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Organoboron-Based Allylation Approach to the Total Synthesis of the Medium-Ring Dilactone (+)-Antimycin A_{1b}

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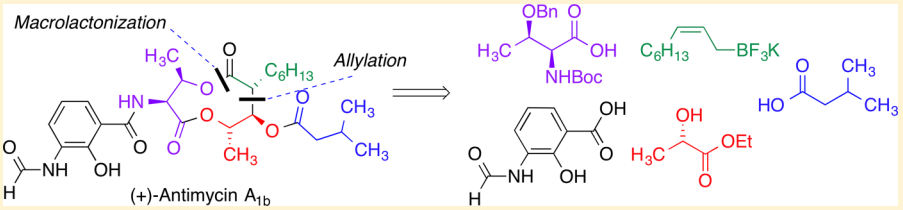
Supporting Information



ABSTRACT: The stereoselective synthesis of (+)-antimycin A_{1b} has been accomplished in 12 linear steps and 18% overall yield from (−)-ethyl lactate. A robust, scalable, and highly diastereoselective montmorillonite K10-promoted allylation reaction between an α-silyloxy aldehyde and a substituted potassium allyltrifluoroborate salt provides a general approach to the core stereochemical triad of the antimycin A family. The requisite (Z)-substituted potassium allyltrifluoroborate salt was synthesized using a *syn*-selective hydroboration/protodeboration of an alkynylboronate ester, followed by a Matteson homologation reaction. The total synthesis leverages an MNBA (Shiina's reagent)-mediated macrolactonization to generate the 9-membered dilactone ring and a late-stage PyBOP-mediated amide coupling employing an unprotected 3-formamidosalicylic acid fragment, thereby shortening the longest linear sequence and, perhaps most notably, generating the antimycin A C7−C8−C9 stereotriad in a single step using a single chiral pool-derived stereocenter.

INTRODUCTION

Leben and Keitt first described the antimycins in 1948 when they reported a bioactive preparation obtained from an unidentified *Streptomyces* strain.[1] At the time of discovery, the family of 9-membered dilactones was shown to have potent antifungal activity against *Nigrospora sphaerica*. As a result, members of the antimycin family have been studied extensively, with a wealth of additional bioactivity being revealed. Seminal studies suggested that antimycin A was able to potently inhibit mitochondrial respiration[2] by binding to the cytochrome bc_1 complex at its Q_i site.[3] More recently, several groups showed that various members of the antimycin A family and their derivatives exhibit biological activities including blocking angiogenesis,[4] inhibiting autophagy,[5] conferring cardioprotection,[6] and stimulating apoptosis by inhibiting Bcl-x_L.[7] Hockenbery and co-workers elegantly demonstrated that antimycin A was able to inhibit the antiapoptotic effects of Bcl-x_L by binding to its Bcl-2 *h*omology domain 3 (BH3)-binding hydrophobic groove, facilitating the loss of mitochondrial membrane fidelity and ultimately leading to the onset of apoptotic cell death.[7b] These studies also demonstrated promise for the use of an antimycin A analogue for the treatment of neoplastic or other proliferative diseases reliant on Bcl-2 protein overexpression by showing that, at least in the context of antimycin A_3, methylation of the phenol abolished its inhibition of cellular respiration while retaining its ability to stimulate apoptosis in cells with enhanced levels of Bcl-x_L (Bcl-x_L^{high}).[7b] More recent findings suggested the mechanism of action involved mitochondrial membrane hyperpolarization as evidenced by the accumulation of NAD(P)H. Interestingly, this gain-of-function cytotoxicity was only observed in cells overexpressing Bcl-x_L.[7a]

To date, there are several dozen known members of the antimycin A family, each differing in the nature of the alkyl chain at C7 (R^1) or the acyl group at C8 (R^2) (Figure 1).[8] More recently, Fenical and co-workers described a related family of anti-inflammatory natural products, the splenocins,[9] which differ from the antimycins in that they incorporate an aryl moiety at either their C7 or C8 side chains. Several related structures have also been reported, including UK-2A (a derivative of splenocin B),[10] as well as related neoantimycins, such as JBIR-52,[11] prunustatin A,[12] kitastatin 1,[13] and respirantin,[14] which share the 1,2,3-trisubstituted aryl fragment with the antimycins and splenocins (Figure 1).

RESULTS AND DISCUSSION

Due to the breadth and potency of their biological activities, the antimycins have garnered significant synthetic attention,[8a] both in the synthesis of natural members[15−18] and novel analogues.[19] The main synthetic challenges associated with antimycin synthesis are (i) the formation of the nine-membered ring, (ii) the synthesis of the C7−C8−C9 stereotriad, and (iii) the attachment of the formamidosalicylate ring. Our goal was to

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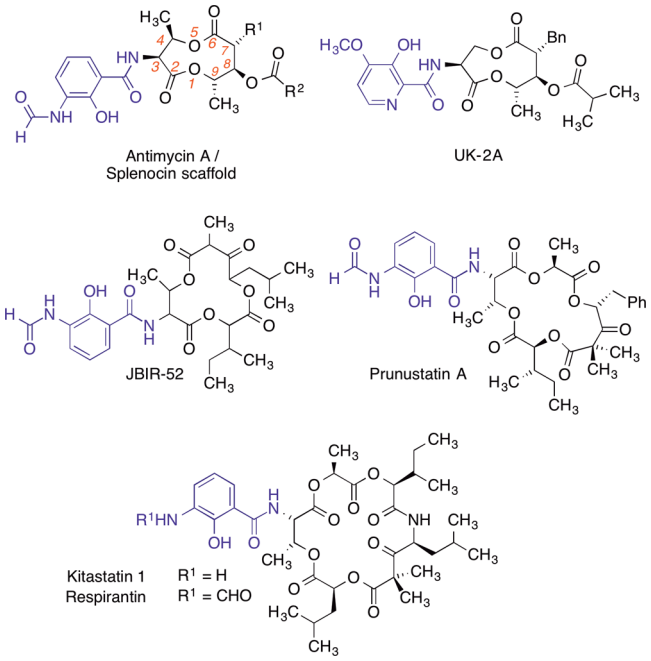
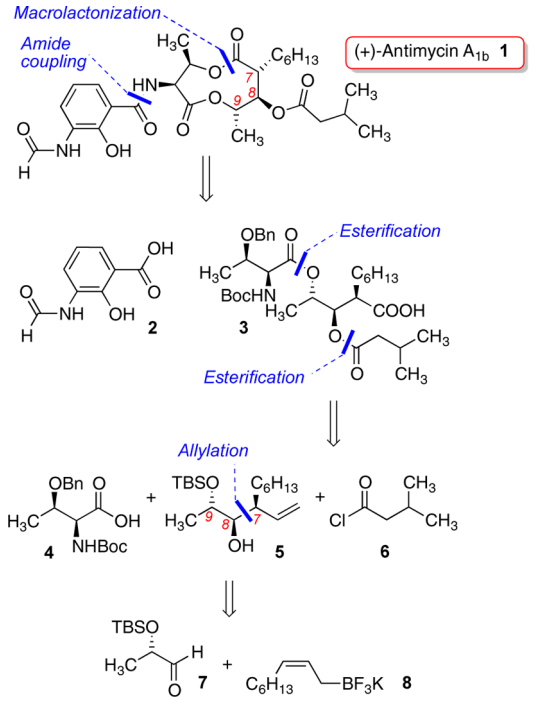


Figure 1. Structures of antimycins and related natural products.

develop a general route to the antimycin family, targeting the specific example of antimycin A_{1b} (R^1 = *n*-hexyl, R^2 = $CH_2CH(CH_3)_2$), a major component of the antimycin A mixture that, at the onset of this work, had not yet been chemically synthesized.[15c] We envisaged a retrosynthetic approach from chiral pool-derived precursors **4** and **7** using a diastereoselective organotrifluoroborate[20]-based allylation approach with the *Z*-configured reagent **8** to establish the key C7−C8−C9 stereotriad of antimycin A_{1b}, (+)-**1**, via **5** (Scheme 1). Sequential esterification of **5** followed by oxidative cleavage to protected *seco*-acid **3**, macrolactonization, and late-stage

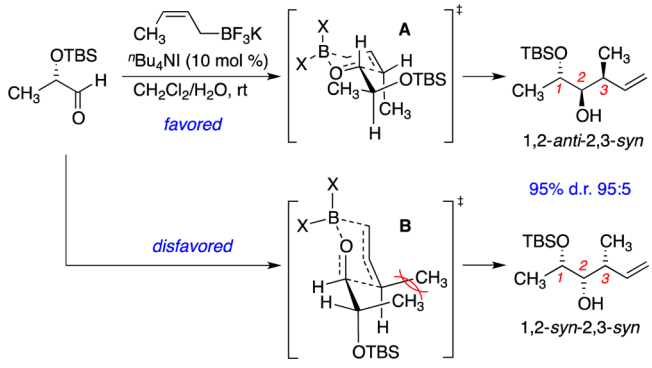
Scheme 1. Retrosynthesis of Antimycin A_{1b}



coupling of the unprotected substituted salicylic acid fragment **2** would then give (+)-**1** (Scheme 1). Such an approach would both address the limitations of some of the previous antimycin syntheses and showcase the practical utility of recently developed robust and scalable organotrifluoroborate-based allylation and crotylation methods.[21]

