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Synthetic studies towards Zetekitoxin AB: preparation of 4,5-epi-11-hydroxy-saxitoxinol

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Abstract

A concise synthesis of 4,5-epi-11-hydroxy-saxitoxinol utilizing D-ribose to direct an asymmetric Mannich reaction. This approach allows many modes of reactivity, which can be used to access various analogs of saxitoxin.

Keywords

Saxitoxin; Zetekitoxin AB; Mannich reaction; Sodium channel; Diamino acid

1. Introduction

Saxitoxin (**2**) and its analogs have attracted the interest of organic chemists due to its dense, heteroatom-rich structure.[1–10] Zetekitoxin AB (**1**), isolated from Panamanian golden frog (*Atelopus zeteki*), was found to be an analog of saxitoxin however, significantly more biologically potent.[11] Due to the endangerment of the Panamanian golden frog there is no source of Zetekitoxin AB, preventing further studies. Due to the complexity, potency and rarity of this molecule we were attracted to tackling the challenge of its synthesis.

Our retrosynthetic analysis reveals that Zetekitoxin AB could arise from core structure **4**. This substrate could arise from the condensation of two guanidines on a central carbonyl and the nucleophilic ring-closure on carbon-10, displacing a leaving group (Scheme 1). Ketone **5** could be derived from protected diamino ester **6**, which in turn could be formed from a Mannich-type reaction on ribose-derived imine **7**. The Mannich precursor could be formed from D-ribose (**8**) in a few steps.

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Supplementary Material
Supplementary data associated with this Letter can be found, in the online version, at doi:xxxxxxx.

2. Results and Discussion

D-Ribose was treated with sulfuric acid, benzyl alcohol and acetone to give the corresponding O-benzyl-protected ribose acetal, which was oxidized with TEMPO and TCC to give aldehyde **9** (Scheme 2). This aldehyde was converted to several benzyl imines or oximes and then added to a solution of the enolate of glycine template **11**, resulting only in the recovery of starting material.

These results indicated that imines or oximes were not electrophilic enough, so more reactive imines were sought out. Since carbamates are good electron-withdrawing groups and versatile amine protecting groups it was thought that N-acylimines would constitute a suitable Mannich substrate. A literature survey revealed that the N-acylimines are generally not stable, but they could be masked and generated *in situ*. Amido sulfones, in particular, seemed to be the most promising because they are stable and can be prepared with mild conditions.[12]

When ribose-derived aldehyde **9** was treated with *tert*-butyl carbamate, phenylsulfinic acid, and anhydrous magnesium sulfate in dichloromethane, amido sulfone **10** was generated in good yield (Scheme 2).[13] Amido sulfone **10** was added to the enolate of glycine template **11** giving desired Mannich product **12** in good yield and as a single diastereomer. The absolute stereochemistry of product **12** was determined by X-ray crystallography.

With Mannich product **12** in hand, the Boc group was removed *via* Ohfune's conditions followed by the hydrolysis of the benzophenone imine to give the diamine. This diamine was then guanidinylated with reagent **13**, mercuric chloride and triethylamine in DMF to give bisguanidine **14** (Scheme 3). Hydrogenation of compound **14**, followed by reduction of the lactol gave the diol, which was selectively protected with TBSOTf. The resulting alcohol was then oxidized to the ketone using Dess-Martin's periodinane giving ketone **15**, which embodies all the functionality to make the core of Zetekitoxin AB.

With ketone **15** in hand the next step was removal of the methyl carbamate protecting groups, followed by treatment with an acid to form bicyclic species **16** (Scheme 4). This bicyclic substance could then be submitted to Mitsunobu conditions giving compound **17**. This promising synthetic approach was abandoned at this stage because another approach, being run in parallel, showed greater potential.

Starting with Mannich product **12,** the benzophenone imine was hydrolyzed and then treated with methyl chloroformate to give methyl carbamate **18** (Scheme 5). The ethyl ester was then reduced with lithium borohydride giving a mixture of oxazolidinone **19** and the primary alcohol. This mixture could be converted to oxazolidinone **19** by heating in a solution of potassium hydroxide in methanol.

Exposure of oxazolidinone **19** to Ohfune's conditions afforded the corresponding amine, which was then guanidinylated with reagent **20** giving oxazolidinone **21** in good yield (Scheme 6). The benzyl ether was then removed *via* hydrogenation at high pressure with Pearlman's catalyst to give lactol **22**.

Installation of an amino group at the lactol position was not as straightforward as expected. Initial attempts for a one pot reductive amination failed, so a two-step procedure was utilized. Treatment of the lactol **22** with hydroxylamine-HCl and sodium acetate afforded the corresponding oxime. The oxime proved recalcitrant to reduction with a number of hydride reducing reagents or by hydrogenation with either palladium or platinum catalysts. The best conditions found to reduce the oxime was hydrogenation over Raney nickel (Scheme 7). Unfortunately, the yield of amine **23** was only 25% over the two steps and suffered from poor reproducibility.

After screening many conditions, a one-pot reductive amination protocol was developed. When lactol **22** was stirred with a benzyl amine and sodium cyanoborohydride in methanol there was no reaction. It was discovered that adding ~150 equivalents of acetic acid to the reaction gave the desired amine, in a reasonable amount of time (Scheme 8). Many different benzylamines were tested however the o-nitrobenzyl (oNB) was the only protecting group that proved later, could be removed efficiently.

Amines **23** and **24** were elaborated to nine-membered ring species **26** and **27** in a one-pot reaction (Scheme 9). This was accomplished by the treatment of the amine with reagent **25** followed by a mercury-promoted cyclization and ring opening of the resulting oxazolidinone with ammonia in water. These nine-membered ring structures are reminiscient of the intermediate in DuBois's elegant synthesis of saxitoxin.[5,6] Alcohols **26** and **27** were efficiently oxidized to ketone **28** and **29** with Dess-Martin periodinane. Ketone **28** spontaneously undergoes ring contraction to give hemiaminal **30,** as a mixture of diastereomers, due to the lack of the benzyl-protecting group. Irradiating compound **29** with UV light cleanly afforded the desired free guanidine which cyclized to the hemiaminal **30**.

The first reaction conditions tested to enact the global deprotection and cyclization to the tricycle was 0.5M $B(TFA)_3$ in TFA, which had literature precedence.[6] Unfortunately, these conditions failed to give the desired result. To simplify this complex reaction a stepwise approach was taken allowing each individual product to be characterized. Treatment of the mixture of **29/30** with 6M HCl in methanol gave a single product. This product showed loss of the Boc groups, the acetonide and a water molecule by NMR and MS analysis. The NMR spectrum indicated the presence of an olefin, but no hemiaminal or aminal. Since the identity of the compound couldn't be determined easily, it was treated with TFA. This product still contained the olefin and showed the loss of another water molecule. Since hemiaminal **30** is presumably in equilibrium with ketone **29**, two different pathways can be imagined (Scheme 10). Hemiaminal **30** could lose both Boc groups and the acetonide followed by dehydration to form enamine **31**. A very similar pathway could occur with ketone **29** giving enamine **35**. These enamines when treated with TFA also could undergo very similar reactions. Elimination of water could give reactive intermediates **32** or **36**, which could then cyclize to compound **33** or **37**. These compounds are structurally similar and distinguishing between them by NMR proved to be not straightforward.

To identify the pathway that is operative we endeavored to narrow down the possibilities (Scheme 11). Leaving the o-NB protecting group intact until after the cyclizations eliminated the possibility of pathway A. Treatment of compound **28** with 6M HCl/MeOH

followed by uv irradiation gave compound **35** which matched the previously made substance. Furthermore, treatment of compound **35** with TFA led to compound **37**. These results indicated that pathway B was the preferred route.

This result although interesting was not synthetically useful for this synthesis. To avoid this side-reaction we speculated that if we could prevent z the hemiaminal **30** from opening to the 9-member ring we could force the compound through an alternative pathway, which might lead to the desired product. We envisioned that using an oxophilic reagent the hemiaminal could be stabilized. We decided to reexamine the $B(TFA)_3$ in TFA conditions because boron is very oxophilic and should be capable of trapping hemiaminal **30.** It was found that a slight modification in the procedure gave the desired result. Originally, the compound was cooled, dissolved in TFA and the $B(TFA)_3$ was added. It is presumed that the Boc deprotection is so fast that the more stable hemiaminal **34** was probably forming before the boron reagent was added. Instead, the $B(TFA)_3$ in TFA was added directly to a cooled mixture of **29**/**30**, which after stirring for 15h. resulted in the formation of tricycle **40** and enamine **41**.

This result was exciting, but the stereogenic centers at C-8 and C-9 in compound **40** possess the wrong configuration. It was reasoned that the enamine (**41**) formation might be reversible. If this is the case it could lead to epimerization of the incorrect stereogenic center and give the desired tricycle **43** which should be more stable than tricycle **40**, since its steric interactions between the newly formed 5-member spiro-guanidine ring and the proximal substituents could be obviated (Scheme 13).

Mixture **29**/**30** was allowed to stir for 48h, but instead of giving the desired tricycle, compound **44** was formed exclusively. Unfortunately, this reaction proved to be irreversible.

The undesirable elimination/cyclization steps could theoretically be slowed down with cooling, but unfortunately when the same reaction was stirred for 48h. at 4°C the result was a nearly 1:1 mixture of tricycle **40** and compound **44**. This result indicated that tricycle **40** was fairly stable and only a small fraction converted to enamine **41**, which easily eliminates water irreversibly giving the undesirable compound **44**. Compound **40** is of 4,5-epi-11-hydroxy-saxitoxinol.

3. Conclusions

In conclusion, we have explored a strategy for the synthesis of Saxitoxin analogs utilizing a diastereoselective Mannich-type reaction on a ribose-derived imine. This approach allows for the efficient assembly of the Saxitoxin backbone in four steps, which can be elaborated to the tricyclic core of Saxitoxin in a total of fifteen steps. Future efforts will focus on rectifying stereochemical issues at C-8 in the early stages of the synthesis.

4. Experimental

4.1 General

Unless otherwise noted, materials were obtained from commercial sources and used without purification. All reactions requiring anhydrous conditions were performed under positive

pressure of argon using flame dried glassware. Dichloromethane, diisopropylamine, triethylamine, tetrahydrofuran, dimethylformamide, diethyl ether, and toluene were degassed with argon and passed through a solvent purification system (J.C. Meyer of Glass Contour) containing either alumina or molecular sieves. Flash chromatography was performed on Merck silica gel Kieselgel 60 (230–400 mesh) from EM science with the indicated solvent.

^{1}H-NMR spectra were recorded on Varian, 300, 400, or 500 MHz spectrometers as indicated. The chemical shifts (δ) of proton resonances are reported relative to CDCl3, DMSO-d5, D_2O, CD_3OD, and acetone-d6 using the following format: chemical shift [multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet), coupling constant(s) (J in Hz), integral]. ^{13}C-NMR spectra were recorded at 100 or 125 MHz. The chemical shifts of carbon resonances are reported relative to the deuterated solvent peak, except D_2O, which was internally referenced.

