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A convergent approach to huperzine A and analogues †

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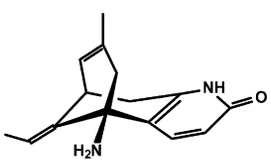
We describe a concise and convergent synthesis of (*rac*)-5-methoxy-6-azatricyclco[7.3.1.$0^{2,7}$]trideca-2(7),3,5,11-tetraen-13-ol, which has the basic ring system of huperzine A, a potent inhibitor of acetylcholinesterase. We also describe the synthesis of the novel system 5-methoxy-6-azatricyclo[7.2.2.$0^{2,7}$]trideca-2(7),3,5-trien-10-one and a series of related systems.

Introduction



(-)-Huperzine A

Huperzine A **1** from the club moss *Huperzia serrata*[1] has proven activity as an inhibitor of the enzyme acetylcholinesterase, and extracts of the moss have been used as the basis of Chinese folk remedies for memory loss in elderly patients. In the USA huperzine A is undergoing clinical trials as a potential treatment for Alzheimer's disease (AD), while in China the natural product has already been approved for the treatment of AD. Huperzine A 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 Bai[3] and Kozikowski.[4] All of the synthetic approaches to date have been essentially linear, and are thus not ideal for analogue preparation. We have been trying to devise a more convergent approach to this interesting molecule and structural analogues and our overall approach is summarised in Scheme 1.

Results and discussion

We have already recorded our attempts to proceed *via* route A, in which a 3-pyridylcuprate was successfully reacted with a 4-substituted-cyclohexa-2,5-dienone, though the subsequent chemistry was not productive.[5] However, this work did provide multi-gram quantities of 3-bromo-6-methoxy-2-methylpyridine **2**, which was also the starting material for route B. This second strategy involves attachment of a trisubstituted pyridine to a 4-susbtituted cyclohexenone with a subsequent intramolecular Heck reaction to complete the construction of the basic skeleton.

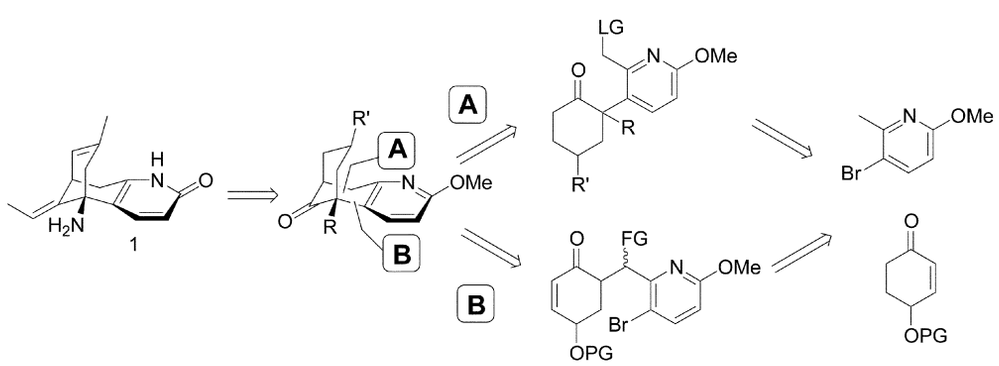
Our starting material **2** was oxidised to the aldehyde **3** *via* formation of the *N*-oxide **4** (*m*CPBA), rearranged to provide the acetate **5** (acetic anhydride), and thence the aldehyde by hydrolysis and oxidation with manganese dioxide. The overall yield for the process was 61% (Scheme 2).

In order to establish the optimum conditions for the intramolecular Heck-type reaction,[6] we carried out model studies on the aldol product **6** (X = halogen, Y = CH, R = H) produced by reaction of the enolate of cyclohexenone **7** and either 2-bromobenzaldehyde or 2-iodobenzaldehyde. As shown in the Table 1, there was only modest stereoselectivity in this reaction. The *syn*-aldol product could be distinguished from the *anti*-product since the coupling constant between H-6 and H-7 observed by ^{1}H NMR was less than 4 Hz for the former products and greater than 6 Hz for the latter products. Initial attempts to achieve an intramolecular Heck reaction with aldol adduct **6** or its acetate derivative proved unsuccessful. It became apparent that the hydroxy group of **6** must be protected and that only the

Table 1 Syntheses of the Heck precursors from cyclohexenone

Product	Y	X	R	Yield (%)	Ratio *syn* : *anti*
9a	CH	Br	H	62	3 : 2
9b	CH	I	H	36	4 : 1
10	N	Br	OMe	45	3 : 2

† Electronic supplementary information (ESI) available: further experimental details. See http://www.rsc.org/suppdata/ob/b3/b305869g/



Scheme 1 Retrosynthetic analysis.

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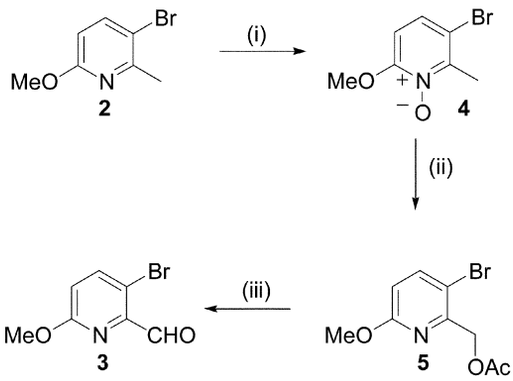
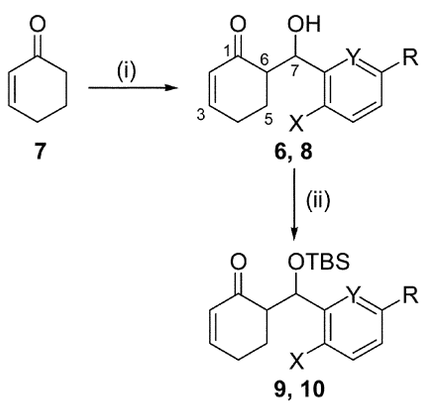
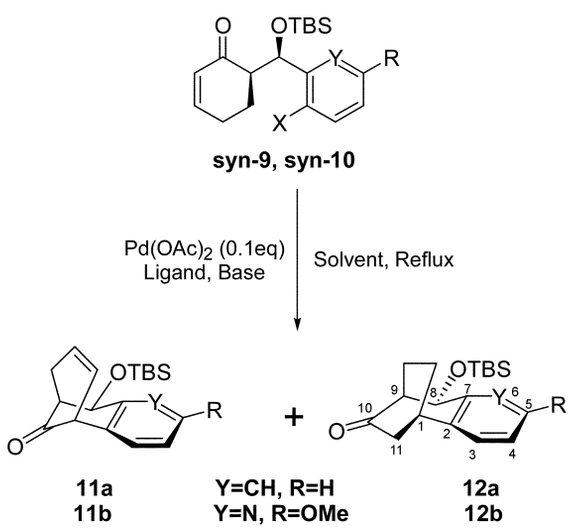


Scheme 2 *Reagents and conditions*: (i) *m*-CPBA, $CHCl_3$, rt, 15 h, 91%; (ii) Ac_2O, 120 °C, 2 h, 80%; (iii) a) K_2CO_3, MeOH, rt, 40 min, quant., b) MnO_2, $CHCl_3$, rt, 12 h, 84%.

syn-aldol product as its TBS ether **9** (Scheme 3) would provide the desired tricycle **11** (Y = CH, R = H) (Scheme 4). Molecular modelling studies suggest that there is steric impedance to the *anti*-isomer cyclising.



Scheme 3 *Reagents and conditions*: (i) LDA, THF, −78 °C, 1 h, then aldehyde, −78 °C, 2 h; (ii) TBSOTfl, Et_3N, THF, 0 °C, 2 h.



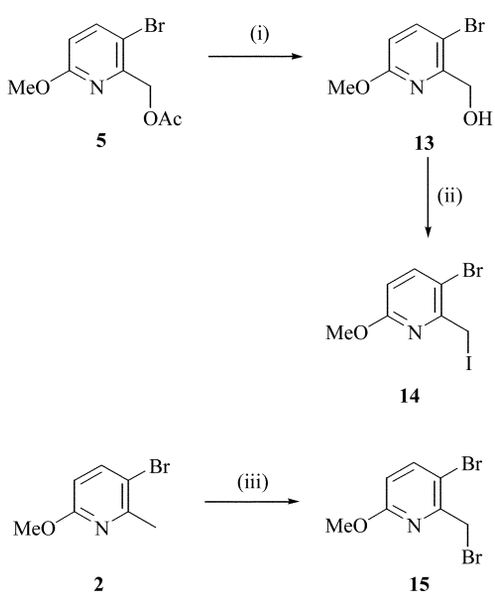
Scheme 4 Intramolecular Heck ring closure with TBS silyl ethers precursors.

The highest yield (46%) of **11** (Y = CH, R = H) from the precursor **9a** was produced when palladium acetate (0.1 equiv.) was used in conjunction with tri-(*o*-tolyl)phosphine (0.2 equiv.) as ligand and triethylamine (12 equiv.) as base in dimethylformamide. However, this poor yield could be raised to around 60% when the same palladium complex and iodide **9b** were employed in the presence of pentamethylpiperidine (2 equiv.) in dimethylacetamide. Around 10% of an alternative reduced tricycle **12** (Y = CH, R = H) was also produced. The results of the key experiments are summarised in Table 2. These model studies suggested that the overall strategy was viable and we thus turned our attentions to the huperzine precursor **10** (Y = N, X = Br, R = OMe).

Reaction of the pyridine aldehyde **3** with the enolate of cyclohexenone **7** (LDA, THF, −78 °C) provided the aldol products **8** (Y = N, X = Br, R = OMe) as a separable mixture of isomers in the ratio of 2 : 3 (*syn* : *anti*). The disappointing yield of the desired *syn*-isomer was unexpected from previous results in the benzene series. Each isomer was converted into its TBS ethers **10** in good yield.

Huperzine precursor **10** was reacted under the optimised conditions as described for **9b**, but failed to provide any cyclisation products. With triphenylphosphine and triethylamine in dimethylformamide, reaction did occur to produce two major tricyclic products : the novel system 5-methoxy-8-*tert*-butyldimethylsilyloxy-6-azatricyclo[7.2.2.$0^{2,7}$]trideca-2(7),3,5-trien-10-one **12b** (Y = N, R = OMe), and the desired tricycle **11b** (Y = N and R = OMe), which has the skeleton of huperzine A (Scheme 4 and Table 2).[7] However, the yield of tricycle **11b** was less than 10% in all experiments, and it was clear that major modifications would be required if the natural product and analogues were to be obtained in useful quantities.

The acetate **5** was hydrolysed to the alcohol **13** and then converted into the iodide **14**. Alternatively, bromide **15** was synthesised by NBS bromination[8] of 3-bromo-6-methoxy-2-methylpyridine **2** (Scheme 5).



