A Radical Cyclization Approach to Isoindolobenzazepines. Synthesis of Lennoxamine†

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The alkaloid lennoxamine (**1**) was synthesized by transannular cyclization of a 10-membered lactam obtained by intramolecular addition of an aryl radical to a (trimethylsilyl)acetylene. The isoindolo-[1,2-*b*][3]benzazepine skeleton present in lennoxamine was also obtained by means of regioselective 7-*endo-trig* radical cyclization of methylenephthalimidines.

Introduction

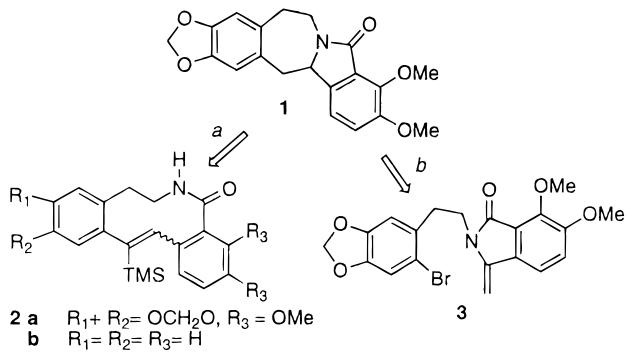
Isoindolobenzazepine alkaloids, exemplified by lennoxamine (**1**, see Scheme 1), are a class of alkaloids belonging to the aporhoedane series isolated from Chilean Berberidaceae.[1] Although biogenetically related to protoberberines,[2,3] and usually classified as isoquinoline alkaloids, they are distinguished by the presence of an isoindolo-[1,2-*b*][3]benzazepine system. This system has been the objective of several synthetic approaches based on biomimetic pathways,[4] electrophilic alkylation,[5] photochemistry of enamides,[6] or vinyl azide chemistry.[7] More recently, the five-membered ring has also been formed by a combination of intramolecular aromatic substitution and radical cyclization.[8] We now report the total synthesis of lennoxamine (**1**) by two new approaches in which radical cyclizations are used either to prepare the macrocyclic lactam intermediate **2a** (route a) or as the final step in the construction of the azepine nucleus from the methylenephthalimidine **3** (route b).

Results and Discussion

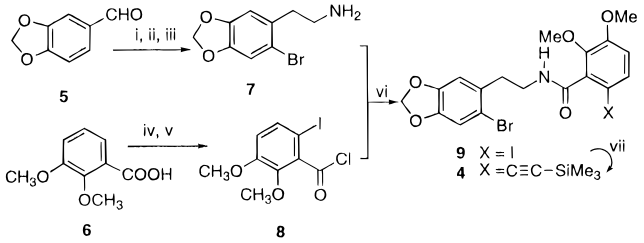
We recently showed that the unsubstituted 10-membered lactam **2b**, obtained by radical macrocyclization, could be regioespecifically converted by transannular cyclization into products with either the isoindolobenzazepine or the protoberberine skeletons.[9] We therefore pursued this strategy to obtain the alkaloid lennoxamine (**1**). The precursor to the required 10-membered lactam **2a** is the trimethylsilyl derivative **4**, which was prepared from piperonal (**5**) and 2,3-dimethoxybenzoic acid (**6**) as shown in Scheme 2.

Piperonal (**5**) was converted in three steps into the corresponding bromophenethylamine **7** (62% overall yield).

Scheme 1



Scheme 2[a]



[a] Reagents: (i) CH_3NO_2, NaOAc, $CH_3NH{\cdot}HCl$, rt, 94%; (ii) Zn−Hg, CH_3OH, HCl, 85%; (iii) Br_2, AcOH, rt, 78%; (iv) (a) $Tl(OCOCF_3)_3$, CF_3COOH; (b) NaI, 94%, (v) $SOCl_2$; (vi) Et_3N, THF, 83%; (vii) (trimethylsilyl)acetylene, $PdCl_2(PPh_3)_2$, CuI, Et_3N, 89%.

2,3-Dimethoxybenzoic acid (**6**) was iodinated[10] (94% yield) and subsequently converted into the acid chloride **8**. The amide **9** was readily obtained in 83% yield by condensation of **7** and **8** in THF at room temperature in the presence of triethylamine. Finally, treatment of the dihalogenated amide **9** with (trimethylsilyl)acetylene (1.1 equiv) in the presence of CuI (0.05 equiv) and $PdCl_2(PPh_3)_2$ (0.05 equiv)[11] in triethylamine at room temperature under argon gave the bromo amide **4** chemoselectively in 89% yield (Scheme 2).

