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Stannyl Radical-Mediated Cleavage of π-Deficient Heterocyclic Sulfones. Synthesis of α-Fluoro Esters

Stanislaw F. Wnuk,* Jeannette M. Rios, Jahanzeb Khan, and Ya-Li Hsu

Department of Chemistry, Florida International University, Miami, Florida 33199

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Treatment of ethyl 2-(pyridin-2-ylsulfonyl)hexanoate with tributylstannane and azobis(2-methyl-2-propanitrile) (AIBN) in benzene at reflux for 36 h resulted in hydrogenolysis to give ethyl hexanoate (60%), whereas no reaction was observed after 48 h at reflux with ethyl 2-(phenylsulfonyl)-hexanoate. Ethyl 2-(pyrimidin-2-ylsulfonyl)hexanoate underwent quantitative hydrogenolysis within 1 h under these conditions. This represents a mild new methodology for removal of the synthetically useful sulfone moiety. Substitution of Bu_3SnD for Bu_3SnH gave access to α-deuterium-labeled esters. Treatment of the α-(pyrimidin-2-ylsulfonyl) enolates derived from several esters with Selectfluor gave high yields of the 2-fluoro-2-(pyrimidin-2-ylsulfonyl)alkanoates, which were smoothly desulfonylated [Bu_3SnH (2 equiv)/AIBN/benzene/Δ] to give 2-fluoroalkanoates. "Catalytic" tin hydride, generated from tribuytltin chloride (0.15 equiv) and excess polymethylhydrosiloxane in the presence of potassium fluoride, also effected removal of the π-deficient α-(pyrimidin-2-ylsulfonyl) moiety from acid derivatives in high yields. Desulfonylation is suggested to proceed via alkoxy ketyl-type radicals and tin enolates.

Introduction

The sulfone group is a well-established activating moiety for construction of carbon−carbon skeletons and other transformations.[1] During recent work on synthesis of a 6′-deoxy-6′-fluorohomonucleoside phosphonate from uridine, we found that standard procedures for desulfonylation[1d] [e.g., Al(Hg) or Na(Hg); or base-promoted elimination] were ineffective for removal of the pyridin-2-ylsulfonyl group from the α-carbon of phosphonic esters.[2] We then explored the feasibility of a radical-mediated cleavage of sulfonyl groups from the α-carbon of carboxylic and phosphonic esters with tributyltin hydride. Our initial success prompted us to investigate the broader potential of radical cleavage of π-deficient heterocyclic sulfones.

Tributylstannane is used routinely for hydrogenolysis of carbon−halogen, carbon−sulfur, carbon−selenium, and carbon−nitro bonds,[3] but is generally recognized as ineffective for cleavage of saturated sulfones.[1d] Recently, desulfonylation of β-ketosulfones,[4] *N*-sulfonylated amides,[5] and 2-(alkyl and aryl)sulfonylpyrroles with Bu_3SnH[6] as well stannodesulfonylations of vinyl sulfones[7] have been reported. Desulfonylations of allylic sulfones[8a] with tributylstannane are known, and sulfonyl radicals are versatile intermediates in organic synthesis.[8b]

Selective introduction of fluorine into organic molecules often causes significant changes in biological activity.[9] In particular, α-fluoro carbonyl compounds are important since they have been utilized as diagnostic tools in metabolic processes and serve as building blocks in the synthesis of more complex molecules.[9a,b,e] α-Fluoro esters have been prepared from toxic fluoroacetate ions,[10] by reaction of α-hydroxy esters with DAST,[11] electrophilic fluorination of stabilized carbanions, enolates or silyl enol ethers,[12] metal-catalyzed addition of fluoroiodoacetates to alkenes,[13] and Reformatsky reactions with bromofluoroacetates.[14] Other methods also exist.[9]

* To whom correspondence should be addressed. E-mail: wnuk@fiu.edu. Fax: (305) 348−3772.

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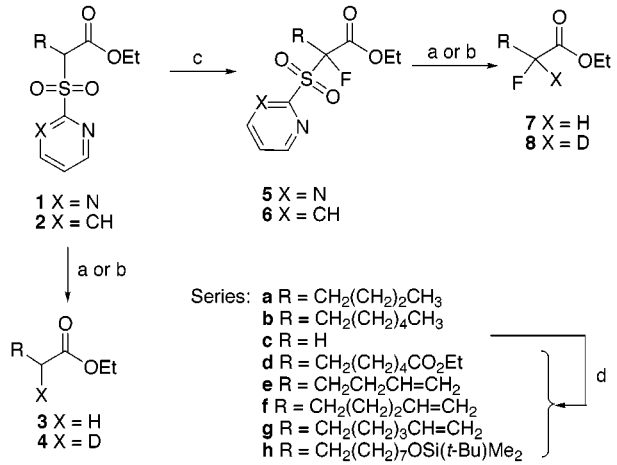
Scheme 1[a]



[a] Key: (a) $Bu_3SnH(D)$/AlBN/benzene or toluene/Δ; (b) Bu_3SnCl/PMHS/KF/H_2O/toluene/Δ; (c) KH/Selectfluor/THF/DMF; (d) **1c**/RBr/NaH/DMF.

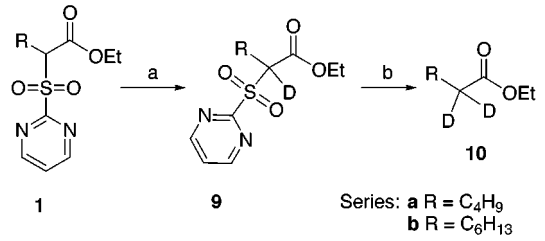
We now report convenient and efficient methodologies for synthesis of carboxylate α-pyrimidin-2-yl sulfones, their α-fluorination with Selectfluor, and their desulfonylation with tributylstannane or a "catalytic" tin equivalent. This provides a facile new route for the preparation of α-[^{2}H], α-[$^2H_2$], and α-fluoro-α-[^{2}H] carbonyl compounds. Mechanistic considerations for this novel radical desulfonylation procedure are suggested.

