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Stereocontrolled Synthesis of Kalihinol C

Christopher A. Reiher and Ryan A. Shenvi*

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

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.[1,2] Kalihinol A[3a] also exhibits the highest reported potency of the ICTs against *Plasmodium falciparum*,[3b] killing with an EC_{50} 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[4] or copper chelation,[5] 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.[6] 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[2,6,7] and associated methods[8] to produce and modify three main structural classes: amphilectenes, adocianes, and kalihinols.[1,2] Prior syntheses[9] 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.[10] 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)[1] would arise from bisabolyl cation intermediate **3** via cation-olefin cyclization and concomitant stereoselective capture of water.[11] 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.[12]

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

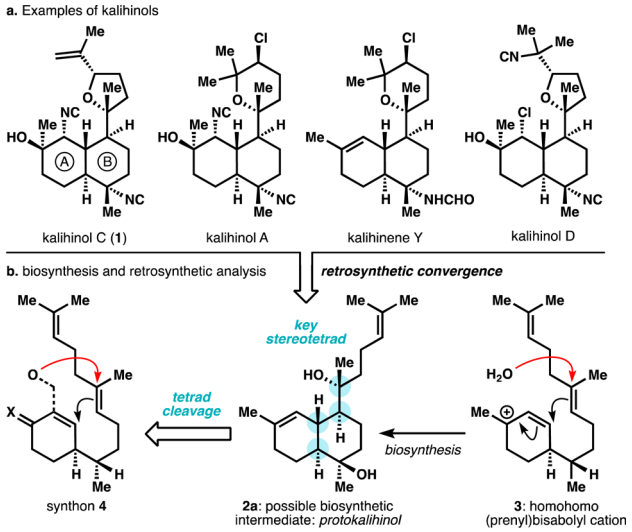
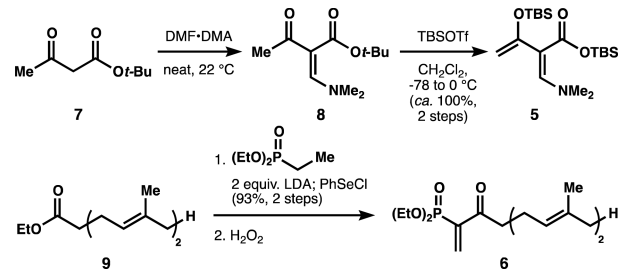


Figure 1. (a) Kalihinol congeners; (b) hypothetical biosynthesis that informs a proposed chemical synthesis.

Scheme 1. Routes to Building Blocks



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[15] 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**

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

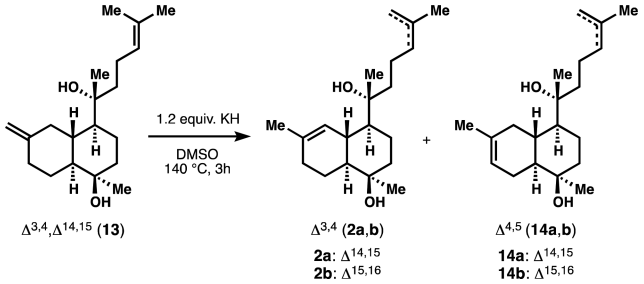
Building block **5** was synthesized by condensation of *tert*-butyl acetoacetate **7** with dimethylformamide dimethyl acetal (DMF-DMA) to yield vinylogous amide **8**, which was doubly silylated to **5** with loss of the *tert*-butyl group. Geranyl-phosphonate **6** was also synthesized in two steps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

Cycloaddition of **5** to **6** occurred at 22 °C in CH_2Cl_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[17] to provide, after tautomerization, β-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.[18]

Lactone **10** was converted to diol **11** by (1) Krapcho-like dephosphonylation, (2) stereoselective methyl addition to the B-ring ketone, and (3) lactone hydrolysis/decarboxylation; each step deserves some comment. First, the desphonylation is a little-precedented transformation that required the development of a new procedure [LiCl, Py·HCl (aq.), 90→110 °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,[2,9,10] 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[19] as well as alkene isomerizations in the heavily studied amorphane sesquiterpenes.[20] Attempts to generate endocyclic alkene **2** by ionization of the tertiary alcohol derived from ketone **11** delivered the isomeric $\Delta^{4,5}$ alkene with unrelenting regularity. Because Brønsted bases can mediate alkene isomerization at high temperatures,[21] 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 °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 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[22] or HAT isomerization[23] (entries 6 and 7) delivered mixtures of alkenes or the $\Delta^{4,5}$ isomer exclusively.

