Sulfur-controlled 5-*exo* selective aryl radical cyclisation of *N*-vinylic 2-bromobenzamides: synthesis of lennoxamine and chilenine

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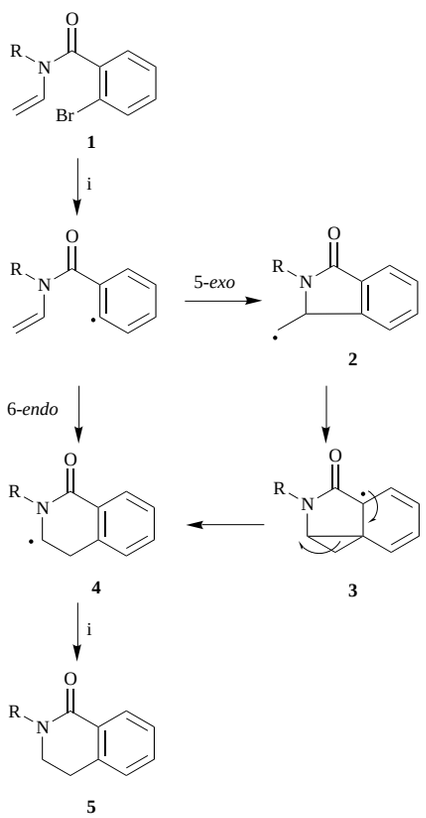
Bu_3SnH-mediated aryl radical cyclisation of *N*-[2,2-bis(phenylsulfanyl)ethenyl]-2-bromobenzamides 12a–d and 16 takes place in a 5-*exo* manner to give exclusively the isoindolones 15a–d and 17, respectively. The isoindolone 17 is converted into lennoxamine and a key intermediate 20 for the synthesis of chilenine.

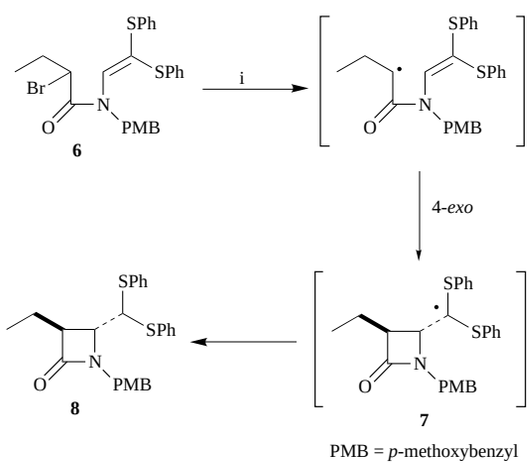
Introduction

Bu_3SnH-mediated aryl radical cyclisations are now widely used in organic synthesis for the construction of fused aromatic compounds. With only a few exceptions,[1] a 5-*exo*-*trig* cyclisation is generally preferred over a 6-*endo*-*trig* ring closure in those systems having an alkenic bond at the 5-position relative to the aryl radical centre.[2] The corresponding *N*-vinylic benzamide systems **1**, however, have been reported to cyclise in a 6-*endo*-*trig* manner exclusively or predominantly, leading to the isoquinolones **5**.[3] The exact reason why the 6-*endo* cyclisation predominates in the systems **1** is not clear at the present time, but one possible explanation involves an assumption that the initially formed aryl radicals cyclise in the usual 5-*exo* manner to give radicals **2**, which then undergo a neophyl rearrangement[4] through the intermediates **3** to give more stable radicals **4** (Scheme 1). If this hypothesis is correct, the stabilisation of the radicals **2** might prevent further rearrangement to give the 5-*exo* cyclisation products.



Scheme 1 *Reagents:* i, Bu_3SnH, AIBN

Previously, we demonstrated that, when two phenylsulfanyl groups were introduced at the terminus of the vinyl group of *N*-vinylic α-halogenoacetamides such as **6**, the 4-*exo* cyclisation becomes favoured over the 5-*endo* cyclisation to give exclusively the β-lactams **8** (Scheme 2).[5] This is considered to be a result of stabilisation of the intermediate radicals **7** by means of two phenylsulfanyl groups. We have now examined whether or not the radical cyclisation of bromides **1** can be shifted from a *endo* mode to an *exo* mode by using this methodology. Herein, we report the sulfur-directed 5-*exo* selective radical cyclisation onto enamides which provides new entries to the isoindolones and the application of this method to the synthesis of lennoxamine **21** and chilenine **22**.[6]



Scheme 2 *Reagents:* i, Bu_3SnH, AIBN

Results and discussion

We began our investigations by examining the cyclisation of several model compounds **12a–d**, which were readily prepared in 59–92% overall yield by condensation of appropriate alkylamines **9a–d** with bis(phenylsulfanyl)acetaldehyde **10**,[5a] followed by N-acylation of the resulting enamines **11a–d** with *o*-bromobenzoyl chloride.

