Total Synthesis of Dragocins A–C via Electrochemical Cyclization

Brendyn P. Smith‡, Nathanyal J. Truax‡, Alexandros S. Pollatos, Michael Meanwell†, Pranali Bedekar, Alberto F. Garrido-Castro§, and Phil S. Baran

Department of Chemistry, Scripps Research, La Jolla, California 92037, United States

ABSTRACT: The first total synthesis of dragocins A–C, remarkable natural products containing an unusual C-4'oxidized ribose architecture bridged by a polyhydroxylated pyrrolidine, is presented through a route featuring a number of uncommon maneuvers. Several generations towards the target molecules are presented including the spectacular failure of a key C–H oxidation on a late-stage intermediate. The final route features rapid, stereocontrolled access to a densely functionalized pyrrolidine and an unprecedented diastereoselective oxidative electrochemical cyclization to forge the hallmark 9-membered ring. Preliminary studies suggest this electrochemical oxidation protocol is generally useful.

Dragocins A–C (**1A-1C**, Figure 1) belong to a peculiar hybrid structural class of secondary metabolites.[1] These intriguing molecules were isolated off the Caribbean coast near Boca del Drago from a marine cyanobacterium and were found to possess modest cytotoxic activity against human lung cancer cells (H-460). Thus far, the only related natural product to the dragocin family is AB-3217A[2] (**2**) (previously synthesized in 26 steps by Nakata[3]), an anti-mite substance which features a near identical framework, but lacks the unique C-4' oxidation found on dragocins A–C. Notably, this C-4' functionalization is unprecedented in the natural product space, with the exception of nucleocidin,[4] a C-4' fluorinated nucleoside. Aside from this unusual feature, the dragocins contain an alluring central 9-membered ring system which consists of a highly oxidized pyrrolidine harboring four contiguous stereocenters and an electron-rich arene, all cemented upon a polar ribose moiety. In this Communication we disclose a 13-14 step route to dragocins A–C enabled by an unprecedented electrochemical oxidative cyclization.

Secondary metabolites containing more than eight atoms in a skeletal ring have captured the imagination of synthetic organic chemists for nearly a century. Among ring systems containing eight or more atoms, medium-sized (eight to eleven atoms) rings are regarded as the most difficult to access due to entropic and enthalpic barriers.[5] Consequently, embarking on the syntheses of such complex structures requires careful consideration of route choreography, strategy, and tactics for success. Practitioners engaging in such pursuits have few available general strategies for such ring formations: ring-expansion, ring-contraction, and direct cyclization of the acyclic precursors.[6] However, reduction of these strategies to practice is often not straightforward.

With this historical context in mind, multiple retrosynthetic plans hinging upon disparate cyclization strategies were pursued as briefly illustrated in Figure 1 and more extensively described in the SI. For instance, direct construction of the

