(3*H*)-furanone (*trans*-2-methyl-2-(phenylthio)-4-phenylbutyrolactone, 5-trans): mp 115 °C; IR (KBr) 1762 cm^{-1}; ^{13}C NMR ($CDCl_3$) 175.67 (C=O), 77.78 (C-4), 51.57 (C-2), 46.22 (C-3), 23.43 (CH_3), phenyl group 138.56 (C_i), 129.07 (C_o), 128.60 (C_p), 125.52 (C_m), phenylthio group 129.32 (C_i), 137.25 (C_o), 130.21 (C_p), 128.78 (C_m) ppm; ^1H NMR ($CDCl_3$) δ 1.55 (3 H, s, CH_3), 5.52 (1 H, dd, H-4), 2.76 (1 H, dd, H-3α), 2.31 (1 H, dd, H-3β); (C_6D_6) δ 1.29 (3 H, s, CH_3), 5.37 (1 H, dd, H-4), 2.24 (1 H, dd, H-3α), 1.75 (1 H, dd, H-3β).

Phenylsulfenylation of *trans*-Dihydro-3-methyl-5-phenyl-2(3*H*)-furanone (*trans*-2-methyl-4-phenylbutyrolactone, 2-trans). A solution of lactone **2** (0.4 g, 2.27 mmol) in 5 mL of dry THF was cooled to −78 °C and added to a solution of LDA prepared as reported before [diisopropylamine (0.33 mL, 2.35 mmol) and *n*-BuLi (0.67 mL, 2.35 mmol, 3.5 M) in 10 mL of THF], and the reaction mixture was stirred at −78 °C over 1 h. Diphenyl disulfide (0.49 mL, 2.27 mmol) was dissolved in 5 mL of dry THF, cooled to −78 °C, and added dropwise to the reaction mixture. Then, the solution was stirred at −78 °C for 3 h, and the reaction was quenched as reported for phenylsulfenylation of **1**. The mixture was extracted with $CHCl_3$ (10 mL) and washed with water (4 × 5 mL) and the solvent dried and removed. After separation of the crude product by column chromatography, 0.60 g of **5**-trans was obtained (93%).

Methylsulfenylation of *trans*-Dihydro-3-methyl-5-phenyl-2(3*H*)-furanone (*trans*-2-Methyl-4-phenylbutyrolactone, 2-trans). A solution of lactone **2** (0.4 g, 2.27 mmol) in 5 mL of dry THF was cooled to −78 °C and added to a solution of LDA prepared as reported before [diisopropylamine (0.33 mL, 2.35 mmol) and *n*-BuLi (0.67 mL, 2.35 mmol, 3.5 M) in 10 mL of THF], and the reaction mixture was stirred at −78 °C over 1 h. Dimethyl disulfide (0.22 mL, 2.27 mmol) was dissolved in 5 mL of dry THF, cooled to −78 °C, and added dropwise to the reaction mixture. Then the solution was stirred at −78 °C for 3 h, and the reaction was quenched as reported for phenylsulfenylation. The mixture was extracted with $CHCl_3$ (10 mL) and washed with water (4 × 5 mL) and the solvent dried and removed. Purification of the reaction mixture by column chromatography afforded **6**-trans as a liquid (3.88 g, 77%).

***trans*-Dihydro-3-methyl-3-(methylthio)-5-phenyl-2-(3*H*)-furanone (*trans*-2-methyl-2-(methylthio)-4-phenylbutyrolactone, 6-trans)**: IR ($CHCl_3$) 1775 cm^{-1}; ^{13}C NMR ($CDCl_3$) 174.98 (C=O), 77.94 (C-4), 46.69 (C-2), 46.41 (C-3), 21.95 (CH_3), 11.96 (methylthio), phenyl group 138.42 (C_i), 128.73 (C_o), 128.57 (C_p), 125.53 (C_m) ppm; ^1H NMR ($CDCl_3$) δ 1.60 (3 H, s, CH_3), 2.21 (3 H, s, CH_3S), 2.25 (1 H, dd, H-3β), 2.57 (1 H, dd, H-3α), 5.63 (1 H, dd, H-4), 7.30 (5 H, m, H-aromatic) ppm.

Protonation Reactions. General Procedure. A solution of the lactone **3**-cis (0.10 g, 0.37 mmol) in 5 mL of THF was cooled to −78 °C and added to a solution of LDA prepared as reported before [diisopropylamine (0.037 g, 0.37 mmol) and *n*-Buli 1.4 M (0.26 mL, 0.37 mmol) in 10 mL of THF], and the reaction mixture was stirred at the same temperature over 1 h under a nitrogen atmosphere and quenched at −78 °C with a mixture of AcOH/MeOH/THF (1:1:1). The mixture was extracted with $CHCl_3$ (20 mL) and the solvent dried and removed. The crude product was observed directly by proton NMR (90 MHz, CW) and the isomer ratio measured from the analyses of the signals of H-2 or methyl.

Lactones **3**-cis and **3**-trans afforded a 60/40 (cis/trans) ratio, whereas the **4**-cis and **4**-trans mixture (80/20) gave 68/32, respectively. The reaction of the lactone mixture **2**-cis and **2**-trans gave an isomer ratio cis/trans of 90/10. The cis isomer was separated and analyzed by NMR spectrscopy.

