Chiral Succinate: A Precursor for Enantiomerically Pure β²-Amino Acids

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Abstract: Five suitably protected enantiomerically pure β²-amino acids, homologues of proteinogenic α-amino acids, were synthesized from the common chiral precursor, *tert*-butyl succinyloxazolidinone.

Key words: β-amino acids, rearrangements, regioselectivity, ring closure, stereoselective synthesis

While it has been known for about five decades[1] that β³-amino acids can be obtained by various methods of simple homologation of proteinogenic α-amino acids,[2] methods for the synthesis of β²-amino acids with proteinogenic sidechains have been established only recently.[3] Much of the work regarding the stereoselective preparation of β²-amino acids, their properties, and biological importance has been reviewed.[4]

Most of the methods known for the synthesis of α-substituted β-amino acids may be classified as two main approaches. The more straightforward one comprises the stereoselective alkylation of a synthetic β-alanine equivalent introducing the sidechain. The amino group in such a β-alanine derivative is usually suitably protected[5] or included into a heterocycle,[6] but may also be unprotected[7] or masked as a nitro group.[8]

The stereoselective introduction of an amino or methylamino group into a carboxylic acid equivalent bearing the desired sidechain is the less straightforward method. In each case a different precursor for each amino acid has to be synthesized. Nevertheless, this is the most frequently used approach to β²-amino acids.[9] The key step of most of these syntheses is the amidomethylation of Ti-enolates of acylated chiral oxazolidinones first developed by Evans.[10] The ease of cleavage of the chiral auxiliary leading to the enantiomerically pure product was probably the main reason for the success of this method. Later on, this method underwent various modifications concerning the amidomethylating reagent[11] or the chiral auxiliary.[12]

Reactions of chiral *N*-acyl-oxazolidinones with the corresponding acid derivatives in combination with Curtius rearrangement proved to be a highly effective method for the introduction of an amino (carbamate) group in the synthesis of amino acids. This method was for the first time described by Evans and used for a synthesis of γ-amino acids.[13] Most of the related syntheses of β-amino acids published later included the alkylation of lithium or sodium enolates of chiral acyl-oxazolidinones with *tert*-butyl bromoacetate. The second step involved the selective removal of either imine or newly introduced ester functionality followed by Curtius degradation of the free carboxy group. Thus, the substituted succinate formed serves as a common precursor for β³-amino acids[14] or β²-amino acids.[11b] In contrast, the synthesis published by Sibi[15] is based on the stereoselective and regioselective alkylation of Na-enolates of *tert*-butyl succinyloxazolidinone as chiral equivalent of β-alanine, followed by Curtius rearrangement of one of the carboxylic groups leading to a β²- or β³-amino acid.

In spite of the relatively large number of published 'general' methods for the synthesis of enantiopure β²-amino acids, most of them are limited to rather simple alkyl-, aryl- or benzyl-substituted amino acids. The first attempt to synthesize a β²-amino acid with a functional group in the sidechain, as a homologue of the corresponding proteinogenic α-amino acid was published by Arvanitis.[16] The alkylation of the chiral oxazolidinones derived from vinyl or dimethoxyphenyl substituted acids, equivalents of succinic acid, with bromoacetates and subsequent oxidation provides enantiopure tricarballylic acid.[17] After Curtius degradation and cleavage of the chiral auxiliary, the *N*-Cbz-protected β²-homo-aspartic acid was obtained.

Recently, Seebach presented the syntheses of suitably protected β²-amino acids with 17 of the 20 proteinogenic sidechains.[3] The amino acids were prepared by diastereoselective reactions of Li-, B-, or Ti-enolates of the corresponding 3-acyl-4-isopropyl-5,5-diphenyloxazolidin-2-ones with appropriate electrophiles [amidomethylation, hydroxyalkylation, (benzyloxycarbonyl)methylation] in good yields and with diastereoselectivities of 80–97%.

We developed, independently from Seebach et al., a methodology for the synthesis of some β²-amino acids with proteinogenic sidechains.[18] Among the various methods described above, we found the concept of Sibi et al.[15] to be most suitable for our purposes. Thus, we tried to extend their synthesis of methyl, allyl and benzyl substituted β²-amino acids to derivatives with functionalized sidechains. We focused our investigation on reactions of chiral succinyloxazolidinones. The parent (4*R*)-4-benzyl-1,3-oxazolidin-2-one was chosen as the source of chirality because of its stability against common deprotecting reagents such as TFA or H_2, Pd/C (see ref.[19]) and better diastereoselection in some cases. Moreover, it is commercially available or can be easily synthesized from phenylalanine.

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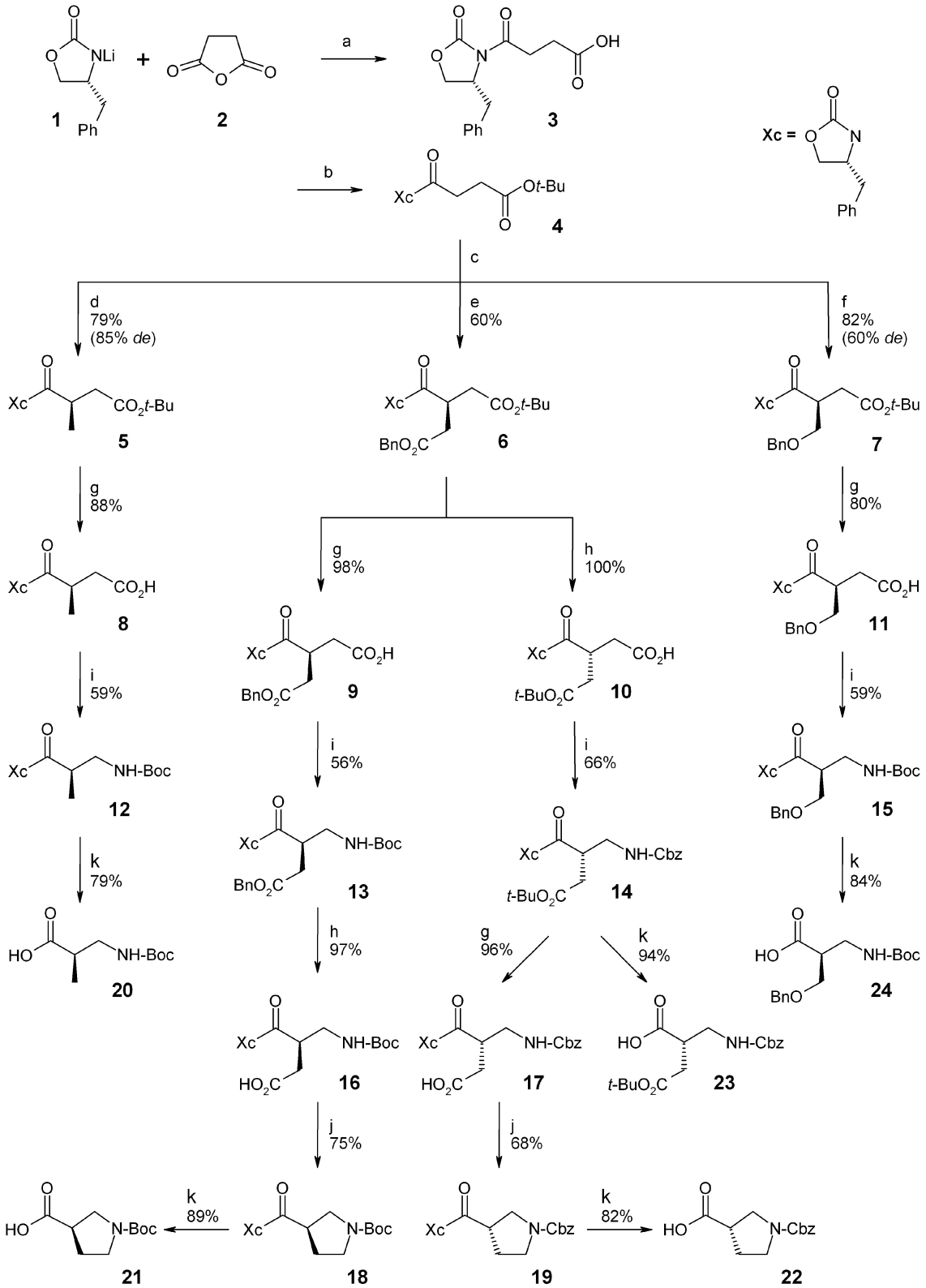

Scheme 1 *Reagents and conditions*: a) THF, –78 °C–r.t.; b) $CHCl_3$, *t*-BuOH, P_2O_5, see also ref.[20]; c) THF, NaHMDS, –78 °C; d) MeI, –78 °C to –50 °C; e) NaI, $BrCH_2CO_2Bn$, –95 °C to –78 °C; f) NaI, $ClCH_2OBn$, –95 °C to –78 °C; g) CH_2Cl_2, TFA; h) EtOAc, H_2, Pd/C (10%); i) 1. THF, $ClCO_2Et$, Et_3N, –15 °C to r.t.; 2. NaN_3, H_2O, 0 °C; 3. toluene, *t*-BuOH for **12**, **13**, **15**, $C_6H_5CH_2OH$ for **14**, reflux; j) THF, $BH_3{\cdot}Me_2S$, 0 °C to r.t.; k) THF, H_2O_2, $LiOH{\cdot}H_2O$, 0 °C.

