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First asymmetric syntheses of 6-substituted nipecotic acid derivatives

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Dedicated with the very best wishes to Professor Wolfgang Steglich on the occasion of his 70th birthday

Abstract—Various nipecotic acid derivatives are known to be potent GABA uptake inhibitors thus being useful in the treatment of a number of neurological and psychological disorders. In this paper, the first asymmetric syntheses of 6-substituted nipecotic acid derivatives are presented. The synthetic strategy was designed to provide access to a large variety of enantiomerically pure 6-substituted nipecotic acid derivatives. The synthesis starts from the chiral *N*-acyldihydropyridines **15** and **16** obtained via asymmetric electrophilic α-amidoalkylation reaction of a chiral *N*-acylpyridinium ion. These were utilized for the preparation of enantiomerically pure 6-(4,4-diphenylbutyl)nipecotic acids and 6-(4,4-diphenylbutenyl)nipecotic acids in a multistep synthesis, including the removal of the dimethylphenylsilyl blocking group from the dihydropyridine ring, the reduction of the dihydropyridine heterocycle, a Horner–Wittig reaction and the removal of the chiral auxiliary. The obtained target molecules, however, showed only negligible affinity to the GAT-1- and GAT-3 transport proteins.

1. Introduction

γ-Aminobutyric acid (GABA) is recognized as the predominant inhibitory neurotransmitter in the mammalian brain. Malfunctions in GABAergic neurotransmission are likely to contribute to the development of certain psychiatric and neurological disorders such as epilepsy, Huntington's Chorea and Parkinson's disease.[1] One of the various pharmacological approaches to palliate GABA deficiency in vivo is to inhibit the uptake of the neurotransmitter, thereby increasing the synaptic level of GABA and enhancing inhibitory neurotransmission. In contrast to the direct enhancement of GABA neurotransmission by $GABA_A$ agonists or benzodiazepines, GABA uptake inhibition results in a selective potentiation of endogenously released GABA and therefore is thought not to give rise to the development of tolerance.[2] Four different GABA transporters have been identified so far (GAT-1, GAT-2, GAT-3 and BGT-1), which differ in their cellular distribution in the brain and in their sensitivity to pharmacological agents.[3] A number of cyclic amino acids such as (*RS*)-piperidine-3-carboxylic acid (nipecotic acid, **1**) and 1,2,5,6-tetrahydropyridine-3-carboxylic acid (guvacine, **2**), which may be considered as conformationally restricted GABA analogues, display in vitro activity as inhibitors of [^{3}H]-GABA uptake.[4] These cyclic amino acids do not readily cross the blood brain barrier, but have been used as the basis for the design of some lipophilic and highly potent GABA uptake inhibitors, e.g. SK&F-89976-A[5] (**3**) and Tiagabine[6] (**5**) with GAT-1-selectivity and (*S*)-SNAP-5114[7] (**4**) with GAT-3-selectivity. Using structure-activity data and molecular modeling, Wermuth et al.[8] developed a pharmacophore model of GABA uptake inhibitors which suggests that for binding the lipophilic side chain is located in the vicinity of position 6 of the piperidine ring. He successfully confirmed his model by synthesizing 6-[(3,3-diphenyl)propyl]guvacine (**6**) which he found to be a potent GABA uptake inhibitor. The biological evaluation of compound **6** was performed, however, with a test system not clearly distinguishing between GAT-1 and GAT-3 uptake. Dhar and coworkers[9] synthesized quinolizidine derivatives (e.g., **7**) with a diphenylmethyl substituent in position 8 as conformationally restricted analogues of the nipecotic acid derivative **6**. Although, these analogues were in accordance with the pharmacophore model proposed by Wermuth, their affinity for GAT-1 or GAT-3 was very low. In the context with a study aimed at the development of new GABA uptake inhibitors we were interested in 6-substituted nipecotic acid derivatives. Since it is well known that (*R*)-nipecotic acid derivatives are more potent for GAT-1 than (*S*)-nipecotic acid derivatives and that the opposite is true for (*S*)-nipecotic acid derivatives exhibiting higher affinity to GAT-3 than compounds derived from (*R*)-nipecotic acid, it seemed reasonable to evaluate the enantiopure compounds. Thus, we performed the first asymmetric synthesis of 6-substituted nipecotic acid derivatives, which we,

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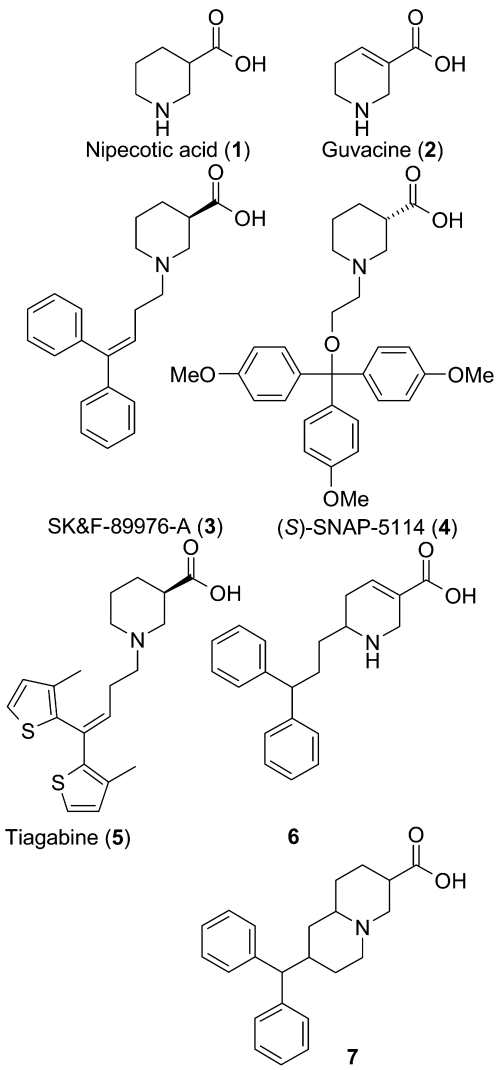
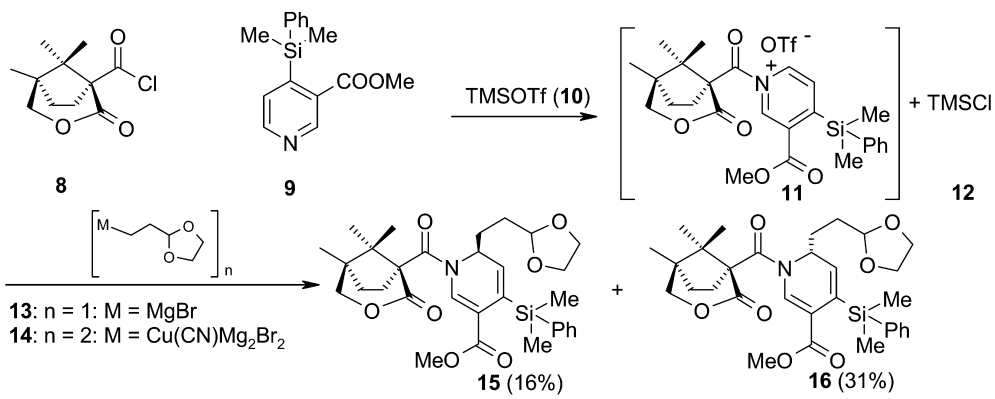


Scheme 1.

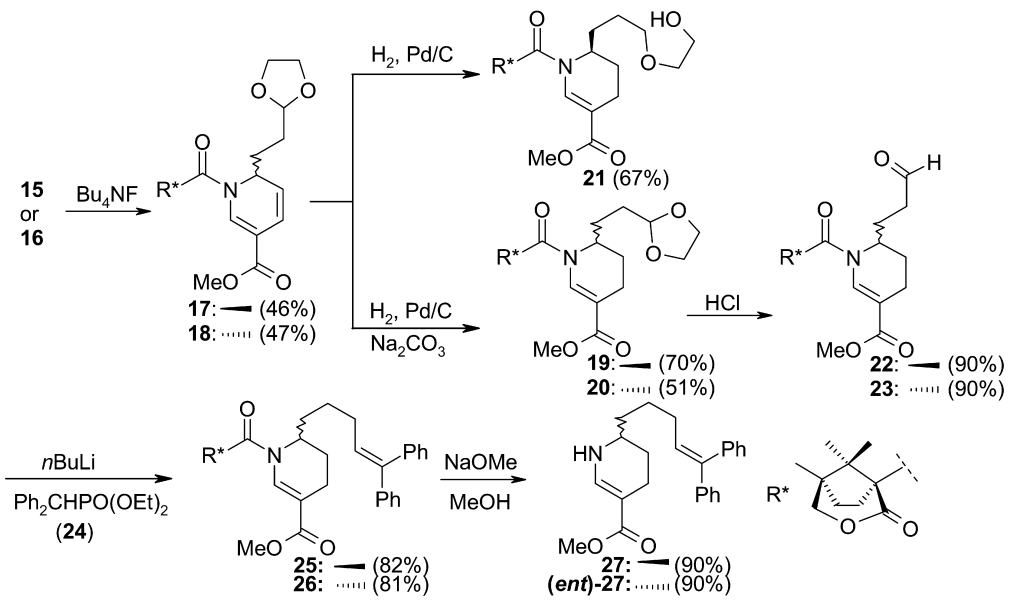
furthermore, investigated for their biological potential (Scheme 1).

