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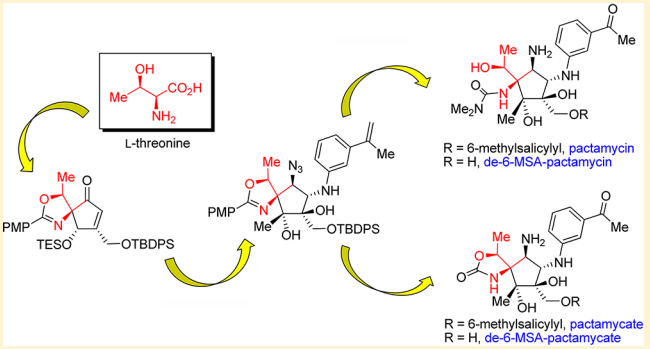
Total Synthesis of Pactamycin and Pactamycate: A Detailed Account

Stephen Hanessian,* Ramkrishna Reddy Vakiti, Stéphane Dorich, Shyamapada Banerjee, and Benoît Deschênes-Simard

Department of Chemistry, Université de Montréal, Montreal, Quebec, Canada H3C 3J7

Supporting Information

ABSTRACT: This article describes synthetic studies that culminated in the first total synthesis of pactamycin and pactamycate and, in parallel, the two known congeners, de-6-MSA-pactamycin and de-6-MSA-pactamycate, lacking the 6-methylsalicylyl moiety. Starting with L-threonine as a *chiron*, a series of stereocontrolled condensations led to a key cyclopentenone harboring a spirocyclic oxazoline. A series of systematic functionalizations led initially to the incorrect cyclopentanone epoxide, which was "inverted" under solvolytic conditions. Installation of the remaining groups and manipulation of the oxazoline eventually led to pactamycin, pactamycate, and their desalicylyl analogues.



INTRODUCTION

The plethora of microbial secondary metabolites produced by the soil bacterium of the *Streptomyces* family comprise a family of highly substituted aminocyclopentitol-containing natural products.[1] Among these are pactamycin (**1**) and pactamycate (**2**), two structurally unique and functionally rich metabolites (Figure 1). Related cyclopentane core structures, albeit with simpler substitution patterns, are encountered in allosamizoline (**5**),[2] mannostatin A (**6**),[2] and trehazolamine (**7**).[3] Early studies on the biosynthesis of pactamycin were reported by Rinehart and co-workers in 1978.[4] More recently, Kudo and co-workers[5] cloned the biosynthetic gene cluster involved in the formation of the cyclopentane ring of pactamycin. Mahmud and co-workers[6] have shown pactamycin (**1**), pactamycate (**2**), de-6-MSA-pactamycin (**3**), and de-6-MSA-pactamycate (**4**) are produced from the same gene cluster.

Pactamycin was isolated in 1961 from a fermentation broth of *Streptomyces pactum var. pactum* by scientists at the former Upjohn Company.[7] Although it exhibited in vitro activity against certain Gram-positive and Gram-negative bacteria, as well as cytotoxicity toward cancer cell lines, its further development was curtailed due to its toxicity.[8] This can be attributed to its effect in arresting protein biosynthesis in eukaryotes as well as in prokaryotes.[9] Pioneering X-ray crystallographic studies by Ramakrishnan and co-workers[10] involving pactamycin bound to the 30S site of *Thermus thermophilus* showed unique interactions, whereby its two aromatic moieties are π-stacked against each other like consecutive RNA bases, while the core aminocyclopentitol motif mimics the RNA sugar−phosphate backbone. This results in an intricate network of H-bonded interactions with specific bases within the 30S site of the ribosome, as well as intramolecularly.

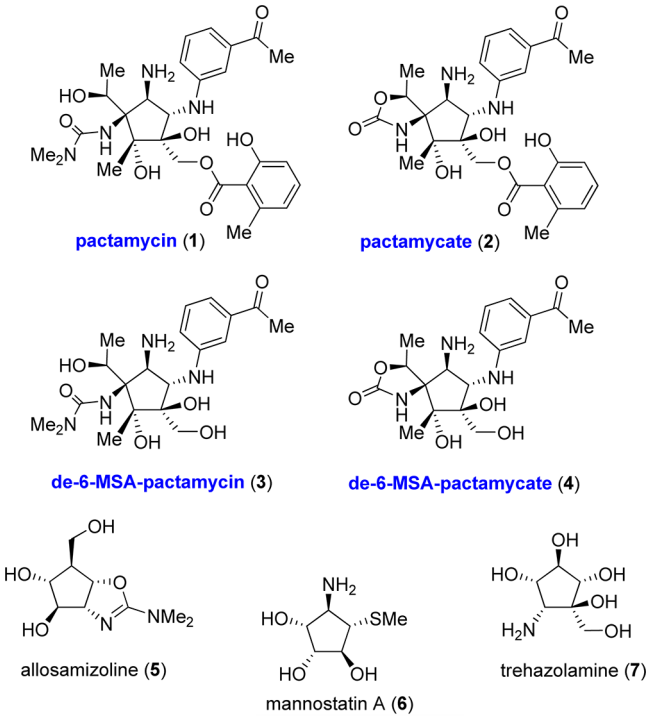


Figure 1. Structures of pactamycin, pactamycate, de-6-MSA-pactamycin, de-6-MSA-pactamycate, allosamizoline, mannostatin A, and trehazolamine.

An initially proposed structure for pactamycin by the Upjohn scientists in 1970 based on chemical degradation studies[11] was

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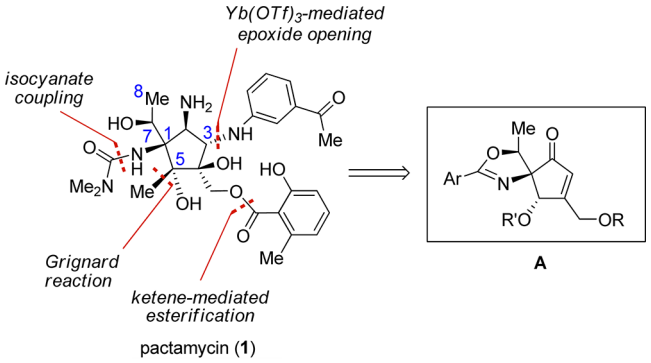
subsequently corrected in 1972 as a result of an X-ray crystal structure of a derivative.[12] To the best of our knowledge, pactamycin is the most densely functionalized naturally occurring aminocyclopentitol.[13] In spite of its unique architecture and rich history in the realm of other RNA-binding natural products, efforts toward its synthesis have been sparse. Conceptually different approaches toward the construction of the aminocyclopentitol core of pactamycin were reported by Isobe,[14] Knapp,[15] and more recently by Johnson,[16] Looper,[17] Nishikawa,[18] and their respective co-workers.

In a preliminary communication, we reported the first total synthesis of pactamycin (**1**) and pactamycate (**2**).[19] Herein, we provide a detailed account of our efforts, delineating initial studies that were met with a number of unexpected dead ends and road blocks, necessitating revisions of synthetic approaches. Analysis of the structure of pactamycin reveals a number of challenges, not the least of which are the presence of three contiguous tertiary centers at C4, C5, and C1 (Scheme 1). We

Scheme 1. Strategic Bond Disconnections to Key Intermediate Cyclopentenone A



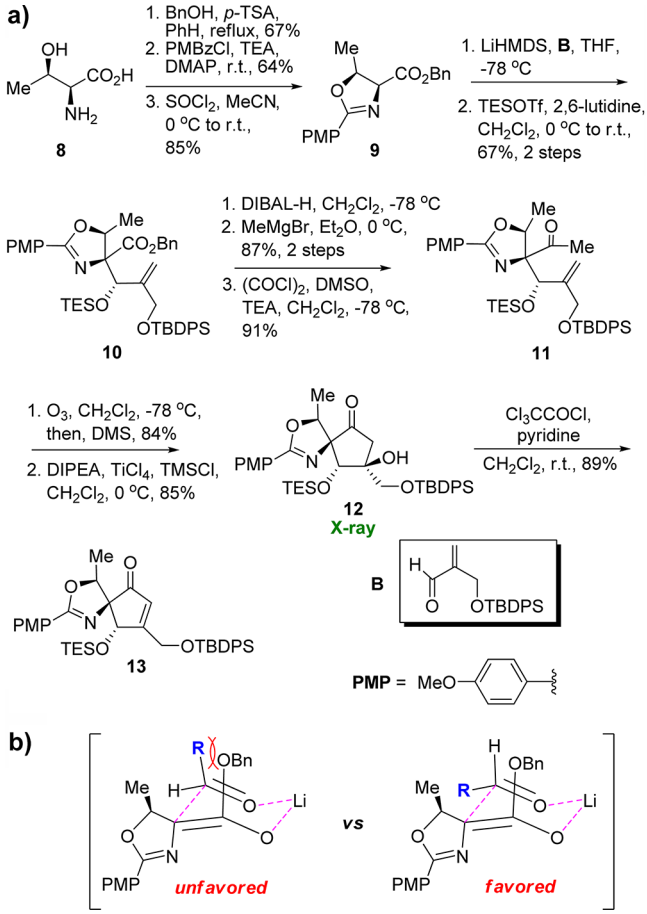
were cognizant that the densely functionalized core motif would require a judicious choice of carefully orchestrated bond-forming sequences, in which the order of execution would be crucial. On the basis of the existing functional groups and substituents on the cyclopentane core of pactamycin, a series of bond-forming sequences could be envisaged, as shown in Scheme 1.

Straightforward as this plan may have appeared to be at the outset, we were unaware of the potential difficulties associated with effecting seemingly routine transformations as new substituents and appendages were sequentially introduced on the cyclopentane core. Considering the nature and placement of the substituents, we chose to secure the aminoalcohol unit comprising C1 and extending toward C2 (or C5) that could be further elaborated into the cyclopentane core motif. With this initial objective in mind, we chose L-threonine as a suitable *chiron* that would provide a hydroxyethyl appendage with the desired absolute configuration and allowed further elaboration of the α-amino acid segment to introduce C-branching via enolate or Claisen condensation. Since the aminoalcohol portion of pactamycin was considered to be an inherent part of the molecule, we wanted to adopt a modular approach for the introduction of substituents around the cyclopentane core to allow for diversification in preparing potentially bioactive analogues and congeners with diminished toxicity. To this end, we chose the cyclopentenone core motif **A** as our initial objective for synthesis (Scheme 1).

RESULTS AND DISCUSSION

Cyclopentenone Core. A known three-step sequence starting with L-threonine (**8**) led to the PMP-oxazoline derivative **9** (Scheme 2a).[20] Formation of the enolate with

Scheme 2. (a) Synthesis of the Cyclopentenone Intermediate 13 and (b) Suggested Transition State for the Formation of 10



LiHMDS and condensation with O-TBDPS-2-hydroxymethyl acrolein (**B**), followed by protection with TESOTf, afforded **10** as a single isomer. The observed stereoselectivity can be rationalized based on a favored Zimmerman–Traxler transition state model (Scheme 2b). Reduction of the benzyl ester to the aldehyde, treatment with MeMgBr, and oxidation of the resulting alcohol afforded the methyl ketone **11**. Ozonolytic cleavage of the exocyclic methylene group, followed by a highly stereoselective Mukaiyama-type intramolecular aldol condensation, proceeding via a presumed Ti-coordinated Si-enol ether or the corresponding Ti-enolate, afforded **12** as a shelf-stable crystalline product which was fully characterized by X-ray crystallography.[21] Treatment of **12** with trichloroacetyl chloride in pyridine led to the corresponding ester, which underwent in situ β-elimination to give the intended cyclopentenone **13**.

Elaboration of the Cyclopentenone Core (Plan A). We started by exploring a sequence of reactions to introduce functional groups in a "clockwise manner" commencing with the carbonyl group at C2 in **13** (Scheme 3). Under a variety of conditions, reduction led almost exclusively to the (*R*)-allylic alcohol **14**. This result augured well for the introduction of an azide group at C2 (and eventually an amine), by an S_N2

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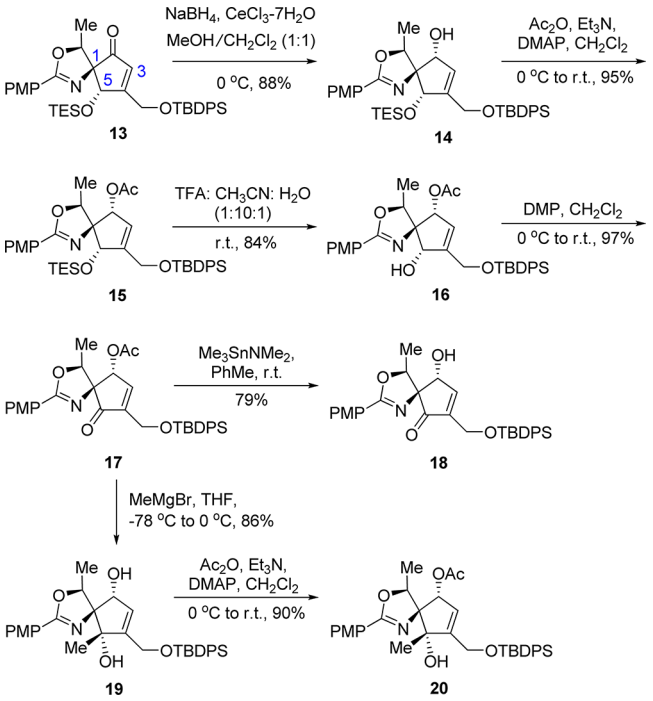
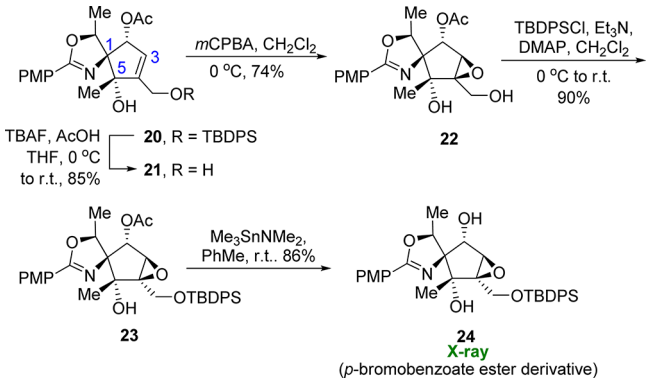
Scheme 3. Toward the Pactamycin Core, Plan A (Part 1)



reaction to secure the correct stereochemistry as found in pactamycin. Unfortunately, all attempts to prepare the triflate ester from **14** led to complex mixtures. Conversion to the acetate ester **15** and treatment of the latter with $Pd(PPh_3)_4$ and NaN_3 or $TMSN_3$ under classical Tsuji–Trost conditions[22] was also unsuccessful, as starting material remained intact and could be recovered. Selective deprotection of the TES ether in **15** gave **16**, which was oxidized under Dess–Martin conditions to give ketone **17**. Deacetylation to **18** with trimethylstannyl dimethylamine,[23] followed by attempted conversion to the triflate ester led to decomposition. However, treatment of **17** with MeMgBr afforded **19** as a single isomer with the required orientation as found in pactamycin. Unfortunately, formation of the corresponding triflate or mesylate esters also failed, giving a complex mixture of products.

We next decided to postpone the introduction of the azide group, in favor of the aniline moiety at C3. The acetate **20**, prepared from **19**, was transformed to the corresponding allylic alcohol **21**, which was treated with *m*CPBA to afford epoxide **22** (Scheme 4). Reprotection of the primary hydroxyl group as

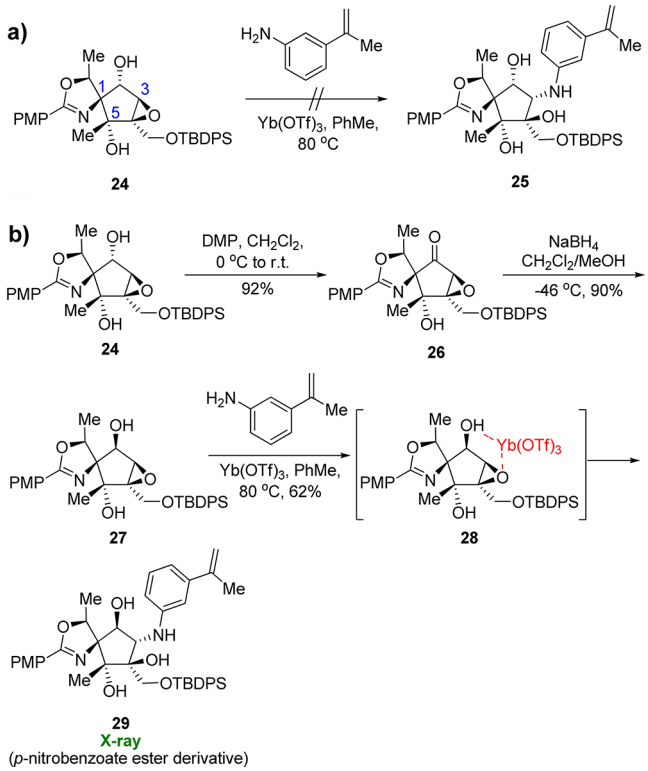
Scheme 4. Toward the Pactamycin Core, Plan A (Part 2)



in **23**, followed by deacetylation, led to **24**, whose structure was ascertained by X-ray crystallography of the corresponding *p*-bromobenzoate ester.[21] It is noteworthy that the direct epoxidation of **20** gave only trace amounts of **23** and mainly entailed slow decomposition. Disappointingly, attempts to prepare the C2 triflate ester of **24** led to a complex mixture of products.

