OL Organic Letters

pubs.acs.org/OrgLett Letter

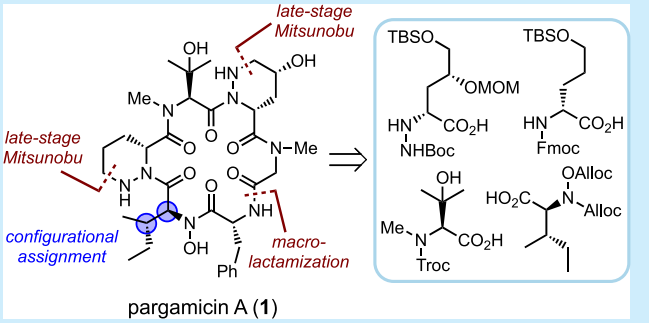
Total Synthesis of Pargamicin A

Yassin M. Elbatrawi, Taylor Gerrein, Avraz Anwar, Kamlesh M. Makwana, David Degen, Richard H. Ebright, and Juan R. Del Valle*

Cite This: *Org. Lett.* 2022, 24, 9285–9289 Read Online

ACCESS | Metrics & More | Article Recommendations | Supporting Information

ABSTRACT: We report the total synthesis and configurational assignment of pargamicin A, a highly oxidized nonribosomal peptide that potently inhibits the growth of drug-resistant bacteria. Our synthetic approach relies on late-stage piperazine ring formation and careful selection of condensation reagents to assemble the densely substituted hexapeptide backbone. This work enables the synthesis of pargamicin congeners for the development of structure–activity relationships and informs strategies for accessing other sterically congested piperazic acid-containing natural products.



Antimicrobially resistant infections are associated with approximately 3500 deaths per day, outpacing malaria and HIV/AIDS as a leading cause of mortality worldwide.[1] Methicillin-resistant *Staphylococcus aureus* (MRSA) and vancomycin-resistant *Enterococci* (VRE) are both designated as high-priority threats by the World Health Organization and now contribute to approximately 400 000 hospitalizations annually in the United States.[2] Given their prevalence in hospital settings, significant co-colonization of MRSA and VRE is frequently encountered in critically ill patients.[3] Only a handful of drugs are currently approved to treat both pathogens, with strains resistant to these therapeutics already emerging in the clinic.[4]

Naturally occurring nonribosomal peptides (NRPs) represent a privileged class of antimicrobial lead compounds for drug development.[5] Novel NRPs with promising antibiotic activity are regularly isolated and characterized, but challenges associated with their chemical synthesis continue to hinder detailed biological and structure–activity relationship (SAR) studies. This is particularly true in the case of NRPs harboring dense backbone substitution patterns, where sterically demanding condensation reactions, proclivity toward Cα epimerization, and amide bond lability complicate traditional peptide assembly approaches. Pargamicin A [PrgA (**1**)] is a nonribosomal cyclic hexapeptide isolated in 2002 from the fermentation broth of *Amycolatopsis* sp. (Figure 1).[6] Although initially identified as a weak inhibitor of poly-ADP ribose glycohydrolase, PrgA was later found to exhibit submicromolar growth inhibitory activity against several MRSA and VRE bacterial strains.[7] PrgA belongs to a family of more than 200 NRPs harboring one or more piperazic acid (Piz) residues.[8] In addition to D-Piz, PrgA features γ-hydroxy-D-piperazic acid (γ-OH-D-Piz) and *N*-hydroxyisoleucine [(*N*-OH)-Ile] residues,

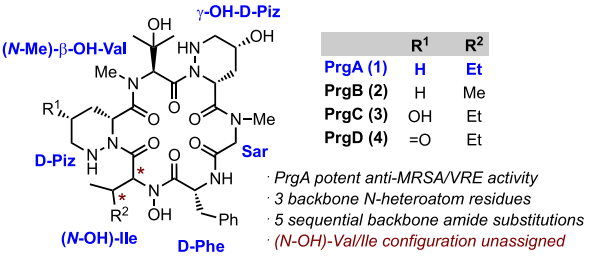
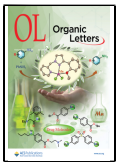


