DOI: 10.1002/ejoc.200700104

Azabicycloalkenes as Synthetic Intermediates – Synthesis of Conformationally Constrained Glutamate Analogues

Wolfgang Maison*[a]

Keywords: Glutamate mimetics / Amino acids / Tumour marker / Peptidomimetics / Neurotransmitter

As a part of our study of the cancer-specific protease PSMA (prostate-specific membrane antigen) we present a stereoselective synthesis of conformationally constrained glutamate mimetics. Key intermediates are azabicycloalkenes which are synthesized via diastereoselective or enantioselective *imino*-Diels–Alder protocols. The versatility of the route is demonstrated with the preparation of Asp, Glu and *H*Glu-mimetics based on proline or pipecolic acid scaffolds. These scaffolds are assembled by an oxidative cleavage of azabicycloalkenes and subsequent conversions of the resulting dialdehydes via chlorite oxidation or Wittig olefination. The resulting cyclic amino acids are obtained as Cbz-protected derivatives or free amines ready for further manipulation at their *N*-terminus and are useful as building blocks for the assembly of conformationally rigid PSMA ligands.

Introduction

Strained and unsaturated heterocycles of the azabicycloalkene type are extremely versatile synthetic intermediates for a number of different target structures. As ideal synthetic intermediates, they are easy to synthesize in large quantities by Diels–Alder chemistry from low-cost starting materials[1] and have functional groups that can be addressed by a number of different chemical reactions. In this respect, 2-azabicycloalkenes are particularly valuable, because of their rich follow-up chemistry resulting from their unique strained bicyclic structure.[2] In addition, diastereoselective and enantioselective *imino*-Diels–Alder protocols to azabicycloalkenes are well established[3] and a practical catalytic enantioselective approach to carbamate-protected 2-azabicycloalkenes has recently been communicated by our group.[4]

A selection of accessible target structures starting from 2- and 3-substituted azabicycloalkenes **1** is shown in Figure 1 and a lot more transformations are known for higher substituted analogs of **1**. The azabicycloalkene scaffold has a unique reactivity with respect to the strained double bond. This feature has been explored by several groups with rearrangement reactions to give hydroisoquinolines **2**[5] or bicyclic urea derivatives **3**.[6] Oxidative conversions of the double bond are also valuable methods for the preparation of cyclic amino acids **4** in peptide[7] and non-peptide context.[8] In addition, bicyclic amines **1** are useful for the preparation of diazabicycloalkanes **5**.[9] Oxidative domino processes involving 2-azabicycloalkenes have been reported by our group to give diazabicycloalkanes **6**.[10] Other known domino reactions with scaffolds **1** include metathesis sequences, which are excellent methods for the synthesis of indolizidine scaffolds **7**.[11] In addition, bicyclic amino alcohol derivatives like **8** have been prepared from **1** and are used as ligands for asymmetric catalyses.[12]

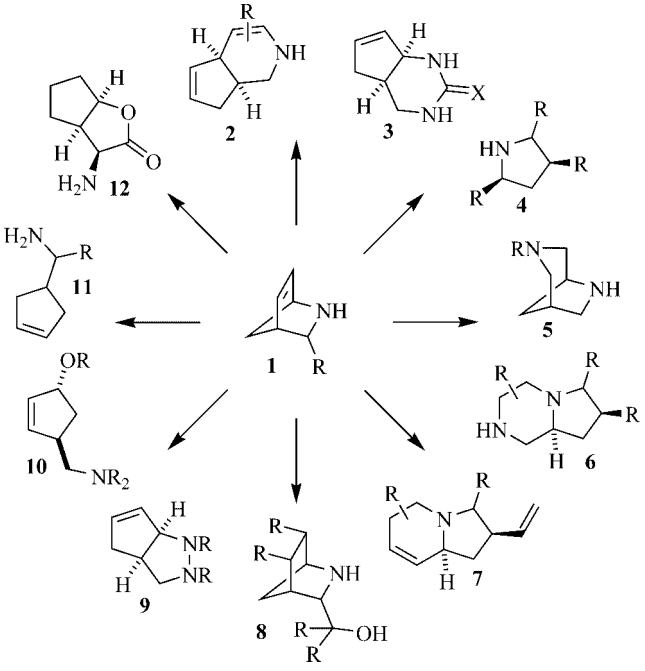


Figure 1. Scaffolds accessible from 2-azabicycloalkenes.

[a] Justus-Liebig-Universität Gießen, Institut für Organische Chemie,
Heinrich-Buff-Ring 58, 35392 Giessen
Fax: +49-641-9919864
E-mail: wolfgang.maison@org.chemie.uni-giessen.de

Special reactivity is also observed with respect to the strained nitrogen heterocycle, a fact that has been explored in different ring opening reactions. Bicyclic hydrazines like **9**[13] and amino alcohols **10**[14] are thus accessible from *N*-amino or *N*-hydroxy-azabicycloalkenes. Acidic and reductive cleavage of azabicycloalkenes gives cyclopentene derivatives or chiral amines like **11**,[15] which are valuable building blocks for carbocyclic nucleosides[16] and lactones **12**.[17] In this context it should also be noted that the 2-azabicycloalkene scaffold can be used as a general protection group for primary amines that is cleaved off via acid catalysed *retro*-Diels–Alder reaction.[18]

In this paper we report the application of the above mentioned oxidative cleavage strategy of 2-azabicycloalkenes to the synthesis of conformationally constrained aspartate, glutamate and *homo*glutamate derivatives. These compounds are interesting building blocks for the synthesis of Asp-Glu dipeptide mimetics. In this context we have been investigating conformationally constrained mimetics of *N*-acetylaspartyl glutamate (NAAG) for a while.[19] NAAG is an important neurotransmitter and the natural substrate of a cancer-specific protease called prostate-specific membrane antigen (PSMA) which we have used successfully for imaging of prostate cancer cells with low molecular weight ligands.[20]

In addition, aspartate and glutamate are the major excitatory neurotransmitters and our targeted mimetics might thus be of general interest as new ligands for glutamate receptors which are known to play an important role in several neurological disorders.[21] In this context, Hodgson has reported an elegant racemic synthesis of kainoids starting from 7-azabicycloalkenes recently.[22]

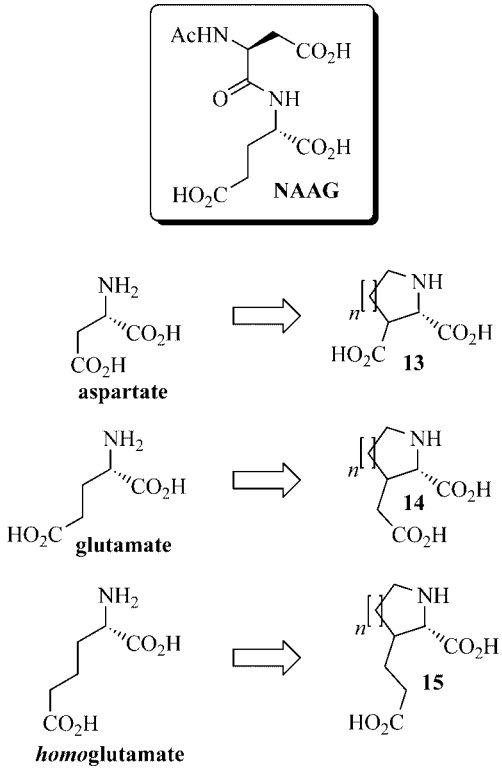


Figure 2. Conformationally constrained amino acids and the dipeptide NAAG, the natural substrate of PSMA.

The most successful inhibitors of PSMA are analogs of the transition state for peptide bond hydrolysis of NAAG (Figure 2) and are thus based on phosphonates, phosphanates and phosphoramidates.[23] However, conformational constraint of the native substrate NAAG is also a valuable strategy for the design of new PSMA inhibitors. With conformationally constrained glutamate analogs like **13**–**15** we would like to synthesize building blocks for a combined strategy of PSMA binding by conformationally constrained transition state analogues which would be accessible by *N*-terminal phosphorylation of cyclic amino acids of type **13**–**15**.

Results and Discussion

Figure 3 shows two stereoselective strategies to **19**. Key steps are either enantioselective (route A) or diastereoselective (route B) *imino*-Diels–Alder reactions to bicyclic intermediates **16** and **17**, respectively. Both routes are short (4–6 steps) and should give amino acids **18** or **19** with two additional side chains attached to a proline or pipecolic acid scaffold. This adds an additional negative charge to our glutamate mimetics, which is known to enhance the binding properties of PSMA ligands. For later phosphorylation at the *N*-terminus, the desired amino acids **19** would have to be synthesized with a free amine and base labile protection at the carboxylic acids.[24]

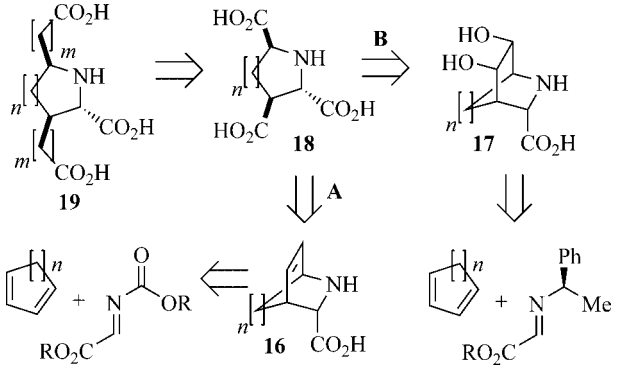
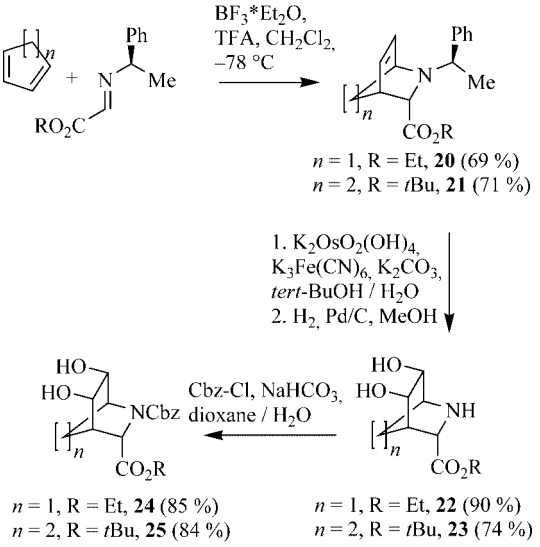


Figure 3. Retrosynthesis of cyclic amino acids **18**–**19**.

