Efficient Synthesis of Medium-Sized Cyclic Ether Diamines

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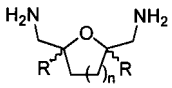
The diamine group is a ubiquitous structure in many natural products, pharmaceutical drugs, agricultural chemicals, and polymers. Within this class of compounds, cyclic diamines that possess either C_2-symmetrical or pseudo-C_2-symmetrical structures have received attention for their use as ligands and antifungal agents and their incorporation within macromonocycles, macropolycyclic cryptands, and HIV protease inhibitors.[1−6] We report a simple protocol for the construction of symmetrical diamines **1** that are bridged by a medium-sized

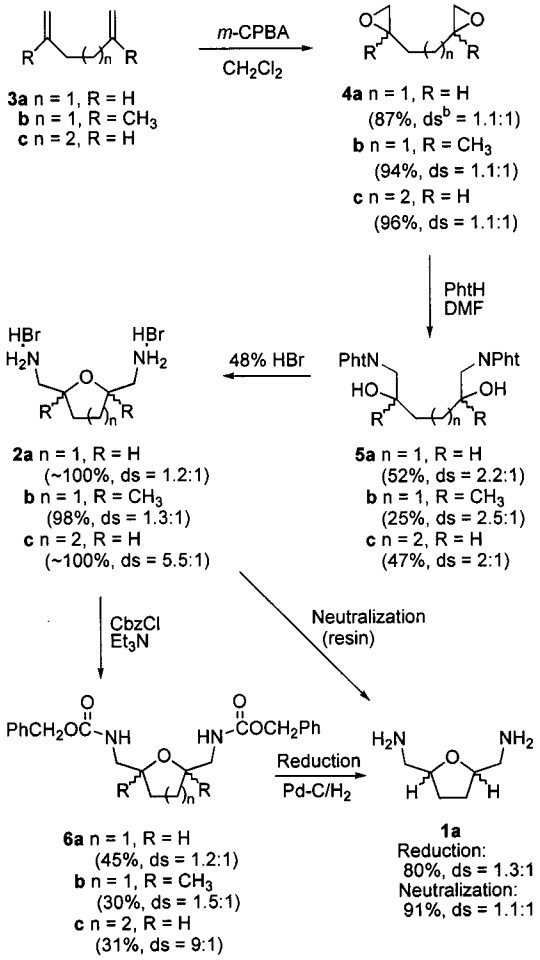


1
n = 1, 2
R = H, CH_3

cyclic ether unit. Introduction of the ether oxygen within the diamine scaffold provides a central site for substrate binding (hydrogen bond, dipole−dipole) and metal complexation. Our synthesis of **1** proceeded in three steps from commercial starting materials, with amine generation and ring cyclization occurring in the final step. The advantages of the procedure are discussed in the context of existing routes,[2,3,7,8] and information is provided on the pathway for diamine formation.

Synthetic Method. The route developed to construct cyclic ether diamine salts **2** from dialkenes **3** is outlined in Scheme 1. Adding *m*-chloroperbenzoic acid to **3** provided diepoxide **4**,[9a,b] which was then ring opened with phthalimide to give **5**.[9c] Treatment of **5** with hot, aqueous HBr led to the removal of the phthalimido units and

Scheme 1. Synthesis of Cyclic Ether Diamine Salts 2[a]



[a] All yields correspond to isolated products. [b] ds = diastereomeric selectivity, ratio of the diastereomeric products.

subsequent diol cyclization to ether diamine salt **2**. We used this protocol to prepare **2a**−**c** in 23−45% overall yields.

