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An Original Synthesis of *trans*-1,2-Diaminocyclobutane

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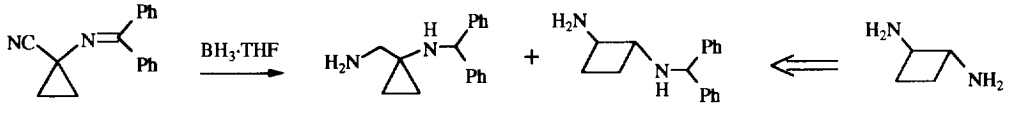
Abstract: A new synthesis of *trans*-1,2-diaminocyclobutane **1** is described, in which the key feature is the novel stereoselective borane-induced reductive ring-expansion reaction of the cyclopropane-iminonitrile **2** to give the cyclobutane **4**. This latter intermediate was also used to prepare a *trans*-fused rigid analogue of moclobemide.

Introduction. An ever-increasing number of 1,2-diamino compounds are finding applications as auxiliaries in organic synthesis[1] and as structural units in medicinal chemistry.[2] As a conformationally-restricted analogue of ethylenediamine, *trans*-1,2-diaminocyclobutane **1** has been used to probe structure-activity relationships in several therapeutic agents,[3,4] and appears as a linker unit in polymeric photoconductors.[5] Surprisingly, only one low-yielding synthesis of **1** has been described,[6] in slightly varying forms according to Buchman[6a] and Shuikina,[6b] requiring either a Schmidt or Curtius rearrangement on an appropriate derivative of *trans*-1,2-cyclobutanedicarboxylic acid.[7] This precursor is not readily available — its synthesis from adipic acid requires eight steps — and some authors have encountered problems with the key rearrangement step.[4]

During our work on cyclopropane-containing diamines,[8] we discovered that the reduction of 1-(diphenylmethylene)amino-1-cyclopropanecarbonitrile **2** with borane yielded, in addition to the reduced cyclopropane **3**, a small quantity of an unexpected diaminocyclobutane byproduct **4** (Scheme 1). Inspired by the unusual ring-expansion reaction, we pursued our investigations, and in this paper we describe our results leading to a new synthesis of the title compound **1** and the convenient preparation of a representative *N,N'*-difunctionalised derivative.

