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An Improved Synthesis of Pyridine−Thiazole Cores of Thiopeptide Antibiotics

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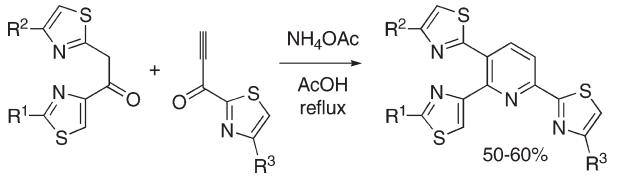

The oxidation of 2-methylthiazoles to 2-formylthiazoles simplifies the implementation of the Bagley variant of the Bohlmann−Rahtz reaction as a key step in a concise new route to pyridine cores of thiopeptide antibiotics.

The biomedical potential of thiopeptide antibiotics[1] and the manifold chemical issues associated with a synthetic attack on these molecules have elicited considerable activity during the past decade.[2] These efforts have produced noteworthy methods for the assembly of the pyridine−thiazole core of those antibiotics. Remarkable biomimetic cycloadditions of azadienes have been key to the expeditious construction of the core thiostrepton and congeners incorporating a reduced pyridine.[3] On the other hand, fully aromatic cores are best obtained either by functionalization of an existing pyridine[4] or by a de novo construction thereof. Approaches of the latter type that rely on variants of the Hantzch[5] and, especially, the Bohlmann−Rahtz[6] reactions tend to be particularly direct. Still, more than 10 linear steps are needed to reach the desired objectives. Efforts toward the thiopeptide antibiotics would surely benefit from the advent of more concise routes.

Incisive work by Bagley[7] has unveiled a remarkable variant of the Bohlmann−Rahtz synthesis, wherein an enolizable ketone, **1**, an ynone, **2**, and NH_4OAc combine in refluxing ethanol to afford a pyridine in excellent yield (Scheme 1). The transformation presumably involves the initial formation of enamine **3**, which then participates in an actual Bohlmann−Rahtz reaction with **2**, i.e., 1,4-addition to the ynone and cyclodehydration of the emerging **4** to the ultimate **5**. This chemistry could deliver the complete pyridine−thiazole cluster of thiopeptide antibiotics, if it were to prove serviceable with variants of **1** and **2** wherein the R groups are thiazolyl residues. Bagley utilized a similar transformation to assemble the core motif of amythiamycin,[8] except that an enamine such as **3** was prepared separately as a discrete intermediate, and subsequently it was caused to react with a thiazolyl ynone in refluxing EtOH. These important findings beg the question of whether the union of thiazolyl analogues of **1** and **2** could be effected by the one-step method. Herein, we detail a procedure that accomplishes such a goal.

The first objective of this study was the establishment of a more direct route to 2-formylthiazoles of the type **7** and **12**. These compounds are crucial building blocks of the pyridine−thiazole core of thiopeptides, but their preparation has been fairly laborious.[9] We concentrated on the oxidation of 2-methylthiazoles as an avenue to the corresponding aldehydes (Scheme 2). Curiously, this transformation appears to be undocumented. We found that commercially available **6** or the derived bis-thiazole **11** were largely immune to the action of SeO_2 in refluxing ethanol or dioxane. However, they were smoothly converted into the known **7**[10a] and **12**,[5] upon exposure to SeO_2 in refluxing acetic acid. Conduct of the oxidation of **6** in concentrated solutions (1 M or greater) caused the formation of much carbethoxythiazole **8**[10b,10c] as a byproduct. The genesis of **8** is attributable to overoxidation of **7** to the corresponding acid and ensuing decarboxylation. The problem may be contained by operating at concentrations

