Vinyl Azides in Heterocyclic Synthesis. Part 10.[1] Synthesis of the Isoindolobenzazepine Alkaloid Lennoxamine[2]

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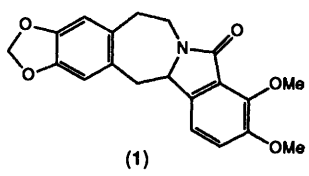
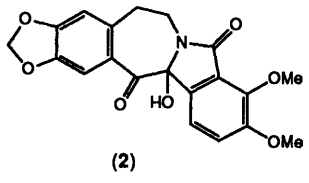
A total synthesis of the isoindolobenzazepine alkaloid lennoxamine (**1**), by a route involving vinyl azide chemistry, is described. Model studies on the azidocinnamates (**12**) and (**13**) revealed a striking difference between the (*E*)- and (*Z*)-isomers; whereas the (*Z*)-isomer (**12**) and gave largely the 1-benzylisoquinoline (**15**) on decomposition, the (*E*)-isomer (**13**) gave the 2-aryl-3-benzazepine (**14**) as the major product. Consequently, in the lennoxamine synthesis, the azidocinnamate (**26**) bearing the (*E*)-alkenyl side chain, prepared from 6-bromopiperonal *via* the (*E*)-stilbene aldehyde (**25**) (Scheme 4), was decomposed to give the key 2-aryl-3-benzazepine (**27**). Reduction of the double bonds in (**27**) was accompanied by cyclisation to the tetrahydroisoindolo[1,2-*b*][3]benzazepine (**30**), which was converted into lennoxamine (**1**) by reduction of the ester group to an aldehyde, and decarbonylation.

Members of the plant family *Berberidaceae* are a rich source of alkaloids, and recently the first examples of a new class of alkaloid, the isoindolobenzazepines lennoxamine (**1**) and chilenine (**2**), have been isolated from the Chilean barberries *Berberis darwinii* Hook and *Berberis empetrifolia* Lam, respectively.[3–5] The isoindolobenzazepines, also known as aporhoeadanes, which are accessible *in vivo* and *in vitro* by oxidation of berberine alkaloids[5–7] and from phthalide–isoquinoline alkaloids,[8] have recently been the subject of some new synthetic approaches.[9–12] We now report the full details of a total synthesis of lennoxamine (**1**) by a route involving vinyl azide chemistry.[13–15]



(1)

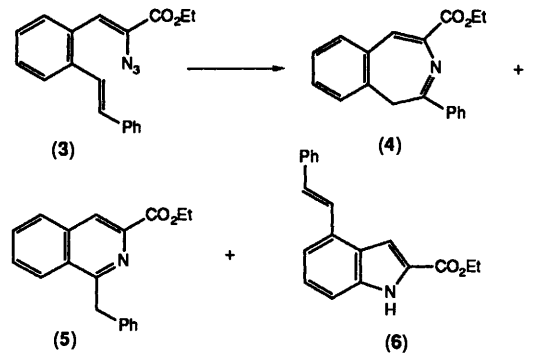


(2)

Results and Discussion

In our earlier studies on the decomposition of azidocinnamates bearing *ortho*-alkenyl side chains, we have shown that the major reaction pathway involves interaction of the azide or nitrene with the substituent double bond rather than with the aromatic ring.[13–15] In particular, the *ortho*-styryl azide (**3**) gave the 2-phenyl-3-benzazepine (**4**) (37%) and the 1-benzylisoquinoline (**5**) (36%) as the major products, resulting from attack of the azide or intermediate nitrene on the alkenyl double bond. Only a small amount (9%) of the indole (**6**) derived by competing attack at the free *ortho*-position of the aromatic ring was observed (Scheme 1).[15] We therefore investigated the use of this type of reaction as a route to the 2-aryl-3-benzazepine portion of lennoxamine (**1**).

Model Studies.—Since the precursor to the 2-aryl-3-benzazepine required for the synthesis of lennoxamine is a highly substituted stilbene aldehyde (*q.v.*), our initial studies on the benzazepine-forming reaction were carried out with a slightly simpler substrate. Thus the monoprotected dialdehyde (**7**), prepared from 6-bromoveratraldehyde[16] as shown in Scheme 2, underwent Wittig reaction with the ylide derived from 2-bromobenzyltriphenylphosphonium bromide[17] to give a mixture of the (*Z*)- and (*E*)-stilbenes (**8**) and (**9**) in good yield (90%) in the ratio of 4:1, from which the pure (*Z*) isomer (**8**) could be separated by chromatography. The pure (*E*)-stilbene (**9**) was better obtained by a Wadsworth–Emmons reaction on the aldehyde (**7**) using dimethyl (2-bromobenzyl)phosphonate. Hydrolysis of the acetals, followed by condensation with methyl azidoacetate then gave the (*Z*)- and (*E*)-isomers (**12**) and (**13**) of the model azidocinnamate. Thermolysis of the (*Z*)-azide (**12**) in boiling toluene for 45 min resulted in the formation of three products: the 2-arylbenzazepine (**14**) (22%) (or its 5*H*-tautomer), the 1-benzylisoquinoline (**15**) (39%), and the debenzylated isoquinoline (**16**) (6%). No 4-substituted indole (**17**) was detected. The azide (**12**) is also unstable at room temperature so that its decomposition in deuteriochloroform could be conveniently followed by ^{1}H NMR spectroscopy. After 15 d at 20 °C, the mixture contained (by NMR) the benzazepine (**14**) (10%), the isoquinoline (**15**) (57%), and the isoquinoline (**16**) (19%), together with an unknown compound (*ca.* 14%). The (*E*)-azide (**13**) also decomposed at room temperature over several days, although the product distribution, as determined by NMR spectroscopy, was strikingly



Scheme 1.

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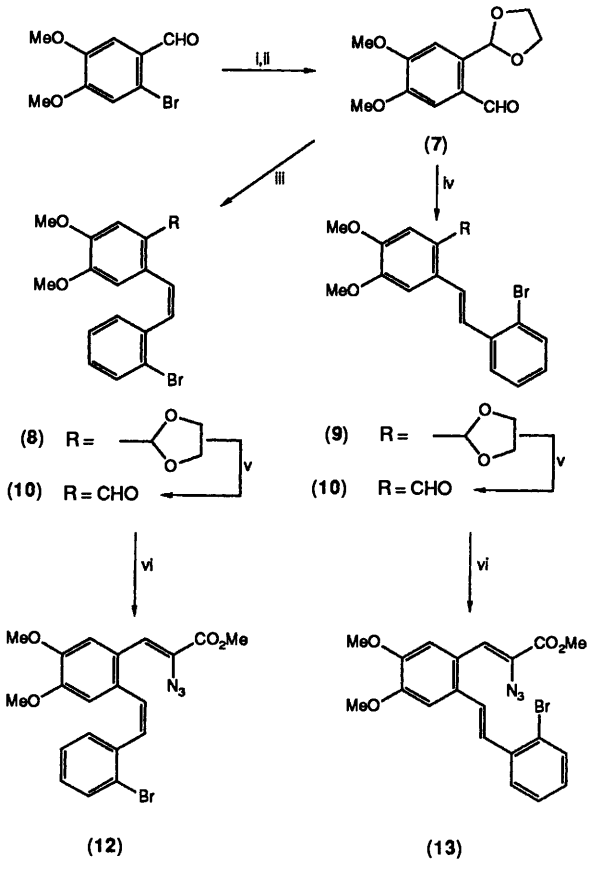
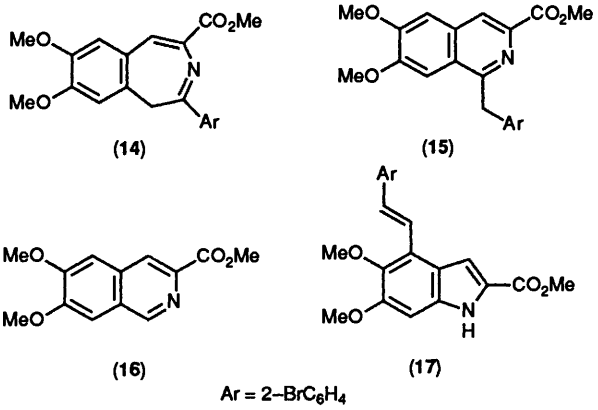
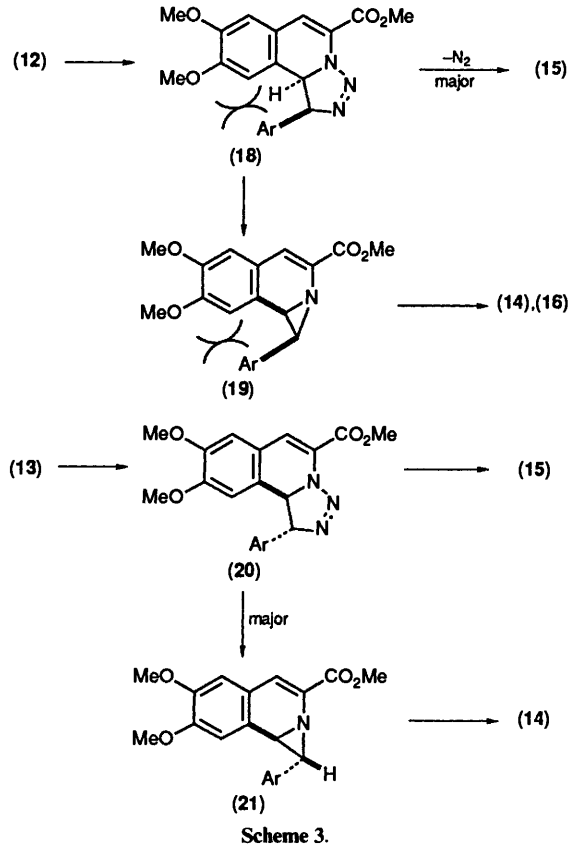


