A One-Pot Synthesis of Symmetrical and Unsymmetrical Dipeptide Ureas

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Dedication ((optional))

We describe a flexible and high yielding synthesis of 1,3-disubstituted ureas,[1]that allows for the construction of both symmetrical and unsymmetrical dipeptide ureas, including easy access to ^{13}C labelled ureas, from amino acids and carbon dioxide at atmospheric pressure.

Introduction

The usefulness of ureas in materials chemistry,[1,2,3] pharmaceutical chemistry,[4–6] and biology[7,8] is evident from the publication of many more than a thousand papers reporting their synthesis and applications. These diverse series of compounds have wide series of applications ranging from plasticisers to pharmaceuticals. Importantly, ureas are also a key component of several bioactive natural products (Figure 1),[9] including mozamide A (**1**), oscillamide Y (**2**) and the uridyl peptide antibiotics (of which pacidamycin 4 (**3**) is a member).[10–12] In the uridyl peptide series of antibiotics the incorporation of a diaminoacid *N* to *N* inverts the sense of the peptide, the *N* to *C* directionality is restored by the incorporation of a urea; this double inversion in the sense of the peptide potentially confers a level of resistance to degradation by proteases.[12]

The vast majority of methods to synthesise ureas rely upon the use of phosgene or isocyanates as staring materials[13–20] Alternatively, approaches based on activated carbamates which can be generated from various carbonylation reagent such as carbonates[21] chloroformates[22] and N,N-carbonyldiimidazole (CDI)[23] have been described for the synthesis of peptide ureas. Newer methods have been developed using carbon monoxide or carbon dioxide with transition metal catalysts.[24–27] These procedures are generally accompanied by the disadvantage that they require either the use of very high temperatures or pressures, expensive catalysts, highly specialised apparatus or do not afford the flexibility to synthesise unsymmetrical ureas.

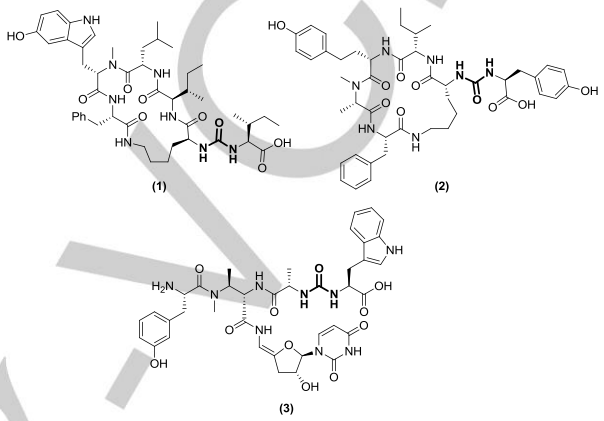
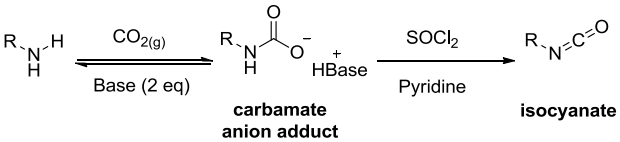


Figure 1. Urea-containing natural products. Mozamide A (1), oscillamide Y (2) and pacidamycin 4 (3), the urea moiety is highlighted.

Herein, we describe a simple procedure that allows for the ready formation of symmetrical and unsymmetrical ureas from amino acids or amines and carbon dioxide.

Results and Discussion

Our simple one-pot, sequential, low temperature and atmospheric pressure route to ureas is inspired by the work of McGhee *et al.*,[28] which involves first the deprotonation of an amine with base and reaction with carbon dioxide to form the carbamate anion, followed by its conversion to an isocyanate using thionyl chloride (Scheme 1).



Scheme 1. Conversion of amines to isocyanate using thionyl chloride.[28]

The utility of this route to access carbamates has been elegantly demonstrated by Taylor *et al.*[29,30] In the present work, once the isocyanate is formed, by removal of the solvent and all volatiles, *in vacuo*, re-dissolving the residue in pyridine and then introducing a second amino acid, we demonstrated that ready access to the urea formation could be afforded. This approach enabled us to access a series of 1,3-disubstituted urea analogues (Scheme 2).

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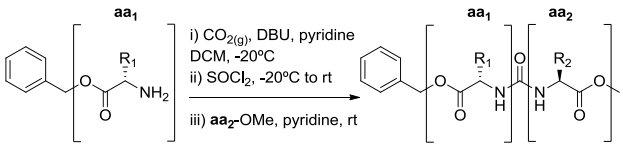


Scheme 2. Synthesis of unsymmetrical 1,3-disubstituted ureas.

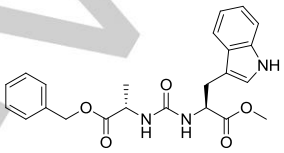
Firstly, optimisation of the reaction conditions was carried out by exploring the synthesis of the unsymmetrical alanine-urea-tryptophan (**4**) as a model system. Dried carbon dioxide, generated from CO_2(s) was bubbled into a cooled solution of L-alanine benzyl ester *p*-toluenesulfonate in dichloromethane (DCM) with 1,8-diazabicycloundec-7-ene (DBU) and pyridine. It is noteworthy that DBU facilitates the formation and stabilisation of the carbamate anion adduct of the amine with $CO_{2(g)}$, whereas pyridine liberates the free amine from its *p*-toluenesulfonate salt. Thionyl chloride was then added and the reaction was allowed to warm to room temperature. Volatiles were removed under reduced pressure, anhydrous pyridine was added to solvate the isocyanate, and then L-tryptophan methyl ester was added as a solution in anhydrous pyridine. Using this pre-optimized method, next, the effect of altering temperature and reagent concentrations was systematically investigated. This screening revealed that the temperature at which the carbon dioxide and thionyl chloride are added have a great impact on the overall yield (Table 1). Under the same reaction conditions, low yields were obtained at -10ºC and -50ºC (Table 1, entries 2 and 15 respectively). A slightly increase in the total yield was afforded at -30ºC (Table 1, entry 13) but, to our delight, when the reaction was performed at -20ºC the yield dramatically increased to 74% (Table 1, entry 6). The need for the subtle tuning of temperature is curious and can perhaps be explained by low reactivity and/or solubility of the reactants at -30ºC, balanced against the instability and decomposition of intermediates at the higher temperature of -10ºC.

