Synthesis of Enantiopure Functionalized Pipecolic Acids via Amino Acid Derived *N*-Acyliminium Ions

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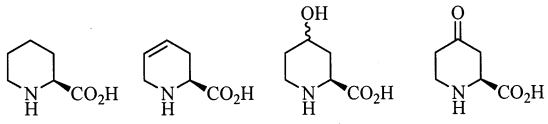
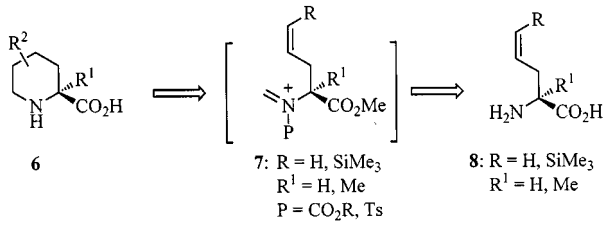
The synthesis and enzymatic resolution of a novel vinylsilane-containing amino acid is described. Derivatization of this and other olefinic amino acids followed by subjection to standard *N*-acyliminium ion cyclization conditions provides the corresponding pipecolic acid derivatives with – in most cases – complete conservation of enantiopurity. In addition to studying the scope of this reaction, details of the *N*-acyliminium ion cyclization including an aza Cope equilibrium are highlighted.

Pipecolic acids (hexahydropyridine-2-carboxylic acids) are cyclic α-amino acids that are frequently encountered in nature and often display interesting and potent biological activity.[1] Some examples of natural products are shown such as (*S*)-pipecolic acid (**1**),[2] baikiain (**2**),[3] the *cis*- and *trans*-4-hydroxypipecolic acids (**3**[4] and **4**[5]) and the 4-oxo derivative **5**, which is found in the virginiamycins.[6] Pipecolic acids that are functionalized at the 4-position form the major focus of this article. These types of heterocycles have been applied as building blocks in biologically active compounds[7] and may also function as rigid scaffolds for the introduction of functional group diversity in combinatorial chemistry approaches.[8]



1 **2** **3**: R = α-OH, **4**: R = β-OH **5**

The general interest in these types of heterocycles has aroused a great deal of research focused on the synthesis of a wide range of differently functionalized pipecolic acid derivatives both in racemic[9] and enantiopure form.[10] A particular pathway that has frequently been applied consists of the use of cationic cyclization reactions via iminium[11] and *N*-acyliminium ion intermediates.[12] The latter type of transformation is the subject of this research. As a part of our program to utilize non-natural amino acids for synthetic purposes, we set out to investigate the possibility of using the enantiomerically pure, nucleophile-containing amino acids **8** as starting materials for the construction of different pipecolic acid derivatives **6**. The non-natural amino acids **8** – available in enantiopure form by enzymatic resolution of the corresponding amino acid amides – should after functionalization lead to the desired heterocycles **6** via the *N*-acyliminium intermediates **7**.[13]



6 **7**: R = H, $SiMe_3$; R^1 = H, Me; P = CO_2R, Ts **8**: R = H, $SiMe_3$; R^1 = H, Me

Scheme 1. Retrosynthetic approach

This work was inspired by previous research in the Hiemstra/Speckamp group on cationic cyclization reactions of the glyoxylate adducts of the homoallylic carbamates **9** (Scheme 2).[12a–12c] These molecules smoothly cyclized upon treatment with Lewis acids[12b] or protic acids[12c] to give the cyclic products **12** as an approximately 1:1 mixture of the *cis*/*trans* isomers. This reaction proceeds via the achiral chair-like *N*-acyliminium ion **10**, which can undergo a [3,3]-sigmatropic rearrangement (aza Cope rearrangement) to the chiral isomeric *N*-acyliminium ion **11**. Nucleophilic attack of the olefin at the cation, followed by trapping of a formate ion then leads to the mixture of products **12**. The existence of the aza Cope rearrangement was proven by a trapping experiment: TFA-mediated generation of the cationic species in the presence of the hydride donor Et_3SiH gave the *N*-methylated allylglycine derivative **13** as the only reaction product, showing that the rearrangement must have taken place.[14]

The purpose of this research was to investigate whether the enantiomerically pure amino acids **8**, despite the possibility of the aza Cope rearrangement, would lead to enantiopure pipecolic acids. To the best of our knowledge, there is no literature precedent for this type of cyclization

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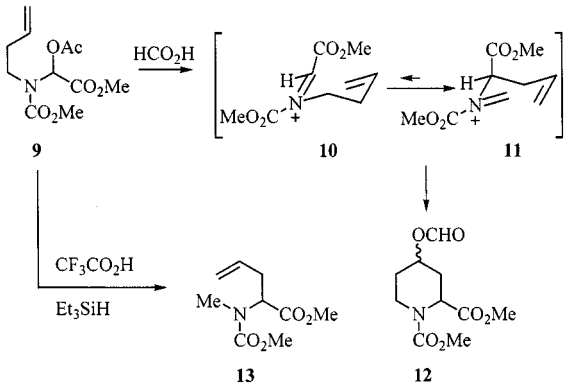
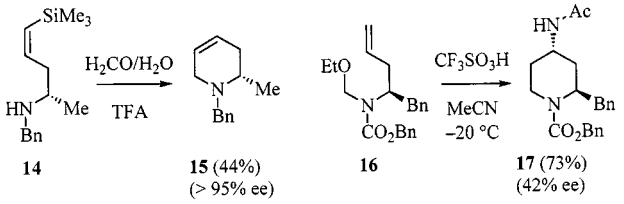


Scheme 2. Proof for the aza Cope rearrangement

with ester-substituted *N*-acyliminium ions and olefins as the nucleophiles. Similar reactions with alkyl-substituted iminium ions have been carried out by Overman and co-workers to arrive at enantiomerically pure α-Me-substituted tetrahydropyridines (**15**) by a vinylsilane-terminated cyclization of precursor **14** (Scheme 3). Initially, this reaction was reported to yield racemic products,[15a] but in a later publication complete retention of enantiopurity was claimed.[15b] An *N*-acyliminium version of this reaction was more recently pursued by Veenstra et al. at Novartis,[16] with the aim of preparing enantiopure 2-benzyl-substituted 4-aminopiperidines. Application of this method with the enantiomerically pure olefinic precursor **16** led to a 73% yield of the desired acetamido-substituted piperidine **17**, but in a low *ee* of 42%, which must be a result of the aza Cope equilibrium.

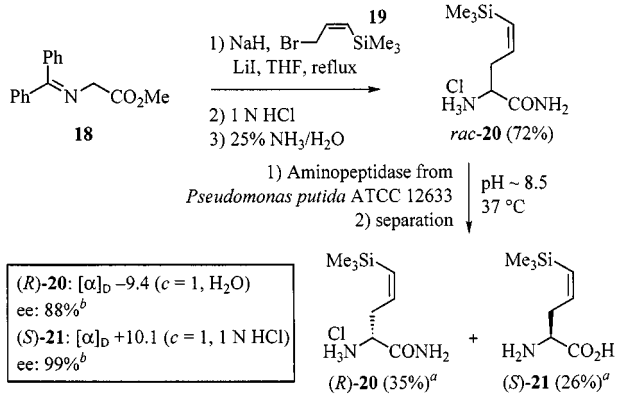


Scheme 3. Literature examples

We reasoned that with an α-ester instead of an α-benzyl substituent racemization would be more difficult: The strong electron-withdrawing effect of the ester relative to that of the benzyl function causes a large electronic difference between the two possible cations, thus preventing the aza Cope equilibrium to take place. As a result, the stereochemistry at the α-center will be retained. This reasoning is in agreement with the fact that in the trapping experiment starting from compound **9** a single product was obtained, despite the stronger electrophilic character of the *N*-acyliminium ion **10**.

Results and Discussion

In order to verify this hypothesis, three enantiomerically pure amino acids with different nucleophilic side chains were used: allylglycine (**8**, R = R^1 = H), α-Me-allylglycine (**8**, R = H, R^1 = Me) and the novel vinylsilane-containing amino acid **21**.



Scheme 4. [a] Based on a maximum theoretical yield of 50%; [b] ee determined by chiral HPLC [Crownpak CR(+)]

Enantiopure (*R*)-allylglycine was prepared according to a literature procedure by an enzymatic resolution (aminopeptidase from *Pseudomonas putida*) of racemic allylglycine amide,[17] while (*S*)-α-Me-allylglycine was accessible by a related resolution (aminopeptidase from *Mycobacterium neoaurum*).[18] The novel amino acid **21** was synthesized in enantiomerically pure form by a similar resolution of the racemic vinylsilane-containing amino acid amide **20** (Scheme 4). The sequence commenced with the glycine-derived ketimine **18** developed by O'Donnell.[19] Alkylation with (*Z*)-3-bromo-1-trimethylsilyl-1-propene (**19**)[20] followed by acid hydrolysis of the ketimine provided the corresponding methyl ester. The crude ester was treated with aqueous ammonia to give the amino acid amide, which was purified by formation of the Schiff base (PhCHO, H_2O, pH ≈ 9), extraction from the water layer and precipitation by acid hydrolysis in acetone. Thus, the racemic amide **20** was efficiently synthesized on a multigram scale in 72% overall yield without using column chromatography.

