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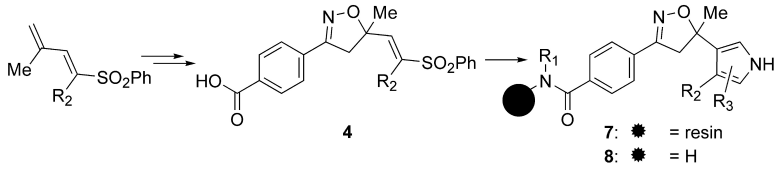
J. Comb. Chem., **2004**, 6 (1), 142-148• DOI: 10.1021/cc034023w • Publication Date (Web): 20 November 2003



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Solid-Phase Synthesis of an Isoxazolinopyrrole Library

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Received June 30, 2003

A four-step solid-phase synthesis of isoxazolinopyrroles **8** that employs an acid-labile 2-(4-formyl-3-methoxyphenoxy)ethyl polystyrene HL resin **1** is reported. Resin-bound vinyl sulfone **5** is obtained by DIC coupling with acid **4**, which was in turn synthesized in solution phase by a regioselective nitrile oxide 1,3-dipolar cycloaddition. The resin-bound pyrrole **7** was synthesized on solid phase by pyrrole annulation with various isocyano derivatives and potassium *t*-butoxide in which the sulfone α-anion generated by Michael addition gives the desired pyrrole through internal condensation followed by a sigmatropic [1,5]-hydrogen shift. The resulting isoxazolinopyrroles **8** were released from resin **7** by 10% TFA in moderate to excellent overall yields from 2-(4-formyl-3-methoxyphenoxy)ethyl polystyrene HL resin **1**.

Introduction

Combinatorial chemistry and related parallel synthesis techniques are important drug discovery tools for lead generation, target validation, and lead optimization,[1] and solid-phase organic synthesis (SPOS)[2] is arguably the most important method in combinatorial synthesis. The target of this investigation, isoxazolinopyrrole **8**, contains isoxazoline and pyrrole heterocycles that constitute important structural moieties occurring frequently in natural products and other biologically active compounds.[3] We, therefore, believe these isoxazolinopyrroles **8** may prove useful as a molecular scaffold for library production. Indeed, a solid-phase synthesis of isoxazolinopyrroles has already been described by our group[4] in which a sulfinate-functionalized resin [from styrene/2% divinylbenzene copolymer beads (PS/DVB)][5] was employed. Four problems were encountered in using this sulfinate-functionalized resin: (i) low yields (6−24%), (ii) a necessity for flash column chromatography purification after the cleavage step, (iii) difficulty in introducing diversity on the pyrrole moiety (e.g., **8i**, **8j**, **8k**, **and 8l**), and (iv) an inability to functionalize the pyrrole nitrogen prior to resin cleavage.

Results and Discussion

Herein, we report an efficient solution-/solid-phase synthesis of isoxazolinopyrroles **8** from acid-labile 2-(4-formyl-3-methoxyphenoxy)ethyl polystyrene HL resin **1** in which pyrrole annulation[4,6] is employed as the key solid-phase step, and nitrile oxide 1,3-dipolar cycloaddition[7] is employed as the key solution-phase step. In the first solid-phase step, 2-(4-formyl-3-methoxyphenoxy)ethyl polystyrene HL resin **1** (1.1 mmol/g) was loaded with various primary amines **2** by repeated reductive amination[8] (Scheme 1). It is generally known that imine formation of resin-bound aldehyde is slower than imine formation on resin-bound amine in reductive aminations; in the present example, repeat treatment was needed.[9] Complete reductive amination was confirmed by IR (disappearance of C═O peak at 1678 cm^{-1}) as well as by positive *p*-chloranil test (deep blue color).[10] The first real challenge confronted was development of a reliable route to the requisite polymer-bound vinyl sulfone **5**. Indeed, all attempts to introduce the vinyl sulfone moiety on polymer support were problematic. For example, attempts to introduce the vinyl sulfone moiety by reaction between the resin-bound oxime and excess phenylsulfonyl 1,3-diene through 1,3-dipolar cycloaddition was troublesome as a result of the polymerization of phenylsulfonyl-1,3-diene under the requisite basic conditions (e.g., I in Scheme 2). In an attempt to introduce the vinyl phenylsulfonyl moiety under neutral conditions by amide coupling, the preparation of carboxylic acid or free amine containing phenylsulfonyl 1,3-dienes was also investigated, but these compounds resulted in decomposition or polymerization by their own acidity or basicity (e.g., II in Scheme 2).

In light of these problems, we decided to introduce the required vinyl sulfone moiety as well as the isoxazoline moiety in solution phase by regioselective nitrile oxide 1,3-dipolar cycloaddition on phenyl sulfone-1,3-dienes as the key step (Scheme 3).[11] The resulting acids **4** were obtained from commercially available benzenesulfinic acid sodium salt **9** by S-alkylation with alkyl iodide; sulfone monoanion electrophilic 1,2-addition to methacrolein; acetylation followed by in situ (in the case of acid **4a**) or stepwise (in the case of acid **4b**) *β*-elimination; regioselective 1,3-dipolar cycloaddition to the distal C═C; and finally, saponification.[11] It should be noted that phenylsulfonyl 1,3-diene **12b**, the precursor for acid **4b**, could not be obtained unless a base stronger than DBU was employed.[12] Both phenylsulfonyl 1,3-dienes **12a** and **12b** were kept in solution because of their tendency to polymerize.[13] As anticipated, 1,3-dipolar cycloaddition of diene compounds **12a** and **12b** with the nitrile oxide derived from methyl 4-(hydroxyiminomethyl)benzoate (+ bleach) gave only isoxazolines **13a** and **13b**, respectively;