Infrared spectra were recorded on a Bruker Tensor 27 FTIR spectrometer. All absorptions are reported in cm^{-1}. Spectra were recorded as films deposited from deuterated NMR solvent solutions on NaCl plates followed by solvent evaporation. Peaks reported in the IR are described using the following conventions: w = weak, m = medium, s = strong, vs = very strong, sh = shoulder, and br = broad.

Mass spectra were obtained at the Colorado State University CIF on a Fisons VG Autospec. Optical rotations were obtained with a 1mL, 1 dm cell on a Rudolf Research Autopol III polarimeter operating at 589 nm in $CHCl_3$. HPLC separations were obtained on a Waters 600E HPLC system using the indicated column and eluent conditions.

4.2 Experimental procedures

((3a*R*,4*R*,6*R*,6a*R*)-6-(benzyloxy)-2,2-dimethyltetrahydrofuro[3,4-*d*] [1,3]dioxol-4-yl)methanol (8a)—To a suspension of D-ribose (150 g) in benzyl alcohol (990 mL) and acetone (600 mL) was added sulfuric acid (12 mL) drop wise. The mixture was heated to 70–75°C and was allowed to stir for 4–5h. The reaction was allowed to cool to room temperature and was neutralized with Et_3N. The acetone was removed under vacuum and the solution was washed with H_2O (3x). The benzyl alcohol was removed under high vacuum. The product was crashed out with Et_2O and the solids were washed with 20% EtOAc/hexanes to give 141.7 grams (51%) of an off white solid. $[\alpha]_D^{25} = -96$ (c 0.44, $CHCl_3$) ^{1}H-NMR (400 MHz; $CDCl_3$): δ 7.38-7.30 (m, 5H), 5.18 (s, 1H), 4.86 (d, *J* = 5.9 Hz, 1H), 4.77 (d, *J* = 11.6 Hz, 1H), 4.67 (d, *J* = 5.9 Hz, 1H), 4.58 (d, *J* = 11.6 Hz, 1H), 4.45 (t, *J* = 2.9 Hz, 1H), 3.72 (dd, *J* = 12.5, 2.4 Hz, 1H), 3.63 (dd, *J* = 12.5, 3.6 Hz, 1H), 3.11 (s, 1H), 1.48 (s, 3H), 1.32 (s, 3H). 13-C NMR (101 MHz; cdcl3): δ 136.5, 128.8, 128.41, 128.35, 112.3, 108.2, 88.6, 86.1, 81.7, 70.3, 64.2, 26.5, 24.8 IR (Dep. $CDCl_3$): 3487 (br), 2930.17 (s), 2888 (s), 1454 (s), 1403 (s), 1375 (s).

tert-butyl ((R)-((3aS,4S,6R,6aR)-6-(benzyloxy)-2,2-dimethylte trahydrofuro[3,4-d][1,3]dioxol-4-yl)(phenylsulfonyl)methyl)c arbamate (9)—To a solution of aldehyde **8a** (36.9 g, 1 eq.) in CH_2Cl_2 (1.3L) was added t-butyl carbamate (18.3 g, 1.2 eq.),

phenylsulfinic acid (28.3 g, 1.5 eq.), and magnesium sulfate (19 g). This mixture was allowed to stir overnight and was filtered through glass wool. The solution was then evaporated in vacuo and the product was crashed out with ether (500mL) to give 42.4 g (62%) of **9** as a white powder and taken on crude.[1] ^{1}H-NMR (400 MHz; $CDCl_3$): δ 7.81 (s, *J* = 8.2, 1.4 Hz, 1H), 7.74 (d, *J* = 7.4 Hz, 1H), 7.47 (d, *J* = 5.1 Hz, 2H), 7.40-7.23 (m, 6H), 7.03 (dd, *J* = 7.5, 1.9 Hz, 1H), 4.99 (s, 1H), 4.88 (d, *J* = 5.9 Hz, 1H), 4.75 (d, *J* = 5.9 Hz, 1H), 4.53 (s, 1H), 4.44 (ddd, *J* = 11.6, 9.7, 1.9 Hz, 1H), 4.11 (dq, *J* = 10.6, 10.0, 7.0 Hz, 1H), 4.06 (d, *J* = 13.3 Hz, 1H), 3.90 (dq, *J* = 10.7, 7.1 Hz, 1H), 1.45 (s, 9H), 1.44 (s, 3H), 1.29 (s, 3H), 1.08 (t, *J* = 7.1 Hz, 3H). 13-C NMR (101 MHz; cdcl3): δ 170.2, 155.7, 137.0, 132.4, 130.0, 128.32, 128.23, 128.10, 127.9, 127.56, 127.49, 112.0, 108.0, 86.3, 85.4, 81.9, 79.5, 69.5, 64.8, 61.1, 54.3, 28.2, 26.2, 24.6, 13.9. IR (Dep. $CDCl_3$): 3428 (s), 2980(s), 2938(s), 1739(s), 1714(s), 1491(s),1714(s), 1491(s).

(2R,3R) -ethyl 3- ((3aR,4R,6R,6aR) -6- (benzyloxy) -2,2-dimethyltetrahydrofuro[3,4-d][1,3]dioxol-4-yl)-3-((tert-butoxycarbonyl)amino)-2-((diphenylmethylene) amino)propanoate (12)—To a solution of LDA (0.1M, 192.3 mL) in dry THF at −78°C was added a glycine **11** (5.14 g, 2 eq.) in THF (−78°C) dropwise. The resulting yellow solution was stirred for 1 hour and amido sulfone **9** (5 g, 1 eq.) in THF (−78°C) was added dropwise. The reaction was stirred 20 min. and then quenched with sat. NH_4Cl (100mL) and allowed to warm to rt. The organic phase was separated and washed with brine. The aqueous phase was extracted with EtOAc (3x, 50mL) followed by brine. The combined organic extracts were dried over sodium sulfate and evaporated. The resulting oil was dissolved in hexanes and was evaporated. This process was repeated until solids formed which were removed by filtration to give **12** (4.8 g, 78%) as a white powder, which could be recrystallized from hexanes. $[\alpha]_D^{25} = -31$ (c 0.38, $CHCl_3$). ^{1}H-NMR (400 MHz; $CDCl_3$): δ7.74 (d, J = 7.4 Hz, 1H), 7.49-7.26 (m, 11H), 7.03 (dd, J = 7.5, 1.9 Hz, 2H), 6.15 (s, 1H), 5.80 (d, J = 9.7 Hz, 1H), 4.99 (s, 1H), 4.88 (d, J = 6.0 Hz, 1H), 4.75 (d, J = 5.9 Hz, 1H), 4.53 (s, 1H), 4.44 (ddd, J = 11.6, 9.7, 1.9 Hz, 1H), 4.10 (dq, J = 10.6, 7.1 Hz, 1H), 4.09 (d, J =12.0 Hz, 1H), 4.05 (d, J = 11.2 Hz, 1H), 4.03 (d, J = 11.6 Hz, 1H), 3.90 (dq, J = 10.7, 7.1 Hz, 1H), 1.45 (s, 9H), 1.44 (s, 3H), 1.29 (s, 3H), 1.08 (t, J = 7.1 Hz, 3H). 13-C NMR (101 MHz; cdcl3): δ 170.4, 155.9, 137.2, 132.5, 130.2, 128.60, 128.51, 128.42, 128.28, 128.07, 128.01, 127.81, 127.75, 127.67, 112.2, 108.2, 86.5, 85.5, 82.1, 79.7, 69.7, 65.0, 61.3, 54.5, 28.4, 26.4, 24.8, 14.1. IR (Dep. $CDCl_3$): 3428 (br), 2980 (vs), 2938 (vs), 1739 (vs), 1714 (vs), 1491 (s). HRMS (FAB^+): Calcd for $C_{37}H_{45}N_2O_8$ [M +H]: 645.3176; Found 645.3172.

(2*R*,3*R*)-ethyl 2,3-diamino-3-((3a*R*,4*R*,6*R*,6a*R*)-6-(benzyloxy)-2,2-dimethyltetrahydrofuro[3,4-*d*][1,3]dioxol-4-yl)propanoate (12a)—Compound **12** (1000mg, 1eq.) was dissolved in CH_2Cl_2 (15.5mL) and 2,6-lutidine (0.67g, 4eq.) was added followed by TMSOTf (1.2g, 3.5eq.). The mixture was stirred 1 hr. and quenched with sat. $NaHCO_3$ (20mL). The mixture was extracted with EtOAc (3x, 50mL) dried over Na_2SO_4, evaporated in vacuo. The product was dissolved in THF (5mL) and 1M HCl (5mL) was added. The mixture was stirred for ~20 min. until complete by TLC. The mixture was washed with diethyl ether (3x, 20mL) to remove the benzophenone and then the aqueous layer was basified with $NaHCO_3$. The mixture was extracted with n-butanol (5x, 20mL) and

the organic extracts were combined, dried over Na_2SO_4 and evaporated in vacuo to give diamine **12a** (570mg, 97%), which was taken on crude. ^{1}H-NMR (300 MHz; $CDCl_3$): δ 7.34-7.29 (m, 5H), 5.19 (s, 1H), 4.97 (dd, *J* = 6.0, 1.1 Hz, 1H), 4.76 (d, *J* = 11.9 Hz, 1H), 4.71 (d, *J* = 6.0 Hz, 1H), 4.50 (d, *J* = 11.9 Hz, 1H), 4.14 (q, *J* = 7.1 Hz, 2H), 4.07 (dd, *J* = 10.7, 1.2 Hz, 1H), 3.98 (d, *J* = 2.0 Hz, 1H), 3.20 (dd, *J* = 10.7, 2.0 Hz, 1H), 1.49 (s, 3H), 1.33 (s, 3H), 1.17 (t, *J* = 7.1 Hz, 3H). HRMS (FAB$^+$): Calcd. for $C_{19}H_{29}N_2O_6$ [M+H]: 381.2026; Found 381.2022.