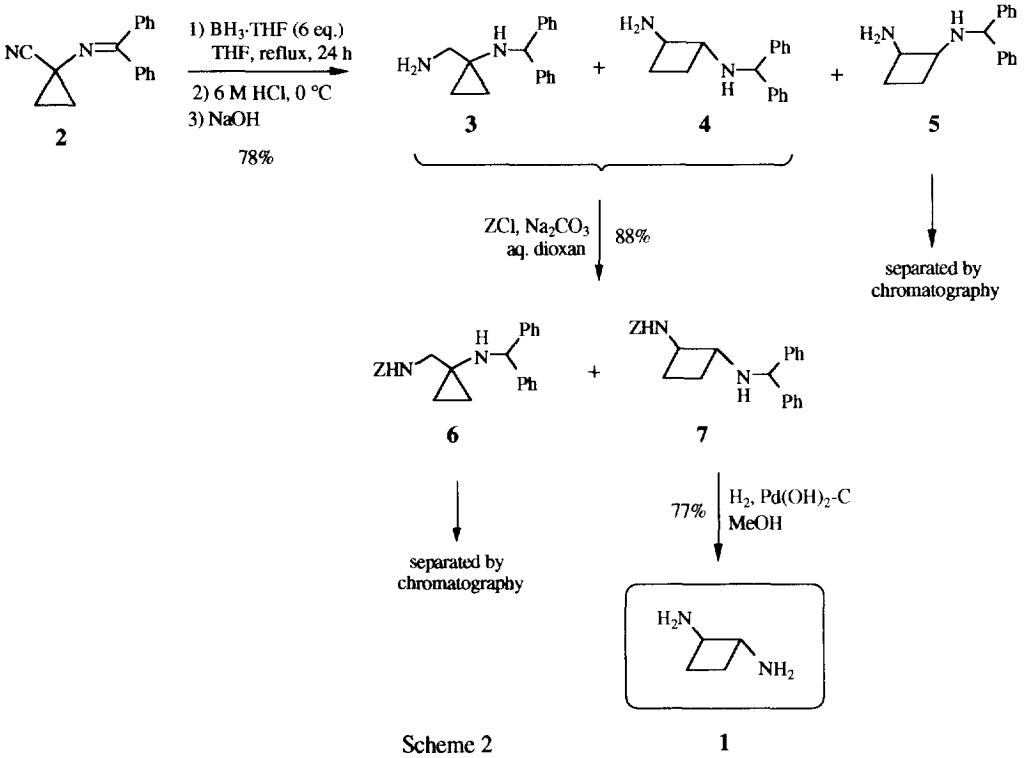


2 **3** **4** **1**

Scheme 1

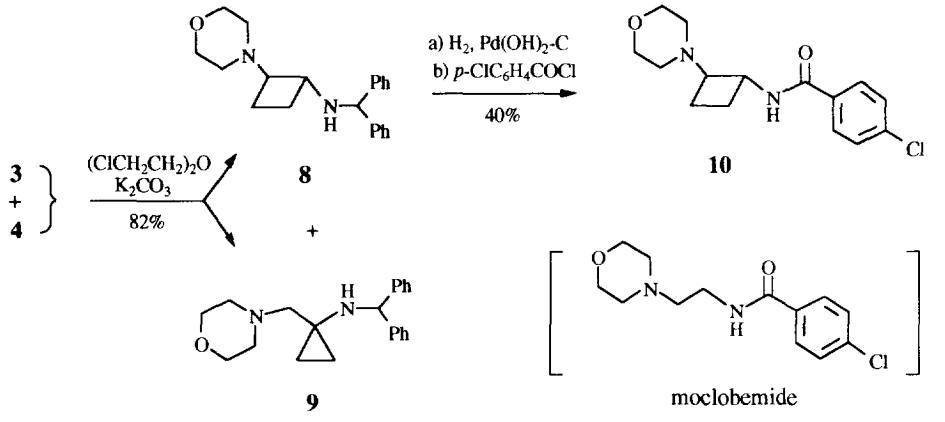
Synthesis. The original reaction conditions for reduction of **2** (addition of an excess of BH_3·THF at rt)[8] gave an 80% yield of a **3**:**4** mixture in which the cyclopropane predominated (85:15). A series of empirical experiments was carried out to find conditions which increased the proportion of **4** in the mixture without lowering the overall yield. The critical stage was found to be at the start of the reaction, and the optimum conditions are as follows: 6 equiv. BH_3·THF are added *as rapidly as possible* to a solution of **2** in THF at reflux under nitrogen. After 24 hours reflux and standard hydrolytic workup, a mixture of **3**, **4** and **5** is obtained in 78% overall yield with a cyclopropane:cyclobutane ratio of 40:60 (Scheme 2). Cyclobutane formation was highly stereoselective, with a **4**:**5** ratio of greater than 11:1. Deviation from these conditions (*e.g.* changing order or rate of addition, use of less than 6 equiv. BH_3·THF, reaction carried out at rt) resulted in an increase in the cyclopropane:cyclobutane ratio, or a lowering of the overall yield through degradation (*e.g.* use of 12 equiv. BH_3·THF).

The best reproducible yield of **4** from **2** (45%) was considered sufficient to pursue the synthesis of the title compound (Scheme 2). Diamines **3** and **4** were not conveniently separated from the mixture, but flash chromatography allowed the removal of the less polar minor *cis* isomer **5**. Mixture **3**:**4** was converted into the less polar benzyl carbamates **6** and **7**, readily separated by chromatography. Hydrogenation of **7** over Pearlman's catalyst gave **1** as a volatile oil, most easily handled as its dihydrochloride. The *trans* geometry was confirmed by reaction with CS_2 to form the known dithiocarbamate.[6a] The overall yield of **1** from **2** was 30% for three steps and two chromatographies.



