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Synthesis of Conformationally Constrained Diaminodicarboxylic Acid Derivatives

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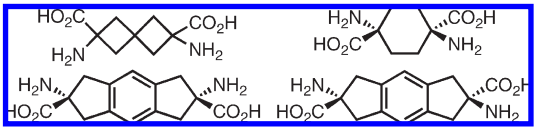
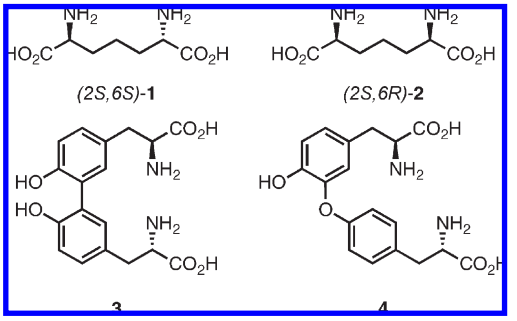


Functionally protected forms of three conformationally constrained diaminodicarboxylic acids were synthesized and characterized. 2,2′-Diaminospiro[3.3]heptane-2,2′-dicarboxylic acid, an analogue of diaminopimelic acid, was prepared in racemic form and the structure established by X-ray crystallographic analysis of the methyl ester hydrochloride. *trans*-1,4-Diaminocyclohexane-1,4-dicarboxylic acid was prepared and its structure established by X-ray crystallographic analysis of the corresponding Cbz-protected ethyl ester. *cis*- and *trans*-2,6-diamino-1,2,3,5,6,7-hexahydro-*s*-indacene-2,6-dicarboxylic acids were synthesized and the structures assigned by X-ray crystallographic analysis of the corresponding Boc-protected ethyl ester and Cbz-protected ethyl ester, respectively.

Introduction

Interest in the chemistry of diaminodicarboxylic acids has grown following the recognition that these are important biological agents. Diaminopimelic acids (DAPs) such as (2*S*,6*S*)-**1** and (2*S*,6*R*)-**2** are essential for the growth of bacteria and plants.[1] Dityrosine (**3**) and isodityrosine (**4**) stabilize structural proteins in bacteria and plants.[2] DAP- and isodityrosine-containing peptides exhibit antibiotic and antitumor activities.[3] These compounds inspired syntheses of a number of structurally related unnatural diaminodicarboxylic acids intended to enhance bioactivity and/or control peptide secondary structure.[4]



Novel diaminodicarboxylic acids have also been used in assembly of nanoscale structures.[5] Our interest in crystal engineering using 1,4-piperazine-2,5-dione scaffolds[6] led to a need for compounds **5**−**7** for construction of linear piperazinedione oligomers.[7] 2,2′-Diaminospiro[3.3]heptane-2,

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(4) (a) Cox, R. J.; Sutherland, A.; Vederas, J. C. *Bioorg. Med. Chem.* **2000**, *8*, 843–871. (b) Lygo, B.; Crosby, J.; Peterson, J. A. *Tetrahedron* **2001**, *57*, 6447–6453. (c) Williams, R. M.; Fegley, G. J.; Gallegos, R.; Schaefer, F.; Pruess, D. L. *Tetrahedron* **1996**, *52*, 1149–1164.
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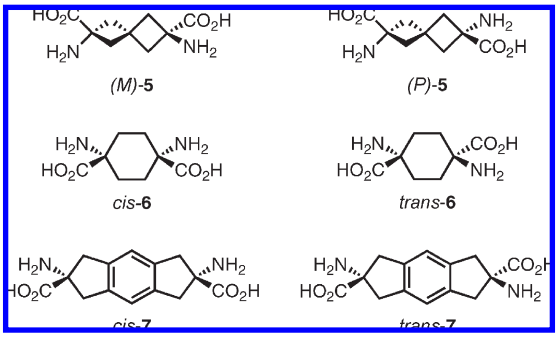
2′-dicarboxylic acid (**5**) is a DAP analogue that is capable of supporting enantiomerism, and to the best of our knowledge is unknown. 1,4-Diaminocyclohexane-1,4-dicarboxylic acid (**6**) is achiral, but can exist as cis and trans diastereomers. Both diastereomers have previously been prepared.[8] However, the issue of stereochemistry was unresolved at the time our work began.[7b] 2,6-Diamino-1,2,3,5,6,7-hexahydro-*s*-indacene-2,6-dicarboxylic acid (**7**) is similar to **6** in that it is achiral but can exist as cis and trans diastereomers. Precursors to these diastereomers have previously been prepared,[9] but stereochemistry remains unassigned to the diastereomeric products.[10] We report herein syntheses of derivatives of racemic **5**, *trans*-**6**, *cis*-**7**, and *trans*-**7**, along with crystallographic analyses that establish the structures of these four compounds.