Figure 1. Structures of pargamicins A–D [PrgA–D, respectively (**1**–**4**)]. Residue abbreviations for PrgA provided in blue.

resulting in a peptide macrocycle with five sequential backbone amide substitutions. The stereochemistry of the (*N*-OH)-Ile residue remains unassigned. Preliminary mechanism-of-action studies showed that PrgA induces bacterial cell membrane depolarization and loss of function in a manner distinct to that of daptomycin.[9] In 2017, Hashizume and co-workers identified additional family members [PrgB–D (**2**–**4**, respectively)] from the same culture broth.[10] Although PrgC retains much of the antimicrobial activity of the parent compound, subtle changes to the (*N*-OH)-Ile and γ-OH-D-Piz residues in PrgB and PrgD result in diminished potency.

Despite their promising anti-MRSA/VRE activity, there remains no reported chemical synthesis of a member of the pargamicin family.[11] Our goal was to develop an approach

Received: November 12, 2022
Published: December 14, 2022



https://doi.org/10.1021/acs.orglett.2c03861
Org. Lett. 2022, 24, 9285–9289

amenable to SAR studies through residue substitution. Candidate sites for macrolactamization in PrgA are limited due to the presence of a single secondary amide linkage between the D-Phe and Sar residues. Moreover, difficulties associated with incorporating preformed Nε-protected Piz residues into such sequences are well-documented and are attributed to steric bulk and strong electronic deactivation from the N^{α}-(acyloxy)amino group.[8a,12] We expected that a more efficient assembly of the peptide chain could be achieved using protected linear precursors to the D-Piz and γ-OH-D-Piz residues and formation of the diazinane rings at a late stage of the synthesis (Figure 2). At the outset of our campaign, we also

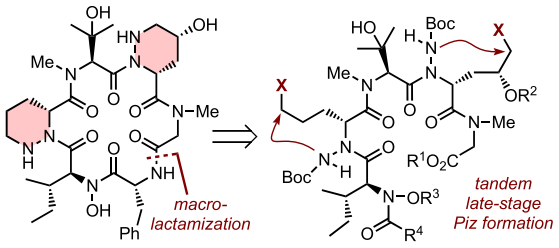
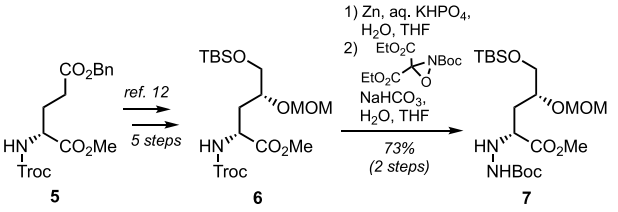


Figure 2. Late-stage Piz formation approach to PrgA (**1**).

hypothesized the configuration of the unassigned (*N*-OH)-Ile residue to be 2*S*,3*S* based on the alternating L/D pattern found in related macrocyclic nonribosomal hexapeptide natural products.[8b]

We recently reported the synthesis of a linear precursor to γ-OH-D-Piz that can be incorporated into a growing peptide chain.[13] This approach relies on diastereoselective Cγ electrophilic hydroxylation of a D-Glu derivative. We employed this protocol to prepare intermediate **6** in five steps from Troc-D-Glu(Bn)-OMe (Scheme 1). Removal of the Troc group in **6**

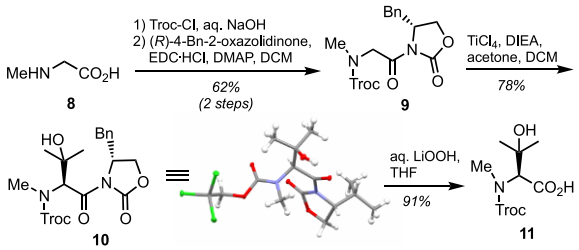
Scheme 1. Synthesis of γ-OH-D-Piz Precursor 7



was followed by electrophilic amination with 2-*tert*-butyl-3,3-diethyl oxaziridine-2,3,3-tricarboxylate (TBDOT)[14] to provide building block **7** in 73% yield over two steps.