Keeping -20ºC as the optimal temperature, we then studied the effect of the concentration of reagents. We found that for DBU, the best yield was obtained upon using 5 eq since, under the same reaction conditions, neither the use of an increased amount (8 eq) nor a decreased amount (3 eq) was beneficial to the overall reaction yield (Table 1, entries 6, 7 and 8 respectively). In the case of pyridine, the optimal quantity was found to be 3 eq. since increased amounts (4 and 5 eq) resulted in very poor yields (Table 1 entries 6, 9 and 10 respectively). This effect could be attributed to the reaction of the overexcess base with $SOCl_2$, thus lowering the concentration of the later for the generation of the desired isocyanate. Addition of 1.5 eq of $SOCl_2$ was enough to afford high yields of the desired urea compound (Table 1, entry 6). Upon using a larger excess of this reagent (2 and 3 eq) the obtained yields were comparable (Table 1, entries 11 and 12 respectively). It is important to note that a high excess of $SOCl_2$ resulted in a very dark reaction mixture and further problems in the workup procedure. Thus, 1.5 eq of $SOCl_2$ was determined as the optimal amount as demonstrated through the reactions reported in Table 1.

Depending upon reagent availabilities, rather than generate the CO_2(g) from CO_2(s), dry CO_2(g) from a cylinder can be directly used. We noted that upon using a CO_2(g) cylinder an improvement of 10% in yield was obtained (Table 1, entry 6 was elevated from 74 to 85% yield).

Finally, we explored the effect of replacing thionyl chloride with *p*-toluenesulfonyl chloride (*p*-TsCl) or 1-[bis(dimethylamino)methylene]-1*H*-1,2,3-triazolo[4,5-*b*]pyridinium 3-oxid hexafluorophosphate (HATU) as alternative activators (Table 2). In all cases, formation of the desired product was observed but generally the isolated yields were considerably lower, even upon using larger excess, in comparison to the use of $SOCl_2$ (Table 2, entries 2 to 6 and 1 respectively).

Table 1. Reaction optimisation. Compound **4**, aa_1 = Ala, aa_2 = Trp



(4)

Entry	Temp, ºC	DBU, eq	Pyridine, eq	$SOCl_2$, eq	Yield, %[a],[b]
1	-10	3	2	1.5	15
2	-10	5	3	1.5	22
3	-10	5	3	3	28
4	-10	3	2	1.5	22
5	-10	5	2	1.5	35
6	**-20**	**5**	**3**	**1.5**	**74**
7	-20	8	3	1.5	20
8	-20	3	3	1.5	69
9	-20	5	4	1.5	8
10	-20	5	5	1.5	6
11	-20	5	3	2	73
12	-20	5	3	3	76
13	-30	5	3	1.5	40
14	-30	5	3	3	42
15	-50	5	3	1.5	15

[a] Reactions were carried out using alanine benzyl ester *p*-toluenesulfonate (1 eq) and tryptophan methyl ester hydrochloride (1 eq) in DCM as specified above. [b] Isolated are reported after flash chromatography

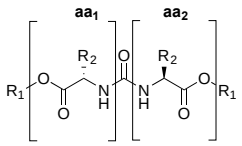
Table 2. Screening of alternative activators for synthesis of compound **4**. aa_1 = Ala, aa_2 = Trp

Entry	Activator	eq	Yield, %[a],[b]
1	**$SOCl_2$**	**1.5**	**74**
2	p-TsCl	1.5	28
3	p-TsCl	2	35
4	p-TsCl	3	30
5[c]	HATU	1.5	45
6	HATU	2	48

[a] Reactions were carried out using alanine benzyl ester *p*-toluenesulfonate (1 eq), tryptophan methyl ester hydrochloride (1 eq), DBU (5 eq), pyridine (3 eq) in DCM at -20ºC as specified above. [b] Isolated yields are reported after flash chromatography. [c] A slightly different procedure was used, see experimental section.

Using the optimized conditions with thionyl chloride, access to symmetrical ureas was shown to be particularly high yielding, over 90% in all cases (Table 3, entries 1-3).

Table 3. One-pot synthesis of symmetrical urea analogues, aa_1=aa_2.



Entry	R_1	R_2	aa_1=aa_2	Yield, %[a],[b]
1	Me	Bn	Phe	96± 0.03 (**5**)
2	Me	$CH_2CH_2SCH_3$	Met	93± 0.1 (**6**)
3	Bn	Me	Ala	95± 0.07 (**7**)

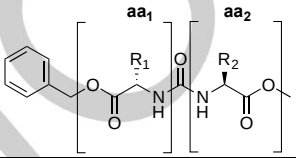
[a] Reactions were carried out using aa_1 (1 eq), aa_2 (1 eq), DBU (5 eq), pyridine (3 eq) and $SOCl_2$ (1.5 eq) in DCM as specified above. [b] Isolated yields are reported after flash chromatography from reactions carried out in triplicate.

Encouraged by these results, we next focused on expanding the scope of the reaction on the synthesis of unsymmetrical ureas. A series of six methyl ester and benzyl ester protected amino acids were synthesised and using these, a range of ureas were prepared in modest to good yields (Table 4, entries 1-11).

As shown in Table 4, reacting Ala as aa_1 with Trp (Tryptophan), Phe (Phenylalanine) and Met (Methionine) as aa_2 afforded high yields of the corresponding 1,3-disubstituted urea analogues (Table 4, entries 1, 2 and 3).

Notably, the coupling of Ala as aa_1 with halogenated Trp (generated by biocatalysis through a well established protocol previously developed in our group)[31,32] as aa_2 also afforded the corresponding desired urea analog with moderate yields (Table 4, entries 4 to 7).

Table 4. One-pot synthesis of unsymmetrical urea analogues.



Entry	aa_1	aa_2	Yield, %[a],[b]
1	Ala	Trp	74 ± 0.8 (**4**)
2	Ala	Phe	78 ± 0.5 (**8**)
3	Ala	Met	68 ± 1.0 (**9**)
4	Ala	5-Br-Trp	55 ± 0.8 (**10**)
5	Ala	5-Cl-Trp	52 ± 1.1 (**11**)
6	Ala	5-F-Trp	58 ± 0.5 (**12**)
7	Ala	7-I-Trp	72 ± 0.9 (**13**)
8	Met	Phe	60 ± 0.7 (**14**)
9	Met	Trp	63 ± 0.5 (**15**)
10	Leu	Phe	55 ± 0.9 (**16**)
11	Leu	Met	40 ± 1.2 (**17**)
12	Ala ($^{13}CO_2$)	Trp	90 (**18**)

[a] Reactions were carried out using aa_1 (1 eq), aa_2 (1 eq), DBU (5 eq), pyridine (3 eq) and $SOCl_2$ (1.5 eq) in DCM as specified above. [b] Isolated yields are reported after flash chromatography from reactions carried out in triplicate.

Changing aa_1 to Leu (Leucine) and Met successfully resulted in the formation of the desired urea product but in lower yields (Table 4, entries 8-10 respectively). This decrease in yield upon changing aa_1 could be explained mainly due to the steric effects of the side chain in α position (R_1).

