The Synthesis of Functionalised Bicyclo[3.3.1]nonanes Related to Huperzine A

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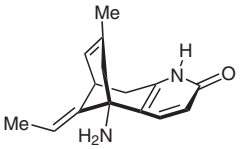
Abstract: Radical cyclisation-based synthetic routes to the core structure of huperzine A, are described. Cyclisation of (2-pyridyl)methyl radicals derived from two model [(2-phenylselenomethyl)-3-pyridyl]cyclohexenones, proceeds in 6-*exo-trig* mode to give bicyclo[3.3.1]nonanes. Cyclisation yields are related to the substitution pattern and relative stereochemistry about the enone ring. Cyclisation precursors were accessed by either conjugate addition of a (3-pyridyl)cuprate onto an enone or by Diels–Alder cycloaddition of a (3-pyridyl)-substituted alkene with Rawal's diene.

Key words: huperzine A, radical cyclisation, cuprate, selenium, Diels–Alder

Huperzine A (**1**; Figure 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, which exhibits potent inhibition of acetcholinesterase[3] and neuroprotective properties,[4] is a useful lead in the search for treatment of Alzheimer's disease. Indeed, clinical studies have shown that huperzine A effectively improves cognitive function in the elderly.[5] In addition, huperzine A has been used as a pretreatment for organophosphate poisoning.[6] The medicinal potential and unique structure of huperzine A have stimulated the development of a number of synthetic approaches.[7]

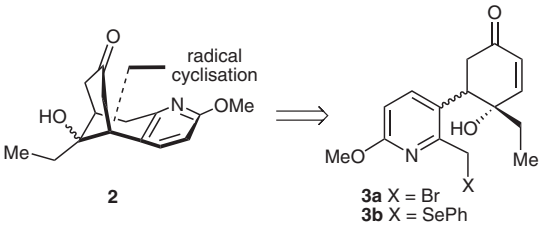


huperzine A (**1**)

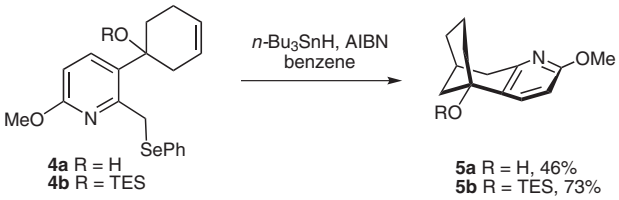
Figure 1

We have designed a strategy toward *des*-aminohuperzine A which centres on the synthesis of core structure target **2**. Our approach to **2** hinges on the conjugate, 6-*exo-trig* cyclisation of (2-pyridyl)methyl radicals derived from (3-pyridyl)cyclohexenones such as **3a**,**b** (Equation 1).

As the generation and reactions of (2-pyridyl)methyl radicals had not been reported prior to our studies, we initially focused on probing the validity of our disconnection by investigating the 6-*exo-trig* cyclisation of simplified model phenylselenides **4a**,**b** (Equation 2).[8]



Equation 1



Equation 2

These preliminary studies revealed that cyclisation yields dramatically improve on protection of the hydroxy moiety. We attributed this effect to increasing preference for the most reactive radical conformer, in which the pyridyl moiety is pseudo-axial, on increasing bulk of the geminal substituent.[8b]

While these initial investigations demonstrated that the (2-pyridyl)methyl radical can be formed quantitatively from phenylselenomethylpyridines under standard conditions, enone-based substrates more structurally akin to **3a**,**b**, were not studied. We now wish to report our studies on the radical cyclisation of a model (3-pyridyl)cyclohexenone and a more functionalised radical precursor.

This phase of our investigation initially focused on a synthesis of model enone **6**. Our approach to **6** centred on the functionalisation of known enone **7** (Scheme 1).[9] Stereoselective conjugate addition of the mixed cyano-Gilman cuprate, derived from 3-bromopyridine **8**,[10] onto **7** followed by retro-Diels–Alder reaction of the resulting adduct **9**, yielded enone **10**. Direct selenation at the (2-pyridyl)methyl position of **10**, using our previously developed deprotonation/selenation sequence,[8] was precluded by the presence of the carbonyl system. However, a more circuitous strategy, based on the nucleophilic displacement of a prefunctionalised 2-methylpyridine, proved successful. Thus, oxidation of **10** using *m*-chloroperoxybenzoic acid (MCPBA) was achieved selectively at the nitrogen, despite the presence of the enone moiety.[11] Rearrangement of the resulting *N*-oxide **11** occurred upon treatment with acetic anhydride to give acetoxymethylpy-

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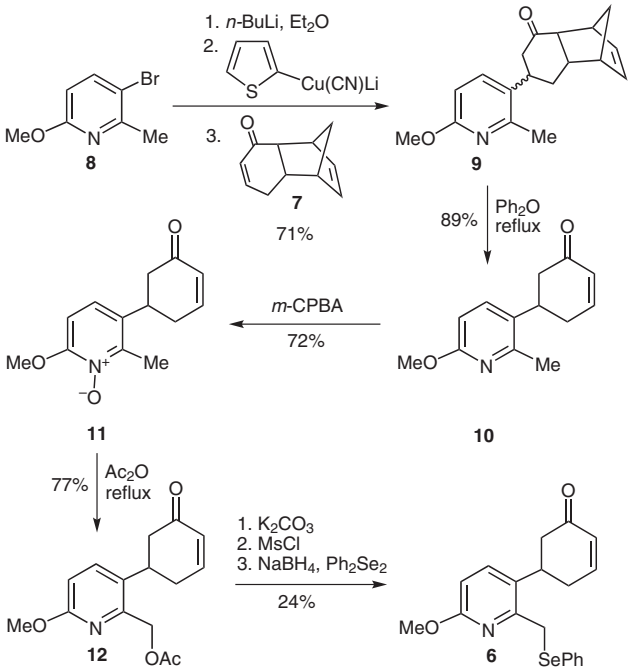
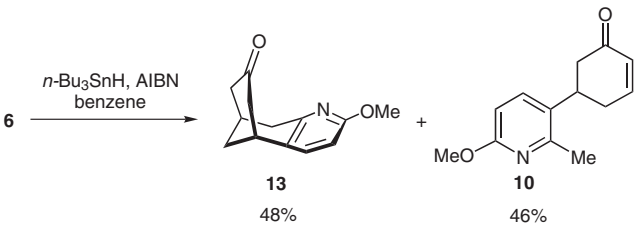
ridine **12**.[12] Finally, immediate treatment of the unstable alcohol derived from **12**, with mesyl chloride followed by sodium phenylselenolate, gave the model phenylselenide **6** in 24% yield over three steps.



Scheme 1

Subjecting model selenide **6** to the standard radical cyclisation conditions previously applied,[8] resulted in the formation of bicyclo[3.3.1]nonane **13** in moderate yield, along with reduction product **10** (Equation 3).



