Preparation of β^2-Homotryptophan Derivatives for β-Peptide Synthesis[1])

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In view of the prominent role of the 1*H*-indol-3-yl side chain of tryptophan in peptides and proteins, it is important to have the appropriately protected homologs H-β^2-HTrp–OH and H-β^3-HTrp–OH (*Fig.*) available for incorporation in β-peptides. The β^2-HTrp building block is especially important, because β^2-amino acid residues cause β-peptide chains to fold to the unusual *12/10* helix or to a hairpin turn. The preparation of Fmoc– and Z–β^2-HTrp(Boc)–OH by *Curtius* degradation (*Scheme 1*) of a succinic acid derivative is described (*Schemes 2–4*). To this end, the (*S*)-4-isopropyl-3-[(*N*-Boc-indol-3-yl)propionyl]-1,3-oxazolidin-2-one enolate is alkylated with Br–CH_2CO_2Bn (*Scheme 3*). Subsequent hydrogenolysis, *Curtius* degradation, and removal of the *Evans* auxiliary group gives the desired derivatives of (*R*)-H–β^2-HTrp–OH (*Scheme 4*). Since the (*R*)-form of the auxiliary is also available, access to (*S*)-β^2-HTrp-containing β-peptides is provided as well.

Introduction. – The tryptophan side chain, a (1*H*-indol-3-yl)methyl group, is hydrophobic and lipophilic, and, at the same time, it is capable of engaging in H-bonding. Of all amino acids, tryptophan has the highest affinity for the membrane–water interface [2]. That makes tryptophan residues especially important for membrane proteins, where they are believed to serve as anchors on the periplasmic side of the membranes [3], and, indeed, membrane proteins have a significantly higher tryptophan content compared to soluble proteins. Also, antimicrobial peptides [4], containing several tryptophan residues, are widely distributed among living organisms and are believed to play important roles in the protection against potentially pathogenic microorganisms by disrupting the structural integrity of the microbial membranes. For example, indolicidin, which has antibiotic activity against bacteria [5], fungi [6], proteazoae [7], and viruses [8], is a cationic peptide amide consisting of only 13 amino acids, five of which are tryptophans; it also causes lysis of erythrocytes and is cytotoxic to human T lymphocytes [6]. Although tryptophan residues are localized at the membrane interface and are not inserted in the lipid bilayer [9], the peptide causes disruption of the cytoplasmic membrane [10], and the tryptophan residues appear to be essential for the hemolytic activity [11]. Another tryptophan-rich cationic peptide is tritrpticin, which possesses strong antimicrobial activity against bacteria and fungi [12]; it adopts four conformations in solution, but when it binds to membrane-mimetic sodium dodecyl sulfate micelles, only one major conformer is present [13]. Other peptides, such as lactoferricin B [14], mastoparan B [15], the 20-residue hybrid peptide

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[1]) Incorporation of a β^2-HTrp residue into a turn-mimicking structure has been mentioned in a preliminary communication [1].

[2]) Postdoctoral co-worker at ETH-Zürich (2001/02), financed by the *Swiss National Science Foundation*, Grant No. 2000-058831.99/1.

CA(1–8)-MA(1–12) [16], and PMAP-23 [17] have been found to have antimicrobial activity, and the importance of at least part of their tryptophans for the observed activity indicates that the side chains of this amino acid function as anchors to the microbial membrane. Tryptophans are also essential for the formation of H_2O_2 by a variety of antibodies, which can participate in antibody-mediated cell killing [18].

Another important property of tryptophans is the fluorescence of the indole ring [19], which is highly sensitive to microenvironmental conditions and can, therefore, be used to study conformational changes of proteins and protein-membrane interactions: for instance, when tryptophan is inside a hydrophobic environment, a blue shift is observed[3]).

In view of the central role that tryptophan plays in peptides and proteins it is necessary to have access to the two homologs, 3-amino-4-(1*H*-indol-3-yl)butanoic acid (H–β^3-HTrp–OH) and 3-amino-2-[(1*H*-indol-3-yl)methyl]propionic acid (H–β^2-HTrp–OH) (*Fig.*), for incorporation into β-peptides. These analogs of α-peptides consist of homologated proteinogenic amino acids and have recently been shown to form two types of helices [21], turns [22][23], and parallel as well as antiparallel sheets [22][24] with short chain lengths, to be stable to peptidases [25], and to be able to mimic α-peptide turns [26], amphipathic helices [27], and cell-penetrating oligoarginines [28]. With β-peptides carrying tryptophan side chains, we have the means of mimicking yet other α-peptidic activities. Whereas the H–β^3-HTrp–OH is available by *Arndt-Eistert* homologation of the natural tryptophan [29], the β^2-analog has not been described[1]); on the other hand, β^2-amino acid residues are especially important for the construction of turns [22] and of *12/10* helices [21]. The preparation of β^2-HTrp derivatives in either enantiomeric form is described herein.

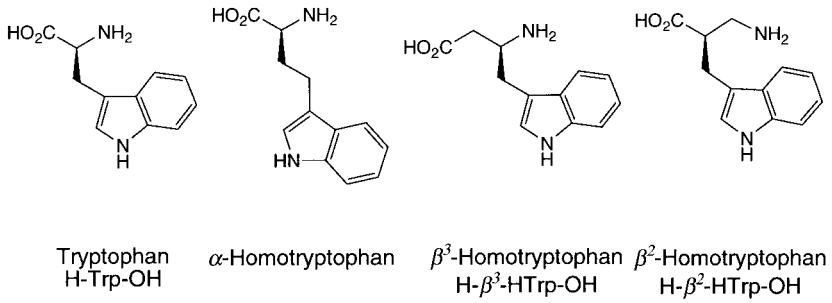

Figure. *Tryptophan and three of its homologs*

Results and Discussion. – We chose to prepare Z-protected β^2-HTrp **1a**, suitable for solution-phase synthesis of β-peptides, and the Fmoc derivative **1b** for solid-phase synthesis. The Boc group was applied for protection on the indole N-atom, since it is orthogonal to both Fmoc and Z protective groups. Moreover, Boc was expected to help diminish some side reactions known to occur with the Trp side chain during acidic

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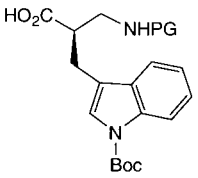
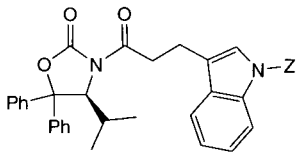
[3]) Positively charged residues close to the benzene part or negative charges close to the pyrrole part of the indole ring cause λ_{max} shift to longer wavelengths (red shift) with the opposite configuration leading to a blue shift [20].

cleavage of peptides from resins[4]), a step in which the Boc group itself is readily removed.

We first tried to build the desired β-amino acid skeleton by diastereoselective aminomethylation [31] of the corresponding propionyl-oxazolidinone **2** [31a], a method we had previously applied for the preparation of other β^2-amino acids, but experiments under various conditions were as fruitless as our preliminary attempts [31a]. We then tried to carry out the C,C-bond formation the other way around, *i.e.*, by indolylmethylation (with bromide **4** [32]) of 3-(3-aminopropionyl)-oxazolidinone derivatives **3a** [31a] and **3b**, again without success[5]).





