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Synthesis of Dianionic and Trianionic Chiral, Chelating Ligands Based on Amino Acids

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The synthesis of two new families of amino acid-containing chiral ligands, based on methyliminodiacetic acid and nitrilotriacetic acid cores, has been accomplished using a simple protection, solution-phase amide coupling, and deprotection strategy. The amino acids glycine, leucine, aspartic acid, and phenylalanine were used to demonstrate the versatility of the synthetic route, and that no epimerization occurs. The tridentate ligands bear C_3 symmetry, whereas the bidentate ligands have C_1 symmetry.

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Introduction

Amino acids form a cheap and ubiquitous source of chirality, and use has been made of amino acids as metal-binding components of ligands for classical coordination chemistry.[1–4] Free amino acids and derivatives thereof have also been used extensively as ligands and chiral auxiliaries in a variety of asymmetric syntheses; this field has been reviewed.[5–7] For example, chiral amino acids have been incorporated into phosphine and phosphite ligands for asymmetric catalysis.[8,9] However, in many cases the amino acids are not incorporated into the ligand by amide bonds, and most of these ligands contain other functional groups. In addition, many bear the chiral amino acids remote from the metal. In this project, we sought to prepare ligands that resemble peptides in only having amide bonds as functional groups, with the goal that these ligands should be biologically compatible. The ligands are designed to bind to the metal through the deprotonated acid groups of their amino acids.

Incorporation of more than one amino acid into the ligand leads to multiple chiral centres and also to multiple charges. Our final goal is to prepare neutral complexes of divalent and trivalent metals. Thus, we require dianionic and trianionic ligands. For dianionic ligands, iminodiacetic acid (IDA), which resembles glycine, was selected as a basis for the core of the ligands (Fig. 1a); however, the NH bond can participate in peptide coupling and so the methyl substituted methyliminodiacetic acid (MIDA) (Fig. 1b) was prepared. MIDA structurally resembles half an ethylenediaminetetraacetate (EDTA) molecule and was reported 60 years ago.[10] The chelate nitrilotriacetic acid (NTA) (Fig. 1c) was selected as the core for trianionic ligands, because it is extremely cheap, readily available, and also structurally resembles glycine. Thus, amino acids protected at their C-terminus can be coupled to MIDA and NTA. We have adopted the nomenclature A-[X(OY)]$_n$ where A is NTA or MIDA, X is the amino acid, Y is the protecting group or H for the free acid, and $n = 2$ or 3 for MIDA and NTA, respectively.

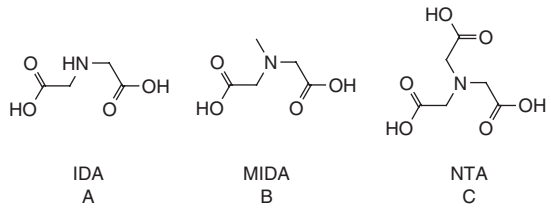

Fig. 1. Cores of ligands synthesized.

IDA has previously been used as the core of small peptide mimics with several different groups as the third substituent on the central nitrogen atom, such as oxycarbonyls.[11,12] However, until now MIDA has not been used as a ligand core. NTA has previously been used as the core of some C_3 symmetric ligands based on a similar synthetic procedure to that reported here, with further synthetic steps to form oxazolines[13–15] or to reduce the amide groups to amines.[16] An NTA-based methyl protected ester of valine, very similar to some of the compounds prepared in this work, NTA-[Val(OMe)]$_3$, has been reported as an intermediate on route to the corresponding oxazoline;[13] the phenylalanine and alanine analogues have also been synthesized.[15] Other C_3 symmetric tripodal peptide bundles have been prepared, using ammonia as the core,[17] and used as metalloenzyme mimics.[18] The current interest in C_3 symmetric compounds as biomimetic ligands and catalysts 'inspired by nature' has been reviewed.[19] Achiral cryptands have recently been reported using NTA in Ugi-type multiple multicomponent macrocyclizations.[20,21] However, simple amino acid derivatives such as those reported here have not been used as ligands. The protected ligands and the acid ligands described here are

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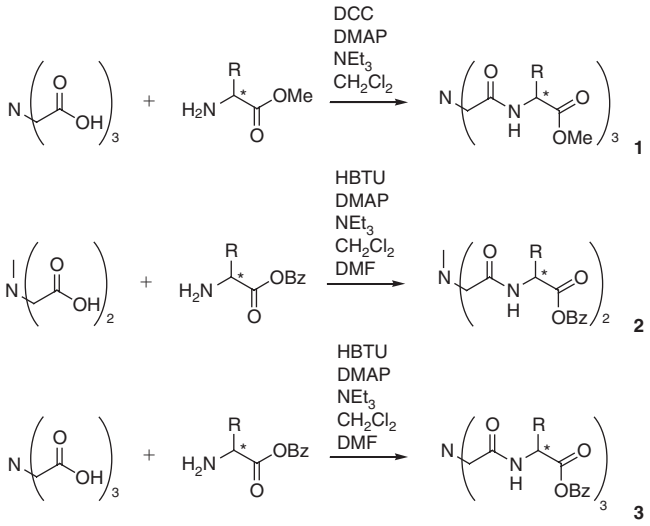