***cis*-Dihydro-3-methyl-5-phenyl-2(3*H*)-furanone (*trans*-2-methyl-4-phenylbutyrolactone, 2-cis)**: IR ($CHCl_3$) 1767 cm^{-1}; MS *m/z* (rel intensity) 176 (M^+, 90), 132 (48), 117 (100), 105 (80), 77 (37), 42 (50); ^{13}C NMR ($CDCl_3$) 179.64 (C=O), 79.60 (C-4), 41.35 (C-2), 36.80 (C-3), 15.40 (CH_3), phenyl group 139.88 (C_i), 129.22 (C_o), 128.88 (C_p), 126.18 (C_m) ppm; ^1H NMR (C_4D_8O/C_6D_6) δ 1.27 (3 H, d, CH_3), 1.78 (1 H, td, H-3β), 2.74 (1 H, ddd, H-3α), 2.76 (1 H, qdd, H-2), 5.29 (1 H, dd, H-4), 7.32 (5 H, m, H-aromatic) ppm.

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Synthesis of 1-Amino-1-(aminomethyl)cyclopropane and Its Monobenzamides†

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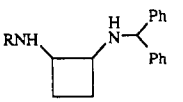
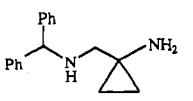
An increasing number of therapeutic agents, including antiarrythmic, antipsychotic, and antitumor compounds, have structures which incorporate a 1,2-diamine function. As an extension of our program[1] dealing with the preparation of cyclopropane compounds of biological interest,[2] we required a method for the synthesis of a series of 1,2-diaminoethanes in which one of the carbon atoms is incorporated into a cyclopropane ring. Here we report on the preparation of the simplest such compound, the previously unknown 1-amino-1-(aminomethyl)cyclopropane, **1**, by a simple and efficient synthetic strategy which allows regiospecific functionalization of *either* primary amine group.

Existing methods for the synthesis of vicinal diamines are rather limited and usually involve the introduction of two nitrogen functions onto a preformed carbon skeleton.[3] We propose an alternative strategy, whereby a variety of target molecules might be constructed from a single C_2N_2 unit, an objective which calls for an ethylenediamine synthon having nonequivalent nitrogen and carbon atom reactivities. A possible candidate was (dibenzylamino)-acetonitrile which can be alkylated with certain electrophiles under strongly basic conditions,[1b] but recent observations indicate that this synthon is not applicable to cyclopropane-forming reactions in which 1,2-dibromoethane is used as the electrophile.[4] We adopted instead the related compound [*N*-(diphenylmethylene)amino]-acetonitrile, **2**, as our 1,2-diamine precursor, since it also has the requisite differential reactivity of all four central atoms. Synthon **2** was first prepared in 1978 by O'Donnell[5a] and has been used by his group[5] and others[6] as a synthetic glycine equivalent in the preparation of a number of amino acid derivatives.

The various approaches to the synthesis of **1** are shown in Scheme I. Double alkylation of **2** with 1,2-dibromoethane and base under phase-transfer conditions according to O'Donnell[5b] gave the cyclopropane derivative **3**. Complete multiple-bond reduction of **3** with lithium aluminum hydride was inefficient, giving a mixture of products from which **4** was isolated only in low yield (35%). A high yield of diamine **4** was obtained using a borane–tetrahydrofuran complex[7] which allowed the reaction to go to completion without complication from reductive decyanation.[8] We were intrigued to find, however, that a small amount (15–20%) of a secondary product was formed, corresponding to a cyclobutanediamine **7a**, which was characterized as its benzamide **7b**.



7a R=H
7b R=PhCO



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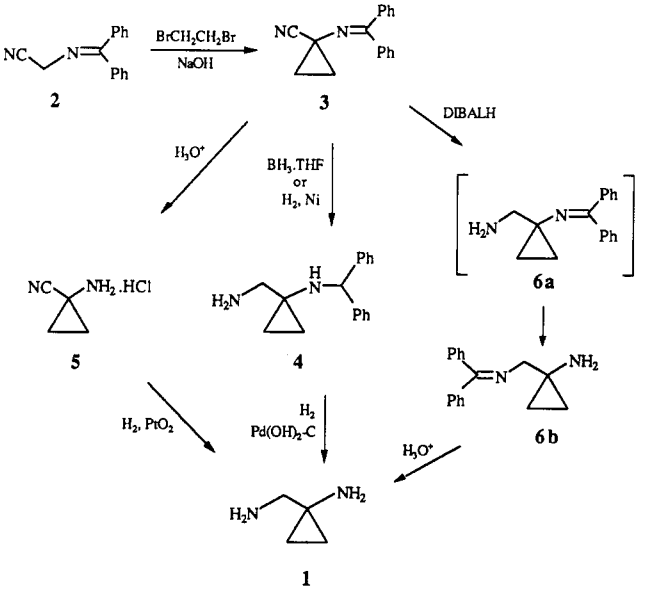
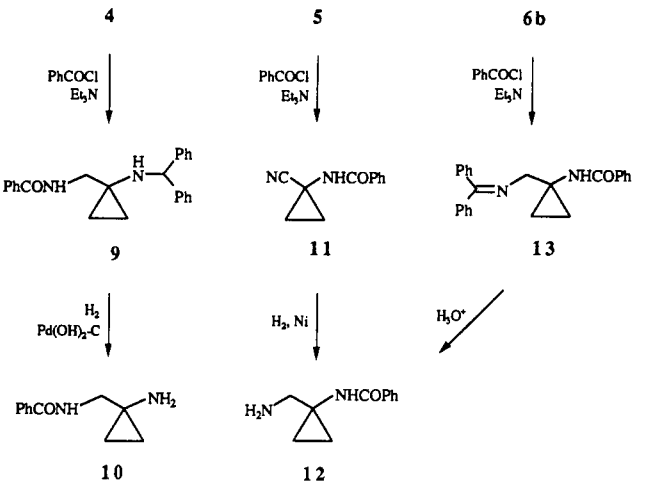
Scheme I



Scheme II



The benzylic substituent of the secondary amino function of 4 was removed conveniently by hydrogenation over Pearlman's catalyst to give the title compound as a volatile colorless liquid in methanolic solution. The dihydrochloride salt was more convenient to handle and characterize and allowed purification by recrystallization to remove the 1,2-diaminocyclobutane impurity. The overall yield of pure 1·2HCl from 3 by this route was 60%.