The requisite 9,8-*anti*-8,7-*syn* stereochemical configuration of the key intermediate **5** necessary to form the C7−C8−C9 antimycin A stereotriad suggested an approach based on the use of a (*Z*)-substituted organoboron reagent. Previous studies, on the synthesis of (−)-tetrahydrolipstatin, had established that diastereoselective crotylation of *α*- and *β*-silyloxy aldehydes using (*E*)- and (*Z*)-crotyltrifluoroborate salts[21f] could be achieved under phase-transfer-catalyzed conditions.[21f,g] The stereochemical outcome of addition to *α*-substituted aldehydes was rationalized by invoking Cornforth-like transition states **A** and **B** (Scheme 2).[21f,h,22] This model is supported by the

Scheme 2. Stereocontrolled Crotylation of *α*-Silyloxy Aldehydes



observation that with a (*Z*)-configured crotylboron reagent there is a strong preference for the formation of the 1,2-*anti*-2,3-*syn* diastereomer. The preferred 2,3-*syn* relationship is controlled by the (*Z*)-geometry of the crotylboron reagent, and the 1,2-*anti* relationship predominates as a result of the disfavored *syn*-pentane like interaction present in the 1,2-*syn* transition state **B**. Notably, in Kiyota's formal synthesis of antimycin A_{3b}, a chelation-controlled allylstannane addition was employed to generate the C7−C8−C9 stereotriad. However, in their case the addition, while quite stereoselective, produced the incorrect *all-syn* diastereomer and required a Mitsunobu inversion at C9 and the use of ethyl (*R*)-lactate as a starting material in order to obtain the natural stereotriad configuration.[15e]

We envisioned the final step in the synthesis of (+)-**1** to be the union of **2** and a macrocyclic amine. However, this route required the coupling of an unprotected phenol where previous syntheses bore this functional group in a protected form, as a benzyl ether.[15] Our initial approach to the arene fragment involved the saponification of the nitrosalicyl ester, **9**, followed by hydrogenolysis of the resulting 3-nitrosalicylic acid. Unfortunately, this chemistry failed to provide practical quantities of 3-aminosalicylic acid with poor batch-to-batch reproducibility and challenges in handling the resulting amino acid. Similarly, reversal of the reduction and saponification steps proved unsuitable due to the significant aqueous solubility of 3-aminosalicylic acid. We ultimately opted for a route in which **9** was subjected to hydrogenolysis, followed by metal silanolate-mediated ester hydrolysis[23] and subsequent acidification to

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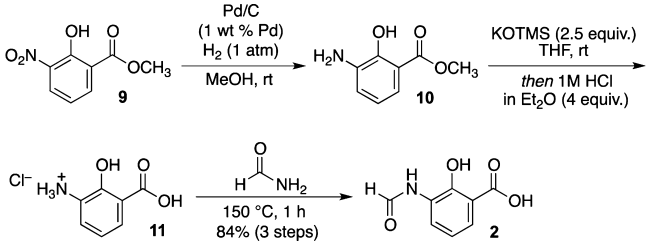
provide the corresponding hydrochloride salt **11** after a simple filtration (Scheme 3). Lastly, conversion of **11** to **2** was then

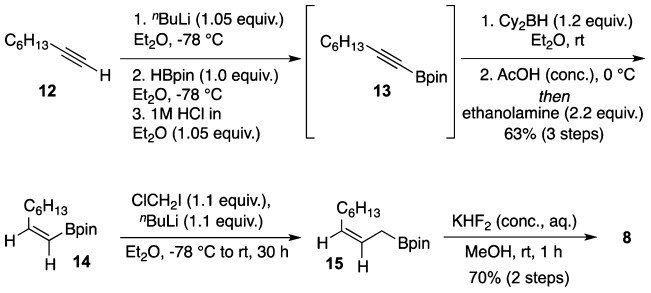
Scheme 3. Synthesis of 3-Formamidosalicylic Acid (2)



achieved as described by Petitt.[14] This route enabled rapid and robust access to multigram quantities of **2** without the need for chromatographic purification steps. Interestingly, the ^{1}H NMR spectrum of **2** was complicated by the fact that the formamide moiety can adopt two distinct rotomeric species, which interconvert on the NMR-time scale, in about a 4:1 ratio, as shown by ^{1}H–^{1}H EXSY NMR (NOESY pulse sequence, see the Supporting Information for details).

For the preparation of the requisite boron reagent **8**, we sought to identify a robust and scalable route that would enable access to multigram quantities with the highest possible stereochemical purity. While numerous methods could be envisioned for the generation of *cis*-alkenyl boronates, we opted for a hydroboration/protodeboration route previously described by Molander and Ellis.[24] Metalation of **12**, trapping of the alkynyllithium with pinacol borane, and subsequent protonolysis of the borohydride afforded large quantities of the labile alkynyl boronate **13** (Scheme 4). Subjecting crude **13** to

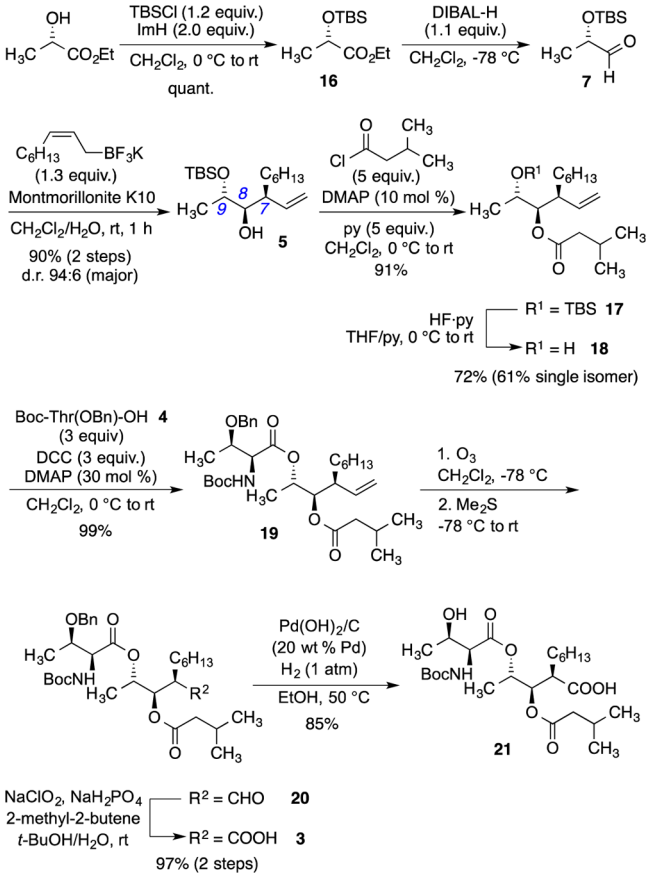
Scheme 4. Synthesis of Boron Reagent 8



hydroboration with dicyclohexylborane followed by selective protodeboration afforded **14** as a single detectable stereoisomer[25] on a multigram scale. Matteson homologation to allylic boronate **15**, using in situ generated (chloromethyl)-lithium,[26] was followed by conversion into the corresponding (*Z*)-configured potassium trifluoroborate salt **8** which exhibits superior stability and ease of handling relative to **15**.[20]

Synthesis of the core fragment began with the conversion of (−)-ethyl lactate to silyl-protected aldehyde **7** (Scheme 5). We were pleased to find allylation with boron reagent **8** proceeded smoothly, using our recently described montmorillonite K10 clay-based allylation method,[21d] to give **5** as the major diastereomer on multigram scale. The benefits of the montmorillonite K10-promoted allylation method include low cost, low toxicity, and facile reaction setup (open-air flask). Perhaps more notable is the fact that this reaction is fast yet highly diastereoselective[27] at room temperature in contrast to

Scheme 5. Synthesis of *seco*-Acid 21



other allylmetal additions, as evidenced by the cryogenic temperature used for the allylstanne addition in Kiyota's synthesis.[15e]

Optimized conditions were able to remedy the initially sluggish acylation encountered for the conversion of the hindered secondary alcohol in **5** to **17**. However, desilylation of **17** was complicated by a 1,2-acyl migration when either TBAF or aqueous HF were used. Fortunately, reports by Trost and Carreira,[28] who had observed similar acyl migrations, led us to examine buffered HF·pyridine conditions, enabling the smooth conversion of **17** to **18** without significant observable acyl transfer. Various conditions for coupling of the threonine moiety **4** were explored including PyBOP, EDC, HBTU, BOP, BOP-Cl, and DCC. Ultimately, DCC proved to be the optimal reagent for the coupling of **4** with **18**, affording **19** in nearly quantitative yield. Terminal olefin oxidation of **19** proved challenging, with the use of Sudan III[29] being essential for obtaining **3** in good yield[30] after subjecting the crude aldehyde to Pinnick oxidation.[29] Removal of the threonine benzyl ether occurred under surprisingly mild conditions,[15b] giving access to multigram quantities of **21**.