Results and Discussion

The 2-(pyrimidin-2-ylsulfonyl) **1a**−**c** and 2-(pyridin-2-ylsulfonyl) **2a** esters were prepared from the corresponding ethyl 2-bromoalkanoates and pyrimidin- or pyridin-2-thiolates, followed by oxidation (*m*-CPBA) of the ethyl 2-(arylthio)alkanoates. Alkylation of ethyl 2-(pyrimidin-2-ylsulfonyl)acetate (**1c**) with the corresponding alkyl bromides gave sulfones **1d**−**h** (Scheme 1). Treatment of ethyl 2-(pyridin-2-ylsulfonyl)hexanoate (**2a**) with Bu_3SnH/AIBN/benzene at reflux for 36 h gave ethyl hexanoate (**3a**, 60%) plus unchanged **2a** and minor decomposition products. Analogous treatment of ethyl 2-(pyrimidin-2-ylsulfonyl)hexanoate (**1a**) gave complete conversion to **3a** within 1 h and in toluene desulfonylation was completed in 30 min. Parallel treatment of standard ethyl 2-(phenylsulfonyl)hexanoate (48 h) caused no observed change in the starting material. Other 2-(pyrimidin-2-ylsulfonyl)alkanoates (e.g., **1b**,**e**−**g**) also underwent clean desulfonylation with Bu_3SnH (∼1.5−2.0 equiv) to give esters **3b**,**e**−**g** (81−91%).

π-Deficient heterocyclic sulfones also were found to be advantageous in reactions that involve generation of sulfonyl-stabilized carbanions (acidifying effects of pyridin- and pyrimidin-2-ylsulfonyl groups on α-carbon are greater than that of the phenylsulfonyl group). Thus, 2-(pyrimidin-2-ylsulfonyl) **1a**,**b**,**d**−**h** and 2-(pyridin-2-ylsulfonyl) **2a** esters were treated with potassium hydride, and the enolates were quenched with Selectfluor[12c] to give ethyl 2-fluoro-2-(pyrimidin-2-ylsulfonyl)alkanoates (**5a**,**b**,**d**−**h**) and ethyl 2-fluoro-2-(pyridin-2-ylsulfonyl)-hexanoate (**6a**) in good yields (72−92%). Tributylstannane-mediated desulfonylation of **5a** (1 h) and **6a** (28 h) gave ethyl 2-fluorohexanoate (**7a**; 95% and 60%, respectively). Treatment of α-fluoro-α-(pyrimidin-2-ylsulfonyl) esters **5b**,**d-h** by this procedure gave α-fluoro esters **7b**,**d**−**h** (77−91%). Isolated double bonds, a carboxylate ester, and a silyl protected hydroxyl were tolerated under the fluorination and desulfonylation conditions.

Scheme 2[a]



[a] Key: (a) KH/THF/D_2O; (b) Bu_3SnD/AlBN/benzene/Δ.

It is noteworthy that an α-fluoro substituent has no effect on the time required and yield of the radical desulfonylation reactions in contrast to the impact of the second nitrogen atom in the heterocyclic ring [**1a**/**5a** (1 h, 95%) versus **2a**/**6a** (36/28 h, 60%)]. Although removal of the pyridin-2-ylsulfonyl group is less efficient, easy access to the pyridin-2-yl thioethers with the radical-stabilizing group at α-carbon (via Barton's thiohydroxamic ester chemistry)[15,16] enhances the versatility of our mild radical-mediated removal of the pyridin-2-ylsulfonyl group. In an attempt to facilitate removal of the pyridin-2-ylsulfonyl group, compound **2a** was oxidized to the *N*-oxide. However, treatment of the latter with Bu_3SnH (2 equiv, 1 h) gave **2a** (∼80%) plus **3a** (∼12%). Deoxygenation of *N*-oxides with tin reagents (including Bu_3SnH)[17a] is known.[17]

Tributylstannane-mediated desulfonylation also gives access to deuterium-labeled[18] esters. Thus, treatment of **1a** and **5a** with Bu_3SnD gave ethyl 2-deuteriohexanoate (**4a**, ∼95% [^{2}H]) and 2-fluoro-2-deuteriohexanoate (**8a**, ∼90% [^{2}H]), respectively. Quenching enolates derived from **1a** and **1b** with D_2O yielded α-deuterated sulfone **9a** and **9b** (∼90% [^{2}H]) which upon treatment with Bu_3SnD gave ethyl 2,2-dideuterioalkanoates **10a** (∼80% [$^2H_2$]) and **10b** (∼85% [$^2H_2$]), respectively (Scheme 2).

Disadvantages associated with the use of Bu_3SnH are toxicity[19] and purification[20] of organotin species. To alleviate these problems, processes that are "catalyzed" by Bu_3SnH have been developed. One approach utilizes the ability of borohydrides to reduce tributyltin halides,[4b,21] and Fu's procedures exploit silicon hydride reduction of species with a Sn−O (or Sn−N) bond to regenerate Bu_3SnH.[22] $(TMS)_3SiH$ also can serve as a substitute for Bu_3SnH in a number of radical-mediated processes.[23] Recently, in situ generation of tin hydride by treatment

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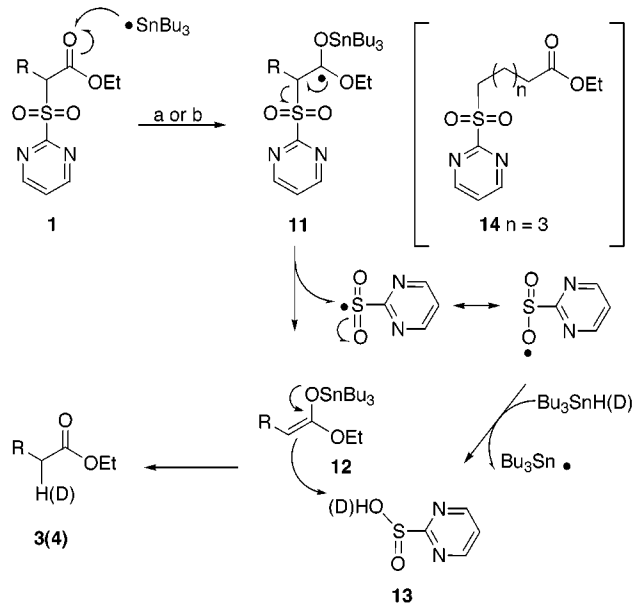
Scheme 3[a]



[a] Key: (a) $Bu_3SnH(D)$/AIBN/benzene/Δ; (b) Bu_3SnCl/PMHS/KF/H_2O/toluene/Δ.

of catalytic Bu_3SnCl with excess polymethylhydrosiloxane (PMHS) in the presence of potassium fluoride has been reported.[24]

To reduce the amount of tributyltin hydride, a modification of our stannyl radical-mediated desulfonylation has been developed. Treatment of the **1a** or **1b** with catalytic Bu_3SnH or Bu_3SnCl (0.2 equiv) and excess Bu_4NBH_3CN (benzene/AIBN/Δ) did not effect desulfonylation in good yields. The amounts of products formed (**3a** or **3b**) were proportional to the quantities of Bu_3SnH used. Treatment of **1a** and **5a** with Ph_3SiH or $(TMS)_3SiH$ [benzene/AIBN or $(BzO)_2/\Delta$] also resulted in recovery of unchanged sulfones (80−90%). However, treatment of **1b** with another "catalytic" tin hydride system [Bu_3SnCl (0.15 equiv.)/PMHS/KF/H_2O/toluene/Δ][24] effected hydrogenolysis to give **3b** (85%) which was readily purified. Analogous treatment of 2-(pyrimidin-2-ylsulfonyl) **1d**,**f** and 2-fluoro-2-(pyrimidin-2-ylsulfonyl) **5b**,**f** resulted in smooth desulfonylation to give esters **3d**,**f** and α-fluoro esters **7b**,**f** (84−89%), respectively.

