(m, 15 H, $P(CH_2CH_2CH_2CH_3)_3$, C(2′)CH_3), 1.70–1.80 (m, 1 H, C(4)*H*H′), 1.90–2.03 (m, 2 H, C(4)H*H*′, C(5)H), 2.12–2.32 (m, 6 H, $P(CH_2CH_2CH_2CH_3)_3$), 2.45–2.60 (m, 1 H, C(5a)*H*H′), 2.62–2.78 (m, 1 H, C(5a)H*H*′), 3.53 (d, 1 H, C(3′)*H*H′, J = 12.0 Hz), 3.52–3.62 (m, 1 H, C(3)*H*H′), 3.69 (d, 1 H, C(3′)H*H*′, J = 12.0 Hz), 3.86 (s, 1 H, C(1′)*H*), 3.90–4.00 (m, 1 H, C(3)H*H*′).

General Procedure for the Competition Experiments of 1 with Phosphorus- and Sulfur-Containing Nucleophiles in THF–H_2O (3:1) Mixtures. The reactions were carried out in THF–H_2O (3:1) mixtures (1.5 mL) containing **1**, **3**, and the sulfur-containing nucleophile (**9** or **11**). The "pH" of the solution was adjusted to 8 using aqueous dilute NaOH (or HCl) solutions. The solution was deaerated with Ar, capped, and stirred at rt. The solvents were removed in vacuo, and the residue was subjected to preparative TLC (20% MeOH–$CHCl_3$). The identities of these reaction products were verified by ^{1}H NMR analysis.

Reactions of 1, $(nBu)_3P$ (3), and EtSNa (9). Using **1** (10.0 mg, 0.03 mmol), **3** (30.3 mg, 0.15 mmol), and **9** (12.6 mg, 0.15 mmol) gave **12** (2.4 mg, 21%), **13** (1.6 mg, 14%), recovered **1** (2.8 mg, 28%), and an unidentified ethanethiolate–bicyclomycin adduct (1.2 mg) after 24 h. TLC analysis did not indicate the presence of **4** and **5**. The "pH" at the conclusion of the reaction was 9.6.

Bicyclomycin (1): R_f 0.40 (20% MeOH–$CHCl_3$); ^{1}H NMR (CD_3OD) δ 1.35 (s, 3 H, C(2′)CH_3), 2.60–2.68 (m, 2 H, C(4)H_2), 3.52 (d, 1 H, C(3′)*H*H′, J = 12.0 Hz), 3.68 (d, 1 H, C(3′)H*H*′, J = 12.0 Hz), 3.82–3.96 (m, 2 H, C(3)H_2), 4.10 (s, 1 H, C(1′)H), 5.16 (s, 1 H, C(5a)*H*H′), 5.58 (s, 1 H, C(5a)H*H*′).

Compound 12:[6a] R_f 0.85 (20% MeOH–$CHCl_3$); ^{1}H NMR (CD_3OD) δ 1.15 (s, 3 H, C(2′)CH_3), 1.24 (t, 3 H, CH_3CH_2S, J = 7.5 Hz), 1.91 (br d, 1 H, C(4)*H*H′, J = 14.1 Hz), 2.32 (dt, 1 H, C(4)H*H*′, J = 6.5, 14.1 Hz), 2.57 (q, 2 H, CH_3CH_2S, J = 7.5 Hz), 2.90 (d, 1 H, C(5a)*H*H′, J = 13.8 Hz), 3.02 (d, 1 H, C(5a)H*H*′, J = 13.8 Hz), 3.62 (d, 1 H, C(3′)*H*H′, J = 12.3 Hz), 3.72 (dt, 1 H, C(3)*H*H′, J = 2.1, 14.1 Hz), 3.90 (s, 1 H, C(1′)H), 3.97–4.10 (m, 2 H, C(3)H*H*′, C(3′)H*H*′).

Compound 13: R_f 0.55 (20% MeOH–$CHCl_3$); ^{1}H NMR (CD_3OD) δ 1.20, 1.22 (2 t, 3 H, CH_3CH_2S, J = 7.0 Hz), 1.34 (s, 3 H, C(2′)CH_3), 1.80–1.92 (m, 1 H, C(4)*H*H′), 2.20–2.30 (m, 1 H, C(4)H*H*′), 2.45–2.60 (m, 4 H, CH_3CH_2S, C(5a)*H*H′, C(5)H), 2.80–2.85 (m, 1 H, C(5a)H*H*′), 3.90–4.00 (m, 2 H, C(3)*H*H′, C(3′)*H*H′), 4.02–4.12 (m, 1 H, C(3)H*H*′), 4.36 (d, 1 H, C(3′)H*H*′, J = 9.0 Hz), 4.62, 4.63 (2 s, 1 H, C(1′)H).

Reaction of 1, $(nBu)_3P$ (3), and Et_2S (11). Employing **1** (10.0 mg, 0.033 mmol), **3** (13.4 mg, 0.066 mmol), and **11** (5.9 mg, 0.066 mmol) afforded **4** (1.8 mg, 13%) and **5** (1.0 mg, 17%) after 48 h. No other products were observed by TLC analysis. The "pH" at the conclusion of the reaction was 9.8.