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(2) Major synthetic achievements. Promothiocin A: (a) Moody, C. J.; Bagley, M. C. *Chem. Commun.* **1998**, 2049. (b) Bagley, M. C.; Bashford, K. E.; Hesketh, C. L.; Moody, C. J. *J. Am. Chem. Soc.* **2000**, *122*, 3301. Amythiamycin D: (c) Hughes, R. A.; Thompson, S. P.; Alcaraz, L.; Moody, C. J. *J. Am. Chem. Soc.* **2005**, *127*, 15644. (d) Hughes, R. A.; Thompson, S. P.; Alcaraz, L.; Moody, C. J. *Chem. Commun.* **2004**, 946. Thiostrepton: (e) Nicolaou, K. C.; Safina, B. S.; Zak, M.; Lee, S. H.; Nevalainen, M.; Bella, M.; Estrada, A. A.; Funke, C.; Zecri, F. J.; Bulat, S. *J. Am. Chem. Soc.* **2005**, *127*, 11159. (f) Nicolaou, K. C.; Zak, M.; Safina, B. S.; Estrada, A. A.; Lee, S. H.; Nevalainen, M. *J. Am. Chem. Soc.* **2005**, *127*, 11176. (g) Nicolaou, K. C.; Safina, B. S.; Zak, M.; Estrada, A. A.; Lee, S. H. *Angew. Chem., Int. Ed.* **2004**, *43*, 5087. (h) Nicolaou, K. C.; Zak, M.; Safina, B. S.; Lee, S. H.; Estrada, A. A. *Angew. Chem., Int. Ed.* **2004**, *43*, 5092. Siomycin A: (i) Mori, T.; Higashibayashi, S.; Goto, T.; Kohno, M.; Satouchi, Y.; Shinko, K.; Suzuki, K.; Suzuki, S.; Tohmiya, H.; Hashimoto, K.; Nakata, M. *Tetrahedron Lett.* **2007**, *48*, 1331. GE2270A and GE 2270T: (j) Nicolaou, K. C.; Zou, B.; Dethe, D. H.; Li, D. B.; Chen, D. Y. K. *Angew. Chem., Int. Ed.* **2006**, *45*, 7786. (k) Muller, H. M.; Delgado, O.; Bach, T. *Angew. Chem., Int. Ed.* **2007**, *46*, 4771. (l) Delgado, O.; Muller, H. M.; Bach, T. *Chem.—Eur. J.* **2008**, *14*, 2322. Micrococcin P1: (m) Lefranc, D.; Ciufolini, M. A. *Angew. Chem., Int. Ed.* **2009**, *48*, 4198.

(3) (a) Nicolaou, K. C.; Nevalainen, M.; Safina, B. S.; Zak, M.; Bulat, S. *Angew. Chem., Int. Ed.* **2002**, *41*, 1941. (b) Moody, C. J; Hughes, R. A.; Thompson, S. P.; Alcaraz, L. *Chem. Commun.* **2002**, 1760. See also ref 2d.

(4) Noteworthy in this regard is the Bach approach (refs 2k and 2l). See ref 1 for a thorough bibliography.

(5) Ciufolini, M. A.; Shen, Y. C. *J. Org. Chem.* **1997**, *62*, 3804.

(6) (a) Bohlmann, F.; Rahtz, D. *Chem. Ber.* **1957**, *90*, 2265. Review: (b) Bagley, M. C.; Glover, C.; Merritt, E. A. *Synlett* **2007**, 2459. Moody introduced the reaction into current synthetic practice during his pioneering synthesis of promothiocin A (ref 2a).

(7) Bagley, M. C.; Dale, J. W.; Bower, J. *Chem. Commun.* **2002**, 1682.

(8) Bagley, M. C.; Dale, J. W.; Jenkins, R. L.; Bower, J. *Chem. Commun.* **2004**, 102.

(9) For representative methods see the preparation of compounds **7** and **12** (Scheme 2 herein) as described in ref 5 (**12**, 8 steps from glycolonitrile, 25%), ref 8, and in the following: Merritt, E. A.; Bagley, M. C. *Synlett* **2007**, 954 (**7**, 4 steps from diethoxyacetonitrile, 83%).