(2R,3R)-ethyl 3-((3aR,4R,6R,6aR)-6-(benzyloxy)-2,2-dimethyl tetrahydrofuro[3,4-d][1,3]dioxol-4-yl)-2,3-bis(2-(tert-butoxyc arbonyl)-3-(methoxycarbonyl)guanidino)propanoate (14)—To a solution of diamine **12a** (570mg, 1eq.) in DMF (15 ml) was added reagent **13** (1.12g, 1.1eq.), $HgCl_2$ (1.22g, 1.1eq.) and triethylamine (1.36g, 3.3 eq.). The mixture was stirred 30 min and the mercury salts were crashed out with ethyl acetate (25mL). The mixture was filtered and the filtrate was washed with H_2O. The organic layer was washed with brine (25mL), dried over Na_2SO_4 and solvents were removed in vacuo. The crude material was purified via flash chromatography to give product 14 (844mg, 72%). $[\alpha]_D^{25} = -58$ (c 0.53, $CHCl_3$). ^{1}H-NMR (500 MHz; $CDCl_3$): δ 11.34 (s, 1H), 11.30 (s, 1H), 9.14 (d, *J* = 8.9 Hz, 1H), 8.85 (d, *J* = 9.7 Hz, 1H), 7.40 (d, *J* = 7.2 Hz, 2H), 7.33 (t, *J* = 7.3 Hz, 2H), 7.28 (d, *J* = 7.2 Hz, 1H), 5.40 (dd, *J* = 8.9, 2.1 Hz, 1H), 5.24 (s, 1H), 5.04 (td, *J* = 10.3, 1.6 Hz, 1H), 4.96 (d, *J* = 12.2 Hz, 1H), 4.77 (dd, *J* = 6.0, 1.0 Hz, 1H), 4.73 (d, *J* = 6.0 Hz, 1H), 4.59 (d, *J* = 12.2 Hz, 1H), 4.21 (dd, *J* = 10.7, 1.1 Hz, 1H), 4.14-4.04 (m, 2H), 3.76 (d, *J* = 5.7 Hz, 1H), 3.70 (s, 3H), 3.65 (s, 3H), 1.50 (s, 9H), 1.48 (s, 9H), 1.46 (s, 3H), 1.29 (s, 3H), 1.13 (t, *J* = 7.2 Hz, 3H). 13-C NMR (126 MHz; cdcl3): δ 170.1, 164.29, 164.21, 156.94, 156.88, 152.77, 152.67, 137.5, 128.5, 127.89, 127.73, 112.9, 108.1, 86.0, 85.4, 83.8, 83.6, 81.9, 70.1, 62.3, 53.86, 53.81, 52.9, 28.1, 26.6, 25.3, 13.9. IR (Dep. $CDCl_3$): 2987 (w), 2946 (w), 1722 (vs), 1644 (vs), 1620 (s), 1572 (s). HRMS (FAB$^+$): Calcd for $C_{35}H_{53}N_6O_{14}$ [M+H]: 781.3620; Found 781.3625

(2*R*,3*R*)-ethyl 2,3-bis(2-(*tert*-butoxycarbonyl)-3-(methoxycarb onyl)guanidino)-3-((3a*R*,4*R*,6*R*,6a*R*)-6-hydroxy-2,2-dimethylt etrahydrofuro[3,4-*d*][1,3]dioxol-4-yl)propanoate (14a)—Benzyl ether **14** (540mg) was dissolved in 5:1 THF/MeOH (6mL) and 20% $Pd(OH)_2$/C (270mg) was added. Argon was bubbled through the suspension for 5 min. and the mixture was hydrogenated at 100 psi hydrogen for 24h. The mixture was then filtered through celite, evaporated, and purified via flash chromatography (30% EtOAc/Hexane) to give 404 mg (85%) of lactol **14a**. $[\alpha]_D^{25} = -1$ (c 0.54, $CHCl_3$) 1H NMR (500 MHz; CDCl3): δ 11.51 (s, 1H), 11.37 (s, 1H), 9.31 (d, J = 9.7 Hz, 1H), 8.97 (d, J = 9.0 Hz, 1H), 5.63 (s, 1H), 5.13 (dd, J = 8.9, 2.0 Hz, 1H), 4.93 (ddd, J = 11.6, 9.6, 2.3 Hz, 1H), 4.89 (d, J = 6.0 Hz, 1H), 4.68 (d, J = 5.9 Hz, 1H), 4.41 (s, 1H), 4.32 (q, *J* = 7.1 Hz, 2H), 4.12 (d, *J* = 11.4 Hz, 1H), 3.69 (s, 3H), 3.67 (s, 3H), 1.50 (s, 8H), 1.49 (s, 8H), 1.45 (s, 4H), 1.35 (t, *J* = 7.1 Hz, 3H), 1.31 (s, 3H). 13-C NMR (126 MHz; cdcl3): δ 169.3, 164.27, 164.11, 156.4, 155.5, 153.6, 152.5, 112.8, 104.0, 88.1, 85.6, 84.6, 83.7, 82.3, 62.6, 55.7, 52.91, 52.77, 52.3, 28.2, 26.8, 25.5, 14.1 IR (Dep. $CDCl_3$): 1724 (s), 1619 (m), 1440 (s), 1413 (s), 1370 (s). HRMS (FAB$^+$): Calcd. for $C_{28}H_{47}N_6O_{14}$ [M+H]: 691.3150; Found 691.3147.

(2*R*,3*R*)-ethyl 2,3-bis(2-(*tert*-butoxycarbonyl)-3-(methoxycarb onyl)guanidino)-4-((4*R*,5*S*)-5-(((*tert*-butyldimethylsilyl)oxy)m ethyl)-2,2-dimethyl-1,3-dioxolan-4-yl)-4-hydroxybutanoate (14b)—To a solution of diol **14a** (240mg, 1 eq.) in CH_2Cl_2 (20 mL) was added 2,6-lutidine (223mg, 6 eq.). The solution was cooled to −78°C and TBSOTf (446mg, 5 eq.) was added. The reaction was stirred 1 hr. and was quenched with sat. NH_4Cl. The mixture was extracted with ethyl acetate (3x, 10mL), dried over sodium sulfate and evaporated in vacuo. The crude compound was purified via column chromatography (10–30% EtOAc/Hexanes) to give TBS ether **14b** (230 mg, 82%). ^{1}H-NMR (500 MHz; $CDCl_3$): δ 11.32 (s, 1H), 11.18 (s, 1H), 8.91 (d, *J* = 7.3 Hz, 1H), 8.80 (d, *J* = 6.1 Hz, 1H), 5.17 (t, *J* = 7.5 Hz, 1H), 4.82 (dd, *J* = 8.5, 7.0 Hz, 1H), 4.73 (q, *J* = 7.0 Hz, 1H), 4.64 (dd, *J* = 8.8, 6.3 Hz, 1H), 4.33-4.22 (m, 2H), 3.95 (dd, *J* = 10.7, 2.6 Hz, 1H), 3.85 (dd, *J* = 11.7, 5.0 Hz, 1H), 3.80-3.78 (m, 1H), 3.65 (s, 6H), 1.49 (s, 6H), 1.48 (s, 5H), 1.46 (t, *J* = 9.3 Hz, 3H), 1.37 (s, 3H), 1.32 (s, 3H), 0.89 (s, 9H), 0.08 (s, 3H), 0.07 (s, 3H). 13-C NMR (126 MHz; cdcl3): δ 171.6, 163.7, 163.5, 155.9, 155.6, 152.9, 152.7, 108.9, 83.98, 83.94, 78.1, 76.7, 61.5, 56.7, 54.6, 52.75, 52.66, 28.12, 28.06, 27.3, 26.00, 25.94, 25.2, 18.4, −5.2. HRMS (FAB$^+$): Calcd. for $C_{34}H_{63}N_6O_{14}Si$ [M+H]: 807.4172; Found 807.4168.

(2*R*,3*R*)-ethyl 2,3-bis(2-(*tert*-butoxycarbonyl)-3-(methoxycarb onyl)guanidino)-4-((4*S*,5*S*)-5-(((*tert*-butyldimethylsilyl)oxy)m ethyl)-2,2-dimethyl-1,3-dioxolan-4-yl)-4-oxobutanoate (15)—To a solution of compound **14b** (49 mg, 1 eq.) in CH_2Cl_2 (5 mL) was added Dess-Martin periodinane (51.5 mg, 2 eq.). The solution turned cloudy over time and was allowed to stir for 2h. The reaction was quenched with 10% $Na_2S_2O_3$ (5mL) and was allowed to stir until the biphasic system turned clear. The mixture was extracted with EtOAc (3x, 10mL), dried over sodium sulfate and evaporated in vacuo to give ketone **15** (47 mg, 96%). ^{1}H-NMR (500 MHz; $CDCl_3$): δ 11.24 (s, 1H), 11.10 (s, 1H), 9.24 (d, *J* = 5.0 Hz, 1H), 9.00 (d, *J* = 6.5 Hz, 1H), 5.77 (d, *J* = 7.2 Hz, 1H), 5.72 (d, *J* = 8.0 Hz, 1H), 5.24 (d, *J* = 8.6 Hz, 1H), 4.46 (d, *J* = 8.6 Hz, 1H), 4.38-4.31 (m, 1H), 4.27-4.20 (m, 1H), 3.72 (dd, *J* = 11.7, 2.1 Hz, 1H), 3.67 (dd, *J* = 11.7, 2.1 Hz, 1H), 3.63 (s, 3H), 3.62 (s, 3H), 1.47 (s, 9H), 1.47 (s, 9H), 1.43 (s, 3H), 1.41 (s, 3H), 1.32 (t, *J* = 7.1 Hz, 3H), 0.76 (s, 9H), −0.00 (s, 3H), −0.01 (s, 3H). 13-C NMR (126 MHz; cdcl3): δ 203.7, 169.5, 164.2, 163.7, 156.0, 155.7, 152.39, 152.36, 110.0, 83.6, 83.2, 79.78, 79.71, 62.4, 61.5, 59.7, 53.2, 52.6, 52.3, 28.34, 28.31, 28.1, 26.5, 25.82, 25.78, 24.6, 18.8, 13.9, −5.1, −5.8 HRMS (FAB$^+$): HRMS (FAB$^+$): Calcd. for $C_{34}H_{61}N_6O_{14}Si$ [M+H]: 805.4015; Found 805.4014.