Compound 4: R_f 0.55 (25% MeOH–$CHCl_3$); ^{1}H NMR (CD_3OD) δ 0.90–1.11 (m, 9 H, $P(CH_2CH_2CH_2CH_3)_3$), 1.38–1.65 (m, 14 H, $P(CH_2CH_2CH_2CH_3)_3$, OCH_2CH_2CH), 1.82–1.95 (m, 1 H, CH), 2.13–2.45 (m, 8 H, $P(CH_2CH_2CH_2CH_3)_3$, $CH_2P(nBu)_3$), 3.88–3.94 (m, 1 H, OC*H*H′), 4.00–4.09 (m, 1 H, OCH*H*′).

Compound 5:[7] R_f 0.40 (25% MeOH–$CHCl_3$); ^{1}H NMR (CD_3OD) δ 1.28 (s, 3 H, CH_3), 3.78–3.88 (m, 3 H, CH_2, C(OH)*H*).

Reaction of Bicyclomycin (1) with EtSNa (9). Bicyclomycin (**1**) (20.0 mg, 0.066 mmol) and EtSNa (**9**) (11.1 mg, 0.132 mmol) were dissolved in a THF–H_2O (3:1) mixture (2.5 mL). The "pH" of this solution was adjusted to 10 using a dilute aqueous HCl solution, deaerated with Ar, capped, and stirred at rt (48 h). The solvents were removed in vacuo, and the residue was separated by preparative TLC (20% MeOH–$CHCl_3$) to give unreacted **1** (7.1 mg (36%), R_f 0.40 (20% MeOH–$CHCl_3$)), **12**, **13**, and an unidentified ethanethiolate–bicyclomycin adduct (1.0 mg).

Compound 12:[6a] 5.2 mg (23%); R_f 0.85 (20% MeOH–$CHCl_3$); ^{1}H NMR (CD_3OD) δ 1.15 (s, 3 H, C(2′)CH_3), 1.24 (t, 3 H, CH_3CH_2S, J = 7.3 Hz), 1.90 (br d, 1 H, C(4)*H*H′, J = 14.0 Hz), 2.33 (dt, 1 H, C(4)H*H*′, J = 6.4, 14.0 Hz), 2.56 (q, 2 H, CH_3CH_2S, J = 7.3 Hz), 2.90 (d, 1 H, C(5a)*H*H′, J = 14.0 Hz), 3.01 (d, 1 H, C(5a)H*H*′, J = 14.0 Hz), 3.61 (d, 1 H, C(3′)*H*H′, J = 12.3 Hz), 3.76 (dt, 1 H, C(3)*H*H′, J = 2.0, 14.0 Hz), 3.90 (s, 1 H, C(1′)H), 4.03 (dd, 1 H, C(3)H*H*′, J = 6.4, 14.0 Hz), 4.05 (d, 1 H, C(3′)H*H*′, J = 12.3 Hz).

Compound 13: 2.8 mg (12%); R_f 0.55 (20% MeOH–$CHCl_3$); FT-IR (KBr) 1686 cm^{-1}; ^{1}H NMR (CD_3OD) δ 1.21, 1.22 (2 t, 3 H, CH_3CH_2S, J = 7.2 Hz), 1.32 (s, 3 H, C(2′)CH_3), 1.80–1.92 (m, 1 H, C(4)*H*H′), 2.20–2.32 (m, 1 H, C(4)H*H*′), 2.45–2.60 (m, 4 H, CH_3CH_2S, C(5a)*H*H′, C(5)H), 2.78–2.83 (m, 1 H, C(5a)H*H*′), 3.90–4.00 (m, 2 H, C(3)*H*H′, C(3′)*H*H′), 4.02–4.12 (m, 1 H, C(3)H*H*′), 4.35 (d, 1 H, C(3′)H*H*′, J = 9.0 Hz), 4.63 (s, 1 H, C(1′)H). ^{1}H NMR analysis indicated that the product existed as approximately a 1:1 diastereomeric mixture; the ^{1}H NMR assignments were verified by a COSY experiment: ^{1}H NMR (DMSO-d_6) δ 1.20–1.40 (m, 6 H, CH_3CH_2S, C(2′)CH_3), 1.80–1.95 (m, 1 H, C(4)*H*H′), 2.18–2.30 (m, 1 H, C(4)H*H*′), 2.50–2.65 (m, 4 H, CH_3CH_2S, C(5a)*H*H′, C(5)H), 2.70–2.80 (m, 1 H, C(5a)H*H*′), 3.80–3.95 (m, 2 H, C(3)*H*H′, C(3′)*H*H′), 4.00–4.10 (m, 1 H, C(3)H*H*′), 4.32 (d, 1 H, C(3′)H*H*′, J = 12.0 Hz), 4.55, 4.56 (2 s, 1 H, C(1′)H); ^{13}C NMR (CD_3OD) 15.06 (CH_3CH_2S), 21.15 (C(2′)CH_3), 26.96 (CH_3CH_2S), 31.46 (C(5a)), 68.73 (C(3)), 78.69 (C(1′)), 80.14 (C(2′)), 81.51 (C(3′)), 94.74 (C(1)), 103.38 (C(6)), 173.07 (C(7) or C(9)) ppm; the other carbonyl resonance was not observed, and the C(5) signal is believed to be beneath the solvent peak. Additional unassigned peaks detected at 31.53, 68.36, 78.08, 103.67, and 173.21 ppm may be attributable to the other diastereomer present in solution. ^{13}C NMR (DMSO-d_6) 14.58 (CH_3CH_2S), 20.86 (C(2′)CH_3), 25.32 (CH_3CH_2S), 29.97 (C(5a)), 45.93 (C(5)), 67.04 (C(3)), 77.20 (C(1′)), 78.74 (C(2′)), 78.99 (C(3′)), 92.40 (C(1)), 102.12 (C(6)), 169.65 (C(7) or C(9)), 170.46 (C(7) or C(9)) ppm. Additional unassigned peaks detected at 25.27, 30.07, 66.96, and 92.53 ppm may be attributable to the other diastereomer present in solution. MS (+FAB) 365 [M + 1]$^+$, 347 [M – H_2O + 1]$^+$; M_r (+FAB) 365.138 69 [M + 1]$^+$ (calcd for $C_{14}H_{25}N_2O_7S$ 365.138 25), 347.127 53 [M – H_2O + 1]$^+$ (calcd for $C_{14}H_{23}N_2O_6S$ 347.127 68). MS–MS (+FAB) indicated that the 347 ion emanated from the 365 ion.

