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A convenient route to α-amino acids with β-alkyne substituents from a serine derived aziridine

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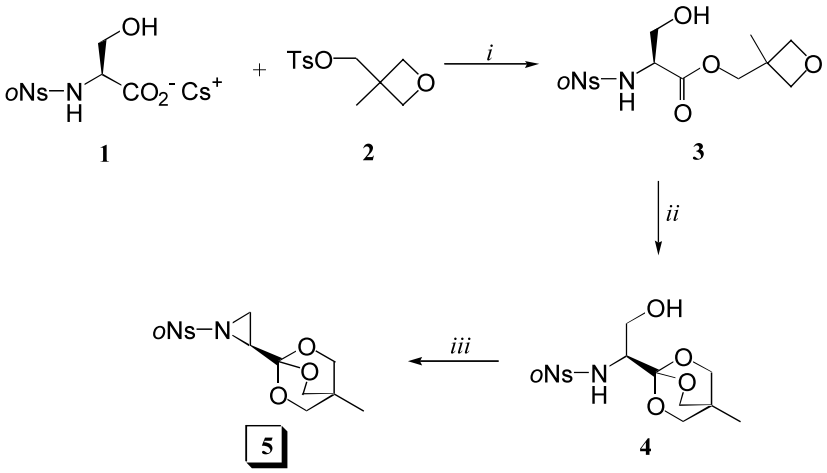
Abstract—1-[(*S*)-1-(2-Nitrobenzenesulfonyl)-aziridin-2-yl]-4-methyl-2,6,7-trioxabicyclo[2.2.2]octane **5** was ring opened regioselectively with a variety of lithium acetylides to give α-amino acids bearing γ,δ-unsaturation in very good to excellent yields. The 2-nitrobenzenesulfonyl and OBO ester protecting groups were removed in excellent overall yield.

The synthesis of α-amino acids with novel β-side chains has aroused much interest over the last couple of decades. Of the many modifications known, amino acids with unsaturated side chains are of particular interest due to their potential biological activity as specific irreversible enzyme inhibitors, also known as 'suicide substrates'.[1] Specifically it has been found that compounds containing carbon–carbon triple bonds serve to deactivate a variety of enzymes.[2] Consequently, there have been many reports on the synthesis of α-amino acids with β-side chains containing alkyne functionality;[1,3] however, general stereoselective routes to these compounds are not available. A potentially general route to α-amino acids bearing γ,δ-unsaturation might be realised via the ring opening of an aziridine-2-carboxylate with lithium acetylides. Previous reports concerning the ring opening of such compounds with carbon nucleophiles indicate that the use of tosyl-*N*-aziridine-2-carboxylate esters results in unwanted attack at the ester functionality.[4,5] However, it has been shown that this problem can be circumvented by employing no carboxylate protection.[4a–b,6] On the other hand, Lajoie and co-workers[7] have demonstrated that masking the carboxylic acid functionality utilising the



Scheme 1. *Reagents and conditions*: (i) NaI (0.2 equiv.), DMF, rt, 2 days, 45%; (ii) $BF_3{\cdot}OEt_2$ cat., DCM, rt, 4 h, 78%; (iii) Ph_3P (1.2 equiv.), DEAD (1.2 equiv.), 0°C, 1 h, 98%.

Keywords: Mitsunobu reaction; nitrobenzenesulfonamides; carbon nucleophiles; aziridine; ring opening.

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base-stable 2,6,7-trioxabicyclo[2.2.2]octane (OBO-ester) Corey protecting group also prevents attack on the carboxylate by organometallic reagents. Crucially, cleavage of the *ortho*-ester proceeded with minimal racemisation. It was therefore envisaged that an attractive substrate for ring opening with lithium acetylides would comprise of an aziridine with the carboxylic acid protected as the OBO ester. In addition, replacement of the tosyl group for the 2-nitrobenzenesulfonyl (*o*Ns) group would avoid the harsh conditions required[4,6] for the removal of the former. We here report a convenient synthesis of α-amino acids bearing a β-alkyne substituent via regioselective ring opening of serine derived aziridine **5** with lithium acetylides.

