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ORIGINAL RESEARCH

Sulfamate-tethered *aza*-Wacker approach towards analogs of Bactobolin A

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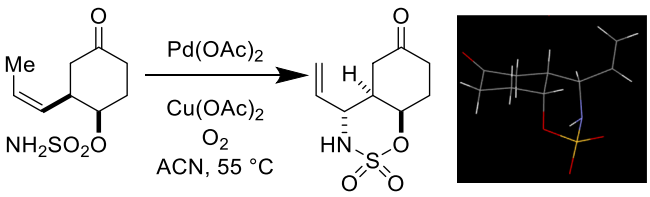
Abstract

Here, we describe an approach towards analogs of the potent antibiotic Bactobolin A. Sulfamate-tethered *aza*-Wacker cyclization reactions furnish key synthons, which we envision can be elaborated into analogs of Bactobolin A. Docking studies show that the C4 epimer of Bactobolin A and the C4/C6 diastereomer interact with different residues of the 23S rRNA (bacterial ribosome 50S subunit) than the natural product, suggesting that these molecules could be valuable tool compounds for fundamental studies of the bacterial translational machinery.

Graphical Abstract



Keywords aza-Wacker · Sulfamate · Bactobolin · Antibiotic synthesis

Introduction

Over the last twenty years, analogs-oriented synthetic strategies have gained favor over "make- the-molecule" approaches, which predominated organic chemistry in the twentieth century [1–3]. Our laboratory is deeply invested in developing *tethered* olefin functionalization methodology, which we envision as key steps in analogs-oriented syntheses of antibiotics [4–7]. Bactobolin A is an unusual dichlorinated polyketide antibiotic that was first isolated from the culture broth of *Pseudomonas yoshidomiensis* and has been demonstrated to have broad antibacterial activity against a variety of pathogenic gram-positive and gram-negative organisms (Fig. 1) [8–11]. Unfortunately, marked cytotoxicity to eukaryotic cells has precluded its clinical use [12, 13]. Recent work has pinpointed the antibacterial activity of Bactobolin A to inhibition of bacterial protein translation *via* binding to an unprecedented site on the bacterial ribosome 50S subunit (L2 protein) [9, 14]. A crystal structure shows this interaction [15]. It is hypothesized that binding to the L2 homolog of the eukaryotic ribosome (L8e) is responsible for eukaryotic cytotoxicity. Despite such rich biological activity, there exists only one racemic synthesis (Weinreb) [16–18] and one enantiospecific synthesis (Švenda) [19] of Bactobolin A [20–23]. Furthermore, few studies of Bactobolin derivatives have been reported; thus far, most analyses have focused on modifying side chains attached to the amino and hydroxy functionalities with few attempts at modifying other aspects of the core structures [24–26]. In addition, most exploration

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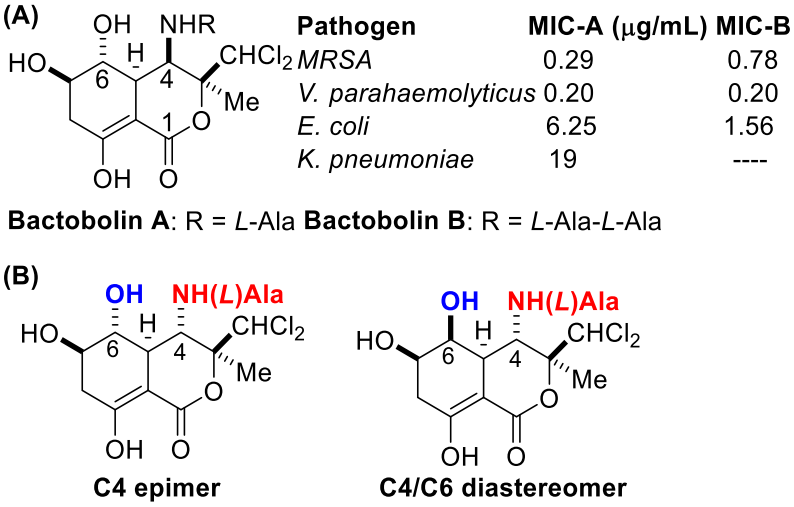
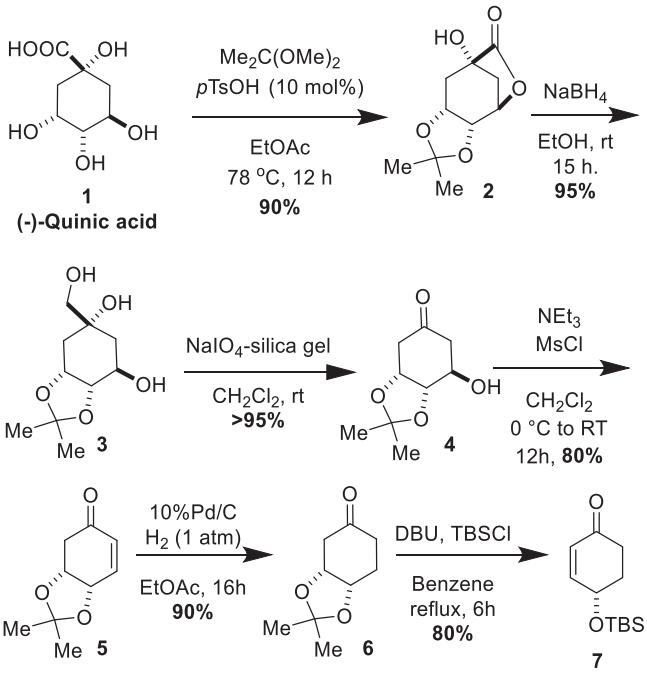


Fig. 1 **A** Bactobolin A is a potent antibiotic. **B** Analogs of Bactobolin A may have useful biological properties and may serve as tool compounds for studying the L2 protein of the bacterial ribosome (50S subunit)



Scheme 1 Opening sequence of reactions patterned on literature precedent

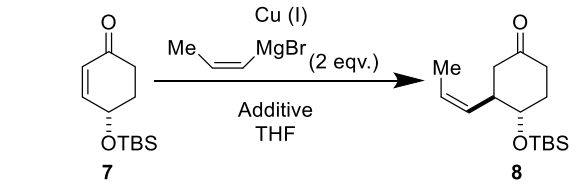
of Bactobolin analogs has centered on directly modifying the natural product, obtained from fermentation.