Faced with yet another impasse in our attempts to functionalize C2, we proceeded to study conditions for the regioselective ring opening of the epoxide **24** with various anilines.[24] Preliminary model studies, to be discussed in a separate publication, with simple 1-hydroxy-2,3-epoxy-3-methyl cyclopentanes, with and without protecting groups utilizing various Lewis acids and anilines, resulted in exclusive opening at the tertiary carbon atom. Nevertheless, we hoped that the selectivity could be reversed due to the different topology, substitution pattern, and steric effects in **24**. However, treatment with 3-isopropenyl aniline in the presence of $Yb(OTf)_3$ in toluene at 80 °C did not lead to **25** but resulted in the formation of a complex mixture of products (Scheme 5a).

Scheme 5. Toward the Pactamycin Core, Plan A (Part 3): Introduction of the Aniline Moiety



Oxidation of **24** to the corresponding ketone **26** and reduction with $NaBH_4$ led to the C2 epimeric alcohol **27**. Much to our delight, treatment with 3-isopropenyl aniline in the presence of $Yb(OTf)_3$ now led to the expected aniline **29**. Definitive confirmation of structure and stereochemistry was obtained from a single X-ray crystal structure determination of a *p*-nitrobenzoate ester derivative.[21] The successful regio- and stereoselective opening of the *syn*-oriented epoxyalcohol **27** can be explained by a favorable Yb-coordinated complex (**28**),[24] which presumably was not formed in the case of **24** with an

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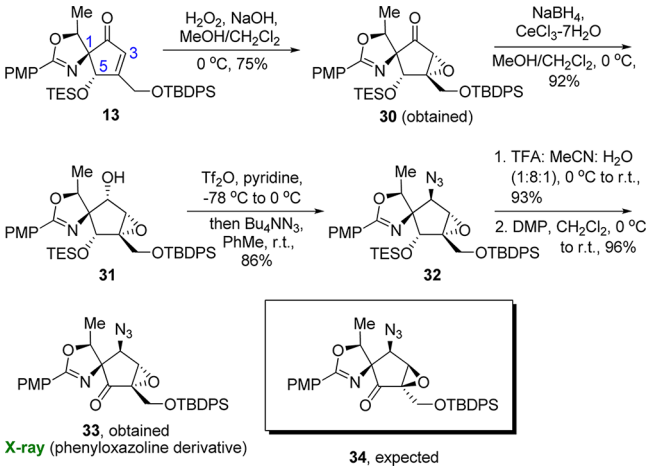
anti-orientation of the C2 alcohol compared to **27** (Scheme 5b).

Reassessing our options, it was clear that substantial progress had been made in reaching the advanced stage of intermediate **29**, which possessed all of the required functional appendages except at C2. Introduction of an azide group would require reinversion of the C2 hydroxyl group in order to attempt S_N2 substitution on the triflate ester. However, our prior negative experiences along those lines (vide supra) dissuaded us from continuing this approach.

Elaboration of the Cyclopentenone Core (Plan B). We returned to the cyclopentenone core motif **13** and considered a different sequence of funtionalizations. Treatment of **13** with H_2O_2 cleanly afforded a product which we believed to be the "*up*" epoxide analogue of **30** as observed for **21**, due to the orientation of the bulky O-TES group (Scheme 6). Reduction

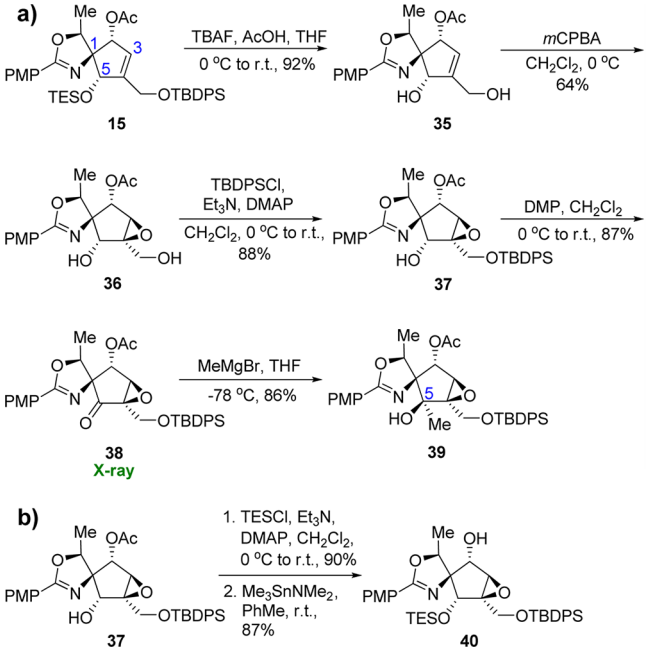
Scheme 6. Toward the Pactamycin Core, Plan B (Part 1): Introducing Azide on the Wrong Epoxide



of the ketone with $NaBH_4$ in the presence of $CeCl_3 \cdot 7H_2O$ gave a single alcohol at C2, which upon triflation and treatment with Bu_4NN_3 afforded a product containing the elusive azide group for the first time. However, not until the O-TES group was deprotected, and the resulting alcohol was oxidized, did we become aware that epoxidation had occurred from the *opposite face* of the enone in **13**, as evidenced from an X-ray structure.[21] Thus, epoxidation had led to **30**, which was reduced to **31**, and introduction of azide had led to **32** and **33** after silyl deprotection and oxidation, rather than the expected **34**. We presume that the combination of the spiro-oxazoline and the bulky O-TBDPS group may have disfavored the approach of the hydroperoxide ion from the same side, eventually leading to the wrong epoxide **30**.

We therefore once again changed our order of reactions, now starting with **15** (Scheme 7a). Deprotection of the silyl ethers led to **35**, which was smoothly epoxidized to **36** with *m*CPBA then reprotected to give **37**. Oxidation to **38** and X-ray analysis confirmed the required "*up*" orientation of the epoxide. However, deprotection of the acetate ester in **38** and attempted triflation led to decomposition. Having the ketone **38** in hand, we also attempted to introduce the methyl group at C5 using a Grignard reaction. In this case, however, attack occurred from the side *opposite* to the epoxide and the spiro-oxazoline to give the **39**, epimeric at C5 with **23**. Conversion of **37** to **40** (a

Scheme 7. Toward the Pactamycin Core, Plan B (Part 2): Introducing the Correct Epoxide



diastereomer of **31**) followed by attempted triflation led to yet another complex mixture (Scheme 7b).

Inverting the Epoxide (Plan C). From the various attempts to introduce an azide group at C2 with the correct stereochemistry, it was clear that a successful triflation and S_N2 azide displacement was possible only with a specific relative orientation of the epoxy alcohol as found in **31**. We were therefore faced with an "*epoxide inversion*" issue. Treatment of the ketone **33** with MeMgBr, then silyl ether deprotection, cleanly gave **41** (Scheme 8). For the "inversion" of the epoxide, we would rely on a regioselective solvolytic ring opening, followed by placing a leaving group at the resulting C3 alcohol, then treatment with an appropriate base to effect epoxide formation with the tertiary hydroxyl group at C4, acting as an internal nucleophile. A variety of conditions were tried to effect these transformations, but without success.[25] We then resorted to an activation of the epoxide with a Lewis acid in the presence of acetic acid as a nucleophile in the hope of obtaining the C4-inverted tertiary alcohol as the acetate ester. In the event, treatment of **41** with $Zn(OTf)_2$ in acetic acid[26] led directly to the primary acetate ester **44** in excellent yield.

Thus, configurational inversion at C3 and C4 had indeed been achieved, albeit by an alternative pathway than the one initially envisaged (vide supra). Presumably, solvolysis proceeded by initial activation of the epoxide by $Zn(OTf)_2$, as in **42**, followed by formation of a spiroepoxide **43** by intramolecular attack of the primary hydroxyl group with inversion of configuration of the tertiary C4 center. Subsequent regioselective ring opening with acetic acid at the primary carbon atom of the spiroepoxide, possibly activated by $Zn(OTf)_2$, led to **44** as the only product in good overall yield. A two-step sequence restored the TBDPS ether group, and the resulting triol was converted to the C3,C4-"inverted" epoxide **46** via the corresponding triflate (71% overall yield from **33**). An X-ray structure of **46** confirmed the structure of the latter intermediate. Highly regio- and stereoselective epoxide opening at C3 with 3-isopropenyl aniline in the

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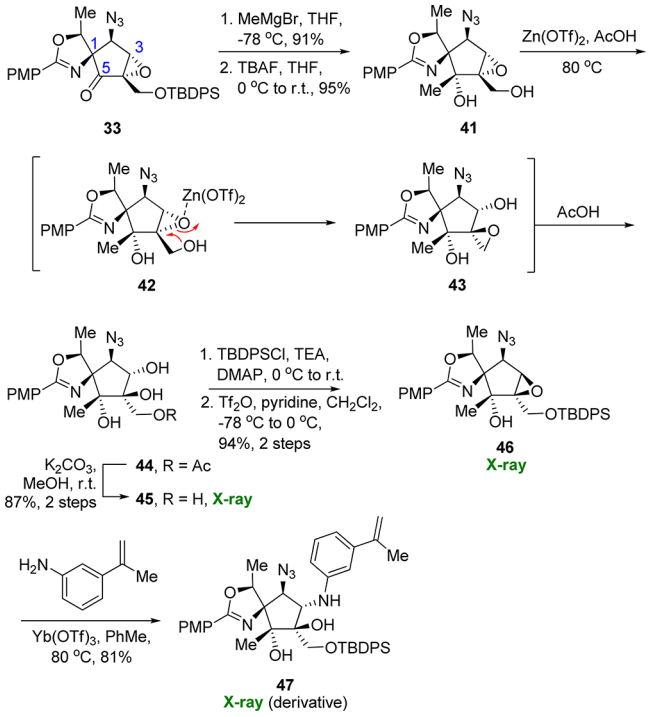
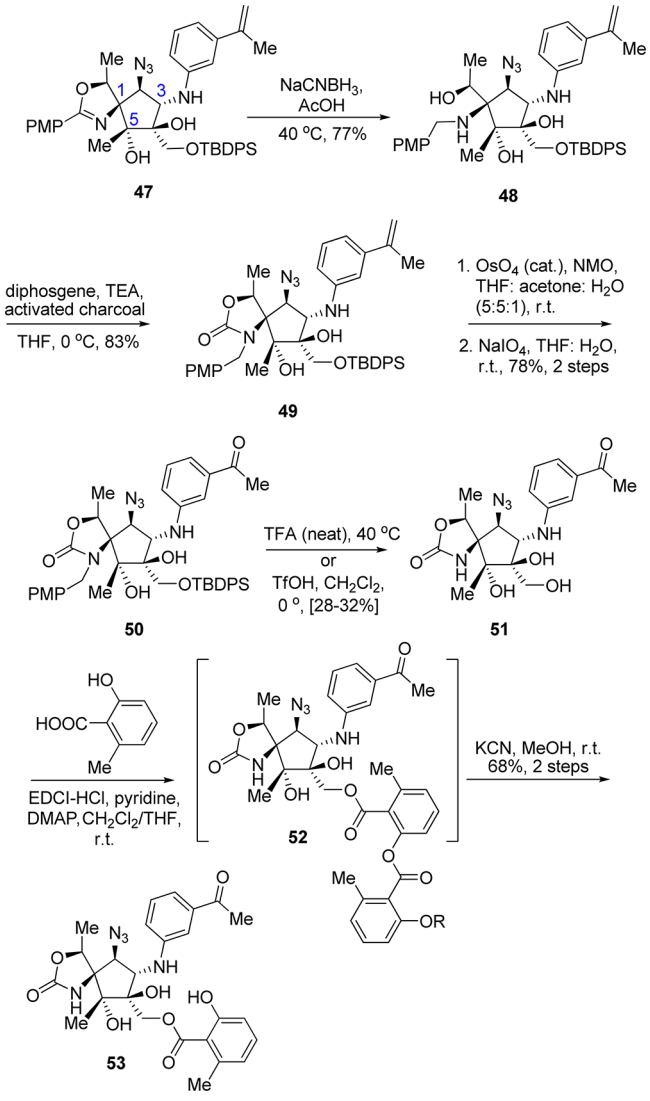
Scheme 8. Obtaining the Core Structure of Pactamycin



Scheme 9. Toward Pactamycate (First Approach)



presence of $Yb(OTf)_3$ afforded the advanced core structure **47** as the sole product.[21] It should be noted that activation of the epoxide **46** with $Yb(OTf)_3$ occurred in the absence of a coordinating hydroxyl group, and the regioselective opening with the aniline could be due to the inductive effect of the neighboring azido group and to steric effects.

Toward Pactamycate. Having secured the full complement of substituents directly attached to the cyclopentane core motif, we set our next objective toward the naturally occurring congener, pactamycate, previously obtained by acid treatment of pactamycin.[11] Studies by Mahmud and co-workers[6] on the biosynthesis of pactamycin led to the identification and isolation of pactamycate and its de-6-MSA-counterpart from the same gene cluster.

Our first steps toward pactamycate consisted of the conversion of **47** to the N-PMB derivative **48** by treatment with $NaCNBH_3$ in AcOH[20] (Scheme 9). Formation of the cyclic carbamate **49** using diphosgene in the presence of activated charcoal[27] was followed by an oxidative cleavage of the exocyclic methylene group to afford **50**. Treatment of **50** with ceric ammonium nitrate resulted in decomposition. However, treatment under strong acidic conditions removed the N-PMB group, albeit in modest yield, to furnish the 2-azido analog of de-6-MSA-pactamycate **51**. There remained to esterify the primary hydroxyl group and to reduce the azide group to reach pactamycate. Thus, treatment of **51** with 6-methylsalicylic acid in the presence of EDCI under standard conditions led to the formation of **52** as a mixture of oligomers containing two or more 6-MSA units as a result of multiple esterifications of the phenolic hydroxyl group in the initially formed 2-azido pactamycate. Treatment of **52** with KCN in MeOH[28] effected selective cleavage of the phenolic esters to afford the desired 2-azido pactamycate **53**.

In view of the modest yield of deprotection of the N-PMB group, coupled with the unwanted double esterification of **51**, we sought an alternative approach to pactamycate (Scheme 10). The oxazoline group in **47** was cleaved under acidic conditions to afford the *p*-methoxybenzoate ester **54**. Treatment with DIBAL-H led to **55**, which when treated with diphosgene in the presence of activated charcoal gave the cyclic carbamate **56**. Oxidative cleavage of the exocyclic methylene group, followed by cleavage of the OTBDPS group in the presence of TASF[29] afforded **51**, which had been obtained in lower yields by the earlier route (see Scheme 9). Esterification of **51** was successfully achieved using cyanomethyl 2-hydroxy-6-methylbenzoate (**57**) according to Porco and co-workers[30] to afford **53**. Reductive cleavage of the azido group in presence of Zn powder in aqueous NH_4Cl[31] gave crystalline pactamycate (**2**) whose structure and absolute stereochemistry was validated by X-ray crystallography for the first time. De-6-MSA-pactamycate (**4**) could be obtained by reductive cleavage of the azido group in **51**, adopting the same methods used for **53**.

Onward to Pactamycin. The advanced intermediates **54** and **55** were exquisitely poised for a straightforward completion of the total synthesis of pactamycin. All that would be required was the formation of the dimethylurea by suitable functionalization of the exposed primary amino group. The availability of N,N-dimethylcarbonyl chloride as a reagent would practically ensure access to the desired N,N-dimethylurea from one or

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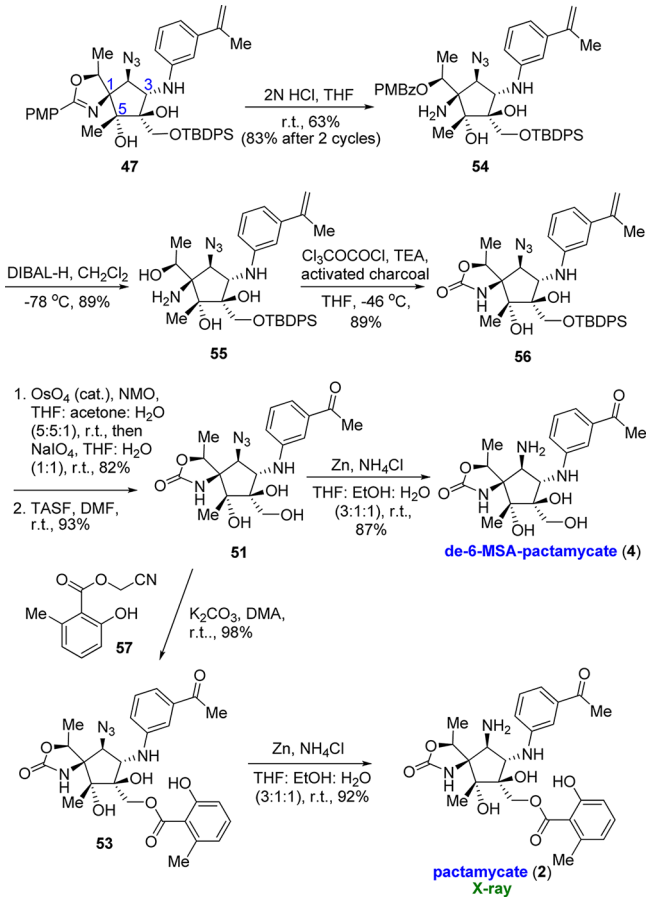
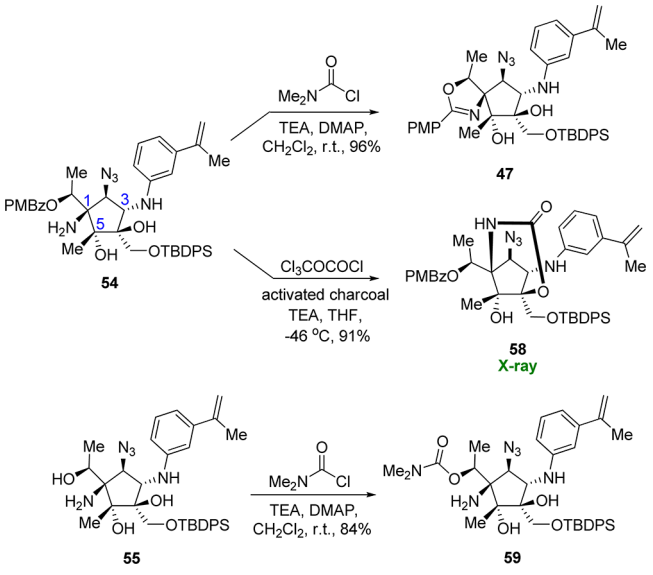
Scheme 10. Toward Pactamycate (Second Approach)



more of the aforementioned intermediates.[32] However, in practice, this turned out to be a frustrating experience and a reflection of the unexpected reactivities of an otherwise commonly reactive primary amino group in densely functionalized core motifs, such as **54** and **55** (Scheme 11). When **54** was treated with N,N-dimethylcarbamoyl chloride under a variety of conditions, none of the desired N,N-dimethylurea was observed. Instead, the oxazoline **47**, formed by an intramolecular attack of the amino group on the PMBz ester and elimination of water, was recovered. Under forcing conditions, using NaH, TBAI, and N,N-dimethylcarbamoyl chloride, only carbamoylation of **54** was observed. In an effort to obtain the intended urea via an intermediate isocyanate, we treated **54** with diphosgene in the presence of activated charcoal. Surprisingly, this led to the six-membered cyclic carbamate **58**, resulting from an intramolecular attack of the tertiary alcohol on the isocyanate group. The structure of **58** was ascertained by X-ray analysis. Treatment of the aminotriol **55** with N,N-dimethylcarbamoyl chloride led to the formation of the carbamate **59**, leaving the amino group unperturbed.