In practice, epoxidation of dialkenes **3a**−**c** (Aldrich Chemical Co.) to **4a**−**c** with *m*-chloroperbenzoic acid occurred in high yields (87−96%) and with little diastereomeric differentiation. Treatment of **4a**−**c** with phthalimide in DMF (135 °C) led to regioselective epoxide ring opening to give the terminally bisphthalimido-substituted diols **5a**−**c** in moderate yields (25−52%). NMR analyses (^{1}H, ^{13}C) of the isolated product mixtures indicated that one diastereomer predominated (2.0−2.5:1), suggesting that either one diastereomer is preferentially formed or the different solubilities of the ring-opened products **5** led to the selective loss of product under the workup conditions used to rapidly remove the unreacted phthalimide. Diastereomeric **5** was converted to the cyclic ether diamine salts **2** with aqueous 48% HBr (70−120 °C) in near quantitative yields. NMR analyses of the crude product showed that the diastereomeric ratio of the cyclic ether diamine salts prior to recrystallization was 1.2:1 for **2a**, 1.3:1 for **2b**, and 5.5:1 for **2c**. We have assigned the predominant isomer for **2c** as the *cis*-isomer on the basis of the ^{1}H and ^{13}C NMR chemical shifts for the C(2)

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(C(6)) methine hydrogen and carbon signals, respectively, and comparable values reported for *cis*- and *trans*-1,3-dimethylcyclohexanes[10] and 2,6-dimethyltetrahydropyrans.[11] For *cis*-**2c** the C(2) (C(6)) methine hydrogen resonated upfield (Δppm = 0.40) from the corresponding signal for *trans*-**2c**, while the C(2) (C(6)) carbon signal for *cis*-**2c** appeared downfield from that of *trans*-**2c** (Δppm = 5.50).

Diamine salts **2a**−**c** were converted to di-Cbz derivatives **6a**−**c**, respectively. We showed that free diamine **1a** could be prepared by catalytic removal (Pd−C, H_2) of the Cbz protecting groups from **6a** (80% yield) and by passage of hydrobromide salt **2a** through an Amberlite ion-exchange resin (IRA-67) (91% recovery).

Preparative routes for cyclic diamine **1a** (or salt form) have been reported,[2,3,7,8] and a brief mention of **1c** has appeared, but no experimental data have been given.[2] These routes either began with a cyclic starting material or generated a cyclic intermediate[12] at an early stage in the synthesis. Overall yields for **1a** including synthetic intermediates were 6−13% and required 4−9 steps.[3,7,8,12] The most efficient of these began with 5-(hydroxymethyl)-furfural[12a,e] and gave **1a** in four steps in 13% overall yield.[7] By comparison, our synthesis for the corresponding hydrogen bromide salt **2a** proceeded in three steps in 45% overall yield from 1,5-hexadiene, with ring cyclization proceeding in the final step. Further differentiating this protocol is the versatility of the method, permitting the placement of additional substituents at carbon sites adjacent to the ether oxygen (i.e., C(2) (C(5)) in **2b**). Compound **2b** is one such compound that has not been reported and cannot be prepared by the previous methods.[2,3,7,8] This latitude in the synthetic procedure permits the preparation of a wide range of cyclic ether diamines.

Cyclization Step. The key step in the synthesis is the final one. Treatment of **5** with acid led to phthalimide deprotection and cyclodehydration to give diamine salts **2** in near quantitative yield without cyclic amine production. We studied the ring closure of **5** to **2**. First, we learned that **5b** was converted to product **2b** faster than **5a** to **2a** (**5b**, 2 d, 90 °C; **5a**, 10 d, 90 °C). Second, we documented (^{1}H NMR) that HBr-mediated phthalimide removal proceeded faster than diol cyclization (e.g., **5a** → **2a**, rate of phthalimide removal:diol cyclization ≈ 5:1).[13] Third, we showed that HBr cyclization of an enriched *meso*-**5a** sample (^{13}C NMR, *meso:dl* = >9:1; X-ray analysis[14]) gave a 1.2:1 diastereomeric mixture of cyclic diamine salts **2a** after 24 h (120 °C), with the *trans*-product being the major adduct. Interestingly, when the reaction was monitored by NMR (^{1}H, ^{13}C), the extent of diastereomeric enrichment of the diamine salt *trans*-**2a** progressively decreased from 2.0:1 (0.5 h) to 1.2:1 (24 h). Similarly, beginning with enriched *dl*-**5a** (^{13}C NMR, *dl:meso* = 3.7:1), we obtained a 1.2:1 *trans*:*cis* diastereomeric mixture of cyclic diamine salts **2a** after 24 h (120 °C), with the *cis*-**2a** initially being formed as the major product (i.e., 0.5 h, *cis*-**2a**:*trans*-**2a** = 1.5:1). We have again assigned the stereochemistry of the *cis*- and *trans*-cyclic diamine salts **2a** on the basis of the ^{1}H and ^{13}C NMR spectra. We observed that the C(2) (C(5)) methine hydrogen for the *cis*-isomer **2a** resonated upfield from that of the *trans*-adduct in the ^{1}H NMR (Δppm = 0.12) while the corresponding carbon signal in *cis*-**2a** appeared downfield from that of *trans*-**2a** (Δppm = 0.70). Similar NMR findings have been observed for *cis*- and *trans*-1,3-dimethylcyclopentanes[15] and 2,5-dimethyltetrahydrofurans.[16]