Equation 3

Recrystallisation of **13** from hexane yielded crystals of suitable quality for X-ray crystal structure analysis, which further confirmed the structure of this cyclisation product (Figure 2). The overall yield of **13** and reduction product **10** indicates that the (2-pyridyl)methyl radical was again generated quantitatively under these conditions. Moreover, incorporation of an enone as acceptor did not adversely affect the cyclisation, as the yield of **13** was found to be comparable to that of **5a**. The decrease in bicyclononane yield in moving from **4b** to **6** provides further proof that a bulky substituent geminal to the pyridine moiety on the cyclohexene ring, favours radical cyclisation.

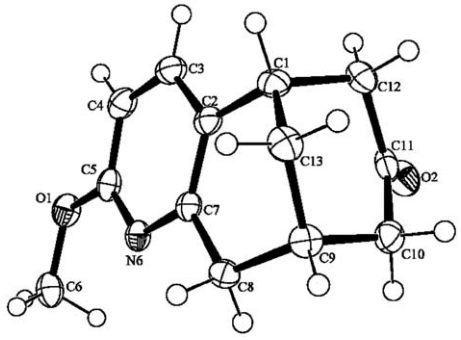
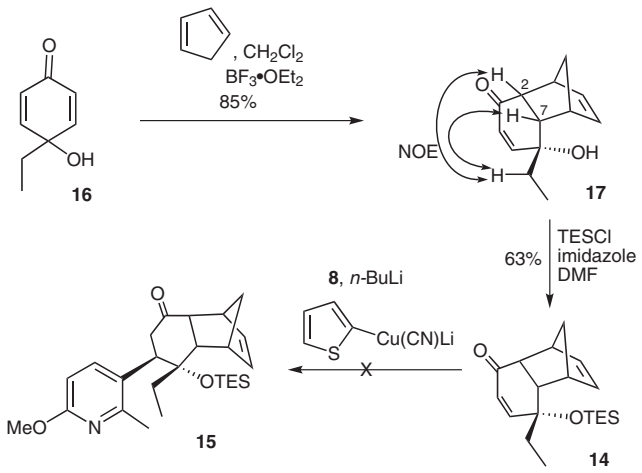


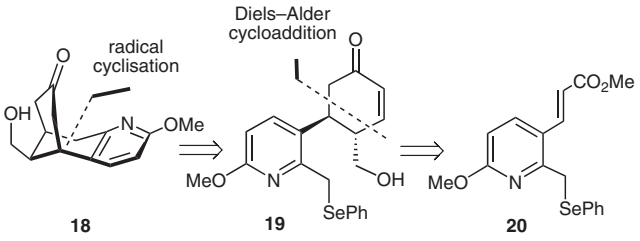
Figure 2 Molecular structure of **13** from the X-ray crystal structure analysis showing 50% probability displacement ellipsoids for non-hydrogen atoms and hydrogen atoms as arbitrary spheres. All bond lengths and angles are normal, and there are no hydrogen bonds in the crystal.

Despite the moderate yields obtained in the model study, we next investigated the synthesis and cyclisation of a more functionalised substrate in an effort to access the target core structure **2** of huperzine A. It was envisaged that O-protected **3b** could be accessed in a similar manner to that of **6**, by conversion of tricycle **14** into **15** followed by retro-Diels–Alder reaction and selenation. Compound **14** was prepared as a single diastereoisomer by cycloaddition of 4-hydroxycyclohexadienone **16**[13] with cyclopentadiene in the presence of $BF_3{\cdot}OEt_2$[14] followed by O-protection (Scheme 2). The stereochemistry of cycloaddition was confirmed by the observation of strong correlations between protons of the ethyl group and those at C2 and C7 in the 2D-NOESY NMR spectrum of **17**. The preferential addition of the diene *syn* to the oxygen at C4 of the dienophile has been previously observed in related systems and was attributed to stereoelectronic effects.[15] Unfortunately, all attempts at addition of the cuprate, derived from pyridine **8**, onto enone **15** failed, possibly due to steric hindrance around the β-position of the enone moiety.

This setback led us to revise our retrosynthesis and focus our attention on the synthesis of an alternate target, bicyclo[3.3.1]nonane **18**. We envisaged that the requisite cyclisation substrate **19** could be constructed by Diels–Alder



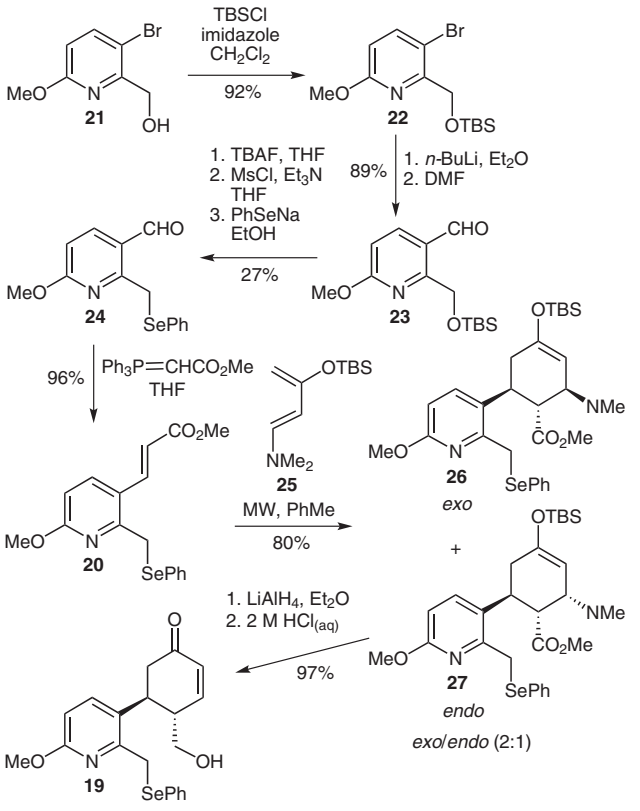
Scheme 2



Scheme 3

cycloaddition of an appropriate silyloxydiene with alkene **20** (Scheme 3).

The synthesis of alkene **20** commenced with O-protection of known alcohol **21** (Scheme 4).[16] Formylation of the resulting silyl ether **22** by lithium–halogen exchange followed by addition of DMF, yielded aldehyde **23**. Deprotection of the silyl ether, followed by mesylation/selenation gave phenylselenide **24**, which was converted into *trans*-alkene **20** on treatment with methyl(triphenylphosphoranylidene)acetate. After some experimentation, it was discovered that optimum yields of Diels–Alder cycloadducts were obtained on microwave irradiation of a mixture of **20** and Rawal's diene **25**[17] in toluene, to give a mixture of *exo*/*endo* isomers **26** and **27** in an overall yield of 80%. Assignment of stereochemistry to cycloadducts **26**/**27** was readily achieved on examination of the ^{1}H NMR coupling constants between H2 and H3 (Figure 3). Finally, reduction of this mixture of isomers with lithium aluminium hydride, followed by acidic work-up, afforded cyclisation substrate **19**.



