Enantioselective Synthesis of Azamerone

Matthew L. Landry, Grace M. McKenna, Noah Z. Burns*

Department of Chemistry, Stanford University, Stanford, California 94305, United States

ABSTRACT: A concise and selective synthesis of the dichlorinated meroterpenoid azamerone is described. The paucity of tactics for the synthesis of chiral organochlorides motivated the development of unique strategies for accessing these motifs in enantioenriched forms. The route features a novel enantioselective chloroetherification reaction, a Pd-catalyzed cross-coupling between a quinone diazide and a boronic hemiester, and a late-stage tetrazine [4+2]-cycloaddition/oxidation cascade.

The napyradiomycins are a diverse class of halogenated meroterpenoids that have been isolated from terrestrial and marine actinomycetes (Figure 1A).[1] Initial isolation efforts were driven by a desire to identify novel antibiotic scaffolds; the napyradiomycins have since demonstrated potent inhibition of gastric (H^+-K^+)-ATPase, nonsteroidal estrogen antagonism, cancer cell cytotoxicities, and activity against Gram-positive bacteria.[1c-f] Of the over 40 members within this class, only napyradiomycin A1 has succumbed to synthesis (**2**, Figure 1A).[2] Syntheses of more highly oxidized members of the napyradiomycins (e.g. **1** and **3**, Figure 1A), which feature densely functionalized, chiral halocycle appendages, remain elusive, representing an exciting arena for synthetic development.

Azamerone is structurally unique among the napyradiomycins. It is the lone example of a phthalazinone-containing natural product and only the second known example of a pyridazine-containing natural product.[3] Moore has postulated that this nitrogen–nitrogen bond-containing heterocycle arises from oxidative rearrangement of SF2415A1 (**5**) via intermediate **6** (Figure 1B).[3] In addition to its unusual hetereocycle, azamerone's highly oxidized structure, diversity of heteroatoms, two chiral tertiary alcohols, and two distinct chlorine-bearing stereogenic centers pose significant synthetic challenges. To address these demanding structural elements, we devised a convergent synthesis of azamerone. We envisaged that azamerone could be retrosynthetically traced to a chlorobenzopyran, tetrazine, and chlorocyclohexane of general forms **7**, **8**, and **9** (Figure 1C). A challenging enantioselective chloroetherification on trisubstituted olefin-containing hydroxyquinone **10**, a hindered carbon–carbon bond formation between **9** and **7**, and an electronically mismatched late-stage tetrazine Diels–Alder reaction were thus identified as the key challenges for this chemical synthesis.

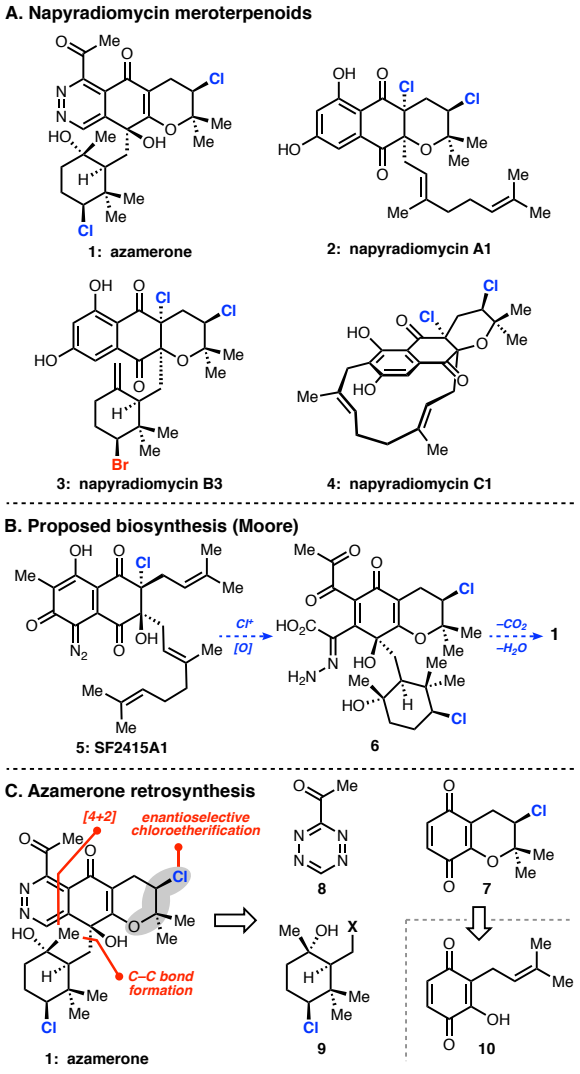
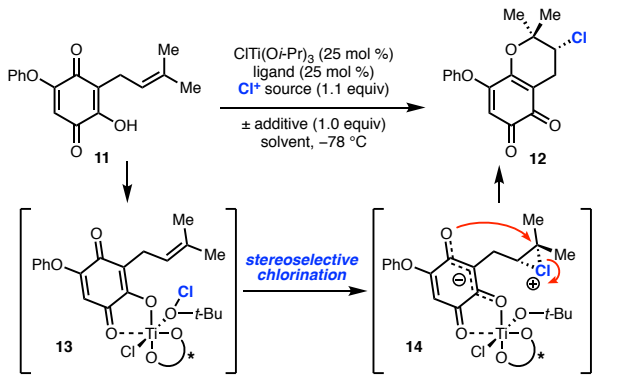


