Diastereoselective Synthesis of Cyclopentanoids with Hydantoin and Isoxazoline Substituents

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Exploiting 1,3-dipolar cycloaddition and urea → hydantoin cyclization transformations, novel spiro-[cyclopenta[*d*]isoxazole-4′,5-imidazolindine] heterocycles of generalized structure **I** have been prepared. The 1-amino-3-cyclopentenecarboxylate precursor **II** was prepared from a suitably activated/protected derivative of glycine and the bis-alkylating agent *cis*-1,4-dichloro-2-butene.

The hydantoin nucleus is an important structural element with medicinal (cf., anticonvulsant[1]) as well as agrochemical (cf., fungicidal[2] and herbicidal[3]) activities. Indeed a large number of hydantions adorned with diverse substituents have been synthesized for a wide variety of biological applications.[4] These activities, coupled with our observation that the isoxazoline heterocycle has been used extensively to modulate various other biologically active motifs,[5] led us to explore synthetic strategies for constructing hydantoin−isoxazoline heterocycles about a central carbocyclic core.

Isoxazoline heterocycles can be synthesized from the 1,3-dipolar cycloaddition reaction of a nitrile oxide to an alkene using reaction protocols which perform nicely with a variety of reaction partners.[6] The requisite nitrile oxides can be generated in situ by either (i) base-induced dehydrohalogenation of hydroximoyl chlorides (Huisgen methodology,[7] originally reported for aromatic nitrile oxides) or (ii) dehydration of primary nitroalkane derivatives (Mukaiyama methodology, originally reported for aliphatic nitrile oxides).[8] Hydantoin heterocycles are generally prepared by cyclization of 2-[5-aryl (or alkyl)-ureido] acetate derivatives or carbamate derivatives in the presence of acid or base.[9]

Exploiting these transformations for heterocycle construction, we set out to develop a protocol for elaboration

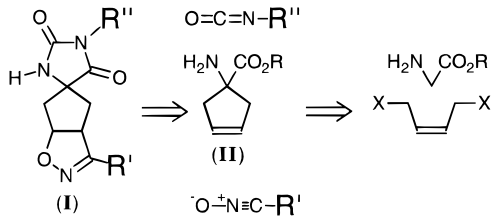

Figure 1.

of the novel spiro(cyclopenta[*d*]isoxazole-4′,5-imidazolindine) heterocycle of generalized structure **I**. We envisioned the 1-amino-3-cyclopentenecarboxylate precursor (**II**) as deriving from a suitably activated/protected derivative of glycine and a bis-alkylating agent such as *cis*-1,4-dichloro-2-butene (Figure 1).

Drawing on the extensive glycine alkylation studies for the synthesis of α-amino acid derivatives,[10] we began our studies with the condensation of 4-bromobenzaldehyde with ethyl glycine hydrochloride to give Schiff base **1** (Scheme 1). Subsequent bis-alkylation of this active methylene compound by treating a THF suspension of sodium hydride with **1** followed by dropwise addition of *cis*-1,4-dichloro-2-butene delivered cyclopentenecarboxylate **2** with no trace (as judged by ^{1}H NMR) of the potential cyclopropanecarboxylate side product. The Schiff base moiety in **2** proved rather labile to silica gel chromatography and therefore was most effectively used without purification in the subsequent phenyl isocyanate-mediated 1,3-dipolar cycloaddition reaction.

Thus, treating crude **2** with 1-nitrobutane, phenyl isocyanate, and triethylamine (Mukaiyama method) in dimethoxyethane (DME) at room temperature for 10 h followed by reflux for 30 h delivered a nearly 1:1 mixture of diastereomeric cycloaddition products (**3**) in 60% crude yield. Again, the Schiff base moiety of **3** proved labile during attempted silica gel purification so the crude product was taken up in THF and treated with aqueous hydrochloric acid to effect imine to amine conversion. The resulting ammonium salts were neutralized with aqueous sodium hydroxide and, following workup and solvent exchange (EtOAc → CH_2Cl_2), the resulting primary

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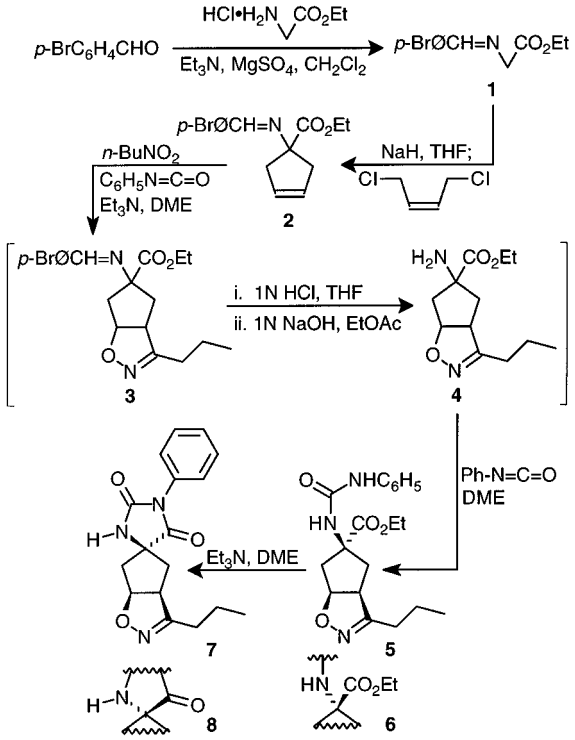
Scheme 1.



amines (**4**) were intercepted with phenyl isocyanate to deliver ureas **5** (16% overall yield from **1**) and **6** (14% overall yield from **1**) which proved easily separable by silica gel chromatography. Alternatively, this mixture of ureas could be cyclized to hydantoins **7** and **8** by base treatment; specifically, triethylamine in DME at reflux caused **5**/**6** → **7**/**8**.

