Tandem Reductive Alkylation−Cyclization for the Preparation of Unsymmetrical 1,4-Disubstituted 2,3-Diketopiperazines

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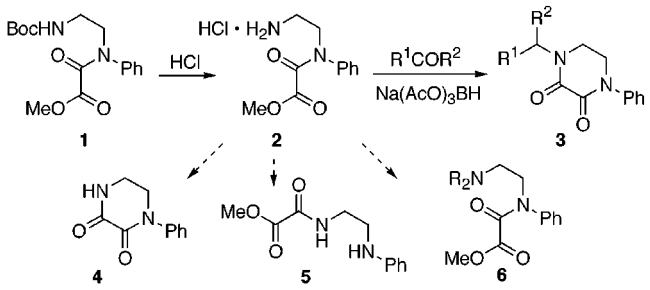
Derivatives of piperazine have found wide use in medicinal chemistry as molecular scaffolds for the positioning of substituents in biologically active molecules.[1] During the course of an ongoing drug discovery project, we required a general method for the preparation of unsymmetrical 1,4-disubstituted 2,3-diketopiperazines. While the Riebsomer condensation of a 1,2-diamine with dialkyl oxalate is frequently employed,[2] it generally requires elevated reaction temperature as well as prior construction of the appropriate *N,N′*-disubstituted 1,2-diamine. We felt that a more flexible approach, featuring simultaneous amine derivatization and ring construction, would enable the more efficient synthesis of 1,4-disubstituted analogues. Here, we describe a modified protocol (Scheme 1) involving the conversion of protected *N*-(2-aminoethyl)oxamates (e.g., **1**) to stable amine salts (e.g., **2**), followed by tandem reductive amination and cyclization to provide 1,4-disubstituted 2,3-diketopiperazines **3**. This coupling reaction enables the rapid convergent synthesis of a diverse array of adducts from readily available monoalkylethylenediamine derivatives and aldehydes or ketones.

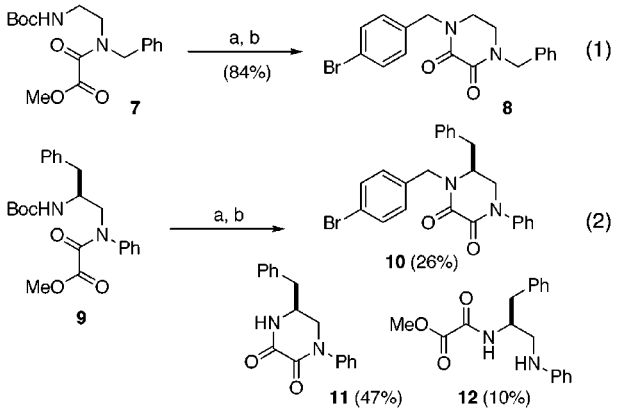
The performance of this reaction was first explored using the protected amine **1**, available in a single step from 1-phenylethylenediamine.[3] Reductive coupling of the derived amine salt **2** with benzaldehyde using sodium triacetoxyborohydride and molecular sieves cleanly provided product **3a** within several hours in 72% isolated yield (Table 1, entry 1). At the outset of these studies, it seemed plausible that under the mildly acidic reaction conditions the amine **2** could undergo either competitive cyclization to give **4** or acyl transfer to produce **5**.[4,5] Gratifyingly, these side reactions were largely precluded

Scheme 1



in the presence of most aldehydes and ketones.[6] Substituted benzaldehydes (entries 2−5) were efficiently converted to the corresponding *N*-benzyl-2,3-diketopiperazines (**3b**−**e**) regardless of their electronic nature (cf. entries 1−3) or steric environment (entries 4 vs 5). Additionally, 2,3-diketopiperazines were prepared from cinnamaldehyde (**3f**) and aliphatic aldehydes (**3g**−**i**). While the less hindered aldehydes also underwent bisalkylation to produce acyclic oxamate byproducts **6** as minor components (entries 6 and 7), the branched aldehydes performed more smoothly (entries 8 and 9). Reactions with ketones were more sensitive; although acetophenone failed to react, enabling the predominant formation of byproducts **4** and **5** (entry 10), the cyclic *N*-Boc-4-piperidone led to **3k** in high yield (entry 11).

Other *N*-(2-aminoethyl)oxamates were evaluated to further probe the utility of the transformation. Modification of the nitrogen substituent from phenyl in **1** to benzyl in **7** was well tolerated, leading to 2,3-diketopiperazine **8** in good yield (eq 1). Thus, the amide *cis*−*trans* conformational mobility has little influence on the course of the reaction.[7] Installation of a substituent on the aminoethyl chain (e.g., **9**) reduces the efficiency of the reductive amination−cyclization sequence (eq 2). Although the desired product was obtained (**10**, 26%), a combination of premature cyclization (**11**) and acyl migration (**12**) preceded reductive amination, possibly by virtue of the Thorpe−Ingold effect.[8]



(a) HCl, EtOAc, 0 °C; (b) 4-Br-C_6H_4CHO, $Na(AcO)_3BH$, $ClCH_2CH_2Cl$, 4 Å molecular sieves, 0 °C to rt, ca. 10 h.

