Synthesis of 1-(*m*-Hydroxybenzyl)-Substituted 1,2,3,4-Tetrahydroisoquinoline-3-carboxylic Acid Derivatives as Opioid Peptide Mimetics − Unexpected Amide Bond Cleavages under Mild Conditions

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N-Glycyl-(1*R*,3*S*)-1-(*m*-hydroxybenzyl)-1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid (Tic) was prepared as a Tyr-Tic dipeptide mimetic for exploration of its potential as a delta opioid receptor selective ligand. The compound was successfully obtained by a stereoselective synthesis starting from L-Tic. In the course of the reactions, unusual peptide bond cleavages were observed under mild conditions, and reaction mechanisms have been proposed.

Introduction

The development of peptide mimetics starting from the structure of a bioactive peptide remains a considerable challenge. In the past decade, delta opioid receptor antagonists have attracted much attention because of their potential to suppress the addiction and tolerance associated with the use of mu opioid agonists such as morphine as analgesics.[1] Non-peptide delta antagonists such as naltrindole (NTI) as well as peptide antagonists have been reported. In the prototype Tyr-Tic-Phe-Phe-OH peptide antagonist sequence, the antagonism has been shown to be due to the cyclic, and therefore conformationally restricted, nature of the Tic (1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid) residue. Several pharmacophoric models have been proposed, based on comparison of the calculated low-energy conformations of the flexible peptide with the rigid structure of NTI.[2,3,4] There is general agreement about the importance of the relative orientation of three pharmacophores: the *N*-terminal amine, the Tyr[1] phenolic ring, and the Tic[2] aromatic ring. The model for the bioactive conformation of the Tyr-Tic-Phe-OH (TIP) tripeptide proposed by Wilkes[2] shows a close proximity of the Tyr[1] phenolic ring and the saturated ring of the tetrahydroisoquinoline ring. This observation led us to the design of *N*-glycyl-1-(*m*-hydroxybenzyl)-1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid (**2**) as a mimetic for the Tyr-Tic dipeptide **1** (Figure 1).

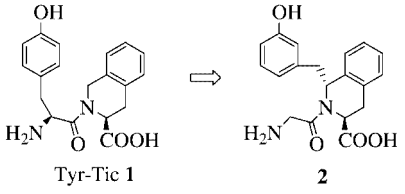
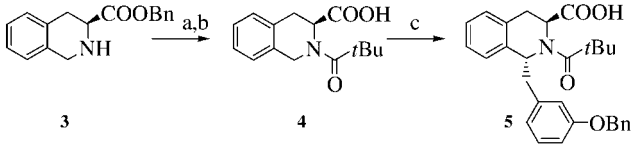


Figure 1. Design of a new Tyr-Tic dipeptide mimetic **2**

Results and Discussion

The 1-substituted (1*R*,3*S*)-stereoconfigured 1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid derivative was stereoselectively prepared as depicted in Scheme 1.[5]



Scheme 1. **5** (a) *t*BuCOCl, Et_3N (98%); (b) H_2, Pd/C (99%); (c) *t*BuLi, −78 °C, 3-benzyloxybenzyl bromide (80−84%)

(*S*)-2-Pivaloyl-Tic **4** was prepared from enantiomerically pure (*S*)-Tic-OBn,[6] followed by hydrogenolysis as described by Seebach.[5] Direct pivaloyl protection of unprotected (*S*)-Tic to provide **4** was tried, but failed. 2-Pivaloyl-Tic **4** was subsequently stereoselectively alkylated[5] by use of *t*BuLi and *m*-benzyloxybenzyl bromide[7] in THF at −78 °C to give (1*R*,3*S*)-1-(*m*-benzyloxybenzyl)-2-pivaloyl-Tic **5** in good yields (80−84%). The reaction needed 3 days for

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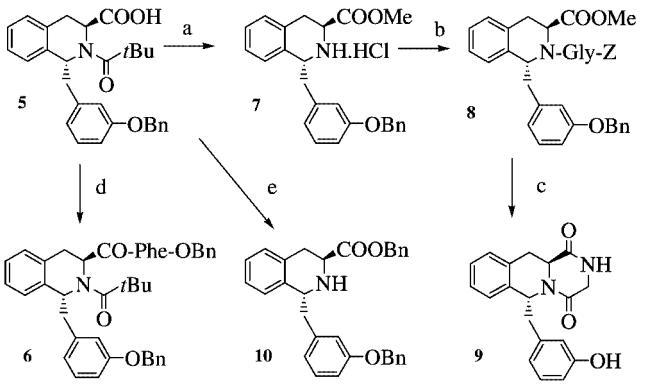
completion at −78 °C. The reaction time could be decreased to 1 h by addition of 2 equiv. of 1,3-dimethyl-3,4,5,6-tetrahydro-2(1H)-pyrimidinone (DMPU), but the yield then dropped to 40−62%.

The stereochemical outcome of the alkylation reaction was confirmed after coupling of Phe-OBn to **5** with *O*-(benzotriazol-1-yl)-1,1,3,3-tetramethyluronium tetrafluoroborate (TBTU) as coupling reagent (Scheme 2). Crystallization by vapor diffusion from ethyl acetate/petroleum ether gave single crystals of **6** suitable for X-ray diffraction analysis. The determined X-ray structure confirmed the (1*R*,3*S*) stereochemistry (Figure 2).

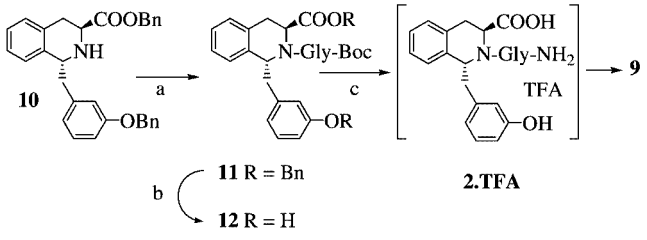


Scheme 2. (a) MeOH, HCl(g), 0 °C (90%); (b) Z-Gly-OH, EDC (97%); (c) H_2, Pd/C (95%); (d) Phe-OBn, TBTU, NMM (94%); (e) BnOH, pTosOH, benzene reflux, then $NaHCO_3$ (99%)

Removal of the pivaloyl group of (1*R*,3*S*)-1-(*m*-benzyloxybenzyl)-2-pivaloyl-Tic **5** was unexpectedly easy. Stirring of the compound in HCl(g)-saturated MeOH at room temperature resulted in a mixture of (1*R*,3*S*)-1-(*m*-benzyloxybenzyl)Tic-OMe **7** and (1*R*,3*S*)-1-(*m*-hydroxybenzyl)Tic-OMe in 57% and 25% yields, respectively. When the cleavage reaction was performed at 0 °C for 21 h, pure (1*R*,3*S*)-1-(*m*-benzyloxybenzyl)Tic-OMe **7** was obtained as its HCl salt in 70 to 90% yield (Scheme 2). These mild cleavage conditions are remarkable, since Seebach reported difficult pivalamide cleavages of 2-pivaloyl-1,2,3,4-tetrahydroisoquinolines.[5,8]

Coupling of benzyloxycarbonyl-protected glycine (Z-Gly) to (1*R*,3*S*)-1-(*m*-benzyloxybenzyl)Tic-OMe **7** failed when TBTU or benzotriazol-1-yloxytris(dimethylamino)phosphonium hexafluorophosphate (BOP) were used as coupling reagents, but was successful when *N*-ethyl-*N*′-(3-dimethylaminopropyl)carbodiimide (EDC) in dichloromethane was used. The glycine-coupled compound **8** was prepared in yields of 86 to 97% after purification by flash column chromatography. Removal of the benzyl ether and the benzyloxycarbonyl groups by hydrogenolysis resulted in immediate cyclization to diketopiperazine **9**.

