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Robust Asymmetric Synthesis of Unnatural Alkenyl Amino Acids for Conformationally Constrained α-Helix Peptides

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The efficient asymmetric synthesis of unnatural alkenyl amino acids required for peptide 'stapling' has been achieved using alkylation of a fluorine-modified Ni^{II} Schiff base complex as the key step.

Introduction

The asymmetric synthesis of enantiomerically pure unnatural α-amino acids using chiral auxiliaries or catalysts is an important field of bio-organic chemistry. These amino acids provide the starting materials required to generate peptidomimetic tools for the investigation of protein form and function. Conformationally constraining peptides to adopt the appropriate bioactive conformation decreases the entropic penalty of folding and can provide enhanced binding affinity to target receptors.[1] Employing synthetic, unnatural functionality as the constraining moiety has also been demonstrated to provide a range of other favourable physicochemical and pharmacological properties including improved stability toward peptidase degradation, increased bioavailability and membrane permeability.[2] Conformationally constrained peptides have thus come of age as tools for chemical biology and drug discovery.

Figure 1. (S)-Alkenyl α-methyl α-amino acids required for i, i+4 and i, i+7 peptide conformational constraints.

The majority of research in this area focuses on the regulation of α-helix-mediated protein-protein interactions (PPIs). A plethora of synthetic approaches have therefore been developed to promote α-helical structure in peptides. Examples include: triazole bridge,[3] lactam bridge,[4] hydrogen bond surrogates,[5] disulphide bridges,[6] electrostatic interaction between side chains,[7] and incorporation of α,α-disubstituted amino acids.[8] Blackwell and Grubbs developed an i, i+4 cross-linked peptide via cross metathesis of O-allyl functionalised residues.[9]

Verdine and co-workers expanded this method through the develop of an all hydrocarbon peptide "staple", determining the optimal chain length of α-methyl α-disubstituted unnatural amino acids bearing alkenes for i, i+3, i, i+4, and i, i+7 staples.[10] These hydrocarbon stapled peptides were found to exhibit increased α-helicity and resistance to proteolysis.[11]

Recent literature suggests that peptides stapled with mono-substituted alkenyl amino acids can demonstrate similar improvements in α-helicity and proteolytic stability as their α-methyl α-disubstituted counterparts.[12,13]

During our research into the design and synthesis of peptide conformational constraints we required unnatural alkenyl α-methyl α-amino acids **1** & **2** (Figure 1). The synthesis of these amino acids has previously been achieved by alkylation of alanine-derived oxazinones.[14] We disregarded this method due to the potential for over-reduction of the olefin moiety during the required metal reduction step.[15]

Belekon and co-workers have developed a more convenient method for the synthesis of α-methyl α-disubstituted amino acids that involves α-C-alkylation of chiral Ni^{II} Schiff base complexes derived from alanine. However, in our hands the key alkylation step gave low yield (42%) and poor diastereoselectivity (72% d.e.). The diastereoselectivity of this reaction originates from the benzylproline moiety that sterically hinders one face of the complex. Attempts to increase selectivity have thus focused on modification of the benzylproline functionality within the Ni^{II} Schiff base complex. Introduction of the sterically bulky naphthylmethyl[16] or 2,4,6-trimethylbenzyl[17] functionality are reported to result in either poor chemical yield or complexes with limited solubility. Introduction of halogens onto the aromatic ring of the N-benzylproline moiety have been more successful in enhancing diastereoselectivity.[18] The aim of this work was to develop a robust asymmetric synthesis of enantiopure unnatural alkenyl amino acids required for peptide stapling. Here we report the use of Ni^{II} Schiff base complexes, derived from a 2-fluorobenzyl ligand[18] for the diastereoselective synthesis
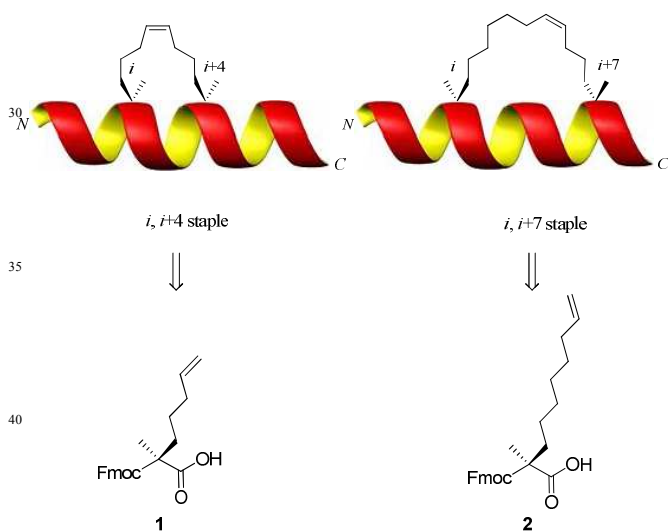
of four alkenyl amino acids required for *i* - *i* + 4 and *i* - *i* + 7 peptide hydrocarbon staples.

The method is notable for the high diastereoselectivities of the alkylation reactions and the fluorinated substituent in the Ni^{II} Schiff base complexes facilitate purity and d.e. analysis by ^{19}F NMR. Insights into the origin of the diastereoselectivity were observed from the X-ray crystal structure of the alkylated Ni^{II} Schiff base complex **9**.

Results and discussion

Our initial aim was the efficient synthesis of the chiral auxiliary (*S*)-*N*-(2-benzoylphenyl)-1-(2-fluorobenzyl)-pyrrolidine-2-carboxamide **4** (2-FBPB) from L-proline (Scheme 1).

N-alkylation of L-proline with 2-fluorobenzyl bromide gave tertiary amine **3** in very good yield. Condensation of **3** with 2-aminobenzophenone using methanesulfonyl chloride and *N*-methylimidazole gave 2-FBPB **4** in respectable yield given the sterically cumbersome nature of the aniline nucleophile. However, the enantiopurity of 2-FBPB **4** was a disappointing 97% e.e. as determined by chiral HPLC and has not previously been reported. We therefore undertook a slow recrystallisation to enrich the desired enantiomer to >99% e.e. (see SI).
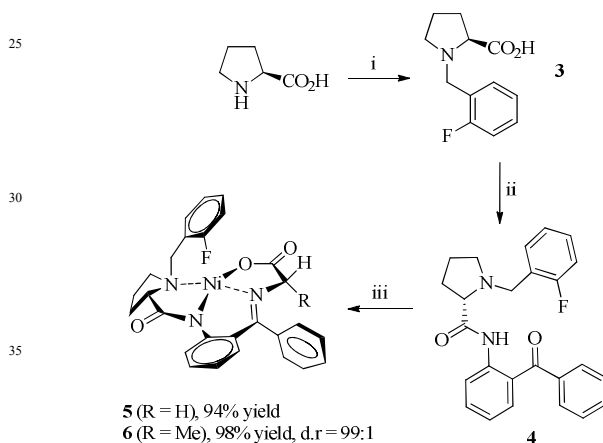
Scheme 1. *Reagents and conditions*: i. 2-fluorobenzylbromide, KOH, ^{i}PrOH, 93%; ii. 2-aminobenzophenone, 1-Me-imidazole, MsCl, CH$_2$Cl$_2$, 50 ^{o}C, 55%; iii. glycine (**5**) or L-alanine (**6**), Ni(NO$_3$)$_2$, KOH, MeOH, 70 ^{o}C.

Complexation of **4** with nickel nitrate and either glycine or L-alanine under basic conditions gave a thermodynamic mixture of diastereomers of nickel Schiff base complexes (*S*)-Ni-Gly-2FBPB **5** and (*S*)-Ni-Ala-2FBPB **6**, respectively, in excellent yield as red crystals that could be stored in air without any significant decomposition (Scheme 1).

With the nickel Schiff base complexes **5** and **6** in hand, we turned our attention to asymmetric alkylation reactions with the appropriate electrophiles to provide the desired alkenyl amino acids required to synthesise stapled peptides.

