Asymmetric Synthesis of β^2-homo-*tert*-Leucine *via* Radical Addition to Enantiopure *N*-Fumaroylhexahydrobenzooxazolidin-2-one

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Dedicated to Professor *Dieter Seebach*, on the joyful occasion of his 75th birthday – an opportunity to celebrate half a century of his relevant contributions to organic chemistry

β-Amino acids are key structural elements in unnatural peptides, peptidomimetics, and many other physiologically active compounds. In view of their importance, we have developed an efficient synthetic route that provides highly enantiomerically enriched (*R*)- and (*S*)-H-β^2-h^{t}Leu-OH *via* highly diastereo- and regioselective addition of *tert*-butyl radical to enantiomerically pure *N*-fumaroyloxazolidinones, followed by removal of the chiral auxiliary, *Curtius* rearrangement, ester hydrolysis, and catalytic hydrogenolysis.

Introduction. – β-Amino acids might be regarded as the building blocks that Nature 'overlooked', since essentially all biomolecules present in living organisms are made up of α-amino acids. Nevertheless, chemists have recently recognized the importance of β-amino acids in the design of many molecules of interest. Indeed, it has been realized that β-Amino acids are key structural elements of unnatural peptides, peptidomimetics, and many other physiologically active compounds. In particular, during the last decade, β-peptides have received much attention in several scientific areas owing to their ability to form various and interesting secondary structures, and also due to their physiological activity that renders them as promising peptidomimetics [1]. All these relevant applications are, of course, dictated by the structural properties of the β-amino acid components and their corresponding sequence in the unnatural peptide.

β^2-Amino acids, like their counterparts, β^3-amino acids, are of immense chemical and biological interest. Their highly potent biological effects are observed in both naturally occurring and synthetic derivatives [2]. As a consequence, the synthesis of rare and unnatural amino acids in their stereochemically pure form has been the subject of intense research in the last two decades.

tert-Leucine is a chiral non-proteinogenic α-amino acid. As a result of its bulky and hydrophobic *tert*-butyl side chain, *tert*-leucine finds increasing use as a building block for the synthesis of chiral auxiliaries, as ligands in asymmetric catalysts, as an effective chiral organocatalyst, and as building block for the synthesis of chiral drugs [3]; for example, acting as protease inhibitors in various medical protocols. Therefore, a significant number of synthetic approaches to *tert*-leucine have been reported [4–6].

In view of the interesting biological role played by *tert*-leucine, we deemed it necessary to have access to both enantiomers of the β-homolog, 2-(aminomethyl)-3,3-dimethylbutanoic acid (H-β^2-h^{t}Leu; *Fig. 1*). The synthesis of these β^2-analogs has not been previously described, probably as a consequence of the significant synthetic challenge due to the presence of the sterically demanding ^{t}Bu group. By contrast, enantiomerically pure H-β^3-h^{t}Leu-OH is readily available by resolution of the racemic β-amino acid with L-norephedrine [7].

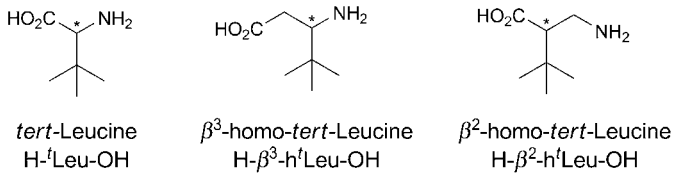
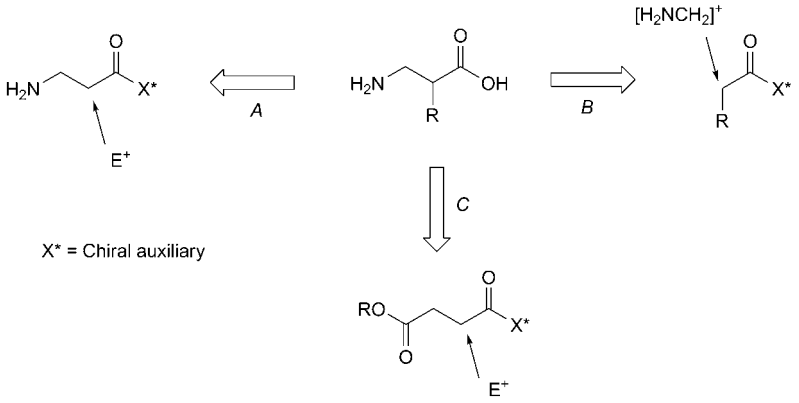