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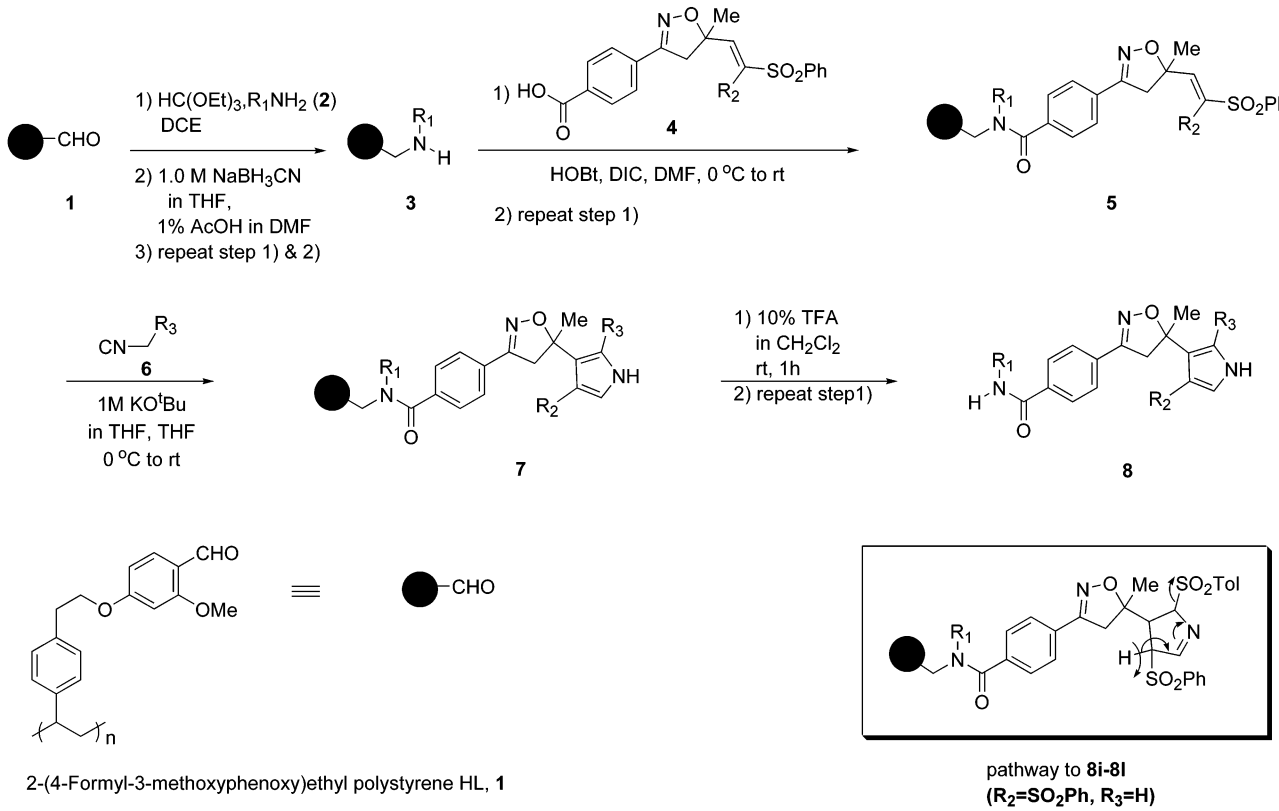
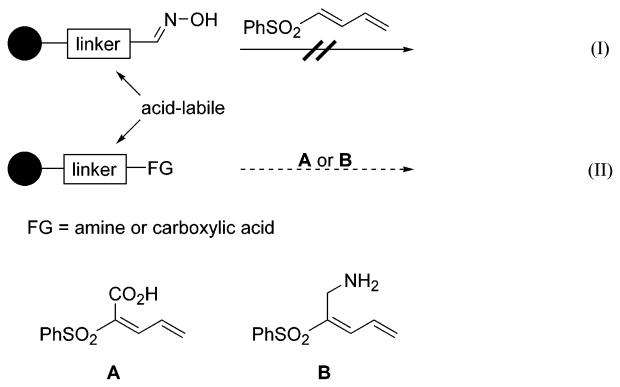
10.1021/cc034023w CCC: $27.50
Published on Web 11/20/2003

Scheme 1



Scheme 2

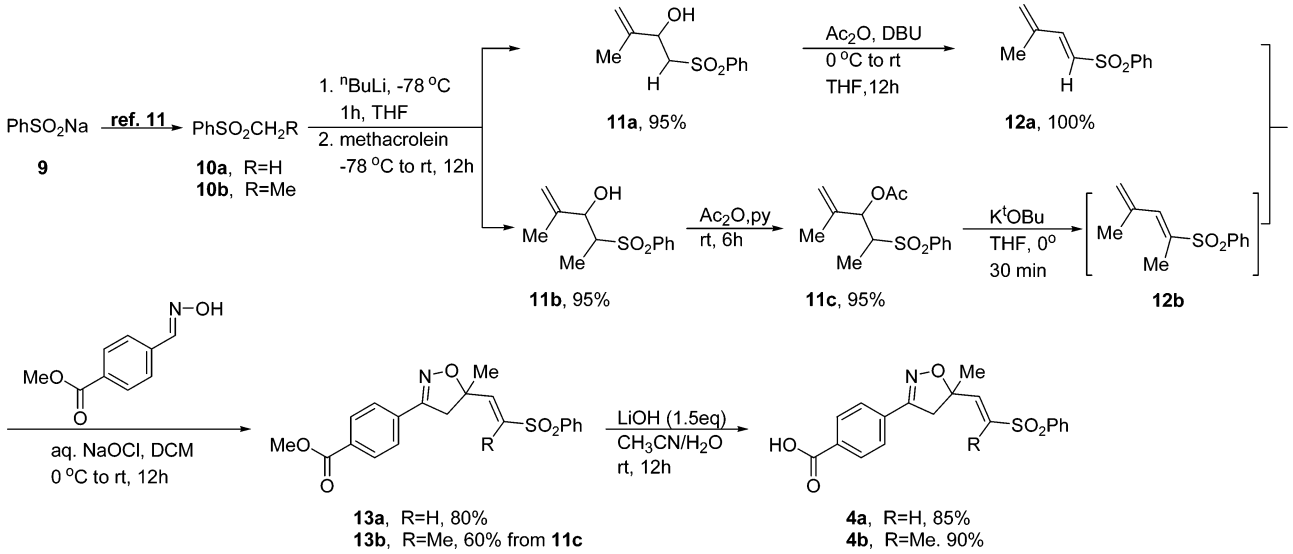


none of the regioisomeric or dicyclized alternatives were detected (e.g., we observed complete chemo- and regioselectivity; see **4a** in Figure 1 and **13b** in Figure 2).

Indeed, attempts to form the bis(isoxazoline) adduct of **13b** failed because nitrile oxide dimerization occurred in lieu of 1,3-dipolar cycloaddition to the vinyl sulfone moiety. Presumably, nitrile oxide dimerization is favored because of not only the steric hindrance imparted by the two bulky groups on the internal double bond, but also by sulfone deactivation of this dipolarophile. The methyl group at the C-5 isoxazoline position on acid **4** was necessary because sulfone elimination takes place in the presence of base if there is a proton at this position.[11] Targeted acids **4a** and **4b** were both obtained from commercially available benzenesulfinic acid sodium salt **9** in excellent yield (Scheme 3).

