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Model studies for the synthesis of the antibiotic lactonamycin and the discovery of new reactions and mechanisms for the construction of substituted heterocycles

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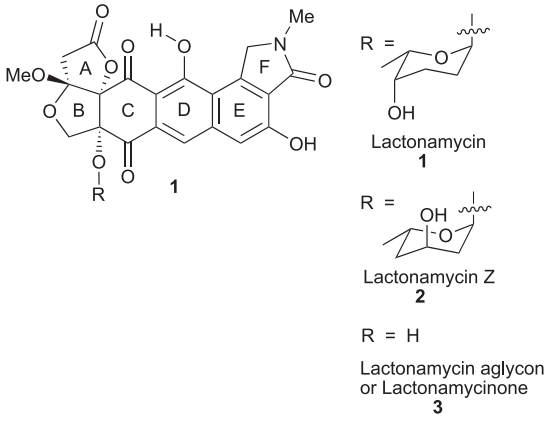
ABSTRACT

A new and highly efficient route for the construction of a model for the synthesis of lactonamycin **1** is reported. The chemistry has been utilised for the synthesis of heterocyclic rings, and new reactions for the synthesis of dienes and alkynes are reported.

1. Introduction

Lactonamycin **1** was isolated from bacterium *Streptomyces rishiriensis* and its structure was reported by Matsumoto in 1996.[1] Lactonamycin was shown to possess potent antibiotic activity and good efficacy against Gram-positive bacteria including most notably Methicillin-Resistant *Staphylococcus Aureus* (MRSA) and Vancomycin-Resistant *Enterococcus* (VRE).[1] Matsumoto and co-workers published the structure of lactonamycin **1** in detail in 1999 together with its biological properties and production procedures.[2,3] In 2003, an analogue of lactonamycin, lactonamycin Z **2** was isolated from pine wood samples collected from Hamsterley Forest in England.[4] Although lactonamycin Z **2** showed weak Gram-positive activity, it proved to be very active against gastric adenocarcinoma (HMO2) (IC50, 0.19 mg mL^{-1}) in human cell lines.

The biological profile of the lactonamycins is of great interest and because the search for new antibiotics is now of paramount importance due to the dramatic increase in post operative hospital infections[5] great interest has been shown from the chemical community in the synthesis of the lactonamycins.



In 2002, Behar and Deville published a synthesis of the ABCD ring system precursor of lactonamycin **1**.[6] A different approach was published by Kelly and co-workers,[7] which involved a Diels–Alder reaction as the key step for the formation of the ABCD ring. Kelly and his co-workers subsequently published a route to the EF ring system of lactonamycin **1**[8] but they have hitherto not reported a total synthesis of lactonamycin **1**. Notable contributions to the synthesis of lactonamycin **1** have also been made by Barrett and Danishefsky.

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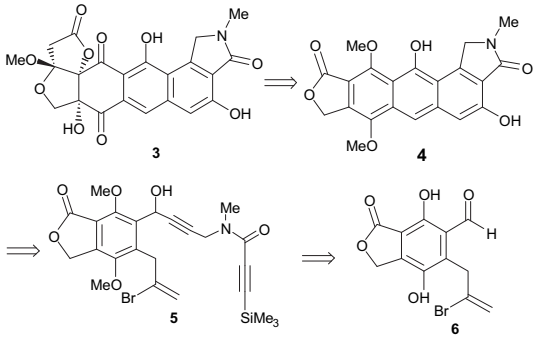
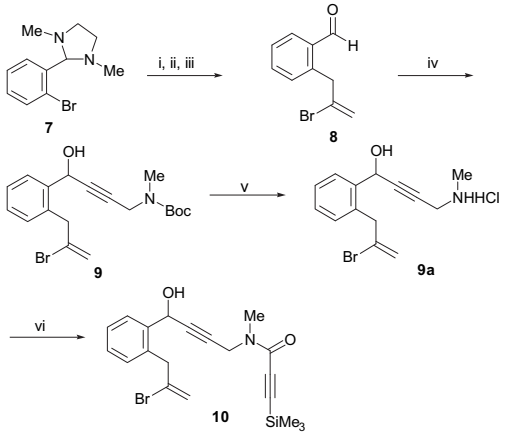
1.1. Cyclisation studies and the new synthetic approach

We devised a novel approach to the core of lactonamycin **1** together with an approach to the total synthesis of this important natural substance[9] (Scheme 1).



Scheme 1.

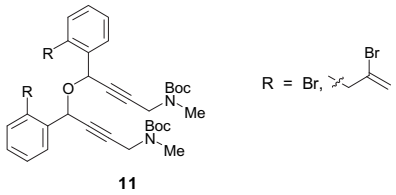
Retrosynthetic analysis of lactonamycin **3** led to the idea that a palladium[10] or tin[11] mediated cyclisation of the ene diyne **5** would after suitable chemical transformations give the tetracycle **4**. We envisaged that the ene diyne **5** could easily be prepared from the aldehyde **6**. In order to test this hypothesis the chemistry outlined in Scheme 2 was carried out.



Scheme 2. Reagents and conditions: (i) *n*-BuLi, (1.05 equiv), THF, −78 °C; (ii) CuCN, (1.05 equiv), −78 °C to −40 °C; (iii) 2,3-di bromopropene, (1.2 equiv), −78 °C to room temperature, HCl/H_2O quench then 2 M HC1 (73%); (iv) $LiC{\equiv}C{-}CH_2NMe(Boc)$, then ^tBuBr (80%); (v) 4 M HCl dioxane (2 equiv), 2 h (69%); (vi) $TMS{-}C{\equiv}C{-}CO_2H$, oxalyl chloride/DMF/Et_3N (86%).

Treatment of the aminal **7** with *n*-butyllithium in tetrahydrofuran at −78 °C, followed by transmetallation with cuprous cyanide[12] gave an intermediate cuprate, which upon reaction with 2,3-dibromopropene, gave the aldehyde **8** after acidic workup. Addition of the lithium salt of *N*-Boc-methylpropargylamine[13] to the aldehyde **8** followed by workup with *tert*-butyl bromide gave the alcohol **9** in high yield. *tert*-Butyl bromide acts as a bulky proton source and is entirely neutral as a quenching agent.[9] Other methods that were used to quench this reaction gave lower yields of the desired alcohol **9** and when ammonium chloride in water was used to work up the reaction mixture the ether **11** was isolated.

The alcohol **9** was treated with hydrogen chloride in dioxane to afford the amine hydrochloride salt **9a**. Treatment of the alcohol **9a** with trimethylsilylpropynoyl chloride generated from the parent acid and oxalyl chloride in dimethylformamide gave the desired alchol **10**.



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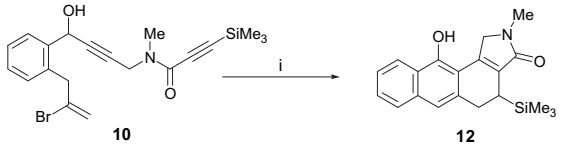
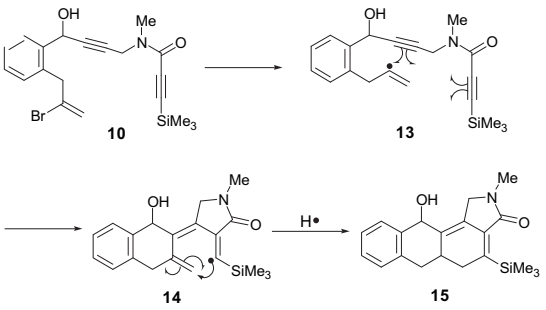
With the cyclisation precursor **10** in hand, we investigated a radical cascade sequence mediated with tri-*n*-butyltin hydride (Scheme 3).



Scheme 3. Reagents and conditions: (i) Bu_3SnH, AIBN, benzene (14%).

The reaction between tri-*n*-butyltin hydride and the alcohol **10** in boiling benzene gave the tetracyclic amide **12** in 14% isolated yield. This result was surprising because the lactam **12** was not the expected product **15** of the radical cyclisation depicted in Scheme 4.



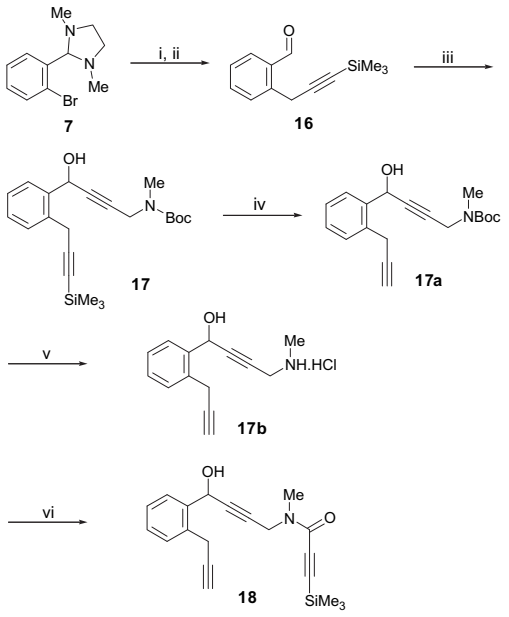
Scheme 4.

