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New Scalable Asymmetric Aminomethylation Reaction for the Synthesis of β²-Amino Acids

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β-Amino acids are useful tools in the design of peptidomimetics, and the development of new methods for their syntheses, particularly the synthesis of β²-amino acids, remains an important challenge. Here we report a new scalable route based on the aminomethylation of silyl ketene N,O-acetals by Mannich-type iminium electrophiles.

Introduction

The development of scalable syntheses of β-amino acids has constituted an important challenge since oligomers of these compounds were reported to be excellent peptidomimetics.[1,2] This goal has been reached in the case of β³-amino acids; indeed, the Arndt–Eistert homologation of natural amino acids allows the large-scale synthesis of all the β³-amino acids, which are now commercially available.[3] This has permitted an extensive study of oligomers of these compounds and their use for the development of interesting peptidomimetics.

On the other hand, it is known that different β-peptide secondary structures,[4] especially the design of β-turn-type structures,[5] require the introduction of β²-amino acid isomers. Use of these compounds, however, is still highly limited for practical reasons, as no general methodology for the multigram preparation of these compounds has yet been reported (especially those bearing suitably protected functionalities on their side chains), even though it is a prerequisite for peptide synthesis. Although Seebach et al. succeeded in preparing all of the β²-amino acids bearing proteinogenic side chains, the syntheses of some are not straightforward, and are limited to laboratory scales.[6] Many other methods have been reported,[7] including a recent elegant organocatalytic one developed by Gellman et al.,[8] but none of them seems amenable to large-scale synthesis, especially in view of the purification steps required. The most widely used route involves aminomethylation of an enolate equivalent bearing the side chain of the amino acid. Many aminomethylating agents for this purpose have been reported, but their use presents severe limitations that hinder up-scaling, such as their low stabilities and/or reactivities and the harsh conditions required to deprotect the amine moieties.[9] We recently reported our preliminary results on the homologation of α-amino acids to β²-amino acids by means of Reformatsky-type reactions using highly reactive preformed iminium ions as aminomethylating agents.[10] Here we disclose the scope and limitations of this approach, together with its extension to the aminomethylation of silyl enol ethers, which has allowed the development of a highly efficient and scalable synthesis of a wide range of optically pure β²-amino acids.

Results and Discussion

The classical Reformatsky reaction involves nucleophilic species produced through zinc insertion into the carbon–halogen bonds in α-haloacetate esters.[11] This reaction is usually conducted under very mild conditions, the major proviso being that highly reactive electrophiles are usually needed. The addition of Reformatsky reagents to reactive imine derivatives has been widely used for the preparation of β³- or disubstituted β²,³-amino acids (Gilman–Speeter reaction),[12] but the aminomethylation of such reagents is limited by the inaccessibility of stable and reactive formylimine equivalents. Interestingly, Mannich-type iminium ions are very reactive aminomethylating agents: Knochel et al. have reported the aminomethylation of organozinc and

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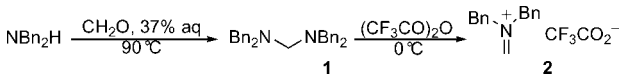
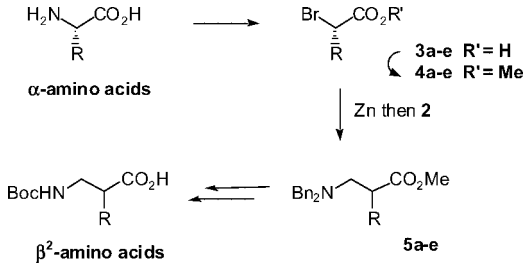
Grignard reagents through the use of iminium trifluoroacetates generated in situ.[13] We have thus explored the scope of these iminium trifluoroacetate salts with regard to the Reformatsky reaction.

Aminal **1** was generated by heating dibenzylamine and aqueous formaldehyde at reflux, as reported by Knochel et al.,[13] and isolated by crystallization as a stable solid compound (Scheme 1). Treatment of this aminal with trifluoroacetic anhydride produced the corresponding trifluoroacetate iminium salt, which was directly used in the Reformatsky reaction without further purification.



Scheme 1. Synthesis of the iminium trifluoroacetate salt.

α-Bromo esters **4a**–**e**, bearing proteinogenic side chains, if not commercially available, were easily obtained from the corresponding α-amino acids by diazotization,[14] and subsequent esterification under conditions compatible with classical protective groups for peptide synthesis.[15] The zinc intermediate was generated, as reported by Dardoize et al.,[16] in formaldehyde dimethylacetal at room temperature and then treated with dibenzylideneiminium trifluoroacetate, providing compounds **5a**–**e** in good yields (Scheme 2 and Table 1). Subsequent debenzylation with ammonium formate in the presence of palladium on charcoal,[17] followed by ester saponification and *N*-Boc protection, provided racemic β²-amino acids suitably protected for peptide synthesis.

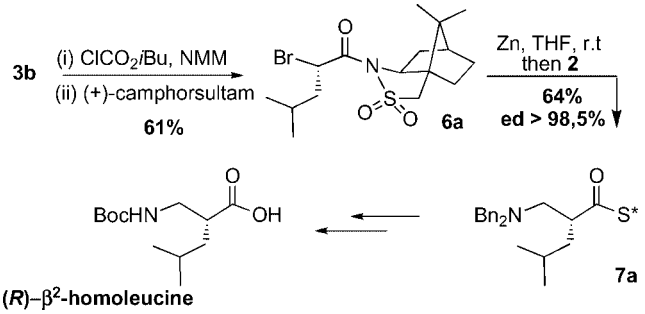


Scheme 2. Synthesis of racemic β²-amino acids through Reformatsky reactions with the iminium trifluoroacetate salt.

Table 1. Yields for the Reformatsky reactions with iminium trifluoroacetate.

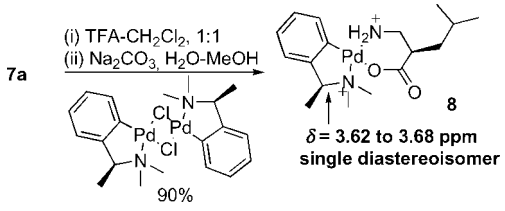
Entry	R	*rac*-**5** (%)
a	CH_3 (**4a**)	**5a** (43)
b	*i*Bu (**4b**)	**5b** (66)
c	CH_2Ph (**4c**)	**5c** (74)
d	CH_2-(3-indolyl-*N*-Boc) (**4d**)	**5d** (73)
e	CH_2CO_2-*t*Bu (**4e**)	**5e** (72)

The ease of this reaction prompted us to explore its asymmetric version for the synthesis of β²-homoleucine, which was needed for our structure/activity relationship studies of biologically active peptides. In classical Reformatsky reactions, the attachment of chiral auxiliaries (derived from menthol, oxazolidines or oxazinanes) to halo precursors had previously given rise to some diastereoselectivity and enantiofacial differentiation.[11] We chose Oppolzer's sultam, easily obtained on multigram scales for laboratory needs and used on kilogram scales for industrial purposes (Scheme 3).[18] Good to excellent diastereoselectivities are usually observed with this chiral auxiliary. Sulfonamide **6a** was thus obtained by coupling 2-bromo-3-methylbutanoic acid with (+)-camphorsultam as shown in Scheme 3.



Scheme 3. Synthesis of optically pure β²-homoleucine through a Reformatsky reaction using the iminium trifluoroacetate salt. S* = (+)-camphorsultam.

Treatment of sulfonamide **6a** under the conditions described above resulted in the corresponding β²-amino acid derivative **7a** as a single diastereoisomer. The stereochemistry of compound **7a** was deduced by comparison of the optical rotation of the *N*-Boc-β²-homoleucine (obtained through deprotection/reprotection steps) with that of an authentic sample.[19] The optical purity was confirmed by NMR analysis by the methodology reported by Seebach et al. (Scheme 4).[20] It should be noted that the stereochemical course of this aminomethylation reaction is identical to that usually observed with Oppolzer's sultam for glycinate-derived enolates.[21]



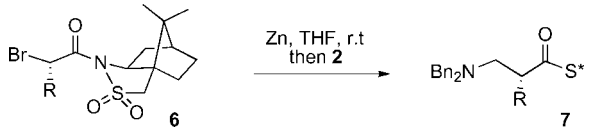
Scheme 4. Enantiomeric excess.

We then studied the scope of this aminomethylation reaction with different α-bromosulfonamides (Scheme 5 and Table 2). The mild conditions required for the Reformatsky reaction are compatible with many of the sensitive protecting groups typically used in peptide synthesis. This could allow for the direct synthesis of β²-amino acids bearing functional groups on their side chains, avoiding many deprotection/reprotection steps usually required for their preparation.

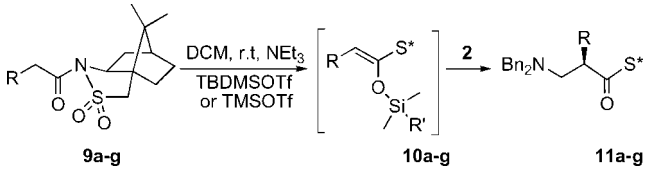
Table 2. Levels of conversion and *dr* values for asymmetric Reformatsky reactions with the iminium trifluoroacetate salt.

