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SYNTHESIS OF THE ISOINDOLOBENZAZEPINE ALKALOID LENNOXAMINE

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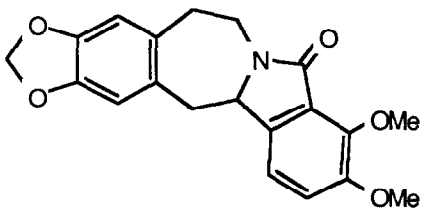
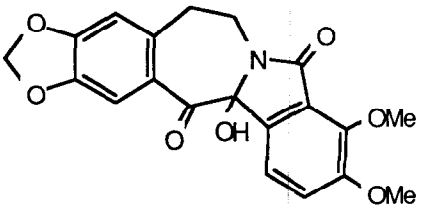
Summary: The naturally occurring isoindolobenzazepine lennoxamine (1) has been synthesised from 6-bromopiperonal in 9 steps by a route which involves formation of the 2-arylbenzazepine (**10**) from the azide (**9**) as the key step.

Barberries are a rich source of alkaloids, and recent studies of Chilean Berberidaceae have provided the first members of a new class of alkaloid, the isoindolobenzazepines,[1-3] exemplified by lennoxamine (**1**) and chilenine (**2**). The ring system, which is accessible *in vivo* and *in vitro* by oxidation of berberine alkaloids[3-5] and from phthalide-isoquinoline alkaloids,[6] has recently been the subject of several synthetic approaches.[7-10] We now report a total synthesis of the alkaloid lennoxamine (**1**), isolated from *Berberis darwinii* Hook,[2] by a route based on vinyl azide chemistry.[11-13]

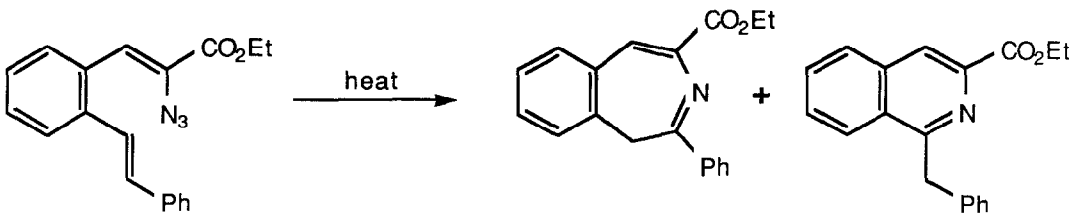


(1)



(2)

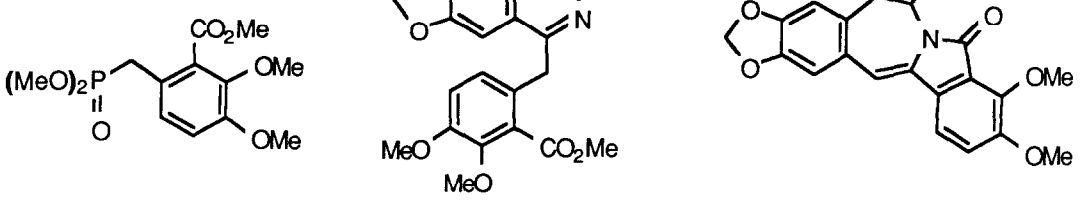
We have recently shown that in the thermolysis of azidocinnamates bearing *ortho*-alkenyl side chains, the major reaction pathway involves interaction of the azide/nitrene with the substituent double bond rather than with the aromatic ring. In particular, the *ortho*-styryl azide (**3**) gave the 3-benzazepine (**4**) (37%) and the 1-benzylisoquinoline (**5**) (36%) as the major products (Scheme 1),[13] and therefore we investigated the use of this type of reaction as a route to the 3-benzazepine portion of lennoxamine (**1**).



(3) (4) (5)

