

# Stereocontrolled Synthesis of Kalihinol C

Christopher A. Reiher and Ryan A. Shenvi\*<sup>1b</sup>

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

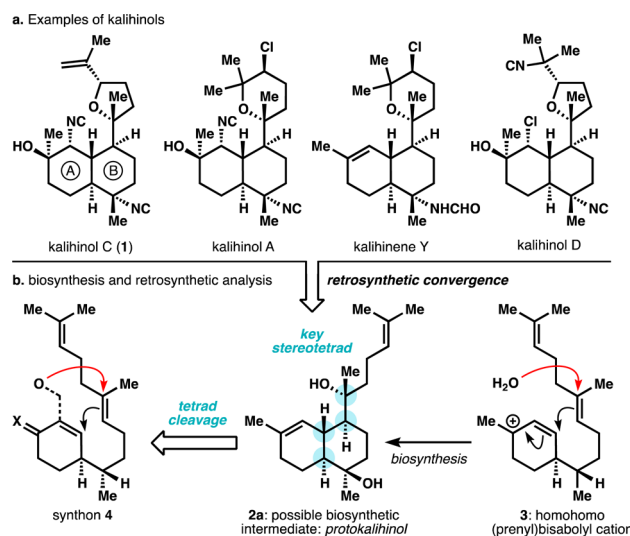
**S** Supporting Information

**ABSTRACT:** We report a concise chemical synthesis of kalihinol C via a possible biosynthetic intermediate, “protokalihinol”, which was targeted as a scaffold en route to antiplasmodial analogs. High stereocontrol of the kalihinol framework relies on a heterodendralene cascade to establish the target stereotetrad. Common problems of regio- and chemoselectivity encountered in the kalihinol class are explained and solved.

The kalihinols (Figure 1) possess the highest skeletal and functional group complexity of the biologically enigmatic isocyanoterpene (ICT) class.<sup>1,2</sup> Kalihinol A<sup>3a</sup> also exhibits the highest reported potency of the ICTs against *Plasmodium falciparum*,<sup>3b</sup> killing with an EC<sub>50</sub> of 1 nM, but the mechanism of action has not been rigorously assigned. Proposed mechanisms to explain phenotypic effects of the ICTs include inhibition of heme detoxification<sup>4</sup> or copper chelation,<sup>5</sup> but these proposals do not fully account for the structure–activity relationships and life-cycle activities reported. For example, our discovery that the amphilectenes and adocianes are cytotoxic against liver-stage parasites militates against heme detoxification inhibition as the exclusive antiplasmodial mechanism.<sup>6</sup> Copper chelation is simply not possible for congeners with distant isonitriles. As part of a program to investigate the biological activity of ICTs, we have begun to develop effective chemical syntheses<sup>2,6,7</sup> and associated methods<sup>8</sup> to produce and modify three main structural classes: amphilectenes, adocianes, and kalihinols.<sup>1,2</sup> Prior syntheses<sup>9</sup> of the kalihinol class have fought to control stereochemistry in the functionally dense scaffolds, and each contains at least one uncontrolled (ca. 1:1 d.r.) stereogenic step.<sup>10</sup> Here we report a short and fully stereocontrolled synthesis of kalihinol C (1) enabled by a new heterodendralene building block, a directed alkene isomerization, and a new method for isonitrile synthesis.

The kalihinols appear to derive from a common intermediate, a “protokalihinol” (2a) where the tetrahydrofurans or -pyrans derive from oxidative cyclization of a pendant prenyl unit. The protokalihinol framework (a dihydroxy-bifloran diterpene)<sup>1</sup> would arise from bisabolyl cation intermediate 3 via cation-olefin cyclization and concomitant stereoselective capture of water.<sup>11</sup> Although such a pathway might globally simplify formation of the kalihinol stereotetrad (in blue), we thought intramolecular capture of oxygen in synthon 4 might be more realistic than stereoselective carbocation hydration.<sup>12</sup>

Recently, our lab reported short syntheses of amphilectene<sup>7</sup> and adociane<sup>6</sup> ICTs that relied on a new class of polarized dendrimeric polyene<sup>13</sup> (Danishefsky dendralenes) that forged the stereochemically dense core of these and other terpenes<sup>14</sup> in

