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Stereoselective synthesis of both enantiomers of *trans*-2-(diphenylmethylideneamino)cyclopropanecarboxylic acid using a chiral pool approach and their incorporation in dipeptides

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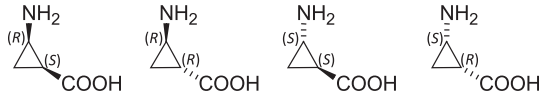
ABSTRACT

The stereoselective synthesis of (1*R*,2*R*)- and (1*S*,2*S*)-*trans*-2-(diphenylmethylideneamino)cyclopropanecarboxylic acid has been accomplished in six steps starting from (2*S*)- and (2*R*)-β-benzyl *N*-(*tert*-butoxycarbonyl)aspartate, respectively. The key-step in the reaction sequence is a stereoselective base-induced ring closure with a good trans diastereoselectivity. These novel *trans*-β-ACC derivatives could be incorporated in dipeptides employing a standard peptide coupling technique.

1. Introduction

β-Aminocyclopropanecarboxylic acid (β-ACC) **1** is a carbocyclic analogue of β-alanine possessing a severe ring strain. β-ACC **1** itself has never been synthesized due to the inherent instability of this small-membered ring caused by its 1,2-donor-acceptor substituted cyclopropane structure.[1,2] Therefore, a suitable stabilizing group at nitrogen is essential to avoid spontaneous ring opening of the cyclopropane core, which complicates the synthesis of β-ACC derivatives and their incorporation in peptides.[3–9] Moreover, due to the presence of two stereogenic centres in the cyclopropane ring, β-aminocyclopropanecarboxylic acid **1** exists as four stereoisomers (Fig. 1). This entails an extra challenge in the development of a strategy for the synthesis of enantiopure β-ACC derivatives.



1a (1*S*,2*R*) **1b** (1*R*,2*R*) **1c** (1*S*,2*S*) **1d** (1*R*,2*S*)

Fig. 1. The four stereoisomers of β-ACC **1**.

Although different asymmetric synthetic approaches towards 2-aminocyclopropanecarboxylates have been reported,[10,11] the elaboration of synthetic pathways towards β-ACC derivatives with no extra functionalization of the cyclopropane core remains rather scarce. An enantiomerically enriched *cis*-2-aminocyclopropanecarboxylic acid derivative (63% ee) was synthesized using a chemoselective hydrolysis of a cyclopropane *meso*-diester with Pig Liver Esterase (PLE) followed by appropriate functional group transformation.[12] Enamides have proved to serve as valuable precursors in the synthesis of unsubstituted *N*-stabilized β-ACC derivatives via a cyclopropanation reaction using ethyl diazoacetate as a carbene source in the presence of a catalyst, which is of great importance for the diastereoselective outcome of this reaction.[13,14] An asymmetric cyclopropanation reaction of styrene with ethyl diazoacetate afforded an unsubstituted *trans*-β-ACC derivative (90% ee) in five steps using a chiral (salen)Ru(II) cyclopropanation catalyst.[15] Noteworthy, only one synthetic route towards an unsubstituted chiral β-aminocyclopropanecarboxylic acid using a chiral pool approach has been described in the literature, more specifically starting from the expensive chiral building block benzyl (*S*)-(+)-glycidyl ether.[16,17] The only other synthesis starting from a chiral building block, D-glyceraldehyde, leads to an enantiomerically pure *trans*-1-methyl-β-ACC derivative in nine steps.[12]

Next to their synthesis, also the incorporation of *cis*-,[10,18–22] and to a lesser extent *trans*-β-aminocyclopropanecarboxylates[10] in peptides, allowing to influence their structural conformation, has received a lot of attention in recent years. The synthesis of a *cis*-β-ACC-containing pseudopeptide, starting from a *meso*-anhydride and (*S*)-prolinate is the only example that can be mentioned regarding the incorporation of an unsubstituted β-ACC building block in peptides.[23,24]

In view of these important gaps in the chemistry of chiral β-ACCs, herein, the synthesis of a new enantiopure unsubstituted (−)-*trans*-β-aminocyclopropanecarboxylic acid via a stereoselective base-induced ring closure is described, starting from an *S*-aspartic acid

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derivative as chiral building block. The (+)-*trans*-β-ACC enantiomer could be synthesized via the same pathway starting from the *R*-aspartic acid derivative. Surprisingly, *S*-aspartic acid, one of the twenty proteinogenic amino acids and a naturally occurring β-amino acid, has never been used as a chiral building block in the synthesis of enantiopure β-aminocyclopropanecarboxylic acids. Moreover, the incorporation of these new *trans*-β-amino-cyclopropanecarboxylic acids in dipeptides was studied as well.