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Supplementary Material Available: ^{1}H and ^{13}C NMR spectra for compounds **4**, **8**, and **13** (9 pages). This material is contained in many libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

An Enantioselective Synthesis of Vicinal Diamines

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Chiral C_2-symmetric vicinal diamines and their derivatives, notably the bisaldimines, constitute an important class of bidentate ligands having broad application as chiral auxiliaries in metal-induced asymmetric synthesis.[1] Traditionally, enantiomerically pure vicinal diamines have

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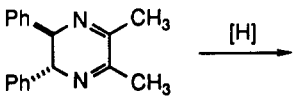
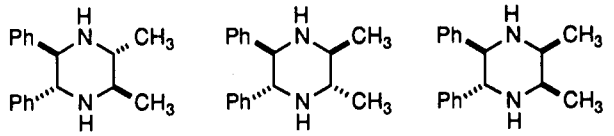
0022-3263/92/1957-6653$03.00/0

Scheme I



1a



2a 3a 4a

been obtained through optical resolution of diamine racemates which may be prepared using a number of synthetic methods.[2] The resolution process, however, is time consuming, often requiring repeated recrystallizations of the corresponding ammonium salts formed on treatment of the racemate with an optically active carboxylic acid such as mandelic or tartaric acid.[3] Asymmetric synthesis of vicinal diamines is an attractive alternative to resolution, yet few methods have been reported.[4] Recently, Sharpless[5] and Reetz[6] have described enantioselective approaches to vicinal diamines which proceed from enantiopure vicinal diols and amino acids, respectively. A limitation inherent to these approaches is the availability of the optically pure starting material. Thus, we have sought a flexible approach to 1,2-dialkyl-1,2-diamines from readily accessible *achiral* starting materials which may be converted into either diamine enantiomer.

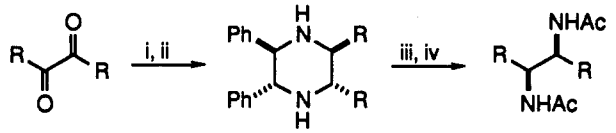
We report herein a general, self-immolative method for synthesis of enantiomerically pure C_2-symmetric vicinal diamines involving chirality transfer from a single chiral source, 1,2-diphenylethane-1,2-diamine (DPEDA). Hydride reduction of a chiral imine in which a stereogenic center is attached to nitrogen has been shown to occur with excellent diastereoselectivity to afford the chiral amine.[7] By analogy, we felt the diastereoselective reduction of a chiral 1,2-diimine might constitute a reasonable approach to chiral 1,2-diamines. DPEDA was chosen as our chiral diimine precursor (eq 1) on the basis of its availability[8] in

Table I. Diastereoselection in the Reduction of 1a

entry	reaction conditions	% yield[a] (3a + 4a)	ratio[b] 3a:4a
1	$NaBH_4$, MeOH, 25 °C	77	3:1
2	$NaBH_3CN$, PPTS[c], MeOH, 25 °C	72	9:1
3	$NaBH_3CN$, PPTS, MeOH, −20 °C	85	15:1
4	DIBAL, THF, −78 °C → 25 °C	51	2:1
5	$LiAlH_4$, THF, 40 °C	73	1:1
6	H_2, Pd-C 10%, EtOH	55	1:3
7	1:1 $LiAlH_4$-$AlMe_3$,[d] THF	71	1:33

[a] Isolated yield. [b] Determined by GC analysis (30 m × 0.25 mm, DB-5). [c] Pyridinium *p*-toluenesulfonate. [d] Reference 7.