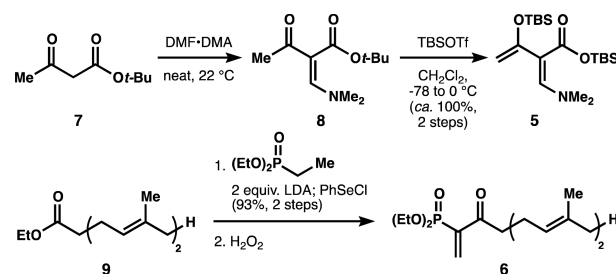


**Figure 1.** (a) Kalihinol congeners; (b) hypothetical biosynthesis that informs a proposed chemical synthesis.

highly diastereoselective Diels–Alder cascades. Given the structural correspondence between amphilectenes and kalihinols, we realized that a dendralene-based approach might emulate the proposed biosynthetic pathway if the oxynucleophile of 4 were embedded in a dendralene.

Short and efficient routes to the heterodendralene and double-dienophile partners are shown in Scheme 1. Preliminary reconnaissance identified two important features of each component. First, the dimethylamine substituent<sup>15</sup> in 5 was necessary to offset the electron-withdrawing carboxylate, which rendered the dendralene less reactive with electron-deficient dienophiles. Second, the diethylphosphonate substituent in 6

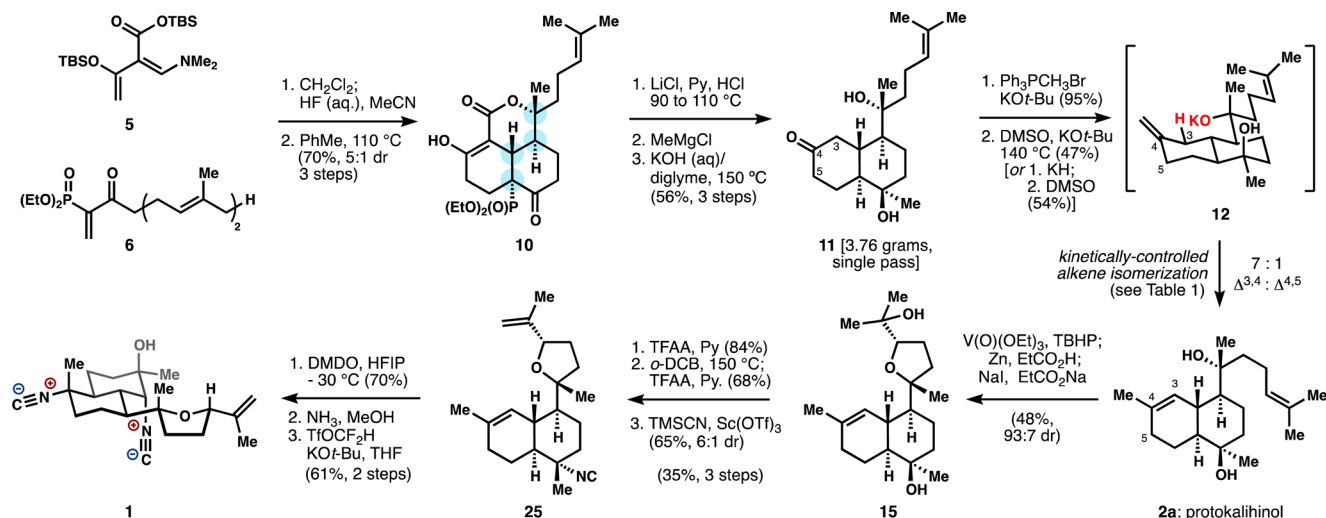
## Scheme 1. Routes to Building Blocks



Received: February 1, 2017

Published: March 2, 2017

Scheme 2. Synthesis of Kalihinol C



activated the dienophile for ambient-temperature cycloaddition but was not so destabilizing as to complicate isolation.