Scheme 11. Attempts To Form the Urea (Part 1)



We then reasoned that treatment of the cyclic carbamates **47**, **56**, and **58** with dimethylamine or trimethylstannyl dimethylamine (Me_3SnNMe_2) could result in the formation of the elusive N,N-dimethylurea via a direct attack on the carbonyl group of the carbamate or via a four-center activation mode with transfer of the dimethylamine group (Scheme 12). However, in the presence of Me_3SnNMe_2 in refluxing toluene, **56** was found to be completely stable, while **58** gave the O-PMBz deprotected carbamate **60**.

The unsuccessful attempts to prepare the N,N-dimethylurea derivative by selective acylation of the seemingly more nucleophilic primary amino group at C1 underscore the importance of proximity and steric effects in the densely functionalized cyclopentane core intermediates such as **54** and **55**. The extreme shielding of the amino group was further demonstrated in a last resort effort to achieve urea formation (Scheme 13). Thus, benzylation of the aminoester **54** in the presence of BnBr, NaH, and Bu_4NI in THF led unexpectedly to **62**, the structure of which was confirmed only after effecting two additional steps (vide infra). Realizing that benzylation had not occurred on the amino group from independent analysis, but as yet unaware of the exact placement of the two benzyl groups, we treated the product **62** with NaH, TBAI, and N,N-dimethylcarbamoyl chloride, which resulted in recovery of starting material. Then, the amine **62** was reduced with DIBAL-H to cleave the PMB ester, and the resulting amino alcohol **63** was treated with N,N-dimethylcarbamoyl chloride in the presence of NaH and Bu_4NI at rt. The product turned out to be the carbamate **64**, the structure of which was confirmed by X-ray analysis. Remarkably, and against all predictions, benzylation had spared the primary amino group and, instead, had occurred on two adjacent diols, albeit with an internal functional adjustment. Thus, the alkoxide initially formed from the tertiary alcohol at C4 of **54** had undergone an intramolecular silyl transfer reaction[33] via **61**, transposing the TBDPS group and exposing a primary alkoxide which was benzylated to give **62**!

In an alternative approach, benzylation of intermediate **63** under the same conditions as for **54** gave the tribenzyl ether **65** (Scheme 14). Treatment with diphosgene led to a chromatographically stable isocyanate **66** which was treated with neat dimethylamine to give the N,N-dimethylurea **67** for the first time. Oxidative cleavage of the exocyclic methylene group led to the ketone, which was desilylated to give the crystalline urea derivative **68**. Clearly, without X-ray crystallographic evidence, it would have been very difficult to interpret the results shown in Schemes 13 and 14, spectroscopically or otherwise.

Although we became aware of the inertness of the primary amino group toward acylation and alkylation, we also learned that in the absence of an interfering hydroxyl at C4, we could

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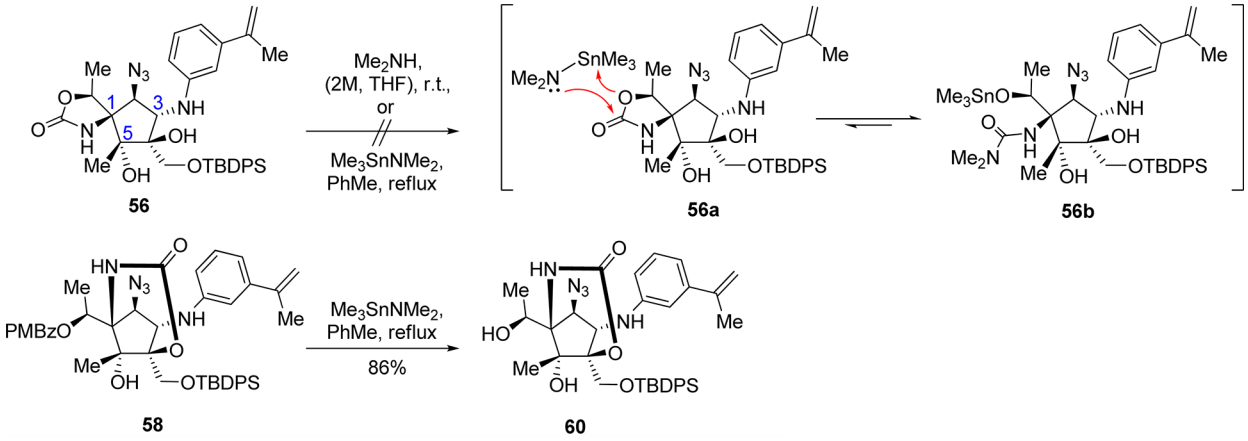
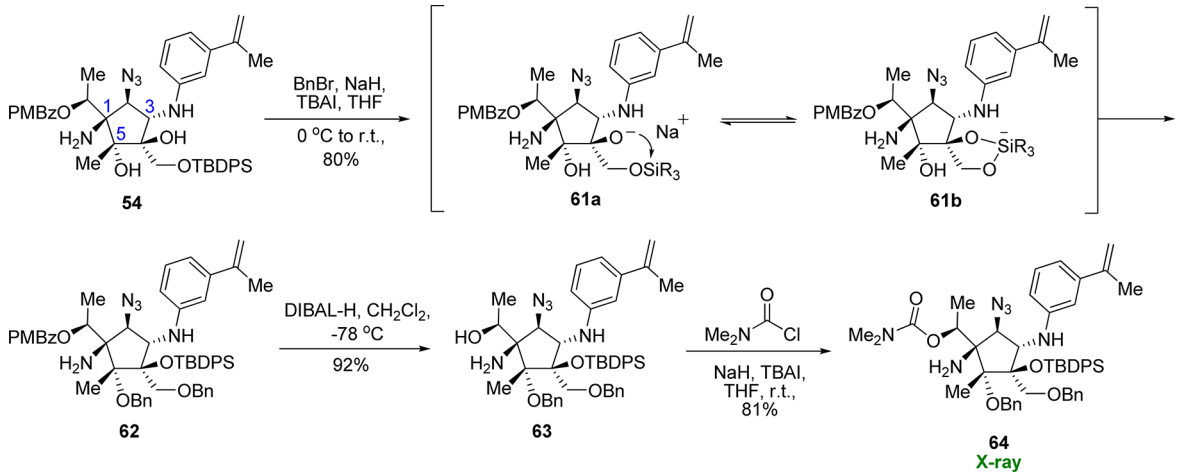
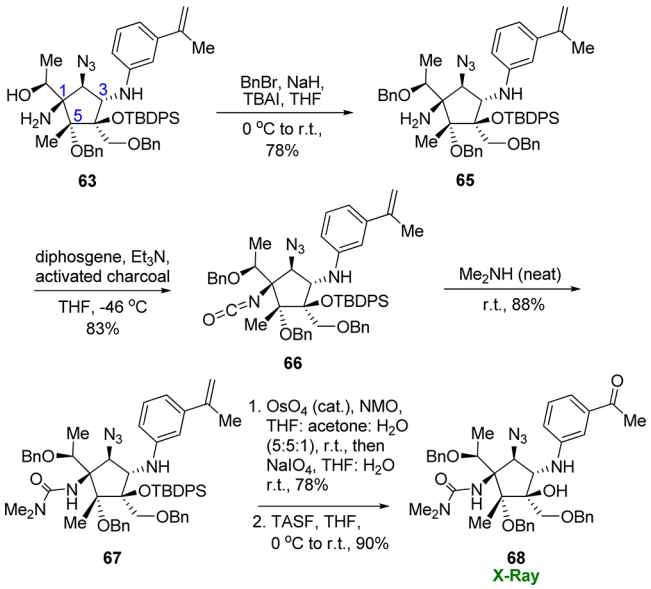
Scheme 12. Attempts To Form the Urea (Part 2)



Scheme 13. Attempts To Form the Urea (Part 3)



Scheme 14. Formation of the Urea via the Isocyanate



nevertheless form isocyanates and even the desired N,N-dimethylurea, as shown in Scheme 14. Rather than continuing with the fully protected intermediate **68**, we turned our attention instead to "neutralizing" the offending tertiary hydroxyl group at C4.

Deprotection of the TBDPS ether in **54** led to an aminotriol, which was converted to the acetonide **69** (Scheme 15). Formation of the isocyanate, then treatment with neat dimethylamine, afforded the N,N-dimethylurea derivative **70** in 86% yield. Reductive cleavage of the PMB ester followed by the oxidative cleavage of the methylene group, and finally, hydrolysis of the acetonide group gave **71**. Esterification as described for pactamycate (**2**), followed by reduction of the azido group, gave pactamycin (**1**) in excellent yield.[21] In parallel, reduction of the azide group in **71** led to de-6-MSA-pactamycin (**3**).

CONCLUSION

We described a detailed account of our efforts toward the total synthesis of pactamycin, pactamycate, and their de-esterified counterparts. Starting with L-threonine as the chiral cornerstone, we proceeded to construct the cyclopentenone core motif **A** (Scheme 1), which served as the pivotal scaffold upon which we attempted to introduce the required substituents in a systematic way. Initial failures and unexpected results forced us to explore alternative approaches to install functional groups in regio- and stereocontrolled reactions. At times, the difference between triumph and disaster hinged upon the judicious choice of methods and order of execution, such as the solvolytic

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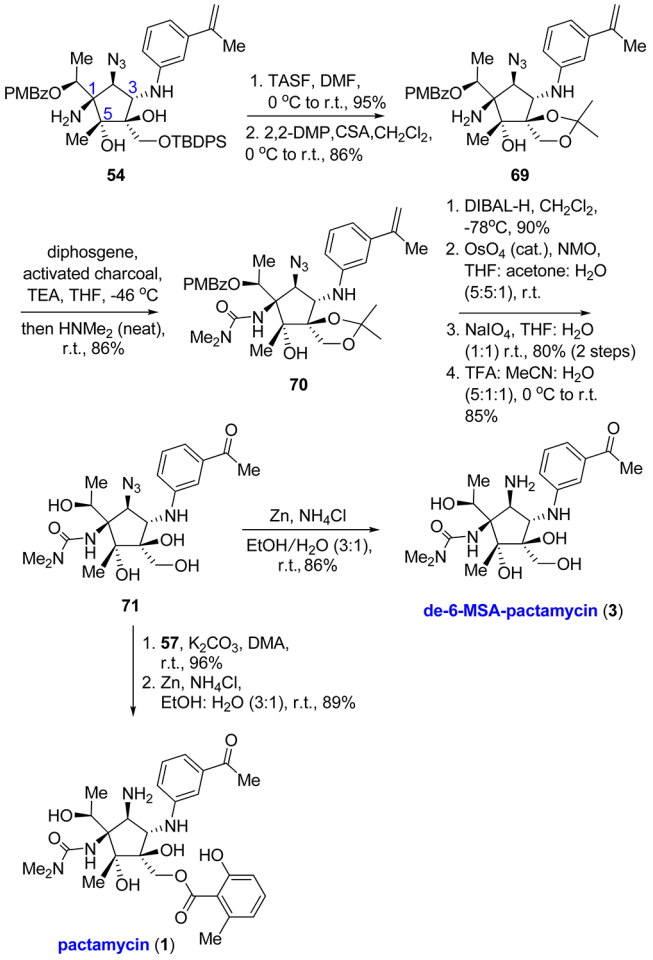
Scheme 15. Completion of the Total Synthesis of Pactamycin



"inversion" of the epoxide in presence of $Zn(OTf)_2$ and AcOH. The capricious S_N2 displacement of C2 triflate esters became cooperative when the substituents in the cyclopentanone ring provided a favored trajectory of approach for the azide ion. Epoxide opening with an aniline moiety was possible only when a neighboring hydroxy group had a *syn* relationship, favoring a coordination with the Lewis acid $Yb(OTf)_3$, or when an azide group was present, exerting an inductive effect. Finally, the importance of proximity effects and steric shielding became manifest in the numerous vain attempts to acylate or benzylate the presumably more basic and nucleophilic primary amino group in the presence of highly hindered tertiary hydroxyl groups. In spite of these humbling experiences, logic, deductive reasoning, and a strong resolve prevailed in the end. Pactamycin (**1**) and pactamycate (**2**) were synthesized in 29 steps (3.1%) and 26 steps (4.0%), respectively, starting with the known oxazoline **9**. With the recent reports on the antiprotozoal activities of pactamycin,[6] the study of this unique amino cyclopentitol and its analogues expands their scope as valuable biological probes to interact with RNAs of diverse sources. Studies relative to such objectives are in progress and will be reported in due course.

EXPERIMENTAL SECTION

Experimental procedures and characterization data for the preparation of compounds **1**, **2**, **8**−**13**, **30**−**33**, **41**−**47**, **51**, **53**−**56**, **58**, and **69**−**71** have been reported previously.[19]

(4*S*,5*R*,6*R*,9*S*)-8-((*tert*-Butyldiphenylsilyloxy)methyl)-2-(4-methoxyphenyl)-4-methyl-9-(tripropylsilyloxy)-3-oxa-1-azaspiro[4.4]nona-1,7-dien-6-ol (14). To a solution of cyclopentenone **13** (3.81 g, 5.81 mmol) in MeOH/CH_2Cl_2 (30 mL, 1:1) was added $CeCl_3{\cdot}7H_2O$ (4.33 g, 11.63 mmol) at 0 °C under argon atmosphere, and the mixture was stirred for 10 min. Then, $NaBH_4$ (220 mg, 5.81 mmol) was added portionwise and stirred for 1 h at the same temperature. The reaction was then quenched with slow addition of a saturated aqueous NH_4Cl solution and extracted three times with EtOAc. The organic layer was dried over Na_2SO_4 and concentrated under reduced pressure. Flash column chromatography using 25% EtOAc in hexanes eluent afforded the allylic alcohol **14** (3.37 g, 88%) as a viscous liquid: $[\alpha]_D^{20}$ −6.8 (*c* 1.00, acetone); IR (neat) ν_{max} 3178 (br, s), 3071, 2957, 2877, 1635, 1610, 1513, 1463, 1427, 1372, 1350, 1307, 1257, 1172, 1144, 1112, 1065, 1039, 1008, 974, 908, 875, 841, 741, 702, 611 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.86 (2H, d, J = 8.8 Hz), 7.75−7.72 (4H, m), 7.47−7.40 (6H, m), 6.90 (2H, d, J = 8.8 Hz), 6.30 (1H, d, J = 1.9 Hz), 5.10 (1H, q, J = 6.6 Hz), 4.72 (1H, s), 4.37−4.34 (3H, m), 3.86 (3H, s), 2.28 (1H, br s), 1.61 (3H, d, J = 6.6 Hz), 1.11 (9H, s), 0.85 (9H, t, J = 7.9 Hz), 0.56−0.49 (6H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ 163.9, 162.0, 147.5, 135.6, 135.4, 133.5, 133.3, 130.1, 129.6, 129.2, 128.5, 127.6, 127.5, 120.4, 113.4, 86.0, 79.8, 78.9, 78.2, 61.3, 55.2, 26.7, 19.2, 16.6, 6.6, 4.7; HRMS-ESI (m/z) calcd for $C_{38}H_{52}NO_5Si_2$ $[M + H]^+$ 658.33785, found 658.33952.