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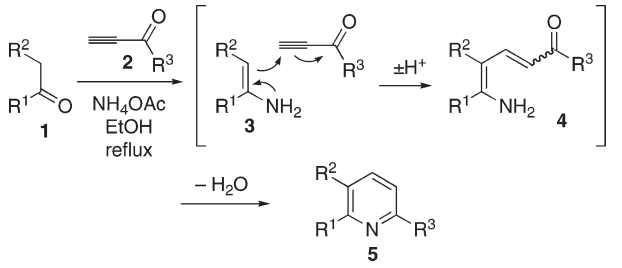
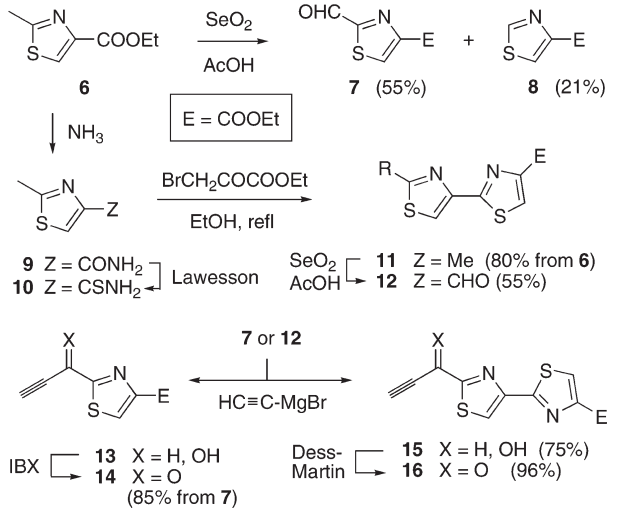
SCHEME 1. The Bagley Variant of the Bohlmann−Rahtz Pyridine Synthesis



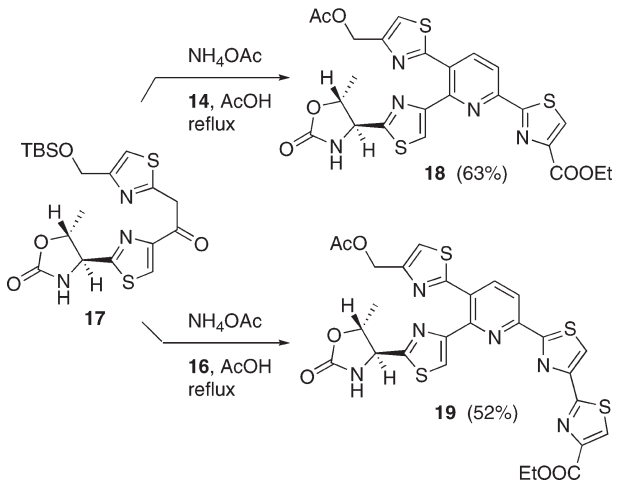
SCHEME 2. SeO_2 Oxidation of 2-Methylthiazoles and Preparation of Thiazolyl Ynones



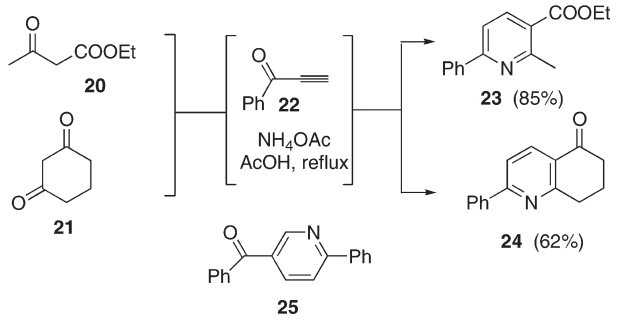
of ca. 0.5 M. The desired **7** (55% yield after purification) is then accompanied by 21% of **8**, which is readily separated by chromatography. The oxidation of **11**[10d] also proceeded in 55% yield (after chromatography), but no discrete byproducts could be detected in this reaction.[11] Addition of ethynylmagnesium bromide to **7** and **12** and oxidation of the resulting carbinols (IBX[12] for **13**; Dess−Martin for **16**) gave ynones **14**[8] and **16**.