Building block 5 was synthesized by condensation of *tert*-butyl acetoacetate 7 with dimethylformamide dimethyl acetal (DMF-DMA) to yield vinylogous amide 8, which was doubly silylated to 5 with loss of the *tert*-butyl group. Geranyl-phosphonate 6 was also synthesized in two steps by addition of diethyl ethylphosphonate to ethyl geranylacetate (9), followed by in situ selenation and subsequent oxidation/elimination of the selenoxide.<sup>16</sup>

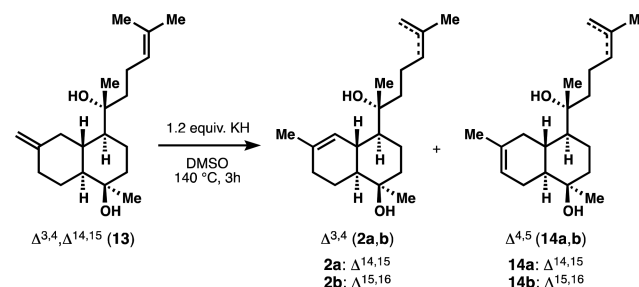
Cycloaddition of 5 to 6 occurred at  $22^\circ\text{C}$  in  $\text{CH}_2\text{Cl}_2$  to yield an inconsequential mixture of diastereomers at the dimethylamino group, which was eliminated to an enone (see synthon 4) by treatment with hydrogen fluoride. The silylester was also cleaved to the corresponding unsaturated carboxylic acid, which engaged in a nearly quantitative intramolecular Diels–Alder cycloaddition<sup>17</sup> to provide, after tautomerization,  $\beta$ -keto-lactone 10, possessing the targeted stereotetrad of the kalihinols. The stereoisomers (5:1 ratio) corresponded to epimers at the C–P bond, and were converged in the next step.<sup>18</sup>

Lactone 10 was converted to diol 11 by (1) Krapcho-like dephosphonylation, (2) stereoselective methyl addition to the  $\beta$ -ring ketone, and (3) lactone hydrolysis/decarboxylation; each step deserves some comment. First, the desphosphonylation is a little-precedented transformation that required the development of a new procedure [LiCl, Py·HCl (aq.),  $90\rightarrow 110^\circ\text{C}$ ] to spare the acid-sensitive *tert*-alkyl lactone and the electrophilic ketones, which underwent retro-Dieckmann reactions under other conditions. Addition of a methyl group prior to decarboxylation preserved the *trans*-decalin geometry, whereas the corresponding ketone weakly favored the *cis*-decalin after lactone cleavage. Preferential formation of the disfavored *trans*-decalin (of 11) has remained unsolved in prior work,<sup>2,9,10</sup> and in this case is enabled by the fused lactone, which locks the geometry. Through this short process, multigram quantities of decalone 11 could be generated in a single pass for elaboration to protokalihinol 2a and the metabolite itself (1).

However, establishment of the required  $\Delta^{3,4}$  unsaturation was undermined by formation of the  $\Delta^{4,5}$  isomer, which predominated upon enolization of ketone 11. Such preference is well-precedented for 2-decalone enolizations<sup>19</sup> as well as alkene isomerizations in the heavily studied amorphane sesquiterpenes.<sup>20</sup> Attempts to generate endocyclic alkene 2 by ionization

of the tertiary alcohol derived from ketone 11 delivered the isomeric  $\Delta^{4,5}$  alkene with unremitting regularity. Because Brønsted bases can mediate alkene isomerization at high temperatures,<sup>21</sup> we wondered if the tertiary alcohol proximal to the C3 methylene of 11 could mediate a selective alkene isomerization as its strongly basic alkoxide. Indeed, we found that the potassium salt 12 could be heated to  $140^\circ\text{C}$  in DMSO to deliver protokalihinol 2a with 7:1 selectivity for  $\Delta^{3,4}$  unsaturation (2) over  $\Delta^{4,5}$  (14, Table 1). Consistent with this

Table 1. Alkoxide-Directed Alkene Isomerization



entry	variations (and % conversion)	2:14	%2a
1	none (78)	7:1	54
2 <sup>a</sup>	4 equiv. KOt-Bu, no KH (82)	5:1	55
3 <sup>a</sup>	16 equiv. KOt-Bu, no KH (86)	1:1	28
4	1.2 equiv. <i>n</i> -BuLi, no KH (0)		0
5	DMPU instead of DMSO (0)		0
alternate conditions			
6 <sup>b</sup>	20 mol % RhCl <sub>3</sub> , EtOH/H <sub>2</sub> O, $70^\circ\text{C}$ (56)	1:1	28
7 <sup>a</sup>	2 mol % [Co], <sup>c</sup> 4 mol % PhSiH <sub>3</sub> , PhH (42)	<1:20	<5