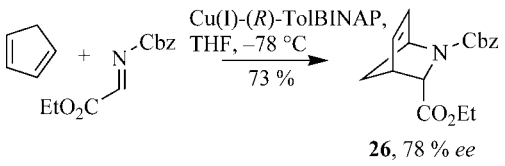
The synthesis of intermediate amino diols **17** was accomplished by a diastereoselective *imino*-Diels–Alder reaction followed by a twofold hydroxylation and deprotection as described previously.[25] Diastereoselective Diels–Alder conversions of *imino*-dienophiles are known to proceed with a high degree of stereoselectivity if the chiral information is present at the *N*-terminus of the starting imine. We chose phenylethylamine as a cheap source of chirality, following known procedures for the cycloaddition to azabicycloheptene **20** and azabicyclooctene **21**.[26] An advantage of this diastereoselective approach is its easy scale up especially for *tert*-butyl esters like **23** because all intermediates are easy

to purify by crystallisation. *N*-terminal protection was achieved with Cbz-Cl following a standard procedure to give both diols **24** and **25** (Scheme 1) in good yields.



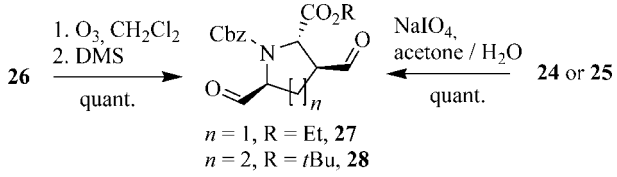
Scheme 1. Diastereoselective synthesis of Cbz-protected aminodiols **24** and **25**.

A much shorter alternative is the enantioselective synthesis of Cbz-protected azabicycloalkene **26** via the copper-catalyzed Diels–Alder reaction depicted in Scheme 2. Copper-catalyzed enantioselective *imino*-Diels–Alder reactions have been developed by Jørgensen[27] and a useful protocol for the application of this approach to the synthesis of carbamate-protected azabicycloalkenes has recently been communicated by our group.[4] However, this approach is limited to azabicycloheptenes, which are obtained in good yield and enantioselectivity. For the corresponding Diels–Alder conversions with cyclohexadiene to azabicyclooctenes, yields and enantioselectivities were generally found to be low. In consequence, we use the diastereoselective approach outlined in Scheme 1 for the synthesis of azabicyclooctenes like **21** and if large quantities of enantiomerically pure intermediates **20** or **21** are needed.



Scheme 2. Enantioselective synthesis of carbamate-protected azabicycloalkene **26**.

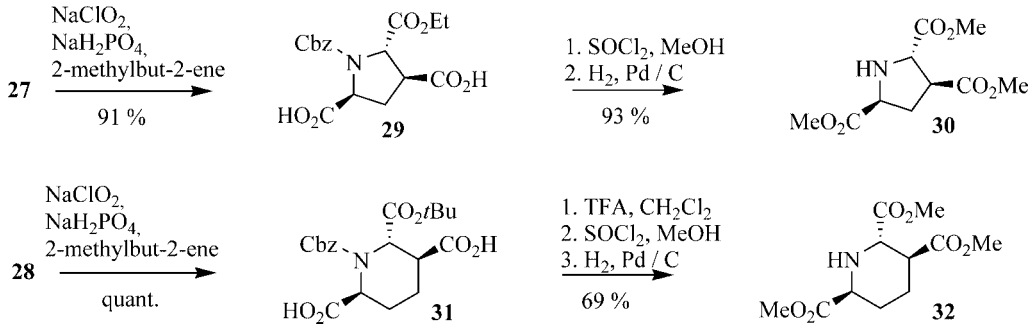
Intermediate diols **24**, **25** and the olefine **26** are all suitable for conversion to dialdehydes **27** or **28** as shown in Scheme 3. Either ozonolysis of azabicycloalkene **26** or periodate cleavage of diols **24** or **25** gave dialdehydes **27** or **28** in very clean conversions as determined by ^{1}H-NMR of the crude product which is more than 90% pure. Crude dialdehydes **27** and **28** can be stored at –18 °C for a month. However, they are configurationally labile on silica gel and were therefore used for further transformations without purification.



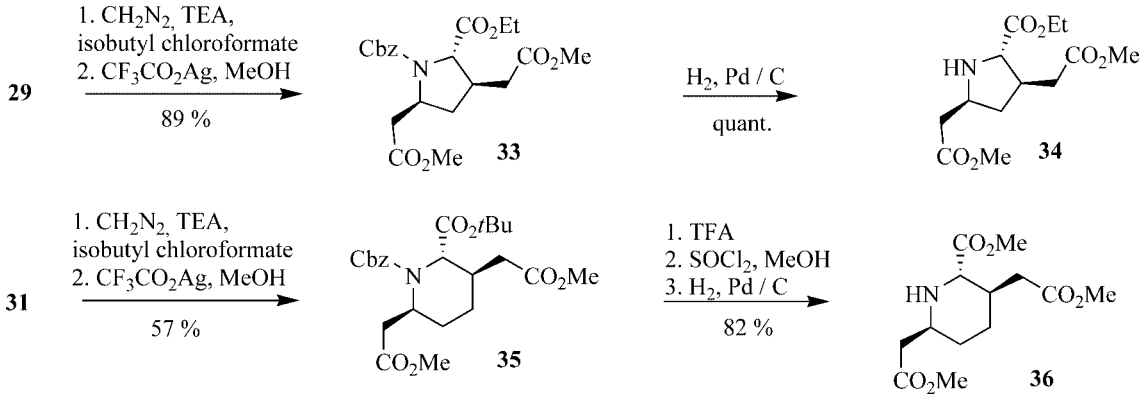
Scheme 3. Oxidative cleavage to dialdehydes **27** and **28**.

Dialdehydes **27** and **28** are versatile intermediates for the synthesis of different amino acid mimetics, because the aldehyde may be converted into almost any functionality present in amino acid side chains.

Our first target structures were aspartate mimetics **30** and **32** which were synthesized as depicted in Scheme 4. Chlorite oxidation of dialdehydes **27** and **28** gave carboxylic acids **29** and **31** in excellent yields and without epimerisation of the relatively labile α-amino aldehyde moiety. In the proline series the carboxylic acid **29** was converted into the methyl ester using thionyl chloride in methanol. Under these conditions a transesterification of the ethyl ester in **29** occurred to give an *all*-methyl ester intermediate which was deprotected with hydrogen and Pd/C to give **30** as the free amine.



Scheme 4. Synthesis of aspartate mimetics **30** and **32**.



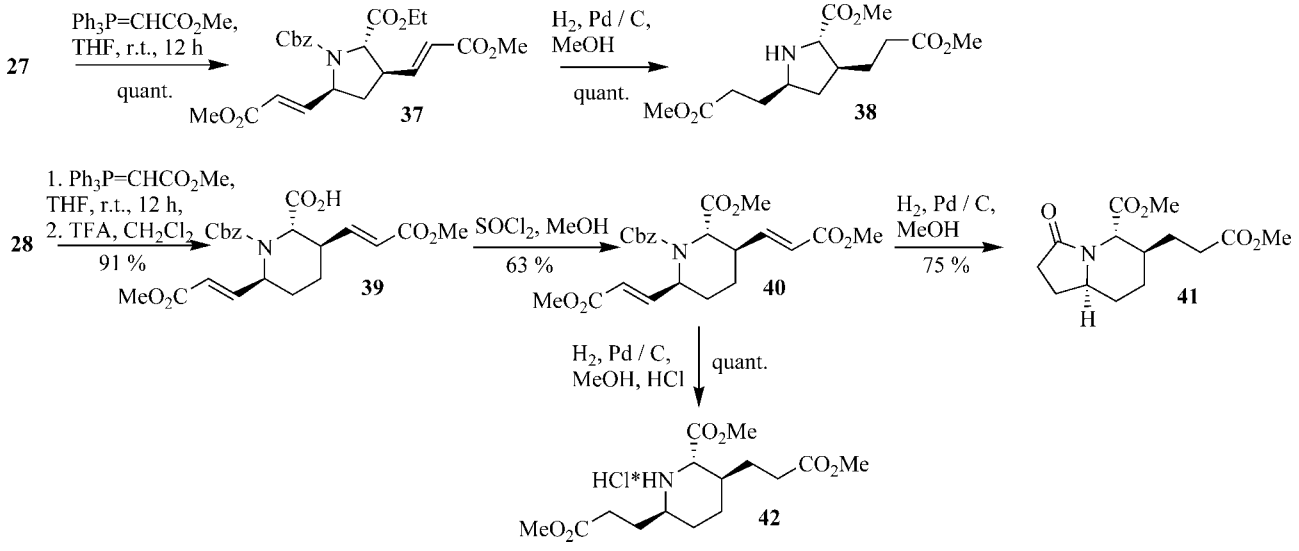
Scheme 5. Synthesis of glutamate mimetics **34** and **36**.

