Diastereoselective Solid-Phase Synthesis of Novel Hydantoin- and Isoxazoline-Containing Heterocycles

Kyung-Ho Park, Marilyn M. Olmstead, and Mark J. Kurth*

Department of Chemistry, University of California, Davis, California 95616

Received April 17, 1998

Exploiting 1,3-dipolar cycloaddition and carbanilide cyclization transformations, we have prepared novel spirocyclic isoxazoloimidazolidinedione heterocycles of generalized structures **II** and **III** on solid phase starting from Merrifield resin. Cyclopentanoid isoxazoloimidazolidinedione **II** was obtained with complete diastereoselectivity, and cyclopropanoid isoxazoloimidazolidinedione **III** was obtained as an ≈2:1 mixture of diastereomers.

The hydantoin moiety has important medicinal[1] as well as agrochemical[2,3] activities; a large number of hydantions have been synthesized for various biological applications,[4] and the isoxazoline heterocycle has been used extensively to modulate various other biologically active motifs.[5] In preliminary solution studies, we developed a novel route[6] to cyclopentanoids adjoined to hydantoin[7] and isoxazoline heterocycles. The key control element in this approach to these spiro[cyclopenta[*d*]isoxazole-4′,5-imidazoline] heterocycles was the utilization of an intermolecular hydrogen-bond to control alkene face selectivity in the nitrile oxide cycloaddition step.

We are interested in developing synthetic strategies[8] which can be applied to combinatorial chemistry, and our main objective in the work reported here is the development of a stereoselective synthetic strategy for the construction of polyfunctional heterocycles on solid-phase. With reliable solid-phase chemistry in hand, library preparation would set the stage for a thorough exploration of the biological properties of the isoxazoloimidazolidinedione heterocycles targeted here.

A basic tenant of combinatorial chemistry is to design analogue libraries using chemistry which allows for the incorporation of two or more elements of diversification. As illustrated in isoxazoloimidazolidinedione target structure **I**, a key synthetic questions in this study addressed the issues of developing a solid-phase synthetic protocol which would allow for peripheral diversification at "X" and "Y" and core diversification at "Z". Our initial solid-phase target was **II**, where "Z" is a cyclopentyl moiety, and from the outset, several important synthetic questions were apparent in the planning of this solid-phase synthetic study: (i) Would it be possible to α,α-dialkylate polymer-bound glycinate **1** with *cis*-1,4-dichloro-2-butene to give the corresponding cyclopentenyl amino acid? (ii) Would the resulting polymer-bound cyclopentenyl moiety participate in a nitrile oxide 1,3-dipolar cycloaddition reaction, or would we only see nitrile oxide dimerization? (iii) As a particularly key question, would we see intermolecular hydrogen-bond control of alkene face selectivity in the solid-phase cycloaddition step leading to the diastereoselective preparation of **II**? (iv) Would an ester substrate−polymer tether allow for both cyclative release of substrate from the resin as well as traceless delivery of cyclopentanoid isoxazoloimidazolidinedione **II**? Once data addressing these synthetic questions were in hand, the question of incorporating "X", "Y", and "Z" diversification could be addressed. Clearly, the main issue here centers on the question of whether a solid-phase synthetic strategy can be developed to accommodate core diversification (i.e., at "Z" in **I**). As detailed in Scheme 1, we planned to address this question of "Z" diversity by targeting cyclopropanoid isoxazoloimidazolidinediones of generalized structure **III**.

All of our attempts at solid-phase α,α-dialkylation of **1** were unsuccessful because of ester hydrolysis with concomitant removal of product from the resin. For example, treating **1** with either LDA/THF or potassium *tert*-butoxide/THF resulted in substantial ester hydrolysis. In contrast, the solution-phase alkylation of imino ester **7** with *cis*-1,4-dichloro-2-butene was highly effective (80% yield of **8**) and subsequent imine hydrolysis (**8** → **9**), amine protection (**9** → **10**), and ester saponification delivered carboxylic acid **11** (Scheme 2). *O*-Alkylation of the carboxylate salt of **11** with Merrifield resin in the presence of 18-crown-6[9] readily produced **2** (FTIR 1711

(1) (a) Ware, E. *Chem. Rev.* **1950**, *46*, 403. (b) Spinks, A.; Waring, W. S. *Prog. Med. Chem.* **1963**, *3*, 313. (c) Karolakwojciechowska, J.; Kwiatkowski, W.; Kieckonono, K. *Pharmazie* **1995**, *50*, 114. (d) Brouillette, w. J.; Jestkov, V. P.; Brown, M. L.; Akhtar, M. S. *J. Med. Chem.* **1994**, *37*, 3289. (e) Brouillette, W. J.; Brown, G. B.; Deloreg, T. M.; Liang, G. *J. Pharm. Sci.* **1990**, *79*, 871.

(2) Mappes, C. J.; Pommer, E. H.; Rentzea, C.; Zeeh, B. U.S. Patent 4, 198, 423, 1980.

(3) Ohta, H.; Jikihara, T.; Wakabayashi, Ko.; Fujita, T. *Pestic. Biochem. Physiol.* **1980**, *14*, 153.

(4) Avendano Lopez, C.; Gonzalez Trigo, G. *Adv. Heterocycl. Chem.* **1985**, *38*, 177.

(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.; Yooder, 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.; Tranielo, F.; Nastruzzi, C.; Feriotto, G.; Gambari, R. *Top. Mol. Org. Eng.* **1991**, *8 (Chem. Prop. Biomol. Syst.)*, 119.

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

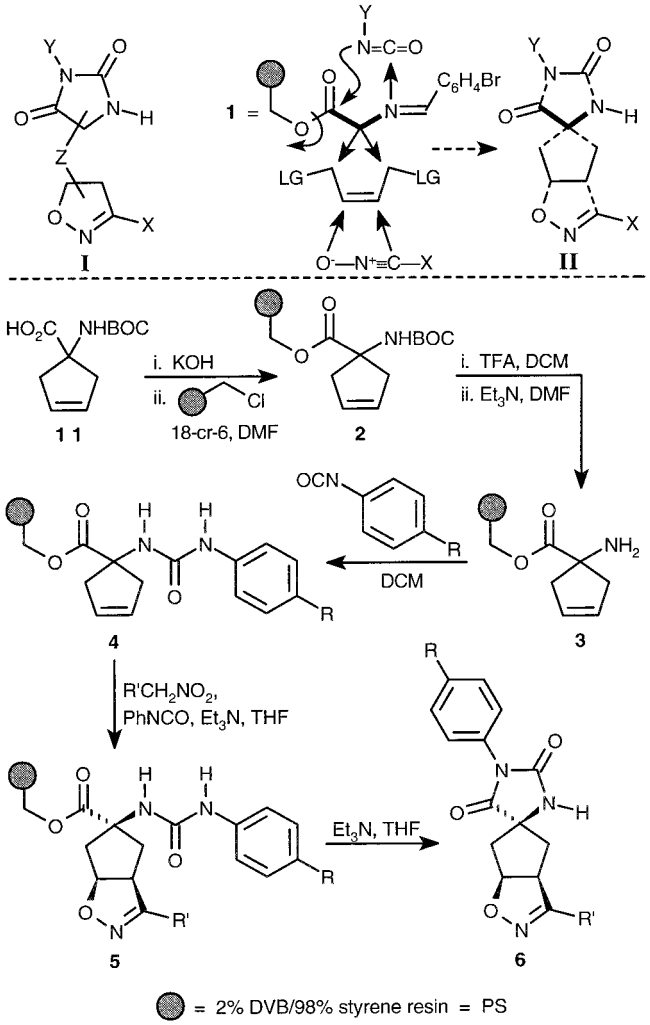
(7) For solid-phase routes to hydantoins, see: (a) DeWitt, S. H.; Kiely, J. S.; Stankovic, C. J.; Schroeder, M. C.; Cody, D. R.; Pavia, M. R. *Proc. Natl. Acad. Sci. U.S.A.* **1993,** *90*, 6909. (b) Dressman, B. A.; Spangle, L. A.; Kaldor, S. W. *Tetrahedron Lett.* **1996**, *37*, 937.