(2*R*,3*R*)-ethyl 3-((3a*R*,4*R*,6*R*,6a*R*)-6-(benzyloxy)-2,2-dimethylt etrahydrofuro[3,4-*d*][1,3]dioxol-4-yl)-3-((*tert*-butoxycarbonyl) amino)-2-((methoxycarbonyl)amino)propanoate (18)—To a solution of compound **12** (5 g, 1 eq.) in THF (150 mL) was added 1M HCl (150 mL). The mixture was stirred 30 min. and quenched with $NaHCO_3$ (15 g). Methyl chloroformate (733 mg, 1 eq.) was added to the mixture and stirred an additional 2h. The layers were separated and the aqueous layer was extracted with CH_2Cl_2 (3x, 50mL) the combined extracts were washed with brine, dried over sodium sulfate and evaporated. The crude material was purified via flash chromatography (20–50% EtOAc/Hexanes) to give methyl carbamate **18** (4.07 g, 97%) as a

white powder. $[\alpha]_D^{25} = -96$ (c 1.04, $CHCl_3$) ^{1}H-NMR (400 MHz; $CDCl_3$): δ 7.38-7.27 (m, 4H), 5.61 (s, 1H), 5.25 (s, 1H), 4.90 (d, *J* = 12.3 Hz, 2H), 4.86 (d, *J* = 7.7 Hz, 1H), 4.77 (d, *J* = 5.9 Hz, 1H), 4.74 (d, *J* = 5.8 Hz, 1H), 4.60 (d, *J* = 12.3 Hz, 1H), 4.33 (td, *J* = 10.9, 2.1 Hz, 1H), 4.15-4.06 (m, 1H), 4.06-3.99 (m, 1H), 4.01 (d, *J* = 7.7 Hz, 1H), 3.72 (s, 3H), 1.46 (s, 3H), 1.40 (s, 9H), 1.29 (s, 3H), 1.13 (t, *J* = 7.1 Hz, 3H). 13-C NMR (101 MHz; cdcl3): δ 171.3, 157.3, 155.2, 137.4, 128.5, 127.78, 127.64, 112.6, 108.3, 85.73, 85.55, 82.1, 80.3, 77.4, 70.1, 62.1, 54.67, 54.56, 54.52, 52.83, 52.76, 28.3, 26.5, 25.0, 14.0. IR (Dep. $CDCl_3$): 3584 (br), 3362 (s), 2980(s), 2940(s), 1715(s), 1514(s). HRMS (FAB^+): Calcd. for $C_{26}H_{39}N_2O_{10}$ [M+H]: 539.2605; Found 539.2602.

***tert*-butyl ((*R*)-((3a*R*,4*R*,6*R*,6a*R*)-6-(benzyloxy)-2,2-dimethylte trahydrofuro[3,4-*d*][1,3]dioxol-4-yl)((*R*)-2-oxooxazolidin-4-yl) methyl)carbamate (19)—**To a solution of methyl carbamate **18** (1.08 g, 1 eq.) in THF (20 mL) was added lithium borohydride (436 mg, 10 eq.). The mixture was allowed to stir 10h or until complete by TLC. The mixture was poured over cracked ice and sat. ammonium chloride (100 mL) was added and allowed to stir for 30 min.. The mixture was extracted with EtOAc (3x, 50mL) and the combined extracts were washed with brine dried over sodium sulfate and evaporated. The crude alcohol was dissolved in MeOH (20 mL) and finely powdered KOH (1.02 g, 10 eq.) was added. The mixture was refluxed until complete by 1 hr., allowed to cool and evaporated. The crude oxazolidinone was purified via a plug of silica gel (10% MeOH/DCM) to give oxazolidinone **19** (906 mg, 98%) as a white solid. $[\alpha]_D^{25} = -72$ (c 0.45, $CHCl_3$) ^{1}H-NMR (400 MHz; $CDCl_3$): δ 7.38-7.26 (m, 5H), 5.52 (s, 1H), 5.20 (s, 1H), 4.85 (d, *J* = 10.4 Hz, 1H), 4.74 (d, *J* = 6.0 Hz, 1H), 4.73 (d, *J* = 6.0 Hz, 1H), 4.65 (d, *J* = 12.2 Hz, 1H), 4.62 (d, *J* = 12.2 Hz, 1H), 4.16 (t, *J* = 7.6 Hz, 1H), 4.09 (t, *J* = 8.8 Hz, 1H), 4.00 (dd, *J* = 8.5, 6.2 Hz, 1H), 3.87 (d, *J* = 11.2 Hz, 1H), 3.74 (td, *J* = 10.8, 1.7 Hz, 1H), 1.46 (s, 3H), 1.45 (s, 9H), 1.31 (s, 3H). 13-C NMR (101 MHz; cdcl3): δ 160.0, 156.2, 137.0, 128.8, 128.2, 127.4, 112.8, 109.0, 86.5, 85.2, 82.4, 80.9, 70.7, 67.0, 53.1, 52.0, 28.4, 26.6, 25.0. IR (Dep. $CDCl_3$): 3305 (br), 2980 (s), 2938 (s), 1756 (s), 1708 (s), 1499 (s), 1455 (s). HRMS (FAB^+): Calcd. for $C_{23}H_{33}N_2O_8$ [M+H]: 465.2237; Found 465.2240.

(*R*)-4-((*R*)-(2,3-bis(*tert*-butoxycarbonyl)guanidino)((3a*R*,4*R*,6 *R*,6a*R*)-6-(benzyloxy)-2,2-dimethyltetrahydrofuro[3,4-*d*][1,3] dioxol-4-yl)methyl)oxazolidin-2-one (21)—To a solution of oxazolidinone **19** (245 mg, 1eq.) and 2,6-lutidine (226 mg, 3eq.) in CH_2Cl_2 (5 mL) was added TMSOTf (352 mg, 3 eq.). The mixture was allowed to stir 1 hr. and quenched with sat. sodium bicarbonate, extracted with EtOAc (3x, 15mL). The combined extracts were dried over sodium sulfate and evaporate. The crude amine was dissolved in DMF (5mL) and triethylamine (240 mg, 4.5 eq.) and guanylating reagent **20** (153.3 mg, 1eq.) was added. The mixture was cooled to 0°C and mercuric chloride (157.5mg, 1.1 eq.) was added. The cloudy suspension was allowed to room temperature and stirred 1 hr. The reaction was quenched by adding sat. sodium chloride and ethyl acetate. After stirring the mixture for 20 min. the reaction was filtered through celite to remove all the mercury salts. The biphasic solution was separated and the organic layer was washed with H_2O (3x, 20mL), brine (20 mL), dried over sodium sulfate and evaporated in vacuo. The crude material was purified via column chromatography (20–

50% EtOAc/Hexanes) to give compound **21** (216 mg, 68%). $[\alpha]_D^{25} = -91$ (c 0.23, $CHCl_3$) ^{1}H-NMR (400 MHz; $CDCl_3$): δ 11.45 (s, 1H), 8.77 (d, *J* = 9.4 Hz, 1H), 7.39-7.29 (m, 5H), 5.21 (s, 1H), 5.07 (s, 1H), 4.83 (dd, *J* = 6.0, 1.1 Hz, 1H), 4.75 (d, *J* = 6.0 Hz, 1H), 4.70 (d, *J* = 12.4 Hz, 1H), 4.64 (d, *J* = 12.3 Hz, 1H), 4.50 (td, *J* = 10.0, 1.5 Hz, 1H), 4.17 (ddt, *J* = 8.7, 6.7, 2.0 Hz, 1H), 4.09 (t, *J* = 8.8 Hz, 1H), 4.04 (dd, *J* = 8.8, 6.7 Hz, 1H), 3.99 (dd, *J* = 10.2, 1.1 Hz, 1H), 1.49 (s, 9H), 1.49 (s, 9H), 1.47 (s, 3H), 1.32 (s, 3H). 13-C NMR (101 MHz; cdcl3): δ 163.3, 159.2, 157.2, 153.0, 136.9, 128.8, 128.2, 127.6, 113.1, 108.9, 98.7, 86.6, 85.2, 84.2, 82.0, 70.6, 66.8, 52.33, 52.17, 28.4, 28.20, 28.14, 26.7, 25.2. IR (Dep. CDCl3): 3263 (br), 2981 (s), 2936(s), 1763(s), 1725(s), 1641(s), 1613(s). HRMS (FAB^+): Calcd. for $C_{29}H_{43}N_4O_{10}$ [M+H]: 607.2979; Found 607.2968.

(*R*)-4-((1*R*,2*R*)-1-(2,3-bis(*tert*-butoxycarbonyl)guanidino)-2-((4*R*,5*S*)-2,2-dimethyl-5-(((2-nitrobenzyl)amino)methyl)-1,3-dio xolan-4-yl)-2-hydroxyethyl)oxazolidin-2-one (24)—To a solution of benzyl ether **331** (300 mg) in 4:1 THF/methanol (5 mL) was added 20% $Pd(OH)_2/C$ (150 mg). Argon was bubbled through the resulting suspension and then it was hydrogenated at 100 psi overnight. The mixture was filtered evaporated and to give lactol **22**, which was taken on crude.

A solution of lactol **22**, o-nitrobenzylamine HCl (456.4 mg, 5 eq.), AcOH (727 mg, 25 eq.), sodium acetate (397 mg, 10 eq.) and sodium cyanoborohydride (152 mg, 5 eq.) in MeOH (2.4 mL) was allowed to stir 1.5h. The reaction was carefully quenched with sat. sodium bicarbonate, extracted with EtOAc (3x, 20mL) and the combined extracts were dried over sodium sulfate and evaporated. The crude product wad purified via prep. TLC (10% MeOH/DCM) to give benzylamine **24** (276 mg, 86%). $[\alpha]_D^{25} = -23$ (c 0.54, $CHCl_3$). ^{1}H-NMR (400 MHz; cd3cn): δ 11.59 (s, 1H), 8.72 (d, *J* = 9.6 Hz, 1H), 8.00 (dd, *J* = 8.2, 1.0 Hz, 1H), 7.69 (td, *J* = 7.5, 1.1 Hz, 1H), 7.58 (dd, *J* = 7.7, 1.2 Hz, 1H), 7.55-7.50 (m, 1H), 5.79 (s, 1H), 4.44-4.36 (m, 3H), 4.30 (ddd, *J* = 9.9, 5.9, 3.9 Hz, 1H), 4.18 (dd, *J* = 9.7, 5.7 Hz, 1H), 4.10 (dd, *J* = 7.2, 4.9 Hz, 1H), 4.05 (d, *J* = 13.5 Hz, 1H), 3.98 (d, *J* = 13.5 Hz, 1H), 3.75 (dd, *J* = 9.7, 3.7 Hz, 1H), 2.87 (dd, *J* = 12.1, 10.1 Hz, 1H), 2.81 (dd, *J* = 12.2, 3.7 Hz, 1H), 1.51 (s, 9H), 1.43 (s, 9H), 1.36 (s, 3H), 1.28 (s, 3H). 13-C NMR (101 MHz; cd3cn): δ 164.6, 159.9, 157.9, 153.8, 150.0, 134.7, 134.5, 133.2, 129.9, 125.9, 109.6, 84.3, 79.7, 78.5, 76.7, 71.6, 67.9, 53.0, 52.2, 50.7, 49.3, 28.4, 28.20, 28.18, 25.4 HRMS (FAB^+): Calcd. for $C_{29}H_{45}N_6O_{11}$ [M+H]: 653.3146; Found 653.3138.

