An efficient copper-catalysed pyrrole synthesis

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Dedicated to Professor Keith Smith on the occasion of his 65th anniversary

Abstract
Copper-catalysed cyclisations of β-hydroxyhomopropargylic sulfonamides can be carried out using copper(II) acetate in hot toluene to provide generally excellent yields of the corresponding pyrroles.

Keywords: Pyrroles, 5-endo-dig cyclization, copper catalysis, acetylenes, sulfonamides

Introduction
The development of efficient and environmentally acceptable syntheses of heteroaromatics continues to be of enormous importance because of the value of compounds containing such residues in most areas of ‘effect’ chemicals. Despite many years of effort, there still remain a number of deficiencies in the methods available for the elaboration of such compounds, especially in a general sense in a number of structural types. In the area of pyrroles, it is still not unusual to see quite poor yields reported for the synthesis of relatively simple pyrroles when these are used as precursors of more complex derivatives. These limitations in existing pyrrole synthesis are evident from the large number of reactions types which have recently been applied to their preparation. Further, it is often the case that when an ‘effect’ chemical contains a pyrrole residue, its synthesis is quite inefficient and used simply to provide sufficient material; in some cases one wonders what would happen if a commercial scale-up actually became necessary. Our own recent contributions have been focussed on the use of iodonium and selenium electrophilic species to trigger 5-endo-dig cyclisations, illustrated by the conversion of the alkynyl sulfonamides 1 into iodopyrroles 2 (Scheme 1) which, while usually providing excellent yields of substituted iodopyrroles, does suffer from some limitations.
Scheme 1. An iodocyclization route to β-iodopyrroles.

Efficient though these are, with the presence of the iodine atom suggesting a number of opportunities for further elaboration, the requirement for three equivalents of iodine rather detracts from this methodology, which would probably not be viable on a large scale on cost grounds alone. We therefore initiated a series of studies aimed at defining heterogeneous catalysts which are suitable for triggering such cyclisations of homopropargylic sulfonamides of the same type as 1, with a view to forming pyrroles (3) (Scheme 2). These could in particular offer the crucial advantages of defining a catalyst which could be both recoverable and reusable and thereby carry some significant ‘green’ credentials. Herein, we report a new cyclisation protocol for the very efficient generation of pyrroles from 3-alkynyl 2-hydroxysulfonamides.

Scheme 2. A possible catalysed route pyrroles by 5-endo-dig cyclisation.

Fortunately, we had available a range of suitable precursors 6 from a separate study having the amine function protected by a toluenesulfonyl group. This was especially advantageous, as this group has provided very stable protection, and also apparently activation, in cyclisations previously studied by us, and can also be readily removed from pyrroles under, effectively, basic saponification conditions. These precursors were readily obtained from 1-alkynes 4 by sequential formylation and condensation of the resulting ynals 5 with the tin(II) enolate of ethyl N-tosyl-glycinate, as summarized in Scheme 3.

Scheme 3. Synthesis of amino-ester precursors: i, ref. 5; ii, ref. 6.
This methodology, perhaps surprisingly, also works very well when applied to ketones; hence, we were also readily able to obtain more substituted precursors [e.g. 8] (Scheme 4).

\[ \text{7} \quad \xrightarrow{\text{Ph}} \quad \text{8} \]

**Scheme 4.** Synthesis of a more substituted precursor.

Ethyl N-tosylglycinate 9 was also used as the precursor to a pair of pseudosymmetrical precursors but by acting as an electrophile this time, in condensations with two equivalents of a lithiated alkyne, which gave excellent yields of the potential pyrrole precursors 10 (Scheme 5).

\[ \text{MeO}_2C \quad \xrightarrow{3 \text{R}^1 \text{Li}} \quad \text{R}^1 \quad \text{HO} \quad \text{TSHN} \quad \text{10} \quad \text{a)} \ R^1 = \text{Bu} \quad \text{b)} \ R^1 = \text{Ph} \]

**Scheme 5.** Synthesis of pseudosymmetrical precursors.

Finally, two representative alkyl-substituted precursors, 13, were prepared from the amino-aldehyde 11, readily derived from 2-amino-1-butanol (Scheme 6). The rather irritating exchange of protecting groups was necessary because the N-tosyl aldehydes corresponding to the N-Boc aldehydes 11 were highly unstable and failed to deliver acceptable yields of the desired amino-alcohols 13 in a direct fashion.

\[ \text{BocHN} \quad \xrightarrow{\text{O}} \quad \text{R}^1 \quad \text{HO} \quad \text{BocHN} \quad \xrightarrow{\text{R}^1 \text{Li}} \quad \text{R}^1 \quad \text{HO} \quad \text{TSHN} \quad \text{13} \quad \text{a)} \ R^1 = \text{Bu} \quad \text{b)} \ R^1 = \text{Ph} \]

**Scheme 6.** Synthesis of 2-alkyl precursors.
Our first success in this area, reported a while ago, was the finding that various copper salts were capable of cyclising such substrates (e.g. 6a) but to give, most often, a predominance of the hydroxy-dihydropyrroles 14a, accompanied by varying but generally much smaller returns of the corresponding pyrroles 15a (Scheme 7). Of a succession of copper salts tested, copper(II) acetate appeared to be an optimum choice, typically delivering overall yields of up to 90% and a ratio of products of ~9:1. Further, the best reaction conditions we found in these initial studies were somewhat inconvenient, consisting of heating the copper salt with a precursor such as ester 6a in a mixture of diethyl ether and pyridine held in a sealed tube at around 90 °C for a few hours. This somewhat bizarre solvent system was suggested by similar mixtures which are used in some of the classical acetylene coupling reactions; our reasoning was simply that under such conditions, alkynes are probably activated by metal complexation, with copper ions at least, and hence that these might be effective in triggering the desired type of cyclisation.

$$\text{Bu} \equiv \text{OH} \xrightarrow{\text{Cu(OAc)}_2 \text{ (cat.)}} \text{Et}_2\text{O, py, 90 °C}} \text{Bu} \equiv \text{TsHN} \text{CO}_2\text{Et} \quad + \quad \text{Bu} \equiv \text{Ns} \text{CO}_2\text{Et} \quad + \quad \text{Bu} \equiv \text{TsHN} \text{CO}_2\text{Et}$$

**Scheme 7.** Initial trials of the copper-catalysed cyclisation.

We were very surprised to isolate to intermediate hydroxy-dihydropyrroles such as 14a, as these have not been previously recorded and would be expected to very easily lose water to give the corresponding pyrroles (e.g. 15a). This is certainly the case in related furan syntheses, when no traces of such dihydro intermediates were observed, despite a number of attempts. However, such dihydrofuran species have been prepared and used in synthesis, for examples, as substrates in Claisen rearrangements. While these hydroxy-dihydropyrroles 14 will very likely turn out to be useful intermediates, their conversions into the corresponding pyrroles 15 were not, in our hands, completely efficient, despite trying many methods involving exposure to acid or various derivatisations followed by base-induced elimination. Although the major diastereoisomer shown from the Kazmaier method is not particularly well set up for such eliminations by reason of its syn-stereochemistry, we thought that the thermodynamic driving force of aromatization would be quite sufficient to trigger such transformations; evidently such eliminations were not so facile in these cases. We therefore wished to further develop this chemistry with the duel aims of rendering it a one-pot, two-step sequence of cyclisation and dehydration, thus avoiding a separate elimination step, and also of finding much simpler, greener and more convenient reaction conditions. Herein, we report a successful outcome of this study.

We first carried out a simple screen, using the representative substrate 6a and a higher boiling solvent, to determine how essential the use of ether was and if we could remove the requirement of using a sealed tube (Table 1). Only toluene proved to be useful, giving complete
conversion although predominantly to the hydroxy-dihydropyrrole 14a along with much smaller amounts of the pyrrole 15a, in direct contrast of the failures associated with the other solvents tested. Ethyl acetate, ethanol and dimethylformamide were partly successful but were clearly not solvents of choice. Hence, at least, the need for a sealed tube was obviated as the use of a toluene-pyridine combination permitted the reaction mixture to be heated to a necessary temperature under a reflux condenser.

**Table 1.** An initial solvent study

<table>
<thead>
<tr>
<th>Entry</th>
<th>Co-solvent</th>
<th>6a</th>
<th>14a</th>
<th>15a</th>
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<tbody>
<tr>
<td>1</td>
<td>THF</td>
<td>100</td>
<td>0</td>
<td>trace</td>
</tr>
<tr>
<td>2</td>
<td>MeCN</td>
<td>100</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>3</td>
<td>Water</td>
<td>100</td>
<td>0</td>
<td>0</td>
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<tr>
<td>4</td>
<td>Toluene</td>
<td>0</td>
<td>89</td>
<td>11</td>
</tr>
</tbody>
</table>

We therefore initiated a more extensive systematic study of all features of the cyclisation, the results of which are presented in Table 2.

The original sealed tube conditions in ether (Entry 1)\(^7\) were found to have too long a reaction time; one hour was sufficient (Entry 2), although the reaction was significantly slower in hot toluene (Entry 3) but at least the drawback of the sealed tube requirement had been obviated and the yield was very similar to those which had been obtained using ether; the cyclisation was also successful using the phenyl-substituted precursor 6b (Entry 4), which also gave significantly more pyrrole 15b, presumably because of greater conjugation. We were surprised to find that lowering the amount of pyridine to only two equivalents, based on the amount of precursor 6a, resulted in an equally efficient cyclisation in refluxing toluene, but gave a product containing much more pyrrole 15a (Entry 5). At the same time, we found that copper(II) acetate, which we presumed might be more stable with respect to its oxidation state, was equally effective in triggering the cyclisation and also gave a preponderance of pyrrole 15a (Entry 6). By contrast, copper(I) iodide gave no trace of cyclised products in two runs (Entries 7 and 8). We then questioned the need for including any pyridine at all and were delighted to find that it was indeed unnecessary (Entry 9) when we reverted back to using copper(II) acetate as the catalyst. A considerable bonus was that the product now consisted entirely of the pyrrole 15a, which could be isolated in a pure state in around 93% yield. The eight hour heating period was also unnecessary: simply refluxing the reaction mixture for an hour produced the same result (Entry
Finally, we checked that the copper acetate could indeed be used ‘catalytically’ as, up to this stage, we had routinely used one equivalent of this reagent. Happily, we found that only 10mol% was perfectly adequate to drive the combined cyclisation and dehydration steps to completion during one hour at reflux (Entry 11). That this temperature was required to achieve complete reaction in such a short time was confirmed when a reaction carried out at 70 °C overnight only resulted in 80% conversion to the pyrrole 15a (Entry 12).