Scheme 5 *Reagents and conditions*: (i) K_2CO_3, MeOH, 95%; (ii) imidazole, Ph_3P, iodine, DCM, 66%; (iii) NBS, AIBN, CCl_4, AcOH, hν 71%.

Attempted alkylations with the kinetic enolate from cyclohexenone provided a number of products in low yield, but alkylation with cyclohexanone was very effective to provide the ketone **16** (Scheme 6). Reaction of ketone **16** with LDA and PhSeCl in THF–DMPU produced the *syn*- and *anti*-phenylseleno-derivatives **17** as a separable mixture of isomers (*syn* : *anti* 2 : 3).[9] The ^{1}H NMR spectra of these two isomers were quite different, and most significantly, for compound ***syn*-17** 2-H appeared at 4.11 ppm (dd) with 6-H at 3.20 ppm (m), while for compound ***anti*-17** both 2-H and 6-H appeared as a complex multiplet at 3.95 ppm. The *syn–anti* mixture readily yielded the alkylated cyclohexenone **18** (77% isolated yield) upon treatment with sodium periodate.[9]

The carbocyclic model compound **21** was produced in a similar way from 2-bromobenzyl bromide *via* the alkylated product

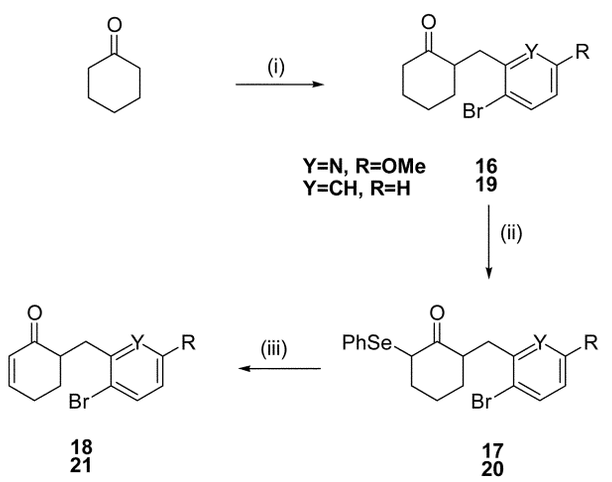
Table 2 Study of intramolecular Heck ring closure with TBS silyl ethers precursors

Precursor	Y	X	R	Ligand[a]	Base[b]	Solvent	Yield **11** : **12** (%)
***syn*-9a**	CH	Br	H	PPh_3	Et_3N	CH_3CN	21 : 23
				POT	Et_3N	DMF	47 : 27
***syn*-9b**	CH	I	H	PPh_3	Et_3N	CH_3CN	30 : 11
				POT	PMP	DMA	60 : 11
***syn*-10**	N	Br	OMe	PPh_3	Et_3N	DMF	8 : 40

[a] 0.4 equivalent of PPh_3 or 0.2 equivalent of tri(*o*-tolyl)phosphine (POT) was used. [b] 12 equivalents of Et_3N or 2 equivalents of 1,2,2,6,6-pentamethylpiperidine (PMP) were used.

Table 3

Product	Y	R	Yield (%)	Ratio *syn* : *anti*
16	N	OMe	81	
17	N	OMe	86	2 : 3
18	N	OMe	77	
19	CH	H	83	
20	CH	H	85	2 : 3
21	CH	H	78	



Scheme 6 *Reagents and conditions*: (i) LDA, −78 °C, DMPU–HMPA, then **14**/**15** or benzyl bromide; (ii) LDA, −78 °C, PhSeCl; (iii) $NaIO_4$, MeOH, H_2O

19 and the selenides **20** (*syn* : *anti* 2 : 3). Oxidation of **20** provided enone **21** in 78% yield. All these results are collected in Table 3.

The model compound **21** was then used to explore the intramolecular Heck reaction in a series of parallel reactions. Using a large variety of conditions including those used in the first series of Heck reactions, the major product was always the reduced tricycle **22** with smaller amounts of the desired tricycle **23**. In some cases, and in particular with the ligand tri(*o*-tolyl)-phosphine, the double bond isomer **24** was also isolated (Table 4 and Scheme 7).

The structure of compound **22** was determined by analysis of its NMR data. It was clearly not the desired tricycle as it contained no signals in the olefin region of the ^1H NMR spectrum. The spectrum contained four aromatic protons and ten others. ^{13}C NMR spectroscopy confirmed the presence of four CH_2 groups and two CH groups. From analysis of COSY and HetCor couplings the structure **22** was proposed and this was confirmed by mass spectrometry and microanalysis. The ^1H NMR spectrum of molecule **23** showed two olefinic signals at 5.71 and 5.87 ppm. Analysis of the ^{13}C NMR spectrum confirmed the presence of 2 olefinic carbons 11-C and 12-C, as well as two C-H groups and two CH_2 groups. Together with HetCor and COSY data, the structure **23** was assigned to the molecule.

Table 4 Study of intramolecular Heck ring closure with alkylated precursor **21**

			Yield (%)		
Base (equiv.)	Ligand (equiv.)[a]	Solvent	**22**	**23**	**24**
Et_3N (12)	PPh_3 (0.2)	DMF	14	8	—
Et_3N (12)	PPh_3 (0.4)	DMF	48	19	—
Et_3N (12)	POT (0.2)	DMF	22	4	3
PMP (2)	PPh_3 (0.4)	DMF	44	5	—
PMP (2)	POT (0.2)	DMF	21	16	16
Et_3N (12)	PPh_3 (0.4)	DMA	63	25	6

[a] POT = tri(*o*−tolyl)phosphine. PMP = 1,2,2,6,6-pentamethylpiperidine.

The mechanisms suggested for formation of cycloadducts **22**, **23** and **24** are outlined in Scheme 8.

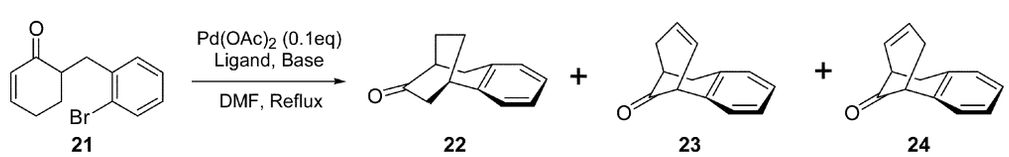
A 6-*exo-trig* cyclisation affords compound **23**, due to *syn*-elimination of proton Hb and the palladium(II) species from intermediate **25** (Scheme 8). *syn* β-Elimination with Ha was impossible.

Formation of intermediate **26** involves a 7-*endo-trig* cyclisation. However, this intermediate does not possess a *syn* β-hydrogen and furthermore it is difficult to form a double bond at such a bridgehead position. It is then proposed that nucleophilic displacement of the palladium(II) species by a hydride ion yields the tricycle **22**, although the source of the hydride ion has not been resolved.

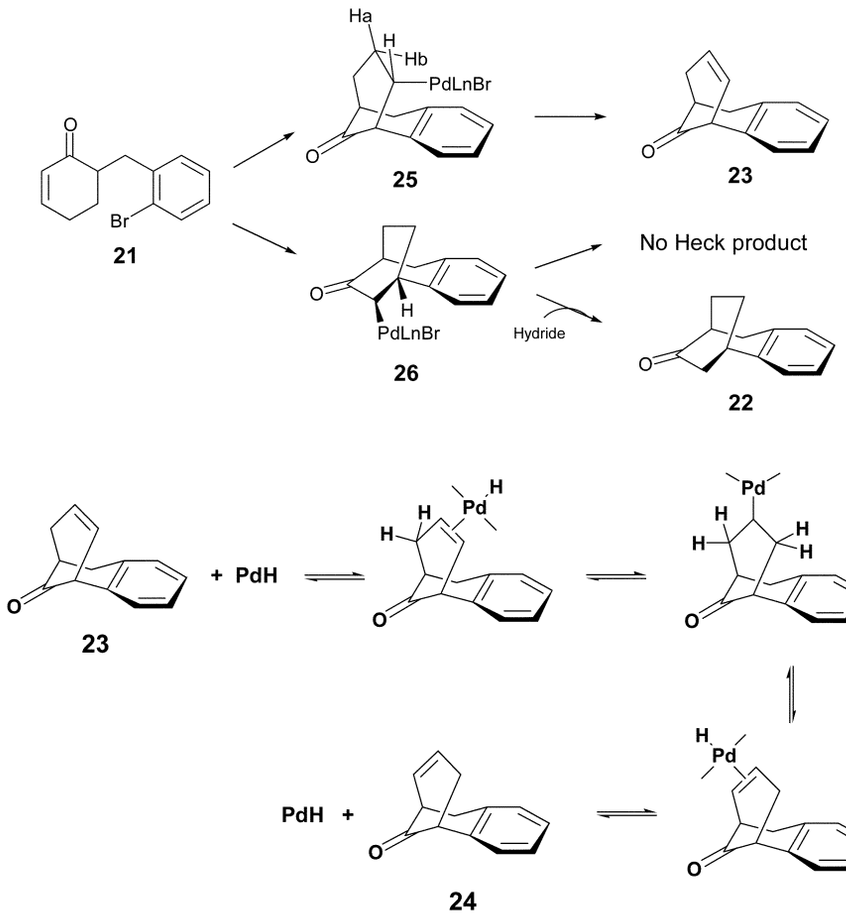
Tricycle **24** is most likely to be formed *via* double bond migration from **23**. The mechanism probably involves a Pd metal hydride addition–elimination (Scheme 8), since palladium hydride species are often intermediates in catalytic reactions. The hydride adds to the double bond of **23**, providing an unstable alkylpalladium species with a β-hydrogen. As a result an equilibrium is set up between the alkene and the alkylpalladium species. The hydride elimination (olefin insertion) is believed to proceed by way of an olefin π-complex to yield alkene **24**.

Using the same reaction conditions with the substituted pyridine **18** provided a poor yield of the desired tricycle **27** and the reduced tricycle **28** as the major product (Table 5 and Scheme 9).

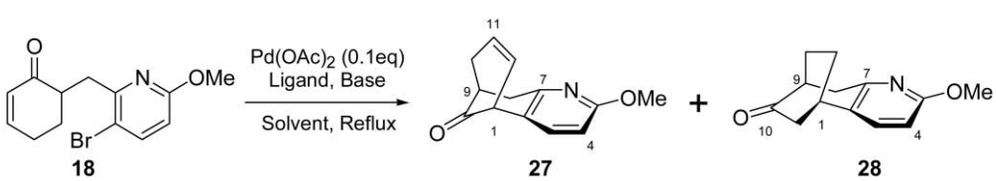
We reasoned that the preference for the 'Michael-type' adducts could be overturned if we removed the conjugated carbonyl, and so the ketones **18** and **21** were reduced with



Scheme 7 Intramolecular Heck ring closure with alkylated benzene precursor **21**.



