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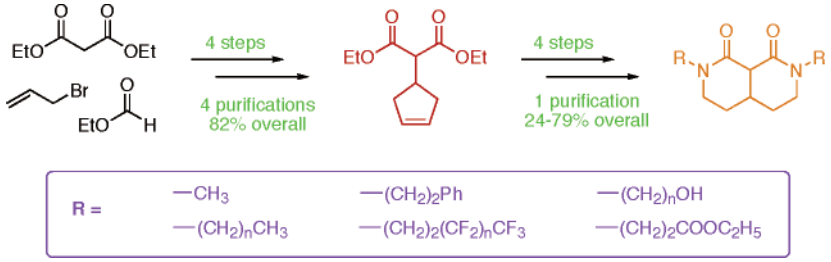
Convenient Synthesis of 6,6-Bicyclic Malonamides: A New Class of Conformationally Preorganized Ligands for f-Block Ion Binding

Bevin W. Parks, Robert D. Gilbertson,† Dylan W. Domaille,‡ and James E. Hutchison*

Chemistry Department, University of Oregon, Eugene, Oregon 97403-1253

hutch@uoregon.edu

Received August 20, 2006



A general synthetic approach was developed for the preparation of a series of 6,6-bicyclic malonamides, a class of ligands that provide a preorganized binding site for f-block ions (particularly trivalent lanthanides). The approach described is convenient to introduce a variety of functional groups at the amide nitrogens to tune the properties of the ligand without altering the preorganized binding. Each of the ten derivatives (that represent a range of functionality, including R = alkyl, hydroxy, phenyl, ester, perfluorocarbon) reported here derives from a single, readily prepared dialdehyde intermediate. This intermediate is converted to the final products via reductive amination with an appropriately functionalized benzylamine, followed by hydrogenolysis and lactam formation. Because derivatization occurs late in the synthesis, the approach is general, requiring only modification of the purification procedures for each new derivative. To aid in the purification of the bicyclic malonamides, we report a novel complexation-based purification method that takes advantage of the high affinity of the ligand for f-block metals.

Introduction

The design and synthesis of ligand architectures that present an organized array of donor atoms to enhance the interactions between the ligand and a metal is an important, ongoing challenge in molecular design.[1−3] The type and geometric arrangement of donor atoms is crucial to controlling the properties of both the ligand and the resulting metal−ligand complex.[1−3] The application of these new architectures requires that their designs permit functionalization of the metal-binding moiety to tune the properties of the ligand without adversely impacting the binding characteristics.[1,4] Although new developments, including computer modeling approaches (e.g., molecular mechanics strategies such as HostDesigner),[5] facilitate the selection of new targets, each design must still be refined by coupling modeling studies with synthesis and physical testing. Each iteration of modeling−synthesis−testing affords a greater understanding of ligand−metal interactions, improves design models, and accelerates the transition into de novo ligand design.

During the last two decades, significant effort has been directed toward developing design strategies for f-block ion binders, primarily based upon diamide structures such as the malonamides. Malonamides were originally chosen for development because they are completely incinerable, relatively easy to synthesize, selective for trivalent lanthanides, stable to

† Present address: Los Alamos National Laboratory, Los Alamos, NM 87545.
‡ Present address: Department of Chemistry, University of California, Berkeley, CA 94720.

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10.1021/jo0617262 CCC: $33.50
Published on Web 12/02/2006

CHART 1. Preorganized 6,6-Bicyclic Malonamides 1 and the Acyclic Malonamides used as Models (2a and 2d) for the Malonamides used in the Diamex Process (2b and 2c)

1a R = $(CH_2)_7CH_3$
1b R = CH_3

2a $R_1 = R_2 = (CH_2)_5CH_3$, $R_3 = H$
2b $R_1 = CH_3$, $R_2 = (CH_2)_7CH_3$, $R_3 = C_2H_4OC_6H_{13}$
2c $R_1 = CH_3$, $R_2 = (CH_2)_3CH_3$, $R_3 = C_{14}H_{29}$
2d $R_1 = R_2 = CH_3$, $R_3 = H$

radiolysis, and able to bind in acidic aqueous media.[6−10] A large number of derivatives of the acyclic malonamide substructure (see, for example, **2a**−**d** in Chart 1) have been prepared with the aim of improving the extraction characteristics (primarily the binding characteristics and solubility) for radionuclide separation (e.g., the DIAMEX (diamide extraction) process for minor actinide separation).[6−8,10−15] The coordination chemistry and extraction efficiency of these derivatives have been explored, and the influence of ligand structure (the identity of the substituents on the amide nitrogens and the central methylene) upon binding affinity has been described.[4,6,9,10,16,17] Despite considerable effort, only modest improvements in the extraction of trivalent lanthanides have been realized.[6−9,11,13,15,18]

Our approach to this problem derives from the premise that preorganization of the malonamide moiety into a conformation resembling that required in the metal−ligand complex will enhance the binding interaction.[3,19−21] In effect, the strain energy, which acyclic ligands **2** experience upon chelation to a metal center, is minimized in the bicyclic ligands **1**.[3,20−22] Initial studies with **1a** and **1b** showed large enhancements in extraction efficiencies and binding affinities for the bicyclic structures relative to the acyclic analogues, providing strong support for our initial premise.[3,21−24]