Fig. 1. tert-*Leucine and its β-homo amino acid analogs*

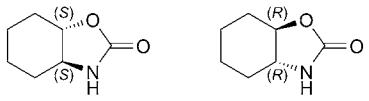
On the other hand, β^2-, in contrast to β^3-amino acids, cannot be prepared stereoselectively by a general synthetic methodology from the corresponding, readily available α-amino acids. β^2-Amino acids have frequently been prepared *via* reaction of an appropriate electrophile with cyclic or acyclic enolates derived from 3-amino-propanoic acid (*cf. Path A* in *Scheme 1*) [8–16]. Thus, most methods are applicable only to the preparation of β^2-amino acids with alkyl or benzyl (Bn) side chains. In another approach, the amino acid side chain is first attached to an auxiliary as part of an acyl group, followed by aminomethylation with a synthetic equivalent of $[H_2NCH_2]^+$ cation (*Mannich* reaction; *cf. Path B* in *Scheme 1*) [17]. Also, alkylation of an enolate with the appropriate side chain of a haloacetate electrophile, followed by *Curtius* degradation, leads to the net attachment of an aminomethyl group [18][19]. Another synthetic approach towards the β^2-amino acids involves the regioselective coupling of an electrophile containing the amino acid side chain with a dissymmetric succinic acid derivative, which is then subjected to a regioselective *Curtius* rearrangement (*cf. Path C* in *Scheme 1*) [20].

Scheme 1. *Synthetic Approaches towards the Preparation of β²-Amino Acids*



Previous investigations have shown the effectiveness of various methods for the intermolecular addition of alkyl radicals to enoyl oxazolidinones [21]. Additionally, convenient methods based on the employment of chiral auxiliaries are at hand for the control of the absolute configuration at the stereogenic β-center that is created [22–25]. With these precedents, we anticipated that diastereoselective radical addition to enoyl derivatives of chiral oxazolidinones (*S*,*S*)-**1** and (*R*,*R*)-**1** could afford an efficient entry to enantiomerically pure β^2-amino acids incorporating bulky and hydrophobic side chains that are not accessible by other methods.

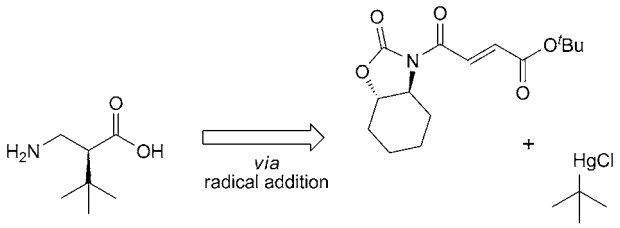
The use of *trans*-hexahydrobenzoxazolidin-2-ones (*R*,*R*)-**1** and (*S*,*S*)-**1** as chiral auxiliaries (*Fig. 2*) has been shown to be an efficient methodology in the asymmetric synthesis of β-amino acids, *e.g.*, H-β^2-hVal-OH, H-β^2-hLeu-OH, and H-β^2-hTrp-OH [26][27]. Furthermore, *trans*-hexahydrobenzoxazolidin-2-ones (*R,R*)-**1** and (*S,S*)-**1** have also been shown to induce high stereoselectivity in alkylation, acylation, and aldol condensation reactions [28]. We now describe asymmetric radical addition reactions promoted by this auxiliary (*Scheme 2*). In particular, when attached to an electrophilic fumarimide, (*R*,*R*)-**1** and (*S*,*S*)-**1** provided high regio- and stereocontrol in radical additions. This strategy was employed for the preparation of H-β^2-h^{t}Leu-OH in both enantiomeric forms, as reported herein.



(*S,S*)-**1** (*R,R*)-**1**

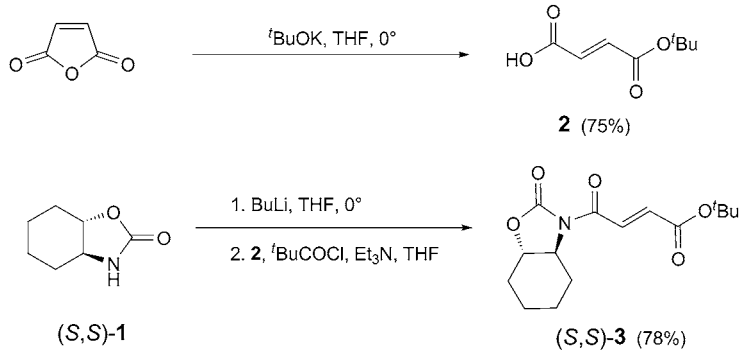
Fig. 2. trans-*Hexahydrobenzoxazolidin-2-ones*

Scheme 2. *Retrosynthetic Analysis for the Preparation of H-β^2-h^{t}Leu-OH* via *Radical Addition to Chiral Acyl-oxazolidinones*



