Synthesis of *cis,cis,cis*-Tetrasubstituted Cyclobutanes. Trapping of Tetrahedral Intermediates in Intramolecular Nucleophilic Addition

Dorothée Laurenti, Christiane Santelli-Rouvier, Gérard Pèpe,† and Maurice Santelli*

Laboratoire de Synthèse Organique, ESA au CNRS no. 6009, Faculté des Sciences de St Jérôme, 13397 Marseille Cedex 20, France

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The intramolecular [2 + 2] photocycloaddition of bismaleimides leads to cage diimides **2**. Nucleophilic addition on these compounds ($NaBH_4$, RLi, or MeONa) gives rise to various diazatetracyclic **4** and **11** or oxadiazapentacyclic **3** "bowl shaped" alcohols. X-ray analyses of **3c** and **11a** provide definite structural data concerning these two highly functionalized compounds.

Multiple dentates containing hybrid P−N ligands are of considerable interest in coordination chemistry, and part of our research work involves the development of new tetrapodal ligands containing different donor systems.[1,2]

As the conformational properties of ligands are well-known to influence the reactivity and selectivity of transition metal catalysis, we hope to prepare a cyclobutane ring system as a backbone in tetrapodal ligands. The rigid cyclobutane ring offers a choice of stereochemically interesting substitution patterns, which have not been exploited for designing multifunctional ligands.[3] We report here the preparation of new cyclobutane derivatives in which four functionalized carbon atoms are stereospecifically bound to the *cis,cis,cis*-1,2,3,4-positions of the cyclobutane ring.[4]

The [2 + 2] photocycloaddition of actived alkenes is arguably the most useful route to cyclobutane derivatives.[5,6] However, the main impediment for the use of photoannelations in synthesis remains the generally poor regio- and stereochemical control.[7] Finally, the intramolecular [2 + 2] photocycloaddition of bismaleimides, involving the intramolecular photosensitized cycloaddition of suitable oriented double bonds, was evaluated as a simple access to a *cis,cis,cis*-tetrasubstituted cyclobutane backbone.[8]

In this aim, two bismaleimides **1a**,**b** were obtained from the corresponding anhydrides and 1,3-diaminopropane (Scheme 1). A solution of bismaleimide **1a** or **1b** in a mixture of acetone/acetonitrile was photodimerized at 0 °C under nitrogen with UV irradiation (20 h) (high-pressure mercury lamp, Pyrex filter). Removal of the solvent followed by column chromatography through silica gel afforded **2a** or **2b** as crystalline material. These cage diimides have a low reactivity, and we were unable

* To whom correspondence should be addressed. E-mail: m.santelli@lso.u-3mrs.fr.

† Address X-ray correspondence to this author. E-mail: pepe@luminy.univ-mrs.fr.

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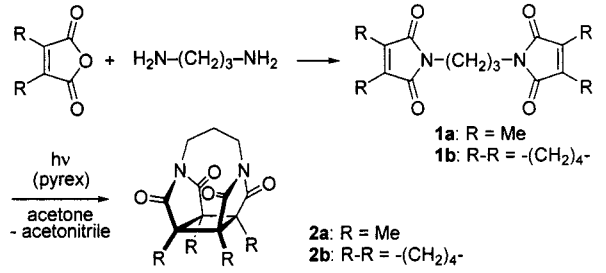
Scheme 1



Scheme 2

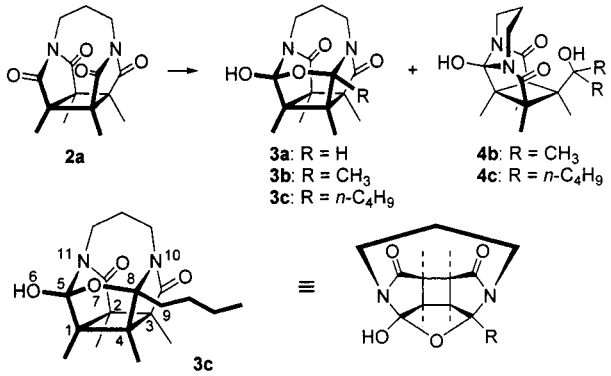


Table 1. Selected Bond Lengths and Angles for Compound 3c[a]