Stereoselective alkylation of (*S*)-Ni-Gly-2FBPB **5** through formation of the enolate using sodium hydroxide as base followed by nucleophilic substitution reaction with 5-bromopentene gave complex **7** in excellent isolated yield and

diastereoselectivity (>95:5 d.r.) (Scheme 2, entry 1). Under the same reaction conditions, (*S*)-Ni-Gly-2FBPB **5** also underwent efficient, stereoselective alkylation with 8-bromooctene (Scheme 2, entry 2). The α-proton of the amino acid of the glycine derived Schiff base moiety has a pKa of around 11 and can be deprotonated relatively easily under basic reaction conditions. The second α-proton has a pKa of around 15 and so is more difficult to deprotonate, however is labile using these reaction conditions. Addition of alkyl halide at room temperature prevented formation of α,α–dialkylation product.

Thus, the diastereomeric ratio of products obtained from these reactions reflects the position of the thermodynamic equilibrium. The nickel Schiff base complexes produced from these alkylation reactions were isolated in diastereomerically pure form, as red crystalline solids after flash column chromatography.

A further advantage of the 2-FBPB ligand **4** is that ^{19}F NMR spectroscopy can be used to monitor both reaction progression and also diastereoselectivity and constitutes an extremely useful tool functionality.

Alkylation of (*S*)-Ni-Ala-2FBPB **6** with 5-bromopent-1-ene or 8-bromopent-1-ene was also found to be successful when the enolate was formed at 0 ^{o}C and then alkylation at 50 ^{o}C to produce complexes **9** and **10** with good diastereoselectivity and yield (Scheme 2, entries 3 & 4). The α-methyl-α-substituted amino acid functionality produced during these alkylation reactions lacks an α-proton and so no epimerisation can occur, resulting in the kinetic diastereomer as the major product. (*S*)-Ni-Gly-2FBPB **5** gives better diastereoselectivity in comparison with (*S*)-Ni-Ala-2FBPB **6** in part, due to increased temperature of the alkylation reaction required for the latter.


7 R = H,   n = 3
8 R = H,   n = 6
9 R = Me, n = 3
10 R = Me, n = 6
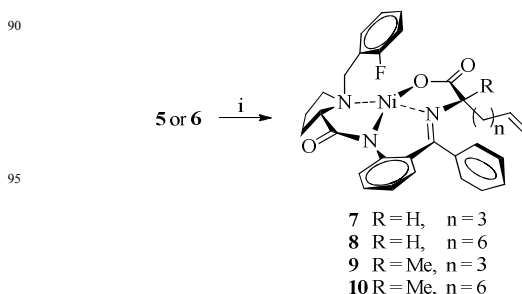
Entry	Initial complex	Alkyl bromide	Product	Isolated yield	d.r
1	**5**	5-Br-pentene	**7**	83%	>95:5
2	**5**	8-Br-octene	**8**	72%	>95:5
3	**6**	5-Br-pentene	**9**	62%	88:12
4	**6**	8-Br-octene	**10**	42%	89:11

Scheme 2. *Reagents and conditions*: i. Br(CH$_2$)$_n$CH=CH$_2$, NaOH, DMF, 0 ^{o}C to RT (R = H) or 50 ^{o}C (R = Me). Alkylation of chiral complexes **5** and **6** (d.r *was determinated by* ^{19}F NMR on crude materials).

The absolute stereochemistry of complexes **7**, **8** and **9** were determined from the x-ray crystal structures (Figure 2 and SI). The crystal structure also gives an insight into the origin of the asymmetric induction. The 2-F-benzyl moiety is positioned across the *Re*-face of the complex and sterically restricts access to the electrophile, forcing reaction from the *Si*-face of the complex

to give the 2*S* configuration at the amino acid α-carbon. It has been proposed that an interaction between the halide atom and the central Ni-atom constrains the complex,[19] however the distance between these two atoms in the crystal structure of complex **9** (3.1 Å) exactly matches the sum of the Van-der-Waals radii and suggests that no such attractive interaction exists in the solid state. Our preferred explanation for the increase in diastereoselectivity using the 2-FBPB ligand, over the BPB ligand is a displaced π- π stacking interaction between the *N*-benzyl functionality and the proline amide bond that constrains the complex. The fluorine atom creates a dipole with positive charge situated on the aromatic that may interact with ionised amide bond oxygen and so will facilitate this interaction.
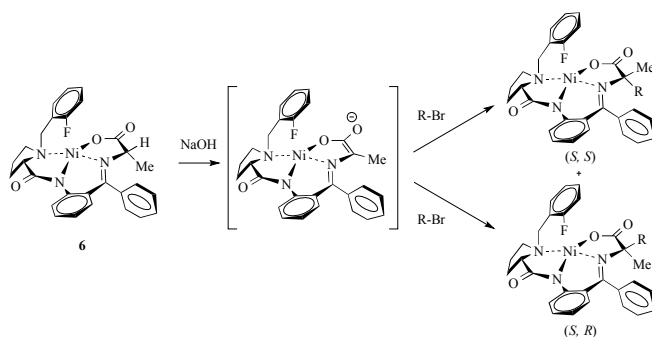
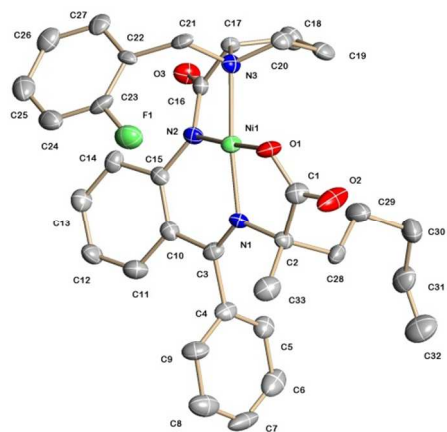**Scheme 3**. Deprotonation and alkylation pathway of **6.**

Figure 2. Crystal structure of compound **9** (hydrogen atoms have been omitted from diagrams).

Alkylated complexes **7-10** were readily decomposed under acidic conditions to give amino acids **11-14** and the chiral auxiliary **4.** Chiral ligand **4** was easily extracted from the crude mixture (enantiomerically pure as assessed by chiral HPLC) and can be reused, thus providing added value to this synthetic method. Purification via ion exchange chromatography gave amino acids **11-14,** which were subsequently treated with Fmoc succinimide under mildly basic conditions to afford Fmoc protected amino acids **1-2**, **15-16** (Scheme 4).
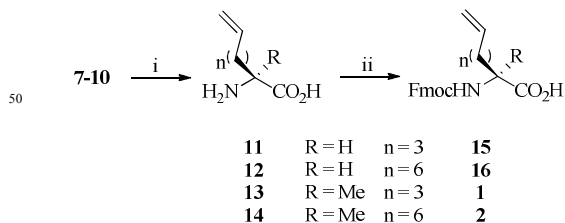
Alkylated complex	Amino acid	Yield	Fmoc-AA	Yield
7	11	60%	15	65%
8	12	67%	16	63%
9	13	65%	1	82%
10	14	68%	2	62%

Scheme 4. *Reagents and conditions*: i. 3 M HCl/MeOH; ii. Fmoc-OSu, K_2CO_3, dioxane/H_2O. Decomposition of alkylated complexes **7-10** to amino acids **11-14** and Fmoc protection to compounds **1-2**, **15-16**.

Conclusions

In summary, the outlined method enabled the diastereoselective synthesis of a range of enantiopure unnatural alkenyl amino acids required for peptide stapling in six steps from proline in up to 17% yield. Incorporation of a fluorine atom on the chiral ligand of the nickel Schiff base complex increases diastereoselectivity of the key alkylation reactions and also facilitates chiral analysis by ^{19}F NMR. Moreover, we observed that the directing effect of the key alkylation step is the result of the electrophile approaching the enolate complex from the opposite face of the proline *N*-benzyl moiety. These features make this method applicable to the large-scale synthesis of custom α,α-disubstituted amino acids. Efforts to establish in-depth structural understanding of the role played by the fluorine atom on diastereoselectivity are currently under active investigation in our laboratories. We are also currently using this method to synthesis other α,α-disubstituted amino acids to develop new peptide conformational constraints.