Scheme 8 Mechanisms for formation of cycloadducts **22**, **23** and **24**.



Scheme 9 Intramolecular Heck ring closure with alkylated pyridine precursor **18**.

Table 5 Study of intramolecular Heck ring closure with alkylated precursor **18**

Base (equiv.)	Ligand[a]	Solvent[b]	Yield **27** : **28** (%)
Et_3N (12)	PPh_3	DMF	0 : 33
Et_3N (12)	PPh_3	DMA	6 : 60
PMP (2)	POT	DMA	0 : 41

[a] 0.2 equivalent of ligand was used for all experiments. [b] DMF at 120 °C, DMA at 140 °C.

sodium borohydride under Luche conditions to provide a mixture of alcohols **29** and **30** respectively (Scheme 10).

To our delight, the intramolecular Heck reaction using *syn–anti*-**29** produced a mixture of alcohols **31** and **32** with the desired skeleton. Small amounts of the alternative tricycle **33** and the previously synthesised tricycle **22** were also isolated (Scheme 11 and Table 6).

The ^{1}H NMR and ^{13}C signals for tricycles **31** and **32** exhibited all of the expected signals for both the desired tricyclic compounds. The stereoisomers were separated by column chromatography and both showed two olefinic ^{1}H NMR signals in the region δ_H 5.5–δ_H 5.8. Both ^{13}C spectra also showed two olefinic signals. Apparent singlets are observed at δ_H 3.94 and δ_H 4.22, corresponding to H-13 for the respective stereoisomers, which are deshielded due to the electron withdrawing effect of their respective alcohol groups.

Determination of the stereochemistry of H-13 proved more difficult. NOE studies were undertaken on both **31** and **32** (Fig. 1). A molecular model demonstrated that H-13 in both isomers was a similar distance in space away from H-1 and H-9, and that the tricyclic framework was quite rigid and inflexible. From the model, it seemed that irradiation of the H-13 signals of the *endo* isomer **31** and the *exo* isomer **32** would give identical enhancements for H-1 and H-9. The experiment was run in $CDCl_3$, and as expected, enhancements were almost identical and so proved of no use for ascertaining the stereochemistry H-13.

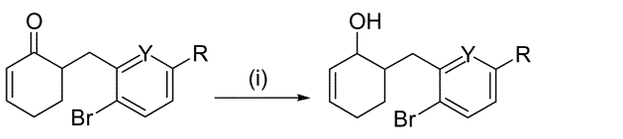
Signals for H-8, H-9 and H-10 overlapped in the ^{1}H NMR spectrum run in $CDCl_3$ and the NOE experiment was repeated in C_6D_6. Now, irradiation of H-13 of the *endo* isomer led to a small but significant enhancement of H-10″, confirming tricycle **31** as the *endo* stereoisomer. Enhancement of H-8″ was observed when H-13 of the *exo* isomer was irradiated. The corresponding effect on H-13 from H-8″ was also seen, confirming the *exo*-stereochemistry of compound **32**. Irradiation of H-8′ of **32** led to enhancement of H-10′ and *vice versa*, confirming the position of the bridge double bond.

Tricycles **31** and **32** are formed *via* a 6-*exo*-*trig* cyclisation to give the palladium(II) intermediate, which undergoes *syn*

Table 6 Study of intramolecular Heck closure with allylic alcohol precursor *syn–anti***29**

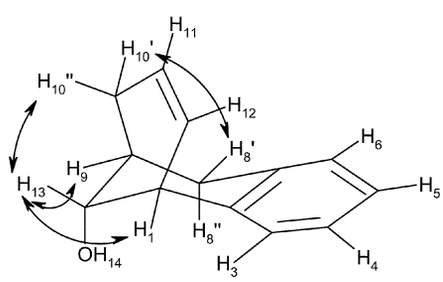
Precursor	Solvent	Base (equiv.)	Ligand (equiv.)	Yield (%) **31**	**32**	**33**	**22**
syn–anti **29**	DMA	Et_3N (12)	PPh_3 (0.4)	50	26	15	5
syn–anti **29**	DMA	Et_3N (12)	PPh_3 (0.2)	49	21	14	13

β-hydride elimination to yield the products (Scheme 12). The cycloadduct **22** is likely to have been formed *via* a 7-*endo*-*trig* cyclisation. The Pd(II) intermediate does possess a *syn* β-hydrogen which undergoes the elimination step to give the enol, which converts to the more stable ketone **22**. Tricycle **33** is probably formed *via* an intramolecular π-allyl substitution reaction (Scheme 12).

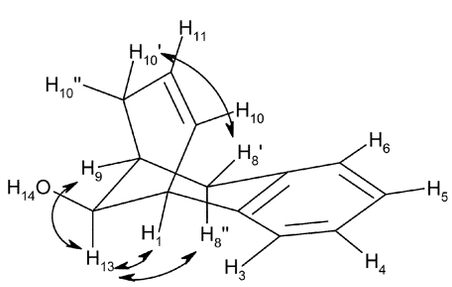


29 R=H Y=CH 87% (ratio syn:anti 1:1)
30 R=OMe Y=N 91% (ratio syn:anti 1:1)

Scheme 10 *Reagents and conditions*: (i) $NaBH_4$, $CeCl_3$, MeOH–DCM.



endo-31



exo-32

Fig. 1

Encouraged by these results, a series of reactions were carried out on the pyridine system using precursors *syn*- and *anti*-**30** (Tables 7, 8 and 9).

Reaction of *syn*-**30** with triethylamine in acetonitrile (entry 1, Table 7) provided the correct skeleton **34**, with a small amount of the novel tricycle **36**. The major product of the reaction, however, was compound **37**, the result of reductive dehalogenation (hydrodehalogenation) of the starting material (Scheme 13).

Carrying out the reaction on *syn*-**30** in refluxing DMA had a considerable effect on the reaction. Compound **36** was synthesised in excellent yield with the use of 0.2 equiv. tri(*o*-tolyl)-phosphine and triethylamine as base (entry 2). The double bond isomer **35** was isolated along with an equal amount of the desired tricycle **34**. The isolation of the isomer **35** was a new development in our intramolecular Heck cyclisation investigations. Importantly, the compound has the double bond in the correct position for the natural product huperzine A. The reduced tricycle **28** was also identified as a minor side product of the reaction.

Using 0.2 equivalents of PPh_3 (entry 3), the major product was again the two-carbon bridged tricycle **36**. The two compounds **34** and **35** with the huperzine A core, were isolated in low yield along with some of the reduced tricycle **28**. A considerable amount of starting material was recovered.

It is known that increasing ligand concentration can inhibit double bond isomerisation. We were gratified to find that by increasing the ligand concentration to 0.4 equivalents, isomerisation to **35** was completely suppressed and the expected tricycle **34** was isolated in excellent yield (entry 4).

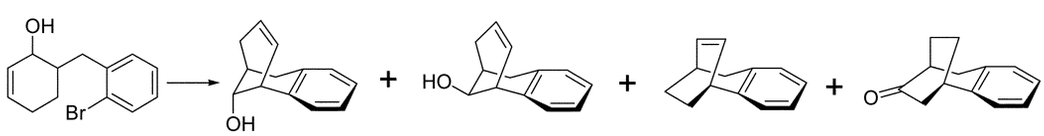
Reaction of *anti*-**30** with 0.2 equivalents of both tri(*o*-tolyl)-phosphine and PPh_3 led to equal amounts of the tricycles **38** and **39** (Scheme 14, entries 5 and 6 in Table 8). The stereochemistry of the alcohol group was determined by a series of NOE experiments.

A striking difference was observed between the reactions of *syn* and *anti*-**30** with tri(*o*-tolyl)phosphine (entries 3 and 5). The novel tricycle **36**, isolated in 50% yield with the *syn*-**30** isomer, was only a trace product when *anti*-**30** was subject to identical conditions. For the *anti*-**30** isomer in general, compound **36** is only isolated in trace amounts.

Increasing the ligand concentration to 0.4 equivalents led to an excellent yield of compound **38** (entry 7, Table 8). In all reactions with the *anti*-isomer, the reduced tricycle **28** was isolated in modest yield (entries 5, 6 and 7).

When comparing the reaction of *anti* and *syn* isomers under the best Heck conditions (entry 4 and 7), it was clear that the 6-*exo*-*trig* cyclisation performed better with *anti*-**30**. To reinforce these results, the Heck reaction was carried out on a *syn–anti* mixture of alcohols. Indeed, the tricycle **38** was shown to be the major product when a *syn–anti* mixture was subjected to cyclisation under our best Heck conditions (Table 9).

It is likely that this can be explained if one considers the steric requirement for cyclisation. It is probable than the steric crowding caused by the OH group pointing inward towards the pyridyl-bromide accounts for the lower yield obtained for the reaction of the *syn* alcohol compared to that of the *anti* alcohol where the OH group points away and does not interfere (Scheme 15).



29 **31** **32** **33** **22**

Scheme 11 Intramolecular Heck closure with *syn–anti*-**29**.

Table 7 Study of intramolecular Heck ring closure with allylic alcohol *syn*-**30**

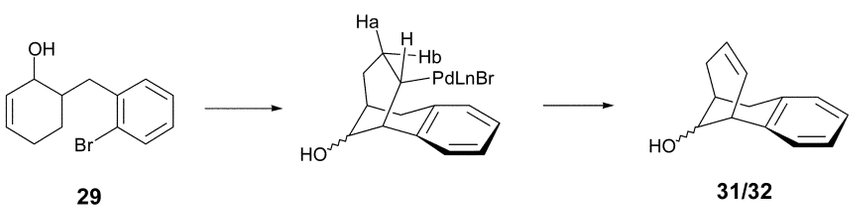
Entry	Precursor	Solvent	Base (equiv.)	Ligand (equiv.)	Yield (%) **34**	**35**	**36**	**28**	**37**
1	*syn*-**30**	CH_3CN	Et_3N (12)	PPh_3 (0.4)	18		4		25
2	*syn*-**30**	DMA	Et_3N (12)	POT (0.2)	19	19	50	9	
3	*syn*-**30**	DMA	Et_3N (12)	PPh_3 (0.2)	7	7	27	11	
4	*syn*-**30**	DMA	Et_3N (12)	PPh_3 (0.4)	61		20	15	

Table 8 Study of intramolecular Heck ring closure with allylic alcohol *anti*-**30**