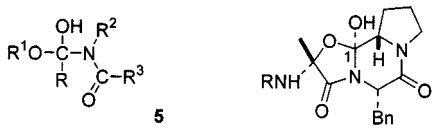
type	bond length (Å)	type	angle (deg)
C1−C2	1.567 (2)	C2−C1−C4	92.41 (11)
C2−C3	1.615 (2)	C1−C2−C3	87.12 (10)
C3−C4	1.553 (2)	C2−C3−C4	89.95 (10)
C1−C4	1.535 (2)	C1−C4−C3	90.52 (10)
C1−C5	1.548 (2)	C1−C5−O6	119.96 (12)
C5−O6	1.364 (2)	C1−C5−O7	105.68 (11)
C5−O7	1.422 (2)	C1−C2−C3−C4	−0.11 (11)
C5−N11	1.485 (2)	C4−C1−C5−O7	−19.4 (13)
C8−N10	1.493 (2)	C3−C4−C8−N10	−1.49 (13)

[a] Atom numbering is as in Scheme 2.

to perform some classical reactions (esterification with sulfuric acid in methanol, hydrazinolysis, etc.) in synthetically useful yields. Surprisingly, when **2a** was exposed to $NaBH_4$, the alkoxy group of the tetrahedral intermediate added to the adjacent imide group and led to the oxadiazapentacyclic "bowl-shaped" alcohol **3a**, which was the only isolated product, in 65% yield. In the same way, MeLi and *n*-BuLi added to **2a** gives rise to alcohol **3b,c** (Scheme 2). The compounds **4b** or **4c** were isolated as side products.

The cage products **3a**−**c** were characterized on the basis of their spectroscopic properties, including a series of 2D NMR (COSY and HMQC experiments (400 MHz)). Moreover, the structure of **3c** was confirmed by a single-crystal X-ray diffraction. Selected bond lengths and angles are presented in Table 1. The salient finding is the extraordinary value of 1.615 Å for the C−C bond of the cyclobutane ring. This value corresponds to an increase of 5% of the bond length of cyclobutane.[9] A survey of the literature indicates that only few cyclobutane rings have a long bond equal to or exceeding 1.6 Å.[10] In a number of instances, these cyclobutanes are the result of a photodimerization and they give the monomer

Scheme 3



on heating.[11] In our case, **3c** is bridged, in the sense that cleavage of one long bond would not allow the molecule to fall apart. Thus, the molecules survive despite the presence of what is most likely a severely weakened bond.[12] The cyclobutane ring is almost flat, with a dihedral angle of 0.11(10)°. Another interesting finding is the increased length of the C−N bond (1.493 Å) relative to the expected value of 1.45 Å.[13] To our knowledge, only two aminocarbinols present a C−N bond length close to 1.50 Å.[14] In contrast, we note that C−O(H) bond is shortened to 1.364 Å.

Although carbopolycyclic and oxapolycyclic cage compounds have attracted considerable attention in recent years,[15] the synthesis and chemistry of the azapolycyclic cage compounds have received less attention. Interestingly, for **3**, we note the presence of *N*-amidoalkoxycarbinol moiety (ortho-amide) **5**, an unstable intermediate in the reaction of ester with amide anion or imide with alkoxy anion (Scheme 3).[16,17] To the best of our knowledge, this structural feature has been observed only in the peptide part **6** of ergot alkaloids[18,19] and related compounds.[20] This acid-sensitive function[21] plays a central role in the acid-catalyzed isomerization of ergot alkaloids called *aci* isomerization.[22]

(9) C−C bond length in the cyclobutane: 1.551 Å, see: Stein, A.; Lehmann, C. W.; Luger, P. *J. Am. Chem. Soc.* **1992**, *114*, 7684−7687.

(10) For results before 1976, see footnote 30 in (a) Hounshell, W. D.; Dougherty, D. A.; Hummel, J. P.; Mislow, K. *J. Am. Chem. Soc.* **1977**, *99*, 1916−1924. For more recent works, the experimental bond lengths (in Å) are given before each reference: (b) 1.608, Jones, D. W.; McDonald, W. S. *J. Chem. Soc., Chem. Commun.* **1980**, 417−418. (c) 1.606, Hasegawa, E.; Mukai, T.; Yanagi, K. *J. Org. Chem.* **1989**, *54*, 2053−2058. (d) 1.593, Fessner, W. D.; Sedelmeier, G.; Spurr, P. R.; Rihs, G.; Prinzbach, H. *J. Am. Chem. Soc.* **1987**, *109*, 4626−4642. (e) 1.59, Fritz, H.-G.; Hutmacher, H.-M.; Musso, H.; Ahlgren, G.; Åkermark, B.; Karlsson, R. *Chem. Ber.* **1976**, *109*, 3781−3792.

