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Stereocontrolled Synthesis of the Aminocyclopentitol Core of Jogyamycin *via* an Ichikawa Rearrangement Reaction

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Abstract

Jogyamycin is a member of the aminocyclopentitol class of natural products that exhibits significant antiprotozoal activities against diseases that include African sleeping sickness and malaria. Herein, we report a route to the core of this natural product *via* an underutilized Ichikawa rearrangement as a key step. This route efficiently forms the cyclopentane ring from simple and easily accessible starting materials, and rapidly installs the C1/C4/C5 polar functional groups. In addition, this strategy shows excellent potential for the preparation of analogues of jogyamycin to study how structural changes impact the selectivity in binding to the ribosome.

Graphical Abstract

Introduction

In 2012, Otogura, the mura group reported the structure of a new natural product that was isolated from a strain of *Streptomyces* bacteria.¹ This complex aminocyclopentitol was named jogyamycin (**1**, Figure 1) after the city of Jogjakarta in Indonesia, where the bacteria was first discovered. Jogyamycin displays significant activity against the protozoa responsible for malaria and African sleeping sickness, while pactamycin **2** and analogs **3–5** also show anticancer, antiviral and antimicrobial activities.^{1,2} X-ray crystal structures that show the co-crystallation of **2** with the ribosomal 30S subunit indicates that it behaves as a universal inhibitor of translocation in a region of the ribosome that is highly conserved

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Supporting Information

The supporting information contains NMR characterization data for all new and old compounds, reaction optimization conditions, unsuccessful substrates, and relevant references.

between bacterial and mammalian ribosomes, explaining the diverse bioactivities exhibited by these types of aminocyclopentitol natural products.³ Intriguingly, minor changes to the core of the aminocyclopentitol ring can significantly alter the activity as compared to the parent compound.^{2d-h} Continued explorations of structure-activity relationships in this class of compounds are directed towards attenuating cytotoxicity and providing a better understanding of how selectivity between binding to pathogen vs. human ribosomes may be achieved. In this communication, we report an enantioselective synthesis of the core of **1** using an Ichikawa rearrangement as a key step. While this strategy ultimately did not deliver **1**, the concise and efficient installation of polar functionality at C1/C4/C5 renders this approach convenient for targeting analogues.

In addition to their biological activities, aminocyclopentitols **1–5** are challenging synthetic targets,⁴ as each carbon of the cyclopentane core bears either a stereodefined amine or alcohol. C1-C3 in **1** is comprised of three contiguous carbons with distinct amine functional groups, while C4/C5/C1 displays three contiguous fully substituted carbons. The stereochemical relationships between these adjacent stereocenters pose their own challenges, including the *cis* C1 urea/C2 amine and the *trans* C4/C5 tertiary alcohols. Despite many elegant studies directed towards **2**, most approaches to pactamycin utilize the stereodefined C7 alcohol as an effective lynchpin early in the synthesis to set the remaining stereocenters through diastereoselective reactions. The lack of this C7 alcohol in **1** requires a different strategy to construct the core, but only two approaches towards **1** have been reported (Scheme 1).

Results and discussion

In 2016, our group reported an approach to the core of **1**, where the versatile intermediate **6** contains the required C1/C5 heteroatoms, a C2 alcohol, and a flexible C3/C4 alkene that can be employed for analogue synthesis (Scheme 1A). A key step in our group's strategy for the synthesis of **6** involved an oxidative amination of **9** to install polar functionality at the three carbons of the allene, which correspond to C1/C2/C5 of **1**. Other key steps involved a highly diastereoselective addition of an isopropenyl organometallic reagent to **12** to set the C5 stereochemistry in **13** and a ring-closing metathesis of **7** to furnish **6**.⁵ The only other route to the core of **1** was reported by Trost in 2018 (Scheme 1B).⁶ The C1 urea was proposed to form through a clever late-stage Hofmann rearrangement of **14**, while the key cyclopentane ring of **16** arises from a Pd-catalyzed [3+2] cycloaddition of **17** and **18**. In the forward sense, cyclization was achieved with catalytic [Pd(allyl)Cp] in the presence of a chiral Trost ligand; interestingly, the product (*ent*)-**16** was the opposite enantiomer required for **1**. Oxidation state manipulations of the C2/C3 groups to furnish the *trans* diamine was followed by protection to an oxalamide in (*ent*)-**15**. Installation of a C4 alkene and dihydroxylation delivered **19**. The key Hofmann rearrangement of **20** to **21** was successfully promoted using PhINTs, where the oxalamide prevents competing formation of a cyclic urea. Installation of the *N,N*-dimethylurea of **22** proceeded smoothly; unfortunately, the ketone of **22** proved resistant towards nucleophilic attack, likely due to steric hindrance posed by the flanking, fully substituted C1/C4 stereocenters. Despite this setback, the Trost

route rapidly accessed four of the stereocenters on the ring and successfully differentiated the C1-C3 amines.

The challenges inherent in dealing with intermolecular manipulations of polar functionalities in the highly congested cyclopentane ring of **1** at a late stage in the synthesis inspired us to consider a new strategy to set the key C1/C2 amines through the use of sequential Ichikawa⁷ and Overman rearrangements (Scheme 2). We were fully aware of the hurdles that might be encountered employing this approach, particularly in such a compact and densely functionalized environment. However, the benefits of successful implementation, including the use of easily accessible starting materials, potential for enantioselective synthesis, minimal oxidation state manipulations, the opportunity to showcase a lesser known [3,3]-sigmatropic rearrangement in a complex molecule, and the ability to rapidly obtain a variety of new analogues of **1**, outweighed the potential risks.

In the retrosynthetic analysis (Scheme 2), transformation of **23** to **1** relies on chemistry reported by Hanessian in his total synthesis of **2** to install the heteroatoms at C3/C4.^{4a} An Overman rearrangement of **24** was proposed to concomitantly install the C2 amine with the correct stereochemistry and position the C3/C4 alkene in **23**. The rationale for this particular disconnection was strengthened by the potential to form the C2 amine *via* an Ichikawa rearrangement, should the Overman fail. Installation of the C1 urea of **24** would proceed through an Ichikawa rearrangement of **25**. This variation on the more well-known Overman rearrangement is underutilized in the broader synthetic community, but proceeds at significantly lower temperatures and produces a useful isocyanate intermediate that offers product diversity, depending on the subsequent nucleophile selection. In addition, while both sequential Overman and Ichikawa rearrangements have been reported,⁸ to our knowledge, there are no examples of tandem Ichikawa/Overman rearrangements, a transformation that could prove to be a convenient and general solution for differentiating two adjacent nitrogen-bearing stereocenters. Finally, the *cis* C3/C4 diol in **25** would be formed in a series of steps from enone **26**, accessible in a few steps from 2-methyl-2-cyclopenten-1-one. In the forward route directed towards the preparation of the Ichikawa rearrangement precursor (Scheme 3), enone **27** was subjected to a known enantioselective cuprate addition using Cu(OTf)₂ and ligand **28**, as reported by Alexakis and co-workers, to give **30** in 80% *ee*.⁹ The easy accessibility of this ligand was the primary reason it was utilized in these studies; if we should use the tandem Ichikawa/Overman strategy for the syntheses of enantioenriched analogues of **1**, we plan to survey more specialized ligands reported by Alexakis that yield higher *ee*.⁹ The intermediate magnesium enolate was trapped as the silyl enol ether **29**; the crude material was then treated with DMDO in a Rubottom oxidation to give a mixture of diastereomers. While **30** was confirmed as the major diastereomer^{10,11} through a NOESY analysis of a later intermediate (see the Supplementary Information for further details), the *dr* was unfortunately low. Nonetheless, the ready accessibility, low cost, and easy separation of the diastereomers rendered this reaction sufficient to assess the viability of this approach to **1**. We did undertake initial attempts to utilize *m*-CPBA or MoOPH as alternative oxidants; however, these reagents resulted in predominant formation of the undesired diastereomer from reaction at the more hindered face of the silyl enol ether. Inoue observed similar stereochemistry in oxidations of silyl enol ethers derived from a cyclopentenones with *m*-