We were unable to make unambiguous stereochemical assignments at **5**/**6** using ^{1}H NMR experiments. Fortunately, **5** is crystalline and single-crystal X-ray analysis (Figure 2) established the relative stereochemistry of urea **5** (and hence **6**) and, by relating **5** → **7** and **6** → **8**, the relative stereochemistry of hydantoins **7** and **8**.

Before proceeding with the preparation of R′ and R″ analogues of **I**, we felt it would be advantageous to address the Schiff base lability issue and, reflecting on the transformations employed in Scheme 1, an attractive alternative appeared to be imine → urea conversion earlier in the sequence. Specifically, our idea was to react aminocyclopentenecarboxylate **II** with an isocyanate to replace the sensitive imine with a stable urea. This change in sequence, however, introduces the question of how the urea moiety would behave in the nitrile oxide cycloaddition step. Intrigued by the potential, we set out to prepare urea **10** (Scheme 2).

Treatment of cyclopentenecarboxylate **2** with aqueous hydrochloric acid in THF followed by aqueous sodium hydroxide delivered amino ester **9**. Urea formation followed in straightforward fashion by treatment with phenyl isocyanate yielded **10** which, unlike imine analogue **2**, was easily purified by silica gel chromatography (60% overall yield from imino ester **1**). In the key step, the urea moiety of **10** proved to be additionally advantageous in that it provides facial direction in the reaction of the in situ generated nitrile oxide with the cyclopentenoid moiety. Thus, we were pleased to find that **10** gave one major cycloaddition product which, by comparison with the results of Scheme 1, proved to be isoxazoline

Scheme 2.

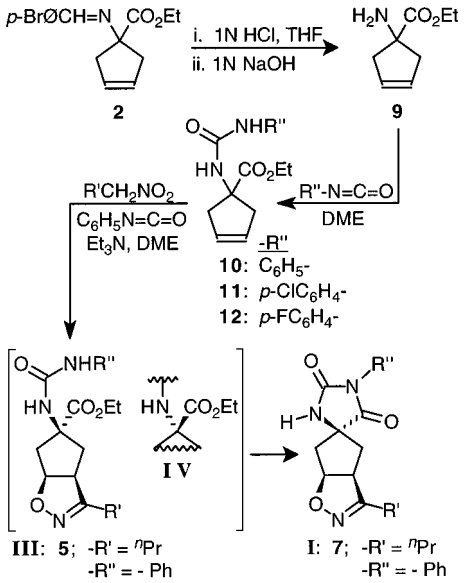


Table 1. Diastereoselective Formation of Cyclopenta[*d*]isoxazoles (III)

compound	R′	R″	% yield (**III**)	% yield (**IV**)
5 (**III**), **6** (**IV**)	$CH_2CH_2CH_3$	C_6H_5	54	3
13 (**III**)	CH_3	C_6H_5	58	
14 (**III**)	C_6H_5	C_6H_5	60	
15 (**III**), **16** (**IV**)	$CH_2CH_2CH_3$	*p*-ClC_6H_4	55	5
17 (**III**)	$CH_2CH_2CH_3$	*p*-FC_6H_4	56	6

Table 2. Diastereoselective Formation of Spirocyclopenta[*d*]isoxazole-4′,5-imidazolidines (I)

compound	R′	R″	% yield (**I**)
7 (**I**)	$CH_2CH_2CH_3$	C_6H_5	82
18 (**I**)	CH_3	C_6H_5	73
19 (**I**)	C_6H_5	C_6H_5	60
20 (**I**)	$CH_2CH_2CH_3$	*p*-ClC_6H_4	78
21 (**I**)	$CH_2CH_2CH_3$	*p*-FC_6H_4	80

5. One final advantage of the imine/urea switch also surfaced in this cycloaddition step. Namely, urea **5** can be caused to undergo cyclization to hydantoin **7** without intermediate isolation. By treating cyclopentenecarboxylate **10** with the nitroalkane, isocyanate, and triethylamine first at room temperature followed by warming the reaction mixture (12 h delivers **5**) to reflux without isolation results in conversion of **5** to **7**.

Thus, as a result of our "early" imine to urea switch, imino ester **2** can be converted with diastereoselectivity to heterocycle **I** by an efficient three-pot sequence which has the potential of introducing variable R′ substituents in the selection of the nitroalkane (**10** → **7**) and variable R″ substituents in the selection of the isocyanate (**9** → **10**). We have established the validity of this synthetic potential by preparing the heterocycles listed in Tables 1 and 2. Moreover, **2** → **7** can be effected as a two-pot sequence by hydrolysis of **2** to **9** followed by a one-pot conversion of **9** to **7**; treatment of **9** with PhN=C=O (3 equiv) in DME at room temperature (0.5 h), addition of 1-nitrobutane and triethylamine at room temperature (10 h), and finally warming to reflux (3 d) delivered **7** in 30% yield from **2**.