Total multiple-bond reduction of 3 was also achieved in near-quantitative yield by hydrogenation over Raney nickel,[9] and the product was obtained as a mixture of 4 and 8 in widely-varying ratios.[10] The occurrence of the latter suggests that **6a** is an intermediate product in the hydrogenation reaction and undergoes partial transimination to **6b** before reduction of the imine moiety (vide infra). Although the two isomeric diamines could be separated by chromatography, this proved unnecessary for the preparation of the target molecule: hydrogenation of 4/8 mixture over Pearlman's catalyst furnished 1 in 75% yield for two steps.

In an alternative approach, imino nitrile 3 was treated with dilute mineral acid to produce the amino nitrile **5**, as its stable hydrochloride.[11] For the transformation of the nitrile to a primary amine, hydrogenation over Raney nickel was inappropriate, leading to a poorly-defined mixture of oligomeric materials. Reduction was best achieved by hydrogenation over Adam's catalyst in ethanolic HCl, which gave 1·2HCl (76% yield from 3) in high purity even before recrystallization. Provided intermediate **5** is not kept for long periods, which results in degradation, this route represents the simplest and most efficient synthesis of the title compound in its dihydrochloride form.

In our third approach to 1, we reasoned that the size of the diphenylmethylene moiety of 3 should make the imine double bond less accessible than the nitrile center and that by using a bulky reducing agent under mild conditions we should be able to effect regioselective total reduction of the nitrile to an amine whilst leaving the imine intact. Selective reduction was achieved with diisobutylaluminum hydride (3.5 equiv, 7 h at −78 °C and then overnight at rt). The isolated product had the structure **6b**, apparently the result of a facile transimination reaction of the initially formed imino amine **6a**. This made no difference to the preparation of the title compound: acid hydrolysis of **6b** provided 1, once again as its dihydrochloride. Although the reaction was complete, purification proved difficult due to the persistence of the byproduct benzophenone. Pure 1·2HCl was obtained in approximately 35% yield by recrystallization of the crude reaction product.

We obtained further evidence concerning the transimination reaction.[12] Imino nitrile 3 was reduced with DIBALH, and the resulting imino amine was isolated and then treated with borane–tetrahydrofuran. This furnished diamine 8, distinguishable from 4 by TLC and NMR spectroscopy, which implicates intermediate structure **6b**. In contrast, imino amine generated by the same DIBALH procedure and then further reduced in situ by $LiAlH_4$ in

(1) (a) Aitken, D. J.; Royer, J.; Husson, H.-P. *J. Org. Chem.* **1990**, *55*, 2814. (b) Guillaume, D.; Aitken, D. J.; Husson, H.-P. *Synlett* **1991**, 747.

(2) (a) Stammer, C. H. *Tetrahedron* **1990**, *46*, 2231. (b) Suckling, C. J. *Angew. Chem., Int. Ed. Engl.* **1988**, *27*, 537. (c) Lin, H.-W.; Walsh, C. T. In *The Chemistry of the Cyclopropyl Group*; Rappoport, Z., Ed.; Wiley: New York, 1987; pp 959–1025.

(3) For recent examples and leading references concerning 1,2-diamine synthesis, see: (a) Bruni, E.; Cardillo, G.; Orena, M.; Sandri, S.; Tomasini, C. *Tetrahedron Lett.* **1989**, *30*, 1679. (b) Pini, D.; Iuliano, A.; Rosini, C.; Salvadori, P. *Synthesis* **1990**, 1023. (c) Imamoto, T.; Nishimura, S. *Chem. Lett.* **1990**, 1141. (d) Jones, D. S.; Srinivasan, A.; Kasina, S.; Fritzberg, A. R.; Wilkening, D. W. *J. Org. Chem.* **1989**, *54*, 1940. (e) Fazio, M. J. *J. Org. Chem.* **1984**, *49*, 4889. (f) Asaro, M. F.; Nakayama, I.; Wilson, R. B., Jr. *J. Org. Chem.* **1992**, *57*, 778. (g) Benalil, A.; Carboni, B.; Vaultier, M. *Tetrahedron* **1991**, *47*, 8177. (h) Dieter, R. K.; Deo, N.; Lagu, B.; Dieter, J. W. *J. Org. Chem.* **1992**, *57*, 1663.

(4) Brum-Bousquet, M.; Guillaume, D.; Aitken, D. J.; Husson, H.-P., unpublished results.

(5) (a) O'Donnell, M. J.; Eckrich, T. M. *Tetrahedron Lett.* **1978**, 4625. (b) O'Donnell, M. J.; Bruder, W. A.; Eckrich, T. M.; Shullenberger, D. F.; Staten, G. S. *Synthesis* **1984**, 127.

(6) (a) Ferroud, D.; Genet, J. P.; Kiolle, R. *Tetrahedron Lett.* **1986**, *27*, 23. (b) Genet, J. P.; Juge, S.; Achi, S.; Mallart, S.; Ruiz Montes, J.; Levif, G. *Tetrahedron* **1988**, *44*, 5263. (c) Leduc, R.; Bernier, M.; Escher, E. *Helv. Chim. Acta* **1983**, *66*, 960. (d) Dryanska, V. *Synth. Commun.* **1990**, *20*, 1055. (e) Osuko Opio, J.; Labidalle, S.; Galons, H.; Miocque, M.; Zaparucha, A.; Loupy, A. *Synth. Commun.* **1991**, *21*, 1743.