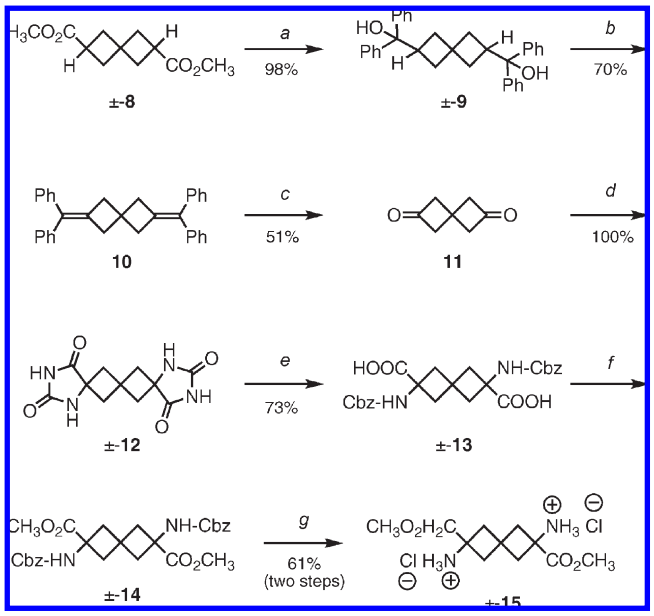


Results

The synthesis of functionally protected forms of 2,2′-diaminospiro[3.3]heptane-2,2′-dicarboxylic acid is depicted in Scheme 1. The dimethyl ester of Fecht acid, ±-**8**,[11] was treated with an excess of phenylmagnesium bromide, producing diol ±-**9**[12] in 98% yield. Acid-catalyzed double elimination produced diene **10**[12] in 70% yield. Rhodium-catalyzed oxidative cleavage of the alkene groups gave dione **11**[13] in 51% yield. Application of the Bucherer−Bergs reaction to **11** produced the bis-hydantoin ±-**12** quantitatively. Base hydrolysis, followed by *N*-acylation with Cbz-Cl gave dicarboxylic acid ±-**13** in 73% yield over the two steps. Treatment of ±-**13** with cesium carbonate, lyophilization, and reaction of the salt with iodomethane in DMF produced diester ±-**14**. Hydrogenolysis over Pd/C in ethyl acetate, followed by treatment with gaseous HCl, provided the bis-amine hydrochloride ±-**15** in 61% yield from ±-**13**.

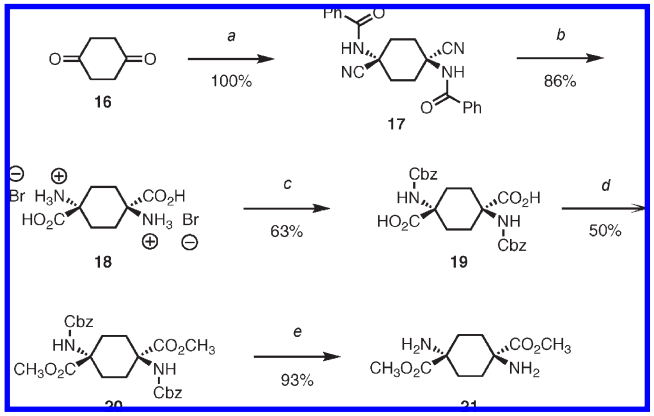
The synthesis of functionally protected forms of *trans*-1,4-diamino-1,4-cyclohexanedicarboxylic acid is depicted in Scheme 2. Following the procedure of Paventi et al.,[14] application of the Strecker reaction to 1,4-cyclohexanedione (**16**), followed by treatment of the crude product with benzoyl chloride and base, gave a single isomer of dinitrile **17** in quantitative yield over the two steps. Hydrolysis under strongly acidic conditions produced the hydrobromide salt **18** in 86% yield. Reaction of **18** with Cbz-Cl gave dicarboxylic acid **19** in 63% yield. Treatment with cesium carbonate, lyophilization, and reaction of the salt with iodomethane in DMF produced diester **20** in 50% yield. Hydrogenolysis over Pd/C in ethyl acetate provided the diaminodicarboxylic ester **21** in 93% yield.

SCHEME 1. Synthesis of Derivatives 12−15 of 2,2′-Diaminospiro[3.3]heptane-2,2′-dicarboxylic Acid[a]



[a]Reagents: (a) PhMgBr, Et_2O. (b) $(COOH)_2$, $Na_2(COO)_2$, heat. (c) $RuCl_3$, $NaIO_4$, acetonitrile, CCl_4, water. (d) KCN, $(NH_4)_2CO_3$, EtOH, water. (e) NaOH, water, heat; Cbz-Cl, acetone. (f) Cs_2CO_3, water; CH_3I, DMF. (g) H_2, Pd/C, EtOAc; HCl (g), Et_2O.

SCHEME 2. Synthesis of Derivatives 17−21 of *trans*-1,4-Diamino-1,4-cyclohexanedicarboxylic Acid[a]



[a]Reagents: (a) KCN, NH_4Cl, water; Ph(CO)Cl, K_2CO_3, THF, water. (b) concd HBr, heat. (c) Cbz-Cl, $NaHCO_3$, water. (d) Cs_2CO_3, water; CH_3I, DMF. (e) H_2, Pd/C, EtOAc.

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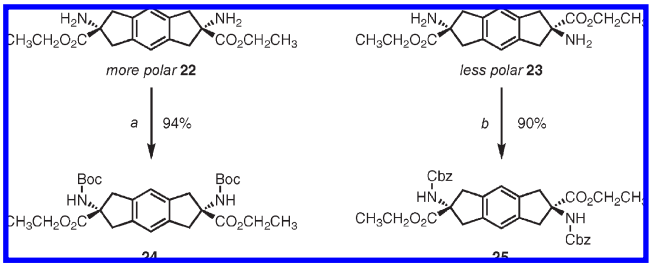
SCHEME 3. Synthesis of Derivatives 22−25 of *cis*- and *trans*-2,6-Diamino-1,2,3,5,6,7-hexahydro-*s*-indacene-2,6-dicarboxylic Acid[a]



[a]Reagents: (a) $(Boc)_2O$, CH_2Cl_2, heat. (b) $(Cbz)_2O$, CH_2Cl_2, heat.

The synthesis of functionally protected forms of *cis*- and *trans*-2,6-diamino-1,2,3,5,6,7-hexahydro-*s*-indacene-2,6-dicarboxylic acids is depicted in Scheme 3. A mixture of aminoesters **22** and **23** was produced from a mixture of the corresponding isonitrile-esters according to the procedure of Kotha and Brahmachary.[9] Aminoesters **22** and **23** were easily separated by chromatography, and were converted to the corresponding carbamates **24** and **25** by treatment with Boc anhydride and Cbz anhydride in 94% and 90% yields, respectively.

A summary of crystallographic data for compounds ±-**15**, **20**, **24**, and **25** is given in Table 1. Structures drawn from crystal structure data illustrating molecular conformations appear in Figure 1. Complete crystallographic data (CIF files) and brief descriptions of the molecular conformations and the supramolecular assemblies observed in the crystals appear in the Supporting Information that accompanies this article.