Scheme 1. Solution-phase coupling to form protected ligands NTA-[X(OMe)]$_3$ **1**, MIDA-[X(OBz)]$_2$ **2**, and NTA-[X(OBz)]$_3$ **3**. R = H (Gly), CH_2CHMe_2 (Leu), CH_2Ph (Phe), CH_2COOMe (AspOMe).

previously unreported, although the achiral NTA-[Gly(OH)]$_3$ has been mentioned in a 1992 patent without any characterization data.[22]

To allow access to a wide range of amino acid-containing ligands, solution-phase coupling of the free carboxylic acids of the cores MIDA and NTA with C-protected amino acids was adopted. Both methyl and benzyl protected esters were used in coupling reactions with NTA, and benzyl esters were coupled to MIDA. Standard coupling conditions from solid-phase peptide synthesis were adapted for the coupling reactions. The protected esters were fully characterized and deprotected by standard techniques to form the free di- and tri-acids, which have also been fully characterized. Our synthesis has the advantages of using only cheap and safe starting materials, giving access to a small library of di- and tri-anionic chiral ligands, and was conducted by undergraduate students.

Results and Discussion

Typical solution-phase peptide coupling conditions (DCC or HBTU, DMAP, NEt_3, CH_2Cl_2 solution, overnight, room temperature, see Experimental) were successfully used to couple the methyl and benzyl C-protected amino acids to the carboxylic acids of NTA and MIDA (Scheme 1). Use of DCC as a coupling agent was successful for the methyl esters; however, for the benzyl esters HBTU was adopted because DCC coupling led to low yields. This is presumably because of the steric bulk of the benzyl ester, which limits access of the N-terminus of the amino acid to the activated ester for coupling.

The protected products, other than NTA-[Gly(OMe)]$_3$, are soluble in organic solvents, such as CH_2Cl_2, and were purified by silica gel chromatography and characterized by NMR and IR spectroscopy and high-resolution mass spectrometry. The ^{1}H NMR spectra of these compounds show well resolved coupling constants and all resonances can be unambiguously assigned using a combination of one- and two-dimensional spectra; Fig. 2 shows a typical example. This indicates that no epimerization occurs under the coupling conditions. This is to be expected using conditions adapted from solid-phase peptide synthesis. Methyl-protected D,L-phenylalanine was used in one reaction to verify that an epimerized amino acid leads to a mixture of diastereomers after coupling. In that case the ^{1}H NMR spectrum of the resulting NTA-[Phe(OMe)]$_3$ was very complicated and the coupling constants were not resolved.

Deprotection of the six methyl esters of the protected NTA-[Asp(OMe)(OMe)]$_3$ was achieved using 1.0 M NaOH or LiOH solution (Scheme 2) to form the alkali metal salt of the C_3 ligand. These salts were not suitable for use in metal complexation studies with higher valent metals because the alkali metals were difficult to remove. Thus, the methyl esters were not pursued further.

The benzyl esters were removed by hydrogenolysis over Pd/C (Scheme 3) in ethanol. The protected phenylalanine derivatives MIDA-[Phe(OBz)]$_2$ and NTA-[Phe(OBz)]$_3$ are only sparingly soluble in ethanol but this did not affect the reaction. The solubility of the products of hydrogenolysis is substantially different from the protected compounds; none are soluble in CH_2Cl_2, and all are somewhat soluble in water. The glycine derivatives MIDA-[Gly(OH)]$_2$ and NTA-[Gly(OH)]$_3$ are extremely hygroscopic and could only be isolated as powders when not exposed to air. Upon air exposure, they became sticky oils.

The NMR spectra of the free acids were recorded in D_2O, (D_6)acetone, or deuterated dimethyl sulfoxide ((D_6)DMSO). The resolved coupling constants observed in the ^{1}H NMR spectra indicate that no epimerization occurred during hydrogenolysis, so the newly prepared ligands have C_3 and C_1 symmetry for the NTA and MIDA cores, respectively.

Conclusions

We have demonstrated a cheap, simple, and reliable route to the synthesis of a small library of chiral C_1 dianionic and C_3 trianionic chelating ligands, based on MIDA and NTA cores respectively, with amino acid substituents. Benzyl esters were the most suitable protecting groups for the amino acids because upon deprotection, the free acids are formed. The metal complexation behaviour and acidity of these ligands are currently under investigation.

Experimental

General

2-(1*H*-Benzotriazole-1-yl)-1,1,3,3-tetramethylaminium hexafluorophosphate (HBTU), Leu(OBz)·TsOH and Phe(OBz)·HCl were purchased from NovaBioChem; *N*,*N*-dicyclohexylcarbodiimide (DCC) was purchased from Fluka. All other chemicals and solvents including dimethylaminopyridine (DMAP), triethylamine (NEt_3), and palladium over carbon (Pd/C) were purchased from Aldrich. Gly(OBz)·TsOH was prepared according to the reported method using BzOH and TsOH in C_6H_6.[23] The hydrochloric acid salts of the methyl protected amino acids Gly(OMe)·HCl, Leu(OMe)·HCl, Phe(OMe)·HCl, and Asp(OMe)(OMe)·HCl were prepared from the free amino acids by stirring overnight at room temperature in methanol with 2 equiv. of thionyl chloride, followed by removal of all volatile material under vacuum. Silica gel 60, 0.04–0.06 mm (230–400 mesh) from Scharlau was used for flash column chromatography. Eluents were optimized by TLC on silica gel 60 F_{254} sheets from Merck. A phosphomolybdic acid (PMA) in EtOH dip followed by charring with a hot air gun was used to visualize TLC plates. NMR spectra were collected on Bruker AMX-300, DRX-400, and DRX-500 instruments at room temperature in the solvent specified, and are referenced to residual protons of the proteosolvent for ^{1}H spectra, or to the carbon of the solvent for ^{13}C{^{1}H}

