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A Route to the Heterocyclic Cluster of the E-Series of Thiopeptide Antibiotics

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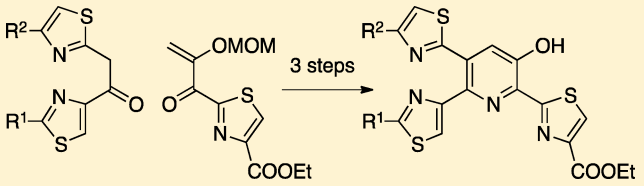
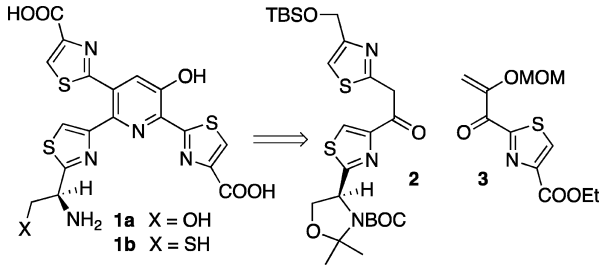
Supporting Information

ABSTRACT: A concise route to the 3-hydroxypyridine core of thiopeptide antibiotics such as nocathiacin is described. Key phases of the sequence involve a modified Hantzsch pyridine construction and a chemoselective Peng deprotection of a phenolic MOM ether.



The E-series of thiopeptide antibiotics[1] includes those substances that exhibit a core consisting of a 3-hydroxypyridine ring embedded in a heterocyclic cluster of the type **1** (Scheme 1). In compounds such as MJ347-81F4,[2]

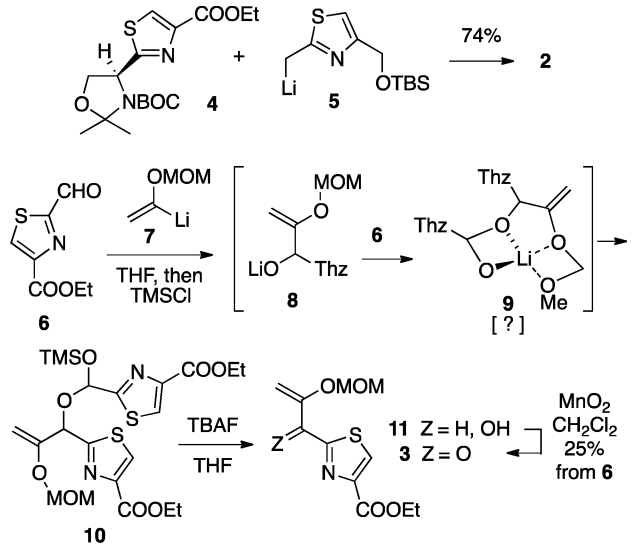
Scheme 1. Retrosynthetic Logic for the Pyridine Cores of Nocathiacin (1) and of Nosiheptide (2)



nocathiacin,[3] and thiazomycin,[4] substituent X is an OH group (cf. **1a**), whereas in nosiheptide,[5] X = SH (**1b**). The assembly of such motifs is fraught with difficulties that translate into fairly elaborate routes.[6] Our interest in thiopeptides[7] prompted us to seek a more direct avenue to orthogonally protected forms of **1**, in which the COOH functionalities are suitably differentiated. To that end, we revisited a modified Hantzsch pyridine synthesis, which had served us well[8] for the assembly of analogs of **1** lacking the pyridine C-3 OH group.[9] Accordingly, structure **1** would result through the union of fragments **2** and **3**.

The requisite fragments were prepared as delineated in Scheme 2. Reaction of the known thiazole **4**[10] with a 2-fold molar excess[11] of organolithium species **5**[8] afforded **2** in 74% yield. Proton and ^{13}C NMR spectra revealed that the product existed as a mixture of keto- and enol tautomers, each of which gave rise to two slow-interconverting BOC rotamers at room temperature. Therefore, the NMR spectra of **2** were recorded both at rt and at 60−80 °C.[12] Segment **3** was obtained starting with addition of lithiated methoxymethyl vinyl ether, **7**,[13] to the known[14] aldehyde **6**. The yield of alcohol **11** thus obtained was consistently around 50%, even when the reaction was carried

Scheme 2. Preparation of Ketones 2 and 3



out using multiple equivalents of **7**. Furthermore, all such reactions returned about half of the starting aldehyde **6**. This phenomenon was observed only with organometallic agent **7**: The addition of other organo-Li species to **6** occurred normally and proceeded to completion.[7,8] It was determined that this peculiar behavior was due to a rapid, irreversible addition of initially formed alkoxide **8** to a second molecule of highly electrophilic **6**. This resulted in formation of an unusually stable hemiacetal anion, which was intercepted *in situ* with TMSCl to afford **10** (partially characterized) as a 1:1 mixture of diastereomers.[15] The unusual stability of the foregoing anion may be due to its existence as chelated complex **9**.[16] Upon treatment with TBAF, substance **10** unraveled to an equimolar mixture of aldehyde **6** and carbinol **11**, a sensitive compound that was not amenable to purification. Most residual **6** could be

