Sulfur-controlled 6-*exo* aryl radical cyclisation of *N*-ethenyl-2-(2-bromophenyl)acetamides: synthesis of (±)-tetrahydropalmatine and saulatine

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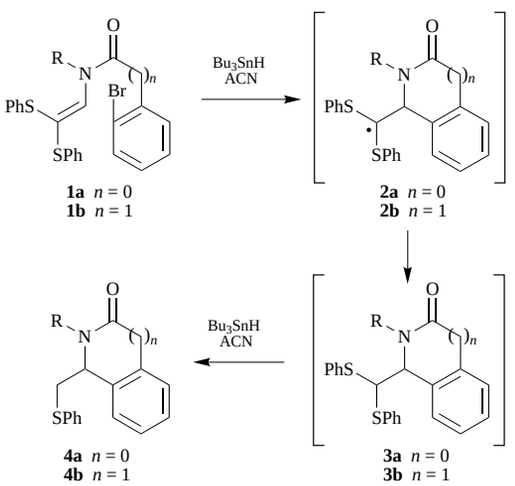
Bu_3SnH-mediated aryl radical cyclisation of 2-(2-bromophenyl)-*N*-[2,2-bis(phenylsulfanyl)ethenyl]-acetamide 7 takes place in a 6-*exo*-*trig* manner to give the isoquinolinone 9. The method has been applied to the synthesis of (±)-tetrahydropalmatine 16 and saulatine 24.

Introduction

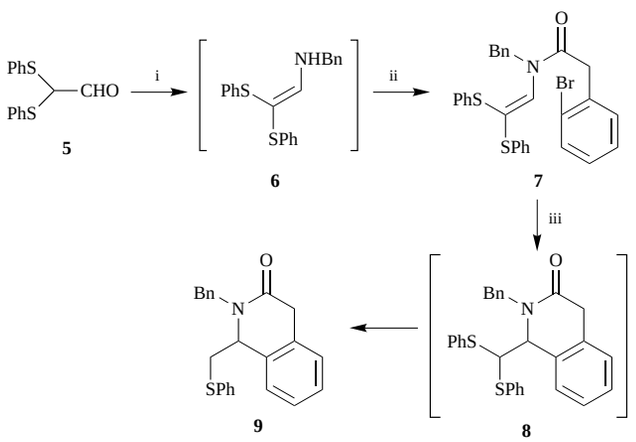
Previous reports from our laboratory[1] have described that treatment of the 2-bromobenzamides **1a**, having two phenylsulfanyl groups at the terminus of the *N*-ethenyl group, with tributyltin hydride (Bu_3SnH; 3.3 mol equiv.) in the presence of azo(cyclohexanecarbonitrile) (ACN) gave, in good yields (49–66%), the isoindolones **4a** as a result of the partial desulfurisation of the initially formed 5-*exo* aryl radical cyclisation products **3a**. The sulfur substituent incorporated into the products **4a** served as a handle for the elaboration of the functionality required for the synthesis of isoindolobenzazepine alkaloids chilenine and lennoxamine. As an extension of the method, we turned our attention to the homologous systems **1b** and found that the cyclisation of **1b** occurred smoothly in a 6-*exo*-*trig* manner to give the isoquinolinones **4b** *via* **3b**. The present paper describes an application of this method to the synthesis of a protoberberine alkaloid (±)-tetrahydropalmatine **16** and an isoquinobenzazepine alkaloid saulatine **24**.



1a $n = 0$ **1b** $n = 1$ **2a** $n = 0$ **2b** $n = 1$ **3a** $n = 0$ **3b** $n = 1$ **4a** $n = 0$ **4b** $n = 1$

Results and discussion

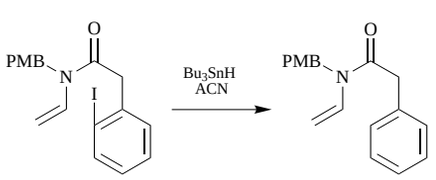
The enamide **7** was prepared by condensation of bis(phenylsulfanyl)acetaldehyde **5**[2] and benzylamine followed by *N*-acylation of the resulting enamine **6** with 2-(2-bromophenyl)acetyl chloride. When the enamide **7** was treated with Bu_3SnH (3.3 mol equiv.) in the presence of ACN in boiling toluene, the expected partially desulfurised 6-*exo* cyclisation product **9** was obtained (58%). The structure of **9** was assigned on the basis of its ^1H NMR spectrum which revealed an ABX pattern due to the PhSCH_2C*H* system similar to that observed for the isoindolones **4a**.[1]



5 **6** **7** **8** **9**

Scheme 1 *Reagents and conditions:* i, $PhCH_2NH_2$, $MgSO_4$, Et_2O, room temp.; ii, 2-(2-bromophenyl)acetyl chloride, $PhNEt_2$, toluene, reflux; iii, Bu_3SnH, ACN, toluene, reflux

In order to clarify the role of the phenylsulfanyl groups in the cyclisation of the enamide **7**, the reaction of **10** having no sulfur substituent on the *N*-ethenyl group was examined. Surprisingly, no cyclisation product was formed from **10** when treated with Bu_3SnH (2.2 mol equiv.) in the presence of ACN in boiling toluene; the reduction product **11** and an unidentified product were obtained. It has been well recognised that, since aryl radicals are very reactive species the product distribution of the aryl radical reactions reflects the rotamer population of the starting amides.[3] It appears, however, that there is little difference in the geometry between the enamides **7** and **10**. Therefore,