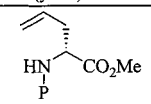
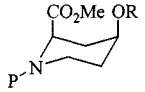
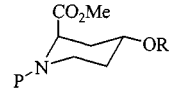
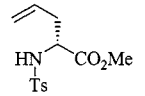
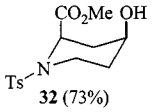
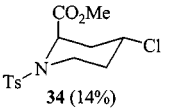
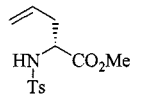
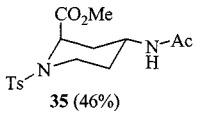
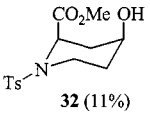
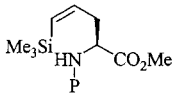
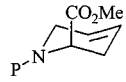
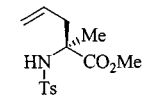
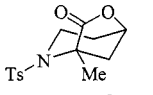
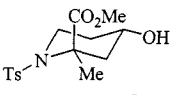
The racemic amino acid amide **20** was then subjected to the enzymatic resolution conditions (amidase produced by *Pseudomonas putida* ATCC 12633)[21][22] to give a mixture of the (*S*)-acid **21** and the corresponding (*R*)-amide. Separation occurred by the addition of benzaldehyde, followed by extraction of the resulting amide-derived Schiff base with CH_2Cl_2. The water layer was then concentrated and the residue purified by ion-exchange chromatography to yield the pure (*S*)-acid **21**. The Schiff base was hydrolyzed to give the (*R*)-amide **20**. As shown in Scheme 4, the amide was hydrolyzed with good enantioselectivity: This procedure afforded the amino acid (*S*)-**21** in an excellent *ee* of 99%,[25] while the (*R*)-amide **20** was shown to be slightly less pure (*ee*: 88%).

With these enantiopure amino acids in hand, the cyclization precursors **22**–**26** were obtained by standard methodology in good yields (shown in Table 1) and without detectable racemization according to chiral HPLC analysis (Chiralcel OD). In most cases (all except **23**) the amino acids were esterified, followed by reaction with methyl chloroformate or tosyl chloride. The Fmoc-protected precursor **23**

was obtained by reaction of the amino acid with FmocOSu, followed by esterification. In addition to these monosubstituted amino acids, the disubstituted amino acid α-Me-allylglycine was used to prepare precursor **27** by a similar procedure. Although the sulfonyl substituent will be more difficult to be removed in a later stage, this protecting group was deliberately chosen for the majority of the reactions since the absence of rotamers in the NMR spectra significantly simplified the interpretation of the results.

Having thus established the validity of this approach, different cyclization conditions were investigated to introduce other functionalities into the piperidine ring. For example, treatment of **24** with a formaldehyde equivalent and $SnCl_4$ should provide the corresponding chloride.[12b] Because paraformaldehyde itself is not compatible with such Lewis

Table 1 . Precursors, conditions and products of the cyclization reactions

Entry	Precursor (yield)[a]	Reaction Conditions	Reaction Time (h)	Product(s) (yield %)[b]	
					
1	**22**: P = CO_2Me (80%)	1.5 equiv $(H_2CO)_n$, HCOOH, rt	16	**28**: R = CHO (37%)[c]	**29**: R = CHO (40%)[c]
2	**23**: P = Fmoc (82%)	10 equiv $(H_2CO)_n$, HCOOH, rt	16	**30**: R = CHO (43%)	**31**: R = CHO (41%)
3	**24**: P = Ts (76%)	10 equiv $(H_2CO)_n$, HCOOH, 50 °C	18	**32**: R = H (54%)[d]	**33**: R = H (36%)[d]
					
4	**24**	1 equiv 1,3,5-trioxane, 4 equiv $SnCl_4$, CH_2Cl_2, rt	20	**32** (73%)	**34** (14%)
					
5	**24**	1 equiv 1,3,5-trioxane, 3 equiv $SnCl_4$, MeCN, 50 °C	18	**35** (46%)	**32** (11%)
					
6	**25**: P = CO_2Me (68%)	1.5 equiv $(H_2CO)_n$, HCOOH, rt	24	**36**: P = CO_2Me (40%)[e]	
7	**26**: P = Ts (59%)	1.5 equiv $(H_2CO)_n$, HCOOH, rt	60	**37**: P = Ts (60%)[f]	
					
8	**27** (76%)	10 equiv $(H_2CO)_n$, HCOOH, 50 °C	22	**38** (50%)[g]	**39** (32%)[g]

[a] Yields starting from the amino acids. – [b] *ee* > 98% (Chiralcel OD), unless stated otherwise. – [c] *ee* > 95% (^{1}H NMR). – [d] After treatment with NH_3/MeOH. – [e] *ee* not determined. – [f] *ee* = 88% = (Chiralcel OD). – [g] After treatment with NH_3/MeOH, heating in toluene with catalytic *p*TSA.

The results of the cyclization reactions are depicted in Table 1. The carbamate-protected amino esters **22** and **23** readily cyclized with the standard cyclization conditions (1.5 or 10 equiv of paraformaldehyde, HCO_2H, room temp.) to give approximately 1:1 mixtures of *cis* and *trans* products in comparable overall yields (entries 1 and 2). Both reactions proceeded with complete retention of stereochemistry at the C-2 center. This was proven for **28** and **29** by conversion of the corresponding alcohols (NH_3/MeOH, 0°C) into the camphanic esters [(1*S*)-camphanic chloride, DMAP, pyridine, CH_2Cl_2] and analysis by ^{1}H NMR (> 95% *de*). The enantiopurity of **30** and **31** was unambiguously established by analysis with chiral HPLC (Chiralcel OD), which was also the method of choice for analysis of the other cyclization products. The tosyl-protected amino ester **24** reacted more sluggishly at room temp., which is probably due to the more strongly electron-withdrawing effect of the tosyl group. At 50°C, however, the reaction was completed in 18 h, leading to a mixture of *cis* and *trans* products, which prior to purification were hydrolyzed to the alcohols **32** and **33**. Again, despite the higher reaction temperature, the cyclization did not lead to any loss of enantiopurity as was proven by chiral HPLC.

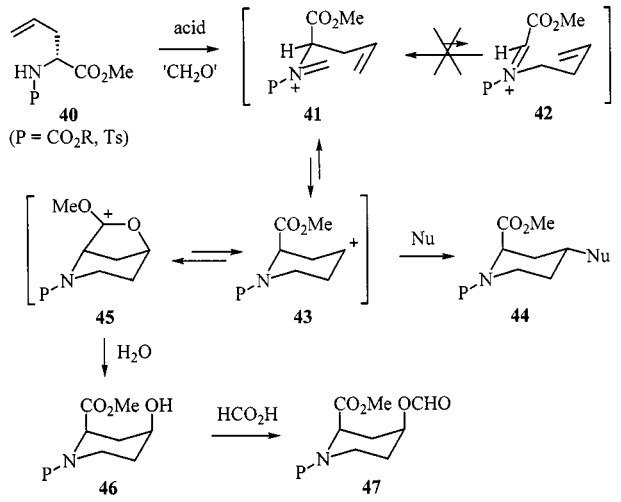
acids, *s*-trioxane was used as the source of the required C_1 moiety (entry 4). Surprisingly, reaction with *s*-trioxane and $SnCl_4$ yielded the desired chloride **34** only as a by-product (14% yield). Instead, the enantiopure axial alcohol **32** was obtained as the major product (73% yield), regardless of any modification in the reaction conditions. Other temperatures or amounts of Lewis acid did not lead to an improvement of this ratio. Alternatively, this reaction was carried out in MeCN with the aim of introducing an N substituent at the 4-position by a Ritter-type reaction. This time, the reaction did not proceed at room temp., but at 50°C a reasonable yield (46%) of the enantiopure acetamide **35** was obtained together with a small amount of the axial alcohol **32** (11%), which could be readily separated by chromatography (entry 5). Once again, also in these Lewis acid mediated cyclizations, no racemization could be detected.

The (*Z*)-vinylsilane-substituted amino acids **25** and **26** cyclized upon subjection to HCO_2H to afford the anticipated baikiain derivatives **36** and **37**, albeit in somewhat lower yields (entries 6 and 7). Apparently, the vinylsilane group

is not as good a nucleophile as the unsubstituted olefin. Unfortunately, the *ee* of the protected unsaturated pipecolic acid derivative **36** could not be determined, while the tosylated analog **37** was shown to be partly racemized (88% *ee*).

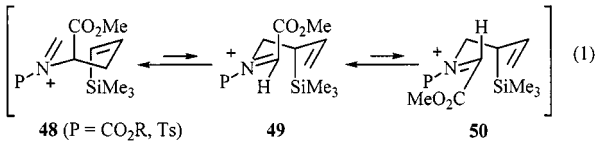
The disubstituted amino acid derivative **27** cyclized smoothly under the previously optimized conditions to give the expected mixture of *cis*/*trans* isomers, which could not be separated by chromatography (entry 8). Therefore, the formate esters were hydrolyzed and the resulting alcohols subjected to lactonization conditions to give lactone **38** and alcohol **39**. Separation by chromatography now led to the pure products, both of which were shown to be of more than 98% enantiopurity by chiral HPLC.