The *tert*-butyl ester in **28** caused an additional deprotection step in the pipecolic acid series, because we needed base labile protection for the carboxylic acids in our final products. This is due to the planed derivatisation of the amino termini to transition state analogs like phosphoramidates. However, derivative **28** is useful due to the easy purification of *tert*-butyl ester derivatives in this series. Oxidation of dialdehyde **28** gave the diacid **31** which was deprotected with TFA to give a tricarboxy piperidine in quantitative yield. Esterification to the methyl ester was again performed with thionyl chloride in methanol followed by Cbz-deprotection using Pd/C and hydrogen to give the free amine **32** ready for further manipulation at the *N*-terminus. The stereochemistry of pyrrolidine and piperidine derivatives **30** and **32** was at this point determined unambiguously by 2D-NOESY experiments.

Dicarboxylic acids **29** and **31** are ideal intermediates for Arndt–Eistert homologation to give Cbz-protected glutamate mimetics **33** and **35**. We have used a standard method for homologation of carboxylic acids with isobutyl chloroformiate giving a mixed anhydride intermediate that was treated with diazomethane. The resulting diazo ketone was not isolated, but treated subsequently with silver trifluoroacetate in methanol to give methyl esters **33** and **35** in Scheme 5. In the proline series, **33** was deprotected at the *N*-terminus with Pd/C and hydrogen to give the free amine **34** in quantitative yield.

In the pipecolic acid series, **35** was treated with TFA to deprotect the *tert*-butyl ester, followed by reprotection of the resulting carboxylic acid as the methyl ester and Cbz-deprotection under standard hydrogenolytic conditions to give the free amine **36**.

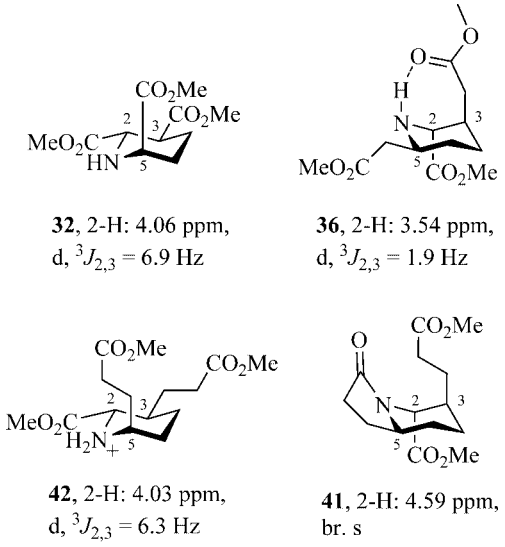
Further homologation to *homo*glutamate mimetics is depicted in Scheme 6 and was achieved by a Wittig olefination of aldehydes **27** and **28** to give both diolefines **37** and **39** in excellent yields. Treatment of **37** with hydrogen and Pd/C in methanol gave directly the *homo*glutamate mimetic **38**. Again two steps more were needed in the pipecolic acid series. Carboxylic acid **39** was obtained in a two step sequence by treatment of an intermediate Wittig adduct synthesized from dialdehyde **28** with TFA. Subsequent treatment of carboxylic acid **39** with MeOH and $SOCl_2$ then gave the trimethyl ester **40** in acceptable 63% yield. In this case we learned that, unlike the conversion of **37** to **38** in



Scheme 6. Synthesis of *homo*glutamate mimetics **38** and **42**.

the proline series, hydrogenolysis of the Cbz-protected trimethyl ester **40** under standard conditions in MeOH leads to almost complete cyclization to the undesired lactam **41**. However, the target *homo*glutamate mimetic **42** is obtained quantitatively as a hydrochloride salt upon hydrogenolysis of **40** in acidic methanol. It should be noted that intramolecular lactam formation occurs spontaneously in the pipecolic acid series if the Cbz-group in **40** is cleaved under alkaline or neutral conditions. It is, however, no problem in the proline series and deprotection of Cbz-protected **37** under neutral conditions to pyrrolidine **38** proceeds quantitatively without any observable pyrrolizidine side product.

A closer look at the NMR-data of our target products reveals interesting conformational preferences of the pipecolic acid derivatives. The chemical shift and multiplicity of 2-H is a good indicator of the ring conformation in piperidines like **32**, **36**, **41** and **42**.[28] As depicted in Figure 4, the chemical shift of 2-H in our targeted aspartate and *homo*glutamate mimetics **32** and **42** is generally around 4.0–4.1 ppm and the $^3J_{2,3}$ coupling constant is 6–7 Hz. This indicates a *trans*-coupling and is in accordance with a chair conformation of the six-membered ring and the substituents at C2 and C3 in equatorial position. In contrast, acylated piperidines like **41** show a significant downfield shift for 2-H and prefer a conformation with substituents at C2 in the axial position to avoid pseudo allylic 1,3-strain.[29] This results in a small $^3J_{2,3}$ coupling constant, which is for **41** (broad singlet for 2-H) not resolved. Surprisingly, glutamate mimetic **36** shows the same small coupling constant (1.9 Hz) indicating an axial position of the carboxymethyl group at C2. We attribute this, for a non-acylated piperidine untypical, conformation to an intramolecular hydrogen bond of either the ester at C3 (shown in Figure 4) or the ester at C5 (not shown) to the piperidine NH in $CDCl_3$. Support for an intramolecular hydrogen bond comes from an additional finding: the chemical shift (δ =3.93 ppm) and the coupling constant (6.3 Hz) change to the expected values for non-acylated piperidines if the ^{1}H NMR spectrum of **36** is measured in [D_4]MeOH instead of $CDCl_3$.



32, 2-H: 4.06 ppm, d, $^3J_{2,3}$ = 6.9 Hz

36, 2-H: 3.54 ppm, d, $^3J_{2,3}$ = 1.9 Hz

42, 2-H: 4.03 ppm, d, $^3J_{2,3}$ = 6.3 Hz

41, 2-H: 4.59 ppm, br. s

Figure 4. Representative ^{1}H NMR-data (500 MHz in $CDCl_3$) of pipecolic acids.

Conclusions

Within this paper we describe an efficient general approach to conformationally rigid amino acid mimetics. The approach is stereoselective and principally suitable for the preparation of various amino acid analogues based on proline or pipecolic acid scaffolds. We have focussed on aspartate (**30** and **32**), glutamate (**34** and **36**) and *homo*glutamate (**38** and **42**) mimetics in this study which were obtained as free amines with base labile protection of the carboxyl groups. As a part of our study of the cancer-specific protease PSMA, we are going to use these amino acids as building blocks for the assembly of dipeptide mimetics for NAAG, the natural substrate of PSMA. In addition, our amino acids might be of general interest as new analogues of aspartate, glutamate and natural products like the kainates.[30] They are thus interesting ligands for neurologically important glutamatergic receptors. In this context, it should be noted that the targeted proline and pipecolic acid derivatives have an additional side chain (besides the one mimicking the native amino acid side chain) suitable for further structural modification.

Experimental Section

General: Melting points were determined in open capillaries in a Dr. Lindström instrument and are uncorrected. ^{1}H NMR and ^{13}C-NMR spectra were recorded with a Bruker-Karlsruhe AMX 400 spectrometer (400 MHz/100.6 MHz) or on a Bruker-Karlsruhe DRX 5001 spectrometer (500 MHz/125.8 MHz). Chemical shifts, δ, are presented in part per million (ppm) and coupling constants, *J*, in Hertz (Hz) from tetramethylsilane (TMS, 0 ppm) as the internal standard for $CDCl_3$ and residual solvent peaks for other deuterated solvents. – Mass spectra were obtained with a Varian MS MAT 311A in EI mode or a VG/70–250 F (VG Analytical) instrument in FAB mode in a *p*-nitrobenzylalkohol matrix. – Elemental analyses were performed with a C,H,N Analyser EA 1108 from Carlo–Erba. The following starting materials were synthesized according to literature procedures: methyl (triphenylphosphoranylidene)acetate,[31] ethyl (1*S*,3*S*,4*R*)-2-[(1*R*)-phenylethyl]-2-azabicyclo[2.2.1]hept-5-ene-3-carboxylate **20**,[32] ethyl (1*S*,3*S*,4*S*,5*S*,6*R*)-5,6-dihydroxy-2-azabicyclo[2.2.1]heptane-3-carboxylate **22**,[25] 2-benzyl 3-ethyl (1*S*,3*S*,4*R*)-2-azabicyclo[2.2.1]hept-5-ene-2,3-dicarboxylate **26**.[4]

Azabicyclooctene 21: The title compound was prepared according to a recently published protocol[25] in 71% (51.3 g) yield as a colourless solid. R_f = 0.34 (hexane/EtOAc, 10:1). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 0.90–0.98 (m, 1 H), 1.17–1.24 (m, 13 H), 1.49–1.55 (m, 1 H), 1.95 (br., 1 H), 2.64 (s, 1 H), 2.71 (s, 1 H), 3.34 (br., 1 H), 3.54 (br., 1 H), 6.18 (dd, ^3J = 6.9 Hz, 1.9 Hz, 1 H), 6.33 (dd, ^3J = 6.9 Hz, 6.9 Hz, 1 H), 7.09–7.36 (m, 5 H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 18.9, 19.4, 26.6, 28.2, 34.1, 47.9, 63.1, 65.6, 128.8, 128.1, 128.6, 132.6, 133.0 ppm. HRMS (FAB) calcd. for $C_{20}H_{28}NO_2$ [MH^+] 314.2120, found 314.2143. $C_{20}H_{27}NO_2$ (313.4): calcd. C 76.64, H 8.68, N 4.47; found C 76.37, H 8.91, N 4.38.