The loss of stereochemistry for the conversion of *meso*-**5a** to **2a** indicated that the reaction proceeds, in part, by an S_N1-type pathway. Nonetheless, the detection of a modest diastereoselective preference for **5a** → **2a** suggested that either the initial cyclization step is governed by a preferred kinetic S_N1 pathway or both S_N1 and S_N2 cyclization pathways are operative. There is support in the literature for both cyclization routes.[17−22] Mihailović and co-workers studied the conversion of secondary diols to cyclic ethers in H_2SO_4 and H_3PO_4 solutions.[18a] A similar investigation has been reported using HBr.[19] Both studies documented that cyclodehydration proceeded by a S_N2 pathway either in dilute acid solutions or when low molar ratios of acid to diol were used. Correspondingly, use of high molar ratios of concentrated H_2SO_4[19] with respect to the diol or use of tertiary substituted diols[21] led to a loss in stereoselective ring closure and cyclization by a S_N1-mediated pathway. While our data do not permit us to differentiate these and other cyclization pathway(s),[22] the decrease in diastereomeric enrichment of tetrahydrofuran diamine salt **2a** with time indicated that under the reaction conditions (HBr, 120 °C) the final product undergoes isomerization to give a *thermodynamic* mixture of diamine salts **2a**. A similar finding has been observed by Mihailović and co-workers for 2,5-dimethyltetrahydrofurans in DMSO solutions.[18a] This notion is supported by the finding that crude **2a** contained both the *cis*- and *trans*-isomers in near-equal amounts. Energy minimization calculations (Tripos, Sybyl

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6.7) for **2a** indicated that the two isomers had comparable energy, in agreement with the corresponding energy (computational, thermodynamic) values reported for 1,3-dimethylcyclopentanes[23,24] and the thermodynamic measurements for 2,5-dialkyltetrahydrofurans.[16c] Similarly, we learned that the *cis*-to-*trans* ratio for crude tetrahydropyran salt **2c** was 5.5:1, a finding predicted by the energy minimization calculations (Tripos, Sybyl 6.7) for **2c** and the reported thermodynamic measurements for 1,3-dimethylcyclohexanes.[24,25] The observed diastereomeric ratios for **2a** and **2c** likely reflect the thermodynamic consequences of the bis(aminomethyl) substituents in five-memberd puckered[16c] and six-membered chair[25] conformations, respectively.

In summary, we report a novel, concise method (Scheme 1) for the construction of cyclic diamines bridged by an ether unit. This is a general preparative route for medium-sized ether ring diamines, employs commercially available dienes as starting materials, provides moderate overall yields of cyclic ether diamine salts in three steps, and is compatible with a wide range of ring substitution patterns.

Experimental Section

^{1}H and ^{13}C NMR spectra were recorded on a General Electric QE-300 spectrometer. Mass spectrometry (MS) data were obtained by Dr. Mehdi Moini at the University of Texas at Austin. The low-resolution MS studies were run on a Finnegan TSQ-70 triple quadrupole mass spectrometer, and the high-resolution MS studies were conducted on a Micromass ZAB-E mass spectrometer. FT-IR spectra were run on a Mattson Galaxy Series FT-IR 5000 spectrometer. Melting points were determined in open capillary tubes using a Thomas-Hoover melting point apparatus and are uncorrected. Microanalyses were provided by Atlantic Microlab, Inc. (Norcross, GA).

