Sequential 1,3-Dipolar Cycloadditions in the Synthesis of Bis-Isoxazolo Substituted Piperidinones

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Received September 8, 1999

A strategy for the efficient synthesis of novel bis-isoxazolo substituted piperidinones has been developed. The protocol consists of the Michael addition of an unsaturated alkoxide to β-nitrostyrene followed by an intramolecular nitrile oxide cycloaddition (INOC) or an intramolecular silyl nitronate olefin cycloaddition (ISOC) to give **III**. Grignard addition to this isoxazoline intermediate followed by DCC coupling of the resulting isoxazolidine with nitroacetic acid gave **II**, and a second intramolecular cycloaddition via 1,3-dipoles result in the formation of the targeted novel tetracycles (**I**). A solid-supported scavenger was employed to increase the efficiency and yield of the Michael addition step.

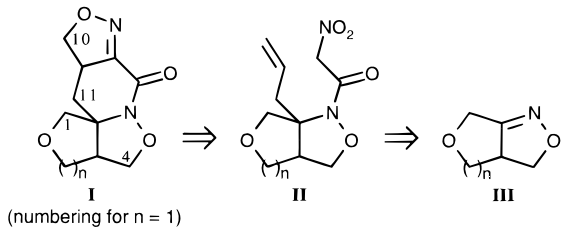
Introduction

Isoxazolidine and isoxazoline heterocycles are commonly found in polycyclic compounds with biological activity. Some examples include the immuno-suppressive cyclolignans[1] and steroidal antiflammatory drugs.[2] There are also numerous examples of these *N*,*O*-heterocycles being used as key building blocks in the total synthesis of natural and unnatural compounds such as β-lactam antibiotics,[3] quinolizidine and indolizine tricycles,[4] testosterone,[5] sarkomycin,[6] and biotin.[7] The potential for control of two (isoxazoline) or three (isoxazolidine) contiguous stereocenters in these heterocycles affords additional synthetic opportunities.

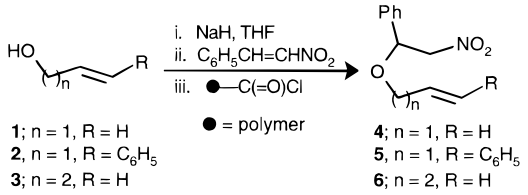
The biological and synthetic utility apparent for isoxazolidine and isoxazoline heterocycles has prompted us to develop a synthetic route to novel polycyclic compounds which incorporate these subfragments. Herein we report the results of that investigation which constitutes a strategic route for the synthesis of isoxazoloisoxazoline-containing tetracyclic targets of general structure **I** (Scheme 1). Enroute, we compare the diastereoselectivity of an intramolecular nitrile oxide olefin cycloaddition (INOC) with a silyl nitronate olefin cycloaddition (ISOC).

Our retrosynthetic approach to **I** engaged furano- or pyranoisoxazolidine **II** (n = 1 or 2, respectively) as the key intermediate which in turn would be derived from furano- or pyranoisoxazoline **III**. The commercial starting points for this plan were *trans*-β-nitrostyrene and allyl alcohols **1**−**3** which collectively deliver **I** with a phenyl substituent on the furan/pyran ring (i.e., **1** and **2** → **I** with a C1 phenyl substituent and n = 1; **3** → **I** with C1 phenyl substituent and n = 2).

Scheme 1. Retrosynthetic Approach to Isoxazoloisoxazoline-Containing Tetracycle I



Scheme 2. Nitroether Formation



Results and Discussion

The first step in the preparation of furano- or pyranoisoxazoline **III** (n = 1 or 2, respectively) is depicted in Scheme 2. Michael addition of excess sodio allyl (**1**), cinnamyl (**2**), or 3-butenyl (**3**) alkoxide to β-nitrostyrene in dry THF at −78 °C affords nitroethers **4**−**6**. We have found that excess sodio or potassio (but not litho) alkoxide effectively avoids the competing Michael addition of the nitronate intermediate to β-nitrostyrene.[8] By employing a polymer-supported acyl chloride as a polymer sponge, this excess alkoxide can be easily removed from the reaction mixture[9] [−C(═O)Cl at 1760 cm^{-1} → −C(═O)OR at 1721 cm^{-1}] to deliver the targeted nitroethers in 75−93% yield.

With these nitroethers in hand, attention was turned to the second step in the preparation of **III** (Scheme 3), the intramolecular 1,3-dipolar cycloaddition reaction. Both the ISOC (intermediacy of silyl nitronate **7** and

