

A concise and convergent (formal) total synthesis of huperzine A†

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The first convergent synthesis of the tricyclic skeleton of huperzine A is described and includes, as the key step, an efficient regioselective intramolecular Heck reaction of 2-(*tert*-butyldimethylsilyloxymethyl)-6-(2-methoxy-5-bromopyridin-6-yl)methylcyclohex-2-enol.

Introduction

There is considerable interest in the natural product huperzine A **1** (Fig. 1) from the club moss *Huperzia serrata*, since this has proven activity as an inhibitor of the enzyme acetylcholine esterase, and is currently undergoing clinical evaluation in the USA as a potential treatment for Alzheimer's disease. In China it has already been approved for this condition. To date the best synthesis of the natural product is the route published by Kozikowski in 1993,¹ which has been used by his group and by others to prepare a large number of analogues. Comprehensive reviews of structure–activity data for these analogues have been provided by Kozikowski² and by Bai.³ The basic Kozikowski route is shown in Scheme 1 and is essentially linear in nature, thus making access to the widest range of analogues more difficult. In 2003, we described a new convergent approach to the basic skeleton of huperzine,⁴ but this earlier approach did not allow access to the (apparently) essential bridgehead amino functionality. In this paper we report a modified approach that allows access to the full tricyclic skeleton of huperzine A by a concise and convergent route to the key keto-ester **2** used by Kozikowski in his ground-breaking synthesis.

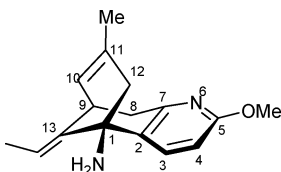
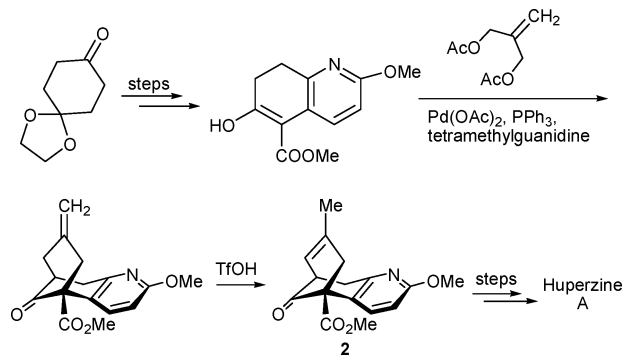


Fig. 1 (–)-Huperzine A: structure and numbering.

Results and discussion

Our overall synthesis is shown in Scheme 2 and includes, as its key step, a regioselective intramolecular Heck reaction of 2-(*tert*-butyldimethylsilyloxymethyl)-6-(2-methoxy-5-bromopyridin-6-yl)methylcyclohex-2-enol **7**. The alicyclic portion of this molecule was prepared from cyclohex-2-enone **3** using a Baylis–Hillman reaction⁵ to insert the requisite hydroxymethyl group, followed by protection of the hydroxyl as its *tert*-butyldimethylsilyl ether, thus providing the 2-substituted cyclo-



Scheme 1 Summary of Kozikowski's synthesis.

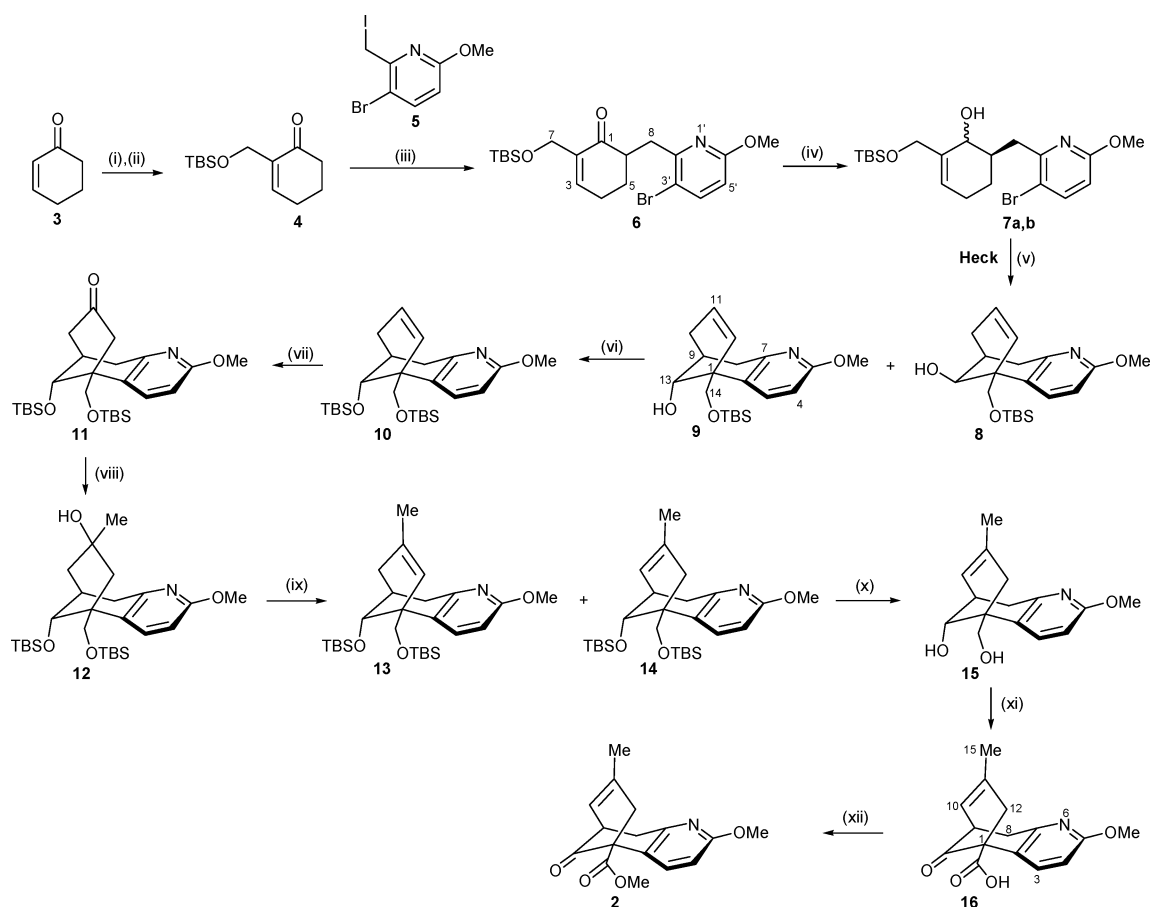
hexenone **4**. The synthesis of the substituted picoline derivative **5** was previously described in our 2003 paper.⁴ Alkylation of the cyclohexenone **4** with the iodide **5** to yield the adduct **6** was accomplished using sodium hexamethyldisilazide as base in THF at -50°C , although the best yield was only 65%. Attempted alkylations with LDA and with potassium *tert*-butoxide gave complex reaction mixtures where proton removal had also occurred γ to the ketone group.