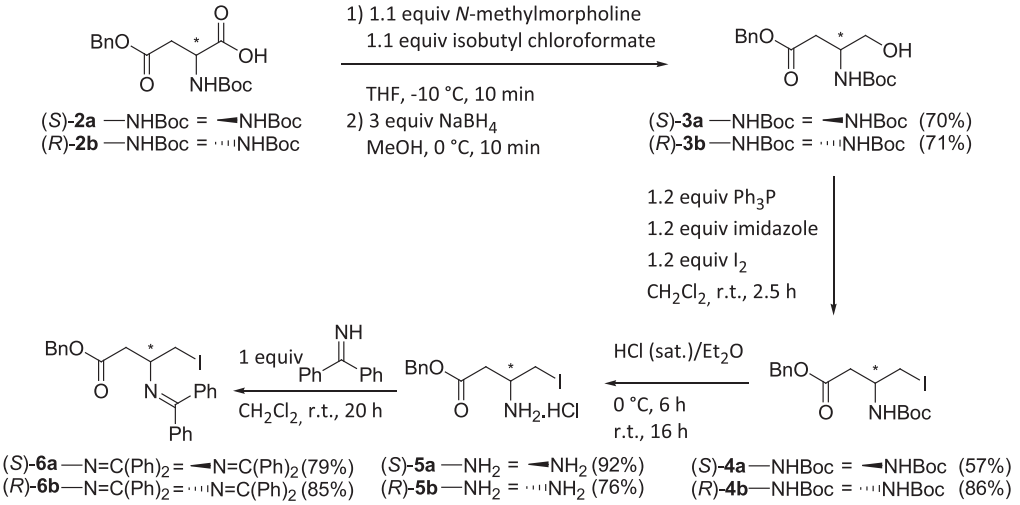
2. Results and discussion

By using acyclic aspartic acid derivatives as chiral building blocks for the synthesis of β-ACCs, the introduction of the cyclopropane core is envisaged to proceed via a 1,3-cyclization reaction. Therefore, the synthesis of an eligible precursor, bearing a leaving group in γ-position and a suitably stabilized amino group in β-position, starting from these aspartic acid derivatives had to be developed. Similar β-aminobutanoates have already been used as precursors in the synthesis of another class of β-amino acids with a three-membered ring as a core structure, more specifically 2-carboxymethylaziridines.[25–27] In the literature, the conversion of (2*S*)-β-benzyl *N*-(*tert*-butoxycarbonyl)aspartate **2a** towards the functionalized iodide **4a** has been reported. The carboxylic acid moiety of aspartate **2a** was converted into the alcohol **3a** by reduction using $NaBH_4$ after activation with isobutyl chloroformate.[28] Conversion of β-amino alcohol **3a** into iodide **4a** was achieved using a PPh_3/I_2 complex using triphenylphosphine instead of a polymer bound triaryl phosphine (Scheme 1).[29,30] In theory, this *N*-Boc protected iodide could serve as a direct precursor in the synthesis of β-ACCs, although competition with formation of the corresponding aziridines is expected.[31] However, it has been demonstrated that the presence of only one electron-withdrawing group at nitrogen in such type of precursors is not sufficient to allow cyclization to 1,2-donor–acceptor substituted cyclopropanes.[32,33] Therefore, another group at nitrogen was introduced, more specifically a diphenylmethylidene group, which has already been used previously as a stabilizing group in the synthesis of donor–acceptor substituted cyclopropanes.[7,32] Boc-deprotection of the amino group of β-amino ester **4a** under acidic conditions afforded β-iodoammonium salt **5a**. Subsequent transimination of **5a** with benzophenone imine yielded enantiopure benzyl (3*S*)-3-diphenylmethylideneamino-4-iodobutanoate **6a**, as a direct precursor for the synthesis of novel chiral unsubstituted β-aminocyclopropanecarboxylates (Scheme 1).

The same synthetic pathway was applied on (2*R*)-β-benzyl *N*-(*tert*-butoxycarbonyl)aspartate **2b** and afforded (3*R*)-benzyl 3-diphenylmethylideneamino-4-iodobutanoate **6b** in 39% overall yield (Scheme 1).

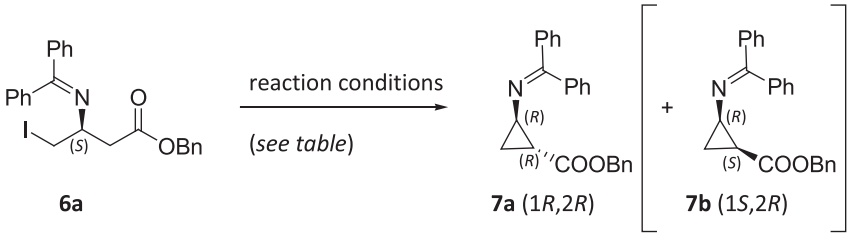
With γ-iodo β-amino esters **6a**–**b** in hand, the base-induced ring closure of these precursors towards the envisaged chiral benzyl cyclopropanecarboxylates was investigated and optimized (Table 1 and 2).