Highly diastereoselective cycloaddition reactions of nitrile oxides to alkenes are rare.[11] We believe the facial diastereoselectivity observed in the reaction of cyclopen-

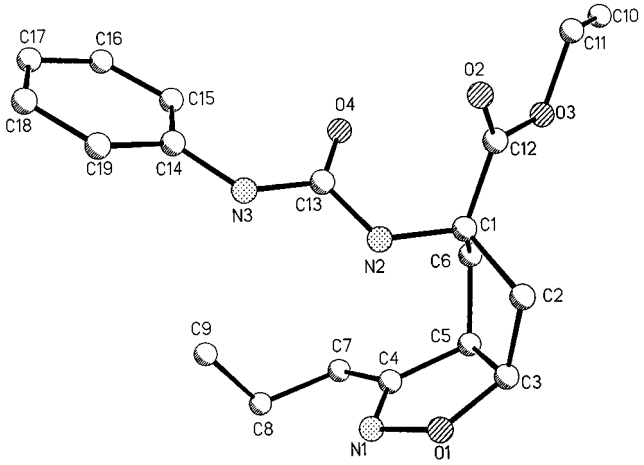
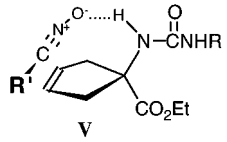


Figure 2. Single-Crystal X-ray Diffraction of Urea **5**.



V

Figure 3. H-Bonding Contolled Cycloaddition.

tenyl ureas such as **10** with nitrile oxides can be understood based on H-bonded direction of the cycloaddition step as depicted in **V** (Figure 3).

Experimental Section

Ethyl 2-[[(*E*)-1-(4-Bromophenyl)methylidene]amino]-acetate (1). Anhydrous magnesium sulfate (5 g) and triethylamine (7.2 g, 71.6 mmol) were added to a solution of *p*-bromobenzaldehyde (6.63 g, 35.8 mmol) and ethyl glycine hydrochloride (5 g, 35.8 mmol) in methylene chloride (100 mL). The reaction mixture was stirred for 10 h at room temperature at which time the magnesium sulfate was removed by filtration. The solvent was removed by rotary evaporation, ether (100 mL) and brine (50 mL) were added, the ether layer was separated, and the organic layer was dried ($MgSO_4$). Filtration and removal of the solvent (rotary evaporation) yielded Schiff base **1** (9 g, 33.3 mmol, 93%) as a white liquid. **1**: IR (neat) 2981, 1742, 1648, 1590 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ 8.23 (s, 1H), 7.64 (d, J = 8.3 Hz, 2H), 7.55 (d, J = 8.2 Hz, 2H), 4.38 (s, 2H), 4.23 (q, J = 7.1 Hz, 2H), 1.29 (t, J = 7.1 Hz, 3H). ^{13}C NMR (300 MHz, $CDCl_3$) δ 169.8, 164.0, 134.4, 131.7, 129.7, 125.6, 61.8, 61.0, 14.1.

Ethyl 1-[[(*E*)-1-(4-Bromophenyl)methylidene]amino]-cyclopent-3-ene-1-carboxylate (2). Schiff base **1** (1 g, 3.7 mmol) in THF (5 mL) was added to a reaction flask containing sodium hydride (0.19 g, 8.1 mmol) in THF (30 mL) under nitrogen. After 5 min, *cis*-1,4-dichloro-2-butene (0.46 g, 3.7 mmol) was added dropwise, and the reaction mixture was stirred at room temperature for 2 h and refluxed for 1 h. After cooling and solvent removal (rotary evaporation), ether (80 mL), ice (20 g), and cold water (20 mL) were added to the reaction mixture. The layers were separated, and the organic layer was dried ($MgSO_4$). Filtration, removal of the solvent (rotary evaporation), and column chromatography (silica gel, 5% triethylamine in hexane) of the residue gave cyclopentenecarboxylate **2** (0.96 g, 2.98 mmol, 80%) as a yellow liquid. **2**: IR (neat) 3059, 2979, 2935, 1728, 1640, 1589 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ 8.16 (s, 1H), 7.62 (d, J = 8.4 Hz, 2H), 7.53 (d, J = 8.4 Hz, 2H), 5.71 (s, 2H), 4.23 (q, J = 7.1 Hz, 2H), 3.18 (d, J = 15.5 Hz, 2H), 2.69 (d, J = 15.5 Hz, 2H), 1.27 (t, J = 7.1 Hz, 3H). ^{13}C NMR (300 MHz, $CDCl_3$) δ 173.9, 157.6, 135.2, 131.7, 129.7, 127.9, 125.2, 74.9, 61.2, 43.9, 14.1.

Ethyl (3a*R,5*S**,6a*S**)-5-(3-Phenylureido)-3-propyl-3a,5,6,6a-tetrahydro-4*H*-cyclopenta[*d*]isoxazole-5-carboxylate (5) and Ethyl (3a*R**,5*R**,6a*S**)-5-(3-Phenylureido)-3-propyl-3a,5,6,6a-tetrahydro-4*H*-cyclopenta-[*d*]isoxazole-5-carboxylate (6) from 2.** A DME (30 mL) solution of imine **2** (1.4 g, 4.3 mmol) was added to phenyl isocyanate (1.0 g, 8.7 mmol) and 1-nitrobutane (0.45 g, 4.3 mmol) followed by triethylamine (0.043 g, 0.43 mmol) under nitrogen. The reaction mixture was stirred for 10 h at room temperature and then refluxed for 30 h. DME was removed by rotary evaporation to give crude **3** which was dissolved in THF (20 mL) and treated with aqueous HCl (1N, 5 mL). After stirring 20 min at room temperature, the reaction mixture was transferred to a separatory funnel, and water (30 mL) and ethyl acetate (50 mL) were added. The water layer was removed by separation, and aqueous NaOH (1N) was added to adjust the pH to 9. The resulting water layer was extracted with ethyl acetate (2 × 30 mL), and the combined organic layer was dried ($MgSO_4$) and filtered.