In our earlier studies with unsubstituted cyclohexenone and also in the present work, attempts to carry out the intramolecular Heck reaction resulted in a variety of products resulting from bond formation both α and β to the carbonyl. In consequence, we chose to reduce the ketone under Luche conditions,⁶ and this provided a 92 : 8 ratio of the *syn*- and *anti*-alcohols **7a,b** in good yield. (These assignments were confirmed by NOE experiments carried out on the Heck products **8** and **9**). The intramolecular Heck reaction now proceeded in good yield to produce exclusively the desired huperzine A skeleton in the form of the two epimeric alcohols **8** and **9**, depending on the Heck substrate used (*i.e.* *anti*- or *syn*-). Interestingly, when a microwave reactor was employed the reaction times could be reduced from 24 hours to around 20 minutes with little diminution in the isolated yield, and Tables 1 and 2 provide a comparison of the various reaction conditions employed.

The predominant epimer **9** was first converted into the bis-TBS ether **10** and thence into the ketone **11**. This oxidation was most efficiently achieved *via* a one-pot process involving borane–dimethylsulfide in THF followed by the *N*-methylmorpholine oxide/tetrabutylammonium perruthenate combination introduced by Yates⁷ (60% overall yield on a 3.5 g scale). Several other methods were also explored including Wacker oxidation, formation of

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Scheme 2 Formal convergent synthesis of huperzine A. *Reagents and conditions:* (i) 37% aq. HCHO, DMAP, THF, r.t., 15 h, 63%; (ii) TBS-Cl, imidazole, DMF, r.t., 18 h, 74%; (iii) NaHMDS, THF, -78°C to -50°C , 2 h; then **5**, -50°C , 3 h, 64%; (iv) NaBH₄, CeCl₃·7H₂O, MeOH–DCM, r.t., 89%; (v) Pd(OAc)₂ (10 mol%), PPh₃, Et₃N, DMA, 167°C , 24 h, 72% **9** or 57% **8**; (vi) TBS-OTf, DMAP, Et₃N, DCM, 0°C to r.t., 18 h, 93%; (vii) BH₃·DMS, Et₂O, 37°C , 1 h; then NMO, crushed 4 Å mol. sieves, DCM, r.t., 1 h; then TPAP (5 mol%), r.t., 15 h, 60%; (viii) MeMgI, Et₂O, r.t. to reflux, 24 h, 55% **12** and 36% recovered **11**; (ix) SOCl₂, pyridine, 0°C , 3 h, 11% **13**, 63% **14**; (x) TBAF, THF, r.t., 15 h, 90%; (xi) PDC, DMF, r.t., 20 h, 53%; (xii) CH₂N₂, Et₂O, 0°C , 1 h, 80%.

the epoxide and Lewis-acid-catalysed rearrangement, but none of these proved successful. The ketone **11** was now reacted with excess methyl magnesium iodide to produce the alcohol **12** (55% yield with 36% recovery of starting material), which was efficiently dehydrated using thionyl chloride and pyridine to provide the alkenes **13** and **14** (11% and 63%), the latter alkene possessing

the complete tricyclic skeleton of huperzine A. Completion of the formal total synthesis was achieved by removal of the silyl ether protecting groups using TBAF and oxidation of the resultant diol **15** with PDC in DMF to yield keto acid **16** (53% unoptimised yield). Esterification of this with diazomethane then provided the keto ester **2** used by Kozikowski in his 1993 synthesis of huperzine A, which employed a Curtius rearrangement to insert the requisite bridgehead amino functionality and a Wittig reaction to provide the required ethylidene group. Comparison of the NMR data for

Table 1 Study of intramolecular Heck cyclisation under standard heating conditions

Entry	Precursor ^a	Ligand (equiv.) ^b	Yield (%)	
			8	9
1	(<i>syn</i>) 7a	PPh ₃ (0.2)	—	22
2	(<i>syn</i>) 7a	PPh ₃ (0.4)	—	56
3	(<i>syn</i>) 7a	PPh ₃ (0.6)	—	72
4	(<i>syn</i>) 7a	PPh ₃ (0.8)	—	63
5	(<i>syn</i>) 7a	POT (0.2)	—	30
6	(<i>anti</i>) 7b	PPh ₃ (0.4)	57	—
7	(<i>anti</i>) 7b	PPh ₃ (0.6)	53	—

^a Precursor, ligand, Pd(OAc)₂ (10 mol%) and Et₃N (12 equiv.) were refluxed in DMA for 24 h under standard heating conditions. ^b POT = tri(*o*-tolyl)phosphine.