Aminodiol 23: The title compound was prepared according to a recently published protocol[25] from azabicyclooctene **21** in 26.8 g (74%) yield as a colourless solid. R_f = 0.50 (dichloromethane/MeOH, 9:1). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.22–1.31 (m, 2 H), 1.38 (s, 9 H), 1.50–1.59 (m, 1 H), 1.78–1.95 (m, 2 H), 2.11–2.14 (m, 1 H), 2.95–2.99 (m, 1 H), 3.53 (t, ^3J = 2.0 Hz, 1 H), 4.06–4.09 (m, 2 H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 13.5, 20.1, 28.4, 35.1, 49.3, 57.4, 66.0, 67.0, 82.8, 173.5 ppm. HRMS (FAB) calcd. for $C_{12}H_{22}NO_4$ [MH$^+$] 244.1549, found 244.1552. $C_{12}H_{21}NO_4$ (243.3): calcd. C 59.24, H 8.70, N 5.76; found C 59.14, H 8.93, N 5.69.

Cbz-Protected Diol 24: Aminodiol **22** (2.00 g, 9.9 mmol) was dissolved in dioxane/water, 1:1 (50 mL) and cooled to 0 °C. $NaHCO_3$ (0.92 g, 11.0 mmol) was added and the solution was stirred for 5 min at 0 °C before Cbz-Cl (1.88 g, 11.0 mmol) were slowly added via an addition funnel. The resulting mixture was stirred for two hours at 0 °C and additional two hours at room temp. Dioxane was removed in vacuo and the residue was treated with water (50 mL) and extracted four times with dichloromethane (each 50 mL). The combined organic phases were washed with 0.5 N HCl (50 mL) and water (50 mL). The organic phase was dried with $NaSO_4$, filtered and the solvent removed in vacuo to give 3.2 g of a yellow oil that was purified by chromatography on silica gel (dichloromethane/MeOH, 96:4) to give 2.83 g (85% yield) of the title compound **24** as a colourless oil. R_f = 0.47 (dichloromethane/MeOH, 95:5). ^{1}H NMR (500 MHz, $CDCl_3$, 2:1 mixture of rotamers): δ = 1.09 (t, ^3J = 7.1 Hz, 2 H), 1.19 (t, ^3J = 7.1 Hz, 1 H), 1.72–1.81 (m, 2 H), 2.51 (br. s, 1 H), 3.42 (br. s, 2 H), 3.65–3.70 (m, 1 H), 3.76–3.87 (m, 2 H), 3.97–4.15 (m, 3 H), 4.89–4.93 (m, 0.7 H), 5.05–5.10 (m, 1.3 H), 7.16–7.29 (m, 5 H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$, 2:1 mixture of rotamers): δ = 14.1, 14.2, 28.2, 28.9, 47.6, 48.2, 60.0, 60.1, 60.2, 60.3, 61.6, 61.7, 67.4, 67.5, 71.1, 72.2, 72.5, 72.9, 127.7, 128.1, 128.2, 128.3, 128.6, 128.7, 136.0, 136.4, 154.3, 154.6, 170.2, 170.7 ppm. HRMS (FAB) calcd. for $C_{17}H_{22}NO_6$ [MH$^+$] 336.1447, found 336.1449. $C_{17}H_{21}NO_6$ (335.4): calcd. C 60.89, H 6.31, N 4.18; found C 60.96, H 6.41, N 4.09.

Cbz-Protected Diol 25: Aminodiol **23** (2.00 g, 8.2 mmol) was dissolved in dioxane/water, 1:1 (50 mL) and cooled to 0 °C. $NaHCO_3$ (0.76 g, 9.0 mmol) was added and the solution was stirred for 5 min at 0 °C before Cbz-Cl (1.54 g, 9.0 mmol) were slowly added via an addition funnel. The resulting mixture was stirred for two hours at 0 °C and additional two hours at room temp. Dioxane was removed in vacuo and the residue was treated with water (50 mL) and extracted four times with dichloromethane (each 50 mL). The combined organic phases were washed with 0.5 N HCl (50 mL) and water (50 mL). The organic phase was dried with $NaSO_4$, filtered and the solvent removed in vacuo to give 3.9 g of a yellow oil that was purified by chromatography on silica gel (dichloromethane/MeOH, 96:4) to give 2.78 g (84% yield) of the title compound **25** as a colourless foam. R_f = 0.21 (dichloromethane/MeOH, 96:4). ^{1}H NMR (500 MHz, $CDCl_3$, 7:3 mixture of rotamers): δ = 1.26–1.38 (m, 1 H), 1.36 (s, 7 H), 1.47 (s, 2 H), 1.78–1.91 (m, 2 H), 1.95–2.09 (m, 1 H), 2.23–2.25 (m, 0.7 H), 2.28–2.31 (m, 0.3 H), 2.59 (br. s, 2 H), 3.89–4.01 (m, 2 H), 4.07–4.10 (m, 0.7 H), 4.10–4.12 (m, 0.3 H), 4.16–4.20 (m, 0.3 H), 4.22–4.25 (m, 0.7 H), 5.02–5.06 (m, 0.6 H), 5.10–5.17 (m, 1.4 H), 7.28–7.38 (m, 5 H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$, 2:1 mixture of rotamers): δ = 13.0, 13.1, 18.8, 18.9, 28.3, 28.4, 36.6, 36.8, 48.6, 49.0, 59.1, 59.2, 65.0, 65.7, 67.1, 67.3, 67.7, 67.9, 82.1, 82.2, 128.2, 128.3, 128.4, 128.5, 128.8, 128.9, 136.4, 136.5, 155.3, 155.4, 169.9, 170.3 ppm. HRMS (FAB) calcd. for $C_{20}H_{28}NO_6$ [MH$^+$] 378.1917, found 378.1923. $C_{20}H_{27}NO_6$ (377.4): calcd. C 63.64, H 7.21, N 3.71; found C 63.96, H 7.31, N 3.79.

Dialdehyde 27: Cbz-protected diol **24** (1.66 g, 4.9 mmol) was dissolved in acetone/water (2.5:1, 25 mL), cooled to 0 °C and treated with $NaIO_4$ (2.1 g, 9.8 mmol). The resulting suspension was stirred for 2 h at 0 °C and 2 h at room temp. Water (50 mL) was added and the resulting solution was extracted with ethyl acetate four times with each 50 mL. The combined organic phases were washed with brine, dried with $NaSO_4$, filtered and the solvent was removed in vacuo to give the title compound **27** (1.65 g) as a colourless oil, which was used without further purification in the next step.

Dialdehyde 28: Cbz-protected diol **25** (2.20 g, 5.8 mmol) was dissolved in acetone/water (2.5:1, 30 mL), cooled to 0 °C and treated with $NaIO_4$ (2.1 g, 9.8 mmol). The resulting suspension was stirred for 3 h at room temp. Water (50 mL) was added and the resulting solution was extracted with ethyl acetate four times with each 50 mL. The combined organic phases were washed with brine, dried with $NaSO_4$, filtered and the solvent was removed in vacuo to give the title compound **28** (2.40 g) as a colourless oil, which was used without further purification in the next step.

Dicarboxylic Acid 29: Dialdehyde **27** (1.20 g, 3.6 mmol) and 2-methyl-2-butene (1.01 g, 14.4 mmol) were dissolved in *t*BuOH (250 mL) and treated with a solution of $NaClO_2$ (0.85 g, 9.4 mmol) and NaH_2PO_4 (1.09 g, 8.6 mmol) in water. The resulting yellow solution was stirred at room temp. for 12 h. *t*BuOH was removed in vacuo and the resulting solution treated with 0.1 N aqueous NaOH solution (50 mL) and washed three times with dichloromethane. The remaining aqueous phase was adjusted to pH ca. 1 with HCl and extracted four times with EtOAc (each 50 mL). The combined organic phases were washed with brine (50 mL), dried with $NaSO_4$, filtered and the solvent was removed in vacuo to give 1.20 g (91%) of the title compound **29** as a colourless solid. ^{1}H NMR (400 MHz, $CDCl_3$, 3:3 mixture of rotamers): δ = 1.03 (t, ^3J = 7.3 Hz, 1.8 H), 1.18 (t, ^3J = 7.3 Hz, 1.2 H), 2.38–2.68 (m, 2 H), 3.03–3.10 (m, 1 H), 3.91–4.19 (m, 2 H), 4.41–4.56 (m, 1 H), 4.91–5.21 (m, 3 H), 7.14–7.30 (m, 5 H), 8.23 (br. s, 2 H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$, mixture of rotamers): δ = 14.1, 14.3, 20.7, 21.2, 30.2, 31.2, 46.0, 47.0, 58.5, 59.0, 61.6, 62.1, 67.9, 68.2, 127.8, 127.9, 128.0, 128.2, 128.3, 128.6, 135.8, 136.0, 154.7, 154.8, 171.0, 171.1, 175.3, 175.4, 175.6, 175.7 ppm. HRMS (FAB) calcd. for $C_{17}H_{20}NO_8$ [MH$^+$] 366.1189, found 366.1183. $C_{17}H_{19}NO_8$ (365.3): calcd. C 55.89, H 5.24, N 3.83; found C 55.93, H 5.35, N 3.71.