An alternative pathway (Scheme 3), making use of the mild simultaneous pivaloyl deprotection and benzyl ester formation to **10** catalyzed by *p*-toluenesulfonic acid (Scheme 2), followed by coupling of Boc-Gly to give **11** and subsequent hydrogenolysis to **12**, indicated that after Boc-deprotection, lactamization to **9** by attack of the amine onto the free carboxylic acid in **2** occurred on standing.



Scheme 3. (a) Boc-Gly-OH, EDC (60%); (b) H_2, Pd/C (92%); (c) TFA, H_2O (99%)

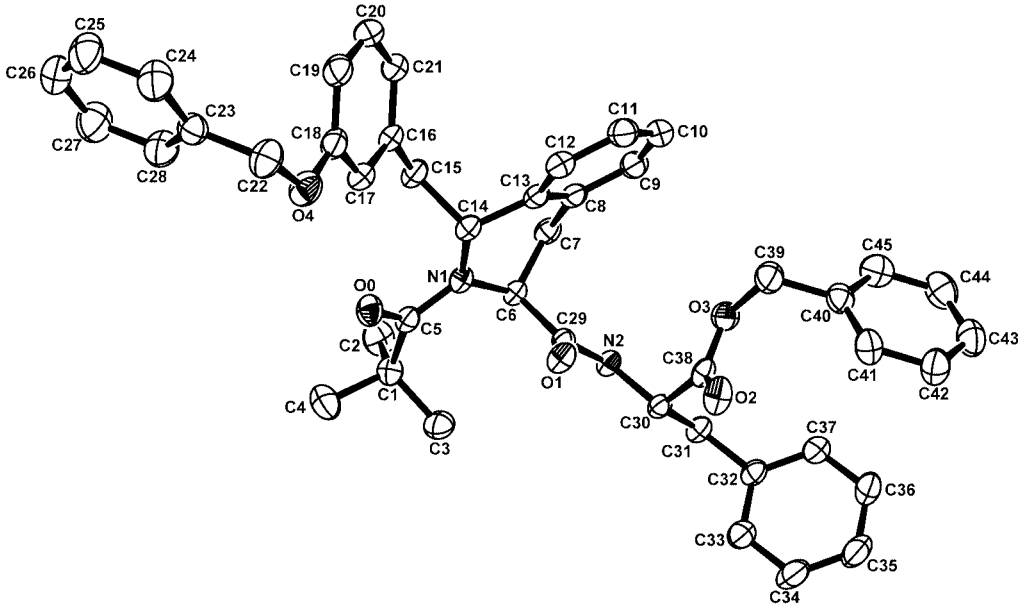
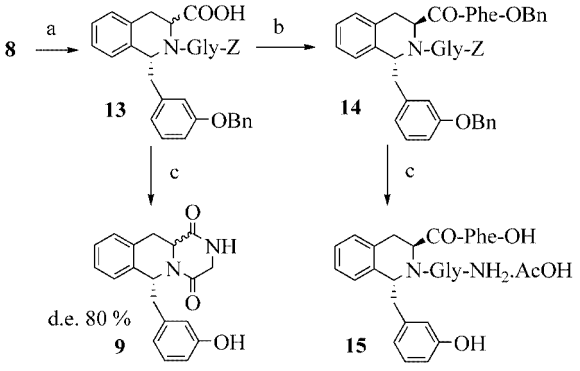


Figure 2. X-ray diffraction structure of (**6**) with numbering of the atoms; thermal ellipsoids are traced at the 30% probability level

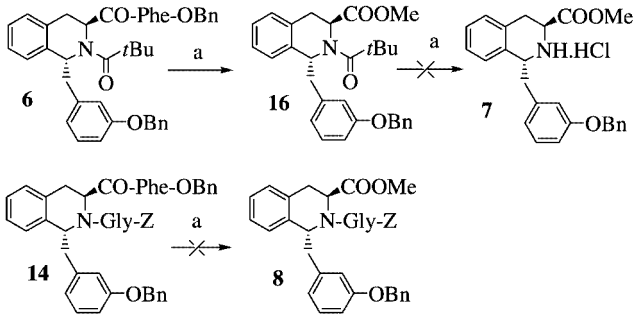
The dipeptide mimetic **2** could not therefore be obtained for biological testing.

We therefore focussed our attention on the tripeptide mimetic **15**, containing an additional *C*-terminal phenylalanine. (Scheme 4). Saponification of the methyl ester in **8** resulted in partial epimerization of the α-C atom independently of the conditions used: 1.1 equiv. of KOH in EtOH/water at room temperature for 6 days, 1.5 equiv. of KOSiMe$_3$ in Et$_2$O at room temperature for 30 min,[9] or 1.5 equiv. of *n*Bu$_4$NOH in THF at 0 °C for 50 min.[10] LC/MS analysis after coupling of Phe-OBn with TBTU and NMM in DMF showed a diastereomeric ratio of 9:1 in which the major isomer was the (1*R*,3*S*)-stereoconfigured Z-Gly-1-(*m*-benzyloxybenzyl)Tic-Phe-OBn **14**. This was verified by transformation of the epimeric mixture of **13** into the diketopiperazine **9**. The major isomer was identical to the one formed from ester **8** (Scheme 2). Crystallization of the mixture of diastereomers obtained after the coupling of Phe-OBn to **13** yielded 70% of the pure Z-Gly-[(1*R*,3*S*)-1-(*m*-benzyloxybenzyl)Tic]-Phe-OBn **14**. Subsequent hydrogenolysis afforded the tripeptide mimetic Gly-[(1*R*,3*S*)-1-(*m*-hydroxybenzyl)Tic]-Phe **15** in 45% yield after column chromatography.

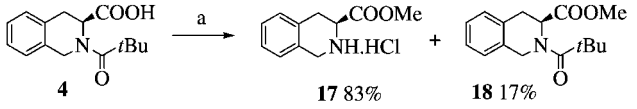


Scheme 4. (a) saponification (84−94%); (b) Phe-OBn, TBTU, *N*-methylmorpholine, then crystallization (70%); (c) H$_2$, Pd/C, AcOH (45%)

To avoid the saponification step, which causes epimerization, and to exploit the anticipated mild cleavage of the pivaloyl group, a more convergent pathway starting from **6** was proposed (Scheme 5). Treatment of **6** in HCl-saturated methanol, however, did not result in the selective cleavage of the pivaloyl-Tic amide bond, but the Tic-Phe amide bond was rather unexpectedly cleaved to yield **16**. Moreover, prolonged treatment of this ester also did not result in the removal of the pivaloyl group to give **7**. To investigate the nature of these amide bond cleavages in more detail, other test reactions were performed. In the case of Z-Gly-(1*R*,3*S*)-1-(*m*-benzyloxybenzyl)Tic-Phe-OBn **14**, no cleavage of the Tic-Phe amide bond was observed under these conditions. Similarly, in Z-Gly-(1*R*,3*S*)-1-(*m*-benzyloxybenzyl)Tic-OH **13**, no cleavage of the Gly-Tic amide bond was observed, indicating a role of the pivaloyl group in both cases. A minor influence of the 1-(*m*-benzyloxybenzyl) substituent was indicated by partial cleavage in 2-pivaloyl-Tic-OH **4** (Scheme 6).



