OL Organic Letters

pubs.acs.org/OrgLett Letter

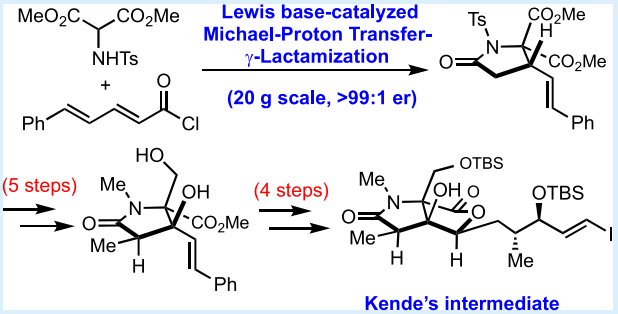
Enantioselective, Organocatalytic Strategy for the Oxazolomycin Core: Formal Synthesis of (+)-Neooxazolomycin

Christian M. Chaheine, Paul T. Gladen, Mikail E. Abbasov, and Daniel Romo*

Cite This: *Org. Lett.* 2020, 22, 9282–9286 Read Online

ACCESS | Metrics & More | Article Recommendations | Supporting Information

ABSTRACT: A concise, organocatalytic, enantioselective route to the γ-lactam core of the oxazolomycins was developed. Key steps include a Lewis base-catalyzed, Michael proton transfer−lactamization organocascade, a one-pot N-methylation and diastereoselective α-alkylation, a diastereotopic group-selective reduction, a substrate-directed allylic hydroxylation, and a lanthanide-mediated organolithium addition to append the side chain. A formal synthesis of (+)-neooxazolomycin via interception of a Kende intermediate, accessed in 10 steps (previously 24 steps from α-D-glucose), enabled confirmation of the relative and absolute stereochemistry.



Since the isolation and structural assignment of the peptide−polyketide natural products oxazolomycin A[1] and neooxazolomycin[2] by Uemura and co-workers in 1985, several congeners have been identified from both marine and terrestrial *Streptomyces* bacteria and are known collectively as the "oxazolomycins" (Figure 1).[3] Across the various congeners

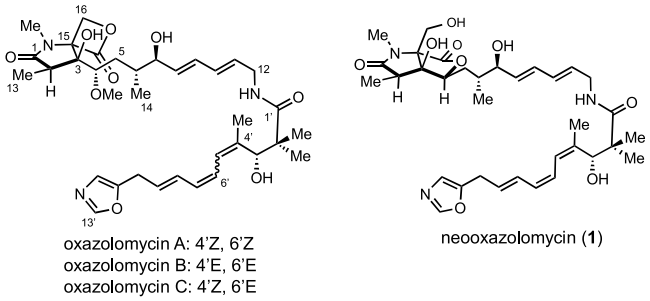


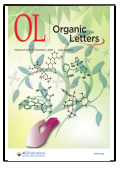
Figure 1. Structures of selected oxazolomycin family members and neooxazolomycin.

that have been identified to date, the main structural differences are substitution at C16 of the spiro-β-lactone, the geometry of the conjugated triene, and the terminal group of the side chain. The stereochemically rich spiro-β-lactone pyroglutamate core is common to all oxazolomycin family members with the exception of neooxazolomycin, which instead possesses a fused γ-lactone. The only reports regarding the bioactivity of neooxazolomycin, to the best of our knowledge, include the original isolation paper that reports *in vivo* activity against Ehrlic ascites tumor cells but without quantitative data.[2] In addition, a study evaluating the inhibition of plant tumorigenesis by oxazolomycin A states that neooxazolomycin did not display this activity.[4] In contrast, there are many reports of spiro-β-lactone-containing oxazolomycins that demonstrate a wide range of bioactivities, including antiviral, anticancer, and antibacterial activity.[5] Thus, an efficient, stereoselective synthetic route to access both spiro-β-lactone and fused γ-lactone γ-lactam core structures of the oxazolomycins and neooxazolomycins, respectively, is desirable for a more complete understanding of the structure−activity relationship of these natural products.

Numerous elegant synthetic strategies targeting the densely functionalized γ-lactam core have been described,[6] culminating in a formal synthesis of neooxazolomycin by Taylor[7] and total syntheses of oxazolomycin A[8] and lajollamycin[9] by Hatakeyama and neoxazolomycin by Kim,[10] Hatakeyama,[11] and Kende.[12] Despite these various synthetic strategies, only a few studies directed toward an understanding of the biological mode of action[13] of the oxazolomycin family have been reported. Futhermore, no catalytic, enantioselective routes to the oxazolomycin core have been described. Previous synthetic routes employed chiral pool starting materials and required redox manipulations to invert the C4 or C7 carbinol stereocenters. In contrast, our approach sets all six stereogenic centers in the C1−C17 core with a high degree of stereocontrol and with the natural configurations.