The radical reaction was performed by slow (5 h) dropwise addition of a benzene solution of tributyltin hydride (2 equiv) and AIBN (20% by weight) to a refluxing benzene solution (5 mM) of the bromo amide **4** under argon. This gave a 74% yield of the desired macrocycle **2a**, derived by *endo* cyclization resulting from intramolecular attack by the aryl radical on the terminal end of the triple bond (Scheme 3). A single geometric

† Dedicated to Prof. Antonio González González in celebration of his half-century of contribution to natural product chemistry.

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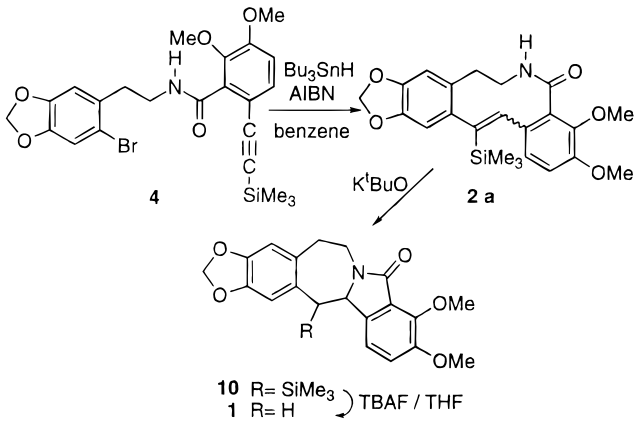
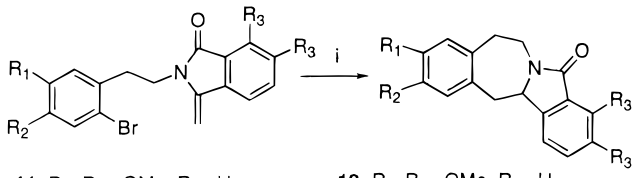
Scheme 3



Scheme 4



11 R_1, R_2= OMe, R_3= H
3 R_1+ R_2= -OCH_2O-, R_3= OMe
i) Bu_3SnH, AIBN, benzene, reflux

12 R_1, R_2= OMe, R_3= H
1 R_1+ R_2= -OCH_2O-, R_3= OMe

isomer of unknown stereochemistry was obtained, which contrasts with the *E*/*Z*-mixture observed when the corresponding desilylated acetylene[9] was subjected to the same cyclization conditions.

Having prepared the macrolactam **2a**, we next investigated how to achieve transannular cyclization through nucleophilic attack by the nitrogen atom. We found that under basic conditions (0.2 equiv of potassium *tert*-butoxide in THF under argon at room temperature), addition at the β-position of the vinylsilane occurred to give **10**. Desilylation by addition of tetrabutylammonium fluoride (1.1 equiv in THF) to the crude reaction mixture at room temperature[12] led to the isoindolobenzazepine lennoxamine (**1**) in 60% yield (over two steps). The spectroscopic data of synthetic **1** agree with those reported for the natural alkaloid.[13]

Our second approach to lennoxamine is based on our previous results concerning the efficient synthesis of benz[*d*]indeno[1,2-*b*]azepines by intramolecular addition of an aryl radical to an enamide double bond.[14] We were intrigued by the possibility of generating the 3-benzazepine unit of lennoxamine by a related cyclization in the methylenephthalimidine **3** (Scheme 1). This type of precursor has previously been used by Snieckus,[6] who reported its photochemical transformation into isoindolobenzazepines, albeit in poor yields (20%).

As a preliminary, we investigated the behavior of the dimethoxy derivative **11** (see Scheme 4), which was prepared by heating 6-bromohomoveratrylamine with 2-acetylbenzoic acid at 140 °C for 1 h (94% yield).[15] When **11** (0.05 M in benzene) was subjected to the radical conditions, regioselective *7-endo-trig* cyclization gave the desired 3-benzazepine **12** in 81% yield (Scheme 4).

We therefore proceeded to apply this strategy to the synthesis of lennoxamine (**1**). The methylenephthalimidine **3** was readily obtained by desilylation and further cyclization of **4** under basic conditions (95% yield)[16] and was then subjected to radical cyclization under the same conditions as for **11**, giving a 61% yield of lennoxamine (**1**).

