Synthetic Studies Toward Pactamycin Highlighting Oxidative C–H and Alkene Amination Technologies

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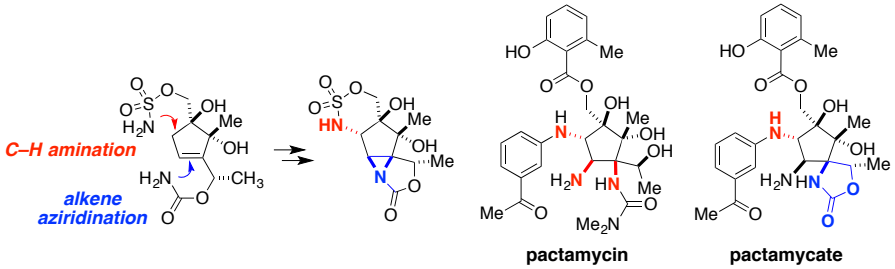
Abstract
A strategy enabled by C–H and alkene amination technologies for synthesizing the aminocyclitol natural product, pactamycin, is disclosed. This work features two disparate approaches for assembling the five-membered ring core of the target, the first of which utilizes acyl anion catalysis and a second involving β-ketoester aerobic hydroxylation. Installation of the C3–N bond, one of three contiguous nitrogen centers, is made possible through Rh-catalyzed allylic C–H amination of a sulfamate ester. Subsequent efforts are presented to introduce the C1,C2 *cis*-diamino moiety en route to pactamycin, including carbamate-mediated alkene aziridination. In the course of these studies, assembly of the core of C2-*epi*-pactamycate, which bears the carbon skeleton and all of the requisite nitrogen and oxygen functional groups found in the natural product, has been achieved.



Introduction
Reaction methods for the selective functionalization of both C–H and π-bonds have shaped the modern practice of synthetic chemistry.[1,2] As part of our efforts to advance such technologies, we have engaged in developing C–H and alkene amination methods for general use in synthesis.[3] Given the structural intricacies and prevalence of nitrogen functional groups in aminocyclitol targets, these molecules present ideal, albeit considerably challenging, problems for the application of such chemistries. Herein, we outline a strategic analysis of pactamycin that features the use of oxidative C–N bond-forming reactions. The following disclosure highlights the successful application of sulfamate and carbamate amination methods for preparing functionally complex carbocyclic structures, and culminates in the preparation of an advanced intermediate comprising the fully substituted cyclopentane core of the natural product.

Background
The ornate chemical structure and pronounced biological activity of pactamycin (**1**), an isolate from the fermentation broth of *Streptomyces pactum* var. *pactum*, distinguish this natural product among the larger family of aminocyclitol metabolites (Figure 1).[4,5] Pactamycin is a potent cytotoxin that displays antibiotic, antiprotozoal, and antiproliferative properties. Biochemical and structural biology studies have shown that this compound blocks both prokaryotic and eukaryotic protein synthesis by binding to a conserved region in the E site of the 30S ribosomal subunit.[6,7] A small number of analogs of **1** display reduced cytotoxicity towards mammalian cells, thus renewing interest in pactamycin-derived compounds for possible therapeutic applications.[8]

Related congeners of pactamycin include: 1) cranomycin (**2**), which lacks a hydroxyl group at C7; 2) the spiro-fused oxazolidinone compound, pactamycate (**3**); and 3) jogyamycin (**4**), which is absent both the 6-methylsalicylate and C7 hydroxyl moieties (Figure 1). Each of these compounds possesses a congested cyclopentane frame replete with heteroatom substitution and stereochemical information at each carbon

center, three of which are tetrasubstituted. A contiguous triamine motif at C1, C2, and C3 is an additional characteristic feature of these molecules. Elegant asymmetric syntheses of pactamycin have been achieved by the Hanessian and Johnson groups, and several creative approaches to this family of natural products have been reported.[9,10,11] The outstanding accomplishments of these works notwithstanding, challenges remain in developing efficient routes to highly substituted, heteroatom-rich frameworks such as those found in pactamycin and other aminocyclitol products. These types of targets have compelled us to evaluate strategies enabled by stereospecific C–H and alkene amination, emergent technologies for simplifying the synthesis of complex amines and amine derivatives.[12]

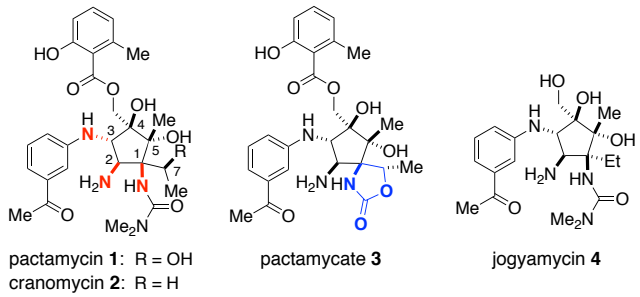


Figure 1. Structures of pactamycin and related congeners.

Results and Discussion

A. Retrosynthetic analysis.

In planning a synthesis of pactamycin, cyclic sulfamate **5** was identified as a strategic intermediate. An advantage of this particular structure was its seeming versatility for installing the array of functional groups across C1, C2, and C7 (*vide infra*). Access to **5** would allow for introduction of the C3-arylamine and C6-salicylate ester groups in the final stages of the assembly process (Figure 2A). This plan exploits the electrophilic nature of [1,2,3]-oxathiazinane-2,2-dioxides, heterocyclic structures, which can be ring-opened under mild conditions through nucleophilic displacement of the C–O bond.[12a, 13] The oxathiazinane unit also functions as a convenient mask of both the C3-N and C4–O centers, thus allowing for manipulation of **5** to install the requisite C1, C2, and C7 groups. Access to oxathiazinane **5** would feature allylic C–H amination with sulfamate ester **6**, exploiting the intramolecular nature of this reaction to control site and stereochemical selectivity. The preparation of **6** could follow from cyclopentanone **7** through enol triflate cross coupling to add the two-carbon unit at C1.

Two strategies were examined for constructing cyclopentenone **6**. The first exploited an acyl anion cyclization reaction of an acyclic keto-aldehyde **8**. The salient feature of this approach was to transform a complex problem in cyclic stereocontrolled synthesis to one involving the assembly of an acyclic substrate **8** bearing a single tetrasubstituted stereocenter. Alternatively, the cyclopentane core of pactamycin could derive from an ester such as **10** (Figure 2B). Following this retrosynthetic logic, **10** would be obtained from inexpensive 2-oxo-cyclopentanecarboxylate **11** through a series of maneuvers that included enantioselective β-ketoester hydroxylation.[14]

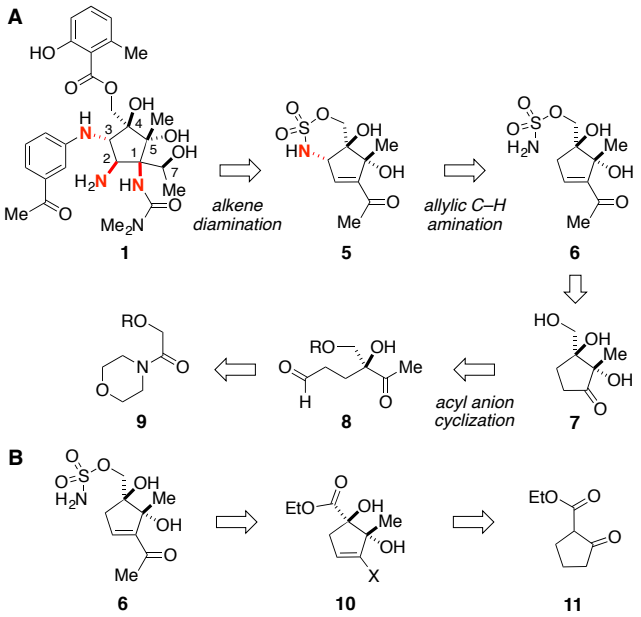


Figure 2A. Retrosynthetic analysis of **1**. **2B.** An alternative strategy for assembling the cyclopentane core of **1**.

Several tactics were considered for executing the critical diamination of the C1,C2 alkene.[15] This problem, along with a general interest in developing methods for synthesizing 1,2-diamines, prompted us to devise an oxidative protocol that relies on a novel bifunctional nitrogen reagent, $H_2NS(O)_2NHBoc$, for converting olefins to cyclic sulfamides (Figure 3A).[16] Hydrolytic ring opening of the sulfamide affords differentially-protected vicinal diamines. Pactamycin offers a compelling test for the application of this technology. An alternative plan could utilize a C7 1° carbamate to promote intramolecular C1,C2 alkene aziridination (Figure 3B). Subsequent aziridine ring opening through a double-inversion process would afford a vicinal diamine derivative in the proper *cis*-stereochemical configuration. As installation of the C1 and C2 amino groups has proven a roadblock in our efforts to synthesize pactamycin and pactamycate, other ideas were also examined for manipulating enone **5** and the corresponding allylic alcohol, and are briefly highlighted in the relevant sections below.[17]

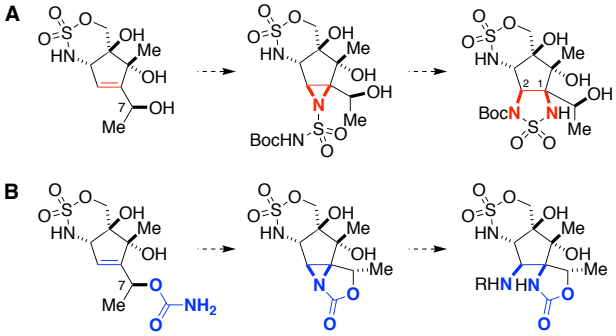
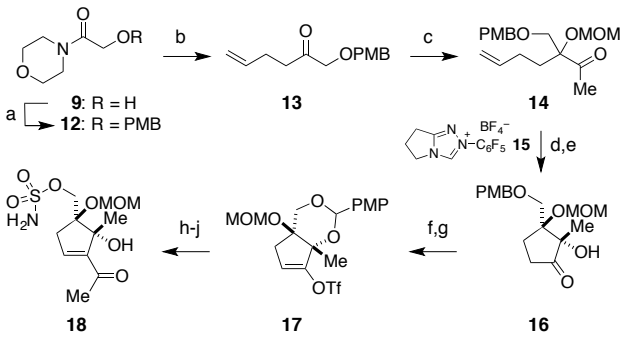


Figure 3A. Sulfamide aziridination/isomerization for vicinal diamination of the C1,C2 alkene. **3B.** C1,C2 alkene aziridination through carbamate oxidative cyclization.

B. Cyclopentane assembly: 1st and 2nd generation syntheses.

In a first approach to the assembly of a polyfunctionalized cyclopentanone analogous to **7,** we exploited chemistry developed by Rovis and coworkers to promote intramolecular acyl anion addition of a ketoaldehyde intermediate.[18] To initiate this synthesis, morpholine amide **9**, a commercially available

compound that is also readily prepared in two steps from glycolic acid, served as the starting material (Scheme 1).[19] A straightforward sequence involving *para*-methoxybenzyl (PMB) protection of the 1° alcohol in **9** followed by 3-butenyl Grignard addition delivered ketone **13**. Using a protocol developed by Brandsma, ethyl vinyl ether was metalated and added to **13** in the presence of LiBr to mitigate competitive enolization.[20] The resultant alkoxide was directly trapped as the mixed acetal upon addition of methoxymethyl chloride (MOMCl). Addition of citric acid to hydrolyze the ethyl enol ether delivered methyl ketone **14** in 86% overall yield. The efficiency of this sequential 'one-pot' process enabled access to large quantities of this material (>13 g). Following Os-catalyzed oxidative cleavage of the terminal alkene in **14**, treatment of the unpurified ketoaldehyde with triazolium catalyst **15** effected the key cyclization reaction.[18,21] Under these conditions, the desired cyclopentanone **16** was obtained in 53% isolated yield.[22] Oxidation of the PMB ether with DDQ enabled protection of both the 1° and 3° alcohol groups in the form of a benzylidene acetal. This reaction, along with subsequent enol triflate formation, proceeded smoothly in 79% (two steps) to afford **17**. Stille cross-coupling of enol triflate **17** with tributyl(1-ethoxyvinyl)tin was followed by hydrolysis of both the enol ether and benzylidene acetal.[23,24,25] Finally, the resultant diol was selectively converted to sulfamate **18**. Overall, this effective, albeit somewhat lengthy process (10 steps) for synthesizing **18**, proved capable of delivering sufficient amounts of racemic material for exploration of both C–H and π-bond amination chemistries.

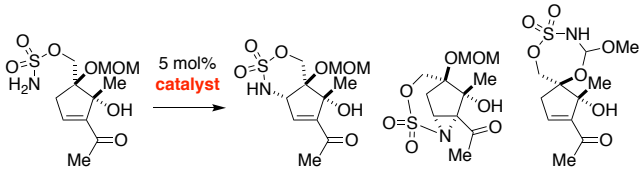


Scheme 1. *Reagents and conditions:* (a) PMBCl, NaH, THF, 65 °C; (b) 4-bromo-1-butene, Mg, THF, 0 °C, 85% (2 steps); (c) ethyl vinyl ether, *t*-BuOK, *n*-BuLi, LiBr, THF, –78 °C; then **13**, THF; then MOMCl, 0 °C; then 1.0 M aqueous citric acid, 86%; (d) 1 mol% OsO_4, $NaIO_4$, 2,6-lutidine, dioxane, H_2O; (e) 20 mol% **15**, 20 mol% NaOAc, $CHCl_3$, 53% (2 steps), 3.5:1 dr; (f) DDQ, CH_2Cl_2, 4 Å molecular sieves, 85%; (g) $KN(SiMe_3)_2$, $PhNTf_2$, THF, –78 °C, 93%; (h) tributyl(1-ethoxyvinyl)tin, 10 mol% $Pd(PPh_3)_4$, LiCl, CuCl, DMSO; (i) 1.0 M aqueous HCl, dioxane, 52% (2 steps); (j) $ClSO_2NH_2$, pyridine, DMA, 83%. PMB = *para*-methoxybenzyl, PMP = *para*-methyoxphenyl, MOM = methoxymethyl, DDQ = 2,3-dichloro-5,6-dicyano-*p*-benzoquinone, Tf = trifluoromethanesulfonate.