(8) For recent examples, see: (a) Gong, Y.-D.; Najdi, S.; Olmstead, M. M.; Kurth, M. J. *J. Org. Chem.* **1998**, *63*, 3081. (b) Lorsbach, B. A.; Bagdanoff, J. T.; Miller, R. B.; Kurth, M. J. *J. Org. Chem.* **1998**, *63*, 2244. (c) Halm, C.; Evarts, J.; Kurth, M. J. *Tetrahedron Lett.* **1997**, *38*, 7709. (d) Kantorowski, E. J.; Kurth, M. J. *J. Org. Chem.* **1997**, *62*, 6797.

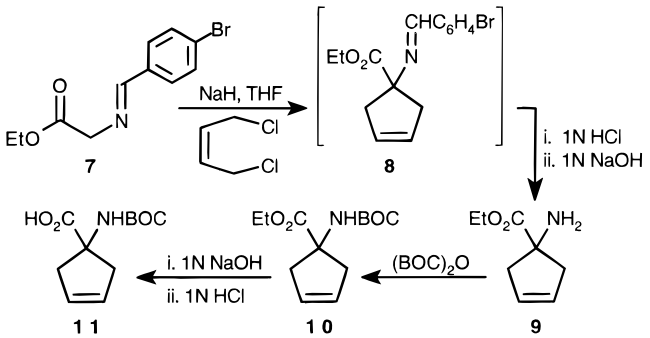
(9) Roeske, R. W.; Gesellchen, P. D. *Tetrahedron Lett.* **1976**, *38*, 3369.

S0022-3263(98)00716-6 CCC: $15.00
Published on Web 08/25/1998

Scheme 1. Cyclopentanoid Isoxazoloimidazolidinediones 6: Solid-Phase Reactions



Scheme 2. Synthesis of Cyclopentenyl Amino Acid



cm^{-1}). The BOC group in amino ester **2** was then cleaved by 50% TFA in CH_2Cl_2 and the resulting ammonium salt was neutralized by a triethylamine/CH_2Cl_2 wash to give amino ester **3**. At this point, various isocyanates were reacted with amino ester **3** to give urea **4** (**4a**: R = H, FTIR 1736, 1700, 1654 cm^{-1}). A hydrogen bond-directed intermolecular 1,3-dipolar cycloaddition reaction (i.e., urea NH···O—N≡CR)[6] of the alkene in **4** with a Mukaiyama-generated nitrile oxide[10] was carried out to give intermediate **5**. This transformation (**4** → **5**) proceeds with complete face diastereoselective as evidenced by the base-mediated cyclative release of only **6**; no trace of the other diastereomer was detected. Six analogues of **6** were prepared in this way, and these results are summarized in Table 1.

Table 1. Cyclopentanoid Isoxazoloimidazolidinedione 6 Prepared by SPOS

compd	−R	−R′	yield (%)[a]
6a	−Cl	$-CH_3$	21
6b	−F	$-CH_3$	27
6c	−H	$-CH_2CH_3$	30
6d	−H	$-CH_2CH_2CH_3$	21
6e	−Cl	$-CH_2CH_2CH_3$	25
6f	−F	$-CH_2CH_2CH_3$	26

[a] Overall yield from PS−CH_2Cl.

This solid-phase synthesis of **II** from **11** accommodates peripheral diversification at "X" and "Y" from simple nitroalkane and isocyanate reagents, respectively. We next turned to the question of incorporating core diversification at "Z" (see **I**; Scheme 1) and decided to explore routes to cyclopropanoids of general structure **III**.

Dialkylation of **7** with *cis*-1,4-dichloro-2-butene delivers **8** and what we believed to be a trace of the cyclopropanoid analogue **12**. Thus, we were delighted to find that substituting *cis*-1,4-bis(methylsulfonyl)oxy)-2-butene[11] for *cis*-1,4-dichloro-2-butene resulted in formation of cyclopropyl imino ester **12** (Scheme 3) as the major α,α-dialkylation product.[12] This completely diastereoselective alkylation (i.e., there was no evidence for the cyclopropyl imino ester with *trans* carboethoxy and vinyl moieties) did produce cyclopentenyl imino ester **8** as a minor side product. However, the R_f values for these two structurally isomeric products were same, so hydrolysis of those intermediate imines gave two different values of compound **9** ($R_f \approx 0.1$ in 50% ethyl acetate in hexane) and compound **13** ($R_f \approx 0.3$), which were easily separated by flash chromatography (overall yield from **7**; 18%:39% = **9**:**13**).

Imine hydrolysis to **13** followed by addition of phenyl isocyanate delivered urea **14**. Unlike cyclopentenoid **4** where the urea moiety is ideally positioned for diastereofacial selective delivery of the nitrile oxide to the alkene, the *trans* configuration of the urea and vinyl moieties precludes H-bonding delivery of the nitrile oxide. Consequently, isoxazoline formation from **14** proceeds with only minimal selectivity giving mixtures of C1′α- and C1′β-isomers **15** and **16**, respectively (see Table 2). This solution-phase route to cyclopropanoid isoxazoloimidazolidinedione **III** was completed by base-mediated cyclization of **15** to **17** and **16** to **18**. Single-crystal X-ray chrystallographic analysis of **17a** (R′ = $CH_2CH_2CH_3$; see Figure 1) verified the relative cyclopropane stereochemistries of **12**−**18** and established the C1′ stereochemistries of **15**−**18**.

Our solid-phase approach to cyclopropanoid isoxazoloimidazolidinediones **III** began with amino ester **13** which was BOC-protected (→**19**), saponified (→**20**), and coupled with Merrifield resin to give resin **21** (Scheme 4). Deprotection to amino ester **22** delivered the solid-phase analogue of **13** which, upon isocyanate treatment, gave urea **23**. 1,3-Dipolar cycloaddition with a Mukaiyama-

(10) For reviews of nitrile oxide−isoxazoline methodology, see: (a) Curran, D. P. *Adv. Cycladdit.* **1988**, *1*, 129. (b) Torssel, K. B. G. *Nitrile Oxides, Nitrones and Nitronates in Organic Synthesis*; VCH Publishers: Weinheim, Germany, 1988.

(11) Ding, Z.; Tufariello, J. J. *Synth. Commun.* **1990**, *20*, 227.

(12) Nantz, M. H.; Radisson, X.; Fuchs, P. L. *Synth. Commun.* **1987**, *17*, 55.

Scheme 3. Cyclopropanoid Isoxazoloimidazolidinediones 17/18; Solution-Phase Reactions

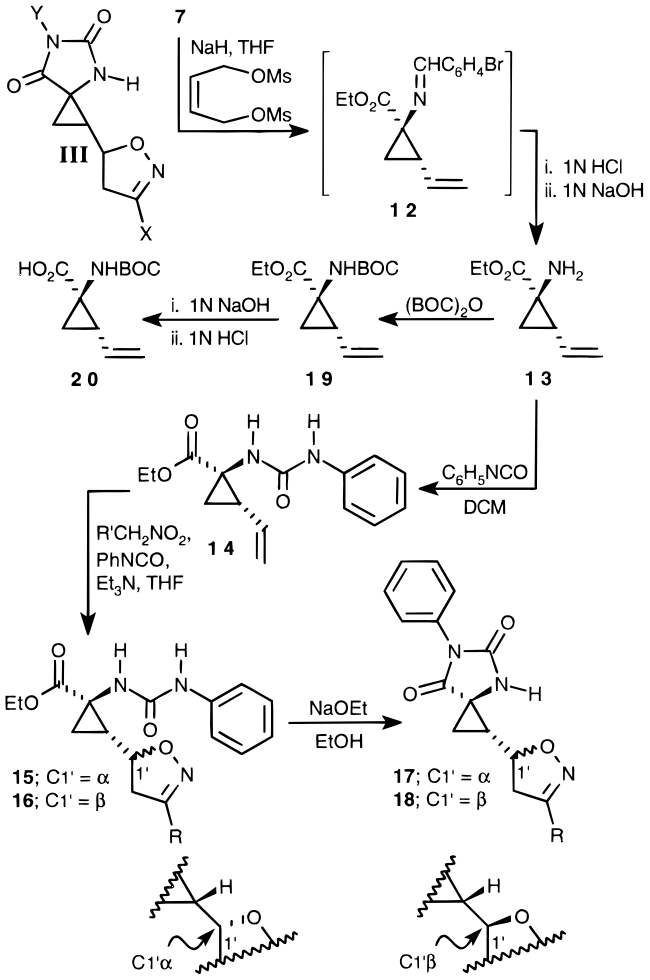


Table 2. Cyclopropanoid Isoxazoloimidazolidinedione Prepared by Solution-Phase Reactions