(11) To our knowledge, the longest C−C bonds (*l*) are observed for cyclobutane photodimers which underwent clean thermal cycloreversion to the monomer: (a) photodimer of [6](1,4)-anthracenophane, l = 1.637 Å, see Tobe, Y.; Takahashi, T.; Kobiro, K.; Kakiuchi, K. *J. Am. Chem. Soc.* **1991**, *113*, 5804−5808. (b) photodimer of methyl orotate, l = 1.628 Å, see Birnbaum, G. I.; Dunston, J. M.; Szabo, A. G. *Tetrahedron Lett.* **1971**, 947−950. Birnbaum, G. I. *Acta Crystallogr.* **1972**, *B28*, 1248−1254.

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(13) The C(OH)−N bond length in 3-hydroxyphthalimidine is 1.469 Å, see: Orzeszko, A.; Maurin, J. K.; Niedzwiecka-Kornas, A.; Kazimierczuk, Z. *Tetrahedron* **1998**, *54*, 7517−7524. Dr Maurin, J. K., University of Warsaw, Poland, private communication.

(14) The experimental C(OH)−N bond lengths (in Å) are given before each reference. (a) 1.502, De Kimpe, N.; Palamareva, M.; Sulmon, P.; Verhe, R.; De Buyck, L.; Schamp, N. Declecq, J.-P.; Tinant, B.; Van Meerssche, M. *Tetrahedron* **1986**, *42*, 71−80. (b) 1.53, Sakurai, H.; Sakabe, N.; Hirata, Y. *Tetrahedron Lett.* **1966**, 6309−6314.

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(19) X-ray analysis of the ergotamine: bond distance between the atom C(1) and neighboring atoms (see **6**): C(1)−N, 1.454 (8) Å; C(1)−C, 1.518 (8) Å; C(1)−OR, 1.424 (8) Å; C(1)−OH, 1.387 (8) Å; see: Pakhomova, S.; Ondracek, J.; Husak, M.; Kratochvil, B.; Jegorov, A.; Stuchlik, J. *Acta Crystallogr., Sect. C* **1995**, *51*, 308−311.

Scheme 4

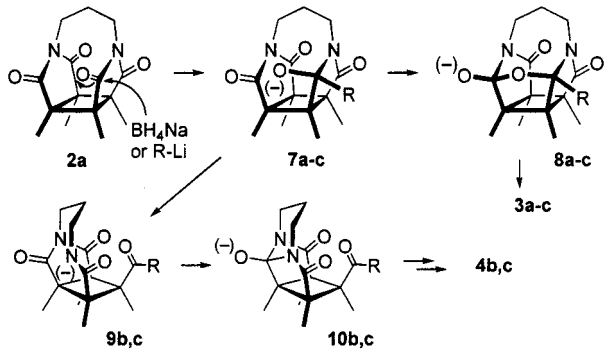


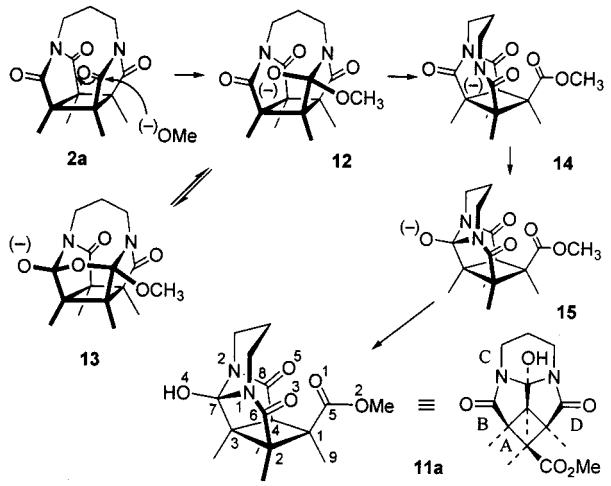
Table 2. Selected Bond Lengths and Angles for Compound 11a[a]

type	bond length (Å)	type	angle (deg)
C1−C2	1.598 (6)	C1−C2−C3	89.7 (3)
C2−C3	1.544 (5)	C2−C3−C4	91.6 (3)
C3−C4	1.555 (6)	C1−C4−C3	89.8 (3)
C1−C4	1.587 (6)	C2−C1−C4	88.5 (3)
C1−C5	1.516 (6)	N1−C7−N2	109.0 (3)
C3−C7	1.536 (5)	C3−C7−O4	118.2 (3)
C7−N1	1.443 (5)	N1−C7−C3	105.3 (3)
C7−O4	1.392 (5)	C9−C1−C5−O1	−152.4 (5)
C6−N1	1.352 (5)	C1−C2−C3−C4	−4.8 (3)

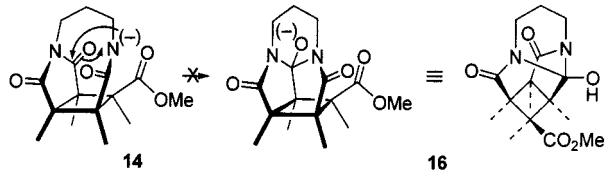
[a] Atom numbering is as in Scheme 5.