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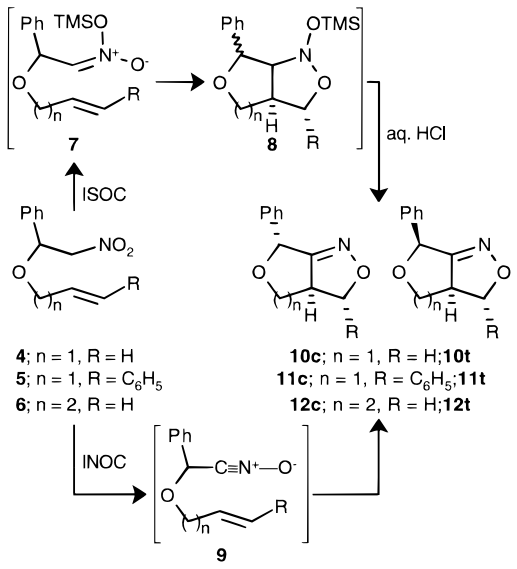
(5) Ihara, M.; Tokunaga, Y.; Fukumoto, K. *J. Org. Chem.* **1990**, *15*, 4497.
(6) Curran, D. P. *J. Am. Chem. Soc.* **1987**, *109*, 5280.
(7) Confalone, P. N.; Pizzolato, G.; Confalone, D. L.; Uskokovic, M. R. *J. Am. Chem. Soc.* **1980**, *102*, 1954.
(8) Duffy, J. L.; Kurth, J. A.; Kurth, M. J. *Tetrahedron Lett.* **1993**, *34*, 1259.
(9) (a) Kaldor, S. W.; Siegel, M. G.; Fritz, J. E.; Dressman, B. A.; Hahn, P. J. *Tetrahedron Lett.* **1996**, *37*, 7193. (b) Bunin, B. A. *The Combinatorial Index*; Academic Press: San Diego; p 275.

10.1021/jo991418m CCC: $19.00
Published on Web 12/29/1999

Scheme 3. ISOC vs INOC Stereoselectivity



N-silyloxy isoxazolidine **8**) and INOC (intermediacy of nitrile oxide **9**) reactions of nitroether **4** have been reported.[10] In our hands, the INOC of **4** delivers **10** as a 9:1 mixture of *cis* and *trans* furanoisoxazolines **10c** and **10t**, respectively, in 88% combined yield. This result was obtained utilizing 1,4-phenylene diisocyanate as the dehydrating agent as we have found that the resulting urea polymer can be removed by simple filtration[11] whereas the use of the more standard phenyl isocyanate Mukayiyama dehydrating agent[12] requires a difficult chromatographic removal of the phenyl urea byproduct.[13]

We next investigated the ISOC and INOC reactions of nitroether **5** and found that the stereoselectivity paralleled that of **4**. That is, the ISOC on **5** gave **11c** (and a trace of **11t**) in 82% combined, while the INOC on **5** gave **11c** and **11t** in a 6:1 ratio, respectively (75% combined yield). Thus, with nitroether **5**, the INOC requires a longer reaction time and a higher temperature than the corresponding ISOC. With these substrates **4** and **5**, the INOC is not as effective as the ISOC in the construction of furanoisoxazolines. In contrast, the ISOC and INOC stereoselectivities with nitroether **6**, which now delivers pyranoisoxazolines, were quite different. Here, the ISOC on **6** gave **12c** and **12t** in a 1:1 ratio, respectively (40% combined yield), while the INOC reaction on **6** gave essentially only **12t** (**12c**:**12t** = 3:97) in 77% yield. Our rationale for these results with **6** is summarized in

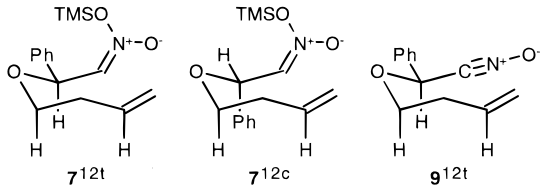


Figure 1. ISOC vs INOC for **6** → **12**.

Scheme 4. Preparation of Isoxazolidines II

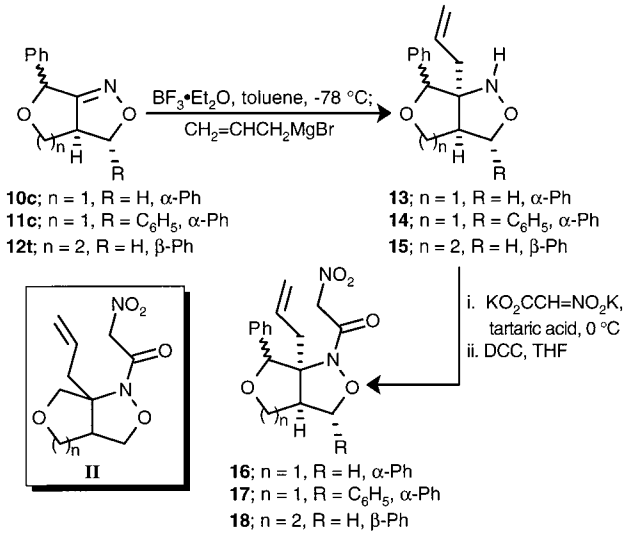


Figure 1. ISOC **6** → **12** is disfavored by a "TMSO || Ph" nonbonding interaction in intermediate conformation $\mathbf{7}^{12t}$ or by "Ph axial interactions" in $\mathbf{7}^{12c}$. As a result, ISOC **6** → **12** is an ineffective (40% yield) and nonselective (1:1 product ratio) transformation. In contrast, the linear nitrile oxide intermediate $\mathbf{9}^{12t}$ which is operative in INOC **6** → **12** avoids both of these destabilizing interactions and is both effective (77% yield) and stereoselective (94% de).