TABLE 1. Crystallographic Data for Compounds ±-15, 20, 24, and 25

compd	±-**15**	**20**	**24**	**25**
formula	$C_{11}H_{20}Cl_2N_2O_4$	$C_{26}H_{30}N_2O_8$	$C_{31}H_{47}N_3O_9$	$C_{34}H_{36}N_2O_8$
wt (g mol^{-1})	315.19	498.52	605.72	600.65
temp (K)	293(2)	100(2)	170(2)	170(2)
radiation	Mo Kα	Mo Kα	Mo Kα	Mo Kα
cryst syst	monoclinic	monoclinic	monoclinic	triclinic
space group	$P2_1/c$	$P2_1/c$	$P2_1/c$	$P\bar{1}$
a (Å)	8.681(6)	10.2758(6)	10.7517(11)	7.7824(8)
b (Å)	16.982(12)	7.1597(4)	36.694(4)	9.1091(9)
c (Å)	11.343(8)	16.6143(10)	9.4807(10)	11.1134(11)
α (deg)	90	90	90	98.037(2)
β (deg)	90.511(13)	92.7750(10)	115.835(2)	106.442(2)
γ (deg)	90	90	90	100.826(2)
V (Å^3)	1672(2)	1220.91(12)	3366.5(6)	726.43(13)
Z	4	2	4	1
R_1 (obsd data)	0.0643	0.0393	0.0678	0.0418
wR_2 (all data)	0.1310	0.1043	0.2258	0.0864
GOF on F^2	0.774	0.997	0.895	0.867

Discussion

Synthesis of diaminodicarboxylic ester ±-**15** was more difficult than anticipated. We planned to construct the spiro[3.3]heptane ring system from pentaerythritol tetrabromide using protocols established for monocyclic small-ring systems.[15] This approach failed, and so a longer route was employed (Scheme 1). Others had previously described the conversion of Fecht acid to diene **10**.[11,12] While oxidation of similar systems yielded pinacol rearranged products,[16] ruthenium-catalyzed oxidative cleavage of diene **10** generated dione **11** in good yield.[17] Bis-hydantoin ±-**12** formed under Bucherer−Bergs conditions in high yield, but hydrolysis and protection were difficult to scale up, and so generation of the *N*-Cbz acid ±-**13** proved to be a bottleneck. Esterification to ±-**14** and hydogenolysis provided ±-**15**.

Synthesis of diaminodicarboxylic ester **21** was previously described,[8] but by somewhat different methods. One synthesis prepared compound **20** and confirmed its trans stereochemistry by X-ray crystallographic analysis.[8c] However, the structure reported here is polymorphic with the previously reported structure.

Although the synthesis of diaminodicarboxylic esters **22** and **23** was previously described,[9] and a crystal structure of the isonitrile precursor to **23** was recently published,[10] no definitive structural identification linked to the chromatographic behavior of **22** and **23** or precursors to these compounds has appeared. The crystal structures of **24** and **25** now provide this identification.

These compounds will be used in our future crystal engineering efforts, and may also be useful to investigators working to design and produce bioactive peptide ligands.

Experimental Section[18]

Dimethyl Spiro[3.3]heptane-2,6-dicarboxylate (±-8).[11] Oxalyl chloride (7.0 mL, 80 mmol) was added to a solution of spiro[3.3]heptane-2,6-dicarboxylic acid[11] (5.71 g, 31 mmol) in dry CH_2Cl_2 (40 mL) under argon. The solution was stirred at room temperature for 3 h. The majority of solvent was then removed in vacuo, the flask was cooled in an ice−water bath, and dry MeOH (40 mL) was slowly added. The solution was allowed to warm to room temperature and was stirred overnight. Volatiles were then removed under vacuum. The residue was taken up in EtOAc (250 mL) and the solution was washed with $NaHCO_3$ (2 × 250 mL) and brine (250 mL), dried ($MgSO_4$), filtered, and concentrated to give 6.56 g (31 mmol, 100%) of ±-**8** as a pale yellow oil, R_f 0.46 (50% EtOAc/hexanes, blue in anisaldehyde stain). IR (NaCl) (cm^{-1}) 1733; ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.13 (8H, m), 2.87 (2H, pentet, J = 8.5 Hz), 3.53 (6H, s); ^{13}C NMR (75 MHz, $CDCl_3$) δ 32.4, 36.5, 37.1, 37.7, 51.4, 175.4; HRMS (FAB+) calcd for $C_{11}H_{17}O_4$ $(M + H)^+$ 213.1127, found 213.1134 (+3.2 ppm).

2,6-Di(diphenylhydroxy)methylspiro[3.3]heptane (±-9).[12] A solution of PhMgBr in Et_2O (2.9 M, 100 mL, 0.29 mol) was injected into a solution of ±-**8** (12.4 g, 58 mmol) in Et_2O (100 mL) under argon and the mixture was cooled in an ice−water bath. The reaction was warmed to room temperature and heated at reflux for 1.5 h. The solution was then cooled in an ice−water bath and a saturated aqueous solution of ammonium chloride was slowly added until the reaction was quenched (exothermic reaction ceased). The solution was stirred for an additional 10 min at room temperature, then diluted with brine (1 L) and extracted with EtOAc (5 × 200 mL). The organic extracts were washed with brine (500 mL), dried ($MgSO_4$), filtered, and concentrated to leave a yellow oil. This material was subjected to flash chromatography (230−400 mesh silica) using 100%

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(18) The General Experimental Section appears in the Supporting Information.