The vinyl sulfone moiety was tethered to resin by amide bond formation between resin **3** and acid **4** (4 equiv) in the presence of DIC (4 equiv) and HOBt (4 equiv). This transformation can be monitored by a negative *p*-chloranil test (disappearance of blue color) and was confirmed by TFA cleavage. Fortunately, no Michael addition of amine to the vinyl sulfone moiety occurred during this transformation. It should also be noted that amide bond formation required repeat treatment at higher resin loading (1.1 mmol/g), whereas it was not necessary at lower resin loading (0.51 mmol/g).[14] To obtain the desired pyrrole moiety on polymer support, pyrrole annulation[16] was performed with various isocyano derivatives (3 equiv) in the presence of K^{t}OBu (3 equiv) as base. Greater equivalents of K^{t}OBu resulted in lower yields. The desired isoxazolinopyrroles were obtained by resin cleavage with 10% TFA (see Table 1). As hoped, pure isoxazolinopyrroles (**8**) were obtained without the need for chromatographic purification.[15] Not surprisingly, the yields of isoxazolinopyrroles derived from vinyl sulfones lacking an α-methyl group (entries **8a**−**8l**) were lower than those obtained from α-methyl-substituted vinyl sulfones (entries **8m**−**8x**) because, as previously observed by Zard et al with α-substituted nitroalkenes,[16] cyclization in the case of a primary α-sulfonylcarbanion is inefficient [e.g., no product with **8e**−**8h**; low yield with **8a**, **8c**, **8d**, **8v**, and **8w**]. When isocyanoacetylpiperidine was used as the isocyano derivative in reaction with resin bound vinyl sulfone **5** having no methyl group on the vinyl sulfone, no product was obtained (entries **8e**−**8h**). Extending the observations of Magnus et al.,[13] isoxazolinopyrroles **8i**, **8j**, **8k**, and **8l** were obtained by exclusive elimination of the (4-methyl)phenyl sulfinate rather than the phenylsulfinate (see Scheme 1). Additionally, in the case of **8n**, no desired product was obtained. It should also be noted that attempted functionalization of the pyrrole nitrogen in resin **7** was problematic.

Scheme 3



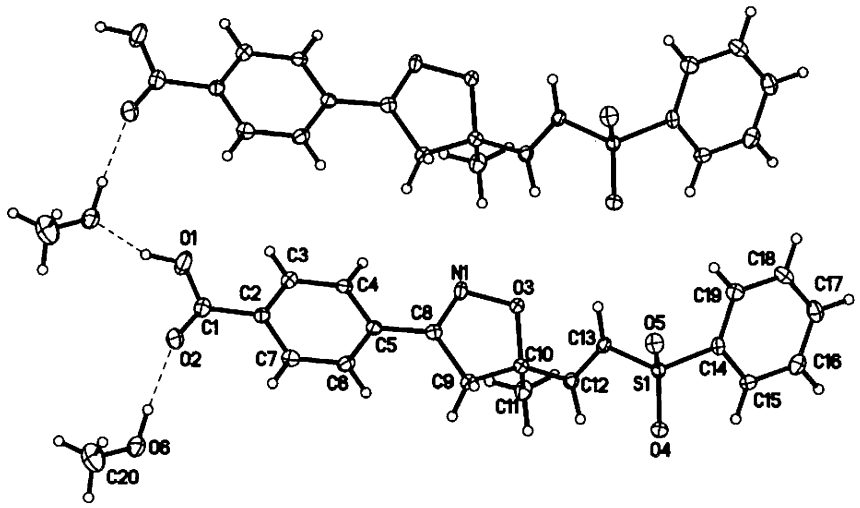


Figure 1. X-ray crystal structure of **4a**.

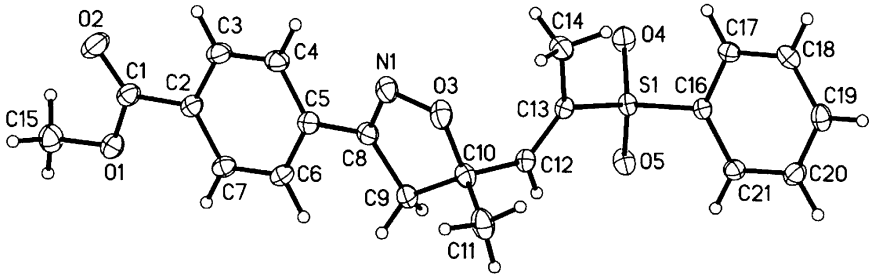


Figure 2. X-ray crystal structure of **13b**.

In contrast, there was no problem in the solution-phase model studies of this reaction using benzyl or benzoyl halide as the electrophiles. This provides yet another example of reactivity differences between solution- and solid-phase transformations.[17]

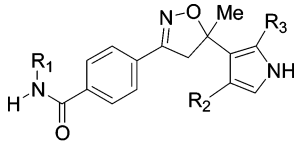
Conclusions

In summary, an efficient solid-phase parallel synthetic route to an isoxazolinopyrrole library has been developed. The advantages of this method include moderate to high product yields, excellent crude product purities, and the improved ability to C-functionalize the pyrrole scaffold.

Experimental Section

General. 2-(4-Formyl-3-methoxyphenoxy)ethyl polystyrene HL resin (100−200 mesh, 1% cross-linked; 1.1 mmol/g, batch no. A28821) and 2-(4-formyl-3-methoxyphenoxy)-ethyl polystryene resin (100−200 mesh, 1% cross-linked; 0.51 mmol/g, batch no. A25465) were purchased from Novabiochem. Hexamethyldisiloxane was purchased from Aldrich. Tetrahydrofuran was distilled from sodium/benzophenone ketyl immediately prior to use. The following reagents were prepared by literature methods: methyl vinyl sulfone **10a**,[11] ethyl vinyl sulfone **10b**,[11] (3-methylbuta-1,3-