Experimental

(*S*)-1-(2-Fluorobenzyl)pyrrolidine-2-carboxylic acid (3)

L-Proline (100.0 g, 869.0 mmol) was added to a solution of potassium hydroxide (146.0 g, 2607.0 mmol, 3.0 equiv.) dissolved in isopropyl alcohol (1.0 L) at 40 °C. 2-Fluorobenzyl bromide (15.6 mL, 130 mmol, 1.0 equiv.) was added to the solution drop wise. The solution was allowed to stir at 40 °C for 18 hours and progress was monitored by TLC (MeOH:CH_2Cl_2, 1:4). Aqueous hydrochloric acid (37%) was added drop wise to the mixture until the solution reached pH 6–5 (as determined using a pH probe). The suspension was then cooled in an ice bath, filtered and the filtrate concentrated *in vacuo* to give (*S*)-1-(2-fluorobenzyl)pyrrolidine-2-carboxylic acid as a yellow solid (209.0 g, 93%). m.p: 78-80 °C (EtOH); $[\alpha]^{20}_D$ −24.1 (*c* 0.1 in MeOH); ^{1}H NMR (300 MHz; $CDCl_3$) δ 8.42 (1H, br s, OH), 7.52 (1H, td, *J* = 7.5, 1.3 Hz, Ar-C*H*), 7.35 (1H, m, Ar-C*H*), 7.12 (1H, t, *J*= 7.5 Hz, Ar-C*H*), 7.08 (1H, t, *J* = 8.8 Hz, Ar-C*H*), 4.37 (1H, d, *J* = 13.5 Hz, N-C*H₂*), 4.20 (1H, d, *J* = 13.5 Hz, N-C*H₂*), 3.74 (1H, dd, *J* = 9.2, 6.3 Hz, α-C*H*), 3.59 (1H, ddd, *J* = 10.6, 6.9, 3.8 Hz, δ-C*H₂*), 2.85 (1H, dt, *J*= 9.3, 8.5 Hz, δ-C*H₂*), 2.39-2.13 (2H, m, β-C*H₂*), 2.06-1.81 (2H, m, γ-C*H₂*); ^{13}C NMR (75 MHz;

CDCl$_3$) δ 171.9 (s), 163.0 (s), 132.8 (d), 131.4 (d), 124.8 (d), 119.4 (s), 115.9 (d), 67.3 (d), 53.5 (t), 50.9 (t), 29.0 (t), 23.0 (t). Additional peaks arise from rotamers at 131.2, 119.2 and 115.6; ^{19}F NMR (282 MHz; CDCl$_3$) −116.3 (s); IR (ν$_{max}$/cm^{-1}, neat): 3458, 3013, 2970, 1736, 1618, 1443, 1369, 1229, 1109, 898, 758; HRMS-ESI (calcd for C$_{12}$H$_{15}$NO$_2$F [M+H]$^+$) 224.1087, found 224.1091 (Δ = 1.8 ppm).

(*S*)-*N*-(2-Benzoylphenyl)-1-(2-fluorobenzyl)pyrrolidine-2-carboxamide ((2*S*)-FBPB) (4)

Methanesulfonyl chloride (1.0 mL, 13.4 mmol, 1.0 equiv.) was added to a solution of (*S*)-1-(2-fluorobenzyl)pyrrolidine-2-carboxylic acid **3** (3.0 g, 13.4 mmol) and *N*-methylimidazole (2.4 mL, 29.6 mmol, 2.2 equiv.) in CH$_2$Cl$_2$ (30.0 mL) at 0 °C. After 5 minutes 2-aminobenzophenone (2.4 g, 12.1 mmol, 0.9 equiv.) was added. The reaction mixture was heated to 50 °C for 12 hours, cooled and then saturated aqueous sodium hydrogen carbonate solution (30.0 mL) was added. The two layers were separated and the aqueous layer extracted with CH$_2$Cl$_2$ (3 x 30.0 mL). The combined organic layers were dried (MgSO$_4$) and concentrated *in vacuo*. Purification by flash column chromatography (15% ethyl acetate/hexane) followed by a recrystallisation with hexane and few drops of EtOAc gave the title compound as a pale yellow crystals (2.7 g, 55%). m.p: 88-90 °C (hexane/EtOAc); [α]$_D$ ^{30} −125.1 (*c* 0.25, MeOH); ^{1}H NMR (300 MHz; CDCl$_3$) δ 11.41 (1H, s, NH), 8.56 (1H, dd, *J* = 8.4, 1.0 Hz, Ar-C*H*), 7.79-7.73 (2H, m, Ar-C*H*), 7.61 (1H, td, *J* = 6.9, 1.1 Hz), 7.57-7.44 (5H, m, Ar-C*H*), 7.15-7.04 (2H, m, Ar-C*H*), 6.93 (1H, td, *J* = 7.4, 1.2 Hz, Ar-C*H*), 6.80 (1H, td, *J* = 9.0, 1.2 Hz, Ar-C*H*), 3.89 (1H, d, *J* = 13.3 Hz, N-C*H*$_2$), 3.73 (1H, dd, *J* = 13.3, 1.2 Hz, N-C*H*$_2$), 3.36 (1H, dd, *J* = 10.2, 4.7 Hz, α-C*H*), 3.24 (1H, m, β-C*H*$_2$), 2.48 (1H, m, β-C*H*$_2$), 2.25 (1H, m, δ-C*H*$_2$), 1.96 (1H, m, δ-C*H*$_2$), 1.89-1.73 (2H, m, γ-C*H*$_2$).; ^{13}C NMR (75 MHz; CDCl$_3$) δ 197.8 (s), 174.3 (s), 139.0 (s), 138.6 (s), 133.2 (d), 132.4 (d), 131.6 (d), 130.0 (d), 128.9 (d), 128.8 (d), 128.2 (d), 125.6 (s), 124.9 (s), 124.8 (s), 123.9 (d), 123.8 (d), 122.2 (d), 121.4 (d), 115.2 (d), 114.9 (d), 67.9 (d), 53.7 (t), 52.0 (t), 31.0 (t), 24.2 (t); ^{19}F NMR (376 MHz; CDCl$_3$) −117.5 (s); IR (ν$_{max}$/cm^{-1}, neat): 3276, 1682, 1647, 1577, 1512, 1444, 1286, 1266, 1102, 923, 768, 697; HRMS-ESI (calcd for C$_{25}$H$_{24}$N$_2$O$_2$F [M+H]$^+$) 403.1822, found 403.1825 (Δ = 0.7 ppm); HPLC (OD-H column, hexane (5%)/^{i}PrOH isocratic): 15.2 min. X-rays: see SI.

General method of formation of Gly-Ni or Ala-Ni complexes (5)-(6).

(*S*)-*N*-(2-Benzoylphenyl)-1-(2-fluorobenzyl)pyrrolidine-2-carboxamide (2-FBPB) **4** (9.0 g, 22.4 mmol, 1.0 equiv.), Ni(NO$_3$)$_2$.6H$_2$O (13.0 g, 44.7 mmol, 2.0 equiv.) and glycine (3.4 g, 44.7 mmol, 2.0 equiv.) were dissolved in methanol (225.0 mL, 0.1 M) at 50 °C. Potassium hydroxide (8.8 g, 156.5 mmol, 7.0 equiv.) was added and the mixture was heated to 70 °C for 1 hour. The reaction mixture was cooled and then concentrated. The resulting residue was taken up in water (200.0 mL) and extracted with EtOAc (3 x 200.0 mL). The combined organic layers were washed with saturated brine solution (3 x 600.0 mL), dried (MgSO$_4$) and concentrated *in vacuo* to give the title compound as a red crystalline solid.