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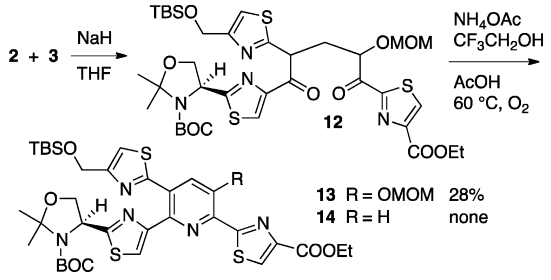
removed by washing with water, in which it is soluble probably due to hydrate formation. Crude **11** thus obtained was immediately oxidized to **3** (MnO_2), a delicate substance (oil) which was partially purified by rapid elution through deactivated (Et_3N) silica gel, in order to contain losses to an acceptable level.[17]

Enones of the type **3**, but lacking the OMOM functionality, are problematic substrates for 1,4-addition, because their extremely electrophilic character causes them to polymerize rapidly under Michael conditions.[7,8] This had necessitated the development of a heterogeneous catalytic system to achieve their union with ketones such as **2**.[7,8] It was unclear, at the onset of the present investigation, whether the alkoxy group in **3** might exacerbate the foregoing characteristics and possibly bar the feasibility of the desired transformation. Fortunately, this proved not to be the case: Enone **3** was a good substrate for Michael addition, indicating that the alkoxy group actually moderates the electrophilic character of the molecule. Indeed, the union of **2** with **3** was easily achieved with NaH in THF at room temperature. Diketone **12** thus obtained (mixture of diastereomers, keto−enol−, and ring−chain tautomers as well as slow-interconverting BOC rotamers; NMR) was advanced to the pyridine-forming step in crude form.

Scheme 3. Synthesis of Pyridine13

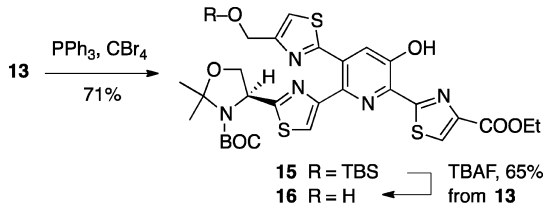


The Hantzsch-type conditions developed earlier[7,8] for the assembly of pyridines lacking the 3-OH functionality proved to be inadequate for the conversion of **12** into **13**. However, pyridine **13** emerged in 28% yield from **2** and **3** over 2 steps, after chromatography, upon slow addition (3 h, syringe pump) of a solution of crude **12** in a 4:1 mixture of 2,2,2-trifluoroethanol and acetic acid into a solution of NH_4OAc (12.5 equiv) and PPTS[18] (1 equiv) in the same solvent system, maintained 60 °C under an O_2 atmosphere (balloon), followed by stirring for 14 h at 60 °C. The acidic medium effectively suppressed formation of desoxypyridine **14**, a major byproduct obtained from reactions carried out under less acidic conditions.[19] The room-temperature NMR spectra of **13** exhibited broadened lines (BOC rotamers), but excellent spectra were obtained at 80 °C (DMSO-d_6).

The release of the *O*-MOM group from **13** by the use of traditional acidic reagents (aq. HCl, HBr/AcOH, BBr_3) resulted in rapid destruction of the substrate. Remarkably, the unusually mild method for MOM release described by Peng and co-workers[20] performed well and delivered **15** in 71% yield. The survival of the TBS group under these conditions is noteworthy.

The room-temperature NMR spectra of **15** again indicated the presence of slow-interconverting BOC rotamers. When a solution of **15** in DMSO-d_6 was heated to 80 °C in an NMR probe, with the intent of obtaining clearer spectra, partial release of the TBS group was observed (ca. 20% after 30 min).

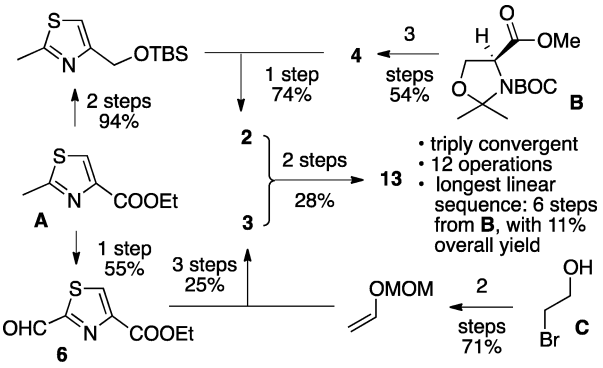
Scheme 4. Selective Deblocking of Pyridine 13



This prevented proper characterization. Therefore, pyridine **15** was fully deblocked, and complete characterization was carried out at the stage of **16**.