1a PG = CO_2Bn (Z)
b PG = (9*H*-fluoren-9-yl)CH_2OCO (Fmoc)
(Boc = *t*-BuOCO)

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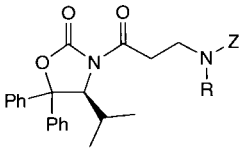

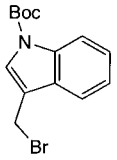

3a R = H
b R = Bn

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Another route for the attachment of a H_2NCH_2 group to a carboxylic acid (the *Mannich* transformation) is based on *Curtius* degradation of enantiomerically pure and regioselectively protected succinic acids, a route that can lead to either β^2- or β^3-amino acids [33] (*Scheme 1*). The precursors for the degradation can be obtained, for instance, by diastereoselective carboxymethylation of suitable chiral carboxylic acid derivatives [33a,b], by regio- and diastereoselective alkylation of chiral succinates [33c], or from malic acid [33d].

Preparation of the indolyl-substituted 3-propionyl-oxazolidinones **8a**,**b** was straightforward: esterification of 3-(1*H*-indol-3-yl)propionic acid (**5**) with CH_2N_2 [34], followed by Boc protection of the indole nucleus, provided the methyl indole-propionate **6** in 92% yield (*Scheme 2*). Hydrolysis of the ester function, followed by

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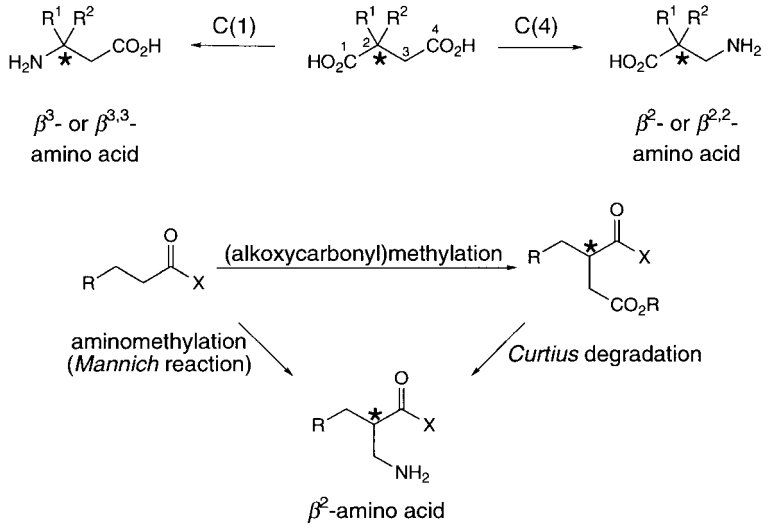
[4]) During *N*-Boc deprotection with CF_3COOH the *t*-Bu moiety is removed, leaving the indole nucleus protected with a COOH group, thus preventing it from being alkylated, and from undergoing peptide reattachement or sulfonation. The COOH group is lost as CO_2 in H_2O to give the unprotected indole nucleus [30]. The Boc group could also protect the indole ring from being reduced to dihydroindole by silanes, which are often used as so-called scavengers in the removal/deprotection of peptides from resins [30b].

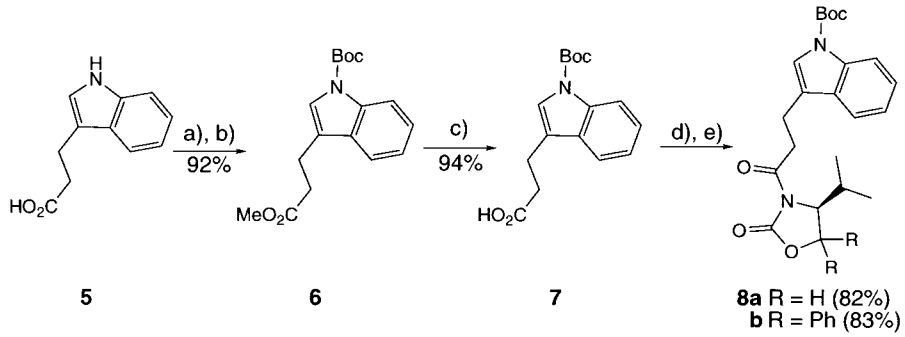
[5]) With a methylsulfonyl group at the indole N-atom ($MeSO_2$ instead of Boc in **4**), a small amount (< 10%) of alkylated product was detected in the reaction mixture.

Scheme 1. Curtius *Degradation of Succinic Acid Derivatives for the Preparation of β^2- or β^3-Amino Acids*



attachment of the oxazolidinone auxiliaries, led to the chiral derivatives **8a**,**b** in *ca.* 80% yield (*Scheme 2*). Since both enantiomeric forms of valine, the precursor of the oxazolidinones, are available, all enantiomers of the products reported herein are also accessible.

Scheme 2. *Preparation of Indolepropionic Acid Derived Oxazolidinones* **8**



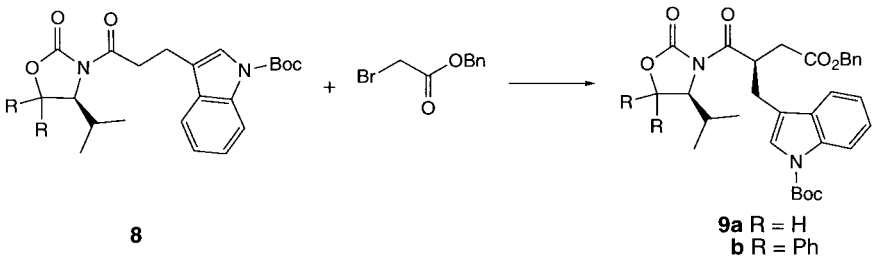
a) CH_2N_2, Et_2O. b) Boc_2O, DMAP, MeCN. c) $LiOH \cdot H_2O$, THF/H_2O. d) Et_3N, *t*-BuCOCl. e) Auxiliary, LiCl.

For the carboxymethylation of indole-propionic acid derivatives **8** (*Scheme 3*), the benzyl bromoacetate was chosen, so that hydrogenolytic deprotection in the presence of the Boc group would be possible (under basic conditions, the auxiliary could be lost and/or partial epimerization of the newly formed stereogenic center could occur)[6]). In

[6]) The trimethylsilylethyl ester of bromoacetic acid [35] was also used for the carboxymethylation of **8b**. However, attempts to cleave the silylated ethyl ester group in the resulting product with Bu_4NF led to complete detachment of the auxiliary.

the optimization of the alkylation conditions, it was found that the NaHMDS-generated Na enolate provided best yields and diastereoselectivities. Within experimental error, single diastereoisomers **9a**,**b** were present in the reaction mixture. Lithium and zinc enolates[7]) gave less-satisfactory results: the selectivity was excellent, but prolonged reaction times (5–7 days) were necessary, which led to low conversion (36%) and required laborious separation from unreacted starting material **8**.

