoisomeric mixtures were determined by NMR analysis on crude products before any purification. Mass spectra were recorded on a Hewlett-Packard MS Engin HP5989B equipped with an ESI source Analytica Branford. HRMS

spectra were performed by the "Service de spectrometrie de masse" in Strasbourg University. Elementary analyses were performed by the "Service de Microanalyses" in Gif sur Yvette.

General procedure for the preparation of chlorides (GP-1)

A solution of amino alcohol (1 mmol) in DCM (5 mL) was cooled to 0°C under argon. Thionyl chloride (2.05 mmol) was added dropwise and the resulting mixture was refluxed for 2 h. After the completion of the reaction, the reaction mixture was cooled to room temperature and quenched by addition of saturated aqueous solution of $NaHCO_3$ (10 mL). The aqueous layer was extracted with diethylether (2 × 15 mL) followed by usual workup gave a mixture of chlorides that was purified by flash chromatography. The formed chlorides (1 mmol) were then dissolved in DMF (10 mL) and heated at 60 °C for the time specified in Table 1. After completion of the reaction, DMF was removed under vacuo and the crude residue was purified by flash chromatography.

(*R*)-(–)-[*N*-(2-Chloro-4-methyl-pentyl)-benzylamino]acetonitrile 21. (Table 1, Entry 1) Prepared according to GP-1. The pure compound was obtained after flash chromatography (SiO_2, PE/AcOEt, 9:1) as a colourless oil. Yield: 1.94 g (85%); R_f = 0.82 (PE/AcOEt, 9:1); $[\alpha]_D^{20}$: – 2.0 (c = 0.80, $CHCl_3$). ^{1}H NMR (200 MHz, $CDCl_3$, 25 °C): δ = 0.91 (d, *J* = 6.6 Hz, 3H, C*H*$_3$) 0.95 (d, *J* = 6.6 Hz, 3H, C*H*$_3$), 1.50-1.69 (m, 2H, C*H*$_2$CH(CH$_3$)$_2$), 1.82-2.20 (m, 1H, C*H*(CH$_3$)$_2$), 2.90 (dd, *J* = 7.5 Hz, *J* = 2.7 Hz, 2H, NC*H*$_2$CHCl) 3.53 (s, 2H , NC*H*$_2$CN), 3.76 (s, 2H, NC*H*$_2$Ph), 3.81-4.10 (m, 1H, NCH$_2$C*H*Cl), 7.28-7.48 (m, 5H, Ph*H*) ppm. ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C): δ = 21.3 (*C*H$_3$), 23.2 (*C*H$_3$), 25.1 (*C*H(CH$_3$)$_2$), 42.3 (N*C*H$_2$CN), 45.1 (*C*H$_2$CH(CH$_3$)$_2$), 58.6 (NCH$_2$*C*HCl), 58.8 (N*C*H$_2$Ph), 61.2 (N*C*H$_2$CHCl), 115.0 (CN), 128.0, 128.2, 128.5, 128.7, 129.0 (*C*Ph) 136.8 (*ipso*-*C*Ph) ppm. CIMS: *m*/*z* (%) = 265 (100) [MH$^+$], 238 (10), 159 (70), 158 (23), 108 (16), 91 (78). HRMS (ESI) calcd. for $C_{15}H_{22}ClN_2$ [MH$^+$]: 265.1472; found 265.1466.

(*R*)-(–)-[*N*-(2-Chloro-propyl)-benzylamino]acetonitrile 22. (Table 1 , Entry 2) Prepared according to GP-1. The pure compound was obtained after flash chromatography (SiO_2, PE/AcOEt, 9:1) as a colourless oil. Yield: 1.63 g (88%); R_f = 0.75 (PE/AcOEt, 9:1); $[\alpha]_D^{20}$: – 79.8 (c = 1.30, $CHCl_3$). ^{1}H NMR (200 MHz, $CDCl_3$, 25 °C): δ = 1.54 (d, *J* = 6.6 Hz, 3H, C*H*$_3$), 2.89 (dd, *J* = 6.9 Hz, *J* = 3.1 Hz, 2H, NC*H*$_2$CHCl) 3.52 (s, 2H , NC*H*$_2$CN), 3.76 (s, 2H, NC*H*$_2$Ph), 4.03-4.10 (m, 1H, CH$_3$C*H*Cl), 7.22-7.32 (m, 5H, Ph*H*) ppm. ^{13}C NMR (50 MHz, $CDCl_3$, 25 °C): δ = 23.0 (*C*H$_3$), 42.1 (N*C*H$_2$CN), 54.9 (NCH$_2$*C*HCl), 58.7 (N*C*H$_2$Ph), 61.9 (N*C*H$_2$CHCl), 114.9 (CN), 128.0, 128.7, 129.0 (*C*Ph),136.7 (*ipso*-*C*Ph) ppm. CIMS: *m*/*z* (%) = 225 (31), 223 (100) [MH$^+$], 196 (14), 159 (32), 91 (31). HRMS (ESI) calcd. for $C_{12}H_{16}ClN_2$ [MH$^+$]: 223.1002; found 223.1012.

(*R*)-(–)-[(*N*-(2-Chloro-3methylbutyl)-benzylamino]acetonitrile 23. (Table 1, Entry 3) Prepared according to GP-1. The pure compound was obtained after flash chromatography (SiO_2, PE/AcOEt, 9:1) as a colourless oil. Yield: 1.46 g (88%); R_f = 0.75 (PE/AcOEt, 9:1); $[\alpha]_D^{20}$: – 92.2 (c = 0.70, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C): δ = 0.95 (d, *J* = 6.6 Hz, 3H, C*H*$_3$), 1.07 (d, *J* = 6.8 Hz, 3H, C*H*$_3$), 2.07-2.16 (m, 1H, C*H*(CH$_3$)$_2$), 2.90 (dd, *J* = 6.8 Hz, *J* = 3.2 Hz,

2H, NC*H*$_2$CHCl), 3.50 (s, 2H, NC*H*$_2$CN), 3.75 (s, 2H, NC*H*$_2$Ph), 3.94-4.00 (m, 1H, NCH$_2$C*H*Cl), 7.22-7.45 (m, 5H, Ph*H*) ppm. ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C): δ = 16.5 (*C*H$_3$), 20.3 (*C*H$_3$), 31.9 (*C*H(CH$_3$)$_2$) 42.0 (N*C*H$_2$CN), 58.7 (N*C*H$_2$Ph), 66.5 (NCH$_2$*C*HCl), 114.9 (*C*N), 128.0, 128.5, 128.7, 128.8, 129.0 (*C*Ph),136.8 (*ipso*-*C*Ph) ppm. CIMS: *m*/*z* (%) = 251 (22) [MH$^+$], 224 (5), 159 (68), 91 (100). HRMS (ESI) calcd. for $C_{14}H_{20}ClN_2$ [MH$^+$]: 251.1315; found 251.1310.

(1*S*,2*S*)-(+)-(*N*-(2-Chloro-1-phenylpropyl)-methylamino)acetonitrile 24. (Table 1, Entry 4) Prepared according to GP-1. The pure compound was obtained after flash chromatography (SiO_2, PE/AcOEt, 9:1) as colourless oil. Yield: 1.43 g (85%); R_f = 0.85 (PE/AcOEt, 9:1); $[\alpha]_D^{20}$: + 370.0 (c = 0.60, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C): δ = 1.27 (d, *J* = 6.7 Hz, 3H, C*H*$_3$CHCl), 2.48 (s, 3H, NC*H*$_3$), 3.46 (d, *J* = 17.3 Hz, 1H, NC*H*HCN), 3.47 (d, *J* = 8.0 Hz, 1H, PhC*H*N), 3.63 (d, *J* = 17.3 Hz, 1 H, NCH*H*CN), 4.42-4.62 (m, 1H, CH$_3$C*H*Cl), 7.28-7.45 (m, 5H, Ph*H*) ppm. ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C): δ = 22.8 (*C*H$_3$), 40.1 (N*C*H$_3$), 44.1 (N*C*H$_2$CN), 56.6 (CH$_3$*C*HCl), 72.0 (Ph*C*HN), 114.6 (*C*N), 128.3, 128.7, 129.7 (*C*Ph), 135.2 (*ipso*-*C*Ph) ppm.; EIMS: *m*/*z* (%) = 196 (16) (M–HCN)$^+$, 187 (100), 153 (28), 117(23). HRMS (ESI) calcd. for $C_{12}H_{16}ClN_2$ [MH$^+$]: calcd. 223.0997; found 223.0996.