In none of the examples herein was the accumulation of an intermediate secondary amine observed. Further-

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(1)) Giannis, A.; Kolter, T. *Angew, Chem., Int. Ed. Engl.* **1993**, *32*, 1244−1267.

(2) (a) Riebsomer, J. L. *J. Org. Chem.* **1950**, *15*, 68−73. (b) Hori, T.; Yoshida, C.; Murakami, S.; Takeno, R.; Nakano, J.; Nitta, J.; Tsuda, H.; Kishimoto, S.; Saikawa, I. *Chem. Pharm. Bull.* **1981**, *29*, 684−698. (c) Mueller-Westerhoff, U.; Zhou, M. *J. Org. Chem.* **1994**, *59*, 4988−4992.

(3) Substituted 1-arylethylenediamines are also readily prepared. See: Poindexter, G. S.; Owens, D. A.; Dolan, P. L.; Woo, E. *J. Org. Chem.* **1992**, *57*, 6257−6265.

(4) Base treatment of the amine·HCl **2** (e.g., $Et_3N/CDCl_3$ or EtOAc/aqueous $NaHCO_3$) resulted in immediate (<3 min) cyclization to give 2,3-diketopiperazine **4**.

(5) For intramolecular cyclizations of oxamides: (a) N-Acylation: Lewis, R. T.; Macleod, A. M.; Merchant, K. J.; Kelleher, F.; Sanderson, I.; Herbert, R. H.; Cascieri, M. A.; Sadowski, S.; Ball, R. G.; Hoogsteen, K. *J. Med. Chem.* **1995**, *38*, 923−933. (b) *C*-Acylation: Southwick, P. L.; Fitzgerald, J. A.; Madhav, R.; Welsh, D. A. *J. Org. Chem.* **1969**, *34*, 3279−3285. (c) Harada, T.; Morimoto, M.; Nagasawa, M.; Inoue, H.; Ohishi, T.; Takeda, M.; Takamura, N. *Chem. Pharm. Bull.* **1992**, *40*, 1986−1989.

(6) In most cases, reactions in Table 1 also produced minor amounts of **4** and **5** in up to 10% yields, as judged by HPLC and ^1H NMR analyses.

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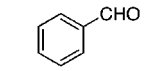
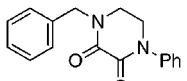
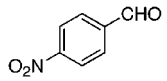
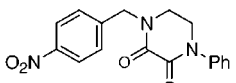
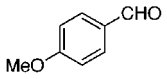
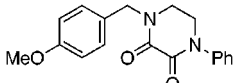
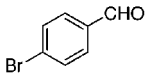
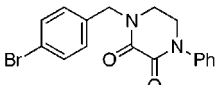
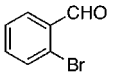
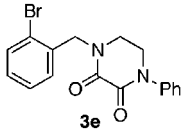
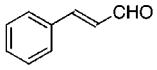
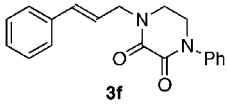
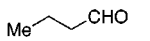
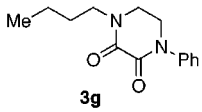
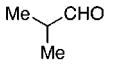
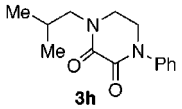
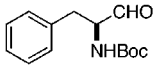
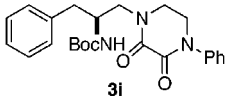
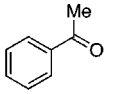
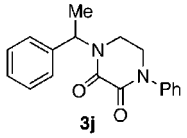
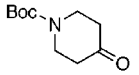
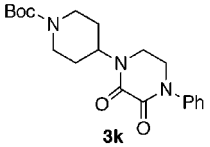
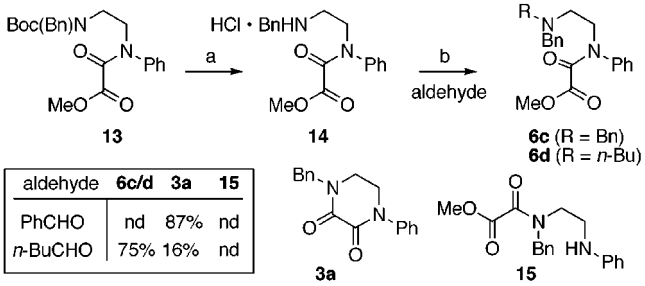
Table 1. Reductive Amination-cyclization of Amine 2 with Aldehydes and Ketones to Give 2,3-diketopiperazines 3[a]

entry	aldehyde/ketone	product	yield (%)[b]
1		 **3a**	72
2		 **3b**	72
3		 **3c**	61
4		 **3d**	72
5		 **3e**	62
6		 **3f**	20[c]
7		 **3g**	43[d]
8		 **3h**	78
9		 **3i**	60
10		 **3j**	0[e]
11		 **3k**	90