Initially, (3*S*)-benzyl 4-iodobutanoate **6a** was treated with 1.05 equiv of KO*t*Bu in THF for 1 h at room temperature. After work-up, four reaction products could be detected in the crude reaction mixture (based on ^{1}H NMR analysis). To our satisfaction, the intended β-aminocyclopropanecarboxylic ester **7** was formed under the present reaction conditions, albeit as a mixture of two diastereomers in moderate diastereomeric ratio (dr *trans*:*cis* 74:26) (Table 1, entry 1) from which (1*R*,2*R*)-*trans*-2-(diphenylmethylideneamino)cyclopropanecarboxylate **7a** could be isolated in 26% yield (dr>99:1). Due to a reaction conversion of only 73%, iodide **6a** was still present in the crude reaction mixture and via ^{1}H NMR analysis of the reaction mixture, a *tert*-butyl cyclopropanecarboxylate resulting from transesterification could tentatively be identified as a side product, which was not isolated. In an attempt to drive the ring closure reaction to completion, iodide **6a** was treated with 1.5 equiv KO*t*Bu in THF at room temperature for 1 h (Table 1, entry 2). In this case, a reaction conversion of 100% was noticed, but again cyclopropane **7** was obtained in a moderate diastereomeric ratio (dr *trans*:*cis* 79:21). Furthermore, the formation of the side product mentioned above could not be avoided under these modified reaction conditions. After extensive column chromatography and subsequent recrystallization, (1*R*,2*R*)-*trans*-cyclopropane **7a** (24%) and a very small amount of (1*S*,2*R*)-*cis*-cyclopropane **7b** (2%) could be isolated in pure form (dr>99:1). In order to suppress the occurrence of the side reaction, the ring closure reaction was performed at a lower temperature. Unfortunately, the use of KO*t*Bu at 0 °C did not lead to better results (Table 1, entry 3). Following these moderate results, the use of another base, more specifically the strong nitrogen base potassium hexamethyldisilazide (KHMDS), was evaluated in the ring closure reaction of iodide **6a**. When (3*S*)-benzyl 4-iodobutanoate **6a** was reacted with 1.1 equiv KHMDS in THF for 5 min at −78 °C, 92% of the starting product was converted towards cyclopropane **7**, with no formation of side products. Moreover, an improvement of the diastereomeric ratio of cyclopropane **7** could be observed (dr *trans*:*cis* 88:12) (Table 1, entry 4). Prolongation of the reaction time to 10 min led to a full



Scheme 1. Synthesis of (3*S*)-benzyl 4-iodobutanoate **6a** and (3*R*)-benzyl 4-iodobutanoate **6b**.

Table 1
Ring closure of (3*S*)-benzyl 3-(diphenylmethylideneamino)-4-iodobutanoate **6a**

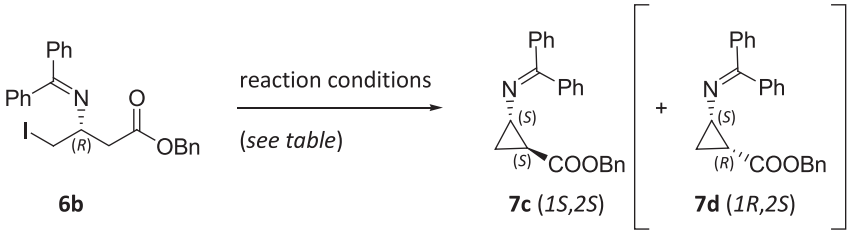


6a **7a** (1*R*,2*R*) **7b** (1*S*,2*R*)

Entry	Reaction conditions	dr *trans*:*cis*[a]	Yield (%) *trans* **7a**[b]
1	1.05 equiv KO*t*Bu, THF, rt, 1 h	74:26[c]	26
2	1.5 equiv KO*t*Bu, THF, rt, 1 h	79:21[d]	24
3	1.05 equiv KO*t*Bu, THF, 0 °C, 2 h	61:39[e]	22
4	1.1 equiv KHMDS, THF, −78 °C, 5 min	88:12[f]	70
5	1.1 equiv KHMDS, THF, −78 °C, 10 min	91:9	79
6	1.1 equiv KHMDS, THF, −78 °C, 1 h	95:5	81
7	1.1 equiv KHMDS, THF, −78 °C, 2 h	99:1	80
8	1.1 equiv KHMDS, THF, 0 °C, 5 min	99:1	74
9	1.5 equiv KHMDS, THF, −78 °C, 1 h	93:7	65

[a] Determinated by ^{1}H NMR spectroscopy of the crude reaction mixture.
[b] dr *trans*:*cis*>99:1.
[c] 73% conversion.
[d] *cis*-**7b** was isolated in 2% yield (dr>99:1).
[e] 82% conversion.
[f] 92% conversion.

Table 2
Ring closure of (3*R*)-benzyl 3-(diphenylmethylideneamino)-4-iodobutanoate **6b**



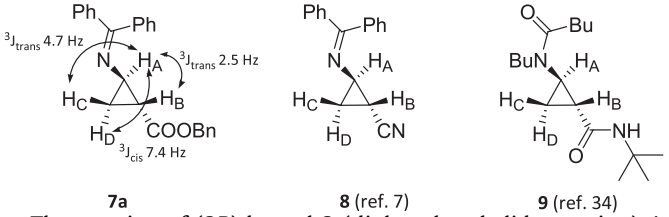
6b **7c** (*1S*,*2S*) **7d** (*1R*,*2S*)

Entry	Reaction conditions	dr *trans*:*cis*[a]	Yield(%) *trans* **7c**[b]
1	1.1 equiv KHMDS, THF, −78 °C, 1 h	97:3	75
2	1.1 equiv KHMDS, THF, rt, 1 h	87:13	56

[a] Determinated by ^{1}H NMR spectroscopy of the crude reaction mixture.
[b] dr *trans*:*cis*>99:1.