Table 2. Optimisation of catalyst, solvent and conditions

<table>
<thead>
<tr>
<th>Entry</th>
<th>Cu salt (eq.)</th>
<th>Solvent</th>
<th>Pyridine</th>
<th>Time (h)</th>
<th>Temp (°C)</th>
<th>14a</th>
<th>15a</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>CuOAc (1.0)</td>
<td>ether</td>
<td>1:1</td>
<td>6</td>
<td>90</td>
<td>86</td>
<td>14</td>
</tr>
<tr>
<td>2a</td>
<td>CuOAc (1.0)</td>
<td>ether</td>
<td>1:1</td>
<td>1</td>
<td>90</td>
<td>95</td>
<td>5</td>
</tr>
<tr>
<td>3</td>
<td>CuOAc (1.0)</td>
<td>toluene</td>
<td>1:1</td>
<td>4</td>
<td>90</td>
<td>89</td>
<td>11</td>
</tr>
<tr>
<td>4a</td>
<td>CuOAc (1.0)</td>
<td>toluene</td>
<td>1:1</td>
<td>4</td>
<td>90</td>
<td>67</td>
<td>33</td>
</tr>
<tr>
<td>5</td>
<td>CuOAc (1.0)</td>
<td>toluene</td>
<td>2 eq.</td>
<td>4</td>
<td>reflux</td>
<td>17</td>
<td>83</td>
</tr>
<tr>
<td>6</td>
<td>Cu(OAc)_2 (1.0)</td>
<td>toluene</td>
<td>1:1</td>
<td>4</td>
<td>90</td>
<td>20</td>
<td>80</td>
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<tr>
<td>7</td>
<td>CuI (1.0)</td>
<td>toluene</td>
<td>1:1</td>
<td>18</td>
<td>90</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>8</td>
<td>CuI (1.0)</td>
<td>toluene</td>
<td>1:1</td>
<td>18</td>
<td>reflux</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>9</td>
<td>Cu(OAc)_2 (1.0)</td>
<td>toluene</td>
<td>0</td>
<td>8</td>
<td>90</td>
<td>0</td>
<td>100</td>
</tr>
<tr>
<td>10</td>
<td>Cu(OAc)_2 (1.0)</td>
<td>toluene</td>
<td>0</td>
<td>1</td>
<td>reflux</td>
<td>0</td>
<td>100</td>
</tr>
<tr>
<td>11</td>
<td>Cu(OAc)_2 (0.1)</td>
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<td>0</td>
<td>1</td>
<td>reflux</td>
<td>0</td>
<td>100</td>
</tr>
<tr>
<td>12</td>
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<td>toluene</td>
<td>0</td>
<td>18</td>
<td>70</td>
<td>0</td>
<td>80</td>
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</table>

*a* In entries 2 and 4, a phenyl group replaced the butyl group.

*b* Overall recoveries were typically >90%.
Having established what appeared to be an optimum set of conditions, we turned to an exploration of application of these to a more general series of cyclisation-dehydrations using a diversity of precursors, the results of which are set out in Table 3. The initial optimisation substrate 6a, when reacted on a preparative scale, gave the desired pyrrole 15a in a 98% isolated yield, without the need for any purification beyond a filtration through a short pad of silica gel (Entry 1). Similarly, the 5-phenyl pyrrole 15b was formed slightly more slowly but in comparable yield (Entry 2). Cyclisation of the enyne (entry 3) was strangely retarded, as the previous conjugated substrate 6b (Entry 2) also contained a conjugated alkyne and reacted more rapidly. The example with a terminal alkyne (entry 4) also required a much longer reaction time and one equivalent of catalyst to secure a good yield. Protection of a potentially competing 5-endo-dig cyclisation of a hydroxyl group was not necessary (Entries 5 and 6) but was needed in the case of competing 5-exo-dig or 6-endo-dig cyclisations (Entry 7). Although the alternative products proved too sensitive to isolate and characterize, the attempt to cyclise the free alcohol derivative 6h gave only a 30% return of the expected pyrrole 15h (Entry 8).

2,4-Disubstituted pyrroles (entries 9 and 10) can also be prepared using this method; the necessary precursors to these ‘pseudo-symmetrical’ pyrroles were prepared by a double addition of the corresponding lithio-alkyne to N-tosyl ethyl glycinate. Unfortunately, the completely substituted precursors (entries 11 and 12) failed to cyclise despite prolonged heating and so it would seem that this method may be limited to the synthesis of products which do not contain adjacent substituents. Most of the entries contain an ester group, which is positioned at the 2-position of the final pyrroles 4. This was due purely to synthetic expedience as the precursors 1 were readily prepared using the Kazmaier method.6 To demonstrate that the ester group is not necessary for cyclisation, the two alkyl-substituted precursors (entries 13 and 14) derived from commercial 2-amino-1-butanol were found to undergo comparably rapid and clean cyclisations when heated in toluene. This should mean that this methodology will find plenty of applications as the elaboration of such relatively simple pyrroles is often beset by poor yields.

Although many of the foregoing cyclisations were carried out using mixtures of stereoisomers, no difference in the rates of cyclisation of such pairs were observed under the reaction conditions used. At lower temperatures or perhaps by an earlier work up, it might be possible to observe such a rate difference.
Table 3. The copper(II)-catalysed conversion of 3-alkynyl-2-hydroxysulfonamides 6, 10, 13 into pyrroles 15

![Diagram](image)

<table>
<thead>
<tr>
<th>Entry</th>
<th>Precursor</th>
<th>R&lt;sup&gt;1&lt;/sup&gt;</th>
<th>R&lt;sup&gt;2&lt;/sup&gt;</th>
<th>R&lt;sup&gt;3&lt;/sup&gt;</th>
<th>Time, h</th>
<th>Pyrrole</th>
<th>Yield, %</th>
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<tr>
<td>1</td>
<td>6a</td>
<td>Bu</td>
<td>CO&lt;sub&gt;2&lt;/sub&gt;Et</td>
<td>H</td>
<td>0.75</td>
<td>15a</td>
<td>98</td>
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<tr>
<td>2&lt;sup&gt;a&lt;/sup&gt;</td>
<td>6b</td>
<td>Ph</td>
<td>CO&lt;sub&gt;2&lt;/sub&gt;Et</td>
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<td>1.2</td>
<td>15b</td>
<td>97</td>
</tr>
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<td>6c</td>
<td>MeC(=CH&lt;sub&gt;2&lt;/sub&gt;)</td>
<td>CO&lt;sub&gt;2&lt;/sub&gt;Et</td>
<td>H</td>
<td>3.5</td>
<td>15c</td>
<td>75&lt;sup&gt;a&lt;/sup&gt;</td>
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<tr>
<td>4&lt;sup&gt;a&lt;/sup&gt;</td>
<td>6d</td>
<td>H</td>
<td>CO&lt;sub&gt;2&lt;/sub&gt;Et</td>
<td>H</td>
<td>12</td>
<td>15d</td>
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<tr>
<td>5</td>
<td>6e</td>
<td>(CH&lt;sub&gt;2&lt;/sub&gt;)&lt;sub&gt;2&lt;/sub&gt;OTBS</td>
<td>CO&lt;sub&gt;2&lt;/sub&gt;Et</td>
<td>H</td>
<td>0.75</td>
<td>15e</td>
<td>98</td>
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<tr>
<td>6</td>
<td>6f</td>
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<td>CO&lt;sub&gt;2&lt;/sub&gt;Et</td>
<td>H</td>
<td>1.0</td>
<td>15f</td>
<td>96</td>
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<tr>
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<td>6g</td>
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<td>CO&lt;sub&gt;2&lt;/sub&gt;Et</td>
<td>H</td>
<td>1.0</td>
<td>15g</td>
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<td>Et</td>
<td>H</td>
<td>1.0</td>
<td>15m</td>
<td>96</td>
</tr>
</tbody>
</table>

<sup>a</sup> The remaining product was the hydroxy-dihydropyrrole [cf. structure 14a].

<sup>b</sup> One equivalent of catalyst was used; with 10 mol%, the yield was 50% after 12 h.

Similar cyclisations under the present conditions using carbamate derivatives in place of sulfonamides were unsuccessful in the case of both methoxycarbonyl and N-Boc derivatives 16 (Scheme 8); no traces of either the hydroxyl-dihydropyrroles 17 or the derived pyrroles 18 were
observed by NMR analysis of the crude products, which were essentially unchanged starting materials. Although it is not clear why this is, it may be associated with the higher pKa values of such derivatives. To check that the catalyst was indeed necessary, the first two substrates 6a and 6b (entries 1 and 2) were separately heated in toluene alone when no cyclisation was observed. We are not certain of the exact nature of the catalyst: although high purity copper(II) acetate was used throughout, it is of course possible that small amounts of copper(I) are responsible for the catalytic effect. However, the greater electrophilicity of copper(II) ions suggest that these would be more effective catalyst species.

\[
\text{Bu} = \text{Me}, \text{Bu}^t
\]

**Scheme 8.** Carbamates are not effective precursors in this copper-catalysed cyclisation.

Finally, we should point out that this type of cyclisation is not entirely new. In related work, a Japanese group have reported that copper(II) acetate in hot toluene is a most effective catalytic system for the cyclisation of sulfonamide derivatives of 2-alkynylanilines to give indoles.\(^{12}\) In similar fashion, they too found that the corresponding carbamate derivatives did not cyclise anything like as efficiently using this system. Although the copper catalyst was not recovered, it very likely could be and then reused. Hence, overall, this can be regarded as a very environmentally friendly procedure for pyrrole synthesis. Of course, as it usually the case, this only contributes one ‘clean’ step to the overall sequence required to reach the final pyrroles; as ever, there are necessary prior steps which produce the routine levels of waste, so there is still much to do!