When the alcohol **10** was heated in toluene solution in the absence of tri-*n*-butyltin hydride, the tetracyclic lactam **12** was formed in 41% isolated yield. In order to prevent the acid catalysed decomposition of intermediates or the starting material with liberated hydrogen bromide, we elected to carry out the reaction in the presence of the high boiling epoxide epoxyhexene. In the presence of epoxyhexene in hot toluene the alcohol **10** underwent cyclisation to give the amide **12** in 76% yield. By analogy, epoxypropene served as an efficient acid trap in Corey's synthesis of gibberellic acid.[14]

In order to rule out the possibility of an acid catalysed cyclisation the alcohol **18** was prepared according to Scheme 5.

The alkyne **18** was heated in boiling toluene for four hours to give two products **12** and **19**.

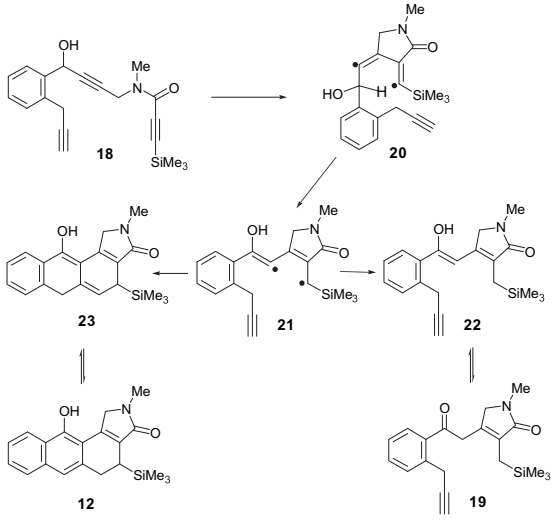
12 **19**



Scheme 5. Reagents and conditions: (i) *n*-BuLi (1.05 equiv), CuCN (1.05 equiv); $Me_3SiC{\equiv}C{-}CH_2Br$ (1.1 equiv), THF −60 °C (69%); (ii) H_2O; (iii) $LiC{\equiv}C{-}CH_2NMe(Boc)$, ^{t}BuBr, −95 °C (90%); (iv) MeONa (0.3 equiv), MeOH, DCM 1:1 (97%); (v) HCl, Et_2O (60%); (vi) oxalyl chloride (1.1 equiv), DMF, $TMSC{\equiv}C{-}CO_2H$ (28%).

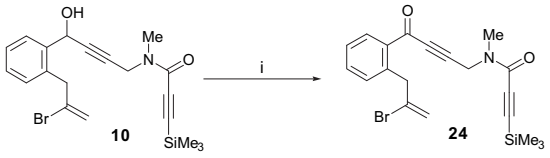
1.2. A mechanistic discussion and the discovery of new reactions

The isolation of the ketone **19** was very interesting because this indicated that a radical mechanism could be in operation. The isolation of **12** in low yield in the presence of tri-*n*-butyltin hydride also points towards a radical cyclisation (Scheme 6).



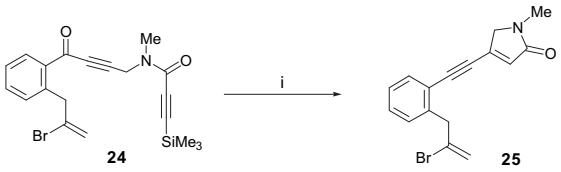
Scheme 6.

The alkyne **18** could cyclise to give a concentration of the biradical **20**, which in turn could give the biradical **21** by hydrogen atom abstraction. The biradical **21** could then cyclise to give the intermediate **23** and hence isomerise to the phenol **12** or by hydrogen atom abstraction from the solvent (toluene) from the enol **22**, which would form the ketone **19** by tautomerism. We decided to test the mechanism of this intriguing reaction further by removing the benzylic hydrogen in **10** by benzylic oxidation to afford the ketone **24** (Scheme 7).



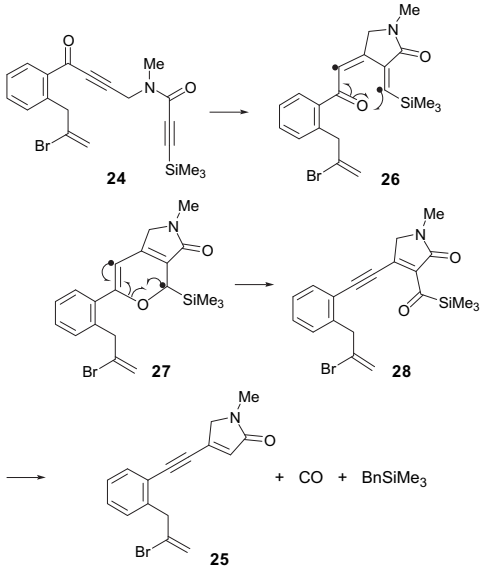
Scheme 7. Reagents and conditions: (i) MnO_2 (21 equiv), DCM (97%).

When the ketone **24** was heated in toluene solution for 6 h under reflux a remarkable transformation was observed; the alkyne **25** was isolated in 30% isolated yield (Scheme 8).



Scheme 8. Reagents and conditions: (i) Toluene, reflux, 6 h (30%).

The formation of the alkyne **25** was totally unexpected and the mechanism outlined in Scheme 9 was proposed to account for this unprecedented transformation.



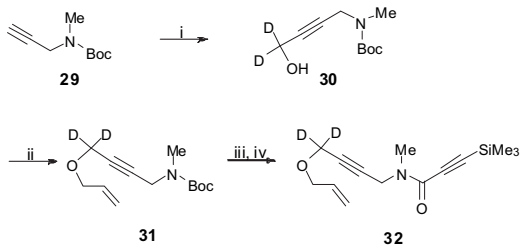
Scheme 9.

The biradical **26** could be formed as described in Scheme 6; instead of hydrogen atom abstraction the alkenyl radical could add to the carbonyl group as shown in structure **26** to form the new biradical **27**. Fragmentation of **27** would give the acyl silane **28**, which on loss of carbon monoxide and benzylsilane (from benzyl radical addition to silicon) would give the observed product **25**.

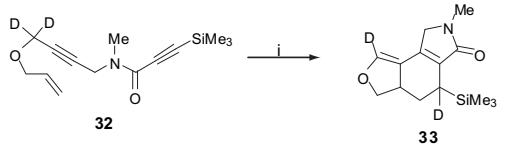
In order to further investigate the cyclisation the deuterated amide **32** was prepared according to Scheme 10.[15]

When the amide **32** was heated in hot toluene, cyclisation occurred to give the dihydrofuran **33** in 94% isolated yield (Scheme 11).

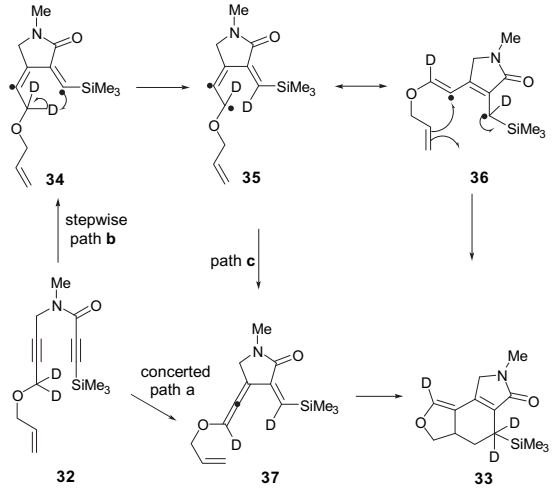
The deuterium transfer observed in lactam **33** coupled with a slower rate of reaction compared with its hydrogen analogue adds support to a concerted mechanism, which could operate in the absence of a radical stabilizing aromatic ring (Scheme 12).



Scheme 10. Reagents and conditions: (i) *n*-BuLi, THF, −78 °C, paraformaldehyde D_2 (94%); (ii) NaH, allyl bromide (quant); (iii) TFA, CH_2Cl_2; (iv) Et_3N, TMSC≡CCOCl (68%).



Scheme 11. Reagents and conditions: (i) Toluene, 110 °C, 3.5 h, (94%).



Scheme 12.

