 Resistance to clinical antibiotics has emerged as one of the major challenges confronting global health. As a result, this problem has become a top priority for international governing bodies. The Centers for Disease Control and Prevention estimates annually, in the United States, 2 million adults infected with drug-resistant bacteria and, of those infected, there is a 12% morbidity rate. These numbers will increase yearly. Antibiotic resistance mechanisms, many of which can be transferred between different bacteria, have greatly outpaced drug development, as a result of this disease being deprioritized by the pharmaceutical industry. Government efforts to incentivize the development of new antibiotics have been approached in large part by rejuvenating existing clinically employed antibiotics providing a lower barrier for entering the market. However, the development of new chemical entities represent a significantly better solution and is expected to have the largest impact on the current resistance dilemma.

An approach to develop a new class of antibiotics for use in humans has been inspired by the natural product nosiheptide. Nosiheptide, initially named multhiomycin, was first identified as a member of the thiazolyl peptide (thiopeptide) class of antibiotics and reported to possess potent antibiotic activity in 1970. The bactericidal activity occurs through the inhibition of ribosomal protein synthesis in a manner distinct from other clinical protein synthesis inhibitors. Nosiheptide has pronounced antibiotic effects against a large number of clinically relevant strains including those derived from patients. Potent activity is present against numerous methicillin-resistant Staphylococcus aureus (MRSA) and other multidrug resistant strains. Single digit, nanomolar activity is achieved against Clostridium difficile (C. difficile), a difficult bacterium to kill. Remarkably, no toxicity is seen when dosing animals at the extremely high level of 2.5 g/kg. As a result, the compounds have been used outside of the United States to increase feed conversion in livestock. With desirable activity and no apparent toxicity, chemistry is now needed to deliver derivatives that possess improved solubility but maintain the potent antibacterial effects. With the characterization of the potential pharmacophore of nosiheptide and related thiazolyl peptide natural products, total syntheses achieved for some of the most structurally complex members, and paths forward for development, now is the opportune time to advance this compound class through chemistry.

Toward the goal of developing new derivatives the structural requirements for antibiotic activity are required. Through significant effort by multiple research groups an understanding of the pharmacophore of thiazolyl peptides...
similar to nosiheptide has been developed. Key structural similarities across this class are highlighted in red. In addition to the compounds shown in Figure 1, the related natural products thiostrepton, nocathiacins, and siomycins also possess a similar core, a 26-membered macrocycle with multiple thiazoles. Recently identified or prepared members of this class include lactocillin9 from the human microbiome (absolute configuration yet to be reported) and QN3323A (YM-266183),10 a compound undergoing development.

Important structure-activity relationships have been achieved accessing unnatural thiocillins and thiostrepton derivatives through prepeptide gene replacement. These compounds were tested for structural modifications to the antibiotics and were achieved by exchanging amino acids within the natural products precursors and determining the new, designed compounds' activity.11 Remarkably the use of prepeptide gene replacement techniques has even yielded thiocillin derivatives with variations in the size of the macrocycle, however, as expected these compounds were devoid of antibiotic activity.12 Evolved cross-resistance to the parent natural products has provided information with respect to interactions with the ribosome.13 Semi-synthesis of active analogues, starting from QN3323A (YM-266183), have undoubtedly built upon these findings.8,10

The total syntheses of thiazolyl peptide antibiotics have been achieved with synthetic creativity and through these studies numerous transformations have been developed and adapted. To date, arguably, the most structurally challenging thiazolyl peptide natural product to be synthesized is thiostrepton by Nicolaou and co-workers.14 The total synthesis of nosiheptide has also been achieved15 after significant efforts were made in an attempt to prepare it through total synthesis.16 In addition, many notable accomplishments have been made through the total syntheses of other thiazolyl peptide natural products.17 While a great deal of chemistry has been learned from these syntheses the application of these findings to drug development is still devel-

Biographical Sketches

**Trevor Johnson** was born in Sacramento, California. He completed his undergraduate degree at the University of California, Santa Cruz in Biochemistry and Molecular Biology and completed research under the mentorship of Professor Needhi Bhalla (Molecular Biology). He joined the labs of Professor Dionicio Siegel in 2012, where his research focused on the total synthesis of complex natural products, bioactive small molecules, and reaction methodology and he received his Ph.D. in chemistry in 2016. He joined the Process Chemistry Department at Gilead Sciences in 2016 where he is currently working on the development of innovative therapeutics for patients worldwide.