Entry	R	Product	Conversion (yield)[a]	*dr*[a]
a	*i*Bu (**6a**)	**7a**	69% (64%)	>98:2
b	CH_3 (**6b**)	**7b**	71% (nd)	72:28
c	CH_2Ph (**6c**)	**7c**	71% (57%)	87:13
d	CH_2(*N*-Boc-indolyl) (**6d**)	**7d**	nd[b]	nd[c]
e	$(CH_2)_4NHBoc$ (**6e**)	**7e**	69% (47%)	nd[c]

[a] Calculated from the NMR spectrum of the crude mixture. [b] A complex mixture that contained the product was obtained. [c] Complex mixture of diastereoisomers with *cis*/*trans*-*N*-Boc isomerism.



Scheme 5. Asymmetric synthesis of β^2-amino acids through Reformatsky reactions using the iminium trifluoroacetate salt. S* = (+)-camphorsultam.



Scheme 6. Aminomethylation of chiral silyl ketene N,O-acetal with the iminium trifluoroacetate salt. S* = (+)-camphorsultam.

Unfortunately, use of α-bromo sulfonamides bearing less hindered side chains gave disappointing results. Indeed, with all the compounds tested, inseparable mixtures of diastereoisomers were obtained. Screening of different reaction conditions (solvents, temperature, reagent loading) and use of other chiral auxiliaries (Evans oxazolidinone, menthol) did not improve the diastereoselectivities of the aminomethylations.[22]

We anticipated that the use of classical enolate chemistry with this aminomethylating reagent should solve the problem, but all the attempts to achieve reactions with ester enolates generated from various bases with the iminium trifluoroacetate ion failed. Silyl enol ethers have been reported as an alternative to ester enolates,[23] so we examined the reactivity of the chiral silyl ketene N,O-acetals, generated in situ from Oppolzer's sultam derivatives, toward the iminium trifluoroacetate salt (Scheme 6 and Table 3).

In a first attempt the silyl ketene acetal was generated from the corresponding alkanoylsultam sulfonamide[24] by treatment with *tert*-butyldimethylsilyl triflate and triethylamine at room temperature.[25] After addition of the iminium trifluoroacetate salt, the protected β^2-homoalanine derivative **11a** was obtained in moderate yield (60%) and with virtually complete diastereoselectivity. In the case of derivatives bearing hindered side chains (**11b**–**d**, **11f**–**g**), the formation of the corresponding ketene acetal was not observed. Replacement of *tert*-butyldimethylsilyl triflate with the cheaper trimethylsilyl triflate allowed the formation of the silylenol intermediates of all other alkanoylsultam sulfonamides. Indeed, *tert*-butyldimethylsilyl triflate was inefficient, probably because of the steric hindrance developed in the transition state, preventing the formation of the (*Z*)-silylenol ether. These intermediates reacted with the iminium salt to give the corresponding protected β^2-amino acids as single diastereoisomers, with all compounds being obtained in excellent yields as solids. The stereochemical

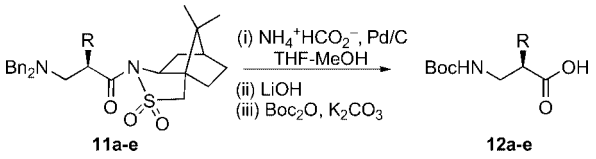
Table 3. Yields of the asymmetric aminomethylations of silyl ketene N,O-acetals.

Entry	R	R′Me_2SiOTf	Product (yield)	*dr*[b]
a	CH_3 (**9a**)	TBDMSOTf	**11a** (60%)	>98:2
b		TMSOTf	(91%)	>98:2
c	*i*Pr (**9b**)	TBDMSOTf	**11b** (0%)	
d		TMSOTf	(81%)	>98:2
e	*i*Bu (**9c**)	TBDMSOTf	**11c** (0%)	
f		TMSOTf	(82%)	>98:2
g	Bn (**9d**)	TBDMSOTf	**11d** (0%)	
h		TMSOTf	(72%)	>98:2
i	hexyl (**9e**)	TBDMSOTf	**11e** (61%)	>98:2
j		TMSOTf	(74%)	>98:2
k	Br-$(CH_2)_4$ (**9f**)	TMSOTf	**11f** (76%)	>98:2
l	*N*-benzylindolyl-3-methylene (**9g**)[a]	TMSOTf	**11g** (88%)	>98:2

[a] Use of 2 equiv. of TMSOTf. [b] Calculated from NMR data of the crude mixture.

course of this aminomethylation reaction is identical to that observed in the Reformatsky strategy,[10] and also to that usually observed with glycine enolates derived from Oppolzer's sultam.[21]

The obtained derivatives were then debenzylated with ammonium formate in the presence of palladium on charcoal, with the chiral auxiliary being removed by saponification. All compounds were isolated by simple crystallization after Boc protection of their amine moieties (Scheme 7). The optical purities were confirmed by measurement of the optical rotations and comparison with the literature data.



Scheme 7. Deprotection and Boc protection.

Conclusions

We have developed a straightforward synthesis of β²-amino acids, which has been easily scaled up for the preparation of the β²-homophenylalanine derivative in 100 g quantities in the laboratory by use of the same procedure as described for smaller scales. All reactions may be performed at room temperature and the compounds can be isolated by simple precipitation or crystallization. With the strategy described here we have shown that β²-amino acids with various side chains can be obtained, establishing the versatility of this aminomethylation reaction. This route opens a new avenue to explore the potential of β²-amino acids in various fields.

Experimental Section

General Considerations: Tetrahydrofuran (THF) was distilled from sodium/benzophenone and kept over molecular sieves (4 Å). Dichloromethane (CH_2Cl_2) and triethylamine (NEt_3) were distilled from CaH_2. Anhydrous methylal, anhydrous DMF and other reagents were obtained from commercial suppliers and used without further purification. Compound **4a** is commercially available. Oppolzer's sultams were a gift from Senn Chemicals. Anhydrous reactions were performed under argon, and glassware was dried in an oven prior to use. Prior to preparation of the HBr solution, the commercial concentrated HBr was washed with a solution of tributyl phosphate in $CHCl_3$ (5%) to remove contaminating Br_2. Reaction progress was monitored by TLC on precoated silica plates (Merck 60 F_{254} 0.25 μm). Spots were detected by UV, molybdophosphoric acid oxidation or ninhydrin reagent. Flash column chromatography was carried out with Merck 60 F_{254} 0.040–0.063 μm silica gel. ^1H and ^{13}C NMR spectra were recorded with Bruker Avance 250 or 400 MHz spectrometers. Chemical shifts (δ) are reported in ppm relative to internal TMS. Optical rotations were determined at 20 °C with a Perkin–Elmer Model 141 polarimeter with a 10 cm path-length cell. Microanalyses were obtained from CNRS central service. HR mass spectra were recorded at the Université Pierre et Marie Curie with an LTQ Orbitrap™ (Thermoelectron Corporation, Bremen, Germany). Cy = cyclohexane; EA = ethyl acetate.

General Procedure for the Conversion of α-Amino Acids with Nonfunctionalized Side Chains into α-Bromo Acids: Sodium nitrite (1.25 equiv.) in H_2O was added dropwise at 0 °C to a stirred solution of L-amino acid and sodium bromide (3.5 equiv.) in H_2SO_4 (2.5 M, 1.3 mL per mmol). After stirring at 0 °C for 1 h, the reaction mixture was brought to room temperature and stirred for 6 h. The mixture was extracted with ethyl acetate, and the combined organic solutions were washed with brine, dried ($MgSO_4$) and concentrated in vacuo.

General Procedure for the Conversion of Amino Acids with Functionalized Side Chains into the Corresponding α-Bromo Acids: NaBr (3.7 equiv.) was dissolved in an aqueous solution of HBr (0.75 M) in a three-necked flask with an overhead stirrer. The solution was cooled to –15 °C and sodium nitrite (1.3 equiv.) was added in one portion. The amino acid (1 equiv.) was then added and the reaction mixture was kept between –15 °C and –10 °C for 1.5 h. The mixture was extracted twice with precooled EtOAc (0 °C) and the combined organic layers were washed with saturated aqueous solution of NH_4Cl, dried ($MgSO_4$) and concentrated in vacuo.

Protection of the Acid Function for Compounds with Nonfunctionalized Side Chains: The α-bromo acid was treated with a solution of concentrated sulfuric acid (30 μL per mmol) in methanol (2 mL per mmol) and the mixture was heated at reflux for 1 h. The solution was allowed to cool to room temperature and concentrated in vacuo, Et_2O was added, and the organic layer was washed with aqueous $NaHCO_3$ (5%) followed by brine, dried with $MgSO_4$ and concentrated in vacuo.

Protection of the Acid Function for Compounds with Functionalized Side Chains: The α-bromo acid was treated with a solution of acetyl chloride (30 μL per mmol) in methanol (2 mL per mmol) for 1 h. The solution was allowed to cool to room temperature and concentrated in vacuo.

General Procedure for the Acylation of Oppolzer's Sultam Starting from Acid Chloride Derivatives: A solution of 10,2-camphorsultam (1 equiv.) in dimethoxyethane (3 mL per mmol) was added slowly at room temperature to a stirred suspension of NaH (1.1 equiv.) in the same solvent. After the mixture had been stirred at room temperature for 1 h, the acid chloride derivative (1.1 equiv.) was added. The mixture was stirred at room temperature for an additional 1 h, and was then quenched with water and concentrated. After addition of ethyl acetate, the solution was washed with saturated aqueous NH_4Cl, and the organic layer was dried with anhydrous $MgSO_4$ and concentrated. The acylsultam derivatives were obtained by precipitation from diethyl ether/pentane.