The formation of the isolated compounds can be rationalized as taking place through intermediate **7** (Scheme 4). In contrast, treatment of **2a** or **2b** by a methanolic solution of sodium methylate gives rise to compounds **11a** or **11b** of "bowl-like" topology. The gross structure of **11a**,**b** was revealed by a series of 2D NMR (COSY and HMQC experiments (400 MHz)). According to the ^{1}H and ^{13}C NMR spectra, **11a** has a plane of symmetry in solution. In addition, the structure of **11a** was confirmed by a single-crystal X-ray diffraction. Select bond distances and angles are given in Table 2. This molecule is chiral and asymmetric since it has no plane of symmetry (the value of the dihedral angle C9−C1−C5−O1 being −152.4°). The main feature shown is the great distances C1−C2 or C1−C4 of the cyclobutane moiety, perhaps due to repulsion within the congested concave surface with the *gem*-methoxycarbonyl and methyl groups. Rings A and C assume a puckered and chair conformation, respectively.[23] Only a few aliphatic compounds possess the tetrahedral structure of diazacyclols (1,3-diazacycloalkan-1-ols).[24,25] Such a structure corresponds to the unstable intermediate for the reaction

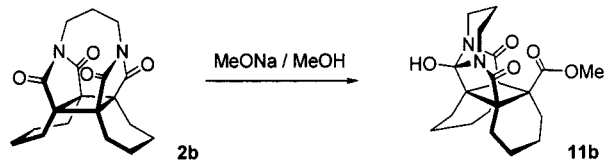
Scheme 5



Scheme 6



Scheme 7



of amide with amine (aminolysis of amide).[26] The formation of **11a** resulted from the addition of methylate anion followed by an intramolecular addition of the resulting amide anion **14** to the adjacent imide function leading to **15** (Scheme 5).

In theory, the amide anion addition could also occur transversely on the second imide function, giving rise to **16** (Scheme 6). This competing reaction is presumably suppressed by the considerable repulsion of the aza-bridge and the methoxycarbonyl group. We have calculated the relative energies of the two isomeric structures **11a** and **16**. According to the semiempirical PM3 method,[27] the **11a** isomer is favored by 14.5 kcal/mol (final heat of formation for **11a**, −204.66 kcal/mol; for **16**, −190.14 kcal/mol). Similarly, **2b** led to the hexacyclic globular compound **11b** (Scheme 7).

With the aim of understanding the origin of the stability of **3**, we have carried out molecular orbital calculations by the AM1[28] and PM3 methods. These calculations indicated that **7** can be very easily cyclized to **8**. For **7b**, the minimization of the energy led to a modification of the starting structure (from molecular mechanics geometry optimization) in favor of **8b**. Calcu-

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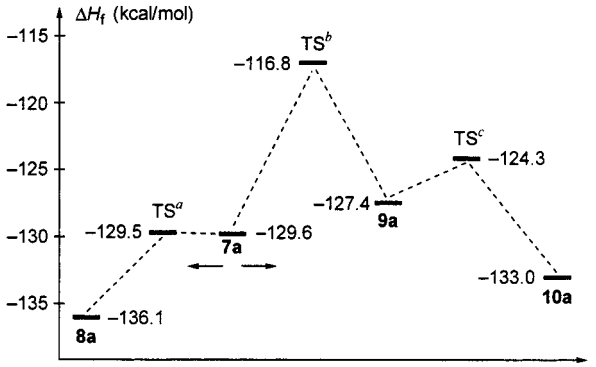

Figure 1. Reaction profile for addition of $NaBH_4$ to **2a** and evolution of the first intermediate **7a**. (*a*) Imaginary frequency of transition state (IF), −158.0 cm^{-1}. (*b*) IF, −329.8 cm^{-1}. (*c*) IF, −325.3 cm^{-1}.