To explore the coordination chemistry of this new ligand-system and prepare ligands that have properties that are tailored for particular applications, it was necessary to prepare a number of derivatives. Thus, we aimed to develop a convenient, efficient, and general approach that could be accomplished in only a few steps, required limited purifications, and made use of shelf-stable, common intermediates close to the end of the synthesis. The design of the synthesis was geared toward easy modification because one derivative might be the best choice for studying the solid-state structure of the ligand (e.g., **1b**),[3,22] whereas another derivative may be necessary for evaluating the extraction efficiency (e.g., **1a**).[3] In addition, it is desirable to manipulate the physical properties such as solubility or melting point or to introduce additional functionalization without altering the structure of the binding moiety. The synthesis was also designed to be scaleable and efficient because multigram quantities of material were required for exploring the fundamental coordination chemistry, comparing the new structures to those of existing ligand architectures, and further developing the ligands for a wide variety of applications.

Here, we report the synthesis and purification of a unique series of 10 functionalized malonamide ligands designed to be preorganized for chelation of f-block ions. Each derivative can be accessed through a stable cyclopentene derivative that can be prepared easily on a large scale. Conversion of this derivative to a dialdehyde allows introduction of a range of functional groups through reductive amination. Because derivatization occurs late in the synthesis, our approach is general for a wide range of derivatives, only requiring modification of the purification process for the final products. Purification is facilitated by a complexation-based purification method we developed that takes advantage of the high affinity of the ligand for f-block metals.

Results and Discussion

To obtain the desired 6,6-bicyclicmalonamide (BMA) in quantities sufficient for use in physical studies and potential applications, we aimed for the synthesis to be general to multiple functionalities and high yielding, with few steps and minimal purifications. Surprisingly, few examples of BMAs are found in the literature.[25] The synthesis of a representative example, an unsubstituted 5,6-BMA with a cis ring junction, **5**, is shown in Scheme 1.[25] Although this approach was not directly extendable to our targets, the synthesis provides the basis for the retrosynthetic analysis of our desired 6,6-BMA.

Upon the basis of this precedent, the bisfunctionalized 6,6-bicyclic malonamide (R_2BMA, **1**) could be prepared by intramolecular ring closing of the bisamine **6** shown in Scheme 2. Bisamine **6** might be obtained through either of two routes. These routes differ mainly in whether the coupling to diethyl malonate occurs before or after the incorporation of the amine

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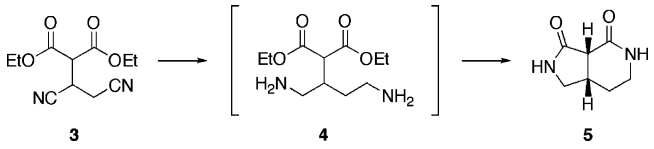
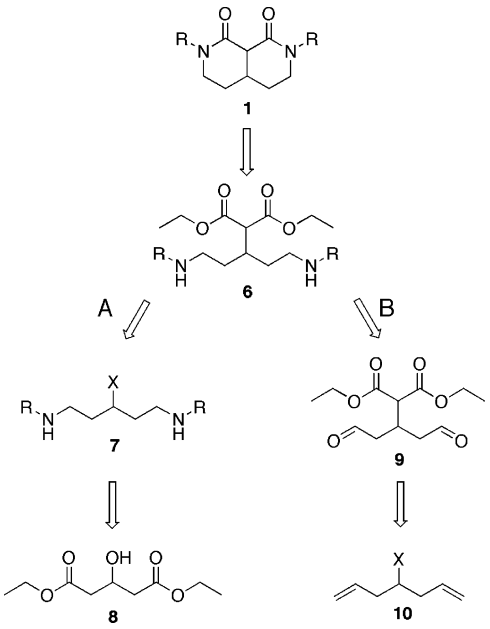
SCHEME 1. Reductive Cyclization of a Cyanoester Producing a Bicyclic Diamide Based on a Fused Five- and Six-Membered Ring System



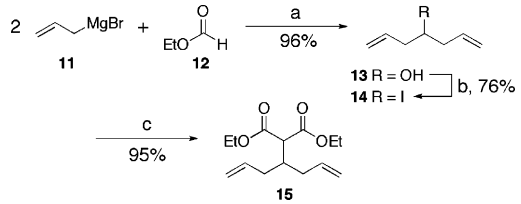
SCHEME 2. Retrosynthetic Analysis Showing Two Possible Routes to the Bisfunctionalized 6,6-BMAs Based upon the Literature Precedent of the 5,6-BMA



functionality. In route A, diethyl glutarate **8** is converted to a bisamide that is subsequently reduced to the bisamine. Once the hydroxyl is transformed to a good leaving group, **7** is then coupled to diethyl malonate to form **6**. For route B, diene **10** is coupled to diethyl malonate and the alkenes oxidize to form dialdehyde intermediate **9**. Dialdehyde **9** is then transformed to **6** via reductive amination. Route B was ultimately chosen because route A is complicated by intramolecular reactions involving displacement of the leaving group, X, by the amines to form an azetidine and because route B offers several desirable attributes. It allows us to add the amine functionality later in the reaction sequence, provides more shelf-stable intermediates, and has overall fewer transformations—synthesis of the dialdehyde **9**, reductive amination to form **6**, and ring closing to the product **1**.