Scheme 2. *Reagents and conditions:* i, ethylene glycol, TsOH (cat.), toluene, reflux; ii, BuLi, THF, −78 °C, then DMF; iii, 2-bromobenzyltriphenylphosphonium bromide, NaOEt, EtOH; iv, dimethyl (2-bromobenzyl)phosphonate, NaH, THF; v, aq. HCl, Et_2O; vi, $MeO_2CCH_2N_3$, NaOMe, MeOH, −15 °C.



different to that obtained from the (*Z*)-azide (**12**). Thus, after 15 d in deuteriochloroform solution at 20 °C, the azide (**13**) had decomposed to the benzazepine (**14**) (38%) and the 1-benzylisoquinoline (**15**) (6%), and three unknown compounds (*ca.* 40, 13, and 2%). No debenzylated isoquinoline (**16**) was detected in the product mixture.

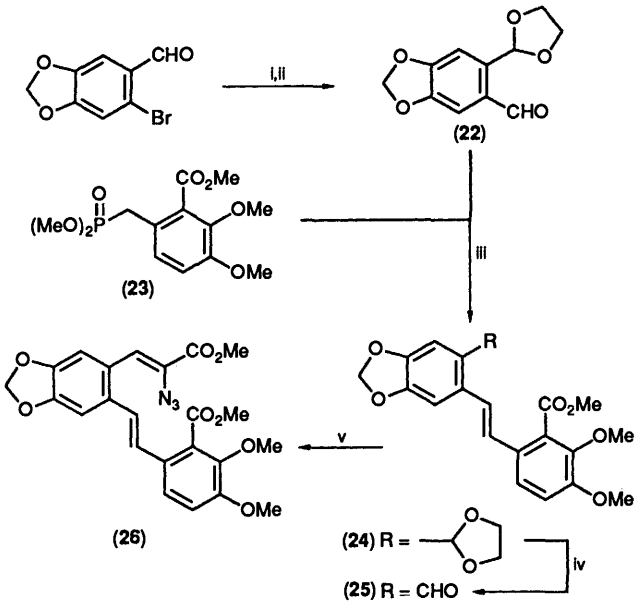
In mechanistic terms, these results fit in with our previous suggestions[14,15] that the decomposition of *ortho*-alkenyl azidocinnamates involves initial 1,3-dipolar cycloaddition to give a triazoline. In the (*Z*)-series, the resulting triazoline (**18**) would be sterically hindered due to the *cis*-disposition of the two aryl groups, and would be expected to undergo loss of nitrogen acccompanied by a [1,2]-shift of hydrogen to give the 1-benzylisoquinoline (**15**) directly. The alternative elimination of nitrogen to give aziridine (**19**) does not result in any immediate relief of steric strain, which has to occur subsequently by C–N bond cleavage to give the benzazepine (**14**). Presumably the debenzylated isoquinoline (**16**) results from C–C bond cleavage in the aziridine (**19**) followed by decomposition of the resulting isoquinolinium ylide. In the (*E*)-series of compounds, the initially formed triazoline (**20**) is less sterically strained and may decompose to the *trans*-aziridine (**21**) and hence the benzazepine (**14**) (Scheme 3). As relief of strain in aziridine (**21**) is less important than in the *cis*-isomer (**19**), no C–C bond cleavage is observed. Hence the model study revealed a striking difference



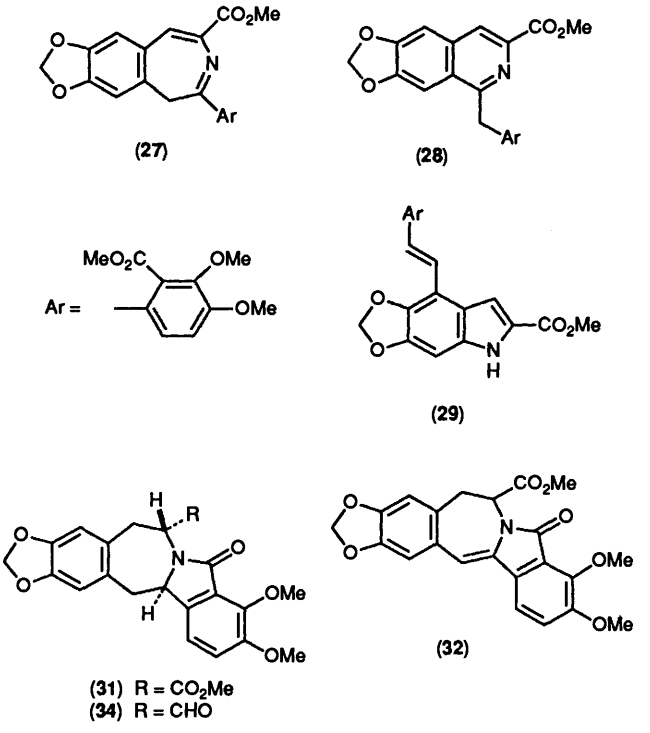
Scheme 3.

in the decomposition pathways of azidocinnamates bearing *cis*- or *trans*- *ortho*-styryl groups; the *cis*-isomer (**12**) giving the 1-benzylisoquinoline (**15**) as the major product, whereas the *trans*-isomer (**13**) gave largely the 2-aryl-3-benzazepine (**14**).

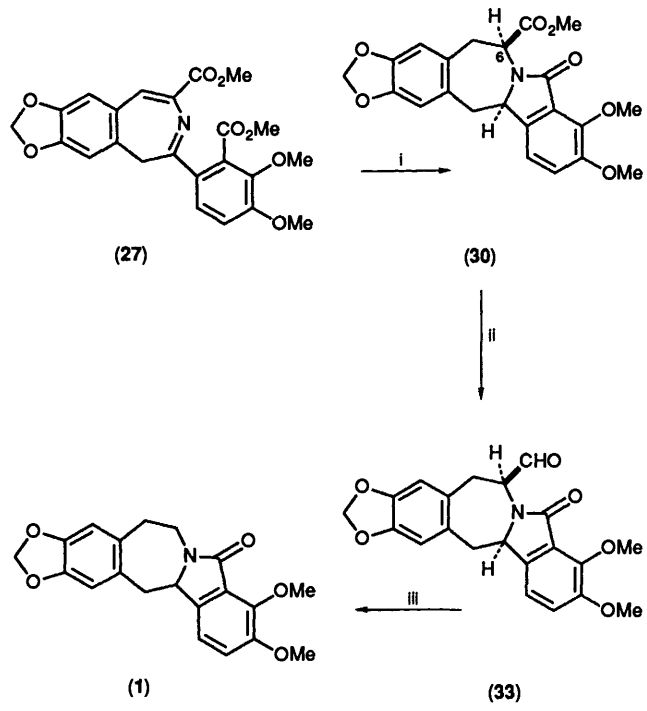
Synthesis of Lennoxamine (**1**).—The precursor to the required azidocinnamate (**26**) bearing the *trans*-alkenyl substituent is the highly substituted (*E*)-stilbene aldehyde (**25**), which was prepared from 6-bromopiperonal[18] as shown in Scheme 4. Thus the ethylene acetal derived from 6-bromopiperonal was lithiated, and the aryl lithium quenched with dimethylformamide (DMF) to give the mono-protected dialdehyde (**22**). Wadsworth–Emmons reaction of the aldehyde (**22**) with the phosphonate (**23**)[11] gave, after acid hydrolysis of the acetal, the (*E*)-stilbene aldehyde (**25**) in good overall yield. Condensation with methyl azidoacetate gave the unstable azide (**26**) in 66% yield. When heated in boiling xylene for 30 min, the azide (**26**) decomposed to give the required 2-aryl-3-benzazepine (**27**) as the major product (55%). The benzazepine (**27**) was accompanied by the 1-benzylisoquinoline (**28**) (29%) and the 4-substituted indole (**29**) (4%).