CPBA;¹⁰ calculations indicated torsional strain in the transition state is responsible for the unexpected selectivity.

The desired diastereomer of the α -hydroxy ketone **30** was then converted to the enone, first by protection of the tertiary alcohol as a BOM ether to furnish **31**, followed by formation of a silyl enol ether and subsequent oxidation with IBX and 4-methoxypyridine oxide to deliver **26**.¹² Any remaining starting material **31** could be easily separated from **26** and re-subjected to the reaction conditions to improve the overall yield of the transformation. The BOM group was essential to moving the material forward to the key Ichikawa rearrangement step, as the use of other standard protecting groups resulted in problems with deprotection later in the synthesis.

The next sequence of reactions was designed to install the C-4/C-6 bond in **32** through the addition of MeMgBr to **26**. The absence of CeCl₃-2LiCl¹³ resulted in a 3:1 mixture of 1,2- and 1,4-addition products, albeit in >20:1 *dr* for both of the C4 alcohols. In contrast, while the inclusion of an equimolar amount of CeCl₃-2LiCl also resulted in a high *dr* of the product, the regioselectivity was significantly improved to completely favor the desired 1,2-addition product **32**. Our previous experience with the isolation of sensitive cyclopentenols in other routes to **1**, where any adventitious acid gave decomposition of the product, led us to carry out the directed epoxidation immediately on the crude **32** to give the epoxide **33** in good isolated yield and a high *dr* of >20:1; none of the other diastereomer was observed by ¹H NMR. The extreme facial bias in the organometallic addition to **26** is noteworthy, in that it occurs adjacent to a quaternary carbon bearing two groups of similar size. The preference may be due to the C-1 Et group effectively blocking the approach of the organometallic along the Bürgi-Dunitz angle, although chelation between the adjacent ether and the carbonyl may also be operative. Similar diastereoselectivity for the 1,2-addition has been observed in other cyclopentenones.¹⁴

The preparation of the substrate for the key Ichikawa rearrangement required conversion of the epoxide of **33** to allylic alcohol **36**. The C4 alcohol was first protected with an orthogonal -CH₂OPMB group to give **34**, which was followed by a highly regioselective ring-opening with PhSeNa to afford **35**, likely due to less steric congestion at C2 compared to C3 in **34**.¹⁵ Finally, **35** was transformed to the allylic alcohol **36** by oxidation of the intermediate selenide with H₂O₂.

Treatment of the alcohol **36** with trichloroacetyl isocyanate (TAI) delivered the carbamate **25** in excellent yield (Scheme 4). The Ichikawa rearrangement was promoted with a combination of CBr₄/PPh₃/Et₃N;^{8,16} gratifyingly, **25** was smoothly converted to the isocyanate intermediate **37**, which was then trapped with Me₂NH to efficiently install the C1 urea in **38**. Removal of the PMBOCH₂ group with DDQ unmasked the 3° alcohol in **39**;¹⁷ use of a buffered solution was important for improving the yield of the deprotection. Overall, this sequence proceeds in a sequence from **27** that requires ten purifications by column chromatography, installs all three of the fully substituted stereocenters at C1/C4/C5, and offers opportunities for new analogues via manipulation of the C2/C3 alkene.

The next challenge involved implementing the Overmann rearrangement sequence to ideally convert **39** to **42** after hydrolysis of the resulting trichloroacetimidate (Scheme 5).¹⁸ Attempts to form the trichloroimidate of **39** in the presence of various bases unfortunately led to formation of the proposed oxazoline **40**. We hypothesize that the C4 tertiary alcohol does not compete effectively with the urea oxygen for attack on the trichloroacetonitrile, even when the reagent used in large excess; this results in activation of the urea towards nucleophilic attack by the C4 alcohol to furnish **40**, as determined by NMR of the reaction mixture. Attempts to limit the nucleophilicity of the urea by protecting the -NH via alkylation led only to extensive decomposition.

In light of these issues with the Overman rearrangement, we surmised that a second Ichikawa rearrangement of the C4 alcohol of **39** might provide an alternative solution to installing the C2 amine (Scheme 5, right). While the presence of the free -NH in the C1 urea would result in the formation of a second urea between C1 and C2, as shown in **43**, success would nonetheless illustrate the feasibility of the second rearrangement event. However, attempts to form the C4 carbamate from **39** resulted in the isolation of a trisubstituted alkene that did not contain an additional urea carbonyl. NMR spectroscopy of the crude isolated material supported the formation of **41**, indicating that the oxygen of the urea carbonyl is sufficiently nucleophilic to displace even a relatively poor carbamate leaving group at C4 via an S_N2' allylic substitution reaction.

Ultimately, these studies highlighted two major issues in the second rearrangement event, irrespective of whether an Overman or Ichikawa protocol was adopted. The first involved the potential for a C4 alkoxide to engage with the urea, while the second problem was the propensity of the urea oxygen to displace even poor leaving groups at C4. To circumvent these complications, the C4 heteroatom cannot be nucleophilic or easily displaced by the urea oxygen. A possible solution is to exchange the C4 alcohol for an azide, as this functional group is non-nucleophilic, will not react with the C1 isocyanate intermediate, and is already primed for the subsequent azide [3,3]-sigmatropic rearrangement.¹⁹ This potential work-around of a sequential Ichikawa/azide [3.3]-sigmatropic rearrangement is further supported by Hanessian's ability to form the C1 urea from an isocyanate in the presence of a C2 azide.^{4a} Exploration of this alternative route is currently underway in our group and will be reported in due course, should it successfully achieve the total synthesis of jogyamycin.

Conclusions

In conclusion, we have established a reliable and concise route to a densely functionalized cyclopentene motif **39** which maps onto the core of jogyamycin **1**. In addition, access to this late stage intermediate may enable facile syntheses of novel analogs of **1**. Early installation of the C1 stereocenter in an asymmetric manner enables the challenging C1, C4, and C5 quaternary stereocenters to be set in a diastereoselective manner. Successful implementation of an Ichikawa rearrangement was complicated by transannular reactions in the densely functionalized core; however, the insight gleaned in these investigations point towards a viable route to finally complete the total synthesis of **1**.