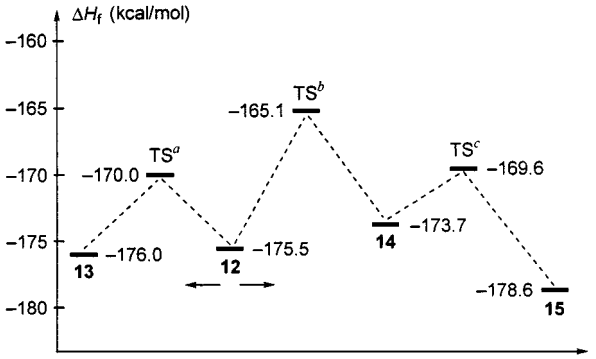

Figure 2. Reaction profile for the addition of methylate anion to **2a** and evolution of the first intermediate **12**. (*a*) Imaginary frequency of transition state (IF), −258.0 cm^{-1}. (*b*) IF, −361.4 cm^{-1}. (*c*) IF, −327.5 cm^{-1}.

lations on **7a** show that the O−C distance is near to the sum of the van der Waals radii for the two groups. Thus the "proximity effect" is strongly efficient since the distance and the angle of approach are particularly favorable. The term of near attack conformation (NAC) has been introduced to define the required conformation for juxtaposed reactants to enter a transition state. When the ground state consists of only NACs, the rate enhancement can be as large as 10^8.[29] In Figure 1, we reported calculated optimized energy of reactants and products and transition structure **7a**/**8a**, **7a**/**9a** and **9a**/**10a** using the AM1 method.

In Figure 1, we note that the reaction profile for the addition of hydride anion is favorable to the formation of **8a**. In contrast, the opening of the ansa bridge (formation of **9a**) is an endothermic process with an appreciable energy barrier. These investigations indicate that the overall change in strain energy from **7a** to **8a** provides the closure driving force. This suggest that increasing conformational rigidity imposed on the system by the annelation favorably affects the stability of cyclols **3**.

The reaction profile is different for the addition of methylate anion to **2a** (Figure 2). First, the pentacyclic anion **13** presents a weak stability and the cyclization **12**/**13** is reversible. Second, the tetracyclic anion **15** is the more stable.

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Conclusion

We have described a simple method for the preparation of bowl-shaped polyheterocyclic derivatives. The X-ray crystal structure determination revealed that a bond length in cyclobutane ring is one of the longest in this class of compounds.

Experimental Section

General. All reactions were run under argon in oven-dried glassware. ^1H and ^{13}C NMR spectra were recorded at 200 or 400 MHz and at 50 and 100 MHz, respectively. Flash chromatography was performed on silica gel (Merk 60 GF_{254} 230−400 mesh) and TLC on silica gel (Merck 60 F_{254}). 3,4,5,6-Tetrahydrophthalic anhydride was prepared by a known procedure.[30,31] Dimethylmaleic anhydride was synthesized by the reaction of pyruvic acid with succinic anhydride.[32]

General Procedure for the Preparation of Bisimide 1a,b. To a stirred solution of dimethylmaleic anhydride or 3,4,5,6-tetrahydrophthalic anhydride (100 mmol) in toluene (40 mL) was added 1,3-diaminopropane (3.7 g, 50 mmol). The solution was heated until the formation of a clear solution. A Dean−Stark apparatus was added, and water was removed. After 6 h of heating, 0.5 mL of 1,3-diaminopropane was added. The solution was heated for 2 h, and the toluene was removed by distillation. The crude product was crystallized in EtOH to give bismaleimide. **1,3-Bis(dimethylmaleimido)propane (1a):** using dimethylmaleic anhydride (12.6 g), 8.7 g (60 mmol) was obtained (60% yield) after chromatography on silica gel (diethyl ether/petroleum ether 4:1); white crystals, mp 114 °C. **1,3-Bis(3,4,5,6-tetrahydrophthaleimido)propane (1b):** using 3,4,5,6-tetrahydrophthalic anhydride (15.2 g), 11.8 g (0.69 mmol) was obtained (69% yield) after chromatography on silica gel (diethyl ether/petroleum ether 4:1); white crystals, mp 130 °C.

General Procedure for the Preparation of Cage Photoproducts 2a,b. Two grams of bisimide **1a** or **1b** in anhydrous acetone (230 mL) and acetonitrile (300 mL) containing a crystal of benzophenone was cooled to 0 °C and irradiated by a UV lamp (mercury lamp Philips HPK, 125 W) equipped with a Pyrex filter for 20 h. The solvent was removed under vacuum, and the crude solid was chromatographed on silica gel (diethyl ether/petroleum ether 4:1).