To sum up, we obtained good yields of the isoindolo[1,2-*b*][3]benzazepine skeleton by both radical macrocyclization (route a) and aryl-radical cyclization of an enamide double bond (route b). Both cyclizations were regioselective, giving 10-*endo-dig* or 7-*endo-trig* adducts, respectively. In the former case, the resulting macrocycle was finally transformed into lennoxamine by transannular cyclization. We are currently exploring the utility of these reactions for the synthesis of other natural products.

Experimental Section

General. All reactions were carried out under argon. Solvents were dried by distillation from a drying agent: THF and benzene from Na/benzophenone, Et_3N from CaH_2. Slow additions were carried out using a syringe pump (Harvard 11). Melting points are uncorrected. ^1H and ^{13}C NMR spectra were recorded in $CDCl_3$.

***N*-[2-(6-Bromo-1,3-benzodioxol-5-yl)ethyl]-2-iodo-5,6-dimethoxybenzamide (9).** To a cold, stirred solution of **7**[17] (1 g, 4.09 mmol) and triethylamine (1.2 mL, 8.6 mmol) in THF (5 mL) under argon was added dropwise (via a cannula) a solution of **8** (1.5 g, 4.6 mmol) in 5 mL of THF. Once addition was finished, stirring was continued for 12 h at room temperature. The residue obtained by removal of volatiles under reduced pressure was dissolved in CH_2Cl_2, and this solution was washed with 5% HCl, dried over Na_2SO_4 and evaporated to dryness to yield 1.81 g of **9** (83%), which was crystallized as fine crystals of mp 155−157 °C (MeOH). IR (KBr) ν 3260, 3080, 2940, 1640, 1480 cm^{-1}. ^1H NMR δ 7.46 (d, J = 8.7 Hz, 1H), 6.99 (s, 1H), 6.89 (s, 1H), 6.66 (d, J = 8.7 Hz, 1H), 5.94 (s, 2H), 5.78 (m, N*H*), 3.84 (s, 6H), 3.69 (m, 2H), 3.01 (t, J = 7 Hz, 2H). ^{13}C NMR δ 167.3, 153.1, 147.5, 147.2, 146.6, 137.8, 134.6 (CH), 131.1, 114.9 (CH), 114.6, 112.8 (CH), 110.7 (CH), 101.6 (CH_2), 81.1, 62.0 (CH_3), 55.9 (CH_3), 39.6 (CH_2), 35.6 (CH_2). MS *m*/*z* (relative intensity) 454 (M^+ − Br, 19), 291 (100), 228 (90), 226 (90). Anal. Calcd for $C_{18}H_{17}NO_5BrI$, C 40.47, H 3.2, N 2.62. Found: C 40.14, H 3.12, N 2.84.

***N*-[2-(6-Bromo-1,3-benzodioxol-5-yl)ethyl]-5,6-dimethoxy-2-[(trimethylsilyl)ethynyl]benzamide (4).** Compound **9** (0.2 g, 0.37 mmol), $PdCl_2(PPh_3)_2$ (13 mg, 0.02 mmol), CuI (4 mg, 0.02 mmol), and (trimethylsilyl)acetylene (160 μL, 1.11 mmol) were placed in a flask containing 5.5 mL of degassed Et_3N, and this reaction mixture was stirred under argon for 6 h at room temperature. The resulting suspension was vacuum filtered through a pad of Celite. The filtrate was concentrated and dissolved in CH_2Cl_2. The resulting solution was washed with 5% HCl, dried over Na_2SO_4, and chromatographed on silica gel. Benzamide **4** (0.17 g, 89%) was obtained as colorless crystals of mp 133−135 °C (MeOH). IR (KBr) ν 3260, 2960, 2940, 2160, 1680, 1485, 855, 850 cm^{-1}. ^1H NMR δ 7.22 (d, J = 8.5 Hz, 1H), 6.99 (s, 1H), 6.88 (s, 1H), 6.84 (d, J = 8.5 Hz, 1H), 5.94 (s, 2H), 5.88 (m, N*H*), 3.87 (s, 3H), 3.85 (s, 3H), 3.65 (m, 2H), 2.99 (t, J = 7.1 Hz, 2H), 0.2 (s, 9H). ^{13}C NMR δ 166.1, 153.4, 147.5, 147.2, 145.8, 135.1, 131.2, 129.3 (CH), 114.5, 113.3, 112.7 (2 x CH), 110.7 (CH), 102.1, 101.6 (CH_2), 96.4, 61.9 (CH_3), 55.8 (CH_3), 39.6 (CH_2), 35.8 (CH_2), −0.15 (CH_3). MS *m*/*z* (relative intensity) 505 (M^+, 3), 424 (6), 278 (45), 261 (100), 228 (28), 226 (28). Anal. Calcd for $C_{23}H_{26}NO_5BrSi$, C 54.76, H 5.19, N 2.78. Found: C 54.51, H 5.18, N 2.84.