Figure 1. (**A**) Representative napyradiomycin meroterpenoids. (**B**) Proposed biosynthesis of azamerone. (**C**) Retrosynthetic analysis of azamerone.

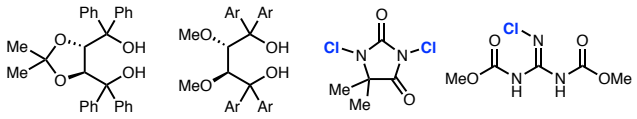
Our synthetic approach first required the assembly of enantioenriched chlorocycles **7** and **9**. Biosynthetically, the chlorocycle motifs found in **7** and **9** are proposed to derive from chloronium-initiated cyclizations of the prenyl and geranyl fragments within **5** (Figure 1B,C).[4] Neither of these transformations have enantioselective,

synthetic parallels.[5] In fact, the use of enantioselective halogenation in natural product synthesis has been limited thus far to the enantioselective bromochlorination and dichlorination of olefins.[2b,6] Cognizant of these methodological gaps and the challenge of chiral organochloride synthesis in general, we set out to develop a new method for enantioselective chloroetherification to produce a benzochloropyran akin to **7** and to discover a means for resolving the enantiomers of chlorocycle **9**, which was previously made in racemic form (**9**, **X** = OAc, Figure 1C).[9a]

Table 1. Enantioselective chloroetherification optimization



entry[a]	conditions	yield (%)	ee (%)
1	**A**, *t*-BuOCl, DCM	29	10
2	**B**, *t*-BuOCl, DCM	39	7
3	**B**, *t*-BuOCl, hexanes	11	<1
4	**B**, *t*-BuOCl, PhMe	38	16
5	**B**, *t*-BuOCl, Et$_2$O	36	14
6	**B**, *t*-BuOCl, *t*-BuOMe	25	16
7	**B**, *t*-BuOCl, THF	18	22
8	**B**, *t*-BuOCl, 2-Me-THF	33	57
9	**B**, NCS, 2-Me-THF	<5	–
10	**B**, DCDMH, 2-Me-THF	42	33
11	**B**, Palau'Chlor, 2-Me-THF	28	29
12	**B**, *t*-BuOCl, 2-Me-THF, pyridine	20	78
13	**B**, *t*-BuOCl, 2-Me-THF, quinoline	24	81
14[b]	**B**, *t*-BuOCl, 2-Me-THF, quinoline	68	84
15[c]	**B**, *t*-BuOCl, 2-Me-THF, quinoline	45	79
16[c,d]	**B**, *t*-BuOCl, 2-Me-THF, quinoline	40[e]	84