Table 2 Study of intramolecular Heck cyclisation under microwave heating conditions

Entry	Precursor ^a	Ligand (equiv.) ^b	Yield (%)	
			8	9
1	(<i>syn</i>) 7a	PPh ₃ (0.6)	—	54
2	(<i>syn</i>) 7a	POT (0.2)	—	30
3	(<i>anti</i>) 7b	PPh ₃ (0.4)	55	—

^a Precursor, ligand, Pd(OAc)₂ (10 mol%), Et₃N (12 equiv.) and DMA were subjected to microwave radiation (200 W, 167°C) for 20 mins; ^b POT = tri(*o*-tolyl)phosphine.

our product **2** and those reported by Kozikowski are shown in Fig. 2.

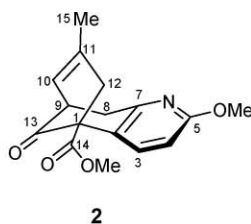
Our convergent route yields not only the complete huperzine A skeleton but also provides the key tricycle **9**, which should allow access to a wide range of analogues not hitherto available, including a range of novel tricycles with one or more integral nitrogen atoms produced *via* Beckmann rearrangements. Our initial investigations in this area are shown in Scheme 3.

Finally, resolution of our key intermediate **9** was achieved through formation of the camphanate esters **20** (Scheme 3) which after separation by chromatography, were hydrolysed to

produce the discrete enantiomers of **9**. (We have not yet been able to obtain crystals of (+)- and (–)-**20** good enough for X-ray characterisation.) This now opens up the possibility of preparing stereochemically defined analogues of huperzine A.

Experimental

Where possible, dry solvents were obtained from MBraun MB-SPS dry solvent machines. Where this was not possible, solvents were pre-dried according to procedures described in *Purification of Laboratory Chemicals* (D. D. Perrin and W. L. F. Armarego, 3rd



Mann *et al.*:

δ_{H} (ppm)	Signal
1.62	3H singlet, H-15
2.51	1H doublet, $J = 17.5$ Hz, H-12
3.12	2H multiplet, H-8 and H-9
3.36	2H multiplet, H-8 and H-12
3.76	3H singlet, OMe
3.92	3H singlet, CO ₂ Me
5.42	1H multiplet, H-10
6.61	1H doublet, $J = 8.5$ Hz, H-4
7.10	1H doublet, $J = 8.5$ Hz, H-3

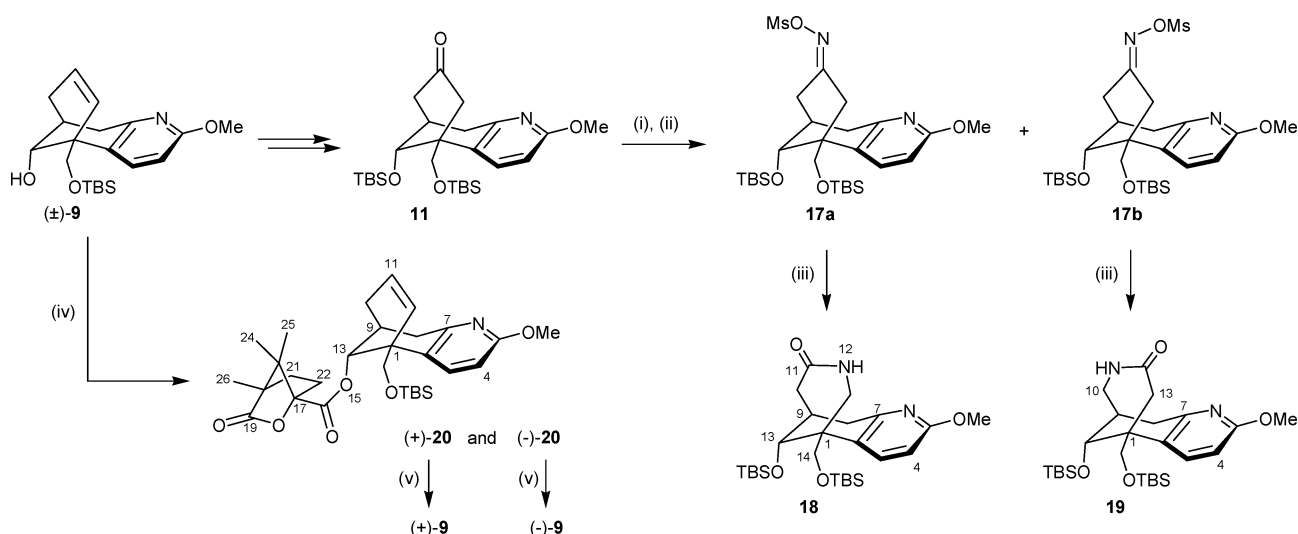
Kozikoski *et al.*:

δ_{H} (ppm)	Signal
1.60	3H singlet, H-15
2.53	1H doublet, $J = 17.5$ Hz, H-12
3.15	1H multiplet, H-9
3.18	1H doublet, $J = 18.2$ Hz, H-8
3.36	2H multiplet, H-8 and H-12
3.76	3H singlet, OMe
3.92	3H singlet, CO ₂ Me
5.42	1H multiplet, H-10
6.62	1H doublet, $J = 8.6$ Hz, H-4
7.11	1H doublet, $J = 8.6$ Hz, H-3

