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SYNTHESIS OF THE BICYCLO[3.3.1]NONANE CORE OF HUPERZINE A AND NOVEL PYRIDINE-FUSED TRICYCLES BY CYCLISATION OF PYRIDINE-BASED RADICALS‡

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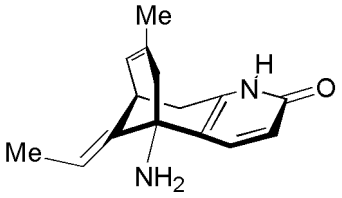
Abstract – The cyclisation of 3-pyridyl radicals and (2-pyridyl)methyl radicals, generated from (pyridyl)cyclohexenols **5** to **8**, has been examined as part of a model study directed towards the synthesis of huperzine A. The 3-pyridyl radical, generated from 3-bromopyridine **5**, undergoes 5-*exo-trig* cyclisation to give hexahydroindenopyridine **10**. Related pyridine-fused tricycle **12** is formed by 5-*exo-trig* cyclization of the (2-pyridyl)methyl radical derived from selenide **7b**, while the radicals generated from selenides **8b** and **19** undergo 6-*exo-trig* cyclisation to give the bicyclo[3.3.1]nonane core of huperzine A.

INTRODUCTION

Huperzine A **1** is a *Lycopodium* alkaloid isolated from the Chinese club moss *Huperzia serrata*[1] and the New Zealand club moss *Lycopodium varium*.[2] This compound is a potent, selective and reversible inhibitor of acetylcholine esterase[3] and is a useful lead in the palliative treatment of disorders, such as Alzheimer's disease, that are attributed, in part, to a depletion of brain levels of acetylcholine. Indeed, clinical studies have shown that huperzine A effectively improves cognitive function in the elderly.[4] In addition, huperzine A functions as a pretreatment for organophosphate poisoning[5] and recent studies have shown that this compound also displays neuroprotective properties.[6]

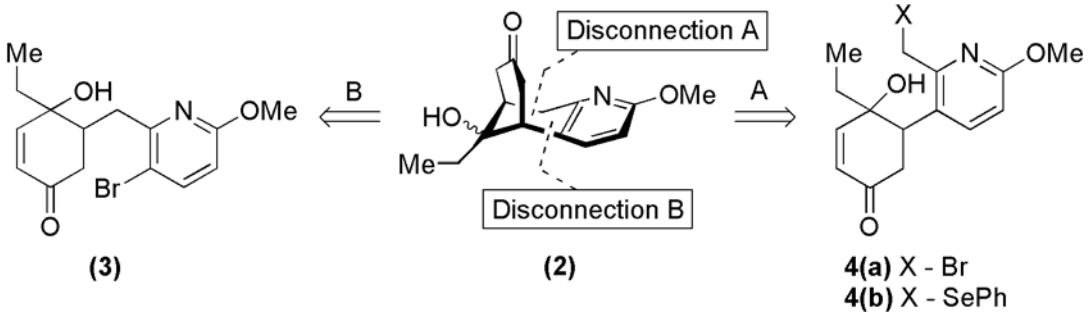


(1)

Figure 1

‡This paper is dedicated to the memory of Dr. John Daly.

The important bioactivity of huperzine A has stimulated the development of a number of total[7] and partial syntheses of this compound[8] and analogues.[9] In an effort to develop a novel synthesis of **1**, and as part of a research programme aimed at probing the scope and utility of pyridine-based radicals in synthesis, we have investigated a novel synthetic approach to core structure **2**. This strategy centres on the 6-*exo-trig* cyclisation of either the 3-pyridyl radical generated from intermediate **3**, or the (2-pyridylmethyl) radical generated from **4a/b** (Scheme 1).



Scheme 1. Retrosynthesis of core structure **2**

While there are a small number of reports documenting the generation and reaction of 3-pyridyl radicals,[10] the use of (2-pyridyl)methyl radicals has not been studied. Thus, prior to embarking on a synthesis of **2**, we have carried out a programme of model studies to validate the proposed strategy.[11]These studies, reported in full herein, have focused on investigating the synthesis of compounds **5**-**8** and the predominant mode of cyclisation of the radicals generated from each (Figure 2).

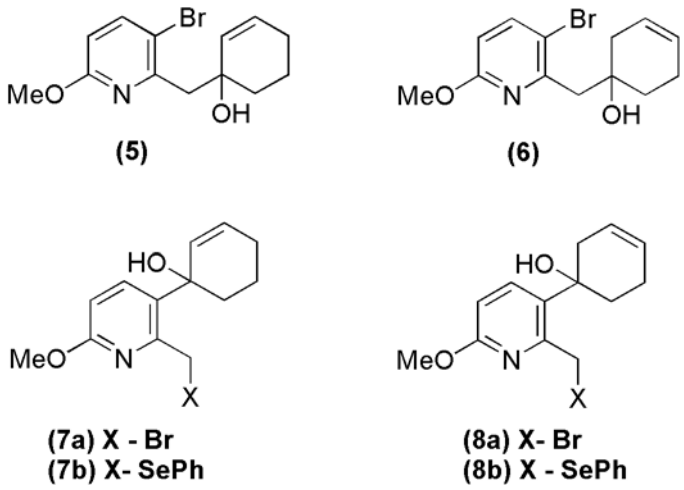
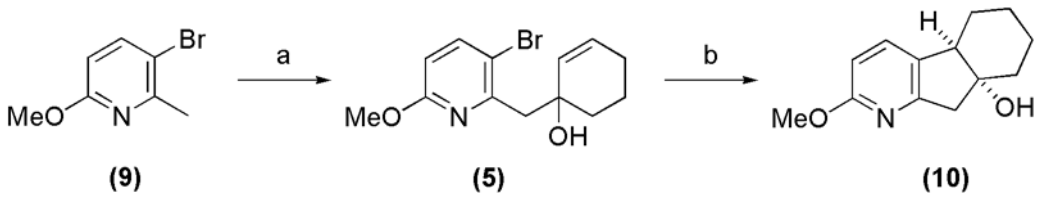