We next examined various conditions for forming the 9-membered ring of antimycin A. The use of Shiina's reagent, MNBA,[31] which was previously found to be optimal in the synthesis of antimycin A$_{3b}$,[15b] again proved optimal in our hands (Scheme 6) amidst the other macrolactonization conditions examined. It is noteworthy that MNBA has been used by many groups for the construction of challenging medium and large rings.[31,32] Macrolactonization occurred to give **22** in good yield using slow addition techniques. The

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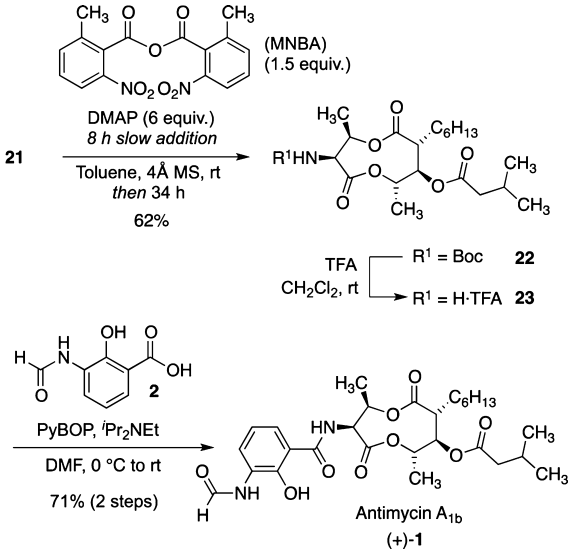
Scheme 6. Synthesis of Antimycin A_{1b}



somewhat modest yield for macrolactonization can be attributed to the competing formation of an 18-member ring dimer that was observed in the crude reaction mixtures both by MS and NMR. Removal of the Boc group and subsequent amide bond coupling with **2** using PyBOP provided synthetic (+)-antimycin A_{1b}, which exhibited spectral and physical properties matching those reported for the natural compound.[8c]

Previous antimycin A syntheses described in the literature, notably even the most recent reports, rely on the use of chiral auxiliaries for the generation of the core antimycin A stereochemical triad. In contrast, we present here an approach in which the intrinsic properties of the substrates are exploited with the single chiral center from the ethyl (*S*)-lactate starting material being used to set the correct C7−C8−C9 configuration with a single practical transformation. We also describe a streamlined and chromatography-free route to **2**, which can be coupled to the antimycin A core directly, in contrast to previous uses of a protected derivative.

With a longest linear sequence of 12 steps (19 steps overall) and 18% overall yield (linear sequence), this constitutes one of the shortest syntheses of a member of the antimycin A family. Key steps included a diastereoselective addition of a (*Z*)-substituted potassium allyltrifluoroborate salt under clay catalysis to establish the C7−C8−C9 stereotriad, an MNBA-promoted macrolactonization, and the use of an unprotected formamidosalicylic acid for the final coupling step. The absolute stereochemistry of the stereotriad was established by the use of the chiral pool reactant ethyl lactate. The synthesis constitutes the first total synthesis application of the use of a nonstandard (*Z*)-substituted potassium allyltrifluoroborate species. Efforts are currently underway to use this flexible allylboron based strategy to access novel analogues with the antimycin A core structure and medicinally interesting neoantimycins and related natural products.

EXPERIMENTAL SECTION

General Considerations. The following general experimental considerations apply for all experiments described in this paper. Unless otherwise stated, all reactions were performed under nitrogen or argon atmosphere using oven-dried (140 °C) and subsequently flame-dried glassware. Reaction solvents were distilled under an inert atmosphere before use and transferred via syringe using standard Schlenk techniques. Dichloromethane, toluene, and acetonitrile were distilled from CaH_2 under nitrogen atmosphere. Tetrahydrofuran, diethyl ether, and benzene were distilled from sodium under nitrogen atmosphere. All reagents and starting materials, unless otherwise stated, were used as received from their respective providers. Anhydrous methanol was used as received. Anhydrous *tert*-butyl alcohol was either freshly distilled from sodium under argon and stored under argon over activated 4 Å molecular sieves or purchased and used as received. Alkyllithium reagents were titrated according to the method by Watson and Eastham[33] prior to use.

Infrared spectra were recorded either as neat samples or from thin films. Strong bands are noted by the abbreviation "str". NMR spectra were obtained as a solution in deuterated solvent ($CDCl_3$, CD_3CN, CD_3OD, $(CD_3)_2SO$), as indicated. Chemical shifts are expressed in parts per million (ppm) relative to Me_4Si (TMS) and referenced by the residual solvent peak (^1H, ^{13}C), $BF_3{\cdot}OEt_2$ (^{11}B), or $CFCl_3$ (^{19}F). Peak multiplicities are designated by the following abbreviations: m, multiplet; s, singlet; d, doublet; t, triplet; q, quartet; dd, doublet of doublets; dt, doublet of triplets and so forth. Additional descriptions include br, broad (this abbreviation is also used for designation of IR peaks), and app, apparent. Apparent multiplicities are described when complex splitting is simplified by averaging or coincidental equivalence. Coupling constants, *J*, are expressed in hertz (Hz) to the nearest 0.5 Hz. Mass spectra, low-resolution (LRMS) and high-resolution (HRMS), were recorded on either a Q-TOF mass spectrometer (ESI), a GC TOF mass spectrometer (EI), or an AccuTOF (DART). LRMS analysis includes peaks of significant relative intensity only with relative intensities given in parentheses (EI only). Accurate masses were determined in all cases to be within ±5 ppm of the calculated high-resolution mass. Stated melting points are uncorrected. Since **5** and **17** were obtained as diastereomeric mixtures no optical rotations are reported.

Flash column chromatography on silica gel (60 Å, 230−400 mesh) was performed with reagent-grade solvents. Chromatography was either run manually or using a flash purification system. Analytical thin-layer chromatography (TLC) was performed on precoated aluminum-backed silica gel plates (Alugram SIL G/UV_{254}), visualized with one of more of the following methods: UV lamp (254 nm), iodine, ninhydrin, potassium permanganate, *p*-anisaldehyde, phosphomolybdic acid, vanillin, Hanessian's stain (cerium molybdate), 2,4-dinitrophenylhydrazine, or bromocresol green. References following compound names indicate literature articles where full-characterization, including all spectral and physical properties, is reported.

Preparation of Boron Reagents. *4,4,5,5-Tetramethyl-2-(oct-1-yn-1-yl)-1,3,2-dioxaborolane (**13**).*[34] A 250 mL three-neck round-bottomed flask, equipped with a thermocouple, for internal temperature monitoring, and a large Teflon stir bar, was flame-dried under vacuum and refilled with dry argon. Anhydrous ether (100 mL) was added followed by 1-octyne (**12**, 14.8 mL, 100 mmol). The stirred solution was then cooled to −78 °C, and *n*-BuLi (38.0 mL, ca. 2.63 M in hexanes, 100 mmol) was added dropwise over 1 h to this solution to form the corresponding lithium acetylide. This solution was then stirred for 1 h before being transferred via cannula to a 500 mL round-bottomed flask, dried as described above, and charged with pinacolborane (14.5 mL, 100 mmol) in 100 mL of anhydrous ether prechilled to −78 °C. This addition occurs over approximately 1 h, during which stirring in the recipient flask became labored due to the gel-like nature of the borohydride complex.[35] After the addition, the mixture was stirred at −78 °C for 1 h and then slowly warmed to room temperature, at which point stirring became facile. The solution was then cooled to 0 °C, and hydrogen chloride (100 mL, ca. 1.0 M in ether) was added dropwise. Over the course of the addition LiCl precipitated and vigorous gas evolution was observed. The reaction mixture was then stirred for an additional 30 min before being filtered through Celite to remove lithium chloride and subsequently concentrated in vacuo to afford crude **13** (21.4 g) as a colorless oil which was used without further purification.

^1H NMR ($CDCl_3$, 400 MHz): δ 2.25 (2H, t, J = 7.0 Hz), 1.57−1.48 (2H, m), 1.44−1.20 (21H, m), 0.88 (3H, t, J = 7.0 Hz). ^{13}C NMR

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($CDCl_3$, 100 MHz): (carbon directly bound to boron not observed) δ 84.0, 31.3, 28.5, 28.0, 24.6, 24.5, 22.4, 19.5, 14.0. ^{11}B NMR ($CDCl_3$, 128 MHz): (major) δ 29.7.