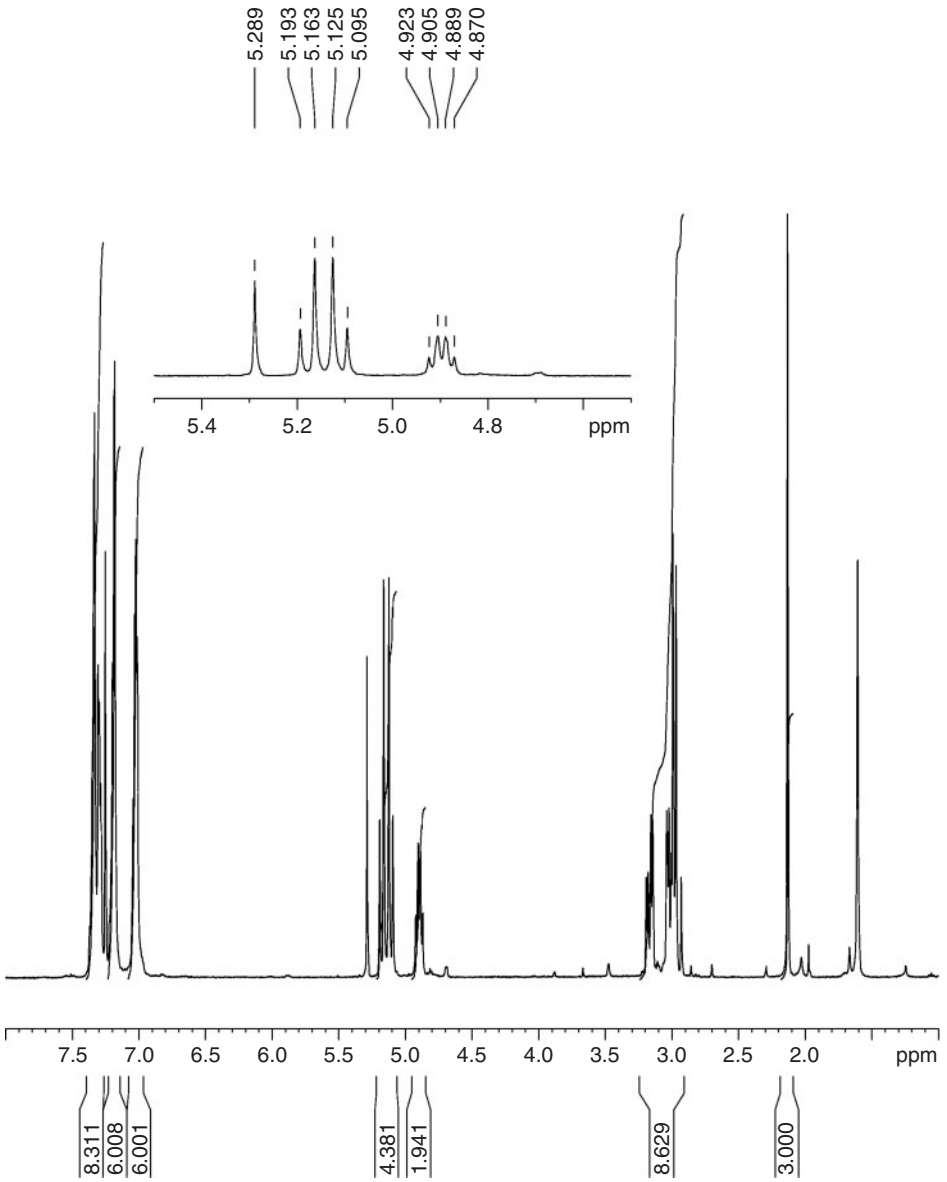
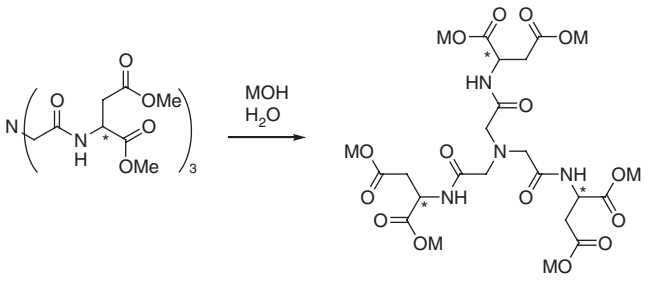


Fig. 2. ^{1}H NMR spectrum of NTA-[Leu(OBz)]$_3$ in $CDCl_3$. The inset shows the resolved coupling of the benzylic protons and the α-proton of the amino acid. The resonance at δ 5.29 is residual CH_2Cl_2.