Scheme 3. *Preparation of Succinic Acid Derivatives* **9** via *Carboxymethylation of the* N-*Acyl-oxazolidinone* **8**



8 **9a** R = H **b** R = Ph

Contrary to our previous experience [31a], hydrogenolysis of the BnOCO group (in THF for 2 h) with the diphenyl-substituted oxazolidinone derivative **9b** also led to the cleavage of $Ph_2C(5)-O$ bond in the auxiliary group[8]). This forced us to switch to the original *Evans* auxiliary with its less well-crystallizing derivatives. Thus, the Bn group of succinate **9a** was cleaved by hydrogenolysis in dry THF with Pd/C as the catalyst (*Scheme 4*). From the resulting acid **10**, an azide was generated *in situ* [33a] and decomposed with *Curtius* rearrangement in the presence of BnOH to give the Z-protected amino acid derivative **12**. Removal of the auxiliary by $LiOH/H_2O_2$ afforded Z–β^2-HTrp(Boc)–H (**1a**). Alcoholysis (BnOLi) of the intermediate **12** led to the benzyl ester **13** in 81% yield, which was converted to Fmoc–β^2-HTrp(Boc)–H (**1b**) in 80% yield, by hydrogenolysis of both the ester Bn and the Z protecting groups, followed by Fmoc protection of the amino group [37]. Hydrogenolyses of succinate **9a** in THF/MeOH 1:1 between 0° and room temperature produced a mixture of epimeric indoline derivatives **11**; although these could be used for the *Curtius* rearrangement, followed by re-oxidation with DDQ, the overall yield was poorer.

Thus, we have developed a useful route from commercial 3-(1*H*-indol-3-yl)propionic acid to the desired *N*-Fmoc- and *N*-Z-protected β^2-homotryptophans for β-peptide synthesis[9]). It is remarkable that the preparation of compounds as simple as the amino-acid derivatives **1** in enantiomerically pure form takes nine (for **1a**) and eleven steps (for **1b**) from commercial precursors, using an auxiliary approach.

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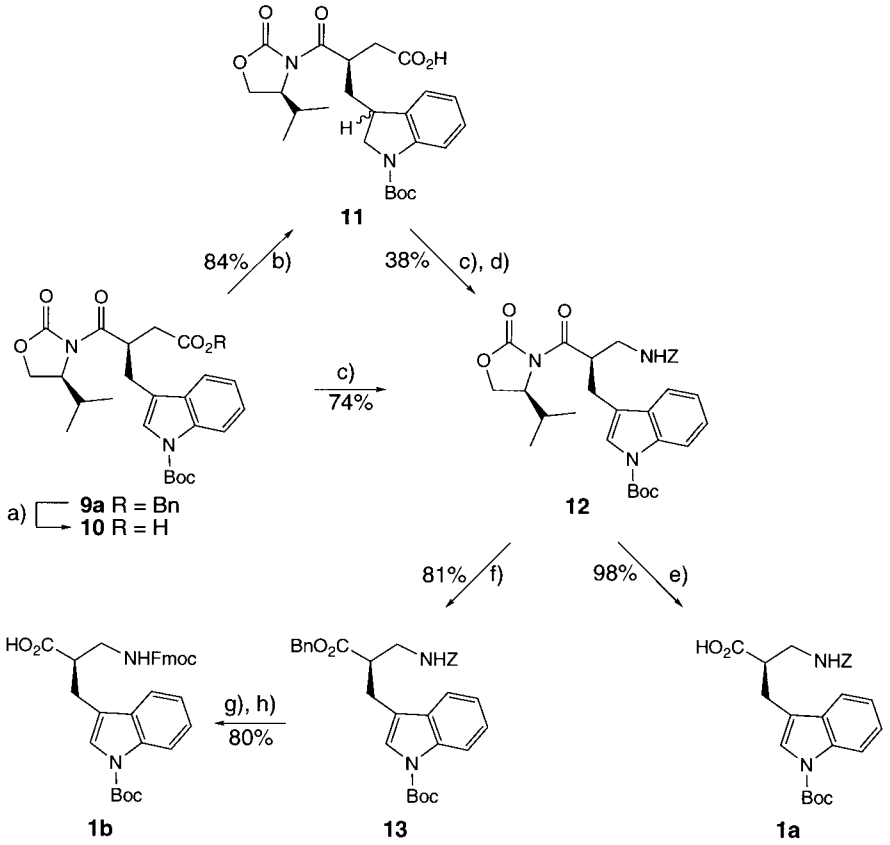
[7]) 'Zinc enolates' were generated by addition of $ZnCl_2$ to the solutions of the lithium enolates.

[8]) Hydrogenolysis of the $Ph_2C(5)-O$ bond of 4-substituted 5,5-diphenyloxazolidin-2-ones has been used to prepare chiral, diphenylmethyl-substituted amines [36].

[9]) The enantiomer purity of **1a** and **1b** was not determined, but we know that β-peptides prepared with incorporation of β-HTrp (from **1a**) are diastereoisomerically pure [1].

Scheme 4. *Preparation of β^2-Homotryptophan Derivatives* **1**



a) H_2 (1 atm), 10% Pd/C, THF. b) H_2 (1 atom), 10% Pd/C, THF/MeOH 1:1. c) $(PhO)_2P(O)N_3$, Et_3N, BnOH, toluene, reflux. d) DDQ, CH_2Cl_2. e) $LiOH \cdot H_2O$, 30% H_2O_2, THF/H_2O. f) BnOH, BuLi, THF. g) H_2, 10% Pd/C, EtOH. h) Fmoc-OSu, Na_2CO_3, acetone/H_2O. DDQ = 2,3-Dichloro-5,6-dicyano-1,4-benzoquinone, Su = *N*-succinimidyl.

Experimental Part

1. *General. Abbreviations:* Boc_2O: di(*tert*-butyl) dicarbonate, DCTB: 2-{(2*E*)-3-[4-(*tert*-butyl)phenyl]-2-methylprop-2-enylidene}malonitrile, DDQ: 2,3-dichloro-5,6-dicyano-1,4-benzoquinone, DHB: 2,5-dihydroxybenzoic acid, DMAP: 4-dimethylaminopyridine, FC: flash chromatography, h.v.: high vacuum, 0.01–0.1 Torr, NaHMDS: sodium hexamethyldisilazan. Solvents for chromatography and workup procedures were distilled from *Sikkon* (anh. $CaSO_4$; *Fluka*); Et_2O was distilled from $KOH/FeSO_4$. Et_3N was distilled from CaH_2 and stored over molecular sieves (4 Å). Pivaloyl chloride was distilled and stored under Ar. LiCl and $ZnCl_2$ were dried under h.v. at 200° for 24 h. All other reagents were used as received from *Fluka*. The methyl 3-(1*H*-indol-3-yl)-propionate was prepared according to the procedure in [34]. TLC: *Merck* silica gel *60 F_{254}* plates; detection with UV and anisaldehyde or I_2. FC: *Fluka* silica gel *60* (40–63 μm); at *ca.* 0.5 bar. M.p.: *Büchi 510* apparatus; uncorrected. Optical rotations: *Perkin-Elmer 241* polarimeter (10 cm, 1-ml cell) at r.t. IR Spectra: *Perkin-Elmer 782* spectrophotometer. NMR Spectra: *Bruker AMX-500* (^{1}H: 500 MHz, ^{13}C: 125 MHz), *AMX-400* (^{1}H: 400 MHz, ^{13}C: 100 MHz); chemical shifts δ in ppm downfield from internal Me_4Si (= 0 ppm); *J* values in Hz; some compounds show the presence of rotamers, which are indicated. MS: *IonSpec Ultima-Maldi FT/ICR* mass

spectrometer, matrix DHB or DCTB, 4.7 T, N_2 laser at 337 nm. Elemental analyses were performed by the Microanalytical Laboratory of the Laboratorium für Organische Chemie, ETH-Zürich.