We were attracted to Bactobolin A because of its complex, functional-group laden architecture and its useful antibacterial activity. We were most interested in designing a route to access the C4 epimer and the C4/C6 diastereomer of Bactobolin A (Fig. 1). Docking studies (see *Results and Discussion* section) establish that these compounds interact with bacterial 23S rRNA differently from Bactobolin A, suggesting that these compounds may have divergent biological properties relative to the natural isomer. Furthermore, these molecules and their derivatives could serve as biological tool compounds for fundamental studies of the bacterial L2 protein, a rare and unique target for antibacterial action. It is unlikely that these unnatural isomers could be accessed from modifications of fermented Bactobolin A, making de novo synthesis necessary. We envisioned our laboratory's sulfamate-tethered *aza*-Wacker cyclization would serve as a key step in the construction of the 1,3-amino alcohol motif found in these analogs [4, 27, 28].

Results and discussion

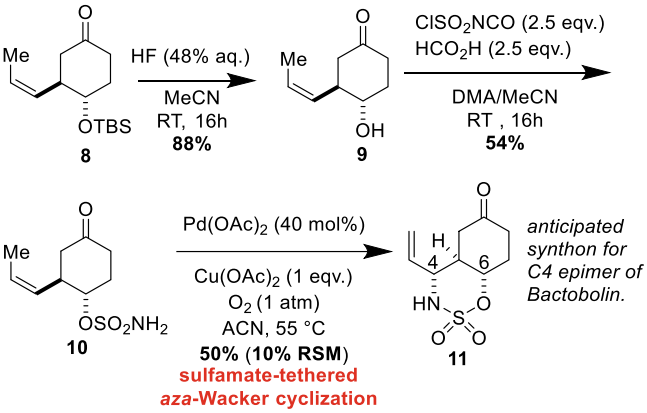
Our synthesis commenced from D-(-)-quinic acid, a commercially available cyclitol chiron (Scheme 1). Following literature precedent, quinic acid was transformed into tricyclic lactone **2**, which was reduced into triol **3** using $NaBH_4$ [29]. Cleavage with $NaIO_4$-impregnated silica gel,

Scheme 2 Optimization of a conjugate addition reaction of *cis*-1-propenyl magnesium bromide



Cu (I)	Additive	T (°C)/Time	Yield
1. $CuBr{\cdot}SMe_2$ (2.5 eqv.)	LiCl (2.5 eqv.)	-40 °C to RT/16h	40%
2. $CuBr{\cdot}SMe_2$ (2.5 eqv.)	LiCl (2.5 eqv.)	-20 °C to RT/16h	NR
3. $CuBr{\cdot}SMe_2$ (2.5 eqv.)	LiCl (2.5 eqv.)	0 °C to RT/16h	NR
4. CuCN (0.5 eqv.)	None	-78 °C/ 3h	45%
5. **CuCl (0.2 eqv.)**	**None**	**-78 °C/ 1h**	**60%**

Scheme 3 Tethered *aza*-Wacker technology furnishes an anticipated synthon for the C4 epimer of Bactobolin A



mesylation, and elimination afforded enone **5** [29]. Removal of the double bond proceeded smoothly with 10% Pd/C under 1 atm of H_2. Acetonide elimination coupled with in situ TBS protection of the resulting alkoxide afforded enone **7** [30].

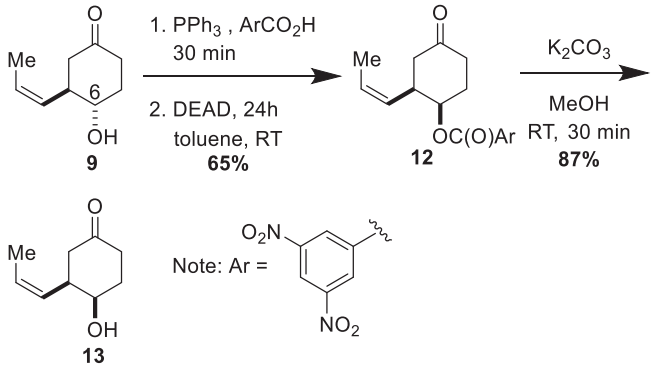
Diastereoselective conjugate addition of *cis*-1-propenyl magnesium bromide into enone **7** proved to be a challenge, as, curiously, there is sparse precedent for 1,4-addition with this reagent. We tested a variety of conditions, a portion of which are shown (Scheme 2). We were pleased to find that a combination of super-stoichiometric $CuBr{\bullet}SMe_2$, LiCl, and *cis*-1-propenyl-magnesium bromide afforded desired product **8** in 40% yield and as the single *trans*-diastereomer (Scheme 2, **Entry 1**). Attempts to further optimize this transformation using variations in temperature were invariably unsuccessful (Scheme 2, **Entries 2-3**). We observed a modest improvement in yield upon switching to CuCN, eliminating LiCl, and reducing the temperature to −78 °C (Scheme 2, **Entry 4**). The most dramatic improvement in this reaction was afforded by switching to catalytic CuCl (Scheme 2, **Entry 5**). With only 0.2 equivalents, the reaction was complete within 1 h at −78 °C. Importantly, these optimized conditions could be used reliably on scales as large as one gram, allowing for more convenient material throughput. We note that the use of *cis*-1-propenyl-magnesium bromide was *critical* for achieving high diastereoselectivity in the conjugate addition. Using commercial preparations containing undisclosed ratios of *cis*- and *trans*-1-propenyl magnesium bromide afforded intractable mixtures of diastereomers and geometric isomers.