[a] See ref 6. All reactions were carried out on 1.5 mmol scale using 2 equiv of $Na(AcO)_3BH$, 1.1 equiv of aldehyde or ketone, and 4 Å powdered sieves at 0 °C→rt as described in the Experimental Section. [b] Purified yield based on **1**→**3**. [c] The byproduct **6a** (R = cinnamyl) was also islolated in 35% yield. [d] The byproduct **6b** (R = *n*-Bu) was also islolated in 16% yield. [e] HPLC analysis indicated complete conversion of **2** to approximately equal amounts of **4** and **5**. Although **4** was lost in the aqueous workup, **5** was isolated in 37% yield.

more, products derived from acyl transfer from such an intermediate were not detected, and only unhindered aldehydes produced tertiary amine byproducts **6** emanating from a second reductive amination. This suggests that intramolecular cyclization of the putative secondary amine is fast relative to competing transformations. To explore this further, an example of such an entity (**14**) was prepared for study (Scheme 2).

Scheme 2[a]



aldehyde	6c/d	3a	15
PhCHO	nd	87%	nd
n-BuCHO	75%	16%	nd

[a] (a) HCl, EtOAc, 0 °C; (b) RCHO, $Na(AcO)_3BH$, $ClCH_2CH_2Cl$, 4 Å molecular sieves, 0 °C to rt, 1 h; nd = not detected.

Compound **13**, available from the hydrolysis and refunctionalization of **3a**, was deprotected to provide the corresponding stable HCl salt **14**. An initial control experiment demonstrated that when an equimolar mixture of **2** and **14** was stirred with 4 Å powdered sieves, cyclization and acyl transfer (**2** → **4** + **5** and **14** → **3a**) occurred at similar rates over the course of several hours.[9a,b] The same transformations were much more rapid in the presence of $Na(AcO)_3BH$, suggesting that $Na(AcO)_3BH$ contributes to accelerating the cyclizations of **2** and **14**.[9c] Second, exposure of **14** to the reductive amination conditions in the presence of benzaldehyde provided **3a** in less than 1 h as the sole product, which was isolated in 87% yield (Scheme 2). None of **6c** or **15** was detected, indicating rapid cyclization. Third, the same experiment with butyraldehyde produced a mixture of **3a** and **6d**, reflecting the enhanced susceptibility of the secondary amine in **14** to a second reductive alkylation in cases of more reactive aldehydes (e.g., Table 1, entries 6 and 7).

The tandem reductive coupling−cyclization provides convenient access to a diverse array of 1,4-disubstituted 2,3-diketopiperazines in convergent fashion. The mild reaction conditions employed and the wide availablity of aldehydes and ketones are attractive features. Aromatic aldehydes, branched aliphatic aldehydes, and cyclic ketones were the most successful substrates for the transformation. Application of this methodology to the preparation of biologically active molecules will be described elsewhere.

Experimental Section

Methyl *N*-[2-(*tert*-Butoxycarbonylamino)ethyl]-*N*-(phenyl)oxamate (1). To a solution of 1-phenylethylenediamine (10.0 mL, 70.5 mmol) in 120 mL of CH_2Cl_2 at 0 °C was added di-*tert*-butyl dicarbonate (15.4 g, 70.5 mmol). After 4 h, triethyl-

(7) Analysis of the ^1H NMR spectra of oxamates **1** and **6** (23 °C, $CDCl_3$) indicates conformational homogeneity for **1**, but a 45:55 mixture for **6**. The *cis*-amide preference in amides of *N*-alkylanilines (cf. **1**) is well-known: Saito, S.; Toriumi, Y.; Tomioka, N.; Itai, A. *J. Org. Chem.* **1995**, *60*, 4715−4720 and references therein.

(8) Detar, D. F.; Luthra, N. P. *J. Am. Chem. Soc.* **1980**, *102*, 4505−4512.

(9) (a) The use of molecular sieves as a neutral acid scavenger for the absorption of HCl has been documented: Weinstock, L. M.; Karady, S.; Roberts, F. E.; Hoinowski, A. M.; Brenner, G. S.; Lee, T. B. K.; Lumma, W. C.; Sletzinger, M. *Tetrahedron Lett.* **1975**, 3979−3982. (b) Compounds **2** and **14** were stirred with 4 Å molecular sieves in $ClCH_2CH_2Cl$ (0 °C to rt) and assayed by RP-HPLC (**2** and **3** are stable to the chromatography conditions). After 16 h, both had undergone ca. 70% conversion. (c) In the presence of $Na(AcO)_3BH$, complete conversion occurred within 1 h.

amine was added (14.7 mL, 106 mmol), followed by dropwise addition of methyl oxalyl chloride (6.81 mL, 74.0 mmol). After 45 min, the solution was poured into EtOAc, washed with water, a 10% HCl solution, a saturated $NaHCO_3$ solution, and brine, dried over Na_2SO_4, filtered, and concentrated. The product was crystallized from a stirred 5% EtOAc/hexane solution to afford **1** (15.39 g, 68%) as a white powder: R_f 0.36 (50% EtOAc/hexane); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.35−7.42 (m, 3H), 7.25 (bd, J = 8 Hz, 2H), 4.87 (bs, 1H), 3.91 (t, J = 6.0 Hz, 2H), 3.53 (s, 3H), 3.37 (dt, J = 5.8 and 6 Hz, 2H), 1.41 (s, 9H); ES HRMS exact mass calcd for $C_{16}H_{23}N_2O_5$ (M + H$^+$) 323.1601, found 323.1603. Anal. Calcd for $C_{16}H_{22}N_2O_5$: C, 59.62; H, 6.88; N, 8.69. Found: C, 59.23; H, 6.65; N, 8.57.