Scheme 4. *Reagents and conditions:* i, ethylene glycol, TsOH (cat.), toluene, reflux; ii, BuLi, ether, −60 °C, then DMF; iii, KOBu^t, THF; iv, dilute HCl, CH_2Cl_2; v, $MeO_2CCH_2N_3$, NaOMe, MeOH–THF, 5 °C.



The synthesis of lennoxamine (**1**) was completed as shown in Scheme 5. Reduction of the 3-benzazepine (**27**) with sodium cyanoborohydride in acetic acid resulted in reduction of both double bonds, and concomitant cyclisation of the NH moiety onto the ester group of the 2-substituent to give the *cis*-tetrahydroisoindolo[1,2-b][3]benzazepine (**30**) in 80% yield, together with small amounts of the *trans*-diastereoisomer (**31**) (epimeric at C-6) (4%) and the dihydro derivative (**32**) (3%). It is not known whether the *trans*-isomer (**31**) is formed in the reduction or during isolation because it was subsequently found that the *cis*-isomer rapidly epimerised to the more stable *trans*-isomer on treatment with base. The relative stereochemistries



Scheme 5. *Reagents and conditions:* i, $NaBH_3CN$, AcOH; ii, DIBAL, toluene, −70 °C; iii, $Rh(PPh_3)_2(CO)Cl$, dppp, xylene, reflux.

of the esters (**30**) and (**31**) were assigned by correlation with the corresponding aldehydes (**33**) and (**34**) (*q.v.*).

It only remained to remove the unwanted ester group at C-6, and this was achieved by decarbonylation of the corresponding aldehyde; hydrolysis and decarboxylation of the ester were unsatisfactory. Thus reduction of the *cis*-ester (**30**) using diisobutylaluminium hydride (DIBAL) in toluene at low temperature gave the *cis*-aldehyde (**33**) (70%). The aldehyde (**33**) readily epimerised to the *trans*-diastereoisomer (**34**) on treatment with base, and with both aldehydes available the relative stereochemistries were confirmed by NOE difference spectroscopy. The *cis*-aldehyde (**33**) was smoothly decarbonylated using a rhodium(I) catalyst in the presence of 1,3-bis(diphenylphosphino)propane (dppp)[19] to give lennoxamine (**1**) (51%). Since the stereochemical centre at C-6 is not present in the natural product, separation of the diastereoisomers of the tetrahydroisoindolinobenzazepines formed in the cyanoborohydride reduction step is unnecessary, and without this separation, the 2-aryl-3-benzazepine (**27**) was converted into lennoxamine (**1**) in 43% overall yield. The sample of lennoxamine was identical (m.p., TLC, 200 MHz ^{1}H NMR) to material from natural sources.

Experimental

For general points see ref. 14.

Model Studies.—6-Bromoveratraldehyde was prepared in 80% yield, m.p. 148–150 °C (lit.,[16] m.p. 148–150 °C) by the bromination of veratraldehyde in acetic acid at *ca.* 10 °C.

2-(1,3-Dioxolan-2-yl)-4,5-dimethoxybromobenzene was prepared in 94% yield, m.p. 105–111 °C (from diethyl ether–hexane) (lit.,[20] m.p. not recorded) from 6-bromoveratraldehyde and ethylene glycol in toluene with azeotropic removal of water; ν_{max}(Nujol) 1 599, 1 262, 1 211, 1 169, 1 097, 886, and 837 cm^{-1} (lit.,[20] IR not recorded).

(2-Bromobenzyl)triphenylphosphonium bromide was pre-

pared in 95% yield, m.p. 193–195 °C (lit.,[17] m.p. 193–195 °C) by treating 2-bromobenzyl bromide with triphenylphosphine in toluene at reflux.

2-(1,3-*Dioxolan*-2-*yl*)-4,5-*dimethoxybenzaldehyde* (**7**).—Butyl-lithium (1.55M solution in hexane, 115 ml, 0.178 mol, 1.04 equiv.) was added at *ca.* −70 °C to a solution of 2-(1,3-dioxolan-2-yl)-4,5-dimethoxybromobenzene (50.0 g, 0.173 mol) in THF (400 ml) under nitrogen. The mixture was stirred at −78 °C for a further 0.5 h, then treated with anhydrous DMF (15.0 g, 0.205 mol) and allowed to warm to room temperature during 1.5 h. The reaction mixture was poured into hydrochloric acid (0.05M; 500 ml) and immediately extracted with ether (1 × 400 ml, 3 × 100 ml), dried (K_2CO_3), and concentrated under reduced pressure to give a pale yellow solid. Trituration with ether gave the *benzaldehyde* (**7**) (40.6 g, 99%) as a white solid, m.p. 95–97 °C which crystallised as colourless needles from diethyl ether, m.p. 98–99 °C (Found: C, 60.8; H, 6.0. $C_{12}H_{14}O_5$ requires C, 60.5; H, 5.9%); ν_{max}(Nujol) 1 677, 1 592, 1 287, 1 219, 1 118, 876, 745, and 720 cm^{-1}; δ_H($CDCl_3$) 3.95 (3 H, s, OMe), 3.99 (3 H, s, OMe), 4.0–4.25 (4 H, m, OCH_2CH_2O), 6.36 (1 H, s, OCHO), 7.22 (1 H, s, ArH), 7.47 (1 H, s, ArH), and 10.34 (1 H, s, ArCHO).

Dimethyl (2-*Bromobenzyl*)*phosphonate*.—Trimethyl phosphite (49.7 g, 0.40 mol) was added dropwise to a solution of 2-bromobenzyl bromide (50.0 g, 0.40 mol) in diethyl ether (500 ml) at *ca.* 0 °C. The mixture was stirred at room temperature overnight and then concentrated under reduced pressure. The residual oil was distilled to afford the *phosphonate* (91.6 g, 82%) as a colourless oil, b.p. 124 °C at 0.45 mmHg (Found: C, 39.1; H, 4.3. $C_9H_{12}BrO_3P$ requires C, 38.7; H, 4.3%); ν_{max}(neat) 2 951, 1 471, 1 438, 1 254br, 1 030br, 830br, and 539 cm^{-1}; δ_H($CDCl_3$) 3.42 (2 H, d, *J* 22 Hz, $ArCH_2P$), 3.68 (3 H, s, OMe), 3.73 (3 H, s, OMe), 7.08–7.16 (1 H, m, ArH), 7.24–7.32 (1 H, m, ArH), 7.41–7.47 (1 H, s, ArH), 7.55–7.59 (1 H, s, ArH *ortho* to Br).

(Z)- *and* (E)-*Isomers of* 2-*Bromo*-2′-(1,3-*dioxolan*-2-*yl*)-4′,5′-*dimethoxystilbene* (**8**) and (**9**).—A solution of sodium ethoxide [prepared from sodium (2.0 g, 87 mmol) in ethanol (100 ml)] was added during 0.5 h to a stirred mixture of the benzaldehyde (**7**) (20.0 g, 84.0 mmol) and 2-bromobenzyl(triphenyl)phosphonium bromide (43.0 g, 84.0 mmol) in ethanol (200 ml) at room temperature. The mixture was stirred for a further 0.5 h and concentrated under reduced pressure. The residue was purified by chromatography (neutral Al_2O_3; ether) to afford a pale yellow syrup which slowly crystallised. Trituration with hexane gave the stilbenes (**8**) and (**9**) (*Z*–*E*, 4:1) (29.54 g, 90%) as colourless prisms, m.p. 76–78 °C (from hexane) (Found: C, 58.2; H, 5.1. $C_{19}H_{19}BrO_4$ requires C, 58.3; H, 4.9%); ν_{max}(Nujol) 1 601, 1 511, 1 205, 1 110, 1 001, 880, 776, and 750 cm^{-1}; δ_H($CDCl_3$) (data for *Z*-isomer) (**8**) 3.46 (3 H, s, OMe *meta* to olefin), 3.88 (3 H, s, OMe *meta* to dioxolane), 4.0–4.2 (4 H, m, OCH_2CH_2O), 5.96 (1 H, s, OCHO), 6.44 (1 H, s, ArH *ortho* to OMe and olefin), 6.72 (1 H, d, *J* 12 Hz, olefinic H geminal to ArBr), 6.95 (1 H, d, *J* 12 Hz, olefinic *H* geminal to methoxylated aromatic ring), 7.00–7.05 (3 H, m, ArH *ortho*, *meta*, and *para* to olefin), 7.09 (1 H, s, ArH *ortho* to OMe and acetal), and 7.5–7.6 (1 H, m, ArH *ortho* to Br); irradiation of the signal at δ 5.96 caused NOE effects at δ 4.0–4.2, 7.09, and 6.95; irradiation of the signal at δ 7.09 caused NOE effects at δ 3.88 and 5.95; irradiation of the signal at δ 6.44 caused NOE effects at δ 3.46, and 7.0–7.05.