In Scheme 12 concerted path a would proceed by an intramolecular ene reaction to give the allene intermediate **37**, which could also result from the radical pathway b. Either a Diels–Alder reaction from allene **37** to lactam **33** could occur, or the cycloaddition pathway from the biradical **36** would also result in the formation of the lactam **33**.[16–20]

2. Conclusion

We have discovered a new cyclisation reaction together with a novel route to substituted alkynes. The mechanism of the cyclisation of the aryl substituted diynes appear to follow a radical pathway, which is also postulated for the formation of the alkyne **25**. The facile formation of the lactam **33** occurs with deuterium transfer and the cyclisation requires a longer reaction time (3.5 h) compared to less than one hour for its hydrogen analogue. The formation of **33** is consistent with a radical or a concerted pathway.

3. Experimental

3.1. General

Reactions were conducted at room temperature under an atmosphere of nitrogen unless otherwise stated. They were monitored using analytical thin layer chromatography with visualisation by UV light and either alkaline potassium permanganate ($KMnO_4$), vanillin or phosphomolybdic acid (PMA) dips. Reaction solvents were purified and dried according to literature methods. Tetrahydrofuran and diethyl ether were distilled from sodium with benzophenone as indicator; dichloromethane and acetonitrile were distilled from calcium hydride. Petrol refers to distilled petroleum 40–60 °C. All other solvents and reagents were used as supplied. Flash chromatography was performed using silica gel 60, 230–400 mesh. ^{1}H NMR spectra were recorded on a Bruker 300 MHz machine operating at ambient probe temperature using an internal deuterium lock. Chemical shifts were reported in parts per million (ppm) using residual solvent as an internal standard. Standard abbreviations were used throughout (s singlet; br d broad doublet, br s broad singlet; d doublet; dd doublet of doublets; dt doublet of triplets; dq doublet of quartets; t triplet; q quartet; m multiplet). Coupling constants were measured in hertz (Hz). ^{13}C NMR spectra were recorded at 75 MHz. Chemical shifts were reported in parts per million (ppm). Dept and correlation experiments were used for assignment of spectra. In some cases amide splitting caused doubling of peaks. Suppression of this was not possible using conventional variable temperature experiments and as such the relevant peaks have been assigned together. ESI mass spectra were recorded on a Bruker Daltonics Apex III spectrometer with methanol as solvent. EI mass spectra were recorded on a Fisons VG Autospec spectrometer. Infra red spectra were recorded on a Perkin ELMER Spectrum One FT-IR spectrometer. Crystal structures were obtained from a Bruker/Enraf Nonius FR590 KappaCCD. Structures were named using the ACD labs 'ACD/IUPAC Name v8.05'. The result of ACD/IUPAC Name v8.05 was obtained using the ACD/I-Lab service.

*3.1.1. 2-(2-Bromophenyl)-1,3-dimethylimidazolidine (**7**).* A solution of 2-bromobenzaldehyde (10.1 g, 55 mmol) and *N*,*N*′-dimethylethylenediamine (7.0 ml. 66 mmol) in ethanol (100 ml) was stirred at room temperature for 18 h. The reaction mixture was dried over $MgSO_4$ and the solvent was removed under reduced pressure to give a yellow oil. This was purified using Kugelröhr distillation (0.2 mbar, 110 °C) to yield **7** (12.9 g, 92%) as a transparent colourless oil. Spectra were consistent with those previously reported. IR (neat) ν (cm^{-1}): 3396, 3134, 3064, 2970, 2942, 2840, 2778, 2695, 2671, 2627, 2566, 2473, 1670, 1589, 1568; δ_H (300 MHz, $CDC1_3$): 7.72–7.15 (dd, 1H, J_1=7.8 Hz, J_2=1.7 Hz, *Ar*), 7.51–7.48 (dd, 1H, J_1=8.0 Hz, J_2=0.9 Hz, *Ar*), 7.35–7.30 (m, 1H, *Ar*), 7.16–7.11 (m, 1H, *Ar*), 4.05 (s, 1H, 7-CH), 3.40–3.34 (m, 2H, 8-CH_2), 2.65–2.60 (m, 2H, 9-CH_2), 2.21 (s, 6H, 10-CH_3-11-CH_3). δ_C (75 MHz, $CDC1_3$): 138.6 (q, *Ar*), 132.1 (CH, *Ar*), 129.6 (CH, *Ar*), 127.8 (CH, *Ar*), 125.4 (q, *Ar*), 88.3 (CH, 7-*C*), 53.4 (CH_3, 8-*C*-9-*C*), 39.4 (10-*C*-11-*C*). MS (EI) *m*/*z* (rel int.): 255 (M), 210, 132, 88, 42. HRMS (ESI^+): calcd for $C_{11}H_{15}N_2Br$, *m*/*z* 255.0491, found 255.0499.

*3.1.2. 2-(2-Bromoprop-2-en-1-yl)benzaldehyde (**8**).* *n*-Butyllithium (2.5 M in hexanes, 16.5 ml, 41.2 mmol) was added to a cooled (−78 °C) solution of 2-(2-bromophenyl)-1,3-dimethylimidazolidine (**7**) (10.0 g, 39.2 mmol) in THF (100 ml) and the reaction mixture stirred for 20 min. Copper cyanide (3.7 g, 41.2 mmol) was added and the reaction mixture allowed to warm to between −45 °C and 38 °C and stirred for 90 min. The reaction mixture was again cooled to −78 °C and 2,3-dibromopropene (4.9 ml, 47.0 mmol) was added. The reaction mixture was allowed to warm slowly to room temperature, quenched with saturated ammonium chloride solution (100 ml) and extracted with diethyl ether (2×100 ml). The combined organic phases were washed with brine, HCl (2 M, 4×40 ml) with vigorous shaking, saturated sodium hydrogen carbonate solution and brine, dried over magnesium sulfate and the solvent

removed under reduced pressure to give an orange oil. This was purified using flash column chromatography (24:1 petroleum ether 40/60/diethyl ether) and then with Kugelröhr distillation (0.8 mbar, 90–115 °C) to yield **8** (6.4 g, 73%) as a transparent colourless oil. IR (neat) ν (cm^{-1}): 3382, 3069, 3024, 2858, 2742, 1698, 1629, 1599, 1576. δ_H (300 MHz, $CDC1_3$) 10.20 (s, 1H, 10-CH), 7.87–7.84 (d, 1H, J=7.6 Hz, *Ar*), 7.60–7.55 (dt, 1H, J_1=7.5 Hz, J_2=1.4 Hz, *Ar*), 7.50–7.45 (t, 1H, J=7.4 Hz, *Ar*), 7.38–7.35 (d, 1H, J=7.5 Hz, Ar), 5.52–5.46 (m, 2H, 1-CH), 4.21 (s, 2H, 3-CH). δ_C (75 MHz, $CDC1_3$) 192.1 (CH, 10-*C*), 138.9 (q), 133.8 (CH, *Ar*), 132.6 (CH, *Ar*), 131.6 (CH, *Ar*), 131.6 (CH, *Ar*), 131.5 (q), 127.7 (CH, *Ar*), 118.8 (CH_2, 1-*C*), 43.7 (CH_2, 3-*C*). MS (EI) m/z (rel int.): 225, 208, 145, 115, 91, 51, 39. HRMS (ESI^+): calcd for $C_{10}H_9OBrNa$, m/z 246.9729, found 246.9723.

*3.1.3. tert-Butyl {4-[2-(2-bromoprop-2-en-1-yl)phenyl]-4-hydroxybut-2-yn-1-yl}methylcarbamate (**9**).* *n*-Butyllithium (2.5 M in hexanes, 4.8 ml, 12.0 mmol) was added to a cooled (−95 °C) solution of *tert*-butyl methyl(prop-2-yn-1-yl)carbamate (1.9 g, 11.5 mmol) in THF (200 ml) and stirred for 90 min. 2-(Bromoprop-2-en-1-yl) benzaldehyde **8** (2.5 g, 11.1 mmol) was added (reaction mixture <−95 °C) to the reaction mixture and stirred for 60 min. 2-Bromo-2-methylpropane (2.0 ml, 17.2 mmol) was added and the reaction mixture allowed to slowly warm to room temperature. The reaction mixture was partitioned between water (100 ml) and diethyl ether (200 ml) and the phases separated. The aqueous phase was extracted with diethyl ether (50 ml) and the combined organic phases were washed with brine and dried over magnesium sulfate. This was purified using flash column chromatography (2:3 diethyl ether/petroleum ether 40/60) to yield **9** (3.4 g, 77%) as a yellow oil. IR (neat) ν (cm^{-1}) 3396, 3066, 2977, 2930, 2248, 1679, 1630, 1604, 1581. δ_H (300 MHz, $CDC1_3$): 7.73–7.70 (m, 1H, *Ar*), 7.35–7.28 (m, 2H, *Ar*), 7.26–7.23 (m, 1H, *Ar*), 5.65 (s, 1H, 10-CH), 5.54 (s, 1H, 1a-CH), 5.44 (s, 1H, 1b-CH), 4.11 (s, 2H, 13-CH_2), 4.03–3.87 (m, 2H, 3-CH_2), 2.90 (s, 3H, 14-CH_3), 1.46 (s, 9H, 17-CH_3). δ_C (75 MHz, $CDC1_3$): 155.2 (q, 15-*C*), 138.7 (q), 134.7 (q), 131.8 (q), 130.6 (CH, *Ar*), 128.6 (CH, *Ar*), 127.6 (CH, *Ar*), 127.2 (CH, Ar), 118.3 (CH_2, 1-*C*), 83.0 (q, alkyne), 80.2 (q, 16-*C*), 61.8 (CH, 10-*C*), 40.0 (CH_2, 3-*C*), 38.2 (CH_2 b, 13*C*), 33.6 (CH_3, 14-*C*), 28.3 ($3CH_3$, 17-*C*). MS (EI) m/z (rel int.): 336, 320, 293, 258, 240, 214, 196, 183, 165, 153, 141, 129, 115. HRMS (ESI^+): calcd for $C_{19}H_{24}BrO_3NNa$, m/z 416.0832, found 416.0814.