Removal of the TBS group proceeded smoothly with aqueous HF affording alcohol **9** (Scheme 3). Sulfamoyl chloride was generated upon treatment of chlorosulfonyl isocyanate with formic acid [31] after which a solution of **9** in DMA was added, forming sulfamate **10**. To our delight (and perhaps some relief), the sulfamate-tethered *aza*-Wacker cyclization of **10** afforded oxathiazinane **11** in synthetically useful yields and as a single diastereomer. We anticipate that **11** will serve as a key synthon for future elaboration into C4-*epi*-Bactobolin.

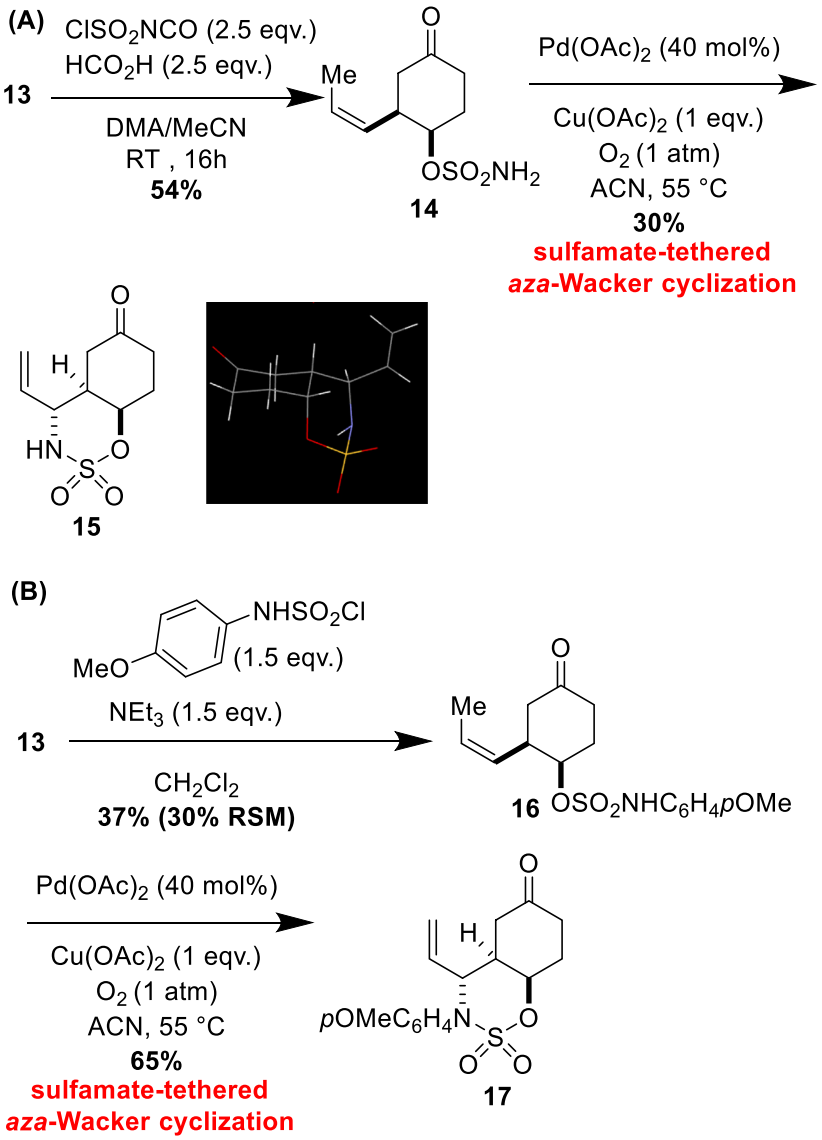
In order to invert the C6 stereocenter, a Mitsunobu protocol involving pre-treatment of **9** with PPh_3 and 3,5-dinitrobenzoic acid followed by addition of DEAD was developed (Scheme 4) [32]. Rapid hydrolysis of the 3,5-dinitrobenzoate ester occurred upon addition of K_2CO_3 in anhydrous MeOH.

Condensation of **13** with sulfamoyl chloride in a mixture of DMA/acetonitrile yielded primary sulfamate **14** (Scheme 5). Treatment with 40 mol% of $Pd(OAc)_2$ and 1 equivalent of $Cu(OAc)_2$ under 1 atmosphere of O_2 afforded bicyclic oxathiazinane **15** in a modest yield of

Scheme 4 Mitsunobu inversion of the C6 alcohol



Scheme 5 C4/C6 diastereomer synthons. **A** *aza*-Wacker cyclization reaction of primary sulfamate **14**. **B** Using *p*OMe-phenyl sulfamate **16** dramatically improves the yield of the tethered *aza*-Wacker cyclization reaction



30%. X-ray crystallography (CCDC Number: 2045973) established its absolute configuration. Our previous work has shown that primary sulfamates perform poorly in the *aza*-Wacker cyclization relative to secondary sulfamates [4]. Accordingly, we prepared *N*-*p*OMe-phenyl sulfamate **16** via condensation of **13** with *p*OMe-phenylsulfamoyl chloride and NEt_3. In line with our previous results, we found a dramatic improvement in reaction performance