The enamide **12a**, when treated with 1.1 mol equiv. of Bu_3SnH and a small amount of 1,1′-azobis(cyclohexanecarbonitrile) (ACN) in boiling toluene, gave the cyclised products **14a** (30%) and **15a** (8%), in addition to the unchanged starting material **12a** (28% recovery). Since a partial desulfurisation of the cyclisation product **14a** to the mono(phenylsulfanyl) compound **15a** was unavoidable possibly because of slow generation of the aryl radical from **12a**, the enamide **12a**

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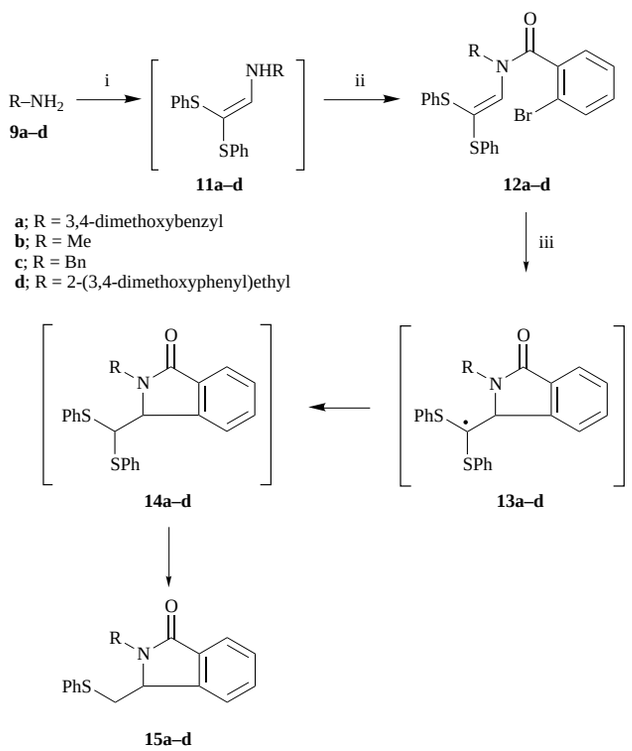
was treated with 3.3 mol equiv. of Bu_3SnH in the presence of ACN to give compound **15a** as the sole product in 64% yield. The structure of compound **15a** was determined on the basis of spectroscopic evidence; a carbonyl absorption in its IR spectrum appeared at 1700 cm^{-1} (a five-membered lactam) and the ^1H NMR spectrum revealed an AMX pattern consisting of three doublets at δ 3.19 (*J* 13.8 and 6.6 Hz), 3.54 (*J* 13.8 and 3.3 Hz), and 4.56 (*J* 6.6 and 3.3 Hz), indicating the presence of a $PhSCH_2CH$ moiety.

Similar treatment of compounds **12b–d** with Bu_3SnH gave the corresponding isoindolones **15b–d** in 49–59% yield.

Thus we found that the Bu_3SnH-induced aryl radical cyclisation of the enamides **12** having two phenylsulfanyl groups at the terminus of the *N*-vinylic bond provided exclusively the isoindolones **14**. Because aryl radicals are very reactive species with very early transition states their products are not generally determined by the product radical stability. Thus, a thermodynamic argument[5] used to explain the predominance of 4-*exo*

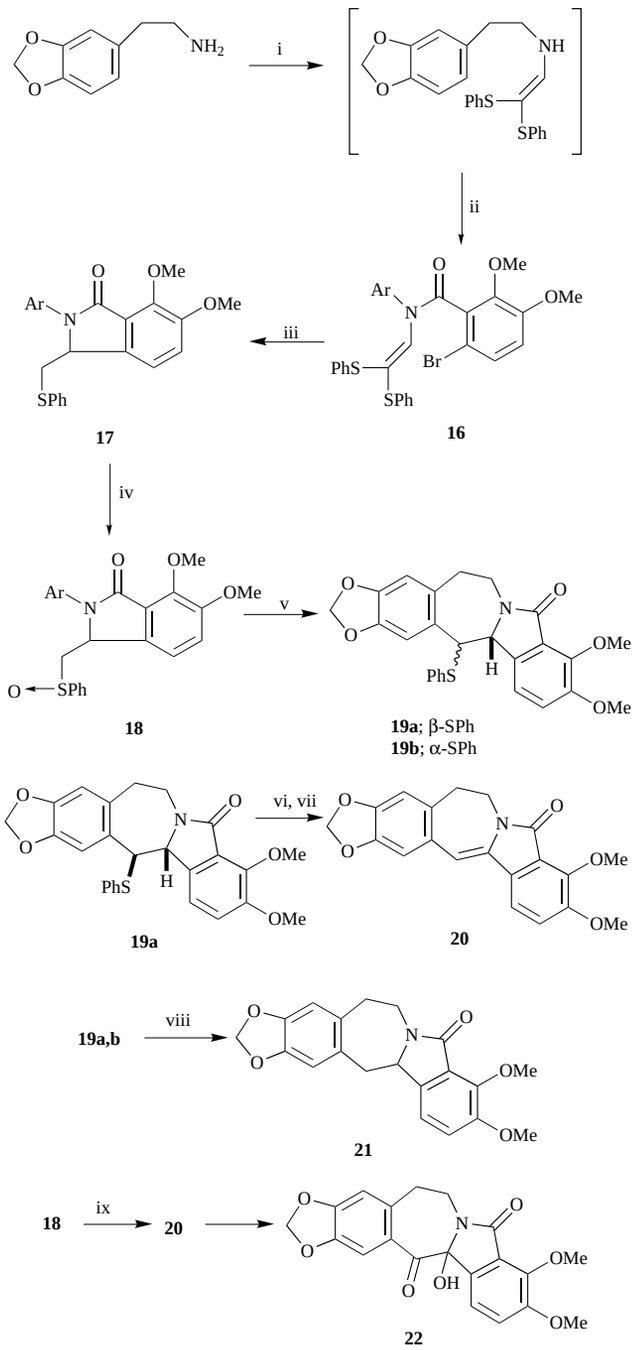


Scheme 3 *Reagents and conditions:* i, $(PhS)_2CHCHO$ (**10**), $MgSO_4$, CH_2Cl_2, room temp.; ii, *o*-bromobenzoyl chloride, $PhNEt_2$, benzene, reflux; iii, Bu_3SnH, ACN, toluene, reflux