*(*R*)-3-{[(Benzyloxy)carbonyl]amino}-2-({1-[(*tert*-butoxy)carbonyl]-1*H*-indol-3-yl}-methyl)propionic Acid* (**1a**). To a stirred soln. of amide **12** (627 mg, 1.108 mmol) in THF (16 ml), H_2O_2 (30% aq. sol.; 0.45 ml, 4.37 mmol) and soln. of $LiOH \cdot H_2O$ in 5.6 ml H_2O were added at 0°. The mixture was stirred at 0° for 2.5 h before addition of a sat. aq. soln. of Na_2SO_3 (5 ml). The soln. was partially conc. *in vacuo*, diluted with H_2O and acidified to pH 1–2 with 10% HCl at 0°. A white solid precipitated, was extracted with EtOAc (2×), the org. layer was dried ($MgSO_4$) and concentrated *in vacuo* to yield 639 mg of an oil. FC (pentane/Et_2O/AcOH 100:100:1) yields **1a** (494 mg, 98%). White foam. M.p. 63–65°. $[\alpha]_D^{r.t.} = +0.57$ ($c = 0.6$, $CHCl_3$). IR ($CHCl_3$): 3448*w*, 2982*w*, 1724*s*, 1514*m*, 1453*m*, 1371*m*, 1157*m*, 1092*m*, 1040*w*, 1020*w*, 855*w*. ^{1}H-NMR (400 MHz, $CDCl_3$; signals of rotamers in italics): 1.66 (*s*, *t*-Bu); *2.81–2.89*, 2.90–2.94 (*m*, 1 H, indCH_2); 3.0–3.15 (*m*, 2 H, indCH_2, C(O)CH); *3.2–3.35*, 3.4–3.5 (*m*, 1 H, NCH_2); 3.5–3.6 (*m*, 1 H, NCH_2); 5.04–5.11 (*m*, OCH_2); 5.22–5.30, *6.6–6.7* (*m*, NH); 7.13–7.52 (*m*, 9 arom. H); 8.12 (br. *s*, arom. NCH). ^{13}C-NMR (100 MHz, $CDCl_3$): 24.9, 25.2 (CH_2); 28.2 (Me); 41.8, 42.3 (CH_2); 45.3, 45.6 (CH); 66.9, 67.3 (CH_2); 83.7 (C); 115.4 (CH); 116.7 (C); 118.7, 122.6, 123.7, 123.9, 124.5, 127.8, 128.2, 128.4, 128.5 (CH); 130.2, 135.5, 136.3, 149.7, 156.5, 157.8, 177.5, 178.4 (C). HR-MALDI-MS: 475.1845 (+1.05 ppm) ($C_{25}H_{28}N_2O_6Na^+$; calc. 475.1840). Anal. calc. for $C_{25}H_{28}N_2O_6$ (452.50): C 66.36, H 6.24, N 6.19; found: C 66.00, H 6.19, N 6.09.

*(*R*)-3-({[(9*H*-Fluoren-9-yl)methoxy]carbonyl}amino)-2-({1-[(*tert*-butoxy)carbonyl]-1*H*-indol-3-yl}methyl)propionic Acid* (**1b**). To a stirred soln. of BnOH (0.15 ml, 1.45 mmol, 2.36 equiv.) in THF (6 ml) at −78°, BuLi (1.6M in hexane, 0.6 ml, 1.56 equiv.) was added, followed by a soln. of amide **12** (347 mg, 0.613 mmol, 1 equiv.) in 2 ml of THF. After 5 min, the temp. was allowed to rise to 0°, and stirring was continued for 3 h before NH_4Cl soln. was added, and the mixture was diluted with H_2O and Et_2O. The org. phase was separated, washed with brine, dried ($MgSO_4$), and concentrated *in vacuo*. FC (pentane/Et_2O 3:1 to 2:1) yielded the benzyl ester **13** as a colorless oil (269 mg, 81%). Part of this oil (157 mg, 0.289 mmol) was dissolved in EtOH (5 ml) and stirred under H_2 atmosphere (1 atm, balloon) with 10% Pd/C (15 mg) for 2 h at r.t. Pd/C was filtered off, washed with EtOH, and the filtrate was concentrated *in vacuo* to yield the crude amino acid, which was suspended in 0.15M aq. Na_2CO_3 (3.9 ml, 0.585 mmol, 2 equiv.). The suspension was treated with a soln. of Fmoc-OSu (117 mg, 0.347 mmol, 1.2 equiv.) in acetone (3.5 ml); all solids dissolved. The soln. was stirred for 21 h at r.t., the solvent was partially evaporated *in vacuo* and diluted with H_2O (100 ml) and Et_2O (50 ml). The org. phase was washed with 0.15M Na_2CO_3 (35 ml). Combined H_2O phases were acidified to pH 2–3 with 1M HCl and extracted with AcOEt (2 × 60 ml). AcOEt phases were dried ($MgSO_4$) and concentrated *in vacuo* to yield 158 mg of colorless solid. Recrystallization (cyclohexane/AcOEt) yielded **1b** (125 mg, 80% from **13**). Colorless solid. M.p. 125–128°. $[\alpha]_D^{r.t.} = -5.0$ ($c = 1.04$, $CHCl_3$). IR ($CHCl_3$): 3451*w*, 3007*w*, 1723*s*, 1516*m*, 1452*m*, 1371*m*, 1156*m*, 1090*m*, 1019*w*, 857*w*. ^{1}H-NMR (400 MHz, CD_3OD; signals of rotamers in italics): *1.57*, 1.64 (*s*, *t*-Bu); *2.5*, *2.7*, 2.85–3.05, *3.25* (*m*, indole-CH_2, C(O)CH); *3.94*, 4.19 (*t*, $J = 6.8$, C*H*CH_2O); 4.32–4.34 (*m*, CHC*H*$_2$O); 7.17–7.40 (*m*, 6 arom. H); 7.47 (*s*, 1 arom. H); 7.55 (*d*, $J = 7.7$, 1 arom. H); 7.63 (*d*, $J = 7.4$, 2 arom. H); 7.70–7.80 (*m*, 2 arom. H); *8.00*, 8.07 (br. *d*, $J = 8.1$, arom. NCH). ^{13}C-NMR (100 MHz, CD_3OD): 26.0 (CH_2); 28.4 (Me); 43.6, 47.3 (CH); 67.8 (CH_2); 84.7 (C); 116.1 (CH); 119.3 (C); 120.1, 120.9, 123.6, 124.6, 125.4, 126.3, 128.2, 128.8 (CH); 131.8, 136.9, 142.6, 145.4, 151.1, 158.9, 177.6 (C). HR-MALDI-MS: 563.2465 (+55 ppm) ($C_{32}H_{32}N_2O_6Na^+$; calc. 563.2153). Anal. calc. for $C_{32}H_{32}N_2O_6 \cdot 1/2\ H_2O$ (549.62): C 69.93, H 6.05, N 5.10; found: C 69.77, H 6.18, N 5.16.