**Mitchell P. Christy** was born in Houston, Texas and completed his undergraduate degree in chemistry (B.S. 2014) from the University of Texas at Austin where he undertook research in organometallic reaction methodology under Dr. Guangbin Dong. He then moved to California to complete his Ph.D. in organic chemistry at UC San Diego under the direction of Dr. Dionicio Siegel where he worked on the total synthesis of natural products and drug development in the areas of malaria and cancer in collaboration with the Winzeler and Ideker labs in the school of medicine. He completed his Ph.D. in 2019 and is currently a postdoc in the Gerwick lab at the Scripps Institute of Oceanography in La Jolla where he is pursuing the isolation and synthesis of novel marine natural products and medicinal chemistry development of protease inhibitors against SARS-CoV-2.

**Dionicio Siegel**, born in 1974 in Truchas New Mexico, studied chemistry starting at Reed College and earned his Ph.D. in chemistry with Andy Myers at Harvard University. Postdoctoral work with Samuel Danishefsky at the Memorial Sloan-Kettering Cancer Center was followed, from 2007 to 2014, with a faculty position at The University of Texas at Austin. In 2014 he transitioned to the University of California, San Diego in the Skaggs School of Pharmacy and Pharmaceutical Sciences where he is currently Chair of the Division of Pharmaceutical Chemistry. His research interests focus on synthetic organic chemistry applied to natural product-based drug discovery and medicinal chemistry.
oping. In our group, we have succeeded synthesizing micrococcin P1 implementing cysteine nitrile condensation reactions to form thiazoles. This provided guidance in the synthesis of the common core of the 26-membered thiopeptides that we believe to be a fundamentally important substrate to assess structure-activity relationships present in this class of natural products as they are related to anti-proliferative effects.

Our approach to synthesizing the fragments of thiazolyl peptides, chiral carboxyaminothiazoles, used a general strategy that has proven both reliable and scalable; cysteine-nitrile condensation reactions followed by aromatization. For comparison, the Hantzch thiazole synthesis has proven useful in the past for the syntheses of this class of natural products as the method is highly reliable, however, conducting these thiazole forming reactions on the multi-decagram scale proved difficult in our hands in maintaining...
yields achieved at smaller scales. As the cysteine-nitrile condensation links easily into the syntheses of all thiazoles except for one we also utilized the addition of thiazole-based Grignard reagents into chiral \( N \)-sulfinylimines, which has similarly proven reliable and scalable.\(^{21}\)

As an example, starting from threonine in a seven-step sequence that does not require chromatography we accessed 30 grams of amino alcohol \( 4 \) as its hydrochloride salt (Scheme 1). The cysteine/nitrile condensation onto nitrile \( 2 \) followed by aromatization with trichlorobromomethane and DBU was conducted on a 38 gram scale to generate pure thiazole \( 3 \). The reaction was both clean and the product readily separated from reactants and by-products. Notably, the purification is greatly simplified compared to the Hantzch thiazole synthesis that employs Lawesson's reagent and results in the generation of poorly behaved spent reagents. Simple acidic liberation of the amino alcohol provides \( 4 \) as the hydrochloride salt with the acid masked as the methyl ester.

Coupling of the amino alcohol \( 4 \) to a compound generated earlier in the route, carboxylic acid \( 1 \), proceeded uneventfully using EDC and HOBt to generate amide \( 5 \) (Scheme 2). Dehydrative elimination to form alkene \( 6 \) on large scale failed to provide good yields under multiple conditions used for the syntheses dehydroamino acids, however, in situ formation of the tert-butyl carbonate followed by reaction with DBU led to facile elimination and the reaction scaled well, conducted as shown on 28 grams of material.\(^ {22} \) Saponification of the ester of \( 6 \) generated carboxylic acid \( 7 \) that was combined with the previously synthesized amino alcohol \( 4 \) using EDC/HOBt coupling to yield amide \( 8 \). The resulting amide product \( 8 \) was then hydrolyzed at the thiazole methyl ester to yield carboxylic acid \( 9 \).