(4*S*,5*S*,6*R*,9*S*)-8-((*tert*-Butyldiphenylsilyloxy)methyl)-2-(4-methoxyphenyl)-4-methyl-9-(tripropylsilyloxy)-3-oxa-1-azaspiro[4.4]nona-1,7-dien-6-yl acetate (15). To a solution of allylic alcohol **14** (3.12 g, 4.75 mmol) in CH_2Cl_2 (20 mL) were added Et_3N (3.31 mL, 23.73 mmol), Ac_2O (0.67 mL, 7.12 mmol), and DMAP (58.6 mg, 0.48 mmol) at 0 °C under argon atmosphere. The reaction mixture was stirred for 1 h at rt. The reaction was quenched with aqueous saturated NH_4Cl solution and extracted twice with CH_2Cl_2. The residue was purified by flash chromatography on silica gel using 15% EtOAc in hexanes to afford acetate **15** (3.16 g, 95%) as clear oil: $[\alpha]_D^{20}$ −22.4 (*c* 1.00, $CHCl_3$); IR (neat) ν_{max} 3072, 2957, 2935, 2877, 1743, 1640, 1610, 1513, 1462, 1427, 1369, 1306, 1254, 1238, 1169, 1145, 1112, 1071, 1034, 968, 911, 875, 841, 823, 741, 703, 613 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.92 (2H, d, J = 8.9 Hz), 7.73−7.71 (4H, m), 7.47−7.40 (6H, m), 6.93 (2H, d, J = 8.9 Hz), 6.04 (1H, s), 5.73 (1H, s), 5.13 (1H, q, J = 6.8 Hz), 4.65 (1H, s), 4.33 (2H, q, J = 6.8 Hz), 3.86 (3H, s), 2.07 (3H, s), 1.56 (3H, d, J = 6.8 Hz), 1.12 (9H, s), 0.82 (9H, t, J = 7.9 Hz), 0.54−0.48 (6H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.2, 164.0, 162.0, 148.2, 135.5, 135.4, 133.3, 133.2, 129.9, 129.7, 127.7, 127.6, 124.1, 120.5, 113.5, 86.3, 80.7, 79.0, 77.8, 61.2, 55.3, 26.7, 21.2, 19.2, 16.5, 6.6, 4.7; HRMS-ESI (m/z) calcd for $C_{40}H_{54}NO_6Si_2$ $[M + H]^+$ 700.34842, found 700.34801.

(4*S*,5*S*,6*R*,9*S*)-8-((*tert*-Butyldiphenylsilyloxy)methyl)-9-hydroxy-2-(4-methoxyphenyl)-4-methyl-3-oxa-1-azaspiro[4.4]-nona-1,7-dien-6-yl acetate (16). The disilyl ether **15** (1.72 g, 2.46 mmol) was dissolved in a 1:10:1 mixture of TFA/MeCN/H_2O (18 mL) at rt and stirred for 3 h at the same temperature. The transformation was monitored on ESI-MS, and the reaction mixture was slowly quenched with a saturated solution of $NaHCO_3$ at 0 °C. The reaction mixture was extracted three times with EtOAc, dried over Na_2SO_4, and concentrated in vacuo. The residue was purified by flash chromatography on silica gel using 20% EtOAc in hexanes to afford allylic alcohol **16** (1.21 g, 84%) as a colorless oil: $[\alpha]_D^{20}$ −65.1 (*c* 1.00, $CHCl_3$); IR (neat) ν_{max} 3072, 3014, 2959, 2933, 2857, 1739, 1632, 1610, 1513, 1462, 1427, 1371, 1307, 1255, 1236, 1171, 1112, 1031, 840, 823, 744, 703, 612 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.86 (2H, d, J = 8.9 Hz), 7.75−7.73 (4H, m), 7.47−7.42 (6H, m), 6.92 (2H, d, J = 8.9 Hz), 6.18 (1H, d, J = 1.9 Hz), 5.63 (1H, s), 5.19 (1H, q, J = 6.7 Hz), 4.50 (2H, s), 4.24 (1H, s), 3.86 (3H, s), 3.02 (1H, br s), 2.07 (3H, s), 1.44 (3H, d, J = 6.7 Hz), 1.12 (9H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.7, 164.0, 162.2, 150.3, 135.5, 135.4, 133.1, 133.0, 130.1, 129.7, 127.7, 127.6, 126.2, 83.4, 81.0, 80.0, 77.7, 61.6, 55.3, 26.7, 21.2, 19.1, 16.0; HRMS (ESIMS) calcd for $C_{34}H_{40}NO_6Si$ $[M + H]^+$ 586.26194, found 586.26182.

(4*S*,5*S*,6*R*)-8-((*tert*-Butyldiphenylsilyloxy)methyl)-2-(4-methoxyphenyl)-4-methyl-9-oxo-3-oxa-1-azaspiro[4.4]nona-1,7-dien-6-yl acetate (17). To a stirred solution of allylic alcohol **16**

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(1.13 g, 1.93 mmol) in CH_2Cl_2 (20 mL) was added Dess–Martin periodinane (900 mg, 2.12 mmol) at 0 °C under argon atmosphere, and the reaction mixture was stirred at rt for 2 h. The reaction mixture was quenched with $Na_2S_2O_3$/$NaHCO_3$ (7:1) aqueous saturated solution (20 mL) at 0 °C. The mixture was stirred vigorously until the two layers were separated at rt. The crude product was extracted with ether (60 mL × 3). The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4, and concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel using 15% EtOAc in hexanes afforded the enone **17** (1.09 g, 97%) as a colorless viscous foam: $[\alpha]_D^{20}$ −183.5 (*c* 1.00, $CHCl_3$); IR (neat) ν_{max} 2932, 1733, 1723, 1633, 1609, 1513, 1427, 1369, 1257, 1226, 1112, 1027, 839, 742, 703, 668 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.88 (2H, d, *J* = 8.9 Hz), 7.69–7.65 (5H, m), 7.47–7.39 (6H, m), 6.91 (2H, d, *J* = 8.9 Hz), 5.93 (1H, d, *J* = 1.9 Hz), 5.06 (1H, q, *J* = 6.7 Hz), 4.56–4.48 (2H, m), 3.86 (3H, s), 2.13 (3H, s), 1.50 (3H, d, *J* = 6.7 Hz), 1.12 (9H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ 201.9, 169.5, 165.5, 162.5, 150.7, 147.4, 135.5, 135.4, 132.9, 132.7, 130.4, 129.9, 129.8, 127.9, 127.8, 119.4, 113.6, 81.3, 79.4, 59.0, 55.4, 26.8, 21.1, 19.3, 16.1; HRMS-ESI (*m*/*z*) calcd for $C_{34}H_{38}NO_6Si$ $[M + H]^+$ 584.2463, found 584.2467.

(4*S*,5*R*,9*R*)-7-((*tert*-Butyldiphenylsilyloxy)methyl)-9-hydroxy-2-(4-methoxyphenyl)-4-methyl-3-oxa-1-azaspiro[4.4]nona-1,7-dien-6-one (18). To a solution of enone **17** (70 mg, 0.12 mmol) in toluene (3 mL) was added (dimethylamino)trimethyltin (0.1 mL, 0.60 mmol) dropwisely at rt under argon atmosphere and stirred for 3 h. Toluene was removed under reduced pressure, and the residue was purified by flash column chromatography on silica gel using 25% EtOAc in hexanes afforded the allylic alcohol **18** (51.4 mg, 79%) as colorless oil: $[\alpha]_D^{20}$ −147.9 (*c* 1.00, $CHCl_3$); IR (neat) ν_{max} 3222 (br s), 3072, 2958, 2932, 2858, 1715, 1626, 1609, 1513, 1462, 1427, 1360, 1307, 1258, 1172, 1113, 1030, 906, 868, 839, 823, 736, 702, 610 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.88 (2H, d, *J* = 8.9 Hz), 7.71–7.67 (4H, m), 7.65 (1H, d, *J* = 1.9 Hz), 7.47–7.41 (6H, m), 6.90 (2H, d, *J* = 8.9 Hz), 4.98 (1H, d, *J* = 1.9 Hz), 4.94 (1H, q, *J* = 6.7 Hz), 4.56–4.48 (2H, m), 3.85 (3H, s), 2.24 (1H, br s), 1.60 (3H, d, *J* = 6.7 Hz), 1.13 (9H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ 202.8, 165.7, 162.5, 154.4, 145.7, 135.5, 133.0, 132.8, 130.3, 129.9, 129.8, 127.9, 127.8, 119.6, 113.6, 83.2, 80.6, 76.4, 58.9, 55.3, 26.8, 19.2, 16.0; HRMS-ESI (*m*/*z*) calcd for $C_{32}H_{36}NO_5Si$ $[M + H]^+$ 542.23573, found 542.23740.

(4*S*,5*R*,6*S*,9*R*)-7-((*tert*-Butyldiphenylsilyloxy)methyl)-2-(4-methoxyphenyl)-4,6-dimethyl-3-oxa-1-azaspiro[4.4]nona-1,7-diene-6,9-diol (19). To a stirred solution of enone **17** (823 mg, 1.41 mmol) in dry THF (15 mL) was added MeMgBr (2.35 mL, 3.0 M solution in ether, 7.06 mmol) at −78 °C under argon atmosphere and stirred for 30 min. Then the temperature was raised to 0 °C and stirred for 20 min. The reaction mixture was quenched with saturated aqueous NH_4Cl solution and extracted with EtOAc (50 mL × 3). The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4, and concentrated in vacuo. Purification by column chromatography on silica gel using 35% EtOAc in hexanes afforded allylic alcohol **19** (676 mg, 86%) as a colorless liquid: $[\alpha]_D^{20}$ +29.4 (*c* 1.00, $CHCl_3$); IR (neat) ν_{max} 3402 (br), 3072, 2960, 2932, 2857, 1634, 1610, 1513, 1462, 1427, 1361, 1334, 1308, 1256, 1171, 1112, 1034, 996, 952, 912, 840, 824, 743, 702, 612 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.88 (2H, d, *J* = 8.9 Hz), 7.75–7.70 (4H, m), 7.49–7.43 (6H, m), 6.91 (2H, d, *J* = 8.9 Hz), 6.22 (1H, br s), 5.25 (1H, q, *J* = 6.6 Hz), 4.52 (1H, d, *J* = 8.0 Hz), 4.44 (2H, s), 3.86 (3H, s), 2.90 (1H, s), 2.07 (1H, d, *J* = 8.0 Hz), 1.63 (3H, d, *J* = 6.6 Hz), 1.21 (3H, s), 1.11 (9H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ 163.2, 162.1, 150.6, 135.6, 135.5, 132.8, 132.7, 131.7, 130.1, 130.0, 129.9, 127.8, 120.4, 113.6, 85.1, 83.9, 79.1, 77.7, 61.2, 55.3, 26.8, 19.1, 17.9, 17.2; HRMS-ESI (*m*/*z*) calcd for $C_{33}H_{40}NO_5Si$ $[M + H]^+$ 558.26703, found 558.26887.

(4*S*,5*S*,6*R*,9*S*)-8-((*tert*-Butyldiphenylsilyloxy)methyl)-9-hydroxy-2-(4-methoxyphenyl)-4,9-dimethyl-3-oxa-1-azaspiro-[4.4]nona-1,7-dien-6-yl acetate (20). To a solution of allylic alcohol **19** (658 mg, 1.18 mmol) in CH_2Cl_2 (20 mL) were added Et_3N (0.82 mL. 5.90 mmol), Ac_2O (0.17 mL, 1.77 mmol), and DMAP (14 mg, 0.12 mmol) at 0 °C under argon atmosphere. The reaction mixture was stirred for 1 h at rt. The reaction was quenched with aqueous saturated NH_4Cl solution and extracted twice with CH_2Cl_2. The residue was purified by flash chromatography on silica gel using 25% EtOAc in hexanes to afford acetate **20** (637 mg, 90%) as clear oil: $[\alpha]_D^{20}$ −37.0 (*c* 1.00, $CHCl_3$); IR (neat) ν_{max} 3220 (br), 2933, 2857, 1739, 1643, 1609, 1513, 1454, 1427, 1370, 1336, 1309, 1254, 1226, 1169, 1112, 1086, 1028, 950, 840, 824, 744, 703, 671, 612 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.88 (2H, d, *J* = 8.9 Hz), 7.74–7.70 (4H, m), 7.48–7.41 (6H, m), 6.92 (2H, d, *J* = 8.9 Hz), 6.30 (1H, d, *J* = 2.3 Hz), 5.60 (1H, d, *J* = 2.3 Hz), 5.23 (1H, q, *J* = 6.6 Hz), 4.45 (2H, s), 3.87 (3H, s), 2.11 (3H, s), 1.92 (1H, s), 1.43 (3H, d, *J* = 6.6 Hz), 1.11 (9H, s), 1.08 (3H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.4, 162.9, 162.2, 154.6, 135.6, 135.5, 133.2, 133.1. 130.1, 129.8, 129.7, 127.7, 127.6, 126.1, 84.9, 83.5, 80.9, 77.4, 60.4, 55.4, 26.8, 21.5, 19.2, 17.2, 17.1; HRMS-ESI (*m*/*z*) calcd for $C_{35}H_{42}NO_6Si$ $[M + H]^+$ 600.2776, found 600.2790.

(4*S*,5*S*,6*R*,9*S*)-9-Hydroxy-8-(hydroxymethyl)-2-(4-methoxyphenyl)-4,9-dimethyl-3-oxa-1-azaspiro[4.4]nona-1,7-dien-6-yl acetate (21). To a solution of silyl ether **20** (624 mg, 1.04 mmol) in THF (10 mL) were added AcOH (2 drops) and TBAF (1.15 mL, 1.0 M in THF, 1.15 mmol) at 0 °C under argon atmosphere. The reaction mixture was stirred at rt for 1 h, a saturated aqueous NH_4Cl solution was then added, and the aqueous phase was extracted three times with EtOAc. The combined organic layers were dried over Na_2SO_4 and concentrated in vacuo. The residue was purified by flash chromatography on silica gel using 60% EtOAc in hexanes to afford allylic alcohol **21** (320 mg, 85%) as clear oil: $[\alpha]_D^{20}$ −56.5 (*c* 1.00, $CHCl_3$); IR (neat) ν_{max} 3401 (br), 2973, 2936, 2840, 1732, 1634, 1609, 1514, 1454, 1422, 1371, 1338, 1308, 1255, 1172, 1090, 1022, 953, 910, 842, 732 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.88 (2H, d, *J* = 8.9 Hz), 6.92 (2H, d, *J* = 8.9 Hz), 6.26 (1H, d, *J* = 2.2 Hz), 5.57 (1H, d, *J* = 2.2 Hz), 5.25 (1H, q, *J* = 6.6 Hz), 4.37 (2H, d, *J* = 9.7 Hz), 3.85 (3H, s), 3.21 (1H, br s), 2.08 (3H, s), 1.44 (3H, d, *J* = 6.6 Hz), 1.18 (3H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.3, 163.5, 162.4, 155.0, 130.2, 126.4, 119.7, 113.7, 84.7, 83.7, 77.5, 58.6, 55.4, 21.4, 17.2, 17.0; HRMS-ESI (*m*/*z*) calcd for $C_{19}H_{24}NO_6$ $[M + H]^+$ 362.15981, found 362.16011.

(1*R*,2*R*,3*S*,4*S*,5*R*,5′*S*)-2-Hydroxy-1-(hydroxymethyl)-2′-(4-methoxyphenyl)-2,5′-dimethyl-5′*H*-6-oxaspiro[bicyclo[3.1.0]-hexane-3,4′-oxazole]-4-yl acetate (22). To the solution of allylic alcohol **21** (316 mg, 0.875 mmol) in CH_2Cl_2 (15 mL) was added *m*CPBA (647 mg, 70% in water, 2.63 mmol) at 0 °C under argon atmosphere. The reaction mixture was stirred for 2 h at the same temperature. A saturated aqueous Na_2SO_3 solution was added to the reaction mixture at 0 °C and stirred for 30 min. The reaction mixture was then diluted with EtOAc and washed with a saturated aqueous $NaHCO_3$ solution. The aqueous phase was extracted two times with EtOAc, and the combined organic layers were dried over Na_2SO_4 and concentrated in vacuo. The residue was purified by flash chromatography on silica gel using 80% EtOAc in hexanes to afford epoxy alcohol **22** (244 mg, 74%) as a colorless oil: $[\alpha]_D^{20}$ −15.0 (*c* 1.00, $CHCl_3$); IR (neat) ν_{max} 3418 (br), 2937, 1738, 1634, 1610, 1514, 1455, 1422, 1372, 1308, 1255, 1226, 1172, 1092, 1030, 908, 841, 732 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.91 (2H, d, *J* = 8.9 Hz), 6.92 (2H, d, *J* = 8.9 Hz), 5.43 (1H, s), 5.24 (1H, q, *J* = 6.5 Hz), 4.17 (1H, d, *J* = 12.7 Hz), 4.07 (1H, d, *J* = 12.7 Hz), 3.86 (3H, s), 3.75 (1H, s), 2.44 (1H, s), 2.16 (3H, s), 1.33 (3H, d, *J* = 6.5 Hz), 1.22 (3H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.9, 163.0, 162.4, 130.4, 119.8, 113.6, 84.0, 81.0, 77.8, 67.7, 59.6, 58.0, 55.4, 21.2, 17.5, 16.7; HRMS-ESI (*m*/*z*) calcd for $C_{19}H_{24}NO_7$ $[M + H]^+$ 378.1547, found 378.1558.