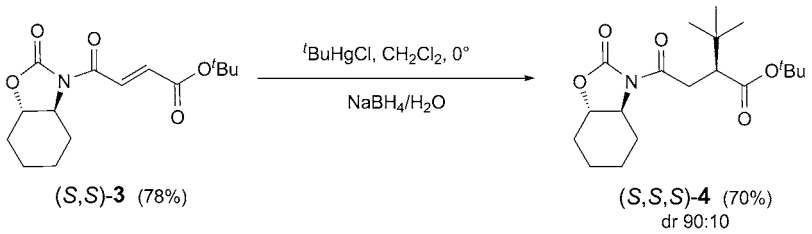
Results and Discussion. – *N*-Fumaroylhexahydrobenzo-2-oxazolidinone (*S*,*S*)-**3** was initially prepared through the coupling of (*S*,*S*)-**1** with maleic anhydride in a one-pot procedure, as described by *Knol* and *Feringa* [29]. Under these conditions, the yield of the desired product was only 23%. In contrast, when mono-*tert*-butyl fumarate **2**, prepared by isomerization of maleic anhydride with ^{t}BuOK according to procedure of *Clarke et al.* [30] was activated *via* the pivaloyl mixed anhydride method, followed by attachment to the lithiated auxiliary (using BuLi at $-30°$), *N*-fumaroylhexahydrobenzo-2-oxazolidinone (*S*,*S*)-**3** was obtained in 78% yield (*Scheme 3*). The same procedure was followed for the preparation of (*R*,*R*)-**3** in 80% yield.

Scheme 3. *Preparation of the* N-*Fumaroylhexahydrobenzooxazolidin-2-one (*S,S*)-***3***



Radical addition of ^{t}BuHgCl [31] to *N*-fumaroylhexahydrobenzo-2-oxazolidinone (*S*,*S*)-**3** (in CH_2Cl_2 at 0° with an excess of solid $NaBH_4$ and H_2O) afforded the expected addition product (*S*,*S*,*S*)-**4** in 70% yield (*Scheme 4)*. The reaction proceeded with complete regioselectivity to give exclusively addition at the *β*-center. Furthermore, the radical addition reaction was also highly diastereoselective, dr 9:1, in favor of diastereoisomer (*S*,*S*,*S*)-**4** as deduced from the ^{1}H-NMR spectrum of the crude product and confirmed by single-crystal X-ray diffraction analysis (*Fig. 3*)[1]).

Scheme 4. *Diastereoselective Radical Addition of* ^{t}*BuHgCl to (*S,S*)-***3***



Removal of the chiral auxiliary from (*S*,*S*,*S*)-**4** and (*R*,*R*,*R*)-**4** was achieved by hydrolytic cleavage with $LiOH \cdot H_2O_2$, as suggested by *Evans et al.* [32]. These reactions proceed in 95% yield for both diastereomers. From the resulting acids (*S*)-**5** and (*R*)-**5**, an azide derivative was generated with $(PhO)_2P(O)N_3$ which decomposed *in situ* to give rise to a *Curtius* rearrangement in the presence of BnOH, to afford the *N*-(benzyloxycarbonyl)(Z)-protected amino acid derivatives (*R*)-**6** and (*S*)-**6**, in good yields (*Scheme 5*).

The resulting products (*R*)-**6** and (*S*)-**6** were deprotected with CF_3COOH (TFA) and hydrogenolyzed (H_2, Pd/C) to give H-β^2-homo-*tert*-leucine (*R*)-**7** and (*S*)-**7**.

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[1]) CCDC-895646 contains the supplementary crystallographic data for this work. These data can be obtained free of charge *via* http://www.ccdc.cam.ac.uk/data_request/cif.

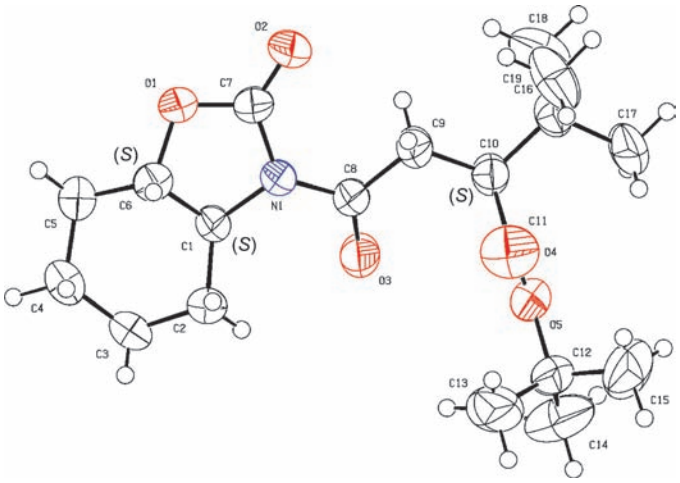
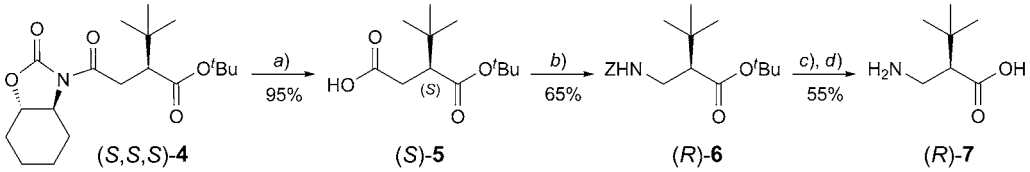


