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Synthesis of polysubstituted pyrroles from sulfinimines (*N*-sulfinyl imines)

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Abstract

Polysubstituted 2-carboxylate and 2-phosphonate pyrroles are prepared by aromatization of the corresponding 3-oxo 2-carboxylate and 2-phosphonate NH-pyrrolidines using air. Reaction of electrophiles with 3-oxo pyrrolidine dianions readily introduces substituents, regioselectively at C-4 in these pyrrolidines.

Keywords

pyrroles; aromatization; dianions; *N*-sulfinyl imines

1. Introduction

The current focus of our research efforts is the design and synthesis of sulfinimine-derived building blocks, templates, and scaffolds for the asymmetric synthesis of nitrogen heterocycles.^{1,2} In this context we reported the synthesis of *N*-sulfinyl δ -amino β -ketoesters **1**³ and *N*-sulfinyl δ -amino β -ketophosphonates **2**⁴ for the asymmetric synthesis of 3-oxo pyrrolidine 2-carboxylates **3**⁵ and 3-oxo pyrrolidine 2-phosphonates **4**,⁶ respectively (Scheme 1).¹ The oxo pyrrolidines **3** were elaborated to *cis*-5-substituted prolines^{5a,b} and the anti-fungal alkaloid (+)-preussin.^{5c} Pyrrolidine 2-phosphonates **4** were transformed into *cis*-5-substitute pyrrolidine 2-phosphonates (proline surrogates)⁶ and into polyfunctionalized pyrrolidines, including the ant alkaloid pyrrolidine 225C.⁷ We describe here details of a new method for preparing polysubstituted pyrroles **5** from **4**. The advantage of this methodology is that electrophiles can be regioselectively introduced at C-4 of **3** and **4** via the corresponding dianions and that aromatization is accomplished at room temperature under non-aqueous conditions. Pyrroles are heterocyclic compounds that exhibit a broad range of biological properties including antibacterial, antiviral, antitumor, anti-inflammatory, and antioxidant activities.⁸ They are also important intermediates in the synthesis of natural products.⁹ For these reasons many methods have been devised for their preparation, which include the classical Hantzsch, Knorr, and Paal-Knorr procedures.¹⁰ While newer methods provide access to ring substitute examples, their synthesis continues to be a challenge.^{11,12} Some of these newer procedures involve aromatization of stable preformed pyrrolidines.¹³ Although phosphonopyrrolidines have been examined as HIV protease inhibitors,¹⁴ only a few procedures have been reported for their preparation.^{11,15} Furthermore, much less is known concerning the properties of phosphonopyrroles, undoubtedly due to the fact that there is no general method for their preparation.^{11,16}

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2. Results and discussion

2.1. Synthesis of 3-oxo pyrrolidines

cis-3-Oxo pyrrolidine 2-carboxylates **13** and *cis*-3-oxo pyrrolidine 2-phosphonates **14** were prepared as previously described using the highly diastereoselective intramolecular metal carbenoid NH insertion reaction of *N*-Boc δ -amino α -diazo β -ketoesters and phosphonates **11** and **12**, respectively (Scheme 2).^{5,6,7} While a number of these compounds were originally prepared as pure diastereoisomers from the corresponding enantiopure sulfinimines (*p*-Tolyl-S(O)N=CHR), this is not necessary.¹⁷ Racemic sulfinimines are readily available from the corresponding racemic sulfinamide (*p*-Tolyl-S(O)NH₂) prepared using the procedure described by Garcia Ruano and co-workers.¹⁸

2.2. Synthesis of 4-substituted 3-oxo 2,5-disubstituted pyrrolidines

The presence of the 3-oxo group in **13** and **14** provides an avenue for functionalization of these building blocks via the corresponding 2,4-carbonyl dianions.¹⁹ Regioselective reaction of electrophiles at the C-4 carbanions of **13/14** is expected because of the lower nucleophilicity and steric hindrance of the C-2 β -dicarbonyl anion. Optimized yields of products were obtained when the dianions were generated by treatment of **13/14** with 3 equiv of LDA at -78°C . At this temperature 1.5 equivalents of the appropriate electrophiles (E^+) were added (Scheme 3). In each case only a single regioisomer was detected resulting in exclusive reaction at C-4 affording **15** and **16** in moderate to good yields (Table 1).²⁰ However, attempts to introduce a hydroxy group at C-4 in **13a** ($\text{R} = \text{Ph}$) using 8.8-(dichlorocamphorsulfonyl)oxaziridine (Oxaz)²¹ and a benzyl group at C-4 in **13c** ($\text{R} = t\text{-Bu}$) were unsuccessful and likely due to increased steric demands of oxaziridine and the pyrrolidine. These results are summarized in Table 1.

In another study, it was found possible to introduce a chlorine atom at C-4 in **19** by treatment of the 2,4-dicarbonyl dianion with 0.75 equiv of 1,3-dichloro-5,5-dimethylhydantoin (DMDCH) affording 4-chloropyrrolidine **20** in 53% yield as a single isomer (Scheme 4). The reason that chlorination was carried out with the *N*-Cbz 3-oxo pyrrolidine **19** was to demonstrate that the intramolecular metal carbenoid NH insertion reaction, **18** to **19**, is also compatible with this protecting group (Scheme 4).

2.2. Aromatization of 3-oxo pyrrolidines to pyrroles

Treatment of **13a** ($\text{R} = \text{Ph}$) with 10 equiv of TFA, neutralization with NaHCO_3 , and concentration removed the *N*-Boc group to give the intermediate 3-oxo pyrrolidine **21** (Scheme 5). The ^1H NMR of this material has the NH protons at δ 9.41 ppm (D_2O exchangeable), and the C-2 proton appears at δ 5.42 ppm suggesting that the enol **22** was not formed in detectable amounts. Under these conditions, in an NMR tube in CDCl_3 , **21** was stable for more than 48 h. However, attempts to purify this material resulted in decomposition. When pyrrolidine **21** was stirred for 4 h in EtOAc, in the presence of SiO_2 in an open flask exposed to the atmosphere 5-phenyl-3-hydroxy-1*H*-pyrrole-2-carboxylate (**23**) was isolated in 88% yield (Table 2, entry 1). The structure of **23** is supported by the downfield shift of the C-4 protons from δ 2.59 and 3.70 ppm to one proton at δ 6.13 ppm.

The influence of the reaction parameters on the aromatization of **21** to **23** was next explored to optimize yields and determine the mechanism of the reaction. In the absence of air, formation of pyrrole **23** was not detected (Table 2, entries 2 and 5). In the absence of SiO_2 or TFA, even in the presence of air, the pyrrole was not formed (Table 2, entries 3 and 7). The only exception was with Et_3N , but the yield was low, 33% (Table 2, entry 6). Optimum yields of **23** were obtained using the combination of SiO_2 and air in EtOAc.

Most mechanisms proposed for the aromatization of stable and unstable hydroxy and oxo pyrrolidines invoke a base promoted elimination of a nitrogen (9-phenylfluorene, TsOH) or ring substituent.^{11c,13b,d} The results summarized in Table 2 suggest a different mechanism, an acid catalyzed radical mechanism. We suggest that SiO₂ promotes formation of the enol **22**, required for aromatization, and that molecular oxygen abstracts hydrogen atoms with concomitant formation of the pyrrole **23** and hydrogen peroxide.²² In support of this hypothesis is the fact that *N*-Boc pyrrolidine **13a** in the presence of SiO₂-air does not form the pyrrole. Perhaps interaction between the large *N*-Boc and the CO₂Me may sterically inhibit enol formation. The radical mechanism is further supported by the fact that peroxide was detected in the reaction mixture using a KI peroxide test.²³ In the absence of pyrrolidine **21**, the SiO₂-air system did not produce detectable amounts of peroxide.