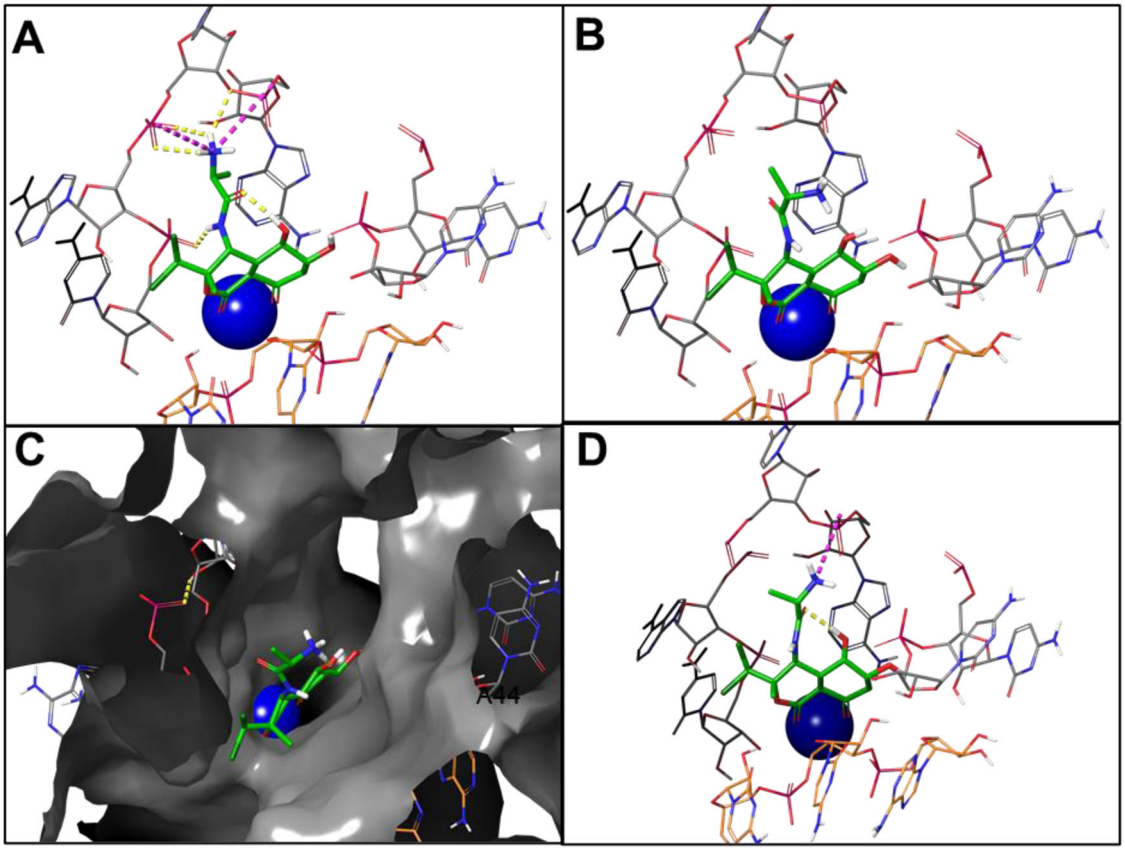


Fig. 2 **A** Bactobolin A binds in a cleft between the 23S rRNA (gray sticks) and the tRNA (orange sticks), coordinating with a magnesium ion (blue sphere) and forming several internal and external hydrogen bonds (yellow dashes) and salt bridge interactions (magenta dashes). **B** The Bactobolin epimer is oriented away from the sub-pocket, interacting with different regions of the rRNA. **C** The space fill representation with the Bactobolin epimer suggests the potential to interrogate other sub-pockets. **D** The C4/C6 diastereomer regains interactions that were lost in the C4 epimer

when sulfamate **16** was subject to the *aza*-Wacker protocol, with oxathiazinane **17** forming in 65% yield. There is ample precedent for oxidative removal of *p*OMe-phenyl groups from amines [33, 34] and amides [35, 36]; we anticipate analogous deprotection at some later stage of the synthesis of the C4/C6 diastereomer.

Docking studies (Fig. 2) of Bactobolin, the C4 epimer, and the C4/C6 diastereomer show that the three molecules interact with the 23S rRNA (bacterial ribosome 50S subunit) in different regions. All three coordinate to a Mg^{2+} ion and form van der Waals interactions with the bacterial 23S rRNA. With Bactobolin A, the alanine side chain is oriented towards a small sub-pocket (Fig. 2A). With both the C4 epimer (Fig. 2B, C) and the C4/C6 diastereomer (Fig. 2D), the alanine residue is pointed towards a larger open space. Thus, appending longer side chains onto the nitrogen would allow for interrogation of different regions of the 23S rRNA. This suggests that both analogs could have divergent biological properties relative to Bactobolin A and that they could serve as valuable tool compounds for fundamental studies of the bacterial ribosome L2 protein, an unusual and rare antibiotic target. Such data gives us the impetus to continue pursuing analogs-oriented syntheses of the Bactobolin family.

Conclusion

In summary, we present our progress towards analogs of Bactobolin A. Stereospecific sulfamate-tethered *aza*-Wacker cyclization reactions furnish key synthons, which we envision can be elaborated into the C4 epimer and the C4/C6 diastereomer. Docking studies show that these isomers interact with the bacterial 23S rRNA in disparate ways relative to Bactobolin A, suggesting that access to these molecules could provide valuable tool compounds for fundamental biological studies of the bacterial ribosome.

