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γ-Aminoadamantanecarboxylic Acids Through Direct C–H Bond Amidations

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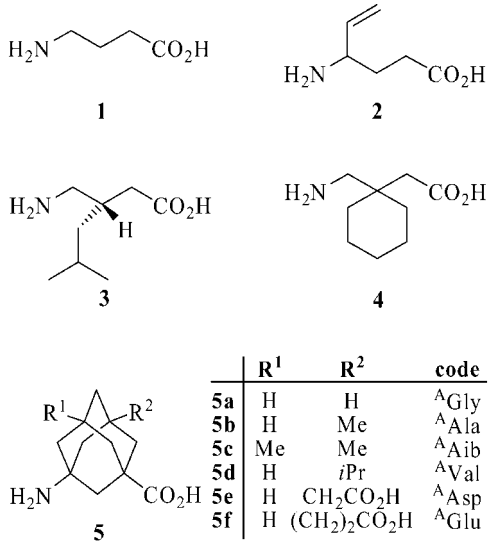
Utilizing bromine-free, direct C–H bond amidations we have synthesized a large variety of adamantane amides. Depending on the precursors used these amides directly yield pharmaceutically active aminoadamantanes or γ-aminoadamantanecarboxylic acids after hydrolytic cleavage. These rigid analogues of γ-aminobutyric acid (GABA) were protected at the C- and N-termini and we synthesized a number of peptides incorporating γ-aminoadamantanecarboxylic acids in solution as well as via solid phase peptide synthesis. These peptides are promising scaffolds for applications in medicinal chemistry as well as in organocatalysis.

Introduction

Unnatural amino acids are most welcome building blocks to expand on structural motifs, chemical properties and pharmaceutical activities attainable by their natural, proteinogenic counterparts.[1] Artificial scaffolds based on novel amino acids often display well-defined secondary and even tertiary structures; pertinent examples are oligopeptides of β- or higher amino acids.[2] The seminal syntheses and structure elucidations of β- and γ-peptide foldamers[3–9] led to the discovery of alternative peptide backbones. One particular class of γ-amino acids is represented by γ-aminobutyric acid (GABA) analogues such as Vigabatrin® (**2**), Pregabalin® (**3**), and Gabapentin® (**4**, Scheme 1) that have proven effective, e.g., as potent anticonvulsants.[10]

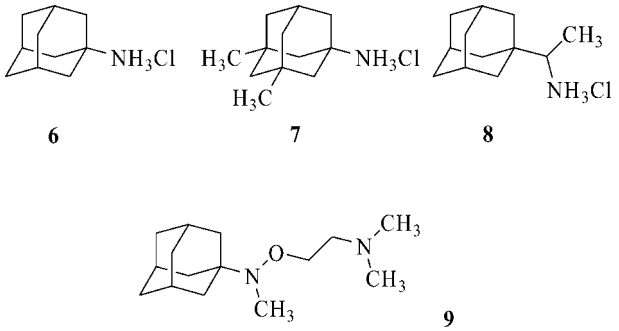
γ-Amino acids based on the adamantane framework are rigid GABA analogues and, although simple representatives have already been prepared decades ago,[11] they have not been utilized as peptide building blocks or pharmaceutically active compounds until very recently,[12] despite the fact that *all* adamantane derivatives currently used as pharmaceuticals are amino derivatives (Scheme 2).[13–19]

Here, we report the synthesis of a number of representative γ-aminoadamantane-1-carboxylic acids (we use the short-hand designation "^{A}Xaa" to emphasize the functional group relationship to α-amino acids) through tertiary C–H bond amidation protocols of the adamantane core. The adamantane C–H bond amidation is conducted in a



	R^1	R^2	code
5a	H	H	^{A}Gly
5b	H	Me	^{A}Ala
5c	Me	Me	^{A}Aib
5d	H	*i*Pr	^{A}Val
5e	H	CH_2CO_2H	^{A}Asp
5f	H	$(CH_2)_2CO_2H$	^{A}Glu

Scheme 1. GABA (**1**) and analogues **2**–**4** used as anticonvulsants. γ-Aminoadamantanecarboxylic acids **5a**–**5f** as GABA analogues.



Scheme 2. Aminoadamantanes used as pharmaceuticals. Anti-Influenza-A pharmaceuticals Amantadine (**6**) and Rimantadine (**8**), Tromantadine (**9**), used against *Herpes simplex*, and Memantine (**7**), a non-competitive NMDA-receptor antagonist used in the therapy of Alzheimer's disease; **6** is also being used in Parkinson's disease therapy.

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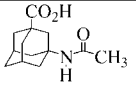
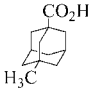
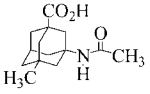
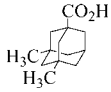
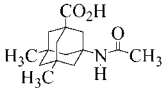
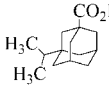
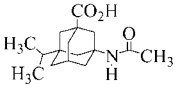
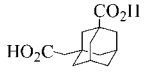
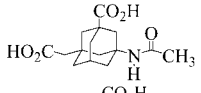
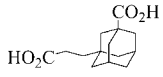
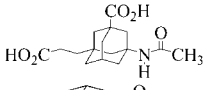
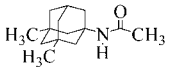
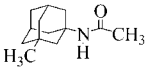
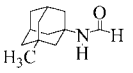
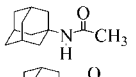
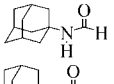
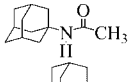
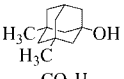
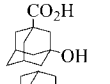
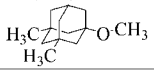
direct way, that is, without prior halogenation of the desired tertiary position, and it solely utilizes technical grade reagents which allows for large-scale preparation of adamantyl amides in straightforward procedures. We report two C–H bond amidation protocols utilizing acetonitrile or amides as nitrogen nucleophiles. As an additional benefit, these amidation protocols can also be applied to the preparation of closely related pharmacologically active amino adamantanes. Additionally, alcohols and ethers can also easily be prepared in satisfactory to good yields when using oxygen nucleophiles. The ^{A}Xaa's use as building blocks in liquid- as well as solid-phase peptide syntheses is exemplified by the synthesis of homooligomeric ^{A}Xaas and hybrid peptides incorporating both ^{A}Xaas and α-amino acids.

Results and Discussion

For the preparation of pharmaceutically active amino adamantanes, a number of syntheses have been reported. By far the most abundant method is the formation of C–N bonds via Ritter-type[20] reactions and subsequent conversions. For instance, bromination of the tertiary positions of adamantane proceeds with excellent yields and selectivities, and consequently one usually uses halogenations to direct the newly introduced nitrogen functionalities into these positions.[11] A major drawback of this approach (also in view of medicinal applications or large-scale reactions) is the use of excess of bromine. Since the molecularity of the electrophilic bromination of adamantane with elemental bromine

Table 1. Direct C–H bond functionalizations of adamantane derivatives.[a,c]

Entry	Starting compound		Nucleophile	Product		Yield [%][b]
1		**10**	CH_3CN		**19**	84
2		**11**	CH_3CN		(±)-**20**	93
3		**12**	CH_3CN		**21**	92
4		**13**	CH_3CN		(±)-**22**	39
5		**14**	CH_3CN		(±)-**23**	77
6		**15**	CH_3CN		(±)-**24**	37
7		**16**	CH_3CN		**25**	90
8		**16**			**26**	89
9		**17**	CH_3CN		**27**	42
10		**17**			**28**	45
11		**18**	CH_3CN		**29**	15
12		**18**			**30**	13
13		**18**			**29**	38
14		**16**	H_2O		**31**	81
15		**10**	H_2O		**32**	70
16		**16**	CH_3OH		**33**	38

[a] Experimental procedures and workup vary; for details, see Exp. Section. [b] Yields of isolated product after recrystallization or silica gel column chromatography. [c] For racemic compounds, only one enantiomer is shown.

is about 7,[21] usually 10 equivalents of bromine are used. Moreover, bromine has to be distilled prior to use to avoid overfunctionalization due to traces of Lewis acids;[21–23] excess bromine has to be redistilled or disposed after the reaction. In view of these limitations, we set out to advance a Ritter-type protocol[24,25] that allows for *direct* C–H bond amidation of various adamantane derivatives *without* a prior halogenation step (Table 1). In order to activate the adamantane tertiary C–H bonds, we decided to use nitrating acid (HNO_3/H_2SO_4) of various compositions, because under these conditions the key single electron oxidizer NO_2^+ is generated in situ.[26] Treating the appropriate precursors with these mineral acid mixtures yields a "(radical)-cation[27] solution" that can be quenched with a number of nucleophiles. Acetonitrile is historically used in most Ritter-type amidations of adamantane derivatives; upon aqueous workup, adamantane acetamides are usually isolated in good yields.[28] Our direct functionalization protocol presumably is currently the most convenient approach as it avoids halogenation, does not depend on expensive and sometimes poisonous SET acceptors [$Pb(OAc)_4$,[29] NO_2BF_4,[26] etc.] or operationally difficult anodic oxidation;[30,31] only technical grade reagents are employed.[32] Yields of the acetamides are generally high when using adamantane precursors whose solubility in the polar mineral acid medium is enhanced by one or more carboxylic acid groups (Table 1, entries 1–6) or when the intermediate radical cation is hyperconjugatively stabilized[21] through alkyl substitution of the remaining tertiary positions (entry 7). In some cases, the isolated product yields are lowered due to the pronounced volatility of the amides (entries 9 and 11).

Strikingly, an unprecedented variant of direct C–H to C–N bond functionalization by quenching the solution with amides, e.g., formamide and acetamide as the nitrogen nucleophiles[33] is also possible with only minor changes in the reaction conditions (somewhat larger amount of the amide). Formamides and acetamides (Table 1, entries 8, 10, 12, 13) form in yields comparable to the other amidation protocol. Acidic hydrolysis of amides **19**–**24** directly yields ^{A}Xaas **5a**–**5f** as their respective hydrochlorides (Scheme 1; Figure 1). When using 1,3-dimethyladamantane or adamantane, hydrolysis of the respective amides (Table 1, entries 7 and 8; Figure 2) yields 1-amino-3,5-dimethyladamantane (**7**) (Memantine®,Axura®, Akatinol®, Ebixa®, Namenda®) that is used as an NMDA-receptor antagonist for the treatment of Alzheimer's disease[34,35] and 1-aminoadamantane (**6**, Amantadine®), respectively, which is used as an antiviral agent[13] and to combat Parkinsonism.[36] Acid hydrolysis of formamido adamantanes is advantageous over the hydrolysis of the corresponding acetamides as it proceeds much more smoothly at lower concentration of acid, which again is important for large-scale syntheses.

The reactions can also be quenched with other nucleophiles such as water and alcohols (Table 1, entries 14–16), yielding hydroxy as well as alkoxy adamantanes. This method also appears to be an operationally simpler synthesis of alcohols and adamantyl ethers than procedures previously reported.[37–39]

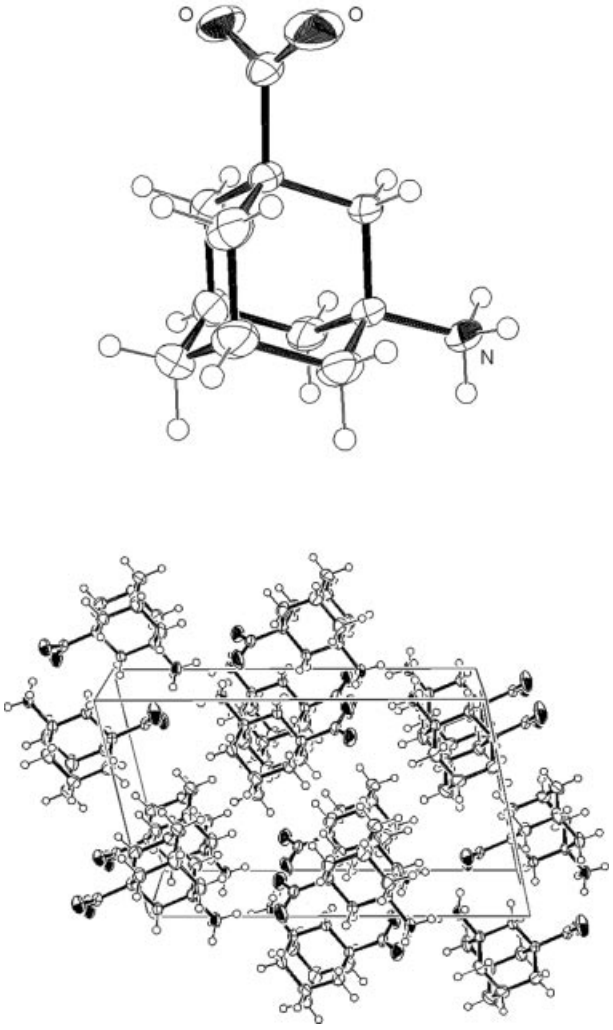


Figure 1. ORTEP diagram of ^{A}Gly (**5a**) and its packing in the crystal. Displacement ellipsoids drawn with 50% probability.

An alternative strategy to ^{A}Xaas utilizes phase-transfer catalyzed halogenations developed in our group;[40,41] this allows for a larger variety of R^1 and R^2 for future applications (vide infra). The strategy is exemplified in Scheme 3 by the synthesis of ^{A}Aib ($R^1 = R^2$ = Me) and ^{A}Val (R^1 = H, R^2 = *i*Pr). Hence, we have iodinated bromoadamantanes (available via the above-mentioned electrophilic bromination protocol using elemental bromine or via PTC bromination for sensitive substrates) with iodoform and solid sodium hydroxide in fluorobenzene suspension under PTC conditions and ultrasound acceleration[42] to yield bromoiodoadamantanes in satisfactory yields. Nitrosonium ion induced oxidative Ritter-type reaction[28] allowed for selective substitution of the iodine in **35a**,**b** to give the corresponding bromo acetamido adamantanes in good yields (**36a**: $R^1 = R^2$ = Me, 94%; **36b**: R^1 = H, R^2 = *i*Pr, 66%). Koch–Haaf substitution gives the acetylated ^{A}Xaas (**21**, 72%, **22**, 62%).

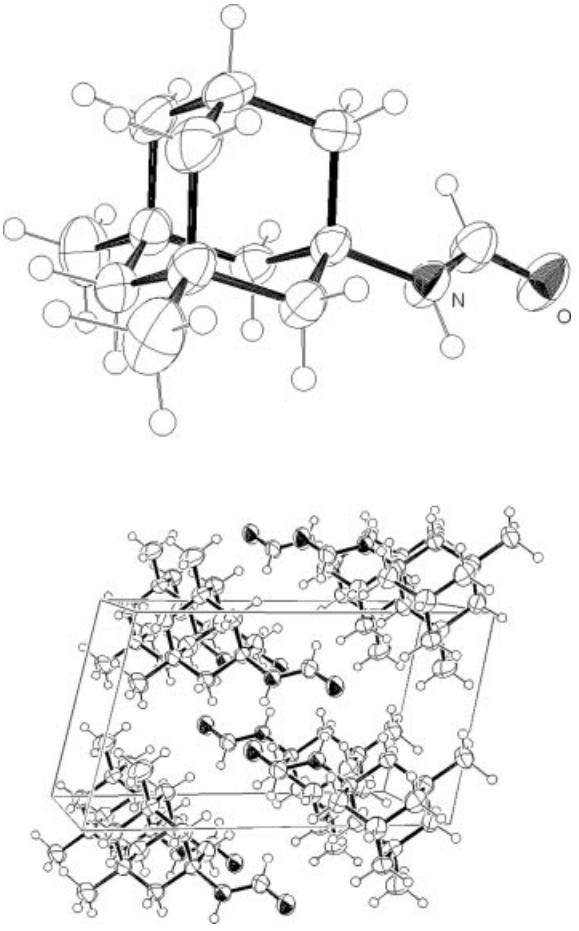
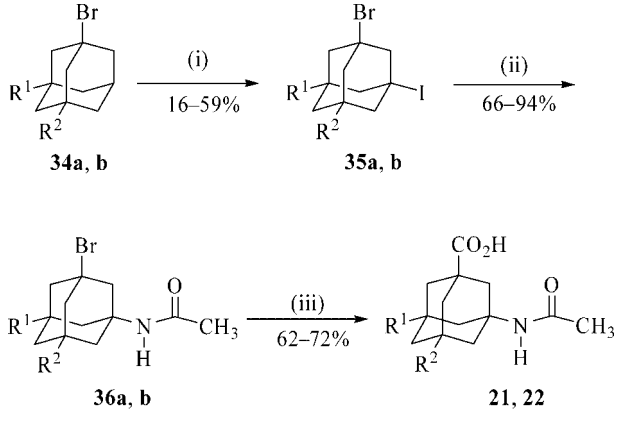
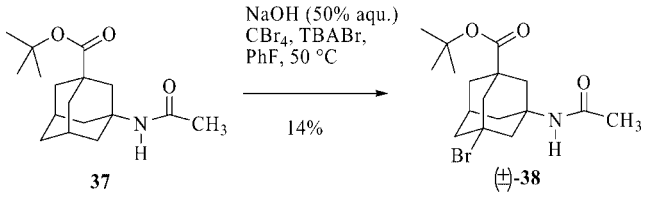


Figure 2. ORTEP diagram of **26** and its packing in the crystal. Displacement ellipsoids drawn with 50% probability.



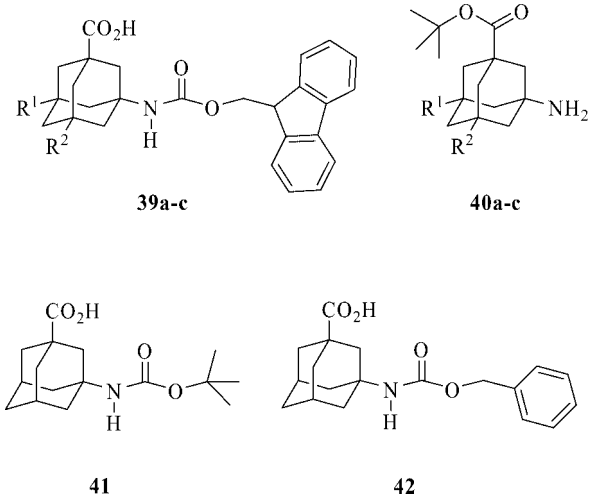
Scheme 3. PTC strategy towards acetamido precursors of γ-aminoadamantanecarboxylic acids. **a**: $R^1 = R^2 = Me$; **b**: $R^1 = H$, $R^2 = i$Pr. Reagents and conditions: (i) NaOH, CHI_3, tetra-*n*-butylammonium bromide (TBABr), ultrasound; (ii) 1. $NOBF_4$, MeCN, –50 to –15 °C, 2. H_2O; (iii) 1. H_2SO_4, HCO_2H, 2. H_2O.