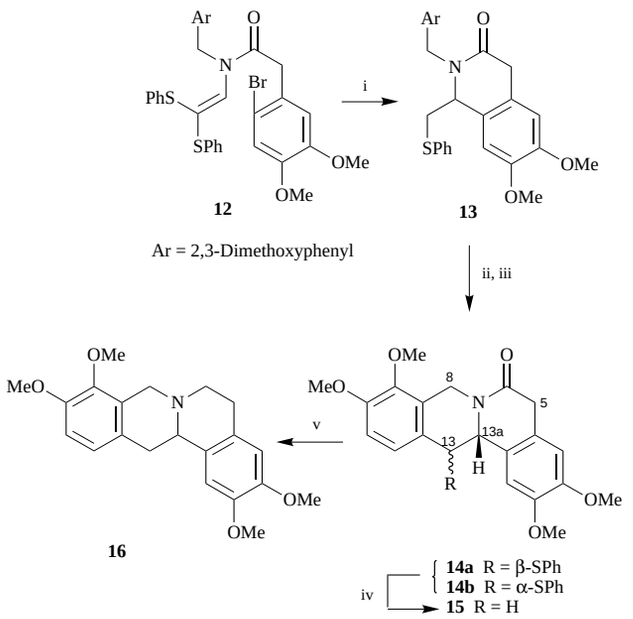
10 **11**

PMB = *p*-Methoxybenzyl

we assume that the effectiveness of formation of **8** from **7** is ascribed to the high stability of the intermediate sulfur-substituted radical **2b**.

Encouraged by the success of the 6-*exo* aryl radical cyclisation of the enamide **7**, we then applied this method to the synthesis of a protoberberine alkaloid (±)-tetrahydropalmatine **16**[4] and an isoquinobenzazepine alkaloid saulatine **24**[5,6] isolated from *Abuta bullata*.

The requisite enamide **12** was prepared from 2,3-dimethoxybenzylamine according to a procedure similar to that described for **7**. The compound **12**, upon treatment with Bu_3SnH (3.3 equiv.)/ACN (catalytic amount) in boiling toluene, gave the isoquinolinone **13** (67%). Oxidation of **13** with MCPBA in dichloromethane at −30 °C followed by treatment of the resulting sulfoxide with trifluoroacetic anhydride (TFAA) in dichloromethane at room temperature gave, in 65% overall yield, a diastereoisomeric mixture of the tetracyclic compounds **14a**,**b** as a result of the intramolecular electrophilic aromatic substitution of the Pummerer rearrangement intermediate (α-thiocarbocation).[7] The mixture could be separated by column chromatography on silica gel, and the stereochemistry of **14a**,**b** was assigned on the basis of the coupling constants between 13-H and 13a-H: *J* 10.1 Hz for **14a** and *J* 1.8 Hz for **14b**. Each of the sulfides **14a,b** was desulfurised with Bu_3SnH–ACN to give the same lactam **15**, reduction of which with BH_3·THF complex furnished (±)-tetrahydropalmatine **16**, whose spectroscopic data were identical with the reported values.†[8]



Scheme 2 *Reagents and conditions:* i, Bu_3SnH, ACN, toluene, reflux; ii, MCPBA, CH_2Cl_2, −30 °C; iii, TFAA, CH_2Cl_2, 0 °C and then room temp.; iv, Bu_3SnH, AIBN, toluene, reflux; v, BH_3-THF

Radical cyclisation of the enamide **17** gave the isoquinolinone **18** (66%). Repetition of the same sequence with **18** as that used for the preparation of **14a**,**b** from **13** afforded the tetracyclic compound **19** (36%; based on **18**) as a single stereoisomer, although the exact stereochemistry is unknown. Oxidation of **19** with MCPBA followed by treatment of the resulting sulfoxide **20** with TFAA in dichloromethane gave the trifluoroacetate **22** (ν_{max}/cm^{-1} 1780). The formation of **22** may be rationalised by assuming a cationic intermediate **21** which arises by elimination of the sulfenic acid derivative from **20**.[9] A subsequent attack of trifluoroacetate ion on the cation **21** gives **22**. The trifluoroacetate **22** was then hydrolysed with potassium carbonate in dichloromethane–methanol to give the alcohol **23** as a single stereoisomer in 56% overall yield from **20**. Finally, Swern oxidation of the alcohol **23** gave saulatine **24** (73%), whose melting point and ^{1}H NMR spectral data were in accord with the reported values.[10]

In summary, we have found that the sulfur-substituents at the terminus of the *N*-ethenyl group of the enamide **7** play a crucial role in effecting the Bu_3SnH-mediated 6-*exo* aryl radical cyclisation due to the high stability of the intermediate radical to give the isoquinolinone **9** in good yield. With the establishment of the use of the sulfur-substituent incorporated into the products, (±)-tetrahydropalmatine **16** and saulatine **24** have been synthesized.

Experimental

Mps were measured on a Yanako MP-J3 micro-melting point apparatus and are uncorrected. IR spectra were recorded on a JASCO-IR-A-100 spectrophotometer. ^{1}H NMR (60 and 300 MHz) spectra were measured on a JEOL-JNM-PMX 60 or a Varian XL-300 spectrometer for solutions in $CDCl_3$. δ-Values quoted are relative to tetramethylsilane, and *J*-values quoted are given in Hz. Exact mass determinations (EI and FAB mass spectra) were obtained on a JEOL-SX 102A instrument. Column chromatography was performed on silica gel 60 PF_{254} (Nacalai Tesque) under pressure.