Possible reaction mechanisms might involve formation of either stabilized α-carboxylate or alkoxy ketyl-type intermediate radicals. The absence of 5-*exo*-trig ring-closure during radical desulfonylation of ethyl 2-(pyrimidin-2-sulfonyl)hept-6-enoate (**1f**) to **3f** [Bu_3SnH (84% isolated yield), Bu_3SnCl/PMHS (89%)] argues against an α-carboxylate radical intermediate. Similarly, α-fluoro analogue **5f** produced **7f** (84−91%; ^{19}F NMR of the crude reaction mixture showed peaks only for **7f**). Attack by the tin radical on the carbonyl oxygen of **1** (or **5**) would generate a ketyl-type radical **11**, and β-elimination of a sulfonyl radical would produce the tin enolate **12** (Scheme 3). In a propagation step, hydrogen (deuterium) transfer[8b,25] from tributyltin hydride or deuteride to the sulfonyl radical would give the pyrimidin-2-ylsulfinic acid **13** (isolated from the reaction mixture). Protonation of **12** by **13** would yield products **3**/**4** (or **7**/**8**). Desulfonylation of β-ketosulfones[4] and *N*-sulfonylated amides[5] with Bu_3SnH have been proposed to proceed via analogous ketyl-type radicals and tin-enolates. The ability of PMHS to reduce oxygen−tin bonds is well documented.[22b,c,24] The fact that ethyl 6-(pyrimidin-2-ylsulfonyl)hexanoate (**14**) did not undergo the radical-mediated desulfonylation is consistent with the proposed mechanism. A further possibility might involve single electron transfer from the tin radical to the ester group, again leading to enolate formation.

Reductive cyclization of ketyl radicals arising from δ,ϵ-unsaturated ketones and aldehydes (as well esters having an auxiliary α-hydroxymethyl group)[26a] are known to give the corresponding substituted cyclopentanols.[26b] Intramolecular 1,5-cyclization of 5-hexenoyl chloride to 2-methylcyclopentanone[27a] and reductive cyclization of unsaturated aldehydes and ketones with Bu_3SnH have been reported.[27b,c] However, desulfonylation of hex-5-enoates **1e** and **5e** occurred without observed formation of cyclization products (**3e** and **7e** were isolated in 81% yields). Apparently, β-elimination of a sulfonyl radical is much faster than intramolecular cyclization involving *O*-stannyl ketyl radicals of type **11**.

In summary, we have developed convenient and efficient methodologies for synthesis of heterocyclic α-sulfones of carboxylate esters, their α-fluorination with Selectfluor, and their desulfonylation with tributylstannane or catalytic tin reagents in the presence of polymethylhydrosiloxane. This provides a facile new route for the preparation of α-[^2H], α-[$^2H_2$], and α-fluoro-α-[^2H] esters. Desulfonylation is suggested to proceed via alkoxy ketyl-type radicals and tin enolates.

Experimental Section

Uncorrected melting points were determined with a capillary tube apparatus. ^1H NMR spectra were determined with solution in $CDCl_3$ at 200 or 400 MHz, ^{13}C at 100.6 MHz, and ^{19}F (CCl_3F) at 376.4 MHz unless otherwise noted. Mass spectra (MS) were obtained by electron impact (EI), atmospheric pressure chemical ionization (APCI) or CI (CH_4), or fast atom bombardment (FAB, 5% trifluoroacetic acid/thioglycerol matrix) techniques. Reagent-grade chemicals were used, and solvents were dried by reflux over and distillation from CaH_2 under an argon atmosphere. Selectfluor fluorinating reagent (>95% active [F^+]) was purchased from Aldrich. TLC was performed on Merck kieselgel 60-F_{254} with MeOH/$CHCl_3$ (1:19) and EtOAc/hexane (1:2) as developing systems, and products were detected with 254 nm light or by development of color with I_2. Merck kieselgel 60 (230−400 mesh) was used for column chromatography. Elemental analyses were determined by Galbraith Laboratories, Knoxville, TN. Purity and identity of the products (crude and/or purified) were established using GC/MS (EI) system [capillary column (30 m × 0.25 mm × 25 μm), program: 40 °C for 1 min with increase

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15 °C/min to 300 °C]. Typical t_R for the series of octanoate compounds are as follow: **1b** (16.8 min), **3b** (7.6 min), **5b** (16.7 min), and **7b** (7.9 min). CAUTION! All procedures involving benzene and tributyltin hydride should be carried out in a well-ventilated hood.