In summary, the complete heterocyclic cluster of the E-class of thiopeptide antibiotics may be accessed in orthogonally protected form, and via a triply convergent approach, from inexpesive commercial materials **A**, **B**, and **C** (Scheme 5). The

Scheme 5. Summary of the Present Route to 13



route entails 12 distinct operations and six steps along the longest linear sequence (**B** → **13**, Scheme 5), with an 11% overall yield along this path. In terms of length and yields, this route is competitive with known alternatives.[21] We are actively endeavoring to parlay these results into a synthesis of representative members of the E-series of thiopeptide antibiotics.

EXPERIMENTAL SECTION

Experimental Protocols. These are provided as Supporting Information.

*tert-Butyl (S)-4-(4-(ethoxycarbonyl)thiazol-2-yl)-2,2-dimethyloxazolidine-3-carboxylate (**4**).* A solution of (4*S*)-4-(aminothioxomethyl)-2,2-dimethyl-3-oxazolidinecarboxylic acid-1,1-dimethyl-ethyl ester[10a,d] (1.3 g, 5.0 mmol) in DME (30 mL) containing suspended $KHCO_3$ (3.6 g, 35.0 mmol, 7.0 equiv) was stirred at rt for 10 min. Neat ethyl bromopyruvate (Caution: toxic; 2.9 g, 15.0 mmol, 3.0 equiv, 2.1 mL) was added dropwise over a period of 3 min, and the mixture was stirred for 16 h at rt. The solvent was removed *in vacuo*, the residue was redissolved in EtOAc (65 mL), and the solution was sequentially washed with brine (20 mL) and water (15 mL), dried (Na_2SO_4), and evaporated *in vacuo*. The residue was placed under high vacuum to remove all remaining EtOAc, then it was redissolved in DME (30 mL). The solution was cooled to 0 °C, and pyridine (3.1 mL, 3.0 g, 37.5 mmol, 7.5 equiv) was added slowly over a period of 3 min. After 5 min, TFAA (4.1 g, 20.0 mmol, 2.8 mL, 4.0 equiv) was added slowly. The mixture was stirred at 0 °C for 3 h, then it was brought to rt. Triethylamine (1.2 g, 10.0 mmol, 1.7 mL, 2.0 equiv) was slowly added, and stirring at rt was continued for another hour, whereupon the reaction was complete (TLC). The mixture was evaporated, and the residue was dissolved in EtOAc (70 mL) and washed with 1 M HCl (15 mL), sat. aq. $NaHCO_3$ (15 mL), and brine (15 mL). The organic phase was dried (Na_2SO_4) and concentrated *in*

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vacuo. Flash column chromatography (25% EtOAc: 75% Hex, R_f = 0.31) of the residue afforded **4** (1.7 g, 4.6 mmol, 97%) as a yellow solid, mp 105−109 °C (lit. mp not reported);[10d] $[\alpha]_D^{22}$ = −13.1° (CH_2Cl_2, *c* = 1.05) (lit. $[\alpha]_D$ not reported).[10d] ^{1}H: 8.09 (s, 1H), 5.36 (bs, minor rotamer) and 5.29−5.25 (m, major rotamer; 1H), 4.42 (q, 2H, *J* = 7.0 Hz), 4.32−4.28 (m, major rotamer) and 4.17−4.14 (m, minor rotamer; 2H), 1.79 (bs, major rotamer) and 1.73 (bs, minor rotamer, 3H), 1.57 (bs, major rotamer) and 1.50 (bs, minor rotamer; 6H), 1.38 (t, 3H, *J* = 7.0 Hz), 1.30 (bs, 6H). ^{13}C: 175.3, 161.3, 151.5, 147.2, 127.1, 95.2 (major rotamer) and 94.8 (minor rotamer), 81.4 (minor rotamer) and 81.0 (major rotamer), 69.3 (major rotamer) and 68.9 (minor rotamer), 61.5, 59.4, 28.2, 27.3 (minor rotamer) and 26.5 (major rotamer), 23.9 (minor rotamer) and 22.7 (major rotamer), 14.4. IR: 1701, 1364 cm^{-1}. LRMS: 379.1 [M + Na$^+$].