Representative Procedure for the Preparation of 2,3-Diketopiperazines from Oxamates: 4-Benzyl-1-phenyl-2,3-diketopiperazine (3a). Through a solution of **1** (500 mg, 1.55 mmol) in 10 mL of EtOAc at 0 °C was bubbled anhydrous HCl gas for 3 min. After being stirred for an additional 20 min, the solution was concentrated to provide **2** as a white foam (400 mg, 100%): ^{1}H NMR (400 MHz, CD_3OD) δ 7.42−7.51 (m, 3H), 7.37 (bd, J = 8 Hz, 2H), 4.11 (t, J = 6.4 Hz, 2H), 3.52 (s, 3H), 3.15 (t, J = 6.4 Hz, 2H); ES HRMS exact mass calcd for $C_{11}H_{15}N_2O_3$ (M + H$^+$) 223.1077, found 223.1068. Anal. Calcd for $C_{11}H_{14}N_2O_3$·1.0HCl·0.1H_2O: C, 50.72; H, 5.88; N, 10.75. Found: C, 50.82; H, 5.85; N, 10.75. To a 0 °C solution of **2** in 3.0 mL of 1,2-dichloroethane were added 0.50 g of 4 Å powdered molecular sieves, benzaldehyde (174 μL, 1.70 mmol), and sodium triacetoxyborohydride (439 mg, 2.33 mmol). After 30 min, the ice bath was removed, and the reaction was stirred for 4 h. The solution was poured into EtOAc, washed with a saturated $NaHCO_3$ solution and brine, dried over Na_2SO_4, filtered, and concentrated. Flash chromatography (25 × 80 mm silica, 75% EtOAc/hexanes) provided **3a** (313 mg, 72%) as a white solid: R_f 0.48 (5% MeOH/$CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.31−7.43 (m, 9H), 7.27 (tt, J = 8.4 and 1.1 Hz, 1H), 4.75 (s, 2H), 3.87−3.90 (m, 2H), 3.55−3.58 (m, 2H); ES HRMS exact mass calcd for $C_{17}H_{17}N_2O_2$ (M + H$^+$) 281.1283, found 281.1284. Anal. Calcd for $C_{17}H_{16}N_2O_2$: C, 72.84; H, 5.75; N, 9.99. Found: C, 72.99; H, 5.92; N, 10.15.

4-(4-Nitrobenzyl)-1-phenyl-2,3-diketopiperazine (3b). Crystallization of the crude reaction mixture from EtOAc provided **3b** (72%) as a white solid: R_f 0.19 (5% MeOH/CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.24 (d, J = 8.8 Hz, 2H), 7.54 (d, J = 8.8 Hz, 2H), 7.42 (bt, J = 7.5 Hz, 2H), 7.27−7.34 (m, 3H), 4.84 (s, 2H), 3.94−3.96 (m, 2H), 3.62−3.65 (m, 2H); ES HRMS exact mass calcd for $C_{17}H_{16}N_3O_4$ (M + H$^+$) 326.1135., found 326.1118. Anal. Calcd for $C_{17}H_{15}N_3O_4$: C, 62.76; H, 4.65; N, 12.92. Found: C, 62.36; H, 4.52; N, 12.77.

4-(4-Methoxybenzyl)-1-phenyl-2,3-diketopiperazine (3c). Flash chromatography (25 × 80 mm silica, 75−100% EtOAc/hexane) provided **3c** (61%) as a white solid: R_f 0.43 (5% MeOH/$CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.40 (bt, J = 8 Hz, 2H), 7.32 (bd, J = 8 Hz, 2H), 7.28 (d, J = 8.7 Hz, 2H), 7.26 (m, 1H), 6.89 (d, J = 8.7 Hz, 2H), 4.68 (s, 2H), 3.85−3.88 (m, 2H), 3.82 (s, 3H), 3.53−3.56 (m, 2H); ES HRMS exact mass calcd for $C_{18}H_{19}N_2O_3$ (M + H$^+$) 311.1390, found 311.1394.

4-(4-Bromobenzyl)-1-phenyl-2,3-diketopiperazine (3d). Crystallization of the crude reaction mixture from EtOAc provided **3d** (72%) as a white solid: R_f 0.44 (5% MeOH/$CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.50 (bt, J = 8.4 Hz, 2H), 7.41 (bt, J = 8 Hz, 2H), 7.28−7.33 (m, 3H), 7.23 (d, J = 8.6 Hz, 2H), 4.70 (s, 2H), 3.88−3.91 (m, 2H), 3.55−3.58 (m, 2H); ES HRMS exact mass calcd for $C_{17}H_{16}BrN_2O_2$ (M + H$^+$) 359.0390, found 359.0404. Anal. Calcd for $C_{17}H_{15}BrN_2O_2$: C, 56.84; H, 4.21; N, 7.80. Found: C, 57.05; H, 4.31; N, 7.69.