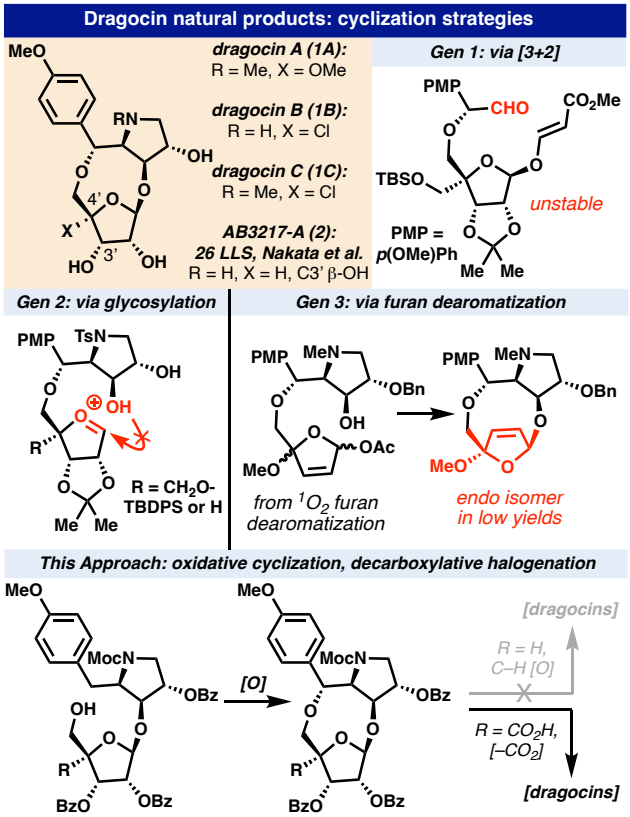
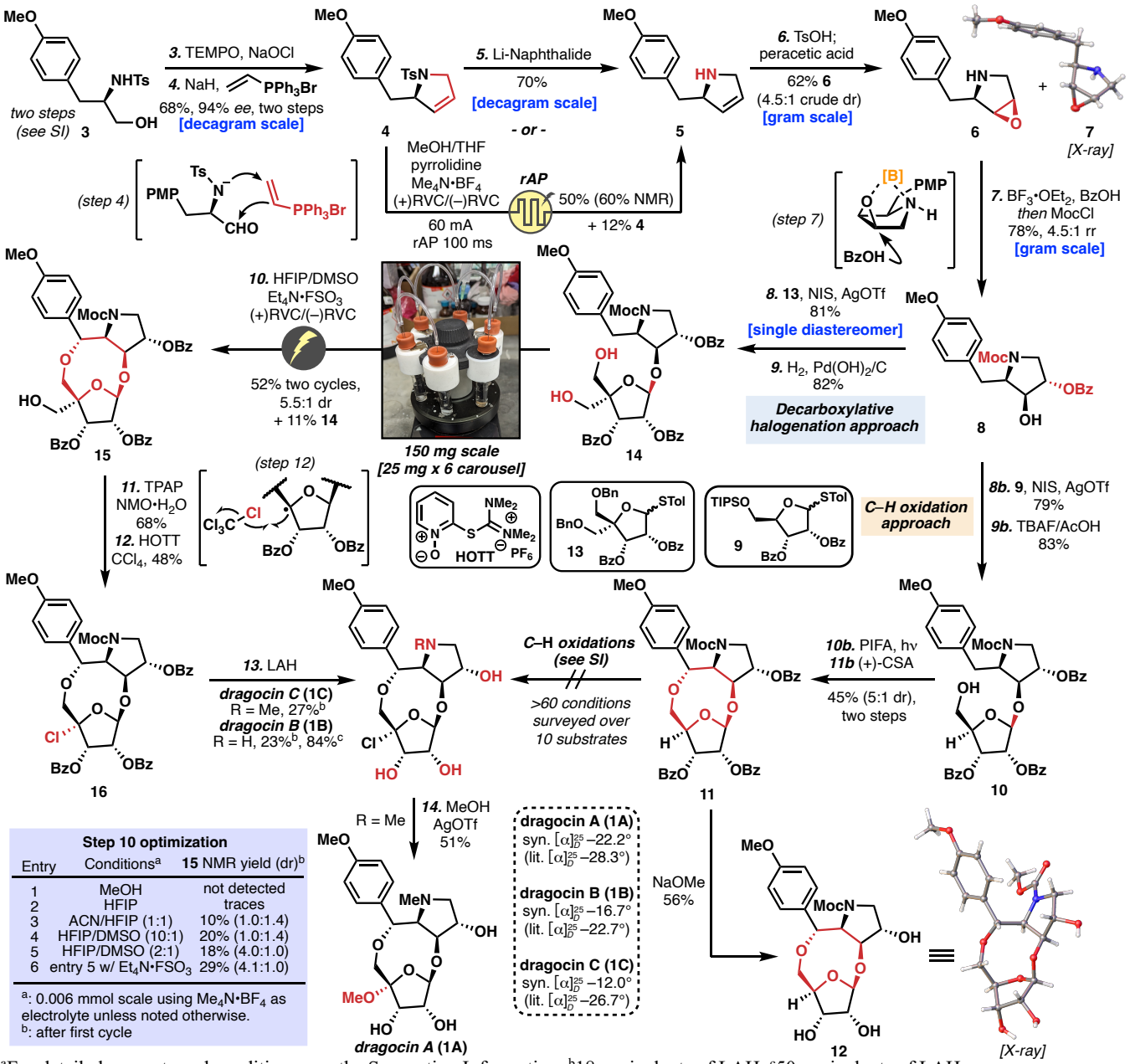