A small sample was subjected to chromatography (SiO_2; ether–hexane) to afford the pure (*Z*)-stilbene (**8**), m.p. 98–99 °C.

(E)-2-*Bromo*-4′,5′-*dimethoxy*-2′-(1,3-*dioxolan*-2-*yl*)*stilbene* (**9**).—A solution of dimethyl 2-bromobenzylphosphonate (11.0 g, 36.0 mmol) in THF (40 ml) was added dropwise at 0 °C to a mixture of the benzaldehyde (**7**) (8.50 g, 35.7 mmol) and sodium hydride (80% dispersion in oil) (1.08 g, 36 mmol) in THF (100 ml). The reaction mixture was stirred at room temperature for 2 h then water (100 ml) and chloroform (100 ml) were added. The organic phase was separated, combined with a further extract (50 ml), and the extract was washed with brine (25 ml), dried (Na_2SO_4), and concentrated *in vacuo* to afford a pale yellow syrup which was recrystallised from hexane to give the (E)-*stilbene* (**9**) (12.84 g, 92%) as colourless flakes, m.p. 125–132 °C (Found: C, 58.3; H, 4.9. $C_{19}H_{19}BrO_4$ requires C, 58.3; H, 4.9%); ν_{max}(Nujol) 1 602, 1 510, 1 275, 1 202, 1 120, 963, 875, and 760 cm^{-1}; δ_H($CDCl_3$ 3.94 (3 H, s, OMe), 3.97 (3 H, s, OMe), 4.0–4.25 (4 H, m, OCH_2CH_2O), 6.06 (1 H, s, OCHO), 7.08 (1 H, dd, *J* 2 and 7 Hz, ArH), 7.15 (1 H, s, ArH *ortho* to OMe), 7.17 (1 H, s, ArH *ortho* to OMe), 7.26 (1 H, d *J* 16 Hz, olefinic H), 7.30 (1 H, dt, *J* 2 and 7 Hz, ArH), 7.40 (1 H, d, *J* 16 Hz, olefinic H), 7.58 (1 H, dd, *J* 1 and 8 Hz, ArH), and 7.65 (1 H, dd, *J* 2 and 8 Hz, ArH).

(Z)- *and* (E)-*Isomers of* 2-*Bromo*-4,5-*dimethoxystilbene*-2-*carbaldehyde* (**10**) *and* (**11**).—A solution of the acetals (**8**) and (**9**) (*Z*–*E*, 4:1) (6.00 g, 15.34 mmol) in ether (200 ml) was stirred with hydrochloric acid (2M; 150 ml) for 1 h at room temperature. A white solid precipitated and was filtered off, dissolved in dichloromethane (25 ml), and dried (K_2CO_3). The solvent was removed under reduced pressure to give the (E)-*stilbene* (**11**) (0.75 g, 14%) as white needles, m.p. 153–155 °C (from hexane) (Found: C, 58.95; H, 4.35. $C_{17}H_{15}BrO_3$ requires C, 58.8; H, 4.35%); ν_{max}(Nujol) 1 664, 1 591, 1 511, 1 276, 1 103, 965, 878, and 761 cm^{-1}; δ_H($CDCl_3$) 3.98 (3 H, s, OMe), 4.05 (3 H, s, OMe), 7.15 (1 H, s, ArH), 7.16 (1 H, dt, *J* 7 and 2 Hz), 7.31 (1 H, d, *J* 16 Hz, ArCH=C), 7.35 (1 H, dt, *J* 7 and 2 Hz, ArH), 7.39 (1 H, s, ArH), 7.61 (1 H, dd, *J* 7 and 2 Hz, ArH), 7.71 (1 H, dd, *J* 7 and 2 Hz, ArH), 7.85 (1 H, d, *J* 16 Hz, ArCH=C), and 10.31 (1 H, s, ArCHO).

The filtrate was extracted with dichloromethane (75 ml), and the extract dried (K_2CO_3), and concentrated under reduced pressure to give the *stilbenes* (*Z*–*E*, 5:1) (3.75 g, 70%). A small sample of the mixture was subjected to radial TLC (SiO_2; hexane–ether) to afford a sample of the pure (Z)-*stilbene* (**10**) as colourless needles, m.p. 114–115 °C (from hexane) (Found: C, 58.8; H, 4.4%); ν_{max}(Nujol) 1 671, 1 594, 1 511, 1 264, 1 095, 857, 780, and 769 cm^{-1}; δ_H($CDCl_3$) 3.64 (3 H, s, OMe), 3.92 (3 H, s, OMe), 6.55 (1 H, s, ArH *ortho* to OMe and olefin), 6.93 (1 H, d, *J* 12 Hz, olefinic H), 6.88–7.10 (3 H, m, ArH), 7.16 (1 H, d, *J* 12 Hz, olefinic H), 7.33 (1 H, s, ArH *ortho* to OMe and CHO), 7.53–7.63 (1 H, m, ArH), and 10.15 (1 H, s, ArCHO).

The pure (*E*)-acetal (**9**) from the Wadsworth–Emmons reaction was hydrolysed as above to afford the pure (*E*)-benzaldehyde (**11**) in 93% yield.

(Z)-2-(2-*Azido*-2-*methoxycarbonylvinyl*)-2′-*bromo*-4,5-*dimethoxystilbene* (**12**).—A solution of sodium methoxide [prepared from sodium (0.68 g, 29.5 mmol) in methanol (75 ml)] was cooled to −15 °C and a suspension of the (*Z*)-benzaldehyde (**10**) (2.60 g, 7.49 mmol) in methyl azidoacetate (3.4 g, 29.5 mmol) and methanol (50 ml) was added in one portion under nitrogen. The reaction mixture was allowed to warm to room temperature over 2 h and stirred overnight. A pale yellow precipitate was filtered off, washed with methanol, and dried *in vacuo* to afford the (*Z*)-*azide* (**12**) (1.58 g, 48%) as unstable pale yellow needles, m.p. 122–124 °C (decomp.) (from methanol) (Found: C, 54.2; H, 3.85; N, 9.5. $C_{20}H_{18}BrN_3O_4$ requires C, 54.1; H, 4.1; N, 9.5%); ν_{max}(Nujol) 2 123, 1 715, 1 611, 1 596, 1 511, 1 258, 1 000, 875, 793, and 760 cm^{-1}; δ_H($CDCl_3$) 3.63 (3 H, s, OMe), 3.90 (3 H, s, OMe), 3.92 (3 H, s, OMe), 6.61 (1 H, s, ArH *ortho* to OMe and styrene), 6.82 (2 H, s, coincident signals CH=CH), 6.85–6.93 (1 H, m, ArH), 6.93–7.1 [2 H, m, ArH and 1 H, s, C*H*=C(CO_2Me) (δ 6.99)], 7.47–7.56 (1 H, m, ArH), and 7.60 (1 H, s, ArH *ortho* to vinyl azide).

(E)-2-(2-*Azido*-2-*methoxycarbonylvinyl*)-2′-*bromo*-4,5-*dimethoxystilbene* (**13**).—A solution of sodium methoxide [prepared from sodium (0.66 g, 28.8 mmol) in methanol (75 ml)] was cooled to −15 °C and treated with a solution of the (*E*)-benzaldehyde (**11**) (2.50 g, 7.20 mmol) and methyl azidoacetate (3.31 g, 28.8 mmol) in THF (50 ml). The mixture was stored at *ca.* 4 °C overnight, the precipitate collected and washed with methanol to afford the (E)-*azide* (**13**) (2.05 g, 64%) as pale yellow needles, m.p. 115–118 °C (Found: C, 54.0; H, 4.1; N, 9.6. $C_{20}H_{18}BrN_3O_4$ requires C, 54.1; H, 4.1; N, 9.5%); ν_{max}(Nujol) 2 133, 1 713, 1 595, 1 509, 1 252, 1 207, 1 108, and 747 cm^{-1}; $\delta_H(CDCl_3)$ 3.91 (3 H, s, OMe), 3.95 (3 H, s, OMe), 3.98 (3 H, s, OMe), 7.08 (1 H, s, ArH *ortho* to OMe), 7.14 (1 H, dt, *J* 8 and 2 Hz, ArH), 7.22 (2 H, s, coincident signals, CH=CH), 7.26 (1 H, s, ArH *ortho* to OMe), 7.34 (1 H, dt, *J* 7.5 and 1 Hz, ArH), 7.61 (1 H, dd, *J* 8 and 1 Hz, ArH), 7.63 [1 H, s, CH=C(CO_2Me)], and 7.65 (1 H, dd, *J* 8 and 1.5 Hz, ArH); λ_{max}(95% EtOH) 347 (ε 20 040 dm^3 mol^{-1} cm^{-1}), 293 (28 080), 237 (14 800), and 206 nm (28 070).