General Procedure for the Preparation of Diepoxides 4.[9a,b] To a stirred solution of diene **3** (8.4 mmol) in dry CH_2Cl_2 (17 mL) was added *m*-chloroperbenzoic acid (*m*-CPBA; 5.30 g, 68% by wt, 21.0 mmol) at 4 °C in four portions. The reaction was maintained at either 4 °C or rt (3−24 h), then H_2O (15 mL) was added, and the mixture was extracted with CH_2Cl_2 (2 × 15 mL). The combined organic layers were washed with aqueous 1.0 N KOH (3 × 25 mL), dried ($MgSO_4$), and concentrated to give the diepoxide **4**, which was used without further purification.

General Procedure for the Preparation of Bis(phthalimido)alkanediols 5. To a DMF (11 mL) solution of phthalimide (6.44 g, 44 mmol) maintained at 135 °C was added dropwise **4** (18 mmol) with vigorous stirring. The reaction mixture was heated (1 h, 135 °C) and then cooled. The precipitate was filtered and successively washed with aqueous 1.0 N NaOH, H_2O, EtOH, and Et_2O to give **5**.

1,6-Bis(phthalimido)-2,5-hexanediol (5a). Using **4a**[9a] (2.00 g, 18 mmol) and the general procedure, **5a** (white solid) was obtained as a mixture of diastereomers (2.2:1, ^{13}C NMR analysis): yield 3.80 g (52%); mp 235−240 °C; R_f 0.30 (2:1 EtOAc/hexanes); IR (KBr) 3502, 2931, 1770 (sh), 1705, 1427, 1392, 1076, 960, 728 cm^{-1}; ^{1}H NMR (DMSO-d_6) δ 1.25−1.65 (m, 4 H), 3.42−3.56 (m, 4 H), 3.74 (br s, 2 H), 4.87−4.90 (m, 2 H), 7.82−7.88 (m, 8 H); ^{13}C NMR (DMSO-d_6) δ 30.2, 30.7, 44.1, 66.8, 67.5, 122.8, 131.7, 134.1, 167.9; the other signals were not detected and are believed to overlap with the observed peaks; the ^{1}H and ^{13}C NMR data are in agreement with the COSY and DEPT spectra; MS (+CI) *m*/*z* 409 [M + 1]$^+$; M_r (+CI) 409.13898 [M + 1]$^+$ (calcd for $C_{22}H_{21}N_2O_6$ 409.13996).

2,5-Dimethyl-1,6-bis(phthalimido)-2,5-hexanediol (5b). Using **4b**[9b] (2.56 g, 18 mmol) and the general procedure, **5b** (white solid) was obtained as a mixture of diastereomers (2.5:1, ^{13}C NMR analysis): yield 1.96 g (25%); mp 222−226 °C; R_f 0.36 (2:1 EtOAc/hexanes); IR (KBr) 3468, 2933, 1767 (sh), 1710, 1421, 1388, 1318, 1042, 719 cm^{-1}; ^{1}H NMR (DMSO-d_6) δ 1.04 (s, 6 H), 1.53 (s, 4 H), 3.48−3.58 (m, 4 H), 4.37, 4.38 (2 s, 2 H), 7.80−7.96 (m, 8 H); ^{13}C NMR (DMSO-d_6) δ 25.0, 33.5, 33.6, 47.8, 71.6, 122.9, 131.7, 134.2, 168.2; the other signals were not detected and are believed to overlap with the observed peaks; the ^{13}C NMR data are in agreement with the DEPT spectrum; MS (+CI) *m*/*z* 437 [M + 1]$^+$; M_r (+CI) 437.17172 [M + 1]$^+$ (calcd for $C_{24}H_{25}N_2O_6$ 437.17126).