Initial attempts to induce the union of **14** and **16** with the known **17**[2m,5] (Scheme 3) in refluxing EtOH (original Bagley conditions) were unsuccessful. Yet, in our hands the Bagley reaction performed admirably well when a mixture of, e.g., 1-phenyl-2-propyn-1-one[13] and ethyl acetoacetate, was treated with NH_4OAc under the prescribed conditions. The fact that none of the desired product was obtained from the reaction of **17** with **14** or **16** was attributed to the failure of **17** to combine with NH_4OAc sufficiently rapidly to furnish a requisite enamine of the type **3**. Perhaps for this reason, the Bagley synthesis of the core of amythiamycin[8] necessitated the formation of the enamine in question as a separate step. On the other hand, protonic acids are known to facilitate the formation of such enamines. Indeed, some modified Bohlmann−

SCHEME 3. One-Step Bohlmann−Rahtz Assembly of Thiopeptide Cores



SCHEME 4. Other Pyridines Obtained by the Procedure



Rahtz reactions proceed best in a 5:1 mixture of toluene and acetic acid as the solvent.[14] This induced us to study the combination of **14** and **16** with **17** and NH_4OAc in progressively more acidic media. In the event, it transpired that the reaction is best carried out in refluxing acetic acid, in a manner similar to the Eiden−Herdeis pyridine construction.[15] As seen in Scheme 3, pyridines **18** and **19** were thus obtained in 63% and 52% yield, respectively, after chromatographic purification. Notice that under the present conditions the TBS protecting group present in **17** was replaced by an acetate, probably as a consequence of acid-promoted cleavage and consequent Fischer-type esterification of the liberated alcohol. Compound **19** is recognized as a protected form of the core cluster of micrococcin P1−P2,[2m,5,9] thiocillin I, and YM266183.[16] The same procedure was satisfactory also for the synthesis of known pyridines **23**[6a] and **24**[10e] (Scheme 4). Interestingly, pyridine **25**[10f] was isolated as a byproduct in 22% yield from the reaction of **21** with **22**, but it was not detected in the crude reaction mixture obtained from **20**.

(11) This reaction forms a black precipitate of Se byproducts. Perhaps this precipitate entrains byproducts arising from **11**.

(12) The use of IBX for the oxidation of such carbinols was introduced by Moody (refs 2a and 2b). We found that the Dess−Martin periodinane performed better than IBX in the oxidation of **15**.

(13) This known compound was made as detailed in the Supporting Information.

(14) (a) Bagley, M. C.; Chapaneri, K.; Dale, J. W.; Xiong, X.; Bower, J. *J. Org. Chem.* **2005**, *70*, 1389. See also: (b) Bagley, M. C.; Brace, C.; Dale, J. W.; Ohnesorge, M.; Phillips, N. G.; Xiong, X.; Bower, J. *J. Chem. Soc., Perkin Trans. 1* **2002**, 1663.

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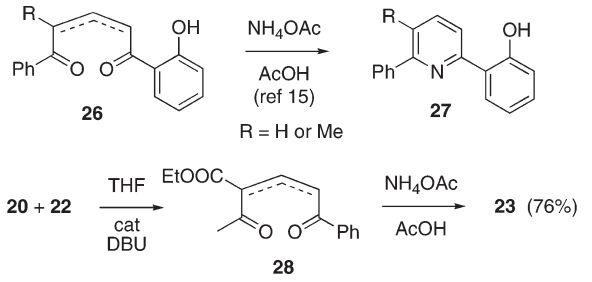
(16) Thiocillin, I.; Shoji, J.; Kato, T.; Yoshimura, Y.; Tori, K. *J. Antibiot.* **1981**, *34*, 1126. YM-266183: Nagai, K.; Kamigiri, K.; Arao, N.; Suzumura, K.-I.; Kawano, Y.; Yamaoka, M.; Zhang, H.; Watanabe, M.; Suzuki, K. *J. Antibiot.* **2003**, *56*, 123.

SCHEME 5. Eiden−Herdeis Pyridine Construction



A final aspect of this chemistry is worthy of note. Given that enediones **26** advance to pyridines **27** upon reaction with NH_4OAc in refluxing AcOH (Scheme 5),[15] we evaluated a variant of the chemistry of Schemes 3 and 4, in which a preformed substrate of the type **27** is converted into a pyridine in a separate step. Thus, treatment of the crude Michael adduct **28** of ethyl acetoacetate and **22** with NH_4OAc in refluxing AcOH[17] furnished pyridine **23** in *lower* yield relative to the direct synthesis (76% vs. 85%). This suggests that the variant of Bagley protocol detailed herein is superior to the Eiden−Herdeis method.