With routes to furanoisoxazolines and pyranoisoxazolines in hand, attention was directed toward the conversion of **III** to furano- and pyranoisoxazolidines **II** (Scheme 4). Not surprisingly, the isoxazoline ring of **III** is quite unreactive toward carbon nucleophiles.[14] Reports of oxime activation by Lewis acid complexation[15] led us to pretreat a toluene solution of furanoisoxazoline **10c** with boron trifluoride etherate at −78 °C. Subsequent addition of an ethereal solution of allylmagnesium bromide delivered furanoisoxazolidine **13** with no evidence of the C6a-epimer in the crude reaction mixture (88% yield). Likewise, furanoisoxazoline **11c** and pyranoisoxazoline **12t** gave only *cis*-fused allyl addition products **14** (80% yield) and **15** (80% yield), respectively.

Next, the nitroacetamide moiety in isoxazolidines **16**−**18** was introduced by a DCC-mediated *N*-acylation of **13**−**15**. Nitroacetic acid, which was generated by treatment of nitromethane with potassium hydroxide (formation of the dipotassium salt of nitroacetic acid) followed by treatment with tartaric acid,[16] and DCC were added to an ice-cold, dry THF solution of isoxazolidines **13**−**15**.

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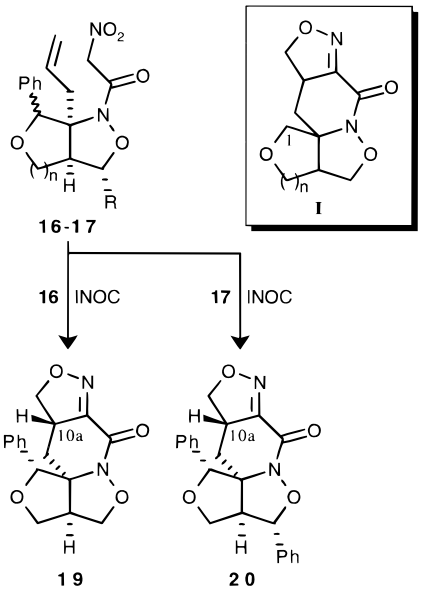
Scheme 5. Preparation of Bis-Isoxazolo Substituted Piperidonone I



Filtration and flash column chromatography removed the DCU byproduct leading to crystalline nitroacetamides **16**−**18** in excellent yield (86−90%).

The phenylisocyanate-mediated dehydration of nitroacetates is known to deliver the corresponding nitrile oxide [i.e., $ROC(=O)CH_2NO_2 + PhNCO \rightarrow ROC(=O)C{\equiv}N^+-O^-$].[17] Drawing on this precedent, we were optimistic that a similar dehydration of the nitroacetamide moiety in isoxazolidines **16**−**18** would deliver the analogous amido nitrile oxide. Indeed, we were pleased to find that treatment of nitroacetamide **16** with our modified Mukaiyama protocol of 1,4-phenylene diisocyanate instead of phenyl isocyanate produced (furoisoxazolidino)isoxazolopiperidinone **19** as the sole product in 65% yield. Conformational biases clearly dictate complete facial selectivity for this INOC reaction. In similar fashion, the INOC of nitroacetamide **17** delivered (furoisoxazolidino)-isoxazolopiperidinone **20**, again as the sole product. Thus, in the reaction sequence beginning with nitroether **5**, the lone stereocenter of this starting material played forward by a highly stereoselective ISOC reaction on **5**, a completely stereoselective Grignard addition to **11c**, and a completely stereoselective INOC reaction on **17**, rendering heterocycle **20** as the sole product. INOC reactions of **16** and **17** produced none of the C10a-epimeric cycloaddition products of **19** and **20** (Scheme 5**)**.

In conclusion, we have reported an efficient and highly stereoselective route to novel bis-isoxazolo substituted pyridinone tetracycles of general structure **I**. The reaction sequence consists of alkoxide Michael addition to *β*-nitrostyrene, INOC or ISOC to give furano- or pyranoisoxazolines (**III**), facial-selective Grignard addition to the oxime moiety in **III**, *N*-acylation of the resulting furano- or pyranoisoxazolidines with nitroacetic acid to give **II**, and INOC or ISOC to give **I**.

Experimental Section

General Experimental. Unless otherwise noted, starting materials were obtained from commercial suppliers and used as received. All reactions were carried out under nitrogen atmosphere. Tetrahydrofuran (THF) was distilled under nitrogen from potassium/benzophenone immediately prior to use. Benzene and toluene were distilled under nitrogen from sodium immediately prior to use. Triethylamine was distilled under nitrogen from calcium hydride immediately prior to use. Silica gel chromatography was performed according to the method of Still.[18] All melting points are uncorrected.