2. Synthetic strategy

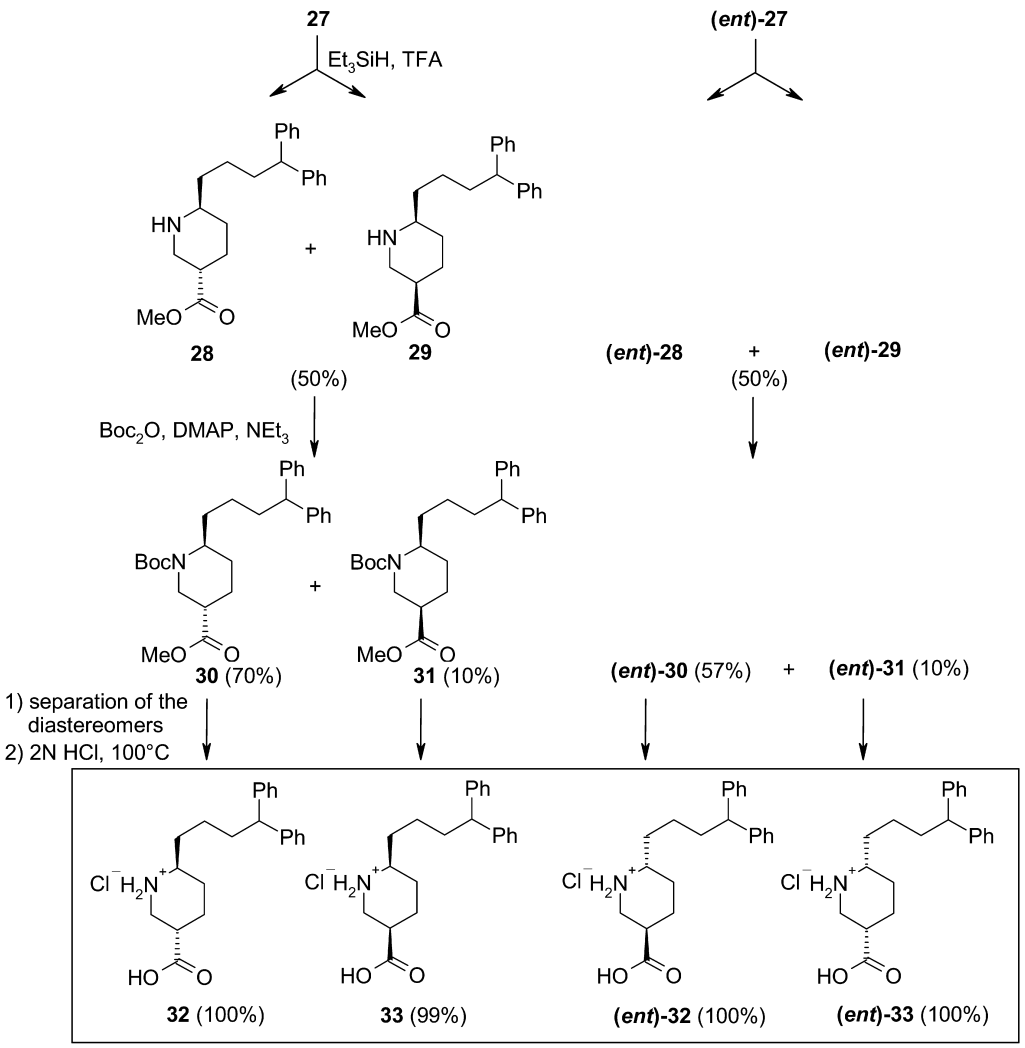
The overall strategy used for the stereoselective preparation of the 6-substituted nipecotic acid derivates is based on a method termed as asymmetric electrophilic α-amidoalkylation (AEαA).[10] In this type of reaction the new stereocenter is formed by stereoselectively adding a suitable nucleophile to a chiral *N*-acyliminium ion. In former studies of our group the carboxylic acid depicted as acid chloride **8** has proven to be a useful chiral auxiliary for the synthesis of pyrrolidines, piperidines, 1,2,3,4-tetrahydroisoquinolines and β-carbolines via AEαA.[11] Previously, we reported the successful generation of the chiral *N*-acylpyridinium ion **11** from acid chloride **8** and methyl (4-dimethylphenylsilyl)-nicotinate (**9**)[12] by means of trimethylsilyl triflate.[13] The dimethylphenylsilyl group, served as a blocking substituent in subsequent trapping reactions preventing addition reactions to position 4 of the pyridinium ring. Reaction of the *N*-acyl-4-dimethylphenylsilylpyridinium salt **11** with {[1,3]-dioxolan-2-ylethyl}magnesium bromide (**13**) led to the *N*-acyl-1,6-dihydropyridines **15** as the main product (**15**/**16**=87.2/12.8).[13] Meanwhile further experiments revealed that the sense of asymmetric induction is switched and compound **16** becomes the major diastereomer when the higher order cyanocuprate **14** (Scheme 2) is employed (see below). Having both diastereomers **15** and **16** available in reasonable amounts we set out to utilize these compounds as the basis for the synthesis of a series of 6-substituted nipecotic acid derivates. With regard to the above mentioned [6-(3,3-diphenylpropyl)]guvacine (**6**) and considering the structure of the GABA uptake inhibitor SK&F-89976-A (**3**) with a diphenylbutenyl substituent bound to the nitrogen atom we planned to transform the side chain present in **15** and **16**—via the respective aldehyde—to a diphenylbutenyl residue by employing a Horner–Emmons-reaction or to a diphenylbutyl substituent. Besides, the [1,3]-dioxolan-2-ylethyl substituent may open the way to various functional groups, e. g. alcohols or ethers, or to bicyclic ring systems either by intramolecular Schiff-Base-reaction or by α-aminonitrile formation according to the method of Husson et al.[14] The dimethylphenylsilyl substituent, which serves as a blocking group in the trapping reaction as described above, may either be removed thereby providing access to nipecotic acid derivatives unsubstituted in the 4-position or it may serve as a masked hydroxyl group[15] leading to 4-hydroxynipecotic acid derivatives. Furthermore, elimination of the generated hydroxyl group might afford guvacine derivatives. Both, 4-hydroxynipecotic acid as well as guvacine, are promising substructures for potential GABA uptake inhibitors.



Scheme 2.



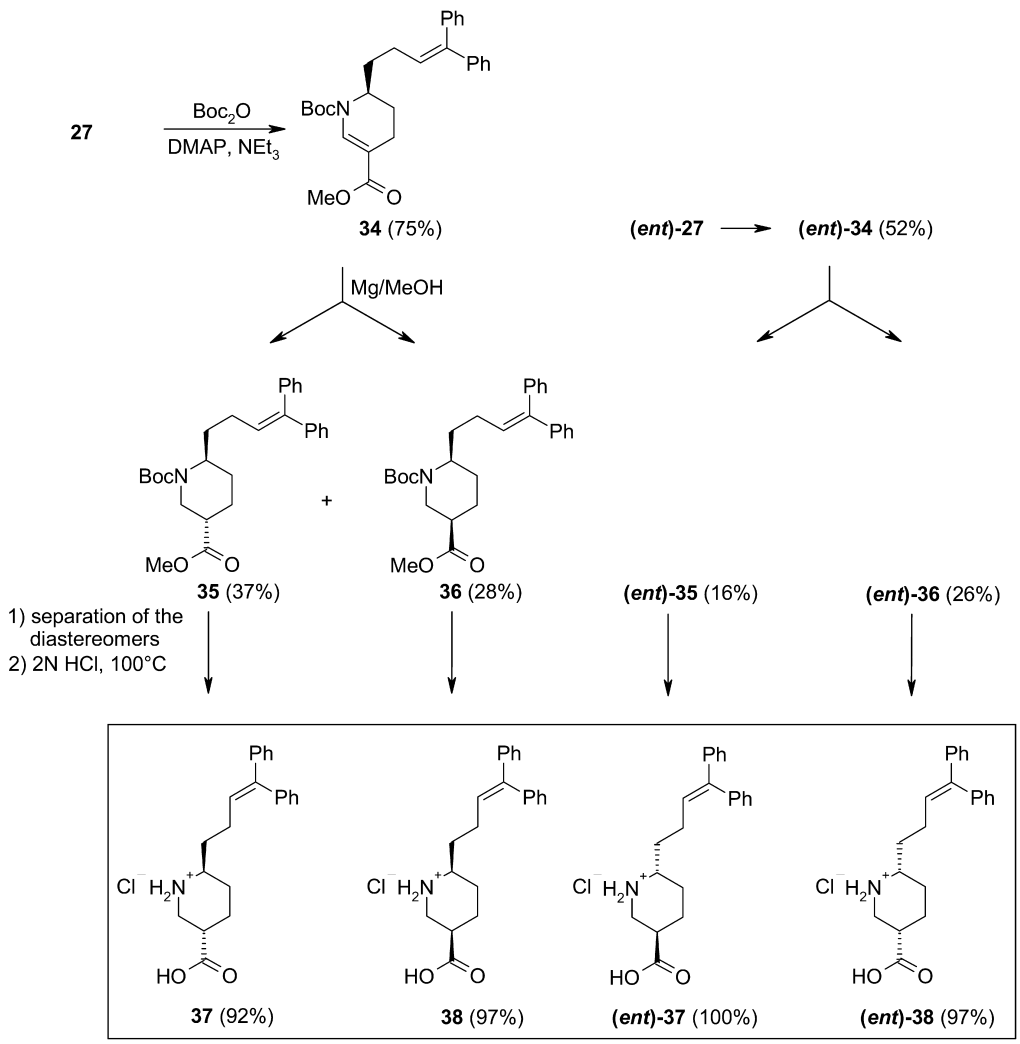
Scheme 3.



Scheme 4.

3. Results and discussion

Diastereomer **15** was available from a trapping reaction of **11** employing the Grignard reagent **13**,[16] which yielded a mixture of **15** and **16** in a ratio of 87.2 to 12.8. Interestingly, the sense of asymmetric induction observed for the Grignard reagent was inverted when the cyanocuprate **14** was used (**15**/**16**=34.0/66.0, total yield: 47%). Consequently, the reaction mixture resulting from this addition reaction was utilized to get access to diastereomer **16** in pure form which became available upon chromatography in a yield of 31%. Both diastereomers, **15** and **16**, were separately converted to the target molecules **32**, **33**, (*ent*)-**32** and (*ent*)-**33** in a multi-step synthesis. Though in the following only one of the two sequences, the one starting from **15** and leading to **32** and **33** is described, the synthesis of the enantiomers (*ent*)-**32** and (*ent*)-**33** was performed accordingly starting with the *N*-acyl-1,6-dihydropyridine **16**. The dimethylphenylsilyl group was removed by treating **15** with tetrabutyl-ammonium fluoride leading to product **17** (46%). In the next step compound **17** was subjected to catalytic hydrogenation, which yielded the 1,4,5,6-tetrahydropyridine derivative **19** in 70% yield, but only when Na_2CO_3 was present. Otherwise, in the absence of Na_2CO_3, only alcohol **21** was obtained by hydrogenolysis of the acetal moiety (68% yield, see Scheme 3). Following cleavage of the acetal group in compound **19** (90%), the resulting aldehyde **22** was successfully converted to the diphenylbutenyl derivative **25** carrying out a Wittig–Horner reaction. Deprotonation of phosphonate **24** with *n*BuLi[17] and reaction of the resulting carbanion with the aldehyde **22** gave the desired product **25** in 82% yield. The removal of the chiral auxiliary was achieved straightforwardly in a yield of 90% by heating compound **25** with NaOMe in methanol at 120 °C in a sealed tube (Scheme 3).[13,18] As the resulting enamino ester **27** was unstable, it became necessary to immediately reduce the double bond of the enamino ester unit. Thus compound **27** was treated with triethylsilane in trifluoroacetic acid at 50 °C using a method developed by Rosentreter[19] for the synthesis of piperidine derivatives from 1,4-dihydropyridines. Employing these reaction conditions, the enamine-double bond and the double bond in the side chain were reduced yielding diastereomers **28** and **29** (total yield for amide cleavage and reduction: 50%, d.s.=83/17 determined by ^{1}H NMR). The reduction of both double bonds was not very surprising but quite useful, as it provided an even easier access to the desired nipecotic acid derivates with a saturated side chain. Since we were not able to separate the diastereomers at this stage, we decided to convert them to the Boc-protected derivatives **30** and **31**.[20] Compounds **30** and **31** were then

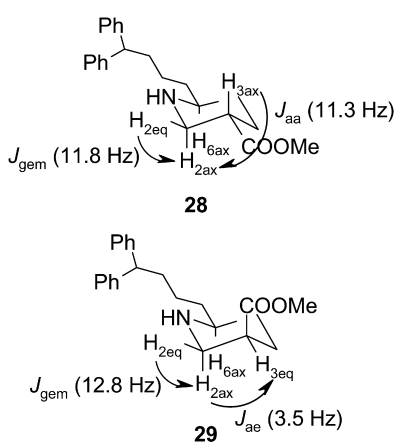


Scheme 5.

easily separable by chromatography. By refluxing in 2 M HCl the methyl ester and the carbamate function were simultanously cleaved yielding the target molecules **32** and **33**, each in 99% yield (Scheme 4).