General Procedure for the Acylation of Oppolzer's Sultam Starting from Carboxylic Acid Derivatives: A solution of 10,2-camphorsultam (1 equiv.) in dimethoxyethane (3 mL per mmol) was added slowly at room temperature to a stirred suspension of NaH (1.1 equiv.) in the same solvent. The solution was stirred for 1 h. In parallel, isobutyl chloroformate (1.1 equiv.) and *N*-methylmorpholine (1.1 equiv.) were added at –15 °C to a solution of the carboxylic acid (1 equiv.) in dimethoxyethane (3 mL per mmol). After 15 min of stirring at –15 °C, this preformed mixed anhydride was rapidly introduced, after filtration through a Celite pad, into the sultam sodium salt solution. After 1 h of stirring at –15 °C and 1 h at room temperature, the crude mixture was quenched with water and concentrated. Ethyl acetate was added and the organic layer was washed with saturated aqueous NH_4Cl, dried with anhydrous $MgSO_4$ and concentrated. Acylsultam derivatives were obtained by precipitation from diethyl ether/pentane.

General Procedure for the Reformatsky Reaction: Dibromoethane (20 μL per mmol) was added to a suspension of zinc dust (1.5 equiv.) in methylal (0.5 mL per mmol) and the mixture was heated at reflux for a few minutes. A solution of the α-bromo acid (1 equiv.) in methylal (1 mL per mmol) was added dropwise, the reaction mixture was stirred at room temperature for 15 min, and a solution of the iminium trifluoroacetate, freshly prepared from *N*,*N*,*N*′,*N*′-tetrabenzylmethanediamine,[13] was added. The reaction mixture was stirred at room temperature for 1.5 h, and was then quenched with a saturated solution of NH_4Cl and extracted with Et_2O. The combined organic layers were washed with saturated aqueous $NaHCO_3$, aqueous $Na_2S_2O_3$ (5%) and saturated aqueous NH_4Cl, and were then dried ($MgSO_4$) and concentrated.

General Procedure for the Aminomethylation: Trimethylsilyl triflate (1.5 equiv.) and triethylamine (1.1 equiv.) were added successively to a stirred solution of the sulfonamide derivative (1 equiv.) in CH_2Cl_2 (1 mL per mmol) and the mixture was stirred at room temperature for 6 h. A solution of *N*,*N*-dibenzyliminium trifluoroacetate salt (1.1 equiv.) in CH_2Cl_2 (1 mL per mmol) freshly prepared from *N*,*N*,*N*′,*N*′-tetrabenzylmethanediamine[13] was added and the mixture was stirred for 15 min. TBAF in THF (1 M, 1 equiv.) was added, the reaction was quenched with water, and CH_2Cl_2 was removed in vacuo. The aqueous layer was extracted with diethyl ether and the combined organic solutions were washed with a saturated solution of NH_4Cl, dried ($MgSO_4$) and concentrated in vacuo.

General Procedure for the Deprotection and Boc Protection: Pd/C (10%, 100 mg per mmol) and ammonium formate (5 equiv.) were added to a solution of the amine in a THF/MeOH mixture (1:4, 5 mL per mmol) and the reaction mixture was stirred at room temperature. The solution was filtered through Celite and concentrated to give the corresponding amine, which was dissolved in a THF/water mixture (1:1, 5 mL per mmol). After addition of LiOH (2 equiv.), the reaction mixture was stirred at room temperature overnight, the THF was then evaporated, and dioxane (2 mL per mmol) was added. After addition of Boc_2O (1.1 equiv.) and K_2CO_3 (1.1 equiv.), the solution was stirred for 5 h and then concentrated to remove organic solvents. After addition of water and extraction with Et_2O, the aqueous layer was cooled to 0 °C, acidified to pH = 2 with HCl (1 M), and extracted with ethyl acetate. The combined organic layers were dried and concentrated in vacuo to afford the Boc-protected amino acid, which was purified by recrystallization from diethyl ether/pentane.

(*S*)-2-Bromopropionic Acid (3a):[26] This compound was prepared from L-alanine (50 g, 562 mmol), the crude product being purified by distillation under reduced pressure (P = 0.06 Torr, T = 63–64 °C) to give an oil (58.7 g, 68%); R_f = 0.24 (Cy/EA/AcOH, 8:2:0.1). $[\alpha]_D^{20}$ = –28.5 (c = 1, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 11.54 (br. s, 1 H), 4.42 (q, J = 6.8 Hz, 1 H), 1.85 (d, J = 6.8 Hz, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 176.6, 39.4, 21.4 ppm. $C_3H_5BrO_2$ (152.97): calcd. C 23.55, H 3.29; found C 23.60, H 3.55.

(*S*)-2-Bromo-4-methylpentanoic Acid (3b):[27] This compound was prepared from L-leucine (20 g, 153 mmol), the crude product being purified by distillation under reduced pressure (P = 0.03 Torr, T = 96 °C) to give an oil (20.8 g, 70%); R_f = 0.60 (CH_2Cl_2/EtOH, 9:1). $[\alpha]_D^{20}$ = –39.9 (c = 2, MeOH). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 9.80–10.50 (br. s, 1 H), 4.30 (t, J = 7.5 Hz, 1 H), 1.93 (t, J = 7.5 Hz, 2 H), 1.76–1.90 (m, 1 H), 0.98 (d, J = 6.5 Hz, 3 H), 0.94 (d, J = 6.25 Hz, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 176.4, 44.0, 43.2, 26.3, 22.3, 21.5 ppm.

(*S*)-2-Bromo-3-phenylpropionic Acid (3c):[28] This compound was prepared from L-phenylalanine (20 g, 121.2 mmol), the crude product being purified by flash column chromatography (Cy/EA/AcOH, 99:1) to give an oil (19 g, 68%), R_f = 0.33 (CH_2Cl_2/EtOH/AcOH, 9:1:0.1). $[\alpha]_D^{20}$ = –11.4 (c = 2, MeOH). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.18–7.36 (m, 5 H), 4.42 (t, J = 7.7 Hz, 1 H), 3.47 (dd, J = 8 Hz, 14.2 Hz, 1 H), 3.24 (dd, J = 7.2 Hz, 14.2 Hz, 1 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 175.5, 136.3, 129.4, 129.0, 128.5, 127.5, 44.8, 40.7 ppm. $C_9H_9BrO_2$ (229.07): calcd. C 47.19, H 3.96; found C 47.21, H 3.60.

(*S*)-2-Bromo-3-[*N*-(*tert*-butoxycarbonyl)indol-3-yl]propionic Acid (3d):[14b] This compound was prepared from H-Trp(Boc)-OH (5 g, 16.4 mmol), the crude product being purified by flash column chromatography (Cy/EA/AcOH, 7:3:0.1) to give compound **3d** as an oil (4 g, 67%); R_f = 0.21 (Cy/EA/AcOH, 7:3:0.1). $[\alpha]_D^{20}$ = –13.2 (c = 1, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.87 (br. s, 1 H), 8.10 (br. s, 1 H), 7.51–7.53 (m, 2 H), 7.32 (t, J = 7.3 Hz, 1 H), 7.24 (t, J = 6.8 Hz, 1 H), 4.52 (t, J = 7.6 Hz, 1 H), 3.58 (dd, J = 8.1 Hz, 14.9 Hz, 1 H), 2.93 (dd, J = 6.8 Hz, 14.9 Hz, 1 H), 1.65 (s, 9 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 174.5, 149.6, 135.3, 129.7, 124.7, 124.5, 122.7, 118.5, 115.5, 115.4, 84.0, 43.3, 30.5, 28.2 ppm.

(*S*)-2-Bromo-3-(*tert*-butoxycarbonyl)propionic Acid (3e):[14b] This compound was prepared from H-Asp(O*t*Bu)-OH (5 g, 26.4 mmol), the crude product being purified by flash column chromatography (Cy/EA/AcOH, 7:3:0.1) to give compound **3e** as an oil (11.5 g, 86%); R_f = 0.48 (Cy/EA/AcOH, 6:4:0.1). $[\alpha]_D^{20}$ = –45.4 (c = 2, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 10.60 (br. s, 1 H), 4.55 (dd, J = 9.1 Hz, 6.1 Hz, 1 H), 3.18 (dd, J = 9.1 Hz, 16.9 Hz, 1 H), 2.93 (dd, J = 6.1 Hz, 16.9 Hz, 1 H), 1.40 (s, 9 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 174.8, 168.7, 82.5, 40.7, 38.1, 27.9 ppm. $C_9H_{13}BrO_2$ (233.10): calcd. C 37.96, H 5.18; found C 37.70, H 5.33.

Methyl (*S*)-2-Bromo-4-methylpentanoate (4b): Ester **4b** was purified by flash column chromatography (Cy/EA, 99:1) to give an oil (2.5 g, 79%), R_f = 0.67 (Cy/EA, 8:2). $[\alpha]_D^{20}$ = –49.6 (c = 1, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 4.29 (t, J = 7.6 Hz, 1 H), 3.78 (s, 3 H), 1.86–2.05 (m, 2 H), 1.71–1.81 (m, 1 H), 0.96 (d, J = 6.8 Hz, 3 H), 0.91 (d, J = 6.8 Hz, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 170.6, 52.9, 44.3, 43.5, 26.3, 22.3, 21.5 ppm.