Although this PTC pathway is more laborious and relies on halogenated adamantanes, it broadens the pool of substrates to be converted to ^{A}Xaas due to the remarkable functional group tolerance of the PTC halogenation step. Furthermore, it allows for post-functionalization of an appropriately protected amino acid (e.g., **37**) for further conversions (Scheme 4). While this reaction is not yet optimized, it still is an example for a highly remarkable functional group tolerance in a direct C–H functionalization. The range of accessible ^{A}Xaas by substituting the bromine using, e.g., TMS-substituted reagents following Sasaki's procedures[43,44] is appealing. When synthesizing chiral ^{A}Xaa derivatives (e.g., **20** and **38**), both direct C–H bond amidations and PTC strategy necessarily yield racemic mixtures. However, resolution via chiral HPLC in principle is possible (*tert*-butyl ester of compound **20** was resolved analytically using a Macherey–Nagel Nucleodex® β-PM column). Preparative scale resolution via cocrystallization with quinine as reported in the literature for closely related adamantanecarboxylic acids[45] appears to be a reasonable approach.



Scheme 4. "Post-functionalization" of protected ^{A}Gly via PTC bromination. For racemic **38**, only one enantiomer is shown.

Carboxy- and amino-protective groups can easily be introduced into ^{A}Xaas with standard methods, yielding, e.g., (Scheme 5) Fmoc-^{A}Xaas (**39a**–**c** and Figure 3), *tert*-butyl esters of ^{A}Xaas (**40a**–**c**), Boc-^{A}Gly (**41**), and Cbz-^{A}Gly (**42**). We have initially performed peptide couplings in solution utilizing the DIC/HOBt methodology with unsatisfactory results in terms of yield and reaction time. Using an uronium salt (HBTU) as the coupling reagent, solution phase peptide synthesis is accomplished in good yields, even for the ^{A}Xaa–^{A}Xaa coupling step that is supposed to resemble a difficult sequence due to steric hindrance.



Scheme 5. Protected ^{A}Xaas as building blocks for peptide synthesis. See Exp. Section for preparative details.

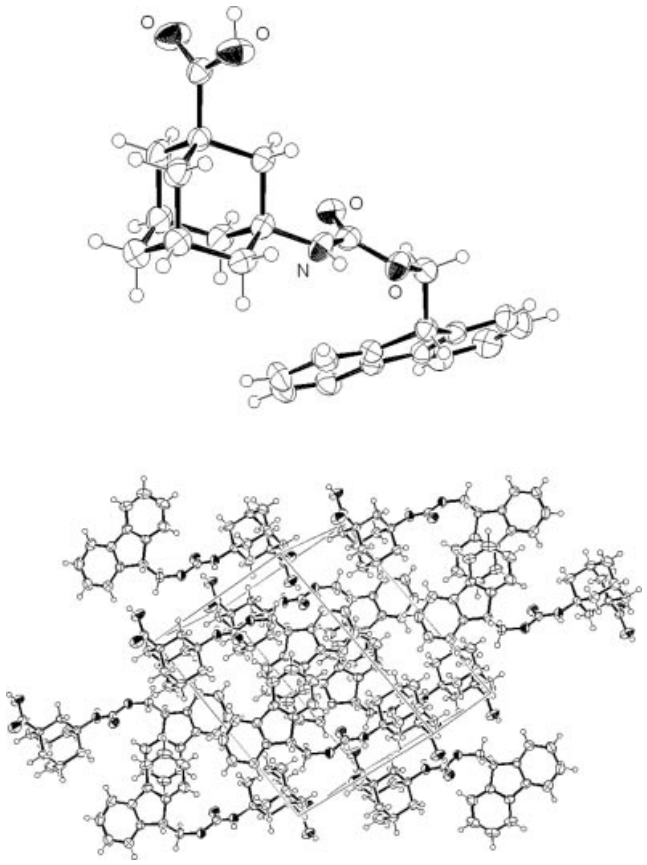
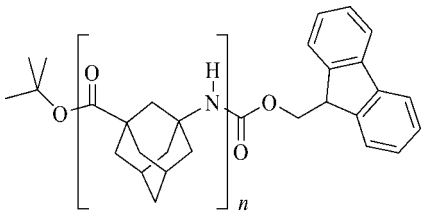


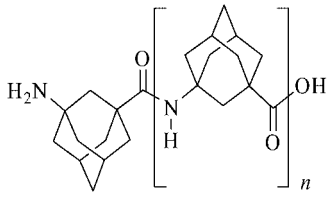
Figure 3. ORTEP diagram of **39a** and its packing in the crystal. Displacement ellipsoids drawn with 50% probability.

With these results and the appropriate building blocks at hand, we went on to apply SPPS methods to the synthesis of peptides incorporating ^{A}Xaas. Among others, we synthesized homooligomeric ^{A}Xaas as well as hybrid peptides by standard procedures using 2-chlorotrityl chloride- or Wang-resin following the Fmoc strategy (see supporting information for details). When assembling homooligomeric ^{A}Gly on 2-chlorotrityl resin, quantitative controls by HPLC and MS of small portions of the Fmoc-protected growing chain revealed incomplete acylation reactions starting from the tetramer. This might indicate the formation of a rigid conformation of the tetramer on the resin, thereby reducing the accessibility of the terminal amino group for the next coupling step. However, when modifying the procedures (elongation of reaction times, double couplings starting from the trimer), satisfactory purities of the desired homooligomers **44** were realized as monitored by analytical HPLC. Apart from being valuable targets for medicinal applications, peptides incorporating ^{A}Xaas are interesting substrates for structural investigations. Currently, we explore homooligomers **43a**–**d** (Scheme 6) via NMR methods.

The quasi-tetrahedral symmetry of ^{A}Xaas and their rigidity are likely to induce turn-like structures when incorporated into small peptides. As a first application, we are currently investigating peptidic structures based upon ^{A}Xaas as organocatalysts for various reactions (Scheme 7).

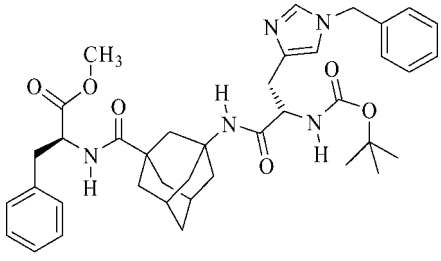


43a: n = 2; **43b:** n = 3
43c: n = 4; **43d**: n = 6

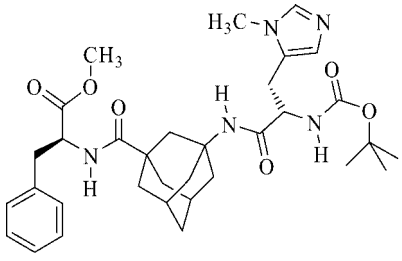


44a: n = 4
44b: n = 6

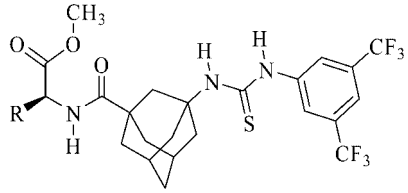
Scheme 6. Orthogonally protected ^{A}Gly homooligomers **43a**–**d** synthesized in solution (see Exp. Sect. for preparative details) and deblocked homooligomers **44a**,**b** prepared via SPPS (see supporting information for details).



45



46



47a: R = H
47b: R = CH_2Ph

Scheme 7. Peptidic organocatalysts incorporating ^{A}Gly. See Exp. Section for preparative details.

At first, we synthesized two hybrid peptides incorporating His residues (**45** and **46**) for organocatalyzed transacylation reactions that are reported to benefit from rigid turn structures.[46,47] Organocatalysts incorporating a thiourea motif[48] (**47**) can be synthesized in three steps from **39a**. The bulky, rigid γ-amino acid prevents peptide degradation through thiazolone formation (Edman degradation[49–51]) rendering compounds **47** bench-top stable. We have already successfully tested His-containing peptidic organocatalysts **45** and **46** in stereoselective transacylation reactions and peptidic thioureas **47a** and **47b** in Morita–Baylis–Hillman reactions. Results of these and other organocatalysis studies will be reported elsewhere in due course.

Conclusions and Outlook

We have prepared monomeric γ-aminoadamantanecarboxylic acids (^{A}Xaas) that are rigid GABA analogues. The amidation protocols utilized for the synthesis of ^{A}Xaas represent halogen-free and operationally facile direct syntheses for pharmaceutically active aminoadamantanes. The ^{A}Xaa's protection is straightforward and they can be used for the solution- as well as solid-phase synthesis of rigid, highly lipophilic peptides that are promising for medicinal applications. When equipped with catalytically active groups like histidine or thiourea moieties, ^{A}Xaas provide a scaffold for the design of novel organocatalysts incorporating a multitude of thiourea and peptide moieties with the ^{A}Xaas as the orientating tether.

Experimental Section

All chemicals were purchased from Acros Organics, Aldrich, Lancaster, Merck or Fluka at the highest purity grade available and were used without further purification. The nitric acid used in all cases was technical grade (65%), the sulfuric acid used also was technical grade (95–98%). All solvents were distilled prior to use. Column chromatography was conducted using J.T. Baker silica gel (0.063–0.200 mm) or, for flash column chraomatography, Merck silica gel 60 (0.040–0.063 mm), respectively. Melting points (< 200 °C) were measured using a Büchi SMP 20 apparatus and are not corrected; melting points above 200 °C were measured by using a Bunsen burner melting point apparatus and are also not corrected. ^{1}H and ^{13}C NMR spectra were recorded on Bruker AV400 or AV200 spectrometers, respectively, using TMS or 3-(trimethylsilyl)-[D_4]propanoic acid sodium salt as the internal standard with chemical shifts given in ppm relative to TMS or the respective solvent residual peaks. Assignments have been made using DEPT 135 spectra. Infrared spectra were recorded on a Bruker IFS25 spectrometer. MS/HRMS were recorded on a Finnigan MAT95 sectorfield spectrometer, ESI mass spectra on a Finnigan LCQDuo spectrometer using methanol/acetic acid solutions of the respective compounds. Elemental analyses were measured by using a Carlo–Erba 1106 CHN analyzer.

Direct C–H to C–N Bond Amidations

3-Acetamidotricyclo[3.3.1.1^{3,7}]decane-1-carboxylic Acid (19): 25.0 g (138.7 mmol) adamantane-1-carboxylic acid (**10**) was suspended in 20 mL nitric acid and cooled to 0 °C with an ice bath. Using an addition funnel, 150 mL sulfuric acid was added over the course of 90 min while keeping the reaction mixture at 0 °C. The reaction mixture was stirred for another 2 h at 0 °C, whereupon 100 mL of technical grade acetonitrile was added via an addition funnel within 3 h at 0 °C. After another 3 h of stirring at 0 °C, the reaction mixture was poured onto ice (ca. 1 kg) with shaking. The colorless precipitate was collected via suction filtration, washed with water, recrystallized from a mixture of acetic acid/water/acetone (5:5:2) and dried over potassium hydroxide at 110 °C/15 mbar overnight to give 27.58 g (116.23 mmol, 83.8%) of the acetamide as colorless crystals, m.p. 251 °C (ref.[11] 255–256 °C). ^{1}H NMR (400 MHz, [D_6]DMSO): δ = 10.29 (br. s, 1 H, CO_2H), 7.38 (br. s, 1 H, N*H*), 2.08 (m, 2 H), 1.99 (s, 2 H), 1.86 (m, 4 H), 1.74 (s, 3 H, CH_3), 1.70 (d, J = 2.4 Hz, 4 H), 1.56 (br. s, 2 H) ppm. ^{13}C NMR (100 MHz, [D_6]DMSO): δ = 177.6 (C=O), 168.7 (C=O), 50.8 (C_q), 42.1, 41.4 (C_q), 40.1, 37.7, 35.0, 28.5, 23.7 (*C*H_3) ppm. IR (KBr): $\tilde{\nu}$ = 3337, 2950, 2920, 2858, 1700, 1688, 1630, 1552, 1238 cm^{-1}. MS (EI, 70 eV): *m*/*z* = 237 (100%), 219 (14.9%), 191 (98.6%), 180 (47.5%), 162 (57.6%), 150 (40.6%), 136 (55.4%), 94 (69.7%). HRMS: found 237.1373, calcd. 237.1365.

3-Acetamido-5-methyltricyclo[3.3.1.1^{3,7}]decane-1-carboxylic Acid (20): 1-Methyladamantane was synthesized according to a literature procedure,[52] 3-brominated with excess bromine,[53] and converted into 3-methyladamantane-1-carboxylic acid.[11] 2.576 g of 3-methyladamantane-1-carboxylic acid (**11**, 13.3 mmol) was suspended in 10 mL nitric acid and cooled to 0 °C with an ice bath. After the addition of 13 mL sulfuric acid, the mixture was stirred at 0 °C for 10 min. 11 mL of oleum (20% SO_3) was then added and the mixture was stirred for 1 h at 0 °C and 3 h at room temp. After cooling to 0 °C, 10 mL of technical grade acetonitrile was added, the mixture was stirred for 10 min at 0 °C and 3 h at room temp. Finally, the mixture was poured onto ca. 300 g of ice with shaking and left standing in a refrigerator overnight. The colorless precipitate was collected via suction filtration and recrystallized from a mixture of acetic acid/water/acetone (5:5:3). After drying over potassium hydroxide at 110 °C/15 mbar for about 12 h, 2.8765 g (12.3 mmol, 92.6%) of acetamide **20** was isolated as colorless crystals, m.p. 262 °C (ref.[11] 265–266 °C). ^{1}H NMR (400 MHz, [D_6]DMSO): δ = 12.08 (br. s, 1 H, CO_2H), 7.40 (br. s, 1 H, N*H*), 2.11 (m, 1 H), 1.92 (m, 2 H), 1.85–1.68 (m, 2 H), 1.74 (s, 3 H, CH_3), 1.67–1.55 (m, 4 H), 1.44 (s, 2 H), 1.38–1.27 (m, 2 H), 0.83 (s, 3 H, CH_3) ppm. ^{13}C NMR (100 MHz, [D_6]DMSO): δ = 177.5 (C=O), 168.6 (C=O), 51.6 (C_q), 46.9, 44.5, 42.07 (C_q), 42.04, 41.5, 39.3, 37.0, 31.3 (C_q), 29.9, 28.9, 23.6 ppm. IR (KBr): $\tilde{\nu}$ = 3340, 2947, 2936, 2921, 2902, 2863, 1692, 1615, 1553, 1268, 1230 cm^{-1}. MS (EI, 70 eV): *m*/*z* = 251 (92.9%), 206 (100%), 194 (30.3%), 176 (27.5%), 164 (28.10%), 150 (76.8%), 108 (42.6%). HRMS: found 251.1527, calcd. 251.1521.

3-Acetamido-5,7-dimethyltricyclo[3.3.1.1^{3,7}]decane-1-carboxylic Acid (21): 1-Bromo-3,5-dimethyladamantane was converted into the corresponding 3,5-dimethyladamantane-1-carboxylic acid according to a literature procedure.[11] 20.66 g (99.2 mmol) of 3,5-dimethyladamantane-1-carboxylic acid (**12**) was suspended in 60 mL of nitric acid and cooled to 0 °C with an ice bath. After the addition of 100 mL sulfuric acid, the mixture was stirred at 0 °C for 10 min. 35 mL of oleum (25% SO_3) was then added and the mixture stirred for 30 min at 0 °C and 1 h at room temp. After cooling to 0 °C, 60 mL of technical grade acetonitrile was added, the mixture was stirred for 10 min at 0 °C and 3 h at room temp. Finally, the mixture was poured onto ca. 2 kg of ice with shaking and left standing in a refrigerator overnight. The colorless precipitate was collected via suction filtration and recrystallized from a mixture of acetic acid/water/acetone (5:5:4). After drying over potassium hydroxide at 110 °C/15 mbar overnight, 24.2866 g

(91.5 mmol, 92.3%) of acetamide **21** was isolated as colorless crystals, m.p. 306 °C (ref.[11] 307–308 °C). ^{1}H NMR (400 MHz, [D$_6$]DMSO): δ = 12.09 (br. s, 1 H, CO_2H), 7.35 (br. s, 1 H, N*H*), 1.85 (m, 2 H), 1.73 (s, 3 H, CH_3), 1.60–1.46 (m, 4 H), 1.42–1.31 (m, 4 H), 1.12–1.03 (m, 2 H), 0.84 (s, 6 H, 2 × CH_3) ppm. ^{13}C NMR (100 MHz, [D$_6$]DMSO): δ = 177.4 (C=O), 168.7 (C=O), 52.4 (C$_q$), 49.3, 46.2, 43.9, 42.7 (C$_q$), 40.9, 31.9 (C$_q$), 29.5 (2 × *C*H$_3$), 23.6 (*C*H$_3$) ppm. IR (KBr): $\tilde{\nu}$ = 3340, 2942, 2898, 2860, 2848, 2477, 1687, 1611, 1553, 1271, 1261, 1225, 711 cm^{-1}. MS (EI, 70 eV): *m*/*z* = 265 (85.7%), 220 (78.6%), 207 (10.4%), 194 (20.2%), 176 (31.7%), 164 (100.0%), 150 (35.2%), 122 (31.1%), 107 (30.0%). HRMS: found 265.1670, calcd. 265.1678. $C_{15}H_{23}NO_3$ (265.35): calcd. C 67.90, H 8.74, N 5.28; found C 68.12, H 9.12, N 5.32.

