Combined Enzyme- and Transition Metal-Catalyzed Strategy for the Enantioselective Syntheses of Nitrogen Heterocycles: (−)-Coniine, DAB-1, and Nectrisine

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ABSTRACT: The enantioselective syntheses of (−)-coniine, DAB-1, and nectrisine have been developed, utilizing a complementary strategy of enzyme- and transition metal-catalyzed reactions. The initial stereocenter was set with >99% enantioselectivity via an enzyme-catalyzed hydrocyanation reaction. Substrate incompatibilities with the natural enzyme were overcome by tactical utilization of ruthenium-catalyzed olefin metathesis to functionalize an enzyme-derived (R)-allylic fragment. The piperidine and pyrrolidine alkaloid natural products were obtained by a route that leveraged regio- and stereoselective palladium-catalyzed 1,3-substitutive reactions.

INTRODUCTION

Functionalized piperidine and pyrrolidine alkaloids are a broad and diverse class of molecules that typically exhibit high levels of biological activity. Nitrogen heterocycles are ubiquitous among natural products and are found in countless pharmaceutical compounds. Importantly, the biological activity of these molecules is often tied to a specific enantiomer. Therefore, deeper understanding of the importance of piperidine and pyrrolidine alkaloids is reliant on the development of new strategies for their enantioselective synthesis. Enzymatic reactions are a prime source of enantioenriched material, and their use has been critical to the development of enantioselective reactions. One significant drawback of enzymes, however, is their often-limited substrate compatibility toward small organic molecules. Our group has focused on augmenting the high enantioselectivities of enzyme-catalyzed reactions with transition metal-catalyzed processes that are able to stereospecifically alter the position and substitution of enzymatically derived stereochemistry.

We targeted (−)-coniine (1), DAB-1 (2), and nectrisine (3) as platforms to demonstrate the general applicability of our synthetic strategy toward the larger classes of saturated nitrogen heterocycles (Figure 1). Coniine has a storied past in toxicology circles as the active poison of spotted hemlock and is known most notably for its role in the death of Socrates. Furthermore, the de novo chemical synthesis of coniine remains a touchstone for the synthesis of substituted piperidines. DAB-1 (2) and nectrisine (3) are polyhydroxylated pyrrolidine iminosugars isolated from terrestrial sources. DAB-1 is a potent inhibitor (IC$_{50}$ = 9.3 μM) against a specific glycosidase, rabbit muscle glycogen phosphorylase, while being mostly ineffective toward glycogen synthesis enzymes. Structurally related nectrisine (3) is also a strong inhibitor of α-glucosidases. Selective inhibitors of this type are implicated in the treatment of diabetes as well as other sugar-related diseases. As a result, DAB-1 and nectrisine have been the targets of many synthetic efforts and remain useful targets to demonstrate stereoselective reaction methods in complex settings. A majority of these approaches utilized the chiral pool to establish many of the stereocenters; however, a small subset of more recent syntheses has used other enantioselective methods to install the requisite stereo-
chemistry.\(^{32-35}\) As for our own approach, we envisioned the rapid, highly stereocontrolled syntheses of these molecules that would diverge from a single enantiopure precursor. More precisely, we would blend the utility of a highly enantioselective enzymatic reaction with the specificity of modern transition metal-catalyzed reactions to achieve this goal.

Our unified synthetic plan for (−)-coniine and DAB-1 incorporates three catalytic methodologies for the construction of the heterocyclic rings and stereocenters (Scheme 1).

### Scheme 1. Retrosynthetic Analysis of (−)-Coniine and DAB-1

![Scheme 1](image)

The six-membered ring of 1 would be synthesized by ruthenium-catalyzed ring-closing metathesis of diene precursor 4, while five-membered rings would be accessed by cyclization of a γ-amino ester such as 5 after appropriate functionalization of the alkene. We were encouraged by the validation of some of these late-stage approaches in synthetic efforts toward related nitrogen heterocycles.\(^{36-39}\) The allylic amine stereocenters of 4 and 5 could be constructed by a palladium-catalyzed nucleophilic substitution reaction with concomitant 1,3-transposition from carbonate esters 6. In this reaction, a palladium π-allyl complex generated from 6 would be trapped by a nitrogen nucleophile at the distal position, providing the conjugated enolate 4 or 5, depending on the choice of nucleophile. This reaction would serve as a point of strategic divergence that would allow synthesis of piperidines and nucleophiles that react directly with the chiral π-allyl intermediate that led to competitive formation of the (S)-cis product than the more compact nitrile. Accordingly, α-hydroxyster 9a was converted to carbonate 6a with ethyl chloroformate without event.\(^{8,9}\)

Our next challenge was to develop optimal conditions for maximum stereocontrol in the crucial palladium-catalyzed 1,3-chirality transfer step. Although many methods exist for the 1,3-chirality transfer of allylic alcohol derivatives,\(^{40-43}\) we believed that the palladium-catalyzed method provides the greatest flexibility in terms of scope of nucleophile choice and general mildness of the reaction conditions.\(^{52}\) Of special concern to us were the competing inner- and outer-sphere nucleophilic addition processes to the cationic palladium π-allyl intermediate generated by exposure of carbonate 6a to palladium(0) catalysts (Figure 2). Specifically, amine nucleophiles that react directly with the chiral π-allyl complex 10a generate C–N bond formation products ((R)-11) with a net retention of stereochemistry (pathway A). On the other hand, Lewis basic amines that are inclined to coordinate to the metal (e.g., 10b) undergo an inner-sphere reductive elimination to give (S)-11 (pathway B). Products of pathway B would be delivered with a net inversion of configuration. We understood