Fig. 3. *X-Ray crystal structure of the major diastereoisomer* (S,S,S)-**4** *permitting configurational assignment*

Scheme 5. *Preparation of* (R)-β^2-h^t*Leu-OH* ((*R*)-**7**)



a) $LiOH \cdot H_2O$, THF/H_2O 1:1, H_2O_2, 0°. *b*) Et_3N, $(PhO)_2P(O)N_3$, BnOH, Toluene, 100°. *c*) TFA/CH_2Cl_2 1:1, 0 → r.t. *d*) Pd/C, H_2, MeOH, r.t.

HPLC Analysis of (*R*)-**6** and (*S*)-**6** on a *Chiracel OD-H* column confirmed the efficiency of the present strategy for the preparation of enantiomerically enriched (*R*)-**7** and (*S*)-**7**, which were obtained in 80 and 98% ee, respectively (*Fig. 4*).

Conclusions. – In this work, we have developed an efficient synthetic route to both enantiomers of H-β^2-h^{t}Leu-OH *via* highly diastereo- and regioselective radical addition of *tert*-butyl radical to enantiomerically pure *N*-fumaroyl-oxazolidinones.

Experimental Part

General. Flasks, stirring bars, and hypodermic needles used for the generation and reactions of organometallic compounds were dried for *ca.* 12 h at 120° and allowed to cool in a desiccator over anh. $CaSO_4$. Anh. solvents were obtained by distillation from benzophenone/ketyl radical. BuLi was titrated according to the method of *Juaristi et al.* [33]. TLC: *Merck DC* F_{254} plates, detection by UV light, I_2 vapor, or ninhydrin spray. Flash chromatography (FC): *Merck* silica gel (0.040–0.063 mm). M.p. *Melt Temp* apparatus; not corrected. Anal. HPLC: *Water* 600 instrument fitted with UV/VIS detector, *Chiracel OD-H* column. IR Spectra: FT-IR Spectrometer *Varian 640-IR*; $\tilde{\nu}$ in cm^{-1}. ^{1}H-NMR Spectra:

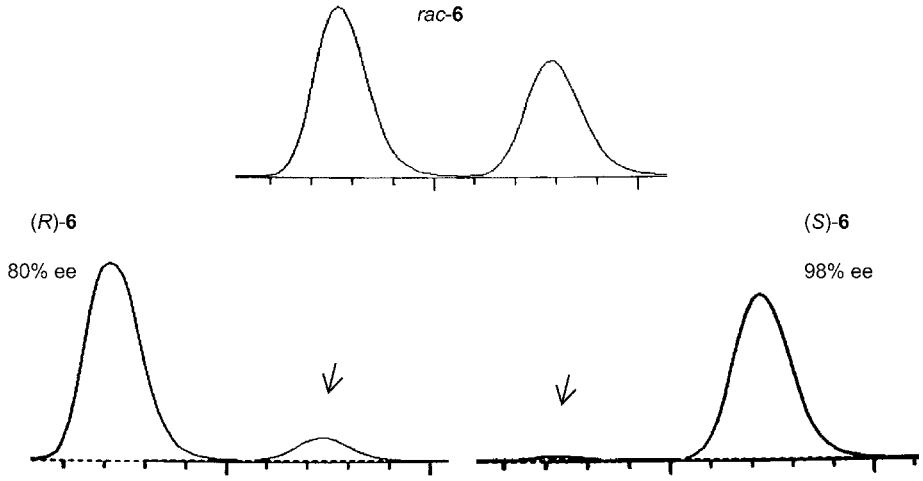


Fig. 4. *HPLC Analysis of (*R*)-***6*** and (*S*)-***6*** on a* Chiracel OD-H *column*

Jeol ECA-400 (500 MHz) spectrometer; ^{13}C-NMR spectra: *Jeol ECA-500* (125 MHz) spectrometer; chemical shifts δ in ppm rel. to Me_4Si (0 ppm) as an internal reference; coupling constants *J* in Hz. MS: *Hewlett–Packard HP-5986* instrument, high-resolution (HR) MS: *HPLC 1100* coupled to MSD-TOF *Agilent Technologies* mod. *1969A*; in *m*/*z*. Combustion Analysis: *Thermo-Finnigan* model *Flash CHNS/O 1112*.