Experimental section

I. General information.

All glassware was either oven dried at 130 °C, or flame dried under vacuum and purged with nitrogen before use. All glassware was then allowed to cool in a desiccator filled with Drierite as a desiccant or under nitrogen after placing under vacuum. Unless otherwise specified, reagents were used as obtained from the vendor without further purification. Tetrahydrofuran was passed through an alumina column before use or freshly distilled from a Na/benzophenone ketyl. Diethyl ether was freshly distilled from a Na/benzophenone ketyl. Dichloromethane was freshly distilled from calcium hydride or passed through an alumina column before use. Acetonitrile, toluene and benzene were all freshly distilled from calcium hydride before use. Other solvents were purified using accepted procedures from the sixth edition of "Purification of Laboratory Chemicals".²⁰ Air- and moisture-sensitive reactions were performed using standard Schlenk Techniques under nitrogen atmosphere. Analytical thin layer chromatography (TLC) was performed using pre-coated silica gel 60 F₂₄ plates containing a fluorescent indicator. Either KMnO₄ or ceric ammonium molybdate (CAM stain) were used to visualize the reaction products. Preparative chromatography for most compounds, unless otherwise specified, was performed using SilicaFlash P60 silica gel (230–400 mesh) via Still's method.²¹ Unless stated otherwise, columns were typically run using a gradient method using EtOAc/hexanes.

¹H NMR and ¹³C NMR spectra were obtained using Bruker Avance III 400 and 500 spectrometers. For ¹H NMR, chemical shifts are reported relative to the tetramethylsilane peak (δ 0.00 ppm), except in some cases when there was no tetramethylsilane peaks in some samples of C₆D₆ where the chemical shifts are reported relative to the residual protiated solvent peak (7.16 ppm). ¹³C NMR spectra were measured at 125 MHz on the same instruments noted above for recording ¹H NMR spectra. Chemical shifts are reported relative to the solvent peaks (δ 77.16 ppm for CDCl₃ and 128.06 ppm for C₆D₆). Accurate mass measurements were acquired at the University of Wisconsin, Madison using a Micromass LCT (electrospray ionization or electron impact methods with electrospray ionization - quadrupole - ion trap (orbitrap)). The NMR and Mass Spectrometry facilities are funded by the NSF (CHE-1048642), the University of Wisconsin as well as a generous gift by Paul J. Bender.

II. Experimental procedures for the synthesis of all compounds.

(2R,3S)-3-ethyl-2-hydroxy-2-methylcyclopentan-1-one (30).—An oven-dried, 3-neck round bottom flask was equipped with a mechanical stirrer, an oven-dried addition funnel, and a septum.⁹ The flask was evacuated and refilled with dry nitrogen three times, then charged with **28** (599.3 mg, 1.17 mmol, 0.010 equiv) and Cu(OTf)₂ (329.3 mg, 0.910 mmol, 0.0078 equiv). The set-up was again evacuated and refilled with dry nitrogen. The addition funnel was charged with 2-methyl-2-cyclopenten-1-one **27** (11.4 mL, 116 mmol, 1.0 equiv) and Et₂O (110 mL), while the flask was charged with additional Et₂O (280 mL). The mixture was cooled to –30 °C with vigorous stirring using a Cryocool. After the temperature stabilized at –30 °C, ethylmagnesium bromide (48.0 mL, 3.0 M in Et₂O, 144 mmol, 1.24 equiv) was added to the mixture; a color change from a dark brown to yellow

and back to a dark brown was noted within the addition of the first few mL of the Grignard solution. After 25 min, a solution of the enone **27** in Et₂O was added dropwise over 1 h. After stirring for 4 h, distilled HMPA (42.0 mL, 241 mmol, 2.08 equiv) was added to the reaction and the mixture stirred for 25 min. The addition funnel was then charged with Et₃N (34.0 mL, 244 mmol, 2.10 equiv) and trimethylchlorosilane (29.5 mL, 232 mmol, 2.0 equiv, freshly distilled from CaH₂) and the mixture added dropwise to the reaction. The mixture was stirred for 2 h, 600 mL of pentanes added, and then the cold slurry poured into 150 mL of pentanes and 350 mL of water. The layers were separated, and the aqueous layer extracted with 400 mL of pentanes. The combined organics were washed with 200 mL of water, then 200 mL of brine. The organics were dried over Na₂SO₄ and the solvent was removed under reduced pressure. The crude material was stored in a -78 °C freezer overnight. A fritted funnel was loaded with 100 g of silica gel that had been thoroughly wetted with pentanes. The crude material was loaded onto the silica and rapidly filtered through the plug using 1.5 L of pentanes. The solvent was removed under reduced pressure to yield a slightly peach-colored liquid consisting of the silyl enol ether **29** (14.3 g, 72.1 mmol, 62% crude yield).

The second step of the sequence involves oxidation of the silyl enol ether **29** to the α -hydroxyketone **30**. Due to the dilute nature of solutions of DMDO, the oxidation reaction was split between two separate flasks that were later combined for a single purification. A stock solution of 3.86 g of NH₄F in 700 mL of MeOH was prepared and set aside. A round bottom flask equipped with a stir bar was cooled to -78 °C and charged with the DMDO solution (1.25 L, 0.046 M in acetone, 57.5 mmol, 1.3 equiv) and CH₂Cl₂ (88 mL). A portion of the silyl enol ether **29** (8.78 g, 44.2 mmol, 1.0 equiv) was added slowly once the internal temperature of the solution had reached -75 °C. After 1.5 h, the NH₄F solution (370 mL) was added and the flask was allowed to warm to room temperature over 11 h. A second round bottom flask equipped with a stir bar was cooled to -78 °C and charged with the remainder of the DMDO solution (625 mL, 0.059 M in acetone, 36.9 mmol, 1.3 equiv) and CH₂Cl₂ (56 mL). Again, once the internal temperature of the solution had reached -75 °C, the balance of the silyl enol ether **29** (5.53 g, 27.9 mmol, 1.0 equiv) was added. After 1.5 h, the NH₄F solution (230 mL) was added and the solution was allowed to warm to room temperature over 11 h. At this point, the two reaction solutions were combined and the solvent was carefully removed under reduced pressure. When ~100 mL of solution remained, the crude material was diluted with CH₂Cl₂ (600 mL) and water (400 mL). The layers were separated, and the aqueous layer was extracted two more times with CH₂Cl₂ before the combined organics were washed with brine. The organics were dried over Na₂SO₄ and the solvent carefully removed under reduced pressure. The crude material was dry loaded with Celite (30 g) and purified *via* column chromatography (330 g column, 0 to 100% Et₂O/hexanes). The major diastereomer **30** (5.03 g, 35.4 mmol, 30% yield) and the minor diastereomer (3.71 g, 26.1 mmol, 22% yield) were completely separable as yellow oils. The combined material (8.74 g, 61.4 mmol, 53% yield from the enone, 85% yield from the crude silyl enol ether) was obtained in a 1.36:1 *dr*. Major diastereomer **30**: ¹H NMR (500 MHz, CDCl₃) δ 2.50 (s, 1H), 2.44 (ddd, *J* = 19.5, 9.9, 1.6 Hz, 1H), 2.24 (dt, *J* = 19.6, 9.8 Hz, 1H), 2.17 – 2.10 (m, 1H), 1.86 (dddd, *J* = 12.1, 8.9, 7.0, 5.4 Hz, 1H), 1.70 (dq, *J* = 12.9, 7.5, 5.3 Hz, 1H), 1.42 – 1.30 (m, 2H), 1.08 (s, 3H), 1.02 (t, *J* = 7.4 Hz, 3H). ¹³C{¹H} NMR (126 MHz, CDCl₃) δ 221.3, 79.5, 48.0, 33.4, 23.3, 22.5, 18.0, 12.1. HRMS (ESI) *m/z*