The (*N*-Me)-β-OH-Val residue in PrgA is encountered in other biologically active NRPs such as the luzopeptins, quinoxapeptins, and the fungicidal aureobasidin A. Two previous enantioselective syntheses of protected derivatives of (*N*-Me)-β-OH-Val have been achieved in six and eight steps.[15] We developed a four-step chiral auxiliary approach that relies on aldol reaction between a protected sarcosine (Sar) derivative and acetone. Thus, Troc protection of **8** followed by EDC/DMAP-mediated condensation with Evans' (*R*)-4-benzyl-2-oxazolidinone auxiliary provided **9** in 62% yield over two steps (Scheme 2). Reaction of the titanium enolate of **9** with acetone afforded the desired aldol product **10** as a single diastereomer, whose configuration was confirmed by X-ray crystallography.[16] Removal of the auxiliary with LiOOH then provided **11** in 91% yield.

Scheme 2. Synthesis of 11



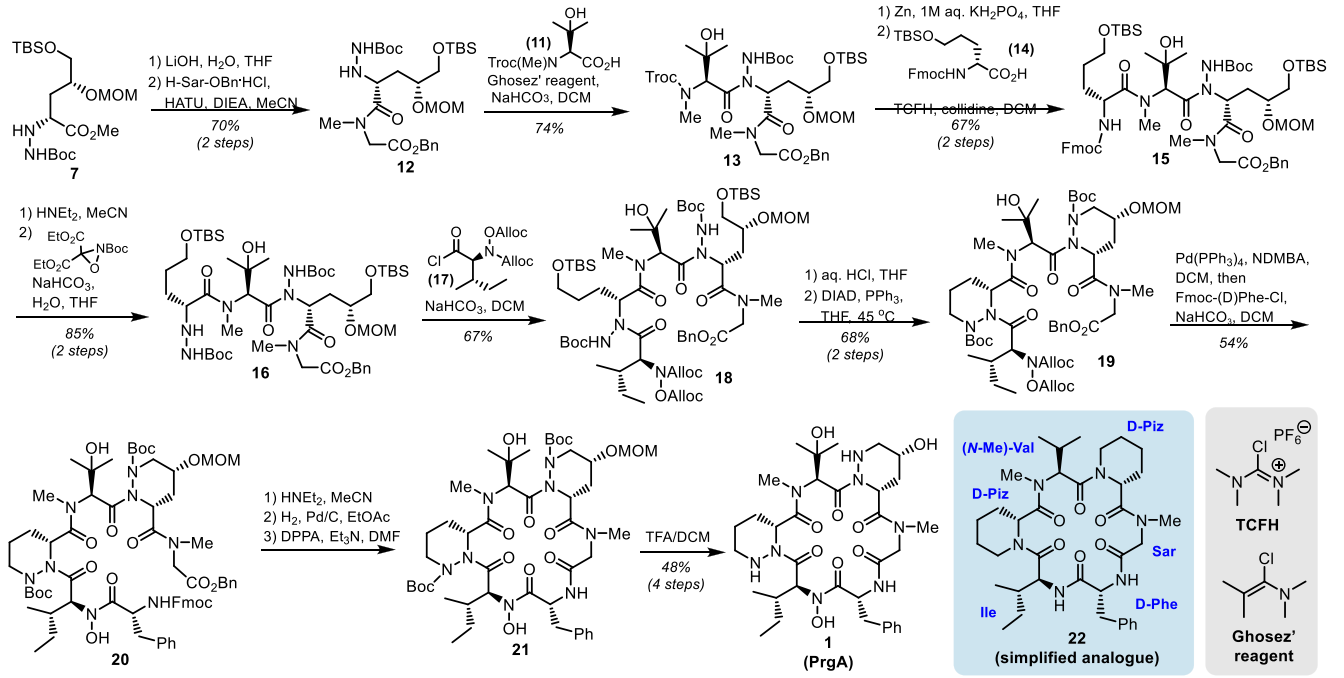
With building blocks **7** and **11** in hand, we proceeded with assembly of the linear hexapeptide precursor to PrgA. Methyl ester hydrolysis of **7** followed by HATU-mediated condensation with H-Sar-OBn afforded dipeptide **12** in 70% yield over two steps (Scheme 3). Activation of **11** with Ghosez's reagent and condensation with **12** in the presence of sodium bicarbonate afforded **13** in 74% yield without detectable epimerization. Troc deprotection with activated Zn was followed by condensation with Fmoc-protected hydroxynorvaline derivative **14**[17] in the presence of chloro-*N*,*N*,*N*′,*N*′-tetramethylformamidinium hexafluorophosphate (TCFH) and 2,4,6-collidine to afford tetrapeptide **15** in 67% yield over two steps. Activation with TCFH was critical to the success of this sterically demanding condensation. Other coupling reagent/base combinations such as HATU/DIPEA, Ghosez's reagent/$NaHCO_3$, PyBrOP/DIPEA, BEP/NMI, or *i*-BuOCOCl/NMM failed to afford **15** in any appreciable amount. Removal of the Fmoc group was followed directly by treatment with TBDOT to provide di-N-aminated tetrapeptide **16** in 85% yield over two steps. Condensation of Alloc-(*N*-OAlloc)-Ile-Cl (**17**)[17] with the hydrazide group in **16** provided **18** in 67% yield. The stability of acid chloride **17** is noteworthy given the proclivity of *N*-Alloc-protected α-amino acid chlorides to undergo *N*-carboxyanhydride (NCA) formation. Indeed, Alloc-Ile-OH and the Alloc-protected analogue of **11** both rapidly converted to their NCA derivatives upon treatment with either thionyl chloride or Ghosez's reagent. In the case of **17**, strong induction from the allyl carbonate substituent on Nα likely inhibits cyclization.[18]