Figure 1. The dragocin natural products (**1A-1C**) and related natural product AB-3217A (**2**). Failed cyclization strategies towards the hallmark skeleton of the dragocin family and the final successful approach.

https://doi.org/10.26434/chemrxiv-2024-mvf2m **ORCID:** https://orcid.org/0000-0001-9193-9053

Scheme 1. Total synthesis of dragocins A–C (1A-1C) and the failed late-stage C–H oxidation strategy[a]



Step 10 optimization

Entry	Conditions[a]	15 NMR yield (dr)[b]
1	MeOH	not detected
2	HFIP	traces
3	ACN/HFIP (1:1)	10% (1.0:1.4)
4	HFIP/DMSO (10:1)	20% (1.0:1.4)
5	HFIP/DMSO (2:1)	18% (4.0:1.0)
6	entry 5 w/ $Et_4N•FSO_3$	29% (4.1:1.0)

[a]: 0.006 mmol scale using $Me_4N•BF_4$ as electrolyte unless noted otherwise.
[b]: after first cycle

[a]For detailed reagents and conditions, see the Supporting Information. [b]18 equivalents of LAH. [c]50 equivalents of LAH.

hallmark 9-membered ring using a bold dipolar cycloaddition approach (Gen 1) failed due to instability of the acyclic precursor. Next, intramolecular glycosylation (the successful strategy employed by Nakata) was explored, but unfortunately the completely functionalized precursor did not form the desired ring (Gen 2). Reasoning that an abundance of functional groups prevented cyclization, an oxidative furan-based approach was evaluated which also failed due to the formation (in low yield) of the undesired endo-cyclization product (Gen 3).

Ultimately, the final synthetic design was guided by plastic models of potential precursors suggesting that glycosylation prior to cyclization would render the system conformationally poised to furnish the desired skeletal ring. Further, the electron-rich arene opened the possibility of installing the requisite benzylic ether at a late stage via stereoselective oxidative cyclization. The challenging C-4' oxidation state was envisaged to arrive either through a late-stage C–H oxidation or through decarboxylative functionalization. As both strategies relied on similar intermediates they were pursued in parallel.

Scheme 1 presents the realization of these plans resulting in the first total synthesis of dragocins A–C (**1A–1C**). A scalable and enantiocontrolled route to the linchpin pyrrolidine **8** was required to evaluate both approaches. Historically, the routes to similar structures are either over 10 steps or are plagued with exhaustive functional group interconversions.[7] As such, distinct strategies were evaluated (see SI for details), all of which failed due to stereochemical challenges, protecting group complications, or time-consuming sequences. A simple and direct stereoselective five-step route to **8** was devised starting from D-tyrosine-derived alcohol **3** (two steps from commercial). Thus, annulation of the corresponding aldehyde (TEMPO, NaOCl, used crude) with triphenylvinylphosphonium bromide[8] delivered dihydropyrrole **4** in 68% yield (94% *ee*). Subsequent Ts-

https://doi.org/10.26434/chemrxiv-2024-mvf2m **ORCID:** https://orcid.org/0000-0001-9193-9053

removal was accomplished using metal-free electrochemical Birch conditions enabled by rapid alternating polarity[9] (rAP, 50% yield). These rAP-based conditions for Ts-amide deprotection are without precedent and represent a safer alternative to conventional Li-naphthalide (which was employed for scale-up before rAP conditions were developed, see SI). This also constitutes the first use of the rAP waveform in total synthesis. Subsequent Brønsted acid-assisted diastereoselective epoxidation of **5** (62% **6**, 4.5:1 crude dr) proved superior to epoxidation of **4** which led to a ca. 1:1 inseparable mixture of epoxide diastereomers in low conversion. Undesired diastereomer **7** was separable at this point, which set the stage for a free amine-assisted Lewis-acid mediated epoxide opening of **6** to furnish the key pyrrolidine **8** after *in situ* Moc protection (78% yield, 4.5:1 rr, gram-scale).