Methyl (*S*)-2-Bromo-3-phenylpropanoate (4c):[29] Ester **4c** was purified by flash column chromatography (Cy/EA, 99:1) to give an oil (6.8 g, 94%); R_f = 0.33 (Cy/EA, 95:5). $[\alpha]_D^{20}$ = –11.1 (c = 1, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.17–7.29 (m, 5 H), 4.39 (t, J = 8.3 Hz, 1 H), 3.36 (s, 3 H), 3.45 (dd, J = 8.3 Hz, 14.1 Hz, 1 H), 3.22 (dd, J = 7.1 Hz, 13.9 Hz, 1 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 169.8, 136.7, 129.1, 128.6, 127.3, 52.8, 45.1, 41.0 ppm.

Methyl (*S*)-2-Bromo-3-[*N*-(*tert*-butoxycarbonyl)indol-3-yl]propionate (4d): The crude product was purified by flash column chromatography (Cy/EA, 97:3) to give compound **4d** as an oil (1 g, 59%); R_f = 0.58 (Cy/EA, 8:2). $[\alpha]_D^{20}$ = –18.6 (c = 1, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.12–8.13 (m, 1 H), 7.47–7.53 (m, 2 H), 7.31–7.34 (m, 2 H), 4.50 (dd, J = 8.6 Hz, 6.6 Hz, 1 H), 3.73 (s, 3 H), 3.58 (dd, J = 8.6 Hz, 14.9 Hz, 1 H), 3.35 (dd, J = 6.6 Hz, 14.9 Hz, 1 H), 1.66 (s, 9 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 170.0, 150.0, 135.5, 129.7, 124.7, 124.5, 122.7, 118.6, 115.8, 115.4, 83.8, 53.0, 43.5, 30.8, 20.2 ppm. $C_{17}H_{20}BrNO_4$ (382.25): calcd. C 53.42, H 5.27, N 3.66; found C 53.00, H 5.43, N 3.27.

Methyl (*S*)-2-Bromo-4-(*tert*-butoxycarbonyl)propionate (4e): The crude product was purified by flash column chromatography (Cy/EA, 97:3) to give compound **4e** as an oil (2.9 g, 51%); R_f = 0.53 (Cy/EA, 8:2). $[\alpha]_D^{20}$ = –53.5 (c = 1, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 4.53 (dd, J = 9.1 Hz, 6.1 Hz, 1 H), 3.80 (s, 3 H), 3.19 (dd, J = 9.1 Hz, 16.9 Hz, 1 H), 2.91 (dd, J = 6.1 Hz, 16.9 Hz, 1 H), 1.44 (s, 9 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 169.7, 168.6,

82.0, 53.1, 40.9, 38.3, 27.9 ppm. $C_9H_{15}BrO_4$ (267.12): calcd. C 40.47, H 5.66; found C 40.89, H 5.68.

Methyl 2-[(Dibenzylamino)methyl]propionate (5a): The crude product was treated with a solution of TFA in EA (1%) and purified by flash column chromatography (Cy/EA, 8:2; then Cy/EA/NEt_3, 8:2:0.1) to give **5a** as an oil (3 g, 43%); R_f = 0.61 (Cy/EA, 8:2). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.19–7.30 (m, 10 H), 3.62 (d, J = 13.4 Hz, 2 H), 3.61 (s, 3 H), 3.46 (d, J = 13.4 Hz, 2 H), 2.73–2.70 (m, 2 H), 2.37–2.44 (m, 1 H), 1.07 (d, J = 6.3 Hz, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 176.1, 139.2, 128.9, 128.1, 126.9, 58.4, 57.3, 51.4, 38.6, 15.3 ppm. $C_{19}H_{23}NO_2$ (297.39): calcd. C 76.73, H 7.80, N 4.71; found C 76.87, H 7.99, N 4.65.

Methyl 2-[(Dibenzylamino)methyl]-4-methylpentanoate (5b): The crude product was treated with a solution of TFA in EA (1%) and purified by flash column chromatography (Cy/EA, 8:2; then Cy/EA/NEt_3, 8:2:0.1) to give **5b** as an oil (4.8 g, 66%); R_f = 0.69 (Cy/EA, 8:2). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.20–7.30 (m, 10 H), 3.72 (d, J = 13.6 Hz, 2 H), 3.63 (s, 3 H), 3.36 (d, J = 13.6 Hz, 2 H), 2.73–2.80 (m, 2 H), 2.36–2.39 (m, 1 H), 1.39–1.49 (m, 2 H), 1.15–1.22 (m, 1 H), 0.85 (d, J = 6.6 Hz, 3 H), 0.82 (d, J = 6.6 Hz, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 175.9, 139.2, 128.9, 128.1, 126.9, 58.4, 56.8, 51.3, 42.9, 39.6, 26.3, 23.0, 22.0 ppm. $C_{22}H_{29}NO_2$ (339.47): calcd. C 77.84, H 8.61, N 4.13; found C 77.61, H 8.73, N 4.04.

Methyl 2-[(Dibenzylamino)methyl]-3-phenylpropionate (5c): Compound **5c** was obtained after precipitation in MeOH/$CHCl_3$ as a white powder (14.6 g, 74%); R_f = 0.65 (Cy/EA, 8:2); m.p. 83 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.1–7.3 (m, 15 H), 3.66 (d, J = 13.6 Hz, 2 H), 3.42 (d, J = 13.6 Hz, 2 H), 3.55 (s, 3 H), 2.95–3.00 (m, 3 H), 2.79–2.85 (m, 1 H), 2.75–2.76 (m, 2 H), 2.50–2.54 (m, 1 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 174.9, 139.2, 139.0, 129.0, 128.7, 128.4, 128.2, 127.0, 126.3, 58.5, 55.9, 51.3, 46.9, 36.4 ppm. $C_{25}H_{27}NO_2$ (373.49): calcd. C 80.40, H 7.29, N 3.75; found C 80.16, H 7.34, N 3.67.

Methyl 3-[*N*-(*tert*-Butoxycarbonyl)indol-3-yl]-2-[(dibenzylamino)-methyl]propionate (5d): Compound **5d** was obtained after flash column chromatography (Cy/EA, 98:2) as an oil (14.6 g, 73%); R_f = 0.53 (Cy/EA, 8:2). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.1 (br. s, 1 H), 7.43 (d, J = 7.6 Hz, 1 H), 7.19–7.31 (m, 14 H), 3.67 (d, J = 13.6 Hz, 2 H), 3.45 (d, J = 13.6 Hz, 2 H), 3.59 (s, 3 H), 3.07–3.13 (m, 1 H), 2.80–2.90 (m, 1 H), 2.59 (dd, 1 H, 5.8 Hz, 12.6 Hz), 1.65 (s, 9 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 175.1, 149.7, 138.0, 130.3, 128.9, 128.1, 127.0, 124.3, 123.1, 122.4, 118.8, 115.2, 83.4, 58.4, 56.0, 51.5, 44.8, 28.2, 25.7 ppm. MS (CI; NH_3): m/z = 513 $[M + H]^+$, 413 $[M – Boc]^+$.

Methyl 3-(*tert*-Butoxycarbonyl)-2-[(dibenzylamino)methyl]propionate (5e): Compound **5e** was obtained after flash column chromatography (Cy/EA, 97:3) as an oil (1.3 g, 72%); R_f = 0.49 (Cy/EA, 8:2). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.2–7.4 (m, 10 H), 3.59 (d, J = 13.6 Hz, 2 H), 3.51 (d, J = 13.6 Hz, 2 H), 3.3 (s, 3 H), 3.0–3.1 (m, 1 H), 2.7 (dd, J = 7.3 Hz, 10.2 Hz, 1 H), 2.4–2.6 (m, 3 H), 1.4 (s, 9 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 174.4, 171.2, 138.9, 128.9, 128.2, 127.0, 126.3, 80.7, 58.3, 55.1, 51.7, 40.5, 35.6, 28.0 ppm. $C_{24}H_{31}NO_4$ (397.51): calcd. C 72.52, H 7.86, N 3.52; found C 72.72, H 7.89, N 3.46.

(2*S*)-*N*-(2-Bromo-4-methylpentanoyl)camphorsultam 6a:[30] 61% yield (8 g); R_f = 0.23 (Cy/EA, 9:1); m.p. 132 °C. $[\alpha]_D^{20}$ = 59.5 (c = 1, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 4.91 (t, J = 7.3 Hz, 1 H), 3.93 (dd, J = 4.8 Hz, 7.3 Hz, 1 H), 3.49 (d, J = 13.9 Hz, 2 H), 3.39 (d, J = 13.9 Hz, 2 H), 1.94–2.09 (m, 3 H), 1.88–1.94 (m, 4 H), 1.74 (m, 1 H), 1.36–1.45 (m, 2 H), 1.20 (s, 3 H), 0.98 (s, 3 H), 0.97 (d, J = 6.8 Hz, 3 H), 0.92 (d, J = 6.6 Hz, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 168.3, 64.9, 53.0, 48.7, 47.9, 44.5, 43.7, 42.4, 37.5, 32.7, 26.5, 26.4, 22.4, 22.0, 20.7 19.9 ppm. $C_{16}H_{26}BrNO_3S$ (392.35): calcd. C 48.98, H 6.68, N 3.57; found C 48.60, H 6.72, N 3.53.