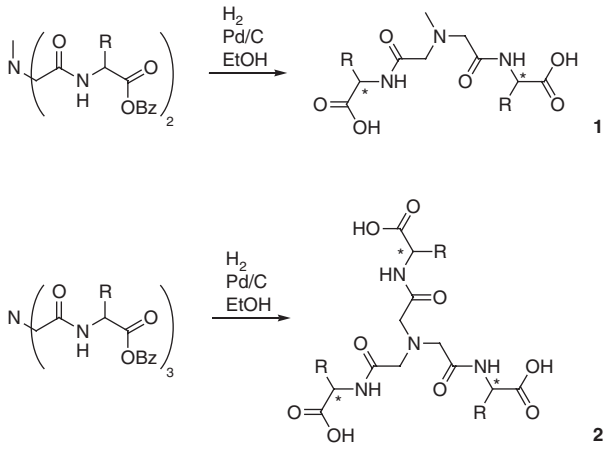


Scheme 2. Deprotection of NTA-[Asp(OMe)(OMe)]$_3$ with NaOH or LiOH (M = Na or Li).

spectra. Assignments are based on a combination of one- and two-dimensional spectra. Infrared spectra were collected on a Perkin–Elmer 1600 or 1000 FTIR using CsF plates or in solution as specified, and only carbonyl stretches are reported. High-resolution mass measurements were obtained from a Finnigan MAT 900 XL-Trap electrospray (ESI) mass spectrometer with a Finnigan API III electrospray source. Low-resolution ESI mass spectrometry was conducted on a Quattro II triple-quadruple liquid chromatography–mass spectrometer (Micromass, Manchester, UK) or a Finnigan MAT 900 XL-Trap electrospray mass spectrometer with a Finnigan API III electrospray source.

Synthesis of MIDA (Modification of a Reported Technique[10])

Iminodiacetic acid (6.65 g, 0.05 mol) was weighed into a round-bottomed flask equipped with a magnetic stirrer bar. Water (6.7 mL, 0.38 mol), formic acid (3.8 mL, 0.10 mol), and formaldehyde (7.5 mL, 0.27 mol) were added and the mixture was stirred overnight at reflux. Ethanol (50 mL) was added to the resulting pale yellow solution, which led to the formation of a white precipitate, which was collected by filtration and washed with ethanol. Yield: 4.18 g (57%). δ_H (500 MHz, 298 K,



Scheme 3. Deprotection of benzyl protected ligands by hydrogenolysis to form free acids MIDA-[X(OH)]$_2$ **1**, and NTA-[X(OH)]$_3$ **2**.

D_2O) 3.83 (s, 4H, MeNCH_2), 2.87 (s, 3H, NMe), carboxylic acid protons not observed. δ_C (125 MHz, 298 K, D_2O) 169.1 (*C*OOH), 57.3 (MeN*C*H_2), 42.4 (NMe).

Typical Conditions for Coupling Benzyl-Protected Amino Acids to MIDA

MIDA (1.10 g, 6.8 mmol) and HBTU (5.69 g, 15 mmol, 2.2 equiv.) were weighed into a flask equipped with a magnetic stirrer bar and dichloromethane (50 mL) was added, followed by DMAP (0.138 g, 1.5 mmol, 0.22 equiv.), NEt_3 (4.17 mL, 30 mmol, 4.4 equiv.), and the benzyl ester of the amino acid to be coupled (15 mmol, 2.2 equiv.). The mixture was stirred overnight at room temperature, after which it was a yellow solution. If a solid precipitated, this was removed by filtration. The product was purified using silica gel chromatography (CH_2Cl_2/MeOH, 96:4). Yield: 45–60% after chromatography. The later column fractions were sometimes contaminated with tetramethylurea, a by-product of coupling by HBTU.

$Me_2NCONMe_2$: δ_H (500 MHz, 298 K, $CDCl_3$) 2.71 (s, NMe_2). δ_C (126 MHz, 298 K, $CDCl_3$) 165.4 (CO), 38.3 (NMe_2).

MIDA-[Gly(OBz)]$_2$: ν_{max}/cm^{-1} (CsF) 1747, 1660. δ_H (400 MHz, 298 K, $CDCl_3$) 7.40 (t, 2H, ^3J 5.8, NH), 7.33–7.30 (m, 10H, $CH_2C_6H_5$), 5.12 (4H, CH_2C$_6$H$_5$), 4.09 (d, 4H, ^3J 5.8, NHCH_2), 3.17 (s, 4H, MeNCH_2), 2.44 (s, 3H, NMe). δ_C (101 MHz, 298 K, $CDCl_3$) 170.3 (CO), 170.0 (CO), 135.0 (*ipso*-C of C_6H_5), 128.6, 128.5, 128.3 (*ortho*, *meta*, *para*-C of C_6H_5), 67.2 (*C*H_2C$_6$H$_5$), 61.2 (MeN*C*H_2), 43.9 (NMe), 40.8 (NHCH). *m*/*z* (ESI$^+$) 480 [M + K], 464 [M + Na], 442 [M + H]. Calc. for $C_{23}H_{28}N_3O_6$: 442.1973 [M + H]. Found: 442.1980.