cyclisation in the *N*-vinylic enamides **6** seems to be not directly applied to the present case. One possible rationalisation for the observed behaviour of the enamides **12** would involve the postulated neophyl rearrangement: the presence of two phenylsulfanyl groups would make the radical **13** much more stable and less prone to undergo the rearrangement, hence allowing the formation of isoindolone rather than the neophyl rearrangement. An alternative explanation could involve steric factors: the presence of two large phenylsulfanyl groups kinetically favours attack at the proximate end of the double bond to give the isoindolones **14** (Scheme 3).

Encouraged by the success of the 5-*exo* cyclisation of the enamides **12**, we then applied this method to the synthesis of isoindolobenzazepine alkaloids lennoxamine **21**[7] and chilenine **22**,[8] isolated as racemates from the Chilean barberries *Berberis darwinii* Hook[7b] and *Berberis empetrifolia* Lam,[9] respectively.

Compound **16**, prepared from 2-(3,4-methylenedioxyphenyl)ethylamine, the aldehyde **10**, and 6-bromo-2,3-dimethoxybenzoyl chloride[10] in 90% yield, was treated with Bu_3SnH (3.3 mol equiv.)/ACN in boiling toluene to give the



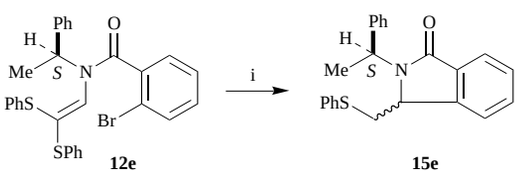
Scheme 4 *Reagents and conditions:* i, $(PhS)_2CHCHO$ (**10**), $MgSO_4$, Et_2O, room temp.; ii, 6-bromo-2,3-dimethoxybenzoyl chloride, $PhNEt_2$, toluene, reflux (90%); iii, Bu_3SnH, ACN, toluene, reflux; iv, MCPBA, CH_2Cl_2, −20 °C (quant.); v, TFAA, CH_2Cl_2, 0 °C and then room temp. (80%); vi, MCPBA, CH_2Cl_2, −20 °C; vii, toluene, reflux; viii, Bu_3SnH, AIBN, toluene, reflux (94%); ix, TFAA, toluene, 0 °C and then reflux, 10 h (69%)

isoindolone **17** in 66% yield. Oxidation of compound **17** with *m*-chloroperbenzoic acid MCPBA gave the sulfoxide **18** (quant.), which was then treated with trifluoroacetic anhydride (TFAA) in dichloromethane at room temperature for 1.5–2 days to give the benzazepine **19** in 80% yield as a mixture of two diastereoisomers (Scheme 4). This mixture was separated by silica gel column chromatography to give isomers **19a**, mp 226–227 °C, and **19b**, mp 202–203 °C. The formation of benzazepines **19a**,**b** from sulfoxide **18** can be explained in terms of the Pummerer rearrangement of compound **18** with TFAA followed by an intramolecular electrophilic aromatic substitution of the resulting α-trifluoroacetoxy sulfide.[11] The stereochemistry of benzazepines **19a**,**b** was determined based on the

thermal behaviour of the corresponding sulfoxides. Thus, heating of the sulfoxide derived from compound **19a** in boiling toluene gave the unsaturated lactam **20** in 57% yield as a result of a *syn*-elimination of sulfenic acid, while similar treatment of the sulfoxide derived from compound **19b** recovered unchanged under the same conditions. Desulfurisation of a mixture of isomers **19a** and **19b** with Bu_3SnH and azobisisobutyronitrile (AIBN) in boiling toluene gave lennoxamine **21** in 94% yield, whose mp and ^{1}H NMR spectral data were in accord with the reported values.[7d]

On the other hand, heating of the sulfoxide **18** with TFAA in toluene gave compound **20** in 69% yield. Since compound **20** has already been converted into chilenine **22** in a one-pot procedure (dimethyldioxirane and then aq. $NaHCO_3$) by Fang and Danishefsky,[8] the whole sequence of reactions constitutes, in a formal sense, a total synthesis of chilenine.

Since relatively high asymmetric inductions were observed with the 4-*exo*-*trig*[5] and 5-*endo*-*trig* radical cyclisations[12] of *N*-vinylic α-halogenoacetamides bearing a chiral auxiliary group on the nitrogen atom, it was of interest to investigate the diastereoselectivity of the 5-*exo* aryl radical cyclisation. Therefore, we prepared the enamide **12e** bearing an (*S*)-1-phenylethyl group on the nitrogen atom as a chiral auxiliary group. Treatment of compound **12e** with Bu_3SnH/ACN in boiling toluene gave the isoindolone **15e** as a two-diastereomer mixture in 59% combined yield (Scheme 5). The ^{1}H NMR spectrum of this mixture showed the ratio of the two diastereoisomers to be ~2:1, though the exact stereochemistry of the major diastereoisomer of compound **15e** was not determined. Thus, no remarkable diastereoselectivity was observed for the cyclisation of compound **12e**. In order to improve the diastereoselectivity, a synthesis of the enamide bearing an (*S*)-1-(1-naphthyl)ethyl group on the nitrogen atom was attempted without success.