1-(Allyloxy)-2-nitrophenylethane (4).[19] A three-necked 50 mL round-bottom flask equipped with a magnetic stir bar was charged with NaH (160 mg, 4 mmol, 60% in mineral oil), and the oil was removed by washing with dry hexane (5 × 3 mL). The resulting solid NaH was dried under vacuum, and the flask was flushed with nitrogen and charged with dry THF (20 mL). Allyl alcohol (300 μL, 4 mmol) was added slowly via syringe, and the mixture was allowed to stir for 1 h at room temperature. The solution was cooled to −78 °C, and nitrostyrene (290 mg, 2 mmol) in dry THF (5 mL) was added via syringe pump at a rate of 510 μL per minute. After an additional 1 h at −78 °C, the mixture was warmed to 0 °C. Polymer-supported acyl chloride (1.3 g, 2 mmol) was added in portions, and the solution was stirred at for 2 h at 0 °C. The mixture was quenched with 1 N HCl (20 mL) and filtered to remove the polymer. The aqueous layer was separated and extracted with ethyl ether (3 × 10 mL). The combined organic washes were washed with saturated $NaHCO_3$ and brine, dried ($MgSO_4$), filtered, and concentrated by rotatory evaporation to give **4** (330 mg, 1.6 mmol, 80%) as a yellow oil which was used in the next step without further purification: ^{1}H NMR δ 3.81 (dd, J = 13, 6 Hz, 1H), 3.98 (dd, J = 13, 5 Hz, 1H), 3.98, 4.39 (dd, J = 13, 3 Hz, 1H), 4.63 (dd, J = 13, 10 Hz, 1H), 5.16 (m, 3H), 5.82 (m, 1H), 7.38 (m, 5H); ^{13}C NMR δ 69.9, 76.7, 77.5, 80.3, 117.3, 126.8, 128.9, 133.8, 136.5; IR (neat) 3081, 3031, 2923, 2865, 1558, 1380, 1100 cm^{-1}.

1-(Cinnamyloxy)-2-nitro-1-phenylethane (5).[19] The procedure described for the preparation of **4** was employed with the following reagents and quantities: NaH (5 g, 125 mmol; 60% in mineral oil), cinnamyl alcohol (18 g, 134 mmol), and nitrostyrene (8.9 g, 59.4 mmol). Workup and column chromatography (hexane/ethyl acetate 10:1) gave **5** (15 g, 55.4 mmol, 93%) as a yellow oil: ^{1}H NMR δ 3.97 (ddd, J = 13, 7, 1 Hz, 1H), 4.13 (ddd, J = 13, 6, 1 Hz, 1H), 4.37 (dd, J = 13, 3 Hz, 1H), 4.64 (dd, J = 13, 10 Hz, 1H), 5.17 (dd, J = 10, 3 Hz, 1H), 6.18 (m, 1H), 6.50 (d, 16 Hz, 1H), 7.33 (m, 10 H); ^{13}C NMR δ 69.5, 76.8, 77.3, 80.3, 125.0, 126.6, 126.9, 127.8, 128.6, 129.1, 133.0, 136.3, 136.5; IR (thin film) 3030, 2920, 2860, 1556, 1381, 1103 cm $^{-1}$.

1-(But-3-enyloxy)-2-nitro-1-phenylethane (6).[19] The procedure described for the preparation of **4** was employed with the following reagents and quantities: NaH (2 g, 50 mmol; 60% in mineral oil), 3-buten-1-ol (4 mL, 46.50 mmol), and nitrostyrene (3 g, 19.80 mmol). Workup gave **6** (4 g, 18.10 mmol, 93%) as a yellow oil which was used in the next step without further purification: ^{1}H NMR δ 2.30 (m, 2H), 3.42 (m, 2H), 4.37 (dd, J = 13, 3 Hz, 1H), 4.60 (dd, J = 13, 10 Hz, 1H), 5.02 (m, 3H), 5.74 (m, 1H), 7.38 (m, 5H); ^{13}C NMR δ 33.8, 68.9, 78.5, 80.4, 116.4, 126.6, 128.9, 128.9, 134.6, 136.8, IR (thin film) 3074, 3034, 2916, 2872, 1556, 1380, 1107 cm $^{-1}$.

General Procedure for INOC. A 250 mL round-bottom flask equipped with a magnetic stir bar was charged with nitroether, dry benzene, 1,4-phenylene diisocyanate (3 equiv), and a catalytic amount of triethylamine (3 drops). The resulting solution was stirred under a blanket of nitrogen at room temperature for 3 d at which time additional 1,4-phenylene diisocyanate (1 equiv) was added. The mixture was then refluxed for 1 d, quenched with water (10 mL), and stirred at 70 °C for 3 h. Polymeric phenylurea was removed by filtration and washed with diethyl ether. The combined organic washes were washed with brine, dried ($MgSO_4$), filtered, and concentrated by rotatory evaporation. Column chromatography afforded the desired isoxazoline.

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General Procedure for ISOC. A 100 mL round-bottom flask equipped with a magnetic stir bar was charged with nitroether, dry benzene, chlorotrimethylsilane (3 equiv), and triethylamine (3 equiv). The resulting solution was stirred under a blanket of nitrogen at room temperature for 2 d at which time 1 N aq HCl was added. Rapid stirring was continued for an additional 1 h at room temperature at which time the layers were separated, and the aqueous layer was extracted with diethyl ether (3 × 20 mL). The combined organic washes were washed with brine, dried ($MgSO_4$), filtered, concentrated by rotatory evaporation, and purified by column chromatography.