Table 1. Isoxazolinopyrroles Generated on Solid Support



8

entry	R_1	R_2	R_3	MW (calcd)	MW (found) (MH^+)	yield (%)[a]	purity (%)[b]
8a	CH_2Ph	H	CO_2Et	431.2	432.2	32	99
8b	CH_2-2-Fu[c]	H	CO_2Et	421.2	422.2	44	99
8c	$CH_2CH(CH_3)_2$	H	CO_2Et	397.2	398.2	15	97
8d	$CH_2CH_2OCH_3$	H	CO_2Et	399.2	400.2	14	96
8e	CH_2Ph	H	C(O)-1-Pip[c]	470.2			
8f	CH_2-2-Fu[c]	H	C(O)-1-Pip[c]	460.2			
8g	$CH_2CH(CH_3)_2$	H	C(O)-1-Pip[c]	436.3			
8h	$CH_2CH_2OCH_3$	H	C(O)-1-Pip[c]	438.2			
8i	CH_2Ph	SO_2Ph[d]	H[d]	499.2	500.1	68	98
8j	CH_2-2-Fu[c]	SO_2Ph[d]	H[d]	489.1	490.1	26	97
8k	$CH_2CH(CH_3)_2$	SO_2Ph[d]	H[d]	465.2	466.2	30	98
8l	$CH_2CH_2OCH_3$	SO_2Ph[d]	H[d]	467.2	468.1	53	99
8m	CH_2Ph	Me	CO_2Et	445.2	446.2	44	95
8n	CH_2-2-Fu[c]	Me	CO_2Et	435.2			
8o	$CH_2CH(CH_3)_2$	Me	CO_2Et	411.2	412.3	70	89
8p	$CH_2CH_2OCH_3$	Me	CO_2Et	413.2	414.2	22	90
8q	CH_2Ph	Me	C(O)-1-Pip[c]	484.3	485.3	56	96
8r	CH_2-2-Fu[c]	Me	C(O)-1-Pip[c]	474.2	475.3	34	93
8s	$CH_2CH(CH_3)_2$	Me	C(O)-1-Pip[c]	450.3	451.3	100	84
8t	$CH_2CH_2OCH_3$	Me	C(O)-1-Pip[c]	452.2	453.3	27	78
8u	CH_2Ph	Me	SO_2Tol	527.2	528.3	26	98
8v	CH_2-2-Fu[c]	Me	SO_2Tol	517.2	518.3	31	99
8w	$CH_2CH(CH_3)_2$	Me	SO_2Tol	493.2	494.3	58	93
8x	$CH_2CH_2OCH_3$	Me	SO_2Tol	495.2	496.2	45	97

[a] Reported yields are determined by ^{1}H NMR integration with internal standard (hexamethyldisiloxane). The overall yields are based on the initial loading of the 2-(4-formyl-3-methoxyphenoxy)ethyl polystyrene HL resin **1**. [b] Purities were determined by HPLC [220−320 nm, on an Xterra MS C_{18} column; Waters, 2.1 mm × 50 mm × 3.5 μm) using a linear gradient from 5% CH_3CN (0.01% TFA) in water (0.01% TFA) to 100% CH_3CN (0.01% TFA) in 18 min (flow rate, 0.2 mL/min)]. [c] Fu = furan and Pip = piperidine. [d] In the case of entries **8i**−**8l**, the $-SO_2Ph$ moiety of the vinyl sulfone is retained, and the $-SO_2Tol$ moiety, derived from TosMIC, is eliminated.

diene-1-sulfonyl)benzene **12a**,[18,11] methyl 4-(hydroxyiminomethyl)benzoate,[19] and isocyanoacetylpiperidine.[20] Other solvents and reagents were used as received from commercial suppliers. Reactions in the solid phase were performed on a Trident automated library synthesizer (Argonaut Technologies). All reactions, unless otherwise described, were performed under an inert atmosphere of dry nitrogen. Melting points are uncorrected. All infrared spectra were determined on a Genesis II Mattson FTIR. ^{1}H and ^{13}C NMR were measured in $CDCl_3$ at 400 and 100 MHz, respectively. Yields were determined by ^{1}H NMR integration with internal standard (hexamethyldisiloxane). In the case of isoxazolinopyrroles (**8a** to **8l**), 5 μL (0.0235 mmol) of hexamethyldisiloxane was used. In the case of isoxazolinopyrroles (**8m**−**8x**), 10 μL (0.0471 mmol) of hexamethylsiloxane was used. Elemental analyses were determined at MidWest Microlab, Indianapolis, IN. The specifications of the LC/MS are as follows: LC/MS (with a Waters 2695 and a Waters PDA 996), ionization mode; electrospray (+), mass range 200−900 Da, 32-V cone voltage, column; XTerra MS C_{18} (Waters, 2.1 mm × 50 mm × 3.5 μm).

Methyl 4-[5-(2-Benzenesulfonylvinyl)-5-methyl-4,5-dihydroisoxazol-3-yl]benzoate (13a). Aqueous NaOCl (5.25%, 38.7 g) was added dropwise at 0 °C to a stirred mixture of methyl 4-(hydroxyiminomethyl)benzoate (2.52 g, 14.1 mmol) and (3-methylbuta-1,3-diene-1-sulfonyl)benzene **12a** (1.62 g, 7.8 mmol) in CH_2Cl_2 (78 mL). The mixture was vigorously stirred overnight at room temperature, at which time the phases were separated, and the aqueous phase was extracted with CH_2Cl_2 (30 mL × 2). The combined organic extracts were dried over $MgSO_4$, and the solvent was removed under reduced pressure. Triturating the resulting residue with Et_2O gave **13a** (2.4 g, 80%) as a white solid: mp 184 °C; IR (neat) 1713, 1611, 1591, 1282, 1147, 1085 cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 8.03 (d, J = 8 Hz, 2H), 7.87−7.84 (m 2H), 7.64 (d, J = 8 Hz, 2H), 7.63−7.50 (m, 3H), 7.01 (d, J = 15 Hz, 1H), 6.67 (d, J = 15 Hz, 1H), 3.91 (s, 3H), 3.35 (d, J = 17 Hz, 1H), 3.28 (d, J = 17 Hz, 1H), 1.62 (s, 3H); ^{13}C NMR δ 166.44, 155.50, 145.60, 139.84, 133.88, 133.23, 131.77, 130.55, 130.14, 129.56, 127.92, 126.65, 85.65, 52.49, 46.14, 25.38. Anal. Calcd for $C_{20}H_{19}NO_5S$: C, 62.32; H, 4.97; N, 3.63; S, 8.32. Found: C, 62.14; H, 4.99; N, 3.54; S, 8.07.