This aromatization procedure is remarkable general working with various substituted pyrrolidine 2-carboxylates **13** and **15** and pyrrolidine 2-phosphonates **14** and **16** to afford the corresponding pyrroles **25** and **26** in good yields (Scheme 6). Only in the case of **15d** (R = *t*-Butyl, E = Me) was the isolated yield modest, i.e. 50%.

When *N*-Cbz chloropyrrolidine **20** was treated with SiO₂-air for 5 h the *N*-CBz pyrrole **27** was obtained in 82% yield. Heating **20** with Et₃N at 45° C for 6 h in the absence of air also gave the pyrrolidine **27** in 68% yield (Scheme 7). In these examples aromatization is induced by elimination of the C-3 chlorine atom.

3. Summary

In summary, the dianions of 2,5-disubstituted 3-oxo pyrrolidines regioselectively undergo electrophilic substitution at the C-4 position affording tetrasubstituted pyrrolidines. Air oxidation of these pyrrolidines affords the corresponding tetrasubstituted pyrroles at room temperature without the need for a pyrrolidine leaving group. Importantly, this methodology provides convenient access to the relatively unexplored 2-phosphopyrroles **26** for further biological and chemical evaluation.

4. Experimental

Column chromatography was performed on silica gel, Merck grade 60 (230–400 mesh). TLC plates were visualized with UV, in an iodine chamber, or with phosphomolybdic acid, unless otherwise noted. Melting points were recorded on a Mel-Temp apparatus and are uncorrected. IR spectra were recorded, using NaCl plates or as KBr disks on a Mattson 4020 FTIR. ¹H NMR and ¹³C NMR spectra were recorded on a Bruker Avance-400, operating at 400 and 125 MHz, respectively. HRMS were performed in the Department of Chemistry, Drexel University, Philadelphia, PA, using a Fissions ZAB HF double-focusing mass spectrometer. Solvents, DCM, THF, and diethyl ether were purified by filtration on a Glass Contour Seca solvent purification system. Unless stated otherwise, all reagents were purchased from commercial sources and used without additional purification.

Methyl-(±)-*N*-(*p*-toluenesulfinyl)-3-amino-3-phenylpropanoate (**6a**),^{5a} methyl-(+)-3-(furan-2-yl)-3-(*p*-toluenesulfinylamino)propanoate (**6b**),^{5a} methyl-(+)-4,4-dimethyl-*N*-(*p*-toluenesulfinyl)-3-aminopentanoate (**6c**),^{5b} methyl-(+)-3-(*p*-toluenesulfinyl)-pent-4-enoate (**6d**),^{5d} methyl-(+)-3-oxo-5-(*p*-toluenesulfinylamino)-5-phenylpentanoate (**7a**),^{5a} methyl-(+)-6,6-dimethyl-3-oxo-5-(*p*-toluenesulfinylamino) heptanoate (**7c**),^{5b} dimethyl-(−)-2-oxo-4-(*p*-toluenesulfinylamino)-4-phenylbutylphosphonate (**8a**),⁶ dimethyl-(−)-*N*-(*tert*-butoxycarbonyl)-3-oxo-5-*tert*-butylpyrrolidine-2-phosphonate (**8c**),⁶ methyl-(+)-3-oxo-5-(*tert*-butyloxycarbonylamino)-5-phenylpentanoate (**9a**),^{5a} methyl-(+)-5-*tert*-butoxycarbonyl)-6,6-dimethyl-3-oxoheptanoate (**9c**),^{5b} dimethyl-(+)-2-oxo-*N*-(*tert*-butoxycarbonyl)-4-amino-4-phenylbutylphosphonate (**10a**),⁶ dimethyl-(−)-2-oxo-*N*-(*tert*-

butoxycarbonyl)-4-amino-5,5-dimethylhexylphosphonate (**10c**),⁶ methyl-(+)-2-diazo-3-oxo-5-(*tert*-butoxycarbonylamino)-5-phenylpentanoate (**11a**),^{5a} methyl-(+)-2-diazo-6,6-dimethyl-3-oxo-*N*-(*tert*-butoxycarbonyl)-5-aminoheptanoate (**11c**),^{5b} dimethyl-(+)-1-diazo-2-oxo-*N*-(*tert*-butoxycarbonyl)-4-amino-4-phenylbutylphosphonate (**12a**),⁶ (+)-diazo-2-oxo-*N*-(*tert*-butoxycarbonyl)-4-amino-5,5-dimethylhexylphosphonate (**12c**),⁶ methyl-(+)-*N*-(*tert*-butoxycarbonyl)-3-oxo-5-phenylpyrrolidine-2-carboxylate (**13a**),^{5a} methyl-(+)-5-*tert*-butyl-3-hydroxypyrrolidine-1-dicarboxylate (**13c**),^{5b} dimethyl-(+)-*N*-(*tert*-butoxycarbonyl)-3-oxo-5-phenylpyrrolidine-2-phosphonate (**14a**),⁶ dimethyl-(+)-*N*-(*tert*-butoxycarbonyl)-3-oxo-5-*tert*-butylpyrrolidine-2-phosphonate (**14c**),⁶ 5-*tert*-butyl-3-hydroxy-1*H*-pyrrole-2-carboxylic acid methyl ester (**25f**),^{5b} dimethyl 5-*tert*-butyl-3-hydroxy-1*H*-pyrrole-2-phosphonate (**26c**)⁶ were previously synthesized as enantiomerically and diastereomerically pure compounds. The racemic forms of these materials exhibited identical physical and spectral properties when compared to their optically active counterparts.

4.1. Methyl-(±)-5-(2-furyl)-5-(*p*-toluenesulfinylamino)-3-oxopentanoate (**7b**). Typical procedure

In an oven-dried, 250-mL, single necked round-bottom flask equipped with a magnetic stirring bar, rubber septum, and argon balloon was placed NaHMDS (14.70 mL, 14.70 mmol) in anhydrous THF (15 mL). The reaction mixture was cooled to -78°C and methyl acetate (1.20 mL, 15.13 mmol) was added. After stirring at this temperature for 1 h, **6b** (1.129 g, 3.67 mmol) in THF (35 mL) was added. The solution was stirred at -78°C for 4 h, quenched with saturated NH_4Cl (5 mL), and warmed to rt. Water (10 mL) was added and the solution was extracted with EtOAc (3×10 mL). The combined organic phases were washed with brine (10 mL), dried (Na_2SO_4), and concentrated. Flash chromatography (50% EtOAc/hexanes) afforded 1.077 g (84%) as an orange oil; IR (neat) 3423, 3224, 1748, 1716 cm^{-1} ; ^1H NMR (CDCl_3) δ 2.27 (s, 3 H), 3.08 (qd, 2 H), 3.29 (s, 2 H), 3.57 (s, 3 H), 4.78–4.82 (m, 2 H), 6.13 (d, $J = 8.1$, 1 H), 6.26 (d, $J = 8.0$ Hz, 1 H), 7.15 (d, $J = 8.4$ Hz, 2 H), 7.22 (s, 1 H), 7.45 (d, $J = 8.4$ Hz, 2 H); ^{13}C NMR (CDCl_3) δ 21.7, 47.7, 49.5, 52.7, 108.2, 110.9, 126.0, 129.9, 141.8, 142.6, 153.4, 167.5, 200.5. HRMS calcd for $\text{C}_{17}\text{H}_{20}\text{NO}_5\text{S}$ (M+H) 350.1062. Found 350.1059.