(*S*)-({2-[1-(2-Fluorobenzyl)benzyl)pyrrolidine-2-carboxamide]phenyl}phenylmethylene)-glycinato-*N,N',N'',O*}nickel (II) (Ni-Gly-2-FBPB) (5)

Yield 94%; m.p: 124-126 °C (hexane/EtOAc) (lit: 125-127 °C)[18]; [α]$_D$ ^{20} +1897.9 (*c* 0.05, CHCl$_3$) (lit: +1300.0 (*c* 0.05, CHCl$_3$)[18]; ^{1}H NMR (400 MHz, CDCl$_3$) δ 8.40 (1H, dd, *J* = 7.8, 1.6 Hz, Ar-C*H*), 8.35 (1H, d, *J* = 9.0 Hz, Ar-C*H*), 7.63-7.50 (3H, m, Ar-C*H*), 7.37 (1H, m, Ar-C*H*), 7.33-7.23 (2H, m, Ar-C*H*), 7.21-7.10 (2H, m, Ar-C*H*), 7.03 (1H, m, Ar-C*H*), 6.87 (1H, d, *J* = 8.2 Hz, Ar-C*H*), 6.76 (1H, t, *J* = 7.8 Hz, Ar-C*H*), 4.52 (1H, d, *J* = 12.9 Hz, N-C*H*$_2$), 3.98 (1H, d, *J* = 12.9 Hz, N-C*H*$_2$), 3.82 (1H, d, *J* = 20.3 Hz, CH$_2$), 3.72 (1H, m, δ-C*H*$_2$), 3.70 (1H, d, *J* = 20.3 Hz, CH$_2$), 3.5 (1H, dd, *J* = 10.6, 5.9 Hz, α-C*H*$_2$), 3.41 (1H, m, γ-C*H*$_2$), 2.71 (1H, m, β-C*H*$_2$), 2.51 (1H, m, β-C*H*$_2$), 2.24-2.06 (2H, m, δ-C*H*$_2$); ^{13}C NMR (100 MHz, CDCl$_3$) δ 181.0 (s), 177.9 (s), 171.7 (s), 142.5 (s), 134.6 (s), 134.3 (s), 133.3 (d), 132.3 (d), 131.5 (d), 131.4 (d), 129.8 (d), 129.7 (d), 129.4 (d), 126.3 (s), 125.7 (s), 125.3 (d), 124.6 (d), 121.0 (d), 120.4 (s), 116.3 (d), 116.0 (d), 70.1 (d), 61.3 (t), 57.3 (t), 55.8 (t), 30.7 (t), 23.7 (t); ^{19}F NMR (376 MHz; CDCl$_3$) −113.6 (s).; IR (ν$_{max}$/cm^{-1}, neat): 2935, 2354, 1672, 1634, 1588, 1490, 1471, 1440, 1362, 1334, 1256, 1165, 1111, 1063, 962, 754, 723, 704.; HRMS-ESI (calcd for C$_{27}$H$_{24}$N$_3$O$_3$F^{58}Ni [M+H]$^+$) 516.1233, found 516.1224 (Δ = −1.7 ppm); HPLC (OD-H column, hexane (50%)/^{i}PrOH isocratic): 18.76 min. X-rays: see SI.

(*S*)-({2-[1-(2-Fluorobenzyl)pyrrolidine-2-carboxamide]phenyl}phenylmethylene)-(*S*)-alaninato-*N,N',N'',O*}nickel(II) and (*S*)-({2-[1-(2-Fluorobenzyl)pyrrolidine-2-carboxamide]phenyl}phenylmethylene)-(*R*)-alaninato-*N,N',N'',O*}nickel(II) (Ni-Ala-2-FBPB) (6)

Yield 98%, 99:1 d.r; m.p: 284-286 °C (hexane/EtOAc) (lit: 283-285 °C)[18]; [α]$_D$ ^{20} + 3664.5 (*c* 0.05 in CHCl$_3$) (lit: + 3126.6 (*c* 0.05 in CHCl$_3$)[18]; ^{1}H NMR (400 MHz, CDCl$_3$) δ 8.33 (1H, td, *J* = 7.3 Hz, Ar-C*H*), 8.13 (1H, dd, *J* = 8.6 Hz, Ar-C*H*), 7.53-7.49 (2H m, Ar-C*H*), 7.46 (1H, m, Ar-C*H*), 7.27-7.20 (2H, m, Ar-C*H*), 7.20-7.13 (2H,m, Ar-C*H*), 7.06 (1H, ddd, *J* = 9.8, 8.2 Hz, Ar-C*H*), 6.96 (1H, m, Ar-C*H*), 6.71-6.63 (2H, m, Ar-C*H*), 4.41 (1H, dd, *J* = 12.9, 1.2, N-C*H*H), 3.91 (1H, q, *J* = 7.0 Hz, α-C(Me)*H*), 3.83 (1H, dd, *J* = 12.9, 0.8, N-CH*H*), 3.70 (1H, m, β(Pro)-C*H*H), 3.55-3.46 (2H, m, α(Pro)-C*H*, γ(Pro)-CH*H*), 2.38 (1H, m, δ(Pro)-C*H*H), 2.57 (1H, m, δ(Pro)-CH*H*), 2.22 (1H, m, γ(Pro)-CH*H*), 2.07 (1H, m, β(Pro)-CH*H*), 1.58 (3H, d, *J* = 7.0 Hz, C*H*$_3$); ^{13}C NMR (100 MHz, CDCl$_3$) δ 180.4 (s), 180.1 (s), 170.3 (s), 142.1 (s), 134.2 (d), 133.5 (s), 133.2 (d), 132.1 (d), 129.7 (d), 128.9 (d), 127.5 (d), 127.2 (d), 126.6 (s), 124.5 (d), 123.9 (d), 120.8 (d), 120.5 (s), 119.8 (s), 117.9 (d), 116.2 (d), 116.0 (d), 70.3 (d), 66.6 (d), 57.1 (t), 55.6 (t), 30.7 (t), 24.1 (t), 21.8 (q); ^{19}F NMR (376 MHz, CDCl$_3$) δ −113.9 (s); IR (ν$_{max}$/cm^{-1}, neat) 1680, 1626, 1593, 1440, 1359, 1330, 1302, 1266, 1231, 1168, 1064, 7621, 748, 710, 682; HRMS-ASAP (calcd for C$_{28}$H$_{27}$N$_3$O$_3$F^{58}Ni [M+H]$^+$) 530.1390, found 530.1397 (Δ = 1.3 ppm), (calcd for C$_{28}$H$_{27}$N$_3$O$_3$F^{60}Ni [M+H]$^+$) 532.1344, found 532.1381 (Δ = 7.0 ppm); HPLC: OD-H column, hexane (50%)/^{i}PrOH isocratic: 14.71 min. X-rays: see SI.

General method of alkylation of (5)-(6) with alkyl bromides.

Freshly ground sodium hydroxide (0.54 g, 13.4 mmol, 4.0 equiv.) was taken up in DMF (20.0 mL) with stirring at 0 °C under an atmosphere of nitrogen. (*S*)-({2-[1-(2-Fluorobenzyl)pyrrolidine-2-carboxamide]phenyl}phenylmethylene)-glycinato-*N,N',N'',O*}nickel(II) **5** (1.73 g, 3.4 mmol, 1.0 equiv.) was added and stirred for 2 minutes; the solution darkened in colour and the ice bath was removed. A solution of 1-bromo-4-pentene (1.2 mL, 10.1 mmol, 3.0 equiv.) was added to reaction mixture. The solution was left to stir for 15 minutes at room temperature (for Gly-Ni-2-FBPB **5**), or for 1 h at 50 °C (for Ala-Ni-2-FBPB **6**) then quenched with the addition of water. The mixture was concentrated *in vacuo*, taken up in water (20.0 mL) and extracted with dichloromethane (3 x 25.0 mL). The combined organic

extracts were washed with aqueous lithium chloride solution (5% v/v) (3 x 50.0 mL), brine (3 x 50.0 mL), dried (MgSO₄) and concentrated *in vacuo*. Purification by flash column chromatography (EtOAc/hexane 1:1) gave the title compound as a deep red-orange solid.

(S)-({2-[1-(2-Fluorobenzyl)benzyl)pyrrolidine-2-carboxamide]phenyl}phenylmethylene)-(S)-pentenylglycinato-*N,N',N'',O*}nickel (II) (Ni-α-pent-4-enyl gly-2-FBPB) (7)