Scheme 2

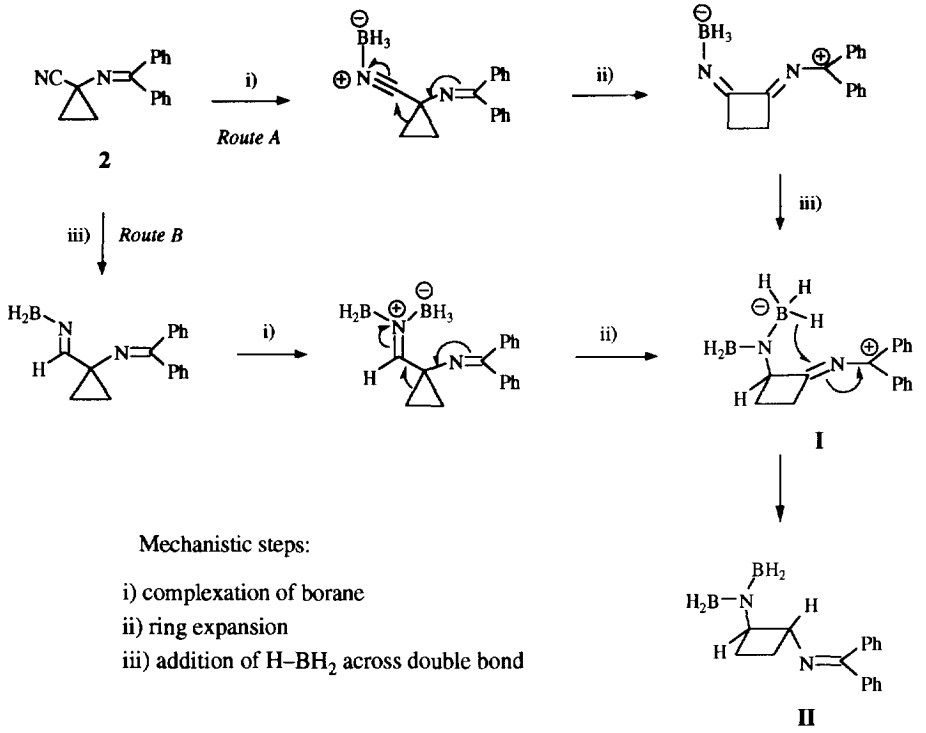
An interesting feature of this synthetic route is that it permits differentiation of amine reactivities, an important factor in the preparation of dissymmetric derivatives of **1**. To illustrate this point, we carried out the short synthesis of a conformationally-restrained analogue of moclobemide,[9] a reversible MAO-A inhibitor used clinically as a short-acting antidepressant (Scheme 3). Treatment of a **3**:**4** mixture with 2-chloroethyl ether under prolonged reflux gave in 82% total yield the corresponding morpholine derivatives **8** and **9**, separable at this stage. Hydrogenolysis of **8** followed by acylation of the primary amine led smoothly to the required structure **10**.



Scheme 3

Mechanistic aspects. A plausible mechanism for the formation of cyclobutane[10] is shown in Scheme 4. Initial complexation[11] (*Route A*) of borane to the nitrile function of **2** activates a ring-expansion process involving the π-electrons of the imine, with the developing positive charge conveniently delocalised on the diphenylcarbenium system.[12] Regioselective reduction of the more electron-rich double bond of the cyclobutanediimine by a second equivalent of borane leads to intermediate **I**. Alternatively (*Route B*), normal reduction of **2** by one equivalent of borane to give an *N*-borylimine is followed by complexation of a second borane molecule, which activates an analogous push-pull ring-expansion to give intermediate **I**. The postulate of the key intermediate **I** helps to explain the high *trans* stereoselectivity of the reaction, since intramolecular hydride transfer leads to the neutral intermediate **II**. Reduction of the remaining benzophenone-imine type double bond, a relatively slow process,[8,13] completes the formation of **4**.

The reaction system is highly reagent-sensitive: the presence of Lewis acids (BF_3·OEt_2, $ZnCl_2$, $GaCl_3$, $SnCl_4$, $RuCl_3$, LiI) diminished the proportion of cyclobutane and/or the overall yield,[14] while no other reducing agent ($LiAlH_4$, DIBALH, H_2-Ni) produced any trace of **4** or **5**. Even the solvent appears to play an important role: treatment of **2** with BH_3·SMe_2 in CH_2Cl_2 gave an 80% yield of a **3**:**4** mixture in a ratio of 97:3. We conclude that cyclobutane formation is the result of a fine balance of the dual Lewis acid and reducing agent properties of borane, mediated through association with THF solvent. At all times, of course, this reactivity competes with the usual straightforward reduction of **2** to cyclopropane **3**.