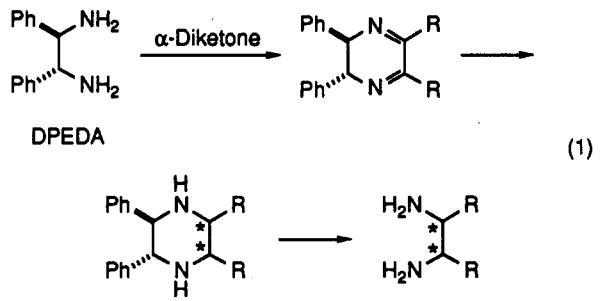
Scheme II



5a: R = CH_3 **3a-c** **6a-c**
b: R = $CH(CH_3)_2$
c: R = $CH_2CH(CH_3)_2$

(i) DPEDA, C_6H_6; (ii) $NaBH_3CN$, PPTS, MeOH; (iii) AcCl, Py.; (iv) Li°, NH_3.

either enantiomeric form and its necessary ability to undergo a double benzylic C–N bond cleavage once the new stereocenters (*) had been established. Excision of bibenzyl from a chiral piperazine formed on reduction of a DPEDA derived 1,2-diimine would liberate the chiral vicinal diamine.



DPEDA (1)

Initially, we evaluated the diastereoselectivity of the reduction process using 5,6-dimethyl-2,3-diphenyl-2,3-dihydropyrazine (**1a**) (Scheme I). A number of standard hydride conditions[9] were used to reduce **1a** followed by GLC analysis of the crude reaction mixtures. In all cases, only the same two products, **3a** and **4a**, of the three possible diastereomeric piperazines, **2a–4a**, were obtained. The unsymmetric piperazine **4a** was readily identified by examination of its ^1H NMR and ^{13}C NMR spectra. The spectral data for **3a** indicated a high degree of symmetry consistent with a C_2 axis of symmetry. It was anticipated that a preferential attack of the hydride reagents on the imine π faces opposite each of the trans-diequatorial phenyl group steric biases would favor the formation of piperazine **3a** over **2a**.[10] The assignment of **3a** as the

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Table II. Individual Yields for Transformations 5 → 3 and 3 → 6 (Scheme II) and Enantiomeric Excess of Bisacetamides 6

	starting materials		% yield[a]		bisacetamides 6a–c		
entry	R	DPEDA	5 → 3	3 → 6	$[\alpha]^{25}_D$,[b] deg	% ee[c]	confgn
a_1	Me	(+)-*R,R*	80	80	−54.8 (*c* 0.10)[d]	99	*S,S*
a_2	Me	(−)-*S,S*	84	83	+54.7 (*c* 0.098)[d]	99	*R,R*
b	iPr	(+)-*R,R*	82	82	−85.7 (*c* 0.78)	99	*S,S*
c	iBu	(+)-*R,R*	80	85	−116.9 (*c* 0.98)	98	*S,S*

[a] Chromatographed yield. [b] Taken in $CHCl_3$ unless otherwise indicated. [c] Determined by GC analysis (30 m × 0.25 mm, Chirasil-D-Valine). [d] Taken in butanone, maximum reported[16] value: $[\alpha]^{25}_D = -56.8°$ (*c* 0.0095).

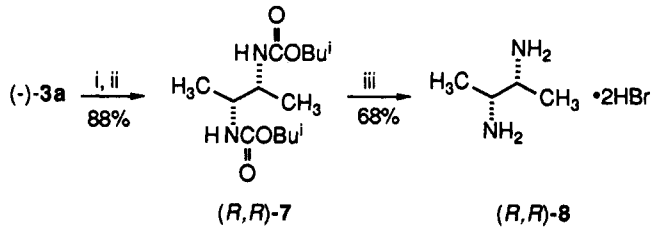
second diastereomeric product was supported by NOE measurements and by spectral comparison with similar piperazines for which X-ray crystallographic data had been obtained (vide infra).

The **3a**:**4a** selectivity in the reduction experiments was found to be highly dependent on the choice of reducing agent (Table I). Acid-catalyzed $NaBH_3CN$[11] reduction at −20 °C (entry 3) affords the diaxial reduction product, piperazine **3a**, with excellent selectivity. The minor diastereomer **4a**, a precursor to the *meso*-1,2-diamine, was separated from **3a** using silica gel chromatography. The preponderance of piperazine **3a** in entries 1–6 is consistent with models[10] for preferential axial reduction of unsaturation in cyclic systems. The reagent combination of $LiAlH_4$ and $AlMe_3$ in equimolar quantities (entry 7) reverses this trend to yield piperazine **4a** as the major diastereomer. Presumably, the axial preference in the delivery of the second hydride equivalent is diminished by the nitrogen·$AlMe_3$ complexation which results in pertubation of the imine π orbitals.[7] Consequently, the second hydride is delivered from the least hindered face to yield the *cis*-5,6-dialkyl product.

Having established a stereoselective route to 5,6-dialkyl-2,3-diphenylpiperazines, we next examined a number of conditions to selectively cleave the benzylic C–N bonds on piperazine **3a**. Hydrogenolysis using $Pd(OH)_2$-C[12] was sluggish and afforded only trace amounts of the diamine. However, a dissolving metal C–N cleavage[13] could be accomplished by prior activation of (+)-**3a** as the corresponding bisacetamide, then treatment with Li^0 in NH_3 liberated the diamine as its bisacetamide, (−)-**6a** (Scheme II), in 80% yield from **3a**.