Remarkably, in all cases, this one-pot method is highly reproducible as shown by the very low error obtained from performing the reactions in triplicate.

Most importantly, using ^{13}C carbon dioxide we successfully generated isotopically labelled urea in almost a quantitively manner (Table 4, entry 12). The obtained higher yield over the unlabelled system (90% and 74% respectively) can be rationalised by the fact that rigorously dry $^{13}CO_2$(g) was provided

directly from a gas cylinder rather from simply evaporating and drying CO_2(s).

Conclusions

In summary, we have developed a simple and efficient synthetic approach enabling easy access to symmetrical and the more challenging unsymmetrical 1,3-disubstiuted ureas from amino acids and carbon dioxide in moderate to high yields at atmospheric pressure. Moreover, the utility of this one-pot approach for accessing ^{13}C labelled urea has also been demonstrated. Although the current methodology is applied to the synthesis of dipeptide ureas, in principle, it could potentially be extended to other types of building blocks to generate 1,3 disubstituted ureas apart from amino acids.

Experimental Section

General experimental methods: TLC analysis was carried out on Merck aluminium-backed silica gel 60 F_{254} and was visualised by ultraviolet light (UV) using a model UVGL-58 MINERLIGHT® LAMP multiband UV-254/365 nm, by ninhydrin stain (50 mg of ninhydrin dissolved in 40 ml of acetone). Column chromatography was carried out on Davisil® chromatographic silica media LC60A 40-63µm. Anhydrous DCM was obtained using a MBRAUN SPS 800 filtered over pre-packed alumina columns. Anhydrous pyridine was distilled over calcium hydride under argon atmosphere and stored over activated 4 Å molecular sieves. Anhydrous DMF was purchased. All other solvents were SLR grade and used without further purification unless stated otherwise. When anhydrous solvents were used, all glassware was oven dried and cooled under argon. L-7-Iodotryptophan, L-5-bromotryptophan, L-5-chlorotryptophan, and L-5-fluorotryptophan were prepared as previously described. [31,32]

***N*-[[(1*S*)-1-[(Benzyloxy)carbonyl]ethyl]aminocarbonyl]-L-tryptophan methyl ester (4):**

Dry ice was placed in a 500 ml round-bottom flask connected to a paraffin oil bubbler then to a drying tube containing pellets of activated 4 Å molecular sieves. Using the Teflon tubing, $CO_{2\,(g)}$ derived from dry ice was bubbled into a stirred solution of L-alanine benzyl ester *p*-toluenesulfonate salt (0.20 g, 0.57 mmol), 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) (0.43 ml, 2.85 mmol) and pyridine (0.14 ml, 1.71 mmol) in anhydrous DCM (30 ml) at -20 °C, for a period of 30 minutes whilst keeping the mixture at -20 °C. Subsequently, a solution of thionyl chloride (0.08 ml, 1.14 mmol) in anhydrous DCM (5 ml) was carefully added to the reaction over a period of 20 minutes under an atmosphere of argon. The reaction was then left stirring under an atmosphere of argon for 2 hours while it was allowed to warm up to room temperature. Upon addition of thionyl chloride, the color of the reaction mixture gradually changed from clear to yellow to brown as the reaction warms up to room temperature. Afterwards, the solvent was removed under reduced pressure and the brown, oily residue was dissolved in anhydrous pyridine (8 ml). Under an atmosphere of argon, a solution of L-tryptophan methyl ester hydrochloride salt (0.15 g, 0.57 mmol) in anhydrous pyridine (2 ml) was added over a period of 10 minutes at room temperature. The mixture was left stirring under an atmosphere of nitrogen at room temperature for 4 hours. The solvent was then removed under reduced pressure and the brown residue was dissolved in ethyl acetate (50 ml) and washed five times with a saturated sodium bicarbonate solution (40 ml). The organic layer was dried over magnesium sulfate, filtered, concentrated under reduced pressure and purified using flash chromatography (SiO_2, hexane / ethyl acetate 3:1 to 1:1, ninhydrin/UV) to yield the target compound (**4**)(0.19 g, 0.44 mmol, 74%) as a white powder.

^1H NMR (500 MHz, $CDCl_3$)δ 8.62 (s, 1H), 7.48 (d, J = 7.9 Hz, 1H), 7.29 – 7.36 (m, 4H), 7.19 – 7.21 (m, 2H), 7.15 (t, J = 7.6 Hz, 1H), 7.07 (t, J = 7.4 Hz, 1H), 6.87 (s, 1H), 5.78 (d, J = 8.4 Hz, 1H), 5.64 (d, J = 8.0 Hz, 1H), 5.06 (d, J = 12.3 Hz, 1H), 4.85 (dt, J = 7.9, 5.3 Hz, 1H), 4.72 (d, J = 12.3 Hz, 1H), 4.64 (p, J = 7.4 Hz, 1H), 3.62 (s, 3H), 3.28 (dd, J = 14.8, 5.3 Hz, 1H), 3.18 (dd, J = 14.8, 5.1 Hz, 1H), 1.30 (d, J = 7.3 Hz, 3H); ^{13}C-NMR (126 MHz, $CDCl_3$) δ 175.0, 173.4, 156.8, 135.9, 135.2, 128.5, 128.3, 128.1, 127.4, 123.6, 121.9, 119.3, 118.4, 111.4, 109.2, 67.2, 53.1, 52.3, 48.5, 28.0, 19.0; HRMS (ESI, +ve) $C_{23}H_{25}N_3O_5$ $[M+Na]^+$ calculated for 446.1679, found 446.1680.

***N*,*N*'-Carbonyl bis(L-phenylalanine methyl ester) (5):**

N,*N*'-Carbonyl bis(L-phenylalanine methyl ester) (**5**) (0.09 g, 0.23 mmol, 96%), white powder, was prepared following the same procedure as described for compound (**4**)

^1H NMR (500 MHz, $CDCl_3$) δ 7.20 – 7.30 (m, 6H), 7.09 (d, J = 7.1 Hz, 4H), 5.51 (d, J = 8.4 Hz, 2H), 4.82 (dt, J = 8.4, 5.8 Hz, 2H), 3.63 (s, 6H), 3.00 (d, J = 5.9 Hz, 4H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 173.3, 156.2, 136.1, 129.3, 128.4, 126.9, 53.9, 52.2, 38.7; HRMS (ESI, +ve) $C_{21}H_{24}N_2O_5$ $[M+H]^+$ calculated for 385.1758, found 385.1761.

***N*,*N*'-Carbonyl bis(L-methionine methyl ester) (6):**

N,*N*'-Carbonyl bis(L-methionine methyl ester) (**6**) (0.16 g, 0.46 mmol, 93%), white powder, was prepared following the same procedure as described for compound (**4**).