Ethyl 2-(Pyrimidin-2-ylsulfonyl)hexanoate (1a). Procedure A. NaH (1.01 g, 50%/mineral oil, 21 mmol) was washed (dried Et_2O, 1 × 25 mL) and suspended in dried DMF (35 mL) under N_2. Two equal portions of 2-mercaptopyrimidine (2.24 g, 20 mmol) were added slowly at ∼0 °C (ice bath). The resulting solution was stirred at ambient temperature for 1 h and cooled to ∼0 °C, and ethyl 2-bromohexanoate (3.65 mL, 4.46 g, 20 mmol) was added. After 1 h, the mixture was allowed to warm to ambient temperature, stirred overnight, and evaporated, and the residue was partitioned (EtOAc/H_2O). The organic layer was washed ($NaHCO_3$/H_2O; brine), dried ($MgSO_4$), and evaporated to give the viscous thioether (4.83 g, 95%) that was dissolved ($CHCl_3$, 50 mL), cooled (∼−20 °C), and treated dropwise with *m*-CPBA (9.66 g/75% reagent, 42 mmol) in $CHCl_3$/CH_2Cl_2 (1:1, 100 mL). After 2 h, the mixture was allowed to warm to ambient temperature and stirred for 18 h. Saturated $NaHCO_3$/H_2O (100 mL) was added, stirring was continued for 30 min, the organic layer was separated, and the aqueous layer was extracted ($CHCl_3$, 50 mL). The combined organic phase was washed ($NaHCO_3$/H_2O; brine), dried ($MgSO_4$), evaporated, and chromatographed (50% hexanes/EtOAc → EtOAc) to give **1a** (5.15 g, 90% overall) as a solidified oil: mp 50−51 °C; ^{1}H NMR δ 0.90 (t, J = 6.6 Hz, 3H), 1.09 (t, J = 7.1 Hz, 3H), 1.28−1.51 (m, 4H), 2.16−2.28 (m, 2H), 4.10 (q, J = 7.1 Hz, 2H), 4.61 (dd, J = 6.2, 8.7 Hz, 1H), 7.60 (t, J = 4.9 Hz, 1H), 8.97 (d, J = 4.9 Hz, 2H); ^{13}C NMR δ 13.8, 13.9, 22.4, 24.8, 29.3, 62.4, 66.1, 124.1, 158.8, 165.3; IR (Nujol) 2924, 1731, 1556, 1456, 1316, 1113 cm^{-1}; MS (CI) *m*/*z* 287 (100, MH^+). Anal. Calcd for $C_{12}H_{18}N_2O_4S$ (286.35): C, 50.33; H, 6.34; N, 9.78. Found: C, 50.33; H, 6.15; N, 9.60.

Ethyl 2-(Pyrimidin-2-ylsulfonyl)acetate (1c). The 2-mercaptopyrimidine (1.12 g, 10 mmol) was added to a solution of EtONa in EtOH [Na (330 mg, 14 mmol) in EtOH (30 mL)], and the resulting solution was stirred at ambient temperature for 1 h. Ethyl 2-bromoacetate (1.11 mL, 1.67 g, 10 mmol) was added, stirring was continued overnight, and volatiles were evaporated. The residue was subjected to the remaining part of procedure A to give **1c** (1.95 g, 84%) as a white solid: mp 40−41 °C; ^{1}H NMR δ 1.14 (t, J = 7.2 Hz, 3H), 4.12 (q, J = 7.2 Hz, 2H), 4.58 (s, 2H), 7.60 (t, J = 5.2 Hz, 1H), 8.96 (d, J = 4.9 Hz, 2H); ^{13}C NMR δ 14.2, 56.1, 62.7, 124.9, 159.2, 162.7, 165.0; MS (FAB) *m*/*z* 231 (100, MH^+). Anal. Calcd for $C_8H_{10}N_2O_4S$ (230.25): C, 41.73; H, 4.38; N, 12.17. Found: C, 41.69; H, 4.43; N, 12.10.

Diethyl 2-(Pyrimidin-2-ylsulfonyl)octanedioate (1d). Procedure B. NaH (264 mg, 50%/mineral oil, 5.5 mmol) was washed (dried Et_2O, 1 × 25 mL) and suspended in dried DMF (20 mL) under N_2. Compound **1c** (1.15 g, 5 mmol) was added slowly at ∼0 °C (ice bath), and the resulting solution was stirred at ambient temperature for 30 min. Ethyl 6-bromohexanoate (0.98 mL, 1.23 g, 5.5 mmol) was added (syringe), and after being stirred for 16 h the mixture was heated for 2 h at 50 °C. Volatiles were evaporated, and the residue was partitioned (EtOAc/NH_4Cl/H_2O). The organic layer was washed ($NaHCO_3$/H_2O; brine), dried ($MgSO_4$), evaporated, and chromatographed (40% hexanes/EtOAc → EtOAc) to give **1d** (1.32 g, 71%) as an oil: ^{1}H NMR δ 1.04 (t, J = 7.1 Hz, 3H), 1.19 (t, J = 7.3 Hz, 3H), 1.30−1.62 (m, 6H), 2.11−2.20 (m, 2H), 2.24 (t, J = 7.4 Hz, 2H), 4.02−4.09 (m, 4H), 4.59 (dd, J = 3.9, 9.6 Hz, 1H), 7.60 (t, J = 4.8 Hz, 1H), 8.93 (d, J = 4.9 Hz, 2H); ^{13}C NMR δ 14.1, 14.6, 24.8, 25.1, 27.1, 28.9, 34.4, 60.6, 62.7, 66.1, 124.5, 159.1, 165.4, 165.5, 173.9; IR (neat) 2938, 1734, 1566 cm^{-1}; MS (EI) *m*/*z* 327 (30, M^+ − OEt), 185 (100). Anal. Calcd for $C_{16}H_{24}N_2O_6S$ (372.45): C, 51.60; H, 6.50; N, 7.52. Found: C, 51.87; H, 6.46; N, 7.72.

Ethyl 2-(Pyrimidin-2-ylsulfonyl)hept-6-enoate (1f). Treatment of **1c** (1.15 g, 5 mmol) with 5-bromo-1-pentene (0.77 mL, 968 mg, 6.5 mmol) by procedure B gave **1f** (1.22 g, 82%) as a solidified oil: ^{1}H NMR δ 1.06 (t, J = 7.2 Hz, 3H), 1.54 (quint, J = 7.7 Hz, 2H), 2.04−2.26 (m, 4H), 4.08 (q, J = 7.2 Hz, 2H), 4.62 (dd, J = 6.2, 8.7 Hz, 1H), 4.93 (dm, J = 9.9 Hz, 1H), 5.00 (dm, J = 16.5 Hz, 1H), 5.73 (ddt, J = 16.9, 10.1, 6.5 Hz, 1H), 7.62 (t, J = 5.1 Hz, 1H), 8.96 (d, J = 5.1 Hz, 2H); ^{13}C NMR δ 14.2, 24.8, 26.7, 33.6, 62.8, 66.3, 116.0, 124.3, 137.8, 159.0, 165.5, 165.6; MS (FAB) *m*/*z* 299 (100, MH^+). Anal. Calcd for $C_{13}H_{18}N_2O_4S$ (298.37): C, 52.33; H, 6.08; N, 9.39. Found: C, 52.71; H, 6.41; N, 9.08.