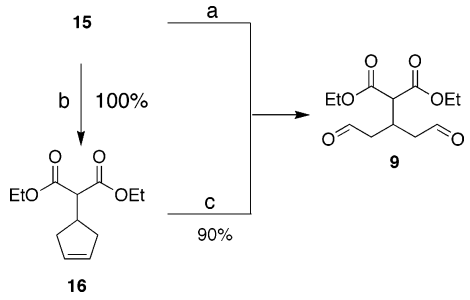
Preparation of the Diene 15. Our first target, dialdehyde **9**, should be readily obtained through the reaction of ozone with diethyl malonate-diene **15**. Large quantities (30 g) of **15** can be synthesized in excellent yield over three steps (Scheme 3). Although 1,6-heptadien-4-ol **13** is commercially available, it is convenient (and inexpensive) to prepare at a large scale via the high-yielding Grignard reaction of allyl bromide with ethyl formate. Alcohol **13** was then converted to iodide **14** by standard methods in good yield.[26] Iodide **14** can be stored at −20 °C in the presence of a stabilizer (copper or hydroquinone) to prevent decomposition or used immediately. Refluxing **14** with diethyl

SCHEME 3[a]



[a] Reagents and conditions: (a) THF, reflux; (b) PPh_3, I_2, imidazole, CH_2Cl_2; (c) diethyl malonate, NaH, THF, reflux.

SCHEME 4[a]



[a] Reagents and conditions: (a) (*i*) O_3, EtOAc, −78 °C, (*ii*) PPh_3; (b) bis(tricyclohexylphosphine)benzylidine ruthenium(IV) dichloride, CH_2Cl_2; (c) (*i*) O_3, EtOAc, 78 °C, (*ii*) H_2 (30 psi), 5% Pd/carbon.

malonate and NaH in THF over a period of several days afforded **15** in 95% yield. Although the rates of enolate substitutions, such as the one shown here, are enhanced in the presence of a polar aprotic solvent such as DMSO, in this case, THF was preferred because it prevents formation of a side product believed to result from O-alkylation of the malonate ester.

Ozonolysis and Reduction to Dialdehyde 9. Early attempts to convert diene **15** to dialdehyde **9** directly via ozonolysis with a reductive workup (Scheme 4, a) were problematic. Neither dimethyl sulfide nor catalytic hydrogenation readily reduces the ozonide intermediate, possibly due to the formation of bisperoxide or oligomeric species instead of the typical ozonide following fragmentation of the initial ozone adduct. Triphenylphosphine effected the reduction of the ozonolysis intermediate, but separation of the produced triphenylphosphine oxide from the product was troublesome.

All of these problems were overcome by adding a step to the reaction sequence. Ring-closing metathesis (RCM) of diene **15** with Grubbs' catalyst (bis(tricyclohexylphosphine) benzylidine ruthenium(IV) dichloride)[27] produced the cyclopentene ring (Scheme 4, b) of **16** quantitatively within 30 min. When olefin **16** is treated with ozone at low temperature, it reacts quantitatively to give the ozonide, which is easily reduced to **9** by catalytic hydrogenation (Scheme 4, c). Dialdehyde **9** was obtained in excellent yield with little impurity (by ^1H NMR) and was carried forward to the next reaction in crude form after vacuum filtration to remove the Pd/C catalyst.

The RCM was initially performed only on a 5 mmol scale, and **16** was used in crude form; therefore, the main contaminant in **9** was the catalyst. It has since been found that the RCM on a 0.2 mol scale requires only slightly more catalyst than the small-scale reaction. The larger amount of product from the scale-up also made it possible to distill cyclopentene **16** away

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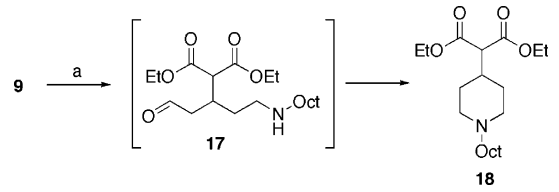
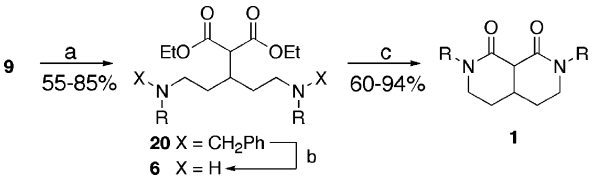
SCHEME 5. Piperidine Formation from Dialdehyde 10 and a Primary Amine[a]



[a] Conditions: (a) (*i*) 1,2-DCE, octylamine, (*ii*) $NaBH(OAc)_3$.

SCHEME 6[a]



[a] Reaction conditions: (a) (*i*) benzyl amine **19**, (*ii*) $NaBH(OAc)_3$, 1,2-DCE; (b) H_2 (50 psi), 20% $Pd(OH)_2$/carbon, EtOH; (c) EtOH, reflux.