−R	isoxazoline	**15** or **16** yield (%)	isoxazoloimid azolidinedione	**17** or **18** yield (%)
-$CH_2CH_2CH_3$	**15a** (α1′)	12	**17a** (α1′)	82
-$CH_2CH_2CH_3$	**16a** (β1′)	61	**18a** (β1′)	85
-CH_3	**15b** (α1′)	9	**17b** (α1′)	78
-CH_3	**16b** (β1′)	65	**18b** (β1′)	75
-C_6H_5	**15c** (α1′)	33	**17c** (α1′)	81
-C_6H_5	**16c** (β1′)	51	**18c** (β1′)	75

generated nitrile oxide gave an α/β-mixture of C1′ epimeric isoxazolines as evidenced by obtaining a mixture of **17** and **18** upon cyclative release from the resin. However, in the case of R = Cl, the C1′-epimer of **18** (i.e., **17**) readily decomposed[13] and could not be isolated in a substantial amount. The overall yield of isoxazoloimidazolidinediones **17**/**18** was ≈19% (see Table 3) from Merrifield resin which translates to an ≈76% yield per transformation in this six step solid-phase procedure.

In summary, we have developed synthetic strategies for the solid-phase preparation of novel heterocycles of generalized structures **II** and **III**. The solid-phase methods developed provide fast, reliable access to an array of

(13) Crude reaction mixtures of **17**/**18** (R = Cl) rapidly turn deep brown as a result of decomposition of **17**. In contrast, isolated **18** is stable when stored dark and in the cold. This decomposition explains the lower yield for R = Cl (< yield for R = H; see Table 3).

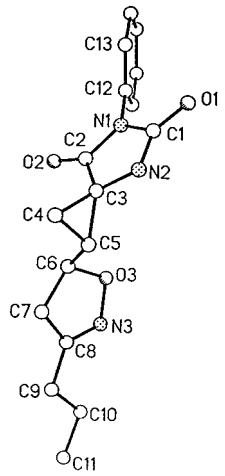


Figure 1. Computer-generated single-crystal X-ray structure of **18a**.

Scheme 4. Cyclopropanoid Isoxazoloimidazolidinediones 17/18; Solid-Phase Reactions

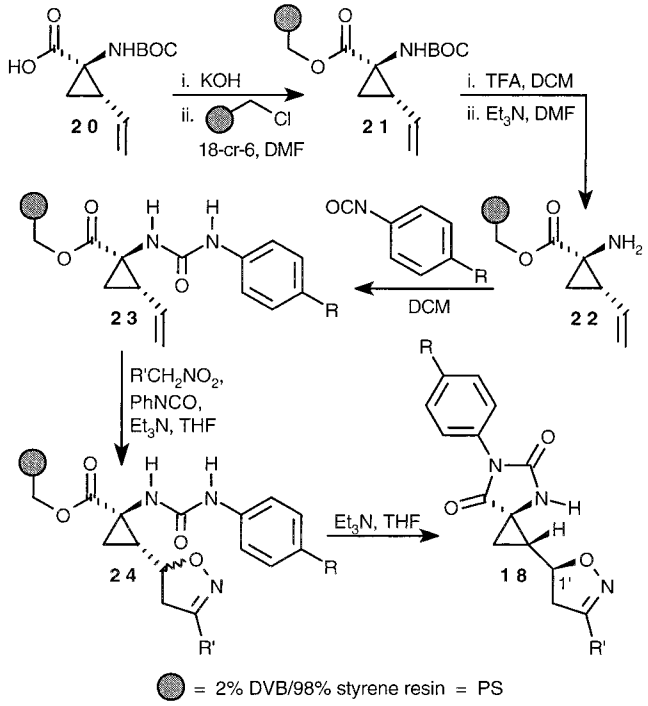


Table 3. Cyclopropanoid Isoxazoloimidazolidinedione Prepared by SPOS

compd	−R	−R′	yield (%)[a]	≈C1′α/β ratio[b]
17a/**18a**	−H	−$CH_2CH_2CH_3$	22	1/2.6
18d	−Cl	−CH_2CH_3	18	*b*
18e	−Cl	−$CH_2CH_2CH_3$	15	*b*
18f	−Cl	−C_6H_5	19	*b*

[a] Overall yield from PS−CH_2Cl. [b] The C1′ epimer of **18** (i.e., **17**) was negligible.[13]

structurally interesting isoxazoloimidazolidinediones with a number of advantages over the corresponding solution-phase chemistry. These include easy reaction workup manipulations (i.e., filtration and solvent washing), ready access to milligram quantities of isoxazoloimidazolidinediones with labor efficient procedures, overall yields comparable to our one-pot solution-phase protocol[6] but with improved product purity and much simpler product

isolation/purification, and the practical ability to use excess reagents to drive solid-phase chemical reactions to completion. Our cyclative release strategy (i.e., **5** → **6** and **24** → **18**) affords another important synthetic advantage to this solid-phase chemistry in that products with ≈95% purity are obtained from the resin after the five solid-phase steps required for conversion of **11** to **6** or **20** to **18**. Moreover, we have shown that **6** is obtained with complete diastereoselectivity because the urea moiety in solid-phase **4** is a powerful control element which utilizes an intermolecular hydrogen-bond to control alkene face selectivity in the nitrile oxide cycloaddition step. The work reported here secures the first stage in a program aimed at the solid-phase diversification of hydantoin- and isoxazoline-based pharmocophores. By employment of this general and expedient solid-phase synthetic methodology, construction of a large combinatorial library of isoxazoloimidazolidinedione derivatives is currently in progress. The solid-phase synthesis of other classes of biologically important organic compounds is also under investigation and will be reported in due course.

Experimental Section

Resin 2. Boc acid (**11**) (1 g, 4.40 mmol) was treated with KOH (1.0 equiv) in EtOH/H_2O (10 mL/5 mL, 2:1) at ambient temperature for 1 h. After removal of the solvent, the potassium salt of **11** was dried under vacuum to give 1.15 g (4.33 mmol) of a solid which was dissolved in DMF (40 mL). Merrifield resin (2.16 g, 2.16 mmol; loading = 1 mmol of Cl/g) and 18-crown-6 (1.136 g, 4.3 mmol) were added to this DMF solution, and the reaction mixture was stirred with a magnetic stir bar at 70 °C for 50 h. The resin was washed with DMF (2 × 30 mL), THF (30 mL), THF/H_2O (2 × 30 mL), THF (30 mL), and finally ether (30 mL). The resin was dried under vacuum to give 2.4 g of the desired resin. FTIR (KBr): 1711 cm^{-1}.