4-[5-(2-Benzenesulfonylvinyl)-5-methyl-4,5-dihydroisoxazol-3-yl]benzoic Acid 4a. Lithium hydroxide (47 mg, 1.95 mmol) was added at room temperature to a solution of ester **13a** (0.5 g, 1.3 mmol) in CH_3CN/H_2O (30 mL, 3:1). The mixture was stirred overnight at room temperature, at which time the reaction was quenched by addition of TFA (0.15 mL). The solvent was removed under reduced pressure, and the resulting white precipitate formed was collected by filtration and recrystallized with MeOH to give **4a** (0.41 g, 85%) as a white solid. mp 191.8 °C; IR (neat) 2875, 1677,

1612, 1593, 1282, 1143, 1087 cm^{-1}; ^1H NMR ($CDCl_3$): δ 8.12 (d, $J = 8$ Hz, 2H), 7.88 (d, $J = 8$ Hz, 2H), 7.69 (d, $J = 8$ Hz, 2H), 7.64−7.53 (m, 3H), 7.04 (d, $J = 15$ Hz, 1H), 6.70 (d, $J = 15$ Hz, 1H), 3.39 (d, $J = 17$ Hz, 1H), 3.31 (d, $J = 17$ Hz, 1H), 1.65 (s, 3H); ^{13}C NMR δ 171.11, 155.46, 145.57, 139.82, 134.11, 133.90, 130.77, 130.59, 129.58, 127.94, 126.77, 85.80, 46.09, 25.38. Anal. Calcd for $C_{19}H_{17}NO_5S$: C, 61.44; H, 4.61; N, 3.77; S, 8.63. Found: C, 61.56; H, 4.72; N, 3.66; S, 8.48.

4-Benzenesulfonyl-2-methylpent-1-en-3-ol (11b). To a solution of ethyl phenyl sulfone **10b** (10.9 g, 64 mmol) in THF (300 mL) was added *n*-butyllithium (48 mL, 76.8 mmol) at −78 °C. After stirring 1 h at −78 °C, methacrolein (6.1 mL, 70.4 mmol) was added, and the reaction mixture was allowed to warm to room temperature with stirring for 30 min. Water was added, and the THF was removed under reduced pressure. The resulting aqueous mixture was extracted with EtOAc (300 mL × 3), and the combined extracts were dried over $MgSO_4$, filtered, and evaporated under reduced pressure. The colorless oil (**11b**; 14.6 g, 95%) was used without further purification. IR (neat) 3481, 1645, 1282, 1141 cm^{-1}; ^1H NMR ($CDCl_3$): δ 7.94 (d, $J = 8$ Hz, 2H), 7.73−7.59 (m, 3H), 5.18 (br s, 0.5H), 5.00 (br q, $J = 1$ Hz, 0.5H), 4.94−4.90 (m, 1H), 4.71 (br s, 0.5H), 4.38 (dd, $J =$ 9 and 1 Hz, 0.5H), 4.16 (d, $J = 1$ Hz, 0.5H), 3.24 (dq, $J =$ 9 and 7 Hz, 0.5H), 3.16 (dq, $J = 7$ and 1 Hz, 0.5H), 2.97−2.94 (m, 0.5H), 1.72 (s, 1.5H), 1.60 (s, 1.5H), 1.25 (d, $J =$ 7 Hz, 1.5H), 1.03 (d, $J = 7$ Hz, 1.5H); ^{13}C NMR δ 142.34, 141.92, 137.45, 136.98, 134.30, 134.15, 129.42, 129.40, 129.17, 128.87, 116.29, 112.89, 75.79, 70.25, 63.10, 61.70, 19.54, 16.18, 12.60, 6.20. Anal. Calcd for $C_{12}H_{16}O_3S$: C, 59.97; H, 6.71; S, 13.34. Found: C, 60.03; H, 6.68; S, 13.12.

1-(1-Benzenesulfonylethyl)-2-methylallyl Acetate (11c). To a solution of 4-benzenesulfonyl-2-methyl-pent-1-en-3-ol **11b** (2.23 g, 9.3 mmol) in pyridine (10 mL) was added acetic anhydride (10 mL) and a catalytic amount of DMAP at room temperature. The mixture was stirred at room temperature overnight. The reaction was quenched by H_2O. EtOAc was added, and the organic layer was washed with H_2O (× 2) and with saturated aqueous $CuSO_4$ solution until the water layer remained a light blue color and then washed with saturated $NaHCO_3$ solution until the bubbles ceased. The organic layer was dried with $MgSO_4$ and evaporated under reduced pressure. It was used without further purification and 2.5 g (95%) of **11c** was obtained as a white oil. IR (neat) 1735, 1651, 1298, 1286, 1240, 1138 cm^{-1}; ^1H NMR ($CDCl_3$): δ 7.91−7.86 (m, 2H), 7.70−7.55 (m, 3H), 5.69 (s, 0.5H), 5.46 (d, $J = 9.5$ Hz and 0.5H), 5.06 (s, 0.5H), 5.03−5.01 (m, 0.5H), 4.94−4.92 (m, 0.5H), 4.84−4.83 (m, 0.5H), 3.49 (dq, $J = 9.5$ and 7 Hz, 0.5H), 3.23 (dq, $J = 7$ and 1.5 Hz, 0.5H), 1.86 (s, 1.5H), 1.68−1.65 (m, 4.5H), 1.39 (d, $J = 7$ Hz, 1.5H), 1.27 (d, $J = 7$ Hz, 1.5H); ^{13}C NMR δ 169.15, 169.12, 140.18, 139.45, 139.34, 137.64, 133.94, 133.67, 129.22, 129.20, 128.70, 117.96, 112.67, 76.07, 71.65, 61.40, 61.08, 20.75, 20.71, 19.55, 17.37, 11.02, 7.74. Anal. Calcd for $C_{14}H_{18}O_4S$: C, 59.55; H, 6.43; S, 11.36. Found: C, 59.92; H, 6.28; S, 11.07.

(4-Methyl-penta-2,4-diene-2-sulfonyl)benzene (12b). To a solution of acetic acid 1-(1-benzenesulfonyl-ethyl)-2-methyl-allyl ester **11c** (5.92 g, 21 mmol) in THF (210 mL), 1 M K^tOBu in THF (21 mL, 21 mmol) was added at 0 °C. The reaction mixture was stirred for 30 min and then quenched by adding H_2O. The solvent was removed under reduced pressure, and the aqueous residue was extracted with CH_2Cl_2 (50 mL × 3). The combined extracts were dried with $MgSO_4$ and evaporated under reduced pressure. It was used without further purification. This product was characterized by ^1H NMR ($CDCl_3$): δ 7.88−7.85 (m, 2H), 7.63−7.50 (m, 4H), 5.30 (dd, $J = 1.6$ Hz, 1H), 5.15 (s, 1H), 2.00 (d, $J =$ 1.6 Hz, 3H), 1.95 (s, 3H) and IR (neat) disappearance of the C═O peak (1735 cm^{-1}).