(*R*)-(–)-[*N*-(2-Chloro-4-methyl-pentyl)-benzylamino] Acetic acid tert-butyl ester 25. (Table 1, Entry 5) Prepared according to GP-1. The pure compound was obtained after flash chromatography (SiO_2, PE/AcOEt, 9:1) as colourless oil. Yield: 4.15 g (76%); R_f = 0.82 (PE/AcOEt, 9:1); $[\alpha]_{365}^{20}$: – 25.4 (c = 0.90, $CHCl_3$). ^{1}H NMR (200 MHz, $CDCl_3$, 25 °C): δ = 0.88 (d, *J* = 6.4 Hz, 3H, C*H*$_3$CH(CH$_3$)), 0.94 (d, *J* = 6.8 Hz, 3H, CH$_3$CH(C*H*$_3$), 1.50 (s, 9H, C(C*H*$_3$)$_3$), 1.51-1.71 (m, 2H, C*H*$_2$CHCl), 1.85-2.00 (m, 1H, C*H*(CH$_3$)$_2$), 3.00 (dd, *J* = 15.0 Hz, *J* = 6.7 Hz, 1H, NC*H*HCHCl), 3.06 (dd, *J* = 15.0 Hz, *J* = 6.7 Hz, 1H, NCH*H*CHCl), 3.33 (s, 2H, NC*H*$_2$COO^{t}Bu), 3.86-4.08 (m, 3H, NC*H*$_2$Ph, NCH$_2$C*H*Cl), 7.27-7.30 (m, 5H, Ph*H*) ppm. ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C): δ = 21.1 (*C*H$_3$), 23.4 (*C*H$_3$), 25.1 (*C*H(CH$_3$)$_2$), 28.1 (C(*C*H$_3$)$_3$), 45.1 (CH*C*H$_2$CHCl), 55.9 (N*C*H$_2$COO*t*Bu), 58.7 (N*C*H$_2$Ph), 59.9 (NCH$_2$*C*HCl), 61.8 (N*C*H$_2$CHCl), 81.0 (COO*C*(CH$_3$)$_3$), 127.2, 128.3, 128.9 (*C*Ph), 139.1 (*ipso*-*C*Ph), 170.8 (CO) ppm. EIMS: *m*/*z* (%) = 340 (28) [MH$^+$], 284 (20), 238 (100), 234 (41), 178 (32), 91 (85). HRMS (ESI) calcd. for $C_{19}H_{31}ClNO_2$ [MH$^+$]: calcd. 340.2038; found 340.2045.

(*R*)-(–)-[*N*-(2-Chloro-propyl)-benzylamino]-acetic acid *tert*-butyl ester 26. (Table 1, Entry 6) Prepared according to GP-1. The pure compound was obtained after flash chromatography (SiO_2, PE/AcOEt, 9:1) as colourless oil. Yield: 1.09 g (85%); R_f = 0.85 (Petroleum ether/AcOEt, 9:1); $[\alpha]_D^{20}$: –6.6 (c = 0.70, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C): δ = 1.37 (s, 12H, C(C*H*$_3$)$_3$, C*H*$_3$CHCl), 2.80 (dd, *J* = 13.7 Hz, *J* = 6.8 Hz, 1H, NC*H*HCHCl), 3.19 (s, 2H, NC*H*$_2$COOtBu), 3.75 (d, *J* = 16.8 Hz, 1H, A of AB system, NC*H*HPh), 3.81 (d, *J* = 16.8 Hz, 1H, B of AB system, NCH*H*Ph), 3.90 (sextet, *J* = 6.8 Hz, 1H, CH$_3$C*H*(CH$_2$)Cl), 7.14-7.20 (m, 5H, Ph*H*) ppm. ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C): δ = 23.0 (*C*H$_3$), 28.2 (C(*C*H$_3$)$_3$), 55.7 (N*C*H$_2$COO*t*Bu), 56.2 (CH$_3$*C*HCl), 58.7 (N*C*H$_2$Ph), 62.5 (N*C*H$_2$CHCl), 81.0 (COO*C*(CH$_3$)$_3$), 127.2, 128.7, 128.9 (*C*Ph), 136.8 (*ipso*-*C*Ph), 170.7 (CO) ppm. EIMS: *m*/*z* (%) = 320 (27) [M+K$^+$], 264 (8), 242 (61). HRMS (ESI) calcd. for $C_{16}H_{25}ClNO_2$ [MH$^+$]: 298.1568; found 298.1590.

(*S*)-(+)-[*N*-(2-Chloro-butyl)-benzylamino]-acetic acid *tert*-butyl ester 27. (Table 1, Entry 7) Prepared according to GP-1. The pure compound was obtained after flash chromatography (SiO_2, PE/AcOEt, 9:1) as colourless oil. Yield: 1.47 g (83%); R_f = 0.85 (PE/AcOEt, 9:1); $[\alpha]_D^{20}$: + 2.8 (c = 1.00, $CHCl_3$). ^{1}H NMR (200 MHz, $CDCl_3$, 25 °C): δ = 1.06 (t, *J* = 7.3 Hz, 3H, C*H*$_3$), 1.53 (s, 9H, C(C*H*$_3$)$_3$), 1.60-1.74 (m, 1H, C*H*HCH$_3$), 1.95-2.10 (m, 1H, CH*H*CH$_3$), 3.05 (dd, *J* = 14.1 Hz, *J* = 6.9 Hz, 1H, NC*H*HCHCl), 3.08 (dd, *J* = 14.1 Hz, *J* = 6.9 Hz, 1H, NCH*H*CHCl), 3.35 (s, 2H, NC*H*$_2$COOtBu), 3.85-4.03 (m, 3H, NC*H*$_2$Ph, CH$_2$C*H*Cl), 7.24-7.51 (m, 5H, Ph*H*) ppm. ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C): δ = 10.8 (*C*H$_3$), 28.3 (C(*C*H$_3$)$_3$), 28.9 (CH$_3$*C*H$_2$CHCl), 55.7 (N*C*H$_2$COO^{t}Bu), 58.7 (N*C*H$_2$Ph), 60.9 (N*C*H$_2$CHCl), 63.3 (*C*HClCH$_2$CH$_3$), 81.0 (COO*C*(CH$_3$)$_3$), 127.3, 128.4, 128.9 (*C*Ph), 139.1 (*ipso*-*C*Ph), 170.8 (CO) ppm. EIMS: *m*/*z* (%) = 350 (13), 336 (35), 334 (100), 312 (11) [MH$^+$], 278 (26), 256 (75), 254 (26), 242 (10), 220 (14). HRMS (ESI) calcd. for $C_{17}H_{27}ClNO_2$ [MH$^+$]: 312.1730; found 312.1718.

(*R*)-(+)-{*N*-[3-(4-benzyloxy-phenyl)-2-chloro-propyl]-benzylamino}-acetic acid *tert*-butylester 28. (Table 1, Entry 8) Prepared according to GP-1. The pure compound was obtained after flash chromatography (SiO_2, PE/AcOEt, 9:1) as colourless oil. Yield: 1.09 g (88%); R_f = 0.80 (PE/AcOEt, 9:1); $[\alpha]_D^{20}$: + 5.7 (c = 0.20, $CHCl_3$). ^{1}H NMR (200 MHz, $CDCl_3$, 25 °C): 1.59 (s, 9H, C(C*H*$_3$)$_3$), 2.89 (dd, *J* = 14.3 Hz, *J* = 8.6 Hz, 1H, A of AB System, OPhC*H*HCHCl), 3.18 (dd, *J* = 6.4 Hz, *J* = 1.8 Hz, 2H, NC*H*$_2$CHCl), 3.35 (dd, *J* = 14.3 Hz, *J* = 4.4 Hz, 1H, B of AB System, OPhCH*H*CHCl), 3.45 (s, 2H, NC*H*$_2$COOtBu), 4.01 (s, 2H, NC*H*$_2$Ph), 4.05-4.27 (m, 1H, NCH$_2$C*H*Cl), 5.12 (s, 2H, OC*H*$_2$Ph), 7.02 (d, *J* = 8.6 Hz, 2H, OPh*H*), 7.22 (d, *J* = 8.6 Hz, 2H, OPh*H*), 7.30-7.60 (m, 10H, Ph*H*) ppm. ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C): δ = 28.0 (C(*C*H$_3$)$_3$), 41.1 (Ph*C*H$_2$CHCl), 55.7 (NCH$_2$*C*HCl), 58.5 (N*C*H$_2$COO^{t}Bu), 60.6 (N*C*H$_2$*C*HCl), 62.0 (N*C*H$_2$Ph), 69.7 (O*C*H$_2$Ph), 80.8 (COO*C*(CH$_3$)$_3$), 114.5, 127.1, 127.3, 127.7, 128.2, 128.4, 128.7 (*C*Ph), 130.2, 137.0, 138.8, 157.4 (*ipso*-*C*Ph), 170.4 (CO) ppm. EIMS: *m*/*z* (%) = 480 (100) [MH$^+$], 388(24), 378 (10), 352 (11). HRMS (ESI) calcd. for $C_{29}H_{35}ClNO_3$ [MH$^+$]: 480.2305; found 480.2308.