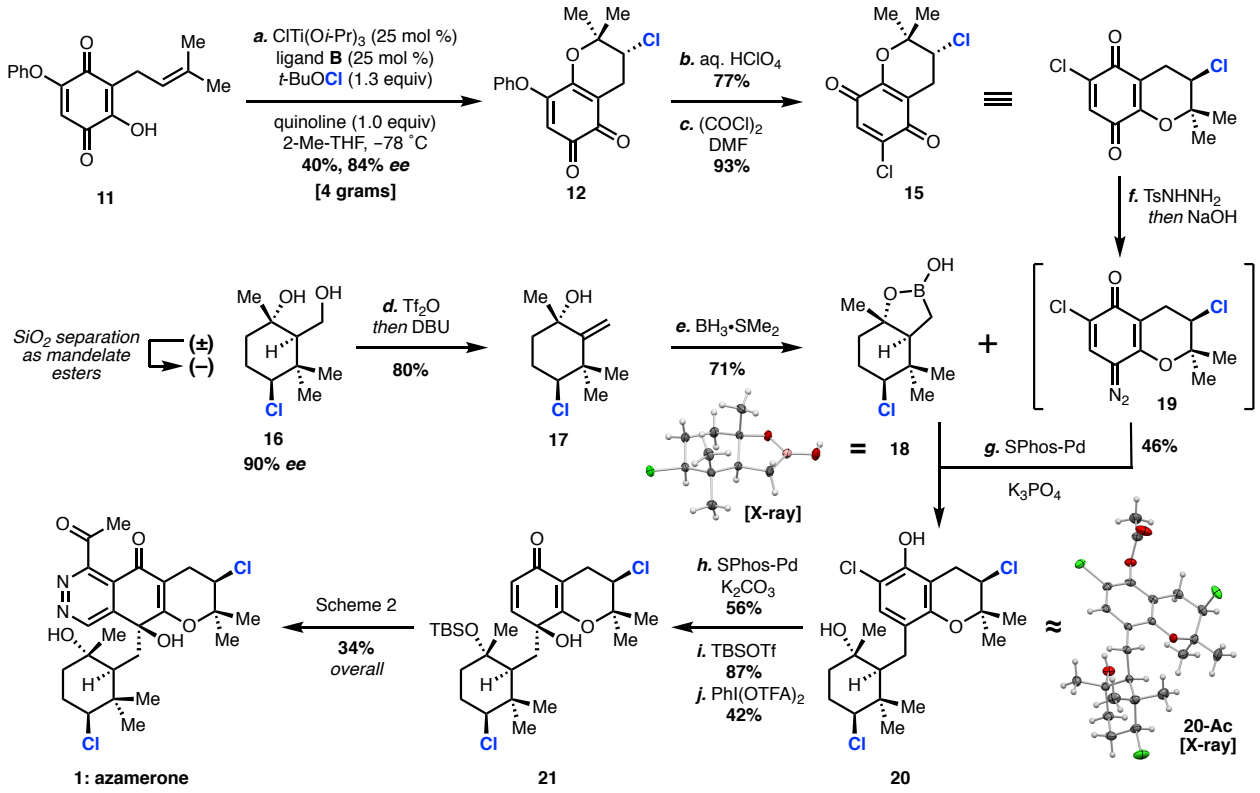
a. Reactions were conducted on 0.035–0.176 mmol scale, and ^{1}H-NMR yields are reported based on 1,4-dinitrobenzene as internal standard; *b.* 100 mol % ClTi(O*i*-Pr)$_3$, 100 mol % **B**; *c.* 1.3 equiv *t*-BuOCl; *d.* reaction conducted on 4.0 grams **11**; *e.* isolated yield.

De novo development of an enantioselective chloroetherification required the identification of a substrate that was not only amenable to asymmetric halogenation but also could be parlayed into a synthesis of azamerone. Although considerable advances have been made in the area of catalytic, enantioselective chlorolactonization and chloroetherification, high selectivity has been achieved only for styrenyl substrates; use of non-stabilized olefins is accompanied by a precipitous drop in enantioselectivity.[5,7] After extensive investigation of potential substrate structures and chiral catalysts, we discovered that prenylated hydroxyquinone **11** could be chlorocyclized to a benzochloropyran by a TADDOL-ligated titanium complex and *tert*-butyl hypochlorite in modest yield and 10% ee (entry 1, Table 1). Application of other common systems for enantioselective chlorofunctionalization returned racemic product.[7] Unexpectedly, under these conditions *ortho*-quinone **12** was formed as the major product. Initial formation of intermediate **13** is proposed, as this is consistent with our hypothesis in a related dihalogenation system that a coordinatively saturated octahedral titanium complex is necessary for high selectivity.[6d] Chloroether **12** likely arises via trapping of the chloronium by the vinylogous carboxylate carbonyl oxygen in **14**; however, titanium is not necessary for such regioselectivity, as the racemic product could be produced in 52% yield solely by the action of *tert*-butyl hypochlorite (see Supporting Information). We anticipated that **12** could be leveraged as a precursor to a *para*-quinone intermediate for the synthesis of azamerone and, therefore, pursued optimization of this chloroetherification.

A survey of chiral ligands afforded optimal TADDOL ligand **B**,[8] which produced chloropyran **11** in increased yield but with similarly low enantioselectivity (entry 2, Table 1). Although comparable to ligand **A** under the conditions of entry 1 and 2, acyclic ligand **B** proved to be more selective and higher yielding across a broader range of conditions and was selected for further optimization efforts. Screening of reaction solvents revealed that 2-methyl-tetrahydrofuran increased the selectivity of the chloroetherification to 57% ee (entries 3–8, Table 1). Use of other electrophilic chlorine sources led to a reduction in the yield or enantioselectivity of the process (entries 9–11, Table 1). Inclusion of heterocyclic base additives, such as pyridine and quinoline, increased the enantioselectivity of chlorocyclization (entries 12, 13, Table 1); the precise role of these additives is unclear, but they could serve as general bases, activating agents for transfer of electrophilic chlorine, or ligands on titanium. Employing a stoichiometric amount of titanium and chiral ligand delivered only a modest increase in selectivity but a dramatic improvement in yield (entry 14, Table 1). Increasing the amount of *tert*-butyl hypochlorite to 1.3 equivalents provided an improvement in yield when using 25 mol % titanium and ligand (entry 15, Table 1). Gratifyingly, performing the reaction on 4-gram scale under these conditions resulted in an isolated 40% yield (entry 16, Table 1).

