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Scalable Access to Arylomycins via C−H Functionalization Logic

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Supporting Information

ABSTRACT: Arylomycins are a promising class of "latent" antibacterial natural products currently in preclinical development. Access to analogues within this family has previously required a lengthy route involving multiple functional group manipulations that is costly and time-intensive on scale. This study presents a simplified route predicated on simple C−H functionalization logic that is enabled by a Cu-mediated oxidative phenol coupling that mimics the putative biosynthesis. This operationally simple macrocyclization is the largest of its kind and can be easily performed on gram scale. The application of this new route to a formal synthesis of the natural product and a collection of new analogues along with their biological evaluation is also reported.

The arylomycin class of antibiotics are a group of bacterially derived natural product lipopeptides that inhibit bacterial type 1 signal peptidase (SPase).[1] Their spectrum was initially thought to be narrow, but they were later shown to exhibit broad spectrum activity that was masked by the pre-existence of a resistance-conferring mutation in the SPase of many of the test organisms.[2] It was hypothesized that the presence of these resistance-conferring mutations was the result of previous selection pressure, suggesting that the arylomycins once had broad spectrum activity and thus, with optimization, they might again (i.e., a "latent" antibiotic family[3]). Indeed, initial optimization efforts yielded analogues with increased activity and spectrum,[4] including activity against the important Gram-negative human pathogen *Escherichia coli*.[5] However, the main challenge to the development of novel analogues is the lengthy and low-yielding synthesis of the macrocyclic core. This Communication presents a simplified, scalable route to arylomycins and analogues thereof displaying potent Gram-negative activity enabled by a pivotal Cu-mediated oxidative macrocyclization.

The peptidic structure of the arylomycins points to amino acids as logical precursors for synthesis (Figure 1). These natural products are comprised of a lipophilic tail connected to a 14-membered, biaryl-bridged macrocyclic core. Whereas the former is trivial to install, the latter represents the primary challenge for synthesis. This type of problem has been encountered before, such as in the AB ring system of vancomycin.[6] Those classic studies taught that three general approaches are strategic: (1) macrolactamization; (2) cross-coupling; and (3) oxidative phenol coupling. Initial studies toward the synthesis of the arylomycins demonstrated that macrolactamization is not a viable route, and ultimately the use of an intramolecular Suzuki−Miyaura coupling provided access to the macrocycle.[7] While this route provided the first access to synthetic arylomycins and has enabled all of the optimization efforts to date, it suffers from several drawbacks. First, the Suzuki−Miyaura coupling used to forge the macrocycle proceeds, in the best case, in 51% yield using 20 mol% of Pd catalyst (the mass balance is protodeborylation byproduct that cannot be recycled).[8] Next, installation of the requisite functional and protecting groups for this coupling requires extensive manipulation of the amino acid precursors (including an additional Pd-catalyzed step to install the boronic ester). This results in a lengthy 14-step synthesis of the macrocycle with an overall yield of 6.4% (36% ideality).[9] This costly and labor-intensive route has delayed development efforts and would be prohibitive of any large-scale synthesis efforts necessary to advance to preclinical or clinical studies.

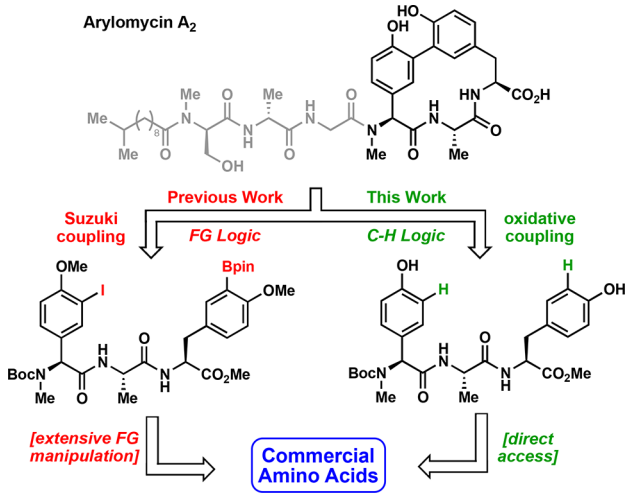

Figure 1. Contrasting retrosynthetic analyses of the arylomycin macrocycle (illustrated with natural variant arylomycin A_2).