4.2. Methyl-(±)-5-(*p*-toluenesulfinylamino)-3-oxo-hept-6-enoate (**7d**)

Yield 85% of a yellow liquid; IR (neat) 1735, 1718 cm^{-1} ; ^1H NMR (CDCl_3) δ 2.28 (s, 3 H), 2.78–2.75 (m, 2 H), 3.29 (s, 2 H), 3.58 (s, 3 H), 4.16–4.13 (m, 1 H), 4.67 (d, $J = 9$ Hz, 1 H), 5.07 (m, 1 H), 5.16 (m, 1 H), 5.77 (m, 1 H), 7.15 (d, $J = 10$ Hz, 2 H), 7.43 (d, $J = 10$ Hz, 2 H); ^{13}C NMR (CDCl_3) δ 21.8, 48.8, 49.7, 52.6, 53.2, 117.3, 125.9, 129.8, 138.1, 141.7, 142.3, 168.9, 200.9. HRMS calcd for $\text{C}_{15}\text{H}_{19}\text{NO}_4\text{S}$ (M + H) 310.1113. Found 310.1115.

4.3. Dimethyl-(±)-2-oxo-4-(*p*-toluenesulfinylamino)-4-(2-furyl butylphosphonate (**8b**)

In a 50-mL, single-necked, round-bottom flask equipped with a magnetic stirring bar, rubber septum, and argon balloon was placed *n*-BuLi (2 M in cyclohexane, 2.70 mL, 5.40 mmol) in anhydrous THF (5 mL). The mixture was cooled to -78°C and dimethyl methylphosphonate (0.60 mL, 5.61 mmol) was added. After stirring at this temperature for 1 h, **6b** (0.207 g, 0.67 mmol) in THF (15 mL) was added via cannula. The reaction mixture was stirred at this temperature for 4 h, quenched with saturated NH_4Cl (0.5 mL), and warmed to rt. Water (5 mL) was added and the solution was extracted with EtOAc (3×10 mL). The combined organic phases were washed with brine (5 mL), dried (Na_2SO_4), and concentrated. Flash chromatography (EtOAc) afforded a colorless oil that was subjected to Kugelrohr vacuum distillation (60°C under 2.5 mmHg) to remove dimethyl menthylphosphonate, affording 0.219 g (82%) as an orange oil; IR (neat) 3379, 3192, 1753, 1717, 1246, 1089 cm^{-1} ; ^1H NMR (CDCl_3) δ 2.32 (s, 3 H), 2.85 (s, 1 H), 2.89 (s, 1 H), 3.65 (m, 6 H), 5.15 (m, 2 H), 6.11 (m, 1 H), 6.23 (m, 1 H), 7.24 (s, 1 H), 7.29 (m, 2 H), 7.37 (m, 2 H); ^{13}C NMR (CDCl_3) δ 20.3, 38.5,

48.1, 50.9, 106.6, 109.5, 124.6, 125.0, 128.6, 140.5, 141.4, 201.3; ^{31}P NMR (CDCl_3) δ 22.06. HRMS calcd for $\text{C}_{17}\text{H}_{23}\text{NO}_6\text{P}$ (M+H) 400.0984. Found 400.0987.

4.4. Methyl-($\pm$)-5-(*tert*-butoxycarbonyl)-5-(2-furyl)-3-oxopentanoate (9b). Typical procedure

In an oven-dried, 25-mL, single-necked, round-bottom flask equipped with a magnetic stirring bar, rubber septum, and argon balloon was placed **7b** (0.097 g, 0.28 mmol) in anhydrous methanol (2 mL). The solution was cooled to 0 °C and TFA (0.06 mL, 0.78 mmol) was added. The reaction mixture was stirred for 1 h, concentrated, and anhydrous THF (2 mL) was added. The solution was cooled to 0 °C, Et_3N (0.20 mL, 1.43 mmol) and Boc_2O (0.60 mL, 0.60 mmol) were added, and the solution was warmed to rt. After 8 h, H_2O (0.5 mL) was added and the solution was extracted with EtOAc (3×2 mL). The combined organic phases were washed with brine (2 mL), dried (Na_2SO_4), and concentrated. Flash chromatography (20% EtOAc/hexanes) afforded 0.071 g (82%) of a yellow oil; IR (neat) 3421, 3226, 1745, 1716 cm^{-1} ; ^1H NMR (CDCl_3) δ 1.36 (s, 9 H), 3.07 (m, 2 H), 3.37 (s, 2 H), 3.64 (s, 3 H), 5.18 (m, 2 H), 6.18 (d, $J = 8.1$ Hz, 1 H), 6.21 (d, $J = 8.0$ Hz, 1 H), 7.19 (s, 1 H); ^{13}C NMR (CDCl_3) δ 28.5, 40.3, 47.8, 48.4, 52.6, 80.1, 106.9, 109.8, 140.5, 141.8, 156.3. HRMS calcd for $\text{C}_{15}\text{H}_{22}\text{NO}_6$ (M + H) 312.1447. Found 312.1441.

4.5. Methyl-($\pm$)-(tert-butoxycarbonyl)-3-oxohept-6-enoate (9d)

Yield 92% of a slight yellow oil; IR (neat) 3123, 1720, 1707, 1649 cm^{-1} ; ^1H NMR (CDCl_3) δ 1.49 (s, 9H), 2.90 (m, 2H), 3.52 (s, 2 H), 3.79 (s, 3 H), 4.55 (br s, 1 H), 5.15 (m, 1 H), 5.19 (m, 1 H), 5.26 (m, 1 H), 5.90-5.70 (m, 1 H); ^{13}C NMR (CDCl_3) δ 28.4, 47.5, 49.6, 52.7, 80.3, 115.7, 137.5, 155.4, 167.6, 201.2. HRMS calcd for $\text{C}_{13}\text{H}_{21}\text{NO}_5$ (M + H) 272.1498. Found 272.1491.

4.6. Dimethyl-($\pm$)-2-oxo-N-(tert-butoxycarbonyl)-4-amin-o-4-(2-furyl)-butylphosphonate (10b)

Yield 97% of a yellow oil; IR (neat) 3306, 1716, 1255, 1031 cm^{-1} ; ^1H NMR (CDCl_3) δ 1.37 (s, 9H), 3.01 (m, 2 H), 3.38 (s, 2 H), 3.61 (m, 6 H), 5.14 (m 2 H), 6.16 (m, 1 H), 6.22 (m, 1 H), 7.25 (s, 1 H); ^{13}C NMR (CDCl_3) δ 28.7, 41.9, 50.2, 51.1, 53.3, 53.6, 126.6, 127.7, 129.0, 141.6, 155.5, 200.2; ^{31}P NMR (CDCl_3) δ 23.82. HRMS calcd for $\text{C}_{17}\text{H}_{27}\text{NO}_6\text{P}$ (M + H) 372.1576. Found 372.1575.

4.7. Methyl-($\pm$)-5-(tert-butoxycarbonyl)-2-diazo-5-(2-furyl)-3-oxopentanoate (11b). Typical procedure

In an oven-dried, 25-mL, single-necked, round-bottom flask equipped with a magnetic stirring bar, rubber septum, and argon balloon was placed **9b** (0.020 g, 0.06 mmol) in anhydrous CH_3CN (3 mL). The reaction mixture was cooled to 0 °C, and 4-carboxybenzenesulfonazide (4-CBSA) (0.019 g, 0.09 mmol) and Et_3N (0.05 mL, 0.36 mmol) were added. The reaction mixture was warmed to rt, and after 4 h H_2O (0.5 mL) was added and the solution was extracted with EtOAc (3×5 mL). The combined organic phases were washed with brine (5 mL), dried (Na_2SO_4), and concentrated. Flash chromatography (20% EtOAc/hexanes) afforded 0.015 g (76%) of a yellow oil; IR (neat) 3421, 3226, 1745, 1716, 1316, 1201 cm^{-1} ; ^1H NMR (CDCl_3) δ 1.36 (s, 9 H), 3.11 (qd, 2 H), 3.68 (s, 3 H), 4.70 (m, 2 H), 6.23 (s, 1 H), 7.18 (m, 2 H); ^{13}C NMR (CDCl_3) δ 21.7, 48.5, 53.1, 106.0, 111.3, 146.1, 166.7, 201.8. HRMS calcd for $\text{C}_{15}\text{H}_{20}\text{N}_3\text{O}_6$ (M + H) 338.1352. Found 338. 1355.