Scheme 1  Chromatography-free, multi-decagram synthesis of chiral carboxyaminothiazole \( 4 \)

Scheme 2  Five step conversion of amino alcohol \( 4 \) into acid \( 9 \)
Synthesis of the double thiazole-substituted pyridyl core was also greatly simplified using the cysteine/nitrile condensation-aromatization sequence (Scheme 3). Starting from inexpensive 2-chloro-3-pyridinecarbonitrile (10) seven steps arrived at the appropriately modified pyridine with the differentially protected esters, compound 14. Condensation of cysteine and 2-chloro-3-pyridinecarbonitrile (10) and oxidation of the thiazoline generated thiazole 11. Protection of the free acid as the tert-butyl ester and oxidation of the pyridine nitrogen to the N-oxide proceeded smoothly setting up a modified Reissert reaction with trimethylsilyl cyanide and diethylcarbamoyl chloride to provide nitrile 13 as a crystalline, off-white solid. The sequence was scalable with all intermediates crystallized from the reaction mixture or purified by trituration. A second cysteine/nitrile condensation followed by MnO2 oxidation (proved optimal for this system) generated the second appended thiazole ester.

The last required fragment possessed a thiazole with an alternative substitution pattern. Although a Hunsdiecker reaction could, in theory, generate this compound following a cysteine/nitrile condensation-aromatization the broad utility of the Ellman auxiliary led us to the route shown in Scheme 4 for the synthesis of the coupling fragment, stannane 18. Diastereoselective delivery of the Grignard derived from 2,4-dibromothiazole (Turbo Grignard exchange) provided a 4:1 ratio of diastereomers and a 66% isolated yield of the major diastereomer.

Coupling of the three fragments chloropyridine 14, stannane 18, and acid 9 followed by macrocyclization generated the core structure triol ester 21 (Scheme 5). Stille coupling of chloropyridine 14 and stannane 18 was optimal using Pd2(dba)3 with Cy-JohnPhos, cleanly generating the tri-thiazole bearing pyridine 19. Selective cleavage of the tert-butylsulfinyl group (and TBPS) with hydrochloric acid provided an amine that was directly coupled to carboxylic acid 9 using HATU to provide the cyclization precursor in protected form, compound 20. Deprotection of both Boc groups and acetonide was followed by cyclization, again using HATU, providing the desired triol compound 21 in 27% yield over two steps, conducted on the gram scale.

With access to ample quantities of core compound 21, which we envision to be the key pharmacophore for the 26-membered thiopeptide natural products functionalization can be achieved through modifications to the ester position and the primary alcohol. This follows from previous efforts to increase the water solubility of thiazolyl peptides, which succeeded in developing an antibiotic that reached Phase II clinical trials for the treatment of C. difficile, LFF571. The compound, developed by Norvartis, function through a

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**Scheme 3** Tri-substituted thiazole-pyridine 14 synthesis from commercial pyridine 10

**Scheme 4** Diastereoselective Grignard addition into chiral N-sulfinylimine 16 and stannylation of bromide 17 generating 18
different mechanism of ribosome inhibition and like most of the thiazolyl peptides was initially too insoluble for development.

All reactions were performed in flame-dried round-bottomed flasks fitted with rubber septa under a positive pressure of argon or N₂ unless otherwise indicated. Air and moisture sensitive liquids and solutions were transferred via syringe or cannula. Organic solutions were concentrated by rotary evaporation at 20 torr in a water bath heated to 40 °C, unless otherwise noted. Et₂O, CH₂Cl₂, THF, and toluene were washed with H₂O (500 mL) and brine (500 mL), dried (Na₂SO₄), and concentrated to provide a colorless oil. The crude material (175.4 g) was used directly in the next reaction without further purification.

(4S,5R)-3-(tert-Butyloxycarbonyl)-2,2,5-trimethyloxazolidine-4-carboxylic Acid (1)

Solid l-threonine (100 g, 839 mmol, 1 equiv) was dissolved in 1:7:1 THF/2 M NaOH and cooled in an ice bath. Boc anhydride was added as a solid portionwise (220g, 1.01 mol, 1.2 equiv) over 10 min and the reaction mixture was stirred for 1 h. The reaction vessel was removed from ice bath and stirred at 23 °C for 48 h. THF was removed under vacuum, the residue taken up in aq 2 M HCl (2 L), and the mixture was washed with H₂O (750 mL) and brine (750 mL), dried (Na₂SO₄) and concentrated to provide a colorless oil. The crude material (175.4 g) was used directly in the next reaction without further purification.