δ_{C} (ppm)	Signal
22.7	CH ₃ , C-15
40.9	CH ₂ , C-8
46.5	CH, C-9
47.3	CH ₂ , C-12
53.0	CH ₃ , OCH ₃
53.9	CH ₃ , CO ₂ CH ₃
60.6	C, C-1
110.1	CH, C-4
124.2	CH, C-10
126.9	C, C-2
134.0	C, C-11
138.1	CH, C-3
151.2	C, C-7
163.7	C, C-5
171.8	CO ₂ Me, C-14
207.9	C=O, C-13

δ_{C} (ppm)	Signal
22.3	CH ₃ , C-15
40.4	CH ₂ , C-8
46.0	CH, C-9
46.9	CH ₂ , C-12
52.7	CH ₃ , OCH ₃
53.4	CH ₃ , CO ₂ CH ₃
60.1	C, C-1
109.6	CH, C-4
123.8	CH, C-10
126.4	C, C-2
133.6	C, C-11
137.7	CH, C-3
150.7	C, C-7
163.2	C, C-5
171.4	CO ₂ Me, C-14
207.5	C=O, C-13

Fig. 2 Comparison of ¹H and ¹³C NMR data for **2** *via* the Mann synthesis and *via* the Kozikowski synthesis.



Scheme 3 Resolution of key intermediate **9** and initial analogue investigation. *Reagents and conditions:* (i) $\text{NH}_2\text{OH}\cdot\text{HCl}$, pyridine, $\text{EtOH-H}_2\text{O}$ (1 : 1), reflux, 3 h, 91%; (ii) MeSO_2Cl , pyridine, DCM, -10°C to r.t., 18 h, 94% **17a** or 72% **17b**; (iii) aq. KH_2PO_4 (pH 7.4), THF, 76°C , 20 h, 83% **18** or 84% **19**; (iv) (1*S*)-(–)-camphanic chloride, DMAP, DCM, 0°C to r.t., 18 h, 34% (+)-**20** and 37% (–)-**20**; (v) K_2CO_3 , MeOH, r.t., 24 h, 49% (+)-**9** or 41% (–)-**9**.

edition, 1988). Anhydrous *N,N*-dimethylformamide (DMF) and *N,N*-dimethylacetamide (DMA) were purchased from Aldrich Chemical company and were supplied under argon in Sure-Seal bottles. Thin layer chromatography was used to monitor reactions using Polygram® SIL G/UV₂₅₄ precoated plastic sheets with a 0.2 mm layer of silica gel containing fluorescent indicator UV₂₅₄. Plates were visualised using a 254 nm UV lamp and a potassium permanganate stain. Flash column chromatography was carried out using Sorbisil® C60 silica gel (40–60 µm mesh). Petroleum ether 40–60 °C (pet. ether), diethyl ether, ethyl acetate, dichloromethane and methanol were used as eluents. NMR spectra were recorded on a Bruker DPX 300 or a Bruker DRX 500 spectrometer. Samples were dissolved in deuterated chloroform with tetramethylsilane as a reference. Chemical shift values (δ) are given in ppm. IR spectra were recorded using a Perkin Elmer RX 1 FT-IR spectrophotometer. Melting points were recorded on a Mettler Toledo FF62 melting point apparatus. EI-MS and CI-MS experiments were carried out on a VG Autospec spectrometer. Elemental analyses were carried out by ASEP (Queen's University Belfast) with a precision of 0.3%. Optical rotations were measured on a Perkin Elmer polarimeter (Na lamp (589 nm) at 20°C).

Intramolecular Heck cyclisation

The experimental procedures described below for the Heck reaction, using either standard heating conditions or microwave radiation, are general and can be applied to different Heck substrates, catalysts, ligands, bases and solvents (for more details see Results and discussion).

(13*R*)*-1-[(*tert*-Butyldimethylsilyloxy)methyl]-5-methoxy-6-azatricyclo[7.3.1.0^{2,7}]trideca-2(7),3,5,11-tetraen-13-ol (9**).** *Standard heating:* Freshly distilled triethylamine (14.55 ml, 104 mmol, 12 eq.) was added *via* syringe to a stirred solution of *syn*-6-[(3-bromo-6-methoxypyridin-2-yl)methyl]-2-[(*tert*-butyldimethylsilyloxy)methyl]cyclohex-2-en-1-ol **7a** (3.85 g, 8.70 mmol, 1 eq.), triphenylphosphine (1.37 g, 5.22 mmol, 0.6 eq.) and palladium(II) acetate (0.20 g, 0.87 mmol, 10 mol%) in anhydrous DMA

(250 ml) under argon. The reaction mixture was heated to reflux and stirred at this temperature for 24 h. After cooling to room temperature, the reaction was quenched with saturated aqueous sodium bicarbonate solution (200 ml). The organic layer was taken up with diethyl ether, washed with water and brine, dried over MgSO_4 and concentrated under reduced pressure to give a crude brown oil. Purification by flash chromatography (40% Et_2O –pet. ether) yielded the pure Heck product **9** as a white solid (2.31 g, 73% yield), mp 96.5°C .

Microwave Heck reaction: *Syn*-6-[(3-bromo-6-methoxypyridin-2-yl)methyl]-2-[(*tert*-butyldimethylsilyloxy)methyl]cyclohex-2-en-1-ol **7a** (0.10 g, 0.23 mmol, 1 eq.) in anhydrous DMA (2 ml), followed by freshly distilled triethylamine (0.38 ml, 2.72 mmol, 12 eq.) were added *via* syringe to a mixture of palladium(II) acetate (0.005 g, 0.02 mmol, 10 mol%) and triphenylphosphine (0.04 g, 0.14 mmol, 0.6 eq.) in a sealed, inert microwave tube, which also contained a magnetic stirring bar. The reaction mixture was then heated rapidly to 167°C under microwave radiation (200 W) and maintained at this temperature for 20 min. On cooling to room temperature, the reaction mixture was diluted with Et_2O (3 ml), washed successively with sodium bicarbonate, water and brine, dried over MgSO_4 and concentrated under reduced pressure. Purification by flash chromatography (40% Et_2O –pet. ether) gave the Heck product **9** (0.04 g, 54% yield).