Methyl 4-[5-(2-Benzenesulfonylpropenenyl)-5-methyl-4,5-dihydro-isoxazol-3-yl]benzoate (13b). Compound **13b** (2.22 g, 60%) as a white solid was synthesized from **11c** (2.63 g) by the same method as that described for **13a** after purification by column chromatography (30% EtOAc in hexanes). mp 154 °C; IR (neat) 1713, 1610, 1592, 1282, 1157, 1085 cm^{-1}; ^1H NMR ($CDCl_3$): δ 8.07 (d, $J = 8$ Hz, 2H), 7.88−7.84 (m, 2H), 7.69 (d, $J = 8$ Hz, 2H), 7.66−7.61 (m, 1H), 7.56−7.52 (m, 2H), 7.12−7.09 (m, 1H), 3.94 (s, 3H), 3.43 (d, $J = 17$ Hz, 1H), 3.35 (d, $J = 17$ Hz, 1H), 2.06−2.04 (m, 3H), 1.64 (s, 3H); ^{13}C NMR δ 166.41, 155.65, 141.35, 139.78, 138.36, 133.70, 133.38, 131.59, 130.08, 129.42, 128.35, 126.62, 86.32, 52.46, 47.09, 26.75, 12.47. Anal. Calcd for $C_{21}H_{21}NO_5S$: C, 63.14; H, 5.30; N, 3.51; S, 8.03. Found: C, 62.79; H, 5.28; N, 3.39; S 7.90.

4-[5-(2-Benzenesulfonylpropenenyl)-5-methyl-4,5-dihydroisoxazol-3-yl]-benzoic Acid 4b. The title compound was prepared in 90% isolated yield as a white solid (1.25 mmol scale) from 4-[5-(2-Benzenesulfonyl-propenenyl)-5-methyl-4,5-dihydro-isoxazol-3-yl]-benzoic acid methyl ester **13b** and LiOH following a procedure similar to that described above for **4a**, except product was washed with Et_2O instead of recrystallization with MeOH. mp 189 °C; IR (neat) 2865, 1682, 1616, 1592, 1286, 1158, 1086 cm^{-1}; ^1H NMR ($CDCl_3$): δ 8.14 (d, $J = 8$ Hz, 2H), 7.87−7.84 (m, 2H), 7.73 (d, $J = 8$ Hz, 2H), 7.65−7.52 (m, 3H), 7.12 (s, 1H), 3.45 (d, $J = 17$ Hz, 1H), 3.36 (d, $J = 17$ Hz, 1H), 2.05 (s, 3H), 1.65 (s, 3H); ^{13}C NMR δ 171.14, 155.44, 141.00, 139.84, 138.20, 134.13, 133.60, 130.65, 129.32, 128.29, 126.61, 86.35, 47.02, 26.70, 12.37. Anal. Calcd for $C_{20}H_{19}NO_5S$: C, 62.32; H, 4.97; N, 3.63; S, 8.32. Found: C, 62.30; H, 5.03; N, 3.63; S, 8.26.

General Procedure for Solid-Phase Synthesis of Isoxazolinopyrroles. Ethyl 3-[3-(4-Benzylcarbamoylphenyl)-5-methyl-4,5-dihydroisoxazol-5-yl]-1H-pyrrole-2-carboxylate 8a. (A) Reductive Amination. 2-(4-Formyl-3-methoxyphenoxy) ethyl polystyrene HL **1** beads (80 mg) (IR (neat) 1678, 1601, 1492, 1452 cm^{-1}) were swollen in DCE for 1 h. The DCE was drained, and triethylorthoformate (3.45 mL) was added to the resin, followed by addition of 0.9 M benzylamine in DCE (3.910 mL) at room temperature, and then agitated for 2 h. The solution was removed by suction, and the resin was treated with 1 M $NaBH_3CN$ in THF (3.52 mL) and 1% AcOH in DMF (3.52 mL) overnight under N_2. The resin was washed five times with DMF, MeOH, and

DCM. The procedure was repeated, affording polymer-bound amine **3** as yellow beads (positive *p*-chloranil test): IR (neat) 1601, 1492, 1452 cm^{-1}.

(B) Coupling. Polymer **3** (80 mg) was swollen in DMF (3.5 mL) and 0.2 M HOBt·H_2O in DMF (1.76 mL) and 0.12 M 4-[5-(2-benzenesulfonyl-vinyl)-5-methyl-4,5-dihydro-isoxazol-3-yl]-benzoic acid **4a** in DMF (2.93 mL) were added at room temperature, after which 0.2 M DIC in DMF (1.76 mL) was added at 0 °C. The resulting solution was agitated overnight at room temperature. The solution was removed by suction. The procedure was repeated. The resin was washed three times with DMF, MeOH, and DCM (negative *p*-chloranil test), affording polymer **7** as yellow beads: IR (neat) 1679, 1636, 1602, 1493, 1452,1262,1148 cm^{-1}.

(C) Pyrrole Annulation. Polymer **5** (80 mg) was swollen in THF (3.5 mL) for 30 min. 0.1 M ethyl isocyanoacetate in THF (2.640 mL) and 1 M potassium *tert*-butoxide in THF (0.264 mL) were added at −5 °C. The reaction mixture was stirred at the same temperature for 1 h. The reaction mixture was warmed to room temperature and then agitated for 15 h. The reaction was quenched by adding water and then agitated for 1 h. The solution was removed. The resin was washed three times with THF/H_2O (1:1) and then three times with DMF, water, THF, MeOH, and DCM, affording polymer **7** as yellow beads: IR (neat) 1703, 1634, 1601, 1493, 1452 cm^{-1}.

(D) Cleavage. Polymer **7** (80 mg) was treated with a 10% v/v solution of TFA in CH_2Cl_2 (3 mL). The reaction was agitated for 1 h. The solution was collected, and the remaining resin was retreated with a 10% TFA in CH_2Cl_2 for an additional 1 h. The solution was collected, and the resins were washed and collected with CH_2Cl_2 (2 × 3 mL). The combined solution was concentrated under pressure using a Genevac DD-4 centrifugal evaporator, affording isoxazolinopyrrole **8a**.

8a. HPLC: RT = 0.97 min. ^{1}H NMR ($CDCl_3$): δ 9.15 (br s, 1H), 7.78 (d, J = 9 Hz, 2H), 7.72 (d, J = 9 Hz, 2H), 7.38−7.35 (m, 5H), 6.83 (t, J = 3 Hz, 1H), 6.55 (t, J = 3 Hz, 1H), 6.54−6.49 (m, 1H), 4.66 (d, J = 5.5 Hz, 2H), 4.35 (q, J = 7 Hz, 2H), 3.63 (d, J = 5 Hz, 2H), 1.85 (s, 3H), 1.38 (t, J = 7 Hz, 3H). MS (ESI) m/z: 432.2 (M + H^+).