N-Benzyl-2-(2-bromophenyl)-*N*-[2,2-bis(phenylsulfanyl)-ethenyl]acetamide 7

Benzylamine (622 mg, 5.8 mmol) and magnesium sulfate (10 g) were added to a solution of bis(phenylsulfanyl)acetaldehyde **5**[2] (1.51 g, 5.8 mmol) in diethyl ether (30 cm^3) and the mixture was stirred at room temperature for 3 h. Magnesium sulfate was removed by filtration of the mixture and the filtrate was concentrated *in vacuo*, and the resulting crude enamine **6** was dissolved in toluene (50 cm^3). *N*,*N*-Diethylaniline (1.30 g, 8.7 mmol) and 2-(2-bromophenyl)acetyl chloride (1.99 g, 8.7 mmol) were successively added to the refluxing solution and the whole was refluxed for 2 h. The reaction mixture was washed with 10% aq. HCl, saturated aq. $NaHCO_3$, and brine, dried ($MgSO_4$) and concentrated. The residue was chromatographed on silica gel [hexane–AcOEt (15:1)] to give **7** (3.17 g, 90%) as an oil [Found: $(M + H)^+$, 546.0569. $C_{29}H_{25}{}^{79}BrNOS_2$ requires *m/z*, 546.0561]; $\nu_{max}(CCl_4)$/cm^{-1} 1660; δ_H(60 MHz) 3.85 (2 H, s, $NCOCH_2$), 4.90 (2 H, s, NCH_2Ph) and 6.7–7.6 (20 H, m, olefinic H and ArH).

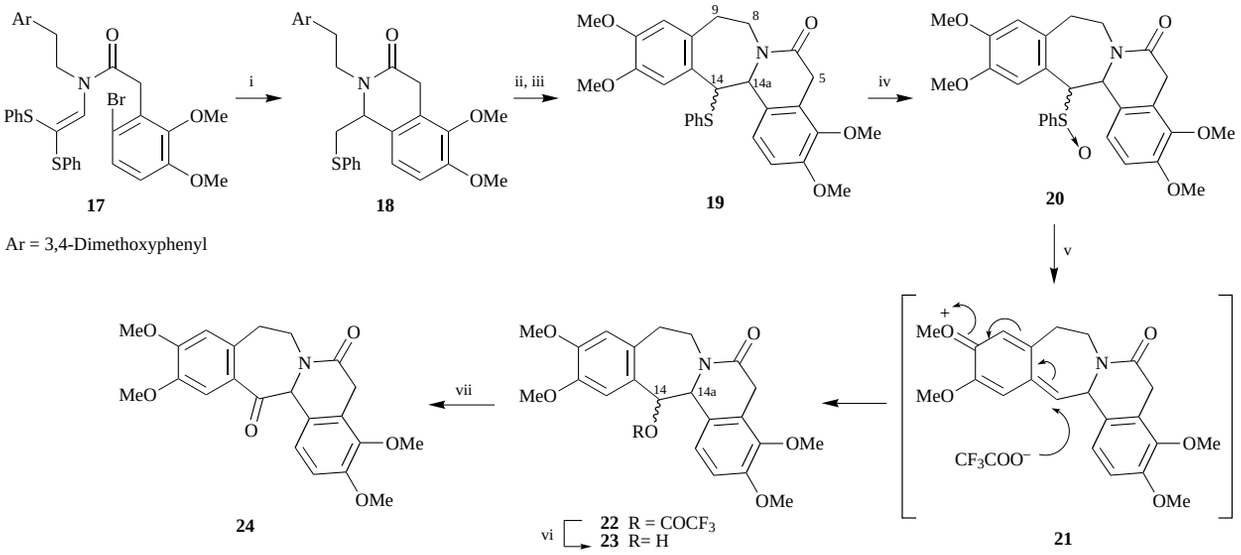
Radical cyclisation of compound 7

General procedure. A solution of Bu_3SnH (1.01 g, 3.47 mmol) and ACN (76 mg, 0.31 mmol) in toluene (150 cm^3) was added dropwise to a solution of **7** (596 mg, 1.09 mmol) in boiling toluene (100 cm^3) *via* a syringe during 3 h, and the mixture was refluxed for 5 h. After concentration of the mixture by removal of the solvent, diethyl ether (50 cm^3) and 8% KF (50 cm^3) were added to the residue, and the whole was vigorously stirred at room temperature for 30 min. The organic layer was separated, dried ($MgSO_4$) and concentrated. The residue was chromatographed on silica gel [hexane–AcOEt (3:1)] to give 2-*benzyl*-1,4-*dihydro*-1-(*phenylsulfanylmethyl*)*isoquinolin*-3(2H)-*one* **9** (228 mg, 58%) as an oil (Found: M^+, 359.1331. $C_{23}H_{21}NOS$ requires *M*, 359.1344); $\nu_{max}(CCl_4)$/cm^{-1} 1655; δ_H(300 MHz) 3.16 (1 H, dd, *J* 13.8 and 7.8, one of CH_2SPh), 3.31 (1 H, dd, *J* 13.8 and 4.5, one of CH_2SPh), 3.70 (1 H, d, *J* 19.2, one of 4-H_2), 3.90 (1 H, d, *J* 19.2, one of 4-H_2), 4.14 (1 H, d, *J* 15.3, one of CH_2Ph), 4.45 (1 H, dd, *J* 7.8 and 4.5, 1-H), 5.32 (1 H, d, *J* 15.3, one of CH_2Ph) and 7.03–7.30 (14 H, m, ArH).