Experimental section

All reagents were obtained commercially unless otherwise noted. Solvents were purified by passage under 10 psi N_2

through activated alumina columns. Infrared (IR) spectra were recorded on a Thermo Scientific™ Nicolet™ iS™5 FT-IR Spectrometer; data are reported in frequency of absorption (cm^{-1}). Optical rotations were determined by a Rudolph Polarimeter AUTOPOL IV. NMR spectra were recorded on a Bruker Avance 400 operating at 400 and 100 MHz. ^{1}H NMR spectra were recorded at 400 MHz. Data are recorded as: chemical shift in ppm referenced internally using residue solvent peaks, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet or overlap of nonequivalent resonances), integration, coupling constant (Hz). ^{13}C NMR spectra were recorded at 100 MHz. Exact mass spectra were recorded using an electrospray ion source (ESI) either in positive mode or negative mode and with a time-of-flight (TOF) analyzer on a Waters LCT PremierTM mass spectrometer and are given in m/z. TLC was performed on pre-coated glass plates (Merck) and visualized either with a UV lamp (254 nm) or by dipping into a solution of $KMnO_4$–K_2CO_3 in water followed by heating. Flash chromatography was performed on silica gel (230–400 mesh). (-)-Quinic acid was purchased from ACROS and *cis*-1-bromo propene was purchased from Sigma-Aldrich. Compounds **2-7** were prepared using reported procedures [29, 30].

(3*R*,4*S*)-4-((*tert*-butyldimethylsilyl)oxy)-3-((*Z*)-prop-1-en-1-yl)cyclohexan-1-one (8)

To a solution of CuCl (87.4 mg, 0.884 mmol, 0.2 equiv.) in dry THF (5 mL) was added freshly prepared (Z)-prop-1-en-1-ylmagnesium bromide (0.44 M in THF, 20 mL, 8.8 mmol, 2.4 equiv.) at −78 °C. A solution of **7** (1 g, 4.42 mmol) in THF (3 mL) was added to the reaction mixture at −78 °C and the resulting mixture was stirred for 1 h at same temperature. After 1 h, the reaction was quenched with saturated aqueous ammonium chloride (40 mL) at 0 °C. The mixture was transferred to a separatory funnel. The organic layer was removed, and the aqueous layer was extracted with ethyl acetate (2 × 100 mL). The combined organic layers were washed with brine solution (50 mL), dried over anhydrous Na_2SO_4, filtered, and the solvent was removed in vacuo. The residue was purified through silica gel column chromatography (hexane/ethyl acetate = 95:5) to afford 700 mg (60%) of **8** as a colorless oil. $[\alpha]_D = +39.82$ (*c* 0.625, $CHCl_3$); FT-IR (KBr): 3012, 2958, 2886, 1717, 1471 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 5.52 (ddd, *J* = 10.8, 6.9, 1.2 Hz, 1H), 5.14 (ddd, *J* = 11.0, 9.5, 1.8 Hz, 1H), 3.78 (td, *J* = 5.8, 2.9 Hz, 1H), 2.99 (dddd, *J* = 11.8, 6.5, 5.4, 4.2 Hz, 1H), 2.70 (ddd, *J* = 14.1, 5.4, 1.6 Hz, 1H), 2.61 (dddd, *J* = 14.3, 9.9, 5.9, 1.7 Hz, 1H), 2.25 (dddd, *J* = 14.2, 6.9, 5.3, 1.9 Hz, 1H), 2.18 – 1.98 (m, 2H), 1.85 (dqd, *J* = 13.7, 5.9, 1.3 Hz, 1H), 1.62 (dd, *J* = 6.9, 1.8 Hz, 3H), 0.90 (s, 9H), 0.09 (d, *J* = 2.3 Hz, 6H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 211.4, 130.6, 126.3, 70.4, 43.1, 42.9, 37.4, 31.7, 25.9, 18.1, 13.3, −4.5. HRMS calculated for $C_{15}H_{28}O_2SiNa^+$ 291.1756 Found 291.1745 (MNa^+).

(3R,4S)-4-hydroxy-3-((Z)-prop-1-en-1-yl)cyclohexan-1-one (9)

48% aq. HF (4 mL) was added dropwise to a solution of compound **8** (500 mg, 1.86 mmol) in acetonitrile (40 mL) (Note: teflon tube) at 0 °C. The resulting solution was stirred at room temperature for 16 h. After 16 h, the reaction mixture was cooled to 0 °C and quenched with saturated $NaHCO_3$ (20 mL). The reaction mixture was transferred to a separatory funnel. The organic layer was removed, and the aqueous layer was extracted with DCM (3 × 20 mL). The combined organic layers were washed with brine solution (2 × 20 mL), dried over anhydrous Na_2SO_4, filtered, and the solvent was removed in vacuo. The residue was purified through silica gel column chromatography (hexane/ethyl acetate = 60:40) to afford 250 mg (1.62 mmol, 88%) of **9** as a white solid. $[\alpha]_D = +124$ (*c* 0.5, $CHCl_3$); FT-IR (KBr): 3416, 3017, 2825, 1705, 1420 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.74 (dqd, *J* = 10.8, 6.9, 1.0 Hz, 1H), 5.22 (ddt, *J* = 12.6, 9.7, 1.8 Hz, 1H), 3.75 (ddd, *J* = 10.1, 8.9, 3.9 Hz, 1H), 2.88 – 2.77 (m, 1H), 2.52 – 2.40 (m, 2H), 2.40 – 2.35 (m, 1H), 2.32 – 2.26 (m, 1H), 2.22 (ddd, *J* = 14.7, 11.8, 1.1 Hz, 1H), 1.86 – 1.76 (m, 2H), 1.68 (dd, *J* = 6.9, 1.8 Hz, 3H).; ^{13}C NMR (101 MHz, $CDCl_3$) δ 209.4, 130.1, 128.9, 71.6, 44.1, 43.6, 38.7, 32.0, 13.5. HRMS calculated for $C_9H_{14}O_2Na^+$ 177.0892 Found 177.0896 (MNa^+).