conversion of the starting material towards cyclopropane **7** in a good diastereomeric ratio (dr *trans*:*cis* 91:9) (Table 1, entry 5). In an attempt to improve the diastereomeric ratio, the reaction time was prolonged towards 1 and 2 h, with some improvement of the diastereomeric ratio (up to 99:1), but no improvement of the yield of cyclopropanecarboxylate **7a** (Table 1, entry 6–7). From these attempts, (1*R*,2*R*)-*trans*-cyclopropanecarboxylate **7a** could be isolated in a good yield of 81% (resp. 80%) (dr>99:1). When (3*S*)-benzyl 4-iodobutanoate **6a** was reacted with KHMDS at a higher temperature, a similar variable diastereomeric ratio was observed (dr *trans*:*cis* up to 99:1) and (1*R*,2*R*)-*trans*-benzyl 2-(diphenylmethylideneamino)cyclopropanecarboxylate **7a** was isolated in 74% yield (dr>99:1) after recrystallization (Table 1, entry 8). The use of more equivalents of the base was also evaluated but did not lead to an improvement of the diastereomeric ratio or the yield (Table 1, entry 9). Noteworthy, treatment of pure *trans*-benzyl 2-(diphenylmethylideneamino)cyclopropanecarboxylate **7a** with KHMDS under similar reaction conditions (THF, −78 °C, 1 h) only led to degradation of this cyclopropane derivative.

The relative configuration of cyclopropane **7a** was assigned based on comparison of the coupling constants in the ^{1}H NMR signal corresponding to H_A with literature values. The values of the vicinal coupling constants *trans*-$^3J_{HA,HB}$ (=2.5 Hz), *trans*-$^3J_{HA,HC}$ (=4.7 Hz) and *cis*-$^3J_{HA,HD}$ (=7.4 Hz) are comparable to the values of the observed vicinal coupling constants *trans*-$^3J_{HA,HB}$ (=3.0–3.2 Hz), *trans*-$^3J_{HA,HC}$ (=4.7–4.9 Hz) and *cis*-$^3J_{HA,HD}$ (=7.5–7.7 Hz) of the similar racemic *trans*-β-ACC derivatives **8**,[7] and **9**.[34]



7a **8** (ref. 7) **9** (ref. 34)

The reaction of (3*R*)-benzyl 3-(diphenylmethylideneamino)-4-iodobutanoate **6b** with KHMDS, performed under similar reaction conditions (1.1 equiv KHMDS, −78 °C, 1 h), afforded cyclopropane **7**

in a good diastereomeric ratio (dr 97:3) from which (1*S*,2*S*)-benzyl 2-(diphenylmethylideneamino)cyclopropanecarboxylate **7c** could be isolated in 75% yield after recrystallization (dr>99:1) (Table 2, entry 1). Enantiomer **6b** was also treated with KHMDS at room temperature for 1 h, which resulted in a lower diastereomeric ratio (dr *trans*:*cis* 87:13) (Table 2, entry 2).

In an attempt to isolate (1*S*,2*R*)-*cis*-benzyl 2-(diphenylmethylideneamino)cyclopropanecarboxylate **7b** in a better yield, some other reaction conditions were evaluated in order to invert the diastereomeric ratio of cyclopropane **7**. Addition of KCl (1 equiv) or $ZnCl_2$ (1.1 equiv) to the reaction of (3*S*)-benzyl butanoate **6a** with KHMDS in THF at −78 °C or 0 °C did not increase the amount of *cis*-isomer **7b** and resulted in a sluggish reaction with the formation of unidentified side products. Also the addition of 18-crown-6, a crown ether with affinity for potassium cations, to the cyclization reaction did not lead to an inversion of the diastereomeric ratio and only lowered the conversion of the reaction. By adding these additives to the reaction, it was attempted to create a more 'naked' anion in the intermediate, so that internal solvation by the benzophenone imine function might take place, which could lead to preferential formation of the *cis*-cyclopropane.[35]

In a last step towards the synthesis of the unprotected *C*-terminal β-aminocyclopropanecarboxylic acids, a saponification reaction of cyclopropanecarboxylic esters **7a** and **7c** was performed by treatment with aqueous NaOH (in methanol). To our satisfaction, this reaction proceeded smoothly and afforded cyclopropanecarboxylic acids **10a**–**b** in 61–77% yield without observation of *trans*/*cis* isomerisation (based on detailed analysis of the well-resolved signals in the ^{1}H NMR spectrum) (Scheme 2 and Scheme 3). Subsequently, the stability of cyclopropanecarboxylic acids **10a**–**b** towards a peptide coupling reaction with methyl glycinate hydrochloride **11** was evaluated. In a first attempt, (1*R*,2*R*)-*trans*-cyclopropanecarboxylic acid **10a** was reacted with glycinate **11** in the presence of 1.05 equiv dicyclohexylcarbodiimide (DCC) and Et_3N in EtOAc. After detailed analysis of the reaction mixture, it could be concluded that carboxylic acid **10a** had reacted with DCC but the subsequent coupling of the activated acid with methyl glycinate failed, and peptide **12a** could not be detected. The use of another coupling reagent, more specifically 1-ethyl-3-(3-*N*,*N*-dimethylaminopropyl)carbodiimide (HCl salt) (EDC.HCl), proved to be more successful. Reaction of cyclopropanecarboxylic acid **10a** with 1 equiv of methyl glycinate (HCl salt) in CH_2Cl_2 for 24 h at room temperature in the presence of EDC·HCl afforded dipeptide **12a**, which could be isolated, albeit in a very low yield of 2% (dr>99:1). Addition of the base *N*-methylmorpholine (NMM) to the reaction mixture decreased the reaction time to 3 h and increased the yield of peptide **12a** up to 58% after column chromatography (Scheme 2). Peptide **12b** was formed under similar reaction conditions and was isolated in 68% yield (Scheme 3).