Ethyl 2-(Pyridin-2-ylsulfonyl)hexanoate (2a). Treatment of ethyl 2-bromohexanoate (3.65 mL, 4.46 g, 20 mmol) with 2-mercaptopyridine (2.22 g, 20 mmol) and oxidation (20 h) with *m*-CPBA (9.66 g/75% reagent, 42 mmol) by procedure A gave **2a** (5.07 g, 89%; oil): ^{1}H NMR δ 0.85−0.93 (m, 3H), 1.11 (t, J = 7.1 Hz, 3H), 1.31−1.45 (m, 4H), 2.10−2.21 (m, 2H), 4.21 (q, J = 7.1 Hz, 2H), 4.46 (dd, J = 5.5, 9.4 Hz, 1H), 7.58 (ddd, J = 1.3, 4.7, 7.6 Hz, 1H), 7.97 (td, J = 7.7, 1.7 Hz, 1H), 8.08 (dt, J = 7.8, 1.3 Hz, 1H), 8.78 (ddd, J = 1.3, 1.7, 4.8 Hz, 1H); ^{13}C NMR δ 14.11, 14.12, 22.6, 25.6, 29.5, 62.6, 67.2, 123.8, 128.2, 138.6, 150.7, 156.8, 165.9; IR (neat) 2961, 1740, 1580, 1325, 1164 cm^{-1}; MS (CI) *m*/*z* 286 (100, MH^+). Anal. Calcd for $C_{13}H_{19}NO_4S$ (285.36): C, 54.72; H, 6.71; N, 4.91. Found: C, 54.63; H, 6.52; N 5.09.

Treatment of **2a** (285 mg, 1 mmol) with *m*-CPBA (460 mg/75% reagent, 2 mmol) in $CHCl_3$/CH_2Cl_2 (1:1, 15 mL) at ambient temperature for 72 h followed by geantly heating at reflux for 3 h and workup (procedure A) gave **2a** *N*-oxide (184 mg, 61%) and unchanged **2a** (88 mg, 31%). ^{1}H NMR spectrum of **2a**-*N*-oxide show significant downfield shift for the proton at C2: δ 5.31 (dd, J = 4.3, 9.6 Hz, 1H).

Ethyl hexanoate (3a). Procedure C. Argon was bubbled through a solution of **1a** (286 mg, 1.0 mmol) in benzene (5.0 mL) for 30 min, and Bu_3SnH (0.467 mL, 509 mg, 1.75 mmol) was added. Deoxygenation was continued for 5 min, AIBN (25 mg, 0.15 mmol) was added, and the solution was refluxed for 1 h (TLC showed complete conversion of **1a**). Volatiles were evaporated (<25 °C, ∼20 mmHg), and the residue was dissolved (EtOAc, 5 mL). The solution was stirred overnight with KF/H_2O (30 mg/0.3 mL), evaporated, and chromatographed (pentane → 3% EtOAc/pentane) to give **3a** (137 mg, 95%) with spectral data identical to those of an authentic sample.[28] Evaporation of the reaction mixture and direct column chromatography [hexane (100 mL) → 5% EtOAc/hexane] also gave **3a** with similar yield and purity. A ratio of 1.35 equiv. of Bu_3SnH also gave essentially quantitative conversion of **1a** to **3a** within 1 h.

Treatment of **2a** (285 mg, 1 mmol) with Bu_3SnH (1.65 mmol) by procedure C (30 min) using toluene instead of benzene gave **3a** (131 mg, 91%).

Analogous treatment (36 h, benzene) of **2a** (285 mg, 1 mmol) with Bu_3SnH (2.0 mmol) and AIBN (0.2 mmol) [additional Bu_3SnH (1.0 mmol) and AIBN (0.2 mmol) after 15h] by procedure C gave **3a** [87 mg, 60%; further elution (EtOAc/pentane, 1:1) gave recovered **2a** (85 mg, 30%)]. Treatment of **2a** *N*-oxide (90 mg, 0.3 mmol) by procedure C [1h, Bu_3SnH (2 equiv)] gave **2a** (68 mg, 80%) and **3a** (5 mg, 12%).

Treatment of ethyl 2-(phenylsulfonyl)hexanoate [prepared by procedure A (thiophenol, 10 mmol; 2.41 g, 85%) with data as described][29] by procedure C (48 h, benzene) gave recovered starting material (∼95%).

Ethyl Octanoate (3b). Procedure D. Nitrogen was bubbled through a solution of **1b** (314 mg, 1 mmol), Bu_3SnCl (49 mg, 0.041 mL, 0.15 mmol), and AIBN (5 mg, 0.03 mmol) in toluene (2 mL) for 15 min. The solution was heated at reflux for 3 h, and PMHS (0.2 mL) and KF [116 mg (2 mmol) in H_2O (0.5 mL)] were added in three equal portions immediately after reaching the boiling point and after 1 and 2 h. Volatiles were evaporated, and the residue was partitioned (EtOAc//$NaHCO_3$/H_2O). The organic layer was washed (brine), dried ($MgSO_4$), evaporated, and chromatographed [hexane (100 mL) → 10% EtOAc/hexane] to give **3b** [(147 mg, 85%): GC/MS purity (>99%); MS *m*/*z* 172 (10, M^+), 127 (42, M^+ − OEt), 88 (100)] with spectral data identical to those of an authentic sample.[28]

(28) *The Aldrich Library of ^{13}C and ^{1}H FT-NMR Spectra*; Pouchert, C. J., Behnke, J., Eds.; Aldrich Chemical: Milwaukee, WI, 1993.

(29) Wang, Y.; Jiang, Y. *Synth. Commun.* **1992**, *22*, 2287−2291.

Further elution (EtOAc/hexane, 1:1) gave recovered **1b** (31 mg, 10%). Evaporation of the reaction mixture and direct column chromatography also gave **3b** with similar yield and purity.

Treatment of **1b** (157 mg, 0.5 mmol) by procedure C gave **3b** (78 mg, 91%).

Diethyl Octanedioate (Diethyl Suberate) (3d). Treatment of **1d** (186 mg, 0.5 mmol) by procedure D gave **3d** (101 mg, 88%) with spectra identical to those of an authentic sample:[28] GC/MS purity (>99%); MS *m*/*z* 185 (80, $M^+ - OEt$), 143 (100).