(*R*)-(+)- [*N*-(2-Chloro-3-phenoxy-propyl)-isopropyl-amino]-acetic acid *tert*-butyl ester 29. (Table 1, Entry 9) Prepared according to GP-1. The pure compound was obtained after flash chromatography (SiO_2, PE/AcOEt, 9:1) as colourless oil. Yield: 300 mg (85%); R_f = 0.50 (PE/AcOEt, 95:5); $[\alpha]_D^{20}$: + 19.5 (c = 0.90, $CHCl_3$). ^{1}H NMR (200 MHz, $CDCl_3$, 25 °C): δ = 1.02 (d, *J* = 4.6 Hz, 3H, NCHC*H*$_3$(CH$_3$)), 1.05 (d, *J* = 4.8 Hz, 3H, NCHCH$_3$(C*H*$_3$), 1.45 (s, 9H, C(C*H*$_3$)$_3$), 2.92-3.18 (m, 3H, NC*H*(CH$_3$)$_2$ NC*H*$_2$CHCl), 3.29 (dd, *J* = 17.1 Hz, *J* = 11.2 Hz, 2H, NC*H*$_2$COOtBu), 4.15-4.28 (quintet, *J* = 4.5 Hz, 1H, NCH$_2$C*H*(Cl)CH$_2$), 4.32 (dd, *J* = 10.2 Hz, *J* = 3.9 Hz, 1H, A of AB system, PhOC*H*H), 4.40 (dd, *J* = 10.2 Hz, *J* = 3.9 Hz, 1H, B of AB system, PhOCH*H*), 6.90-7.02 (m, 3H, Ph*H*), 7.22-7.36 (m, 2H, Ph*H*) ppm. ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C): δ = 19.1 (NCH*C*H$_3$(CH$_3$)), 19.7 (NCHCH$_3$(*C*H$_3$)), 28.1 (C(*C*H$_3$)$_3$), 53.2 (N*C*H(CH$_3$)$_2$), 54.0 (N*C*H$_2$CHCl), 55.4 (NCH$_2$COOtBu), 58.5 (NCH$_2$*C*HCl), 69.3 (OCH$_2$CHCl), 80.7 (COO*C*(CH$_3$)$_3$), 114.8, 121.1, 129.5 (*C*Ph), 158.5 (*ipso*-*C*Ph), 171.7 (CO) ppm. EIMS: *m*/*z* (%) = 364 (90) (M+Na)$^+$, 346 (100), 308 (45), 290 (82), 286 (72), 272 (23). HRMS (ESI) calcd. for $C_{18}H_{29}ClNO_3$ [MH$^+$]: 342.1836; found 342.1828.

(*R*)-(+)-[N-(2-Chloro-3-phenoxy-propyl)-benzyl-amino]-acetic acid *tert*-butyl ester 30. (Table 1, Entry 10) Prepared according to GP-1. The pure compound was obtained after flash chromatography (SiO_2, PE/AcOEt, 9:1) as colourless oil. Yield: 300 mg (64%); R_f = 0.45 (PE/AcOEt, 95:5); $[\alpha]_D^{20}$: + 10.6 (c = 0.80, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C): 1.48 (s, 9H, C(C*H*$_3$)$_3$), 3.06 (dd, *J* = 14.2 Hz, *J* = 5.3 Hz, 1H, NC*H*HCHCl), 3.19 (dd, *J* = 14.2 Hz, *J* = 5.3 Hz, 1H, NCH*H*CHCl), 3.32 (s, 2H, NC*H*$_2$COOtBu), 3.92 (s, 2H, NCH$_2$Ph), 4.03-4.13 (m, 2H, NCH$_2$C*H*Cl, PhOC*H*H), 4.14-4.22 (m, 1H, PhOCH*H*), 6.82-7.04 (m, 3H, OPh*H*), 7.10-7.30 (m, 7H, OPh*H*, Ph*H*) ppm. ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C): δ = 28.3 (C(*C*H$_3$)$_3$), 55.2 (N*C*H$_2$COO^{t}Bu), 56.8 (NCH$_2$*C*HCl), 58.1 (N*C*H$_2$CHCl), 59.0 (N*C*H$_2$Ph), 70.1 (PhO*C*H$_2$CHCl), 81.1 (COO*C*(CH$_3$)$_3$), 114.8, 121.0, 126.2, 128.5, 129.0, 129.5 (*C*Ph), 158.0 (*ipso*-*C*Ph), 171.0 (CO) ppm. EIMS: *m*/*z* (%) = 390 (100) [MH$^+$], 362(30), 354 (56), 334 (99), 288 (24), 234 (10). HRMS (ESI) calcd. for $C_{22}H_{29}ClNO_3$ [MH$^+$]: 390.1836; found 390.1830.

2*R*,3*R*)-(–)-[(3-Benzyloxy-2-chloro-butyl)-benzyl amino]-acetic acid *tert*-butyl ester 31. (Table 1, Entry 11) Prepared according to GP-1. The pure compound was obtained after flash chromatography (SiO_2, PE/AcOEt, 9:1) as colourless oil. Yield: 179 mg (95%); R_f = 0.82 (PE/AcOEt, 9:1); $[\alpha]_D^{20}$: – 11.9 (c = 0.80, $CHCl_3$). ^{1}H NMR (200 MHz, $CDCl_3$, 25 °C): 1.22 (d, *J* = 6.2 Hz, 3H, CH$_3$), 1.51 (s, 9H, C(C*H*$_3$)$_3$), 3.07 (dd, *J* = 14.3 Hz, *J* = 7.0 Hz, 1H, NC*H*HCHCl), 3.15 (dd, *J* = 14.3 Hz, *J* = 6.6 Hz, 2H, NCH*H*CHCl)), 3.30 (s, 2H, NC*H*$_2$COO^{t}Bu), 3.79-3.98 (m, 3H, NC*H*$_2$Ph, CH$_3$C*H*OCH$_2$Ph), 4.14-4.25 (m, 1H, NCH$_2$C*H*Cl), 4.54 (d, *J* = 12.1 Hz, 1H, A of AB system, PhOC*H*HPh), 4.61 (d, *J* = 12.1 Hz, 1H, B of AB system, PhOCH*H*Ph), 7.23-7.42 (m, 10H, Ph*H*) ppm. ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C): δ = 14.9 (*C*H$_3$), 28.1 (C(*C*H$_3$)$_3$), 55.5 (N*C*H$_2$CHCl), 57.5 (N*C*H$_2$COO^{t}Bu), 58.5 (NCH$_2$*C*HCl), 63.4 (N*C*H$_2$Ph), 70.6 (Ph*C*H$_2$O), 74.9 (CH$_3$*C*HOCH$_2$Ph), 80.9 (COO*C*(CH$_3$)$_3$), 127.2, 127.5, 127.6, 128.3, 128.8 (*C*Ph), 138.2, 138.7 (*ipso*-*C*Ph), 170.4 (CO) ppm. EIMS: *m*/*z* (%) = 440 (100) (M+Na)$^+$, 384(32), 362 (19). HRMS (ESI) calcd. for $C_{24}H_{33}ClNO_3$ [MH$^+$]: 418.2149; found 418.2138.

General procedure for the synthesis of azetidines (GP-2)

To a solution of chloride (1 mmol) in pure THF (10 mL for chloro nitriles) or 8/2 THF/HMPA (for chloro esters) was added dropwise at – 90 °C a solution of LiHMDS (1M solution in THF, 1.5 mL, 1.5 mmol). The reaction was monitored by TLC and then quenched after completion by the addition of an aqueous saturated solution of NH_4Cl at 0 °C. Extraction of the reaction mixture using ether followed by usual workup gave azetidine **34**-**45**.

(2*R* and *2S*, 3*S*)1-Benzyl-3-isobutyl-azetidine-2-carbonitrile 34 and 35. (Table 2, Entry 1) Prepared according to GP-2 and flash chromatographic purification of the reaction mixture gave an inseparable mixture of *cis* and *trans* diasteromers (3:2) (SiO_2, PE/AcOEt, 95:5) as colourless oil. Yield: 103 mg (95%); R_f = 0.60 (PE/AcOEt, 9:1); ^{1}H NMR (200 MHz, $CDCl_3$, 25 °C, mixture of *cis* and *trans* diasteromers (3:2)): 0.94 (d, *J* = 6.2 Hz, 6H, (C*H*$_3$)$_2$CH), 1.46-1.70 (m, 3H, (CH$_3$)$_2$C*H*C*H*$_2$), 2.72 (Appt triplet, *J* = 7.3 Hz 1H, H-4, *cis*-isomer), 2.77-2.94 (m, 1H, H-3), 3.02 (Appt triplet, *J* = 6.8 Hz 1H, H-4′, *cis*-isomer), 3.38 (Appt triplet, *J* = 6.7 Hz, 1H, H-4,

trans-isomer), 3.47 (d, *J* = 7.0 Hz, 1H, H-2, *cis*-isomer), 3.53 (Appt triplet, *J* = 7.0 Hz, 1H, H-4′, *trans*-isomer), 3.54 (d, *J* = 12.8 Hz, 1H, A of AB system, NC*H*HPh), 3.71 (d, *J* = 12.8 Hz, 1H, B of AB system, NCH*H*Ph), 4.19 (d, *J* = 7.3 Hz, 1H, H-2, *trans*-isomer), 7.14-7.46 (m, 5H, Ph*H*) ppm. ^{13}C NMR (50 MHz, $CDCl_3$, 25 °C, *cis*-isomer): δ = 22.4 (2×*C*H_3), 26.5 ($(CH_3)_2$*C*H), 32.2 (C-3), 42.5 ($(CH_3)_2$CH*C*H_2), 57.3 (C-2), 58.8 (C-4), 61.8 (N*C*H_2Ph), 116.8 (CN), 127.5, 128.5, 128.8 (*C*Ph), 136.6 (*ipso*-*C*Ph) ppm. CIMS: *m*/*z* (%) = 229 (89) [MH^+], 202 (18), 172 (5), 137 (45), 91 (100). HRMS (ESI) calcd. for $C_{15}H_{21}N_2$ [MH^+]: 229.1699; found: 229.1697.

