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# Stereoselectivity in the photoinduced electron transfer (PET) promoted intramolecular cyclisations of 1-alkenyl-2-silyl-piperidines and -pyrrolidines: rapid construction of 1-azabicyclo[*m.n.*0]alkanes and stereoselective synthesis of (±)-isoretronecanol and (±)-epilupinine

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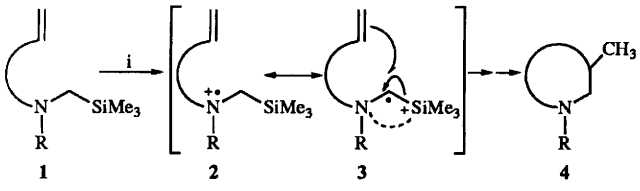
**PET promoted cyclisations of 1-alkenyl-2-silyl-pyrrolidines and -piperidines 9a–d to 1-azabicyclo[*m.n.*0]alkanes have been found to be stereoselective. The five-membered ring formation gives predominantly *cis* products while six-membered rings are *trans*. Application of such cyclisations to the synthesis of (±)-isoretronecanol 22a, (±)-epilupinine 29 and related alkaloids has been demonstrated.**

Recently we reported [1] an efficient cyclisation of α-silylmethylamines of type **1** to construct piperidine and pyrrolidine skeletons **4** by PET initiation and utilising the singlet excited state of 1,4-dicyanonaphthalene (DCN) as an electron acceptor (Scheme 1). The delocalised amine radical-cation **3**, formed by

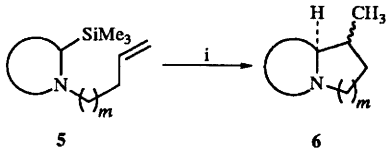



1 2 3 4

**Scheme 1** *Reagents and conditions:* i, *hv*, DCN, Pr$^i$OH

the vertical overlap of the C–Si σ bond and the empty p orbital of nitrogen, was suggested to be the intermediate in these cyclisations.[1]

The heterocyclisation of substituted **1** (both at α- and α′-positions) was found to be non-stereoselective due to a low energy barrier between the two possible transition states,[1] caused by the flipping of the lone pair of electrons on the nitrogen. However, a study of the cyclic analogues **5**,[2] for which the flipping of the lone pair of electrons on the nitrogen would be restricted due to the rigidity imposed in the transition state structure, gave the 1-azabicyclo[*m.n.*0]alkane skeletons [3–6] stereoselectively in fairly good yields (Scheme 2).



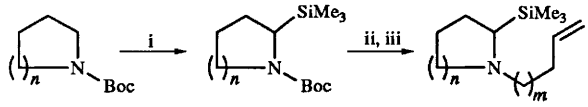

5 6

**Scheme 2** *Reagents and conditions:* i, PET, Pr$^i$OH

A communication from Hoegy and Mariano [7] in which they mention difficulty in reproducing the conversion of **5** into **6** has prompted us to disclose the full experimental details of our intial study [2] along with the application of this methodology for the stereoselective synthesis of (±)-isoretronecanol **22a**, (±)-1-azabicyclo[4.3.0]non-7-ylmethanol **22b** and (±)-epilupinine **29**.

## Results and discussion

We initiated our study by monitoring the PET cyclisation of 1-(but-3-enyl)-2-silylpyrrolidine **9a**, synthesised by the following



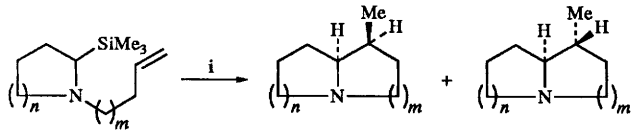

7 8 9

a $n=1$ a $n=m=1$ b $n=m=2$
b $n=2$ c $m=2, n=1$ d $m=1, n=2$

**Scheme 3** *Reagents and conditions:* i, Bu$^s$Li, TMEDA, $Et_2O$, −78 °C, $Me_3SiCl$, 3 h; ii, $CF_3CO_2H$, $CH_2Cl_2$, O °C; iii, $CH_2{=}CH(CH_2)_mBr$, $CH_3CN$, $K_2CO_3$, reflux

procedure (see Scheme 3). *N*-Boc-protected pyrrolidine **7a** was metallated [8] with Bu$^s$Li, and then treated with trimethylsilyl chloride to produce **8a** (92%). *N*-Boc deprotection of this, followed by alkylation with 4-bromobut-1-ene gave **9a** (75%).

In the PET reaction a solution of **9a** and DCN in propan-2-ol was irradiated with Pyrex-filtered light ($\lambda > 280$ nm, all light absorbed by DCN only) from a 450 W Hanovia medium-pressure mercury lamp at room temperature without removal of the dissolved oxygen from the solution, until *ca.* 90% (2.5 h) of **9a** was consumed (monitored by GC and TLC). Evaporation of the mixture under reduced pressure and silica gel column chromatography of the crude product gave the cyclised product **10** (90%) (Scheme 4). DCN was recovered quantitatively (98%)




9

| | | |
|---|---|---|
| a $n=m=1$ | **10a** | **10b** |
| b $n=m=2$ | **11a** | **11b** |
| c $m=2, n=1$ | **12a** | **12b** |
| d $m=1, n=2$ | **13a** | **13b** |

**Scheme 4** *Reagents and conditions:* i, *hv*, DCN, Pr$^i$OH

by the procedure reported by us.[9] $^1$H NMR and $^{13}$C NMR spectra of **10** indicated it to be a mixture of two diastereoisomers whose ratio was determined as 97:3 by analysis with capillary GC (methyl silicone, fused silica, 25 m). Pure **10a** was finally obtained by careful column chromatography on silica gel. However, **10b** could not be isolated in pure form for spectroscopic characterisation. The discrepancy described by Mariano,[7] intriguing to us since all our PET reactions using **9a** have only given **10** as the product, may arise from their use of radiation of a different wavelength (*i.e.* 240 nm), all

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**Table 1** Data for conversion of **9** into **10–13**

| Compound | Ratio of **a**:**b** | Yield (%) |
|---|---|---|
| **10** | 97:3 | 90 |
| **11** | 0:100 | 88 |
| **12** | 2:98 | 85 |
| **13** | 95:5 | 87 |

our reported[2] work having been carried out with Pyrex-filtered (>280 nm) light.