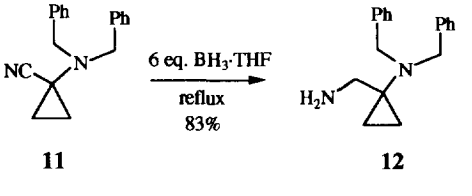


Mechanistic steps:

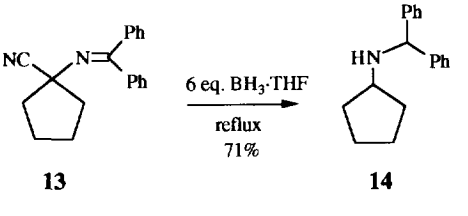
i) complexation of borane
ii) ring expansion
iii) addition of H–BH_2 across double bond

Scheme 4

The ring expansion reaction can only proceed through the cooperativity of the ternary cyclopropane-imine-nitrile combination. The unique nature of the system is underlined by comparative studies carried out on two control substrates, neither of which produced a ring-expanded product. Compound **11**, lacking the imine π-electrons, was reduced by BH_3·THF to cyclopropane **12** exclusively (Scheme 5), while cyclopentane **13** underwent decyanation[15,16] before reduction, yielding amine **14** as the sole product (Scheme 6).



Scheme 5



Scheme 6

In conclusion, this work provides a useful access to the title compound, convenient for gram-scale preparations, and allows for sequential, non-equivalent functionalisation of both amine centres. We are presently investigating the scope of this latter reactivity, in application to selected 1,2-diamine structures of pharmacological interest.

EXPERIMENTAL SECTION

General. ^1H and ^{13}C NMR spectra were recorded at 300 MHz and 75 MHz respectively. IR spectra were recorded as thin films (for oils) or as KBr discs (for solids). Chemical ionisation mass spectra were recorded at 30 eV using ammonia as the vector gas. Elemental analyses were performed by Service de Microanalyse, I.C.S.N.-C.N.R.S., Gif-sur-Yvette, France. Analytical TLC was performed on silica gel F-254 plates and components visualized using ethanolic phosphomolybdic acid solution. Flash chromatography was carried out on 230-400 mesh silica gel. Iminonitriles **2** and **13** were prepared by the method of O'Donnell,[17] and compound **11** was obtained as previously reported.[18] Triethylamine, dichloromethane and THF were dried and redistilled under nitrogen before use. All other commercial reagents and solvents were used as supplied.

Cyclobutane-optimized reduction of 2. A solution of **2** (20.0 g, 81.2 mmol) in THF (350 mL) was heated at reflux under nitrogen, while a 1 M solution of BH_3·THF (487 mL, 487 mmol) was added as rapidly as possible (*CAUTION:* vigorous evolution of gas). After 24 h at reflux, the mixture was cooled to 0 °C and 6 M HCl (300 mL) was added slowly, and the mixture allowed to warm to rt. Solid sodium hydroxide was added portionwise to give pH 14, and the mixture diluted with water (100 mL). The organic phase was collected, and the aqueous phase was extracted with ethyl acetate (3 x 100 mL). Combined organic phases were washed with water (150 mL), then brine (200 mL), dried over $MgSO_4$, and evaporated to give a clear oil. Flash chromatography using EtOAc:MeOH (95:5) containing a gradient of concentrated NH_4OH (0–3%) gave the following:

3 and **4**. (40:60 mixture) (15.2 g, 74%) as a clear syrup (R_f = 0.32; EtOAc-MeOH-NH_4OH 95:5:1); physicochemical data for **3** have previously been described;[8] the following were deduced for **4** from the mixture: ^1H NMR ($CDCl_3$) δ 1.18 (m, 2 H), 1.57 (br s, 3 H), 1.96 (m, 2 H), 2.76 (m, 1 H), 3.01 (m, 1 H), 4.93 (s, 1 H), 7.15-7.46 (m, 10 H); ^{13}C NMR ($CDCl_3$) δ 23.5 (t), 25.8 (t), 57.2 (d), 63.5 (d), 65.2 (d), 126.7, 127.2, 128.2 (each d), 144.3 (s).