To access target molecules with a diphenylbutenyl side chain, the enamino ester **27** was first protected with a Boc group providing **34** (yield: 75%). Upon subsequent reduction of the enamido ester double bond in **34** with magnesium in methanol the piperidine derivatives **35** and **36** were obtained (yield: 65%, d.s.=57/43, determined by ^{1}H NMR). Chromatographic separation of the diastereomers followed by the concurrent cleavage of the amide and the ester bond by HCl yielded 92% of the target molecule **37** and 97% of the target molecule **38**. The enantiomers (*ent*)-**37** and (*ent*)-**38** were synthesized accordingly starting from compound (*ent*)-**27** (Scheme 5).

The relative stereochemistry of the piperidine derivatives **28** and **29** became apparent from their ^{1}H NMR spectra. The absolute stereochemistry of the precursor **15** had been established in a former study by X-ray analysis.[13] Thus, piperidine derivative **28** obtained from **15** must be of (*S*)-configuration in position 6 of the heterocycle, as it is the case for **15**. In the ^{1}H NMR spectrum of **28** the signal of 6-H (δ=2.28–2.45 ppm) is a multiplet due to coupling with 5-H and the hydrogen atoms of the alkyl chain. A large coupling constant of J=12.1 Hz was identified to the hydrogen atoms in position 5. Thus, 6-H must adopt an axial orientation. The signal of one hydrogen in position 2 (δ=2.60 ppm) of the heterocycle is split to a doublet of doublets by a geminal (J=11.8 Hz) and by a vicinal coupling (J=11.3 Hz). Consequently, this proton (2-H) and the proton in position 3 of the piperidine ring must be in an axial position. Therefore, the residues in position 3 and 6 must both occupy equatorial positions and diastereomer **28**, as the major diastereomer of the reduction, must, consequently, be of (3*S*,6*S*)-configuration. As the minor isomer **29** differs from **28** only with respect to the stereochemistry at 3-C of the ring system, it must have the stereochemistry indicated [(3*R*,6*S*)], which in further support of this assignment could also be delineated from the ^{1}H NMR spectrum of this compound. (6-H: δ=2.30–2.45 ppm, J=12.1 Hz in addition to small coupling constants; 2-H_{ax}: δ=2.71 ppm, J=12.8/3.5 Hz; 2-H_{eq}: δ=3.31 ppm, J=12.8/2.5 Hz) (Scheme 6).



Scheme 6.

The configuration of the nipecotic acid derivatives **37** and **38** was determined from the ^{1}H NMR spectra of the Boc-protected compounds **35** and **36**. Analysis of the coupling pattern of the 2-H and 6-H signal in the ^{1}H NMR spectrum leads to the configuration of **35**. For 6-H (δ=4.15–4.24 ppm) only small coupling constants (J=2.0/8.1 Hz) are observed for the hydrogen atoms in position 6 indicating, that the diphenylbutenyl substituent is positioned axially. This orientation of the side chain is to be seen as a result of the allylic strain arising from the carbamate function.[21] As the ester function at 3-C adopts an axial position which becomes apparent from the coupling constants between 2-H and 3-H (2-H_{ax}: 2.93 ppm, J=14.0/4.1 Hz; 2-H_{eq}: 4.41 ppm, J=14.0/1.2 Hz) compound **35** must, consequently, be (3*S*,6*S*)-configurated. Finally compound **36** by differing from the aforementioned diastereomer **35** only in the configuration at 3-C exhibiting the ester function must be the (3*R*,6*S*)-stereoisomer.

4. Biological test results

The enantiomerically pure nipecotic acid derivates were evaluated for their in vitro activity as GABA uptake inhibitors by a radioligand-receptor binding assay.[22] The results are depicted in Table 1 and are given as percentage of GABA uptake compared to the control experiment without test substance. To determine IC_{50} values did not seem appropriate as none of the 6-substituted nipecotic acid derivatives **32**, **33**, (*ent*)-**32**, (*ent*)-**33**, **37**, **38**, (*ent*)-**37** and (*ent*)-**38** displayed a reasonable potency neither at GAT-1 nor at GAT-3 (see Table 1). For comparison purposes in Table 1 also the data for SK&F-89976A (**3**), 6-[(3,3,-diphenylpropyl)]guvacine (**6**) and (*S*)-SNAP-5114 (**4**) from the literature are included. The low potency of the herein synthesized target molecules is surprising considering the high affinity of 6-[(3,3-diphenylpropyl)]guvacine (**6**). However, our results are in accordance with biological test results reported by Dhar[9] for conformationally restricted 6-substituted nipecotic acid derivatives (e.g., **7**) also having low affinity for GAT-1 and GAT-3.

Table 1.

Compound	IC_{50}±SEM	
	GAT-1	GAT-3
6	0.1 μM[a,8,23]	
3	0.13±0.03 μM[b]	944±110 μM[b]
4	388±92 μM[b,7]	5±1 μM[b,7]
32	100 μM: 96.5%[c]	100 μM: 97.6%[c]
33	100 μM: 75.3%[c]	100 μM: 95.3%[c]
(*ent*)-**32**	100 μM: 98.3%[c]	100 μM: 85.5%[c]
(*ent*)-**33**	100 μM: 86.0%[c]	100 μM: 94.8%[c]
37	100 μM: 91.6%[c]	100 μM: 71.8%[c]
38	100 μM: 77.7%[c]	100 μM: 74.5%[c]
(*ent*)-**37**	100 μM: 89.7%[c]	100 μM: 65.0%[c]
(*ent*)-**38**	100 μM: 93.4%[c]	100 μM: 69.9%[c]

[a] [^{3}H]GABA-synaptosomal uptake in rat brain given as IC_{50}.
[b] determined for hGAT-1 and hGAT-3 given as IC_{50} according to Borden.[24]
[c] % uptake compared to a control experiment without test substance, each experiment performed as triplicate.[22]

5. Conclusion

In summary, the first asymmetric synthesis for 6-substituted nipecotic acid derivatives was developed. The synthetic strategy was designed to provide a flexible access to a wide range of nipecotic acid derivatives. The educts **15** and **16** were prepared by asymmetric electrophilic α-amidoalkylation via the chiral *N*-acylpyridinium ion **11**. In multistep syntheses the four enantiomerically pure isomers of 6-(4,4-diphenylbutyl)nipecotic acid and of 6-(4,4-diphenylbutyl)-nipecotic acid were obtained. The synthesized nipecotic acid derivatives were evaluated for their in vitro activity at the GAT-1 and GAT-3 transport proteins, but did not show any reasonable potency.

6. Experimental

6.1. General

All reactions were carried out in vacuum dried glassware sealed with rubber septa under argon atmosphere whenever necessary. All reagents were used as commercially available. The solvents were dried and distilled. Mp (uncorrected values): Büchi melting point apparatus no. 510 (Dr. Tottoli). Optical rotations: Polarimeter 241 MC (Perkin–Elmer). IR: Perkin–Elmer FT-IR spectrophotometer Paragon 1000. ^{1}H NMR: JEOL JNMR-GX 400 spectrometer (400 MHz) with TMS as internal standard. MS spectra: Hewlett Packard 5989 with 59980 B particle beam LC/MS interface. Elemental analysis: CHN Rapid (Heraeus). TLC: TLC plates Merck 60 F-254. Column chromatography (CC): Flash chromatography on silica gel (Merck 60 F-254, 0.040–0.063 mm). Analytical HPLC: L-6000 pump, L-4000 UV/VIS detector, D-7500 Chromato Integrator (Merck–Hitachi), column: LiChroCart® with Lichrospher® Si 60 cartridge (5 μm, 250×4 mm with precolumn 4×4 mm), (Merck). Preparative HPLC: L-6000 pump, L-4000 UV/Vis, D-2000 Chromato Integrator (Merck–Hitachi), column: Hibar RT LiChrosorb® Si 60 (7 μm, 250×25 mm) (Merck).

6.1.1. Methyl (*S*)-(4-(dimethylphenylsilyl)-6-(2-[1,3]dioxolan-2-ylethyl)-1-[(1*S*,5*R*)-5,8,8-trimethyl-2-oxo-3-oxabicyclo[3.2.1]octylcarbonyl]-1,6-dihydropyridine-3-carboxylate (15) and methyl (*R*)-(4-(dimethylphenylsilyl)-6-(2-[1,3]dioxolan-2-ylethyl)-1-[(1*S*,5*R*)-5,8,8-trimethyl-2-oxo-3-oxabicyclo[3.2.1]octylcarbonyl]-1,6-dihydropyridine-3-carboxylate (16). The generation of the *N*-acylpyridinium triflate **11** was performed according to literature[13] starting from 3.0 mmol of acylchloride **8**, 816 mg (3.0 mmol) of pyridine **9** and 543 μl (3.0 mmol) of trimethylsilyl triflate in 15 ml CH_2Cl_2. To this solution another solution was added at −78 °C over 3 min, that had been prepared by addition of 18 ml (18.0 mmol, 2.0 equiv.) of 2-([1,3]dioxolan-2-yl)ethylmagnesium bromide (1.0 M in THF) to a suspension of 806 mg (9.0 mmol, 1.0 equiv.) of CuCN in 35 ml THF at −78 °C and had been allowed to react at 0 °C for 10 min. After 3 h at −30 °C the reaction mixture was quenched at −30 °C with phosphate buffer (pH=7, c=1.0 M). Work up, purification and separation of the diastereomers according to literature[13] afforded 272 mg (16%) of **15** and 528 mg (31%) of **16**, which were identical in all respect with authentic samples.[13]

6.1.2. Methyl (*S*)-6-(2-[1,3]dioxolan-2-ylethyl)-1-[(1*S*,5*R*)-5,8,8-trimethyl-2-oxo-3-oxabicyclo[3.2.1]octylcarbonyl]-1,6-dihydropyridine-3-carboxylate (17). 880 μl (0.880 mmol, 5 equiv.) of Bu_4NF (1 M in THF) were slowly added to a solution of 100 mg (0.176 mmol) of **15** in 1760 μl THF over a period of 3 h. Phosphate buffer (pH=7, c=1.0 M) was added. The reaction mixture was extracted with CH_2Cl_2. The combined organic layer were dried (Na_2SO_4) and concentrated in vacuo. Purification by CC (*n*-heptane/EtOAc)=50:50) afforded 35 mg (46%) of compound **17**.

Compound **17**. Colorless oil. TLC: R_f=0.20 (*n*-heptane/EtOAc=50:50). $[\alpha]_D^{20}$=+436.3 (c=0.16, CH_2Cl_2). IR (KBr): $\tilde{\nu}$=2955 cm^{-1}, 1718, 1677, 1219. ^{1}H NMR (nitrobenzene-d$_5$, 140 °C): δ=0.90 ppm (s, 3H, CH_3), 1.07 (s, 3H, CH_3), 1.42 (s, 3H, CH_3), 1.77–2.00 (m, 6H, CH_2CH_2, CH_2CH$_2$), 2.28–2.40 (m, 1H, CH$_2$CH_2), 2.50–2.60 (m, 1H, CH$_2$CH_2), 3.77 (s, 3H, COOCH_3), 3.74–3.80 (m, 2H, OCH$_2$CH$_2$O), 3.86–3.93 (m, 2H, OCH$_2$CH$_2$O), 3.99 (d, J=10.9 Hz, 1H, OCH$_2$), 4.19 (dd, J=10.9/1.9 Hz, 1H, OCH$_2$), 4.87 (t, 1H, J=4.8 Hz, OCHO), 5.13–5.16 (m, 1H, NCHCH$_2$), 5.84 (dd, J=9.9/5.6 Hz, 1H, NCHCH=CH), 6.53 (d, J=9.9 Hz, 1H, NCH=CCH), 7.94 (s, 1H, NCH=C). MS (70 eV); *m/z* (%): 433 [M$^+$] (1), 332 (23), 195 (100), 167 (28), 139 (31). $C_{23}H_{31}NO_7$ (433.50): calcd C 63.73, H 7.21, N 3.23; found C 63.90, H 7.26, N 2.96.