Figure 2. Structures of model cyclisation precursors (**5**) to (**8**)

RESULTS AND DISCUSSION

Cyclisation precursor **5** was synthesized, according to the method of Gray *et al.*,[12] by addition of the ((2-pyridyl)methyl)lithium, generated from bromopyridine **9**,[8e,12] to 2-cyclohexenone. Radical cyclisation of **5** was initiated under standard conditions, using $^{n}Bu_3SnH$ and AIBN. As predicted, cyclisation proceeded *via* a 5-*exo-trig* pathway to give novel annulated pyridine **10**, with *cis*-stereochemistry at the ring junction (Scheme 2). The stereochemistry of cyclisation was assigned by analysis of 2D-NOESY spectral data (Figure 3.)



Scheme 2. Reagents and conditions: (a) (i) LDA, THF, -78 ºC, (ii) 2-cyclohexen-1-one, THF, -78 ºC; (b) $^{n}Bu_3SnH$, AIBN, benzene, reflux, 64%

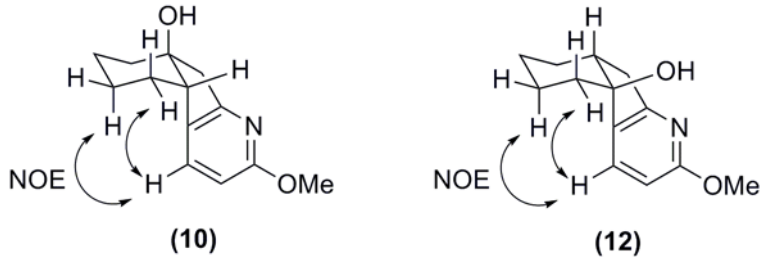
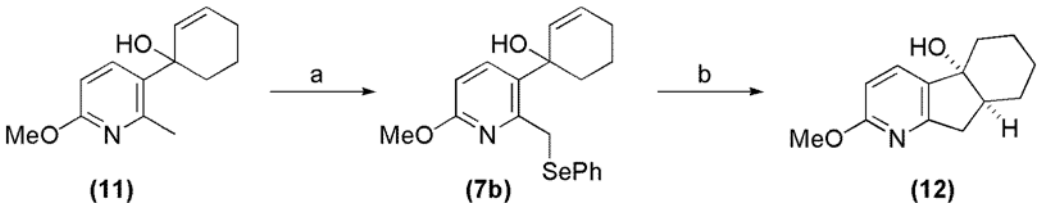


Figure 3. Key NOE correlations for compounds (**10**) and (**12**)

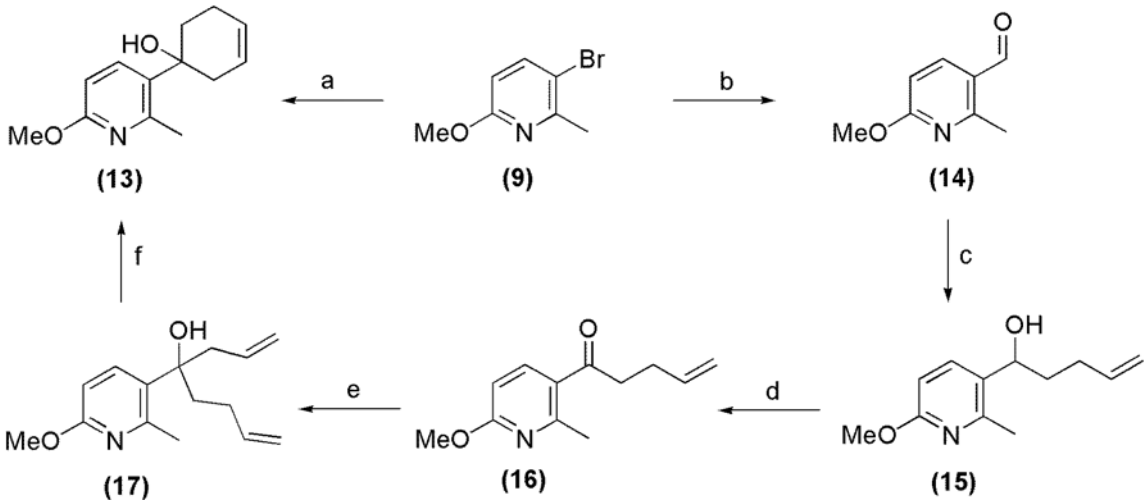
Unfortunately, attempts to probe the 6-*exo-trig* cyclisation of 3-pyridyl radicals, using compound **6**, were stymied by the difficulty in accessing this compound. We planned to synthesise **6**, in similar fashion to **5**. However, addition of the 3-lithiopyridine, generated from **9**,[8e,12] to 3-cyclohexenone[13] only proceeded in a poor yield of 6%.