Table 1. Alkoxide-Directed Alkene Isomerization



entry	variations (and % conversion)	2:14	%2a
1	none (78)	7:1	54
2[a]	4 equiv. KO*t*-Bu, no KH (82)	5:1	55
3[a]	16 equiv. KO*t*-Bu, no KH (86)	1:1	28
4	1.2 equiv. *n*-BuLi, no KH (0)		0
5	DMPU instead of DMSO (0)		0
	alternate conditions		
6[b]	20 mol % $RhCl_3$, $EtOH/H_2O$, 70 °C (56)	1:1	28
7[a]	2 mol % [Co],[c] 4 mol % $PhSiH_3$, PhH (42)	<1:20	<5

[a] ^{1}H NMR. [b] GC–MS. [c] Co(Sal$^{t\text{-Bu},t\text{-Bu}}$)Cl·$H_2O$.

A Sharpless-type directed epoxidation[24] 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 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).

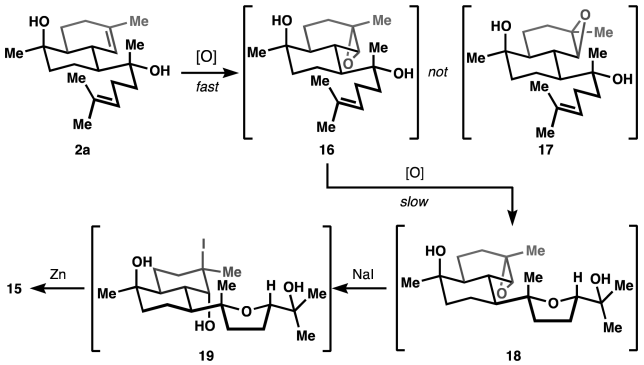


Figure 2. Stereoselective oxidative cyclization to **15**.

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 stereoinver-

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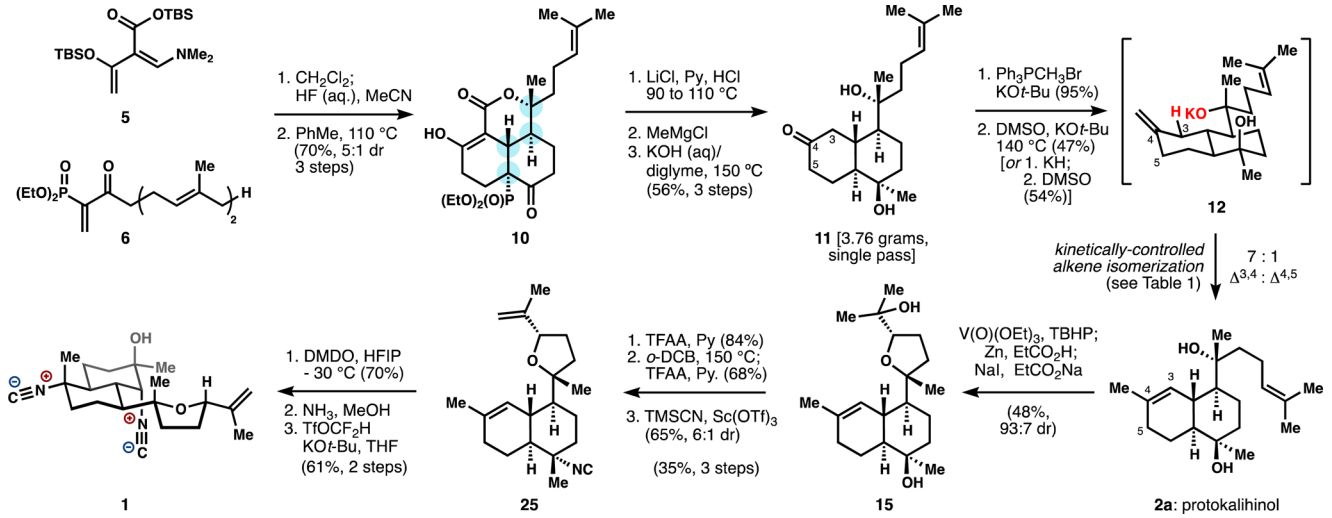
Scheme 2. Synthesis of Kalihinol C



sion.[8] 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.[9e] 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[8] was low-yielding by virtue of competitive elimination (**22**→**23**).[25] Because the epoxide opening occurred faster than trifluoroacetate ionization, and the resulting isocyanohydrin caused elimination in ring B, we concluded that the B-ring C–N bond must be in place prior to epoxidation.