Toward our goal of elucidating the cellular target(s) and delineating the minimal structural features required for the bioactivity of the oxazolomycin family, we report herein a

Received: October 21, 2020
Published: November 23, 2020



https://dx.doi.org/10.1021/acs.orglett.0c03511
Org. Lett. 2020, 22, 9282–9286

scalable, organocatalytic, enantioselective approach to the pyroglutamate core of the oxazolomycins. A vinyl iodide intermediate **2** utilized by Kende in the first total synthesis of neooxazolomycin was intercepted in 10 steps (longest linear sequence; previously obtained in 24 steps from glucose) from the known sulfonamido malonate **7**.[14] This enabled correlation of the absolute stereochemistry of the C1−C9 core of the oxazolomycins obtained through the described synthetic route.

We adopted a common retrosynthetic disconnection for all oxazolomycins utilized to date, namely the side-chain amide bond that appends the core (C1−C17) to the conjugated triene oxazole fragment (C1′−C13′). With a goal of methodically increasing the complexity of the side chain in a version of pharmacophore-directed retrosynthesis,[15] we next chose a C9−C10 disconnection of the diene,[16] leading to the initial synthetic target of our study, Kende's vinyl iodide **2** that would enable correlation of the absolute and relative configuration corresponding to that of neoxazolomycin and by extension oxazolomycin (Figure 2). Disconnection of the

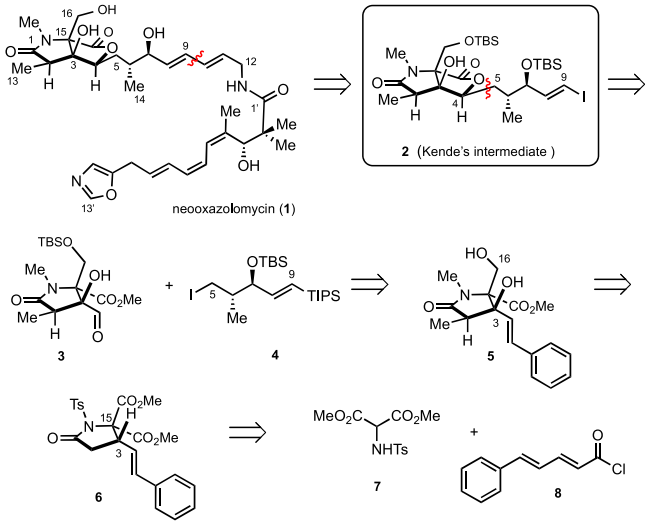
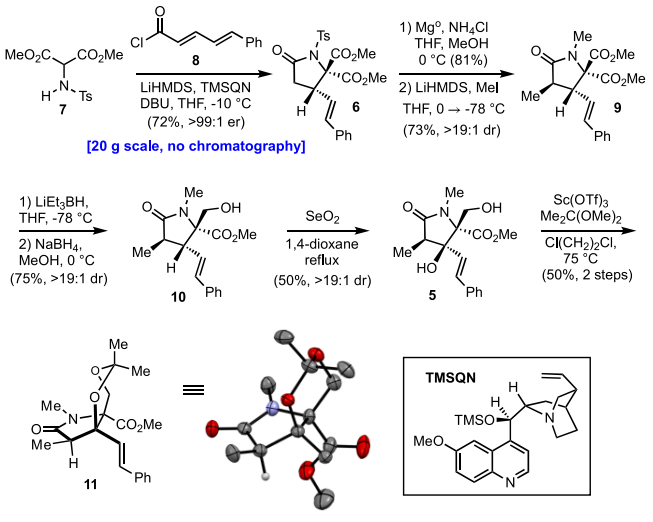


Figure 2. Retrosynthetic analysis of the γ-lactam core of the oxazolomycins intercepting Kende's vinyl iodide intermediate **2**.

C4−C5 bond through a facially selective addition to aldehyde **3** of an alkylmetal species derived from a C5−C9-bearing iodide **4** builds on precedent from the Donohoe lab.[6d] The appropriately functionalized aldehyde-bearing γ-lactam **3** would be derived from diol **5**, in turn derived from substrate-controlled alkylation and functional group manipulation of diester **6**. Finally, our previously described nucleophile (Lewis base)-catalyzed Michael proton transfer lactamization (NCMPL) organocascade[17] would deliver diester lactam **6** in enantiopure form from aminomalonate **7**[14] and acid chloride **8**, each accessible in one step from commercial materials. The single C3-stereogenic center would impart diastereoselectivity during α-methylation at C2 and guide a diastereotopic group-selective reduction[18] of the geminal diester. The styrenyl moiety in the NCMPL was chosen to control the regioselectivity for the allylic C−H hydroxylation at C3 and serve as a masked aldehyde.