6.1.3. Methyl (*R*)-6-(2-[1,3]dioxolan-2-ylethyl)-1-[(1*S*,5*R*)-5,8,8-trimethyl-2-oxo-3-oxabicyclo[3.2.1]octylcarbonyl]-1,6-dihydropyridine-3-carboxylate (18). Synthesis as described for the preparation of **17** from 985 mg (1.734 mmol) of **16** and 8.67 ml (8.670 mmol, 5 equiv.) of Bu_4NF (1 M in THF). Purification by CC (*iso*-hexane/Et_2O=25:75) afforded 355 mg (47%) of **18**.

Compound **18**. Colorless oil. TLC: R_f=0.20 (*iso*-hexane/Et_2O=25:75). $[\alpha]_D^{20}$=−357.6 (c=0.88, CH_2Cl_2). IR (KBr): $\tilde{\nu}$=2958 cm^{-1}, 1718, 1676, 1578, 1210. ^{1}H NMR (CD_2Cl_2, 120 °C): δ=0.93 ppm (s, 3H, CH_3), 0.97 (s, 3H, CH_3), 1.22 (s, 3H, CH_3), 1.62–1.81 (m, 4H, CH_2CH_2), 1.87–2.00 (m, 2H, CH_2CH$_2$), 2.31–2.44 (m, 1H, CH$_2$CH_2), 2.73–2.87 (m, 1H, CH$_2$CH_2), 3.78 (s, 3H, COOCH_3), 3.80–3.85 (m, 2H, OCH$_2$CH$_2$O), 3.92–3.96 (m, 2H, OCH$_2$CH$_2$O), 3.98 (d, J=11.0 Hz, 1H, OCH$_2$), 4.20 (dd, J=11.0/2.1 Hz, 1H, OCH$_2$), 4.88 (t, 1H, J=4.7 Hz, OCHO), 5.25–5.33 (m, 1H, NCHCH$_2$), 5.70 (dd, J=9.9/5.6 Hz, 1H, NCHCH=CH), 6.44 (d, J=9.9 Hz, 1H, NCH=CCH), 7.66 (s, 1H, NCH=C). MS (70 eV); *m/z* (%): 433 [M$^+$] (2), 402 (2), 332 (29), 195 (100), 167 (27), 139 (30). $C_{23}H_{31}NO_7$ (433.50): calcd C 63.73, H 7.21, N 3.23; found C 64.01, H 7.42, N 2.74.

6.1.4. Methyl (*R*)-6-(2-[1,3]dioxolan-2-ylethyl)-1-[(1*S*,5*R*)-5,8,8-trimethyl-2-oxo-3-oxabicyclo[3.2.1]octylcarbonyl]-1,4,5,6-tetrahydropyridine-3-carboxylate (19). 681 mg Pd/C (10% Pd) were added to a suspension of 681 mg (1.571 mmol) of compound **17** and 666 mg (6.284 mmol, 4 equiv.) of Na_2CO_3 in 31 ml of CH_3OH. The resulting mixture was hydrogenated for 48 h under normal pressure. Then the mixture was filtered and concentrated in vacuo. Purification by CC (*iso*-hexane/Et_2O=20:80) afforded 478 mg (70%) of **19**.

Compound **19**. Colorless crystals, mp 68 °C. TLC: R_f=0.22 (*iso*-hexane/Et_2O=20:80). $[\alpha]_D^{20}$=+195.1 (*c*=0.61, CH_2Cl_2). IR (KBr): $\tilde{\nu}$=2954 cm^{-1}, 1728, 1623, 1244, 1187. ^1H NMR ($C_2D_2Cl_4$, 120 °C): δ=0.94 ppm (s, 3H, CH_3), 1.03 (s, 3H, CH_3), 1.36 (s, 3H, CH_3), 1.60 (m, 1H, NCHCH_2CH$_2$C=), 1.69–1.81 (m, 5H, CH_2CH_2, NCHCH_2-CH$_2$C=), 1.86–1.97 (m, 2H, CH_2CH$_2$), 2.01 (dd, *J*=12.9/5.6 Hz, 1H, NCH=CCH_2), 2.32 (dd, *J*=12.9/6.4 Hz, 1H, NCH=CCH_2), 2.38–2.47 (m, 2H, CH$_2$CH_2), 3.76 (s, 3H, COOCH_3), 3.81–3.86 (m, 2H, OCH$_2$CH$_2$O), 3.93–3.98 (m, 2H, OCH$_2$CH$_2$O), 3.97 (d, *J*=11.0 Hz, 1H, OCH$_2$), 4.18 (d, *J*=11.0 Hz, 1H, OCH$_2$), 4.51–4.59 (m, 1H, NC*H*CH$_2$), 4.92 (t, 1H, *J*=4.0 Hz, OCHO), 7.76 (s, 1H, NC*H*=C). MS (70 eV); *m*/*z* (%): 435 [M^+] (1), 404 (4), 336 (100), 240 (13), 195 (81), 167 (25). $C_{23}H_{33}NO_7$ (435.52): calcd C 63.43, H 7.63, N 3.22; found C 63.23, H 7.74, N 3.05.

6.1.5. Methyl (*S*)-6-(2-[1,3]dioxolan-2-ylethyl)-1-[(1*S*,5*R*)-5,8,8-trimethyl-2-oxo-3-oxabicyclo[3.2.1]octylcarbonyl]-1,4,5,6-tetrahydropyridine-3-carboxylate (20). Synthesis as described for the preparation of **19** from 129 mg (0.298 mmol) of **18**, 129 mg of Pd/C (10% Pd) and 126 mg (1.192 mmol, 4 equiv.) of Na_2CO_3 in 6 ml CH_3OH, hydrogenation time: 24 h. Purification by CC (*iso*-hexane/Et_2O=25:75) afforded 67 mg (51%) of **20**.

Compound **20**. Colorless crystals, mp 160–161 °C. TLC: R_f=0.24 (*iso*-hexane/Et_2O=25:75). $[\alpha]_D^{20}$=−36.1 (*c*=0.51, CH_2Cl_2). IR (KBr): $\tilde{\nu}$=2950 cm^{-1}, 1717, 1676, 1610, 1238, 1173. ^1H NMR ($C_2D_2Cl_4$, 120 °C): δ=0.94 ppm (s, 3H, CH_3), 1.00 (s, 3H, CH_3), 1.30 (s, 3H, CH_3), 1.61 (m, 1H, NCHCH_2CH$_2$C=), 1.63–1.76 (m, 4H, CH_2CH_2), 1.92 (m, 1H, NCHCH_2CH$_2$C=), 1.90–2.06 (m, 2H, CH_2CH$_2$), 2.26 (ddd, *J*=18.3/7.4/5.9 Hz, 1H, NCH=CCH_2), 2.31–2.43 (m, 1H, CH$_2$CH_2), 2.46 (dd, *J*=18.3/5.9 Hz, 1H, NCH=CCH_2), 2.57–2.80 (m, 1H, CH$_2$CH_2), 3.76 (s, 3H, COOCH_3), 3.81–3.86 (m, 2H, OCH$_2$CH$_2$O), 3.92–3.97 (m, 2H, OCH$_2$CH$_2$O), 3.97 (d, *J*=11.0 Hz, 1H, OCH$_2$), 4.20 (d, *J*=11.0 Hz, 1H, OCH$_2$), 4.76–4.83 (m, 1H, NC*H*CH$_2$), 4.90 (t, 1H, *J*=4.2 Hz, OCHO), 7.79 (s, 1H, NC*H*=C). MS (CI, CH_5^+); *m*/*z* (%): 436 [M^++1] (6), 404 (4), 336 (100), 195 (89). $C_{23}H_{33}NO_7$ (435.52): calcd C 63.43, H 7.63, N 3.22; found C 63.36, H 7.74, N 3.14.

6.1.6. Methyl (*R*)-6-[3-(1-hydroxyethoxy)propyl]-1-[(1*S*,5*R*)-5,8,8-trimethyl-2-oxo-3-oxabicyclo[3.2.1]octylcarbonyl]-1,4,5,6-tetrahydropyridine-3-carboxylate (21). Synthesis as described for the preparation of **19** from 84 mg (0.194 mmol) of **17** in 3.8 ml CH_3OH, 168 mg of Pd/C (10% Pd) and without Na_2CO_3, hydrogenation time: 48 h. Purification by CC (*iso*-hexane/Et_2O=20:80) afforded 57 mg (67%) of **21**.

Compound **21**. Colorless oil. TLC: R_f=0.25 (*iso*-hexane/Et_2O=20:80). $[\alpha]_D^{20}$=+170.1 (*c*=0.64, CH_2Cl_2). IR (film): $\tilde{\nu}$=3532 cm^{-1}, 2953, 1730, 1676, 1624, 1244, 748, 706. ^1H NMR (nitrobenzene-d_5, 140 °C): δ=0.91 ppm (s, 3H, CH_3), 1.09 (s, 3H, CH_3), 1.41 (s, 3H, CH_3), 1.59–1.84 (m, 4H, CH_2CH_2), 1.87–1.94 (m, 1H, NCH=CCH$_2$CH_2), 1.89–2.00 (m, 2H, CH_2CH$_2$), 2.01–2.11 (m, 1H, NCH=CCH$_2$-CH_2), 2.29–2.47 (m, 2H, NCH=CCH_2), 2.47–2.62 (m, 2H, CH$_2$CH_2), 3.26–3.36 (m, 5H, NCHCH$_2$CH$_2$CH_2O, OCH$_2$-CH$_2$O), 3.36–3.45 (m, 1H, NCHCH$_2$CH$_2$CH_2O), 3.74 (s, 3H, COOCH_3), 3.99 (d, *J*=11.1 Hz, 1H, OCH$_2$), 4.19 (d, *J*=11.1 Hz, 1H, OCH$_2$), 4.39–4.47 (br, 1H, OH), 4.58–4.68 (m, 1H, NC*H*CH$_2$), 8.07 (s, 1H, NC*H*=C). MS (70 eV); *m*/*z* (%): 437 [M^+] (3), 406 (100), 334 (6), 195 (16), 167 (9), 139 (8). $C_{23}H_{35}NO_7$ (437.53): calcd C 63.14, H 8.06, N 3.20; found C 63.48, H 8.00, N 3.16.

6.1.7. Methyl (*R*)-6-(3-oxopropyl)-1-[(1*S*,5*R*)-5,8,8-trimethyl-2-oxo-3-oxabicyclo[3.2.1]octylcarbonyl]-1,4,5,6-tetrahydropyridine-3-carboxylate (22). 3.6 ml of HCl (5% in H_2O) were added to a solution of 478 mg (1.102 mmol) of **19** in 7.3 ml THF. The reaction mixture was stirred for 18 h and was then quenched with phosphate buffer (pH 7, *c*=1.0 M). The reaction mixture was extracted with CH_2Cl_2. The combined organic layers were dried ($MgSO_4$) and concentrated in vacuo. Purification by CC (*iso*-hexane/Et_2O=25:75) afforded 389 mg (90%) of **22**.