**Experimental Section**

**General.** NMR spectra were recorded using a Bruker DPX spectrometer operating at 400 MHz for \(^1H\) spectra and at 100.6 MHz for \(^{13}C\) spectra respectively. Unless stated otherwise, NMR spectra were measured using dilute solutions in deuteriochloroform. All NMR measurements were carried out at 30 °C and chemical shifts are reported as ppm on the delta scale downfield from tetramethylsilane (TMS: \(\delta 0.00\)) or relative to the resonances of CHCl\(_3\) (\(\delta_H 7.27\) ppm in proton spectra and \(\delta_C 77.0\) ppm for the central line of the triplet in carbon spectra respectively). Coupling constants (\(^3J_{HH}\)) are reported in Hz. Infrared spectra were recorded as thin films on sodium chloride plates for liquids and as KBr disks for solids, using a Perkin-Elmer 1600 series FTIR spectrophotometer and sodium chloride plates. Low resolution mass spectra were obtained
using a VG Platform II Quadrupole spectrometer operating in the electron impact (EI; 70 eV) or atmospheric pressure chemical ionization (ApCI) modes, as stated. High resolution mass spectrometric data was obtained from the EPSRC Mass Spectrometry Service, University College, Swansea, using the electrospray ionisation (ES) mode unless otherwise stated. Melting points were determined using a Kofler hot stage apparatus and are uncorrected. Elemental analyses were obtained using a Perkin Elmer 240C Elemental Microanalyser.

All reactions were conducted in oven-dried apparatus under an atmosphere of dry nitrogen unless otherwise stated. All organic solutions from aqueous work-ups were dried by brief exposure to dried magnesium sulfate, followed by gravity filtration. The resulting dried solutions were evaporated using a Büchi rotary evaporator under water aspirator pressure and at ambient temperature unless otherwise stated. Column chromatography was carried out using Merck Silica Gel 60 (230-400 mesh). TLC analyses were carried out using Merck silica gel 60 F254 pre-coated, aluminium-backed plates, which were visualized using ultraviolet light or potassium permanganate or ammonium molybdate sprays.

Ether refers to diethyl ether and petrol to the fraction boiling 60-80°C unless stated otherwise.

2-Alkyn-1- al synthesis. General procedure

To a stirred solution of a 1-alkyne (1.0 equiv.) in dry tetrahydrofuran (3 ml mmol\(^{-1}\)) maintained at -78°C was added butyl lithium (2.5 M in hexanes, 1.0 equiv.) and the resulting solution stirred for 0.5 h. Anhydrous dimethylformamide (2.0 equiv.) was then added dropwise, the cooling bath was removed and stirring continued for 0.5 h. The reaction mixture was then poured into a vigorously stirred, ice-cold 1:1 v/v biphasic mixture of 10% aqueous potassium dihydrogen phosphate (4.0 equiv.) and ether. The organic layer was separated and the aqueous layer extracted with an additional portion of ether. The combined ether solutions were dried, filtered and evaporated at ambient temperature. The residue was taken up in 10% ether-hexanes and filtered through a short pad of silica gel. Evaporation of the filtrate left the pure alkynal, which could be further purified by distillation.

Hept-2-ynal (5a).\(^{13}\) By the general procedure, condensation between 1-hexyne (4.20 ml, 36.3 mmol) and dimethylformamide (5.65 ml, 73.2 mmol) in tetrahydrofuran (120 ml) followed by quenching with potassium dihydrogen phosphate (25.29 g, 145.2 mmol) in water (250 ml) gave the ynal 5a, obtained as a pale orange oil (2.80 g, 66%), b.p. 80°C (kugelrohr oven temp.) at 0.6 mm Hg, \(\delta_H\) (400 MHz, CDCl\(_3\)) 9.05 (app. s, 1H, CHO), 2.29 (t, \(^3J_{HH}\) 7.3 Hz, 2H, 4-CH\(_2\)), 1.45 (quint., \(^3J_{HH}\) 7.3 Hz, 2H, 5-CH\(_2\)), 1.35 (sext., \(^3J_{HH}\) 7.3 Hz, 2H, 6-CH\(_2\)), 0.81 (t, \(^3J_{HH}\) 7.3 Hz, 3H, 7-Me).\(^{13}\)

3-Phenylprop-2-ynal (5b).\(^{13}\) By the general procedure, starting with phenylacetylene (3.23 ml, 29.0 mmol), the ynal 5b was obtained as an orange oil (2.81 g, 74%), b.p. 190°C (oven temp.) at 0.6 mm Hg, \(\delta_H\) (400 MHz, CDCl\(_3\)) 9.30 (app. s, 1H, CHO), 7.49-7.26 (m, 5H).

4-Methylpent-4-en-2-ynal (5c).\(^{14}\) By the general procedure, condensation between 3-methylbut-3-en-1-yne (3.00 g, 45.5 mmol) and dimethylformamide (7.04 ml, 90.9 mmol) gave the ynal 5c.
as an orange oil (2.60 g, 60%), $\delta _{1}$ (400 MHz, CDCl$_3$) 9.29 (s, 1H, CHO), 5.60 (app. s, 1H, 5-H$_a$), 5.53 (app. s, 1H, 5-H$_b$), 1.96 (s, 3H, Me).

3-(Trimethylsilyl)prop-2-ynal.$^{15}$ By the general procedure starting with trimethylacetylene (2.90 ml, 20.4 mmol), the ynal was obtained as an orange oil (1.705 g, 66%), $\delta _{1}$ (400 MHz, CDCl$_3$) 9.01 (s, 1H, CHO), 0.11 (s, 9H, Me$_3$Si).

5-(t-Butyldimethylsilyloxy)pent-2-ynal (5e).$^{16}$ by the general procedure, condensation between O-t-butyldimethylsilyl-3-butyn-1-ol (2.00 g, 10.8 mmol) and dimethylformamide (1.70 ml, 21.7 mmol) gave the ynal 5e (2.10 g, 87%) as a yellow oil, $\delta _{1}$ (400 MHz, CDCl$_3$) 9.09 (s, 1H, CHO), 3.72 (t, $^3J_{HH}$ 6.7 Hz, 2H, 5-CH$_2$), 2.54 (t, $^3J_{HH}$ 6.7 Hz, 4-CH$_2$), 0.82 (s, 9H, 3 × Me), 0.00 (s, 6H, 2 × Me).

N-Sulfonyl-$\beta$-hydroxy-$\alpha$-amino ester synthesis using tin(II) enolates of glycine and other precursor syntheses: General procedure.$^6$

To a stirred solution of lithium diisopropylamide (2.2 equiv.) in tetrahydrofuran (4-5 ml mmol$^{-1}$) maintained at -78 °C was added a solution of ethyl N-tosylglycinate (1.00 equiv.) in tetrahydrofuran (1.0 ml mmol$^{-1}$) followed by a solution of tin(II) chloride (2.50 equiv.) in tetrahydrofuran (0.50 ml mmol$^{-1}$). The resulting mixture was stirred at the same temperature for 0.5h before the dropwise addition of an ynal or ynone (1.10 equiv.) in tetrahydrofuran (1.0 ml mmol$^{-1}$). Stirring was then continued overnight without further addition of coolant. The resulting cloudy yellow solution was then quenched using phosphate buffer (pH 7), filtered through a pad of silica gel and the bulk of the tetrahydrofuran was evaporated. The aqueous residue was extracted with ether (3 × equal volume) and the combined organic solutions dried, filtered and evaporated. The crude product was purified by combinations of column chromatography and crystallisations.

(2$^SR$, 3$^SR$)-Ethyl 2-(4-toluenesulfonylamino)-3-hydroxy-5-phenylpent-4-ynoate (6a). By the general procedure, reaction between LDA (27.3 mmol) in tetrahydrofuran (200 ml), ethyl N-tosylglycinate (3.19 g, 12.4 mmol) in tetrahydrofuran (13 ml), tin(II) chloride (5.88 g, 31.0 mmol) in tetrahydrofuran (16 ml) and hept-2-ynal 5a (1.50 g, 13.6 mmol) in tetrahydrofuran (14 ml) gave the $\beta$-hydroxy-$\alpha$-amino ester 6a (3.60 g, 79%) as a single diastereoisomer, m.p. 66 -67 °C after crystallization (EtOAc-petrol) as a yellow crystalline solid, $\delta _{1}$ (400 MHz, CDCl$_3$) 7.69 (d, $^3J_{HH}$ 8.3 Hz, 2H, 2 × CHAr), 7.25 (d, $^3J_{HH}$ 8.3 Hz, 2H, 2 × CHAr), 5.45 (d, $^3J_{HH}$ 9.3 Hz, 1H, NH), 4.59 (br. m, 1H, 3-H), 4.05 (dd, $^3J_{HH}$ 9.3, 3.8 Hz, 1H, 2-H), 4.01-3.95 (m, 2H, OCH$_2$), 2.70 (d, $^3J_{HH}$ 10.3 Hz, 1H, OH), 2.41 (s, 3H, TsMe), 2.12 (td, $^3J_{HH}$ 7.0, 2.0 Hz, 2H, 6-CH$_2$), 1.43-1.28 (m, 4H, 7- and 8-CH$_2$), 1.09 (t, $^3J_{HH}$ 7.0 Hz, OCH$_2$Me), 0.83 (t, $^3J_{HH}$ 7.1 Hz, 3H, 9-Me); $\delta _{C}$ (100 MHz, CDCl$_3$) 168.4 (C=O), 144.4 (C), 136.7 (C), 130.1 (2 × ArCH), 127.7 (2 × ArCH), 89.1 (C), 75.9 (C), 63.5 (3-CH), 62.5 (OCH$_2$), 61.1 (2-CH), 30.7 (6-CH$_2$), 22.3 (7-CH$_2$), 21.9 (ArMe), 18.7 (8-CH$_2$), 14.3 (OCH$_2$Me), 13.9 (9-Me); $\nu _{max}$/cm$^{-1}$ (CHCl$_3$) 3492, 1739, 1598, 1445, 1342, 1164, 1093; $m/z$ (CI) 385 (M + NH$_4^+$, 75%), 275 (100), 189 (30), 119 (70), 102 (40) [Found: [M + NH$_4^+$], 385.1794; C$_{18}$H$_{20}$N$_2$O$_4$S requires M, 385.1797].