Resin 3. Resin **2** (1.8 g) was treated with 50% TFA/CH_2Cl_2 (30 mL) using a magnetic stirrer at ambient temperature for 1 h. The resin was washed with CH_2Cl_2 (30 mL), dioxane/CH_2Cl_2 (1:1, 2 × 30 mL), dioxane (30 mL), and CH_2Cl_2 (2 × 30 mL), followed by treatment with 10% Et_3N in CH_2Cl_2 (30 mL) for 1 h. The resin was washed with DMF (2 × 30 mL), CH_2Cl_2 (2 × 30 mL) and ether (30 mL) and dried under vacuum to give the desired resin (1.6 g). FTIR (KBr): 3459, 3380, 1726 cm^{-1}.

Resin 4 (R = H). Resin **3** (300 mg) was treated with 0.5 M phenyl isocyanate using a magnetic stirrer in CH_2Cl_2 (30 mL) for 10 h at ambient temperature. The resin was washed with DMF (2 × 30 mL), THF (2 × 30 mL), CH_2Cl_2 (30 mL), and ether (30 mL). Drying in vacuo gave the desired resin (0.31 g). FTIR (KBr): 1736, 1700, 1654 cm^{-1}.

Resin 4 (R = Cl). Following the same procedure used for making resin **4** (R = H) but using 0.5 M 4-chlorophenyl isocyanate gave the desired resin (320 mg). FTIR (KBr): 1737, 1702 cm^{-1}.

Resin 4 (R = F). Following the same procedure used for making resin **4** (R = H) but using 0.5 M 4-fluorophenyl isocyanate gave the desired resin (310 mg). FTIR (KBr): 1734, 1654 cm^{-1}.

Resin 5 (R = Cl, R′ = Me). To a mixture of resin **4** (R = Cl, 300 mg), 0.5 M nitroethane, and 0.5 M of phenyl isocyanate in THF (20 mL) was added Et_3N (10 μL). The reaction mixture was stirred with a magnetic stir bar at 60 °C overnight and then washed with DMF (2 × 30 mL), THF (2 × 30 mL), CH_2Cl_2 (30 mL), and ether (30 mL). Drying in vacuo gave the desired resin (310 mg). FTIR (KBr): 1735, 1700 cm^{-1}.

Resin 5 (R = F, R′ = Me). Following the same procedure used for making resin **5** (R = Cl, R′ = Me) gave the desired resin (290 mg). FTIR (KBr): 1734, 1699 cm^{-1}.

Resin 5 (R = H, R′ = Et). Following the same procedure used for making resin **5** (R = Cl, R′ = Me) gave the desired resin (300 mg). FTIR (KBr): 1737, 1697 cm^{-1}.

Resin 5 (R = H, R′ = Propyl). Following the same procedure used for making resin **5** (R = Cl, R′ = Me) gave the desired resin (305 mg). FTIR (KBr): 1738, 1698 cm^{-1}.

Resin 5 (R = Cl, R′ = Propyl). Following the same procedure used for making resin **5** (R = Cl, R′ = Me) gave the desired resin (303 mg). FTIR (KBr): 1735, 1700 cm^{-1}.

Resin 5 (R = F, R′ = Propyl). Following the same procedure used for making resin **5** (R = Cl, R′ = Me) gave the desired resin (280 mg). FTIR (KBr): 1734, 1699 cm^{-1}.

(3a*R,5*S**,6a*S**)-Spiro[1′-(*p*-chlorophenyl)-3-methyl-4,5,6,-6a-tetrahydro-3a*H*-cyclopenta[*d*]isoxazole-4′,5-imidazolidine-2′,5′-dione] (6a) from Resin 5 (R = Cl, R′ = Me).** Using the same procedures described for the synthesis of resins **1**−**4** from Merrifield resin (300 mg, 1 mmol of Cl/g) delivered resin **5** (340 mg; R = Cl, R′ = Me). This resin was treated with Et_3N (1 mL) using a magnetic stirrer in THF at 60 °C overnight. After filtration and washing of the resin with THF (2 × 30 mL), the solvent was removed under reduced pressure and the residue was purified by short silica gel column to give **6a** (20 mg, 0.063 mmol, overall 20% yield) as a solid: Mp >260 °C; FTIR (KBr) 3104, 2931, 1777, 1709 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.45−7.38 (m, 4H), 5.99 (s, 1H), 5.27 (dd, 1H, J = 8.3, 4.4 Hz), 3.76 (t, 1H, J = 9.17 Hz), 2.63−2.45 (m, 3H), 2.18 (d, 1H, J = 14.14 Hz), 2.07 (s, 3H); ^{13}C NMR (300 MHz, DMSO-d_6) δ 175.3, 157.1, 154.0, 132.1, 130.8, 128.6, 128.3, 83.8, 67.3, 54.5, 11.3. Anal. Calcd for $C_{15}H_{14}ClN_3O_3$: C, 56.34; H, 4.41; N, 13.14. Found: C, 56.40; H, 4.37; N, 13.09.

(3a*R,5*S**,6a*S**)-Spiro[1′-(*p*-fluorophenyl)-3-methyl-4,5,6,6a-tetrahydro-3a*H*-cyclopenta[*d*]isoxazole-4′,5-imidazolidine-2′,5′-dione] (6b) from Resin 5 (R = F, R′ = Me).** Using the same procedures described for the synthesis of **6a**, resin **5** (R = F, R′ = Me) gave **6b** (35 mg, 0.083 mmol, overall 27% yield) as a solid: Mp 248−249 °C; FTIR (KBr) 3208, 2962, 1774, 1714 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.43−7.38 (m, 2H), 7.18−7.12 (m, 2H), 5.99 (s, 1H), 5.27 (dd, 1H, J = 7.47, 4.54 Hz), 3.76 (t, 1H, J = 9.23 Hz), 2.64−2.45 (m, 3H), 2.18 (d, 1H, J = 14.11), 2.07 (s, 3H); ^{13}C NMR (300 MHz, $CDCl_3$) δ 173.9, 162.0 (d, J = 249 Hz), 158.6, 154.6, 127.8 (d, J = 8.6 Hz), 127.4, 116.1 (d, J = 22.86 Hz), 86.0, 67.8, 55.2, 45.1, 41.2, 12.1. Anal. Calcd for $C_{15}H_{14}FN_3O_3$: C, 59.40; H, 4.65; N, 13.85. Found: C, 59.50; H, 4.67; N, 13.77.

(3a*R,5*S**,6a*S**)-Spiro[3-ethyl-1′-phenyl-4,5,6,6a-tetrahydro-3a*H*-cyclopenta-[*d*]isoxazole-4′,5-imidazolidine-2′,5′-dione] (6c) from Resin 5 (R = H, R′ = Et).** Using the same procedures described for the synthesis of **6a**, resin **5** (R = H, R′ = Et) gave **6c** (27 mg, 0.091 mmol, overall 30% yield) as a solid: Mp 196 °C; FTIR (KBr) 3225, 2971, 1776, 1714 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.50−7.35 (m, 5H), 6.02 (s, 1H), 5.26 (dd, 1H, J = 8.28, 4.37 Hz), 3.79 (t, 1H, J = 8.98 Hz), 2.64−2.46 (m, 4H), 2.39−2.27 (m, 1H), 2.17 (d, 1H, J = 14.12 Hz), 1.24 (t, 3H, J = 7.5 Hz); ^{13}C NMR (300 MHz, $CDCl_3$) δ 173.9, 163.2, 154.7, 131.4, 129.1, 128.3, 126.0, 86.1, 67.8, 53.8, 44.9, 41.4, 20.4, 10.78. Anal. Calcd for $C_{16}H_{17}N_3O_3$: C, 64.20; H, 5.72; N, 14.03. Found: C, 64.06; H, 5.71; N, 13.95.

(3a*R,5*S**,6a*S**)-Spiro[1′-phenyl-3-propyl-4,5,6,6a-tetrahydro-3a*H*-cyclopenta[*d*]isoxazole-4′,5-imidazolidine-2′,5′-dione] (6d) from Resin 5 (R = H, R′ = Propyl).** Using the same procedures described for the synthesis of **6a**, resin **5** (R = H, R′ = propyl) gave **6d**[6] (20 mg, 0.064 mmol, overall 21% yield) as a solid.