The results of entries 1−5 can be largely explained by invoking the mechanism shown in Scheme 5. Upon subjection to the cyclization conditions, precursor **40** will initially lead to the chairlike *N*-acyl- or *N*-tosyliminium intermediate **41**, which according to these results does not convert into the achiral ester-substituted iminium ion **42**. Cyclization of **41** then leads to the secondary cation **43**, which on the one hand can be trapped from the least hindered equatorial side by a nucleophile (formate, chloride or acetonitrile) to eventually give the *trans* product **44**. On the other hand, stabilization by the ester carbonyl group might take place, giving rise to the dioxycarbenium ion **45**. The latter intermediate can then be hydrolyzed under the reaction conditions (HCO_2H reactions) or during the workup ($SnCl_4$ reactions) to give the axial formate **47** or alcohol **46**, respectively.[12b,12c]



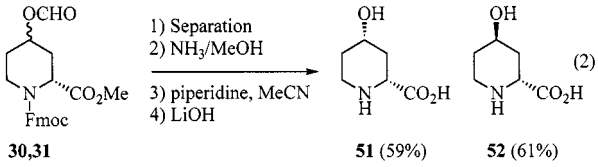
Scheme 5. Proposed mechanism of the cyclizations

Comparing these results with the cyclization described by Veenstra,[16] one can conclude that the ester substituent has a significant beneficial effect on the conservation of the enantiopurity. As stated before, this is probably the result of an electronic effect due to the electron-withdrawing properties of the ester function, thus preventing the aza Cope rearrangement to take place. In the case of the precursors **25** and **26**, the reaction is slightly different. The equilibrium now involves the (compared to the olefin) moderately nucleophilic vinylsilane **48**, which due to the low rate of cyclization can form the achiral allylsilane-containing intermediate **49**. (*E*)/(*Z*) Isomerization of the iminium double bond (viz. intermediates **49** and **50**) then can cause some epimerization at the C-2 carbon atom.[24] As expected, the disubstituted precursor **27** behaved similarly to the monosubstituted precursors, where equilibria as shown in Scheme 5 apply.



(1)

Finally, it was shown that the Fmoc moiety is a suitable protecting group to arrive at the free pipecolic acids. The Fmoc-protected cyclization products **30** and **31** were − after separation by column chromatography − further converted into the corresponding *cis*- and *trans*-4-hydroxypipecolic acids **51** and **52**, respectively. The sequence involved subsequent (i) hydrolysis of the formyl ester, (ii) deprotection of the nitrogen and (iii) hydrolysis of the methyl ester. The crude amino acids were then purified by using a strongly acidic ion-exchange column (Dowex 50 W×4) to yield the unnatural (*R*)-pipecolic acids **51** and **52** in 59 and 61% yield, respectively, over three steps. Thus, starting from (*R*)-allylglycine, the enantiomers of these natural products were obtained in an efficient sequence in eight steps.



(2)

Conclusions

In summary, we have shown that a novel vinylsilane-containing amino acid can be readily obtained in enantiopure form by an enzymatic resolution of the corresponding amino acid amide. This and two other olefinic amino acids served as versatile precursors in *N*-acyliminium ion cyclizations to arrive at the corresponding pipecolic acid derivatives without loss of optical activity in most cases. Thus, differently functionalized pipecolic acids such as baikiain and other natural products were synthesized in protected form. By applying the readily removable Fmoc protecting group, the unnatural enantiomers of *cis*- and *trans*-4-hydroxypipecolic acid were obtained.

Experimental Section

General: All reactions were carried out under dry nitrogen, unless described otherwise. Standard syringe techniques were applied for transfer of dry solvents and air- or moisture-sensitive reagents. − IR: Bruker IFS 28. − NMR: Bruker AC 200, Bruker WM 250, Bruker ARX 400 (200, 250 or 400 MHz for ^1H; 50, 63 or 100 MHz for ^{13}C, respectively). − HRMS: JEOL JMS SX/SX102A, coupled

to a JEOL MS-MP7000. − Elemental analyses: Vario EL. − Optical rotations: Perkin−Elmer 241 (at ambient temperature). − Melting points and boiling points are uncorrected. − Ethyl acetate and petroleum ether (boiling range 60−80°C) were distilled prior to use. THF and Et_2O were freshly distilled from sodium benzophenone ketyl prior to use. CH_2Cl_2 and MeCN were dried and distilled from CaH_2 and stored over 4-Å molecular sieves under nitrogen. Paraformaldehyde was converted to the monomer prior to use by heating for 1 min in HCO_2H. Purification of the amino acids by ion-exchange chromatography using a strongly acidic Dowex 50 W×4 resin involved the following sequence: The resin was treated with the HCl salt and washed with water until no more HCl was detected. Then the resin was eluted with 2 N NH_4OH, the ninhydrin-positive fractions were collected and concentrated to give the free amino acid. The *ee* values of the free amino acids were determined by HPLC on a Crownpak CR(+) column (aqueous $HClO_4$, at 0−7°C).[23] The *ee* values of compounds **22**−**39** (except for **28**, **29** and **36**) were determined by HPLC on a Chiralcel OD column (10−20% *i*PrOH in heptane).

(*Z*)-2-Amino-5-(trimethylsilyl)-4-pentenamide · Hydrochloride (20): A mixture of the glycine-derived imine **18**[19] (25.2 g, 99.6 mmol), LiI (1.33 g, 9.96 mmol), NaH (4.32 g, 108 mmol of a 60% dispersion in mineral oil) and 3-bromo-1-(trimethylsilyl)-1-propene (**19**,[20] 23.0 g, 119 mmol) in THF (500 mL) was refluxed for 26 h. It was cooled down to room temp., poured into saturated aqueous NH_4Cl (500 mL) and the organic layer was separated. The aqueous layer was extracted with diethyl ether (3 × 400 mL) and the combined organic layers were washed with H_2O (300 mL). The solution was dried ($MgSO_4$) and concentrated to give the crude alkylated product as a light yellow oil (40.4 g, 111 mmol), which was directly used for the next step. − R_f = 0.58 (50% diethyl ether in petroleum ether). − IR (film): $\tilde{\nu}$ = 2952 cm^{-1}, 1741 (C=O), 1248 (C−Si), 838 (C−Si). − ^1H NMR ($CDCl_3$): δ = 0.10 (s, 9 H, $SiMe_3$), 2.75−2.79 (m, 2 H, CH_2), 3.73 (s, 3 H, CO_2Me), 4.20 (dd, *J* = 7.3, 5.8 Hz, 1 H, NCH), 5.58 (d, *J* = 14.1 Hz, 1 H, SiCH), 6.17 (dt, *J* = 14.1, 7.3 Hz, 1 H, SiCH=C*H*), 7.18−7.83 (m, 10 H, ArH). − A solution of the crude imine (40.4 g, 111 mmol) in Et_2O (500 mL) was treated at 0°C with 1 N HCl (120 mL, 120 mmol) and the reaction mixture was stirred for 3 h at room temp. Separation of the two layers and concentration of the water layer provided the crude amino ester (24.0 g, 100 mmol) as the hydrochloride salt. − R_f = 0.13 (70% diethyl ether in petroleum ether). − IR (KBr): $\tilde{\nu}$ = 3405 cm^{-1} (NH), 2955, 1749 (C=O), 1248 (C−Si), 839 (C−Si). − ^1H NMR (CD_3OD) δ = 0.15 (s, 9 H, $SiMe_3$), 2.78−2.82 (m, 2 H, CH_2), 3.82 (s, 3 H, CO_2Me), 4.15 (t, *J* = 6.5 Hz, 1 H, NCH), 5.78 (dt, *J* = 14.1, 1.5 Hz, 1 H, SiCH), 6.29 (dt, *J* = 14.1, 7.1 Hz, 1 H, SiCH=C*H*). − A solution of the crude methyl ester (24.0 g, 100 mmol) was stirred in 25% aqueous NH_3 (200 mL) for 18 h. After concentration, the residue was dissolved in aqueous NaOH (200 mL), benzaldehyde (11.7 g, 110 mmol) was added and the mixture was vigorously stirred for 3 h. Extraction with CH_2Cl_2 (3 × 300 mL), drying ($MgSO_4$) and concentration provided the corresponding Schiff base. The latter was dissolved in acetone and 10 M HCl (10 mL, 100 mmol) was added. After stirring for 10 h, the resulting suspension was filtered to give pure **20** as the HCl salt (16.1 g, 72 mmol, 72%) as a white solid. − R_f = 0.93 ($CHCl_3$/MeOH/25% NH_4OH, 60:45:20). − Mp. 180°C (subl.). − IR (KBr) $\tilde{\nu}$ = 3390, 3272, 3189 cm^{-1} (NH), 2956, 1702 (C=O), 1249, 840 (C−Si). − ^1H NMR (CD_3OD) δ = 0.15 (s, 9 H, $SiMe_3$), 2.71−2.75 (m, 2 H, CH_2), 3.98 (t, *J* = 6.2 Hz, 1 H, NCH), 5.79 (dt, *J* = 14.2, 1.5 Hz, 1 H, SiCH), 6.30 (dt, *J* = 14.2, 6.9 Hz, 1 H, SiCH=C*H*). − ^{13}C NMR (CD_3OD) δ = 0.13 (q, $SiMe_3$), 36.0 (t, CH_2), 53.9 (d, NCH), 135.9 (d, SiCH), 140.6 (d, SiCH=*C*H), 171.6 (s, CO). − $C_8H_{19}ClN_2OSi$ (222.79): calcd. C 43.13, N 12.57, H 8.60; found C 43.02, N 13.06, H 8.61.