(2$^SR$, 3$^SR$)-Ethyl 3-hydroxy-2-(4-toluenesulfonylamino)-5-phenylpent-4-ynoate (6b). By the general procedure, condensation
between ethyl N-tosylglycinate (1.06 g, 4.12 mmol) and 3-phenylprop-2-ynal 5b (0.91 g, 4.28 mmol) gave the \(\beta\)-hydroxy-\(\alpha\)-amino ester 6b (1.31 g, 82%) as a single diastereoisomer, m.p. 119 °C after crystallization (EtOAc-petrol) as a colourless crystalline solid. [Found: C, 61.98; H, 5.40; N, 3.59. C\(_{20}\)H\(_{21}\)NO\(_5\)S requires C, 62.00; H 5.47; N, 3.62%]; \(\delta\)\(_H\) (400 MHz, CDCl\(_3\)) 7.79 (d, \(3\)\(J_{HH}\) 8.3 Hz, 2H, 2 × CHAr), 7.42-7.31 (m, 5H, 5 × CHAr), 7.33 (d, \(3\)\(J_{HH}\) 8.2 Hz, 2H, 2 × CHAr), 5.60 (d, \(3\)\(J_{HH}\) 9.5 Hz, 1H, NH), 4.92 (dd, \(3\)\(J_{HH}\) 10.7, 3.9 Hz, 1H, 3-H), 4.24 (dd, \(3\)\(J_{HH}\) 9.5, 3.9 Hz, 1H, 2-H), 4.08 (q, \(3\)\(J_{HH}\) 7.2 Hz, 2H, OCH\(_2\)), 2.93 (d, \(3\)\(J_{HH}\) 10.7 Hz, 1H, OH), 2.45 (s, 3H, ArMe), 1.17 (t, \(3\)\(J_{HH}\) 7.2 Hz, 3H, OCH\(_2\)Me); \(\delta\)\(_C\) (100 MHz, CDCl\(_3\)) 167.9 (C=O), 144.1 (C), 136.2 (C), 131.8 (2 × ArCH), 129.8 (2 × ArCH), 129.0 (ArCH), 128.4 (2 × ArCH), 127.3 (2 × ArCH), 121.4 (C), 87.5 (C), 84.2 (C), 63.6 (2(3)-CH), 62.4 (OCH\(_2\)), 60.7 (3(2)-CH), 21.6 (ArMe), 14.0 (OCH\(_2\)Me); \(\nu_{\text{max/cm}}\) (nujol) 3273, 1743, 1598, 1444, 1322, 1162, 1020; m/z (ES) 388 (M + H\(^+\), 50%), 370 (M + H\(^+\) - H\(_2\)O, 100). Found: (M + H\(^+\)), 388.1222; C\(_{20}\)H\(_{22}\)NO\(_5\)S requires 388.1218.

\(2SR\), \(3SR\)-Ethyl 3-hydroxy-6-methyl-2-(4-toluenesulfonylamino)hept-6-en-4-ynoate (6c). According to the general procedure, condensation between ethyl N-tosylglycinate (3.73 g, 14.50 mmol) and 4-methylpent-4-2-ynal 6c (1.50 g, 16.00 mmol) gave the \(\beta\)-hydroxy-\(\alpha\)-amino ester 6c (3.60 g, 71%) as a colourless crystalline solid, m.p. 73-74 °C (EtOAc-petrol), \(\delta\)\(_H\) (400 MHz, CDCl\(_3\)) 7.81 (d, \(3\)\(J_{HH}\) 8.2 Hz, 2H, 2 × CHAr), 7.33 (d, \(3\)\(J_{HH}\) 8.2 Hz, 2H, 2 × CHAr), 5.54 (d, \(3\)\(J_{HH}\) 9.0 Hz, 1H, NH), 5.31 (app. br. s, 1H, 7-H\(_a\)), 5.29 (m, 1H, 7-H\(_b\)), 4.80 (dd, \(3\)\(J_{HH}\) 10.1, 3.9 Hz, 1H, 3-H), 4.16 (dd, \(3\)\(J_{HH}\) 9.0, 3.9 Hz, 1H, 2-H), 4.05 (m, 2H, OCH\(_2\)H), 2.82 (d, \(3\)\(J_{HH}\) 10.1 Hz, 1H, OH), 2.45 (s, 3H, ArMe), 1.86 (app. s, 3H, 6-Me), 1.16 (t, \(3\)\(J_{HH}\) 7.0 Hz, 3H, OCH\(_2\)CH\(_3\)); \(\delta\)\(_C\) (100 MHz, CDCl\(_3\)) 168.3 (C=O), 144.5 (C), 136.6 (C), 130.2 (2 × ArCH), 127.8 (2 × ArCH), 125.8 (6-C), 123.9 (=CH\(_2\)), 88.9 (C), 83.6 (C), 63.8 (3(2)-CH), 62.7 (OCH\(_2\)), 61.0 (2(3)-CH), 23.4 (ArMe), 22.0 (6-Me), 14.3 (Me); \(\nu_{\text{max/cm}}\) (nujol) 3480, 2368, 2228, 1737, 1598, 1445, 1342, 1163, 1093; m/z (ES) 352 (M + H\(^+\), 100%), 334 (M + H\(^+\) - H\(_2\)O, 40). Found: [M + H\(^+\)], 352.1222; C\(_{17}\)H\(_{22}\)NO\(_5\)S requires M, 352.1218.

\(2SR\), \(3SR\)-Ethyl 3-hydroxy-2-(4-toluenesulfonylamino)-5-trimethylsilylpent-4-ynoate. By the general procedure, condensation between ethyl N-tosylglycinate (1.48 g, 5.77 mmol) and 3-trimethylsilyl-2-propynal (0.80 g, 6.34 mmol) gave the silylated \(\beta\)-hydroxy-\(\alpha\)-amino ester (2.21 g, 83%) as an 85:15 mixture of diastereoisomers after separation by column chromatography (10% EtOAc-petrol) as a pale yellow oil. The major (2SR, 3SR) isomer showed \(\delta\)\(_H\) (400 MHz, CDCl\(_3\)) 7.60 (d, \(3\)\(J_{HH}\) 8.2 Hz, 2H, 2 × CHAr), 7.16 (d, \(3\)\(J_{HH}\) 8.2 Hz, 2H, 2 × CHAr), 5.34 (d, \(3\)\(J_{HH}\) 9.5 Hz, 1H, NH), 4.88-4.84 (m, 1H, 3-H), 4.52 (dd, \(3\)\(J_{HH}\) 10.6, 3.9 Hz, 1H, 2-H), 3.97-3.91 (m, 2H, OCH\(_2\)H), 2.63 (d, \(3\)\(J_{HH}\) 10.6 Hz, 1H, OH), 2.28 (s, 3H, ArMe), 1.04 (t, \(3\)\(J_{HH}\) 7.1 Hz, 3H, OCH\(_2\)Me), 0.00 (s, 9H, Me\(_3\)Si); \(\delta\)\(_C\) (100 MHz, CDCl\(_3\)) 168.8 (C=O), 143.8 (C), 136.2 (C), 129.8 (2 × ArCH), 127.3 (2 × ArCH), 100.3 (C), 93.0 (C), 63.4 (2(3)-CH), 62.3 (OCH\(_2\)H), 60.3 (3(2)-CH), 21.6 (ArMe), 14.0 (OCH\(_2\)Me), -0.4 (3 × Me\(_3\)Si); \(\nu_{\text{max/cm}}\) (CHCl\(_3\)) 3343, 3055, 2358, 2341, 1740, 1421, 1347; m/z (ES) 401 (M + NH\(_4\)\(^+\), 100%), 384 (M + H\(^+\), 30). Found: [M + H\(^+\)], 384.1294; C\(_{17}\)H\(_{26}\)NO\(_5\)Si requires 384.1301. The minor (2SR, 3RS) diastereoisomer was distinguishable by resonances at \(\delta\)\(_H\) (400 MHz, CDCl\(_3\)) 5.23 (d, \(3\)\(J_{HH}\) 9.1 Hz, 1H, NH), 4.47 (dd, \(3\)\(J_{HH}\) 8.0, 4.1 Hz, 1H, 2-H), 2.58 (d, \(3\)\(J_{HH}\) 8.1 Hz, 1H, OH).
(2SR, 3SR)-Ethyl 3-hydroxy-2-(4-toluenesulfonylamino)pent-4-ynoate (6d). Potassium carbonate (0.02 g, 0.14 mmol) was added to a stirred solution of the foregoing trimethylsilyl-alkynyl derivative (0.28 g, 0.73 mmol) in ethanol cooled in an ice bath. After 1.5h, the cooling bath was removed and when the mixture had warmed to ambient temperature the mixture was filtered and the filtrate and washings evaporated. The residue was dissolved in ether (10 ml) and the resulting solution washed with water (10 ml) and brine (10 ml), then dried, filtered and evaporated. Column chromatography of the residue (30% EtOAc-hexanes) then separated the alkyne 6d (0.20 g, 88%) as a clear, colourless oil, $\delta_H$ (400 MHz, CDCl$_3$) 7.77 (d, $^3$J$_{HH}$ 8.2 Hz, 2H, 2 × CHAr), 7.32 (d, $^3$J$_{HH}$ 8.2 Hz, 2H, 2 × CHAr), 5.42 (d, $^3$J$_{HH}$ 8.0 Hz, 1H, NH), 4.69 (app. dt, $^3$J$_{HH}$ 8.0, 4.0 Hz, 1H, 3-H), 4.17-4.08 (m, 3H, 2-H and OCH$_2$), 2.73 (d, $^3$J$_{HH}$ 8.0 Hz, 1H, OH), 2.49 (d, $^3$J$_{HH}$ 4.0 Hz, 1H, 5-H), 2.44 (s, 3H, ArMe), 1.18 (t, $^3$J$_{HH}$ 7.0 Hz, 3H, OCH$_2$CH$_3$); $\delta_C$ (100 MHz, CDCl$_3$) 168.7 (C=O), 143.8 (C), 136.9 (C), 129.6 (2 × ArCH), 127.4 (2 × ArCH), 80.2 (5-CH), 75.5 (C), 63.7 (3-CH), 62.5 (OCH$_2$), 60.1 (2-CH), 21.6 (ArMe), 13.9 (Me); $\nu_{max}$/cm$^{-1}$ (film) 3277, 2961, 2346, 1736, 1453, 1310, 1266, 1162, 1093; m/z (APCI) 329 (M + NH$_4^+$, 70%), 312 (M + H$_2$O, 100), 294 (M – H$_2$O, 25). Found: [M + H$_2$O], 312.0920; C$_{14}$H$_{18}$NO$_5$S requires 312.0906.