^1H NMR (500 MHz, $CDCl_3$) δ 5.67 (d, J = 8.2 Hz, 2H), 4.60 (td, J = 7.7, 5.0 Hz, 2H), 3.76 (s, 6H), 2.53 (t, J = 7.5 Hz, 4H), 2.06 – 2.17 (m, 8H), 1.94 (dq, J = 14.6, 7.4 Hz, 2H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 173.8, 156.8, 52.5, 52.2, 32.3, 29.9, 15.4; HRMS (ESI, +ve) $C_{13}H_{24}N_2O_5S_2$ $[M+H]^+$ calculated for 353.1199 found 353.1202.

***N*,*N*'-Carbonyl-bis(L-alanine benzyl ester) (7):**

N,*N*'-Carbonyl bis(L-alanine benzyl ester) (**7**) (0.10 g, 0.27 mmol, 95%), white powder, was prepared following the same procedure as described for compound (**4**).

^1H NMR (500 MHz, $CDCl_3$) δ 7.32 – 7.40 (m, 10H), 5.35 (d, J = 7.7 Hz, 2H), 5.22 (d, J = 12.4 Hz, 2H), 5.15 (d, J = 12.4 Hz, 2H), 4.55 (p, J = 7.3 Hz, 2H), 1.39 (d, J = 7.2 Hz, 6H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 174.1, 156.4, 135.4, 128.6, 128.3, 128.1, 67.0, 48.8, 18.9; HRMS (ESI, +ve) $C_{21}H_{24}N_2O_5$ $[M+H]^+$ calculated for 385.1758, found 385.1761.

_N_-[[(1_S_)-1-[(Benzyloxy)carbonyl]ethyl]aminocarbonyl]-L-phenylalanine methyl ester (8):

_N_-[[(1_S_)-1-[(Benzyloxy)carbonyl]ethyl]aminocarbonyl]-L-phenylalanine methyl ester (**8**) (0.17 g, 0.42 mmol, 78%), white powder, was prepared following the same procedure as described for compound (**4**).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.34 – 7.39 (m, 5H), 7.22 – 7.26 (m, 3H), 7.11 (d, _J_ = 7.1 Hz, 2H), 5.24 – 5.08 (m, 4H), 5.02 (d, _J_ = 8.1 Hz, 1H), 4.80 (dt, _J_ = 5.7, 8.2 Hz, 1H), 4.50 – 4.58 (m, 1H), 3.71 (s, 3H), 3.09 (dd, _J_ = 2.6, 5.8 Hz, 2H), 1.37 (d, _J_ = 7.5 Hz, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 173.8, 172.9, 156.1, 135.9, 135.4, 129.3, 128.6, 128.5, 128.3, 128.1, 127.0, 67.0, 53.8, 52.2, 48.8, 38.5, 19.0; HRMS (ESI, +ve) $C_{21}H_{24}N_2O_5$ $[M+Na]^+$ calculated for 407.1565, found: 407.1566.

_N_-[[(1_S_)-1-[(Benzyloxy)carbonyl]ethyl]aminocarbonyl]-L-methionine methyl ester (9):

_N_-[[(1_S_)-1-[(Benzyloxy)carbonyl]ethyl]aminocarbonyl]-L-methionine methyl ester (**9**) (0.15 g, 0.40 mmol, 68%), white powder, was prepared following the same procedure as described for compound (**4**).

^{1}H NMR (500 MHz, $CDCl_3$) δ7.30 – 7.40 (m, 5H), 5.57 (d, _J_ = 8.1 Hz, 1H), 5.48 (d, _J_ = 7.7 Hz, 1H), 5.11 – 5.24 (m, 2H), 4.62 (td, _J_ = 7.7, 4.9 Hz, 1H), 4.51 – 4.58 (m, 1H), 3.76 (s, 3H), 2.53 (t, _J_ = 7.5 Hz, 2H), 2.06 – 2.16 (m, 4H), 1.93 (dq, _J_ = 14.6, 7.4 Hz, 1H), 1.39 (d, _J_ = 7.1 Hz, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 174.0, 173.9, 156.6, 135.4, 128.6, 128.3, 128.0, 67.0, 52.5, 52.2, 48.9, 32.3, 29.9, 18.9, 15.4; HRMS (ESI, +ve) $C_{17}H_{24}N_2O_5S[M+Na]^+$ calculated for 391.1292, found 391.1290.

_N_-[[(1_S_)-1-[(Benzyloxy)carbonyl]ethyl]aminocarbonyl]-L-5-bromotryptophan methyl ester (10):

_N_-[[(1_S_)-1-[(Benzyloxy)carbonyl]ethyl]aminocarbonyl]-L-5-bromotryptophan methyl ester (**10**) (0.08 g, 0.16 mmol, 55%), white powder, was prepared following the same procedure as described for compound (**4**).

^{1}H NMR (500 MHz, $CDCl_3$) δ 8.74 (s, 1H), 7.58 (s, 1H), 7.31 – 7.35 (m, 3H), 7.13 – 7.23 (m, 4H), 6.86 (s, 1H), 5.86 (d, _J_ = 8.7 Hz, 1H), 5.67 (d, _J_ = 7.9 Hz, 1H), 5.04 (d, _J_ = 12.3 Hz, 1H), 4.83 (dt, _J_ = 7.9, 5.0 Hz, 1H), 4.63 – 4.73 (m, 2H), 3.68 (s, 3H), 3.21 (dd, _J_ = 14.9, 5.0 Hz, 1H), 3.12 (dd, _J_ = 14.9, 5.0 Hz, 1H), 1.35 (d, _J_ = 7.2 Hz, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 175.2, 173.0, 156.7, 135.0, 134.4, 129.1, 128.5, 128.4, 128.0, 125.0, 124.7, 121.0, 112.8, 112.6, 108.8, 67.4, 52.9, 52.4, 48.5, 27.9, 19.2; HRMS (ESI, +ve) $C_{23}H_{24}BrN_3O_5$ $[M+Na]^+$ calculated for 524.0786, found 524.0788.

_N_-[[(1_S_)-1-[(Benzyloxy)carbonyl]ethyl]aminocarbonyl]-L-5-chlorotryptophan methyl ester (11):

_N_-[[(1_S_)-1-[(Benzyloxy)carbonyl]ethyl]aminocarbonyl]-L-5-chlorotryptophan methyl ester (**11**) (0.09 g, 0.2 mmol, 52%), white powder, was prepared following the same procedure as described for compound (**4**).