Scheme 4

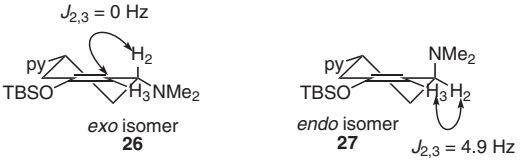
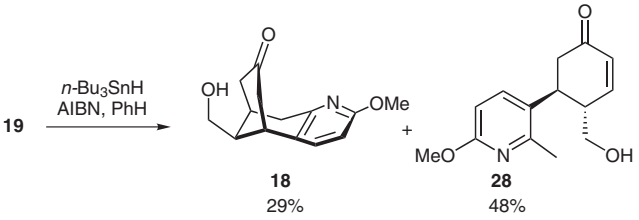


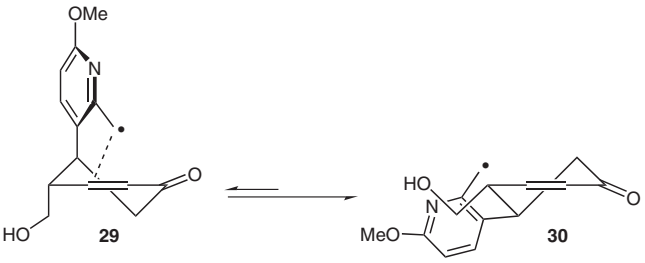
Figure 3

The radical generated from selenide **19** under standard conditions underwent 6-*exo-trig* cyclisation to give bicyclononane **18** in 29% yield, along with reduction product **28** in 48% yield (Equation 4).



Equation 4

The low cyclisation yield can be attributed to the *trans*-substitution pattern across the enone ring. In this instance, the most reactive conformer **29** contains both enone substituents in pseudo-axial positions and is therefore of much higher energy than the preferred diequatorial conformer **30** (Equation 5). The results reported herein, in combination with those obtained in earlier studies,[8] indicates radical cyclisation yields should improve on using the *cis*-isomer of **19** and should increase even further on incorporation of a bulky moiety geminal to the pyridine group on the enone ring.



Equation 5

In conclusion, we have shown that cyclisation of functionalised (2-pyridyl)methyl radicals proceeds in 6-*exo-trig* mode onto cyclohexenone-based acceptors, to give bicyclo[3.3.1]nonanes closely related to huperzine A. Moreover, this study serves to further support our postulate that cyclisation yields are affected by the position and relative stereochemistry of substituents about the cyclohexenone ring. Thus, this study has proved to be of great value in illuminating future avenues of investigation which will focus on the synthesis of other substituted cyclisation precursors in an attempt to access the fully functionalised core structure of huperzine A in high overall yield.

All reactions were performed under a nitrogen atmosphere using oven-dried glassware. All solvents were dried by distillation from CaH_2 (CH_2Cl_2, $CHCl_3$, DMF, toluene, benzene) or sodium-benzophenone (THF and Et_2O). 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 TMS peak (δ = 0.00 ppm). ^{1}H NMR values are reported as follows: chemical shift (d), multiplicity (s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet), coupling constant (*J*), relative integral and assignment. 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%). For the X-ray diffraction experiment, a suitable single crystal was placed in a cold N_2 gas stream of the Siemens SMART diffractometer (Mo K_α radiation, l = 0.71073 Å). The structure was solved by direct methods.[18] All non-hydrogen atoms were refined anisotropically.[18] A riding model was employed in the refinement of the hydrogen atoms.

(2*S,5*R**,7*S**)-5-(6′-Methoxy-2′-methylpyridin-3′-yl)tricyclo[6.2.1^{2,7}]undec-9-en-3-one (9)**

A solution of *n*-BuLi (1.43 M in hexane, 39.0 mL, 52.3 mmol) was added dropwise to a solution of thiophene (4.13 mL, 52.3 mmol) in THF (30 mL) at –30 °C. The reaction mixture was stirred at –30 °C for 30 min then added dropwise to a stirred suspension of CuCN (4.26 g, 52.3 mmol) in THF (50 mL) at –78 °C. The resulting slurry was warmed to r.t. to give the thienylcyanocuprate as a tan coloured solution.

A solution of *n*-BuLi (1.43 M in hexane, 39.0 mL, 52.3 mmol) was added dropwise to a solution of bromopyridine **8** (10.5 g, 52.3 mmol) in Et_2O (110 mL) at –78 °C. The reaction mixture was warmed to –40 °C and stirred at this temperature for 1 h. The reaction mixture was re-cooled to –78 °C and the thienylcyanocuprate prepared above was added dropwise. The mixture was then warmed to –40 °C and stirred at this temperature for 30 min. A solution of enone **7** (9.21 g, 57.5 mmol) in Et_2O was then added dropwise. The reaction mixture was slowly warmed to r.t. and stirred for a further 2 h. A mixture of sat. aq NH_4Cl and sat. aq NH_4OH (1:9, 250 mL) was added. The organic layer was separated and the aqueous layer further extracted with Et_2O (3 × 250 mL). The combined organic extracts were dried ($MgSO_4$), the solvent removed under reduced pressure and the residue purified by column chromatography on silica gel (Et_2O–hexane, 3:97), to afford compound **9**.

Yield: 10.56 g (71%); colourless solid; mp 83–84 °C.

IR (film): 2961, 1699, 1476, 1305, 1041 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.32 (d, *J* = 8.4 Hz, 1 H, H-11$_a$), 1.43–1.70 (m, 1 H, H-11$_b$), 1.67–1.84 (m, 1 H, H-6$_a$), 1.97–2.19 (m, 1 H, H-6$_b$), 2.32–3.64 (m, 2 H, H-4), 2.38 (s, 3 H, CH_3), 2.65–2.69 (m, 1 H, H-7), 2.85 (d, *J* = 4.1 Hz, 1 H, H-1), 2.89–3.16 (m, 1 H, H-8), 3.18–3.34 (m, 1 H, H-5), 3.41–3.55 (m, 1 H, H-2), 3.89 (s, 3 H, OCH_3), 6.25–6.32 (m, 2 H, H-9, H-10), 6.53 (d, *J* = 8.5 Hz, 1 H, H-5′), 7.25 (d, *J* = 8.5 Hz, 1 H, H-4′).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 21.8, 32.3, 33.9, 37.2, 46.0, 46.7, 48.7, 49.4, 51.4, 53.2, 107.5, 129.6, 135.0, 135.8, 138.3, 153.3, 161.7, 213.3.

MS (EI, 70 eV): *m*/*z* (%) = 283 (38) [M$^+$], 216 (84), 149 (100), 66 (33).

HRMS-EI: *m*/*z* [M$^+$] calcd for $C_{18}H_{21}NO_2$: 283.1572; found: 283.1563.

5-(6′-Methoxy-2′-methylpyridin-3′-yl)cyclohex-2-en-1-one (10)

A solution of adduct **9** (10.6 g, 37.3 mmol) in Ph_2O (40 mL) was stirred under reflux for 45 min. The mixture was then cooled to r.t. and the solvent was removed under reduced pressure. The residue was purified by column chromatography on silica gel (Et_2O–hexane) to afford compound **10**.

Yield: 7.23 g (89%); orange solid; mp 71–78 °C.