calculated for $C_8H_{14}O_2$ $[M+NH_4]^+$ 160.1332, found 160.1332. Minor diastereomer (**SI-30**): 1H NMR (500 MHz, $CDCl_3$) δ 2.38 (ddd, $J = 19.3, 8.7, 4.7$ Hz, 1H), 2.25 (ddd, $J = 19.3, 9.3, 7.4$ Hz, 1H), 2.09 – 1.99 (m, 1H), 1.90 (d, $J = 1.7$ Hz, 1H), 1.82 – 1.75 (m, 1H), 1.75 – 1.65 (m, 2H), 1.27 (s, 3H), 1.26 – 1.18 (m, 1H), 0.98 (t, $J = 7.4$ Hz, 3H). $^{13}C\{^1H\}$ NMR (126 MHz, $CDCl_3$) δ 219.6, 77.7, 48.3, 33.7, 23.2, 22.8, 20.8, 12.2. HRMS (ESI-Q-IT) m/z : $[M+NH_4]^+$ Calcd for $C_8H_{14}O_2$ 160.1332; Found 160.1331. For confirmation of the stereochemistry of Compound **30**, please see the information on Compound **36**.

(2R,3S)-2-[(benzyloxy)methoxy]-3-ethyl-2-methylcyclopentan-1-one (31).—A flame-dried, round bottom flask equipped with a stir bar and a reflux condenser was charged with $i\text{-Pr}_2\text{NEt}$ (17.5 mL, 100 mmol, 5.0 equiv) and **30** (2.86 g, 20.1 mmol, 1.0 equiv) in CH_2Cl_2 (100 mL). Benzyl chloromethylether (8.25 mL, 59.8 mmol, 3.0 equiv) was added and the solution was refluxed. After confirming complete conversion by NMR after 6 h, the solution was cooled to room temperature and diluted with Et_2O and saturated NH_4Cl . The aqueous layer was extracted three times with portions of Et_2O . The combined organics were washed with water and brine, followed by drying over Na_2SO_4 . The solvent was removed under reduced pressure, the crude material dry loaded with Celite (20 g) and purified *via* column chromatography (330 g column, 0 to 60% Et_2O /hexanes). The acetal **31** (4.14 g, 15.8 mmol, 79% yield) was isolated as a slightly cloudy liquid. 1H NMR (500 MHz, $CDCl_3$) δ 7.36 – 7.30 (m, 4H), 7.30 – 7.26 (m, 1H), 5.00 (d, $J = 7.7$ Hz, 1H), 4.77 (d, $J = 7.7$ Hz, 1H), 4.62 (ABq, $\delta_{AB} = 0.02$, $J_{AB} = 11.8$ Hz, 2H), 2.38 – 2.13 (m, 4H), 1.67 (dq, $J = 14.8, 7.4, 4.1$ Hz, 1H), 1.39 – 1.21 (m, 2H), 1.16 (s, 3H), 0.98 (t, $J = 7.4$ Hz, 3H). $^{13}C\{^1H\}$ NMR (126 MHz, $CDCl_3$) δ 219.1, 138.0, 128.5, 128.1, 127.8, 90.4, 84.0, 70.2, 44.6, 35.0, 23.2, 22.2, 16.5, 12.1. HRMS (ESI-Q-IT) m/z : $[M+NH_4]^+$ Calcd for $C_{16}H_{22}O_3$ 280.1907; Found 280.1905.

(4S,5R)-5-[(benzyloxy)methoxy]-4-ethyl-5-methylcyclopent-2-en-1-one (26).—A flame-dried, round bottom flask equipped with stir bar was taken into the glovebox and charged with **31** (264.7 mg, 1.01 mmol, 1.0 equiv). The flask was capped with a septum, removed from the box and charged with THF (10 mL). The solution was cooled to $-45^\circ C$ and NaHMDS (1.30 mL, 1 M in THF, 1.30 mmol, 1.3 equiv) added in a dropwise fashion. After 30 min, chlorotrimethylsilane (0.20 mL, 1.6 mmol, 1.6 equiv, freshly distilled from CaH_2) was added and the reaction stirred for 1 h. The cold mixture was then poured into pentanes (25 mL) and saturated NH_4Cl (12 mL). The phases were quickly separated and the aqueous layer extracted two more times with pentanes (15 mL). The combined organics were washed with water, then saturated NH_4Cl , dried over Na_2SO_4 and the solvent removed under reduced pressure. The crude material was azeotroped with toluene (2.0 mL) under high vacuum to remove any silanol byproducts. A second flask equipped with a stir bar was charged with IBX (424.5 mg, 1.52 mmol, 1.5 equiv) and 4-methoxypyridine *N*-oxide hydrate (218.4 mg, 1.5 equiv). The flask was covered with aluminum foil and the light in the hood was extinguished prior to the addition of DMSO (3.75 mL). Once the IBX-MPO solution was homogenous, the silyl enol ether was diluted with DMSO (0.50 mL) and CH_2Cl_2 (0.20 mL). The IBX-MPO solution was then poured into the silyl enol ether solution and the flask covered with aluminum foil. After stirring for 18 h, the solution was diluted with Et_2O (25 mL), saturated $NaHCO_3$ (15 mL), and saturated $Na_2S_2O_3$ (15 mL). The layers

were separated and the aqueous layer further extracted three times with Et₂O. The combined organics were washed once with saturated NaHCO₃, twice with water, and one time with brine. The organics were then dried over Na₂SO₄ and the solvent removed under reduced pressure. The crude material was dry loaded with Celite and purified *via* column chromatography (40 g column, 0 to 50% Et₂O/hexanes). A portion of the ketone **31** (54.7 mg, 0.209 mmol, 21%) was recovered in addition to the desired enone product **26** (151.9 mg, 0.583 mmol, 58% yield, 73% based on recovered starting material). ¹H NMR (500 MHz, CDCl₃) δ 7.59 (dd, *J* = 6.2, 2.2 Hz, 1H), 7.38 – 7.25 (m, 5H), 6.18 (dd, *J* = 6.2, 2.3 Hz, 1H), 4.99 (d, *J* = 7.6 Hz, 1H), 4.79 (d, *J* = 7.6 Hz, 1H), 4.61 (ABq, δ_{AB} = 0.03, *J*_{AB} = 11.8 Hz, 2H), 3.08 (ddt, *J* = 10.1, 5.8, 2.3 Hz, 1H), 1.84 – 1.72 (m, 1H), 1.34 (dtd, *J* = 13.7, 7.2, 2.4 Hz, 1H), 1.29 (s, 3H), 1.08 (t, *J* = 7.4 Hz, 3H). ¹³C{¹H} NMR (126 MHz, CDCl₃) δ 209.2, 164.7, 137.9, 130.7, 128.5, 128.0, 127.8, 90.9, 82.9, 70.1, 51.4, 22.0, 19.3, 12.4. HRMS (ESI-Q-IT) *m/z*: [M+NH₄]⁺ Calcd for C₁₆H₂₀O₃ 278.1751; Found 278.1747.

