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Total synthesis of cytotoxic sponge alkaloids hachijodines F and G

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Abstract—The total synthesis of two cytotoxic sponge alkaloids hachijodines F and G has been achieved. The synthesis of both compounds utilises a common intermediate alkyne. By comparison of spectra the structure of the natural product has been confirmed.

1. Introduction

Marine sponges (Phylum Porifera) are an extremely rich source of novel secondary metabolites, many of which display potent biological activities. One major category of such compounds is the 3-alkylpyridine alkaloids.[1–3] Recently Fusetani[4] et al. isolated seven 3-alkylpyridine alkaloids from two marine sponges of the genera *Xestospongia* and *Amphimedon*. The sponges were collected off Hachijo-jima, Japan and the alkaloids were subsequently named hachijodines A–G. Their structures were determined on the basis of NMR spectroscopy and mass spectrometry measurements. Hachijodines F (**1**) and G (**2**) (Fig. 1) share the same acetylene moiety and were both isolated from the sponge *Amphimedon* (0.0058 and 0.017% yield, wet weight, respectively). They exhibit moderate toxicity against P388 murine leukaemia cells with IC_{50} values of 1.0–2.3 μg/ml. We have previously communicated the synthesis of these two compounds.[5] Herein we disclose the full details of our investigation. Retrosynthetic analysis shows that the alkaloids can be synthesised via a common alkyne intermediate **3**.

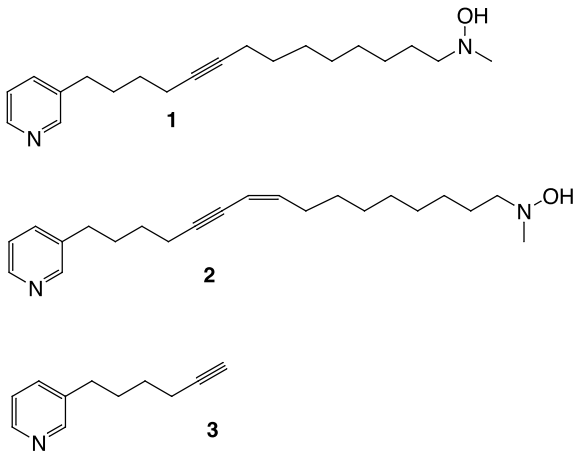
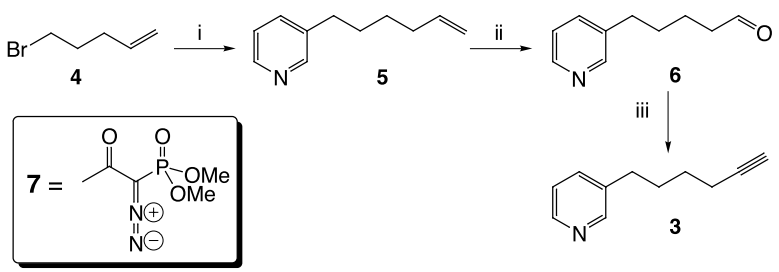


Figure 1. Hachijodines F (**1**) and G (**2**). Common intermediate **3**.

2. Results and discussion

2.1. Synthesis of 5-(pyridin-3-yl)-hex-1-yne (3)

The synthesis commenced with 5-bromopent-1-ene **4** being subjected to S_N2 displacement by the anion derived from 3-picoline[6] to give the 5-(pyridin-3-yl)-hex-1-ene **5**[7] (Scheme 1). Deprotonation of 3-picoline was affected by



Scheme 1. *Reagents and conditions*: (i) LDA, DMPU, 3-picoline, THF, 70%; (ii) OsO_4, $NaIO_4$, ^tBuOH, H_2O, 73%; (iii) K_2CO_3, MeOH, dimethyldiazo-2-oxopropylphosphonate **7**, 79%.

Keywords: marine sponge alkaloid; Sonogashira coupling.

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Table 1. Range of conditions for Lemieux–Johnson oxidation

Co-solvent	$NaIO_4$ (equiv.)	Yield of aldehyde **6** (%)
Et_2O	3.0	47
Et_2O	6.0	57
THF	3.0	44
^{t}BuOH	3.0	44
^{t}BuOH	4.5	73
^{t}BuOH	6.0	49

using lithium diisopropylamine (LDA) in THF with 1,3-dimethyl-3,4,5,6-tetrahydro-2(1*H*)-pyrimidinone (DMPU). The reaction proceeded in 55–70% yield depending on the scale. The lowering of the yield on a large-scale preparation of **5** is probably due to a competing elimination reaction to give 1,5-pentadiene. When the reaction mixture was left for 60 h (20 h in excess of the literature precedent), it was observed that isomerisation of the product to give the thermodynamically stable internal double bond occurred in about 50% (estimated by ^{1}H NMR spectroscopy). The amount of lithiated 3-picoline affects the outcome of the reaction greatly. Too little and the yield is low, but too much and degradation of product occurs. The reaction time was limited to less than 18 h to avoid isomerisation and the quantity of lithiated 3-methyl picoline was optimised. Reactions with 1.5 equiv. of the anion were found to give the best results with no isomerisation product as detected by ^{1}H NMR spectroscopy, with a reasonable yield of **5**.

Oxidation of compound **5** was first attempted using ozonolysis,[8] however yields of aldehyde **6** were low, with a range of unidentified degradation products. As an alternative approach compound **5** was subjected to the Lemieux–Johnson oxidation.[9] Osmium tetroxide was added to a homogeneous mixture of water and a co-solvent, containing the alkene **5** and sodium periodate, then stirred at room temperature for one hour. The reaction was attempted with several organic solvents, Et_2O, THF and ^{t}BuOH and a different amount of sodium periodate equivalents (Table 1). The best yield of **6** (73%) was obtained using 4.5 equiv. of $NaIO_4$ with ^{t}BuOH as co-solvent. Care was taken in the reaction work-up since the aldehyde **6** was quite water-soluble.

Conversion to the acetylene **3** was effected in 79% yield by use of the Bestmann procedure.[10] The alkyne forming reaction was performed as a one-pot procedure by adding anhydrous potassium carbonate to a solution of dimethyl-diazo-2-oxopropylphosphonate **7** and aldehyde **6** in anhydrous methanol. Dimethyldiazo-2-oxopropylphosphonate **7** was prepared according to the literature from tosyl azide and the commercially available dimethyl-2-oxopropylphosphonate.[11]

Table 2. Conditions for coupling of **3** and **11**, showing the amount of starting material recovered

Iodide	DMPU	^{n}BuLi	Alkyne (%)	Iodide (%)	**12** (%)
1.5	5.0	1.1	0	34	42
2.6	5.0	1.2	12	27	48
2.7	6.0	1.5	32	63	36

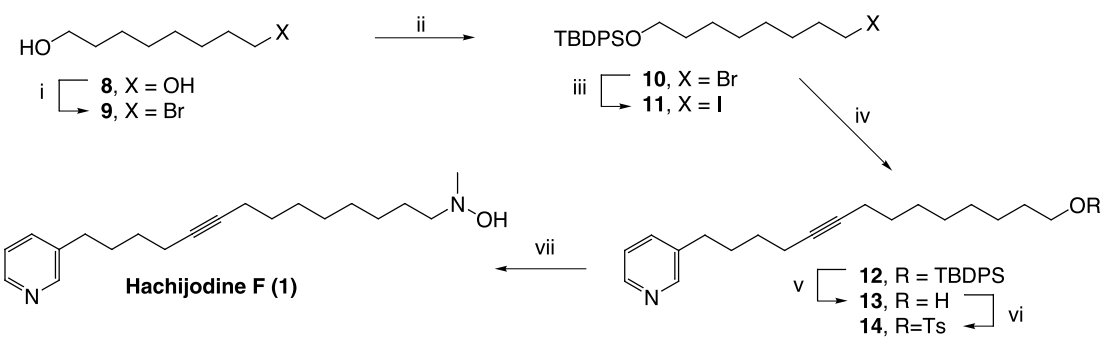
2.2. Synthesis of hachijodine F (1)

The synthesis of hachijodine F **1** commenced with the selective monobromination[12] of octane-1,8-diol **8** to give 8-bromooctan-1-ol **9** in 95% yield (Scheme 2). Experimentally, concentrated hydrobromic acid was added to a mixture of the diol **8** in toluene and the mixture was heated under gentle reflux. In the original protocol, the reaction was conducted as an open system, but we found this produced low yields presumably due to the loss of HBr. The yield of this reaction was greatly improved by conducting the reaction in a closed system at atmospheric pressure. Less than 1% of dibrominated product was isolated when the reaction was carried out on a large scale.

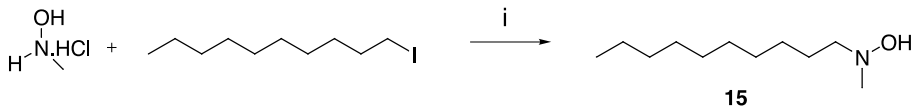
Compound **9** was converted to its *tert*-butyldiphenylsilyl ether **10** in 89% yield by reaction with imidazole and *tert*-butyldiphenylsilyl chloride (TBDPSCl) in THF.[13] Iodide **11** was obtained in 95% yield via a Finklestein[14] reaction, with bromide **10** and 5 equiv. of NaI in acetone at reflux.

Iodide **11** was reacted with the acetylide anion generated from **3** (**3**+^{n}BuLi in THF/DMPU)[15] to deliver the coupled compound **12**. We found that following the method of Liljefors, by adding ^{n}BuLi to **3** followed by DMPU and **11** produced low yields of **12**. However by adding the DMPU first followed by ^{n}BuLi gave much better results. The amounts of DMPU, iodide and ^{n}BuLi were varied, to optimise the reaction and the best yield achieved was 48% (Table 2). In this reaction remaining **3** and **11** were both recovered and recycled.

Deprotection of **12** was affected by the method of Zhang, with ammonium fluoride in methanol[16] to afford alcohol **13**



Scheme 2. *Reagents and conditions*: (i) $HBr_{(aq)}$, toluene, reflux, 95%; (ii) TBDPSCl, imidazole, THF, 89%; (iii) NaI, acetone, reflux, 95%; (iv) **3**, ^{n}BuLi, DMPU, 48%; (v) NH_4F, MeOH, 90%; (vi) TsCl, Et_3N, CH_2Cl_2, 67%; (vii) Et_4NI, Et_3N, MeNHOH·HCl, DMPU, 61%.



Scheme 3. *Reagents and conditions*: (i) DMPU, E_3N, 67%.