(*S*)-(*Z*)-2-Amino-5-(trimethylsilyl)-4-pentenoic Acid [(*S*)-21] and (*R*)-(*Z*)-2-Amino-5-(trimethylsilyl)-4-pentenamide [(*R*)-20]: A mixture of racemic **20** (5.00 g, 22.5 mmol) and $MnSO_4$ (ca. 10 mass-% of an 8 mM solution) in H_2O (50 mL) was adjusted to pH ≈ 8.5 with aqueous 1 N NaOH. Then a crude enzyme paste from *Pseudomonas putida* ATCC 12633 (ca. 1 g) was added and the mixture was shaken at 37°C for 72 h. The reaction was monitored by analyzing small samples of the reaction mixture with ^1H NMR in D_2O. After a conversion of approximately 50%, the enzyme residues were removed by centrifugation. The resulting solution was treated with benzaldehyde (1.15 mL, 11.3 mmol) and vigorously stirred for 5 h, after which the Schiff base of the remaining amide was extracted with CH_2Cl_2 (3 × 100 mL). The water layer was concentrated and the residue was purified on a strongly acidic ion-exchange column (Dowex 50 W×4) to give the amino acid (*S*)-**21** (1.11 g, 5.93 mmol, 26%) as a white solid. The combined organic layers were dried ($MgSO_4$), concentrated, dissolved in acetone, treated with 10 N HCl (1.13 mL, 11.3 mmol) and after stirring for 5 h filtered to give (*R*)-**20** (1.73 g, 7.79 mmol, 35%) as a white solid. − (*S*)-**21**: R_f = 0.77 ($CHCl_3$/MeOH/25% NH_4OH, 60:45:20). − $[\alpha]_D$ = +10.1 (*c* = 1, 1 N HCl). − *ee*: 99%. − Mp. 210°C (dec.). − IR (KBr): $\tilde{\nu}$ = 3450 cm^{-1} (NH), 3300−2900 (CO_2 H) 1591 (C=O), 1248, 837 (C−Si). − ^1H NMR (CD_3OD) δ = 0.15 (s, 9 H, $SiMe_3$), 2.62−2.80 (m, 2 H, CH_2), 3.57 (dd, *J* = 7.1, 5.6 Hz, 1 H, NCH), 5.73 (d, *J* = 14.2 Hz, 1 H, SiCH) 6.33 (dt, *J* = 14.2, 6.9 Hz, 1 H, SiCH=C*H*). − ^{13}C NMR (CD_3OD) δ = 0.13 (q, $SiMe_3$), 35.8 (t, CH_2), 56.1 (d, NCH), 134.6 (d, SiCH), 142.8 (d, SiCH=*C*H), 173.9 (s, C=O). − HRMS (EI); $C_8H_{18}NO_2Si$ (188.1107): found 188.1111. − (*R*)−**20**: R_f = 0.93 ($CHCl_3$/MeOH/25% NH_4OH, 60:45:20). − $[\alpha]_D$ = −9.4 (*c* = 1, H_2O). − *ee*: 88% (determined by conversion into (*R*)-allylglycine (6 N HCl, 90°C, 4 h).

Methyl (*R*)-2-(Methoxycarbonyl)amino-4-pentenoate (22): A solution of (*R*)-allylglycine (200 mg, 1.74 mmol) in MeOH (3 mL) was treated dropwise at 0°C with $SOCl_2$ (253 μL, 3.48 mmol) and refluxed for 4 h. The mixture was concentrated to give the crude methyl ester hydrochloride (ca. 1.74 mmol) as a dark yellow oil. A solution of the crude residue (1.74 mmol) in CH_2Cl_2 (3 mL) was treated at 0°C with Et_3N (485 μL, 3.48 mmol) and methyl chloroformate (161 μL, 2.09 mmol). After stirring at room temp. for 1 h, the mixture was poured into saturated aqueous NH_4Cl (10 mL) and extracted with CH_2Cl_2 (3 × 10 mL). The combined organic layers were dried ($MgSO_4$), concentrated and purified by flash chromatography (50% diethyl ether in petroleum ether) to give **22** (260 mg, 1.39 mmol, 80%) as a colorless oil. − R_f = 0.35 (50% diethyl ether in petroleum ether). − $[\alpha]_D$ = +19.5 (*c* = 1.9, CH_2Cl_2). − IR (film): $\tilde{\nu}$ = 3310 cm^{-1} (NH), 2955, 1737 (CO), 1698 (CO), 1267, 1221, 779. − ^1H NMR ($CDCl_3$): δ = 2.42−2.57 (m, 2 H, CH_2), 3.64 (s, 3 H, NCO_2Me), 3.71 (s, 3 H, CO_2Me), 4.40 (q, *J* = 6.4 Hz, 1 H, NCH), 5.08−5.12 (m, 2 H, =CH_2), 5.29 (br d, *J* = 6.4 Hz, 1 H, NH), 5.60−5.71 (m, 1 H, =CH). − ^{13}C NMR ($CDCl_3$): δ = 36.5 (t, CH_2), 52.2, 53.1 (d, NCH, 2 × q, CO_2Me), 119.1 (t, =CH_2), 132.0 (d, =CH), 156.2 (s, NCO), 172.1 (s, CO). − HRMS (EI); $C_8H_{13}NO_4$ (187.0845): found 187.0847.

Methyl (*R*)-2-(9-Fluorenylmethoxycarbonyl)amino-4-pentenoate (23): A mixture of (*R*)-allylglycine (500 mg, 4.35 mmol) and Et_3N (0.61 mL, 4.35 mmol) in H_2O (4 mL) was treated with a solution of Fmoc-OSu (1.42 g, 4.35 mmol) in MeCN (4 mL). The mixture was vigorously stirred for 2 h and concentrated to yield the crude acid (1.19 g, 3.53 mmol, 82%) as a white solid. A portion of the crude acid (250 mg, 0.74 mmol) was dissolved in MeOH (2 mL),

treated at 0°C with $SOCl_2$ (108 μL, 1.48 mmol) and refluxed for 3 h. The mixture was concentrated and purified by flash chromatography (30% ethyl acetate in petroleum ether) to yield **23** (270 mg, 0.74 mmol, 100%) as a white solid. − R_f = 0.56 (50% ethyl acetate in petroleum ether). − $[\alpha]_D$ = −7.7 (*c* = 0.65, CH_2Cl_2). − Mp. 99−100°C. − IR (film): $\tilde{\nu}$ = 3320 (NH) cm^{-1}, 2947, 1742 (C=O), 1699 (C=O), 1537, 1225. − ^1H NMR ($CDCl_3$): δ = 2.42−2.62 (m, 2 H, CH_2), 3.76 (s, 3 H, CO_2Me), 4.32 (t, *J* = 7.0 Hz, 1 H, ArCH), 4.39 (d, *J* = 6.9 Hz, 2 H, OCH_2), 4.45−4.48 (m, 1 H, NCH), 5.13−5.17 (m, 2 H, $=CH_2$), 5.32 (d, *J* = 7.2 Hz, 1 H, NH), 5.65−5.73 (m, 1 H, =CH), 7.25−7.77 (m, 8 H, ArH). − ^{13}C NMR ($CDCl_3$): δ = 36.8 (t, CH_2), 47.2 (d, $CHCH_2O$), 52.4, 53.3 (2 × d, NCH, CO_2Me), 67.1 (t, CH_2O), 119.4 (t, $=CH_2$), 120.0, 125.1, 127.1, 127.7 (d, ArCH), 132.0 (d, =CH), 143.8, 143.9 (s, ArC), 156.0 (s, NCO), 172.2 (s, CO). − HRMS (EI); $C_{21}H_{21}NO_4$ (351.1471): found 351.1464.