4-(2-Bromobenzyl)-1-phenyl-2,3-diketopiperazine (3e). Crystallization of the crude reaction mixture from EtOAc provided **3e** (62%) as a white solid: R_f 0.49 (5% MeOH/$CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.60 (bd, J = 8 Hz, 1H), 7.47 (bt, J = 8 Hz, 2H), 7.32−7.43 (m, 4H), 7.28 (m, 1H), 7.21 (bt, J = 8 Hz, 1H), 4.91 (s, 2H), 3.94 (m, 2H), 3.65 (m, 2H); ES HRMS exact mass calcd for $C_{17}H_{16}BrN_2O_2$ (M + H$^+$) 359.0390, found 359.0371. Anal. Calcd for $C_{17}H_{15}BrN_2O_2$: C, 56.84; H, 4.21; N, 7.80. Found: C, 57.23; H, 4.27; N, 7.71.

4-(3-Phenyl-2-propen-1-yl)-1-phenyl-2,3-diketopiperazine (3f) and Methyl *N*-[2-(Bis(3-phenyl-2-propenyl)amino)ethyl]-*N*-(phenyl)oxamate (6a). Crystallization of the crude reaction mixture from EtOAc provided **3f** (20%) as a white solid. Flash chromatography of the mother liquor (25 × 80 mm silica, 50−100% EtOAc/hexane) provided **6a** (35%) as a colorless oil. For **3f**: R_f 0.41 (5% MeOH/$CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.26−7.43 (m, 10H), 6.63 (d, J = 15.9 Hz, 2H), 6.21 (dt, J = 15.9 and 6.9 Hz, 2H), 4.33 (d, J = 6.9 Hz, 4H), 3.95 (m, 2H), 3.68 (m, 2H); ES HRMS exact mass calcd for $C_{19}H_{19}N_2O_2$ (M + H$^+$) 307.1441, found 307.1433. For **6a**: R_f 0.25 (25% EtOAc/hexane); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.20−7.35 (m, 15H), 6.46 (d, J = 15.9 Hz, 2H), 6.18 (dt, J = 15.9 and 6.6 Hz, 2H), 3.95 (t, J = 6.6 Hz, 2H), 3.52 (s, 3H), 3.31 (d, J = 6.6 Hz, 4H), 2.75 (t, J = 6.6 Hz, 2H); ES HRMS exact mass calcd for $C_{29}H_{31}N_2O_3$ (M + H$^+$) 455.2329, found 455.2310.

4-(*n*-Butyl)-1-phenyl-2,3-diketopiperazine (3g) and Methyl *N*-[2-(Di-*n*-Butylamino)ethyl]-*N*-(phenyl)oxamate (6b). Flash chromatography (40 × 70 mm silica, 2−4% MeOH/CH_2Cl_2) provided an inseparable mixture of **3g** (43%) and **6b** (16%) as a colorless oil. For **3g**: R_f 0.30 (5% MeOH/CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.24−7.42 (m, 5H), 3.95 (m, 2H), 3.66 (m, 2H), 3.54 (t, J = 7.5 Hz, 2H), 1.62 (m, 2H), 1.39 (m, 2H), 0.96 (t, J = 7.3 Hz, 3H); ES HRMS exact mass calcd for $C_{14}H_{19}N_2O_2$ (M + H$^+$) 247.1441, found 247.1449. For **6b**: R_f 0.30 (5% MeOH/CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.24−7.42 (m, 5H), 3.83 (t, J = 6.8 Hz, 2H), 3.52 (s, 3H), 2.62 (t, J = 6.8 Hz, 2H), 2.38 (t, J = 7.2 Hz, 4H), 1.62 (m, 4H), 1.45 (m, 4H), 0.87 (t, J = 7.2 Hz, 6H); ES HRMS exact mass calcd for $C_{19}H_{31}N_2O_3$ (M + H$^+$) 335.2329, found 335.2329.

4-(2-Methyl-1-propyl)-1-phenyl-2,3-diketopiperazine (3h). Crystallization of the crude reaction mixture from EtOAc provided **3h** (78%) as white flakes: R_f 0.17 (5% MeOH/CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.41 (bt, J = 8 Hz, 2H), 7.35 (bd, J = 8 Hz, 2H), 7.28 (bt, J = 8 Hz, 1H), 3.95−3.98 (m, 2H), 3.66−3.68 (m, 2H), 3.37 (d, J = 7.5 Hz, 2H), 2.06 (m, 1H), 0.98 (d, J = 6.6 Hz, 6H); ES HRMS exact mass calcd for $C_{14}H_{19}N_2O_2$ (M + H$^+$) 247.1434, found 247.1441. Anal. Calcd for $C_{14}H_{18}N_2O_2$: C, 68.27; H, 7.37; N, 11.37. Found: C, 67.94; H, 7.48; N, 11.44.