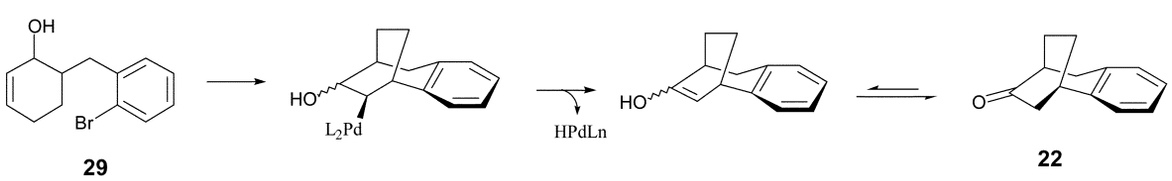
Entry	Precursor	Solvent	Base (equiv.)	Ligand (equiv.)	Yield (%) **38**	**39**	**36**	**28**
5	*anti*-**30**	DMA	Et_3N (12)	POT (0.2)	29	29	2	20
6	*anti*-**30**	DMA	Et_3N (12)	PPh_3 (0.2)	30	30	3	19
7	*anti*-**30**	DMA	Et_3N (12)	PPh_3 (0.4)	66	—	2	25

Table 9 Study of intramolecular Heck ring closure with *syn–anti*-**30**

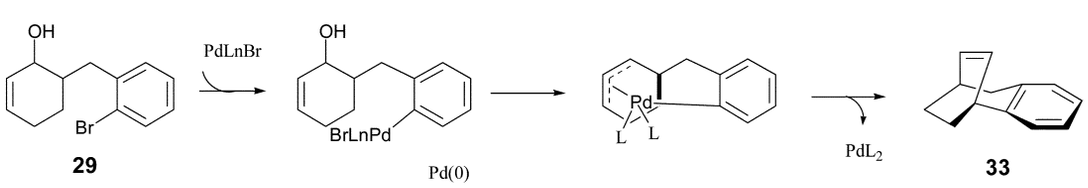
Entry	Precursor	Solvent	Base (equiv.)	Ligand (equiv.)	Yield (%) **38**	**34**	**36**	**28**
1	*syn*/*anti*-**30**	DMA	Et_3N (12)	PPh_3 (0.4)	39	33	15	10



Formation of cycloadducts **31** and **32**: 6-exo trig cyclisation



Formation of cycloadduct **22**: 7-endo trig cyclisation



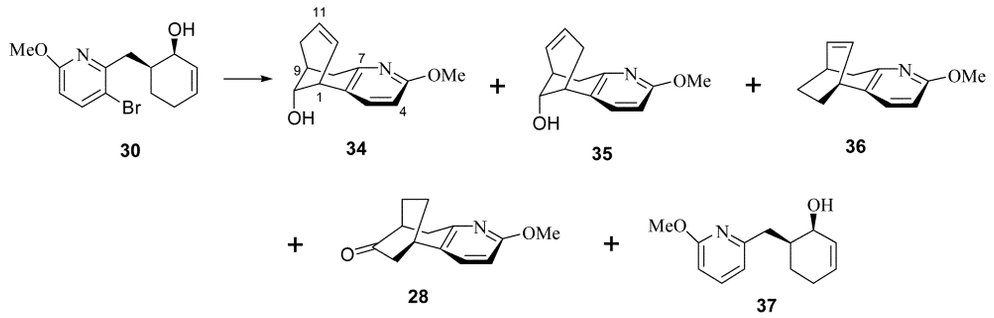
Formation of cycloadduct **33**

Scheme 12 Mechanisms for formation of compounds **31**, **32**, **33** and **22**.

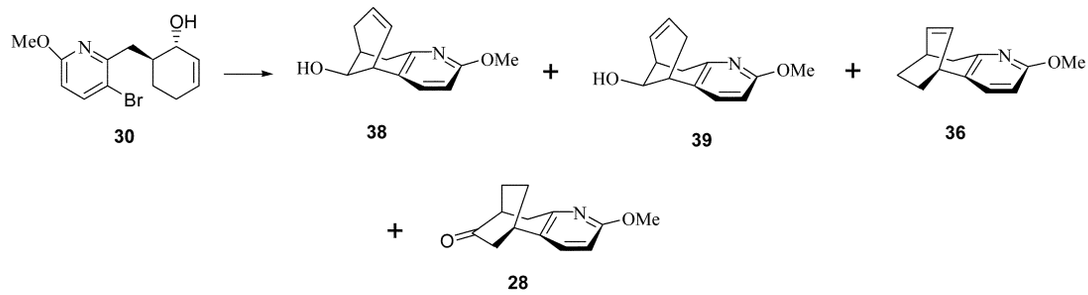
Conclusion

Since compounds **34** and **38** can be oxidised with PCC to produce the same ketone **27**, and compounds **35** and **39** can be oxidised to ketone **40**[10] (Scheme 16), we have achieved a highly convergent synthesis of the basic tricyclic skeleton of huperzine A, with most reactions carried out on at least the half gram scale. Comparison of the structure of compound **40** with huperzine A reveals that it lacks a methyl group at C-11, an ethylidene group at C-13, and most importantly an amino group at C-1.

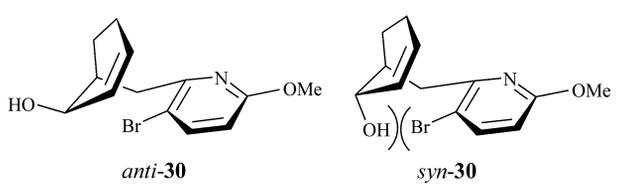
In consequence, our present investigations are directed towards the synthesis of the key intermediate **41**, which we hope to convert into both the natural product and a variety of analogues. In addition, our investigations have shown that by subtle manipulation of the conditions employed in the intramolecular Heck reaction, it is possible to produce a number of novel ring systems. We propose converting these into a range of



Scheme 13 Intramolecular Heck ring closure with *syn*-**30**.



Scheme 14 Intramolecular Heck ring closure with *anti*-**30**.



Scheme 15

new compounds that incorporate at least two nitrogen atoms, for assessment of their structure–biological activity profiles.

Experimental

All solvents were pre-dried. Acetonitrile, dichloromethane, diethyl ether and methanol were distilled from calcium hydride under nitrogen or argon. Tetrahydrofuran was dried by distillation in the presence of sodium and benzophenone. DMF was dried over 4 Å molecular sieves. For flash column chromatography, ether and petroleum ether 40–60 °C (Pet.Ether) was used. Thin layer chromatography was used to monitor reactions using Polygram® SIL G/UV_{254} precoated plastic sheets with a 0.2 mm layer of silica gel containing fluorescent indicator UV_{254}. Plates were visualised using a 254 nm UV lamp, potassium permanganate and phosphomolybdic acid stain. Flash column chromatography was carried out using Sorbsil™ C60 silica gel (40–60 mesh) with the eluent or the gradient of eluents reported. NMR spectra were recorded using JEOL EX400, Bruker DPX250, Bruker WM250, Brucker Avance300 and Brucker DRX500 spectrometers. Samples were dissolved in $CDCl_3$ with tetramethylsilane as a reference or in D_4-methanol. IR spectra were recorded using a Perkin-Elmer 881 series double beam spectrophotometer, Perkin-Elmer 1720-X FT-IR spectrophotometer. CI-MS experiments as well as and EI-MS experiments were carried out on a VG Autospec spectrometer. Elemental analyses were carried out by Medac Ltd (Brunel University) and ASEP (Queen's University of Belfast). Analyses with ASEP were carried out with a precision of 0.3%. Melting points were recorded on a Kofler hot plate or Stuart melting point apparatus and are uncorrected.

3-Bromo-6-methoxy-2-methylpyridine *N*-oxide (4)

m-CPBA (18.13 g, 63.03 mmol) was added portionwise to a solution of 3-bromo-6-methoxy-2-methylpyridine (8.49 g, 42.02 mmol) in $CHCl_3$ (130 mL) over a period of 3 h. The reaction mixture was stirred overnight and the solvent was removed under reduced pressure. The crude product was purified by flash chromatography (20–100% diethyl ether–petroleum ether solvent gradient) to afford the *N*-oxide as a yellow oil (5.61 g, 91% based on recovered starting material).

ν_{max}(film)/cm^{-1} 3503, 1605, 1493; δ_H(400 MHz; CD_3OD) 2.69 (3H, s, 7-H), 4.09 (3H, s, OCH_3), 7.10 (1H, d, *J* 9.2 Hz, 5-H), 7.76 (1H, d, *J* 9.2 Hz, 4-H); *m*/*z* (CI) 218 (MH^+, 100%), 202 (31), 171 (24), 93 (11), 65 (10); $C_7H_9BrNO_2$ [MH^+ and ^{79}Br] *required* 217.9817, found 217.9806.

2-(Acetoxymethyl)-3-bromo-6-methoxypyridine (5)

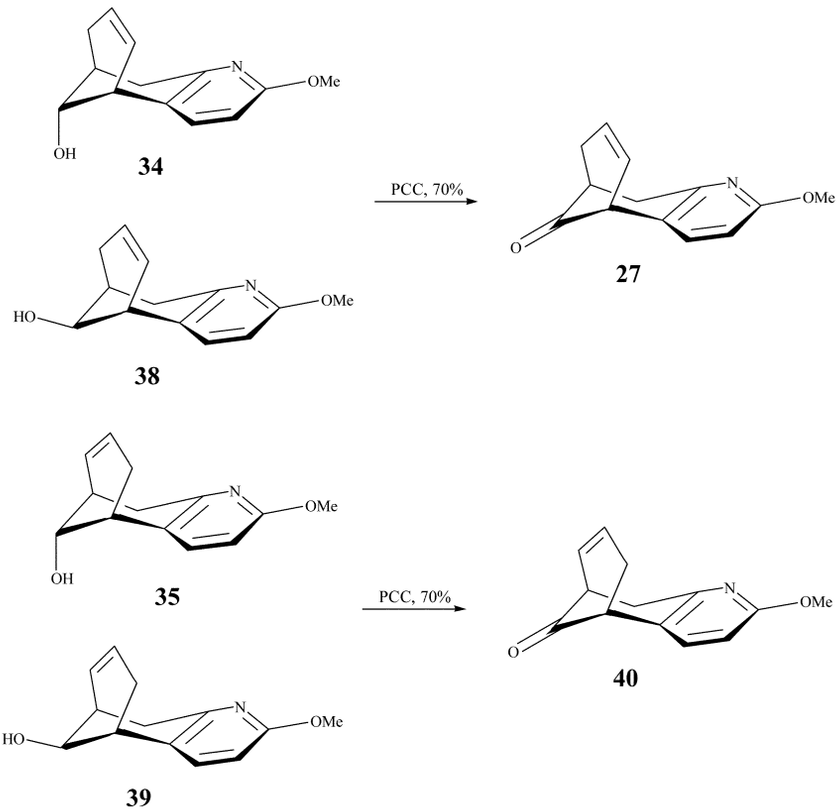
A solution of *N*-oxide **4** (5.61 g, 25.72 mmol) in acetic anhydride (32 mL) was heated to 120 °C for 3 h under nitrogen. Methanol was added to the reaction mixture and the solvent was then removed under reduced pressure. The crude product was taken up in Et_2O and the resulting solution was washed successively with a saturated aqueous solution of sodium bicarbonate (3 × 60 mL), water (80 mL) and brine (50 mL). Finally the organic extract was dried over $MgSO_4$ and concentrated under reduced pressure to produce the pure acetate as an yellow oil (5.33 g, 80%).