*3.1.4. 1-[2-(2-Bromoprop-2-en-1-yl)phenyl]-4-(methylamino)but-2-yn-1-ol hydrochloride (**9a**).* Hydrogen chloride (2 M solution in ether, 53 ml, 105.2 mmol) was added to *tert*-butyl{4-[2-(2-bromoprop-2-en-1-yl)phenyl]-4-hydroxybut-2-yn-1-yl}methylcarbamate **9** (6.9 g, 17.5 mmol) and the resulting solution stirred for 18 h. Pentane (50 ml) was added to the reaction mixture and the precipitate purified by filtration and washing with diethyl ether (30 ml) and pentane (50 ml). Residual solvent was removed under reduced pressure to yield **9a** (4.7 g, 81%) as an off white solid, mp 96 °C. IR (Nujol) ν, (cm^{-1}): 3584, 3297, 3110, 2923, 2855, 2781, 2725, 2441, 1808, 1731, 1633, 1570, 1462, 1440, 1413, 1401, 1378, 1296, 1212, 1179, 1155, 1116, 1107, 1078, 1017, 969, 961, 903, 884, 867, 764, 655. δ_H (300 MHz, DMSO-d_6): 9.52 (s, 2H, 14-NH_2), 7.65–7.62 (m, 1H, *Ar*), 7.30–7.27 (m, 2H, *Ar*), 7.22–7.20 (m, 1H, *Ar*), 6.28 (br s, 1H, 16-OH), 5.69 (s, 1H, 10-CH), 5.56 (s, 2H, 1-CH_2), 4.03–3.82 (m, 4H, 3-CH_2-13-CH_2), 2.50 (s, 4H, 15-NCH_3-DMSO). δ_C (75 MHz, DMSO-d_6): 139.4 (q), 134.4 (q), 131.8 (q), 129.8 (CH, *Ar*), 128.0 (CH, *Ar*), 127.1 (CH, *Ar*), 127.0 (CH, *Ar*), 119.3 (CH_2, 1-C), 88.6 (q, alkyne), 76.0 (q, alkyne), 59,8 (CH, 10C), 43.1 (CH_2, 3-C), 36.8 (CH_2, 13-C), 31.3 (CH_3, 15-C). MS (EI) m/z (rel int.): 214, 196, 194, 181, 155, 141, 128, 115, 68, 44. HRMS (ES^+): calcd for $C_{14}H_{17}BrNO$, m/z, 294/0488, found 294.0479.

*3.1.5. N-{4-[2-(2-Bromoprop-2-en-1-yl)phenyl]-4-hydroxybut-2-yn-1-yl}-N-methyl-3-(trimethylsilyl)prop-2-ynamide (**10**).* DMF (15 drops) was added to a solution of 3-(trimethylsilyl)prop-2-ynoic acid (1.7 g, 12.2 mmol) and oxalyl chloride (1.1 ml, 12.2 mmol) in DCM (32 ml) and stirred for 30 min. This was added to a solution of 1-[2-(2-bromoprop-2-en-1-yl)phenyl]-4-(methylamino)but-2-yn-1-ol hydrochloride (4.2 g, 12.2 mmol) and triethylamine (4.3 ml, 30.5 mmol) in DCM (48 ml) that had itself been stirring for 10 min. The reaction mixture was stirred for 180 min and quenched with water (100 ml). The phases were separated and the organic phase washed with HC1 (1 M, 2×100 ml), saturated sodium hydrogen carbonate solution and brine. The solvent was removed to give a red oil, which was purified using flash column chromatography (1:1 diethyl ether/petroleum ether 40/60) to yield **10** (4.4 g, 86%) as a highly viscous yellow oil. IR (neat) ν (cm^{-1}): 3382, 2962, 2923, 2247, 1744, 1625, 1485, 1441, 1400, 1347, 1252, 1121, 996, 847, 760, 733, 665. δ_H (300 MHz, $CDC1_3$): 7.69–7.66 (m, 1H, *Ar*), 7.36–7.32 (m, 2H, *Ar*), 7.27–7.23 (m, 1H, *Ar*), 5.69–5.65 (d, 1H, J=11.4 Hz, 10-CH), 5.34–5.44 (d, 2H, J=29.1 Hz, 1-CH_2), 4.48–4.31 (d, 2H, J=51.8 Hz, 13-CH_2), 4.02–3.86 (m, 2H, 3-CH_2), 3.26–3.01 (d, 3H, J=76.2 Hz, 18-CH_3), 2.37 (s, 1H, 19-OH), 0.25–0.24 (d, 9H, J=3.1 Hz, 17-$3CH_3$). δ_C (75 MHz, $CDC1_3$): 153.6+153.4 (q, 14-*C*), 138.4+138.3 (q.), 134.8 (q), 131.8 (q), 130.8+130.7 (CH, *Ar*), 128.9–128.8 (CH, *Ar*), 127.8–127.7 (CH, *Ar*), 127.3–127.2 (CH, *Ar*), 118.5 (CH, 1-*C*), 98.3 (q, alkyne), 95.4–95.2 (q, alkyne), 84.3–83.5 (q, alkyne), 80.7–80.5 (q, alkyne), 61.9 (CH, 10-*C*), 44.1 (CH_2, 3-*C*), 41.0+35.5 (CH_2, 13-*C*), 35.7–31.7 (CH_3, 18-*C*). MS (EI) m/z (rel int.): 418, 402, 338,320, 304, 194, 183, 165, 155, 138, 125, 115, 97, 73, 42. MS (EI) m/z (rel int.): 460, 459, 458, 457, 456, 444, 443, 442, 441, 440. HRMS (ESI^+): calcd for $C_{20}H_{24}BrNO_2SiNa$, m/z 440.0652, found 440.0639.

*3.1.6. tert-Butyl{oxybis[4-(2-bromophenyl)but-2-yne-4,1-diyl]}bis (methylcarbamate) (**11**).* The title compound was tentatively assigned as the structure of a substance isolated in 6% yield as part of the synthesis of *tert*-butyl [4-(2-bromophenyl)-4,4-hydroxybut-2-yn-1-yl]methylcarbamate **9**. δ_H (300 MHz, $CDC1_3$): 7.63–7.61 (d, 2H, J=7.7 Hz, *Ar*), 7.50–7.47 (d, 2H, J=7.8 Hz, *Ar*), 7.35–7.30 (t, 2H, J=7.5 Hz, *Ar*), 7.15–7.09 (m, 2H, *Ar*), 5.58–5.54 (m, 1H, 7-CH), 4.68 (br s, 1H, 15-CH), 4.09 (br s, 4H, 10-$2CH_2$), 2.91–2.87 (d, 6H, J=10.4 Hz, 11-$2CH_3$) 1.44 (s, 18H, 14-$6CH_3$). δ_C (75 MHz, $CDC1_3$): 142.8 (q, *Ar*), 132.6 (CH, *Ar*), 128.8 (CH, *Ar*), 127.7 (CH, *Ar*), 127.5 (CH, *Ar*), 121.2 (q, *Ar*), 84.0 (q, alkyne), 83.6 (q, alkyne), 80.3 (q, 13-*C*), 71.0 (CH, 7-*C*), 61.1 (CH_2 15-*C*), 42.5 (CH_2, 10-*C*), 29.7 (CH_2, 10-*C*), 28.4 (CH_3, 14-*C*). It is believed that the missing peaks in the carbon NMR spectrum may have been lost in the baseline. The spectra are only temporarily assigned.