Our synthesis commenced with the NCMPL, employing acid chloride **8** and *N*-tosyl aminomalonate **7** as substrates with 20 mol % TMS-quinine (TMSQN) as the chiral Lewis base, reliably delivering γ-lactam **6** on a 20 g scale in 72% yield [>99:1 er (Scheme 1)]. Sufficiently pure, crystalline lactam **6** could be obtained by simple trituration (MeOH) of the crude

Scheme 1. Scalable, Enantioselective Synthesis of Pyroglutamate Core 5[a]



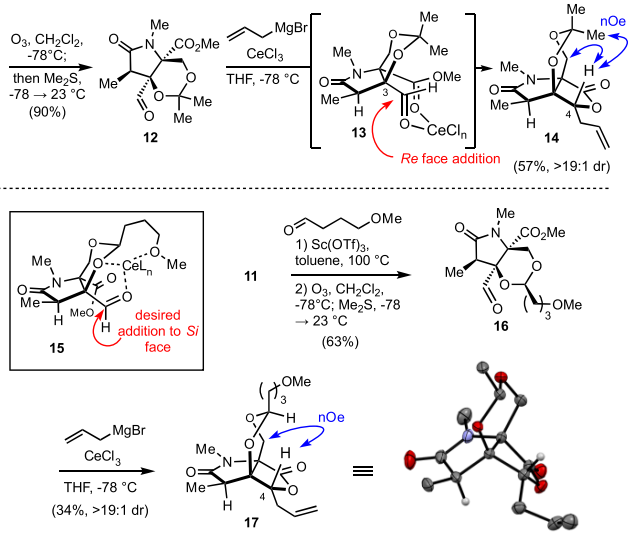
[a]The inset shows an ORTEP representation of the single-crystal X-ray structure of dioxane **11**, with 50% probability ellipsoids, PhCH═ omitted for the sake of clarity.

solid following aqueous workup. The absolute stereochemistry was confirmed by X-ray analysis as recently described.[17a] Desulfonylation of lactam **6** on a decagram scale by stirring with Mg^0 turnings in cold MeOH/THF[19] was followed by a one-pot *N*-methylation on the pyrrolidinone nitrogen and highly diastereoselective methylation at C2 to deliver dimethyl γ-lactam **9** on a multigram scale in 73% yield (>19:1 dr). A diastereotopic group-selective monoreduction of the more sterically accessible methyl ester was possible through use of a bulky hydride source ($LiEt_3BH$, superhydride) at a low temperature, giving an intermediate aldehyde that was directly reduced with $NaBH_4$ to the targeted β-hydroxy ester **10**. A subsequent allylic CH hydroxylation with SeO_2, presumably directed by the adjacent primary alcohol,[20] provided multigram quantities of pyroglutamate diol **5** with the desired C3 configuration [confirmed by X-ray analysis of an acetonide derivative **11** (Scheme 1, inset)]. Notably, diester **9**, upon being exposed to SeO_2, led to the desired stereochemistry at C3 but as a 4:1 mixture of epimers, supporting the directing effect of the C16 primary alcohol. Simple trituration of crude diol **5** with CH_2Cl_2 provided sufficiently pure material for use in subsequent reactions.

With pyroglutamate diol **5** available in gram quantities, the stage was set for exploration of the key C4−C5 alkylmetal addition reaction, which required a careful choice of a C3,C16 alcohol protecting group scheme. Initially, we studied the formation of acetonide from **5** and the styrenyl moiety was oxidatively cleaved with ozone to yield aldehyde **12**. Exposure to several Grignard or organolithium reagents led to only reduction or no reaction, respectively (Scheme 2). The sterically hindered nature of the C4 aldehyde presumably led to low reactivity; therefore, we turned to the use of anhydrous lanthanide halides, known to assist in nucleophilic additions to hindered carbonyls through Lewis acid activation of the carbonyl oxygen and/or the *in situ* generation of an