### RESULTS AND DISCUSSION

The syntheses began with the installation of the first chiral center by an enzyme-catalyzed hydrocyanation reaction (Scheme 2).\(^{44-48}\) The enzyme oxynitrilase [EC 4.1.2.10],\(^{49}\)

![Scheme 2. Synthesis of Building Blocks Utilizing the Oxynitrilase Enzyme](image)

found in raw bitter almonds, has been shown to provide cyanohydrins of α,β-unsaturated aldehydes in good yields with remarkable enantiopurity.\(^{50}\) trans-2-Hexenal (8a) and crotonaldehyde (8b) are both excellent substrates for this process. Exposure of these aldehydes to oxynitrilase in the presence of excess HCN furnished cyanohydrins 7 in good yields and >99% enantiomeric excess.\(^{8}\) This reaction is particularly serviceable because of the low cost and ready availability of the enzyme from store-bought raw almonds, which, after grinding and removal of fats by extraction, are ready to use in the natural enzymatic matrix. The conversion of cyanohydrins 7 into their analogous α-hydroxyster 9 was conducted under anhydrous Pinner conditions using TMSCl in ethanol. It is important to stress that the anhydrous Pinner conditions are compulsory if the erosion of enantiomeric purity that occurs under aqueous conditions is to be avoided. This functional group interconversion was necessitated by our earlier studies that found α,β-unsaturated cyanohydrin carbonates were poor substrates for stereo-controlled, palladium-catalyzed allylic substitution reactions. The corresponding ethyl ester carbonate (6), however, demonstrated excellent stereocontrol.\(^{8,51}\)

The more sterically demanding ethyl ester was better suited to attenuate π-σ-π isomerization of the π-allyl intermediate that found α,β-unsaturated cyanohydrin carbonates were poor substrates for stereo-controlled, palladium-catalyzed allylic substitution reactions. The corresponding ethyl ester carbonates (6), however, demonstrated excellent stereocontrol.\(^{8,51}\)

The allylic amine stereocenters of 4 and 5 could be constructed by a palladium-catalyzed nucleophilic substitution reaction with concomitant 1,3-transposition from carbonate esters 6. In this reaction, a palladium π-allyl complex generated from 6 would be trapped by a nitrogen nucleophile at the distal position, providing the conjugated enolate 4 or 5, depending on the choice of nucleophile. This reaction would serve as a point of strategic divergence that would allow synthesis of piperidines and pyrrolidines from similar carbonate precursors. The stereo-divergence that would allow synthesis of piperidines and nucleophiles that react directly with the chiral π-allyl intermediate that led to competitive formation of the (S)-cis product than the more compact nitrile. Accordingly, α-hydroxyster 9a was converted to carbonate 6a with ethyl chloroformate without event.\(^{8,9}\)
that this stereospecificity could be governed by hard-—soft acid base theory, with softer nucleophiles reacting more preferentially with the π-allyl ligand directly (pathway A) and harder nucleophiles operating through an inner-sphere process (pathway B). It was not clear to us at the outset whether amines would have the requisite hardness or softness to be selective for one pathway over the other, and it was thought that judicious choice of nitrogen-protecting groups could be used to modulate the stereospecificity.

Our initial attempts at palladium-catalyzed C–N bond formation began with the reaction between 3-butenylamine and allylic carbonate 6a (Table 1, entry 1). Although the yield of the resulting allylic amine (12a) was acceptable, all efforts to improve the stereospecificity of the reaction were unsuccessful. We, therefore, turned our attention to more highly resonance-stabilized versions of the 3-butenylamine moiety in order to soften the nucleophile and promote preferential outer-sphere substitution. Although carbamates are significantly more acidified relative to primary amines, the reduced nucleophilicity of the bulky tert-butyl carbamate-protected 3-butenylamine provided only trace amounts of C–N bond formation (entry 2). We then further increased the acidity of the butenyl nitrogen, and therefore its base-mediated nucleophilicity, by converting it to the corresponding 2,4-dinitrobenzenesulfonamide (DNs) using 2,4-dinitrobenzenesulfonyl chloride. Upon exposure to the palladium catalyst in dichloromethane at room temperature, allylic carbonate 6a and the DNs-derived nucleophile quickly reacted to form 12c in 80% yield and 80% ee (entry 3). Although these numbers reflect similar results to those obtained under analogous conditions in the 3-butenylamine experiment, we found that the rate of reaction with the DNs-sulfonamide to be superior. We also looked into alternative ligands for the palladium catalyst, but the results were disappointing and detrimental to the yields (entries 4 and 5). Ultimately, we found that reducing the reaction temperature to −10 °C and employing the reactive sulfonamide nucleophile enabled us to obtain excellent enantiospecificity of 96% with only a modest reduction in overall yield (entry 6). Any further decrease in temperature resulted in poor yields (entry 7). We anticipate that secondary sulfonamides of this type will have broad utility in palladium-catalyzed allylic substitution reactions where high levels of stereospecificity are desired. The appeal of this reaction is further enhanced by the ease of both the synthesis and removal of the DNs group under mildly nucleophilic conditions.