The minor (2SR, 3RS) diastereoisomer could be distinguished by $\delta_H$ (400 MHz, CDCl$_3$) 5.56 (d, $^3$J$_{HH}$ 9.4 Hz, 1H, NH), 2.96 (d, $^3$J$_{HH}$ 10.8 Hz, 1H, OH), 2.51 (d, $^3$J$_{HH}$ 2.3 Hz, 1H, 5-H).

(2SR, 3SR)-Ethyl 7-(t-butyldimethylsilyloxy)-3-hydroxy-2-(4-toluenesulfonylamino)hept-4-ynoate (6e). By the general procedure, condensation between ethyl N-tosylglycinate (1.00 g, 3.89 mmol) and 5-t-butyldimethylsilyloxypent-2-ynal 5e (0.91 g, 4.28 mmol) gave the $\beta$-$\alpha$-hydroxy-$\alpha$-amino ester 6e (1.51 g, 83%) as an 86:14 mixture of diastereoisomers after separation by column chromatography (25% EtOAc-petrol) as a clear, colourless oil. The major (2SR, 3SR) isomer showed $\delta_H$ (400 MHz, CDCl$_3$) 7.69 (d, $^3$J$_{HH}$ 8.2 Hz, 2H, 2 × CHAr), 7.24 (d, $^3$J$_{HH}$ 8.2 Hz, 2H, 2 × CHAr), 5.50-5.47 (br. res., 1H, NH), 4.60-4.57 (m, 1H, 3-H), 4.07-3.90 (m, 3H, 3-H and OCH$_2$), 3.59 (t, $^3$J$_{HH}$ 7.1 Hz, 2H, 7-CH$_2$), 2.75 (d, $^3$J$_{HH}$ 10.1 Hz, 1H, OH), 2.36 (s, 3H, ArMe), 2.32 (td, $^3$J$_{HH}$ 7.1, 2.0 Hz, 2H, 6-CH$_2$), 1.07 (t, $^3$J$_{HH}$ 7.0 Hz, 3H, OCH$_2$Me), 0.83 (s, 9H, t-BuSi), 0.00 (s, 6H, Me$_3$Si); $\delta_C$ (100 MHz, CDCl$_3$) 167.9 (C=O), 144.0 (C), 136.3 (C), 129.8 (2 × ArCH), 127.4 (2 × ArCH), 85.5 (C), 76.7 (C), 63.2 (2(3)-CH), 62.2 (CH$_2$), 61.5 (CH$_2$), 60.7 (3(2)-CH), 25.9 (3 × MeC), 23.0 (6-CH$_2$), 21.6 (ArMe), 18.1 (CSi), 13.9 (OCH$_2$Me), -5.3 (2 × MeSi); $\nu_{max}$/cm$^{-1}$ (film) 3490, 2357, 1736, 1598, 1458, 1338; m/z (ES) 487 (M + NH$_4^+$, 100%), 470 (M + H$_2$O, 35). Found: [M + H$_2$O], 470.2010; C$_{22}$H$_{36}$NO$_6$SSi requires 470.2033.

The minor (2SR, 3RS) diastereoisomer was distinguishable by a resonance at $\delta_H$ (400 MHz, CDCl$_3$) 2.64 (d, $^3$J$_{HH}$ 7.5 Hz, 1H, OH).

(2SR, 3SR)-Ethyl 3-hydroxy-3-isopropyl-5-phenyl-2-(4-toluenesulfonylamino)pent-4-ynoate (8). i) To a mixture of 4-methyl-1-phenylpent-1-yn-3-ol$^{17}$ (3.00 g, 17.2 mmol) and powdered 4 Å molecular sieves (5.00 g) in dry dichloromethane (90 ml) was added pyridinium chlorochromate (12.97 g, 34.50 mmol) portionwise and the resulting mixture stirred at ambient temperature overnight and then passed through a thick pad of silica gel which was subsequently washed with dichloromethane. The combined filtrates were evaporated to leave 4-methyl-1-phenylpent-1-yn-
3-one 7\(^{17}\) (2.60 g, 88\%) as a yellow oil which was sufficiently pure to be used in the next step and which showed \(\delta_H\) (400 MHz, CDCl\(_3\)) 7.45 (d, \(^3J_HH\) 7.6 Hz, 2H, 2 × CHAr), 7.36-7.24 (m, 3H), 2.63 (sept., \(^3J_HH\) 7.0 Hz, 1H, 4-H), 1.14 (d, \(^3J_HH\) 7.0 Hz, 6H, 2 × Me).

ii) According to the general procedure, condensation between ethyl N-tosylglycinate (3.73 g, 14.50 mmol) and the foregoing ketone 7 (2.00 g, 11.6 mmol) gave the \(\beta\)-hydroxy-\(\alpha\)-amino ester 8 (4.02 g, 82\%) as an orange crystalline solid, m.p. 126-127 °C (EtOAc-petrol) [Found: C, 64.3; H, 6.4; N, 3.2. C\(_{23}\)H\(_{27}\)NO\(_3\)S requires C, 64.5; H, 6.1; N, 3.3%]; \(\delta_H\) (400 MHz, CDCl\(_3\)) 7.76 (d, \(^3J_HH\) 8.2 Hz, 2H, 2 × CHAr), 7.38-7.27 (m, 7H), 5.63 (d, \(^3J_HH\) 10.7 Hz, 1H, NH), 4.21 (d, \(^3J_HH\) 10.7 Hz, 1H, 2-H), 3.90 (dq, \(^3J_HH\) = 10.8, 7.2 Hz, 1H, OCH\(_3\)), 3.76 (dq, \(^3J_HH\) 10.8, 7.2 Hz, 1H, OCH\(_3\)), 3.25 (br. s, 1H, OH), 2.51 (d, \(^3J_HH\) 10.8 Hz, 1H, OH), 2.15 (t, \(^3J_HH\) 7.2 Hz, 3H, OCH\(_2\)CH\(_3\)) ; \(\Delta\) (100 MHz, CDCl\(_3\)) 171.2 (C=O), 144.2 (C), 138.1 (C), 132.1 (2 × ArCH), 130.0 (2 × ArCH), 129.3 (CH), 128.8 (2 × ArCH), 127.9 (2 × ArCH), 122.2 (C), 88.4 (C), 86.2 (C), 76.2 (C), 62.2 (OCH\(_2\)), 60.1 (2-CH), 33.7 (CH), 22.0 (ArMe), 18.1 (Me), 17.3 (Me), 14.2 (Me); \(v_{max}/cm^{-1}\) (film) 3476, 3276, 2359, 1732, 1598, 1338, 1164, 1092; \(m/z\) (APCI) 412 (M + H\(^+\) - H\(_2\)O, 100%) [Found: [M + NH\(_4\)\(^+\)], 447.1956; C\(_{23}\)H\(_{31}\)N\(_2\)O\(_3\)S requires 447.1953].

The minor (2SR, 3RS) diastereoisomer could be distinguished by \(\delta_H\) (400 MHz, CDCl\(_3\)) 5.56 (d, \(^3J_HH\) 9.4 Hz, 1H, NH), 2.96 (d, \(^3J_HH\) 10.8 Hz, 1H, OH), 2.51 (d, \(^3J_HH\) 2.3 Hz, 1H, 5-H).

(2SR, 3SR)-Ethyl 3,7-dihydroxy-2-(4-toluenesulfonylamino)hept-4-ynoate (6f). A solution of tetrabutylammonium fluoride (TBAF) (1.0 M in tetrahydrofuran, 1.17 ml, 1.17 mmol) was added dropwise to an ice-cooled, stirred solution of the hydroxy-aminoester 6e (0.50 g, 1.07 mmol) in dry tetrahydrofuran (10 ml). The resulting solution was stirred overnight without additional cooling then the solvent evaporated. The residue was dissolved in ether (20 ml) and the solution washed with water (2 × 10 ml) and brine (10 ml) then dried, filtered and evaporated. Column chromatography (1:1 EtOAc-hexanes) of the residue then separated the alcohol 6f (0.32 g, 85\%) as a colourless oil, \(\delta_H\) (400 MHz, CDCl\(_3\)) 7.69 (d, \(^3J_HH\) 8.2 Hz, 2H, 2 × CHAr), 7.33 (d, \(^3J_HH\) 8.2 Hz, 2H, 2 × CHAr), 6.01-5.83 (br. res., 1H, NH), 4.62-4.59 (m, 1H, 3-H), 4.10 (app. d, \(^3J_HH\) 3.6 Hz, 1H, 2-H), 3.99-3.90 (m, 2H, OCH\(_2\)), 3.74-3.69 (m, 2H, 7-CH\(_2\)), 2.59 (dt, \(^3J_HH\) 7.5, 5.7 Hz, 2H, 6-CH\(_2\)), 2.33 (s, 3H, ArMe), 1.02 (t, \(^3J_HH\) 7.1 Hz, 3H, OCH\(_2\)Me). \(\Delta\) (100 MHz, CDCl\(_3\)) 168.9 (C=O), 143.9 (C), 136.2 (C), 129.6 (2 × ArCH), 127.1 (2 × ArCH), 86.0 (C), 77.8 (C), 63.2 (2-CH\(_3\)), 62.3 (CH\(_2\)), 61.0 (3(2)-CH\(_2\)), 60.6 (CH\(_2\)), 22.9 (6-CH\(_2\)), 21.6 (ArMe), 13.9 (OCH\(_2\)Me); \(v_{max}/cm^{-1}\) (film) 3482, 2358, 1734, 1598, 1458, 1338; \(m/z\) (APCI) 378 (M + Na\(^+\), 5\%), 177 (60), 130 (100). Found: [M + Na\(^+\)], 378.1002; C\(_{16}\)H\(_{21}\)NNaO\(_3\)S requires 378.0987.

