

A radical mediated approach to the core structure of huperzine A

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Abstract—The synthesis of the core structure of huperzine A by cyclisation of 2-pyridylmethyl radicals is described. (2-Methylpyridin-3-yl)cyclohexenols are directly selenated at the benzylic position by deprotonation/selenation and the products undergo either 5-*exo-trig* or 6-*exo-trig* radical cyclisations giving access to hexahydroindenopyridines and the bicyclo[3.3.1]nonane core of huperzine A, respectively.

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Huperzine A **1**, a *Lycopodium* alkaloid isolated from the Chinese club moss *Huperzia serrata*¹ and recently from the New Zealand club moss *Lycopodium varium*,² is a potent and reversible acetylcholinesterase inhibitor that also displays neuroprotective properties (Fig. 1).³ Clinical trials have revealed the efficacy of this alkaloid as a treatment for Alzheimer's disease⁴ and huperzine A also shows promise as a protective agent against organo-

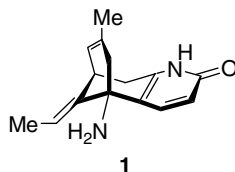


Figure 1.

phosphate poisoning.⁵ A number of total syntheses of huperzine A⁶ and synthetic approaches to the bicyclo[3.3.1]nonane core structure⁷ and analogues⁸ have been developed.

We are currently investigating a synthetic approach to core structure **2** that centres on the 6-*exo-trig* cyclisation of pyridylmethyl radicals generated from intermediates

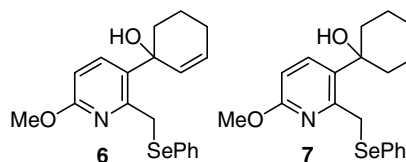
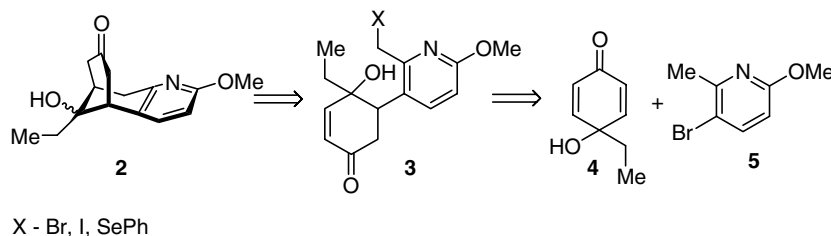


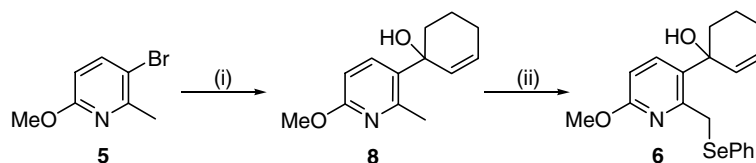
Figure 2.



Scheme 1.

Keywords: Huperzine A; Pyridylmethyl radicals; Selenation; Radical cyclisation.

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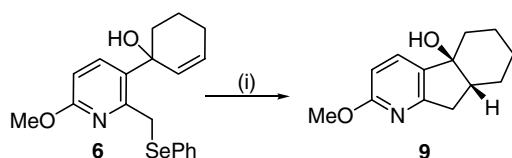


Scheme 2. Reagents and conditions: (i) n BuLi, 2-cyclohexen-1-one, THF, 1 h, -78 °C, 59%; (ii) 2.2 equiv LDA, THF, -78 °C, Ph_2Se_2 , 1 h, 20%.

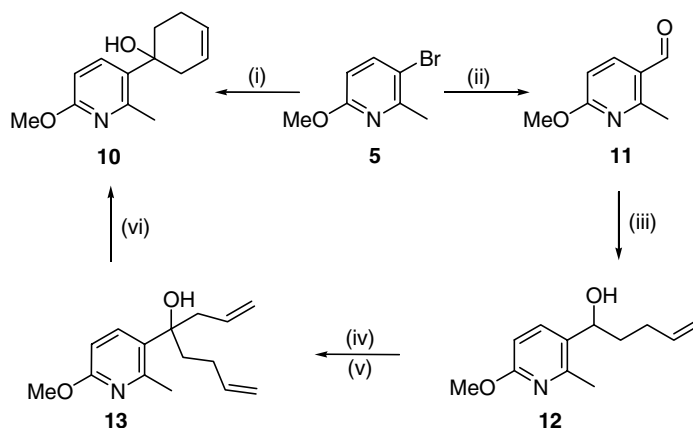
of general structure **3**. It is planned to derive intermediate **3** from quinol **4** and trisubstituted pyridine **5**—a compound previously utilised in synthetic approaches to huperzine A (Scheme 1).^{7a,f,i}

While the generation and use of pyridyl radicals in synthesis has been reported⁹ the utilisation of pyridylmethyl radicals, has to our knowledge, not been documented. Thus, before embarking on a synthesis of the target, we decided to both probe the synthetic utility of such radicals and the validity of our key disconnection by studying the radical cyclisation of model selenides **6** and **7** (Fig. 2).