TABLE 1. Reagents Used and Isolated Yields (from Cyclopentene 16) in the Preparation of Malonamides 1

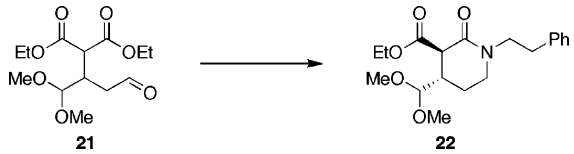
	reagent	product	R	% yield
1	**19a**	**1a**	$(CH_2)_7CH_3$	51
2	**19b**	**1b**	CH_3	79
3	**19c**	**1c**	$(CH_2)_9CH_3$	44
4	**19d**	**1d**	$(CH_2)_{15}CH_3$	40
5	**19e**	**1e**	$(CH_2)_2Ph$	49
6	**19f**	**1f**	$(CH_2)_2OH$	40
7	**19g**	**1g**	$(CH_2)_4OH$	35
8	**19h**	**1h**	$(CH_2)_2(CF_2)_5CF_3$	35
9	**19i**	**1i**	$(CH_2)_2(CF_2)_7CF_3$	43
10	**19j**	**1j**	$(CH_2)_2COOC_2H_5$	48

from the residual catalyst without loss of yield (99.6% isolated yield). The increased purity of **16** increases the reaction rates of both the ozonolysis and catalytic hydrogenation and increases the stability of **9**.

Synthesis of Bicyclic Malonamides via Reductive Amination and Lactam Formation. We found it convenient to add the desired functionality of the BMA via reductive amination of the dialdehyde. Although it was expected that dialdehyde **9** could be reacted with an excess of amine to give the desired bisamine intermediate **6**, reaction of primary amines with **9** results in formation of piperidine **18** (Scheme 5). The intramolecular reaction of the second aldehyde with the secondary amine in intermediate **17** is much faster than the intermolecular reaction with the second equivalent of primary amine even when a large excess of the amine is used. The use of benzyl-protected amines eliminates this problem. Benzyl-protected amines that are not commercially available can be synthesized from the corresponding amines or iodides (see Supporting Information).[28−30]

Various derivatives of **1** have been synthesized with no change to the reaction conditions (Scheme 6) and were isolated in good yields (Table 1). A modest excess (2.2 mol equiv) of benzyl-protected amine **19** was added to **9**, and the intermediate was then reduced to the amine by addition of $NaBH(OAc)_3$ to

SCHEME 7. Stepwise Ring Closure Used to Investigate the Stereochemistry of the Ring Formation[a]



[a] The initial cyclization leads to the trans configuration. Formation of the second ring always leads to a cis configuration.

give bistertiary amine **20**. Diamine **20** was purified to remove excess secondary amine **19**, though it was not necessary because use of the crude material in a repeated experiment did not hinder the yield of the following reactions nor alter the purification of the final product. The benzyl-protecting groups were removed via catalytic hydrogenolysis to form bis-secondary amine **6**. The close proximity of the amines to the esters and the favorable ring size of the product resulted in spontaneous lactam formation, even before reflux. In fact, a derivative of **6** was only isolated in one instance (see Supporting Information). Heating to reflux in absolute ethanol for 2−18 h afforded **1** in overall good yield (see Table 1).

Attempts to Prepare the *trans*-6,6-BMA. It was expected that the synthetic method would produce a mixture of stereoisomers, with the hydrogens on the bridgehead carbons being either cis or trans to each other. To our surprise, the ^1H NMR indicated only one stereoisomer (see Supporting Information), and multiple crystal structures have shown evidence of only the cis structure.[22] Molecular mechanics indicates that both stereoisomers are preorganized for metal ion binding, though the trans stereoisomer of **1** is ideally preorganized and the cis stereoisomer must undergo slight rearrangement upon binding.[3] The ideal conformation of the trans stereoisomer should lead to further enhanced binding and extraction properties, so the ring closing was further examined.

Using a model compound to study the ring-closing reactions that lead to the bicyclic system, we have found that the substituents on the monocyclic amide have a trans relationship to each other upon closure of the first ring (Scheme 7). When aldehyde **21** was treated with an excess of phenethylamine and $NaBH(OAc)_3$ in 1,2-dichloroethane (DCE), amide **22** was produced (along with a small amount of material in which the amine had been alkylated by 2 equiv of the aldehyde). The trans relationship of the ring substituents in **22** was established by the magnitude of the J_3 coupling constant of 10 Hz between the bridgehead protons (a cis relationship of these protons would be expected to exhibit a smaller J_3 coupling constant).

Yet, closure of the second ring consistently leads to the cis product. It is possible that the trans stereoisomer cannot adopt a conformation that allows the amine to attack the ester, but epimerization to the cis conformation allows the ring-closing amide formation to occur. Another possible explanation is that the ideal binding conformation of *trans*-**1**, demonstrated by intersecting carbonyl dipoles,[3] leads to a dipole−dipole interaction that is unfavorable. This interaction could be enough to shift the equilibrium of the epimerization to the cis conformation of **1**. In any case, this type of approach does not appear to be viable for synthesis of the trans conformation of **1**.

Purification Strategies for Functionalized BMAs. The diversity of BMA **1** functionality has necessitated the development of several purification strategies, including Kugelrohr distillation and complex-mediated precipitation in addition to

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recrystallization and chromatography. No single technique for purification worked for all synthesized derivatives. The main impurities in the final product **1** were benzylamine **19**, the corresponding primary amine, and an ethyl ester characterized by a 4.2 ppm peak in the ^{1}H NMR. It seems likely that this ester is incompletely cyclized **1**. Although many of the derivatives of **1** are solids, recrystallization was not a consistent method of purification. Owing to differences in impurity profiles and the low melting points of some of the derivatives, recrystallization was time-consuming and often unsuccessful (crystals were often contaminated with the ester-amide side product). The remaining derivatives of **1** are oils, and purification via chromatography was also problematic. Kugelrohr distillation has been used in the case of the octyl derivative, but the temperature must be closely monitored and carefully controlled to avoid decomposition.