*tert-Butyl (S)-4-(4-(2-(4-(((tert-butyldimethylsilyl)oxy)methyl)-thiazol-2-yl)acetyl)thiazol-2-yl)-2,2-dimethyloxazolidine-3-carboxylate (**2**).* Commercial *n*-BuLi solution (1.1 M in hexanes, 7.2 mL, 7.7 mmol) was added over 3 min to a cold (−78 °C) solution of 2-methyl-4-(*tert*-butyldimethylsilyl-oxy)methyl thiazole (1.9 g, 7.7 mmol, 2.0 equiv) in THF (12 mL), the mixture was stirred at −78 °C for 40 min, then a solution of compound **4** (1.3 g, 3.6 mmol, 1 equiv) in THF (4 mL) was slowly added over a period of 3 min. The mixture was slowly brought up to rt over a period of 2 h, then it was quenched with aq. sat. NH_4Cl solution (5 mL). The mixture was diluted with EtOAc (50 mL), transferred to a separatory funnel, and carefully acidified with 0.5 M HCl to pH 5. The organic layer was collected, dried (Na_2SO_4), and concentrated *in vacuo*. Flash column chromatography (15% EtOAc: 85% hexanes, R_f = 0.33) of the residue afforded unreacted 2-methyl-4-(*tert*-butyldimethylsilyl-oxy)methyl thiazole (378 mg, 1.6 mmol, 38%, R_f = 0.50) and the desired ketone **2** (1.5 g, 2.7 mmol, 74%) as a thick yellow oil, $[\alpha]_D^{22}$ = −6.1° (CH_2Cl_2, *c* = 1.78). Proton and ^{13}C NMR spectra of this material revealed that it existed as a mixture BOC rotamers of the keto- (minor) and enol forms (major; ca. 1:2 ratio). ^{1}H: [8.20(br. s, keto), 7.67 (br. s, enol) (1H)], [7.16 (br. s, keto), 6.95 (br. s, enol) (1H)], [6.69 (s, enol) (0.6H)], [5.24 (br. s, keto), 5.21 (br. s, enol) (1H)], [4.85−4.80 (m, contains keto form of enol at 6.69) (2.5H)], [4.34−4.27 (m, enol), 4.22−4.16 (m, keto) (2H)], [1.81−1.77 (m, enol), 1.76−1.71 (m, keto) (3H)], [1.59, 1.51 (br. 2s of equal intensity, (6H)], 1.32 (br. s, enol and keto), (6H), [0.95(s, enol), 0.93 (s, keto) (9H)], [0.13 (s, enol), 0.09 (s, keto) (6H)]. ^{13}C NMR (100 MHz, CD_3CN, 65 °C): 190.4, 175.3, 175.0, 169.4, 163.6, 157.9, 156.7, 156.3, 154.6, 153.1, 151.7, 128.1, 119.2, 116.6, 112.4, 96.1, 96.0, 94.0, 81.7, 69.8, 62.9, 62.4, 60.6, 60.5, 45.0, 28.8, 27.4, 26.5, 24.1, 19.2, −4.8. IR: 3126, 1694, 1630, 1090, 837 cm^{-1}. LRMS: 554.3 [M + H$^+$]. HRMS: calcd for 554.2179 $C_{25}H_{40}N_3O_5SiS_2$; found: 554.2179 [M + H$^+$].

*Ethyl 2-(2-(methoxymethoxy)acryloyl)thiazole-4-carboxylate (**3**).* Commercial *tert*-BuLi in pentane (1.24 M, 7.0 mL, 8.7 mmol, 5.8 equiv) was carefully added over 3 min to a cold (−78 °C) solution of methoxymethyl vinyl ether[13] (385 mg, 8.7 mmol, 5.8 equiv) in dry tetrahydropyran (3.5 mL). A bright yellow solution resulted. The mixture was stirred at −78 °C for 10 min, then it was warmed to −10 °C (NaCl/ice bath) and stirred at that temperature for 23 min, during which time the bright yellow color disappeared. The mixture was then cooled back to −78 °C and diluted with dry THF (2.5 mL). A solution of aldehyde **6** (277 mg, 1.5 mmol, 1 equiv) in THF (1.5 mL) was added dropwise, whereupon the color of the solution turned light red. The mixture was stirred at −78 °C for 20 min, then it was quenched with TMSCl (1.1 mL, 8.2 mmol, 5.5 equiv) and stirred for 10 more min. Aqueous sat. NH_4Cl (1.5 mL) was added, and the mixture was rapidly warmed to rt (warm water bath). More aq. sat. NH_4Cl (3 mL) was added during the warming process. The mixture was then diluted with EtOAc (25 mL) and transferred to a separatory funnel and the aqueous layer was discarded. The organic phase was washed with more aq. sat. NH_4Cl (3 mL), dried (Na_2SO_4) and concentrated *in vacuo*. In crude form, the sensitive product **10** (not fully characterized)[15] was immediately taken up in THF (6 mL), treated with 1 M TBAF in THF (1.8 mL, 1.8 mmol), and stirred at rt for 3 h. The mixture was quenched with aq. sat. NH_4Cl (3 mL), diluted with EtOAc (25 mL), transferred into a separatory funnel, and washed with water (5 mL) to remove ammonium salts, then the organic phase was dried (Na_2SO_4) and concentrated *in vacuo* to afford crude alcohol **11** (410 mg). This compound was immediately dissolved in CH_2Cl_2 (15 mL) and treated with MnO_2 (1.30 g, 15 mmol, 10 equiv relative to **6**). The mixture was stirred at rt for 48 h, then it was filtered over Celite. The filtrate was evaporated *in vacuo*, and the residue was immediately applied to a column of silica gel (10 g) that had been deactivated by eluting with 3.5% Et_3N in hexanes (20 mL). Elution with 3.5% Et_3N:50% EtOAc:46.5% hexanes yielded enone **3** (101 mg, 375 μmol, 25% over 3 steps) as a yellow oil (R_f = 0.63). ^{1}H: 8.43 (s, 1H), 6.57 (d, 1H, *J* = 3.0 Hz), 5.63 (d, 1H, *J* = 3.0 Hz), 5.17 (s, 2H), 4.43 (q, 2H, *J* = 7.3 Hz), 3.50 (s, 3H), 1.41 (t, 3H, *J* = 7.3 Hz). ^{13}C: 179.0, 165.9, 160.8, 153.1, 148.6, 132.9, 107.2, 94.6, 61.8, 56.5, 14.3. IR: 1733, 1721, 1658, 1610, 1152, 1011 cm^{-1}. LRMS: 272.2 [M + H$^+$], 294.2 [M + Na$^+$]. HRMS: calcd for 272.0593 $C_{11}H_{14}NO_5S$; found: 272.0590 [M + H$^+$].