$\nu_{\text{max}}/\text{cm}^{-1}$: 3480, 3054, 2956, 2930, 2859, 2305, 1594, 1447, 1427, 1307, 1265, 1102, 1069, 1044, 837, 738; δ_{H} (CDCl_3 , 500 MHz): 0.00 (3H, s, $(\text{CH}_3)_3\text{Si}$), 0.02 (3H, s, $(\text{CH}_3)_3\text{Si}$), 0.72 (9H, s, $(\text{CH}_3)_3\text{CSi}$), 1.99 (1H, dd, $J = 18.0, 4.5$ Hz, H-10), 2.37–2.45 (2H, m, H-9 and H-10), 2.42 (1H, d, $J = 19.0$ Hz, H-8), 3.24 (1H, dd, $J = 19.0, 8.0$ Hz, H-8), 3.75 (3H, s, OCH_3), 3.78 (1H, d, $J = 10.5$ Hz, H-14), 4.05 (1H, d, $J = 3.5$ Hz, H-13), 4.17 (1H, d, $J = 10.5$ Hz, H-14), 5.06–5.09 (1H, m, H-12), 5.47–5.50 (1H, m, H-11), 6.34 (1H, d, $J = 8.5$ Hz, H-4), 7.23 (1H, d, $J = 8.5$ Hz, H-3); δ_{C} (CDCl_3 , 125 MHz): -5.66 (2CH_3 , $(\text{CH}_3)_3\text{Si}$), 18.05 (C, $(\text{CH}_3)_3\text{C}$), 25.75 (3CH_3 , $(\text{CH}_3)_3\text{CSi}$), 31.71 (CH, C-9), 35.03 (CH_2 , C-10), 36.94 (CH_2 , C-8), 43.74 (C, C-1), 53.26 (CH_3 , OCH_3), 68.38 (CH_2 , C-14), 74.65 (CH, C-13), 106.75 (CH, C-4), 125.32 (C, C-2), 126.51 (CH, C-11),

130.78 (CH, C-12), 135.49 (CH, C-3), 156.78 (C, C-7), 161.50 (C, C-5); m/z (EI): 362 (M^+ , 74%), 361 (43), 347 (25), 346 (100), 328 (41), 316 (17), 305 (16), 304 (69), 274 (29), 212 (57), 200 (41), 105 (56), 75 (100); CHN Analysis required C 66.44, H 8.64, N 3.87%, found C 66.22, H 8.57, N 3.79%.

(13R)*-1-[(*tert*-Butyldimethylsilyloxy)methyl]-5-methoxy-6-aza-13-(*tert*-butyldimethylsilyloxy)tricyclo[7.3.1.0^{2,7}]trideca-2(7),3,5-trien-11-one (11). Borane–dimethyl sulfide (3.64 ml of a 2 M solution, 7.276 mmol, 1 eq.) was added slowly *via* syringe to a stirred solution of **10** (3.46 g, 7.28 mmol, 1 eq.) in dry Et₂O (70 ml) at room temperature and under argon. The reaction mixture was heated to a gentle reflux and refluxed for 1 h. After cooling to room temperature, dry DCM (70 ml) was added followed by crushed 4 Å molecular sieves (*ca.* 0.5 g) and *N*-methylmorpholine *N*-oxide (8.52 g, 72.76 mmol, 10 eq.). The reaction mixture was stirred under argon at room temperature for 1 h. Tetra-*n*-butylammonium perruthenate (0.13 g, 0.364 mmol, 5 mol%) was then added and the reaction mixture stirred overnight. The following morning, activated charcoal was added and the reaction mixture filtered through Celite. The Celite was then rinsed with ethyl acetate and the reaction mixture concentrated under reduced pressure. The crude product was purified by flash chromatography (35% Et₂O–pet. ether) to give the pure ketone **11** as a white solid (2.13 g, 60% yield), mp 128.4 °C.

$\nu_{\max}/\text{cm}^{-1}$: 2953, 2928, 2856, 1720, 1598, 1577, 1478, 1428, 1313, 1257, 1096, 1028, 872, 834, 776; δ_{H} (CDCl₃, 500 MHz): 0.11 (3H, s, (CH₃)₃Si), 0.12 (3H, s, (CH₃)₃Si), 0.14 (3H, s, (CH₃)₃Si), 0.15 (3H, s, (CH₃)₃Si), 0.81 (9H, s, (CH₃)₃CSi), 0.96 (9H, s, (CH₃)₃CSi), 2.20 (1H, dd, J = 14.5, 3.0 Hz, H-12), 2.38 (1H, dd, J = 13.5, 3.0 Hz, H-10), 2.58 (1H, d, J = 18.0 Hz, H-8), 2.65–2.70 (2H, m, H-9 and H-10), 2.58 (1H, d, J = 14.5 Hz, H-12), 3.33 (1H, dd, J = 18.0, 6.5 Hz, H-8), 3.80 (1H, d, J = 10.0 Hz, H-14), 3.87 (3H, s, OCH₃), 3.89 (1H, d, J = 10.0 Hz, H-14), 4.49 (1H, d, J = 3.5 Hz, H-13), 6.50 (1H, d, J = 8.5 Hz, H-4), 7.41 (1H, d, J = 8.5 Hz, H-3); δ_{C} (CDCl₃, 125 MHz): –5.05 (CH₃, (CH₃)₃Si), –4.68 (CH₃, (CH₃)₃Si), –4.50 (CH₃, (CH₃)₃Si), –3.80 (CH₃, (CH₃)₃Si), 18.52 (C, (CH₃)₃C), 18.87 (C, (CH₃)₃C), 26.18 (3CH₃, (CH₃)₃CSi), 26.52 (3CH₃, (CH₃)₃CSi), 35.32 (CH₂, C-8), 36.46 (CH, C-9), 46.14 (C, C-1), 47.31 (CH₂, C-10), 50.73 (CH₂, C-12), 53.64 (CH₃, OCH₃), 66.44 (CH₂, C-14), 70.82 (CH, C-13), 109.15 (CH, C-4), 125.77 (C, C-2), 136.60 (CH, C-3), 152.10 (C, C-7), 162.42 (C, C-5), 210.04 (C=O, C-11); m/z (EI): 492 (56%, M^+), 435 (42), 434 (100), 302 (15), 228 (24), 200 (22), 186 (28), 160 (26), 147 (66), 74 (59); C₂₆H₄₅O₄Si₂N [M^+] required 491.2887, found 491.2882.