(1R,2R,3R,4S,5R)-3-[(benzyloxy)methoxy]-4-ethyl-2,3-dimethyl-6-

oxabicyclo[3.1.0]hexan-2-ol (33).—A flame-dried, round bottom flask equipped with a stir bar was taken into the glovebox and charged with anhydrous CeCl₃ (2.91 g, 11.8 mmol, 1.53 equiv)¹³ and LiCl (1.02 g, 24.0 mmol, 3.10 equiv). The flask was sealed with a septum, removed from the glovebox and charged with THF (47 mL). The mixture was stirred at room temperature for 19 h, eventually turning into a homogenous, yellow, opaque solution. A flame-dried conical flask was taken into the glovebox and charged with **26** (2.01 g, 7.73 mmol, 1.0 equiv). The flask was sealed with a septum, removed from the box and charged with THF (3.0 mL). The solution was transferred *via* cannula to the CeCl₃-2LiCl solution using a rinse of THF (3.0 mL). After stirring for 1 h, the flask was cooled to –78 °C and stirred for an additional 50 min before dropwise addition of methylmagnesium bromide (7.0 mL, 3 M in Et₂O, 21 mmol, 2.7 equiv). A pH 7 buffer solution (10 mL, 0.1 M phosphate buffer) was added after 5 h and the reaction warmed to room temperature before pouring it into a mixture of Et₂O and pH 7 buffer. The aqueous layer was extracted three times with Et₂O. The combined organics were washed with brine, diluted with CH₂Cl₂, dried over Na₂SO₄, and the solvent was removed under reduced pressure. The crude alcohol **32** was diluted with CH₂Cl₂ (26 mL) and transferred to a flame-dried round bottom flask equipped with a stir bar. The flask was cooled to 0 °C and charged with *t*-BuOOH (1.60 mL, ~5.5 M in decane, 8.80 mmol, 1.14 equiv). A separate flask was charged with VO(acac)₂ (83.5 mg, 0.315 mmol, 0.041 equiv) and CH₂Cl₂ (77 mL). The VO(acac)₂ solution was added *via* cannula transfer to the allylic alcohol to give a red solution, which was gradually warmed to room temperature. After 4.5 h, another batch of VO(acac)₂ (82.5 mg, 0.311 mmol, 0.040 equiv) was added to restore the red color to the solution. After 2.5 h, more *t*-BuOOH (1.60 mL, ~5.5 M in decane, 8.80 mmol, 1.14 equiv) and VO(acac)₂ (85.3 mg, 0.322 mmol, 0.042 equiv) were added. After 1.5 h, an additional aliquot of *t*-BuOOH (1.60 mL, ~5.5 M in decane, 8.80 mmol, 1.14 equiv) and VO(acac)₂ (80.1 mg, 0.302 mmol, 0.039 equiv) was added, followed by more VO(acac)₂ (83.2 mg, 0.314 mmol, 0.041 equiv) after the mixture was stirred for another 1.5 h. The reaction mixture was quenched with saturated Na₂S₂O₃ and the aqueous layer was extracted three times with Et₂O. The combined organics were washed with water, then brine. CH₂Cl₂ was added to the combined organics, which were then dried over Na₂SO₄. The solvent was removed under reduced pressure and the crude

material dry loaded with Celite (13 g). The product was purified *via* column chromatography (120 g column, 0 to 70% EtOAc/hexanes) to yield the epoxy alcohol **33** (1.76 g, 6.03 mmol, 78% yield) as an oil. *Note: Attempts to circumvent the portionwise addition of VO(acac)₂ and t-BuOOH by adding an equivalent amount at the beginning of the epoxidation resulted in a stalled reaction that still required additional portions of catalyst and oxidant to be added periodically. We hypothesize this is due to the extremely hindered tertiary alcohol in 32, as the same batch of VO(acac)₂ and t-BuOOH did not display these issues with less hindered allylic alcohols.* ¹H NMR (500 MHz, CDCl₃) δ 7.37 – 7.27 (m, 5H), 4.93 (d, *J* = 6.9 Hz, 1H), 4.75 (d, *J* = 6.9 Hz, 1H), 4.66 (d, *J* = 11.8 Hz, 1H), 4.52 (d, *J* = 11.8 Hz, 1H), 3.44 (dd, *J* = 3.4, 1.4 Hz, 1H), 3.30 (d, *J* = 3.4 Hz, 1H), 2.22 (s, 1H), 1.93 (ddd, *J* = 10.4, 4.9, 1.4 Hz, 1H), 1.67 – 1.58 (m, 1H), 1.57 – 1.50 (m, 1H), 1.31 (s, 3H), 1.26 (s, 3H), 1.05 (t, *J* = 7.4 Hz, 3H). ¹³C{¹H} NMR (126 MHz, CDCl₃) δ 137.9, 128.6, 127.9, 127.9, 89.8, 84.4, 81.6, 69.7, 60.8, 55.2, 50.0, 21.1, 19.7, 17.7, 12.5. HRMS (ESI-Q-IT) *m/z*: [M+NH₄]⁺ Calcd for C₁₇H₂₄O₄ 310.2013; Found 310.2011.