Scheme 5. (a) MeOH, HCl(g), 0 °C



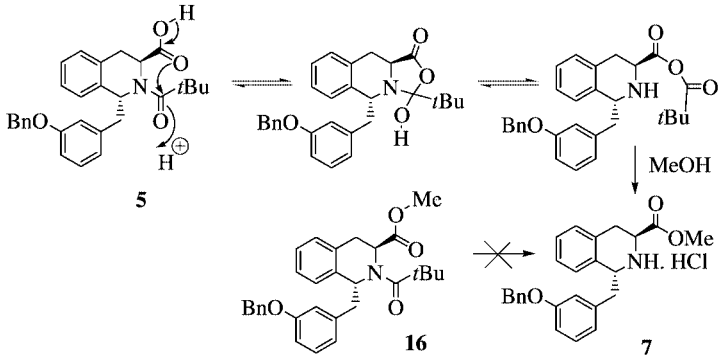
Scheme 6. (a) MeOH, HCl(g), 0 °C

These observations cannot be ascribed to a twisted amide bond involving the pivaloyl group. Indeed the X-ray data of **6** reveal a normal geometry for the Tic-Phe amide bond (which is cleaved) and a slightly distorted pivaloyl-Tic amide bond with a torsion angle of −19.3°and a CO−N bond length (1.372 Å) slightly longer than a typical amide bond (1.346 Å).[11] Moreover, the ^{13}C NMR chemical shift of the pivaloyl carbonyl in 2-pivaloyl-Tic-OH **4** is 177.8 ppm, and in the corresponding 1-(*m*-benzyloxybenzyl) substituted compound **5** it is 178.9 ppm, revealing very little change in resonance overlap.

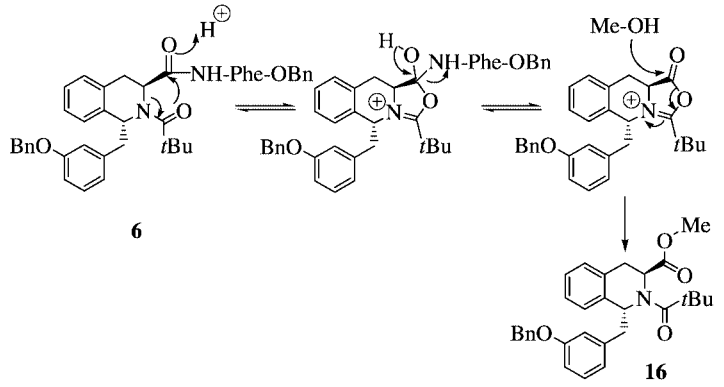
These observations can be explained by assuming a mechanism involving intramolecular formation of a tetrahedral intermediate, as demonstrated for acylated *N*-methyl-α-aminoisobutyryl residues by Goodman.[12] (Scheme 7)

In (1*R*,3*S*)-1-(*m*-benzyloxybenzyl)-2-pivaloyl-Tic **5**, the pivaloyl carbonyl experiences an acid-catalyzed nucleophilic addition reaction by the oxygen of the 3-carboxylic acid, producing an oxazolidinone intermediate. This rearranges with cleavage of the pivaloyl−Tic amide bond to a mixed anhydride, which is converted into the methyl ester. This mechanism is consistent with the fact that the methyl ester **16** is stable under these reaction conditions. In the case of **6**, it is the pivaloyl carbonyl oxygen that attacks the carbonyl carbon atom of the Tic residue, creating a cyclic oxazolinium/oxazolidinium ion intermediate that loses Phe-OBn and that subsequently opens by attack of a solvent molecule (Scheme 8).

The target compound **15** was tested for its ability to displace [^{3}H]Ile^{5,6}deltorphin II as a delta opioid selective ligand in rat brain homogenates, but displays very weak affinity (IC_{50} = 17 μM).[13] The signal transduction properties of **15** were evaluated by DPDPE-receptor-activated [^{35}S]GTPγS binding to cloned human delta receptors in C6 glioma cells, and indicated that **15** was a weak delta opioid



Scheme 7. Proposal for the mechanism involved in the cleavage of the pivaloyl−Tic amide bond



Scheme 8. Proposal for the mechanism involved in the cleavage of the Tic−Phe amide bond

antagonist (Kb = 1.3 μm).[14] The in vivo analgesic effect was tested in the tail withdrawal test after intrathecal injection in rats. At a dose of 40 μg per rat, full analgesia was reached at 15 min after injection, and lasted for more than 2 h. In comparison to intrathecally administered morphine, compound **15** is about six times less potent.[14]

Conclusion

A convenient stereoselective method has been developed for the synthesis of the tripeptide mimetic Gly-(1*R*,3*S*)-1-(*m*-hydroxybenzyl)Tic-Phe-OH **15**, starting from 2-pivaloyl-L-Tic **4**. The key step in the pathway was the stereoselective alkylation of *2*-pivaloyl-Tic **4** to yield the *trans*- or (1*R*,3*S*)-configured 1-(*m*-benzyloxybenzyl)-2-pivaloyl-Tic derivative **5**. Confirmation of the stereoselectivity of the reaction was obtained by the X-ray structure after coupling of Phe-OBn to **10** to give **6**. The pivalamide bond of (1*R*,3*S*)-1-(*m*-benzyloxybenzyl)-2-pivaloyl-Tic **5** was cleaved under surprisingly mild acidolytic conditions. In contrast, the pivaloyl group of (1*R*,3*S*)-1-(*m*-benzyloxybenzyl)-2-pivaloyl-Tic-Phe-OBn **6** was not cleaved under these mild conditions but rather cleavage of the Tic-Phe peptide bond was observed. These cleavages under unusually mild conditions could be explained by an acid-catalyzed intramolecular nucleophilic addition of a carbonyl oxygen to the adjacent carbonyl carbon. The tripeptide mimetic **15** was shown to have weak delta opioid affinity and antagonist properties. Its in vivo analgesic potency is about six times less than that of morphine. These data indicate that the peptide mimetic effectively interacts with the target receptor. However the orientation of the pharmacophoric groups is not optimal. Further modifications based on this design principle are currently under investigation.

Experimental Section

General Methods: Unless stated otherwise, solvents and reagents were used as supplied. Ethanol and methanol were dried by distillation from magnesium and stored over activated 3 Å molecular sieves (10 wt%). THF was heated at reflux with 0.1% w/v $LiAlH_4$ for 24 h, distilled over sodium wire, and distilled again just before use. DMF was distilled from benzene-1,2,4-tricarboxylic anhydride and stored over activated molecular sieves. Diethyl ether and benzene were shaken with $CaCl_2$ (5−10% w/v) before being dried on sodium wire. DMSO was purified and dried by distillation and over activated molecular sieves (5% w/v). Triethylamine was distilled from CaH_2 and stored over KOH pellets. Dichloromethane was heated at reflux with CaH_2 (5% w/v) and distilled onto activated molecular sieves.