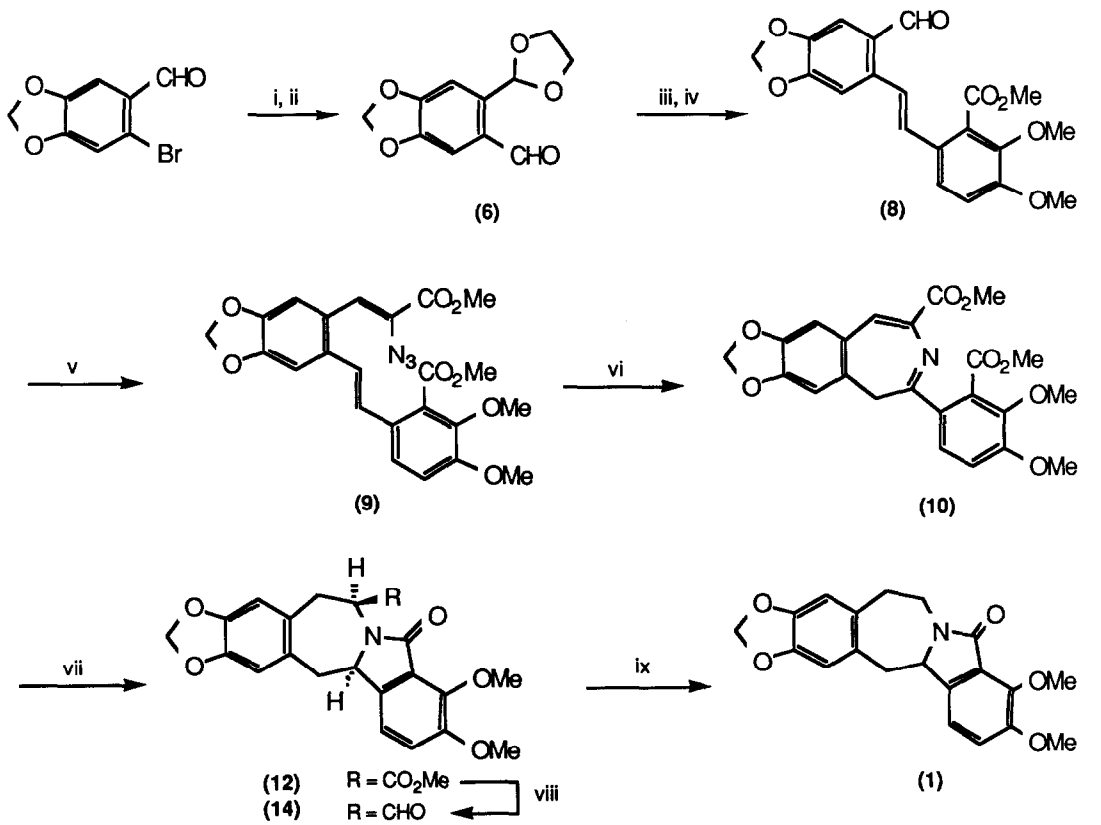
Scheme 1

The precursor to the required azidocinnamate (**9**) is the highly substituted (E)-stilbene aldehyde (**8**), and this was prepared from 6-bromopiperonal as shown in Scheme 2. Thus the ethylene acetal derived from 6-bromopiperonal[14] was converted into the mono-protected dialdehyde (**6**) (88%), which underwent Wadsworth-Emmons reaction with the known[9] phosphonate (**7**) to give, after acid hydrolysis of the acetal, the (E)-stilbene aldehyde (**8**) (74% over 2 steps). Condensation of the aldehyde (**8**) with methyl azidoacetate gave the unstable azide (**9**) in 66% yield. On heating in boiling xylene, the azide (**9**) rapidly decomposed to give the required 2-aryl-3-benzazepine (**10**) as the major product (55%). The benzazepine (**10**) was accompanied by the benzylisoquinoline (**11**) (29%) and the corresponding 4-styryl indole-2-carboxylate (4%). Treatment of the 3-benzazepine (**10**) with sodium cyanoborohydride in acetic acid resulted in reduction of both double bonds, and concomitant cyclisation of the NH onto the ester group of the 2-substituent to give the *cis*-tetrahydroisoindolo[1,2-*b*][3]benzazepine (**12**) in 80% yield.[15] The *cis*-diastereomer of the benzazepine (**12**) was accompanied by small amounts of the *trans*-isomer (epimeric at C-6) (4%) and the dihydro compound (**13**) (3%). It is not clear whether the *trans*-tetrahydro isoindolobenzazepine 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.



(7) (11) (13)

The total synthesis of lennoxamine (**1**) now simply required the removal of the unwanted ester group at C-6, and this was achieved by reduction of the *cis*-ester (**12**) to the *cis*-aldehyde[15] (**14**) (70%) using di-isobutylaluminium hydride in toluene, followed by decarbonylation using a rhodium (I) catalyst[16] to give lennoxamine (**1**) (51%). Since the stereochemical centre at C-6 is removed in the final step, separation of the diastereomers of the tetrahydro isoindolobenzazepine formed in the cyanoborohydride reduction step is unnecessary, and without this separation, the 2-aryl-3-benzazepine (**10**) was converted into lennoxamine (**1**) in 43% overall yield. The sample of lennoxamine was identical (m.p., t.l.c., 200 MHz ^{1}H n.m.r.) to material from natural sources.[17]



Scheme 2. *Reagents:* i, ethylene glycol, TsOH (cat), toluene, reflux; ii, *n*-BuLi, -60°C, ether, then DMF; iii, KO^{t}Bu/phosphonate (**7**), THF; iv, dilute HCl, CH_2Cl_2; v, $MeO_2CCH_2N_3$, NaOMe, MeOH, THF, 5°C; vi, xylene, reflux; vii, $NaBH_3CN$, AcOH; viii, DIBAL, toluene, -70°; ix, $(Ph_3P)_2Rh(CO)Cl$, $Ph_2P(CH_2)_3PPh_2$, xylene, reflux.

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