(2*S*,3*S*)-(–)-1-Benzyl-3-methylazetidine-2-carbonitrile 36 and (2*R*,3*S*)-(+)-1-benzyl-3-methylazetidine-2-carbonitrile 37. (Table 2, Entry 2) Prepared according to GP-2. Analytical samples of each diastereoisomer could be obtained after flash chromatography (SiO_2, PE/AcOEt, 9:1) as colourless oils. Overall yield: 179 mg (60%). Compound **36** (2,3-*trans* isomer) R_f = 0.75 (PE/AcOEt, 9:1); $[\alpha]_{578}^{20}$: – 48.2 (c = 0.40, $CHCl_3$). ^{1}H NMR (200 MHz, $CDCl_3$, 25 °C): 1.25 (d, *J* = 6.6 Hz, 3H, C*H*$_3$), 2.75 (dd, *J* = 13.6 Hz, *J* = 7.2 Hz, 1H, H-4), 2.86 (septet, *J* = 6.8 Hz, 1H, H-3), 3.45 (d, *J* = 6.8 Hz, 1H, H-2), 3.53 (Appt triplet, *J* = 6.6 Hz, 1H, H-4′), 3.64 (d, *J* = 12.7 Hz, 1H, A of AB system, NC*H*HPh), 3.76 (d, *J* = 12.7 Hz, 1H, B of AB system, NCH*H*Ph), 7.22-7.42 (m, 5H, Ph*H*) ppm. ^{13}C NMR (50 MHz, $CDCl_3$, 25 °C): δ = 18.0 (*C*H_3), 32.5 (C-3), 58.1 (C-4), 59.5 (C-2), 61.5 (N*C*H_2Ph), 118.8 (*C*N), 127.6, 128.4, 128.5, 128.8 (*C*Ph), 136.2 (*ipso*-*C*Ph) ppm. EIMS: *m*/*z* (%) = 187 (19) [MH^+], 161 (13), 160 (100), 159 (23), 91 (3). HRMS (ESI) calcd. for $C_{12}H_{15}N_2$ [MH^+]: 187.1235; found 187.1240. Compound **37** (2,3-*cis* isomer): R_f = 0.72 (PE/AcOEt, 9:1); $[\alpha]_{578}^{20}$: + 76.1 (c = 0.90, $CHCl_3$). ^{1}H NMR (200 MHz, $CDCl_3$, 25 °C): 1.38 (d, *J* = 6.8 Hz, 3H, C*H*$_3$), 2.82 (septet, *J* = 7.2 Hz, 1H, H-3), 2.99 (Appt triplet, *J* = 6.5 Hz, 1H, H-4), 3.32 (Appt triplet, *J* = 6.5 Hz, 1 H, H-4′), 3.69 (d, *J* = 12.7 Hz, 1H, A of AB system, NC*H*HPh), 3.76 (d, *J* = 12.7 Hz, 1H, B of AB system, NCH*H*Ph), 4.11 (d, *J* = 7.5 Hz, 1H, H-2), 7.21-7.41 (m, 5H, Ph*H*) ppm. ^{13}C NMR (50 MHz, $CDCl_3$, 25 °C): δ = 16.2 (*C*H_3), 28.4 (C-3), 57.2 (C-4), 59.2 (C-2), 59.9 (N*C*H_2Ph), 127.5, 128.5, 128.8 (*C*Ph, *C*N), 136.4 (*ipso*-*C*Ph) ppm. EIMS: *m*/*z* (%) = 187 (8) [MH^+], 161 (15), 160 (100), 159 (21), 91 (6). HRMS (ESI) calcd. for $C_{12}H_{15}N_2$ [MH^+]: 187.1235; found 187.1238.

(2*R* and *2S*, 3*S*)-1-Benzyl-3-isopropyl-azetidine-2-carbonitrile 38 and **39.** (Table 2, Entry 3) Prepared according to GP-2 and flash chromatographic purification of the reaction mixture gave an inseparable mixture of *cis* and *trans* diasteromers (3:2) (SiO_2, PE/AcOEt, 95:5) as colourless oil. Yield: 20 mg (25%); R_f = 0.44 (PE/AcOEt, 9:1); ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C, mixture of *cis* and *trans* diasteromers (3:2)): 0.70 (d, *J* = 6.6 Hz, 3H, C*H*$_3$), 0.80 (d, *J* = 6.5 Hz, 3H, C*H*$_3$), 1.50-1.65 (m, 1H, $(CH_3)_2$C*H*, *cis*-isomer), 1.80-1.96 (m, 1H, $(CH_3)_2$C*H*, *trans*-isomer), 2.22-2.40 (m, 1H, H-3), 2.65 (Appt triplet, *J* = 7.3 Hz, 1H, H-4, *cis*-isomer), 2.92 (Appt triplet, *J* = 7.5 Hz, 1H, H-4′, *cis*-isomer), 3.32 (Appt triplet, *J* = 7.1 Hz, 1H, H-4, *trans*-isomer), 3.39 (Appt triplet, *J* = 7.1 Hz, 1H, H-4′, *trans*-isomer), 3.41 (d, *J* = 7.3 Hz, 1H, H-2, *cis*-isomer), 3.48 (d, *J* = 12.5 Hz, 1H, A of AB system, NC*H*HPh), 3.62 (d, *J* = 12.5 Hz, 1H, B of AB system, NCH*H*Ph), 4.10 (d, *J* = 7.3 Hz, 1H, H-2, *trans*-isomer), 7.04-7.30 (m, 5H, Ph*H*) ppm. ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C, *cis*-isomer): δ = 20.3 (*C*H_3), 20.9 (*C*H_3), 32.7 ($(CH_3)_2$*C*H), 44.5 (C-3), 56.8 (C-2), 57.9 (C-4), 61.8 (N*C*H_2Ph), 119.3 (CN), 127.5, 128.1, 128.5 (*C*Ph), 137.4 (*ipso*-*C*Ph) ppm.

CIMS: *m*/*z* (%) = 214 (8) [M^+], 213 (11), 190 (13), 188 (100), 121 (14). HRMS (ESI) calcd. for $C_{14}H_{19}N_2$ [MH^+]: 215.1548; found 215.1536.

(2*R*, 3*S*)-(+)-1-Benzyl-3-isobutyl-azetidine-2-carboxylic acid *tert*-butyl ester 40. (Table 2, Entry 5) Prepared according to GP-2. The pure compound was obtained after flash chromatography (SiO_2, PE/AcOEt, 9:1) as colourless oil. Yield: 131 mg (73%); R_f = 0.82 (PE/AcOEt, 9:1); $[\alpha]_{365}^{20}$: + 197.0 (c = 0.70, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C): 0.73 (d, *J* = 6.7 Hz, 3H, C*H*$_3$), 0.79 (d, *J* = 6.7 Hz, 3H, C*H*$_3$), 1.31 (s, 9H, C(C*H*$_3$)$_3$), 1.32-1.63 (m, 3H, C*H*(CH$_3$)$_2$, C*H*$_2$CH(CH$_3$)$_2$), 2.49-2.68 (m, 1H, H-3), 2.95 (Appt triplet, *J* = 7.0 Hz, 1H, H-4), 3.15 (dd, *J* = 6.6 Hz, *J* = 3.1 Hz, 1H, H-4´), 3.54 (d, *J* = 12.7 Hz, 1H, A of AB system, NC*H*HPh), 3.63 (d, *J* = 12.7 Hz, 1H, B of AB system, NCH*H*Ph), 3.66 (d, *J* = 8.5 Hz, 1 H, H-2), 7.14-7.32 (m, 5H, Ph*H*). ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C): δ = 21.9 (*C*H$_3$), 23.2 (*C*H$_3$), 26.0 (*C*H(CH$_3$)$_2$), 28.1 (COOC(*C*H$_3$)$_3$), 31.9 (C-3), 38.3 (*C*H$_2$CH(CH$_3$)$_2$), 55.4 (C-4), 61.5 (N*C*H$_2$Ph), 67.3 (C-2), 80.7 (COO*C*(CH$_3$)$_3$), 127.1, 128.2, 129.3 (*C*Ph), 137.4 (*ipso*-*C*Ph), 170.8 (CO) ppm. CIMS: *m*/*z* (%) = 304 (24) [MH^+], 248 (13), 202 (100), 91 (54). HRMS (ESI) calcd. for $C_{19}H_{30}NO_2$ [MH^+]: 304.2277; found 304.2271.