(2*S*)-*N*-(2-Bromopropionyl)camphorsultam 6b: 68% yield (12.3 g); R_f = 0.26 (Cy/EA, 9:1); m.p. 132 °C. $[\alpha]_D^{20}$ = 81.0 (c = 1, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 4.98 (q, J = 6.6 Hz, 1 H), 3.93 (dd, J = 5.3 Hz, 7.3 Hz, 1 H), 3.44 (d, J = 13.9 Hz, 1 H), 3.56 (d, J = 13.9 Hz, 1 H), 1.98–2.11 (m, 2 H), 1.86–1.95 (m, 3 H), 1.82 (d, J = 6.8 Hz, 3 H), 1.34–1.46 (m, 2 H), 1.20 (s, 3 H), 0.99 (s, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 168.7, 64.9, 52.9, 48.8, 47.8, 44.5, 39.4, 37.5, 32.8, 26.5, 20.7, 20.5, 19.9 ppm. $C_{13}H_{20}BrNO_3S$ (350.27): calcd. C 44.58, H 5.76, N 4.00; found C 44.59, H 5.83, N 3.95.

(2*S*)-*N*-(2-Bromo-3-phenylpropionyl)camphorsultam 6c:[30] 82% yield (6.7 g); R_f = 0.23 (Cy/EA, 9:1); m.p. 156–157 °C. $[\alpha]_D^{20}$ = 84.1 (c = 1, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.32–7.23 (m, 5 H), 5.07 (t, J = 7.1 Hz, 1 H), 3.88 (dd, J = 7.6 Hz, 5 Hz, 1 H), 3.53 (dd, J = 14.2 Hz, 7.0 Hz, 1 H), 3.39 (d, J = 13.9 Hz, 1 H), 3.49 (d, J = 13.9 Hz, 1 H), 3.25 (dd, J = 7.3 Hz, 14.2 Hz, 1 H), 2.01–2.09 (m, 2 H), 1.89–1.94 (m, 3 H), 1.30–1.41 (m, 2 H), 1.18 (s, 3 H), 0.96 (s, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 167.7, 136.5, 129.6, 128.5, 127.2, 64.8, 52.9, 48.7, 47.8, 44.8, 44.5, 39.8, 37.5, 32.7, 26.4, 20.7, 19.9 ppm. $C_{19}H_{24}BrNO_3S$ (426.37): calcd. C 53.52, H 5.67, N 3.29; found C 53.31, H 5.80, N 3.35.

(2*S*)-*N*-{2-Bromo-3-[*N*-(*tert*-butoxycarbonyl)indol-3-yl]propionyl}-camphorsultam 6d: Compound **6d** was obtained after purification by flash column chromatography (Cy/EA, 85:15) as a white powder (2.3 g, 44%); R_f = 0.18 (Cy/EA, 9:1); m.p. 79 °C. $[\alpha]_D^{20}$ = 53.8 (c = 1, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.1 (m, 1 H), 7.54–7.60 (m, 2 H), 7.24–7.33 (m, 2 H), 5.15–5.20 (m, 1 H), 3.91 (dd, J = 5.3 Hz, 7.1 Hz, 1 H), 3.63 (dd, J = 15.2 Hz, 7.1 Hz, 1 H), 3.50 (d, J = 13.6 Hz, 1 H), 3.44 (d, J = 13.6 Hz, 1 H), δ = 3.35 (dd, J = 15.4 Hz, 7.6 Hz, 1 H), 2.01–2.10 (m, 2 H), 1.82–1.94 (m, 3 H), 1.66 (s, 9 H), 1.30–1.42 (m, 2 H), 1.18 (s, 3 H), 0.96 (s, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 167.7, 149.6, 135.3, 129.9, 124.7, 124.4, 122.6, 118.9, 115.6, 115.2, 83.6, 64.9, 52.9, 48.8, 47.8, 44.5, 43.2, 37.5, 32.7, 29.6, 28.2, 26.4, 20.7, 19.8 ppm.

(2*S*)-*N*-{2-Bromo-6-[(*tert*-butoxycarbonyl)amino]hexanoyl}-camphorsultam 6e: Compound **6e** was obtained after purification by flash column chromatography (Cy/EA, 9:1) as a powder (430 mg, 70%); R_f = 0.37 (Cy/EA, 8:2); m.p. 110–112 °C. $[\alpha]_D^{20}$ = 42.2 (c = 1, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 4.79 (t, J = 7.1 Hz, 1 H), 3.93 (dd, J = 5.3 Hz, 7.3 Hz, 1 H), 3.69 (t, J = 7.3 Hz, 2 H), 3.53 (d, J = 13.6 Hz, 1 H), 3.43 (d, J = 13.6 Hz, 1 H), 2.04–2.09 (m, 3 H), 1.90–1.99 (m, 4 H), 1.65 (s, 9 H), 1.19–1.44 (m, 6 H), 1.19 (s, 3 H), 0.98 (s, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 168.1, 152.1, 85.2, 64.9, 53.0, 48.8, 47.9, 44.5, 44.3, 40.2, 37.6, 33.2, 32.8, 28.1, 26.4, 24.6, 20.7, 19.9 ppm.

(2*S*)-*N*-{(2*R*)-2-[(Dibenzylamino)methyl]-4-methylpentanoyl}-camphorsultam 7a: Compound **7a** was obtained by precipitation from methanol/chloroform as a single diastereoisomer (7.2 g, 64%); R_f = 0.21 (Cy/EA, 9:1); m.p. 108 °C. $[\alpha]_D^{20}$ = 69.9 (c = 1, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.18–7.33 (m, 10 H), 3.87 (dd, J = 5 Hz, 7.6 Hz, 1 H), 3.68 (d, J = 13.9 Hz, 2 H), 3.41–3.52 (m, 5 H), 2.76 (dd, J = 6.3 Hz, 12.4 Hz, 1 H), 2.50 (dd, J = 12.4 Hz, 7.3 Hz, 1 H), 2.00–2.11 (m, 2 H), 1.86–1.92 (m, 4 H), 1.46–1.56 (m, 3 H), 1.31–1.42 (m, 2 H), 1.22 (s, 3 H), 0.97 (s, 3 H), 0.87 (d, J = 5.8 Hz, 6 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 174.9, 139.1, 129.1, 128.0, 126.8, 65.5, 58.1, 56.5, 53.2, 48.2, 47.8, 44.6, 42.6, 38.8, 38.6, 32.9, 26.5, 26.0, 23.0, 22.7, 21.0, 19.9 ppm.

$C_{31}H_{42}N_2O_3S$ (522.74): calcd. C 71.23, H 8.10, N 5.36; found C 71.05, H 8.30, N 5.11.

(2*S*)-*N*-{2-[(Dibenzylamino)methyl]propionyl}camphorsultam 7b: Compound **7b** was obtained as a mixture of diastereoisomers (72:28); R_f = 0.39 (Cy/EA, 8:2); major diastereoisomer. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.2–7.3 (m, 10 H), 3.9 (dd, J = 7.6 Hz, 5.1 Hz, 1 H), 3.6 (s, 4 H), 3.4–3.5 (m, 3 H), 2.9 (dd, J = 7.6 Hz, 12.6 Hz, 1 H), 2.4 (dd, J = 6.3 Hz, 12.6 Hz, 1 H), 2.0–2.1 (m, 1 H), 2.0 (dd, J = 7.6 Hz, 13.9 Hz, 1 H), 2.02–2.11 (m, 2 H), 1.86–1.91 (m, 3 H), 1.3–1.4 (m, 2 H), 1.2 (s, 3 H), 1.1 (s, 3 H), 1.0 (s, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 175.3, 138.9, 128.0, 126.8, 65.4, 57.9, 57.8, 53.1, 48.2, 47.7, 44.7, 38.6, 38.4, 32.9, 26.4, 21.0, 19.9, 15.5 ppm.

(2*S*)-*N*-{2-[(Dibenzylamino)methyl]-3-phenylpropionyl}camphorsultam 7c: Compound **7c** was obtained after purification by flash column chromatography (Cy/EA, 9:1) as a mixture of diastereoisomers (87:13, 5.1 g, 57%), R_f = 0.41 (Cy/EA, 8:2). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.16–7.26 (m, 15 H), 3.86 (dd, J = 7.6 Hz, 5.1 Hz, 1 H), 3.73 (m, 1 H), 3.41–3.54 (m, 6 H), 3.04 (dd, J = 13.6 Hz, 5.6 Hz, 1 H), 2.92 (dd, J = 12.6 Hz, 8.1 Hz, 1 H), 2.65 (dd, J = 13.6 Hz, 8.6 Hz, 1 H), 2.49 (dd, J = 12.6 Hz, 5.3 Hz, 1 H), 2.02–2.11 (m, 2 H), 1.87–1.91 (m, 3 H), 1.31–1.38 (m, 2 H), 1.24 (s, 3 H), 0.98 (s, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 174.1, 139.3, 138.7, 129.4, 129.1, 128.3, 128.0, 126.8, 126.2, 65.4, 57.7, 55.7, 53.2, 48.3, 47.8, 44.9, 44.8, 38.6, 36.0, 32.9, 26.5, 20.1, 19.9 ppm.