We have developed a purification strategy that is reliable, convenient, and broadly applicable that exploits the strong binding of the whole class of ligands to f-block metal ions. This method has been applied successfully to the majority of the derivatives described here (with the exception of the alcohol derivatives) and is especially advantageous when purifying derivatives that are low-melting solids or oils. It is less sensitive than the other methods to varying impurity profiles, making it a rapid and general method for isolating new derivatives. The higher selectivity of the desired product for uranyl binding relative to all other byproducts permits one to isolate derivatives of **1** from complex reaction mixtures very quickly.

Binding to uranyl nitrate ($UO_2(NO_3)_2$·$6H_2O$) is fast in MeOH and results in a precipitate of the desired product bound to the uranyl ion. This precipitate can be washed with MeOH to remove impurities which cannot bind the metal ion, such as benzylamine **19** or the ester-amide which did not undergo the second lactam formation to become **1**. The solid, dried UO_2·**1** complex is then stirred with a 0.1 M aqueous EDTA solution (pH 8.0). EDTA binds the uranyl much more tightly than BMA **1**, and the resulting UO_2·EDTA complex is too polar to be extracted from the aqueous solution. Extraction with $CHCl_3$ removes **1**, the only remaining organic compound, from the aqueous solution. Evaporation of the dried solution typically results in a high-purity, colorless oil or solid.

In summary, we have demonstrated a convenient synthetic method for a range of BMA derivatives where the R groups are identical. Work is currently underway to modify the synthetic method, extending it to a variety of BMAs with nonequivalent R groups. This would be useful to introduce multiple (different) functionalities into the BMA, making it easier to incorporate the molecules into functional materials.

Experimental

The general experimental conditions and synthesis of all previously reported compounds are given in the Supporting Information.

1,6-Heptadiene-4-ol (13). Clear, colorless oil. Bp 150−151 °C. 96% yield. ^{1}H NMR ($CDCl_3$) δ 5.837 (m, 2H), 5.156 (m, 2H), 5.112 (triplet, J = 0.9 Hz, 2H), 3.711 (tt, J_S = 5.1 Hz, J_L = 7.5 Hz, 1H), 2.14−2.34 (m, 4H). Anal. Calcd for $C_7H_{12}O$: C, 74.95; H, 10.78. Found: C, 74.83; H, 11.02.

4-Iodo-1,6-heptadiene (14). Triphenylphosphine (70.0 g, 0.267 mol), imidazole (18.2 g, 0.267 mol), and **13** (25.0 g, 0.223 mol) were dissolved in dichloromethane (500 mL) and cooled to 0 °C. Iodine crystals (67.5 g, 0.266 mol) were slowly added (ca. 30 min), then the reaction was allowed to stir at ambient temperature for 6 h. Most of the dichloromethane was removed by rotary evaporation, and the resulting brown slurry was poured into rapidly stirred ether (500 mL). The precipitated solids were removed by vacuum filtration through a pad of Celite, and the filter cake was washed with ether (50 mL). The remaining solvent was removed by rotary evaporation, and distillation of the residue (in the presence of hydroquinone or copper) provided 37.8 g (76.3%) of colorless liquid (bp 65−70 °C at 20 mmHg). **14** is indefinitely stable when stored at −25 °C over copper; however, rapid discoloration was observed when the compound was allowed to stand at room temperature with no inhibitor present. ^{1}H NMR ($CDCl_3$) δ 5.81 (m, 2H), 5.18−5.10 (m, 4H), 4.08 (pentet, J = 6.5 Hz, 1H), 2.62 (t, J = 6.5 Hz, 4H). ^{13}C NMR ($CDCl_3$) δ 136.1, 117.8, 43.9, 34.2. Anal. Calcd for $C_7H_{11}I$: C, 37.86; H, 4.99. Found: C, 38.06; H, 5.13.

Diethyl 2-(4-(1,6-Heptadiene)) Malonate (15). Diethyl malonate (40.1 g, 0.250 mol) was dissolved in THF (750 mL) and cooled to 0 °C. Solid sodium hydride (5.67 g, 0.236 mol) was slowly added, and the flask was warmed to ambient temperature. After stirring for 1 h, **14** (37.0 g, 0.167 mol) was added and the reaction was stirred at reflux for 5 days. The reaction was then cooled to 0 °C and quenched with water. The layers were separated, and the aqueous phase was extracted with ether (2 × 100 mL). The combined organics were washed with 10% NaOH (100 mL) and brine (100 mL), then dried ($MgSO_4$) and filtered through Celite. Solvents were removed by rotary evaporation, and the resulting oil was distilled to yield 42.4 g (94.8%) of diethyl(4-(1,6-heptadiene)) malonate **15** (bp 103−105 °C at 0.3 mmHg) as a colorless oil after a forerun of diethyl malonate. ^{1}H NMR ($CDCl_3$) δ 5.74 (m, 2H), 5.07−5.00 (m, 4H), 4.20 (q, J = 7.0 Hz, 4H), 3.42 (d, J = 7.3 Hz, 1H), 2.34−2.11 (m, 5H), 1.26 (t, J = 7.0 Hz, 6H). ^{13}C NMR ($CDCl_3$) δ 168.8, 135.7, 117.4, 61.2, 54.3, 37.6, 35.1, 14.1. IR (neat) cm^{-1} 3077, 2981, 1753, 1732. Anal. Calcd for $C_{14}H_{22}O_4$: C, 66.12; H, 8.72. Found: C, 65.86; H, 8.43.