The stereochemistry of the major isomer **10a** was determined by comparing the $^1$H NMR and $^{13}$C NMR chemical shift values of the methyl group with the minor isomer **10b**. The methyl group in **10a** appeared ($\delta_H$ 1.07, d, $J$ 6.9; $\delta_C$ 13.07) upfield from that of **10b** ($\delta_H$ 1.12, d, $J$ 7.1; $\delta_C$ 14.86). It has been reported[10] that, within a given series, the axial proton and carbon signals appear upfield of those of equatorial groups, so the methyl group could be assigned as in **10a** and equatorial in **10b**. Considering the bridge head proton 5-H to be equatorial in such bicyclic compounds, the relative stereochemistry between 4-H and 5-H in **10a** can be assigned *cis* and *trans* for **10b**. This assignment is further supported by comparing the $^1$H NMR and $^{13}$C NMR values of **10a** with the reported values of (±)-heliotridane.[11]

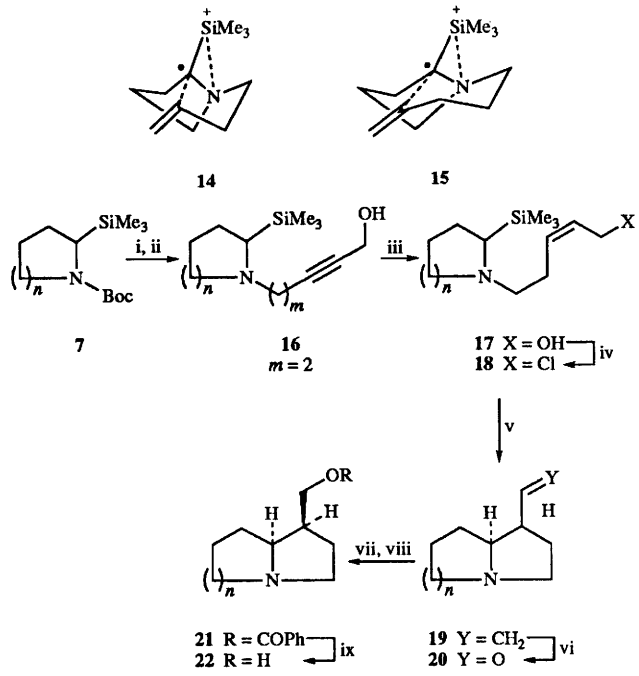
Similarly, to probe the stereochemistry of the 1,6-cyclisations, **9b** was prepared and cyclised to a single compound **11b** (purity checked by analysis on capillary GC column) by following the procedure described for **9a** exactly. The 5,6-*trans* stereochemistry of **11b** is suggested for similar reasons to those discussed for **10a**, by assigning to the methyl group an equatorial position because of its appearance at low chemical shift ($\delta_C$ 18.00) in the $^{13}$C NMR spectrum. This assignment is further confirmed by comparison of the C-5 chemical shift value of $\delta_C$ 34.00 with the reported values for the lupin series of alkaloids.[12] To confirm the generality of this stereochemistry, compound **9c–d** were studied and the results are given in Table 1.

From the above results, it appears that the stereochemistry of products **10a–13b** depends upon the size of the new ring formed, *i.e.* a 1,5-cyclisation gives predominantly *cis* products while 1,6-cyclisation gives *trans* isomers. The 4,5-*cis* diastereoselectivity for **10a** and **13a** can be rationalized by invoking 'chair-like' transition states **14** analogous to the ring closure of 2-but-3-enylcycloalkyl radicals.[10] Similarly the origin of the *trans* stereochemistry for **11b** and **12b** could also be explained in terms of the 'chair-like' transition state **15** where the effective overlap between the SOMO of the radical cation centre and olefin π-orbitals results in a 5,6-*trans* stereochemistry. In order to demonstrate the synthetic potentials of such stereoselective cyclisations and also to confirm our stereochemical assignments, the total syntheses of the racemic alkaloids **22a**, **22b** and **29** were undertaken.

### Synthesis of (±)-isoretronecanol[13] 22a and (±)-1-azabicyclo-[4.3.0]nonan-7-ylmethanol[14] 22b

The synthesis of **22a** and **22b** was achieved by following the procedure shown in Scheme 5. Precursor compounds **18a–b** were prepared from **7a–b** by deprotection, alkylation with 5-iodopent-2-yn-1-ol, partial hydrogenation of the acetylenic bond using Lindlar's catalyst (Pd–$CaCO_3$) and finally chlorination of resultant alcohols **17a–b**.[15]

The PET cyclisations of **18a–b** were carried out using DCN in propan-2-ol and a small amount of $K_2CO_3$ (to neutralize the HCl formed during the reaction) in a manner identical with that described for **9a**. GC (methyl silicone capillary column, fused silica, 25 m) analysis of each of the products **19a** and **19b** showed each to be a mixture of two diastereoisomers, in the ratio of 96:4 and 95:5, respectively. Attempts to obtain pure