(13R)*-1-[(*tert*-Butyldimethylsilyloxy)methyl]-5-methoxy-6-aza-11-methyl-13-(*tert*-butyldimethylsilyloxy)tricyclo[7.3.1.0^{2,7}]trideca-2(7),3,5-trien-11-ol (12). Freshly prepared methylmagnesium iodide in Et₂O (0.16 ml of 1.47 M solution, 0.24 mmol, 1.2 eq.) was added dropwise to a solution of ketone **11** (0.097 g, 0.20 mmol) in dry Et₂O at room temperature under argon. The reaction mixture was stirred at room temperature for 3 h. A further 1 eq. of methylmagnesium iodide (0.13 ml of 1.47 M solution, 0.20 mmol) was then added and the reaction mixture stirred at room temperature overnight. In the morning, a further 2 eq. of the Grignard reagent was added. The reaction mixture was heated to gentle reflux and stirred at this temperature for 24 h. The reaction was quenched with a saturated aqueous solution of ammonium chloride. The two phases were separated and the aqueous phase

washed with Et₂O. The combined organic phases were washed with water and brine, dried over MgSO₄ and concentrated under reduced pressure. Purification by flash chromatography (40% Et₂O–pet. ether) gave the pure tertiary alcohol **12** as a colourless oil (0.06 g, 55% yield), and also recovered starting ketone **11** (0.03 g, 36%).

Alcohol **12**: $\nu_{\max}/\text{cm}^{-1}$: 3445 (br.), 2955, 2929, 2857, 1596, 1477, 1426, 1306, 1256, 1094, 1037, 836, 775; δ_{H} (CDCl₃, 500 MHz): 0.05 (3H, s, (CH₃)₃Si), 0.08 (3H, s, (CH₃)₃Si), 0.10 (3H, s, (CH₃)₃Si), 0.12 (3H, s, (CH₃)₃Si), 0.75 (9H, s, (CH₃)₃CSi), 0.95 (9H, s, (CH₃)₃CSi), 1.11 (3H, s, CH₃), 1.69 (1H, dd, J = 14.4, 3.2 Hz, H-12), 1.83 (1H, dd, J = 14.7, 4.8 Hz, H-10), 1.90 (1H, d, J = 14.4 Hz, H-12), 1.92–1.96 (1H, m, H-10), 2.29–2.33 (1H, m, H-9), 2.77 (1H, d, J = 18.1 Hz, H-8), 3.24 (1H, dd, J = 18.1, 7.9 Hz, H-8), 3.73 (1H, d, J = 9.5 Hz, H-14), 3.84 (1H, d, J = 9.5 Hz, H-14), 3.87 (3H, s, OCH₃), 3.89 (1H, d, J = 3.9 Hz, H-13), 6.48 (1H, d, J = 8.5 Hz, H-4), 7.57 (1H, d, J = 8.5 Hz, H-3); δ_{C} (CDCl₃, 125 MHz): –5.06 (CH₃, (CH₃)₃Si), –4.74 (CH₃, (CH₃)₃Si), –4.56 (CH₃, (CH₃)₃Si), –3.81 (CH₃, (CH₃)₃Si), 18.47 (C, (CH₃)₃C), 18.88 (C, (CH₃)₃C), 26.15 (3CH₃, (CH₃)₃CSi), 26.52 (3CH₃, (CH₃)₃CSi), 33.14 (CH₃, C-15), 34.66 (CH, C-9), 35.03 (CH₂, C-8), 42.98 (C, C-1), 45.02 (CH₂, C-10), 47.90 (CH₂, C-12), 53.70 (CH₃, OCH₃), 68.31 (CH₂, C-14), 70.10 (C, C-11), 72.94 (CH, C-13), 107.73 (CH, C-4), 128.00 (C, C-2), 136.58 (CH, C-3), 155.52 (C, C-7), 162.04 (C, C-5); m/z (EI): 507 (11%, M^+), 490 (12), 475 (13), 474 (31), 452 (14), 451 (34), 450 (100), 432 (61), 244 (16), 226 (100), 212 (19), 160 (12), 147 (55), 73 (68); C₂₇H₄₉O₄Si₂N [M^+] required 507.3200, found 507.3206.