8b. HPLC: RT = 0.95 min. ^{1}H NMR ($CDCl_3$): δ 9.14 (br s, 1H), 7.78 (d, J = 8 Hz, 2H), 7.72 (d, J = 8 Hz, 2H), 7.40−7.38 (m, 1H), 6.83 (t, J = 3 Hz, 1H), 6.56 (t, J = 3 Hz, 1H), 6.52−6.48 (m, 1H), 6.36−6.31 (m, 2H), 4.65 (d, J = 5.5 Hz, 2H), 4.35 (q, J = 7 Hz, 2H), 3.63 (d, J = 5 Hz, 2H), 1.86 (s, 3H), 1.38 (t, J = 7 Hz, 3H). MS (ESI) m/z: 422.2 (M + H^+).

8c. HPLC: RT = 0.99 min. ^{1}H NMR ($CDCl_3$): δ 9.10 (br s, 1H), 7.77 (d, J = 9 Hz, 2H), 7.72 (d, J = 9 Hz, 2H), 6.83 (t, J = 3 Hz, 1H), 6.57 (t, J = 3 Hz, 1H), 6.20−6.10 (m, 1H), 4.36 (q, J = 7 Hz, 2H), 3.64 (d, J = 3 Hz, 2H), 3.30 (dd, J = 7 Hz and 6 Hz, 2H), 1.96−1.88 (m, 1H), 1.86 (s, 3H), 1.39 (t, J = 7 Hz, 3H), 0.99 (d, J = 7 Hz, 6H). MS (ESI) m/z: 398.2 (M + H^+).

8d. HPLC: RT = 0.98 min. ^{1}H NMR ($CDCl_3$): δ 9.11 (br s, 1H), 7.78 (d, J = 8 Hz, 2H), 7.72 (d, J = 8 Hz, 2H), 6.83 (t, J = 3 Hz, 1H), 6.56 (t, J = 3 Hz, 1H), 6.54−6.49 (m, 1H), 4.35 (q, J = 7 Hz, 2H), 3.68−3.63 (m, 4H), 3.57 (t, J = 5 Hz, 2H), 3.40 (s, 3H), 1.86 (s, 3H), 1.39 (t, J = 7 Hz, 3H). MS (ESI) m/z: 400.2 (M + H^+).

8i. HPLC: RT = 0.96 min. ^{1}H NMR ($CDCl_3$): δ 8.64 (br s, 1H), 7.91−7.88 (m, 2H), 7.78 (d, J = 8 Hz, 2H), 7.62 (d, J = 8 Hz, 2H), 7.58−7.48 (m, 4H), 7.38−7.30 (m, 5H), 6.98 (t, J = 3 Hz, 1H), 6.42−6.38 (m, 1H), 4.66 (d, J = 6 Hz, 2H), 3.69 (d, J = 17 Hz, 1H), 3.35 (d, J = 17 Hz, 1H), 1.70 (s, 3H). MS (ESI) m/z: 500.1 (M + H^+).

8j. HPLC: RT = 0.95 min. ^{1}H NMR ($CDCl_3$): δ 8.87 (br s, 1H), 7.89 (d, J = 8 Hz, 2H), 7.76 (d, J = 8 Hz, 2H), 7.75−7.40 (m, 4H), 7.61 (d, J = 8 Hz, 2H), 7.34−7.31 (m, 1H), 6.95 (s, 1H), 6.62−6.56 (m, 1H), 6.36−6.31 (m, 2H), 4.65 (d, J = 5 Hz, 2H), 3.69 (d, J = 17 Hz, 1H), 3.33 (d, J = 17 Hz, 1H), 1.69 (s, 3H). MS (ESI) m/z: 490.1 (M + H^+).

8k. HPLC: RT = 0.96 min. ^{1}H NMR ($CDCl_3$): δ 8.90 (br s, 1H), 7.91−7.88 (m, 2H), 7.75 (d, J = 8 Hz, 2H), 7.62 (d, J = 8 Hz, 2H), 7.56−7.48 (m, 4H), 6.96 (t, J = 3 Hz, 1H), 6.26−6.20 (m, 1H), 3.69 (d, J = 17 Hz, 1H), 3.34 (d, J = 17 Hz, 1H), 3.29 (t, J = 7 Hz, 2H), 1.91 (septet, J = 7 Hz, 1H), 1.69 (s, 3H), 0.99 (d, J = 7 Hz, 6H). MS (ESI) m/z: 466.2 (M + H^+).

8l. HPLC: RT = 0.97 min. ^{1}H NMR ($CDCl_3$): δ 8.95 (br s, 1H), 7.92−7.48 (m, 11H), 6.91−6.88 (m, 1H), 3.65−3.52 (m, 6H), 3.41 (s, 3H), 1.64 (s, 3H). MS (ESI) m/z: 468.1 (M + H^+).

8m. HPLC: RT = 0.98 min. ^{1}H NMR ($CDCl_3$): δ 8.93 (br s, 1H), 7.79 (d, J = 9 Hz, 2H), 7.74 (d, J = 9 Hz, 2H), 7.40−7.34 (m, 5H), 6.61 (d, J = 3 Hz, 1H), 6.57−6.51 (m, 1H), 4.66 (d, J = 6 Hz, 2H), 4.34 (dq, J = 7 and 2 Hz, 2H), 3.78 (d, J = 17 Hz, 1H), 3.67 (d, J = 17 Hz, 1H), 2.30 (s, 3H), 1.83 (s, 3H), 1,39 (t, J = 7 Hz, 3H). MS (ESI) m/z: 446.2 (M + H^+).

8o. HPLC: RT = 1.00 min. ^{1}H NMR ($CDCl_3$): δ 8.94 (br s, 1H), 7.77−7.74 (m, 4H), 6.62 (d, J = 2 Hz, 1H), 6.40−6.32 (m, 1H), 4.34 (dq, J = 7 and 2 Hz, 2H), 3.78 (d, J = 17 Hz, 1H), 3.67 (d, J = 17 Hz, 1H), 3.31 (t, J = 7 Hz, 2H), 2.31 (s, 3H), 1.98−1.86 (m, 1H), 1.83 (s, 3H), 1.39 (t. J = 7 Hz, 3H), 0.99 (d, J = 7 Hz, 6H). MS (ESI) m/z: 412.3 (M + H^+).