methyl *N*-(((4*S*,5*R*)-5-((1*R*,2*R*)-2-(2,3-bis(*tert*-butoxycarbonyl) guanidino)-1-hydroxy-2-((*R*)-2-oxooxazolidin-4-yl)ethyl)-2,2-dimethyl-1,3-dioxolan-4-yl)methyl)-*N*′-((4-methoxyphenyl)sul fonyl)-*N*-(2-nitrobenzyl)carbamimidothioate (24a)—To a solution of amine **24** (209 mg, 1 eq.) and triethylamine (124 mg, 3 eq.) in CH_2Cl_2 (4 mL, 0.1M) was added **25** (229.1 mg, 2 eq.). The mixture was allowed to stir for 45 min and evaporated. The crude compound purified via flash chromatography (1–5% MeOH/DCM) to give the isothiourea **24a** (235 mg, 82%). ^{1}H-NMR (400 MHz; CD_3CN): δ 11.49 (s, 1H), 8.62 (d, *J* = 8.7 Hz, 1H), 8.00 (d, *J* = 8.1 Hz, 1H), 7.65 (t, *J* = 7.4 Hz, 1H), 7.55 (s, 1H), 7.48 (t, *J* = 7.7 Hz, 1H), 7.25 (d, *J* = 7.6 Hz, 1H), 6.87 (d, *J* = 8.1 Hz, 1H), 5.72 (s, 1H), 5.22 (d, *J* = 16.3 Hz, 1H), 5.02 (d, *J* = 17.6 Hz, 1H), 4.42 (t, *J* = 8.6 Hz, 1H), 4.41 (s, 1H), 4.31-4.27 (m, 1H), 4.22 (dd, *J* = 14.4, 1.8 Hz, 1H),

4.00 (dd, *J* = 8.5, 7.2 Hz, 1H), 3.94 (s, 1H), 3.83 (s, 3H), 3.68 (d, *J* = 8.8 Hz, 1H), 2.64 (s, 3H), 1.49 (s, 9H), 1.41 (s, 3H), 1.39 (s, 9H), 1.21 (s, 3H). 13-C NMR (101 MHz; cd3cn): δ 168.6, 164.3, 162.9, 159.8, 157.9, 153.7, 148.7, 137.2, 134.9, 133.0, 129.4, 129.0, 128.6, 126.2, 114.7, 110.5, 84.5, 79.8, 76.88, 76.74, 70.6, 68.0, 56.4, 54.3, 54.0, 53.0, 51.9, 28.4, 28.15, 28.05, 25.6, 19.0. (Dep. MeCN): 3317 (br), 2980 (s), 2935 (s), 1762 (s), 1727 (s), 1639 (s), 1613 (s), 1579 (s), 1529 (s). HRMS (FAB^+): Calcd. for $C_{38}H_{54}N_7O_{14}S_2$ [M+H]: 896.3170; Found 896.3177.

((3a*S*,8*R*,9*R*,10*R*,10a*R*)-9-(2,3-(tert-butoxycarbonyl)guanidin o)-10-hydroxy-6-(((4-methoxyphenyl)sulfonyl)imino)-2,2-dim ethyl-5-(2-nitrobenzyl)octahydro-3a*H*-[1,3]dioxolo[4,5-*e*][1,3] diazonin-8-yl)methyl carbamate (27)—To a solution of compound **24a** (22 mg, 1eq.) and triethylamine (22.5 mg, 5 eq.) in acetonitrile (2 mL) was added mercury (II) chloride (13.3 mg, 2 eq.). The reaction was stirred ~20 min. until the disappearance of stating material by TLC. The reaction was quenched with conc. ammonium hydroxide (2 mL) and stirred an additional 20 min. until the disappearance of stating material by TLC. The reaction mixture was filtered through celite to remove mercury salts and the was extracted 3x (5mL) with EtOAc. The combined organic layers were dried over sodium sulfate and evaporated. The crude material was purified by flash chromatography (1–5% MeOH/DCM) to give **27** as a white solid (15.1 mg, 71%). ^{1}H-NMR (400 MHz; CD_3CN): δ 11.48 (s, 1H), 8.64 (d, *J* = 8.8 Hz, 1H), 8.08 (d, *J* = 8.0 Hz, 1H), 7.65 (d, *J* = 8.2 Hz, 2H), 7.56 (t, *J* = 7.4 Hz, 1H), 7.48 (t, *J* = 7.5 Hz, 1H), 7.15 (d, *J* = 7.3 Hz, 1H), 6.94 (d, *J* = 8.7 Hz, 2H), 6.75 (s, 2H), 5.76 (s, 1H), 4.95 (s, 1H), 4.42 (t, *J* = 8.6 Hz, 1H), 4.36 (ddd, *J* = 9.7, 6.1, 1.7 Hz, 1H), 4.34-4.28 (m, 2H), 4.03 (dd, *J* = 9.6, 5.7 Hz, 1H), 3.99 (dd, *J* = 8.2, 6.7 Hz, 1H), 3.84 (s, 3H), 3.76 (d, *J* = 10.0 Hz, 1H), 3.40 (s, 2H), 1.49 (s, 9H), 1.45 (s, 3H), 1.39 (s, 1H), 1.22 (s, 3H). 13-C NMR (101 MHz; cd3cn): δ 164.2, 163.0, 159.8, 158.3, 157.9, 153.7, 149.0, 137.1, 134.9, 133.8, 129.3, 128.67, 128.62, 126.2, 114.7, 110.5, 84.5, 79.9, 77.7, 76.8, 70.9, 68.0, 56.3, 54.3, 52.0, 51.1, 50.2, 28.4, 28.14, 28.04, 25.5. HRMS (FAB^+): Calcd. for $C_{37}H_{53}N_8O_{14}S$ [M+H]: 865.3402 Found 865.3413.

((3a*S*,8*R*,9*R*,10*R*,10a*R*)-9-(2,3-bis(*tert*-butoxycarbonyl)guanid ino)-10-hydroxy-6-(((4-methoxyphenyl)sulfonyl)imino)-2,2-di methyloctahydro-3a*H*-[1,3]dioxolo[4,5-*e*][1,3]diazonin-8-yl)m ethyl carbamate (26)—Argon was bubbled through a vial containing **27** (53 mg) in THF (6 mL, wet) for 5 min. The vial was sealed and irradiated by a Hg vapor lamp for 30 min. The mixture was evaporated and purified via flash chromatography (1–5% MeOH/DCM) to give **26** (40 mg, 89%, 97% brsm) and recovered starting material (4 mg). ^{1}H-NMR (400 MHz; CD_3CN): δ 11.53 (s, 1H), 8.67 (d, *J* = 8.8 Hz, 2H), 7.75 (d, *J* = 8.9 Hz, 2H), 6.98 (d, *J* = 8.9 Hz, 2H), 6.22 (s, 2H), 5.84 (s, 1H), 4.51 (s, 1H), 4.45 (d, *J* = 8.6 Hz, 1H), 4.43 (d, *J* = 8.6 Hz, 1H), 4.37-4.35 (m, 1H), 4.30 (dt, *J* = 8.9, 2.7 Hz, 1H), 4.18 (dd, *J* = 12.5, 5.5 Hz, 1H), 4.07 (dd, *J* = 9.8, 5.7 Hz, 1H), 4.03 (dd, *J* = 8.3, 7.1 Hz, 1H), 3.83 (s, 3H), 3.78 (d, *J* = 10.3 Hz, 1H), 3.32 (dd, *J* = 7.7, 5.9 Hz, 1H), 3.28 (d, *J* = 5.7 Hz, 1H), 1.51 (s, 9H), 1.42 (s, 3H), 1.41 (s, 9H), 1.27 (s, 3H). HRMS (FAB^+): Calcd. for $C_{30}H_{48}N_7O_{12}S$ [M+H]: 730.3082; Found 730.3085

(4*R*,9*S*,10*R*)-4-((carbamoyloxy)methyl)-9,10-dihydroxy-6-(((4 -methoxyphenyl)sulfonyl)imino)-3,4,5,6,7,8,9,10-octahydroim idazo[4,5-*e*] [1,3]diazonin-2(1*H*)-iminium 2,2,2 trifluoro-acetate (35)—To a solution of **29** (29 mg) in THF (3 mL) was added 6M HCl (3 mL). The mixture was allowed to stir for 24h. and then evaporated. The mixture was purified via RP-18 flash chromatography (100-80% 0.1% TFA in H_2O/MeCN) to give **35** (16 mg, 86%) as the TFA salt. ^{1}H-NMR (400 MHz; D_2O): δ 7.67 (d, *J* = 9.0 Hz, 2H), 6.95 (d, *J* = 9.0 Hz, 2H), 5.01 (s, 1H), 4.53 (t, *J* = 9.5 Hz, 1H), 4.44 (s, 1H), 4.14 (dd, *J* = 9.2, 7.2 Hz, 1H), 3.78-3.74 (m, 1H), 3.73 (s, 3H), 3.31 (d, *J* = 12.8 Hz, 1H), 3.11 (dd, *J* = 13.9, 5.8 Hz, 1H). 13-C NMR (101 MHz; D_2O): δ 162.3, 161.0, 157.3, 147.4, 133.0, 127.9, 123.5, 121.8, 114.3, 71.4, 69.5, 64.7, 55.6, 46.6, 43.7. HRMS (FAB^+): Calcd. for $C_{17}H_{24}N_7O_7S$ [M+H]: 470.1458 Found 470.1445.

(1*S*,5*R*,8a*R*)-5-((carbamoyloxy)methyl)-1-hydroxy-4,5,8,8a-tet rahydro-1*H*-2a, 4,6,8-tetraazaacenaphthylene-3,7(2*H*,6*H*)-dii minium 2,2,2-trifluoroacetate (44) —Ketone **29** (10 mg) was cooled to 0°C and 0.25 $B(TFA)_3$ in TFA (1 mL) was added. The mixture was allowed to warm to r.t. slowly (leave in the ice bath) and stirred a total of 48h. The mixture was cooled to 0°C and quenched with methanol (2mL). The reaction was evaporated and diluted with methanol (3mL) and evaporated three times. The crude solid was purified via RP-18 flash chromatography (100-80% 0.1% TFA in H_2O/MeCN) to give **44** (5 mg, 92%). ^{1}H-NMR (500 MHz; D_2O): δ 5.26 (dd, *J* = 9.5, 7.3 Hz, 1H), 4.87 (d, *J* = 2.9 Hz, 1H), 4.77 (t, *J* = 9.5 Hz, 1H), 4.35 (dd, *J* = 9.5, 7.4 Hz, 1H), 4.22 (q, *J* = 3.1 Hz, 1H), 3.58 (dd, *J* = 13.6, 2.1 Hz, 1H), 3.38 (dd, *J* = 13.5, 3.8 Hz, 1H). 13-C NMR (126 MHz; d2o): δ 161.84, 161.75, 158.01, 158.01, 157.54, 157.54, 91.80, 91.80, 72.57, 72.57, 69.84, 69.84, 68.09, 68.09, 63.05, 63.05, 51.62, 51.62, 44.85, 44.85. Calcd. for $C_{10}H_{16}N_7O_3$ [M+H]: 282.1304 Found 282.1311.