1,6-Diaza-3,4,8,9-tetramethyltetracyclo[4.4.3.$0^{3,9}$.$0^{4,8}$]-trideca-2,5,7,10-tetraone (2a): 1.3 g (4.5 mmol, 65%) obtained; white crystals, mp 295 °C; ^1H NMR ($CDCl_3$) δ 3.85 (4H, t, J = 5.8 Hz), 2.24 (2H, quint., J = 5.8 Hz), 1.32 (12H, s); ^{13}C NMR ($CDCl_3$) δ 177.4 (s), 50.9 (s), 40.4 (t), 20.5 (t), 9.9 (q). Anal. Calcd for $C_{15}H_{18}N_2O_4$: C, 62.06; H, 6.25; N, 9.65. Found: C, 61.99; H, 6.21; N, 9.61.

1,6-Diaza-hexacyclo[4.4.3.$4^{3,9}$.$4^{4,8}$.$0^{3,9}$.$0^{4,8}$]heneicosa-2,5,7,-10-tetraone (2b): 160 mg (0.47 mmol, 8%) obtained; white crystals, mp 250 °C; ^1H NMR ($CDCl_3$) δ 3.89 (4H, t, J = 5.8 Hz), 2.26 (2H, q, J = 5.8 Hz), 2.0 (8H, m), 1.65 (4H, m), 1.25 (4H, m); ^{13}C NMR ($CDCl_3$) δ 177.7 (s), 50.6 (s), 40.6 (t), 20.6 (t), 20.4 (t), 19.2 (t). Anal. Calcd for $C_{19}H_{22}N_2O_4$: C, 66.66; H, 6.43; N, 8.19. Found: C, 66.72; H, 6.42; N, 8.14.

1,6-Diaza-14-oxa-3,4,8,9-tetramethylpentacyclo[4.4.3.-$1^{2,5}$.$0^{3,9}$.$0^{4,8}$]tetradeca-2-ol-7,10-dione (3a). To a stirred solution of 250 mg (0.86 mmol) of **2a** in 2-propanol (7.7 mL) and water (1.3 mL) was added $NaBH_4$ (0.16 g, 4.3 mmol). The reaction mixture was stirred 1 day and then evaporated to dryness. Finally, CH_2Cl_2 (10 mL) and saturated aqueous NH_4Cl (5 mL) were added, and after stirring the phases were separated. The aqueous phase was extracted with CH_2Cl_2 (3 × 10 mL), and the organic fractions were dried ($MgSO_4$). The reaction mixture was filtered and rotary evaporated to a

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solid. Purification was achieved by recrystallization in CH_2Cl_2/methanol to give **3a** (164 mg, 0.56 mmol, 65%); white crystals, mp 215 °C; ^{1}H NMR ($CDCl_3$) δ 4.89 (1H, s), 3.79 (1H, dd, J = 14.1, 3.6 Hz), 3.66 (1H, br. d, J = 13.6 Hz), 3.37 (1H, td, J = 13.7, 2.7 Hz), 3.20 (1H, td, J = 13.4, 3.10 Hz), 2.86 (1H, m), 1.19 (1H, m), 1.13 (6H, s), 1.11 (3H, s), 1.04 (3H, s); ^{13}C NMR ($CDCl_3$) δ 175.7 (s), 174.8 (s), 117.2 (s), 94.5 (d), 50.4 (s), 49.7 (s), 49.6 (s), 48.5 (s), 41.6 (t), 40.1 (t), 19.3 (t), 12.2 (q), 10.1 (q), 9.95 (q), 8.9 (q); HRMS calcd for $C_{19}H_{28}N_2O_4$ 292.1423, found 292.1440.

Addition of Methyllithium and *n*-Butyllithium to 2a. To a stirred solution of 0.25 g (0.86 mmol) of **2a** in anhydrous THF (10 mL) cooled to −30 °C was slowly added MeLi or *n*-BuLi (0.65 mL, 1.04 mmol, 1.2 equiv, 1.6 M). The solution was allowed to warm to ambient temperature in 12 h. Then, the reaction mixture was poured into cold NH_4Cl solution and extracted with CH_2Cl_2 (3 × 15 mL). The combined organic phases were dried ($MgSO_4$), filtered, and rotary evaporated to a solid. After dissolution in CH_2Cl_2, the solution was purified by flash chromatography (98:2 to 90:10 CH_2Cl_2/MeOH).