Flash column chromatography was performed on Merck Kieselgel 60 (0.040−0.063 mm). TLC was performed on precoated polyethylene-backed silica plates (Merck Kieselgel 60 F_{254}) with viewing by UV light or by use of iodine. Mass spectra were recorded on a VG Quattro II spectrometer (ESP ionization, cone voltage 70 V, capillary voltage 3.5 kV, source temperature 80 °C). Data collection was done with the aid of Masslynx software. Exact mass measurements

(EMM) were recorded al low resolution by electrospray ionization with PEG-Na or PEG-Me as standard.[15] RP-HPLC analyses were performed on a Spectra-Physics P-4000 analytical system. A Vydac 218TP54RP column (C_{18}, 5 μm, d = 0.46 cm, l = 25 cm) was used with a flow rate of 1 mL/min. and a gradient going from 100% water containing 0.1% TFA to a water/CH_3CN mixture (80:20) containing 0.1% TFA in 30 min, followed by 10 min isocratic run under these conditions. UV detection was performed at 215 nm. ^{1}H NMR and ^{13}C NMR spectra were recorded at 25 °C on a Bruker Avance DRX 250 or AMX 500 spectrometer, with the residual isotopic solvent signal as internal standard. Chemical shifts (δ) are given in ppm, the coupling constants (J) in Hz. ^{1}H NMR signals were assigned by 2D COSY and NOESY. Melting points were determined on a Büchi B-540 melting point apparatus with a temperature gradient of 2 °C/min. Optical rotations (α_D) were measured on an automatic polarimeter (Optical Activity AA-5) at a wavelength of 289 nm with a cell length of 10 cm, concentration is in g/mL. In vitro δ-opioid receptor binding studies were performed on homogenized rat (Wistar) brain cells with use of Ile^{5,6}deltorphin II as δ-selective ligand, as described before.[13] Antagonist properties were determined in the GTPγS assay on human δ-receptor transfected C6 glioma cells, while the in vivo analgesia was determined in rats after intrathecal injection.[14]

(1*R*,3*S*)-1-(*m*-Benzyloxybenzyl)-2-pivaloyl-1,2,3,4-tetrahydroisoquinoline-3-carboxylic Acid (5): *t*BuLi (1.7 M solution in pentane, 7.8 mL, 11.49 mmol) was added under Ar atmosphere at −78 °C to a solution of L-2-pivaloyl- 1,2,3,4-tetrahydroisquinoline-3-carboxylic acid[5] (**4**, 1.50 g, 5.75 mmol) and DMPU (1.4 mL, 11.49 mmol) in anhydrous THF (40 mL). After the mixture had been stirred for 1.5 h, a solution of *m*-benzyloxybenzyl bromide[7] (3.18 g, 11.49 mmol, 2 equiv.) in dry THF (30 mL) was added and the mixture was left stirring for 1.5 h at −78 °C. (If no DMPU was added, the reaction took 3 days to complete.) The cooling was stopped, and the reaction mixture was poured into water (50 mL) and washed with Et_2O (3 × 40 mL). The water fraction was acidified to pH 2 with 1 N HCl_{aq} and extracted with Et_2O (3 × 50 mL). The combined Et_2O fractions were then dried ($MgSO_4$) and filtered, and the solvents were evaporated. Excess DMPU could be removed by redissolving the residue in water and extracting extensively with Et_2O. The compound was crystallized from EtOAc or Et_2O.

Yields varied from 1.05 to 1.58 g or 40 to 62% (with DMPU, 1 h) or 2.10 to 2.21 g or 80 to 84% (without DMPU, 3 days), white solid; m.p. 189.2−189.8 °C. $[\alpha]_D$ = −3.5 (c = 2, CH_2Cl_2). R_f (EtOAc/petroleum ether, 4:1 +1% AcOH) 0.43. HPLC: R_t = 28.4 min. MS (ES^+): 122, 269, 290, 310, 440, 458 [M + H$^+$]. EMM (m/z): [M + H$^+$] calcd. for $C_{29}H_{32}NO_4$, 458.2331; found, 458.2345. ^{1}H NMR ([D$_6$]DMSO): δ = 1.26 (s, 9 H, *t*Bu), 2.26 and 2.75−3.12 (m, 4 H, C-CH_2-Ar, Hβ and Hβ′), 4.88−4.95 (m, 3 H, N-CH and O-CH_2-Ph), 5.40 (m, 1 H, Hα), 6.15−6.24 (m, 2 H, H arom.), 6.76−6.83 (m, 2 H, H arom.), 7.06−7.17 (m, 4 H, H arom.), 7.33 (s, 5 H, H arom.) ppm. ^{13}C NMR ($CDCl_3$): δ = 28.1 (3 CH_3), 31.9 (CH_2), 42.0 (CH_2), 56.0 (CH), 57.9 (CH), 67.0 (C, *t*Bu), 70.0 (CH_2, OBn), 112.9 (CH, arom.), 116.9 (CH, arom.), 122.5 (CH, arom.), 126.2 (CH, arom.), 127.0 (CH, arom.), 127.4 (3 CH, arom.), 127.6 (2 CH, arom.), 128.3 (3 CH, arom.), 133.4 (C, arom.), 137.0 (C, arom.), 139.0 (C, arom.), 157.7 (C, arom.), 173.2 (C=O, carboxylic acid), 178.9 (C=O, pivaloyl) ppm.

Methyl (1*R*,3*S*)-1-(*m*-Benzyloxybenzyl)-1,2,3,4-tetrahydroisoquinoline-3-carboxylate Hydrochloride (7): A solution of (1*R*,3*S*)-1-(*m*-benzyloxybenzyl)-2-pivaloyl-1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid (**5**, 2.0 g, 4.38 mmol) in dry MeOH (120 mL) was cooled to 0 °C. Dry HCl gas was flushed through the mixture until the medium was saturated. The reaction mixture was stirred overnight at 0 °C, then again some HCl gas was flushed through it for final completion and the mixture was stirred for an additional 4 h. The solvent was evaporated. MeOH (40 mL) was added to the residue, and the solution was evaporated again. Finally, the residue was crystallized from EtOAc. Additional purification was not generally necessary but could be carried out by flash chromatography with cyclohexane/EtOAc (6:1 to 3:1) containing 1% Et_3N as eluent. Yields varied from 1.19 to 1.52 g or 70 to 90%, beige solid; m.p. the compound decomposed at 240 °C. R_f (EtOAc) 0.60; R_f (CH_3CN/MeOH/water, 4:1:1) 0.86. HPLC: R_t = 23.2 min. MS (ES^+): 388 [M + H$^+$]. EMM (m/z): [M + H$^+$] calcd. for $C_{25}H_{26}NO_3$, 388.1912; found, 388.1932. ^{1}H NMR ($CDCl_3$, free amine): δ = 2.54 (br. s, 1 H, NH), 2.89−3.10 (m, 4 H, Hβ, Hβ′, C-CH_2-Ar), 3.71 (s, 3 H, $COOCH_3$), 3.97 (dd, 1 H, J_1 = 5.8, J_2 = 13.7, Hα), 4.37 (dd, 1 H, J_1 = 3.7, J_2 = 10.6, N-CH), 5.06 (s, 2 H, Ph-CH_2-O), 6.87 (m, 3 H, H arom.), 7.16 (m, 5 H, H arom.), 7.20−7.46 (s, 5 H, H arom.). ^{13}C NMR ($CDCl_3$, the free amine): δ = 31.9 (CH_2), 43.1 (CH_2), 51.2 (CH), 52.1 (CH_3), 56.2 (CH), 70.1 (CH_2, OBn), 113.3 (CH, arom.), 116.1 (CH, arom.), 122.0 (CH, arom.), 126.1 (CH, arom.), 126.6 (CH, arom.), 126.8 (CH, arom.), 127.6 (2CH, arom.), 128.0 (CH, arom.), 128.6 (2CH, arom.), 129.2 (CH, arom.), 129.8 (CH, arom.), 133.1 (C, arom.), 137.2 (C, arom.), 137.7 (C, arom.), 140.5 (C, arom.), 159.2 (C-O, arom.), 173.5 (C=O) ppm.