(3a*R,5*S**,6a*S**)-Spiro[1′-(*p*-chlorophenyl)-3-propyl-4,5,6,6a-tetrahydro-3a*H*-cyclopenta[*d*]isoxazole-4′,5-imidazolidine-2′,5′-dione] (6e) from Resin 5 (R = Cl, R′ = Propyl).** Using the same procedures described for the synthesis of **6a**, resin **5** (R = Cl, R′ = propyl) gave **6e**[6] (26 mg, 0.075 mmol, overall 25% yield) as a solid.

(3a*R,5*S**,6a*S**)-Spiro[1′-(*p*-fluorophenyl)-3-propyl-4,5,6,6a-tetrahydro-3a*H*-cyclopenta[*d*]isoxazole-4′,5-imidazolidine-2′,5′-dione] (6f) from Resin 5 (R = F, R′ = Propyl).** Using the same procedures described for the synthesis of **6a**, resin **5** (R = F, R′ = propyl) gave **6f**[6] (26 mg, 0.078 mmol, overall 26% yield) as a solid.

Ethyl 1-((*tert*-Butoxycarbonyl)amino)cyclopenta-3-ene-1-carboxylate (10) from 9. Compound **9** (4 g, 25.8 mmol) was treated with di-*tert*-butyl dicarbonate (5.63 g, 25.8 mmol) in CH_2Cl_2 (100 mL) at reflux overnight. The solvent was removed in vacuo, and the residue was recrystallized (ethyl acetate/hexane) to give **10** (6 g, 23.5 mmol, 91%) as a solid. Mp 82 °C; FTIR (KBr) 3279, 2981, 1735, 1701 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 5.65 (s, 2H), 5.10 (s, br, 1H), 4.20 (q, 2H, J = 7.1 Hz), 3.05 (d, 2H, J = 15.6 Hz), 2.6 (d, 2H, J = 15.6 Hz), 1.43 (s, 9H), 1.27 (t, 3H, J = 7.1 Hz); ^{13}C NMR (300 MHz, $CDCl_3$) δ 174.3, 154.9, 127.7, 64.3, 61.5, 44.9, 28.3, 27.4, 14.2.

1-((*tert*-Butoxycarbonyl)amino)cyclopenta-3-ene-1-carboxylic Acid (11) from 10. Compound **10** (3.5 g, 13.72 mmol) and sodium hydroxide (1.09 g, 27.4 mmol) in EtOH/H_2O (20 mL/20 mL) were refluxed overnight. The solvent was removed under reduced pressure, and 1 N HCl was added to the reaction mixture until the pH reached 2−3. Ethyl acetate (40 mL × 2) extraction, drying over anhydrous $MgSO_4$, and removal of solvent under reduced pressure gave **11** (2.7 g, 11.8 mmol, 87%) as a solid: Mp 137 °C; FTIR (KBr) 3258, 3066, 2975, 1708, 1653 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 5.66 (s, 2H), 5.14 (s, br, 1H), 3.13 (d, 2H, J = 16.3 Hz), 2.64 (d, 2H, J = 16.3 Hz), 1.44 (s, 9H); ^{13}C NMR (300 MHz, $CDCl_3$) δ 155.8, 127.6, 64.4, 44.8, 28.3, 27.4. Anal. Calcd for $C_{11}H_{17}NO_4$: C, 58.13; H, 7.54; N, 6.16. Found: C, 57.98; H, 7.64; N, 6.12.

Ethyl (1*R,2*S**)-1-Amino-2-vinylcyclopropane-1-carboxylate (13) from 7.** Compound **7** (1.10 g, 4.09 mmol) was treated with NaH (0.216 g, 9 mmol) in THF (30 mL) at ambient temperature. A solution of *cis*-1,4-bis(methylsulfonyl)oxy)-2-butene (1 g, 4.09 mmol) in DMF (5 mL) was added dropwise to the solution at ambient temperature. After 12 h, ether (80 mL) and cold water (40 mL) were added to the reaction mixture and the ether layer was separated and dried (anhydrous $MgSO_4$). After removal of the ether at reduced pressure, the residue was passed through a silica gel column which was presaturated with 10% Et_3N in hexane. Removal of the solvent under reduced pressure gave compounds **8** and **12** (1 g of crude) as an inseparable mixture which was treated with 1 N HCl (10 mL) in THF (10 mL) for 30 min. Ethyl acetate (40 mL) and water (30 mL) 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 (30 mL × 2), drying over anhydrous $MgSO_4$, and silica gel column chromatography (1:1 ethyl acetate/hexane) gave **9**[6] (0.12 g, 0.77 mmol, 18%) and **13** (0.25 g, 1.61 mmol, 39%) as liquids.

13: FTIR (neat) 3381, 3322, 2983, 1720 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 5.69 (ddd, 1H, J = 17.41, 10.29, 10.25 Hz), 5.21 (dd, 1H, J = 17.41, 1.8 Hz), 5.03 (dd, 1H, J = 10.29, 1.8 Hz), 4.17 (m, 2H), 2.08 (s, 2H), 2.01 (m, 1H), 1.55 (dd, 1H, J = 7.44, 4.70 Hz), 1.33 (dd, 1H, J = 9.38, 4.70 Hz), 1.27 (t, 3H, 7.21 Hz); ^{13}C NMR (300 MHz, $CDCl_3$) δ 173.8, 135.1, 116.3, 61.1, 42.5, 35.7, 23.1, 14.4.

Ethyl (1*R,2*S**)-1-((*N*-Phenylcarbamoyl)amino)-2-vinylcyclopropane carboxylate (14) from 13.** Compound **13** (0.2 g, 1.29 mmol) in CH_2Cl_2 (20 mL) was treated with phenyl isocyanate (0.153 g, 1.29 mmol) at ambient temperature for 1 h. Removal of the solvent under the reduced pressure, followed by recrystallization (1:1 ethyl acetate/hexane) gave **14** (317 mg, 1.15 mmol, 90%) as a solid: Mp 150 °C; FTIR (KBr) 3348, 3087, 2981, 1729, 1642 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.04−7.36 (m, 5H), 6.83 (s, 1H), 5.76 (m, 1H), 5.62 (s, 1H), 5.33 (d, 1H, J = 17.16 Hz), 5.17 (d, 1H, J = 11.61 Hz), 4.18 (q, 2H, J = 7.11 Hz), 2.21 (m, 1H), 1.91 (dd, 1H, J = 7.91, 5.31 Hz), 1.59 (dd, 1H, J = 9.56, 5.31 Hz), 1.24 (t, 3H, J = 7.11 Hz); ^{13}C NMR (300 MHz, $CDCl_3$) δ 171.4, 155.8, 138.3, 133.4, 129.2, 123.8, 120.5, 118.4, 61.8, 40.9, 34.9, 23.4, 14.3.

Ethyl (1*R,2*S**,1′*R**)-2-(4′-propyl-2′,3′-oxazolinyl)-1-((*N*-phenylcarbamoyl)amino)cyclopropanecarboxylate (15a) and Ethyl (1*R**,2*S**,1′*S**)-2-(4′-Propyl 2′,3′-oxazolinyl)-1-((*N*-phenylcarbamoyl)amino)cyclopropanecarboxylate (16a) from 14.** Compound **14** (150 mg, 0.54 mmol) in DME (10 mL) was treated with 1-nitrobutane (56 mg, 0.54 mmol), phenyl isocyanate (130 mg, 1.09 mmol), and Et_3N (0.01 mL) at 70 °C overnight. Removal of the solvent at reduced pressure, followed by the silica gel column chromatography (3:7 ethyl acetate/hexane) gave **15a** (25 mg, 0.07 mmol, 13%) as a liquid and **16a** (12 mg, 0.33 mmol, 62%) as a solid.