IR (film): 2943, 1681, 1477, 1307, 1040 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.47 (s, 3 H, CH_3), 2.53–2.66 (m, 2 H, H-4), 2.60–2.87 (m, 2 H, H-6), 3.49–3.70 (m, 1 H, H-5), 3.91 (s, 3 H, OCH_3), 6.13 (dd, *J* = 10.1, 5.7 Hz, 1 H, H-2), 6.58 (d, *J* = 8.3 Hz, 1 H, H-5′), 7.05 (ddd, *J* = 10.1, 5.7, 2.5 Hz, 1 H, H-3), 7.43 (d, *J* = 8.5 Hz, 1 H, H-4′).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 21.8, 32.8, 36.0, 44.4, 53.3, 107.9, 128.4, 129.8, 136.1, 149.4, 153.3, 162.0, 198.9.

MS (EI, 70 eV): *m*/*z* (%) = 217 (44) [M$^+$], 149 (100), 120 (21).

HRMS-EI: *m*/*z* [M$^+$] calcd for $C_{13}H_{15}NO_2$: 217.1103; found: 217.1097.

6-Methoxy-3-(1-oxocyclohex-2′-en-5′-yl)-2-methylpyridine-1-oxide (11)

A solution of MCPBA (8.62 g, 49.9 mmol) in $CHCl_3$ (50 mL) was added to a solution of enone **10** (7.2 g, 33.3 mmol) in $CHCl_3$ (300 mL) at r.t. and the reaction mixture was stirred for 22 h. The solvent was removed under reduced pressure and the residue was purified by column chromatography on silica gel (MeOH–CH_2Cl_2, 1:99), to afford compound **11**.

Yield: 5.55 g (72%); yellow solid; mp 146–149 °C.

IR (film): 3402, 2951, 1671, 1605, 1508, 1319, 1082 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.39–2.45 (m, 2 H, H-4′), 2.49 (s, 3 H, CH_3), 2.52–2.69 (m, 2 H, H-6′), 3.43–3.53 (m, 1 H, H-5′), 3.98 (s, 3 H, OCH_3), 6.01 (dd, *J* = 10.2, 2.1 Hz, 1 H, H-2′), 6.81 (d, *J* = 8.8 Hz, 1 H, H-5), 7.01 (ddd, *J* = 10.2, 5.6, 2.5 Hz, 1 H, H-3′), 7.32 (d, *J* = 8.8 Hz, 1 H, H-4).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 21.8, 32.8, 35.9, 45.3, 53.3, 107.6, 128.4, 129.4, 136.3, 149.4, 153.3, 162.0, 197.7.

MS (EI, 70 eV): *m*/*z* (%) = 233 (65) [M$^+$], 46 (100), 148 (92), 68 (71).

HRMS-EI: *m*/*z* [M$^+$] calcd for $C_{13}H_{15}NO_3$: 233.1052; found: 233.1058.

6-Methoxy-3-(1-oxocyclohex-2′-en-5′-yl)-2-acetoxymethylpyridine-1-oxide (12)

A solution of *N*-oxide **11** (5.55 g, 24.8 mmol) in Ac_2O (100 mL) was stirred at 120 °C for 22 h. The reaction was cooled to r.t. and the solvent was removed under reduced pressure. The residue was dissolved in Et_2O (50 mL) and sat. aq $NaHCO_3$ (100 mL) was added. The organic layer was separated and the aqueous layer further extracted with Et_2O (3 × 50 mL). The combined organic extracts were washed with H_2O (150 mL), dried ($MgSO_4$) and the solvent removed under reduced pressure. The residue was purified by column chromatography on silica gel (EtOAc–hexane, 1:4), to afford compound **12**.

Yield: 5.24 g (77%); colourless oil.

IR (film): 2946, 1740, 1679, 1599, 1481, 1233, 1043 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 2.12 (s, 3 H, $COCH_3$), 2.52–2.54 (m, 2 H, H-6′), 2.60–2.83 (m, 2 H, H-4′), 3.49 (m, 1 H, H-5′), 3.95 (s, 3 H, OCH_3), 5.21 [d, *J* = 3.8 Hz, 2 H, $CH_2OC(O)CH_3$], 6.18 (dt, *J* = 10.2, 1.7 Hz, 1 H, H-2′), 6.75 (d, *J* = 8.6 Hz, 1 H, H-5), 7.04 (ddd, *J* = 10.2, 5.4, 2.7 Hz, 1 H, H-3′), 7.56 (d, *J* = 8.6 Hz, 1 H, H-4).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 20.9, 33.3, 35.4, 44.8, 53.5, 65.3, 111.2, 129.9, 130.0, 136.9, 149.4, 153.3, 169.9, 187.3, 193.2.

MS (EI, 70 eV): *m*/*z* (%) = 275 (16) [M^+], 232 (37), 215 (93), 164 (100), 43 (53).

HRMS-EI: *m*/*z* [M^+] calcd for $C_{15}H_{17}NO_4$: 275.1158; found: 275.1161.

5-[6′-Methoxy-2′-(phenylselenylmethyl)pyridine-3-yl]cyclohex-2-en-1-one (6)

Solid K_2CO_3 (0.53 g, 3.81 mmol) was added in one portion to a solution of acetate **12** (0.50 g, 1.82 mmol) in MeOH–H_2O (1:1, 50 mL) at r.t. and the reaction mixture was stirred for 1 h. The solvent was removed under reduced pressure and the solid residue was dissolved in $CHCl_3$–H_2O (1:1, 50 mL). The layers were separated and the aqueous phase extracted with $CHCl_3$ (2 × 50 mL). The combined organic extracts were dried ($MgSO_4$) and the solvent removed under reduced pressure. The residue was purified by column chromatography on silica gel (EtOAc–hexane, 2:3), to afford the alcohol. MsCl (0.1 mL, 1.39 mmol) was added to a solution of the alcohol then Et_3N (0.39 mL, 2.79 mmol) in THF (25 mL) at 0 °C, and the reaction mixture was stirred at this temperature for 30 min. The mixture was warmed to r.t. and stirred for an additional 30 min then filtered. The filtrate was added to a solution of PhSeNa [prepared from Ph_2Se_2 (0.18 g, 0.59 mmol) and $NaBH_4$ (0.04 g, 1.07 mmol) in EtOH (25 mL)], at –30 °C. The reaction mixture was warmed to r.t. and stirred for 2 h. Sat. aq $NaHCO_3$ (10 mL) was added and the layers separated. The aqueous phase was extracted with Et_2O (2 × 25 mL) and the combined organic extracts were dried ($MgSO_4$) and the solvent removed under reduced pressure. The residue was purified by column chromatography on silica gel (Et_2O–hexane, 1:99), to afford compound **6**.

Yield: 0.16 g (24%); yellow oil.

IR (film): 2940, 1678, 1595, 1478, 1316, 1275, 1032 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 2.21–2.51 (m, 2 H, H-6), 2.40–2.49 (m, 2 H, H-4), 3.32–3.52 (m, 1 H, H-5), 3.79 (s, 3 H, OCH_3), 4.20 (s, 2 H, CH_2SePh), 6.32 (dd, *J* = 10.2, 2.1 Hz, 1 H, H-2), 6.61 (d, *J* = 8.6 Hz, 1 H, H-5′), 6.96 (dd, *J* = 10.2, 2.8 Hz, 1 H, H-3), 7.18–7.30 (m, 3 H, H-Ar), 7.43 (d, *J* = 8.6 Hz, 1 H, H-4′), 7.53–7.58 (m, 2 H, H-Ar).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 30.9, 33.0, 35.6, 44.7, 52.1, 109.4, 127.3, 128.3, 128.5, 129.8 (2 × C), 133.7, 136.7, 149.1, 152.9, 161.6, 198.4.