We next explored the possibility of forming both Piz heterocycles under Mitsunobu conditions at the linear pentapeptide stage. Acidolysis of the TBS ethers in **18** was thus followed by gentle heating of the diol in the presence of DIAD and PPh_3 to provide **19** in 68% yield. We observed no elimination across the Cα−Nα bond of the base-labile Alloc-(*N*-OAlloc)-Ile residue under these conditions.[18] We later confirmed the synthetic timing of this tandem cyclization to be important, as attempts to form the Piz heterocycles at the linear hexapeptide or macrocyclic hexapeptide stage were unsuccessful. Removal of both Alloc groups in **19** with Pd_0 in the presence of 1,3-dimethylbarbituric acid (NDMBA) was followed by selective N-acylation of the terminal hydroxylamine with Fmoc-D-Phe-Cl to afford **20** in 54% yield. The C- and N-termini of hexapeptide **20** were then deprotected by treatment with Et_2NH followed by hydrogenolysis to give the corresponding linear zwitterion.

Initial attempts at macrolactamization resulted in poor yields and significant cyclo-oligomer formation even at high dilutions. We then used LCMS to screen the relative efficiency of macrocyclization effected by a variety of condensation reagents at a substrate concentration of 1 mM (Figure 3). Activation of the C-terminal carboxylate with diphenylphosphoryl azide

https://doi.org/10.1021/acs.orglett.2c03861
Org. Lett. 2022, 24, 9285−9289

Scheme 3. Total Synthesis of PrgA (1)



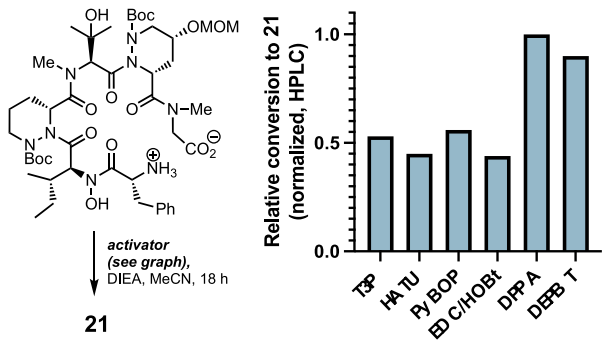


Figure 3. Screening of macrocyclization conditions.