Our approach to pactamycin was contingent on sulfamate **18** undergoing selective, intramolecular allylic C–H amination to install the C3–N center of the natural product. This substrate presents a challenging test for C–H amination chemistry, as electron withdrawing groups proximal to the desired site of oxidation generally have deleterious effects on reaction efficiency.[26] In addition, reactions of homoallylic sulfamates are often marred by competing π-bond oxidation to generate aziridine products. High levels of chemoselectivity for allylic C–H amination over alkene aziridination have been noted, however, in reactions utilizing Ru, Fe, Ag, and Co catalysts.[12c–f, 27] Accordingly, we examined a variety of these catalyst systems to effect conversion of **18** to **19** (Table 1). Somewhat surprisingly, the application of $[Ru_2(esp)_2]SbF_6$ to promote oxidative cyclization of **18** led to exclusive functionalization of the methoxymethyl protecting group (Table 1, entry 1). Switching to the 2-hydroxypyridine-derived catalyst, $[Ru_2(hp)_4Cl]$, altered the reaction outcome to favor allylic amine **19**, but only a trace amount of the desired product was generated under these conditions (entry 2). Experiments with both AgOTf/phenanthroline and Fe phthalocyanine catalysts afforded no isolable oxidation products (entries 3 and 4).[12d,e] Three dirhodium tetracarboxylate complexes were also tested, among which $[Rh_2(esp)_2]$

afforded oxathiazinane **19** as a single diastereomer along with aziridine **20** and MOM insertion product **21** in a 2:2:1 ratio (entry 5).[28] The formation of aziridine **20** was somewhat unexpected given the electron-deficient nature of the reacting π-bond.[29] Screening additional dirhodium tetracarboxylate complexes showed that the sterically bulky catalyst [$Rh_2(O_2CCPh_3)_4$] was optimal, providing the highest ratio of the allylic C–H amination product while suppressing oxidation of the MOM-acetal. By employing this particular complex, oxathiazinane **19** could be obtained in 50% isolated yield (entry 6). Given the success of [$Rh_2(O_2CCPh_3)_4$] for facilitating oxidation of **18**, we also examined [Rh_2(*S*-BTPCP)$_4$], a catalyst of considerable steric size developed by the Davies group.[30] Using this system, both the allylic amine **19** and MOM insertion **21** products were generated; unfortunately, formation of the latter negated any beneficial effect of suppressing aziridine formation (entry 7). Although no catalyst was identified to bias exclusive formation of **19**, the effectiveness of [$Rh_2(O_2CCPh_3)_4$] allowed us to advance sufficient quantities of material for evaluating subsequent reactions. Notably, sulfamate **18** represents one of the more complex substrates successfully subjected to allylic C–H amination.[12,31] Further efforts are warranted to identify catalyst systems that enable higher levels of chemoselectivity in allylic oxidation reactions.

Table 1. Transition metal-catalyzed oxidation of **18**.



Entry	Catalyst	Conditions[a]	Ratio (19/20/21)[b]
1	[Ru_2(esp)$_2$]SbF_6	A	0:0:1[c]
2	[Ru_2(hp)$_4$Cl]	A	1:0:0[d]
3	AgOTf, phen (1:3)	B	decomposition
4	[FePc]Cl	C	no conversion
5	[Rh_2(esp)$_2$]	D	2:2:1[c]
6	**[$Rh_2(O_2CCPh_3)_4$]**	**D**	**2:1:0[e]**
7	[Rh_2(*S*-BTPCP)$_4$]	D	3:1:3[c]

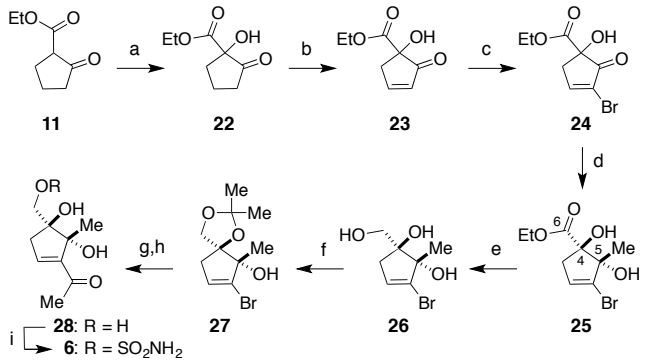
[a]Condition A: PhI(OPiv)$_2$, 5 Å molecular sieves, CH_2Cl_2, 40 °C; Condition B: PhIO, 4 Å molecular sieves, CH_2Cl_2; Condition C: PhI(OPiv)$_2$, $AgSbF_6$, 4:1 PhMe/MeCN; Condition D: PhI(OAc)$_2$, MgO, *i*-PrOAc. [b]Product ratio determined by ^{1}H NMR integration. [c]Starting material consumed. [d]Product formation is < 5%. [e]50% isolated yield of **19**. esp = α,α,α',α'-tetramethyl-1,3-benzenedipropionate, hp = 2-oxypyridinate, phen = 1,10-phenanthroline, Pc = phthalocyanine, *S*-BTPCP = (1*S*)-1-(4-bromophenyl)-2,2-diphenylcyclopropanecarboxylato.

Having established a 'proof-of-concept' synthesis of **19**, we desired a more concise sequence to this product as well as a route that would afford optically enriched material. Our second-generation approach commenced from ethyl 2-oxo-cyclopentanecarboxylate **11**, an inexpensive starting material that can be oxidized under aerobic conditions to give decagram quantities of ketoalcohol **22** (Scheme 2).[32] Asymmetric variants of this process that rely on terminal oxidants such as 4-chloro-nitrosobenzene have been reported and afford the alcohol product in high enantiomeric excess (93% ee).[14] For our purposes, racemic **22** was used throughout the development phase of this work.

Extensive efforts to manipulate **22** to enone **23** using standard ketone desaturation conditions (e.g., Saegusa-Ito, α-selenoxide elimination, halogenation/elimination) failed to deliver appreciable amounts of the desired product.[33] Fortunately, a modified procedure developed by Diao and Stahl employing $Pd(OAc)_2$ and DMSO in AcOH furnished enone **23** in 79% yield.[34] Subsequent α-bromination of this product provided **24**. Installation of the C5 3° alcohol (pactamycin numbering) on bromoenone **24** would necessitate chemo- and diastereoselective 1,2-addition of a Me-nucleophile. To accomplish this rather

demanding transformation, we envisioned utilizing the C4 hydroxyl group to 'deliver' an appropriate organometallic reagent to the C5 carbonyl from the requisite stereoface.[35] Initial attempts to effect this reaction focused on the use of either Me_3Al or Me_2Zn (or the corresponding anionic '-*ate* complexes' generated by addition of MeLi) as Me-anion equivalents. Reactions with these reagents and reagent combinations, however, failed to promote 1,2-addition, instead either returning unreacted starting material **24** or leading to mixtures of unidentifiable products. Treatment of **24** with MeMgCl fared better, giving some of the desired alcohol product (< 35%). In combination with a lanthanide additive such as $LaCl_3$•2LiCl, reaction performance was markedly improved, and diol **25** was isolated in 50% yield.[36] The majority of the mass balance is attributed to competing 1,4- and ester addition reactions – none of the *cis*-diol diastereomer was obtained.

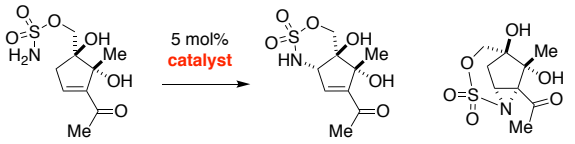
Conversion of the ester moiety to the C6 hydroxymethyl group was achieved with *i*-Bu_2AlH, which smoothly supplied triol **26** (Scheme 2). After acetonide protection of the C4,C6 diol**,** Stille cross-coupling of vinyl bromide **27** with tributyl(1-ethoxyvinyl)tin proceeded in 65% yield.[37] Concomitant acetonide and enol ether hydrolysis with trifluoroacetic acid then afforded enone **28**. Alternatively, subjecting triol **26** to the Stille cross-coupling conditions followed by an acidic aqueous workup gave **28** in a single-step process in 46% yield. The three-step sequence, however, proved more reproducible and amenable to scale-up. Finally, selective sulfamoylation of triol **28** delivered sulfamate **6** in 55% yield.[38] This sequence affords **6** in seven steps from ketoester **11** (nine if one includes the optional acetonide protection/deprotection steps) and is amenable to production of either enantiomer of the sulfamate ester.



Scheme 2. *Reagents and conditions:* (a) 5 mol% $CeCl_3$•$7H_2O$, O_2 (1 atm), *i*-PrOH, 70%; (b) $Pd(OAc)_2$, DMSO, AcOH, 80 °C, 79%; (c) Br_2, Et_3N, CH_2Cl_2, 0→23 °C, 91%; (d) MeMgCl, $LaCl_3$•2LiCl, THF, −40 °C, 50%; (e) *i*-Bu_2AlH, THF, −78→23 °C, 67%. (f) 2,2-dimethoxypropane, CSA, THF, CH_2Cl_2, 86%; (g) tributyl(1-ethoxyvinyl)tin, 10 mol% $Pd(OAc)_2$, 11 mol% XPhos, CsF, 1,4-dioxane, 80 °C, 65%; (h) CF_3CO_2H, MeCN, H_2O, 70%; (i) H_2NSO_2Cl, pyridine, MeCN, 0→23 °C, 55%. CSA = camphorsulfonic acid.

Following our earlier study of amination conditions with sulfamate **18**, a small number of dirhodium and diruthenium catalysts were tested with the closely related structure **6** to promote the desired cyclization reaction (Table 2). Reactions with $[Ru_2(esp)_2]SbF_6$ and $[Ru_2(hp)_2Cl]$ failed to give either the insertion **5** or aziridination **29** products, and simply resulted in decomposition of starting material (entries 1 and 2). By contrast, use of $[Rh_2(esp)_2]$ furnished oxathiazinane **5** and aziridine **29** as a 1.1:1 mixture in high conversion (>95%, entry 3). Use of the sterically encumbered $[Rh_2(O_2CCPh_3)_4]$ complex resulted in a slight improvement in the product ratio (1.6:1 **5**/**29**) and allowed for the isolation of oxathiazinane **5** in 56% yield (entry 4).

Table 2. Allylic C–H amination of sulfamate **6**.



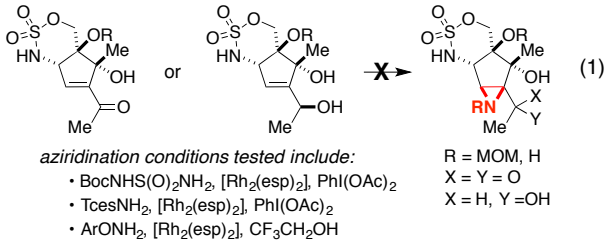
6 **5** **29**

Entry	Catalyst	Conditions[a]	Ratio (5/29)[b]
1	$[Ru_2(esp)_2]SbF_6$	A	decomposition
2	$[Ru_2(hp)_4Cl]$	A	decomposition
3	$[Rh_2(esp)_2]$	B	1.1:1
4	$[Rh_2(O_2CCPh_3)_4]$	B	1.6:1[c]

[a]Condition A: $PhI(OPiv)_2$, 5 Å molecular sieves, CH_2Cl_2, 40 °C; Condition B: $PhI(OAc)_2$, MgO, *i*-PrOAc, 40 °C. [b]Product ratio determined by ^1H NMR integration. [c]Isolated **5** in 56% yield and **29** in 35%.

C. Studies to install the C1,C2 diamine.

With the availability of cyclic sulfamate **5**, conditions for introducing the two amino groups at C1 and C2 were examined. In our initial attempts, aziridination of the C1,C2 alkene using different nitrogen sources was attempted with both enone **5** and the corresponding C7 allylic alcohol (Figure 3). These protocols included ones previously developed by our lab using either $H_2NS(O)_2NHBoc$ or $TcesNH_2$ (Tces = $S(O)_2CH_2CCl_3$), as well as a method for N–H aziridination described by Kürti and Falck employing *O*-(2,4-dinitrophenyl)hydroxylamine (DPH).[16,39,40] With either the ketone or allylic alcohol substrate, no aziridine products were generated under the conditions tried (eq 1). The electron-withdrawn and sterically crowded nature of the C1,C2 alkene in **5** (and the related C7 allylic alcohol) make this a particularly challenging substrate for electrophilic aziridination.



(1)

aziridination conditions tested include:
- $BocNHS(O)_2NH_2$, $[Rh_2(esp)_2]$, $PhI(OAc)_2$
- $TcesNH_2$, $[Rh_2(esp)_2]$, $PhI(OAc)_2$
- $ArONH_2$, $[Rh_2(esp)_2]$, CF_3CH_2OH

In considering alternative tactics for modifying the C1,C2 alkene in **5** and analogous structures, our focus turned to intramolecular oxidative chemistry of allylic carbamates.[41] A successful reaction of this type would deliver the spiro-fused oxazolidinone heterocycle found in pactamycate **3**. Acccordingly, two different ideas were envisioned, the first of which would involve an initial 1,4-addition (aza-Michael) to enone **5** to install the C2 amino group; introduction of the C1–N center could then be accomplished through carbamate C–H insertion (Figure 4).[42] A second approach would follow through an unusual oxazolidinone-aziridine intermediate (see Figure 3B) and rely on a stereoretentive ring opening reaction (i.e., double displacement) to introduce the C2 amine. Given the complexity of the substrates involved, each of these proposals would present a stringent test of methods for carbamate oxidative cyclization.

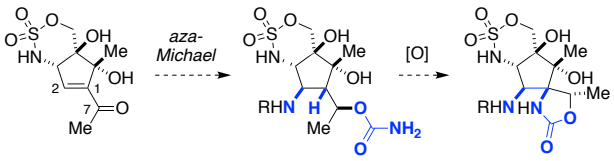
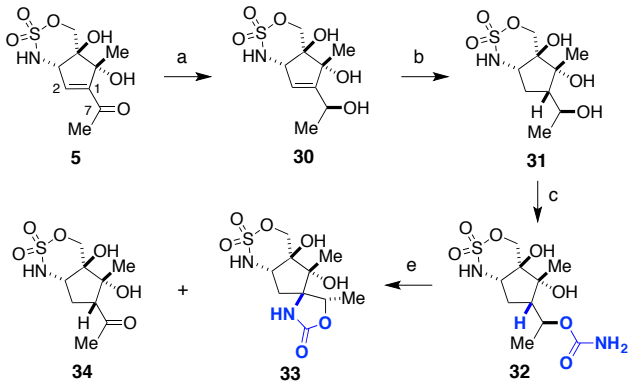


Figure 4. Aza-Michael/stereospecific carbamate C–H amination approach for installing the C1,C2 *cis*-diamine.