MIDA-[Leu(OBz)]$_2$: δ_H (500 MHz, 298 K, $CDCl_3$) 7.28 (m, 10H, Bz), 7.20 (br d, 2H, ^3J 8.6, NH), 5.12 (d, 2H, ^2J 27, CH_2Ph), 5.07 (d, 2H, ^2J 27, CH_2Ph), 4.64 (m, 2H, NHC*H*), 3.15 (d, 2H, ^2J 15, MeNCH_2), 3.02 (d, 2H, ^2J 15, MeNCH_2), 2.36 (s, 3H, NMe), 1.61 (m, 2H, C*H*Me$_2$), 1.55 (m, 4H, CHCH_2CH), 0.87 (d, 6H, ^3J 1.7, CHCH_3), 0.86 (d, 6H, ^3J 1.7, CHCH_3). δ_C (125 MHz, 298 K, $CDCl_3$) 172.6 (*C*OOCH$_2$Ph), 169.7 (CONH), 135.1 (*ipso*-C of C_6H_5), 128.1, 127.9, 127.7 (*ortho*, *meta*, *para*-C of C_6H_5), 66.5 (*C*H_2C$_6$H$_5$), 60.7 (MeN*C*H_2), 50.1 (NHCH), 43.2 (NMe), 40.4 (CH*C*H_2CH), 24.5 (*C*HMe$_2$), 22.5 (CHCH_3), 21.2 (CHCH_3). *m*/*z* (ESI$^+$) 1129 [2M + Na], 576 [M + Na], 554 [M + H]. Calc. for $C_{31}H_{43}N_3O_6Na$: 576.3050 [M + Na]. Found: 576.3047.

MIDA-[Phe(OBz)]$_2$: ν_{max}/cm^{-1} (CsF) 1741, 1663. δ_H (400 MHz, 298 K, $CDCl_3$) 7.33–7.01 (m, 22H, Ph and NH), 5.17 (d, 2H, ^2J 12, OCH_2Ph), 5.11 (d, 2H, ^2J 12, OCH_2Ph), 4.90 (m, 2H, NHC*H*), 3.19–2.92 (m, 8H, MeNCH_2 and CHCH_2Ph), 2.13 (s, 3H, NCH_3). δ_C (101 MHz, 298 K, $CDCl_3$) 171.6 (*C*OOCH$_2$Ph), 169.4 (*C*ONH), 135.9 and 135.1 (*ipso*-C of C_6H_5), 129.1, 128.6, 128.6, 128.5, 128.5, 127.0 (*ortho*, *meta*, *para*-C of C_6H_5), 67.3 (OCH_2C$_6$H$_5$), 61.2 (MeN*C*H$_2$), 52.8 (NHCH), 43.6 (NMe), 37.6 (CH*C*H$_2$Ph). *m*/*z* (ESI$^+$) 622.4 [M + H]. Calc. for $C_{37}H_{39}N_3O_6Na$: 644.2731 [M + Na]. Found: 644.2729.

Typical Coupling Conditions of Benzyl Esters to NTA

The solids, NTA (0.15 g, 0.76 mmol) and HBTU (0.96 g, 2.54 mmol, 3.3 equiv.), were placed in a flask equipped with a magnetic stirrer bar. Dichloromethane (50 mL) was added, followed by DMAP (0.062 g, 0.51 mmol, 0.67 equiv.), NEt_3 (1.42 mL, 10.2 mmol, 13 equiv.), and the benzyl-protected amino acid (2.54 mmol, 3.3 equiv.). The mixture was stirred overnight at room temperature, and then washed with dilute HCl (1.0 M) and $NaHCO_3$ (1.0 M), followed by distilled water. The product was purified by silica gel chromatography (CH_2Cl_2/MeOH, 96/4). Yield: 40–60% after chromatography. The later column fractions were sometimes contaminated with tetramethylurea, a by-product of coupling by HBTU.

NTA-[Gly(OBz)]$_3$: δ_H (300 MHz, 298 K, $CDCl_3$) 7.67 (t, 3H, ^3J 6.0, NH), 7.31 (m, 15H, $CH_2C_6H_5$), 5.12 (s, 6H, CH_2C$_6$H$_5$), 4.06 (d, 6H, ^3J 6.0, NHCH_2), 3.37 (s, 6H, NCH_2). δ_C (125 MHz, 298 K, $CDCl_3$) 170.5 (NHCO and *C*OOBz), 135.1 (*ipso*-C of C_6H_5), 128.7, 128.6, 128.3 (*ortho*, *meta*, *para*-C of C_6H_5), 67.3 (*C*H_2C$_6$H$_5$), 58.6 (NCH_2), 41.1 ($NHCH_2$). *m*/*z* (ESI$^+$) 655 [M + Na]. Calc. for $C_{33}H_{36}N_4O_9Na$: 655.2380 [M + Na]. Found: 655.2371.