7,8-Dihydro-13-(trimethylsilyl)dibenz[*c*,*g*]azecin-5(6*H*)-one (2a). To a solution of **4** (0.1 g, 0.2 mmol) in 40 mL of dry

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degassed benzene, refluxing under argon, a solution of n-Bu_3-SnH (0.11 mL, 2 equiv) and AIBN (20 mg, 20% by weight) in 10 mL of benzene was added via a syringe pump over 5 h. Once addition had finished, refluxing was kept up for a further 4 h. The benzene was evaporated under vacuum, and the resulting residue was dissolved in CH_3CN. This solution was washed with hexane, dried over Na_2SO_4, concentrated, and chromatographed on silica gel using 1:2 EtOAc/hexane as eluent. Macrolactam **2a** (64 mg, 74%) was obtained as colorless crystals of mp 187−189 °C (MeOH). IR (KBr) ν 3380, 2940, 1695, 1505, 1480, 845 cm^{-1}. ^1H NMR δ 6.93 (s, 2H), 6.85 (s, 1H), 6.67 (s, 1H), 6.58 (s, 1H), 5.93 (m, 2H), 5.50 (m, N*H*), 4.14 (m, 1H), 3.96 (s, 3H), 3.89 (s, 3H), 3.30 (m, 1H), 2.98 (m, 1H), 2.34 (m, 1H), −0.10 (s, 9H). ^{13}C NMR δ 167.9, 152.2, 149.9, 147.3, 145.7, 145.5, 145.1 (CH), 139.8, 132.7, 132.6, 130.7, 122.3 (CH), 113.3 (CH), 110.9 (CH), 107.2 (CH), 100.8 (CH_2), 61.9 (CH_3), 55.9 (CH_3), 43.7 (CH_2), 31.2 (CH_2), −0.7 (CH_3). MS *m*/*z* (relative intensity) 425 (M^+, 19), 382 (23), 352 (100), 351 (23), 337 (29), 336 (35), 73 (23). Anal. Calcd for $C_{23}H_{27}NO_5Si$, C 64.92, H 6.39, N 3.29. Found: C 64.93, H 6.56, N 3.46.

Lennoxamine (1). A suspension of **2a** (0.2 g, 0.5 mmol) and potassium *tert*-butoxide (11.5 mg, 0.1 mmol) in 4 mL of dry THF was stirred under argon for 1 h, concentrated under vacuum, and dissolved in CH_2Cl_2. This solution was washed with NH_4Cl and brine, dried over Na_2SO_4, and finally concentrated at reduced pressure to give crude **10**. IR ν 2954, 2857, 1684, 1491, 1429, 1267, 1040, 844 cm^{-1}. ^1H NMR δ 7.16 (d, J = 8.2 Hz, 1H), 7.12 (d, J = 8.2 Hz, 1H), 6.65 (s, 2H), 5.95 (m, 2H), 4.64 (m, 2H), 4.09 (s, 3H), 3.91 (s, 3H), 2.98−2.77 (m, 4H), −0,32 (s, 9H). ^{13}C NMR δ 165.8, 152.8, 147.4, 146.1, 145.5, 137.9, 135.8, 133.1, 125.0, 117.8 (CH), 115.9 (CH), 111.1 (CH), 110.6 (CH), 101.0 (CH_2), 62.7 (CH_3), 62.5 (CH_3), 56.7 (CH), 44.0 (CH), 41.1 CH_2), 35.8 (CH_2), 0.8 (CH_3). MS *m*/*z* (relative intensity) 425 (M^+, 67), 424 (100), 410 (30), 394 (18), 352 (13), 336 (12), 264 (27), 149 (11), 76 (56).