**Scheme 5** *Reagents and conditions:* i, $CF_3CO_2H$, $CH_2Cl_2$, 0 °C, 30 min; ii, $I(CH_2)_2C{\equiv}CCH_2OH$, $K_2CO_3$, $CH_3CN$, reflux; iii, Pd–$CaCO_3$, MeOH, $H_2$ (35 psi); iv, $PPh_3$, $CCl_4$–$CH_2Cl_2$ (4:1), $K_2CO_3$, reflux; v, *hν*, DCN, $Pr^iOH$, $K_2CO_3$; vi, $O_3$, MeOH–$CH_2Cl_2$ (1:1), $Me_2S$, −78 °C; vii, $NaBH_4$, $C_2H_5OH$, reflux; viii, $Et_3N$, THF, PhCOCl, room temp., 8 h; ix, 1% NaOH, MeOH

diastereoisomers at this stage failed and crude **19a–b** was used for the next step. Ozonolysis of **19a–b** at −78 °C in the presence of dimethyl sulfide, followed by the reduction of the crude material with $NaBH_4$ in ethanol gave the corresponding alcohols **22a** and **22b**, again as mixtures of diastereoisomers. Since the pure diastereoisomers could still not be isolated, the alcohols were esterified, using benzoyl chloride in $CH_2Cl_2$ in the presence of $Et_3N$, to give compounds **21a–b**, which were then purified by column chromatography (silica gel, light petroleum–acetone as eluent). The minor isomers could not be isolated pure in sufficient quantity to be fully characterised. Debenzoylation of the benzoyl esters **21a–b**, by stirring in 1% methanolic NaOH solution, gave pure **22a** and **22b** and the spectral data ($^1$H NMR, $^{13}$C NMR, mass spectra) of these compounds compared well with the reported values for these compounds.[13d,14]

### Synthesis of (±)-epilupinine[16] 29

Compound **29** was synthesised (Scheme 6) from **25** by a procedure identical with that described above for **22a–b**. The precursor compound **25** was obtained by alkylation of deprotected **7b** with 6-iodohex-2-yne-1-ol and purification of crude **29** was achieved by its conversion to the benzoyl ester **28** which could then be column chromatographed.

## Experimental

The chemicals and reagents used in this study were of commercial grade and some of them were purified further. 1,4-Dicyanonaphthalene (DCN) was prepared by the standard procedure.[17] Chromatography was performed using silica gel (Acme India, finer than 200 mesh). The solvents used during the experiments were purified, unless otherwise stated, by standard literature procedures. Ether refers to diethyl ether. NMR spectra obtained for $^1$H and $^{13}$C were recorded on Bruker 200 MHz, Varian Gemini 200 MHz and FT 80 MHz spectrometers in $CDCl_3$, using tetramethylsilane as internal reference. $J$ Values are reported in Hz. IR spectra were recorded on Perkin-Elmer model 283B spectrometer and are reported in $cm^{-1}$. Mass spectra were recorded on a VG-Micro Mass 7070 spectrometer

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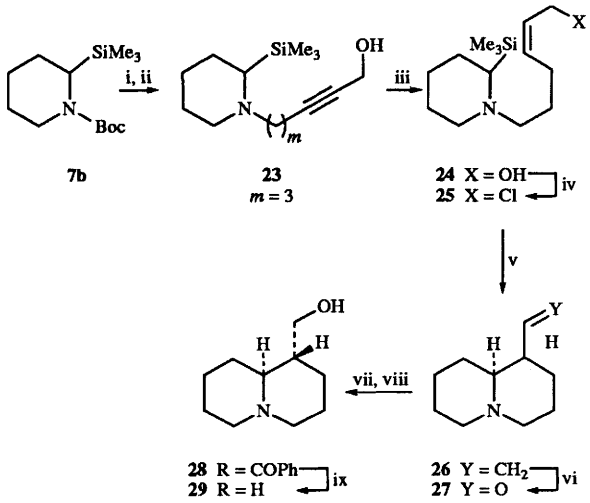


**Scheme 6** *Reagents and conditions:* i, $CF_3CO_2H$, $CH_2Cl_2$, 0 °C, 30 min; ii, $I(CH_2)_3C{\equiv}CCH_2OH$, $K_2CO_3$, $CH_3CN$, reflux; iii, Pd–$CaCO_3$, MeOH, $H_2$ (35 psi); iv, $PPh_3$, $CCl_4$–$CH_2Cl_2$ (4:1), $K_2CO_3$, reflux; v, *hv*, DCN, $Pr^iOH$, $K_2CO_3$; vi, $O_3$, MeOH–$CH_2Cl_2$ (1:1), $Me_2S$, −78 °C; vii, $NaBH_4$, $C_2H_5OH$, reflux; viii, $Et_3N$, THF, PhCOCl, room temp., 8 h; ix, 1% NaOH, MeOH

and GC analyses were performed using OV-17 (10%, 10 × 1/8 in) and methyl silicone (fused silica, 25 m) capillary columns. Photolysis equipment consisted of a 450 W Hanovia medium pressure lamp, Pyrex-filtered immersion well and Pyrex reaction vessels, all procured from ACE glass USA.

**General method for the syntheses of 1-Boc-protected 2-trimethylsilyl-pyrrolidines and -piperidines 8a–b**

To a stirred solution of *tert*-butyl carbazate (104.12 mmol), dissolved in a mixture of acetic acid (41.6 $cm^3$) and water (82.5 $cm^3$), sodium nitrite ($NaNO_2$, 114.12 mmol) was added portionwise at 0 °C. After being stirred for 30 min, the reaction mixture was extracted with ether twice (2 × 100 $cm^3$). The combined extracts were washed successively with water, aq. $NaHCO_3$ (1 mol $dm^{-3}$) and brine, dried ($Na_2SO_4$) and concentrated to give *tert*-butoxy azide as a brown oily liquid (92%), which was used for the next step without further purification.