In contrast to Sibi et al., we simplified the synthesis of the chiral succinate **4**. The Li imide of the chiral auxiliary **1** was almost quantitatively acylated with succinic anhydride **2** (Scheme 1) and the resulting carboxylic acid **3** was subsequently converted to its *tert*-butyl ester using the procedure described by Wright.[20] Despite the moderate conversion (50%) and yield of **4**, we preferred this method over others because the ester **4** and unconverted starting material **3** were easily separable and were obtained essentially pure after the reaction. Thus, about 35% of unconverted **3** can be recycled. This new procedure avoids the additional synthesis of mono-*tert*-butyl succinate.

In general, enolate reactions with iodomethane are the least stereoselective processes and serve as a probe for the method. It is also known that alkylations of Na enolates are superior to analogous reactions of the corresponding Li enolates.[15,19,21] Therefore, firstly the chiral succinate **4** was treated with NaHMDS and allowed to react with iodomethane. This reaction provided **5** as the single regioisomer with good diastereoselectivity (85% de, according to ^{1}H NMR spectra of the crude product). The mixture of **5** and its diastereomer (overall yield 79%) was inseparable by column chromatography and used as obtained in the next step. Relatively good results of this experiment encouraged us to examine the reactions of **4** with other electrophiles. The enolate of **4** was treated with benzyl bromoacetate. However, the first experiments were disappointing not only due to moderate stereoselectivity and incomplete regioselectivity but especially due to a low reaction rate. It appeared that benzyl bromoacetate reacts too slowly with the Na enolate of **4** at –50 °C and a detectable amount of starting material was present in the reaction mixture even after 30 hours. The presence of regioisomers and probably non-volatile benzyl bromoacetate in the crude product encumbered the determination of diastereomeric purity. Up to seven partially overlapping signals corresponding to a benzylic proton were observed in the ^{1}H NMR spectra.

The reaction of **4** with benzyl bromoacetate in the presence of NaI proceeds much faster and only traces of starting material **4** were detectable after 3 hours, even at low temperatures (–100 °C to –78 °C; see also ref.[22,23]). Essentially the same results were achieved, when benzyl iodoacetate was prepared separately beforehand. However, only moderate improvements of diastereoselectivity and regioselectivity were observed in both cases. Six compounds were present in the crude product in a ratio of about 59:7:6:3:3:1 (according to ^{1}H NMR spectra). The lack of regioselectivity of this reaction was somehow astonishing as the reaction with iodomethane was completely regioselective. A possible explanation may be that the formed product **6** and its minor diastereomer in the reaction mixture undergo partial *trans*-enolization of the benzyl ester and react with a second molecule of benzyl iodoacetate.[24] It was not possible to completely overcome this problem. Hence, the reaction conditions were optimized to maximum conversion and minimum amounts of by-products. This allows obtaining of diastereomerically pure **6** in 60% yield after column chromatography and crystallization.

The reaction of the enolate of **4** with benzyl chloromethyl ether (benzyloxymethyl chloride), which was converted to benzyloxymethyl iodide in situ was carried out successfully. The benzyloxymethylated succinate **7** and its diastereomer (in a ratio of about 4:1, according to ^{1}H NMR) were obtained as an inseparable mixture in 82% yield and used as obtained in the next step.

The *tert*-butyl ester of the diastereomeric mixtures of both succinates **5** and **7** was cleaved with TFA in CH_2Cl_2 in excellent yields. At this point the diastereomeric mixture of the obtained intermediate acids could be easily separated by column chromatography to provide the diastereomerically pure products **8** and **11**. The *tert*-butyl ester of **6** was cleaved using the same method as mentioned above. Alternatively, the benzyl ester protection was removed by hydrogenolysis to give carboxylic acid **10** quantitatively. Subsequent Curtius rearrangement provided the imides of protected β^2-amino acids **12–15** in moderate yields.

The orthogonally protected tricarboxylic acid **6** is in fact derived from the parent *meso* compound permitting the selective synthesis of both enantiomers of the corresponding protected β^2-homo-aspartic acid **13** and **14**. The remaining ester groups of **13** and **14** were cleaved as described previously and the resulting acids **16** and **17** were subjected to further transformations, for example to give a variety of homo-aspartate derivatives.[25] In our attempts to reduce the carboxylic group of intermediate acids **16** and **17** with a series of reduction agents, we found out, that treatment with $BH_3 \cdot Me_2S$ causes a ring closure reaction, leading to the pyrrolidines **18** and **19** (see also ref.[26]). This provided us with a relatively straightforward method for the synthesis of both enantiomers of β-proline (β^2-isoproline). However, we were not able to obtain the primary alcohols from any reduction reaction.

Thus, after cleavage of the chiral auxiliary with lithium hydroperoxide according to a numerously employed procedure (see ref.[15]), five suitably protected β^2-amino acids **20**, **21**, **22**, **23** and **24** with proteinogenic sidechains were synthesized in acceptable overall yields. Notably, all amino acids were obtained starting from the single precursor **4**. Moreover, some β^2-amino acids were synthesized from **6**, the product of one single diastereoselective reaction. As the stereoselective creation of a new stereogenic center is usually the most difficult procedure in the synthesis of enantiomerically pure compounds, this feature of the synthesis presented is of great value.

In summary, we have explored a highly versatile synthesis of some proteinogenic β^2-amino acids. A number of β^2-amino acids were synthesized from a single intermediate using efficient procedures with a minimum of efforts for stereoselection.

All chemicals were reagent grade and used as purchased, except for succinic anhydride, which was sublimated and iodomethane, benzyl bromoacetate and benzyl chloromethyl ether, which were distilled

prior to use. The solvents were purified by standard procedures. All moisture-sensitive experiments were performed under anhydrous conditions in flame-dried glassware under a dry Ar atmosphere, employing standard techniques for handling air-sensitive materials. ^{1}H NMR and ^{13}C NMR spectra were recorded on the following instruments: Bruker AC 250P (^{1}H: 250 MHz, ^{13}C: 62.9 MHz), Bruker DRX 500 (^{1}H: 500 MHz, ^{13}C: 125.8 MHz) and Bruker Avance 600 (^{1}H: 600 MHz). All chemical shifts are reported as ppm values (δ) relative to TMS or residual solvent. IR spectra were recorded on a JASCO FT/IR-410 spectrophotometer, either using KBr discs or films on NaCl plates. Optical rotations were measured on a Jasco DIP-360 polarimeter at the sodium D-line (589 nm) (*c* in g/100 mL). Mass spectral data were obtained either on a VG Autospec X (CI), on a Bruker Esquire 3000 (ESI) or on a Bruker APEX III instrument (ESI–FT–ICR, for HRMS). Melting points were determined in open capillaries on a Büchi Melting Point apparatus B 540 and are uncorrected. Reactions were monitored by TLC on Merck silica gel 60 F_{254} plates, using a combination of UV- and chemical detection (dipping the plate into a 5% ninhydrine solution in EtOH and subsequent heating). Petroleum ether (PE) used had a boiling point range of 30–60 °C.