(*S*)-4-[(2-*tert*-Butoxycarbonylamino-3-phenyl)propyl]-1-phenyl-2,3-diketopiperazine (3i). Flash chromatography (40 × 70 mm silica, 1.5−3% MeOH/CH_2Cl_2) provided **3i** (60%) as a white solid: R_f 0.13 (5% MeOH/CH_2Cl_2); $[\alpha]^{20}_D = -106.4°$ (*c* 0.10, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.40 (bt, J = 8.4 Hz, 2H), 7.22−7.34 (m, 8H), 4.79 (bd, J = 9 Hz, 1H), 4.19 (m, 1H), 3.94−4.06 (m, 2H), 3.80 (m, 1H), 3.71 (m, 1H), 3.57 (m, 1H), 3.11 (dd, J = 13.9 and 4 Hz, 1H), 2.98 (dd, J = 13.8 and 6.4 Hz, 1H), 2.78 (dd, J = 13.8 and 7.7 Hz, 1H), 1.40 (s, 9H); ES HRMS exact mass calcd for $C_{24}H_{30}N_3O_4$ (M + H$^+$) 424.2231, found 424.2234.

4-[(4-*tert*-Butoxycarbonyl)-1-piperidinyl]-1-phenyl-2,3-diketopiperazine (3k). Flash chromatography (40 × 70 mm silica, 2−4% MeOH/CH_2Cl_2) provided **3k** (90%) as a white solid: R_f 0.11 (5% MeOH/CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.41 (bt, J = 8 Hz, 2H), 7.35 (bt, J = 8 Hz, 2H), 7.28 (bt, J = 8 Hz, 1H), 4.67 (tt, J = 12.3 and 4.0 Hz, 1H), 4.24 (m, 1H), 3.92−3.94 (m, 2H), 3.85 (m, 1H), 3.56−3.58 (m, 2H), 3.03 (dt, J = 3.2 and 9.7 Hz, 1H), 2.84 (bt, J = 12 Hz, 1H), 1.85 (m, 1H), 1.76 (bd, J = 10 Hz, 1H), 1.55−1.68 (m, 2H), 1.46 (s, 9H); ES HRMS exact mass calcd for $C_{20}H_{28}N_3O_4$ (M + H$^+$) 374.2074, found 374.2069.

Methyl *N*-Benzyl-*N*-[2-(*tert*-butoxycarbonylamino)ethyl]oxamate (7). To a solution of Boc-glycine (5.71 g, 32.6 mmol) in 50 mL of DMF at 0 °C were added benzylamine (4.27 mL, 39.1 mmol), HOBt·H_2O (5.72 g, 42.4 mmol), and EDC·HCl (8.71, 45.6 mmol). After stirring overnight, allowing the reaction to warm to room temperature, the solution was poured into EtOAc and washed with water, a 10% HCl solution, a saturated $NaHCO_3$ solution, and brine. The solution was dried over Na_2SO_4, filtered, and concentrated to provide a pale yellow waxy solid (8.27 g, 96%): ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.24−7.33 (m, 5H), 6.62 (bs, 1H), 5.28 (bs, 1H), 4.44 (d, J = 5.9 Hz, 2H), 3.81 (d, J = 5.5 Hz, 2H), 1.42 (s, 9H). The product (7.30 g, 27.6 mmol) was taken up in 50 mL of THF and then added dropwise to a 0 °C suspension of $LiAlH_4$ (8.37 g, 226 mmol) in 40 mL of THF. After the solution was overnight, allowing the reaction to warm to room temperature, it was quenched by dropwise addition of a saturated NH_4Cl solution [CAUTION]. The solution was poured into EtOAc, washed with a saturated $NaHCO_3$ solution and brine, dried over Na_2SO_4, filtered, and concentrated to provide a yellow oil (4.22 g, 61%): ^{1}H NMR (400 MHz, $CDCl_3$)

δ 7.23−7.34 (m, 5H), 4.96 (bs, 1H), 3.79 (d, J = 6 Hz, 2H), 3.23 (m, 2H), 2.74 (m, 2H), 1.57 (bs, 1H), 1.44 (s, 9H). The product (4.22 g, 16.9 mmol) was taken up in 50 mL of EtOAc and 50 mL of saturated $NaHCO_3$ solution and cooled to 0 °C. Methyl oxalyl chloride (2.83 mL, 30.8 mmol) was added dropwise. After 10 min, the layers were separated, and the organic phase was washed with a saturated NH_4Cl solution, a saturated $NaHCO_3$ solution, and brine, dried over Na_2SO_4, filtered, and concentrated. Purification by flash chromatography (60 × 80 mm silica, 30−40% EtOAc/hexanes) provided **7** (53%) as a colorless oil: R_f 0.36 (50% EtOAc/hexane); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.27−7.37 (m, 5H), 4.80 (bs, 1H), 4.67 (s, 45% of 2H), 4.52 (s, 55% of 2H), 3.90 (s, 45% of 3H), 3.85 (s, 55% of 3H), 3.43 (t, J = 5.8 Hz, 55% of 2H), 3.27−3.32 (m, 2H and 45% of 2H), 1.44 (s, 9H); ES HRMS exact mass calcd for $C_{17}H_{25}N_2O_5$ (M + H^+) 337.1758, found 337.1761.