15a: FTIR (neat) 3357, 2963, 1724, 1662 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.33−7.04 (m, 5H), 6.99 (s, 1H), 5.71 (s, 1H), 4.79 (m, 1H), 4.15 (m, 2H), 3.39 (dd, 1H, J = 17.15, 6.54 Hz), 3.0 (dd, 1H, J = 17.15, 10.35 Hz), 2.33 (t, 2H, J = 7.22 Hz), 1.87−1.79 (m, 1H), 1.67−1.53 (m, 3H), 1.41 (dd, 1H, J = 9.27, 5.20 Hz), 1.25 (t, 3H, 7.15 Hz), 0.94 (t, 3H, 7.39 Hz); ^{13}C NMR (300 MHz, $CDCl_3$) δ 171.8, 160.2, 156.0, 138.3, 129.2, 124.0, 120.9, 79.2, 61.8, 42.1, 37.7, 35.5, 29.8, 23.4, 19.8, 14.3, 13.8.

16a: Mp 152 °C; FTIR (KBr) 3303, 2961, 2873, 1724, 1659 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.76 (s, br, 1H), 7.6−7.0 (m, 5H), 5.63 (s, br, 1H), 4.7 (m, 1H), 4.34−4.11 (m, 2H), 3.17 (dd, 1H, J = 17.03, 10.4 Hz), 2.83 (dd, 1H, J = 17.03, 7.24 Hz), 2.34 (t, 3H, J = 7.3 Hz), 1.89−1.77 (m, 2H), 1.66−1.51 (m, 3H), 1.22 (t, 3H, J = 7.1 Hz), 0.95 (t, 3H, J = 7.2 Hz); ^{13}C NMR (300 MHz, $CDCl_3$) δ 170.8, 159.5, 156.1, 139.1, 128.9, 122.9, 119.6, 79.2, 62.2, 42.3, 38.3, 35.5, 29.7, 21.6, 19.8, 14.2, 13.8. Anal. Calcd for $C_{19}H_{25}N_3O_4$: C, 63.49; H, 7.01; N, 11.69. Found: C, 63.26; H, 7.05; N, 11.61.

Ethyl (1*R,2*S**,1′*R**)-2-(4′-Methyl-2′,3′-oxazolinyl)-1-((*N*-phenylcarbamoyl)amino)cyclopropanecarboxylate (15b) and Ethyl (1*R**,2*S**,1′*S**)-2-(4′-Methyl-2′,3′-oxazolinyl)-1-((*N*-phenylcarbamoyl)amino)cyclopropane carboxylate (16b) from 14.** Following the same procedure described **15a** and **16a**, nitroethane (41 mg, 0.54 mmol) gave **15b** (17 mg, 0.05 mmol, 9%) and **16b** (117 mg, 0.35 mmol, 65%) as solids.

15b: Mp 174−175 °C; FTIR (KBr) 3356, 2978, 1694 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.31−7.06 (m, 5H), 6.95 (s, 1H), 5.67 (s, 1H), 4.81 (m, 1H), 4.17 (q, 2H, J = 7.1 Hz), 3.39 (dd, 1H, J = 17.29, 6.64 Hz), 3.0 (dd, 1H, J = 17.29, 10.12 Hz), 2.0 (s, 3H), 1.84 (m, 1H), 1.65 (m, 1H), 1.42 (dd, 1H, J = 9.32, 5.26 Hz), 1.25 (t, 3H, J = 7.1 Hz); ^{13}C NMR (300 MHz, $CDCl_3$) δ 171.8, 157.6, 156.0, 138.2, 129.3, 124.1, 121.1, 79.5, 61.8, 43.7, 37.7, 35.5, 23.4, 14.3, 13.3. Anal. Calcd for $C_{17}H_{21}N_3O_4$: C, 61.61; H, 6.38; N, 12.68. Found: C, 61.49; H, 6.47; N, 12.45.

16b: Mp 149 °C; FTIR (KBr) 3304, 2983, 1716, 1662 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.75 (s, br, 1H), 7.57 (m, 2H), 7.31−7.28 (m, 2H), 7.02 (t, 1H, J = 7.36 Hz), 5.47 (s, br, 1H), 4.76 (m, 1H), 4.24 (m, 2H), 3.17 (dd, 1H, J = 17.16, 10.53 Hz), 2.85 (dd, 1H, J = 17.16, 7.26 Hz), 2.02 (s, 3H), 1.88 (m, 1H), 1.78 (dd, 1H, J = 7.79, 5.07 Hz), 1.53 (dd, 1H, J = 9.55, 5.07 Hz), 1.23 (t, 3H, J = 7.1 Hz); ^{13}C NMR (300 MHz, $CDCl_3$) δ 171.0, 156.3, 156.0, 139.2, 128.8, 122.8, 119.5, 77.9, 62.1, 43.9, 38.3, 36.2, 21.4, 14.2, 13.3. Anal. Calcd for $C_{17}H_{21}N_3O_4$: C, 61.61; H, 6.38; N, 12.68. Found: C, 61.46; H, 6.41; N, 12.57.

Ethyl (1*R,2*S**,1′*R**)-2-(4′-phenyl-2′,3′-oxazolinyl)-1-((*N*-phenylcarbamoyl)amino)cyclopropane carboxylate (15c) and Ethyl (1*R**,2*S**,1′*S**)-2-(4′-Phenyl-2′,3′-oxazolinyl)-1-((*N*-phenylcarbamoyl)amino)cyclopropanecarboxylate (16c) from 14.** Following the same procedure described for **15a** and **16a**, α-nitrotoluene (74 mg, 0.54 mmol) gave **15c** (73 mg, 0.18 mmol, 33%) and **16c** (109 mg, 0.28 mmol, 51%) as solids.

15c: Mp 204 °C; FTIR (KBr) 3360, 3094, 2980, 1721, 1652 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.69−7.04 (m, 10H), 6.94 (s, 1H), 5.72 (s, 1H), 5.00 (m, 1H), 4.16 (m, 2H), 3.80 (dd, 1H, J = 16.86, 6.83 Hz), 3.38 (dd, 1H, J = 16.86, 10.51 Hz), 1.90 (m, 1H), 1.70 (dd, 1H, J = 7.99, 5.34 Hz), 1.45 (dd, 1H, J = 9.27, 5.34 Hz), 1.25 (t, 3H, J = 7.13 Hz); ^{13}C NMR (300 MHz, $CDCl_3$) δ 171.8, 157.6, 156.1, 138.1, 130.1, 129.6, 129.3, 128.7, 126.9, 124.2, 121.2, 80.6, 61.9, 40.0, 37.9, 35.5, 23.4, 14.3. Anal. Calcd for $C_{22}H_{23}N_3O_4$: C, 67.16; H, 5.89; N, 10.68. Found: C, 66.99; H, 5.81; N, 10.54.

16c: Mp 199−200 °C; FTIR (KBr) 3373, 3059, 2984, 1719, 1660 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.66−7.01 (m, 11H), 5.40 (s, br, 1H), 4.95 (m, 1H), 4.36−4.15 (m, 2H), 3.60 (dd, 1H, J = 16.65, 10.53 Hz), 3.24 (dd, 1H, J = 16.65, 7.08 Hz), 2.02 (m, 1H), 1.87 (dd, 1H, J = 7.77, 5.1 Hz), 1.58 (dd, 1H, J = 9.51, 5.1 Hz), 1.26 (t, 3H, J = 7.15 Hz); ^{13}C NMR (300 MHz, $CDCl_3$) δ 171.2, 157.1, 155.8, 138.9, 130.4, 129.1, 128.9, 128.8, 126.8, 123.1, 119.8, 78.9, 62.4, 40.3, 38.4, 35.7, 21.8, 14.2.