Crude Boc-l-threonine was dissolved in 2.2-dimethoxypropane (1.03 L) and PPTS (recrystallized from acetone) was added as a solid in one portion (60.3 g, 0.3 equiv) and the reaction mixture was heated to reflux for 14 h. The mixture was cooled to 23 °C and then concentrated and the residue was dissolved in EtOAc (2 L). The EtOAc solution was washed with H₂O (500 mL) and brine (500 mL), dried (Na₂SO₄), and
concentrated. Recrystallization of the residue from hexanes yielded 113.1 g of product and an additional 58 g collected from a 2nd recrystallization to provide 1 as a white solid (85% yield over 2 steps).

1H NMR (600 MHz, MeOD): δ (rotamers) = 4.21–4.13 (m, 1 H), 3.90–3.80 (m, 1 H), 1.58 (br s, 3 H), 1.54 (br s, 3 H), 1.45 (br d, 9 H), 1.37 (d, J = 6.1 Hz, 3 H).

tert-Butyl (4R,5R)-4-Cyano-2,2,5-trimethyloxazolidine-3-carboxylate (2)

Solid 1 (58 g, 224 mmol, 1 equiv) was dissolved in THF (447 mL, 0.5 M) and cooled in an ice bath. Ethyl chloroformate (25.8 mL, 269 mmol, 1.0 M) was added followed by dropwise addition of Et\textsubscript{3}N (37.5 mL, 269 mmol, 1.2 equiv) with vigorous stirring over 20 min to ensure stirring was not hindered. After the addition of ethyl chloroformate, the reaction mixture was warmed to 23 °C and stirred for 4 h when full consumption of starting material was observed by TLC (ninyhydrin stain). The mixture was cooled again in an ice bath and 25% aq NH\textsubscript{4}OH (48.8 mL, 1.4 equiv) was added in a single portion and the mixture was stirred with slow warming over 12 h. The solvent was removed under reduced pressure and the residue was dissolved in EtOAc (1 L). The combined extracts were washed with H\textsubscript{2}O (2 L, 500 mL) and brine (350 mL), dried (Na\textsubscript{2}SO\textsubscript{4}), and concentrated to give 47.8 g of thiazole as a white solid (85% yield over 2 steps); mp 41–43 °C.

IR (film): 2358, 1715 cm\textsuperscript{-1}.

HRMS (ESI): m/z calcd for C\textsubscript{16}H\textsubscript{24}N\textsubscript{2}O\textsubscript{5}SNa [M + Na]\textsuperscript{+}: 239.0461; found: 239.0463.

Methyl 2-[[53R,2S]-1-Amino-2-hydroxypropyl]thiazole-4-carboxylate Hydrochloride (4)

1,4-Dioxane (1 mL/g) was added to thiazole 3 (30 g, 84 mmol, 1 equiv) to solubilize the material. A 4 M solution of HCl in 1,4-dioxane was added (105 mL, 5 equiv) followed by dropwise addition of distilled H\textsubscript{2}O (11 mL, 10% v/v). The reaction mixture was stirred at 23 °C for 2 h. An oil or solid might appear to precipitate from the reaction, which was the desired HCl salt. The mixture was concentrated from 4:1 benzene/MeOH (3 × 100 mL). The solid crude material was of sufficient purity to be used directly in the next reaction without further purification (99%).

1H NMR (600 MHz, MeOD): δ = 8.54 (s, 1 H), 4.88 (s, 1 H), 4.76 (d, J = 6.6 Hz, 1 H), 4.32–4.26 (m, 1 H), 3.92 (s, 3 H), 1.23 (d, J = 6.4 Hz, 3 H).

13C NMR (150 MHz, MeOD): δ = 165.2, 162.9, 147.3, 131.7, 68.5, 58.8, 53.0, 19.9.

HRMS (ESI): m/z calcd for C\textsubscript{8}H\textsubscript{12}N\textsubscript{2}O\textsubscript{5}Na\textsuperscript{+} [M + Na]\textsuperscript{+}: 379.1295; found: 379.1295.

tert-Butyl (4S,5R)-4-[4-([Methoxy]carbonyl)thiazol-2-yl]propyl]carbamoyl)-2,2,5-trimethyloxazolidine-3-carboxylate (5)

Nitrile 2 (37.7 g, 157 mmol, 1.0 equiv) was dissolved in a 1:5 mixture of i-ProOH/pH 7 phosphate buffer (785 mL, 0.2 M buffer, 0.1 M concentration) and solid cysteine methyl ester hydrochloride was added in a single portion (40.4 g, 236 mmol, 1.5 equiv). The reaction mixture was stirred and heated to 50 °C for 14 h. The solvent was removed under reduced pressure and the residue was partitioned between H\textsubscript{2}O (1 L) and EtOAc (500 mL) and the aqueous layer was extracted with EtOAc (3 × 250 mL). The combined organic layers were dried (Na\textsubscript{2}SO\textsubscript{4}) and concentrated to give the thiazoline (50.9 g) as a colorless oil that solidifies upon standing. This crude material was used directly in the next reaction without further purification.