MS (EI, 70 eV): *m*/*z* (%) = 373 (15) [M^+], 292 (100), 251 (20), 216 (35), 183 (62), 174 (58).

HRMS-EI: *m*/*z* [M^+] calcd for $C_{19}H_{19}NO_2{}^{80}Se$: 373.0581: found 373.0580.

(1*R,9*S**)-5-Methoxy-6-azatricyclo[7.3.1.0^{2,7}]trideca-2,4,6-trien-11-one (13)**

A solution of *n*-Bu_3SnH (0.07 mL, 0.27 mmol) and AIBN (0.01 g, 0.05 mmol) in degassed benzene (80 mL) was added dropwise over 4 h using a syringe pump, to a solution of selenide **6** (0.10 g, 0.27 mmol) in degassed benzene (300 mL) under reflux. The reaction mixture was stirred under reflux for a further 2 h then cooled to r.t. and the solvent was removed under reduced pressure. Sat. aq KF (25 mL) was added to the residue and the mixture was stirred at r.t. overnight. The reaction mixture was extracted with Et_2O (3 × 25 mL) and the combined organic extracts were washed with brine (25 mL), dried ($MgSO_4$) and the solvent removed under reduced pressure. The residue was purified by flash column chromatography on silica gel (EtOAc–hexane, 1:9), to afford compound **13** (0.03 g, 48%) as a white solid. Further elution provided compound **10** (0.031 g, 46%) as an orange solid. Recrystallisation of compound **13** from hexane yielded crystals suitable for X-ray crystallography.

Data for compound **13**:

Mp 97–99 °C.

IR (film): 2924, 1710, 1600, 1477, 1421, 1311, 1259, 1031 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 2.05–2.30 (m, 2 H, H-13), 2.38–2.43 (m, 2 H, H-10), 2.61–2.69 (m, 2 H, H-12), 2.65 (d, *J* = 18.4 Hz, 1 H, H-8_a), 2.82–2.88 (m, 1 H, H-9), 3.10 (dd, *J* = 18.4, 6.6 Hz, 1 H, H-8_b), 3.32–3.42 (m, 1 H, H-1), 3.86 (s, 3 H, OCH_3), 6.50 (d, *J* = 8.8 Hz, 1 H, H-4), 7.19 (d, *J* = 8.8 Hz, 1 H, H-3).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 30.3, 30.5, 34.9, 38.8, 48.9, 49.6, 53.2, 108.9, 126.5, 138.9, 151.2, 162.7, 210.5.

MS (EI, 70 eV): *m*/*z* (%) = 217 (40) [M^+], 160 (100), 228 (20).

HRMS-EI: *m*/*z* [M^+] calcd for $C_{13}H_{15}NO_2$: 217.1103; found: 217.1101.

Anal. Calcd for $C_{13}H_{15}NO_2$: C, 71.9; H, 7.0; N, 6.45; O, 14.7. Found: C, 72.0; H, 6.9; N, 6.5; O, 14.6.

X-ray Crystal Structure Analysis[19]

A single crystal with dimensions 0.34 × 0.20 × 0.12 mm was obtained by slow evaporation of **13** from hexane solution. Empirical formula: $C_{13}H_{15}NO_2$; M_r = 217.26; monoclinic; space group $P2_1/c$ (no. 14); *a* = 12.6525(1), *b* = 5.7506(1), *c* = 15.6757(1) Å, *β* = 104.545(1)°; *V* = 1104.00(2) $Å^3$; *Z* = 4; ρ_{calcd} = 1.307 mg/cm^3; μ = 0.088 mm^{-1}; *F*(000) = 217.26, θ range 3.71–25.04°; 6550 collected reflections, 1938 unique reflections (R_{int} = 0.0231); refinement by full-matrix least-squares methods on F^2 for all unique reflections; *S* = 1.050, R_1 = 0.0373 [$I > 2\sigma(I)$], wR_2 (all data) = 0.0972; max/min electron density 0.191/–0.199 e $Å^{-3}$.

(2*S,6*S**,7*R**)-6-Ethyl-6-hydroxytricyclo[6.2.1.0^{2,7}]undeca-4,9-dien-3-one (17)**

Freshly distilled cyclopentadiene (2 mL, 37.4 mmol) and $BF_3{\cdot}OEt_2$ (2.70 mL, 21.3 mmol), were added to a solution of alcohol **16**[11] in CH_2Cl_2 (20 mL) at –78 °C. The reaction mixture was stirred at this temperature for 30 min and sat. aq $NaHCO_3$ (50 mL) was added. The layers were separated, the organic layer dried ($MgSO_4$) and the solvent removed under reduced pressure. The residue was purified by column chromatography on silica gel (EtOAc–hexane), to afford compound **17**.

Yield: 1.69 g (85%); colourless crystals; mp 70–71 °C.

IR (film): 3418, 2968, 2938, 1651, 1257, 1136, 737 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 0.88 (t, *J* = 8.4 Hz, 3 H, CH_2CH_3), 1.35 (d, *J* = 8.4 Hz, 1 H, H-11_a), 1.45 (dt, *J* = 8.4, 1.7 Hz, 1 H, H-11_b), 1.70 (q, *J* = 7.4 Hz, 1 H, CH_2CH_3), 2.71 (ddd, *J* = 8.8, 3.4, 0.9 Hz, 1 H, H-7), 2.98 (dd, *J* = 8.8, 4.3 Hz, 1 H, H-2), 3.18–3.24 (m, 1 H, H-8), 3.33–3.38 (m, 1 H, H-1), 5.84 (dd, *J* = 5.5, 2.9 Hz, 1 H, H-10), 5.86 (d, *J* = 10.3 Hz, 1 H, H-4), 6.15 (dd, *J* = 5.5, 2.8 Hz, 1 H, H-9), 6.38 (dd, *J* = 10.3, 0.9 Hz, 1 H, H-5).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 7.7, 39.9, 46.0, 46.8, 48.5, 48.8, 50.7, 72.2, 129.3, 134.7, 135.2, 153.1, 200.3.

MS (EI, 70 eV): *m*/*z* (%) = 204 (8) [M^+], 139 (25), 66 (100).

HRMS-EI: *m*/*z* [M^+] calcd for $C_{13}H_{16}O_2$: 204.1150; found: 214.1145.

(2*S,6*S**,7*R**)-6-Triethylsilyloxy-6-ethyltricyclo[6.2.1.0^{2,7}]undeca-4,9-dien-3-one (14)**

A solution of alcohol **17** (1.60 g, 7.84 mmol), imidazole (4.00 g, 58.8 mmol) and Et_3SiCl (2.63 mL, 16.0 mmol) in DMF (50 mL) was stirred at r.t. for 12 h. H_2O (50 mL) was added and the reaction mixture was extracted with Et_2O (3 × 50 mL). The combined organic extracts were dried ($MgSO_4$), the solvent was removed under reduced pressure and the residue was purified by column chromatography on silica gel (Et_2O–hexane, 1:9), to afford compound **14**.