With key pyrrolidine **8** in hand, two distinct approaches to the natural product were explored, differentiated by the means with which the C-4'oxidation would be installed: (1) C–H oxidation and (2) decarboxylative chlorination. To set the stage for the C–H oxidation, glycosylation with donor **9** (AgOTf, NIS, 79% yield) followed by desilylation (TBAF/AcOH, 83%) delivered cyclization precursor **10**. The electron-rich benzylic system present in **10** is innately primed to achieve a benzylic C–H functionalization to provide the 9-membered ring through either direct or indirect means. For instance, the use of DDQ (DCE, 100 °C, μW) led to 3-10% yield of the desired product **11** but unfortunately was not reproducible or scalable despite extensive efforts. Switching to an I(III)-based oxidant (PIFA, benzene, hν)[10] delivered a mixture of diastereomeric benzylic trifluoroacetates that were purified before exposure to (+)-CSA (1.0 equiv, ACN, 60 °C) to afford **11** in 45% yield (over two steps) as a 5:1 mixture of diastereomers. This two-step process was serviceable for exploring the downstream C-4' oxidation chemistry. The structure of **11** was confirmed by X-ray crystallographic analysis after debenzoylation (**12**).

At this juncture the pivotal C–H oxidation of the tertiary C–H bond at C-4' was explored using nearly every set of conditions that could conceivably function in such a chemoselectively demanding setting. Thus, radical, dioxirane, halogenative, directing group-based, and others were evaluated to no avail (across a range of differentially protected analogs, see SI). Even enzymatic systems were studied which so far have proven fruitless.[11] With this spectacular failure in hand, attention thus turned to the decarboxylative chlorination approach.

Returning to intermediate **8**, glycosylation with donor **13** (AgOTf, NIS, 81% yield, single diastereomer) and debenzylation (H_2, $Pd(OH)_2$, 82% yield) afforded cyclization precursor **14**. In this instance, the PIFA-based conditions that allowed for a two-step cyclization for substrate **9**, functioned poorly on **14** delivering **15** in 32% yield (1.5:1 crude dr, diastereomers separable). As this two-step sequence was inconvenient for material throughput and exploration of the downstream steps, an alternative tactic was pursued. Specifically, a chemoselective electrochemical 9-membered etherification-cyclization was explored. Remarkably, anodic oxidation of key acyclic precursor **14** proceeded smoothly in the presence of multiple electron-rich C–H bonds and a pyrrolidine moiety (Shono products[12] not observed) to deliver the 9-membered skeleton in 52% yield with a 5.5:1 dr at the benzylic position (44% isolated **15**) after two cycles.

The development of optimized conditions for this unique electrochemical oxidative cyclization warrants further comment. Initial electrolysis of **14** to electrolysis in methanol or HFIP resulted in benzylic solvent trapping, alongside trace **15** in the latter case. Nevertheless, the clean benzylic oxidation was encouraging, and after screening a series of solvent mixtures, it was discovered that ACN:HFIP (1:1) afforded a 1:1.4 ratio of diastereomers (undesired favored, 26% total NMR yield). At this point, nearly 100 additional conditions were explored including waveform, temperature, electrolytes, solvents, electrodes, current density, and additives (see SI for details). These studies revealed that the desired product yield was diminished at higher conversions due to overoxidation. Therefore, all further efforts were focused on the suppression of overoxidation, reasoning that a solvent with a suitable oxidation window[13] might prevent undesired over-reactivity. This hypothesis proved fruitful, with substantial suppression of the overoxidized byproducts when enlisting an HFIP:DMSO mixture. Careful titration of the DMSO quantity proved essential to maintain oxidative efficiency whilst suppressing the formation of undesired products. More facile over-oxidation of the desired diastereomer was observed as evidenced by an apparent drop in dr at higher conversions, so reactions were run to partial conversion (ca. 50%) followed by recycling. Finally, the reaction was further enhanced using an uncommon ammonium fluorosulfate electrolyte.