*Methyl 3-{1-[(*tert*-Butoxy)carbonyl]-1*H*-indol-3-yl}propionate* (**6**). A stirred soln. of methyl 3-(1*H*-indol-3-yl)propionate [34] (1.233 g, 6.018 mmol, 1 equiv.) in MeCN (10 ml) was treated with a soln. of Boc_2O (1.379 g, 6.318 mmol, 1.05 equiv.) in 2 ml of MeCN and with DMAP (40 mg, 0.327 mmol, 0.05 equiv.). After stirring at r.t. for 1 h, additional Boc_2O (156 mg, 0.715 mmol, 0.1 equiv.) was added, and stirring was continued for 90 min. The mixture was concentrated *in vacuo*, diluted with AcOEt (40 ml), washed with 1M HCl (2 × 30 ml) and brine (30 ml), dried ($MgSO_4$), and concentrated *in vacuo*. FC (pentane/Et_2O 10:1) yielded **6** (1.678 g, 92%). Colorless oil. IR ($CHCl_3$): 3005*w*, 2982*w*, 1729*s*, 1477*w*, 1453*m*, 1371*m*, 1309*w*, 1086*m*, 1019*w*, 856*w*. ^{1}H-NMR (400 MHz, $CDCl_3$): 1.67 (*s*, *t*-Bu); 2.70–2.75 (*m*, CH_2); 3.01–3.06 (*m*, CH_2); 3.70 (*s*, OMe); 7.24 (*ddd*, $J = 1.1$, 7.2, 7.7, 1 arom. H); 7.29–7.34 (*m*, 1 arom. H); 7.38 (*s*, 1 arom. H); 7.52 (*ddd*, $J = 0.8$, 1.3, 7.7, 1 arom. H); 8.11 (br. *d*, $J = 7.7$, arom. NCH). ^{13}C-NMR (100 MHz, $CDCl_3$): 20.4 (CH_2); 28.2 (Me); 33.8 (CH_2); 51.7 (Me); 83.5 (C); 115.3, 118.8 (CH); 119.4 (C); 122.4, 122.5, 124.4 (CH); 130.3, 135.5, 149.8, 173.4 (C). HR-MALDI-MS: 326.1360 (−0.92 ppm) ($C_{17}H_{21}NO_4Na^+$; calc. 326.1363). Anal. calc. for $C_{17}H_{21}NO_4$ (303.35): C 67.31, H 6.98, N 4.62; found: C 67.53, H 7.00, N 4.45.

*3-{1-[(*tert*-Butoxy)carbonyl]-1*H*-indol-3-yl}propionic Acid* (**7**). A stirred soln. of **6** (1.575 g, 5.192 mmol) in THF (15 ml) was diluted with H_2O (5 ml) and treated with $LiOH \cdot H_2O$ (500 mg, 11.916 mmol, 2.3 equiv.). After stirring at r.t. for 9 h, most of the THF was removed *in vacuo*, and the residue was acidified to pH 2–3 by

10% soln. of tartaric acid and extracted with CH_2Cl_2 (3×25 ml). Each org. phase was washed with H_2O (25 ml). The combined org. phases were dried ($MgSO_4$) and concentrated *in vacuo* to yield **7** (1.406 g, 94%) of colorless oil, which solidified while standing. Crude product was pure by ^{1}H-NMR spectrum and was used in the next reaction without further purification. FC (pentane/Et_2O/AcOH 2:1:0.02) and recrystallization from hexane/AcOEt of small sample yielded anal. pure **7**. White solid. M.p. 117°. IR ($CHCl_3$): 3008*w*, 2981*m*, 2932*w*, 1725*s*, 1475*w*, 1453*s*, 1371*s*, 1340*w*, 1309*w*, 1086*s*, 1043*w*, 1020*w* . ^{1}H-NMR (400 MHz, $CDCl_3$): 1.66 (*s*, *t*-Bu); 2.78 (*m*, CH_2); 3.04 (*m*, CH_2); 7.24 (*ddd*, $J = 1.1$, 7.3, 7.7, 1 arom. H); 7.32 (*ddd*, $J = 1.2$, 7.2, 8.3, 1 arom. H); 7.41 (*s*, 1 arom. H); 7.52 (*ddd*, $J = 0.7$, 1.3, 7.7, 1 arom. H); 8.11 (br. *d*, $J = 7.5$, arom. NCH). ^{13}C-NMR (100 MHz, $CDCl_3$): 20.1 (CH_2); 28.2 (Me); 33.6 (CH_2); 83.6 (C); 115.3, 118.7 (CH); 119.1 (C); 122.5, 122.6, 124.5 (CH), 130.2, 135.5, 149.8, 178.7 (C). HR-MALDI-MS: 312.1205 (−0.32 ppm) ($C_{16}H_{19}NO_4Na^+$; calc. 312.1206). Anal. calc. for $C_{16}H_{19}NO_4$ (289.33): C 66.42, H 6.62, N 4.84; found: C 66.39, H 6.59, N 4.84.