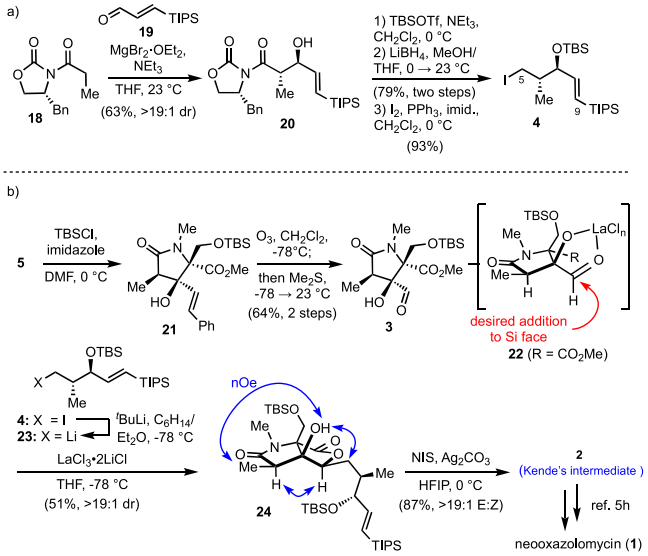
https://dx.doi.org/10.1021/acs.orglett.0c03511
Org. Lett. 2020, 22, 9282−9286

Scheme 2. Facially Selective Additions to Aldehydes 12 and 16 and Stereochemical Assignments through nOe and X-ray Analysis[a]



[a]The inset shows an ORTEP representation of single-crystal X-ray structure of lactone **17**, with 50% probability ellipsoids. Methoxymethylene side chain omitted for the sake of clarity.

Scheme 3. (a) Enantioselective Synthesis of the C5−C9 Fragment of the Oxazolomycins and (b) Formal Total Synthesis of (+)-Neooxazolomycin (1)



organolanthanide of enhanced nucleophilicity and reduced basicity.[21] A combination of excess allylmagnesium bromide[22] and anhydrous $CeCl_3$[23] in THF led to a single diastereomer of γ-lactone **14** through a nucleophilic addition/γ-lactonization sequence (Scheme 2). Spectroscopic analysis, including NOESY, unfortunately indicated that γ-lactone **14** had the undesired C4 configuration, presumably the product of addition to the *re* face of aldehyde **13** induced by formation of seven-membered chelate **13** with the pendant ester. We speculated that the gem-dimethyl group in the acetonide of diol **5** sterically precluded the C3-ether oxygen from coordination to the cerium(III) ion that would induce the desired facial selectivity. An acetal protecting group bearing a pendant methoxy functionality was next considered with the aim of templating the chelation of the cerium(III) ion onto aldehyde **16** via chelated intermediate **15** (Scheme 2), leading to *si* face addition to the aldehyde; however, this tactic did not override the competing seven-membered chelate. The NOESY spectra and X-ray single-crystal analysis of lactone **17** confirmed that the undesired C4-relative configuration was again formed during the allylation.

Building on work by Donohoe, we considered the possibility that the C3-tertiary alcohol, once deprotonated, could enforce a chelated α-hydroxy aldehyde intermediate [cf. **22** (Scheme 3b)], which would be expected to deliver the desired facial selectivity. This chelated α-alkoxy aldehyde was first proposed by Donohoe employing a similar α-hydroxy aldehyde and a primary alkylcerium reagent generated *in situ*.[6d] We studied this tactic beginning with selective silyl protection of 1,3-diol **5**, yielding silyl ether **21**, followed by ozonolysis to afford the α-hydroxyaldehyde **3**. Initial studies with allylmagnesium bromide were inconclusive with regard to the stereochemical outcome at C4 so we proceeded to correlate the stereochemical outcome by comparison to Kende's intermediate **2** through addition of the required side chain as described below.

The required enantioenriched C5−C9 iodide **4** was synthesized through application of an Evans anti-aldol reaction[24] utilizing oxazolidinone[25] **18** and the β-triisopropylsilyl acrolein[26] **19** [63% yield, >19:1 dr (Scheme 2a)]. Silyl protection of the resulting secondary alcohol and reductive cleavage of the auxiliary gave a primary alcohol that was converted to iodide **4** under typical Appel conditions.[27]

The optimized procedure for this key fragment coupling involved lithium−halogen exchange of the primary iodide **4** at −78 °C in a mixture of dry hexanes and ether.[28] α-Hydroxyaldehyde **3** was dissolved in a solution of $LaCl_3$·2LiCl in THF,[29] and this mixture was then slowly added to the alkyllithium solution maintained at −78 °C (Scheme 3b). The desired fused γ-lactone γ-lactam **24** was generated through a highly diastereoselective nucleophilic addition/γ-lactonization sequence, and the conformational rigidity of lactone **24** enabled the initial determination of the C4 stereochemistry through NOESY analysis (blue arrows). The relative and absolute stereochemical assignment of this fragment was further corroborated by intercepting Kende's vinyl iodide intermediate **2**. Iododesilylation of the vinylsilane in **24** with NIS and Ag_2CO_3 in hexafluoroisopropanol[30] (HFIP) at 0 °C delivered (*E*)-vinyl iodide **2** (87% yield, >19:1 *E*:*Z*) and spectroscopicaly correlated well with that previously reported (see Table S1).