(7) Although the original article by Brown (Brown, H. C.; Krishnamurthy, S.; Yoon, N. M. *J. Org. Chem.* **1976**, *41*, 1778) on the use of borane–THF in synthesis stated that "nitriles are reduced [to amines] slowly", the reagent can still be very convenient for such transformations; see: Brown, H. C.; Choi, Y. M.; Narasimhan, S. *Synthesis* **1981**, 605. We based our procedure on that used by Ganem for polyamine synthesis: Nagarajan, S.; Ganem, B. *J. Org. Chem.* **1986**, *51*, 4856.

(8) Ogura, K.; Shimamura, Y.; Fujita, M. *J. Org. Chem.* **1991**, *56*, 2920.

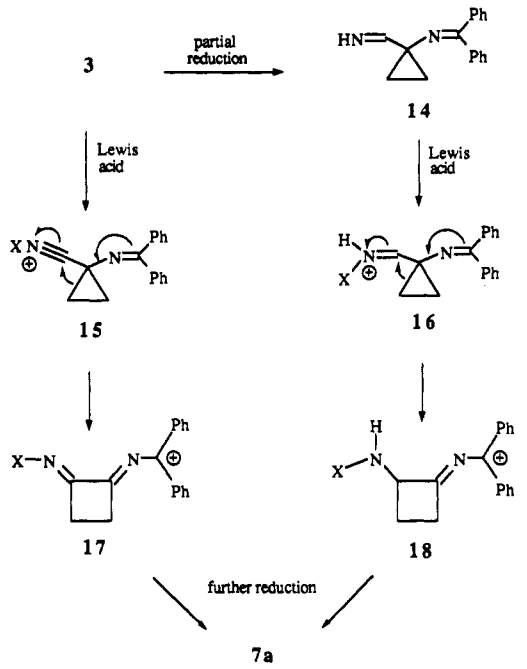
(9) Best results were obtained when the reduction was carried out in the presence of sodium hydroxide; use of ammonia to suppress secondary amine formation gives a lower yield. See: Bergeron, R. J.; Garlich, J. R. *Synthesis* **1984**, 782.

(10) For example, in one run we obtained a product containing 95% of 4, while the next run, under identical conditions, gave 80% of 8. Results of repeated experiments fluctuated between these extremes.

(11) Salaün, J.; Marguerite, J.; Karkour, B. *J. Org. Chem.* **1990**, *55*, 4276.

(12) For a discussion of transimination reactions, see: Hogg, J. L.; Jencks, D. A.; Jencks, W. P. *J. Am. Chem. Soc.* **1977**, *99*, 4772.

Scheme III



a one-pot reaction provided **4** as the sole product. Thus it seemed that the conversion of **6a** to **6b** occurs during workup of the DIBALH reaction.

Differentiation of amino group reactivity is a challenging problem in the preparation of pharmacologically active compounds, so it was important to demonstrate that the intermediates in our scheme allow regiospecific functionalization of one or other nitrogen atom. We selected the introduction of a benzamide group as an illustrative example (Scheme II). As a result of the steric bulk of the substituents on the secondary amine center, reaction of **4** (in this case separated from **8** by chromatography) under standard benzoylating conditions provided a single benzamide **9**. Hydrogenation over Pearlman's catalyst cleaved diphenylmethane cleanly and gave the α-primary benzamide **10** in 84% yield for the two steps. In the intermediate amino nitrile **5**, the α-tertiary nitrogen center is free for functionalization, and benzoylation gave amido nitrile **11**. Chemoselective reduction of the nitrile was achieved in excellent yield using hydrogen and Raney nickel[9] to provide the α-tertiary benzamide **12** in 56% overall yield from **3**.

The consequences of the **6a**/**6b** transimination reaction became apparent when a freshly prepared imino amine sample was exposed to standard benzoylating conditions: a single amido imine **13** was obtained, corresponding to a derivative of **6b**. Thus subsequent hydrolysis of the benzophenone imine with dilute mineral acid yielded benzamide **12**, and not benzamide **10**, as the final product in this sequence.

The formation of the cyclobutane diamine in the BH_3·THF reduction warrants further comment. Acid-catalyzed cyclopropyl imine rearrangements to pyrrolines are well documented[13] and give some insight into our observed ring expansion. We believe that borane acts not only as a reducing agent but also as a Lewis acid, activating the nitrile of **3** and/or the primary imine of the partially-reduced intermediate **14** (Scheme III). Ring expansion of **15** or **16** is promoted by delocalization of the positive charge onto the (diphenylmethylene)amino function,[14] to give intermediate cyclobutane structures **17** or **18**, either of which is subsequently reduced by borane to **7a**. This mechanism is similar to that suggested by Wasserman[15] for (1-aminocyclopropyl)iminium to pyrroline rearrangements, in which a diaminocyclobutane intermediate analogous to **18** is invoked. In the present case, reduction by borane precludes further skeletal rearrangement of **17** or **18**. We are aware of only one other very recent example where participation of a neighboring (diphenylmethylene)amino group provides the driving force for a cyclopropane to cyclobutane ring enlargement.[16] Further support for our explanation was provided in an experiment whereby **3** was refluxed for several hours with 1 equiv of BF_3·Et_2O, a stronger Lewis acid with no reducing properties, during treatment with borane–tetrahydrofuran. In this case the yield of **7a** rose to 50%, attesting to considerable rearrangement before reduction.

In conclusion, we have prepared a new diamine and both of its monobenzamide derivatives in high yield from a single starting material, in a synthetic scheme which allows for initial C-functionalization followed by further development on one or other amino group according to choice. We are presently applying this strategy to the synthesis of other diamines and derivatives thereof.

Experimental Section

Synthon **2** is commercially available (Aldrich), but for large-scale work we prefer to prepare it according to the method of O'Donnell.[17] Pearlman's catalyst, Adam's catalyst, Raney nickel, BH_3·THF, and DIBALH–hexane solutions were used as supplied commerically (all Aldrich). All chromatographic manipulations were carried out using silica as the stationary phase. TLC R_f values are given for the column chromatography eluent, unless otherwise stated. For further details of general experimental procedures, see the Experimental Section in ref 1a.