4-[(4*R*)-4-Benzyl-2-oxo-1,3-oxazolidin-3-yl]-4-oxobutanoic Acid (3)

A solution of (4*R*)-4-benzyl-1,3-oxazolidin-2-one (**2**; 2.00 g, 11.29 mmol) in anhyd THF (40 mL) was cooled to –78 °C and a solution of *n*-BuLi (7.5 mL of 15% solution in hexane, 12.29 mmol) was added dropwise. The obtained mixture was stirred for 30 min at –78 °C. A solution of succinic anhydride (1.35 g, 13.49 mmol) in anhyd THF (90 mL) was slowly added at this point and the mixture was stirred overnight allowing gradual warming to r.t. After the reaction, water (90 mL) was added, THF was evaporated and sat. aq $NaHCO_3$ solution was added to adjust pH to 9. The basic aqueous solution was washed with EtOAc (2 × 30 mL), then acidified with concd HCl to adjust pH < 2 and extracted with CH_2Cl_2 (4 × 200 mL). The combined CH_2Cl_2 extracts were dried over anhyd Na_2SO_4, filtered and evaporated to dryness. The oily residue was crystallized from toluene–PE (25 mL, 7:1), affording **3** (3.01 g, 96%) as colorless crystals; mp 56 °C; $[\alpha]_D^{24}$ –63.6 (*c* = 1.0, $CHCl_3$).

IR (KBr): 3029, 1784, 1701, 1604, 1583, 1497, 1455, 1389, 1351, 1250, 1215, 1182, 1116, 990, 943, 845, 761, 730, 698 cm^{-1}.

^{1}H NMR (250 MHz, $CDCl_3$): δ = 2.73–2.85 (m, 3 H), 3.22–3.30 (m, 3 H), 4.14–4.25 (m, 2 H), 4.67 (m, 1 H), 7.15–7.36 (m, 5 H).

^{13}C NMR (62.9 MHz, $CDCl_3$): δ = 28.1, 30.7, 37.8, 55.1, 66.4, 127.4, 129.0, 129.5, 135.1, 153.5, 171.7, 177.9.

MS (CI, NH_3): *m*/*z* (%) = 178 (37), 195 (100), 278 (23) $[M + H]^+$, 295 (46) $[M + NH_4]^+$.

***tert*-Butyl 4-[(4*R*)-4-Benzyl-2-oxo-1,3-oxazolidin-3-yl]-4-oxobutanoate (4)**

A solution of **3** (7.50 g, 27.05 mmol) in anhyd $CHCl_3$ (100 mL) was added to a suspension of P_2O_5 (4.20 g, 29.59 mmol) in anhyd $CHCl_3$ (100 mL), followed by slow addition of anhyd *t*-BuOH (13.0 mL, 10.0 g, 135 mmol). The reaction mixture was stirred for 60 h at r.t. in a tightly stoppered flask and subsequently poured into sat. aq $NaHCO_3$ solution (300 mL). After separation of the phases, the aqueous phase was extracted with CH_2Cl_2 (3 × 100 mL). The combined organic extracts were washed with brine, dried over anhyd Na_2SO_4 and evaporated to dryness. The obtained yellow oil was purified by flash chromatography (EtOAc–PE, 1:1), yielding **4** (4.48 g, 50%) as white crystals after recrystallization from Et_2O–PE (16 mL, 1:1).

The aqueous phase was acidified with concd HCl solution (pH 2) and extracted with CH_2Cl_2 (4 ×). The combined extracts were dried over anhyd Na_2SO_4 and evaporated to dryness. The oily residue was crystallized from a mixture of toluene (10 mL) and PE (1.5 mL), thus recovering unreacted starting material **3** (2.48 g, 33%).

Mp 56.5–58 °C; $[\alpha]_D^{22}$ –55.1 (*c* = 1.0, $CHCl_3$).

IR (KBr): 3030, 3005, 2979, 2931, 1783, 1733, 1718, 1696, 1457, 1387, 1365, 1263, 1242, 1224, 1153, 996, 847, 761, 701 cm^{-1}.

^{1}H NMR (250 MHz, $CDCl_3$): δ = 1.47 (s, 9 H), 2.59–2.65 (m, 2 H), 2.78 (dd, *J* = 13.5, 9.5 Hz, 1 H), 3.18–3.21 (m, 2 H), 3.29 (dd, *J* = 13.5, 3.2 Hz, 1 H), 4.14–4.25 (m, 2 H), 4.68 (m, 1 H), 7.19–7.37 (m, 5 H).

^{13}C NMR (62.9 MHz, $CDCl_3$): δ = 28.1, 29.5, 31.0, 37.8, 55.1, 66.3, 80.7, 127.4, 129.0, 129.5, 135.3, 153.5, 171.6, 172.1.

MS (CI, NH_3): *m*/*z* (%) = 178 (4), 195 (11), 278 (20), 295 (100), 334 (9) $[M + H]^+$, 351 (29) $[M + NH_4]^+$.

***tert*-Butyl (3*R*)-4-[(4*R*)-4-Benzyl-2-oxo-1,3-oxazolidin-3-yl]-3-methyl-4-oxobutanoate (5)**

A solution of **4** (3.33 g, 9.99 mmol) in anhyd THF (100 mL) was cooled to –78 °C and NaHMDS (12.00 mL of 1 M solution in THF, 12.00 mmol) was added dropwise. The mixture was stirred for 1 h at the same temperature. A solution of MeI (3.12 mL, 7.11 g, 50.12 mmol) in THF (10 mL) was added dropwise. The mixture was stirred at –78 °C for 5 h, then allowed to warm to –50 °C and stirred overnight. The reaction was quenched with sat. aq NH_4Cl (50 mL), the mixture was allowed to warm to r.t. and THF was evaporated. The resulting aq solution was extracted with CH_2Cl_2 (3 × 70 mL), the combined organic extracts were washed successively with 5% aq solutions of $KHSO_4$, $NaHCO_3$, Na_2SO_3 and brine, then dried over anhyd Na_2SO_4, filtered and evaporated. The obtained oil containing a mixture of the diastereomers **5** and *epi*-**5** (85% de) (2.74 g, 79%) solidified upon a standing in a fridge. The mixture was inseparable by column chromatography and was used as such in the next step.

^{1}H NMR (250 MHz, $CDCl_3$): δ = 1.24 (d, *J* = 6.9 Hz, 3 H), 1.42 (s, 9 H), 2.35 (dd, *J* = 16.9, 4.4 Hz, 1 H), 2.80 (dd, *J* = 13.2, 9.4 Hz, 1 H), 2.85 (dd, *J* = 16.6, 10.4 Hz, 1 H), 3.23 (dd, *J* = 13.5, 3.5 Hz, 1 H), 4.06 (m, 1 H), 4.18 (dd, *J* = 9.1, 2.8 Hz, 1 H), 4.25 (m, 1 H), 4.71 (m, 1 H), 7.19–7.36 (m, 5 H).

^{13}C NMR (62.9 MHz, $CDCl_3$): δ = 17.4, 28.1, 34.4, 38.0, 38.6, 55.2, 66.1, 80.7, 127.3, 128.9, 129.5, 135.2, 153.0, 171.2, 176.2.

1-Benzyl 5-*tert*-Butyl (3*R*)-3-{[(4*R*)-4-Benzyl-2-oxo-1,3-oxazolidin-3-yl]carbonyl}pentanedioate (6)

A solution of **4** (3.00 g, 9.00 mmol) in anhyd THF (50 mL) was added to a solution of anhyd NaI (1.60 g, 10.67 mmol) in anhyd THF (130 mL). The mixture was cooled to –78 °C (acetone–dry ice) and NaHMDS (12.00 mL of 1 M solution in THF, 12.00 mmol) was added dropwise. This mixture was stirred for 1 h at –78 °C, and then cooled to –95 °C by addition of liquid N_2 to the cooling bath. A solution of benzyl bromoacetate (1.74 mL, 2.54 g, 11.44 mmol, 1.27 equiv) in anhyd THF (8 mL) was added within 2 h (syringe pump, 4 mL/h) and the reaction mixture was stirred for additional 4 h, while it was allowed to warm to –75 °C. The reaction was quenched by addition of sat. aq NH_4Cl solution (80 mL), allowed to warm to r.t. and THF was evaporated. The remaining aqueous mixture was diluted with water (10 mL) and extracted with EtOAc (3 × 300 mL). The combined organic extracts were washed successively with 5% aq $KHSO_4$, 5% aq $NaHCO_3$ and brine (80 mL of each), dried over anhyd Na_2SO_4 and evaporated to dryness. The crude yellow oil was purified by flash column chromatography (CH_2Cl_2–Et_2O, 40:1). Crystallization of the obtained oil from Et_2O–PE (50 mL, 1:1) gave **6** (2.60 g, 60%) as colorless crystals; mp 90–91 °C; $[\alpha]_D^{23}$ –26.6 (*c* = 1.0, $CHCl_3$).