To examine the feasibility of constructing the C1–N bond through carbamate C–H amination, a simplified model substrate lacking the C2 nitrogen group was initially prepared from enone **5**. Reduction of this compound with $CeCl_3$ and $NaBH_4$ afforded allylic alcohol **30** in 74% yield, along with 21% yield of the undesired C7 epimer (Scheme 3).[43,44] Catalytic hydrogenation of allylic alcohol **30** occurred exclusively from the convex face of the bicycle to furnish the saturated product **31**. Subsequent carbamoylation of the C7 alcohol with trichloroacetyl isocyanate afforded carbamate **32** in 78% yield over two steps. Subjecting **32** to conditions for C–H amination gave oxazolidinone **33** in 25% yield as a single diastereomer along with 25% of methyl ketone **34** and 50% recovered starting carbamate **32**.[45] Although these results confirmed to our satisfaction the viability of the C–H amination reaction, the product yield was less than desired and we assumed that the introduction of a polar functional group at C2 would further diminish the performance of this process.[26,46] This was indeed the case, as attempts to promote carbamate oxidative cyclization on C2-substituted intermediates (prepared through aza-Michael addition reactions and C2-ketone reductive amination) uniformly failed.[17] Thus, we turned to alternative tactics for installing the C1,C2 *cis*-diamine. The inability to promote efficient oxidation with substrates such as **32** encourages further exploration of C–H amination catalysis.

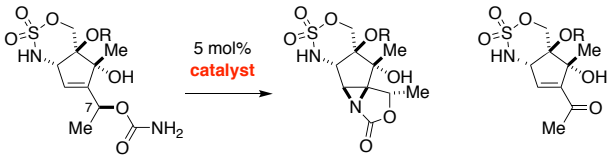


Scheme 3. Exploratory study for intramolecular carbamate C–H amination. *Reagents and conditions:* (a) $NaBH_4$, $CeCl_3$•$7H_2O$, MeOH, THF, −78 °C, 74%; (b) H_2 (1 atm), PtO_2, EtOH; (c) $Cl_3CC(O)NCO$, THF, CH_2Cl_2; then K_2CO_3, MeOH, 78% over 2 steps; (d) 5 mol% [$Rh_2(HNCOCF_3)_4$], $PhI(OAc)_2$, MgO, *i*-PrOAc, 25%.

Parallel explorations with substrates derived from both enones **19** and **5** were conducted to find a solution for installing the C1,C2 nitrogen centers. Carbamate **35** was readily obtained from enone **19** in two steps, and this compound was subjected to a series of conditions capable of promoting intramolecular aziridination. Upon treating carbamate **35** with 5 mol% [$Rh_2(esp)_2$], $PhI(OAc)_2$ oxidant, and MgO, aziridine **36** formed as a single diastereomer, albeit in a modest 10% isolated yield (Table 3, entry 1). A rationale for the high stereoselectivity noted in this transformation posits that the desired transition structure is favored by the topology of the bicyclic ring system and minimization of an $A^{1,2}$-interaction (Figure 5).[47] Rather remarkably, this seemingly ring-strained tetracyclic product could be purified by silica gel chromatography and was amenable to prolonged storage at −20 °C. A major side product of the oxidative cyclization reaction was enone **19**. Of the four different dirhodium catalysts (entries 1–3, 5) tested, the trifluorocarboxamidate complex, [$Rh_2(NHCOCF_3)_4$] proved most effective, yielding an ~1:1 ratio of oxazolidinone **36**/enone **19**. The former product was isolated as a single stereoisomer in 37% yield along with 36% yield of enone **19**. Interestingly, the sterically largest catalyst, [$Rh_2(O_2CCPh_3)_4$],

failed to deliver any of the desired product (entry 5). Similar results were noted with carbamate **37** (derived from enone **5**), with [$Rh_2(NHCOCF_3)_4$] proving most effective at generating aziridine **38** (entry 6).

Table 3. Intramolecular carbamate aziridination.



35: R = MOM
37: R = H

36: R = MOM
38: R = H

19: R = MOM
5: R = H

Entry	Catalyst	Conditions[a]	R	Ratio (36/19/35)[b]
1	[$Rh_2(esp)_2$]	A[c]	MOM	1:2.7:2
2	[$Rh_2(OAc)_4$]	A	MOM	1:1:0.9
3	[$Rh_2(HNCOCF_3)_4$]	A	MOM	1:0.9:1.8
4	**[$Rh_2(HNCOCF_3)_4$]**	**B**	**MOM**	**1:0.9:0[d]**
5	[$Rh_2(O_2CCPh_3)_4$]	B	MOM	0:1:0.6
6	**[$Rh_2(HNCOCF_3)_4$]**	**C**	**H**	**3.5:1:2.4[e]**

[a]Condition A: $PhI(OAc)_2$, MgO, CH_2Cl_2; Condition B: $PhI(OAc)_2$, MgO, C_6H_6, 65 ºC; Condition C: $PhI(OAc)_2$, MgO, *i*-PrOAc. [b]Product ratio determined by ^1H NMR integration. [c]Reaction performed with *i*-PrOAc as solvent. [d]Isolated **36** in 37% yield. [e]Ratio of **38**/**5**/**37**. Isolated **38** in 38% yield.

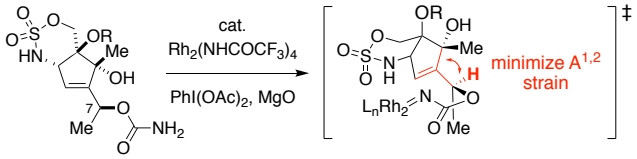
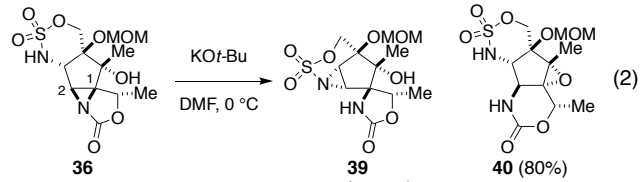


Figure 5. Favored transition structure for alkene aziridination minimizes allylic strain.

Transforming aziridine **36** (or **38**) to the proper C2 amine epimer was envisioned through a S_N2 double inversion sequence. In our original manifestation of this process, we surmised that the C3–N of the oxathiazinane ring could facilitate aziridine ring opening (eq 2). Subsequent addition at C2 of a nitrogen-based nucleophile (e.g., N_3^-) would afford the fully elaborated core of the natural product. The product of the isomerization reaction **39** was speculated to be less strained that the starting material given the 'plasticity' of the S-center in the oxathiazinane ring and known stability of related aziridines derived from homoallylic sulfamates.[11h,29,48] The enforced spatial positioning and relative orientation of the C3–N would also favor this isomerization reaction. To accomplish the desired rearrangement of **36**, this intermediate was treated with KO*t*-Bu, which resulted in clean consumption of the starting material. The isolated product, however, was determined to be the tetrasubstituted epoxide **40** (80%) and not aziridine **39**. Although nucleophilic opening of the epoxide at C1 could, in principle, deliver the fully substituted core of pactamycin, attempts to achieve such a transformation using different combinations of azide and Lewis acids (e.g., $MgCl_2$, $LiClO_4$) only led to decomposition and/or recovery of starting material.[49]



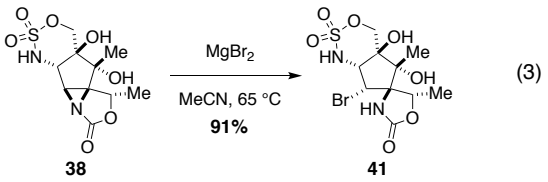
36

39
not observed

40 (80%)

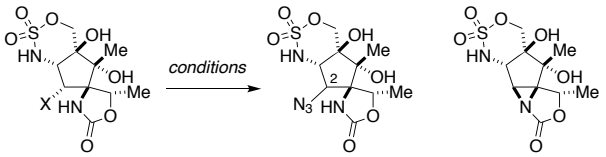
(2)

In a second approach for elaborating aziridine **36** (or **38**) into pactamycin, we examined conditions that would introduce a halide substituent at C2. Ring opening to form the C2 alkyl halide could then be followed by azide displacement (eq 3). Much of this work was performed with aziridine **38** to minimize potential complications with azide addition stemming from the steric encumbrance of the MOM-protecting group. We were pleased to find that the first step of this process was straightforward, as treatment of **38** with $MgBr_2$ in MeCN at 75 °C efficiently furnished bromide **41** in 91% yield.[50] In contrast, when other bromide sources including $LiBr/LiClO_4$ and *n*-Bu_4NBr were surveyed, little to no amounts of the desired bromide **41** were obtained. Unfortunately and despite evaluating a number of conditions for S_N2 reactions, most attempts to displace the C2 alkyl bromide resulted in decomposition of the starting material (Table 4). The use of *n*-Bu_4NN_3 in MeCN cleanly provided an azide product, but ^1H NMR analysis confirmed that the stereochemical configuration at C2 was undesired (entry 2). We assume that this product results from the surprisingly facile regeneration of aziridine **38** followed by azide ring opening. To mitigate this process, protic solvents were evaluated to temper the basicity of N_3^- and disfavor ionization of the oxazolidinone. Conditions employing alcohol solvent such as *i*-PrOH and H_2O only led to unproductive consumption of the starting material (entry 3). Other ideas that included the use of Ag salts to facilitate halide ionization and C2 radical generation followed by trapping with $PhSO_2N_3$ also proved unsuccessful (entries 4 and 5).[51]



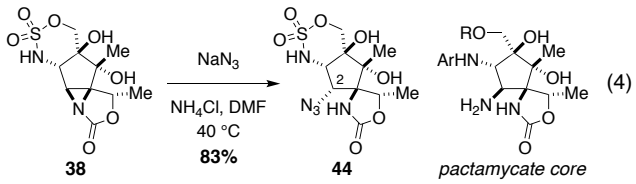
(3)

Table 4. Attempts to form the C2–N bond.



Entry	X	Conditions	Result
1	Br	NaN_3, DMF, 70 °C	decomposition
2	Br	*n*-Bu_4NN_3, MeCN, 55 °C	**44**
3	Br	NaN_3, *i*-PrOH, H_2O, 45 °C	decomposition
4	I	NaN_3, $AgNO_3$, DMF	recovered **42** + **38**
5	I	$PhSO_2N_3$, $(Bu_3Sn)_2$, C_6H_6/EtOAc, hv	decomposition

Absent a viable pathway for introducing the C1,C2 *cis*-diamine, the epimeric C2-azide **44** was prepared directly from **38** upon treatment with NaN_3 and NH_4Cl. These conditions furnish the azide product in 83% yield (eq 4). Azide **44** embodies the complete carbon skeleton of pactamycin with all of the requisite heteroatom connectivity, and should function as an intermediate en route to C2-*epi*-pactamycate and C2-*epi*-pactamycin. Using the second-generation route for the synthesis of the cyclopentane core, azide **44** was prepared in 12 steps from commercially available ethyl 2-oxo-cyclopentanecarboxylate without the use of protecting group manipulations (or 14 steps with an optional protection/deprotection in converting triol **26** to enone **28**). Few pactamycin analogues with variation of the aminocyclitol core have been reported and thus the chemistry described herein offers a possible entry to such compounds.



Conclusions

A strategy featuring the application of contemporary technologies for the selective oxidation of C–H and π-bonds to access structurally elaborate, nitrogen-rich molecules has been outlined for the synthesis of pactamycin. We have demonstrated that the cyclopentane core of this natural product can be assembled through two disparate routes, both of which converge on a key sulfamate ester. Oxidative cyclization of this intermediate under dirhodium-catalyzed conditions results in chemoselective allylic C–H amination to install the first of three nitrogen centers. Efforts to introduce two additional nitrogen groups at C1 and C2 aimed to capitalize on analogous amination reactions of carbamate derivatives. Although the implementation of these ideas did not give way to the natural product, in the course of these studies we have successfully assembled the core of C2-*epi*-pactamycate – a structure that bears all of the requisite nitrogen and oxygen functional groups present in the target molecule.

The many challenges associated with the synthesis of pactamycin and related aminocyclitol natural products continue to drive innovation. In this regard, we expect that an efficient route to the desired target will be realized in parallel with the identification of new catalysts for controlling C–H amination as well as new methods for vicinal diamination of alkenes.

Experimental Section

General Information: All reagents were obtained commercially unless otherwise noted. Reactions were performed using glassware that was flame-dried under vacuum (~1 Torr). Air- and moisture-sensitive liquids and solutions were transferred via syringe or stainless steel cannula. Organic solutions were concentrated under reduced pressure (~15 Torr) by rotary evaporation. Solvents were purified by passage under 12 psi N_2 through activated alumina columns. Chlorosulfonyl isocyanate was purchased from Acros Chemicals, transferred via cannula to a Schlenk flask, and stored at –20 ºC. Chromatography was performed on either Silicycle Silia-P Silica Gel (40-63 μm) or Fisher Davisil Grade 643 Type 150A silica gel (200-425 mesh). Compounds purified by chromatography were typically applied to the adsorbent bed using the indicated solvent conditions with a minimum amount of added chloroform as needed for solubility. Thin layer chromatography was performed on either Whatman Partisil K6F Silica Gel 60 Å plates (250 μm) or EMD Chemicals Silica Gel 60 F_{254} plates (250 μm). Visualization of the developed chromatogram was accomplished by fluorescence quenching or by staining with butanolic ninhydrin, aqueous potassium permanganate, or aqueous ceric ammonium molybdate (CAM).

Nuclear magnetic resonance (NMR) spectra were acquired on either a Varian Inova-600 operating at 600 and 150 MHz, a Varian Inova-300 operating at 300 and 75 MHz, a Varian Mercury-400 operating at 400 and 100 MHz, or a Varian Inova-500 operating at 500 and 125 MHz for ^{1}H and ^{13}C, respectively, and are referenced internally according to residual solvent signals. Data for ^{1}H NMR are recorded as follows: chemical shift (δ, ppm), multiplicity (s, singlet; br s, broad singlet; d, doublet; t, triplet; q, quartet; quint, quintet; sext, sextet; m, multiplet), integration, coupling constant (Hz). Data for ^{13}C NMR are reported in terms of chemical shift (δ, ppm). Melting points were obtained on a Thomas-Hoover apparatus in open capillary tubes and are uncorrected. Infrared spectra were recorded on either a Thermo-Nicolet IR100 spectrometer or a Thermo-Nicolet IR300 spectrometer as thin films using NaCl salt plates or as KBr pellets and are reported in frequency of absorption. High-resolution mass spectra were obtained from the Vincent Coates Foundation Mass Spectrometry Laboratory at Stanford University using a microTOF-Q II or a Thermo Exactive Orbitrap mass spectrometer.

1-((4-Methoxybenzyl)oxy)hex-5-en-2-one (13). To a suspension of NaH (2.82 g, 0.12 mol, 1.1 equiv) in 100 mL of THF was added a solution of 2-hydroxy-1-morpholinoethanone (15.49 g, 0.11 mol) in 100 mL of THF at 0 ºC with vigorous stirring. After warming the solution to room temperature, ^{n}Bu$_4$NI (0.99 g, 2.7 mmol, 0.025 equiv) was added followed by dropwise addition of *p*-methoxybenzylchloride (15.9 mL, 0.12 mol, 1.1 equiv). The solution was stirred at reflux for 17 h, cooled to room temperature, transferred to a separatory funnel with 300 mL of a 1:1 mixture of saturated aqueous NH_4Cl and water. The aqueous solution was extracted with 4 x 100 mL of EtOAc. The combined organic extracts were dried over $MgSO_4$, filtered, and concentrated under reduced pressure to afford the desired PMB ether **12** as a yellow/orange oil. This material was analyzed by ^{1}H NMR and used without additional purification. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.27 (d, 2H, *J* = 8.9 Hz), 6.89 (d, 2H, *J* = 8.9 Hz), 4.52 (s, 2H), 4,14 (s, 2H), 3.81 (s, 3H), 3.70-3.65 (m, 2H), 3.65-3.58 (m, 4H), 3.52-3.47 (m, 2H) ppm.