(1*R*,2*R*,3*S*,4*S*,5*R*,5′*S*)-1-((*tert*-Butyldiphenylsilyloxy)methyl)-2-hydroxy-2′-(4-methoxyphenyl)-2,5′-dimethyl-5′*H*-6-oxaspiro[bicyclo[3.1.0]hexane-3,4′-oxazole]-4-yl acetate (23). To a solution of epoxy alcohol **22** (220 mg, 0.583 mmol) in CH_2Cl_2 (10 mL) were added Et_3N (0.2 mL. 1.46 mmol), TBDPSCl (0.16 mL, 0.64 mmol), and DMAP (7 mg, 0.06 mmol) at 0 °C under argon atmosphere. The reaction mixture was stirred for 4 h at rt, then quenched with aqueous saturated NH_4Cl solution and extracted twice with CH_2Cl_2. The combined organic layers were dried over Na_2SO_4 and concentrated in vacuo. The residue was purified by flash chromatography on silica gel using 25% EtOAc in hexanes to afford

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silyl ether **23** (323 mg, 90%) as clear oil: $[\alpha]_D^{20}$ −11.6 (*c* 1.00, $CHCl_3$); IR (neat) ν_{max} 3486 (br), 3072, 2960, 2934, 2858, 1746, 1641, 1610, 1513, 1455, 1428, 1372, 1334, 1308, 1254, 1232, 1170, 1113, 1064, 1030, 910, 841, 823, 735, 703, 614 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.93 (2H, d, *J* = 8.9 Hz), 7.74−7.69 (4H, m), 7.48−7.42 (6H, m), 6.92 (2H, d, *J* = 8.9 Hz), 5.42 (1H, s), 5.30 (1H, q, *J* = 6.5 Hz), 4.25 (1H, d, *J* = 11.6 Hz), 3.90 (1H, d, *J* = 11.6 Hz), 3.86 (3H, s), 3.58 (1H, s), 3.21 (1H, s), 2.17 (3H, s), 1.35 (3H, d, *J* = 6.5 Hz), 1.24 (3H, s), 1.09 (9H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.9, 162.4, 161.9, 135.3, 135.2, 132.0, 131.9, 130.0, 129.7, 129.6, 127.5, 119.7, 113.2, 83.7, 80.6, 77.5, 76.5, 66.3, 61.1, 60.0, 55.0, 26.4, 20.9, 18.8, 17.3, 17.2; HRMS-ESI (*m*/*z*) calcd for $C_{35}H_{42}NO_7Si$ $[M + H]^+$ 616.2725, found 616.2733.

(1*R*,2*R*,3*R*,4*S*,5*R*,5′*S*)-1-((*tert*-Butyldiphenylsilyloxy)methyl)-2′-(4-methoxyphenyl)-2,5′-dimethyl-5′*H*-6-oxaspiro[bicyclo[3.1.0]hexane-3,4′-oxazole]-2,4-diol (24). To a solution of acetate **23** (270 mg, 0.44 mmol) in toluene (5 mL) was added (dimethylamino)trimethyltin (0.36 mL, 2.19 mmol) dropwisely at rt under argon atmosphere and stirred for 3 h. Toluene was removed under reduced pressure, and the residue was purified by flash column chromatography on silica gel using 50% EtOAc in hexanes afforded the epoxy alcohol **24** (216 mg, 86%) as colorless oil: $[\alpha]_D^{20}$ +4.4 (*c* 1.00, $CHCl_3$); IR (neat) ν_{max} 3326 (br), 2933, 2858, 1632, 1610, 1513, 1454, 1427, 1361, 1332, 1308, 1257, 1174, 1113, 1045, 944, 910, 841, 824, 735, 703, 614 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.92 (2H, d, *J* = 8.8 Hz), 7.73−7.70 (4H, m), 7.50−7.42 (6H, m), 6.91 (2H, d, *J* = 8.8 Hz), 5.27 (1H, q, *J* = 6.5 Hz), 4.43 (1H, br s), 4.33 (1H, d, *J* = 11.3 Hz), 4.32 (1H, s), 3.85 (3H, s), 3.80 (1H, d, *J* = 11.3 Hz), 3.55 (1H, s), 1.55 (3H, d, *J* = 6.5 Hz), 1.27 (3H, s), 1.11 (9H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ 163.4, 162.3, 135.5, 135.4, 131.8, 130.3, 130.2, 128.1, 128.0, 120.2, 113.5, 83.4, 81.7, 77.9, 74.8, 65.3, 63.1, 62.4, 55.3, 26.8, 19.1, 17.5, 17.2; HRMS-ESI (*m*/*z*) calcd for $C_{33}H_{40}NO_6Si$ $[M + H]^+$ 574.26194, found 574.26272.

(1*R*,2*R*,3*R*,5*S*,5′*S*)-1-((*tert*-Butyldiphenylsilyloxy)methyl)-2-hydroxy-2′-(4-methoxyphenyl)-2,5′-dimethyl-5′*H*-6-oxaspiro-[bicyclo[3.1.0]hexane-3,4′-oxazol]-4-one (26). To a stirred solution of epoxy alcohol **24** (125 mg, 0.218 mmol) in CH_2Cl_2 (5 mL) was added Dess−Martin periodinane (102 mg, 0.24 mmol) at 0 °C under argon atmosphere, and the reaction mixture was stirred at rt for 2 h. The reaction mixture was quenched with $Na_2S_2O_3/NaHCO_3$ (7:1) aqueous saturated solution (10 mL) at 0 °C. The mixture was stirred vigorously until the two layers were separated at rt. The crude product was extracted with Et_2O (20 mL × 3). The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4, and concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel using 25% EtOAc in hexanes afforded the epoxy ketone **26** (115 mg, 92%) as a colorless oil: $[\alpha]_D^{20}$ +142.5 (*c* 1.00, $CHCl_3$); IR (neat) ν_{max} 3478 (br), 3072, 2933, 2858, 1753, 1627, 1610, 1513, 1462, 1427, 1362, 1306, 1257, 1170, 1113, 1033, 910, 840, 823, 800, 737, 703, 612 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.91 (2H, d, *J* = 9.0 Hz), 7.74−7.69 (4H, m), 7.52−7.46 (6H, m), 6.89 (2H, d, *J* = 9.0 Hz), 4.94 (1H, q, *J* = 6.6 Hz), 4.46 (1H, d, *J* = 11.8 Hz), 3.85 (3H, s), 3.82 (1H, d, *J* = 11.8 Hz), 3.20 (1H, s), 1.68 (3H, d, *J* = 6.6 Hz), 1.52 (3H, s), 1.11 (9H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ 204.0, 165.4, 162.3, 135.5, 131.6, 131.4, 130.5, 130.4, 128.1, 128.0, 119.9, 113.4, 82.7, 78.8, 78.5, 67.4, 61.9, 59.7, 55.3, 26.7, 19.4, 19.1, 16.4; HRMS-ESI (*m*/*z*) calcd for $C_{33}H_{38}NO_6Si$ $[M + H]^+$ 572.24629, found 572.24675.

(1*R*,2*R*,3*R*,4*R*,5*R*,5′*S*)-1-((*tert*-Butyldiphenylsilyloxy)methyl)-2′-(4-methoxyphenyl)-2,5′-dimethyl-5′*H*-6-oxaspiro[bicyclo-[3.1.0]hexane-3,4′-oxazole]-2,4-diol (27). To a solution of epoxy ketone **26** (78 mg, 0.137 mmol) in MeOH/CH_2Cl_2 (1:1, 3 mL) was added $NaBH_4$ (5.2 mg, 0.137 mmol) at −46 °C under argon atmosphere and stirred for 1 h. The reaction was then quenched with slow addition of saturated aqueous NH_4Cl solution and extracted three times with EtOAc. The combined organic layers were washed with brine, dried over Na_2SO_4, and concentrated under reduced pressure. Flash column chromatography on silica gel using 35% EtOAc in hexanes eluent afforded the epoxy alcohol **27** (71 mg, 90%) as a colorless oil: $[\alpha]_D^{20}$ +31.0 (*c* 1.00, $CHCl_3$); IR (neat) ν_{max} 3474 (br), 2931, 1638, 1610, 1513, 1427, 1361, 1256, 1112, 1030, 840, 744, 702, 614 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.96 (2H, d, *J* = 8.9 Hz), 7.73−7.68 (4H, m), 7.51−7.43 (6H, m), 6.91 (2H, d, *J* = 8.9 Hz), 5.08 (1H, q, *J* = 6.5 Hz), 4.46 (1H, d, *J* = 8.0 Hz), 4.33 (1H, d, *J* = 11.5 Hz), 4.01 (1H, s), 3.86 (3H, s), 3.66 (1H, d, *J* = 11.5 Hz), 3.37 (1H, s), 2.66 (1H, d, *J* = 8.0 Hz), 1.52 (3H, d, *J* = 6.5 Hz), 1.30 (3H, s), 1.11 (9H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.1, 162.3, 135.6, 135.5, 131.9, 131.7, 130.4, 130.3, 130.2, 128.0, 127.9, 120.0, 113.5, 81.5, 80.7, 78.4, 72.3, 64.3, 64.0, 62.8, 55.4, 26.8, 19.0, 18.8, 17.3; HRMS-ESI (*m*/*z*) calcd for $C_{33}H_{40}NO_6Si$ $[M + H]^+$ 574.26194, found 574.26343.

(4*S*,5*R*,6*R*,7*S*,8*S*,9*S*)-7-((*tert*-Butyldiphenylsilyloxy)methyl)-2-(4-methoxyphenyl)-4,6-dimethyl-8-(3-(prop-1-en-2-yl)-phenylamino)-3-oxa-1-azaspiro[4.4]non-1-ene-6,7,9-triol (29). To a stirred solution of epoxy alcohol **27** (56 mg, 0.098 mmol) in toluene (3 mL) were added the aniline derivative (130 mg, 0.98 mmol) and $Yb(OTf)_3$ (61 mg, 0.049 mmol) at rt under argon atmosphere. The reaction mixture was heated to 80 °C and stirred for 9 h, then cooled to rt, quenched with water (5 mL), and extracted with EtOAc (50 mL × 2). The combined organic layers were washed with 0.5 N HCl, saturated aqueous $NaHCO_3$ solution, dried over anhydrous Na_2SO_4, and concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel using 40% EtOAc in hexanes to afford the aniline **29** (43 mg, 62%) as a pale yellow viscous liquid: $[\alpha]_D^{20}$ +20.5 (*c* 1.00, $CHCl_3$); IR (neat) ν_{max} 3421 (br), 2932, 1635, 1604, 1586, 1514, 1427, 1364, 1257, 1171, 1105, 1038, 822, 737, 702 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.92−6.69 (18H, aromatic protons), 5.32 (1H, s), 5.07 (1H, q, *J* = 6.4 Hz), 5.03 (1H, s), 4.68−4.58 (2H, m), 4.40 (1H, dd, *J* = 11.2, 4.8 Hz), 4.17−4.12 (2H, m), 3.99 (1H, br s), 3.88 (3H, s), 3.83 (1H, d, *J* = 10.8 Hz), 2.25 (1H, d, *J* = 11.6 Hz), 2.10 (3H, s), 1.60 (3H, d, *J* = 6.4 Hz), 1.19 (3H, s), 1.12 (9H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.2, 162.9, 147.8, 143.8, 142.3, 135.8, 135.6, 131.4, 131.3, 130.4, 130.2, 130.0, 129.1, 128.0, 127.9, 118.9, 114.9, 113.8, 112.4, 111.9, 111.0, 84.4, 83.6, 80.9, 80.3, 79.4, 72.8, 66.7, 55.5, 27.0, 21.9, 19.0, 17.3, 17.1; HRMS-ESI (*m*/*z*) calcd for $C_{42}H_{51}N_2O_6Si$ $[M + H]^+$ 707.35235, found 707.35109.

(4*S*,5*S*,6*R*,9*S*)-9-Hydroxy-8-(hydroxymethyl)-2-(4-methoxyphenyl)-4-methyl-3-oxa-1-azaspiro[4.4]nona-1,7-dien-6-yl acetate (35). To the solution of silyl ether **15** (1.07g, 1.53 mmol) in THF (10 mL) was added TBAF (3.21 mL, 1.0 M in THF, 3.21 mmol) at 0 °C under argon atmosphere. The reaction mixture was stirred at rt for 1.5 h, a saturated aqueous NH_4Cl solution was then added, and the aqueous phase was extracted three times with EtOAc. The combined organic layers were dried over Na_2SO_4 and concentrated in vacuo. The residue was purified by flash chromatography on silica gel using 80% EtOAc in hexanes to afford diol **35** (489 mg, 92%) as colorless viscous liquid: $[\alpha]_D^{20}$ −87.7 (*c* 1.00, $CHCl_3$); IR (neat) ν_{max} 3351 (br), 1733, 1631, 1514, 1422, 1372, 1308, 1255, 1173, 1028, 914, 841, 746 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.80 (2H, d, *J* = 8.9 Hz), 6.86 (2H, d, *J* = 8.9 Hz), 6.06 (1H, s), 5.54 (1H, s), 5.21 (1H, q, *J* = 6.7 Hz), 4.34 (3H, br s), 4.18 (1H, br s), 3.82 (3H, s), 2.03 (3H, s), 1.43 (3H, d, *J* = 6.7 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.0, 164.7, 162.4, 150.6, 130.2, 126.7, 119.5, 113.6, 83.28, 80.89, 79.38, 78.17, 59.37, 55.32, 21.16, 16.11; HRMS-ESI (*m*/*z*) calcd for $C_{18}H_{22}NO_6$ $[M + H]^+$ 348.14416, found 348.14499.

(1*S*,2*R*,3*S*,4*S*,5*R*,5′*S*)-2-Hydroxy-1-(hydroxymethyl)-2′-(4-methoxyphenyl)-5′-methyl-5′*H*-6-oxaspiro[bicyclo[3.1.0]hexane-3,4′-oxazole]-4-yl acetate (36). To the solution of diol **35** (431 mg, 1.24 mmol) in CH_2Cl_2 (15 mL) was added *m*CPBA (918 mg, 70% in water, 3.73 mmol) at 0 °C under argon atmosphere. The reaction mixture was stirred for 2 h at the same temperature. A saturated aqueous Na_2SO_3 solution was added to the reaction mixture at 0 °C and stirred for 30 min. The reaction mixture was then diluted with EtOAc and washed with saturated aqueous $NaHCO_3$ solution. The aqueous phase was extracted two times with EtOAc, and the combined organic layers were dried over Na_2SO_4 and concentrated in vacuo. The residue was purified by flash chromatography on silica gel using 90% EtOAc in hexanes to afford epoxy diol **36** (286 mg, 64%) as a colorless oil: $[\alpha]_D^{20}$ −41.5 (*c* 1.00, $CHCl_3$); IR (neat) ν_{max} 3364 (br), 3008, 2937,

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1746, 1633, 1610, 1514, 1455, 1422, 1373, 1334, 1308, 1256, 1230, 1173, 1088, 1029, 904, 842, 732, 688 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.84 (2H, d, J = 8.8 Hz), 6.85 (2H, d, J = 8.8 Hz), 5.30 (1H, s), 5.20 (1H, q, J = 6.5 Hz), 4.26 (1H, d, J = 12.7 Hz), 4.24 (1H, br s), 3.93 (1H, s), 3.82 (1H, d, J = 12.7 Hz), 3.80 (3H, s), 3.65 (1H, s), 2.11 (3H, s) 1.27 (3H, d, J = 6.5 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.7, 163.5, 162.4, 130.4, 119.7, 113.6, 82.3, 78.4, 76.9, 76.3, 67.3, 60.5, 59.7, 55.3, 21.1, 16.4; HRMS-ESI (m/z) calcd for $C_{18}H_{22}NO_7$ $[M + H]^+$ 364.13908, found 364.13963.

(1*S*,2*R*,3*S*,4*S*,5*R*,5′*S*)-1-((*tert*-Butyldiphenylsilyloxy)methyl)-2-hydroxy-2′-(4-methoxyphenyl)-5′-methyl-5′*H*-6-oxaspiro-[bicyclo[3.1.0]hexane-3,4′-oxazole]-4-yl acetate (37). To a solution of epoxy alcohol **36** (269 mg, 0.74 mmol) in CH_2Cl_2 (10 mL) were added Et_3N (0.31 mL. 2.22 mmol), TBDPSCl (0.21 mL, 0.82 mmol) and DMAP (9 mg, 0.074 mmol) at 0 °C under argon atmosphere. The reaction mixture was stirred for 4 h at rt, then quenched with aqueous saturated NH_4Cl solution and extracted twice with CH_2Cl_2. The combined organic layers were dried over Na_2SO_4 and concentrated in vacuo. The residue was purified by flash chromatography on silica gel using 30% EtOAc in hexanes to afford silyl ether **37** (392 mg, 88%) as clear oil: $[\alpha]_D^{20}$ −28.7 (c 1.00, $CHCl_3$); IR (neat) ν_{max} 3466 (br), 3071, 3011, 2932, 2857, 1747, 1630, 1609, 1512, 1462, 1427, 1373, 1332, 1308, 1254, 1228, 1171, 1113, 1087, 1031, 841, 823, 744, 703, 612 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.92 (2H, d, J = 8.9 Hz), 7.72−7.68 (4H, m), 7.47−7.41 (6H, m), 6.90 (2H, d, J = 8.9 Hz), 5.39 (1H, s), 5.36 (1H, q, J = 6.5 Hz), 4.21 (1H, d, J = 11.6 Hz), 4.03 (1H, d, J = 11.6 Hz), 3.96 (1H, d, J = 3.1 Hz), 3.85 (3H, s), 3.58 (1H, s), 3.27 (1H, d, J = 3.1 Hz), 2.15 (3H, s), 1.31 (3H, d, J = 6.5 Hz), 1.09 (9H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.5, 163.1, 162.3, 135.5, 135.4, 132.3, 132.2, 130.3, 130.1, 130.0, 127.9, 120.1, 113.5, 82.5, 78.5, 77.9, 76.5, 65.3, 62.8, 60.6, 55.3, 26.7, 21.1, 19.1, 16.4; HRMS-ESI (m/z) calcd for $C_{34}H_{40}NO_7Si$ $[M + H]^+$ 602.25686, found 602.25821.