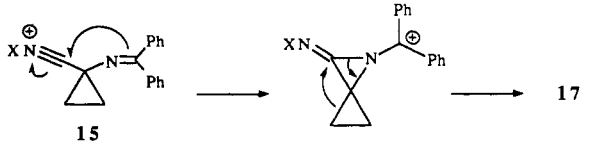
1-[(Diphenylmethylene)amino]-1-cyclopropanecarbonitrile (3). This compound was prepared by reaction of **2** with dibromoethane and NaOH under phase-transfer conditions according to the procedure of O'Donnell.[5b] After purification by flash chromatography using cyclohexane–EtOAc (95:5), the product was obtained in 80% yield as a yellow solid: R_f 0.46 (90:10 cyclohexane–EtOAc); mp 81–83 °C (lit.[11] mp 81 °C).

1-Amino-1-cyclopropanecarbonitrile Hydrochloride (5). Via the procedure of Salaün,[11] a mixture of **3** (1.00 g, 4.06 mmol), Et_2O (12 mL), and 1 M HCl (25 mL) was stirred at rt for 16 h. The aqueous phase was collected, washed with CH_2Cl_2 (3 × 10 mL), evaporated, and dried in vacuo over P_2O_5 to give a white solid, 462 mg (96%): mp 168 °C (lit.[11] mp 170–172 °C).

1-(Aminomethyl)-1-[(diphenylmethyl)amino]cyclopropane (4). Method A. To a solution of NaOH (1.02 g, 25.5 mmol) in absolute EtOH (40 mL) were added **3** (2.97 g, 12.1 mmol) and then Raney nickel (700 mg). The mixture was subjected to Parr hydrogenation at 50 psi of overpressure and monitored by TLC for the disappearance of starting material and intermediate **6a**. After 30 h, reduction was complete, and the catalyst was removed

(13) Boeckman, R. K., Jr.; Walter, M. A. In *Advances in Heterocyclic Natural Product Synthesis, Volume 1*; Pearson, W. H., Ed.; Jai Press, Inc.: Greenwich, CT, 1991; pp 1–41.

(14) Prof. de Meijere (Georg-August-Universität, Germany) has suggested to us that the ring expansion of **15** to **17** may proceed via a spiroaziridine intermediate:



An analogous intermediate can be proposed for the rearrangement of **16** to **18**.

(15) Wasserman, H. H.; Dion, R. P. *Tetrahedron Lett.* **1983**, *24*, 3409.

(16) (a) de Meijere, A.; Wessjohann, L. *Synlett* **1990**, 20. (b) Giller, K. Dissertation, Universität Hamburg, Germany, 1991.

(17) O'Donnell, M. J.; Polt, R. L. *J. Org. Chem.* **1982**, *47*, 2663.

by careful vacuum filtration through Celite. The Celite was then washed with MeOH (4 × 20 mL). The filtrate was concentrated, 1 M NaOH solution (30 mL) was added, and the mixture was extracted with EtOAc (4 × 15 mL). Combined organic extracts were dried over $MgSO_4$ and then concentrated. Flash chromatography of the resulting oil using EtOAc–MeOH (95:5) containing a gradient of concentrated NH_4OH (0–3%) gave (in variable proportions[10]) the following two compounds in a total yield of 2.67 g (88%).

4 as a pale yellow oil: R_f 0.16 (95:5:3 EtOAc–MeOH–NH_4OH); IR (film) 3321, 3386 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.33 (m, 2 H), 0.62 (m, 2 H), 1.66 (br s, 3 H), 2.46 (s, 2 H), 5.00 (s, 1 H), 7.15–7.63 (m, 10 H); ^{13}C NMR ($CDCl_3$) δ 12.5 (t), 41.4 (s), 46.8 (t), 64.3 (d), 126.7, 127.2, 128.2 (each d), 145.2 (s); MS (CI) m/e 253 (MH^+). A sample was treated with ethanolic HCl then evaporated to give the dihydrochloride. Anal. Calcd for $C_{17}H_{20}N_2 \cdot 2HCl$: C, 62.77; H, 6.82; N, 8.61. Found: C, 63.37; H, 6.88; N, 8.26.

8 as a pale yellow oil: R_f 0.48 (95:5:3 EtOAc–MeOH–NH_4OH); IR (film) 3357, 3310 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.38 (m, 2 H), 0.60 (m, 2 H), 1.80 (br s, 3 H), 2.52 (s, 2 H), 4.90 (s, 1 H), 7.18–7.50 (m, 10 H); ^{13}C NMR ($CDCl_3$) δ 12.6 (t), 33.8 (s), 57.0 (t), 66.8 (d), 126.6, 126.9, 128.1 (each d), 143.9 (s); MS (CI) m/e 253 (MH^+).

Method B. A solution of **3** (3.00 g, 12.2 mmol) in THF (40 mL) was added to a 1 M BH_3·THF solution (73 mL, 73 mmol) under a nitrogen atmosphere. The mixture was stirred at rt and monitored periodically by TLC for disappearance of starting material and intermediate **6a**. Reduction was complete after 24 h. The mixture was cooled to 0 °C, and 6 M HCl (30 mL) was added to destroy excess borane. The mixture was then made basic with 1 M NaOH solution and extracted with EtOAc (3 × 20 mL). Combined organic extracts were washed with water (2 × 15 mL) and brine (15 mL), dried over $MgSO_4$, and then concentrated. Flash chromatography as for method A gave 2.65 g (86%) of an inseparable mixture of **4** and **7a** in a ratio of approximately 85:15, respectively; for **7a** the following was deduced: R_f 0.14 (95:5:3 EtOAc–MeOH–NH_4OH); ^{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).