(2*S*)-*N*-{6-[(*tert*-Butoxycarbonyl)amino]-2-[(dibenzylamino)-methyl]hexanoyl}camphorsultam 7e: Compound **7e** was obtained after purification by flash column chromatography (Cy/EA, 9:1) as a mixture of diastereoisomers (251 mg, 47%); R_f = 0.41 (Cy/EA, 8:2). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.18–7.34 (m, 10 H), 3.86 (t, J = 7.2 Hz, 1 H), 3.54–3.80 (m, 4 H), 3.45–3.53 (m, 3 H), 2.29–3.34 (m, 2 H), 2.75 and 2.69 (dd, J = 12.2 Hz, 6.2 Hz and dd, J = 13.5 Hz, 4.7 Hz, 1 H), 2.57 and 2.48 (dd, J = 13 Hz, 8.7 Hz and dd, J = 12.5 Hz, 7.2 Hz, 1 H), 2.03–2.06 (m, 2 H), 1.86–1.89 (m, 3 H), 1.52–1.64 (m, 13 H), 1.13–1.37 (m, 7 H), 0.96 and 0.98 (s and s, 3 H) ppm.

(2*S*)-*N*-Propionylcamphorsultam 9a:[31] 91% yield (5.7 g); R_f = 0.43 (Cy/EA, 8:2); m.p. 145 °C. $[\alpha]_D^{20}$ = 116.5 (c = 1, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 3.86 (dd, J = 7.6 Hz, 5.1 Hz, 1 H), 3.49 (d, J = 13.9 Hz, 1 H), 3.43 (d, J = 13.9 Hz, 1 H), 2.69–2.81 (m, 2 H), 2.04–2.16 (m, 1 H), 2.07 (dd, J = 13.6 Hz, 7.6 Hz, 1 H), 1.85–1.96 (m, 3 H), 1.32–1.44 (m, 2 H), 1.16 (t, 3 H, 7.3 Hz), 1.16 (s, 3 H), 0.97 (s, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 172.6, 65.2, 52.9, 48.5, 47.7, 44.6, 38.5, 32.8, 28.9, 26.4, 20.8, 19.9, 8.39 ppm. $C_{13}H_{21}NO_3S$ (271.38): calcd. C 57.54, H 7.80, N 5.16; found C 57.60, H 7.83, N 5.07.

(2*R*)-*N*-(3-Methylbutanoyl)camphorsultam 9b:[31] 93% yield (6.4 g), R_f = 0.45 (Cy/EA, 8:2), m.p. 114 °C. $[\alpha]_D^{20}$ = –88.4 (c = 1, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 3.88 (t, J = 6.3 Hz, 1 H), 3.50 (d, J = 13.6 Hz, 1 H), 3.43 (d, J = 13.6 Hz, 1 H), 2.66 (dd, J = 15.6 Hz, 7.0 Hz, 1 H), 2.51 (dd, J = 15.6 Hz, 6.8 Hz, 1 H), 2.18–2.28 (m, 1 H), 2.08–2.1 (m, 2 H), 1.87–1.96 (m, 3 H), 1.32–1.44 (m, 2 H), 1.16 (s, 3 H), 0.97 (s and t, 9 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 171.5, 65.2, 53.0, 48.2, 47.7, 44.6, 44.2, 38.6, 32.8, 26.4, 25.5, 22.3, 22.2, 20.8, 19.8 ppm. $C_{15}H_{25}NO_3S$ (299.43): calcd. C 60.17, H 8.42, N 4.68; found C 60.15, H 8.48, N 4.61.

(2*S*)-*N*-(4-Methylpentanoyl)camphorsultam 9c:[31] 81% yield (5.84 g); R_f = 0.44 (Cy/EA, 8:2); m.p. 44 °C. $[\alpha]_D^{20}$ = 97.6 (c = 1, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 3.85–3.88 (m, 1 H), 3.50 (d, J = 13.9 Hz, 1 H), 3.43 (d, J = 13.9 Hz, 1 H), 2.66–2.76 (m, 2 H), 2.04–2.13 (m, 2 H), 1.86–1.96 (m, 3 H), 1.54–1.63 (m, 2 H), 1.16 (s, 3 H), 0.97 (s, 3 H), 0.90 (d, J = 6.3 Hz, 3 H), 0.89 (d, J = 6.3 Hz, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 172.3, 65.2, 53.0, 48.4, 47.7, 44.6, 38.5, 33.6, 33.2, 32.8, 27.6, 26.5, 22.3, 22.2, 20.8, 19.9 ppm. $C_{16}H_{27}NO_3S$ (313.46): calcd. C 61.31, H 8.68, N 4.47; found C 61.15, H 8.85, N 4.41.

(2*S*)-*N*-(3-Phenylpropanoyl)camphorsultam 9d:[31] 92% yield (11.9 g); R_f = 0.37; (Cy/EA, 8:2); m.p. 149 °C. $[\alpha]_D^{20}$ = 82.2 (c = 1, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.2–7.3 (m, 5 H), 3.86 (t, J = 6.3 Hz, 1 H), 3.48 (d, J = 13.6 Hz, 1 H), 3.41 (d, J = 13.6 Hz, 1 H), 3.0–3.1 (m, 4 H), 2.0–2.1 (m, 2 H), 1.8–1.9 (m, 3 H), 1.3–1.4 (m, 2 H), 1.08 (s, 3 H), 0.95 (s, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 171.1, 140.1, 128.5, 128.4, 126.2, 65.2, 52.9, 48.4, 47.7, 44.6, 38.4, 36.9, 32.8, 30.4, 26.4, 20.8, 19.9 ppm. $C_{19}H_{25}NO_3S$ (347.47) calcd. C 65.68, H 7.25, N 4.03; found C 65.40, H 7.35, N 3.99.

(2*S*)-*N*-Octanoylcamphorsultam 9e: This compound, obtained as an oil, was purified by flash column chromatography (Cy/EA, 95:5), 92% yield (7.32 g); R_f = 0.61 (Cy/EA, 8:2). $[\alpha]_D^{20}$ = 88.4 (c = 1, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 3.86 (dd, J = 7.3 Hz, 5.3 Hz, 1 H), 3.49 (d, J = 13.9 Hz, 1 H), 3.43 (d, J = 13.9 Hz, 1 H), 2.68–2.73 (m, 2 H), 2.08–2.12 (m, 2 H), 1.86–1.91 (m, 2 H), 1.63–1.69 (m, 2 H), 1.21–1.41 (m, 12 H), 1.16 (s, 3 H), 0.97 (s, 3 H), 0.87 (t, J = 7.1 Hz, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 65.2, 52.9, 48.3, 47.7, 44.6, 38.5, 35.4, 32.8, 31.6, 28.97, 28.92, 26.9, 26.4, 24.4, 22.5, 20.8, 19.8, 14.0 ppm. $C_{18}H_{31}NO_3S$ (341.51): calcd. C 63.31, H 9.15, N 4.10; found C 63.40, H 9.28, N 4.07.

(2*S*)-*N*-(6-Bromohexanoyl)camphorsultam 9f: Compound **9f** was obtained by crystallization from ethanol, 82% yield (7.56 g); R_f = 0.49 (Cy/EA, 8:2); m.p. 54–55 °C. $[\alpha]_D^{20}$ = 87.8 (c = 1, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 3.86 (dd, J = 7.4 Hz, 5.3 Hz, 1 H), 3.50 (d, J = 13.6 Hz, 1 H), 3.43 (d, J = 13.6 Hz, 1 H), 3.40 (t, J = 6.8 Hz, 2 H), 2.71–2.75 (m, 2 H), 2.04–2.12 (m, 2 H), 1.85–1.92 (m, 5 H), 1.65–1.74 (m, 2 H), 1.33–1.53 (m, 4 H), 1.15 (s, 3 H), 0.97 (s, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 171.6, 65.2, 52.9, 48.4, 47.7, 44.6, 38.5, 35.1, 33.5, 32.8, 32.4, 27.5, 26.4, 23.5, 20.8, 19.9 ppm. $C_{16}H_{26}NO_4SBr$ (408.35): calcd. C 48.98, H 6.68, N 3.57; found C 48.93, H 6.75, N 3.57.