Ethyl Hept-6-enoate (3f). Treatment of **1f** (170 mg, 0.57 mmol) with Bu_3SnH (1.14 mmol) by procedure C (chromatography: pentane → 10% EtOAc/pentane) gave **3f**[30] (75 mg, 84%) contaminated (∼5−10%, ^1H NMR) by tin compound(s). Hydrolysis ($NaOH/H_2O$/MeOH) of this material gave 6-heptenoic acid with spectra identical to those of authentic sample.[28]

Analogous treatment of **1f** by procedure C in C_6D_6 and direct analysis of the aliqouts (0.25 h, 0.5 h, 1 h) by ^1H NMR (C_6D_6) showed that integration of the characteristic signals for the vinylic protons at δ 5.54−5.75 (m, 1, H6) and 4.90−5.02 (m, 3, H2,7,7′) remained constant (±5%) compared with the signals for the methylene protons at δ 3.88 (**1f**) and 4.01 (**3f**) from the ester groups. Washing of the C_6D_6 solution with $D_2O/NaHCO_3$ and ^1H NMR of D_2O layer showed only signals for **13**.

Treatment of **1f** (149 mg, 0.5 mmol) by procedure D also gave **3f** (69 mg, 89%): GC/MS purity (99%); MS *m*/*z* 156 (5), 88 (100).

Ethyl 2-Deuteriohexanoate (4a). Treatment of **1a** (143 mg, 0.5 mmol) with Bu_3SnD (0.268 mL, 291 mg, 1 mmol) by procedure C (2 h) gave **4a** (65 mg, 90%): ^1H NMR spectra corresponded with those of **3a** with 50% reduction in the intensity of signals[28] at δ 2.26 (t, *J* = 7.7 Hz, 1H, 2-CHD); MS (CI) *m*/*z* 146 (100, MH^+ [$C_8H_{16}DO_2$]).

Ethyl 2-Fluoro-2-(pyrimidin-2-ylsulfonyl)hexanoate (5a). Procedure E. KH [(571 mg, 35%/mineral oil, 5 mmol) or (220 mg, 5.5 mmol, dried/pressed between filter paper)] in a flame-dried flask under Ar was washed (dried hexane, dried Et_2O), and dried THF (25 mL) was added. The suspension was cooled (∼0 °C, ice bath), and compound **1a** (1.14 g, 4 mmol) in dried THF (15 mL) was added (syringe). The solution was stirred (0 °C for 15 min, ambient temperature for 60 min, cooled to 0 °C), and Selectfluor (2.13 g, 6 mmol) was added in one portion. After 15 min, dried DMF (15 mL) was added (syringe), the ice bath was removed after 5 min, and stirring was continued at ambient temperature for 2 h. The reaction mixture was cooled to ∼0 °C (ice bath), and $CHCl_3$ (30 mL) and saturated NH_4Cl/H_2O (15 mL) were slowly added. The organic layer was separated after 5 min, and the aqueous layer was extracted ($CHCl_3$, 2 × 25 mL). The combined organic phase was washed (saturated $NaHCO_3/H_2O$, brine), dried ($MgSO_4$), evaporated, and chromatographed (50 → 90% EtOAc/hexanes)] to give **5a** (1.12 g, 92%) as a slightly yellow solidified oil: ^1H NMR δ 0.91 (t, *J* = 6.6 Hz, 3H), 1.30 (t, *J* = 7.1 Hz, 3H), 1.25−1.60 (m, 4H), 2.43−2.72 (m, 2H), 4.35 (q, *J* = 7.1 Hz, 2H), 7.62 (t, *J* = 4.9 Hz, 1H), 8.98 (d, *J* = 4.9 Hz, 2H); ^{13}C NMR δ 14.1, 14.4, 22.8, 25.1, 30.9 (d, ^2J = 19.7 Hz), 63.9, 107.6 (d, ^1J = 232.8 Hz), 125.0, 159.3, 163.7, 163.9 (d, ^2J = 25.2 Hz); ^{19}F NMR δ −158.8 (dd, $^3J_{F-3a}$ = 10.9 Hz, $^3J_{F-3b}$ = 37.8 Hz); IR (neat) 2963, 1751, 1567, 1347 cm^{-1}; MS (EI) *m*/*z* 304 (42, M^+), 197 (50), 79 (100). Anal. Calcd for $C_{12}H_{17}FN_2O_4S$ (304.3): C, 47.36; H, 5.63; N, 9.20. Found: C, 47.57; H, 5.72; N, 9.19.

Diethyl 2-Fluoro-2-(pyrimidin-2-ylsulfonyl)octanedioate (5d). Treatment of **1d** (186 mg, 0.5 mmol) by procedure E gave **5d** (166 mg, 85%): ^1H NMR δ 1.22 (t, *J* = 7.1 Hz, 3H), 1.30 (t, *J* = 7.2 Hz, 3H), 1.40 (quint, *J* = 7.3 Hz, 2H), 1.52−1.66 (m, 4H), 2.26 (t, *J* = 7.4 Hz, 2H), 2.48−2.66 (m, 2H), 4.08 (q, *J* = 7.1 Hz, 2H), 4.34 (q, *J* = 7.1 Hz, 2H), 7.65 (t, *J* = 4.8 Hz, 1H), 8.95 (d, *J* = 4.9 Hz, 2H); ^{13}C NMR δ 14.3, 14.6, 22.6 (d, ^3J = 2.0 Hz), 24.8, 28.9, 30.9 (d, ^2J = 19.8 Hz), 34.3, 60.7, 63.9, 107.3 (d, ^1J = 234.4 Hz), 125.1, 159.3, 163.4, 163.7 (d, ^2J = 25.1 Hz), 173.8; ^{19}F NMR δ −158.9 (dd, $^3J_{F-3a}$ = 11.3 Hz, $^3J_{F-3b}$ = 37.6 Hz); MS (APCI) *m*/*z* 391 (100, MH^+). Anal. Calcd for $C_{16}H_{23}FN_2O_6S$ (390.44): C, 49.22; H, 5.94; N, 7.18. Found: C, 48.88; H, 6.30; N, 6.84.

Ethyl 2-Fluoro-2-(pyrimidin-2-ylsulfonyl)hept-6-enoate (5f). Treatment of **1f** (596 mg, 2.0 mmol) by procedure E gave **5f** (556 mg, 88%) as an oil: ^1H NMR δ 1.28 (t, *J* = 7.1 Hz, 3H), 1.35−1.68 (m, 2H), 2.08−2.18 (m, 2H), 2.45−2.68 (m, 2H), 4.32 (q, *J* = 7.1 Hz, 2H), 4.95 (dm, *J* = 9.9 Hz, 1H), 5.01 (dm, *J* = 16.6 Hz, 1H), 5.65−5.75 (m, 1H), 7.65 (t, *J* = 4.8 Hz, 1H), 8.98 (d, *J* = 4.9 Hz, 2H); ^{13}C NMR δ 14.4, 22.3 (^3J = 2.0 Hz), 30.5 (d, ^2J = 19.8 Hz), 33.4, 63.9, 107.4 (d, ^1J = 234.2 Hz), 116.4, 124.9, 137.3, 159.2, 163.5, 163.8 (d, ^2J = 25.3 Hz); ^{19}F NMR δ −158.6 (dd, $^3J_{F-3a}$ = 11.9 Hz, $^3J_{F-3b}$ = 36.9 Hz); MS (APCI) *m*/*z* 317 (100, MH^+). Anal. Calcd for $C_{13}H_{17}FN_2O_4S$ (316.36): C, 49.36; H, 5.42; N, 8.86. Found: C, 49.39; H, 5.51; N, 8.80.