1. *General* N*-Acylation Procedure for the Preparation of (*R,R*)- or (*S,S*)-***3*** (*GP 1*). To a suspension of *mono*-tert-*butyl fumarate* (**2**; 3.59 g, 20.9 mmol, 1 equiv.) in THF (0.25M) at $-30°$, Et_3N (3.21 ml, 23.0 mmol, 1.1 equiv.) and pivaloyl chloride (2.6 ml, 20.9 mmol, 1 equiv.) were added dropwise, and the mixture was stirred for 120 min at $-30°$. Meanwhile, a soln. of BuLi (2.49M in hexane; 8.39 ml, 1 equiv.) was added to an ice-bath-cooled suspension of hexahydrobenzoxazolidin-2-one (*R,R*)- or (*S,S*)-**1** (2.95 g, 20.9 mmol, 1 equiv.) in THF (0.25M), and the resulting mixture was stirred for 30 min at $-30°$. The resulting soln. was added to the mixed anhydride soln. prepared previously. Stirring was continued for 15 h, and the mixture was allowed to warm to r.t. The reaction was then quenched with sat. aq. NH_4Cl soln. (100 ml), and the mixture was diluted with AcOEt (200 ml). The org. phase was separated and washed with brine (100 ml), and each aq. fraction was re-extracted with AcOEt (2×200 ml). The combined org. extracts were dried (Na_2SO_4) and concentrated under reduced pressure.

tert-*Butyl (*2E*)- 4-[(*3a*S,*7a*S*)-Hexahydro-2-oxo-1,3-benzoxazol-3(*2H*)-yl]-4-oxobut-2-enoate* ((*S,S*)-**3**). *GP 1* was followed, and the crude product was purified by FC (AcOEt/hexane 80:20) to give 4.81 g (78%) of (*S,S*)-**3**. White solid. R_f (AcOEt/hexane 3:7) 0.5. M.p. 80–81°. $[\alpha]_D^{r.t.} = +85$ ($c = 1.0$, $CHCl_3$). IR (ATR): 2978*w*, 2936*w*, 2872*w*, 1793*s*, 1712*s*, 1681*s*, 1305*m*, 1146*s*, 1036*s*, 681*s*, 619*s*. ^{1}H-NMR ($CDCl_3$): 1.42 (*m*, 3 H); 1.48 (*s*, ^{t}Bu); 1.66 (*m*, 1 H); 1.85 (*m*, 1 H); 1.94 (*m*, 1 H); 2.23 (*m*, 1 H); 2.79 (*m*, 1 H); 3.60 (*m*, 1 H); 3.93 (*td*, $J = 3.6, 11.2$, 1 H); 6.78 (*d*, $J = 15.5$, 1 H); 7.75 (*d*, $J = 15.5$, 1 H). ^{13}C-NMR ($CDCl_3$): 23.60; 23.73; 28.05; 28.47; 28.49; 63.16; 81.93; 132.81; 135.48; 154.43; 164.17; 165.93. HR-ESI-TOF-MS: 296.1494 ($[M + H]^+$, $C_{15}H_{22}NO_5^+$; calc. 296.1492), 318.1315 ($[M + Na]^+$, $C_{15}H_{21}NNaO_5^+$; calc. 318.1311). Anal. calc. for $C_{15}H_{22}NO_5$ (295.1420): C 61.0, H 7.17, N 4.74; found: C 60.85, H 7.12, N 4.8.

tert-*Butyl (*2E*)-4-[(*3a*R,*7a*R*)-Hexahydro-2-oxo-1,3-benzoxazol-3(*2H*)-yl]-4-oxobut-2-enoate* ((*R,R*)-**3**). *GP 1* was followed, and the crude product was purified by FC (AcOEt/hexane 20:80) to give 4.93 g (80%) of (*R,R*)-**3**. White solid. R_f (AcOEt/hexane 7:3) 0.5. M.p. 80–81°. $[\alpha]_D^{r.t.} = -98$ ($c = 1.1$, $CHCl_3$). IR (ATR): 2978*w*, 2936*w*, 2872*w*, 1793*s*, 1712*s*, 1681*s*, 1305*m*, 1146*s*, 1036*s*, 681*s*, 619*s*. ^{1}H- and ^{13}C-NMR data: identical to those recorded for (*S,S*)-**3**. HR-ESI-TOF-MS: 296.1494 ($[M+H]^+$, $C_{15}H_{22}NO_5^+$; calc. 296.1492), 318.1314 ($[M+Na]^+$, $C_{15}H_{21}NNaO_5^+$; calc. 318.1311).