To a stirred solution of pyrrolidine or piperidine (80 mmol) in dioxane (40 $cm^3$) and triethylamine (100 mmol), a solution of *tert*-butoxy azide (100 mmol) in dioxane (35 $cm^3$) was added dropwise. The mixture was stirred until a clear solution was obtained after which it was evaporated and the residue was extracted twice with ether. The extracts were washed with water and brine, dried ($Na_2SO_4$) and evaporated to give the corresponding *N*-Boc-protected pyrrolidines and piperidines **7a–b** as clear liquids. The crude products were purified by vacuum distillation (88–90%).

To a stirred solution of **7a** or **7b** (58.4 mmol) in dry ether (60 $cm^3$) under argon at −78 °C, *N*,*N*,*N*′,*N*′-tetramethylethylenediamine (TMEDA, 132.5 mmol) and $Bu^sLi$ in ether (1.5 mol $dm^{-3}$; 46.7 $cm^3$, 70.4 mmol) were successively added *via* a syringe. The mixture was stirred for 3.5 h at −78 °C after which trimethylsilyl chloride (TMSCl, 87.7 mmol) was added to it slowly. After being allowed to warm to room temp., the mixture was treated with water, (10 $cm^3$), to quench the reaction, and extracted with ether (3 × 50 $cm^3$). The combined ethereal extracts were dried ($Na_2SO_4$) and concentrated to give compounds **8a–b** (90–92%), purification of which was effected by vacuum distillation.

**Deprotection of compounds 8a–b**

To a stirred solution of **8a–b** (41.15 mmol) in dry $CH_2Cl_2$ (50 $cm^3$), trifluoroacetic acid (123.6 mmol) was added slowly at 0 °C under an argon atmosphere. After being stirred for 30 min at room temp., the reaction mixture was diluted with $CH_2Cl_2$ (100 $cm^3$) and adjusted to pH 10 with aq. NaOH (10%). The aqueous layer was extracted three times with $CH_2Cl_2$ and the combined organic extracts were washed with water and brine, dried ($Na_2SO_4$) and evaporated to give the corresponding 2-(trimethylsilyl)-pyrrolidine and -piperidine (92–95%) as clear liquids, which were used as obtained for the following reactions.

**General method for the preparation of 1-alkenyl-2-(trimethylsilyl)-pyrrolidines and -piperidines 9a–d**

A mixture of the 2-silylated pyrrolidine or piperidine (34.8 mmol), the appropriate bromoalkene (34.8 mmol) and anhydrous $K_2CO_3$ (52.4 mmol) in dry acetonitrile was refluxed for 10 h. The reaction mixture was allowed to cool to room temp. and any solid material was filtered off and washed with ethyl acetate (3 × 50 $cm^3$). The combined filtrates were concentrated and purified by column chromatography, using ethyl acetate–hexane as eluent, to give **9a–d** (72–75%) as clear liquids.

**1-(But-3-enyl)-2-(trimethylsilyl)pyrrolidine 9a.** Yield 75%; $\delta_H$(200 MHz) 0.09 (9 H, s), 1.51–1.85 (6 H, m), 1.95–2.15 (3 H, m), 2.69–2.85 (1 H, m), 3.05–3.20 (1 H, m), 4.87–5.05 (2 H, m) and 5.71–5.90 (1 H, m); $\delta_C$(50.4 MHz) 2.5, 24.19, 27.29, 33.56, 55.47, 56.25, 56.48, 114.53 and 138.36; $\nu_{max}$(neat) 2900, 2800, 1255 and 850; *m*/*z* 197 ($M^+$, 1%), 158 (20), 126 (100), 73 (50) and 55 (70).

**1-(Pent-4-enyl)-2-(trimethylsilyl)piperidine 9b.** Yield 72%; $\delta_H$(200 MHz) 0.065 (9 H, s), 1.42–1.75 (9 H, m), 1.92–2.10 (2 H, m), 2.15–2.30 (1 H, m), 2.65–2.79 (1 H, m), 2.95–3.07 (2 H, m), 4.90–5.05 (2 H, m) and 5.71–5.91 (1 H, m); $\delta_C$(50.4 MHz) 1.13, 25.17, 25.55, 25.97, 27.39, 31.71, 54.05, 55.39, 56.98, 114.47 and 138.55; $\nu_{max}$(neat) 2900, 2800, 1620, 1420 and 840; *m*/*z* 225 ($M^+$, 2%), 151 (100), 84 (40) and 73 (30).

**1-(Pent-4-enyl)-2-(trimethylsilyl)pyrrolidine 9c.** Yield 73%; $\delta_H$(200 MHz) 0.08 (9 H, s), 1.62–1.80 (6 H, m), 1.85–2.05 (2 H, m), 2.12–2.20 (3 H, m), 2.80–2.95 (1 H, m), 3.15–3.30 (1 H, m), 4.90–5.10 (2 H, m) and 5.75–5.95 (1 H, m); $\delta_C$(50.4 MHz) 2.5, 24.19, 27.29, 27.74, 31.56, 55.47, 56.25, 56.48, 114.43 and 138.47; $\nu_{max}$(neat) 2900, 2800, 1255 and 850; *m*/*z* 211 ($M^+$, 5%), 138 (100), 84 (30), 73 (30), 69 (20) and 57 (30).

**1-(But-3-enyl)-2-(trimethylsilyl)piperidine 9d.** Yield 75%; $\delta_H$(200 MHz) 0.065 (9 H, s), 1.45–1.65 (7 H, m), 1.71–1.82 (1 H, m), 1.95–2.12 (1 H, m), 2.19–2.25 (1 H, m), 2.30–2.45 (1 H, m), 2.62–2.80 (1 H, m), 2.85–2.95 (1 H, m), 4.85–5.05 (2 H, m) and 5.6–5.82 (1 H, m); $\delta_C$(50.4 MHz) 1.58, 24.94, 25.59, 27.14, 29.91, 53.73, 54.43, 56.41, 115.31 and 136.80; $\nu_{max}$(neat) 2900, 2800, 1620, 1420 and 840; *m*/*z* 212 ($M^+$ + 1, 10%), 138 (100), 84 (50), 73 (40), 55 (40) and 69 (30).