With optimized conditions for the palladium-catalyzed 1,3-chirality transfer in hand, we moved forward with the completion of the synthesis (Scheme 3). Ring-closing metathesis with the second-generation Hoveyda–Grubbs catalyst excised the α,β-unsaturated ester as expected to provide DNs-protected saturated piperidine 13. In a single pot, 13 was rapidly deprotected with excess allyl amine followed by reprotection with Boc2O to afford the corresponding tert-butyl carbamate (14) in 75% yield. This functional group interconversion was initiated to avoid difficulties inherent with the purification and handling of volatile-free amines. Palladium-catalyzed hydrogenation of the remaining alkene readily yielded Boc-protected coniine 15. Because this intermediate has itself been transformed into (−)-coniine (1) via acid-mediated removal of the tert-butyl carbamate, this inclusive synthetic effort, leading to (−)-15, represents a formal total synthesis of (−)-coniine (1). The measured optical rotation of 15 ([α]D 20 = −31.6 (c 0.86, CHCl3)); lit. [α]D 20 = −31.6 (c 0.86, CHCl3) is in convincing agreement with the reported value, suggesting a high level of enantiopurity initially derived from the enzyme-catalyzed hydroxylation reaction.

Our approach to polyhydroxylated iminosugar DAB-1 (2) required additional considerations to account for the introduction of the stereodefined dihydroxyl groups and exocyclic hydroxymethylene functionality. The first challenge could be satisfied with stereoselective dihydroxylation, but the second one required more thought. It was decided that a protected version of the hydroxymethylene group should be incorporated directly into the unsaturated aldehyde starting material with oxygen substitution in the 4-position. Unfortu-
nately, early experiments revealed that oxynitrilase was not able to hydrocyanate aldehydes with tolerable enantioselectivities when adorned with the requisite oxygen substitution. In order to overcome this complication, we envisioned that a ruthenium-catalyzed cross-metathesis between a protected allyl alcohol and an enzyme-derived (R)-β,γ-unsaturated-(α)-hydroxyester should furnish our ideal starting material (Scheme 4). Consequently, we were delighted to find that the cross-metathesis reaction amongst hydroxyester 9b and allyl benzyl ether supplied the needed alkene acetate, allyl alcohol, or and pleasing trans/cis selectivity. Other partners, such as allyl alcohol and an enzyme-derived (R)-β,γ-unsaturated-(α)-hydroxyester should furnish our ideal starting material (Scheme 4). Consequently, we were delighted to find that

**Scheme 4. Catalytic Reactions to Generate the Key Nitrogen Stereocenter**

\[
\begin{align*}
\text{CO}_2\text{Et} & \quad \text{OH} \\
\text{BnO} & \quad \text{BnO} \\
\text{HGI} & \quad \text{BnO} \\
\text{9b} & \quad \text{9c} \\
(69\%, 95.5\text{ trans:cis}) & \quad (97\%, 95\text{ trans:cis}) \\
\end{align*}
\]

Although the optimized metathesis reaction leading to (R)-9c generated a trans/cis ratio of 95:5, this inseparable material could not be carried forward to the palladium transposition step. Any cis isomer present would undergo π−σ−π equilibration of the palladium π-allyl intermediate, ultimately eroding enantiopurity with the formation of the undesired enantiomer. Fortunately, the undesired cis isomer was separable by careful chromatographic purification after conversion to the carbonate (6b). Palladium-catalyzed allylic azidation of carbonate 6b was achieved following our previously reported conditions. Stereospecificity in this allylic transposition was high, providing azide 16 in good yield and enantiopurity. This sequence provided the key amine stereocenter in short order from the enzymatically derived chiral fragment.

The next stage of the synthesis focused on the introduction of the two remaining alcohol stereocenters (Scheme 5). Conversion of azide 16 to carbamate 17 prior to dihydroxylation was necessary to exert a greater influence on the stereoselectivity of the crucial dihydroxylation step. Under the standard Upjohn conditions, however, the diastereoselectivity ratio was a disappointing 1.3:1, marginally favoring the unwanted diol 19. Fortunately, dihydroxylation with AD-mix β delivered the desired diastereomer (18) in good yield and excellent diastereoselectivity (>20:1 dr).

With all heteroatoms and stereocenters correctly positioned, completion of the DAB-1 synthesis rested on three remaining steps: lactam formation, amide reduction, and benzyl deprotection (Scheme 6). One-pot cyclization of aminoester 18 to lactam diol 20 was efficaciously accomplished in 87% yield via facile removal of the Boc group followed by a cyanide-catalyzed lactamization. Reduction of the resultant lactam (20) was achieved under classic borane-mediated conditions. Finally, deprotection of the benzyl-protecting group was performed under a hydrogen atmosphere with a 10% loading of palladium on carbon. We were gratified to discover that this two-step reaction sequence produced our target molecule, DAB-1 (2), in a 63% yield, isolated as the hydrochloride salt. The observed optical rotation of synthetic DAB-1 was in good agreement with literature-reported values.