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.84 (s, 1H), 7.42 (d, _J_ = 2.0 Hz, 1H), 7.30 – 7.34 (m, 3H), 7.21 (d, _J_ = 8.6 Hz, 1H), 7.13 – 7.20 (m, 2H), 7.07 (dd, _J_ = 8.6, 2.0 Hz, 1H), 6.87 (d, _J_ = 2.4 Hz, 1H), 5.97 (d, _J_ = 7.9 Hz, 1H), 5.77 (d, _J_ = 7.9 Hz, 1H), 5.05 (d, _J_ = 12.3 Hz, 1H), 4.84 (1 H, _J_ = 7.9, 5.0 Hz, dt), 4.61 – 4.74 (m, 2H), 3.66 (s, 3H), 3.21 (dd, _J_ = 14.9, 5.1 Hz, 1H), 3.11 (dd, _J_ = 14.9, 5.0 Hz, 1H), 1.33 (d, _J_ = 7.2 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 175.3, 173.1, 135.0, 134.2, 128.5, 128.4, 128.3, 128.0, 125.2, 125.1, 122.1, 117.9, 112.4, 108.9, 67.4, 52.9, 52.4, 48.5, 27.9, 19.1; HRMS (ESI, +ve) $C_{23}H_{24}ClN_3O_5$ $[M+H]^+$ calculated for 458.1477, found 458.1478.

_N_-[[(1_S_)-1-[(Benzyloxy)carbonyl]ethyl]aminocarbonyl]-L-5-fluorotryptophan methyl ester (12):

_N_-[[(1_S_)-1-[(Benzyloxy)carbonyl]ethyl]aminocarbonyl]-L-5-fluorotryptophan methyl ester (**12**) (0.10 g, 0.23 mmol, 58%), white powder, was prepared following the same procedure as described for compound (**4**).

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.73 (s, 1H), 7.32 (m, 3H), 7.16 – 7.25 (m, 3H), 7.10 (dd, _J_ = 9.8, 2.6 Hz, 1H), 6.87 – 6.92 (m, 2H), 5.89 (d, _J_ = 8.5 Hz, 1H), 5.71 (d, _J_ = 8.1 Hz, 1H), 5.07 (d, _J_ = 12.4 Hz, 1H), 4.83 (dt, _J_ = 8.0, 5.1 Hz, 1H), 4.75 (d, _J_ = 12.4 Hz, 1H), 4.61 – 4.70 (m, 1H), 3.65 (s, 3H), 3.20 (dd, _J_ = 14.9, 5.1 Hz, 1H), 3.12 (dd, _J_ = 14.9, 5.0 Hz, 1H), 1.32 (d, _J_ = 7.2 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 175.1, 173.2, 156.8, 156.7 (d, _J_ = 32.2 Hz), 133.8 (d, _J_ = 277.9 Hz), 128.5, 128.3, 128.0, 127.8 (d, _J_ = 9.6 Hz), 125.5, 123.9, 112.04 (d, _J_ = 9.7 Hz), 110.30 (d, _J_ = 26.2 Hz), 109.37 (d, _J_ = 4.7 Hz), 103.2 (d, _J_ = 23.6 Hz), 67.3, 53.0, 52.4, 48.5, 28.0, 19.1; ^{19}F NMR (377 MHz, $CDCl_3$, decoupled ^{1}H) δ -124.89; ^{19}F NMR (377 MHz, $CDCl_3$, coupled ^{1}H) δ -124.90 (td, _J_ = 9.4, 4.3 Hz); HRMS (ESI, +ve) $C_{23}H_{24}FN_3O_5$ $[M+H]^+$ calculated for 442. 7713, found 442.7768.

_N_-[[(1_S_)-1-[(Benzyloxy)carbonyl]ethyl]aminocarbonyl]-L-7-iodotryptophan methyl ester (13):

_N_-[[(1_S_)-1-[(Benzyloxy)carbonyl]ethyl]aminocarbonyl]-L-7-iodotryptophan methyl ester (**13**) (0.11 g, 0.19 mmol, 72%), white powder, was prepared following the same procedure as described for compound (**4**).

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.64 (s, 1H), 7.50 (d, _J_ = 7.5 Hz, 1H), 7.43 (d, _J_ = 7.9 Hz, 1H), 7.35 (m, 2H), 7.25 – 7.32 (m, 3H), 6.91 (d, _J_ = 2.4 Hz, 1H), 6.83 (t, _J_ = 7.7 Hz, 1H), 5.79 (d, _J_ = 8.1 Hz, 1H), 5.66 (d, _J_ = 8.2 Hz, 1H), 5.11 (d, _J_ = 12.4 Hz, 1H), 4.91 (dt, _J_ = 8.2, 5.0 Hz, 1H), 4.80 (d, _J_ = 12.3 Hz, 1H), 4.70 (apparent p, _J_ = 7.4 Hz, 1H), 3.59 (s, 3H), 3.23 (dd, _J_ = 14.8, 4.9 Hz, 1H), 3.14 (dd, _J_ = 14.9, 5.3 Hz, 1H), 1.29 (d, _J_ = 7.2 Hz, 2H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 174.9, 173.3, 156.7, 137.8, 135.3, 130.5, 128.6, 128.4, 128.1, 127.5, 124.1, 121.0, 118.6, 110.9, 76.7, 67.2, 52.9, 52.3, 48.5, 28.5, 19.1; HRMS (ESI, +ve) $C_{23}H_{24}IN_3O_5$ $[M+H]^+$ calculated for 550.0833, found 550.0826.

_N_-[[(1_S_)-1-[(Benzyloxy)carbonyl]-4-(methylthio)propyl]-aminocarbonyl]-L-phenylalanine methyl ester (14):

_N_-[[(1_S_)-1-[(Benzyloxy)carbonyl]-4-(methylthio)propyl]-aminocarbonyl]-L-phenylalanine methyl ester (**14**) (0.07 g, 0.16 mmol, 60%), white powder, was prepared following the same procedure as described for compound (**4**).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.36 – 7.41 (m, 5H), 7.25 – 7.29 (m, 3H), 7.11 (d, *J* = 6.6 Hz, 2H), 5.23 (d, *J* = 12.2 Hz, 1H), 5.17 (d, *J* = 12.1 Hz), 5.02 (d, *J* = 8.0 Hz, 1H), 4.87 (d, *J* = 8.0 Hz, 1H), 4.78 (dt, *J* = 7.9, 5.6 Hz, 1H), 4.63 (td, *J* = 7.7, 4.9 Hz, 1H), 3.73 (s, 3H), 3.11 (d, *J* = 5.6 Hz, 2H), 2.44 – 2.55 (m, 2H), 2.10 – 2.18 (m, 1H), 2.04 (s, 3H), 1.89 – 1.97 (m, 1H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 174.1, 173.0, 156.1, 142.6, 135.8, 135.5, 129.3, 128.6, 128.5, 128.4, 128.3, 127.0, 67.3, 53.9, 52.4, 52.2, 38.4, 29.8, 15.4; HRMS (ESI, +ve) $C_{23}H_{28}N_2O_5S[M+Na]^+$ calculated for 467.1608, found 467.1606.