(DPPA) resulted in optimal conversion to the desired product relative to other reagents tested (see the Supporting Information for details). Because of difficulties in purifying **21** to homogeneity, C- and N-terminal deprotection of **20** was followed by treatment with DPPA/DIEA and subsequent global deprotection of the crude macrocycle with TFA/DCM. In this way, we obtained pure **1** in 48% overall yield from **20** following column chromatography.

We acquired ^{1}H NMR spectra of **1** to compare chemical shift assignments with those previously reported for PrgA (Table S1).[7] Gratifyingly, all proton signals for **1** in D_2O and $CDCl_3$ were in excellent agreement with those of the natural isolate. Analytical HPLC analysis via co-injection with an authentic sample of natural PrgA further confirmed the identity of synthetic **1**. Our synthesis thus enables the first complete configurational assignment of PrgA and establishes the presence of a (2*S*,3*S*)-(*N*-OH)Ile residue in the natural product.

Finally, we carried out bacterial growth inhibition assays to obtain MIC values for synthetic PrgA. In addition to **1**, we prepared a simplified analogue [**22** (Scheme 3)] by conventional SPPS for comparison to PrgA. Cyclic hexapeptide **22**

Table 1. MIC Values Determined for 1 and 22 against Selected Pathogens

		MIC (μg/mL)				
bacterial strain	antibiotic resistance	**1**	**22**	vancomycin	daptomycin	linezolid
S. aureus ATCC BAA-1717	methicillin, erythromycin	3.13	>50	–	–	–
S. aureus ATCC 12600-rpoB D"516"G	rifampin	3.13	>50	1.56	3.13	6.25
S. aureus NRS121	methicillin, ceftriaxone, ciprofloxacin, doxycylcline, linezolid, cotrimoxazole	3.13	>50	3.13	3.13	50
S. aureus CB1540	methicillin, ceftriaxone, daptomycin	3.13	>50	6.25	25	0.78
S. aureus VRS1	methicillin, ceftriaxone, rifampin, erthromycin, ciprofloxacin, clindamycin, daptomycin, mupirocin, vancomycin	3.13	>50	>50	3.13	3.13
Enterococcus faecalis DSM 13591	rifampin, streptomycin, mupirocin, vancomycin	3.13	>50	>50	12.5	3.13
E. faecalis AR-0782	vancomycin, quinupristin-dalfopristin	3.13	>50	12.5	12.5	1.56
Enterococcus faecium AR-0783	vanomycin, rifampin, doxycycline	3.13	>50	50	12.5	3.13
Streptococcus pneumoniae ATCC 49619	–	3.13	>50	–	–	–
Streptococcus pyogenes ATCC 12344	–	1.56	>50	–	–	–
M. catarrhalis ATCC 25238	–	12.5	>50	>50	25	6.25
E. coli D21f2tolC	tetracycline, streptomycin	6.25	>50	>50	>50	25