We were thus drawn to the third and final tactic employed in biaryl-fused macrocyclic peptide synthesis: oxidative phenol coupling. This process is known to underlie the biosynthetic origin of the macrocycle[10] and is a classic example of C−H functionalization logic applied to synthesis.[11] Since Barton's first example of this type of reactivity,[12] many methods have become available for oxidative phenolic coupling, including the use of organic oxidants,[13] stoichiometric[13b,14] and catalytic[15] metal oxidants, and electrochemical oxidation.[16] Additional precedence for intramolecular oxidative coupling of short

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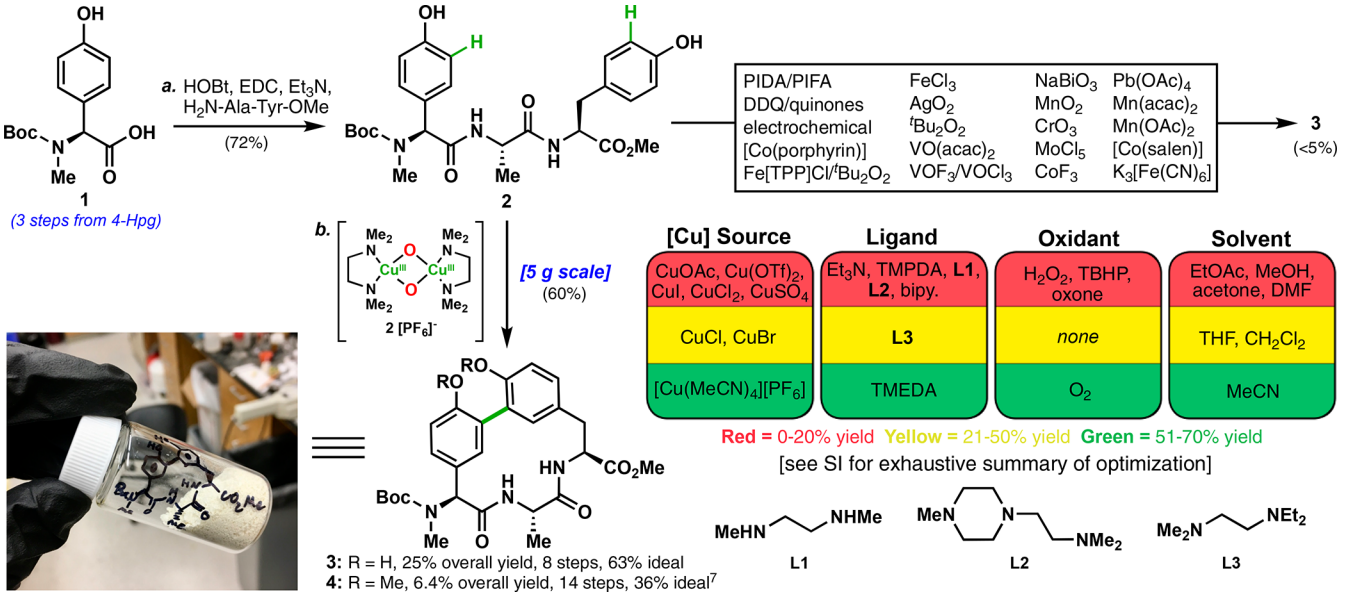
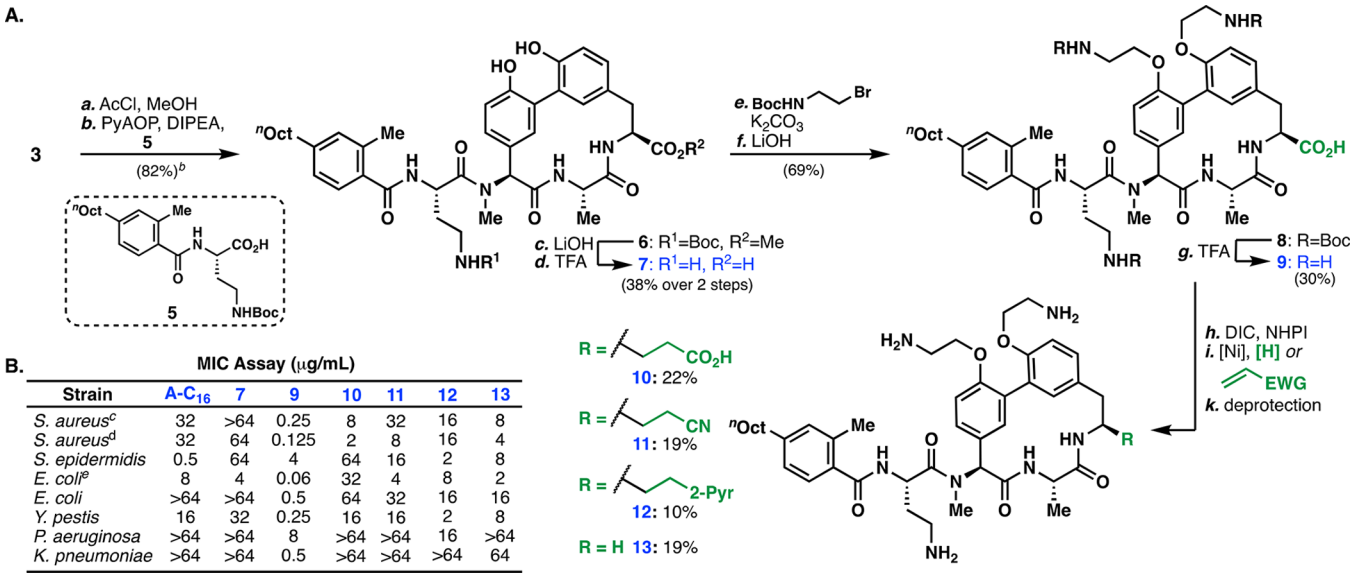
Scheme 1. Synthesis of the Arylomycin Core via Oxidative Macrocyclization[a]