5 (0.82 g, 4%) as an oil (R_f = 0.65; EtOAc-MeOH-NH_4OH 95:5:1); IR 3367, 3311, 1602, 1490, 1455 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.48 (m, 1 H), 1.90 (m, 2 H), 2.06 (m, 1 H), 2.23 (br s, 3 H), 3.22 (m, 1 H), 3.51 (m, 1 H), 4.82 (s, 1 H), 7.11-7.45 (m, 10 H); ^{13}C NMR ($CDCl_3$) δ 25.8 (t), 27.0 (t), 50.9 (d), 54.1 (d), 64.5 (d), 126.9, 127.0, 127.4, 128.4, 128.5 (each d), 144.2 (s); MS(CI) *m/e* 253 $[MH]^+$. Anal. Calcd for $C_{17}H_{20}N_2$: C, 80.90; H, 7.99; N, 11.10. Found: C, 80.76; H, 7.66; N, 10.97.

Preparation of carbamates 6 and 7. To a solution of **3**:**4** mixture (40:60) (5.26 g, 20.8 mmol) in a mixture of dioxan (11 mL) and 2 M aqueous sodium carbonate solution (52 mL) at 0 °C was added benzyl chloroformate (3.6 mL, 25.0 mmol). The mixture was stirred at 0 °C for 3 h then at rt for 12 h. More sodium carbonate solution was added (70 mL), and the mixture extracted with ethyl acetate (4 x 45 mL). Combined extracts were dried over $MgSO_4$, and evaporated to dryness. Flash chromatography of the residue using EtOAc-heptane (25:75) as eluent gave the following two compounds (40:60) in an overall yield of 88%:

6 (2.82 g) as white crystals (R_f = 0.48; EtOAc-heptane 30:70), mp 116-118 °C (EtOAc-petroleum ether); IR 3340, 3424, 1708, 1518, 1237 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.46 (m, 2 H), 0.61 (m, 2 H), 1.86 (br s, 1 H), 3.05 (d, 2 H, J = 5.6 Hz), 4.95 (s, 1 H), 5.01 (s, 1 H), 5.07 (s, 2 H), 7.10-7.42 (m, 15 H); ^{13}C NMR ($CDCl_3$) δ 12.9 (t), 39.1(t), 46.2 (s), 64.6 (d), 66.8 (t), 127.2, 127.4, 128.2, 128.6, (each d), 136.8, 144.8, 156.6 (each s);

MS(CI) *m/e* 387 $[MH]^+$. Anal. Calcd for $C_{25}H_{26}N_2O_2$: C, 77.69; H, 6.78; N, 7.24. Found: C, 77.34; H, 6.76; N, 7.19.

7 (4.23 g) as colourless crystals (R_f = 0.33; EtOAc-heptane 30:70), mp 118-119 °C (EtOAc-heptane); IR 3324, 3310, 1710, 1523, 1263 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.30 (m, 2 H), 1.86 (s, 1 H), 1.96 (m, 1 H), 2.08 (m, 1 H), 2.98 (dd, 1 H, *J* = 16.0 and 7.8 Hz), 3.89 (dt, 1 H, *J* = 15.9 and 7.9 Hz), 4.86 (d, 1 H, *J* = 7.3 Hz), 4.95 (s, 1 H), 5.12 (2d, 2 H, *J* = 12.1 Hz, *AB* system), 7.12-7.41 (m, 15 H); ^{13}C NMR ($CDCl_3$) δ 23.5 (t), 23.9 (t), 54.8 (d), 60.3 (d), 64.6 (d), 66.7 (t), 127.2, 127.4, 128.3, 128.6 (each d), 136.7, 143.6, 144.2, 155.4 (each s); MS(CI) *m/e* 387 $[MH]^+$. Anal. Calcd for $C_{25}H_{26}N_2O_2$: C, 77.69; H, 6.78; N, 7.24. Found: C, 77.63; H, 6.77; N, 7.24.