*(*S*)-3-(3-[1-[(*tert*-Butoxy)carbonyl]-1*H*-indol-3-yl]-1-oxopropyl)-4-isopropyloxazolidin-2-one* (**8a**). To a soln. of **7** (6.106 g, 21.104 mmol, 1.05 equiv.) in THF (100 ml), Et_3N (7.3 ml, 52.37 mmol, 2.6 equiv.) and pivaloyl chloride (2.60 ml, 21.13 mmol, 1.05 equiv.) were added at −30°. The resulting white suspension was stirred at −30° for 90 min; LiCl (980 mg, 23.12 mmol, 1.15 equiv.) and (*S*)-4-isopropyloxazolidin-2-one (2.596 g, 20.099 mmol, 1 equiv.) were added, and the mixture was allowed to warm slowly to r.t. over 11 h. The mixture was treated with sat. NH_4Cl (50 ml), diluted with H_2O (100 ml) and Et_2O (250 ml). The org. phase was separated, washed with 1M HCl (2×100 ml), 1M NaOH (2×100 ml), and brine (100 ml). Each H_2O phase was re-extracted with Et_2O (250 ml). Combined org. phases were dried ($MgSO_4$) and concentrated *in vacuo*. FC (pentane/Et_2O 2:1) yielded **8a** (6.675 g, 83%). White solid. M.p. 44°. $[\alpha]_D^{r.t.} = +48.0$ ($c = 0.9$, $CHCl_3$). IR ($CHCl_3$): 3032*w*, 2972*m*, 2877*w*, 1780*s*, 1724*s*, 1608*w*, 1486*w*, 1453*s*, 1387*s*, 1308*m*, 1086*s*, 1032*m*, 1019*m*. ^{1}H-NMR (400 MHz, $CDCl_3$): 0.85 (*d*, $J = 6.9$, Me); 0.91 (*d*, $J = 7.0$, Me); 1.66 (*s*, *t*-Bu); 2.31–2.43 (*m*, Me_2CH); 3.01–3.13 (*m*, CH_2); 3.29 (*ddd*, $J = 7.1$, 7.8, 17.0, 1 H, CH_2); 3.41 (*ddd*, $J = 6.8$, 8.4, 17.0, 1 H, CH_2); 4.20 (*dd*, $J = 3.3$, 9.1, 1 H, OCH_2); 4.25 (*dd*, $J = 8.1$, 9.1, 1 H, OCH_2); 4.44 (*ddd*, $J = 3.3$, 3.9, 8.1, NCH); 7.24 (*ddd*, $J = 1.1$, 7.2, 7.7, 1 arom. H); 7.28–7.33 (*m*, 1 arom. H); 7.42 (*s*, 1 arom. H); 7.58 (*ddd*, $J = 0.7$, 1.3, 7.7, 1 arom. H); 8.12 (br. *d*, $J =$ 7.8, arom. NCH). ^{13}C-NMR (100 MHz, $CDCl_3$): 14.7, 18.0 (Me); 19.8 (CH_2); 28.2 (Me); 28.4 (CH); 35.3 (CH_2); 58.5 (CH); 63.5 (CH_2); 83.4 (C); 115.2, 119.0 (CH); 119.4 (C); 122.4, 122.9, 124.3 (CH); 130.3, 135.8, 149.7, 154.1, 172.4 (C). HR-MALDI-MS: 423.1891 (+0.24 ppm) ($C_{22}H_{28}N_2O_5Na^+$; calc. 423.1890). Anal. calc. for $C_{22}H_{28}N_2O_5$ (400.47): C 65.98, H 7.05, N 7.00; found: C 65.97, H 7.07, N 7.15.

*(*S*)-3-(3-[1-[(*tert*-Butoxy)carbonyl]-1*H*-indol-3-yl]-1-oxopropyl)-4-isopropyl-5,5-diphenyloxazolidin-2-one* (**8b**). Analogously to the preparation of **8a**, **7** (308 mg, 1.064 mmol) and (*S*)-4-isopropyl-5,5-diphenyloxazolidin-2-one (285 mg, 1.013 mmol) were reacted. FC (pentane/Et_2O 8:1) yielded **8b** (459 mg, 82%). White solid. M.p. 78–80°. $[\alpha]_D^{r.t.} = -134.9$ ($c = 0.77$, $CHCl_3$). IR ($CHCl_3$): 3008*w*, 1781*s*, 1724*s*, 1494*w*, 1452*s*, 1371*s*, 1320*w*, 1087*m*, 1048*w*, 1019*w*, 991*w*, 859*w*. ^{1}H-NMR (500 MHz, $CDCl_3$): 0.75 (*d*, $J = 6.8$, Me); 0.87 (*d*, $J = 7.0$, Me); 1.65 (*s*, *t*-Bu); 1.94–2.01 (*m*, Me_2CH); 2.89–2.95 (*m*, 1 H, CH_2); 2.99–3.05 (*m*, 1 H, CH_2); 3.11 (*ddd*, $J =$ 5.8, 9.2, 16.4, 1 H, CH_2); 3.35 (*ddd*, $J = 6.1$, 9.5, 16.4, 1 H, CH_2); 5.40 (*d*, $J = 3.4$, NCH); 7.19–7.40 (*m*, 11 arom. H); 7.44–7.48 (*m*, 2 arom. H); 7.53 (*ddd*, $J = 0.7$, 1.2, 7.8, 1 arom. H); 8.1 (br. *d*, $J = 6.5$, arom. NCH). ^{13}C-NMR (125 MHz, $CDCl_3$): 16.4 (Me); 20.0 (CH_2); 21.7, 28.2 (Me); 29.9 (CH); 35.0 (CH_2); 64.6 (CH); 83.3, 89.5 (C); 115.2, 119.0 (CH); 119.3 (C); 122.4, 122.8, 124.3, 125.6, 125.9, 126.6, 128.0, 128.4, 128.6, 128.9 (CH); 130.3, 135.5, 138.1, 142.3, 149.7, 153.0, 172.3 (C). HR-MALDI-MS: 575.2522 (+1.04 ppm) ($C_{34}H_{36}N_2O_5Na^+$; calc. 575.2516). Anal. calc. for $C_{34}H_{36}N_2O_5$ (552.66): C 73.89, H 6.57, N 5.07; found: C 74.00, H 6.78, N 5.03.

*Benzyl (*R*)-3-({1-[(*tert*-Butoxy)carbonyl]-1*H*-indol-3-yl}methyl)-4-[(*S*)-4-isopropyl-2-oxooxazolidin-3-yl)-4-oxobutanoate* (**9a**). NaHMDS (2M in THF, 9.1 ml, 18.2 mmol, 1.1 mmol) was added to a cold (−78°) soln. of **8a** (6.646 g, 16.596 mmol) in THF (80 ml) over 18 min, and the mixture was stirred for an additional 50 min at −78°. A soln. of benzyl bromoacetate (5.3 ml, 33.45 mmol, 2 equiv.) in THF (5 ml) was added during 15 min, and the soln. was stirred for another 3 h at −78°, sat. NH_4Cl (50 ml) was added, and the mixture was warmed to r.t. and diluted with H_2O (100 ml) and Et_2O (250 ml). The org. phase was separated and washed with brine (100 ml). Each H_2O fraction was re-extracted with Et_2O (200 ml). Combined org. phases were dried ($MgSO_4$) and concentrated *in vacuo* to yield a yellowish solid, which was washed with pentane/Et_2O 3:1 ($3 \times$ 40 ml) to provide crude **9a** containing traces of unreacted benzyl bromoacetate, which were evaporated *in vacuo* with heating (100°). This procedure led to **9a** (6.965 g, 76%) with 1.7% (*w*/*w*) of bromoacetate. FC (pentane/Et_2O 3:1) yielded anal. pure **9a**. White solid. M.p. 141–142°. $[\alpha]_D^{r.t.} = +63.6$ ($c = 1.0$, $CHCl_3$). IR ($CHCl_3$): 3037*w*, 2970*w*, 1779*s*, 1730*s*, 1454*m*, 1385*s*, 1370*s*, 1309*m*, 1159*s*, 1085*m*, 1017*w*. ^{1}H-NMR (400 MHz, $CDCl_3$): 0.87 (*d*, $J = 2.0$, Me); 0.88 (*d*, $J = 2.2$, Me); 1.66 (*s*, *t*-Bu); 2.25–2.35 (*m*, Me_2CH); 2.50 (*dd*, $J = 4.3$, 17.1, 1 H, $C(O)CH_2$); 2.73 (*dd*, $J = 9.1$, 14.0, 1 H, indole-CH_2); 2.97 (*dd*, $J = 10.4$, 17.1, 1 H, $C(O)CH_2$); 3.16 (*ddd*, $J = 1.0$,