With the complete skeleton of the dragocin natural product family in hand, bearing a synthetic handle at C-4', a classic Barton decarboxylative chlorination[14] was pursued. Oxidation of the free primary alcohol in **15** to the carboxylic acid was achieved using TPAP•NMO (69% yield). Conveniently, simple exposure of this acid to HOTT[15] in CCl_4 at 80 °C led smoothly to the elusive tertiary chloride **16** (48% isolated yield). In general, Barton decarboxylative chlorinations involve the use of acid chlorides or coupling reagents such as DCC,[16] all of which were unsuccessful in our hands, likely due to the sterically encumbered environment. The use of HOTT in CCl_4 followed by simple heating, although a seemingly incremental modification, proved essential in this case. To complete the synthesis of dragocin B (**1B)** and C (**1C**), global reduction using LAH was successful in delivering the natural products (**1B:** observed $[a]_D^{25}$–16.7°; lit. $[a]_D^{25}$–22.7° **1C:** observed $[a]_D^{25}$–12.0°; lit. $[a]_D^{25}$–26.7°). As the related natural product dragocin A bears a methoxy group at the C-4' position, the exchange of the C-4'-Cl to -OMe was explored. To this end, preparing methanolic solutions of **1C** led to only traces of **1A** after several hours, even at elevated temperatures. Thus, the addition of halophilic activators was explored, and it was found that simple exposure of **1C** to AgOTf in refluxing methanol furnished **1A** in 51% yield ($[a]_D^{25}$–22.2°; lit. $[a]_D^{25}$–28.3°)

Returning to the pivotal electrochemical cyclization reaction, the premise that these conditions may be amenable towards the preparation of benzylic β-hydroxy amino acids was explored (Figure 2). Typical conditions employed for such a transformation often suffer from poor reactivity[17] or require a stepwise protocol.[18] Slight modification of the conditions presented above proved successful in generating a small series of oxazolidinones which may prove useful in the synthesis of functionalized β-hydroxy amino acid building blocks (**17-20**). A more in-depth study of this method is therefore warranted to fully tease out its generality.

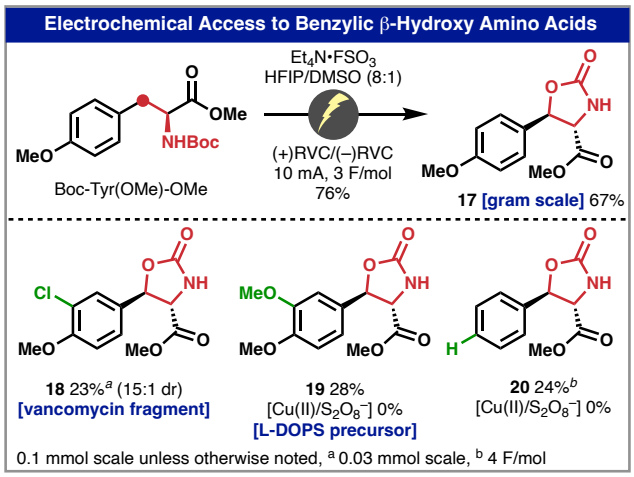


Figure 2. Application of the benzylic electrochemical oxidative C–H functionalization reaction towards β-hydroxy amino acid building blocks.

A simple solution to the challenge posed by the dragocin natural product family has been presented. The successful route features a number of interesting transformations that may find application in other settings, such as: (1) rapid, stereocontrolled entry to polyhydroxylated pyrrolidines through diastereoselective and regioselective reactions, (2) rAP-mediated electrochemical metal-free tosylamide removal, (3) one-pot decarboxylative Barton chlorination, and, most remarkably, (4) oxidative, diastereoselective C–H functionalizing electrochemical cyclization to form a 9-membered ring.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website.