Our attention next turned to a study of the cyclisation of (2-pyridyl)methyl radicals. We planned to access compounds **7a/b** by direct functionalisation at the methyl position of (3-pyridyl)cyclohexenol **11**.[12] Attempts to access bromide **7a**, by NBS bromination of **11**,[12] were unsuccessful. However, synthesis of selenide **7b** was achieved, albeit in low yield, by deprotonation of **11** with ^{n}BuLi followed by addition of diphenyl diselenide (Scheme 3). Radical cyclisation of **7b** was, again, achieved under standard conditions, to give the *cis*-fused product **12**, arising from 5-*exo-trig* cyclisation, in near quantitative yield. Stereochemistry at the ring junction was, again, assigned with the aid of 2D-NOESY data (Figure 3).



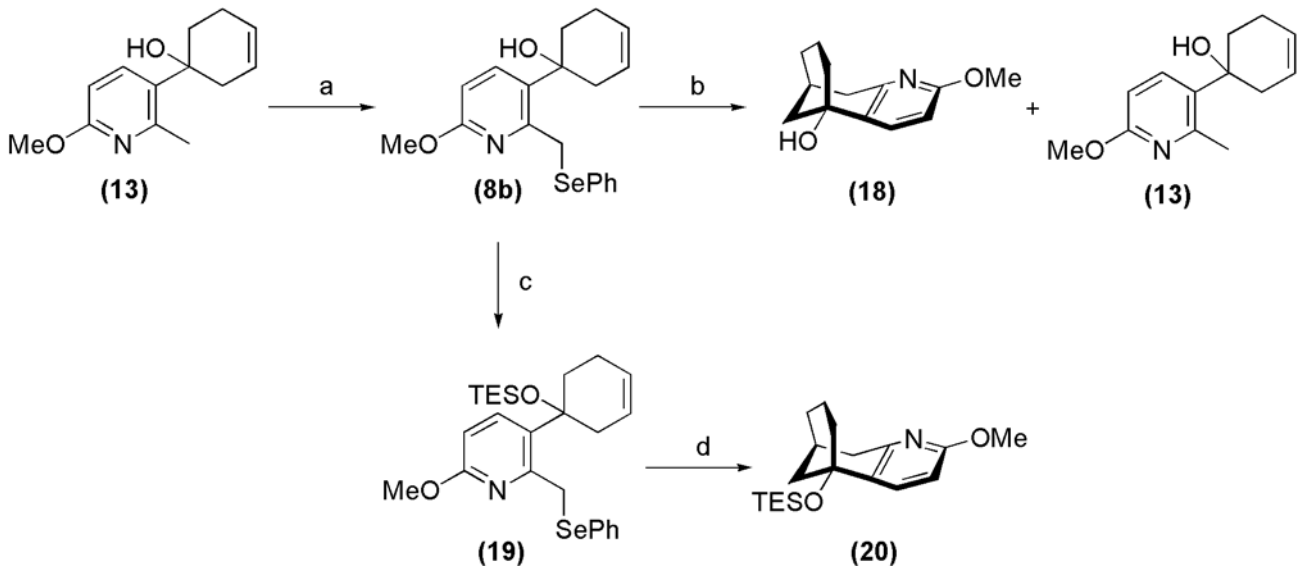
Scheme 3. Reagents and conditions: (a) (i) ^{n}BuLi, THF, -78 °C, (ii) Ph_2Se_2, THF, -78 °C, 20%; (b) $^{n}Bu_3SnH$, AIBN, benzene, reflux, 97%.

The third stage of this model study involved an investigation of the cyclisation of **8a/b**, which we planned to access by selective functionalisation at the benzylic position of (3-pyridyl)cyclohexenol **13**. The most direct synthesis of **13**, by addition of 3-cyclohexenone to the 3-pyridyllthium derived from bromopyridine **9**,[8e,12] met with limited success, proceeding in a maximum yield of 20%. This prompted us to develop a more circuitous route to **13**, utilizing an iterative nucleophilic addition/oxidation sequence followed by ring-closing metathesis, to construct the cyclohexene moiety (Scheme 4). Thus, formylation of **9**,[12] followed by addition of but-3-enylmagnesium bromide, gave alcohol **15**. Oxidation of **15**, to ketone **16**, followed by addition of allylmagnesium bromide gave RCM substrate **17**. Grignard addition to **16** initially proved difficult, owing to additional allylation by displacement of the 6-methoxy group on the pyridine ring. This problem was overcome, by performing the reaction under higher dilution, to give the required addition product in high yield. Ruthenium-catalysed ring closing metathesis of pyridine-containing substrates has been reported as problematic, owing to competing coordination of the pyridine nitrogen to the catalyst.[14] Nevertheless, diene **17** underwent smooth RCM using 3 mol% Grubbs' first generation catalyst to give (3-pyridyl)cyclohexenol **13** in excellent yield.



Scheme 4. Reagents and conditions: (a) (i) ^{n}BuLi, THF, -78 °C, (ii) 3-cyclohexenone -78 °C, 18%; (b) (i) ^{n}BuLi, THF, -78 °C, (ii) DMF, THF, -78 °C, 98%; (c) but-3-enylmagnesium bromide, Et_2O, 0 °C, 77%; (d) DMP, py, CH_2Cl_2, rt, 84%; (e) allylmagnesium bromide, Et_2O, 0 °C, 79%; (f) $(Cl)_2(PCy_3)_2Ru{=}CHPh$, CH_2Cl_2, 94%.