N-Ethenyl-2-(2-iodophenyl)-*N*-(4-methoxybenzyl)acetamide 10

Following a procedure similar to that described for the preparation of **7**, the imine, prepared from 4-methoxybenzylamine (760 mg, 7 mmol) and acetaldehyde (790 mg, 18 mmol), was treated with 2-(2-iodophenyl)acetyl chloride (2.24 g, 8 mmol) to give **10** (284 mg, 10%) as an oil, whose ^{1}H NMR spectrum showed the presence of two rotamers in a ratio of *ca.* 4:1 [Found: $(M + H)^+$, 408.0469. $C_{18}H_{19}INO_2$ requires *m/z*,

† The authors thank Professor M. Hanaoka (Kanazawa University) for providing spectra of compound **16**.



Ar = 3,4-Dimethoxyphenyl

Scheme 3 *Reagents and conditions:* i, Bu_3SnH, ACN, toluene, reflux; ii, MCPBA, CH_2Cl_2, −20 °C; iii, TFAA, CH_2Cl_2, 0 °C and then room temp.; iv, MCPBA, CH_2Cl_2, −20 °C; v, TFAA, CH_2Cl_2, 0 °C and then room temp.; vi, K_2CO_3–CH_2Cl_2, MeOH; vii, $(COCl)_2$, DMSO, Et_3N, CH_2Cl_2

408.0460]; $\nu_{max}(CCl_4)/cm^{-1}$ 1670 and 1625; δ_H(300 MHz) for the major rotamer 3.78 (3 H, s, OMe), 4.02 (2 H, s, $COCH_2$), 4.39 (1 H, d, *J* 9.1, one of C=CH_2), 4.57 (1 H, d, *J* 14.9, one of C=CH_2), 4.87 (2 H, s, NCH_2Ar), 6.8–7.05 (4 H, m, NCH= and ArH), 7.1–7.4 (4 H, m, ArH) and 7.86 (1 H, d, *J* 7.8, ArH).

Radical cyclisation of compound 10

Following the general procedure, compound **10** (276 mg, 0.68 mmol) was treated with Bu_3SnH (433 mg, 1.49 mmol) and ACN (33 mg, 0.14 mmol) in toluene (34 cm^3) and the crude material was chromatographed on silica gel [hexane–AcOEt (1:1)]. The first eluent gave N-*ethenyl*-N-(4-*methoxybenzyl*)-2-*phenylacetamide* **11** (43 mg, 22%) as an oil, whose ^{1}H NMR spectrum showed the presence of two rotamers in a ratio of *ca*. 4:1 [Found: $(M + H)^+$, 282.1501. $C_{18}H_{20}NO_2$ requires *m/z*, 282.1494]; $\nu_{max}(CCl_4)/cm^{-1}$ 1670 and 1625; δ_H(300 MHz) for the major rotamer 3.77 (3 H, s, OMe), 3.93 (2 H, s, $COCH_2$), 4.30 (1 H, d, *J* 9.0, one of C=CH_2), 4.49 (1H, d, *J* 15.4, one of C=CH_2), 4.84 (2 H, s, NCH_2Ar) and 6.8–7.4 (10 H, m, NCH= and ArH). The second eluent gave an unidentified product (34 mg).

2-(6-Bromo-3,4-dimethoxyphenyl)-*N*-(2,3-dimethoxybenzyl)-*N*-[2,2-bis(phenylsulfanyl)ethenyl]acetamide 12

Following a procedure similar to that described for the preparation of **7**, the enamine, prepared from 2,3-dimethoxybenzylamine (1.26 g, 7.5 mmol) and the aldehyde **5** (1.96 g, 7.5 mmol), was treated with 2-(6-bromo-3,4-dimethoxyphenyl)-acetyl chloride[11] (4.41 g, 15.0 mmol) to give **12** (3.39 g, 68%) as an oil (Found: C, 59.9; H, 5.05; N, 2.0. $C_{33}H_{32}BrNO_5S_2$ requires C, 59.5; H, 4.8; N, 2.1%); $\nu_{max}(CCl_4)/cm^{-1}$ 1660; δ_H(60 MHz) 3.7–3.9 (14 H, m, 4 × OMe, $NCOCH_2$), 4.99 (2 H, s, NCH_2Ar) and 6.7–7.3 (16 H, m, alkenic H and ArH).