When 2 equiv of (*R*)-4-(9-anthryl)-2,2,2-trifluoroethanol [(*R*)-Pirkle alcohol] were added to a prepared mixture (1:1) of peptides **12a** and **12b**, spectral nonequivalences of the signals from the NH-proton and NCH_2-protons appeared in the ^{1}H NMR spectrum (300 MHz, $CDCl_3$). When 2 equiv of (*R*)-Pirkle alcohol were added to peptide **12a** or peptide **12b**, no chemical shift nonequivalences could be observed in the ^{1}H NMR spectrum, confirming the enantiomeric purity of peptides **12a** and **12b**.

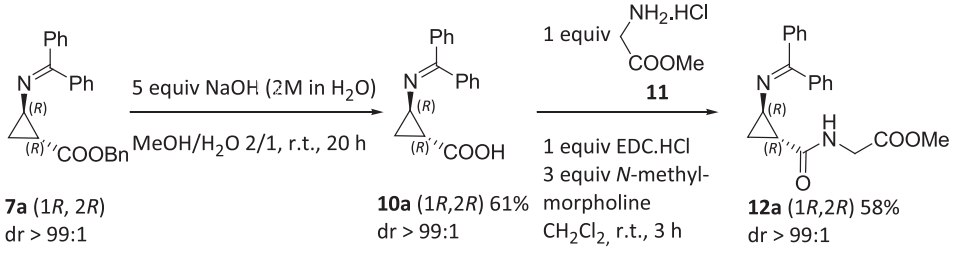
3. Conclusion

In conclusion, a stereoselective synthesis of novel *trans*-β-aminocyclopropanecarboxylic acids **7** was developed, using a chiral pool approach. The key step in the reaction sequence, more specifically the base-induced ring closure was optimized and afforded (1*R*,2*R*)- and (1*S*,2*S*)-*trans*-2-(diphenylmethylideneamino)cyclopropanecarboxylates **7a** and **7c** in very good diastereoselectivity and high yield. These new unsubstituted *N*-stabilized β-ACC derivatives could be converted into the *C*-terminal unprotected β-ACCs **10a**–**b** and were incorporated in dipeptides **12** using standard peptide coupling reaction conditions. The coupling of the novel β-aminocyclopropanecarboxylic acid derivatives **10** into peptides via the N-terminus is currently under investigation in our group.

4. Experimental

4.1. General

Commercially available solvents and reagents were purchased from common chemical suppliers and used without further purification. Diethyl ether and tetrahydrofuran (THF) were freshly distilled from sodium/benzophenone ketyl. CH_2Cl_2 was freshly

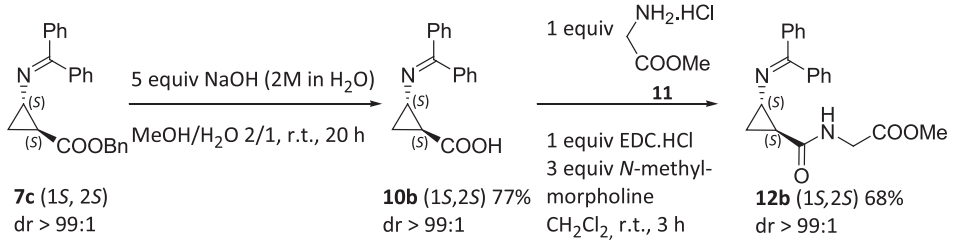


7a (1*R*, 2*R*)
dr > 99:1

10a (1*R*,2*R*) 61%
dr > 99:1

12a (1*R*,2*R*) 58%
dr > 99:1

Scheme 2. Saponification of ester **7a** and peptide formation.



7c (1*S*, 2*S*)
dr > 99:1

10b (1*S*,2*S*) 77%
dr > 99:1

12b (1*S*,2*S*) 68%
dr > 99:1

Scheme 3. Saponification of ester **7c** and peptide formation.

distilled from CaH_2. Petroleum ether refers to the 40–60 °C boiling fraction. ^{1}H NMR (300 MHz), ^{13}C NMR (75 MHz) spectra were recorded in deuterated solvents with tetramethylsilane (TMS, δ=0 ppm) as internal standard. Mass spectra were recorded using a direct inlet system (ESI, 4000 V). IR spectra were obtained from samples in neat form with an ATR (Attenuated Total Reflectance) accessory or on a Perkin–Elmer Spectrum One spectrophotometer. HRMS analysis was performed using an Agilent 1100 series HPLC coupled to an Agilent 6220 TOF-Mass Spectrometer equipped with ESI/APCI-multimode source. Melting points of crystalline compounds were determined in open-end capillary tubes using a hot stage apparatus and were not corrected. The purification of the reaction mixtures was performed by column chromatography with silica gel (particle size 0.035–0.070 mm, pore diameter ca. 6 nm). Thin layer chromatography (TLC) was performed on glass plates coated with silica gel 60 F_{254}, using UV and $KMnO_4$ as a visualizing agent.