Hydroxy-7-(4-toluenesulfonylaminomethyl)trideca-5,8-diyne (10a). A solution of 1-hexyne (1.70 ml, 14.4 mmol) in dry tetrahydrofuran (60 ml) was cooled to -78 °C and butyl lithium (5.80 ml of a 2.5 M solution, 14.4 mmol) was added dropwise. After stirring at this temperature for 0.5h, a solution of methyl N-tosylglycinate 9 (1.00 g, 4.11 mmol) in tetrahydrofuran (10 ml) was added dropwise and the resulting solution stirred without the addition of further coolant for 16h. The reaction was quenched by the addition of saturated aqueous ammonium chloride (5 ml) and the bulk of the tetrahydrofuran evaporated. The residue was taken up in ether (30 ml) and the
solution washed with water (2 × 20 ml) and brine (20 ml) then dried, filtered through a pad of silica gel and evaporated to leave the diynyl alcohol 10a (1.51 g, 98%) as a pale orange oil, δ_{H} (400 MHz, CDCl$_3$) 7.65 (d, 3J$_{HH}$ 8.1 Hz, 2H, 2 × CHAr), 7.18 (d, 3J$_{HH}$ 8.1 Hz, 2H, 2 × CHAr), 4.82 (t, 3J$_{HH}$ 6.7 Hz, 1H, NH), 3.14 (d, 3J$_{HH}$ 6.7 Hz, 2H, CH$_2$N), 2.30 (s, 3H, ArMe), 2.05 (t, 3J$_{HH}$ 7.1 Hz, 4H, 4- and 10-CH$_2$), 1.51 (br. res., 1H, OH), 1.38-1.20 (m, 8H), 0.77 (t, 3J$_{HH}$ 7.1 Hz, 6H, 1- and 13-Me); δ_{C} (100 MHz, CDCl$_3$) 143.9 (C), 137.1 (C), 129.7 (2 × ArCH), 127.2 (2 × ArCH), 86.0 (C), 78.2 (C), 62.7 (7-C), 53.9 (CH$_3$), 53.7 (CH$_3$), 129.8 (CH$_2$), 129.0 (CH), 128.3 (CH), 127.2 (C), 121.5 (C), 118.6 (C), 86.5 (C), 85.1 (C), 63.6 (3-C), 53.7 (CH$_2$N), 21.5 (ArMe); v$_{max}$/cm$^{-1}$ (film) 3404, 3287, 3059, 2234, 1598, 1470, 1443, 1374, 1332, 1257, 1161, 1094; m/z (ES) 439 (M + MeCN and Na$^+$, 90%), 414 (M + K$^+$, 30), 393 (M + NH$_4^+$, 80), 358 (M – H$_2$O, 100). [Found: [M + NH$_4^+$], 393.2208; C$_{21}$H$_{33}$N$_2$O$_3$S requires 393.2212].

Diphenyl-3-hydroxy-3-(4-toluenesulfonylamino)methyl)penta-1,4-diynyl (10b).

Using exactly the same method as described in the foregoing preparation and on the same scale, addition of phenylacetylene to the glycinate 9 gave, after column chromatography (10% EtOAc-hexanes), the diynyl alcohol 10b (1.31 g, 77%) as an orange oil, δ_{H} (400 MHz, CDCl$_3$) 7.69 (d, 3J$_{HH}$ 8.1 Hz, 2H, 2 × CHAr), 7.38-7.31 (m, 4H), 7.22-7.19 (m, 4H), 7.18 (d, 3J$_{HH}$ 8.1 Hz, 2H, 2 × CHAr), 7.06 (d, 3J$_{HH}$ 8.1 Hz, 2H, 2 × CHAr), 5.50 (t, 3J$_{HH}$ 6.7 Hz, 1H, NH), 3.66 (s, 1H, OH), 3.44 (d, 3J$_{HH}$ 6.7 Hz, 2H, CH$_2$N), 2.20 (s, 3H, ArMe); δ$_{C}$ (100 MHz, CDCl$_3$) 143.6 (C), 137.0 (C), 132.0 (CH), 129.8 (CH), 129.0 (CH), 128.3 (CH), 127.2 (CH), 121.5 (C), 86.5 (C), 85.1 (C), 63.6 (3-C), 53.7 (CH$_2$N), 21.5 (ArMe); v$_{max}$/cm$^{-1}$ (film) 3404, 3287, 3059, 2234, 1598, 1470, 1443, 1374, 1332, 1257, 1161, 1092; m/z (APCI) 433 (M + NH$_4^+$, 30%), 243 (40), 229 (100). [Found: [M + NH$_4^+$], 433.1598; C$_{25}$H$_{35}$N$_2$O$_3$S requires 433.1586].

Copper-catalysed pyrrole synthesis: General procedure

A solution of the acetylenic precursor (1.00 equiv.) and copper(II) acetate (0.10 equiv.) in dry toluene (10 ml g$^{-1}$ of precursor) was stirred and gently refluxed under a slow stream of dry nitrogen. Once tlc indicated completion of reaction, typically after around one hour, the resulting brown mixture was cooled and filtered through a pad of silica gel. The solid was washed with ether and the combined filtrates evaporated to leave (usually) clean pyrrole. When impurities were present, short column chromatography secured pure products.

Ethyl 5-butyl-1-(4-toluenesulfonyl)-1H-pyrrole-2-carboxylate (15a).

By the general procedure, the β-hydroxy-α-amino ester 6a (0.15 g, 0.41 mmol) and copper(II) acetate (5 mg, 0.04 mmol) were heated together in toluene (2 ml) for 40 minutes to give the pyrrole 15a (0.14 g, 98%) as a thick, colourless oil, δ$_{H}$ (400 MHz, CDCl$_3$) 7.85 (d, J 8.3 Hz, 2H, 2 × CHAr), 7.25 (d, 3J$_{HH}$ 8.3 Hz, 2H, 2 × CHAr), 6.73 (d, 3J$_{HH}$ 3.6 Hz, 1H, 3-H), 5.92 (d, 3J$_{HH}$ 3.6 Hz, 1H, 4-H), 4.21 (q, 3J$_{HH}$ 7.1 Hz, 2H, OCH$_2$), 2.76 (t, 3J$_{HH}$ 7.8 Hz, 2H, 1′-CH$_2$), 2.36 (s, 3H, ArMe), 1.54-1.46 (m, 2H), 1.32-1.22 (m, 2H), 1.24 (t, 3J$_{HH}$ 7.1 Hz, 3H, OCH$_2$Me), 0.83 (t, 3J$_{HH}$ 7.4 Hz, 3H, 4′-Me); δ$_{C}$ (100 MHz, CDCl$_3$) 160.8 (C=O), 144.8 (C), 143.8 (C), 136.8 (C), 129.6 (2 × ArCH), 127.9 (C), 127.4 (2 × ArCH), 120.3 (3-CH), 110.8 (4-CH), 61.1 (OCH$_2$), 30.9 (CH$_2$), 29.7 (CH$_2$), 28.3 (CH$_2$), 21.7 (Me), 14.1 (Me), 13.8 (Me); v$_{max}$/cm$^{-1}$ (film) 3055, 1721, 1496, 1368, 1318, 1264, 1176, 1106, 895; m/z (APCI) 433 (M + NH$_4^+$, 30%), 243 (40), 229 (100). [Found: [M + NH$_4^+$], 433.1598; C$_{25}$H$_{35}$N$_2$O$_3$S requires 433.1586].
Ethyl 5-phenyl-1-(4-toluenesulfonyl)-1H-pyrrole-2-carboxylate (15b). By the general procedure, the β-hydroxy-α-amino ester 6b (0.24 g, 0.62 mmol) and copper(II) acetate (8 mg, 0.06 mmol) were heated together in toluene (2 ml) for 70 minutes to give the pyrrole 15b (0.22 g, 97%) as a thick, colourless oil, δ_H (400 MHz, CDCl₃) 7.32 (d, 3_J_HH 8.2 Hz, 2H, 2 × CHAr), 7.29-7.08 (5H, m), 7.05 (d, 3_J_HH 8.2 Hz, 2H, 2 × CHAr), 6.28 (d, 3_J_HH 3.4 Hz, 1H, 3-H), 6.04 (d, 3_J_HH 3.4 Hz, 1H, 4-H), 4.33 (q, 3_J_HH 7.2 Hz, 2H, OCH₂), 2.28 (s, 3H, ArMe), 1.35 (t, 3_J_HH 7.2 Hz, 3H, OCH₂Me); δ_C (100 MHz, CDCl₃) 161.8 (CO), 145.4 (C), 144.0 (C), 136.1 (C), 131.7 (C), 131.5 (C), 130.5 (2 × ArCH), 129.5 (2 × ArCH), 129.2 (ArCH), 128.1 (2 × ArCH), 128.0 (2 × ArCH), 121.9 (3-CH), 114.8 (4-CH), 62.0 (OCH₂), 2.0 (ArMe), 14.6 (Me); ν_max/cm⁻¹ (film) 3085, 2987, 1719, 1550, 1470, 1369, 1237, 1139, 1092; m/z (APCI) Found: M + NH₄⁺, 387.1385; C₂₀H₂₃N₂O₄S requires M, 387.1379.

Ethyl 5-(prop-1-en-2-yl)-1-(4-toluenesulfonyl)-1H-pyrrole-2-carboxylate (15c). By the general procedure, heating the hydroxy-amino-ester 6c (0.15 g, 0.43 mmol) and copper(II) acetate (10 mg, 0.04 mmol) in toluene (2 ml) was refluxed for 3.5 h. The usual work up of the cooled mixture gave the pyrrole 15c (0.12 g, 84%) as a pale yellow oil, δ_H (400 MHz, CDCl₃) 7.72 (d, 3_J_HH 8.3 Hz, 2H, 2 × CHAr), 7.19 (d, 3_J_HH 8.3 Hz, 2H, 2 × CHAr), 6.75 (d, 3_J_HH 3.5 Hz, 1H, 3-H), 5.96 (d, 3_J_HH 3.5 Hz, 1H, 3-H), 5.11 (app. s, 1H), 4.86 (app. s, 1H), 4.25 (q, 3_J_HH 7.1 Hz, 2H, OCH₂), 2.34 (s, 3H, ArMe), 1.91 (br. s, 3H), 1.28 (t, 3_J_HH 7.1 Hz, 3H, OCH₂Me); δ_C (100 MHz, CDCl₃) 129.8 (2 × ArCH), 128.2 (2 × ArCH), 122.8 (3-CH), 119.4 (5-CH₂), 114.2 (4-CH), 62.6 (OCH₂), 22.9 (ArMe), 20.9 (Me), 14.3 (Me) (quaternary carbons not measured); ν_max/cm⁻¹ (film) 2927, 2855, 1732, 1532, 1495, 1446, 1304, 1192, 1020, 914, 815; m/z (APCI) Found: M + H⁺, 334.1114; C₁₇H₂₅NO₄S requires M, 334.1113.