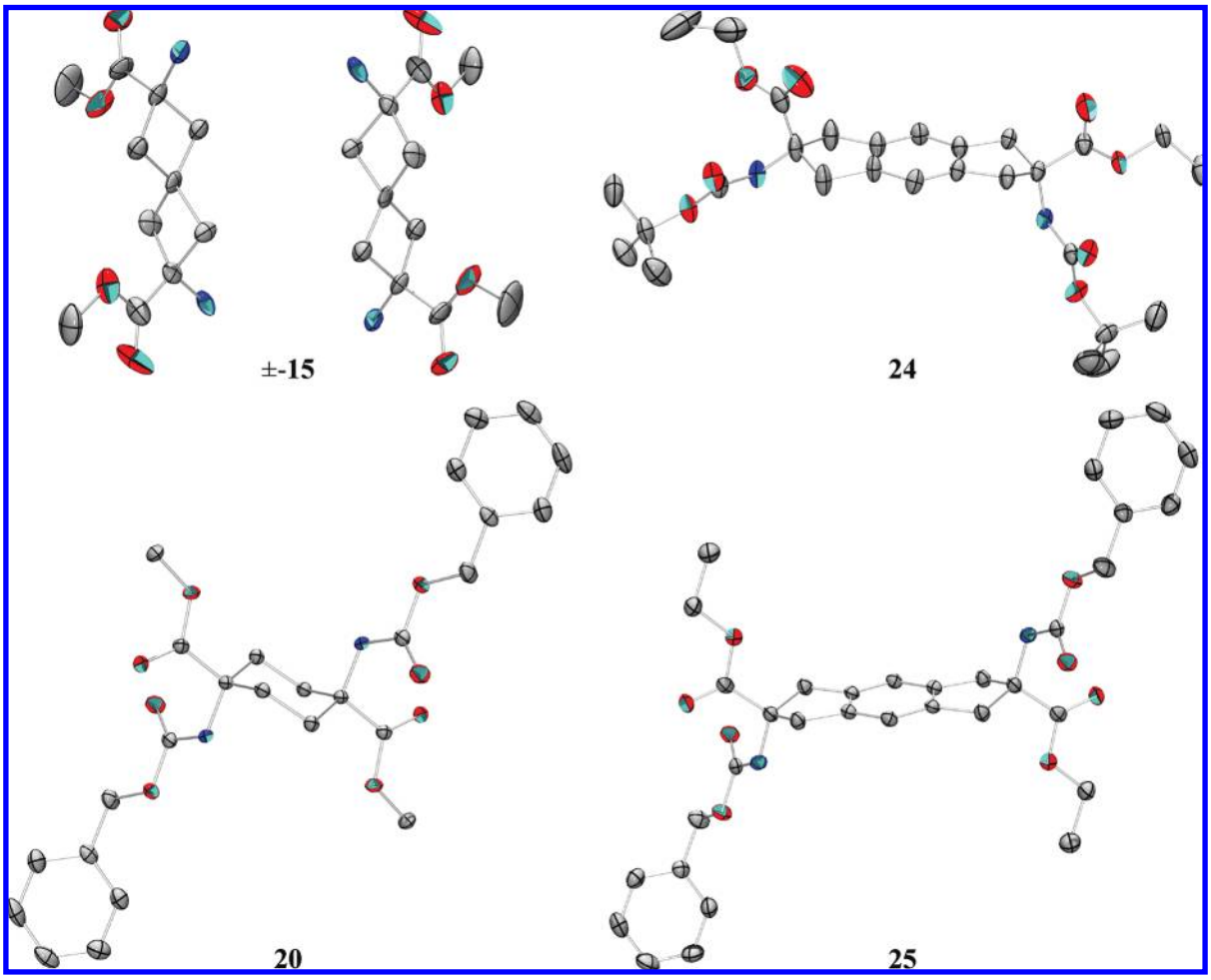

FIGURE 1. Conformers of compounds ±-**15**, **20**, **24**, and **25** observed by X-ray crystallography.

hexanes as elutant until all UV active byproduct was removed. The elutant was then changed to 20% EtOAc/hexanes, giving 26.4 g (57 mmol, 98%) of ±-**9** as a light yellow foam, R_f 0.13 (10% EtOAc/hexanes, brown in anisaldehyde stain), mp 52−55 °C (lit.[12] mp 56 °C), which was used without further purification. IR (KBr) (cm^{-1}) 3506 (br), 1449, 751, 702; ^{1}H NMR (300 MHz, DMSO-d_6) δ 1.54 (2H, dt, J = 3.9, 7.2 Hz), 1.82 (2H, dt, J = 3.9, 7.3 Hz), 1.95 (2H, t, J = 10.1 Hz), 2.07 (2H, t, J = 9.9 Hz), 3.18 (2H, pentet, J = 8.5 Hz), 5.33 (2H, s), 7.12 (4H, m), 7.21 (4H, t, J = 7.4 Hz), 7.24 (4H, t, J = 7.4 Hz), 7.32 (4H, d, J = 7.8 Hz), 7.34 (4H, d, J = 7.6 Hz); ^{13}C NMR (75 MHz, DMSO-d_6) δ 32.6, 34.3, 35.9, 38.3, 76.7, 126.0, 126.1, 126.2, 127.6, 147.4; HRMS (FAB+) calcd for $C_{33}H_{31}O$ $(M - OH)^+$ 443.2375, found 443.2363 (−2.6 ppm).

2,6-Di(benzhydrylidene)spiro[3.3]heptane (10).[12] A ground mixture of oxalic acid (88.1 g, 0.71 mol) and sodium oxalate (15.5 g, 0.12 mol) was deposited in a beaker containing oily solid ±-**9** (22.9 g, 50 mmol), and the contents were intermixed. A watch glass was placed over the beaker and the neat mixture thermolyzed in an oil bath heated to 175−180 °C for 2 h. The material was then cooled to room temperature and partitioned between water (500 mL) and Et_2O (1 L). The heterogeneous solvent system was vacuum filtered, the filtrate was washed thoroughly with Et_2O, the organic phase was separated, and the aqueous phase was extracted with Et_2O (3 × 250 mL). The Et_2O fractions were combined, washed with $NaHCO_3$ (2 × 250 mL) and brine (250 mL), treated with charcoal, dried ($MgSO_4$), filtered, and concentrated under vacuum to leave a yellow oil. The oil was dried to a sticky solid by azeotroping with MeOH, and the material was further purified by trituration with hot MeOH to give eventually a yellow solid. The MeOH slurry was cooled in a freezer (−22 °C) overnight and filtered, then the solid was washed sparingly with cold MeOH to give 14.9 g (35 mmol, 70%) of **10** as a light yellow solid, R_f 0.54 (20% Et_2O/hexanes, black in PMA stain), mp 112−113 °C (lit.[12] mp 116−116.5 °C). IR (KBr) (cm^{-1}) 3086, 3018, 1499, 1443, 702; ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.02 (8H, s), 7.22 (20H, m); ^{13}C NMR (75 MHz, $CDCl_3$) δ 35.3, 44.9, 126.3, 128.0, 128.8, 134.0, 135.2, 140.6.