_N_-[[(1_S_)-1-[(Benzyloxy)carbonyl]-4-(methylthio)butyl]-aminocarbonyl]-L-tryptophan methyl ester (15):

_N_-[[(1_S_)-1-[(Benzyloxy)carbonyl]-4-(methylthio)propyl] aminocarbonyl]-L-tryptophan methyl ester (**15**) (0.07 g, 0.15 mmol, 63%), white powder, was prepared following the same procedure as described for compound (**4**).

^{1}H NMR (500 MHz, $CDCl_3$) δ8.59 (s, 1H), 7.48 (d, *J* = 7.9 Hz, 1H), 7.29 – 7.41 (m, 4H), 7.15 – 7.21 (m, 3H), 7.09 (t, *J* = 7.5 Hz, 1H), 6.89 (s, 1H), 5.81 (d, *J* = 8.9 Hz, 1H), 5.63 (d, *J* = 8.0 Hz, 1H), 5.03 (d, *J* = 12.2 Hz, 1H), 4.87 (dt, *J* = 8.6, 5.2 Hz, 1H), 4.77 (td, *J* = 8.3, 4.8 Hz, 1H), 4.69 (d, *J* = 12.2 Hz, 1H), 3.64 (s, 3H), 3.30 (dd, *J* = 14.9, 5.1 Hz), 3.20 (dd, *J* = 14.9, 5.2 Hz), 2.40 – 2.47 (m, 2H), 2.00 – 2.10 (m, 4H),1.83 (dq, *J* = 14.5, 7.5 Hz); ^{13}C NMR (126 MHz, $CDCl_3$) δ 174.0, 173.1, 156.9, 135.9, 135.0, 128.6, 128.5, 128.4, 127.4, 123.5, 122.0, 119.4, 118.4, 111.4, 109.2, 67.5, 53.2, 52.3, 51.9, 32.4, 29.8, 28.0, 15.4; HRMS (ESI, +ve) $C_{25}H_{29}N_3O_5S[M+Na]^+$ calculated for 506.1717, found 506.1715.

_N_-[[(1_S_)-1-[(Benzyloxy)carbonyl]-4,4-(dimethyl)propyl] aminocarbonyl-L-phenylalanine methyl ester (16):

_N_-[[(1_S_)-1-[(Benzyloxy)carbonyl]-4,4-(dimethyl)propyl]aminocarbonyl]-L-pheny-lalanine methyl ester (**16**) (0.08 g, 0.18 mmol, 55%), white powder, was prepared following the same procedure as described for compound (**4**).

^{1}H NMR (500 MHz, $CDCl_3$) δ7.32 – 7.42 (m, 5H), 7.20 – 7.27 (m, 3H), 7.07 – 7.12 (m, 2H), 5.20 (d, *J* = 12.3 Hz, 1H), 5.09 – 5.15 (m, 3H), 4.82 (dt, *J* = 8.1, 5.5 Hz, 1H), 4.55 (td, *J* = 8.9, 5.2 Hz), 3.69 (s, 3H), 3.08 (t, *J* = 5.5 Hz, 2H), 1.63 – 1.71 (m, 1H), 1.58 (ddd, *J* = 13.6, 8.4, 5.2 Hz), 1.44 (ddd, *J* = 13.5, 9.3, 5.7 Hz, 1H), 0.90 (dd, *J* = 8.2, 6.5 Hz, 6H); ^{13}C NMR (126 MHz, $CDCl_3$) δ174.2, 172.9, 156.4, 135.9, 135.4, 129.4, 128.5, 128.4, 128.3, 128.1, 127.0, 67.0, 53.9, 52.2, 51.6, 41.9, 38.5, 24.7, 22.8, 21.8; HRMS (ESI, +ve) $C_{24}H_{30}N_2O_5$ $[M+H]^+$ calculated for 427.2227, found 427.2226.

_N_-[[(1_S_)-1-[(Benzyloxy)carbonyl]-4,4-(diemthyl)propyl]-aminocarbonyl]-L-methionine methyl ester (17):

_N_-[[(1_S_)-1-[(Benzyloxy)carbonyl]-4,4-(diemthyl)propyl]aminocarbonyl]-L-methionine methyl ester (**17**) (0.10 g, 0.24 mmol, 40%), white powder, was prepared following the same procedure as described for compound (**4**).

^{1}H NMR (500 MHz, $CDCl_3$) δ7.31 – 7.43 (m, 5H), 5.12 – 5.23 (m, 3H), 4.92 (d, *J* = 8.5 Hz, 1H), 4.61 (td, *J* = 7.7, 4.9 Hz, 1H), 4.54 (td, *J* = 8.9, 5.2 Hz, 1H), 3.77 (s, 3H), 2.51 – 2.58 (m, 2H), 2.08 – 2.20 (m, 4H), 1.95 (dq, *J* = 14.4, 7.4 Hz, 1H), 1.64 – 1.73 (m, 2H), 1.51 (ddd, *J* = 13.5, 9.2, 5.7 Hz, 1H), 0.93 (dd, *J* = 6.5, 4.7 Hz, 6H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 173.9, 173.4, 156.6, 135.4, 128.5, 128.3, 128.1, 67.0, 52.5, 52.3, 51.7, 41.9, 32.2, 29.9, 24.7, 22.8, 21.9, 15.4; HRMS (ESI, +ve) $C_{20}H_{30}N_2O_5S$ $[M+Na]^+$ calculated for 411.1948, found 411.1946.

_N_-[[(1_S_)-1-[(Benzyloxy)carbonyl]ethyl](^{13}C)aminocarbonyl]-L-tryptophan methyl ester (18):

_N_-[[(1_S_)-1-[(Benzyloxy)carbonyl]ethyl](^{13}C)aminocarbonyl]-L-tryptophan methyl ester (**18**) (0.70 g, 1.65 mmol, 90%), white powder, was prepared following the same procedure as described for compound (**4**). ^{13}C labelled carbon dioxide, $^{13}CO_2$, (carbon dioxide (^{13}C, 99 %) (< 1 % ^{18}O) purchased from Cambridge Isotope Laboratories, Inc.) was used instead of CO_2 derived from dry ice.