Failed routes, optimization, detailed experimental procedures, and analytical data

Accession Codes

CCDC 2264982 and 2218603 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

Phil S. Baran − *Department of Chemistry, Scripps Research, La Jolla, California 92037, United States;* orcid.org/0000-0001-9193-9053; Email: pbaran@scripps.edu

Authors

Brendyn P. Smith − *Department of Chemistry, Scripps Research, La Jolla, California 92037, United States; orcid.org/0009-0006-4619-9547*

Nathanyal J. Truax − *Department of Chemistry, Scripps Research, La Jolla, California 92037, United States; orcid.org/0000-0002-8510-2326*

Alexandros S. Pollatos − *Department of Chemistry, Scripps Research, La Jolla, California 92037, United States; orcid.org/0000-0002-3688-3218*

Michael Meanwell − *Department of Chemistry, Scripps Research, La Jolla, California 92037, United States; orcid.org/0000-0002-4217-8478*

Pranali Bedekar − *Department of Chemistry, Scripps Research, La Jolla, California 92037, United States*

Alberto Garrido-Castro − *Department of Chemistry, Scripps Research, La Jolla, California 92037, United States; orcid.org/0000-0001-7262-7986*

Present Addresses

[†]Department of Chemistry, University of Alberta, Edmonton, Canada

[§]Laboratorium für Organische Chemie, ETH Zürich, Vladimir-Prelog-Weg 3, HCI, 8093 Zürich, Switzerland

Author Contributions

‡B.P.S. and N.J.T. contributed equally to this work.

Notes

The authors declare no competing financial interest.

ACKNOWLEDGMENT

Financial support of this work was provided by NIH (GM-118176). A.S.P. was supported by NSF Graduate Research Fellowship (DGE2235200). P.B. was supported by NSF Graduate Research Fellowship (DGE1842471 and DGE2235200). M.M. was supported by a Banting Postdoctoral Fellowship (NSERC). A.F.G.-C. thanks the European Commission for a Marie Skłodowska-Curie Global Fellowship (H2020-MSCA-IF-2020-GF-101027337-CatToSat). The authors are grateful to Dr. Dee-Hua Huang, Dr. Laura Pasternack, and Dr. Gerard Kroon (Scripps Research) for assistance with NMR spectroscopy; to Dr. Jason Chen, Brittany Sanchez, Quynh Nguyen, and Jason Lee (Scripps Research ASF) for assistance with UPLC and HRMS analysis; to The Center for Metabolomics and Mass Spectrometry, Scripps Research for HRMS analysis; and to Dr. Milan Gembicky and Dr. Jake Bailey (UCSD) for X-ray crystallographic analysis. We would also like to acknowledge Gohith Boga and Tim Oleksenko for assistance with starting material preparation. Professor Hans Renata and Junhong Yang (Rice University) are acknowledged for investigations involving enzymatic C–H oxidations. Finally, we thank Professor Bill Gerwick (Scripps Institute for Oceanography, Skaggs School of Pharmacy and Pharmaceuticals, UCSD) for prompt correspondences regarding the availability of authentic dragocin samples.

REFERENCES

(1) Choi, H.; Engene, N.; Byrum, T.; Hwang, S.; Oh, D. C.; Gerwick, W. H. Dragocins A-D, Structurally Intriguing Cytotoxic Metabolites from a Panamanian Marine Cyanobacterium. *Org. Lett.* **2019**, *21*, 266-270. DOI: 10.1021/acs.orglett.8b03712

(2) Kanbe, K.; Mimura, Y.; Tamamura, T.; Yatagai, S.; Sato, Y.; Takahashi, A.; Sato, K.; Naganawa, H.; Nakamura, H.; Takeuchi, T.; Iitaka, Y. AB3217-A, a novel anti-mite substance produced by a strain of Streptomyces platensis. *J. Antibiot.* **1992**, *45*, 458-464. DOI: 10.7164/antibiotics.45.458