12e **15e**

Scheme 5 *Reagents and conditions:* i, Bu_3SnH, ACN, toluene, reflux

In summary, we have found that Bu_3SnH-mediated aryl radical cyclisation of *N*-[2,2-bis(phenylsulfanyl)ethenyl]-2-bromobenzamides **12a**–**d** and **16** took place in a 5-*exo* manner to give exclusively the isoindolones **15a**–**d** and **17**, respectively. The isoindolone **17** was converted into lennoxamine **21** and a key intermediate **20** for the synthesis of chilenine **22**. This work raises some mechanistic questions concerning the aryl radical cyclisation of the enamides, and we hope to pursue these problems in a continuation of this study.

Experimental

Mps were measured on a Yanaco MP-J3 micro melting point apparatus and uncorrected. IR spectra were recorded on a JASCO-IR-A-100 spectrophotometer. ^{1}H NMR (60 and 300 MHz) and ^{13}C NMR (75.4 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 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.

General procedure for the preparation of *N*-[2,2-bis(phenylsulfanyl)ethenyl]-2-bromobenzamides 12a–e

Appropriate amine **9** (5.5 mmol) and magnesium sulfate (10 g) were added to a solution of bis(phenylsulfanyl)acetaldehyde **10** (1.44 g, 5.5 mmol) in dichloromethane (70 cm^3) and the mixture was stirred at room temperature for 2 h. Magnesium sulfate was removed by filtration, the filtrate was concentrated *in vacuo*, and the resulting crude enamine was dissolved in benzene (70 cm^3). *N*,*N*-Diethylaniline (1.64 g, 11 mmol) and then *o*-bromobenzoyl chloride (2.14 g, 11 mmol) were successively added to the refluxing solution and the whole was refluxed for 1 h. The reaction mixture was washed successively with 1 mol dm^{-3} HCl, saturated aq. $NaHCO_3$, and brine, dried ($MgSO_4$) and concentrated. The residue was chromatographed on silica gel [hexane–AcOEt (2:1)]. The following compounds were thus obtained.

***N*-(3,4-Dimethoxybenzyl)-*N*-[2,2-bis(phenylsulfanyl)ethenyl]-2-bromobenzamide 12a.** Yield 92%, *crystals* mp 88–90 °C (from hexane–AcOEt) (Found: C, 60.5; H, 4.4; N, 2.6. $C_{30}H_{26}BrNO_3S_2$ requires C, 60.8; H, 4.4; N, 2.4%); $\nu_{max}(CCl_4)$/cm^{-1} 1650; δ_H(60 MHz) 3.80 (3 H, s, OMe), 3.85 (3 H, s, OMe), 4.98 (2 H, br s, NCH_2Ar) and 6.4–7.7 (18 H, m, olefinic H and ArH).

***N*-Methyl-*N*-[2,2-bis(phenylsulfanyl)ethenyl]-2-bromobenzamide 12b.** Yield 59 %, an *oil* (Found: C, 57.4; H, 3.7; N, 2.95. $C_{22}H_{18}BrNOS_2$ requires C, 57.9; H, 4.0; N, 3.1%); $\nu_{max}(CCl_4)$/cm^{-1} 1665; δ_H(60 MHz) 3.35 (3 H, br s, NMe) and 6.7–7.7 (15 H, m, olefinic H and ArH).

***N*-Benzyl-*N*-[2,2-bis(phenylsulfanyl)ethenyl]-2-bromobenzamide 12c.** Yield 74%, *crystals* mp 64–65 °C (from hexane–AcOEt) (Found: C, 63.3; H, 4.4; N, 2.3. $C_{28}H_{22}BrNOS_2$ requires C, 63.15; H, 4.2; N, 2.6%); $\nu_{max}(CCl_4)$/cm^{-1} 1660; δ_H(60 MHz) 5.05 (2 H, br s, NCH_2Ar) and 6.4–7.65 (20 H, m, olefinic H and ArH).

***N*-[2-(3,4-Dimethoxyphenyl)ethyl]-*N*-[2,2-bis(phenylsulfanyl)ethenyl]-2-bromobenzamide 12d.** Yield 75%, *crystals* mp 85–86 °C (from hexane–AcOEt) (Found: C, 61.3; H, 4.6; N, 2.25. $C_{31}H_{28}BrNO_3S_2$ requires C, 61.4; H, 4.65; N, 2.3%); $\nu_{max}(CCl_4)$/cm^{-1} 1655; δ_H(60 MHz) 2.8–3.2 (2 H, m), 3.77 (3 H, s, OMe), 3.82 (3 H, s, OMe), 3.9–4.3 (2 H, m) and 6.5–7.7 (18 H, m, olefinic H and ArH).