(1S,2R)-4-oxo-2-((Z)-prop-1-en-1-yl)cyclohexyl sulfamate (10)

Formic acid (61 µL, 1.62 mmol, 2.5 equiv.) was added to neat Chlorosulfonyl isocyanate (140 µL, 1.62 mmol, 2.5 equiv.) at 0 °C and the mixture was stirred for 5 minutes. Vigorous gas evolution was observed during the addition, and the mixture turned into a white solid after 5 to 10 minutes. Anhydrous acetonitrile (2 mL) was added to the solid. The resulting solution was stirred at room temperature for 12 h. After 12 h, the reaction mixture was cooled to 0 °C, and alcohol **9** (100 mg, 0.649 mmol) dissolved in 0.5 mL of DMA was added dropwise using a syringe. The resulting solution was stirred at room temperature for 5 h. The reaction was quenched with ice water (10 mL). The reaction mixture was transferred to a separatory funnel, the organic layer was separated, and the aqueous layer was extracted with ethyl acetate (2 × 10 mL). The combined organic layers were washed with brine solution (2 × 10 mL), dried over anhydrous Na_2SO_4, filtered, and the solvent was removed in vacuo. The residue was purified through silica gel column chromatography (hexane/ethyl acetate = 50:50)

to afford 82 mg (54%) of **10** as a colorless oil. $[\alpha]_D = +18.5$ (*c* 0.4, $CHCl_3$); FT-IR (KBr): 3260, 2910, 1710, 1210 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 5.65 (dqd, *J* = 10.7, 6.9, 1.2 Hz, 1H), 5.20 (ddq, *J* = 11.0, 9.3, 1.8 Hz, 1H), 4.97 (s, 2H), 4.70 (td, *J* = 6.4, 3.1 Hz, 1H), 3.42 – 3.30 (m, 1H), 2.74 – 2.53 (m, 2H), 2.45 – 2.28 (m, 2H), 2.22 (tddd, *J* = 13.8, 7.3, 4.7, 1.4 Hz, 2H), 1.68 (dd, *J* = 6.9, 1.8 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 208.6, 128.7, 128.1, 81.1, 42.9, 40.1, 37.1, 28.8, 13.3. HRMS calculated for $C_9H_{15}NO_4SNa^+$ 256.0620 Found 256.0617 (MNa^+).

(1R,2R)-4-oxo-2-((Z)-prop-1-en-1-yl)cyclohexyl 3,5-dinitrobenzoate (12)

A mixture of **9** (0.4 g, 2.59 mmol), PPh_3 (3.4 g, 12.98 mmol, 5 equiv.) and 3,5-dinitro-benzoic acid (2.75 g, 12.98 mmol, 5 equiv.) in dry toluene (40 mL) was stirred at room temperature for 30 min under N_2 atmosphere. After 30 min, diethyl azodicarboxylate (2 mL, 12.74 mmol, 5 equiv.) was added dropwise to the reaction mixture at 0 °C. The resulting mixture was stirred at room temperature for 24 h under N_2 atmosphere. After 24 h, the reaction mixture was concentrated under reduced pressure. The residue was taken in 20% EtOAc/hexanes (200 mL) and filtered through a celite pad. The filtrate was concentrated under reduced pressure. The resulting residue was purified through silica gel column chromatography (hexane/ethyl acetate = 85:15) to afford 588 mg (1.69 mmol, 65%) of **12** as a white solid. $[\alpha]_D = -91.0$ (*c* 0.5, $CHCl_3$); FT-IR (KBr): 3110, 3023, 1712, 1719, 1460 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 9.26 (t, *J* = 2.1 Hz, 1H), 9.14 (d, *J* = 2.2 Hz, 2H), 5.68 – 5.59 (m, 1H), 5.52 (dt, *J* = 5.8, 3.1 Hz, 1H), 5.37 (ddt, *J* = 12.7, 9.3, 1.8 Hz, 1H), 3.30 (tt, *J* = 9.4, 4.5 Hz, 1H), 2.69 – 2.52 (m, 3H), 2.47 (dddd, *J* = 14.8, 13.3, 8.1, 3.5 Hz, 2H), 2.17 (ddt, *J* = 16.3, 9.6, 3.9 Hz, 1H), 1.65 (dd, *J* = 6.9, 1.8 Hz, 3H); ^{13}C NMR (126 MHz, $CDCl_3$): δ 208.2, 162.1, 148.9, 133.9, 129.4, 127.9, 127.3, 122.8, 74.2, 43.3, 38.6, 36.5, 28.9, 13.4; HRMS calculated for $C_{16}H_{16}N_2O_7Na^+$ 371.0855 Found 371.0855 (MNa^+).

(3R,4R)-4-hydroxy-3-((Z)-prop-1-en-1-yl)cyclohexan-1-one (13)

A mixture of **12** (0.350 g, 1 mmol) and K_2CO_3 (207 mg, 1.5 mmol, 1.5 equiv.) in dry methanol (10 mL) was stirred at room temperature for 1 h. After 1 h, the solvent was evaporated under reduced pressure. The resulting residue was dissolved in DCM and extracted with 1 N HCl (30 mL). The organic layer was separated, and the aqueous layer was extracted with DCM (2 × 40 mL). The combined organic layers were washed with brine solution (2 × 20 mL), dried over anhydrous Na_2SO_4, filtered, and the solvent was removed in vacuo. The residue was purified through silica gel column chromatography (hexane/ethyl acetate = 1:1) to afford 134 mg (0.87 mmol, 87%) of **13** as a colorless oil. $[\alpha]_D = +26.4$ (*c* 0.5, $CHCl_3$); FT-IR (KBr): 3450, 3012, 2958, 2886, 1717, 1471 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 5.60 (ddddd, *J* = 10.8, 8.1, 6.8, 5.6, 1.3 Hz, 1H), 5.42 (ddq, *J* = 11.0, 9.2, 1.8 Hz, 1H), 4.02 (dt, *J* = 4.7, 2.7 Hz, 1H), 2.99 – 2.89 (m, 1H), 2.71 – 2.54 (m, 2H), 2.29 – 2.17 (m, 2H), 2.12 (ddt, *J* = 14.7, 5.9, 4.4 Hz, 1H), 2.03 (d, *J* = 9.6 Hz, 1H), 1.91 (tdd, *J* = 13.8, 5.2, 2.6 Hz, 1H), 1.62 (dt, *J* = 6.9, 1.5 Hz, 3H);^{13}C NMR (101 MHz, $CDCl_3$) δ 211.3, 129.3, 126.9, 68.3, 42.4, 40.8, 36.0, 32.4, 13.4; HRMS calculated for $C_9H_{14}O_2Na^+$ 177.0892 Found 177.0894 (MNa^+).