Methyl (*R*)-2-(Toluenesulfonylamino)-4-pentenoate (24): A solution of (*R*)-allylglycine (608 mg, 5.29 mmol) in MeOH (25 mL) was treated at 0°C with $SOCl_2$ (0.77 mL, 10.6 mmol). The mixture was refluxed for 4 h and concentrated to give the crude methyl ester (1.01 g) as a viscous oil. The product was dissolved in pyridine (25 mL), TsCl (3.02 g, 15.9 mmol) was added and the mixture was heated at 40°C for 24 h. The mixture was concentrated, dissolved in EtOAc (50 mL) and washed with aqueous $CuSO_4$ (2 × 25 mL) and H_2O (25 mL). The organic layer was dried, concentrated and purified by flash chromatography (50 → 70% ethyl acetate in petroleum ether) to give **24** (1.13 g, 4.01 mmol, 76%) as a white solid. − R_f = 0.33 (30% ethyl acetate in petroleum ether). − Mp. 68−69°C. − $[\alpha]_D$ = −15.5 (*c* = 1, CH_2Cl_2). − IR (film): $\tilde{\nu}$ = 3278 cm^{-1} (NH), 2953, 1742 (C=O). − ^1H NMR ($CDCl_3$): δ = 2.40 (s, 3 H, ArMe), 2.45 (t, *J* = 6.6 Hz, 2 H, CH_2), 3.51 (s, 3 H, CO_2Me), 4.02 (dt, *J* = 9.0, 5.9 Hz, 1 H, NCH), 5.04−5.10 (m, 2 H, $=CH_2$), 5.22 (d, *J* = 8.9 Hz, 1 H, NH), 5.69 (m, 1 H, =CH), 7.28 (d, *J* = 8.0 Hz, 2 H, ArH), 7.71 (d, *J* = 8.0 Hz, 2 H, ArH). − ^{13}C NMR ($CDCl_3$): δ = 21.4 (q, ArMe), 37.4 (t, CH_2), 52.3 (q, CO_2Me), 55.1 (d, NCH), 119.6 (t, $=CH_2$), 127.1, 129.5 (d, ArH), 131.2 (d, =CH), 136.7, 143.5 (s, ArC), 171.2 (s, CO). − $C_{13}H_{18}NO_4S$ (284.1): calcd. C 55.11, H 6.05, N 4.94; found C 55.10, H 6.11, N 4.91.

Methyl (*S*)-(*Z*)-2-(Methoxycarbonylamino)-5-(trimethylsilyl)-4-pentenoate (25): A solution of (*S*)-**21** (300 mg, 1.69 mmol) in MeOH (20 mL) was treated with diazomethane (freshly prepared from Diazald® [5.0 mmol in diethyl ether (15 mL) and KOH (31.5 mmol dissolved in EtOH (45 mL)][25] at 0°C until the solution became slightly yellow. The solution was acidified with 1 N HCl and concentrated to afford the methyl ester hydrochloride (250 mg, 1.24 mmol) as a yellow solid. A portion of the crude methyl ester (106 mg, 0.53 mmol) in CH_2Cl_2 (10 mL) was treated at 0°C with Et_3N (180 μL, 1.28 mmol) and methyl chloroformate (50 μL, 0.64 mmol). After stirring at room temp. for 3 h, the solution was poured into aqueous saturated NH_4Cl (10 mL) and extracted with CH_2Cl_2 (3 × 10 mL). The combined organic layers were dried ($MgSO_4$), concentrated and purified by flash chromatography (20 → 50% diethyl ether in petroleum ether) to give methyl carbamate **25** (93 mg, 0.36 mmol, 68%) as a colorless oil. − R_f = 0.29 (50% diethyl ether in petroleum ether). − $[\alpha]_D$ = +12.2 (*c* = 1, CH_2Cl_2). − IR (film): $\tilde{\nu}$ = 3341 cm^{-1} (NH), 2954, 1729 (C=O), 1249 and 850 (C−Si). − ^1H NMR ($CDCl_3$): δ = 0.10 (s, 9 H, $SiMe_3$), 2.54−2.65 (m, 2 H, CH_2), 3.67 (s, 3 H, CO_2Me), 3.74 (s, 3 H, CO_2Me), 4.44 (q, *J* = 7.1 Hz, 1 H, NCH), 5.23 (br. d, *J* = 6.6 Hz, 1 H, NH), 5.69 (d, *J* = 14.1 Hz, 1 H, SiCH), 6.14 (dt, *J* = 14.1, 7.2 Hz, 1 H, SiCH=C*H*). − ^{13}C NMR ($CDCl_3$): δ = −0.10 (q, $SiMe_3$), 35.7 (t, CH_2), 52.1 and 52.2 (2 × q, CO_2Me), 53.1 (d, NCH), 134.1 (d, SiCH), 140.8 (d, SiCH=*C*H), 156.0 (NCO) 171.5 (CO). − HRMS (EI); $C_{11}H_{21}NO_4Si$ (259.1239): found 259.1258.

Methyl (*S*)-(*Z*)-2-(Toluenesulfonylamino)-5-(trimethylsilyl)-4-pentenoate (26): A portion of the crude methyl ester hydrochloride derived from (*S*)-**21** (144 mg, 0.62 mmol) in pyridine (6 mL) was treated with tosyl chloride (142 mg, 0.74 mmol). After stirring for 18 h, the mixture was concentrated and purified by flash chromatography (20 → 50% diethyl ether in petroleum ether) to give the tosylamide **26** (124 mg, 0.37 mmol, 59%) as a colorless oil. − R_f = 0.23 (50% diethyl ether in petroleum ether). − $[\alpha]_D$ = +12.8 (*c* = 1, CH_2Cl_2). − IR (film): $\tilde{\nu}$ = 3274 cm^{-1} (NH), 2953, 1743 (C=O), 1248 (C−Si), 1163, 839 (C−Si). − ^1H NMR ($CDCl_3$): δ = 0.09 (s, 9 H, $SiMe_3$), 2.41 (s, 3 H, ArMe), 2.49−2.58 (m, 2 H, CH_2), 3.50 (s, 3 H, CO_2Me), 4.00 (dt, *J* = 9.1, 6.1 Hz, 1 H, NCH), 5.13 (d, *J* = 9.1 Hz, 1 H, NH), 5.66 (d, *J* = 14.5 Hz, 1 H, SiCH), 6.10 (dt, *J* = 14.2, 7.1 Hz, 1 H, SiCH=C*H*), 7.28 (d, *J* = 8.1 Hz, 2 H, ArH), 7.71 (d, *J* = 8.3 Hz, 2 H, ArH). − ^{13}C NMR ($CDCl_3$): δ = −0.10 (q, $SiMe_3$), 21.3 (q, ArMe), 36.5 (t, CH_2), 52.3 (q, CO_2Me), 55.1 (NCH), 127.1 (d, ArC), 129.4 (d, ArC), 134.3 (d, SiCH), 136.6 (s, ArC), 140.0 (d, SiCH=*C*H), 143.5 (s, ArC), 171.3 (s, C=O). − HRMS (EI); $C_{16}H_{25}NO_4SSi$ (355.1274): found 355.1260.

Methyl (*S*)-2-Methyl-2-(toluenesulfonylamino)-4-pentenoate (27): A solution of (*S*)-α-methylallylglycine[25] (97 mg, 678 μmol) in MeOH (5 mL) was treated at 0°C with $SOCl_2$ (100 μL, 1.37 mmol). The mixture was refluxed for 16 h and concentrated to give the crude methyl ester (128 mg) as a viscous oil. The product was dissolved in pyridine (5 mL), TsCl (381 mg, 2.0 mmol) was added and the mixture was heated at 40°C for 70 h. The mixture was concentrated, dissolved in EtOAc (25 mL) and washed with aqueous $CuSO_4$ (2 × 25 mL) and H_2O (25 mL). The organic layer was dried, concentrated and purified by flash chromatography (30% ethyl acetate in petroleum ether) to give **27** (154 mg, 0.52 mmol, 76%) as a light yellow oil. − R_f = 0.35 (30% ethyl acetate in petroleum ether). − $[\alpha]_D$ = +2.4 (*c* = 1.05, CH_2Cl_2). − IR (film): $\tilde{\nu}$ = 3274 cm^{-1} (NH), 1738 (C=O). − ^1H NMR ($CDCl_3$): δ = 1.41 (s, 3 H, Me), 2.40 (s, 3 H, ArMe), 2.46 (dd, 1 H, *J* = 7.2, 13.8 Hz, CH_2), 2.58 (dd, 1 H, *J* = 7.5, 13.9 Hz, CH_2), 3.64 (s, 3 H, CO_2Me), 5.06−5.13 (m, 2 H, $=CH_2$), 5.35 (s, 1 H, NH), 5.60 (ddt, 1 H, *J* = 7.0, 7.4, 10.2 Hz, =CH), 7.27 (d, 2 H, *J* = 8.3 Hz, ArH), 7.75 (d, 2 H, *J* = 8.3 Hz, ArH). − ^{13}C NMR ($CDCl_3$): δ = 21.4 (q, ArMe), 22.0 (q, Me), 44.1 (t, CH_2), 52.6 (q, CO_2Me), 61.9 (s, NC), 120.1 (t, $=CH_2$), 126.9, 129.4 (d, ArCH), 131.2 (d, =CH), 139.4, 143.1 (s, ArC), 173.3 (s, CO). − HRMS (EI); $C_{14}H_{20}NO_4S$ (298.1113): found 298.1107.