Ethyl acetate was removed (rotary evaporation), and methylene chloride (20 mL) was added to the residue followed by phenyl isocyanate (0.52 g, 4.35 mmol). The solution was stirred for 30 min at room temperature, the solvent removed (rotary evaporation), and the residue purified by column chromatography (silica gel, EtOAc:hexanes = 1:3) to give **5** (0.28 g, 0.79 mmol, 16%) and **6** (0.25 g, 0.69 mmol, 14%) as a white solid. **5**: mp 122 °C; IR (KBr) 3379, 2961, 1733, 1676, 1616, 1549 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ 7.59 (bs, 1H), 7.31 (d, J = 7.3 Hz, 2H), 7.23 (dd, J = 7.1, 7.3 Hz, 2H), 6.98 (t, J = 7.1 Hz, 1H), 5.92 (bs, 1H), 5.20 (dd, J = 9.2, 5.4 Hz, 1H), 4.27−4.15 (m, 2H), 3.80 (dd, J = 9.2, 9.0 Hz, 1H), 2.92 (d, J = 14.4 Hz, 1H), 2.69 (dd, J = 14.4, 9.2 Hz, 1H), 2.42−2.21 (m, 2H), 2.28 (t, J = 7.8 Hz, 2H), 1.66−1.55 (m, 2H), 1.24 (t, J = 7.1 Hz, 3H), 0.91 (t, J = 7.3 Hz, 3H). ^{13}C NMR (300 MHz, $CDCl_3$) δ 172.9, 162.5, 154.7, 139.0, 128.4, 122.7, 119.4, 84.1, 65.3, 61.6, 54.5, 46.1, 36.9, 28.2, 19.5, 14.1, 13.8. Anal. Calcd for $C_{19}H_{25}N_3O_4$: C, 63.49; H, 7.01; N, 11.69. Found: C, 63.43; H, 6.93; N, 11.64. **6**: mp 155 °C; IR (KBr) 3354, 2961, 1742, 1638, 1554 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ 7.40−6.91 (m, 6H), 5.78 (bs, 1H), 5.12−5.05 (m, 1H), 4.14−4.07 (m, 2H), 3.63 (m, 1H), 2.54 (d, J = 9.2 Hz, 1H), 2.50−2.15 (m, 3H), 1.59−1.46(m, 2H), 1.16 (t, J = 7.2 Hz, 3H), 0.89 (t, J = 7.3 Hz, 3H). ^{13}C NMR (300 MHz, $CDCl_3$) δ 173.0, 161.7, 155.5, 138.5, 129.0, 123.2, 119.6, 84.5, 66.1, 61.9, 53.9, 45.1, 39.0, 28.3, 19.4, 13.9, 13.8. Anal. Calcd for $C_{19}H_{25}N_3O_4$: C, 63.49; H, 7.01; N, 11.69. Found: C, 63.31; H, 7.04; N, 11.53.

Ethyl (3a*R,5*S**,6a*S**)5-(3-Phenylureido)-3-propyl-3a,5,6,6a-tetrahydro-4*H*-cyclopenta[*d*]isoxazole-5-carboxylate (5) from 10.** To a solution of urea **10** (0.5 g, 1.8 mmol) in DME (30 mL) were added phenyl isocyanate (0.43 g, 3.6 mmol) and 1-nitrobutane (0.19 g, 1.8 mmol) followed by the addition of triethylamine (18 mg, 0.18 mmol) under nitrogen. The reaction mixture was stirred for 10 h at room temperature and then refluxed for 30 h. DME was removed (rotary evaporation) and the residue purified by column chromatography (silica gel, EtOAc:hexanes = 1:3) to give **5** (0.33 g, 0.93 mmol, 51%) as a white solid. **5**: mp 122 °C; IR (KBr) 3379, 2961, 1733, 1676, 1616, 1549 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ 7.59 (bs, 1H), 7.31 (d, J = 7.3 Hz, 2H), 7.23 (dd, J = 7.1, 7.3 Hz, 2H), 6.98 (t, J = 7.1 Hz, 1H), 5.92 (bs, 1H), 5.20 (dd, J = 9.2, 5.4 Hz, 1H), 4.27−4.15 (m, 2H), 3.80 (dd, J = 9.2, 9.0 Hz, 1H), 2.92 (d, J = 14.4 Hz, 1H), 2.69 (dd, J = 14.4, 9.2 Hz, 1H), 2.42−2.21 (m, 2H), 2.28 (t, J = 7.8 Hz, 2H), 1.66−1.55 (m, 2H), 1.24 (t, J = 7.1 Hz, 3H), 0.91 (t, J = 7.3 Hz, 3H). ^{13}C NMR (300 MHz, $CDCl_3$) δ 172.9, 162.5, 154.7, 139.0, 128.4, 122.7, 119.4, 84.1, 65.3, 61.6, 54.5, 46.1, 36.9, 28.2, 19.5, 14.1, 13.8. Anal. Calcd for $C_{19}H_{25}N_3O_4$: C, 63.49; H, 7.01; N, 11.69. Found: C, 63.43; H, 6.93; N, 11.64.