(2*R*, 3*S*)-(+)-1-Benzyl-3-methyl-azetidine-2-carboxylic acid *tert*-butyl ester 41. (Table 2, Entry 6) Prepared according to GP-2. The pure compound was obtained by flash chromatography (SiO_2, PE/AcOEt, 9:1) as colourless oil. Yield: 1.050 g (80%); R_f = 0.80 (PE/AcOEt, 9:1); $[\alpha]_D^{20}$: +91.3 (c = 0.40, $CHCl_3$). ^{1}H NMR (200 MHz, $CDCl_3$, 25 °C): 1.23 (d, *J* = 7.0 Hz, 3 H, C*H*$_3$), 1.40 (s, 9 H, C(C*H*$_3$)$_3$), 2.58-2.69 (m, 1H, H-3), 2.90-3.10 (m, 2H, H-4, H-4´), 3.54 (d, *J* = 12.5 Hz, 1H, A of AB system, NC*H*HPh), 3.68 (d, *J* = 8.0 Hz, 1H, H-2), 3.74 (d, *J* = 12.5 Hz, 1H, B of AB system, NCH*H*Ph), 7.18-7.39 (m, 5H, Ph*H*). ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C): δ = 15.5 (*C*H$_3$), 28.2 (COOC(*C*H$_3$)$_3$), 28.6 (C-3), 56.8 (C-4), 61.6 (N*C*H$_2$Ph), 67.3 (C-2), 80.6 (COO*C*(CH$_3$)$_3$), 127.0, 128.2, 129.2 (*C*Ph), 137.5 (*ipso*-*C*Ph), 170.8 (CO) ppm. CIMS: *m*/*z* (%) = 300 (10), 284 (74), 262 (28) [MH^+], 206 (100). HRMS (ESI) calcd. for $C_{16}H_{24}NO_2$ [MH^+]: 262.1802; found 262.1796.

(2*S*, 3*R*)-(–)-1-Benzyl-3-ethyl-azetidine-2-carboxylic acid *tert*-butyl ester 42. (Table 2, Entry 7) Prepared according to GP-2. The pure compound was obtained after flash chromatography (SiO_2, PE/AcOEt, 9:1) as colourless oil. Yield: 272 mg (85%); R_f = 0.75 (PE/AcOEt, 9:1); $[\alpha]_D^{20}$: – 91.1 (c = 0.90, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C): 0.75 (t, *J* = 7.3 Hz, 3 H, C*H*$_3$), 1.30 (s, 9H, C(C*H*$_3$)$_3$), 1.49-1.68 (m, 2H, C*H*$_2$CH$_3$), 2.30-2.46 (m, 1 H, H-3), 2.89 (Appt triplet, *J* = 7.1 Hz, 1H, H-4), 3.01 (dd, *J* = 6.6 Hz, *J* = 2.8 Hz, 1H, H-4´), 3.52 (d, *J* = 12.5 Hz, 1H, A of AB system, NC*H*HPh), 3.63 (d, *J* = 12.5 Hz, 1H, B of AB system, NCH*H*Ph), 3.64 (d, *J* = 7.0 Hz, 1H, H-2), 7.24-7.51 (m, 5H, Ph*H*). ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C): δ = 11.4 (*C*H$_3$), 22.4 (*C*H$_2$CH$_3$), 28.1 (COOC(*C*H$_3$)$_3$), 35.5 (C-3), 54.7 (C-4), 61.7 (N*C*H$_2$Ph), 67.2 (C-2), 80.7 (COO*C*(CH$_3$)$_3$), 127.1, 128.2, 129.3 (*C*Ph), 137.5 (*ipso*-*C*Ph), 170.8 (CO) ppm. CIMS: *m*/*z* (%) = 298 (100), 242 (37), 220 (34). HRMS (ESI) calcd. for $C_{17}H_{26}NO_2$ [MH^+]: 276.1964; found 276.1954.

(2*R*, 3*S*)-(+)-1-Benzyl-3-(4-benzyloxy-benzyl)-azetidine-2-carboxylic acid *tert*-butyl ester 43. (Table 2, Entry 8) Prepared according to GP-2. The pure compound was obtained after flash chromatography (SiO_2, PE/AcOEt, 9:1) as colourless oil. Yield: 93 mg (50%); R_f = 0.70

(PE/AcOEt, 9:1); $[\alpha]_D^{20}$: + 160.0 (c = 0.30, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C): 1.32 (s, 9H, C(C*H*$_3$)$_3$), 2.62-2.90 (m, 5H, CHC*H*2Ph, H-3, H-4), 3.51 (d, *J* = 12.5 Hz, 1H, A of AB system, NC*H*HPh), 3.66 (d, *J* = 13.0 Hz, 1H, B of AB system, NCH*H*Ph), 3.69 (d, *J* = 8.3 Hz, 1H, H-2), 4.92 (s, 2H, PhC*H*$_2$O), 6.77 (d, *J* = 8.5 Hz, 2H, OPh*H*), 6.98 (d, *J* = 8.5 Hz, 2H, OPh*H*), 7.18-7.39 (m, 10H, Ph*H*). ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C): δ = 28.2 (COOC(*C*H$_3$)$_3$), 34.4 (CH*C*H$_2$PhO), 34.8 (C-3), 54.2 (C-4), 61.7 (N*C*H$_2$Ph), 66.8 (C-2), 70.0 (O*C*H$_2$Ph), 81.1 (COO*C*(CH$_3$)$_3$), 114.8, 127.2, 127.5, 127.7, 128.0, 128.3, 128.6, 129.4 (*C*Ph), 129.8, 132.2, 137.2, 157.3 (*ipso*-*C*Ph), 170.7 (CO) ppm. CIMS: *m*/*z* (%) = 444 (100) [MH$^+$], 419 (7), 388 (7), 354 (7), 342 (30). HRMS (ESI) calcd. for $C_{29}H_{34}NO_3$ [MH$^+$]: 444.2539; found 444.2542.

(2*R*, 3*S*)-(+)-1-Isopropyl-3-phenoxymethyl-azetidine-2-carboxylic acid *tert*-butyl ester 44. (Table 2, Entry 9) Prepared according to GP-2. The pure compound was obtained after flash chromatography (SiO_2, PE/AcOEt, 4:1) as colourless oil. Yield: 40 mg (50%); R_f = 0.80 (PE/AcOEt, 4:1); $[\alpha]_D^{20}$: + 50.8 (c = 1.30, $CHCl_3$). ^{1}H NMR (200 MHz, $CDCl_3$, 25 °C): 0.93 (d, *J* = 6.4 Hz, 3H, C*H*$_3$), 0.98 (d, *J* = 6.4 Hz, 3 H, C*H*$_3$) 1.42 (s, 9H, C(C*H*$_3$)$_3$), 2.32-2.56 (septet, *J* = 6.4 Hz, 1H, NC*H*(CH$_3$)$_2$), 2.88-3.11 (m, 2H, H-3, H-4), 3.35 (d, *J* = 5.3 Hz, 1H, H-4′), 3.75 (d, *J* = 7.5 Hz, 1H, H-2), 4.18 (Appt triplet, *J* = 8.0 Hz, 1H PhOC*H*HCH), 4.37 (Appt triplet, *J* = 8.0 Hz, 1H PhOCH*H*CH), 6.78-7.12 (m, 3H, Ph*H*), 7.27 (t, *J* = 10 Hz, 2H, Ph*H*). ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C): δ = 19.3 (*C*H$_3$), 19.8 (*C*H$_3$), 28.0 (COOC(*C*H$_3$)$_3$), 31.6 (C-3), 52.1 (C-4), 57.8 (NC*H*(CH$_3$)$_2$), 65.6 (C-2), 67.4 (ArO*C*H$_2$CH), 81.0 (COO*C*(CH$_3$)$_3$), 114.5, 120.7, 129.3 (*C*Ph), 158.7 (*ipso*-*C*Ph), 170.4 (CO) ppm. CIMS: *m*/*z* (%) = 328 (20), 272 (100), 250 (55), 290 (82), 204 (25). HRMS (ESI) calcd. for $C_{18}H_{28}NO_3$ [MH$^+$]: 306.2069; found 306.2077.

(2*R*, 3*S*)-(+)-1-Isopropyl-3-phenoxymethyl-azetidine-2-carboxylic acid *tert*-butyl ester 45. (Table 2, Entry 10) Prepared according to GP-2. The pure compound was obtained after flash chromatography (SiO_2, PE/AcOEt, 4:1) as colourless oil. Yield: 87 mg (75%); R_f = 0.45 (PE/AcOEt, 9:1); $[\alpha]_D^{20}$: + 48.7 (c = 1.10, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C): 1.26 (s, 9H, C(C*H*$_3$)$_3$), 2.86-3.07 (m, 2H, H-3, H-4), 3.18 (dd, *J* = 4.8 Hz, *J* = 1.9 Hz, 1H, H-4′), 3.58 (d, *J* = 12.5 Hz, 1H, A of AB system, NC*H*HPh), 3.69 (d, *J* = 12.5 Hz, 1H, B of AB system, NCH*H*Ph), 3.74 (d, *J* = 8.0 Hz, 1H, H-2), 4.12 (Appt triplet, *J* = 8.5 Hz, 1H PhOC*H*HCH), 4.29 (dd, *J* = 9.2 Hz, *J* = 6.5 Hz, 1H PhOCH*H*CH), 6.82-7.04 (m, 3H, Ph*H*), 7.10-7.30 (m, 7H, Ph*H*). ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C): δ = 28.0 (COOC(*C*H$_3$)$_3$), 33.3 (C-3), 53.1 (C-4), 61.9 (N*C*H$_2$Ph), 65.7 (C-2), 67.3 (ArO*C*H$_2$CH), 81.0 (COO*C*(CH$_3$)$_3$), 114.5, 120.7, 127.2, 128.3, 129.3, 129.4 (*C*Ph), 137.1, 158.8 (*ipso*-*C*Ph), 170.0 (CO) ppm. CIMS: *m*/*z* (%) = 392 (6), 376 (100), 354 (3) [MH$^+$], 298 (72), 204 (25). HRMS (ESI) calcd. for $C_{22}H_{28}NO_3$ [MH$^+$]: 354.2069; found 354.2071.