4.2. Experimental procedures

*4.2.1. Synthesis of (3S)-benzyl 4-iodo-3-N-(tert-butoxycarbonyl)butanoate **4a**.* (3*S*)-4-Iodobutanoate **4a** was synthesized in two steps following a slightly modified literature procedure starting from (2*S*)-β-benzyl *N*-(*tert*-butoxycarbonyl)aspartate **2a** using PPh_3 instead of polymer bound triphenylphosphine.[28–30]

*4.2.2. Synthesis of (3S)-benzyl 3-amino-4-iodobutanoate hydrochloride **5a**.* (3*S*)-Benzyl 4-iodo-3-*N*-(*tert*-butoxycarbonyl)butanoate **4a** (1.53 g, 3.4 mmol) was dissolved in 34 mL of a saturated solution of HCl in Et_2O at 0 °C and stirred for 6 h at 0 °C. After stirring the reaction mixture for another 16 h at room temperature, the solvent was evaporated *in vacuo*. Subsequently, dry Et_2O (20 mL) was added and the solution was filtered. After washing the filter cake with dry Et_2O (20 mL), (3*S*)-benzyl 3-amino-4-iodobutanoate hydrochloride **5a** was obtained as white crystals in a yield of 92%.

*4.2.2.1. (3S)-Benzyl 3-amino-4-iodobutanoate hydrochloride **5a**.* White crystals. Yield 92%. Mp=129–130 °C ^{1}H NMR (300 MHz, DMSO-d_6): δ 2.77–2.92 (2H, m, CH_2C=O), 3.46–3.61 (3H, m, CH_2I and CH), 5.15 (2H, s, CH_2O), 7.32–7.43 (5H, m, CH_{arom}), 8.51 (3H, br s, NH_3). ^{13}C NMR (75 MHz, DMSO-d_6): δ 6.3 (CH_2I), 37.3 (*C*H_2C=O), 47.6 (CH), 66.2 (CH_2O), 128.0, 128.1, 128.4 (CH_{arom}), 135.5 ($C_{q,arom}$), 169.0 (C=O). IR (ATR, cm^{-1}): ν=3028 (NH_3), 1731 (C=O). MS (ES, pos. mode): *m*/*z* (%): 320 (M+H$^+$–HCl, 100), 192 (M+H$^+$–HCl–HI, 46).

Optical rotation could not be determined due to instability of the HCl salt in MeOH.

*4.2.3. Synthesis of (3S)-benzyl 3-(diphenylmethylideneamino)-4-iodobutanoate **6a**.* To a solution of (3*S*)-benzyl 3-amino-4-iodobutanoate hydrochloride **5a** (0.23 g, 0.6 mmol, 1 equiv) in CH_2Cl_2 (5 mL) was added benzophenone imine (0.11 g, 0.6 mmol, 1 equiv). After stirring the reaction mixture for 20 h at room temperature, the solvent was evaporated *in vacuo* and the residue was redissolved in dry Et_2O (5 mL). Filtration of the solids and subsequent removal of the solvent *in vacuo* afforded (3*S*)-benzyl 4-iodobutanoate **6a** in 97% yield.

*4.2.3.1. (3S)-Benzyl 3-(diphenylmethylideneamino)-4-iodobutanoate **6a**.* Yellow crystals. Yield 97%. Mp=82–83 °C $[\alpha]_D$ 41±1 (*c* 0.8, CH_2Cl_2). ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.76 (1H, dxd, *J*=7.2, 15.3 Hz, C*H*(H)C=O), 2.81 (1H, dxd, *J*=5.5, 15.1 Hz, CH(*H*)C=O), 3.26 (1H, dxd, *J*=6.1, 9.9 Hz, C*H*(H)I), 3.32 (1H, dxd, *J*=6.1, 9.6 Hz, CH(*H*)I), 3.84–3.92 (1H, m, CH), 5.06 (1H, d, *J*=12.4 Hz, C*H*(H)O), 5.10 (1H, d, *J*=12.4 Hz, CH(*H*)O), 7.15–7.20 (2H, m, CH_{arom}), 7.25–7.51 (11H, m, CH_{arom}), 7.57–7.62 (2H, m, CH_{arom}). ^{13}C NMR (75 MHz, $CDCl_3$): δ 10.9 (CH_2I), 41.2 (*C*H_2C=O), 58.5 (CH), 66.1 (CH_2O), 127.5, 127.9, 128.0, 128.3, 128.5, 128.7, 130.3 (CH_{arom}), 135.6, 136.0, 139.3 ($C_{q,arom}$), 169.6 and 170.6 (C=N and C=O). IR (ATR, cm^{-1}): ν=1737 (C=O), 1616 (C=N). MS (ES, pos. mode): *m*/*z* (%): 484 (M+H$^+$, 100). HRMS (ESI) calcd for $C_{24}H_{22}INO_2$ 484.0774 (M+H$^+$), found 484.0764.

*4.2.3.2. (3R)-Benzyl 3-(diphenylmethylideneamino)-4-iodobutanoate **6b**.* $[\alpha]_D$ −40±1 (*c* 0.8, CH_2Cl_2).