3-Acetamido-5-isopropyltricyclo[3.3.1.1^{3,7}]decane-1-carboxylic Acid (22): 3-Bromo-1-isopropyladamantane was synthesized according to literature procedures.[54] It was then converted into 3-isopropyladamantane-1-carboxylic acid according to the procedure described above.[11] 3.7 g (16.64 mmol) of 3-isopropyladamantane-1-carboxylic acid (**13**) was suspended in 10 mL nitric acid and cooled to 0 °C with an ice bath. After the addition of 17 mL sulfuric acid, the mixture was stirred at 0 °C for 10 min. 6 mL of oleum (25% SO_3) was then added and the mixture was stirred for 1 h at 0 °C and 3 h at room temp. After cooling to 0 °C, 10 mL of technical grade acetonitrile was added, the mixture was stirred for 10 min at 0 °C and 1.5 h at room temp. Finally, the mixture was poured over ca. 400 g of ice with shaking and left standing in a refrigerator overnight. The yellowish precipitate was extracted with ethyl acetate, the combined organics were dried (Na_2SO_4), and the solvent was evaporated under reduced pressure. The residual solid was dissolved with 5% aqueous NaOH, filtered and precipitated with concentrated hydrochloric acid. It was then collected via suction filtration and recrystallized from a mixture of acetic acid/water/acetone (5:5:2). After drying over potassium hydroxide at 110 °C/15 mbar overnight, 1.815 g (6.5 mmol, 39.0%) of acetamide **22** was isolated as colorless crystals, m.p. 188–189 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 12.14 (br. s, 1 H, COO*H*), 7.42 (br. s, 1 H, N*H*), 2.14 (m, 1 H, C*H*), 2.00–1.88 (m, 2 H), 1.88–1.70 (m, 2 H), 1.74 (s, 3 H, CH_3), 1.68–1.53 (m, 4 H), 1.45 (br. s, 2 H), 1.40–1.31 (m, 2 H), 1.28 [sept, *J* = 6.8 Hz, 1 H, C*H*(CH$_3$)$_2$], 0.79 [d, *J* = 7.2 Hz, 6 H, CH(CH_3)$_2$] ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 181.6 (*C*OOH), 170.3 (*C*=O), 53.4 (C$_q$), 42.9, 42.6, 41.9, 40.2, 39.6, 37.5 (2 signals), 37.05, 37.01, 29.2, 24.4 (*C*H$_3$), 16.4 [CH(*C*H$_3$)$_2$] ppm. IR (KBr): $\tilde{\nu}$ = 3367, 2969, 2933, 2908, 2859, 1694, 1616, 1549, 1254, 1225 cm^{-1}. MS (EI, 70 eV): *m*/*z* = 279 (65.6%), 236 (87.2%), 194 (81.6%), 190 (100%), 178 (16.6%), 162 (9.7%), 138 (18.5%). HRMS: found 279.1830, calcd. 279.1834. $C_{16}H_{25}NO_3$ (279.37): calcd. C 68.79, H 9.02, N 5.01; found C 69.09, H 9.26, N 4.55.

3-Acetamido-5-(carboxymethyl)tricyclo[3.3.1.1^{3,7}]decane-1-carboxylic Acid (23): 3-(Carboxymethyl)adamantane-1-carboxylic acid was prepared following literature procedures.[55] 10.739 g (45.1 mmol) of 3-(carboxymethyl)adamantane-1-carboxylic acid (**14**) was suspended in 36 mL of nitric acid and cooled to 0 °C with an ice bath. After the addition of 50 mL sulfuric acid, the mixture was stirred at 0 °C for 10 min. 30 mL of oleum (25% SO_3) was then added and the mixture was stirred for 1 h at 0 °C and 3 h at room temp. After cooling to 0 °C, 35 mL of technical grade acetonitrile was added, the mixture was stirred for 10 min at 0 °C and 3 h at room temp. Finally, the mixture was poured onto ca. 1 kg of ice with shaking and left standing in a refrigerator overnight. The colorless precipitate was collected via suction filtration and recrystallized from a mixture of acetic acid/water/acetone (5:5:2). After drying over potassium hydroxide at 110 °C/15 mbar overnight, 10.2955 g (34.9 mmol, 77.4%) of acetamide **23** was isolated as colorless crystals, m.p. 148–150 °C. ^{1}H NMR (400 MHz, [D$_6$]DMSO): δ = 12.0 (br. s, 2 H, 2 × CO_2H), 7.45 (br. s, 1 H, N*H*), 2.16–2.09 (m, 1 H), 2.06 (s, 2 H), 1.98–1.87 (m, 2 H), 1.87–1.65 (m, 4 H), 1.74 (s, 3 H, CH_3), 1.65–1.53 (m, 4 H), 1.51–1.40 (m, 2 H) ppm. ^{13}C NMR (100 MHz, [D$_6$]DMSO): δ = 177.4 (C=O), 172.2 (C=O), 168.8 (C=O), 51.4 (C$_q$), 47.0, 44.5, 42.2, 41.9 (C$_q$), 41.5, 39.9, 39.3, 37.0, 33.7 (C$_q$), 28.6, 23.6 ppm. IR (KBr): $\tilde{\nu}$ = 3495, 3437, 3396, 2948, 1727, 1628, 1609, 1544, 1234, 1184, 575 cm^{-1}. MS (EI, 70 eV): *m*/*z* = 295 (20%), 193 (8.5%), 149 (7.8%), 91 (11.0%), HRMS: found 295.1436, calcd. 295.1420. $C_{15}H_{21}NO_5$ (295.33): calcd. C 61.00, H 7.17, N 4.47; found C 61.43, H 7.35, N 4.45.

3-(3-Acetamido-5-carboxy-1-tricyclo[3.3.1.1^{3,7}]decane)propanoic Acid (24): Adamantane-1-propanoic acid was synthesized by homologization of adamantane-1-acetic acid as described in the literature.[56] The propanoic acid was then brominated using excess bromine and converted into the dicarboxylic acid via Koch–Haaf reaction as described above. 2.311 g (9.2 mmol) of dicarboxylic acid **15** was suspended in 7.5 mL of nitric acid and cooled to 0 °C with an ice bath. After the addition of 10.5 mL sulfuric acid, the mixture was stirred at 0 °C for 10 min. 7 mL of oleum (25% SO_3) was then added, the mixture was stirred for 1 h at 0 °C and 3 h at room temp. After cooling to 0 °C, 8 mL of technical grade acetonitrile was added, the mixture was stirred for 10 min at 0 °C and 3 h at room temp. Finally, the mixture was poured onto ca. 250 g of ice with shaking and left standing in a refrigerator overnight. The colorless precipitate was collected via suction filtration and recrystallized from a mixture of acetic acid/water/acetone (5:5:2). After drying over potassium hydroxide at 110 °C/15 mbar overnight, 1.039 g (3.36 mmol, 36.7%) of acetamide **24** was isolated as colorless crystals, m.p. 222–223 °C. ^{1}H NMR (400 MHz, [D$_6$]DMSO): δ = 12.03 (br. s, 2 H, 2 × CO_2H), 7.40 (br. s, 1 H, N*H*), 2.16–2.07 (m, 3 H), 1.93 (br. s, 2 H), 1.87–1.70 (m, 2 H), 1.74 (s, 3 H, CH_3), 1.70–1.53 (m, 4 H), 1.45–1.34 (m, 2 H + 2 H), 1.32 (br. s, 2 H) ppm. ^{13}C NMR (100 MHz, [D$_6$]DMSO): δ = 177.5 (C=O), 174.8 (C=O), 168.7 (C=O), 51.5 (C$_q$), 44.4, 42.1 (C$_q$), 41.9. 41.7, 39.5, 37.4, 37.2, 33.6 (C$_q$), 28.6, 27.6, 23.7 ppm. IR (KBr): $\tilde{\nu}$ = 3396, 3122, 2935, 2861, 1742, 1726, 1591, 1554, 1227, 1162, 1134, 852, 580 cm^{-1}. MS (EI, 70 eV): *m*/*z* = 309 (17.5%), 291 (27.1%), 249 (50.1%), 192 (43.3%), 148 (100%), 105 (39.4%). HRMS: found 309.1569, calcd. 309.1576. $C_{16}H_{23}NO_5$ (309.36): calcd. C 62.12, H 7.49, N 4.53; found C 61.87, H 7.44, N 4.66.

1-Acetamido-3,5-dimethyltricyclo[3.3.1.1^{3,7}]decane (25): This acetamide is known from the literature.[57] 6.572 g (40 mmol) of 1,3-dimethyladamantane (**16**) was suspended in 8 mL of nitric acid and cooled to 0 °C with an ice bath. 44 mL of sulfuric acid was then added with an addition funnel over the course of 4 h at 0 °C and stirring was continued for another 2 h at 0 °C. 44 mL of technical grade acetonitrile was then added with an addition funnel within 90 min. To complete the reaction, the mixture was stirred 1 h at 0 °C and another 1 h at room temp. Finally, the mixture was poured over ca. 250 g of crushed ice with shaking. The mixture was extracted with diethyl ether (3 × 100 mL), the combined organic phases were washed with water, 5% $NaHCO_3$, water and brine and dried (Na_2SO_4). After evaporation of the solvent, 7.99 g (36.11 mmol, 90.3%) of the acetamide **25** was obtained as a slightly yellowish powder, m.p. 109 °C (ref.[57] 109–110 °C). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 5.27 (br. s, 1 H, N*H*), 2.13 (quint, *J* = 3 Hz, 1 H), 1.90 (s, 3 H, CH_3), 1.83 (d, *J* = 3 Hz, 2 H), 1.68–1.58 (m, 4 H), 1.42–1.24 (m, 4 H), 1.21–1.08 (m, 2 H), 0.84 (s, 6 H, 2 × CH_3) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 169.3 (C=O), 53.5 (C$_q$), 50.7, 47.6, 42.7, 40.2, 32.4, 30.2 (C$_q$), 30.1 (2 × *C*H$_3$), 24.7 (*C*H$_3$) ppm. IR (KBr): $\tilde{\nu}$ = 3294, 3259, 2945, 2904, 2862, 2843, 2834, 1653, 1632, 1556, 1455, 1359, 1310, 605 cm^{-1}. MS (EI, 70 eV):

m/*z* = 221 (64.5%), 164 (100%), 150 (93.7%), 122 (15.6%), 107 (28.2%). HRMS: found 221.1773, calcd. 222.1780.

1-Formamido-3,5-dimethyltricyclo[3.3.1.1^{3,7}]decane (26): This compound is known from the literature.[58] However, since it was neither isolated nor characterized and was prepared previously via a different route, its preparation and full characterization is reported here. 6.572 g (40 mmol) of 1,3-dimethyladamantane (**16**) was suspended in 5 mL of nitric acid and cooled to 0 °C with an ice bath. 50 mL sulfuric acid was then added with an addition funnel over the course of 1 h at 0 °C and stirring was continued for another 5 h at 0 °C. The mixture was then upon vigorous stirring and cooling with an ice bath poured into 100 mL of technical formamide. The resulting mixture was stirred under argon for 30 min at 0 °C and another 2 h at room temp. After addition of 200 mL dichloromethane and 200 mL of water, the layers were separated. The aqueous phase was extracted twice with 100 mL of dichloromethane, the combined organic phases were washed with water (3 × 200 mL) and brine (200 mL). After drying with Na_2SO_4, the solvent was removed and the residual yellowish oil was purified via silica gel column chromatography eluting with ethyl acetate (R_f = 0.42) to yield 7.384 g (35.6 mmol, 89.0%) of formamide **26** as a colorless powder, m.p. 69.5 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.14, 8.17, 7.98 and 7.97 (4 × s, 1 H, NHC*H*O), 6.72–6.31 and 5.51–5.23 (m/br. s, 1 H, N*H*CHO), 2.24–2.10 (m, 1 H), 1.89–1.83 (m, 1 H), 1.72–1.63 (m, 3 H), 1.51–1.40 (m, 2 H), 1.39–1.30 (m, 4 H), 1.20–1.13 (m, 1 H), 0.83 and 0.81 (2 s, 6 H, C*H*$_3$) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 162.3 and 160.4 (C=O), 53.6 and 52.3 (C_q), 50.5 and 50.1, 47.7, 42.6 and 42.5, 40.3, 32.5 and 32.4 (C_q), 30.04 and 29.95 ppm. IR (KBr): $\tilde{\nu}$ = 3198, 3103, 2946, 2909, 2864, 2847, 1691, 1451, 1326, 795 cm^{-1}. MS (EI, 70 eV): *m*/*z* = 207 (53.3%), 192 (6.6%), 162 (7.6%), 150 (100%), 136 (90.9%), 106 (9.9%). HRMS: found 207.1617, calcd. 207.1623. $C_{13}H_{21}NO$ (207.31): calcd. C 75.32, H 10.21, N 6.76; found C 75.06, H 10.42, N 6.71.

1-Acetamido-3-methyltricyclo[3.3.1.1^{3,7}]decane (27): 0.751 g (5 mmol) of 1-methyladamantane (**17**) was suspended in 1 mL of nitric acid and cooled to 0 °C with an ice bath. 7 mL of sulfuric acid was then added with an addition funnel over the course of 3 h at 0 °C and stirring was continued for another 3 h at 0 °C. 7 mL of technical grade acetonitrile was then added with an addition funnel within 1 h. To complete the reaction, the mixture was stirred 5 h at 0 °C. Finally, the mixture was poured onto ca. 100 g of crushed ice with shaking. The mixture was extracted with diethyl ether (3 × 50 mL), the combined organic phases were washed with water, 5% $NaHCO_3$, water and brine and dried (Na_2SO_4). After evaporation of the solvent, the residue was purified by column chromatography eluting with diethyl ether (R_f = 0.30). 0.431 g (2.08 mmol, 41.6%) of the acetamide **27** was isolated as slightly yellowish powder, m.p. 108 °C (ref.[53] 108–109 °C). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 5.15 (br. s, 1 H, N*H*), 2.13–2.08 (m, 2 H), 1.97–1.86 (m, 4 H), 1.90 (s, 3 H, C*H*$_3$), 1.70 (br. s, 2 H), 1.66–1.49 (m, 2 H), 1.45–1.35 (m, 4 H), 0.83 (s, 3 H, C*H*$_3$) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 169.3 (C=O), 52.7 (C_q), 48.4, 43.4, 41.0, 35.7, 31.9 (C_q), 30.4, 29.8 (*C*H$_3$), 24.7 (*C*H$_3$) ppm. IR (KBr): $\tilde{\nu}$ = 3286, 3078, 2944, 2910, 2862, 2841, 1639, 1559, 1456, 1371, 1306 cm^{-1}. MS (EI, 70 eV): *m*/*z* = 207 (35.9%), 150 (100%), 136 (13.5%), 108 (22.2%), 93 (11.3%). HRMS: found 207.1609, calcd. 207.1623.

1-Formamido-3-methyltricyclo[3.3.1.1^{3,7}]decane (28): 1.503 g (10 mmol) of 1-methyladamantane (**17**) was suspended in 1 mL of nitric acid and cooled to 0 °C with an ice bath. 25 mL of sulfuric acid was then added with an addition funnel over the course of 3 h and stirring was continued at 0 °C for another 3 h. The mixture was then upon intensive stirring and cooling to 0 °C added to 50 mL technical formamide. The resulting mixture was stirred at 0 °C for 30 min and another 2 h at room temp. The resulting mixture was extracted with dichloromethane (3 × 100 mL), the combined organic phases were washed with water and dried (Na_2SO_4). After evaporation of the solvent, the residue was purified by column chromatography eluting with ethyl acetate, R_f(**28**) = 0.37. 0.864 g (45%) 1-formamido-3-methyladamantane was isolated as a colorless solid, m.p. 66 °C (sealed capillary). ^{1}H NMR (200 MHz, $CDCl_3$): δ = 8.25 (d, *J* = 12.4 Hz) and 8.05 (d, *J* = 9.0 Hz), 1 H, NHC*H*O (2 isomers), 6.62 (br. s) and 5.33 (br. s), 1 H, N*H*CHO (2 isomers), 2.22–1.33 (m, 14 H, CH/CH$_2$ of adamantane), 0.87 (s) and 0.85 (s), 3 H, -CH$_3$ (2 isomers) ppm. ^{13}C NMR (50 MHz, $CDCl_3$): δ = 162.6 and 160.4 (C=O), 53.0 and 51.6, 50.7 and 48.4, 43.3 and 43.2, 42.9 and 41.1, 35.5 and 35.1, 32.0 and 31.9, 30.4 and 30.3, 29.7 and 29.6 (2 isomers) ppm. IR (KBr): $\tilde{\nu}$ = 3439, 3211, 3083, 2902, 2849, 1696, 1675, 1536, 1456, 1313 cm^{-1}. MS (EI, 70 eV): *m*/*z* = 193 (66.5%), 178 (2.9%), 148 (5.7%), 136 (100%), 122 (18.4%), 108 (11.6%), 92 (19.8%). HRMS: found 193.14625, calcd. 193.14666. $C_{12}H_{19}NO$ (193.29): calcd. C 74.57, H 9.91, N 7.25; found C 74.62, H 10.04, N 7.05.

1-Acetamidotricyclo[3.3.1.1^{3,7}]decane (29). (a) Ritter-Type Reaction: 5.4492 g (40 mmol) adamantane (**18**) was suspended in 50 mL nitric acid and cooled to 0 °C with an ice bath. After the addition of 60 mL sulfuric acid, the mixture was stirred at 0 °C for 10 min. 40 mL of oleum (25% SO_3) was then added and the mixture was stirred for 1 h at 0 °C and 3 h at room temp. After cooling to 0 °C, 40 mL of technical grade acetonitrile was added, the mixture was stirred for 10 min at 0 °C and 4 h at room temp. Finally, the mixture was poured over ca. 600 g of ice with shaking. The mixture was extracted with diethyl ether (3 × 100 mL), the combined organic phases were washed with water, 5% $NaHCO_3$, water and brine and dried (Na_2SO_4). After evaporation of the solvent, the residue was purified by column chromatography eluting with diethyl ether (R_f = 0.29). 1.3301 g (6.88 mmol, 17.2%) of the acetamide **29** was isolated as slightly yellowish powder, m.p. 142 °C (ref.[14] 149–149.5 °C). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 5.18 (br. s, 1 H, N*H*), 2.10–2.02 (m, 3 H), 2.02–1.94 (m, 6 H), 1.90 (s, 3 H, C*H*$_3$), 1.70–1.61 (m, 6 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 169.4 (C=O), 52.0 (C_q), 41.7, 36.4, 29.5, 24.7 ppm. IR (KBr): $\tilde{\nu}$ = 3280, 3079, 2906, 2847, 1643, 1560, 1304 cm^{-1}. MS (EI, 70 eV): *m*/*z* = 193 (35.9%), 150 (6.9%), 136 (100%), 94 (46.6%). HRMS: found 193.1465, calcd. 193.14666.