8p. HPLC: RT = 1.00 min. ^{1}H NMR ($CDCl_3$): δ 8.92 (br s, 1H), 7.78 (d, J = 9 Hz, 2H), 7.74 (d, J = 9 Hz, 2H), 6.66−6.60 (m, 2H), 4.34 (dq, J = 7 and 2 Hz, 2H), 3.81−3.57(m, 6H), 3.40 (s, 3H), 2.31 (s, 3H), 1.83 (s, 3H), 1.39 (t, J = 7 Hz, 3H). MS (ESI) m/z: 414.2 (M + H^+).

8q. HPLC: RT = 1.00 min. ^{1}H NMR ($CDCl_3$): δ 8.64 (br s, 1H), 7.78 (d, J = 8 Hz, 2H), 7.68 (d, J = 8 Hz, 2H), 7.39−7.30 (m, 5H), 6.65−6.59 (m, 1H), 6.58 (br s, 1H), 4.65 (d, J = 6 Hz, 2H), 3.61−3.50 (m, 4H), 3.46 (d, J = 17 Hz, 1H), 3.41 (d, J = 17 Hz, 1H), 2.13 (s, 3H), 1.73 (s, 3H), 1.69−1.58 (m, 6H). MS (ESI) m/z: 485.3 (M + H^+).

8r. HPLC: RT = 0.99 min. ^{1}H NMR ($CDCl_3$): δ 8.57 (br s, 1H), 7.72 (d, J = 8 Hz, 2H), 7.62 (d, J = 8 Hz, 2H), 7.33−7.32 (m, 1H), 6.55−6.49 (m, 2H), 6.29−6.25 (m, 2H), 4.65 (d, J = 6 Hz, 2H), 3.61−3.51 (m, 4H), 3.51 (d, J = 17 Hz, 1H), 3.41 (d, J = 17 Hz, 1H), 2.07 (s, 3H), 1.67 (s, 3H), 1.64−1.50 (m, 6H). MS (ESI) m/z: 475.3 (M + H^+).

8s. HPLC: RT = 1.02 min. ^{1}H NMR ($CDCl_3$): δ 8.66 (br s, 1H), 7.75 (d, J = 8 Hz, 2H), 7.69 (d, J = 8 Hz, 2H), 6.59−6.57 (m, 1H), 6.44−6.37 (m, 1H), 3.61−3.50 (m, 4H), 3.50 (d, J = 17 Hz, 1H), 3.41 (d, J = 17 Hz, 1H), 3.30 (t, J = 7 Hz, 2H), 2.13 (s, 3H), 1.92 (septet, J = 7 Hz, 1H), 1.73 (s, 3H), 1.70−1.58 (m, 6H), 0.98 (d, J = 7 Hz, 6H). MS (ESI) m/z: 451.3 ($M + H^+$).

8t. HPLC: RT = 1.01 min. ^{1}H NMR ($CDCl_3$): δ 8.53 (br s, 1H), 7.78 (d, J = 8 Hz, 2H), 7.70 (d, J = 8 Hz, 2H), 6.74−6.66 (m, 1H), 6.59−6.56 (m, 1H), 3.67 (q, J = 5 Hz, 2H), 3.60−3.53 (m, 8H), 3.40 (s, 3H), 2.13 (s, 3H), 1.74 (s, 3H), 1.70−1.56 (m, 6H). MS (ESI) m/z: 453.3 ($M + H^+$).

8u. HPLC: RT = 0.96 min. ^{1}H NMR ($CDCl_3$): δ 9.35 (br s, 1H), 7.77−7.72 (m, 6H), 7.57 (d, J = 9 Hz, 2H), 7.40−7.32 (m, 5H), 6.79 (d, J = 3 Hz, 1H), 6.67−6.59 (m, 1H), 4.66 (d, J = 6 Hz, 2H), 3.49 (d, J = 17 Hz, 1H), 3.42 (d, J = 17 Hz, 1H), 2.38 (s, 3H), 2.22 (s, 3H), 1.58 (s, 3H). MS (ESI) m/z: 528.3 ($M + H^+$).

8v. HPLC: RT = 0.96 min. ^{1}H NMR ($CDCl_3$): δ 9.32 (br s, 1H), 7.80−7.68 (m, 4H), 7.57 (d, J = 8 Hz, 2H), 7.39 (s, 1H), 7.30−7.26 (m, 2H), 6.81−6.78 (m, 1H), 6.62−6.54 (m, 1H), 6.38−6.31 (m, 2H), 4.66 (d, J = 5 Hz, 2H), 3.50 (d, J = 17 Hz, 1H), 3.42 (d, J = 17 Hz, 1H), 2.38 (s, 3H), 2.22 (s, 3H), 1.59 (s, 3H). MS (ESI) m/z: 518.3 ($M + H^+$).

8w. HPLC: RT = 0.97 min. ^{1}H NMR ($CDCl_3$): δ 9.23 (br s, 1H), 7.74 (d, J = 8 Hz, 4H), 7.57 (d, J = 8 Hz, 2H), 7.28 (d, J = 8 Hz, 2H), 6.80−6.77 (m, 1H), 6.24−6.14 (m, 1H), 3.50 (d, J = 17 Hz, 1H), 3.42 (d, J = 17 Hz, 1H), 3.30 (t, J = 7 Hz, 2H), 2.39 (s, 3H), 2.23 (s, 3H), 1.96−1.82 (m, 1H), 1.60 (s, 3H), 0.99 (d, J = 7 Hz, 6H). MS (ESI) m/z: 494.3 ($M + H^+$).

8x. HPLC: RT = 0.98 min. ^{1}H NMR ($CDCl_3$): δ 9.35 (br s, 1H), 7.78−7.69 (m, 4H), 7.57 (d, J = 9 Hz, 2H), 7.30−7.26 (m, 2H), 6.79 (d, J = 3 Hz, 1H), 6.78−6.64 (m, 1H), 3.70−3.66 (m, 2H), 3.62−3.56 (m, 2H), 3.52−3.40 (m, 2H), 3.41 (s, 3H), 2.38 (s, 3H), 2.23 (s, 3H), 1.60 (s, 3H). MS (ESI) m/z: 496.2 ($M + H^+$).

Acknowledgment. We thank the National Science Foundation and Cystic Fibrosis Foundation for financial support of this research. The 400- and 300-MHz NMR spectrometers used in this study were funded in part by a grant from NSF (CHE-9808183).

Supporting Information Available. X-ray crystallographic data for **4a** and **13b** as well as ^{1}H spectra and LC/MS spectra for isoxazolinopyrroles **8** (57 pages). This material is available free of charge via the Internet at http://pubs.acs.org.

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CC034023W