ν_{max}/cm^{-1} 2915, 1745, 1652, 1580; δ_H(400 MHz; $CDCl_3$) 2.18 (3H, s, $OCOCH_3$), 3.89 (3H, s, OCH_3), 5.22 (2H, s, 7-H), 6.59 (1H, d, *J* 8.8 Hz, 5-H), 7.66 (1H, d, *J* 8.8 Hz, 4-H); δ_C(125 MHz; $CDCl_3$) 20.7 (CH_3, $OCOCH_3$), 53.6 (CH_3, OCH_3), 65.7 (CH_2, 7-C), 110.7 (C, 3-C), 111.8 (CH, 5-C), 142.6 (CH, 4-C), 150.2 (C, 2-C), 162.7 (C, 6-C), 170.6 (C, $OCOCH_3$).

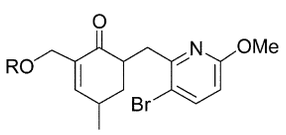
3-Bromo-2-formyl-6-methoxypyridine (3)

A 1 M aqueous solution of potassium carbonate (58 mL, 58 mmol) was added to a solution of acetate **5** (8.76 g, 33.68 mmol) in MeOH at room temperature and the resulting solution was stirred for 1 h. The solvent was removed under reduced pressure and the residue was dissolved in $CHCl_3$. The resulting solution was washed with brine (70 mL), dried over $MgSO_4$ and concentrated under reduced pressure to produce the pure alcohol as an orange oil (7.26 g, quant.).

ν_{max}/cm^{-1} 3460, 1575, 1468; δ_H(400 MHz; $CDCl_3$) 3.97 (3H, s, OCH_3), 4.68 (2H, s, 7-H), 6.61 (1H, d, *J* 8.6 Hz, 5-H), 7.68 (1H, d, *J* 8.6 Hz, 4-H); δ_C(100 MHz; $CDCl_3$) 53.8 (CH_3, OCH_3), 62.9 (CH_2, 7-C), 110.9 (C, 3-C), 111.0 (CH, 5-C), 142.6 (CH, 4-C),



Scheme 16



41

153.5 (C, 2-C), 162.4 (C, 6-C); *m*/*z* (CI) 218 (MH^+, 100%), 202 (13), 188 (39), 170 (21), 119 (12), 80 (12), 58 (15), 43 (32). $C_7H_9BrNO_2$ [MH^+ and ^{79}Br] *required* 217.9817, found 217.9821.

Manganese dioxide (20.1 g, 0.23 mol) was added to a solution of the alcohol (4.2 g, 0.19 mol) in $CHCl_3$ (1.5 L). The reaction mixture was stirred for 3 days and was filtered through a pad of Celite. The filtrate was concentrated under reduced pressure to afford the pure aldehyde as a white solid (3.52 g, 84%).

ν_{max}/cm^{-1} 2924, 1715, 1582, 1466; δ_H(400 MHz; $CDCl_3$) 4.02 (3H, s, OCH_3), 6.85 (1H, d, *J* 8.8 Hz, 5-H), 7.82 (1H, d, *J* 8.8 Hz, 4-H), 10.15 (1H, s, C*H*O); δ_C(100 MHz; $CDCl_3$) 54.1 (CH_3, OCH_3), 114.0 (C, 3-C), 117.4 (CH, 5-C), 144.5 (CH, 4-C), 145.2 (C, 2-C), 163.0 (C, 6-C), 190.5 (CH, C*H*O); $C_7H_7BrNO_2$ [MH^+ and ^{79}Br] *required* 215.9660, found 215.9666.

2-(Hydroxymethyl)-3-bromo-6-methoxypyridine (13)

Stirring 2-(acetoxymethyl)-3-bromo-6-methoxypyridine **5** (1.10 g, 4.23 mmol) with K_2CO_3 (1 M solution, 7.28 mL, 7.28 mmol) in methanol (110 mL) for 50 min provided the alcohol (0.88 g, 96% yield) as a white solid.

Mp 45–47 °C; ν_{max}/cm^{-1} 3447, 2949, 2860, 1575, 1467, 1405, 1321, 1196, 1121, 1070, 1022, 954, 823, 668; δ_H(500 MHz; $CDCl_3$) 3.97 (3H, s, OCH_3), 4.01 (1H, br s, O*H*), 4.68 (2H, s, 7-H), 6.60 (1H, d, *J* 8.7 Hz, 5-H), 7.68 (1H, d, *J* 8.7 Hz, 4-H); δ_C(125 MHz; $CDCl_3$) 53.9 (CH_3, OCH_3), 63.0 (CH_2, 7-C), 108.8 (C, 3-C), 110.9 (CH, 5-C), 142.7 (CH, 4-C), 153.7 (C, 2-C), 162.5 (6-C); *m*/*z* (EI) 217 (86%), 190 (100), 173 (45), 63 (38), 40 (48); $C_7H_8BrNO_2$ [M^+, ^{79}Br] *required* 216.9738, found 216.9742.

2-(Iodomethyl)-3-bromo-6-methoxypyridine (14)

To a solution of iodine (1.71 g, 6.74 mmol) and imidazole (0.46 g, 6.74 mmol) in dry dichloromethane (15 mL) at 0 °C was added portionwise triphenylphosphine (1.77 g, 6.74 mol) and the resultant solution was stirred at this temperature for 20 min prior to the addition of the alcohol (1.23 g, 5.63 mmol). The reaction mixture was quenched with water (15 mL), taken up with ether, washed with water, dried over $MgSO_4$, and concentrated under reduced pressure to yield a crude brown oil. Purification through a plug silica column yielded the iodomethyl pyridine as a yellow oil (1.22 g, 66%).

ν_{max}/cm^{-1} 2982, 2948, 1579, 1465, 1416, 1321, 1262, 1037, 1010, 823, 643, 574, 508; δ_H(500 MHz; $CDCl_3$) 3.91 (3H, s, OCH_3), 4.56 (2H, s, 7-H), 6.54 (1H, d, *J* 8.7 Hz, 5-H), 7.61 (1H, d, *J* 8.7 Hz, 4-H); δ_C(125 MHz; $CDCl_3$) 6.3 (CH_2, 7-C), 53.9 (CH_3, OCH_3), 110.3 (C, 2-C), 112.2 (CH, 5-C), 143.1 (CH, 4-C), 153.1 (C, 3-C), 162.7 (6-C); *m*/*z* (EI) 329 (32%), 202 (70), 127 (68), 78 (100), 63 (61), 51 (56), 38 (53); C_7H_7BrINO [M^+, ^{79}Br] *required* 326.8758, found 326.8756; CHN analysis found C 26.24, H 2.20, N 4.50 required C 25.64, H 2.15, N 4.27%.

2-(Bromomethyl)-3-bromo-6-methoxypyridine (15)

5-Bromo-6-methyl-2-methylpyridine (1.22 g, 6.05 mmol), *n*-bromosuccinimide (1.08 g, 6.05 mmol), 2,2′-azobisisobutyronitrile (0.15 g, 0.91 mmol), acetic acid (1.75 mL) in CCl_4 (60 mL) under argon was irradiated (150 W Hg lamp) for 4 hours. Flash chromatography (5%, EtOAc–hexane) and concentration under reduced pressure gave pure 2-bromomethyl-3-bromo-6-methoxypyridine as a brown oil (1.21 g, 71%).

ν_{max}/cm^{-1} 2983, 2950, 2857, 1581, 1464, 1417, 1324, 1263, 1219, 1105, 1037, 1013, 835; δ_H(500 MHz; $CDCl_3$) 3.92 (3H, s, OCH_3), 4.60 (2H, s, 7-H), 6.58 (1H, d, *J* 8.7 Hz, 5-H), 7.66 (1H, d, *J* 8.7 Hz, 4-H); δ_C(125 MHz; $CDCl_3$) 33.4 (CH_2, 7-C), 53.9 (CH_3, OCH_3), 109.5 (C, 3-C), 112.8 (CH, 5-C), 143.0 (CH, 4-C), 151.8 (C, 2-C), 162.8 (C, 6-C); *m*/*z* (EI) 280 (100%), 200 (72), 78 (36); $C_7H_7Br_2NO$ [M^+ and ^{79}Br] *required* 278.8894, found 278.8907.

Synthesis of alkylated adducts

n-BuLi was added to a solution of diisopropylamine in dry THF at 0 °C, and stirred under nitrogen at this temperature for 15 min. The reaction mixture was cooled to −78 °C and HMPA or DMPU was then added. After stirring for a further 15 min cyclohexanone was added. After stirring for 45 min at −78 °C the halide reagent was slowly added. The reaction mixture was stirred for 2 h at −78 °C, allowed to warm to room temperature overnight, and then quenched with aqueous ammonium chloride. The organic layer was taken up with diethyl ether, washed with water and brine, dried over $MgSO_4$ and concentrated under reduced pressure to yield the crude ketone. Purification by flash chromatography (10% EtOAc–hexane) yielded the pure ketone.

2-[(3-Bromo-6-methoxypyridin-2-yl)methyl]cyclohexanone (16)

6-(Iodomethyl)-5-bromo-2-methoxypyridine (18.0 g, 0.055 mol), with a solution of LDA [diisopropylamine (8.30 mL, 0.059 mol), *n*-BuLi (23.2 mL, 2.5 M in hexane, 0.058 mol)] and cyclohexanone (5.40 mL, 0.055 mol) in THF (230 mL) and HMPA (19.5 mL, 0.112 mol) yielded after flash chromatography the pure ketone **16** as a white solid (13.3 g, 81%).