(2*S*)-*N*-[3-(*N*-Benzylindol-3-yl)propanoyl]camphorsultam 9g: Compound **9g** was obtained from 3-(*N*-benzylindol-3-yl)propionic acid. A stirred solution of 3-(indol-3-yl)propionic acid (10 g, 52.9 mmol) in DMF (55 mL) was cooled to 0 °C and NaH (4.66 g, 116.4 mmol) was added in small portions. The mixture was stirred at 0 °C for 30 min and benzyl bromide (6.6 mL, 55.54 mmol) was added. After the mixture had been stirred for 1 h, the reaction was quenched with water, the mixture acidified to pH = 2, and extracted with diethyl ether. The combined organic layers were washed with saturated aqueous NH_4Cl, dried and concentrated in vacuo. Purification by flash column chromatography (Cy/EA/AcOH, 7:3:0.1) gave 3-(*N*-benzylindol-3-yl)propionic acid as a white solid, 75% yield (11 g); R_f = 0.25 (Cy/EA, 8:2); m.p. 117 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.60 (d, J = 7.6 Hz, 1 H), 7.22–7.29 (m, 5 H), 7.17 (t, J = 7.1 Hz, 1 H), 7.11 (t, J = 7.6 Hz, 1 H), 7.07 (d, J = 7.1 Hz, 1 H), 6.93 (s, 1 H), 5.24 (s, 2 H), 3.71 (t, J = 7.6 Hz, 2 H), 2.76 (t, J = 7.6 Hz, 2 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 179.5, 137.6, 136.7, 128.7, 127.7, 127.5, 126.7, 125.6, 121.9, 119.1, 118.8, 113.8, 109.7, 49.9, 34.8, 20.4 ppm. $C_{18}H_{17}NO_2$: calcd. C 77.40, H 6.13, N 5.01; found C 77.12, H 6.37, N 4.89. Compound **9g** was obtained from this compound according to the general procedure and purified by flash column chromatography (Cy/EA, 8:2), white solid, 70% yield (4.7 g), R_f = 0.42 (Cy/EA/NEt_3, 8:2:0.1), m.p. 123 °C. $[\alpha]_D^{20}$ = 57.4 (c = 1, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$):

δ = 7.63–7.65 (m, 1 H), 7.20–7.28 (m, 4 H), 7.07–7.16 (m, 4 H), 6.97 (s, 1 H), 5.23 (s, 2 H), 3.85 (t, *J* = 6.3 Hz, 1 H), 3.45 (d, *J* = 13.9 Hz, 1 H), 3.42 (d, *J* = 13.9 Hz, 1 H), 3.06–3.19 (m, 4 H), 2.03–2.05 (m, 2 H), 1.81–1.87 (m, 3 H), 1.29–1.39 (m, 2 H), 1.05 (s, 3 H), 0.92 (s, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 171.5, 137.7, 136.6, 128.7, 127.9, 127.4, 126.7, 125.8, 121.7, 119.1, 119.0, 113.8, 109.5, 65.2, 52.9, 49.8, 48.4, 47.7, 44.6, 38.5, 36.1, 32.8, 26.4, 20.7, 20.2, 19.8 ppm. $C_{28}H_{32}N_2O_3S$ (476.63): calcd. C 70.56, H 6.77, N 5.88; found C 70.31, H 6.98, *N*, 5.67.

(2*S*)-*N*-{(2*R*)-2-[(Dibenzylamino)methyl]propanoyl}camphorsultam 11a: Crystallization from $CHCl_3$/MeOH, 91% yield (16.7 g); R_f = 0.39 (Cy/EA, 8:2); m.p. 143 °C. $[\alpha]_D^{20}$ = 50.2 (*c* = 1, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.2–7.3 (m, 10 H), 3.9 (dd, *J* = 7.6 Hz, 5.1 Hz, 1 H), 3.6 (s, 4 H), 3.4–3.5 (m, 3 H), 2.9 (dd, *J* = 7.6 Hz, 12.6 Hz, 1 H), 2.4 (dd, *J* = 6.3 Hz, 12.6 Hz, 1 H), 2.0–2.1 (m, 1 H), 2.0 (dd, *J* = 7.6 Hz, 13.9 Hz, 1 H), 2.02–2.11 (m, 2 H), 1.86–1.91 (m, 3 H), 1.3–1.4 (m, 2 H), 1.2 (s, 3 H), 1.1 (s, 3 H), 1.0 (s, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 175.3, 138.9, 128.0, 126.8, 65.4, 57.9, 57.8, 53.1, 48.2, 47.7, 44.7, 38.6, 38.4, 32.9, 26.4, 21.0, 19.9, 15.5 ppm. $C_{28}H_{36}N_2O_3S$ (480.66): calcd. C 69.96, H 7.55, N 5.83; found C 69.85, H 7.67, N 5.92.

(2*R*)-*N*-{(2*S*)-2-[(Dibenzylamino)methyl]-3-methylbutanoyl}-camphorsultam 11b: Purification by flash column chromatography (Cy/EA, 92:8), 81% yield (8.3 g); R_f = 0.45 (Cy/EA, 8:2); m.p. 96 °C. $[\alpha]_D^{20}$ = –41.4 (*c* = 1, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.19–7.31 (m, 10 H), 3.88 (dd, *J* = 5.0 Hz, 7.6 Hz, 1 H), 3.64 (d, *J* = 13.6 Hz, 1 H), 3.51 (d, *J* = 13.6 Hz, 1 H), 3.49 (d, *J* = 13.9 Hz, 1 H), 3.43 (d, *J* = 13.6 Hz, 1 H), 3.27–3.29 (m, 1 H), 2.93 (dd, *J* = 9.1 Hz, 12.6 Hz, 1 H), 2.59 (dd, *J* = 3.8 Hz, 12.9 Hz, 1 H), 2.16–2.20 (m, 1 H), 1.98–2.08 (m, 2 H), 1.87–1.94 (m, 3 H), 1.31–1.41 (m, 2 H), 1.25 (s, 3 H), 0.97 (s, 3 H), 0.91 (d, *J* = 7.1 Hz, 3 H), 0.88 (d, *J* = 7.1 Hz, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 174.3, 138.9, 129.3, 128.0, 126.8, 65.7, 57.8, 53.4, 53.3, 48.5, 48.0, 47.7, 44.7, 38.7, 32.9, 29.1, 26.5, 21.1, 20.9, 19.9, 18.5 ppm. $C_{30}H_{40}N_2O_3S$ (508.72): calcd. C 70.83, H 7.93, N 5.51; found C 70.22, H 7.99, N 5.45. MS (ESI$^+$): *m*/*z* = 509 [MH$^+$].

(2*S*)-*N*-{(2*R*)-2-[(Dibenzylamino)methyl]-4-methylpentanoyl}-camphorsultam 11c: Purification by flash column chromatography (Cy/EA, 9:1), 82% yield (2.7 g); analytical data are identical to those of compound **7a** obtained by the Reformatsky reaction.

(2*S*)-*N*-{(2*R*)-2-[(Dibenzylamino)methyl]-3-phenylpropanoyl}-camphorsultam 11d: Purification by flash column chromatography (Cy/EA, 9:1), 76% yield (9.3 g); R_f = 0.41 (Cy/EA, 8:2); m.p. 59 °C. $[\alpha]_D^{20}$ = 45.6 (*c* = 1, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.16–7.26 (m, 15 H), 3.86 (dd, *J* = 7.6 Hz, 5.1 Hz, 1 H), 3.73 (m, 1 H), 3.41–3.54 (m, 6 H), 3.04 (dd, *J* = 13.6 Hz, 5.6 Hz, 1 H), 2.92 (dd, *J* = 12.6 Hz, 8.1 Hz, 1 H), 2.65 (dd, *J* = 13.6 Hz, 8.6 Hz, 1 H), 2.49 (dd, *J* = 12.6 Hz, 5.3 Hz, 1 H), 2.02–2.11 (m, 2 H), 1.87–1.91 (m, 3 H), 1.31–1.38 (m, 2 H), 1.24 (s, 3 H), 0.98 (s, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 174.1, 139.3, 138.7, 129.4, 129.1, 128.3, 128.0, 126.8, 126.2, 65.4, 57.7, 55.7, 53.2, 48.3, 47.8, 44.9, 44.8, 38.6, 36.0, 32.9, 26.5, 20.1, 19.9 ppm. $C_{34}H_{40}N_2O_3S$ (556.76): calcd. C 73.35, H 7.24, N 5.03; found C 73.01, H 7.31, N 4.90.

(2*S*)-*N*-{(2*R*)-2-[(Dibenzylamino)methyl]octanoyl}camphorsultam 11e: Purification by flash column chromatography (Cy/EA, 95:5), 74% yield (12.98 g); R_f = 0.5 (Cy/EA, 8:2); m.p. 60 °C. $[\alpha]_D^{20}$ = 13.7 (*c* = 1, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.21–7.32 (m, 10 H), 3.88 (dd, *J* = 7.6 Hz, 5.3 Hz, 1 H), 3.65 (d, *J* = 13.6 Hz, 1 H), 3.51 (d, *J* = 13.6 Hz, 1 H), 3.50 (d, *J* = 13.9 Hz, 1 H), 3.43 (d, *J* = 13.9 Hz, 1 H), 3.34–3.38 (m, 1 H), 2.80 (dd, *J* = 12.6 Hz, 7.1 Hz, 1 H), 2.52 (dd, *J* = 12.6 Hz, 6.8 Hz, 1 H), 2.01–2.12 (m, 2 H), 1.86–1.93 (m, 3 H), 1.55 (m, 2 H), 1.27–1.42 (m, 2 H), 1.22 (m, 11 H), 0.97 (s, 3 H), 0.86 (t, *J* = 7.1 Hz, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 174.8, 139.0, 129.1, 128.0, 126.8, 65.4, 58.0, 56.4, 53.3, 48.2, 47.8, 44.7, 44.2, 38.6, 38.6, 32.9, 31.6, 30.1, 29.4, 27.2, 26.5, 21.0, 19.9, 14.1 ppm. $C_{33}H_{46}N_2O_3S$ (550.79): calcd. C 71.96, H 8.42, N 5.09; found C 71.67, H 8.62, N 4.94.