Radical cyclisation of compound 12

Following the general procedure, compound **12** (705 mg, 1.06 mmol) was treated with Bu_3SnH (1.02 g, 3.49 mmol) and ACN (77 mg, 0.14 mmol) in toluene (53 cm^3) and the crude material was chromatographed on silica gel [hexane–AcOEt (1:1)] to give 1,4-*dihydro*-6,7-*dimethoxy*-2-(2,3-*dimethoxybenzyl*)-1-[(*phenylsulfanyl*)*methyl*]*isoquinolin*-3(2H)-*one* **13** (341 mg, 67%), mp 108–109 °C (from hexane–AcOEt) [Found: $(M + H)^+$, 480.1855. $C_{27}H_{29}NO_5S$ requires *m/z*, 480.1845]; $\nu_{max}(CCl_4)/cm^{-1}$ 1645; δ_H(300 MHz) 3.37 (2 H, d, *J* 6.1, CH_2SPh), 3.59 (1 H, d, *J* 19.8, one of 4-H_2), 3.78, 3.79 (3 H each, both s, 2 × OMe), 3.85 (6 H, s, 2 × OMe), 3.89 (1 H, d, *J* 19.8, one of 4-H_2), 4.29 (1 H, d, *J* 15.3, one of NCH_2), 4.55 (1 H, t, *J* 6.1, 1-H), 5.28 (1 H, d, *J* 15.3, one of NCH_2), 6.53 (1 H, s, ArH), 6.58 (1 H, s, ArH), 6.71 (1 H, dd, *J* 7.8 and 1.5, ArH), 6.80 (1 H, dd, *J* 8.1 and 1.5, ArH), 6.92 (1 H, dd, *J* 8.1 and 7.8, ArH) and 7.12–7.27 (5 H, m, SPh).

5,6,13,13a-Tetrahydro-2,3,9,10-tetramethoxy-13-phenylsulfanyl-8*H*-dibenzo[*a*,*g*]quinolizin-6-ones 14a,b

To a solution of **13** (217 mg, 0.44 mmol) in dichloromethane (40 cm^3) was added dropwise a solution of MCPBA (95 mg, 0.44 mmol) in dichloromethane (20 cm^3) at −30 °C during 1 h, after which the mixture was washed with saturated aq. $NaHCO_3$ and brine, dried ($MgSO_4$) and concentrated. The residue was chromatographed on silica gel [hexane–AcOEt (1:3)] to give the sulfoxide (168 mg, 75%) as an oily mixture of two diastereoisomers, which was used immediately in the next step.

TFAA (143 mg, 0.68 mmol) was added to a solution of the crude sulfoxide (113 mg, 0.23 mmol) in dichloromethane (8 cm^3) at 0 °C and the mixture was stirred for 3 d at room temperature. The mixture was concentrated by evaporation of the solvent and the residue was chromatographed on silica gel [hexane–AcOEt (1:1)]. The first fraction gave **14a** (36 mg, 33%), mp 212–213 °C (from AcOEt) [Found: $(M + H)^+$, 478.1704. $C_{27}H_{28}NO_5S$ requires *m/z*, 478.1688]; $\nu_{max}(CHCl_3)/cm^{-1}$ 1640; δ_H(300 MHz) 3.59 (2 H, s, 5-H_2), 3.82, 3.87 (3 H each, both s, 2 × OMe), 3.88 (1 H, d, *J* 16.4, one of 8-H_2), 3.89, 3.91 (3 H each, both s, 2 × OMe), 4.35 (1 H, d, *J* 10.1, 13-H), 4.77 (1 H, d, *J* 10.1, 13a-H), 5.82 (1 H, d, *J* 16.4, one of 8-H_2), 6.59 (1 H, s, ArH), 6.87 (1 H, d, *J* 8.4, ArH), 6.95–7.00 (2 H, m, ArH), 7.07 (1 H, s, ArH), 7.11–7.14 (3 H, m, ArH) and 7.55 (1 H, d, *J* 8.4, ArH). The second fraction gave **14b** (59 mg, 54%), mp 247–248 °C (from AcOEt) [Found: $(M + H)^+$, 478.1682. $C_{27}H_{28}NO_5S$ requires *m/z*, 478.1688]; $\nu_{max}(CHCl_3)/cm^{-1}$ 1630; δ_H(300 MHz) 3.65 (3 H, s, OMe), 3.66 (1 H, d, *J* 20.5, one of 5-H_2), 3.88 (6 H, s, 2 × OMe), 3.90 (3 H, s, OMe), 4.06–4.15 (2 H, m, one of 5-H_2 and 8-H_2), 4.70 (1 H, d, *J* 1.8, 13-H), 5.02 (1 H, d, *J* 1.8, 13a-H), 5.83 (1 H, d, *J* 18.3, one of 8-H_2), 6.35 (1 H, s, ArH), 6.55 (1 H, s, ArH), 6.85 (1 H, d, *J* 8.7, ArH) and 6.98–7.13 (6 H, m, ArH).

5,6,13,13a-Tetrahydro-2,3,9,10-tetramethoxy-8*H*-dibenzo[*a*,*g*]-quinolizin-6-one 15

From 14a. A solution of Bu_3SnH (37 mg, 0.13 mmol) and ACN (0.013 mmol) in toluene (10 cm^3) was added all at once to a solution of **14a** (30 mg, 0.063 mmol) in boiling toluene (5 cm^3) and the mixture was refluxed for 22 h. Work-up and purification

by column chromatography on silica gel [hexane–AcOEt (1:1)] gave **15** (13 mg, 57%), mp 216–217 °C (from AcOEt) [Found: $(M + H)^+$, 370.1664. $C_{21}H_{24}NO_5$ requires *m/z*, 370.1654]; $\nu_{max}(CHCl_3)/cm^{-1}$ 1625; δ_H(300 MHz) 2.89 (1 H, dd, *J* 15.6 and 12.3, one of 13-H_2), 3.10 (1 H, dd, *J* 15.6 and 3.5, one of 13-H_2), 3.66 (2 H, s, 5-H_2), 3.87 (3 H, s, OMe), 3.90 (6 H, s, 2 × OMe), 3.91 (3 H, s, OMe), 4.14 (1 H, d, *J* 18.3, one of 8-H_2), 4.63–4.71 (1 H, m, 13a-H), 5.84 (1 H, d, *J* 18.3, one of 8-H_2), 6.63 (1 H, s, ArH), 6.71 (1 H, s, ArH), 6.81 (1 H, d, *J* 8.6, ArH) and 6.85 (1 H, d, *J* 8.6, ArH).