With an enantioselective chloroetherification in hand, we commenced our synthesis of azamerone. Prenylquinone **11**, which is made in two steps from commercially available materials, was cyclized to chloropyran **12** using our optimized conditions (Scheme 1). Treatment of this *ortho*-quinone with aqueous acid induced hydrolysis and isomerization to an intermediate 2-hydroxy-*para*-quinone, which was smoothly converted to its corresponding 2-chloro-*para*-quinone **15** with oxalyl chloride and DMF. Pyranoquinone **15** is embedded within nearly all members of the napyradiomycins (e.g. **1**–**4**, Figure 1).

Scheme 1. Short enantioselective synthesis of azamerone.[a]



[a]Reagents and conditions: (a) ClTi(O*i*-Pr)$_3$ (0.25 equiv), **B** (0.25 equiv), quinoline (1.0 equiv), *t*-BuOCl (1.3 equiv), 2-Me-THF, –78 ˚C, 40%, 84% ee; (b) aq. $HClO_4$ (1.3 equiv), Et_2O, 77%; (c) oxalyl chloride (1.1 equiv), DMF (1.4 equiv), MeCN, 0 ˚C, 93%; (d) Tf_2O (1.05 equiv), 2,6-lutidine (1.2 equiv), DBU (2.5 equiv), DCM, –78 ˚C to RT, 80%; (e) $BH_3{\cdot}SMe_2$ (2.0 equiv), THF, 0 ˚C to RT, 71%; (f) $TsNHNH_2$ (1.1 equiv), MeOH; (g) (SPhos)Pd-G3 (0.1 equiv), K_3PO_4 (1.3 equiv), dioxane, 60 ˚C, 46% over 2 steps, 10:1 dr; (h) (SPhos)Pd-G3 (0.1 equiv), K_2CO_3 (2.0 equiv), *i*-PrOH, 90 ˚C 56%; (i) TBSOTf (3.0 equiv), (*i*-Pr)$_2$NEt (4.0 equiv), DCM then aq. NaOH (7.5 equiv), *i*-PrOH, 87%; (j) PhI(OTFA)$_2$ (1.1 equiv), 3:1 MeCN/H_2O, 42%.

Our synthesis of the chlorocyclohexane of azamerone focused on first establishing a means to resolve racemic **16** (Scheme 1). In 2010, the Snyder group reported the direct chlorocyclization of geranyl acetate with chlorodiethylsulfonium hexachloroantimonate (see Scheme S2 in Supporting Information).[9a] This reaction provides the primary acetate of diol **16** in racemic form. Important recent work by Gulder,[9b] along with a report by Snyder[9c] on a mercury-based two-step mimic for halopolyene cyclizations, provided additional strategies for accessing racemic chlorocycle **16** (see Schemes S1 and S2 in Supporting Information). Attempts to catalytically resolve diol **16** by either chemical or enzymatic means were met with limited success. Investigations into resolution by chiral derivatization revealed the methoxy mandelate of diol **16** to be uniquely competent in providing chromatographic resolution of diastereomers on silica gel.[10] This result is noteworthy given the challenges associated with resolving primary alcohols,[11] and we anticipate that access to enantioenriched diol **16** will enable syntheses of other chlorinated natural products. Using this approach, multigram quantities of racemic diol **16** can be separated into its constituent enantiomers.