Dimethyl (2*R*,4*S*)-4-Formyloxy-1,2-piperidinedicarboxylate (28) and Dimethyl (2*R*,4*R*)-4-Formyloxy-1,2-piperidinedicarboxylate (29): A solution of carbamate **22** (75 mg, 400 μmol) and paraformaldehyde (18 mg, 600 μmol) in HCO_2H (2 mL) was stirred at room temp. for 16 h. The reaction mixture was concentrated and purified by flash chromatography (30 → 70% diethyl ether in petroleum ether) to give **28** (36 mg, 147 μmol, 37%) and **29** (40 mg, 160 μmol, 40%) as colorless oils. − **28**: R_f = 0.32 (70% diethyl ether in petroleum ether). − $[\alpha]_D$ = +7.2 (*c* = 1, CH_2Cl_2). − IR (film): $\tilde{\nu}$ = 2956 cm^{-1}, 1746 (C=O), 1713 (C=O). − ^1H NMR ($CDCl_3$): δ = 1.68−1.90 (m, 2 H, 2 × 5-H), 1.95 (ddd, *J* = 1.9, 6.9, 14.8 Hz, 1 H, 3-H_{ax}), 2.58 (br. d, *J* = 14.8 Hz, 1 H, 3-H_{eq}), 3.27, 3.36 (rotamers, t, *J* = 13.2 Hz, 1 H, 6-H_{ax}), 3.67, 3.70, 3.72 (rotamers, s, 6 H, 2 × CO_2Me), 3.92, 4.05 (rotamers, br. d, *J* = 10.9 Hz, 1 H, 6-H_{eq}), 4.74, 4.89 (rotamers, m, 1 H, 2-H), 5.21(t, *J* = 2.7 Hz, 1 H, 4-H), 7.92 (s, 1 H, CHO). − ^{13}C NMR ($CDCl_3$): δ = 28.5, 30.1 (t, C-3 and C-5), 35.9, 36.1 (rotamers, t, C-6), 50.7, 51.0, 52.1, 52.9 (rotamers, C-2 and 2 × CO_2Me), 66.1 (d, C-4), 156.0 (s, NCO), 159.6

(s, HCO), 171.4 (s, CO). − HRMS (EI); $C_{10}H_{15}NO_6$ (245.0899): found 245.0875. − **29**: R_f = 0.35 (70% diethyl ether in petroleum ether). − $[\alpha]_D$ = −17.7 (*c* = 1, CH_2Cl_2). − IR (film): $\tilde{\nu}$ = 2956 cm^{-1}, 1743 (C=O), 1709 (C=O). − ^1H NMR ($CDCl_3$): δ = 1.52 (dq, *J* = 4.8. 12.5 Hz, 1 H, 5-H_{ax}), 1.78 (dt, *J* = 6.3, 12.5 Hz, 1 H, 3-H_{ax}), 1.97−2.05 (m, 1 H, 5-H_{eq}), 2.51 (br. d, *J* = 12.2 Hz, 1 H, 3-H_{eq}), 3.07, 3.15 (rotamers, br. t, *J* = 13.3 Hz, 1 H, 6-H_{ax}), 3.72 (s, 3 H, CO_2Me), 3.75 (s, 3 H, CO_2Me), 4.09, 4.22 (rotamers, br. d, *J* = 13.2 Hz, 1 H, 6-H_{eq}), 4.86 (tt, *J* = 4.4, 11.5 Hz, 1 H, 4-H_{ax}), 4.92, 5.08 (rotamers, br. s, 1 H, 2-H), 7.95 (s, 1 H, CHO). − ^{13}C NMR ($CDCl_3$): δ = 30.2, 31.5 (t, C-3 and C-5), 39.7 (t, C-6), 52.5, 53.0, 53.7 (q, 2 × CO_2Me and d, C-2), 67.9 (d, C-4), 155.9 (s, NCO), 160.0 (s, HCO), 170.9 (s, CO). − HRMS (EI); $C_{10}H_{15}NO_6$ (245.0899): found 245.0904.

1-(9-Fluorenylmethyl) 2-Methyl (2*R*,4*S*)-4-Formyloxy-1,2-piperidinedicarboxylate (30) and 1-(9-Fluorenylmethyl) 2-Methyl (2*R*,4*R*)-4-Formyloxy-1,2-piperidinedicarboxylate (31): A solution of carbamate **23** (130 mg, 0.37 mmol) and paraformaldehyde (111 mg, 3.70 mmol) in HCO_2H (3 mL) was stirred at room temp. for 16 h. The reaction mixture was concentrated and purified by flash chromatography (30 → 50% ethyl acetate in petroleum ether) to give **30** (67 mg, 0.16 mmol, 43%) and **31** (61 mg, 0.15 mmol, 41%) as colorless oils. − **30**: R_f = 0.37 (50% ethyl acetate in petroleum ether). − $[\alpha]_D$ = +2.0 (*c* = 1, CH_2Cl_2). − Mp. 51−52°C. − IR (film): $\tilde{\nu}$ = 2952 cm^{-1}, 1715 (C=O), 1704 (C=O). − ^1H NMR ($CDCl_3$): δ = 1.64−2.00 (m, 3 H, 2 × 5-H and 3-H_{ax}), 2.57, 2.63 (rotamers, br. d, *J* = 14.4 Hz, 1 H, 3-H_{eq}), 3.29, 3.46 (rotamers, t, *J* = 13.4 Hz, 1 H, 6-H_{ax}), 3.69, 3.73 (rotamers, s, 3 H, CO_2Me), 3.96, 4.09 (rotamers, dd, *J* = 13.6, 4.0 Hz, 1 H, 6-H_{eq}), 4.22−4.55 (m, 3 H, OCH_2CH), 4.62, 4.94 (rotamers, d, *J* = 5.9 Hz, 1 H, 2-H), 5.24 (br. s, 1 H, 4-H), 7.28−7.78 (m, 8 H, ArH), 7.93, 7.96 (rotamers, s, 1 H, CHO). − ^{13}C NMR ($CDCl_3$): δ = 28.3, 28.5, 30.1 (rotamers, t, C-3 and C-5), 35.9, 36.3 (rotamers, t, C-6), 47.1 (d, ArCH), 50.8, 51.0, 52.1 (rotamers, d, C-2 and q, CO_2Me), 66.0, 66.1 (rotamers, d, C-4), 67.5, 67.7 (rotamers, t, CH_2O), 119.9, 124.8, 127.0, 127.6 (d, ArC), 141.2, 143.0 (s, ArC), 156.0 (s, NCO), 159.6 (s, HCO), 171.3 (s, CO). − HRMS (EI); $C_{23}H_{23}NO_6$ (409.1525): found 409.1547. − **31**: R_f = 0.44 (50% ethyl acetate in petroleum ether). − $[\alpha]_D$ = +12.5 (*c* = 1, CH_2Cl_2). − Mp. 47−48°C. − IR (film): $\tilde{\nu}$ = 2952 cm^{-1}, 1742 (C=O), 1707 (C=O). − ^1H NMR ($CDCl_3$): δ = 1.47−1.58 (m, 1 H, 5-H_{ax}), 1.65−1.82 (m, 1 H, 3-H_{ax}), 2.04 (br. d, *J* = 6.7 Hz, 1 H, 5-H_{eq}), 2.46, 2.53 (rotamers, br. d, *J* = 12.3 Hz, 1 H, 3-H_{eq}), 3.08, 3.22 (rotamers, br. t, *J* = 12.9 Hz, 1 H, 6-H_{ax}), 3.73, 3.77 (rotamers, s, 3 H, CO_2Me), 4.06−4.52 (m, 4 H, CH_2O, ArCH, 6-H_{eq}), 4.80, 5.10 (rotamers, d, *J* = 4.7 Hz, 1 H, 2-H), 4.84−4.93 (m, 1 H, 4-H_{ax}), 7.25−7.42 (m, 4 H, ArH), 7.47−7.61 (m, 2 H, ArH), 7.74−7.77 (m, 2 H, ArH), 8.02 (s, 1 H, CHO). − ^{13}C NMR ($CDCl_3$): δ = 30.3, 31.5 (t, C-3 and C-5), 39.8 (t, C-6), 47.1 (d, ArCH), 52.5, 53.8 (q, CO_2Me and d, C-2), 67.7 (t, CH_2O), 67.9 (d, C-4), 119.9, 124.8, 127.0, 127.6 (d, ArC), 141.2, 143.6 (s, ArC), 155.1 (s, NCO), 160.0 (s, HCO), 171.2 (s, CO). − HRMS (EI); $C_{23}H_{23}NO_6$ (409.1525): found 409.1518.