Preparation of *trans*-1,2-diaminocyclobutane 1. A solution of **7** (2.4 g, 6.2 mmol) in methanol (75 mL) containing 10% $Pd(OH)_2$-C catalyst (1.0 g) was hydrogenated at rt for 48 h, then the mixture was filtered through celite. The filtrate was concentrated by careful distillation through a 25 cm Vigreux column to remove the major part of the methanol. The residue, consisting of diphenylmethane, methanol and the title product, was distilled using a Kugelrohr apparatus at atmospheric pressure, collecting the fraction bp 100-140 °C. This material was nearly-pure diamine **1**, containing trace amounts of methanol. The dihydrochloride was prepared by treatment with dry HCl-MeOH then evaporation of the solvent, to give 0.76 g (77%) of **1**·2HCl: mp 248-251 °C (MeOH-Et_2O) (lit.[6b] mp 240 °C); IR 3410 cm^{-1}; ^1H NMR (D_2O) δ 1.80 (m, 2 H), 2.14 (m, 2 H), 3.78 (m, 2 H); ^{13}C NMR (D_2O) δ 20.5 (d), 48.3 (t); MS(CI) *m/z* 87 $[MH]^+$. Anal. Calcd for $C_4H_{10}N_2$·2HCl: C, 30.21; H, 7.60; N, 17.61. Found: C, 30.46; H, 7.24; N, 17.24.

A solution of the free diamine in methanol was treated with a large excess of carbon disulphide (10 equiv.) to form the dithiocarbamate salt: mp 259-261 °C (H_2O) (lit.[6a] mp 263 °C).

Preparation of morpholines 8 and 9. To a solution of **3**:**4** mixture (40:60) (1.31 g, 5.19 mmol) in absolute ethanol (40 mL) under nitrogen were added sucessively potassium iodide (0.18 g, 1.08 mmol), potassium carbonate (3.03 g, 21.9 mmol) and 2-chloroethyl ether (0.79 mL, 6.74 mmol). The mixture was heated at reflux for at least 7 days, then cooled and filtered. The solids were rinsed with THF and the combined filtrate was evaporated. Flash chromatography of the residue using EtOAc:cyclohexane (10:90 then 50:50) gave the following two compounds (61:39) in an overall yield of 82%:

8 (0.84 g) as an oil (R_f = 0.33; EtOAc-cyclohexane 50:50); IR 3385, 1454 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.09 (m, 1 H), 1.22 (m, 1 H), 1.69 (m, 1 H), 1.78 (br s, 1 H), 1.92 (m, 1 H), 2.26 (m, 2 H), 2.38 (m, 3 H), 2.95 (dd, 1 H, *J* = 15.1 and 7.2 Hz), 3.56 (t, 4 H, *J* = 4.7 Hz), 4.70 (s, 1 H), 7.10-7.29 (m, 10 H); ^{13}C NMR ($CDCl_3$) δ 19.5 (t), 24.7 (t), 51.2 (t), 56.2 (d), 64.8 (d), 66.9 (t), 68.8 (d), 127.1, 127.2, 127.5, 128.5 (each d), 144.6, 144.9 (each s); MS(CI) *m/e* 323 $[MH]^+$. Anal. Calcd for $C_{21}H_{26}N_2O$: C, 78.22; H, 8.13; N, 8.69. Found: C, 77.85; H, 8.27; N, 8.71.

9 (0.53 g) as an oil (R_f = 0.75; EtOAc-cyclohexane 50:50); IR 3388, 1455 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.21 (dd, 2 H, *J* = 6.9 and 4.6 Hz), 0.61 (dd, 2 H, *J* = 6.9 and 3.8 Hz), 2.21 (s, 2 H), 2.39 (t, 4 H, *J* = 4.7 Hz), 2.60 (br s, 1 H), 3.68 (t, 4 H, *J* = 4.7 Hz), 5.03 (s, 1 H), 7.25 (m, 10 H); ^{13}C NMR ($CDCl_3$) δ 12.4 (t), 35.8 (s), 53.9 (t), 63.0 (t), 64.1 (d), 67.2 (t), 126.8, 127.9, 128.3 (each d), 145.4 (s); MS(CI) *m/e* 323 $[MH]^+$. Anal. Calcd for $C_{21}H_{26}N_2O$: C, 78.22; H, 8.13; N, 8.69. Found: C, 77.93; H, 8.16; N, 8.56.