[a]Reagents and conditions: (*a*) **1** (1 equiv), HCl·NH_2-Ala-Tyr-OMe (1 equiv), HOBt (1 equiv), EDC (1.5 equiv), Et_3N (3.3 equiv), MeCN/DMF, 25 °C (72%); (*b*) $[Cu(MeCN)_4][PF_6]$ (2 equiv), TMEDA (2 equiv), O_2, MeCN, then **2** (1 equiv), 25 °C (60%). Abbreviations: HOBt = 1-hydroxybenzotriazole, EDC = *N*-ethyl-*N*′-(3-(dimethylamino)propyl)carbodiimide hydrochloride, TMEDA = *N,N,N′,N′*-tetramethylethylenediamine.

Scheme 2. Development of Arylomycin Analogues: (A) Synthesis of Analogues via Decarboxylative Methods[a] **and (B) MIC Assay of Antibacterial Activity**



B. MIC Assay (μg/mL)

Strain	A-C_{16}	7	9	10	11	12	13
S. aureus[c]	32	>64	0.25	8	32	16	8
S. aureus[d]	32	64	0.125	2	8	16	4
S. epidermidis	0.5	64	4	64	16	2	8
E. coli[e]	8	4	0.06	32	4	8	2
E. coli	>64	>64	0.5	64	32	16	16
Y. pestis	16	32	0.25	16	16	2	8
P. aeruginosa	>64	>64	8	>64	>64	16	>64
K. pneumoniae	>64	>64	0.5	>64	>64	>64	64

[a]Reagents and conditions: (*a*) **3** (1 equiv), AcCl (10 equiv), MeOH, 0 to 25 °C; (*b*) **5** (2 equiv), PyAOP (2 equiv), DIPEA (6 equiv), DMF, 50 °C (82%, 2 steps); (*c*) **6** (1 equiv), LiOH (10 equiv), THF/H_2O, 0 to 25 °C; (*d*) TFA/CH_2Cl_2 (1:6), 0 to 25 °C (41%, 2 steps); (*e*) *N*-Boc-2-bromoethan-1-amine (4 equiv), K_2CO_3 (5 equiv), DMF, 50 °C; (*f*) LiOH (10 equiv), THF/H_2O, 0 to 25 °C (69%, 2 steps); (*g*) TFA/CH_2Cl_2 (1:6), 0 to 25 °C (40%); (*h*) **8** (1 equiv), DIC (1.1 equiv), NHPI (1.1 equiv), CH_2Cl_2, 25 °C; (*i*) and (*k*) see Supporting Information for details. Abbreviations: DIPEA = *N,N*-diisopropylethylamine, DIC = *N,N′*-diisopropylcarbodiimide, NHPI = *N*-hydroxyphthalimide. [b]**6** isolated as a 1:1 mixture of diastereomers at α-C of diaminobutyric acid; all assayed compounds diastereomerically pure in configuration shown (see Supporting Information for details).[19] [c]MRSA USA 300. [d]MRSA COL. [e]*E. coli* BAS901 (perm.).