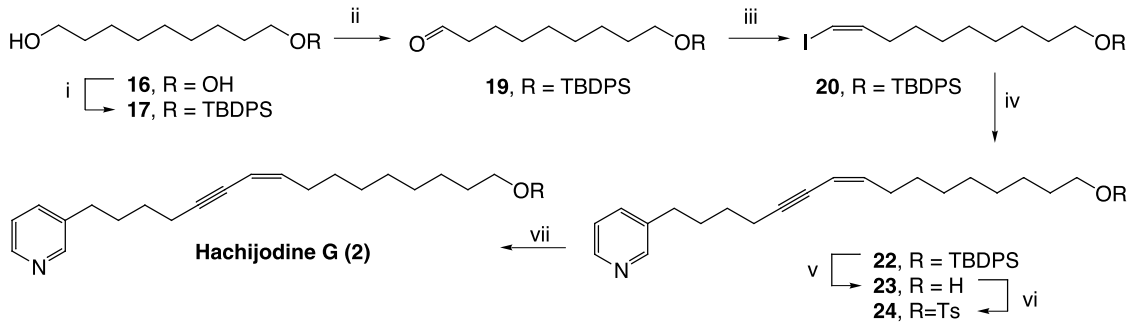
in 90% yield. Reaction of alcohol **13** with *p*-toluenesulphonyl chloride and triethylamine[17] gave tosylate **14** in 67% yield. Next, the introduction of the hydroxylamino group was investigated. Mukiyama et al.[18] examined the best solvent for the reaction of *N*-alkylhydroxylamines with bromides and found hexamethylphosphoric triamide (HMPA) gave the best yields. However, as HMPA is carcinogenic and can cause heritable genetic damage, it was decided to test if DMPU could be used as a HMPA substitute in this particular reaction.[15,19] A trial reaction was carried out between *N*-methylhydroxylamine (as the hydrochloride) and iododecane in DMPU with triethylamine, giving the expected product 1-(*N*-methylhydroxylamine)-decane **15** in 67% yield (Scheme 3). Thus compound **14** was subjected to nucleophilic displacement with *N*-methylhydroxylamine under the modified Mukiyama conditions (triethylamine and a catalytic amount of tetraethylammonium iodide in DMPU) to afford hachijodine F (**1**) in 61% yield.

2.3. Synthesis of hachijodine G (2)

The synthesis of hachijodine G (**2**) began with the selective monoprotection[20] of nonanediol **16**. A mild and convenient biphasic process was employed according to Yu et al. (Scheme 4). The diol **16** was dissolved in a biphasic mixture of diisopropylethylamine and *N*,*N*-dimethylformamide. *tert*-Butyldiphenylsilylchloride was added dropwise into the mixture at room temperature and stirred vigorously for 28 h. On a small scale yields of 75% of the 9-(*tert*-butyldiphenylsilyloxy)-nonan-1-ol **17** were achieved, however on a large scale the yield of **17** was just 55% with the di-protected diol **18** isolated in a 20% yield. No mechanistic rationale or working model was given in the protocol, but it could be conjectured that the diol **16** initially resides in the diisopropylethylamine (DIEA) phase and upon monoprotection moves into the dimethyl sulfoxide (DMF) phase. If the TBDPSCl remains in the DIEA phase then little diprotection would occur. As the volume of the solution increases the surface to volume ratio decreases, hence the diffusion rate decreases and more diprotection occurs.

The oxidation of **17** to aldehyde **19** was effected in 83% yield by treating monoprotected diol **16** with 2-iodoxybenzoic acid (IBX)[21,22] in a mixture of DMSO and THF. Compound **19** was converted into *cis*-vinyl iodide **20** by using the Stork and Zhao olefination protocol.[23] Again DMPU successfully replaced HMPA as reported by Holmes et al.[24] The required Wittig reagent $[Ph_3PCH_2I^+]^-$ **21** was prepared in 96% yield by refluxing triphenylphosphine with diiodomethane in benzene at 100°C.[25] The aldehyde **19** was then reacted with the ylide generated from **21** with sodium bis(trimethylsilyl)amide to afford the vinyl iodide **20** in 65% yield. The geometry of the alkene was confirmed as *Z* by measuring the vincinal-coupling constant of the vinyl hydrogens in the ^1H NMR spectrum (J=7.0 Hz).

The projected Sonogashira[26] coupling of compounds **3** and **20** was found to be non-trivial. A range of conditions was screened (Table 3). Using Sonogashira's methodology (experiment 1)[27] no desired product was formed and the spectroscopic data suggested that the iodine had been replaced. Unfortunately the due to the rapid fragmentation of this molecule in mass spectrometry measurements, we were unable to fully determine what this side product was, solely on the basis of NMR spectroscopy. Using Et_3N instead of Et_2NH has been successful in the coupling of



Scheme 4. *Reagents and conditions*: (i) $^iPr_2Et$, DMF, TBDPSCl, 55%; (ii) IBX, DMSO, THF, 83%; (iii) $NaN(TMS)_2$, $[PH_3PCH_2I]^+I^-$, THF, DMPU, 65%; (iv) $Pd(PPh_3)_4$, pyrrolidine, CuI, **3**, 87%; (v) NH_4F, MeOH, 92%; (vi) TsCl, Et_3N, DCM, 81%; (vii) Et_4NI, Et_3N, MeNHOH·HCl, DMPU, 46%.

Table 3. Reagents and conditions for the Sonogashira coupling

Experiment	Reagents and conditions	Yield
1	$Pd(PPh_3)_4$, CuI, Et_2NH, rt, 39 h	Side product
2	$Cl_2Pd(PPh_3)_2$, CuI, Et_3N, DCM, reflux 50°C, 22 h	No reaction
3	$Pd(PPh_3)_4$, CuI, $BnEt_3N^+Cl^-$, 10% $NaOH_{(aq)}$, rt, 22 h	No reaction
4	$Pd(PPh_3)_4$, CuI, pyrrolidine, rt, 20 h	90% **22**

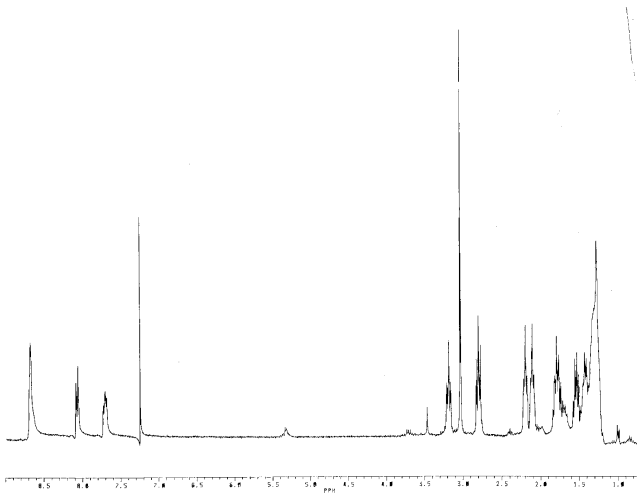


Figure 2. Proton NMR spectrum of authentic hachijodine F.

alkynes and bromoalkenes,[7] but when applied in this reaction (experiment 2) only the starting materials were recovered. Rossi[28] reported the use of phase transfer conditions to avoid the production of a diethylamine side product. This protocol was adopted for experiment 3 but again no coupling was observed. Following the work of Alami,[29] when pyrrolidine was used as solvent, 87% of the desired coupling product **22** was formed. No reaction was observed until the copper (I) iodide was added showing that it plays a key role in the mechanism.

Compound **22** was deprotected with ammonium fluoride in methanol[16] to deliver the alcohol **23** in 92% yield. Alcohol **23** was then converted to its tosylate **24** in 81% yield with *p*-toluenesulphonyl chloride and triethylamine.[17] Compound **24** was treated with *N*-methylhydroxylamine[18] under our modified conditions, to give hachijodine G **2** in 46% yield.

3. Conclusion

The ^{1}H NMR data of hachijodines F (**1**) and G (**2**) (in $CDCl_3$ with traces of trifluoroacetic acid added) are consistent with the literature data (Figs. 2–5). The structures of the natural products have been confirmed, and efficient syntheses of **1** (7%), and **2** (9%) have been developed via the common intermediate **3**.

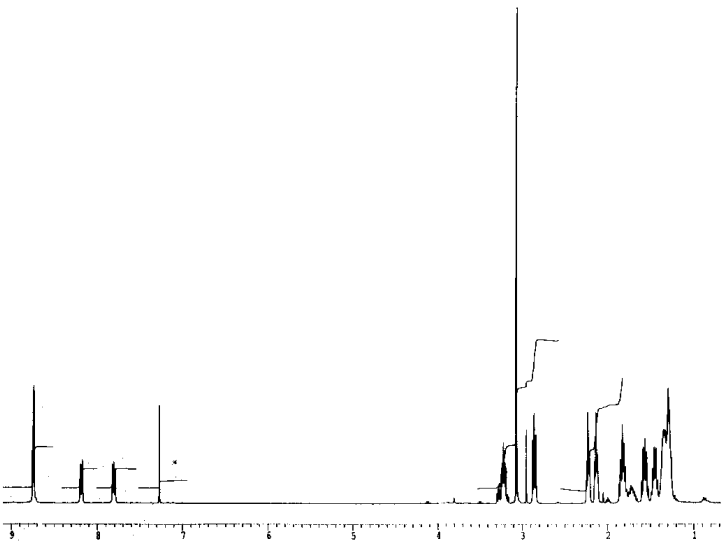


Figure 3. Proton NMR spectrum of synthetic hachijodine F.

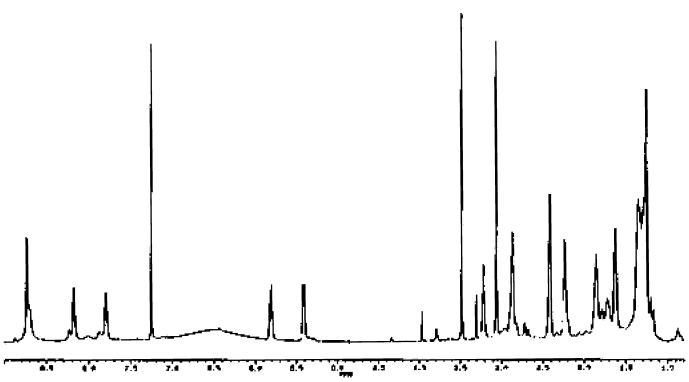


Figure 4. Proton NMR spectrum of authentic hachijodine G.