1,7-Bis(phthalimido)-2,6-heptanediol (5c). Using **4c**[9b] (2.31 g, 18 mmol) and the general procedure, **5c** (white solid) was obtained as a mixture of diastereomers (2:1, ^{13}C NMR analysis): yield 3.57 g (47%); mp 165−170 °C; R_f 0.28 (2:1 EtOAc/hexanes); IR (KBr) 3533, 2933, 1771 (sh), 1718, 1430, 1395, 1048, 721 cm^{-1}; ^{1}H NMR (DMSO-d_6) δ 1.25−1.70 (m, 6 H), 3.41−3.58 (m, 4 H), 3.74 (br s, 2 H), 4.84−4.87 (m, 2 H), 7.81−7.88 (m, 8 H); ^{13}C NMR (DMSO-d_6) δ 21.2, 21.3, 34.3, 44.1, 67.1, 122.8, 131.7, 134.1, 167.9; the other signals were not detected and are believed to overlap with the observed peaks; MS (+CI) *m*/*z* 423 [M + 1]$^+$; M_r (+CI) 423.15639 [M + 1]$^+$ (calcd for $C_{23}H_{23}N_2O_6$ 423.15561).

General Procedure for the Preparation of Cyclic Ether Diamine Hydrobromide Salts 2. Bis(phthalimido)alkanediol **5** (2.7 mmol) and aqueous 48% HBr (38 mL) were heated (70−125 °C) for 2−27 d. After completion of reaction, the reaction mixture was cooled to 4 °C (1 h) and then the precipitate removed by filtration. The aqueous filtrate was washed with Et_2O (2 × 20 mL) and concentrated in vacuo to give **2**.

2,5-Bis(aminomethyl)tetrahydrofuran Dihydrobromide (2a).[3,7] **Method A**. Using **5a** (1.10 g, 2.7 mmol) and the general procedure (90 °C, 10 d), crude **2a** (yellow solid) was obtained as a mixture of diastereomers (1.2:1, ^{1}H NMR analysis): yield 0.79 g (∼100%); mp > 230 °C dec; IR (KBr) 3029, 1696, 1575, 1503, 1401, 1053, 1015, 967, 918, 788 cm^{-1}; ^{1}H NMR (CD_3OD) δ 1.73−1.83 (m, 2 H), 2.17−2.26 (m, 2 H), 2.95−3.21 (m, 4 H), 4.20−4.37 (m, 2 H); ^{13}C NMR (CD_3OD) δ 29.6, 29.8, 44.2, 44.9, 76.8, 77.5; the ^{1}H and ^{13}C NMR data are in agreement with the COSY, HMQC, and DEPT spectra; MS (+CI) *m*/*z* 131 [M + 1]$^+$; M_r (+CI) 131.11850 [M + 1]$^+$ (calcd for $C_6H_{15}N_2O$ 131.11844). A sample (104 mg) was further purified by recrystallization (EtOH−Et_2O) to give **2a** (21 mg) as a mixture of diastereomers (1.2:1, ^{13}C NMR analysis). Anal. Calcd for $C_6H_{16}Br_2N_2O$: C, 24.68; H, 5.52; N, 9.59. Found: C, 24.66; H, 5.36; N, 9.48.

Method B. Using **5a** (1.10 g, 2.7 mmol) and the general procedure (120−125 °C, 1 d), crude **2a** (yellow solid) was obtained as a mixture of diastereomers (1.3:1, ^{1}H NMR analysis): yield 0.78 g (99%); ^{1}H NMR (CD_3OD) δ 1.75−1.85 (m, 2 H), 2.17−2.28 (m, 2 H), 2.97−3.23 (m, 4 H), 4.23−4.40 (m, 2 H); ^{13}C NMR (CD_3OD) δ 29.6, 29.8, 44.2, 44.9, 76.7, 77.4.