**General method of photolysis**

A solution of the amine **9** (2.5 mmol) and DCN (0.56 mmol) in propan-2-ol was irradiated in a 500 $cm^3$ irradiation vessel using a 450 W Hanovia medium-pressure lamp at ambient temperature for 3 h without removal of any dissolved oxygen. The lamp was housed in a Pyrex-jacketed immersion well which allowed only light of wavelength >280 nm to pass through. The progress of the reaction was monitored by TLC and GC and when almost 90% of the starting material was consumed, the irradiation was discontinued. Evaporation of the mixture under reduced pressure and purification by silica gel column chromatography (eluting with $CHCl_3$–MeOH) gave the corresponding 1-azabicyclo[*m.n.*0]alkanes as viscous liquids (85–90%). Compound **10a** was obtained in pure form by careful chromatography using silica gel finer than 200 mesh and eluting with 4% $CH_3OH$–$CHCl_3$; **10b** could not be isolated in sufficient quantity for characterisation.

**4-Methyl-1-azabicyclo[3.3.0]octane 10a.** Yield 90%; $\delta_H$(200 MHz) 1.07 (3 H, d, *J* 6.9), 1.32–1.41 (2 H, m), 1.60–1.81 (2 H, m), 1.91–2.22 (2 H, m), 2.40–2.60 (1 H, m), 2.72–2.85 (1 H, m), 2.95–3.10 (1 H, m), 3.40–3.60 (1 H, m), 3.85–3.95 (1 H, m) and 4.12–4.30 (1 H, m); $\delta_C$(50.4 MHz) 13.07, 25.4, 25.5, 30.31, 34.4,

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53.65, 55.85 and 70.07; $\nu_{max}$(neat) 2950, 2855, 1255 and 1015; *m/z* 125 ($M^+$, 48%), 110 (10), 97 (15), 83 (100) and 55 (37) (Found: C, 76.6; H, 11.9; N, 11.4. Calc. for $C_8H_{15}N$: C, 76.74; H, 12.08; N, 11.19%).

**5-Methyl-1-azabicyclo[4.4.0]decane 11b.** Yield 88%; $\delta_H$(200 MHz) 0.90 (3 H, d, *J* 6.8), 1.52–2.25 (11 H, m), 2.30–2.40 (1 H, m), 2.55–2.75 (2 H, m) and 3.35–3.55 (2 H, m); $\delta_C$(50.4 MHz) 18.00, 22.28, 22.37, 22.50, 26.60, 31.52, 34.0, 55.70, 55.87 and 69.9; $\nu_{max}$(neat) 2900, 2810, 1420, 1235 and 1030; *m/z* 153 ($M^+$, 18%), 152 (28), 124 (20), 111 (35), 97 (50), 83 (100), 69 (29), 60 (35) and 55(80) (Found: C, 78.2; H, 12.3; N, 9.4. Calc. for $C_{10}H_{19}N$: C, 78.36; H, 12.50; N, 9.14%).

**5-Methyl-1-azabicyclo[4.3.0]nonane 12b.** Yield 85%; $\delta_H$(200 MHz) 0.95 (3 H, d, *J* 6.8), 1.20–1.42 (3 H, m), 1.82–2.05 (4 H, m), 2.51–2.72 (2 H, m), 2.90–3.05 (1 H, m), 3.21–3.35 (2 H, m) and 3.62–3.82 (2 H, m); $\delta_C$(50.4 MHz) 17.52, 22.37, 23.25, 25.40, 30.05, 34.2, 55.25, 55.30 and 69.55; $\nu_{max}$(neat) 2900, 2810, 1355 and 840; *m/z* 139 ($M^+$, 10%), 125 (21), 84 (60), 61 (58), 43 (100) and 28 (100) (Found: C, 77.5; H, 12.2; N, 10.2. Calc. for $C_9H_{17}N$: C, 77.63; H, 12.31; N, 10.06%).

**7-Methyl-1-azabicyclo[4.3.0]nonane 13a.** Yield 87%; $\delta_H$(200 MHz) 1.05 (3 H, d, *J* 6.8), 1.50–1.85 (8 H, m), 2.12–2.25 (1 H, m), 2.42–2.55 (1 H, m), 2.65–2.85 (2 H, m) and 3.45–3.62 (2 H, m); $\delta_C$(50.4 MHz) 14.85, 21.50, 22.12, 23.52, 29.15, 33.95, 51.75, 51.80 and 68.95; $\nu_{max}$(neat) 2940, 2855, 1355 and 940; *m/z* 139 ($M^+$, 11%), 125 (14), 84 (78), 61 (40), 43 (100) and 28 (98) (Found: C, 77.4; H, 12.4; N, 10.2. Calc. for $C_9H_{17}N$: C, 77.63; H, 12.31; N, 10.06%).

**General method for the syntheses of 5- and 6-iodo-alk-2-yn-1-ols**
Lithium (220 mmol) was slowly added to liquid ammonia (500 $cm^3$) containing a catalytic amount of $Fe(NO_3)_3$ and the reaction mixture was stirred for 1 h. The solution of $LiNH_2$ was cooled to −78 °C, prop-2-yn-1-ol (103.0 mmol) in THF (15 $cm^3$) was added and the mixture stirred at the same temperature for an additional 70 min. A solution of the appropriate bromochloroalkane (78.0 mmol) in THF (70 $cm^3$) was added slowly and the reaction mixture stirred for a further 1 h at −78 °C, after which it was diluted with ether (400 $cm^3$). After evaporation of the ammonia from the mixture, aq. $NH_4Cl$ was added and the reaction mixture was extracted with ether (2 × 200 $cm^3$). The combined organic extracts were washed successively with water and brine, dried ($Na_2SO_4$) and evaporated to give the corresponding ω-chloroalkynols. The crude products were purified by vacuum distillation to give the desired products as clear liquids (80–82%).