Spiro[3.3]heptane-2,6-dione (11).[13] To a solution of **10** (7.97 g, 19.0 mmol) in a mixture of acetonitrile (120 mL), CCl_4 (120 mL), and water (180 mL) were added $RuCl_3$ dihydrate (0.65 g, 3.1 mmol, 16 mol %) and $NaIO_4$ (40 g, 0.19 mol) in one portion. The solution was stirred at room temperature for 5 min, and then heated at reflux for 1.5 h. The solution was then cooled to room temperature and the insoluble salts were collected by filtration and extracted with CH_2Cl_2 in a Soxhlet extractor overnight. The CH_2Cl_2 phases were combined and concentrated to leave a brown residue. The material was dry loaded onto silica, and subjected to gravity chromatography (230−400 mesh silica) with 35% EtOAc/hexanes as elutant to give the product as a yellow oil (contaminated with I_2). The oil was purified by trituration with hot hexanes to give a light yellow solid. The slurry was cooled in the freezer (−22 °C) overnight, then the solid was collected by filtration, washed with hexanes, and dried to give 1.2 g (9.7 mmol, 51%) of **11** as a light yellow solid, R_f 0.5 (40% EtOAc/hexanes, black in anisaldehyde stain),

mp 59−62 °C (lit[13] mp 81 °C), which was used without further purification. IR (KBr) (cm^{-1}) 1781; ^1H NMR (300 MHz, $CDCl_3$) δ 3.34 (8H, s); ^{13}C NMR (75 MHz, $CDCl_3$) δ 23.4, 58.6, 204.7. Anal. Calcd for $C_7H_8O_2$: C 67.73, H 6.50. Found: C 66.90, H 6.59.

Bis(spiro-2,6-hydantoin)spiro[3.3]heptane (±-12). Potassium cyanide (1.65 g, 25 mmol) and ammonium carbonate (13.3 g, 85 mmol) were added to a solution of **11** (1.05 g, 8.5 mmol) in absolute EtOH (30 mL) and water (30 mL). The solution was heated in an oil bath at 60 °C. The solution cleared after 3 h of heating, and then a white precipitate gradually formed. After 3 d, the reaction was cooled to room temperature, and further cooled in an ice−water bath, then concd HCl (ca. 20 mL) added dropwise to the solution over a 1 h period until a pH of 2 was reached. The reaction mixture was cooled in a freezer (−22 °C) overnight, Et_2O (60 mL) was added, the cold mixture was vacuum filtered, and the precipitate was washed with Et_2O. The white solid was further purified by vigorous stirring with absolute EtOH (100 mL) at room temperature overnight. The mixture was filtered to give 2.28 g (8.6 mmol, 100%) of ±-**12** as a white solid, mp 358 °C dec. IR (KBr) (cm^{-1}) 3188 (br), 1781, 1725; ^1H NMR (300 MHz, DMSO-d_6) δ 2.21 (2H, d, J = 12.5 Hz), 2.28 (2H, d, J = 12.7 Hz), 2.39 (2H, dd, J = 3.4, 12.6 Hz), 2.54 (2H, dd, J = 3.2, 12.5 Hz), 8.15 (2H, s), 10.45 (2H, s); ^{13}C NMR (75 MHz, DMSO-d_6) δ 27.4, 44.0, 44.2, 57.1, 156.1, 178.5; HRMS (EI) calcd for $C_{11}H_{12}N_4O_4$ (M^+) 264.0853, found 264.0865 (+4.5 ppm).

2,6-Di(benzyloxycarbonyl)aminospiro[3.3]heptane-2,6-dicarboxylic Acid (±-13). (Note: Successful reaction is limited to this scale.) Compound ±-**12** (136 mg, 0.52 mmol) was mixed with 3 M NaOH solution (1 mL) and heated at vigorous reflux for 24 h. A trace amount of precipitate developed after this time. The solution was cooled in an ice−water bath, and a solution of benzyl chloroformate (1 mL, 7.0 mmol) in acetone (5 mL) followed by NaOH (400 mg, 10 mmol) in water (5 mL) were added. The reaction was warmed to room temperature and stirred overnight. The reaction mixture was washed with Et_2O (10 mL), the Et_2O phase was back-extracted with water (10 mL), and the aqueous fractions were combined, diluted with water (100 mL), and acidified with concd HCl until a white precipitate was observed (pH 2). The acidified solution was extracted with EtOAc (3 × 100 mL). Extraction forms an emulsion that was collected together with the EtOAc layer. The emulsified organic phase was dried ($MgSO_4$), filtered, and concentrated to give an opaque oil, which was freeze−pump−thawed (twice) and triturated with hot hexanes to produce 178 mg (0.37 mmol, 73% for two steps) of ±-**13** as a white solid, mp 192−194 °C. IR (KBr) (cm^{-1}) 3292, 1709, 1644; ^1H NMR (300 MHz, CD_3OD) δ 2.37 (4H, t, J = 11.7 Hz), 2.74 (4H, d, J = 9.5 Hz), 5.05 (4H, s), 7.32 (10H, m); ^{13}C NMR (75 MHz, CD_3OD) δ 33.0, 45.0, 45.5, 55.4, 67.3, 128.6, 128.9, 129.4, 138.1, 157.8, 177.2; HRMS (FAB+) cacld for $C_{25}H_{27}N_2O_8$ $(M + H)^+$ 483.1767, found 483.1744 (−4.9 ppm).

