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An unexpected product from attempted reductive etherification of a silyl alcohol with an aldehyde

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Abstract—Reductive etherification, using $BiBr_3/Et_3SiH$, between two modified amino acids, one with a silyl alcohol side chain and one with an aldehyde side chain, gave, not the desired bis-amino acid, but a tetrahydrooxazine, in good yield.

1. Introduction

Many different approaches to generating short peptides with defined conformational properties have been reported. One important strategy is the synthesis of peptides where two or more side chains are linked together. The synthesis of such peptides has previously relied on the preparation of a linear peptide, followed by the development of chemistry for linking two side chains that would be both regioselective and compatible with the underlying peptide.[1–3]

We have recently developed a complementary approach to the synthesis of side-chain bridged peptides. This entails, firstly, the synthesis of a bis-amino acid with the desired side-chain link in place between the two Cα positions. The bis-amino acid is protected at one end with a transient (Fmoc) protecting group, whilst the NH_2 and COOH groups at the other end are protected with groups orthogonal to both Fmoc and to the permanent ^{t}Bu/Boc groups on other amino acid side chains. These amino acids can then be incorporated into the desired peptide by standard solid-phase methods, with the desired bridge being generated by removal of the orthogonal protecting groups followed by on-resin cyclisation. We have so far used this approach to synthesise peptides bridged by aliphatic links,[4] norlanthionine[5] and lanthionine.[6]

Constrained cyclic peptides with aliphatic ether linkages between two side chains have rarely been reported, probably due to the difficulties inherent in forming the ether between two amino acid side chains of a linear peptide. As this motif could potentially provide an interesting conformational constraint, we sought to synthesise the ether-linked bis-amino acid **1** and use this in the solid-phase synthesis of cyclic peptides with aliphatic ether linkages. We envisaged that the key step in the synthesis would be the formation of the ether linkage itself, using the reductive etherification of a silyl alcohol with an aldehyde recently reported by several groups for intermolecular[7–9] and intramolecular[10] etherification.

2. Results

To carry out the reductive etherification, a silyl alcohol fragment **2** and an aldehyde **3** were required. It seemed expedient to prepare both of these from aspartic acid. However, it was important not to use the same protecting group chemistry on the two fragments, as after the etherification reaction it would be necessary to differentiate the two amino groups, and likewise the two carboxyl groups. Careful choice of protection for the α-COOH groups was also necessary. We envisaged that the synthetic routes to both **2** and **3** would have homoserine derivatives as key intermediates. These are known to lactonise rapidly[11] unless bulky α-COOH protecting groups are employed.

The silyl alcohol was prepared in the following manner (Scheme 1). Selective β-esterification[12] of aspartic acid afforded **4**, followed by Boc protection to give **5** and α-esterification to give **6**. As the reduction of **6** with DIBAL did not give a clean reaction, it was decided to install a second Boc protecting group to remove any possibility of interference by the acidic NH.[13] Accordingly, **6** was protected under mild conditions[14] to give **7**,[15] which was then reduced using DIBAL[15] to give alcohol **8**.[16] Silylation under standard conditions[17] gave the desired **9**.

