Diastereoselective Synthesis of Hydantoin- and Isoxazoline-Substituted Dispirocyclobutanoids

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Synthetic strategies for constructing novel achiral cyclobutanoid isoxazolidinoimidazolidinedione heterocycles, with a generalized structure of **II**, have been developed via 1,3-dipolar cycloaddition and carbanilide cyclization transformations from methylenecyclobutane **13**. The exo methylene cyclobutane system has made the realization of some diasteroselectivity possible, such that the H-bond (Boc-NH) directed product (i.e., **14**) was obtained with 3:1 selectivity relative to the non-H-bond directed product (i.e., **15**).

Introduction

In the field of drug discovery, considerable efforts have been focused on the synthesis of hydantoin derivatives,[1] using both solution- and solid-phase organic synthesis.[2] As part of our efforts toward the preparation and evaluation of hydantoin containing heterocycles, we recently reported synthetic strategies for the solution,[3] as well as solid-phase,[4] routes for the construction of hydantoin- and isoxazoline-containing heterocycles (**I**) arrayed about a central core (R_3). This interesting structural motif incorporates the hydantoin nucleus, which plays an important role in agrochemical,[2a−b] as well as medicinal,[2c−g] applications and the isoxazoline motif, which has been used extensively to modulate various other biological active targets.[5] The need to further diversify these compounds, together with recent reports regarding the biological activities of the spirohydantoins[6] and spiroisoxazolines,[7] led us to explore development of synthetic strategies for constructing hydantoin- and isoxazoline-containing heterocycle **II** with its central cyclobutane core (Figure 1). In the 5−4−5 dispiro system **II**, the target molecule is achiral and thus may simplify the synthetic aspects of drug discovery with this scaffold.

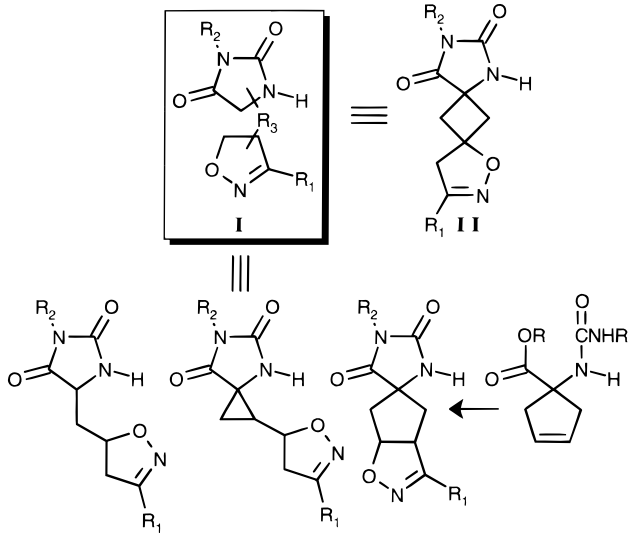

Figure 1.

Results and Discussion

We envisioned employing amino acid **III** in our construction of novel 2,4,9-triaza-8-oxa-dispiro[4.1.4.1]dodec-9-ene-1,3-dione heterocycles of generalized structure **II**. This core building block would be derived from a suitably activated/protected derivative of glycine and a bis-alkylating agent such as 3-chloro-2-chloromethyl-1-propene

(1) (a) Dressman, B. A.; Spangle, L. A.; Kaldor, S. W. *Tetrahedron Lett.* **1996**, *37*, 937. (b) Hanessian, S.; Yang, R. Y. *Tetrahedron Lett.* **1996**, *37*, 5835. (c) Matthews, J.; Rivero, R. A. *J. Org. Chem.* **1997**, *62*, 6090. (d) Xiao, X.; Ngu, K.; Chao, C.; Patel, D. V. *J. Org. Chem.* **1997**, *62*, 6968. (e) Stadlwieser, J.; Ellmerer-Muller, E. P.; Taco, A.; Maslouh, N.; Bannwarth, W. *Angew. Chem., Int. Ed. Engl.* **1998**, *37*, 1402. (f) Wilson, L. J.; Li, M.; Portlock, D. E. *Tetrahedron Lett.* **1998**, *39*, 5135. (g) Nefzi, A.; Dooley, C.; Ostresh, J. M.; Houghten, R. A. *Bioorg. Med. Chem. Lett.* **1998**, *8*, 2273. (h) Boeijen, A.; Kruijtzer, A. W.; Liskamp, R. M. J. *Bioorg. Med. Chem. Lett.* **1998**, *8*, 2375 (i) Park, K.-H.; Olmstead, M. M.; Kurth, M. J. *J. Org. Chem.* **1998**, *63*, 6579. (j) Park, K.-H.; Abbate, E.; Najdi, S.; Olmstead, M. M.; Kurth, M. J. *Chem. Commun.* **1998**, 1679. (k).Park, K.-H.; Kurth, M. J. *Tetrahedron Lett.* **1999**, *40*, 5841.

(2) (a) Mappes, C. J.; Pommer, E. H.; Rentzea, C.; Zeeh, B. *U.S. Patent* **1980**, 4, 198, 423. (b) Ohta, H.; Jikihara, T.; Wakabayashi, Ko.; Fujita, T. *Pestic. Biochem. Physiol.* **1980**, *14*, 153. (c) Brouillette, W. J.; Brown, G. B.; DeLorey, T. M.; Liang, G. *J. Pharm. Sci.* **1990**, *79*, 871. (d) Coudert, P.; Rubat, C.; Couquelet, J. M.; Bastide, J.; Bastide, P. *Pharm. Acta Helv.* **1991**, *66*, 155. (e) Carrera, G. M., Jr.; Garvey, D. S. *J. Heterocycl. Chem.* **1992**, *29*, 847. (f) Brouillette, W. J.; Jestkov, V. P.; Brown, M. L.; Akhtar, M. S.; DeLorey, T. M.; Brown, G. B. *J. Med. Chem.* **1994**, *37*, 3289. (g) Karolak-Wojciechowska, J.; Kwiatkowski, W.; Kiec-Kononowicz, K. *Pharmazie* **1995**, *50*, 114.

(3) Park, K.-H.; Olmstead, M. M.; Kurth, M. J. *J. Org. Chem.* **1998**, *63*, 113.

(4) See refs 1i and j.