Trimethyl Ester 30: Dicarboxylic acid **29** (0.35 g, 0.96 mmol) was dissolved in a mixture of $SOCl_2$ (0.40 g, 3.4 mmol) and abs. MeOH (10 mL) at 0 °C. The resulting solution was allowed to reach room temp. and was stirred for 24 h. The solvent was removed in vacuo and the resulting crude product 0.34 g (93%) was used without further purification in the next step. ^{1}H NMR (400 MHz, $CDCl_3$, 1:1 mixture of rotamers): δ = 2.39–2.59 (m, 2 H), 3.01–3.07 (m, 1 H), 3.46 (s, 3 H), 3.65 (s, 1.5 H), 3.66 (s, 4.5 H), 4.46 (dd, ^3J = 1.8 Hz, 9.1 Hz, 0.5 H), 4.52 (dd, ^3J = 2.3 Hz, 9.1 Hz, 0.5 H), 4.89–4.99 (m, 2 H), 5.12–5.20 (m, 1 H), 7.18–7.31 (m, 5 H) ppm.

The crude Cbz-protected triester (0.30 g, 0.79 mmol) was dissolved in MeOH (10 mL) and treated with 5% Pd/C (10 mg). The resulting mixture was stirred for 24 h under hydrogen (balloon technique) at room temp. The mixture was filtered, the solvent was removed in vacuo and the resulting residue purified by chromatography on silica gel (Et_2O) to give 0.19 g (100%) of the title compound **30** as a colourless oil. R_f = 0.57 (Et_2O). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 2.25–2.32 (m, 1 H), 2.41–2.52 (m, 2 H), 3.20 (ddd, ^3J = 6.3 Hz, 6.9 Hz, 2.5 Hz, 1 H), 3.71 (s, 3 H), 3.73 (s, 3 H), 3.74 (s, 3 H), 3.98 (dd, ^3J = 7.3 Hz, 1 H), 4.28 (d, ^3J = 6.3 Hz, 1 H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$): δ = 33.3, 47.1, 52.5, 52.6, 52.7, 59.7, 62.7, 173.0, 173.3, 173.9 ppm. HRMS (FAB) calcd. for $C_{10}H_{16}NO_6$

[MH$^+$] 246.0978, found 246.0979. $C_{10}H_{15}NO_6$ (245.2): calcd. C 48.98, H 6.17, N 5.71; found C 48.69, H 6.31, N 5.70.

Dicarboxylic Acid 31: Dialdehyde **28** (1.60 g, 4.3 mmol) and 2-methyl-2-butene (1.63 g, 23.2 mmol) were dissolved in *t*BuOH (150 mL) and treated with a solution of $NaClO_2$ (1.37 g, 15.1 mmol) and NaH_2PO_4 (1.91 g, 13.9 mmol) in water. The resulting yellow solution was stirred at room temp. for 12 h. *t*BuOH was removed in vacuo and the resulting solution treated with 0.1 N aqueous NaOH solution (50 mL) and washed three times with dichloromethane. The remaining aqueous phase was adjusted to pH ca. 1 with HCl and extracted four times with EtOAc (each 50 mL). The combined organic phases were washed with brine (50 mL), dried with $NaSO_4$, filtered and the solvent was removed in vacuo to give 1.75 g (100%) of the title compound **31** as a colourless solid. ^{1}H NMR (400 MHz, $CDCl_3$, 3:1 mixture of rotamers): δ = 1.27 (s, 6 H), 1.37 (s, 3 H), 1.58–1.69 (m, 0.7 H), 1.74–2.00 (m, 2.6 H), 2.03–2.12 (m, 0.7 H), 3.10–3.18 (m, 0.3 H), 3.20–3.25 (m, 0.7 H), 4.20 (dd, ^3J = 6.5 Hz, 0.7 H), 4.43 (br. s, 0.3 H), 4.94–5.25 (m, 3 H), 7.16–7.28 (m, 5 H), 8.44 (br. s, 2 H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$, mixture of rotamers): δ = 17.2, 17.6, 25.9, 38.8, 39.7, 53.1, 53.3, 53.9, 66.2, 80.7, 81.0, 126.1, 126.2, 126.6, 133.9, 134.0, 154.9, 155.4, 168.4, 168.6, 175.6, 175.9, 176.1 ppm. HRMS (FAB) calcd. for $C_{20}H_{26}NO_8$ [MH$^+$] 408.1658, found 408.1651. $C_{20}H_{25}NO_8$ (407.4): calcd. C 58.96, H 6.18, N 3.44; found C 58.93, H 6.25, N 3.37.

Trimethyl Ester 32: *tert*-Butyl ester **31** (0.58 g, 1.4 mmol) was dissolved in dichloromethane (5 mL) and treated with TFA (5 mL). The resulting solution was stirred at room temp. for 2 h. The solvent was removed in vacuo to give 0.50 g (100%) of the Cbz-protected tricarboxylic acid as a colourless solid. R_f = 0.26 (dichloromethane/MeOH, 95:5). ^{1}HNMR (400 MHz, D_2O, 1:1 mixture of rotamers): δ = 1.61–2.00 (m, 4 H), 2.68–2.75 (m, 0.5 H), 2.82–2.88 (m, 0.5 H), 4.09 (dd, ^3J = 5.3 Hz, 8.2 Hz, 0.5 H), 4.35 (dd, ^3J = 5.5 Hz, 5.5 Hz, 0.5 H), 4.54 (d, ^3J = 6.8 Hz, 0.5 H), 4.85 (d, ^3J = 4.3 Hz, 0.5 H), 5.10–5.22 (m, 2 H), 7.40–7.52 (m, 5 H) ppm. ^{13}CNMR (101 MHz, D_2O, mixture of rotamers): δ = 22.3, 22.7, 25.8, 45.9, 47.7, 58.6, 59.1, 60.6, 60.7, 67.8, 127.8, 128.5, 129.0, 136.7, 159.7, 160.0, 180.5, 180.6, 181.0, 181.3, 182.0, 182.2 ppm. HRMS (FAB) calcd. for $C_{16}H_{18}NO_8$ [MH$^+$] 352.1032, found 352.1027. $C_{16}H_{17}NO_8$ (351.31): calcd. C 54.70, H 4.88, N 3.99; found C 54.93, H 4.92, N 3.87.

The resulting triacid (0.60 g, 1.7 mmol) was dissolved in a mixture of $SOCl_2$ (1.19 g, 10 mmol) and abs. MeOH at 0 °C. The solution was allowed to reach room temp. and was stirred for 24 h at room temp. The solvent was removed in vacuo and the resulting residue purified by chromatography on silica gel (PE/EtOAc, 7:3) to give 0.46 g (69%) of the Cbz-protected trimethyl ester as a colourless oil. R_f = 0.16 (PE/EtOAc, 7:3). ^{1}H NMR (400 MHz, $CDCl_3$, 1:1 mixture of rotamers): δ = 1.61–2.07 (m, 4 H), 2.88–3.09 (m, 1 H), 3.44 (br. s, 3 H), 3.66 (br. s, 6 H), 4.28–4.35 (m, 0.5 H), 4.53–4.59 (m, 0.5 H), 4.70–4.75 (m, 0.5 H), 4.94–5.20 (m, 2.5 H), 7.20–7.30 (m, 5 H) ppm. ^{13}C NMR (101 MHz, D_2O, mixture of rotamers): δ = 20.5, 21.1, 24.5, 24.7, 42.1, 43.5, 52.7, 52.9, 55.7, 55.9, 56.4, 56.8, 68.4, 128.6, 128.9, 157.1, 172.3, 172.6 ppm. HRMS (FAB) calcd. for $C_{19}H_{24}NO_8$ [MH$^+$] 394.1502, found 394.1503. $C_{19}H_{23}NO_8$ (393.39): calcd. C 58.01, H 5.89, N 3.56; found C 58.15, H 5.96, N 3.46.

The resulting Cbz-protected triester (0.30 g, 0.8 mmol) was dissolved in MeOH (15 mL) and treated with 5% Pd/C (10 mg). The resulting mixture was stirred for 24 h under hydrogen (balloon technique) at room temp. The mixture was filtered, the solvent was removed in vacuo and the resulting residue purified by chromatography on silica gel (Et_2O) to give 0.20 g (100%) of the title compound **32** as a colourless oil. R_f = 0.68 (Et_2O). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.75–1.84 (m, 3 H), 1.85–1.95 (m, 1 H), 2.49 (br., 1 H), 2.78–2.83 (m, 1 H), 3.64 (dd, ^3J = 6.9 Hz, 4.1 Hz, 1 H), 3.67 (s, 3 H), 3.70 (s, 3 H), 3.71 (s, 3 H), 4.06 (d, ^3J = 6.9 Hz, 1 H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$): δ = 23.9, 25.2, 42.3, 52.1, 52.2, 52.4, 54.7, 56.4, 172.4, 173.4, 173.6 ppm. HRMS (FAB) calcd. for $C_{11}H_{18}NO_6$ [MH$^+$] 260.1134, found 260.1136. $C_{11}H_{17}NO_6$ (259.3): calcd. C 50.96, H 6.61, N 5.40; found C 50.79, H 6.34, N 5.54.