The synthesis of aziridine **5** (Scheme 1) was realised by Mitsunobu-mediated intramolecular condensation of 2-nitrobenzenesulfonyl protected L-serine OBO ester **4**.[8] Compound **4** was obtained following a similar procedure to that described previously[7] for the synthesis of the corresponding Fmoc, Boc and benzyloxylcarbonyl derivatives. Thus, reaction of the caesium salt of 2-nitrobenzenesulfonyl L-serine **1** with 3-methyl-3-(toluenesulfonyloxymethyl)oxetane **2** in the presence of a catalytic amount of sodium iodide afforded the oxetane ester **3**. The latter compound was then rearranged catalytically with boron trifluoride ethyl etherate to the corresponding OBO ester **4**. Treatment of **4** with triphenyl phosphine and diethylazodicarboxylate in THF afforded aziridine **5** in an overall yield of 34%.

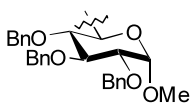
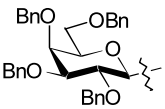
The ring opening of aziridine **5** (Scheme 2) was first attempted with an excess of lithium trimethylsilyl acetylide **6a**, in THF (entry 1, Table 1). The reaction afforded the expected product **7a** in 42% yield, but this was also accompanied by **7b** and dimer **8** in 8 and 30% yields, respectively. The formation of **7b** presumably arises from in situ silyl–lithium exchange. The lithium anion of **7b** successfully competes with **6a** in opening aziridine **5** leading to dimer **8**. However, formation of **8** could be suppressed by using a large excess of **6a**, with ring opened products **7a** and **7b** being obtained in 48 and 46% yields, respectively (entry 2).

In order to optimise reaction conditions and prevent similar in situ decomposition and side product formation to that described above, the use of more stable lithio-alkyne reagents was explored. To this end, lithium acetylide **6c** was reacted with aziridine **5** (entry 3) providing a homogenous ring opened product, **7c**, in very good yield. However, when ring opening was attempted with known (3-tetrahydropyran-2-yloxy-prop-1-ynyl)-lithium (**6d**) in the same amount, no reaction was observed (entry 4). The desired product could be obtained simply by increasing the amount of **6d** used (entries 5 and 6) with the optimum being 4 equiv., whereupon **7d** was isolated in 98% yield. A similar trend was also observed for the synthesis of the corresponding homologue, **7e**, where the same excess of reagent (**6e**) was necessary for efficient ring opening (entry 7).

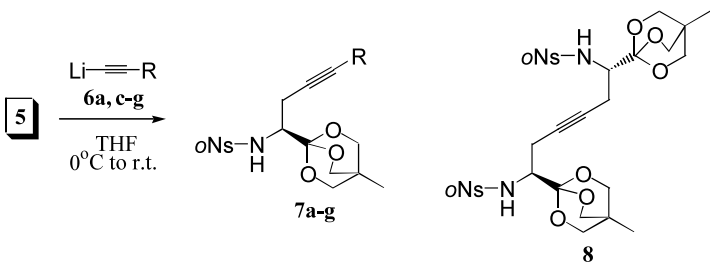
Having examples of the successful ring opening of **5** with simple lithium acetylides in hand, attention was turned to lithio-alkynes bearing more functionality and steric hindrance. Accordingly, an excess of the lithium anion of fully benzylated methyl 6,7-dideoxy-α-D-gluco-hept-6-ynopyranoside[9] **6f** was reacted with **5**, providing the desired product **7f** in 85% yield (entry 8). In contrast, only 2 equiv. of the anion of fully benzylated β-D-galactopyranosyl-ethyne[10] **6g** (entry 9) were needed to effect efficient ring opening of **5**, furnishing **7g** in 82% yield. It is noteworthy (entry 8) that when ring opening of **5** was attempted with 2 equiv. of **6f**, formation of **7f** could not be observed.