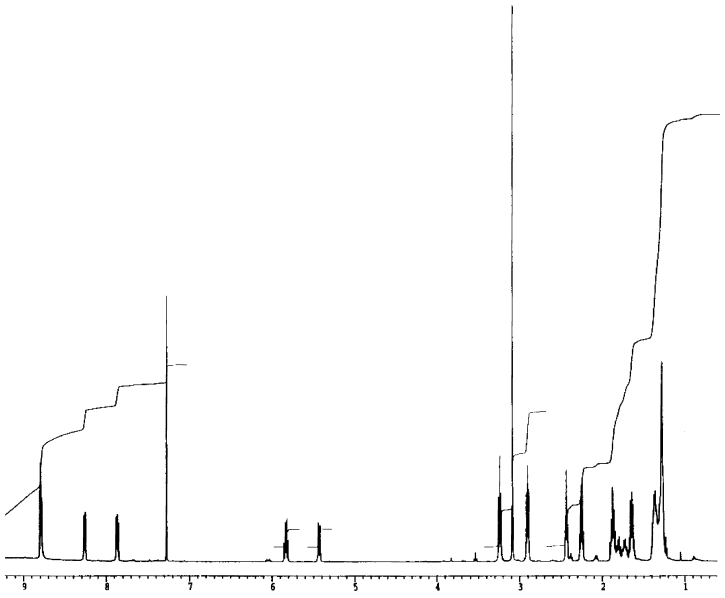


Figure 5. Proton NMR spectrum of synthetic hachijodine G.

4. Experimental

4.1. General experimental

Proton magnetic resonance spectra were recorded on a Varian Gemini 200 (200 MHz), Brüker DPX200 (200 MHz), Brüker DPX400 (400 MHz), and Brüker AMX500 (500 MHz) spectrometers at ambient temperatures. Proton spectra assignments are supported by $^{1}H-^{1}H$ COSY where necessary. Chemical shifts (δ_H) are reported in parts per million (ppm) and are referenced to the residual solvent peak. Coupling constants (J) are recorded to the nearest 0.5 Hz.

Carbon magnetic resonance spectra were recorded on Varian Gemini 200 (50.3 MHz), Brüker DPX200 (50.3 MHz), Brüker DPX400 (100.6 MHz), and Brüker AMX500 (125.8 MHz), spectrometers at ambient temperatures. Chemical shifts (δ_C) are reported in parts per million (ppm) and are referenced to the residual solvent peak. Carbon spectra assignments are supported by DEPT analysis and $^{13}C-^{1}H$ correlations where necessary.

Low resolution mass spectra were recorded using a TRIO-1 GCMS spectrometer, a Micromass Platform (APCI) Spectrometer, Micromass Autospec spectrometer (CI^+) and a micromass ZAB spectrometer (CI^+, EI). Only molecular ions (M^+), fragments from molecular ions and other major peaks are reported. High-resolution mass spectra were recorded on a Micromass Autospec spectrometer and are accurate to ± 10 ppm.

Microanalyses were carried out by Elemental Microanalysis Limited, and are quoted to the nearest 0.1% for all elements except hydrogen which is quoted to the nearest 0.05%.

Infrared spectra were recorded on a Perkin–Elmer Paragon 1000 Fourier Transform spectrometer as a thin film between NaCl plates, and where necessary as KBr discs. Absorption maxima (ν_{max}) of the major peaks are reported in wavenumbers (cm^{-1}).

Melting points were measured using a Cambridge Instruments Gallen™ III hot stage melting point apparatus and are uncorrected.

Thin layer chromatography (TLC) was performed using Merck aluminium foil backed plates pre-coated with silica gel 60 F_{254} (1.05554). Visualisation was affected by quenching of UV fluorescence (λ_{max}=254 nm), staining with 10% w/v ammonium molybdate in 1 M sulphuric acid, followed by heating. Retention factors (R_f) are reported to two decimal places.

Column chromatography was performed using ICN silica 32–63, 60 Å. Kugelröhr distillations were performed using Büchi Glass Oven B-580 distillation apparatus at the temperature and pressure specified.

Anhydrous diethyl ether, and THF were obtained by distillation from sodium/benzophenone ketyl under nitrogen, anhydrous dichloromethane (DCM) was distilled from calcium hydride under nitrogen. PE refers to the fraction of light petroleum ether boiling between 40 and 60°C, and was distilled before use. IPA refers to isopropyl alcohol. All water used was distilled except where otherwise indicated. Solvents were evaporated on a Büchi R110 Rotavaporator.

Diisopropylamine, diisopropylethylamine (DIEA), diethylamine, triethylamine, dimethyl formamide (DMF), dimethyl sulfoxide, pyrrolidine, 1,3-dimethyl-3,4,5,6.tetrahydro-2(1*H*)-pyrimidinone (DMPU), benzene, EtOH, and MeOH were distilled from calcium hydride under argon or reduced pressure and stored over 4 Å molecular sieves under argon until used. Toluene and dimethylacetylmethylphosphonate were dried over 4 Å molecular sieves under argon. Anhydrous K_2CO_3 was flame dried and cooled under

argon before use. 2-Iodobenzoic acid was recrystallised from acetone/water.

4.2. Experimental procedure

4.2.1. Preparation of 5-(pyridin-3-yl)-hex-1-ene (5). To a stirred solution of diisopropylamine (0.84 ml, 6.00 mmol) in THF (5 ml) at 0°C under argon was added ^{n}BuLi (2.65 ml, 2.29 M, 6.00 mmol) in hexanes via a syringe. The resulting pale yellow solution was maintained at 0°C for 30 min, then treated with DMPU (0.72 ml, 6.00 mmol). The yellow solution was stirred at 0°C for 15 min then treated with 3-methylpyridine (0.58 ml, 6.00 mmol) over 10 min to give a deep red solution. After 30 min at 0°C, the mixture containing the lithiated 3-methylpyridine was cooled to −78°C and treated with 5-bromo-1-pentene **4** (0.60 ml, 5.00 mmol). The resulting solution was stirred for 17 h, being allowed to gradually warm to room temperature. The mixture was quenched with water (20 ml) and $NH_4Cl_{(aq)}$ (sat., 20 ml), then extracted into Et_2O (3×30 ml). The combined organic extracts were washed with brine (sat., 15 ml) and dried over Na_2SO_4. Removal of solvent in vacuo afforded the crude product which was purified by flash chromatography (20% PE, 80% Et_2O) to yield 5-(pyridin-3-yl)-hex-1-ene **5** (4.69 g, 63%) as a yellow/brown oil; R_f=0.35 (20% PE, 80% Et_2O); ν_{max}/cm^{-1} (thin film) 3077 (m), 3028 (m), 2995 (m), 2977 (m), 2932 (s), 2858 (s), 1641 (m), 1592 (w), 1575 (m), 1478 (m), 1462 (m), 1438 (m), 1422 (s), 1190 (w), 1110 (w), 1026 (m), 993 (s), 911 (s), 796 (m), 714 (s), 629 (m); *m/z* Probe APCI 162.16 ([MH]$^+$ 100%); HRMS found [MH]$^+$=162.1282, $C_{11}H_{15}N$ requires [MH]$^+$=162.1283; δ_H (200 MHz, $CDCl_3$) 1.40 (2H, qui, *J*=7.0 Hz, H-4), 1.60 (2H, qui, *J*=7.0 Hz, H-5), 2.04 (2H, q, J_1=7.0 Hz J_2=6.0 Hz, H-3), 2.56 (2H, t, *J*=7.5 Hz, H-6), 4.83–5.04 (2H, m, H-1), 5.60–5.87 (1H, m, H-2), 7.15 (1H, dd, J_1=5.0 Hz, J_2=8.0 Hz, H-5), 7.45 (1H, dt, J_1=8.0 Hz, J_2=2.0 Hz, H-4′), 8.32–8.49 (2H, m, H-2′,6′); δ_C (50.3 MHz, $CDCl_3$) 28.3 (*C*H_2), 30.5 (*C*H_2), 32.8 (*C*H_2), 33.4 (*C*H_2), 114.6 (1C, C-1), 123.2 (1C, C-5′), 135.7 (1C, C-4′), 137.7 (1C, C-3′), 138.5 (1C, C-2), 147.2, 149.9 (2C, C-2′,6′).

4.2.2. Preparation of 5-(pyridin-3-yl)-pentanal (6). To a stirred solution of the alkene **5** (300 mg, 1.86 mmol) in ^{t}BuOH/H_2O (8 ml/2.67 ml) was added a catalytic amount of osmium tetroxide. To the resulting brown solution was added $NaIO_4$ (3×600 mg, 8.38 mmol) at intervals of 15 min. The reaction was allowed to stir under argon for 1 h. The mixture was quenched with water (80 ml), then extracted with DCM /IPA mixture (9:1, 6×25 ml). The combined organic extracts were washed with $Na_2S_2O_{3(aq)}$ (sat., 10 ml) and brine (sat., 10 ml), then dried over Na_2SO_4. Removal of solvent in vacuo afforded the crude product which was purified by flash chromatography (40% EtOAc, 60% Et_2O) to yield 5-(pyridin-3-yl)-pentanal **6** (220 mg, 73%) as a yellow oil; R_f=0.38 (40% EtOAc, 60% Et_2O); ν_{max}/cm^{-1} (thin film) 3420 (w), 3029 (w), 2937 (s), 2861 (m), 2724 (w), 1926 (w, br), 1723 (s), 1576 (m), 1479 (m), 1461 (m), 1423 (m), 1391 (w), 1270 (w), 1189 (w), 1127 (w), 1108 (w), 1027 (m); *m/z* Probe APCI 164.02 ([MH]$^+$ 100%); HRMS found [MH]$^+$=164.1075, $C_{10}H_{13}NO$ requires [MH]$^+$=164.1075; δ_H (200 MHz, $CDCl_3$) 1.46–1.72 (4H, m, H-4, H-3), 2.30–2.49 (2H, m, H-2), 2.60 (2H, t, *J*=7.5 Hz, H-5), 7.14 (1H, dd, J_1=5.0 Hz, J_2=7.5 Hz, H-5′), 7.45 (1H, dt, J_1=8.0 Hz, J_2=2.0 Hz, H-4′), 8.30–8.47 (2H, br s, H-2′, H-6′), 9.69 (1H, t, *J*=1.5 Hz, H-1); δ_C (50.3 MHz, $CDCl_3$) 21.4 (*C*H_2), 30.4 (*C*H_2), 32.6 (*C*H_2), 43.5 (1C, C-2), 123.3 (1C, C-5′), 135.8 (1C, C-4′), 137.1 (1C, C-3′), 147.2, 149.7 (2C, C-2′,6′), 202.1 (1C, C-1).