peptides is provided in the Evans group's efforts toward the synthesis of vancomycin.[6d,17]

Our investigation of this route began with synthesis of the linear tripeptide precursor, which is quickly assembled via amide bond formation between **1** and an NH_2-Ala-Tyr-OMe dipeptide (Scheme 1). This delivered **2** in good yield on multigram scale, enabling a broad screen of conditions known to promote oxidative coupling. First attempts were made with strong metal oxidants (VOF_3, MnO_2, $Pb(OAc)_4$, etc.), which resulted in decomposition of the substrate. Additionally, peroxides, hypervalent iodine reagents, and quinone oxidants all resulted in nonproductive consumption of **2**. Milder metal

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oxidants ($FeCl_3$, $VO(acac)_2$, $K_3[Fe(CN)_6]$, etc.) generally demonstrated no reactivity with **2**, with the exception of CuCl, which produced trace amounts of the desired macrocycle.

This result prompted an extensive investigation of Cu-mediated oxidative coupling, an area of study most prevalent in the synthesis of BINOL and its derivatives. Employing conditions reported by Nakajima,[15b] utilizing [Cu(OH)Cl·TMEDA] in dichloromethane open to the air provided isolable amounts of **3**, albeit in very low yields (ca. 10%). The previously reported "open flask" procedure, where air served as the oxidant, unfortunately could not be applied in our hands since the macrocyclization was found to be sensitive to water. Performing the reactions under a dry oxygen atmosphere resulted in over-oxidation of the product. Because oxygen seemed to be the only competent terminal oxidant (Scheme 1), preformed copper-oxo complexes were generated using O_2 and subsequently reacted with **2** under an inert atmosphere. Screening of copper sources identified $[Cu(MeCN)_4][PF_6]$ as optimal, likely owing to its high solubility in organic solvents. Bidentate tertiary amines were the most competent ligands, with TMEDA ultimately providing the highest yields. Finally, acetonitrile as a solvent gave the best results, even over dichloromethane which is extensively used in similar reactions. These results ultimately point to the formation of a bis(μ-oxo)dicopper(III) species (**O**) (Scheme 1) known to be favored by bidentate amines, weak counteranions, and polar solvents.[18] The optimized conditions are robust and allow macrocyclization of **2** to be performed on a 5 g scale, providing **3** in a 60% isolated yield. To the best of our knowledge, this represents the largest peptide macrocycle to be forged via a Cu-mediated oxidative process. By obviating all prefunctionalizations and several protecting group manipulations en route to the macrocycle, 6 steps were excised from the previous route, bringing the ideality to 63%. Additionally, the yield for the macrocyclization is higher than that of the optimized Suzuki coupling, which provided **4** (with phenols protected as methyl ethers). All of these factors lead to a 6-fold increase in the overall yield (from 4-hydroxyphenylglycine). Metrics aside, the previous route required approximately twice the labor and involved manipulating unstable intermediates across multiple steps.

With large quantities of the macrocycle now readily available, we turned our attention to making derivatives of the arylomycin A structure. In particular, the C-terminal end of the arylomycins is known to hydrogen-bond with the catalytic Ser-Lys dyad of SPase (Figure S1), and only simple amide derivatives have been made to explore optimization.[1c] Starting from **3**, removal of the Boc group and coupling with **5** provided **6**, containing an optimized lipophilic side chain reported previously.[20] While the Cu-mediated macrocyclization yielded a mixture of interconverting atropisomers, appending an amino acid to the hydroxyphenylglycine residue provided only a single atropisomer matching the natural products. Double alkylation of **6** followed by saponification yielded the free acid **8** (Scheme 2). This free acid was then subjected to the decarboxylative Giese reaction recently described by our group (P.S.B.) to yield **10**, **11**, and **12** after deprotection.[21] We also utilized the decarboxylation method to deliver **13** after deprotection. Finally, deprotection of **6** and **8** provided compounds **7** and **9**, respectively.