(2*R*, 3*S*)-(+) 3-Methyl-azetidine-1,2-dicarboxylic acid di-*tert*-butyl ester 46. To a mixture of azetidine (100 mg, 0.38 mmole), Boc anhydride (104 mg, 0.48 mmol) in absolute ethanol (10 mL) was added $Pd(OH)_2$ and the reaction mixture was stirred under hydrogen ballon pressure for 2 h. After the completion of the reaction, the reaction mixture was filtered through Celite and the filtrate was concentrated and dried under vacuo. The crude residue was then purified by silica gel column chromatography using petroleum ether and ethyl acetate (8:2) gave *N*-Boc azetidine as a

thick oil. Yield: 92 mg (89%); R_f = 0.45 (PE/AcOEt, 4:1); $[\alpha]_D^{20}$: + 67.4 (c = 0.40, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C): 0.90 (d, *J* = 7.3 Hz, 3H, C*H*$_3$), 1.12 (s, 9H, COOC(C*H*$_3$)$_3$), 1.27 (s, 9H, NCOOC(C*H*$_3$)$_3$), 2.70 (septet, *J* = 6.0 Hz, 1H, H-3), 3.35 (Appt triplet, *J* = 6.7 Hz, 1H, H-4), 3.72 (Appt triplet, *J* = 6.7 Hz, 1H, H-4′), 4.28 (d, *J* = 8.9 Hz, 1H, H-2). ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C): δ = 14.3 (*C*H$_3$), 27.1 (COOC(*C*H$_3$)$_3$), 27.8 (NCOOC(*C*H$_3$)$_3$), 28.0 (C-3), 54.0 (C-4), 65.2 (C-2), 79.6 (COO*C*(CH$_3$)$_3$), 81.6 (NCOO*C*(CH$_3$)$_3$), 155.4 (*C*OOC(CH$_3$)$_3$), 168.8 (N*C*OOC(CH$_3$)$_3$) ppm. CIMS: *m*/*z* (%) = 271 (100) [M^+], 272 (16) [MH^+]. $C_{14}H_{25}NO_4$ (271.35): calcd. C 61.97, H 9.29, N 5.56; found C 61.89, H 9.36, N 5.61.

(2*R*,3*S*)-(+)-3-Methyl-azetidine-2-carboxylic acid 47. To a solution of *N*-Boc azetidine **46** (92 mg, 0.34 mmole) in THF (5 mL) was added TFA (3 mL) and stirred overnight. The reaction mixture was concentrated under vacuo. The traces of TFA in the reaction mixture were removed by adding acetone and subsequent removal of the solvents from the mixture. The obtained triflate salt was purified using ion exchange Dowex resin. The column was first eluted with distilled water to get rid of trifluoroacetic acid and then the column was eluted with EtOH/NH_4OH (30% aq.soln)/H_2O, 9:3:1 solution to elute the azetidinic amino acid. The pure compound was obtained as a colourless solid. Yield: 33 mg (94%); Mp: 65 °C; R_f = 0.45 (EtOH/NH_4OH (30% aq.soln)/H_2O, 9:3:1); $[\alpha]_D^{20}$: + 210 (c = 0.10, H_2O). ^{1}H NMR (300 MHz, D_2O, 25 °C): 1.07 (d, *J* = 7.4 Hz, 3H, C*H*$_3$), 3.09 (septet, *J* = 7.2 Hz, 1H, H-3), 3.48 (dd, *J* = 10.4 Hz, *J* = 6.3 Hz, 1H, H-4), 4.11 (Appt triplet, *J* = 9.8 Hz, 1H, H-4′), 4.75 (d, *J* = 9.4 Hz, 1H, H-2). ^{13}C NMR (75 MHz, D_2O, 25 °C): δ = 14.3 (*C*H$_3$), 29.3 (C-3), 49.9 (C-4), 62.9 (C-2), 171.7 (CO) ppm. CIMS: *m*/*z* (%) = 133 (20) [$MH+NH_3^+$], 116 (100) [MH^+]. HRMS (ESI) calcd. for $C_5H_{10}NO_2$ [MH^+]: 116.0712; found 116.0721.

Dipeptide 49

To a solution of *N*-Benzyl azetidine **41** (219 mg, 0.84 mmole) in DCM (5 mL) was added TFA (1 mL) and stirred for 30 min. The reaction mixture was concentrated under vacuo. Traces of TFA in the reaction mixture were removed by adding acetone and subsequent removal of the solvents from the mixture. To a solution of crude *N*-Benzyl azetidinic triflate salt **48**, (270 mg, 0.88 mmol) in acetonitrile (10 mL) were added BOP reagent (777 mg, 1.76 mmol), *L*-Ala-OMe, HCl (247 mg, 1.76 mmol), and triethylamine (0.218 mL, 1.57 mmol). After 16h of stirring at r.t., the reaction was quenched by the addition of saturated aq. sodium chloride solution. The reaction mixture was extracted with ethyl acetate and the combined organic layer was washed successively with 2N HCl, water, 5% $NaHCO_3$, and water and dried over Na_2SO_4. The solvent was removed under reduced pressure to give the crude dipeptide. Purification of the crude product on flash silica gel column chromatography (AcOEt/PE: 1:1) gave dipeptide **49**.Yield: 166 mg (65%); R_f = 0.70 (PE/AcOEt, 9:1); $[\alpha]_D^{20}$: + 42.1 (c = 1.30, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C): 1.01 (d, *J* = 7.3 Hz, 3H, CH_3), 1.50 (d, *J* = 7.3 Hz, 3H, CH_3), 2.62-2.78 (septet, *J* = 7.3 Hz, 1H, H-3), 3.01 (dd, *J* = 6.9 Hz, *J* = 2.1 Hz, 1H, H-4), 3.14 (Appt triplet, *J* = 7.6 Hz, 1H, H-4′), 3.51 (d, *J* = 12.3 Hz, 1H, A of AB system, NC*H*HPh), 3.58 (d, *J* = 12.5 Hz, 1H, B of AB system, NCH*H*Ph), 3.66 (s, 3H, OC*H*$_3$), 3.70 (d, *J* = 8.9 Hz, 1H, H-2), 4.38 (quintet, *J* = 7.5 Hz,

1 H, $CH_3CHCOOCH_3$), 7.10-7.30 (m, 5H, Ph*H*), 7.40 (br. s, 1H, N*H*). ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C): δ = 15.2 (CH_3), 18.1 (CH_3), 27.9 (C-3), 46.9 ($CH_3CHCOOCH_3$), 52.3 (OCH_3), 57.4 (C-4), 62.4 (NCH_2Ph), 69.0 (C-2), 127.5, 128.7, 129.0 (*C*Ph) 137.7 (*ipso*-*C*Ph), 170.6 (CO), 173.3 (CO) ppm. CIMS: *m*/*z* (%) = 330 (9), 313 (100), 291 (51) [MH^+]. HRMS (ESI) calcd. for $C_{16}H_{23}N_2O_3$ [MH^+]: 291.1709; found 291.1694.

Tripeptide 50

To a mixture of dipeptide **49** (140 mg, 0.48 mmole) and acetic acid (0.27 mL, 4.80 mmol) in methanol (10 mL) was added $Pd(OH)_2$ (50 mg) and the reaction mixture was stirred under hydrogen ballon pressure for 2 h. After the completion of the reaction, the reaction mixture was filterd through Celite and the filtrate was concentrated and dried under vacuo to give crude *N*-debenzylated intermediate as an ammonium acetate salt (118 mg, 95 %). To a mixture of this dipeptide acetate salt (55 mg, 0.21 mmol), BOP reagent (188 mg, 0.42 mmol), *N*-Boc alanine (81 mg, 0.42 mmol) in acetonitrile (2 mL) was added triethylamine (0.12 mL, 0.85 mmole). The reaction mixture was stirred at rt for overnight. The reaction mixture was quenched by the addition of saturated aq. sodium chloride solution and the reaction mixture was extracted with ethyl acetate (2 × 15 mL). The combined organic layer were washed successively with 2N HCl, water, 5% $NaHCO_3$, and water and dried with Na_2SO_4. The solvent was removed under reduced pressure to give the crude dipeptide. Purification of the crude product on flash silica gel column chromatography (AcOEt/PE: 8:2) gave tripeptide (39 mg, 50%).; R_f = 0.70 (AcOEt); $[\alpha]_D^{20}$: +85.0 (c = 0.30, $CHCl_3$). ^{1}H NMR (300 MHz, Acetone-d_6, 25 °C, mixture of rotamers): 0.68 (d, *J* = 6.8 Hz, 3H, CH_3), 1.03 (d, *J* = 7.3 Hz, 3H, CH_3), 1.06 (d, *J* = 6.8 Hz, 3H , CH_3), 1.14 (d, *J* = 7.0 Hz, 3H, CH_3), 1.29 (s, 9H, $C(CH_3)_3$), 2.90 (septet, *J* = 8.0 Hz, 1H, H-3), 3.24 (septet, *J* = 6.6 Hz, 1H, H-3), 3.54 (s, 3H, OCH_3), 3.56 (s, 3H, OCH_3), 3.71 (t, *J* = 6.7 Hz, 1H, H-4), 3.76-3.96 (m, 2H, H-4′, $CH(CH_3)NH$), 4.23 (quintet, *J* = 6.7 Hz, 1H, $CH(CH_3)NH$), 4.31 (quintet, *J* = 6.7 Hz, 1H, $CH(CH_3)NH$), 4.47 (d, *J* = 9.4 Hz, 1H, H-2), 5.08 (d, *J* = 9.0 Hz, 1H, H-2), 5.90 (br.s, NH), 6.25 (br.s, NH), 7.34 (br.s, NH), 7.71 (br.s, NH). ^{13}C NMR (75 MHz, Acetone-d_6, 25 °C, mixture of rotamers): δ = 14.0, 16.1, 17.2, 17.4 (CH_3), 28.2 ($C(CH_3)_3$), 29.0 (C-3), 29.4 ($C(CH_3)_3$), 46.0, 47.2, 47.7, 47.9 ($NCH(CH_3)$, 52.5 (OCH_3), 54.0 (C-4), 55.1 (C-4), 64.5 (C-2), 67.0 (C-2), 78.6 ($OC(CH_3)_3$), 156.0 (NCOO), 168.5, 170.6, 172.5, 173.3 (CO) ppm. CIMS: *m*/*z* (%) = 372 (9) [MH^+], 333 (30), 316 (35), 260 (100), 91 (15), 82 (3). HRMS calcd. for $C_{17}H_{30}N_3O_6$ [MH^+]: 372.2135; found 372.2132.