4.2.3. Preparation of dimethyldiazo-2-oxopropylphosphonate (7). Sodium hydride (2.64 g, 60% in oil, 66.3 mmol) was washed with THF (anhydrous, 2×15 ml) under argon. To a cold suspension (0–5°C) of NaH in benzene (100 ml) and THF (20 ml) was added dimethyl acetylmethylphosphonate (8.60 ml, 62.0 mmol) in anhydrous THF (7.5 ml) via cannula. After stirring for 1 h at 0°C, tosylazide (13.0 g, 10.1 ml, 66.0 mmol) was added in anhydrous THF (7.5 ml) via cannula. The solution was allowed to warm to room temperature with stirring over 18 h. The mixture was filtered through a celite pad and the pad was washed with benzene (3×20 ml) and EtOAc (14×30 ml). Removal of solvent in vacuo afforded the crude product which was purified by flash chromatography (100% EtOAc) to yield dimethyldiazo-2-oxopropylphosphonate **7** (10.4 g, 87%) as a bright yellow oil; R_f=0.28 (100% EtOAc); ν_{max}/cm^{-1} (thin film) 3496 (w, br), 3302 (w), 3007 (w), 2960 (m), 2856 (w), 2415 (w), 2344 (w), 2224 (w), 2125 (s), 1660, (s), 1462 (m), 1366 (m), 1272 (s, br), 1183 (s), 1028 (s, br), 971 (m), 929 (w), 837 (s), 804 (s), 784 (m); *m/z* Probe CI$^+$ (NH_3) 193.0 (M$^+$ 13%), 183.4 (38%), 173.8 (100%), 149.1 (26%), 128.0 (16%), 111.0 (14%), 57.9 (14%); δ_H (400 MHz, $CDCl_3$) 2.20 (3H, s, H-1), 3.78 (6H, d, *J*=12.0 Hz, OMe); δ_C (100.6 MHz, $CDCl_3$), 27.0 (1C, C-1), 53.5 (2C, d, *J*=5.0 Hz, OMe), 63.4 (1C, d, *J*=222.5 Hz, C-3), 189.8 (1C, d, *J*=13.0 Hz, C-2).

4.2.4. Preparation of 5-(pyridin-3-yl)-hex-1-yne (3). To a stirred solution of the aldehyde **6** (1.07 g, 6.56 mmol) and dimethyl-1-diazo-2-oxopropylphosphonate **7** (1.52 g, 7.92 mmol) in anhydrous methanol (5 ml), was added anhydrous K_2CO_3 (1.88 g, 13.6 mmol). The resulting pale yellow solution was stirred for 22 h. The mixture was quenched with water (40 ml) and extracted with Et_2O (4×25 ml). The combined extracts were washed with $NaHCO_{3(aq)}$ (sat., 10 ml) and brine (sat., 10 ml), then dried over Na_2SO_4. Removal of solvent in vacuo afforded the crude product which was purified by flash chromatography (20% PE, 80% Et_2O) to yield 3-hex-5-ynylpyridine **3** (824 mg, 79%) as a pale yellow oil; R_f=0.36 (20% PE, 80% Et_2O); ν_{max}/cm^{-1} (thin film) 3305 (s), 3030 (w), 2941 (s), 2862 (m), 2217 (w), 2117 (w), 1592 (w), 1576 (m), 1479 (m), 1462 (m), 1423 (s), 1328 (w), 1190 (w), 1106 (w), 1026 (m), 912 (m), 795 (m), 733 (s), 714 (s), 644 (m); *m/z* Probe APCI 160.08 (MH$^+$ 100%); HRMS found MH$^+$=160.1133, $C_{11}H_{13}N$ requires [MH]$^+$=160.1126; δ_H (200 MHz, $CDCl_3$) 1.44–1.62 (2H, m, H-4), 1.62–1.81 (2H, m, H-5), 1.94 (1H, t, *J*=2.5 Hz, H-1), 2.20 (2H, dt, J_1=3.0 Hz J_2=7.0 Hz, H-3), 2.60 (2H, t, *J*=7.5 Hz, H-6), 7.18 (1H, dd, J_1=7.0 Hz, J_2=5.0 Hz, H-5′), 7.43–7.53 (1H, m, H-4′), 8.35–8.50 (2H, m, H-2′,6′); δ_C (50.3 MHz, $CDCl_3$) 18.1 (*C*H_2), 27.7 (*C*H_2), 30.0 (*C*H_2), 32.4 (1C, C-6), 68.6 (1C, C-1), 84.0 (1C, C-2), 123.2 (1C, C-5′), 135.7 (1C, C-4′), 137.3 (1C, C-3′), 147.3, 149.8 (2C, C-2′,6′).

4.2.5. Preparation of 8-bromooctan-1-ol (9). To 1,9-octane

diol **8** (5.2 g, 35.6 mmol) in toluene (80 ml) was added concentrated HBr (5 ml, 45 mmol, 48% 9 M aq). The heterogeneous mixture was heated at reflux for 21 h (with a rubber balloon fitted to the condenser). The reaction mixture was diluted with water (50 ml), and extracted with Et_2O (2×40 ml). The combined organics were then washed with $NaOH_{(aq)}$ (1 M, 30 ml), and brine (sat., 40 ml), dried over Na_2SO_4, and concentrated in vacuo. The crude product was purified by flash chromatography (40% PE, 60% Et_2O) to give 8-bromooctan-1-ol **9** as a colourless oil (7.00 g, 95%); R_f=0.30 (40% PE, 60% Et_2O); ν_{max}/cm^{-1} (thin film) 3339 (br, s), 2930 (s), 2856 (s), 2361 (w), 1654 (w), 1464 (m), 1246 (m), 1057 (m), 878 (w), 724 (w); δ_H (200 MHz, $CDCl_3$) 1.21–1.60 (10H, m, H-2, 3, 4, 5, 6), 1.81 (2H, qui, J=7.0 Hz, H-7), 3.37 (2H, t, J=7.0 Hz, H-8), 3.57 (2H, t, J=6.5 Hz, H-1); δ_C (50.3 MHz, $CDCl_3$) 25.7 (CH_2), 28.1 (CH_2), 28.7 (CH_2), 29.2 (CH_2), 32.6 (CH_2), 32.8 (CH_2), 34.0 (1C, C-8), 62.7 (1C, C-1).

4.2.6. Preparation of 8-bromo-1-(*tert*-butyldiphenylsilyloxy)-octane (10). To 8-bromooctan-1-ol **9** (6.84 g, 32.7 mmol) in THF (70 ml) was added imidazole (6.65 g, 97.7 mmol) and *tert*-butyldiphenylsilyl chloride (10.3 g, 10.7 ml, 39 mmol). The solution was stirred at room temperature for 3.5 h. The reaction mixture was diluted with $NH_4Cl_{(aq)}$ (sat., 30 ml), and extracted with a 50% PE 50% Et_2O mixture (3×60 ml). The combined extracts were washed with brine (sat., 40 ml), dried over $MgSO_4$, and concentrated in vacuo. The crude material was purified by flash chromatography (100% PE) to give 1-bromo-8-(*tert*-butyldiphenylsilyloxy)-octane **10** as a colourless oil (13.0 g, 89%); R_f=0.20 (100% PE); ν_{max}/cm^{-1} (thin film) 3071 (s), 3850 (m), 2999 (m), 2931 (s), 2857 (s), 2739 (w), 1959 (w), 1890 (w), 1825 (w), 1655 (w), 1590 (m), 1472 (s), 1428 (s), 1390 (s), 1361 (m), 1250 (m), 1226 (w), 1188 (w), 1111 (s), 1008 (m), 998 (m), 939 (w), 824 (s), 740 (s), 703 (s), 688 (s), 614 (s); *m/z* Probe CI$^+$ (NH_3) 464.2, 466.2 (15%, $[MNH_4]^+$, Br^{79}, Br^{81}), 447.4, 449.4 (100%, MH^+, Br^{79}, Br^{81}); HRMS found $[MH]^+$=447.1704, $C_{24}H_{35}OSiBr$ requires $[MH]^+$=447.1719; δ_H (200 MHz, $CDCl_3$) 1.09 (9H, s, $C(CH_3)_3$), 1.22–1.50 (8H, m, H-3, 4, 5, 6), 1.50–1.69 (2H, m, H-2), 1.88 (2H, qui, J=8.0 Hz, H-7), 3.43 (2H, t, J=7.0 Hz, H-8), 3.70 (2H, t, J=6.5 Hz, H-1), 7.35–7.48 (6H, m, *o*, *p*-Ph), 7.67–7.77 (4H, m, *m*-Ph); δ_C (50.3 MHz, $CDCl_3$) 19.3 (1C, $C(CH_3)_3$), 25.7 (CH_2), 26.9 (3C, $C(CH_3)_3$), 28.2 (CH_2), 28.8 (CH_2), 29.2 (CH_2), 32.6 (CH_2), 32.9 (CH_2), 34.1 (1C, C-8), 64.0 (1C, C-1), 127.6 (4C, *o*-Ph), 129.6 (2C, *p*-Ph), 134.2 (2C, *i*-Ph), 135.6 (4C, *m*-Ph).

4.2.7. Preparation of 8-iodo-1-(*tert*-butyldiphenylsilyloxy)-octane (11). To 1-bromo-8-*tert*-butyldiphenylsilyloxy-octane **10** (2.02 g, 4.52 mmol) in acetone (dry, 15 ml) was added NaI (3.27 g, 21.8 mmol) and the solution was refluxed for 20 min. The reaction mixture was diluted with Et_2O and then filtered to give the crude product. The crude product was purified by flash chromatography (90% PE, 10% Et_2O), to give 1-iodo-8-(*tert*-butyldiphenylsilyloxy)-octane **11** as a colourless oil (2.11 g, 95%); R_f=0.8 (90% PE, 10% Et_2O); ν_{max}/cm^{-1} (thin film) 3071 (m), 2999 (m), 2930 (s), 2856 (s), 2739 (w), 1958 (w), 1888 (w), 1823 (w), 1658 (w), 1590 (w), 1472 (m), 1428 (s), 1390 (m), 1361 (m), 1260 (w), 1193 (m), 1111 (s), 1007 (m), 824 (s), 740 (s), 702 (s), 614 (s); *m/z* Probe CI$^+$ (NH_3) 512.3 ($[MNH_4]^+$, 5%), 495.2 ($[MH]^+$, 47%), 368.4 ($[MH-I]^+$, 100%), 328.3 (25%); HRMS found $[MH]^+$=495.1591, $C_{24}H_{35}OSiI$ requires $[MH]^+$=495.1580; δ_H (200 MHz, $CDCl_3$) 1.09 (9H, s, $C(CH_3)_3$), 1.22–1.50 (8H, m, H-3, 4, 5, 6), 1.50–1.68 (2H, m, H-2), 1.82 (2H, qui, J=7.0 Hz, H-7), 3.20 (2H, t, J=7.0 Hz, H-8), 3.67 (2H, t, J=6.5 Hz, H-1), 7.32–7.48 (6H, m, *o*, *p*-Ph), 7.65–7.74 (4H, m, *m*-Ph); δ_C (50.3 MHz, $CDCl_3$) 7.4 (1C, C-8), 19.3 (1C, $C(CH_3)_3$), 25.7 (CH_2), 26.9 (3C, $C(CH_3)_3$), 28.5 (CH_2), 29.2 (CH_2), 30.5 (CH_2), 32.5 (CH_2), 33.6 (CH_2), 64.0 (1C, C-1), 127.6 (4C, *o*-Ph), 129.5 (2C, *p*-Ph), 134.2 (2C, *i*-Ph), 135.6 (4C, *m*-Ph).