*(Z)-4,4,5,5-Tetramethyl-2-(oct-1-en-1-yl)-1,3,2-dioxaborolane (**14**).*[36] In a nitrogen-filled glovebox, a 250 mL, round-bottomed flask equipped with a large Teflon stir bar was charged with dicyclohexylborane[37] (19.4 g, 108.9 mmol). The flask was covered with a rubber septum, removed from the glovebox, and connected to a Schlenk line. Under an argon atmosphere, diethyl ether (160 mL, anhydrous) was added via syringe. To the stirring slurry was added **13** (21.4 g, 90.7 mmol) slowly via cannula as a solution in anhydrous ether (50 mL). The reaction was stirred for 1 h before being cooled to 0 °C. Acetic acid (glacial, 6.7 mL, 117.8 mmol) was then added dropwise, the solution was stirred for 20 min before ethanolamine (14.1 mL, 235.7 mmol) was added, and the mixture was allowed to warm to room temperature. Hexanes (20 mL) was added, and the white precipitate that formed upon addition of ethanolamine was removed by filtration through Celite. The filtrate was concentrated in vacuo to afford a crude residue, which was purified by flash chromatography on silica to afford **14** (15.2 g) as a colorless to pale yellow oil in 70% yield over two steps and in accordance with spectral data previously reported.

R_f = 0.44 (10% ethyl acetate in hexanes). ^1H NMR ($CDCl_3$, 400 MHz): δ 6.43 (1H, dt, J = 13.5, 7.5 Hz), 5.32 (1H, dt, J = 13.5, 1.0 Hz), 2.49−2.46 (2H, m), 1.42−1.22 (20H, m), 0.88 (3H, m). ^{13}C NMR ($CDCl_3$, 100 MHz): (major) δ 155.3, 120.0−116.0 (1C, br), 82.8, 32.2, 31.7, 29.4, 28.7, 24.8, 22.6, 14.1. ^{11}B NMR ($CDCl_3$, 128 MHz): (major) δ 29.7.

*(Z)-4,4,5,5-Tetramethyl-2-(non-2-en-1-yl)-1,3,2-dioxaborolane (**15**).* To a 1 L, three-neck, round-bottomed flask, equipped with a large Teflon stir bar that had previously been flame-dried under vacuum, was added **14** (14.4 g, 60.4 mmol) followed by anhydrous ether (400 mL). Chloroiodomethane (4.84 g, 66.5 mmol), which had been freshly dried over 3 Å molecular sieves, was then added via syringe. The system was cooled to −78 °C and protected from light. *n*-BuLi (28.0 mL, ca. 2.34 M in hexanes, 66.5 mmol) was then slowly added dropwise. If the addition rate is too rapid a sudden flash of yellow color will be observed. After the addition was complete, the reaction mixture was stirred for an additional 1 h at this temperature before gradually being warmed to room temperature. Once at room temperature, the reaction mixture was stirred for an additional 24 h (LiI precipitated over the course of the addition). The reaction was quenched by the addition of distilled water (50 mL) (to dissolve salts), and the two phases were separated. The aqueous phase was washed once with diethyl ether (100 mL), and the combined organic layers were dried over anhydrous sodium sulfate, filtered by gravity, and concentrated in vacuo to afford the crude product (10.8 g). NMR analysis showed about 95% conversion of the starting alkenylboronate. In addition to trace quantities of unreacted starting material, residual butyl iodide (3.18, 1.79, 1.38, 0.91 ppm) was also present. This mixture was characterized and used in the following step without further purification.

^1H NMR ($CDCl_3$, 400 MHz): δ 5.52−5.32 (2H, m), 1.99 (2H, app q, J = 7.0 Hz), 1.65 (2H, d, J = 7.5 Hz), 1.46−1.12 (20H, m), 0.86 (3H, t, J = 7.0 Hz). ^{13}C NMR ($CDCl_3$, 100 MHz): (major) δ 130.0, 123.9, 83.1, 31.8, 29.5, 29.0, 27.0, 24.7, 22.6, 14.1. ^{11}B NMR ($CDCl_3$, 128 MHz): (major) δ = 33.0. IR (thin film): ν_{max} 2978, 2957, 2926, 2360, 2341, 1467, 1459, 1388, 1370, 1345, 1325, 1273, 1215, 1165, 1146, 1111, 968, 882, 848 cm^{-1}. LRMS (EI): m/z 195.2 (33.9), 124.1 (13.8), 101.1 (13.7), 95.1 (11.0), 85.1 (25.2), 84.1 (100), 83.1 (32.9), 82.1 (10.5), 81.1 (17.0), 69.1 (17.5), 67.1 (22.6), 57.1 (18.0), 55.1 (20.1), 54.0 (10.2), 44.0 (10.8). HRMS (EI): m/z calcd for $C_{15}H_{29}BO_2$ $[M]^+$ 252.2261, found 252.2261.

*Potassium (Z)-2-(Non-2-en-1-yl)trifluoroborate (**8**).* To a 250 mL round-bottomed flask, equipped with a large Teflon stir bar, were added crude **15** (10.8 g), methanol (50 mL), and a saturated aqueous solution of KHF_2 (18 mL, ca. 4.5 M). Almost immediately, an exothermic reaction took place with appreciable frothing and formation of a white solid. Stirring was permitted for 2 h after which the flask was placed on ice for about 1 h prior to filtration. Vacuum filtration and subsequent washing of the filter cake with cold diethyl ether (2 × 50 mL) followed by drying on-frit (for at least 30 min) afforded a clumpy, white solid. After transfer to a suitable container, the solid was allowed to dry overnight under high vacuum to afford the crude, yet now free-flowing, product. This solid was then "dissolved" in a minimal quantity of hot anhydrous acetonitrile such that most of the organic reagent was dissolved but residual inorganic salts remained suspended. Hot filtration, followed by concentrating the filtrate in vacuo, afforded **8** as a powdery white solid (11.9 g, 83% over two steps, ≥ 85% purity as determined by ^{19}F NMR).

^1H NMR (DMSO-d_6, 400 MHz): δ 5.58−5.46 (1H, m), 5.11−5.01 (1H, m), 1.97−1.86 (2H, m), 1.32−1.20 (8H, m), 0.90−0.78 (5H, m). ^{13}C NMR (DMSO-d_6, 100 MHz): (major) δ 133.2, 123.2, 31.3, 29.6, 28.6, 26.5, 22.1, 22.0−19.0 (br), 14.0. ^{11}B NMR (DMSO-d_6, 128 MHz): (major) δ = 4.03; ^{19}F NMR (DMSO-d_6, 376 MHz): (major) δ −135.6 to −136.6 (m). IR (neat): ν_{max} 3002, 2957, 2922, 2853, 1646, 1404, 1229, 1169, 1068, 963, 917, 788, 752, 670 cm^{-1}. LRMS (ESI^-): m/z 425.2, 408.3, 278.1, 193.1, 173.1. HRMS (ESI^-): m/z calcd for $C_9H_{17}BF_3$ $[M]^-$ 193.1380, found 193.1377.

Preparation or Arene Fragment. *Methyl 3-Amino-2-hydroxybenzoate (**10**).* A 250 mL round-bottomed flask, equipped with a magnetic stir bar, was flame-dried under vacuum and refilled with argon. To this, degassed, wet methanol (100 mL) was transferred via cannula or syringe. The methanol was degassed by bubbling argon or nitrogen through the solution for a minimum of 10 min to remove dissolved oxygen. To the stirring solvent was added **9** (2.7 g, 13.7 mmol) to afford a pale yellow solution. While an argon atmosphere was maintained in the reaction vessel, Pd/C (10 wt %, 270 mg, of 10 wt % Pd/C − 1 wt % Pd) was added in one portion to give a black suspension. At this time, the atmosphere was exchanged to hydrogen (1 atm) by bubbling hydrogen gas into the solution (with a gas outlet connected) for at least 5 min. A balloon of hydrogen gas was then used to maintain the hydrogen atmosphere, and the reaction was allowed to stir at room temperature for 12 h. After 12 h, the reaction was judged complete by TLC analysis. The balloon of hydrogen was removed and dry argon bubbled through the solution for at least 5 min. The vessel was opened to the air, and the suspension was filtered through a fritted glass funnel packed to about half its volume with Celite into a round-bottomed receiving flask. The reaction vessel and filter cake were washed with methanol to ensure complete transfer of the materials (3 × 60 mL). Care was taken to not let the filter cake dry completely. The resultant green-yellow filtrate was concentrated in vacuo to afford a beige solid. This solid was then dissolved in methylene chloride (120 mL), and a magnetic stir bar was added. To the stirring solution was added activated carbon (4.0 g), and the suspension was allowed to stir at room temperature under an air atmosphere for 5 h and then filtered (as above) through a fritted glass funnel packed with Celite into a preweighed round-bottomed flask. The flask and filter cake were washed with methylene chloride (3 × 20 mL) to ensure quantitative transfer, and the resultant yellow-orange filtrate was concentrated in vacuo to afford **10** (2.13 g, 93%) as a peach-colored solid (after drying under high vacuum) that was used without further purification.