4.8. Methyl-($\pm$)-5-(tert-butoxycarbonylamino)-2-diazo-3-oxohept-6-enoate (11d)

Yield 95% of a yellow oil; IR (neat): 3278, 2132, 1730, 1715, 1653 cm^{-1} ; ^1H NMR (CDCl_3) δ 1.49 (s, 9 H), 3.06 (m, 2 H), 3.80 (s, 3 H), 4.65 (br s, 1 H), 5.05 (m, 1 H), 5.13 (m, 1 H), 5.15 (m, 1 H), 5.45 (m, 1 H); ^{13}C NMR δ 28.6, 44.8, 49.7, 50.0, 52.6, 115.2, 138.1, 155.5, 162.0,

190.8 ($C=N_2$ was not observed). HRMS calcd for $C_{13}H_{19}N_3O_5$ ($M + H$) 298.1403. Found 298.1409.

4.9. Dimethyl-(±)-1-diazo-2-oxo-*N*-(*tert*-butoxycarbonyl)-4-amino-4-(2-furyl)-butylphosphonate (**12b**). Typical procedure

In a 50-mL, single-necked, round-bottom flask equipped with a magnetic stirring bar, rubber septum, and argon balloon was placed NaH (60% in mineral oil, 0.020 g, 0.50 mmol), which was washed by petroleum ether (2 mL). After removal of the petroleum ether by syringe, the flask was placed under vacuum for 2 min, and THF (5 mL) was added by syringe. In another 50-mL round-bottom flask was placed **8b** (0.075 g, 0.24 mmol) and 4-acetamidobenzenesulfonyl azide (4-ABSA, 0.058 g, 0.24 mmol) in THF (10 mL). The solution was transferred to the 50-mL, round-bottom flask containing NaH and THF via cannula quickly at rt. After stirring for 1 h, the reaction mixture was quenched by addition of saturated aqueous NH_4Cl (0.5 mL) and extracted with Et_2O (20 mL) and $EtOAc$ (2×20 mL). The combined organic phases were washed with brine (10 mL), dried (Na_2SO_4), and concentrated. To the residue was added $CHCl_3$ (5 mL), and the solution was filtered and concentrated. Flash chromatography ($EtOAc$) afforded 0.065 g (71%) of a yellow oil; IR (neat) 3317, 1710, 1314, 1256 cm^{-1} ; 1H NMR ($CDCl_3$) δ 1.33 (s, 9H), 3.02 (m, 2 H), 3.64 (d, $J = 12.1$ Hz, 3 H), 3.70 (d, $J = 12.1$ Hz, 3 H), 4.74 (m, 2 H), 6.24 (s, 1 H), 7.17 (m, 2 H); ^{13}C NMR ($CDCl_3$) δ 21.6, 48.6, 53.5, 106.2, 111.5, 146.7, 166.9, 202.0; ^{31}P NMR ($CDCl_3$) δ 14.32. HRMS calcd for $C_{15}H_{22}N_3O_7PNa$ ($M + Na$) 410.1093. Found 410.1089.

4.10. 1-*tert*-Butyl-2-methyl-5-(2-furyl)-3-oxopyrrolidine-1,2-dicarboxylate (**13b**). Typical procedure

In an oven-dried, 100-mL, single-necked round-bottom flask equipped with a magnetic stirring bar, rubber septum, and argon balloon was placed **11b** (0.813 g, 2.41 mmol) and $Rh_2(OAc)_4$ (0.107 g, 0.24 mmol) in CH_2Cl_2 (30 mL), and the reaction mixture was warmed to 35 °C. After stirring for 8 h at this temperature the solution was concentrated. Flash chromatography (20% $EtOAc$ /hexanes) afforded 0.552 g (74%) of a yellow oil; IR (neat) cm^{-1} 3094, 1737, 1667, 1314; 1H NMR ($CDCl_3$) δ 1.17 (s, 9 H), 2.67 (m, 1 H), 3.15 (m, 1 H), 3.73 (s, 3 H), 4.72 (m, 1 H), 5.30 (m, 1 H), 6.14 (s, 1 H), 7.08 (m, 2 H); ^{13}C NMR ($CDCl_3$) δ 28.5, 43.1, 46.8, 51.6, 79.8, 106.1, 142.8, 155.3, 170.9, 202.1. HRMS calcd for $C_{15}H_{19}NO_6Na$ ($M + Na$) 332.1111. Found 332.1114.

4.11. 1-*tert*-Butyl 2-methyl 3-oxo-5-vinylpyrrolidine-1,2-dicarboxylate (**13d**)

Yield 87% of a yellow oil; IR (neat) 2956, 1735, 1710, 815 cm^{-1} ; Rotamers were observed. 1H NMR ($CDCl_3$) δ 1.45 (d, $J = 10$ Hz, 9 H), 2.56-2.46 (m, 1 H), 3.02 (dd, $J = 3.15$ Hz, 1 H) 3.83 (d, $J = 3.0$ Hz, 3 H), 4.71 (m, 2 H), 5.26 (m, 2 H), 5.98 (m, 1 H); ^{13}C NMR ($CDCl_3$) δ 28.5, 43.2, 53.3, 55.6, 66.4, 66.6, 81.6, 81.7, 116.0, 116.8, 137.1, 137.6, 153.4, 167.1, 167.9, 203.4, 203.9. HRMS calcd for $C_{13}H_{20}NO_5$ ($M + H$) 271.1341. Found 271.1340.

4.12. Dimethyl-(±)-*N*-(*tert*-butoxycarbonyl)-3-oxo-5-(2-furyl)-pyrrolidine-2-phosphonate (**14b**)

In an oven-dried, 25-mL, single-necked round-bottom flask equipped with a magnetic stirring bar, rubber septum, and argon balloon was placed **12b** (0.070 g, 0.18 mmol) and $Rh_2(OAc)_4$ (0.008 g, 0.02 mmol) in CH_2Cl_2 (5 mL), and the reaction mixture was warmed to 35 °C. After stirring for 8 h at this temperature the solution was concentrated, and flash chromatography (50% $EtOAc$ /hexanes) afforded 0.043 g (67%) of a yellow oil; IR (neat) 1762, 1701, 1668, 1315, 1032 cm^{-1} ; 1H NMR ($CDCl_3$) δ 1.41 (s, 9 H), 2.70 (m, 1 H), 3.19 (m, 1 H), 3.72 (m, 6 H), 4.79 (m, 1 H), 5.31 (m, 1 H), 6.15 (s, 1 H), 7.09 (m, 2 H); ^{13}C NMR ($CDCl_3$) δ 28.5, 43.1, 47.6, 53.1, 62.8, 80.1, 105.8, 112.6, 142.6, 151.2, 154.9, 201.8; ^{31}P NMR ($CDCl_3$) δ 17.52. HRMS calcd for $C_{15}H_{22}NO_7PNa$ ($M + Na$) 382.1032. Found 382.1027.