It was planned to access compounds **6** and **7** by selenylation of a ring-functionalised 2-methylpyridine late in the reaction sequence. Selenation at the benzylic position of a 2-methylpyridine has been previously achieved by reaction of the corresponding bromomethylpyridine with sodium phenylselenolate¹⁰ or by treatment of a hydroxymethylpyridine with *N*-PSP in the presence of tri-*n*-butylphosphine.¹¹ Either approach requires the presence of prior functionality at the benzylic position and our desire for a rapid and efficient synthesis of



Scheme 3. Reagents and conditions: (i) n Bu₃SnH, AIBN, benzene, 80 °C, 2 h, 97%.



Scheme 4. Reagents and conditions: (i) n BuLi, 3-cyclohexen-1-one, THF, -78 °C, 1 h, 9%; (ii) n BuLi, DMF, THF, -78 °C, 1 h, 80%; (iii) but-3-enylmagnesium bromide, Et_2O , 0 °C, 1 h, 73%; (iv) Dess–Martin periodinane, pyridine, CH_2Cl_2 , 25 °C, 0.5 h, 80%; (v) allylmagnesium bromide, Et_2O , 0 °C, 1 h, 40%; (vi) 3 mol % $(\text{Cl})_2(\text{PCy}_3)_2\text{Ru}=\text{CHPh}$, CH_2Cl_2 , 25 °C, 1 h, 94%.

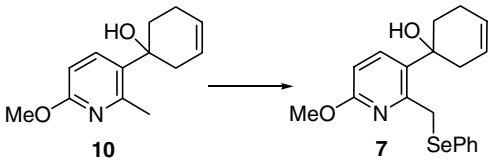
model compounds prompted us to investigate a more direct approach to both **6** and **7** centred on the one step deprotonation/selenation of a 2-methylpyridine.

We initially investigated the synthesis and radical cyclisation of compound **6**; as the potential precursor, pyridylcyclohexenol **8**, was readily accessed in multi-gram quantities from bromopyridine **5**.⁷ⁱ Lithium–halogen exchange of **5** followed by the addition of 2-cyclohexen-1-one, according to the method of Gray et al.,¹² gave adduct **8** in moderate yield (Scheme 2). Direct selenation of **8** was successfully achieved using LDA as base and diphenyl diselenide as the electrophile giving selenide **6**, albeit in low yield (Scheme 2).

Radical cyclisation of selenide **6** was then attempted by slow addition of tributyltin hydride using AIBN as initiator in benzene under reflux. Compound **6** underwent 5-*exo-trig* radical cyclisation under these conditions to give hexahydroindenopyridinol **9** in excellent yield with no trace of products arising from 6-*endo-trig* cyclisation or reduction detected (Scheme 3).

We planned to access selenide **7** in a similar manner to compound **6** by direct selenylation of adduct **10** which, in turn, would be derived in one step from bromide **5**. Unfortunately, treatment of the 3-pyridyllithium, derived from lithium–halogen exchange of **5**,¹² with 3-cyclohexen-1-one¹³ gave the desired adduct **10** in poor yield. This prompted us to develop an alternative approach to **10** utilising a RCM methodology (Scheme 4).

Formylation of bromopyridine **5**¹² and reaction with but-3-enylmagnesium bromide gave alcohol **12**. Oxida-

Table 1. Optimisation of the deprotonation/selenation of compound **10**


| Base ^a | Additive ^b | Electrophile ^c | Yield ^d (%) |
|-------------------|-----------------------|---------------------------------|------------------------|
| LDA | — | Ph ₂ Se ₂ | 9 |
| ^t BuLi | — | Ph ₂ Se ₂ | 7 |
| ^t BuLi | — | Ph ₂ Se ₂ | 33 |
| ^t BuLi | — | PhSeCl | 40 |
| ^t BuLi | TMEDA | PhSeCl | 30 |
| ^t BuLi | DMPU | PhSeCl | 75 |

^a All deprotonations were performed by the addition of 2.2 equiv of base in THF at -78°C and stirring for 1 h.

^b 2.2 equiv of additive was used.