To demonstrate the feasibility of liberating the amino and carboxylic acid functionalities of these ring opened

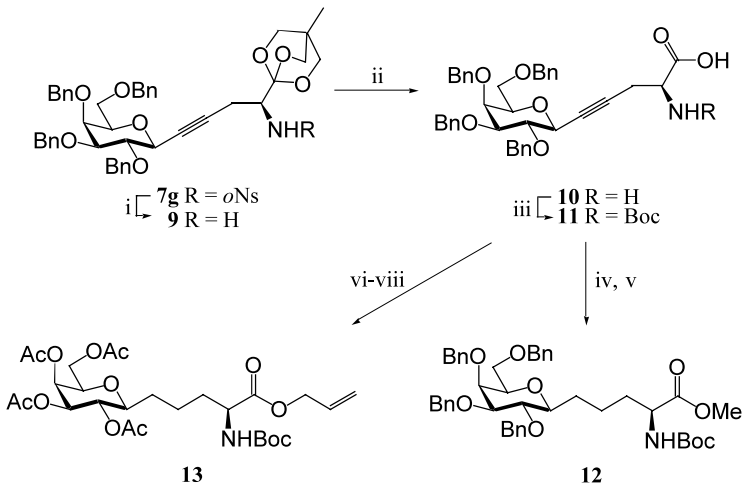
Table 1. Ring-opening of aziridine **5**

Entry	Lithium acetylide **6**, R =	Equiv. (reagent)	Yield (%)
1	TMS (**6a**)	2	**7a** R = TMS, 42 **7b** R = H, 8 **8**, 30
2	TMS (**6a**)	10	**7a**, 48 **7b**, 46
3	Ph (**6c**)	2	**7c**, 84
4	CH_2OTHP (**6d**)	2	0
5	CH_2OTHP (**6d**)	3	**7d**, 49
6	CH_2OTHP (**6d**)	4	**7d**, 98
7	CH_2CH_2OTHP (**6e**)	4	**7e**, 86
8	(**6f**) 	4[a]	**7f**, 85
9	(**6g**) 	2	**7g**, 82

[a] Using 2 equiv. of **6f**, only starting compounds were recovered.



Scheme 2.



Scheme 3. *Reagents and conditions*: (i) K_2CO_3 (4 equiv.), PhSH (3 equiv.), 0.05 M ACN/DMSO 49/1 (v/v), 50°C, 4 h; (ii) a. TFA/DCM/H_2O (v/v/v), rt, 30 min, b. Cs_2CO_3 (5 equiv.), dioxane/MeOH/H_2O 1/1/2 (v/v/v), rt, 16 h, 89% (three steps from **7g**); (iii) Boc_2O (1.5 equiv.), Na_2CO_3 (1.5 equiv.), dioxane/H_2O 1/1 (v/v), rt, 5 h, 92%; (iv) Pd/C, H_2, dioxane/EtOH/H_2O 2/2/1 (v/v/v), rt, 4 h; (v) CH_2N_2, Et_2O/DCM, rt, 10 min 96% (two steps from **11**); (vi) $Pd(OH)_2$/C, H_2, dioxane/EtOH/H_2O 2/2/1 (v/v/v), rt, 16 h; (vii) allylbromide (2 equiv.), $KHCO_3$ (2 equiv.), DMF, rt, 16 h; (viii) Ac_2O (2 equiv. per OH), pyridine, rt 16 h, 81% (three steps from **11**).

products, *ortho*-nitrobenzenesulfonyl (*o*Ns) cleavage conditions were applied to **7g**, as previously described for primary nosyl sulfonamides,[11] to give **9** (Scheme 3). Subsequent acid and base treatment[7] to cleave the OBO ester in **9** furnished novel unsaturated *C*-glycosyl amino acid **10** in excellent yield over the three steps. For additional proof of the structure and stereochemistry, the latter compound was converted to the corresponding Boc protected derivative **11**, subjected to partial hydrogenation followed by esterification of the carboxyl group, to furnish known fully benzylated β-D-galactose-$(CH_2)_2$-asparagine methyl ester **12** with full agreement of analytical data to that reported previously.[12] Furthermore, compound **11** could be readily converted to the corresponding *O*-acetylated fully saturated *C*-glycosylated amino acid derivative **13** by subsequent hydrogenation, allyl ester formation and acetylation. It should be noted that omission of carboxylic acid protection prior to acetylation resulted in an inseparable mixture of products. This problem was circumvented by protection of the carboxylic acid before acetylation.