(b) Direct Amidation with Acetamide: 2.725 g (20 mmol) of adamantane (**18**) was suspended in 2 mL nitric acid and cooled to 0 °C with an ice bath. Within 10 min, 25 mL sulfuric acid was added and stirring was continued for 10 min at 0 °C. 10 mL oleum (25% SO_3) was added, the reaction vessel was closed and stirring at 0 °C was continued for 18 h. The resulting mixture was added within 30 min at 0 °C to 20 g of solid acetamide upon vigorous stirring. Stirring was continued for 30 min at 0 °C and 90 min at room temp. 100 mL dichloromethane and 100 mL ice water was added, the layers were separated and the aqueous layer was extracted with dichloromethane (2 × 20 mL). The combined organic phases were washed with water, 5% $NaHCO_3$ and brine (50 mL each) and dried with Na_2SO_4. After evaporation of the solvent, the residual yellowish oil was purified by silica gel column chromatography eluting with diethyl ether, R_f(**29**) = 0.29. 1.448 g (38%) of **29** was isolated as slightly yellowish powder, m.p. 143.5 °C. The spectroscopic data are in accordance with those obtained for **29** obtained by the method described under **(a)**.

1-Formamidotricyclo[3.3.1.1^{3,7}]decane (30): 2.725 g (20 mmol) adamantane was suspended in 2 mL nitric acid and cooled to 0 °C

with an ice bath. 25 mL of sulfuric acid was added within 10 min and stirring at 0 °C was continued for another 10 min. 5 mL oleum (25% SO_3) was then added, the reaction vessel was closed and intensively stirred for 18 h at 0 °C. The resulting mixture was added to 50 mL of technical formamide under vigorous stirring within 30 min at 0 °C. Stirring was continued for 30 min at 0 °C and 90 min at room temp., whereupon 100 mL of dichloromethane and 100 mL ice water was added. The layers were separated, the aqueous layer was extracted with dichloromethane, the combined organic phases were washed with water, 5% $NaHCO_3$ and brine (50 mL each) and dried (Na_2SO_4). The yellowish oil obtained after evaporation was purified by silica gel column chromatography eluting with ethyl acetate, R_f(**30**) = 0.33. 480 mg (13%) of 1-formamidoadamantane was isolated as slightly yellowish powder, m.p. 134 °C (ref.[14] 139.4–141.5 °C). ^{1}H NMR (200 MHz, [D$_6$]DMSO): δ = 8.28 (d, J = 12.5 Hz) and 8.03 (d, J = 1.9 Hz, 1 H, NHC*H*O, 2 isomers), 6.21 and 5.24 (br. s, 1 H, N*H*CHO, 2 Isomers), 2.24–1.44 (m, 15 H, CH-/CH$_2$) ppm. ^{13}C NMR (50 MHz, [D$_6$]DMSO): δ = 162.4 and 160.33 (C$_q$, NH*C*HO), 52.2 and 50.8 (C$_q$, *C*-NHCHO), 44.1, 41.8, 36.2 and 35.9, 29.4 and 29.3 ppm. ^{1}H-NMR spectroscopic data are in accordance with the literature.[59]

Direct C–H to C–O Functionalizations

3,5-Dimethyltricyclo[3.3.1.1^{3,7}]decane-1-ol (31): 6.572 (40 mmol) of 1,3-dimethyladamantane (**16**) was mixed with 8 mL of nitric acid and cooled to 0 °C with an ice bath. 44 mL of sulfuric acid was added via an addition funnel within 2 h and stirring at 0 °C was continued for 3 h. The mixture was poured over ca. 800 g ice and the colorless precipitate was collected via suction filtration and dried with P_2O_5 under reduced pressure. 5.846 g (81%) of **31** was isolated as a colorless powder, m.p. 94 °C (ref.[60] 96.8–97.1 °C). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.19 (sept, J = 3.2 Hz, 1 H, CH), 1.58–1.54 (m, 2 H, adamantane-CH_2), 1.53 (br. s, 1 H, -O*H*), 1.42–1.18 (m, 8 H, 4×adamantane-CH_2), 1.11 (s, 2 H, adamantane-CH_2), 0.87 (s, 6 H, 2×CH_3) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 69.9 (*C*-OH), 51.5, 50.5, 43.8, 42.5, 33.8 (C$_q$), 31.1, 29.9 ppm. ^{13}C NMR shifts are in accordance with literature values.[61]

3-Hydroxytricyclo[3.3.1.1^{3,7}]decane-1-carboxylic Acid (32): 7.210 g (40 mmol) **10** was suspended in 4 mL nitric acid at 0 °C. Upon stirring, 50 mL sulfuric acid was added within 2 h at 0 °C. Stirring at 0 °C was continued for another 3 h and the mixture was poured over ca. 100 g of ice. The colorless precipitate was collected via suction filtration, washed with water and dried with P_2O_5 in a dessicator at reduced pressure. 5.507 g (70%) **32** was isolated. ^{1}H NMR (200 MHz, [D$_6$]DMSO): δ = 7.19 (br. s, 3 H, CO_2H and O*H*), 2.19–2.01 (m, 2 H, adamantane-CH_2) 1.63–1.54 (m, 6 H, 3×adamantane-CH_2), 1.54–1.40 (m, 6 H, adamantane-CH$_2$) ppm. ^{13}C NMR (50 MHz, [D$_6$]DMSO): δ = 177.7 (*C*O$_2$H), 66.3 (*C*-OH), 46.5 (*C*-CO$_2$H), 44.2, 42.8, 37.6, 34.8, 29.7 ppm. ^{1}H-NMR spectroscopic data are in accordance with the literature.[62]

3,5-Dimethyltricyclo[3.3.1.1^{3,7}]decane-1-yl Methyl Ether (33): 1.643 g (10 mmol) **16** was mixed with 1 mL nitric acid at 0 °C. 12.5 mL sulfuric acid was added with an addition funnel over the course of 3 h upon stirring at 0 °C. Stirring was continued for another 3 h, whereupon the mixture was added to 25 mL of methanol upon cooling to 0 °C. The mixture was stirred at 0 °C for 30 min and at room temp. for 90 min. 50 mL dichloromethane and 50 mL water was added, the layers were separated and the aqueous layer was extracted with dichloromethane (3×20 mL). The combined organic phases were washed with water, 5% $NaHCO_3$ and brine (50 mL each) and dried (Na_2SO_4). The slightly yellowish oil obtained after evaporation of the solvent was purified by silica gel column chromatography eluting with *n*-pentane/diethyl ether (95:5), R_f(**33**) = 0.22. 0.735 g (38%) **33** was isolated as a colorless liquid. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 3.23 (s, 3 H, OCH_3), 2.20 (sept, J = 3.0 Hz, adamantane-CH), 1.60–1.55 (m, 2 H, adamantane-CH_2), 1.43–1.24 (m, 8 H, adamantane-CH_2), 1.12 (br. s, 2 H, adamantane-CH_2), 0.87 (s, 6 H, 2×CH_3) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 73.6 (*C*OCH$_3$), 50.8 (*C*H$_2$), 48.0 (O*C*H$_3$), 47.0 (*C*H$_2$), 42.8 (*C*H$_2$), 39.4 (*C*H$_2$), 33.4 (*C*-CH$_3$), 30.8 (*C*H$_3$), 30.1 (*C*H) ppm. IR (film): $\tilde{\nu}$ = 2945, 2920, 2902, 2863, 2845, 1455, 1197, 10095, 1089 cm^{-1}. MS (EI, 70 eV): m/z = 194 (35.6%), 163 (41.8%), 137 (96.1%), 107 (28.6%). HRMS: found 194.16664, calcd. 194.16707. $C_{13}H_{22}O$ (194.31): calcd. C 80.72, H 11.73; found C 80.42, H 11.72.

Synthesis of ^{A}Xaas 5a–5f

General Procedure: The respective precursors **19**–**24** were refluxed in concentrated hydrochloric acid (36–38%)/water as described below. After evaporation of the acid under reduced pressure to dryness, the crude products were treated with an organic solvent and collected via suction filtration. All compounds were dried in a desiccator over P_2O_5 and paraffin pellets at reduced pressure for 48 h.

3-Aminotricyclo[3.3.1.1^{3,7}]decane-1-carboxylic Acid Hydrochloride (5a): 12.396 g (52.2 mmol) **19**, 140 mL of aqueous HCl, 60 mL water, 72 h reflux. Workup by treating the crude product with acetone. Yield: 10.58 g (45.7 mmol, 87.4%), m.p. 332 °C (ref.[25] 338–340 °C).

(1) Hydrochloride: ^{1}H NMR (400 MHz, [D$_6$]DMSO): δ = 12.33 (br. s, 1 H, CO_2H), 8.37 (br. s, 3 H, NH_3Cl), 7.43 [t, J(^{15}N-H) = 50.8 Hz], 2.23–2.14 (m, 2 H), 1.96–1.87 (m, 2 H), 1.86–1.70 (m, 6 H), 1.70–1.48 (m, 4 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 176.8 (C=O), 51.2 (C$_q$), 41.3, 41.0 (C$_q$), 38.9, 36.9, 34.1, 28.0 ppm. IR (KBr): $\tilde{\nu}$ = 3391, 3144, 3103, 2924, 1700, 1601, 1510, 1227 cm^{-1}. ^{1}H NMR spectroscopic data are in accordance with the literature.[12] The hydrochloride was neutralized by heating with an equimolar amount of NaOH in water. The zwitterion was then recrystallized from water and dried at 110 °C under reduced pressure over phosphorus pentaoxide; m.p. > 355 °C (ref.[63] > 300 °C).

(2) Zwitterion: ^{1}H NMR (400 MHz, D_2O, sodium 3-(trimethylsilyl)-[D$_4$]propanoate): δ = 2.32–2.25 (m, 2 H), 1.96–1.91 (m, 2 H), 1.89–1.80 (m, 6 H), 1.75–1.60 (m, 4 H) ppm. ^{13}C NMR (100 MHz, D_2O, sodium 3-(trimethylsilyl)-[D$_4$]propanoate): δ = 187.9 (C=O), 55.7 (C$_q$), 46.8 (C$_q$), 45.0, 42.0, 40.5, 36.8, 31.6 ppm. IR (KBr): $\tilde{\nu}$ = 3438, 2929, 2898, 2858, 2634, 1620, 1547, 1511, 1391 cm^{-1}. MS (EI, 70 eV): m/z = 195 (46.7%), 150 (30.0%), 138 (63.5%), 108 (14.5%), 94 (100%). HRMS: found 195.1248, calcd. 195.1259. $C_{11}H_{17}NO_2$ (195.26): calcd. C 67.66, H 8.77, N 7.17; found C 67.57, H 8.94, N 7.21.

3-Amino-5-methyltricyclo[3.3.1.1^{3,7}]decane-1-carboxylic Acid Hydrochloride (5b): 3.015 g (12.9 mmol) of acetamide **20**, 100 mL of aqueous HCl, 75 h reflux. Workup by treatment of the crude product with acetone. Yield: 2.545 g (10.4 mmol, 80.5%), m.p. 315 °C (ref.[11] 320–322 °C).

(1) Hydrochloride: ^{1}H NMR (400 MHz, [D$_6$]DMSO): δ = 12.34 (br. s, 1 H, CO_2H), 8.38 (br. s, 3 H, NH_3Cl), 7.39 [t, J(^{15}N-H) = 50.8 Hz], 2.21 (br. s, 1 H), 1.92–1.77 (m, 2 H), 1.77–1.56 (m, 4 H), 1.56–1.44 (m, 2 H), 1.44–1.24 (m, 4 H), 0.88 (s, 3 H, CH_3) ppm. ^{13}C NMR (100 MHz, [D$_6$]DMSO): δ = 176.7 (C=O), 51.8 (C$_q$), 45.6, 43.8, 42.0 (C$_q$), 41.2, 40.4, 38.2, 36.3, 31.4 (C$_q$), 29.3, 28.4 ppm. The hydrochloride was neutralized by heating with an equimolar amount of NaOH in water. The zwitterion was then recrystallized from water and dried at 110 °C under reduced pressure over phosphorus pentoxide; m.p. 336 °C (ref.[11] 338–339 °C).

(2) Zwitterion: ^{1}H NMR (400 MHz, D_2O and [D_6]DMSO): δ = 2.31–2.23 (m, 1 H), 1.88–1.76 (m, 2 H), 1.76–1.57 (m, 4 H), 1.57–1.46 (m, 2 H), 1.46–1.30 (m, 4 H), 0.92 (s, 3 H, CH_3) ppm. ^{13}C NMR (100 MHz, D_2O and [D_6]DMSO): δ = 184.3 (C=O), 54.8 (C_q), 47.3, 46.3, 45.7 (C_q), 43.2, 42.7, 39.7, 38.6, 33.4 (C_q), 30.9, 30.6 ppm. IR (KBr): $\tilde{\nu}$ = 3416, 2942, 2912, 2860, 2153, 1635, 1558, 1530, 1389, 1350, 732 cm^{-1}. MS (EI, 70 eV): *m*/*z* = 209 (19.8%), 164 (40.1%), 152 (35.1%), 138 (14.2%), 122 (8.8%), 108 (100%), 94 (18.4%). HRMS: found 209.1409, calcd. 209.1416. $C_{12}H_{19}NO_2$ (209.28): calcd. C 68.87, H 9.15, N 6.69; found C 68.57, H 9.51, N 7.08.

3-Amino-5,7-dimethyltricyclo[3.3.1.1^{3,7}]decane-1-carboxylic Acid Hydrochloride (5c): 7.730 g (29.1 mmol) of acetamide **21**, 170 mL of aqueous HCl, 80 h reflux. Workup by treating the crude product with ethyl acetate. Yield: 6.425 g (24.7 mmol, 84.9%), m.p. 337 °C (ref.[11] 346–347 °C).

(1) Hydrochloride: ^{1}H NMR (400 MHz, [D_6]DMSO): δ = 12.36 (br. s, 1 H. CO_2H), 8.42 (br. s, 3 H, NH_3Cl), 7.39 [t, J(^{15}N-H) = 50.7 Hz], 1.79 (br. s, 2 H), 1.53–1.32 (m, 8 H), 1.19–1.06 (m, 2 H), 0.89 (s, 6 H, 2 × CH_3) ppm. ^{13}C NMR (100 MHz, [D_6]DMSO): δ = 176.6 (C=O), 52.5 (C_q), 48.5, 44.9, 43.2, 42.6, 39.8 (C_q), 32.0 (C_q), 29.0 (2 × CH_3) ppm. The hydrochloride was neutralized by heating with an equimolar amount of NaOH in water. The zwitterion was then recrystallized from water and dried at 110 °C under reduced pressure over phosphorus pentoxide. M.p. 337 °C (ref.[11] 352–353 °C).

(2) Zwitterion: ^{1}H NMR (400 MHz, D_2O, sodium 3-(trimethylsilyl)-[D_4]propanoate): δ = 1.80 (br. s, 2 H), 1.55–1.40 (m, 8 H), 1.27–1.18 (m, 2 H), 0.90 (s, 6 H, 2 × CH_3) ppm. ^{13}C NMR (100 MHz, D_2O, sodium 3-(trimethylsilyl)-[D_4]propanoate): δ = 187.9 (C=O), 57.1 (C_q), 51.1, 48.3 (C_q), 48.0, 46.9, 44.0, 35.2 (C_q), 31.5 (2 × CH_3) ppm. IR (KBr): $\tilde{\nu}$ = 3428, 2946, 2922, 2864, 2849, 2652, 2559, 2120, 1638, 1564, 1538, 1455, 1382, 1348, 726 cm^{-1}. MS (EI, 70 eV): *m*/*z* = 223 (9.7%), 178 (35.8%), 152 (34.6%), 134 (4.8%), 122 (100%), 108 (35.5%). HRMS: found 223.1567, calcd. 223.1572. $C_{13}H_{21}NO_2$ (223.31): calcd. C 69.92, H 9.48, N 6.27; found C 69.72, H 9.67, N 6.34.

3-Amino-5-(2-propyl)tricyclo[3.3.1.1^{3,7}]decanecarboxylic Acid Hydrochloride (5d): 1.276 g (4.57 mmol) of acetamide **22**, 20 mL of aqueous HCl, 10 mL of H_2O, 69 h reflux. Workup by treating the crude product with acetone. Yield: 657 mg (2.40 mmol, 52.5%), m.p. 274 °C. ^{1}H NMR (400 MHz, [D_6]DMSO): δ = 12.35 (br. s, 1 H, CO_2H), 8.38 (br. s, 3 H, NH_3^+Cl), 7.41 [t, J(^{15}N-H) = 43.6 Hz], 2.28–2.20 (m, 2 H), 1.91–1.27 (m, 11 H), 0.75 (d, J = 6.8 Hz, 6 H, 2 × CH_3) ppm. ^{13}C NMR (100 MHz, [D_6]DMSO): δ = 176.9 (C=O), 52.1 (C_q), 41.8 (C_q), 40.8, 40.7, 38.9, 38.6, 36.7, 36.4 (C_q), 36.1, 36.0, 28.2, 16.2 ppm. IR (KBr): $\tilde{\nu}$ = 3442, 3006, 2945, 2860, 1734, 1702, 1472, 1200, 663 cm^{-1}. MS (EI, 70 eV): *m*/*z* = 237 (40.0%), 213 (27.9%), 194 (48.4%), 192 (81.1%), 180 (43.8%), 150 (33.6), 136 (85.1%), 108 (14.0%), 94 (65.7%). HRMS: found 237.1732, calcd. 237.1729 (M^+ – HCl).