Yield 83%; m.p: 170-172 °C (hexane/EtOAc).; [α]$_D^{20}$ +2813.2 (*c* 0.05 in CHCl₃) (lit: +2172 (*c* 0.1, MeOH, 25 °C)[20]; ¹H NMR (400 MHz, CDCl₃) δ 8.31 (1H, t, *J* = 6.7 Hz, Ar-C*H*), 8.18 (1H, d, *J* = 8.6 Hz, Ar-C*H*), 7.57-7.41 (3H, m, Ar-C*H*), 7.32-7.20 (2H, m, Ar-C*H*), 7.16 (2H, t, *J* = 7.0 Hz, Ar-C*H*), 7.05 (1H, t, *J* = 8.8 Hz, Ar-C*H*), 6.92 (1H, d, *J* = 7.0 Hz, Ar-C*H*), 6.72-6.60 (2H, m, Ar-C*H*), 5.72 (1H, tdd, *J* = 13.3, 5.9, 4.3 Hz, C*H*=CH₂), 5.06-4.91 (2H, m, CH=C*H₂*), 4.44 (1H, d, *J* = 12.9 Hz, N-C*H₂*), 3.91 (1H, dd, *J* = 7.6, 3.3 Hz), 3.85 (1H, d, *J* = 12.9 Hz, N-C*H₂*), 3.61-3.40 (3H, m), 2.84 (1H, m), 2.56 (1H, m), 2.31-1.84 (6H, m), 1.78-1.55 (2H, m); ¹³C NMR (100 MHz, CDCl₃) δ 180.0 (s), 179.2 (s), 170.4 (s), 160.3 (s), 142.2 (s), 137.7 (d), 134.2 (d), 133.8 (s), 133.3 (d), 132.1 (d), 131.2 (d), 129.7 (d), 128.9 (d), 128.8 (d), 127.6 (d), 127.1 (d), 126.6 (s), 124.5 (d), 123.6 (d), 120.7 (d), 120.4 (s), 116.2 (d), 115.9 (d), 115.2 (t), 70.4 (d), 56.7 (t), 55.6 (t), 34.7 (t), 33.3 (t), 30.6 (t), 24.5 (t), 23.6 (t); ¹⁹F NMR (376 MHz; CDCl₃) −113.9 (s).; IR (ν$_{max}$/cm⁻¹, neat): 2920, 2854, 1645, 1333, 1256, 1168, 752; HRMS-ESI (calcd for C₃₂H₃₃N₃O₃F⁵⁸Ni [M+H]⁺) 584.1895, found 584.1893 (Δ = 4.6 ppm), (calcd for C₃₂H₃₃N₃O₃F⁶⁰Ni [M+H]⁺) 586.1814, found 586.1841(Δ = −1.7 ppm); HPLC (OD-H column, hexane (50%)/*ⁱ*PrOH isocratic): 14.23 min. X-rays: see SI.

(S)-({2-[1-(2-Fluorobenzyl)benzyl)pyrrolidine-2-carboxamide]phenyl}phenylmethylene)-(S)-octenylglycinato-*N,N',N'',O*}nickel (II) (Ni-α-oct-7-enylgly-2-FBPB) (8)

Yield 72%; **m.p**: 144-146 °C (hexane/EtOAc; **[α]$_D^{20}$** +3013.3 (*c* 0.05 in CHCl₃); ¹H NMR (400 MHz, CDCl₃) δ 8.31 (1H, td, *J* = 7.3, 1.8 Hz, Ar-C*H*), 8.18 (1H, d, *J* = 8.6 Hz, Ar-C*H*), 7.56-7.42 (3H, m, Ar-C*H*), 7.26-7.14 (4H, m, Ar-C*H*), 7.04 (1H, t, *J* = 9.4 Hz, Ar-C*H*), 6.92 (1H, d, *J* = 6.7 Hz, Ar-C*H*), 6.67 (2H, m, Ar-C*H*), 5.79 (1H, tdd, *J* = 10.2, 7.0, 3.1 Hz, C*H*=CH₂), 5.04-4.91 (2H, m, CH=C*H₂*), 4.45 (1H, d, *J* = 12.9 Hz), 3.92 (1H, dd, *J* = 7.8, 3.1 Hz), 3.86 (1H, d, *J* = 12.9 Hz), 3.62-3.44 (3H, m), 2.86 (1H, m), 2.57 (1H, m), 2.23-2.12 (2H, m), 2.11-1.99 (3H, m), 1.93 (1H, m), 1.73-1.57 (2H, m), 1.41-1.24 (4H, m), 1.23-1.07 (2H, m); ¹³C NMR (100 MHz, CDCl₃) δ 180.0 (s), 179.4 (s), 170.3 (s), 160.4 (s), 142.3 (s), 138.9 (d), 134.2 (d), 133.9 (s), 133.3 (d), 132.1 (d), 131.2 (d), 139.7 (d), 129.7 (d), 128.8 (d), 127.6 (d), 127.2 (d), 126.7 (s), 124.5 (d), 123.7 (d), 120.7 (d), 120.4 (s), 116.2 (d), 116.0 (d), 114.3 (t), 70.5 (d), 56.8 (t), 55.6 (t), 35.3 (t), 33.7 (t), 30.7 (t), 29.2 (t), 28.9 (t), 28.8 (t), 25.3 (t), 23.6 (t). Additional peaks arise from rotamers at 131.1 (d), 128.9 (d), 124.4 (d), 120.3 (s), 70.4 (d); ¹⁹F NMR (376 MHz; CDCl₃) 113.7 (s); IR (ν$_{max}$/cm⁻¹, neat): 3020, 1741, 1365, 1222; HRMS-ESI (calcd for C₃₅H₃₉N₃O₃F⁵⁸Ni [M+H]⁺) 626.2329, found 626.2321 (Δ = −1.3 ppm), (calcd for C₃₅H₃₈N₃O₃FNa⁵⁸Ni [M+Na]⁺) 648.2148, found 648.2155 (Δ = 1.1 ppm); HPLC (OD-H column, hexane (50%)/*ⁱ*PrOH isocratic): 13.62 min. X-rays: see SI.

(S)-({2-[1-(2-Fluorobenzyl)benzyl)pyrrolidine-2-carboxamide]phenyl}phenylmethylene)-(S)-

pentenylalaninato-*N,N',N'',O*}nickel (II) (Ni-α-pent-4-enyl Ala-2-FBPB) (9)

Yield 62%; m.p: 190-192 °C (hexane/EtOAc); [α]$_D^{20}$ +2271.2 (*c* 0.05, CHCl₃); ¹H NMR (500 MHz, CDCl₃) δ 8.29 (1H, td, *J* = 7.4, 1.0 Hz, Ar-C*H*), 8.03 (1H, d, *J* = 8.5 Hz, Ar-C*H*), 7.51-7.44 (2H, m, Ar-C*H*), 7.38 (1H, m, Ar-C*H*), 7.33 (1H, m, Ar-C*H*), 7.29 (1H, m Ar-C*H*), 7.20 (1H, t, *J* = 7.4 Hz, Ar-C*H*), 7.16 (1H, ddd, *J* = 8.4, 6.2, 2.2 Hz, Ar-C*H*), 7.06 (1H, t, *J* = 9.1 Hz, Ar-C*H*), 6.97 (1H, d, *J* = 7.6 Hz, Ar-C*H*), 6.68-6.61 (2H, m, Ar-C*H*), 5.86 (1H, ddt, *J* = 17.0, 10.3, 6.5 Hz, C*H*=CH₂), 5.08 (1H, dd, *J* = 17.0, 1.0 Hz, CH=C*H₂cis*), 5.02 (1H, d, *J* = 10.3 Hz, CH=C*H₂trans*), 4.52 (1H, d, *J* = 13.1 Hz, N-C*H*H*), 3.95 (1H, d, *J* = 13.1 Hz, N-CH*H*), 3.60 (1H, dd, *J* = 9.9, 6.5 Hz, α(Pro)-C*H*), 3.41 (1H, dd, *J* = 10.7, 6.4 Hz, δ(Pro)-C*H*H), 3.26 (1H, m, β(Pro)-C*H*H), 2.78 (1H, m, γ(Pro)-C*H*H), 2.52 (1H, m, γ(Pro)-CH*H*), 2.40 (1H, m, γ-CH*H*), 2.17-1.98 (5H, m, δ-C*H₂*, γ-CH*H*, δ(Pro)-CH*H*, β(Pro)-CH*H*), 1.75-1.62 (2H, m, β-C*H₂*), 1.23 (3H, s, C*H₃*); ¹³C NMR (126 MHz, CDCl₃) δ 182.3 (s), 180.1 (s), 172.4 (s), 141.5 (s), 137.8 (d), 136.5 (s), 134.2 (d), 133.4 (d), 131.6 (d), 131.3 (d), 130.3 (d), 129.4 (d), 128.7 (s), 127.9 (d), 127.3 (s), 126.9 (d), 124.5 (d), 124.0 (d), 120.8 (d), 120.3 (s), 116.2 (d), 116.0 (d), 115.4 (t), 78.1 (s), 70.1 (d), 56.7 (t), 55.9 (t), 39.8 (t), 33.7 (t), 30.5 (t), 29.6 (q), 25.2 (t), 23.2 (t); ¹⁹F NMR (376 MHz, CDCl₃) δ −113.7 (s); IR (ν$_{max}$/cm⁻¹, neat) 2927, 2854, 1662, 1635, 1435, 1354, 1334, 1254, 1234, 1163, 1111, 1064, 765, 745, 708, 698, 673; HRMS-ASAP (calcd for C₃₃H₃₅N₃O₃F⁵⁸Ni [M+H]⁺) 598.2016, found 598.2004 (Δ = −2.0 ppm), (calcd for C₃₃H₃₅N₃O₃F⁶⁰Ni [M+H]⁺) 600.1970, found 600.1999 (Δ = 4.8 ppm); HPLC (OD-H column, hexane (60%)/*ⁱ*PrOH isocratic): 10.78 min. X-rays: see SI.