2. *General Procedure for the Stereoselective* tert-*Butyl Radical Additions* (*GP 2*). According to the procedure described in [34][35], (*R*,*R*)- or (*S*,*S*)-**3** (2 g, 6.77 mmol, 1 equiv.) was dissolved in CH_2Cl_2 (0.2M) and cooled to 0°, before the addition of ^{t}BuHgCl (2.97 g, 10.15 mmol, 1.5 equiv.). The mixture was stirred for 30 min at 0°, and then solid $NaBH_4$ (0.3820 g, 10.15 mmol, 1.5 equiv.) and H_2O (3 ml) were added, and the resulting mixture was stirred for another 2 h at 0°. The mixture was diluted with CH_2Cl_2 (25 ml), dried (Na_2SO_4), filtered, and concentrated under reduced pressure.

tert-*Butyl (2*S*)-2-{2-[(3a*S*,7a*S*)-Hexahydro-2-oxo-1,3-benzoxazol-3(2*H*)-yl]-2-oxoethyl}-3,3-dimethylbutanoate* ((*S*,*S*,*S*)-**4**). *GP 2* was followed, and the crude product was purified by FC (AcOEt/hexane 10:90) to give 1.67 g (70%) of (*S*,*S*,*S*)-**4**. White solid. R_f (AcOEt/hexane 3:7) 0.52. M.p. 148–149°. $[\alpha]_D^{r.t.} = +48$ ($c = 1.0$, $CHCl_3$). IR (ATR): 2960*w*, 2900*w*, 1781*s*, 1763*s*, 1362*s*, 1221*m*, 1121*s*, 1110*s*, 860*s*, 763*s*, 705*s*, 695*s*. ^{1}H-NMR ($CDCl_3$): 0.98 (*s*, ^{t}Bu); 1.34 (*m*, 3 H); 1.42 (*s*, ^{t}BuO); 1.63 (*m*, 1 H); 1.80 (*m*, 1 H); 1.91 (*m*, 1 H); 2.21 (*m*, 1 H); 2.60 (*dd*, $J = 4.1, 11.3$, 1 H); 2.73 (*m*, 1 H); 3.1 (*m*, 2 H); 3.49 (*td*, $J = 3.3, 11$, 1 H); 3.93 (*td*, $J = 3.6, 11.6$, 1 H). ^{13}C-NMR ($CDCl_3$): 23.63; 23.76; 28.09; 28.18; 28.51; 28.63; 32.49; 35.64; 51.62; 63.13; 80.28; 81.57; 154.87; 173.52; 174.75. HR-ESI-TOF-MS: 354.2279 ($[M + H]^+$, $C_{19}H_{32}NO_5^+$; calc. 354.2274), 376.2099 ($[M + Na]^+$, $C_{19}H_{31}NNaO_5^+$; calc. 376.2094).

tert-*Butyl (2*R*)-2-{2-[(3a*R*,7a*R*)-Hexahydro-2-oxo-1,3-benzoxazol-3(2*H*)-yl]-2-oxoethyl}-3,3-dimethylbutanoate* ((*R*,*R*,*R*)-**4**). *GP 2* was followed, and the crude product was purified by FC (AcOEt/hexane 90:10) to give 1.64 g (69%) of (*R*,*R*,*R*)-**4**. White solid. R_f (AcOEt/hexane 3:7) 0.52. M.p. 149–150°. $[\alpha]_D^{r.t.} = -51$ ($c = 1.0$, $CHCl_3$). IR (ATR): 2955*w*, 2874*w*, 1758*s*, 1704*s*, 1365*s*, 1238*m*, 1143*s*, 1115*s*, 860*s*, 763*s*, 705*s*, 695*s*. The ^{1}H- and ^{13}C-NMR data: identical to those recorded for (*S*,*S*,*S*)-**4**. HR-MS: 376.2094 ($[M + Na]^+$, $C_{19}H_{31}NNaO_5^+$; calc. 376.2094). Anal. calc. for $C_{19}H_{31}NO_5$ (353.2202): C 64.56, H 8.84, N 3.96; found: C 64.57, H 9.16, N 3.91.