3-Amino-5-(carboxymethyl)tricyclo[3.3.1.1^{3,7}]decane-1-carboxylic Acid Hydrochloride (5e): 1.846 g (6.24 mmol) of acetamide **23**, 70 mL of aqueous HCl, 25 mL of H_2O. Workup by treating the crude product with acetone. Yield: 1.662 g (5.74 mmol, 92%), m.p. 252 °C. ^{1}H NMR (400 MHz, [D_6]DMSO): δ = 12.28 (br. s, 2 H, 2 × CO_2H), 8.33 (br. s, 3 H, NH_3Cl), 2.27–2.19 (m, 1 H), 2.13 (s, 2 H, CH_2CO_2H), 1.94–1.78 (m, 2 H), 1.78–1.55 (m, 8 H), 1.53–1.42 (m, 2 H) ppm. ^{13}C NMR (100 MHz, [D_6]DMSO): δ = 176.6 (C=O), 171.9 (C=O), 51.7 (C_q), 46.3, 43.1, 41.8, 41.6 (C_q), 40.4, 39.0, 38.3, 36.3, 33.7 (C_q), 28.2 ppm. IR (KBr): $\tilde{\nu}$ = 3427, 3020, 2938, 2863, 2598, 1726, 1709, 1368, 1200 cm^{-1}. MS (EI, 70 eV): *m*/*z* = 253 (37.6%), 208 (75.7%), 196 (30.8%), 166 (17.5%), 152 (70.2%), 138 (19.2%), 106 (43.1%). HRMS: found 253.1320, calcd. 253.1314 (M^+ – HCl). $C_{13}H_{20}ClNO_4$ (289.60): calcd. C 53.89, H 6.96, N 4.83; found C 53.75, H 6.98, N 4.46.

3-Amino-5-carboxytricyclo[3.3.1.1^{3,7}]decane-1-propanoic Acid Hydrochloride (5f): 453 mg (1.47 mmol) of acetamide **24**, 10 mL of aqueous HCl, 5 mL of H_2O, 69 h reflux. Workup by treating the crude product with acetone. Yield: 375 mg (1.23 mmol, 83.9%), m.p. 265 °C. ^{1}H NMR (400 MHz, [D_6]DMSO): δ = 12.21 (br. s, 2 H, 2 × CO_2H), 8.34 (br. s, 3 H, NH_3Cl), 7.37 [t, J(^{15}N-H) = 50.8 Hz], 2.28–2.19 (m, 1 H), 2.16 (t, J = 8.0 Hz, 2 H, $CH_2CH_2CO_2$H), 1.92–1.79 (m, 2 H), 1.78–1.22 (m, 10 H), 1.44 (t, J = 8.2 Hz, 2 H, $CH_2CH_2CO_2$H) ppm. ^{13}C NMR (100 MHz, [D_6]DMSO): δ = 176.7 (C=O), 174.5 (C=O), 51.8 (C_q), 43.3, 42.0, 41.4, 40.6 (C_q), 38.6, 38.4, 36.8, 36.5, 33.8 (C_q), 28.2, 27.5 ppm. IR (KBr): $\tilde{\nu}$ = 3142, 2997, 2920, 2864, 2585, 1728, 1704, 1494, 1218, 1187, 1155, 667 cm^{-1}. MS (EI, 70 eV): *m*/*z* = 267 (20.2%), 222 (44.0%), 204 (16.1%), 192 (22.3%), 180 (12.5%), 166 (39.0%), 148 (40.6%), 138 (16.7%), 120 (11.1%), 106 (16.5%). HRMS: found 267.1476, calcd. 267.1471 (M^+ – HCl).

PTC Strategy Towards ^{A}Xaas

3-Bromo-1-iodo-5,7-dimethyltricyclo[3.3.1.1^{3,7}]decane (35a): 2.432 g (10 mmol) of 1-bromo-3,5-dimethyladamantane, 15.76 g (40 mmol) of CHI_3, 10 g of powdered NaOH and 484 mg (15 mol-%) of tetra-*n*-butylammonium bromide was mixed with 80 mL of fluorobenzene in a 250 mL flask. The flask was equipped with a condenser, put into an ultrasonic cleaning bath (Bender & Hobein Laboson 200) and agitated at 45 °C. After 3, 4, 5, 6, 7 and 8 days the mixture was filtered through a glass frit and the solvent was evaporated under reduced pressure. The residue was then mixed with the same amount of reagents as described above. After agitation for 9 days the mixture was worked up as described above and purified through silica gel column chromatography eluting with *n*-pentane, R_f = 0.31. After evaporation of the solvent, 2.192 g (5.94 mmol, 59.4%) of **35a** was isolated as a colorless powder, m.p. 98–99 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.91 (br. s, 2 H), 2.28–2.14 (m, 4 H), 2.03 (br. s, 4 H), 1.38–1.19 (m, 2 H), 0.89 (s, 6 H, 2 × CH_3) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 61.5 (C_q), 60.1, 56.0, 53.1, 48.0, 43.1 (C_q), 39.1 (2 × C_q), 28.8 (2 × CH_3) ppm. IR (KBr): $\tilde{\nu}$ = 2951, 2924, 2863, 2841, 1452, 1442, 1315, 1167, 891, 828, 703 cm^{-1}. MS (EI, 70 eV): *m*/*z* = 289 (4.4%, M^+ – Br), 243/241 (100) [M^+ – I], 185 (15.6%), 161 (42.2%), 119 (20.0%). $C_{12}H_{18}BrI$ (369.08): calcd. C 39.05, H 4.91; found C 39.14, H 4.72.

3-Bromo-1-iodo-5-(1-methylethyl)tricyclo[3.3.1.1^{3,7}]decane (35b): 3.858 g (15 mmol) of 1-bromo-3-(1-methylethyl)adamantane, 29.5 g (75 mmol) of CHI_3, 730 mg (2.25 mmol) of tetra-*n*-butylammonium bromide and 21 g powdered NaOH was suspended in 80 mL fluorobenzene, equipped with a condenser, put into an ultrasonic cleaning bath and agitated at 45 °C for 16 h. The mixture was filtered through a glass frit and the solvent was evaporated under reduced pressure. The reaction was restarted twice with the same amounts of solvent and reagent. The residue was then purified by silica gel column chromatography eluting with *n*-pentane, R_f = 0.31. After evaporation of the solvent, 0.93 g (2.42 mmol, 16.2%) of **35b** was isolated as a colorless powder. NMR and GC/MS analyses proved the identity of the product that was used for further conversions without additional purification. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 3.09–2.95 (m, 2 H), 2.54–2.35 (m, 2 H), 2.34–2.18 (m, 4 H), 2.19–2.06 (m, 3 H), 1.61–1.50 (m, 2 H), 1.34 [sept, J = 7.0 Hz, 1 H, CH(CH_3)$_2$], 0.84 [d, J = 7.0 Hz, 6 H, CH(CH_3)$_2$] ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 62.9 (C_q), 61.5, 52.1, 49.6, 49.2, 46.8, 44.9 (C_q), 44.7 (C_q), 36.9, 35.5, 35.45, 16.4 ppm. MS (HP 5971):

m/*z* = 303 (4) [M^+ – Br], 257/255 (100) [M^+ – I], 175 (56%), 91 (77%).

1-Bromo-3-acetamido-5,7-dimethyltricyclo[3.3.1.1^{3,7}]decane (36a): 58.4 mg (0.5 mmol) $NOBF_4$ was suspended in 3 mL of dry acetonitrile and cooled to –50 °C. 185 mg (0.5 mmol) **35a** in 15 mL dry acetonitrile was slowly added and the resulting mixture was stirred under argon upon warming to –15 °C within ca. 2 h. The reaction was then quenched with 20 mL water and extracted three times with 20 mL diethyl ether. The combined organic phases were washed with saturated $NaHSO_3$ (2 × 20 mL) until the organic layer turned colorless. After washing with water (5 × 20 mL) and brine (20 mL), the solution was dried (Na_2SO_4). The solvents were then evaporated under reduced pressure and the residue was purified by silica gel column chromatography eluting with diethyl ether, R_f = 0.27. After evaporation of the solvent, 142 mg (0.47 mmol, 94.4%) of **36a** was collected as a colorless powder, m.p. 178–179 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 5.24 (br. s, 1 H, N*H*), 2.49–2.42 (m, 2 H), 2.03–1.88 (m, 4 H), 1.91 (s, 3 H, COCH_3), 1.78–1.58 (m, 4 H), 1.25–1.14 (m, 2 H), 0.92 (s, 6 H, 2 × CH_3) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 169.4 (C=O), 62.7 (C_q), 55.3 (C_q), 54.0, 50.8, 48.9, 46.0, 35.8 (2 × C_q), 29.0 (2 × *C*H_3), 24.5 (CO*C*H_3) ppm. IR (KBr): $\tilde{\nu}$ = 3295, 3081, 2947, 2928, 2902, 2865, 1676, 1655, 1639, 1558, 1370, 1323, 606 cm^{-1}. MS (EI, 70 eV): *m*/*z* = 301 (2.8%), 299 (2.6%), 220 (100%), 178 (19.5%), 164 (26.7%), 121 (25.9%), 105 (9.7%). HRMS: found 299.0906, calcd. 299.0884. $C_{14}H_{22}BrNO$ (300.23): calcd. C 56.00, H 7.38, N 4.66; found C 55.84, H 7.35, N 4.59.

3-Acetamido-1-bromo-5-(1-methylethyl)tricyclo[3.3.1.1^{3,7}]decane (36b): 230 mg (1.93 mmol) of $NOBF_4$ was suspended in dry acetonitrile and cooled to –50 °C. A solution of 740 mg (1.93 mmol) **35b** was slowly added and the resulting mixture was stirred under argon upon warming to 0 °C within ca. 2 h. The reaction was then quenched with 20 mL water and extracted three times with 20 mL diethyl ether. The combined organic phases were washed with saturated aqueous $NaHSO_3$ (2 × 20 mL) until the organic layer turned colorless. After washing with water (5 × 20 mL) and brine (20 mL), the solution was dried (Na_2SO_4). The solvents were then evaporated under reduced pressure and the residue was purified by silica gel column chromatography eluting with ethyl acetate/*n*-hexane (1:1), R_f = 0.26. After evaporation of the eluent, 400 mg (1.27 mmol, 65.9%) of **36b** was obtained as a colorless powder, m.p. 135 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 5.27 (br. s, 1 H, N*H*), 2.63–2.49 (m, 2 H), 2.30–2.13 (m, 3 H), 2.09–1.97 (m, 3 H), 1.92 (s, 3 H, COCH_3), 1.87–1.66 (m, 3 H), 1.45 (br. s, 2 H), 1.37 [sept, *J* = 7.0 Hz, C*H*(CH_3)$_2$], 0.85 [d, *J* = 7.0 Hz, 6 H, CH(CH_3)$_2$] ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 169.3 (C=O), 64.1 (C_q), 55.0 (C_q), 52.0, 50.0, 47.6, 42.0, 41.1 (C_q), 39.5, 36.8, 36.3, 32.1, 24.6 (CO*C*H_3), 16.6 [CH(*C*H_3)$_2$] ppm. IR (KBr): $\tilde{\nu}$ = 3266, 3085, 2977, 2957, 2933, 2922, 2867, 1654, 1638, 1566, 1370, 606 cm^{-1}. MS (EI, 70 eV): *m*/*z* = 315 (0.7%), 313 (0.7%), 234 (100%), 220 (8.3%), 192 (27.5%), 175 (16.7%), 150 (14.8%), 136 (12.0%), 119 (7.8%), 108 (8.5%), 93 (15.8%). HRMS: found 313.1040, calcd. 313.1041 $C_{15}H_{24}BrNO$ (314.26): calcd. C 57.33, H 7.70, N 4.46; found C 57.39, H 7.68, N 4.80.

***tert*-Butyl 3-Acetamidotricyclo[3.3.1.1^{3,7}]decane-1-carboxylate (37):** In an oven-dried 250 mL flask under argon, 11.865 g (50 mmol) of acetamide **19** was suspended in 100 mL of dry THF. 7.03 mL (50 mmol) of dry triethylamine was added and the mixture was refluxed for 45 min. After cooling to room temp., 3.65 mL (50 mmol) of freshly distilled $SOCl_2$ was added and the mixture was refluxed another 45 min. After cooling to room temp., 50 mL of *tert*-butyl alcohol was added and the reaction mixture was heated for another 2 h at reflux temperature. The mixture was then cooled to room temp. and 150 mL water was added. Extraction with ethyl acetate (3 × 100 mL), washing of the combined organics with water, sat. aqueous $NaHCO_3$, water and brine (100 mL each), drying (Na_2SO_4) and evaporation of the solvents under reduced pressure yielded a yellowish oil that was purified by silica gel column chromatography by eluting with *tert*-butyl methyl ether, R_f = 0.28. After evaporation of the eluent, 7.383 g (25.2 mmol, 50.3%) of **37** was obtained as a colorless powder, m.p. 129.5–130.5 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 5.23 (br. s, 1 H, N*H*), 2.09–2.03 (m, 2 H), 2.02–1.92 (m, 4 H), 1.91 (s, 3 H, COCH_3), 1.86–1.73 (m, 4 H), 1.69–1.55 (m, 2 H), 1.42 [s, 9 H, C(CH_3)$_3$] ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 175.8 (C=O), 169.3 (C=O), 79.9 [*C*(CH_3)$_3$], 52.2 (C_q), 43.1 (C_q), 42.7, 40.8, 38.0, 35.4, 29.2, 28.0 [C(*C*H_3)$_3$], 24.7 (CO*C*H_3) ppm. IR (KBr): $\tilde{\nu}$ = 3277, 3207, 3085, 2955, 2918, 2863, 1723, 1648, 1561, 1269, 1242, 1172, 1139, 850 cm^{-1}. MS (EI, 70 eV): *m*/*z* = 293 (9.6%), 237 (27.9%), 192 (100%), 150 (79.5%), 136 (30.1%), 129 (18.7%), 94 (34.5%). HRMS: found 293.1942, calcd. 293.1991. $C_{17}H_{27}NO_3$ (293.40): calcd. C 69.59, H 9.27, N 4.77; found C 69.54, H 9.43, N 4.93.

***tert*-Butyl 5-Acetamido-3-bromotricyclo[3.3.1.1^{3,7}]decane-1-carboxylate (38):** A mixture of 586 mg (2 mmol) of **37**, 3.0 g (9 mmol) of CBr_4, and tetra-*n*-butylammonium bromide (96 mg, 15 mol-%) was dissolved in 20 mL of fluorobenzene, then 10 mL of 50% aqueous NaOH was added. The mixture was stirred intensively at 50 °C for 6 d in a 50 mL flask equipped with a condenser, then diluted with water and extracted with ethyl acetate. The extract was washed with water and dried (Na_2SO_4). The filtrate was concentrated under reduced pressure and the reaction was restarted with the same amounts of solvents and reagents as above and kept stirring at 50 °C for another 5 d. After workup as described above, the residue was purified by silica gel column chromatography eluting with ethyl acetate, R_f = 0.42. After evaporation of the eluent under reduced pressure, 100.5 mg (2.7 mmol, 13.5%) of **38** was collected as a colorless powder, m.p. 140.5 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 5.32 (br. s, 1 H, N*H*), 2.65–2.53 (m, 2 H), 2.44–2.33 (m, 2 H), 2.33–2.28 (m, 1 H), 2.28–2.00 (m, 6 H), 1.93 (s, 3 H, COCH_3), 1.85–1.77 (m, 2 H), 1.43 [s, 9 H, C(CH_3)$_3$] ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 173.6 (C=O), 169.4 (C=O), 80.8 [*C*(CH_3)$_3$], 61.1 (C_q), 54.3 (C_q), 51.4, 48.8, 46.9, 46.1 (C_q), 41.3, 39.0, 36.4, 31.6, 28.0 [C(*C*H_3)$_3$], 24.4 (CO*C*H_3) ppm. IR (KBr): $\tilde{\nu}$ = 3267, 3085, 2978, 2941, 2869, 1724, 1654, 1566, 1370, 1311, 1271, 1168, 849 cm^{-1}. MS (EI, 70 eV): *m*/*z* = 373 (0.7%), 371 (0.7%), 315 (0.8%), 300 (0.8%), 292 (22.2%), 109 (12.2%), 236 (100%), 190 (60.1%), 148 (12.3%), 133 (7.1%). HRMS: found 371.1105, calcd. 371.1096. $C_{17}H_{26}BrNO_3$ (372.30): calcd. C 54.84, H 7.04, N 3.76; found C 54.90, H 7.00, N 4.41.

Protective Group Chemistry

General Procedure for Fmoc-Protection: The amino acid hydrochlorides **5a**–**5c** were mixed with 4.5 equiv. of Na_2CO_3 and suspended in water and acetone (2:1). Under vigorous stirring and cooling in an ice bath, 1.1 equiv. of 9-fluorenylmethyl chloroformate in acetone was added with an addition funnel within ca. 1 h. The mixture was then stirred at room temp. overnight, whereupon it was heated to 50 °C for 2 h to evaporate most of the acetone. The mixture was then poured over ice and carefully extracted with diethyl ether. The aqueous phase was acidified with concd. aqueous HCl (pH 5) and the yellowish precipitate extracted with ethyl acetate. The combined organic phases were washed with water, dried (Na_2SO_4), and concentrated. The residue was purified by recrystallization from nitromethane. Drying in a desiccator over paraffin wax and P_2O_5 under reduced pressure overnight yielded the Fmoc-protected amino acids.

3-[(9-Fluorenyl)methoxycarbonylamino]tricyclo[3.3.1.1^{3,7}]decane-1-carboxylic Acid (39a): 8.347 g (36 mmol) of amino acid **5a**. Yield: 10.177 g (24.4 mmol, 67.7%) of **39a** as slightly yellowish crystals, m.p. 185 °C. ^{1}H NMR (400 MHz, [D$_6$]DMSO): δ = 12.23 (br. s, 1 H, CO_2H), 7.88 (d, J = 7.4 Hz, 2 H), 7.71 (d, J = 7.2 Hz, 2 H), 7.41 (t, J = 7.2 Hz, 2 H), 7.33 (t, J = 7.4 Hz, 2 H), 7.11 (br. s, 1 H, NH), 4.31–4.13 (m, 3 H), 2.21–1.38 (m, 14 H, adamantane) ppm. ^{13}C NMR (100 MHz, [D$_6$]DMSO): δ = 177.6 (C=O), 154.2 (C=O), 144.0, 140.7, 127.5, 126.9, 125.2, 120.0, 64.8 (Fmoc-CH_2), 50.1 (C$_q$), 46.7, 42.3, 41.5, 40.1 (C$_q$), 37.6, 34.9, 28.5 ppm. IR (KBr): $\tilde{\nu}$ = 3318, 3068, 2913, 2856, 1719, 1677, 1556, 1450, 1264, 1091, 733 cm^{-1}. MS (EI, 70 eV): m/z = 417 (2.2%), 208 (3.1%), 178 (100%), 165 (9.7%), 128 (4.4%), 93 (7.9%). HRMS: found 417.1900, calcd. 417.1900. $C_{26}H_{27}NO_4$ (417.50): calcd. C 74.52, H 6.52, N 3.39; found C 74.63, H 6.57, N 3.39.