6-Phenyl-3a,6-*trans*-3,3a-dihydro-4*H*,6*H*-furo[3,4-*c*]-isoxazole (10c).[20] The INOC procedure described above was employed with the following reagents and quantities: nitroether **4** (3 g, 15 mmol), dry benzene (100 mL), 1,4-phenylene diisocyanate (5.3 g, 33.10 mmol), catalytic amount of triethylamine (3 drop), and additional 1,4-phenylene diisocyanate (2.4 g, 15 mmol $T_0 + 24$ h). Column chromatography (hexane/ethyl acetate 3:1) afforded **10c** as a white solid (1.5 g, 7.98 mmol, 53%): $R_f = 0.31$, mp 77−78 °C; ^{1}H NMR δ 3.74 (m, 1 H), 4.00 (m, 1H), 4.17 (m, 1 H), 4.36 (m, 1 H), 4.52 (m, 1 H), 5.55 (s, 1 H), 7.35 (m, 5 H); ^{13}C NMR δ 54.6, 69.9, 73.1, 73.6, 125.8, 128.4, 128.7, 137.8, 170.0; IR (CH_2Cl_2) 3006, 2914, 2862, 1458, 1009 cm^{-1}.

3,6-Diphenyl-3,3a-*trans*-3a,6-*trans*-3,3a-dihydro-4*H*,6*H*-furo[3,4-*c*]isoxazole (11c).[19] The ISOC procedure described above was employed with the following reagents and quantities: nitroether **5** (2.7 g, 9.51 mmol), dry benzene (50 mL), chlorotrimethylsilane (4.20 mL, 33.09 mmol), and triethylamine (4.60 mL, 33 mmol). The resulting solution was stirred under a blanket of nitrogen at room temperature for 2 d at which time 1 N HCl (32 mL) was added. Column chromatography (hexane/ethyl acetate 5:1) afforded **11c** as a pale yellow oil (2.1 g, 7.91 mmol, 82%): $R_f = 0.30$; ^{1}H NMR δ 3.99 (dd, J = 9, 8 Hz, 1H); 4.22 (m, 1H), 4.43 (t, $J = 8$, 1H), 5.52 (d, J = 12 Hz, 1H), 5.64 (s, 1H), 7.38, (m, 10H); ^{13}C NMR δ 60.3, 69.4, 73.2, 89.0, 125.6, 126.6, 128.4, 128.7, 136.8, 137.3, 170.9; IR (thin film) 3062, 3032, 2873, 1456, 1022 cm^{-1}.

7-Phenyl-3a,7-*cis*-3,3a,4,5-tetrahydro-7*H*-pyran[3,4-*c*]-isoxazole (12t).[19] The INOC procedure described above was employed with the following reagents and quantities: nitroether **6** (3.6 g, 16.36 mmol), dry benzene (100 mL), 1,4-phenylene diisocyanate (7.9 g, 49.08 mmol), catalytic amount of triethylamine (3 drop), and additional 1,4-phenylene diisocyanate (2.6 g, 16.36 mmol $T_0 + 24$ h**)**. Column chromatography (hexane/ethyl acetate 3:1) afforded **12t** as a white solid [2.6 g, 12.59 mmol, 77%; $R_f = 0.25$; mp 88−89 °C; ^{1}H NMR δ 1.91 (m, 1H), 2.21 (m, 1H), 3.51 (m, 1H), 3.73 (m, 1H), 3.83 (dd, J = 12, 8 Hz, 1H), 4.21 (m, 1H), 4.64 (dd, J = 10, 8 Hz, 1H), 5.11 (s, 1H), 7.39 (m, 5H); ^{13}C NMR δ 33.0, 46.6, 66.5, 73.8, 77.2, 127.6, 128.1, 128.4, 136.7, 158.2; IR (thin film) 3032, 2927, 2856, 1454, 1070 cm^{-1}].

6a-Allyl-3a,6a-*cis*-6-phenyl-3a,6-*trans*-3,3a-dihydro-1*H*,4*H*,6*H*-furo[3,4-*c*]isoxazole (13). A toluene (100 mL) solution of **10c** (1.7 g, 8.83 mmol) was cooled to −78 °C under a blanket of nitrogen, and boron triflouride etherate (3.40 mL, 27.6 mmol) was added over 10 min via syringe pump. Upon complete addition, the solution was stirred for an additional 30 min at which time allylmagnesium bromide (1 M in diethyl ether; 28.0 mL, 28.0 mmol) was added at −78 °C over 20 min via syringe pump. The resulting mixture was stirred for 24 h with gradual warming to room temperature. The reaction was quenched by a slow addition of water (5 mL), and the aqueous layer was separated and extracted with diethyl ether (3 × 50 mL). The combined organic extracts were washed with brine, dried ($MgSO_4$), filtered, and concentrated by rotatory evaporation. Column chromatography (hexane/ethyl acetate 3:1) afforded isoxazolidine **13** as a colorless oil (1.8 g, 7.76 mmol, 88%): $R_f = 0.32$; ^{1}H NMR δ 1.64 (dd, J = 15, 9 Hz, 1H), 2.07 (dd, J = 15, 6, 1H), 3.01 (q, J = 14, 8 Hz, 1H), 3.53 (dd, J = 9, 6, 1H), 3.62 (t, J = 9 Hz, 1H), 3.98 (d, J = 9 Hz, 1H), 4.64 (t, J = 9 Hz, 1H), 4.66 (s, 1H), 4.99 (dd, J = 17, 1 Hz, 1H), 5.07 (s, 1H), 5.13 (dd, J = 10, 1 Hz, 1H), 5.60 (m, 1H), 7.33 (m, 5H); ^{13}C NMR δ 34.9, 51.7, 72.5, 77.0, 78.2, 86.5, 120.6, 125.9, 127.3, 127.8, 131.9, 137.6; IR (thin film) 3214, 3032, 2929, 2856, 1063 cm^{-1}. Anal. Calcd for $C_{14}H_{17}NO_2$: C, 72.70; H, 7.41; N, 6.06. Found: C, 72.52; H, 7.39; N, 5.84.