4.13. Methyl-(±)-*N*-(*tert*-butoxycarbonyl)-3-oxo-4-methyl-5-phenylpyrrolidine-2-carboxylate (15a). Typical procedure

In an oven-dried, 25-mL, single-necked, round-bottom flask equipped with a magnetic stirring bar, rubber septum, and argon balloon was placed **13a** (0.021 g, 0.06 mmol) in THF (1 mL). The reaction flask was cooled to -78°C , and LDA (0.20 mL, 0.20 mmol, in THF) was added. The solution was stirred for 1 h at which time methyl iodide (0.01 mL, 0.16 mmol) was added. After stirring at -78°C for 2 h, the solution was quenched with saturated NH_4Cl (0.5 mL) and warmed to rt. Water (0.5 mL) was added, and the solution was extracted with EtOAc (3×1 mL). The combined organic phases were washed with brine (1 mL), dried (Na_2SO_4), and concentrated. Preparative TLC (20% EtOAc/hexanes) afforded 0.017 g (83%) of a slight yellow oil; IR (neat) 1774, 1746, 1699, 1391, 1157 cm^{-1} ; ^1H NMR (CDCl_3) δ 1.09 (2s, 9 H), 2.09 (m, 3 H), 3.12 (m, 1 H), 3.84 (2s, 3 H), 4.72 (m, 2 H), 5.51 (m, 1 H), 7.04 (m, 2 H), 7.24 (m, 2 H), 7.41 (m, 1 H); ^{13}C NMR (CDCl_3) δ 10.3, 27.8, 52.6, 64.6, 67.9, 79.5, 126.7, 128.1, 128.2, 129.4, 129.5, 141.9, 154.3, 166.8, 203.8; ^{31}P NMR (CDCl_3) δ 17.21. HRMS calcd for $\text{C}_{18}\text{H}_{24}\text{NO}_5$ (M + H) 334.1654. Found 334.1658.

4.14. 1-*tert*-Butyl-2-methyl-5-(2-furyl)-4-methyl-3-oxopyrrolidine-1,2-dicarboxylate (15c)

Yield 88% of a yellow oil; IR (neat) 1763, 1703, 1667, 1315, 1032 cm^{-1} ; ^1H NMR (CDCl_3) δ 1.16 (d, $J = 5.0$ Hz, 3 H), 1.41 (s, 9 H), 3.40 (m, 1 H), 3.77 (s, 3 H), 3.99 (m, 1 H), 5.34 (m, 1 H), 6.11 (s, 1 H) 7.09 (m, 2 H); ^{13}C NMR (CDCl_3) δ 10.2, 28.3, 46.9, 52.1, 56.6, 72.5, 79.3, 106.8, 109.4, 145.1, 156.2, 172.0, 200.9. HRMS calcd for $\text{C}_{16}\text{H}_{22}\text{NO}_6$ (M + H) 324.1447. Found 324.1441.

4.15. Methyl-(±)-*N*-(*tert*-butoxycarbonyl)-3-oxo-4-methyl-5-(*tert*-butyl)pyrrolidine-2-carboxylate (15d)

Yield 50% of a colorless oil; IR (neat) 1755, 1716 cm^{-1} ; ^1H NMR (CDCl_3) δ 0.95 (s, 9 H), 1.21 (d, $J = 5.1$ Hz, 3 H), 1.41 (s, 9 H), 3.25 (m, 1 H), 3.89 (s, 3 H), 4.19 (m, 1 H), 4.71 (m, 1 H); ^{13}C NMR (CDCl_3) δ 11.1, 26.9, 29.0, 37.5, 41.6, 53.2, 62.9, 67.4, 82.1, 156.3, 167.4, 203.9. HRMS calcd for $\text{C}_{16}\text{H}_{28}\text{NO}_5$ (M + H) 314.1967. Found 314.1958.

4.16. Methyl-(±)-*N*-(*tert*-butoxycarbonyl)-3-oxo-4-benzyl-5-phenylpyrrolidine-2-carboxylate (15b)

Yield 79% of a slight yellow oil; IR (neat) 1743, 1711, 1401 cm^{-1} ; ^1H NMR (CDCl_3) δ 1.10 (2s, 9 H), 3.40 (m, 1 H) 3.85 (2s, 3 H), 4.30 (m, 2 H), 5.02 (m, 1 H) 5.61 (m, 1 H), 7.33 (m, 8 H), 7.53 (m, 2 H); ^{13}C NMR (CDCl_3) δ 29.5, 32.7, 57.6, 65.3, 80.7, 128.3, 128.4, 128.5, 128.8, 129.0, 129.1, 129.2, 129.3, 141.1, 141.8, 157.4, 171.9, 202.1. HRMS calcd for $\text{C}_{24}\text{H}_{28}\text{NO}_5$ (M + H) 410.1967. Found 410.1964.

4.17. (±)-*tert*-Butyl-4-benzyl-2-(dimethoxyphosphoryl)-3-oxo-5-phenylpyrrolidine-1-carboxylate (16a)

Yield 41% of an oil; IR (neat) 3252, 1568, 1180, 1024 cm^{-1} ; ^1H NMR (CDCl_3) δ 1.24 (s, 9 H), 3.01 (d, $J = 10.8$ Hz, 3 H), 3.03 (s, 1 H), 3.30 (q, $J = 6.4$ Hz, 1 H), 3.79 (d, $J = 10.8$ Hz, 3 H), 3.80 (d, $J = 10.8$ Hz, 3 H), 4.57 (d, $J = 18.0$ Hz, 1 H), 4.72 (m, 1 H), 7.21 (m, 8 H), 7.36 (m, 2 H); ^{13}C NMR (CDCl_3) δ 28.3, 30.0, 33.7, 54.0, 58.0, 64.4, 81.8, 127.1, 127.1, 127.6, 128.6, 128.9, 129.8, 137.6, 142.5, 155.0, 205.2; ^{31}P NMR (CDCl_3) δ 17.21. HRMS calcd for $\text{C}_{24}\text{H}_{31}\text{NO}_6\text{P}$ (M + H) 460.1889. Found 460.1890.

4.19. (±)-tert-Butyl-3-methyl-5-(dimethoxyphosphoryl)-4-oxo-2-(2-furyl)-pyrrolidine-1-carboxylate (16b)

Yield 40% of a yellow oil; IR (neat) cm^{-1} 1736, 1668, 1315; ^1H NMR (CDCl_3) δ 1.18 (d, J = 5.1 Hz, 3 H), 1.40 (s, 9 H), 3.56 (m, 1 H), 3.81 (d, J = 10.8 Hz, 3 H), 3.84 (d, J = 10.8 Hz, 3 H), 4.02 (s, 1 H), 5.36 (m, 1 H), 6.12 (s, 1 H) 7.08 (m, 2 H); ^{13}C NMR (CDCl_3) δ 10.5, 28.3, 46.9, 52.3, 56.7, 72.5, 79.3, 106.8, 109.4, 145.1, 156.2, 172.0, 201.1; ^{31}P NMR (CDCl_3) δ 17.19. HRMS calcd for $\text{C}_{16}\text{H}_{25}\text{NO}_7\text{P}$ ($M + \text{H}$) 374.1369. Found 374.1360.

4.18. (±)-tert-Butyl-4-benzyl-2-(dimethoxyphosphoryl)-3-oxo-5-(2-furyl)-pyrrolidine-1-phosphonate (16c)

Yield 40% of a yellow oil; IR (neat) 3256, 1736, 1668; ^1H NMR (CDCl_3) 1.40 (s, 9 H), 2.82 (d, J = 10.6 Hz, 1 H), 3.10 (s, 1 H), 3.16 (d, J = 17.8 Hz, 1 H), 3.71 (m, 6 H), 3.96 (m, 1 H), 6.17 (s, 1 H), 6.27 (s, 1 H), 7.16 (m, 6 H); ^{13}C NMR (CDCl_3) δ 28.5, 29.9, 33.7, 54.1, 60.1, 62.6, 80.4, 105.9, 112.4, 127.1, 127.1, 127.6, 128.6, 128.9, 129.8, 142.6, 151.2, 154.8, 202.0; ^{31}P NMR (CDCl_3) δ 17.36. HRMS calcd for $\text{C}_{22}\text{H}_{29}\text{NO}_7\text{PNa}$ ($M + \text{Na}$) 450.1682. Found 450.1674.