(1*R*,3*S*,4*S*,5*R*,5′*S*)-1-((*tert*-Butyldiphenylsilyloxy)methyl)-2′-(4-methoxyphenyl)-5′-methyl-2-oxo-5′*H*-6-oxaspiro[bicyclo-[3.1.0]hexane-3,4′-oxazole]-4-yl acetate (38). To a stirred solution of epoxy alcohol **37** (132 mg, 0.22 mmol) in CH_2Cl_2 (5 mL) was added Dess−Martin periodinane (140 mg, 0.33 mmol) at 0 °C under argon atmosphere, and the reaction mixture was stirred at rt for 2 h. The reaction mixture was quenched with $Na_2S_2O_3/NaHCO_3$ (7:1) aqueous saturated solution (5 mL) at 0 °C. The mixture was stirred vigorously until the two layers were separated at rt. The crude product was extracted with Et_2O (30 mL × 3). The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4, and concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel using 25% EtOAc in hexanes to afford the epoxy ketone **38** (115 mg, 87%) as colorless crystals: mp 123−125 °C; $[\alpha]_D^{20}$ −136.4 (c 1.00, $CHCl_3$); IR (neat) ν_{max} 3072, 3010, 2959, 2933, 2858, 1754, 1723, 1631, 1609, 1513, 1463, 1427, 1372, 1353, 1309, 1257, 1220, 1170, 1113, 1086, 1058, 1030, 908, 864, 842, 739, 703, 616 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.91 (2H, d, J = 8.9 Hz), 7.71−7.67 (4H, m), 7.47−7.39 (6H, m), 6.90 (2H, d, J = 8.9 Hz), 5.57 (1H, s), 5.16 (1H, q, J = 6.5 Hz), 4.36 (1H, d, J = 12.4 Hz), 4.10 (1H, s), 4.03 (1H, d, J = 12.4 Hz), 3.86 (3H, s), 2.14 (3H, s), 1.37 (3H, d, J = 6.5 Hz), 1.09 (9H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ 203.8, 169.3, 164.7, 162.6, 135.6, 135.2, 132.9, 132.6, 130.6, 129.9, 129.8, 127.8, 127.7, 119.2, 113.6, 79.4, 79.1, 73.3, 61.2, 59.6, 57.2, 55.4, 26.7, 20.9, 19.3, 16.8; HRMS-ESI (m/z) calcd for $C_{34}H_{38}NO_7Si$ $[M + H]^+$ 600.24121, found 600.24208.

(1*R*,2*S*,3*S*,4*S*,5*R*,5′*S*)-1-((*tert*-Butyldiphenylsilyloxy)methyl)-2-hydroxy-2′-(4-methoxyphenyl)-2,5′-dimethyl-5′*H*-6-oxaspiro[bicyclo[3.1.0]hexane-3,4′-oxazole]-4-yl acetate (39). To a stirred solution of epoxy ketone **38** (66 mg, 0.11 mmol) in dry THF (3 mL) was added MeMgBr (0.07 mL, 3.0 M solution in ether, 0.22 mmol) at −78 °C under argon atmosphere and stirred for 1 h. The reaction mixture was quenched with saturated aqueous NH_4Cl solution and extracted with EtOAc (20 mL × 3). The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4, and concentrated in vacuo. Purification by column chromatography on silica gel using 30% EtOAc in hexanes afforded epoxy alcohol **39** (58 mg, 86%) as a colorless liquid: $[\alpha]_D^{20}$ −56.8 (c 1.00, $CHCl_3$); IR (neat) ν_{max} 3444 (br), 2957, 2932, 2857, 1745, 1636, 1609, 1513, 1462, 1427, 1373, 1337, 1309, 1255, 1236, 1171, 1113, 1080, 1049, 906, 841, 823, 741, 704, 687, 609 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.87 (2H, d, J = 8.9 Hz), 7.79−7.75 (4H, m), 7.45−7.41 (6H, m), 6.93 (2H, d, J = 8.9 Hz), 5.12 (1H, s), 5.11 (1H, q, J = 6.5 Hz), 4.49 (1H, d, J = 11.6 Hz), 4.33 (1H, s), 3.87 (3H, s), 3.71 (1H, d, J = 11.6 Hz), 2.15 (3H, s), 1.37 (3H, d, J = 6.5 Hz), 1.20 (3H, s), 1.09 (9H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.8, 163.4, 162.8, 135.7, 135.6, 133.2, 133.1, 130.4, 129.7, 129.6, 127.7, 127.6, 118.9, 113.8, 81.7, 78.9, 78.1, 75.3, 69.2, 68.9, 60.5, 55.4, 26.7, 21.3, 19.3, 17.1, 9.9; HRMS-ESI (m/z) calcd for $C_{35}H_{42}NO_7Si$ $[M + H]^+$ 616.27251, found 616.27303.

(1*R*,3*R*,4*S*,5*R*,5′*S*)-1-((*tert*-Butyldiphenylsilyloxy)methyl)-4-hydroxy-2′-(4-methoxyphenyl)-5′-methyl-5′*H*-6-oxaspiro-[bicyclo[3.1.0]hexane-3,4′-oxazol]-2-one (Alcohol of 38). To a solution of epoxy ketone **38** (40 mg, 0.067 mmol) in toluene (3 mL) was added (dimethylamino)trimethyltin (0.055 mL, 0.33 mmol) dropwisely at rt under argon atmosphere and stirred for 3 h. Toluene was removed under reduced pressure, and the residue was purified by flash column chromatography on silica gel using 35% EtOAc in hexanes afforded the epoxy alcohol (32.5 mg, 87%) as a colorless oil: $[\alpha]_D^{20}$ −93.7 (c 1.00, $CHCl_3$); IR (neat) ν_{max} 3230 (br), 3072, 2932, 2858, 1753, 1614, 1513, 1462, 1427, 1355, 1309, 1259, 1174, 1113, 1058, 1030, 996, 863, 841, 823, 798, 743, 702 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.90 (2H, d, J = 8.8 Hz), 7.72−7.70 (4H, m), 7.46−7.39 (6H, m), 6.88 (2H, d, J = 8.8 Hz), 5.12 (1H, q, J = 6.5 Hz), 4.65 (1H, s), 4.35 (1H, d, J = 12.5 Hz), 4.09 (1H, d, J = 12.5 Hz), 4.08 (1H, s), 3.84 (3H, s), 2.85 (1H, br s), 1.50 (3H, d, J = 6.5 Hz), 1.06 (9H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ 205.4, 164.9, 162.6, 135.7, 135.6, 133.0, 132.6, 130.6, 129.9, 129.8, 127.8, 119.4, 113.6, 80.7, 79.7, 71.4, 62.4, 61.5, 57.4, 55.3, 26.7, 19.2, 17.0; HRMS-ESI (m/z) calcd for $C_{32}H_{36}NO_6Si$ $[M + H]^+$ 558.23064, found 558.23177.

(1*R*,2*R*,3*S*,4*S*,5*R*,5′*S*)-1-((*tert*-Butyldiphenylsilyloxy)methyl)-2′-(4-methoxyphenyl)-5′-methyl-2-(tripropylsilyloxy)-5′*H*-6-oxaspiro[bicyclo[3.1.0]hexane-3,4′-oxazole]-4-yl acetate (TES Ether of 37). To a solution of epoxy alcohol **37** (223 mg, 0.37 mmol) in CH_2Cl_2 (10 mL) were added Et_3N (0.1 mL. 0.74 mmol), TESCl (0.075 mL, 0.45 mmol), and DMAP (5 mg, 0.04 mmol) at 0 °C under argon atmosphere. The reaction mixture was stirred for 4 h at rt, then quenched with aqueous saturated NH_4Cl solution and extracted twice with CH_2Cl_2. The combined organic layers were dried over Na_2SO_4 and concentrated in vacuo. The residue was purified by flash chromatography on silica gel using 25% EtOAc in hexanes to afford silyl ether (239 mg, 90%) as clear oil: $[\alpha]_D^{20}$ −33.8 (c 1.00, $CHCl_3$); IR (neat) ν_{max} 3071, 3000, 2956, 2935, 2877, 1746, 1637, 1610, 1512, 1460, 1427, 1372, 1323, 1308, 1254, 1228, 1169, 1112, 1075, 1031, 1009, 901, 841, 740, 703, 613 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ = 7.94 (2H, d, J = 8.8 Hz), 7.74−7.72 (4H, m), 7.45−7.40 (6H, m), 6.93 (2H, d, J = 8.8 Hz), 5.31 (1H, s), 5.10 (1H, q, J = 6.5 Hz), 4.21 (1H, d, J = 12.0 Hz), 3.94 (1H, s), 3.90 (1H, d, J = 12.0 Hz), 3.87 (3H, s), 3.71 (1H, s), 2.09 (3H, s), 1.34 (3H, d, J = 6.5 Hz), 1.08 (9H, s), 0.90 (9H, t, J = 7.9 Hz), 0.65−0.61 (6H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.7, 162.9, 162.2, 135.8, 135.7, 133.2, 133.1, 130.3, 129.6, 127.6, 120.3, 113.5, 84.3, 78.5, 78.1, 76.2, 67.7, 60.0, 59.9, 55.3, 26.8, 21.0, 19.3, 16.3, 6.7, 4.8; HRMS-ESI (m/z) calcd for $C_{40}H_{54}NO_7Si_2$ $[M + H]^+$ 716.34333, found 716.34461.

(1*R*,2*R*,3*R*,4*S*,5*R*,5′*S*)-1-((*tert*-Butyldiphenylsilyloxy)methyl)-2′-(4-methoxyphenyl)-5′-methyl-2-(tripropylsilyloxy)-5′*H*-6-oxaspiro[bicyclo[3.1.0]hexane-3,4′-oxazol]-4-ol (40). To a solution of disilyl ether (186 mg, 0.26 mmol) in toluene (5 mL) was added (dimethylamino)trimethyltin (0.21 mL, 1.3 mmol) dropwise at rt under argon atmosphere and stirred for 3 h. Toluene was removed under reduced pressure, and the residue was purified by flash column chromatography on silica gel using 30% EtOAc in hexanes ot afford the epoxy alcohol **40** (152 mg, 87%) as a colorless oil: $[\alpha]_D^{20}$ −10.2 (c 1.00, $CHCl_3$); IR (neat) ν_{max} 3256, 2956, 1630, 1513, 1462, 1427, 1328, 1307, 1256, 1173, 1112, 841, 741, 702 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.95 (2H, d, J = 8.9 Hz), 7.76−7.72 (4H, m), 7.45−7.38 (6H, m), 6.93 (2H, d, J = 8.9 Hz), 5.03 (1H, q, J = 6.5 Hz), 4.30 (1H, d, J = 11.8 Hz), 4.28 (1H, d, J = 11.7 Hz), 3.91 (1H, s), 3.87 (3H,

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s), 3.86 (1H, d, J = 11.8 Hz), 3.73 (1H, s), 1.89 (1H, d, J = 11.8 Hz), 1.52 (3H, d, J = 6.5 Hz), 1.09 (9H, s), 0.92 (9H, t, J = 7.9 Hz), 0.70−0.63 (6H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ 163.0, 162.2, 135.8, 135.7, 133.3, 133.0, 130.3, 129.7, 129.6, 127.6, 120.6, 113.5, 83.4, 78.7, 78.4, 74.6, 67.2, 61.0, 60.5, 55.4, 26.8, 19.3, 16.4, 6.8, 4.8; HRMS-ESI (m/z) calcd for $C_{38}H_{52}NO_6Si_2$ $[M + H]^+$ 674.33277, found 674.33367.

(1*S*,2*R*,3*R*,4*S*,5*S*)-4-Azido-1-((*tert*-butyldiphenylsilyloxy)-methyl)-3-((*S*)-1-hydroxyethyl)-3-(4-methoxybenzylamino)-2-methyl-5-(3-(prop-1-en-2-yl)phenylamino)cyclopentane-1,2-diol (48). To a stirred solution of oxazoline **47** (170 mg, 0.232 mmol) in dry AcOH (4 mL) was added $NaCNBH_3$ in portions (59 mg, 0.93 mmol) at rt under argon atmosphere. The reaction mixture was heated to 40 °C and stirred for 12 h. Then, the reaction mixture was quenched with saturated aqueous $NaHCO_3$ solution and extracted with EtOAc (50 mL × 3). The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4, and concentrated in vacuo. Purification by column chromatography on silica gel using 30% EtOAc in hexanes afforded *N*-PMB amino alcohol **48** (132 mg, 77%) as a colorless liquid: $[\alpha]_D^{20}$ +60.8 (c 1.00, $CHCl_3$); IR (neat) ν_{max} 3413 (br), 2932, 2858, 2106, 1602, 1581, 1513, 1471, 1428, 1373, 1327, 1250, 1175, 1113, 1071, 1035, 890, 822, 738, 702 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.64−6.58 (18H, aromatic protons), 5.30 (1H, s), 5.04 (1H, s), 5.01 (1H, s), 4.54 (1H, q, J = 6.7 Hz), 4.36 (1H, d, J = 10.1 Hz), 4.29 (1H, d, J = 6.5 Hz), 4.21 (1H, d, J = 10.1 Hz), 4.14 (1H, m), 4.04 (1H, d, J = 11.1 Hz), 3.98 (1H, d, J = 12.4 Hz), 3.81 (3H, s), 3.76 (1H, d, J = 11.1 Hz), 2.09 (3H, s), 1.62 (3H, s), 1.52 (3H, d, J = 6.7 Hz), 1.11 (9H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ 158.9, 146.8, 143.6, 142.5, 135.8, 135.6, 132.2, 131.1, 131.0, 130.3, 130.0, 129.3, 129.2, 128.0, 127.9, 115.4, 114.1, 112.2, 112.1, 111.0, 86.0, 80.4, 73.4, 69.7, 69.5, 66.0, 55.3, 47.5, 27.0, 21.9, 20.7, 19.5, 19.0; HRMS-ESI (m/z) calcd for $C_{42}H_{54}N_5O_5Si$ $[M + H]^+$ 736.38887, found 736.38914.

(4*S*,5*R*,6*R*,7*S*,8*S*,9*S*)-9-Azido-7-((*tert*-butyldiphenylsilyloxy)-methyl)-6,7-dihydroxy-1-(4-methoxybenzyl)-4,6-dimethyl-8-(3-(prop-1-en-2-yl)phenylamino)-3-oxa-1-azaspiro[4.4]nonan-2-one (49). To a stirred solution of *N*-PMB amino alcohol **48** (125 mg, 0.17 mmol) in dry THF (4 mL) were added activated charcoal (12 mg), Et_3N (0.17 mL, 1.19 mmol) and diphosgene (0.02 mL, 0.17 mmol) added slowly at 0 °C under argon atmosphere and stirred for 1 h. Then, the reaction was quenched by slow addition of a saturated aqueous $NaHCO_3$ solution and extracted with EtOAc (50 mL × 2). The combined organic layers were washed with brine, filtered, dried over anhydrous Na_2SO_4, and concentrated in vacuo. Flash column chromatography on silica gel using 25% EtOAc in hexanes eluted the cyclic carbamate **49** (108 mg, 83%) as a colorless liquid: $[\alpha]_D^{20}$ +5.8 (c 1.00, $CHCl_3$); IR (neat) ν_{max} 3366 (br), 2932, 2858, 2106, 1725, 1603, 1584, 1514, 1428, 1407, 1362, 1247, 1178, 1113, 1086, 1051, 908, 821, 782, 738, 702 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.54−6.39 (18H, aromatic protons), 5.33 (1H, s), 5.09 (1H, s), 4.87 (1H, d, J = 15.8 Hz), 4.78 (1H, d, J = 15.8 Hz), 4.77 (1H, d, J = 12.4 Hz), 4.76 (1H, q, J = 6.2 Hz), 4.15 (1H, d, J = 10.9 Hz), 3.97 (1H, d, J = 10.9 Hz), 3.74 (3H, s), 3.71 (1H, s), 3.40 (1H, br s), 2.86 (1H, s), 2.78 (1H, s), 2.12 (3H, s), 1.54 (3H, d, J = 6.2 Hz), 1.44 (3H, s), 1.07 (9H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.3, 158.4, 146.2, 143.4, 142.1, 135.3, 131.8, 131.4, 130.2, 129.8, 129.1, 128.9, 128.0, 127.9, 115.9, 113.6, 112.7, 112.0, 110.8, 84.4, 81.9, 75.4, 74.6, 66.7, 66.2, 65.9, 55.1, 46.7, 26.9, 21.8, 19.8, 19.1, 17.2; HRMS-ESI (m/z) calcd for $C_{43}H_{52}N_5O_6Si$ $[M + H]^+$ 762.36814, found 762.36649.