NTA-[Leu(OBz)]$_3$: ν_{max}/cm^{-1} (CsF) 1746, 1666. δ_H (300 MHz, 298 K, $CDCl_3$) 7.77 (d, 3H, ^3J 8.4, NH), 7.35 (m, 15H, $CH_2C_6H_5$), 5.20 (d, 3H, ^2J 12, CH_2Ph), 5.11 (d, 3H, ^2J 12, CH_2Ph), 4.65 (m, 3H, NHC*H*), 3.41 (d, 3H, $^2J_{HH}$ 15, NCH_2), 3.25 (d, 3H, ^2J 15, NCH_2), 1.73–1.57 (m, 9H, C*H*Me$_2$ and CHCH_2CH), 0.92 (d, 9H, ^3J 3.4, CHCH_3), 0.90 (d, 9H, ^3J 3.4, CHCH_3). δ_C (125 MHz, 298 K, $CDCl_3$) 174.7 (NHCO and *C*OOBz), 140.1 (*ipso*-C of C_6H_5), 128.7, 127.8, 127.4 (*ortho*, *meta*, *para*-C of C_6H_5), 63.8 (*C*H_2C$_6$H$_5$), 58.5 (NCH_2), 52.9 (NHCH), 39.6 (CH*C*H$_2$CH), 24.0 (*C*H(CH$_3$)$_2$), 21.8 (CH*C*H$_3$), 20.8 (CH*C*H$_3$). *m*/*z* (ESI$^+$) 823 [M + Na], 801 [M + H]. Calc. for $C_{45}H_{61}N_4O_9$: 801.4433 [M + H]. Found: 801.4422.

NTA-[Phe(OBz)]$_3$: ν_{max}/cm^{-1} (CsF) 1732, 1660. δ_H (400 MHz, 298 K, $CDCl_3$) 7.60 (d, 3H, ^3J 8.4, N*H*), 7.35–7.12 (m, 30H, C_6H_5), 5.19 (d, 3H, ^2J 12.2, OCH_2Ph), 5.13 (d, 3H, ^2J 12.2, OCH_2Ph), 4.90 (m, 3H, NHC*H*), 3.19–2.91 (m, 12H, NCH_2 and CHCH_2Ph). δ_C (100 MHz, 298 K, $CDCl_3$) 172.6 (*C*H$_3$OOBz), 170.1 (NH*C*H$_3$O), 136.1 and 135.0 (*ipso*-C of C_6H_5), 129.0, 128.5, 128.4, 128.4, 128.2, 126.9 (*ortho*, *meta*, *para*-C of C_6H_5), 67.3 (OCH$_3$H$_2$C$_6$H$_5$), 57.6 (NCH_2), 53.4 (NHCH$_3$H), 37.3 (CH*C*H$_3$H$_2$Ph). *m*/*z* (ESI$^+$) 903 [M + H]. Calc. for $C_{54}H_{55}N_4O_9$: 903.3964 [M + H]. Found: 903.3962.

Typical Coupling Conditions of Methyl Esters to NTA

The solids, NTA (0.27 g, 1.41 mmol) and DCC (1.05 g, 5.10 mmol, 3.6 equiv.), were placed in a flask equipped with a magnetic stirrer bar under nitrogen. Distilled dichloromethane (50 mL) was added, followed by DMAP (0.12 g, 0.98 mmol, 0.7 equiv.), triethylamine (1.29 mL, 9.27 mmol, 6.6 equiv.), and the methyl protected amino acid (4.63 mmol, 3.3 equiv.). The mixture was stirred under nitrogen overnight at room

temperature, and then filtered and washed with dilute acid followed by distilled water. The product was purified by silica gel chromatography (CH_2Cl_2/MeOH, 96/4). Yield: 40–60% after chromatography.

NTA-[Gly(OMe)]$_3$: δ_H (500 MHz, 298 K, $CDCl_3$) 7.77 (br t, 3H, ^3J 3.4, NH), 4.04 (d, 6H, ^3J 3.6, NHCH_2), 3.71 (s, 9H, OMe), 3.39 (s, 6H, NCH_2). δ_H (500 MHz, 298 K, D_2O) 3.98 (s, 6H, NHCH_2), 3.67 (s, 9H, OMe), 3.44 (s, 6H, NCH_2). δ_C (125 MHz, 298 K, $CDCl_3$) 171.2 (*C*OOMe), 170.9 (NH*C*O), 58.7 (NCH_2), 52.4 (COOCH_3), 40.8 ($NHCH_2$). δ_C (125 MHz, 298 K, D_2O) 173.1 (*C*OOMe), 171.4 (NHCO), 57.1 (NCH_2), 52.3 (COOCH_3), 40.5 ($NHCH_2$). *m/z* 427 [M + Na].

NTA-[Phe(OMe)]$_3$ (Mixture of Diastereomers):[15] ν_{max}/cm^{-1} (CH_2Cl_2 solution): ν_{CO} 1738, 1680. δ_H (300 MHz, 298 K, $CDCl_3$) 7.36–7.08 (m, 18H, NH and C_6H_5), 4.79 (m, 3H, NHC*H*), 3.72 (s, 9H, OMe), 3.25–2.90 (m, 12H, CH_2Ph and NCH_2). *m/z* (ESI^+) 697 [M + Na], 675 [M + H]. Calc. for $C_{36}H_{42}N_4O_9Na$ [M + Na]: 697.2849. Found: 697.2839.