4.2.8. Preparation of 14-(pyridin-3-yl)-1-*tert*-butyldiphenylsilyloxy-tetradec-9-yne (12). To a stirred solution of 5-(pyridin-3-yl)-hex-1-yne **3** (78.3 mg, 0.49 mmol) in THF (1 ml) was added DMPU (300 μl, 314 mg, 2.45 mmol) and the solution was cooled to −78°C. After 10 min to this was added ^{n}BuLi in hexanes (250 μl, 0.58 mmol, 2.3023 M) with a colour change from pale yellow to orange. After 30 min 8-iodo-1-(*tert*-butyldiphenylsilyloxy)-octane **11** (635 mg, 1.29 mmol) was added via cannula in THF (2×1 ml). The reaction mixture was left stirring for 17.5 h and warmed to room temperature. The reaction mixture was diluted with water (10 ml) and extracted with PE (3×10 ml). The organics were washed with brine (sat., 10 ml), then dried over Na_2SO_4 and filtered. Removal of solvent in vacuo afforded the crude product which was purified by flash chromatography (60% PE, 40% Et_2O) to yield 14-(pyridin-3-yl)-1-*tert*-butyldiphenylsilyloxy-tetradec-9-yne **12** as a colourless oil (124 mg, 48%); R_f=0.25 (60% PE, 40% Et_2O); ν_{max}/cm^{-1} (thin film) 3071 (w), 3050 (w), 2998 (w), 2931 (s), 2857 (s), 1590 (w), 1576 (w), 1473 (m), 1463 (m), 1428 (s), 1390 (w), 1361 (w), 1332 (w), 1189 (w), 1112 (s), 1026 (w), 1008 (w), 940 (w), 824 (m), 793 (w), 741 (m), 703 (s), 688 (m); Microanalysis found C 80.0%, H 9.50%, $C_{35}H_{47}NOSi$ requires C 79.9%, H 9.00%; *m/z* Probe electrospray 548.18 (15%, $[M+Na]^+$) 526.23 (100%, $[M+H]^+$); HRMS found $[MH]^+$=526.3497, $C_{35}H_{47}NOSi$ requires $[MH]^+$=526.3505; δ_H (200 MHz, $CDCl_3$) 1.05 (9H, s, $C(CH_3)_3$), 1.20–1.65 (14H, m, H-2, 3, 4, 5, 6, 7, 12), 1.65–1.85 (2H, m, H-13), 2.08–2.26 (4H, m, H-8,11), 2.63 (2H, t, J=8.0 Hz, H-14), 3.65 (2H, t, J=6.5 Hz, H-1), 7.16–7.24 (1H, m, H-5′), 7.31–7.45 (6H, m, *o*, *p*-Ph), 7.50 (1H, d, J=7.5 Hz, H-4′), 7.62–7.72 (4H, m, *m*-Ph), 8.40–8.47 (2H, m, H-2′,6′); δ_C (100.6 MHz, $CDCl_3$) 18.6 (CH_2), 18.8 (CH_2), 19.3 (1C, $C(CH_3)_3$), 25.8 (CH_2), 26.9 (3C, $C(CH_3)_3$), 28.5 (CH_2), 28.9 (CH_2), 29.2 (CH_2), 29.3 (CH_2), 30.2 (CH_2), 32.5 (CH_2), 32.6 (CH_2), 64.0 (1C, C-1), 79.6, 80.8 (2C, C-9, 10), 123.3 (1C, C-5′), 127.6 (4C, *o*-Ph), 129.5 (2C, *p*-Ph), 134.2 (2C, *i*-Ph), 135.6 (4C, *m*-Ph), 135.8 (1C, C-4″), 137.6 (1C, C-3′), 147.3 (1C, C-6′), 150.0 (1C, C-2′). Also recovered were 8-iodo-1-(*tert*-butyldiphenylsilyloxy)-octane (171.2 mg, 27%) and 5-(pyridin-3-yl)-hex-1-yne (18.3 mg, 12%).

4.2.9. Preparation of 14-(pyridin-3-yl)-tetradec-9-yne-1-ol (13). To a stirred solution of 14-(pyridin-3-yl)-1-*tert*-butyldiphenylsilyloxy-tetradec-9-yne **12** (477 mg, 0.9 mmol) in methanol (5 ml) was added ammonium fluoride (635 mg, 17 mmol). The mixture was kept at 70°C for 3 h under argon. The reaction was quenched with $NaHCO_{3(aq)}$ (sat., 40 ml) and water (40 ml) and extracted with EtOAc (3×50 ml). The organics were washed with brine (sat.,

40 ml), then dried over Na_2SO_4. Removal of solvent in vacuo afforded the crude product which was purified by flash chromatography (Gradient eluted, 50% PE, 50% EtOAc to 95% EtOAc, 5% MeOH) to afford 14-(pyridin-3-yl)-tetradec-9-yne-1-ol **13** (234 mg, 90%) as a colourless oil; R_f=0.20 (50% PE, 50% EtOAc); ν_{max}/cm^{-1} (thin film) 3326 (br, m), 3031 (w), 2930 (s), 2857 (s), 2360 (w), 1672 (w), 1594 (w), 1577 (m), 1479 (m), 1462 (m), 1424 (s), 1368 (w), 1332 (m), 1190 (w), 1058 (s), 1028 (s), 795 (m), 714 (s), 637 (m); *m/z* Probe CI$^+$ (NH_3) 289.40 (33%), 288.21 (100%, MH^+); HRMS found $[MH]^+$=288.2325, $C_{19}H_{29}NO$ requires $[MH]^+$=288.2327; δ_H (200 MHz, $CDCl_3$) 1.20–1.64 (14H, m, 2, 3, 4, 5, 6, 7, 12), 1.74 (2H, qui, J=7.0 Hz, H-13), 2.08–2.28 (4H, m, H-8, 11), 2.63 (2H, t, J=7.5 Hz, H-14), 3.64 (2H, t, J=6.5 Hz, H-1), 7.21 (1H, dd, J_1=8.0 Hz, J_2=5.0 Hz, H-5′), 7.51 (1H, dt, J_1=8.0 Hz, J_2=2.0 Hz, H-4′), 8.36–8.55 (2H, m, H-2′,6′); δ_C (125.7 MHz, $CDCl_3$) 19.0, 19.1 (2C, C-8,13), 26.1 (CH_2), 28.9 (CH_2), 29.2 (CH_2), 29.5 (2C, CH_2), 29.7 (CH_2), 30.6 (CH_2), 33.0, 33.2 (2C, C-2,14), 63.3 (1C, C-1), 80.0, 81.1 (2C, C-9, 10), 123.8 (1C, C-5′), 136.3 (1C, C-4′), 138.1 (1C, C-3′), 147.6 (1C, C-6′), 150.2 (1C, C-2′).

4.2.10. Preparation of 14-(pyridin-3-yl)-1-tosyl-tetradec-9-yne (14). To a solution of 14-(pyridin-3-yl)-tetradec-9-yne-1-ol **13** (90.0 mg, 0.31 mmol) in anhydrous DCM (2 ml) under an argon atmosphere was added Et_3N (87 μl, 0.62 mmol), and tosyl chloride (90 mg, 0.47 mmol). The reaction was stirred at 0°C for 19 h under argon. The reaction was diluted with $Na_2CO_{3(aq)}$ (sat., 20 ml) and extracted with DCM (3×20 ml). The organics were washed with brine (sat., 20 ml), then dried over Na_2SO_4. Removal of solvent in vacuo afforded the crude product which was purified by flash chromatography (100% Et_2O) to yield 14-(pyridin-3-yl)-1-tosyl-tetradec-9-yne **14** (90.6 mg, 67%) as a pale orange oil; R_f=0.27 (100% Et_2O); ν_{max}/cm^{-1} (thin film) 3022 (m), 2919 (s), 2849 (s), 1593 (m), 1570 (m), 1459 (m), 1430 (m), 1360 (s), 1180 (s), 1105 (m), 1028 (w), 942 (m), 814 (m), 721 (m), 669 (s); *m/z* Probe APCI 442.20 (100%, MH^+); HRMS found $[MH]^+$=442.2428, $C_{26}H_{35}NO_3S$ requires $[MH]^+$=442.2416; δ_H (200 MHz, $CDCl_3$) 1.13–1.85 (16H, m, H-2, 3, 4, 5, 6, 7, 12, 13), 2.03–2.27 (4H, m, H-8, 11), 2.45 (3H, s, C(CH_3)), 2.63 (2H, t, J=7.5 Hz, H-14), 4.01 (2H, t, J=6.5 Hz, H-1), 7.21 (1H, dd, J_1=8.0 Hz, J_2=5.0 Hz, H-5′), 7.44 (2H, d, J=8.5 Hz, *m*-Ph), 7.50 (1H, dt, J_1=8.5 Hz, J_2=2.0 Hz, H-4′), 7.86 (2H, d, J=8.0 Hz, *o*-Ph), 8.40–8.50 (2H, m, H-2′,6′); δ_C (125.7 MHz, $CDCl_3$) 18.4, 18.6 (2C), 21.5 (1C, C(CH_3)), 25.2 (CH_2), 28.3 (CH_2), 28.6 (CH_2), 28.7 (2C, CH_2), 28.8 (CH_2), 28.9 (CH_2), 30.0, 32.4 (2C, C-2, 14), 70.5 (1C, C-1), 79.5, 80.5 (2C, C-9, 10), 123.2 (1C, C-5′), 127.8 (2C, *o*-Ph), 129.7 (2C, *m*-Ph), 133.1 (1C, *p*-Ph), 135.7 (1C, C-4′), 137.5 (1C, C-3′), 144.5 (1C, *i*-Ph), 147.2 (1C, C-6′), 149.8 (1C, C-2′).