(2*S*)-*N*-{(2*R*)-6-Bromo-2-[(dibenzylamino)methyl]hexanoyl}-camphorsultam 11f: Purification by flash column chromatography (Cy/EA, 9:1), 76% yield (14.6 g); R_f = 0.47 (Cy/EA, 8:2); m.p. 90 °C. $[\alpha]_D^{20}$ = 57.3 (*c* = 1, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.20–7.40 (m, 10 H), 3.87 (dd, *J* = 7.3 Hz, 5.3 Hz, 1 H), 3.68 (d, *J* = 13.6 Hz, 2 H), 3.51 (d, *J* = 13.9 Hz, 1 H), 3.47 (d, *J* = 13.6 Hz, 2 H), 3.43 (d, *J* = 13.9 Hz, 1 H), 3.31–3.37 (m, 3 H), 2.77 (dd, *J* = 12.6 Hz, 6.6 Hz, 1 H), 2.52 (dd, *J* = 12.6 Hz, 7.3 Hz, 1 H), 2.03–2.07 (m, 2 H), 1.86–1.90 (m, 3 H), 1.77–1.81 (m, 2 H), 1.56–1.60 (m, 2 H), 1.33–1.42 (m, 4 H), 1.21 (s, 3 H), 0.97 (s, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 174.4, 139.0, 129.0, 128.1, 126.9, 65.4, 58.2, 56.3, 53.2, 48.2, 47.7, 44.6, 44.0, 38.5, 33.5, 32.9, 32.8, 28.9, 26.4, 25.7, 21.0, 19.9 ppm. MS (ESI$^+$): *m*/*z* = 603 [M + H]$^+$.

(2*S*)-*N*-{(2*R*)-3-(*N*-Benzylindol-3-yl)-2-[(dibenzylamino)methyl]-propanoyl}camphorsultam 11g: Purification by flash column chromatography (Cy/EA, 9:1), 88% yield (5.8 g); R_f = 0.35 (Cy/EA, 8:2); m.p. 80–81 °C. $[\alpha]_D^{20}$ = 25.0 (*c* = 1, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.78–7.80 (m, 1 H), 7.09–7.34 (m, 16 H), 6.99–7.01 (m, 2 H), 6.85 (s, 1 H), 5.20 (s, 2 H), 3.88 (m, 2 H), 3.42–3.52 (m, 6 H), 3.21 (dd, *J* = 14.4 Hz, 3.8 Hz, 1 H), 2.94 (dd, *J* = 12.4 Hz, 10.3 Hz, 1 H), 2.86 (dd, *J* = 14.4 Hz, 9.1 Hz, 1 H), 2.56 (dd, *J* = 12.6 Hz, 4.5 Hz, 1 H), 2.06–2.15 (m, 2 H), 1.85–1.87 (m, 3 H), 1.30–1.37 (m, 2 H), 1.23 (s, 3 H), 0.96 (s, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 174.7, 138.7, 137.9, 136.6, 129.1, 128.6, 128.4, 127.9, 127.0, 126.7, 126.6, 121.6, 119.6, 112.4, 109.4, 65.4, 57.5, 55.8, 53.2, 49.8, 48.3, 47.7, 44.7, 38.6, 32.8, 26.5, 25.8, 21.0, 19.9 ppm. $C_{43}H_{47}N_3O_3S$ (685.92): calcd. C 75.29, H 6.91, N 6.13; found C 75.45, H 7.20, N 5.81.

(*R*)-2-{[(*tert*-Butoxycarbonyl)amino]methyl}propionic Acid (12a): 68% yield (4.6 g), R_f = 0.20 (CH_2Cl_2/MeOH/AcOH, 99:1:0.1); m.p. 89–90 °C. $[\alpha]_D^{20}$ = –17.7 (*c* = 1, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 10.6 (br. s, 1 H), 6.43 and 5.08 (br. s, 1 H), 3.21–3.39 (m, 2 H), 2.65–2.74 (m, 1 H), 1.47 and 1.44 (s, 9 H), 1.2 (d, *J* = 7.5 Hz, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 180.9, 179.6, 157.8, 156.1, 81.1, 79.6, 44.1, 42.7, 40.3, 40.0, 28.4, 14.6 ppm. $C_9H_{17}NO_4$ (203.24): calcd. C 53.19, H 8.43, N 6.89; found C 53.41, H 8.42, N 6.85.

(*S*)-2-{[(*tert*-Butoxycarbonyl)amino]methyl}-4-methylbutanoic Acid (12b): 59% yield (1.7 g), R_f = 0.30 (Cy/EA/AcOH, 7:3:0.1); m.p. 78 °C. $[\alpha]_D^{20}$ = 6.9 (*c* = 1, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.89 and 5.05 (br. s, 1 H), 3.37–3.47 (m, 1 H), 3.20–3.27 (m, 0.3 H), 3.06–3.17 (m, 0.6 H), 2.42–2.49 (m, 1 H), 1.87–2.03 (m, 1 H), 1.48 and 1.44 (s, 9 H), 0.97 and 0.99 (d, *J* = 6.6 Hz, 6 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 178.2, 158.3, 81.1, 52.7, 52.0, 40.6, 39.5, 28.9, 28.4, 26.4, 20.4, 20.3, 19.8 ppm. $C_{10}H_{19}NO_4$ (217.26): calcd. C 57.12, H 9.15, N 6.06; found C 56.98, H 9.29, N 5.98.

(*R*)-2-{[(*tert*-Butoxycarbonyl)amino]methyl}-4-methylpentanoic Acid (12c): 80% yield (2.3 g), R_f = 0.21 (Cy/EA/AcOH, 8:2:0.1); m.p. 74 °C. $[\alpha]_D^{20}$ = –3.1 (*c* = 1, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.76 and 5.02 (br. s, 1 H), 3.32–3.41 (m, 1 H), 3.19–3.26 and 3.00–3.07 (m, 1 H), 2.68–2.70 (m, 1 H), 1.64–1.72 (m, 1 H), 1.52–1.60 (m, 1 H), 1.44–1.48 (s, 9 H), 1.19–1.35 (m, 3 H), 0.93 (d, *J* = 6.1 Hz, 3 H), 0.92 (d, *J* = 6.6 Hz, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 180.8, 179.4, 155.9, 158.1, 79.6, 81.1, 43.7, 44.1, 41.7, 43.0, 38.6, 39.0, 28.4, 25.8, 22.4 ppm. $C_{12}H_{23}NO_4$ (245.32): calcd. C 58.75, H 9.45, N 5.71; found C 58.84, H 9.59, N 5.61.

(*R*)-2-{[(*tert*-Butoxycarbonyl)amino]methyl}-3-phenylpropionic acid (12d): 73% yield (1.6 g); R_f = 0.21 (Cy/EA/AcOH, 8:2:0.1); m.p. 74 °C. $[\alpha]_D^{20}$ = 16.9 (c = 1, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$): δ = 9.65 (br. s, 1 H), 7.18–7.30 (m, 5 H), 6.67 and 5.01 (br. s, 1 H), 3.37–3.41 (m, 0.5 H), 3.22–3.27 (m, 1 H), 2.80–3.11 (m, 3 H), 2.63–2.72 (m, 0.5 H), 1.37–1.42 (s, 9 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 179.01, 179.28, 155.91, 157.98, 138.19, 138.06, 128.91, 128.77, 126.62, 79.73, 81.19, 47.17, 47.53, 41.25, 42.01, 35.66, 35.82 ppm. $C_{15}H_{21}NO_4$ (279.33): calcd. C 64.50, H 7.58, N 5.01; found C 64.19, H 7.62, N 4.90.

(*R*)-2-{[*N*-(*tert*-Butoxycarbonyl)amino]methyl}octanoic Acid (12e): Purification by flash column chromatography (Cy/EA/AcOH, 85:15:1), 44% yield (0.87 g). ^1H NMR (400 MHz, $CDCl_3$): δ = 6.63 and 5.01 (br. s, 1 H), 3.34–3.40 (m, 2 H), 3.23–3.28 (m, 2 H), 3.10–3.12 (m, 2 H), 2.61 (m, 1 H), 1.27–1.64 (m, 19 H), 0.88 (t, J = 6.8 Hz, 6 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 180.7, 180.0, 158.2, 156.1, 81.3, 79.7, 45.8, 42.8, 41.5, 31.7, 29.8, 29.3, 28.5, 27.1, 22.7, 14.2 ppm. The amino acid was crystallized as its dicyclohexylamine (DCHA) salt from diethyl ether (700 mg, 24%); m.p. 103 °C. $[\alpha]_D^{20}$ = –3.73 (c = 1, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$): δ = 8.10 (br. s, 2 H), 5.51 and 5.20 (br. s, 1 H), 3.29–3.35 (m, 1 H), 3.11–3.18 (m, 1 H), 2.89–2.96 (m, 2 H), 2.62–2.31 (m, 1 H), 1.99–2.02 (m, 4 H), 1.78–1.81 (m, 4 H), 1.58–1.66 (m, 3 H), 1.12–1.42 (m, 28 H), 0.86 (t, J = 6.8 Hz, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 180.02, 156.1, 78.5, 52.5, 47.6, 42.5, 31.8, 30.8, 29.6, 28.5, 27.7, 25.3, 24.8, 22.6, 14.1 ppm. $C_{26}H_{50}N_2O_4$ (454.69): calcd. C 68.68, H 11.48, N 6.13; found C 68.44, H 11.63, N 6.05.)

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