Compound **22**. Colorless crystals, mp 83 °C. TLC: R_f=0.22 (*iso*-hexane/Et_2O=25:75). $[\alpha]_D^{20}$=+191.8 (*c*=0.34, CH_2Cl_2). IR (KBr): $\tilde{\nu}$=2954 cm^{-1}, 2724, 1723, 1673, 1621, 1246, 1180. ^1H NMR ($C_2D_2Cl_4$, 120 °C): δ=0.94 ppm (s, 3H, CH_3), 1.04 (s, 3H, CH_3), 1.37 (s, 3H, CH_3), 1.71–1.84 (m, 2H, NCHCH_2CH$_2$C=, CH_2CH$_2$-CHO), 1.85–1.98 (m, 4H, CH_2CH$_2$, CH_2CH$_2$CHO, NCHCH_2CH$_2$C=), 2.27–2.40 (m, 2H, CH$_2$CH_2, CH$_2$CH_2-CHO), 2.40–2.55 (m, 3H, NCH=CCH_2, CH$_2$CH_2, CH$_2$-CH_2CHO), 2.56–2.67 (m, 1H, NCH=CCH_2), 3.78 (s, 3H, COOCH_3), 3.98 (d, *J*=11.0 Hz, 1H, OCH$_2$), 4.19 (dd, *J*=1.7, 11.0 Hz, 1H, OCH$_2$), 4.57–4.63 (m, 1H, NC*H*(CH$_2$)), 7.75 (s, 1H, NC*H*=C), 9.80 (s, 1H, CHO). MS (CI, CH_5^+); *m*/*z* (%): 392 [M^++1] (35), 360 (100), 305 (9), 195 (57), 167 (44), 139 (51). $C_{21}H_{29}NO_6$ (391.46): calcd C 64.43, H 7.47, N 3.58; found C 64.16, H 7.46, N 3.44.

6.1.8. Methyl (*S*)-6-(3-oxopropyl)-1-[(1*S*,5*R*)-5,8,8-trimethyl-2-oxo-3-oxabicyclo[3.2.1]octylcarbonyl]-1,4,5,6-tetrahydropyridine-3-carboxylate (23). Synthesis as described for the preparation of **22** from 132 mg (0.302 mmol) of **20** in 2 ml THF with 1.0 ml of HCl (5% in H_2O). Purification by CC (*iso*-hexane/ethyl acetate=55:45) afforded 106 mg (90%) of **23**.

Compound **23**. Colorless crystals, mp 52–55 °C. TLC: R_f=0.27 (*iso*-hexane/ethyl acetate=55:45). $[\alpha]_D^{20}$=−40.2 (*c*=0.53, CH_2Cl_2). IR (KBr): $\tilde{\nu}$=2958 cm^{-1}, 1725, 1670, 1618, 1243, 1184. ^1H NMR ($C_2D_2Cl_4$, 120 °C): δ=0.95 ppm (s, 3H, CH_3), 0.98 (s, 3H, CH_3), 1.29 (s, 3H, CH_3), 1.76–2.03 (m, 6H, NCHCH_2CH$_2$C=, CH_2CH$_2$CHO, CH_2CH$_2$), 2.20–2.39 (m, 2H, CH$_2$CH_2, CH$_2$CH_2CHO), 2.42–2.60 (m, 3H, CH$_2$CH_2, CH$_2$CH_2CHO, NCH=CCH_2), 2.64–2.85 (m, 1H, NCH=CCH_2), 3.77 (s, 3H, COOCH_3), 3.98 (d, *J*=11.1 Hz, 1H, OCH$_2$), 4.22 (dd, *J*=11.1/1.8 Hz, 1H, OCH$_2$), 4.80–4.85 (m, 1H, NC*H*CH$_2$), 7.78 (s, 1H, NC*H*=C), 9.79 (s, 1H, CHO). MS (CI, CH_5^+); *m*/*z* (%): 392 [M^++1] (22), 360 (31), 195 (536), 180 (100), 167 (26), 139 (14). $C_{21}H_{29}NO_6$ (391.46): calcd C 64.43, H 7.47, N 3.58; found C 64.11, H 7.75, N 3.22.

6.1.9. Methyl (*S*)-6-(4,4-diphenylbut-3-enyl)-1-[(1*S*,5*R*)-5,8,8-trimethyl-2-oxo-3-oxabicyclo[3.2.1]octylcarbonyl]-1,4,5,6-tetrahydropyridine-3-carboxylate (25).

722 μl (1.156 mmol, 1.2 equiv.) of *n*BuLi (1.6 M in hexane) were added to 700 μl of THF. After cooling to 0 °C 327 mg (1.156 mmol, 1.2 equiv.) of ethyl benzhydrylphosphonate (**24**) in 1.6 ml THF were added. The reaction mixture was warmed to room temperature. After 2.5 h a solution of 377 mg (0.963 mmol) of **22** in 4.6 ml THF were added dropwise and the reaction mixture was stirred for 18 h. The reaction was quenched with phosphate buffer (pH 7, c=1.0 M). Then it was extracted with CH_2Cl_2 and the combined organic layers were dried ($MgSO_4$) and concentrated in vacuo. Purification by CC (*iso*-hexane/Et_2O=40:60) afforded 429 mg (82%) of **25**.

Compound **25**. Colorless crystals, mp 185 °C. TLC: R_f=0.22 (*iso*-hexane/Et_2O=40:60). $[\alpha]_D^{20}$=+136.9 (c=0.49, CH_2Cl_2). IR (KBr): $\tilde{\nu}$=2951 cm^{-1}, 1731, 1707, 1674, 1622, 1243, 1186, 810, 764, 702. ^1H NMR (nitrobenzene-d_5, 140 °C): δ=0.92 ppm (s, 3H, CH_3), 1.09 (s, 3H, CH_3), 1.43 (s, 3H, CH_3), 1.81–1.87 (m, 2H, NCHCH_2CH$_2$C=), 1.87–2.04 (m, 4H, CH_2CH_2), 2.22–2.36 (m, 3H, NCH=CCH_2, CH_2CH$_2$), 2.41 (dd, J=17.3/5.8 Hz, 1H, NCH=CCH_2), 2.48–2.59 (m, 2H, CH$_2$CH_2), 3.76 (s, 3H, $COOCH_3$), 3.99 (d, J=11.1 Hz, 1H, OCH_2), 4.21 (d, J=11.1 Hz, 1H, OCH_2), 4.56–4.64 (m, 1H, NCHCH$_2$), 6.19 (t, J=6.8 Hz, 1H, HC=CPh$_2$), 7.18–7.37 (m, 8H, $H_{arom.}$), 7.37–7.45 (m, 2H, $H_{arom.}$), 8.07 (s, 1H, NCH=C). MS (CI, CH_5^+); m/z (%): 542 [M^++1] (27), 510 (37), 346 (37), 271 (12), 195 (100), 167 (40), 139 (38). $C_{34}H_{39}NO_5$ (541.69): calcd C 75.39, H 7.26, N 2.59; found C 75.14, H 7.26, N 2.47.

6.1.10. Methyl (*R*)-6-(4,4-diphenylbut-3-enyl)-1-[(1*S*,5*R*)-5,8,8-trimethyl-2-oxo-3-oxabicyclo[3.2.1]octylcarbonyl]-1,4,5,6-tetrahydropyridine-3-carboxylate (26). Synthesis as described for the preparation of **25** using 137 μl (0.218 mmol, 1.2 equiv.) of *n*BuLi (1.6 M in hexane), 137 μl of THF, 66 mg (0.218 mmol, 1.2 equiv.) of ethyl benzhydrylphosphonate (**24**) in 296 μl THF, 71 mg (0.182 mmol) of **23** in 865 μl THF. Purification by CC (*iso*-hexane/Et_2O=40:60) afforded 80 mg (81%) of **26**.

Compound **26**. Colorless crystals, mp 75 °C. TLC: R_f=0.30 (*iso*-hexane/Et_2O=40:60). $[\alpha]_D^{20}$=−23.9 (c=0.93, CH_2Cl_2). IR (KBr): $\tilde{\nu}$=2952 cm^{-1}, 1729, 1682, 1235, 1178, 763, 701. ^1H NMR ($C_2D_2Cl_4$, 120 °C): δ=0.93 ppm (s, 3H, CH_3), 0.95 (s, 3H, CH_3), 1.29 (s, 3H, CH_3), 1.50–1.70 (m, 3H, CH_2CH$_2$, NCHCH_2CH$_2$C=), 1.80–1.97 (m, 3H, CH$_2$CH_2, NCHCH_2CH$_2$C=), 2.04–2.22 (m, 3H, NCH=CCH_2, CH_2CH$_2$), 2.28–2.56 (m, 3H, CH$_2$CH_2, NCH=CCH_2), 3.76 (s, 3H, $COOCH_3$), 3.96 (d, J=11.0 Hz, 1H, OCH_2), 4.18 (dd, J=11.1/1.2 Hz, 1H, OCH_2), 4.71–4.79 (m, 1H, NCHCH$_2$), 6.12 (t, J=7.5 Hz, 1H, HC=CPh$_2$), 7.14–7.44 (m, 10H, $H_{arom.}$), 7.77 (s, 1H, NCH=C). MS (CI, CH_5^+); m/z (%): 542 [M^++1] (100), 510 (23), 195 (20), 167 (14), 139 (14). $C_{34}H_{39}NO_5$ (541.69): calcd C 75.39, H 7.26, N 2.59; found C 75.37, H 7.56, N 2.44.

6.1.11. Methyl (*S*)-6-(4,4-diphenylbut-3-enyl)-1,4,5,6-tetrahydropyridine-3-carboxylate (27). A mixture of 600 μl of freshly prepared NaOMe (0.5 M in CH_3OH_{abs}) and 25 mg (0.046 mmol) of **25** in 230 μl THF was reacted at 120 °C for 18 h in a sealed tube. The reaction was quenched with phosphate buffer (pH 7, c=1.0 M). The reaction mixture was extracted with CH_2Cl_2. The combined organic layers were dried ($MgSO_4$) and concentrated in vacuo. Purification by CC (CH_2Cl_2/CH_3OH=95:5) afforded 15 mg (90%) of **27**. As product **27** appeared to be labile, it could not be fully characterized. It was immediately transformed to either the compounds **28** and **29** or **34**.

Compound **27**. Colorless oil. TLC: R_f=0.68 (CH_2Cl_2/CH_3OH=95:5). ^1H NMR (CD_2Cl_2): δ=1.53–1.62 ppm (m, 3H, NCHCH_2CH$_2$C=, NCHCH$_2$CH_2CH–CPh$_2$), 1.70–1.78 (m, 1H, NCHCH_2CH$_2$C=), 2.14–2.21 (m, 3H, NCH=CCH_2, NCHCH_2CH$_2$CHCPh$_2$), 2.22–2.31 (m, 1H, NCH=CCH_2), 3.12–3.21 (m, 1H, NCHCH$_2$), 3.58 (s, 3H, $COOCH_3$), 4.16 (br, 1H, NH), 6.07 (t, J=6.8 Hz, 1H, HC=CPh$_2$), 7.12–7.29 (m, 7H, $H_{arom.}$, NCH=C), 7.29–7.45 (m, 4H, $H_{arom.}$). MS (CI, CH_5^+); m/z (%): 348 [M^++1] (100), 316 (13), 237 (1), 138 (12).