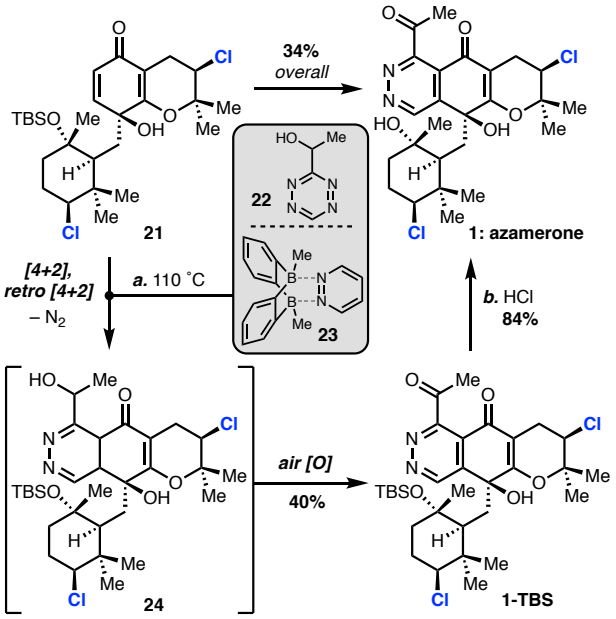
We next investigated the coupling of quinone **15** and an appropriate derivative of chlorocyclohexane **16**. Initial studies attempted to unite these pieces through a 1,2-addition of generalized organometallic **9** (**X** = metal, Figure 1C) into the more electrophilic carbonyl of **15**. These efforts were hampered due to Grob-type fragmentation of organometallic **9**, which occurs at temperatures above –78 ˚C, and due to preferential reduction of the quinone by organometallic reagents. Owing to these obstacles, a cross-coupling approach was adopted for the union of these fragments (Scheme 1). Chemoselective dehydration of the primary alcohol in **16** with triflic anhydride and DBU provided olefin **17**, which was hydroborated to form boronic hemiester **18** in good yield and diastereoselectivity. Boronic hemiester **18** is stable to column chromatography, allowing for facile removal of a minor diastereomer; X-ray crystallographic analysis of racemic **18** unambiguously verified its relative configuration. This cross-coupling partner has precedent in the synthesis of sclareolide derivatives and was chosen to attenuate Grob-type fragmentation.[12]

Quinone **15** was joined with boronic hemiester **18** through a quinone diazide-based coupling strategy (Scheme 1). Chemoselective condensation of tosyl

hydrazide with quinone **15** followed by treatment with base provided intermediate quinone diazide **19**, which was directly used as a cross-coupling electrophile without purification. Screening of conditions revealed that SPhos-ligated palladium was able to catalyze C_{sp^3}–C_{sp^2} bond formation between sterically hindered boronic hemiester **18** and quinone diazide **19**, providing phenol **20** in 46% overall yield from **15**. The structure and relative configuration of phenol **20** was confirmed via X-ray crystallography of its acetate. Small amounts of another diastereomer were produced due to the presence of minor enantiomers of each substrate. Limited precedent exists for Suzuki reactions with quinone diazides, and to the best of our knowledge, this represents the first example of this reaction type with a C_{sp^3} nucleophile.[13]

Subsequent dechlorination, silylation, and hypervalent iodine-mediated *para* oxidation[14] of phenol **20** provided the desired stereoisomer of *para*-quinol **21** as the major product in 42% yield (Scheme 1). Protection of the tertiary alcohol of **21** was necessary to prevent two undesired pathways: (1) the unprotected tertiary alcohol in **21** acting as a nucleophile during arene oxidation to exclusively form a diastereomeric mixture of spirocycles; (2) in oxidized quinol structures such as **21**, free tertiary alcohols are prone to oxa-Michael additions into the proximal enone (see Schemes S11, S15, S16 in Supporting Information). Two diastereomeric products from the latter of these undesired pathways were verified via X-ray crystallography (see Supporting Information), enabling relative stereochemical assignments.

Scheme 2. Tetrazine cycloaddition sequence.[a]



[a]Reagents and conditions: (a) **22** (15.0 equiv), **23** (2.0 equiv), CF_3Ph, 110 °C, 40%; (b) 12N HCl, MeOH, 84%, 34% from **21**.

We envisioned that quinol **21** could be expediently translated to azamerone through a Boger-inspired [4+2]-cycloaddition with an appropriately functionalized tetrazine.[15] Although it is a direct means for phthalazinone construction, we recognized that electron-deficient enone **21** was ill-matched to participate in this inverse electron-demand cycloaddition. After discovering that acyltetrazine **8** (Figure 1) had limited stability, we chose its reduced variant **22** for further study (Scheme 2). Unfortunately, initial attempts to thermally induce reactivity between **21** and tetrazine **22** were unsuccessful. During our studies, Wegner and coworkers reported that bisboron complex **23** is able to catalyze the cycloaddition of tetrazines with naphthoquinones.[16] Encouraged by their auspicious results, we applied complex **23** to our system and were delighted to observe formation of silyl-azamerone **1-TBS**. This cascade is presumed to occur through initial [4+2]-cycloaddition, subsequent expulsion of dinitrogen via [4+2]-retrocycloaddition (to provide diimine **24**), and both in situ oxidative aromatization and benzyl alcohol oxidation to **1-TBS**. The alcohol oxidation occurred to a varying extent in some experiments but could also be accomplished with Dess–Martin periodinane (see Supporting Information). Treatment with hydrochloric acid affected desilylation and provided azamerone **1**[17] in 34% overall yield from **21**.