The preparation of **19** outlined in Scheme 3 (7 linear steps from **6**; 16% overall yield) compares favorably with earlier routes (12 linear steps from glycolonitrile,[5] 9% overall yield; 11 linear steps from diethoxyacetonitrile,[9] 15% overall yield). Applications of these findings to the synthesis of thiopeptide antibiotics are being actively pursued and will be disclosed in due course.

Experimental Section[18]

Aldehyde 7. A solution of compound **6** (4.0 g, 23.6 mmol) and SeO_2 (7.8 g, 70.8 mmol) in AcOH (95 mL) was refluxed for 12 h, then it was evaporated. The residue was neutralized with aqueous saturated $NaHCO_3$ solution (30 mL) and extracted with EtOAc. The combined extracts were dried (Na_2SO_4) and evaporated. Flash chromatographic purification of the residue (30% EtOAc/ hexanes) afforded **7** (2.4 g, 55%) as a white solid, mp 65−66 °C (lit.[10a] mp 67−68 °C), and **8** (780 mg, 21%) as a pale yellow solid, mp 49−50 °C (lit.[10c] mp 52−54 °C). ^{1}H NMR ($CDCl_3$) δ 10.08 (d, 1H, J = 1.3 Hz), 8.52 (d, 1H, J = 1.3 Hz), 4.50 (q, 2H, J = 7.1 Hz), 1.45 (t, 3H, J = 7.1 Hz). ^{13}C NMR ($CDCl_3$) δ 183.6, 166.1, 160.6, 149.6, 133.0, 62.1, 14.3. IR 1717, 1694. ESIMS 207.9 $[M + Na]^+$. HRMS calcd for $C_7H_8NO_3S$ $[M + H]^+$ 186.0225, found 186.0224.

Aldehyde 12. A solution of compound **11** (4.9 g, 19.2 mmol) and SeO_2 (6.4 g, 57.8 mmol) in AcOH (40 mL) was refluxed for 12 h. The mixture was filtered through Celite to remove a dark precipitate and the filtrate was evaporated. The residue was treated with aqueous saturated $NaHCO_3$ solution (30 mL) and extracted with EtOAc. The combined extracts were dried (Na_2SO_4) and evaporated to give the known **12**[2m,5] (2.8 g, 55%). A sample recrystallized from EtOAc/heptanes had mp 156−157 °C. ^{1}H NMR ($CDCl_3$) δ 10.06 (d, 1H, J = 1.0 Hz), 8.55 (d, 1H, J = 1.1 Hz), 8.26 (s, 1H), 4.47 (q, 2H, J = 7.1 Hz), 1.45 (t, 3H, J = 7.1 Hz). ^{13}C NMR ($CDCl_3$) δ 183.2, 165.9, 161.9, 161.1, 151.1, 148.2, 128.5, 123.9, 61.7, 14.3. IR 1723, 1702. ESIMS 301 $[M+MeOH+H]^+$. HRMS calcd for $C_{10}H_8N_2O_3S_2Na$ $[M+Na^+]$ 290.9874, found 290.9865.