6.1.12. Methyl (*R*)-6-(4,4-diphenylbut-3-enyl)-1,4,5,6-tetrahydropyridine-3-carboxylate [(*ent*)-27]. Synthesis as described for the preparation of **27** from 37 mg (0.067 mmol) of **26** in 340 μl THF with 1.2 ml of freshly prepared NaOMe (0.5 M in $CH_3OH_{abs.}$). Purification by CC (CH_2Cl_2/ CH_3OH=95:5) afforded 22 mg (90%) of (*ent*)-**27**. As product (*ent*)-**27** appeared to be labile, it could not be fully characterized. It was immediately transformed to either the compounds (*ent*)-**28** and (*ent*)-**29** or (*ent*)-**34**.

Compound (*ent*)-**27**. Colorless oil. ^1H NMR as described for **27**. MS (CI, CH_5^+); m/z (%): 348 [M^++1] (100), 316 (12), 237 (21), 138 (23).

6.1.13. Methyl (3*S*,6*S*)-6-(4,4-diphenylbutyl)piperidine-3-carboxylate (28) and methyl (3*R*,6*S*)-6-(4,4-diphenylbutyl)piperidine-3-carboxylate (29). The starting material **27** was prepared as described above from 430 mg (0.794 mmol) of **25** in 4 ml THF and 18 ml of freshly prepared NaOMe (0.5 M in $CH_3OH_{abs.}$). Following purification by CC (CH_2Cl_2/CH_3OH=95:5) the solvent was removed in vacuo and the residue was dissolved in 1.8 ml of CF_3CO_2H. 380 μl (278 mg, 2.392 mmol, 3 equiv.) of Et_3SiH were added dropwise and the reaction mixture was stirred for 3 h at 50 °C. The reaction was quenched with saturated $NaHCO_3$ solution. The reaction mixture was extracted with CH_2Cl_2 and the combined organic layers were dried ($MgSO_4$) and concentrated in vacuo. Purification by CC (Et_2O/$EtMe_2N$=98:2) afforded 140 mg (50%) of a mixture of **28** and **29**.

Compounds **28** and **29**. Colorless oil. TLC: R_f=0.28 (Et_2O/$EtMe_2N$=98:2). ^1H NMR (CD_2Cl_2): δ=0.93–1.05 ppm (m, 1H, NCHCH_2 (**28**), NCHCH_2 (**29**)), 1.22–1.40 (m, 4H, CH_2CH_2), 1.40–1.52 (m, 0.8×1H, NCHCH_2 (**28**)), 1.53–1.61 (m, 0.2×1H, NCHCH_2 (**29**)), 1.65–1.75 (m, 1H, NCH$_2$CHCH_2 (**28**), NCH$_2$CHCH_2 (**29**)), 1.96–2.15 (m, 3H, NCH$_2$CHCH_2 (**28**), NCH$_2$CHCH_2 (**29**), CH_2CHPh$_2$ (**28**), CH_2CHPh$_2$ (**29**)), 2.28–2.37 (m, 1.8H, NHCH_{ax} (**28**) one large coupling J=12.1 Hz was identifiable, CHCOO (**28**), CHCOO (**29**)), 2.38–2.43 (m, one large coupling J=12.1 Hz was identifiable, 0.2H, NHCH_{ax} (**29**)), 2.60 (dd, J=11.8/11.3 Hz, 0.8×1H, NCH$_{2ax}$ (**28**)), 2.71 (dd, J=12.8/3.5 Hz, 0.2×1H, NCH$_{2ax}$ (**29**)), 3.20 (dd, J=11.8/4.1 Hz, 0.8×1H, NCH$_{2eq}$ (**28**)), 3.31 (dd, J=12.8/2.5 Hz,

0.2×1H, NCH_{2eq} (**29**)), 3.61 (s, 0.8×3H, $COOCH_3$ (**28**)), 3.66 (s, 0.2×3H, $COOCH_3$ (**29**)), 3.89 (t, J=7.7 Hz, 0.2×1H, Ph_2CH (**29**)), 3.90 (t, J=7.7 Hz, 0.8×1H, Ph_2CH (**28**)), 7.11–7.20 (m, 2H, $H_{arom.\ para}$), 7.21–7.35 (m, 8H, $H_{arom.\ ortho,\ meta}$); **28/29**=83/17. MS (CI, CH_5^+); *m/z* (%): 352 [M^++1] (100), 320 (3), 274 (3), 142 (20). HRM (70 eV) for $C_{23}H_{29}NO_2$: calcd 351.2198; found 351.2195 (M^+). $C_{23}H_{29}NO_2$ (355.22): calcd C 78.65, H 8.31, N 3.99; found C 77.36, H 8.66, N 3.68.

6.1.14. Methyl (3*R*,6*R*)-6-(4,4-diphenylbutyl)piperidine-3-carboxylate [(*ent*)-28] and methyl (3*S*,6*R*)-6-(4,4-diphenylbutyl)piperidine-3-carboxylate [(*ent*)-29]. Synthesis as described for the preparation of **28** and **29** from 203 mg (0.345 mmol) of **26** in 1.9 ml of THF with 6.7 ml of freshly prepared NaOMe (0.5 M in $CH_3OH_{abs.}$), 950 μl of CF_3CO_2H and 193 μl (141 mg, 1.214 mmol, 3.5 equiv.) of Et_3SiH. Purification by CC (Et_2O/$EtMe_2N$=98:2) afforded 66 mg (50%) of a mixture of (*ent*)-**28** and (*ent*)-**29**.

Compounds (*ent*)-**28** and (*ent*)-**29**. ^{1}H NMR and IR as described for **28** and **29**, respectively. Colorless oil. HRM (70 eV) for $C_{23}H_{29}NO_2$: calcd 351.2198; found 351.2193 (M^+).

6.1.15. Methyl (3*S*,6*S*)-1-*tert*-butyloxycarbonyl-6-(4,4-diphenylbutyl)piperidine-3-carboxylate (30) and methyl (3*R*,6*S*)-1-*tert*-butyloxycarbonyl-6-(4,4-diphenylbutyl)-piperidine-3-carboxylate (31). 44 μl (32 mg, 0.313 mmol, 1.0 equiv.) of NEt_3, 307 mg (1.407 mmol, 4.4 equiv.) of di-*tert*-butyldicarbonate and 39 mg (0.319 mmol, 1.0 equiv.) of DMAP were added to a solution of 110 mg (0.313 mmol) of a mixture of **28** and **29** (**28/29**=83/17) in 1.7 ml of THF. The reaction mixture was stirred for 3 days at room temperature. Phosphate buffer (pH 7, c=1.0 M) was added. The reaction mixture was extracted with CH_2Cl_2. The combined organic layers were dried ($MgSO_4$) and concentrated in vacuo. Purification by CC (*iso*-hexane/Et_2O/$EtMe_2N$=80:20:2) afforded 81 mg (70%) of **30** and 17 mg (10%) of **31**.

Compound **30**. Colorless oil. TLC: R_f=0.14 (*iso*-hexane/Et_2O/dimethylethyl amine=80:20:2). $[\alpha]_D^{20}$=+38.7 (c=1.16, CH_2Cl_2). IR: $\tilde{\nu}$=2932 cm^{-1}, 1736, 1688, 1418, 1365, 1162, 741, 702. ^{1}H NMR (CD_2Cl_2): δ=1.10–1.25 ppm (m, 2H, $CH_2CH_2CHPh_2$), 1.29–1.36 (m, 1H, $NCHCH_2$), 1.34 (s, 9H, *t*Bu), 1.36–1.44 (m, 1H, $NCHCH_2$), 1.64–1.84 (m, 3H, NCH_2CHCH_2, $CH_2CH_2CH_2CHPh_2$), 1.89–1.92 (m, 1H, NCH_2CHCH_2), 1.98–2.14 (m, 2H, CH_2CHPh_2), 2.47–2.53 (m, 1H, $CHCOO$), 2.89 (dd, J=14.0/4.0 Hz, 1H, NCH_2CHCOO), 3.66 (s, 3H, $COOCH_3$), 3.87 (t, J=7.7 Hz, 1H, Ph_2CH), 4.06–4.16 (m, 1H, $NCHCH_2$), 4.32 (d, J=14.0 Hz, 1H, NCH_2CHCOO), 7.09–7.20 (m, 2H, $H_{arom.\ ortho}$), 7.21–7.30 (m, 8H, $H_{arom.\ meta,\ para}$). MS (CI, CH_5^+); *m/z* (%): 452 [M^++1] (2), 396 (91), 352 (100), 142 (89). $C_{28}H_{37}NO_4$ (451.61): calcd C 74.47, H 8.26, N 3.10; found C 74.66, H 8.52, N 3.09.

Compound **31**. Colorless oil. TLC: R_f=0.26 (*iso*-hexane/Et_2O/$EtMe_2N$=80:20:2). $[\alpha]_D^{20}$=−22.6 (c=0.73, CH_2Cl_2). IR: $\tilde{\nu}$=2933 cm^{-1}, 1731, 1682, 1420, 1265, 1161, 740, 706. ^{1}H NMR (CD_2Cl_2): δ=1.09–1.24 ppm (m, 2H, $CH_2CH_2CHPh_2$), 1.33 (s, 9H, *t*Bu), 1.30–1.45 (m, 1H, $NCHCH_2$), 1.51–1.79 (m, 4H, $NCHCH_2$, NCH_2CHCH_2, $CH_2CH_2CH_2CHPh_2$), 1.79–1.88 (m, 1H, NCH_2CHCH_2), 1.97–2.16 (m, 2H, CH_2CHPh_2), 2.35 (dddd, J=11.9/11.6/4.3/4.0 Hz, 1H, $CHCOO$), 2.63–2.86 (br_{koal}, 1H, NCH_2CHCOO), 3.66 (s, 3H, $COOCH_3$), 3.88 (t, J=7.7 Hz, 1H, Ph_2CH), 3.96–4.34 (br_{koal}, 2H, $NCHCH_2$, NCH_2CHCOO), 7.11–7.40 (m, 10H, $H_{arom.}$). ^{1}H NMR (CD_2Cl_2, −78 °C): 0.93–1.09 ppm (m, 2H, $CH_2CH_2CHPh_2$), 1.15 (s, 0.65×9H, *t*Bu), 1.30 (s, 0.35×9H, *t*Bu), 1.41–1.67 (m, 4H, $CH_2CH_2CH_2CHPh_2$, $NCHCH_2$), 1.71–1.82 (m, 2H, CH_2CHPh_2), 1.82–1.94 (m, 1H, NCH_2CHCH_2), 1.95–2.06 (m, 1H, NCH_2CHCH_2), 2.23–2.35 (m, 1H, $CHCOO$), 2.65 (dd, J=13.7/12.5 Hz, 0.65×1H, NCH_2CHCOO_{ax}), 2.73 (dd, J=13.7/12.5 Hz, 0.35×1H, NCH_2CHCOO_{ax}), 3.57 (s, 0.65×3H, $COOCH_3$), 3.58 (s, 0.35×3H, $COOCH_3$), 3.79 (t, J=6.4 Hz, 1H, Ph_2CH), 3.95 (dd, J=13.7/2.9 Hz, 0.35×1H, NCH_2CHCOO_{eq}), 3.98–4.06 (m, 0.65×1H, $NCHCH_2$), 4.05–4.17 (m, 1H, $NCHCH_2$, NCH_2CHCOO_{eq}), 7.04–7.16 (m, 2H, $H_{arom.\ ortho}$), 7.15–7.30 (m, 8H, $H_{arom.\ meta,\ para}$); ratio of rotamers: 65/35. MS (CI, CH_5^+); *m/z* (%): 452 [M^++1] (1), 396 (86), 352 (100), 142 (75). HRM (70 eV) for $C_{28}H_{37}NO_4$: calcd 451.2723; found 451.2721 (M^+).