<sup>a</sup><sup>1</sup>H NMR. <sup>b</sup>GC–MS. <sup>c</sup>Co(Sal<sup>f-Bu,f-Bu</sup>)Cl·H<sub>2</sub>O.

mechanistic model, increased equivalents of base led to increased amounts of 14 (entries 1–3), which would derive from intermolecular deprotonation. Small amounts (ca. 15%) of isomers derived from chain isomerization ( $\Delta^{15,16}$ : 2b, 14b) also were observed, but could be removed from 2a (or carried forward and removed from 15). Other alkali metals besides potassium and other solvents besides DMSO performed poorly (entries 4 and 5; see SI for a list of other variations). Methods like coordinative isomerization<sup>22</sup> or HAT isomerization<sup>23</sup>

(entries 6 and 7) delivered mixtures of alkenes or the  $\Delta^{4,5}$  isomer exclusively.

A Sharpless-type directed epoxidation<sup>24</sup> was identified as the only method capable of controlling the stereochemistry of the targeted tetrahydrofuran. But to our chagrin, the  $\Delta^{3,4}$  ring-alkene reacted faster than the  $\Delta^{14,15}$  chain-alkene and delivered a C3,4 epoxide opposite to that required for elaboration to the isocyano-hydrin of **1** (**16**, see Figure 2). Fortunately, these

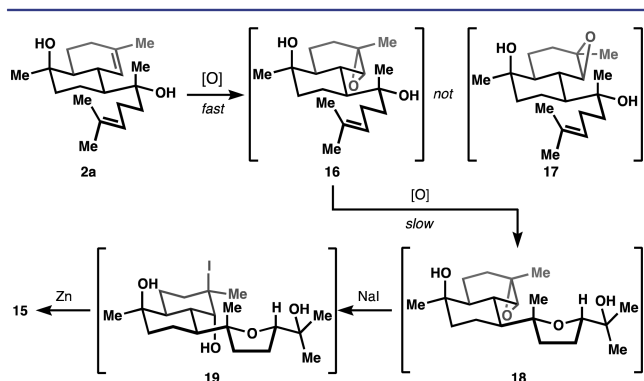


Figure 2. Stereoselective oxidative cyclization to **15**.

same conditions also mediated a slower, but stereoselective (93:7 d.r.) epoxidation of the side-chain alkene, as well as concomitant 5-*exo*-tet cyclization to the targeted tetrahydrofuran, whereas the A-ring epoxide was spared attack. Consequently, a sodium iodide/zinc metal-mediated epoxide deoxygenation selectively removed the unwanted ring epoxide, whereas the C14,15 oxidation was retained as the incipient hydroxy-tetrahydrofuran (see Figure 2).

The full kalihinol skeleton and correct oxidation state were thus established in eight steps from heterodendralene **5**; we next investigated elaboration to a known metabolite. Elimination of the exocyclic tertiary alcohol was effected by selective trifluoroacetylation and *syn*-elimination via thermolysis since ionizing conditions resulted in hydride shift from the tetrahydrofuran methine. In the same flask, we trifluoroacetylated the remaining alcohol and then installed the B-ring equatorial *tert*-alkyl isonitrile with our solvolytic stereoinversion.<sup>8</sup> The logic leading to this route (Scheme 2) requires some discussion.

We had originally targeted a tandem epoxide opening/trifluoroacetate stereoinversion of **20** (Figure 3) using our solvolysis conditions to install the bis-isonitrile motif. This approach was reported by Vanderwal to be successful, but low-yielding in his kalihinol B synthesis.<sup>9e</sup> We similarly found that this tandem reaction yielded only small amounts of the bis-isonitrile **21** (5–6%). The basis of the low yield was not the epoxide opening step, which was efficient and regioselective in substrate **20**. Instead, the subsequent B-ring stereoinversion<sup>8</sup> was low-yielding by virtue of competitive elimination (**22**→**23**).<sup>25</sup> Because the epoxide opening occurred faster than trifluoroacetate ionization, and the resulting isocyano-hydrin caused elimination in ring B, we concluded that the B-ring C–N bond must be in place prior to epoxidation.