In a separate flask, 4-bromo-1-butene (16.2 mL, 0.16 mol, 1.5 equiv) and 1,2-dibromoethane (250 μL, 2.9 mmol, 0.027 equiv) were added to a suspension of Mg turnings (2.85 g, 0.12 mol, 1.7 equiv) in 930 mL of THF. The mixture was stirred at reflux for 4 h, then cooled to 0 ºC and cannulated into an ice-cold solution of the PMB-protected morpholine amide (0.117 mol) in 140 mL of THF over 1 h. After stirring at 0 ºC for an additional 30 min, the reaction was slowly quenched by the addition of 500 mL of aqueous citric acid (1.0 M, pH = 3). The solution was transferred to a separatory funnel and extracted with 4 x 200 mL of EtOAc. The organic extracts were divided into two equal volumes and separately washed with 2 x 100 mL of saturated aqueous $NaHCO_3$ and 1 x 100 mL of saturated aqueous NaCl. The combined EtOAc extracts were dried over $MgSO_4$, filtered, and concentrated under reduced pressure to a light

yellow/orange oil. Purification of this material by chromatography on silica gel (8:1 hexanes/EtOAc) afforded ketone **13** as a transparent colorless oil (21.3 g, 85% over 2 steps). TLC R_f = 0.36 (4:1 hexanes/EtOAc); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.28 (d, 2H, *J* = 9.2 Hz), 6.89 (d, 2H, *J* = 9.2 Hz), 5.85-5.74 (m, 1H), 5.06-4.95 (m, 2H), 4.52 (s, 2H), 4.03 (s, 2H), 3.81 (s, 3H), 2.56 (t, 2H, *J* = 7.4 Hz), 2.37-2.30 (m, 2H) ppm; ^{13}C NMR ($CDCl_3$, 100 MHz) δ 208.3, 159.6, 137.0, 129.7, 129.3, 115.5, 114.0, 74.8, 73.1, 55.4, 38.2, 27.3 ppm; IR (thin film) ν 3077, 3001, 2912, 2837, 1719, 1613, 1514, 1303, 1175, 1097, 1035 cm^{-1}; HRMS (ESI-TOF) calcd for $C_{14}H_{18}O_3Na^+$ 257.1148 found 257.1160 (MNa^+).

3-(((4-Methoxybenzyl)oxy)methyl)-3-(methoxymethoxy)hept-6-en-2-one (14). Potassium *tert*-butoxide (8.93 g, 79.6 mmol, 1.6 equiv) was dissolved in 166 mL of THF and the solution was cooled to −78 °C. Ethyl vinyl ether (15.2 mL, 159.2 mmol, 3.2 equiv) was added dropwise. A solution of *n*-butyllithium (2.08 M in hexanes, 38.0 mL, 79.6 mmol, 1.6 equiv) was then added dropwise over 10 min. The resulting yellow, transparent mixture was stirred for 1 h at −78 °C. Following this time, a solution of lithium bromide[52] (9.50 g, 109.4 mmol, 2.2 equiv) in 50 mL of THF was added via syringe. The reaction mixture was warmed to 0 °C and stirred for 20 min and then cooled slowly (~10 min) to −78 °C. An ice-cold solution of ketone **13** (11.65 g, 49.7 mmol) in 130 mL of THF was added dropwise via cannula over 15 min. Transfer of **13** was made quantitative with two 15 mL portions of THF. After stirring for 2.5 h at −78 °C, a solution of methoxymethyl chloride[53] (2.1 M in toluene, 107.0 mL, 4.5 equiv) was added dropwise via addition funnel over 15 min. The mixture was warmed to room temperature and stirred for 6 h. The reaction was then cooled to 0 °C and 65 mL of 1.0 M aqueous citric acid was added dropwise via addition funnel over 5 min. After stirring for 10 min at 0 °C, the reaction was warmed to room temperature over 20 min and quenched by the successive addition of 50 mL of saturated aqueous NaCl and 210 mL of saturated aqueous $NaHCO_3$. The contents were transferred to a separatory funnel, the organic phase was collected, and the aqueous layer was extracted with 3 x 150 mL of EtOAc. The combined organic extracts were dried over $MgSO_4$, filtered, and concentrated under reduced pressure. Purification of the oily residue by chromatography on silica gel (gradient elution: 19:1→8:1 hexanes/EtOAc) afforded methyl ketone **14** as a pale yellow oil (13.8 g, 86%). TLC R_f = 0.52 (4:1 hexanes/EtOAc); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.19 (d, *J* = 8.5 Hz, 2H), 6.86 (d, *J* = 8.4 Hz, 2H), 5.72 (ddt, *J* = 16.9, 10.2, 6.6 Hz, 1H), 4.98 (dq, *J* = 17.1, 1.6 Hz, 1H), 4.93 (ddd, *J* = 10.2, 1.6, 1.0 Hz, 1H), 4.85 (d, *J* = 7.1 Hz, 1H), 4.75 (d, *J* = 7.1 Hz, 1H), 4.39 (d, *J* = 2.0 Hz, 2H), 3.79 (s, 3H), 3.67 (d, *J* = 9.8 Hz, 1H), 3.60 (d, *J* = 10.4 Hz, 1H), 3.42 (s, 3H), 2.23 (s, 3H), 2.12-1.99 (m, 1H), 1.95-1.78 (m, 2H), 1.75-1.61 (m, 1H) ppm; ^{13}C NMR ($CDCl_3$, 100 MHz) δ 211.6, 159.3, 137.8, 129.9, 129.3, 115.0, 113.8, 92.3, 86.7, 73.1, 72.2, 56.2, 55.3, 32.1, 27.7, 27.3 ppm; IR (thin film) ν 3077, 2931, 1719, 1612, 1513, 1248, 1173, 1154, 1092, 1032, 918 cm^{-1}; HRMS (ESI-TOF) calcd for $C_{18}H_{26}O_5Na^+$ 345.1672 found 345.1673 (MNa^+).

(2*S*,3*S*)-2-Hydroxy-3-(((4-methoxybenzyl)oxy)methyl)-3-(methoxymethoxy)-2-methylcyclopentan-1-one (16). To a solution of olefin **14** (5.13 g, 15.9 mmol) in 160 mL of a 3:1 mixture of dioxane/H_2O was added 2,6-lutidine (3.7 mL, 31.8 mmol, 2.0 equiv), OsO_4 (1.01 mL of a 4% solution in H_2O, 160 μmol, 0.01 equiv), and $NaIO_4$ (13.61 g, 63.4 mmol, 4.0 equiv).[54] The resulting mixture was stirred for 2 h, then transferred to a separatory funnel with 600 mL of H_2O. The aqueous phase was extracted with 4 x 180 mL of Et_2O. The combined organic extracts were washed successively with 2 x 90 mL of 1.0 M aqueous citric acid and 1 x 90 mL of saturated aqueous NaCl, dried over MgSO4, filtered, and concentrated under reduced pressure to afford a dark brown translucent oil. The ketoaldehyde product was analyzed by ^{1}H NMR and used without further purification. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 9.70 (t, 1H, J = 1.3 Hz), 7.19 (d, 2H, J = 8.8 Hz), 6.86 (d, 2H, J = 8.8 Hz), 4.83 (d, 1H, J = 7.0 Hz), 4.72 (d, 1H, J = 7.0 Hz), 4.42-4.36 (m, 2H), 3.80 (s, 3H), 3.69 (d, 1H, J = 10.2 Hz), 3.59 (d, 1H, J = 10.2 Hz), 3.39 (s, 3H), 2.52-2.43 (m, 1H), 2.39-2.30 (m, 1H), 2.23 (s, 3H), 2.11-1.96 (m, 2H) ppm.

The ketoaldehyde (15.9 mmol) was dissolved in 160 mL of HPLC grade $CHCl_3$. To this solution was added triazolium catalyst **15**[18] (1.16 g, 3.18 mmol, 0.2 equiv) and NaOAc (261 mg, 3.18 mmol, 0.2 equiv). The mixture was sonicated for 3 min and stirred vigorously for 17 h, then filtered through a Celite plug. The flask and filter cake were rinsed with 100 mL of Et_2O and the combined filtrates were concentrated under reduced pressure to dark brown viscous oil. Purification by chromatography on silica gel (gradient elution: 3:1→1:1 hexanes/EtOAc) afforded cyclopentanone **16** as a transparent light yellow viscous oil (2.76 g, 53% of isolated diastereomer over 2 steps, 3.5:1 dr). TLC R_f = 0.34 (1:1 hexanes/EtOAc); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.17 (d, *J* = 8.6 Hz, 2H), 6.87 (d, *J* = 8.6 Hz, 2H), 4.92 (d, *J* = 7.2 Hz, 1H), 4.69 (d, *J* = 7.2 Hz, 1H), 4.40 (s, 3H), 3.80 (s, 3H), 3.73 (dd, *J* = 9.4, 0.9 Hz, 1H), 3.64 (d, *J* = 9.4 Hz, 1H), 3.37 (s, 3H), 2.82 (s, 1H), 2.55-2.18 (m, 3H), 2.13-1.99 (m, 1H), 1.26 (s, 3H) ppm; ^{13}C NMR ($CDCl_3$, 125 MHz) δ 216.0, 159.4, 129.7, 129.3, 114.0, 92.5, 83.8, 81.2, 73.5, 71.5, 55.9, 55.4, 32.4, 27.4, 19.6 ppm; IR (thin film) ν 3463, 2932, 1752, 1613, 1514, 1463, 1248, 1173, 1140, 1099, 1032 cm^{-1}; HRMS (ESI-TOF) calcd for $C_{17}H_{24}O_6Na^+$ 347.1465 found 347.1473 (MNa^+).

(4a*S*,7a*S*)-4a-(Methoxymethoxy)-2-(4-methoxyphenyl)-7a-methyltetrahydrocyclopenta[*d*][1,3]dioxin-7(4*H*)-one (SI-1). To a solution of starting cyclopentanone **16** (0.62 g, 1.9 mmol) and freshly activated[55] 3Å molecular sieves (0.76 g) was added 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (0.65 g, 2.9 mmol, 1.5 equiv). The dark green reaction mixture was stirred for 1.5 h then transferred to a separatory funnel with 150 mL of CH_2Cl_2. The organic layer was washed with 2 x 100 mL of half-saturated aqueous sodium bicarbonate, dried over $MgSO_4$, filtered, and concentrated under reduced pressure to an oil. Purification by chromatography on silica gel (gradient elution: 3:1→1:1 hexanes/EtOAc) afforded the desired benzylidene acetal **SI-1** (0.52 g, 85%, 3.3:1 dr). While it is possible to separate the two diastereomers, in practice, the material is used as a mixture in subsequent transformations.

Major diastereomer isolated as a clear oil (stereochemistry unassigned at acetal carbon). TLC R_f = 0.50 (1:1 hexanes/EtOAc); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.35 (d, 2H, *J* = 8.8 Hz), 6.86 (d, 2H, *J* = 8.8 Hz), 5.64 (s, 1H), 4.77 (d, 1H, *J* = 7.8 Hz), 4.59 (d, 1H, *J* = 7.8 Hz), 4.16 (d, 1H, *J* = 11.4 Hz), 4.00 (d, 1H, *J* = 11.4 Hz), 3.77 (s, 3H), 3.36 (s, 3H), 2.86-2.76 (m, 1H), 2.59 (ddd, 1H, *J* = 19.3, 9.8, 1.0 Hz), 2.41-2.30 (m, 1H), 2.23 (dd, 1H, *J* = 14.2, 9.1 Hz), 1.46 (s, 3H) ppm; ^{13}C NMR ($CDCl_3$, 100 MHz) δ 211.8, 160.2, 129.7, 127.6, 113.6, 95.3, 91.1, 81.1, 77.9, 67.9, 55.8, 55.3, 33.1, 23.7, 10.3 ppm; IR (thin film) ν 2939, 1757, 1518, 1251, 1153, 1124, 1105, 1060, 1038, 1018 cm^{-1}.

Minor diastereomer isolated as a white solid (stereochemistry unassigned at acetal carbon). TLC R_f = 0.30 (1:1 hexanes/EtOAc); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.24 (d, 2H, *J* = 8.8 Hz), 6.87 (d, 2H, *J* = 8.8 Hz), 5.40, (s, 1H), 5.18 (d, 1H, *J* = 7.1 Hz), 4.91 (d, 1H, *J* = 7.1 Hz), 4.51 (d, 1H, *J* = 13.5 Hz), 3.78 (s, 3H), 3.65 (d, 1H, *J* = 13.5 Hz), 3.49 (s, 3H), 2.60 (ddd, 1H, *J* = 20.6, 11.0, 2.1 Hz), 2.37-2.26 (m, 1H), 2.17-2.08 (m, 1H), 1.91 (ddd, 1H, *J* = 13.5, 10.1, 2.1 Hz), 1.35 (s, 3H) ppm; ^{13}C NMR ($CDCl_3$, 100 MHz) δ 215.0, 160.2, 130.1, 127.7, 113.7, 98.5, 92.7, 85.5, 74.8, 70.0, 56.0, 55.4, 33.1, 25.8, 18.1 ppm; IR (thin film) ν 2936, 2842, 1754, 1615, 1518, 1250, 1172, 1153, 1132, 1075, 1027 cm^{-1}.

(4a*S*,7a*S*)-4a-(Methoxymethoxy)-2-(4-methoxyphenyl)-7a-methyl-4,4a,5,7a-tetrahydrocyclopenta[*d*][1,3]dioxin-7-yl trifluoromethanesulfonate (17). A solution of the benzylidine acetal of cyclopentanone **16** (0.52 g, 1.6 mmol) in 6.0 mL of THF was added dropwise via syringe to a –78 °C solution of $KN(SiMe_3)_2$ (0.36 g, 1.8 mmol, 1.1 equiv) in 4.3 mL of THF. The mixture was stirred at –78 °C for 10 min before a solution of $PhNTf_2$ (0.70 g, 1.9 mmol, 1.2 equiv) in 6 mL of THF was added dropwise. After stirring at –78 °C for 1 h, the reaction was quenched at this temperature by the addition of 50 mL of H_2O and 50 mL of saturated aqueous NaCl. The mixture was transferred to a separatory funnel, and the aqueous layer was extracted with 4 x 40 mL of EtOAc. The combined organic extracts were dried over $MgSO_4$, filtered, and concentrated under reduced pressure. Purification by chromatography on Davisil silica gel (6:1 hexanes/EtOAc) afforded the desired product **17** (0.69 g, 93%,

2:1 dr). While it is possible to separate the diastereomers, in practice, the material is used as a mixture in subsequent transformations.