Yield: 1.58 g (63%); colourless oil.

IR (film): 2957, 2876, 1672, 1459, 1134, 1088, 1055, 740 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.65 (q, *J* = 7.7 Hz, 6 H, SiC*H*$_2$CH$_3$), 0.79 (t, *J* = 7.4 Hz, 3 H, CH$_2$C*H*$_3$), 1.03 (t, *J* = 7.7 Hz, 9 H, SiCH$_2$C*H*$_3$), 1.30 (d, *J* = 8.4 Hz, 1 H, H-11$_a$), 1.38 (dt, *J* = 8.4, 1.7 Hz, 1 H, H-11$_b$), 1.58–1.80 (m, 2 H, C*H*$_2$CH$_3$), 2.65 (ddd, *J* = 8.9, 3.5, 1.1 Hz, 1 H, H-7), 2.88 (dd, *J* = 8.9, 3.5 Hz, 1 H, H-2), 3.17–3.24 (m, 1 H, H-8), 3.27–3.34 (m, 1 H, H-1), 5.78 (dd, *J* = 5.6, 2.9 Hz, 1 H, H-10), 5.86 (d, *J* = 10.4 Hz, 1 H, H-4), 6.15 (dd, *J* = 5.6, 2.8 Hz, 1 H, H-9), 6.22 (dd, *J* = 10.4, 1.1 Hz, 1 H, H-5).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 7.1 (2 × C), 8.6, 39.4, 47.1, 47.8, 49.2, 48.3, 50.8, 75.7, 129.4, 133.7, 136.3, 152.6, 201.4.

MS (EI, 70 eV): *m*/*z* (%) = 318 (4) [M$^+$], 289 (20), 223 (100), 115 (32).

HRMS-EI: *m*/*z* [M$^+$] calcd for $C_{19}H_{30}O_2Si$: 318.2005; found: 318.2015.

3-Bromo-2-[(*tert*-butyldimethylsilyloxy)methyl]-6-methoxypyridine (22)

A solution of alcohol **21**[16] (1.57 g, 7.15 mmol), imidazole (1.94 g, 28.6 mmol), and TBSCl (3.30 g, 21.4 mmol) in CH_2Cl_2 (30 mL) was stirred at r.t. for 3 h. H_2O (20 mL) was added and the layers separated. The aqueous phase was extracted with CH_2Cl_2 (3 × 20 mL) and the combined organic extracts were dried ($MgSO_4$) and the solvent removed under reduced pressure. The residue was purified by column chromatography on silica gel (Et_2O–hexane, 1:19), to afford compound **22**.

Yield: 2.27 g (92%); colourless oil.

IR (film): 2956, 1643, 1581, 1252, 1036 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.12 [s, 6 H, Si(CH$_3$)$_2$], 0.94 [s, 9 H, Si(CH$_3$)$_2$C(C*H*$_3$)$_3$], 3.94 (s, 3 H, OCH$_3$), 4.81 (s, 2 H, CH$_2$OTBS), 6.54 (d, *J* = 8.6 Hz, 1 H, H-5), 7.63 (d, *J* = 8.6 Hz, 1 H, H-4).

^{13}C NMR (75 MHz, $CDCl_3$): δ = –5.1, 18.5, 25.9, 53.7, 65.9, 110.6, 111.2, 142.5, 154.6, 162.7.

MS (EI, 70 eV): *m*/*z* (%) = 332 (48) [M$^+$], 276 (100), 200 (22), 154 (63), 136 (52), 89 (22).

HRMS-EI: *m*/*z* [M$^+$] calcd for $C_{13}H_{23}{}^{79}BrNO_2$: 332.0681; found: 332.0674.

2-[*tert*-Butyldimethylsilyloxy)methyl]-3-formyl-6-methoxypyridine (23)

A solution of *n*-BuLi (1.5 M in hexane, 4.31 mL, 6.03 mmol) was added dropwise to a solution of bromide **22** (2.00 g, 6.03 mmol) in Et_2O (150 mL) at –78 °C and the mixture was stirred at this temperature for 1 h. DMF (1.40 mL, 18.1 mmol) was added in one portion and the reaction mixture was warmed to r.t. and stirred for 30 min. Sat. aq NH_4Cl (50 mL) was added and the layers separated. The aqueous phase was further extracted with Et_2O (2 × 20 mL) and the combined organic extracts were dried ($MgSO_4$) and the solvent removed under reduced pressure. The residue was purified by column chromatography on silica gel (Et_2O–hexane, 1:19), to afford compound **23**.

Yield: 1.50 g (89%); colourless oil.

IR (film): 2954, 1691, 1594, 1460, 1327, 1085 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.10 [s, 6 H, Si(CH$_3$)$_2$], 0.89 [s, 9 H, Si(CH$_3$)$_2$C(C*H*$_3$)$_3$], 4.01 (s, 3 H, OCH$_3$), 5.04 (s, 2 H, CH$_2$OTBS), 6.75 (d, *J* = 8.6 Hz, 1 H, H-5), 8.10 (d, *J* = 8.6 Hz, 1 H, H-4), 10.0 (s, 1 H, CHO).

^{13}C NMR (75 MHz, $CDCl_3$): δ = –5.3, 18.5, 25.8, 54.0, 65.6, 110.3, 124.5, 139.1, 162.3, 165.9, 190.2.

MS (CI, NH_3): *m*/*z* (%) = 282 (100) [MH$^+$], 224 (42).

HRMS-FAB: *m*/*z* [M$^+$] calcd for $C_{14}H_{24}NO_3Si$: 282.1526; found: 282.1524.

6-Methoxy-2-(phenylselenylmethyl)nicotinaldehyde (24)

A solution of TBAF (1 M in THF, 13.6 mL, 13.6 mmol) was added in one portion to a solution of silyl ether **23** (3.48 g, 12.4 mmol) in THF (100 mL) at 0 °C. The mixture was stirred at this temperature for 1 h and then sat. aq NH_4Cl (20 mL) was added. The reaction mixture was extracted with $CHCl_3$ (2 × 25 mL), the combined organic extracts were dried ($MgSO_4$) and the solvent was removed under reduced pressure. The residue was purified by column chromatography on silica gel (EtOAc–hexane, 3:7), to afford the alcohol as a yellow oil. MsCl (1.36 mL, 17.57 mmol) was added to a solution of the alcohol (2.26 g, 13.53 mmol) then Et_3N (4.90 mL, 35.1 mmol) in THF (50 mL) at 0 °C, and the reaction mixture was stirred at this temperature for 30 min then warmed to r.t. The mixture was filtered and the filtrate was added to a solution of PhSeNa [prepared from Ph_2Se_2 (2.15 g, 6.89 mmol) and $NaBH_4$ (0.51 g, 13.5 mmol) in EtOH (50 mL)], at –30 °C. The mixture was warmed to r.t. and stirred for 2 h then sat. aq $NaHCO_3$ (10 mL) was added and the reaction mixture was extracted with Et_2O (2 × 25 mL). The combined organic extracts were dried ($MgSO_4$), and the solvent was removed under reduced pressure. The residue was purified by column chromatography (Et_2O–hexane), to afford compound **24**.