Cbz-Protected Triester 33: The title compound was prepared following a known procedure for Arndt–Eistert homologation from diacid **29** (0.70 g, 1.9 mmol).[33] The resulting residue was purified by chromatography on silica gel (PE/EtOAc, 8:2) to give 0.71 g (89%) of the title compound **33** as a colourless oil. R_f = 0.29 (PE/EtOAc, 7:3). ^{1}H NMR (500 MHz, $CDCl_3$, 2:1 mixture of rotamers): δ = 1.03 (t, ^3J = 7.2 Hz, 2 H), 1.80 (t, ^3J = 7.2 Hz, 1 H), 2.15–2.49 (m, 3 H), 2.82–3.16 (m, 4 H), 3.60 (s, 3 H), 3.69 (s, 3 H), 3.88–3.99 (m, 1.4 H), 4.09–4.17 (m, 0.6 H), 4.33–4.40 (m, 1 H), 4.74 (d, ^3J = 19.3 Hz, 0.7 H), 4.78 (d, ^2J = 19.3 Hz, 0.3 H), 4.92 (d, ^3J = 12.3 Hz, 1 H), 5.09 (d, ^3J = 19.3 Hz, 0.7 H), 5.12 (d, ^3J = 19.3 Hz, 0.3 H), 7.19–7.31 (m, 5 H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$, mixture of rotamers): δ = 14.1, 14.2, 31.9, 32.6, 38.1, 39.1, 45.5, 46.4, 51.7, 52.9, 54.3, 55.1, 61.6, 61.7, 62.2, 62.6, 67.3, 67.5, 127.9, 128.1, 128.2, 128.5, 128.6, 136.2, 136.3, 154.2, 154.6, 171.2, 171.5, 171.6, 171.8, 172.7 ppm. HRMS (FAB) calcd. for $C_{21}H_{28}NO_8$ [MH$^+$] 422.1815, found 422.1809. $C_{21}H_{27}NO_8$ (421.4): calcd. C 59.85, H 6.46, N 3.32; found C 59.97, H 6.35, N 3.40.

Triester 34: Cbz-protected triester **33** (0.15 g, 0.36 mmol) was dissolved in MeOH (10 mL) and treated with 5% Pd/C (10 mg). The resulting mixture was stirred for 24 h under hydrogen (balloon technique) at room temp. The mixture was filtered and the solvent was removed in vacuo to give 0.10 g (100%) of the title compound as a colourless oil. ^{1}H NMR (400 MHz, [D$_4$]MeOH): δ = 1.19 (t, ^3J = 7.2 Hz, 3 H), 1.62–2.00 (m, 3 H), 2.31–2.64 (m, 4 H), 3.60 (s, 3 H), 3.62–3.75 (m, 1 H), 3.65 (s, 3 H), 4.10–4.14 (m, 1 H), 4.24 (q, ^3J = 7.2 Hz, 2 H) ppm. HRMS (FAB) calcd. for $C_{13}H_{22}NO_6$ [MH$^+$] 288.1447, found 288.1451. $C_{13}H_{21}NO_6$ (287.3): calcd. C 54.35, H 7.37, N 4.88; found C 54.15, H 7.48, N 4.66.

Cbz-Protected Triester 35: The title compound was prepared following a known procedure for Arndt–Eistert homologation from diacid **31** (1.40 g, 3.4 mmol).[33] The resulting residue was purified by chromatography on silica gel (PE/EtOAc, 8:2) to give 0.91 g (57%) of the title compound **35** as a colourless oil. R_f = 0.23 (PE/EtOAc, 8:2). ^{1}H NMR (400 MHz, $CDCl_3$, due to rotational isomerism most signals are extremely broadened): δ = 1.38 (s, 4.5 H), 1.41 (s, 4.5 H), 1.63–1.90 (m, 4 H), 2.0 (br., 1 H), 2.4 (br., 1 H), 2.49–2.61 (m, 2 H), 2.8 (br., 1 H), 3.2 (br., 1 H), 3.63 (s, 3 H), 3.65 (s, 1.5 H), 3.70 (s, 1.5 H), 4.4 (br., 1 H), 5.03–5.21 (m, 2 H), 7.24–7.38 (m, 5 H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$): δ = 22.2, 24.8, 27.8, 27.9, 37.2, 38.3, 49.9, 51.7, 51.8, 52.4, 56.2, 56.7, 67.5, 81.9, 82.3, 127.9, 128.0, 128.1, 128.2, 128.5, 136.4, 136.5, 156.2, 156.9, 170.7, 171.8, 172.3, 174.0 ppm. HRMS (FAB) calcd. for $C_{24}H_{34}NO_8$ [MH$^+$] 464.2284, found 464.2290. $C_{24}H_{33}NO_8$ (463.5): calcd. C 62.19, H 7.18, N 3.02; found C 61.99, H 7.12, N 3.06.

Trimethyl Ester 36: Cbz-protected triester **35** (0.50 g, 1.1 mmol) was dissolved in dichloromethane (5 mL) and treated with TFA (5 mL). The resulting solution was stirred for 2 h at room temp. and the solvent was removed in vacuo to give crude acid which was used without further purification in the next step. This acid was dissolved in a mixture of $SOCl_2$ (0.50 g, 4.0 mmol) and abs. MeOH (10 mL) at 0 °C. The resulting solution was allowed to reach room temp. and was stirred for 24 h at room temp. The solvent was re-

moved in vacuo and the resulting crude product was purified by column chromatography on silica gel (PE/EtOAc, 7:3) to give the Cbz-protected trimethyl ester as a colourless oil (0.38 g, 82% yield). R_f = 0.19 (PE/EtOAc, 7:3). ^{1}H NMR (400 MHz, $CDCl_3$, due to rotational isomerism most signals are extremely broadened): δ = 1.65–2.03 (m, 4 H), 2.26–2.39 (m, 1 H), 2.45–2.62 (m, 2 H), 2.26–2.39 (m, 1 H), 2.8 (br., 1 H), 3.1 (br., 1 H), 3.42–3.55 (m, 1 H), 3.64 (s, 3 H), 3.65 (s, 3 H), 3.70 (s, 3 H), 4.5 (br., 1 H), 5.06–5.20 (m, 2 H), 7.28–7.38 (m, 5 H) ppm. ^{13}C NMR (101 MHz, mixture of rotamers $CDCl_3$): δ = 22.7, 25.2, 26.0, 31.0, 36.8, 37.9, 50.1, 51.8, 51.9, 52.4, 52.5, 52.6, 55.4, 59.1, 67.8, 68.1, 128.1, 128.2, 128.3, 128.4, 128.6, 136.2, 136.3, 156.1, 171.5, 172.1, 172.2 ppm. HRMS (FAB) calcd. for $C_{21}H_{28}NO_8$ [MH^+] 422.1815, found 422.1812. $C_{21}H_{27}NO_8$ (421.45): calcd. C 59.85, H 6.46, N 3.32; found C 59.65, H 6.71, N 3.23.

The resulting Cbz-protected trimethyl ester (0.35 g, 0.83 mmol) was dissolved in MeOH (10 mL) and treated with 5% Pd/C (10 mg). The resulting mixture was stirred for 24 h under hydrogen (balloon technique) at room temp. The mixture was filtered, the solvent was removed in vacuo and the resulting residue purified by chromatography on silica gel (Et_2O) to give 0.24 g (100%) of the title compound **36** as a colourless oil. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.29–1.55 (m, 3 H), 1.62–1.70 (m, 1 H), 2.34–2.43 (m, 2 H), 2.47 (dd, ^2J = 15.3 Hz, ^3J = 6.3 Hz, 1 H), 2.65–2.71 (m, 1 H), 2.76 (dd, ^2J = 15.3 Hz, ^3J = 7.9 Hz, 1 H), 3.16–3.21 (m, 1 H), 3.54 (d, ^3J = 1.9 Hz, 1 H), 3.67 (s, 3 H), 3.68 (s, 3 H), 3.74 (s, 3 H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$): δ = 25.6, 26.8, 30.8, 36.4, 40.9, 49.0, 51.7, 51.8, 52.2, 59.3, 172.5, 173.5, 174.0 ppm. HRMS (FAB) calcd. for $C_{13}H_{22}NO_6$ [MH^+] 288.1447, found 288.1442. $C_{13}H_{21}NO_6$ (287.3): calcd. C 54.35, H 7.37, N 4.88; found C 54.69, H 7.30, N 4.59.