(1R,2R,3R,4S,5R)-3-[(benzyloxy)methoxy]-4-ethyl-2-[(4-methoxyphenyl)methoxy]-2,3-dimethyl-6-oxabicyclo[3.1.0]hexane (34).—A round bottom flask equipped with a stir bar and a reflux condenser was charged with **33** (121.9 mg, 0.417 mmol, 1.0 equiv) and *i*-Pr₂NEt (0.36 mL, 2.1 mmol, 5.0 equiv). A separate round bottom flask equipped with a stir bar was charged with PMBOCH₂SMe (249.7 mg, 1.26 mmol, 3.0 equiv), the vessel subjected to three cycles of evacuation/nitrogen back-fills, and then charged with CH₂Cl₂ (3.10 mL). This flask was cooled to –78 °C for 10 min before the addition of SO₂Cl₂ (0.11 mL, 1.4 mmol, 3.4 equiv) dropwise over 2 min. The reaction mixture was stirred for 1 h, then the flask warmed to room temperature and the solvent removed under reduced pressure. Once the solvent had been removed, the crude PMBOCH₂Cl was subjected to three evacuation/nitrogen back-fill cycles, then diluted with CH₂Cl₂ (2.25 mL). The solution was transferred to the tertiary alcohol *via* cannula and followed by a CH₂Cl₂ rinse (2.0 mL). The reaction was refluxed for 51 h, then quenched with water. The aqueous layer was extracted three times with CH₂Cl₂, the combined organics dried over Na₂SO₄, and the solvent removed under reduced pressure. The crude material was dry loaded with Celite (1 g) and purified *via* column chromatography (40 g column, 0 to 15% Et₂O/toluene). The protected alcohol **34** (149.2 mg, 0.337 mmol, 81% yield) was isolated as a slightly impure sample. *Note: The reaction is lengthy and does take the full time allotted. The use of saturated NH₄Cl during the workup is not recommended, as this led to rapid ring-opening of the epoxide with chloride to give a byproduct that was challenging to separate.* ¹H NMR (500 MHz, CDCl₃) δ 7.37 – 7.26 (m, 7H), 6.90 – 6.86 (m, 2H), 5.04 (d, *J* = 7.2 Hz, 1H), 4.96 (ABq, δ_{AB} = 0.01, *J*_{AB} = 7.6 Hz, 2H), 4.76 – 4.70 (m, 2H), 4.68 (d, *J* = 11.2 Hz, 1H), 4.55 (d, *J* = 11.2 Hz, 1H), 4.49 (d, *J* = 11.8 Hz, 1H), 3.80 (s, 3H), 3.55 (d, *J* = 3.4 Hz, 1H), 3.42 (dd, *J* = 3.4, 1.4 Hz, 1H), 1.89 (ddd, *J* = 10.5, 4.7, 1.4 Hz, 1H), 1.75 – 1.64 (m, 1H), 1.64 – 1.56 (m, 1H), 1.37 (s, 3H), 1.28 (s, 3H), 1.07 (t, *J* = 7.4 Hz, 3H). ¹³C{¹H} NMR (126 MHz, CDCl₃) δ 159.4, 138.3, 130.1, 129.9, 128.5, 127.9, 127.7, 114.0, 90.2, 89.9, 86.2, 85.2, 69.6, 69.2, 58.4, 55.4, 54.9, 49.4, 19.6, 19.3, 18.6, 12.6. HRMS (ESI-Q-IT) *m/z*: [M+NH₄]⁺ Calcd for C₂₆H₃₈NO₆ 460.2694; Found 460.2691.

(1S,2R,3R,4R,5S)-3-[(benzyloxy)methoxy]-4-ethyl-2-[(4-methoxyphenyl)methoxy]-2,3-dimethyl-5-(phenylselenanyl)cyclopentan-1-ol (35).

—A flame-dried round bottom flask equipped with a stir bar was charged with Ph_2Se_2 (276.3 mg, 0.885 mmol, 5.75 equiv) and NaH (47.7 mg, 1.19 mmol, 7.73 equiv). Three cycles of evacuation/back-filling with argon were carried out before DMSO (1.80 mL) was added to the flask and the reaction heated to 50 °C. A separate flame-dried flask equipped with a stir bar was taken into the glovebox and charged with **34** (68.3 mg, 0.154 mmol, 1.0 equiv). The flask was sealed with a septum and evacuated/back-filled with argon. After 1 h, the solution of PhSeNa was cooled to room temperature and 1.0 mL added to the flask containing **34**. The resulting solution was heated to 100 °C for 17 h before the mixture was cooled to room temperature and quenched with brine. The aqueous layer was extracted three times with EtOAc, the combined organics washed one additional time with brine, and dried over Na_2SO_4 . The solvent was removed under reduced pressure and the crude material dry loaded with Celite (1 g). The crude material was purified *via* column chromatography (40 g column, 0 to 60% Et_2O /hexanes) to yield the selenoether **35** (53.5 mg, 0.0892 mmol, 58% yield) as an oil. ^1H NMR (500 MHz, CDCl_3) δ 7.64 – 7.59 (m, 2H), 7.37 – 7.26 (m, 5H), 7.24 – 7.17 (m, 5H), 6.88 – 6.84 (m, 2H), 4.93 (d, J = 7.3 Hz, 1H), 4.75 (d, J = 7.3 Hz, 1H), 4.64 (d, J = 7.6 Hz, 1H), 4.62 (d, J = 11.8 Hz, 1H), 4.53 (ABq, δ_{AB} = 0.04, J_{AB} = 11.8 Hz, 2H), 4.49 (d, J = 7.4 Hz, 1H), 4.46 (d, J = 11.4 Hz, 1H), 4.05 (dd, J = 8.3, 7.4 Hz, 1H), 3.80 (s, 3H), 3.62 (d, J = 8.4 Hz, 1H), 2.94 (t, J = 7.4 Hz, 1H), 1.88 (ddd, J = 8.9, 7.3, 5.9 Hz, 1H), 1.66 (ddd, J = 13.6, 7.5, 6.0 Hz, 1H), 1.54 (ddt, J = 13.5, 8.9, 7.4 Hz, 1H), 1.28 (s, 3H), 1.28 (s, 3H), 1.06 (t, J = 7.5 Hz, 3H). $^{13}\text{C}\{^1\text{H}\}$ NMR (126 MHz, CDCl_3) δ 159.6, 138.1, 135.5, 129.7, 129.5, 129.0, 128.5, 128.0, 127.7, 127.7, 114.1, 89.4, 89.0, 88.6, 87.1, 82.2, 70.3, 69.7, 55.4, 52.6, 52.0, 25.8, 14.9, 14.7, 13.6. HRMS (ESI-Q-IT) m/z : $[\text{M}+\text{H}]^+$ Calcd for $\text{C}_{32}\text{H}_{40}\text{O}_6\text{Se}$ 601.2063; Found 601.2059.

(1R,4R,5R)-4-[(benzyloxy)methoxy]-3-ethyl-5-[(4-methoxyphenyl)methoxy]-4,5-dimethyl-cyclopent-2-en-1-ol (36).