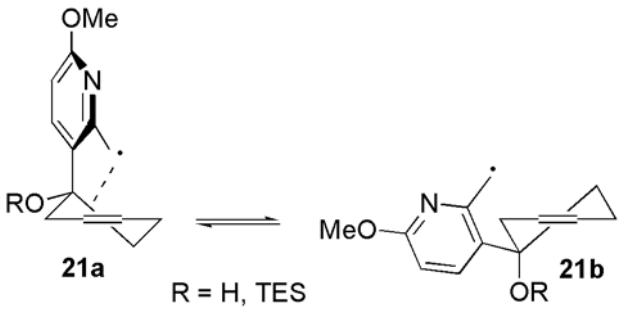
Again, direct bromination of **13**, using NBS, failed. We thus turned our attention to effecting a direct selenation *via* deprotonation of **13** at the benzylic position. As selenophenylmethylpyridine **7b** was only obtained in low yield, by direct selenation of **11**, a variety of bases and electrophiles were screened in an effort to more efficiently access selenide **8b**.[11] After some optimization, it was discovered that use of 2.2 equivalents of ^{t}BuLi as base, THF/DMPU as solvent and phenylselenium chloride as electrophile furnished **8b** in 79% yield (Scheme 5).[11] With quantities of selenide **8b** in hand, we next embarked on a study of the 6-*exo-trig* radical cyclisation of this compound, in an effort to access the bicyclo[3.3.1]nonane core of huperzine A. Cyclisation of **8b**, under the conditions previously developed for cyclisation of **5** and **7b**, gave the desired bicyclo[3.3.1]nonane **18** in 46% yield along with the reduced product **13** in 54% yield. While the yield of cyclised product is only moderate, this result, and the excellent yield achieved during cyclisation of **7b**, indicates that the (2-pyridyl)methyl radical is being formed quantitatively under these reaction conditions. In an effort to more fully probe the 6-*exo-trig* radical cyclisation of compounds of type **8b** we also investigated the triethylsilyl ether **19**, readily accessed by treatment of alcohol **8b** with TESCl in the presence of imidazole. We were delighted to find that 6-*exo-trig* radical cyclisation of **19** occurs in 79% yield.



Scheme 5. Reagents and conditions. (a) (i) 2.2 equiv ^{t}BuLi, 2.2 equiv DMPU, THF, -78 °C, 77%. (ii) PhSeCl, -78 °C, 75%; (b) $^{n}Bu_3SnH$, AIBN, benzene, reflux, 46% for **18** 46%, 54% for **13** (c) TESCl, imidazole, DMF, rt, 63%; (d) $^{n}Bu_3SnH$, AIBN, benzene, reflux, 73%.

The increase in yield may be attributable to stereoelectronic factors. It is probable that the optimal conformation for SOMO-LUMO overlap is **21a**, with the pyridylmethyl moiety occupying a pseudo-axial position. However, when R = H, the more stable transition-state conformer is likely to be **21b**, and thus,

reduction of the radical with tributyltin hydride, or intramolecular abstraction of an allylic hydrogen,[15] competes with cyclisation. However, the transition state conformer **21a** may be more favourable when a bulky geminal substituent such as a silyloxy ether is present. Unfortunately, attempts to further verify this theory have, so far, been thwarted by difficulties encountered in the conversion of tertiary alcohol **8b** to the more bulky *tert*-butyldimethylsilyl ether under a variety of reaction conditions.



Scheme 6. Proposed transition-state conformations of radical **21**.

In conclusion, we have further broadened the scope and utility of 3-pyridyl radicals by the use of these species in the synthesis of novel hexahydroindenopyridines. Furthermore, we have shown that, hitherto unaccessed, (2-pyridyl)methyl radicals can be formed quantitatively from 2-(phenylselenylmethyl)pyridines under standard conditions. These species undergo 5-*exo-trig* cyclisation, in excellent yield, to give hexahydroindenopyridines and have also been revealed to undergo 6-*exo-trig* cyclisation to give bicyclo[3.3.1]nonanes related to the core structure of huperzine A. Future work will concentrate on further optimizing the yield of the latter mode of cyclisation and on investigating the radical cyclisation of more functionalized substrates in an effort to achieve a total synthesis of huperzine A.

EXPERIMENTAL

General. All reactions were performed under a nitrogen atmosphere using oven-dried glassware. All solvents were dried by distillation from calcium hydride (CH_2Cl_2, benzene, DMF) or sodium-benzophenone (THF and diethyl ether). Benzene was degassed by sonication before use. Flash chromatography was performed using Scharlau 60 (230-400 mesh ASTM) silica gel and thin layer chromatography was performed on Merck silica gel 60 F_{254} plates. IR spectra were recorded using a Perkin-Elmer Spectrum 1000 Fourier-Transform IR spectrometer. NMR spectra were recorded using a Bruker Avance 300 Spectrometer or a Bruker DRX 400 Spectrometer. ^{1}H NMR chemical shifts are reported in parts per million (ppm) relative to the tetramethylsilane peak (δ 0.00 ppm). ^{1}H NMR values are reported as chemical shift δ, multiplicity (s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet),

coupling constant $(J)_2$ and relative integral. Coupling constants were taken directly from the spectra. Assignments were made with the aid of DEPT, COSY, HSQC, HMBC and NOESY experiments. Low resolution and accurate mass data were recorded on a VG70SE spectrometer operating at a nominal accelerating voltage of 70 eV. Ionisation was effected using electron impact (EI^+), or chemical ionisation (CI^+) using ammonia as a carrier gas. Major and significant fragments are quoted in the form *x* (*y*), where *x* is the mass to charge ratio (*m*/*z*) and *y* is the percentage abundance relative to the base peak (100%).