In summary, the ring opening of aziridine **5** was shown to proceed with complete regioselectivity and high yield using lithium acetylides. The facile conversion of **7g** via novel unsaturated *C*-glycosylated amino acid **11** to known *C*-glycosylated amino acid **12**, and the corresponding acetylated allyl ester derivative **13**, demonstrates the potential of this methodology towards the construction of glycopeptide isosteres suitable for incorporation into peptide sequences.

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8. All new compounds were fully characterised by ^{1}H and ^{13}C NMR spectroscopy as well as mass spectrometry. Data for selected examples are as follows.

1-[(*S*)-1-(2-Nitrobenzenesulfonyl)-aziridin-2-yl]-4-methyl-2,6,7-trioxabicyclo[2.2.2]octane **5**: ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.31–8.28 (m, 1H, *o*Ns), 7.75–7.72 (m, 3H, *o*Ns), 3.90 (s, 6H, 3×CH_2 OBO), 3.19 (dd, 1H, H_2, $J_{2,3}=7.2$ Hz, $J_{2,3'}=4.6$ Hz), 2.85 (d, 1H, H_3), 2.69 (d, 1H, $H_{3'}$), 0.80 (s, 3H, CH_3 OBO). ^{13}C NMR (75 MHz, $CDCl_3$): δ 147.9 (C-NO_2), 134.4, 131.9, 130.8 (3×CH_{arom} *o*Ns), 130.5 (C-SO_2), 123.9 (1×CH_{arom} *o*Ns), 104.7 (C_q OBO), 72.3 (3×CH_2 OBO), 40.6 (C_2), 31.2 (C_3), 30.3 (C_q OBO), 13.5 (CH_3 OBO). MS (ESI) *m*/*z* 356.9 $[M+H]^+$, 379.0 $[M+Na]^+$.

1-[*N*-(2-Nitrobenzenesulfonyl)-(1*S*)-1-amino-4-trimethylsilanyl-but-3-ynyl]-4-methyl-2,6,7-trioxabicyclo[2.2.2]-octane **7a**: ^{1}H NMR (200 MHz, $CDCl_3$): δ 8.16–8.12 (m, 1H, *o*Ns), 7.97–7.93 (m, 1H, *o*Ns), 7.78–7.74 (m, 2H, *o*Ns), 6.03 (d, 1H, NH, $J_{NH,1}=9.5$ Hz), 3.77–3.52 (m, 7H, H_1, 3×CH_2 OBO), 2.59 (ABX, 2H, H_2, $J_{2,1}=4.4$ Hz, $J_{2',1}=9.1$ Hz), 0.69 (s, 3H, CH_3 OBO), 0.16 (s, 9H, 3×CH_3 TMS). ^{13}C NMR (50 MHz, $CDCl_3$): δ 147.1 (C-NO_2), 136.6 (C-SO_2), 132.7, 132.4, 131.0, 124.8 (4×CH_{arom} *o*Ns), 107.3 (C_q OBO), 102.4, 87.2 (2×C_q alkyne), 72.4 (3×CH_2 OBO), 57.2 (C_1), 30.4 (C_q OBO), 22.3 (C_2), 14.0 (CH_3 OBO), −0.1 (3×CH_3 TMS). MS (ESI) *m*/*z* 477.1 $[M+Na]^+$.