Preparation of moclobemide analogue 10. A solution of **8** (0.30 g, 0.93 mmol) in methanol (27 mL) containing 10% $Pd(OH)_2$-C catalyst (70 mg) was hydrogenated at rt for 48 h, then the mixture was filtered through celite. The filtrate was evaporated, finally at 0.5 mm Hg, to remove all residual solvent. The residuewas dissolved in dichloromethane (15 mL) under nitrogen, and triethylamine (0.16 mL, 1.11 mmol) was added. The mixture was stirred at 0 °C while 4-chlorobenzoyl chloride (0.14 mL, 1.11 mmol) was added dropwise. The mixture was left at rt for 24 h, then the solvent was evaporated. Flash chromatography of the residue using EtOAc:MeOH (90:10) as eluent gave **10** (109 mg, 40%) as colourless crystals (R_f = 0.28; EtOAc-MeOH 90:10), mp 116-119 °C (EtOAc-cyclohexane); IR 3350, 1660, 1518 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.63 (m, 2 H), 1.97 (m, 1 H), 2.34 (m, 1 H), 2.51 (m, 4 H), 2.73 (dd, 1 H, J = 16.2 and 8.2 Hz), 3.69 (t, 4 H, J = 4.4 Hz), 4.56 (dt, 1 H, J = 17.2 and 8.7 Hz), 6.33 (d, 1 H, J = 8.7 Hz), 7.40 (d, 2 H, J = 8.5 Hz), 7.70 (d, 2 H, J = 8.5 Hz); ^{13}C NMR ($CDCl_3$) δ 19.8 (t), 23.9 (t), 48.7 (d), 50.3 (t), 66.8 (t), 69.2 (d), 128.4, 128.9 (each d), 132.9, 165.3 (each s); MS(CI) *m/e* 295 $[MH]^+$. Anal. Calcd for $C_{15}H_{19}ClN_2O_2$: C, 61.11; H, 6.50; N, 9.50. Found: C, 60.88; H, 6.51; N, 9.21.

Reduction of 11. The procedure for the reduction of **2** was repeated using aminonitrile **11** to obtain **12** (83%) as a white microcrystalline solid (R_f = 0.44; EtOAc-MeOH-NH_4OH 95:5:1), mp 74-76 °C (toluene-heptane); IR 3388, 3022, 1502, 1454 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.36 (m, 2 H), 0.57 (m, 2 H), 1.80 (s, 2 H), 2.77 (s, 2 H), 3.79 (s, 4 H), 7.19 (m, 10 H); ^{13}C NMR ($CDCl_3$) δ 12.6 (t), 45.4 (s), 45.7 (t), 56.9 (t), 126.7, 128.0, 128.8 (each d), 140.6 (s); MS(CI) *m/e* 267 $[MH]^+$. Anal. Calcd for $C_{18}H_{22}N_2$: C, 81.16; H, 8.32; N, 10.52. Found: C, 79.21; H, 8.21; N, 9.96.

Reduction of 13. The procedure for the reduction of **2** was repeated using iminonitrile **13** to obtain **14** (71%) as an oil (R_f = 0.63; EtOAc-cyclohexane 20:80); IR 3368, 3022, 1605, 1500, 1454 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.39-1.50 (m, 4 H), 1.53-1.74 (m, 3 H), 1.82 (m, 2 H), 3.00 (quintet, 1 H, J = 7.1 Hz), 4.89 (s, 1 H), 7.12-7.40 (m, 10 H); ^{13}C NMR ($CDCl_3$) δ 23.9 (t), 33.4 (t), 57.7 (d), 65.8 (d), 126.9, 127.2, 127.5, 128.5 (each d), 144.6 (s); MS(CI) *m/e* 252 $[MH]^+$. Anal. Calcd for $C_{18}H_{21}N$: C, 86.01; H, 8.42; N, 5.57. Found: C, 85.82; H, 8.52; N, 5.53.

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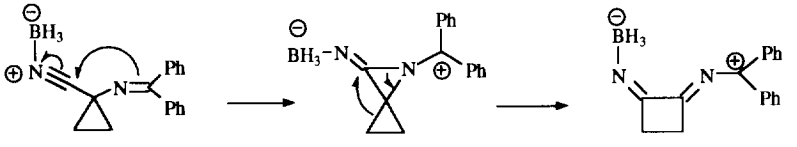

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14. In the preliminary communication (ref. 8) we observed that the addition of BF_3·Et_2O to a refluxing reaction mixture improved the cyclobutane:cyclopropane ratio from the original 15:85 to 50:50. In light of the results presented here, this observation seems more likely due to the reflux conditions than the presence of the Lewis acid. The overall yield of **3** and **4** was, in any case, considerably diminished.
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