2,5-Bis(aminomethyl)-2,5-dimethyltetrahydrofuran Dihydrobromide (2b). Using **5b** (1.18 g, 2.7 mmol) and the general procedure (70 °C, 9 d), crude **2b** (brown solid) was obtained as a mixture of diastereomers (1.3:1, ^{13}C NMR analysis): yield 0.85 g (98%); ^{1}H NMR (D_2O) δ 1.29, 1.33 (2 s, 6 H), 1.95−2.13 (m, 4 H), 2.69 (s, impurity, 1.5 H), 3.02−3.14 (m, 4 H); ^{13}C NMR (D_2O) δ 23.9, 24.0, 34.4, 34.7, 47.5, 47.8, 81.1, 81.3. The product was purified for analysis by recrystallization (EtOH−Et_2O) to give a flocculent solid as an apparent single diastereomer (>9:1, ^{13}C NMR analysis): yield 0.10 g (11%); mp > 270 °C dec; IR (KBr) 3427, 3029, 2971, 2922, 2655, 2559, 1581, 1495, 1467, 1396, 1145, 1056, 981, 764 cm^{-1}; ^{1}H NMR (CD_3OD) δ 1.38 (s, 6 H), 2.09 (s, 4 H), 3.00−3.13 (m, 4 H); ^{13}C NMR (CD_3OD) δ 25.2, 36.5, 49.4, 82.9; no signals were detected for the other diastereomer; the ^{1}H and ^{13}C NMR data are in agreement with the HMQC spectrum; MS (+CI) *m*/*z* 159 [M + 1]$^+$; M_r (+CI) 159.14896 [M + 1]$^+$ (calcd for $C_8H_{19}N_2O$ 159.14974). Anal. Calcd for $C_8H_{20}Br_2N_2O$: C, 30.02; H, 6.30; N, 8.75. Found: C, 30.21; H, 6.32; N, 8.75.

2,6-Bis(aminomethyl)tetrahydropyran Dihydrobromide (2c). Using **5c** (1.14 g, 2.70 mmol) and the general procedure (90 °C, 25 d), crude **2c** (brown solid) was obtained as a mixture of diastereomers (5.5:1, ^{13}C NMR analysis): yield 0.83 g (∼100%); ^{13}C NMR (CD_3OD) δ 18.3, 22.9, 27.9, 28.9, 42.7, 44.9, 69.3, 74.7.

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The product was purified for analysis by recrystallization (EtOH−Et_2O) to give a brown solid as a mixture of diastereomers (5.2:1, ^1H and ^{13}C NMR analysis): yield 0.11 g (13%); mp > 280 °C dec; IR (KBr) 3400, 3029, 2937, 1590, 1507, 1450, 1400, 1158, 1067, 985, 924 cm^{-1}; ^1H NMR (CD_3OD) δ 1.20−2.00 (m, 6 H), 2.92−3.18 (m, 4 H), 3.75 (t, J = 10.2 Hz, 1.7 H), 4.15 (br s, 0.3 H); ^{13}C NMR (CD_3OD) δ 23.0, 27.8, 29.0, 42.6, 45.0, 69.7, 75.0; one signal for the minor diastereomer was not detected; the ^1H and ^{13}C NMR data are in agreement with the COSY and HMQC spectra; MS (+CI) m/z 145 $[M + 1]^+$; M_r (+CI) 145.13443 $[M + 1]^+$ (calcd for $C_7H_{17}N_2O$ 145.13409).

General Procedure for the Preparation of Cbz-Protected Cyclic Ether Diamines 6. To a stirred aqueous solution (1 mL) of cyclic ether diamine dihydrobromide **2** (0.2 mmol) was added Et_3N (164 μL, 1.2 mmol), and then the reaction was stirred (rt, 30 min). Acetonitrile (1 mL) was added to the reaction and the mixture cooled (4 °C), and then benzyl chloroformate (71 μL, 0.5 mmol) was added dropwise with stirring. The mixture was stirred (4 °C, 1 h, and then rt, 3 h). EtOAc (20 mL) and H_2O (20 mL) were added to the reaction, and the organic layer was separated. The organic layer was successively washed with aqueous 0.05 N HCl, aqueous 0.5 N NaOH, and aqueous saturated brine, and then concentrated in vacuo. The crude product was purified by PTLC.