(S)-({2-[1-(2-Fluorobenzyl)benzyl)pyrrolidine-2-carboxamide]phenyl}phenylmethylene)-(S)-octenylalaninato-*N,N',N'',O*}nickel (II) (Ni-α-oct-4-enyl-Ala- 2-FBPB) (10)

Yield 42%; m.p: 70-72 °C (hexane/EtOAc); [α]$_D^{20}$ +1978.1 (*c* 0.05, CHCl₃); ¹H NMR (500 MHz, CDCl₃) δ 8.29 (1H, td, *J* = 7.5, 1.2 Hz, Ar-C*H*), 8.03 (1H, d, *J* = 9.1 Hz, Ar-C*H*), 7.50-7.44 (2H, m, Ar-C*H*), 7.38 (1H, m, Ar-C*H*), 7.34 (1H, m, Ar-C*H*), 7.29 (1H, m, Ar-C*H*), 7.20 (1H, td, *J* = 7.6, 1.2 Hz, Ar-C*H*), 7.15 (1H, ddd, *J* = 8.5, 6.2, 2.4 Hz, Ar-C*H*), 7.09 (1H, t, *J* = 9.1 Hz, Ar-C*H*), 6.95 (1H, d, *J* = 7.9 Hz, Ar-C*H*), 6.68-6.61 (2H, m, Ar-C*H*), 5.81 (1H, ddt, *J* = 17.1, 10.3, 6.8 Hz, C*H*=CH₂), 5.01 (1H, dq, *J* = 17.1, 1.6 Hz, CH=C*H₂cis*), 4.94 (1H, m, CH=C*H₂trans*), 4.52 (1H, d, *J* = 13.1 Hz, N-C*H*H), 3.96 (1H, d, *J* = 13.1 Hz, N-CH*H*),), 3.59 (1H, dd, *J* = 10.1, 6.6 Hz, α(Pro)-C*H*), 3.41 (1H, dd, *J* = 10.5, 6.6 Hz, δ(Pro)-C*H*H), 3.27 (1H, m, β(Pro)-C*H*H), 2.77 (1H, m, γ(Pro)-C*H*H), 2.52 (1H, m, γ(Pro)-CH*H*), 2.35 (1H, m, γ-CH*H*),), 2.12-1.97 (5H, m, δ-C*H₂*, γ-CH*H*, δ(Pro)-CH*H*, β(Pro)-CH*H*), 1.69 (1H, td, *J* = 13.3 Hz, η-C*H*H), 1.58 (1H, m, η-CH*H*), 1.48-1.37 (4H, m, β-C*H₂*, ε-C*H₂*),1.37-1.27 (2H, m, ζ-C*H₂*), 1.23 (3H, s, C*H₃*); ¹³C NMR (126 MHz, CDCl₃) δ 182.5 (s), 180.1 (s), 172.4 (s), 141.5 (s), 138.9 (d), 136.5 (s), 134.2 (d), 133.4 (d), 131.6 (d), 131.3 (d), 130.4 (d), 129.4 (d), 128.5 (s), 128.0 (d), 127.3 (s), 126.9 (d), 124.6 (d), 124.0 (d), 120.8 (d), 120.5 (s), 116.3 (d), 116.1 (d), 114.4 (t), 78.3 (s), 70.1 (d), 56.7 (t), 55.9 (t), 40.3 (t), 33.8 (t), 30.6 (t), 29.7 (q), 29.6 (t), 29.2 (t), 28.9 (t), 20.0 (t), 23.22 (t); ¹⁹F NMR (376 MHz, CDCl₃) δ −113.7 (s); IR (ν$_{max}$/cm⁻¹, neat) 2923, 2858, 1672, 1639, 1574, 1490, 1456, 1438, 1352, 1251, 1165, 1112, 1062, 903, 750, 711, 669; HRMS-ASAP: (calcd for C₃₆H₄₁N₃O₃F⁵⁸Ni [M+H]⁺) 640.2485, found 640.2485 (Δ = 0 ppm), (calcd for C₃₆H₄₁N₃O₃F⁶⁰Ni [M+H]⁺) 642.2440, found 642.2471 (Δ = 4.8 ppm); HPLC (OD-H column, hexane (50%)/*ⁱ*PrOH isocratic): 8.34 min.

General method of formation of amino acids (11)-(14).

(*S*)-({2-[1-(2-Fluorobenzyl)pyrrolidine-2-carboxamide]phenyl}phenylmethylene)-(*S*)-pentenylglycinato-*N,N',N'',O*}nickel(II) **5** (0.49 g, 0.87 mmol, 1.0 equiv.) was dissolved in methanol (52 mL) and added drop wise to 3 M
5 hydrochloric acid (7.0 mL) at 70 °C, over 5 minutes. The solution was stirred for 30 minutes, a colour change of red to a transparent green/yellow was observed. The reaction was cooled to room temperature and methanol removed *in vacuo*. The residue was taken up in water (25.0 mL) and extracted with dichloromethane
10 (3 x 25.0 mL). The organic extracts were combined, dried (MgSO₄) and concentrated *in vacuo* to reclaim compound **4** for re-use. The aqueous solution was added to a Dowex 50WX2 200 H⁺ column (prewashed with H₂O to pH 7) and washed with H₂O:EtOH (1:1, v/v, 250.0 mL) to remove the nickel salts. The
15 amino acid product was eluted with 20% NH₄OH:EtOH (1:1 v/v, 350.0 mL). Fractions containing product were identified by staining with ninhydrin. The fractions where combined and concentrated *in vacuo*, triturated with Et₂O to give (*S*)-2-aminohept-6-enoic acid as a white powder.
20

(*S*)-2-aminohept-6-enoic acid (11)
Yield 60%; m.p: 225-226 °C (Et₂O) (lit: 224-225 °C)[12]; $[\alpha]_D^{30}$ +1.5 (*c* 0.1, H₂O) (lit: + 9.5 (*c* 0.5, H₂O, 26 °C)[12]; ¹H NMR (300 MHz, D₂O) δ 5.85 (1H, ddt, *J* = 17.5, 10.5, 6.7 Hz, C*H*=CH₂),
25 5.06 (1H, d, *J* = 19.3 Hz, CH=C*H*₂ *trans*), 4.99 (1H, d, *J* = 10.5 Hz, CH=C*H*₂ *cis*), 3.67 (1H, t, *J* = 6.1 Hz, C*H*CH₂CH₂), 2.08 (2H, q, *J* = 7.0 Hz, C*H*₂CH=CH₂), 1.92-1.70 (2H, m, CHC*H*₂CH₂), 1.56-1.32 (2H, m, CH₂C*H*₂CH₂). NH₂ and OH protons are missing from spectrum; ¹³C NMR (75 MHz, CDCl₃) δ
30 175.5 (s, *C*=O), 138.6 (d, *C*H=CH₂), 115.0 (t, CH=*C*H₂), 54.8 (d, *C*HCH₂CH₂), 32.5 (t, *C*H₂CH=CH₂), 30.1 (t, CH*C*H₂CH₂), 23.6 (t, CH₂*C*H₂CH₂); IR (ν$_{max}$/cm⁻¹, neat): 2929 (br), 1579, 1514, 1407, 1355, 1322, 989, 912, 839; HRMS-ESI (calcd for C₇H₁₄NO₂ [M+H]⁺) 144.1025, found 144.1028 (Δ = 2.1 ppm).
35