6a-Allyl-3a,6a-*cis*-3,6-diphenyl-3,3a-*trans*-3a,6-*trans*-3,3a-dihydro-1*H*,4*H*,6*H*-furo[3,4-*c*]isoxazole (14). The procedure described for the preparation of **13** was employed with the following reagents and quantities: isoxazoline **11c** (2.5 g, 9.50 mmol), dry toluene (100 mL), boron triflouride etherate (3.60 mL, 29.27 mmol), and allylmagnesium bromide (1 M in diethyl ether; 30 mL, 30 mmol). Column chromatography (hexane/ethyl acetate 8:1) afforded **14** as a colorless oil (2.3 g, 7.60 mmol, 80%): $R_f = 0.30$; ^{1}H NMR δ 1.58 (dd, J = 15, 9 Hz, 1H), 1.99 (dd, J = 15, 6 Hz, 1H), 3.30 (t, J = 8 Hz, 1H), 3.74 (t, J = 8 Hz, 1H), 4.67 (m, 3H), 4.85 (s, 1H), 5.01 (m, 1H), 5.17 (s, 1H), 5.49 (m, 1H), 7.33, (m, 10H); ^{13}C NMR δ 35.0, 58.2, 72.9, 79.4, 86.1, 88.4, 119.5, 125.3, 126.0, 127.4, 127.5, 127.9, 128.8, 131.8, 137.5, 139.2; IR (thin film) 3086, 3029, 2847, 1065, cm^{-1}.

7a-Allyl-3a,7a-*cis*-7-phenyl-3a,7-*cis*-3,3a,4,5-tetrahydro-1*H*,7*H*-pyrano[3,4-*c*]isoxazole (15). The procedure described for the preparation of **13** was employed with the following reagents and quantities: isoxazoline **12t** (2.4 g, 11.66 mmol), dry toluene (100 mL), boron triflouride etherate (4.40 mL, 38.28 mmol), and allylmagnesium bromide (1 M in diethyl ether; 35 mL, 35 mmol). Column chromatography (hexane/ethyl acetate 2:1) afforded **15** as a colorless oil (2.3 g, 9.33 mmol, 80%): $R_f = 0.30$; ^{1}H NMR δ 1.84 (m, 2H), 2.49 (m, 2H), 2.78 (m, 1H), 3.69 (m, 2H), 4.09 (m, 2H), 4.66 (s, 1H), 5.13 (m, 2H), 5.90 (m, 2H), 7.31 (m, 5H); ^{13}C NMR δ 27.0, 38.6, 41.9, 66.1, 66.9, 74.1, 79.7, 119.4, 127.8, 128.2, 133.0, 137.4; IR (thin film) 3219, 3032, 2931, 2873, 1097 cm^{-1}. Anal. Calcd for $C_{15}H_{19}NO_2$: C, 73.44; H, 7.81; N, 5.71. Found: C, 73.08; H, 7.82; N, 5.64.

6a-Allyl-3a,6a-*cis*-1-(α-nitroacetyl)-6-phenyl-3a,6-*trans*-3,3a-dihydro-4*H*,6*H*-furo[3,4-*c*]isoxazole (16). A 500 mL Erlenmeyer flask equipped with a magnetic stir bar was charged with potassium hydroxide (226 g, 4.02 mol) and water (300 mL). The solution was cooled to room temperature, nitromethane (60 g, 983 mmol) was added dropwise over 1.5 h, and the solution was refluxed until crystals appeared. Upon cooling to room temperature, the light yellow crystals were collected by filtration and either used immediately or stored in the refrigerator to prevent decomposition.

To the nitroacetic acid dipotassium salt (3 g, 71.37 mol) was added ice cold water (10 mL), and the solution was then cooled to −8 °C (dry ice/ethanol). Tartaric acid (21.43 g, 142.8 mmol dissolved in 40 mL of water) was added over a period of 20 min at which time the mixture was filtered and the mother liquor was extracted with ice cold diethyl ether (5 × 30 mL). The combined organic washes were dried (Na_2SO_4) and concentrated by rotatory evaporation (at room temperature) to afford a yellow oil which was dissolved in chloroform (1 mL), concentrated again, and dried under high vacuum at 0 °C for 6 h to afford pale yellow crystals (67−70% by mass) which was used immediately without purification.