(4*R*,9*S*)-4-((carbamoyloxy)methyl)-9-hydroxy-6-(((4-methoxy phenyl)sulfonyl)imino)-4,6,7,8,9,9a-hexahydro-1*H*-imidazo[4′,5′: 3,4]pyrrolo[1,2-*c*]pyrimidin-2(3*H*)-iminim 2,2,2-trifluoroacetate (37)—To a flask containing compound 409 (10 mg) was added TFA (2 mL). The reaction was stirred 48 hr. and evaporated. The compound was purified via HPLC (YMC-Pack ODS-AM-322, 150x10mm, 5Å; 95-0% 0.1% TFA H_2O/MeCN over 45 min; t_r= 14.409 min.) to give **37** (9 mg, 94%) as an inseparable mixture (1:1) of diastereomers.

anti-37: ^{1}H-NMR (500 MHz; D_2O): δ 7.80 (d, *J* = 9.0 Hz, 2H), 7.07 (d, *J* = 8.9 Hz, 2H), 5.32 (d, *J* = 4.1 Hz, 1H), 5.22 (dd, *J* = 9.2, 6.9 Hz, 1H), 4.77 (t, *J* = 9.4 Hz, 1H), 4.27 (dd, *J* = 9.2, 7.2 Hz, 1H), 4.15 (dd, *J* = 7.3, 3.1 Hz, 1H), 3.80 (s, 3H), 3.29 (dd, *J* = 14.2, 3.2 Hz, 1H), 3.16 (dd, *J* = 14.2, 4.1 Hz, 2H). 13-C NMR (126 MHz; d2o): δ 165.5, 162.7, 161.0, 152.0, 130.6, 125.6, 123.1, 119.1, 115.1, 69.4, 63.7, 56.0, 54.1, 46.5, 42.0

syn-37: ^{1}H-NMR (500 MHz; D_2O): δ 7.74 (d, *J* = 9.0 Hz, 2H), 7.05 (d, *J* = 9.0 Hz, 2H), 5.49 (d, *J* = 5.1 Hz, 1H), 5.21 (dd, *J* = 9.2, 6.0 Hz, 1H), 4.63 (t, *J* = 9.5 Hz, 1H), 4.24 (dt, *J* = 7.9, 4.1 Hz, 1H), 4.17 (dd, *J* = 7.9, 6.8 Hz, 1H), 3.80 (s, 3H), 3.26 (dd, *J* = 13.0, 3.5 Hz, 1H), 2.98 (dd, *J* = 13.4, 7.6 Hz, 1H). 13-C NMR (126 MHz; d2o): δ 165.5, 162.7, 161.0, 152.0,

148.2, 130.6, 125.6, 123.1, 119.1, 115.1, 69.4, 63.7, 56.0, 54.1, 46.5, 42.0. HRMS (FAB^+): Calcd. for $C_{17}H_{22}N_7O_6S$ [M+H]: 452.1347 Found 452.1353.

(3a*R*,4*R*,9*S*,10*R*,10a*R*)-4-((carbamoyloxy)methyl)-9,10-dihydroxyhexahydropyrrolo[1,2-*c*]purine-2,6(1*H*,8*H*)-diiminium 2,2,2-trifluoroacetate and (3*R*,5*R*,6*S*)-4-((amino(iminio)-methyl)amino)-3-((carbamoyloxy)methyl)-5,6-dihydroxy-2,3, 6,7-tetrahydropyrrolo[1,2-*c*]pyrimidin-1(5*H*)-iminium 2,2,2-trifluoroacetate (40)—Ketone **29** (10 mg) was cooled to 0°C and 0.25 $B(TFA)_3$ in TFA (1 mL) was added. The mixture was allowed to warm to r.t. slowly (leave in the ice bath) and stirred a total of 20h. The mixture was cooled to 0°C and quenched with methanol (2mL). The reaction was evaporated and diluted with methanol (3mL) and evaporated three times. The crude solid was purified via RP-18 flash chromatography (100-80% 0.1% TFA in H_2O/MeCN) to give an inseparable mixture of 40/41 (3:1, 5mg, 69%)

40: ^{1}H-NMR (500 MHz; D_2O): δ 4.65 (dd, *J* = 9.7, 8.6 Hz, 1H), 4.43 (ddd, *J* = 8.9, 5.0, 3.8 Hz, 1H), 4.35 (dd, *J* = 9.5, 4.8 Hz, 1H), 4.27 (d, *J* = 3.5 Hz, 1H), 4.02 (ddd, *J* = 8.8, 6.5, 3.0 Hz, 1H), 3.69 (d, *J* = 8.8 Hz, 1H), 3.54 (dd, *J* = 14.6, 3.1 Hz, 1H), 3.44 (dd, *J* = 14.6, 6.6 Hz, 1H). 13-C NMR (126 MHz; d2o): δ 161.84, 161.75, 158.01, 158.01, 157.54, 157.54, 91.80, 91.80, 72.57, 72.57, 69.84, 69.84, 68.09, 68.09, 63.05, 63.05, 51.62, 51.62, 44.85, 44.85. HRMS (FAB^+): Calcd. for $C_{10}H_{18}N_7O_4$ [M+H]: 300.1409 Found 300.1414.

41: ^{1}H-NMR (500 MHz; D_2O): δ 5.28 (dd, *J* = 9.5, 7.0 Hz, 1H), 4.79 (t, *J* = 9.5 Hz, 1H), 4.66 (d, *J* = 7.4 Hz, 1H), 4.38 (dd, *J* = 9.5, 7.0 Hz, 1H), 3.96 (td, *J* = 7.2, 3.0 Hz, 1H), 3.52 (dd, *J* = 14.4, 3.0 Hz, 1H), 3.31 (dd, *J* = 14.5, 7.2 Hz, 1H). HRMS (FAB^+): Calcd. for $C_{10}H_{18}N_7O_4$ [M+H]: 300.1409 Found 300.1414.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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References and notes

1. Hong CY, Kishi Y. J Am Chem Soc. 1992; 114:7001.
2. Tanino H, Nakata T, Kaneko T, Kishi Y. J Am Chem Soc. 1977; 99:2818. [PubMed: 850038]
3. Jacobi PA, Martinelli MJ, Polanc S. J Am Chem Soc. 1984; 106:5594.
4. Mulcahy JV, Du Bois J. J Am Chem Soc. 2008; 130:12630. [PubMed: 18759394]
5. Fleming JJ, McReynolds MD, Du Bois J. J Am Chem Soc. 2007; 129:9964. [PubMed: 17658800]
6. Fleming JJ, Du Bois J. J Am Chem Soc. 2006; 128:3926. [PubMed: 16551097]
7. Bhonde VR, Looper RE. J Am Chem Soc. 2011; 133:20172. [PubMed: 22098556]
8. Iwamoto O, Nagasawa K. Organic Letters. 2010; 12:2150. [PubMed: 20355743]
9. Iwamoto O, Shinohara R, Nagasawa K. Chemistry - An Asian Journal. 2009; 4:277.
10. Sawayama Y, Nishikawa T. Angew Chem Int Ed. 2011; 50:7176.

11. Yotsu-Yamashita M, Kim YH, Dudley SC Jr, Choudhary G, Pfahnl A, Oshima Y, Daly JW. Proc Natl Acad Sci U S A. 2004; 101:4346. [PubMed: 15070720]
12. Petrini M. Chemical Reviews. 2005; 105:3949. [PubMed: 16277367]
13. Foresti E, Palmieri G, Petrini M, Profeta R. Org Biomol Chem. 2003; 1:4275. [PubMed: 14685331]

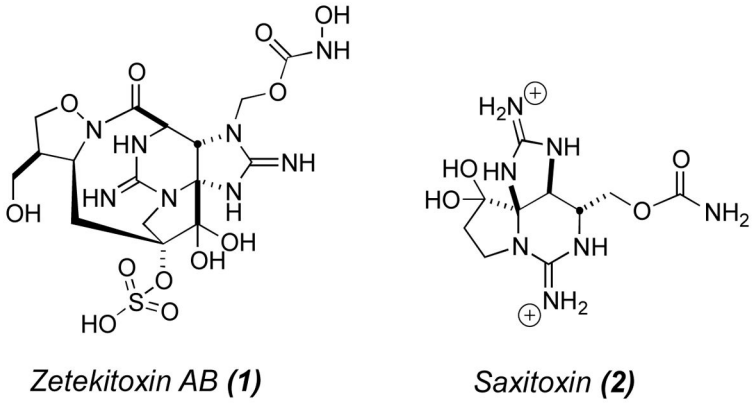
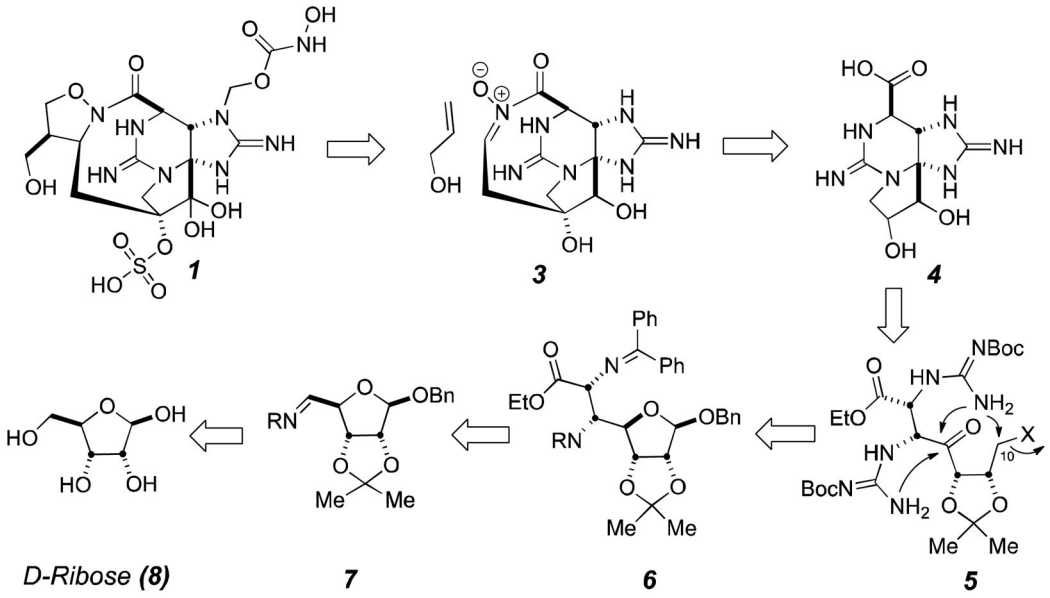
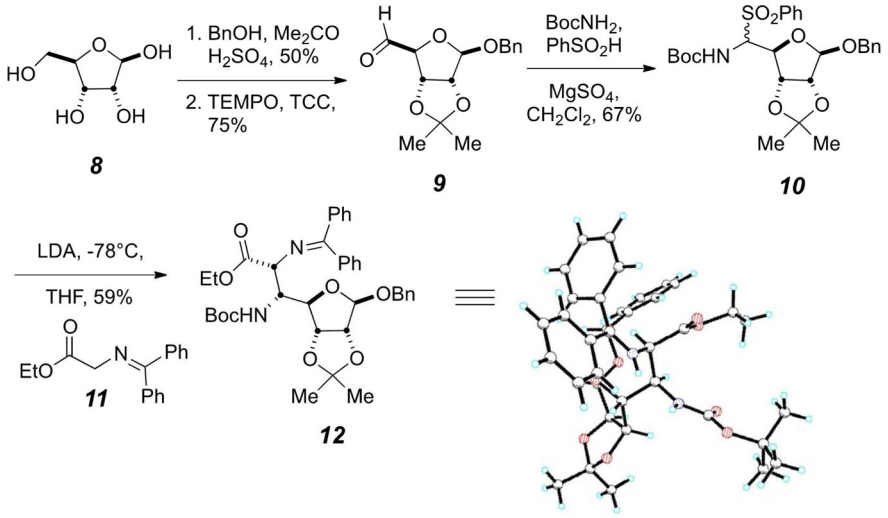