Tetrabutylammonium fluoride (0.22 g, 0.84 mmol) (1 M solution in THF, from Acros Chimica) was added to a solution of this crude product in 3 mL of THF, and this mixture was stirred at room temperature for 15 min, concentrated, and dissolved in CH_2Cl_2. This solution was washed, dried over Na_2SO_4, concentrated under vacuum, and finally chromatographed on silica gel using 1:2 EtOAc/hexane as eluent. Lennoxamine (**1**) (0.1 g, 60%) was obtained as colorless crystals of mp 223−225 °C (lit.[13] 225 °C) (MeOH). IR (KBr) ν 2950, 1685, 1430, 1290, 1270, 1040 cm^{-1}. ^1H NMR δ 7.17 (d, J = 8.2 Hz, 1H), 7.12 (d, J = 8.2 Hz, 1H), 6.77 (s, 1H), 6.72 (s, 1H), 5.95 (d, J = 1.4 Hz, 1H), 5.94 (d, J = 1.4 Hz, 1H), 4.73 (m, 1H) 4.29 (dd, $J_{13a,13\alpha}$ = 1.3, $J_{13a,13\beta}$ = 10.6 Hz, H_{13a}), 4.09 (s, 3H), 3.91 (s, 3H), 3.09 (dd, $J_{13a,13\alpha}$ = 1.3, $J_{13\alpha,13\beta}$ = 14.6 Hz, $H_{13\alpha}$), 2.81 (dd, $J_{13a,13\beta}$ = 10.6, $J_{13\alpha,13\beta}$ = 14.6 Hz, $H_{13\beta}$), 2.99−2.77 (m, 3H). ^{13}C NMR δ 165.2, 152.7, 147.4, 146.4, 146.2, 138.3, 134.9, 131.0, 124.2, 117.1 (CH), 116.4 (CH), 110.4 (2 × CH), 101.1 (CH_2), 62.5 (CH_3), 60.1 (CH), 56.8 (CH_3), 42.7 (CH_2), 41.1 (CH_2), 35.9 (CH_2). MS *m*/*z* (relative intesity) 353 (M^+, 100), 352, 23), 338 (67), 335 (43), 162 (76), 161 (90), 131 (73). Anal. Calcd for $C_{20}H_{19}NO_5$, C 67.98, H 5.42, N 3.96. Found: C 68.18; H 5.17, N 3.88.

***N*-[2-(2-Bromo-4,5-dimethoxyphenyl)ethyl]-2,3-dihydro-3-methylene-1*H*-isoindol-1-one (11).** A mixture of 6-bromohomoveratrylamine (0.97 g, 3.74 mmol) and 2-acetylbenzoic acid (0.66 g, 4.02 mmol) was heated at 140 °C for 1 h. Once the mixture had cooled to room temperature, EtOAc (2 mL) was added and the mixture was then left at 0 °C overnight, affording a crystalline solid (1.36 g, 94%) which was identified as **11**. Mp 123 °C (EtOAc). IR (KBr) ν 3416, 1720, 1507, 1216 cm^{-1}. ^1H NMR δ 7.82 (d, J = 7.4 Hz, 1H), 7.67 (d, J = 7.5 Hz, 1H), 7.57 (dt, J = 7.4, J = 1 Hz, 1H), 7.49 (dt, J = 7.5, J = 1 Hz, 1H), 7.00 (s, 1H), 6.68 (s, 1H), 5.16 (d, J = 2.4 Hz, 1H), 4.98 (d, J = 2.4 Hz, 1H), 3.99 (t, J = 7.4 Hz, 2H), 3.85 (s, 3H), 3.68 (s, 3H), 3.04 (t, J = 7.4 Hz, 2H). ^{13}C NMR δ 167.5, 148.9, 148.8, 142.0, 136.7, 132.3 (CH), 130.1, 129.9 (CH), 129.6, 123.4 (CH), 120.3 (CH), 115.7 (CH), 114.5, 113.9 (CH), 89.6 (CH_2), 56.5 (CH_3), 56.4 (CH_3), 39.7 (CH_2), 34.9 (CH_2). MS *m*/*z* (relative intensity) 308 (M^+ − Br, 100), 244 (28), 242 (28), 158 (40). Anal. Calcd for $C_{19}H_{18}NO_3Br$, C 58.76, H 4.64, N 3.61. Found: C 59.10, H 4.63, N 3.61.