(5) (a) Khalil, M. A.; Maponya, M. F.; Ko, D.-H.; You, Z.; Oriaku, E. T.; Lee, H. J. *Med. Chem. Res.* **1996**, *6*, 52. (b) Groutas, W. C.; Venkataraman, R.; Chong, L. S.; Yoder, J. E.; Epp, J. B.; Stanga, M. A.; Kim, E.-H. *Bioorg. Med. Chem.* **1995**, *3*, 125. (c) Levin, J. I.; Chan, P. S.; Coupet, J.; Bailey, T. K.; Vice, G.; Thibault, L.; Lai, F.; Venkatesan, A. M.; Cobuzzi, A. *Bioorg. Med. Chem. Lett.* **1994**, *4*, 1703. (d) Simoni, D.; Manfredini, S.; Tabrizi, M. A.; Bazzanini, R.; Guarneri, M.; Ferroni, R.; Traniello, F.; Nastruzzi, C.; Feriotto, G.; Gambari, R. *Top. Mol. Organ. Eng.* **1991**, *8 (Chem. Prop. Biomol. Syst.)*, 119.

(6) (a) Brandstetter, T. W.; Kim, Y.; Son, J. C.; Taylor, H. M.; Lilley, P. M. de Q.; Watkin, D. J.; Johnson, L. N.; Oikonomakos, N. G.; Fleet, G. W. J. *Tetrahedron Lett.* **1995**, *36*, 2149. (b) Haruyama, H.; Takayama, T.; Kinoshita, T.; Kondo, M.; Nakajima, M.; Haneishi, T. *J. Chem. Soc., Perkin Trans. 1* **1991**, 1637. (c) Mio, S.; Sano, H.; Shindou, M.; Honma, T.; Sugai, S. *Agric. Biol. Chem.* **1991**, *55*, 1105.

(7) (a). Wityak, J.; Sielecki, T. M.; Pinto, D. J.; Emmett, G.; Sze, J. Y.; Liu, J.; Tobin, A. E.; Wang, S.; Jiang, B,; Ma, P.; Mousa, S. A.; Wexler, R. R.; Olson, R. E. *J. Med. Chem.* **1997**, *40*, 50. (b) Ciminiello, P.; Dell'Aversano, C.; Fattorusso, E.; Magno, S.; Pansini, M. *J. Nat. Prod.* **1999,** *62*, 590.

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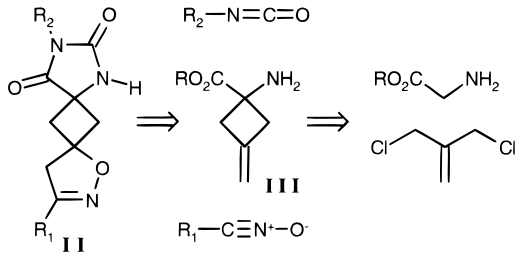
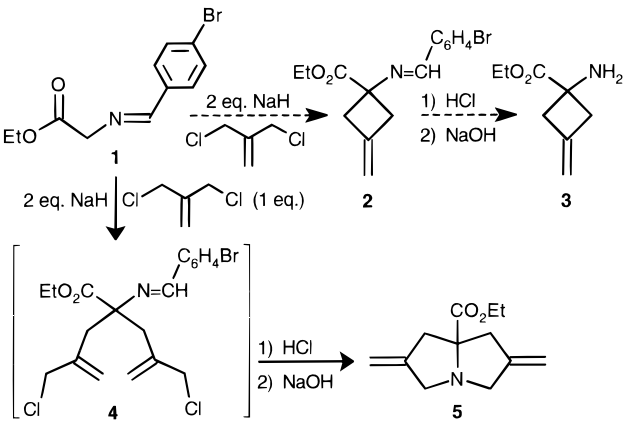


Figure 2.

Scheme 1



(Figure 2). Subsequent isoxazoline formation by a nitrile oxide 1,3-dipolar cycloaddition and hydantoin formation by isocyanate treatment would then deliver **II**.

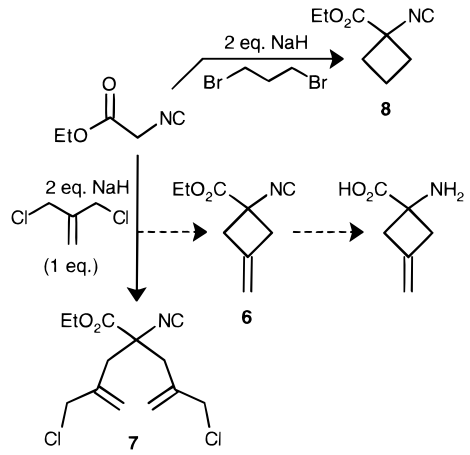
Unfortunately, bis-alkylation of Schiff base **1**[8] with 3-chloro-2-chloromethyl-1-propene resulted in pyrrolizidine **5** instead of the desired cyclobutane product **2** (Scheme 1).

The intermediate bis-alkylated Schiff base (**4**) gave pyrrolizidine **5** by an acid-catalyzed hydrolysis of the Schiff base and, upon base treatment to neutralize the resulting hydrochloride salt, spontaneous intramolecular bis-*N*-alkylation. This unoptimized reaction delivered **5** in 35% yield from **1**.

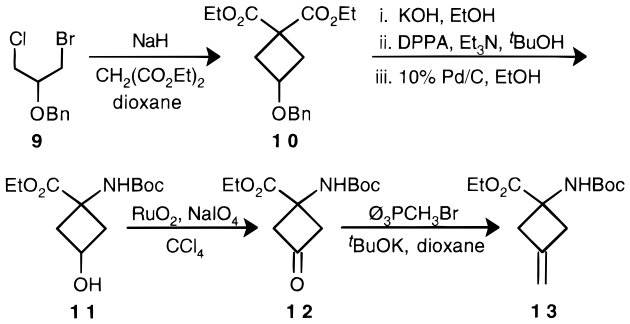
Next, a route targeting cyclobutane intermediate **6** starting from ethyl isocyanoacetate was attempted as outlined in Scheme 2. Again, base treatment in the presence of 3-chloro-2-chloromethyl-1-propene gave dialkylated product **7** as the major product; none of the desired cyclobutane product **6** was obtained. This failure to form the desired *exo*-methylene substituted cyclobutane ring (i.e., **2** or **6**) can be attributed to problems in accommodating sp^2 geometry at C3 in the cyclobutane ring system. Indeed, the alkylation reaction of ethyl isocyanoacetate with 1,3-dibromopropane results in formation of the desired cyclobutane ring system **8**, which can be hydrolyzed to the corresponding amino acid.[9]