4.20. Methoxy-(±)-3-oxo-5-(*N*-benzyloxycarbonylamino)-5-phenylpentanoate (17)

In an oven-dried, 300-mL, single-necked, round-bottom flask equipped with a magnetic stirring bar, rubber septum, and argon balloon was placed **7a** (1.170 g, 3.26 mmol) in anhydrous methanol (100 mL). The solution was cooled to 0 °C, and TFA (1.3 mL, 16.87 mmol) was added. After stirring for 1 h, the mixture was concentrated. The residue was dissolved in THF (100 mL), cooled to 0 °C, and Et_3N (2.8 mL, 20.09 mmol), DMAP (0.415 g, 3.40 mmol), and benzyl chloroformate (0.6 mL, 3.40 mmol) were added. After warming to rt, the solution was stirred for 5 h and quenched by addition of sat. NH_4Cl (5 mL). Water (30 mL) was added; the solution was extracted with EtOAc (3 $\times$ 30 mL); and the combined organic phases were washed with brine (30 mL), dried (Na_2SO_4), and concentrated. Flash chromatography (30% EtOAc/hexanes) afforded 0.892 g (77%) of a white solid, mp 82–84 °C; IR (neat) 3314, 1747, 1716, 1688 cm^{-1} ; ^1H NMR (CDCl_3) δ 3.07 (d, J = 5.4 Hz, 1 H), 3.13 (d, J = 6.5 Hz, 1 H), 3.40 (s, 2 H), 3.69 (s, 3 H), 5.09 (m, 1 H), 5.20 (m, 1 H), 5.67 (m, 2 H), 7.24 (m, 2 H), 7.32 (m, 6 H), 7.41 (m, 2 H); ^{13}C NMR (CDCl_3) δ 48.6, 49.8, 51.7, 52.8, 67.3, 126.5, 128.1, 128.7, 129.1, 129.2, 136.7, 141.1, 155.9, 167.6, 200.9. HRMS calcd for $\text{C}_{20}\text{H}_{21}\text{NO}_5\text{Na}$ ($M + \text{H}$) 378.1317. Found 378.1314.

4.21. Methyl-(±)-2-diazo-3-oxo-5-(*N*-benzyloxycarbonylamino)-5-phenylpentanoate (18)

In an oven-dried, 250-mL, single-necked, round-bottom flask equipped with a magnetic stirring bar, rubber septum, and argon balloon was placed **17** (0.866 g, 2.44 mmol) in anhydrous CH_3CN (80 mL). The reaction mixture was cooled to 0 °C, 4-carboxybenzenesulfonazide (4-CBSA) (0.665 g, 2.92 mmol) and Et_3N (1.1 mL, 7.89 mmol) were added, and the solution was warmed to rt. After stirring for 4 h H_2O (10 mL) was added, and the solution was extracted with EtOAc (3 $\times$ 20 mL). The combined organic phases were washed with brine (10 mL), dried (Na_2SO_4), and concentrated. Flash chromatography (20% EtOAc/hexanes) afforded 0.770 g (83%) of a colorless oil; IR (neat) 3312, 2138, 1720, 1654 cm^{-1} ; ^1H NMR (CDCl_3) δ 3.34 (m, 1 H), 3.44 (dd, J = 15.0, 15.5 Hz, 1 H), 3.83 (s, 3 H), 5.08 (dd, J = 21.5, 21.0 Hz, 2 H), 5.25 (m, 1 H), 5.74 (m, 1 H), 7.29 (m, 2 H) 7.34 (m, 6 H), 7.42 (m, 2 H); ^{13}C NMR (CDCl_3) δ 30.1, 46.1, 52.3, 52.7, 67.2, 126.5, 127.9, 128.4, 128.7, 128.8, 129.0, 136.8, 141.7, 155.9, 162.1, 190.4. HRMS calcd for $\text{C}_{20}\text{H}_{20}\text{N}_3\text{O}_5$ ($M + \text{H}$) 382.1403. Found 382.1398.

4.22. Methyl-(±)-(*N*-benzyloxycarbonyl)-3-oxo 5-phenylpyrrolidine-2-carboxylate (19)

In an oven-dried, 100-mL, single-necked, round-bottom flask equipped with a magnetic stirring bar, rubber septum, and argon balloon was placed **18** (0.018 g, 0.05 mmol) and $\text{Rh}_2(\text{OAc})_4$

(0.004 g, 0.01 mmol) in CH_2Cl_2 (2 mL). After stirring for 8 h at 35 °C, the solution was concentrated, and flash chromatography (20% EtOAc/Hexanes) afforded 0.016 g (93%) of a clear oil; IR (neat) 3256, 1772, 1747, 1700, 1391, 1159 cm^{-1} ; ^1H NMR (CDCl_3) δ 2.56 (m, 1 H), 3.17 (m, 1 H), 3.86 (s, 3 H), 4.60 (m, 2 H), 4.95 (m, 1 H), 5.36 (m, 1 H), 7.14 (m, 8 H), 7.22 (m, 2 H); ^{13}C NMR (CDCl_3) δ 45.8, 46.8, 52.5, 67.9, 68.0, 83.6, 125.8, 126.0, 126.5, 126.8, 127.3, 127.9, 128.2, 128.4, 129.3, 130.0, 142.4, 143.1, 154.9, 165.1, 203.6, 204.0. HRMS calcd for $\text{C}_{20}\text{H}_{19}\text{NO}_5\text{Na}$ (M + Na) 376.1161. Found 376.1156.

4.23. Methyl-(±)-(N-benzyloxycarbonyl)-3-oxo-4-chloro-5-phenylpyrrolidine-2-carboxylate (20)

In an oven-dried, 50-mL, single-necked, round-bottom flask equipped with a magnetic stirring bar, rubber septum, and argon balloon was placed **19** (0.242 g, 0.68 mmol) in anhydrous THF (5 mL), and the solution was cooled to −78 °C. At this time LDA (2.00 mL, 2.00 mmol, in THF) was added, and the solution was stirred for 1 h. 1,3-Dichloro-5,5-dimethyl hydantoin (0.201 g, 1.02 mmol) was added, and the reaction mixture was stirred at −78 °C for 2 h.²⁰ At this time sat. NH_4Cl (0.5 mL) was added, and the solution was warmed to rt. Water (2 mL) was added; the solution was extracted with EtOAc (3 × 2 mL); and the combined organic phases were washed with brine (2 mL), dried (Na_2SO_4), and concentrated. Flash chromatography (20% EtOAc/hexanes) afforded 0.140 g (53%) of a slight yellow oil; IR (neat) 3256, 1772, 1747, 1700, 1391, 1159 cm^{-1} ; ^1H NMR (CDCl_3) δ 3.89 (s, 3 H), 4.60 (m, 2 H), 5.36 (m, 1 H), 5.38 (d, J = 16.1 Hz, 1 H), 5.48 (d, J = 8.0 Hz, 1 H), 7.16 (m, 8 H), 7.22 (m, 2 H); ^{13}C NMR (CDCl_3) δ 45.8, 52.5, 67.9, 68.0, 75.8, 75.9, 83.6, 125.8, 126.0, 126.5, 126.8, 127.3, 127.9, 128.2, 128.4, 129.3, 130.0, 142.4, 143.1, 154.9, 165.1, 203.6, 204.0. HRMS calcd for $\text{C}_{20}\text{H}_{19}\text{NO}_5\text{Cl}$ (M + H) 388.0952. Found 388.0944.