The first synthesis of azamerone has been reported. Our successful route relied on development of an enantioselective chloroetherification with a substrate suitable for elaboration into the target. Identification of a scalable resolution process provided access to an enantioenriched chlorocyclohexane that had been made previously in racemic form. A convergent cross-coupling between a quinone diazide and a hindered boronic hemiester, followed by a late-stage arene oxidation and bisboron-mediated tetrazine [4+2]-annulation installed the fully-oxidized framework of azamerone. We anticipate that this sequence and the strategies leveraged herein will find use in syntheses of other members of the napyradiomycin meroterpenoids.

ASSOCIATED CONTENT

Supporting Information. Experimental procedures, characterizations, spectral data, and CIF files.

AUTHOR INFORMATION

Corresponding Author

*nburns@stanford.edu

Funding Sources

No competing financial interests have been declared. This work was supported by Stanford University, the National Institutes of Health (R01 GM114061), the National Science Foundation (DGE-114747 GRF to MLL), and the Center for Molecular Analysis and Design (GRF to GMM).

ACKNOWLEDGMENT

This work is dedicated to Prof. Dale Boger on the occasion of his 65th birthday. We are grateful to Dr. A. Oliver (Notre Dame) and Dr. N. Settineri (UC Berkeley) for X-ray crystallographic analysis, Dr. S. Lynch (Stanford University) for assistance with NMR spectroscopy, Prof. B. Moore (Scripps

Institute for Oceanography) for providing an authentic sample of **1**, Prof. Dr. H. Wegner (Justus Liebig University Giessen) for providing an initial amount of bisboron complex **23**, Sajan Patel (Stanford University) for the synthesis of additional **23**, and Prof. Y. Xia (Stanford University) for assistance with LCMS.

REFERENCES

(1) (a) Shiomi, K.; Iinuma, H.; Hamada, M.; Naganawa, H.; Manabe, M.; Matsuki, C.; Takeuchi, T.; Umezawa, H.; Matsuki, C.; Takeuchi, T. Novel antibiotics napyradiomycins production, isolation, physicochemical properties and biological activities. *J. Antibiot.* **1986**, *39*, 487–493. (b) Shiomi, K.; Nakamura, H.; Iinuma, H.; Naganawa, H.; Isshiki, K.; Takeuchi, T.; Umezawa, H. Structures of new antibiotics napyradiomycins. *J. Antibiot.* **1986**, *39*, 494–501. (c) Dantzig, A. H.; Minor, P. L.; Garrigus, J. L.; Fukuda, D. S.; Mynderse, J. S. Studies on the mechanism of action of A80915A, a semi-naphthoquinone natural product, as an inhibitor of gastric (H^+-K^+)-ATPase. *Biochem. Pharmacol.* **1991**, *42*, 2019–2026. (d) Hori, Y.; Abe, Y.; Shigematsu, N.; Goto, T.; Okuhara, M.; Kohsaka, M. Napyradiomycins A and B1: Non-steroidal estrogen-receptor antagonists produced by a Streptomyces. *J. Antibiot.* **1993**, *46*, 1890–1893. (e) Cheng, Y.-B.; Jensen, P. R.; Fenical, W. Cytotoxic and antimicrobial napyradiomycins from two marine-derived Streptomyces strains. *Eur. J. Org. Chem.* **2013**, 3751–3757. (f) Farnaes, L.; Coufal, N. G.; Kauffman, C. A.; Rheingold, A. L.; DiPasquale, A. G.; Jensen, P. R.; Fenical, W. Napyradiomycin derivatives, produced by a marine-derived actinomycete, illustrate cytotoxicity by induction of apoptosis. *J. Nat. Prod.* **2014**, *77*, 15–21.

(2) (a) Tatsuta, K.; Tanaka, Y.; Kojima, M.; Ikegami, H. The first total synthesis of (±)-napyradiomycin A1. *Chem. Lett*. **2002**, 14–15. (b) Snyder, S. A.; Tang, Z. Y.; Gupta, R. Enantioselective total synthesis of (–)-napyradiomycin A1 via asymmetric chlorination of an isolated olefin. *J. Am. Chem. Soc*. **2009**, *131*, 5744–5745. (c) Miles, Z. D.; Diethelm, S.; Pepper, H. P.; Huang, D. M.; George, J. H.; Moore, B. S. A unifying paradigm for naphthoquinone-based meroterpenoids biosynthesis. *Nat. Chem.* **2017**, *9*, 1235–1242.