Major diastereomer isolated as a clear oil (stereochemistry unassigned at the acetal carbon). TLC R_f = 0.60 (1:1 hexanes/EtOAc); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.36 (d, 2H, *J* = 8.8 Hz), 6.88 (d, 2H, *J* = 8.8 Hz), 5.92 (dd, 1H, *J* = 3.4, 2.1 Hz), 5.59 (s, 1H), 4.76 (d, 1H, *J* = 7.7 Hz), 4.66 (d, 1H, *J* = 7.7 Hz), 4.11 (d, 1H, *J* = 11.9 Hz), 3.95 (d, 1H, *J* = 11.9 Hz), 3.80 (s, 3H), 3.38 (s, 3H), 2.94 (dd, 1H, *J* = 16.8, 2.1 Hz), 2.73 (dd, 1H, *J* = 16.8, 3.3 Hz), 1.54 (s, 3H) ppm; ^{13}C NMR ($CDCl_3$, 100 MHz) δ 160.2, 150.0, 130.1, 127.6, 117.5, 117.0, 113.7, 94.6, 91.8, 84.8, 77.9, 68.0, 55.8, 55.4, 32.9, 12.8 ppm; IR (thin film) ν 2940, 1518, 1423, 1250, 1217, 1141, 1063, 1045, 1013 cm^{-1}.

Minor diastereomer isolated as a clear oil (stereochemistry unassigned at the acetal carbon). TLC R_f = 0.62 (1:1 hexanes/EtOAc); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.41 (d, 2H, *J* = 8.8 Hz), 6.89 (d, 2H, *J* = 8.8 Hz), 5.77 (dd, 1H, *J* = 3.6, 2.0 Hz), 5.62 (s, 1H), 5.18 (d, 1H, *J* = 7.0 Hz), 4.84 (d, 1H, *J* = 7.0 Hz), 4.49 (d, 1H, *J* = 13.0 Hz), 3.98 (d, 1H, *J* = 13.0 Hz), 3.80 (s, 3H), 3.47 (s, 3H), 2.55 (dd, 1H, *J* = 15.8, 1.9 Hz), 2.23 (dd, 1H, *J* = 15.8, 3.6 Hz), 1.44 (s, 3H) ppm; ^{13}C NMR ($CDCl_3$, 100 MHz) δ 160.3, 148.7, 130.1, 127.6, 114.1, 113.8, 97.7, 93.1, 84.8, 76.7, 71.6, 56.0, 55.4, 34.7, 20.1 ppm; IR (thin film) ν 2937, 1519, 1423, 1251, 1218, 1143, 1084, 1031 cm^{-1}.

1-((4*S*,5*R*)-5-Hydroxy-4-(hydroxymethyl)-4-(methoxymethoxy)-5-methylcyclopent-1-en-1-yl)ethan-1-one (SI-2). To solid LiCl (0.16 g, 3.72 mmol, 6.0 equiv), CuCl (0.31 g, 3.1 mmol, 5.0 equiv), and $Pd(PPh_3)_4$ (72 mg, 0.062 mmol, 0.1 equiv) was added enol triflate **17** (0.28 g, 0.62 mmol) in 4.4 mL of DMSO via syringe. Neat tributyl(1-ethoxyvinyl)tin (0.42 mL, 1.24 mmol, 2.0 equiv) was then added and the black suspension was subjected to 3 freeze/pump/thaw cycles. The mixture was stirred for 1.5 h. Following this time, the contents were transferred to a separatory funnel with 120 mL of a 5:1 mixture of saturated aqueous NaCl and 5% aqueous NH_4OH. The aqueous layer was extracted with 4 x 25 mL of EtOAc. The organic extracts were combined, dried over $MgSO_4$, filtered over Celite, and concentrated under reduced pressure. The isolated residue was re-dissolved in 4.0 mL of a 3:1 mixture of dioxane and 1.0 M HCl. The reaction was stirred for 1.5 h, then poured slowly into a separatory funnel containing ~10 mL of a 1:1 solution of saturated aqueous $NaHCO_3$ and saturated aqueous NaCl. The aqueous layer was extracted with 6 x 20 mL of CH_2Cl_2. The combined organic extracts were concentrated under reduced pressure to a dark brown oil. Immediate purification by chromatography on Davisil silica gel (gradient elution: 1:1 hexanes/EtOAc→100% EtOAc) afforded the desired diol product **SI-2** as a clear oil (75 mg, 52%). TLC R_f = 0.35 (EtOAc); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 6.68 (dd, 1H, *J* = 3.6, 2.2 Hz), 5.03 (d, 1H, *J* = 7.2 Hz), 4.70 (d, 1H, *J* = 7.2 Hz), 4.02 (dd, 1H, *J* = 13.2, 3.3, 1.2 Hz), 4.01 (s, 1H), 3.57 (dd, 1H, *J* = 13.2, 11.1 Hz), 3.45 (s, 3H), 3.26 (dd, 1H, *J* = 11.1, 3.4 Hz), 2.83 (dd, 1H, *J* = 18.8, 3.6 Hz), 2.44 (ddd, 1H, *J* = 18.8, 2.3, 1.2 Hz), 2.31 (s, 3H), 1.37 (s, 3H) ppm; ^{13}C NMR ($CDCl_3$, 100 MHz) δ 198.6, 146.0, 142.1, 93.0, 89.4, 85.6, 62.6, 56.0, 37.9, 26.6, 23.4 ppm; IR (thin film) ν 3481, 2932, 1656, 1375, 1121, 1074, 1027 cm^{-1}.

((1*S*,2*R*)-3-Acetyl-2-hydroxy-1-(methoxymethoxy)-2-methylcyclopent-3-en-1-yl)methyl sulfamate (18). To an ice-cold solution of primary alcohol (386 mg, 1.68 mmol) and pyridine (410 μL, 5.03 mmol, 3.0 equiv) in 12 mL of DMA was added solid $ClSO_2NH_2$[56] (581 mg, 5.03 mmol, 3.0 equiv). The mixture was stirred at 0 °C for 5 min, then warmed to room temperature over 25 min. The reaction contents were then diluted with 20 mL of EtOAc and transferred to a separatory funnel with 160 mL of an 18:1:1 mixture of saturated aqueous NaCl, H_2O, and saturated aqueous $NaHCO_3$. The aqueous layer was extracted with 7 x 20 mL of EtOAc. The combined organic extracts were dried over $MgSO_4$, filtered, and concentrated under reduced pressure to an oily residue. Purification by chromatography on silica gel (gradient elution: 3:2→2:3 hexanes/EtOAc) afforded sulfamate **18** as a pale yellow solid (431 mg, 83%). TLC R_f = 0.60 (EtOAc); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 6.68 (dd, 1H, *J* = 3.6, 2.1 Hz), 5.21 (br s, 2H),

5.07 (d, 1H, J = 7.3 Hz), 4.73 (d, 1H, J = 7.3 Hz), 4.58 (dd, 1H, J = 11.2, 1.5 Hz), 4.25 (d, 1H, J = 11.2 Hz), 4.02 (br s, 1H), 3.43 (s, 3H), 2.97 (dd, 1H, J = 18.8, 3.6 Hz), 2.57 (dt, 1H, J = 18.8, 1.7 Hz), 2.32 (s, 3H), 1.37 (s, 3H) ppm; ^{13}C NMR ($CDCl_3$, 100 MHz) δ 198.6, 145.9, 141.3, 93.2, 87.9, 85.0, 70.9, 56.0, 36.7, 26.7, 23.1 ppm; IR (thin film) ν 3270, 2928, 2852, 1657, 1373, 1182, 1141, 1017, 982, 920 cm^{-1}.

1-((4a*S*,5*R*,7a*S*)-5-Hydroxy-4a-(methoxymethoxy)-5-methyl-2,2-dioxido-4,4a,5,7a-tetrahydro-1*H*-cyclopenta[*d*][1,2,3]oxathiazin-6-yl)ethan-1-one (19). To a suspension of sulfamate **18** (408 mg, 1.32 mmol) and MgO (122 mg, 3.03 mmol, 2.3 equiv) in 26.4 mL of *i*-PrOAc was sequentially added [$Rh_2(O_2CCPh_3)_4$] (89 mg, 66 μmol, 0.05 equiv) and $PhI(OAc)_2$ (467 mg, 1.45 mmol, 1.1 equiv). After stirring for 15 h, the reaction mixture was filtered through a pad of Celite, washing the flask and filter cake with 100 mL of CH_2Cl_2. The combined filtrates were concentrated under reduced pressure to an oily residue. Purification by chromatography on silica gel (gradient elution: 1:1→1:3 hexanes/Et_2O) afforded the desired oxathiazinane **19** as a white solid (202 mg, 50%). TLC R_f = 0.66 (1:2 hexanes/EtOAc); mp = 123–126 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.84 (d, J = 2.0 Hz, 1H), 5.34 (br d, J = 7.6 Hz, 1H), 5.08 (d, J = 14.0 Hz, 1H), 4.85 (dd, J = 14.0, 2.0 Hz, 1H), 4.82 (d, J = 7.6 Hz, 1H), 4.34 (dt, J = 5.9, 2.0 Hz, 1H), 3.91 (br s, 1H), 3.51 (s, 3H), 2.39 (s, 3H), 1.37 (s, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 198.4, 143.5, 140.7, 93.5, 83.4, 79.1, 75.4, 65.0, 56.5, 27.0, 22.5 ppm; IR (thin film) ν 3494, 3248, 2926, 1669, 1447, 1383, 1256, 1188, 1057 cm^{-1}; HRMS (ESI-TOF) calcd for $C_{11}H_{17}NO_7SNa^+$ 330.0618 found 330.0620 (MNa^+).

Ethyl 1-hydroxy-2-oxocyclopentane-1-carboxylate (22). This compound was prepared as described in reference 32.

Ethyl 1-hydroxy-2-oxocyclopent-3-ene-1-carboxylate (23). To a solution of cyclopentanone **22** (7.42 g, 43.1 mmol) in 216 mL of AcOH was successively added DMSO (6.4 mL, 90.6 mmol, 2.1 equiv) and $Pd(OAc)_2$ (10.07 g, 44.8 mmol, 1.04 equiv). The dark brown heterogeneous mixture was stirred at 80 °C for 18 h. Following this time, the reaction was cooled to room temperature and concentrated under reduced pressure in a 50 °C water bath. The unpurified product was filtered through a plug of silica gel using 3:2 hexanes/EtOAc as the eluent. The filtrate was concentrated under reduced pressure to a dark yellow oil. Purification by chromatography on silica gel (gradient elution: 4:1→3:2 hexanes/EtOAc) afforded the enone product **23** as a light yellow oil (5.83 g, 79%). TLC R_f = 0.28 (2:1 hexanes/EtOAc); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.84 (dt, J = 5.9, 2.7 Hz, 1H), 6.26 (dt, J = 5.9, 2.2 Hz, 1H), 4.24 (qd, J = 7.2, 0.5 Hz, 2H), 3.83 (br s, 1H), 3.25 (ddd, J = 19.1, 2.9, 2.2 Hz, 1H), 2.81 (dt, J = 19.0, 2.4 Hz, 1H), 1.25 (t, J = 7.1 Hz, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 204.0, 171.0, 164.4, 130.8, 77.4, 62.7, 41.5, 14.0 ppm; IR (thin film) ν 3459, 2985, 1743, 1587, 1263, 1194, 1117, 1016 cm^{-1}; HRMS (ESI) calcd for $C_8H_{10}O_4H^+$ 171.0652 found 171.0652 (MH^+).

Ethyl 3-bromo-1-hydroxy-2-oxocyclopent-3-ene-1-carboxylate (24). A solution of enone **23** (2.99 g, 17.6 mmol) in 21 mL of CH_2Cl_2 was cooled to 0 °C. Bromine (0.92 mL, 17.9 mmol, 1.02 equiv) and Et_3N (3.7 mL, 26.4 mmol, 1.5 equiv) were successively added dropwise via syringe and the reaction was then warmed to room temperature. After stirring for 1 h, the mixture was concentrated under reduced pressure to a volume of ~2 mL. Addition of 35 mL of Et_2O to this solution resulted in formation of a white crystalline precipitate. The precipitate was removed by filtration of the suspension through a pad of Celite, washing the flask and filter cake with 80 mL of Et_2O. The combined filtrates were concentrated under reduced pressure to an oily residue. Purification by chromatography on silica gel (gradient elution: 99:1→14:1 CH_2Cl_2/EtOAc) provided bromoenone **24** as a viscous yellow oil (3.97 g, 91%). TLC R_f = 0.58 (14:1 CH_2Cl_2/EtOAc); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.89 (t, J = 3.1 Hz, 1H), 4.25 (qd, J = 7.1, 2.4 Hz, 2H), 3.21 (dd, J = 18.8, 3.2 Hz, 1H), 2.79 (dd, J = 18.8, 2.9 Hz, 1H), 1.25 (t, J = 7.2 Hz, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 196.9, 170.2, 161.3, 122.6, 76.2, 63.4, 41.1, 14.1 ppm; IR (thin film) ν 3458,

3075, 2984, 1755, 1588, 1368, 1279, 1197, 1119, 1017 cm^{-1}; HRMS (ESI) calcd for $C_8H_9O_4BrNa^+$ 270.9576 found 270.9577 (MNa^+).

Ethyl (1*R*,2*S*)-3-bromo-1,2-dihydroxy-2-methylcyclopent-3-ene-1-carboxylate (25). Bromoenone **24** (2.36 g, 9.52 mmol) was dissolved in 40 mL of a 0.6 M THF solution of $LaCl_3$•2LiCl (23.79 mmol, 2.5 equiv) and stirred for 1 h. The reaction mixture was cooled to −40 °C and 10.0 mL of a 2.38 M THF solution of MeMgCl (23.8 mmol, 2.5 equiv) was added dropwise via syringe over 5 min. After stirring for 45 min at −40 °C, the reaction was quenched by the addition of 120 mL of 0.5 M aqueous citric acid. The mixture was warmed to room temperature and transferred to a separatory funnel with 60 mL of Et_2O. The organic fraction was collected and the aqueous layer was extracted with 4 x 60 mL of Et_2O. The combined organic extracts were washed with 60 mL of saturated aqueous NaCl, dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The amber yellow oil was purified by chromatography on silica gel (gradient elution: 19:1→9:1 CH_2Cl_2/EtOAc) to provide vinyl bromide **25** as a pale yellow solid (1.25 g, 50%). TLC R_f = 0.60 (14:1 CH_2Cl_2/EtOAc); ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.00 (t, *J* = 2.7 Hz, 1H), 4.28 (q, *J* = 7.2 Hz, 2H), 3.62 (br s, 1H), 3.01 (dd, *J* = 17.0, 2.9 Hz, 1H), 2.44 (dd, *J* = 17.0, 2.5 Hz, 1H), 2.17 (br s, 1H), 1.38 (s, 3H), 1.30 (t, *J* = 7.2 Hz, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.8, 129.9, 127.3, 86.8, 83.8, 62.6, 41.3, 21.2, 14.3 ppm; IR (thin film) ν 3416, 2989, 2940, 1743, 1270, 1185, 1088 cm^{-1}; HRMS (ESI) calcd for $C_9H_{13}O_4BrNa^+$ 286.9889 found 286.9892 (MNa^+).