3. *General Procedure for the Hydrolytic Cleavage of the Radical Addition Products in the Preparation of* **5** (*GP 3*). The reaction was carried out in two steps: flask *A:* to a stirred soln. of $LiOH \cdot H_2O$ (0.47 g, 11.3 mmol, 2 equiv.) in 70 ml of a mixture of THF/H_2O 1:1 was added H_2O_2 (30% aq. soln.; 2.56 ml, 2.6 mmol, 4 equiv.) at 0°. The resulting mixture was stirred at 0° for 3 min. Flask *B:* a stirred soln. of (*S*,*S*,*S*)- or (*R*,*R*,*R*)-**4** (2.0 g, 5.6 mmol, 1 equiv.) in THF (70 ml) was cooled to 0° before the addition of the soln. previously prepared in flask *A* (*via* cannula). The mixture was stirred at 0° for 30 min before the addition of Na_2SO_3 (2.31 g, 22.6 mmol, 4 equiv.) in H_2O (20 ml). The mixture was stirred a 0° for another 30 min, treated with H_2O (70 ml), and extracted with AcOEt (2 × 70 ml). The aq. phase was acidified to pH 2 with 1M HCl at 0°. A white solid precipitated that was extracted with AcOEt (3 × 70 ml), and the org. phase was separated, washed with a sat. soln. of sodium and potassium tartrate, dried (Na_2SO_4), and concentrated under reduced pressure.

*(3*S*)-3-[(*tert-*Butoxy)carbonyl]-4,4-dimethylpentanoic Acid* ((*S*)-**5**). *GP 3* was followed to give 1.23 g (95%) of (*S*)-**5**. Pale yellow oil. $[\alpha]_D^{r.t.} = +10$ ($c = 1.0$, $CHCl_3$). IR (ATR): 2966*w*, 2875*w*, 1717*w*, 1367*s*, 1291*m*, 1241*s*, 1145*s*, 848*s*, 763*s*, 591*s*, 557*s*. ^{1}H-NMR ($CDCl_3$): 0.95 (*s*, ^{t}Bu); 1.42 (*s*, ^{t}BuO); 2.44 (1 H); 2.49 (*dd*, $J = 3.3, 26.7$, 1 H); 2.47 (*d*, $J = 1.3$, 1 H); 2.75 (*AMX*, $J_{AM} = 13.5$, $J_{MX} = 22$, 1 H). ^{13}C-NMR ($CDCl_3$): 27.96; 28.07; 32.59; 32.75; 51.94; 80.70; 172.98; 178.97. HR-ESI-TOF-MS: 253.1412 ($[M + Na]^+$, $C_{12}H_{22}NaO_4^+$; calc. 253.1410).

*(3*R*)-3-(*tert-*Butoxycarbonyl)-4,4-dimethylpentanoic Acid* ((*R*)-**5**). *GP 3* was followed to give 1.23 g (95%) of (*R*)-**5**. Pale yellow oil. $[\alpha]_D^{r.t.} = -14$ ($c = 1.0$, $CHCl_3$). IR (ATR): 2960*w*, 2900*w*, 1781*s*, 1763*s*, 1362*s*, 1221*m*, 1121*s*, 1110*s*, 860*s*, 763*s*, 705*s*, 695*s*. ^{1}H- and ^{13}C-NMR data: identical to those recorded for (*S*)-**5**. HR-ESI-TOF-MS: 253.1411 ($[M + Na]^+$, $C_{12}H_{22}NaO_4^+$; calc. 253.1410).

4. *General Procedure for the* Curtius *Rearrangement of* **5** (*GP 4*). *Preparation of Protected β-Amino Acids* **6**. To a stirred soln. of (*S*)- or (*R*)-**5** (0.400 g, 1.73 mmol, 1 equiv.) in toluene (15 ml) and Et_3N (0.48 ml, 3.47 mmol, 2 equiv.), were added ($(PhO)_2P(O)N_3$, 0.44 ml, 2.07 mmol, 1.2 equiv.) and BnOH (0.35 ml, 3.47 mmol, 2 equiv.). The resulting mixture was stirred for 1 h at r.t. and then heated to reflux for an additional 3 h. The toluene solvent was evaporated under vacuum, and the residue was dissolved in AcOEt (30 ml) and 2M HCl (15 ml). The org. phase was separated, washed with aq. sat. soln. of $NaHCO_3$, dried (Na_2SO_4), and concentrated under reduced pressure.

tert-*Butyl (2*R*)-2-({[(Benzyloxy)carbonyl]amino}methyl)-3,3-dimethylbutanoate* ((*R*)-**6**). *GP 4* was followed, and the crude product was purified by FC (AcOEt/hexane 10:90) to give to 0.126 g (66%) of (*R*)-**6**. Yellow oil. $[\alpha]_D^{r.t.} = -41$ ($c = 1.0$, $CHCl_3$) for 80% ee. *Chiracel OD-H* (hexane/^{i}PrOH 90:10; 0.7 ml/