IR (KBr): 3029, 2972, 2933, 1792, 1700, 1604, 1587, 1498, 1485, 1400, 1353, 1304, 1261, 1208, 1159, 1121, 1064, 1009, 958, 843, 729, 697 cm^{-1}.

^1H NMR (250 MHz, $CDCl_3$): δ = 1.42 (s, 9 H), 2.48 (dd, *J* = 16.3, 5.6 Hz, 1 H), 2.57 (dd, *J* = 13.4, 10.0 Hz, 1 H), 2.65 (dd, *J* = 16.2, 5.9 Hz, 1 H), 2.74 (dd, *J* = 16.3, 8.3 Hz, 1 H), 2.89 (dd, *J* = 16.4, 8.1 Hz, 1 H), 3.25 (dd, *J* = 13.4, 3.3 Hz, 1 H), 4.11 (dd, *J* = 9.1, 3.0 Hz, 1 H), 4.19 (m, 1 H), 4.47 (m, 1 H), 4.64 (m, 1 H), 5.12 (s, 2 H), 7.17–7.36 (m, 10 H).

^{13}C NMR (62.9 MHz, $CDCl_3$): δ = 28.4, 36.4, 36.7, 37.3, 38.0, 55.9, 66.6, 67.1, 81.5, 127.6, 128.7, 129.0, 129.3, 129.8, 136.0, 136.1, 153.5, 170.7, 171.3, 174.4.

MS (CI, NH_3): *m*/*z* (%) = 178 (42), 195 (10), 266 (59), 334 (7), 426 (31), 443 (97), 482 (1) $[M + H]^+$, 499 (27) $[M + NH_4]^+$.

HRMS (ESI): *m*/*z* $[M + Na]^+$ calcd for $C_{27}H_{31}NO_7Na$: 504.1991; found: 504.1993.

tert-Butyl (3*S*)-4-[(4*R*)-4-Benzyl-2-oxo-1,3-oxazolidin-3-yl]-3-[(benzyloxy)methyl]-4-oxobutanoate (7)

NaHMDS (5.40 mL of a 1 M solution in THF, 5.40 mmol) was added dropwise to a solution of **4** (1.50 g, 4.50 mmol) in anhyd THF (25 mL) at –78 °C and the solution was stirred for 1 h. At the same time benzyl chloromethyl ether (0.77 mL, 0.85 g, 5.40 mmol) was added separately to a solution of anhyd NaI (0.81 g, 5.40 mmol) in anhyd THF (60 mL) and this mixture was stirred for 1 h at r.t. The resulting slurry was added dropwise within 30 min to the solution of Na enolate of **4** which had been pre-cooled to –95 °C. After stirring the mixture for 4 h at a temperature below –75 °C, the reaction was quenched by addition of sat. aq NH_4Cl (40 mL). THF was evaporated in vacuo, the aqueous residue was diluted with water (10 mL) and extracted with EtOAc (4 × 200 mL). The combined organic extracts were washed successively with 5% aq solutions of $KHSO_4$, $NaHCO_3$, Na_2SO_3 and with brine (50 mL of each), and finally dried over anhyd Na_2SO_4, filtered and evaporated. The crude product was chromatographed through a silica gel column (CH_2Cl_2–Et_2O, 40:1). An inseparable mixture of the diastereomers **7** and *epi*-**7** (4:1) (1.67 g, 82%) was obtained as a colorless oil and was used in the next step.

^1H NMR (250 MHz, $CDCl_3$): δ = 1.42 (s, 9 H), 2.51 (dd, *J* = 17.0, 4.3 Hz, 1 H), 2.67 (dd, *J* = 13.4, 9.3 Hz, 1 H), 2.93 (dd, *J* = 16.9, 10.4 Hz, 1 H), 3.20 (dd, *J* = 13.4, 3.3 Hz, 1 H), 3.58–3.66 (m, 2 H), 4.12 (dd, *J* = 9.1, 3.3 Hz, 1 H), 4.21 (m, 1 H), 4.48 (m, 1 H), 4.54 (s, 2 H), 4.72 (m, 1 H), 7.15–7.33 (m, 10 H).

^{13}C NMR (62.9 MHz, $CDCl_3$): δ = 28.0, 34.5, 37.9, 40.3, 55.1, 66.0, 70.2, 73.0, 80.7, 127.2, 127.6, 128.3, 128.8, 129.4, 135.2, 137.9, 153.1, 171.0, 173.3.

MS (CI, isobutane): *m*/*z* (%) = 91 (41), 178 (30), 290 (28), 380 (20), 398 (100), 454 (13) $[M + H]^+$, 488 (3) $[M + Na]^+$.

HRMS (ESI): *m*/*z* $[M + Na]^+$ calcd for $C_{26}H_{31}NO_6Na$: 476.2044; found: 476.2043.

Cleavage of *tert*-Butyl Ester; General Procedure 1 (GP1)

TFA (2.4 mL, 31.0 mmol) was added dropwise to a solution of *tert*-butyl ester **5**–**7** or **14** (3.1 mol) in anhyd CH_2Cl_2 (50 mL). The solution was stirred overnight at r.t., evaporated and subsequently co-evaporated with toluene.

(3*R*)-4-[(4*R*)-4-Benzyl-2-oxo-1,3-oxazolidin-3-yl]-3-methyl-4-oxobutanoic Acid (8)

Target compound **8** was obtained from a mixture of **5** and *epi*-**5** (85% de) (2.60 g, 7.48 mmol) following GP1. The crude product was purified by flash column chromatography (PE–EtOAc, 2:3 + 0.5% AcOH), simultaneously resolving the mixture of diastereomers: the minor diastereomer *epi*-**8** was eluted first, followed by **8** (1.91 g, 88%) which was obtained as a colorless foam after co-evaporation with toluene and drying under high vacuum for 4 h.

IR (film): 3030, 2978, 2932, 1781, 1699, 1390, 1351, 1255, 1204, 1110, 979, 761, 747, 704 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): δ = 1.27 (d, *J* = 6.9 Hz, 3 H), 2.47 (dd, *J* = 16.9, 4.4 Hz, 1 H), 2.79 (dd, *J* = 13.5, 9.1 Hz, 1 H), 2.97 (dd, *J* = 17.6, 10.7 Hz, 1 H), 3.22 (dd, *J* = 13.2, 3.1 Hz, 1 H), 4.02–4.12 (m, 1 H), 4.18 (dd, *J* = 9.1, 2.8 Hz, 1 H), 4.26 (dd, *J* = 8.5, 8.5 Hz, 1 H), 4.72 (m, 1 H), 7.18–7.36 (m, 5 H), 10.3 (br, 1 H).

^{13}C NMR (126 MHz, $CDCl_3$): δ = 17.4, 34.3, 37.0, 37.9, 55.1, 66.3, 127.4, 128.9, 129.5, 135.1, 153.1, 175.9, 178.0.

MS (ESI): *m*/*z* = 292.0 $[M + H]^+$, 313.9 $[M + Na]^+$.

MS (ESI, negative mode): *m*/*z* = 290.0 $[M – H]^–$, 325.9 $[M + Cl]^–$.

(3*S*)-3-{[(4*R*)-4-Benzyl-2-oxo-1,3-oxazolidin-3-yl]carbonyl}-5-(benzyloxy)-5-oxopentanoic Acid (9)

Compound **9** was obtained from **6** (2.00 g, 4.15 mol) following GP1. Purification by flash column chromatography (PE–EtOAc, 2:3 + 0.5% AcOH) followed by co-evaporation with toluene and drying under high vacuum afforded **9** (1.73 g, 98%) as a colorless solid; mp 69–72 °C; $[\alpha]_D^{22}$ –35.1 (*c* = 1.0, $CHCl_3$).