***N*-[(*S*)-1-Phenylethyl]-*N*-[2,2-bis(phenylsulfanyl)ethyl]-2-bromobenzamide 12e.** Yield 57%, *crystals* mp 123 °C (from hexane–AcOEt) (Found: C, 63.4; H, 4.3; N, 2.5. $C_{29}H_{24}BrNOS_2$ requires C, 63.7; H, 4.4; N, 2.6%); $\nu_{max}(CCl_4)$/cm^{-1} 1650; δ_H(60 MHz) 1.73 (3 H, d, *J* 8, CHCH_3), 6.09 (1 H, q, *J* 8.0, C*H*CH$_3$) and 6.3–7.7 (20 H, m, olefinic H and ArH).

Radical cyclisation of compound 12a

General procedure. To a stirred and boiling solution of compound **12a** (579 mg, 0.97 mmol) in toluene (100 cm^3) was added a solution of Bu_3SnH (960 mg, 3.3 mmol) and ACN (73 mg, 0.3 mmol) in toluene (50 cm^3) *via* a syringe during 3 h, and the mixture was refluxed for 5 h. After removal of the solvent, diethyl ether (50 cm^3) and 8% aq. 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 (2:1)] to give 2,3-*dihydro*-N-(3,4-*dimethoxybenzyl*)-3-[(*phenylsulfanyl*)*methyl*]-1H-*isoindol*-1-*one* **15a** (251 mg, 64%) as an oil (Found: C, 71.1; H, 5.9; N, 3.75. $C_{24}H_{23}NO_3S$ requires C, 71.1; H, 5.7; N, 3.45%); $\nu_{max}(CCl_4)$/cm^{-1} 1700; δ_H(300 NHz) 3.19 (1 H, dd, *J* 13.8 and 6.6, one of CH_2SPh), 3.54 (1 H, dd, *J* 13.8 and 3.3, one of CH_2SPh), 3.79 (3 H, s, OMe), 3.85 (3 H, s, OMe), 4.01 (1 H, d, *J* 15.0, one of CH_2Ar), 4.56 (1 H, dd, *J* 6.6 and 3.3, 3-H), 5.23 (1 H, d, *J* 15.0, one of CH_2Ar), 6.72–6.81 (3 H, m, ArH), 7.23 (5 H, s, ArH), 7.46–7.53 (3 H, m, ArH) and 7.89–7.92 (1 H, m, ArH).

When compound **12a** (592 mg, 1.0 mmol) was treated with Bu_3SnH (320 mg, 1.1 mmol) and ACN (24 mg, 0.1 mmol) in toluene (150 cm^3), 2,3-*dihydro*-N-(3,4-*dimethoxybenzyl*)-3-[*bis*(*phenylsulfanyl*)*methyl*]-1H-*isoindol*-1-*one* **14a** (73 mg, 30%), compound **15a** (18 mg, 8%), and the unchanged starting material **12a** (76 mg, 28% recovery) were obtained. Compound **14a** had mp 89–91 °C (from hexane–AcOEt) (Found: C, 70.2;

H, 5.3; N, 2.7. $C_{30}H_{27}NO_3S_2$ requires C, 70.15; H, 5.3; N, 2.7%); $\nu_{max}(CCl_4)/cm^{-1}$ 1705; δ_H(300 MHz) 3.72 (3 H, s, OMe), 3.84 (3 H, s, OMe), 4.10 (1 H, d, *J* 15.3, one of CH_2Ar), 4.81 [2 H, s, C*H*C*H*(SPh)$_2$], 5.02 (1 H, d, *J* 15.3, one of CH_2Ar), 6.52 (1 H, d, *J* 8.3, ArH), 6.62 (1 H, d, *J* 8.3, ArH), 6.68 (1 H, s, ArH), 7.26 (10 H, s, ArH), 7.53–7.61 (2 H, m, ArH), 7.93–7.97 (1 H, m, ArH) and 8.03–8.07 (1 H, m, ArH).

Radical cyclisation of compound 12b

Following the general procedure, compound **12b** (525 mg, 1.15 mmol) was treated with Bu_3SnH (1.10 g, 3.79 mmol) and ACN (84 mg, 0.34 mmol) in toluene (170 cm^3) and the crude material was chromatographed on silica gel [hexane–AcOEt (2:1)] to give 2,3-*dihydro*-N-*methyl*-3-[(*phenylsulfanyl*)*methyl*]-1H-*isoindol*-1-*one* **15b** (153 mg, 50%) as an oil (Found: C, 71.0; H, 5.8; N, 5.7. $C_{16}H_{15}NOS$ requires C, 71.35; H, 5.6; N, 5.2%); $\nu_{max}(CCl_4)/cm^{-1}$ 1695; δ_H(300 MHz) 3.02 (3 H, s, NMe), 3.31 (1 H, dd, *J* 13.7 and 6.0, one of CH_2SPh), 3.55 (1 H, dd, *J* 13.7 and 3.5, one of CH_2SPh), 4.60 (1 H, dd, *J* 6.0 and 3.5, 3-H), 7.20–7.53 (8 H, m, ArH) and 7.82–7.85 (1 H, m, ArH).