A 250 mL round-bottom flask equipped with a magnetic stir bar was charged with **13** (620 mg, 2.69 mmol) and dry cold THF (100 mL). This solution was cooled to 0 °C, and DCC (700 mg, 3.39 mmol) and freshly prepared nitroacetic acid (340 mg, 3.24 mmol) were added. After 24 h at 0 °C, additional DCC (1.2 g, 5.96 mmol) and nitroacetic acid (614 mg, 5.84 mmol) were added and stirring was continued for an additional 24 h from 0 °C to room temperature. The mixture was then filtered to remove DCU. Column chromatography (hexane/ethyl acetate 3:2) and subsequent recrystallization with hot ethyl acetate/hexane afforded **16** as colorless crystals (730 mg, 2.30 mmol, 86%): $R_f = 0.25$, mp 124−125 °C; ^{1}H NMR δ 1.81 (dd, J = 15, 8 Hz, 1H), 2.80 (dd, J = 15, 6 Hz, 1H), 3.24 (m, 1H), 3.75 (t, J = 9 Hz, 1H), 3.90 (d, J = 8 Hz, 1H), 4.00 (dd, J = 9, 5 Hz, 1 H), 4.48 (t, J = 8 Hz, 1H), 5.06 (d, J = 17 Hz, 1H), 5.07 (s, 1 H), 5.12 (d, J = 10 Hz, 1H), 5.25 (d, J = 14 Hz, 1H),

(20) Hassner, A.; Murthy, K. S. K.; Padwa, A.; Chiacchio, U.; Dean, D. C.; Schoffstall, A. M. *J. Org. Chem.* **1989**, *54*, 5277.

5.33 (d, $J = 14$ Hz, 1H), 5.63 (m, 1 H), 7.36 (m, 5 H); ^{13}C NMR δ 36.1, 54.2, 70.4, 71.6, 78.1, 82.8, 120.0, 127.1, 127.9, 128.0, 131.8, 136.5, 155.0; IR (CH_2Cl_2) 2360, 2336, 1671, 1559, 1375, 1066 cm^{-1}. Anal. Calcd for $C_{16}H_{18}N_2O_5$: C, 60.37; H, 5.70; N, 8.80. Found: C, 60.12; H, 5.67; N, 8.70.

6a-Allyl-3a,6a-*cis*-1-(α-nitroacetyl)-3,6-diphenyl-3,3a-*trans*-3a,6-*trans*-3,3a-dihydro-4*H*,6*H*-furo[3,4-*c*]isoxazole (17). The procedure described for the preparation of **16** was employed with the following reagents and quantities: isoxazolidine **14** (850 mg, 2.77 mmol), dry THF (35 mL), DCC (900 mg, 4.32 mmol; T_0 + 24 h 590 mg, 2.86 mmol), and nitroacetic acid (420 mg, 3.99 mmol; T_0 + 24 h 330 mg, 3.14 mmol). Column chromatography (hexane/methylene chloride 5:1) and subsequent recrystallization with hot ethyl acetate/hexane afforded **17** as colorless crystals (1.2 g, 3.67 mmol, 90%): $R_f = 0.25$; mp 129−130 °C; ^{1}H NMR δ 1.76 (dd, $J = 15$, 8 Hz, 1H), 2.87 (dd, $J = 15$, 6 Hz, 1H), 3.31 (dd, $J = 9$, 5 Hz, 1H), 4.13 (d, $J = 10$ Hz, 1H), 4.29 (dd, $J = 10$, 5 Hz, 1H), 5.11 (m, 3H), 5.31 (d, $J = 14$ Hz, 1H), 5.40 (d, $J = 14$ Hz, 1H), 5.69 (s, 1H), 5.72 (m, 1H), 7.40, (m, 10H); ^{13}C NMR δ 36.8, 61.7, 68.5, 76.6, 80.1, 86.8, 87.8, 120.2, 126.8, 127.0, 127.7, 128.1, 129.0, 129.6, 132.6, 134.5, 137.8, 155.1; IR (CH_2Cl_2) 2850, 2837, 1672, 1560, 1374, 1037 cm^{-1}. Anal. Calcd for $C_{22}H_{22}N_2O_5$: C, 66.99; H, 5.62; N, 7.10. Found: C, 66.82; H, 5.62; N, 7.11.

7a-Allyl-3a,7a-*cis*-1-(α-nitroacetyl)-7-phenyl-3a,7-*cis*-3,3a,4,5-tetrahydro-7*H*-pyrano[3,4-*c*]isoxazole (18). The procedure described for the preparation of **16** was employed with the following reagents and quantities: isoxazolidine **15** (300 mg, 1.22 mmol), dry THF (50 mL), DCC (379 mg, 1.84 mmol; T_0 + 24 h, additional DCC was added; 251 mg, 1.22 mmol), and nitroacetic acid (200 mg, 1.90 mmol; T_0 + 24 h, additional nitroacetic acid was added; 128 mg, 1.22 mmol). Column chromatography (hexane/methylene chloride 3:1) and subsequent recrystallization with hot ethyl acetate/hexane afforded **18** as colorless crystals (365 mg, 1.09 mmol, 90%): $R_f = 0.33$; mp 120−121 °C; ^{1}H NMR δ 1.88 (m, 1H), 2.11 (m, 1H), 2.61 (dd, $J = 14$, 9 Hz, 1H), 3.09 (m, 2H), 4.04 (m, 4H), 4.52 (s, 1H), 4.91 (d, $J = 14$ Hz, 1H), 5.20 (d, $J = 14$ Hz, 1H), 5.24 (m, 2H), 5.72 (m, 1H), 7.32, (s, 5H); ^{13}C NMR δ 21.8, 36.7, 42.9, 62.6, 69.7, 72.2, 80.4, 120.8, 127.3, 128.0, 128.4, 132.0, 137.2, 144.1, 156.5; IR (CH_2Cl_2) 2873, 2844, 1673, 1549, 1377, 1055 cm^{-1}. Anal. Calcd for $C_{17}H_{20}N_2O_5$: C, 61.43; H, 6.06; N, 8.43. Found: C, 61.29; H, 6.05; N, 8.41.