On the basis of these results, it appeared desirable to maintain sp^3 hybridization at C3 of the cyclobutane ring during ring formation and subsequently rehybridize to sp^2 hybridization. Drawing on extensive bis-alkylation studies for the synthesis of cyclobutanone derivatives, precursor **10**[10] (Scheme 3) was synthesized from 1,3-

Scheme 2



Scheme 3



dihalogenated propane **9**[11] by bis-alkylation of diethylmalonate. Partial hydrolysis of diester **10** was followed by Curtius rearrangement in *tert*-butyl alcohol (giving the Boc-protected amine), and subsequent debenzylation[11] over 10% Pd/C at 1 atm delivered hydroxy cyclobutane **11**. Oxidation of this 2°-alcohol to ketone **12**[12] was achieved by treatment with ruthenium dioxide/sodium metaperiodate.[13] Finally, a Wittig[14] reaction on cylobutanone **12** afforded the exo methylene-substituted cyclobutane target **13**.

In previous studies,[1i,3] we discovered that a urea-NH in cyclopentenyl amino acids (see Figure 1) can be a very effective stereocontrol element in intermolecular nitrile oxide[15] 1,3-dipolar cycloaddition reactions.[16] We showed that this selectivity arose via a facial selective urea-NH-mediated hydrogen-bond delivery of the nitrile oxide moiety (i.e., urea-N—H···$^-$O—$^+$N≡CR). With **13** in hand, we were positioned to probe whether the Boc-NH moiety

(8) (a) O'Donnel, M. J.; Wu, S.; Huffman, J. C. *Tetrahedron Lett.* **1994**, *50*, 4507. (b) Bey, P.; Vevert, J. P. *Tetrahedron Lett.* **1977**, *17*, 1455.

(9) Kalvin, D.; Ramalingam, K.; Woodard, R. *Synth. Commun.* **1985**, *15*, 267.

(10) Beard, C.; Burger, A. *Chem. Ber.* **1962**, *95*, 2535.

(11) (a) Avram, M.; Nenitzescu, C. D.; Maxim, M. *Chem. Ber.* **1957**, *90*, 1424. (b) Michejda, C. D.; Comnick, R. W. *J. Org. Chem.* **1975**, *40*, 1046.

(12) Allan, R. D.; Hanrahan, J. R.; Hambley, T. W.; Johnston, G. A. R.; Mewett, K. N.; Mitrovic, A. D. *J. Med. Chem.* **1990**, *33*, 2905.

(13) (a) Moriarty, R. M.; Gopal, H.; Adams, T. *Tetrahedron Lett.* **1970**, 4003. (b) Dormoy, J.-R.; Castro, B. *Synthesis.* **1986**, 81.

(14) (a) Greenwald, R.; Chaykovsky, M.; Corey, E. J. *J. Org. Chem.* **1963**, *28*, 1128. (b) Maryanoff, B. E.; Reitz, A. B. *Chem. Rev.* **1989**, *89*, 863.

(15) For reviews of nitrile oxide-isoxazoline methodology, see: (a) Curran, D. P. In *Advances in Cycladdition*; Curran, D. P., Ed.; JAI Press Inc.: Greenwich, Connecticut, 1988; Vol. 1, p 129−189. (b) Torssel, K. B. G. In *Organic Nitro Chemistry Series. Nitrile Oxides, Nitrones, and Nitronates in Organic Synthesis. Novel Strategies in Synthesis*; Feuer, H., Ed.; VCH Publishers: Weinheim, 1988; p 55−74.

(16) *1,3-Dipolar Cycloaddition Chemistry*; Padwa, A., Ed.; Wiley: New York, 1984; Vol. 1 and 2.

Scheme 4

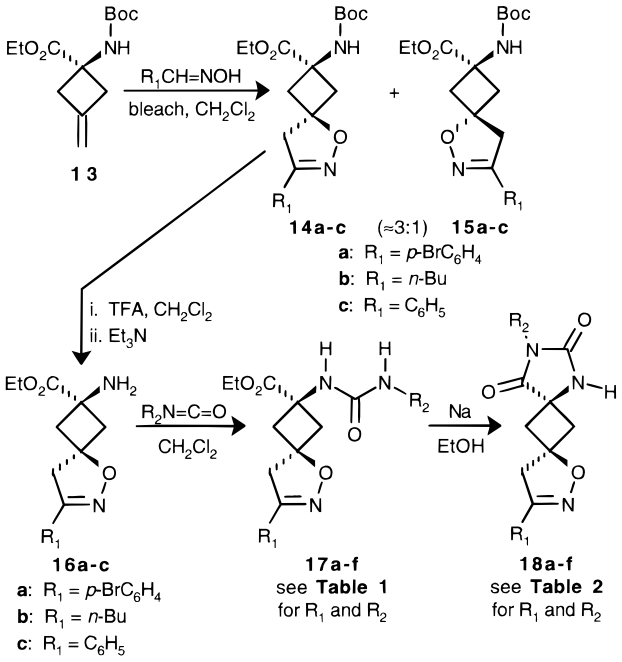
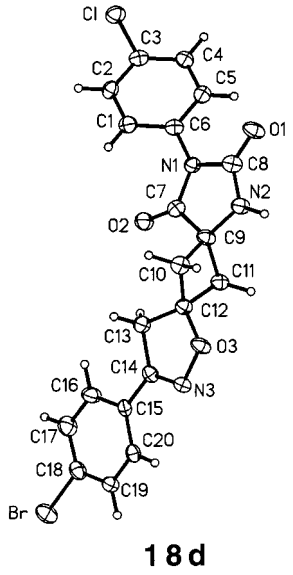