From 14b. Similar treatment of **14b** (35 mg, 0.073 mmol) with Bu_3SnH/ACN gave **15** (19 mg, 70%).

(±)-Tetrahydropalmatine 16

To a solution of **15** (46 mg, 0.12 mmol) in THF (15 cm^3) was added dropwise a BH_3·THF solution (a 1 mol dm^{-3} solution in THF; 1 cm^3, 1.0 mmol) and the mixture was stirred at room temperature for 15 min and then refluxed for 1.5 h. After this, the reaction mixture was diluted with water and concentrated. The residue was dissolved in AcOEt and the organic layer was washed with brine, dried ($MgSO_4$) and concentrated. The residue was purified by chromatography on silica gel [hexane–AcOEt (1:1)] and the product was recrystallised from methanol to give **16** (23 mg, 52%), mp 147–148 °C (lit.,[8a] mp 151–151.5 °C; lit.,[8b] mp 147 °C; lit.,[8d] mp 146–148 °C and lit.,[8e] mp 150–152 °C); δ_H(300 MHz) 2.62–2.73 (2 H, m), 2.84 (1 H, dd, *J* 15.5 and 12.0, one of 13-H_2), 3.09–3.23 (2 H, m), 3.28 (1 H, dd, *J* 15.9 and 3.6, one of 13-H_2), 3.53–3.58 (2 H, m), 3.86 (6 H, s, 2 × OMe), 3.88, 3.90 (3 H each, both s, 2 × OMe), 4.26 (1 H, d, *J* 15.9, one of 8-H_2), 6.63 (1 H, s, ArH), 6.74 (1 H, s, ArH), 6.79 (1 H, d, *J* 8.3, ArH) and 6.89 (1 H, d, *J* 8.3, ArH).

2-(6-Bromo-2,3-dimethoxyphenyl)-*N*-[2-(3,4-dimethoxyphenyl)-ethyl]-*N*-[2,2-bis(phenylsulfanyl)ethenyl]acetamide 17

Following a procedure similar to that described for the preparation of **7**, the enamine, prepared from 2-(3,4-dimethoxyphenyl)ethylamine (632 mg, 3.5 mmol) and the aldehyde **5** (908 mg, 3.5 mmol), was treated with 2-(6-bromo-2,3-dimethoxyphenyl)acetyl chloride[12] (2.80 g, 9.5 mmol) to give **17** (1.34 g, 61%) as an oil (Found: C, 60.2; H, 5.2; N, 2.0. $C_{34}H_{34}BrNO_5S_2$ requires C, 60.0; H, 5.0; N, 2.1%); $\nu_{max}(CCl_4)/cm^{-1}$ 1660; δ_H(300 MHz) 2.87–2.84 (2 H, m, NCH_2CH_2), 3.80 (3 H, s, OMe), 3.81 (3 H, s, OMe), 3.85 (6 H, s, 2 × OMe), 3.90 (2 H, s, $COCH_2$), 3.9–4.0 (2 H, m, NCH_2), 6.7–6.8 (4 H, m, ArH), 6.96 (1 H, br s, alkenic H) and 7.2–7.35 (11 H, m, ArH).

Radical cyclisation of 17

Following the general procedure, compound **17** (1.14 g, 1.67 mmol) was treated with Bu_3SnH (1.61 g, 5.52 mmol) and ACN (122 mg, 0.50 mmol) in toluene (250 cm^3) and the crude material was chromatographed on silica gel [hexane–AcOEt (1:2)] to give 1,4-*dihydro*-5,6-*dimethoxy*-2-[2-(3,4-*dimethoxyphenyl*)*ethyl*]-1-[(*phenylsulfanyl*)*methyl*]*isoquinolin*-3(2H)-*one* **18** (543 mg, 66%), mp 108–109 °C (hexane–AcOEt) (Found: C, 68.0; H, 6.4; N, 2.7. $C_{28}H_{31}NO_5S$ requires C, 68.1; H, 6.3; N, 2.8%); $\nu_{max}(CCl_4)/cm^{-1}$ 1630; δ_H(300 MHz) 2.73 (2 H, t, *J* 6.8, NCH_2CH_2), 2.93–3.03 (1 H, m, one of NCH_2), 3.02 (1 H, dd, *J* 13.7 and 7.5, one of CH_2SPh), 3.22 (1 H, dd, *J* 13.7 and 4.8, one of CH_2SPh), 3.47 (1 H, d, *J* 19.8, one of 4-H_2), 3.50, 3.81, 3.83, 3.85 (3H each, all s, 4 × OMe), 3.93 (1 H, d, *J* 19.8, one of 4-H_2), 3.94 (1 H, dd, *J* 7.5 and 4.8, 1-H), 4.30 (1 H, dt, *J* 13.2 and 6.0, one of NCH_2), 6.41 (1 H, d, *J* 1.5, ArH), 6.54 (1 H, dd, *J* 8.4 and 1.5, ArH), 6.58 (1 H, d, *J* 8.4, ArH), 6.66 (1 H, d, *J* 8.4, ArH), 6.74 (1 H, d, *J* 8.4, ArH) and 7.18–7.30 (5 H, m, ArH).