(1R,2R)-4-oxo-2-((Z)-prop-1-en-1-yl)cyclohexyl sulfamate (14)

Formic acid (61 µL, 1.62 mmol, 2.5 equiv.) was added to neat chlorosulfonyl isocyanate (140 µL, 1.62 mmol, 2.5 equiv.) at 0 °C and the mixture was stirred for 5 minutes. Vigorous gas evolution was observed during the addition, and the mixture turned into a white solid after 5–10 min. Anhydrous acetonitrile (2 mL) was added to the solid. The resulting solution was stirred at room temperature for 12 h. After 12 h, the reaction mixture was cooled to 0 °C, and alcohol **13** (100 mg, 0.65 mmol) dissolved in 0.5 mL of DMA was added dropwise using a syringe. The resulting solution was stirred at room temperature for 5 h. The reaction was quenched with ice water (10 mL) and transferred to a separatory funnel. The organic layer was separated, and then the aqueous layer was extracted with ethyl acetate (2 × 10 mL). The combined organic layers were washed with brine solution (2 × 10 mL), dried over anhydrous Na_2SO_4, filtered, and the solvent was removed in vacuo. The residue was purified through silica gel column chromatography (hexane/ethyl acetate = 1:1) to afford 82 mg (0.35 mmol, 54%) of **14** as a colorless oil. $[\alpha]_D = -38.2$ (*c* 0.5, $CHCl_3$); FT-IR (KBr): 3264, 2926, 1708, 1180 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 5.63 (dq, *J* = 10.7, 6.9 Hz, 1H), 5.45 (ddq, *J* = 10.8, 9.0, 1.8 Hz, 1H), 4.94 (d, *J* = 6.8 Hz, 2H), 4.83 (d, *J* = 2.4 Hz, 1H), 3.13 – 3.01 (m, 1H), 2.78 – 2.49 (m, 3H), 2.33 (dddd, *J* = 29.9, 14.8, 4.9, 2.3 Hz, 2H), 2.00 (dddd, *J* = 14.8, 12.9, 6.2, 2.3 Hz, 1H), 1.65 (dd, *J* = 6.9, 1.8 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 209.0, 128.1, 127.2, 80.3, 42.4, 39.5, 35.6, 30.0,13.3; HRMS calculated for $C_9H_{15}NO_4SNa^+$ 256.0620 Found 256.0618 (MNa^+).

(1R,2R)-4-oxo-2-((Z)-prop-1-en-1-yl)cyclohexyl(4-methoxyphenyl)sulfamate (16)

A mixture of **13** (0.1 g, 0.649 mmol) and (4-methoxyphenyl)sulfamoyl chloride (214 mg, 0.973 mmol, 1.5 equiv.) in dry DCM (3 mL) was added NEt_3 (0.135 mL,

0.973 mmol, 1.5 equiv.) at 0 °C. The reaction mixture was stirred at room temperature for 12 h. Then, the reaction was quenched with cold water (20 mL). The mixture was transferred to a separatory funnel, the organic layer was separated, and then the aqueous layer was extracted with DCM (2 × 15 mL). The combined organic layers were washed with brine solution (15 mL), dried over anhydrous Na_2SO_4, filtered, and the solvent was removed in vacuo. The residue was purified through silica gel column chromatography (hexane/ethyl acetate = 70:30) to afford 82 mg (37%) of **16** as a semi solid. $[\alpha]_D = -41.2$ (*c* 0.5, $CHCl_3$); FT-IR (KBr): 3288, 2965, 1708, 1511 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.22 – 7.16 (m, 2H), 6.91 – 6.85 (m, 2H), 6.63 (s, 1H), 5.47 (dqd, *J* = 10.8, 6.9, 1.1 Hz, 1H), 5.25 (ddq, *J* = 10.8, 9.0, 1.8 Hz, 1H), 4.80 (q, *J* = 2.7 Hz, 1H), 3.80 (s, 3H), 2.98 (td, *J* = 8.9, 7.3, 3.9 Hz, 1H), 2.54 – 2.34 (m, 3H), 2.24 (ddd, *J* = 15.0, 5.3, 3.2 Hz, 2H), 1.95 – 1.80 (m, 1H), 1.57 (dd, *J* = 6.9, 1.8 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 208.7, 158.0, 128.6, 127.7, 126.8, 124.1, 114.7, 80.6, 55.5, 42.3, 39.5, 35.4, 29.8, 13.1; HRMS calculated for $C_{16}H_{20}NO_5S^-$ 338.1068 Found 338.1010 (M-H).