*3-Amino-2-hydroxybenzoic Acid, Hydrochloride Salt (**11**).* A 250 mL round-bottomed flask, equipped with a magnetic stir bar, was flame-dried under vacuum and refilled with nitrogen. Anhydrous THF (120 mL) was then transferred via syringe, and solid **10** was added under a positive-pressure of nitrogen to afford a yellow-orange solution. To this solution was added solid KOTMS (90% purity) (5.4 g, 2.5 equiv) portionwise. Upon addition the reaction mixture turned from yellow-orange to light green up to the addition of the first equivalent. Addition of subsequent reagent resulted in an orange-red solution that darkened with time and as additional KOTMS was added. Upon complete addition of the KOTMS, the reaction was then stirred at room temperature for 24 h before a solution of hydrogen chloride in diethyl ether (65 mL, ca. 1.0 M, 4.25 equiv) was added via syringe at room temperature. The heterogeneous suspension was stirred for 48 h at room temperature and then sonicated for an additional 2 h to ensure conversion to a homogeneous brown suspension. The suspension was then filtered with a Buchner funnel, and the filter cake was washed with cold Et_2O (3 × 20 mL) to remove any organic byproducts and obtain **11** (5.96 g) as a fine gray solid

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(along with the KCl byproduct of the reaction) after drying under vacuum and used without further purification.

*3-Formamido-2-hydroxybenzoic Acid (**2**).*[14] To a 50 mL round-bottomed flask, equipped with a magnetic stir bar, under an atmosphere of air, was added **11** (5 g, mixture of **11**·KCl−ca 12.83 mmol). To the solid was added formamide (12 mL). The flask was fitted with a reflux condenser and placed in an oil bath held at 150 °C. The reaction was monitored as follows: at a given time, an aliquot from the reaction mixture was diluted with methanol, filtered through Celite, and analyzed by ESI-MS (positive-mode). After 1 h, the reaction was stopped by removing the flask from the oil bath and allowing it to cool to room temperature. The resultant solution was dissolved in 6% $NaHCO_3$ (aq) (100 mL), acidified with 1 M $KHSO_4$ (verified by litmus paper), and extracted with ethyl acetate (3 × 100 mL). The combined extracts were washed with 50% satd NaCl (aq) (2 × 25 mL), dried over anhydrous Na_2SO_4, and concentrated in vacuo. The residue was then coevaporated with toluene (or benzene) to afford **2** (2.1 g, 92%) as a fine gray solid whose spectral data were consistent with those previously described and as an ∼4:1 mixture of conformers (see the Supporting Information).[38]

^{1}H NMR (DMSO-d_6, 400 MHz): δ (major conformer) 12.12 (1H, br s), 9.80 (1H, s), 8.42−8.31 (2H, m), 7.53 (1H, d, J = 7.8 Hz), 6.90 (1H, t, J = 8.0 Hz). ^{13}C NMR (DMSO-d_6, 100 MHz): δ (major conformer) 172.7, 160.8, 151.7, 127.0, 126.2, 125.0, 119.0, 113.1. LRMS (DART$^+$): m/z 138.1, 164.0, 182.0, 199.1. HRMS (DART$^+$): m/z calcd for $C_8H_8NO_4$ [MH$^+$] 182.04533, found 182.04422.

Total Synthesis of Antimycin A$_{1b}$. *(S)-Ethyl 2-((tert-Butyldimethylsilyl)oxy)propanoate (**16**).*[39] To a 500 mL round-bottomed flask equipped with a magnetic stirring bar was added (−)-ethyl lactate (6.8 mL, 60 mmol) followed by dichloromethane (220 mL) and imidazole (8.2 g, 120 mmol). The resultant solution was then cooled in an ice bath, and TBSCl (11.8 g, 78 mmol) was subsequently added portionwise with vigorous stirring. Over the course of the addition a white precipitate formed. The ice bath was removed, and the reaction mixture was allowed to warm to room temperature with continuous stirring over 20 h. After this time, the reaction was filtered (vacuum filtration) to remove the white precipitate. The solid was washed with dichloromethane (50 mL), and the filtrate was collected and transferred to a separatory funnel. The organic layer was washed sequentially with 1.0 M HCl (100 mL), $NaHCO_3$ (satd aq, 100 mL), and NaCl (satd aq, 100 mL). The resulting organic phase was collected, dried over anhydrous sodium sulfate, and filtered by gravity. The filtrate was concentrated in vacuo to afford a colorless oil, **12** (13.95 g, quant), whose spectral data matched those previously reported.

^{1}H NMR ($CDCl_3$, 400 MHz): δ 4.31 (1H, q, J = 6.5 Hz), 4.24−4.14 (2H, m), 1.40 (3H, d, J = 6.5 Hz), 1.28 (3H, t, J = 7.0 Hz), 0.91 (9H, s), 0.10 (3H, s), 0.07 (3H, s). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 174.4, 68.7, 61.0, 26.0, 21.6, 18.6, −4.7, −5.0. Optical rotation $[\alpha]^{27}_D$ = −21.7 (c = 1.17, $CHCl_3$) [lit.[39] $[\alpha]^{20}_D$ = −32.0 (c = 1.98, $CHCl_3$)].

*(2S,3R,4S)-2-((tert-Butyldimethylsilyl)oxy)-4-vinyldecan-3-ol (**5**).* Compound **5** was prepared in two steps from **16** as described below. To a 500 mL round-bottomed flask was added **16** (10.9, 46.7 mmol). The colorless oil was dried by coevaporation with ca. 100 mL (2 × 50 mL) of anhydrous benzene. The flask was then evacuated and refilled with argon three times before anhydrous CH_2Cl_2 was added (250 mL) via syringe. A thermocouple was inserted into the flask through the rubber septum to monitor the internal temperature of the system. The flask was then cooled to −78 °C, and DIBAL-H (53 mL, ca. 1.1 equiv, 1.0 M in CH_2Cl_2) was added dropwise via syringe over approximately 2 h while maintaining an internal temperature of ∼−75 °C. After the addition was complete, the reaction mixture was stirred for an additional 1 h at this temperature. Methanol (25 mL) was added dropwise via syringe prior to allowing the reaction to warm to 0 °C. Saturated potassium sodium tartrate (100 mL) was added, and the reaction was allowed to continue warming to room temperature. Though a gel formed initially, vigorous stirring while warming to room temperature eventually led to the formation of two distinct phases. The two phases were separated, and the aqueous phase was washed with dichloromethane (2 × 100 mL). The combined organic phases were washed with NaCl (satd aq) (200 mL), dried over anhydrous sodium sulfate, filtered by gravity, and concentrated in vacuo to afford compound **7** as a colorless oil, which was used immediately without further purification.

To a solution of **7** (6.58 g, 35.0 mmol) in dichloromethane (98 mL) were added **8** (10.8 g, 42 mmol), montmorillonite K10 (7 g), and distilled water (7 mL). The slurry was then stirred at room temperature for 10 h.[40] TLC analysis showed the reaction was complete, and the reaction mixture was filtered through a pad of Celite. The reaction vessel was washed with additional dichloromethane (ca. 250 mL). This solution was concentrated in vacuo to afford a crude oil, which was purified directly by flash chromatography on silica (10% v/v ethyl acetate in hexanes) to afford **5** as a colorless oil in good analytical purity contaminated only with a minor quantity of the diastereomeric compounds as impurities (9.9 g, 90% over two steps).[41]

R_f = 0.34 (10% ethyl acetate in hexanes). ^{1}H NMR ($CDCl_3$, 400 MHz): (major) δ 5.45 (1H, dt, J = 17.0, 10.0 Hz), 5.08−4.96 (2H, m), 3.89 (1H, qd, J = 6.0, 3.0 Hz), 3.42−3.36 (1H, ddd, J = 9.5, 3.0, 1.5 Hz), 2.43 (1H, d, J = 1.0 Hz), 2.14−1.80 (2H, m), 1.40−1.10 (11H, m), 1.05 (3H, d, J = 6.0 Hz), 0.91−0.84 (5H, m), 0.88 (9H, s), 0.054 (3H, s), 0.048 (3H, s). ^{13}C NMR ($CDCl_3$, 100 MHz): (major) δ 138.4, 116.5, 77.15, 69.8, 46.9, 31.9, 31.0, 29.4, 26.7, 25.86, 22.7, 18.0, 15.2, 14.1; −4.5, −4.9. IR (thin film) ν_{max} 3576, 3078, 2956, 2929, 2858, 2361, 1642, 1463, 1383, 1362, 1327, 1257, 1123, 1087, 1003, 965, 863, 809, 776, 678 cm^{-1}. LRMS (ESI$^+$) m/z 337.3, 315.3, 297.3, 183.2. HRMS (ESI$^+$) m/z calcd for $C_{18}H_{38}O_2SiNa$ [MNa]$^+$ 337.2540, found 337.2533.