(4*S*,5*R*,6*R*,7*S*,8*S*,9*S*)-8-(3-Acetylphenylamino)-9-azido-7-((*tert*-butyldiphenylsilyloxy)methyl)-6,7-dihydroxy-1-(4-methoxybenzyl)-4,6-dimethyl-3-oxa-1-azaspiro[4.4]nonan-2-one (50). To a stirred solution of olefin **49** (103 mg, 0.135 mmol) in THF (2 mL), acetone (2 mL), and H_2O (0.4 mL) were added NMO (79 mg, 0.677 mmol) and OsO_4 (0.1 mL, 4 wt % in H_2O) at 0 °C and stirred for 2 h at rt. A saturated aqueous sodium bisulfite solution was added to the reaction mixture and stirred for 30 min. The reaction mixture was extracted with EtOAc (50 mL × 3), and the combined organic layers were washed with water and brine, dried over anhydrous Na_2SO_4, and concentrated in vacuo. Flash column chromatography on silica gel using 70% EtOAc in hexanes eluted the tetrol as clear oil, which was directly used for the next reaction without characterization. To the stirred solution of above tetrol in THF (1.5 mL) and H_2O (1.5 mL) was added $NaIO_4$ (43 mg, 0.2 mmol) at rt and stirred for 3 h. The reaction mixture was extracted with EtOAc (50 mL × 3), and the combined organic layers were washed with brine, dried over anhydrous Na_2SO_4, and concentrated in vacuo. Flash column chromatography on silica gel using 30% EtOAc in hexanes eluted the methyl ketone **50** (81 mg, 78% in 2 steps) as a colorless liquid: $[\alpha]_D^{20}$ +7.5 (c 1.00, $CHCl_3$); IR (neat) ν_{max} 3365 (br), 2933, 2106, 1727, 1715, 1673, 1604, 1514, 1247, 1179, 1084, 909, 821, 735, 703 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.54−7.14 (15H, aromatic protons), 6.80 (1H, d, J = 8.7 Hz), 6.65 (1H, m), 4.85 (1H, d, J = 23.1 Hz), 4.80 (1H, d, J = 23.1 Hz), 4.77 (1H, q, J = 6.4 Hz), 4.15 (1H, d, J = 10.8 Hz), 4.14 (1H, d, J = 11.0 Hz), 4.02 (1H, d, J = 10.8 Hz), 3.73 (3H, s), 3.70 (1H, s), 3.64 (1H, d, J = 11.0 Hz), 3.05 (1H, br s), 2.82 (1H, br s), 2.53 (3H, s), 1.54 (3H, d, J = 6.4 Hz), 1.44 (3H, s), 1.06 (9H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ 198.2, 159.2, 158.5, 146.4, 138.0, 135.4, 135.3, 131.6, 131.2, 130.4, 129.8, 129.3, 129.2, 128.1, 128.0, 118.7, 117.9, 113.6, 112.9, 84.5, 81.9, 75.3, 74.5, 66.8, 65.9, 65.7, 55.2, 46.7, 26.9, 26.7, 20.1, 19.1, 17.3; HRMS-ESI (m/z) calcd for $C_{42}H_{50}N_5O_7Si$ $[M + H]^+$ 764.3474, found 764.34611.

De-6-MSA-pactamycate (4). To a stirred solution of azide **51** (35 mg, 0.086 mmol) in THF/EtOH/H_2O (3:1:1, 2.5 mL) were added ammonium chloride (14 mg, 0.26 mmol) and zinc powder (8.5 mg, 0.13 mmol) at rt and stirred for 6 h. Then, the reaction mixture was quenched with aqueous ammonia (10 mL) and extracted with CH_2Cl_2 (50 mL × 2). The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4, and concentrated in vacuo. The residue was purified by flash column chromatography on silca gel using 8% MeOH in $CHCl_3$ to afford de-6-MSA-pactamycate **4** (28.5 mg, 87%) as a pale yellow solid: mp 93−95 °C; $[\alpha]_D^{20}$ −16.5 (c 1.00, MeOH); IR (neat) ν_{max} 3372 (br), 2939, 1732, 1674, 1602, 1385, 1359, 1335, 1267, 1063, 894, 777, 690 cm^{-1}; ^{1}H NMR (400 MHz, CD_3OD) δ 7.38 (1H, s), 7.21−7.18 (2H, m), 7.00 (1H, m), 4.82 (1H, q, J = 6.6 Hz), 3.91 (1H, d, J = 11.5 Hz), 3.53 (1H, d, J = 11.5 Hz), 3.52 (1H, d, J = 7.9 Hz), 3.49 (1H, d, J = 7.9 Hz), 2.54 (3H, s), 1.53 (3H, d, J = 6.6 Hz), 1.34 (3H, s); ^{13}C NMR (100 MHz, CD_3OD) δ 201.6, 161.1, 150.8, 139.1, 130.2, 119.2, 117.9, 113.2, 84.0, 83.0, 78.5, 72.6, 71.2, 63.8, 60.7, 26.9, 17.6, 17.2; HRMS-ESI (m/z) calcd for $C_{18}H_{26}N_3O_6$ $[M + H]^+$ 380.18161, found 380.18276.

(*S*)-1-((1*R*,2*R*,3*S*,4*S*,5*S*)-1-Amino-5-azido-3-((*tert*-butyldiphenylsilyloxy)methyl)-2,3-dihydroxy-2-methyl-4-(3-(prop-1-en-2-yl)phenylamino)cyclopentyl)ethyl dimethylcarbamate (59). To a solution of amino triol **55** (48 mg, 0.078 mmol) in CH_2Cl_2 (3 mL) were added Et_3N (0.065 mL. 0.47 mmol), *N*,*N*-dimethylcarbamoyl chloride (0.02 mL, 0.23 mmol), and DMAP (2 mg, 0.016 mmol) at rt under argon atmosphere and stirred for 12 h. The reaction was then quenched with aqueous saturated NH_4Cl solution and extracted twice with CH_2Cl_2. The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4, and concentrated in vacuo. The residue was purified by flash chromatography on silica gel using 40% EtOAc in hexanes afforded carbamate **59** (45 mg, 84%) as a clear oil: $[\alpha]_D^{20}$ +86.2 (c 1.00, $CHCl_3$); IR (neat) ν_{max} 3385 (br), 2931, 2857, 2105, 1687, 1601, 1580, 1488, 1396, 1330, 1268, 1195, 1112, 887, 822, 738, 703 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.63−6.56 (15H, aromatic protons and NH_2), 5.36 (1H, q, J = 6.5 Hz), 5.33 (1H, s), 5.04 (2H, s), 4.60 (1H, d, J = 11.2 Hz), 4.18 (1H, dd, J = 11.2, 3.6 Hz), 3.97 (1H, d, J = 10.9 Hz), 3.87 (1H, d, J = 10.9 Hz), 3.74 (1H, d, J = 11.2 Hz), 2.98 (3H, s), 2.96 (3H, s), 2.11 (3H, s), 1.29 (3H, d, J = 6.5 Hz), 1.26 (3H, s), 1.04 (9H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ 156.2, 146.4, 143.6, 142.5, 135.8, 135.6, 132.2, 132.0, 129.9, 129.7, 129.3, 127.8, 127.7, 115.3, 112.3, 112.1, 111.0, 83.8, 82.1, 74.2, 72.6, 69.4, 67.9, 64.4, 36.7, 35.9, 26.9, 21.9, 19.1, 17.9, 15.7; HRMS-ESI (m/z) calcd for $C_{37}H_{51}N_6O_5Si$ $[M + H]^+$ 687.36847, found 687.37043.

(1*S*,5*R*,6*S*,7*S*,8*R*)-6-Azido-1-((*tert*-butyldiphenylsilyloxy)-methyl)-8-hydroxy-5-((*S*)-1-hydroxyethyl)-8-methyl-7-(3-(prop-1-en-2-yl)phenylamino)-2-oxa-4-azabicyclo[3.2.1]octan-3-one (60). To a solution of cyclic carbamate **58** (47 mg, 0.06 mmol) in dry toluene (3 mL) was added (dimethylamino)trimethyltin (0.1 mL, 0.6 mmol) dropwise at rt under argon atmosphere, then the

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reaction mixture was heated to reflux and stirred for 3 h. Toluene was removed under reduced pressure, and the residue was purified by flash column chromatography on silica gel using 55% EtOAc in hexanes to afford diol **60** (33 mg, 86%) as a colorless oil: $[\alpha]_D^{20}$ +88.4 (*c* 1.00, $CHCl_3$); IR (neat) ν_{max} 3398 (br), 2931, 2857, 2107, 1699, 1602, 1582, 1390, 1326, 1263, 1113, 891, 822, 759, 702 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.61−6.74 (15H, aromatic protons and OH), 6.18 (1H, s), 5.30 (1H, s), 5.06 (1H, t, *J* = 1.5 Hz), 4.85 (1H, s), 4.47 (1H, d, *J* = 5.1 Hz), 4.31 (1H, d, *J* = 11.0 Hz), 4.20 (1H, m), 4.19 (1H, d, *J* = 11.2 Hz), 4.01 (1H, m), 3.83 (1H, d, *J* = 11.2 Hz), 2.10 (3H, s), 1.52 (3H, d, *J* = 6.6 Hz), 1.30 (3H, s), 1.09 (9H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ 150.7, 145.7, 143.3, 143.0, 135.8, 135.5, 130.6, 130.4, 130.2, 129.6, 128.2, 128.0, 116.3, 112.6, 111.8, 110.9, 85.0, 78.5, 74.5, 67.1, 66.8, 65.9, 64.0, 27.0, 21.9, 20.7, 18.9, 16.8; HRMS-ESI (*m*/*z*) calcd for $C_{35}H_{44}N_5O_5Si$ $[M + H]^+$ 642.31062, found 642.31084.

(*S*)-1-((1*R*,2*R*,3*S*,4*S*,5*S*)-1-Amino-5-azido-2-(benzyloxy)-3-(benzyloxymethyl)-3-(*tert*-butyldiphenylsilyloxy)-2-methyl-4-(3-(prop-1-en-2-yl)phenylamino)cyclopentyl)ethyl 4-methoxybenzoate (62). To a solution of amino diol **54** (330 mg, 0.44 mmol) in THF (10 mL) were added NaH (88 mg, 60% dispersion in mineral oil, 2.2 mmol), benzyl bromide (0.13 mL, 1.1 mmol), and TBAI (81 mg, 0.22 mmol) at 0 °C. The reaction mixture was stirred for 2 h at rt, then quenched with aqueous saturated NH_4Cl solution and extracted with EtOAc (100 mL × 2). The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4, and concentrated in vacuo. The residue was purified by flash chromatography on silica gel using 15% EtOAc in hexanes to afford the dibenzyl ether **62** (328 mg, 80%) as colorless viscous liquid: $[\alpha]_D^{20}$ +106.7 (*c* 1.00, $CHCl_3$); IR (neat) ν_{max} 3416 (br), 2934, 2858, 2098, 1707, 1604, 1580, 1511, 1318, 1276, 1257, 1168, 1103, 1029, 771, 738, 702 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.16−6.66 (28H, aromatic protons), 5.78 (1H, s), 5.68 (1H, q, *J* = 6.4 Hz), 5.43 (1H, dd, *J* = 8.0, 1.8 Hz), 5.17(1H, s), 5.00 (1H, t, *J* = 1.4 Hz), 4.16 (1H, d, *J* = 8.9 Hz), 4.11 (1H, d, *J* = 8.9 Hz), 3.97 (1H, q, *J* = 11.6 Hz), 3.91 (3H, s), 3.71 (1H, d, *J* = 12.3 Hz), 3.62 (1H, d, *J* = 1.8 Hz), 3.53 (1H, d, *J* = 9.9 Hz), 3.43 (1H, d, *J* = 9.9 Hz), 3.26 (1H, d, *J* = 12.3 Hz), 2.01 (3H, s), 1.92 (3H, s), 1.39 (3H, d, *J* = 6.4 Hz), 1.13 (9H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.2, 163.5, 145.7, 143.4, 141.9, 137.2, 136.8, 136.7, 135.7, 135.0, 134.1, 131.7, 129.7, 129.0, 128.9, 128.8, 128.7, 128.2, 128.0, 127.6, 127.3, 127.0, 122.9, 114.7, 113.8, 111.8, 111.3, 110.8, 91.9, 90.6, 76.9, 74.2, 71.9, 70.2, 67.7, 67.6, 66.6, 55.5, 27.6, 21.9, 20.0, 14.7, 13.5; HRMS-ESI (*m*/*z*) calcd for $C_{56}H_{64}N_5O_6Si$ $[M + H]^+$ 930.46204, found 930.45989.

(*S*)-1-((1*R*,2*R*,3*S*,4*S*,5*S*)-1-Amino-5-azido-2-(benzyloxy)-3-(benzyloxymethyl)-3-(*tert*-butyldiphenylsilyloxy)-2-methyl-4-(3-(prop-1-en-2-yl)phenylamino)cyclopentyl)ethanol (63). To a stirred solution of *p*-methoxy benzyl ester **62** (307 mg, 0.33 mmol) in dry CH_2Cl_2 (12 mL) was added DIBAL-H (1.65 mL, 1.0 M in toluene, 1.65 mmol) slowly at −78 °C under argon atmosphere and stirred for 1.5 h. The reaction mixture was then quenched with slow addition of MeOH and warmed to room temperature. A saturated aqueous potassium sodium tartrate solution was added to the reaction mixture and stirred for 1 h. The reaction mixture was extracted with CH_2Cl_2 (100 mL × 2), and the combined organic layers were washed with brine, dried over anhydrous Na_2SO_4, and concentrated in vacuo. The residue was purified by flash column chromatography on silica gel using 35% EtOAc in hexanes afforded amino alcohol **63** (242 mg, 92%) as colorless liquid: $[\alpha]_D^{20}$ +27.8 (*c* 1.00, $CHCl_3$); IR (neat) ν_{max} 3399 (br), 3029, 2933, 2858, 2097, 1600, 1580, 1492, 1453, 1427, 1328, 1258, 1109, 1027, 975, 784, 739, 702 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.92−6.65 (24H, aromatic protons), 5.93 (1H, t, *J* = 1.9 Hz), 5.42 (1H, dd, *J* = 8.0, 2.0 Hz), 5.19 (1H, s), 5.00 (1H, t, *J* = 1.5 Hz), 4.76 (1H, d, *J* = 9.7 Hz), 4.41 (1H, d, *J* = 9.7 Hz), 4.08 (1H, m), 4.05 (1H, d, *J* = 11.2 Hz), 3.98 (1H, d, *J* = 11.2 Hz), 3.61 (1H, d, *J* = 12.1 Hz), 3.55 (1H, d, *J* = 10.0 Hz), 3.47 (1H, d, *J* = 2.0 Hz), 3.46 (1H, d, *J* = 10.0 Hz), 2.02 (3H, s), 1.90 (3H, s), 1.12 (3H, d, *J* = 6.5 Hz), 1.09 (9H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ 145.8, 143.4, 141.9, 137.8, 137.3, 136.7, 135.6, 135.0, 134.0, 129.6, 129.1, 129.0, 128.4, 128.2, 128.0, 127.9, 127.6, 127.3, 127.0, 114.7, 111.8, 111.2, 111.0, 91.5, 90.7, 78.0, 71.9, 69.7, 69.4, 67.6, 67.3, 66.8, 27.6, 21.8, 20.0, 18.6, 13.7; HRMS-ESI (*m*/*z*) calcd for $C_{48}H_{58}N_5O_4Si$ $[M + H]^+$ 796.42526, found 796.42568.

(*S*)-1-((1*R*,2*R*,3*S*,4*S*,5*S*)-1-Amino-5-azido-2-(benzyloxy)-3-(benzyloxymethyl)-3-(*tert*-butyldiphenylsilyloxy)-2-methyl-4-(3-(prop-1-en-2-yl)phenylamino)cyclopentyl)ethyl dimethylcarbamate (64). To a solution of amino alcohol **63** (42 mg, 0.053 mmol) in dry THF (2 mL) were added NaH (8.5 mg, 60% dispersion in mineral oil, 0.21 mmol), *N*,*N*-dimethylcarbamoyl chloride (0.01 mL, 0.106 mmol), and TBAI (4 mg, 0.01 mmol) at rt under argon atmosphere and stirred for 6 h. The reaction was then quenched with aqueous saturated NH_4Cl solution and extracted twice with EtOAc. The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4, and concentrated in vacuo. The residue was purified by flash column chromatography on silica gel using 20% EtOAc in hexanes to afford carbamate **64** (37 mg, 81%) as pale yellow crystals: mp 153−155 °C; $[\alpha]_D^{20}$ +42.5 (*c* 1.00, $CHCl_3$); IR (neat) ν_{max} 3416 (br), 2933, 2099, 1698, 1600, 1493, 1393, 1270, 1187, 1109, 909, 736, 702 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.98−6.67 (24H, aromatic protons), 5.78 (1H, s), 5.42 (1H, d, *J* = 8.0 Hz), 5.38 (1H, q, *J* = 6.4 Hz), 5.16 (1H, s), 4.99 (1H, s), 4.36 (1H, d, *J* = 8.7 Hz), 4.22 (1H, d, *J* = 8.7 Hz), 3.98 (1H, d, *J* = 11.2 Hz), 3.90 (1H, d, *J* = 11.2 Hz), 3.71 (1H, d, *J* = 12.3 Hz), 3.56 (1H, s), 3.55 (1H, d, *J* = 9.9 Hz), 3.42 (1H, d, *J* = 9.9 Hz), 3.29 (1H, d, *J* = 12.3 Hz), 3.07 (3H, s), 3.00 (3H, s), 2.00 (3H, s), 1.90 (3H, s), 1.31 (3H, d, *J* = 6.4 Hz), 1.11 (9H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ 155.4, 145.7, 143.4, 141.8, 137.3, 137.0, 136.7, 136.5, 135.7, 135.1, 134.1, 129.6, 129.1, 129.0, 128.9, 128.7, 128.2, 128.1, 128.0, 127.6, 127.3, 127.0, 114.6, 111.8, 111.2, 110.9, 91.7, 90.5, 76.6, 74.5, 71.9, 70.0, 67.7, 67.5, 66.6, 36.6, 36.1, 27.6, 21.8, 20.0, 15.4, 13.2; HRMS-ESI (*m*/*z*) calcd for $C_{51}H_{63}N_6O_5Si$ $[M + H]^+$ 867.46237, found 867.4628.