Crude thiazoline was dissolved in DCM (475 mL, 0.3 M) and cooled in an ice bath. Br\textsubscript{CCl\textsubscript{3}} was added (21 mL, 188 mmol, 1.2 equiv) followed by DBU (25.4 mL, 188 mmol, 1.2 equiv) dropwise over several min. The reaction was allowed to warm to 23 °C as the ice bath melts. After completion, the mixture was poured intoaq 1 M HCl (500 mL) and extracted with additional DCM (3 × 200 mL). The combined organic layers were washed with H\textsubscript{2}O (250 mL) and brine (250 mL), dried (Na\textsubscript{2}SO\textsubscript{4}), and concentrated to give 47.8 g of thiazole 3 as an off-white solid (134 mmol, 85% over 2 steps); mp 120–123 °C. The crude material was of sufficient purity to be used directly in the next reaction without further purification.

1H NMR (600 MHz, CDCl\textsubscript{3}): δ = 8.17 (br s, 1 H), 4.78 (m, 1 H), 4.16 (m, 1 H), 3.94 (s, 3 H), 1.69 (br s, 6 H), 1.42 (br s, 9 H), 1.18 (br s, 3 H).

13C NMR (150 MHz, CDCl\textsubscript{3}): δ = 173.3, 161.3, 151.0, 146.1, 127.3, 95.0, 80.4, 77.6, 65.7, 52.1, 27.8, 26.2, 25.6, 17.6.

HRMS (ESI): m/z calcd for C\textsubscript{16}H\textsubscript{24}N\textsubscript{2}O\textsubscript{5}SNa\textsuperscript{+} [M + Na]\textsuperscript{+}: 379.1298; found: 379.1295.

The reaction was allowed to warm to 23 °C as the ice bath melts. After completion, the mixture was poured intoaq 1 M HCl (500 mL) and extracted with additional DCM (3 × 200 mL). The combined organic layers were washed with H\textsubscript{2}O (250 mL) and brine (250 mL), dried (Na\textsubscript{2}SO\textsubscript{4}), and concentrated to give 47.8 g of thiazole 3 as an off-white solid (134 mmol, 85% over 2 steps); mp 120–123 °C. The crude material was of sufficient purity to be used directly in the next reaction without further purification.

1H NMR (600 MHz, CDCl\textsubscript{3}): δ = 8.17 (br s, 1 H), 4.78 (m, 1 H), 4.16 (m, 1 H), 3.94 (s, 3 H), 1.69 (br s, 6 H), 1.42 (br s, 9 H), 1.18 (br s, 3 H).

13C NMR (150 MHz, CDCl\textsubscript{3}): δ = 173.3, 161.3, 151.0, 146.1, 127.3, 95.0, 80.4, 77.6, 65.7, 52.1, 27.8, 26.2, 25.6, 17.6.

HRMS (ESI): m/z calcd for C\textsubscript{16}H\textsubscript{24}N\textsubscript{2}O\textsubscript{5}SNa\textsuperscript{+} [M + Na]\textsuperscript{+}: 379.1298; found: 379.1295.
tert-Butyl (45,SR)-4-((Z)-1-[4-(Methoxy carbonyl)thiazol-2-yl)prop-1-en-1-yl]carbamoyl)-2,2,5-trimethyloxazolidine-3-carboxylate (6)

Solid 5 (28.1 g, 61.4 mmol, 1 equiv.) was dissolved in MeCN (205 mL, 0.3 M). Boc anhydride (16.1 g, 73.7 mmol, 1.2 equiv.) was added in a single portion followed by DMAP (1.5 g, 12.3 mmol, 0.2 equiv.) and the reaction mixture was stirred until all starting materials were consumed. After full conversion of starting materials by TLC, DBU (45.8 mL, 307.0 mmol, 5 equiv.) was added and the reaction mixture was stirred for 1 h. The mixture was diluted with EtOAc (500 mL) and washed with aq 1 M HCl (200 mL), H2O (200 mL) and brine (200 mL), dried (Na2SO4), and concentrated. The crude material was purified by column chromatography with 15–35% EtOAc/hexane on a medium length column to give 18.38 g of intermediate 6 as a colorless oil (41.8 mmol, 68%).