Dimethyl 2,6-Diaminospiro[3.3]heptane-2,6-dicarboxylate Hydrochloride (±-15). Dicarboxylic acid ±-**13** (190 mg, 0.39 mmol) was dissolved in a 5% Cs_2CO_3 solution (15 mL) by heating. Lyophilization gave a white salt. Dry DMF (10 mL) and iodomethane (0.5 mL, 8.0 mmol) were injected into the flask containing the salt under argon and the reaction was stirred at room temperature overnight. After 24 h, additional iodomethane (0.5 mL, 8.0 mmol) was added, and the reaction was stirred an additional 24 h. Volatiles were removed under vacuum, the yellow residue was partitioned between water (100 mL) and EtOAc (100 mL), and the aqueous phase was separated and extracted with EtOAc (3 × 100 mL). The EtOAc phases were combined, washed with Na_2SO_3 (100 mL) and brine (100 mL), dried ($MgSO_4$), filtered, and concentrated to a yellow sticky solid that was purified by flash chromatography (230−400 mesh silica, pretreated 1% NEt_3) with 50% EtOAc/hexanes as elutant to give 173 mg of the crude diester ±-**14** as a sticky, clear oil, R_f 0.34 (50% EtOAc/hexanes, blue-yellow in PMA stain). This material was taken up in EtOAc (10 mL) and treated with 10% Pd/C (40 mg) under H_2 (55 psi) in a hydrogenator. After 20 h, the contents were filtered, solids were washed with CH_2Cl_2, and the filtrate was concentrated. The resulting oil was dissolved in Et_2O (25 mL), the solution was cooled in an ice−water bath, and anhydrous HCl gas was bubbled through the solution until a white precipitate was observed. The Et_2O solvent was decanted and the sticky solid was dried under vacuum to give a dry tan solid. The solid was triturated with hot acetonitrile, then the solution was cooled to room temperature and filtered to give 74.1 mg (0.24 mmol, 61% for two steps) of ±-**15** HCl salt as an off-white solid, R_f 0.13 (50% EtOH/EtOAc, yellow in ninhydrin stain), mp 226−228 °C. IR (KBr) (cm^{-1}) 3421(br), 1741; ^1H NMR (300 MHz, CD_3OD) δ 2.63 (2H, d, J = 15.1 Hz), 2.71 (2H, d, J = 13.7 Hz), 2.78 (1H, d, J = 4.4 Hz), 2.82 (1H, d, J = 4.4 Hz), 2.93 (1H, d, J = 3.4 Hz), 2.97 (1H, d, J = 3.4 Hz), 3.87 (6H, s); ^{13}C NMR (75 MHz, CD_3OD) δ 31.2, 43.3, 44.1, 54.0, 54.1, 172.3; HRMS (FAB+) calcd for $C_{11}H_{19}N_2O_4$ $(M + H)^+$ 243.1345, found 243.1343 (−0.8 ppm).

***trans*-1,4-Di(phenylcarbonyl)aminocyclohexane-1,4-dinitrile (17).**[8] Potassium cyanide (5.3 g, 81 mmol) was added with stirring to a solution of 1,4-cyclohexanedione (4.35 g, 39 mmol) and ammonium chloride (4.3 g, 81 mmol) in water (25 mL) cooled in an ice−water bath. A thick white precipitate formed after a few minutes. The ice bath was removed and the reaction mixture was stirred at room temperature for 2 d. The mixture was filtered, then the white precipitate was washed with a minimum of cold water and cold $CHCl_3$ and dried in vacuo to leave a white solid (6.4 g). This material was immediately deposited into a mixture of K_2CO_3 (15.6 g, 110 mmol) in THF (780 mL) and water (1 L). Benzoyl chloride (9.5 mL, 82 mmol) was added to the mixture, and the reaction was vigorously stirred at room temperature. After a few minutes, a white precipitate formed. After 3 d, the mixture was filtered, then the precipitate was washed with water and dried in vacuo to give 13.6 g (37 mmol, 100%) of **17** as a white solid, mp 316−318 °C, R_f 0.78 (5% MeOH/EtOAc, light purple in anisaldehyde). IR (KBr) (cm^{-1}) 1659; ^1H NMR (300 MHz, DMSO-d_6) δ 1.74 (pentet, minor salt impurity), 2.06 (4H, d, J = 10.3 Hz), 2.61 (4H, d, J = 10.0 Hz), 3.58 (pentet, minor salt impurity), 7.49 (4H, t, J = 7.6 Hz), 7.57 (2H, d, J = 7.3 Hz), 7.90 (4H, d, J = 7.3 Hz); ^{13}C NMR (75 MHz, DMSO-d_6) δ 30.7, 50.4, 119.4, 127.8, 128.3, 131.9, 133.26, 166.8; HRMS (EI+) calcd for $C_{22}H_{20}N_4O_2$ (M^+) 372.1586, found 372.1573 (−3.4 ppm).

***trans*-1,4-Diaminocyclohexane-1,4-dicarboxylic Acid Dihydrobromide (18).**[8c] A solution of **17** (15.8 g, 42.0 mmol) in concd HBr (160 mL) was heated at reflux for 4 d. (Benzoic acid was observed as a white crystalline material in and around the lip of the flask after 24 h.) The solution was cooled to room temperature and volatiles were removed in vacuo aided by azeotroping with *t*-BuOH, to leave a brown solid, which was purified by trituration with absolute EtOH. The suspension was filtered and the solid was washed thoroughly with EtOH to leave a white solid. Due to the presence of a salt impurity (observable by ^1H NMR as signals present in the 6−8 ppm range), the white solid was vigorously stirred in absolute EtOH (150 mL) overnight. The slurry was then filtered to give 13.3 g (36 mmol, 86%) of **18** as a white solid, mp 303 °C dec. IR (KBr) (cm^{-1}) 3018 (br), 1715; ^1H NMR (200 MHz, CD_3OD) δ 2.21 (2H, d, J = 9.4 Hz), 2.26 (2H, d, J = 9.6 Hz), 2.29 (2H, d, J = 9.8 Hz), 2.34 (2H, d, J = 9.5 Hz), 4.95 (6H, s); ^{13}C NMR (50 MHz, CD_3OD) δ 29.2, 58.0, 172.2; HRMS (FAB+) calcd for $C_8H_{15}N_2O_4$ $(M+H)^+$ 203.1032, found 203.1031 (−0.5 ppm).