Figure 1.
Structures of Zetekitoxin AB (left) and saxitoxin (right)

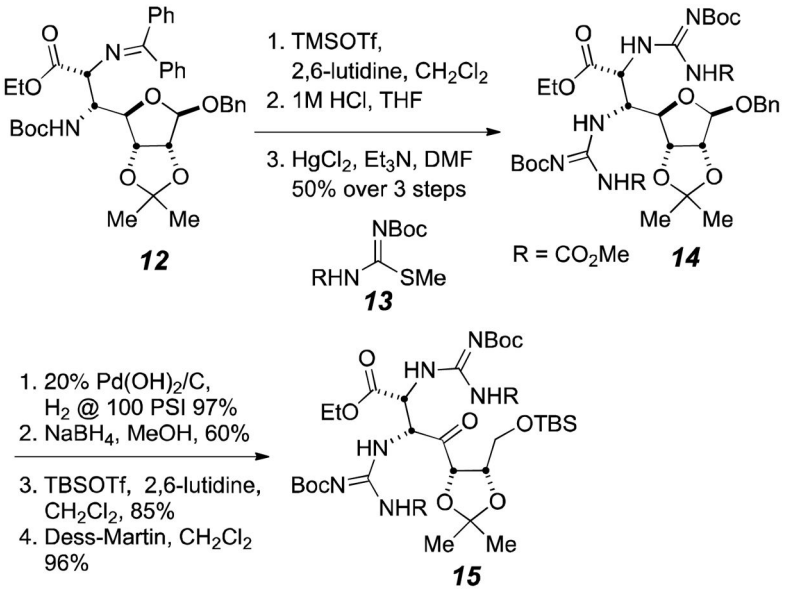


Scheme 1.
Retrosythetic analysis of zetekitoxin AB



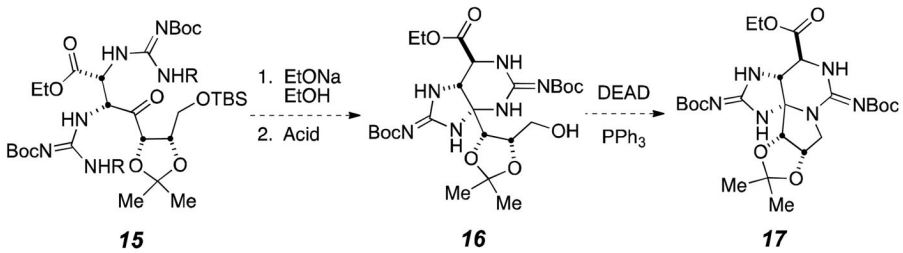
Scheme 2.

Preparation of Mannich product **12** from D-Ribose **(8)**



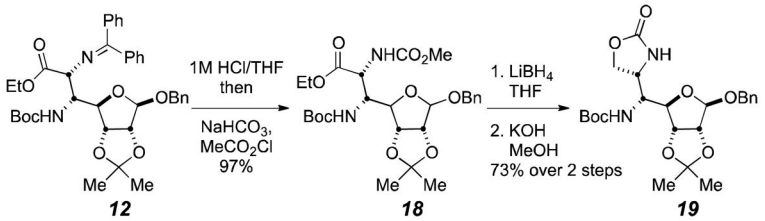
Scheme 3.

Elaboration of Mannich product **12** to ketone **15**



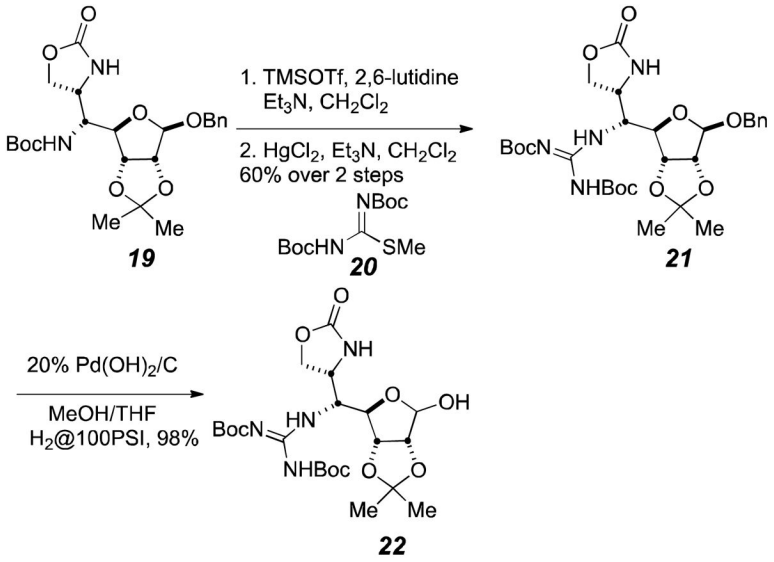
15 ***16*** ***17***

Scheme 4.
Hypothetical formation of tricycle

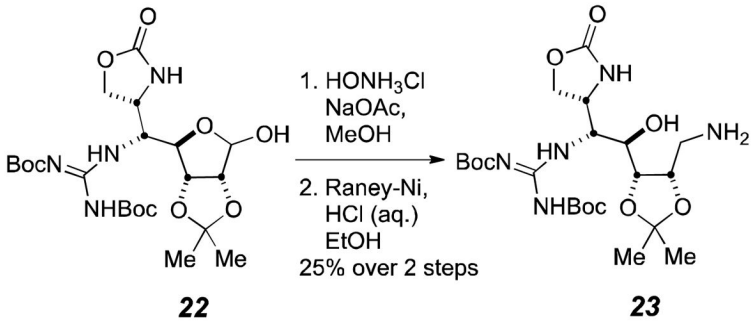


Scheme 5.

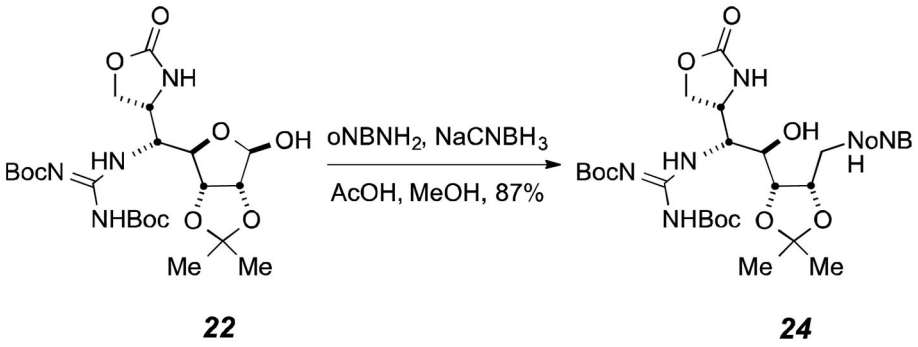
Synthesis of oxazolidinone **19**



Scheme 6.
Preparation of lactol **22**

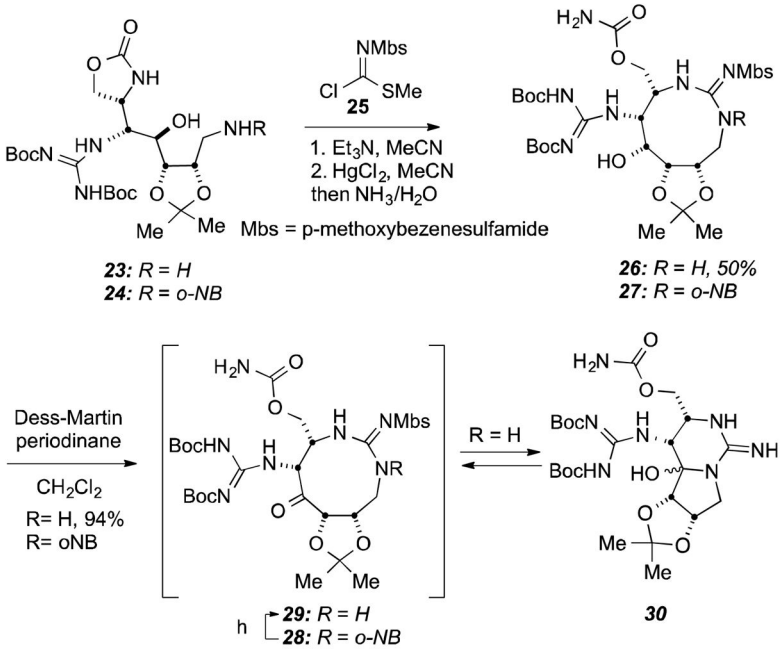


Scheme 7.
Two step installation of amine.