Keywords: Reductive etherification; Cyclic aminal.
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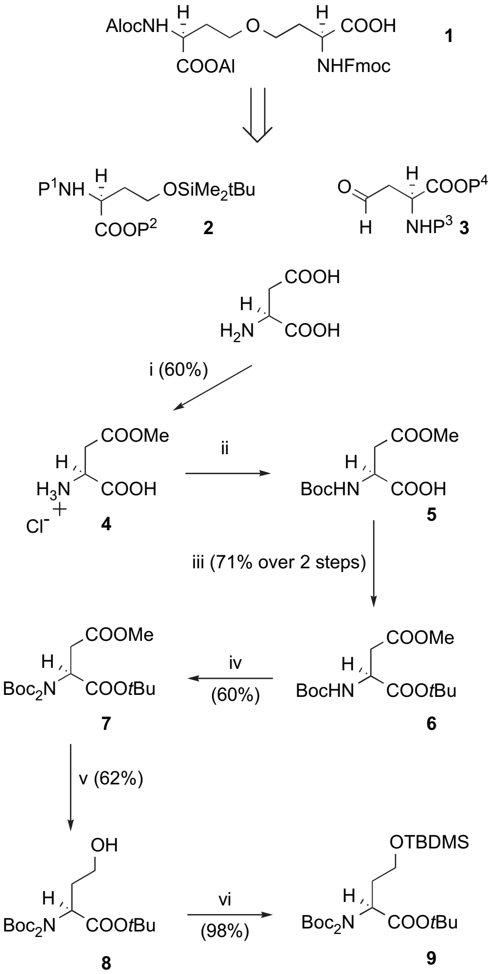
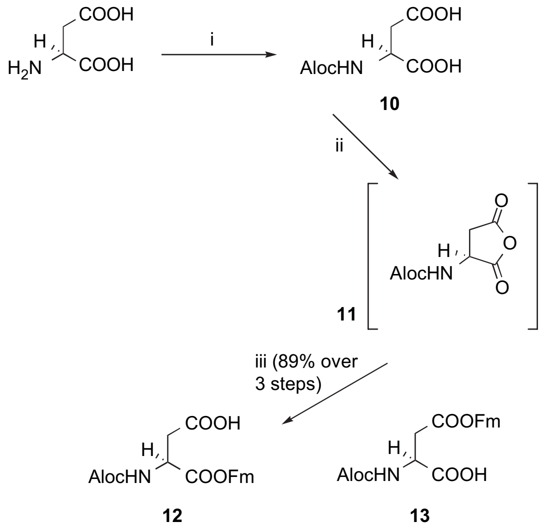
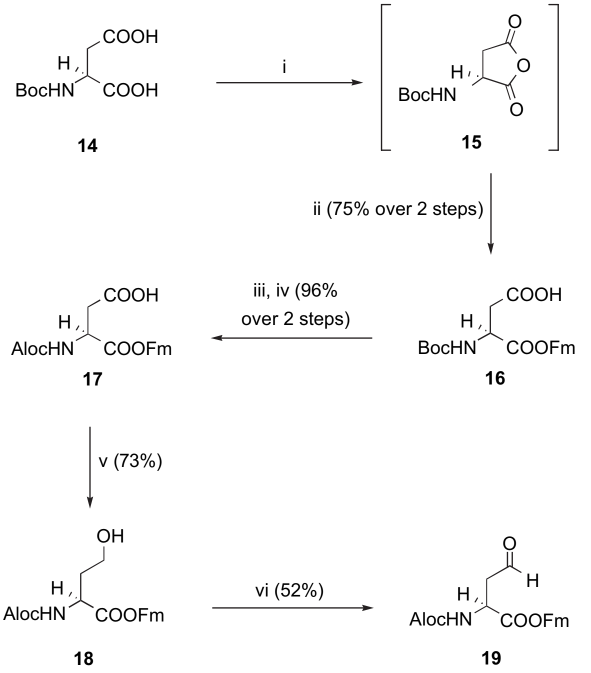


Scheme 1. (i) $SOCl_2$, MeOH, −10 °C to rt; (ii) $(Boc)_2O$, Na_2CO_3, THF/H_2O (2:1), rt, 48 h; (iii) ^{t}BuOH, DCC, DMAP, CH_2Cl_2, 0 °C to rt, 48 h; (iv) $(Boc)_2O$, DMAP, MeCN, rt, 24 h; (v) DIBAL, THF, −45 °C, 1 h; (vi) TMDMS-Cl, DMF, imidazole, rt, 18 h.

A recent publication[2b] suggested that use of the Fm protecting group at the α-COOH of homoserine would prevent the inherent problem of lactonisation. As the Fm and ^{t}Bu esters are orthogonal, this appeared to be an ideal way to prepare the aldehyde fragment from aspartic acid. A reported procedure for synthesis of Boc-Asp-OFm[18] involved conversion of Boc-Asp-OH to its anhydride, followed by ring-opening with Fm-OH to give predominantly the α-ester, which could be separated from the β-ester by selective recrystallisation. We initially wished to modify this procedure by using the Aloc group on the α-NH_2, as this was more useful for our purposes. Heating Aloc-Asp-OH **10** with acetic anhydride (Scheme 2) gave the anhydride **11**, which was immediately treated with 9-fluorenylmethanol to give a mixture of **12** and **13**. Unfortunately, this mixture could not be separated by either recrystallisation or by flash column chromatography. We therefore reverted to the protecting group used in the original paper. Dehydration of Boc-Asp-OH **14** to give the intermediate anhydride **15** (Scheme 3) proceeded cleanly using DIC; ring-opening with 9-fluorenylmethanol gave predominantly the desired regioisomer **16**, which was isolated pure after four recrystallisations in excellent yield. The Boc group was then exchanged for the Aloc group to give **17**, and careful control of the reaction conditions ensured no transesterification took place. Reduction of the free β-COOH via mixed anhydride formation followed by $NaBH_4$ gave the homoserine derivative **18**. This was stable indefinitely at −20 °C, however at room temperature in solution some lactonisation was observed. Finally, Swern reaction[19] of **18** afforded the desired aldehyde **19**.