6.0, 14.0, 1 H, indole-CH_2); 4.01–4.06 (*m*, 1 H, OCH_2CH); 4.15 (*dd*, *J* = 2.7, 9.1, 1 H, OCH_2CH); 4.33 (*ddd*, *J* = 2.7, 3.7, 8.4, NCH); 4.59–4.68 (*m*, C(O)CH); ν_A = 5.02, ν_B = 5.06 (*AB*, *J* = 12.3, PhCH_2); 7.19–7.35 (*m*, 7 arom. H); 7.43 (*s*, 1 arom. H); 7.74 (*ddd*, *J* = 0.7, 1.3, 7.7, 1 arom. H); 8.11 (br. *d*, *J* = 8.0, arom. NCH). ^{13}C-NMR (100 MHz, $CDCl_3$): 14.5, 18.0 (Me); 27.3 (CH_2); 28.2 (CH); 28.2 (Me); 35.8 (CH_2); 39.7, 58.9 (CH); 63.2, 66.5 (CH_2); 83.6 (C); 115.1 (CH); 116.7 (C); 119.5, 122.7, 124.5, 124.5, 128.2, 128.2, 128.5 (CH); 130.1, 135.5, 135.7, 149.6, 153.6, 171.7, 175.0 (C). HR-MALDI-MS: 571.2421 (+1.05 ppm) ($C_{31}H_{36}N_2O_7Na^+$; calc. 571.2415). Anal. calc. for $C_{31}H_{36}N_2O_7$ (548.63): C 67.87, H 6.61, N 5.11; found: C 67.88, H 6.59, N 5.11.

*Benzyl (*R*)-3-({1-[(*tert*-Butoxy)carbonyl]-1*H*-indol-3-yl}methyl)-4-[(*S*)-4-isopropyl-5,5-diphenyl-2-oxooxazolidin-3-yl]-4-oxobutanoate* (**9b**). Analogously to the preparation of **9a**, **8b** (534 mg, 0.966 mmol) was reacted. FC (pentane/Et_2O 10:1 to 6:1) yielded **9b** (608 mg, 89%). White solid. M.p. 77–79°. $[\alpha]_D^{r.t.} = -102.9$ (*c* = 0.75, $CHCl_3$). IR ($CHCl_3$): 3036*m*, 2982*m*, 2933*m*, 1780*s*, 1727*s*, 1606*w*, 1494*w*, 1452*s*, 1370*s*, 1319*m*, 1085*s*, 1053*w*, 1019*w*, 1002*w*, 939*w*. ^{1}H-NMR (400 MHz, $CDCl_3$): 0.83 (*d*, *J* = 6.7, Me); 0.89 (*d*, *J* = 7.0, Me); 1.65 (*s*, *t*-Bu); 1.95–2.03 (*m*, Me_2CH); 2.29 (*dd*, *J* = 10.4, 14.2, 1 H, indole-CH_2); 2.39 (*dd*, *J* = 4.1, 17.2, 1 H, C(O)CH_2); 2.55 (*ddd*, *J* = 1.0, 4.8, 14.2, 1 H, indole-CH_2); 2.89 (*dd*, *J* = 10.7, 17.2, 1 H, C(O)CH_2); 4.51–4.61 (*m*, C(O)CH); ν_A = 4.99, ν_B = 5.06 (*AB*, *J* = 12.3, PhCH_2); 5.39 (*d*, *J* = 3.1, NCH); 7.16–7.47 (*m*, 18 arom. H); 7.62–7.65 (*m*, 1 arom. H); 8.06 (br. *d*, *J* = 7.8, arom. NCH). ^{13}C-NMR (100 MHz, $CDCl_3$): 16.1, 21.5 (Me); 26.7 (CH_2); 28.2 (Me); 30.0 (CH); 35.2 (CH_2); 39.3, 65.2 (CH); 66.5 (CH_2); 83.5, 89.5 (C); 115.1 (CH); 116.5 (C); 119.5, 122.7, 124.2, 124.4, 125.4, 125.9, 128.0, 128.2, 128.3, 128.4, 128.5, 128.6, 128.6, 128.8 (CH); 130.0, 135.4, 135.7, 138.0, 142.3, 149.5, 153.0, 171.7, 174.7 (C). HR-MALDI-MS: 723.3039 (−0.28 ppm) ($C_{43}H_{44}N_2O_7Na^+$; calc. 723.3041). Anal. calc. for $C_{43}H_{44}N_2O_7$ (700.83): C 73.69, H 6.33, N 4.00; found: C 73.70, H 6.54, N 3.92.

*(*R*)-3-({1-[(*tert*-Butoxy)carbonyl]-1*H*-indol-3-yl}methyl)-4-[(*S*)-4-isopropyl-2-oxooxazolidin-3-yl]-4-oxobutyric Acid* (**10**). The soln. of **9a** (6.436 g, 11.731 mmol) in THF (130 ml) was stirred under H_2 (1 atm., ballon) in the presence of 10% Pd/C (510 mg) for 4 h. Pd/C was filtered off, washed with THF, and filtrate was concentrated *in vacuo* to yield an oil. Et_2O was added and evaporated *in vacuo* to yield **10** (5.838 g, quant.; pure by ^{1}H-NMR) as a white solid. An anal. sample was obtained by recrystallization from cyclohexane/AcOEt. M.p. 144–145°. IR ($CHCl_3$): 2974*m*, 1779*s*, 1726*s*, 1453*s*, 1386*s*, 1360*s*, 1308*m*, 1158*s*, 1085*m*, 1057*w*, 1018*w*, 984*w*, 946*w*. ^{1}H-NMR (400 MHz, $CDCl_3$): 0.85 (*d*, *J* = 6.9, Me); 0.88 (*d*, *J* = 7.0, Me); 1.66 (*s*, *t*-Bu); 2.29–2.38 (*m*, Me_2CH); 2.46 (*dd*, *J* = 3.9, 17.8, 1 H, C(O)CH_2); 2.70 (*dd*, *J* = 9.7, 14.0, 1 H, indole-CH_2); 2.96 (*dd*, *J* = 11.0, 17.8, 1 H, C(O)CH_2); 3.13–3.18 (*m*, 1 H, indole-CH_2); 4.05 (*t*, *J* = 8.8, 1 H, CH_2O); 4.16 (*dd*, *J* = 2.7, 9.0, 1 H, CH_2O); 4.33 (*m*, NCH); 4.53–4.61 (*m*, C(O)CH); 7.22–7.27 (*m*, 1 arom. H); 7.28–7.33 (*m*, 1 arom. H); 7.44 (*s*, 1 arom. H); 7.73–7.76 (*m*, 1 arom. H); 8.11 (br. *d*, *J* = 7.6, arom. NCH). ^{13}C-NMR (100 MHz, $CDCl_3$): 14.1, 17.9 (Me); 27.3 (CH_2); 27.9 (CH); 28.2 (Me); 35.3 (CH_2); 39.3, 58.8 (CH); 63.1 (CH_2); 83.7 (C); 115.2 (CH); 116.4 (C); 119.4, 122.7, 124.5, 124.5 (CH); 130.1, 135.5, 149.6, 153.6, 175.6, 177.6 (C). HR-MALDI-MS: 481.1943 (−0.42 ppm) ($C_{24}H_{30}N_2O_7Na^+$; calc. 481.1945). Anal. calc. for $C_{24}H_{30}N_2O_7$ (458.50): C 62.87, H 6.59, N 6.11; found: C 62.84, H 6.60, N 6.14.