*3.1.7. 11-Hydroxy-2-methyl-4-(trimethylsilyl)-1,2,4,5-tetrahydro-3H-naphtho[2,3,-e]isoindol-3-one (**12**).* Using tributyltin hydride: A solution of tributyltin hydride (0.15 ml. 0.96 mmol) and AlBN (spatula end) in benzene (4 ml) was added over 390 min to a degassed, boiling solution of *N*-{4-[(2-bromoprop-2-en-1-yl) phenyl]-4-hydroxybut-2-yn-1-yl}-*N*-methyl-3-(trimethylsilyl)prop-2-ynamide **10** (0.40 g, 0.96 mmol) in benzene (50 ml) and stirred for 30 min. A further solution of tributyltin hydride (0.23 ml, 1.4 mmol) and AlBN (spatula end) in benzene (5 ml) was added to the boiling reaction mixture over 240 min and the reaction mixture allowed to cool to room temperature. Solvent was removed under reduced pressure and the residue purified using flash column chromatography (gradient; pentane 100% to diethyl ether 100% in 25% increments) to yield **12** (45 mg, 14%) as an off white solid, mp 278–282 °C (decomp.). Using tris(trimethylsilyl)silane: A solution of tris(trimethylsilyl)silane (0.28 ml, 0.92 mmol), AlBN (spatula end and *N*-{4-[(2-bromoprop-2-en-1-yl)phenyl]-4-hydroxybut-2-yn-1-yl}-*N*-methyl-3-(trimethylsilyl)prop-2-ynamide **10** (0.35 g, 0.84 mmol) in benzene (20 ml) was degassed and heated to reflux for 3 days. Solvent was removed under reduced pressure and

residue was purified using flash column chromatography (gradient; 1:3 diethyl ether/pentane to diethyl ether 100%) to yield **12** (62 mg 22%) as an off white solid. Using heat in benzene: A solution of *N*-{4-[2-bromoprop-2-en-1-yl)phenyl]-4-hydroxybut-2-yn-1-yl}-*N*-methyl-3-(trimethylsilyl)prop-2-ynamide **10** (0.50 g, 1.2 mmol) in benzene (30 ml) was heated at reflux for 40 h. Solvent was removed under reduced pressure, hexane added to the residue and the precipitate purified by filtration and washing with diethyl ether and hexane to yield **12** (202 mg, 50%). Using heat in toluene: A solution of *N*-{4-[2-bromoprop-2-en-1-yl)phenyl]-4-hydroxybut-2-yn-1-yl}-*N*-methyl-3-(trimethylsilyl)prop-2-ynamide **10** (0.50 g, 1.2 mmol) and butyl oxirane (2.9 ml, 23.9 mmol) in toluene (10 ml) was heated at reflux for 3 h. Solvent was removed under reduced pressure and the residue purified using flash column chromatography (gradient; diethyl ether/hexane 1:1. 2:1, 4:1, 1:0, then 1:1 diethyl ether/THF) to yield **12** (207 mg, 76%). IR (Nujol) ν, (cm^{-1}): 3043, 2955, 2925, 2868, 2855, 1943, 1921, 1647, 1570, 1501, 1487, 1463, 1442, 1416, 1403, 1371, 1336, 1286, 1247, 1219, 1162, 1147, 1118, 1084, 1028, 905, 868, 854, 835, 747, 721. δ_H (300 MHz, DMSO-d_6): 9.79 (br s, 1H, 19-OH), 8.22–8.19 (d, 1H, *J*=8.6 Hz, *Ar*), 7.74.7.71 (m, 1H, *Ar*), 7.34–7.41 (m, 2H, *Ar*), 7.26 (s, 1H, *Ar*, 6-CH), 4.82–4.35 (dd, 2H, J_1=20.1 Hz, J_2=122.3 Hz, 16-CH_2), 3.29–3.22 (m, 2H, 4-CH_2), 3.09–2.96 (m, 3H, N–Me), 2.20 (d, 1H, *J*=7.3 Hz, 3-CH), −0.19 (s, 9H, 17-3CH_3). δ_C (75 MHz, DMSO-d_6): 169.7 (q, 1-*C*), 148.3 (q), 141.6 (q), 135.6 (q), 134.2 (q), 133.9 (q), 127.3 (CH, *Ar*), 126.5 (CH, *Ar*), 124.8 (q), 124.7 (CH, *Ar*), 122.2 (CH, *Ar*, 114.9 (q) 54.7 (CH_2, 16-*C*), 31.1 (CH_2, 4-*C*), 28.8 (CH_3, 18-*C*), 21.2 (CH, 3-*C*), −2.1 (3CH_3, 17-C). MS (EI) *m*/*z* (rel int.): 360, 338, 322, 232. HRMS (ESI^+): calcd for $C_{20}H_{23}NO_2SiNa$, *m*/*z* 360.1390, found 360.1388. calcd for $C_{20}H_{24}NO_2Si$, *m*/*z* 338.1571, found 338.1566.

*3.1.8. 2-[3-(Trimethylsilyl)prop-2-yn-1-yl]benzaldehyde (**16**).* *n*-Butyllithium (8.23 ml, 20.58 mmol) was added dropwise to a cooled (CO_2/acetone) solution of 2-(2-bromophenyl)-1,3-dimethylimidazolidine **7** (5.0 g, 19.60 mmol) in THF (100 ml) and the reaction mixture stirred for 20 min. Copper cyanide (1.84 g, 20.58 mmol) was added and the reaction mixture allowed to warm to 30 °C and stirred at this temperature for 45 min. The reaction mixture was again cooled fully and 3-(trimethylsilyl) propargyl bromide (3.43 ml, 21.56 mmol) added. The reaction mixture was allowed to warm slowly to room temperature and quenched with saturated ammonium chloride solution (50 ml). The reaction mixture was extracted with diethyl ether (2×150 ml), the combined organic fractions washed with hydrochloric acid (2 M, 3×100 ml with vigorous shaking), saturated sodium hydrogen carbonate solution and brine, dried over magnesium sulfate, filtered and the solvent removed under reduced pressure to give a red oil. This was purified using Kugelröhr distillation (0.09 mbar, 140–150 °C) to yield **16** (2.9 g, 69%) as a clear colourless oil. IR (neat) ν (cm^{-1}): 3377, 3071, 2961, 2899, 2834, 2737, 2488, 2343, 2178, 1947, 1695, 1601, 1576, 1487, 1454, 1406, 1320, 1295, 1251, 1198, 1105, 1030, 958, 843, 758, 701, 646. δ_H (300 MHz, $CDC1_3$): 10.21 (s, 1H, 10-CH), 7.82–7.79 (d, 1H, *J*=7.6 Hz, *Ar*), 7.74–7.72 (d, 1H, *J*=7.6 Hz, *Ar*), 7.62–7.57 (m, 1H, *Ar*), 7.48–7.43 (t, 1H, *J*=7.4 Hz, *Ar*), 4.11 (s, 2H, 3-CH_2), 0.18 (s, 9H, 11-3CH_3). δ_C (75 MHz, $CDC1_3$): 192.7 (CH, 10-*C*), 138.3 (q, *Ar*), 134.O (CH, *Ar*), 133.4 (CH, *Ar*), 133.1 (q, *Ar*), 129.7 (CH, *Ar*), 127.2 (CH, *Ar*), 103.3 (q, alkyne), 88.5 (q, alkyne), 23.9 (CH_2, 3-*C*), 0.02 (3CH_3, 11-C). MS (EI) *m*/*z* (rel int.): 239, 217, 102, 79. HRMS (ESI^+): calcd for $C_{13}H_{16}OSiNa$, *m*/*z* 239.0863, found 239.0861.

*3.1.9. tert-Butyl(4-hydroxy-4-{2-[3-(trimethylsilyl)prop-2-yn-1-yl] phenyl}but-2-yn-1-yl)methylcarbamate (**17**).* *n*-Butyllithium (5.1 ml, 12.71 ml) was added (reaction mixture <−90 °C throughout) to a cooled (N_2/methanol) solution of *tert*-butyl methyl(prop-2-yn-1-yl)carbamate (2.15 g, 12.7 mmol) in THF (200 ml) and stirred for 30 min. A solution of 2-[3-(trimethylsilyl)prop-2-yn-1-yl] benzaldehyde **16** (2.50 g, 11.56 mmol) in THF (5 ml) was added dropwise and the reaction mixture allowed to stir for 60 min. The reaction was quenched with 2-bromo-2-methylpropane (2.0 ml, 17.33 mmol) and allowed to slowly warm to room temperature. The reaction mixture was diluted with diethyl ether (2×150 ml). The combined organic phases were washed with brine, dried over magnesium sulfate, filtered and the solvent removed under reduced pressure to give a dark orange oil. This was purified using flash column chromatography (3:2 hexane/diethyl ether) to yield **17** (4.01 g, 90%) as a transparent yellow oil. IR (neat) ν (cm^{-1}): 3396, 2963, 2931, 2248, 2177, 1678, 1483, 1455, 1393, 1368, 1251, 1152, 1026, 954, 911, 844, 759, 734. δ_H (300 MHz, $CDC1_3$): 7.66 (m, 1H, *Ar*), 7.49–7.46 (m, 1H, *Ar*), 7.34–7.28 (m, 2H, *Ar*), 5.71 (s, 1H, 10-CH), 4.11 (br s, 2H, 13-CH_2), 3.82 (s, 2H, 11–3-CH_2), 2.90 (s with long tail, 4H, 14-CH_3 and 19-OH), 1.44 (s, 9H, 17.3CH_3), 0.17 (s, 9H, 3CH_3). δ_C (75 MHz, $CDC1_3$): 155.2 (q, 15-C), 137.8 (q, *Ar*), 134.2 (q, *Ar*), 129.3 (CH, *Ar*), 127.3 (2CH, 2*Ar*), 104.2 (q, alkyne), 87.7 (q, alkyne), 82.5–82.2 (q, alkyne), 80.2 (q, 16-*C*), 62.1 (CH, 10-*C*), 38.6–37.9 (CH_2, br d, 13-*C*), 33.6 (CH_3, 14-*C*), 28.3 (3CH_3, 17-*C*), 23.5 (CH_2, 3-*C*), −0.03 (3CH_3, 18-*C*). MS (EI) I (rel int.): 410, 409, 408, 354, 353, 352, 136. HRMS (ESI^+): calcd for $C_{22}H_{31}NO_3SiNa$, *m*/*z* 408.1965, found 408, 1958.