4.2.11. Preparation of 1-(*N*-methylhydroxylamine)-decane (15). To a solution of *N*-methylhydroxylamine hydrochloride (34.0 mg, 0.41 mmol) in DMPU (1.5 ml) with Et_3N (120 μl, 0.86 mmol) under argon was added 1-iododecane (50 μl, 0.377 mmol). The mixture was left stirring for 48 h. The reaction mixture was diluted with water, then extracted with Et_2O (3×20 ml). The combined organic extracts were washed with water (2×15 ml), and brine (sat., 15 ml), then dried over Na_2SO_4. Removal of solvent in vacuo afforded the crude product which was purified by flash chromatography (50% PE, 50% EtOAc) to yield 1-(*N*-methylhydoxylamine)-decane **15** (47 mg, 83%) as a white powder, mp 57–58°C; R_f=0.38 (50% PE, 50% EtOAc); ν_{max}/cm^{-1} (thin film) 3192 (s, br), 3010 (s), 2925 (s), 2854 (s), 1466 (s), 1378 (m), 1216 (s), 1143 (w), 1040 (w), 958 (w), 758 (s), 668 (s); *m/z* Probe APCI 188.13 (100%, MH^+), 172.1 (89%), 170.1 (24%); HRMS found MH^+=188.2009, $C_{11}H_{26}NO$ requires MH^+=188.2014; microanalysis found H=13.40, C=70.2, N=7.3, $C_{11}H_{25}NO$ requires H=13.45, C=70.5, N=7.5; δ_H (200 MHz, $CDCl_3$) 0.94 (3H, t, J=6.5 Hz, H-1), 1.27–1.48 (14H, m, H-2, 3, 4, 5, 6, 7, 8), 1.51–1.70 (2H, m, H-9), 2.56–2.70 (5H, m, H-10, N(CH_3)), 4.98 (1H, br, s, OH); δ_C (50.3 MHz, $CDCl_3$) 14.9, 24.2, 28.8, 28.8, 30.9, 31.2, 33.5 (9CH_2), 49.4 (1C, C–NCH_3), 63.9 (1C, C-1).

4.2.12. Preparation of hachijodine F (1). To a mixture of *N*-methylhydroxylamine hydrochloride (67 mg, 0.8 mmol) and tetraethylammonium iodide (8.7 mg, 0.03 mmol) in DMPU (1 ml) was added a mixture of 14-(pyridin-3-yl)-1-tosyl-tetradec-9-yne **14** (70.6 mg, 0.21 mmol) and Et_3N (225 μl, 1.61 mmol) in DMPU (1.5 ml) under an argon atmosphere. The mixture was left stirring for 41 h. The reaction mixture was diluted with water (20 ml), then extracted with Et_2O (3×20 ml). The combined organic extracts were washed with water (2×20 ml), brine (sat., 15 ml), then dried over Na_2SO_4. Removal of solvent in vacuo afforded the crude product which was purified by flash chromatography (gradient eluted, 100% Et_2O to 100% EtOAc) to yield hachijodine F (**1**) (30.9 mg, 61%) as a colourless oil; R_f=0.26 (100% Et_2O); ν_{max}/cm^{-1} (thin film) 3228 (m, br), 2931 (s), 2856 (s), 1739 (m), 1576 (m), 1527 (m), 1479 (w), 1462 (m), 1423 (m), 1371 (w), 1332 (w), 1318 (w), 1253 (w), 1190 (w), 1132 (w), 1106 (w), 1046 (w), 1027 (m), 796 (m), 755 (w), 715 (s); *m/z* Probe APCI 3.17.2 (100%, $[MH]^+$), 301.2 (95%); HRMS found MH^+=317.2595, $C_{22}H_{35}N_2O$ requires MH^+=317.2593; δ_H (200 MHz, $CDCl_3$) 1.20–1.62 (14H, m, H-2, 3, 4, 5, 6, 7, 12), 1.69 (2H, qui, J=7.5 Hz, H-13), 2.05–2.24 (4H, m, H-8, 11), 2.52–2.68 (7H, m, H-1,14, NCH_3), 7.19 (1H, dd, J_1=8.0 Hz, J_2=5.0 Hz, H-5′), 7.49 (1H, dt, J_1=8.0 Hz, J_2=2.0 Hz, H-4), 8.39–8.48 (2H, m, H-2′,6′); δ_C (125.7 MHz, $CDCl_3$) 18.5, 18.7 (2C, CH_2), 27.2 (CH_2), 27.3 (CH_2), 28.5 (CH_2), 28.8 (CH_2), 29.1 (2C, CH_2), 29.5 (CH_2), 30.2, 32.6 (2C, CH_2), 48.6 (1C, NCH_3), 62.3 (1C, C-1), 79.6 (1C, C-10), 80.7 (1C, C-9), 123.3 (1C, C-5′), 135.9 (1C, C-4′), 137.6 (1C, C-3′), 147.2 (1C, C-6′), 149.8 (1C, C-2′); δ_H (400 MHz, $CDCl_3$, doped with TFA) 1.20–1.40 (10H, m, CH_2), 1.45 (2H, qui, J=7.5 Hz, H-7), 1.56 (2H, qui, J=7.5 Hz, H-12), 1.64–1.86 (4H, m, H-2, 13), 2.13 (2H, tt, J_1=7.0 Hz, J_2=2.5 Hz, H-8), 2.23 (2H, tt, J_1=7.0 Hz, J_2=2.5 Hz, H-11), 2.86 (2H, t, J=8.0 Hz, H-14), 3.05 (3H, s, N(CH_3)), 3.21 (2H, t, J=8.5 Hz, H-1), 7.80 (1H, dd, J_1=8.0 Hz, J_2=6.0 Hz, H-5′), 8.19 (1H, d, J=8.0 Hz, H-4′), 8.73–8.76 (2H, m, H-2′,6′).

4.2.13. Preparation of 9-(*tert*-butyldiphenylsilyloxy)-nonan-1-ol (17). A solution of 1,9-nonanediol **16** (1.46 g, 0.91 mmol) in anhydrous DMF (1.5 ml) was charged with DIEA (1.2 mmol, 2.1 ml) forming a biphasic mixture at room temperature. TBDPSCl (1.05 mmol, 0.28 ml) was

added dropwise into the biphasic mixture with vigorous stirring under argon. The resulting solution was stirred for 40 h. The mixture was quenched with water (20 ml) and extracted with Et_2O (3×30 ml). The combined extracts were washed with $HCl_{(aq)}$ (2 M, 2×15 ml), $NaHCO_{3(aq)}$ (sat., 20 ml) and brine (sat., 15 ml), then dried over Na_2SO_4. Removal of solvent in vacuo afforded the crude product which was purified by flash chromatography (80% PE, 20% Et_2O) to yield 9-(*tert*-butyldiphenylsilyloxy)-nonan-1-ol **16** (2.03 g, 55%) as a colourless oil; R_f=0.29 (40% PE, 60% Et_2O); ν_{max}/cm^{-1} (thin film) 3338 (br, m), 3071 (w), 2931 (s), 2857 (s), 2362 (w), 1590 (w), 1472 (m), 1428 (m), 1390 (w), 1361 (w), 1188 (w), 1112 (s), 938 (w), 824 (m), 740 (m), 702 (s), 614 (s); *m/z* Probe CI$^+$ (NH_3) 416 (MNH_4^+ 70%), 321 ([MH−PhH]$^+$ 100%), 216 (26%); HRMS found $[MNH_4]^+$=416.2980, $C_{25}H_{38}O_2Si$ requires $[MNH_4]^+$=416.2985; δ_H (200 MHz, $CDCl_3$) 1.06 (9H, s, C(CH_3)$_3$), 1.21–1.40 (10H, m, H-3, 4, 5, 6, 7), 1.45–1.68 (4H, m, H-2,8), 3.64 (2H, t, *J*=6.5 Hz, H-9), 3.66 (2H, t, *J*=6.5 Hz, H-1), 7.32–7.50 (6H, m, *o*, *p*-Ph), 7.63–7.73 (4H, m, *m*-Ph); δ_C (50.3 MHz, $CDCl_3$) 19.2 (1C, *C*(CH$_3$)$_3$), 25.7 (*C*H$_2$), 26.9 (3C, C(*C*H$_3$)$_3$), 29.3 (*C*H$_2$), 29.4 (*C*H$_2$), 32.6, 32.8 (2C, C-2, 8), 63.1, 64.0 (1C, C-1, 9), 127.6 (4C, *o*-Ph), 129.5 (2C, *p*-Ph), 134.2 (2C, *i*-Ph), 135.6 (4C, *m*-Ph).

In addition 1,9-(*tert*-butyldiphenylsilyloxy)-nonane **18** was isolated (1.43 g, 25%) as a colourless oil; R_f=0.31 (80% PE, 20% toluene); ν_{max}/cm^{-1} (thin film) 3071 (m), 2931 (s), 2857 (s), 2361 (w), 1742 (m), 1590 (m), 1472 (m), 1428 (s), 1390 (m), 1361 (w), 1240 (w), 1188 (w), 1112 (s), 1008 (m) 938 (w), 823 (m), 739 (m), 701 (s), 613 (m); *m/z* Probe CI$^+$ (NH_3) 654.5 (MNH_4^+ 100%), 637.5 (MH^+, 16%), 501.3 (16%), 381.3 (20%); HRMS found $[MNH_4]^+$=654.4167, $C_{41}H_{56}O_2Si_2$ requires $[MNH_4]^+$=654.4163; δ_H (200 MHz, $CDCl_3$) 1.07 (18H, s, C(CH_3)$_3$), 1.20–1.40 (10H, m, H-3, 4, 5, 6, 7), 1.49–1.63 (4H, m, H-2,8), 3.66 (4H, t, *J*=6.5 Hz, H-1,9), 7.33–7.48 (12H, m, o, *p*-Ph), 7.65–7.75 (8H, m, *m*-Ph); δ_C (50.3 MHz, $CDCl_3$) 19.2 (2C, *C*(CH$_3$)$_3$), 25.7 (3C, C-4,5,6), 26.9 (6C, C(*C*H$_3$)$_3$), 29.3 (2C, C-3,7), 32.6 (2C, C-2,8), 64.0 (2C, C-1,9), 127.5 (8C, *o*-Ph), 129.5 (4C, *p*-Ph), 134.2 (4C, *i*-Ph), 135.6 (8C, *m*-Ph).