Thermolysis of the (Z)-*Azide* (**12**).—The azidocinnamate (**12**) (190 mg, 0.43 mmol) was dissolved in toluene (5 ml) and the pale yellow solution was heated to reflux for 0.75 h under nitrogen. The solvent was removed under reduced pressure to leave an orange semi-solid residue. A ^{1}H NMR (200 MHz) spectrum of the crude mixture was obtained and the residue chromatographed (SiO_2; dichloromethane–chloroform) to afford: (*a*) *methyl* 2-(2-*bromophenyl*)-7,8-*dimethoxy*-1H-3-*benzazepine*-4-*carboxylate* (**14**) (39 mg, 22%) as a pale yellow amorphous solid, m.p. 126–142 °C (from diethyl ether–hexane) (Found: C, 57.7; H, 4.3; N, 3.4. $C_{20}H_{18}BrNO_4$ requires C, 57.7; H, 4.4; N, 3.4%); ν_{max}(Nujol) 1 709, 1 601, 1 512, 1 280, 1 202, 1 102, 832, and 775 cm^{-1}; $\delta_H(CDCl_3)$ 3.6 (2 H, vbr s, $ArCH_2$), 3.85 (3 H, s, OMe), 3.90 (3 H, s, OMe), 3.96 (3 H, s, OMe), 6.87 (1 H, s), 6.91 (1 H, s), and 7.01 (1 H, s) (2 × ArH *ortho* to OMe + ArCH=C), 7.21 (1 H, dt, *J* 2 and 8 Hz, ArH), 7.40 (1 H, dt, *J* 1 and 8 Hz, ArH), 7.61 (1 H, dd *J* 1 and 8 Hz, ArH), and 7.80 (1 H, dd, *J* 2 and 8 Hz, ArH); $\delta_C(CDCl_3)$ 36.4 (t), 53.1 (q), 56.1 (q), 56.2 (q), 109.9 (d), 110.2 (d), 122.2 (d), 122.7 (d), 123.2 (s), 127.4 (s), 127.5 (d), 129.5 (d), 130.8 (d), 133.1 (d), 140.9 (s), 142.6 (s), 146.5 (s), 148.4 (s), 152.4 (s), and 163.8 (s); (*b*) *methyl* 1-(2-*bromobenzyl*)-6,7-*dimethoxyisoquinoline*-3-*carboxylate* (**15**) (77 mg, 39%) as colourless needles, m.p. 197–199 °C (from dichloromethane–diethyl ether) (Found: C, 57.5; H, 4.05; N, 3.6. $C_{20}H_{18}BrNO_4$ requires C, 57.7; H, 4.05; N, 3.4%); ν_{max}(Nujol) 2 923 1 727, 1 612, 1 509, 1 238, 1 163, 990, 847, 763, and 739 cm^{-1}; $\delta_H(CDCl_3)$ 3.90 (3 H, s, OMe), 4.02 (3 H, s, OMe), 4.07 (3 H, s, OMe), 4.83 (2 H, s, $ArCH_2$), 6.92–7.10 (3 H, m, ArH), 7.18 (1 H, s, isoquinoline 5-H or 8-H), 7.23 (1 H, s, isoquinoline 5-H or 8-H), 7.55–7.65 (1 H, m, ArH), and 8.42 (1 H, s, isoquinoline 4-H); $\delta_C(CDCl_3)$ 42.2 (t), 52.8 (q), 56.2 (q), 56.4 (q), 104.7 (d), 106.5 (d), 122.6 (d), 124.1 (s), 124.9 (s), 127.6 (d), 128.1 (d), 130.5 (d), 132.6 (d), 132.9 (s), 138.7 (s), 139.7 (s), 151.9 (s), 153.0 (s), 157.8 (s), and 166.8 (s); (*c*) *methyl* 6,7-*dimethoxyisoquinoline*-3-*carboxylate* (**16**) (6 mg, 6%) as colourless plates, m.p. 211–211.5 °C (from dichloromethane–diethyl ether) (Found: C, 63.1; H, 5.4; N, 5.7. $C_{13}H_{13}N_3O_4$ requires C, 63.1; H, 5.3; N, 5.7%); ν_{max}(KBr) 2 921, 2 852, 1 709, 1 612, 1 512, 1 286, 1 253, 1 155, 1 004, 902, and 852 cm^{-1}; $\delta_H(CDCl_3)$ 4.05 (3 H, s, OMe), 4.06 (3 H, s, OMe), 4.07 (3 H, s, OMe), 7.22 (1 H, s, isoquinoline 5-H), 7.30 (1 H, s, isoquinoline 8-H), 8.48 (1 H, s, isoquinoline 4-H), and 9.13 (1 H, s, isoquinoline 1-H). Irradiation of the signal at δ 9.13 caused a NOE of the signal at δ 7.30.

The ^{1}H NMR spectrum of the crude reaction mixture indicated that the yield of each component was (**15**) 56, (**14**) 22, and (**16**) 15%. An unidentified component was estimated to be present at *ca.* 7%.

When the *Z*-azide (**12**) was allowed to stand in deuteriochloroform solution at room temperature, slow decomposition ensued. The decomposition was monitored by recording ^{1}H NMR spectra at regular intervals over *ca.* 2 weeks. After 15 d the NMR spectrum indicated that the mixture consisted of the isoquinoline (**15**) (57%), the benzazepine (**14**) (10%), the 1-unsubstituted isoquinoline (**16**) (19%), and an unknown compound (*ca.* 14%) which could not be isolated.

Thermolysis of the (E)-*Azide* (**13**).—A solution of the azidocinnamate (**13**) (26 mg) in toluene (5 ml) was heated to reflux for 2 h. The reaction mixture was concentrated under reduced pressure and a ^{1}H NMR spectrum obtained. This indicated that the mixture consisted of the benzazepine (**14**) (55%), the 1-benzylisoquinoline (**15**) (*ca.* 35%), and an unknown compound (5%). Signals attributable to the debenzylated isoquinoline (**16**) were not present in the spectrum.

A solution of the *trans*-azide (**13**) in deuteriochloroform was allowed to stand at room temperature and the subsequent decomposition monitored by obtaining ^{1}H NMR spectra at regular intervals. After 15 d the NMR spectrum indicated that the mixture consisted of the 1-benzylisoquinoline (**15**) (6%), the benzazepine (**14**) (38%), and three unidentified compounds estimated to be present at 40 [possibly a tautomer of the benzazepine (**14**)], 2, and 13%. No signals due to the 1-unsubstituted isoquinoline (**16**) were observed.

Synthesis of Lennoxamine.—6-Bromopiperonal was prepared by the method of Parijs[18] in 42% yield.

Dimethyl 2-methoxycarbonyl-3,4-dimethoxybenzylphosphonate (**23**) was obtained in four steps from 3,4-dimethoxybenzyl alcohol as described by Napolitano *et al.*[11] (63% overall yield) as colourless prisms m.p. 92 °C (lit.,[11] m.p. 91–93 °C).

2-(1,3-*Dioxolan*-2-*yl*)-4,5-(*methylenedioxy*)*benzaldehyde* (**22**).—A solution of 2-(1,3-dioxolan-2-yl)-4,5-(methylenedioxy)bromobenzene (78.0 g, 0.286 mol) in diethyl ether (600 ml) was cooled to −70 °C and treated with butyl lithium (1.5M solution in hexane) (200 ml, 0.300 mol) at −60 °C. After the mixture had been stirred for a further 0.25 h at −70 °C, anhydrous DMF (30 ml, 0.388 mol) was added at < −60 °C and the mixture was allowed to warm to room temperature overnight. The mixture was poured into saturated aqueous ammonium chloride (300 ml) and the organic phase separated. The aqueous phase was further extracted with dichloromethane (2 × 200 ml) and the combined organic phases were washed with brine (50 ml), dried (Na_2SO_4), and concentrated under reduced pressure to give a pale brown oil. The oil was dissolved in methanol (350 ml) and allowed to crystallise to give the *benzaldehyde* (**22**) (55.9 g, 88%) as colourless prisms, m.p. 69–71 °C (Found: C, 59.7; H, 4.6. $C_{11}H_{10}O_5$ requires C, 59.5; H, 4.5%); ν_{max}(Nujol) 1 681, 1 618, 1 589, 1 256, 1 216, 1 156, 918, and 889 cm^{-1}; $\delta_H(CDCl_3)$ 4.0–4.2 (4 H, m, OCH_2CH_2O), 6.07 (2 H, s, OCH_2O), 6.35 (1 H, s, OCHO), 7.18 (1 H, s, ArH), 7.40 (1 H, s, ArH *ortho* to CHO), and 10.27 (1 H, s, ArCHO).