Mp 53–55 °C. ν_{max}/cm^{-1} 2939, 2859, 1712, 1575, 1459, 1417, 1297, 1268, 1191, 1125, 1036, 1011, 820, 664, 642; δ_H(500 MHz; $CDCl_3$) 1.51 (1H, m, 3-H), 1.65–1.71 (2H, m, 4-H and 5-H), 1.86 (1H, m, 4-H), 2.09 (2H, m, 5-H and 3-H), 2.42 (2H, m, 6-H), 2.74 (1H, dd, *J* 7.7 and 15.6 Hz, 7-H), 3.12 (1H, m, 2-H), 3.35 (1H, dd, *J* 5.8 and 15.6, Hz, 7-H), 3.97 (3H, s, OCH_3), 6.45 (1H, d, *J* 8.6 Hz, 5′-H), 7.61 (1H, d, *J* 8.6 Hz, 4′-H); δ_C(75 MHz, $CDCl_3$) 25.1 (CH_2, 4-C), 28.0 (CH_2, 5-C), 33.5 (CH_2, 3-C), 35.9 (CH_2, 7-C), 41.9 (CH, 6-C), 49.1 (CH, 2-C), 53.2 (CH_3, OCH_3), 109.4 (CH, 5′-C), 112.1 (C, 3′-C), 142.0 (CH, 4′-C), 155.2 (C, 2′-C) 162.0 (C, 6′-C); *m*/*z* (EI) 299 (70%), 297 (68), 271 (56), 269 (61), 242 (64), 240 (61), 218 (40), 203 (100), 201 (86), 190 (51), 162 (35); $C_{13}H_{16}BrNO_2$ [M^+, ^{79}Br] *required* 297.0364, found 297.0365.

Synthesis of phenylseleno derivatives

n-BuLi was added to a solution of diisopropylamine in dry THF at 0 °C and stirred under nitrogen at this temperature for 30 min. HMPA was then added at −78 °C and stirred for 30 min. The ketone was slowly added at −78 °C and stirred for 1 h at this temperature. Phenylselenyl chloride in THF was slowly added to the reaction mixture, stirred for 30 min at −78 °C, and then quenched with aqueous ammonium chloride. The organic layer was taken up with diethyl ether, washed with water and brine, dried over $MgSO_4$ then concentrated under reduced pressure to yield the crude diastereomeric mixture. Purification by flash chromatography yielded the *syn*-selenide and the *anti*-selenide.

6-[(3-Bromo-6-methoxypyridin-2-yl)methyl]-2-phenylselenocyclohexanone (17)

Phenylselenyl chloride (9.29 g, 0.049 mol), with a solution of LDA [diisopropylamine (7.29 mL, 0.051 mol), *n*-BuLi (2.5 M in hexane, 20.4 mL, 0.051 mol)] and 2-[(3-bromo-6-methoxypyridin-2-yl)methyl]cyclohexanone (13.2 g, 0.044 mol) in THF (7.0 mL) and HMPA (17.1 mL, 0.098 mol) yielded after chromatography the *syn*-isomer as a white solid (10.8 g, 54% yield) and *anti*-isomer as a white solid (6.54 g, 32% yield). ν_{max}/cm^{-1} (*syn*–*anti* mixture) 2931, 2856, 1709, 1575, 1460, 1417, 1298, 1269, 1123, 1022, 910, 821, 736, 692.

syn-Isomer: δ_H(500 MHz; $CDCl_3$) 1.50 (1H, m, 5-H), 1.81 (2H, m, 3-H and 4-H), 2.08 (2H, m, 4-H and 5-H), 2.27 (1H, m, 3-H), 2.72 (1H, dd, *J* 7.1 and 15.8 Hz, 7-H), 3.20 (1H, m, 6-H), 3.31 (1H, dd, *J* 6.2 and 15.8 Hz, 7-H), 3.76 (3H, s, OCH_3), 4.11 (1H, dd, *J* 5.9 and 12.9 Hz, 2-H), 6.39 (1H, d, *J* 8.6 Hz, 5′-H), 7.18 (3H, m, H_{arom}), 7.50 (2H, m, H_{arom}), 7.54 (1H, d, *J* 8.6 Hz, 4′-H); δ_C(75 MHz, $CDCl_3$) 22.1 (CH_2, 4-C), 33.3 (CH_2, 5-C), 34.0 (CH_2, 7-C), 36.2 (CH, 3-C), 44.5 (CH, 2-C), 51.1 (CH, 6-C), 53.6 (CH_3, OCH_3), 109.7 (CH, 5′-C), 112.2 (C, 3′-C), 127.0–134.0 (5 × CH, C_{arom}), 142.2 (CH, 4′-C), 155.3 (C, 2′-C), 162.2 (C, 6′-C), 208.7 (C, 1-C).

anti-Isomer: δ_H(500 MHz; $CDCl_3$) 1.52 (1H, m, 5-H), 1.80 (1H, m, 4-H), 1.95 (1H, m, 4-H), 2.09 (1H, m, 5-H), 2.24 (1H, m, 3-H), 2.32 (1H, m, 3-H), 2.70 (1H, dd, *J* 7.5 and 15.5 Hz, 7-H), 3.38 (1H, dd, *J* 5.7 and 15.5 Hz, 7-H), 3.87 (1H, s, OCH_3), 3.94 (2H, m, 6-H and 2-H), 6.45 (1H, d, *J* 8.6 Hz, 5′-H), 7.25 (3H, m, H_{arom}), 7.49 (2H, m, H_{arom}), 7.61 (1H, d, *J* = 8.6 Hz, 4′-H); δ_C(75 MHz, $CDCl_3$) 22.5 (CH_2, 4-C), 33.7 (CH_2, 3-C), 34.0 (CH_2, 5-C), 36.7 (CH_2, 7-C), 45.0 (CH, 2-C), 52.0 (CH, 6-C), 54.1 (CH_3, OCH_3), 110.1 (CH, 5′-C), 112.6 (C, C_{arom}), 128.4–134.4 (5 × CH, C_{arom}), 142.7 (CH, 4′-C), 155.8 (C, 2′-C), 162.6 (C, 6′-C), 209.1 (C, 1-C).

Oxidation of phenylseleno derivatives

The phenylseleno derivative was dissolved in methanol and cooled to 0 °C. Sodium periodate dissolved in a minimum of water was added dropwise. The reaction mixture was warmed to room temperature and allowed stir for 5 hours. The mixture was filtered, washed with methanol, diluted with ether and dried over $MgSO_4$. Purification by wet flash chromatography (Et_2O–Pet. Ether) yielded the pure α,β unsaturated ketone.

6-[(3-Bromo-6-methoxypyridin-2-yl)methyl]cyclohex-2-enone (18)

6-[(3-Bromo-6-methoxypyridin-2-yl)methyl]-2-phenylselenocyclohexanone (8.61 g, 0.020 mol) dissolved in methanol (250 mL) with sodium periodate (4.89 g, 0.023 mol) in a minimum water yielded after work up and chromatography the pure α,β unsaturated ketone as an orange oil (4.34 g, 77%).

ν_{max}/cm^{-1} 2944, 1682, 1575, 1457, 1417, 1387 1297, 1118, 1037, 897, 820, 740; δ_H(500 MHz; $CDCl_3$) 1.85 (1H, m, 5-H), 2.01 (1H, m, 5-H), 2.40 (2H, m, 4-H), 2.89 (1H, dd, *J* 9.1 and 15.3 Hz, 7-H), 3.05 (1H, m, 6-H), 3.48 (1H, dd, *J* 4.1 and 15.3 Hz, 7-H), 3.85 (3H, s, OCH_3), 6.06 (1H, ddd, *J* 1.4, 2.6 and 10.0 Hz, 2-H), 6.47 (1H, d, *J* 8.6 Hz, 5′-H), 6.96 (1H, m, 3-H), 7.62 (1H, d, *J* 8.6 Hz, 4′-H); δ_C(75 MHz, $CDCl_3$) 25.7 (CH_2, 4-C), 27.7 (CH_2, 5-C), 36.0 (CH_2, 7-C), 45.7 (CH, 6-C), 53.6 (CH_3, OCH_3), 109.8 (CH, 5′-C), 112.4 (C, 3′-C), 129.6 (CH, 2-C), 142.3 (C, 4′-C), 149.6 (CH, 3-C), 155.1 (C, 2′-C), 162.3 (C, 6′-C), 200.7 (C, 1-C); *m*/*z* (EI) 297 (58%), 227 (40), 217 (94), 210 (85), 188 (57), 123 (80), 68 (67), 39 (100); $C_{13}H_{13}BrO$ [M^+, ^{79}Br] *required* 295.2079, found 295.0204.

Synthesis of allylic alcohols

Sodium borohydride was added to a solution of ketone and cerium(III) chloride heptahydrate in a mixture of dichloromethane–methanol. The resulting suspension was stirred for 20 min. The reaction was concentrated by rotary evaporation and diluted with water and 2.5 M HCL. The layers were separated, and the aqueous phase was extracted with diethyl ether. The combined organic portions were washed with brine, dried over $MgSO_4$, filtered and concentrated under reduced pressure.

6-[(3-Bromo-6-methoxypyridin-2-yl)methyl]cyclohex-2-en-1-ol (30)

2-[6-(Cyclohex-2-enone)]methyl-3-bromo-6-methoxypyridine (4.30 g, 0.014 mol) in dichloromethane–methanol (100 mL–100 mL) with sodium borohydride (0.57 g, 0.015 mol) and cerium(III) chloride heptahydrate (5.56 g, 0.015 mol) yielded after work up and chromatography the *syn*-alcohol as a white solid (1.96 g, 46%) and the *anti*-alcohol as a white solid (1.96 g, 46%).

syn-Isomer: ν_{max}/cm^{-1} 3419, 2924, 2874, 1575, 1464, 1417, 1320, 1260, 1118, 1037, 1013, 820; δ_H(400 MHz; $CDCl_3$) 1.56 (1H, m, 5-H), 1.66 (1H, m, 5-H), 2.04 (1H, m, 4-H and 6-H), 2.15 (1H, m, 4-H), 2.87 (1H, dd, *J* 10.8 and 13.2 Hz, 7-H), 3.08 (1H, dd, *J* 5.2 and 13.2 Hz, 7-H), 3.78 (1H, m, 1-H), 3.90 (3H, s, OCH_3), 5.81 (1H, m, 2-H), 5.92 (1H, m, 3-H), 6.52 (1H, d, *J* 8.7 Hz, 5′-H), 7.64 (1H, d, *J* 8.7 Hz, 4′-H); δ_C(100 MHz, $CDCl_3$) 23.8 (CH_2, 5-C), 25.8 (CH_2, 4-C), 39.0 (CH_2, 7-C), 39.3 (CH, 6-C), 53.7 (CH_3, OCH_3), 64.1 (CH, 1-C), 110.4 (CH, 5′-C), 111.9 (C, 3′-C), 127.7 (CH, 3-C), 131.4 (CH, 2-C), 143.1 (CH, 4′-C), 155.9 (C, 2′-C), 162.3 (C, 6′-C); *m*/*z* (EI) 299 (30%), 297 (31), 280 (15), 228 (57), 203 (97), 201 (100); $C_{13}H_{15}BrO$ [M^+, ^{79}Br] *required* 297.0364, found 297.0363; CHN analysis found C 52.45, H 5.44, N 4.80 required C 52.36, H 5.41, N 4.70%.

anti-Isomer: mp 77–78 °C; ν_{max}/cm^{-1} 3423, 3024, 2924, 1574, 1464, 1416, 1320, 1260, 1118, 1037, 1013, 820; δ_H(400 MHz; $CDCl_3$) 1.51 (1H, m, 5-H), 1.83 (1H, m, 5-H), 2.06 (3H, m, 4-H and 6-H), 2.94 (1H, dd, *J* 6.3 and 14.5 Hz, 7-H), 3.10 (1H, dd, *J* 5.9 and 14.5 Hz, 7-H), 3.27 (1H, br s, 7-H), 3.90 (3H, s, OCH_3), 4.08 (1H, m, 1-H), 5.70 (1H, m, 2-H), 5.77 (1H, m, 3-H), 6.49 (1H, m, *J* 8.7 Hz, 5-H), 7.64 (1H, d, *J* 8.7 Hz, 4-H); δ_C(100 MHz, $CDCl_3$) 24.9 (CH_2, 4-C), 26.7 (CH_2, 5-C), 40.7 (CH_2, 7-C), 41.4 (CH, 6-C), 53.7 (CH_3, OCH_3), 72.1 (CH, 1-C), 110.1 (CH, 5′-C), 112.2 (C, 3′-C), 128.8 (CH, 3-C), 130.3 (CH, 2-C), 142.7 (CH, 4′-C), 156.2 (C, 2′-C), 162.4 (C, 6′-C); *m*/*z* (EI) 297 (12%), 280 (8), 228 (42), 201 (100), 188 (10); $C_{13}H_{15}BrO$ [M^+, ^{79}Br] *required* 297.0364, found 297.0357; CHN analysis C 52.24, H 5.49, N 4.69 required C 52.36, H 5.41, N 4.70%.