In summary, we developed a scalable, organocatalytic, enantioselective route to a versatile pyroglutamate diol **5** that is serviceable for the synthesis of the oxazolomycin family of natural products. Diol **5** was converted in four steps to an advanced vinyl iodide **2** first synthesized by Kende in the first total synthesis of neooxazolomycin, confirming the relative and absolute stereochemistry of the C1−C17 fragment.[12] A simplified procedure involving a lanthanide-mediated alkyllithium addition, building on work by Donohoe, enabled a highly diastereoselective installation of the C4−C5 bond that initiates construction of the oxazolomycin side chain. This C4−C5 bond disconnection will allow for variation of the side chain in the synthesis of simplified derivatives toward facilitating a more in-depth understanding of the structure−activity relationships and the various reported biological

https://dx.doi.org/10.1021/acs.orglett.0c03511
Org. Lett. 2020, 22, 9282−9286

activities for this family of unique peptide−polyketide natural products.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.0c03511.

Experimental procedures, compound characterization data, ^{1}H, ^{13}C, and select 2D (NOESY, HMBC, and HSQC) NMR spectra for all new compounds reported, and X-ray data for intermediates **11** and **17** (PDF)

Accession Codes

CCDC 2034834−2034835 contain 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

Daniel Romo − *Department of Chemistry and Biochemistry, Baylor University, Waco, Texas 76798-7046, United States;* orcid.org/0000-0003-3805-092X; Email: Daniel_Romo@baylor.edu

Authors

Christian M. Chaheine − *Department of Chemistry and Biochemistry, Baylor University, Waco, Texas 76798-7046, United States*

Paul T. Gladen − *Department of Chemistry and Biochemistry, Baylor University, Waco, Texas 76798-7046, United States*

Mikail E. Abbasov − *Department of Chemistry and Biochemistry, Baylor University, Waco, Texas 76798-7046, United States*

Complete contact information is available at: https://pubs.acs.org/10.1021/acs.orglett.0c03511

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

The authors gratefully acknowledge support by the National Institute of General Medical Sciences of the National Institutes of Health (R37 GM052964 and R35 GM134910) and the Robert A. Welch Foundation (AA-1280) and support by the National Science Foundation (CHE-1800411) for development of the NCMPL. The authors thank Dr. Joe Reibenspies (Texas A&M University, College Station, TX) and Prof. Kevin Klausmeyer (Baylor University) for single-crystal X-ray structure determination.

■ REFERENCES

(1) (a) Aizawa, S.; Shibuya, M.; Shirato, S. Resistaphilin, A New Antibiotic. I, Production, Isolation and Properties. *J. Antibiot.* **1971**, *24* (6), 393−396. (b) Mori, T.; Takahashi, K.; Kashiwabara, M.; Uemura, D.; Katayama, C.; Iwadare, S.; Shizuri, Y.; Mitomo, R.; Nakano, F.; Matsuzaki, A. Structure of Oxazolomycin, a Novel Beta-Lactone Antibiotic. *Tetrahedron Lett.* **1985**, *26* (8), 1073−1076.

(2) Takahashi, K.; Kawabata, M.; Uemura, D.; Iwadare, S.; Mitomo, R.; Nakano, F.; Matsuzaki, A. Structure of Neooxazolomycin, an Antitumor Antibiotic. *Tetrahedron Lett.* **1985**, *26* (8), 1077−1078.