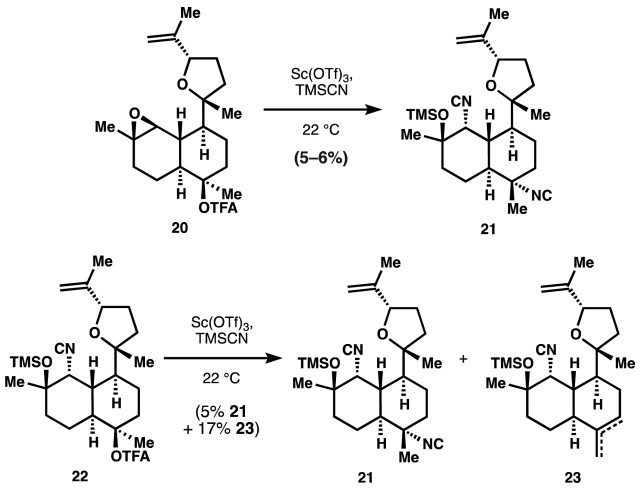
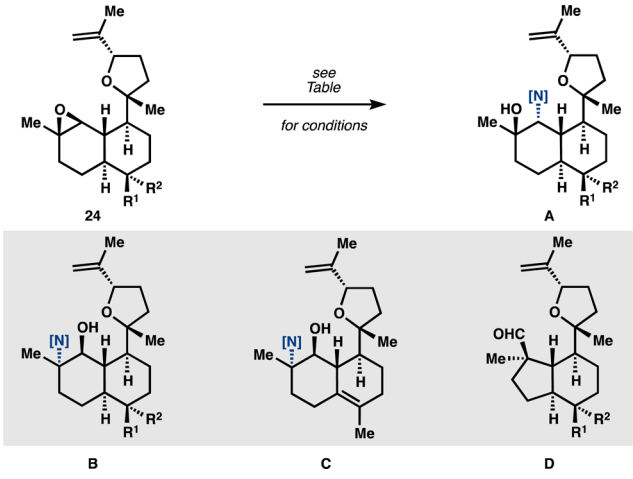


Figure 3. Tandem isonitrile formation is very low yielding.

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**.[26] So, the A- and B-ring substituents proved mutually incompatible in the tandem solvolysis sequence reported by Vanderwal.[9e]

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).

Table 2. Isocyanohydrin Installation[a]



R^1/R^2	conditions [N]	R^1/R^2	A:B:C:D
OTFA/Me	TMSCN, Sc(OTf)$_3$ [NC]	OTFA/Me	83:0:17:0
OH/Me	TMSCN, Sc(OTf)$_3$ [NC]	OTMS/Me	100:0:0:0
Me/NC	TMSCN, Sc(OTf)$_3$ [NC]	Me/NC	61:0:39:0
Me/NHCHO	TMSCN, Sc(OTf)$_3$ [NC]	Me/NHCHO	54:31:0:15
Me/NC	NH_3, MeOH [NH_2]	Me/NC	100:0:0:0

[a]Any silylethers were converted to alcohols with TBAF.

Aminolysis in methanol cleanly opened the epoxide to deliver a *sec*-alkyl amino *tert*-alcohol,[27] which was converted to the isocyanohydrin of **1** via difluorocarbene derived from difluoromethyl triflate[28] and KO*t*-Bu. More orthodox methods for amine to isonitrile conversion worked poorly: chloroform/sodium hydroxide[29] generated appreciable amounts of a

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dichlorocyclopropane and an amide; formylation of the hindered amine occurred slowly due to buildup of acid (isonitriles are produced by subsequent formamide dehydration).[30] 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 chemoselective 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 $C_{19}H_{26}O_4$ (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

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Notes

The authors declare no competing financial interest.

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