Radical cyclisation of compound 12c

Following the general procedure, compound **12c** (416 mg, 0.78 mmol) was treated with Bu_3SnH (768 mg, 2.64 mmol) and ACN (58 mg, 0.24 mmol) in toluene (120 cm^3) and the crude material was chromatographed on silica gel [hexane–AcOEt (5:1)] to give 2,3-*dihydro*-N-*benzyl*-3-[(*phenylsulfanyl*)*methyl*]-1H-*isoindol*-1-*one* **15c** (159 mg, 59%) as an oil (Found: C, 76.5; H, 5.7; N, 4.0. $C_{22}H_{19}NOS$ requires C, 76.5; H, 5.5; N, 4.05%); $\nu_{max}(CCl_4)/cm^{-1}$ 1695; δ_H(300 MHz) 3.19 (1 H, dd, *J* 13.8 and 6.6, one of CH_2SPh), 3.53 (1 H, dd, *J* 13.8 and 3.5, one of CH_2SPh), 4.03 (1 H, d, *J* 15.0, one of CH_2Ph), 4.54 (1 H, dd, *J* 6.6 and 3.5, 3-H), 5.31 (1 H, d, *J* 15.0, one of CH_2Ph), 7.18–7.30 (10 H, m, ArH), 7.45–7.53 (3 H, m, ArH) and 7.89–7.92 (1 H, m, ArH).

Radical cyclisation of compound 12d

Following the general procedure, compound **12d** (714 mg, 1.17 mmol) was treated with Bu_3SnH (1.13 g, 3.88 mmol) and ACN (85 mg, 0.35 mmol) in toluene (170 cm^3) and the crude material was chromatographed on silica gel [hexane–AcOEt (2:1)] to give 2,3-*dihydro*-N-[2-(3,4-*dimethoxyphenyl*)*ethyl*]-3-[(*phenylsulfanyl*)*methyl*]-1H-*isoindol*-1-*one* **15d** (229 mg, 49%) as an oil (Found: M^+, 419.1561. $C_{25}H_{25}NOS$ requires M, 419.1555); $\nu_{max}(CCl_4)/cm^{-1}$ 1690; δ_H(300 MHz) 2.75–2.96 (2 H, m, CH_2Ar), 3.18 (1 H, dd, *J* 13.8 and 6.3, one of CH_2SPh), 3.26 (1 H, dt, *J* 14.4 and 7.3, one of NCH_2), 3.39 (1 H, dd, *J* 13.8 and 3.9, one of CH_2SPh), 3.72 (3 H, s, OMe), 3.83 (3 H, s, OMe), 4.07–4.18 (1 H, m one of NCH_2), 4.40 (1 H, dd, *J* 6.3 and 3.9, 3-H), 6.64 (1 H, d, *J* 1.8, ArH), 6.68 (1 H, dd, *J* 8.25 and 1.8, ArH), 6.74 (1 H, d, *J* 8.25, ArH), 7.22–7.33 (5 H, m, ArH), 7.44–7.51 (3 H, m, ArH) and 7.84–7.87 (1 H, m, ArH).

***N*-[2-(3,4-Methylenedioxyphenyl)ethyl]-*N*-[2,2-bis(phenylsulfanyl)ethenyl]-6-bromo-2,3-dimethoxybenzamide 16**

Following the general procedure for the preparation of compounds **12**, bromide **16** (792 mg, 90%) was obtained by acylation of the enamine [pepared from 2-(3,4-methylenedioxyphenyl)ethylamine (908 mg, 5.5 mmol) and the aldehyde **10** (1.43 g, 5.5 mmol)] with 6-bromo-2,3-dimethoxybenzoyl chloride (1.13 g, 3.36 mmol) as an oil (Found: C, 58.6; H, 4.3; N, 2.2. $C_{32}H_{28}BrNO_5S_2$ requires C, 59.1; H, 4.3; N, 2.15%); $\nu_{max}(CCl_4)/cm^{-1}$ 1670; δ_H(60 MHz) 2.8–3.2 (2 H, m), 3.93 (6 H, s, OMe), 4.1–4.5 (2 H, m), 5.90 (2 H, s) and 6.7–7.4 (16 H, m, olefinic H and ArH).

Radical cyclisation of compound 16

Following the general procedure, bromide **16** (309 mg, 0.47 mmol) was treated with Bu_3SnH (457 mg, 1.57 mmol) and ACN (34 mg, 0.14 mmol) in toluene (75 cm^3) and the crude material was chromatographed on silica gel [hexane–AcOEt (2:1)] to give 2,3-*dihydro*-N-[2-(3,4-*methylenedioxyphenyl*)*ethyl*]-6,7-*dimethoxy*-3-[(*phenylsulfanyl*)*methyl*]-1H-*isoindol*-1-*one* **17** (114 mg, 66%) as an oil (Found: C, 67.45; H, 5.8; N, 3.0. $C_{26}H_{25}NO_5S$ requires C, 67.4; H, 5.4; N, 3.0%); $\nu_{max}(CCl_4)/cm^{-1}$ 1690; δ_H(300 MHz) 2.71–2.89 (2 H, m, CH_2Ar), 3.16 (1 H, dd, *J* 13.7 and 6.0, one of CH_2SPh), 3.16–3.26 (1 H, m, one of NCH_2), 3.36 (1 H, dd, *J* 13.7 and 3.8, one of CH_2SPh), 3.88 (3 H, s, OMe), 3.99 (1 H, ddd, *J* 14.6, 8.6 and 6.5, one of NCH_2), 4.11 (3 H, s, OMe), 4.40 (1 H, dd, *J* 6.0 and 3.8, 3-H), 5.91 (2 H, s, OCH_2O), 6.60 (1 H, dd, *J* 7.8 and 1.8, ArH), 6.66 (1 H, d, *J* 1.8, ArH), 6.69 (1 H, d, *J* 7.8, ArH), 6.99 (1 H, d, *J* 8.4, ArH), 7.15 (1 H, d, *J* 8.4, ArH) and 7.22–7.34 (5 H, m, ArH).