***trans*-1,4-Di(benzyloxycarbonyl)aminocyclohexane-1,4-dicarboxylic Acid (19).**[8c] A slurry of **18** (1.04 g, 2.9 mmol) in sat. aq $NaHCO_3$ (250 mL) was heated to boiling until the solution became clear. The solution was cooled to room temperature, then further in an ice−water bath. Benzyl chloroformate (3.0 mL, 27 mmol) was slowly added by pipet, and the solution was warmed to room temperature. After 48 h, the reaction mixture was diluted with water (250 mL) and extracted with Et_2O (250 mL). The organic phase was discarded. The aqueous phase was acidified with concd HCl to pH 2, and the solution was extracted with EtOAc (3 × 250 mL). MeOH (200 mL) was added to the opaque EtOAc phase until it became clear. The organic solution was then dried (Na_2SO_3) and concentrated under vacuum to leave 850 mg (1.8 mmol, 63%) of **19** as an off-white solid, mp 254 °C dec. IR (KBr) (cm^{-1}) 3320, 1733, 1665; ^1H NMR (200 MHz, DMSO-d_6) δ 1.89 (8H, m), 5.20 (4H, s), 7.36 (10, s), 7.59 (2H, s), 12.38 (2H, br s); ^{13}C NMR (50 MHz, DMSO-d_6) δ 26.4, 57.4, 65.1, 127.6, 127.7, 128.3, 137.0, 155.4, 175.9; HRMS (FAB+) calcd for $C_{24}H_{27}N_2O_8$ $(M + H)^+$ 471.1767, found 471.1770 (+0.6 ppm).

Dimethyl *trans*-1,4-Di(benzyloxycarbonyl)aminocyclohexane-1,4-dicarboxylate (20).[8c] A slurry of **19** (10.4 g, 22 mmol) in 5% aqueous Cs_2CO_3 (75 mL) was heated until solution was effected. The aqueous solution was then lyopholized to give a white solid. Iodomethane (27.4 mL, 0.44 mol) was injected into a slurry of the salt in DMF (100 mL) under argon, and the reaction mixture was stirred at room temperature for 48 h. Volatiles were removed under vacuum to leave a yellow residue, which was taken up in water (200 mL) and extracted with EtOAc (3 × 200 mL). The organic extracts were dried ($MgSO_4$), filtered, and concentrated to give a yellow solid. The solid was triturated with hot Et_2O, then the suspension was cooled to room temperature and filtered to give a light yellow solid. This material was further purified by trituration with a minimum of cold EtOAc to provide 5.53 g (11.1 mmol, 50%) of **20** as a white solid, mp 266 °C, R_f 0.4 (40% EtOAc/hexanes, black in PMA stain). IR (KBr) (cm^{-1}) 3307, 1732, 1689; ^1H NMR (200 MHz, $CDCl_3$) δ 2.10 (4H, d, J = 12.7 Hz), 2.09 (4H, d, J = 12.5 Hz), 3.67 (6H, s), 5.02 (2H, s), 5.09 (4H, s), 7.35 (10H, s); ^{13}C NMR (50 MHz, $CDCl_3$) δ 27.2, 52.6, 58.1, 66.9, 128.1, 128.2, 128.5, 136.0, 155.5, 174.2; HRMS (FAB+) calcd for $C_{26}H_{31}N_2O_8$ $(M + H)^+$ 499.2080, found 499.2086 (+1.2 ppm).

Dimethyl *trans*-1,4-Diaminocyclohexane-1,4-dicarboxylate (21).[8b,c] Ester **20** (1.77 g, 3.6 mmol) and 10% Pd/C (0.42 g) in a mixture of MeOH (50 mL) and EtOAc (80 mL) were shaken under H_2 (55 psi) in a hydrogentator for 20 h. The reaction mixture was treated with charcoal and filtered, then the solids were washed with CH_2Cl_2. The solution was concentrated under vacuum to 20 mL and filtered through a cotton plug. Volatiles were removed under vacuum to give 770 mg (3.3 mmol, 93%) of **21** as an off-white solid, mp 116−118 °C (lit.[8b] mp 122 °C). IR (KBr) (cm^{-1}) 3420, 3359, 3299, 1732; ^1H NMR (300 MHz, $CDCl_3$) δ 1.49 (4H, dd, J = 4.0, 13.5 Hz), 2.15 (4H, dd, J = 3.9, 13.4 Hz), 3.72 (6H, s), 4.85 (4H, br s); ^{13}C NMR (75 MHz, $CDCl_3$) δ 32.1, 52.7, 57.6, 177.9; HRMS (FAB+) calcd for $C_{10}H_{19}N_2O_4$ $(M + H)^+$ 231.1345, found 231.1344 (−0.4 ppm).