4.24. 5-Phenyl-3-hydroxy-1H-pyrrole-2-carboxylic acid methyl ester (23). Typical procedure

In an oven-dried, 25-mL, single-necked, round-bottom flask equipped with a magnetic stirring bar, rubber septum, and argon balloon was placed **13a** (0.050 g, 0.16 mmol) in CH_2Cl_2 (5 mL), and TFA (0.06 mL, 0.79 mmol) was added. The reaction mixture was stirred at rt for 3 h; at which time aqueous sat. NaHCO_3 (3 mL) and H_2O (1 mL) were added. The phases were separated; the aqueous phase was extracted with CH_2Cl_2 (2 × 3 mL); and the combined organic phases were dried (Na_2SO_4) and concentrated in a 25 mL round-bottom flask. To the residue was added ca. 1 g of silica gel (0.035–0.07 mm for column chromatography pore diameter ca 6 nm) and EtOAc (6 mL). The suspension in the reaction flask, open to the atmosphere, was stirred for 5 h, filtered and concentrated. Flash chromatography (20% EtOAc/hexanes) afforded 0.030 g (88%) of a white solid, mp 77–79 °C; IR (neat) 3496, 1672, 2934 cm^{-1} ; ^1H NMR (CDCl_3) δ 2.56 (br, 2 H), 3.81 (s, 3 H), 6.17 (s, 1 H), 7.30 (m, 3 H), 7.44 (d, J = 6.1 Hz, 2 H); ^{13}C NMR (CDCl_3) δ 96.5, 103.1, 148.9, 158.2, 164.9. HRMS calcd for $\text{C}_{12}\text{H}_{11}\text{NO}_3\text{Na}$ (M + Na) 240.0637. Found 240.0634.

4.25. 5-(2-Furyl)-3-hydroxy-1H-pyrrole-2-carboxylic acid methyl ester (25a)

Yield, 75% of a yellow solid, mp 128–129 °C; IR (neat) 3492, 1669, 1254 cm^{-1} ; ^1H NMR (CDCl_3) δ 3.01 (br, 1 H), 3.82 (s, 3 H), 6.12 (s, 1 H), 6.48 (s, 1 H), 6.24 (s, 1 H), 7.25 (s, 1 H), 7.89 (br, 1 H); ^{13}C NMR (CDCl_3) δ 51.5, 96.3, 105.2, 105.8, 110.0, 131.6, 149.4, 154.8, 157.7, 165.1 cm^{-1} . HRMS calcd for $\text{C}_{10}\text{H}_9\text{NO}_4\text{Na}$ (M + Na) 230.0429. Found 230.0422.

4.26. 5-Vinyl-3-hydroxy-1H-pyrrole-2-carboxylate acid methyl ester (25c)

Yield 81% of a white solid mp 121–123 °C; IR (neat) 3483, 3354, 3034, 1678 cm^{-1} ; ^1H NMR (CDCl_3) δ 3.27 (m, 1 H), 3.88 (s, 3 H), 4.21 (m, 1 H), 4.71 (m, 1 H), 5.70 (s, 1 H), 6.33 (br, 2 H); ^{13}C NMR (CDCl_3) δ 51.4, 105.9, 116.7, 121.0, 129.8, 130.1, 134.7, 154.9. HRMS calcd for $\text{C}_8\text{H}_9\text{NO}_3\text{Na}$ (M + Na) 190.0480. Found 190.0471.

4.27. 4-Methyl-5-phenyl-3-hydroxy-1H-pyrrole-2-carboxylic acid methyl ester (25d)

Yield 78% of a white solid, mp 112–114 °C; IR (neat) 3492, 1674 cm^{-1} ; ^1H NMR (CDCl_3) δ 2.59 (br, 2 H), 3.69 (s, 3 H), 3.84 (s, 3 H), 7.27 (m, 3 H), 7.42 (d, $J = 6.0$ Hz, 2 H); ^{13}C NMR (CDCl_3) δ 9.9, 51.5, 96.5, 103.4, 120.6, 124.8, 125.3, 137.6, 148.9, 158.2, 164.9. HRMS calcd for $\text{C}_{13}\text{H}_{13}\text{NO}_3\text{Na}$ ($M + \text{Na}$) 254.0793. Found 254.0782.

4.28. 4-Benzyl-5-phenyl-3-hydroxy-1H-pyrrole-2-carboxylic acid methyl ester (25e)

Yield 67% of a white solid, mp 115–117 °C; IR (neat) 3487, 1678 cm^{-1} ; ^1H NMR (CDCl_3) δ 2.59 (br, 2 H), 3.79 (s, 3 H), 4.03 (s, 2 H), 7.27 (m, 2 H), 7.34 (m, 6 H), 7.52 (m, 2 H); ^{13}C NMR (CDCl_3) δ 29.3, 51.4, 120.3, 121.4, 125.6, 126.5, 126.8, 127.3, 127.9, 128.0, 128.2, 128.4, 128.5, 128.7, 128.8, 136.4. HRMS calcd for $\text{C}_{19}\text{H}_{18}\text{NO}_3$ ($M + \text{H}$) 308.1287. Found 308.1281.

4.29. 4-Methyl-5-(2-furyl)-3-hydroxy-1H-pyrrole-2-carboxylic acid methyl ester (25f)

Yield 67% of a yellow solid, mp 132–134 °C; IR (neat) 3493, 1672, 1254 cm^{-1} ; ^1H NMR (CDCl_3) δ 3.03 (br, 1 H), 3.71 (s, 3 H), 3.81 (s, 3 H), 6.47 (s, 1 H), 6.24 (s, 1 H), 7.23 (s, 1 H), 7.92 (br, 1 H); ^{13}C NMR (CDCl_3) δ 10.1, 51.4, 96.4, 105.2, 110.0, 120.3, 131.5, 149.4, 154.9, 157.6, 164.9. HRMS calcd for $\text{C}_{11}\text{H}_{11}\text{NO}_4\text{Na}$ ($M + \text{Na}$) 244.0586. Found 244.0578.

4.30. 4-Methyl-5-tert-butyl-3-hydroxy-1H-pyrrole-2-carboxylate acid methyl ester (25g)

Yield 50% of a white solid, mp 114–116 °C; IR (neat) 3480, 3326, 1679 cm^{-1} ; ^1H NMR (CDCl_3) δ 1.27 (s, 9 H), 3.69 (s, 3 H), 3.86 (s, 3 H), 6.49 (br, 2 H); ^{13}C NMR (CDCl_3) δ 10.0, 30.4, 33.6, 51.5, 95.3, 120.6, 149.2, 154.6, 164.4. HRMS calcd for $\text{C}_{11}\text{H}_{18}\text{NO}_3$ ($M + \text{H}$) 212.1287. Found 212.1284.

4.31. Dimethyl 5-Phenyl-3-hydroxy-1H-pyrrole-2-phosphonate (26a)

Yield 75% of a clear oil; IR (neat) 3256, 3026, 1716 cm^{-1} ; ^1H NMR (CDCl_3) δ 3.73 (s, 3 H), 3.75 (s, 3 H), 5.59 (s, 1 H), 6.53 (br, 2 H), 7.24 (m, 3 H), 7.45 (m, 2 H); ^{13}C NMR (CDCl_3) δ 53.0, 93.4, 93.5, 95.2, 112.5, 112.9, 120.6, 125.9, 126.1, 126.7, 127.2, 133.1; ^{31}P NMR (CDCl_3) δ 16.38. HRMS calcd for $\text{C}_{12}\text{H}_{15}\text{NO}_4\text{P}$ ($M + \text{H}$) 268.0739. Found 268.0735.