Diolefine 37: Dialdehyde **27** (0.44 g, 1.2 mmol) was dissolved in absol. THF (30 mL) and treated with methyl triphenylphosphanylidene acetate (1.77 g, 5.3 mmol). The resulting solution was stirred under nitrogen for 24 h at room temp. The solvent was removed in vacuo and the resulting crude product was purified by column chromatography on silica gel (PE/EtOAc, 7:3) to give the title compound **37** as a colourless oil (0.55 g, 100% yield). ^{1}H NMR (500 MHz, $CDCl_3$, 1:1 mixture of rotamers): δ = 1.07 (t, ^3J = 7.1 Hz, 1.5 H), 1.25 (t, ^3J = 7.1 Hz, 1.5 H), 1.75–1.84 (m, 1 H), 2.43–2.54 (m, 1 H), 3.01–3.08 (m, 1 H), 3.71 (s, 1.5 H), 3.72 (s, 1.5 H), 3.73 (s, 1.5 H), 3.74 (s, 1.5 H), 3.93–3.98 (m, 1 H), 4.21 (q, ^3J = 7.1 Hz, 1 H), 4.28 (d, ^3J = 4.3 Hz, 0.5 H), 4.32 (d, ^3J = 5.8 Hz, 0.5 H), 4.58–4.72 (m, 1 H), 4.98 (d, ^3J = 12.2 Hz, 0.5 H), 5.02 (d, ^3J = 12.2 Hz, 0.5 H), 5.15 (d, ^3J = 12.2 Hz, 0.5 H), 5.16 (d, ^3J = 12.2 Hz, 0.5 H), 5.78–5.98 (m, 2 H), 6.77 (dd, ^3J = 7.4 Hz, 15.8 Hz, 0.5 H), 6.86 (dd, ^3J = 7.6 Hz, 15.5 Hz, 1.5 H), 7.24–7.36 (m, 5 H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$, mixture of rotamers): δ = 14.1, 14.3, 21.2, 36.4, 37.5, 44.2, 45.2, 51.8, 51.9, 58.8, 59.4, 61.7, 61.8, 64.7, 65.0, 67.6, 67.8, 121.4, 121.6, 122.9, 123.0, 128.1, 128.2, 128.3, 128.5, 128.6, 135.9, 146.2, 146.4, 147.6, 148.2, 154.2, 166.2, 166.4, 166.5, 171.1, 171.3 ppm. HRMS (FAB) calcd. for $C_{23}H_{28}NO_8$ [MH^+] 446.1815, found 446.1817. $C_{23}H_{27}NO_8$ (445.5): calcd. C 62.01, H 6.11, N 3.14; found C 62.13, H 6.04, N 3.10.

Trimethyl Ester 38: Olefine **37** (0.35 g, 0.8 mmol) was dissolved in absol. MeOH (30 mL) and treated with 5% Pd/C (10 mg). The resulting mixture was stirred under hydrogen (balloon technique) for 24 h at room temp. The suspension was filtered and the solvent was removed in vacuo to give the title compound **38** as a colourless oil (0.28 g, 100% yield). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.64–1.80 (m, 3 H), 1.95–2.13 (m, 3 H), 2.27–2.36 (m, 4 H), 2.44–2.58 (m, 2 H), 3.17–3.24 (m, 1 H), 3.44 (d, ^3J = 6.9 Hz, 1 H), 3.60 (s, 3 H), 3.61 (s, 3 H), 3.67 (s, 3 H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$, mixture of rotamers): δ = 30.0, 31.2, 31.7, 32.7, 38.7, 43.9, 51.7, 51.8, 52.4, 58.1, 64.6, 173.7, 174.0, 175.5 ppm. HRMS (FAB) calcd. for $C_{14}H_{24}NO_6$ [MH^+] 302.1604, found 302.1601. $C_{14}H_{23}NO_6$ (301.3): calcd. C 55.80, H 7.69, N 4.65; found C 55.89, H 7.60, N 4.71.

Carboxylic Acid 39: Dialdehyde **28** (0.80 g, 2.1 mmol) was dissolved in absol. THF (30 mL) and treated with methyl triphenylphosphanylidene acetate (3.90 g, 11.6 mmol). The resulting solution was stirred under nitrogen for 24 h at room temp. The solvent was removed in vacuo and the resulting crude product was purified by column chromatography on silica gel (PE/EtOAc, 8:2) to give the diolefine as a colourless oil (0.93 g, 91% yield). R_f = 0.20 (PE/EtOAc, 8:2). ^{1}H NMR (400 MHz, $CDCl_3$, due to rotational isomerism most signals are extremely broadened): δ = 1.41 (s, 9 H), 1.49–1.79 (m, 4 H), 2.8 (br., 1 H), 3.71 (s, 3 H), 3.74 (s, 3 H), 4.5 (br., 2 H), 5.03–5.20 (m, 2 H), 5.7 (br., 1 H), 5.91 (dd, ^3J = 1.0 Hz, 15.8 Hz, 1 H), 6.84–6.99 (m, 2 H), 7.27–7.36 (m, 5 H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$): δ = 15.4, 23.4, 27.1, 28.0, 51.7, 51.8, 59.3, 66.0, 68.0, 82.5, 122.4, 128.3, 128.4, 128.6, 136.0, 148.2, 157.3, 166.6, 170.2, 170.5 ppm. HRMS (FAB) calcd. for $C_{26}H_{34}NO_8$ [MH^+] 488.2284, found 488.2286. $C_{26}H_{33}NO_8$ (487.55): calcd. C 64.05, H 6.82, N 2.87; found C 64.23, H 6.80, N 2.94.

The resulting diolefine (0.90 g, 1.8 mmol) was dissolved in dichloromethane (5 mL) and treated with TFA (5 mL). The solution was stirred for 2 h at room temp. The solvent was removed in vacuo and the resulting crude product was purified by column chromatography on silica gel (PE/EtOAc, 1:1) to give the title compound **39** as a colourless oil (0.78 g, 100% yield). R_f = 0.13 (PE/EtOAc, 7:3). ^{1}H NMR (400 MHz, $CDCl_3$, due to rotational isomerism most signals are extremely broadened): δ = 1.50–1.62 (m, 1 H), 1.71–1.90 (m, 3 H), 2.2 (br., 1 H), 3.74 (s, 3 H), 3.76 (s, 3 H), 4.3 (br., 1 H), 4.7 (br., 1 H), 5.08 (d, ^3J = 12.1 Hz, 1 H), 5.18 (d, ^3J = 12.1 Hz, 1 H), 5.74 (br. d, ^3J = 14.5 Hz, 1 H), 5.94 (dd, ^3J = 1.3 Hz, 15.7 Hz, 1 H), 6.91 (dd, ^3J = 7.5 Hz, 15.7 Hz, 2 H), 7.24–7.35 (m, 5 H), 8.2 (br., 1 H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$): δ = 23.4, 26.9, 27.7, 52.2, 52.3, 58.6, 68.8, 122.8, 128.5, 128.6, 128.7, 135.2, 147.8, 157.6, 167.3, 176.0 ppm. HRMS (FAB) calcd. for $C_{22}H_{26}NO_8$ [MH^+] 432.1658, found 432.1652. $C_{22}H_{25}NO_8$ (431.4): calcd. C 61.25, H 5.84, N 3.25; found C 61.23, H 5.76, N 3.17.

Cbz-Protected Trimethyl Ester 40: Carboxylic acid **39** (0.85 g, 2.0 mmol) was dissolved in a mixture of $SOCl_2$ (0.47 g, 3.9 mmol) and abs. MeOH (15 mL) at 0 °C. The resulting solution was allowed to reach room temp. and was stirred for 24 h at room temp. The solvent was removed in vacuo and the resulting crude product was purified by column chromatography on silica gel (PE/EtOAc, 7:3) to give the title compound **40** as a colourless oil (0.55 g, 63% yield). R_f = 0.18 (PE/EtOAc, 7:3). ^{1}H NMR (400 MHz, $CDCl_3$, due to rotational isomerism most signals are extremely broadened): δ = 1.44–1.59 (m, 1 H), 1.64–1.86 (m, 3 H), 2.8 (br., 1 H), 3.6 (br., 3 H), 3.71 (s, 3 H), 3.73 (s, 3 H), 4.2 (br., 1 H), 4.7 (br., 1 H), 5.04 (d, ^3J = 12.1 Hz, 1 H), 5.16 (d, ^3J = 12.1 Hz, 1 H), 5.73 (br. d, ^3J = 15.1 Hz, 1 H), 5.88 (dd, ^3J = 1.3 Hz, 15.8 Hz, 1 H), 6.83 (dd, ^3J = 8.0 Hz, 15.8 Hz, 2 H), 7.26–7.34 (m, 5 H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$): δ = 23.6, 27.1, 51.7, 51.8, 52.3, 53.8, 58.8, 68.2, 122.7, 128.4, 128.5, 128.6, 135.7, 147.3, 157.0, 166.5, 171.6 ppm. HRMS (FAB) calcd. for $C_{23}H_{28}NO_8$ [MH^+] 446.1815, found 456.1819. $C_{23}H_{27}NO_8$ (445.5): calcd. C 62.01, H 6.11, N 3.14; found C 61.86, H 6.00, N 3.19.

Lactam 41: Cbz-protected triester **40** (0.20 g, 0.5 mmol) was dissolved in MeOH (15 mL) and treated with 5% Pd/C (10 mg). The resulting mixture was stirred for 24 h under hydrogen (balloon

technique) at room temp. The mixture was filtered, the solvent was removed in vacuo and the resulting residue purified by chromatography on silica gel (Et_2O/MeOH, 95:5) to give 0.10 g (75%) of the title compound **41** as a colourless oil. R_f = 0.47 (Et_2O). ^1H NMR (500 MHz, $CDCl_3$): δ = 1.49–1.85 (m, 8 H), 2.20–2.45 (m, 6 H), 3.66 (s, 3 H), 3.69–3.78 (m, 1 H), 3.70 (s, 3 H), 4.59 (s, 1 H) ppm. HRMS (FAB) calcd. for $C_{14}H_{22}NO_5$ [MH^+] 284.1498, found 284.1492. $C_{14}H_{21}NO_5$ (283.3): calcd. C 59.35, H 7.47, N 4.94; found C 59.51, H 7.57, N 4.88.