We were dismayed to find that the B-ring functional groups influenced the course of epoxide ionization. As shown in Table 2, the B-ring axial trifluoroacetate and alcohol led to **A** with high selectivity, whereas the equatorial isonitrile or formamide skewed the ratio to favor substantial quantities of regioisomers **B** and **C**, as well as semipinacol product **D**.<sup>26</sup> So, the A- and B-

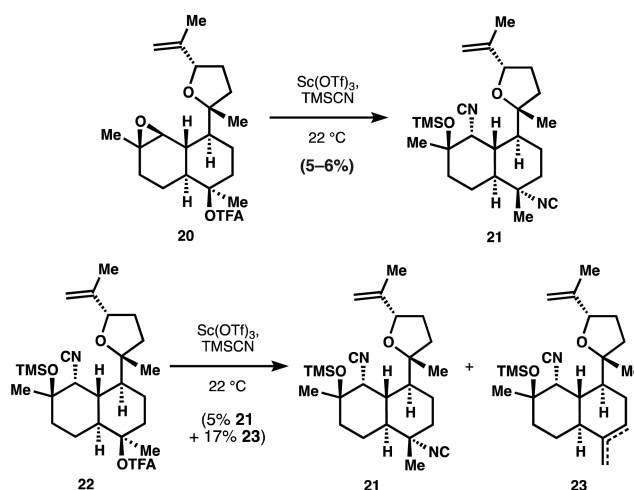


Figure 3. Tandem isonitrile formation is very low yielding.

Table 2. Isocyano-hydrin Installation<sup>a</sup>

R <sup>1</sup> /R <sup>2</sup>	conditions [N]	R <sup>1</sup> /R <sup>2</sup>	A:B:C:D
OTFA/Me	TMSCN, Sc(OTf) <sub>3</sub> [NC]	OTFA/Me	83:0:17:0
OH/Me	TMSCN, Sc(OTf) <sub>3</sub> [NC]	OTMS/Me	100:0:0:0
Me/NC	TMSCN, Sc(OTf) <sub>3</sub> [NC]	Me/NC	61:0:39:0
Me/NHCHO	TMSCN, Sc(OTf) <sub>3</sub> [NC]	Me/NHCHO	54:31:0:15
Me/NC	NH <sub>3</sub> , MeOH [NH <sub>2</sub> ]	Me/NC	100:0:0:0

<sup>a</sup>Any silylethers were converted to alcohols with TBAF.

ring substituents proved mutually incompatible in the tandem solvolysis sequence reported by Vanderwal.<sup>9e</sup>

Consequently, we relied on a simple but effective aminolysis to generate regioselectively the requisite A-ring functionality (Scheme 2 and Table 2, entry 5). First, chemoselective oxidation of the alkene of **25** occurred in preference to the isonitrile if carried out with dimethyldioxirane (DMDO) in the strongly hydrogen bond-donating solvent HFIP, which we posit deactivates the isonitrile against oxidation (Scheme 2). Aminolysis in methanol cleanly opened the epoxide to deliver a *sec*-alkyl amino *tert*-alcohol,<sup>27</sup> which was converted to the isocyano-hydrin of **1** via difluorocarbene derived from difluoromethyl triflate<sup>28</sup> and KO*t*-Bu. More orthodox methods for amine to isonitrile conversion worked poorly: chloroform/sodium hydroxide<sup>29</sup> generated appreciable amounts of a dichlorocyclopropane and an amide; formylation of the hindered amine occurred slowly due to buildup of acid (isonitriles are produced by subsequent formamide dehydration).<sup>30</sup> Our alternative use of



difluorocarbene for isonitrile synthesis therefore offers some advantages over existing methods, especially when multiple functional groups are present or the amine is hindered. This three-step procedure provides an efficient, stereo- and chemo-selective strategy to install the kalihinol A-ring isocyanohydrin motif.