(1*S*,2*S*,3*R*,4*R*,5*S*)-2-Azido-4-(benzyloxy)-3-((*S*)-1-(benzyloxy)-ethyl)-5-(benzyloxymethyl)-5-(*tert*-butyldiphenylsilyloxy)-4-methyl-N1-(3-(prop-1-en-2-yl)phenyl)cyclopentane-1,3-diamine (65). To a solution of amino alcohol **63** (186 mg, 0.234 mmol) in dry THF (5 mL) were added NaH (38 mg, 60% dispersion in mineral oil, 0.94 mmol), BnBr (0.04 mL, 0.35 mmol), and TBAI (9 mg, 0.02 mmol) at 0 °C under argon atmosphere and stirred for 3 h. The reaction was then quenched with aqueous saturated NH_4Cl solution and extracted twice with EtOAc. The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4, and concentrated in vacuo. The residue was purified by flash chromatography on silica gel using 10% EtOAc in hexanes to afford amino tribenzyl ether **65** (162 mg, 78%) as clear oil: $[\alpha]_D^{20}$ +67.5 (*c* 1.00, $CHCl_3$); IR (neat) ν_{max} 3417 (br), 3029, 2933, 2858, 2098, 1600, 1579, 1494, 1453, 1427, 1329, 1266, 1109, 976, 909, 820, 784, 736, 701 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.00−6.68 (29H, aromatic protons), 5.96 (1H, s), 5.53 (1H, dd, *J* = 8.0, 2.0 Hz), 5.22 (1H, s), 5.03 (1H, t, *J* = 1.4 Hz), 4.77 (1H, d, *J* = 11.4 Hz), 4.47 (1H, d, *J* = 9.9 Hz), 4.40 (1H, d, *J* = 11.4 Hz), 4.32 (1H, d, *J* = 9.9 Hz), 4.16 (1H, q, *J* = 6.3 Hz), 4.13 (1H, d, *J* = 11.7 Hz), 4.01 (1H, d, *J* = 11.7 Hz), 3.69 (1H, d, *J* = 12.2 Hz), 3.56 (1H, d, *J* = 2.1 Hz), 3.53 (1H, d, *J* = 9.9 Hz), 3.47 (1H, d, *J* = 9.9 Hz), 3.28 (1H, d, *J* = 12.2 Hz), 2.05 (3H, s), 1.96 (3H, s), 1.35 (3H, d, *J* = 6.3 Hz), 1.11 (9H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ 145.9, 143.4, 141.8, 138.6, 137.8, 137.3, 136.7, 135.6, 135.2, 134.8, 134.2, 129.5, 129.0, 128.9, 128.7, 128.4, 128.1, 127.9, 127.8, 127.7, 127.6, 127.5, 127.4, 127.2, 126.9, 114.5, 111.8, 111.1, 111.0, 92.5, 90.5, 78.4, 71.8, 70.9, 70.0, 67.7, 67.2, 66.3, 27.6, 21.9, 20.0, 13.8, 13.4; HRMS-ESI (*m*/*z*) calcd for $C_{55}H_{64}N_5O_4Si$ $[M + H]^+$ 886.47221, found 886.47332.

***N*-((1*S*,2*S*,3*R*,4*R*,5*S*)-5-Azido-3-(benzyloxy)-4-((*S*)-1-(benzyloxy)ethyl)-2-(benzyloxymethyl)-2-(*tert*-butyldiphenylsilyloxy)-4-isocyanato-3-methylcyclopentyl)-3-(prop-1-en-2-yl)aniline (66).** To a stirred solution of amine **65** (146 mg, 0.165 mmol) in dry THF (5 mL) were added activated charcoal (15 mg), Et_3N (0.07 mL, 0.49 mmol), and diphosgene (0.04 mL, 0.33 mmol) slowly at −46 °C under argon and stirred for 20 min. Then, the reaction was quenched with saturated aqueous $NaHCO_3$ solution and extracted with EtOAc (50 mL × 2). The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4, and concentrated in vacuo. Flash column chromatography on silica gel using 8% EtOAc in hexanes eluted the stable isocyanate **66** (125 mg, 83%) as a colorless

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liquid: $[\alpha]_D^{20}$ +49.5 (*c* 1.00, $CHCl_3$); IR (neat) ν_{max} 3417 (br), 3029, 2933, 2858, 2258, 2098, 1600, 1581, 1454, 1329, 1267, 1110, 909, 821, 737, 701 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.93−6.73 (29H, aromatic protons), 6.07 (1H, s), 5.65 (1H, dd, *J* = 8.0, 1.9 Hz), 5.20 (1H, s), 5.02 (1H, s), 4.82 (1H, d, *J* = 11.5 Hz), 4.44 (1H, d, *J* = 10.3 Hz), 4.39 (1H, d, *J* = 11.5 Hz), 4.37 (1H, d, *J* = 10.3 Hz), 4.28 (1H, q, *J* = 6.2 Hz), 4.10 (1H, dd, *J* = 11.7, 4.0 Hz), 3.83 (1H, d, *J* = 11.7 Hz), 3.70 (1H, d, *J* = 12.0 Hz), 3.52 (1H, d, *J* = 4.0 Hz), 3.50 (1H, d, *J* = 9.9 Hz), 3.44 (1H, d, *J* = 12.0 Hz), 3.33 (1H, d, *J* = 9.9 Hz), 2.04 (3H, s), 1.96 (3H, s), 1.41 (3H, d, *J* = 6.2 Hz), 1.14 (9H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ 145.7, 143.3, 142.0, 137.9, 137.6, 137.4, 136.8, 136.0, 135.3, 134.6, 129.4, 129.1, 129.0, 128.7, 128.5, 128.1, 128.0, 127.6, 127.5, 127.4, 127.3, 127.1, 127.0, 125.4, 115.1, 112.0, 111.3, 111.1, 93.0, 88.3, 77.7, 75.6, 73.6, 72.1, 69.6, 68.7, 67.5, 66.8, 27.2, 21.8, 19.9, 14.8, 13.9.

3-((1*R*,2*R*,3*S*,4*S*,5*S*)-5-Azido-2-(benzyloxy)-1-((*S*)-1-(benzyloxy)ethyl)-3-(benzyloxymethyl)-3-(*tert*-butyldiphenylsilyloxy)-2-methyl-4-(3-(prop-1-en-2-yl)phenylamino)-cyclopentyl)-1,1-dimethylurea (67). To an isocyanate **66** (96 mg, 0.105 mmol) was added neat 0.2 mL of dimethyl amine (upon condensing the gas at −46 °C), and the reaction mixture was left warming to room temperature. It was directly subjected to flash column chromatography using 20% EtOAc in hexanes to afford urea **67** (89 mg, 88%) as a colorless oil: $[\alpha]_D^{20}$ +8.6 (*c* 1.00, $CHCl_3$); IR (neat) ν_{max} 3400 (br), 3030, 2931, 2857, 2100, 1666, 1602, 1581, 1524, 1496, 1454, 1361, 1334, 1243, 1172, 1108, 1028, 909, 821, 780, 733, 701 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.68−6.41 (29H, aromatic protons), 5.58 (1H, s), 5.39 (1H, s), 5.08 (1H, s), 4.89 (1H, d, *J* = 11.8 Hz), 4.68 (1H, q, *J* = 6.1 Hz), 4.62 (1H, d, *J* = 11.8 Hz), 4.50 (1H, d, *J* = 11.0 Hz), 4.42 (1H, br s), 4.11−3.97 (4H, m), 3.87 (1H, d, *J* = 10.1 Hz), 3.64 (1H, d, *J* = 10.1 Hz), 2.90 (6H, s), 2.18 (3H, s), 1.91 (3H, s), 1.14 (3H, d, *J* = 6.1 Hz), 0.92 (9H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ 158.9, 147.2, 143.9, 141.5, 139.2, 139.0, 137.1, 136.2, 135.9, 135.3, 134.7, 129.2, 129.1, 128.6, 128.5, 128.3, 128.1, 128.0, 127.9, 127.2, 127.1, 127.0, 126.8, 126.7, 114.2, 111.7, 111.4, 110.7, 91.0, 86.1, 74.9, 72.9, 70.9, 70.4, 69.2, 67.2, 65.7, 62.3, 36.5, 27.5, 21.9, 19.9; HRMS-ESI (*m*/*z*) calcd for $C_{58}H_{69}N_6O_5Si$ $[M + H]^+$ 957.50932, found 957.5084.

3-((1*R*,2*R*,3*S*,4*S*,5*S*)-4-(3-Acetylphenylamino)-5-azido-2-(benzyloxy)-1-((*S*)-1-(benzyloxy)ethyl)-3-(benzyloxymethyl)-3-(*tert*-butyldiphenylsilyloxy)-2-methylcyclopentyl)-1,1-dimethylurea (methylketone of 67). To a stirred solution of olefin **67** (70 mg, 0.073 mmol) in THF (1 mL), acetone (1 mL), and H_2O (0.2 mL) were added NMO (60 mg, 0.51 mmol) and OsO_4 (0.05 mL, 4 wt % in H_2O) at 0 °C and stirred for 2 h at rt. A saturated aqueous sodium bisulfite solution was added to the reaction mixture and stirred for 30 min. The reaction mixture was extracted with EtOAc (30 mL × 3), and the combined organic layers were washed with water and brine, dried over anhydrous Na_2SO_4, and concentrated in vacuo. Flash column chromatography on silica gel using 70% EtOAc in hexanes eluted the diol as clear oil, which was directly used for the next reaction without characterization. To the stirred solution of the above diol in THF (1 mL) and H_2O (1 mL) was added $NaIO_4$ (24 mg, 0.11 mmol) at rt and stirred for 2 h. The reaction mixture was extracted with EtOAc (30 mL × 3), and the combined organic layers were washed with brine, dried over anhydrous Na_2SO_4, and concentrated in vacuo. Flash column chromatography on silica gel using 30% EtOAc in hexanes eluted the methyl ketone (55 mg, 78% in 2 steps) as a colorless liquid: $[\alpha]_D^{20}$ +23.2 (*c* 1.00, $CHCl_3$); IR (neat) ν_{max} 3434 (br), 2931, 2857, 2099, 1665, 1603, 1585, 1524, 1358, 1272, 1237, 1172, 1108, 910, 821, 733, 701, 607 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.62−7.08 (29H, aromatic protons), 6.62 (1H, br s), 6.38 (1H, s), 4.84 (1H, d, *J* = 8.0 Hz), 4.66 (1H, d, *J* = 12.1 Hz), 4.56 (1H, m), 4.45 (1H, d, *J* = 11.1 Hz), 4.19 (1H, m), 4.04−3.98 (2H, m), 3.92 (1H, d, *J* = 11.3 Hz), 3.86 (1H, d, *J* = 10.1 Hz), 3.59 (1H, d, *J* = 10.1 Hz), 2.94 (6H, s), 2.62 (3H, s), 1.89 (3H, s), 1.12 (3H, d, *J* = 6.4 Hz), 0.91 (9H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ 199.3, 158.6, 147.3, 139.3, 138.8, 137.6, 137.0, 136.1, 136.0, 135.1, 134.4, 129.3, 129.2, 128.8, 128.7, 128.4, 128.3, 128.1, 128.0, 127.2, 127.1, 126.9, 126.8, 126.5, 117.2, 116.7, 112.8, 90.9, 85.8, 73.0, 70.9, 68.9, 67.9, 65.7, 61.7, 36.6, 27.4, 26.8, 19.9.

3-((1*R*,2*R*,3*S*,4*S*,5*S*)-4-(3-Acetylphenylamino)-5-azido-2-(benzyloxy)-1-((*S*)-1-(benzyloxy)ethyl)-3-(benzyloxymethyl)-3-hydroxy-2-methylcyclopentyl)-1,1-dimethylurea (68). To a stirred solution of silyl ether (44 mg, 0.046 mmol) in dry DMF (2 mL) was added TASF (38 mg, 0.138 mmol) at 0 °C under argon and allowed to come to room temperature. After being stirred for 1 h at rt, the reaction mixture was cooled to 0 °C, quenched with a pH 7 phosphate buffer solution, and extracted with EtOAc (50 mL × 3). The combined organic layers were washed with water (30 mL × 3) and brine, dried over anhydrous Na_2SO_4, and concentrated in vacuo. The residue was purified by flash column chromatography on silica gel using 50% EtOAc in hexanes to afford the pure keto alcohol **68** (30 mg, 90%) as pale yellow crystals: mp 127−128 °C; $[\alpha]_D^{20}$ +53.1 (*c* 1.00, $CHCl_3$); IR (neat) ν_{max} 3385 (br), 2931, 2102, 1674, 1602, 1538, 1358, 1269, 1173, 1111, 910, 734, 697 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.37−7.15 (19H, aromatic protons), 6.92 (1H, d, *J* = 7.6 Hz), 6.32 (1H, s), 5.64 (1H, s), 4.81 (1H, q, *J* = 6.3 Hz), 4.68 (1H, d, *J* = 11.0 Hz), 4.66 (1H, d, *J* = 10.8 Hz), 4.59 (1H, d, *J* = 10.8 Hz), 4.52−4.49 (2H, m), 4.37 (1H, dd, *J* = 11.1, 4.3 Hz), 3.94 (1H, d, *J* = 10.0 Hz), 3.85 (1H, d, *J* = 7.1 Hz), 3.54 (1H, d, *J* = 10.0 Hz), 2.97 (6H, s), 2.56 (3H, s), 1.72 (3H, s), 1.40 (3H, d, *J* = 6.3 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 198.6, 158.4, 147.3, 138.5, 138.1, 138.0, 129.6, 128.6, 128.5, 128.2, 127.8, 127.7, 127.6, 127.5, 127.4, 118.0, 117.4, 113.0, 92.3, 82.4, 76.6, 74.0 72.4, 71.4, 71.2, 70.5, 68.5, 66.8, 36.7, 26.7, 14.9, 14.4; HRMS-ESI (*m*/*z*) calcd for $C_{41}H_{49}N_6O_6$ $[M + H]^+$ 721.37081, found 721.37077.

De-6-MSA-pactamycin (3). To a stirred solution of azide **71** (24 mg, 0.044 mmol) in EtOH/H_2O (3:1, 2 mL) were added NH_4Cl (7 mg, 0.133 mmol) and zinc powder (4.5 mg, 0.067 mmol) at rt and stirred for 6 h. Then, the reaction mixture was quenched with aqueous ammonia (10 mL) and extracted with CH_2Cl_2 (30 mL × 2). The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4, and concentrated in vacuo. The residue was purified by flash column chromatography on silca gel using 5% MeOH in $CHCl_3$ to afford de-6-MSA-pactamycin **3** (19.5 mg, 86%) as a pale yellow oil: $[\alpha]_D^{20}$ +32.5 (*c* 1.00, $CHCl_3$); IR (neat) ν_{max} 3383 (br), 2935, 1678, 1603, 1520, 1440, 1359, 1334, 1269, 1091, 1042, 912, 782, 732, 689 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.86 (1H, br s), 7.29−6.85 (5H, aromatic protons and NH_2), 5.56 (1H, br s), 5.48 (1H, d, *J* = 9.9 Hz), 4.13 (1H, d, *J* = 11.7 Hz), 3.93 (1H, m), 3.76 (1H, d, *J* = 9.9 Hz), 3.75 (1H, d, *J* = 11.7 Hz), 3.01 (6H, s), 2.97 (1H, s), 2.56 (3H, s), 1.47 (3H, s), 1.06 (3H, d, *J* = 6.4 Hz); ^1H NMR (400 MHz, $CDCl_3$+D_2O) δ = 7.29−6.85 (4H, aromatic protons), 4.14 (1H, d, *J* = 11.8 Hz), 3.92 (1H, q, *J* = 6.4 Hz), 3.75 (1H, s), 3.70 (1H, d, *J* = 11.8 Hz), 3.00 (6H, s), 2.93 (1H, s), 2.52 (3H, s), 1.45 (3H, s), 1.04 (3H, d, *J* = 6.4 Hz); ^1H NMR (400 MHz, CD_3OD) δ = 7.27−7.24 (3H, aromatic protons), 6.93 (1H, m), 4.07 (1H, q, *J* = 6.5 Hz), 3.94 (1H, d, *J* = 11.5 Hz), 3.74 (1H, d, *J* = 2.1 Hz), 3.68 (1H, d, *J* = 11.5 Hz), 3.01 (1H, d, *J* = 2.1 Hz), 2.98 (6H, s), 2.56 (3H, s), 1.42 (3H, s), 1.04 (3H, d, *J* = 6.5 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 198.8, 159.3, 146.9, 138.1, 129.5, 119.1, 118.4, 110.6, 88.5, 84.9, 73.9, 71.7, 68.1, 62.9, 61.7, 36.9, 26.6, 21.3, 18.2; ^{13}C NMR (100 MHz, CD_3OD) δ 201.7, 161.2, 149.4, 139.5, 130.7, 119.7, 118.5, 113.3, 89.6, 85.6, 74.4, 72.9, 69.4, 64.1, 62.3, 37.3, 27.1, 22.0, 18.9; HRMS-ESI (*m*/*z*) calcd for $C_{20}H_{33}N_4O_6$ $[M + H]^+$ 425.23946, found 425.23998.

■ ASSOCIATED CONTENT

Supporting Information

Copies of the ^1H and ^{13}C NMR spectra of new compounds (PDF) and CIF files for compounds **2**, **12**, **24** (*p*-bromobenzoate ester derivative), **29** (*p*-nitrobenzoate ester derivative), **33** (phenyloxazoline derivative), **38**, **45**, **46**, **47** (derivative), **58**, **64**, and **68**. This material is available free of charge via the Internet at http://pubs.acs.org.

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AUTHOR INFORMATION

Corresponding Author

*E-mail: stephen.hanessian@umontreal.ca.

Notes

The authors declare no competing financial interest.

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