^c 1.2 equiv of electrophile was added as a 0.02 M solution in THF at -78°C and the mixture stirred for 1 h then warmed to room temperature and stirred for a further 30 min.

^d Isolated, chromatographically pure product.

tion with Dess–Martin periodinane buffered with pyridine and treatment of the resulting ketone with allylmagnesium bromide gave RCM precursor **13**. While difficulties have been reported during attempts to perform olefin metatheses on pyridine-containing substrates,¹⁴ the RCM reaction of **13** proceeded smoothly in the presence of 3 mol % Grubb's 1st generation catalyst in dichloromethane at room temperature to give cyclohexenol **10** in excellent yield. Deprotonation of **10** using LDA followed by addition of diphenyl diselenide resulted in a poor yield of selenide **7**. This result prompted us to screen a variety of bases, additives and electrophiles in an attempt to optimise this transformation. The results are summarised in Table 1. After some experimentation it was discovered that optimum conditions for the synthesis of **7** involved deprotonation of **10** with 2.2 equiv. of *tert*-butyllithium in THF at -78°C in the presence of DMPU as additive followed by the addition of 1.2 equiv of phenylselenium chloride. The use of other bases or alternative electrophiles in the absence of DMPU resulted in much lower yields of product.

Treatment of selenide **7** with tributyltin hydride and AIBN under the conditions developed for cyclisation of **6** gave bicyclo[3.3.1]nonane **14**, that has the basic core structure of huperzine A in moderate yield, along with similar quantities of reduction product **10** (Scheme 5).¹⁵

In conclusion, pyridylmethyl radicals have been shown to have utility in synthesis, undergoing both 5-*exo-trig*

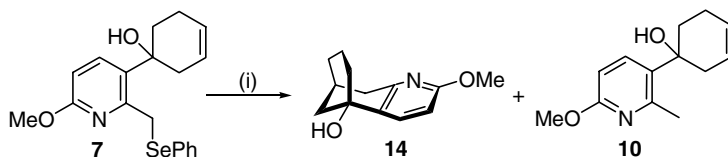
and 6-*exo-trig* cyclisation under standard conditions. The latter mode of cyclisation of such radicals has been used to access efficiently the bicyclo[3.3.1]nonane framework of huperzine A and future work will focus on optimising this transformation and on using more highly functionalised substrates in an effort to access the natural product and analogues. Furthermore, a novel approach to the radical precursors by direct selenation of 2-methylpyridines has been developed using a deprotonation/selenylation sequence and efforts towards probing the scope and utility of this transformation will be reported in due course.

Acknowledgements

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Scheme 5. Reagents and conditions: (i) ^tBu₃SnH, AIBN, benzene, 80 °C, 2 h, **14** 46%, **10** 54%.

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15. Synthesis of bicyclononane **14**: A solution of tributyltin hydride (0.051 g, 0.18 mmol) and AIBN (3.5 mg, 0.021 mmol) in degassed benzene (20 mL) was added, via syringe pump over 4 h, to a solution of selenide **7** (0.044 g, 0.12 mmol) in degassed benzene (60 mL) under reflux. The mixture was stirred under reflux for 2 h, cooled to room temperature and concentrated under reduced pressure. A saturated aqueous solution of potassium fluoride (25 mL) was added to the residue and the mixture stirred overnight then extracted with diethyl ether (3 × 25 mL). The combined organic extracts were washed with brine (2 × 25 mL), dried over anhydrous magnesium sulfate and concentrated under reduced pressure to give a yellow oil which was purified by flash column chromatography using ethyl acetate–hexane (0.5:9.5) to give reduced product **10** (14.6 mg, 54%) and cyclised product **14** (12 mg, 46%). Characterisation data for **14**: ¹H NMR (300 MHz, CDCl₃): δ 7.73 (1H, d, *J* = 8.5 Hz), 6.56 (1H, d, *J* = 8.5 Hz), 3.90 (3H, s), 3.15 (1H, dd, *J* = 7.1, 18.6 Hz), 2.60 (1H, d, *J* = 18.6 Hz), 2.55–2.45 (1H, m), 1.90 (1H, d, *J* = 11.5 Hz), 1.85 (1H, ddd, *J* = 1.3, 3.5, 11.5 Hz), 1.70–1.50 (5H, m), 1.00–1.75 (1H, m); ¹³C NMR (75 MHz, CDCl₃): δ 162.5, 154.3, 135.1, 130.9, 107.9, 70.9, 53.3, 41.0, 40.8, 38.0, 32.4, 29.4, 20.8; HRMS *m/z* (EI) calcd for [C₁₃H₁₇NO₂]⁺: 219.1259. Found: 219.1262.