1-Amino-1-[[(diphenylmethylene)amino]methyl]cyclopropane (6b). A solution of **3** (2.02 g, 8.20 mmol) in toluene (40 mL) was added dropwise to a mixture of 1 M DIBALH–hexane solution (32.5 mL, 32.5 mmol) and toluene (60 mL) under a nitrogen atmosphere at −78 °C. The reaction was stirred at −78 °C for 7 h and then allowed to warm to rt. The evolution of the reaction was monitored by TLC to ensure that overreduction to the diamine **4** did not occur. After 12 h at rt the mixture was cooled to 0 °C and the reaction was quenched by slow addition of a saturated sodium tartrate solution buffered at pH 8.5 (80 mL). The solution was extracted with EtOAc (100 mL), saturated with NaCl, and extracted further with CH_2Cl_2 (2 × 35 mL). Combined organic extracts were washed with saturated tartrate solution (20 mL) and brine (2 × 20 mL), dried over $MgSO_4$, and concentrated to give **6b** as a pale yellow oil, 1.98 g (96%), used without further purification: R_f 0.67 (95:5:3 EtOAc–MeOH–NH_4OH); IR (film) 3381, 3310, 1624 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.47 (dd, 2 H, J = 4 and 6 Hz), 0.61 (dd, 2 H, J = 4 and 6 Hz), 2.05 (br s, 2 H), 3.32 (s, 2 H), 7.15–7.50 (m, 8 H), 7.68 (m, 2 H); ^{13}C NMR ($CDCl_3$) δ 12.8 (t), 35.5 (s), 62.8 (t), 126.9, 127.8, 128.1, 128.4, 128.6, 130.0 (each d), 137.0, 139.8, 168.7 (each s); MS (CI) m/e 251 (MH^+).

1-Amino-1-(aminomethyl)cyclopropane (1). Method A. A solution of **4**/**8** mixture (1.73 g, 6.85 mmol) in MeOH (60 mL) was treated with $Pd(OH)_2$–C catalyst (900 mg), and the mixture was subjected to Parr hydrogenation at 25 psi of overpressure for 24 h. The catalyst was removed by filtration through Celite, and the Celite was washed several times with MeOH. The filtrate was concentrated by slow distillation through a Vigreux column (20 cm). The residue, consisting of diphenylmethane, MeOH, and the diamine, was distilled at atmospheric pressure in a Kugelrohr apparatus, collecting the fraction boiling at 110–140 °C ot. The distillate was diamine **1** (ca. 75% yield overall from **3**) as a 50% solution in MeOH. Treatment with methanolic HCl gave the dihydrochloride: mp 234 °C (MeOH); IR (mull) 2500 br cm^{-1}; ^1H NMR (D_2O) δ 1.12 (m, 2 H), 1.21 (m, 2 H), 3.34 (s, 2 H); ^{13}C NMR (D_2O) δ 11.2 (t), 33.0 (s), 45.2 (t); MS (FAB-glycerol) m/e 87 (MH^+). Anal. Calcd for $C_4H_{10}N_2 \cdot 2HCl$: C, 30.20; H, 7.60; N, 17.61. Found: C, 30.16; H, 7.62; N, 17.81.

When this procedure was repeated using **4**/**7a** mixture, the product was obtained as a mixture of **1** and 1,2-diaminocyclobutane (combined yield ca. 70% overall from **3**) in methanol, from which pure **1**·2HCl was obtained by treatment with methanolic HCl and then double recrystallization from MeOH.

Method B. To a solution of **5** (250 mg, 2.11 mmol) in EtOH (40 mL) was added PtO_2 (53 mg) and then concentrated HCl (1.05 mL), and the mixture was subjected to Parr hydrogenation at 45 psi of overpressure for 24 h. The catalyst was removed by filtration through Celite, and the Celite was washed several times with MeOH. The filtrate was evaporated to dryness, and the residual white solid (330 mg) was dried in vacuo over P_2O_5. Recrystallization from MeOH gave the pure dihydrochloride salt, 262 mg (79%).

Method C. A mixture of unpurified **6b** [freshly prepared from **3** (480 mg, 1.95 mmol)], Et_2O (12 mL), and 1 M HCl (12 mL) was stirred at rt for 24 h. The aqueous phase was collected, washed with CH_2Cl_2 (3 × 7 mL), and evaporated to dryness, and the residual white solid (311 mg) was dried in vacuo over P_2O_5. Recrystallization from MeOH gave a first batch of pure dihydrochloride salt, 107 mg (35%); subsequent batches from the mother liquor were impure semisolids or separated as oils. Evaporation of the mother liquor and examination by NMR showed significant quantities of **1** mixed with benzophenone.

Standard Benzoylation Procedure. A solution of amine (or amine hydrochloride) and freshly-distilled triethylamine in CH_2Cl_2 (10 mL) was treated dropwise at 0 °C with benzoyl chloride under a nitrogen atmosphere. The reaction mixture was stirred at rt for the prescribed time and then filtered through a pad of silica, and the silica was washed with EtOAc. The filtrate was concentrated to give crude product.