Scheme II depicts a general approach to chiral C_2-symmetric bisacetamides from the symmetric α-dicarbonyl compounds **5a–c**. For those α-diketones not commercially available, an acyloin condensation and oxidation sequence was used to prepare the starting diones from the corresponding esters.[14] In practice, the crude, unpurified dihydropyrazines[15] derived from **5a–c** were reduced using the $NaBH_3CN$ conditions (Table I, entry 3). The resultant piperazines were purified by silica gel column chromatography followed by recrystallization. X-ray crystallographic analyses of the highly crystalline piperazines **3b** and **3c** confirmed the structural assignments. Treatment with AcCl yielded the corresponding bisacetamides which, without purification, were subjected to Li^0 in NH_3. Table II summarizes the transformations of the 1,2-diketones to the corresponding 1,2-bisacetamides. Entries a_1 and a_2 serve to exemplify the use of enantiomerically pure DPEDA to dictate the ultimate vicinal diamine stereochemical configuration. The optical purities of the bisacetamides were readily determined by direct chiral capillary GC analysis.

Scheme III



(i) ClC(O)OBu^i, Py.; (ii) Li^0, NH_3; (iii) 30% HBr, HOAc, 80°C

Hydrolysis of the bisacetamides **6a–c** to the corresponding vicinal diamines was attempted using a number of amide hydrolysis procedures.[17] However, the various base- and acid-catalyzed procedures did not result in a clean hydrolysis of the acetamide groups in **6a–c**. These results prompted us to prepare the biscarbamate derivative **7** from piperazine (−)-**3a** (Scheme III). Application of the same procedure described above for the cleavage of bibenzyl gave the biscarbamate **7** in 88% overall yield from **3a**. Subsequent treatment of **7** with 30% HBr in HOAc resulted in hydrolysis to afford the vicinal diamine as its bishydrobromide salt **8** in 68% yield (99% ee,[18] $[\alpha]_D$ +8.2° (H_2O, *c* 1.4)). In summary, a method for the conversion of a 1,2-diketone to the corresponding enantiomerically enriched 1,2-diamine has been demonstrated.

Experimental Section

General. NMR spectra were recorded (^1H at 300 MHz and ^{13}C at 75 MHz) using tetramethylsilane as the internal standard. Optical rotations were recorded at 589 nm. Melting points are uncorrected. Gas chromatographic analyses were performed with a capillary column (30 m × 0.25 mm, DB-5). Flash column chromatography was carried out on silica gel 60 (230–400 mesh) purchased from EM Science. Sodium cyanoborohydride, pyridinium *p*-toluenesulfonate, and 2,3-butanedione were purchased from Aldrich Chemical Co. and used without further purification. DPEDA was prepared using the method of Corey.[8b] DPEDA optical resolution was accomplished by the formation and re-

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(15) During the course of this work it was noted that prolonged exposure of the crude dihydropyrazines to temperatures in excess of 80 °C resulted in formation of the corresponding pyrazines. Similar aromatization reactions had been previously documented; see, for example: Baliah, V.; Pandiarajan, K. *Indian J. Chem.* **1978**, *Vol. 16B*, 73 and references therein.

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(18) A small quantity of the dihydrobromide salt **8** was converted to bisacetamide **6a** by treatment with AcCl. The optical purity of **6a** derived from **8** was determined via GC analysis using a Chirasil-D-Valine fused silica capillary column.

crystallization of the mandelic acid–DPEDA salts as described by Saigo.[8c]

Preparation of Substrates. General Procedure for the Formation of Piperazines 3. A solution of DPEDA (500 mg, 2.36 mmol) and α-diketone (2.40 mmol) in benzene (125 mL) was heated to reflux under a Dean–Stark trap. After 12 h the solvent was removed in vacuo to yield the crude dihydropyrazine which was immediately reduced.

Pyridinium *p*-toluenesulfonate (1.18 g, 4.71 mmol) was added in one portion to a solution of the crude dihydropyrazine (2.36 mmol) and $NaBH_3CN$ (312 mg, 4.71 mmol) in MeOH (30.0 mL) at −30 °C. The reaction mixture was subsequently warmed to −20 °C. After stirring for 2 h at −20 °C, the reaction mixture was quenched by the addition of saturated aqueous $NaHCO_3$ and extracted (3×) with Et_2O. The combined organic layer was washed successively with saturated aqueous $NaHCO_3$ and brine and then dried over KOH pellets. Removal of the solvent by rotary evaporation afforded the crude product which was purified by SiO_2 chromatography.

(+)-(2*R*,3*R*,5*S*,6*S*)-5,6-Dimethyl-2,3-diphenylpiperazine [(+)-3a]: mp 100–101 °C; $[\alpha]^{25}_D$ + 111.5° (*c* 1.03, $CHCl_3$); IR ($CHCl_3$) 3088, 3066, 3033, 3010, 2963, 2932, 2827 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.13 (m, 5 H), 3.82 (s, 1 H), 2.73 (m, 1 H), 1.81 (br s, NH), 1.15 (d, *J* = 5.7 Hz, 3 H); ^{13}C NMR ($CDCl_3$) δ 141.5, 128.0, 127.7, 127.0, 68.5, 58.1, 19.0; HRMS M + 1 observed 267.1861, M + 1 calculated 267.1861.

(−)-(2*S*,3*S*,5*R*,6*R*)-5,6-Dimethyl-2,3-diphenylpiperazine [(−)-3a]: mp 99–100 °C; $[\alpha]^{25}_D$ −109.4° (*c* 0.265, $CHCl_3$); HRMS M + 1 observed 267.1865, M + 1 calculated 267.1861.