6.1.16. Methyl (3*R*,6*R*)-1-*tert*-butyloxycarbonyl-6-(4,4-diphenylbutyl)piperidine-3-carboxylate [(*ent*)-30] and methyl (3*S*,6*R*)-1-*tert*-butyloxycarbonyl-6-(4,4-diphenyl-butyl)piperidine-3-carboxylate (32). Synthesis as described for **30** and **31** from 59 mg (0.167 mmol) of a mixture of (*ent*)-**28** and (*ent*)-**29** [(*ent*)-**29**/(*ent*)-**28**=79/21] in 290 μl of THF with 23 μl (17 mg, 0.167 mmol, 1.0 equiv.) of NEt_3, 164 mg (0.751 mmol, 4.4 equiv.) of di-*tert*-butyldicarbonate and 21 mg (0.319 mmol, 1.9 equiv.) of DMAP, reaction time: 2 days. Purification by CC (*iso*-hexane/Et_2O/$EtMe_2N$=80:20:2) afforded 43 mg (57%) of (*ent*)-**30** and 17 mg (10%) of (*ent*)-**31**.

Compound (*ent*)-**30**. Colorless Oil. ^{1}H NMR and IR as described for **30**. $[\alpha]_D^{20}$=−37.8° (c=0.68, CH_2Cl_2). $C_{28}H_{37}NO_4$ (451.61): calcd C 74.47, H 8.26, N 3.10; found C 74.07, H 8.23, N 3.08.

Compound (*ent*)-**31**. Colorless Oil. ^{1}H NMR and IR as described for **31**. $[\alpha]_D^{20}$=+22.8 (c=0.365, CH_2Cl_2). HRM (70 eV) for $C_{28}H_{37}NO_4$: calcd 451.2723; found 451.2721 (M^+).

6.1.17. (3*S*,6*S*)-6-(4,4-Diphenylbutyl)piperidine-3-carboxylic acid hydrochloride (32). 34 mg (0.075 mmol) of **30** in 9 ml of 2 M HCl were refluxed for 3 h. After cooling to room temperature the solvent was removed in vacuo and the residue was dried over P_2O_5. Yield: 28 mg (100%).

Compound **32**. Colorless crystals, mp 249 °C. $[\alpha]_D^{20}$=+7.6 (c=0.38, DMSO). IR: $\tilde{\nu}$=3423 cm^{-1}, 2940, 2804, 2501, 1724, 1200, 1180, 765, 699. ^{1}H NMR (DMSO-d_6): δ=1.15–1.29 ppm (m, 2H, $Ph_2CHCH_2CH_2$), 1.28–1.40 (m, 1H, $NCHCH_2$), 1.42–1.55 (m, 2H, $NCHCH_2$, $Ph_2CH(CH_2)_2CH_2$), 1.60–1.71 (m, 1H, $Ph_2CH(CH_2)_2CH_2$), 1.74–1.84 (m, 1H, NCH_2CHCH_2), 1.93–2.09 (m, 3H, Ph_2CHCH_2, NCH_2CHCH_2), 2.59–2.69 (m, 1H, $CHCOOH$), 2.86 (dd, J=13.7/12.0 Hz, 1H, $NCH_{2ax}CHCOO$), 2.90–3.00 (m, 1H, $NCHCH_2$), 3.30 (d, J=13.7 Hz, 1H, $NCH_{2eq}CHCOO$), 3.92 (t, J=7.0 Hz, 1H, Ph_2CH), 7.02–7.19 (m, 2H, $H_{arom.}$), 7.20–7.35 (m, 8H, $H_{arom.}$), 8.62–9.03 (br, 2H,

NH_2^+), 12.54–12.89 (br, 1H, COOH). MS (70 eV); *m/z* (%): 337 [M^+−HCl] (5), 319 (4), 260 (1) 167 (12), 128 (100). $C_{22}H_{28}NO_2Cl{\cdot}0.5H_2O$ (382.93): calcd C 69.00, H 7.63, N 3.66; found C 68.87, H 7.57, N 3.54.

6.1.18. (3*R*,6*S*)-6-(4,4-Diphenylbutyl)piperidine-3-carboxylic acid hydrochloride (33). Synthesis as described for the preparation of **32** from 14 mg (0.031 mmol) of **31** in 3.8 ml of 2 M HCl. Yield: 12 mg (99%).

Compound **33**. Colorless crystals, mp 215 °C. $[\alpha]_D^{20}=-0.5$ (c=0.38, DMSO). $[\alpha]_D^{20}=-0.5$ (c=0.19, DMSO). IR: $\tilde{\nu}$=3423 cm^{-1}, 2928, 2862, 1710, 1223, 1107, 762, 701. ^1H NMR (DMSO-d_6): δ=1.18–1.26 ppm (m, 2H, $Ph_2CHCH_2CH_2$), 1.28–1.37 (m, 1H, NCHCH_2), 1.51–1.65 (m, 2H, $Ph_2CH(CH_2)_2CH_2$), 1.67–1.77 (m, 2H, NCHCH_2, NCH_2CHCH_2), 1.87–1.98 (m, 1H, NCH_2CHCH_2), 1.98–2.11 (m, 2H, Ph_2CHCH_2), 2.77–2.84 (m, 1H, C*H*COOH), 3.00–3.12 (m, 2H, NCH_2CH, NCH_{2ax}CHCOO), 3.30 (d, J=13.7 Hz, 1H, NCH_{2eq}CHCOO), 3.93 (t, J=7.6 Hz, 1H, Ph_2CH), 7.11–7.22 (m, 2H, $H_{arom.}$), 7.21–7.37 (m, 8H, $H_{arom.}$), 7.88–8.06 (br, 1H, NH_2^+), 8.84–9.05 (br, 1H, NH_2^+), 12.78–12.98 (br, 1H, COOH). MS (70 eV); *m/z* (%): 337 [M^+−HCl] (10), 167 (11), 128 (100). HRM (70 eV) for $C_{22}H_{27}NO_2$: calcd 337.2035; found 337.2030 (M^+).

6.1.19. (3*R*,6*R*)-6-(4,4-Diphenylbutyl)piperidine-3-carboxylic acid hydrochloride [(*ent*)-32]. Synthesis as described for the preparation of **32** from 27 mg (0.060 mmol) of (*ent*)-**30** in 7 ml of 2 M HCl. Yield: 22 mg (100%).

Compound (*ent*)-**32**. Colorless crystals. ^1H NMR and IR as described for **32**. $[\alpha]_D^{20}=-7.4$ (c=0.19, DMSO). $C_{22}H_{28}NO_2Cl{\cdot}0.5H_2O$ (382.93): calcd C 69.00, H 7.63, N 3.66; found C 69.21, H 7.63, N 3.66.

6.1.20. (3*S*,6*R*)-6-(4,4-Diphenylbutyl)piperidine-3-carboxylic acid hydrochloride [(*ent*)-33]. Synthesis as described for the preparation of **33** from 6.6 mg (0.015 mmol) of (*ent*)-**31** in 1.8 ml of 2 M HCl. Yield: 5.5 mg (100%).

Compound (*ent*)-**33**. Colorless crystals. ^1H NMR and IR as described for **33**. $[\alpha]_D^{20}=+0.7$ (c=0.08, DMSO). HRM (70 eV) for $C_{22}H_{27}NO_2$: calcd 337.2035; found 337.2031 (M^+).

6.1.21. (*S*)-Methyl [1-*tert*-butyloxycarbonyl-6-(4,4-diphenylbut-3-enyl)-1,4,5,6-tetrahydropyridine-3-carboxylate] (34). The starting material **27** was prepared as described above from 352 mg (0.650 mmol) of **25** in 3.2 ml of THF with 11.5 ml of freshly prepared NaOMe (0.5 M in $CH_3OH_{abs.}$). After purification by CC (CH_2Cl_2/CH_3OH=95:5) the solvent was removed in vacuo and the residue was dissolved in 1.24 ml of THF. 101 μl (74 mg, 0.728 mmol, 1.12 equiv.) of NEt_3, 716 mg (3.282 mmol, 5.05 equiv.) of di-*tert*-butyldicarbonate and 92 mg (0.755 mmol, 1.16 equiv.) of DMAP were added. The reaction mixture was stirred for 3 days. Phosphate buffer (pH 7, c=1.0 M) was added. The reaction mixture was extracted with CH_2Cl_2. The combined organic layers were dried ($MgSO_4$) and concentrated in vacuo. Purification by CC (*iso*-hexane/Et_2O=80:20) afforded 217 mg (75%) of **34**.

Compound **34**. Colorless oil. TLC: R_f=0.24 (*iso*-hexane/Et_2O=80:20)-$[\alpha]_D^{20}=+48.5$ (c=0.46 in CH_2Cl_2). IR (Film): $\tilde{\nu}$=2946 cm^{-1}, 1634, 1455, 1416, 1028, 739, 700. ^1H NMR ($C_2D_2Cl_4$, 120 °C): δ=1.51 ppm (s, 9H, *t*Bu), 1.57–1.75 (m, 3H, NCHCH_2, $Ph_2CCHCH_2CH_2$), 1.83 (ddt, J=13.5/5.8/2.3 Hz, 1H, NCHCH_2), 2.06–2.27 (m, 3H, NCHCCH_2, Ph_2CCHCH_2), 2.40 (dd, J=18.4/4.9 Hz, 1H, NCHCCH_2), 3.76 (s, 3H, $COOCH_3$), 4.21–4.28 (m, 1H, NC*H*CH_2), 6.11 (t, J=7.6 Hz, 1H, *H*C=CPh_2), 7.17–7 44 (m, 10H, $H_{arom.}$), 8.01 (s, 1H, NC*H*=C). MS (CI, CH_5^+); *m/z* (%): 448 [M^++1] (54), 416 (9), 392 (100), 348 (98), 182 (29), 142 (34), 138 (24). $C_{28}H_{33}NO_4$ (447.57): calcd C 75.14, H 7.45, N 3.13; found C 74.64, H 7.95, N 2.66.

6.1.22. (*R*)-Methyl [1-*tert*-butyloxycarbonyl-6-(4,4-diphenylbut-3-enyl)-1,4,5,6-tetrahydropyridine-3-carboxylate] [(*ent*)-34]. The starting material (*ent*)-**27** was prepared as described above from 118 mg (0.218 mmol) of **26** in 1.2 ml of THF, 4.2 ml of freshly prepared NaOMe (0.5 M in $CH_3OH_{abs.}$). The synthesis of (*ent*)-**34** was performed in analogy to the preparation of **34** from 71 mg of (*ent*)-**27** in 0.4 ml of THF with 101 μl (25 mg, 0.245 mmol, 1.12 equiv.) of NEt_3, 241 mg (1.105 mmol, 5.05 equiv.) of di-*tert*-butyldicarbonate and 31 mg (0.254 mmol, 1.16 equiv.) of DMAP. Purification by CC (*iso*-hexane/Et_2O=80:20) afforded 51 mg (52%) of (*ent*)-**34**.

Compound (*ent*)-**34**. Colorless oil. ^1H NMR and IR as described for **34**. $[\alpha]_D^{20}=-47.4$ (c=1.35, CH_2Cl_2). $C_{28}H_{33}NO_4$ (447.57): calcd C 75.14, H 7.45, N 3.13; found C 74.84, H 7.56, N 3.04.