IR (KBr): 3064, 3031, 1781, 1734, 1700, 1605, 1498, 1456, 1391, 1352, 1212, 1004, 956, 751, 699 cm^{-1}.

^1H NMR (600 MHz, $CDCl_3$): δ = 2.57 (dd, *J* = 13.4, 9.8 Hz, 1 H), 2.61 (dd, *J* = 17.0, 5.6 Hz, 1 H), 2.68 (dd, *J* = 16.4, 6.2 Hz, 1 H), 2.88 (dd, *J* = 14.7, 7.2 Hz, 1 H), 2.89 (dd, *J* = 17.2, 8.9 Hz, 1 H), 3.22 (dd, *J* = 13.6, 3.4 Hz, 1 H), 4.11 (dd, *J* = 8.9, 2.8 Hz, 1 H), 4.18 (m, 1 H), 4.46 (m, 1 H), 4.65 (m, 1 H), 5.11 (s, 2 H), 7.18–7.34 (m, 10 H).

^{13}C NMR (62.9 MHz, $CDCl_3$): δ = 35.2, 35.9, 36.1, 37.6, 55.4, 66.4, 66.9, 127.3, 128.4, 128.6, 128.9, 129.4, 135.4, 135.5, 153.2, 170.8, 173.6, 176.5.

MS (CI, isobutane): *m*/*z* (%) = 91 (97), 178 (100), 249 (4), 426 (0.1) $[M + H]^+$.

HRMS (ESI, negative mode): *m*/*z* $[M+Cl]^–$ calcd for $C_{23}H_{23}NO_7Cl$: 460.1169; found: 460.1173.

(3*S*)-4-[(4*R*)-4-Benzyl-2-oxo-1,3-oxazolidin-3-yl]-3-[(benzyloxy)methyl]-4-oxobutanoic Acid (11)

Compound **11** was obtained from a mixture of **7** and *epi*-**7** (4:1) (1.40 g, 3.09 mmol) following GP1. The crude product was purified by flash column chromatography (CH_2Cl_2–AcOH, 50:1 → 25:1), simultaneously resolving the mixture of diastereomers: *epi*-**11** was eluted first (0.25 g, 20%), followed by **11** (0.99 g, 80%). Both substances were obtained as colorless oils after co-evaporation with toluene and drying under high vacuum.

Compound 11

$[\alpha]_D^{22}$ –32.6 (*c* = 1.0, $CHCl_3$).

IR (film): 3030, 2922, 2864, 1779, 1702, 1497, 1454, 1390, 1353, 1215, 1196, 1104, 743, 700 cm^{-1}.

^1H NMR (250 MHz, $CDCl_3$): δ = 2.64 (dd, *J* = 17.8, 4.3 Hz, 1 H), 2.67 (dd, *J* = 13.5, 9.2 Hz, 1 H), 3.07 (dd, *J* = 17.5, 10.3 Hz, 1 H), 3.18 (dd, *J* = 13.5, 3.4 Hz, 1 H), 3.70–3.72 (m, 2 H), 4.11 (m, 1 H), 4.21 (m, 1 H), 4.44 (m, 1 H), 4.54 (s, 2 H), 4.72 (m, 1 H), 7.13–7.32 (m, 10 H), 10.25 (br s, 1 H).

^{13}C NMR (62.9 MHz, $CDCl_3$): δ = 33.1, 37.9, 40.3, 55.1, 66.3, 69.9, 73.1, 127.3, 127.7, 128.4, 128.9, 129.4, 135.2, 137.8, 153.3, 172.8, 177.7.

MS (CI, NH_3): *m*/*z* (%) = 178 (37), 195 (100), 221 $[M + H – Aux]^+$, 238 (16) $[M + NH_4 – Aux]^+$.

HRMS (ESI): *m/z* [M + Na]$^+$ calcd for $C_{22}H_{23}NO_6Na$: 420.1418; found: 420.1420.

Compound *epi*-11

$[\alpha]_D^{22}$ –62.5 (*c* = 1.0, $CHCl_3$).

IR (film): 3030, 2924, 2866, 1779, 1705, 1497, 1454, 1390, 1351, 1213, 1195, 1104, 742, 700 cm^{-1}.

^{1}H NMR (250 MHz, $CDCl_3$): δ = 2.63 (dd, *J* = 17.6, 4.5 Hz, 1 H), 2.75 (dd, *J* = 13.6, 9.3 Hz, 1 H), 3.05 (dd, *J* = 17.5, 10.0 Hz, 1 H), 3.22 (dd, *J* = 13.5, 3.2 Hz, 1 H), 3.58–3.70 (m, 2 H), 4.00–4.12 (m, 2 H), 4.48 (s, 2 H), 4.50–4.60 (m, 2 H), 7.18–7.34 (m, 10 H), 9.20 (br s, 1 H).

^{13}C NMR (62.9 MHz, $CDCl_3$): δ = 31.4, 35.6, 38.3, 53.8, 64.3, 68.0, 71.2, 125.5, 125.8, 126.6, 127.1, 127.7, 133.6, 136.1, 151.4, 171.2, 175.8.

MS (CI, NH_3): *m/z* (%) = 108 (11), 178 (28), 195 (100), 221 (7) [M + H – Aux]$^+$, 238 (39) [M + NH_4 – Aux]$^+$.

(3*R*)-3-{[(4*R*)-4-Benzyl-2-oxo-1,3-oxazolidin-3-yl]carbonyl}-5-*tert*-butoxy-5-oxopentanoic Acid (10)

Catalyst Pd/C (10% Pd) (10 mg) was added to a solution of **6** (1.30 g, 2.70 mmol) in EtOAc (15 mL). The suspension was deoxygenated and stirred overnight at r.t. under H_2 atmosphere (1 atm). After the reaction, the residual H_2 was removed by bubbling of Ar through the suspension. The reaction mixture was filtered through a Celite® pad and evaporated. The yellow oily residue was purified by flash column chromatography (EtOAc–PE, 2:3 + 0.5% AcOH). The fractions were evaporated and co-evaporated with toluene. Drying under high vacuum gave **10** (1.05 g, 100%) as a colorless semi-solid; $[\alpha]_D^{22}$ –50.1 (*c* = 1.0, $CHCl_3$).

IR (film): 2979, 1781, 1708, 1392, 1368, 1351, 1208, 1154, 1006, 958, 912, 913, 762, 735, 704 cm^{-1}.

^{1}H NMR (250 MHz, $CDCl_3$): δ = 1.42 (s, 9 H), 2.50 (dd, *J* = 16.3, 5.8 Hz, 1 H), 2.62 (dd, *J* = 16.8, 6.3 Hz, 1 H), 2.73 (dd, *J* = 16.3, 8.2 Hz, 1 H), 2.75 (dd, *J* = 13.4, 9.6 Hz, 1 H), 2.88 (dd, *J* = 16.8, 7.8 Hz, 1 H), 3.28 (dd, *J* = 13.4, 3.3 Hz, 1 H), 4.17 (m, 1 H), 4.23 (m, 1 H), 4.41 (m, 1 H), 4.67 (m, 1 H), 7.19–7.36 (m, 5 H).

^{13}C NMR (62.9 MHz, $CDCl_3$): δ = 28.1, 35.4, 36.2, 36.8, 37.6, 55.5, 66.3, 81.3, 127.3, 128.9, 129.5, 135.4, 153.2, 170.4, 177.2, 177.5.

MS (CI, NH_3): *m/z* (%) = 178 (28), 195 (100), 232 (30), 409 (0.2) [M + NH_4]$^+$.

HRMS (ESI): *m/z* [M + Na]$^+$ calcd for $C_{20}H_{25}NO_7Na$: 414.1523; found: 414.1523.