(1*R,3*S**,1′*S**)-5,7-Diaza-1-(4′-propyl-2′,3′-oxazolinyl)-5-phenylspiro[2,4]heptane-4,6-dione (17a) from 15a.** Compound **15a** (100 mg, 0.278 mmol) was treated with sodium (3.2 mg, 0.14 mmol) in EtOH (5 mL) for 4 h. Removal of the solvent under the reduced pressure and silica gel column chromatography (1:2 ethyl acetate/hexane) gave **17a** (71 mg, 0.23 mmol, 82%) as a liquid: FTIR (neat) 3286, 2963, 1777, 1715 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.51−7.37 (m, 5H), 7.23 (s, 1H), 4.85 (m, 1H), 3.05 (dd, 1H, J = 16.85, 10.23 Hz), 2.64 (dd, 1H, J = 16.85, 7.17 Hz), 2.32 (t, 2H, J = 7.30 Hz), 1.93 (m, 1H), 1.79−1.67(m, 2H), 1.58 (q, 2H, J = 7.43 Hz), 0.96 (t, 3H, J = 7.43 Hz); ^{13}C NMR (300 MHz, $CDCl_3$) δ 171.7, 159.1, 156.1, 131.5, 129.2, 128.5, 126.1, 77.5, 43.7, 42.5, 31.2, 29.7, 20.8, 19.7, 13.8.

(1*R,3*S**,1′*R**)-5,7-Diaza-1-(4′-propyl-2′,3′-oxazolinyl)-5-phenylspiro[2,4]heptane-4,6-dione (18a) from 16a.** Following the same procedure described for making compound **17a**, using compound **16a** (100 mg, 0.278 mmol) gave **18a** (74 mg, 0.236 mmol, 85%) as a solid: Mp 158 °C; FTIR (KBr) 3318, 2961, 1785, 1733 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.49−7.35 (m, 5H), 6.9 (s, br, 1H), 4.89 (m, 1H), 3.13 (m, 1H), 2.72 (m, 1H), 2.34 (t, 2H, J = 7.38 Hz), 1.93 (m, 1H), 1.64−1.56 (m, 4H), 0.97 (t, 3H, J = 7.40 Hz); ^{13}C NMR (300 MHz, $CDCl_3$) δ 171.7, 158.7, 157.1, 131.7, 129.1, 128.3, 126.5, 75.9, 44.0, 42.2, 31.4, 29.7, 19.8, 17.4, 13.8. Anal. Calcd for $C_{17}H_{19}N_3O_3$: C, 65.16; H, 6.11; N, 13.40. Found: C, 65.21; H, 6.11; N, 13.35.

17a and 18a (from Resin 24). Using the same procedure described for the preparation of **6a** (DMF, 90 °C), resin **24** (R = H, R′ = propyl) gave **17a** (5 mg, 0.017 mmol, 6% overall) and **18a** (15 mg, 0.047 mmol, 16% overall) as solids.

(1*R,3*S**,1′*S**)-5,7-Diaza-1-(4′-methyl-2′,3′-oxazolinyl)-5-phenylspiro[2,4]heptane-4,6-dione (17b) from 15b.** Following the same procedure described for making compound **17a**, using compound **15b** (100 mg, 0.302 mmol) gave **17b** (67 mg, 0.234 mmol, 78%) as a solid: Mp 116 °C; FTIR (KBr) 3335, 2924, 2886, 1771, 1708 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.51−7.37 (m, 5H), 6.63 (s, 1H), 4.88 (m, 1H), 3.07 (dd, 1H, J = 16.98, 10.32 Hz), 2.68 (dd, 1H, J = 16.98, 7.06 Hz), 2.00 (s, 3H), 1.93 (m, 1H), 1.83 (dd, 1H, J = 7.78, 6.11 Hz), 1.72 (dd, 1H, J = 9.52, 6.11 Hz); ^{13}C NMR (300 MHz, $CDCl_3$) δ 171.5, 155.9, 155.4, 131.5, 129.2, 128.5, 126.1, 77.7, 44.1, 43.7, 31.4, 20.8, 13.3.

(1*R,3*S**,1′*R**)-5,7-Diaza-1-(4′-methyl-2′,3′-oxazolinyl)-5-phenylspiro[2,4]heptane-4,6-dione (18b) from 16b.** Following the same procedure described for making compound **17a**, using compound **16b** (100 mg, 0.302 mmol) gave **18b** (64 mg, 0.224 mmol, 75%) as a solid: Mp 184 °C; FTIR (KBr) 3360, 3078, 2917, 1781, 1710 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.50−7.35 (m, 5H), 6.86 (s, 1H), 4.93 (m, 1H), 3.14 (dd, 1H, J = 17.07, 9.61 Hz), 2.75 (dd, 1H, J = 17.07, 6.77 Hz), 2.01 (s, 3H), 1.94 (dd, 1H, J = 18.23, 9.33 Hz), 1.61−1.56 (m, 2H); ^{13}C NMR (300 MHz, $CDCl_3$) δ 171.5, 156.2, 155.1, 131.5, 129.1, 128.3, 126.5, 76.1, 43.9, 43.8, 31.4, 17.4, 13.3. Anal. Calcd for $C_{15}H_{15}N_3O_3$: C, 63.14; H, 5.29; N, 14.72. Found: C, 63.30; H, 5.32; N, 14.66.

(1*R,3*S**,1′*S**)-5,7-Diaza-1-(4′-phenyl-2′,3′-oxazolinyl)-5-phenylspiro[2,4]heptane-4,6-dione (17c) from 15c.** Following the same procedure described for making compound **17a**, using compound **15c** (100 mg, 0.254 mmol) gave **17c** (71 mg, 0.204 mmol, 81%) as a solid: Mp 169 °C; FTIR (KBr) 3284, 3064, 1777, 1700 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.66−7.36 (m, 10H), 6.85 (s, 1H), 5.07 (m, 1H), 3.47 (dd, 1H, J = 16.54, 10.47 Hz), 3.07 (dd, 1H, J = 16.54, 6.85 Hz), 2.01 (m, 1H), 1.87 (dd, 1H, J = 7.78, 6.19 Hz), 1.74 (dd, 1H, J = 9.49, 6.17 Hz); ^{13}C NMR (300 MHz, $CDCl_3$) δ 171.5, 156.6, 156.1, 138.9, 131.4, 130.4, 129.2, 128.8, 128.5, 126.7, 126.1, 78.6, 43.8, 40.4, 31.3, 20.8.

(1*R,3*S**,1′*R**)-5,7-Diaza-1-(4′-phenyl-2′,3′-oxazolinyl)-5-phenylspiro[2,4]heptane-4,6-dione (18c) from 16c.** Following the same procedure described for making compound **17a**, using compound **16c** (100 mg, 0.254 mmol) gave **18c** (66 mg, 0.19 mmol, 75%) as a solid: Mp 235 °C (dec); FTIR (KBr) 3339, 3062, 1785, 1710 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.68−7.28 (m, 11H), 5.08 (m, 1H), 3.48 (dd, 1H, J = 15.32, 10.63 Hz), 3.13 (dd, 1H, J = 15.32, 6.84), 2.00 (m, 1H), 1.65−1.55 (m, 2H); ^{13}C NMR (300 MHz, $CDCl_3$) δ 171.5, 156.4, 156.3, 132.0, 130.2, 129.7, 129.0, 128.8, 128.2, 126.8, 126.5, 77.2, 44.1, 40.1, 31.4, 17.4. Anal. Calcd for $C_{20}H_{17}N_3O_3$: C, 69.15; H, 4.93; N, 12.09. Found: C, 69.07; H, 5.03; N, 11.70.