Table 1: Formation of Ethyl 6-aza-5-oxa[(amino)-carbonylamino]spiro-[3.4]oct-6-ene-2-carboxylates (17)

compound	R_1	R_2	% yield
17a	$^{p}BrC_6H_4^-$	$C_6H_5^-$	95
17b	$^{n}Bu^-$	$C_6H_5^-$	96
17c	$C_6H_5^-$	$C_6H_5CH_2^-$	96
17d	$^{p}BrC_6H_4^-$	$^{p}ClC_6H_4^-$	97
17e	$^{n}Bu^-$	$^{m}ClC_6H_4^-$	96
17f	$C_6H_5^-$	$^{n}Bu^-$	95

here would mediate similar stereoselectivity in **13** → **14** vs. **15 (**Scheme 4). Indeed, the *exo*-methylene cyclobutane system realized some diastereoselectivity, such that the H-bond directed product (**14**) was obtained with 3:1 selectivity, relative to the non-H-bond directed product (**15**). Although the combined yield for **13** → **14** + **15** is 60−70%, it is generally difficult to separate each isomer at this stage using silica gel column chromatography. Fractional recrystallization, although inefficient, allowed for the isolation of pure **14a** (35%) and **14c** (37%) from these mixtures. In the case of the **14b**/**15b** mixture, separation was not feasible; however, **16b** was obtained in pure form after silica gel column chromatographic purification of the **13** → [**14b**/**15b** (70%)] → **16b** (75%) reaction sequence. Boc-deprotection of major products **14** followed by neutralization with Et_3N afforded free amines **16** and subsequent treatment of these amines with several isocyanates delivered ureas **17** (see Table 1). Base treatment of **17** (sodium ethoxide) delivered dispirocyclobutanoids **18** with hydantoin and isoxazoline substituents (see Table 2). Because of the dispirocyclic nature of butanoids **18**, it was difficult to establish the relative stereochemistry of these heterocycles using NMR techniques.

Fortunately, many of these compounds were crystalline, and single-crystal X-ray crystallographic analysis proved efficacious in determining the 1,3-cyclobutanoid stereochemistry. With this technique, we were able to establish that the major dispirocyclic product obtained from **13** (*vide supra*) was, in all cases, the *cis* diastereomer (see Figure 3).



18d

Figure 3. Computer generated single-crystal X-ray structure of **18d**.

Table 2: Formation of 2,4,9-triaza-8-oxa-dispiro-[4.1.4.1]dodec-9-ene-1,3-diones (18)

compound	R_1	R_2	% yield
18a	$^{p}BrC_6H_4^-$	$C_6H_5^-$	94
18b	$^{n}Bu^-$	$C_6H_5^-$	92
18c	$C_6H_5^-$	$C_6H_5CH_2^-$	95
18d	$^{p}BrC_6H_4^-$	$^{p}ClC_6H_4^-$	93
18e	$^{n}Bu^-$	$^{m}ClC_6H_4^-$	91
18f	$C_6H_5^-$	$^{n}Bu^-$	90

In summary, we have developed a synthetic strategy for the preparation of novel heterocycles of generalized structure **II**. The work reported here secures this stage in a program aimed at the structural diversification of hydantoin- and isoxazoline-based pharmacophores. Employing this general and expedient synthetic methodology with solid-phase techniques and subsequent library production and biological evaluation are underway.

Experimental Section

Ethyl 2,6-Dimethylene-3,5,7,7a-tetrahydropyrrolizin-7a-carboxylate (5) from 1. Compound **1** (2 g, 7.40 mmol) was treated with NaH (0.39 g, 16.28 mmol) in THF (50 mL) under nitrogen at room temperature. After 5 min, 3-chloro-2-chloromethyl-1-propene (0.925 g, 7.40 mol) was added to the reaction mixture. The resulting solution was stirred at 60 °C for 1 h. Ether and cold water were added to the reaction mixture, and the ether layer was separated and dried (anhydrous $MgSO_4$). After removal of ether at reduced pressure, the residue was passed through a silica gel column that was presaturated with 10% Et_3N in hexane. Removal of the solvent under reduced pressure gave compound **4** (1.3 g of crude) as a liquid, which was treated with 1 N HCl (7 mL) in THF (20 mL) for 5 min. Ethyl acetate and water were added to the reaction mixture, and the aqueous layer was treated with 1 N NaOH solution until the pH reached 9−10. Extraction with ethyl acetate, drying over anhydrous $MgSO_4$, and silica gel column chromatography (ethyl acetate/hexane = 1/3) gave the compound **5** (0.27 g, 1.29 mmol, 35%) as a liquid: FTIR (neat) 3014, 2905, 1725, 1444 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 4.99 (dd, 2H, J = 4.2, 2.0 Hz), 4.93 (dd, 2H, J = 4.2, 2.0 Hz), 4.17 (m, 2H), 3.82 (d, 2H, J = 15.0 Hz), 3.25 (d, 2H, J = 15.0 Hz), 2.97 (d, 2H, J = 16.6 Hz), 2.58 (d, 2H, J = 16.6 Hz), 1.26 (m, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 174.3, 147.6, 106.8, 77.9, 61.3, 59.8, 41.2, 14.4.

Ethyl 1-[(*tert*-Butoxy)carbonylamino]-3-methylenecyclobutanecarboxylate (13) from 12. The mixture of potassium *tert*-butoxide (0.73 g, 6.53 mmol) and methyl triphenyl phosphonium bromide (2.33 g, 6.53 mmol) was stirred at 40 °C in dioxane (10 mL) for 30 min under nitorgen. The reaction mixture was cooled to 10 °C, at which point the solution of compound **12** (1.4 g, 5.44 mmol) in dioxane (10 mL) was added over 20 min. The reaction mixture was stirred at 10 °C for 2 h and at room temperature for 30 min. After removal of the solvent under reduced pressure, ether and cold water were added to the residue. The ether layer was separated, and the aqueous phase was extracted with ether. The combined ether extracts were washed with brine, dried over anhydrous $MgSO_4$, and concentrated. Silica gel column chromatography (ethyl acetate/hexane = 1/9) afforded the desired compound **13** (1.25 g, 4.90 mmol, 90%) as a white solid: Mp 83 °C; FTIR (KBr) 3333, 2985, 1726, 1702, 1512 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 5.32 (s, br, 1H), 4.83 (m, 2H), 4.14 (q, 2H, J = 7.1 Hz), 3.26−3.19 (m, 2H), 2.87−2.80 (m, 2H), 1.36 (s, 9H), 1.20 (t, 3H, J = 7.1 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 173.2, 154.9, 140.8, 108.2, 79.9, 61.3, 54.5, 42.1, 28.2, 14.0. Anal. Calcd for $C_{13}H_{21}NO_4$: C, 61.15; H,8.29; N, 5.48. Found: C, 61.28; H, 8.40; N, 5.53.