min), 210 nm, t_R 6.7 min. IR (ATR): 2995*w*, 2638*w*, 1996–1801*w*, 1716*s*, 1616*w*, 1471*w*, 1398*w*, 1367*s*, 1145*s*, 848*s*, 587*s*, 560*s*. ^{1}H-NMR ((D$_6$)DMSO, 120°): 0.93 (*s*, ^{t}Bu); 1.37 (*s*, ^{t}BuO); 2.32 (*dd*, *J* = 4, 10.5, 1 H); 3.17 (*dt*, *J* = 4.5, 13.3, 1 H); 3.28 (*ddd*, *J* = 13.2, 10.5, 7, 1 H); 5.0 (*s*, 2 H); 6.55 (br., 1 H); 7.25 (*m*, 2 H); 7.29 (*m*, 3 H). ^{13}C-NMR ((D$_6$)DMSO, 120°): 28.18; 28.37; 32.39; 57.1; 65.88; 80.29; 127.98; 128.08; 128.67; 137.91; 156.46; 172.76. HR-ESI-TOF-MS: 336.2166 ([*M* + H]$^+$, $C_{19}H_{30}NO_4^+$; calc. 336.2169).

tert-*Butyl (2*S*)-2-({[(Benzyloxy)carbonyl]amino}methyl)-3,3-dimethylbutanoate* ((*S*)-**6**) was followed, and the crude product was purified by FC (AcOEt/hexane 10 : 90) to give to 0.124 g (65%) of (*S*)-**6**. Yellow oil. $[\alpha]_D^{r.t.} = +46$ (*c* = 1.0, $CHCl_3$) for 98% ee. *Chiracel OD-H* (hexane/^{i}PrOH 90 : 10, 0.7 ml/min), 210 nm, t_R 7.2 min. IR (ATR): 2996*w*, 2638*w*, 1996–1801*w*, 1716*s*, 1471*w*, 1396*w*, 1367*s*, 1146*s*, 847*s*, 577*s*, 557*s*. ^{1}H- and ^{13}C-NMR data: identical to those recorded for (*R*)-**6**. HR-ESI-TOF-MS: 358.1990 ([*M* + Na]$^+$, $C_{19}H_{29}NNaO_4^+$; calc. 358.1988).

5. *General Procedure for the Hydrolysis of (*S*)- or (*R*)-**6**, and Catalytic Hydrogenation to Afford Free Amino Acids (*S*)- or (*R*)-**7** (GP 5)*. The substrate (*S*)- or (*R*)-**6** (0.140 g, 1.73 mmol, 1 equiv.), was dissolved in the minimal volume of CH_2Cl_2 and cooled at 0°, and treated with the same amount of CF_3COOH (TFA). The soln. was stirred for 1.5 h at r.t. The excess solvent and TFA were evaporated under vacuum. The residue was dissolved in EtOH (0.1M), and *ca*. 10% (*w*/*w*) Pd/C was added. The resulting mixture was stirred under H_2 (1 atm) at r.t. for 4 h. The catalyst Pd/C was filtered, washed with EtOH, and the combined filtrate was concentrated under vacuum.

*(2*R*)-2-(Aminomethyl)-3,3-dimethylbutanoic Acid* ((*R*)-**7**). *GP 5* was followed, and the crude product was purified trough *DOWEX 50WX8-100* ion-exchange resin to give 0.033 g (55%) of (*R*)-**7**. White foam. $[\alpha]_D^{r.t.} = -6.0$ (*c* = 1.0, H_2O). IR (ATR): 2958*w*, 2638*w*, 1545*w*, 1406*w*, 1308*w*, 1226*s*, 853*w*, 731*s*, 655*s*, 628*s*, 593*s*. ^{1}H-NMR (D_2O): 0.82 (*s*, ^{t}Bu); 2.16 (*dd*, *J* = 4.3, 10.6, 1 H); 3.01 (*m*, 2 H). ^{13}C NMR (D_2O): 27.4 (3C); 31.5; 39.2; 56.4; 179.0. HR-ESI-TOF-MS: 146.1177 ([*M* + H]$^+$, $C_7H_{16}NO_2^+$; calc. 146.1175).

*(2*S*)-2-(Aminomethyl)-3,3-dimethylbutanoic Acid* ((*S*)-**7**). *GP 5* was followed, and the crude product was purified trough *DOWEX 50WX8-100* ion-exchange resin to give 0.032 g (53%) of (*S*)-**7**. White foam. $[\alpha]_D^{r.t.} = +9$ (*c* = 1.0, H_2O). IR (ATR): 2995*w*, 2638*w*, 1996*w*, 1716*s*, 1616*w*, 1471*w*, 1398*w*, 1367*s*, 1145*s*, 848*s*, 587*s*, 560*s*. ^{1}H- and ^{13}C-NMR data: identical to those recorded for (*R*)-**7**. HR-ESI-TOF-MS: 146.1176 ([*M* + H]$^+$, $C_7H_{16}NO_2^+$; calc. 146.1175).

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