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A convergent approach to huperzine A and analogues

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Abstract

An aldol reaction between the enolate of cyclohexenone and 3-bromo-6-methoxy-1-formylpyridine, followed by protection of the resultant alcohol and reaction with Pd(0) yielded 5-methoxy-8-*tert*-butyldimethylsilylanyloxy-6-azatricyclo[7.3.1.$0^{2,7}$]trideca-2,4,6,11-tetraen-13-one, which has the basic skeleton of huperzine A.

Huperzine A **1** from the club moss *Huperzia serrata*[1] has proven activity as an inhibitor of the enzyme acetylcholinesterase, and is undergoing clinical trials as a potential treatment for Alzheimer's disease. It has been the target of several total syntheses and a number of analogues have also been prepared.[2] A comprehensive review of much of the structure activity data presently available has been provided recently by Kozikowskiy.[3] All of the synthetic approaches to date have been essentially linear and we have been trying to devise a more convergent approach to this interesting molecule. Our overall approach is summarised in Scheme 1 and we report in this communication a synthesis of the basic skeleton of huperzine A via route B.

In an earlier attempt to proceed via route A, we prepared 100 g quantities of 3-bromo-6-methoxy-2-methylpyridine **2**,[4] and this was oxidised to the required aldehyde **3** via formation of the *N*-oxide **4** (*m*CPBA), rearrangement to provide acetate **5** (acetic anhydride), and thence the aldehyde by hydrolysis and oxidation with manganese dioxide. The overall yield for the process was 45% (Scheme 2).

In order to try to establish the optimum conditions for the intramolecular Heck-type reaction,[5] we carried out model studies on the aldol product **6** (X=halogen, Y=CH) produced by reaction of the enolate of cyclohexenone **7** and either 2-bromobenzaldehyde or 2-iodobenzaldehyde. It quickly became apparent that the hydroxyl of **6** must be protected and that only the *syn*-aldol product as its TBDMS ether **9** (Scheme 3) would provide the desired tricycle **11** (Y=CH, R=H). Molecular models suggest that this is primarily due to steric hindrance.

The highest yield of **11** (46%) from the precursor **9a** was produced when palladium acetate (0.1 equiv.) was used in conjunction with tri-*o*-tolylphosphine (0.2 equiv.) as ligand and triethylamine (12 equiv.) as

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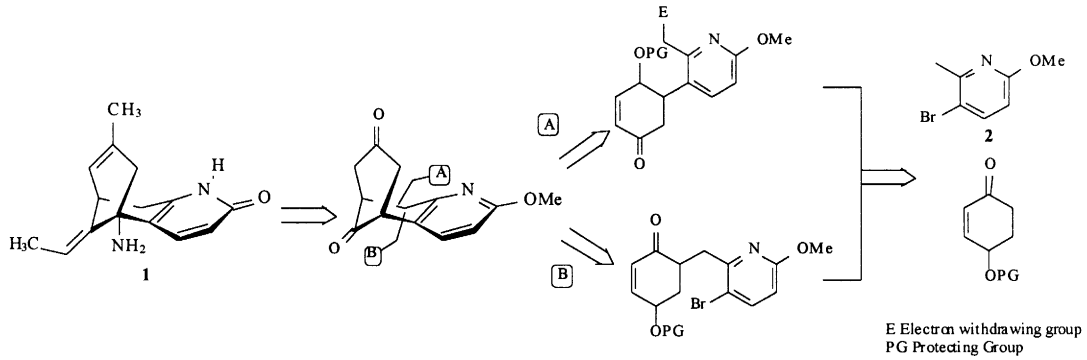
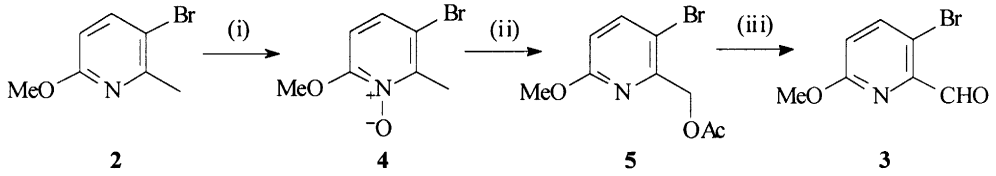
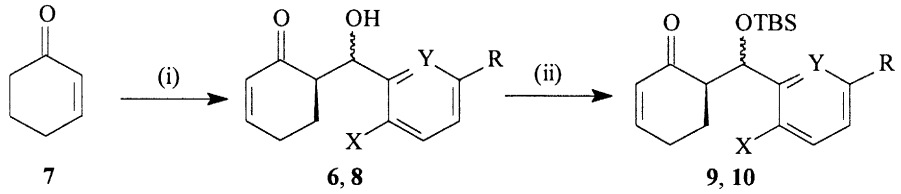


Scheme 1.



Scheme 2. (i) *m*CPBA (1.5 equiv.), $CHCl_3$, rt, 15 h, 61%; (ii) Ac_2O, 120°C, 2 h, 80%; (iii) (a) K_2CO_3, MeOH, rt, 40 min, quant.; (b) MnO_2 (12 equiv.), $CHCl_3$, rt, 12 h, 92%



(i) LDA, THF, -78°C, 1 hour, then aldehyde, -78°C, 2 hours; (ii) TBSOTf, Et_3N, THF, 0°C, 2 hours.