Methyl (E)-3,4-*Dimethoxy*-2′-(1,3-*dioxolan*-2-*yl*)-4′,5′-*methylenedioxystilbene*-2-*carboxylate* (**24**).—A solution of potassium t-butoxide (25.0 g, 0.223 mol) in anhydrous THF (150 ml) was added dropwise to a mixture of the benzaldehyde (**22**) (45.0 g, 0.202 mol) and the phosphonate (**23**) (64.5 g, 0.202 mol) in THF (500 ml) at *ca.* 5 °C under nitrogen. The mixture was stirred for 18 h at room temperature and then partitioned between water (100 ml) and chloroform (200 ml). The organic phase was separated, combined with a further chloroform extract (200 ml), and then washed with brine (25 ml), dried (Na_2SO_4), and concentrated under reduced pressure to give a viscous yellow syrup which was recrystallised from methanol (500 ml) to give the *dioxolane* (**24**) (69.1 g, 82%) as colourless prisms, m.p. 148–

151 °C (Found: C, 63.9; H, 5.3. $C_{22}H_{22}O_8$ requires C, 63.75; H, 5.35%); ν_{max}(Nujol) 1 724, 1 593, 1 487, 1 263, 1 089, 1 062, 1 037, and 886 cm^{-1}; $\delta_H(CDCl_3)$ 3.87 (3 H, s, OMe), 3.89 (3 H, s, OMe), 3.94 (3 H, s, OMe), 4.0–4.15 (4 H, m, OCH_2CH_2O), 5.97 (2 H, s, OCH_2O), 5.99 (1 H, s, OCHO), 6.75 (1 H, d, *J* 16 Hz, C*H*=CH), 6.96 (1 H, d, *J* 9 Hz, ArH), 7.00 (1 H, s, ArH *ortho* to methylenedioxy), 7.10 (1 H, s, ArH *ortho* to methylenedioxy), 7.26 (1 H, d, *J* 16 Hz, C*H*=CH), and 7.35 (1 H, d, *J* 9 Hz, ArH).

Methyl (E)-3,4-*Dimethoxy*-2′-*formyl*-4′,5′-*methylenedioxystilbene*-2-*carboxylate* (**25**).—A solution of the dioxolane (**24**) (30.0 g, 72.4 mmol) in dichloromethane (400 ml) was treated with hydrochloric acid (2M; 200 ml) and the mixture vigorously stirred under nitrogen at room temperature for 1.25 h. The organic phase was separated, combined with a dichloromethane extract (100 ml), and then washed with brine (25 ml), dried (Na_2SO_4), and concentrated under reduced pressure to leave a viscous yellow syrup which rapidly crystallised when dissolved in methanol (500 ml) to afford the *benzaldehyde* (**25**) (24.2 g, 90%) as pale yellow needles, m.p. 107–109 °C (Found: C, 64.7; H, 4.9. $C_{20}H_{18}O_7$ requires C, 64.85; H, 4.9%); ν_{max}(Nujol) 1 722, 1 672, 1 594, 1 281, 1 245, 1 052, 1 031, and 727 cm^{-1}; $\delta_H(CDCl_3)$ 3.89 (3 H, s, OMe), 3.92 (3 H, s, OMe), 3.95 (3 H, s, OMe), 6.07 (2 H, s, OCH_2O), 6.83 (1 H, d, *J* 16 Hz, C*H*=CH), 6.99 (1 H, d, *J* 9 Hz, ArH), 7.03 (1 H, s, ArH *ortho* to olefin), 7.30 (1 H, s, ArH *ortho* to CHO), 7.43 (1 H, d, *J* 9 Hz, ArH), 7.74 (1 H, d, *J* 16 Hz, CH=C), and 10.21 (1 H, s, ArCHO); irradiation of the signal at δ 10.21 caused NOE effects at δ 7.74 and 7.30.

Methyl (E)-2′-(2-*Azido*-2-*methoxycarbonylvinyl*)-3,4-*dimethoxy*-4′,5′-*methylenedioxystilbene*-2-*carboxylate* (**26**).—A mixture of the benzaldehyde (**25**) (7.2 g, 19.4 mmol) and methyl azidoacetate (13.3 g, 0.166 mol) in THF (30 ml) was added dropwise at *ca.* 5 °C to a solution of sodium methoxide [prepared from sodium (2.7 g, 0.177 mol) in methanol (100 ml)] under nitrogen. The reaction mixture was stirred overnight at *ca.* 5 °C and then cooled to −70 °C to induce crystallisation. The precipitate was filtered off, washed with methanol, and dried *in vacuo* to afford the unstable *azide* (**26**) (6.03 g, 66%) as pale yellow needles, m.p. 113–116 °C (Found: C, 59.2; H, 4.5; N, 9.3. $C_{23}H_{21}N_3O_8$ requires C, 59.1; H, 4.5; N, 9.3%); ν_{max}(Nujol) 2 132, 1 727, 1 710, 1 616, 1 594, 1 290, 1 248, and 1 060 cm^{-1}; $\delta_H(CDCl_3)$ 3.88 (3 H, s, OMe), 3.907 (3 H, s, OMe), 3.911 (3 H, s, OMe), 3.94 (3 H, s, OMe), 6.02 (2 H, s, OCH_2O), 6.71 (1 H, d, *J* 16 Hz, C*H*=CH), 6.98 (1 H, d, *J* 8.5 Hz, ArH), 6.98 (1 H, s, ArH *ortho* to methylenedioxy), 7.11 (1 H, d, *J* 16 Hz, C*H*=CH), 7.16 (1 H, s, ArH *ortho* to methylenedioxy), 7.36 (1 H, d, *J* 8.5 Hz, ArH), and 7.55 [1 H, s, ArCH=C(CO_2Me)].

Thermolysis of the Azide (**26**).—The azidocinnamate (**26**) (8.5 g, 18.2 mmol) was suspended in xylene (150 ml) and heated under reflux for 0.5 h under nitrogen. The mixture was cooled to 0 °C whereupon *methyl* 2-(2-*methoxycarbonyl*-3,4-*dimethoxyphenyl*)-7,8-*methylenedioxy*-1H-3-*benzazepine*-4-*carboxylate* (**27**) (4.38 g, 55%) separated as pale yellow *needles*, m.p. 177–204 °C (Found: C, 63.0; H, 5.0; N, 3.3. $C_{23}H_{21}NO_8$ requires C, 62.9; H, 4.8; N, 3.2%); ν_{max}(Nujol) 1 720, 1 595, 1 290, 1 227, 1 056, 924, 844, and 814 cm^{-1}; $\delta_H(CDCl_3)$ 3.84 (3 H, s, OMe), 3.85 (3 H, s, OMe), 3.90 (3 H, s, OMe), 3.91 (3 H, s, OMe), 5.98 (2 H, s, OCH_2O), 6.82, 6.86, and 6.93 (3 × 1 H, 3 × s, 2 × ArH *ortho* to methylenedioxy and ArCH=C), 7.00 (1 H, d, *J* 4 Hz, ArH), and 7.39 (1 H, d, *J* 4 Hz), $ArCH_2$ not observed (very broad signal); $\delta_C(CDCl_3)$ 36.4 (t), 52.2 (q), 52.8 (q), 56.2 (q), 61.6 (q), 101.6 (t), 107.4 (d), 107.5 (d), 113.6 (d), 119.5 (d), 122.8 (s), 124.1 (d), 128.5 (s), 129.4 (s), 130.8 (s), 141.5 (s), 145.5 (s), 146.8 (s), 147.2 (s), 150.6 (s), 152.9 (s), 163.6 (s), and 168.1 (s).