(3) (a) Nakata, M.; Tamai, T.; Kamio, T.; Kinoshita, M.; Tatsuta, K. The Total Synthesis of AB3217-A, a Novel Antimite Substance, Via Intermolecular Etherification and Intramolecular Glycosylation. *Bull. Chem. Soc. Jpn.* **1994**, *67*, 3057-3066. DOI: DOI 10.1246/bcsj.67.3057. (b) Nakata, M.; Tamai, T.; Kamio, T.; Kinoshita, M.; Tatsuta, K. Total Synthesis of AB3217-A, a Novel Antimite Substance, Via Intramolecular Glycosylation.

Tetrahedron Lett. **1994**, *35*, 3099-3102. DOI: 10.1016/S0040-4039(00)76839-0
(4) Thomas, S. O.; Singleton, V. L.; Lowery, J. A.; Sharpe, R. W.; Pruess, L. M.; Porter, J. N.; Mowat, J. H.; Bohonos, N. Nucleocidin, a new antibiotic with activity against Trypanosomes. *Antibiot. Annu.* **1956**, 716-721.
(5) (a) Reyes, R. L.; Iwai, T.; Sawamura, M. Construction of Medium-Sized Rings by Gold Catalysis. *Chem. Rev.* **2021**, *121*, 8926-8947. DOI: 10.1021/acs.chemrev.0c00793. (b) Kleinke, A. S.; Webb, D.; Jamison, T. F. Recent progress in the synthesis of oxepanes and medium ring ethers. *Tetrahedron* **2012**, *68*, 6999-7018. DOI: 10.1016/j.tet.2012.05.081. (c) Illuminati, G.; Mandolini, L. Ring-Closure Reactions of Bifunctional Chain Molecules. *Acc. Chem. Res.* **1981**, *14*, 95-102. DOI: 10.1021/ar00064a001
(6) Huber, T.; Wildermuth, R. E.; Magauer, T. 9-Membered Carbocycles: Strategies and Tactics for their Synthesis. *Chem. Eur. J.* **2018**, *24*, 12107-12120. DOI: 10.1002/chem.201705919
(7) (a) Iida, H.; Yamazaki, N.; Kibayashi, C. Highly Selective Total Synthesis of Enantiomerically Pure (-)-Anisomycin. *J. Org. Chem.* **1986**, *51*, 1069-1073. DOI: 10.1021/jo00357a023. (b) Chandrasekhar, S.; Ramachandar, T.; Reddy, M. V. An efficient synthesis of (-)-deacetylanisomycin starting from D-tyrosine. *Synthesis* **2002**, 1867-1870. DOI: 10.1055/s-2002-33904 (c) Zeng, J.; Zhang, Q.; Zhang, H. K.; Chen, A. Q. Practical synthesis of dihydroxybutyrolactols as chiral C building blocks and their application to the synthesis of polyhydroxylated alkaloids. *RSC Adv.* **2013**, *3*, 20298-20307. DOI: 10.1039/c3ra43232g. (d) Kim, J. H.; Curtis-Long, M. J.; Seo, W. D.; Ryu, Y. B.; Yang, M. S.; Park, K. H. Stereodivergent syntheses of anisomycin derivatives from D-tyrosine. *J. Org. Chem.* **2005**, *70*, 4082-4087. DOI: 10.1021/jo050079w. (e) Baer, H. H.; Zamkanei, M. Stereospecific Synthesis of (-)-Anisomycin from D-Galactose. *J. Org. Chem.* **1988**, *53*, 4786-4789. DOI: 10.1021/jo00255a022. (f) Reddy, J. S.; Kumar, A. R.; Rao, B. V. A new approach to (+)-anisomycin. *Tetrahedron: Asymmetry* **2005**, *16*, 3154-3159. DOI: 10.1016/j.tetasy.2005.08.039. (g) Harit, V. K.; Ramesh, N. G. A common strategy towards the synthesis of 1,4-dideoxy-1,4-imino-L-xylitol, deacetyl (+)-anisomycin and amino-substituted piperidine iminosugars. *Carbohydr. Res.* **2020**, *492*. DOI: 10.1016/j.carres.2020.107988