(*R*)-methyl 3-(benzylamino)butanoate 54. To a solution of (*R*)-methyl 3-aminobutanoate (1.00 g, 9.01 mmol) in MeOH (25 mL) was added benzaldehyde (916 µL, 9.01 mmol) and stirred at rt for 1 h and then sodium borohydride (410 mg, 10.8 mmol) was added portionwise at 0° C. The reaction mixture was allowed to reach rt and stirred overnight. The excess $NaBH_4$ was quenched by NH_4Cl and then it was concentrated under vacuo. The crude residue was then extracted with diethyl ether and the organic layer was concentrated and dried. Flash column chromatographic purification of the residue (SiO_2, PE/AcOEt, 1:4) gave the pure compound as colourless oil. Yield: 1.12 g (60%); R_f = 0.20 (PE/AcOEt, 1:1); $[\alpha]_{578}^{20}$: – 17.7 (c = 1.25, $CHCl_3$). ^{1}H NMR

(300 MHz, $CDCl_3$, 25 °C): 1.16 (d, J = 6.4 Hz, 3H, CH_3), 2.39 (dd, J = 15.1, J = 6.2 Hz, 1H, CHHCOOCH$_3$), 2.52 (dd, J = 15.4, J = 6.8 Hz, 1H, CHHCOOCH$_3$), 3.15 (sextet, J = 6.4 Hz, 1H, CH$_3$CHNCH$_2$Ph), 3.67 (s, 3H, OCH$_3$), 3.81 (d, J = 13.0 Hz, 1H, A of AB system, NCHHPh), 3.88 (d, J = 13.0 Hz, 1H, B of AB system, NCHHPh), 7.20-7.40 (m, 5H, PhH). ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C): δ = 20.5 (*C*H$_3$), 41.4 (*C*H$_2$COOCH$_3$), 49.7 (CH$_3$*C*H), 51.2 (O*C*H$_3$), 51.6 (N*C*H$_2$Ph), 126.9, 128.2, 128.5 (*C*Ph) 140.4 (*ipso*-*C*Ph), 172.8 (CO) ppm. EIMS: *m*/*z* (%) = 315 (45), 293 (100), 208 (30) [MH$^+$], 134 (58). $C_{12}H_{17}NO_2$ (207.27): calcd. C 69.54, H 8.27, N 6.76; found C 69.48, H 8.30, N 6.71.

(*R*)-3-(benzylamino)butan-1-ol 55. To a solution of **54** (946 mg, 4.57 mmol) in THF (10 mL) was added lithium aluminium hydride (347 mg, 9.14 mmol) portionwise at 0 °C. After stirring for ten more minutes at this temperature, the reaction mixture was refluxed for 3 h. After the completion of reaction, the excess LAH was quenched by the addition of 2N NaOH (5 mL) and the reaction mixture was filtered off. The filtrate was concentrated and dried. The crude residue was pure enough for further reactions. Yield: 787 mg (97%); R_f = 0.05 (AcOEt/MeOH, 9:1); $[\alpha]_D^{20}$: – 60.0 (c = 0.31, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C): 1.08 (d, J = 6.4 Hz, 3 H, CH_3), 1.40-1.52 (m, 1 H, CHHCH$_2$OH), 1.58-1.68 (m, CHHCH$_2$OH), 2.86 (sextet, J = 6.7 Hz, 1 H, CH$_3$CHCH$_2$), 3.60-3.78 (m, 4 H, NCH_2Ph, CH$_2$CH_2OH), 7.10-7.30 (m, 5 H, PhH). ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C): δ = 20.3 (*C*H$_3$), 37.1 (CH$_3$CH*C*H$_2$), 51.2 (N*C*H$_2$Ph), 53.6 (CH$_3$*C*HN), 62.2 (CH$_2$*C*H$_2$OH) 127.2, 128.4, 128.6 (*C*Ph) 139.7 (*ipso*-*C*Ph) ppm. EIMS: *m*/*z* (%) = 180 (100) [MH$^+$]. $C_{11}H_{17}NO$ (179.26): calcd. C 73.70, H 9.56, N 7.81; found C 73.72, H 9.45, N 7.76.

(*R*)-*tert*-butyl 2-(*N*-benzyl-*N*-(4-hydroxybutan-2-yl)amino)acetate 56. To a mixture of (*R*)-3-(benzylamino)butan-1-ol **55** (187 mg, 1.06 mmol), sodium iodide (316mg, 2.11mmol), sodium bicarbonate (177 mg, 2.11 mmol) in DMF (10 mL) was added drop wise *t*-butylbromoacetate (310 μL, 2.11 mmol) and the resulting suspension was stirred at rt overnight. After the completion of reaction, the reaction mixture was poured into a 1:1 mixture of saturated aq. NH_4Cl and diethyl ether and the organic layer was concentrated and dried. The crude residue was then purified by silica gel column chromatography (SiO_2, PE/AcOEt, 4:1) to give **56** as a colourless oil. Yield: 177 mg (57%); R_f = 0.50 (PE/AcOEt, 4:1); $[\alpha]_D^{20}$: – 30.0 (c = 0.80, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C): 0.90 (d, J = 6.7 Hz, 3 H, CH_3), 1.38-1.43 (m, 1 H, CH$_3$CHCHH), 1.38 (s, 9 H, C(CH_3)$_3$), 1.58-1.73 (m, 1 H CH$_3$CHCHH), 2.81-2.95 (m, 1 H, CH$_3$CHN), 2.96 (d, J = 16.8 Hz, NCHHCOO^{t}Bu), 3.26 (d, J = 16.8 Hz, NCHHCOO^{t}Bu), 3.30 (d, J = 13.3 Hz, 1 H, A of AB system, NCHHPh), 3.47 (dt, J = 9.7 Hz, J = 3.6 Hz, 1 H, CH$_2$CHHOH), 3.65-3.77 (m, 2 H, CH$_2$CHHOH, NCHHPh), 7.10-7.30 (m, 5 H, PhH). ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C): δ = 12.6 (*C*H$_3$), 28.1 (C(*C*H$_3$)$_3$), 35.6 (CH$_3$CH*C*H$_2$), 51.9 (N*C*H$_2$Ph), 54.3 (N*C*H$_2$COO^{t}Bu), 54.4 (CH$_3$*C*HN), 62.0 (CH$_2$*C*H$_2$OH), 81.7 (*C*(CH$_3$)$_3$), 127.3, 128.5, 129.0 (*C*Ph) 138.6 (*ipso*-*C*Ph), 171.4 (CO) ppm. EIMS: *m*/*z* (%) = 294 (85) [MH$^+$], 248 (9), 238 (30), 220 (9), 193 (17), 192 (100), 148 (13), 91 (30). $C_{17}H_{27}NO_3$ (179.26): calcd. C 69.59, H 9.28, N 4.77; found C 69.62, H 9.30, N 4.74.