*(2S,3R,4S)-2-((tert-Butyldimethylsilyl)oxy)-4-vinyldecan-3-yl 3-methylbutanoate (**17**).* Compound **5** (6.34 g, 29.1 mmol) was dissolved in anhydrous dichloromethane (100 mL). To the solution was added dry pyridine (4.0 mL, 5 equiv) followed by DMAP (247 mg, 2.9 mmol). The solution was cooled to 0 °C, and isovaleryl chloride (17.8 mL, 146 mmol) was added dropwise to the reaction mixture with vigorous stirring. The flask was then allowed to warm gradually to room temperature. After being stirred for 20 h, the reaction, deemed complete by TLC analysis, was quenched by the addition of $NaHCO_3$ (satd aq, 10 mL). The phases were separated, and the aqueous phase was extracted with additional dichloromethane (100 mL). The combined organic extracts were washed with NaCl (satd aq, 3 × 20 mL), dried over anhydrous sodium sulfate, filtered by gravity, and concentrated in vacuo to afford the crude residue that was subsequently purified by flash silica gel chromatography with a gradient from 100% hexanes to 5% (v/v) ethyl acetate in hexanes. This afforded the desired compound **17** as colorless oil in 91% yield (7.27 g).[42]

R_f = 0.47 (5% ethyl acetate in hexanes). ^{1}H NMR ($CDCl_3$, 400 MHz): (major) δ 5.51 (1H, dt, J = 17.5, 9.5 Hz), 5.10−4.96 (2H, m), 3.89 (1H, dd, J = 8.5, 3.5 Hz), 3.96−3.86 (1H, m), 2.26−2.03 (4H, m), 1.48−1.16 (10H, m), 1.09 (3H, d, J = 6.5 Hz), 1.01−0.94 (7H, m), 0.86−0.83 (4H, m), 0.85 (9H, s), 0.021 (6H, s). ^{13}C NMR ($CDCl_3$, 100 MHz): (major) δ 172.6, 138.5, 116.7, 78.3, 68.1, 45.6, 43.8, 31.8, 29.8, 29.3, 29.3, 26.8, 25.8, 25.8, 25.7, 22.6, 22.5, 18.0, 17.4, 14.1, −4.6, −5.0. IR (thin film): ν_{max} 3078, 2956, 2932, 2857, 2361, 1821, 1740, 1642, 1466, 1419, 1381, 1373, 1362, 1292, 1256, 1187, 1168, 1111, 1093, 1034, 1004, 975, 947, 873, 835, 810, 775, 689, 667 cm^{-1}. LRMS (ESI$^+$): m/z 421.3, 399.3, 372.2, 337.2, 297.3, 267.2. HRMS (ESI$^+$): m/z calcd for $C_{23}H_{47}O_3Si$ [MH]$^+$ 399.3289, found 399.3307.[43]

*(2S,3R,4S)-2-Hydroxy-4-vinyldecan-3-yl 3-methylbutanoate (**18**).* In a 500 mL Teflon round-bottomed flask was dissolved compound **17** (7.2 g, 19.6 mmol) in anhydrous THF (100 mL). To the solution was added dry pyridine (19.5 mL). The solution was cooled to 0 °C, and with vigorous stirring, pyridine−hydrogen fluoride complex (8 mL, 70 wt % HF) was added dropwise. The reaction was monitored by TLC until satisfactory conversion was achieved (ca. 10 days for **17** to **18**). At this time, saturated sodium bicarbonate solution was added dropwise until effervescence ceased. After quenching, water (10 mL) and ethyl acetate (100 mL) were added. The organic and aqueous phases were separated, and the aqueous phase was extracted with

additional ethyl acetate (100 mL). The combined organic extracts were washed with NaCl (satd aq, 3 × 20 mL), dried over anhydrous sodium sulfate, filtered by gravity, and concentrated in vacuo to afford the crude residue that was purified using flash silica gel chromatography using a gradient elution from 2% to 20% (v/v%) ethyl acetate in hexanes. This afforded the desired compound **18** as a colorless oil in 61% yield (3.37 g), as a single stereoisomer, after two iterations of chromatography. In addition, 0.662 g of **18** as a mixture of diastereomers that could be further separated and 0.235 g of unconverted **17** that was recycled were obtained affording an overall yield of 72.3% and 75% based on recovered starting material (brsm).

R_f = 0.22 (20% ethyl acetate in hexanes). ^{1}H NMR ($CDCl_3$, 400 MHz): (major) δ 5.55 (1H, dt, J = 17.0, 9.5 Hz), 5.13−5.02 (2H, m), 4.87 (1H, dd, J = 9.0, 3.5 Hz), 4.01−3.92 (1H, m), 2.29−2.06 (5H, m), 1.54−1.06 (10H, m), 1.12 (3H, d, J = 6.5 Hz), 0.99 (6H, d, J = 6.5 Hz), 0.87 (3H, t, J = 7.0 Hz). ^{13}C NMR ($CDCl_3$, 100 MHz): (major) δ 174.0, 138.0, 17.3, 79.2, 68.3, 46.0, 31.7, 30.5, 29.2, 26.5, 25.7, 25.6, 22.6, 22.5, 16.5, 14.0. IR (thin film) ν_{max} 3464 (str, br), 3078, 2955, 2924, 2873, 2858, 1720, 1642, 1466, 1370, 995 cm^{-1}. LRMS (ESI$^+$) m/z 323.2, 307.2, 165.2. HRMS (ESI$^+$) m/z calcd for $C_{17}H_{33}O_3$ $[MH]^+$ 285.2424, found 285.2412. Optical rotation $[\alpha]^{27}_D$ = +4.85 (c = 1.03, $CHCl_3$).

*(2S,3R)-(2S,3R,4S)-3-((3-Methylbutanoyl)oxy)-4-vinyldecan-2-yl 3-(Benzyloxy)-2-((tert-butoxycarbonyl)amino)butanoate (**19**).* Compounds **18** (3.13 g, 11.0 mmol) and **4** (10.2 g, 33.0 mmol) were combined in a flask under argon. Anhydrous dichloromethane (160 mL) was then added, and the resulting solution cooled to 0 °C. Solid DCC (6.81 g, 33 mmol) was then added to the vigorously stirring solution portionwise under a positive pressure of argon. After the mixture was stirred for 1 h at this temperature, solid DMAP (403 mg, 3.30 mmol) was added in one portion, and the reaction mixture was permitted to warm to room temperature slowly. After being stirred for 23 h, the reaction was deemed complete by TLC and was quenched by the addition of water (50 mL) and dichloromethane (100 mL). The organic and aqueous phases were separated, and the aqueous phase was extracted with dichloromethane (100 mL). The combined organic phases were washed with NaCl (satd aq, 3 × 20 mL), and the combined organic components were dried over sodium sulfate and concentrated in vacuo to afford the crude product **19**. The crude residue was purified using flash silica gel chromatography with a gradient elution from 5% to 40% (v/v%) ethyl acetate in hexanes. This afforded the desired **19** as a viscous pale yellow oil in 99% yield (6.31 g) after two sequential iterations of column chromatography.

R_f = 0.47 (20% ethyl acetate in hexanes). ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.37−7.22 (5H, m), 5.42−5.24 (2H, m), 5.16−4.98 (3H, m), 4.89 (1H, dd, J = 10.0, 2.5 Hz), 4.58 (1H, d, J = 11.5 Hz), 4.45 (1H, d, J = 11.5 Hz), 4.22 (1H, dd, J = 10.0, 3.5 Hz), 4.20−4.10 (1H, m), 2.31−2.06 (4H, m), 1.45 (9H, s), 1.30−1.10 (13H, m), 0.98 (6H, d, J = 6.5 Hz), 0.86 (3H, t, J = 6.5 Hz). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 172.4, 170.2, 156.1, 138.5, 137.1, 128.2, 127.4, 127.3, 117.9, 79.7, 75.3, 75.1, 71.8, 71.1, 58.3, 45.8, 43.6, 31.7, 30.3, 29.1, 28.3, 26.4, 25.8, 22.6, 22.40, 22.36, 16.3, 14.0, 13.1. IR (thin film): ν_{max} 3455, 3066, 3032, 2959, 2932, 2872, 2854, 2359, 2341, 1730, 1720, 1499, 1455, 1370, 1292, 1251, 1167, 1096, 989, 920, 735, 696 cm^{-1}. LRMS (ESI$^+$): m/z 598.4, 520.3, 476.3, 267.2. HRMS (ESI$^+$): m/z calcd for $C_{33}H_{53}NO_7Na$ $[MNa]^+$ 598.3714, found 598.3719. Optical rotation $[\alpha]^{26}_D$ = +8.45 (c = 1.1, $CHCl_3$).