*tert-Butyl (S)-4-(4-(3-(4-(((tert-butyldimethylsilyl)oxy)methyl)-thiazol-2-yl)-6-(4-(ethoxycarbonyl)thiazol-2-yl)-5-(methoxymethoxy)-pyridin-2-yl)thiazol-2-yl)-2,2-dimethyloxazolidine-3-carboxylate (**13**).* Commercial NaH (60% oil dispersion, 16 mg, 400 μmol, 1.3 equiv) was dispensed into a flask maintained under inert atmosphere (Ar balloon), washed with hexanes (3 × 400 μL) to remove excess oil, and suspended in THF (400 μL). A solution of ketone **2** (162 mg, 300 μmol, 1 equiv) in THF (500 μL) was slowly added (syringe) at rt over ca. 2 min. Evolution of H_2 was observed, and the color changed from faint green to yellow upon stirring at rt for 15 min. A solution of enone **3** (126 mg, 460 μmol, 1.5 equiv) in THF (0.4 mL) was added at rt over a period of 1 min, whereupon the color of the solution turned from yellow to brown. The mixture was stirred for 90 min at rt, then it was quenched with aq. sat. NH_4Cl (500 μL), diluted with EtOAc (10 mL), and transferred to a separatory funnel. The aqueous layer was discarded, while the organic phase was washed with more aq. sat. NH_4Cl (500 μL), dried (Na_2SO_4), and concentrated *in vacuo*. The crude diketone **12** was immediately taken up in a 4:1 mixture of TFE (1.8 mL) and AcOH (450 μL), and the solution was added over a period of 2.5 h (syringe pump) to a flask containing a warm (60 °C, oil bath temperature) solution of NH_4OAc (288 mg, 3.7 mmol, 12.5 equiv) and PPTS (75 mg, 300 μmol) in 4:1 TFE (2 mL)-AcOH (500 μL), maintained under O_2 atmosphere (balloon). The mixture was stirred at 60 °C for 14 h, then it was concentrated *in vacuo*, and the residue was taken up with EtOAc (15 mL). This solution was washed 2−3 times with 2 mL portions of aq. sat. $NaHCO_3$ until the pH of the aqueous washes (pH paper) stabilized at 7, then it was dried (Na_2SO_4) and concentrated *in vacuo*. Flash column chromatography of the residue (1% Et_3N:25% EtOAc:74% hexanes) afforded pyridine **13** (67 mg, 83 μmol, 28% over 2 steps) as a yellow solid, mp 58−61 °C, $[\alpha]_D^{21}$ = −11.3° (CH_2Cl_2, c = 1.65). This compound was highly UV active (purple under short wavelength, and sky blue under long wavelength), and its elution was readily monitored by TLC (50% EtOAc:50% hexanes; R_f = 0.40). The room-temperature NMR spectra of **13** exhibited broad lines and revealed the presence of BOC rotamers. Therefore, NMR spectra were recorded from DMSO-d_6 solutions at 80 °C. ^{1}H (400 MHz, DMSO-d_6, 80 °C): 8.61 (s, 1H), 8.20 (s, 1H), 7.91 (s, 1H), 7.48 (s, 1H), 5.51 (s, 2H), 5.15 (d of d, 1H,*J* = 6.2 Hz *J* = 1.7 Hz), 4.82 (s, 2H), 4.37 (q, 2H, *J* = 7.1 Hz), 4.22 (d of d, 1H, *J* = 9.0 Hz, *J* = 6.2 Hz), 3.96 (d of d, 1H, *J* = 9.0 Hz, *J* = 1.7 Hz), 3.57(s, 3H), 1.63 (s, 3H), 1.52 (s, 3H), 1.41 (s, 9H), 1.36 (t, 3H, *J* = 7.1 Hz), 0.94 (s, 9H), 0.12 (s, 6H). ^{13}C (100 MHz, DMSO-d_6, 80 °C): 172.0, 164.0, 162.3, 160.5, 156.3, 151.4, 150.9, 149.4, 147.1, 143.9, 139.2, 130.3, 130.2, 125.0, 120.3, 117.4, 95.4, 93.8, 79.7, 68.0, 61.0, 60.3, 58.3, 56.1, 27.6, 26.1, 25.4, 23.1, 17.5, 13.7, −5.7. IR: 1705, 1154, 1088 cm^{-1}. LRMS: 826.4 [M + Na$^+$]. HRMS: calcd for 826.2410 $C_{36}H_{49}N_5O_8SiS_3Na$; found: 826.2411 [M + Na$^+$].