5,6,8,9,14,14a-Hexahydro-3,4,11,12-tetramethoxy-14-phenylsulfanylisoquino[1,2-*b*][3]benzazepin-6-one 19

Following a procedure similar to that described for the preparation of **14a**,**b**, compound **18** (302 mg, 0.61 mmol) was oxidised with MCPBA (132 mg, 0.61 mmol) to give the crude sulfoxide as a diastereoisomeric mixture, which was used immediately in the next step.

The crude sulfoxide was treated with TFAA (1.49 g, 7.08 mmol) in dichloromethane (15 cm^3) and work-up gave **19** (107 mg, 36%) as a single isomer, mp 203–204 °C (from hexane–AcOEt) (Found: M^+, 491.1760. $C_{28}H_{29}NO_5S$ requires *M*, 491.1767); $\nu_{max}(CHCl_3)/cm^{-1}$ 1630; δ_H(300 MHz) 2.75 (1 H, t, *J* 12.3, one of 8-H_2), 2.83 (1 H, dd, *J* 15.5 and 5.4, one of 9-H_2), 3.49–3.58 (1 H, m, one of 9-H_2), 3.64 (3 H, s, OMe), 3.8–4.0 (2 H, overlapped with the following three singlets due to OMe), 3.82, 3.89, 3.91 (3 H each, all s, 3 × OMe), 4.28 (1 H, s, 14-H), 5.04 (1 H, s, 14a-H), 5.07–5.15 (1 H, m, one of 8-H_2), 6.19 (1 H, s, ArH), 6.71 (1 H, s, ArH) and 6.84–7.13 (6 H, m, ArH).

5,6,8,9,14,14a-Hexahydro-14-hydroxy-3,4,11,12-tetramethoxyisoquino[1,2-*b*][3]benzazepin-6-one 23

Following a procedure similar to that described for the preparation of **14a**,**b**, the compound **19** (71 mg, 0.14 mmol) was oxidised with MCPBA (31 mg, 0.14 mmol) to give the crude sulfoxide **20** as a diastereoisomeric mixture, which was used immediately in the next step.

The crude sulfoxide **20** was treated with TFAA (89 mg, 0.42 mmol) in dichloromethane (10 cm^3) and work-up gave 14-*trifluoroacetoxy*-5,6,8,9,14,14a-*hexahydro*-3,4,11,12-*tetramethoxyisoquino*[1,2-b][3]*benzazepin*-6-*one* **22** (107 mg, 36%) as an oil (Found: M^+, 495.1506. $C_{24}H_{24}NO_7F_3$ requires *M*, 495.1505); $\nu_{max}(CHCl_3)/cm^{-1}$ 1780 and 1640.

Potassium carbonate (55 mg) was added to a solution of **22** (37 mg, 0.08 mmol) in dichloromethane (3.5 cm^3) and methanol (3.5 cm^3) and the mixture was stirred at room temperature for 30 min. After this, the reaction mixture was concentrated, the residue was dissolved in AcOEt, and the solution was washed with brine, dried ($MgSO_4$) and concentrated. The residue was chromatographed on silica gel [hexane–AcOEt (1:2)] to give **23** (32 mg, 56%), mp 261–263 °C (from AcOEt) (Found: M^+, 399.1687. $C_{22}H_{25}NO_6$ requires *M*, 399.1682); $\nu_{max}(CHCl_3)/cm^{-1}$ 3400 and 1630; δ_H(300 MHz) 1.77 (1 H, br, OH), 2.69 (1 H, dd, *J* 15.3 and 5.4, one of 9-H_2), 2.83 (1 H, t, *J* 12.3, one of 8-H_2), 3.45–3.56 (1 H, m), 3.72 (1 H, d, *J* 20.7, one of 5-H_2), 3.82 (1 H, d, *J* 20.7, one of 5-H_2), 3.84 (3 H, s, OMe), 3.88 (6 H, s, 2 × OMe), 3.89 (3 H, s, OMe), 4.70 (1 H, s), 4.72 (1 H, s), 4.88–4.96 (1 H, m), 6.70 (1 H, s, ArH), 6.74 (1 H, s, ArH), 6.87 (1 H, d, *J* 8.6, ArH) and 6.97 (1 H, d, *J* 8.6, ArH).