**Scheme 6. Syntheses of DAB-1 and Nectrisine**

With all heteroatoms and stereocenters correctly positioned, completion of the DAB-1 synthesis rested on three remaining steps: lactam formation, amide reduction, and benzyl deprotection (Scheme 6). One-pot cyclization of aminoester 18 to lactam diol 20 was efficaciously accomplished in 87% yield via facile removal of the Boc group followed by a cyanide-catalyzed lactamization. Reduction of the resultant lactam (20) was achieved under classic borane-mediated conditions. Finally, deprotection of the benzyl-protecting group was performed under a hydrogen atmosphere with a 10% loading of palladium on carbon. We were gratified to discover that this two-step reaction sequence produced our target molecule, DAB-1 (2), in a 63% yield, isolated as the hydrochloride salt. The observed optical rotation of synthetic DAB-1 was in good agreement with literature-reported values. Nectrisine, a related iminosugar with important biological activity, was also accessed from lactam 20 by a modified procedure. Hydrogenolysis of the benzyl ether (20) was accomplished to provide lactam triol 21. This triol is a known intermediate in the synthesis of nectrisine. This formal synthesis underscores the general utility of our route to substituted pyrrolidine alkaloids.

In conclusion, we have developed a novel combined enzyme- and metal-catalyzed strategy for the enantioselective syntheses of three notable alkaloid natural products. The inexpensive and readily available oxynitrilase enzyme introduced the first stereocenter in each instance with remarkable enantioselectivity. Alkene cross-metathesis proved a resourceful method to overcome the substrate limitations of the enzyme. Palladium-catalyzed 1,3-allylic substitutive transpositions translated this stereochemistry into the key amine stereocenters using both azide and novel DNs-protected nitrogen nucleophiles. This combined strategy provided functionally dense and stereochemically rich molecular building blocks that were readily elaborated into (−)-coniine, DAB-1, and nectrisine. We anticipate that this strategy could be employed as a template for the synthesis of other piperidine and pyrrolidine alkaloids by taking advantage of the broad scope of the catalytic reactions described as well as a source of functionally dense synthetic intermediates.

**EXPERIMENTAL SECTION**

**General Remarks.** All reactions were carried out in a dry glassware under an argon atmosphere using standard Schlenk techniques unless otherwise specified. Ethanol was purified by distillation from magnesium turnings and iodine. All other
solvents were purified by the passage through solvent purification columns. CDCl₃, CD₂OD, and D₂O were used as received. Compounds 7a, 7b, 9a, 9b, and 6a were prepared according to previously reported literature procedures.¹ The Hoveyda–Grubbs second-generation complex was generously provided by Materia, Inc. All other commercial reagents were used as received.

¹H and ¹³C spectra were recorded on a 300 or 400 MHz spectrometer. Residual CHCl₃ solvent peaks were referenced to 7.27 and 77.23 ppm for ¹H and ¹³C NMR, respectively. Residual CH₂OH solvent peaks were referenced to 3.31 and 49.00 ppm for ¹H and ¹³C NMR, respectively. Infrared spectra were recorded on an FT-IR spectrometer as a thin film on KBr plates. High-resolution mass spectra (HRMS) were provided by the University of California, Irvine Mass Spectrometry Facility. All HRMS were by positive-ion CI or ESI.