Diethyl *cis*-2,6-Diamino-1,2,3,5,6,7-hexahydro-*s*-indacene-2,6-dicarboxylate (22) and Diethyl *trans*-2,6-Diamino-1,2,3,5,6,7-hexahydro-*s*-indacene-2,6-dicarboxylate (23).[9] Concentrated HCl (15 mL) was added to a heterogeneous mixture of diethyl 2,6-diisocyano-1,2,3,5,6,7-hexahydro-*s*-indacene-2,6-dicarboxylate[9] (cis and trans, 5.0 g, 10 mmol) in absolute EtOH (150 mL), and the slurry was stirred at room temperature. Gas was evolved, and the solution gradually became homogeneous. After 24 h, the solvent was removed under vacuum to leave a white solid. This solid was taken up in water (200 mL), then the solution was basified with concd NH_4OH and extracted with EtOAc (3 × 200 mL). The organic phase was dried ($MgSO_4$), filtered, and concentrated under vacuum. The resulting solid was purified by gravity chromatography (230−400 mesh silica) with a 30% EtOH/EtOAc as elutant to give 1.2 g (3.6 mmol) of *cis*-2,6-diamino-1,2,3,5,6,7-hexahydro-*s*-indacene-2,6-dicarboxylic acid diethyl ester (**22**) as an off-white solid, R_f 0.20 (30% EtOH/EtOAc, pink in ninhydrin stain), mp 134 °C (lit.[9] mp 123−125 °C), and 1.4 g (4.2 mmol) of *trans*-2,6-diamino-1,2,3,5,6,7-hexahydro-*s*-indacene-2,6-dicarboxylic acid diethyl ester (**23**) as an off-white solid, R_f 0.40 (30% EtOH/EtOAc, pink in ninhydrin stain), mp 90−91 °C (lit.[9] mp 91−93 °C). Spectral data for **22**: IR (KBr) (cm^{-1}) 3405, 3381, 1725; ^1H NMR (300 MHz, $CDCl_3$) δ 1.27 (6H, t, J = 7.1 Hz), 1.79 (4H, s), 2.80 (4H, d, J = 15.4 Hz), 3.51 (4H, d, J = 15.1 Hz), 4.20 (4H, q, J = 7.1 Hz), 7.04 (2H, s); ^{13}C NMR (75 MHz, $CDCl_3$) δ 14.1, 45.8, 61.2, 65.3, 121.2, 139.1, 176.2; HRMS (FAB+) calcd for $C_{18}H_{25}N_2O_4$ $(M + H)^+$ 333.1814, found 333.1822 (+2.2 ppm). Spectral data for **23**: IR (KBr) (cm^{-1}) 3373, 3300, 3260, 1741; ^1H NMR (300 MHz, $CDCl_3$) δ 1.25 (6H, t, J = 7.2 Hz), 1.78 (4H, s), 2.78 (4H, d, J = 15.4 Hz), 3.45 (4H, d, J = 15.4 Hz), 4.18 (4H, q, J = 7.2 Hz), 7.02 (2H, s); ^{13}C NMR (75 MHz, $CDCl_3$) δ 14.0, 45.5, 61.0, 65.0, 121.1, 139.0, 176.3; HRMS (FAB+) calcd for $C_{18}H_{25}N_2O_4$ $(M + H)^+$ 333.1814, found 333.1824 (+2.9 ppm).

Diethyl *cis*-2,6-Di(*tert*-butoxycarbonyl)amino-1,2,3,5,6,7-hexahydro-*s*-indacene-2,6-dicarboxylate (24). Di-*tert*-butyldicarbonate (206 mg, 0.92 mmol) was added in one portion to a solution of **22** (102 mg, 0.36 mmol) in CH_2Cl_2 (5 mL) and the solution was heated to reflux overnight. The reaction mixture was diluted with CH_2Cl_2 (100 mL) and washed with brine (100 mL), then the organic phase was separated, dried ($MgSO_4$), filtered, and concentrated to give a light yellow solid, which was purified by trituration with hot hexanes. The suspension was cooled to room temperature and filtered to give 154 mg (0.29 mmol, 94%) of **24** as an off-white solid, R_f 0.33 (30% EtOAc/hexanes, light pink in ninhydrin stain), mp 187−188 °C. IR (KBr) (cm^{-1}) 3326, 1727, 1690; ^1H NMR (300 MHz, $CDCl_3$) δ 1.22 (6H, t, J = 7.1 Hz), 1.38 (18H, s), 3.09 (4H, d, J = 16.1 Hz), 3.53 (4H, d, J = 16.1 Hz), 4.18 (4H, q, J = 7.1 Hz), 5.10 (2H, br s), 6.98 (2H, s); ^{13}C NMR (75 MHz, $CDCl_3$) δ 14.1, 28.2, 43.4, 61.4, 66.2, 79.8, 120.6, 138.7, 154.9, 173.3; HRMS (FAB+) cacld for $C_{28}H_{41}N_2O_8$ $(M + H)^+$ 533.2863, found 533.2860 (−0.5 ppm).

Diethyl *trans*-2,6-Di(benzyloxycarbonyl)amino-1,2,3,5,6,7-hexahydro-*s*-indacene-2,6-dicarboxylate (25). Dibenzyl dicarbonate (190 mg, 0.66 mmol) was added in one portion to a solution of **23** (55 mg, 0.17 mmol) in CH_2Cl_2 (5 mL), and the solution was heated to reflux for 1 h. A white precipitate was observed. Volatiles were removed under vacuum to leave a white solid, which was purified by trituration with hot hexanes. The suspension was cooled to room temperature and filtered to give 79 mg (0.15 mmol, 90%) of **25** as a white solid, R_f 0.91 (100% EtOAc, light pink in ninhydrin stain), mp 250 °C dec; IR (KBr) (cm^{-1}) 3340, 1733, 1725; ^1H NMR (300 MHz, $CDCl_3$) δ 1.11 (6H, t, J = 7.0 Hz), 3.15 (4H, d, J = 16.4 Hz), 3.38 (4H, d, J = 16.1 Hz), 4.07 (4H, q, J = 6.9 Hz), 5.01 (4H, s), 6.99 (2H, s), 7.33 (10H, s), 8.03 (2H, s); ^{13}C NMR (75 MHz, $CDCl_3$) δ 13.9, 42.4, 60.7, 65.2, 65.8, 120.4, 127.7, 127.8, 128.3, 136.9, 138.5, 155.6, 173.1. Anal. Calcd for $C_{34}H_{36}N_2O_8$: C 67.99, H 6.04, N 4.66. Found: C 67.50, H 6.18, N 4.87.

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Supporting Information Available: General experimental procedures, proton and carbon NMR spectra for compounds **8**−**13**, **15**, and **17**−**25**, and X-ray crystallographic information files (CIFs) for crystals of **15**, **20**, **24**, and **25**. This material is available free of charge via the Internet at http://pubs.acs.org.