Saulatine 24

Dimethyl sulfoxide (55 mg, 0.70 mmol) was added to a solution of oxalyl chloride (48 mg, 0.38 mmol) in dry dichloromethane (1 cm^3) at −78 °C over a period of 10 min and the mixture was stirred for 10 min. After this, a solution of **23** (15 mg, 0.034 mmol) in dry dichloromethane (1 cm^3) was added to the mixture at −78 °C, and the whole was stirred at the same temperature for 1 h. After addition of triethylamine (108 mg, 1.08 mmol) to the mixture, it was allowed to warm to room temperature. After 2 h, the mixture was diluted with water (5 cm^3) and extracted with ethyl acetate. The extract was dried ($MgSO_4$) and concentrated and the residue was chromatographed on silica gel [hexane–AcOEt (1:2)] to give **24** (11 mg, 73%), mp 224–225 °C (from MeOH) (lit.,[5] mp 226–228 °C; lit.,[10] mp 227–228 °C); $\nu_{max}(CHCl_3)/cm^{-1}$ 1645; δ_H(300 MHz) 3.02–3.10 (1 H, m), 3.04 (1 H, d, *J* 19.3, one of 5-H_2), 3.29–3.42 (2 H, m), 3.8–4.0 (1 H, overlapped with the following four singlets due to OMe), 3.82, 3.86, 3.90, 3.96 (3 H each, all s, 4 × OMe), 4.54–4.66 (1 H, m), 5.21 (1 H, s, 14a-H), 6.74 (1 H, s, ArH), 6.91 (1 H, d, *J* 8.3, ArH), 7.06 (1 H, d, *J* 8.3, ArH) and 7.36 (1 H, s, ArH).

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References

1 H. Ishibashi, H. Kawanami, H. Iriyama and M. Ikeda, *Tetrahedron Lett.*, 1995, **36**, 6733; H. Ishibashi, H. Kawanami and M. Ikeda, *J. Chem. Soc., Perkin Trans. 1*, 1997, 817.

2 H. Ishibashi, C. Kameoka, H. Iriyama, K. Kodama, T. Sato and M. Ikeda, *J. Org. Chem.*, 1995, **60**, 1276.

3 D. P. Curran and N. C. DeMello, *J. Chem. Soc., Chem. Commun.*, 1993, 1314; D. P. Curran and H. Liu, *J. Chem. Soc., Perkin Trans. 1*, 1994, 1377 and references cited therein.

4 M. Shamma, *The Isoquinoline Alkaloids-Chemistry and Pharmacology*, Academic Press, New York, 1972, ch. 16; M. Shamma and L. Moniot, *Isoquinoline Alkaloids Research 1972–1977*, Plenum Press, New York, 1978, ch. 19; T. Kametani, *The Total Synthesis of Natural Products*, ed. by J. ApSimon, John Wiley & Sons Inc., New York, 1977, vol. 3, pp. 1–272; D. S. Bhakuni and S. Jain, *Alkaloids: Chemistry and Pharmacology*, ed. A. Brossi, Academic Press, Orlando, FL, 1986, vol. 28, pp. 95–181; M. Hanaoka, *The Alkaloids: Chemistry and Pharmacology*, ed. A. Brossi, Academic Press, Orlando, FL, 1988, vol. 33, pp. 141–230; C. W. W. Beecher and W. J. Kelleher, *Alkaloids: Chemical and Biological Perspectives*, ed. by S. W. Pelletier, John Wiley & Sons, New York, 1988, vol. 6, pp. 297–337.

5 R. Hocquemiller, A. Cave and A. Fournet, *J. Nat. Prod.*, 1984, **47**, 539.

6 Saulatine was reported as a racemic alkaloid (see ref. 5). However, Shamma claimed that the compound may not be biogenetically formed but is an artifact generated from palmitine during the isolation process: M. Shamma and M. Rahimizadeh, *J. Nat. Prod.*, 1986, **49**, 398.

7 H. Ishibashi and M. Ikeda, *Rev. Heteroatom Chem.*, 1996, **14**, 59; A. W. M. Lee, W. H. Chan and E. T. T. Chan, *J. Chem. Soc., Perkin Trans. 1*, 1992, 309; D. Craig, K. Daniels and A. R. MacKenzie, *Tetrahedron*, 1992, **48**, 7803; S. Takano, H. Iida, K. Inomata and K. Ogasawara, *Heterocycles*, 1993, **35**, 47; H. Ishibashi, K. Takagaki, N. Imada and M. Ikeda, *Tetrahedron*, 1994, **34**, 10 215.

8 (*a*) T. Kametani and M. Ihara, *J. Chem. Soc. C*, 1967, 2036; (*b*) N. S. Narasimhan, R. S. Mali and B. K. Kulkarni, *Tetrahedron*, 1983, **39**, 2770; (*c*) T. Kametani, H. Yukawa, Y. Suzuki, R. Yamaguchi and T. Honda, *Heterocycles*, 1984, **22**, 1067; (*d*) M. Hanaoka, K. Nagami, Y. Hirai, S. Sakurai and S. Yasuda, *Chem. Pharm. Bull.*, 1985, **33**, 2273; (*e*) S. Yasuda, T. Hirasawa and M. Hanaoka, *Tetrahedron Lett.*, 1987, **28**, 2399; (*f*) M. A. Matulenko and A. I. Meyers, *J. Org. Chem.*, 1996, **61**, 573.

9 M. Ikeda, K. Kosaka, M. Sakakibara and M. Okano, *Heterocycles*, 1993, **35**, 81.

10 D. C. Kim, W. H. Yoon, H. Choi and D. H. Kim, *J. Heterocycl. Chem.*, 1993, **30**, 1431.

11 K. Ito and H. Tanaka, *Chem. Pharm. Bull.*, 1974, **22**, 2108; E. Domínguez, E. Lete, M. Jesus Villa and C. Iriondo, *Heterocycles*, 1984, **22**, 1217.

12 J. Kunitomo, Y. Miyata and M. Oshikata, *Chem. Pharm. Bull.*, 1985, **33**, 5245.

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