^{1}H NMR (500 MHz, $CDCl_3$) δ8.62 (s, 1H), 7.48 (d, *J* = 7.9 Hz, 1H), 7.31 – 7.35 (m, 4H), 7.19 – 7.22 (m, 2H), 7.16 (ddd, *J* = 8.1, 7.0, 1.1 Hz, 1H), 7.08 (ddd, *J* = 8.0, 7.0, 1.0 Hz, 1H), 6.87 (d, *J* = 2.4 Hz, 1H), 5.79 (dd, *J* = 8.5, 2.4 Hz, 1H), 5.65 (dd, *J* = 8.1, 2.4 Hz, 1H), 5.06 (d, *J* = 12.3 Hz, 1H), 4.86 (dtd, *J* = 7.9, 5.2, 2.5 Hz, 1H), 4.70 (d, *J* = 12.3 Hz, 1H), 4.62 – 4.68 (m, 1H), 3.62 (s, 3H), 3.28 (dd, 14.9, 5.2 Hz, 1H), 3.19 (dd, 14.9, 5.1 Hz, 1H),1.31 (d, *J* = 7.3 Hz, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 175.1, 173.3, 156.8, 135.9, 135.2, 128.5, 128.3, 128.1, 127.4, 123.6, 121.9, 119.3, 118.4, 111.4, 109.2, 67.2, 53.1, 52.3, 48.5, 28.0, 19.1; HRMS (ESI, +ve) $C_{22}{}^{13}CH_{25}N_3O_5$ $[M+Na]^+$ calculated for 447.1756, found 447.1755.

_N_-[[(1_S_)-1-[(Benzyloxy)carbonyl]ethyl]aminocarbonyl]-L-tryptophan methyl ester using p-toluenesulfonyl chloride (4): *General procedure using p-TsCl as activator.*

Dry ice was placed in a 500 ml round-bottom flask connected to a paraffin oil bubbler then to a drying tube containing pellets of 4 Å molecular sieves. Using the Teflon tubing, $CO_{2\,(g)}$ derived from dry ice was bubbled into a stirred, solution of L-alanine benzyl ester *p*-toluenesulfonate salt (0.20 g, 0.57 mmol), 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) (0.43 ml, 2.85 mmol) and pyridine (0.14 ml, 1.71 mmol) in anhydrous DCM (30 ml) at -20 °C, for a period of 30 minutes whilst keeping the mixture at -20 °C. Subsequently, a solution of *p*-toluenesulfonyl chloride (0.22 g, 1.14 mmol) in anhydrous DCM (5 ml) was added to the reaction over a period of 20 minutes under an atmosphere of argon. The reaction was then left stirring under an atmosphere of argon for 2 hours while it was allowed to warm up to room temperature. Upon addition of *p*-toluenesulfonyl chloride, the color of the reaction mixture gradually changed from clear to yellow as the reaction warms up to room temperature. Afterwards, the solvent was removed under reduced pressure and the brown, oily residue was dissolved in anhydrous pyridine (8 ml). Under an atmosphere of argon, a solution of L-tryptophan methyl ester hydrochloride salt (0.15 g, 0.57 mmol) in anhydrous pyridine (2 ml) was added over a period of 10 minutes at room temperature. The mixture was left stirring under an atmosphere of argon at room temperature for 4 hours. The solvent was then removed under reduced pressure and the brown residue was dissolved in ethyl acetate (50 ml) and washed five times with a saturated sodium bicarbonate solution (40 ml). The organic layer was dried over magnesium sulfate, filtered, concentrated under reduced pressure and purified using flash chromatography (silica, hexane : ethyl acetate 3 : 1 to 1 : 1,

ninhydrin/UV) to yield the target compound (**4**) (0.08 g, 0.2 mmol, 35%) as a white powder.

N*-[[(1*S*)-1-[(Benzyloxy)carbonyl]ethyl]aminocarbonyl]-L-tryptophan methyl ester (4): *General procedure using HATU as activator.

Dry ice was placed in a 500 ml round-bottom flask connected to a paraffin oil bubbler then to a drying tube containing pellets of 4 Å molecular sieves. Using the Teflon tubing, $CO_{2\,(g)}$ derived from dry ice was bubbled into a stirred, solution of L-alanine benzyl ester *p*-toluenesulfonate salt (0.20 g, 0.57 mmol), 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) (0.43 ml, 2.85 mmol) and pyridine (0.14 ml, 1.71 mmol) in anhydrous DCM (30 ml) at -20 °C, for a period of 30 minutes whilst keeping the mixture at -20 °C. The reaction was allowed to warm up to room temperature and the solvent was removed under reduced pressure. The residue obtained was then dissolved in anhydrous DMF, (3 ml) and a solution of HATU (0.43 g, 1.14 mmol) in anhydrous DMF (1 ml) was added to the reaction followed by a solution of *N*,*N*-diisopropylethylamine, DIPEA (0.4 ml, 2.28 mmol) in anhydrous DMF (1 ml) under an atmosphere of argon. The reaction was then left stirring under an atmosphere of argon for 30 minutes. Subsequently, a solution of L-tryptophan methyl ester hydrochloride salt (0.15 g, 0.57 mmol) in anhydrous DMF (2 ml) was added over a period of 10 minutes at room temperature. The mixture was left stirring under an atmosphere of argon at room temperature for 4 hours. The solvent was then removed under reduced pressure and the brown residue was dissolved in ethyl acetate (50 ml) and washed five times with a saturated sodium bicarbonate solution (40 ml). The organic layer was dried over magnesium sulfate, filtered, concentrated under reduced pressure and purified using flash chromatography (silica, hexane : ethyl acetate 3 : 1 to 1 : 1, ninhydrin/UV) to yield the target compound (**4**)(0.11 g, 0.27 mmol, 48%) as a white powder.

L-5-Bromotryptophan methyl ester (19):

Acetyl chloride (0.20 ml, 2.80 mmol) was added over a period of 5 minutes to a stirred solution of L-5-bromotryptophan (0.19 g, 0.70 mmol) in methanol (20 ml) at 0 °C. Following addition, the reaction mixture was allowed to warm up to room temperature then heated to reflux for 3 hours. When no trace of starting material remained (TLC: silica, methanol, ninhydrin, R_f 0.6), the solvent was removed under reduced pressure to leave L-5-bromotryptophan methyl ester (**19**) (0.20 g, 0.69 mmol, >95%), bright red solid. No further purification was required.

^{1}H NMR (500 MHz, CD_3OD) δ 7.69 (s, 1H), 7.35 (d, *J* = 8.6 Hz, 1H), 7.22 – 7.30 (m, 2H), 4.34 (t, *J* = 6.2 Hz, 1H), 3.82 (s, 3H), 3.35 – 3.50 (m, 2H); ^{13}C NMR (126 MHz, CD_3OD) δ 169.3, 135.4, 128.6, 125.9, 124.2, 120.1, 113.0, 112.0, 105.8, 53.1, 52.3, 25.8; HRMS (ESI, +ve) $C_{12}H_{13}BrN_2O_2$ $[M+H]^+$ calculated for 297.0226, found 297.0228.

L-7-Iodotryptophan methyl ester (20):

L-7-Iodotryptophan methyl ester (**20**)(0.09 g, 0.27 mmol, 92%), white powder, was prepared following the same procedure as described for compound (**19**).