6.1.23. (3*S*,6*S*)-Methyl [1-*tert*-butyloxycarbonyl-6-(4,4-diphenylbut-3-enyl)piperidine-3-carboxylate] (35) and (3*R*,6*S*)-methyl [1-*tert*-butyloxycarbonyl-6-(4,4-diphenylbut-3-enyl)piperidine-3-carboxylate] (36). 428 mg of magnesium powder were added to 185 mg (0.141 mmol) of **34** in 1.64 ml of CH_3OH. After 20 min in a sonicator 5 ml of CH_3OH were added, followed by the addition of 4 ml of CH_3OH after 1 h. Following stirring for 18 h phosphate buffer (pH 7, c=1.0 M) was added and the reaction mixture was extracted with CH_2Cl_2. The combined organic layers were dried ($MgSO_4$) and concentrated in vacuo. Purification by CC (*iso*-hexane/Et_2O=70:30) and separation by prep. HPLC (*iso*-hexane/Et_2O=70:30; 9 ml/min) yielded 69 mg (37%) of **35** (t_R=42.14 min) and 51 mg (28%) of **36** (t_R=26.20 min). Analytical HPLC (*iso*-hexane/Et_2O=70:30; 1.0 ml/min); **36**: t_R=10.41 min, 42.4%; **35**: t_R=18.36 min, 57.6%.

Compound **35**. Colorless oil. TLC: R_f=0.21 (*iso*-hexane/Et_2O=70:380)-$[\alpha]_D^{20}=+45.2$ (c=0.5, CH_2Cl_2). IR: $\tilde{\nu}$=2928 cm^{-1}, 1738, 1693, 1418, 1364, 1364, 1168, 764, 701. ^1H NMR (CD_2Cl_2): δ=1.41 ppm (s, 9H, *t*Bu), 1.36–1.45 (m, 2H, NCHCH_2), 1.49–1.60 (m, 1H, CH_2CH_2-$CHCPh_2$), 1.67–1.90 (m, 2H, $CH_2CH_2CHCPh_2$, NCH_2-$CHCH_2$), 1.95–2.16 (m, 3H, NCH_2CHCH_2, CH_2CHCPh_2), 2.52–2.57 (m, 1H, C*H*COO), 2.93 (dd, J=14.0/4.1 Hz, 1H, NCH_2CHCOO), 3.66 (s, 3H, $COOCH_3$), 4.15–4.24 (m, 1H, NC*H*CH_2), 4.41 (d, J=14.0 Hz, 1H, NCH_2CHCOO), 6.10 (t, J=7.6 Hz, 1H, Ph_2C=C*H*), 7.14–7.44 (m, 10H, $H_{arom.}$).

MS (CI, CH_5^+); *m/z* (%): 450 [M^++1] (2), 350 (100), 142 (49). $C_{28}H_{35}NO_4$ (449.59): calcd C 74.80, H 7.85, N 3.12; found C 74.80, H 8.00, N 2.90.

Compound **36**. Colorless oil. TLC: R_f=0.31 (*iso*-hexane/Et_2O=70:30). $[\alpha]_D^{20}$=−12.8 (*c*=0.5, CH_2Cl_2). IR: $\tilde{\nu}$=2924 cm^{-1}, 1734, 1691, 1416, 1164, 765, 701. ^1H NMR (CD_2Cl_2): δ=1.32–1.45 ppm (br_{koal}, 9H, *t*Bu), 1.45–1.75 (m, 4H, NCHCH_2, C$H_2$$CH_2CHCPh_2$), 1.75–1.93 (m, 2H, NCH_2CHCH_2), 1.96–2.15 (m, 2H, CH_2CHCPh_2), 2.30–2.48 (m, 1H, C*H*COO), 2.66–2.86 (br_{koal}, 1H, NCH_2CHCOO), 3.68 (s, 3H, $COOCH_3$), 3.97–4.35 (br_{koal}, 2H, NC*H*CH_2, NCH_2CHCOO), 6.09 ppm (t, *J*=8.1 Hz, 1H, Ph_2C=CH), 7.11–7.40 (m, 10H, $H_{arom.}$). MS (CI, CH_5^+); *m/z* (%): 450 [M^++1] (2), 394 (15), 350 (100), 142 (43). $C_{28}H_{35}NO_4$ (449.59): calcd C 74.80, H 7.85, N 3.12; found C 74.67, H 7.91, N 3.01.

6.1.24. (3*R*,6*R*)-Methyl [1-*tert*-butyloxycarbonyl-6-(4,4-diphenylbut-3-enyl)piperidine-3-carboxylate] [(*ent*)-35] and (3*S*,6*R*)-methyl [1-*tert*-butyloxycarbonyl-6-(4,4-diphenylbut-3-enyl)piperidine-3-carboxylate] [(*ent*)-36]. Synthesis as described for **35** and **36** from 65 mg (0.145 mmol) of (*ent*)-**34** with 150 mg magnesium powder and 0.6 ml of CH_3OH. Purification by CC (*iso*-hexane/Et_2O=70:30) and separation by prep. HPLC (*iso*-hexane/Et_2O=70:30; 9 ml/min) yielded 10 mg (16%) of (*ent*)-**35** (t_R=42.14 min) and 17 mg (26%) of (*ent*)-**36** (t_R=26.20 min). Analytical HPLC (*iso*-hexane/Et_2O=70:30; 1.0 ml/min); (*ent*)-**36**: t_R=10.41 min, 42.6%; (*ent*)-**35**: t_R=18.36 min, 57.4%.

Compound (*ent*)-**35**. Colorless oil. ^1H NMR and IR as described for **35**. $[\alpha]_D^{20}$=−45.6° (*c*=0.82, CH_2Cl_2). HRM (70 eV) for $C_{28}H_{35}NO_4$: calcd 449.2566; found 449.2614 (M^+).

Compound (*ent*)-**36**. Colorless oil. ^1H NMR and IR as described for **36**. $[\alpha]_D^{20}$=+10.2 (*c*=0.50, CH_2Cl_2). HRM (70 eV) for $C_{28}H_{35}NO_4$: calcd 429.2566; found 449.2560 (M^+).

6.1.25. (3*S*,6*S*)-6-(4,4-Diphenylbutyl)piperidine-3-carboxylic acid hydrochloride (37). Synthesis as described for the preparation of **32** from 48 mg (0.107 mmol) of **35** in 13 ml of 2 M HCl. Yield: 38 mg (92%).

Compound **37**. Colorless crystals, mp 234–236 °C (decomp.). $[\alpha]_D^{20}$=+13.6 (*c*=0.53, DMSO). $\tilde{\nu}$=3445 cm^{-1}, 2930, 2730, 2361, 1734, 1162, 766, 703, 696. ^1H NMR (DMSO-d_6): δ=1.26–1.40 ppm (m, one large coupling *J*=12.9 Hz was identifiable, 1H, NCHCH_2), 1.40–1.55 (m, 1H, NCH_2CHCH_2), 1.55–1.67 (m, 1H, Ph_2CCHCH_2CH_2), 1.67–1.77 (m, 1H, NCHCH_2), 1.77–1.87 (m, 1H, Ph_2CCHCH_2CH_2), 1.93–2.03 (m, 1H, NCH_2CHCH_2), 2.09–2.15 (m, 2H, Ph_2CCHCH_2), 2.62–2.72 (m, 1H, C*H*COOH), 2.90 (dd, *J*=13.0/11.6 Hz, 1H, NC$H_2$$CHCOO_{ax}$), 2.95–3.04 (m, 1H, NC*H*CH_2), 3.39–3.44 (m, 1H, NC$H_2$$CHCOO_{eq}$), 6.10 (t, *J*=7.0 Hz, 1H, Ph_2CCH), 7.07–7.50 (m, 10H, $H_{arom.}$), 8.76–9.08 (br, 2H, NH_2^+), 12.61–12.91 (br, 1H, COOH). MS (CI, CH_5^+); *m/z* (%): 336 [M^++1-HCl] (37). $C_{22}H_{28}NO_3Cl$ (389.92): calcd C 67.77, H 7.24, N 3.59; found C 67.97, H 7.02, N 3.59.

6.1.26. (3*R*,6*R*)-6-(4,4-Diphenylbutyl)piperidine-3-carboxylic acid hydrochloride [(*ent*)-37]. Synthesis as described for the preparation of **37** from 10 mg (0.022 mmol) of (*ent*)-**35** in 2.8 ml of 2 M HCl. Yield: 8 mg (100%).

Compound (*ent*)-**37**. Colorless crystals. ^1H NMR and IR as described for **37**. $[\alpha]_D^{20}$=−14.3° (*c*=0.37, DMSO). HRM (70 eV) for $C_{28}H_{35}NO_4$: calcd 335.1885; found 335.1884 (M^+).

6.1.27. (3*R*,6*S*)-6-(4,4-Diphenylbuty-3-enyl)piperidine-3-carboxylic acid hydrochloride (38). Synthesis as described for the preparation of **32** from 32 mg (0.071 mmol) of **36** in 8.7 ml of 2 M HCl. Yield: 28 mg (97%).

Compound **38**. Colorless crystals, mp 150 °C (decomp.). $[\alpha]_D^{20}$=+12.7° (*c*=0.48, DMSO). IR: $\tilde{\nu}$=3425 cm^{-1}, 2926, 2360, 1733, 1445, 767, 698. ^1H NMR (DMSO-d_6): δ=1.21–1.35 ppm (m, 1H, NC*H*CH_2), 1.60–1.73 (m, 3H, NCHCH_2, NCH_2CHCH_2, Ph_2CCHCH_2CH_2), 1.73–1.83 (m, 1H, Ph_2CCHCH_2CH_2), 1.87–1.97 (m, 1H, NCH_2CHCH_2), 2.04–2.17 (m, 2H, Ph_2CCHCH_2), 2.78–2.85 (m, 1H, C*H*COOH), 3.03–3.14 (m, 2H, NC*H*CH_2, NCH_2-$CHCOO_{ax}$), 3.29 (dd, *J*=13.2, 4.8 Hz, 1H, NCH_2-$CHCOO_{eq}$), 6.11 (t, *J*=7.7 Hz, 1H, Ph_2CCH), 7.06–7.57 (m, 10H, $H_{arom.}$), 7.88–8.31 (br, 1H, NH_2^+), 8.88–9.34 (br, 1H, NH_2^+), 12.60–13.15 (br, 1H, COOH). MS (CI, CH_5^+); *m/z* (%): 336 [M^++1-HCl] (72), 167 (11), 128 (100). $C_{22}H_{28}NO_3Cl$ (389.92): calcd. C 67.76, H 6.97, N 3.59; found C 67.70, H 6.93, N 3.77.

6.1.28. (3*S*,6*R*)-6-(4,4-Diphenylbutyl)piperidine-3-carboxylic acid hydrochloride [(*ent*)-38]. Synthesis as described for the preparation of **32** from 13 mg (0.028 mmol) of (*ent*)-**36** in 4.2 ml of 2 M HCl. Yield: 10 mg (99%).

Compound (*ent*)-**38**. Colorless crystals. ^1H NMR and IR as described for **38**. $[\alpha]_D^{20}$=−11.2° (*c*=0.37, DMSO). HRM (70 eV) for $C_{28}H_{35}NO_4$: calcd 335.1885; found 335.1871 (M^+).

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