Curtius Rearrangement; General Procedure 2 (GP2)

A solution of the carboxylic acid **8**–**10** or **11** (3.29 mmol) in anhyd THF (50 mL) was cooled to –15 °C and treated with Et_3N (0.55 mL, 0.40 g, 3.95 mmol, 1.20 equiv). Ethyl chloroformate (0.34 mL, 0.39 g, 3.57 mmol, 1.09 equiv) was added dropwise and the mixture was stirred for 15 min at –15 °C, then allowed to warm to r.t. and stirred for an additional 15 min. The reaction mixture was then cooled to 0 °C, a solution of NaN_3 (0.43 g, 6.61 mmol, 2.00 equiv) in water (8 mL) was added and the mixture was stirred at this temperature for 1 h. THF was evaporated without heating and the aq solution was extracted with Et_2O (4 ×). The combined organic extracts were dried over anhyd $MgSO_4$. Evaporation to dryness (the bath below r.t.) yielded a residue, which was dissolved in anhyd toluene (100 mL). After heating to reflux, several mL of the solvent were distilled off to remove traces of water, followed by addition of 120 equiv of *t*-BuOH or 20 equiv of benzyl alcohol. The reaction mixture was refluxed overnight. After cooling to r.t. the solvent was removed (benzyl alcohol under high vacuum) and the residue was dissolved in CH_2Cl_2 (30 mL). The solution was washed successively with 5% aq $KHSO_4$, 5% aq $NaHCO_3$ and brine, dried over anhyd Na_2SO_4 and evaporated. Purification by flash column chromatography afforded the corresponding urethane-protected amines **12**–**15**.

***tert*-Butyl (2*R*)-3-[(4*R*)-4-Benzyl-2-oxo-1,3-oxazolidin-3-yl]-2-methyl-3-oxopropylcarbamate (12)**

Compound **12** was obtained from **8** (1.91 g, 6.56 mmol) following GP2, using *t*-BuOH. Flash chromatography (EtOAc–PE, 1:2) and crystallization (Et_2O–PE) afforded **12** (1.40 g, 59%) as a colorless solid; mp 87–88.5 °C; $[\alpha]_D^{25}$ –85.0 (*c* = 1.07, $CHCl_3$).

IR (film): 3398, 2983, 2966, 2920, 1786, 1765, 1720, 1689, 1516, 1457, 1389, 1358, 1242, 1215, 1169, 1066, 1032, 972, 760, 746, 729, 717 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.24 (d, *J* = 6.9 Hz, 3 H), 1.43 (s, 9 H), 2.78 (dd, *J* = 13.2, 9.4 Hz, 1 H), 3.25 (dd, *J* = 13.2, 2.5 Hz, 1 H), 3.31 (m, 1 H), 3.46 (m, 1 H), 3.85 (m, 1 H), 4.18 (dd, *J* = 9.4, 2.5 Hz, 1 H), 4.25 (dd, *J* = 8.5, 8.5 Hz, 1 H), 4.67 (m, 1 H), 4.92 (br m, 1 H), 7.16–7.38 (m, 5 H).

^{13}C NMR (62.9 MHz, $CDCl_3$): δ = 14.9, 28.4, 37.9, 39.1, 42.7, 55.3, 66.3, 79.3, 127.4, 128.9, 129.3, 129.4, 135.2, 153.1, 155.9, 175.6.

HRMS (ESI): *m/z* [M + Na]$^+$ calcd for $C_{19}H_{26}N_2O_5Na$: 385.1734; found: 385.1735.

Benzyl (3*R*)-4-[(4*R*)-4-Benzyl-2-oxo-1,3-oxazolidin-3-yl]-3-{[(*tert*-butoxycarbonyl)amino]methyl}-4-oxobutanoate (13)

Target compound **13** was obtained from **9** (1.40 g, 3.29 mmol) following GP2, using *t*-BuOH. Flash column chromatography (EtOAc–PE, 3:2) afforded **13** (0.91 g, 56%) as a yellowish oil; $[\alpha]_D^{22}$ –34.7 (*c* = 1.0, $CHCl_3$).

IR (film): 3389, 2978, 1780, 1733, 1701, 1515, 1455, 1390, 1366, 1351, 1248, 1170, 1107, 753, 700 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.41 (s, 9 H), 2.56 (dd, *J* = 13.2, 10.1 Hz, 1 H), 2.61 (dd, *J* = 17.0, 4.4 Hz, 1 H), 3.04 (dd, *J* = 16.4, 10.1 Hz, 1 H), 3.21 (dd, *J* = 13.2, 3.1 Hz, 1 H), 3.30 (m, 1 H), 3.58 (m, 1 H), 4.10 (dd, *J* = 8.8, 2.5 Hz, 1 H), 4.20 (m, 1 H), 4.34 (m, 1 H), 4.59 (br m, 1 H), 4.92 (br m, 1 H), 5.11 (s, 2 H), 7.19–7.36 (m, 10 H).

^{13}C NMR (125.8 MHz, $CDCl_3$): δ = 28.3, 34.0, 37.5, 40.6, 41.5, 55.7, 66.3, 66.7, 79.5, 127.2, 128.3, 128.6, 128.9, 129.4, 135.6, 135.58, 153.63, 156.0, 171.5, 173.2.

MS (CI, isobutane): *m/z* (%) = 91 (53), 178 (22), 289 (100), 333 (17), 379 (10), 397 (37), 441 (26), 497 (5) [M + H]$^+$.

HRMS (ESI): *m/z* [M + Na]$^+$ calcd for $C_{27}H_{32}N_2O_7Na$: 519.2102; found: 519.2110.

***tert*-Butyl (3*S*)-4-[(4*R*)-4-Benzyl-2-oxo-1,3-oxazolidin-3-yl]-3-({[(benzyloxy)carbonyl]amino}methyl)-4-oxobutanoate (14)**

Compound **14** was obtained from **10** (0.98 g, 2.50 mmol) following GP2, using benzyl alcohol. Flash column chromatography (EtOAc–PE, 2:3) afforded **14** (0.82 g, 66%) as a yellowish gum; $[\alpha]_D^{22}$ –31.2 (*c* = 1.1, $CHCl_3$).

IR (film): 3371, 2979, 1781, 1718, 1524, 1455, 1392, 1352, 1248, 1155, 1107, 1053, 1018, 912, 845, 735, 700 cm^{-1}.

^{1}H NMR (250 MHz, $CDCl_3$): δ = 1.41 (s, 9 H), 2.45 (dd, *J* = 16.8, 4.5 Hz, 1 H), 2.67 (dd, *J* = 13.4, 9.7 Hz, 1 H), 2.86 (dd, *J* = 16.9, 10.0 Hz, 1 H), 3.23 (dd, *J* = 13.4, 3.3 Hz, 1 H), 3.41–3.60 (m, 2 H), 4.13 (dd, *J* = 9.1, 3.0 Hz, 1 H), 4.17–4.27 (m, 2 H), 4.66 (m, 1 H), 5.08 (s, 2 H), 5.17 (m, 1 H), 7.15–7.35 (m, 10 H).

^{13}C NMR (62.9 MHz, $CDCl_3$): δ = 26.2, 33.4, 36.2, 38.4, 40.5, 53.7, 64.7, 65.0, 79.3, 125.5, 126.3, 126.7, 127.1, 127.6, 133.6, 134.7, 151.7, 154.6, 169.0, 171.6.

MS (CI, isobutane): *m/z* (%) = 91 (79), 178 (10), 289 (13), 333 (60), 397 (25), 441 (79), 497 (11) [M + H]$^+$.

HRMS (ESI): *m/z* [M + Na]$^+$ calcd for $C_{27}H_{32}N_2O_7Na$: 519.2102; found: 519.2104.

***tert*-Butyl (2*S*)-3-[(4*R*)-4-Benzyl-2-oxo-1,3-oxazolidin-3-yl]-2-[(benzyloxy)methyl]-3-oxopropylcarbamate (15)**

Target compound **15** was obtained from **11** (0.89 g, 2.24 mmol) following GP2 using *t*-BuOH. Flash chromatography (EtOAc–PE, 3:2) afforded **15** (0.62 g, 59%) as an off-white solid; mp 79–81 °C; $[\alpha]_D^{22}$ –54.4 (*c* = 1.0, $CHCl_3$).

IR (film): 3385, 2976, 2928, 1779, 1702, 1508, 1454, 1390, 1365, 1249, 1212, 1171, 1106, 741, 700 cm^{-1}.