Ethyl *cis*-6-Aza-2-[(*tert*-butoxy)carbonylamino]-7-(4-bromophenyl)-5-oxaspiro[3.4]oct-6-ene-2-carboxylate (14a) and Ethyl *trans*-6-Aza-2-[(*tert*-butoxy)carbonylamino]-7-(4-bromophenyl)-5-oxaspiro[3.4]oct-6-ene-2-carboxylate (15a) from 13. To the solution of compound **13** (1 g, 3.92 mmol), Et_3N (39 mg, 0.39 mmol) and bleach (0.46 g, 6.26 mmol, from 8.8 g of 5.25% NaOCl solution) in CH_2Cl_2 (20 mL) was added the solution of *p*-bromobenzaldehyde oxime (0.28 g, 3.92 mmol) in CH_2Cl_2 (10 mL) over 20 min at 0 °C. The reaction mixture was stirred at 10 °C for 3 h and at room temperature overnight. The inseparable mixture (the same rf value) of compounds **14a** and **15a** (**14a**/**15a** ≈ 3/1, 1.10 g, 2.43 mmol, 62%) was afforded as a white solid using methods including CH_2Cl_2 extraction, drying over anhydrous $MgSO_4$, removal of solvent under reduced pressure, and silica gel column chromatography (ethyl acetate/hexane = 1/9). The solid was fractionally recrystallized (ethyl acetate and hexane) to give compound **14a** (0.621 g, 1.37 mmol, 35%) and **15a** (0.177 g, 0.39 mmol, 10%) as white solid, **14a**: Mp 133−134 °C; FTIR (KBr) 1740, 1675 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.51 (s, 4H), 5.32 (s, br, 1H), 4.24 (q, 2H, J = 7.1 Hz), 3.54 (s, 2H), 3.00 (d, 2H, J = 13.4 Hz), 2.84 (d, 2H, J = 13.4 Hz), 1.44 (s, 9H), 1.31 (t, 3H, J = 7.1 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 173.8, 156.2, 154.6, 131.8, 128.1, 127.9, 124.3, 81.1, 80.2, 61.7, 50.7, 46.9, 46.3, 28.2, 14.1. Anal. Calcd for $C_{20}H_{25}BrN_2O_5$: C, 52.98; H, 5.55; N, 6.17. Found: C, 53.10; H, 5.57; N, 6.14. **15a**: Mp 148 °C; FTIR (KBr) 1736, 1678 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.54 (s, 4H), 5.14 (s, br, 1H), 4.24 (q, 2H, J = 7.1 Hz), 3.54 (s, 2H), 3.22 (d, 2H, J = 13.9 Hz), 2.58 (s, br, 2H), 1.45 (s, 9H), 1.32 (t, 3H, J = 7.1 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 172.4, 156.1, 155.5, 131.8, 128.3, 128.0, 124.2, 81.7, 80.4, 61.7, 51.3, 46.6, 45.7, 28.2, 14.1. Anal. Calcd for $C_{20}H_{25}BrN_2O_5$: C, 52.98; H, 5.55; N, 6.17. Found: C, 52.89; H, 5.49; N, 5.99.

Ethyl *cis*-6-Aza-2-[(*tert*-butoxy)carbonylamino]-5-oxa-7-phenylspiro[3.4]oct-6-en-2-carboxylate (14c) and Ethyl *trans*-6-Aza-2-[(*tert*-butoxy)carbonylamino]-5-oxa-7-phenylspiro-[3.4]oct-6-en-2-carboxylate (15c) from 13. As with **13** → **14a** and **15a**, benzaldehyde oxime gave the inseparable mixture (the same rf value) of compounds **14c** and **15c** (**14c**/**15c** ≈ 3/1, 0.94 g, 2.50 mmol, 64%) as a white solid. The solid was fractionally recrystallized (ethyl acetate and hexane) to give compound **14c** (0.542 g, 1.45 mmol, 37%) and **15c** (0.161 g, 0.43 mmol, 11%) as white solid, **14c**: Mp 128 °C; FTIR (KBr) 1723, 1699 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.66−7.63 (m, 2H), 7.40 (m, 3H), 5.32 (s, br, 1H), 4.25 (q, 2H, J = 7.1 Hz), 3.57 (s, 2H), 3.00 (d, 2H, J = 13.4 Hz), 2.83 (d, 2H, J = 13.4 Hz), 1.44 (s, 9H), 1.32 (t, 3H, J = 7.1 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 173.7, 156.9, 154.6, 129.9, 129.4, 128.5, 126.4, 80.7, 79.9, 61.5, 50.6, 46.8, 46.4, 28.1, 14.0. **15c**: Mp 156−157 °C; FTIR (KBr) 1731, 1721 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.67−7.66 (m, 2H), 7.41−7.40 (m, 3H), 5.16 (s, 1H), 4.24 (q, 2H, J = 7.1 Hz), 3.57 (s, 2H), 3.23 (d, 2H, J = 13.6 Hz), 2.57 (m, br, 2H), 1.46 (s, 9H), 1.32 (t, 3H, J = 7.1 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 172.6, 156.9, 155.5, 130.1, 129.3, 128.7, 126.6, 81.4, 80.5, 61.8, 51.6, 47.2, 45.9, 28.3, 14.2. Anal. Calcd for $C_{20}H_{26}N_2O_5$: C, 64.15; H, 6.99; N, 7.48. Found: C, 64.74; H, 6.96; N, 7.48.

Ethyl *cis*-2-Amino-6-aza-7-(4-bromophenyl)-5-oxaspiro-[3.4]-oct-6-en-2-carboxylate (16a) from 14a. Compound **14a** (0.15 g, 0.33 mmol) was treated with 50% TFA/CH_2Cl_2 (10/10 mL) at 0 °C for 30 min and at room temperature for 2 h. The solvent was removed under reduced pressure, and the residue was dissolved in CH_2Cl_2 (10 mL). At −78 °C, 20% Et_3N in CH_2Cl_2 (10 mL) was added dropwise to the solution and stirred for 20 min. The removal of the solvent under reduced pressure followed by silica gel column chromatography (ethyl acetate/hexane = 4/1) afforded the desired compound **16a** (0.11 g, 0.31 mmol, 94%) as a liquid: FTIR (neat) 3394, 3306, 1723 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.42 (s, 4H), 4.17 (q, 2H, J = 7.1 Hz), 3.40 (s, 2H), 2.87 (d, 2H, J = 14.2 Hz), 2.56 (d, 2H, J = 14.2 Hz), 2.04 (s, 2H), 1.27 (t, 3H, J = 7.1 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 175.2, 156.0, 131.7, 128.4, 127.8, 124.1, 80.1, 61.3, 51.2, 50.0, 45.9, 14.1.