To a solution of dry sodium iodide (94.6 mmol) in dry acetone (150 $cm^3$) was added the appropriate chloroalkynol (75.7 mmol) through a syringe under an argon atmosphere. The stirred reaction mixture was heated at reflux for 10 h, cooled and filtered. Solid material filtered off was washed with a small amount of acetone, the combined filtrates were evaporated and the residue was dissolved in ether (200 $cm^3$). The ether solution was washed with water, dried ($Na_2SO_4$) and concentrated to give the iodo alkynols as clear liquids. The crude products were purified by vacuum distillation (84–85%).

**6-Iodohex-2-yn-1-ol.** (85%), $\delta_H$(200 MHz) 1.87–2.05 (2 H, m), 2.30 (1 H, s), 2.35–2.45 (2 H, m), 3.25 (2 H, t, *J* 7.3) and 4.25 (2 H, s); $\nu_{max}$(neat) 3400, 2950, 2860, 2250, 1460, 1300, 1050 and 600; *m/z* 224.

**5-Iodopent-2-yn-1-ol.** (84%), $\delta_H$(200 MHz) 2.25 (1 H, s), 2.32–2.47 (2 H, m), 3.25 (2 H, t, *J* 7.3) and 4.30 (2 H, s); $\nu_{max}$-(neat) 3430, 2950, 2800, 2250, 1460 and 1290; *m/z* 210.

**General method for the syntheses of compounds 16a–b and 23**
The appropriate iodoalkynol (22.2 mmol) was added dropwise to a stirred refluxing solution of the 2-(trimethylsilyl)-pyrrolidine or -piperidine (22.2 mmol) and anhydrous $K_2CO_3$ (28.5 mmol) in dry acetonitrile (50 $cm^3$) under an argon atmosphere. After refluxing for 10 h, the reaction mixture was cooled to room temp., filtered and the solid material which was filtered off was washed with ethyl acetate. The combined filtrates were concentrated and purified by column chromatography to give **16a–b** or **23** as liquids.

**1-(5-Hydroxypent-3-ynyl)-2-(trimethylsilyl)pyrrolidine 16a.** (77%), $\delta_H$(200 MHz) 0.10 (9 H, s), 1.60–1.85 (7 H, m), 2.25–2.40 (2 H, m), 2.90–3.05 (1 H, m), 3.15–3.25 (2 H, m) and 4.25 (2 H, s); $\nu_{max}$(neat) 3440, 2950, 2800, 2250, 1460 and 1300; *m/z* 225.

**1-(5-Hydroxypent-3-ynyl)-2-(trimethylsilyl)piperidine 16b.** (78%), $\delta_H$(200 MHz) 0.95 (9 H, s), 1.50–1.75 (6 H, m), 2.22–2.45 (6 H, m), 2.75–2.82 (1 H, m), 2.92–3.08 (1 H, m) and 4.25 (2 H, s); $\nu_{max}$(neat) 3440, 2950, 2840, 2250, 1460, 1300 and 840; *m/z* 239.

**1-(6-Hydroxyhex-4-ynyl)-2-(triemthylsilyl)piperidine 23.** (75%), $\delta_H$(200 MHz) 0.10 (1 H, s), 1.52–1.80 (8 H, m), 2.20–2.45 (6 H, m), 2.75–2.85 (1 H, m) , 2.95–3.05 (1 H, m) and 4.25 (2 H, s); $\nu_{max}$(neat) 3440, 2940, 2850, 2250, 1460, 1300 and 847; *m/z* 253.

**General method of hydrogenation of 16a–b and 23**
Compounds **16a–b** or **23** (11.67 mmol), in MeOH (100 $cm^3$) containing a catalytic amount of Pd on $CaCO_3$ (Lindlar catalyst), were hydrogenated using a Parr hydrogenation apparatus at 35 psi of hydrogen at room temperature. The progress of the reaction was monitored by GC analysis. After 1 h (95–98% conversion), the reaction mixture was filtered through Celite and the filtrate was concentrated to give the allylic alcohols **17a–b** or **24** as liquids, which were pure enough to use for the next steps.

**1-(5-Hydroxypent-3-enyl)-2-(trimethyslilyl)pyrrolidine 17a.** (95%), $\delta_H$(200 MHz) 0.10 (9 H, s), 1.65–1.85 (7 H, m), 2.27–2.35 (2 H, m), 2.95–3.10 (1 H, m), 3.20–3.35 (2 H, m), 4.10–4.25 (2 H, m), 5.45–5.55 (1 H, m) and 5.65–5.73 (1 H, m); $\nu_{max}$(neat) 3450, 2950, 2850, 1620, 1480, 1235 and 840; *m/z* 227.

**1-(5-Hydroxypent-3-enyl)-2-(trimethylsilyl)piperidine 17b.** (97%), $\delta_H$(200 MHz) 0.095 (9 H, s), 1.40–1.70 (8 H, m), 1.85–2.20 (4 H, m), 2.75–2.87 (1 H, m), 2.95–3.05 (1 H, m), 4.10–4.20 (2 H, s), 5.39–5.55 (1 H, m) and 5.65–5.75 (1 H, m); $\nu_{max}$(neat) 3450, 2950, 2840, 1620, 1480, 1235 and 840; *m/z* 241.