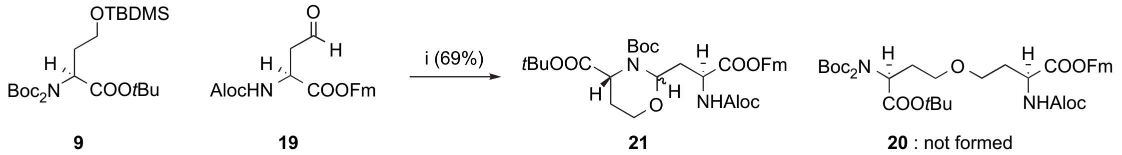


Scheme 2. (i) Allyl chloroformate, Na_2CO_3, H_2O, rt, 24 h; (ii) Ac_2O, THF, reflux, 4 h; (iii) 9-fluorenylmethanol, $^i Pr_2EtN$, THF, rt.



Scheme 3. (i) DIC, $^i Pr_2EtN$, THF, rt, 4 h; (ii) $^i Pr_2EtN$, 9-fluorenylmethanol, THF, 24 h; (iii) TFA/CH_2Cl_2 (1:1), Et_3SiH, 0 °C, 2.5 h; (iv) allyl chloroformate, $NaHCO_3$, THF/H_2O (1:1), 0 °C, 2 h; (v) $^i Pr_2EtN$, isobutylchloroformate, CH_2Cl_2, rt, 1 h, then MeOH, $NaBH_4$, −78 °C; (vi) $(COCl)_2$, DMSO, CH_2Cl_2, −78 °C, 30 min, then **18** added, Et_3N, warm to 0 °C, 2 h.

We then attempted the reductive etherification reaction using the previously reported procedure[7,10] (Scheme 4). This gave a product with four of the five protecting groups (Fm, Aloc, ^{t}Bu and a single Boc) present. However, careful inspection of the spectroscopic data indicated that this was not the desired ether-bridged bis-amino acid, **20**, but the cyclic



Scheme 4. (i) BiBr$_3$, Et$_3$SiH, MeCN, 24 h.

1,3-tetrahydrooxazine **21**. We assume by analogy with our previous work[20] that two diastereoisomers are present, however the NMR spectrum was not well enough resolved to allow this to be unambiguously determined or to allow the ratio to be measured.

3. Discussion

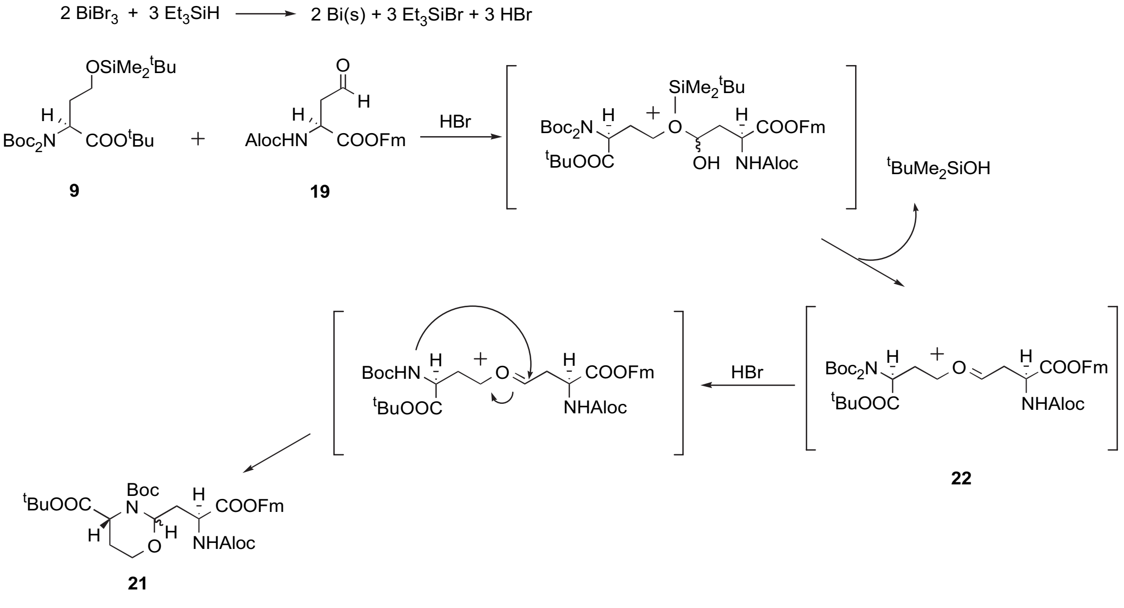
There has recently been some debate about the catalyst formed during the reductive etherification of aldehydes using BiBr$_3$/Et$_3$SiH. Bajwa et al.[7] hypothesised that the active catalyst is Et$_3$SiBr, formed in situ, acting as a Lewis acid catalyst. In this mechanistic scheme, HBr would also be generated, but would be removed by reaction with the solvent, acetonitrile. However, Evans et al.[10] recently demonstrated that the active species is unlikely to be Et$_3$SiBr (which is highly moisture-sensitive) as the reaction will also take place in the presence of 1 equiv of H$_2$O. Moreover, if 4 Å molecular sieves or the base 2,6-di-*tert*-butyl-4-methylpyridine (DTBMP), which should sequester or quench HBr, was added, no reaction takes place. It was therefore demonstrated that the reaction most likely involves Brønsted acid catalysis by HBr.