(1*S*,2*S*)-3-Bromo-1-(hydroxymethyl)-2-methylcyclopent-3-ene-1,2-diol (26). Vinyl bromide **25** (2.61 g, 9.85 mmol) was dissolved in 66 mL of THF and the solution was cooled to −78 °C. A solution of *i*-Bu_2AlH (1.2 M in toluene, 49.2 mL, 59.1 mmol, 6.0 equiv) was added dropwise over 10 min. After stirring for an additional 10 min at −78 °C, the reaction mixture was warmed to room temperature and stirred for 3 h. The reaction was quenched at this temperature by the slow successive addition of 33 mL of EtOAc and 66 mL of 1.0 M aqueous sodium potassium tartrate. The biphasic mixture was stirred vigorously for 0.5 h, following which time the contents were transferred to a separatory funnel with 60 mL of EtOAc. The organic phase was collected and the aqueous layer was extracted with 4 x 60 mL of EtOAc. The combined organic extracts were dried over Na_2SO_4, filtered, and concentrated under reduced pressure to a light orange residue. This material was purified by chromatography on silica gel (gradient elution: 9:1 CH_2Cl_2/THF→19:76:5 CH_2Cl_2/THF/MeOH) to give triol **26** as a pale yellow solid (1.48 g, 67%). TLC R_f = 0.31 (3:1 CH_2Cl_2/acetone); ^{1}H NMR (400 MHz, CD_3OD) δ 5.94 (t, *J* = 2.7 Hz, 1H), 3.74 (dd, *J* = 11.5, 0.6 Hz, 1H), 3.59 (d, *J* = 11.5 Hz, 1H), 2.60 (dd, *J* = 16.6, 2.8 Hz, 1H), 2.19 (ddd, *J* = 16.6, 2.6, 0.6 Hz, 1H), 1.30 (s, 3H) ppm; ^{13}C NMR (100 MHz, CD_3OD) δ 130.6, 130.4, 86.2, 82.4, 66.4, 41.6, 21.3 ppm; IR (thin film) ν 3370, 2951, 1377, 1303, 1154, 1081, 1063, 1019 cm^{-1}; HRMS (ESI) calcd for $C_7H_{11}O_3BrNa^+$ 244.9784 found 244.9783 (MNa^+).

(5*S*,6*S*)-7-Bromo-2,2,6-trimethyl-1,3-dioxaspiro[4.4]non-7-en-6-ol (27). Triol **26** (910 mg, 4.08 mmol) was dissolved in 22 mL of CH_2Cl_2 and 11 mL of THF. The solution was cooled to 0 °C and 10-camphorsulfonic acid (1.14 g, 4.90 mmol) and 6.8 mL of 2,2-dimethoxypropane were added successively. The mixture was warmed to room temperature and stirred for 3.5 h. Following this time, the reaction was cooled to 0 °C and quenched with 30 mL of a 2:1 solution of saturated aqueous $NaHCO_3$ and saturated aqueous NaCl. The contents were transferred to a separatory funnel with 60 mL of CH_2Cl_2. The organic phase was collected and the aqueous layer was extracted with 3 x 60 mL of CH_2Cl_2. The combined organic extracts were dried over Na_2SO_4, filtered, and concentrated under reduced pressure to an orange oil. Purification of this material by chromatography on silica gel (gradient elution: 9:1→3:1 hexanes/EtOAc) afforded acetonide **27** as a yellow oil (903 mg, 84%). TLC R_f = 0.25 (5:1 hexanes/EtOAc); ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.98 (t, *J* = 2.7 Hz, 1H), 4.49 (d, *J* = 9.0 Hz, 1H), 3.81 (d, *J* = 9.0 Hz, 1H), 2.54 (dd, *J* = 2.7, 1.0 Hz, 2H), 1.93 (br s, 1H), 1.43 (s, 3H), 1.41 (s, 3H), 1.34 (s, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 129.7, 129.2, 110.1, 89.2, 83.1, 70.6, 42.9, 26.6, 26.5, 21.9 ppm; IR (thin film) ν 3455, 2987, 2935, 1617, 1451, 1372, 1263, 1144, 1051 cm^{-1}; HRMS (ESI) calcd for $C_{10}H_{15}O_3BrNa^+$ 285.0097 found 285.0096 (MNa^+).

1-((4*S*,5*R*)-4,5-Dihydroxy-4-(hydroxymethyl)-5-methylcyclopent-1-en-1-yl)ethan-1-one (28). Single step procedure from primary alcohol **26**: To a solution of primary alcohol **26** (15 mg, 67 μmol) in 340 μL of deoxygenated 1,4-dioxane (sparged with N_2 for ~20 min) was added successively $Pd(OAc)_2$ (1.5 mg, 7 μmol, 0.10 equiv), XPhos (3.5 mg, 7 μmol, 0.11 equiv), CsF (22 mg, 0.15 mmol, 2.2 equiv), and tributyl(1-ethoxyvinyl)tin (27 μL, 81 μmol, 1.2 equiv). The dark brown suspension was stirred at 80 °C for 4 h. Following this time, the dark brown mixture was cooled to room temperature and 0.25 mL of 2.0 M aqueous HCl was added dropwise. The mixture was stirred for 10 min and transferred to a separatory funnel with 0.2 mL of saturated aqueous $NaHCO_3$, 0.2 mL of saturated aqueous NaCl, and 3 mL of EtOAc. The organic phase was collected and the aqueous layer was extracted with 9 x 3 mL of EtOAc. The combined organic extracts were dried over $MgSO_4$, filtered, and concentrated under reduced pressure to a yellowish brown residue. Purification of this material by chromatography on silica gel (gradient elution: 9:1→1:1 CH_2Cl_2/acetone) furnished methyl ketone **28** as a yellow oil (5.8 mg, 46%). TLC R_f = 0.45 (1:1 CH_2Cl_2/acetone); ^{1}H NMR (400 MHz, CD_3CN) δ 6.78 (dd, *J* = 3.4, 2.4 Hz, 1H), 3.92 (br s, 1H), 3.75 (d, *J* = 11.4 Hz, 2H), 3.37 (br d, *J* = 8.0 Hz, 1H), 3.28 (br s, 1H), 3.14 (br s, 1H), 2.53 (dd, *J* = 18.9, 3.4 Hz, 1H), 2.35 (dd, *J* = 18.9, 2.4 Hz, 1H), 2.26 (s, 3H), 1.34 (s, 3H) ppm; ^{13}C NMR (100 MHz, CD_3CN) δ 199.4, 147.0, 144.1, 85.8, 83.9, 66.9, 40.9, 27.1, 23.0 ppm; IR (thin film) ν 3402, 2936, 1660, 1373, 1251, 1119, 1084, 1036 cm^{-1}; HRMS (ESI) calcd for $C_9H_{14}O_4Na^+$ 209.0784 found 209.0785 (MNa^+).

Two step procedure:
(5*S*,6*R*)-7-(1-ethoxyvinyl)-2,2,6-trimethyl-1,3-dioxaspiro[4.4]non-7-en-6-ol (SI-3). To a solution of acetonide **27** (270 mg, 1.03 mmol) in 1,4-dioxane (6.8 mL, deoxygenated by sparging with N_2) was added sequentially $Pd(OAc)_2$ (23 mg, 103 μmol, 0.10 equiv), XPhos (54 mg, 113 μmol, 0.11 equiv), CsF (343 mg, 2.26 mmol, 2.2 equiv), and tributyl(1-ethoxyvinyl)tin (420 μL, 1.23 mmol, 1.2 equiv). The dark brown suspension was stirred at 80 °C for 4 h. Following this time, the dark brown mixture was cooled to room temperature and filtered through a short plug of silica gel (pre-packed with 99:1 hexanes/Et_3N), eluting with 1:1 CH_2Cl_2/acetone followed by 2:1 $CHCl_3$/*i*-PrOH. The combined filtrates were concentrated under reduced pressure to a red-orange oil. Purification of this material by chromatography on silica gel (gradient elution: 90:10:1→50:50:1 hexanes/EtOAc/Et_3N) furnished the desired enol ether **SI-3** as a yellow oil (164 mg, 63%). TLC R_f = 0.68 (2:1 hexanes/EtOAc); ^{1}H NMR (400 MHz, CD_3CN) δ 5.97 (t, *J* = 2.8 Hz, 1H), 4.65 (d, *J* = 2.0 Hz, 1H), 4.33 (d, *J* = 8.6, 1H), 4.17 (d, *J* = 2.1 Hz, 1H), 3.76 (q, *J* = 7.0 Hz, 2H), 3.69 (d, *J* = 8.6 Hz, 1H), 2.96 (s, 1H), 2.49 (dd, *J* = 17.0, 3.1 Hz, 1H), 2.40 (ddd, *J* = 17.0, 2.5, 0.6 Hz, 1H), 1.36 (t, *J* = 0.7 Hz, 3H), 1.35 (s, 6H), 1.28 (t, *J* = 7.0 Hz, 3H) ppm; ^{13}C NMR (100 MHz, CD_3CN) δ 156.4, 144.6, 127.2, 110.0, 92.9, 85.2, 82.8, 71.3, 63.3, 41.8, 27.0, 26.7, 22.5, 14.8 ppm; IR (thin film) ν 3480, 2984, 2933, 1634, 1584, 1456, 1370, 1325, 1261, 1214, 1146, 1065 cm^{-1}.

To an ice-cold solution of enol ether **SI-3** in 1.8 mL of MeCN and 1.8 mL of H_2O was added 3.0 mL of trifluoroacetic acid dropwise. After stirring at this temperature for 35 min, 40 mL of saturated aqueous $NaHCO_3$ was slowly added. The mixture was warmed to room temperature and transferred to a separatory funnel with 15 mL of EtOAc. The organic phase was collected and the aqueous layer was extracted with 2 x 30 mL of EtOAc and 10 x 30 mL of 3:1 $CHCl_3$/*i*-PrOH. The combined organic extracts were dried over Na_2SO_4, filtered, and concentrated to a yellowish orange residue. Purification of this material by chromatography on silica gel (gradient elution: 99:1→94:6 CH_2Cl_2/MeOH) gave methyl ketone **28** as a yellow oil (115 mg, 70%). The spectral data were consistent with that of material prepared through the single-step procedure (see above).

((1*S*,2*R*)-3-Acetyl-1,2-dihydroxy-2-methylcyclopent-3-en-1-yl)methyl sulfamate (6). Neat pyridine (280 μL, 3.40 mmol, 3.0 equiv) and a solution of $ClSO_2NH_2$ (262 mg, 2.27 mmol, 2.0 equiv) in 5.0 mL of MeCN were added dropwise to an solution of primary alcohol **28** (211 mg, 1.13 mmol) in 11 mL of

MeCN. The reaction was stirred at this temperature for 10 min then warmed to room temperature for 20 min. After this time, a second portion of $ClSO_2NH_2$[56] (66 mg, 0.57 mmol, 0.5 equiv) in 1.3 mL of MeCN was added dropwise and the solution was stirred for an additional 20 min. The mixture was then cooled to 0 °C, diluted with 5 mL of EtOAc, and the reaction quenched with 16 mL of a 3:1 solution of saturated aqueous NaCl/ saturated aqueous $NaHCO_3$. The contents were transferred to a separatory funnel with 30 mL of EtOAc and the organic phase was collected. The aqueous layer was extracted with 4 x 20 mL of EtOAc and 3 x 30 mL of 3:1 $CHCl_3$/*i*-PrOH. The combined organic extracts were dried over Na_2SO_4, filtered, and concentrated under reduced pressure to give an orange-brown oily residue. This material was purified by chromatography on silica gel (gradient elution: 9:1 hexanes/EtOAc→100% EtOAc) to furnish the sulfamate product **6** as a pale yellow solid (164 mg, 55%). TLC R_f = 0.60 (EtOAc); ^{1}H NMR (400 MHz, CD_3OD) δ 6.89 (t, *J* = 2.8 Hz, 1H), 4.26 (dd, *J* = 10.4, 1.0 Hz, 1H), 4.21 (d, *J* = 10.5 Hz, 1H), 2.89 (dd, *J* = 18.8, 3.1 Hz, 1H), 2.40 (ddd, *J* = 18.9, 2.6, 1.0 Hz, 1H), 2.31 (s, 3H), 1.44 (s, 3H) ppm; ^{13}C NMR (100 MHz, CD_3OD) δ 199.2, 148.2, 144.4, 85.1, 83.6, 73.4, 40.6, 27.3, 21.6 ppm; IR (thin film) ν 3459, 3222, 1653, 1373, 1180 cm^{-1}; HRMS (ESI) calcd for $C_9H_{15}NO_6SNa^+$ 288.0512 found 288.0510 (MNa^+).

1-((4a*S*,5*R*,7a*S*)-4a,5-Dihydroxy-5-methyl-2,2-dioxido-4,4a,5,7a-tetrahydro-1*H*-cyclopenta[*d*][1,2,3]oxathiazin-6-yl)ethan-1-one (5). To a solution of sulfamate ester **6** (75 mg, 283 μmol) in 5.7 mL of *i*-PrOAc was added sequentially [$Rh_2(O_2CCPh_3)_4$] (19 mg, 14 μmol, 0.05 equiv), MgO (26 mg, 650 μmol, 2.3 equiv), and $PhI(OAc)_2$ (109 mg, 339 μmol, 1.2 equiv). The resulting green suspension was stirred at 40 °C for 1.5 h, then cooled to room temperature and filtered through a pad of Celite. The flask and filter cake were rinsed successively with 5 mL of CH_2Cl_2 and 30 mL of EtOAc, and the filtrate was concentrated under reduced pressure to an oily green residue. Purification of this material by chromatography on silica gel (gradient elution: 9:1→3:1 CH_2Cl_2/acetone) furnished the product oxathiazinane **5** as a light yellow solid (42 mg, 56%) and aziridine **29** (26 mg, 35%) as a yellow oil. TLC R_f = 0.47 (2:1 CH_2Cl_2/acetone); ^{1}H NMR (400 MHz, CD_3OD) δ 6.87 (d, *J* = 1.9 Hz, 1H), 4.91 (t, *J* = 6.6 Hz, 2H), 4.41 (dd, *J* = 13.1, 1.8 Hz, 1H), 4.17 (t, *J* = 1.9 Hz, 1H), 2.34 (s, 3H), 1.37 (s, 3H) ppm; ^{13}C NMR (100 MHz, CD_3OD) δ 198.9, 146.4, 142.8, 82.9, 77.6, 77.1, 65.9, 27.3, 21.7 ppm; IR (thin film) ν 3447, 1665, 1370, 1249, 1185 cm^{-1}; HRMS (ESI) calcd for $C_9H_{13}NO_6SNa^+$ 286.0356 found 286.0353 (MNa^+).