^{1}H NMR (400 MHz, CD_3OD) δ 7.56 (dd, *J* = 14.8, 7.6 Hz, 1H), 7.34 (s, 1H), 6.88 (t, *J* = 7.6 Hz, 1H), 4.35 (apparent t, *J* = 6.1 Hz, 1H), 3.79 (s, 3H), 3.42 (m, 2H); ^{13}C NMR (101 MHz, CD_3OD) δ 169.2, 138.6, 130.7, 127.2, 125.3, 120.6, 117.8, 107.7, 75.7, 53.2, 52.4, 26.2; HRMS (ESI, +ve) $C_{12}H_{13}IN_2O_2$ $[M+H]^+$ calculated for 345.0094, found 345.0098.

L-5-Chlorotryptophan methyl ester (21):

L-5-Chlorotryptophan methyl ester (**21**)(0.12 g, 0.47 mmol, 94%), white powder, was prepared following the same procedure as described for compound (**19**).

^{1}H NMR (400 MHz, CD_3OD) δ 7.54 (s, 1H), 7.38 (d, *J* = 8.6 Hz, 1H), 7.29 (s, 1H), 7.12 (d, *J* = 7.9 Hz, 1H), 4.35 (t, *J* = 5.8 Hz, 1H), 3.82 (s, 3H), 3.36 – 3.48 (m, 2H); ^{13}C NMR (101 MHz CD_3OD) δ 169.3, 135.2, 127.9, 1206.0, 124.7, 121.6, 117.0, 112.5, 105.9, 53.1, 52.3, 25.9; HRMS (ESI, +ve) $C_{12}H_{13}ClN_2O_2$ $[M+H]^+$ calculated for 253.0738, found 253.0743.

L-5-Fluorotryptophan methyl ester (22):

L-5-Fluorotryptophan methyl ester (**22**)(0.10 g, 0.42 mmol, 94%), white powder, was prepared following the same procedure as described for compound (**19**).

^{1}H NMR (400 MHz, CD_3OD) δ 7.34 – 7.41 (dd, *J* = 8.7, 4.1 Hz, 1H), 7.29 (s, 1H), 7.19 – 7.25 (m, 1H), 6.93 (t, *J* = 9.1 Hz, 1H), 4.34 (t, *J* = 5.8 Hz, 1H), 3.82 (s, 3H), 3.31 – 3.48 (m, 2H); ^{13}C NMR (101 MHz, CD_3OD) δ 169.3, 157.7 (d, *J* = 233.0 Hz), 133.4, 126.2, 124.8, 112.1 (d, *J* = 9.6Hz), 109.6 (d, *J* = 26.5 Hz), 106.3, 102.2 (d, *J* = 23.9 Hz), 53.1, 52.3, 26.0; ^{19}F NMR (377 MHz, CD_3OD, decoupled ^{1}H) δ -126.98; HRMS (ESI, +ve) $C_{12}H_{13}FN_2O_2$ $[M+H]^+$ calculated for 237.1034, found 237.1037.

L-Methionine benzyl ester *p*-toluenesulfonate (23)[33]:

To a stirred solution of L-methionine (0.20 g, 1.34 mmol) and *p*-toluenesulfonic acid (0.27 g, 1.60 mmol) in toluene (50 ml), a solution of benzyl alcohol (0.27 ml, 2.68 mmol) in toluene (10 ml) was added at room temperature over a period of 10 minutes. Following addition the mixture was set to reflux for 20 hours while fitted with a Dean-Stark apparatus to remove water. The reaction mixture was allowed to cool to room temperature, and then stored in the freezer for 3 h. The precipitate was filtered and washed with toluene to yield L-methionine benzyl ester *p*-toluenesulfonate salt (**23**) (0.35 g, 0.85 mmol, 75%) as a white solid. No further purification was required.

^{1}H NMR (500 MHz, $CDCl_3$) δ 8.37 (s, 2H), 7.76 (d, *J* = 7.9 Hz, 2H), 7.18 – 7.35 (m, 5H), 7.08 (d, *J* = 7.9 Hz, 2H), 5.13 (d, *J* = 12.2 Hz, 1H), 5.00 (d, *J* = 12.2 Hz, 1H), 4.18 (q, *J* = 5.9 Hz, 1H), 2.50 (dt, *J* = 14.6, 7.5 Hz, 1H), 2.41 (dt, *J* = 13.9, 7.4 Hz, 1H), 2.31 (s, 3H), 2.12 (apparent hep, *J* = 6.6 Hz, 2H), 1.84 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 168.9, 141.2, 140.4, 134.7, 128.9, 128.5, 128.4, 128.3, 126.0, 67.9, 52.1, 29.4, 28.9, 21.3, 14.8; HRMS (ESI, +ve) $C_{12}H_{17}NO_2S[M+H]^+$ calculated for 240.1053, found 240.1050.

L-Leucine benzyl ester *p*-toluenesulfonate (24)[33]:

L-Leucine benzyl ester *p*-toluenesulfonate (**24**) (0.30 g, 0.76 mmol, 70%), white powderwas prepared following the same procedure as described for compound (**23**).

^{1}H NMR (500 MHz, $CDCl_3$) δ 8.37 (bs, 2H), 7.77 (d, *J* = 7.9 Hz, 2H), 7.25 – 7.32 (m, 5H), 7.08 (d, *J* = 7.9 Hz, 2H), 5.12 (d, *J* = 12.3 Hz, 1H), 5.04 (d, *J* = 12.3 Hz, 1H), 3.97 (t, *J* = 6.9 Hz, 1H), 2.32 (s, 3H), 1.61 –1.74 (m, 3H), 0.75 (dd, *J* = 7.7, 5.8 Hz, 6H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 169.7, 141.4, 140.2, 134.8, 128.8, 128.4, 128.3, 128.2, 126.1, 67.7, 51.7, 39.2, 24.1, 22.0, 21.9, 21.3; HRMS (ESI, +ve) $C_{13}H_{19}NO_2$ $[M+H]^+$ calculated for 222.1485, found 222.1483.

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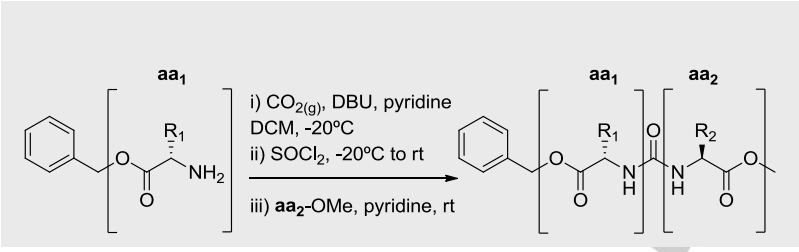

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