1,6-Diaza-14-oxa-3,4,5,8,9-pentamethylpentacyclo[4.4.3.1.^{2,5}0.^{3,9}0^{4,8}]tetradeca-2-ol-7,10-dione (3b). Using MeLi, 158 mg (0.52 mmol, 60%) of **3b** was obtained; white crystals, mp 254 °C; ^{1}H NMR ($CDCl_3$) δ 3.72 (1H, dt, J = 13.9, 2.2 Hz), 3.67 (1H, dt, J = 14.0, 2.0 Hz), 3.32 (1H, td, J = 13.7, 3.1 Hz), 3.16 (1H, td, J = 13.5, 3.1 Hz), 2.91 (1H, qt, J = 13.7, 4.3 Hz), 1.31 (3H, s), 1.21 (1H, m), 1.12 (3H, s), 1.11 (3H, s), 1.05 (3H, s), 1.02 (3H, s); ^{13}C NMR ($CDCl_3$) δ 174.9 (s), 174.8 (s), 115.5 (s), 97.6 (s), 50.6 (s), 50.3 (s), 49.9 (s), 49.8 (s), 40.5 (t), 40.1 (t), 20.6 (q), 19.5 (t), 10.5 (q), 10.3 (q), 10.1 (q), 9.3 (q). Anal. Calcd for $C_{16}H_{22}N_2O_4$: C, 62.74; H, 7.19; N, 9.15. Found: C, 62.80; H, 7.12; N, 9.22.

3,5-Diaza-9-(2-hydroxypropan-2-yl)-1,7,8,9-tetramethyltetracyclo[5.1.1.3^{3,5}.0^{4,8}]dodecan-4-ol-2,6-dione (4b). Using MeLi, 41.5 mg (0.13 mmol, 15%) of **4b** was obtained; white crystals, mp 225 °C; ^{1}H NMR ($CDCl_3$) δ 4.16 (1H, dd, J = 13.7, 5.9 Hz), 3.36 (2H, m), 3.15 (1H, td, J = 13.3, 4.3 Hz), 2.06 (1H, m), 1.40 (3H, s), 1.39 (3H, s), 1.30 (1H, m), 1.20 (3H, s), 1.18 (3H, s), 1.04 (3H, s), 1.03 (3H, s); ^{13}C NMR ($CDCl_3$) δ 176.4 (s), 173.3 (s), 109.3 (s), 83.6 (s), 52.9 (s), 51.7 (s), 49.9 (s), 49.6 (s), 39.5 (t), 36.7 (t), 22.4 (t), 21.8 (q), 18.5 (q), 12.3 (q), 11.9 (q), 11.3 (q); HRMS calcd for $C_{17}H_{24}N_2O_3$ ($M^+ - H_2O$) 304.1787, found 304.1794.

5-Butyl-1,6-diaza-14-oxa-3,4,8,9-tetramethylpentacyclo-[4.4.3.1^{2,5}.0^{3,9}.0^{4,8}]tetradeca-2-ol-7,10-dione (3c). Using *n*-BuLi, 209 mg (0.60 mmol, 70%) of **3c** was obtained; white crystals, mp 208 °C; ^{1}H NMR ($CDCl_3$) δ 3.65 (1H, dd, J = 13.5, 1.6 Hz), 3.63 (1H, br d, J = 13.5 Hz), 3.31 (1H, td, J = 13.5, 3.0 Hz), 3.11 (1H, td, J = 13.5, 3.0 Hz), 2.86 (1H, qt, J = 13.6, 4.2 Hz), 1.82 (1H, ddd, J = 14.8, 11.8, 6.0 Hz), 1.66 (1H, ddd, J = 14.8, 11.0, 4.8 Hz), 1.24 (2H, quint., J = 7.36 Hz), 1.17 (1H, m), 1.09 (3H, s), 1.08 (3H, s), 1.07 (3H, s), 1.01 (3H, s), 0.99 (2H, sext. J = 7.4 Hz), 0.83 (3H, t, J = 7.4 Hz); ^{13}C NMR ($CDCl_3$) δ 175.1 (s), 115.4 (s), 99.4 (s), 50.8 (s), 50.5 (s), 49.9 (s), 49.8 (s), 40.4 (t), 40.1 (t), 32.1 (t), 26.4 (t), 22.7 (t), 19.4 (t), 13.9 (q), 10.3 (q), 10.1 (q), 10.05 (q), 9.2 (q); HRMS calcd for $C_{19}H_{28}N_2O_4$ 348.2049, found 348.2066.