(+)-(2*R*,3*R*,5*S*,6*S*)-5,6-Bis(2-methylethyl)-2,3-diphenylpiperazine [(+)-3b]: mp 166–167 °C; $[\alpha]^{25}_D$ +82.2° (*c* 0.044, $CHCl_3$); IR ($CHCl_3$) 3088, 3065, 3030, 2961, 2930, 2872, 2830 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.04–7.19 (m, 5 H), 3.62 (s, 1 H), 2.73 (s, 1 H), 2.05 (m, 1 H), 1.55 (br s, NH), 1.00 (d, *J* = 6.8 Hz, 3 H), 0.95 (d, *J* = 7.0 Hz, 3 H); ^{13}C NMR ($CDCl_3$) δ 142.4, 128.2, 127.5, 126.9, 68.6, 62.3, 27.2, 20.7, 15.3; HRMS M + 1 observed 323.2490, M + 1 calculated 323.2487.

(+)-(2*R*,3*R*,5*S*,6*S*)-5,6-Bis(2-methylpropyl)-2,3-diphenylpiperazine [(+)-3c]: mp 143–144.5 °C; $[\alpha]^{25}_D$ +1.1° (*c*, 0.295, $CHCl_3$); IR ($CHCl_3$) 3090, 3065, 3030, 2957, 2928, 2883, 2820 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.11 (br s, 5 H), 3.74 (s, 1 H), 2.68 (m, 1 H), 1.70–2.00 (br s, NH), 1.58–1.74 (m, 1 H), 1.22–1.46 (m, 2 H), 0.94 (d, *J* = 6.5 Hz, 3 H), 0.89 (d, *J* = 6.5 Hz, 3 H); ^{13}C NMR ($CDCl_3$) δ 141.7, 128.1, 127.7, 127.0, 68.4, 59.2, 41.3, 24.3, 24.2, 21.4; HRMS M + 1 observed 351.2782, M + 1 calculated 351.2800.

General Procedure for the Formation of Bisacetamides 6. Acetyl chloride (0.31 mL, 4.36 mmol) was added dropwise to a solution of the piperazine **3** (1.71 mmol) and triethylamine (0.48 mL, 3.44 mmol) in CH_2Cl_2 (10 mL) at 0 °C. The reaction mixture was warmed to room temperature and stirred overnight. The reaction mixture was quenched by addition of saturated aqueous $NaHCO_3$ (5.0 mL) and extracted (3×) with Et_2O. The combined organic layer was washed successively with saturated aqueous $NaHCO_3$ and brine and dried over sodium sulfate. The solvent was removed in vacuo to afford the corresponding piperazine bisacetamide which was suitable for subsequent reactions and was reduced without further purification.

Ammonia was condensed (10 mL) in a three-neck flask fitted with a dry ice–acetone condenser and cooled to −78 °C. Li^0 wire (0.026 g, 3.78 mmol) was added to the ammonia, and the reaction mixture was stirred until all the Li^0 had dissolved. To the resultant deep blue solution was added dropwise a solution of the crude piperazine bisacetamide (0.85 mmol) in THF (10.0 mL). The reaction mixture was warmed to the reflux temperature and stirred. After 4 h, the reaction mixture was recooled to −78 °C and quenched by addition of MeOH (1.0 mL) followed by addition of $CHCl_3$ (5.0 mL). The ammonia was allowed to evaporate, and the remaining solution was filtered to remove all solids. The filtrate was concentrated, and the residue was purified by SiO_2 chromatography.

(−)-(2*S*,3*S*)-2,3-Diacetamidobutane [(−)-6a]: mp 203–204 °C (lit.[16] mp 199.3–199.7 °C); $[\alpha]^{25}_D$ −54.8° (*c* 0.10, butanone) [lit.[16] $[\alpha]^{25}_D$ −56.8° (*c* 0.0095, butanone)]; IR ($CHCl_3$) 3436, 3006, 2935, 1663, 1522, 1456, 1374, 1216, 1213 cm^{-1}; ^1H NMR ($CDCl_3$) δ 6.22 (br s, 1 H, NH), 3.81 (m, 1 H), 1.93 (s, 3 H), 1.16 (d, *J* = 6.1 Hz, 3 H); ^{13}C NMR ($CDCl_3$) δ 170.6, 51.0, 23.3, 18.3; HRMS, M + 1 observed 173.1290, M + 1 calculated 173.1290.

(+)-(2*R*,3*R*)-2,3-Diacetamidobutane [(+)-6a]: mp 203.7–204.3 °C; $[\alpha]^{25}_D$ +54.7° (*c* 0.098, butanone); HRMS M + 1 observed 173.1278, M + 1 calculated 173.1290.

(−)-(3*S*,4*S*)-2,5-Dimethyl-3,4-diacetamidohexane [(−)-6b]: mp 200–201 °C; $[\alpha]^{25}_D$ −85.7° (*c* 0.775, $CHCl_3$); IR ($CHCl_3$) 3434, 3006, 2968, 1668, 1519, 1373 cm^{-1}; ^1H NMR ($CDCl_3$) δ 6.44 (d, *J* = 8.6 Hz, 1 H, NH), 3.81 (m, 1 H), 1.92 (s, 3 H), 1.73–1.88 (m, 1 H), 0.88 (d, *J* = 6.7 Hz, 3 H), 0.85 (d, *J* = 6.8 Hz, 3 H); ^{13}C NMR ($CDCl_3$) δ 171.5, 56.4, 28.9, 23.6, 20.8, 17.0; HRMS M + 1 observed 229.1925, M + 1 calculated 229.1916.