N-(But-3-en-1-yl)-2,4-dinitrobenzenesulfonyl amide. To a stirred suspension of 3-butene-1-amine hydrochloride (0.500 g, 4.65 mmol) in CH₂Cl₂ (23 mL, 0.2 M) under nitrogen was added distilled triethylamine (1.62 mL, 11.6 mmol) in drop-wise fashion. When dissolution was complete, the solution was cooled in an ice/water bath, and 2,4-dinitrobenzenesulfonyl chloride (1.49 g, 5.60 mmol) was added portion-wise. The ice bath was then removed, and the reaction was permitted to warm to room temperature for 1 h. The mixture was then diluted with EtOAc (50 mL) and washed with saturated aqueous NH₄Cl (5 mL). The organic phase was extracted with dichloromethane (5 mL) and extracted with ammonium chloride (5 mL). The resulting mixture was stirred at ambient temperature for 10 min, then dissolved in ether (5 mL) and extracted with ammonium chloride (5 mL). The organic phase was dried over MgSO₄, rinsed through a glass-fritted plug of silica gel and MgSO₄, and concentrated. The crude oil was then redissolved in 5:1 THF/dimethylformamide as slightly off-white crystals (55%): mp 91.8 °C; TLC Rf = 0.36 (hexanes/EtOAc, 3:1); IR (film) 3358, 3112, 3101, 1608, 1555, 1530, 1362, 1349, 1341, 1173, 748 cm⁻¹; ¹H NMR (300 MHz, CDCl₃): δ 3.20 (dd, J = 7.1 Hz, 2H), 4.53 (br q, 1H), 4.16 (q, J = 6.8 Hz, 2H), 5.12 (m, 2H), 4.86 (dd, J = 7.1 Hz, 1H), 8.46 (dd, J = 2.2, 8.6 Hz, 1H). ¹³C NMR (75 MHz, CDCl₃): δ 149.9, 148.3, 139.3, 133.7, 132.7, 127.4, 120.9, 118.8, 43.1, 33.9; HRMS (ESI): calcld for C₁₀H₁₅N₄O₆S ([M + H⁺]: 478.1255; found, 478.1250. Cyclohexene was added followed by di-tert-butyl dicarbonate (268 mg, 3 equiv). The resulting mixture was then diluted with dichloromethane (5 mL) and extracted with ammonium chloride (5 mL). The aqueous phase was then extracted with dichloromethane (2 × 5 mL), and the phase was then dried over Na₂SO₄, filtered, concentrated, and purified by automated silica gel chromatography to provide 100 mg (75%) of 12b as colorless oil. IR (KBr): 2975, 2875, 1723, 1697, 1642 cm⁻¹; ¹H NMR (300 MHz, 298K, CDCl₃): δ 5.83 (dd, J = 15.9, 1.7 Hz, 1H), 5.72 (dd, J = 15.1, 9.0, 5.1 Hz, 1H), 5.04 (dd, J = 15.1, 1H), 4.99 (dd, J = 9.0 Hz, 1H), 4.2−4.6 (br s, 1H), 4.19 (q, J = 7.1 Hz, 2H), 3.03 (br s, 2H), 2.11−2.39 (m, 2H), 1.61 (q, J = 7.2 Hz, 2H), 1.45 (s, 3H), 1.41−1.13 (m, 5H), 0.93 (t, J = 7.3 Hz, 3H); ¹³C NMR (75 MHz, CDCl₃): δ 166.5, 155.5, 147.8, 135.5, 121.8, 116.6, 80.1, 60.6, 56.2, 44.3, 36.8, 34.1, 28.6, 19.6, 14.4, 14.0; HRMS (ESI): calcld for C₂₀H₁₈NO₅S ([M + Na⁺]: 478.1255; found, 478.1250. Ethyl (R,E)-4-((N-(But-3-en-1-yl)-2,4-dinitrophenyl)sulfonyl)amido)-hept-2-enoate (12c). A −10 °C solution of dba₃Pd·Cl₂·CHCl₃ (3.2 mg; 1.5 mol %) and triphenylphosphine (3.2 mg; 6 mol %) in THF (0.20 mL, 1 M) was added dropwise to a −10 °C solution of allicine carbonate 6a (50 mg; 0.205 mmol), triethylamine (0.082 mL, 0.615 mmol, 3 equiv), and N-(but-3-en-1-yl)-2,4-dinitrobenzenesulfonyl amide (92 mg; 0.307 mmol, 1.5 equiv) in THF (approx. 0.6 mL, ∼0.3 M). The flask was protected from light with an aluminum foil wrap and held at −10 °C for the duration. The progress of the reaction was monitored by TLC using UV visualization. After 14 h, the reaction was diluted with ethyl acetate (2.5 mL) and rinsed through a short plug of silica gel (60−200 mesh) and MgSO₄ with additional ethyl acetate. The solvent was removed under reduced pressure, and the crude product was chromatographed on silica gel (hexanes/EtOAc, 6:1). Concentration in vacuo afforded 60 mg (67%) of adduct 4 as pale yellow oil: TLC Rf = 0.40 (hexanes/EtOAc, 3:1); [α]D²⁰ +37.6 (c 1.73, CHCl₃) ee = 96% (AD-H Chiralcel HPLC column, 5% IPA in hexane, R = 18.9 min, 20.4 min). Ethyl (R,E)-4-((N-(But-3-en-1-yl)-2,4-dinitrophenyl)sulfonyl)amido)-hept-2-enoate (12d). To a solution of carbonate 1 (447 mg, 0.98 mmol) in CH₂Cl₂ (20 mL) to give a final diene concentration of 0.04 M. The ice bath was then removed, and the flask was allowed to warm to ambient temperature for 3 h.
The reaction was diluted with CH3OH (1 mL) and EtOAc (15 mL) and then rinsed through a glass-fritted plug of silica gel (60–200 mesh) and MgSO4 with additional EtOAc. The solution was concentrated, and the resulting brown oil was purified by silica gel chromatography (hexanes/EtOAc, 6:1) to afford 297 mg (84%) of 13 as pale yellow oil: TLC RF = 0.38 (hexanes/EtOAc, 3:1); [α]D = −195.1 (c 1.445, CHCl3) ee = 95% (AD-H Chiralcel HPLC column, 7.5% IPA in hexane, RF = 7.7 min, 10.4 min); IR (film): 3103, 2960, 2935, 1605, 1553, 1537, 1364, 1352, 1127, 1111, 748 cm⁻¹; 1H NMR (400 MHz, CDCl3): δ 8.46 (dd, J = 2.2, 8.6 Hz, 1H), 8.40 (dd, J = 2.2 Hz, 1H), 8.19 (d, J = 8.6 Hz, 1H), 5.65–5.8 (m, 2H), 4.31 (app br s, 1H), 3.80–3.95 (m, 1H), 3.24–3.34 (m, 1H), 1.88–2.08 (m, 2H), 1.52–1.67 (m, 2H), 1.26–1.47 (m, 2H), 0.90 (t, J = 3.7 Hz, 3H); 13C NMR (100 MHz, CDCl3): δ 149.5, 148.0, 139.9, 132.0, 127.8, 126.3, 124.8, 119.7, 54.8, 39.0, 37.2, 23.9, 19.4, 13.9; HRMS (ESI): calcd for C14H18N2O5S ([M + H]+), 356.0911; found, 356.0918.