(3) (a) Ogura, M.; Nakayama, H.; Furihata, K.; Shimazu, A.; Seto, H.; Otake, N. Structure of a New Antibiotic Curromycin A Produced by a Genetically Modified Strain of *Streptomyces Hygroscopicus* a Polyether Antibiotic Producing Organism. *J. Antibiot.* **1985**, *38* (5), 669−673. (b) Ogura, M.; Nakayama, H.; Furihata, K.; Shimazu, A.; Seto, H.; Otake, N. Isolation and Structural Determination of a New Antibiotic Curromycin-B. *Agric. Biol. Chem.* **1985**, *49* (6), 1909−1910. (c) Ikeda, Y.; Kondo, S.; Naganawa, H.; Hattori, S.; Hamada, M.; Takeuchi, T. New Triene-*β*-lactone Antibiotics, Triedimycins A and B. *J. Antibiot.* **1991**, *44* (4), 453−455. (d) Ryu, G.; Hwang, S.; Kim, S. K. 16-methyloxazolomycin, a new antimicrobial and cytotoxic substance produced by a Streptomyces sp. *J. Antibiot.* **1997**, *50* (12), 1064−1066. (e) Kanzaki, H.; Wada, K.-I.; Nitoda, T.; Kawazu, K. Novel Bioactive Oxazolomycin Isomers Produced by Streptomyces albus JA3453. *Biosci., Biotechnol., Biochem.* **1998**, *62* (3), 438−442. (f) Otani, T.; Yoshida, K. I.; Kubota, H.; Kawai, S.; Ito, S.; Hori, H.; Ishiyama, T.; Oki, T. Novel Triene-*β*-lactone Antibiotics, Oxazolomycin Derivative and Its Isomer, Produced by *Streptomyces* sp. KSM-2690. *J. Antibiot.* **2000**, *53* (12), 1397−1400. (g) Manam, R. R.; Teisan, S.; White, D. J.; Nicholson, B.; Grodberg, J.; Neuteboom, S. T. C.; Lam, K. S.; Mosca, D. A.; Lloyd, G. K.; Potts, B. C. M. Lajollamycin, a nitro-tetraene spiro-beta-lactone-gamma-iactam antibiotic from the marine actinomycete Streptomyces nodosus. *J. Nat. Prod.* **2005**, *68* (2), 240−243. (h) Ko, K.; Lee, S. H.; Kim, S. H.; Kim, E. H.; Oh, K. B.; Shin, J.; Oh, D. C. Lajollamycins, Nitro Group-Bearing Spiro-*β*-lactone-*γ*-lactams Obtained from a Marine-Derived Streptomyces sp. *J. Nat. Prod.* **2014**, *77* (9), 2099−2104. (i) Koomsiri, W.; Inahashi, Y.; Kimura, T.; Shiomi, K.; Takahashi, Y.; Ōmura, S.; Thamchaipenet, A.; Nakashima, T. Bisoxazolomycin A: a new natural product from 'Streptomyces subflavus subsp. irumaensis' AM-3603. *J. Antibiot.* **2017**, *70* (12), 1142−1145.

(4) Kawai, S.; Kawabata, G.; Kobayashi, A.; Kawazu, K. Inhibitory Effect of Oxazolomycin on Crown Gall Formation. *Agric. Biol. Chem.* **1989**, *53* (4), 1127−1133.

(5) Moloney, M. G.; Trippier, P. C.; Yaqoob, M.; Wang, Z. The Oxazolomycins: A Structurally Novel Class of Bioactive Compounds. *Curr. Drug Discovery Technol.* **2004**, *1* (3), 181−199.

(6) (a) Kende, A. S.; Devita, R. J. Synthesis of the Fused Bicyclic Lactam-Lactone Terminus of Neooxazolomycin by a Novel Dianion Cyclocondensation. *Tetrahedron Lett.* **1988**, *29* (21), 2521−2524. (b) Papillon, J. P. B.; Taylor, R. J. K. The first syntheses of the 1-oxo-2-oxa-5-azaspiro[3.4]octane ring system found in oxazolomycin. *Org. Lett.* **2000**, *2* (14), 1987−1990. (c) Donohoe, T. J.; Chiu, J. Y. K.; Thomas, R. E. Synthesis of the Pyrrolidinone Core of KSM-2690 B. *Org. Lett.* **2007**, *9* (3), 421−424. (d) Donohoe, T. J.; O'Riordan, T. J. C.; Peifer, M.; Jones, C. R.; Miles, T. J. Asymmetric Synthesis of the Fully Elaborated Pyrrolidinone Core of Oxazolomycin A. *Org. Lett.* **2012**, *14* (21), 5460−5463. (e) Ishihara, J.; Hatakeyama, S. Total Synthesis of Oxazolomycins. *Chem. Rec.* **2014**, *14* (4), 663−677 (this review cites all synthetic work toward oxazolomycins prior to 2014). (f) Heaviside, E. A.; Moloney, M. G.; Thompson, A. L. Diastereoselective intramolecular aldol ring closures of threonine derivatives leading to densely functionalised pyroglutamates related to oxazolomycin. *RSC Adv.* **2014**, *4* (31), 16233−16249. (g) Josa-Culleré, L.; Towers, C.; Willenbrock, F.; Macaulay, V. M.; Christensen, K. E.; Moloney, M. G. Synthesis and bioactivity of fused- and spiro-*β*-lactone-lactam systems. *Org. Biomol. Chem.* **2017**, *15* (25), 5373−5379. (h) Eto, K.; Ishihara, J.; Hatakeyama, S. Stereoselective synthesis of the right-hand cores of 16-methylated oxazolomycins. *Tetrahedron* **2018**, *74* (7), 711−719.