—A 20 dram vial containing **35** (53.5 mg, 0.0892 mmol, 1.0 equiv) was charged with THF (0.90 mL) and pyridine (0.015 mL, 0.19 mmol, 2.1 equiv). The mixture was stirred at room temperature before adding 30% H_2O_2 (0.028 mL, 0.27 mmol, 3.0 equiv). After 18 h, the reaction was diluted with EtOAc and quenched with a 1:1 mixture of saturated $\text{Na}_2\text{S}_2\text{O}_3$ and NaHCO_3 . The aqueous layer was extracted three times with EtOAc, the combined organics washed with brine, and dried over Na_2SO_4 . The material was purified *via* column chromatography (12 g column, 0 to 50% EtOAc/hexanes) to furnish the allylic alcohol **36** (30.7 mg, 0.0694 mmol, 78% yield) as an oil. ^1H NMR (500 MHz, CDCl_3) δ 7.37 – 7.32 (m, 4H), 7.31 – 7.24 (m, 3H), 6.88 (d, J = 8.6 Hz, 2H), 5.56 (q, J = 2.2 Hz, 1H), 5.02 (d, J = 7.0 Hz, 1H), 4.98 (d, J = 6.8 Hz, 1H), 4.85 (d, J = 6.9 Hz, 1H), 4.78 (d, J = 7.1 Hz, 1H), 4.73 (d, J = 11.8 Hz, 1H), 4.68 (d, J = 11.3 Hz, 1H), 4.55 (d, J = 11.7 Hz, 1H), 4.51 (d, J = 11.2 Hz, 1H), 4.28–4.24 (m, 1H), 3.80 (s, 3H), 2.23 – 2.13 (m, 1H), 2.13 – 2.04 (m, 1H), 1.56 (s, 3H), 1.27 (s, 3H), 1.10 (t, J = 7.3 Hz, 3H). $^{13}\text{C}\{^1\text{H}\}$ NMR (126 MHz, CDCl_3) δ 159.6, 154.9, 138.2, 129.8, 129.2, 128.5, 128.0, 127.7, 123.6, 114.1, 90.2, 90.1, 89.8, 88.4, 78.6, 70.0, 69.5, 55.4, 20.8, 20.0, 18.7, 11.4. HRMS (ESI-Q-IT) m/z : $[\text{M}+\text{NH}_4]^+$ Calcd for $\text{C}_{26}\text{H}_{34}\text{O}_6$ 460.2694; Found 460.2690.

The overall stereochemistry of **36** was confirmed using a NOESY analysis; see the Supplementary Information for details. This analysis also confirms the stereochemical assignment of **30**, even though the C1 stereocenter bearing the ethyl group has been ablated. This is due to two reasons: a) the vanadium-catalyzed, directed epoxidations of allylic alcohols in cyclopentenol scaffolds give exclusively *cis* epoxy alcohols, and b) the selenoxide elimination occurs through *syn* elimination. The proton adjacent to the selenoxide intermediate formed from **35** has too high of a pKa to be epimerized under the reaction conditions employed, meaning that the epoxide and the ethyl group are on the same face in **34**. Since the data above indicates that the allylic alcohol and the C5 methyl are on the same face, this supports our conclusion that the C5 methyl and the ethyl group were also positioned on the same face; thus, the stereochemistry indicated for **30** has been correctly assigned.

(1R,4R,5R)-4-[(benzyloxy)methoxy]-3-ethyl-5-[(4-methoxyphenyl)methoxy]-4,5-dimethyl-cyclopent-2-en-1-yl carbamate (25).—A 20 dram vial containing the allylic alcohol **36** (367.1 mg, 0.830 mmol, 1.0 equiv) and equipped with a stir bar was charged with CH₂Cl₂ (4.5 mL) and cooled to 0 °C. Trichloroacetyl isocyanate (0.12 mL, 0.996 mmol, 1.20 equiv) was added and the reaction stirred for 1 h. When complete consumption of **36** was indicated by TLC, the solvent was removed under reduced pressure. Once dry, the dram vial was charged with K₂CO₃ (69.0 mg, 0.499 mmol, 0.60 equiv) and MeOH (2.10 mL). The reaction was judged complete by TLC after stirring for 5 h at room temperature. The solvent was removed under reduced pressure and the crude mixture dissolved in Et₂O and water. The aqueous layer was extracted three times with Et₂O, the combined organics washed with brine, and dried over Na₂SO₄ before removing the solvent *in vacuo*. The crude material was dry loaded onto Celite before purifying *via* column chromatography (24 g column, 0 to 70% EtOAc/hexanes) to deliver the allylic carbamate **25** (361.4 mg, 0.744 mmol, 90% yield). ¹H NMR (500 MHz, CDCl₃) δ 7.38 – 7.27 (m, 5H), 7.25 (d, *J* = 8.5 Hz, 2H), 6.86 (d, *J* = 8.6 Hz, 2H), 5.54 (dd, *J* = 3.1, 1.8 Hz, 1H), 5.25 (dt, *J* = 2.7, 1.1 Hz, 1H), 5.10 (d, *J* = 7.1 Hz, 1H), 4.91 (d, *J* = 7.3 Hz, 1H), 4.81 (d, *J* = 7.1 Hz, 1H), 4.79 (d, *J* = 7.3 Hz, 1H), 4.76 (d, *J* = 11.8 Hz, 1H), 4.65 (d, *J* = 11.4 Hz, 1H), 4.55 (appt d, *J* = 11.7 Hz, 3H), 4.49 (d, *J* = 11.4 Hz, 1H), 3.79 (s, 3H), 2.27 – 2.16 (m, 1H), 2.16 – 2.06 (m, 1H), 1.54 (s, 3H), 1.39 (s, 3H), 1.10 (t, *J* = 7.3 Hz, 3H). ¹³C{¹H} NMR (126 MHz, CDCl₃) δ 159.3, 158.3, 156.5, 138.2, 130.2, 129.5, 128.6, 128.0, 127.8, 119.9, 114.0, 90.5, 90.3, 90.0, 86.0, 80.3, 69.6, 69.58, 55.4, 20.7, 20.2, 20.1, 11.3. HRMS (ESI-Q-IT) *m/z*: [M+NH₄]⁺ Calcd for C₂₇H₃₅NO₇ 503.2752; Found 503.2744.

1-[(1S,4R,5R)-5-[(benzyloxy)methoxy]-1-ethyl-4-[(4-methoxyphenyl)methoxy]-4,5-di-methylcyclopent-2-en-1-yl]-3,3-dimethylurea (38).—A flame-dried round bottom flask equipped with a stir bar was charged with PPh₃ (488.0 mg, 1.86 mmol, 2.50 equiv) and **25** (361.4 mg, 0.744 mmol, 1.0 equiv) in CH₂Cl₂ (10 mL). The flask was cooled to 0 °C before the addition of Et₃N (0.62 mL, 4.5 mmol, 5.8 equiv). After 15 min, CBr₄ (691.4 mg, 2.08 mmol, 2.80 equiv) in CH₂Cl₂ (5.0 mL) was added in a dropwise fashion. The reaction was warmed to room temperature after 1 h and stirred for an additional 30 min. An aliquot of Me₂NH (3.35 mL, 2 M in THF, 6.70 mmol, 9.0 equiv) was added to the flask, the reaction stirred for 18 h, then quenched with saturated NH₄Cl. The resulting aqueous