Methyl ester 6 (10.0 g, 22.8 mmol, 1 equiv.) was dissolved in MeCN (205 mL, 0.2 M) and solid amine hydrochloride 7 (28.1 g, 61.4 mmol, 1 equiv.) was dissolved in MeCN (205 mL, 0.2 M) and aq 2 M HCl (40 mL) and extracted with EtOAc (3 × 25 mL). The combined organic layers were washed with aq 3 M LiCl (3 × 100 mL), dried (Na2SO4), and concentrated. The crude material was purified by column chromatography with 3:1 THF and MeOH (11.4 mL, 0.2 M) and aq 10% NaOH was added (4.27–422 mL, 1 M). 4.05 (d, J = 8.0 Hz, 1H), 1.91 (d, J = 7.2 Hz, 3H), 1.59–1.39 (m, 18 H), 1.28 (d, J = 6.4 Hz, 3H).

1H NMR (600 MHz, MeOD): δ = 8.40 (dd, J = 4.9, 1.8 Hz, 1H), 8.10 (dd, J = 7.7, 1.8 Hz, 1H), 7.49 (dd, J = 7.7, 4.9 Hz, 1H), 5.36 (t, J = 9.2 Hz, 1H), 3.87–3.80 (m, 2H).

Crude thiazoline (76.9 g, 317 mmol, 1 equiv.) and BrCCl3 (46.9 mL, 476 mmol, 1.5 equiv.) were dissolved in DMF (317 mL, 1 M) in a flask and the flask was immersed in an ice bath. DBU (99 mL, 666 mmol, 2.1 equiv.) was added dropwise via an addition funnel over 20 min. On large scale this addition was significantly exothermic. After addition, the reaction mixture was mixed until 50 °C and stirred for 3 h. After completion, the mixture was slowly introduced dropwise into a vigorously stirring aq 1 M HCl (2 L) at 0 °C to ensure a uniform precipitate. The mixture was stirred for 10 min and the fine brown precipitate was filtered and dried under vacuum at 50 °C and stirred for 1 h. After full conversion of starting materials by TLC, DBU (46.9 mL, 0.25 M) was added dropwise over 30 min via an addition funnel to the reaction mixture. 1H NMR (600 MHz, MeOD): δ = 8.76 (dd, J = 7.9, 1.8 Hz, 1H), 8.58 (s, 1H), 8.50 (dd, J = 4.7, 1.9 Hz, 1H), 7.58 (dd, J = 7.9, 4.7 Hz, 1H).

Crude thiazoline (76.9 g, 317 mmol, 1 equiv.) and BrCCl3 (46.9 mL, 476 mmol, 1.5 equiv.) was dissolved in DMF (317 mL, 1 M) in a flask and the flask was immersed in an ice bath. DBU (99 mL, 666 mmol, 2.1 equiv.) was added dropwise via an addition funnel over 20 min. On large scale this addition was significantly exothermic. After addition, the reaction mixture was mixed until 50 °C and stirred for 3 h. After completion, the mixture was slowly introduced dropwise into a vigorously stirring aq 1 M HCl (2 L) at 0 °C to ensure a uniform precipitate. The mixture was stirred for 10 min and the fine brown precipitate was filtered and dried under vacuum at 50 °C and stirred for 1 h. After full conversion of starting materials by TLC, DBU (46.9 mL, 0.25 M) was added dropwise over 30 min via an addition funnel to the reaction mixture. 1H NMR (600 MHz, MeOD): δ = 8.30 (s, 1H), 8.18 (s, 1H), 6.88–6.54 (m, 1H), 5.35 (br s, 1H), 4.55 (br s, 1H), 4.27–4.22 (m, 1H), 4.05 (d, J = 8.0 Hz, 1H), 1.91 (d, J = 7.2 Hz, 3H), 1.59–1.39 (m, 18 H), 1.28 (d, J = 6.4 Hz, 3H).