**1-(6-Hydroxyhex-4-enyl)-2-(trimethylsilyl)piperidine 24.** (98%), $\delta_H$(200 MHz) 0.09 (9 H, s), 1.45–1.75 (10 H, m), 1.85–2.25 (4 H, m), 2.72–2.85 (1 H, m), 2.95–3.05 (1 H, m), 4.10–4.20 (2 H, m), 5.45–5.60) (1 H, m) and 5.65–5.75 (1 H, m); $\nu_{max}$(neat) 3450, 2950, 2860, 1620, 1480, 1235 and 840; *m/z* 255.

**General method for the syntheses of compounds 18a–b and 25**
To a solution of $PPh_3$ (35.2 mmol) and anhydrous $K_2CO_3$ (23.5 mmol) in $CCl_4$ (40 $cm^3$) and $CH_2Cl_2$ (10 $cm^3$), was added the appropriate allylic alcohol **17a–b** or **24** the mixture was refluxed for 8 h. The reaction mixture was cooled to room temperature and filtered and the solid material which was filtered off was washed with $CH_2Cl_2$. The combined filtrates were concentrated and purified by column chromatography to give the corresponding compounds **18a–b** or **25** as thick liquids.

**1-(5-Chloropent-3-enyl)-2-(trimethylsilyl)pyrrolidine 18a.** (87%), $\delta_H$(200 MHz) 0.12 (9 H, s), 1.60–1.78 (6 H, m) 2.25–2.35 (2 H, m), 2.95–3.10 (1 H, m), 3.25–3.35 (2 H, m), 4.10–4.25 (2 H, m), 5.45–5.60 (1 H, m) and 5.65–5.73 (1 H, m); $\nu_{max}$(neat) 2900, 2850, 1480, 1250 and 750; *m/z* 245.

**1-(5-Chloropent-3-enyl)-2-(trimethylsilyl)piperidine 18b.** (90%), $\delta_H$(200 MHz) 0.12 (9 H, s), 1.70–1.85 (6 H, m), 2.20–2.25 (2 H, m), 2.62–2.87 (2 H, m), 3.10–3.25 (2 H, m), 3.30–3.45 (1 H, m), 4.22 (2 H, d, *J* 7.2), 5.40–5.55 (1 H, m) and 5.75–5.82 (1 H, m); $\nu_{max}$(neat) 2900, 2850, 1480, 1250 and 750; *m/z* 259.

**1-(6-Chlorohex-4-enyl)-2-(trimethylsilyl)piperidine 25.** (85%), $\delta_H$(200 MHz) 0.15 (9 H, s), 1.75–1.85 (8 H, m), 2.20–2.25 (2 H, m), 2.65–2.85 (2 H, m), 3.10–3.25 (2 H, m), 3.30–3.40 (1 H, m), 4.25 (2 H, d, *J* 7.3), 5.40–5.55 (1 H, m) and 5.70–5.78 (1 H, m); $\nu_{max}$(neat) 2950, 2800, 1480, 1235 and 850; *m/z* 273.

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**General method of photolysis of 18a–b and 25**

A mixture of **18a–b** or **25** (2.5 mmol), DCN (0.56 mmol) and $K_2CO_3$ (1.3 mmol) in propan-2-ol was irradiated in a 500 $cm^3$ irradiation vessel using a 450 W Hanovia medium-pressure mercury vapour lamp at ambient temperature for 3 h as described earlier for **9a–d**. The mixture was evaporated under reduced pressure and DCN was filtered off through a column to give the crude products **19a–b** or **26**, which were used for the next step without further purification.

**General method of ozonolysis**

A solution of each of the bicyclic compounds **19a–b** or **26** (1.2 mmol) dissolved in MeOH (2.5 $cm^3$) and $CH_2Cl_2$ (4 $cm^3$) was saturated with ozone (5% in $O_2$) at −78 °C (solution turned blue). The excess of ozone was removed by passage of nitrogen through the mixture which was then treated with dimethyl sulfide (0.6 $cm^3$) and allowed to warm to room temp. After 1 h at room temperature, the mixture was evaporated under reduced pressure to give 80–90% of the crude aldehydes **20a–b** and **27** as viscous liquids which were used for the reduction step without further purification.

**General method for the reduction of aldehydes 20a–b and 27**

To a suspension of $NaBH_4$ (1.07 mmol) in ethanol (10 $cm^3$), a solution of the appropriate crude aldehyde (1.07 mmol) in ethanol (3 $cm^3$) was added dropwise at 0 °C. The mixture was heated at reflux for 3 h, after which it was cooled to 5–10 °C in an ice-bath and treated carefully with water (0.2 $cm^3$). The mixture was filtered through Celite and on a sintered glass funnel. The filtrates were dried ($Na_2SO_4$) and concentrated to afford 86–90% of alcohols **22a–b** and **29** as viscous liquids, which were used for benzoylation without further purification.

**General method of benzoylation of alcohols 22a–b and 29**

To a solution of the appropriate crude alcohol **22a–b** or **29** (0.88 mmol) in triethylamine (1.67 mmol) and dry THF (10 $cm^3$), was added benzoyl chloride (1.67 mmol) at 0 °C under argon. The mixture was stirred overnight at room temp. after which it was diluted with ethyl acetate and filtered through a sintered funnel. The filtrates were concentrated and purified by column chromatography, eluting with light petroleum (bp 60–80 °C)–acetone to afford the benzoyl derivatives **21a–b** or **28** as single isomers.