General method for synthesis of cycloadducts using the Heck reaction.

Palladium acetate was added to a solution of the starting material in the presence of ligand [PPh_3 or P(*o*-tolyl)$_3$] and base (Et_3N, PMP) in a solvent such as acetonitrile, dimethylformamide, dimethylacetamide (for more details see Table 2). The mixture was heated to reflux and the solution was either concentrated under reduced pressure and extracted with diethyl ether or directly extracted with diethyl ether. The combined organic extracts were washed with a saturated aqueous solution of sodium bicarbonate, with brine and dried over $MgSO_4$. The solvent was removed under reduced pressure. The crude products were purified by flash chromatography (eluent, Et_2O : Pet. ether 5 : 95) to yield separately the tricycles in a ratio and yield dependent upon the starting material and experimental conditions (see Tables 2, 4, 5, 6, 7, 8 and 9). The reactions were routinely carried out on 1–3 mmol scale.

8-(*tert*-Butyldimethylsilyloxy)-5-methoxy-6-azatricyclo-[7.3.1.0^{2,7}]trideca-2(7),3,5,11-tetraen-13-one (11b)

Colourless oil; ν_{max}/cm^{-1} 2935, 1736, 1601, 1474; δ_H(250 MHz; $CDCl_3$) −0.19 (3H, s, SiCH_3), 0.00 (3H, s, SiCH_3), 0.64 (9H, s, SiC(CH_3)$_3$), 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, OCH_3), 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* 8.6 Hz, 4-H), 7.02 (1H, d, *J* 8.6 Hz, 3-H); δ_C(62.5 MHz; $CDCl_3$) −5.0 (CH_3, SiCH_3), −4.4 (CH_3, SiCH_3), 18.2 (C, SiC(CH$_3$)$_3$), 25.7 (CH_3, SiC(CH_3)$_3$), 33.3 (CH_2, 10-C), 49.0 (CH, 1-C), 52.3 (CH, 9-C), 53.6 (CH_3, OCH_3), 80.6 (CH, 8-C), 111.2 (CH, 4-C), 126.5 (CH, 11-C), 127.7 (C, 2-C), 131.5 (CH, 12-C), 138.3 (CH, 3-C), 151.4 (C, 5-C), 162.7 (C, 7-C), 208.6 (C, 1-C); *m*/*z* (CI) 346 (MH^+, 28%), 288 (100), 186 (28), 75 (12). $C_{19}H_{28}NO_3Si$ [MH^+] *required* 346.1838, found 346.1824.

8-(*tert*-Butyldimethylsilyloxy)-5-methoxy-6-azatricyclo-[7.2.2.0^{2,7}]trideca-2(7),3,5-trien-10-one (12b)

White solid; mp 95–98 °C ($CHCl_3$) (Found C 65.2, H 8.2, N 3.4; $C_{19}H_{29}NO_3Si$ requires C 65.6, H 8.4, N 4.0%); ν_{max}/cm^{-1} 2935, 1727, 1601, 1479; δ_H (250 MHz; $CDCl_3$) −0.01 (3H, s, SiCH_3), 0.16 (3H, s, SiCH_3), 0.76 (9H, s, SiC(CH_3)$_3$), 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, OCH_3), 4.78 (1H, d, *J* 7.4 Hz, 8-H), 6.53 (1H, d, *J* 8.3 Hz, 4-H), 7.26 (1H, d, *J* 8.3 Hz, 3-H); δ_C (62.5 MHz; $CDCl_3$; Me_4Si) −5.2 (CH_3, SiCH_3), −4.2 (CH_3, SiCH_3), 18.2 (C, SiC(CH$_3$)$_3$), 20.3 (CH_2, 12-C), 25.7 (CH_3, SiC(CH_3)$_3$), 25.8 (CH_2, 13-C), 37.5 (CH, 1-C), 46.4 (CH_2, 11-C), 52.7 (CH, 9-C), 53.4 (CH_3, OCH_3), 77.6 (CH, 8-C), 110.2 (CH, 4-C), 130.0 (C, 2-C), 140.1 (CH, 3-C), 153.9 (C, 7-C), 162.7 (C, 5-C), 213.2 (C, 10-C); *m*/*z* (CI) 348 (MH^+, 32%), 290 (100), 216 (14), 174 (28); $C_{19}H_{30}NO_3Si$ [MH^+] *required* 348.1995, found 348.1984.

5-Methoxy-6-azatricyclo[7.3.1.0^{2,7}]trideca-2(7),3,5,11-tetraen-13-one (27)

Colourless oil; ν_{max}/cm^{-1} 2938, 1732, 1597, 1474, 1421, 1312, 1268, 1030; δ_H(500 MHz; $CDCl_3$) 2.64 (1H, dd, *J* 4.6 and 16.9 Hz, 10-H), 2.95 (2H, m, 9-H and 10-H), 3.23 (1H, d, *J* 18.5 Hz, 8-H), 3.52 (1H, dd, *J* 8.7, 18.5 Hz, 8-H), 3.73 (1H, d, *J* 5.7 Hz, 1-H), 3.88 (3H, s, OCH_3), 5.75 (1H, m, 11-H), 5.89 (1H, m, 12-H), 6.54 (1H, d, *J* 8.4 Hz, 4-H), 7.22 (1H, d, *J* 8.4 Hz, 3-H); δ_C(125 MHz, $CDCl_3$) 39.7 (CH_2, 10-C), 42.3 (CH_2, 8-C), 42.6 (CH, 9-C), 49.9 (CH, 1-C), 53.5 (CH_3, OCH_3), 108.7 (CH, 4-C), 125.8 (CH, 10-C), 126.9 (C, C_{arom}), 131.3 (CH, 11-C), 138.0 (CH, 3-C), 152.5 (C, C_{arom}), 162.8 (C, C_{arom}), 211.0 (C, 13-C); *m*/*z* (EI) 185 (90%), 157 (85), 141 (70), 127 (73), 116 (100), 39 (84); $C_{13}H_{12}O$ *required* 184.0888, found 184.0882; CHN analysis found C 72.54, H 6.21, N 6.50 required C 72.54, H 6.09, N 6.51%.

5-Methoxy-6-azatricyclo[7.2.2.0^{2,7}]trideca-2(7),3,5-trien-10-one (28)

ν_{max}/cm^{-1} 2938, 1710, 1596, 1577, 1477, 1420, 1313, 1270, 1031; δ_H(400 MHz; $CDCl_3$) 2.01 (4H, m, 12-H and 13-H), 2.64 (2H, m, 11-H), 2.81 (1H, m, 9-H), 3.08 (1H, m, 1-H), 3.16 (1H, dd, *J* 3.9 and 18.5 Hz, 8-H), 3.34 (1H, ddd, *J* 1.6, 4.2 and 18.5 Hz, 8-H), 3.86 (3H, s, OCH_3), 6.47 (1H, d, *J* 8.3 Hz, 4-H), 7.26 (1H, d, *J* 8.3 Hz, 3-H); δ_C(125 MHz, $CDCl_3$) 24.2 (CH_2, 13-C), 27.7 (CH_2, 12-C), 36.1 (CH, 1-C), 42.0 (CH_2, 8-C), 45.8 (CH, 9-C), 46.5 (CH_2, 11-C), 53.2 (CH_3, OCH_3), 107.9 (CH, 4-C), 132.0 (C, 2-C), 139.9 (CH, 3-C), 153.4 (C, 5-C), 162.4 (C, 7-C), 214.9 (C, 10-C); *m*/*z* (EI) 217 (100%), 188 (32), 174 (85), 160 (53); $C_{13}H_{15}NO_2$ *required* 217.1103, found 217.1110.

(13*R*)-5-Methoxy-6-azatricyclo[7.3.1.0^{2,7}]trideca-2(7),3,5,11-tetraen-13-ol (34)

White solid; mp 87–89 °C; ν_{max}/cm^{-1} 3292, 2905, 1599, 1582, 1476, 1428, 1308, 1258, 1070, 1034; δ_H(500 MHz; C_6D_6) 1.87 (1H, m, 10-H), 2.31 (2H, m, 9-H and 10-H), 2.73 (1H, d, *J* 19.0 Hz, 8-H), 3.05 (1H, m, 1-H), 3.50 (1H, dd, *J* 8.3 and 19.0 Hz, 8-H), 3.94 (3H, s, CH_3), 4.06 (1H, ap t, *J* 3.3 Hz, 13-H), 5.41 (1H, m, 11-H), 5.73 (1H, m, 12-H), 6.60 (1H, d, *J* 8.2 Hz, 4-H), 6.92 (1H, d, *J* 8.2 Hz, 3-H); δ_C(75 MHz, C_6D_6) 33.9 (CH, 9-C), 37.0 (CH_2, 10-C), 37.7 (CH_2, 8-C), 43.0 (CH, 1-C), 54.2 (CH_3, OCH_3), 69.9 (CH, 13-C), 109.2 (CH, 4-C), 126.0 (C, 11-C), 126.8 (C, 2-C), 132.5 (CH, 10-C), 140.2 (C, 3-C), 155.6 (C, 7-C), 163.6 (C, 5-C); *m*/*z* (EI) 217 (100%), 199 (69), 198 (72), 188 (42), 160 (27), 147 (22); $C_{13}H_{15}NO_2$ *required* 217.1103, found 217.1100.