(8) Burley, I.; Hewson, A. T. Enantiospecific Synthesis of 3-Pyrrolines - a Route to Novel Polyhydroxylated Pyrrolidines. *Tetrahedron Lett.* **1994**, *35*, 7099-7102. DOI: 10.1016/0040-4039(94)88236-3
(9) (a) Kawamata, Y.; Hayashi, K.; Carlson, E.; Shaji, S.; Waldmann, D.; Simmons, B. J.; Edwards, J. T.; Zapf, C. W.; Saito, M.; Baran, P. S. Chemoselective Electrosynthesis Using Rapid Alternating Polarity. *J. Am. Chem. Soc.* **2021**, *143*, 16580-16588. DOI: 10.1021/jacs.1c06572. (b) Hayashi, K.; Griffin, J.; Harper, K. C.; Kawamata, Y.; Baran, P. S. Chemoselective (Hetero)Arene Electroreduction Enabled by Rapid Alternating Polarity. *J. Am. Chem. Soc.* **2022**, *144*, 5762-5768. DOI: 10.1021/jacs.2c02102
(10) Sakamoto, R.; Inada, T.; Selvakumar, S.; Moteki, S. A.; Maruoka, K. Efficient photolytic C-H bond functionalization of alkylbenzene with hypervalent iodine(III) reagent. *Chem. Commun.* **2016**, *52*, 3758-3761. DOI: 10.1039/c5cc07647a
(11) Personal communication with Professor Hans Renata (Rice University)
(12) Shono, T.; Hamaguchi, H.; Matsumura, Y. Electroorganic Chemistry. XX. Anodic-Oxidation of Carbamates. *J. Am. Chem. Soc.* **1975**, *97*, 4264-4268. DOI: 10.1021/ja00848a020
(13) Schotten, C.; Nicholls, T. P.; Bourne, R. A.; Kapur, N.; Nguyen, B. N.; Willans, C. E. Making electrochemistry easily accessible to the synthetic chemist. *Green Chem.* **2020**, *22*, 3358-3375. DOI: 10.1039/d0gc01247e
(14) Barton, D. H. R.; Crich, D.; Motherwell, W. B. A Practical Alternative to the Hunsdiecker Reaction. *Tetrahedron Lett.* **1983**, *24*, 4979-4982. DOI: 10.1016/S0040-4039(01)99826-0
(15) Garner, P.; Anderson, J. T.; Dey, S.; Youngs, W. J.; Galat, K. S-(1-Oxido-2-pyridinyl)-1,1,3,3-tetramethylthiouronium Hexafluorophosphate. A New Reagent for Preparing Hindered Barton Esters. *J. Org. Chem.* **1998**, *63*, 5732-5733. DOI: 10.1021/jo980870n
(16) Varenikov, A.; Shapiro, E.; Gandelman, M. Decarboxylative Halogenation of Organic Compounds. *Chem. Rev.* **2021**, *121*, 412-484. DOI: 10.1021/acs.chemrev.0c00813
(17) Shimamoto, K.; Ohfune, Y. A New Entry to the Synthesis of β-Hydroxytyrosines Via a Novel Benzylic Hydroxylation. *Tetrahedron Lett.* **1988**, *29*, 5177-5180. DOI: 10.1016/S0040-4039(00)80712-1
(18) Crich, D.; Banerjee, A. Expedient synthesis of β-hydroxy-α-amino acid derivatives:: Phenylalanine, tyrosine, histidine, and tryptophan. *J. Org. Chem.* **2006**, *71*, 7106-7109. DOI: 10.1021/jo061159i

Authors are required to submit a graphic entry for the Table of Contents (TOC) that, in conjunction with the manuscript title, should give the reader a representative idea of one of the following: A key structure, reaction, equation, concept, or theorem, etc., that is discussed in the manuscript. Consult the journal's Instructions for Authors for TOC graphic specifications.

Insert Table of Contents artwork here