^{1}H NMR (250 MHz, $CDCl_3$): δ = 1.41 (s, 9 H), 2.70 (dd, *J* = 13.5, 9.4 Hz, 1 H), 3.21 (dd, *J* = 13.7, 3.3 Hz, 1 H), 3.42–3.65 (m, 2 H), 3.77–3.79 (m, 2 H), 4.12 (dd, *J* = 8.9, 3.2 Hz, 1 H), 4.16–4.26 (m, 2 H), 4.54 (s, 2 H), 4.67 (br m, 1 H), 4.87 (br m, 1 H), 7.15–7.33 (m, 10 H).

^{13}C NMR (62.9 MHz, $CDCl_3$): δ = 28.4, 37.9, 39.5, 44.9, 55.3, 66.2, 68.6, 73.3, 79.3, 127.3, 127.7, 128.4, 128.9, 129.4, 135.3, 137.9, 153.4, 156.0, 172.7.

MS (CI, NH_3): *m/z* (%) = 91 (12), 108 (15), 178 (28), 195 (94), 261 (18), 351 (12), 369 (62), 395 (100), 412 (30), 430 (29), 469 (11) [M + H]$^+$.

HRMS (ESI): *m/z* [M + Na]$^+$ calcd for $C_{26}H_{32}N_2O_6Na$: 491.2153; found: 491.2153.

(3*R*)-4-[(4*R*)-4-Benzyl-2-oxo-1,3-oxazolidin-3-yl]-3-{[(*tert*-butoxycarbonyl)amino]methyl}-4-oxobutanoic Acid (16)

An oily yellow residue was obtained from **13** (0.88 g, 1.77 mmol) following the procedure described for **10**. This was purified by flash column chromatography (EtOAc–PE, 3:2). After evaporation of the fractions and drying under high vacuum, **16** (0.70 g, 97%) was obtained as a solid foam; $[\alpha]_D^{22}$ –66.4 (*c* = 1.0, $CHCl_3$).

IR (KBr): 3378, 2979, 2932, 1778, 1703, 1520, 1392, 1367, 1250, 1170, 1108, 1053, 1011, 968, 856, 760, 704 cm^{-1}.

^{1}H NMR (250 MHz, $CDCl_3$): δ = 1.40 (s, 9 H), 2.57 (dd, *J* = 17.2, 4.9 Hz, 1 H), 2.76 (dd, *J* = 13.5, 9.4 Hz, 1 H), 2.98 (dd, *J* = 16.8, 9.3 Hz, 1 H), 3.21–3.34 (m, 2 H), 3.57 (m, 1 H), 4.14 (dd, *J* = 8.9, 2.9 Hz, 1 H), 4.19–4.33 (m, 2 H), 4.63 (br m, 1 H), 4.96 (br m, 1 H), 7.19–7.35 (m, 5 H), 9.20 (br s, 1 H).

^{13}C NMR (62.9 MHz, $CDCl_3$): δ = 28.3, 33.7, 37.5, 40.5, 41.4, 55.6, 66.3, 79.8, 127.2, 128.9, 129.5, 135.5, 153.5, 156.2, 173.2, 176.6.

MS (CI, isobutane): *m/z* (%) = 178 (100), 289 (7), 351 (2), 407 (0.3) [M + H]$^+$.

HRMS (ESI, negative mode): *m/z* [M + Cl]$^-$ calcd for $C_{20}H_{26}N_2O_7Cl$: 441.1434; found: 441.1439.

(3*S*)-4-[(4*R*)-4-Benzyl-2-oxo-1,3-oxazolidin-3-yl]-3-({[(benzyloxy)carbonyl]amino}methyl)-4-oxobutanoic Acid (17)

Compound **17** was obtained from **14** (0.46 g, 0.93 mol) following GP1. The crude product was purified by flash column chromatography (EtOAc–PE, 3:2 + 0.5% AcOH). Successive co-evaporation with toluene, MeOH and MeCN followed by evacuation at the pump afforded **17** (0.39 g, 96%) as a colorless solid; mp 78–83 °C; $[\alpha]_D^{22}$ –35.4 (*c* = 1.0, $CHCl_3$).

IR (KBr): 3361, 3031, 1780, 1700, 1531, 1455, 1392, 1352, 1248, 1108, 1053, 1014, 739, 699 cm^{-1}.

^{1}H NMR (250 MHz, $CDCl_3$): δ = 2.54 (dd, *J* = 17.4, 4.1 Hz, 1 H), 2.65 (dd, *J* = 13.3, 10.1 Hz, 1 H), 2.95 (dd, *J* = 17.2, 10.0 Hz, 1 H), 3.20 (br d, *J* = 13.1 Hz, 1 H), 3.40–3.65 (m, 2 H), 4.08 (dd, *J* = 9.0, 2.6 Hz, 1 H), 4.13–4.24 (m, 2 H), 4.64 (m, 1 H), 5.06 (s, 2 H), 5.31 (br m, 1 H), 7.12–7.35 (m, 10 H), 9.62 (br s, 1 H).

^{13}C NMR (62.9 MHz, $CDCl_3$): δ = 33.5, 37.9, 40.2, 42.2, 55.4, 66.7, 66.9, 127.3, 128.0, 128.5, 128.9, 129.4, 135.4, 136.4, 153.6, 156.6, 173.1, 176.3.

MS (CI, isobutane): *m/z* (%) = 91 (51), 178 (100), 192 (6), 264 (10), 441 (0.1) [M + H]$^+$.

HRMS (ESI): *m/z* [M + Na]$^+$ calcd for $C_{23}H_{24}N_2O_7Na$: 463.1476; found: 463.1482.

***tert*-Butyl (3*R*)-3-{[(4*R*)-4-Benzyl-2-oxo-1,3-oxazolidin-3-yl]carbonyl}-1-pyrrolidinecarboxylate (18)**

BH_3·Me_2S (2.00 mL 2 M solution in THF, 4.00 mmol, 5.42 equiv) was added to a solution of **16** (300 mg, 738 μmol) in anhyd THF (7 mL) and the mixture was stirred for 3 h at r.t. The reaction was quenched by addition of MeOH (3 mL). After stirring for 20 min the solvents were evaporated and the residue was purified by flash column chromatography (Et_2O–PE, 3:1) to give **18** (208 mg, 75%) as a colorless oil; $[\alpha]_D^{23}$ –64.1 (*c* = 1.0, $CHCl_3$).

IR (film): 2977, 2886, 1781, 1695, 1604, 1389, 1247, 1213, 1167, 1115, 881, 761, 703 cm^{-1}.

^{1}H NMR (500 MHz, CD_2Cl_2): δ = 1.45 (s, 9 H), 2.09–2.26 (m, 2 H), 2.86 (dd, *J* = 13.8, 9.4 Hz, 1 H), 3.21 (dd, *J* = 13.2, 3.1 Hz, 1 H), 3.37–3.46 (m, 2 H), 3.54–3.58 (m, 2 H), 4.11 (m, 1 H), 4.19 (m, 1 H), 4.25 (m, 1 H), 4.69 (m, 1 H), 7.20–7.35 (m, 5 H).

^{13}C NMR [125.8 MHz, CD_2Cl_2, (*cis*/*trans*)]: δ = 28.5, 28.7/29.2, 28.8, 38.0, 42.3/43.2, 45.5/45.8, 48.2, 55.5, 66.8, 79.3, 127.6, 129.2, 129.8, 135.7, 153.5, 154.4, 173.3.

MS (CI, NH_3): *m/z* (%) = 178 (5), 275 (100), 336 (43), 375 (4) [M + H]$^+$, 392 (1) [M + NH_4]$^+$.

HRMS (ESI): *m/z* [M + Na]$^+$ calcd for $C_{20}H_{26}N_2O_5Na$: 397.1734; found: 397.1734.

Benzyl (3*S*)-3-{[(4*R*)-4-Benzyl-2-oxo-1,3-oxazolidin-3-yl]carbonyl}-1-pyrrolidinecarboxylate (19)

Compound **19** was obtained from **17** (300 mg, 681 μmol) following a procedure similar to the synthesis of **18**. The raw product was purified by flash column chromatography (EtOAc–PE, 3:2) to give **19** (189 mg, 68%) as a colorless oil; $[\alpha]_D^{22}$ –13.7 (*c* = 1.0, $CHCl_3$).