Ethyl *cis*-2-Amino-6-aza-7-butyl-5-oxaspiro[3.4]oct-6-en-2-carboxylate (16b) from 13. As with **13** → **14a** and **15a**, valeraldehyde oxime (0.396 g, 3.92 mmol) gave the inseparable mixture (the same rf value) of compounds **14b** and **15b** (**14b**/**15b** ≈ 3/1, 0.97 g, 2.74 mmol, 70%) as a liquid. As with **14a** → **16a**, this inseparable mixture (0.34 g, 0.96 mmol) gave compound **16b** (0.18 g, 0.70 mmol, 75%) after silica gel column chromatography (ethyl acetate:hexane = 1:19) as a liquid: FTIR (neat) 3386, 3310, 1726 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 4.22 (q, 2H, J = 7.1 Hz), 3.08 (s, 2H), 2.86 (d, 2H, J = 13.9 Hz), 2.54 (d, 2H, J = 13.9 Hz), 2.32 (t, 2H, J = 7.5 Hz), 1.94 (s, 2H), 1.53 (m, 2H), 1.39−1.30 (m, 5H), 0.92 (t, 3H, J = 7.2 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 175.2, 159.4, 78.2, 61.1, 51.2, 49.8, 48.3, 28.2, 27.3, 22.1, 14.0, 13.5.

Ethyl *cis*-2-Amino-6-aza-5-oxa-7-phenylspiro[3.4]oct-6-en-2-carboxylate (16c) from 14c. As with **14a** → **16a**, compound **14c** (0.24 g, 0.64 mmol) gave compound **16c** (0.156 g, 0.57 mmol, 89%) as a liquid: FTIR (neat) 3386, 3301, 1723 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.64−7.63 (m, 2H), 7.39−7.38 (m, 3H), 4.25 (q, 2H, J = 7.0 Hz), 3.51 (s, 2H), 2.95 (d, 2H, J = 13.9 Hz), 2.63 (d, 2H, J = 13.9 Hz), 2.04 (s, 2H), 1.35 (t, 3H, J = 7.0 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 175.1, 156.7, 129.7, 129.4, 128.4, 126.3, 79.6, 61.1, 51.1, 49.8, 46.0, 13.9.

Ethyl *cis*-6-Aza-7-(4-bromophenyl)-5-oxa-2[(phenylamino)carbonylamino]spiro[3.4]oct-6-en-2-carboxylate (17a) from 16a. To the solution of compound **16a** (90 mg, 0.25 mmol) in CH_2Cl_2 (20 mL) was added phenyl isocyanate (30 mg, 0.25 mmol) at room temperature. After 30 min, the solvent was removed under reduced pressure, and the residue was recrystallized (methanol, ethyl acetate, and hexane) to give compound **17a** (114 mg, 0.24 mmol, 95%) as a solid: Mp 230−231 °C; FTIR (KBr) 1728, 1638 cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6) δ 8.59 (s, 1H), 7.67−7.58 (m, 4H), 7.43−7.41 (m, 2H), 7.24−7.13 (m, 2H), 6.95−6.90 (m, 1H), 4.17 (q, 2H, J = 7.0 Hz), 3.62 (s, 2H), 3.06 (d, 2H, J = 12.7 Hz), 2.66 (d, 2H, J = 12.7 Hz), 1.24 (t, 3H, J = 7.0 Hz); ^{13}C NMR (75 MHz, DMSO-d_6) δ 173.5, 156.6, 154.6, 140.2, 132.0, 128.8, 128.6, 123.6, 121.6, 118.1, 81.8, 61.0, 50.3, 46.6, 45.7, 14.3.

Ethyl *cis*-6-Aza-7-butyl-5-oxa-2-[(phenylamino)carbonyl-amino]spiro[3.4]oct-6-en-2-carboxylate (17b) from 16b. As with **16a** → **17a**, compound **16b** (120 mg, 0.47 mmol) and phenyl isocyanate (56 mg, 0.47 mmol) gave compound **17b** (168 mg, 0.45 mmol, 96%) as a solid: Mp 144−145 °C; FTIR (KBr) 1720, 1673 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.63 (s, 1H), 7.31−7.27 (m, 2H), 7.17 (t, 2H, J = 7.7 Hz), 6.94 (t, 1H, J = 7.2 Hz), 6.34 (s, 1H), 4.21 (q, 2H, J = 7.1 Hz), 3.16 (s, 2H), 2.98 (d, 2H, J = 13.9 Hz), 2.72 (d, 2H, J = 13.9 Hz), 2.33 (t, 2H, J = 7.7 Hz), 1.53 (m, 2H), 1.34 (m, 2H), 1.35 (t, 3H, J = 7.1 Hz), 0.91 (t, 3H, J = 7.3 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 173.9, 160.5, 155.1, 138.8, 128.7, 122.8, 119.5, 79.8, 61.6, 50.5, 48.8, 47.0, 28.3, 27.4, 22.2, 14.1, 13.6. Anal. Calcd for $C_{20}H_{27}N_3O_4$: C, 64.32; H, 7.28; N, 11.25. Found: C, 64.41; H, 7.22; N, 11.11.