2-Methoxy-5,6,7,8,8a,9-hexahydroindeno[2,1-*b*]pyridine-8a-ol (10)

A solution of tributyltin hydride (0.06 mL, 0.21 mmol) and AIBN (0.0041 g, 0.03 mmol) in degassed benzene (40 mL) was added over 4.5 h, using a syringe pump, to a solution of bromopyridine **5** (0.04 g, 0.14 mmol) in degassed benzene (150 mL) under reflux. The reaction mixture was stirred under reflux for a further 2 h then cooled to rt and concentrated *in vacuo*. A saturated aqueous solution of potassium fluoride (25 mL) was added to the residue and the mixture stirred at rt overnight. The reaction mixture was extracted with Et_2O (3 x 25 mL) and the combined organic extracts washed with brine (25 mL), dried over anhydrous magnesium sulfate and concentrated *in vacuo*. The residue was purified by flash column chromatography eluting with diethyl Et_2O:hexane (2:1) to give the *title compound* (0.02 g, 64%) as a colourless oil. IR (neat) 3392, 2929, 2855, 1591, 1472, 1416, 1297 cm^{-1}; ^{1}H-NMR (300 MHz, $CDCl_3$) δ 1.34–1.45 (m, 3H), 1.61-1.72 (m, 3H), 1.82-1.86 (m, 1H), 1.92-1.96 (m, 1H), 2.85 (d, *J* = 16.2 Hz, 1H), 2.90 (t, *J* = 5.7 Hz, 1H), 3.05 (d, *J* = 16.2 Hz, 1H), 3.91 (s, 3H), 6.52 (d, *J* = 8.3 Hz, 1H), 7.31 (d, *J* = 8.3 Hz, 1H); ^{13}C-NMR (75 MHz, $CDCl_3$) δ 22.4, 22.5, 28.5, 35.1, 46.6, 49.6, 53.5, 79.6, 108.1, 131.7, 133.9, 159.3, 164.2; MS (EI) *m/z*: 219 (100, M^+), 190 (53), 176 (75). HRMS (EI): M^+, found 219.1256, $C_{13}H_{17}NO_2$ requires 219.1259.

1-(6-Methoxy-2-(phenylselenylmethyl)pyridin-3-yl)cyclohex-2-en-ol (7b)

A solution of ^{n}BuLi (1.5 M in hexane, 2.31 mL, 3.15 mmol) was added to a solution of (3-pyridyl)cyclohexenol **11**[12] (0.31 g, 1.43 mmol) in THF (10 mL) at -78 °C. The mixture was stirred at -78 °C for 30 min then a solution of diphenyl diselenide (0.33 g, 1.72 mmol) in THF (7 mL) was added dropwise. The reaction mixture was stirred at -78 °C for a further 30 min then warmed to rt and quenched by the addition of a solution of saturated aqueous ammonium chloride (15 mL) The mixture was extracted with Et_2O (2 x 15 mL) and the combined organic layers were dried over anhydrous magnesium sulphate and concentrated *in vacuo*. The residue was purified by flash column chromatography eluting with EtOAc:hexane (3:97) to give the *title compound* (0.11 g, 20%) as a yellow oil; IR (neat) 3400, 2934, 1591, 1475, 1421, 1314, 1262, 1032; ^{1}H-NMR (300 MHz, $CDCl_3$) δ 1.50–2.12 (m, 6H), 3.83 (s, 3H),

4.40 (d, *J* = 11.2 Hz, 1H), 4.61 (d, *J* = 11.2 Hz, 1H), 5.82 (d, *J* = 10.0 Hz, 1H), 5.96-6.03 (m, 1H), 6.53 (d, *J* = 8.4 Hz, 1H), 7.21-7.30 (m, 3H), 7.60-7.65 (m, 2H), 7.69 (d, *J* = 8.4, 1H); ^{13}C-NMR (75 MHz, $CDCl_3$) δ 19.0, 24.7, 33.2, 37.8, 53.1, 71.8, 108.6, 126.7, 128.8, 129.2, 130.8, 132.0, 132.7, 133.0, 138.6, 153.6, 161.9; MS (EI) *m/z*: 375(18, M^+), 314 (68), 200 (82), 176 (93), 157 (93), 97 (91), 77(100). HRMS (EI): M^+, found 375.0736, $C_{19}H_{21}NO_2{}^{80}Se$ requires 375.0738.

2-Methoxy-5,6,7,8,8a,9-hexahydroindeno[2,1-*b*]pyridine-4b-ol (12)

A solution of tributyltin hydride (0.03 mL, 0.01 mmol) and AIBN (0.003 g, 0.02 mmol) in degassed benzene (3 mL) was added dropwise over 4.5 h, using a syringe pump, to a solution of selenide **7b** (0.02 g, 0.01 mmol) in degassed benzene (10 mL) under reflux. The reaction mixture was stirred under reflux for a further 2 h then cooled to rt and concentrated *in vacuo*. A saturated aqueous solution of potassium fluoride (25 mL) was added to the residue and the mixture stirred at rt overnight. The reaction mixture was extracted with Et_2O (3 x 25 mL) and the combined organic extracts washed with brine (25 mL), dried over anhydrous magnesium sulfate and concentrated *in vacuo*. The residue was purified by flash column chromatography eluting with EtOAc:hexane (1:9) to give the *title compound* (0.02 g, 97%) as a colourless oil; IR (neat) 3392, 2929, 2855, 1591, 1472, 1416, 1297; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 1.10-1.32 (m, 4H), 1.52-1.58 (m, 1H), 1.76-1.81 (m, 3H), 2.29-2.33 (m, 1H), 2.51 (dd, *J* = 16.2, 4.9 Hz, 1H), 3.15 (dd, *J* = 16.2, 16.1 Hz, 1H), 3.94 (s, 3H), 6.57 (d, *J* = 8.3 Hz, 1H), 7.48 (d, *J* = 8.3 Hz, 1H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 22.1, 23.0, 28.5, 34.7, 37.6, 46.9, 53.5, 79.8, 109.4, 132.7, 133.0, 156.5, 162.1; MS (EI) *m/z*: 219 (26, M^+), 201 (42), 176 (100). HRMS (EI): M^+, found 219.1259, $C_{13}H_{17}NO_2$ requires 219.1259.