*tert-Butyl (S)-4-(4-(3-(4-(((tert-butyldimethylsilyl)oxy)methyl)-thiazol-2-yl)-6-(4-(ethoxycarbonyl)thiazol-2-yl)-5-hydroxypyridin-2-yl)thiazol-2-yl)-2,2-dimethyloxazolidine-3-carboxylate (**15**).* Solid PPh_3 (2.6 mg, 10 μmol, 0.25 equiv) and CBr_4 (3.3 mg, 10 μmol, 0.25 equiv) were added to a solution of pyridine **13** (32 mg, 40 μmol) in 1,2-dichloroethane (700 μL), and the mixture was heated to 40 °C (oil bath temperature), with good stirring, for 3 h, whereupon TLC (50% EtOAc:50% hexanes) showed complete conversion of **13** into

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15. The solution was then diluted with CH_2Cl_2 (4 mL), washed with aq. sat. $NaHCO_3$ (1 mL), dried (Na_2SO_4), and concentrated *in vacuo*. Flash column chromatography (20% EtOAc:80% hexanes) of the residue afforded pyridine **15** (22 mg, 28 μmol, 71%) as a yellow film, $[\alpha]_D^{25} = -8.9°$ (CH_2Cl_2, $c = 0.350$). The compound, which was very streaky on TLC (R_f = 0.51−0.73 in 50% EtOAc:50% hexanes), is highly UV active. It can be visualized on TLC as a green spot under short wavelength, and a bright green one under long wavelength. ^{1}H: 11.58 (bs, 1H), 8.26 (s, 1H), 7.95 (s, 1H), 7.56 (s, 1H), 7.23 (s, 1H), [5.27−5.22 (m, minor rotamer), 5.16−5.11 (m, major rotamer) (1H)], 4.90 (s, 2H), 4.45 (q, 2H, J = 7.1 Hz), [4.21−4.13 (m, major rotamer), 4.11−4.03 (m, minor rotamor) (2H)], [1.79 (bs, major rotamer), 1.72 (bs, minor rotamer) (3H)], [1.58, 1.54 (bs, rotamers of equal intensity, 6H)], 1.46−1.40 (m, 9H), 0.96 (s, 9H), 0.13 (s, 6H). IR: 3126, 2932 1704, 1365, 839 cm^{-1}. LRMS: 760.3 [M + H$^+$]. HRMS: calcd for $C_{34}H_{46}N_5O_7SiS_3$ 760.2329; found: 760.2324 [M + H$^+$]. Heating a solution of **15** in DMSO-d_6 to 80 °C in an NMR probe caused partial release of the TBS group. An NMR spectrum of the resulting mixture is provided in the Supporting Information.