https://doi.org/10.1021/acs.orglett.2c03861
Org. Lett. 2022, 24, 9285−9289

features pipecolic acid (Pip) in place of both Piz residues and lacks the hydroxyl groups of (*N*-OH)-Ile and (*N*-Me)-*β*-OH-Val in the natural product. Compound **1** exhibited low micromolar MIC values against drug-susceptible, drug-resistant, multidrug-resistant, and pan-drug-resistant strains of *S. aureus*, *Enterococcus* spp., and *Streptococcus* spp. (Table 1 and Table S2). The 50th percentile and 90th percentile minimal inhibitory concentrations (MIC_{50} and MIC_{90}, respectively) of **1** compared favorably to those of vancomycin, linezolid, and daptomycin against a panel of isolates of *S. aureus* (MIC_{50} = MIC_{90} = 3.13 μg/mL), *Enterococcus* spp. (MIC_{50} = MIC_{90} = 3.13 μg/mL), and *Streptococcus* spp. (MIC_{50} = 1.56 μg/mL; MIC_{90} = 3.13 μg/mL). PrgA was inactive or only poorly active against Gram-negative pathogens, with the exception of fastidious Gram-negative *Moraxella catarrhalis* and an influx-proficient/efflux-deficient mutant of *Escherichia coli* (D21f2tolC). Simplified analogue **22** exhibited no appreciable bacterial growth inhibition at 50 μg/mL, highlighting the importance of side chain and backbone oxidations for the activity of PrgA. Synthetic **1** was also evaluated for hemolysis of defibrinated red blood cells. Only minimal hemolytic activity was observed at concentrations of ≤50 μM, with 38% cell lysis evident at 100 μM (Figure S1).

In summary, we achieved the first chemical synthesis and configurational assignment of PrgA. Contiguous backbone amide-modified residues and unusual side chain oxidations posed unique challenges in assembling the hexapeptide natural product. Our ultimately successful route required careful selection of condensation conditions and late-stage Piz heterocycle formation. The order of operations also proved to be critical, as several convergent fragment condensation and preformed Piz incorporation approaches failed to provide desired intermediates. This work should enable the synthesis of PrgA congeners featuring targeted residue substitutions and inform strategies for accessing other sterically congested Piz-containing natural products. Efforts to develop SAR around this family of potent antimicrobial agents are currently underway in our laboratory.

■ ASSOCIATED CONTENT

Data Availability Statement

The data underlying this study are available in the published article and its online Supporting Information.

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.2c03861.

Detailed experimental procedures, characterization data for novel compounds, copies of RP-HPLC, HRMS, and NMR spectra, and biological assay data(PDF)

Accession Codes

CCDC 2217835 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

■ AUTHOR INFORMATION

Corresponding Author

Juan R. Del Valle − *Department of Chemistry & Biochemistry, University of Notre Dame, Notre Dame, Indiana 46556, United States*; orcid.org/0000-0002-7964-8402; Email: jdelvalle@nd.edu

Authors

Yassin M. Elbatrawi − *Department of Chemistry & Biochemistry, University of Notre Dame, Notre Dame, Indiana 46556, United States*

Taylor Gerrein − *Department of Chemistry & Biochemistry, University of Notre Dame, Notre Dame, Indiana 46556, United States*

Avraz Anwar − *Department of Chemistry & Biochemistry, University of Notre Dame, Notre Dame, Indiana 46556, United States*

Kamlesh M. Makwana − *Department of Chemistry & Biochemistry, University of Notre Dame, Notre Dame, Indiana 46556, United States*

David Degen − *Waksman Institute and Department of Chemistry & Chemical Biology, Rutgers University, Piscataway, New Jersey 08854, United States*

Richard H. Ebright − *Waksman Institute and Department of Chemistry & Chemical Biology, Rutgers University, Piscataway, New Jersey 08854, United States*

Complete contact information is available at: https://pubs.acs.org/10.1021/acs.orglett.2c03861

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

This work was supported by grants from the National Science Foundation (CHE2109008 to J.R.D.V.) and the National Institutes of Health (AI142731 to R.H.E.) and by a Welter Family Fellowship (to A.A.). The authors thank Dr. Hideki Hashizume (Institute of Microbial Chemistry, Tokyo, Japan) for providing a sample of natural PrgA and Dr. Allen Oliver (Notre Dame Molecular Structure Facility) for X-ray structure determination. The authors thank Cubist Pharmaceuticals, the Network on Antimicrobial Resistance in *Staphylococcus aureus* (NARSA), and BEI Resources (NIH/NIAID) for bacterial isolates.