NTA-[Leu(OMe)]$_3$: ν_{max}/cm^{-1} (MeOH solution): ν_{CO} 1749, 1664. δ_H (300 MHz, 298 K, $CDCl_3$) 7.71 (br d, 3H, ^3J 8.5, NH), 4.60 (m, 3H, NHC*H*), 3.71 (s, 9H, OMe), 3.41 (d, 3H, ^2J 15, NCH_2), 3.20 (d, 3H, ^2J 15, NCH_2), 1.74–1.56 (m, 9H, C*H*Me_2 and CHCH_2CH), 0.92 (d, 9H, ^3J 2.4, CHCH_3), 0.90 (d, 9H, ^3J 2.3, CHCH_3). δ_C (75 MHz, 298 K, $CDCl_3$) 174.9 (*C*OOMe), 170.5 (*C*ONH), 58.2 (NCH_2), 52.4 (OMe), 50.6 (NHCH), 40.3 (CH*C*H_2CH), 24.8 (*C*HMe_2), 23.0 (CH*C*H_3), 21.3 (CH*C*H_3). *m/z* (ESI^+) 1167 [2M + Na], 1145 [2M + H], 595 [M + Na], 573 [M + H]. Calc. for $C_{27}H_{48}N_4O_9Na$ [M + Na]: 595.3319. Found: 595.3306.

NTA-[Asp(OMe)(OMe)]$_3$: ν_{max}/cm^{-1} (CH_2Cl_2 solution): ν_{CO} 1737, 1681. δ_H (500 MHz, 298 K, $CDCl_3$) 7.72 (d, 3H, ^3J 8.6, NH), 4.92 (m, 3H, NHC*H*), 3.71 (s, 9H, OMe), 3.66 (s, 9H, OMe), 3.46 (d, 3H, ^2J 15, NCH_2), 3.24 (d, 3H, ^2J 15 Hz, NCH_2), 2.99 (dd, 3H, ^2J 17, ^3J 6.0, CHCH_2CO), 2.88 (dd, 3H, ^2J 17, ^3J 4.7, CHCH_2CO). δ_C (125 MHz, 298 K, $CDCl_3$) 171.5 (*C*OOMe), 171.2 (*C*OOMe), 169.8 (NHCO), 58.4 (NCH_2), 52.8 (OMe), 52.1 (OMe), 48.4 (NHCH), 35.8 (CH*C*H_2CO). *m/z* (ESI^+) 643 [M + Na], 621 [M + H]. Calc. for $C_{24}H_{36}N_4O_{15}Na$ [M + Na]: 643.2075. Found: 643.2082.

Typical Deprotection Conditions for Benzyl Esters

A small amount of Pd/C (~2 mg) was added to an ethanol (50 mL) solution or suspension of the compound (~400 mg). The mixture was subjected to a hydrogen atmosphere from a balloon with stirring (NTA-[Gly(OBz)]$_3$, NTA-[Leu(OBz)]$_3$, MIDA-[Leu(OBz)]$_2$), or using a Parr hydrogenator, 30 psi were applied (NTA-[Phe(OBz)]$_3$, MIDA-[Gly(OBz)]$_2$, MIDA-[Phe(OBz)]$_2$). After stirring for 1 h, the solution was filtered through Celite and the solvent was removed under vacuum. The free acids of the glycine derivatives MIDA-[Gly(OH)]$_2$ and NTA-[Gly(OH)]$_3$ are extremely hygroscopic so no yield was recorded. For the other free acids, yields were above 80%.

MIDA-[Gly(OH)]$_2$: δ_H (300 MHz, 298 K, D_2O) 4.01 (s, 4H, CH_2COOH), 3.80 (s, 4H, MeNCH_2), 2.88 (s, 3H, NMe). δ_C (100 MHz, 298 K, D_2O) 175.0 (COOH), 166.1 (CONH), 57.6 (MeN*C*H_2), 43.5 (NMe), 42.7 ($NHCH_2$). *m/z* (ESI^+) 561 [2M + K], 545 [2M + Na], 284 [M + Na], 262 [M + H]. Calc. for $C_9H_{15}N_3O_6Na$: 284.0859 [M + Na]. Found: 284.0868. Because of the hygroscopic nature of this compound, no IR spectrum could be obtained.

MIDA-[Leu(OH)]$_2$: δ_H (300 MHz, 298 K, D_2O) 8.49 (br d, 2H, ^3J 12, NH), 4.17 (m, 2H, NHC*H*), 3.96 (s, 4H, MeNCH_2), 2.86 (s, 3H, N*Me*), 1.49 (m, 6H, C*H*Me_2 and CHCH_2CH), 0.77 (d, 6H, ^3J 10, CHCH_3), 0.74 (d, 6H, ^3J 10, CHCH_3). δ_C (75 MHz, 298 K, D_2O) 177.7 (COOH), 164.8 (CONH), 56.8 (MeN*C*H_2), 52.9 (NHCH), 42.8 (NMe), 39.7 (CH*C*H_2CH), 24.5 (*C*HMe_2), 22.2 (CH*C*H_3), 20.6 (CH*C*H_3). *m/z* (ESI^+) 769 [2M + Na], 747 [2M + H], 396 [M + Na], 374 [M + H]. Calc. for $C_{17}H_{31}N_3O_6Na$: 396.2111 [M + Na]. Found: 396.2116.