Z-Gly-(1*R*,3*S*)-1-(*m*-benzyloxybenzyl)Tic-OMe (8): The HCl salt of methyl (1*R*,3*S*)-1-(*m*-benzyloxybenzyl)-1,2,3,4-tetrahydroisoquinoline-3-carboxylate (**7**, 0.92 g, 2.18 mmol) was washed with a saturated aqueous $NaHCO_3$ solution (100 mL) and extracted with EtOAc (3 × 50 mL). The collected organic fractions were dried ($MgSO_4$) and filtered, and the solvents were evaporated. The residue was dissolved in dichloromethane (5 mL), and Z-Gly-OH (0.68 g, 3.27 mmol) and EDC (0.63 g, 3.27 mmol) were added. The mixture was stirred overnight at room temp. and protected from daylight, as described.[16] After a reaction time of 1 night, additional Z-Gly-OH (0.09 g, 0.44 mmol) and EDC (0.08 g, 0.44 mmol) were added. The reaction was allowed to continue for another 3 to 4 days. When all starting material **7** had been consumed (TLC), the solvents were evaporated. The residue was dissolved in chloroform (40 mL) and extracted with HCl_{aq} (1 N, 3 × 40 mL), H_2O (40 mL), saturated $NaHCO_3$ solution (40 mL), and H_2O (40 mL). The organic phase was then dried and filtered, and the solvents were evaporated. Purification was carried out by flash chromatography, with eluents varying from cyclohexane through cyclohexane/EtOAc (4:1) to cyclohexane/EtOAc (2:1). Yields varied from 1.08 to 1.22 g or 86 to 97%, light yellow oil; R_f (cyclohexane/EtOAc, 4:1) 0.06; R_f (cyclohexane/EtOAc 2:1) 0.20. HPLC: R_t = 30.5 min. MS (ES^+): 388, 579 [M + H$^+$]. EMM (m/z): [M + H$^+$] calcd. for $C_{35}H_{35}N_2O_6$, 579.2495; found, 579.2502. ^{1}H NMR ($CDCl_3$) (500 MHz): compound **8** exists as a mixture of two conformational isomers in a ratio of 7:3. The NMR spectroscopic data on the minor isomer (if resolved) are given between square brackets. δ = 2.41 (dd, 1 H, J_1 = 4.5, J_2 = 16.0, Hβ), 3.00 (m, 3 H, Hβ′, C-CH_2-Ar), 3.48 [3.53] (s, 3 H, $COOCH_3$), 3.80 [4.06] (dd, 1 H, J_1 = 3.4, J_2 = 16.0, Hα of Gly), 4.18−4.25 (m, 1 H, Hα′ of Gly), 4.51 (m, 1 H, Hα of Tic), 4.87 [4.93] (s, 2 H, O-CH_2-Ph), 5.15 [5.13] (s, 2 H, Ph-CH_2-OCO), 5.44 [4.96] (dd, 1 H, J_1 = 3.6, J_2 = 7.2, N-CH-Ar of Tic), 5.99 [5.77] (1 H, b.s., NH), 6.30−6.60 (m, 2 H, H arom.), 6.70−6.85 (m, 2 H, H arom.), 7.00−7.40 (m, 14 H, H arom.) ppm. ^{13}C NMR ($CDCl_3$): δ = 31.4 [30.2] (CH_2,β), 42.8 [44.7] (CH_2), 43.5 (CH_2), 52.7 [52.2] (CHα), 55.2 [54.9] (CH_3), 58.2 [59.0] (CH), 66.9 (CH_2), 69.6 [69.8] (CH_2, OBn), 113.7 [114.3] (CH,

arom.), 116.0 [116.2] (CH, arom.), 122.7 [122.2] (CH, arom.), 126.9−129.5 (15 CH, arom.), 131.9 [131.8] (C, arom.), 136.9 [136.4] (C, arom.), 137.1−138.7 (3 C, arom.), 156.2 (C-O, arom.), 158.3 [158.7] (C=O),168.8 [169.0] (C=O), 170.9 [171.1] (C=O, methyl ester) ppm.

c[Gly-(1*R*,3*S*)-1-(*m*-Hydroxybenzyl)Tic] (9): Methyl Z-Gly-(1*R*,3*S*)-1-(*m*-benzyloxybenzyl)-1,2,3,4-tetrahydroisoquinoline-3-carboxylate (**8**, 0.20 g, 0.35 mmol) was dissolved in EtOH/water (3:1, 40 mL), and Pd/C (10%, 0.10 g) was added. The mixture was placed under 4 atm hydrogen pressure at room temp. for 4 h. After reaction the Pd catalyst was filtered through a layer of celite and rinsed with EtOH. The filtrate was evaporated, some water was added, and the mixture was lyophilized. Yield varied from 1.00 to 1.08 g or 85 to 95%, beige solid; m.p. 111.3−113.7 °C. R_f (acetonitrile/MeOH/water, 4:1:1) 0.78; R_f (EtOAc/MeOH, 9:1) 0.39. HPLC: R_t = 16.9 min. MS (ES^+): 113, 149, 167, 215, 323 [M + H^+]. EMM (*m*/*z*): [M + H^+] calcd. for $C_{19}H_{19}N_2O_3$, 323.1395; found, 323.1399. ^1H NMR ([D_6]DMSO): δ = 2.98−3.11 (m, 4 H, CH_2, Hβ and Hβ′), 3.64 (d, 1 H, Hα of Gly, *J* = 17.6), 3.90 (d, 1 H, Hα′ of Gly, *J* = 17.6), 4.26 (dd, 1 H, Hα, J_1 = 5.3, J_2=10.8), 5.75 (1 H, pseudo-t, *J* = 6.9, N-CH), 6.59 (m, 3 H, H arom.), 7.02 (t, 1 H, H arom., *J* = 7.5), 7.21 (m, 4 H, H arom.), 8.12 (br. s, 1 H, NH), 9.21 (br. s, 1 H, OH) ppm. ^{13}C NMR ([D_6]DMSO): δ = 32.2 (CH_2), 40.2 (CH_2), 43.8 (CH_2), 51.3 (CH), 52.5 (CH), 113.4 (CH, arom.), 116.2 (CH, arom.), 119.9 (CH, arom.), 126.2 (CH, arom.), 126.7 (CH, arom.), 127.1 (CH, arom.), 128.8 (CH, arom.), 128.9 (CH, arom.), 132.3 (C, arom.), 135.7 (C, arom.), 139.0 (C, arom.), 157.1 (C-O, arom.), 162.6 (C=O), 166.2 (C=O) ppm.