Yield: 1.06 g (27%); yellow oil.

IR (film): 2925, 1686, 1590, 1479, 1320, 1022 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 3.65 (s, 3 H, OCH$_3$), 4.32 (s, 2 H, CH$_2$SePh), 6.45 (d, *J* = 8.5 Hz, 1 H, H-5), 7.01–7.12 (m, 3 H, H-Ar), 7.38–7.40 (m, 2 H, Ar-H), 7.75 (d, *J* = 8.5 Hz, 1 H, H-4), 9.75 (s, 1 H, CHO).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 30.1, 53.6, 109.4, 122.7, 126.5, 128.4, 129.3, 134.0, 141.2, 160.9, 165.2, 186.6.

MS (EI, 70 eV): *m*/*z* (%) = 307 (22) [M$^+$], 150 (100).

HRMS-EI: *m*/*z* [M$^+$] calcd for $C_{14}H_{13}NO_2{}^{80}Se$: 307.0112; found: 307.0104.

(*E*)-Methyl 3-[6′-Methoxy-2′-(phenylselenylmethyl)pyridine-3′-yl]acrylate (20)

A solution of aldehyde **24** (1.06 g, 3.64 mmol) and methyl(triphenylphosphoranylidene)acetate (1.74 g, 5.19 mmol) in THF (100 mL) was stirred at r.t. for 12 h. The solvent was removed under reduced pressure and the residue purified by column chromatography on silica gel (Et_2O–hexane, 1:4), to afford compound **20**.

Yield: 1.19 g (96%); white solid; mp 70–71 °C.

IR (film): 2947, 1711, 1591, 1478, 1308, 1170 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 3.78 (s, 3 H, CO$_2$CH$_3$), 3.80 (s, 3 H, OCH$_3$), 4.27 (s, 2 H, CH$_2$SePh), 6.15 (d, *J* = 15.8 Hz, 1 H, H-2), 6.60 (d, *J* = 8.6 Hz, 1 H, H-5′), 7.10–7.25 (m, 3 H, H-Ar), 7.45–7.55 (m, 2 H, H-Ar), 7.70 (d, *J* = 8.6 Hz, 1 H, H-4′), 7.75 (d, *J* = 15.8 Hz, 1 H, H-3).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 30.9, 51.5, 53.5, 109.9, 117.4, 121.1, 127.5, 128.7, 129.3, 134.4, 126.6, 129.4, 155.9, 163.9, 166.9.

MS (EI, 70 eV): *m/z* (%) = 363 (58) [M$^+$], 206 (65), 174 (58), 146 (100).

HRMS-EI: *m/z* [M$^+$] calcd for $C_{17}H_{17}NO_3{}^{80}Se$: 363.0373; found: 363.0378.

(1*R,2*R**,6*S**)-1-Methoxycarbonyl-4-(*tert*-butyldimethylsilyloxy)-2-(*N*,*N*-dimethylamino)-6-[6′-methoxy-2′-(phenylselenylmethyl)pyridine-3′-yl)cyclohex-3-ene (26) and (1*R**,2*S**,6*S**)-1-Methoxycarbonyl-4-(*tert*-butyldimethylsilyloxy)-2-(*N*,*N*-dimethylamino)-6-[6′-methoxy-2′-(phenylselenylmethyl)pyridine-3′-yl]cyclohex-3-ene (27)**

A 10 mL microwave reaction vial was charged with alkene **20** (0.40 g, 1.10 mmol), diene **25** (0.38 g, 1.60 mmol) and toluene (6 mL). The vial was sealed with a cap containing a silicon septum, loaded into the cavity of a focused microwave reactor (Discover® CEM, 300W) and heated at 200 °C for 10 h (microwave reactor conditions: Power: 250 kW, ramp time: 20 min). The reaction mixture was cooled to r.t. and the solvent was removed under reduced pressure. The residue was purified by column chromatography on silica gel (Et_2O–hexane, 1:9), to afford compounds **26** and **27**.

Data for *exo*-Isomer **26**

Yield: 0.34 g (53%); yellow oil.

IR (film): 2949, 2856, 1735, 1595, 1479, 1316, 1193, 1032, 833 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.18 [s, 3 H, $Si(CH_3)_2$], 0.19 [s, 3 H, $Si(CH_3)_2$], 0.93 [s, 9 H, $Si(CH_3)_2C(CH_3)_3$], 2.10–2.21 (m, 2 H, H-5), 2.30 [s, 6 H, $N(CH_3)_2$], 2.68 (t, *J* = 10.5 Hz, 1 H, H-1), 3.35–3.40 (m, 1 H, H-6), 3.37 (s, 3 H, CO_2CH_3), 3.72–3.80 (m, 3 H, H-2), 3.76 (s, 3 H, OCH_3), 4.22 (d, *J* = 12.7 Hz, 1 H, CH_aSePh), 4.61 (d, *J* = 12.7 Hz, 1 H, CH_bSePh), 4.91 (s, 1 H, H-3), 6.57 (d, *J* = 8.6 Hz, 1 H, H-5′), 7.21–7.32 (m, 3 H, H-Ar), 7.46 (d, *J* = 8.6 Hz, 1 H, H-4′), 7.50–7.59 (m, 2 H, H-Ar).

^{13}C NMR (100 MHz, $CDCl_3$): δ = –4.2, –4.5, 18.0, 31.6, 32.4, 37.7, 40.4, 49.3, 53.2, 51.4, 63.7, 102.2, 109.8, 127.0, 127.4, 128.9, 130.6, 132.9, 137.7, 151.5, 153.5, 161.5, 174.7.

MS (EI, 70 eV): *m/z* (%) = 590 (2) [M$^+$], 443 (12), 227 (85), 156 (100).

HRMS-EI: *m/z* [M$^+$] calcd for $C_{29}H_{42}N_2O_4{}^{80}Se$: 590.2079; found: 590.2075.

Data for *endo*-Isomer **27**

Yield: 0.20 g (27%); yellow oil.

IR (film): 2949, 2856, 2856, 1735, 1595, 1479, 1316, 1193, 1032, 833 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.19 [s, 3 H, $Si(CH_3)_2$], 0.20 [s, 3 H, $Si(CH_3)_2$], 0.91 [s, 9 H, $Si(CH_3)_2C(CH_3)_3$], 2.01–2.50 (m, 2 H, H-5), 2.29 [s, 6 H, $N(CH_3)_2$], 2.95 (dd, *J* = 12.8, 6.8 Hz, 1 H, H-1), 3.52 (s, 3 H, CO_2CH_3), 3.65–3.70 (m, 2 H, H-2, H-6), 3.81 (s, 3 H, OCH_3), 4.36 (d, *J* = 11.5 Hz, 1 H, CH_aSePh), 4.66 (d, *J* = 11.5 Hz, 1 H, CH_bSePh), 4.96 (dd, *J* = 4.9, 1.6 Hz, 1 H, H-3), 6.55 (d, *J* = 8.5 Hz, 1 H, H-5′), 7.23–7.29 (m, 5 H, H-Ar), 7.58 (d, *J* = 8.5 Hz, 1 H, H-4′).