General procedure for sulfamate-tethered *aza*-Wacker cyclization

A 10 mL microwave vial containing a magnetic stir-bar was charged with sulfamate [**10**, **14** or **16**] (0.1 mmol), $Pd(OAc)_2$ (0.04 mmol, 0.4 equiv.), and $Cu(OAc)_2$ (0.1 mmol, 1 equiv.) in 2 mL of acetonitrile (final concentration 0.05 M). The reaction vial was sealed and then evacuated and backfilled with oxygen three times. The reaction vessel was then submerged in an oil bath preheated to 55 °C and kept at this temperature under a balloon of O_2 (~1 atm) for 16 h. After 16 h, the reaction mixture was cooled to room temperature and filtered through a small plug of silica. The silica plug was further rinsed with DCM (10 mL). The solvent was removed under reduced pressure. The resulting residue was purified with silica gel chromatography (gradient of 20 to 30% ethyl acetate in hexanes) to afford the cyclized product [**11**, **15** and **17**] in pure form.

(4R, 4aR,8aS)-4-vinylhexahydrobenzo[e][1,2,3]oxathiazin-6 (5H)-one 2,2-dioxide (11)

Following the general procedure, compound **10** (23 mg, 0.1 mmol) furnished cyclized product **11** (11.5 mg, 0.05 mmol, 50%) as an off white solid. $[\alpha]_D = +12.11$ (*c* 1, $CHCl_3$); FT-IR (KBr): 3260, 2910, 1710, 1210 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 5.69 – 5.56 (m, 1H), 5.44 – 5.35 (m, 2H), 4.88 (ddd, *J* = 11.6, 10.4, 4.1 Hz, 1H), 4.50 (d, *J* = 9.3 Hz, 1H), 4.08 – 3.96 (m, 1H), 2.63 – 2.43 (m, 3H), 2.40 (dddd, *J* = 14.9, 6.6, 4.0, 2.3 Hz, 1H), 2.14 – 2.02 (m, 1H), 2.05 – 1.83 (m, 2H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 205.4, 131.9, 121.7, 82.9, 62.1, 42.2, 40.4, 38.6, 30.2; HRMS calculated for $C_9H_{12}NO_4S^-$ 230.0487 Found 230.0461 (M-H).

(4*S*,4a*R*,8a*R*)-4-vinylhexahydrobenzo[e][1,2,3]oxathiazin-6 (5H)-one 2,2-dioxide (15)

Following the general procedure, compound **10** (46 mg, 0.2 mmol) furnished cyclized product **11** (13.6 mg, 0.06 mmol, 30%) as an off white solid $[\alpha]_D = +10.0$ (*c* 0.35, $CHCl_3$); FT-IR (KBr): 3264, 2926, 1708, 1180 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 6.31 (ddd, *J* = 17.2, 10.6, 6.3 Hz, 1H), 5.38 – 5.28 (m, 2H), 5.22 (q, *J* = 2.9 Hz, 1H), 5.02 (d, *J* = 6.0 Hz, 1H), 3.82 – 3.70 (m, 1H), 2.92 – 2.79 (m, 1H), 2.73 – 2.60 (m, 1H), 2.49 (dddd, *J* = 15.0, 6.2, 3.7, 2.3 Hz, 1H), 2.44 – 2.31 (m, 2H), 2.25 – 2.12 (m, 1H), 2.03 (dddd, *J* = 15.0, 13.8, 5.1, 2.7 Hz, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 207.7, 134.9, 118.8, 77.5, 61.4, 40.4, 38.8, 35.4, 30.0; HRMS calculated for $C_9H_{12}NO_4S^-$ 230.0487 Found 230.0476 (M-H).

(4*S*,4a*R*,8a*R*)-3-(4-methoxyphenyl)-4-vinylhexahydrobenzo [e][1,2,3]oxathiazin-6(5H)-one-2,2-dioxide (17)

Following the general procedure, compound **10** (34 mg, 0.1 mmol) furnished cyclized product **17** (22 mg, 0.065 mmol, 65%) as an off-white solid. $[\alpha]_D = +18.6$ (*c* 0.5, $CHCl_3$); FT-IR (KBr): 2954, 2922, 1708, 1509, 1169 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 7.26 – 7.23 (m, 2H), 6.91 – 6.86 (m, 2H), 6.69 (ddd, *J* = 17.1, 10.3, 9.0 Hz, 1H), 5.45 (d, *J* = 3.1 Hz, 1H), 5.32 – 5.27 (m, 1H), 5.05 – 4.99 (m, 1H), 3.80 (s, 3H), 3.72 – 3.64 (m, 1H), 3.29 (t, *J* = 13.8 Hz, 1H), 2.76 (td, *J* = 14.4, 6.5 Hz, 1H), 2.62 – 2.36 (m, 3H), 2.31 – 2.23 (m, 1H), 2.05 (tdd, *J* = 14.3, 5.1, 2.5 Hz, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 207.8, 159.7, 133.8, 131.9, 129.7, 120.7, 114.9, 77.9, 72.2, 55.6, 41.9, 41.0, 35.4, 30.0. HRMS calculated for $C_{16}H_{18}NO_5S^-$ 336.0911 Found 336.0872 (M-H).

Docking studies The structure of Bactobolin A bound to the *T. thermophilus* 70S ribosome-tRNA complex [15] was downloaded from the PDB (PDB ID 4WT8). Because of the size of the complex relative to the size of the interaction site, no residues/bases within 10 Å of Bactobolin were removed, leaving the 23S rRNA, the tRNA, the L2 protein subunit, and the L27 protein subunit. The resulting reduced complex was prepared for modeling using Schrodinger's Protein Preparation Wizard, which adds hydrogens, removes H_2O molecules, optimizes hydrogen bonds, and performs a constrained minimization [37]. A dockable "receptor" was created and centered on Bactobolin A, with a metal coordination constraint with the magnesium ion.

Ligands were prepared using LigPrep, which calculates potential ionization and tautomerization states [37], and these were docked using Glide [38–40] with XP precision. In these docking studies, a core constraint of the fused ring substructure and a metal binding constraint were applied.

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Compliance with ethical standards

Conflict of interest The authors declare no competing interests.

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