IR (film): 2954, 2886, 1778, 1699, 1420, 1389, 1450, 1247, 1212, 1112, 764, 700 cm^{-1}.

^{1}H NMR (250 MHz, $CDCl_3$): δ = 2.09–2.26 (m, 2 H), 2.79 (dd, *J* = 13.3, 9.2 Hz, 1 H), 3.22 (br d, *J* = 13.4 Hz, 1 H), 3.46–3.83 (m, 4 H), 4.11 (dd, *J* = 14.1, 7.1 Hz, 1 H), 4.17–4.27 (m, 2 H), 4.68 (m, 1 H), 5.15 (s, 2 H), 7.15–7.39 (m, 10 H).

^{13}C NMR [62.9 MHz, $CDCl_3$, (*cis*/*trans*)]: δ = 27.8/28.4, 37.9, 42.0/42.9, 45.4/45.9, 48.3/49.0, 55.2, 66.5/66.9, 127.5, 128.0, 128.5, 129.0, 129.4, 135.0, 136.9, 153.2, 154.6, 172.8.

MS (CI, isobutane): *m/z* (%) = 91 (45), 178 (13), 273 (29) [M + H – Cbz]$^+$, 317 (38), 365 (100), 409 (46) [M + H]$^+$.

HRMS (ESI): *m/z* [M + Na]$^+$ calcd for $C_{23}H_{24}N_2O_5Na$: 431.1577; found: 431.1578.

Cleavage of the Chiral Auxiliary; General Procedure 3 (GP3)

H_2O_2 (0.26 mL of 30% aq solution, 2.30 mmol, 4.30 equiv) was added dropwise at 0 °C to a solution of the *N*-acylated oxazolidinone **12**, **14**, **15**, **18** or **19** (0.53 mmol) in THF (10 mL), followed by dropwise addition of aq LiOH·H_2O (49 mg, 1.17 mmol, 2.20 equiv in 3 mL of water). The reaction mixture was stirred at 0 °C for 2.5 h. After addition of sat. aq Na_2SO_3 and sat. aq $NaHCO_3$ (2.5 mL of each), the mixture was stirred for an additional 20 min at r.t. THF was evaporated, the aqueous residue was diluted with water (10 mL) and the basic solution (pH 10) was extracted with CH_2Cl_2 (4 ×). This CH_2Cl_2 extract contained the cleaved chiral auxiliary. The remaining aqueous phase was acidified by addition of 5% aq $KHSO_4$

solution (ca. pH 2) and extracted with EtOAc (4 ×). The combined EtOAc extracts were dried over anhyd Na_2SO_4, evaporated to dryness and purified by flash column chromatography (short column, EtOAc–PE, 3:2 + 0.5% AcOH). Co-evaporation with toluene, MeOH and MeCN and drying under high vacuum afforded the protected β^2-amino acid **20**, **21**, **22**, **23** or **24**, respectively.

(2*R*)-3-[(*tert*-Butoxycarbonyl)amino]-2-methylpropanoic Acid (20)

Compound **20** (0.47 g, 79%) was obtained as a colorless solid from **12** (1.07 g, 2.95 mmol) following GP3 after crystallization from Et_2O; mp 71–73 °C, (ref.[5] mp 79–80 °C; ref.[15] mp 72–73 °C); $[\alpha]_D^{20}$ –19.6 (*c* = 2.09, MeOH), {ref.[5] [α] = –20 (*c* = 2, MeOH), ref.[15] $[\alpha]_D^{26}$ –18.0 (*c* = 1.9, MeOH)}.

HRMS (ESI): *m*/*z* $[M + H]^+$ calcd for $C_9H_{18}NO_4$: 204.1230; found: 204.1234.

(3*R*)-1-(*tert*-Butoxycarbonyl)-3-pyrrolidinecarboxylic Acid (21)

Compound **21** (106 mg, 89%) was obtained as a colorless crystalline solid from **18** (208 mg, 556 μmol) following GP3; mp 139–141 °C; $[\alpha]_D^{22}$ –14.6 (*c* = 1.0, $CHCl_3$), {ref.[27] $[\alpha]_D^{25}$ –8.0 (*c* = 0.5, $CHCl_3$)}.

HRMS (ESI, negative mode): *m*/*z* $[M + Cl]^-$ calcd for $C_{10}H_{17}NO_4Cl$: 250.0852; found: 250.0851.

(3*S*)-1-(Benzyloxycarbonyl)-3-pyrrolidinecarboxylic Acid (22)

Compound **22** (95 mg, 82%) was obtained as a colorless crystalline solid from **19** (189 mg, 463 μmol) following GP3; mp 96–98 °C; $[\alpha]_D^{24}$ +16.5 (*c* = 0.9, $CHCl_3$), {ref.[28] $[\alpha]_D^{25}$ +16.0 (*c* = 9.0, $CHCl_3$)}.

HRMS (ESI, negative mode): *m*/*z* $[M + Cl]^-$ calcd for $C_{13}H_{15}NO_4Cl$: 284.0695; found: 284.0694.

(2*S*)-2-{[(Benzyloxycarbonyl)amino]methyl}-4-*tert*-butoxy-4-oxobutanoic Acid (23)

Compound **23** (178 mg, 94%) was synthesized as a colorless oil from **14** (280 mg, 564 μmol) following GP3; $[\alpha]_D^{22}$ –2.2 (*c* = 1.0, $CHCl_3$).

IR (film): 3341, 2978, 1732, 1538, 1456, 1368, 1259, 1152, 1020, 848, 738, 697 cm^{-1}.

^1H NMR (250 MHz, $CDCl_3$): δ = 1.43 (s, 9 H), 2.51 (dd, *J* = 16.9, 5.7 Hz, 1 H), 2.63 (dd, *J* = 16.7, 7.5 Hz, 1 H), 3.00 (m, 1 H), 3.44–3.49 (m, 2 H), 5.09 (s, 2 H), 5.34 (br m, 1 H), 7.28–7.38 (m, 5 H), 8.67 (br s, 1 H).

^{13}C NMR (62.9 MHz, $CDCl_3$): δ = 27.0, 33.9, 40.6, 40.7, 66.0, 80.6, 127.1, 127.5, 135.3, 155.6, 169.8, 177.0.

MS (CI, isobutane): *m*/*z* (%) = 91 (65), 108 (126), 174 (39), 190 (5), 238 (35), 282 (100), 338 (6) $[M + H]^+$.

HRMS (ESI): *m*/*z* $[M + Na]^+$ calcd for $C_{17}H_{23}NO_6Na$: 360.1418; found: 360.1417.

(2*S*)-3-(Benzyloxy)-2-{[(*tert*-butoxycarbonyl)amino]methyl}propanoic Acid (24)

Compound **24** (111 mg, 84%) was synthesized as a colorless oil from **15** (200 mg, 427 μmol) following GP3; $[\alpha]_D^{22}$ +8.4 (*c* = 1.0, $CHCl_3$).

IR (film): 3333, 2978, 2932, 2871, 1713, 1516, 1454, 1393, 1367, 1253, 1169, 1101, 739, 698 cm^{-1}.

^1H NMR (250 MHz, $CDCl_3$): δ = 1.43 (s, 9 H), 2.88 (m, 1 H), 3.43–3.47 (m, 2 H), 3.69–3.71 (m, 2 H), 4.51 (s, 2 H), 5.08 (br s, 1 H), 7.22–7.36 (m, 5 H), 10.30 (br s, 1 H).

^{13}C NMR [62.9 MHz, $CDCl_3$, (*cis*/*trans*)]: δ = 28.4, 39.4/40.4, 46.0/46.4, 68.6, 73.3, 79.6/81.2, 127.7, 128.4, 137.7, 156.1/157.7, 176.5/177.3.

MS (CI, NH_3): *m*/*z* (%) = 91 (4), 106 (7), 210 (33), 254 (28), 271 (100), 310 (14) $[M + H]^+$, 327 (6) $[M + NH_4]^+$.

HRMS (ESI, negative mode): *m*/*z* $[M + Cl]^-$ calcd for $C_{16}H_{23}NO_5Cl$: 344.1270; found: 344.1268.

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