tert-Butyl (R)-6-Propyl-3,6-dihydroxypridine-1(2H)-carboxylate (14). Allyl amine (0.796 mL; 0.605 g, 10.6 mmol) was added dropwise to an ice-cooled, stirred solution of the DN-protected piperidine 13 (188 mg, 0.531 mmol) in anhydrous CH2Cl2 (5.3 mL, 0.1 M). After 18 min, the initially red solution had turned orange and was carefully concentrated in vacuo (approx. 400 Torr) at room temperature to furnish the volatile dehydroconiine intermediate. To assist in the removal of the excess allyl amine, the crude product was twice dissolved in CH2Cl2 (10 mL) and sequentially evaporated as before. The liquid residue was dissolved in p-dioxane (4.3 mL) and H2O (5.3 mL) and then treated with NaHCO3 (178 mg, 2.12 mmol) and a solution of Boc2O (347 mg, 1.59 mmol) in p-dioxane (1 mL). After 18.5 h of stirring at room temperature, the mixture was diluted with EtOAc (approx. 10 mL) and then quenched by the dropwise addition of H2SO4 (1 M) until the solution reached a pH of 1. The aqueous layer was separated and extracted three times with EtOAc. The combined organic layers were washed with saturated aqueous NaHCO3 (1 M) and MgSO4, dried over Na2SO4, and filtered through silica gel, and concentrated under vacuum. Purification by SiO2 flash chromatography (16% EtOAc/hexanes) afforded 1.9 g (69% yield) of 9c as pale brown oil. 1H NMR (300 MHz, CDCl3): δ 7.36–7.28 (m, 5H), 6.06 (dd, J = 15.5, 5.3, 1.5 Hz, 1H), 5.90–5.82 (m, 1H), 4.69 (t, J = 5.4 Hz, 1H), 4.54 (s, 2H), 4.35–4.19 (m, 2H), 4.08 (d, J = 5.3 Hz, 2H), 3.00 (d, J = 5.9 Hz, 1H), 1.32 (t, J = 7.1 Hz, 3H); 13C NMR (75 MHz, CDCl3): δ 173.4, 138.3, 129.6, 128.6, 128.5, 126.9, 125.8, 125.7, 124.8, 119.7, 54.9, 39.0, 37.2, 23.9, 19.4, 13.9; HRMS (ESI): calcd for C14H15NO4S ([M + Na]+), 273.1093; found, 273.1095.

Ethyl (E)-5-(Benzyloxy)-2-hydroxypent-3-enoate (6b). To a flame-dried 100-mL round-bottomed flask was added hydroxy ester 9c (850 mg, 3.40 mmol, 1.0 equiv) and diluted with pyridine (2.2 mL, 1.5 M). The reaction mixture was cooled to 0 °C and maintained for 10 min before slow drop-wise addition of ethyl chloroformate (0.65 mL, 6.79 mmol, 2.0 equiv). The reaction stirred for 1 h before quenching by pouring into a separatory funnel with saturated aqueous NH4Cl (20 mL). The mixture was diluted with EtOAc (10 mL), the two layers were separated, and the organic layer was washed with saturated NH4Cl (3 × 20 mL) and then saturated NaCl (1 × 15 mL). The organic layer was then dried with Na2SO4, filtered, and concentrated under vacuum. The crude residue was purified using SiO2 flash chromatography (16% EtOAc/hexanes). This material was further purified by radial silica gel chromatography (gradient; 100% hexanes to 5% EtOAc to 10% EtOAc in hexanes) to remove the cis isomer and afford 950 mg (87.3% yield) of 6b as colorless oil: 93% ee (OD-H Chiralcel HPLC column, 5% IPA in hexane, RF = 6.8 min, 8.8 min); 1H NMR (300 MHz, CDCl3): δ 7.36–7.30 (m, 5H), 6.11 (dd, J = 15.6, 5.0, 1.1 Hz, 1H), 5.93–5.86 (ddt, J = 15.6, 6.3, 1.2 Hz, 1H), 5.41 (dd, J = 6.3, 0.9 Hz, 1H), 4.53 (s, 2H), 4.25 (q, J = 7.1 Hz, 4H), 4.08 (d, J = 5.1 Hz, 2H), 3.12–2.67 (m, 1H); 13C NMR (100 MHz, CDCl3): δ 168.4, 154.4, 153.1, 132.9, 128.6, 127.9, 123.5, 75.3, 72.6, 69.4, 64.8, 62.0, 14.3, 14.2; FTIR: 2981, 2854, 1747 cm⁻¹; [α]D = −24.3 (c 0.17, CHCl3); HRMS: calcd for C14H15O4Na ([M + Na]+), 345.1314; found, 345.1320.