In summary, we have demonstrated a concise route to access the kalihinol (bifloran) ICTs via a putative biosynthetic intermediate, protokalihinol (**2a**), that we anticipate can be divergently advanced to the natural series of metabolites. The synthesis compares favorably to the current best approach to the kalihinols by Vanderwal: it is longer in total step count (17 vs 12), but higher in yield by one order of magnitude (1.3% vs 0.13%). The higher efficiency derives from solutions to stereochemical and chemoselectivity problems raised by prior work, but left unsolved. Some of these solutions include (1) a method to synthesize the kalihinol stereotetrad using an iterative cycloaddition of the new building block, "heterodendralene" **5**; (2) an alkoxide-directed isomerization method to access the thermodynamically disfavored  $\Delta^{3,4}$  unsaturated *trans*-bifloran skeleton found throughout the diterpene class, and (3) a short, high-yielding, regio- and stereoselective strategy for installing the A-ring isocyanohydrin motif, including difluorocarbene-mediated isonitrile synthesis. This short and divergent route from protokalihinol **2a** allowed us to generate several analogs related to the metabolite series. We are currently using these compounds to interrogate the antiplasmodial activity and mechanism(s) of the kalihinol class.

## ■ ASSOCIATED CONTENT

### Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/jacs.7b01124.

Data for C<sub>19</sub>H<sub>26</sub>O<sub>4</sub> (CIF)

Detailed experimental procedures, spectral data, chromatograms, and X-ray crystallography (PDF)

## ■ AUTHOR INFORMATION

### Corresponding Author

\*rshenvi@scripps.edu

### ORCID

Ryan A. Shenvi: 0000-0001-8353-6449

### Funding

Financial support for this work was provided by the NIH (GM105766) and the NSF (GRFP to C.A.R.). Additional support was provided by Eli Lilly, Novartis, Bristol-Myers Squibb, Amgen, Boehringer-Ingelheim, the Sloan Foundation and the Baxter Foundation.

### Notes

The authors declare no competing financial interest.

## ■ ACKNOWLEDGMENTS

We thank Dr. Milan Gembicky, Dr. Curtis Moore, and Professor Arnold L. Rheingold for X-ray crystallographic analysis. We thank Chris Vanderwal (UC Irvine) for open communication about his ongoing work on the ICTs.

## ■ REFERENCES

- (1) Emsermann, J.; Kahl, U.; Opatz, T. *Mar. Drugs* **2016**, *14*, 16.
- (2) Shenvi, R. A.; Schnermann, M. J. *Nat. Prod. Rep.* **2015**, *32*, 543.

- (3) (a) Isolation: Chang, C. W. J.; Patra, A.; Roll, D. M.; Scheuer, P. J.; Matsumoto, G. K.; Clardy, J. *J. Am. Chem. Soc.* **1984**, *106*, 4644. (b) Kalihinol antimalarial activity: Miyaoka, H.; Shimomura, M.; Kimura, H.; Yamada, Y.; Kim, H.-S.; Yusuke, W. *Tetrahedron* **1998**, *54*, 13467.

- (4) (a) Wright, A. D.; Wang, H. Q.; Gurrath, M.; Konig, G. M.; Kocak, G.; Neumann, G.; Loria, P.; Foley, M.; Tilley, L. *J. Med. Chem.* **2001**, *44*, 873. (b) Wright, A. D.; McCluskey, A.; Robertson, M. J.; MacGregor, K. A.; Gordon, C. P.; Guenther. *Org. Biomol. Chem.* **2011**, *9*, 400. (c) Young, R. M.; Adendorff, M. R.; Wright, A. D.; Davies-Coleman, M. T. *Eur. J. Med. Chem.* **2015**, *93*, 373.

- (5) Sandoval, I. T.; Manos, E. J.; Van Wagoner, R. M.; Delacruz, R. G. C.; Edes, K.; Winge, D. R.; Ireland, C. M.; Jones, D. A. *Chem. Biol.* **2013**, *20*, 753.

- (6) Lu, H.-H.; Pronin, S. V.; Antonova-Koch, Y.; Meister, S.; Winzeler, E. A.; Shenvi, R. A. *J. Am. Chem. Soc.* **2016**, *138*, 7268.

- (7) Pronin, S. V.; Shenvi, R. A. *J. Am. Chem. Soc.* **2012**, *134*, 19604.

- (8) Pronin, S. V.; Reiher, C. A.; Shenvi, R. A. *Nature* **2013**, *501*, 195.

- (9) (a) White, R. D.; Wood, J. L. *Org. Lett.* **2001**, *3*, 1825. (b) White, R. D.; Keane, G. F.; Slown, C. D.; Wood, J. L. *Org. Lett.* **2004**, *6*, 1123.