Diethyl 2-Cyclopent-3-enylmalonate (16). Bis(tricyclohexylphosphine)benzylidine ruthenium(IV) dichloride (10−15 mg) was added to a solution of **15** (34.403 g, 0.135 mol) in distilled methylene chloride. Immediate bubbling was observed as the produced ethylene escaped. Two additional portions of catalyst were added when the bubbling ceased (ca. 15 min intervals). The reaction mixture was allowed to stir for 2 h and then concentrated in vacuo to yield a dark brown oil. Purification via vacuum distillation (180 mTorr, bp 97 °C) yielded **16** as a clear, colorless oil (30.477 g, 0.135 mol, 99.6% yield). ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.63 (s, 2H), 4.20 (m, 4H), 3.18 (d, 1H), 2.92 (m, 1H), 2.58 (dd, 2H), 2.14 (dd, 2H), 1.24 (m, 6H). ^{13}C NMR ($CDCl_3$) δ 168.9, 129.4, 61.1, 57.1, 36.9, 36.8, 14.0. Anal. Calcd for $C_{12}H_{18}O_4$: C, 63.70; H, 8.02. Found: C, 63.46; H, 8.14.

Diethyl 2-(3-Pentan-1,5-dial) Malonate (9). Pure **16** (5.928 g, 0.0262 mol) was dissolved in ethyl acetate (50 mL) and cooled to −78 °C. Ozone was passed through the solution until a blue color persisted. Excess ozone was removed by purging the solution with N_2 as it was warmed to room temperature. Hydrogenation was carried out at ambient temperature at a H_2 pressure of 30 psi with 5% Pd on the carbon catalyst (150 mg). After 5 min, hydrogen consumption had ceased, at which point the suspension was filtered through Celite and freed of solvent by rotary evaporation. **9** decomposes rapidly under ambient conditions, so the crude product is carried immediately to the next reaction. ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.75 (s, 2H), 4.22 (m, 4H), 3.63 (d, 1H), 3.25 (m, 1H), 2.60−2.90 (dq, 4H), 1.24 (t, 6H).

General Procedure for the Preparation of the Bis-3-amine Diethyl Malonate 20 Based on the Methyl Derivative (20b). To a solution of **9** (6.767 g, 0.026 mol, assuming 100% yield in the previous step) in 1,2-dichloroethane (DCE) (150 mL) was added benzylmethylamine **19b** (7.028 g, 0.058 mol, 2.2 equiv). The bright yellow reaction mixture was cooled to 0 °C, and $NaBH(OAc)_3$ (12.845 g, 0.058 mol, 2.2 equiv) was added slowly (ca. 30 min), then allowed to warm to room temperature and stir overnight. The reaction mixture was diluted with ethyl acetate (∼150 mL) and quenched with saturated aqueous $NaHCO_3$ (100 mL). The layers

were separated, and the organic layer was washed with saturated aqueous $NaHCO_3$ (2 × 100 mL) and brine (100 mL), dried over $MgSO_4$, filtered through celite, and concentrated in vacuo. Purification through a 1 in. plug of silica gel with 1:1 hexanes/ethyl acetate (300 mL) to yield **20b** as a yellow oil (10.436 g, 0.022 mol, 85% yield from cyclopentene **16**) is optional as the crude and purified products give similar results in the final reaction. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.18−7.30 (m, 10H), 4.14 (q, 4H), 3.55 (d, 1H), 3.41 (obs. m, 1H), 3.40 (s, 4H), 2.35 (t, 4H), 2.13 (s, 6H), 1.58 (m, 4H), 1.21 (t, 6H).

General Procedure for the Preparation of 1. All derivatives were synthesized in the same manner; however, purifications are unique and so are listed with the characterization data.

3,9-Diaza-3,9-dimethylbicyclo[4.4.0]decane-2,10-dione (1b). Diamine **20b** (2.51 g, 5.4 mmol) was dissolved in absolute ethanol in a Parr hydrogenation flask, and 20% palladium hydroxide on charcoal (0.15 g) was added. Hydrogenolysis of the benzyl groups was carried out at 55 psi until H_2 uptake had ceased (∼6 h). The suspension was then filtered through Celite to remove the catalyst, and the ethanolic solution was refluxed for 2 h. Removal of solvent by rotary evaporation followed by preparative radial thin-layer chromatography (2 mm rotor, methanol/ethyl acetate) provided 0.985 g (5.0 mmol, 93%) of a colorless solid (mp 108−110 °C). X-ray quality crystals were grown from ethyl acetate, and subsequent purifications via uranyl precipitation (precipitation is rapid) were performed. ^{1}H NMR ($CDCl_3$) δ 3.30 (m, 5H), 2.95 (s, 6H), 2.44 (m, 1H), 1.92 (m, 2H), 1.75 (m, 2H). ^{13}C NMR ($CDCl_3$) δ 166.2, 50.1, 47.5, 34.67, 31.0, 26.0. IR (KBr) 3439 (broad), 2929, 1651 cm^{-1}. Anal. Calcd for $C_{10}H_{16}N_2O_2$: C, 61.20; H, 8.22; N, 14.27. Found: C, 60.94; H, 7.97; N, 14.11.