Ethyl 1-(4-toluenesulfonyl)-1H-pyrrole-2-carboxylate (15d). By the general procedure, when a mixture of the β-hydroxy-α-amino ester 6d (0.05 g, 0.16 mmol) and copper(II) acetate (0.03 g, 0.16 mmol) was heated at 90 °C in dry toluene (1 ml) for 18 h, the usual work up followed by filtration through silica gel gave the pyrrole 15d (0.037 g, 79%), as a pale yellow oil, δ_H (400 MHz, CDCl₃) 7.86 (d, 3_J_HH 8.2 Hz, 2H, 2 × CHAr), 7.70 (dd, 3_J_HH 3.2, 1.8 Hz, 1H, 5-H), 7.25 (d, 3_J_HH 8.2 Hz, 2H, 2 × CHAr), 7.04 (dd, 3_J_HH 3.7, 1.8 Hz, 1H, 3-H), 6.30 (m, 1H, 4-H), 4.19 (q, 3_J_HH 7.0 Hz, 2H, OCH₂), 2.42 (s, 3H, ArMe), 1.26 (t, 3_J_HH 7.0 Hz, 3H, OCH₂Me); ν_max/cm⁻¹ (film) 3055, 2986, 2927, 1726, 1598, 1495, 1446, 1304, 1192, 1020, 914, 815; m/z (APCI) Found: M + H⁺, 334.1114; C₁₇H₂₅NO₄S requires M, 334.1113.

Ethyl 5-(2-(t-Butyldimethylsilyloxyethyl)-1-toluenesulfonyl-1H-pyrrole-2-carboxylate (15e). By the general procedure, reaction of the hydroxy-amino ester 6e (0.20 g, 0.44 mmol) and copper(II) acetate (9 mg, 0.04 mmol) in toluene (2 ml) at reflux for 1.5 h, followed by the usual work up gave clean pyrrole 15e (0.18 g, 95%) as a viscous, pale yellow oil, δ_H (400 MHz, CDCl₃) 7.90 (d, 3_J_HH 8.4 Hz, 2H, 2 × CHAr), 7.35 (d, 3_J_HH 8.4 Hz, 2H, 2 × CHAr), 6.77 (d, 3_J_HH 3.3 Hz, 1H, 3-H), 6.08 (d, 3_J_HH 3.3 Hz, 1H, 3-H), 4.29 (q, 3_J_HH 7.0 Hz, 2H, OCH₂), 3.83 (t, 3_J_HH 6.5 Hz, 2H, 2′-CH₂), 3.08 (t, 3_J_HH 6.5 Hz, 2H, 1′-CH₂), 2.42 (s, 3H, ArMe), 1.30 (t, 3_J_HH 7.0 Hz, 3H, OCH₂Me), 0.85 (s, 9H), 0.00 (s, 6H); δ_C (100 MHz, CDCl₃) 161.0 (C=O), 144.5 (C), 140.0 (C), 137.0 (C), 129.9 (2 × ArCH), 127.3 (2 × ArCH), 120.5 (3-CH), 112.4 (4-CH), 62.2 (CH₂), 61.2 (CH₂), 32.4 (1′-CH₂), 25.9 (3 × Me), 21.8 (ArMe), 18.1 (C), 14.3 (Me), -5.3 (2 × Me);
Ethyl 5-(2-hydroxyethyl)-1-(toluenesulfonyl)-1H-pyrrole-2-carboxylate (15f). By the general procedure, reaction between the hydroxy-amino ester 6f (0.14 g, 0.39 mmol) and copper(II) acetate (8 mg, 0.04 mmol) in toluene (2 ml) at reflux for 1 h gave the pyrrole 15f (0.13 g, 96%) as an orange viscous oil, δ_H (400 MHz, CDCl_3) 7.82 (d, J_{HH} 8.4 Hz, 2H, 2 × CHAr), 7.23 (d, J_{HH} 8.4 Hz, 2H, 2 × CHAr), 6.71 (d, J_{HH} 3.6 Hz, 1H, 3-H), 6.02 (d, J_{HH} 3.6 Hz, 1H, 4-H), 4.19 (q, J_{HH} 7.1 Hz, 2H, OCH_2), 3.79-3.78 (m, 2H, 2'-CH_2), 3.07 (t, J_{HH} 6.3 Hz, 4H, 1'-CH_2), 2.31 (s, 3H, ArMe), 1.94-1.85 (m, 1H, OH), 1.16 (t, J_{HH} 7.1 Hz, 3H, OCH_2Me); δ_C (100 MHz, CDCl_3) 160.7 (C=O), 145.0 (C), 139.6 (C), 136.6 (C), 129.8 (2 × ArCH), 128.4 (C), 127.4 (2 × ArCH), 120.4 (3-CH), 112.4 (4-CH), 61.6 (CH_2), 61.3 (CH_2), 32.0 (1'-CH_2), 21.7 (ArMe), 14.1 (Me); v_{max}/cm^{-1} (film) 3237, 2957, 2962, 2921, 1733, 1638, 1493, 1265, 1109; m/z (APCI) 360 (M + Na, 50%), 355 (M + NH_4, 100), 338 (M + H, 98). [Found: [M + H]^+, 338.1062. C_{14}H_{20}NO_5S requires M, 338.1067].

Ethyl 5-(2-((Butyldimethylsilyloxypropyl)-1-toluenesulfonyl-1H-pyrrole-2-carboxylate (15g). By the general procedure, reaction between the hydroxy-amino ester 6e (0.205 g, 0.44 mmol) and copper(II) acetate (10 mg) in toluene (2 ml) at reflux for 1.5 h, followed by the usual work up gave clean pyrrole 15g (0.185 g, 96%) as a viscous, pale yellow oil, δ_H (400 MHz, CDCl_3) 7.89 (d, J_{HH} 8.3 Hz, 2H, 2 × CHAr), 7.32 (d, J_{HH} 8.3 Hz, 2H, 2 × CHAr), 6.75 (d, J_{HH} 3.3 Hz, 1H, 3-H), 6.05 (d, J_{HH} 3.3 Hz, 1H, 4-H), 4.25 (q, J_{HH} 7.0 Hz, 2H, OCH_2), 3.65 (t, J_{HH} 6.5 Hz, 2H, 2'-CH_2), 3.00 (t, J_{HH} 6.6 Hz, 2H, 1'-CH_2), 2.42 (s, 3H, ArMe), 1.79-1.65 (m, 2H), 1.30 (t, J_{HH} 7.0 Hz, 3H, OCH_2Me), 0.85 (s, 9H), 0.00 (s, 6H); v_{max}/cm^{-1} (film) 2950, 2820, 1708, 1667, 1460; m/z Found: [M + H]^+, 466.2085. C_{19}H_{36}NO_5S requires 466.2083.

2-Butyl-4-(hex-1-yn-1-yl)-1-(toluenesulfonyl)-1H-pyrrole (15i). By the general procedure, reaction between the diyne 10a (0.36 g, 0.96 mmol) and copper(II) acetate (20 mg, 0.10 mmol) in toluene (4 ml) at reflux for 0.75 h gave the pyrrole 15i (0.30 g, 87%) as an orange oil, δ_H (400 MHz, CDCl_3) 7.58 (d, J_{HH} 8.2 Hz, 2H, 2 × CHAr), 7.30 (d, J_{HH} 1.7 Hz, 1H, 5-H), 7.21 (d, J_{HH} 8.2 Hz, 2H, 2 × CHAr), 5.91 (m, 1H, 3-H), 2.52 (t, J_{HH} 7.7 Hz, 2H, CH_2), 2.34 (s, 3H, ArMe), 2.29 (t, J_{HH} 6.9 Hz, 2H, CH_2), 1.50-1.18 (m, 8H, 0.86 (t, J_{HH} 7.3 Hz, 3H, Me), 0.79 (t, J_{HH} 7.3 Hz, 3H, Me); δ_C (100 MHz, CDCl_3) 145.0 (C), 136.0 (C), 135.8 (C), 130.0 (2 × ArCH), 126.9 (2 × ArCH), 124.5 (CH), 114.5 (C), 108.2 (C), 91.0 (C), 30.8 (CH_2), 30.5 (CH_2), 26.6 (CH_2), 22.3 (CH_2), 22.0 (CH_2), 19.2 (ArMe), 19.2 (CH_2), 13.8 (Me), 13.7 (Me) (some resonances obscured); v_{max}/cm^{-1} (film) 2931, 2871, 1596, 1464, 1367; m/z (EI) 357 (M, 10%), 218 (30), 171 (100). [Found: [M]^+, 357.1761. C_{11}H_{27}NO_5S requires M, 357.1763].

2-Phenyl-4-(2-phenylethynyl)-1-(toluenesulfonyl)-1H-pyrrole (15j). By the general procedure, reaction between the diyne 10b (0.10 g, 0.24 mmol) and copper(II) acetate (5 mg, 0.02 mmol) in toluene (1 ml) at reflux for 0.75 h gave the pyrrole 15j (0.098 g, 99%) as an orange oil, δ_H (400 MHz, CDCl_3) 7.61 (d, J_{HH} 1.8 Hz, 1H, 5-H), 7.43-7.40 (m, 2H), 7.31-7.21 (m, 6H), 7.17-7.13 (m, 4H), 7.02 (d, J_{HH} 8.2 Hz, 2H, 2 × CHAr), 6.19 (d, J_{HH} 1.8 Hz, 1H, 3-H), 2.28 (s, 3H, ArMe); δ_C (100 MHz, CDCl_3) 145.2 (C), 136.0 (C), 135.1 (C), 131.5 (2 × ArCH), 130.8 (CH), 129.5 (CH), 128.4 (3-CH), 123.3 (2-CH), 122.2 (2-CH), 119.4 (2-CH), 114.5 (C), 114.0 (C), 108.3 (C), 91.0 (C), 30.8 (CH_2), 30.5 (CH_2), 26.6 (CH_2), 22.2 (CH_2), 22.0 (CH_2), 21.7 (ArMe), 19.2 (CH_2), 13.7 (Me), 13.7 (Me) (some resonances obscured); v_{max}/cm^{-1} (film) 2931, 2871, 1596, 1464, 1367; m/z (EI) 357 (M, 10%), 218 (30), 171 (100). [Found: [M]^+, 357.1761. C_{11}H_{27}NO_5S requires M, 357.1763].
131.0 (2 × ArCH), 130.5 (2 × ArCH), 128.7 ArCH), 128.4 (2 × ArCH), 128.2 (ArCH), 127.4 (2 × ArCH), 126.7 (ArCH), 123.2 (C), 117.8 (ArCH), 108.2 (C), 90.3 (C), 82.4 (C), 21.7 (ArMe); ν\text{max}/\text{cm}^{-1} (film) 3060, 2926, 2853, 1597, 1475, 1443, 1377, 1307, 1226. A molecular ion was not observed using a number of techniques.