- (c) Miyaoka, H.; Abe, Y.; Sekiya, N.; Mitome, H.; Kawashima, E. *Chem. Commun.* **2012**, *48*, 901. (d) Miyaoka, H.; Abe, Y.; Kawashima, E. *Chem. Pharm. Bull.* **2012**, *60*, 1224. (e) Daub, M. E.; Prudhomme, J.; Le Roch, K.; Vanderwal, C. D. *J. Am. Chem. Soc.* **2015**, *137*, 4912. (f) Daub, M. E.; Prudhomme, J.; Mamoun, C. B.; Le Roch, K. G.; Vanderwal, C. D. *ACS Med. Chem. Lett.* **2017**, DOI: 10.1021/acsmchemlett.7b00013.

- (10) Kalihinene X was synthesized with stereocontrol in 35-steps, but lacks the A-ring isocyanohydrin and characteristic *trans*-ring fusion of the kalihinols. See: Miyaoka, H.; Shida, H.; Yamada, N.; Mitome, H.; Yamada, Y. *Tetrahedron Lett.* **2002**, *43*, 2227.

- (11) Dewick, P. M. *Medicinal Natural Products: A Biosynthetic Approach*; Wiley, 2009.

- (12) For an exception, see: Zhao, C.; Toste, F. D.; Raymond, K. N.; Bergman, R. G. *J. Am. Chem. Soc.* **2014**, *136*, 14409.

- (13) For an excellent review of dendralenes, see: Hopf, H.; Sherburn, M. S. *Angew. Chem., Int. Ed.* **2012**, *51*, 2298.

- (14) Newton, C. G.; Drew, S. L.; Lawrence, A. L.; Willis, A. C.; Paddon-Row, M. N.; Sherburn, M. S. *Nat. Chem.* **2015**, *7*, 82.

- (15) Kozmin, S. A.; Rawal, V. H. *J. Org. Chem.* **1997**, *62*, 5252–5253.

- (16) Reich, H. J.; Renga, J. M.; Reich, I. L. *J. Am. Chem. Soc.* **1975**, *97*, 5434.

- (17) For the closest precedent to this stereoselective cycloaddition, see: Tietze, L. F.; Beifuss, U.; Ruther, M. *J. Org. Chem.* **1989**, *54*, 3120.

- (18) The diastereomers of **10** could also be separated and shown to converge to the same product upon dephosphorylation.

- (19) Huffman, J. W.; Balke, W. H. *J. Org. Chem.* **1988**, *53*, 3828.

- (20) Ngo, K.; Brown, G. D. *Tetrahedron* **1999**, *55*, 15109.

- (21) Schriesheim, A.; Muller, R. J.; Rowe, C. A. *J. Am. Chem. Soc.* **1962**, *84*, 3164.

- (22) Harrod, J. F.; Chalk, A. J. *J. Am. Chem. Soc.* **1964**, *86*, 1776.

- (23) Crossley, S. W. M.; Barabé, F.; Shenvi, R. A. *J. Am. Chem. Soc.* **2014**, *136*, 16788.

- (24) Nicolaou, K. C.; Harrison, S. T. *Angew. Chem., Int. Ed.* **2006**, *45*, 3256.

- (25) Stereoselectivity was also poor and the remaining material could not be identified. See ref 9f.

- (26) Stereochemistry depicted assumes a thermally allowed 2-electron suprafacial Wagner-Meerwein shift.

- (27) Wood accesses a related amino alcohol (ref 9b) by epoxide-opening with NaN<sub>3</sub>, followed by Na<sup>0</sup> reduction, conditions which are reported to reduce isonitriles.

- (28) (a) Fier, P. S.; Hartwig, J. F. *Angew. Chem., Int. Ed.* **2013**, *52*, 2092.

- (b) Levin, V. V.; Dilmann, A. D.; Belyakov, P. A.; Struchkova, M. I.; Tartakovsky, V. A. *J. Fluorine Chem.* **2009**, *130*, 667.

- (29) (a) Hofmann, A. W. *Ann. Chem.* **1868**, *298*, 202. (b) Sasaki, T.; Eguchi, S.; Katada, T. *J. Org. Chem.* **1974**, *39*, 1239.

- (30) Hertler, W. R.; Corey, E. J. *J. Org. Chem.* **1958**, *23*, 1221.