1-Phenyl-1,3a-*trans*-3a,10a-*trans*-3a,11a-*cis*-3,3a-dihydro-1*H*-furo[3′,4′:3,4]isoxazolidino[3,2-*f*]-10,10a-dihydroisoxazolo[3,4-*c*]piperidin-7-one (19). The INOC procedure described above was employed with the following reagents and quantities: nitroester **16** (567 mg, 1.78 mmol) dry benzene (15 mL), 1,4-phenylene diisocyanate (600 mg, 3.75 mmol), a catalytic amount of triethylamine (3 drops), and additional 1,4-phenylene diisocyanate (T_0 + 3 d; additional diisocyanate was added; 285 mg, 1.78 mmol). Afterward, the mixture was filtered and concentrated by rotatory evaporator. Column chromatography (ethyl acetate) afforded **19** as a white solid (348 mg, 1.16 mmol 65%): $R_f = 0.35$; mp 265−266 °C; ^{1}H NMR δ 1.81 (dd, $J = 13$, 13 Hz, 1H), 2.29 (m, 1H), 2.59 (dd, $J = 13$, 5 Hz, 1H), 3.09 (m, 1H), 3.69 (dd, $J = 13$, 8 Hz, 1H), 3.79 (dd, $J = 9$, 8 Hz, 1H), 4.17 (s, 1H), 4.18 (d, $J = 3$ Hz, 1H), 4.25 (dd, $J = 10$, 9 Hz, 1H), 4.53 (t, $J = 9$ Hz, 1H), 4.65 (s, 1H), 7.40 (m, 5 H); ^{13}C NMR δ 33.2, 41.8, 56.1, 72.0, 76.0, 78.0, 85.4, 126.7, 128.7, 129.1, 135.3, 152.4, 154.0; IR (CH_2Cl_2) 2995, 2873, 1701, 1456 cm^{-1}. Anal. Calcd for $C_{16}H_{16}N_2O_4$: C, 63.99; H, 5.37; N, 9.33. Found: C, 64.08; H, 5.49; N, 9.35.

1,4-Diphenyl-1,3a-*trans*-3a,4-*trans*-3a,10a-*trans*-3a,11a-*cis*-3,3a-dihydro-1*H*-furo[3′,4′:3,4]isoxazolidino[3,2-*f*]-10,10a-dihydroisoxazolo[3,4-*c*]piperidin-7-one (20). The INOC procedure described above was employed with the following reagents and quantities: nitroester **17** (275 mg, 0.697 mmol) dry benzene (10 mL), 1,4-phenylene diisocyanate (400 mg, 2.50 mmol), a catalytic amount of triethylamine (3 drops), and additional 1,4-phenylene diisocyanate (T_0 + 3 d; additional diisocyanate was added; 112 mg, 0.697 mmol). Afterward, the mixture was filtered, and concentrated by rotatory evaporator. Column chromatography (ethyl acetate) afforded **20** as colorless crystals (178 mg**,** 0.453 mmol 65%): $R_f = 0.30$; mp 231−232 °C; ^{1}H NMR δ 1.58 (dd, $J = 13$, 13 Hz, 1H), 2.18 (m, 1H), 2.57 (dd, $J = 13$, 5 Hz, 1H), 3.13 (m, 1H), 3.58 (dd, $J = 13$, 8 Hz, 1H), 4.14 (dd, $J = 10$, 6 Hz, 1H), 4.23 (dd, $J = 10$, 8 Hz, 1H), 4.69 (dd, $J = 9$, 9 Hz, 1H), 4.89 (s, 1H), 5.48 (d, $J = 3$ Hz, 1H), 7.40 (m, 10H); ^{13}C NMR δ 45.9, 55.0, 75.7, 85.4, 89.5, 90.8, 97.8, 103.2, 138.6, 139.8, 141.9, 142.2, 142.4, 142.5, 142.8, 148.3, 164.4, 165.6; IR (CH_2Cl_2) 2922, 2884, 1680, 1457 cm^{-1}. Anal. Calcd for $C_{22}H_{20}N_2O_4$: C, 70.20; H, 5.36; N, 7.44. Found: C, 70.32; H, 5.40; N, 7.38.

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

Supporting Information Available: Copies of ^{1}H NMR, ^{13}C NMR, and IR spectra for compound **14** . This material is available free of charge via the Internet at http://pubs.acs.org.

JO991418M