It is probable, therefore, that the mechanism for the formation of **21** is as follows (Scheme 5). HBr catalyses the initial formation of an adduct between silyl alcohol **9** and aldehyde **19** as shown previously. Loss of silanol then affords the oxonium species **22**. Concomitant deprotection of the first Boc group by the HBr then gives an intramolecular nucleophile that can react with the oxonium ion, leading to **21**. Clearly the intramolecular cyclisation is much more rapid than reduction of **22** by triethylsilane, which would be the normal course of this reaction. We observed no evidence for silane reduction of the cyclic 1,3-tetrahydrooxazine **21** under these conditions. Furthermore, reductive cleavage of **21** would in all probability lead to cleavage of the C–O bond, affording a secondary amine, via *N*-acetyliminium formation.[21]

It is also likely that the HBr is responsible for the deprotection of the first Boc group. Indeed, there is precedent for this deprotection,[22] whereas Boc groups are generally stable to mild Lewis acids and can, in fact, be prepared using Lewis acids.[23] This reinforces the probability that the HBr formed from the BiBr$_3$ is not buffered by the acetonitrile, but instead is present in the reaction mixture. We attempted to neutralise the HBr formed with K$_2$CO$_3$, however as expected no reaction took place under these conditions.

4. Conclusions

During an attempted reductive etherification reaction between a silyl alcohol and an aldehyde, both derived from protected amino acids, a 1,3-tetrahydrooxazine was unexpectedly formed instead of the desired ether. Although this undesired reaction meant that this route to ether-bridged bis-amino acids had to be abandoned, as it would be impossible to convert the 1,3-tetrahydrooxazine to the desired ether via a ring-opening reaction, the reaction has shed



Scheme 5.

further light on the mechanism of reductive etherification using $BiBr_3/Et_3SiH$. Finally, this reaction also represents a direct and potentially useful route from chiral pool starting materials to 1,3-tetrahydrooxazines, which are useful intermediates in the synthesis of a number of *N*-heterocycles.[21]

5. Experimental

5.1. General procedures and materials

All reagents used for synthesis were purchased from commercial suppliers. Reactions requiring anhydrous conditions were carried out in oven-dried glassware under Ar. Solvents were purified using activated alumina solvent drying columns. NMR spectra were recorded on a Bruker AMX300 spectrometer, chemical shifts (δ) are reported in parts per million (ppm) using residual isotopic solvent as an internal reference. Coupling constants (J) are reported in hertz (Hz). Electrospray mass spectra were recorded on Micromass Quattro LC, Thermo Finnegan MAT 900XP or VG ZAB 2SE instruments, and fast atom bombardment mass spectra on Thermo Finnegan MAT 900XP or VG ZAB 2SE instruments. IR spectra were recorded on a Shimadzu FT-IR 8700.

5.1.1. *tert*-Butyl-*N*,*N*-bis(*tert*-butyloxycarbonyl)-L-homoserinate 8.[16] To a solution of **7**[13,15] (100 mg, 0.248 mmol) in dry CH_2Cl_2 (8.0 mL) at −78 °C under Ar was added DIBAL (1.0 M solution in toluene, 520 μL, 0.521 mmol, 2.1 equiv) slowly over 8 min. The reaction mixture was stirred for 1 h before being quenched with acetone (5.0 mL) and then H_2O (1.0 mL), allowed to warm to room temperature, dried (Na_2SO_4) and filtered through Celite. The solvent was removed in vacuo and the residual oil purified by flash column chromatography (silica gel, 20% EtOAc in hexane, R_f=0.30) to yield **8** as a thick colourless oil (91 mg, 98%); $[\alpha]^{22}_{D}$ −23.3 (c 0.38, in CH_2Cl_2); ^1H NMR (300 MHz, $CDCl_3$) δ 4.90 (1H, dd, J=9.5, 4.9 Hz, CH α), 3.68 (2H, m, CH_2 γ), 2.30 (1H, m, CH_2 β), 1.95 (1H, m, CH_2 β), 1.46 (18H, s, 2×NCOOC(CH_3)$_3$), 1.39 (9H, s, OCOC(CH_3)$_3$); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 170.9, 153.0, 83.6, 81.9, 59.8, 56.9, 32.9, 28.4, 28.3; IR (film) ν_{max} 3543 (O–H), 2979, 2935, (C–H), 1747 (C=O), 1700 (C=O) cm^{-1}; ES$^+$ $C_{18}H_{33}NO_7Na$ m/z [M+Na]$^+$ 398; HRMS calcd for $[C_{18}H_{33}NO_7Na]^+$ 398.21546, found 398.21600.