4-Benzyl-1-(4-bromobenzyl)-2,3-diketopiperazine (8) was prepared from **7** and 4-bromobenzaldehyde using the representative procedure. Recrystallization from hot 80% EtOAc/hexane provided **8** (84%) as a white solid: R_f 0.17 (5% MeOH/CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.45 (d, J = 8.2 Hz, 2H), 7.26−7.34 (m, 5H), 7.16 (d, J = 8.2 Hz, 2H), 4.67 (s, 2H), 4.62 (s, 2H), 3.34 (m, 4H); ES HRMS exact mass calcd for $C_{18}H_{18}BrN_2O_2$ (M + H^+) 373.0533, found 373.0546. Anal. Calcd for $C_{18}H_{17}BrN_2O_2$: C, 57.92; H, 4.59; N, 7.51. Found: C, 57.84; H, 4.69; N, 7.07.

(*S*)-Methyl *N*-[2-(*tert*-Butoxycarbonylamino)-4-phenyl-1-butyl]-*N*-(phenyl)oxamate (9). To a 0 °C solution of (*S*)-2-(*tert*-butoxycarbonylamino)-3-phenyl-1-propionaldehyde[10] (12.18 g, 48.9 mmol) in 200 mL of 1,2-dichloroethane were added 12 g of 4 Å powdered molecular sieves, aniline (4.55 mL, 49.8 mmol), and sodium triacetoxyborohydride (15.5 g, 73.3 mmol). After 20 min, the ice bath was removed, and the reaction was stirred for 2 h. The solution was poured into EtOAc, washed with a saturated $NaHCO_3$ solution and brine, dried over Na_2SO_4, filtered, and concentrated to provide a white solid (14.4 g, 90%): ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.31 (t, J = 7.5 Hz, 2H), 7.13−7.25 (m, 5H), 6.69 (t, J = 7.3 Hz, 1H), 6.56 (d, J = 8.6 Hz, 2H), 4.55 (bs, 1H), 3.8 (bs, 1H), 3.24 (dd, J = 13.0 and 4.6 Hz, 1H), 3.05 (dd, J = 13.0 and 6.9 Hz, 1H), 2.83−2.88 (m, 2H), 1.42 (s, 9H). The product (4.06 g, 12.5 mmol) was taken up in 80 mL of EtOAc and 40 mL of a saturated $NaHCO_3$ solution and cooled to 0 °C. Methyl oxalyl chloride (1.26 mL, 13.7 mmol) was added dropwise. After 30 min, the layers were separated, and the organic phase was washed with brine, dried over Na_2SO_4, filtered, and concentrated to provide **9** (99%) as an oil: R_f 0.15 (20% EtOAc/hexanes); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.34−7.38 (m, 3H), 7.18−7.26 (m, 5H), 7.11 (bd, J = 7 Hz, 2H), 7.31 (t, J = 7.5 Hz, 2H), 4.74 (d, J = 8.6 Hz, 1H), 4.19 (dd, J = 13.8 and 10.4 Hz, 1H), 4.07 (m, 1H), 3.50, (s, 3H), 3.45 (dd, J = 13.8 and 3.7 Hz, 1H), 2.83 (dd, J = 14.1 and 6.8 Hz, 1H), 2.79 (dd, J = 14.1 and 6.6 Hz, 1H), 1.39 (s, 9H); ES HRMS exact mass calcd for $C_{23}H_{29}N_2O_5$ (M + H^+): 413.2071. found 413.2069.