(3a*R,5*S**,6a*S**)-Spiro[3-propyl-1-phenyl-4,5,6,6a-tetrahydro-3a*H*-cyclopenta[*d*]isoxazole-4′,5-imidazolidine-2′,5′-dione] (7) from 5.** Triethylamine (0.11 mL, 0.83 mmol) was added to a DME (20 mL) solution of **5** (0.15 g, 0.41 mmol),

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and the reaction mixture was refluxed for 2 d. DME was removed (rotary evaporation), and the residue was recrystallized (EtOAc:hexanes = 1:3) to give **7** (0.106 g, 0.34 mmol, 82%) as a white solid. **7**: mp 188 °C; IR (KBr) 3223, 2957, 1778, 1712, 1497, 1409 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ 7.49−7.26 (m, 5H), 6.11 (bs, 1H), 5.23 (dd, J = 8.3, 4.5 Hz, 1H), 3.77 (dd, J = 9.0, 9.3 Hz, 1H), 2.61−2.13 (m, 6H), 1.75−1.60 (m, 2H), 1.01 (t, J = 7.3 Hz, 3H). ^{13}C NMR (300 MHz, acetone-d_6) δ 173.9, 161.9, 154.6, 131.4, 129.0, 128.2, 125.9, 85.8, 67.7, 53.7, 44.8, 41.2, 28.6, 19.5, 13.8. Anal. Calcd for $C_{17}H_{19}N_3O_3$: C, 65.16; H, 6.11; N, 13.4. Found: C, 64.89; H, 5.99; N, 13.24.

(3a*R,5*R**,6a*S**)-Spiro[3-propyl-1-phenyl-4,5,6,6a-tetrahydro-3a*H*-cyclopenta[*d*]isoxazole-4′,5-imidazolidine-2′,5′-dione] (8) from 6.** As with **5** → **7**, **8** (0.18 g, 0.6 mmol, 83%) was obtained as a white solid. **8**: mp 166 °C; IR (KBr) 3283, 2962, 1780, 1719, 1501, 1409 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ 7.82 (s, 1H), 7.48−7.34 (m, 5H), 5.10 (m, 1H), 3.60 (m, 1H), 2.42−2.13 (m, 6H), 1.87−1.52 (m, 2H), 0.96 (t, J = 7.3 Hz, 3H). ^{13}C NMR (300 MHz, $CDCl_3$) δ 173.3, 159.7, 155.8, 131.4, 129.1, 128.4, 126.0, 84.3, 68.5, 54.0, 45.0, 40.6, 28.4, 19.4, 13.8. Anal. Calcd for $C_{17}H_{19}N_3O_3$: C, 65.16; H, 6.11; N, 13.41. Found: C, 65.31; H, 6.16; N, 13.38.

Ethyl 1-Aminocyclopent-3-ene-1-carboxylate (9). To a solution of cyclopentenecarboxylate **2** (11 g, 34.1 mmol) in THF (80 mL) was added aqueous HCl (1 N, 35 mL), and the reaction mixture was stirred at room temperature for 30 min. Water (30 mL) was added to the reaction mixture which was extracted with ethyl acetate (2 × 50 mL). The aqueous layer was basified with sodium hydroxide (1 N) until pH = 9, and the resulting solution was extracted with ethyl acetate (2 × 50 mL). The organic layer was dried ($MgSO_4$), filtered, and concentrated (rotary evaporation) to afford amino ester **9** (4.39 g, 28.3 mmol, 83%) as a colorless liquid. **9**: IR (neat) 3058, 2925, 1727, 1207 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ 5.67 (s, 2H), 4.19 (q, J = 7.1 Hz, 2H), 2.97 (d, J = 15.3 Hz, 2H), 2.31 (d, J = 15.3 Hz, 2H), 1.80 (s, 2H), 1.28 (t, J = 7.1 Hz, 3H). ^{13}C NMR (300 MHz, $CDCl_3$) δ 176.9, 127.3, 62.9, 60.6, 46.6, 13.7.

Ethyl 1-(3-Phenylureido)cyclopent-3-ene-1-carboxylate (10). Phenyl isocyanate (2.0 g, 17.0 mmol) was added to a methylene chloride (80 mL) solution of amino ester **9** (2.6 g, 17.0 mmol) at room temperature. After 30 min, the resulting solid was removed by filtration, and the filter cake recrystallized (EtOAc:hexanes = 1:1) to give urea **10** (4.2 g, 15.32 mmol, 90%) as a white solid. **10**: mp 192 °C. IR (KBr) 3365, 3310, 1733, 1644, 1606, 1552 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ 7.30−7.01 (m, 5H), 6.77 (s, 1H), 5.67 (s, 2H), 5.6 (bs, 1H), 4.2 (q, J = 7.1 Hz, 2H), 3.1 (d, J = 15.8 Hz, 2H), 2.7 (d, J = 15.8 Hz, 2H), 1.26 (t, J = 7.1 Hz, 3H). ^{13}C NMR (300 MHz, $CDCl_3$) δ 174.2, 154.9, 140.5, 128.7, 127.7, 121.6, 118.1, 64.1, 60.6, 44.7, 13.7. Anal. Calcd for $C_{15}H_{18}N_2O_3$: C, 65.67; H, 6.61; N, 10.21. Found: C, 65.46; H, 6.49; N, 10.17.