(7) Bastin, R.; Dale, J. W.; Edwards, M. G.; Papillon, J. P. N.; Webb, M. R.; Taylor, R. J. K. Formal synthesis of (+)-neooxazolomycin via a Stille cross-coupling/deconjugation route. *Tetrahedron* **2011**, *67* (51), 10026−10044.

(8) Eto, K.; Yoshino, M.; Takahashi, K.; Ishihara, J.; Hatakeyama, S. Total Synthesis of Oxazolomycin A. *Org. Lett.* **2011**, *13* (19), 5398−5401.
(9) Nishimaru, T.; Eto, K.; Komine, K.; Ishihara, J.; Hatakeyama, S. Total Synthesis of Lajollamycin B. *Chem. - Eur. J.* **2019**, *25* (33), 7927−7934.
(10) Kim, J. H.; Kim, I.; Song, Y.; Kim, M. J.; Kim, S. Asymmetric Total Synthesis of (+)-Neooxazolomycin Using a Chirality-Transfer Strategy. *Angew. Chem., Int. Ed.* **2019**, *58* (32), 11018−11022.
(11) Onyango, E. O.; Tsurumoto, J.; Imai, N.; Takahashi, K.; Ishihara, J.; Hatakeyama, S. Total synthesis of neooxazolomycin. *Angew. Chem., Int. Ed.* **2007**, *46* (35), 6703−6705.
(12) Kende, A. S.; Kawamura, K.; Devita, R. J. Enantioselective Total Synthesis of Neooxazolomycin. *J. Am. Chem. Soc.* **1990**, *112* (10), 4070−4072.
(13) Grigorjev, P. A.; Schlegel, R.; Gräfe, U. On the Protonophoric Activity of Oxazolomycin. *Pharmazie* **1992**, *47* (9), 707−709.
(14) Fritz, S. P.; Moya, J. F.; Unthank, M. G.; McGarrigle, E. M.; Aggarwal, V. K. An Efficient Synthesis of Azetidines with (2-Bromoethyl)sulfonium Triflate. *Synthesis* **2012**, *44* (10), 1584−1590.
(15) (a) Abbasov, M. E.; Alvariño, R.; Chaheine, C. M.; Alonso, E.; Sánchez, J. A.; Conner, M. L.; Alfonso, A.; Jaspars, M.; Botana, L. M.; Romo, D. Simplified immunosuppressive and neuroprotective agents based on gracilin A. *Nat. Chem.* **2019**, *11* (4), 342−350. (b) Tao, Y.; Reisenauer, K. N.; Masi, M.; Evidente, A.; Taube, J. H.; Romo, D. Pharmacophore-Directed Retrosynthesis Applied to Ophiobolin A: Simplified Bicyclic Derivatives Displaying Anticancer Activity. *Org. Lett.* **2020**, *22* (21), 8307−8312. (c) Truax, N. J.; Romo, D. Bridging the Gap Between Natural Product Synthesis and Drug Discovery. *Nat. Prod. Rep.* **2020**, DOI: 10.1039/D0NP00048E.
(16) Kende, A. S.; DeVita, R. J. A mild four-carbon homologation of aldehydes to E, E-dienamines. *Tetrahedron Lett.* **1990**, *31* (3), 307−310.
(17) (a) Chaheine, C. M. S.; Conner, J.; Gladen, P. T.; Romo, D. Enantioselective Michael-Proton Transfer-Lactamization for Pyroglutamic Acid Derivatives: Synthesis of dimethyl-(S,E)-5-oxo-3-styryl-1-tosylpyrrolidine-2,2-dicarboxylate. *Org. Synth.* **2020**. (b) Vellalath, S.; Van, K. N.; Romo, D. Direct Catalytic Asymmetric Synthesis of N-Heterocycles from Commodity Acid Chlorides by Employing α,β-Unsaturated Acylammonium Salts. *Angew. Chem., Int. Ed.* **2013**, *52* (51), 13688−13693.
(18) Horwitz, M. A.; Johnson, J. S. Local Desymmetrization through Diastereotopic Group Selection: An Enabling Strategy for Natural Product Synthesis. *Eur. J. Org. Chem.* **2017**, *2017* (11), 1381−1390.
(19) (a) Lee, G. H.; Youn, I. K.; Choi, E. B.; Lee, H. K.; Yon, G. H.; Yang, H. C.; Pak, C. S. Magnesium in Methanol (Mg/MeOH) in Organic Syntheses. *Curr. Org. Chem.* **2004**, *8* (13), 1263−1287. (b) Leduc, A. B.; Kerr, M. A. Total Synthesis of (±)-Decursivine. *Eur. J. Org. Chem.* **2007**, *2007* (2), 237−240.