■ REFERENCES

(1) Murray, C. J. L.; et al. Global burden of bacterial antimicrobial resistance in 2019: a systematic analysis. *Lancet* **2022**, *399*, 629−655.

(2) World Health Organization. Global action plan on antimicrobial resistance. 2015 (https://ahpsr.who.int/publications/i/item/global-action-plan-on-antimicrobial-resistance). Centers for Disease Control and Prevention. Antibiotic resistance threats in the United States. 2019 (https://www.cdc.gov/drugresistance/biggest-threats.html).

(3) (a) Furuno, J. P.; Perencevich, E. N.; Johnson, J. A.; Wright, M. O.; McGregor, J. C.; Morris, J. G., Jr.; Strauss, S. M.; Roghman, M. C.; Nemoy, L. L.; Standiford, H. C.; Hebden, J. N.; Harris, A. D. Methicillin-resistant Staphylococcus aureus and vancomycin-resistant Enterococci co-colonization. *Emerg. Infect. Dis.* **2005**, *11*, 1539−1544. (b) Yoon, Y. K.; Lee, M. J.; Ju, Y.; Lee, S. E.; Yang, K. S.; Sohn, J. W.; Kim, M. J. Determining the clinical significance of co-colonization of vancomycin-resistant enterococci and methicillin-resistant Staphylococcus aureus in the intestinal tracts of patients in intensive care units: a case-control study. *Ann. Clin. Microbiol. Antimicrob.* **2019**, *18*, 28.

(4) (a) Sun, Y.; Cai, Y.; Liu, X.; Bai, N.; Liang, B.; Wang, R. The emergence of clinical resistance to tigecycline. *Int. J. Antimicrob. Agents* **2013**, *41*, 110−116. (b) Tian, Y.; Li, T.; Zhu, Y.; Wang, B.; Zou, X.; Li, M. Mechanisms of linezolid resistance in staphylococci

and enterococci isolated from two teaching hospitals in Shanghai, China. *BMC Microbiol.* **2014**, *14*, 292. (c) Miller, W. R.; Bayer, A. S.; Arias, C. A. Mechanism of Action and Resistance to Daptomycin in *Staphylococcus aureus* and *Enterococci*. *Cold Spring Harbor Perspect. Med.* **2016**, *6*, a026997. (d) Malbruny, B.; Canu, A.; Bozdogan, B.; Fantin, B.; Zarrouk, V.; Dutka-Malen, S.; Feger, C.; Leclercq, R. Resistance to quinupristin-dalfopristin due to mutation of L22 ribosomal protein in Staphylococcus aureus. *Antimicrob. Agents Chemother.* **2002**, *46*, 2200−2207.

(5) Süssmuth, R. D.; Mainz, A. Nonribosomal Peptide Synthesis—Principles and Prospects. *Angew. Chem., Int. Ed.* **2017**, *56*, 3770−3821.

(6) Masutani, M.; Shimokawa, T.; Igarashi, M.; Hamada, M.; Shibata, A.; Oami, S.; Nozaki, T.; Nakagama, H.; Sugimura, T.; Takeuchi, T.; Hori, M. Inhibition of poly(ADP-ribose) glycohydrolase activity by cyclic peptide antibiotics containing piperazic acid residues. *Proc. Japan Acad. B* **2002**, *78*, 15−17.

(7) Igarashi, M.; Sawa, R.; Kinoshita, N.; Hashizume, H.; Nakagawa, N.; Homma, Y.; Nishimura, Y.; Akamatsu, Y. Pargamicin A, a Novel Cyclic Peptide Antibiotic from Amycolatopsis sp. *J. Antibiot.* **2008**, *61*, 387.