(*S*)-5-Benzyl-4-(4-bromobenzyl)-1-phenyl-2,3-diketopiperazine (10), (*S*)-5-benzyl-1-phenyl-2,3-diketopiperazine (11), and (*S*)-methyl *N*-[3-phenyl-1-(phenylamino)-2-propyl]oxamate (12) were prepared from **9** and 4-bromobenzaldehyde using the representative procedure. Flash chromatography (40 × 70 mm silica, 30−55% EtOAc/hexanes, then 5% MeOH/ CH_2Cl_2) provided **10** (26%) as a white solid, along with **11** (47%) as a white solid and **12** (10%) as a colorless oil. For **10**: R_f 0.13 (50% EtOAc/hexane); $[\alpha]^{20}_D$ = −555.2° (*c* 0.050, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.50 (bd, J = 8.3 Hz, 2H), 7.41 (bt, J = 8 Hz, 2H), 7.23−7.34 (m, 6H), 7.20 (d, J = 8.2 Hz, 2H), 7.02 (bd, J = 8 Hz, 2H), 5.29 (d, J = 14.8 Hz, 1H), 4.00 (dd, J = 13.0 and 3.7 Hz, 1H), 3.81 (d, J = 14.8 Hz, 1H), 3.58 (m, 1H), 3.49 (dd, J = 13.0 and 1.8 Hz, 1H), 3.13 (dd, J = 13.7 and 5.7 Hz, 1H), 3.05 (dd, J = 13.7 and 9.2 Hz, 1H); ES HRMS exact mass calcd for $C_{24}H_{22}BrN_2O_2$ (M + H^+) 449.0859, found 449.0859. For **11**: R_f 0.07 (5% MeOH/CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.39−7.42 (m, 3H), 7.23−7.32 (m, 6H), 7.16 (bd, J = 7 Hz, 2H), 4.08 (m, 1H), 3.91 (dd, J = 12.7 and 3.9 Hz, 1H), 3.84 (dd, J = 12.7 and 7.7 Hz, 1H), 3.01 (dd, J = 14.1 and 5 Hz, 1H), 2.99 (dd, J = 14.1 and 5.7 Hz, 1H); ES HRMS exact mass calcd for $C_{17}H_{16}N_2O_2$ (M + H^+) 281.1284, found 281.1289. Anal. Calcd for $C_{17}H_{16}N_2O_2$: C, 72.84; H, 5.75; N, 9.99. Found: C, 72.58; H, 5.85; N, 10.15. For **12**: R_f 0.31 (50% EtOAc/hexane); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.32 (bt, J = 7.5 Hz, 2H), 7.12−7.27 (m, 5H), 6.72 (bt, J = 7.3 Hz, 1H), 6.59 (bd, J = 7.5 Hz, 2H), 4.43 (m, 1H), 3.97 (bs, 2H), 3.86 (s, 3H), 3.31 (dd, J = 13.0 and 5.1 Hz, 1H), 3.24 (dd, J = 13.0 and 7.3 Hz, 1H), 2.98 (dd, J = 14.2 and 6.6 Hz, 1H), 2.96 (dd, J = 14.2 and 7.0 Hz, 1H); ES HRMS exact mass calcd for $C_{18}H_{21}N_2O_3$ (M + H^+) 313.1558, found 313.1547.

Methyl *N*-(2-Aminoethyl)-*N*-(phenyl)oxamate Hydrochloride (14). A solution of 2,3-diketopiperazine **3a** (350 mg, 1.25 mmol) was refluxed in 4 mL of 4 N HCl for 5 h. The solution was partitioned between CH_2Cl_2 and saturated $NaHCO_3$ solution, and the aqueous layer was extracted four times with CH_2Cl_2. The combined organics were dried over Na_2SO_4, filtered, and concentrated to provide a pale red oil (228.3 mg, 81%): ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.32−7.33 (m, 4H), 7.26 (m, 1H), 7.17 (bt, J = 8 Hz, 2H), 6.70, (bt, J = 7.3 Hz, 1H), 6.63, (bd, J = 8 Hz, 2H), 4.11 (bs, 1H), 3.81 (s, 2H), 3.22 (t, J = 5.7 Hz, 2H), 2.91 (t, J = 5.7 Hz, 2H), 1.44 (bs, 1H). The diamine product was converted to oxamate **13** using the procedure described for the synthesis of **1**. Flash chromatography (40 × 60 mm silica, 20% EtOAc/hexane) provided **13** (84%) as a colorless oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.20−7.39 (m, 9H), 7.14 (m, 1H), 4.48 and 4.43 (2bs, 2H, conformers), 3.93 and 3.78 (2m, 2H, conformers), 3.53 (s, 3H), 3.48 and 3.39 (2m, 2H, conformers), 1.40 (bs, 9H). Through a solution of **13** (54 mg, 0.13 mmol) in 3 mL of EtOAc at 0 °C was bubbled anhydrous HCl gas for 30 min. The solution was concentrated to provide **14** as a white foam (46 mg, 100%): ^{1}H NMR (400 MHz, CD_3OD) δ 7.40−7.50 (m, 9H), 7.36 (m, 1H), 4.88 (bs, 2H), 4.27 (bs, 2H), 3.51 (s, 3H), 3.32 (m, 2H); ES HRMS exact mass calcd for $C_{18}H_{21}N_2O_3$ (M + H^+) 313.1547, found 313.1546.

Methyl *N*-[2-(1-benzyl-1-*n*-butyl)amino)ethyl]-*N*-(phenyl)oxamate (6d) was prepared from **14** and *n*-butyraldehyde using the representative procedure. Flash chromatography (40 × 70 mm silica, 1−3% MeOH/CH_2Cl_2) provided **6d** (75%) as a colorless oil: R_f pending; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.30−7.38 (m, 3H), 7.20−7.30 (m, 5H), 7.14 (bd, J = 8 Hz, 2H), 3.85 (t, J = 6.9 Hz, 2H), 3.56 (s, 2H), 3.52 (s, 3H), 2.66 (t, J = 6.9 Hz, 2H), 2.42 (t, J = 7.3 Hz, 2H), 1.40 (m, 2H), 1.25 (m, 2H), 0.84 (t, J = 7.3 Hz, 3H); ES HRMS exact mass calcd for $C_{22}H_{29}N_2O_3$ (M + H^+) 369.2173, found 369.2166.

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Supporting Information Available: ^{1}H NMR spectra for compounds **3c,f,i,k, 3g/6b, 6a,d, 7, 9, 10, 12**, and **14** (12 pages). This material is contained in 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.

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