(3) (a) Cho, J. Y.; Kwon, H. C.; Williams, P. G.; Jensen, P. R.; Fenical, W. Azamerone, a terpenoid phthalazinone from a marine-derived bacterium related to the genus Streptomyces (actinomycetales). *Org. Lett.* **2006**, *8*, 2471–2474. Using ^{13}C- and ^{15}N-labeled precursors, Moore was able to show that both nitrogen atoms in azamerone originate from the diazo group in **5**: (b) Winter, J. M.; Jansma, A. L.; Handel, T. M.; Moore, B. S. Formation of the pyridazine natural product azamerone by biosynthetic rearrangement of an aryl diazoketone. *Angew. Chem. Int. Ed.* **2009**, *48*, 767–770.

(4) Bernhardt, P.; Okino, T.; Winter, J. M.; Miyanaga, A.; Moore, B. S. A stereoselective vanadium-dependent chloroperoxidase in bacterial antibiotic biosynthesis. *J. Am. Chem. Soc*. **2011**, *133*, 4268–4270.

(5) (a) Denmark, S. E.; Kuester, W. E.; Burk, M. T. Catalytic, asymmetric halofunctionalization of alkenes–a critical perspective. *Angew. Chem. Int. Ed.* **2012**, *51*, 10938–10953. (b) Castellanos, A.; Fletcher, S. P. Current methods for asymmetric halogenation of olefins. *Chem. Eur. J.* **2011**, *17*, 5766–5776. (c) Chung, W. J.; Vanderwal, C. D. Stereoselective halogenation in natural product synthesis. *Angew. Chem. Int. Ed.* **2016**, *55*, 4396–4434.

(6) (a) Bucher, C.; Deans, R. M.; Burns, N. Z. Highly selective synthesis of halomon, plocamenone, and isoplocamenone. *J. Am. Chem. Soc.* **2015**, *137*, 12784–12787. (b) Landry, M. L.; Hu, D. X.; McKenna, G. M.; Burns, N. Z. Catalytic enantioselective dihalogenation and the selective synthesis of (−)-deschloromytilipin A and (−)-danicalipin A. *J. Am. Chem. Soc.* **2016**, *138*, 5150–5158. (c) Burckle, A. J.; Vasilev, V.; Burns, N. Z. A unified approach for the enantioselective synthesis of the brominated chamigrene sesquiterpenes. *Angew. Chem. Int. Ed.* **2016**, *55,* 11476–11479. (d) Landry, M. L.; Burns, N. Z. Catalytic enantioselective dihalogenation in total synthesis. *Acc. Chem. Res.* **2018**, *51*, 1260–1271.

(7) (a) Whitehead, D. C.; Yousefi, R.; Jaganathan, A.; Borhan, B. An organocatalytic asymmetric chlorolactonization. *J. Am. Chem. Soc.* **2010**, *132*, 3298–3300. (b) Zhang, W.; Liu, N.; Schienebeck, C. M.; Decloux, K.; Zheng, S.; Werness, J. B.; Tang, W. Catalytic enantioselective halolactonization of enynes and alkenes. *Chem. Eur. J.* **2012**, *18*, 7296–7305. (c) Zeng, X.; Miao, C.; Wang, S.; Xia, C.; Sun, W. Asymmetric 5-endo chloroetherification of homoallylic alcohols toward the synthesis of chiral β–chlorotetrahydrofurans. *Chem. Commun.* **2013**, *49*, 2418–2420. (d) Han, X.; Dong, C.; Zhou, H. B. C_3-Symmetric cinchonine-squaramide-catalyzed asymmetric chlorolactonization of styrene-type carboxylic acids with 1,3-dichloro-5,5-dimethylhydantoin: an efficient method to chiral isochroman-1-ones. *Adv. Synth. Catal.* **2014**, *356*, 1275–1280.

(8) Teller, H.; Corbet, M.; Mantilli, L.; Gopakumar, G.; Goddar, R.; Thiel, W.; Fürstner, A. One-point binding ligands for asymmetric gold catalysis: phosphoramidites with a TADDOL-related but acyclic backbone. *J. Am. Chem. Soc.* **2012**, *134*, 15331–15342.