5.1.2. *tert*-Butyl-*N*,*N*-bis(*tert*-butyloxycarbonyl)-L-homoserinate *tert*-butyldimethylsilyl ether 9. To a solution of **8** (500 mg, 1.33 mmol) in dry DMF (0.5 mL) was added imidazole (26 mg, 3.33 mmol, 2.5 equiv) and $^tBuMe_2SiCl$ (260 mg, 1.8 mmol, 1.35 equiv). The resulting solution was stirred for 18 h under Ar before being diluted with saturated brine (20 mL) and ethyl acetate (20 mL). The organic layer was then washed with saturated brine (2×50 mL), dried (Na_2SO_4) and concentrated in vacuo. The residual oil (0.98 g) was purified by flash column chromatography (silica gel, 5% EtOAc, 0.001% Et_3N in hexane, R_f=0.25) to yield **9** as a clear colourless oil (640 mg, 98.4%); $[\alpha]^{20}_{D}$ +27.7 (c 1.1, in CH_2Cl_2); ^1H NMR (300 MHz, $CDCl_3$) δ 4.90 (1H, dd, J=8.6, 5.3 Hz, CH α), 3.67 (2H, m, CH_2 γ), 2.34 (1H, m, CH_2 β), 2.00 (1H, m, CH_2 β), 1.49 (18H, s, NCOC(CH_3)$_3$), 1.43 (9H, s, OCOC(CH_3)$_3$), 0.87 (9H, s, Si(CH_3)$_2$C(CH_3)$_3$), 0.03 (6H, s, Si(CH_3)$_2$C(CH$_3$)$_3$); ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.1, 152.4, 82.6, 81.1, 60.2, 55.9, 33.1, 28.0, 27.9, 26.0, 18.3 (Si(CH$_3$)$_2$C(CH$_3$)$_3$ not present); IR (film) ν_{max} 2979, 2956 (C–H), 1737 (C=O), 1705 (C=O) cm^{-1}; HRMS calcd for $[C_{24}H_{47}NO_7SiNa]^+$ 512.30193, found 512.30246.

5.1.3. α-Fluorenylmethyl-*N*-*tert*-butyloxycarbonyl-L-aspartate 16.[18] To a stirred solution of L-aspartic acid (20.0 g, 0.150 mol) and Na_2CO_3 (47.7 g, 0.450 mol, 3 equiv) in H_2O (1.0 L) at 0 °C was added $(Boc)_2O$ (32.8 g, 0.150 mol, 1 equiv) over 20 min. After slow warming to room temperature the reaction was stirred for 24 h. The mixture was then cooled to 0 °C and acidified to pH 2.0 with 0.05 M $KHSO_4$ before being extracted with EtOAc (5×150 mL). The organic layer was then washed with brine (3×200 mL), dried (Na_2CO_3) and concentrated in vacuo to give *N-tert*-butyloxycarbonyl-L-aspartic acid as a clear colourless oil, which was used in the next step without further purification.