1-(6-Methoxy-2-methylpyridin-3-yl)cyclohex-3-enol (13)

Method 1. A solution of ^{n}BuLi (1.5M in hexane, 0.39 mL, 1.48 mmol) was added dropwise to a solution of bromopyridine **9**[8e,12] (0.10 g, 0.49 mmol) in THF (3 mL) at -78 °C. The reaction mixture was stirred at this temperature for 30 min then a solution of 3-cyclohexen-1-one[13] (0.33 mL, 3.39 mmol) in THF (3 mL) was added dropwise. The reaction mixture was stirred for a further 30 min at -78 °C then warmed to rt and quenched by the addition of saturated aqueous ammonium chloride (15 mL). The mixture was extracted with Et_2O (2 x 5 mL) and the combined organic layers were dried over anhydrous magnesium sulfate, concentrated *in vacuo* and the residue purified by flash column chromatography eluting with EtOAc:hexane (1:9) to give the *title compound* (0.02 g, 18%) as a colourless oil.

Method 2. Grubbs' first generation catalyst (0.04 g, 0.05 mmol) was added to a solution of diene **17** (0.40 g, 1.62 mmol) in CH_2Cl_2 (15 mL) at rt. The reaction mixture was stirred at this temperature for 2 h then concentrated *in vacuo*. The residue was purified by flash column chromatography eluting with EtOAc:hexane (1:9) to give the *title compound* (0.34 g, 94%) as a colourless oil; IR (neat) 3421, 2927, 1590, 1475, 1422, 1304; ^{1}H-NMR (300 MHz, $CDCl_3$) δ 2.06–2.12 (m, 4H), 2.46-2.53 (m, 2H), 2.72 (s, 3H), 3.09 (s, 3H), 5.72-5.76 (m, 1H), 5.76-5.82 (m, 1H), 6.53 (d, *J* = 8.6 Hz, 1H), 7.57 (d, *J* = 8.6 Hz, 1H); ^{13}C-NMR (75 MHz, $CDCl_3$) δ 23.1, 25.0, 33.4, 39.2, 53.3, 71.9, 106.7, 124.5, 127.2, 132.0, 136.9, 154.8, 161.9; MS (EI) *m/z*: 219 (17, M^+), 165 (73), 150 (100). HRMS (EI): M^+, found 219.1257, $C_{13}H_{17}NO_2$ requires 219.1259.

1-(6-Methoxy-2-methylpyridin-3-yl)pent-4-en-1-ol (15)

A solution of but-3-enyl bromide (1.48 g, 14.6 mmol) in Et_2O (5 mL) was added dropwise to a mixture of magnesium (0.36 g, 14.6 mmol) and a crystal of iodine in Et_2O (5 mL), at such a rate as to maintain a gentle reflux. The reaction mixture was then stirred under reflux for 1 h then cooled to 0 °C. A solution of aldehyde **14**[12] (1.00 g, 6.62 mmol) in Et_2O (5 mL) was added dropwise and the reaction mixture stirred at 0 °C for 1 h, warmed to rt and quenched by the addition of saturated aqueous ammonium chloride (20 mL). The mixture was extracted with Et_2O (2 x 20 mL) and the combined organic layers washed with brine (2 x 10 mL), dried over anhydrous magnesium sulfate and concentrated *in vacuo*. The residue was purified by column chromatography eluting with Et_2O:hexane (1:9) to give the *title compound* (1.0 g, 77%) as a colourless oil; IR (neat) 3392, 2941, 1597, 1478, 1309, 1041; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 1.82–1.86 (m, 2H), 2.12–2.18 (m, 2H), 2.45 (s, 3H), 3.91 (s, 3H), 4.89-4.92 (m, 1H), 5.08-5.13 (m, 2H), 5.81-5.89 (m, 1H), 6.10 (d, *J* = 8.5, 1H), 7.65 (d, *J* = 8.5, 1H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 21.6, 30.1, 37.1, 53.3, 69.4, 107.8, 115.2, 130.1, 136.5, 137.0, 154.8, 162.4; MS (EI) *m/z*: 207 (8, M^+), 152 (100). HRMS (EI): M^+, found 207.1255, $C_{12}H_{17}NO_2$ requires 207.1259.

1-(6-Methoxy-2-methylpyridin-3-yl)pent-4-en-1-one (16)

Dess-Martin periodinane (4.14 g, 9.74 mmol) was added in one portion to a solution of alcohol **15** (1.0 g, 4.87 mmol) and pyridine (2.35 mL, 29.2 mmol) in CH_2Cl_2 (50 mL) at rt and the reaction mixture stirred at this temperature for 2 h. Saturated aqueous sodium thiosulfate (10 mL) and saturated aqueous sodium hydrogen carbonate (10 mL) were added and the mixture extracted with CH_2Cl_2 (2 x 10 ml). The combined organic extracts were dried over anhydrous magnesium sulfate, concentrated *in vacuo* and the residue purified by flash column chromatography eluting with Et_2O:hexane (1:19) to give the *title*

compound (0.84 g, 84%) as a colourless oil; IR (neat) 2943, 1682, 1587, 1478, 1313, 1128; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 2.46-2.49 (m, 2H), 2.69 (s, 3H), 2.95 (t, *J* = 7.2 Hz, 2H), 4.01 (s, 3H), 5.02-5.11 (m, 2H), 5.88-5.93 (m, 1H), 6.60 (d, *J* = 8.6, 1H), 7.93 (d, *J* = 8.6, 1H); ^{13}C-NMR (100 MHz, $CDCl_3$,) δ 25.0, 28.4, 40.0, 53.7, 107.3, 115.4, 125.8, 137.2, 139.5, 159.0, 164.2, 200.4; MS (EI) *m/z*: 205 (8, M^+), 150 (100), 56 (20). HRMS (EI): M^+, found 205.1110, $C_{12}H_{15}NO_2$ requires 205.1103.