(13*R*)-5-Methoxy-6-azatricyclo[7.3.1.0^{2,7}]trideca-2(7),3,5,10-tetraen-13-ol (35)

Yellow solid; mp 88–90 °C; ν_{max}/cm^{-1} 3273, 2913, 1600, 1579, 1477, 1447, 1425, 1311, 1262, 1079, 1034, 824, 711; δ_H(300 MHz; $CDCl_3$) 1.60 (1H, br s, 14-H), 2.09 (1H, dd, *J* 4.7 and 17.8

Hz, 12-H), 2.64 (1H, m, 12-H), 2.67 (1H, d, *J* 17.6 Hz, 8-H), 2.74 (1H, m, 9-H), 3.04 (1H, m, 1-H), 3.17 (1H, dd, *J* 5.6 and 17.6 Hz, 8-H), 3.90 (3H, s, OCH_3), 4.19 (1H, m, 13-H), 5.50 (1H, m, 11-H), 5.77 (1H, m, 10-H), 6.56 (1H, d, *J* 8.3 Hz, 4-H), 7.44 (1H, d, *J* 8.3 Hz, 3-H); δ_C(125 MHz, $CDCl_3$) 32.7 (CH_2, 8-C), 35.1 (CH, 9-C), 35.5 (CH_2, 12-C), 39.3 (CH, 1-C), 53.3 (CH_3, O*C*H_3), 68.5 (CH, 13-C), 108.8 (CH, 4-C), 124.3 (CH, 11-C), 125.0 (C, 2-C), 130.4 (CH, 10-C), 140.5 (CH, 3-C), 152.4 (C, 7-C), 162.6 (C, 5-C); *m*/*z* (EI) 217 (100%), 199 (69), 198 (72), 188 (42), 160 (27), 147 (22); $C_{13}H_{15}NO_2$ *required* 217.1103, found 217.1100.

5-Methoxy-6-azatricyclo[7.2.2.0^{2,7}]trideca-2(7),3,5,10-tetraene (36)

Orange oil; ν_{max}/cm^{-1} 2935, 1594, 1576, 1474, 1418, 1307, 1256, 1038, 700; δ_H(400 MHz; $CDCl_3$) 1.76 (2H, m, 12-H), 1.79 (1H, m, 13-H), 1.96 (1H, m, 13-H), 2.62 (1H, m, 9-H), 2.94 (2H, m, 8-H), 3.07 (1H, m, 1-H), 3.76 (3H, s, OCH_3), 6.06 (1H, ap t, *J* 7.9 Hz, 10-H), 6.32 (1H, d, *J* 8.2 Hz, 4-H), 6.34 (1H, ap t, *J* 8.2 Hz, 11-H), 7.10 (1H, d, *J* 8.2 Hz, 3-H); δ_C(125 MHz, $CDCl_3$) 26.0 (CH_2, 12-C), 30.9 (CH_2, 13-C), 31.4 (CH, 9-C), 38.9 (CH, 1-C), 42.6 (CH_2, 8-C), 53.6 (CH_3, O*C*H_3), 107.1 (CH, C-10), 131.8 (CH, 11-C), 132.0 (C, 2-C), 136.3 (CH_2, 4-C), 139.3 (CH_2, 3-C), 155.6 (C, 7-C), 162.3 (C, 5-C); *m*/*z* (EI) 201 (100%), 173 (92), 158 (73), 143 (66), 115 (45), 77 (53), 39 (53); $C_{13}H_{15}NO$ *required* 201.1154, found 201.1153.

6-[(6′-Methoxypyridin-2-yl)methyl]cyclohexen-2-en-1-ol (37)

Yellow oil; ν_{max}/cm^{-1} 3401, 2923, 1601, 1579, 1467, 1415, 1313, 1264, 1034; δ_H(500 MHz; $CDCl_3$) 1.54 (1H, m, 5-H), 1.63 (1H, m, 5-H), 1.89 (1H, m, 6-H), 2.02 (1H, m, 4-H), 2.12 (1H, m, 4-H), 2.71 (1H, dd, *J* 4.9 and 13.2 Hz, 7-H), 2.88 (1H, dd, *J* 11.1 and 13.2 Hz, 7-H), 3.86 (1H, ap s, 1-H), 3.92 (3H, s, OCH_3), 4.48 (1H, s, OH), 5.83 (1H, m, 2-H), 5.90 (1H, m, 3-H), 6.60 (1H, d, *J* 8.3 Hz and 11-H), 6.77 (1H, d, *J* 7.2 Hz, 13-H), 7.51 (1H, dd, *J* 7.2 and 8.3 Hz, 12-H); δ_C(125 MHz, $CDCl_3$) 24.2 (CH_2, 5-C), 25.8 (CH_2, 4-C), 40.2 (CH_2, 7-C), 41.2 (CH, 6-C), 53.4 (CH_3, O*C*H_3), 64.0 (CH, 1-C), 108.5 (CH, 11-C), 116.1 (CH, 13-C), 128.2 (CH, 2-C), 131.0 (CH, 3-C), 139.5 (CH, 12-C), 158.3 (C, 10-C), 162.4 (C, 8-C); *m*/*z* (EI) 219 (34%), 200 (21), 150 (67), 123 (100); $C_{13}H_{17}NO_2$ *required* 219.1259, found 219.1256.

(13*S*)-5-Methoxy-6-azatricyclo[7.3.1.0^{2,7}]trideca-2(7),3,5,11-tetraen-13-ol (38)

Orange oil; ν_{max}/cm^{-1} 3400, 2607, 1597, 1475, 1425, 1308, 1254, 1197, 1038, 821, 729, 694; δ_H(500 MHz; C_6D_6) 1.88 (1H, m, 10-H), 2.31 (2H, m, 9-H and 10-H), 2.72 (1H, d, *J* 7.2 Hz, 8-H), 3.05 (1H, m, 1-H), 3.49 (1H, dd, *J* 8.3 Hz and 18.9 Hz, 8-H), 3.94 (3H, s, OCH_3), 4.06 (1H, m, 13-H), 5.41 (1H, m, 11-H), 5.72 (1H, m, 12-H), 6.60 (1H, d, *J* 8.2 Hz, 4-H), 6.92 (1H, d, *J* 8.2 Hz, 3-H); δ_C(75 MHz, C_6D_6) 33.9 (CH, 9-C), 37.0 (CH_2, 10-C), 37.7 (CH_2, 8-C), 43.0 (CH, 1-C), 54.2 (CH_3, O*C*H_3), 69.9 (CH, 13-C), 109.2 (CH, 4-C), 126.0 (CH, 11-C), 132.5 (CH, 12-C), 140.2 (CH, 3-C), 155.6 (C, 7-C), 163.6 (C, 5-C); $C_{13}H_{15}NO_2$ *required* 217.1103, found 217.1101.

(13*S*)-5-Methoxy-6-azatricyclo[7.3.1.0^{2,7}]trideca-2(7),3,5,10-tetraen-13-ol (39)

Yellow oil; ν_{max}/cm^{-1} 3273, 2913, 1600, 1579, 1477, 1447, 1425, 1311, 1262, 1079, 1034, 824, 711; δ_H(300 MHz; $CDCl_3$) 1.91 (1H, dd, *J* 4.5, 17.8 Hz, 12-H), 2.20 (1H, br s, 14-H), 2.64 (2H, m, 9-H, 12-H), 2.85 (1H, d, *J* 18.4 Hz, 8-H), 3.01 (1H, m, 1-H), 3.13 (1H, dd, *J* 5.8, 17.8 Hz, 8-H), 3.87 (3H, s, OCH_3), 4.12 (1H, m, 13-H), 5.66 (2H, m, 10-H, 11-H), 6.55 (1H, d, *J* 8.4 Hz, 4-H), 7.30 (1H, d, *J* 8.4 Hz, 3-H); δ_C(125 MHz, $CDCl_3$) 29.6 (CH_2, 8-C), 36.4 (CH, 9-C), 37.7 (CH_2, 12-C), 38.8 (CH, 1-C), 53.7 (CH_3, O*C*H_3), 68.5 (CH, 13-C), 108.8 (CH, 4-C), 124.3 (CH, 11-C), 126.8 (C, 2-C), 128.0 (CH, 10-C), 140.2 (CH, 3-C), 152.4 (C, 5-C), 162.7 (C, 7-C); $C_{13}H_{15}NO_2$ *required* 217.1103, found 217.1099.

Synthesis of 5-methoxy-6-azatricyclo[7.3.1.0^{2,7}]trideca-2(7),3,5,10-tetraen-13-one (40)

A mixture of alcohols (13*R*)-5-methoxy-6-azatricyclo-[7.3.1.0^{2,7}]trideca-2(7),3,5,10-tetraen-13-ol **35** and (13*S*)-5-methoxy-6-azatricyclo[7.3.1.0^{2,7}]trideca-2(7),3,5,10-tetraen-13-ol **39** (0.08 g, 0.37 mmol) and pyridiniun chlorochromate (0.12 g, 0.55 mmol) in dry dichloromethane (3 ml) was stirred at room temperature for 3 h. The reaction mixture was diluted with ether and filtered through a silica pad with ether–dichloromethane. The product was further purified by wet flash chromatography (Et_2O–Pet. Ether) to yield the pure ketone as a yellow oil (0.055 g, 70%).

Yellow oil; ν_{max}/cm^{-1} 2929, 1734, 1599, 1476, 1421, 1312, 1263, 822, 708; δ_H(500 MHz; $CDCl_3$) 2.56 (1H, ddd, *J* 1.5, 4.6 and 17.6 Hz, 12-H), 2.97 (1H, m, 12-H), 3.12 (1H, m, 9-H), 3.23 (1H, d, *J* 17.5 Hz, 8-H), 3.34 (1H, dd, *J* 5.4 and 17.5 Hz), 3.90 (3H, s, OCH_3), 5.64 (1H, m, 11-H), 5.80 (1H, m, 10-H), 6.62 (1H, d, *J* 8.6 Hz, 4-H), 7.27 (1H, d, *J* 8.6 Hz, 3-H); δ_C(125 MHz, $CDCl_3$) 40.0 (CH_2, 12-C), 41.0 (CH_2, 8-C), 46.2 (CH, 9-C), 48.0 (CH, 1-C), 53.4 (CH_3, OCH_3), 68.5 (CH, 13-C), 109.4 (CH, 4-C), 125.0 (C, 2-C), 125.1 (CH, 11-C), 130.5 (CH, 10-C), 139.0 (CH, 3-C), 155.4 (C, 7-C), 163.2 (C, 5-C), 211.7 (C, 13-C); *m*/*z* (EI) 215 (100%), 186 (80), 172 (75), 158 (60), 51 (53), 39 (55); $C_{13}H_{12}O$ *required* 215.0946, found 215.0955.

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