1-(Benzamidomethyl)-1-[(diphenylmethyl)amino]cyclopropane (9). Reaction of **4** (600 mg, 2.38 mmol), triethylamine (0.40 mL, 2.87 mmol), and benzoyl chloride (0.29 mL, 2.50 mmol) during 5 h gave a crude product (840 mg) which after flash chromatography using EtOAc–cyclohexane (30:70) gave **9** (746 mg, 88%) as clear plates: R_f 0.47; mp 126 °C (EtOAc–petroleum ether); IR ($CHCl_3$ solution) 3438 m, 3318, 3276, 1645 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.61 (dd, 2 H, J = 6 and 11 Hz), 0.72 (dd, 2 H, J = 6 and 11 Hz), 1.77 (br s, 1 H), 3.27 (d, 2 H, J = 5.5 Hz), 5.06 (s, 1 H), 6.42 (m, 1 H), 7.18–7.32 (m, 6 H), 7.38–7.51 (m, 7 H), 7.67 (d, 2 H); ^{13}C NMR ($CDCl_3$) δ 13.5 (t), 39.8 (s), 45.3 (t), 65.0, 127.0, 127.3, 127.4, 128.6, 128.7, 131.4 (each d), 135.0, 145.0, 167.3 (each s); MS (CI) m/e 357 (MH^+). Anal. Calcd for $C_{24}H_{24}N_2O$: C, 80.87; H, 6.79; N, 7.86. Found: C, 80.42; H, 6.76; N, 7.74.

The above procedure was repeated using **4**/**7a** mixture as starting material to give (in addition to **9**) cyclobutane **7b** in about 25% of total yield: R_f 0.26; mp 124 °C (EtOAc–cyclohexane); IR ($CHCl_3$ solution) 3311, 1638 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.48 (m, 2 H), 1.85 (br s, 1 H), 2.11 (m, 1 H), 2.26 (m, 1 H), 3.15 (dd, 1 H, J = 7 and 16 Hz), 4.37 (ddd, 1 H, J = 7, 8, and 16 Hz), 5.08 (s, 1 H), 6.10 (d, 1 H, J = 8 Hz), 7.15–7.30 (m, 6 H), 7.38–7.55 (m, 7 H), 7.71 (d, 2 H); ^{13}C NMR ($CDCl_3$) δ 23.4 (t), 24.1 (t), 53.5, 60.2, 64.6, 127.0, 127.1, 127.3, 127.4, 128.5, 131.4 (each d), 134.6, 143.4, 144.2, 166.6 (each s); MS (CI) m/e 357 (MH^+). Anal. Calcd for $C_{24}H_{24}N_2O$: C, 80.87; H, 6.79; N, 7.86. Found: C, 81.12; H, 6.88; N, 7.92.

1-Benzamido-1-cyclopropanecarbonitrile (11). Reaction of **5** (500 mg, 4.22 mmol), triethylamine (1.30 mL, 9.28 mmol), and benzoyl chloride (0.51 mL, 4.43 mmol) at 0 °C for 5 h and then at rt for 12 h furnished a crude product (745 mg) which was recrystallized from EtOAc–petroleum ether to give fine needles, 601 mg (77%): R_f 0.30 (45:55 EtOAc–cyclohexane); mp 152–153 °C; IR ($CHCl_3$ solution) 3233 w, 2242 m, 1679 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.40 (dd fine structure, 2 H, J = 5 and 9 Hz), 1.63 (dd fine structure, 2 H, J = 5 and 9 Hz), 7.13 (br s, 1 H), 7.39–7.58 (m, 3 H), 7.79 (d, 2 H); ^{13}C NMR ($CDCl_3$) δ 17.0 (t), 21.0 (s), 120.2 (s), 127.3, 128.8, 132.6 (each d), 132.7 (s), 168.2 (s); MS (CI) m/e 187 (MH^+). Anal. Calcd for $C_{11}H_{10}N_2O$: C, 70.95; H, 5.41; N, 15.04. Found: C, 71.03; H, 5.50; N, 14.83.

1-Benzamido-1-[[(diphenylmethylene)amino]methyl]cyclopropane (13). Reaction of **6b** (860 mg, 3.43 mmol), triethylamine (0.58 mL, 4.16 mmol), and benzoyl chloride (0.44 mL, 3.79 mmol) during 10 h gave a sample of **13** (1.19 g, 98%) which was sufficiently pure for use without further purification. A recrystallized sample had the following physicochemical data: R_f

0.45 (50:50 EtOAc–cyclohexane); mp 153 °C (EtOAc–petroleum ether); IR ($CHCl_3$ solution) 3438, 3318, 1658, 1630 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.95 (m, 4 H), 3.60 (s, 2 H), 6.83 (br s, 1 H), 7.09 (m, 2 H), 7.30–7.52 (m, 9 H), 7.62 (dd, 2 H), 7.78 (dd, 2 H); ^{13}C NMR ($CDCl_3$) δ 12.3 (t), 34.9 (s), 58.6 (t), 127.0, 127.7, 128.2, 128.6, 130.1, 131.5 (each d), 135.1, 136.8, 139.6, 167.9, 169.4 (each s); MS (CI) *m/e* 355 (MH^+). Anal. Calcd for $C_{24}H_{22}N_2O$: C, 81.33; H, 6.26; N, 7.90. Found: C, 80.85; H, 6.21; N, 8.09.

1-Amino-1-(benzamidomethyl)cyclopropane (10). A solution of **9** (300 mg, 0.84 mmol) in MeOH (20 mL) was treated with $Pd(OH)_2$–C catalyst (100 mg) and the mixture subjected to Parr hydrogenation at 25 psi of overpressure for 24 h. The catalyst was removed by filtration through Celite, and the Celite was washed several times with MeOH. The filtrate was concentrated, and 1 M HCl (15 mL) was added. The resulting solution was washed with EtOAc (4 × 10 mL) and then lyophilized to leave the hydrochloride hemihydrate salt as a hygroscopic white solid (190 mg, 96%): mp 215 °C (MeOH–Et_2O); IR (mull) 3260, 1647 cm^{-1}; ^1H NMR (D_2O) δ 1.04 (m, 4 H), 3.64 (s, 2 H), 7.51 (t, 2 H), 7.59 (t, 1 H), 7.77 (d, 2 H); ^{13}C NMR (D_2O) δ 9.9 (t), 36.0 (s), 44.9 (t), 128.3, 129.9, 133.5 (each d), 134.0 (s), 172.8 (s); MS (CI) *m/e* 191 (MH^+). Anal. Calcd for $C_{11}H_{14}N_2O{\cdot}HCl{\cdot}0.5H_2O$: C, 56.05; H, 6.84; N, 11.88. Found: C, 56.37; H, 6.41; N, 11.34.