^{13}C NMR (100 MHz, $CDCl_3$): δ = –4.3, 14.1, 25.6, 31.3, 32.7 (2 × C), 43.1, 50.2, 51.1, 51.3, 60.0, 99.3, 109.4, 126.7, 128.9, 130.6, 132.3, 132.9, 136.4, 152.8, 153.9, 161.1, 172.9.

MS (EI, 70 eV): *m/z* (%) = 590 (3) [M$^+$], 227 (90), 156 (100), 70 (48).

HRMS-EI: *m/z* [M$^+$] calcd for $C_{29}H_{42}N_2O_4{}^{80}Se$: 590.2079; found: 590.2085.

(4*S,5*S**)-4-(Hydroxymethyl)-5-(6′-methoxy-2′-phenylselenylmethylpyridin-3′-yl)cyclohex-2-en-1-one (19)**

$LiAlH_4$ (0.08 g, 2.22 mmol) was added to a solution of esters **26/27** (0.52 g, 0.89 mmol) in Et_2O (10 mL) at 0 °C. The mixture was stirred at 0 °C for 1 h then warmed to r.t. and stirred for an additional 1 h. A solution of aq 2 M HCl (10 mL) was added, the mixture was stirred for 12 h and the solvent removed under reduced pressure. The residue was by purified by column chromatography on silica gel ($MeOH–CH_2Cl_2$), to afford compound **19**.

Yield: 0.34 g (97%); yellow oil.

IR (film): 3429, 2938, 2873, 2245, 1673, 1596, 1478, 1317, 1030, 735 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.20–2.31 (m, 1 H, OH), 2.52–2.60 (m, 2 H, H-6), 3.51–3.80 (m, 2 H, CH_2OH), 3.60–3.72 (m, 1 H, H-5), 3.65–3.73 (m, 1 H, H-4), 3.75 (s, 3 H, OCH_3), 4.15 (d, *J* = 11.3 Hz, 1 H, CH_aSePh), 4.35 (d, *J* = 11.3 Hz, 1 H, CH_bSePh), 6.22 (dd, *J* = 10.2, 2.7 Hz, 1 H, H-2), 6.62 (d, *J* = 8.5 Hz, 1 H, H-5′), 7.05 (dd, *J* = 10.2, 2.0 Hz, 1 H, H-3), 7.21–7.32 (m, 3 H, H-Ar), 7.45–7.55 (m, 2 H, H-Ar), 7.53 (d, *J* = 8.5 Hz, 1 H, H-4′).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 31.2, 36.8, 44.6, 44.7, 53.3, 62.2, 110.0, 127.3, 127.6, 129.4 (2 × C), 130.5, 133.6, 137.0, 152.1, 153.5, 161.7, 198.1.

MS (EI, 70 eV): *m/z* (%) = 403 (30) [M$^+$], 322 (92), 246 (100), 150 (40).

HRMS-EI: *m/z* [M$^+$] calcd for $C_{20}H_{21}NO_3{}^{80}Se$: 403.0687; found: 403.0686.

(1*S,1*R**,13*R**)-13-Hydroxymethyl-5-methoxy-6-azatricyclo[7.3.1.0^{2,7}]trideca-2,4,6-trien-11-one (18) and (4*S**,5*S**)-4-Hydroxymethyl-5-(6′-methoxy-2′-methylpyridin-3′-yl)cyclohex-2-en-1-one (28)**

A solution of *n*-Bu_3SnH (0.06 mL, 0.22 mmol) and AIBN (0.01 g, 0.05 mmol) in degassed benzene (80 mL) was added dropwise over 4 h, using a syringe pump, to a solution of selenide **19** (0.09 g, 0.22 mmol) in degassed benzene (300 mL) under reflux. The reaction mixture was stirred under reflux for a further 2 h then cooled to r.t. and the solvent was removed under reduced pressure. Sat. aq KF (25 mL) was added to the residue and the mixture was stirred at r.t. overnight. The reaction mixture was extracted with Et_2O (3 × 25 mL) and the combined organic extracts were washed with brine (25 mL), dried ($MgSO_4$) and the solvent removed under reduced pressure. The residue was purified by flash column chromatography on silica gel ($MeOH–CH_2Cl_2$, 1:19), to afford compound **18**; further elution provided compound **28**.

Data for **18**

Yield: 0.01 g (29%); colourless oil.

IR (film): 3394, 2923, 1706, 1598, 1477, 1423, 1312, 1260, 1112 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.29–2.32 (m, 1 H, H-12$_a$), 2.31–2.34 (m, 1 H, H-13), 2.44–2.48 (m, 1 H, H-12$_b$), 2.58–2.62 (m, 2 H, H-10), 2.70–2.85 (m, 2 H, H-9, H-8$_a$), 3.15 (dd, *J* = 18.3, 6.6 Hz, 3 H, H-8$_b$), 3.32–3.38 (m, 1 H, H-1), 3.86 (s, 3 H, OCH_3), 4.06 (dd, *J* = 8.0, 2.4 Hz, 2 H, CH_2OH), 6.54 (d, *J* = 8.4 Hz, 1 H, H-4), 7.24 (d, *J* = 8.4 Hz, 1 H, H-3).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 31.5, 35.9, 40.1, 40.5, 44.3, 44.9, 53.3, 63.3, 109.1, 127.4, 139.0, 151.3, 162.9, 209.9.

MS (FAB): *m/z* (%) = 248 (100) [MH$^+$], 214 (24).

HRMS-FAB: *m/z* [MH$^+$] calcd for $C_{14}H_{18}NO_3$: 248.1287; found: 248.1283.

Data for **28**

Yield: 0.026 g (48%); yellow oil.

IR (film): 3383, 2940, 1673, 1597, 1478, 1309, 1040 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 2.45 (s, 3 H, CH_3), 2.51–2.59 (m, 2 H, H-6), 2.70–2.85 (m, 1 H, H-4), 3.48–3.52 (m, 1 H, H-5), 3.91 (s, 3 H, OCH_3), 6.15 (dd, *J* = 10.2, 2.7 Hz, 1 H, H-2), 6.60 (d, *J* = 8.5 Hz, 1 H, H-5′), 7.13 (dd, *J* = 10.2, 2.2 Hz, 1 H, H-3), 7.45 (d, *J* = 8.5 Hz, 1 H, H-4′).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 22.0, 37.0, 443, 44.8, 53.3, 62.5, 108.2, 127.3 (2 × C), 136.4, 151.9, 153.9, 161.9, 198.6.

MS (EI, 70 eV): *m*/*z* (%) = 247 (25) [M^+], 149 (100).

HRMS-EI: *m*/*z* [M^+] calcd for $C_{14}H_{17}NO_3$: 247.1208; found: 247.1207.

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