Ethyl (E)-4-Azido-5-(Benzyloxy)pent-3-enoate (16). In a flame-dried 20 mL scintillation vial, carbonate 6b (900 mg,
2.79 mmol, 1.0 equiv) was dissolved in anhydrous dichloromethane (9.3 mL, 0.3 M). The resulting solution was then cooled to 0 °C in an ice/water bath, and Pd(PPh3)4 (161 mg, 0.140 mmol, 5 mol %) was added to the vial. Azidotrimethylsilane (0.741 mL, 5.58 mmol, 2.0 equiv) was then added dropwise, and the solution was allowed to warm to ambient temperature for 4 h. The reaction mixture was quenched by dilution with diethyl ether (10 mL), filtered through silica gel, and concentrated under vacuum. The crude residue was purified by SiO2 flash chromatography (9% EtOAc/hexanes to 25% EtOAc/hexanes) to afford 600 mg (78%) of 16 as colorless oil: 93% ee (OD-H Chiralcel HPLC column, 5% IPA in hexane, Rf = 13.1 min, 15.2 min); 1H NMR (300 MHz, 313 K, CDCl3): δ 7.38–7.31 (m, 5H), 6.10 (dd, J = 15.6, 5.9 Hz, 1H), 1.31 (t, J = 7.1 Hz, 2H), 4.30 (ddd, J = 7.4, 5.9, 4.3, 1.6 Hz, 1H), 4.22 (q, J = 7.1 Hz, 2H), 3.65 (dd, J = 9.9, 4.3 Hz, 1H), 3.54 (dd, J = 9.9, 7.4 Hz, 1H), 1.31 (t, J = 7.1 Hz, 3H); 13C NMR (75 MHz, CDCl3): δ 165.7, 141.3, 137.5, 128.7, 128.1, 127.9, 124.5, 73.7, 71.8, 61.8, 60.9, 14.3; FTIR: 3415, 2926, 1769 cm−1; HRMS: calcld for C19H28NO5 Na ([M + Na]+), 406.1842; found, 406.1844; m/z = 406.1844 (100%), [M + Na]+.

Ethyl (S,E)-5-((Benzyloxy)amino)-2,3-dihydroxypentanoate (19). Potassium osmate dihydrate (11 mg, 0.030 mmol, 0.1 equiv) and N-methylmorpholine oxide (134 mg, 1.14 mmol, 4 equiv) were added to a 20 mL vial equipped with a stir bar. The solids were dissolved in water/tert-butanol (1:1, 3 mL, 0.1 M), and alkene 17 (100 mg, 0.29 mmol 1 equiv) was added. The mixture was stirred at 0 °C for 3 h, before the mixture was cooled with an ice/water bath, diluted with EtOAc, and the solution was transferred to a separatory funnel followed by the addition of 2 M KHSO4 until a pH of 1 was reached. Next, the aqueous phase was extracted with EtOAc, and the solution was washed with MgSO4, and the reaction mixture was washed with sodium thiosulfate (2.47 g, 15.63 mmol, 5 equiv) followed by stirring for 1 h. The layers were separated, and the aqueous layer was extracted with EtOAc (6 × 5 mL). The combined organic layers were then dried over Na2SO4, filtered through silica gel, and concentrated under vacuum to afford crude yellow oil. Purification by SiO2 flash chromatography (25% EtOAc/hexanes) afforded 500 mg (79%) of diol 18 as pale yellow oil: 1H NMR (300 MHz, 313 K, CDCl3): δ 7.38–7.31 (m, 5H), 5.35 (dd, J = 8.4 Hz, 1H), 4.56 (q, J = 9.6 Hz, 2H), 4.22–4.23 (m, 2H), 4.06 (td, J = 9.4, 1.3 Hz, 1H), 3.95 (dd, J = 9.3, 2.6 Hz, 1H), 3.76 (t, J = 8.6, 5.7 Hz, 1H), 3.62 (dd, J = 9.3, 3.8 Hz, 1H), 2.71 (d, J = 10.2 Hz, 1H), 1.45 (s, 9H), 1.33 (t, J = 7.1 Hz, 3H); 13C NMR (75 MHz, CDCl3): δ 172.4, 156.9, 137.8, 128.6, 127.96, 127.84, 80.6, 76.8, 73.6, 72.1, 71.0, 69.0, 61.8, 52.2, 28.4, 14.3; FTIR: 3391, 2978, 1736 cm−1; HRMS: calcld for C18H26NO7Na ([M + Na]+), 406.1842; found, 406.1844; [α]25D −11.4 (c 1.01, CHCl3).