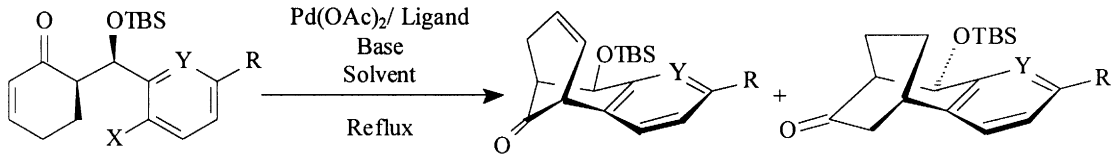
Product	Y	X	R	Overall yield	Ratio *syn/ anti*
9a	CH	Br	H	62%	6:4
9b	CH	I	H	36%	8:2
10	N	Br	MeO	45%	6:4

Scheme 3.

base in dimethylformamide. However, this poor yield could be raised to around 60% when with the same palladium complex the iodide **9b** was employed in the presence of pentamethylpiperidine (2 equiv.) in dimethylacetamide. Around 10% of the alternative tricycle **12** (Y=CH, R=H) was also produced.

Reaction of the aldehyde **3** with the enolate of cyclohexenone **7** (LDA, THF, −78°C) provided the aldol product **8** (Y=N, X=Br, R=OMe) as a mixture of isomers in the ratio of 6:4, and these were converted into their TBDMS ethers 10 (Y=N, X=Br, R=OMe). The major *syn*-product **10** was reacted under the same conditions as described for **9b**, but failed to provide any cyclisation products. With triphenylphosphine and triethylamine in acetonitrile, reaction did occur to produce two major tricyclic products: the 8-alkoxy-tricyclo[7.3.1.0]trideca-2(7),3,5,11-tetraen-13-one **12** (Y=N, R=OMe) and the desired tricycle **11** (Y=N and R=OMe), which has the required basic skeleton of huperzine A (Scheme 4).[6] Although the yield of

11 (Y=N and R=OMe) is only modest, this reaction has yet to be optimised, and this compound promises to be a key intermediate en route to both huperzine A and novel analogues.



9, **10** **11** **12**

Y	X	R	Ligands	Base	Solvent	Yield (**11**:**12**)
CH	Br	H	PPh_3	Et_3N	CH_3CN	21%:23%
CH	Br	H	P(*o*-tolyl)$_3$	Et_3N	DMF	46%:27%
CH	I	H	PPh_3	Et_3N	CH_3CN	30%:11%
CH	I	H	P(*o*-tolyl)$_3$	PMP	DMA	60%:11%
N	Br	MeO	PPh_3	Et_3N	DMF	8%:40%

Scheme 4.

Acknowledgements

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6. Synthesis of cycloadducts **11** and **12** (Y=N and R=OMe): $Pd(OAc)_2$ (0.039 g, 0.1 equiv., 0.17 mmol) was added to a solution of *syn*-aldol **10** (0.740 g, 1.73 mmol) in the presence of triphenylphosphine (0.182 g, 0.4 equiv., 0.69 mmol) and triethylamine (3.144 ml, 13.0 equiv., 22.56 mmol) in dimethylformamide (21 ml). The mixture was then heated until the reaction was complete, and after being quenched with water (20 ml), the solution was extracted with diethyl ether. The combined organic phases were washed with a saturated aqueous solution of sodium hydrogenocarbonate, with brine, dried over magnesium sulphate and concentrated under vacuum to give a black oil as the crude product. The oil was purified by flash chromatography with Et_2O:petroleum ether 40–60 (5:95) to give separately the desired cycloadduct **11** (0.048g, 8% yield) and the side-cycloadduct **12** (0.241g, 40% yield). NMR of product **11** (250 MHz; $CDCl_3$, Me_4Si) −0.19 (3H, s, SiMe), 0.00 (3H, s, SiMe), 0.64 (9H, s, $SiCMe_3$), 2.37 (1H, d, *J*=6.9 Hz, 10-H), 2.68 (2H, m, 10-H and 9-H), 3.43 (1H, d, *J*=6.9 Hz, 1-H), 3.70 (3H, s, OMe), 4.75 (1H, d, *J*=1.9 Hz, 8-H), 5.32 (1H, m, 11-H), 5.74 (1H, m, 12-H), 6.41 (1H, d, *J*=8.4 Hz, 4-H), 7.02 (1H, d, *J*=8.7 Hz, 3-H). NMR of product **12** (250 MHz; $CDCl_3$, Me_4Si) −0.01 (3H, s, SiMe), 0.16 (3H, s, SiMe), 0.76 (9H, s, $SiCMe_3$), 1.66 (3H, m, 12-H and 13-H), 2.00 (1H, m, 13-H), 2.50 (2H, m, 11-H), 2.92 (1H, m, 9-H), 3.07 (1H, m, 1-H), 3.85 (3H, s, OMe), 4.78 (1H, d, *J*=7.4Hz, 8-H), 6.53 (1H, d, *J*=8.3 Hz, 4-H), 7.26 (1H, d, *J*=8.3 Hz, 3-H).