2-[(2-Chloropropin-3-yl)thiazol-4-yl]carboxylic Acid (11)

2-Chlorocinnolinonitrile (10) (50 g, 361 mmol, 1 equiv.) was dissolved in 1.5:1 i-ProOH/pH 7 phosphate buffer (722 mL, 0.5 M) and solid l-cysteine hydrochloride (65.6 g, 542 mmol, 1.5 equiv.) was added in one portion. The reaction mixture was heated to 50 °C and stirred for 16 h. The reaction was then terminated by removing i-ProOH under reduced pressure and diluting with EtOAc (500 mL) and aq 2 M HCl until the solution was acidic (pH > 2). The mixture was extracted with EtOAc (3 × 400 mL), the combined extracts were dried (Na2SO4), and concentrated to give the intermediate thiazoline as a yellow solid (76.9 g, 317 mmol, 88%); mp 156–158 °C. The crude material was of sufficient purity to be used directly in the next reaction without further purification.

1H NMR (600 MHz, MeOD): δ = 8.40 (dd, J = 4.9, 1.8 Hz, 1H), 8.10 (dd, J = 7.7, 1.8 Hz, 1H), 7.49 (dd, J = 7.7, 4.9 Hz, 1H), 5.36 (t, J = 9.2 Hz, 1H), 3.87–3.80 (m, 2H).
in an ice bath. The mixture was then warmed to 23 °C and stirred to completion over 12 h. After completion, the reaction was diluted with additional DCM (175 mL) and aq 10% K2CO3 (175 mL). The organic layer was washed with H2O (2 × 100 mL), sat. aq Na2SO4 (2 × 100 mL) and brine (100 mL), dried (Na2SO4), and concentrated to give 10.1 g of crude N-oxide as a yellow solid (32.1 mmol; 92%; 86% over 2 steps); mp 134–136 °C. The crude material was of sufficient purity to be used directly in the next reaction without further purification.

1H NMR (599 MHz, MeOD): δ = 8.61 (dd, J = 6.5, 1.4 Hz, 1 H), 8.56 (s, 1 H), 8.36 (dd, J = 8.2, 1.4 Hz, 1 H), 7.70 (dd, J = 8.2, 6.5 Hz, 1 H), 1.63 (s, 9 H).

13C NMR (150 MHz, CDCl3): δ = 160.0, 159.9, 148.8, 140.4, 131.6, 128.8, 126.8, 122.9, 82.8, 28.2.


-Butyl 2-{2-Chloro-6-[4-(methoxycarbonyl)thiazol-2-yl]ethyl}-2-methylpropane-2-sulfinamide (18)

Solid 2,4-dibromothiazole (22.8 g, 119 mmol, 1.5 equiv) was dissolved in THF (50 mL, 72 mL/g) and cooled in an ice bath. A 1.3 M solution of i-PrMgClLiC in THF (98 mL, 127 mmol, 1.6 equiv) was added dropwise over 10 min. The reaction mixture was warmed to 23 °C over 30 min. The resulting solution was added dropwise over 2 h to a separate reaction vessel cooled to approximately –50 °C containing a solution of chiral imine (22 g, 79 mmol, 1.0 equiv) in DCM (793 mL, 0.1 M). The mixture was allowed to warm to 23 °C over 12 h, then poured into brine (2 L), and the aqueous layer was extracted with DCM (3 × 500 mL). The combined organic layers were dried (Na2SO4) and concentrated to give 23.1 g of the chiral aminothiazole as a pale-yellow foam.

1H NMR (600 MHz, CDCl3): δ = 7.16 (s, 1 H), 4.83–4.77 (m, 1 H), 4.66 (d, J = 6.0 Hz, 1 H), 4.16 (dd, J = 9.8, 3.6 Hz, 1 H), 4.08 (dd, J = 9.9, 3.5 Hz, 1 H), 1.30 (s, 3 H), 0.81 (s, 3 H), 0.03 (s, 3 H), –0.08 (s, 3 H).

13C NMR (150 MHz, CDCl3): δ = 173.7, 125.0, 117.3, 66.0, 59.0, 56.3, 25.6, 22.5, 18.0, –5.5.


(R)-N-(S)-(1-4-Bromothiazol-2-yl)-2-[(tert-butyldimethylsilyloxy)ethyl]-2-methylpropane-2-sulfonamide (17)

Solid 2,4-dibromothiazole (28.9 g, 119 mmol, 1.5 equiv) was dissolved in THF (50 mL, 72 mL/g) and cooled in an ice bath. A 1.3 M solution of i-PrMgClLiC in THF (98 mL, 127 mmol, 1.6 equiv) was added dropwise over 10 min. The reaction mixture was warmed to 23 °C over 30 min. The resulting solution was added dropwise over 2 h to a separate reaction vessel cooled to approximately –50 °C containing a solution of chiral imine (22 g, 79 mmol, 1.0 equiv) in DCM (793 mL, 0.1 M). The mixture was allowed to warm to 23 °C over 12 h, then poured into brine (2 L), and the aqueous layer was extracted with DCM (3 × 500 mL). The combined organic layers were dried (Na2SO4) and concentrated to give an amber oil. The crude material was purified by flash chromatography with 10 → 30% EtOAc/hexane on a medium length column to give 23.1 g of the chiral aminothiazole as an amber oil (52.3 mmol, 66%).