4.2.14. Preparation of 1-(*tert*-butyldiphenylsilanyloxy)-nonanal (19). To a stirred solution of IBX (1.06 g, 3.79 mmol) in DMSO (8 ml) under argon was added via cannula alcohol **17** (1.00 g, 2.51 mmol) in THF (1 ml, followed by THF 3×0.5 ml). The reaction was left stirring for 2.5 h. The reaction mixture was diluted with water (60 ml) and filtered through a sintered glass funnel, and the residue was washed with EtOAc (30 ml). The combined organics were extracted with EtOAc (3×50 ml), then washed with brine (sat., 20 ml), dried over Na_2SO_4 and filtered. Removal of solvent in vacuo afforded the crude product which was purified by flash chromatography (50% PE, 50% DCM) to yield 1-(*tert*-butyldiphenylsilanyloxy)-nonanal **19** (0.826 g, 83%) as a pale yellow oil; R_f=0.31 (80% PE, 20% toluene); ν_{max}/cm^{-1} (thin film) 3072 (m), 2931 (s), 2857 (s), 2714 (w), 1727 (s), 1590 (w), 1472 (m), 1428 (s), 1390 (m), 1361 (w), 1261 (w), 1188 (w), 1112 (s), 1008 (w), 938 (w), 824 (m), 741 (m), 703 (s), 614 (s); *m/z* Probe CI$^+$ (NH_3) 339.1 ([MH−^{t}Bu]$^+$, 40%), 319.18 (100%), 199.0 (41%); δ_H (200 MHz, $CDCl_3$) 1.08 (9H, s, C(CH_3)$_3$), 1.23–1.47 (8H, m, H-3, 4, 5, 6), 1.49–1.60 (4H, m, H-2,7), 2.43 (2H, dt, J_1=7.5 Hz, J_2=2.0 Hz, H-8) 3.68 (2H, t, *J*=6.5 Hz, H-1), 7.35–7.50 (6H, m, *o*, *p*-Ph), 7.65–7.75 (4H, m, *m*-Ph), 9.78 (1H, t, *J*=1.5 Hz, H-9); δ_C (50.3 MHz, $CDCl_3$) 19.2 (1C, *C*(CH$_3$)$_3$), 22.1, 25.7, 26.9, 29.1, 29.3, 32.5 (9C, C-2, 3, 4, 5, 6, 7, C(*C*H$_3$)$_3$), 43.9 (1C, C-8), 63.9 (1C, C-9), 127.6 (4C, *o*-Ph), 129.5 (2C, *p*-Ph), 134.1 (2C, *i*-Ph), 135.6 (4C, *m*-Ph), 202.9 (1C, C-9).

4.2.15. Preparation of (iodomethyl)triphenylphosphonium iodide (21). A solution of triphenylphosphine (6.01 g, 22.9 mmol) and diiodomethane (2.46 ml, 29.7 mmol) in benzene (10 ml) under argon and protected from light, was heated under reflux at 100°C for 20 h. After this time white crystals had formed. The white crystals were washed with cold benzene (50 ml) and dried in vacuo to yield (iodomethyl)triphenylphosphonium iodide **21** (11.7 g, 96%) as crystals; mp 228°C (lit.=228–230°C); *m/z* Probe Electrospray +ve 403.15 ([M]−I 100%); microanalysis found H=3.20, C=43.1, $C_{16}H_{17}PI_2$ requires H=3.25, C=43.0; δ_H (200 MHz, DMSO-d_6) 5.06 (2H, d, *J*=8.5 Hz, CH_2I), 7.74–8.00 (15H, m, Ph); δ_C (50.3 MHz, DMSO-d_6) −14.3 (1C, d, *J*=50.5 Hz, *C*H$_2$I), 119.3 (3C, d, *J*=90.5 Hz, *i*-Ph), 131.1 (6C, d, *J*=15.0 Hz, *m*-Ph), 134.7 (6C, d, *J*=10.0 Hz, *o*-Ph), 136.1 (3C, s, *p*-Ph).

4.2.16. Preparation of *Z*-10-iodo-1-(*tert*-butyldiphenylsilyloxy)-dec-9-ene (20). To a suspension of iodomethyltriphenylphosphonium iodide **21** (200 mg, 0.38 mmol) in THF (3 ml) at 20°C was slowly added sodium bis-(trimethylsilyl)amide in THF (0.40 ml, 0.943 M). After stirring for 5 min the solution was cooled to −78°C and DMPU (0.23 ml, 1.90 mmol) was added. After a further 15 min aldehyde **19** (100 mg, 0.25 mmol) in THF (1 ml) at −78°C was added via cannula. This was rinsed in with a further 0.5 ml of THF. The reaction was maintained at −78°C for 1hour then was allowed to warm to room temperature. The reaction mixture was diluted with cyclohexane (20 ml). The mixture was filtered through a cellulose pad, and the pad then washed with cyclohexane (8×0 ml). The combined organics were washed with $NH_4Cl_{(aq)}$ (sat., 20 ml), and brine (sat., 20 ml), then dried over Na_2SO_4. Removal of solvent in vacuo afforded the crude product which was purified by flash chromatography (10% benzene, 90% cyclohexane) to yield *Z*-10-iodo-1-(*tert*-butyldiphenylsilyloxy)-dec-9-ene **20** (85.6 mg, 65%) as a colourless oil; R_f=0.34 (10% benzene, 90% cyclohexane); ν_{max}/cm^{-1} (thin film) 3071 (m), 3046 (m), 2930 (s), 2856 (s), 1610 (w), 1590 (w), 1472 (m), 1428 (s), 1389 (m), 1361 (w), 1283 (m), 1189 (w), 1112 (s), 1008 (w), 998 (w), 939 (w), 824 (m), 740 (m), 702 (s), 614 (s); *m/z* Probe CI$^+$ (NH_3) 521.0 (100%, [MH]$^+$), 480.0 (35%), 395.2 (95%), 354.1 (27%), 337.1 (21%), 256.1 (16%), 216.0 (15%), 199.0 (20%); HRMS found $[MH]^+$=521.1727, $C_{26}H_{36}OSiI$ requires $[MH]^+$=521.1737; δ_H (400 MHz, C_6D_6) 1.08–1.18 (6H, m), 1.20 (9H, s, C(CH_3)$_3$), 1.26–1.37 (4H, m,), 1.56 (2H, qui, *J*=7.0 Hz, H-2), 2.02 (2H, q, *J*=7.0 Hz, H-8), 3.68 (2H, t, *J*=6.5 Hz, H-1), 5.74 (1H, q, *J*=7.0 Hz, H-9), 5.89 (1H, d, *J*=7.5 Hz, H-10), 7.20–7.29 (6H, m, *o*, *p*-Ph), 7.76–7.84 (4H, m, *m*-Ph); δ_C (50.3 MHz, C_6D_6) 19.7 (1C, *C*(CH$_3$)$_3$), 26.3 (*C*H$_2$), 27.3 (3C, C(*C*H$_3$)$_3$), 28.4 (*C*H$_2$), 29.5 (*C*H$_2$), 29.8 (*C*H$_2$), 29.9 (*C*H$_2$), 33.2 (1C, C-2), 35.2 (1C, C-8), 64.5 (1C, C-1), 82.6 (1C, C-10), 128.2 (4C, *o*-Ph), 130.1 (2C, *p*-Ph), 134.7 (2C, *i*-Ph), 136.2 (4C, *m*-Ph), 141.6 (1C, C-9).

4.2.17. Preparation of *Z*-16-(pyridin-3-yl)-1-*tert*-butyldiphenylsilyloxy-hexadec-11-yne-9-ene (22). To a stirred solution of iodoalkene **20** (480 mg, 0.92 mmol), $Pd(PPh_3)_4$ (20 mg, 0.017 mmol), and CuI (16 mg, 0.013 mmol) in pyrrolidine (4 ml), under an argon atomosphere, was added via cannula a solution of alkyne **3** (143 mg, 0.90 mmol) in pyrrolidine (3 ml). The reaction was left stirring for 22 h. The reaction mixture was diluted with $NH_4Cl_{(aq)}$ (sat., 40 ml) and extracted with Et_2O (3×50 ml). The organics were washed with brine (sat., 20 ml), then dried over Na_2SO_4 and filtered. Removal of solvent in vacuo afforded the crude product which was purified by flash chromatography (80% PE, 20% EtOAc) to yield *Z*-16-(pyridin-3-yl)-1-*tert*-butyldiphenylsilyloxy-hexadec-11-yne-9-ene **21** (432 mg, 87%) as a colourless oil; R_f=0.34 (80% PE, 20% EtOAc); ν_{max}/cm^{-1} (thin film) 3071 (m), 3021 (m), 2930 (s), 2857 (s), 2361 (w), 1590 (w), 1575 (w), 1473 (m), 1462 (m), 1428 (s), 1390 (w), 1361 (w), 1329 (w), 1261 (w), 1189 (w), 1112 (s), 1026 (w), 1008 (w), 998 (w), 939 (w), 824 (m), 793 (w), 740 (m), 703 (s), 614 (s); *m/z* Probe APCI 552.4 (100%, $[MH]^+$), 474.4 (20%), 314.4 (20%); HRMS found $[MH]^+$=552.3665, $C_{37}H_{49}NOSi$ requires $[MH]^+$=552.3662; δ_H (400 MHz, $CDCl_3$) 1.06 (9H, s, $C(CH_3)_3$), 1.20–1.45 (10H, m, H-3,4,5,6,7), 1.50–1.65 (4H, m, H-2,14), 1.77 (2H, qui, *J*=8.0 Hz, H-15), 2.27 (2H, q, *J*=7.5HZ, H-8), 2.39 (2H, dt, J_1=7.0 Hz, J_2=2.0 Hz, H-13), 2.65 (2H, t, *J*=7.5 Hz, H-16), 3.66 (2H, t, *J*=6.5 Hz, H-1), 5.43 (1H, dt, J_1=1.5 Hz, J_2=10.5 Hz, H-10), 5.83 (1H, dt, J_1=7.5 Hz, J_2=10.5 Hz, H-9), 7.17–7.24 (1H, m, H-5′), 7.37–7.48 (6H, m, *o*, *p*-Ph), 7.50 (1H, d, *J*=7.5 Hz, H-4′), 7.65–7.73 (4H, m, *m*-Ph), 8.46 (2H, br s, H-2′,6′); δ_C (100.6 MHz, $CDCl_3$) 19.2 (1C, $C(CH_3)_3$), 19.3 (1C, C-13), 25.7 (CH_2), 26.8 (3C, $C(CH_3)_3$), 28.2 (1C, C-14), 28.9 (CH_2), 29.1 (CH_2), 29.3 (CH_2), 29.4 (CH_2), 30.1, 30.2 (2C, C-8,15), 32.5, 32.6 (2C, C-16,2), 64.0 (1C, C-1), 77.8 (1C, C-12), 93.6 (1C, C-11), 109.1 (1C, C-10), 123.3 (1C, C-5′), 127.5 (4C, *o*-Ph), 129.5 (2C, *p*-Ph), 134.1 (2C, *i*-Ph), 135.5 (4C, *m*-Ph), 135.7 (1C, C-4′), 137.5 (1C, C-3′), 142.9 (1C, C-9), 147.3 (1C, C-6′), 149.9 (1C, C-2′).