2,3-Dihydro-*N*-[2-(3,4-methylenedioxyphenyl)ethyl]-6,7-dimethoxy-3-[(phenylsulfinyl)methyl]-1*H*-isoindol-1-one 18

To a solution of sulfide **17** (277 mg, 0.60 mmol) in dichloromethane (50 cm^3) was added at −20 °C dropwise a solution of MCPBA (123 mg, 0.60 mmol) in dichloromethane (25 cm^3) during 30 min, and the mixture was stirred at the same temperature for 1 h. The reaction mixture was washed successively with saturated aq. $NaHCO_3$ and brine, dried ($MgSO_4$), and concentrated. The residue was chromatographed on silica gel [hexane–AcOEt (1:2)] to give *sulfoxide* **18** (296 mg, quant.) as an oily mixture of two diastereoisomers [Found: $(M + H)^+$, 480.1472. $C_{26}H_{26}NO_6S$ requires *m*/*z*, 480.1480]; $\nu_{max}(CCl_4)/cm^{-1}$ 1690; δ_H(300 MHz) (for the major diastereoisomer) 2.85–3.12 (2 H, m, CH_2Ar), 3.01 (1 H, dd, *J* 14.1 and 6.8, one of CH_2SPh), 3.22 (1 H, dd, *J* 14.1 and 3.5, one of CH_2SPh), 3.58–3.68 (1 H, m, one of NCH_2), 3.87 (3 H, s, OMe), 4.08 (3 H, s, OMe), 4.19–4.29 (1 H, m, one of NCH_2), 4.82 (1 H, dd, *J* 6.8 and 3.5, 3-H), 5.91 and 5.92 (1 H each, ABq, *J* 1.5, OCH_2O), 6.73–6.76 (3 H, m, ArH), 6.81 (1 H, s, ArH), 7.00 (1 H, d, *J* 7.0, ArH) and 7.53–7.64 (5 H, m, ArH).

5,8,12b,13-Tetrahydro-9,10-dimethoxy-13-phenylsulfanyl-6*H*-1,3-dioxolo[4,5-*h*]isoindolo[1,2-*b*][3]benzazepin-8-ones 19a,b

TFFA (130 mg, 0.61 mmol) was added to a solution of sulfoxide **18** (147 mg, 0.31 mmol) in dichloromethane (8 cm^3) at 0 °C, and the mixture was stirred at room temperature for 36 h. The solvent was evaporated off and the residue was chromatographed on silica gel [hexane–AcOEt (3:1)]. The first fraction gave one of the *diastereoisomers*, **19a** (51 mg, 36%), mp 226–227 °C (from hexane–AcOEt) (Found: C, 67.2; H, 4.9; N, 2.95. $C_{26}H_{23}NO_5S$ requires C, 67.7; H, 5.0; N, 3.0%); $\nu_{max}(CHCl_3)/cm^{-1}$ 1680; δ_H(300 MHz) 2.69–2.79 (1 H, m), 3.29–3.46 (2 H, m), 3.88 (3 H, s, OMe), 4.00 (3 H, s, OMe), 4.03–4.16 (1 H, m), 4.37 (1 H, d, *J* 4.5), 4.83 (1 H, d, *J* 4.5), 5.84 and 5.89 (1 H, each, both d, *J* 1.4, OCH_2O), 6.18 (1 H, s, ArH), 6.62 (1 H, s, ArH), 7.04 and 7.07 (1 H each, ABq, *J* 8.6, ArH) and 7.30–7.45 (5 H, m, ArH). The second fraction gave another *isomer*, **19b** (62 mg, 44%), mp 202–203 °C (from hexane–AcOEt) (Found: M^+, 460.1281. $C_{26}H_{23}NO_5S$ requires M, 461.1297); $\nu_{max}(CHCl_3)/cm^{-1}$ 1680; δ_H(300 MHz), 2.78 (1 H, dd, *J* 15.2 and 4.7), 3.01 (1 H, t, *J* 12.5), 3.53–3.62 (1 H, m), 3.90 (3 H, s, OMe), 4.16 (3 H, s, OMe), 4.43 (1 H, d, *J* 1.8), 4.71–4.78 (1 H, m), 4.75 (1 H, d, *J* 1.8), 5.94 (2 H, s, OCH_2O), 6.54 (1 H, s, ArH), 6.70 (1 H, s, ArH) and 6.94–7.19 (7 H, m, ArH).