Ethyl *cis*-6-Aza-5-oxa-7-phenyl-2-{[benzylamino]-carbonylamino}spiro[3.4]oct-6-en-2-carboxylate (17c) from 16c. As with **16a** → **17a**, compound **16c** (71 mg, 0.26 mmol) and benzyl isocyanate (35 mg, 0.26 mmol) gave compound **17c** (100 mg, 0.25 mmol, 96%) as a solid: Mp 185 °C; FTIR (KBr) 1727, 1625 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.56−7.54 (m, 2H), 7.42−7.24 (m, 3H), 7.17−7.12 (m, 5H), 6.16 (s, 1H), 5.86 (t, 1H, J = 5.3 Hz), 4.23 (d, 2H, J = 5.3 Hz), 4.16 (q, 2H, J = 7.0 Hz), 3.47 (s, 2H), 2.95 (d, 2H, J = 13.4 Hz), 2.74 (d, 2H, J = 13.4 Hz), 1.22 (t, 3H, J = 7.0 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 174.2, 157.6, 157.4, 139.5, 130.1, 129.2, 128.6, 128.3, 127.1, 126.9, 126.5, 81.2, 61.5, 50.6, 47.1, 46.5, 43.8, 14.1.

Ethyl *cis*-6-Aza-7-(4-bromophenyl)-2-{[(4-chlorophenyl)-amino]carbonylamino}-5-oxaspiro[3.4]oct-6-en-2-carboxylate (17d) from 16a. As with **16a** → **17a**, compound **16a** (92 mg, 0.26 mmol) and *p*-chlorophenyl isocyanate (80 mg, 0.26 mmol) gave compound **17d** (127 mg, 0.25 mmol, 97%) as a solid: Mp 243−244 °C; FTIR (KBr) 1729, 1641 cm^{-1}; ^1H NMR (300 MHz, acetone-d_6) δ 8.55 (s, 1H), 7.62 (s, 4H), 7.48 (d, 2H, J = 7.2 Hz), 7.21 (d, 2H, J = 7.2 Hz), 6.94 (s, 1H), 4.19 (q, 2H, J = 7.1 Hz), 3.64 (s, 2H), 3.07 (d, 2H, J = 13.2 Hz), 2.72 (d, 2H, J = 13.2 Hz), 1.26 (t, 3H, J = 7.1 Hz); ^{13}C NMR (75 MHz, acetone-d_6, DMSO-d_6) δ 174.8, 157.5, 155.8, 140.8, 133.1, 130.7, 130.4, 129.7, 126.8, 124.7, 120.6, 83.1, 62.2, 51.8, 48.0, 47.1, 15.0.

Ethyl *cis*-6-Aza-7-butyl-2-{[(3-chlorophenyl)amino]-carbonylamino}-5-oxaspiro[3.4]oct-6-en-2-carboxylate (17e) from 16b. As with **16a** → **17a**, compound **16b** (120 mg, 0.47 mmol) and 3-chlorophenyl isocyanate (72 mg, 0.47 mmol) gave compound **17e** (184 mg, 0.45 mmol, 96%) as a solid: Mp 127 °C; FTIR (KBr) 1726, 1681 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.75 (s, 1H), 7.39 (s, 1H), 7.21 (m, 1H), 7.10 (t, 1H, J = 8.0 Hz), 6.91 (m, 1H), 6.37 (s, 1H), 4.25 (q, 2H, J = 7.1 Hz), 3.21 (s, 2H), 3.05 (d, 2H, J = 14.1 Hz), 2.75 (d, 2H, J = 14.1 Hz), 2.37 (t, 2H, J = 7.8 Hz), 1.53 (m, 2H), 1.37 (m, 2H), 1.28 (t, 3H, 7.1 Hz), 0.93 (t, 3H, 7.3 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 173.8, 161.0, 154.5, 140.2, 134.4, 129.7, 122.6, 119.1, 117.1, 80.0, 61.8, 50.6, 48.9, 47.0, 28.4, 27.5, 22.3, 14.1, 13.6.

Ethyl *cis*-6-Aza-2-[(butylamino)carbonylamino]-5-oxa-7-phenylspiro[3.4]oct-6-en-2-carboxylate (17f) from 16c. As with **16a** → **17a**, compound **16c** (110 mg, 0.40 mmol) and butyl isocyanate (39 mg, 0.40 mmol) gave compound **17f** (146 mg, 0.39 mmol, 98%) as a solid: Mp 171−172 °C; FTIR (KBr) 1734, 1624 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.65−7.62 (m, 2H), 7.40−7.38 (m, 3H), 5.90 (s, 1H), 5.31 (s, br, 1H), 4.25 (q, 2H, J = 7.0 Hz), 3.58 (s, 2H), 3.14−3.11 (m, 2H), 3.06 (d, 2H, 14.0 Hz), 2.82 (d, 2H, 14.0 Hz), 1.46−1.41 (m, 2H), 1.38−1.27 (m, 5H), 0.87 (t, 3H, J = 7.3 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 174.3, 157.6, 157.4, 130.2, 129.3, 128.7, 126.6, 81.3, 61.4, 50.7, 47.2, 46.6, 39.9, 32.3, 19.9, 14.1, 13.7. Anal. Calcd for $C_{20}H_{27}N_3O_4$: C, 64.32; H, 7.28; N, 11.25. Found: C, 64.40; H, 7.19; N, 11.16.

***cis*-2,4,9-Triaza-10-(4-bromophenyl)-8-oxa-2-phenyldispiro[4.1.4.1]dodec-9-en-1,3-dione (18a) from 17a**. To a solution of compound **17a** (100 mg, 0.21 mmol) and EtOH (10 mL) was added sodium (6 mg, 0.25mmol), and the reaction mixture was stirred at room temperature for 2 h. EtOH was removed under reduced pressure. Ethyl acetate and water were added to the residue. Ethyl acetate layer was dried over anhydrous $MgSO_4$, concentrated, and recrystallized to give the compound **18a** (81 mg, 0.19 mmol, 94%) as a solid: Mp 250−251 °C; FTIR (KBr) 1767, 1717 cm^{-1}; ^1H NMR (300 MHz, MeOH d-4, acetone-d_6) δ 7.59 (s. 4H), 7.43−7.34 (m, 6H), 3.75 (s, 2H), 3.03 (d, 2H, J = 13.2 Hz), 2.92 (d, 2H, J = 13.2 Hz); ^{13}C NMR (75 MHz, DMSO-d_6) δ 175.8, 157.0, 154.5, 132.2, 132.0, 128.8, 128.7, 128.6, 127.9, 126.8, 123.6, 79.3, 52.9, 46.7, 45.0. Anal. Calcd for $C_{20}H_{16}BrN_2O_3$: C, 56.35; H, 3.78; N, 9.85. Found: C, 56.11; H, 3.72; N, 9.71.