*(R)-2-((6S,9S,10R)-6-((R)-1-(Benzyloxy)ethyl)-2,2,9,14-tetramethyl-4,7,12-trioxo-3,8,11-trioxa-5-azapentadecan-10-yl)octanoic Acid (**3**).* To a 50 mL round-bottomed flask under argon, equipped with a magnetic stir bar, was added **19** (4.13, 6.95 mmol). Compound **19** was dissolved in anhydrous dichloromethane (10 mL), and sufficient Sudan III was added to obtain a visibly colored solution (ca. < 1 mg). The solution was cooled to −78 °C, and a stream of ozone was bubbled through the open solution at this temperature until the solution became colorless. At this point, the ozone stream was stopped and a stream of argon was blown through the solution to remove excess ozone. The solution, now again under argon, was stirred at this temperature while dimethyl sulfide (1.8 mL, 24.5 mmol) was added to the solution dropwise. The mixture was stirred for an additional 1 h before being allowed to gradually warm to room temperature and then quenched by the addition of water (10 mL). The organic and aqueous phases were separated, and the aqueous phase was extracted with dichloromethane (10 mL). The combined organic extracts were washed with NaCl (satd aq, 1 × 10 mL), dried over anhydrous sodium sulfate, filtered by gravity, and then concentrated in vacuo to afford crude **20** as a slightly colored oil that was used immediately without further purification.

To the crude aldehyde **20**, dissolved in 3:1 t-BuOH/H_2O such that substrate concentration is 5.5 mM (940 mL t-BuOH; 320 mL H_2O), were added 2-methyl-2-butene (3.0 mL, 27.8 mmol), sodium dihydrogen phosphate (1.05 g, 7.65 mmol), and sodium chlorite (2.67 g, 23.6 mmol), sequentially and in the order described. The reaction was then stirred at room temperature for 20 h after which the reaction mixture was concentrated to remove as much of the *tert*-butyl alcohol as possible. The aqueous layer was then extracted with ethyl acetate (3 × 200 mL). The combined organic phases were washed with NaCl (satd aq, 2 × 75 mL), dried over anhydrous sodium sulfate, and filtered by gravity. Concentration in vacuo afforded the desired carboxylic acid, **3**, which was purified using flash silica gel chromatography with a gradient elution from 2 to 10% (v/v%) methanol in dichloromethane. This afforded analytically pure **3** as a heavy colorless oil in 97% yield (3.89 g).

R_f = 0.54 (10% MeOH in CH_2Cl_2, visualized with bromocresol green stain). ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.34−7.22 (5H, m), 5.36−5.26 (2H, m), 5.18−5.04 (1H, m), 4.55 (1H, d, J = 11.5 Hz), 4.44 (1H, d, J = 11.5 Hz), 4.32−4.18 (2H, m), 2.59−2.52 (1H, m), 2.24−2.04 (3H, m), 1.46 (9H, s), 1.33−1.14 (15H, m), 0.97 (6H, d, J = 6.5 Hz), 0.85 (3H, t, J = 7.0 Hz). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 176.1, 171.9, 170.2, 156.7, 138.0, 128.3, 127.7, 127.6, 80.4, 75.1, 73.6, 71.5, 71.3, 58.6, 47.0, 43.3, 31.5, 29.1, 28.3, 28.2, 26.9, 25.6, 22.5, 22.39, 22.38, 16.3, 15.8, 14.0. IR (thin film): ν_{max} 3452, 3100 (br, str), 2957, 2931, 2873, 2860, 2591, 1758, 1689, 1609, 1509, 1164, 992, 736 cm^{-1}. LRMS (ESI$^+$): m/z 623.3, 616.3, 494.3, 360.3, 338.3, 284.3. HRMS (ESI$^+$): m/z calcd for $C_{32}H_{51}NO_9Na$ $[MNa]^+$ 616.3456, found 616.3478. Optical rotation $[\alpha]^{27}_D$ = +11.6 (c = 1.0, $CHCl_3$).

*(R)-2-((6S,9S,10R)-6-((R)-1-Hydroxyethyl)-2,2,9,14-tetramethyl-4,7,12-trioxo-3,8,11-trioxa-5-azapentadecan-10-yl)octanoic Acid (**21**).* To a 250 mL, round-bottomed, two-necked flask, equipped with a magnetic stir bar and fitted with a reflux condenser, was added **3** (3.7 g, 6.23 mmol). Anhydrous ethanol (120 mL) was added under argon, and the resulting solution was degassed by bubbling a stream of argon through it for about 5 min. Under a positive pressure of argon, $Pd(OH)_2$ supported on activated carbon (925 mg, 20 wt % Pd) was added to the stirred solution. The atmosphere was exchanged with hydrogen, and the reaction was then warmed to between 45 and 50 °C with an oil bath. After 12 h, the reaction was complete, as judged by TLC, and the reaction vessel purged with argon while being cooled to room temperature. The reaction mixture was filtered through a pad of Celite and concentrated in vacuo. The resultant residue was purified by flash silica gel chromatography with a gradient elution from 2 to 10% (v/v%) methanol in dichloromethane to afford *seco*-acid **21** as a heavy beige oil (2.7 g, 85%).

R_f = 0.26 (10% MeOH in CH_2Cl_2, visualized with bromocresol green). ^{1}H NMR ($CDCl_3$, 400 MHz): δ 5.45 (1H, d, J = 9.5 Hz), 5.34 (1H, dd, J = 9.5, 3.5 Hz), 5.12 (1H, dd, J = 6.0, 4.0 Hz), 4.32−4.14 (2H, m), 2.56 (1H, dt, J = 10.0, 3.5 Hz), 2.30−2.20 (2H, m), 2.13 (1H, app nonet, J = 7.0 Hz), 1.61 (1H, br s), 1.45 (9H, s), 1.98−1.32 (16H, m), 0.99 (6H, d, J = 6.5 Hz), 0.87 (3H, t, J = 7.0 Hz). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 176.3, 173.2, 170.4, 156.4, 80.0, 73.5, 71.6, 67.1, 59.0, 47.2, 43.4, 31.5, 29.0, 28.6, 28.3, 26.8, 25.6, 22.5, 22.4, 22.3, 19.5, 14.3, 14.0. IR (thin film): ν_{max} 3455, 3364 (br, str), 2960, 2930, 1737 (str), 1688 (str), 1522, 1462, 1368, 1252, 1161, 993, 880, 734 cm^{-1}. LRMS (DART$^+$): m/z 521.2, 504.2, 460.2, 448.2, 404.2, 302.2, 285.2, 164.0. HRMS (DART$^+$): m/z calcd for $C_{25}H_{46}NO_9$ $[MH]^+$ 504.3173, found 504.3175. Optical rotation $[\alpha]^{29}_D$ = −3.49 (c = 0.63, $CHCl_3$).

*(2R,3S,6S,7R,8R)-3-((tert-Butoxycarbonyl)amino)-8-hexyl-2,6-dimethyl-4,9-dioxo-1,5-dioxonan-7-yl 3-Methylbutanoate (**22**).* A 100 mL, round-bottomed, two-necked flask, equipped with a magnetic stir bar, was oven and flame-dried under vacuum prior to the addition of

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activated powdered 4 Å molecular sieves (100 mg). DMAP (46 mg, 0.376 mmol) and MNBA (32 mg, 94 μmol) were added under a positive pressure of argon after the flask had cooled. In a vial under argon, **21** (31.6 mg, 0.063 mmol) was dissolved in anhydrous toluene (20 mL) and transferred to a plastic syringe. The remaining reaction components were suspended in anhydrous toluene (10 mL) and were stirred vigorously at room temperature. Using a syringe pump, the solution of **21** was added dropwise over the course of 8 h to the stirred solution of DMAP and MNBA. After the addition was complete, the reaction was stirred for an additional 34 h before being diluted with ethyl acetate (40 mL) and gravity filtered into a separatory funnel. The organic phase was washed with $NaHCO_3$ (satd aq, 25 mL), water (25 mL), and NaCl (satd aq, 25 mL). The organic phase was dried over anhydrous sodium sulfate, filtered by gravity, and concentrated in vacuo to afford crude **22** which was subsequently purified by flash silica gel chromatography with a gradient from 100% hexanes to 20% (v/v %) ethyl acetate in hexanes to afford **22** as a clear oil with some minor impurities (18.9 mg, 62%).[44]

R_f = 0.16 (10% ethyl acetate in hexanes). Mp = 90−91 °C (from $CHCl_3$). ^{1}H NMR ($CDCl_3$, 400 MHz): δ 5.62−5.45 (1H, m), 5.29−5.18 (1H, m), 5.04 (1H, t, *J* = 9.5 Hz), 4.80−4.96 (2H, m), 2.45 (1H, t, *J* = 10.0 Hz), 2.27−2.20 (2H, m), 2.12 (1H, app nonet, *J* = 6.5 Hz), 1.45 (9H, s), 1.34−1.15 (22H, m), 0.85 (3H, t, *J* = 6.5 Hz). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 173.1, 171.8, 170.7, 155.0, 80.5, 75.8, 74.3, 71.5, 62.3, 54.7, 50.3, 43.4, 31.6, 29.8, 29.1, 28.6, 28.4, 27.2, 25.6, 22.63, 22.58, 18.0, 14.1. IR (thin film) ν_{max} 3354, 2959, 2929, 2872, 2857, 1738 (str), 1696 (str), 1526, 1368, 1350, 1342, 1252, 1161, 1118, 1023 cm^{-1}. LRMS (ESI$^+$) *m*/*z* 146.0, 183.1, 285.2, 430.2, 486.3, 508.3, 570.3. HRMS (ESI$^+$): *m*/*z* calcd for $C_{25}H_{43}NO_8Na$ $[MNa]^+$ 508.2880, found 508.2891. Optical rotation $[\alpha]^{27}_D$ = +8.0 (*c* = 0.46, $CHCl_3$).