1H NMR (600 MHz, CDCl3): δ = 7.16 (s, 1 H), 4.83–4.77 (m, 1 H), 4.66 (d, J = 6.0 Hz, 1 H), 4.16 (dd, J = 9.8, 3.6 Hz, 1 H), 4.08 (dd, J = 9.9, 3.5 Hz, 1 H), 1.30 (s, 3 H), 0.81 (s, 3 H), 0.03 (s, 3 H), –0.08 (s, 3 H).

13C NMR (150 MHz, CDCl3): δ = 173.7, 125.0, 117.3, 66.0, 59.0, 56.3, 25.6, 22.5, 18.0, –5.5.


(R)-N-(S)-{2-[(tert-Butyldimethylsilyloxy)oxy]ethyl}-1-{[trimethylstannyl]thiazol-2-yl}{[ether]yl}-2-methylpropane-2-sulfonamide (18)

Bromide (27.2 g, 5.0 mmol, 1 equiv) was added to a flame-dried, N2-filled flask and dissolved in toluene (25 mL, 0.2 M). Solid Pd(PPh3)4 (576 mg, 0.5 mmol, 0.1 equiv) and neat Me3SnNa (2.19 mL, 10 mmol, 2 equiv) were added and the reaction mixture was heated to 100 °C for 1 h. The mixture was then cooled to 23 °C and partially concentrated. The remaining residue was loaded directly onto a column and purified by flash chromatography with 10 → 20% EtOAc/hexane to give 1.56 g of pure stannane as a slightly yellow oil (2.97 mmol, 66%).

1H NMR (600 MHz, CDCl3): δ = 7.30–7.27 (m, 1 H), 4.89 (dd, J = 10.0, 4.2 Hz, 1 H), 4.70 (d, J = 6.1 Hz, 1 H), 4.15 (dd, J = 9.7, 4.4 Hz, 1 H), 4.07 (dd, J = 9.7, 3.9 Hz, 1 H), 1.29 (s, 9 H), 0.80 (s, 9 H), 0.39–0.28 (m, 9 H), 0.01 (s, 3 H), –0.11 (s, 3 H).

1H NMR (600 MHz, CDCl3): δ = 8.41 (d, J = 8.2 Hz, 1 H), 8.38 (d, J = 8.2 Hz, 1 H), 8.32 (s, 1 H), 8.07 (s, 1 H), 7.92 (s, 1 H), 4.73 (q, J = 5.0 Hz, 1 H), 4.59 (dJ = 5.6 Hz, 1 H), 4.01 (s, 3 H), 3.97–3.89 (m, 2 H), 1.62 (s, 9 H), 1.30 (s, 9 H), 0.86 (s, 9 H), 0.06 (s, 3 H), –0.02 (s, 3 H).

13C NMR (150 MHz, CDCl3): δ = 171.6, 168.9, 164.8, 161.7, 160.1, 153.0, 150.8, 150.4, 148.3, 148.0, 140.2, 130.3, 129.4, 128.2, 121.5, 119.0, 82.1, 66.0, 52.5, 52.4, 28.1, 27.5, 22.5, 18.0.


tert-Butyl (4S,5R)-4-[[2-(12-ethylidene-8,15-diaza-1(2,4),3,7,11(4,2)-tetrathiazole-2(3,2)-pyridine)-1-(4-[[1S,2R,3S,4S]-3-[4-[(tert-Butyloxycarbonyl)thiazol-2-yl]-2-hydroxypropyl]carbamoyl}thiazol-2-yl)]prop-1-en-1-yl]pyridin-2-yl]-2-hydroxyethyl(carbamoyl)thiazol-2-yl)-2-hydroxypropyl(carbamoyl)thiazol-2-yl)prop-1-en-1-yl]carbamoyl-2,2,5-trimethyloxazolidine-3-carboxylate (20)

HRMS (ESI): m/z calcd for C55H64N10O15S5Na [M + Na]+: 945.1006; found: 945.1011.

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