2,5-Bis(*N*-benzyloxycarbonylaminomethyl)tetrahydrofuran (6a). Using **2a** (58 mg, 0.2 mmol) and the general procedure, **6a** (white solid) was obtained as a mixture of diastereomers (1.2:1, ^{13}C NMR analysis) after PTLC using EtOAc/hexanes (1:1) as the eluent: yield 36 mg (45%); mp 86−88 °C; R_f 0.34 (1:1 EtOAc/hexanes); IR (neat) 3333, 3064, 3033, 2938, 2879, 1711, 1533, 1453, 1358, 1256, 1149, 1087, 739, 698 cm^{-1}; ^1H NMR ($CDCl_3$/acetone-d_6) δ 1.62 (br s, 2 H), 1.90−2.05 (m, 2 H), 3.10−3.23 (m, 2 H), 3.30−3.40 (m, 2 H), 3.95−4.13 (m, 2 H), 5.08 (s, 4 H), 5.67 (br s, 1.1 H), 6.00 (br s, 0.9 H), 7.25−7.35 (m, 10 H); ^{13}C NMR ($CDCl_3$) δ 28.1, 28.8, 44.8, 45.1, 66.7, 77.9, 78.6, 128.0, 128.1, 128.5, 136.5, 156.5; the other signals were not detected and are believed to overlap with the observed peaks; MS (+CI) m/z 399 $[M + 1]^+$; M_r (+CI) 399.19135 $[M + 1]^+$ (calcd for $C_{22}H_{27}N_2O_5$ 399.19200). Anal. Calcd for $C_{22}H_{26}N_2O_5$: C, 66.32; H, 6.58; N, 7.03. Found: C, 66.28; H, 6.59; N, 6.93.

2,5-Bis(*N*-benzyloxycarbonylaminomethyl)-2,5-dimethyltetrahydrofuran (6b). Using crude **2b** (64 mg, 0.2 mmol) and the general procedure, **6b** (semisolid) was obtained as a mixture of diastereomers (1.5:1, ^{13}C NMR analysis) after PTLC (2×) using first EtOAc/hexanes (1:1) and then EtOAc/CH_2Cl_2 (1:2) as the eluents: yield 26 mg (30%); R_f 0.45 (1:1 EtOAc/hexanes), R_f 0.62 (1:2 EtOAc/CH_2Cl_2); IR (neat) 3338, 3033, 2970, 2931, 2878, 1712, 1536, 1455, 1375, 1244, 1131, 1024, 884, 739, 698 cm^{-1}; ^1H NMR (acetone-d_6) δ 1.16, 1.18 (2 s, 6 H), 1.67−1.80 (m, 2 H), 1.81−2.02 (m, 2 H), 3.08−3.25 (m, 4 H), 5.07 (s, 4 H), 6.17 (br s, 1.2 H), 6.62 (br s, 0.8 H), 7.26−7.40 (m, 10 H); ^{13}C NMR (actone-d_6) δ 25.8, 26.1, 34.6, 35.0, 50.2, 50.4, 66.5, 84.2, 84.3, 128.5, 128.6, 129.2, 138.5, 157.6; the other signals were not detected and are believed to overlap with the observed peaks; MS (+CI) m/z 427 $[M + 1]^+$; M_r (+CI) 427.22233 $[M + 1]^+$ (calcd for $C_{24}H_{31}N_2O_5$ 427.22330). Anal. Calcd for $C_{24}H_{30}N_2O_5$: C, 67.59; H, 7.07; N, 6.57. Found: C, 67.72; H, 7.03; N, 6.40.

2,6-Bis(*N*-benzyloxycarbonylaminomethyl)tetrahydropyran (6c). Using crude **2c** (61 mg, 0.2 mmol) and the general procedure, **6c** (white solid) was obtained as an apparent single diastereomer (>9:1, ^{13}C NMR analysis) after PTLC using EtOAc/hexanes (1:1) as the eluents: yield 26 mg (31%); mp 95−100 °C; R_f 0.53 (1:1 EtOAc/hexanes); IR (neat) 3334, 3033, 2937, 2861, 1712, 1534, 1454, 1247, 1095, 739, 698 cm^{-1}; ^1H NMR (acetone-d_6) δ 1.10−1.90 (m, 6 H), 2.98−3.10 (m, 2 H), 3.27−3.37 (m, 2 H), 3.38−3.47 (m, 2 H), 5.04 (s, 4 H), 6.38 (br s, 2 H), 7.29−7.40 (m, 10 H); ^{13}C NMR (acetone-d_6) δ 23.3, 29.3, 46.8, 66.5, 77.4, 128.6, 128.8, 129.2, 138.5, 157.3; no signals were detected for the other diastereomer; MS (+CI) m/z 413 $[M + 1]^+$; M_r (+CI) 413.20714 $[M + 1]^+$ (calcd for $C_{23}H_{29}N_2O_5$ 413.20765). Anal. Calcd for $C_{23}H_{28}N_2O_5$: C, 66.97; H, 6.84; N, 6.79. Found: C, 66.82; H, 6.88; N, 6.50.