7,8,13,13a-Tetrahydro-10,11-dimethoxy-5*H*-isoindolo-[1,2-*b*][3]benzazepin-5-one (12). To a solution of **11** (0.29 g, 0.75 mmol) and AIBN (58 mg, 20% by weight) in 80 mL of dry degassed benzene, refluxing under argon, was added n-Bu_3-SnH (0.42 mL, 1.56 mmol) dropwise over 6 min. Once addition had finished, refluxing was kept up for a further 6 h. The benzene was evaporated under reduced pressure, and the resulting residue was taken up in CH_3CN. This solution was washed with hexane, dried over Na_2SO_4, concentrated, and chromatographed on silica gel using 1:1 EtOAc/hexane as eluent. Benzazepine **12** (0.19 g, 81%) was obtained as colorless crystals of mp 179 °C (EtOAc). IR (KBr) v 3455, 1684, 1518, 1293 cm^{-1}. ^1H NMR δ 7.87 (d, J = 7.5 Hz, 1H), 7.59−7.46 (m, 3H), 6.83 (s, 1H), 6.74 (s, 1H), 4.82−4.76 (m, 1H), 4.43 (d, J = 9.8 Hz, 1H), 3.92 (s, 3H), 3.89 (s, 3H), 3.19 (dd, J = 14.7, 1.6 Hz, 1H), 3.05−2.81 (m, 4H). ^{13}C NMR δ 167.5, 148.0, 147.6, 145.3, 134.1, 132.4, 131.9 (CH), 130.1, 128.8 (CH), 124.2 (CH), 122.5 (CH), 114.1 (CH), 113.9 (CH), 61.8 (CH), 56.5 (CH_3), 56.4 (CH_3), 42.6 (CH_2), 41.9 (CH_2), 36.3 (CH_2). MS *m*/*z* (relative intensity) 309 (M^+, 100), 294 (43), 177 (73). Anal. Calcd for $C_{19}H_{19}NO_3$, C 73.79, H 6.15, N 4.53. Found: C 73.86, H 6.33, N 4.58.

***N*-[2-(6-Bromo-1,3-benzodioxol-5-yl)ethyl]-2,3-dihydro-6,7-dimethoxy-3-methylene-1*H*-isoindol-1-one (3).** Potassium carbonate (90 mg, 0.65 mmol) was added to a stirred solution of **4** (91 mg, 0.18 mmol) in methanol (2 mL), and the reaction mixture was kept at room temperature for 30 min. The solid was filtered off, the solvent was removed from the filtrate under reduced pressure, and the resulting residue was chromatographed on silica gel using 1:3 EtOAc/hexane as eluent. Phthalimidine **3** was obtained (74 mg, 95%) as colorless crystals of mp 149 °C (EtOAc). IR (KBr) ν 3459, 1714, 1510, 1220 cm^{-1}. ^1H NMR δ 7.35 (d, J = 8.2 Hz, 1H), 7.13 (d, J = 8.2 Hz, 1H); 7.01 (s, 1H), 6.78 (s, 1H), 5.91 (s, 2H), 5.08 (s, 1H), 4.83 (s, 1H), 4.10 (s, 3H), 3.91 (s, 3H), 3.89 (m, 2H), 3.00 (t, J = 7.7 Hz, 2H). ^{13}C NMR δ 166.1, 154.0, 147.9, 147.7, 141.5, 131.4, 130.6, 123.6, 116.7 (CH); 115.6 (CH), 114.9, 113.1 (CH), 111.0 (CH), 102.1 (CH_2), 87.1 (CH_2), 62.9 (CH_3), 57.1 (CH_3), 39.8 (CH_2), 35.2 (CH_2). MS *m*/*z* (relative intensity) 352 (M^+ − Br, 100), 218 (62). Anal. Calcd for $C_{20}H_{18}BrNO_5$, C 55.55, H 4.17, N 3.24. Found: C 55.27, H 4.32, N 3.17.

Lennoxamine (from **3**). To a solution of **3** (31 mg, 0.07 mmol) and AIBN (7 mg, 20% by weight) in dry degassed benzene (12 mL), refluxing under argon, was added n-Bu_3SnH (50 μL, 0.14 mmol) over 2 min. Once addition had finished refluxing was kept up for 5 h. After the usual workup, the residue was chromatographed on silica gel using 1:1 EtOAc/hexane, which gave lennoxamine (15mg, 61%).

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