Z-Gly-(1*R*)-1-(*m*-benzyloxybenzyl)Tic-OH (13). Procedure 1: Z-Gly-(1*R*,3*S*)-1-(*m*-benzyloxybenzyl)Tic-OMe (**8**, 0.30 g, 0.52 mmol) was dissolved in EtOH/water (2:1, 54 mL). The temperature was lowered to 0 °C, and KOH (0.57 mL of a 1 N aqueous solution, 0.57 mmol) was added dropwise. The mixture was stirred at 0 °C for 1 h and was then allowed to warm to room temp. After 4 to 6 days of stirring, all starting material **8** had been consumed (TLC) and the reaction was quenched with a 10% aqueous acetic acid solution to an acidic pH. The ethanol was evaporated and the water phase was made basic again with a 6% aqueous $NaHCO_3$ solution. The solution was extracted with diethyl ether (30 mL). The water phase was acidified to a pH of 2 with concentrated HCl and again extracted with dichloromethane (3 × 40 mL). The organic phase was dried ($MgSO_4$) and filtered, and the solvents were evaporated. Yield varied from 2.46 to 2.75 or 84 to 94%, oil (mixture of epimers, major/minor = 9:1).

Procedure 2:[9] A solution of Z-Gly-(1*R*,3*S*)-1-(*m*-benzyloxybenzyl)Tic-OMe (**8**, 0.59 g, 1.02 mmol) in dry diethyl ether (60 mL) was placed under nitrogen gas atmosphere, and $KOSiMe_3$ (0.20 g, 1.53 mmol) was added. The mixture was stirred for 30 min at room temp. All starting material **8** had been consumed, but some diketopiperazine (DKP) formation had occurred (4 to 18%). Workup was performed as described in procedure 1 and additional column chromatography was needed for purification. Eluents were varied from cyclohexane/EtOAc (1:1) +1% AcOH until all DKP was washed off, to EtOAc +1% AcOH. Yield: 0.32 g or 55%, oil (mixture of epimers, major/minor = 9:1).

Procedure 3:[10] A solution of Z-Gly-(1*R*,3*S*)-1-(*m*-benzyloxybenzyl)Tic-OMe (**8**, 0.08 g, 0.13 mmol) in THF (3 mL) was cooled to 0 °C and nBu_4NOH_{aq} solution (40%, 0.213 mL, 0.33 mmol) was added dropwise, whereupon formation of a bright yellow color was observed. The mixture was stirred and the reaction was complete after 50 min. All starting material **8** had been consumed and less diketopiperazine formation was observed. The workup was performed as described in procedure 1. A mixture of epimers (major/minor = 9:1) was obtained; R_f (EtOAc/MeOH, 9:1) 0.12; R_f (EtOAc/MeOH, 9:1 + AcOH) 0.37. HPLC: R_t = −28.9 min. (major isomer), 29.0 min (minor isomer). MS (ES^-): 455, 563 [M − H^+]. EMM (*m*/*z*): [M + H^+] calcd. for $C_{34}H_{33}N_2O_6$, 565.2338; found, 565.2347

Z-Gly-(1*R*,3*S*)-1-(*m*-benzyloxybenzyl)Tic-Phe-OBn (14): A solution of Z-Gly-(1*R*)-1-(*m*-benzyloxybenzyl)Tic (**13**, 0.52 g, 0.92 mmol), Phe-OBn·*p*Tos-OH (0.59 g, 1.38 mmol), and TBTU (0.33 g, 1.01 mmol) in THF/acetonitrile (1:1, 8 mL) was cooled to −20 °C. NMM (1.0 mL, 9.20 mmol) was added and the mixture was stirred for 15 min at −20 °C. The mixture was then allowed to warm to room temp. and further stirred overnight. After 24 h all starting material had been consumed. The solvent was evaporated. The residue was dissolved in EtOAc (40 mL) and the solution was washed with HCl_{aq} (1 N, 3 × 30 mL), water (30 mL), saturated $NaHCO_3$ (3 × 30 mL), water (30 mL), and brine (30 mL). After drying ($MgSO_4$), filtration, and evaporation, the residue was crystallized from EtOH, which afforded the major single (1*R*,3*S*) isomer of Z-Gly-1-(*m*-benzyloxybenzyl)Tic-Phe-OBn **14**. Yield 0.52 g or 70%, white needles; m.p. 128.7−129.1 °C. R_f (EtOAc/cyclohexane, 1:1) 0.36. HPLC: R_t = 33.9 min. MS (ES^+): 547, 802 [M + H^+]. EMM (*m*/*z*): [M + H^+] calcd. for $C_{50}H_{48}N_3O_7$, 802.3492; found, 802.3469. ^1H NMR ($CDCl_3$): compound **14** exists as a mixture of two conformational isomers in a ratio of 3:1. The NMR spectroscopic data on the minor isomer (if resolved) are given between square brackets. δ = 2.51 (dd, 1 H, J_1 = 5.2, J_2 = 14.0, Hβ of Phe), 2.64 (dd, 1 H, J_1 = 5.5, J_2 = 15.3, Hβ of Tic or C-CH-Ar of Bn), 2.70-2.93 (m, 2 H, Hβ of Phe and Hβ of Tic or C-CH−Ar of Bn), 3.09−3.19 (m, 2 H, Hβ′ and C-CH′-Ar of Bn), 3.75 (m, 1 H, Hα of Gly), 4.06 [4.11] (m, 1 H, Hα′ of Gly), 4.45 [4.15] (m, 1 H, Hα/N-CH-Ar of Tic), 4.63 [4.70] (m, 1 H, Hα of Phe), 4.89−5.06 (4 H, m. $2CH_2$), 5.12 [5.33] (m, 2 H, CH_2), 5.30 (m, 1 H, Hα/N-CH-Ar of Tic), 5.50 [5.62] (br. s, 1 H, NH of Gly), 5.86 [6.0] (d, *J* = 8.1 Hz, 1 H, NH of Phe), 6.38−7.40 (m, 28 H, H arom.) ppm. ^{13}C NMR ($CDCl_3$): δ = 32.0 [30.9] (CH_2), 37.8 [38.3] (CH_2), 42.9 [43.6] (CH_2), 44.0 [45.1] (CH_2), 53.3 (CH), 57.4 [56.8] (CH), 58.7 [59.7] (CH), 67.4 [67.6] (CH_2), 67.9 (CH_2), 70.2 [70.4] (CH_2), 114.3 [114.6] (CH, arom.), 116.5 (CH, arom.), 123.1 [122.7] (CH, arom.), 127.2−130.2 (25 CH, arom.), 132.4 (C, arom.), 135.2 (2C, arom.), 135.4 (C, arom.), 137.0 (C, arom.), 137.6 (C, arom.), 139.2 (C, arom.), 156.8 (C-O, arom.), 159.0 [159.3] (C=O), 169.9 (C=O), 170.9 (C=O), 171.1 [171.4] (C=O) ppm.