(8) (a) Oelke, A. J.; France, D. J.; Hofmann, T.; Wuitschik, G.; Ley, S. V. Piperazic acid-containing natural products: isolation, biological relevance and total synthesis. *Nat. Prod. Rep.* **2011**, *28*, 1445−1471. (b) Morgan, K. D.; Andersen, R. J.; Ryan, K. S. Piperazic acid-containing natural products: structures and biosynthesis. *Nat. Prod. Rep.* **2019**, *36*, 1628−1653. (c) Handy, E.; Sello, J. *Top. Heterocycl. Chem.* **2015**, *48*, 97.

(9) Hashizume, H.; Adachi, H.; Igarashi, M.; Nishimura, Y.; Akamatsu, Y. Biological activities of pargamicin A, a novel cyclic peptide antibiotic from Amycolatopsis sp. *J. Antibiot.* **2010**, *63*, 279−283.

(10) Hashizume, H.; Sawa, R.; Yamashita, K.; Nishimura, Y.; Igarashi, M. Structure and antibacterial activities of new cyclic peptide antibiotics, pargamicins B, C and D, from Amycolatopsis sp. ML1-hF4. *J. Antibiot.* **2017**, *70*, 699.

(11) Elbatrawi, Y. M.; Gerrein, T.; Anwar, A.; Makwana, K. M.; Degen, D.; Ebright, R. H.; Del Valle, J. R. Total Synthesis of Pargamicin A. *chemRxiv* **2022**, DOI: 10.26434/chemrxiv-2022-dm96r.

(12) (a) Ciufolini, M. A.; Xi, N. Synthesis, chemistry and conformational properties of piperazic acids. *Chem. Soc. Rev.* **1998**, *27*, 437−445. (b) Yoshida, M.; Sekioka, N.; Izumikawa, M.; Kozone, I.; Takagi, M.; Shin-ya, K.; Doi, T. Total Synthesis and Structure Elucidation of JBIR-39: A Linear Hexapeptide Possessing Piperazic Acid and γ-Hydroxypiperazic Acid Residues. *Chem. - Eur. J.* **2015**, *21*, 3031−3041.

(13) Gerrein, T. A.; Elbatrawi, Y. M.; Del Valle, J. R. Diastereoselective Synthesis of (3R,5R)-γ-Hydroxypiperazic Acid. *Synlett* **2021**, *32*, 1747−1750.

(14) Armstrong, A.; Jones, L. H.; Knight, J. D.; Kelsey, R. D. Oxaziridine-Mediated Amination of Primary Amines: Scope and Application to a One-Pot Pyrazole Synthesis. *Org. Lett.* **2005**, *7*, 713−716.

(15) (a) Boger, D. L.; Ledeboer, M. W.; Kume, M.; Searcey, M.; Jin, Q. Total Synthesis and Comparative Evaluation of Luzopeptin A−C and Quinoxapeptin A−C. *J. Am. Chem. Soc.* **1999**, *121*, 11375−11383. (b) Dettwiler, J. E.; Bélec, L.; Lubell, W. D. Synthesis and application of L-N-Boc-N-methyl-β-hydroxyvaline in the preparation of a depsipeptide. *Can. J. Chem.* **2005**, *83*, 793−800.

(16) Evans, D. A.; Urpi, F.; Somers, T. C.; Clark, J. S.; Bilodeau, M. T. New procedure for the direct generation of titanium enolates. Diastereoselective bond constructions with representative electrophiles. *J. Am. Chem. Soc.* **1990**, *112*, 8215−8216.

(17) Elbatrawi, Y. M.; Kang, C. W.; Del Valle, J. R. Total synthesis of L-156,373 and an oxoPiz analog via a submonomer approach. *Org. Lett.* **2018**, *20*, 2707−2710.

(18) Sarnowski, M. P.; Del Valle, J. R. N-Hydroxy peptides: solid-phase synthesis and β-sheet propensity. *Org. Biomol. Chem.* **2020**, *18*, 3690−3696.

https://doi.org/10.1021/acs.orglett.2c03861
Org. Lett. 2022, 24, 9285−9289