Ethyl 2-Fluoro-2-(pyridin-2-ylsulfonyl)hexanoate (6a). Treatment of **2a** (428 mg, 1.5 mmol) with KH (2.0 mmol) and Selectfluor (2.5 mmol) (2 h) by procedure E gave **6a** (414 mg, 91%; viscous oil): ^1H NMR δ 0.90 (t, *J* = 6.8 Hz, 3H), 1.16−1.52 (m, 7H), 2.30−2.73 (m, 2H), 4.31 (q, *J* = 7.2 Hz, 2H), 7.60 (ddd, *J* = 1.4, 4.7, 7.6 Hz, 1H), 7.98 (dt, *J* = 1.7, 7.6 Hz, 1), 8.09 (dt, *J* = 1.1 Hz, 7.8 Hz, 1), 8.73 (ddd, *J* = 1.0, 1.7, 4.8 Hz, 1); ^{13}C NMR δ 14.2, 14.4, 22.8, 25.1 (d, ^3J = 2.0 Hz), 30.7 (d, ^2J = 19.7 Hz), 63.9, 107.5 (d, ^1J = 231.4 Hz), 126.32, 128.8, 138.68, 150.78, 154.2, 164.0 (d, ^2J = 24.1 Hz); ^{19}F NMR δ −159.3 (dd, $^3J_{F-3a}$ = 10.0 Hz, $^3J_{F-3b}$ = 38.7 Hz); IR (neat) 2964, 1758, 1353, 1266, 1174, 734 cm^{-1}; MS (CI) *m*/*z* 304 (100, MH^+). Anal. Calcd for $C_{13}H_{18}FNO_4S$ (303.3): C, 51.47; H 5.98; N, 4.62. Found: C, 51.39; H, 6.12; N, 4.51.

Ethyl 2-Fluorohexanoate (7a). Treatment of **5a** (304 mg, 1 mmol) with Bu_3SnH (1.75 mmol) by procedure C gave **7a** (154 mg, 95%; oil) with data as reported.[31a]

Analogous treatment of **6a** (303 mg, 1 mmol) with Bu_3SnH (2.0 mmol) and AIBN (0.2 mmol) (28 h) [additional Bu_3SnH (1.0 mmol) and AIBN (0.2 mmol) were added after 14 h] gave **7a** (97 mg, 60%). Further elution (EtOAc/pentane, 1:1) gave recovered **5b** (61 mg, 20%).

Treatment of **5a** (1 mmol) with Bu_3SnH (1.3 mmol) gave **7a** (85%) [TLC: **5a** (∼5−10%)].

Ethyl 2-Fluorooctanoate (7b). Treatment of **5b** (664 mg, 2 mmol) with Bu_3SnH (3.5 mmol) by procedure C (chromatography: hexane → 10% EtOAc/hexane) gave **7b** (334 mg, 88%; oil) with data as reported:[13] GC/MS purity (99%); MS *m*/*z* 190 (5, M^+), 106 (100).

Treatment of **5b** (332 mg, 1 mmol) by procedure D gave **7b** [163 mg, 86%; GC (>99%)].

Diethyl 2-Fluorooctanedioate (7d). Treatment of **5d** (195 mg, 0.5 mmol) by procedure C [chromatography (hexane → 10% EtOAc/hexane)] gave **7d** (109 mg, 88%): ^1H NMR δ 1.25 (t, *J* = 7.1 Hz, 3H), 1.31 (t, *J* = 7.2 Hz, 3H), 1.35−1.53 (m, 4H), 1.65 (quint, *J* = 7.5 Hz, 2H), 1.82−1.95 (m, 2H), 2.25 (t, *J* = 7.4 Hz, 2H), 4.12 (q, *J* = 7.2 Hz, 2H), 4.26 (q, *J* = 7.1 Hz, 2H), 4.89 (dt, *J* = 49.4, 5.9 Hz, 1H); ^{13}C NMR δ 14.5, 14.6, 24.4 (d, ^3J = 2.9 Hz), 25.0, 28.9, 32.6 (d, ^2J = 21.1 Hz), 34.5, 60.7, 61.8, 89.3 (d, ^1J = 183.9 Hz), 170.4 (d, ^2J = 23.6 Hz), 174.0; ^{19}F NMR δ −192.6 (dt, $^2J_{F-2}$ = 49.0 Hz, $^3J_{F-3a,b}$ = 25.0 Hz); GC/MS purity (>99%); MS *m*/*z* 203 (45, $M^+ - OEt$), 88 (100). Anal. Calcd for $C_{12}H_{21}FO_4$ (248.30): C, 58.05; H, 8.53. Found: C, 58.25; H, 8.75.

Ethyl 2-Fluorohept-6-enoate (7f). Treatment of **5f** (158 mg, 0.5 mmol) with Bu_3SnH (1 mmol) by procedure C [chromatography (hexane → 10% EtOAc/hexane)] gave **7f** (79 mg, 91%): ^1H NMR δ 1.32 (t, *J* = 7.1 Hz, 3H), 1.58 ("quint" *J* = 8.2 Hz, 2H), 1.85−1.96 (m, 2H), 2.11 ("q", *J* = 6.7 Hz, 2H), 4.29 (q, *J* = 7.1 Hz, 2H), 4.90 (dt, *J* = 49.5, 5.9 Hz, 1H), 4.98 (dm, *J* = 9.9 Hz, 1H), 5.03 (dm, *J* = 16.7 Hz, 1H), 5.79 (ddt, *J* = 16.9, 10.1, 6.6 Hz, 1H); ^{13}C NMR δ 14.6, 23.9 (d, ^3J = 2.8 Hz), 32.1 (d, ^2J = 21.1 Hz), 33.5, 61.9, 89.3 (d, ^1J = 183.9 Hz), 115.7, 138.2, 170.4 (d, ^2J = 23.7 Hz); ^{19}F NMR δ −192.6 (dt, $^2J_{F-2}$ = 49.5 Hz, $^3J_{F-3a,b}$ = 25.4 Hz); IR (neat) 2931, 1758, 1738,

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1640 cm^{-1}; MS (APCI) *m*/*z* 175 (100, MH^+); GC/MS purity (99%); MS *m*/*z* 174 (10, M^+). Anal. Calcd for $C_9H_{15}FO_2$ (174.22): C, 62.05; H, 8.68. Found: C, 61.71; H, 8.81.