1-(Aminomethyl)-1-benzamidocyclopropane (12). Method A. To a solution of NaOH (80 mg, 2.00 mmol) in absolute EtOH (17 mL) was added **11** (187 mg, 1.00 mmol) and then Raney nickel (100 mg). The mixture was subjected to Parr hydrogenation at 50 psi of overpressure for 6 h. The catalyst was removed by careful vacuum filtration through Celite, and the Celite was washed with MeOH (4 × 10 mL). Concentrated HCl (3.2 mL) was added, the solvents were evaporated, and the residue was dried in vacuo over P_2O_5. The hydrated hydrochloride salt was crystallized from a $CHCl_3$ solution containing a minimum of MeOH by slow addition of Et_2O, giving clear plates (186 mg, 76%): mp 136–138 °C; IR (KBr) 3315, 1645 cm^{-1}; ^1H NMR (D_2O) δ 1.08 (s, 4 H), 3.23 (s, 2 H), 7.49 (t, 2 H), 7.60 (t, 1 H), 7.74 (d, 2 H); ^{13}C NMR (D_2O) δ 13.7 (t), 31.8 (s), 47.3 (t), 128.2, 129.8, 133.5 (each d), 134.0 (s), 173.5 (s); MS (CI) *m/e* 191 (MH^+). Anal. Calcd for $C_{11}H_{14}N_2O{\cdot}HCl{\cdot}H_2O$: C, 53.99; H, 7.00; N, 11.45. Found: C, 54.11; H, 6.63; N, 11.35.

Method B. A mixture of unpurified **13** (1.20 g, 3.39 mmol), Et_2O (15 mL), and 1 M HCl (25 mL) was stirred at rt for 18 h. The aqueous phase was collected, washed with Et_2O (3 × 10 mL), and then lyophilized to give a white solid (580 mg). The hydrated hydrochloride salt (428 mg, 52%) was obtained by crystallization as above.

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Synthesis of Bicyclo[2.2.1]heptane-2,3,5,6-tetracarboxylic 2,3:5,6-Dianhydrides

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Aromatic polyimides have been recently noted as high-performance polymers.[1] However, since their utilization has been limited by poor solubility in organic solvents,[2] we have studied the synthesis of aliphatic tetracarboxylic anhydrides with a bicyclic structure in order to enhance the solubility of the polyimides without degrading their thermal stability. Although Florey et al.[3] have reported the synthesis of tetramethyl bicyclo[2.2.1]heptane-2-*exo*,3-*endo*,5-*exo*,6-*endo*-tetracarboxylate, the synthetic route involved more than five steps. Moreover, it would be difficult to convert the tetramethyl ester into the desired dianhydride because of the trans configuration of the vicinal methoxycarbonyl groups. Palladium(0) and palladium(II) chloride are know to catalyze the bismethoxycarbonylation of alkenes and alkynes with carbon monoxide in the presence of CuCl or $CuCl_2$.[4-12] The present work relates the facile synthesis of two novel compounds, bicyclo[2.2.1]heptane-2-*endo*,3-*endo*,5-*exo*,6-*exo*-tetracarboxylic 2,3:5,6-dianhydride (**4**) and its *all-exo* isomer (**8**) from 2-*endo*,3-*endo*- and 2-*exo*,3-*exo*-anhydrides (**1** and **5**), respectively, by bismethoxycarbonylation of the double bond.

Results and Discussion

The synthetic route to the compounds is illustrated in Scheme I. Bismethoxycarbonylation of **1** with carbon monoxide in methanol afforded 2-*endo*,3-*endo*,5-*exo*,6-*exo*-tetracarboxylate **2** in the presence of catalytic amounts of 5% Pd/C and stoichiometric amounts of $CuCl_2$. James and Stille[10] reported that in the palladium(II)-catalyzed bismethoxycarbonylation of norbornene the two methoxycarbonyl groups were introduced with exo configuration to give the 2-*exo*,3-*exo*-dicarboxylate. The stereochemistry of the methoxycarbonyl groups introduced into **2** was shown to be C-5(*exo*) and C-6(*exo*) by their ^{13}C NMR carbon signals at 172.09 (*exo*-CO) and 173.43 (*endo*-CO). The tetracarboxylic acid **3** was prepared by the acid-catalyzed hydrolysis of **2**. Alternatively, base-catalyzed hydrolysis afforded a mixture of the stereoisomers, which was confirmed easily by ^{13}C NMR. The *exo*,*endo*-dianhydride **4** was synthesized by dehydration reaction of **3** with thionyl chloride. It was also prepared from **2** by a one-pot method without isolating **3**.

In a manner similar to that mentioned above, **8** was prepared by employing **5** as a starting material. The *all-exo* ester **6** was synthesized directly by the tetramethoxycarbonylation of norbornadiene (**9**) in the presence of 8 molar equiv of $CuCl_2$, although the yield was somewhat low (30%). Interestingly, thermal dehydration of **3**, at 200 °C for 2 h with removal of water under vacuum, afforded the *all-exo* dianhydride **8**. Isomerization of the two carboxyl groups at the C-2 and C-3 positions was considered to occur by heating, which was confirmed by the ^{13}C NMR spectrum in which only one signal (171.4 ppm) was observed in the carbonyl region. Studies on the preparation of polyimides from these dianhydrides and diamines will be reported elsewhere in the near future.

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