Antibacterial activity of each analogue, and for comparison that of the previously reported analogue arylomycin A-C_{16},[2] was measured by determining the minimal inhibitory concentration (MIC) against a broad panel of bacteria (Scheme 2B, see Supporting Information for the structure of arylomycin A-C_{16}).[2] Compound **7** had lower activity than arylomycin A-C_{16} against all strains tested, with the exception of a marginal increase in activity against permeablized *E. coli* (BAS901). In agreement with a published patent,[5] **9**, which differs from **7** only by the addition of two alkyl amines to the macrocycle, has impressive activity against intact *E. coli*. Remarkably, we found that **9** also gains significant activity against the important Gram-negative human pathogens *Klebsiella pneumoniae* and *Pseudomonas aeruginosa*. All C-terminal derivatizations resulted in reduced activity, likely due to the loss of stabilizing hydrogen bonds with residues in the active site of SPase. If this is correct, it suggests that the cyano group of **11** is better able to compensate for their loss through the formation of other stabilizing interactions. However, the carboxylate is not required for activity, as demonstrated by **13**, which shows the highest activity of the C-terminally modified derivatives. It is possible that the lack of any substituent could allow for retention of water molecules in the active site that are precluded by a substituent. It is therefore suggested that, in order to retain activity, the substituent should possess specifically oriented hydrogen-bond-acceptor functionality to stably engage the active-site hydrogen-bond donors. Nonetheless, **10**–**13** all maintained reasonable activity against all strains tested except *P. aeruginosa*. This, coupled with the dramatic increase of activity of **7** relative to **9**, highlights the importance of the macrocyclic alkyl amine substituents. The alkyl amines likely increase activity against Gram-negative species via increased penetration through outer-membrane porins. The increased activity against the Gram-positive species is more difficult to understand, as based on structural studies they are predicted to be oriented into solution.[1c] However, these studies do not include the machinery of the Sec channel or other membrane proteins that might be proximal under native physiological conditions. Further exploration of this hypothesis, as well as the effort to develop analogues as therapeutics, will be facilitated by the simple and scalable arylomycin synthesis reported herein.[22] This work is yet another example of how scalable synthesis can aid in the evaluation of promising antibacterial leads.[23]

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/jacs.8b00087.

Experimental procedures including a graphical guide for the key oxidative coupling and analytical data (^1H and ^{13}C NMR, MS) for all new compounds, optimization tables, and bioassay procedures (PDF)

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Notes

The authors declare no competing financial interest.

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■ REFERENCES

(1) (a) Schimana, J.; Gebhardt, K.; Holtzel, A.; Schmid, D. G.; Sussmuth, R.; Muller, J.; Pukall, R.; Fiedler, H. P. *J. Antibiot.* **2002**, *55*, 565−70. (b) Kulanthaivel, P.; Kreuzman, A. J.; Strege, M. A.; Belvo, M. D.; Smitka, T. A.; Clemens, M.; Swartling, J. R.; Minton, K. L.; Zheng, F.; Angleton, E. L.; Mullen, D.; Jungheim, L. N.; Klimkowski, V. J.; Nicas, T. I.; Thompson, R. C.; Peng, S. B. *J. Biol. Chem.* **2004**, *279*, 36250−8. (c) Paetzel, M.; Goodall, J. J.; Kania, M.; Dalbey, R. E.; Page, M. G. *J. Biol. Chem.* **2004**, *279*, 30781−90.

(2) Smith, P. A.; Roberts, T. C.; Romesberg, F. E. *Chem. Biol.* **2010**, *17*, 1223−31.

(3) Tan, Y. X.; Romesberg, F. E. *MedChemComm* **2012**, *3*, 916−925.

(4) (a) Roberts, T. C.; Schallenberger, M. A.; Liu, J.; Smith, P. A.; Romesberg, F. E. *J. Med. Chem.* **2011**, *54*, 4954−63. (b) Therien, A. G.; Huber, J. L.; Wilson, K. E.; Beaulieu, P.; Caron, A.; Claveau, D.; Deschamps, K.; Donald, R. G.; Galgoci, A. M.; Gallant, M.; Gu, X.; Kevin, N. J.; Lafleur, J.; Leavitt, P. S.; Lebeau-Jacob, C.; Lee, S. S.; Lin, M. M.; Michels, A. A.; Ogawa, A. M.; Painter, R. E.; Parish, C. A.; Park, Y. W.; Benton-Perdomo, L.; Petcu, M.; Phillips, J. W.; Powles, M. A.; Skorey, K. I.; Tam, J.; Tan, C. M.; Young, K.; Wong, S.; Waddell, S. T.; Miesel, L. *Antimicrob. Agents Chemother.* **2012**, *56*, 4662−70. (c) Liu, J.; Smith, P. A.; Steed, D. B.; Romesberg, F. *Bioorg. Med. Chem. Lett.* **2013**, *23*, 5654−9.