Ynone 14. A solution of **7** (1.7 g, 9.0 mmol) in THF (5 mL) was added dropwise with good stirring to a commercial 0.5 M solution of ethynylmagnesium bromide (27.0 mL, 13.5 mmol) at rt. The mixture was stirred for 30 min at rt, then it was cautiously quenched with aqueous saturated NH_4Cl solution (20 mL). The organic layer was separated and the aqueous phase was extracted with EtOAc (2 × 20 mL). The combined extracts were dried (Na_2SO_4) and concentrated. The crude product, a thick oil, was directly added to a solution of IBX (2.5 g, 18.0 mmol) in DMSO (10 mL) and heated at 35 °C for 12 h. The cooled mixture was diluted with EtOAc (30 mL) and water (40 mL) and stirred vigorously for 10 min, then it was filtered over Celite. The organic phase was separated and the aqueous layer was extracted with ether (3×30 mL). The combined extracts were sequentially washed with saturated aqueous $NaHCO_3$ (30 mL) and saturated aqueous NaCl (30 mL) solution, dried (Na_2SO_4), and concentrated to give a dark solid (1.6 g, 85% over 2 steps). Despite the color, this material was of sufficiently good quality to be used in the next step without purification. A purified sample (flash chromatography, 20% EtOAc/hex), white solid, had mp 114−116 °C. ^{1}H NMR ($CDCl_3$) δ 8.50 (s, 1H), 4.48 (q, 2H, J = 7.2 Hz), 3.68 (s, 1H), 1.44 (t, 3H, J = 7.2 Hz). ^{13}C NMR ($CDCl_3$) δ 169.1, 166.0, 160.5, 149.6, 133.5, 84.8, 78.9, 62.1, 14.3. ESIMS 210.2 $[M + H]^+$, 232.1 $[M + Na]^+$. HRMS calcd for $C_9H_8NO_3S$ $[M+H]^+$ 210.0225, found 210.0175.

Alcohol 15. A solution of **12** (3.5 g, 13.0 mmol) in THF (8 mL) was added dropwise to a commercial 0.5 M solution of ethynylmagnesium bromide in THF (57.6 mL, 28.8 mmol) at rt. The mixture was stirred for 30 min, then it was quenched with aqueous saturated NH_4Cl solution (30 mL). The organic layer was separated and the aqueous phase was extracted with EtOAc (2 × 30 mL). The combined extracts were dried (Na_2SO_4) and evaporated. Flash chromatographic purification of the residue (40% EtOAc/hexanes) gave **15** (2.9 g, 75%) as a white solid, mp 145−148 °C. ^{1}H NMR (DMSO-d_6) δ 8.54 (s, 1H), 8.35 (s, 1H), 7.08 (d, 1H, J = 6.0 Hz), 5.73 (dd, 1H, J = 6.0, 2.2 Hz), 4.32 (q, 2H, J = 7.1 Hz), 3.68 (d, 1H, J = 2.2 Hz), 1.31 (t, 3H, J = 7.1 Hz). ^{13}C NMR (DMSO-d_6) δ 174.0, 162.8, 161.1, 147.8, 147.4, 130.0, 119.4, 83.16, 77.3, 61.3, 60.8, 14.7. ESIMS 295.1 $[M+H]^+$, 317.1 $[M + Na]^+$. HRMS calcd for $C_{12}H_{11}N_2O_3S_2$ $[M + H]^+$ 295.0211, found 295.0191 $[M+1]^+$.

Ynone 16. Dess−Martin periodinane (735 mg, 1.8 mmol) was added in small portions to a suspension of alcohol **15** (435 mg, 1.5 mmol) in CH_2Cl_2 (5 mL) at rt and with good stirring. The solution became clear after 10 min. After 2 h of stirring, the reaction was complete (TLC), whereupon it was diluted with 10 mL each of aqueous saturated $NaHCO_3$ and aqueous saturated $Na_2S_2O_3$ solutions. The organic layer was separated and further washed with aqueous saturated $NaHCO_3$ solution (10 mL), then it was dried (Na_2SO_4) and concentrated to give **16** as an orange solid (415 mg, 96%). A sample purified by flash chromatography (40% EtOAc/ hexanes), white solid, had mp 107−109 °C. ^{1}H NMR ($CDCl_3$) δ 8.54 (s, 1H), 8.26 (s, 1H), 4.46 (q, 2H, J = 7.0 Hz), 3.66 (s, 1H), 1.44 (t, 3H, J = 7.0 Hz). ^{13}C NMR ($CDCl_3$) δ 168.6, 165.7, 161.9, 161.2, 151.1, 148.2, 128.6, 124.7, 84.0, 79.1, 61.7, 14.3. ESIMS 315.1 $[M + Na]^+$. HRMS calcd for $C_{12}H_9N_2O_3S_2$ $[M+H]^+$ 293.0055, found 293.0067.