(9) (a) Snyder, S. A.; Treitler, D. S.; Brucks, A. P. Simple reagents for direct halonium-induced polyene cyclizations. *J. Am. Chem. Soc*. **2010**, *132*, 14303–14314. (b) Arnold, A. M.; Pöthig, A.; Drees, M.; Gulder, T. NXS, morpholine, and HFIP: the ideal combination for biomimetic haliranium-induced polyene cyclizations. *J. Am. Chem. Soc*. **2018**, *140*, 4344–4353. (c) Snyder, S. A.; Treitler, D. S.; Schall, A. A two-step mimic for direct, asymmetric bromonium- and chloronium-induced polyene cyclizations. *Tetrahedron* **2010**, *66*, 4796–4804.

(10) (a) Whitesell, J. K.; Reynolds, D. Resolution of chiral alcohols with mandelic acid. *J. Org. Chem.* **1983**, *48*, 3548–3551. (b) Trost, B. M.; Belletire, J. L.; Godleski, S.; McDougal, P. G.; Balkovec, J. M.; Baldwin, J. J.; Christy, M. E.; Ponticello, G. S.; Varga, S. L.; Springer, J. P. On the use of the *O*-methylmandelate ester for establishment of absolute configuration of secondary alcohols. *J. Org. Chem.* **1986**, *51*, 2370–2374.

(11) (a) Vedejs, E.; Jure, M. Efficiency in nonenzymatic kinetic resolution. *Angew. Chem. Int. Ed.* **2005**, *44*, 3974–4001. (b) Terakado, D.; Koutaka, H.; Oriyama, T. Organocatalytic kinetic resolution of racemic primary alcohols using a chiral 1,2-diamine derived from (*S*)-proline. *Tetrahedron: Asymmetry* **2005**, *16*, 1157–1165. (c) Qayed, W. S.; Aboraia, A. S.; Abdel-Rahman, H. M.; Youssef, A. F. Lipases-catalyzed enantioselective kinetic resolution of alcohols. *J. Chem. Pharm. Res.* **2015**, *7*, 311–322.

(12) Dixon, D. D.; Lockner, J. W.; Zhou, Q.; Baran, P. S. Scalable, divergent synthesis of meroterpenoids via "borono-sclareolide." *J. Am. Chem. Soc.* **2012**, *134*, 8432–8435.

(13) (a) Schmidt, B.; Hölter, F. Suzuki-Miyaura cross coupling reactions with phenoldiazonium salts. *Org. Biomol. Chem.* **2011**, *9*, 4914–4920. For related precedent, see: (b) Xia, Y.; Xia, Y.; Liu, Z.; Zhang, Y.; Wang, J. Palladium-catalyzed cross-coupling reaction of diazo compounds and vinyl boronic acids: an approach to 1,3-diene compounds. *J. Org. Chem.* **2014**, *79*, 7711–7717. (c) Roglans, A.; Pla-Quintana, A.; Moreno-Mañas, M. Diazonium salts as substrates in palladium-catalyzed cross-coupling reactions. *Chem. Rev.* **2006**, *106*, 4622–4643.

(14) Magdziak, D.; Meek, S. J.; Pettus, T. R. R. Cyclohexadienone ketals and quinols: four building blocks potentially useful for enantioselective synthesis. *Chem. Rev.* **2004**, *104*, 1383–1430, and references cited therein.

(15) For reviews, see: (a) Boger, D. L. Diels-Alder reactions of azadienes. *Tetrahedron* **1983**, *39*, 2869–2939. (b) Boger, D. L. Diels-Alder reactions of heterocyclic aza dienes. Scope and applications. *Chem. Rev.* **1986**, *86*, 781–793. For studies on cycloadditions of unsubstituted 1,2,4,5-tetrazine, see: (c) Sauer, J.; Heldmann, D. K.; Hetzenegger, J.; Krauthan, J.; Sichert, H.; Schuster, J. 1,2,4,5-Tetrazine: synthesis and reactivity in [4+2] cycloadditions. *Eur. J. Org. Chem.* **1998**, 2885–2896, and references cited therein.

(16) (a) Hong, L.; Ahles, S.; Strauss, M. A.; Logemann, C.; Wegner, H. A. Synthesis of 2,3-diaza-anthraquinones via the bidentate Lewis acid catalyzed inverse electron-demand Diels-Alder (IEDDA) reaction. *Org. Chem. Front.* **2017**, *4*, 871–875. (b) Hong, L.; Ahles, S.; Heindl, A. H.; Tiétcha, G.; Petrov, A.; Lu, Z.; Logemann, C.; Wegner, H. A. An air-stable bisboron complex: a practical bidentate Lewis acid catalyst. *Beilstein J. Org. Chem.* **2018**, *14*, 618–625.

(17) Synthetic **1**: $[\alpha]_D^{23} = -7.36$ (c = 0.1, MeOH); ref. 3a: $[\alpha]_D = -8.8$ (c = 0.0025, MeOH).