Gly-(1*R*,3*S*)-1-(*m*-hydroxybenzyl)Tic-Phe-OH (15): Z-Gly-(1*R*,3*S*)-1-(*m*-benzyloxybenzyl)Tic-Phe-OBn (**14**, 0.16 g, 0.20 mmol) was dissolved in a mixture of dioxane/water (3:2, 50 mL), and acetic acid (0.011 mL, 0.20 mmol) was added, followed by Pd/C catalyst (10%, 0.08 g). This mixture was shaken in a Parr apparatus under 4 atm of hydrogen pressure at room temp. for 2 h. The catalyst was filtered through a layer of Celite and washed with dioxane and water, and all dioxane was evaporated off. The aqueous solution was then lyophilized. A small amount of diketopiperazine **9** was formed. The tripeptide mimetic **15** was purified by washing of the fraction over a small silica gel column with acetonitrile to remove the diketopiperazine **9** and then with acetonitrile/MeOH/acetic acid (9:1:1) and (5:1:1) to recover the tripeptide **15**. Yield 0.04 g or 45%, beige powder; R_f (EtOAc/MeOH/AcOH 9:1:1) 0.13. HPLC: R_t = 19.0 min. MS (ES^+): 166, 323, 388, 488 [M + H^+]. EMM (*m*/*z*): [M + H^+] calcd. for $C_{28}H_{30}N_3O_5$, 488.2185; found, 488.2181. NMR gave very broad peaks that were not identifiable.

(1*R*,3*S*)-1-(*m*-Benzyloxybenzyl)-2-pivaloyl-Tic-Phe-OBn (6): A solution of (1*R*,3*S*)-1-(*m*-benzyloxybenzyl)-2-pivaloyl-Tic (**5**, 0.50 g, 1.09 mmol), Phe-OBn·*p*TosOH (0.70 g, 1.63 mmol), and TBTU (0.39 g, 1.20 mmol) in dry THF (5 mL) was brought to −20 °C under nitrogen atmosphere. NMM (1.2 mL, 10.90 mmol) was added to the mixture and stirring at −20 °C was continued for 15 min. After the mixture had warmed to room temp. it was stirred for another 20 h. The solvent was evaporated and the residue was dissolved in chloroform (40 mL). The solution was washed with HCl_{aq} (1 N, 2 × 40 mL), aqueous $NaHCO_3$ solution (6%, 2 × 40 mL), and brine (40 mL). After drying, filtration, and evaporation, the residue was crystallized from EtOH. Yield 0.53 g or 70%, white needles; m.p. 128.2−128.7 °C. R_f (EtOAc/cyclohexane, 1:1) 0.55; R_f (EtOAc/cyclohexane, 1:4) 0.15. HPLC: R_t = 36.2 min. MS (ES^+): 288, 440, 695 [M + H^+]. EMM (*m*/*z*): [M + Na^+] calcd. for $C_{45}H_{46}N_2O_5Na$, 717.3304; found, 717.3319−^{1}H NMR ($CDCl_3$): δ = 1.27 (s, 9 H, *t*Bu), 2.40−2.60 (m, 2 H, Hβ and Hβ′ of Phe), 2.75 (m, 2 H, Hβ and C−CH−Ar of Bn), 3.15 (dd, 1 H, J_1 = 3.1, J_2 = 12.5, Hβ′ of Tic), 3.25 (dd, 1 H, J_1 = 2.8, J_2 = 15.3, C-CH′-Ar of Bn), 4.42 (m, 1 H, Hα of Phe), 4.89 (s, 2 H, CO-O-CH_2), 4.99 (m, 3 H, N-CH-Ar of Tic and O-CH_2-Ph), 5.34 (m, 1 H, Hα of Tic), 6.03 (br. s, 1 H, NH), 6.36−7.38 (m, 23 H, H arom.) ppm. ^{13}C NMR ($CDCl_3$): δ = 29.0 (3CH_3, *t*Bu), 33.1 (CH_2), 38.6 (CH_2), 40.8 (C, *t*Bu), 43.2 (CH_2), 54.0 (CH), 59.0 (CH), 59.7 (CH), 67.7 (CH_2), 70.4 (CH_2), 114.0 (CH, arom.), 116.8 (CH, arom.), 123.4 (CH, arom.), 127.6−129.5 (20 CH, arom.) 133.7 (C, arom.), 135.6 (C, arom.), 135.9 (C, arom.), 136.2 (C, arom.), 137.7 (C, arom.), 139.6 (C, arom.), 159.0 (C-O, arom.), 171.0 (C=O), 172.5 (C=O), 178.9 (C=O, piv.) ppm.

Benzyl (1*R*,3*S*)-1-(*m*-Benzyloxybenzyl)-1,2,3,4-tetrahydroisoquinoline-3-carboxylate (10): (1*R*,3*S*)-1-(*m*-Benzyloxybenzyl)-2-pivaloyl-1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid (**5**, 0.46 g, 1.0 mmol), benzyl alcohol (0.53 mL, 5.1 mmol), and *p*-toluenesulfonic acid monohydrate (0.23 g, 1.2 mmol) were heated at reflux in benzene solution (10 mL) for 5 h. The reaction solvents were evaporated. Water (30 mL) was added to the residue, and the solution was basified with a saturated $NaHCO_3$ solution to pH 9. The aqueous suspension was then extracted with diethyl ether (3 × 40 mL). The organic fractions were combined, dried ($MgSO_4$) and filtered, and the solvents were evaporated. A Kugelrohr distillation was performed (p = 0.15 mm, T = 50−70 °C) to distill all benzyl alcohol. The residue was pure **10**. Yield 0.47 g or quantitative, oil; R_f (EtOAc/cyclohexane, 1:1) 0.58. HPLC: R_t = 26.9 min. MS (ES^+): 145, 464 [M + H^+]. EMM (*m*/*z*): [M + H^+] calcd. for $C_{31}H_{30}NO_3$, 464.2225; found, 464.2210. The product was immediately used in the next reaction.

Boc-Gly-(1*R*,3*S*)-1-(*m*-Benzyloxybenzyl)Tic-OBn (11): A mixture of benzyl (1*R*,3*S*)-1-(*m*-benzyloxybenzyl)-1,2,3,4-tetrahydroisoquinoline-3-carboxylate (**10**, 0.46 g, 1.0 mmol), Boc-Gly (0.26 g, 1.5 mmol), and EDC (0.29 g, 1.5 mmol) in dichloromethane (4 mL) was stirred at room temp., with protection from daylight. After 1 night stirring, additional Boc-Gly (0.04 g) and 0.2 equiv. EDC (0.04 g) were added and the mixture was stirred for 2 more days. The solvent was evaporated and the residue was dissolved in chloroform (40 mL). This solution was then washed with HCl_{aq} (1 N, 40 mL), aqueous $NaHCO_3$ (6%, 40 mL) and brine (40 mL), dried ($MgSO_4$), and filtered, and the solvents were evaporated. Purification was carried out by flash chromatography with EtOAc/cyclohexane (1:6) as eluent. Yield 0.37 g or 60%, oil; R_f (EtOAc/cyclohexane 1:1) 0.57; R_f (EtOAc/cyclohexane 1:4) 0.16. HPLC: R_t = 34.3 min. MS (ES^+): 163, 179, 279, 335, 621 [M + H^+]. EMM (*m*/*z*): [M + H^+] calcd. for $C_{38}H_{41}N_2O_6$, 621.2964; found, 621.2973. ^{1}H NMR ($CDCl_3$) (500 MHz): compound **11** exists as a mixture of two conformational isomers in a 6:4 ratio. The NMR spectroscopic data on the minor isomer (if resolved) are given between square brackets. δ = 1.40 [1.39] (s, 9 H, *t*Bu), 2.36 [3.00] (m, 4 H, Hβ, Hβ′, C-CH_2-Ar of Bn), 3.75 (m, 1 H, Hα of Gly), 4.07 (m, 1 H, Hα′ of Gly), 4.48 [4.03] (m, 1 H, Hα/N-CH-Ar of Tic), 4.77−4.85 (m, 4 H, O-CH_2-Ph, CO-O-CH_2-Ph), 5.35 [4.88] (d, 1 H, J_1 = 3.4, J_2 = 7.3, Hα/ N−CH−Ar of Tic), 5.50 (br. s, 1 H, NH of Gly), 6.24−6.50 (m, 2 H, H arom.), 6.64−7.35 (m, 14 H, H arom.) ppm. ^{13}C NMR ($CDCl_3$): δ = 27.5 [30.8] (CH_2), 29.0 (3 CH_3), 32.2 [30.9] (CH_2), 43.5 [45.4] (CH_2), 55.9 [55.7] (CH), 58.9 [59.6] (CH), 68.0 [67.3] (CH_2), 70.3 [70.5] (CH_2), 80.3 (C, *t*Bu.), 114.4 [114.6] (CH, arom.), 116.7 (CH, arom.), 123.4 [122.9] (CH, arom.), 127.4−130.1 (15 CH, arom.), 132.4 (C, arom.), 135.5 (C, arom.), 136.2 (C, arom.), 137.7 (C, arom.), 139.4 (C, arom.), 156.3 (C-O, arom.), 159.0 [159.3] (C=O), 169.8 [170.1] (C=O), 171.0 [171.2] (C=O) ppm.