4.32. Dimethyl 5-(2-furyl)-3-hydroxy-1H-pyrrole-2-phosphonate (26b)

Yield 80% of a yellow oil; IR (neat) 3356, 1718, 1246 cm^{-1} ; ^1H NMR (CDCl_3) δ 3.72 (s, 3 H), 3.75 (s, 3 H), 5.63 (s, 1 H), 6.12 (s, 1 H), 6.42 (br, 1 H), 7.20 (m, 2 H), 7.87 (br, 1 H); ^{13}C NMR (CDCl_3) δ 53.0, 93.4, 93.5, 105.2, 105.8, 108.9, 109.0, 136.9, 156.3; ^{31}P NMR (CDCl_3) δ 16.42. HRMS calcd for $\text{C}_{10}\text{H}_{13}\text{NO}_5\text{P}$ ($M + \text{H}$) 258.0531. Found 258.0533.

4.33. Dimethyl 4-benzyl-5-phenyl-3-hydroxy-1H-pyrrole-2-phosphonate (26d)

Yield 51% of a clear oil; IR (neat) 3257, 3025, 1716 cm^{-1} ; ^1H NMR (CDCl_3) δ 3.72 (s, 3 H), 3.74 (s, 3 H), 4.54 (s, 2 H), 6.59 (br, 2 H), 7.29 (m, 8 H), 7.49 (m, 2 H); ^{13}C NMR (CDCl_3) δ 29.9, 53.0, 93.4, 93.5, 95.2, 95.3, 112.6, 118.9, 120.6, 125.8, 125.9, 126.2, 126.7, 127.1, 128.7, 128.8, 129.0, 129.1, 133.1, 136.4; ^{31}P NMR (CDCl_3) δ 17.26. HRMS calcd for $\text{C}_{19}\text{H}_{21}\text{NO}_4\text{P}$ ($M + \text{H}$) 358.1208. Found 358.1202.

4.34. Dimethyl 4-Methyl-5-(2-furyl)-3-hydroxy-1H-pyrrole-2-phosphonate (26e)

Yield 60% of a yellow oil; IR (neat) 3358, 1716, 1252 cm^{-1} ; ^1H NMR (CDCl_3) δ 2.01 (s, 3 H), 3.72 (s, 3 H), 3.74 (s, 3 H), 6.11 (s, 1 H), 6.47 (br, 1 H), 7.19 (m, 2 H), 7.84 (br, 1 H); ^{13}C NMR (CDCl_3) δ 10.4, 53.0, 93.4, 93.5, 105.2, 108.9, 109.0, 120.4, 136.9, 156.3; ^{31}P NMR (CDCl_3) δ 17.26. HRMS calcd for $\text{C}_{11}\text{H}_{15}\text{NO}_5\text{P}$ ($M + \text{H}$) 272.0688. Found 272.0689.

4.35. Dimethyl 4-Benzyl-5-(2-furyl)-3-hydroxy-1H-pyrrole-2-phosphonate (26f)

Yield 75% of a yellow oil; IR (neat) 3355, 1717, 1247 cm^{-1} ; ^1H NMR (CDCl_3) 3.71 (s, 3 H), 3.74 (s, 3 H), 4.60 (s, 2 H), 6.12 (s, 1 H), 7.19 (m, 2 H), 7.28 (m, 5 H); ^{13}C NMR (CDCl_3) δ 29.8, 53.0, 93.4, 93.5, 105.3, 109.0, 109.1, 120.6, 125.8, 128.6, 128.7, 128.9, 129.0, 136.9, 142.7, 156.3; ^{31}P NMR (CDCl_3) δ 17.28. HRMS calcd for $\text{C}_{17}\text{H}_{19}\text{NO}_5\text{P}$ (M + H) 348.1001. Found 348.1003.

4.36. 5-Phenyl-3-hydroxy-1-benzylloxycarbonyl-pyrrole-2-carboxylate (27)

In an oven-dried, 25-mL, single-necked, round-bottom flask equipped with a magnetic stirring bar, rubber septum, and argon balloon was placed **20** (0.100 g, 0.29 mmol) in anhydrous THF (10 mL), and Et_3N (0.15 mL, 1.08 mmol) was added. The reaction mixture was refluxed for 6 h, H_2O (0.5 mL) was added, and the solution was extracted with EtOAc (3×5 mL). The combined organic phases were washed with brine (5 mL), dried, and concentrated. Flash chromatography (40% EtOAc/Hexanes) afforded 0.041 g (68%) of a clear oil; IR (neat) 3354, 1716, 1668 cm^{-1} ; ^1H NMR (CDCl_3) δ 3.88 (s, 3 H), 4.96 (br, 1, H), 5.51 (br, 2 H), 6.13 (s, 1 H), 7.17 (m, 8 H), 7.23 (m, 2 H); ^{13}C NMR (CDCl_3) δ 52.5, 68.0, 110.2, 118.5, 120.6, 123.6, 125.7, 126.1, 126.6, 126.8, 127.4, 127.9, 128.2, 128.3, 129.3, 130.1, 142.3, 143.1, 154.9. HRMS calcd for $\text{C}_{20}\text{H}_{18}\text{NO}_5$ (M + H) 352.1185. Found 352.1179.

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23. Commercial available LR (low range) tablets from Orbeco Analytical Systems, Inc. were used. The peroxide reacts with KI to produce I_2 , which reacts with diethyl-*p*-phenylenediamine to produce a pink-red color.

Scheme 1.

Scheme 2.

Scheme 3.

Scheme 4.

Scheme 5.

13b: R = 2-Furyl, E = H**13c:** R = Me₃C, E = H**13d:** R = CH₂=CH, E = H**15a:** R = Ph, E = Me**15b:** R = Ph, E = Bn**15c:** R = 2-Furyl, E = Me**15d:** R = Me₃C, E = Me**25a** (75%)**25b** (81%)**25c** (81%)**25d** (78%)**25e** (67%)**25f** (67%)**25g** (50%) **14a:** R = Ph, E = H**14b:** R = 2-Furyl, E = H**14c:** R = Me₃C, E = H**16a:** R = Ph, E = Bn**16b:** R = 2-Furyl, E = Me**16c:** R = 2-Furyl, E = Bn**26a** (75%)**26b** (80%)**26c** (61%)**26d** (51%)**26e** (60%)**26f** (75%)

Scheme 6.

Scheme 7.

Table 1Reaction of electrophiles with the dianions of **13** and **14** at $-78\text{ }^{\circ}\text{C}$ in THF.

entry	Pyrrolidine 13/14 R =	E ⁺	15/16 , E = (% isolated yield)
1	13a , R = Ph	MeI	15a , E = Me (83)
2		BnBr	15b , E = Bn (79)
3		Oxaz ^a	NR ^b
4	13b , R = 2-furan 13c , R = <i>t</i> -Bu	MeI	15c , E = Me (88)
5		MeI	15d , E = Me (50)
6		BnBr	NR ^b
7	14a , R = Ph 14b , R = 2-furyl	BnBr	16a , E = Bn (41)
8		MeI	16b , E = Me (40)
9		BnBr	16c , E = Bn (70)

^a) 3 Equivalents of 8,8-(dichlorocamphorsulfonyl)oxaziridine were used.^b) Starting material was recovered.

Table 2Aromatization of pyrrolidine salt **22** to pyrrole **23** for 5 h in EtOAc at rt.

entry	additives	% isolated yield of pyrrole 23
1	SiO ₂ , air,	88
2	SiO ₂ , argon	No reaction
3	air	No reaction
4	TFA, air	80
5	TFA, argon	No reaction
6	Et ₃ N, air	33
7	pyridine, air	No reaction
8	Cs ₂ CO ₃	20