(13R)*-1-[(*tert*-Butyldimethylsilyloxy)methyl]-5-methoxy-6-aza-11-methyl-13-(*tert*-butyldimethylsilyloxy)tricyclo[7.3.1.0^{2,7}]trideca-2(7),3,5,10-tetraene (14). Thionyl chloride (0.27 ml, 3.72 mmol, 6 eq.) was added dropwise *via* syringe to a solution of **12** (0.32 g, 0.62 mmol, 1 eq.) in dry pyridine (0.6 ml) at 0 °C under argon. The reaction mixture was stirred at 0 °C for 3 h. It was then poured onto ice and the organic layer taken up with Et₂O. Combined organic extracts were washed with brine, dried over MgSO₄ and concentrated under reduced pressure. Purification by flash chromatography (5% Et₂O–pet. ether) gave the pure desired alkene **14** (0.09 g, 28% yield) as a colourless oil, and also a 3 : 1 mixture of **14** and its isomer **13** as a colourless oil (0.14 g, 46% yield).

Olefin **13**: $\nu_{\max}/\text{cm}^{-1}$: 2929, 2857, 1597, 1477, 1307, 1253, 1097, 1033, 835, 775; δ_{H} (CDCl₃, 500 MHz): 0.07 (3H, s, (CH₃)₃Si), 0.10 (3H, s, (CH₃)₃Si), 0.11 (3H, s, (CH₃)₃Si), 0.13 (3H, s, (CH₃)₃Si), 0.82 (9H, s, (CH₃)₃CSi), 0.97 (9H, s, (CH₃)₃CSi), 1.53 (3H, s, CH₃), 1.83 (1H, d, J = 17.4 Hz, H-12), 2.50 (1H, d, J = 17.0 Hz, H-8), 2.53–2.56 (2H, m, H-9 and H-12), 3.21 (1H, dd, J = 17.0, 5.2 Hz, H-8), 3.78 (1H, d, J = 9.6 Hz, H-14), 3.87 (4H, m, OCH₃ and H-14), 4.04 (1H, d, J = 4.6 Hz, H-13), 5.35–5.37 (1H, m, H-10), 6.50 (1H, d, J = 8.5 Hz, H-4), 7.73 (1H, d, J = 8.5 Hz, H-3); δ_{C} (CDCl₃, 125 MHz): –4.99 (CH₃, (CH₃)₃Si), –4.78 (CH₃, (CH₃)₃Si), –4.52 (CH₃, (CH₃)₃Si), –3.68 (CH₃, (CH₃)₃Si), 18.56 (C, (CH₃)₃C), 18.95 (C, (CH₃)₃C), 23.49 (CH₃, C-15), 26.29 (3CH₃, (CH₃)₃CSi), 26.57 (3CH₃, (CH₃)₃CSi), 34.28 (CH₂, C-8), 36.72 (CH, C-9), 42.86 (C, C-1), 42.98 (CH₂, C-12), 53.60 (CH₃, OCH₃), 68.36 (CH₂, C-14), 71.35 (CH, C-13), 108.02 (CH, C-4), 124.57 (CH, C-10), 129.57 (C, C-2), 133.40 (C, C-11), 137.71 (CH, C-3), 153.88 (C, C-7), 162.09 (C, C-5); m/z (EI): 489 (51%, M^+), 488 (26), 476 (15), 475 (37), 474 (100), 466 (12), 432 (37), 227 (20), 226 (100), 212 (13), 147 (44),

73 (55); $C_{27}H_{47}O_3Si_2N$ [M^+] required 489.3095, found 489.3108; CHN Analysis required C 66.20, H 9.67, N 2.86%, found C 65.90, H 9.75, N 2.49%.

(13R)*-1-Hydroxymethyl-5-methoxy-6-aza-11-methyltricyclo[7.3.1.0^{2,7}]trideca-2(7),3,5,10-tetraen-13-ol (15). A 1 M solution of TBAF (0.7 ml, 0.7 mmol, 2.3 eq.) was added dropwise *via* syringe to a solution of **13** (0.15 g, 0.3 mmol, 1 eq.) in dry THF (2 ml) at room temperature. The reaction mixture was stirred at room temperature for 15 h before being quenched with a saturated aqueous solution of ammonium chloride. The organic layer was taken up with ethyl acetate. The combined organic layers were then washed with water and brine, dried over $MgSO_4$ and concentrated under reduced pressure. Purification by flash chromatography (80% ethyl acetate–pet. ether) gave the pure diol **15** as a white solid (0.07 g, 90% yield), mp 160.1 °C.

ν_{max}/cm^{-1} : 3367 (br.), 2915, 1596, 1476, 1423, 1310, 1031; δ_H ($CDCl_3$, 500 MHz): 1.52 (3H, s, CH_3), 1.69 (1H, d, $J = 17.2$ Hz, H-12), 2.13 (1H, d, $J = 17.2$ Hz, H-12), 2.61 (1H, d, $J = 17.4$ Hz, H-8), 2.64–2.66 (1H, m, H-9), 3.24 (1H, dd, $J = 17.4$, 5.5 Hz, H-8), 3.90 (3H, s, OCH_3), 3.98 (1H, d, $J = 11.5$ Hz, H-14), 4.00 (1H, d, $J = 11.5$ Hz, H-14), 4.17 (1H, d, $J = 4.6$ Hz, H-13), 5.43 (1H, d, $J = 5.5$ Hz, H-10), 6.60 (1H, d, $J = 8.5$ Hz, H-4), 7.47 (1H, d, $J = 8.5$ Hz, H-3); δ_C ($CDCl_3$, 125 MHz): 23.12 (CH_3 , C-15), 33.76 (CH_2 , C-8), 36.43 (CH, C-9), 42.22 (C, C-1), 43.33 (CH_2 , C-12), 53.77 (CH_3 , OCH_3), 69.35 (CH_2 , C-14), 74.64 (CH, C-13), 109.11 (CH, C-4), 124.94 (CH, C-10), 125.50 (C, C-2), 132.13 (C, C-11), 137.64 (CH, C-3), 154.62 (C, C-7), 162.65 (C, C-5); m/z (EI): 261 (M^+ , 41%), 260 (15), 242 (18), 224 (22), 213 (18), 212 (100); $C_{15}H_{19}O_3N$ [M^+] required 261.1365, found 261.1361.