Ethyl 1-[3-(*p*-Chlorophenyl)ureido]cyclopent-3-ene-1-carboxylate (11). As with **9** → **10**, *p*-chlorophenyl isocyanate gave **11** (0.8 g, 2.6 mmol, 88%) as a white solid. **11**: mp 135 °C. IR (KBr) 3343, 2979, 1741, 1639, 1598, 1554, 1492 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ 7.23−7.10 (m, 4H), 5.87 (bs, 1H), 5.66 (s, 2H), 4.22 (q, J = 7.1 Hz, 2H), 3.09 (d, J = 15.8 Hz, 2H), 2.65 (d, J = 15.8 Hz, 2H), 1.26 (t, J = 7.1 Hz, 3H). ^{13}C NMR (300 MHz, $CDCl_3$) δ 175.3, 155.0, 137.2, 128.8, 128.2, 127.7, 121.1, 64.3, 61.8, 44.9, 14.0. Anal. Calcd for $C_{15}H_{17}ClN_2O_3$: C, 58.35; H, 5.55; N, 9.07. Found: C, 58.18; H, 5.57; N, 9.01.

Ethyl 1-[3-(*p*-Fluorophenyl)ureido]cyclopent-3-ene-1-carboxylate (12). As with **9** → **10**, *p*-fluorophenyl isocyanate gave **12** (0.75 g, 2.56 mmol, 92%) as a white solid. **12**: mp 146 °C. IR (KBr) 3365, 2985, 1733, 1646, 1624, 1560, 1508 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ 7.25−7.18 (m, 3H), 6.89−6.84 (m, 2H), 5.89 (bs, 1H), 5.64 (s, 2H), 4.20 (q, J = 7.1 Hz, 2H), 3.08 (d, J = 16 Hz, 2H), 2.64 (d, J = 16 Hz, 2H), 1.24 (t, J = 7.1 Hz, 3H). ^{13}C NMR (300 MHz, $CDCl_3$) δ 175.2, 159.0 (d, J = 242.3 Hz), 155.5, 134.5 (d, J = 2.3 Hz), 127.7, 122.1 (d, J = 7.75 Hz), 115.4 (d, J = 22.35 Hz), 64.3, 61.7, 44.9, 14.0. Anal. Calcd for $C_{15}H_{17}FN_2O_3$: C, 61.63; H, 5.86; N, 9.58. Found: C, 61.63; H, 5.95; N, 9.59.

Ethyl (3a*R,5*S**,6a*S**)-5-(3-Phenylureido)-3-methyl-3a,5,6,6a-tetrahydro-4*H*-cyclopenta[*d*]isoxazole-5-carboxylate (13) from 10.** As with **5** → **10**, nitroethane gave **13** (0.35 g, 1.05 mmol, 58%) as a white solid. **13**: mp 145 °C. IR (KBr) 3359, 2981, 1731, 1696, 1670 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ 7.94 (bs, 1H), 7.32 (d, J = 8.2 Hz, 2H), 7.19 (dd, J = 8.0, 7.6 Hz, 2H), 6.94 (dd, J = 7.4, 7.3 Hz, 1H), 6.09 (bs, 1H), 5.20 (dd, J = 8.5, 6.0 Hz, 1H), 4.27−4.13 (m, 2H), 3.77 (dd, J = 9.2, 8.8 Hz, 1H), 2.92 (d, J = 14.2 Hz, 1H), 2.69 (dd, J = 14.2, 9.2 Hz, 1H), 2.35−2.22 (m, 2H), 1.98 (s, 3H), 1.23 (t, J = 7.0 Hz, 3H). ^{13}C NMR (300 MHz, $CDCl_3$) δ 173.0, 159.0, 154.7, 139.1, 128.6, 122.2, 118.8, 84.1, 65.0, 61.4, 55.7, 45.9, 36.7, 13.9, 11.4. Anal. Calcd for $C_{17}H_{21}N_3O_4$: C, 61.61; H, 6.38; N, 12.68. Found: C, 61.82; H, 6.36; N, 12.62.

Ethyl (3a*R,5*S**,6a*S**)-5-(3-Phenylureido)-3-phenyl-3a,5,6,6a-tetrahydro-4*H*-cyclopenta[*d*]isoxazole-5-carboxylate (14) from 10.** As with **5** → **10**, phenylnitromethane gave **14** (0.43 g, 1.09 mmol, 60%) as a white solid. **14**: mp 191 °C. IR (KBr) 3396, 3367, 1731, 1699, 1674, 1596, 1536 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ 7.70−6.86 (m, 11H), 6.00 (bs, 1H), 5.39 (m, 1H), 4.38−4.30 (m, 1H), 4.27−4.15 (m, 2H), 2.94−2.75 (m, 2H), 2.50−2.36 (m, 2H), 1.23 (t, J = 7.1 Hz, 3H). ^{13}C NMR (300 MHz, $CDCl_3$) δ 172.8, 160.9, 154.5, 138.4, 130.4, 128.9, 128.7, 128.0, 127.1, 122.9, 120.0, 86.3, 65.6, 61.6, 52.3, 45.5, 38.8, 14.1. Anal. Calcd for $C_{22}H_{23}N_3O_4$: C, 67.16; H, 5.89; N, 10.68. Found: C, 66.95; H, 5.81; N, 10.66.