(−)-(4*S*,5*S*)-2,7-Dimethyl-4,5-diacetamidooctane [(−)-6c]: mp 153–154 °C; $[\alpha]^{25}_D$ −116.9° (*c* 0.975, $CHCl_3$); IR ($CHCl_3$) 3431, 3006, 2961, 1667, 1372 cm^{-1}; ^1H NMR ($CDCl_3$) δ 6.45 (d, *J* = 8.4 Hz, 2 H, NH), 3.81 (m, 2 H), 1.89 (s, 3 H), 1.51–1.68 (m, 2 H), 1.18–1.38 (m, 4 H), 0.98 (d, *J* = 6.6 Hz, 6 H), 0.97 (d, *J* = 6.4 Hz, 6 H); ^{13}C NMR ($CDCl_3$) δ 170.6, 52.1, 41.6, 25.0, 23.5, 23.0, 21.7; HRMS M + 1 observed 257.2231, M + 1 calculated 257.2229.

(+)-(2*R*,3*R*)-*N*,*N*′-Bis[[(2-methylpropyl)oxy]carbonyl]-2,3-diaminobutane [(+)-7]. Isobutyl chloroformate (3.10 mL, 24.0 mmol) was added dropwise to a solution of (−)-**3a** (1.60 g, 6.00 mmol) in pyridine (15.0 mL) and CH_2Cl_2 (25.0 mL) at 0 °C. The reaction mixture was heated at reflux temperature for 40 min. The reaction mixture was then cooled to 0 °C and quenched by the addition of saturated aqueous NH_4Cl and followed by extraction of the resultant mixture with Et_2O (3×). The combined organic layer was washed successively with saturated aqueous NH_4Cl (2×), saturated aqueous $NaHCO_3$, and brine and dried over sodium sulfate. The solvent was removed in vacuo, and the residue was flashed through a short column of SiO_2, eluting with a 4:1 mixture of hexane/ethyl acetate, to give 2.54 g of the corresponding biscarbamate which was directly reduced without further purification.

Ammonia was condensed (50 mL) in a three-neck flask fitted with a dry ice–acetone condenser and cooled to −78 °C. Li^0 wire (0.207 g, 30.0 mmol) was added portionwise to the ammonia, and the reaction mixture was stirred until all the Li^0 had dissolved. To the resultant deep blue solution was added dropwise a solution of the piperazine biscarbamate (2.54 g, 5.44 mmol) in THF (40.0 mL). The reaction mixture was warmed to reflux temperature and stirred. After 2 h, the reaction mixture was recooled to −78 °C and quenched by addition of MeOH (1.0 mL) followed by addition of $CHCl_3$ (5.0 mL). The ammonia was allowed to evaporate, and the remaining solution was concentrated to afford the crude product which was purified by SiO_2 chromatography, eluting with a 4:1 mixture of hexane/ethyl acetate, to give 1.39 g (88%) of (+)-**7** as a crystalline white solid: mp 83.5–84.5 °C; $[\alpha]^{25}_D$ +32.25° (*c* 0.95, $CHCl_3$); IR ($CHCl_3$) 3350, 2980, 1705, 1530, 1465, 1425, 1390, 1340, 1250, 1095, 1050, 1028 cm^{-1}; ^1H NMR ($CDCl_3$) δ 4.87 (br s, 1 H, NH), 3.81 (d, *J* = 5.7 Hz, 2 H), 3.61 (m, 1 H), 1.88 (m, 1 H), 1.17 (d, *J* = 6.3 Hz, 3 H), 0.90 (d, *J* = 6.6 Hz, 6 H); ^{13}C NMR ($CDCl_3$) δ 157.0, 71.0, 52.0, 28.8, 19.0, 18.8; HRMS M + 1 observed 289.2141, M + 1 calculated 289.2127.

(+)-(2*R*,3*R*)-2,3-Diaminobutane Dihydrobromide [(+)-8]. A pressure tube (Ace, cat. no. 8648-41) was charged with biscarbamate (+)-**7** (0.20 g, 0.69 mmol) and a solution of 30% HBr in acetic acid (1.15 mL). The tube was flushed with a stream of Ar, sealed, and then submersed in an oil bath heated to 85 °C. After 12 h at 85 °C, the tube was cooled to 0 °C and opened. The precipitated crystals were collected by filtration under inert atmosphere (Ar) and dried under vacuum to afford 111 mg of (+)-**8**. An additional 6 mg of (+)-**8** crystallized from the filtrate on standing overnight: mp 288.4–290.8 °C; $[\alpha]^{25}_D$ +8.17° (*c* 1.425, H_2O); ^1H NMR (D_2O) δ 3.76 (m, 1 H), 1.37 (d, *J* = 6.5 Hz, 3 H); ^{13}C NMR (D_2O, DMSO) δ 50.1, 13.9; HRMS M + 1 observed 248.9612, M + 1 calculated 248.9603.