Methyl (2*R*,4*S*)-4-Hydroxy-1-toluenesulfonyl-2-piperidinecarboxylate (32) and Methyl (2*R*,4*R*)-4-Hydroxy-1-toluenesulfonyl-2-piperidinecarboxylate (33): A solution of tosylamide **24** (52 mg, 183 μmol) and paraformaldehyde (55 mg, 1.83 mmol) in HCO_2H (2 mL) was stirred at 50°C for 18 h. The reaction mixture was concentrated and treated with 2 N NH_3/MeOH at 0°C for 30 min. Concentration and purification by flash chromatography (75% ethyl acetate in petroleum ether) afforded **32** (31 mg, 99 μmol, 54%) and **33** (21 mg, 66 μmol, 36%) as colorless oils. − **32**: R_f = 0.38 (75% ethyl acetate in petroleum ether). − $[\alpha]_D$ = +24.1 (*c* = 1, CH_2Cl_2). − IR (film): $\tilde{\nu}$ = 3519 cm^{-1} (OH), 1738 (C=O). − ^1H NMR ($CDCl_3$): δ = 1.66−1.70 (m, 2 H, 5-H_{ax} and 5-H_{eq}), 1.93 (ddd, 1 H, *J* = 2.5, 6.6, 14.3 Hz, 3-H_{ax}), 2.36 (br. d, 1 H, *J* = 14.4 Hz, 3-H_{eq}), 2.41 (s, 3 H, ArMe), 3.48−3.55 (m, 1 H, 6-H_{ax}), 3.53 (s, 3 H, CO_2Me), 3.62 (ddd, 1 H, *J* = 2.9, 3.9, 13.3 Hz, 6-H_{eq}), 4.09−4.11 (m, 1 H, 4-H), 4.68 (d, 1 H, *J* = 6.4 Hz, 2-H), 7.27 (d, 2 H, *J* = 8.3 Hz, ArH), 7.68 (d, 2 H, *J* = 8.3 Hz, ArH). − ^{13}C NMR ($CDCl_3$): δ = 21.37 (q, ArMe), 31.2, 34.1 (t, C.3 and C.5), 37.0 (t, C.6), 51.8 (d, C.2), 52.1 (q, CO_2Me), 62.9 (d, C.4), 127.1, 129.3 (d, ArCH), 137.2, 143.0 (s, ArC), 172.14 (s, CO). − HRMS (EI); $C_{14}H_{20}NO_5S$ (314.1062): found 314.1057. − **33**: R_f = 0.38 (75% ethyl acetate in petroleum ether). − $[\alpha]_D$ = +30.6 (*c* = 0.5, CH_2Cl_2). − IR (film): $\tilde{\nu}$ = 3516 cm^{-1} (OH), 1740 (C=O). − ^1H NMR ($CDCl_3$): δ = 1.44 (ddt, 1 H, *J* = 5.0, 10.9, 12.7 Hz, 5-H_{ax}), 1.64 (ddd, 1 H, *J* = 6.1, 11.6, 12.9 Hz, 3-H_{ax}), 1.9 (ddd, 1 H, *J* = 2.2, 4.4, 12.4 Hz, 5-H_{eq}), 2.36 (dquint, 1 H, *J* = 2.2, 12.9 Hz, 3-H_{eq}), 2.42 (s, 3 H, ArMe), 3.26 (dt, 1 H, *J* = 2.8, 13.1 Hz, 6-H_{ax}), 3.58 (s, 3 H, CO_2Me), 3.66−3.71 (tt, 1 H, 4-H), 3.84−3.89 (dquint, 1 H, 6-H_{eq}), 4.86 (d, 1 H, *J* = 6.0 Hz, 2-H), 7.29 (d, 2 H, *J* = 8.3 Hz, ArH), 7.67 (d, 2 H, *J* = 8.3 Hz, ArH). − ^{13}C NMR ($CDCl_3$): δ = 21.4 (q, ArMe), 33.7, 35.9 (t, C-3 and C-5), 41.3 (t, C-6), 52.1 (q, CO_2Me), 54.9 (d, C-2), 65.2 (d, C-6), 127.0, 129.4 (d, ArCH), 136.8, 143.3 (s, ArC), 170.7 (s, CO). − HRMS (EI); $C_{14}H_{20}NO_5S$ (314.1062): found 314.1078.

Methyl (2*R*,4*R*)-4-Chloro-1-toluenesulfonyl-2-piperidinecarboxylate (34): A solution of *s*-trioxane (20 mg, 222 μmol) and $SnCl_4$ (0.9 mL of a 1.0 M solution in CH_2Cl_2, 0.9 mmol) in CH_2Cl_2 (4 mL) was stirred at room temp. for 15 min. Then, tosylamide **24** (65 mg, 224 μmol) was added and the mixture was stirred at room temp. for 20 h. The reaction mixture was poured into aqueous saturated $NaHCO_3$ (10 mL) and extracted with CH_2Cl_2 (3 × 10 mL). The combined organic layers were dried ($MgSO_4$), concentrated and purified by flash chromatography (25 → 100% ethyl acetate in petroleum ether) to give **32** (71 mg, 162 μmol, 73%) and **34** (11 mg, 34 μmol, 14%) as colorless oils. − **34**: 6:1 mixture of eq/ax chloride, data of the eq chloride; R_f = 0.34 (25% ethyl acetate in petroleum ether). − IR (film): $\tilde{\nu}$ = 1738 cm^{-1} (C=O). − ^1H NMR ($CDCl_3$): δ = 1.77 (ddd, 1 H, *J* = 5.0, 12.8, 24.8 Hz, 5-H_{ax}), 1.99 (ddd, 1 H, *J* = 6.1, 12.4, 18.5 Hz, 3-H_{ax}), 2.10−2.16 (m, 1 H, 5-H_{eq}), 2.43 (s, 3 H, ArMe), 2.55 (dq, 1 H, *J* = 2.1, 13.3 Hz, 3-H_{eq}), 3.27 (dt, 1 H, *J* = 2.8, 13.0 Hz, 6-H_{ax}), 3.58 (s, 3 H, CO_2Me), 3.83−3.92 (m, 2 H, 4-H and 6-H_{eq}), 4.83 (dd, 1 H, *J* = 1.7, 4.2 Hz, 2-H), 7.30 (d, 2 H, *J* = 8.0 Hz, ArH), 7.66 (d, 2 H, *J* = 8.0 Hz, ArH). − ^{13}C NMR ($CDCl_3$): δ = 21.4 (q, ArMe), 35.2, 37.2 (t, C-3 and C-5), 42.1 (t, C-6), 52.2 (q, CO_2Me), 52.4 (d, C-2), 55.3 (d, C-4), 127.1, 129.5 (d, ArCH), 136.4, 143.5 (ArC, s), 170.8 (s, CO). − HRMS (EI); $C_{14}H_{19}ClNO_4S$ (332.0723): found 332.0708.

Methyl (2*R*,4*R*)-4-(*N*-Acetylamino)-1-toluenesulfonyl-2-piperidinecarboxylate (35): A solution of *s*-trioxane (8.5 mg, 94 μmol) and $SnCl_4$ (0.30 mL of a 1.0 M solution in CH_2Cl_2, 0.30 mmol) in MeCN (5 mL) was stirred at room temp. for 30 min. Then, tosylamide **24** (26 mg, 90 μmol) was added and the mixture was stirred at 50°C for 18 h. The reaction mixture was poured into aqueous saturated $NaHCO_3$ (15 mL) and extracted with CH_2Cl_2 (3 × 15 mL). The combined organic layers were dried ($MgSO_4$), concentrated and purified by flash chromatography (25 → 100% ethyl acetate in petroleum ether) to give **35** (16 mg, 41 μmol, 46%) and **32** (3.3 mg, 10 μmol, 11%) as colorless oils. − **35**: R_f = 0.20 (EtOAc). − $[\alpha]_D$ = +12.0 (*c* = 1, CH_2Cl_2). − IR (film): $\tilde{\nu}$ = 3382 cm^{-1} (NH), 3286 (NH), 1741 (C=O), 1652 (C=O). − ^1H NMR ($CDCl_3$, data of the major of a 9:1 mixture of rotamers): δ = 1.36 (ddt, 1 H, *J* = 4.8, 12.4, 12.6 Hz, 5-H_{ax}), 1.61 (dt, 1 H, *J* = 6.1, 12.7 Hz, 3-H_{ax}), 1.94 [s, 3 H, C(O)Me], 1.97−2.01 (m, 1 H, 5-H_{eq}), 2.37−2.43 (m, 1 H, 3-H_{eq}), 2.42 (s, 3 H, ArMe), 3.29 (dt, 1 H, *J* =

2.8, 13.0 Hz, 6-H_{ax}), 3.55 (s, 3 H, CO_2Me), 3.83−3.88 (m, 2 H, 4-H and 6-H_{eq}), 4.87 (d, 1 H, J = 5.9 Hz, 2-H), 5.24 (d, 1 H, J = 7.2 Hz, NH), 7.29 (d, 2 H, J = 8.0 Hz, ArH), 7.67 (d, 2 H, J = 8.0 Hz, ArH). − ^{13}C NMR ($CDCl_3$, data of the major of a 9:1 mixture of rotamers): δ = 21.5 (q, ArMe), 23.3 [q, C(O)Me], 31.6, 33.7 (t, C-3 and C-5), 41.6 (t, C-6), 43.4 (d, C-4), 52.3 (q, CO_2Me), 54.8 (d, C-2), 127.2, 129.6 (d, ArCH), 136.6, 143.5 (s, ArC), 169.4 (s, NCO), 170.3 (s, CO). − HRMS (EI); $C_{13}H_{16}NO_4S$ (355.1328): found 355.1292.