The filtrate was concentrated under reduced pressure and the residue subjected to chromatography (SiO_2; diethyl ether) to afford (*a*) *methyl* 3,4-*dimethoxyphenyl*)-1-(2-*methoxycarbonyl*-6,7-*methylenedioxyisoquinoline*-3-*carboxylate* (**28**) (2.32 g, 29%) as colourless prisms, m.p. 175–178 °C (from methanol) (Found: C, 63.1; H, 5.1; N, 3.4. $C_{23}H_{21}NO_8$ requires C, 62.9; H, 4.8; N, 3.2%); ν_{max}(Nujol) 1 722, 1 489, 1 279, 1 244, 1 061, 1 042, 856, and 783 cm^{-1}; $\delta_H(CDCl_3)$ 3.78 (3 H, s, OMe), 3.88 (3 H, s, OMe), 4.00 (3 H, s, OMe), 4.04 (3 H, s, OMe), 4.53 (2 H, s, $ArCH_2$), 6.09 (2 H, s, OCH_2O), 6.52 (1 H, d, *J* 8.5 Hz, ArH), 6.70 (1 H, d, *J* 8.5 Hz, ArH), 7.17 (1 H, s, isoquinoline H), 7.46 (1 H, s, isoquinoline H), and 8.35 (1 H, s, isoquinoline 4-H); (*b*) *methyl* 4-(E)-[2-(2-*methoxycarbonyl*-3,4-*dimethoxyphenyl*)*vinyl*]-5,6-*methylenedioxyindole*-2-*carboxylate* (**29**) (285 mg, 3.6%) as pale yellow prisms, m.p. 182–185 °C (from methanol) (Found: C, 63.1; H, 4.7; N, 2.9. $C_{23}H_{21}NO_8$ requires C, 62.9; H, 4.8; N, 3.2%); ν_{max}(Nujol) 3 305, 1 709, 1 597, 1 511, 1 485, 1 281, 1 049, and 769 cm^{-1}; $\delta_H(CDCl_3)$ 3.89 (3 H, s, OMe), 3.92 (3 H, s, OMe), 3.95 (3 H, s, OMe), and 3.98 (3 H, s, OMe), 6.08 (2 H, s, OCH_2O), 7.00 (1 H, d, *J* 8.5 Hz, ArH), 7.02 (1 H, s, *J* 16 Hz, C*H*=CH), 7.05 (1 H, s, ArH), 7.27 (1 H, d, *J* 16 Hz, C*H*=CH), 7.43 (1 H, s, ArH), 7.45 (1 H, d, *J* 8.5 Hz, ArH), and 8.76 (1 H, br s, NH).

Reduction of the Benzazepine (**27**) *with Sodium Cyanoborohydride in Glacial Acetic Acid.*—Sodium cyanoborohydride (0.90 g, 14.3 mmol) was added to a suspension of the benzazepine (**27**) (4.194 g, 9.54 mmol) in glacial acetic acid (25 ml) at *ca.* 10 °C. The mixture was stirred for 0.5 h after which the colourless fluorescent solution was basified with aqueous sodium hydroxide (2M) and extracted with dichloromethane (1 × 100 ml, 2 × 25 ml). The combined extracts were washed with brine (25 ml), dried (Na_2SO_4), and concentrated *in vacuo* to afford a pale yellow foam (4.05 g, *ca.* 100%). The foam was triturated with hot methanol (350 ml) and filtered to give *methyl* 5,6-*dihydro*-9,10-*dimethoxy*-8-oxo-8H-1,3-*dioxolo*[4,5-h]*isoindolo*[1,2-b][3]*benzazepine*-6-*carboxylate* (**32**) (131 mg, 3.4%) as fluorescent green microprisms, m.p. 222–245 °C (Found: C, 64.5; H, 4.7; N, 3.45. $C_{22}H_{19}NO_7$ requires C, 64.59; H, 4.7; N, 3.4%); ν_{max}(KBr) 1 735, 1 686, 1 652, 1 500, 1 252, 1 063, 1 038, and 815 cm^{-1}; $\delta_H(CDCl_3)$ ABX system: δ_A 3.11, δ_B 3.54, δ_X 5.66 (J_{AB} 15, J_{AX} 6, J_{BX} 2 Hz, $ArCH_ACH_BCH_X$), 3.53 (3 H, s, CO_2Me), 3.94 (3 H, s, ArOMe *ortho* to aromatic H), 4.11 (3 H, s, ArOMe *ortho* to carbonyl), 5.97 (2 H, s, OCH_2O), 6.37 (1 H, s, ArCH=C), 6.68 (1 H, s, ArH *ortho* to CH_2), 6.78 (1 H, s, ArH *ortho* to olefin), 7.16 (1 H, d, *J* 8 Hz, ArH *ortho* to OMe), and 7.46 (1 H, d, *J* 8 Hz, ArH); irradiation of the signal at δ 3.94 caused NOE effects at δ 7.16 and 4.11; irradiation of the signal at δ 7.46 caused NOE effects at δ 7.16 and 6.37; irradiation of the signal at δ 6.37 caused NOE effects at δ 6.78 and 7.46; λ_{max}(95% EtOH) 270 (ε 10 800 dm^3 mol^{-1} cm^{-1}), 300 (7 820), and 380 nm (22 700).

The filtrate was concentrated *in vacuo* and subjected to chromatography to give (*a*) (6*S**,12a*R**)-*methyl* 5,6,12b,13-*tetrahydro*-9,10-*dimethoxy*-8-*oxo*-8H-1,3-*dioxolo*[4,5-h]*isoindolo*[1,2-b][3]*benzazepine*-6-*carboxylate* (**30**) (3.15 g, 80%) as colourless needles, m.p. 181–183 °C (from methanol) (Found: C, 64.15; H, 5.1; N, 3.4. $C_{22}H_{21}NO_7$ requires C, 64.29; H, 5.1; N, 3.4%); ν_{max}(Nujol) 1 747, 1 686, 1 485, 1 267, 1 222, 1 042, 853, and 721 cm^{-1}; $\delta_H(CDCl_3)$ ABX system: δ_A 3.18, δ_B 3.32, δ_X 5.04 (J_{AB} 17, J_{AX} 11, J_{BX} 3 Hz, $ArCH_AH_BCH_XAr$), A′B′X′ system: $\delta_{A'}$ 3.34, $\delta_{B'}$ 3.61, $\delta_{X'}$ 4.95 ($J_{A'B'}$ 16, $J_{A'X'}$ 6, $J_{B'X'}$ 3 Hz, $ArCH_{A'}H_{B'}CH_{X'}CO_2Me$), 3.60 (3 H, s, OMe), 3.91 (3 H, s, ArOMe), 4.10 (3 H, s, OMe), 5.92 (2 H, ABq, *J* 1.4 Hz, OCH_2O), 6.58 (1 H, s, ArH), 6.59 (1 H, s, ArH), 7.13 (2 H, s, coincident signals, ArH); irradiation of the signal at δ 7.13 (two equivalent aromatic protons on methoxylated ring) caused NOE effects at δ 3.91 (ArOMe, 6.5%), δ 3.32 (CH_ACH_BCHAr, 6%), and δ 5.04 (CH_2CHAr, 5%); decoupling of the signal at δ 4.95 caused the signals at δ 3.61 and 3.34 to collapse to doublets (*J* 16 Hz);

$\delta_C(CDCl_3)$ 34.7 (t), 40.8 (t), 52.3 (q), 55.5 (d), 56.8 (1), 57.5 (d), 62.6 (q), 101.1 (t), 110.2 (d), 111.3 (d), 116.7 (d), 116.9 (d), 123.9 (s), 127.6 (s), 129.6 (s), 138.8 (s), 146.1 (s), 146.9 (s), 147.3 (s), 152.3 (s), 165.8 (s), and 170.7 (s); (*b*) (6*R**,12b*R**)-*methyl* 5,6,12b,13-*tetrahydro*-9,10-*dimethoxy*-8-*oxo*-8H-1,3-*dioxolo*-[4,5-h]*isoindolo*[1,2-b][3]*benzazepine*-6-*carboxylate* (**31**) (151 mg, 3.8%) as colourless plates, m.p. 220–223 °C (from methanol) (Found: C, 64.25; H, 5.05; N, 3.5. $C_{22}H_{21}NO_7$ requires C, 64.2; H, 5.1; N, 3.4%); ν_{max}(Nujol) 1 745, 1 642, 1 492, 1 399, 1 286, 1 253, 1 194, and 1 040 cm^{-1}; $\delta_H(CDCl_3)$ ABX system: δ_A 2.83, δ_B 3.12, δ_X 4.81 (J_{AB} 15, J_{AX} 10, J_{BX} 2 Hz, $ArCH_AH_BCH_XAr$), A′B′X′ system: $\delta_{A'}$ 3.12, $\delta_{B'}$ 3.32, $\delta_{X'}$ 5.59 ($J_{A'B'}$ 15, $J_{A'X'}$ 3, $J_{B'X'}$ 6 Hz, $ArCH_{A'}H_{B'}CH_{X'}CO_2Me$), 3.62 (3 H, s, OMe), 3.92 (3 H, s, OMe), 4.09 (3 H, s, OMe), 5.94 (2 H, ABq, *J* 1.5 Hz, OCH_2O), 6.68 (1 H, s, ArH *ortho* to methylenedioxy), 6.72 (1 H, s, ArH *ortho* to methylenedioxy), 7.17 (1 H, d, *J* 1 Hz, ArH), 7.18 (1 H, d, *J* 1 Hz, ArH); decoupling of the signal at δ 5.59 caused the signals at δ 3.12 and 3.32 to collapse to doublets (*J* 15 Hz).