1-((1*R*,2*S*,6*S*,8*R*,9*R*)-6,9-Dihydroxy-9-methyl-3,3-dioxido-4-oxa-3-thia-2-azatricyclo[4.2.1.0^{2,8}]nonan-1-yl)ethan-1-one (29). ^{1}H NMR analysis of the unpurified reaction mixture from the Rh-catalyzed amination reaction indicated the presence of aziridine **29**, which was isolated following chromatography on silica gel (26 mg, 35%). TLC R_f = 0.56 (2:1 CH_2Cl_2/acetone); ^{1}H NMR (400 MHz, CD_3OD) δ 4.46 (dd, *J* = 11.3, 1.2 Hz, 1H), 3.90 (d, *J* = 11.3 Hz, 1H), 3.42 (dd, *J* = 2.7, 0.6 Hz, 1H), 2.71 (dd, *J* = 15.1, 0.6 Hz, 1H), 2.31 (s, 3H), 2.28 (ddd, *J* = 15.1, 2.7, 1.2 Hz, 1H), 1.43 (s, 3H) ppm; ^{13}C NMR (100 MHz, CD_3OD) δ 202.2, 82.6, 77.5, 72.8, 64.1, 46.6, 36.6, 28.2, 21.9 ppm; IR (thin film) ν 3445, 2978, 1714, 1373, 1186, 1019 cm^{-1}; HRMS (ESI) calcd for $C_9H_{13}NO_6SNa^+$ 286.0356 found 286.0355 (MNa^+).

(4a*S*,5*R*,7a*S*)-4a,5-Dihydroxy-6-((*S*)-1-hydroxyethyl)-5-methyl-4,4a,5,7a-tetrahydro-1*H*-cyclopenta[*d*][1,2,3]oxathiazine 2,2-dioxide (30). To a solution of enone **5** (69 mg, 0.26 mmol) in 2.6 mL of MeOH and 1.3 mL of THF was added $CeCl_3$•$7H_2O$ (117 mg, 0.32 mmol, 1.2 equiv). The mixture was stirred for 30 min, following which time the solution was cooled to −78 °C and $NaBH_4$ (20 mg, 0.52 mmol, 2.0 equiv) was added portionwise. The reaction was stirred for 50 min then quenched at this temperature with 5 mL of a 2:1 solution of saturated aqueous NH_4Cl and saturated aqueous NaCl. The solution was warmed to room temperature in a water bath and transferred to a separatory funnel with 8 mL of EtOAc. The organic layer was collected and the aqueous phase was extracted with 7 x 8 mL of EtOAc. The combined organic extracts were dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The opaque yellow oil was purified by chromatography on silica gel (gradient elution: 4:1→1:1

CH_2Cl_2/acetone) to afford allylic alcohol **30** as a yellow oil (51 mg, 74%). TLC R_f = 0.20 (3:2 CH_2Cl_2/acetone); ^{1}H NMR (400 MHz, CD_3CN) δ 5.78 (br d, *J* = 6.3 Hz, 1H), 5.66 (t, *J* = 1.5 Hz, 1H), 4.85 (d, *J* = 12.9 Hz, 1H), 4.40-4.35 (m, 1H), 4.33 (dd, *J* = 13.0, 1.7 Hz, 1H), 4.04 (dqd, *J* = 6.3, 1.8, 0.4 Hz, 1H), 3.76 (br s, 1H), 3.32 (br s, 1H), 3.08 (d, *J* = 5.2 Hz, 1H), 1.31 (d, *J* = 6.5 Hz, 3H), 1.28 (s, 3H) ppm; ^{13}C NMR (100 MHz, CD_3CN) δ 153.7, 123.3, 83.6, 77.8, 66.1, 65.0, 23.8, 22.2 ppm; IR (thin film) ν 3310, 2979, 2933, 1372, 1281, 1182, 1078, 1034 cm^{-1}; HRMS (ESI) calcd for $C_9H_{15}NO_6SNa^+$ 288.0512 found 288.0514 (MNa^+).

(4a*S*,5*R*,7a*S*)-4a,5-Dihydroxy-6-((*R*)-1-hydroxyethyl)-5-methyl-4,4a,5,7a-tetrahydro-1*H*-cyclopenta[*d*][1,2,3]oxathiazine 2,2-dioxide (SI-4). ^{1}H NMR analysis of the unpurified reaction mixture from the reduction reaction of enone **5** indicated the presence of the C7 epimer of allylic alcohol **30** (**SI-4**), which was isolated following chromatography on silica gel (14 mg, 21%). TLC R_f = 0.32 (3:2 CH_2Cl_2/acetone); ^{1}H NMR (400 MHz, CD_3CN) δ 5.82 (br s, 1H), 5.66 (t, *J* = 1.7 Hz, 1H), 4.90 (d, *J* = 13.0 Hz, 1H), 4.55-4.40 (m, 1H), 4.35 (dd, *J* = 13.0, 1.7 Hz, 1H), 4.04 (br s, 1H), 3.96 (s, 1H), 3.82 (br s, 1H), 3.51 (br d, *J* = 4.4 Hz, 1H), 1.31 (d, *J* = 6.4 Hz, 3H), 1.25 (s, 3H) ppm; ^{13}C NMR (100 MHz, CD_3CN) δ 151.4, 123.8, 84.4, 77.72, 77.68, 66.0, 64.7, 21.8, 21.7 ppm; IR (thin film) ν 3313, 2980, 2934, 1447, 1374, 1283, 1184, 1091, 1033 cm^{-1}; HRMS (ESI) calcd for $C_9H_{15}NO_6SNa^+$ 288.0512 found 288.0513 (MNa^+).

(4a*S*,4b*R*,8*R*,9a*S*)-4a-Hydroxy-4b,6,6,8-tetramethyl-4a,4b,8,9a-tetrahydro-1*H*,4*H*-[1,3]dioxino[4',5':3,4]cyclopenta[1,2-*d*][1,2,3]oxathiazine 2,2-dioxide (SI-5). To a solution of allylic alcohol **30** (10 mg, 38 μmol) in 250 μL of CH_2Cl_2 and 50 μL of THF was added 2,2-dimethoxypropane (100 μL, 750 mmol, 20.0 equiv) and pyridinium *p*-toluenesulfonate (4 mg, 16 μmol, 0.4 equiv). The resulting yellow mixture was stirred for 15 h following which time the reaction was quenched by the addition of 2 mL of a 1:1 solution of saturated aqueous NaCl and saturated aqueous $NaHCO_3$. The contents were transferred to a separatory funnel with 3 mL of EtOAc, the organic phase was collected, and the aqueous layer was extracted with 4 x 3 mL of EtOAc. The combined organic extracts were dried over Na_2SO_4, filtered, and concentrated under reduced pressure to a yellow oil. This material was purified by chromatography on silica gel (gradient elution: 3:2→1:2 hexanes/EtOAc) to afford the acetonide **SI-5** as a yellow oil (9.0 mg, 78%). TLC R_f = 0.74 (2:3 hexanes/EtOAc); ^{1}H NMR (400 MHz, CD_3CN) δ 5.88 (br d, *J* = 6.2 Hz, 1H), 5.61 (t, *J* = 1.7 Hz, 1H), 4.87 (d, *J* = 13.0 Hz, 1H), 4.76 (qdd, *J* = 6.6, 3.0, 1.8 Hz, 1H), 4.31 (dd, *J* = 13.1, 1.8 Hz, 1H), 4.11 (ddd, *J* = 6.2, 3.1, 1.6 Hz, 1H), 3.84 (br s, 1H), 1.35 (d, *J* = 1.3 Hz, 6H), 1.33 (s, 3H), 1.33 (s, 3H) ppm; ^{13}C NMR (100 MHz, CD_3CN) δ 146.6, 121.9, 101.1, 83.8, 77.7, 77.65, 66.9, 66.7, 31.1, 24.9, 23.0, 22.8 ppm; IR (thin film) ν 3278, 2987, 2935, 1437, 1376, 1187, 1108, 1059 cm^{-1}; HRMS (ESI) calcd for $C_{12}H_{19}NO_6SNa^+$ 328.0825 found 328.0826 (MNa^+).

(4a*S*,4b*R*,8*R*,9a*S*)-4a-Hydroxy-4b,6,6,8-tetramethyl-4a,4b,8,9a-tetrahydro-1*H*,4*H*-[1,3]dioxino[4',5':3,4]cyclopenta[1,2-*d*][1,2,3]oxathiazine 2,2-dioxide (SI-6). To a solution of allylic alcohol **SI-4** (33 mg, 0.12 mmol) in 830 μL of CH_2Cl_2 and 150 μL of THF was added 2,2-dimethoxypropane (150 μL, 1.24 mmol, 10.0 equiv) and pyridinium *p*-toluenesulfonate (6 mg, 24 μmol, 0.2 equiv). The resulting yellow mixture was stirred for 12.5 h following which time the reaction was quenched by the addition of 2 mL of a 1:1 solution of saturated aqueous NaCl and saturated aqueous $NaHCO_3$. The contents were transferred to a separatory funnel with 3 mL of EtOAc, the organic phase was collected, and the aqueous layer was extracted with 4 x 3 mL of EtOAc. The combined organic extracts were dried over Na_2SO_4, filtered, and concentrated under reduced pressure to a yellow oil. This material was purified by chromatography on silica gel (gradient elution: 3:2→1:2 hexanes/EtOAc) to afford the acetonide **SI-6** as a yellow crystalline solid (25 mg, 66%). TLC R_f = 0.61 (2:3 hexanes/EtOAc); ^{1}H NMR (400 MHz, CD_3CN) δ 5.89 (br d, *J* = 6.0 Hz, 1H), 5.60 (t, *J* = 1.7 Hz, 1H), 4.88 (dd, *J* = 13.0, 0.4 Hz, 1H), 4.64 (qdd, *J* = 6.2, 3.2, 1.8 Hz, 1H), 4.33 (dd, *J* = 13.1, 1.8 Hz, 1H), 4.17-4.08 (m, 1H), 3.93 (br s, 1H), 1.52 (d, *J* = 0.6 Hz, 3H), 1.34 (s, 3H), 1.29 (d, *J* = 6.2 Hz, 3H), 1.26 (d, *J* = 0.7 Hz, 3H) ppm; ^{13}C NMR (100 MHz, CD_3CN) δ 145.6, 121.3, 100.1, 83.2, 78.0, 77.8, 65.8, 62.9, 30.7,

24.9, 20.7, 18.0 ppm; IR (thin film) ν 3441, 3210, 2998, 2978, 2935, 2873, 1446, 1379, 1288, 1258, 1185, 1092 cm^{-1}; HRMS (ESI) calcd for $C_{12}H_{19}NO_6SNa^+$ 328.0825 found 328.0822 (MNa^+).

(4a*S*,5*R*,5'*S*,6*R*,7a*S*)-4a,5-dihydroxy-5,5'-dimethyltetrahydro-1*H*,4*H*-spiro[cyclopenta[*d*][1,2,3]oxathiazine-6,4'-oxazolidin]-2'-one 2,2-dioxide (33). A solution of carbamate **32** (4.2 mg, 14 μmol) in 190 μL of *i*-PrOAc was charged with $[Rh_2(HNCOCF_3)_4]$ (0.5 mg, 0.7 μmol, 0.05 equiv), MgO (2 mg, 54 μmol, 4.0 equiv), and $PhI(OAc)_2$ (8 mg, 24 μmol, 1.8 equiv). The lavender suspension was vigorously stirred for 2.5 h. Following this time, the resulting yellow-orange suspension was filtered through a small pad of Celite, washing the flask and filter cake successively with 5 mL of EtOAc and 3 mL of CH_2Cl_2. The combined filtrates were concentrated under reduced pressure to an orange oil. Purification of this material by chromatography on silica gel (gradient elution: 9:1 CH_2Cl_2/acetone, then 1:3→1:5 hexanes/EtOAc) furnished oxazolidinone **33** as a white solid (1.1 mg, 25%) along with recovered carbamate **32** (yellow oil, 1.1 mg, 25%) and methyl ketone **34** (yellow oil, 1.8 mg, 50%). TLC R_f = 0.16 (3:1 CH_2Cl_2/acetone); ^{1}H NMR (600 MHz, CD_3OD) δ 4.79 (d, *J* = 12.4 Hz, 1H), 4.36 (d, *J* = 12.4 Hz, 1H), 3.78 (dd, *J* = 9.0, 5.8 Hz, 1H), 2.38 (dd, *J* = 14.8, 9.1 Hz, 1H), 2.27 (dd, *J* = 14.8, 5.8 Hz, 1H), 1.41 (d, *J* = 6.6 Hz, 3H), 1.25 (s, 3H) ppm; IR (thin film) ν 3370, 2928, 2855, 1733, 1557, 1437, 1367, 1250, 1190, 1078 cm^{-1}; HRMS (ESI-TOF) calcd for $C_{10}H_{16}N_2O_7SH^+$ 307.0751 found 309.0747 (MH^+).

1-((4a*S*,5*R*,6*R*,7a*S*)-4a,5-dihydroxy-5-methyl-2,2-dioxidohexahydro-1*H*-cyclopenta[*d*][1,2,3]oxathiazin-6-yl)ethan-1-one (34). ^{1}H NMR analysis of the unpurified reaction mixture from the Rh-catalyzed amination of carbamate **32** indicated the presence of methyl ketone product **34**, which was isolated following chromatography on silica gel (1.8 mg, 50%). TLC R_f = 0.55 (3:1 CH_2Cl_2/acetone); ^{1}H NMR (600 MHz, $CDCl_3$) δ 4.95 (d, *J* = 12.9 Hz, 1H), 4.87 (br s, 1H), 4.38 (br s, 1H), 4.30 (d, *J* = 12.9 Hz, 1H), 3.73 (br s, 1H), 3.27 (dd, *J* = 11.5, 9.0 Hz, 1H), 2.76 (dt, *J* = 14.0, 9.0 Hz, 1H), 2.25 (s, 3H), 1.76 (ddd, *J* = 14.0, 11.5, 4.7 Hz, 1H), 1.31 (s, 3H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$, determined by HMBC and HSQC) δ 212.5, 82.0, 80.7, 74.2, 63.6, 55.3, 31.7, 31.6, 19.5 ppm; IR (thin film) ν 3494, 3298, 3057, 2917, 2849, 1698, 1428, 1367, 1266, 1190, 1078 cm^{-1}; HRMS (ESI-TOF) calcd for $C_9H_{15}NO_6SNa^+$ 288.0512 found 288.0510 (MNa^+).