*4.2.4. Synthesis of (1R,2R)-benzyl 2-(diphenylmethylideneamino)cyclopropanecarboxylate **7a**.* A solution of (3*S*)-benzyl 3-(diphenylmethylideneamino)-4-iodobutanoate **6a** (0.15 g, 0.3 mmol, 1 equiv) in THF (3 mL) was cooled to −78 °C and KHMDS (1 M in THF) (0.33 mmol, 0.33 mL, 1.1 equiv) was added dropwise. Subsequently, the reaction mixture was stirred for 1 h at −78 °C, after which it was quenched with 1 mL $NH_4Cl_{(aq,sat)}$. The mixture was poured in 10 mL NaOH (2 M in H_2O), extracted with Et_2O (3× 10 mL) and the organic layers were dried with $MgSO_4$. After removal of the drying agent and evaporation of the solvent *in vacuo*, a mixture of *trans*- and *cis*-benzyl 2-(diphenylmethylideneamino) cyclopropanecarboxylate **7a** and **7b** was obtained (dr 95:5) from which (1*R*,2*R*)-benzyl 2-(diphenylmethylideneamino)cyclopropanecarboxylate **7a** was isolated in 81% yield (dr>99:1) after recrystallization from hexane.

The diastereomeric ratio was determined based on the well-resolved signal of the benzylic protons in the ^{1}H NMR spectrum.

*4.2.4.1. (1R,2R)-Benzyl 2-(diphenylmethylideneamino)cyclopropanecarboxylate **7a**.* White crystals. Yield 81%. Mp=102–103 °C $[\alpha]_D$ −208±2 (*c* 0.6, CH_2Cl_2). ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.52–1.63 (2H, m, CH_2), 2.29 (1H, dxdxd, *J*=8.6, 6.1, 2.5 Hz, CHC=O), 3.37 (1H, dxdxd, *J*=7.4, 4.8, 2.5 Hz, CHN), 5.08 (2H, s, CH_2O), 7.20–7.55 (15H, m, CH_{arom}). ^{13}C NMR (75 MHz, $CDCl_3$): δ 18.6 (CH_2), 25.2 (*C*HC=O), 45.7 (CHN), 66.4 (CH_2O), 128.2, 128.3, 128.40, 128.43, 128.7, 128.9, 130.1 (CH_{arom}), 136.1, 136.4, 139.6 ($C_{q,arom}$), 169.2 and 172.8 (C=N and C=O). IR (ATR, cm^{-1}): ν=1714 (C=O), 1612 (C=N). MS (ES, pos. mode): *m*/*z* (%): 356 (M+H$^+$, 100). HRMS (ESI) calcd for $C_{24}H_{21}NO_2$ 356.1651 (M+H$^+$), found 356.1644.

*4.2.4.2. (1S,2S)-Benzyl 2-(diphenylmethylideneamino)cyclopropanecarboxylate **7c**.* $[\alpha]_D$ 206 (*c* 1.6, CH_2Cl_2).

*4.2.5. Synthesis of (1S,2R)-benzyl 2-(diphenylmethylideneamino)cyclopropanecarboxylate **7b**.* To a solution of (3*S*)-benzyl 3-(diphenylmethylideneamino)-4-iodobutanoate **6a** (0.24 g, 0.5 mmol, 1 equiv) in THF (3 mL) was added KO*t*Bu (0.084 g, 0.75 mmol, 1.5 equiv). Subsequently, the reaction mixture was stirred for 1 h room temperature, after which it was filtered through a path of Celite®. Evaporation of the solvent *in vacuo* affored a mixture of *trans*- and *cis*-cyclopropane **7a** and **7b**, which could be separated using column chromatography (hexane/Et_2O 8/2), resulting in pure (1*R*,2*R*)-*trans*-cyclopropane **7a** in 24% yield. (1*S*,2*R*)-Benzyl 2-(diphenylmethylideneamino) cyclopropanecarboxylate **7b** was isolated after extra recrystallization in hexane, in 2% yield.

*4.2.5.1. (1S,2R)-Benzyl 2-(diphenylmethylideneamino)cyclopropanecarboxylate **7b**.* White crystals. Yield 2%. Mp=136–138 °C $[\alpha]_D$ 20 (*c* 0.1, CH_2Cl_2). ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.31 (1H, dxdxd, *J*=7.8, 7.3, 5.1 Hz, C*H*(H)), 1.92 (1H, dxdxd, *J*=6.6, 5.1, 5.1 Hz, CH(*H*)), 2.08 (1H, dxdxd, *J*=7.8, 7.8, 6.6 Hz, CHC=O), 3.25 (1H, dxdxd, *J*=7.8, 7.2, 5.1 Hz, CHN), 5.16 (1H, d, *J*=12.4 Hz, C*H*(H)O), 5.29 (1H, d, *J*=12.4 Hz, CH(*H*)O), 7.19–7.52 (15H, m, CH_{arom}). IR (KBr, cm^{-1}):

ν=1730 (C=O), 1615 (C=N). MS (ES, pos. mode): *m*/*z* (%): 356 ($M+H^+$, 100).

4.2.6. Synthesis of (1R,2R)-2-(diphenylmethylideneamino)cyclopropanecarboxylic acid ***10a****.* To an ice-cooled solution of (1*R*,2*R*)-benzyl 2-(diphenylmethylideneamino)cyclopropanecarboxylate **7a** (0.21 g, 0.6 mmol, 1 equiv) in MeOH/H_2O 5/1 (6 mL), aqueous 2 M NaOH (3 mmol, 1.5 mL, 5 equiv) was added. The reaction mixture was stirred at room temperature for 20 h. The organic solvent was evaporated under reduced pressure and the residual aqueous phase was washed with Et_2O (2× 10 mL). Subsequently, the aqueous layer was carefully acidified with a solution of 2 M HCl in H_2O to pH 6, followed by an extraction with CH_2Cl_2 (3× 10 mL). After drying ($MgSO_4$), filtration and evaporation, the pure carboxylic acid **10a** was obtained in 61% yield and dr>99:1.