*3.1.10. tert-Butyl[4-hydroxy-4-(2-prop-2-yn-1-yl-phenyl)but-2-yn-1-yl]methylcarbamate (**17a**).* A solution of *tert*-butyl[4-hydroxy-4-(2-prop-2-yn-1-yl-phenyl)but-2-yn-1-yl]methylcarbamate **17** (2.53 g, 6.7 mmol) and sodium methoxide (0.11 g, 1.97 mmol) in DCM (10 ml) and MeOH (10 ml) was stirred at room temperature for 18 h, diluted with DCM (20 ml), washed with water and the aqueous fractions extracted with DCM (2×20 ml). The combined organic fractions were dried over magnesium sulfate, filtered and, the solvent removed under reduced pressure to yield **17a** (2.04 g, 97%) as a yellow oil. IR (neat) ν (cm^{-1}): 3396, 3303, 2977, 2929, 2248, 2120, 1677, 1483, 1455, 1421, 1393, 1368, 1251, 1152, 1050, 1029, 1004, 872, 755. δ_H (300 MHz, $CDC1_3$): 7.66–7.63 (d, 1H, *J*=6.9 Hz, *Ar*), 7.53–7.51 (d, 1H, *J*=6.8 Hz, *Ar*), 7.36–7.29 (m, 2H, *Ar*), 5.73–5.71 (d, 1H, *J*=4.3 Hz, 10-CH), 4.12 (br s, 2H, 13-CH_2), 3.80 (s, 2H, 3-CH_2), 2.91 (s, 3H, 14-CH_2), 2.46 (br s 1H, 18-OH), 2.23–2.21 (t, 1H, *J*=1.4 Hz, 1-CH), 1.45 (s, 9H, 17.3CH_3). δ_C (75 MHz, $CDC1_3$): 155.2 (q, 15-C), 137.7 (q. *Ar*), 134.0 (q, *Ar*), 129.2 (CH, *Ar*), 128.7 (CH, 2*Ar*), 127.2 (CH, *Ar*), 127.1 (CH, *Ar*), 82.6 (q, alkyne), 82.2 (q, alkyne), 81.7 (q, alkyne), 80.2 (q, 16-*C*), 71.1 (CH_2, 1-*C*), 62.1 (CH, 10-*C*), 38.6–37.9 (CH_2, br d, 13-*C*), 33.6 (CH_3, 14-*C*), 28.3 (3CH_2, 17-*C*), 21.9 (CH_2, 3-*C*). MS (EI) *m*/*z* (rel int.): 336, 330, 280, 112, 101, 58. HRMS (ESI^+): calcd for $C_{19}H_{23}NO_3Na$, *m*/*z* 336.1570, found 336.1552.

*3.1.11. 4-(Methylamino)-1-(2-prop-2-yn-1-yl-phenyl)but-2-1-ol-hydrochloride (**17b**).* A solution of *tert*-butyl[4-hydroxy-4-(2-prop-2-yn-1-yl-phenyl)but-2-yn-1-yl]methylcarbamate **17a** (0.78 g, 2.5 mmol) and hydrochloride acid in diethyl ether (2 M, 2.5 ml, 5.0 mmol) was stirred at room temperature for 3.5 h. Pentane (7 ml) was added and the precipitate removed by filtration. The filter cake was washed with diethyl ether and pentane and sucked dry under nitrogen to yield **17b** (0.37 g, 60%) as an off white solid, mp 96–100 °C. IR (neat) ν (cm^{-1}): 3584, 3303, 3246, 2954, 2925, 2855, 2727, 2561, 2490, 2467, 2397, 1602, 1461, 1398, 1377, 1301, 1205, 1116, 1096, 1021, 795, 749. δ_H (300 MHz, DMSO-d_6): 9.48 (br s, 2H, NH_2), 7.62–7.60 (d, 1H, *J*=6.3 Hz, *Ar*), 7.50.7.48 (d, 1H, *J*=6.5 Hz, *Ar*), 7.34–7.28 (m, 2H, *Ar*), 6.28 (br s, 1H, 16-OH), 5.65 (s, 1H, 10-CH), 3.91 (s, 2H, 13-CH_2), 3.90 (s, 2H, 3-CH_3), 3.15 (s, 1H, 1-CH), 2.52 (s, 3H, 14-CH_3). δ_C (75 MHz, DMSO-d_6): 138.5 (q, *Ar*), 133.7 (q, *Ar*), 128.4 (CH, *Ar*), 128.0 (CH, *Ar*), 126.7 (2CH, 2*Ar*), 88.2 (q, alkyne), 81.8 (CH, 1-*C*), 78.0 (q, alkyne), 73.9 (q, alkyne), 59.9 (CH, 10-*C*), 36.8 (CH_2, 13-*C*), 31.3 (CH_3, 14-*C*), 21.0 (CH_2, 3-*C*). MS (EI) *m*/*z* (rel int.): 213, 194, 181, 165, 153, 141, 128, 115, 103, 94, 77, 68, 44. MS (EI) *m*/*z* (rel int.):

236, 214, 213, 181, 165, 136, 100, 71. HRMS (ESI^+): calcd for $C_{14}H_{16}NO$, *m*/*z* 214.1226, found 214.1217.

*3.1.12. N-[4-Hydroxy-4-(2-prop-2-yn-1-yl-phenyl)but-2-yn-1-yl]-N-methyl-3-(trimethylsilyl)prop-2-ynamide (**18**). Acid chloride method from amine salt* **17b**: DMF (five drops) was added to a solution of 3-(trimethylsilyl)prop-2-ynoic acid (196 mg, 1.38 mmol) and oxalyl chloride (0.13 ml, 1.38 mmol) in DCM (3 ml) and the solution stirred at room temperature for 40 min. This was then added dropwise to a solution of 4-(methylamino)-1-(2-prop-2-yn-1-yl-phenyl)but-2-yn-1-ol-hydrochloride **17b** (327 mg, 1.31 mmol) and triethylamine (0.46 ml, 3.27 mmol) in DCM (4 ml) that had itself been stirring for 20 min. The reaction mixture was stirred at room temperature for 20 min and quenched with water. The phases were separated, the organic phase was washed with hydrochloric acid (2 M, 2×10 ml), saturated sodium hydrogen carbonate solution and brine, dried over magnesium sulfate, filtered and the solvent removed under reduced pressure to give a red oil. This was purified using flash column chromatography (2:3 hexane/diethyl ether) to yield **18** (279 mg, 63%) as a viscous yellow oil. *Hydrogen iodide method from carbamate* **17a**: DMF (five drops) was added to a solution of 3-(trimethylsilyl)prop-2-ynoic acid (1.82 g, 12.76 mmol) and oxalyl chloride (1.1 ml, 12.76 mmol) in MeCN (8 ml) and the solution stirred at room temperature for 30 min. This was added to a cooled (ice/water) solution of *tert*-butyl {4-hydroxy-4-(2-prop-2-yn-1-yl-phenyl)but-2-yn-1-yl]methylcarbamate (1.00 g, 3.19 mmol) and sodium iodide (0.96 ml, 6.38 mmol) and the reaction mixture was stirred at room temperature for 10 min. Triethylamine (1.8 ml, 12.76 mmol) was added and the reaction mixture stirred for a further 30 min. The reaction mixture was quenched with hydrochloric acid (1 M, 25 ml), extracted with diethyl ether (1×100 ml, 2×50 ml), the combined organic fractions were washed with saturated sodium hydrogen carbonate solution and brine, dried over magnesium sulfate, filtered and the solvent removed to give a red oil. This was purified using flash column chromatography (1:1 pentane/diethyl ether) to yield **18** (301 mg, 28%) as a dark red oil. IR (neat) ν (cm^{-1}): 3378, 3306, 2961, 2924, 2853, 2247, 2119, 1716, 1627, 1485, 1455, 1400, 1348, 1253, 1124, 997, 911, 848, 761, 734. δ_H (300 MHz, $CDCl_3$): 7.63–7.60 (m, 1H, *Ar*), 7.53–7.50 (m, 1H, *Ar*), 7.34–7.29 (m, 2H, *Ar*), 5.74–5.70 (d, 1H, *J*=12.9 Hz, 10-CH), 4.48–4.30 (dd, 2H, J_1=1.5 Hz, J_2=52.6 Hz, 13-CH_2), 3.79–3.77 (t, 2H, *J*=2.7 Hz, 3-CH_2), 3.25–3.00 (d, 3H, *J*=75.6 Hz, 18-CH_3), 2.23–2.20 (m, 1H, 1-CH), 0.24–0.23 (d, 9H, *J*=2.8 Hz, 3-CH_3). δ_C (75 MHz, $CDCl_3$): 153.6–153.4 (q, 14-*C*), 137.14–136.36 (q, *Ar*), 134.0 (q, *Ar*), 129.5–29.4 (CH, *Ar*), 129.5–129.4 (CH, 2*Ar*), 129.0–128.9 (CH, Ar), 127.2–127.1 (CH, Ar), 98.35–95.4 (q, alkyne), 84.0–83.3 (q, alkyne), 81.7–81.6 (q, alkyne), 80.7–80.5 (q, alkyne), 71.1 (CH, 1-*C*), 62.1 (CH, 10-*C*), 41.0–35.5 (CH_2, 13-*C*), 35.7–31.7 (CH_3, 18-*C*), 22.0 (CH_2, 3-*C*), −07 ($3CH_3$, 17-*C*), MS (EI) *m*/*z* (rel int.): 725, 697, 530, 461, 360, 330, 242, 120. HRMS (ESI^+): calcd for $C_{20}H_{23}NO_2SiNa$, *m*/*z* 360.1390, found 360.1373.