(1*S*,4a*S*,4b*S*,8a*S*,9*R*,9a*R*)-9-hydroxy-8a-(methoxymethoxy)-1,9-dimethyltetrahydro-1*H*,3*H*,5*H*,8*H*-oxazolo[3'',4'':1',2']azirino[2',3':4,5]cyclopenta[1,2-*d*][1,2,3]oxathiazin-3-one 6,6-dioxide (36). To a solution of carbamate **35** (240 mg, 681 μmol) in 34 mL of benzene was added $[Rh_2(HNCOCF_3)_4]$ (27 mg, 41 μmol , 0.06 equiv), MgO (83 mg, 2.04 mmol, 3.0 equiv), and $PhI(OAc)_2$ (658 mg, 2.04 mmol, 3.0 equiv). The purple suspension was stirred vigorously at 65 ºC for 12 h. Following this time, the resulting orange suspension was cooled to room temperature and filtered through a small pad of Celite, washing the flask and filter cake successively with 40 mL of CH_2Cl_2 and 40 mL of EtOAc. The combined filtrates were concentrated under reduced pressure to an orange residue. Purification of this material by chromatography on silica gel (gradient elution: 2:1→2:3 hexanes/EtOAc) furnished oxazolidinone **36** as a light yellow solid (88 mg, 37%) along with enone **19** (75 mg, 36%). TLC R_f = 0.45 (1:2 hexanes/EtOAc); mp = 156–159 °C; ^{1}H NMR (400 MHz, CD_3CN) δ 6.11 (br d, *J* = 5.8 Hz, 1H), 5.01 (d, *J* = 7.5 Hz, 1H), 4.95 (d, *J* = 14.0 Hz, 1H), 4.90 (q, *J* = 6.3 Hz, 1H), 4.79 (dd, *J* = 14.0, 2.2 Hz, 1H), 4.75 (d, *J* = 7.5 Hz, 1H), 4.02 (br s, 1H), 3.69-3.65 (m, 2H), 3.40 (s, 3H), 1.52 (d, *J* = 6.2 Hz, 3H), 1.29 (s, 3H) ppm; ^{13}C NMR (100 MHz, CD_3CN) δ 164.4, 93.3, 83.4, 79.8, 74.2, 73.6, 63.2, 62.6, 56.3, 48.6, 20.3, 19.1 ppm; IR (thin film) ν 3483, 3375, 2983, 1709, 1602, 1379, 1187, 1049 cm^{-1}; HRMS (ESI-TOF) calcd for $C_{12}H_{18}N_2O_8SH^+$ 351.0857 found 351.0856 (MH^+).

(*S*)-1-((4a*S*,5*R*,7a*S*)-4a,5-Dihydroxy-5-methyl-2,2-dioxido-4,4a,5,7a-tetrahydro-1*H*-cyclopenta[*d*][1,2,3]oxathiazin-6-yl)ethyl carbamate (37). Trichloroacetyl isocyanate (50 μL, 0.41 mmol, 1.2 equiv) was added dropwise to an ice-cold solution of allylic alcohol **30** (91 mg, 343 μmol) in 4.3 mL of 4:1 CH_2Cl_2/THF. The mixture was stirred for 5 min and then warmed to room temperature over

40 min. To this solution were added 8.6 mL of MeOH and K_2CO_3 (19 mg, 0.14 mmol, 0.4 equiv). After stirring vigorously for 2 h, the reaction was quenched by the addition of 12 mL of a 2:1 solution of saturated aqueous NH_4Cl and saturated aqueous NaCl. The contents were transferred to a separatory funnel with 20 mL of EtOAc. The organic phase was collected and the aqueous layer was extracted with 5 x 20 mL of EtOAc. The combined organic extracts were dried over $MgSO_4$, filtered, and concentrated under reduced pressure to a yellow residue. Purification of this material by chromatography on silica gel provided the desired carbamate as a colorless oil (82 mg, 78%). TLC R_f = 0.25 (EtOAc); ^{1}H NMR (400 MHz, CD_3CN) δ 5.84 (br d, *J* = 6.3 Hz, 1H), 5.74 (t, *J* = 1.5 Hz, 1H), 5.28-5.17 (m, 3H), 4.84 (dd, *J* = 13.0, 0.5 Hz, 1H), 4.33 (dd, *J* = 13.0, 1.7 Hz, 1H), 4.07 (dq, *J* = 5.7, 1.7 Hz, 1H), 3.85 (br s, 1H), 3.39 (br s, 1H), 1.36 (d, *J* = 6.6 Hz, 3H), 1.25 (s, 3H) ppm; ^{13}C NMR (100 MHz, CD_3CN) δ 157.3, 150.7, 124.8, 83.0, 77.8, 77.7, 67.0, 65.9, 21.8, 20.5 ppm; IR (thin film) ν 3379, 2984, 1700, 1602, 1374, 1185, 1040 cm^{-1}; HRMS (ESI) calcd for $C_{10}H_{16}N_2O_7SNa^+$ 331.0570 found 331.0571 (MNa^+).

(1*S*,4a*S*,4b*S*,8a*S*,9*R*,9a*R*)-8a,9-Dihydroxy-1,9-dimethyltetrahydro-1*H*,3*H*,5*H*,8*H*-oxazolo[3'',4'':1',2']azirino[2',3':4,5]cyclopenta[1,2-*d*][1,2,3]oxathiazin-3-one 6,6-dioxide (38). To a solution of carbamate (51 mg, 165 μmol) in 1.7 mL of *i*-PrOAc was sequentially added $[Rh_2(HNCOCF_3)_4]$ (5.5 mg, 8 μmol , 0.05 equiv), MgO (27 mg, 662 μmol, 4.0 equiv), and $PhI(OAc)_2$ (96 mg, 298 μmol, 1.8 equiv). The purple suspension turned yellow following the addition of $PhI(OAc)_2$. After stirring for 3.5 h, the mixture was filtered through a small pad of Celite, washing the flask and filter cake successively with 5 mL of CH_2Cl_2 and 10 mL of EtOAc. The combined filtrates were concentrated under reduced pressure to an orange oily residue. Purification of this material by chromatography on silica gel (gradient elution: 9:1→3:1 CH_2Cl_2/acetone→EtOAc) furnished oxazolidinone **38** as a white solid (19 mg, 38%), recovered carbamate (13.5 mg, 26%) as a yellow oil, and enone **5** (4.8 mg, 11%) as a white solid. TLC R_f = 0.40 (5:1 CH_2Cl_2/acetone); ^{1}H NMR (400 MHz, CD_3CN) δ 5.45 (br s, 1H), 5.04 (qt, *J* = 6.2, 0.7 Hz, 1H), 4.67 (d, *J* = 12.6 Hz, 1H), 4.33 (d, *J* = 12.6 Hz, 1H), 4.05 (br s, 1H), 3.93 (br s, 1H), 3.61 (t, *J* = 0.8 Hz, 1H), 3.46 (br s, 1H), 1.56 (d, *J* = 6.3 Hz, 3H), 1.39 (s, 3H) ppm; ^{13}C NMR (100 MHz, CD_3CN) δ 162.9, 80.9, 74.9, 74.3, 73.9, 63.8, 62.9, 48.8, 19.5, 17.3 ppm; IR (thin film) ν 3478, 3128, 1763, 1463, 1364, 1279, 1191, 1070, 1038 cm^{-1}; HRMS (ESI) calcd for $C_{10}H_{14}N_2O_7SH^+$ 307.0594 found 307.0594 (MH^+).

(1a*S*,2*S*,5a*S*,5b*S*,9a*S*,9b*S*)-9a-(methoxymethoxy)-2,9b-dimethylhexahydro-2*H*,4*H*,9*H*-[1,3]oxazino[5',4':4,5]oxireno[2',3':3,4]cyclopenta[1,2-*d*][1,2,3]oxathiazin-4-one 7,7-dioxide (40). To an ice-cold solution of KO*t*-Bu (20 mg, 0.183 mmol, 4.0 equiv) in 750 μL of DMF was added dropwise a solution of aziridine **36** (16 mg, 46 μmol) in 350 μL of DMF. Transfer of **36** was made quantitative by the addition of 2 x 200 μL of DMF. The mixture was stirred at 0 ºC for 30 min, following which time the reaction was diluted with 3 mL of EtOAc and quenched by the addition of 3 mL of a 1:1 solution of 1.0 M aqueous HCl and saturated aqueous NaCl. The mixture was transferred to a separatory funnel containing 12 mL of saturated aqueous NaCl. The organic phase was collected and the aqueous layers were extracted with 5 x 3 mL of EtOAc. The combined organic extracts were dried over $MgSO_4$, filtered, and concentrated under reduced pressure to a yellow residue. Purification of this material by chromatography on silica gel (gradient elution: 1:1→1:5 hexanes/EtOAc) afforded epoxide **40** as a light yellow film (14 mg, 88%). TLC R_f = 0.30 (1:3 hexanes/EtOAc); ^{1}H NMR (400 MHz, CD_3CN) δ 6.10 (br s, 1H), 5.59 (br s, 1H), 4.92 (d, *J* = 7.6 Hz, 1H), 4.86 (d, *J* = 7.6 Hz, 1H), 4.82 (d, *J* = 13.3 Hz, 1H), 4.55 (d, *J* = 13.3 Hz, 1H), 4.31 (q, *J* = 6.7 Hz, 1H), 4.09 (br d, *J* = 7.3 Hz, 1H), 4.04 (br s, 1H), 3.39 (d, *J* = 0.3 Hz, 3H), 1.51 (d, *J* = 6.7 Hz, 3H), 1.44 (s, 3H) ppm; ^{13}C NMR (125 MHz, CD_3CN) δ 151.6, 94.0, 84.9, 74.8, 72.4, 70.7, 70.4, 64.8, 56.4, 55.5, 18.0, 10.5 ppm; IR (thin film) ν 3264, 2927, 1706, 1357, 1193, 1152, 1074, 1004 cm^{-1}; HRMS (ESI-TOF) calcd for $C_{12}H_{18}N_2O_8SH^+$ 351.0857 found 351.0849 (MH^+).

(4a*S*,5*R*,5'*S*,6*R*,7*R*,7a*R*)-7-Bromo-4a,5-dihydroxy-5,5'-dimethyltetrahydro-1*H*,4*H*-spiro[cyclopenta[*d*][1,2,3]oxathiazine-6,4'-oxazolidin]-2'-one 2,2-dioxide (41). To a solution of aziridine **38** (10 mg, 33 μmol) in 650 μL of MeCN was added anhydrous $MgBr_2$ (30 mg, 163 μmol, 5.0

equiv). The suspension was stirred at 70 °C for 15 min. The reaction was then cooled to room temperature and transferred to a separatory funnel with 3 mL of EtOAc and 2 mL of saturated aqueous NH_4Cl. The organic phase was collected and the aqueous layer was extracted with 5 x 3 mL of EtOAc. The combined organic extracts were dried over Na_2SO_4, filtered, and concentrated to a pale yellow residue. This material was purified by chromatography on silica gel (gradient elution: 1:1→1:4 hexanes/EtOAc) to afford bromide **41** as a yellow oil (11.5 mg, 91%). TLC R_f = 0.31 (2:1 CH_2Cl_2/acetone); ^{1}H NMR (400 MHz, CD_3CN) δ 6.00 (br s, 1H), 5.31 (br s, 1H), 4.80 (q, *J* = 6.7 Hz, 1H), 4.76 (d, *J* = 7.1 Hz, 1H), 4.69 (d, *J* = 12.4 Hz, 1H), 4.44 (d, *J* = 12.4 Hz, 1H), 4.11 (s, 2H), 3.98 (br d, *J* = 7.0 Hz, 1H), 1.74 (d, *J* = 6.7 Hz, 3H), 1.26 (s, 3H) ppm; ^{13}C NMR (100 MHz, CD_3CN) δ 158.2, 85.6, 78.4, 76.4, 74.6, 74.3, 66.0, 53.8, 17.7, 17.6 ppm; IR (thin film) ν 3288, 1735, 1368, 1191, 1090 cm^{-1}; HRMS (ESI) calcd for $C_{10}H_{15}N_2O_7BrSH^+$ 386.9856 found 386.9861 (MH^+).

(4a*S*,5*R*,5'*S*,6*R*,7*R*,7a*S*)-7-Azido-4a,5-dihydroxy-5,5'-dimethyltetrahydro-1*H*,4*H*-spiro[cyclopenta[*d*][1,2,3]oxathiazine-6,4'-oxazolidin]-2'-one 2,2-dioxide (44). To a solution of aziridine **38** (10 mg, 33 μmol) in 410 μL of DMF was sequentially added NH_4Cl (3 mg, 49 μmol, 1.5 equiv) and NaN_3 (6.5 mg, 98 μmol, 3.0 equiv). The mixture was stirred at 40 °C for 15 h following which time the reaction was cooled to room temperature and quenched by the addition of 4 mL of EtOAc and 2.5 mL of a 1:1 solution of saturated aqueous NH_4Cl and saturated aqueous NaCl. The organic phase was collected and the aqueous layer was extracted with 5 x 4 mL of EtOAc. The combined organic extracts were dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The orange oily residue was purified by chromatography on silica gel to afford azide **44** as a yellow oil (9.5 mg, 83%). TLC R_f = 0.29 (2:1 CH_2Cl_2/acetone); ^{1}H NMR (400 MHz, CD_3CN) δ 6.00 (br s, 1H), 5.61 (br s, 1H), 4.82 (q, *J* = 6.5 Hz, 1H), 4.77 (d, *J* = 12.7 Hz, 1H), 4.59 (d, *J* = 7.8 Hz, 1H), 4.39 (d, *J* = 12.7 Hz, 1H), 4.34 (s, 1H), 4.09 (d, *J* = 7.8 Hz, 1H), 3.86 (br s, 1H), 1.59 (d, *J* = 6.5 Hz, 3H), 1.20 (s, 3H) ppm; ^{13}C NMR (100 MHz, CD_3CN) δ 157.9, 83.8, 80.5, 76.4, 75.5, 73.7, 67.9, 66.1, 18.1, 16.1 ppm; IR (thin film) ν 3362, 2114, 1739, 1368, 1256, 1190, 1088, 1056 cm^{-1}; HRMS (ESI) calcd for $C_{10}H_{15}N_5O_7SH^+$ 350.0765 found 350.0765 (MH^+).

Supporting information:
NMR spectra

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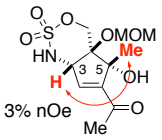

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