(5) Roberts, T. C.; Smith, P. A.; Campbell, D.; Duron, S. G.; Higuchi, R. I. Broad spectrum antibiotics. U.S. Patent Application 15/358,100, Nov 21, 2016.

(6) (a) Boger, D. L.; Miyazaki, S.; Kim, S. H.; Wu, J. H.; Castle, S. L.; Loiseleur, O.; Jin, Q. *J. Am. Chem. Soc.* **1999**, *121*, 10004−10011. (b) Boger, D. L.; Miyazaki, S.; Kim, S. H.; Wu, J. H.; Loiseleur, O.; Castle, S. L. *J. Am. Chem. Soc.* **1999**, *121*, 3226−3227. (c) Nicolaou, K. C.; Natarajan, S.; Li, H.; Jain, N. F.; Hughes, R.; Solomon, M. E.; Ramanjulu, J. M.; Boddy, C. N. C.; Takayanagi, M. *Angew. Chem., Int. Ed.* **1998**, *37*, 2708−2714. (d) Evans, D. A.; Wood, M. R.; Trotter, B. W.; Richardson, T. I.; Barrow, J. C.; Katz, J. L. *Angew. Chem., Int. Ed.* **1998**, *37*, 2700−2704.

(7) Roberts, T. C.; Smith, P. A.; Cirz, R. T.; Romesberg, F. E. *J. Am. Chem. Soc.* **2007**, *129*, 15830−15838.

(8) Dufour, J.; Neuville, L.; Zhu, J. *Synlett* **2008**, *2008*, 2355−2359.

(9) Gaich, T.; Baran, P. S. *J. Org. Chem.* **2010**, *75*, 4657−73.

(10) Liu, W. T.; Kersten, R. D.; Yang, Y. L.; Moore, B. S.; Dorrestein, P. C. *J. Am. Chem. Soc.* **2011**, *133*, 18010−3.

(11) (a) Gutekunst, W. R.; Baran, P. S. *Chem. Soc. Rev.* **2011**, *40*, 1976−91. (b) Brückl, T.; Baxter, R. D.; Ishihara, Y.; Baran, P. S. *Acc. Chem. Res.* **2012**, *45*, 826−839.

(12) Barton, D. H. R.; Deflorin, A. M.; Edwards, O. E. *J. Chem. Soc.* **1956**, 530−534.

(13) (a) Takada, T.; Arisawa, M.; Gyoten, M.; Hamada, R.; Tohma, H.; Kita, Y. *J. Org. Chem.* **1998**, *63*, 7698−7706. (b) Armstrong, D. R.; Cameron, C.; Nonhebel, D. C.; Perkins, P. G. *J. Chem. Soc., Perkin Trans. 2* **1983**, *2*, 563−568.

(14) (a) Bowden, K.; Reece, C. H. *J. Chem. Soc.* **1950**, 2249. (b) Bringmann, G.; Tasler, S. *Tetrahedron* **2001**, *57*, 331−343. (c) Feldman, K. S.; Ensel, S. M. *J. Am. Chem. Soc.* **1994**, *116*, 3357−3366. (d) Richieu, A.; Peixoto, P. A.; Pouysegu, L.; Deffieux, D.; Quideau, S. *Angew. Chem., Int. Ed.* **2017**, *56*, 13833−13837.

(15) (a) Feringa, B.; Wynberg, H. *Bioorg. Chem.* **1978**, *7*, 397−408. (b) Nakajima, M.; Miyoshi, I.; Kanayama, K.; Hashimoto, S.-i.; Noji, M.; Koga, K. *J. Org. Chem.* **1999**, *64*, 2264−2271. (c) Lee, Y. E.; Cao, T.; Torruellas, C.; Kozlowski, M. C. *J. Am. Chem. Soc.* **2014**, *136*, 6782−5. (d) Hwang, D.-R.; Chen, C.-P.; Uang, B.-J. *Chem. Commun.* **1999**, 1207−1208. (e) Barhate, N. B.; Chen, C.-T. *Org. Lett.* **2002**, *4*, 2529−2532. (f) Shalit, H.; Libman, A.; Pappo, D. *J. Am. Chem. Soc.* **2017**, *139*, 13404.