3,5-Diaza-9-(5-hydroxynonan-5-yl)-1,7,8,9-tetramethyltetracyclo[5.1.1.3^{3,5}.0^{4,8}]dodecan-4-ol-2,6-dione (4c). Using *n*-BuLi, 30 mg (0.086 mmol, 10%) of **4c** was obtained; white wax; ^{1}H NMR ($CDCl_3$) δ 4.18 (1H, dd, J = 13.5, 5.6 Hz), 3.26 (2H, dd, J = 10.5, 3.0 Hz), 3.04 (1H, td, J = 13.4, 4.4 Hz), 2.04 (1H, m), 1.82 (4H, m), 1.29 (8H, m), 1.19 (3H, s), 1.16 (3H, s), 1.09 (3H, s), 1.07 (3H, s), 0.88 (3H, t, J = 7.3 Hz), 0.85 (3H, t, J = 7.3 Hz); ^{13}C NMR ($CDCl_3$) δ 176.5 (s), 174.0 (s), 111.9 (s), 85.8 (s), 52.9 (s), 52.4 (s), 49.9 (s), 49.6 (s), 39.8 (t), 37.2 (t), 33.8 (t), 29.7 (t), 29.2 (t), 27.3 (t), 26.6 (t), 22.9 (t), 22.1 (t), 14.0 (q), 13.9 (q), 12.4 (q), 11.9 (q), 11.0 (q), 10.9 (q). Anal. Calcd for $C_{23}H_{38}N_2O_4$: C, 67.98; H, 9.36; N, 6.89. Found: C, 68.04; H, 9.31; N, 6.92.

3,5-Diaza-9-methoxycarbonyl-1,7,8,9-tetramethyltetracyclo[5.1.1.3^{3,5}.0^{4,8}]dodecan-4-ol-2,6-dione (11a). NaMeO (540 mg, 10 mmol) were added to anhydrous methanol (10 mL). After dissolution, bisimide **2a** was added (290 mg, 1 mmol). The mixture was stirred at room temperature for 2 h. Acidic workup and extraction with CH_2Cl_2 give an oil which crystallize in a CH_2Cl_2-Et_2O to give 232 mg (0.72 mmol, 72%) of white crystals, mp 255 °C; ^{1}H NMR ($CDCl_3$) δ 4.10 (2H, ddd, J = 13.9, 5.4, 1.4 Hz), 3.59 (3H, s), 3.41 (2H, td, J = 12.9, 3.8 Hz), 2.26 (1H, qt, J = 13.2, 5.4 Hz), 1.43 (1H, dsept, J = 13.5, 1.87 Hz), 1.34 (3H, s), 1.17 (6H, s), 1.10 (3H, s); ^{13}C NMR ($CDCl_3$) δ 175.3 (s), 171.4 (s), 101.2 (s), 52.5 (s), 52.3 (q), 51.8 (s), 47.3 (s), 37.5 (t), 21.0 (t), 16.1 (q), 12.95 (q), 9.73 (q).). HRMS calcd for $C_{16}H_{22}N_2O_5$ 322.1529, found 322.1538. Anal. Calcd: C, 59.62; H, 6.88; N, 8.69. Found: C, 59.63; H, 6.88; N, 8.64.

3,5-Diaza-8-methoxycarbonylhexacyclo[5.5.5.3^{3,5}.0^{1,8}.0^{4,13}.0^{7,13}]dodecan-4-ol-2,6-dione (11b) was prepared by the same procedure as for **11a** with 374 mg of bisimide **2b** to yield 254 mg (0.68 mmol, 68%) of **11b**; white crystals, mp 145 °C; ^{1}H NMR ($CDCl_3$) δ 4.04 (1H, dd, J = 13.3, 5.1 Hz), 3.99 (1H, dd, J = 13.3, 5.1 Hz), 3.59 (3H, s), 3.40 (2H, td, J = 13.1, 2.8 Hz), 2.13 (2H, m), 1.95 (3H, m), 1.76 (2H, m), 1.72−1.32 (10H, m), 1.29 (1H, m); ^{13}C NMR ($CDCl_3$) δ 176.1 (s), 175.3 (s), 171.2 (s), 101.1 (s), 53.0 (s), 52.3 (q), 51.8 (s), 51.3 (s), 46.9 (s), 37.7 (t), 37.5 (t), 24.6 (t), 22.2 (t), 22.0 (t), 21.2 (t), 19.9 (t), 19.5 (t), 18.9 (t), 17.0 (t), 16.6 (t); HRMS calcd for $C_{20}H_{26}N_2O_5$ 374.1841, found 374.1823.

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Supporting Information Available: NMR spectra for **2a**, **3a**−**c**, **4b**, **4c**, and **11b**. This information is available free of charge via the Internet at http://pubs.acs.org.

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