Lennoxamine 21

To a solution of mixed pentacyclic diastereoisomers **19** (57 mg, 0.12 mmol) in toluene (5 cm^3) were added Bu_3SnH (118 mg, 0.41 mmol) and AIBN (6 mg, 0.04 mmol), and the mixture was refluxed for 2 h. After removal of the solvent, diethyl ether (10 cm^3) and 8% aq. KF (10 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 (2:1)] to give title compound **21** (41 mg, 94%), mp 229–230 °C (from methanol) (lit.,[7a,c] 228–229 °C; lit.,[7b,g] 225 °C);

ν_{max}($CHCl_3$)/cm^{-1} 1675; δ_H(300 MHz), 2.79–2.98 (3 H, m), 2.82 (1 H, dd, *J* 14.6 and 10.8), 3.10 (1 H, dd, *J* 14.6 and 1.5), 3.92 (3 H, s, OMe), 4.10 (3 H, s, OMe), 4.29 (1 H, dd, *J* 10.8 and 1.5), 4.71–4.77 (1 H, m), 5.95 and 5.96 (1 H each, ABq, *J* 1.2, OCH_2O), 6.71 (1 H, s, ArH), 6.78 (1 H, s, ArH), 7.13 (1 H, d, *J* 8.34, ArH) and 7.18 (1 H, d, *J* 8.3, ArH); δ_C 35.9 (CH_2), 41.1 (CH_2), 42.7 (CH_2), 56.7 (CH_3), 60.2 (CH), 62.5 (CH_3), 101.0 (CH_2), 110.3 (2 × CH), 116.2 (CH), 117.1 (CH), 124.1, 130.9, 134.8, 138.2, 146.0, 146.3, 147.2, 152.6 and 165.0 (C=O).

5,8-Dihydro-9,10-dimethoxy-6*H*-1,3-dioxolo[4,5-*h*]isoindolo-[1,2-*b*][3]benzazepin-8-one 20

From compound 19a. Following a procedure similar to that described for the preparation of compound **18**, isomer **19a** (30 mg, 0.065 mmol) was oxidised with MCPBA (14 mg, 0.065 mmol) in dichloromethane (15 cm^3) and work-up gave the crude sulfoxide (32 mg). This sulfoxide was dissolved in toluene (5 cm^3) and the mixture was heated under reflux for 1 h. The reaction mixture was concentrated under reduced pressure, and the residue was chromatographed on silica gel [hexane–AcOEt (3:1)] to give title compound **20** (13 mg, 57%), mp 209–211 °C (from hexane–AcOEt) (Found: M^+, 351.1089. $C_{20}H_{17}NO_5$ requires M, 351.1107); ν_{max}($CHCl_3$)/cm^{-1} 1690; δ_H(300 MHz) 3.04 (2 H, t, *J* 4.8, 5-H_2), 3.93 (3 H, s, OMe), 3.8–4.2 (2 H, br, 6-H_2), 4.11 (3 H, s, OMe), 5.97 (2 H, s, OCH_2O), 6.33 (1 H, s, 13-H), 6.67 (1 H, s, ArH), 6.81 (1 H, s, ArH), 7.13 (1 H, d, *J* 8.4, ArH) and 7.43 (1 H, d, *J* 8.4, ArH); δ_C 35.6 (CH_2), 41.9 (CH_2), 56.8 (CH_3), 62.5 (CH_3), 101.3 (CH_2), 105.0 (CH), 110.2 (CH), 110.3 (CH), 114.4 (CH), 116.4 (CH), 120.4, 127.9, 131.2, 133.3, 134.0, 146.6, 146.9, 147.0, 153.0 and 163.7 (C=O).

From compound 18. TFAA (80 mg, 0.38 mmol) was added to a solution of compound **18** (61 mg, 0.13 mmol) in toluene (10 cm^3) at 0 °C, and the mixture was refluxed for 10 h. The reaction mixture was washed successively with saturated aq. $NaHCO_3$ and brine, dried ($MgSO_4$), concentrated, and the residue was chromatographed on silica gel [hexane–AcOEt (5:1)] to give compound **20** (31 mg, 69%), mp 209–210 °C (from hexane–AcOEt).

Radical cyclisation of compound 12e

Following the general procedure, compound **12e** (474 mg, 0.87 mmol) was treated with Bu_3SnH (835 mg, 2.87 mmol) and ACN (64 mg, 0.26 mmol) in toluene (150 cm^3) and the crude material was chromatographed on silica gel [hexane–AcOEt (5:1)] to give 2,3-*dihydro*-N-[(S)-1-*phenylethyl*]-3-[(*phenylsulfanyl*)-*methyl*]-1H-*isoindol*-1-*one* **15e** (185 mg, 59%) as an oily mixture of two diastereoisomers in the ratio 2:1 (determined by an integrated intensity of the peak heights of the signals due to their C-methyl protons appeared at δ 1.79 and 1.65) (Found: M^+, 359.1352. $C_{23}H_{21}NOS$ requires M, 359.1344); ν_{max}(CCl_4)/cm^{-1} 1690; δ_H(300 MHz) (for the major isomer) 1.79 (3 H, d, *J* 7.5, CHCH_3), 3.05 (1 H, dd, *J* 13.5 and 7.8, one of CH_2SPh), 3.55 (1 H, dd, *J* 13.5 and 3.0, one of CH_2SPh), 4.45 (1 H, dd, *J* 7.8 and 3.0, 3-H), 5.70 (1 H, q, *J* 7.5, C*H*CH_3), 6.99–7.51 (13 H, m, ArH) and 7.86–7.89 (1 H, m, ArH); (for the minor isomer) 1.65 (3 H, d, *J* 7.2, CHCH_3), 2.56 (1 H, dd, *J* 13.8 and 8.1, one of CH_2SPh), 3.16 (1 H, dd, *J* 13.8 and 2.9, one of CH_2SPh), 4.74 (1 H, dd, *J* 8.1, 2.9 and 3-H), 5.60 (1 H, q, *J* 7.2, C*H*CH_3), 6.99–7.51 (13 H, m, ArH) and 7.65–7.68 (1 H, m, ArH).

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