To a stirred solution of *N-tert*-butyloxycarbonyl-L-aspartic acid (10.0 g, 0.0429 mol) in dry THF (175 mL) under an argon atmosphere was added DIC (7.32 mL, 0.0473 mol, 1.1 equiv) dropwise over 20 min. After 4 h the reaction mixture was filtered through a dry sinter funnel and concentrated to approximately 100 mL in vacuo. To the solution was added 9-fluorenylmethanol (9.28 g, 0.0473 mol, 1.1 equiv) in one portion and then $^iPr_2EtN$ (4.1 mL, 0.0452 mol, 1.05 equiv) dropwise over 20 min. The reaction was then stirred for 24 h under argon before being diluted with toluene (50 mL) and quenched with AcOH (5 mL). The solution was concentrated in vacuo until approximately 10 mL remained and was then diluted with EtOAc (100 mL), washed with 0.05 M $KHSO_4$ (3×100 mL), saturated brine (3×100 mL), dried (Na_2SO_4) and the solvent evaporated in vacuo. After 24 h drying on a high vacuum line a pink solid remained, which was subsequently dissolved in a minimum amount of hot EtOAc and recrystallised by addition of hexane. The filtered solid was then washed twice with cold ethyl acetate to give crude **16**. The filtrate was concentrated in vacuo and recrystallised another four times to give **16** as a solid (13.2 g, 75%), mp 138–142 °C [lit.[18b] mp 156 °C]; R_f=0.1–0.3 (silica gel, 50% EtOAc in hexane); $[\alpha]^{20}_{D}$ +19.1 (c 0.45, in MeOH) lit.[18b] $[\alpha]^{20}_{D}$ +15.2 (c 1.00, in THF); ^1H NMR (300 MHz, $CDCl_3$/DMSO (9:1)) δ 7.45 (2H, m, CH Ar), 7.26 (2H, m, CH Ar), 7.10 (2H, t, J=7.4 Hz, CH Ar), 6.98 (2H, t, J=7.4 Hz, CH Ar), 5.74 (1H, br d, J=9.0 Hz, NH), 4.30 (1H, m, CH α), 4.02 (2H, m, COOCH_2CHAr), 3.88 (1H, d, J=7.2 Hz, COOCH$_2$CHAr), 2.66 (1H, dd, J=17.2, 5.2 Hz, CHH β), 2.43 (1H, m, CHH β), 1.11 (9H, s, NCOOC(CH_3)$_3$); ^{13}C NMR (75 MHz, $CDCl_3$/DMSO) δ 171.8, 171.3, 155.3, 143.4, 140.9, 127.7, 127.1, 125.0, 119.8, 82.5, 67.3, 49.9, 46.4, 42.7, 28.2; IR (Nujol mull) ν_{max} 2650–3300 (broad, COOH), 3290 (N–H), 2952, 2922 (C–H), 1737 (C=O), 1504 (C=C, Ar) cm^{-1}; HRMS calcd for $[C_{23}H_{25}NO_6Na]^+$ 434.15795, found 434.15697.

5.1.4. α-Fluorenylmethyl-*N*-allyloxycarbonyl-L-aspartate 17. To a solution of CH_2Cl_2/TFA (1:1, 5.0 mL) at 0 °C was added **16** (200 mg, 0.486 mmol). The mixture was stirred at this temperature for 2.5 h before being poured into ether (300 mL) and cooled to −23 °C in the freezer overnight. After this time a solid precipitate was formed, which was isolated by filtration. The filtrate was diluted with hexane (100 mL) and again cooled to −23 °C in the freezer overnight to produce more solid. The solid was isolated by filtration and this process was performed once more to yield α-fluorenylmethyl-L-aspartate, which was used crude in the following reaction.

To a solution of α-fluorenylmethyl-L-aspartate (270 mg, 0.657 mmol) and $NaHCO_3$ (330 mg, 3.94 mmol, 6 equiv) in H_2O/THF (1:1, 16 mL) at 0 °C was added allyl chloroformate (67 μL, 0.723 mmol, 1.1 equiv) with stirring. After 2 h the reaction was quenched by careful addition of 0.05 M $KHSO_4$ (20 mL) and diluted with EtOAc (50 mL). The organic layer was washed with 0.05 M aqueous $KHSO_4$ (3×40 mL), saturated brine (3×40 mL), dried (Na_2SO_4) and the solvent removed in vacuo to give a thick oil. Purification by flash column chromatography (silica gel, 1% AcOH, 50% EtOAc in hexane (R_f=0.1–0.3 (silica gel, 50% EtOAc in hexane))) provided **17** as a cloudy pink crystalline glass, mp 68 °C (249 mg, 96%); $[\alpha]_D^{20}$ −16.7 (*c* 0.59, in MeOH); ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.25 (1H, br s, COO*H*), 7.73 (2H, d, *J*=7.5 Hz, C*H* Ar), 7.53 (2H, t, *J*=6.6 Hz, C*H* Ar), 7.38 (2H, m, C*H* Ar), 7.28 (2H, m, C*H* Ar), 5.89 (2H, m, N*H*, CH$_2$C*H*=CH$_2$), 5.35–5.2 (2H, m, CH$_2$CH=C*H*$_2$), 4.68 (1H, m, C*H* α), 4.66 (2H, m, C*H*$_2$CH=CH$_2$), 4.54 (2H, m, COOC*H*$_2$CHAr), 4.22 (1H, t, *J*=6.3 Hz, COOCH$_2$C*H*Ar), 2.89 (1H, dd, *J*=17.7, 4.5 Hz, C*H*H β), 2.71 (1H, dd, *J*=17.7, 4.5 Hz, CH*H* β); ^{13}C NMR (75 MHz, $CDCl_3$/DMSO) δ 175.7, 170.7, 156.0, 143.4, 141.3, 132.4, 127.9, 127.2, 124.9, 120.0, 118.2, 67.7, 66.2, 50.2, 46.7, 36.3; IR (Nujol mull) ν_{max} 2650–3200 (broad, COOH), 3305 (N–H), 2952, 2922 (C–H), 1747 (C=O), 1645 (C=C),1506 (C=C, Ar); ES$^+$ $C_{22}H_{21}NO_6Na$ *m/z* [M+Na]$^+$ 418; HRMS calcd for $[C_{22}H_{22}NO_6]^+$ 396.14471, found 396.14642.