***cis*-2,4,9-Triaza-10-butyl-8-oxa-2-phenyldispiro-[4.1.4.1]-dodec-9-en-1,3-dione (18b) from 17b**. As with **17a** → **18a**, compound **17b** (100 mg, 0.26 mmol) and Na (7 mg, 0.32 mmol) gave compound **18b** (80 mg, 0.24 mmol, 92%) as a solid: Mp 162 °C; FTIR (KBr) 1804, 1720 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.48−7.35 (m, 5H), 7.30 (s, 1H), 3.34 (s, 2H), 3.05 (d, 2H, J = 12.2 Hz), 2.90 (d, 2H, J = 12.2 Hz), 2.35 (t, 2H, J = 7.4 Hz), 1.55 (m, 2H), 1.35 (m, 2H), 0.92 (t, 3H, J = 7.2 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 176.0, 160.6, 154.8, 131.5, 129.0, 128.0, 125.9, 77.7, 53.4, 48.1, 46.9, 28.2, 27.4, 22.2, 13.6. Anal. Calcd for $C_{18}H_{21}N_3O_3$: C, 66.03; H, 6.46; N, 12.83. Found: C, 66.24; H, 6.46; N, 12.61.

***cis*-2,4,9-Triaza-8-oxa-10-phenyl-2-benzyldispiro-[4.1.4.1]-dodec-9-en-1,3-dione (18c) from 17c**. As with **17a** → **18a**, compound **17c** (100 mg, 0.24 mmol) and Na (6.7 mg, 0.29 mmol) gave compound **18c** (84 mg, 0.23 mmol, 95%) as a solid: Mp 203−204 °C; FTIR (KBr) 1794, 1712 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.70−7.67 (m, 2H), 7.41−7.39 (m, 5H), 7.35−7.25 (m, 4H), 4.67 (s, 2H), 3.76 (s, 2H), 3.09 (d, 2H, J = 14.0 Hz), 2.92 (d, 2H, J = 14.0 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 176.7, 157.7, 155.8, 135.9, 130.4, 129.0, 128.8, 128.7, 128.4, 127.9, 126.7, 79.1, 53.6, 46.8, 45.8, 42.2. Anal. Calcd for $C_{21}H_{19}N_3O_3$: C, 69.79; H, 5.29; N, 11.62. Found: C, 70.16; H, 5.46; N, 11.37.

***cis*-2,4,9-Triaza-10-(4-bromophenyl)-2-(4-chlorophenyl)-8-oxadispiro[4.1.4.1]dodec-9-en-1,3-dione (18d) from 17d**. As with **17a** → **18a**, compound **17d** (100 mg, 0.19 mmol) and sodium (6 mg, 0.23 mmol) gave compound **18d** (82 mg, 0.18 mmol, 93%) as a solid: Mp 257−258 °C; FTIR (KBr) 1774, 1719 cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6) δ 7.66−7.41 (m, 9H), 3.73 (s, 2H), 3.01 (d, 2H, J = 13.8 Hz), 2.84 (d, 2H, J = 13.8 Hz); ^{13}C NMR (75 MHz, DMSO-d_6) δ 175.7, 157.0, 154.3, 132.3, 132.1, 131.2, 128.9, 128.7, 128.5, 123.7, 79.3, 53.0, 46.8, 45.1. Anal. Calcd for $C_{20}H_{15}BrClN_2O_3$: C, 52.14; H, 3.28; N, 9.12. Found: C, 52.07; H, 3.31; N, 8.99.

***cis*-2,4,9-Triaza-10-butyl-2-(3-chlorophenyl)-8-oxadispiro[4.1.4.1]dodec-9-ene-1,3-dione (18e) from 17e**. As with **17a** → **18a**, compound **17e** (100 mg, 0.24 mmol) and Na (6.7 mg, 0.29 mmol) gave compound **18e** (80 mg, 0.22 mmol, 91%) as a solid: Mp 143 °C; FTIR (KBr) 1778, 1726 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.48 (s, 1H), 7.40−7.33 (m, 3H), 7.07 (s, 1H), 3.34 (s, 2H), 3.07 (d, 2H, J = 12.4 Hz), 2.94 (d, 2H, J = 12.4 Hz), 2.36 (t, 2H, J = 7.4 Hz), 1.57 (m, 2H), 1.37 (m, 2H), 0.93 (t, 3H, 7.2 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 175.5, 160.6, 154.2, 134.6, 132.6, 129.9, 128.2, 126.0, 123.9, 77.9, 53.6, 48.1, 47.0, 28.3, 27.4, 22.3, 13.6. Anal. Calcd for $C_{18}H_{20}ClN_3O_3$: C, 59.75; H, 5.57; N, 11.61. Found: C, 59.88; H, 5.61; N, 11.47.

***cis*-2,4,9-Triaza-2-butyl-8-oxa-10-phenyldispiro[4.1.4.1]-dodec-9-ene-1,3-dione (18f) from 17f**. As with **17a** → **18a**, compound **17f** (100 mg, 0.27 mmol) and Na (7.3 mg, 0.32 mmol) gave compound **18f** (79 mg, 0.24 mmol, 90%) as a solid: Mp 169−170 °C; FTIR (KBr) 1777, 1710 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.72−7.69 (m, 2H), 7.43−7.41 (m, 3H), 7.14 (s, 1H), 3.78 (s, 2H), 3.52 (t, 2H, J = 7.2 Hz), 3.12 (d, 2H, J = 14.0 Hz), 2.94 (d, 2H, J = 14.0 Hz), 1.63 (m, 2H), 1.35 (m, 2H), 0.95 (t, 3H, J = 7.3 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 177.1, 157.7, 156.2, 130.4, 129.0, 128.8, 126.7, 79.2, 53.4, 46.9, 45.8, 38.5, 30.1, 19.9, 13.6. Anal. Calcd for $C_{18}H_{21}N_3O_3$: C, 66.03; H, 6.46; N, 12.83. Found: C, 65.91; H, 6.50; N, 12.69.

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Supporting Information Available: ^1H NMR, ^{13}C NMR, and FTIR spectra for compounds **5**, **14c**, **16a**, **16b**, **16c**, **17a**, **17c**, **17d**, and **17e** as well as X-ray crystallographic data for **18d**. This material is available free of charge via the Internet at http://pubs.acs.org.

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