(9*S*)-9-(4-Methyl-2,6,7-trioxa-bicyclo[2.2.2]oct-1-yl)-9-(2-nitrobenzenesulfonylamino)-6,7,8,9-tetradeoxy-2,3,4-tri-*O*-benzyl-α-D-*gluco*-non-6-ynopyranoside **7f**: ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.13–8.10 (m, 1H, *o*Ns), 7.90–7.88 (m, 1H, *o*Ns), 7.67–7.59 (m, 2H, *o*Ns), 7.41–7.24 (m, 15H, 3×H_{arom} Bn), 5.92 (d, 1H, NH, $J_{NH,9}=9.5$ Hz), 4.94, 4.84, 4.71 (3×AB, 3×2H, 3×CH_2 Bn), 4.55 (d, 1H, H_1, $J_{1,2}=3.5$ Hz), 4.29 (bd, 1H, H_5, $J_{5,4}=9.7$ Hz), 3.85 (m, 1H, H_3), 3.72 (app. dt, 1H, H_9), 3.60–3.49 (m, 8H, 3×CH_2 OBO, H_2, H_4), 3.39 (s, 3H, OMe), 2.59 (ABXY, 2H, H_8 and $H_{8'}$, $J_{8,9}=4.5$ Hz, $J_{8,5}=1.6$Hz, $J_{8',9}=8.8$ Hz, $J_{8',5}=1.7$ Hz), 0.62 (s, 3H, CH_3 OBO). ^{13}C NMR (100 MHz, $CDCl_3$): δ 147.2 (C-NO_2), 138.9, 138.7, 138.2 (3×C_q Bn), 136.4 (C-SO_2), 132.8, 132.3, 131.1 (3×CH_{arom} *o*Ns), 128.4–127.4 (CH_{arom} Bn), 124.8 (1×CH_{arom} *o*Ns), 107.4 (C_q OBO), 98.3 (C_1), 82.4 (C_4), 81.9 (C_q alkyne), 81.0 (C_3), 79.6 (C_q alkyne), 79.3 (C_2), 75.8, 75.3, 73.5 (3×CH_2 Bn), 72.4 (3×CH_2 OBO), 61.9 (C_5), 57.3 (C_9), 55.5 (OMe), 30.4 (C_q OBO), 21.5 (C_8), 13.9 (CH_3 OBO). MS (ESI) *m*/*z* 837.4 $[M+Na]^+$.

(*S*)-2-*tert*-Butoxycarbonylamino-5-(2,3,4,6-tetra-*O*-acetyl-β-D-galactopyranosyl)-pentanoic acid allyl ester **13**: ^{1}H NMR (300 MHz, $CDCl_3$): δ 5.98–5.85 (m, 1H, CH_2=C<u>H</u>), 5.41 (dd, 1H, $H_{4'}$, $J_{4',3'}=3.2$ Hz, $J_{4',5'}=0.9$ Hz), 5.37–5.24 (m, 2H, C<u>H</u>$_2$=CH), 5.11–4.97 (m, 3H, NH, $H_{2'}$, $H_{3'}$), 4.64–4.62 (m, 2H, OC<u>H</u>$_2$ allyl), 4.33–4.20 (m, 1H, H_2), 4.15–4.03 (m, 2H, $2H_{6'}$), 3.86–3.81 (m, 1H, $H_{5'}$), 3.40–3.33 (m, 1H, $H_{1'}$), 2.15, 2.05, 2.05, 1.97 (4×s, 4×3H, 4×CH_3 Ac), 1.81–1.38 (m, 6H, $2H_3$, $2H_4$, $2H_5$), 1.45 (s, 9H, 3×CH_3 ^{t}Bu). ^{13}C NMR (75 MHz, $CDCl_3$): δ 172.4 (C_1), 170.4, 170.2, 170.1, 169.8 (4×C=O Ac), 155.3 (NHC=O), 131.6 (CH_2=<u>C</u>H), 118.7 (<u>C</u>H$_2$=CH), 79.8 (C_q ^{t}Bu), 77.9 ($C_{1'}$), 74.1 ($C_{5'}$), 72.1 ($C_{3'}$), 69.3 ($C_{2'}$), 67.7 ($C_{4'}$), 65.7 (O<u>C</u>H$_2$ allyl), 61.5 ($C_{6'}$), 53.4 (C_2), 32.3 (C_3), 30.8 (C_5), 28.3 (3×CH_3 ^{t}Bu), 21.1 (C_4), 20.7, 20.7, 20.6, 20.5 (4×CH_3 Ac). MS (ESI) *m*/*z* 588.0 $[M+H]^+$, 610.0 $[M+Na]^+$.
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