*tert-Butyl (S)-4-(4-(6-(4-(ethoxy-carbonyl)thiazol-2-yl)-5-hydroxy-3-(4-(hydroxyl-methyl)thiazol-2-yl)pyridin-2-yl)-thiazol-2-yl)-2,2-dimethyloxazolidine-3-carboxylate (**16**).* The partially desilylated pyridine described above was redissolved in THF (100 μL), treated with TBAF (1M, 60 μmol, 60 μL), and stirred at rt for 20 min. The mixture was then diluted with EtOAc (2 mL) and washed with sat. aq. NH_4Cl (500 μL) and water (2 × 500 μL). The organic layer was collected, dried (Na_2SO_4), and concentrated *in vacuo*. The residue was subject to flash column chromatography (40% EtOAc:60% hexanes), and the elution of the desired product was monitored by TLC (70% EtOAc:30% hexanes, R_f = 0.14−0.31, extremely streaky product). Compound **16** appeared as purple spot under short wavelength, and as a yellow one under long wavelength. The product (17 mg, 66% over 2 steps) was isolated as yellow foam, $[\alpha]_D^{21} = -12.1°$ (CH_2Cl_2, c = 0.850). ^{1}H (CD_3CN): 11.71 (bs, 1H), 8.37 (s, 1H), 7.90 (s, 1H), 7.71 (s, 1H), 7.34 (s, 1H), 5.10 (d, 1H, J = 5.9 Hz), 4.64 (s, 2H), 4.39 (q, 2H, J = 7.1 Hz), 4.19 (d of d, 1H, J = 9.0 Hz, J = 6.3 Hz), 3.92 (d of d, 1H, J = 9.0 Hz, J = 1.6 Hz), 1.67 (s, 3H), 1.52 (s, 3H), 1.49 (bs, 3H), 1.41−1.37 (m, 9H). ^{13}C (100 MHz, DMSO-d_6, 65 °C): 172.3, 168.2, 162.0, 159.7, 157.8, 151.5, 151.2, 151.0, 145.4, 142.7, 133.8, 131.5, 130.1, 125.0, 120.2, 117.2, 93.9, 79.8, 68.2, 60.9, 59.4, 58.3, 27.7, 26.3, 23.1, 13.8. IR: 3424, 3115, 2934, 1702, 1366, 1101 cm^{-1}. LRMS: 646.4 [M + H$^+$]. HRMS: cald for 646.1464 $C_{28}H_{32}N_5O_7S_3$; found: 646.1470 [M + H$^+$].

■ ASSOCIATED CONTENT

Supporting Information

Experimental procedures and ^{1}H and ^{13}C NMR spectra for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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■ REFERENCES

(1) Reviews: (a) Just-Baringo, X.; Albericio, F.; Alvarez, M. *Mar. Drugs* **2014**, *12*, 317. (b) Hughes, R. A.; Moody, C. J. *Angew. Chem, Int. Ed.* **2007**, *46*, 7930. (c) Bagley, M. C.; Dale, J. W.; Merritt, E. A.; Xiong, X. *Chem. Rev.* **2005**, *105*, 685.

(2) Sasaki, T.; Otani, T.; Matsumoto, H.; Unemi, N.; Hamada, M.; Takeuchi, T.; Hori, M. *J. Antibiot.* **1998**, *51*, 715.

(3) (a) Constantine, K. L.; Mueller, L.; Huang, S.; Abid, S.; Lam, K. S.; Li, W.; Leet, J. E. *J. Am. Chem. Soc.* **2002**, *124*, 14810. (b) Li, W.; Leet, J. E.; Ax, H. A.; Gustavson, D. R.; Brown, D. M.; Turner, L.; Brown, K.; Clark, J.; Yang, H.; Fung-Tomc, J.; Lam, K. S. *J. Antibiot.* **2003**, *56*, 226.

(4) (a) Jayasuriya, H.; Herath, K.; Ondeyka, J. G.; Zhang, C.; Zink, D. L.; Brower, M.; Gailliot, F. P.; Greene, J.; Birdsall, G.; Venugopal, J.; Ushio, M.; Burgess, B.; Russotti, G.; Walker, A.; Hesse, M.; Seeley, A.; Junker, B.; Connors, N.; Salazar, O.; Genilloud, O.; Masurekar, P.; Barrett, J. F.; Singh, S. B. *J. Antibiot.* **2007**, *60*, 554. (b) Singh, S. B.; Occi, J.; Jayasuriya, H.; Herath, K.; Motyl, M.; Dorso, K.; Gill, C.; Hickey, E.; Overbye, K. M.; Barrett, J. F.; Masurekar, P. *J. Antibiot.* **2007**, *60*, 565. (c) Zhang, C.; Zink, D. L.; Ushio, M.; Burgess, B.; Onishi, R.; Masurekar, P.; Barrett, J. F.; Singh, S. B. *Bioorg. Med. Chem.* **2008**, *16*, 8818. (d) Zhang, C.; Herath, K.; Jayasuriya, H.; Ondeyka, J. G.; Zink, D. L.; Occi, J.; Birdsall, G.; Venugopal, J.; Ushio, M.; Burgess, B.; Masurekar, P.; Barrett, J. F.; Singh, S. B. *J. Nat. Prod.* **2009**, *72*, 841.

(5) Prange, T.; Ducruix, A.; Pascard, C.; Lunel, J. *Nature* **1977**, *265*, 189.