5-Methoxy-6-aza-11-methyl-13-ketotricyclo[7.3.1.0^{2,7}]trideca-2(7),3,5,10-tetraen-14-oic acid (16). To a solution of **15** (0.04 g, 0.17 mmol, 1 eq.) in DMF was added 0.62 g of pyridinium dichromate (1.65 mmol, 10 eq.). The reaction mixture was stirred at room temperature for 20 h. 10 ml of water was added followed by extraction of the product several times with ethyl acetate. The combined organic phases were then washed with brine, dried over $MgSO_4$ and concentrated under reduced pressure. Purification by flash chromatography (40% ethyl acetate–pet. ether) gave the acid **16** as a colourless oil (0.03 g, 53% yield).

ν_{max}/cm^{-1} : 3600–3100 (br), 2919, 2850, 1738 (br), 1601, 1478, 1424, 1326, 1268, 1032; δ_H ($CDCl_3$, 500 MHz): 1.55 (3H, s, CH_3), 2.50 (1H, d, $J = 17.5$ Hz, H-12), 3.12–3.16 (1H, m, H-9), 3.12 (1H, d, $J = 17.5$ Hz, H-8), 3.27 (1H, d, $J = 17.5$ Hz, H-12), 3.32 (1H, dd, $J = 17.5$, 5.3 Hz, H-8), 3.85 (3H, s, OCH_3), 5.36–5.38 (1H, m, H-10), 6.58 (1H, d, $J = 8.7$ Hz, H-4), 7.27 (1H, d, $J = 8.7$ Hz, H-3); δ_C ($CDCl_3$, 125 MHz): 19.81 (CH_3 , C-15), 39.73 (CH_2 , C-8), 44.99 (CH, C-9), 45.88 (CH_2 , C-12), 52.59 (CH_3 , OCH_3), 58.46 (C, C-1), 108.71 (CH, C-4), 122.65 (CH, C-10), 124.83 (C, C-2), 132.48 (C, C-11), 137.08 (CH, C-3), 149.74 (C, C-7), 162.44 (C, C-5), 173.42 (CO_2H , C-14), 207.32 (C=O, C-13); m/z (EI): 273

(M^+ , 30%), 230 (25), 229 (100), 214 (40), 212 (53), 200 (62), 184 (20), 170 (13), 149 (14), 128 (14), 115 (16), 85 (24), 77 (15), 69 (43), 63 (13), 58 (22); $C_{15}H_{16}O_4N$ (ES) [MH^+] required 274.1074, found 274.1074.

5-Methoxy-6-aza-11-methyl-13-ketotricyclo[7.3.1.0^{2,7}]trideca-2(7),3,5,10-tetraen-14-oic acid methyl ester (2). A solution of **16** (0.02 g, 0.07 mmol) in 1 ml of a Et_2O –DCM mixture (1 : 1) was cooled to 0 °C and stirred at this temperature for 20 min before the dropwise addition of a dilute ethereal solution of diazomethane, which had been previously prepared and stored at 0–4 °C until use. The reaction mixture was stirred at 0 °C for 1 h. Three to four drops of acetic acid were then carefully added. Ethyl acetate (3 ml) was added followed by water (1 ml). The two phases were separated, and the organic phase dried over $MgSO_4$ and concentrated under reduced pressure. Purification by flash chromatography (30% Et_2O –pet. ether) yielded keto ester **2** as a colourless oil (0.017 g, 80% yield).

ν_{max}/cm^{-1} : 2917, 2849, 1745, 1731, 1602, 1576, 1478, 1424, 1326, 1262, 1025, 831; δ_H ($CDCl_3$, 500 MHz): 1.62 (3H, s, CH_3), 2.51 (1H, d, $J = 17.5$ Hz, H-12), 3.12–3.20 (2H, m, H-8 and H-9), 3.36–3.43 (2H, m, H-8 and H-12), 3.76 (3H, s, OCH_3 , CO_2Me), 3.92 (3H, s, OCH_3), 5.42–5.44 (1H, m, H-10), 6.61 (1H, d, $J = 8.5$ Hz, H-4), 7.10 (1H, d, $J = 8.5$ Hz, H-3); δ_C ($CDCl_3$, 125 MHz): 22.74 (CH_3 , C-15), 40.87 (CH_2 , C-8), 46.46 (CH, C-9), 47.34 (CH_2 , C-12), 53.01 (CH_3 , OCH_3 , CO_2Me), 53.90 (CH_3 , OCH_3), 60.60 (C, C-1), 110.08 (CH, C-4), 124.24 (CH, C-10), 126.85 (C, C-2), 134.01 (C, C-11), 138.13 (CH, C-3), 151.15 (C, C-7), 163.68 (C, C-5), 171.84 (CO_2Me , C-14), 207.88 (C=O, C-13); m/z (EI): 287 (M^+ , 83%), 255 (86), 244 (16), 228 (65), 226 (16), 212 (15), 200 (100), 184 (43), 170 (25), 156 (18), 128 (20), 91 (12), 77 (16), 65 (15); $C_{16}H_{17}O_4N$ [M^+] required 287.1158, found 287.1139.

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