(*S*)-2-aminodec-9-enoic-acid (12)
Yield 67%; m.p: 255-257 °C (Et₂O); $[\alpha]_D^{30}$ +0.7 (*c* 0.03, MeOH); ¹H NMR (300 MHz, D₂O) δ 5.85 (1H, ddt, *J* = 17.1, 10.3, 6.7 Hz, C*H*=CH₂), 4.97 (1H, dq, *J* = 17.2, 2.3 Hz, CH=C*H*₂ *trans*), 4.90
40 (1H, ddt, *J* = 10.3, 2.5, 1.2 Hz, CH=C*H*₂ *cis*), 3.13 (1H, dd, *J* = 6.8, 6.1 Hz, C*H*CH₂CH₂), 1.97 (2H, qt, *J* = 7.0, 1.2 Hz, C*H*₂CH=CH₂), 1.57-1.41 (2H, m, CHC*H*₂CH₂), 1.37-1.18 (8H, m, CH₂(C*H*₂)₄CH₂). NH₂ and OH protons are missing from spectrum; ¹³C NMR (75 MHz, CDCl₃) δ 184.0 (s, *C*=O), 140.5
45 (d, *C*H=CH₂), 114.0 (t, CH=*C*H₂), 56.1 (d, *C*HCH₂CH₂), 34.7 (t, *C*H₂CH=CH₂), 33.0 (t, CH*C*H₂CH₂), 28.5 (t, *C*H₂), 28.1 (t, *C*H₂), 28.0 (t, *C*H₂), 24.9 (t, *C*H₂); IR (ν$_{max}$/cm⁻¹, neat): 2929 (br), 2925, 2851, 1579, 1513, 1443, 1406, 1319, 1066, 911; HRMS-ESI (calcd for C₁₀H₂₀NO₂ [M+H]⁺) 186.1494, found 186.1493 (Δ = –
50 0.5 ppm).

(*S*)-2-amino-2-methylhept-6-enoic acid (13)
Yield 65%; m.p: 250-252 °C (Et₂O) (lit: >200 °C decomp)[21]; $[\alpha]_D^{20}$ +3.22 (*c* 0.05, MeOH) (lit: +10.8 (*c* 0.83, MeOH, 25 °C)[21];
55 ¹H NMR (300 MHz, D₂O) δ 5.84 (1 H, ddt, *J* = 17.0, 10.2, 6.7 Hz, C*H*=CH₂), 5.11-4.96 (2 H, m, CH=C*H*₂), 2.07 (2 H, q, *J* = 7.0 Hz, δ-C*H*₂), 1.86 (1 H, m, β-C*H*H), 1.71 (1 H, m, , β-CH*H*), 1.54 -1.40 (4 H, m, C*H*₃, γ-C*H*H), 1.31 (1 H, m, γ-CH*H*); ¹³C NMR (100 MHz, D₂O) δ 177.0 (s, *C*=O), 138.7 (d, *C*H=CH₂), 115.1 (t,
60 CH=*C*H₂), 61.6 (s, α-q*C*), 36.7 (t, β-*C*H₂), 32.8 (t, δ-*C*H₂), 22.5 (t, γ-*C*H₂), 22.5 (q, *C*H₃); IR (ν$_{max}$/cm⁻¹, neat) 3124, 3033, 2982, 1738, 1595, 1456, 1397, 1367, 1316, 1232, 912; HRMS-ESI (calcd for C₈H₁₆NO₂ [M+H]⁺) 158.1181, found 158.1175 (Δ = – 3.8 ppm).
65 **(*S*)-2-amino-2-methyldec-9-enoic acid (14)**

Yield 68%; m.p: 262-264 °C (Et₂O); $[\alpha]_D^{20}$ +3.59 (*c* 0.05, MeOH); ¹H NMR (500 MHz, D₂O) δ 5.89 (1 H, ddt, *J* = 17.1, 10.3, 6.8 Hz, C*H*=CH₂), 5.02 (1 H, d, *J* = 17.1 Hz, CH=CH₂*cis*),
70 4.95 (1 H, d, *J* = 10.3 Hz, CH=C*H*₂*trans*), 2.30 (2 H, q, *J* = 6.8 Hz, η-C*H*₂), 1.82 (1 H, m, β-C*H*H), 1.68 (1 H, m, β-CH*H*), 1.44 (3 H, s, C*H*₃), 1.39-1.26 (7 H, m, γ-C*H*H, δ-C*H*₂, ε-C*H*₂, ζ-C*H*₂), 1.19 (1 H, m, γ-CH*H*); ¹³C NMR (126 MHz, D₂O) δ 177.2 (s, *C*=O), 140.3 (d, *C*H=CH₂), 114.0 (t, CH=*C*H₂), 61.7 (s, α-q*C*), 37.2 (t, β-*C*H₂), 33.0 (t, η-*C*H₂), 28.5 (t, δ-*C*H₂), 27.9 (t, ζ-*C*H₂),
75 27.8 (t, ε-*C*H₂), 23.1 (t, γ-*C*H₂), 22.5 (q, α-*C*H₃); IR (ν$_{max}$/cm⁻¹, neat) 3079, 2981, 2922, 2855, 1595, 1457, 1434, 1399, 1367, 1318, 1259, 993, 909, 791; HRMS-ESI: (calcd for C₁₁H₂₂NO₂ [M+H]⁺) 200.1651, found 200.1651 (Δ = 0.0 ppm).

80 **General method of formation of Fmoc protected amino acids (1)-(2), (15)-(16)**
(*S*)-amino hept-6-enoic acid **11** (90 mg, 0.63 mmol, 1.0 equiv.) and potassium carbonate (174 mg, 1.26 mmol, 2.0 equiv) was dissolved in water (2.0 mL) and cooled to 0 °C. 9-
85 Fluorenylmethyl N-succinimidyl carbonate (320 mg, 0.95 mmol, 1.5 equiv.) was dissolved in dioxane (4.0 mL) and added drop wise to aqueous solution over 20 minutes. The reaction was warmed to room temperature and left for 24 hours. An excess volume of water was added and the mixture extracted (2 x 20.0
90 mL) with ethyl acetate. The combined organic fractions were back extracted with saturated bicarbonate solution and the aqueous layers acidified to pH 1 with 3 M HCl. The aqueous fractions were then extracted with EtOAc (3 x 20.0 mL). The organic layers were dried (MgSO₄) and concentrated *in vacuo*.
95 Purification by column chromatography (SiO₂ eluted MeOH/CH₂Cl₂/AcOH (2:97:1)) gave the title compound as a white powder.

(*S*)-2-((((9*H*-fluoren-9-yl)methoxy)carbonyl)amino)hept-6-
100 **enoic acid (15)**
Yield 65%; m.p: 125-127 °C (Et₂O); $[\alpha]_D^{30}$ +0.1 (*c* 0.1, CHCl₃) (lit: +3.1 (1.0, CHCl₃, 22.4 °C)[12]; ¹H NMR (500 MHz, MeOD) δ 7.79 (2 H, d, *J* = 7.6 Hz, Ar-C*H*), 7.68 (2 H, d, *J* = 7.7 Hz, Ar-C*H*), 7.39 (2 H, t, *J* = 7.2 Hz, Ar-C*H*), 7.31 (2 H, t, *J* = 7.5 Hz,
105 Ar-C*H*), 5.81 (1 H, ddt, *J* = 17.0, 10.2, 6.7 Hz, C*H*=CH₂), 5.03 (1 H, d, *J* = 17.5 Hz, CH=C*H*₂ *trans*), 4.96 (1 H, d, *J* = 9.5 Hz, CH=C*H*₂ *cis*), 4.35 (2 H, d, *J* = 7.2 Hz, C*H*₂OCONH), 4.23 (1 H, t, *J* = 6.8 Hz, C*H*CH₂OCONH), 4.14 (1 H, dd, *J* = 9.1, 4.8 Hz, C*H*CH₂CH₂), 2.14-2.05 (2 H, m, C*H*₂CH=CH₂), 1.85 (1 H, m,
110 CHC*H*₂CH₂), 1.69 (1 H, m, CHC*H*₂CH₂), 1.56-1.44 (2 H, m, CH₂C*H*₂CH₂). NH and OH protons are missing from spectrum; ¹³C NMR (125 MHz, MeOD) δ 176.1 (s), 158.8 (s), 145.6 (s), 142.6 (s), 139.4 (d), 128.8 (d), 128.2 (d), 126.3 (d), 120.9 (d), 115.4 (t), 68.0 (t), 55.2 (d), 48.3 (d, *identified by HMQC*), 34.3
115 (t), 32.2 (t), 26.3 (t); IR (ν$_{max}$/cm⁻¹, neat): 3336, 3017, 2971, 1739, 1681, 1532, 1446, 1366, 1229, 1217, 910, 758, 736; HRMS-ESI (calcd for C₂₂H₂₄NO₄ [M+H]⁺) 366.1705, found 366.1705 (Δ = 0.0 ppm), (calcd for C₂₂H₂₃NO₄Na [M+Na]⁺) 388.1525, found 388.1500 (Δ = –6.4 ppm); HPLC (OD-H
120 column, hexane/^{i}PrOH isocratic + 0.1% AcOH): 9.56 min.