Ethyl (2R,3S,4R)-5-((Benzyloxy)methyl)-3,4-dihydroxy-2-pentanoate (17). To a flame-dried 20 mL scintillation vial was added allylic azide 16 (575 mg, 2.09 mmol, 1.0 equiv) and anhydrous EtOH (10 mL, 0.1 M). The solution was cooled to 0 °C, and SnCl2 (792 mg, 4.18 mmol, 2.0 equiv) was added dihydroxylated carbamate (650 mg, 1.72 mmol, 1.0 equiv) and a solution of hydrochloric acid in dioxane (4 M, 21.2 mL, 50 equiv), which was maintained for 1 h. Upon completion via TLC, the solvent was removed under reduced pressure, the residue was washed with saturated aqueous NaCl (1 × 10 mL) and saturated aqueous Na2CO3 (684 mg, 3.13 mmol, 1.5 equiv). The vial was maintained at room temperature for 16 h. The reaction was diluted with EtOAc, and the solution was transferred to a separatory funnel followed by the addition of 2 M KHSO3 until a pH of 1 was reached. The aqueous phase was extracted with EtOAc (3 × 10 mL). The organic layers were combined and washed with saturated aqueous NaHCO3 (3 × 10 mL) and saturated aqueous NaCl (1 × 10 mL). The organic phase was dried with MgSO4, and the reaction mixture was washed through a plug of layered MgSO4 and SiO2. The solvent was removed under reduced pressure, and the residue was purified using SiO2 flash chromatography (50% EtOAc/hexanes) to afford 150 mg (82%) of diol 18 (2 g). Then, equal parts H2O and 19 (2 g). Then, equal parts H2O and 19 (2 g) were added (3.3 mL, 0.5 M), and the biphasic reaction mixture was stirred vigorously for 16 h at ambient temperature. The solution was then diluted with EtOAc (5 mL) and quenched by the addition of sodium thiosulfate (2.47 g, 15.63 mmol, 9.5 equiv) followed by stirring for 1 h. The two layers were separated, and the aqueous layer was extracted with EtOAc (6 × 5 mL). The combined organic layers were then dried over Na2SO4, filtered through silica gel, and concentrated under vacuum to afford crude yellow oil. Purification by SiO2 flash chromatography (25% EtOAc/hexanes) afforded 350 mg (87%) of benzylated lactam 20 as a colorless foam: 1H NMR (300 MHz, CD3OD): δ 7.34–7.25 (m, 5H), 4.53 (s, 2H), 4.06 (d, J = 7.6 Hz, 1H), 3.89 (s, J = 7.1 Hz, 1H), 3.67
(d, J = 9.4, 2.5 Hz, 1H), 3.49–3.38 (m, J = 4.6 Hz, 2H); 13C NMR (75 MHz; MeOD): δ 176.5, 139.5, 129.6, 129.03, 128.90, 77.5, 77.1, 74.5, 71.2, 58.8; FTIR: 3266, 1707 cm\(^{-1}\); [α]\(^D\)_20 +9.5 (c 1.04, MeOH); HRMS: calc for C\(_{12}\)H\(_{15}\)NO\(_4\)Na ([M + Na]\(^+\)), 260.0899; found, 260.0906.

1,4-Dideoxy-1,4-imino-\(\beta\)-arabinono-\(\alpha\)1-HCl (DAB-1) (2). Lactam (20 mg, 0.084 mmol, 1.0 equiv) was dissolved in a solution of borane in THF (1M, 2.1 mL, 2.1 mmol, 25 equiv) under an atmosphere of argon. The vial was sealed and heated to 20 °C. After 48 h, the reaction mixture was quenched by careful addition of MeOH (5 mL) and then concentrated under reduced pressure. The resulting oil was dissolved in MeOH (5 mL), and HCl in dioxane (4 M, 1 mL) was added, followed by a solution of HCl in dioxane (4 M, 5 mL) was added, and the resulting solution was concentrated under reduced pressure to provide 9 mg (63%) of triol as pale yellow oil. 1H NMR (300 MHz, D\(_2\)O): δ 5.5, 3.3 Hz, 1H), 3.79 (t, \(J = 12.2, 4.9, 1.2\) Hz, 1H), 3.56 (dd, \(J = 11.8, 5.0\) Hz, 1H), 3.24–3.09 (m, 2H); 2.93 (dd, \(J = 12.3, 3.2\) Hz, 1H); 13C NMR (75 MHz; D\(_2\)O): δ 76.6, 75.2, 67.5, 59.9, 50.9; [α]\(^D\)_20 +31.1 (c 0.28, H\(_2\)O) lit. +33.3 (c 0.18, H\(_2\)O). Spectroscopic data were an exact match with that previously published in the literature.31

(35,4R,S)-3,4-Di-hydroxy-5-(hydroxymethyl)pyrrolidin-2-one (21). Palladium (10%) on carbon (70 mg) and HCl in dioxane (4 M, 1 mL) was added, and the resulting solution was concentrated under reduced pressure to provide 9 mg (63%) of triol 21 as colorless oil. 1H NMR (300 MHz, D\(_2\)O): δ 4.33 (dd, \(J = 8.0, 1.2\) Hz, 1H), 4.03 (t, \(J = 7.6\) Hz, 1H), 3.81 (dd, \(J = 12.2, 3.1\) Hz, 1H), 3.64 (dd, \(J = 12.2, 4.9\) Hz, 1H), 3.53–3.43 (m, 1H); 13C NMR (75 MHz; D\(_2\)O): δ 178.2, 78.2, 77.2, 62.7, 60.6; FTIR: 3426, 2927, 1740, 1701 cm\(^{-1}\); HRMS: calc for C\(_7\)H\(_9\)NO\(_4\)Na ([M + Na]\(^+\)), 170.0429; found, 170.0430; [α]\(^D\)_20 +10.6 (c 0.63, H\(_2\)O) lit. +15.4 (c 0.12). Spectroscopic data were an exact match with that previously published in the literature.31

**ASSOCIATED CONTENT**

**Supporting Information**
The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acsomega.9b03990.

1H and 13C NMR spectra of novel compounds, 1H NMR spectra of known compounds prepared by new methods, and enantioselective HPLC traces (PDF)

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**Notes**

The authors declare no competing financial interest. D.R.D. has emeritus status.

**ACKNOWLEDGMENTS**

Acknowledgement is made to the donors of the American Chemical Society Petroleum Research Fund (41883-B1) for partial support of this research; Academic Student Project awards and summer research fellowships from Occidental College; the Kenneth T. and Eileen L. Norris Foundation, and the John Stauffer Charitable Trust for research fellowships. NMR data were acquired on instruments purchased with a grant from the NSF (CHE-0321366).

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