**t-Butyl 4-hydroxydec-5-yn-3-yl carbamate (12a).** (i) To an ice-cold, stirred solution of 2-amino-1-butanol (10.00 g, 112 mmol) in dichloromethane (100 ml) triethylamine (17.08 ml, 123 mmol) was added followed by the dropwise addition of a solution of di-t-butyl dicarbonate (24.72 g, 113 mmol) in dichloromethane (10 ml). The resulting solution was stirred without additional cooling for 16 h then diluted with dichloromethane (100 ml) and washed with water (2 × 50 ml) and brine (50 ml) then dried (Na\text{2}SO\text{4}), filtered and evaporated to leave the N-Boc derivative 11 (21.98 g, 99%) as a colourless oil, δ\text{H}(400 MHz, CDCl\text{3}) 4.63 (br. s, 1H, NH), 3.61-3.46 (m, 1H, 2-H), 3.48 (d, 3\text{J}_{\text{HH}}=7.4 Hz, 2H, 1-CH\text{2}), 2.73 (s, 1H, OH), 1.56-1.47 (m, 1H, 3-H\text{a}), 1.42-1.33 (m, 1H, 3-H\text{b}), 1.38 (s, 9H, t-Bu), 0.88 (t, 3\text{J}_{\text{HH}}7.4 Hz, 3H, Me); ν\text{max/cm}^{-1} (film) 3855, 3356, 2970, 2877, 1694, 1679, 1540, 1503, 1454, 1459, 1367.

(ii) A solution of the foregoing alcohol (0.80 g, 5.4 mmol) in dry dimethyl sulfoxide (5 ml) was added dropwise to a solution of IBX (3.05 g, 10.8 m mol) in dimethyl sulfoxide (50 ml). The resulting solution was stirred at ambient temperature for 2 h then poured into an ice-cold, biphasic mixture of ether (100 ml) and water (50 ml). The mixture was stirred for 0.25 h then separated and the aqueous layer extracted with ether (2 × 50 ml). The combined ether solutions were then washed with water (3 × 50 ml) and brine (2 × 50 ml), dried (Na\text{2}SO\text{4}), filtered and evaporated to leave the aldehyde 11 (0.61 g, 77%) as a viscous yellow oil, δ\text{H}(400 MHz, CDCl\text{3}) 9.37 (app. s, 1H, CHO), 3.99 (br. s, 1H, 2-H), 3.88 (br. s, 1H, NH), 1.48-1.39 (m, 2H, 3-CH\text{2}), 1.23 (s, 9H, t-Bu), 0.75 (t, 3\text{J}_{\text{HH}}=7.4 Hz, 3H, 4-CH\text{3}); ν\text{max/cm}^{-1} (film) 3348, 2974, 1697, 1508, 1459, 1392.

(iii) A solution of butyl lithium (2.35 ml of a 2.5M solution in hexanes, 5.88 mmol) was added dropwise to an ice-cold, stirred solution of 1-hexyne (0.68 ml, 5.88 mmol) in tetrahydrofuran (20 ml). After 0.5 h, the resulting solution was cooled to -78 °C and to it was added a solution of the foregoing aldehyde 11 (0.50 g, 2.67 mmol) in tetrahydrofuran (10 ml). The resulting solution was stirred for 16 h without the addition of further coolant, then cooled in ice and quenched by the addition of 2M hydrochloric acid (2 ml). After dilution with ether (40 ml), the solution was washed with water (2 × 20 ml) and brine (20 ml) then dried (Na\text{2}SO\text{4}), filtered and evaporated. Column chromatography (20% EtOAc-hexanes) then separated the propargylic alcohol 12a (0.61 g, 85%) as a colourless, viscous oil and a 4:1 mixture of diastereoisomers which showed δ\text{H} (400 MHz, CDCl\text{3}) 5.01 (br. s, 0.2H, NH), 4.54 (br. s, 0.8H, NH), 4.34 (app. s, 0.2H, 4-H), 4.25 (d, 3\text{J}_{\text{HH}}5.0 Hz, 0.8H, 4-H), 3.64-3.56 (m, 0.2H, 3-H), 3.53-3.44 (m, 0.8H, 3-H), 2.11 (t, 3\text{J}_{\text{HH}}7.0 Hz, 2H, 7-CH\text{2}), 1.74-1.49 (m, 2H, 2-CH\text{2}), 1.45-1.27 (m, 4H, 8- and 9-CH\text{2}), 1.36 (s, 9H, t-Bu), 0.88 (t, 3\text{J}_{\text{HH}}7.5 Hz, 3H, Me), 0.81 (t, 3\text{J}_{\text{HH}}7.2 Hz, 3H, Me); δ\text{C}(100 MHz, CDCl\text{3}) 66.0 (4-CH), 65.4 (4-CH), 57.2 (3-CH), 56.9 (3-CH), 30.7 (CH\text{2}), 30.6 (CH\text{2}), 28.4 3 × Me), 28.3 (3 × Me), 23.8 (CH\text{2}), 23.7 (CH\text{2}), 22.4 (CH\text{2}), 22.0 (CH\text{2}), 18.4 (CH\text{2}), 14.2 (Me), 13.6 (Me), 10.7 (Me), 10.5 (Me); ν\text{max/cm}^{-1} (film) 3390, 2964, 2359, 1694, 1504, 1456, 1392, 1251, 1170, 1056; m/z
(APCI) 561 (M + Na, 30%), 333 (M + MeCN + Na, 20), 270 (M + H, 15), 237 (100). [Found: [M + H]^+, 270.2075. C_{13}H_{28}NO_3 requires M, 270.2069].

**t-Butyl 4-hydroxy-6-phenylhex-5-yn-3-yl carbamate (12b).** This was prepared following exactly the foregoing procedure and on exactly the same scale [0.50 g, 2.67 mmol of aldehyde 11] but using phenylacetylene as the nucleophile precursor, which gave the propargylic alcohol 12b (0.72 g, 93%) as a clear, viscous oil and a 7:3 mixture of diastereoisomers which showed δ_H (400 MHz, CDCl_3) 7.38-7.34 (m, 2H), 7.26-7.21 (m, 3H), 4.68 (app. br. d, 3_J_{HH} 8.6 Hz, 1H, NH), 4.61 (d, 3_J_{HH} 2.7 Hz, 0.3H, 4-H), 4.53 (d, 3_J_{HH} 5.0 Hz, 0.7H, 4-H), 3.80-3.71 (m, 0.3H, 3-H), 3.70-3.59 (m, 0.7H, 3-H), 1.85-1.65 (m, 1H, 2-H_a), 1.55-1.34 (m, 1H, 2-H_b), 1.39 (s, 2.7H, t-Bu), 1.38 (s, 6.3H, t-Bu), 0.96-0.91 (m, 3H, Me); δ_C (100 MHz, CDCl_3) 131.9 (2 × ArCH), 131.8 (2 × ArCH), 128.6 (ArCH), 128.5 (ArCH), 128.3 (2 × ArCH), 128.2 (2 × ArCH), 66.4 (4-CH), 65.6 (4-CH), 57.3 (3-CH), 56.9 (3-CH), 28.4 (3 × Me), 24.5 (2-CH_2), 23.7 (2-CH_2), 10.8 (1-Me), 10.6 (1-Me); ν_{max}/cm^{-1} (film) 3396, 2971, 2934, 1695, 1505, 1456, 1393, 1367, 1249, 1168, 1057; m/z (APCI) 290 (M + H, 15%), 216 (60), 172 (100). [Found: [M + H]^+, 290.1746. C_{17}H_{24}NO requires M, 290.1756].

**2-Butyl-5-ethyl-1-(toluenesulfonyl)-1H-pyrrole (15l).** By the general procedure, reaction between the sulfonylamino propargylic alcohol 13a (0.097 g, 0.30 mmol) and copper(II) acetate (7.5 mg, 0.03 mmol) in toluene (2 ml) at reflux for 1.5 h gave the pyrrole 15l (0.081 g, 89%) as an orange oil, δ_H (400 MHz, CDCl_3) 7.92 (d, 3_J_{HH} 8.2 Hz, 2H, 2 × CHAr), 7.29 (d, 3_J_{HH} 8.2 Hz, 2H, 2 × CHAr), 5.81 (app. s, 2H, 3- and 4-H), 2.33 (s, 3H, ArMe), 2.83-2.62 (m, 4H), 1.56-1.47 (m, 2H), 1.35-1.28 (m, 2H), 1.24 (t, 3_J_{HH} 7.1 Hz, 3H, Me), 1.05 (t, 3_J_{HH} 7.1 Hz, 3H, Me); ν_{max}/cm^{-1} (film) 3050, 2920, 2833, 1590, 1475, 1443, 1377; m/z (APCI) Found: M + H^+, 306.1535; C_{17}H_{24}NO_2S requires M, 306.1528.

**5-Ethyl-2-phenyl-1-(toluenesulfonyl)-1H-pyrrole (15m).** By the general procedure, reaction between the sulfonylamino propargylic alcohol 13b (0.103 g, 0.30 mmol) and copper(II) acetate (7.5 mg, 0.03 mmol) in toluene (2 ml) at reflux for 1.5 h gave the pyrrole 15m (0.093 g, 96%) as an orange oil, δ_H (400 MHz, CDCl_3) 7.85 (d, 3_J_{HH} 8.2 Hz, 2H, 2 × CHAr), 7.58 (d, 3_J_{HH} 3.4 Hz, 1H, 3-H), 5.89 (d, 3_J_{HH} 3.4 Hz, 1H, 4-H), 2.33 (s, 3H, ArMe), 2.79 (q, 3_J_{HH} 7.5 Hz, 2H, 1′-CH_2), 1.19 (t, 3_J_{HH} 7.5 Hz, 3H, 2′-Me), ν_{max}/cm^{-1} (film) 3063, 2978, 2934 2878, 1600, 1480, 1443, 1370; m/z (APCI) Found: M + H^+, 326.1223; C_{19}H_{20}NO_2S requires M, 326.1215.

**Acknowledgements**

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**References and Notes**


11. For an acid-catalysed pyrrole synthesis, see Knight, D. W.; Sharland, C. M. *Synlett* **2003**, 2258.