2,5-Bis(aminomethyl)tetrahydrofuran (1a).[3] **Method A. Deprotection of 6a.** A solution of **6a** (20 mg, 0.05 mmol) in MeOH (1.5 mL) was stirred (5 min) under a slow stream of N_2, and then 10% Pd−C (3.5 mg) was added. The reaction was maintained under a blanket of H_2 (1 atm) for 12 h (20 °C). The catalyst was removed by filtration over Celite, and the filtrate was evaporated under reduced pressure to afford **1a** (viscous oil) as a mixture of diastereomers (1.3:1, ^{13}C NMR analysis): yield 5.2 mg (80%); IR (neat) 3386, 2932, 1567, 1487, 1323, 1070, 820 cm^{-1}; ^1H NMR (CD_3OD) δ 1.55−1.68 (m, 2 H), 1.94−2.08 (m, 2 H), 2.60−2.82 (m, 4 H), 3.90−4.07 (m, 2 H); ^{13}C NMR (CD_3OD) δ 29.5, 30.1, 46.3, 46.7, 80.2, 80.7; MS (+CI) m/z 131 $[M + 1]^+$; M_r (+CI) 131.11816 $[M + 1]^+$ (calcd for $C_6H_{15}N_2O$ 131.11844).

Method B. Use of an Ion-Exchange Resin and 2a. A column was packed with Amberlite IRA-67 ion-exchange resin (5 mL), and the column was eluted with deionized H_2O. An aqueous solution (0.5 mL) of **2a** (24 mg, 0.082 mmol) was loaded onto the column and eluted with deionized H_2O. The basic fractions (pH > 9.0) were collected and concentrated in vacuo to give **1a** (viscous oil) as a mixture of diastereomers (1:1.1, ^{13}C NMR analysis): yield 9.7 mg (91%); ^1H NMR (CD_3OD) δ 1.57−1.70 (m, 2 H), 1.96−2.11 (m, 2 H), 2.63−2.90 (m, 4 H), 3.93−4.10 (m, 2 H); ^{13}C NMR (CD_3OD) δ 29.5, 30.1, 46.1, 46.6, 79.9, 80.4.

Resolution of 1,6-Bis(phthalimido)-2,5-hexanediol (5a) by Fractional Recrystallization. A mixture of crude **5a** (668 mg, a mixture of diastereomers (2.2:1 ratio of *meso*- and *dl*-forms), mp 235−240 °C) and DMF (20 mL) was heated to 80 °C and then filtered to remove the insoluble impurities. The solution was allowed to stand overnight (rt), leading to the precipitation of *meso*-enriched **5a** (430 mg, a mixture of diastereomers (8:1 ratio of *meso*- and *dl*-forms)). The recrystallization was repeated, providing a 9.4:1 mixture of (2*R*,5*S*)-*meso*-**5a** and *dl*-**5a** (318 mg, 48% yield): mp 249−250 °C; ^1H NMR (DMSO-d_6) δ 1.26−1.68 (m, 4 H), 3.47 (dd, J = 13.6, 4.5 Hz, 2 H), 3.56 (dd, J = 13.6, 7.8 Hz, 2 H), 3.74 (br s, 2 H), 4.89 (d, J = 5.1 Hz, 2 H), 7.82−7.89 (m, 8 H); ^{13}C NMR (DMSO-d_6) δ 30.7, 44.1, 67.5, 122.8, 131.7, 134.1, 167.9.

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Supporting Information Available: ^1H and ^{13}C NMR spectroscopic data for all compounds reported. This information is available free of charge via the Internet at http://pubs.acs.org.

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