*3.1.13. 1-Methyl-4-[2-oxo-2-(2-prop-2-yn-1-yl-phenyl)ethyl]-3-[(trimethylsilyl)methyl]-1,5-dihydro-2H-pyrrol-2-one (**19**).* A solution of *N*-[hydroxyl-4-(2-prop-2-yn-1-yl-phenyl)but-2-yn-1-yl]-*N*-methyl-3-(trimethylsilyl)prop-2-ynamide **18** (293 mg, 0.87 mmol) in toluene was heated at reflux for 4 h and the solvent removed under reduced pressure. The mixture was stirred at room temperature for 20 min and quenched with water. The residue was purified using flash column chromatography (24:1 diethyl ether/hexane) to yield **19** as a clear oil (27 mg, 9%). IR (neat) ν (cm^{-1}): 3307, 2954, 2926, 2239, 1681, 1450, 1421, 1399, 1249, 1164, 1073, 987, 910, 842, 734. δ_H (300 MHz, $CDCl_3$): 7.73–7.69 (m, 2H, *Ar*), 7.55–7.50 (m, 1H, *Ar*), 7.41–7.36 (m, 1H, *Ar*), 3.95 (s, 2H, 16-CH_2), 3.91 (s, 2H, 11-CH_2), 3.89–3.88 (d, 2H, *J*=2.6 Hz, 3-CH_2), 3.02 (s, 3H, 17-CH_3), 2.18–2.16 (t, 1H, *J*=2.7 Hz, 1-CH), 1,77 (s, 2H, 15-CH_2), 0.02 (s, 9H, 18-$3CH_3$). δ_C (75 MHz, $CDCl_3$): 199.3 (q, 10-*C*), 171.7 (q, 14-*C*), 137.1 (q), 136.6 (q), 136.6 (q), 136.0 (q), 132.5 (CH, *Ar*), 130.6 (CH, *Ar*), 128.8 (CH, *Ar*), 127.1 (CH, *Ar*), 81.8 (q, 2-*C*), 71.0 (CH, 1-*C*), 54.9 (CH_2, 11-*C*), 40.5 (CH_2, 16-*C*), 29.3 (CH_3, 17-*C*), 23.6 (CH_2, 3-*C*), 14.7 (CH_2, 15-*C*), 1.1 (CH_3, 18-*C*). MS (EI) *m*/*z* (rel int.): 413, 363, 274, 234, 218, 121, 101. HRMS (ESI^+): calcd for $C_{20}H_{25}NO_2SiNa$, *m*/*z* 362.1547, found 362.1533.

*3.1.14. N-{4-[2-(2-Bromoprop-2-en-1-yl)phenyl]-4-oxobut-2-yn-1-yl}-N-methyl-3-(trimethylsilyl)prop-2-ynamide (**24**).* A mixture of *N*-{4-[2-(2-Bromoprop-2-en-1-yl)phenyl]-4-hydroxybut-2-yn-1-yl}-*N*-methyl-3-(trimethylsilyl)prop-2-ynamide **10** (100 mg, 0.24 mmol) and manganese dioxide (438 mg, 5.04 mmol) in DCM was stirred at room temperature for 48 h. The reaction mixture was briefly stirred with magnesium sulfate and then filtered through Celite. The solvent was removed under reduced pressure to yield **24** (97 mg, 97%) as a viscous yellow oil. IR (neat) ν (cm^{-1}): 3278, 2961, 2925, 2230, 1639, 1572, 1484, 11396, 1251, 1128, 902, 849, 761, 735. δ_H (300 MHz, $CDC1_3$): 8.21–8.17 (m, 1H, *Ar*), 7.60–7.52 (m, 1H, *Ar*), 7.46–7.41 (t, 1H, *J*=7.6 Hz, *Ar*), 7.40–7.35 (t, 1H, *J*=6.9 Hz, *Ar*), 5.48–5.44 (m, 2H, 1-CH_2), 4.67–4.51 (d, 2H, *J*=49.7 Hz, 13-CH_2), 4.20–4.19 (d, 2H, *J*=3.9 Hz, 3-CH_2), 3.33–3.09 (d, 3H, *J*=72.5 Hz 18-CH_3), 0.25–0.24 (d, 9H, *J*=2.5 Hz 17-$3CH_3$). δ_C (75 MHz, $CDC1_3$): 178.5–178.3 (q, 10-*C*), 153.7–153.4 (q, 14-*C*), 138.9+138.7 (q), 134.9–134.8 (q), 133.7–133.6 (CH, *Ar*), 133.5–133.4 (CH, *Ar*), 132.0–131.9 (CH, *Ar*), 131.51–31.45 (q), 127.3 (CH, *Ar*), 118.52+118.45 (CH_2, 1-*C*), 99.02–98.96 (q, alkyne), 95.1–94.9 (q, alkyne), 87.2–86.7 (q, alkyne), 83.6–83.0 (q, alkyne), 44.9 (CH_2, 13-*C*), 41.0+35.6 (CH_2, 13-*C*), 35.9–32.1 (CH_3, 18-*C*), −0.8 ($3CH_3$, 17-*C*). MS (EI) *m*/*z* (rel int.): 442, 441, 440, 439, 438, 285, 146, 145. HRMS (ESI^+): calcd for $C_{20}H_{22}BrNO_2SiNa$, *m*/*z* 438.0495, found 438.0486.

*3.1.15. 4-{[2-(2-Bromoprop-2-en-1-yl)phenyl]ethynyl}-1-methyl-1,5-dihydro-2H-pyrrol-2-one (**25**).* A solution of *N*-{4-[2-(2-Bromoprop-2-en-1-yl)phenyl-4-oxobut-2-yn-1-yl}-*N*-methyl-3-(trimethylsilyl)prop-2-ynamide **24** (210 mg, 0.50 mmol) and butyl oxirane (1.2 ml, 10.09 mmol) in toluene (10 ml) was heated at reflux for 6 h. Solvent was removed under reduced pressure and the residue purified using flash column chromatography (1:1 diethyl ether/hexane) to yield **25** as a pale yellow oil (47 mg, 30%). IR (neat) ν (cm^{-1}): 3432, 3067, 2954, 2923, 2853, 2240, 2206, 1682, 1629, 1483, 1447, 1394, 1328, 1287, 1259, 1189, 1109, 1016, 909, 892, 856, 760, 732. δ_H (300 MHz, $CDC1_3$): 7.51–7.48 (d, 1H, *J*=7.7 Hz, *Ar*), 7.40–7.34 (m, 1H, *Ar*), 7.314–7.308 (d, 1H, *J*=1.7 Hz, *Ar*), 7.29–7.28 (m, 1H, *Ar*), 6.35 (s, 1H, 13-CH), 5.51 (s, 1H, 1-CH_2), 5.451–5.446 (d, 1H, *J*=1.5 Hz, 1-CH_2), 4.09 (s, 2H, 15-CH_2), 3.91 (s, 2H, 3-CH_2), 3.05 (s, 3H, 16-CH_3). δ_C (75 MHz, $CDC1_3$): 170.7 (q, 14-*C*), 139.4 (q), 136.4 (q), 132.5 (CH, *Ar*), 131.0 (q), 130.3 (CH, 13-*C*), 129.7 (2CH, 2*Ar*), 127.2 (CH, *Ar*), 121.9 (q), 118.3 (CH_2, 1-*C*), 97.9 (q, alkyne), 85.7 (q, alkyne), 56.8 (CH_2, 15-*C*), 46.0 (CH_2, 3-*C*), 29.0 (CH_3, 16-*C*). MS (EI) m/z (rel int.): 340, 338, 274, 218, 113, 112, 101. HRMS (ESI^+): calcd for $C_{16}H_{14}BrNONa$, *m*/*z* 338.0151, found 338.0129.