3,9-Diaza-3,9-dioctylbicyclo[4.4.0]decane-2,10-dione (1a). 1a was purified by Kugelrohr distillation followed by low-temperature recrystallizations from pentane. It was obtained as a colorless oil and crystallizes below room temperature (mp 22−24 °C). Subsequent purifications via uranyl precipitation (precipitation is slow) were performed. ^{1}H NMR ($CDCl_3$) δ 3.32 (m, 9H), 2.44 (m, 1H), 1.9−2.1 (m, 2H), 1.65 (m, 2H), 1.52 (m, 4H), 1.26 (m, 20H), 0.89 (t, J = 6.6 Hz, 6H). ^{13}C NMR ($CDCl_3$) δ 166.2, 50.1, 47.2, 45.3, 31.7, 30.2, 29.2, 27.2, 27.1, 26.9, 22.5, 22.2, 14.0. Anal. Calcd for $C_{24}H_{44}N_2O_2$: C, 73.42; H, 11.30; N, 7.14. Found: C, 73.16; H, 11.25; N, 7.06.

3,9-Diaza-3,9-didecylbicyclo[4.4.0]decane-2,10-dione (1c). 1c was recrystallized from pentane and obtained as a white powder (mp 46.8−47.5 °C). ^{1}H NMR ($CDCl_3$) δ 3.21−3.42 (m, 9H), 2.44 (m, 1H), 1.95 (m, 2H), 1.66 (m, 2H), 1.52 (m, 4H), 1.25 (m, 28H), 0.89 (t, J = 6.6 Hz, 6H). ^{13}C NMR ($CDCl_3$) δ 166.2, 50.2, 47.2, 45.3, 31.8, 29.5, 29.3, 29.2, 27.3, 27.1, 26.9, 22.6, 14.1. Anal. Calcd for $C_{24}H_{28}N_2O_2$: C, 74.95; H, 11.68; N, 6.24. Found: C, 75.01; H, 12.01; N, 6.13.

3,9-Diaza-3,9-dihexadecylbicyclo[4.4.0]decane-2,10-dione (1d). 1d was recrystallized from *n*-hexane and obtained as a white powder (mp 75.6−76.8 °C). ^{1}H NMR ($CDCl_3$) δ 3.20−3.43 (m, 9H), 2.44 (m, 1H), 1.96 (m, 2H), 1.66 (m, 2H), 1.52 (m, 4H), 1.24 (bs, 56H), 0.88 (t, J = 6.6 Hz, 6H). ^{13}C NMR ($CDCl_3$) δ 166.2, 50.2, 47.2, 45.4, 31.9, 29.66, 29.62, 29.56, 29.52, 29.36, 29.32, 27.3, 27.2, 26.9, 22.6, 14.1. Anal. Calcd for $C_{40}H_{76}N_2O_2$: C, 77.86; H, 12.41; N, 4.54. Found: C, 77.58; H, 12.18; N, 4.42.

3,9-Diaza-3,9-bis(2-phenethyl) Bicyclo[4.4.0]decane-2,10-dione (1e). 1e was purified by uranyl precipitation (precipitation is slow, aided by addition of 3 Å molecular sieves) and obtained as a pale yellow solid (mp 58.9−62.1 °C). ^{1}H NMR ($CDCl_3$) δ 7.15−7.32 (m, 10H), 3.60 (qt, J_t = 7.5 Hz, J_q = 13.5 Hz, 4H), 3.28 (d, J = 6.5 Hz, 1H), 3.08 (m, 4H), 2.91 (t, J = 7.5 Hz), 2.34 (m, J_S = 5.4 Hz, J_L = 8.4 Hz, 1H), 1.79 (dq, J_q = 5.4 Hz, J_d = 13.8 Hz, 2H), 1.49 (dq, J_d = 6.3 Hz, J_q = 8.4 Hz, 2H). ^{13}C NMR ($CDCl_3$) δ 166.2, 133.2, 128.9, 128.4, 126.3, 50.2, 49.5, 46.4, 33.6, 30.2, 26.7.

3,9-Diaza-3,9-bis(2-hydroxyethyl) Bicyclo[4.4.0]decane-2,10-dione (1f). 1f was purified by thin-layer rotary chromatography [0.2 g of crude product on a 2 mm silica plate eluted with 5:3 $CHCl_3$/MeOH (100 mL) followed by 10:6:1 $CHCl_3$/MeOH/$NH_4OH_{(aq)}$ (150 mL)] and trituration with hexanes and obtained as a pale yellow viscous oil.