**1-Azabicyclo[3.3.0]octan-4-ylmethyl benzoate 21a.** (92%), $\delta_H$(200 MHz) 1.75–1.95 (3 H, m), 2.25–2.45 (4 H, m), 2.55–2.75 (2 H, m), 2.95–3.05 (1 H, m), 3.25–3.52 (1 H, m), 3.75–3.85 (1 H, m), 4.25–4.45 (2 H, m), 7.40–7.65 (3 H, m) and 7.96–8.10 (2 H, m); $\delta_C$(50.4 MHz) 25.07, 30.05, 30.90, 41.50, 55.62, 55.74, 65.25, 128.53, 129.30, 129.52, 130.34, 133.14 and 166.62; $\nu_{max}$(neat) 3020, 1720, 1275 and 765; *m/z* 245 ($M^+$, 10%), 244 (12), 124 (100), 105 (70), 83 (100) and 77 (98) (Found: C, 73.5; H, 7.7; N, 5.6. Calc. for $C_{15}H_{19}NO_2$: C, 73.44; H, 7.81; N, 5.71%).

**1-Azabicyclo[4.3.0]nonan-7-ylmethyl benzoate 21b.** (92%), $\delta_H$(200 MHz) 1.25–1.63 (1 H, m), 1.68–2.12 (6 H, m), 2.17–2.40 (1 H, m), 2.65–3.25 (4 H, m), 3.57–3.63 (2 H, m), 4.35–4.65 (2 H, m), 7.36–7.63 (3 H, m) and 7.80–8.22 (2 H, m); $\delta_C$(50.4 MHz) 22.10, 23.55, 24.15, 25.15, 39.27, 50.90, 51.21, 64.85, 65.29, 128.69, 129.88, 132.07, 133.39 and 166.56; $\nu_{max}$(neat) 2985, 1725, 1220 and 770; *m/z* 259 ($M^+$, 5%), 138 (40), 122 (100), 105 (90) and 77 (45) (Found: C, 73.9; H, 8.0; N, 5.3. Calc. for $C_{16}H_{21}NO_2$: C, 74.10; H, 8.16, N, 5.40%).

**1-Azabicyclo[4.4.0]decan-5-ylmethyl benzoate 28.** (90%), $\delta_H$(200 MHz) 1.22–1.62 (2 H, m), 1.70–2.25 (7 H, m), 2.32–2.87 (5 H, m), 3.65–3.95 (2 H, m), 4.30–4.52 (2 H, m), 7.42–7.70 (3 H) and 7.90–8.15 (2 H, m); $\delta_C$(50.4 MHz) 23.31, 23.42, 23.71, 24.52, 27.69, 41.54, 52.13, 52.34, 65.36, 67.83, 128.70–133.52 (ArC) and 166.72 (C=O); $\nu_{max}$(neat) 3010, 2950, 1720, 1390, 1275, 1220 and 760; *m/z* 273 ($M^+$, 2%), 259 (5), 138 (48), 122 (95), 105 (100), 97 (10) and 77 (38) (Found: C, 74.6; H, 8.5; N, 5.2. Calc. for $C_{17}H_{23}NO_2$: C, 74.69; H, 8.48; N, 5.12%).

**General method for debenzoylation**

Each of the bicyclic benzoates **21a–b** or **28** (0.73 mmol) was added to a solution of NaOH (2.9 mmol) in methanol (13 $cm^3$) and the mixture stirred at room temperature for 1.5 h. After evaporation of the mixture under reduced pressure, the residue was extracted with $CH_2Cl_2$ (3 × 20 $cm^3$) and the organic extracts were washed with water, dried ($Na_2SO_4$) and evaporated under reduced pressure. The resulting residue was chromatographed on silica gel, using light petroleum–acetone as eluent, to give the desired alcohol **22a–b** or **29**.

**(±)-Isoretronecanol 22a.** (80%), $\delta_H$(200 MHz) 1.55–1.72 (1 H, m), 1.74–2.12 (7 H, m), 2.55–2.66 (2 H, m), 3.01–3.13 (1 H, m), 3.20–3.28 (1 H, m), 3.45–3.50 (1 H, m) and 3.60–3.64 (2 H, m); $\delta_C$(50.4 MHz) 25.72, 30.20, 31.95, 48.40, 54.33, 56.76, 65.30 and 67.58; $\nu_{max}$(neat) 3340, 2950, 1450 and 1280; *m/z* 141 ($M^+$, 15%), 124 (45), 110 (55), 83 (100), 82 (23) and 55 (67) (Found: C, 68.1; H, 10.8; N, 9.9. Calc. for $C_8H_{15}NO$: C, 68.04; H, 10.71; N, 9.92%).

**(±)-1-Azabicyclo[4.3.0]nonan-7-ylmethanol 22b.** (72%), $\delta_H$(200 MHz) 0.95–2.55 (12 H, m), 2.95–3.30 (3 H, m) and 3.33–3.65 (2 H, m); $\delta_H$(50.4 MHz) 25.55, 26.90, 29.46, 41.24, 53.30, 53.83, 54.17 and 64.70; $\nu_{max}$(neat) 3330, 2950 and 1280; *m/z* 155 ($M^+$, 15%), 124 (100), 97 (45), 83 (36), 69 (23) and 55 (34) (Found: C, 68.9; H, 10.9; N, 9.1. Calc. for $C_9H_{17}NO$: C, 69.63; H, 11.04; N, 9.02%).

**(±)-Epilupinine 29.** (75%), $\delta_H$(200 MHz) 1.15–2.22 (14 H, m), 2.85–2.95 (3 H, m) and 3.55–3.73 (2 H, m); $\delta_C$(50.4 MHz) 24.2, 24.7, 25.2, 28.3, 29.5, 43.5, 56.5, 56.6, 63.7 and 64.5; $\nu_{max}$(neat) 3635, 2950, 2775, 1600, 1450, 1280 and 1010; *m/z* 169 ($M^+$, 20%), 152 (18), 138 (42), 97 (48) and 83 (100) (Found: C, 70.8; H, 11.2; N, 8.3. Calc. for $C_{10}H_{19}NO$: C, 70.96; H, 11.32; N, 8.28%).

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