Pyridine 18. A solution of ketone **17** (256 mg, 564 μmol), ynone **14** (118 mg, 564 μmol), and NH_4OAc (65 mg, 846 μmol) in AcOH (5 mL) was refluxed for 8 h, then it was concentrated, neutralized (aqueous saturated $NaHCO_3$ solution), and extracted with EtOAc (2 × 20 mL). The combined extracts were dried (Na_2SO_4) and evaporated. Flash chromatographic purification of the residue (50% EtOAc/hexanes) afforded **18** (203 mg, 63%) as a light orange solid in >98% purity by HPLC[19] with mp 95−98 °C, $[\alpha]^{25}_D$ +21.1 (*c* 0.99, acetone). ^{1}H NMR

(17) Conduct of the reaction in EtOH again failed to produce pyridines.
(18) Experimental protocols are provided as Supporting Information.
(19) Details of the HPLC analysis are provided as Supporting Information.

($CDCl_3$) δ 8.42 (d, 1H, J = 8.1 Hz), 8.32 (s, 1H), 8.19 (d, 1H, J = 8.1 Hz), 8.01 (s, 1H), 7.39 (s, 1H), 5.59 (s, br, 1H), 5.22 (s, 2H), 4.65 (dd, 1H, J = 6.3, 1.2 Hz), 4.54 (quintet, 1H, J = 6.2 Hz), 4.48 (q, 2H, J = 7.1 Hz), 2.13 (s, 3H), 1.48 (d, 3H, J = 6.3 Hz), 1.46 (t, 3H, J = 7.1 Hz). ^{13}C NMR ($CDCl_3$) δ 170.8, 168.7, 168.5, 165.3, 161.3, 158.0, 154.1, 151.6, 150.5 (2 overlapping peaks), 148.6, 140.0, 130.1, 129.7, 121.5, 119.23, 119.2, 79.6, 61.7, 61.7, 60.8, 20.9, 19.9, 14.4. ESIMS 572 $[M+H]^+$, 594 $[M+Na]^+$. HRMS calcd for $C_{24}H_{22}N_5O_6S_3$ $[M+H]^+$ 572.0732, found 572.0727.

Pyridine 19. A solution of ketone **17** (380 mg, 832 μmol), ynone **12** (248 mg, 832 μmol), and NH_4OAc (97 mg, 1.2 mmol) in AcOH (5 mL) was refluxed for 12 h, then it was concentrated, neutralized (aqueous saturated $NaHCO_3$ solution), and extracted with EtOAc (2 × 25 mL). The combined extracts were dried (Na_2SO_4) and evaporated. Flash chromatographic purification of the residue (70% EtOAc/hexanes) afforded **19** (285 mg, 52%) as a pale yellow solid in >97% purity by HPLC[19] with mp 210−211 °C, $[\alpha]^{25}_D$ +5.5 (*c* 0.91, $CHCl_3$). ^{1}H NMR ($CDCl_3$) δ 8.34 (d, 1H, J = 8.0 Hz), 8.32 (s, 1H), 8.24 (s, 1H), 8.20 (d, 1H, J = 8.0 Hz), 8.03 (s, 1H), 7.40 (s, 1H), 5.78 (s, br, 1H), 5.23 (s, 2H), 4.65 (dd, 1H, J = 6.0, 1.1 Hz), 4.54 (p, 1H, J = 6.1 Hz), 4.47 (q, 2H, J = 7.2 Hz), 2.13 (s, 3H), 1.48 (d, 3H, J = 6.2 Hz), 1.45 (t, 3H, J = 7.2 Hz). ^{13}C NMR ($CDCl_3$) δ 170.8, 168.4, 168.3, 165.4, 163.1, 161.4, 157.7, 154.2, 151.6, 150.7, 150.6, 149.9, 148.1, 140.0, 129.6, 127.9, 121.5, 120.5, 119.1, 118.8, 79.6, 61.8, 61.6, 60.8, 21.0, 19.9, 14.4. ESIMS 655 $[M+H]^+$, 677 $[M+Na]^+$. HRMS calcd for $C_{27}H_{23}N_6O_6S_4$ 655.0562 $[M+H]^+$, found 655.0558.

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Supporting Information Available: Experimental protocols, characterization data, and NMR spectra. This material is available free of charge via the Internet at http://pubs.acs.org.