Ethyl (3a*R,5*S**,6a*S**)-5-[3-(*p*-Chlorophenyl)ureido]-3-propyl-3a,5,6,6a-tetrahydro-4*H*-cyclopenta[*d*]isoxazole-5-carboxylate (15) and Ethyl (3a*R**,5*R**,6a*S**)-5-[3-(*p*-Chlorophenyl)ureido]-3-propyl-3a,5,6,6a-tetrahydro-4*H*-cyclopenta[*d*]isoxazole-5-carboxylate (16) from 11.** To a solution of urea **11** (0.56 g, 1.8 mmol) in DME (30 mL) were added phenyl isocyanate (0.434 g, 3.6 mmol) and 1-nitrobutane (0.18 g, 1.8 mmol) followed by the addition of triethylamine (18 mg, 0.18 mmol) under nitrogen. The reaction mixture was stirred for 10 h at room temperature and then refluxed for 30 h. DME was removed (rotary evaporation), and the residue was purified by column chromatography (silica gel, EtOAc:hexane = 1:3) to give **15** (0.394 g, 1.0 mmol, 55%) and **16** (0.038 g, 0.09 mmol, 5.3%) as white solids. **15**: mp 178 °C. IR (KBr) 3376, 2962, 1739, 1691, 1596 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ 7.59 (s, 1H), 7.16−7.25 (m, 4H), 5.90 (bs, 1H), 5.19 (m, 1H), 4.27−4.15 (m, 2H), 3.81 (t, J = 9.1 Hz, 1H), 2.92 (d, J = 14 Hz, 1H), 2.72−2.64 (dd, J = 14.5, 9.4 Hz, 1H), 2.42−2.20 (m, 4H), 1.68−1.52 (m, 2H), 1.24 (t, J = 7.1 Hz, 3H), 0.91 (t, J = 7.36 Hz, 3H). ^{13}C NMR (300 MHz, $CDCl_3$) δ 172.7, 162.6, 154.4, 137.6, 128.8, 127.8, 120.6, 84.3, 65.5, 61.7, 54.5, 46.1, 37.0, 28.3, 19.5, 14.1, 13.7. Anal. Calcd for $C_{19}H_{24}ClN_3O_4$: C, 57.94; H, 6.14; N, 10.67. Found: C, 58.23; H, 6.28; N, 10.76. **16**: mp 209 °C. IR (KBr) 3382, 2962, 1737, 1698, 1598, 1544 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ 7.25−7.12 (m, 4H), 6.98 (s, 1H), 5.73 (bs, 1H), 5.17(m, 1H), 4.20 (q, J = 7.1 Hz, 2H), 3.75 (m, 1H), 2.62 (m, 2H), 2.46−2.22 (m, 4H), 1.70−1.53 (m, 2H), 1.25(t, J = 7.1 Hz, 3H), 0.97 (t, J = 7.4 Hz, 3H). ^{13}C NMR (300 MHz, $CDCl_3$) δ 173.6, 161.4, 154.9, 137.0, 129.0, 128.5, 121.0, 84.6, 66.4, 62.2, 54.3, 45.6, 39.2, 28.4, 19.5, 13.9, 13.8. Anal. Calcd for $C_{19}H_{24}ClN_3O_4$: C, 57.94; H, 6.14; N, 10.67. Found: C, 57.89; H, 6.20; N, 10.45.

Ethyl (3a*R,5*S**,6a*S**)-5-[3-(*p*-Fluorophenyl)ureido]-3-propyl-3a,5,6,6a-tetrahydro-4*H*-cyclopenta[*d*]isoxazole-5-carboxylate (17) from 12.** As with **11** → **15**, **12** gave **17** (56%) plus its inseparable diastereomer (6%) as a white solid (0.4 g, 1.06 mmol, 62% combined yield). **17** with its diastereomer: mp 136−137 °C. IR (KBr) 3376, 2960, 1735, 1689, 1556, 1508. cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) a mixture of diastereomers (major) δ 7.56 (s, 1H), 7.27−7.22 (m, 2H), 6.95−6.89 (m, 2H), 5.86 (bs, 1H), 5.19 (dd, J = 9.1, 5.7 Hz, 1H), 4.27−4.16 (m, 2H), 3.80 (t, J = 9.1 Hz, 1H), 2.92−2.88 (d J = 14 Hz, 1H), 2.71−2.63 (dd, J = 14, 9.5 Hz, 1H), 2.42−2.20 (m, 4H), 1.78−1.51(m, 2H), 1.25 (t, J = 7.1 Hz, 3H), 0.91 (t, J = 7.3 Hz, 3H). ^{13}C NMR (300 MHz, $CDCl_3$) a mixture of diastereomers (major) δ 172.4, 162.1, 158.3 (d, J = 242 Hz), 154.4, 134.5, 121.1 (d, J = 7.1 Hz), 114.9 (d, J = 22.3 Hz), 83.8, 65.0, 61.2, 54.1, 45.7, 36.6, 27.8, 19.0, 13.7, 13.3. Anal. Calcd for

$C_{19}H_{24}FN_3O_4$: C, 60.47; H, 6.41; N, 11.13. Found: C, 60.31; H, 6.36; N, 11.12.