MIDA-[Phe(OH)]$_2$: ν_{max}/cm^{-1} (CsF) 1667. δ_H (400 MHz, 298 K, (D_6)DMSO) 8.25 (br, 2H, NH), 7.20 (m, 10H, C_6H_5), 4.50 (ddd, ^3J 9.0, ^3J 9.0, ^3J 4.8, 2H, NHC*H*), 3.11 (dd, 2H, ^2J 13.8, ^3J 4.8, CH_2Ph), 3.01 (br, 4H, NCH_2), 2.91 (dd, 2H, ^2J 13.8, ^3J 9.7, CH_2Ph), 2.03 (br s, NMe) (COOH not observed). δ_C (100 MHz, 298 K, (D_6)DMSO) 172.9 (CONH), 169.2 (br, COOH), 137.7 (*ipso*-C of C_6H_5), 129.2, 128.3, 126.5 (*ortho*, *meta*, *para*-C of C_6H_5), 59.9 (br, NCH_2), 53.2 (NHCH), 42.2 (NMe), 36.6 (CH_2Ph). *m/z* (ESI^+) 442.2 [M + H]. Calc. for $C_{23}H_{28}N_3O_6$: 442.1973 [M + H]. Found: 442.1965.

NTA-[Gly(OH)]$_3$: ν_{max}/cm^{-1} (THF) 1752, 1684. δ_H (300 MHz, 298 K, D_2O) 3.92 (s, 6H, N*H*CH_2), 3.50 (s, 6H, NCH_2) (COOH not observed). *m/z* (ESI^+) 385 [M + Na].

NTA-[Leu(OH)]$_3$: δ_H (500 MHz, 298 K, D_2O) 7.32 (m, 3H, NH), 4.31 (m, 3H, NHC*H*), 3.39 (s, 6H, NCH_2), 1.62–1.52 (m, 9H, C*H*Me_2 and CHCH_2CH), 0.83 (d, 9H, ^3J 3.6, CHCH_3), 0.79 (d, 9H, ^3J 3.5, CHCH_3) (COOH not observed). δ_C (125 MHz, 298 K, D_2O) 176.3 (COOH), 172.7 (CONH), 57.7 (NCH_2), 51.4 (NHCH), 39.3 (CHCH_3H$_2$CH), 24.4 (*C*H_3HMe_2), 22.2 (CH*C*H_3), 20.4 (CH*C*H_3). *m/z* (TOF^+) 531 [M + H].

NTA-[Phe(OH)]$_3$: ν_{max}/cm^{-1} (CsF) 1659. δ_H (400 MHz, 298 K, (D_6)acetone) 8.1 (br, not integrated, NH), 7.23–7.08 (m, 15H, C_6H_5), 4.67 (dd, 3H, ^3J 9.6, ^3J 4.5, NHC*H*), 3.19 (dd, 3H, ^2J 13.9, ^3J 4.5, CH_2Ph), 2.91 (m, 9H, CH_2Ph and NCH_2) (COOH not observed). δ_H (400 MHz, 298 K, (D_6)DMSO) 8.32 (br, 3H, NH), 7.22–7.12 (m, 15H, C_6H_5), 4.54 (br dd, 3H, NHC*H*), 3.12 (dd, 3H, ^2J 13.7, ^3J 4.3, CH_2Ph), 2.87 (br, 9H, NCH_2 and CH_2Ph) (COOH not observed). δ_H (400 MHz, 298 K, D_2O) 7.22 (m, 15H, C_6H_5), 4.65 (br dd, 3H, NHC*H*), 3.30 (dd, 3H, ^2J 14.2, ^3J 4.1, CH_2Ph), 2.91 (dd, 3H, ^2J 13.7, ^3J 10.3, CH_2Ph), 2.57 (d, 3H, ^2J 16.8, NCH_2), 2.51 (d, 3H, ^2J 16.1, NCH_2) (NH and COOH not observed). δ_C (100 MHz, 298 K, (D_6)acetone) 174.1 (COOH), 171.1 (CONH), 138.3 (*ipso*-C of C_6H_5), 130.0, 129.1, 127.4 (*ortho*, *meta*, *para*-C of C_6H_5), 58.3 (NCH_2), 54.3 (NHCH), 37.8 (CH_2Ph). *m/z* (ESI^+) 655.4 [M + Na]. Calc. for $C_{33}H_{36}N_4O_9Na$: 655.2376 [M + Na]. Found: 655.2367.

Deprotection Conditions for NTA-[Asp(OMe)(OMe)]$_3$

The methyl ester (0.50 g, 0.81 mmol) was weighed into a round bottomed flask and distilled water (10 mL) was added. The ester was not completely soluble. Six equivalents of the metal hydroxide (NaOH or LiOH) per NTA were weighed into a separate flask and dissolved in water. The base was added to the ester and the mixture was stirred overnight at room temperature. The water was removed under vacuum leaving a hygroscopic white solid that was insoluble in alcohols or THF.

NTA-[Asp(ONa)(ONa)]$_3$: δ_H (500 MHz, 298 K, D_2O) 4.30 (dd, 3H, ^3J 9.9, ^3J 3.9, NHC*H*), 3.30 (s, 6H, NCH_2), 2.54 (dd, 3H, ^2J 16, ^3J 4.0, CHCH_2), 2.35 (dd, 3H, ^2J 16, ^3J 10, CHCH_2). δ_C (125 MHz, 298 K, D_2O) 178.8 (COONa), 178.5 (COONa), 172.3 (CONH), 56.6 (NCH_2), 53.0 (NHCH), 39.5 (CHCH_2).

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