3-[(9-Fluorenyl)methoxycarbonylamino]-5-methyltricyclo[3.3.1.1^{3,7}]-decane-1-carboxylic Acid (39b): 3.686 g (75 mmol) of amino acid **5b**. Yield: 3.858 g (8.94 mmol, 59.6%) of **39b** as slightly yellowish crystals, m.p. 193 °C. ^{1}H NMR (400 MHz, [D$_6$]DMSO): δ = 12.01 (br. s, 1 H, CO_2H), 7.88 (d, J = 7.6 Hz, 2 H), 7.72 (d, J = 6.8 Hz, 2 H), 7.41 (t, J = 7.4 Hz, 2 H), 7.31 (t, J = 7.4 Hz, 2 H), 7.14 (br. s, 1 H, NH), 4.40–4.02 (m, 3 H), 2.23–2.03 (m, 1 H), 2.03–1.01 (m, 13 H, adamantane), 0.85 (s, 3 H, CH_3) ppm. ^{13}C NMR (100 MHz, [D$_6$]DMSO): δ = 177.5 (C=O), 154.2 (C=O), 143.9, 140.7, 127.5, 126.9, 125.2, 120.0, 64.7 (Fmoc-CH_2), 50.9 (C$_q$), 46.9, 46.7, 44.4, 42.1 (C$_q$), 41.9, 41.6, 39.5, 36.9, 31.3 (C$_q$), 29.8, 28.9 ppm. IR: $\tilde{\nu}$ = 3265, 3134, 3066, 3039, 2946, 2907, 2856, 1701, 1450, 1413, 1326, 1288, 1114, 740 cm^{-1}. MS (EI, 70 eV): m/z = 431 (0.2%), 235 (2.3%), 209 (1.9%), 190 (35.1%), 178 (100%), 165 (63.5%), 134 (11.2%), 107 (10.4%). HRMS: found 431.2108 calcd. 431.2097. $C_{27}H_{29}NO_4$ (431.52): calcd. C 75.15, H 6.77, N 3.24; found C 75.41, H 6.75, N 3.55.

3-[(9-Fluorenyl)methoxycarbonylamino]-5,7-dimethyltricyclo-[3.3.1.1^{3,7}]decane-1-carboxylic Acid (39c): 520 mg (2 mmol) of amino acid **5c**. Yield: 408 mg (0.92 mmol, 45.8%) of **39c** as slightly yellowish crystals, m.p. 176 °C. ^{1}H NMR (400 MHz, [D$_6$]DMSO): δ = 12.10 (br. s, 1 H, CO_2H), 7.88 (d, J = 7.2 Hz, 2 H), 7.70 (d, J = 7.6 Hz, 2 H), 7.41 (t, J = 7.2 Hz, 2 H), 7.32 (t, J = 7.4 Hz, 2 H), 7.16 (br. s, 1 H, NH), 4.31–4.13 (m, 3 H), 1.98–1.69 (m, 2 H), 1.69–0.45 (m, 12 H, adamantane), 0.85 (br. s, 6 H, 2 × CH_3) ppm. ^{13}C NMR (100 MHz, [D$_6$]DMSO): δ = 177.4 (CO_2H), 154.2 (C=O), 143.9 (C$_q$), 140.6 (C$_q$), 127.5, 126.9, 125.2, 120.0, 64.7 (Fmoc-CH_2), 51.6 (C$_q$), 49.1, 46.7, 46.2, 43.8, 42.7 (C$_q$), 41.0, 31.9 (C$_q$), 29.4 (2 × CH_3) ppm. IR (KBr): $\tilde{\nu}$ = 3326, 3066, 2941, 2920, 2862, 1728, 1695, 1554, 1540, 1451, 1273, 1253, 1128, 760, 734 cm^{-1}. MS (EI, 70 eV): m/z = 445 (0.1%), 249 (1.8%), 204 (35.0%), 178 (100%), 165 (47.8%), 152 (9.5%), 122 (11.8%), 107 (6.1%). HRMS: found 445.2222, calcd. 445.2253. $C_{28}H_{31}NO_4$ (445.55): calcd. C 75.48, H 7.01, N 3.14; found C 75.53, H 7.22, N 3.28.

General Procedure for the Synthesis of *tert*-Butyl Esters 40a–c: The amino acids **5a**–**5c** (in zwitterionic form) were heated at reflux temperature with excess thionyl chloride for 2 h. After careful evaporation of the excess thionyl chloride under reduced pressure, a large excess of *tert*-butyl alcohol was added and the mixture refluxed for another 4 h. The excess of the alcohol was again removed under reduced pressure. The residue was dissolved in diethyl ether and satd. Na_2CO_3. The aqueous phase was extracted with diethyl ether, the combined organic phases were dried (Na_2SO_4), filtered, and purified by silica gel column chromatography eluting with *tert*-butyl methyl ether/methanol/triethylamine (20:10:1).

***tert*-Butyl 3-Aminotricyclo[3.3.1.1^{3,7}]decane-1-carboxylate (40a):** 1.562 g (8 mmol) of amino acid **5a**, 30 mL of thionyl chloride, 30 mL of *tert*-butyl alcohol. Yield: 1.924 (7.7 mmol, 95.7%) of amino ester **40a** as a slightly yellowish oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.22–2.05 (m, 2 H), 1.83–1.68 (m, 4 H), 1.66 (s, 2 H, NH_2), 1.62–1.50 (m, 4 H), 1.42 [s, 9 H, C(CH_3)$_3$], 1.33–1.24 (m, 2 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 176.3 (CO_2tBu), 79.6 [C(CH$_3$)$_3$], 47.7 (C$_q$), 47.6, 45.2, 43.5 (C$_q$), 37.8, 35.3, 29.6, 28.1 [C(CH$_3$)] ppm. IR (KBr): $\tilde{\nu}$ = 3358, 2977, 2904, 2852, 1718, 1454, 1367, 1267, 1174, 1144, 853 cm^{-1}. MS (EI, 70 eV): m/z = 251 (37.4%), 194 (18.7%), 150 (100%), 138 (37.0%), 127 (8.6%), 108 (9.5%), 94 (67.8%). HRMS: found 251.1905, calcd. 251.1885. $C_{15}H_{25}NO_2$ (251.36): calcd. C 71.76, H 10.02, N 5.57; found C 71.29, H 10.26, N 5.77.

***tert*-Butyl 3-Amino-5-methyltricyclo[3.3.1.1^{3,7}]decane-1-carboxylate (40b):** 1.046 g (5 mmol) of amino acid **5b**, 12.5 mL of thionyl chloride, 12.5 mL of *tert*-butyl alcohol. Yield: 1.169 g (4.4 mmol, 88.1%) of amino ester **40b** as slightly yellowish oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.22–2.15 (m, 1 H), 1.68–1.64 (m, 2 H), 1.64–1.52 (m, 2 H), 1.51–1.44 (m, 2 H) 1.47 (s, 2 H, NH_2), 1.42 [s, 9 H, C(CH_3)$_3$], 1.39–1.30 (m, 2 H), 1.30–1.24 (m, 2 H), 1.24–1.16 (m, 2 H), 0.88 (s, 3 H, CH_3) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 176.2 (CO_2tBu), 79.7 [C(CH$_3$)$_3$], 52.4, 48.6 (C$_q$), 47.0, 44.8, 44.6 (C$_q$), 44.3, 42.5, 37.2, 32.4 (C$_q$), 30.09, 30.07, 28.1 ppm. IR (KBr): $\tilde{\nu}$ = 3360, 2977, 2903, 2847, 1719, 1456, 1367, 1273, 1158, 852 cm^{-1}. MS (EI, 70 eV): m/z = 265 (13.6%), 208 (12.7), 190 (2.7%), 164 (100%), 152 (16.2%), 138 (8.8%), 108 (52.2%). HRMS: found 265.2033, calcd. 265.2042. $C_{16}H_{27}NO_2$ (265.39): calcd. C 72.41, H 10.25, N 5.28; found C 72.10, H 10.30, N 4.83.

***tert*-Butyl 3-Amino-5,7-dimethyltricyclo[3.3.1.1^{3,7}]decane-1-carboxylate (40c):** 2.233 g (10 mmol) of amino acid **5c**, 25 mL of thionyl chloride, 25 mL *tert*-butyl alcohol. Yield: 2.368 g (8.47 mmol, 84.7%) of amino ester **40c** as colorless solid, m.p. 30–31 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.54 (s, 2 H, NH_2), 1.42 [s, 9 H, C(CH_3)$_3$], 1.43–1.37 (m, 4 H), 1.28–1.13 (m, 4 H), 1.12–1–03 (m, 2 H), 0.89 (s, 6 H, 2 × CH_3) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 176.0 (CO_2tBu), 79.6 [C(CH$_3$)$_3$], 51.5, 49.7, 49.3 (C$_q$), 46.2, 44.8 (C$_q$), 44.0, 32.8 (C$_q$), 29.6 (2 × CH_3), 27.9 [C(CH$_3$)$_3$] ppm. IR (KBr): $\tilde{\nu}$ = 3359, 2978, 2946, 2924, 2896, 2864, 2848, 1721, 1456, 1368, 1280, 1162, 850 cm^{-1}. MS (EI, 70 eV): m/z = 279 (6.0%), 208 (3.0%), 164 (3.8%), 152 (12.8%), 122 (100%), 108 (27.8%). HRMS: found 279.2194, calcd. 279.2198. $C_{17}H_{29}NO_2$ (279.42): calcd. C 73.07, H 10.46, N 5.01; found C 72.93, H 10.73, N 4.75.

3-[(*tert*-Butoxycarbonyl)amino]tricyclo[3.3.1.1^{3,7}]decane-1-carboxylic Acid (41): 1.953 g (10 mmol) **5a** (zwitterion) and 2.1 mL (15 mmol) triethylamine was suspended in 40 mL water and 40 mL acetone. 2.463 g (10 mmol) 2-(*tert*-butoxycarbonyloxyimino)-2-phenylacetonitrile ("Boc-ON") was added and the mixture was stirred at room temp. for 24 h. Another 2.463 g Boc-ON was added and stirring at room temp. was continued for 24 h. The mixture was poured over 150 g of crushed ice. 200 mg Na_2CO_3 was added and the acetone was evaporated under reduced pressure. The residual basic solution was extracted three times with diethyl ether and acidified by dropwise addition of concentrated HCl to pH 2. The precipitate was extracted with ethyl acetate, the combined organic phases were washed with water and dried (Na_2SO_4). The solvent was evaporated under reduced pressure and the residue was purified by dissolving it in $CHCl_3$ and reprecipitation through the addition of *n*-hexane. After suction filtration and drying in a dessicator over paraffin wax and P_2O_5, 1.421 g (4.81 mmol, 48.1%) of carbamate **41** was collected as colorless powder, m.p. 180–181 °C. ^{1}H NMR (400 MHz, [D$_6$]DMSO): δ = 12.06 (br. s, 1 H, CO_2H), 6.46 (br. s, 1 H, NH), 2.11–2.03 (m, 2 H), 1.95–1.87 (m, 2 H), 1.87–1.70 (m, 4 H), 1.70–1.61 (m, 4 H), 1.56–1.49 (m, 2 H), 1.37 [s, 9 H,

C(CH_3)$_3$] ppm. ^{13}C NMR (100 MHz, [D$_6$]DMSO): δ = 177.6 (CO_2H), 153.8 (C=O), 77.1 [C(CH$_3$)$_3$], 49.8 (C$_q$), 42.2, 41.5 (C$_q$), 40.3, 37.6, 35.0, 28.4, 28.2 [C(CH_3)$_3$] ppm. IR (KBr): $\tilde{\nu}$ = 3359, 3263, 3130, 3003, 2970, 2949, 2916, 2856, 2643, 1690, 1480, 1541, 1392, 1365, 1284, 1245, 1168, 1071, 776 cm^{-1}. MS (EI, 70 eV): *m*/*z* = 295 (0.7%), 239 (25.5%), 195 (7.5%), 179 (15.4%), 169 (5.9%), 151 (15.2%), 138 (20.8%), 133 (8.1%), 108 (7.4%). HRMS: found 295.1735, calcd. 295.1786. $C_{16}H_{25}NO_4$ (295.37): calcd. C 65.06, H 8.53, N 4.74; found C 64.74, H 8.92, N 4.52.

3-[(Benzyloxycarbonyl)amino]tricyclo[3.3.1.1^{3,7}]decane-1-carboxylic Acid (42): 463 mg (2 mmol) **5a** (hydrochloride) and 1.06 g (10 mmol) Na_2CO_3 were suspended in 10 mL of water and 10 mL of acetone and cooled to 0 °C in an ice bath. 512 mg (30 mmol) of benzyl chloroformate was then added and the mixture was stirred 2 h at 0 °C, 1 h at room temp. and 2 h at 60 °C to evaporate most of the acetone. The mixture was then extracted three times with diethyl ether and acidified by dropwise addition of concd. aqueous HCl (pH 5). The precipitate was extracted with ethyl acetate, the combined organic phases were washed with water an dried (Na_2SO_4). The mixture was concentrated and the crude product was purified by silica gel column chromatography eluting with dichloromethane/*tert*-butyl methyl ether (1:1), R_f = 0.59. After evaporation of the eluent, 561 mg (1.65 mmol, 82.7%) of carbamate **42** was collected as a colorless powder, m.p. 114 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.38–7.28 (m, 5 H), 5.05 (s, 2 H, benzyl CH_2), 4.69 (br. s, 1 H, NH), 2.24–2.15 (m, 2 H), 2.11 (br. s, 2 H), 2.03–1.87 (m, 4 H), 1.87–1.79 (m, 4 H), 1.70–1.57 (m, 2 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 182.0 (CO_2H), 154.4 (C=O), 136.7 (C$_q$), 128.5, 128.1, 128.07, 66.2, 51.0 (C$_q$), 42.52, 42.49 (C$_q$), 40.9, 37.7, 35.2, 29.1 ppm. IR (KBr): $\tilde{\nu}$ = 3386, 3139, 3085, 3031, 2940, 2922, 2855, 1728, 1677, 1531, 1301, 1251, 1242, 1205, 1075, 694 cm^{-1}. MS (EI, 70 eV): *m*/*z* = 329 (1.0%), 279 (0.5%), 228 (1.7%), 221 (6.9%), 194 (8.2%), 176 (59.6%), 149 (6.5%), 133 (12.9%), 120 (17.2%), 108 (100%). HRMS: found 329.1612, calcd. 329.1627. $C_{19}H_{23}NO_4$ (329.39): calcd. C 69.28, H 7.03, N 4.25; found C 69.03, H 6.96, N 4.35.

Peptides Incorporating ^{A}Xaas

***tert*-Butyl 3-{3-[(9-Fluorenyl)methoxycarbonylamino]tricyclo-[3.3.1.1^{3,7}]dec-1-ylcarboxamido}-tricyclo[3.3.1.1^{3,7}]decane-1-carboxylate (Fmoc-^{A}Gly-^{A}Gly-O*t*Bu, 43a):** In an oven-dried 250 mL flask under argon, 3.989 g (15.9 mmol) of ^{A}Gly-O*t*Bu (**40a**), 6.621 g (15.9 mmol) of Fmoc-^{A}Gly (**39a**) and 6.015 g (15.9 mmol) of *O*-(1*H*-benzotriazol-1-yl)-*N*,*N*,*N*′,*N*′-tetramethyluronium hexafluorophosphate (HBTU) were dissolved in 150 mL dry THF. 2.05 g (15.9 mmol) of diisopropyl ethylamine (DIPEA) was added and the mixture was stirred overnight at room temp., then 1 h at 60 °C. After cooling to room temp., 100 mL of brine was added and the mixture was extracted with $CHCl_3$. The combined organic phases were washed with 1 N HCl, 5% $NaHCO_3$, water and brine and dried (Na_2SO_4). The solvents were evaporated under reduced pressure and the residue was purified by silica gel column chromatography eluting with diethyl ether, R_f = 0.59. After careful evaporation of the eluent, 9.453 g (14.5 mmol, 91.6%) of the dipeptide was obtained as a colorless powder, m.p. 139 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.75 (d, *J* = 7.5 Hz, 2 H), 7.58 (d, *J* = 7.4 Hz, 2 H), 7.39 (t, *J* = 7.3 Hz, 2 H), 7.31 (t, *J* = 7.4 Hz, 2 H), 5.24 (br. s, 1 H, NH), 4.70 (br. s, 1 H, NH), 4.45–4.27 (m, 2 H, Fmoc-CH_2), 4.20 (t, *J* = 6.5 Hz, 1 H, fluorenyl-C$H_{aliph.}$), 2.31–1.53 (m, 28 H, 2 × adamantane), 1.42 [s, 9 H, C(CH_3)$_3$] ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 175.8 (CO), 175.7 (C=O), 154.3 (C=O), 144.1 (C$_q$), 141.4 (C$_q$), 127.6, 127.0, 125.0, 120.0, 79.9 [C(CH$_3$)$_3$], 65.9 (Fmoc-CH_2), 51.7 (C$_q$), 51.3 (C$_q$), 47.4, 43.2 (C$_q$), 43.1, 43.0 (C$_q$), 42.6, 40.9, 40.6, 38.3, 38.0, 35.4, 35.3, 29.3, 29.2, 28.0 [C(CH_3)$_3$] ppm. IR (KBr): $\tilde{\nu}$ = 3438, 3349, 2909, 2855, 1718, 1650, 1510, 1451, 1297, 1271, 1252, 1220, 1167, 1103, 1081, 759, 740 cm^{-1}. MS (ESI): *m*/*z* = 673.5 [M + Na]$^+$ (calcd. 673.4). $C_{41}H_{50}N_2O_5$ (650.85): calcd. C 75.66, H 7.74, N 4.30; found C 75.92, H 7.95, N 4.14.