(1*R*)-(–)-1-Benzyl-(3-chloro-1-methyl-propyl)-amino]-acetic acid *tert*-butyl ester 57. Prepared according to GP-1. The pure compound was obtained after flash chromatography (SiO_2,

PE/AcOEt, 9:1) as a colourless oil. Yield: 600 mg (78%); R_f = 0.70 (PE/AcOEt, 9:1); $[\alpha]_D^{20}$: – 39.1 (c = 0.70, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C): 0.95 (d, *J* = 6.6 Hz, 3H, C*H*$_3$), 1.36 (s, 9H, C(C*H*$_3$)$_3$), 1.54-1.68 (m,1H, ClCH$_2$C*H*H), 1.82-1.96 (m, 1H, ClCH$_2$CH*H*), 2.83-2.96 (m, 1H, NC*H*CH$_3$), 2.98 (d, *J* = 16.4 Hz, 1H, NC*H*HCOO(C(CH$_3$)$_3$), 3.10 (d, *J* = 16.4 Hz,1H, NCH*H*COO(C(CH$_3$)$_3$) 3.51 (d, *J* = 13.8 Hz, 1H, A of AB system, NC*H*HPh), 3.92 (d, *J* = 14.1 Hz, 1H, B of AB system, NCH*H*Ph), 3.56-3.67 (m, 2H, CH$_2$Cl), 3.73 (d, *J* = 13.8 Hz, 1H, B of AB system, NC*H*HPh), 7.10-7.34 (m, 5H, Ph*H*). ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C): δ = 14.0 (CH_3), 28.1 (COOC(*C*H$_3$)$_3$), 37.8 (ClCH$_2$*C*H$_2$), 42.8 (Cl*C*H$_2$), 52.2 (N*C*H$_2$ COOC(CH$_3$)$_3$), 53.0 (N*C*HCH$_3$), 54.8 (NCH$_2$Ph), 80.7 (COO*C*(CH$_3$)$_3$), 127.0, 128.3, 128.8 (*C*Ph) 139.5 (*ipso*-*C*Ph), 171.5 (CO) ppm. CIMS: *m*/*z* (%) = 346 (14), 312 (100) [MH$^+$], 311 (40), 256 (17), 210 (93). $C_{17}H_{26}ClNO2$ (311.85): calcd. C 65.48, H 8.40, N 4.49; found C 65.40, H 8.42, N 4.53.

(2*R*, 5*R*) (+)-1-Benzyl-5-methyl-pyrrolidine-2-carboxylic acid *tert*-butyl ester 58. Prepared according to GP-2. The pure compound was obtained after flash chromatography (SiO_2, PE/AcOEt, 9:1) as a colourless oil. Yield: 82 mg (59%); R_f = 0.57 (PE/AcOEt, 9:1); $[\alpha]_D^{20}$: + 13.5 (c = 0.31, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C): 1.15 (d, *J* = 6.0 Hz, 3H, C*H*$_3$), 1.40 (s, 9H, C(C*H*$_3$)$_3$), 1.50-1.68 (m,1H, H-4), 1.80-2.03 (m, 3H, H-3, H-3′, H-4′), 2.68-2.82 (m, 1H, H-5), 3.21 (Appt triplet, *J* = 7.0 Hz, 1H, H-2), 3.79 (d, *J* = 14.1 Hz, 1H, A of AB system, NC*H*HPh), 3.92 (d, *J* = 14.1 Hz, 1H, B of AB system, NCH*H*Ph), 7.22-7.40 (m, 5H, Ph*H*). ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C): δ = 19.9 (CH_3), 27.9 (COOC(*C*H$_3$)$_3$), 28.0 (C-4), 32.5 (C-3), 56.5 (N*C*H$_2$Ph), 59.7 (C-5), 66.4 (C-2), 80.1 (COO*C*(CH$_3$)$_3$), 126.8, 128.0, 129.5 (*C*Ph) 138.6 (*ipso*-*C*Ph), 173.9 (CO) ppm. CIMS: *m*/*z* (%) = 276 (42) [MH$^+$], 220 (26), 174 (100), 91 (34). $C_{17}H_{25}NO_2$ (275.39): calcd. C 74.14, H 9.15, N 5.09; found C 74.10, H 9.09, N 5.17.

(2*S*, 5*R*)-(–)-1-Benzyl-5-methyl-pyrrolidine-2-carboxylic acid *tert*-butyl ester 59. Prepared according to GP-2. The pure compound was obtained after flash chromatography (SiO_2, PE/AcOEt, 9:1) as a colourless oil. Yield: 54 mg (39%); R_f = 0.60 (PE/AcOEt, 9:1); $[\alpha]_D^{20}$: – 81.6 (c = 0.75, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C): 1.11 (d, *J* = 6.2 Hz, 3H, C*H*$_3$), 1.49 (s, 10 H, H-4, C(C*H*$_3$)$_3$), 1.70-1.82 (m,1H, H-4′), 2.05-2.28 (m, 2H, H-3, H-3′), 3.31-3.45 (sextet, *J* = 6.8 Hz, 1H, H-5), 3.50 (dd, *J* = 5.8 Hz, *J* = 2.5 Hz, 1H, H-2), 3.76 (d, *J* = 13.5 Hz, 1H, A of AB system, NC*H*HPh), 3.98 (d, *J* = 13.7 Hz, 1H, B of AB system, NCH*H*Ph), 7.11-7.42 (m, 5H, Ph*H*). ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C): δ = 19.7 (CH_3), 27.4 (C-4), 28.2 (COOC(*C*H$_3$)$_3$), 31.8 (C-3), 52.4 (N*C*H$_2$Ph), 56.6 (C-5), 63.7 (C-2), 80.3 (COO*C*(CH$_3$)$_3$), 126.6, 128.2, 128.8 (*C*Ph) 140.2 (*ipso*-*C*Ph), 174.2 (CO) ppm. CIMS: *m*/*z* (%) = 276 (29) [MH$^+$], 220 (13), 174 (100), 91 (23). $C_{17}H_{25}NO_2$ (275.39): calcd. C 74.14, H 9.15, N 5.09; found C 74.20, H 9.19, N 5.02.

[Benzyl-(3-chloro-butyl)-amino]-acetic acid *tert*-butyl ester 62. Prepared according to GP-1. The pure compound was obtained after flash chromatography (SiO_2, PE/AcOEt, 9:1) as a colourless oil. Yield: 1.77 g (93%); R_f = 0.70 (PE/AcOEt, 9:1); ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C): 1.54 (s, 12 H, C(C*H*$_3$)$_3$), 1.92 (quartet, *J* = 6.7 Hz, 2 H, NCH$_2$C*H*$_2$CHCl), 2.80-2.97 (m, 2 H, NC*H*$_2$CH$_2$), 3.27 (s, 2 H, NC*H*$_2$COOC(CH$_3$)$_3$), 3.85 (s, 2 H, NC*H*$_2$Ph), 4.24 (sextet, *J* = 6.6 Hz, 1 H, CH$_3$C*H*Cl), 7.25-7.45 (m, 5 H, Ph*H*). ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C): δ = 25.5 (CH_3), 28.3 (COOC(*C*H$_3$)$_3$), 38.6 (NCH$_2$*C*H$_2$), 51.3 (N*C*H$_2$CH$_2$), 55.4 (N*C*H$_2$COOC(CH$_3$)$_3$), 56.6

(CH_3CHCl), 58.4 (NCH_2Ph), 80.8 ($COOC(CH_3)_3$), 127.1, 128.3, 128.9 (*C*Ph) 139.2 (*ipso*-*C*Ph), 170.7 (CO) ppm. EIMS: *m*/*z* (%) = 334 (35) [$M+Na^+$], 280 (32), 242 (24), 200 (17). $C_{16}H_{24}ClNO_2$ (297.82): calcd. C, 64.53; H, 8.12; N, 4.70; found C 64.45, H 8.06, N 4.79.

***cis* and *trans*-1-Benzyl-3-methyl-pyrrolidine-2-carboxylic acid *tert*-butyl ester 63.** Prepared according to GP-2. The pure compound was obtained after flash chromatography (SiO_2, PE/AcOEt, 9:1) as a colourless oil. Yield: 54 mg (98%); R_f = 0.60 (PE/AcOEt, 9:1); ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C, 2 : 1 mixture of diasteroisomers): 0.94 (d, *J* = 6.9 Hz, 3H, C*H*$_3$ major isomer), 1.03 (d, *J* = 6.7 Hz, 3 H, C*H*$_3$, minor isomer), 1.11-1.41 (m, 1H, H-4, major isomer), 1.35 (s, 9H, C(C*H*$_3$)$_3$, minor isomer), 1.38 (s, 9H, C(C*H*$_3$)$_3$, major isomer), 1.42-1.60 (m, 1H, H-4, major isomer), 1.83-2.07 (m, 1H, H-4′), 2.18-2.45 (m, 2H, H-3, H-5, major isomer), 2.60 (d, J = 7.3 Hz, 1H, H-2, major isomer), 2.85-3.00 (m, 1H, H-5), 3.19 (d, *J* = 8.3 Hz 1H, H-2, minor isomer), 3.33 (d, *J* = 12.3 Hz, 1H, A of AB system, NC*H*HPh, major isomer), 3.56 (d, *J* = 13.1 Hz, 1H, A of AB system, NC*H*HPh, minor isomer), 3.75 (d, *J* = 12.9 Hz, 1H, B of AB system, NCH*H*Ph, minor isomer) 3.85 (d, *J* = 12.9 Hz, 1H, B of AB system, NCH*H*Ph, minor isomer), 7.10-7.38 (m, 5H, Ph*H*). ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C, major diasteromer): δ = 20.0 (CH_3), 28.2 ($COOC(CH_3)_3$), 31.3 (C-4), 36.1 (C-3), 51.8 (C-5), 58.7 (NCH_2Ph), 74.1 (C-2), 80.5 ($COOC(CH_3)_3$), 126.9, 128.7, 129.2 (*C*Ph) 138.7 (*ipso*-*C*Ph), 172.9 (CO) ppm. CIMS: *m*/*z* (%) = 276 (35) [MH^+], 221 (10), 173 (100), 91 (20). $C_{17}H_{25}NO_2$ (275.39): calcd. C 74.14, H 9.15, N 5.09; found C 74.10, H 9.17, N 5.13.

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