(*S*)-2-((((9*H*-fluoren-9-yl)methoxy)carbonyl)dec-9-enoic acid (16)
Yield 63%; m.p: 225-226 °C (Et₂O); $[\alpha]_D^{30}$ +0.2 (*c* 0.02, CHCl₃);
125 ¹H NMR (500 MHz, MeOD) δ 7.77 (2 H, d, *J* = 7.3 Hz, Ar-C*H*), 7.60 (2 H, d, *J* = 6.7 Hz, Ar-C*H*), 7.41 (2 H, t, *J* = 7.6 Hz, Ar-C*H*), 7.32 (2 H, t, *J* = 7.0 Hz, Ar-C*H*), 5.81 (1 H, ddt, *J* = 17.0, 10.2, 6.7 Hz, C*H*=CH₂), 5.03 (1 H, d, *J* = 17.5 Hz, CH=C*H*₂ *trans*), 4.96 (1 H, d, *J* = 9.5 Hz, CH=C*H*₂ *cis*), 4.35 (2 H, d, *J* =
130 7.2 Hz, C*H*₂OCONH), 4.23 (1 H, t, *J* = 6.8 Hz, C*H*CH₂OCONH),

4.14 (1 H, dd, J = 9.1, 4.8 Hz, C*H*CH$_2$CH$_2$), 2.03 (2 H, q, J = 6.7 Hz, C*H$_2$*CH=CH$_2$), 1.89 (1 H, m, CHC*H$_2$*CH$_2$), 1.67 (1 H, m, CHC*H$_2$*CH$_2$), 1.46-1.18 (8 H, m, CH$_2$(C*H$_2$*)$_4$CH$_2$). NH and OH protons are missing from spectrum; ^{13}C NMR (125 MHz, MeOD) δ 176.4 (s), 158.9 (s), 145.4 (s), 142.8 (s), 140.2 (d), 128.9 (d), 128.3 (d), 126.4 (d), 121.1 (d), 114.9 (t), 68.1 (t), 55.5 (d), 47.4 (d), 35.0 (t), 32.9 (t), 30.1 (3 x t), 27.0 (t); IR (v_{max}/cm^{-1}, neat): 3072, 2931, 2858, 2487, 1687, 1537, 1450, 1264, 1236, 1167, 1086, 1045, 992, 907, 738; HRMS-ESI (calcd for C$_{25}$H$_{30}$NO$_4$ [M+H]$^+$) 408.2175, found 408.2170 (Δ = −1.2 ppm), (calcd for C$_{25}$H$_{29}$NO$_4$Na [M+Na]$^+$) 430.1994, found 430.1989 (Δ = −1.2 ppm); HPLC (OD-H column, hexane/*^{i}*PrOH isocratic + 0.1% AcOH): 7.54 min.

(*S*)-2-((((9*H*-fluoren-9yl)methoxy)carbonyl)amino)-2-methylhept-6-enoic acid (1)

Yield 82%; [α]$_D^{20}$ +3.5 (*c* 1.0 in MeOH); ^{1}H NMR (300 MHz; CDCl$_3$) δ 7.78 (2 H, d, *J* = 7.5 Hz, Ar-C*H*), 7.60 (2 H, d, *J* = 7.2 Hz, Ar-C*H*), 7.41 (2 H, t, *J* = 7.4 Hz, Ar-C*H*), 7.33 (2 H, t, *J* = 7.5, Ar-C*H*), 5.76 (1 H, m, CH$_2$C*H*=CH$_2$), 5.50 (1 H, s, N*H*), 5.09-4.89 (2 H, m, CH$_2$CH=C*H$_2$*), 4.53-4.33 (2 H, m, C(O)OC*H$_2$*CH), 4.23 (1 H, t, *J* = 6.6 Hz, C(O)OCH$_2$C*H*), 2.22-1.95 (2 H, m, C*H$_2$*CH=CH$_2$), 1.95-1.78 (1 H, m, C(Me)CH$_2$C*H$_2$*), 1.60 (3 H, s, C(C*H$_3$*)CH$_2$), 1.50-1.26 (2 H, t, *J* = 7.1 Hz, C(Me)C*H$_2$*); ^{13}C NMR (75 MHz; CDCl$_3$) δ 178.3 (s), 154.8 (s), 143.8 (s), 141.4 (s), 138.0 (d), 127.7 (d), 127.1 (d), 125.0 (d), 120.0 (d), 115.1 (t), 66.5 (t), 59.7 (s), 47.2 (d), 36.2 (t), 33.4 (t), 30.9 (t), 23.3 (q); IR (v_{max}/cm^{-1}, neat) 2932, 1701, 1507, 1450, 1334, 1253, 1074, 910, 758, 737; HRMS-ESI (calcd for C$_{23}$H$_{26}$NO$_4$ [M+H]$^+$) 380.1862, found 380.1860 (Δ = –0.5 ppm), (calcd for C$_{23}$H$_{25}$NO$_4$Na [M+Na]$^+$) 402.1681, found 402.1692 (Δ = 2.7 ppm). HPLC (OD-H column, hexane (50%)/*^{i}*PrOH isocratic + 0.1% AcOH): 8.07 min.

(*S*)-2-((((9*H*-fluoren-9-yl)methoxy)carbonyl)amino)-2-methyldec-9-enoic acid (2)

Yield 62%; [α]$_D^{20}$ +5.89 (*c* 1.0, CHCl$_3$); ^{1}H NMR (500 MHz, CDCl$_3$) δ 7.77 (2 H, d, *J* = 7.5 Hz, Ar-C*H*), 7.59 (2 H, d, *J* = 7.5 Hz, Ar-C*H*), 7.40 (2 H, t, *J* = 7.4 Hz, Ar-C*H*), 7.32 (2 H, t, *J* = 7.4 Hz, Ar-C*H*), 5.79 (1 H, ddt, *J* = 17.1, 10.2, 6.8 Hz, C*H*=CH$_2$), 5.46 (1 H, br s, N*H*), 4.98 (1 H, dd, *J* = 17.1, 1.5 Hz, CH=CH$_2$*cis*), 4.92 (1 H, d, *J* = 10.1 Hz, CH=C*H$_2$trans*), 4.41 (2 H, s, C(O)OC*H$_2$*CH), 4.22 (1 H, t, *J* = 6.8 Hz, C(O)OCH$_2$C*H*), 2.02 (2 H, q, *J* = 6.9 Hz, C*H$_2$*CH=CH$_2$), 1.82 (1 H, m, C*H*HCH$_2$CH=CH$_2$), 1.60 (3 H, s, C*H$_3$*), 1.39-1.10 (9 H, m, CH*H*CH$_2$CH=CH$_2$, CH$_3$C(C*H$_2$*)$_4$); ^{13}C NMR (100 MHz, CDCl$_3$) δ 179.3 (s), 157.7 (s), 143.9 (s), 141.4 (s), 139.0 (d), 127.7 (d), 127.0 (d), 124.9 (d), 120.0 (d), 114.2 (t), 66.5 (d), 59.8 (t), 47.2 (s), 36.8 (t), 33.7 (t), 29.3 (t), 28.9 (t), 28.8 (t), 23.9 (t), 23.2 (q); IR (v_{max}/cm^{-1}, neat) 2926, 1705, 1506, 1450, 1338, 1251, 1105, 1086, 1052, 995, 909, 776, 758, 737, 674; HRMS-ESI (calcd for C$_{26}$H$_{32}$NO$_4$ [M+H]$^+$) 422.2331, found 422.2331 (Δ = 0.0 ppm); HPLC (OD-H column, hexane (50%)/*^{i}*PrOH isocratic + 0.1% AcOH): 7.28 min.

Acknowledgments

Notes and references

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