4-(6-Methoxy-2-methylpyridin-3-yl)octa-1,7-dien-4-ol (17)

A solution of allyl bromide (0.76 mL, 9.02 mmol) in Et_2O (10 mL) was added dropwise to a mixture of magnesium (0.22 g, 9.02 mmol) and a crystal of iodine in Et_2O (40 mL), at such a rate as to maintain a gentle reflux. The reaction mixture was then stirred under reflux for 1 h then cooled to 0 °C and a solution of ketone **16** (0.84 g, 4.10 mmol) in Et_2O (40 mL) added dropwise. The reaction mixture was stirred at 0 °C for 1 h then warmed to rt and quenched by the addition of saturated aqueous ammonium chloride (20 mL) and extracted with Et_2O (2 x 20 mL). The combined organic layers were dried over anhydrous magnesium sulfate, concentrated *in vacuo* and the residue purified by flash column chromatography eluting with Et_2O:hexane (1:9) to give the *title compound* (0.82 g, 79%) as a colourless oil; IR (neat) 3504, 3076, 2944, 1592, 1475, 1307, 1043; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 1.82–2.01 (m, 2H), 2.02–2.15 (m, 2H), 2.55 (dd, *J* = 14.0, 8.3 Hz, 1H), 2.61 (s, 3H), 2.85 (dd, *J* = 14.0, 6.3 Hz, 1H), 3.89 (s, 3H), 4.92-5.00 (m, 2H), 5.05-5.15 (m, 2H), 5.54-5.62 (m, 1H), 5.72-5.83 (m, 1H), 6.52 (d, *J* = 8.6 Hz, 1H), 7.73 (d, *J* = 8.6 Hz, 1H); ^{13}C-NMR (100MHz, $CDCl_3$) δ 24.9, 28.0, 39.8, 45.7, 53.6, 75.3, 106.4, 114.2, 119.5, 130.7, 133.1, 138.2, 138.3, 152.5, 161.5; MS (CI, NH_3) *m/z*: 248 (100, MH^+), 230 (60), 206 (55), 150 (30). HRMS (CI): MH^+, found 248.1647, $C_{15}H_{22}NO_2$ requires 248.1651.

1-(6-Methoxy-2-(phenylselenylmethyl)pyridin-3-yl)cyclohex-3-en-1-ol (8b)

A solution of *tert*-butyllithium (1.5 M in pentane, 0.73 mL, 1.10 mmol) was added to a solution of pyridinylcyclohexenol **13** (0.10 g, 0.46 mmol) and DMPU (0.12 mL, 1.01 mmol) in THF (4 mL) at -78 °C. The mixture was stirred at 78 °C for 30 min then a solution of phenylselenium chloride (0.11 g, 0.55 mmol) was added dropwise. The reaction mixture was stirred for a further 30 min then warmed to rt and quenched by the addition of saturated aqueous ammonium chloride (5 mL). The mixture was extracted with Et_2O (2 x 10 mL), the combined organic layers dried over anhydrous magnesium sulfate and concentrated *in vacuo*. The residue was purified by flash column chromatography using EtOAc:hexane (3:97) to give the *title compound* (0.13 g, 77%) as a yellow oil; IR (neat) 3447, 3014, 2923, 1591, 1475, 1313; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 1.78-1.82 (m, 2H), 2.15-2.19 (m, 2H), 2.47-2.51 (m, 2H), 3.72 (s, 3H), 4.53 (d, *J* = 11.2 Hz, 1H), 4.64 (d, *J* = 11.2 Hz, 1H), 5.68-5.76 (m, 2H), 6.52 (d, *J* = 8.7

Hz, 1H), 7.29-7.28 (m, 2H), 7.48 (d, *J* = 8.7 Hz, 1H), 7.62-7.68 (m, 2H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 23.1, 34.2, 34.3, 40.0, 53.3, 72.2, 108.1, 124.4, 126.7, 127.2, 128.8, 131.3, 131.8, 133.1, 137.3, 155.0, 161.8; MS (EI) *m/z*: 375 (49, M^+), 356 (33), 294 (19), 218 (100), 200 (97); HRMS (EI): M^+, found 375.0736, $C_{19}H_{21}NO_2{}^{80}Se$ requires 375.0738.