***tert*-Butyl 3-{3-[3-[(9-fluorenyl)methoxycarbonylamino]tricyclo-[3.3.1.1^{3,7}]dec-1-ylcarboxamido]-tricyclo[3.3.1.1^{3,7}]dec-1-ylcarboxamido}tricyclo[3.3.1.1^{3,7}]decane-1-carboxylate (Fmoc-^{A}Gly-^{A}Gly-^{A}Gly-O*t*Bu, 43b). (a) *N*-Deprotection. Synthesis of *tert*-Butyl 3-(3-Aminotricyclo[3.3.1.1^{3,7}]dec-1-ylcarboxamido)tricyclo[3.3.1.1^{3,7}]decane-1-carboxylate (H-^{A}Gly-^{A}Gly-O*t*Bu):** 1.953 g (3 mmol) of dipeptide **43a** was dissolved in 40 mL of dry acetonitrile and cooled to 0 °C with an ice bath. 40 mL of diethylamine was slowly added and the mixture was stirred for 1 h at 0 °C and 24 h at room temp. The solvents were evaporated under reduced pressure and the residue was purified by silica gel column chromatography eluting with *tert*-butyl methyl ether/methanol/triethylamine (20:10:1), R_f = 0.36. After careful evaporation of the eluent, 1.198 g (2.8 mmol, 93.1%) of the *N*-deprotected dipeptide was obtained as colorless powder, m.p. 169 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 5.24 (br. s, 1 H, NH), 2.24–2.13 (m, 4 H), 2.06–1.83 (m, 4 H), 2.02 (s, 2 H, NH_2), 1.83–1.65 (m, 10 H), 1.65–1.50 (m, 10 H), 1.42 [s, 9 H, C(CH_3)$_3$] ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 176.3 (C=O), 175.9 (C=O), 79.9 [C(CH$_3$)$_3$], 51.7 (C$_q$), 48.1, 48.0 (C$_q$), 45.1, 43.4 (C$_q$), 43.1 (C$_q$), 42.7, 40.7, 38.4, 38.0, 35.4, 29.7, 29.3, 28.1 [C(CH_3)$_3$] ppm. IR (KBr): $\tilde{\nu}$ = 3320, 2977, 2908, 2853, 1719, 1635, 1534, 1276, 1252, 1171, 854 cm^{-1}. MS (EI, 70 eV): *m*/*z* = 428 (40.3%), 371 (10.5%), 353 (4.0%), 327 (9.9%), 279 (7.3%), 179 (8.5%), 167 (131.3%), 150 (100%), 133 (4.0%), 108 (6.2%), 94 (35.6%). HRMS: found 428.3036, calcd. 428.3039. $C_{26}H_{40}N_2O_3$ (428.61): calcd. C 72.86, H 9.41, N 6.54; found C 72.85, H 9.51, N 6.52.

(b) Peptide Coupling. Synthesis of the Trimer Fmoc-^{A}Gly-^{A}Gly-^{A}Gly-O*t*Bu (43b): 594 mg (1.42 mmol) Fmoc-^{A}Gly (**39a**) and 192 mg (1.42 mmol) 1-Hydroxybenzotriazole (HOBt) were dissolved in 40 mL dry THF under argon. Upon cooling with an ice bath, 179 mg DIC was slowly added with a syringe. The mixture was stirred at room temp. for 1 h. After cooling to 0 °C, 610 mg of H-^{A}Gly-^{A}Gly-O*t*Bu (vide supra) in 30 mL of dry THF was slowly added via an addition funnel. The mixture was stirred at 0 °C for 1 h and at room temp. for 7 d. The solvent was then carefully evaporated under reduced pressure and the residue was dissolved in diethyl ether. The solution was washed 12 times with water, then with brine and dried (Na_2SO_4). Filtration and concentration under reduced pressure yielded a crude product that was purified via silica gel column chromatography eluting with diethyl ether, R_f = 0.34. After careful evaporation of the eluent, 876 mg (1.04 mmol, 73.2%) of tripeptide **43b** was obtained as colorless powder, m.p. 191 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.76 (d, *J* = 7.5 Hz, 2 H), 7.59 (d, *J* = 7.4 Hz, 2 H), 7.40 (t, *J* = 7.4 Hz, 2 H), 7.32 (t, *J* = 7.4 Hz, 2 H), 5.27 (br. s, 2 H, 2 × NH), 4.67 (br. s, 1 H, NH), 4.42–4.27 (m, 2 H, Fmoc-CH_2), 3.46 (t, *J* = 6.4 Hz), 2.37–1.48 (m, 42 H, 3 × adamantane), 1.42 [s, 9 H, C(CH_3)$_3$] ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 175.88 (C=O), 175.85 (2 signals, 2 × C=O), 154.3 (C=O), 144.4 (C$_q$), 141.4 (C$_q$), 127.7, 127.1, 125.0, 120.0, 79.9 [C(CH$_3$)$_3$], 66.0 (Fmoc-CH_2), 51.9 (C$_q$), 51.8 (C$_q$), 51.3 (C$_q$), 47.4, 43.3 (2 signals, 2 × C$_q$), 43.1 (C$_q$), 43.0, 42.9, 42.6, 40.9, 40.7, 40.6, 38.4, 38.3, 38.0, 35.4 (2 signals), 35.3, 29.4, 29.3, 29.25, 28.0 ppm. IR (KBr): $\tilde{\nu}$ = 3377, 2910, 2852, 1714, 1642, 1523, 1451, 1296, 1267, 1253, 1218, 1170, 1079, 740 cm^{-1}. MS (ESI): *m*/*z* = 850.6 [M + Na]$^+$ (calcd. 850.5). $C_{52}H_{65}N_3O_6$ (828.09): calcd. C 75.42, H 7.91, N 5.07; found C 75.56, H 8.13, N 4.83.

Fmoc-^{A}Gly-^{A}Gly-^{A}Gly-^{A}Gly-O*t*Bu (43c). (a) *C*-Deprotection: Synthesis of Fmoc-^{A}Gly-^{A}Gly-OH. 3.254 g (5 mmol) of dipeptide **43a**

was dissolved in 45 mL dichloromethane and cooled to 0 °C. 45 mL trifluoroacetic acid was added and the mixture stirred 1 h at 0 °C and 24 h at room temp. The solvents were carefully evaporated under reduced pressure by repeatedly adding dichloromethane. The residue was then recrystallized from nitromethane/acetone (1:1) to yield 2.386 g (4.0 mmol, 80.2%) of Fmoc-^{A}Gly-^{A}Gly-OH as a colorless powder, m.p. 208 °C. ^{1}H NMR (400 MHz, [D$_6$]DMSO): δ = 12.01 (br. s, 1 H, CO_2H), 7.88 (d, J = 7.5 Hz, 2 H), 7.72 (d, J = 7.4 Hz, 2 H), 7.41 (t, J = 7.5 Hz, 2 H), 7.33 (t, J = 7.4 Hz, 2 H), 7.08 (br. s, NH), 6.44 (br. s, 1 H, NH), 4.31–4.06 (m, 3 H), 2.23–1.39 (m, 28 H, 2 × adamantane) ppm. ^{13}C NMR (100 MHz, [D$_6$]DMSO): δ = 177.7 (C=O), 175.6 (C=O), 154.0 (C=O), 143.9 (C$_q$), 140.6 (C$_q$), 127.5, 126.9, 125.2, 120.0, 64.7 (Fmoc-CH$_2$), 50.9 (C$_q$), 50.5 (C$_q$), 46.7, 42.5 (C$_q$), 42.3, 42.0 (C$_q$), 41.5, 39.7, 39.5, 37.7, 37.5, 35.1, 34.9, 28.8, 28.5 ppm. IR (KBr): $\tilde{\nu}$ = 3358, 3326, 3040, 2906, 2853, 1706, 1693, 1639, 518, 1449, 1295, 1251, 1215, 1087, 737 cm^{-1}. MS (ESI): m/z = 594.3 [M + Na]$^+$. $C_{37}H_{42}N_2O_5$ (594.74): calcd. C 74.72, H 7.11, N 4.71; found C 74.49, H 7.19, N 4.98.

(b) Peptide Coupling. Synthesis of Tetramer Fmoc-^{A}Gly-^{A}Gly-^{A}Gly-^{A}Gly-OtBu (43c): In an oven-dried 250 mL flask under argon, 1.072 g (2.5 mmol) of H-^{A}Gly-^{A}Gly-OtBu, 1.487 g (2.5 mmol) of Fmoc-^{A}Gly-^{A}Gly-OH (vide supra) and 1.0429 g (2.75 mmol) HBTU were dissolved in 200 mL dry acetonitrile. 354 mg (2.75 mmol) DIPEA was added and the mixture was stirred overnight at room temp., then 90 min at 60 °C. After cooling to room temp., 100 mL of brine was added and the mixture was extracted with $CHCl_3$. The combined organic phases were washed with 1 N HCl, 5% $NaHCO_3$, water and brine and dried (Na_2SO_4). The solvents were evaporated under reduced pressure. The crude product was dissolved in $CHCl_3$ and reprecipitated through slow addition of n-hexane. The peptide was collected via suction filtration and dried in vacuo in a desiccator over paraffin wax and P_2O_5. 2.345 g (2.33 mmol, 93.3%) of the tetrapeptide was obtained as a colorless powder, m.p. 235–238 °C (decomp.). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.76 (d, J = 7.5 Hz, 2 H), 7.59 (d, J = 7.4 Hz, 2 H), 7.40 (t, J = 7.4 Hz, 2 H), 7.32 (t, J = 7.5 Hz, 2 H), 5.28 (br. s, 2 H, 2 × NH), 5.26 (br. s, 1 H, NH), 4.68 (br. s, 1 H, NH), 4.46–4.25 (m, 2 H, Fmoc-CH_2), 4.21 (t, J = 6.4 Hz, 1 H), 2.28–1.53 (m, 56 H, 4 × adamantane), 1.42 [s, 9 H, C(CH_3)$_3$] ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 175.96 (C=O), 175.87 (C=O), 175.86 (C=O), 175.83 (C=O), 154.3 (C=O), 144.1 (C$_q$), 141.1 (C$_q$), 127.7, 127.1, 125.0, 120.0, 79.9 [C(CH$_3$)$_3$], 66.0 (Fmoc-CH$_2$), 51.92 (C$_q$), 51.88 (C$_q$), 51.77 (C$_q$), 51.28 (C$_q$), 47.4, 43.2, 43.1, 43.0 (possibly 2 signals), 42.9 (possibly 2 signals), 42.6 (possibly 2 signals), 40.9 (C$_q$), 40.7 (possibly 2 signals, C$_q$), 40.6 (C$_q$), 38.4 (possibly 2 signals), 38.3, 38.0, 35.4 (possibly 2 signals), 35.3 (possibly 2 signals), 29.32 (2 signals), 29.27, 29.23, 28.0 ppm. IR (KBr): $\tilde{\nu}$ = 3439, 3379, 2909, 2853, 1716, 1643, 1522, 1451, 1341, 1295, 1266, 1253, 1220, 1169, 740 cm^{-1}. MS (ESI): m/z = 1027.8 [M + Na]$^+$ (calcd. 1027.6). $C_{63}H_{80}N_4O_7$ (1005.33): calcd. C 75.27, H 8.02, N 5.57; found C 74.98, H 8.15, N 5.68.

Hexamer Fmoc-^{A}Gly-^{A}Gly-^{A}Gly-^{A}Gly-^{A}Gly-^{A}Gly-OtBu (43d). (a) *N*-Deprotection. Synthesis of H-^{A}Gly-^{A}Gly-^{A}Gly-^{A}Gly-OtBu: 2.011 g (2 mmol) of tetrapeptide **43c** was dissolved in 40 mL of dry acetonitrile and cooled to 0 °C with an ice bath. 40 mL of diethylamine was slowly added and the mixture was stirred for 1 h at 0 °C and 24 h at room temp. The solvents were evaporated under reduced pressure and the residue was purified by silica gel column chromatography eluting with *tert*-butyl methyl ether/methanol/triethylamine (20:10:1), R_f = 0.30. After careful evaporation of the eluent, 1.151 g (1.47 mmol, 73.5%) of H-^{A}Gly-^{A}Gly-^{A}Gly-^{A}Gly-OtBu was obtained as colorless powder, m.p. > 360 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.28–2.11 (m, 8 H), 2.07–1.84 (m, 16 H), 2.02 (s, 2 H, NH_2), 1.83–1.52 (m, 32 H), 1.43 [s, 9 H, C(CH_3)$_3$] ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 176.3 (C=O), 176.0 (C=O), 175.9 (2 signals, 2 × C=O), 79.9 [C(CH$_3$)$_3$], 52.0 (C$_q$), 51.9 (C$_q$), 51.8 (C$_q$), 48.4 (C$_q$), 47.6, 44.7, 43.4 (C$_q$), 43.1, 43.0 (3 signals, 2 × C$_q$), 42.97, 42.7, 40.74, 40.69, 40.67, 38.47, 38.44, 38.3, 38.0, 35.4 (3 signals), 35.2, 29.6, 29.38, 29.36, 29.26, 28.1 ppm. IR (KBr): $\tilde{\nu}$ = 3384, 2911, 2851, 1714, 1643, 1522, 1294, 1267, 1253, 1172 cm^{-1}. MS (ESI): m/z = 783.7 [M + H]$^+$ (calcd. 783.5). $C_{48}H_{70}N_4O_5$ (783.09): calcd. C 73.62, H 9.01, N 7.15; found C 73.30, H 9.15, N 7.14.

(b) Peptide Coupling. Fmoc-^{A}Gly-^{A}Gly-^{A}Gly-^{A}Gly-^{A}Gly-^{A}Gly-OtBu (43d): In an oven-dried 250 mL flask under argon, 585 mg (0.75 mmol) of H-^{A}Gly-^{A}Gly-^{A}Gly-^{A}Gly-OtBu, 44 mg (0.75 mmol) of Fmoc-^{A}Gly-^{A}Gly-OH and 312 mg (0.75 mmol) of HBTU were dissolved in 75 mL of dry acetonitrile. 106 mg (0.82 mmol) of DIPEA was added and the mixture was stirred overnight at room temp., then 90 min at 60 °C. After cooling to room temp., 100 mL of brine was added and the mixture was extracted with $CHCl_3$. The combined organic phases were washed with 1 N HCl, 5% $NaHCO_3$, water and brine and dried (Na_2SO_4). The solvents were evaporated under reduced pressure. The crude product was dissolved in $CHCl_3$ and reprecipitated through slow addition of diethyl ether. The peptide was collected via suction filtration and dried in vacuo in a desiccator over paraffin wax and P_2O_5. 2.345 g (2.33 mmol, 93.3%) of the hexapeptide was obtained as a slightly yellowish powder, m.p. 320–325 °C (decomp.). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.76 (d, J = 7.5 Hz, 2 H), 7.58 (d, J = 7.5 Hz, 2 H), 7.40 (t, J = 7.5 Hz, 2 H), 7.31 (t, J = 7.5 Hz, 2 H), 5.28 (br. s, 4 H, 4 × NH), 5.26 (br. s, 1 H, NH), 4.69 (br. s, 1 H, NH), 4.42–4.27 (m, 2 H, Fmoc-CH_2), 4.20 (t, J = 6.4 Hz, 1 H), 2.28–1.49 (m, 84 H, 6 × adamantane), 1.42 [s, 9 H, C(CH_3)$_3$] ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 176.2, 176.0, 175.98, 175.89, 175.83, 175.5, 154.4, 144.1, 141.4, 127.7, 127.1, 125.0, 120.0, 79.9, 66.0, 52.1, 52.0, 51.9, 51.8, 51.3, 47.4, 43.3, 43.2, 43.0, 42.9, 42.7, 40.9, 40.7, 40.68, 40.5, 38.5, 38.4, 38.0, 35.4, 35.3, 29.4, 29.3 28.1 ppm. (Note: due to insufficient resolution of the spectrometer and low solubility of the peptide, the set of resonances is not complete. Groups of resonances are given.) IR (KBr): $\tilde{\nu}$ = 3378, 2928, 2910, 2852, 1719, 1642, 1521, 1450, 1293, 1267, 1255 cm^{-1}. MS (ESI): m/z = 1381.9 [M + Na]$^+$ (calcd. 1381.8).

Solution-Phase Synthesis of Peptidic Organocatalysts

Boc-His(τ-Bn)-^{A}Gly-Phe-OMe (45). (a) Fmoc-^{A}Gly-Phe-OMe: In an oven-dried 100 mL flask under argon, 863 mg (4 mmol) of L-phenylalanine methyl ester hydrochloride, 1.67 g (4 mmol) of Fmoc-^{A}Gly (**13a**) and 1.517 g (4 mmol) of HBTU were dissolved in 50 mL of dry THF. 1.034 g (8 mmol) of DIPEA was added and the mixture was stirred overnight at room temp., then 1 h at 60 °C. After cooling to room temp., 50 mL of brine was added and the mixture was extracted with $CHCl_3$. The combined organic phases were washed with 1 N HCl, 5% $NaHCO_3$, water and brine and dried (Na_2SO_4). The solvents were evaporated under reduced pressure and the residue was purified by silica gel column chromatography eluting with ethyl acetate/hexane (2:1), R_f = 0.47. After evaporation of the eluent, 2.093 g (3.6 mmol, 90.4%) of the dipeptide was obtained as a colorless powder that was analyzed by ^{1}H and ^{13}C NMR and used as such. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.76 (d, J = 7.4 Hz, 2 H), 7.58 (d, J = 7.4 Hz, 2 H), 7.39 (t, J = 7.3 Hz, 2 H), 7.31 (t, J = 7.4 Hz, 2 H), 7.33–7.20 (m, 3 H), 7.07 (d, J = 7.1 Hz, 2 H), 6.02 (br. s, 1 H, NH), 4.91–4.79 [m, 1 H, Hα (Phe)], 4.64 (br. s, 1 H, NH), 4.48–4.25 (m, 2 H, Fmoc-CH_2), 4.21 (t, J = 6.4 Hz, 1 H), 3.73 (s, 3 H, OCH_3), 3.22–3.04 [m, 2 H, Hβ

(Phe)], 2.38–1.41 (m, 14 H, adamantane) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 175.8 (C=O), 172.2 (C=O), 154.3 (C=O), 144.01 (C_q), 141.4 (C_q), 135.9 (C_q), 129.4, 128.6, 127.6, 127.2, 127.1, 125.0, 120.0, 66.0, 52.8, 52.3, 51.1 (C_q), 47.4, 43.0, 42.6 (C_q), 40.7, 38.0, 37.9, 35.2, 29.2 ppm.