(3a*R,5*S**,6a*S**)-Spiro[3-methyl-1-phenyl-4,5,6,6a-tetrahydro-3a*H*-cyclopenta[*d*]isoxazole-4′,5-imidazolidine-2′,5′-dione] (18) from 13.** As with **5** → **7**, **18** (0.063 g, 0.22 mmol, 73%) was obtained as a white solid. **18**: mp 220 °C. IR (KBr) 3347, 2959, 1785, 1713, 1501, 1414 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ 7.49−7.35 (m, 5H), 6.08 (bs, 1H), 5.27 (dd, J = 8.3, 4.8 Hz, 1H), 3.75 (t, J = 9.0 Hz, 1H), 2.63−2.44 (m, 3H), 2.18 (d, J = 15.7 Hz, 1H), 2.06 (s, 3H). ^{13}C NMR (300 MHz, $CDCl_3$) δ 173.8, 158.6, 154.7, 131.3, 129.0, 128.3, 125.9, 86.0, 67.7, 55.1, 45.0, 41.1, 12.1. Anal. Calcd for $C_{15}H_{15}N_3O_3$: C, 63.14; H, 5.29; N, 14.72. Found: C, 63.10; H, 5.32; N, 14.62.

(3a*R,5*S**,6a*S**)-Spiro[1,3-diphenyl-4,5,6,6a-tetrahydro-3a*H*-cyclopenta[*d*]isoxazole-4′,5-imidazolidine-2′,5′-dione] (19) from 14.** As with **5** → **7**, **19** (0.105 g, 30 mmol, 60%) was obtained as a white solid. **19**: mp 245 °C. IR (KBr) 3265, 2972, 1780, 1710, 1500, 1412 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ 7.80−7.26 (m, 10H), 6.05 (bs, 1H), 5.48−5.44 (m, 1H), 4.34−4.28 (m, 1H), 2.80 (dd, J = 14.1, 10.4 Hz, 1H), 2.71−2.57 (m, 2H), 2.33 (dd, J = 14.1, 1.8 Hz, 1H). ^{13}C NMR (300 MHz, $CDCl_3$) δ 174.2, 160.8, 155.0, 131.7, 131.1, 129.5, 128.7, 128.2, 127.5, 127.4, 126.3, 88.1, 68.3, 51.9, 45.2, 42.8. Anal. Calcd for $C_{20}H_{17}N_3O_3$: C, 69.15; H, 4.93; N, 12.09. Found: C, 69.24; H, 4.87; N, 12.08. **(3a*R**,5*S**,6a*S**)-Spiro[3-propyl-1-(*p*-chlorophenyl)-4,5,6,6a-tetrahydro-3a*H*-cyclopenta[*d*]isoxazole-4′,5-imidazolidine-2′,5′-dione] (20) from 15.** As with **5** → **7**, **20** (0.205 g, 0.59 mmol, 78%) was obtained as a white solid. **20**: mp 241 °C. IR (KBr) 3210, 2965, 1778, 1716, 1496, 1403 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ 7.45−7.38 (m, 4H), 6.03 (s, 1H), 5.24(dd, J = 8.2, 4.5 Hz, 1H), 3.77 (dd, J = 9.1, 9.0 Hz, 1H), 2.62−2.14 (m, 6H), 1.73−1.61 (m, 2H), 1.03 (t, J = 7.3 Hz, 3H). ^{13}C NMR (300 MHz, $CDCl_3$) δ 173.6, 162.0, 154.2, 133.9, 130.0, 129.2, 127.0, 85.8, 67.8, 53.8, 44.9, 41.3, 28.7, 19.6, 13.8. Anal. Calcd for $C_{17}H_{18}ClN_3O_3$: C, 58.71; H, 5.21; N, 12.08. Found: C, 58.77; H, 5.27; N, 12.01.

(3a*R,5*S**,6a*S**)-Spiro[3-propyl-1-(*p*-fluorophenyl)-4,5,6,6a-tetrahydro-3a*H*-cyclopenta[*d*]isoxazole-4′,5-imidazolidine-2′,5′-dione] (21) from 17.** As with **5** → **7**, **21** (0.104 g, 0.314 mmol, 80%) was obtained as a white solid. **20**: mp 225 °C. IR (KBr) 3199, 2977, 1774, 1714, 1513, 1415 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ 7.43−7.38 (m, 2H), 7.18−7.12 (m, 2H), 6.06 (s, 1H), 5.25(dd, J = 8.1, 4.5 Hz, 1H), 3.78 (t, J = 8.6 Hz, 1H), 2.62−2.14 (m, 6H), 1.76−1.59 (m, 2H), 1.01 (t, J = 7.3 Hz, 3H). ^{13}C NMR (300 MHz, $CDCl_3$) δ 173.8, 162.0, 161.9 (d, J = 249 Hz), 154.5, 127.7, (d, J = 8.7 Hz), 127.5 (d, J = 2.5 Hz), 116.0 (d, J = 23.1 Hz), 85.9, 67.8, 53.8, 44.9, 41.3, 28.7, 19.6, 13.8. Anal. Calcd for $C_{17}H_{18}FN_3O_3$: C, 61.62; H, 5.48; N, 12.68. Found: C, 61.86; H, 5.47; N, 12.62.

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Supporting Information Available: ^1H NMR/^{13}C NMR and IR spectra for compounds **1**, **2**, **9**, and **15** (12 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.

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