^{19}F NMR of the crude reaction mixture showed only peaks for **7f**.

Analogous treatment of **5f** (158 mg, 0.5 mmol) by procedure D gave **7f** (73 mg, 84%): GC/MS purity (>99%); MS *m*/*z* 174 (10, M^+). ^{19}F NMR of the crude reaction mixture showed peaks for **7f** (~92%) and unchanged **5f** (~8%).

Ethyl 2-Deuterio-2-fluorohexanoate (8a). Treatment of **5a** (152 mg, 0.5 mmol) with Bu_3SnD (0.268 mL, 291 mg, 1.0 mmol) by procedure C gave **8a** (74 mg, 91%; contained ~10% of **7a**). ^1H NMR data for **8a** corresponded to those reported for **7a**[31a] except for small signals (~10%) at δ 4.86 (dt, $^2J_{F-H}$ = 49.2 Hz, $^3J_{F-H}$ = 5.9 Hz, 2-CHF) and simplification of the multiplet at δ 1.87 (3-CH_2); ^{19}F NMR δ −193.2 (tt, $^2J_{F-D}$ = 7.9 Hz, $^3J_{F-H}$ = 24.9 Hz, 0.9, 2-CDF), −192.5 (dt, $^2J_{F-H}$ = 49.2 Hz, $^3J_{F-H}$ = 24.9 Hz, 0.1, 2-CHF); MS (CI) *m*/*z* 164 (100, MH^+ [$C_8H_{15}DFO_2$]).

Ethyl 2-Deuterio-2-(pyrimidin-2-ylsulfonyl)hexanoate (9a). Procedure F. Compound **1a** (356 mg, 1.25 mmol) was treated with KH (1.75 mmol) as described in procedure E. The solution was stirred at 0 °C for 15 min followed by 90 min at ambient temperature and then was cooled to −60 °C, and D_2O (1 mL) was added dropwise. After 5 min, the reaction mixture was allowed to warm to ~0 °C and solid NH_4Cl (1 g) followed by saturated NH_4Cl/H_2O (15 mL) and EtOAc (25 mL) were added. The organic layer was separated, and the aqueous layer was extracted (EtOAc). The combined organic phase was washed (saturated $NaHCO_3/H_2O$, brine), dried ($MgSO_4$), evaporated, and chromatographed (50 → 85% hexanes/EtOAc) to give **9a** (271 mg, 76%): ^1H NMR spectra corresponded with those of **1a** with ~90% reduction in the intensity of signals at δ 4.61 (0.1H) and simplification of multiplet at δ 2.16−2.28 (2H); MS (CI) *m*/*z* 288 (100, MH^+ [$C_{12}H_{17}DN_2O_4S$]).

Ethyl 2,2-Dideuteriohexanoate (10a). Treatment of **9a** (29 mg, 0.1 mmol) with Bu_3SnD (2 equiv) by procedure C gave **10a** (11 mg, 76%). ^1H NMR spectra corresponded with those of **3a** with ~80% reduction in the intensity of signals at δ 2.28 (t, *J* = 7.7 Hz, 0.2H, 2-CD_2); MS (CI) *m*/*z* 147 (100, MH^+ [$C_8H_{15}D_2O_2$]).

Pyrimidin-2-ylsulfinic Acid (13). A sample of **1a** (286 mg, 1 mmol) was treated with Bu_3SnH as described in procedure C, and the crude benzene solution was partitioned (EtOAc// $NaHCO_3/H_2O$). The aqueous phase was washed (EtOAc) and was evaporated to give a white solid. Extraction of this material with MeOH and evaporation gave **13** as a sodium salt (148 mg, 89%): ^1H NMR (D_2O) δ 7.60 (t, *J* = 4.9 Hz, 1H), 8.88 (d, *J* = 4.9 Hz, 2H); ^{13}C NMR (D_2O/Me_2SO-d_6) δ 123.2, 159.1, 177.0. ^1H NMR spectrum of **13** parallels with that reported for potassium pyrimidin-2-ylsulfonate.[31b]

Analogous treatment of **1f** (298 mg, 1 mmol) by procedure C also gave **13** (144 mg, 87%).

Ethyl 6-(Pyrimidin-2-ylsulfonyl)hexanoate (14). Treatment of ethyl 6-bromohexanoate (1.82 mL, 2.23 g, 10 mmol) with 2-mercaptopyrimidine (1.12 g, 10 mmol) and oxidation (20 h) with *m*-CPBA (4.8 g/75% reagent, 21 mmol) by procedure A gave **14** (2.43 g, 85%): ^1H NMR δ 1.23 (t, *J* = 7.1 Hz, 3H), 1.43−1.95 (m, 6H), 2.28 (t, *J* = 7.1 Hz, 3H), 3.52 (dd, *J* = 7.4, 8.2 Hz, 2H), 4.09 (q, *J* = 7.1 Hz, 2H), 7.58 (t, *J* = 4.9 Hz, 1H), 8.95 (d, *J* = 4.9 Hz, 2H); ^{13}C NMR δ 14.7, 22.3, 24.7, 28.3, 34.3, 51.5, 60.8, 124.4, 159.2, 166.2, 173.7; MS (CI) *m*/*z* 287 (100, MH^+). Anal. Calcd for $C_{12}H_{18}N_2O_4S$ (286.35): C, 50.33; H, 6.34; N, 9.78. Found: C, 50.40; H, 6.27; N, 9.56.

Treatment of **14** with Bu_3SnH (2 equiv) by procedure C gave unchanged **14** (89%) contaminated (~10%, ^1H NMR) by tin compound(s).

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Supporting Information Available: Experimental procedures and characterization data for compounds **1b**,**e**,**g**,**h**, **3e**,**g**, **5b**,**e**,**g**,**h**, **7e**,**g**,**h**, **9b**, and **10b** as well as copies of ^1H and ^{13}C NMR spectra of compound **13**. This material is available free of charge via the Internet at http://pubs.acs.org

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