(b) H-^{A}Gly-Phe-OMe: 2.049 g (3.54 mmol) Fmoc-^{A}Gly-Phe-OMe was dissolved in 30 mL of dry acetonitrile and cooled to 0 °C with an ice bath. 30 mL of diethylamine was slowly added and the mixture was stirred for 1 h at 0 °C and 24 h at room temp. The solvents were evaporated under reduced pressure and the residue was purified by silica gel column chromatography eluting with *tert*-butyl methyl ether/methanol/triethylamine (20:10:1), R_f = 0.30. After careful evaporation of the eluent, 1.187 g (3.33 mmol, 94.1%) of the *N*-deprotected dipeptide was obtained as a slightly yellowish solid, m.p. 86 °C. ^{1}H NMR (200 MHz, $CDCl_3$): δ = 7.33–7.15 (m, 3 H), 7.12–6.99 (m, 2 H), 6.12–5.99 (br. d, N*H*), 4.93–4.78 [m, 1 H, Hα (Phe)], 3.72 (s, 3 H, OCH_3), 3.23–3.00 [m, 2 H, Hβ (Phe)], 2.26–2.09 (m, 2 H), 1.79–1.70 (m, 12 H, adamantane) ppm. ^{13}C NMR (50 MHz, $CDCl_3$): δ = 176.3 (C=O), 172.2 (C=O), 135.9 (C_q), 129.3, 128.5, 127.1, 52.7, 52.3, 47.8 (C_q), 47.6, 45.0, 43.0 (C_q), 38.0, 37.8, 29.5 ppm. IR (KBr): $\tilde{\nu}$ = 3329, 3029, 2906, 2851, 1741, 1642, 1529, 1496, 1454, 1216, 702 cm^{-1}. MS (EI, 70 eV): *m*/*z* = 356 (4.8%), 299 (5.0%), 239 (3.3%), 194 (55.6%), 150 (100%), 120 (19.7%), 94 (33.4%). HRMS: found 356.2078, calcd. 356.2030. $C_{21}H_{28}N_2O_3$ (356.46): calcd. C 70.76, H 7.92, N 7.86; found C 70.71, H 7.84, N 7.89.

(c) Boc-His(τ-Bn)-^{A}Gly-Phe-OMe (45): 357 mg (1 mmol) H-^{A}Gly-Phe-OMe (1 mmol), 345 mg Boc-His(τ-Bn)-OH (1 mmol), and 379 mg (1 mmol) HBTU were dissolved in 50 mL dry THF. 171 μL (1 mmol) of DIPEA was added and the mixture was stirred under argon at room temp. for 15 h. 50 mL of brine and 50 mL of chloroform were added, the layers were separated and the aqueous phase was extracted with chloroform (3 × 30 mL). The combined organic phases were washed with 1 N HCl, 5% $NaHCO_3$, water and brine (2 × 30 mL each) and dried (Na_2SO_4). The crude product obtained after evaporation was purified by flash column chromatography eluting with dichloromethane/methanol (95:5), R_f(**45**) = 0.40. 603 mg (0.88 mmol, 88%) of tripeptide **50** were obtained as a colorless powder, m.p. 97 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.46–7.44 (m, 1 H), 7.38–7.22 (m, 6 H), 7.19–7.15 (m, 2 H), 7.11–7.06 (m, 2 H), 6.72 (br. s, 1 H), 6.57 (br. s, 1 H, N*H*), 6.20 (br. s, 1 H, N*H*), 6.04 (d, *J* = 7.4 Hz, 1 H), 5.04 (s, 2 H, CH_2Ph), 4.89–4.82 [m, 1 H, H_α(Phe)], 4.29 [br. s, 1 H, H_α(His)], 3.73 (s, 3 H, OCH_3), 3.20–3.05 [M, 3 H, Hβ(Phe) and Hβ (His)], 2.88–2.80 [m, 1 H, Hβ (His)], 2.22–1.50 (m, 14 H, adamantane), 1.46 [s, 9 H, C(CH_3)$_3$] ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 176.0 (C=O), 172.2 (C=O), 170.8 (C=O), 138.6 (C_q), 136.5, 136.0 (C_q), 135.9 (C_q), 129.3, 129.0, 128.6, 128.3, 127.5, 127.1, 117.3, 79.7 (C_q), 52.8, 52.3, 51.8, 50.9, 42.5, 42.4, 40.3, 40.1, 38.1, 38.0, 37.8, 35.2, 30.7, 29.1, 28.4 ppm. IR (KBr): $\tilde{\nu}$ = 3337, 2976, 2911, 2856, 1741, 1701, 1654, 1507, 1455, 1365, 1249, 1169 cm^{-1}. MS (ESI): *m*/*z* = 684.3 [M + H]$^+$; (calcd. 684.4). $C_{39}H_{49}N_5O_6$ (683.84): calcd. C 68.50, H 7.22, N 10.24; found C 68.01, H 7.21, N 10.03.

Boc-His(π-Me)-^{A}Gly-Phe-OMe (46): 178.2 mg (0.5 mmol) of H-^{A}Gly-Phe-OMe, 134.7 mg (0.5 mmol) of Boc-His(π-Me)-OH and 189.6 mg (0.5 mmol) HBTU were dissolved in 30 mL dry THF. 86 μL (0.5 mmol) of DIPEA was added and the mixture was stirred under argon at room temp. for 16 h. 30 mL of brine and 30 mL of chloroform were added, the layers were separated and the aqueous layer was extracted with chloroform (3 × 20 mL). The combined organic phases were washed with 1 N HCl, 5% $NaHCO_3$, water, and brine (2 × 20 mL each) and dried (Na_2SO_4). The crude product obtained after evaporation of the solvents was purified by flash column chromatography eluting with dichloromethane/methanol (9:1), R_f(**46**) = 0.21. 199.5 mg (0.33 mmol, 66%) of tripeptide **46** was isolated as a colorless powder, m.p. 71 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.39 (br. s, 1 H), 7.33–7.22 (m, 3 H, H_{Ar}), 7.09–7.05 (m, 2 H, H_{Ar}), 6.85 (s, 1 H), 6.04 [d, *J* = 7.6 Hz, N*H*(Phe)], 5.71 [s, 1 H, N*H*(^{A}Gly)], 5.17 [br. s, 1 H, N*H*(His)], 4.88–4.81 [m, 1 H, H_α(Phe)], 4.21–4.08 [m, 1 H, H_α(His)], 3.73 (s, 3 H, O-CH_3), 3.58 (s, 3 H, N-CH_3), 3.20–2.91 [m, 4 H, *Hβ*(Phe) and *Hβ*(His)], 2.21–1.51 (m, 14 H, adamantane), 1.44 [s, 9 H, C(CH_3)$_3$] ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 175.7 (C=O), 172.2 (C=O), 169.5 (C=O), 155.3 (C=O_{Boc}), 138.2, 135.8 (C_q), 129.2, 128.5, 128.2, 127.1, 80.4 (C_q), 52.7, 52.3, 52.2, 42.4, 42.1, 40.24, 40.20, 38.0, 37.9, 37.7, 35.0, 31.4, 29.0, 28.2, 26.7 ppm. IR (KBr): $\tilde{\nu}$ = 3434, 2913, 1740, 1701, 1659, 1509, 1366, 1169 cm^{-1}. MS (ESI): *m*/*z* = 608.3 [M + H]$^+$; (calcd. 608.3). $C_{33}H_{45}N_5O_6$ (607.74): calcd. C 65.22, H 7.46, N 11.52; found C 64.78, H 7.49, N 11.44.

***N*-[3,5-Bis(trifluoromethyl)phenyl]-*N*′-3{[carboxy(glycine methyl ester)amido]tricyclo [3.3.1.1^{3,7}]dec-1-yl}thiourea (47a). (a) Fmoc-^{A}Gly-Gly-OMe:** In an oven-dried 100 mL flask under argon, 126 mg (1 mmol) of glycine methyl ester hydrochloride, 418 mg (1 mmol) of Fmoc-^{A}Gly (**13a**) and 417 mg (1.1 mmol) of HBTU were dissolved in 30 mL dry THF. 259 mg (2 mmol) of DIPEA was added and the mixture was stirred overnight at room temp., then 1 h at 60 °C. After cooling to room temp., 50 mL of brine was added and the mixture was extracted with $CHCl_3$. The combined organic phases were washed with 1 N HCl, 5% aqueous $NaHCO_3$, water and brine and dried (Na_2SO_4). The solvents were evaporated under reduced pressure and the residue was purified by silica gel column chromatography eluting with ethyl acetate, R_f = 0.48. After evaporation of the eluent, 431 mg (0.88 mmol, 88.3%) of the dipeptide was obtained as a colorless powder, m.p. 128 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.75 (d, *J* = 7.5 Hz, 2 H), 7.58 (d, *J* = 7.4 Hz, 2 H), 7.38 (t, *J* = 7.4 Hz, 2 H), 7.32 (t, *J* = 7.4 Hz, 2 H), 6.15 (br. s, 1 H, N*H*), 4.72 (br. s, 1 H, N*H*), 4.44–4.23 (m, 2 H, Fmoc-CH_2), 4.19 (t, *J* = 6.3 Hz, 1 H), 4.00 [d, *J* = 5.1 Hz, 2 H, Hα (Gly)], 3.74 (s, 3 H, OCH_3), 2.40–1.31 (m, 14 H, adamantane) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 176.6 (C=O), 170.6 (C=O), 154.4 (C=O), 144.1 (C_q), 141.4 (C_q), 127.6, 127.1, 124.9, 120.0, 65.9, 52.3, 51.1 (C_q), 47.4, 43.0, 42.6, 41.2, 40.8 (C_q), 38.1, 35.2, 29.2 ppm. IR (KBr): $\tilde{\nu}$ = 3330, 3065, 2947, 2925, 2910, 2857, 1750, 1698, 1637, 1524, 1293, 1272, 1256, 1247, 1222, 1206, 1280, 765, 744 cm^{-1}. MS (ESI): *m*/*z* = 511.5 [M + Na]$^+$ (calcd. 511.2). $C_{29}H_{32}N_2O_5$ (488.57): calcd. C 71.29, H 6.60, N 5.73; found C 70.99, H 6.57, N 5.62.

(b) H-^{A}Gly-Gly-OMe: 977 mg (2 mmol) of Fmoc-^{A}Gly-Gly-OMe was dissolved in 25 mL of dry acetonitrile and cooled to 0 °C with an ice bath. After slow addition of 25 mL of diethylamine the mixture was stirred for 1 h at 0 °C and 15 h at room temp. The solvents were evaporated under reduced pressure and the residue was purified by silica gel column chromatography eluting with *tert*-butyl methyl ether/methanol/triethylamine (20:10:1), R_f = 0.28. After careful evaporation of the eluent, 520 mg (1.95 mmol, 97.6%) of the *N*-deprotected dipeptide was obtained as a slightly yellowish solid, m.p. 104.5 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.18 (br. s, 1 H, N*H*), 4.03 [d, *J* = 5.1 Hz, 2 H, Hα(Gly)], 3.76 (s, 3 H, OCH_3), 2.29–2.13 (m, 2 H), 1.89–1.52 (m, 12 H), 1.71 (s, 2 H, NH_2) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 177.1 (C=O), 170.7 (C=O), 52.4 (OCH_3), 47.9 (C_q), 47.7, 45.0, 43.1 (C_q), 41.2, 38.1, 35.2, 29.6 ppm. IR (KBr): $\tilde{\nu}$ = 3353, 2943, 2916, 2852, 1761, 1635, 1525, 1396, 1207, 1183, 1160, 876 cm^{-1}. MS (EI, 70 eV): *m*/*z* = 266 (23.4%), 252 (2.6%), 239 (6.7%), 209 (26.3%), 177 (21.3%), 150 (100%), 134 (8.9%), 120 (76.1%), 108 (27.8%), 94 (88.3%). HRMS: found

266.1628, calcd. 266.1630. $C_{14}H_{22}N_2O_3$ (266.34): calcd. C 63.13, H 8.33, N 10.52; found C 62.99, H 8.42, N 10.17.

(c) Thiourea Derivative 47a: In an oven-dried 100 mL flask under argon, 1.019 g (3.82 mmol) of H-^{A}Gly-Gly-OMe was dissolved in 20 mL of dry THF, then 493 mg (3.82 mmol) of DIPEA was added. The mixture was cooled to 0 °C with an ice bath and 1.037 g (3.82 mmol) of 3,5-bis(trifluoromethyl)phenyl isothiocyanate in 20 mL of dry THF was added with an addition funnel. The mixture was stirred upon warming to room temp. for 24 h. After careful evaporation of the solvents in vacuo, the crude product was dissolved in $CHCl_3$ and reprecipitated by the addition of *n*-hexane. The product was collected via suction filtration and dried in a desiccator under vacuum over P_2O_5 and paraffin wax. 1.672 g (3.11 mmol, 81.3%) of the thiourea was isolated as a colorless solid, m.p. 189 °C. ^{1}H NMR (400 MHz, [D$_6$]DMSO): δ = 9.89 (s, 1 H), 8.22 (s, 2 H), 77.95 [t, J = 5.7 Hz, N*H* (Gly)], 7.89 (s, 1 H), 7.71 (s, 1 H), 3.79 [d, J = 5.7 Hz, Hα (Gly)], 3.62 (s, 3 H, OC*H*$_3$), 2.54–2.49 (m, 2 H), 2.33–2.14 (m, 6 H), 1.84–1.68 (m, 4 H), 1.68–1.53 (m, 2 H) ppm. ^{13}C NMR (100 MHz, [D$_6$]DMSO): δ = 178.6 (C=S), 176.5 (C=O), 170.4 (C=O), 141.8 (C$_q$), 130.0 (q, $^2J_{C,F}$ = –33 Hz, 2 × *C*-CF$_3$), 123.2 (q, $^1J_{C,F}$ = –273 Hz, 2 × *C*F$_3$), 122.1, 115.9, 54.3 (C$_q$), 51.5 (O*C*H$_3$), 41.8, 40.7, 39.6, 37.6, 34.9, 28.8 ppm. One quaternary ^{13}C signal is overlapped by the DMSO signal. IR (KBr): $\tilde{\nu}$ = 3326, 3213, 3044, 2909, 2857, 1721, 1640, 1531, 1387, 1277, 1175, 1138 cm^{-1}. MS (EI, 70 eV): *m/z* = 537 (0.3%), 466 (0.7%), 387 (0.4%), 309 (0.3%), 271 (100%), 250 (20.4%), 213 (21.2%), 150 (60.6%), 120 (32.1%). HRMS: found 537.1470, calcd. 537.1521. $C_{23}H_{25}F_6N_3O_3S$ (537.52): calcd. C 51.39, H 4.69, N 7.82; found C 51.42, H 4.27, N 8.07.

***N*-[3,5-Bis(trifluoromethyl)phenyl]-*N*′-3{[carboxy(phenylalanine methyl ester)amido]tricyclo[3.3.1.1^{3,7}]dec-1-yl}thiourea (47b):** H-^{A}Gly-Phe-OMe was synthesized as described above. In an oven-dried 100 mL flask under argon, 1.167 g (3.27 mmol) H-^{A}Gly-Phe-OMe was dissolved in 15 mL dry THF and 423 mg (3.27 mmol) of DIPEA was added. The mixture was cooled to 0 °C with an ice bath and 888 mg (3.27 mmol) of 3,5-bis(trifuoromethyl)phenyl isocyanate in 30 mL dry THF was added with an addition funnel. The mixture was stirred upon warming to room temp. for 24 h. After careful evaporation of the solvents in vacuo, the crude product was purified by silica gel column chromatography eluting with ethyl acetate/hexane (2:1), R_f(**47b**) = 0.50. After evaporation of the eluent, 1.859 g (2.96 mmol, 90.6%) of the thiourea was isolated as a colorless powder, m.p. 96–97 °C. ^{1}H NMR (400 MHz, [D$_6$]DMSO): δ = 8.63 (s, 1 H), 7.89 (s, 2 H), 7.62 (s, 1 H), 7.33–7.18 (m, 3 H), 7.08–6.97 (m, 2 H), 6.56 (br. s, 1 H, N*H*), 6.25 (d, J = 7.5 Hz, N*H*), 4.73 [, J = 6.6 Hz, 1 H, Hα (Phe)], 3.71 (s, 3 H, OC*H*$_3$), 3.16–3.01 [s, 2 H, Hβ (Phe)], 2.42–1.56 (m, 14 H, adamantane) ppm. ^{13}C NMR (100 MHz, [D$_6$]DMSO): δ = 179.5 (C=S), 176.9 (C=O), 171.8 (C=O), 140.1 (C$_q$), 135.2 (C$_q$), 132.0 (q, $^2J_{C,F}$ = –34 Hz, 2 × *C*-CF$_3$), 129.1, 128.7, 127.4, 123.0 (q, $^1J_{C,F}$ = –273 Hz, 2 × *C*F$_3$), 124.0, 118.2, 54.9, 53.0 (C$_q$), 52.5 (O*C*H$_3$), 42.8 (C$_q$), 42.7, 40.0, 37.9, 37.5, 35.0, 29.2 ppm. IR (KBr): $\tilde{\nu}$ = 3434, 3331, 3089, 3032, 2914, 2858, 1747, 1640, 1532, 1386, 1278, 1176, 1132, 701, 682 cm^{-1}. MS (ESI): *m/z* = 650.4 [M + Na]$^+$ (calcd. 650.2). $C_{30}H_{31}F_6N_3O_3S$ (627.64): calcd. C 57.41, H 4.98, N 6.69; found C 57.38, H 4.90, N 6.70.

CCDC-626190 to -626192 contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/datarequest/cif.

Supporting Information (see also the footnote on the first page of this article): Experimental details on the solid phase synthesis of pentameric and heptameric ^{A}Gly (**44a**,**b**) as well as HPLC- and MS data. SPPS synthesis of compound **46**.

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