layer was extracted three times with Et₂O, the combined organics washed with brine, dried over Na₂SO₄ and the solvent removed under reduced pressure. The crude material was dry loaded with silica (2.5 g) and purified *via* column chromatography (40 g column, 0 to 100% EtOAc/hexanes) to give **38** (189.1 mg, 0.369 mmol, 50% yield). ¹H NMR (500 MHz, CDCl₃) δ 7.38 – 7.31 (m, 4H), 7.31 – 7.27 (m, 1H), 7.25 (d, *J* = 8.7 Hz, 2H), 6.87 (d, *J* = 8.7 Hz, 2H), 6.27 (d, *J* = 6.4 Hz, 1H), 5.93 (d, *J* = 6.4 Hz, 1H), 5.03 (d, *J* = 7.1 Hz, 1H), 4.98 (d, *J* = 7.2 Hz, 1H), 4.84 (d, *J* = 7.3 Hz, 1H), 4.77 (d, *J* = 7.3 Hz, 1H), 4.72 (d, *J* = 11.5 Hz, 1H), 4.63 (d, *J* = 11.6 Hz, 1H), 4.59 (d, *J* = 11.4 Hz, 1H), 4.48 (d, *J* = 11.4 Hz, 1H), 4.39 (s, 1H), 3.80 (s, 3H), 2.77 (s, 6H), 2.11 (dq, *J* = 14.8, 7.5 Hz, 1H), 1.71 (dq, *J* = 14.6, 7.3 Hz, 1H), 1.42 (s, 3H), 1.40 (s, 3H), 0.93 (t, *J* = 7.4 Hz, 3H). ¹³C{¹H} NMR (126 MHz, CDCl₃) δ 159.3, 158.0, 138.2, 137.4, 131.6, 130.3, 129.6, 128.6, 128.1, 127.9, 113.9, 92.8, 90.7, 90.1, 90.09, 71.9, 70.3, 68.9, 55.4, 36.4, 28.7, 23.1, 16.1, 9.3. HRMS (ESI-Q-IT) *m/z*: [M+Na]⁺ Calcd C₂₉H₄₀N₂O₆ 535.2779; Found 535.2779.

1-[(1S,4R,5R)-5-[(benzyloxy)methoxy]-1-ethyl-4-hydroxy-4,5-

dimethylcyclopent-2-en-1-yl]-3,3-dimethylurea (39).—A round bottom flask equipped with a stir bar was charged with **38** (20.0 mg, 0.0390 mmol, 1.0 equiv), CH₂Cl₂ (0.56 mL), *t*-BuOH (0.06 mL) and a pH 7 buffer (0.06 mL, 0.2 M sodium phosphate buffer). DDQ (14.0 mg, 0.0617 mmol, 1.6 equiv) was added with vigorous stirring. An NMR aliquot after 3 h showed complete conversion of the starting material. The reaction was diluted with Et₂O and filtered through Celite. The filtrate was washed with 5 mL of saturated NaHCO₃ and 10 mL of brine. The aqueous layer was extracted three times with Et₂O, the combined organics dried over Na₂SO₄ and the solvent removed under reduced pressure. The crude material was purified *via* column chromatography (0 to 40% EtOAc/hexanes in 20% increments, then 40 to 100% EtOAc/hexanes in 10% increments) to furnish **39** (9.0 mg, 0.025 mmol, 64% yield) as a thin film. ¹H NMR (500 MHz, CDCl₃) δ 7.37 – 7.27 (m, 5H), 5.90 (d, *J* = 6.1 Hz, 1H), 5.80 (d, *J* = 6.1 Hz, 1H), 4.99 (d, *J* = 7.4 Hz, 1H), 4.89 (d, *J* = 7.3 Hz, 1H), 4.69 – 4.58 (m, 3H), 4.34 (s, 1H), 2.85 (s, 6H), 1.87 – 1.75 (m, 2H), 1.38 (s, 3H), 1.34 (s, 3H), 1.01 (t, *J* = 7.5 Hz, 3H). ¹³C{¹H} NMR (126 MHz, CDCl₃) δ 158.1, 138.1, 137.1, 133.0, 128.6, 127.9, 127.8, 91.5, 90.8, 84.6, 77.2, 72.7, 70.4, 36.4, 29.3, 22.6, 14.5, 9.3. HRMS (ESI-Q-IT) *m/z*: [M+H]⁺ Calcd for C₂₀H₃₀N₂O₄ 363.2278; Found 363.2274.

(3aS,4S,6aS)-4-[(benzyloxy)methoxy]-3a-ethyl-N,N,4,5-tetramethyl-3aH,4H,6aH-cyclo-penta[d][1,3]oxazol-2-amine (41).—A 20 dram vial containing **39** (23.5 mg, 0.065 mmol, 1.0 equiv) and equipped with a stir bar was charged with CH₂Cl₂ (0.32 mL) and cooled to 0 °C. Trichloroacetyl isocyanate (9.3 μL, 0.078 mmol, 1.20 equiv) was added and the reaction stirred for 2.5 h. When complete consumption of **39** was indicated by TLC, the solvent was removed under nitrogen. Once dry, the dram vial was charged with K₂CO₃ (5.4 mg, 0.039 mmol, 0.60 equiv) and MeOH (0.16 mL). The reaction was judged complete by TLC after stirring for 5 h at room temperature. The solvent was removed under reduced pressure and the crude mixture dissolved in Et₂O and water. The aqueous layer was extracted three times with Et₂O, the combined organics washed with brine, and dried over Na₂SO₄ before removing the solvent *in vacuo*. The crude material was analyzed by ¹H NMR (500 MHz, CDCl₃) δ 7.32 – 7.27 (m, 5H), 5.60 (app pent, *J* = 1.6 Hz, 1H), 5.12 (d, *J* = 2.5 Hz, 1H), 4.69 (d, *J* = 7.4 Hz, 1H), 4.61 (d, *J* = 11.8 Hz, 1H), 4.53 (d, *J* = 7.4 Hz, 1H), 4.52

(d, $J=11.8$ Hz, 1H), 2.9 (s, 6H), 1.76 (t, $J=1.6$ Hz, 3H), 1.62 (qd, ABX₃ $J=7.3$, 1.8 Hz, 2H), 1.41 (s, 3H), 0.85 (t, $J=7.4$ Hz, 3H). ¹³C{¹H} NMR (126 MHz, CDCl₃) δ 166.2, 161.1, 149.7, 139.3, 129.4, 128.9, 128.1, 93.3, 91.0, 90.2, 83.3, 70.5, 37.8, 26.6, 20.8, 13.5, 8.7.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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MSA = 6-methyl salicylate

anti-				
R ¹	R ²		antibacterial		malarial	<i>T.b.b.</i>	cytotoxicity
			<i>Staphylococcus</i>		<i>P. f. K1</i> ^a	<i>GUTat 3.1</i> ^b	<i>MRC-5</i>
Et	H	<i>Jogyamycin</i>	1	---	1.5 nM	12.3 nM	4 nM
Me	MSA	<i>Pactamycin</i>	2	10 μM	14.2 nM	7.4 nM	7 nM
Et	MSA	<i>7-Deoxypactamycin</i> (<i>Cranomycin</i>)	3	50 μM	0.4 nM	0.9 nM	74 nM
Me	H	<i>TM-025</i>	4	> 1 mM	25-30 nM	---	>1000 nM
Me	MSA	<i>TM-026</i>	5	> 1 mM	---	---	---

^a *Plasmodium falciparum* K1 (resistant). ^b *Trypanosoma brucei brucei*.

Figure 1.
Bioactive aminocyclopentitol natural products.

Scheme 1.
Two previous approaches to jogyamycin **1**.

Scheme 2.

Retrosynthesis of **1** via an Ichikawa/Overman rearrangement strategy.

Scheme 3.
Preparation of Ichikawa rearrangement precursor.

Scheme 4.
Successful Ichikawa rearrangement.

Scheme 5.
Attempted Overman and Ichikawa rearrangements.