*Antimycin A_{1b}: (2R,3S,6S,7R,8R)-3-(3-Formamido-2-hydroxybenzamido)-8-hexyl-2,6-dimethyl-4,9-dioxo-1,5-dioxonan-7-yl 3-Methylbutanoate (**1**).* Compound **22** (5 mg, 1 μmol) was placed in a 20 mL scintillation vial equipped with a magnetic stir bar and covered by an inverted rubber septum. The vial was purged with argon prior to running the reaction. The residue was dissolved in anhydrous dichloromethane (0.5 mL), and with stirring, TFA (150 μL, 1.96 μmol) was added dropwise. The reaction mixture was stirred at room temperature and monitored by TLC. Additional dichloromethane (0.5 mL) was added after 6 h to compensate for absorption by the septum. After 18 h, the reaction mixture was diluted with wet dichloromethane (1 mL) and transferred to a separatory funnel. The organic phase was washed with $NaHCO_3$ (satd aq, 2 × 5 mL), dried over anhydrous sodium sulfate, filtered by gravity, and concentrated in vacuo to afford the free base of **23**. This material was used immediately without further purification.

A 5 mL microwave vial equipped with a magnetic stir bar and stoppered with a rubber septum was flame-dried under vacuum and refilled with nitrogen. To this, **2** (2.2 mg, 12.3 μmol) and PyBOP (6.4 mg, 12.3 μmol) were added as solids under a positive pressure of nitrogen. Anhydrous DMF (150 μL) was added to afford a red solution. In a separate vial the crude free-base of **23** (3.8 mg, 10.0 μmol), under an atmosphere of nitrogen, was dissolved in anhydrous DMF (100 μL). The solution of amine was added via syringe to the stirred solution of carboxylic acid and coupling reagent at room temperature (total volume of DMF after combining the components should result in a 0.05 M reaction mixture). Upon addition of the amine, the reaction mixture turned from red to yellow. Immediately following complete transfer of the amine, DIEA (2.2 μL, 12.3 μmol) was added to the reaction, and the mixture was allowed to stir for 20 h with routine monitoring of the reaction progress by TLC (50% ethyl acetate in hexanes, CAM staining to detect product and ninhydrin staining to detect the disappearance of amine). After 20 h, phosphate buffer (pH 5.5, 0.1 M, 2 mL) and ethyl acetate (3 mL) were added to quench the reaction. After the mixture was stirred for several minutes at room temperature, the organic layer was separated and washed five times with NH_4Cl (satd aq, 2 mL), $NaHCO_3$ (satd aq, 2 mL), $NaHCO_3$ (50% saturated, aq, 2 mL), and NaCl (50% satd aq, 3 × 2 mL). The combined organic layers were dried over anhydrous sodium sulfate, filtered by gravity, and concentrated in vacuo. The crude residue was then purified by flash column chromatography on silica gel with a gradient of 40% to 60% (v/v%) ethyl acetate in hexanes to give purified **1** (3.9 mg, 71%). In order to obtain analytically pure material, the product was further purified by semipreparative reversed-phase HPLC (see the Supporting Information) to afford synthetic antimycin A_{1b}, which was characterized fully and was found to be in good accordance with the physical and spectral properties previously described for the natural material.[8c]

R_f = 0.42 (40% ethyl acetate in hexanes). Mp = 126−127 °C (from $CDCl_3$). ^{1}H NMR ($CDCl_3$, 500 MHz): (major rotamer) δ 12.62 (1H, s); 8.55 (1H, dd, *J* = 8.0, 1.5 Hz), 8.50 (1H, d, *J* = 1.5 Hz), 7.92 (1H, br s), 7.24 (1H, dd, *J* = 8.0, 1.0 Hz), 7.07 (1H, d, *J* = 7.5 Hz), 6.92 (1H, t, *J* = 8.0 Hz), 5.73 (1H, app pentet, *J* = 6.5 Hz), 5.29 (1H, app t, *J* = 7.5 Hz), 5.09 (1H, app t, *J* = 10.0 Hz), 5.02−4.94 (1H, m), 2.50 (1H, app td, *J* = 11.0, 3.0 Hz), 2.17−2.10 (1H, m), 2.27−2.23 (2H, m), 1.35−1.20 (16H, m), 0.99 (6H, dd, *J* = 7.0, 1.0 Hz), 0.86 (3H, t, *J* = 7.0 Hz). ^{13}C NMR ($CDCl_3$, 125 MHz): δ 172.9, 171.7, 170.1, 169.4, 158.9, 150.6, 127.5, 124.5, 120.1, 119.0, 112.5, 75.5, 74.9, 70.9, 53.7, 50.2, 43.2, 31.5, 29.0, 28.5, 27.0, 25.5, 22.5, 22.4, 17.9, 15.0, 14.0. IR (thin film): ν_{max} 3410, 3348 (br), 2959, 2924, 2853, 1738 (str), 1636 (str), 1609, 1583, 1374, 1285, 1249, 1207, 1167, 1119, 1018, 870, 756 cm^{-1}. LRMS (ESI$^+$): *m*/*z* 223.1, 265.1, 282.3, 295.2, 304.3, 549.3, 571.3. HRMS (ESI$^+$): *m*/*z* calcd for $C_{28}H_{41}N_2O_9$ $[MH]^+$ 549.2806, found 549.2800. Optical rotation $[\alpha]^{24}_D$ = +58.7 (*c* = 0.13, $CHCl_3$) [lit.[15c] $[\alpha]^{23}_D$ +70.4 (*c* = 0.21, $CHCl_3$)].

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

NMR spectra, a comparison of synthetic and natural antimycin A_{1b}, and final HPLC purification conditions. 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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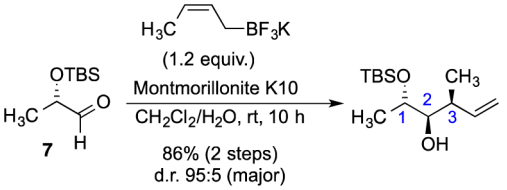

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(40) This reaction was performed in open air without the use of anhydrous manipulations. The reaction time was longer than the 1 h reaction time reported (see ref 21d) as it was run overnight and to ensure full conversion was achieved given the quantity of suspended solids for this large-scale reaction. Smaller scale test reactions reached full conversion in the time previously described.
(41) The diastereoselectivity for the crotylation was determined by integration of the ^{1}H NMR spectrum and using the methine hydrogen bound to the hydroxyl-bearing carbon. In the case of **5**, the peak at 3.37 ppm was assigned as the major diastereomer (9,8-*anti*-8,7-*syn*) and 3.03 ppm as the minor diastereomer (9,8-*syn*-8,7-*syn*). The 8,7-*anti* stereoisomers are difficult to observe, and only what is believed to be the major diastereomer (9,8-*anti*-8,7-*anti*) at 3.21 ppm is even discernible and only in a miniscule quantity. The relative stereochemistry of the major species was assigned based on the J^3 values that were consistent with one *syn* and one *anti* coupling. Similarly, as outlined in ref 27, the ratio was determined by the relative integrations of the protons at 3.30 ppm (1,2-*anti*-2,3-*syn*; major) and 3.02 ppm (1,2-*syn*-2,3-*syn*; minor), with a peak at 3.10 ppm being assigned by analogy to the 1,2-*anti*-2,3-*anti* diastereomer.
(42) Compound **17** was characterized with contamination from the minor diastereomers formed during the allylation step. At this point, the compound could not be purified to a single diastereomer but was used in the subsequent step as obtained. Upon removal of the silyl ether the resulting product, **18**, was purified to essentially a single stereoisomer by flash chromatography.
(43) This compound was originally not detected during HRMS analysis and could only be observed in ESI^+ following a methanol wash after the initial MS injection.
(44) This reaction was highly dependent on scale. An effort to use the more recently described DMAPO (see ref 31h) was met with a very modest 22% yield, even at 0.6 mmol scale (about 10× that reported above). Conditions used were as described above, but with the following alterations: MNBA (417 mg, 1.21 mmol) and DMAPO (167.2 mg, 1.21 mmol), in anhydrous dichloromethane (50 mL), were stirred at room temperature. To the stirred solution was added **21** (290 mg, 0.576 mmol) as a solution in dichloromethane (320 mL) over the course of 18 h. The reaction was stirred an additional 10 h prior to workup and purified as described above.

NOTE ADDED AFTER ASAP PUBLICATION

This paper was published ASAP on July 25, 2014. Figure 1 was updated. The revised paper was reposted on July 29, 2014.