Trimethyl Ester 42: Cbz-protected triester **40** (0.30 g, 0.67 mmol) was dissolved in a mixture of AcCl (0.8 mL) and MeOH (20 mL) and treated with 10% Pd/C (10 mg). The resulting mixture was stirred for 24 h under hydrogen (balloon technique) at room temp. The mixture was filtered, the solvent was removed in vacuo to give 0.23 g (100%) of the title compound **42** as a colourless oil. ^1H NMR (500 MHz, [D_4]MeOH): δ = 1.49–1.57 (m, 1 H), 1.60–1.71 (m, 3 H), 1.73–2.01 (m, 4 H), 2.03–2.09 (m, 1 H), 2.29–2.50 (m, 4 H), 3.44–3.51 (m, 1 H), 3.58 (s, 3 H), 3.60 (s, 3 H), 3.79 (s, 3 H), 4.03 (d, ^3J = 6.3 Hz, 1 H) ppm. ^{13}C NMR (101 MHz, [D_4]MeOH): δ = 24.0, 25.0, 27.2, 27.3, 31.0, 32.0, 36.4, 52.6, 52.8, 54.3, 54.9, 59.2, 170.3, 174.9, 175.4 ppm. $C_{15}H_{26}ClNO_6$ (351.8): calcd. C 51.21, H 7.45, N 3.98; found C 51.71, H 7.72, N 4.06.

Acknowledgments

We are grateful to BASF AG, Degussa AG and Merck KgaA for material support. We thank the Alexander von Humboldt-Stiftung, Fonds der Chemischen Industrie and the Deutsche Forschungsgemeinschaft (DFG) (MA 2529/1-2) for financial support.

[1] Reviews: a) L. F. Tietze, G. Kettschau, *Top. Curr. Chem.* **1997**, *189*, 1–120; b) P. Buonora, J.-C. Olsen, T. Oh, *Tetrahedron* **2001**, *57*, 6099–6138.
[2] D. Blondet, C. Morin, *Heterocycles* **1982**, *19*, 2155–2182.
[3] Review: G. R. Heintzelman, I. R. Meigh, Y. R. Mahajan, S. M. Weinreb, *Org. React.* **2005**, *65*, 141–599.
[4] A. H. G. P. Prenzel, N. Deppermann, W. Maison, *Org. Lett.* **2006**, *8*, 1681–1684.
[5] a) M. M. Cid, E. Pombo-Villar, *Helv. Chim. Acta* **1993**, *76*, 1591–1607; b) S. M. Roberts, C. Smith, R. J. Thomas, *J. Chem. Soc., Perkin Trans. 1* **1990**, 1493–1495; c) E. W. Baxter, D. Labaree, S. Chao, P. S. Mariano, *J. Org. Chem.* **1989**, *54*, 2893–2904; d) P. S. Mariano, D. Dunaway-Mariano, P. L. Huesmann, *J. Org. Chem.* **1979**, *44*, 124–133.
[6] A. M. Bowser, J. S. Madalengoitia, *Tetrahedron Lett.* **2005**, *46*, 2869–2872.
[7] M. Jaeger, K. Polborn, W. Steglich, *Tetrahedron Lett.* **1995**, *36*, 861–864.
[8] a) Y. Arakawa, M. Yasuda, M. Ohnishi, S. Yoshifuji, *Chem. Pharm. Bull.* **1997**, *45*, 255–259; b) W. Maison, G. Adiwidjaja, *Tetrahedron Lett.* **2002**, *43*, 5957–5960; c) M. J. Alves, X. Garcia-Mera, M. L. C. Vale, T. P. Santos, F. R. Aguiar, J. E. Rodriguez-Borges, *Tetrahedron Lett.* **2006**, *47*, 7595–7597.
[9] A. H. Fray, D. J. Augeri, E. F. Kleinman, *J. Org. Chem.* **1988**, *53*, 896–899.
[10] W. Maison, D. Küntzer, D. Grohs, *Synlett* **2002**, 1795–1798.
[11] a) M. Büchert, S. Meinke, A. H. G. P. Prenzel, N. Deppermann, W. Maison, *Org. Lett.* **2006**, *8*, 5553–5556; b) Z. Liu, J. D. Rainier, *Org. Lett.* **2006**, *8*, 459–462; for ROCM of 2-azabicycloalkenes see: A. M. Dunne, S. Mix, S. Blechert, *Tetrahedron Lett.* **2003**, *44*, 2733–2736; 2-azabicycloalkenones have been studied by Plumet: O. Arjona, A. G. Csáky, R. Medel, J. Plumet, *J. Org. Chem.* **2002**, *67*, 1380–1383; for ROCM of 2-azabicycloalkenones see: M. Ishikura, M. Saijo, A. Hino, *Heterocycles* **2003**, *59*, 573–585.
[12] S. J. M. Nordin, P. Roth, T. Tarnai, D. A. Alonso, P. Brandt, P. G. Andersson, *Chem. Eur. J.* **2001**, *7*, 1431–1436.
[13] A. Heesing, L. Keller, *Chem. Ber.* **1986**, *119*, 1413–1423.
[14] A. Heesing, W. Herdering, G. Henkel, B. Krebs, *Chem. Ber.* **1983**, *116*, 1107–1117.
[15] a) M. D. Gaul, K. W. Fowler, P. A. Grieco, *Tetrahedron Lett.* **1993**, *34*, 3099–3102; b) S. K. Bertilsson, J. K. Ekegren, S. A. Modin, P. G. Andersson, *Tetrahedron* **2001**, *57*, 6399–6406.
[16] P. A. Grieco, S. D. Larsen, W. F. Fobare, *Tetrahedron Lett.* **1986**, *27*, 1975–1978.
[17] a) T. Kobayashi, K. Ono, H. Kato, *Bull. Chem. Soc. Jpn.* **1992**, *65*, 61–65; b) M. B. Hursthouse, K. M. A. Malik, D. E. Hibbs, S. M. Roberts, A. J. H. Seago, V. Sik, R. Storer, *J. Chem. Soc., Perkin Trans. 1* **1995**, 2419–2425; c) S. E. Ward, A. B. Holmes, R. McCague, *Chem. Commun.* **1997**, 2085–2086.
[18] P. A. Grieco, J. D. Clark, *J. Org. Chem.* **1990**, *55*, 2271–2272.
[19] W. R. Fair, R. S. Israeli, W. D. Heston, *Prostate* **1997**, *32*, 140–146.
[20] P. Misra, V. Humblet, N. Pannier, W. Maison, J. V. Frangioni, manuscript submitted for publication.
[21] C. J. Swanson, M. Bures, M. P. Johnson, A. M. Linden, J. A. Monn, D. D. Schoepp, *Nat. Rev. Drug Discovery* **2005**, *4*, 131–144.
[22] D. M. Hodgson, S. Hachisu, M. D. Andrews, *J. Org. Chem.* **2005**, *70*, 8866–8876.
[23] Review: J. Zhou, J. H. Neale, M. G. Pomper, A. P. Kozikowski, *Nat. Rev. Drug Discovery* **2005**, *4*, 1015–1026.
[24] J. P. Mallari, C. J. Choy, Y. Hu, A. R. Martinez, M. Hosaka, Y. Toriyabe, J. Maung, J. E. Blecha, S. F. Pavkovic, C. E. Berkman, *Bioorg. Med. Chem.* **2004**, *12*, 6011–6020.
[25] W. Maison, D. C. Grohs, A. H. G. P. Prenzel, *Eur. J. Org. Chem.* **2004**, 1527–1543.
[26] a) H. Waldmann, M. Braun, *Liebigs Ann. Chem.* **1991**, 1045–1048; b) P. D. Bailey, R. D. Wilson, G. R. Brown, *J. Chem. Soc., Perkin Trans. 1* **1991**, 1337–1340; c) H. Abraham, L. Stella, *Tetrahedron* **1992**, *48*, 9707–9718; d) J. K. Ekegren, S. A. Modin, D. A. Alonso, P. G. Andersson, *Tetrahedron: Asymetry* **2002**, *13*, 447–449.
[27] S. Yao, S. Saaby, R. G. Hazell, K. A. Jørgensen, *Chem. Eur. J.* **2000**, *6*, 2435–2448.
[28] E. E. Sugg, J. F. Griffin, P. S. Portoghese, *J. Org. Chem.* **1985**, *50*, 5032–5037.
[29] a) R. W. Hoffmann, *Chem. Rev.* **1989**, *89*, 1841–1860; b) D. Seebach, B. Lamatsch, R. Amstutz, A. K. Beck, M. Dobler, M. Egli, R. Fitzi, M. Gautschi, B. Herradon, P. C. Hidber, J. J. Irwin, R. Locher, M. Maestro, T. Maetzke, A. Mourinho, E. Pfammatter, D. A. Plattner, C. Schickli, W. B. Schweizer, P. Seiler, G. Stucky, W. Petter, J. Escalante, E. Juaristi, D. Qunitana, C. Mriavitlles, E. Molins, *Helv. Chim. Acta* **1992**, *75*, 913–934.
[30] J. Clayden, B. Read, K. R. Hebditch, *Tetrahedron* **2005**, *61*, 5713–5724.
[31] O. Isler, H. Gutmann, M. Montavon, R. Rüegg, G. Ryser, P. Zeller, *Helv. Chim. Acta* **1957**, *40*, 1242–1249.
[32] D. A. Alonso, S. K. Bertilsson, S. Y. Johnsson, S. J. M. Nordin, M. J. Södergren, P. G. Andersson, *J. Org. Chem.* **1999**, *64*, 2276–2280.
[33] M. R. Linder, S. Steurer, J. Podlech, *Org. Synth., Coll. Vol.* **2004**, *10*, 194–199.

Received: February 7, 2007
Published Online: March 22, 2007