(6) (a) Lu, J.-Y.; Riedrich, M.; Mikyna, M.; Arndt, H.-D. *Angew. Chem., Int. Ed.* **2009**, *48*, 8137. (b) Lu, J.-Y.; Riedrich, M.; Mikyna, M.; Arndt, H.-D. *Angew. Chem., Int. Ed.* **2009**, *48*, 9211 (erratum). (c) Kimber, M. C.; Moody, C. J. *Chem. Commun.* **2008**, 591. (d) Taddei, D.; Poriel, C.; Moody, C. J. *ARKIVOC* **2007**, 56. (e) Lu, J.-Y.; Arndt, H.-D. *J. Org. Chem.* **2007**, *72*, 4205. (f) Umemura, K.; Noda, H.; Yoshimura, J.; Konn, A.; Yonezawa, Y.; Shin, C.-G. *Bull. Chem. Soc. Jpn.* **1998**, *71*, 1391. (g) Umemura, K.; Noda, H.; Yoshimura, J.; Konn, A.; Yonezawa, Y.; Shin, C.-G. *Tetrahedron Lett.* **1997**, *38*, 3539.

(7) (a) Lefranc, D.; Ciufolini, M. A. *Angew. Chem., Int. Ed.* **2009**, *48*, 4198. (b) Ciufolini, M. A.; Lefranc, D. *Nat. Prod. Rep.* **2010**, *27*, 330. (c) Aulakh, V. S.; Ciufolini, M. A. *J. Am. Chem. Soc.* **2011**, *133*, 5900.

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

(9) Such "desoxy" heterocyclic clusters are found in the D-series of thiopeptides, which includes thiocillin I and micrococcin P as well as GE2270. See refs 1 and 7.

(10) (a) Shin, C.-G.; Okabe, A.; Ito, A.; Ito, A.; Yonezawa, Y. *Bull. Chem. Soc. Jpn.* **2002**, *75*, 1583. (b) Nicolaou, K. C.; Lee, S. H.; Estrada, A. A.; Zak, M. *Angew. Chem., Int. Ed.* **2005**, *44*, 3736. (c) Nicolaou, K. C.; Estrada, A. A.; Freestone, G. C.; Lee, S. H.; Alvarez-Mico, X. *Tetrahedron* **2007**, *63*, 6088. (d) Lin, C.-C.; Tantisantisom, W.; McAlpine, S. R. *Org. Lett.* **2013**, *15*, 3574.

(11) The second equivalent of **5** serves to deprotonate nascent **2**, which is a rather acidic active methylene compound and/or EtOH formed upon reaction of the EtO$^-$ liberated during the addition of **5** to **4** with nascent **2**. See ref 8 for details.

(12) All subsequent BOC-protected compounds derived from **2** also existed as pairs of slow-interconverting rotamers. Their NMR spectra were thus recorded both at 25 °C and at suitably higher temperatures (see Supporting Information).

(13) Tamao, K.; Nakagawa, Y.; Ito, Y. *Org. Syn.* **1996**, *73*, 94.

(14) Aulakh, V. S.; Ciufolini, M. A. *J. Org. Chem.* **2009**, *74*, 5750.

(15) See Supporting Information. Attempts to contain this phenomenon by simultaneous addition of **6** and TMSCl to a solution of **7**, in the hope of capturing alkoxide **8** before it might add to a second molecule of **6**, were uniformly unsuccessful.

(16) It should be noted that replacement of **7** with lithiated ethyl vinyl ether, Shimano, M.; Meyers, A. I. *Tetrahedron Lett.* **1994**, *35*, 7727 , in an effort to suppress formation of presumed chelate **9**, led to an ultimate 3-ethoxypyridine analog of **13**, which could not be deblocked; contact with acidic agents (HBr, BBr_3, TMSI) caused rapid degradation to an intractable mixture of products.

(17) Initial experiments aiming to produce the desired pyridine were carried out with crude **3**. However, it rapidly became clear that the use of purified material was essential in the pyridine-forming sequence.

(18) Miyashita, M.; Yoshikoshi, A.; Grieco, P. A. *J. Org. Chem.* **1977**, *42*, 3772.

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(19) Pyridine **14** was difficult to separate from a number of other byproducts obtained in the course of reactions run under alternative conditions. Consequently, it was not fully characterized. Its presence was obvious from ^{1}H NMR and MS spectra of crude reaction mixtures, and the extent of its formation was estimated (^{1}H NMR) to be about 5−10% of the total product. In some cases, **14** became the major product (reaction run in a mixture of CF_3CH_2OH and $(CF_3)_2CHOH$, but without PPTS, at 60 °C under O_2; ca. 10% **14** vs 5% **13**).

(20) Peng, Y.; Ji, C.; Chen, Y.; Huang, C.; Jiang, Y. *Synth. Commun.* **2004**, *34*, 4325.

(21) A comparison of known routes to hydroxypyridines of the type found in thiopeptides is provided in the Supporting Information.

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