*3.1.16. (4-Hydroxy-but-2-ynyl)-methyl-carbamic acid tert-butyl ester (**30**).* To *N*-Boc-*N*-methylpropargylamine **29** (1.32 g, 7.81 mmol, 1.0 equiv) in THF (40 ml) at −78 °C was added *n*-butyllithium in hexanes (3.91 ml, 2.3 M, 8.80 mmol, 1.1 equiv). The solution was stirred for 30 min. Powdered *para*-formaldehyde-d_2 (500 mg, 15.6 mmol, 2.0 equiv) was added in one portion. The solution was allowed to warm to room temperature over 1 h upon which water and CH_2Cl_2 were added. The layers were separated and the aqueous layer was extracted over magnesium sulfate and concentrated under reduced pressure. Purification by flash column chromatography (10% diethyl ether in hexanes) gave the title compound **30** as a light yellow oil (1.49 g, 95%). IR (neat) ν (cm^{-1}): 3427, 2977, 2933, 2202, 2096, 1691. δ_H (300 MHz, $CDC1_3$): 4.01 (br s, 2H, 4-CH_2), 2.90 (br s, 1H, OH), 2.86 (s, 3H, 5-NMe), 1.42 (s, 9H, 8-

CH_3). δ_C (75 MHz, $CDC1_3$): 155.7 (6-CO), 82.4 (C), 81.0 (C), 80.6 (C), 38.5 (4-CH_2), 33.9 (5-CH_3), 28.7 (8-CH_3). HRMS (ESI^+): calcd for $C_{10}H_{15}D_2NO_3Na$: *m*/*z* 224.1226, found 224.1227.

*3.1.17. (4-Allyloxy-but-2-ynyl)-methyl-carbamic acid tert-butyl ester (**31**).* To a solution of NaH (60%, 286 mg, 7.16 mmol, 1.3 equiv) in THF was added dropwise D_2 propargylic alcohol **30** (1.11 g, 5.51 mmol, 1.0 equiv). The solution was stirred for 1 h after which time allyl bromide (666 mg, 0.48 ml, 5.51 mmol, 1.0 equiv) was added dropwise over 5 min at 0 °C. The solution was allowed to warm to room temperature over 2 h and was added to a stirring biphasic mixture of 10% aqueous K_2CO_3 solution and diethyl ether. The layers were then separated, the organic layer was washed with water and brine, dried over magnesium sulfate and concentrated under reduced pressure. Purification by flash column chromatography (10% diethyl ether in hexanes) to yield **31** (1.24 g, 93%) as a pale yellow oil. IR (neat) ν (cm^{-1}): 2929, 2249, 2084, 1695, 1455, 1247. δ_H (300 MHz, $CDC1_3$): 5.80–5.97 (m, 1H, 2-CH), 5.14–5.34 (m, 2H, 1-CH_2), 3.94–4.06 (m, 4H, 3,7-CH_2), 2.89 (s, 3H, 8-NMe), 1.45 (s, 9H, 11-CH_3). δ_H (75 MHz, $CDC1_3$): 155.2 (9-CO), 133.9 (2-CH), 117.8 (1-CH_2), 81.7 (C), 80.0 (C), 79.2 (C), 70.5 (3-CH_2), 38.6 (7-CH_2), 33.4 (8-NMe), 28.3 (11-CH_3). HRMS (ESI^+): calcd for $C_{13}H_{19}D_2NO_3Na$: *m*/*z* 264.1539, found 264.1539.

*3.1.18. 3-Trimethylsilanyl-propynoic acid (4-allyloxy-but-2-ynyl)-methyl-amide ester (**32**).* To a solution of D_2 (4-allyloxy-but-2-ynyl)-methyl-carbamic acid *tert*-butyl ester **31** (917 mg, 3.80 mmol, 1.0 equiv) in CH_2Cl_2 (30 ml) was added TFA (2.17 g, 1.41 ml, 19.0 mmol, 5.0 equiv) dropwise over 5 min. The solution was allowed to stir for a further 15 h and the reaction mixture was concentrated under reduced pressure to yield the amine TFA salt as a dark oil, which was used without further purification. To the amine salt was added CH_2Cl_2 (7 ml) followed by a dropwise addition of triethylamine (1.23 g, 1.69 ml, 12.2 mmol, 3.2 equiv) over 10 min under a flow of nitrogen at 0 °C. To the solution was then added freshly prepared trimethylsilylpropynoyl chloride (3.80 mmol, 1.0 equiv) in CH_2Cl_2 (7 ml) dropwise and stirred for a further 30 min, after which time the reaction was washed with 1 M HCl solution, saturated aqueous Na_2CO_3 solution, water and brine, dried over magnesium sulfate and concentrated under reduced pressure. The yellow oil was then purified by flash column chromatography (20% diethyl ether in hexanes) to yield **32** as a light yellow oil (d, 343 mg, 34%). IR (neat) ν (cm^{-1}): 2962, 2923, 2164, 2089, 1638, 1398, 848. δ_H (300 MHz, $CDC1_3$): 5.81–5.98 (m, 1H, 2-CH), 5.17–5.35 (m, 2H, 1-CH_2), 4.22–4.46 (m, 2H, 7-CH_2), 3.99–4.04 (m, 2H, 3-CH_2), 23.26 (s, 1.5H, 8-NMe), 3.01 (s, 1.5H, 8-NMe), 24 (s, 9H, 12-$SiMe_3$). δ_C (75 MHz, $CDC1_3$): 154.2 (9-CO), 133.7 (2-CH), 118.0 (1-CH_2,), 98.0 (C), 95.5 (C), 79.9 (C), 70.6 (3-CH_2), 40.8 (35.5, 7-CH_2), 35.4 (31.5, 8-NMe), −0.8 (112-$SiMe_3$). HRMS (ESI^+): calcd for $C_{14}H_{19}D_2NO_2Na$: *m*/*z* 288.1359, found 288.1358.

*3.1.19. 7-Methyl-5-trimethylsilanyl-3,3a,4,5,7,8-hexahydro-furo-[3,4-e]isoindol-6-one (**33**).* D_2 3-Trimethylsilanyl-propynoic acid (4-allyloxy-but-2-ynyl)-methyl-amide **32** (200 mg, 0.75 mmol, 1.0 equiv) in toluene (10 ml) was heated at reflux for 3.5 h. The reaction mixture was concentrated under reduced pressure to yield **33** (198 mg, 99%) as a colourless oil. IR (neat) ν (cm^{-1}): 3449, 2952, 2237, 1676, 1630. δ_H (300 MHz, $CDC1_3$): 4.58–4.66 (dd, 1H, J_1=8.85, J_2=8.85 Hz, 2a-CH_2), 3.84–4.02 (m, 2H, 6-CH_2), 3.69–3.78 (dd, 1H, J_1=8.67, J_2=12.62 Hz, 2b-CH_2), 3.20–3.38 (m, 1H, 1-CH), 2.98 (s, 3H, 7-NMe), 2.09–2.21 (dd, 1H, J_1=4.14, J_2=12.43 Hz, 11a-CH_2), 1.53–1.65 (dd, 1H, J_1=12.53, J_2=12.53 Hz, 11b-CH_2), 0.04 (s, 9H, 12-$SiMe_3$). δ_C (75 MHz, $CDC1_3$): 171.3 (8-CO), 136.2 (C), 132.7 (C), 76.9 (2-CH_2), 51.6 (6-CH_2), 40.7 (1-CH), 29.4 (7-NMe), 28.9 (11-CH_2), −1.0 (12-$SiMe_3$). HRMS (ESI^+): calcd for $C_{14}H_{19}D_2NO_2Na$: *m*/*z* 288.1359, found 288.1352.

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Supplementary data

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.tet.2010.05.051.

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