*(*R*)-3-({(3*R*/*S*)-1-[(*tert*-Butoxy)carbonyl]-2,3-dihydro-1*H*-indol-3-yl}methyl)-4-[(*S*)-4-isopropyl-2-oxooxazolidin-3-yl]-4-oxobutyric Acid* (**11**). The soln. of **9a** (1.116 g, 2.034 mmol) in MeOH (20 ml) and THF (20 ml) was stirred under H_2 (1 atm, balloon) in the presence of 10% Pd/C (113 mg) at 0° to r.t. for 13 h. Pd/C was filtered off, washed with THF and MeOH, and concentrated *in vacuo*. FC (pentane/Et_2O/AcOH 200:100:1) yielded **11** (787 mg, 84%) as a mixture of epimers. White solid. ^{13}C-NMR (100 MHz, $CDCl_3$): 14.2, 14.3, 17.9, 18.0 (Me); 27.9, 28.0 (CH); 28.4, 28.5 (Me); 36.6 (CH); 37.0, 43.3, 52.6, 54.2 (CH_2); 58.7, 58.8 (CH); 63.0, 63.1, 64.3 (CH_2); 81 (C); 114.7, 114.8, 122.1, 122.3, 124.1, 128.0, 128.1, 128.2, 129.0 (CH); 134, 143, 152.5, 153.4, 153.5, 174.9, 175.1, 177.0 (C). HR-MALDI-MS: 483.2095 (−1.45 ppm) ($C_{24}H_{32}N_2O_7Na^+$; calc. 483.2102). Anal. calc. for $C_{24}H_{32}N_2O_7$ (460.52): C 62.59, H 7.00, N 6.08; found: C 62.55, H 7.01, N 5.91.

*(*S*)-3-[(2*R*)-2-({[(Benzyloxy)carbonyl]amino}methyl)-3-{1-[(*tert*-butoxy)carbonyl]indol-3-yl}-1-oxopropyl]-4-isopropyloxazolidin-2-one* (**12**). *a*) To a stirred soln. of **11** (419 mg, 0.913 mmol) in toluene (5 ml), Et_3N (0.25 ml, 1.79 mmol, 2 equiv.), diphenylphosphoryl azide ($(PhO)_2P(O)N_3$; 0.24 ml, 1.114 mmol, 1.2 equiv.), and BnOH (0.19 ml, 1.84 mmol, 2 equiv.) were added, and the mixture was stirred for 1 h at r.t., followed by refluxing for additional 1 h. Toluene was evaporated *in vacuo*, the residue was dissolved in Et_2O (30 ml) and 2M HCl (20 ml). The org. phase was separated, washed with sat. $NaHCO_3$, dried ($MgSO_4$), and concentrated *in vacuo*. FC (CH_2Cl_2/Et_2O 50:1) yielded **12** (380 mg, 74%).

b) To a stirred soln. of the epimeric acids **11** (596 mg, 1.294 mmol) in toluene (6 ml), Et_3N (0.36 ml, 2.58 mmol, 2 equiv.), $(PhO)_2P(O)N_3$ (0.33 ml, 1.53 mmol, 1.2 equiv.), and BnOH (0.27 ml, 2.61 mmol, 2 equiv.) were added, and the mixture was stirred for 1 h at r.t., followed by refluxing for an additional 1 h. Toluene was evaporated *in vacuo*, and the residue was dissolved in Et_2O (30 ml) and 2M HCl (20 ml). The org. phase was separated, washed with sat. $NaHCO_3$, dried ($MgSO_4$), and concentrated *in vacuo* to yield 860 mg of yellow oil.

FC (CH_2Cl_2/Et_2O 50:1 to 25:1) yielded (*S*)-3-((2*R*)-2-{[(Benzyloxycarbonyl)amino]methyl}-3-{1-[(*tert*-butoxy)carbonyl]-2,3-dihydroindol-3-yl}-1-oxopropyl)-4-isopropyloxazolidin-2-one (493 mg, 67%). HR-MALDI-MS: 588.2681 (+0.17 ppm) ($C_{31}H_{39}N_3O_7Na^+$; calc. 588.2680). This product was dissolved in CH_2Cl_2 (6 ml), and DDQ (207 mg, 0.912 mmol, 1.05 equiv.) was added in 3 portions over 5 min. A black mixture formed and was stirred at r.t. for 1 h, filtered, and concentrated *in vacuo*. FC (CH_2Cl_2/Et_2O 50:1) yielded **12** (276 mg, 38% over two steps). M.p. 83–84°. $[\alpha]_D^{r.t.} = +45.5$ ($c = 0.96$, $CHCl_3$). IR ($CHCl_3$): 3449*w*, 3032*w*, 2975*w*, 1778*s*, 1724*s*, 1608*w*, 1514*m*, 1453*s*, 1386*s*, 1371*s*, 1302*m*, 1157*s*, 1087*m*, 1017*w*. ^{1}H-NMR (500 MHz, $CDCl_3$): 0.79 (*d*, *J* = 6.9, Me); 0.86 (*d*, *J* = 7.0, Me); 1.66 (*s*, *t*-Bu); 2.25–2.33 (*m*, Me_2CH); 2.87–2.95 (*m*, 1 H, indole-CH_2); 3.14 (*dd*, *J* = 8.1, 14.3, 1 H, indole-CH_2); 3.50–3.62 (*m*, NCH_2); 3.91–3.95 (*m*, 1 H, OCH_2CH); 4.09 (*dd*, *J* = 2.4, 9.0, 1 H, OCH_2CH); 4.23–4.26 (*m*, NCH); 4.43–4.46 (*m*, C(O)CH); $\nu_A = 5.06$, $\nu_B = 5.09$ (*AB*, *J* = 12.3, $PhCH_2$); 5.11–5.15 (*m*, NH); 7.20–7.32 (*m*, 7 arom. H); 7.42 (*s*, 1 arom. H); 7.55 (*d*, *J* = 7.6, 1 arom. H); 8.11 (br. *d*, *J* = 7.4, arom. NCH). ^{13}C-NMR (125 MHz, $CDCl_3$): 14.6, 18.0 (Me); 25.2 (CH_2); 28.2 (Me); 28.5 (CH); 43.0 (CH_2); 43.5, 58.9 (CH); 63.4, 66.8 (CH_2); 83.6 (C); 115.2 (CH); 116.8 (C); 119.0, 122.6, 124.1, 124.5, 128.1, 128.5 (CH); 130.2, 135.4, 136.5, 149.6, 153.8, 156.3, 174.3 (C). HR-MALDI-MS: 586.2525 (+0.17 ppm) ($C_{31}H_{37}N_3O_7Na^+$; calc. 586.2524).

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