3,9-Diaza-3,9-bis(4-hydroxybutyl)bicyclo[4.4.0]decane-2,10-dione (1g). 1g was purified by thin-layer rotary chromatography [0.2 g of crude product on a 2 mm silica plate eluted with 9:1 $CHCl_3$/MeOH (200 mL) followed by 10:6:1 $CHCl_3$/MeOH/$NH_4OH_{(aq)}$ (200 mL)] and obtained as a viscous yellow oil. ^{1}H NMR ($CDCl_3$) δ 3.65 (m, 6H), 3.31 (m, 5H), 3.22 (m, 2H), 3.01 (bs, −OH), 2.48 (dq, J_q = 2.7 Hz, J_d = 6.0 Hz, 1H), 1.99 (dq, J_d = 5.4 Hz, J_q = 13.8 Hz, 2H), 1.52−1.73 (m, 10H). ^{13}C NMR ($CDCl_3$) δ 166.8, 62.0, 50.1, 46.6, 45.4, 30.2, 29.4, 27.0, 23.6.

3,9-Diaza-3,9-bis(1*H*,1*H*,2*H*,2*H*-perfluorooctyl) Bicyclo[4.4.0]-decane-2,10-dione (1h). 1h was purified by precipitation from EtOH/H_2O and obtained as a white powder (mp 114.6−115.4 °C). ^{1}H NMR ($CDCl_3$) δ 3.63 (t, J = 6.9 Hz, 4H), 3.38 (m, 5H), 2.32−2.53 (m, 5H), 2.00 (dq, J_S = 5.4 Hz, J_L = 13.8 Hz, 2H), 1.72 (m, 2H). ^{13}C NMR ($CDCl_3$) d 166.3, 50.2, 46.5, 40.7, 30.4, 28.9, 28.6, 28.3, 26.6. Anal. Calcd for $C_{24}H_{18}F_{26}N_2O_2$: C, 33.50; H, 2.11; N, 3.26. Found: C, 33.49; H, 2.07; N, 3.31.

3,9-Diaza-3,9-bis(1*H*,1*H*,2*H*,2*H*-perfluorodecyl)bicyclo[4.4.0]-decane-2,10-dione (1i). 1i was purified by precipitation from EtOH/H_2O and obtained as a white powder (mp 156.8−157.5 °C). ^{1}H NMR ($CDCl_3$) δ 3.64 (m, J = 6.6 Hz, 4H), 3.39 (t, J = 6.6 Hz, 5H), 2.34−2.54 (m, 5H), 2.01 (dq, J_S = 5.4 Hz, J_L = 13.8 Hz, 2H), 1.73 (dq, J_S = 7.5 Hz, J_L = 13.5 Hz, 2H). Anal. Calcd for $C_{28}H_{18}F_{34}N_2O_2$: C, 31.71; H, 1.71; N, 2.64. Found: C, 31.44; H, 1.63; N, 2.92.

3,9-Diaza-3,9-bis(2-ethoxycarbonylethyl)bicyclo[4.4.0]decane-2,10-dione (1j). 1j was purified by uranyl precipitation and obtained as a pale yellow crystalline solid (mp 71.8−73.0 °C). ^{1}H NMR ($CDCl_3$) δ 4.10 (q, J = 7.2 Hz, 4H), 3.60 (m, 4H), 3.37 (dd, J_S = 5.4 Hz, J_L = 7.2 Hz, 4H), 3.25 (m, 1H), 2.62 (td, J_S = 3.0 Hz, J_L = 6.6 Hz, 4H), 2.41 (m, 1H), 1.93 (dq, J_S = 5.4 Hz, J_L = 13.8 Hz, 2H), 1.64 (dq, J_S = 7.8 Hz, J_L = 13.5 Hz, 2H), 1.23 (t, J = 6.9 Hz). ^{13}C NMR ($CDCl_3$) δ 172.2, 166.4, 60.5, 50.2, 46.6, 43.8, 32.5, 30.3, 27.0, 14.1. Anal. Calcd for $C_{18}H_{28}N_2O_6$: C, 58.68; H, 7.66; N, 7.60. Found: C, 58.91.; H, 7.61; N, 7.51.

General Procedure for Uranyl Precipitation Purification of BMA Ligands. A 2 mL methanolic solution of crude Me_2BMA **1b** (150 mg, maximum of 0.76 mmol) was added to a 2 mL methanolic solution of uranyl nitrate ($UO_2(NO_3)_2$·H_2O, 384 mg, 0.76 mmol). The resulting yellow precipitate (forms immediately) was recovered, washed with MeOH (10 mL), and stirred with 0.5 M EDTA (aqueous, pH 8.0, 5 mL) for 30 min. This solution was extracted with $CHCl_3$ (6 × 15 mL), and the organics were combined and concentrated to give Me_2BMA **1b** as a white crystalline solid (71 mg, 48% yield from crude product). [Oct_2BMA **1a** (500 mg, maximum of 1.27 mmol) yielded a colorless viscous oil (356 mg, 71% yield from crude product).] This method was not attempted with any derivative of **1** that gave a readily purified solid (**1c**, **1d**, **1h**, **1i**) and failed with the alcohols (**1e**, **1f**).

Acknowledgment. The authors thank the National Science Foundation (CHE-0213563) and the NSF IGERT (DGE-0114419) for financial support.

Supporting Information Available: Experimental procedures for the synthesis of **13** and **19**; attempted synthesis toward acid-functionalized **1**; ^{1}H NMR, ^{13}C NMR, and EA of propionic acid **6** with experimental details; spectroscopic analysis of **1**; ^{1}H NMR spectra of **1b** in $CDCl_3$ and D_2O for reference; ^{1}H NMR spectra of **1e**−**g** for proof of purity. This material is available free of charge via the Internet at http://pubs.acs.org.

JO0617262