4.2.6.1. (1R,2R)-2-(Diphenylmethylideneamino)cyclopropanecarboxylic acid ***10a****.* White crystals. Yield 61%. Mp=194–195 °C $[\alpha]_D$ −256 (*c* 0.5, MeOH). ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.55 (1H, dxdxd, *J*=7.4, 5.8, 4.4 Hz, C*H*(H)), 1.63 (1H, dxdxd, *J*=8.8, 4.5, 4.4 Hz, CH(*H*)), 2.23 (1H, dxdxd, *J*=8.5, 6.1, 2.5 Hz, CHC=O), 3.38 (1H, dxdxd, *J*=7.3, 4.8, 2.3 Hz, CHN), 7.24–7.55 (10H, m, CH_{arom}). ^{13}C NMR (75 MHz, CD_3OD) δ 17.7 (CH_2), 24.6 (*C*HC=O), 45.4 (CHN), 128.3, 128.5, 128.6, 129.0, 130.5 (CH_{arom}), 136.9, 139.8 ($C_{q,arom}$), 170.7 and 175.6 (C=N and C=O). IR (ATR, cm^{-1}): ν=2850 (OH), 1698 (C=O), 1613 (C=N). MS (ES, pos. mode): *m*/*z* (%): 266 ($M+H^+$, 100). HRMS (ESI) calcd for $C_{17}H_{15}NO_2$ 266.1181 ($M+H^+$), found 266.1176.

4.2.6.2. (1S,2S)-2-(Diphenylmethylideneamino)cyclopropanecarboxylic acid ***10b****.* $[\alpha]_D$ 247 (*c* 0.4, MeOH).

4.2.7. Synthesis of (1′R,2′R)-methyl [(2′-diphenylmethylideneaminocyclopropane)carbonyl]aminoacetate ***12a****.* To a stirred solution of (1*R*,2*R*)-2-(diphenylmethylideneamino)cyclopropanecarboxylic acid **10a** (0.053 g, 0.2 mmol, 1 equiv) and methyl glycinate hydrochloride **11** (0.025 g, 0.2 mmol, 1 equiv) in dry CH_2Cl_2 (5 mL) were added 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (EDC·HCl) (0.038 g, 0.2 mmol, 1 equiv) and *N*-methylmorpholine (0.061 g, 0.6 mmol, 3 equiv), and the reaction mixture was stirred at room temperature for 3 h. The reaction mixture was poured into water (10 mL) and extracted with CH_2Cl_2 (3× 5 mL). The combined organic layers were dried with $MgSO_4$. The drying agent was removed by filtration and the filtrate was concentrated in vacuo. This afforded pure (1′*R*,2′*R*)-methyl [(2′-diphenylmethylideneaminocyclopropane)carbonyl]aminoacetate **12a** (58% yield) after column chromatography on silica gel (petroleum ether/EtOAc 1/1).

4.2.7.1. (1′R,2′R)-Methyl [(2′-diphenylmethylideneaminocyclopropane)carbonyl]aminoacetate ***12a****.* Viscous oil. Yield 58%. $[\alpha]_D$ −168±3 (*c* 0.1, CH_2Cl_2). ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.49 (1H, dxdxd, *J*=8.8, 4.4, 4.4 Hz, C*H*(H)), 1.56 (1H, dxdxd, *J*=7.4, 5.8, 4.4 Hz, CH(*H*)), 2.11 (1H, dxdxd, *J*=8.5, 5.9, 3.0 Hz, CHC=O), 3.36 (1H, dxdxd, *J*=7.2, 4.8, 2.2 Hz, CHN), 3.75 (3H, s, CH_3), 4.03 (2H, d, *J*=5.0 Hz, C*H*$_2$NH), 6.28 (1H, t, *J*=5.0 Hz, NH), 7.23–7.55 (10H, m, CH_{arom}). ^{13}C NMR (75 MHz, $CDCl_3$): δ 17.5 (*C*H$_2$CHN), 26.9 (*C*HC=O), 41.3 (CH_2N), 44.8 (CHN), 52.4 (CH_3), 128.1, 128.3, 128.4, 128.6, 128.8, 129.9 (CH_{arom}), 136.3, 139.7 ($C_{q,arom}$), 168.7, 170.5 and 171.6 (C=N and 2× C=O). IR (ATR, cm^{-1}): ν=3299 (NH), 1752 (C=O), 1648 (C=O). MS (ES, pos. mode): *m*/*z* (%): 337 ($M+H^+$, 100). HRMS (ESI) calcd for $C_{20}H_{20}N_2O_3$ 337.1552 ($M+H^+$), found 337.1548.

4.2.7.2. (1′S,2′S)-Methyl [(2′-diphenylmethylideneaminocyclopropane)carbonyl]aminoacetate ***12b****.* $[\alpha]_D$ 151±1 (*c* 0.3, CH_2Cl_2).

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Supplementary data

Supplementary data associated with this article can be found in the online version, at http://dx.doi.org/10.1016/j.tet.2012.09.078. These data include MOL files and InChiKeys of the most important compounds described in this article.

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