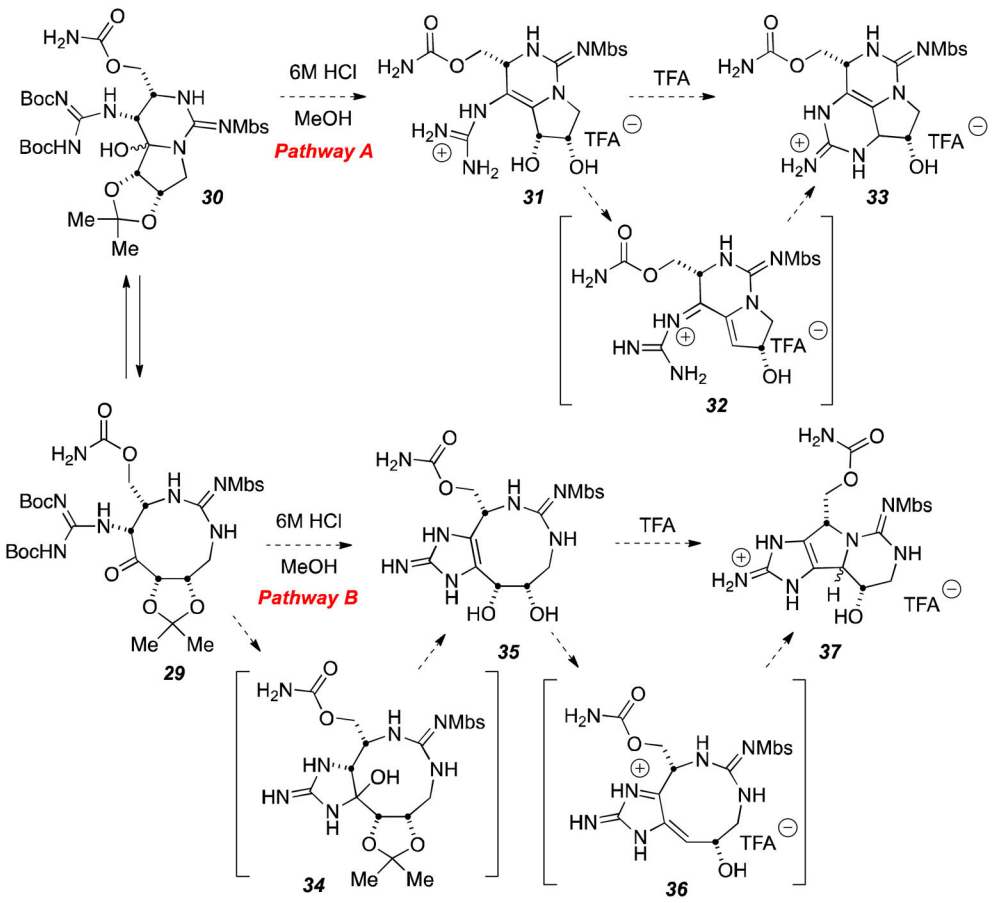


22 **24**

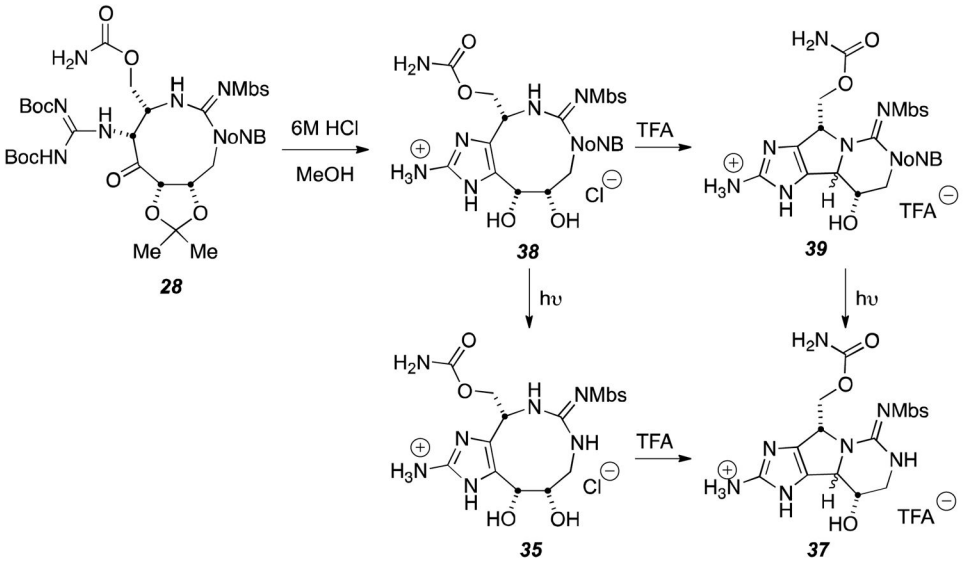
Scheme 8.
Reductive amination with oNB-amine



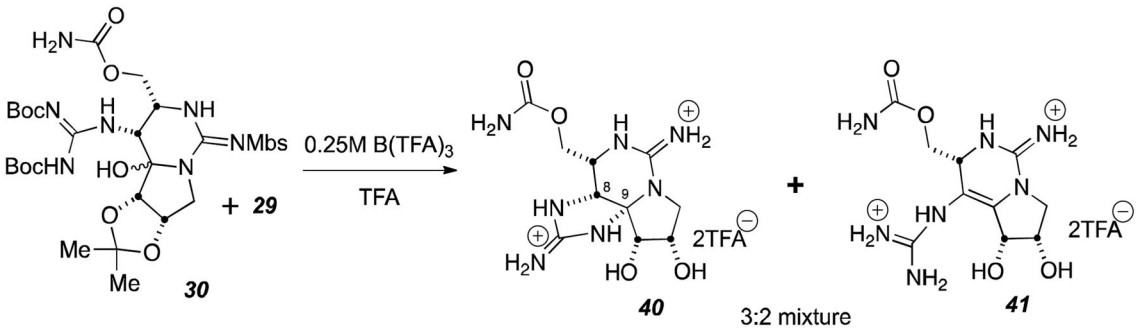
Scheme 9.
Installation and cyclization of the isothiourea



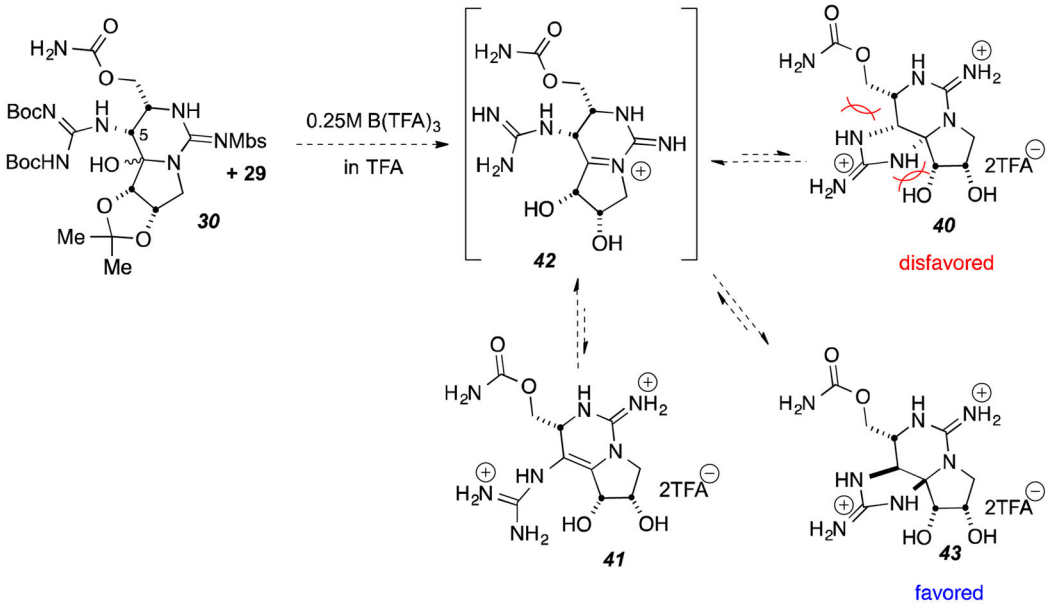
Scheme 10.
Potential cyclization pathways



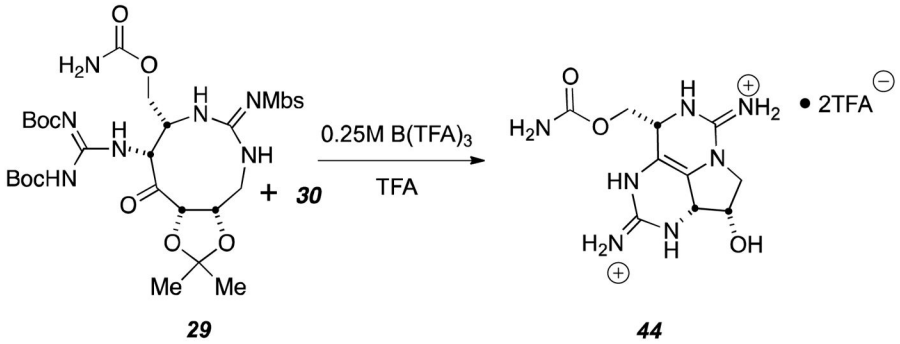
Scheme 11.
Determination of the cyclization pathway



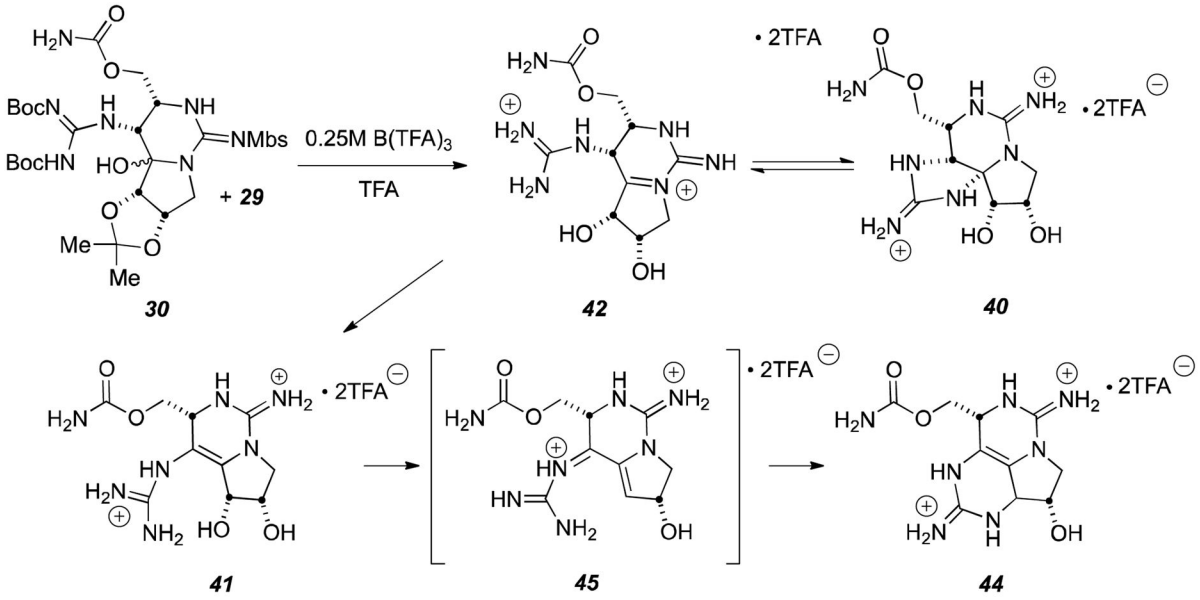
Scheme 12.
Cyclization of hemiaminal **30**



Scheme 13.
Plan to epimerize C-5



Scheme 14.
Preparation of tricycle **44**



Scheme 15.

Modes of reactivity of hemiaminal **30**