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Supplementary Material Available: ^{13}C NMR spectra of **3a–c**, **6a–c**, **7**, and **8** and details for bisacetamide optical purity

determination (9 pages). This material is contained in many libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

The Synthesis of Cerpegin

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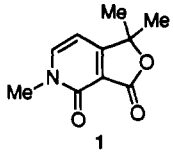
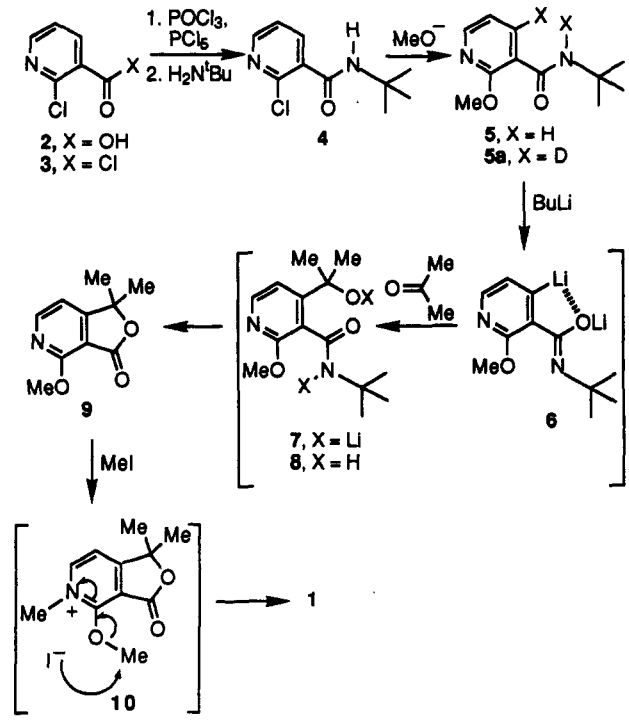
The structure of the pyridone alkaloid cerpegin was recently established as **1**.[1] Apart from some metabolites of pyridoxal,[2] to our knowledge cerpegin is the only naturally occurring example of the bicyclic furo[3,4-*c*]pyridine ring system. Because of the novelty of its structure and our continuing interest in the synthesis of pyridine-containing natural products,[3] we undertook the synthesis of **1**. We now report the first synthesis of cerpegin; the synthesis uses a reaction sequence that requires only about five steps from commercially available starting materials.



1

Thus (Scheme I) 2-chloronicotinic acid (**2**) was converted to its *tert*-butyl amide **4** via the acid chloride **3**.[4] Replacement[5] of the chloride by methoxide then afforded methoxy amide **5**. It had been our hope that **5** could be ortho lithiated[6] to give **6** and that **6** could be condensed with acetone to introduce the dimethylcarbinol side chain. Attempts to achieve that end in tetrahydrofuran using *n*-BuLi for ortho metalation followed by addition of acetone led only to recovery of starting material **5** after workup. In order to establish whether the absence of apparent reaction was due to a failure to ortho metalate **5** or to the quenching of **6** by proton transfer from the acetone, the putative **6** was quenched with D_2O; the deuterated derivative **5a** was isolated in high yield. Evidently, the problem was not in the ortho metalation step but in the quenching of anion **6** by proton transfer from acetone. Buhler[7] had previously established that in the reaction of alkyllithiums with ketones, enolization is diminished by using ether instead of THF as the reaction solvent. Accordingly, we attempted the preparation and reaction of **6** in ether rather than THF. Although some **5** was still

Scheme I



recovered, substantial amounts of **8** and **9** were produced. In the optimized procedure the crude product mixture is treated with acid prior to purification to complete the conversion of **8** to **9**. The overall isolated yield of **9** from **5** is 35%. That the recovery of **5** is due to quenching of **6** rather than incomplete metalation was shown, as before, by monitoring the progress of the metalation by quenching small aliquots of the reaction mixture with D_2O.

With a route to **9** in hand, it remained only to transpose the methyl group from the oxygen to the nitrogen to complete the synthesis. That manipulation was accomplished cleanly by heating a solution of **9** in CH_3I at 140 °C in a sealed tube. The conversion presumably proceeds via **10**.[8] The **1** so produced is identical by direct comparison (including mixed melting point) to a sample of naturally derived cerpegin.

Experimental Section[9]

***N*-*tert*-Butyl-2-chloronicotinamide (4).** 2-Chloronicotinic acid (5.00 g, 31.7 mmol) and PCl_5 (7.28 g, 34.9 mmol) were vigorously stirred in $POCl_3$ (25 mL) at 0 °C under N_2 for 30 min. The mixture was allowed to warm to room temperature and was then heated at reflux with stirring for 60 min during which time a clear solution resulted. The solution was allowed to cool to ambient temperature, and the volatiles were removed in vacuo. The resultant, resinous residue (crude **3**[4]) was cooled to 0 °C, and neat *tert*-butylamine (20 mL, 0.19 mol) was added dropwise over a period of approximately 15 min with vigorous stirring. The suspension was warmed to ambient temperature and then heated at reflux for 30 min. The reaction mixture was cooled to ambient temperature, water (25 mL) was added, and the mixture was partitioned between $CHCl_3$ and water. The aqueous phase was removed and extracted twice with $CHCl_3$. The organic phases were combined, washed with brine, dried over $MgSO_4$, and concentrated to dryness in vacuo to give a yellow solid. Recrystallization was achieved by heating the solid on a steam bath with

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