5.1.5. Fluorenylmethyl-*N*-allyloxycarbonyl-L-homoserinate 18. To a stirred solution of **17** (1.7 g, 4.30 mmol) in dry CH_2Cl_2 (10.0 mL) was added isobutyl chloroformate (614 μL, 4.73 mmol, 1.1 equiv) dropwise over 5 min, followed by *N*-methylmorpholine (373 μL, 4.30 mmol, 1 equiv). The reaction was stirred under argon at room temperature for 30 min and then cooled to −78 °C before $NaBH_4$ (325 mg, 8.6 mmol, 2 equiv) was added in one portion, followed by dropwise addition of MeOH (10.0 mL) over 10 min. After 1.5 h the reaction was quenched by addition of AcOH (3.0 mL) and stirred for 30 min at −78 °C before warming to room temperature and dilution with toluene (40 mL). The solvents were removed in vacuo with the water bath not exceeding 30 °C to give a thick oil. This was taken up in EtOAc (50 mL) and washed with 0.1 M HCl (3×50 mL), saturated brine (3×50 mL), dried (Na_2SO_4) and the solvent evaporated in vacuo to yield a viscous oil. This was purified by flash column chromatography (silica gel, 40% EtOAc in hexane (R_f=0.25 (silica gel, 50% EtOAc in hexane))) to give **18** as a clear colourless oil (1.3 g, 73%); $[\alpha]_D^{20}$ −84.7 (*c* 0.46, in CH_2Cl_2); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.73 (2H, d, *J*=7.5 Hz, C*H* Ar), 7.57 (2H, m, C*H* Ar), 7.36 (2H, m, C*H* Ar), 7.30 (2H, m, C*H* Ar), 5.89 (2H, m, N*H*, CH$_2$C*H*=CH$_2$), 5.37–5.18 (2H, m, CH$_2$CH=C*H*$_2$), 4.57–4.43 (5H, m, C*H*$_2$CH=CH$_2$, COOC*H*$_2$CHAr, C*H* α), 4.21–4.09 (1H, br m, COOCH$_2$C*H*Ar), 3.63 (2H, m, C*H*$_2$OH), 2.03 (1H, m, C*H*$_2$ β), 1.69 (1H, m, C*H*$_2$ β); ^{13}C NMR (75 MHz, $CDCl_3$) δ 172.5, 156.6, 143.6, 141.3, 132.5, 127.9, 127.2, 125.0, 120.1, 118.0, 67.1, 66.0, 58.5, 51.7, 46.8, 34.9; IR (film) ν_{max} 3419 (N–H), 3533 (O–H), 2899 (C–H), 1758 (C=O), 1683 (C=C), 1576 (C=C, Ar); HRMS calcd for $[C_{22}H_{23}NO_5Na]^+$ 404.14738, found 404.14640.