4.2.18. Preparation of *Z*-16-(pyridin-3-yl)-hexadec-11-yne-9-ene-1-ol (23). To a stirred solution of *Z*-16-(pyridin-3-yl)-1-*tert*-butyldiphenylsilyloxy-hexadec-11-yne-9-ene **22** (430 mg, 0.78 mmol) in methanol (5 ml) was added ammonium fluoride (580 mg, 15.6 mmol). The mixture was kept at 70°C for 7 h under argon. The reaction was quenched with $NaHCO_{3(aq)}$ (sat., 40 ml) and water (40 ml) and extracted with EtOAc (3×50 ml). The organics were washed with brine (sat., 30 ml), then dried over Na_2SO_4. Removal of solvent in vacuo afforded the crude product which was purified by flash chromatography (gradient eluted, 50% PE, 50% EtOAc to 100% EtOAc) to afford *Z*-16-(pyridin-3-yl)-hexadec-11-yne-9-ene-1-ol **23** (224 mg, 92%) as a colourless oil; R_f=0.34 (80% PE, 20% EtOAc); ν_{max}/cm^{-1} (thin film) 3326 (br, m), 3021 (m), 2928 (s), 2855 (s), 2211 (w), 1578 (m), 1479 (m), 1462 (m), 1424 (m), 1329 (w), 1190 (w), 1058 (m), 1028 (m), 795 (w), 714 (s); *m/z* Probe APCI 314.38 (100%, $[MH]^+$); HRMS found $[MH]^+$=314.2495, $C_{21}H_{33}NO$ requires $[MH]^+$=314.2484; δ_H (400 MHz, $CDCl_3$) 1.20–1.45 (10H, m, H-3,4,5,6,7), 1.45–1.60 (4H, m, H-2,14), 1.72 (2H, qui, *J*=7.5 Hz, H-15), 2.22 (2H, q, *J*=7.5 Hz, H-8), 2.38 (2H, dt, J_1=7.0 Hz, J_2=2.0 Hz, H-13), 2.60 (2H, t, *J*=7.5 Hz, H-16), 3.58 (2H, t, *J*=6.5 Hz, H-1), 5.38 (1H, apparent d, *J*=10.5 Hz, H-10), 5.77 (1H, dt, J_1=7.5 Hz, J_2=10.5 Hz, H-9), 7.17 (1H, dd, J_1=5.0 Hz, J_2=7.5 Hz, H-5′), 7.47 (1H, dd, J_1=8.0 Hz, J_2=1.5 Hz, H-4), 8.30–8.43 (2H, m, H-2′,6′); δ_C (100.6 MHz, $CDCl_3$) 19.2 (1C, C-13), 25.8 (CH_2), 28.1 (1C, C-14), 28.9 (CH_2), 29.1 (CH_2), 29.3 (CH_2), 29.4 (CH_2), 30.0, 30.1 (2C, C-8,15), 32.4, 32.8 (2C, C-2,16), 62.5 (1C, C-1), 77.8 (1C, C-12), 93.6 (1C, C-11), 109.0 (1C, C-10), 123.3 (1C, C-5′), 135.9 (1C, C-4′), 137.6 (1C, C-3′), 142.8 (1C, C-9), 147.0 (1C, C-6′), 149.6 (1C, C-2′).

4.2.19. Preparation of *Z*-16-(pyridin-3-yl)-1-tosyl-hexadec-11-yne-9-ene (24). To a solution of alcohol **23** (80.0 mg, 0.26 mmol) in anhydrous DCM (8 ml) under an argon atmosphere was added Et_3N (71 μl, 0.51 mmol), and tosyl chloride (71 mg, 0.372 mmol). The reaction was stirred at 0°C for 3 days. The reaction was diluted with $Na_2CO_{3(aq)}$ (sat., 30 ml) and extracted with DCM (3×30 ml). The organics were washed with brine (sat., 30 ml), then dried over Na_2SO_4. Removal of solvent in vacuo afforded the crude product which was purified by flash chromatography (100% Et_2O) to yield *Z*-16-(pyridin-3-yl)-1-tosyl-hexadec-11-yne-9-ene **24** (98.8 mg, 83%) as a pale orange oil; R_f=0.27 (100% Et_2O); ν_{max}/cm^{-1} (thin film) 3022 (m), 2930 (s), 2857 (s), 2211 (w), 1922 (w), 1598 (m), 1575 (m), 1462 (m), 1423 (m), 1360 (s), 1189 (s), 1177 (s), 1098 (s), 1026 (w), 956 (m), 816 (m), 734 (m), 664 (m); *m/z* Probe APCI 468.28 (100%, MH^+); HRMS found $[MH]^+$=468.2586, $C_{28}H_{37}NO_3S$ requires $[MH]^+$=468.2572; δ_H (400 MHz, $CDCl_3$) 1.15–1.45 (10H, m, H-3,4,5,6,7), 1.51–1.70 (4H, m, H-2,14), 1.76 (2H, q, *J*=7.5 Hz, H-15), 2.26 (2H, q, *J*=7.0 Hz, H-8), 2.39 (2H, dt, J_1=1.5 Hz, J_2=7.0 Hz, H-13), 2.45 (3H, s, $C(CH_3)$), 2.65 (2H, t, *J*=7.5 Hz, H-16), 4.02 (2H, t, *J*=6.5 Hz, H-1), 5.43 (1H, d, *J*=10.5 Hz, H-10), 5.81 (1H, dt, J_1=7.5 Hz, J_2=10.5 Hz, H-9), 7.19–7.25 (1H, m, H-5′), 7.35 (2H, d, *J*=8.0 Hz, *m*-Ph), 7.51 (1H, d, *J*=8.0 Hz, H-4), 7.79 (2H, d, *J*=8.0 Hz, *o*-Ph), 8.46 (2H, br s, H-2′,6′); δ_C (50.3 MHz, $CDCl_3$) 19.2 (1C, C-13), 21.5 (1C, $C(CH_3)$), 25.2 (CH_2), 28.1 (1C, C-14), 28.7, 28.9, 29.1 (3C, CH_2), 29.9, 30.1 (2C, CH_2), 32.4 (2C, CH_2), 70.7 (1C, C-1), 77.4 (1C, C-12), 93.8 (1C, C-11), 109.4 (1C, C-10), 123.4 (1C, C-5′), 128.0 (1C, *o*-Ph), 130.0 (1C, *m*-Ph), 133.4 (1C, *p*-Ph), 136.0 (1C, C-4′), 137.7 (1C, C-3′), 142.9 (1C, C-9), 144.9 (1C, *i*-Ph), 147.6 (1C, C-6′), 150.2 (1C, C-2′).

4.2.20. Preparation of hachijodine G (2). To a mixture of *N*-methylhydroxylamine hydrochloride (88 mg, 1.06 mmol) and tetraethylammonium iodide (10.3 mg, 0.04 mmol) in DMPU (1 ml) was added a mixture of tosylate **24** (98.8 mg, 0.21 mmol) and Et_3N (308 μl, 2.24 mmol) in DMPU (1.5 ml) under an argon atmosphere. The mixture was left stirring for 47 h. The reaction mixture was diluted with water (20 ml), then extracted with Et_2O (3×20 ml). The combined organic extracts were washed with water (2×20 ml), brine (sat., 20 ml), then dried over Na_2SO_4. Removal of solvent in vacuo afforded the crude product which was purified by flash chromatography (PE–EtOAc–Et_3N, 1:1:1) to yield hachijodine G (**2**) (33.8 mg, 46%) as a colourless oil; R_f=0.38; (PE–EtOAc–Et_3N, 1:1:1); ν_{max}/cm^{-1} (thin film) 3222 (m, br), 3020 (m), 2928 (s), 2855 (s), 2211 (w), 1739 (m), 1576 (m), 1479 (m), 1462 (s), 1424 (s), 1372 (m), 1329 (w), 1241 (w), 1191 (w), 1136 (w), 1105

(w), 1046 (w), 1027 (m), 957 (w), 795 (m), 714 (s); *m/z* Probe APCI 343.3 ($[MH]^+$ 70%), 327.3 (100%), HRMS found $[MH]^+$=343.2751, $C_{22}H_{34}N_2O$ requires $[MH]^+$= 343.2749; δ_H (500 MHz, $CDCl_3$) 1.20–1.42 (10H, m, H-3, 4, 5, 6, 7), 1.50–1.65 (4H, m, H-2,14), 1.77 (2H, qui, J=7.5 Hz, H-15), 2.26 (2H, q, J=7.0 Hz, H-8), 2.39 (2H, dt, J_1=7.0 Hz, J_2=2.0 Hz, H-13), 2.55–2.70 (7H, m, H-1,16, NCH_3), 5.43 (1H, d, J=10.5 Hz, H-10), 5.82 (1H, dt, J_1= 7.5 Hz, J_2=10.5 Hz, H-9) 7.21 (1H, dd, J_1=7.5 Hz, J_2= 5.0 Hz, H-5′), 7.51 (1H, d, J=8.0 Hz, H-4), 8.41–8.48 (2H, m, H-2′,6′); δ_C (125.7 MHz, $CDCl_3$) 19.8 (1C, CH_2), 27.7 (CH_2), 27.9 (CH_2), 28.7 (CH_2), 29.3 (CH_2), 29.6 (CH_2), 29.8 (CH_2), 30.0 (CH_2), 30.5 (CH_2), 30.6 (CH_2), 33.0 (CH_2), 49.1 (1C, C–NCH_3), 62.8 (1C, C-1), 78.3 (1C, C-12), 94.1 (1C, C-11), 109.6 (1C, C-10), 123.8 (1C, C-5′), 136.3 (1C, C-4′), 138.0 (1C, C-3′), 143.3 (1C, C-9), 147.7, 150.3 (2C, C-2′,6′); δ_H (500 MHz, $CDCl_3$, doped with TFA) 1.20–1.42 (10H, m, CH_2), 1.65 (2H, qui, J=7.0 Hz, H-14), 1.73 (1H, m, H-2), 1.81 (1H, m, H-2), 1.88 (2H, qui, J=7.5 Hz, H-15), 2.25 (2H, q, J=7.0 Hz, H-8), 2.44 (2H, dt, J_1= 7.0 Hz, J_2=2.0 Hz, H-13), 2.91 (2H, t, J=8.0 Hz, H-16), 3.09 (3H, s, N(CH_3), 3.24 (2H, t, J=8.0 Hz, H-1), 5.43 (1H, d, J=11.0 Hz, H-10), 5.83 (1H, dt, J_1=7.5 Hz, J_2=10.5 Hz, H-9), 7.87 (1H, dd, J_1=8.0 Hz, J_2=5.5 Hz, H-5′), 8.26 (1H, d, J=8.0 Hz, H-4), 8.73–8.83 (2H, m, H-2′,6′).

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