(16) (a) Elsler, B.; Schollmeyer, D.; Dyballa, K. M.; Franke, R.; Waldvogel, S. R. *Angew. Chem., Int. Ed.* **2014**, *53*, 5210−5213. (b) Ding, H.; DeRoy, P. L.; Perreault, C.; Larivée, A.; Siddiqui, A.; Caldwell, C. G.; Harran, S.; Harran, P. G. *Angew. Chem., Int. Ed.* **2015**, *54*, 4818−4822.

(17) (a) Evans, D. A.; Dinsmore, C. J. *Tetrahedron Lett.* **1993**, *34*, 6029−6032. (b) Evans, D. A.; Dinsmore, C. J.; Evrard, D. A.; DeVries, K. M. *J. Am. Chem. Soc.* **1993**, *115*, 6426−6427.

(18) Mirica, L. M.; Ottenwaelder, X.; Stack, T. D. *Chem. Rev.* **2004**, *104*, 1013−45.

(19) After the conclusion of this study, our collaborators at Genentech brought to our attention that coupling of diaminobutyric acid with a carbamate protecting group rather than an appended tail yields diastereomerically pure product.

(20) Schwarz, J. B.; Ly, C.; Crawford, J.; Roberts, T. C.; Smith, P. A.; Higuchi, R. I.; Paraselli, P.; Bergeron, P.; Koehler, M. F. T.; Hu, H. Macrocyclic broad spectrum antibiotics. Int. Patent WO2015179441A3, May 19, 2015.

(21) Qin, T.; Malins, L. R.; Edwards, J. T.; Merchant, R. R.; Novak, A. J.; Zhong, J. Z.; Mills, R. B.; Yan, M.; Yuan, C.; Eastgate, M. D.; Baran, P. S. *Angew. Chem., Int. Ed.* **2017**, *56*, 260−265.

(22) Baran, P. S.; Romesberg, F. E.; Peters, D. S. Synthesis of the Arylomycin Macrocyclic Core. Int. Patent WO17/214534, Dec 14, 2017.

(23) (a) Wright, P. M.; Seiple, I. B.; Myers, A. G. *Angew. Chem., Int. Ed.* **2014**, *53*, 8840−69. (b) Sun, C.; Wang, Q.; Brubaker, J. D.; Wright, P. M.; Lerner, C. D.; Noson, K.; Charest, M.; Siegel, D. R.; Wang, Y. M.; Myers, A. G. *J. Am. Chem. Soc.* **2008**, *130*, 17913−27. (c) Seiple, I. B.; Zhang, Z.; Jakubec, P.; Langlois-Mercier, A.; Wright, P. M.; Hog, D. T.; Yabu, K.; Allu, S. R.; Fukuzaki, T.; Carlsen, P. N.; Kitamura, Y.; Zhou, X.; Condakes, M. L.; Szczypiński, F. T.; Green, W. D.; Myers, A. G. *Nature* **2016**, *533*, 338. (d) Okano, A.; Isley, N. A.; Boger, D. L. *Proc. Natl. Acad. Sci. U. S. A.* **2017**, *114*, E5052−E5061. (e) Murphy, S. K.; Zeng, M.; Herzon, S. B. *Org. Lett.* **2017**, *19*, 4980−4983. (f) Zeng, M.; Murphy, S. K.; Herzon, S. B. *J. Am. Chem. Soc.* **2017**, *139*, 16377−16388. (g) Rodriguez, R. A.; Barrios Steed, D.; Kawamata, Y.; Su, S.; Smith, P. A.; Steed, T. C.; Romesberg, F. E.; Baran, P. S. *J. Am. Chem. Soc.* **2014**, *136*, 15403−15413. (h) Li, Q.; Seiple, I. B. *J. Am. Chem. Soc.* **2017**, *139*, 13304−13307. (i) Nicolaou, K. C.; Pulukuri, K. K.; Rigol, S.; Buchman, M.; Shah, A. A.; Cen, N.; McCurry, M. D.; Beabout, K.; Shamoo, Y. *J. Am. Chem. Soc.* **2017**, *139*, 15868−15877. (j) Steele, A. D.; Keohane, C. E.; Knouse, K. W.; Rossiter, S. E.; Williams, S. J.; Wuest, W. M. *J. Am. Chem. Soc.* **2016**, *138*, 5833−5836.

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J. Am. Chem. Soc. 2018, 140, 2072−2075