(1*R,3*S**,1′*R**)-5,7-Diaza-1-(4′-ethyl-2′,3′-oxazolinyl)-5-(*p*-chlorophenyl)spiro[2,4]heptane-4,6-dione (18d) from Resin 24 (R = Cl, R′ = Ethyl).** Using the same procedure described for the preparation of **6a** (DMF, 90 °C), resin **24** (R = Cl, R′ = ethyl) gave **18d** (18 mg, 0.054 mmol, 18% overall) as a solid: Mp 215 °C; FTIR (KBr) 3317, 2976, 1783, 1713 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.45−7.38 (m, 4H), 6.99 (s, 1H), 4.93−4.85 (m, 1H), 3.15 (dd, 1H, J = 16.92, 10.37 Hz), 2.75 (dd, 1H, J = 16.92, 6.66 Hz), 2.38 (q, 2H, J = 7.53 Hz), 1.95 (dd, 1H, J = 18.22, 9.26 Hz), 1.61−1.53 (m, 2H), 1.18 (t, 3H, J = 7.53 Hz); ^{13}C NMR (300 MHz, $CDCl_3$) δ 171.2, 160.0, 156.1, 134.0, 130.3, 129.3, 127.6, 75.9, 44.0, 42.0, 31.5, 21.4, 17.5, 10.9. Anal. Calcd for $C_{16}H_{16}ClN_3O_3$: C, 57.57; H, 4.83; N, 12.58. Found: C,57.63; H, 4.79; N, 12.47.

(1*R,3*S**,1′*R**)-5,7-Diaza-1-(4′-propyl-2′,3′-oxazolinyl)-5-(*p*-chlorophenyl)spiro[2,4]heptane-4,6-dione (18e) from Resin 24 (R = Cl, R′ = Propyl).** Using the same procedure described for the preparation of **6a** (DMF, 90 °C), resin **24** (R = Cl, R′ = propyl) gave **18e** (16 mg, 0.046 mmol, 15% overall) as a solid: Mp 196 °C; FTIR (KBr) 3315, 2959, 1783, 1714 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.45−7.38 (m, 4H), 6.97 (s, 1H), 4.93−4.84 (m, 1H), 3.13 (dd, 1H, J = 16.93, 10.41 Hz), 2.73 (dd, 1H, J = 16.93, 6.69 Hz), 2.34 (t, 2H, J = 7.72 Hz), 1.93 (dd, 1H, J = 18.19, 9.26 Hz), 1.67−1.55 (m, 4H), 0.97 (t, 3H, J = 7.39 Hz); ^{13}C NMR (300 MHz, $CDCl_3$) δ 171.2, 158.7, 156.1, 134.0, 130.1, 129.2, 127.6, 75.8, 43.9, 42.1, 31.5, 29.6, 19.8, 17.5, 13.8 Anal. Calcd for $C_{17}H_{18}ClN_3O_3$: C, 58.70; H, 5.21; N, 12.08. Found: C, 58.94; H, 5.25; N, 11.88.

(1*R,3*S**,1′*R**)-5,7-Diaza-1-(4′-phenyl-2′,3′-oxazolinyl)-5-(*p*-chlorophenyl)spiro[2,4]heptane-4,6-dione (18f) from Resin 24 (R = Cl, R′ = Phenyl).** Using the same procedure described for the preparation of **6a** (DMF, 90 °C), resin **24** (R = Cl, R′ = phenyl) gave **18f** (21 mg, 0.055 mmol, 19% overall) as a solid: Mp 260 °C (dec); FTIR (KBr) 3353, 3109, 1784, 1715 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.68−7.65 (m, 2H), 7.43−7.39 (m, 5H), 6.83 (s, 1H), 5.15−5.06 (m, 1H), 3.56 (dd, 1H, J = 16.62, 10.51 Hz), 3.19 (dd, 1H, J = 16.62, 6.48 Hz), 2.02 (m, 1H), 1.67−1.57 (m, 2H); ^{13}C NMR (300 MHz, $CDCl_3$) δ 171.2, 156.3, 156.1, 134.0, 130.3, 130.1, 129.3, 128.8, 127.6, 126.7, 76.6, 44.0, 40.0, 31.5, 17.6. Anal. Calcd for $C_{20}H_{16}ClN_3O_3$: C, 62.91; H, 4.22 N, 11.00. Found: C,63.01; H, 4.29; N, 10.89.

Ethyl (1*R,2*S**)-1-((*tert*-Butoxycarbonyl)amino)-2-vinylcyclopropane-1-carboxylate (19) from 13.** Following the procedure described for making compound **10**, using compound **13** (4 g, 25.8 mmol) gave **19** (5.8 g, 22.7 mmol, 88%) as a liquid: FTIR (neat) 3360, 3085, 2980, 1726 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 5.82−5.70 (m, 1H), 5.27 (dd, 1H, J = 17.09, 1.32 Hz), 5.10 (dd, 1H, J = 10.3, 1.63 Hz), 4.18 (m, 2H), 2.13 (m, 1H), 1.80 (m, 1H), 1.44 (s, 9H), 1.43 (m, 1H), 1.25 (t, 3H, J = 7.08); ^{13}C NMR (300 MHz, $CDCl_3$) δ 170.9, 155.9, 133.8, 117.6, 80.1, 61.3, 40.9, 34.2, 28.3, 23.3, 14.3.

(1*R,2*S**)-1-((*tert*-Butoxycarbonyl)amino)-2-vinylcyclopropane-1-carboxylic Acid (20) from 19.** Following the procedure described for making compound **11**, using compound **19** (3.5 g, 13.72 mmol) gave compound **20** (2.8 g, 12.33 mmol, 90%) as a solid: Mp 159 °C; FTIR (KBr) 3263, 2986, 1702, 1653 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 9.6 (s, br, 1H), 5.78 (m, 1H), 5.30 (d, 1H, J = 16.71 Hz), 5.31 (dd, 1H, J = 10.27, 1.4 Hz), 2.19 (dd, 1H, J = 17.58, 8.91 Hz), 1.81 (s, br, 1H), 1.53 (s, br, 1H), 1.45 (s, 9H); ^{13}C NMR (300 MHz, $CDCl_3$) δ 176.5, 156.1, 133.5, 118.1, 81.6, 40.7, 35.1, 28.3, 23.5. Anal. Calcd for $C_{11}H_{17}NO_4$: C, 58.13; H, 7.54; N, 6.16. Found: C, 58.26; H, 7.64; N, 6.05.

Resin 21. Following the same procedure described for making resin **2**, **20** gave resin **21** (2.54 g): FTIR (KBr) 1725 cm^{-1}.

Resin 22. Following the same procedure described for making resin **3**, **21** gave resin **22** (2.44 g): FTIR (KBr) 3473, 3385, 1719 cm^{-1}.

Resin 23 (R = H). Following the same procedure described for making resin **4**, **22** gave resin **23** (300 mg): FTIR (KBr) 1727, 1658 cm^{-1}.

Resin 23 (R = Cl). Following the same procedure described for making resin **4**, **22** gave resin **23** (310 mg): FTIR (KBr) 1717, 1654 cm^{-1}.

Resin 24 (R = H, R′ = Propyl). Following the same procedure described for making resin **5** (R = Cl, R′ = Me), **23** gave resin **24** (305 mg): FTIR (KBr) 1727, 1699 cm^{-1}.

Resin 24 (R = Cl, R′ = Ethyl). Following the same procedure described for making resin **5** (R = Cl, R′ = Me), **23** gave resin **24** (302 mg): FTIR (KBr) 1725 cm^{-1}.

Resin 24 (R = Cl, R′ = Propyl). Following the same procedure described for making resin **5** (R = Cl, R′ = Me), **23** gave resin **24** (310 mg): FTIR (KBr) 1726, 1698 cm^{-1}.

Resin 24 (R = Cl, R′ = Phenyl). Following the same procedure described for making resin **5** (R = Cl, R′ = Me), **23** gave resin **24** (308 mg): FTIR (KBr) 1728 cm^{-1}.

Acknowledgment. We are grateful to the National Science Foundation and Novartis Crop Protection AG for financial support of this research.

Supporting Information Available: ^{1}H NMR, ^{13}C NMR, and FTIR spectra for compounds **10**, **13**, **14**, **15a**, **16c**, **17a**−**c**, and **19**, tables of X-ray data, and ORTEP diagrams (38 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

JO9807161