5-Methoxy-6-azatricyclo[7.3.1.0^{2,7}]trideca-2,4,6-trien-1-ol (18)

A solution of tributyltin hydride (0.06 mL, 0.18 mmol) and AIBN (0.0035 g, 0.02 mmol) in degassed benzene (40 mL) was added dropwise over 4.5 h, using a syringe pump, to a solution of selenide **8b** (0.04 g, 0.12 mmol) in degassed benzene (150 mL) under reflux. The reaction mixture was stirred under reflux for a further 2 h then cooled to rt and concentrated *in vacuo*. A saturated aqueous solution of potassium fluoride (50 mL) was added to the residue and the mixture stirred at rt overnight. The reaction mixture was extracted with Et_2O (3 x 50 mL) and the combined organic extracts washed with brine (50 mL), dried over anhydrous magnesium sulfate and concentrated *in vacuo*. The residue was purified by flash column chromatography eluting with EtOAc:hexane (1:9) to give compound **13** (0.02 g, 54%) as a colourless oil and the *title compound* (0.01 g, 46%) as a colourless oil; IR (neat) 3394, 2928, 1579, 1477, 1311; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 1.09-1.12 (m, 1H), 1.52-1.56 (m, 3H), 1.59-1.62 (m, 2H), 1.85 (dd, *J* = 11.5, 1.3 Hz, 1H), 1.90 (d, *J* = 11.5, 1H), 2.47-2.51 (m, 1H), 2.62 (d, *J* = 18.6 Hz, 1H), 3.15 (dd, *J* = 18.6, 7.1 Hz, 1H), 3.92 (s, 3H), 6.56 (d, *J* = 8.5 Hz, 1H), 7.73 (d, *J* = 8.5 Hz, 1H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 20.8, 29.9, 32.4, 38.0, 40.8, 41.6, 53.3, 70.9, 107.9, 130.1, 154.3, 162.5; MS (EI) *m/z*: 219 (8, M^+), 176 (100). HRMS (EI): M^+, found 219.1262, $C_{13}H_{17}NO_2$ requires 219.1259.

1-(6-Methoxy-2-(phenylselenylmethyl)pyridin-3-yl)-3-(1-(triethylsilyloxy)cyclohex-3-ene (19)

A mixture of alcohol **8b** (0.19 g, 0.51 mmol), imidazole (0.26 g, 3.81 mmol) and triethylsilyl chloride (0.51 mL, 2.54 mmol) in DMF (10 mL) was stirred at rt for 12 h. Water (10 mL) was added and the mixture extracted with Et_2O (2 x 15 mL). The combined organic layers were dried over anhydrous magnesium sulfate, concentrated *in vacuo* and the residue purified by flash column chromatography eluting with hexane to give the *title compound* (0.16 g, 63%) as a colourless oil; IR (neat) 2954, 2876, 1591, 1475, 1313, 1237, 1074; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 0.46 (t, *J* = 7.9 Hz, 9H), 0.81 (q, *J* = 7.9 Hz, 6H), 1.51-1.62 (m, 1H), 1.89-1.98 (m, 1H), 2.26-2.33 (m, 1H), 2.41-2.51 (m, 1H), 2.48-2.53 (m, 1H), 2.69-2.71 (m, 1H), 3.81 (s, 3H), 4.58 (d, *J* = 11.7 Hz, 1H), 4.89 (d, *J* = 11.7 Hz, 1H), 5.60-5.72 (m, 1H), 5.70-5.73 (m, 1H), 6.43 (d, *J* = 8.5 Hz, 1H), 7.20-7.29 (m, 2H), 7.63-7.65 (m, 2H), 7.30 (d, *J* = 8.5 Hz, 1H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 6.5, 7.0, 24.6, 33.4, 36.3, 40.0, 53.4, 75.0, 107.1, 124.7, 126.4, 127.9

(2C), 128.8, 130.4, 132.3, 137.7, 155.2, 161.9; MS (EI) *m/z*: 489 (20, M^+), 358 (55), 200 (100). HRMS (EI): M^+, found 489.1598, $C_{22}H_{35}NO_2Si^{80}Se$ requires 489.1602.

1-(Triethylsilyloxy)-5-methoxy-6-azatricyclo[7.3.1.0^{2,7}]trideca-2,4,6-triene (20)

A solution of tributyltin hydride (0.04 mL, 0.15 mmol) and AIBN (0.003 g, 0.02 mmol) in degassed benzene (40 mL) was added dropwise over 4.5 h, using a syringe pump, to a solution of selenide **19** (0.05 g, 0.10 mmol) in degassed benzene (150 mL) under reflux. The reaction mixture was stirred under reflux for a further 2 h then cooled to rt and concentrated *in vacuo*. A saturated aqueous solution of potassium fluoride (50 mL) was added to the residue and the mixture stirred at rt overnight. The reaction mixture was extracted with Et_2O (3 x 50 mL) and the combined organic extracts washed with brine (50 mL), dried over anhydrous magnesium sulfate and concentrated *in vacuo*. The residue was purified by flash column chromatography eluting with EtOAc:hexane (1:19) to give the *title compound* (0.03 g, 73%) as a colourless oil; IR (neat) 2934, 2874, 1594, 1476, 1419, 1312, 1122; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 0.57 (q, *J* = 7.9, 6H), 0.91 (t, *J* = 7.9, 9H), 1.41-1.70 (m, 6H), 1.90-2.05 (m, 2H), 2.41-2.50 (m, 1H), 2.65 (dd, *J* = 18.5, 8.4 Hz, 1H), 3.11 (dd, *J* = 18.5, 7.3 Hz, 1H), 3.91 (s, 3H), 6.54 (d, *J* = 8.5, 1H), 7.69 (d, *J* = 8.5, 1H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 6.2, 7.1, 52.2, 29.1, 29.6, 32.6, 38.1, 40.5, 42.7, 73.3, 107.7, 132.0, 136.0, 154.0, 162.3. MS (EI) *m/z*: 333 (13, M^+), 290 (100), 202 (22). HRMS (EI): M^+, found 333.2124, $C_{19}H_{31}NO_2Si$ requires 333.2124.

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