Dimethyl (2*S*)-1,2,3,6-Tetrahydropyridine-1,2-dicarboxylate (36): A solution of **25** (36.0 mg, 0.14 mmol) and paraformaldehyde (6.3 mg, 0.21 mmol) in HCO_2H (3 mL) was stirred at room temp. for 24 h. The mixture was concentrated and purified by flash chromatography (50% diethyl ether in petroleum ether) to give **36** (11.0 mg, 0.06 mmol, 40%) as a colorless oil. − R_f = 0.20 (50% diethyl ether in petroleum ether). − $[\alpha]_D$ = +2.8 (c = 1, CH_2Cl_2). − IR (film): $\tilde{\nu}$ = 2955 cm^{-1}, 1743 (C=O), 1705 (C=O). − ^{1}H NMR ($CDCl_3$): δ = 2.48−2.67 (m, 2 H, 2 × 3-H), 3.70, 3.72, 3.74, 3.75 (2 rotamers, s, 3 H, 2 × CO_2Me), 3.82−4.15 (m, 2 H, 2 × 6-H), 4.92 and 5.09 (2 rotamers, d, J = 6.3 Hz, 1 H, 2-H), 5.62−5.75 (m, 2 H, 4-H and 5-H). − ^{13}C NMR ($CDCl_3$): δ = 26.3, 26.6 (rotamers, t, C-3), 41.7, 41.8 (rotamers, t, C-6), 51.4, 51.9, 52.2, 52.8 (rotamers, q, 2 × CO_2Me and C-2), 121.7, 122.2, 123.7, 124.1 (rotamers, C-4 and C-5), 157.0 (NCO), 171.8 (C=O). − HRMS (EI); $C_9H_{13}NO_4$ (199.0845): found 199.0844.

Methyl (2*S*)-1-Toluenesulfonyl-1,2,3,6-tetrahydropyridine-2-carboxylate (37): A solution of **26** (57 mg, 0.16 mmol) and paraformaldehyde (7.3 mg, 0.24 mmol) in HCO_2H (3 mL) was stirred at room temp. for 60 h. The mixture was concentrated and purified by flash chromatography (50% diethyl ether in petroleum ether) to give **37** (28 mg, 0.10 mmol, 60%) as a colorless oil. − *ee*: 87%. − R_f = 0.23 (50% diethyl ether in petroleum ether). − $[\alpha]_D$ = +2.2 (c = 1, CH_2Cl_2). − IR (film): $\tilde{\nu}$ = 2921 cm^{-1}, 1732 (C=O). − ^{1}H NMR ($CDCl_3$) δ = 2.41 (s, 3 H, ArMe), 2.54 (br. s, 2 H, 2 × 3-H), 3.49 (s, 3 H, CO_2Me), 3.81 (d, J = 16.9 Hz, 1 H, 6-H), 4.07 (d J = 17.0 Hz, 1 H, 6-H), 4.86 (t, J = 4.6 Hz, 1 H, 2-H), 5.47−5.71 (m, 2 H, 4-H and 5-H), 7.28 (d, J = 8.0 Hz, 2 H, ArH), 7.66 (d, J = 8.1 Hz, 2 H, ArH). − ^{13}C NMR ($CDCl_3$) δ = 21.4 (q, ArMe), 27.6 (t, C-3), 42.0 (t, C-6), 51.9, 52.5 (C-2 and CO_2Me), 122.1, 123.2 (d, C-4 and C-5), 127.1, 129.3 (d, ArC), 136.1, 143.1 (s, ArC), 170.8 (C=O). − HRMS (EI); $C_{14}H_{17}NO_4S$ (295.0878): found 295.0866.

(2*S*,4*S*)-1-Methyl-6-oxo-2-toluenesulfonyl-7-oxa-2-azabicyclo[3.2.1]-octane (38) and Methyl (2*S*,4*R*)-4-Formyloxy-2-methyl-1-toluenesulfonyl-2-piperidinecarboxylate (39): A solution of tosylamide **27** (65 mg, 217 μmol) and paraformaldehyde (65 mg, 2.17 mmol) in HCO_2H (3 mL) was stirred at 50°C for 22 h. The reaction mixture was concentrated and dissolved in a 2 N NH_3/MeOH solution at 0°C. After stirring for 30 min, the mixture was concentrated, dissolved in toluene and heated at reflux in the presence of cat. *p*TSA under azeotropic removal of MeOH. The mixture was concentrated and purified by flash chromatography (50% ethyl acetate in petroleum ether) to give the lactone **38** (24 mg, 93 μmol, 50%) and alcohol **39** (18 mg, 60 μmol, 32%) as colorless oils. − **38**: R_f = 0.40 (50% ethyl acetate in petroleum ether). − $[\alpha]_D$ = −47.7 (c = 1, CH_2Cl_2). − IR (film): $\tilde{\nu}$ = 1773 cm^{-1} (C=O). − ^{1}H NMR ($CDCl_3$): δ = 1.61 (s, 3 H, CH_3), 2.00−2.04 (m, 2 H, 5-H_{ax} and 5-H_{eq}), 2.08 (dd, 1 H, J = 6.0, 12.9 Hz, 3-H_{ax}), 2.40−2.44 (m, 1 H, 3-H_{eq}), 2.41 (s, 3 H, ArMe), 3.17−3.25 (m, 1 H, 6-H_{ax}), 4.30 (ddd, 1 H, J = 2.5, 5.5, 14.0 Hz, 6-H_{eq}), 4.89 (q, 1 H, J = 2.8 Hz, 4-H), 7.30 (d, 2 H, J = 8.2 Hz, ArH), 7.68 (d, 2 H, J = 8.2 Hz, ArH). − ^{13}C NMR ($CDCl_3$): δ = 20.2 (q, Me), 21.3 (q, ArMe), 29.6, 43.0, 43.5 (t, C-3, C-5 and C-6), 62.3 (s, C-2), 75.1 (d, C-4), 126.9, 129.5 (d, ArCH), 137.7, 143.5 (s, ArC), 173.7 (s, CO). − HRMS (EI); $C_{15}H_{22}NO_5S$ (328.1219): found 328.1199. − **39**: R_f = 0.14 (50% ethyl acetate in petroleum ether). − $[\alpha]_D$ = −14.5 (c = 0.91, CH_2Cl_2). − IR (film): $\tilde{\nu}$ = 3515 cm^{-1} (OH), 1738 (C=O). − ^{1}H NMR ($CDCl_3$): δ = 1.54−1.62 (m, 1 H, 5-H_{ax}), 1.66 (dd, 1 H, J = 8.6, 13.4 Hz, 3-H_{ax}), 1.71 (s, 3 H, Me), 1.88−1.93 (m, 1 H, 5-H_{eq}), 2.28 (ddd, 1 H, J = 1.4, 4.0, 13.4 Hz, 3-H_{eq}), 2.41 (s, 3 H, ArMe), 3.09−3.15 (m, 1 H, 6-H_{ax}), 3.68 (s, 3 H, CO_2Me), 3.84−3.90 (m, 2 H, 4-H and 6-H_{eq}), 7.27 (d, 2 H, J = 8.1 Hz, ArH), 7.75 (d, 2 H, J = 8.1 Hz, ArH). − ^{13}C NMR ($CDCl_3$): δ = 21.4 (q, ArMe), 24.6 (q, Me), 29.6, 42.1, 44.9 (t, C-3, C-5 and C-6), 52.4 (q, CO_2Me), 63.4 (s, C-2), 64.7 (d, C-4), 127.2, 129.3 (d, ArCH), 138.6, 143.1 (s, ArC), 173.9 (s, CO). − HRMS (EI); $C_{14}H_{18}NO_4S$ (296.0956): found 296.0942.

(2*R*,4*S*)-4-Hydroxy-2-piperidinecarboxylic Acid (51): Formate **30** (30 mg, 0.07 mmol) was stirred in a saturated NH_3/MeOH solution (3 mL) for 2 h and concentrated. The residue was dissolved in a 20% piperidine/MeOH (v/v) solution (3 mL), stirred for 2 h at room temp. and concentrated. The residue was dissolved in THF (3 mL), treated with 0.15 M aqueous LiOH (1 mL) and stirred vigorously for 3 h at room temp. The mixture was acidified with 2 N HCl and purified on a strongly acidic Dowex 50 W×4 ion-exchange column to yield **51** (6.5 mg, 0.04 mmol, 59%) as a thick gum. All spectroscopic data are in good agreement with those previously reported.[6a]

(2*R*,4*R*)-4-Hydroxy-2-piperidinecarboxylic Acid (52): In a similar procedure as described for **30**, formate **31** (35 mg, 0.09 mmol) was deprotected to afford the free pipecolic acid **52** (8 mg, 0.06 mmol, 61%) as a thick gum. All spectroscopic data are in good agreement with those previously reported.[6a]

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