Boc-Gly-(1*R*,3*S*)-1-(*m*-hydroxybenzyl)Tic-OH (12): A solution of Boc-Gly-(1*R*,3*S*)-1-(*m*-benzyloxybenzyl)-Tic-OBn (**11**, 0.36 g, 0.58 mmol) in EtOH/water (3:1, 40 mL) with Pd/C catalyst (10%, 0.10 g) was shaken in a Parr apparatus under 4 atm hydrogen pressure at room temp. for 1 h. The catalyst was filtered through a layer of Celite and washed with ethanol and water, and all ethanol was evaporated off. The aqueous solution was then lyophilized. Yield 0.23 g or 92%, white powder; m.p. the compound decomposed at 183.6 °C. R_f (EtOAc/MeOH/AcOH, 9:1:1) 0.75; R_f (*n*BuOH/MeOH/AcOH, 4:1:1) 0.71. HPLC: R_t = 21.2 min. MS (ES^+): 130, 164, 186, 341, 385, 441 [M + H^+]. EMM (*m*/*z*): [M − H^+] calcd. for $C_{24}H_{27}N_2O_6$, 439.1869; found, 439.1883. ^{1}H NMR ([D_6]DMSO +2 drops D_2O): compound **12** exists as a mixture of two conformational isomers in a 4:1 ratio. The NMR spectroscopic data on the minor isomer (if resolved) are given between square brackets. δ = 1.38 (s, 9 H, *t*Bu), 2.48−3.09 (m, 4 H, Hβ, Hβ′, C-CH_2-Ar of Bn), 3.97 (m, 2 H, Hα and Hα′ of Gly), 4.42 [4.70] (m, 1 H, Hα of Tic), 5.19 [4.05] (m, 1 H, N-NH-Ar of Tic), 6.15−6.33 (m, 2 H, H arom.), 6.50−6.70 (m, 2 H, H arom), 6.87−7.12 (m, 4 H, H arom.) ppm. ^{13}C NMR ([D_6]DMSO +2 drops D_2O): δ = 30.2 (3 CH_3), 31.5 [30.0] (CH_2), 42.8 (2 CH_2), 55.9 [54.9] (CH), 57.7 (CH), 78.5 (C, *t*Bu.), 113.4 [113.8] (CH, arom.), 116.8 (CH, arom.), 120.8 (CH, arom.), 126.0 (CH, arom.), 126.9 (CH, arom.), 127.2 (CH, arom.), 127.7 (CH, arom.), 128.9 (CH, arom.), 133.8 [132.9] (C, arom.), 136.3 (C, arom.), 139.6 (C, arom.), 156.1 (C-O, arom.), 156.9 [157.2] (C=O), 169.8 [169.5] (C=O), 173.4 [172.9] (C=O) ppm.

Gly-(1*R*,3*S*)-1-(*m*-hydroxybenzyl)Tic TFA (2·TFA): A solution of Boc-Gly-(1*R*,3*S*)-1-(*m*-hydroxybenzyl)-Tic-OH (**12**, 0.10 g, 0.23 mmol) in TFA containing 5% of water (5 mL) was stirred for 15 min at room temp. The solvent was evaporated, acetic acid (10 mL) was added, and the mixture was lyophilized. Yield 0.09 g or quantitative, sticky beige compound. The compound cyclizes spontaneously to its diketopiperazine derivative **9** on standing; no NMR spectroscopic data could therefore be determined; R_f (EtOAc/MeOH/AcOH, 9:1:1) 0.23. HPLC: R_t = 15.5 min. MS (ES^+): 341 [M + H^+].

X-Ray Structure Determination of (1*R*, 3*S*)-1-(*m*-Benzyloxybenzyl)-2-pivaloyl-Tic-(*S*)-Phe-OBn (6): Single crystals of **6** were grown from ethyl acetate/petroleum ether by vapor diffusion. Molecular formula: $C_{45}H_{46}N_2O_5$. Molecular mass: 694.84. Unit cell dimensions: a = 5.6350(10) Å, b = 12.315(2) Å, c = 15.010(2) Å, α = 112.37(3)°, β = 96.50(3)°, γ = 96.54(3)°. Z = 1; d_{calc} = 1.224 Mg/m^3; crystal system: triclinic; space group: *P1*. Crystal size: 0.45 × 0.30 × 0.20 mm. Absorption coefficient: 0.630 mm^{-1}. Data collection was performed on a Philips PW1100 four-circle diffractometer

with use of graphite-monochromated Cu-$K\alpha$ radiation (λ = 1.54178 Å) in the θ-2θ scan mode up to $\theta = 60°$. Limiting indices: $-6 \le h \le 6$, $-13 \le k \le 12$, $0 \le l \le 16$. A total of 2810 reflections were collected, 2801 of which were symmetry-independent and 2653 of which had $I \ge 2\sigma(I)$.

The structure was solved by direct methods with the aid of the SHELXS 97 program,[17] and refined by full-matrix block least-squares on F^2, by using all data, with all non-H atoms anisotropic, by application of the SHELXL 97 program,[18] allowing the positional parameters and the anisotropic displacement parameters of the non-H atoms to refine at alternate cycles. All phenyl rings were constrained to the idealized geometry. H-atoms were placed at idealized positions and refined as riding, with U_{iso} set equal to 1.2 (or 1.5 for methyl groups) times the U_{eq} of the parent atom. Refinement converged to $R_1 = 0.0397$ and $wR_2 = 0.1135$. Data/restraints/parameters ratio: 2801:3:412.

CCDC-200237 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge at www.ccdc.cam.ac.uk/conts/retrieving.html [or from the Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; Fax: (internat.) +44-(0)1223-336-033; E-mail: deposit@ccdc.cam.ac.uk].

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