Epimerisation of the Ester (**30**) *to the Ester* (**31**).—The ester (**30**) (102 mg, 0.25 mmol) was dissolved in warm methanol (20 ml) and treated with a catalytic amount of sodium methoxide. After 0.5 h the solvent was removed under reduced pressure and recrystallised from methanol to afford the ester (**31**) (91 mg, 89%) (data previously given).

Reduction of the Ester (**30**) *to the Aldehyde* (**33**).—Di-isobutylaluminium hydride (1.5M solution in toluene) (0.20 ml, 0.3 mmol) was added dropwise at −70 °C to a solution of the ester (**30**) (105 mg, 0.26 mmol) in toluene (15 ml) under nitrogen. The mixture was stirred at −70 °C for 18 h then quenched with hydrochloric acid (2M; 5 ml). The organic phase was separated, washed with brine (5 ml), dried (Na_2SO_4), and concentrated under reduced pressure to give a white semi-solid (89 mg, 88%). Recrystallisation from methanol afforded (6*S**,12b*R**)-5,6,12b,13-*tetrahydro*-9,10-*dimethoxy*-8-*oxo*-8H-1,3-*dioxolo*[4,5-h]*isoindolo*[1,2-b][3]*benzazepine*-6-*carbaldehyde* (**33**) (71 mg, 70%) as colourless needles, m.p. 182–185 °C (Found: C, 66.0; H, 5.4; N, 3.5. $C_{21}H_{19}NO_6$ requires C, 66.1; H, 5.0; N, 3.7%); ν_{max}(KBr) 2 831, 1 722, 1 675, 1 484, 1 298, 1 269, 1 047, and 912 cm^{-1}; $\delta_H(CDCl_3)$ ABX system: δ_A 2.89, δ_B 3.30, δ_X 4.78 (J_{AB} 16, J_{AX} 9, J_{BX} 3 Hz, $ArCH_AH_BCH_XAr$), A′B′X′ system: $\delta_{A'}$ 3.27, $\delta_{B'}$ 3.43, $\delta_{X'}$ 4.21 ($J_{A'B'}$ 16, $J_{A'X'}$ 7, $J_{B'X'}$ 4 Hz, $ArCH_{A'}H_{B'}CH_{X'}CHO$), 3.91 (3 H, s, OMe), 4.03 (3 H, s, OMe), 5.90 (2 H, ABq, *J* 1.4 and 1.4 Hz, OCH_2O), 6.52 (1 H, s, ArH *ortho* to methylenedioxy), 6.68 (1 H, s, ArH *ortho* to methylenedioxy), 7.16 (2 H, s, 2 × ArH, coincident signals), 9.85 (1 H, s, CHO); irradiation of the signal at δ 7.15 (two equivalent aromatic protons on methoxylated ring) caused a NOE of the signals at δ 4.78 (CH_2CHAr), 3.91 (ArOMe), and 3.30 (CH_ACH_BCHAr); irradiation of the signal at δ 9.85 (ArCHO) caused a NOE at δ 4.21 (*CH*CHO); *m/z* 381 (M^+, 13%) and 352 (100).

Epimerisation of the Aldehyde (**33**)–(**34**).—A suspension of the aldehyde (**33**) (26 mg, 0.06 mmol) in methanol (3 ml) was treated with sodium methoxide (2 mg) and the mixture stirred. After 2 min a fluorescent solution resulted. The mixture was concentrated under reduced pressure and the residue partitioned between water (5 ml) and chloroform (15 ml). The organic phase was separated, washed with brine (5 ml), and dried (Na_2SO_4). Concentration under reduced pressure gave a pale yellow syrup (27 mg, *ca.* 100%) which was recrystallised from ether to afford (6*S**,12b*S**)-5,6,12b,13-*tetrahydro*-9,10-*dimethoxy*-8-*oxo*-8H-1,3-*dioxolo*[4,5-h]*isoindolo*[1,2-b][3]-*benzazepine*-6-*carbaldehyde* (**34**) (21 mg, 81%) as an amorphous white solid, m.p. 122–125 °C (Found: C, 66.0; H, 5.0; N, 3.5. $C_{21}H_{19}NO_6$ requires C, 66.1; H, 5.0; N, 3.7%); ν_{max} 1 662 (shoulder at 1 685), 1 485, 1 271, 1 189, 1 067, 1 039, and 835 cm^{-1}; $\delta_H(CDCl_3)$ ABX system: δ_A 2.82, δ_B 3.10, δ_X 4.65 (J_{AB} 14.5, J_{AX} 10, J_{BX} 2 Hz, $ArCH_AH_BCH_XAr$), A′B′X′ system: $\delta_{A'}$ 3.18, $\delta_{B'}$ 3.45, $\delta_{X'}$ 5.48 ($J_{A'B'}$ 15, $J_{A'X'}$ 4, $J_{B'X'}$ 5 Hz, $ArCH_{A'}H_{B'}CH_{X'}$), 3.92 (3 H, s, OMe), 4.09 (3 H, s, OMe), 5.94 (2 H, s, OCH_2O), 6.68 (1 H, s, ArH *ortho* to methylenedioxy), 6.75 (1 H, s, ArH *ortho* to methylenedioxy), 7.17 (2 H, 2 × ArH, coincident signals), 9.60 (1 H, s, CHO); irradiation of the signal at δ 9.60 (CHO) caused a NOE at δ 5.48 (*CH*CHO) and δ 4.65 (CH_2CHAr) and confirms relative stereochemistry at C-6 and C-12b; *m/z* 381 (M^+, 13%) and 352 (100).

Deformylation of the Aldehyde (**33**) *to Lennoxamine* (**1**).—Bis(triphenylphosphine)(carbonyl)rhodium chloride (5 mg) was added to xylene (2 ml) under nitrogen and the mixture warmed to 80 °C for 0.25 h (until the rhodium complex dissolved). 1,3-Bis-diphenylphosphino)propane (7 mg) was added and the solution stirred at 80 °C for a further 0.5 h when a fine yellow precipitate formed. The aldehyde (**33**) (57 mg, 0.14 mmol) was then added and the mixture heated under reflux for 18 h. The solvent was removed under reduced pressure and the yellow residue subjected to chromatography (SiO_2; chloroform) to afford lennoxamine (**1**) (26 mg, 51%) as a white amorphous solid, m.p. 226–228 °C (from methanol) (lit.,[8] m.p. 228–229 °C; lit.,[4] m.p. 225 °C; lit.,[11] m.p. 228–229 °C) identical by TLC and ^1H NMR with an authentic sample.

Conversion of the Benzapine (**27**) *to Lennoxamine* (**1**).—Sodium cyanoborohydride (300 mg, 4.8 mmol) was added in one portion to a suspension of the benzazepine (**27**) (1.26 g, 2.87 mmol) in glacial acetic acid (25 ml) with ice cooling. After 0.25 h, another portion of sodium cyanoborohydride (100 mg, 1.6 mmol) was added and stirring continued at room temperature. A fluorescent green–blue solution formed after *ca.* 0.5 h. The mixture was basified with aqueous sodium hydroxide (2M) and extracted with dichloromethane (2 × 50 ml, 1 × 25 ml). The combined extracts were washed with saturated aqueous sodium hydrogen carbonate (20 ml), dried (Na_2SO_4), and concentrated under reduced pressure to give a pale yellow foam (1.20 g, *ca.* 100%).

A portion of this product mixture (502 mg, 1.22 mmol) in toluene (40 ml) was treated with di-isobutylaluminium hydride (1.5M solution in toluene; 0.90 ml, 1.35 mmol, 1.08 equiv.) at −70 °C. The mixture was stirred at −70 °C for 5 h and then allowed to warm to room temperature and quenched with hydrochloric acid (2M; 20 ml). The organic phase was separated, washed with brine (10 ml), dried (Na_2SO_4), and concentrated under reduced pressure to give a cream amorphous solid (390 mg, 81%).

Bis(triphenylphosphine)(carbonyl)rhodium chloride (15 mg) was added to xylene (6 ml) under nitrogen and the mixture warmed to 80 °C for 0.25 h. 1,3-Bis(diphenylphosphino)propane (21 mg) was added and the solution stirred at 80 °C for a further 0.5 h when a yellow precipitate formed. The aldehyde mixture (120 mg, 0.30 mmol) obtained above was then added and the mixture heated under reflux for 18 h. The solvent was removed under reduced pressure and the yellow residue subjected to chromatography (SiO_2; chloroform) to afford lennoxamine (**1**) (57 mg, 53%) as a white amorphous solid identical by TLC and ^1H NMR comparisons with the sample previously prepared.

The overall yield for this three step conversion of the benzazepine (**27**) into lennoxamine (**1**) without purification of the intermediates was 43%.

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