(20) Hoveyda, A. H.; Evans, D. A.; Fu, G. C. Substrate-directable chemical reactions. *Chem. Rev.* **1993**, *93* (4), 1307−1370.
(21) (a) Molander, G. A. Application of lanthanide reagents in organic synthesis. *Chem. Rev.* **1992**, *92* (1), 29−68. (b) Imamoto, T.; Sugiura, Y.; Takiyama, N. Organocerium reagents. Nucleophilic addition to easily enolizable ketones. *Tetrahedron Lett.* **1984**, *25* (38), 4233−4236. (c) Liu, H. J.; Shia, K. S.; Shang, X.; Zhu, B. Y. Organocerium Compounds in Synthesis. *Tetrahedron* **1999**, *55* (13), 3803−3830.
(22) Duttwyler, S.; Chen, S.; Takase, M. K.; Wiberg, K. B.; Bergman, R. G.; Ellman, J. A. Proton Donor Acidity Controls Selectivity in Nonaromatic Nitrogen Heterocycle Synthesis. *Science* **2013**, *339* (6120), 678.
(23) (a) Dimitrov, V.; Kostova, K.; Genov, M. Anhydrous Cerium(III) Chloride — Effect of the Drying Process on Activity and Efficiency. *Tetrahedron Lett.* **1996**, *37* (37), 6787−6790. (b) Takeda, N.; Imamoto, T. Use of Cerium(III) Chloride in the Reactions of Carbonyl Compounds with Organolithiums or Grignard Reagents for the Suppression of Abnormal Reactions: 1-butyl-1,2,3,4-tetrahydro-1-napthol. *Org. Synth.* **1999**, *76*, 228.
(24) (a) Evans, D. A.; Downey, C. W.; Shaw, J. T.; Tedrow, J. S. Magnesium Halide-Catalyzed Anti-Aldol Reactions of Chiral N-Acylthiazolidinethiones. *Org. Lett.* **2002**, *4* (7), 1127−1130. (b) Evans, D. A.; Tedrow, J. S.; Shaw, J. T.; Downey, C. W. Diastereoselective Magnesium Halide-Catalyzed anti-Aldol Reactions of Chiral N-Acyloxazolidinones. *J. Am. Chem. Soc.* **2002**, *124* (3), 392−393.
(25) Gage, J. R.; Evans, D. A. Diastereoselective Aldol Condensaiton Using a Chiral Oxazolidinone Auxiliary: (2*S*,3*S*)-3-hydroxy-3-phenyl-2methylpropanoic Acid. *Org. Synth.* **1990**, *68*, 83.
(26) Ogasawara, M.; Okada, A.; Subbarayan, V.; Sorgel, S.; Takahashi, T. Palladium-Catalyzed Asymmetric Synthesis of Axially Chiral Allenylsilanes and Their Application to S(E)2 ' Chirality Transfer Reactions. *Org. Lett.* **2010**, *12* (24), 5736−5739.
(27) Appel, R. Tertiary Phosphane/Tetrachloromethane, a Versatile Reagent for Chlorination, Dehydration, and P-N Linkage. *Angew. Chem., Int. Ed. Engl.* **1975**, *14* (12), 801−811.
(28) (a) Bailey, W. F.; Brubaker, J. D.; Jordan, K. P. Effect of solvent and temperature on the lithium-iodine exchange of primary alkyl iodides: reaction of t-butyllithium with 1-iodooctane in heptane-ether mixtures. *J. Organomet. Chem.* **2003**, *681* (1−2), 210−214. (b) Rathman, T.; Bailey, W. F. Optimization of Organolithium Reactions. *Org. Process Res. Dev.* **2009**, *13* (2), 144−151.
(29) Krasovskiy, A.; Kopp, F.; Knochel, P. Soluble Lanthanide Salts (LnCl3·2 LiCl) for the Improved Addition of Organomagnesium Reagents to Carbonyl Compounds. *Angew. Chem., Int. Ed.* **2006**, *45* (3), 497−500.
(30) (a) Ilardi, E. A.; Stivala, C. E.; Zakarian, A. Hexafluoroisopropanol as a Unique Solvent for Stereoselective Iododesilylation of Vinylsilanes. *Org. Lett.* **2008**, *10* (9), 1727−1730. (b) Sidera, M.; Costa, A. M.; Vilarrasa, J. Iododesilylation of TIPS-, TBDPS-, and TBS-Substituted Alkenes in Connection with the Synthesis of Amphidinolides B/D. *Org. Lett.* **2011**, *13* (18), 4934−4937.

https://dx.doi.org/10.1021/acs.orglett.0c03511
Org. Lett. 2020, 22, 9282−9286