5.1.6. 2-(*S*)-Allyloxycarbonylamino-4-oxo-butyric acid fluorenylmethyl ester 19. To a solution of oxalyl chloride (233 μL, 2.76 mmol, 1.5 equiv) in dry CH_2Cl_2 (0.50 mL) at −78 °C was added dropwise DMSO (145 μL, 2.76 mmol, 1.5 equiv). The resulting solution was stirred for 30 min at this temperature before a solution of **18** (700 mg, 1.84 mmol) dissolved in CH_2Cl_2 (2.0 mL) was added dropwise over 10 min. After 30 min Et_3N (1.28 mL, 9.2 mmol, 5 equiv) was added and the reaction was warmed to 0 °C. After 2 h the solution was quenched with 0.1 M $KHSO_4$ (20 mL) and allowed to warm to room temperature. The resulting solution was diluted with CH_2Cl_2 (100 mL) and the organic layer washed with 0.1 M $KHSO_4$ (3×75 mL), dried (Na_2SO_4) and concentrated in vacuo. The residual oil (650 mg) was purified by flash column chromatography (silica gel, 30% EtOAc in hexane, R_f=0.35) to yield **19** as a dusty brown solid (545 mg, 52%), mp 110 °C; $[\alpha]_D^{20}$ +63.2 (*c* 0.35, in CH_2Cl_2); ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.50 (1H, s, C(=O)*H*), 7.76 (2H, d, *J*=7.5 Hz, C*H* Ar), 7.54 (2H, m, C*H* Ar), 7.41–7.25 (4H, m, C*H* Ar), 5.89 (1H, m, CH$_2$C*H*=CH$_2$), 5.61 (1H, d, *J*=8.6 Hz, N*H*), 5.30–5.10 (2H, CH$_2$CH=C*H*$_2$), 4.62–4.53 (5H, m, C*H*$_2$CH=CH$_2$, COOC*H*$_2$CHAr, C*H* α), 4.23 (1H, t, *J*=6.1 Hz, COOCH$_2$C*H*Ar), 2.9 (2H, m, C*H*$_2$ β); ^{13}C NMR (75 MHz, $CDCl_3$) δ 199.0, 170.6, 155.8, 143.4, 141.3, 132.4, 127.9, 127.2, 124.9, 120.1, 118.1, 67.3, 66.1, 49.0, 46.7, 45.7; IR (Nujol mull) ν_{max} 3305 (N–H), 2952, 2922 (C–H), 1737 (C=O), 1712 (C=O), 1645 (C=C), 1531 (C=C, Ar); HRMS calcd for $[C_{22}H_{21}NO_5Na]^+$ 402.13174, found 402.13277.

5.1.7. Coupling reaction between *tert*-butyl-*N,N*-bis(*tert*-butyloxycarbonyl)-L-homoserinate *tert*-butyldimethylsilyl ether 9 and 2-(*S*)-allyloxycarbonylamino-4-oxo-butyric acid fluorenylmethyl ester 19. To a stirred solution of **9** (56 mg, 0.114 mmol) in MeCN (0.5 mL) at room temperature was added Et_3SiH (27 μL, 0.171 mmol, 1.5 equiv). After 5 min $BiBr_3$ (34.0 mg, 0.076 mmol, 0.67 equiv) was added. A solution of **19** (65 mg, 0.171 mmol, 1.5 equiv) in MeCN (0.5 mL) was then added and the solution stirred for 24 h. The reaction was diluted with EtOAc (50 mL) and then washed with Na_2CO_3 (2×50 mL), dried (Na_2SO_4) and concentrated in vacuo. The residual oil was purified by flash column chromatography (silica gel, 20% EtOAc in hexane, R_f=0.17) to yield **21** as a clear colourless oil (50.2 mg, 69.1%); $[\alpha]_D^{20}$ +11.2 (*c* 0.62, in CH_2Cl_2); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.85 (2H, m, C*H* Ar), 7.60 (2H, d, *J*=7.1 Hz, C*H* Ar), 7.37 (2H, m, C*H* Ar), 7.26 (2H, m, C*H* Ar), 5.92 (1H, m, CH$_2$C*H*=CH$_2$), 5.87 (1H, m, N*H*), 5.44 (1H, m, AlocNHCHCH$_2$C*H*(O)NBoc) 5.28–5.18 (2H, m, CH$_2$CH=C*H*$_2$), 4.71 (1H, br s, ^{t}BuOOCC*H*N-Boc), 4.58–4.48 (5H, m, C*H*$_2$CH=CH$_2$, COOC*H*$_2$CHAr, AlocNHC*H*CH$_2$CH(O)NBoc), 4.29 (1H, br m, COOCH$_2$C*H*Ar), 3.75 (2H, m, ^{t}BuOOCCHCH$_2$C*H*$_2$O), 2.25–2.20 (2H, m, AlocNHCHC*H*$_2$CH(O)NBoc, ^{t}BuOOCCHC*H*$_2$CH$_2$O), 2.10–2.02 (2H, m, AlocNHCHC*H*$_2$CH(O)NBoc, ^{t}BuOOCCHC*H*$_2$CH$_2$O), 1.41 (18H, s, NCOC(C*H*$_3$)$_3$, OCOC(CH_3)$_3$); ^{13}C NMR (75 MHz, CDCl$_3$) δ 172.1, 171.4, 156.0, 153.4, 143.6, 141.3, 132.7, 127.8, 127.2, 125.1, 120.0, 117.8, 82.0, 81.0, 67.6, 65.8, 64.3, 58.1, 51.7, 46.9, 34.4, 34.2, 28.3, 27.9; HRMS calcd for $[C_{35}H_{44}N_2O_9Na]^+$ 659.29444, found 659.29494.

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