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Stereocontrolled Synthesis of Kalihinol C

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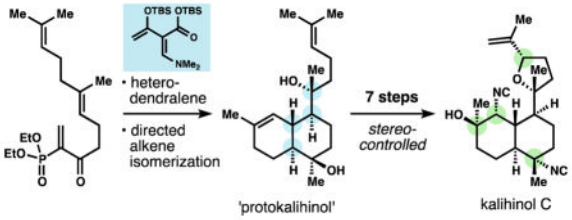
Abstract

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.

Graphical Abstract



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 *P. 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

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Supporting Information. Detailed experimental procedures, spectral data, chromatograms and x-ray crystallography. This material is available free of charge via the Internet at http://pubs.acs.org.

stereocontrolled synthesis of kalihinol C (**1**) enabled by a new hetereodendralene 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] While such a pathway might globally simplify formation of the kalihinol stereotetrad (in blue), we thought *intra*-molecular 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 forges 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.

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** 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 dimethyl formamide dimethyl acetal (DMF-DMA) to yield vinylogous amide **8**, which was doubly silylated to **5** with loss of the *tert*-butyl group. Geranylphosphonate **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-ketolactone **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 3-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. Since 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 *inter*-molecular 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 4–5; see SI for a list of other variations). Methods like coordinative isomerization[22] or HAT isomerization[23] (entries 6–7) delivered mixtures of alkenes or the $\Delta^{4,5}$ isomer exclusively.

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 isocyanohydrin of **1** (**16**, see Figure 2). Fortunately, these same conditions also catalyzed 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 A-ring equatorial *tert*-alkyl isonitrile with our solvolytic stereoinversion.[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] Since 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.

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 semi-pinacol 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 regioselectively generate 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,[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 dichlorocyclopropane and an amide; formylation of the hindered amine occurred slowly due to build up 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 inter-mediate, 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 an 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.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

Funding Sources

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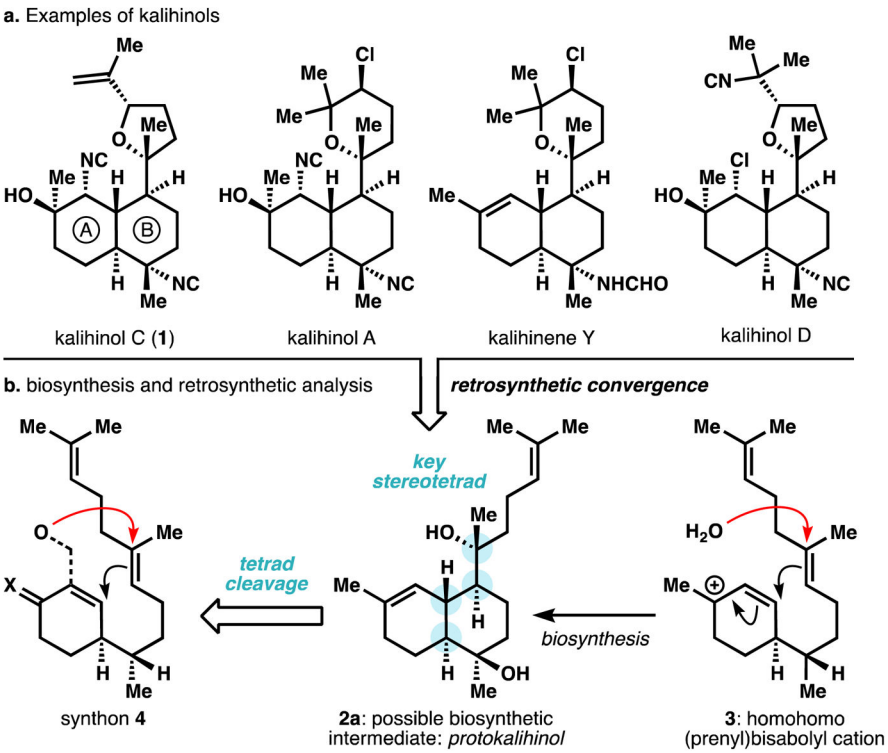


Figure 1.

a. Kalihinol congeners **b.** hypothetical biosynthesis that informs a proposed chemical synthesis.

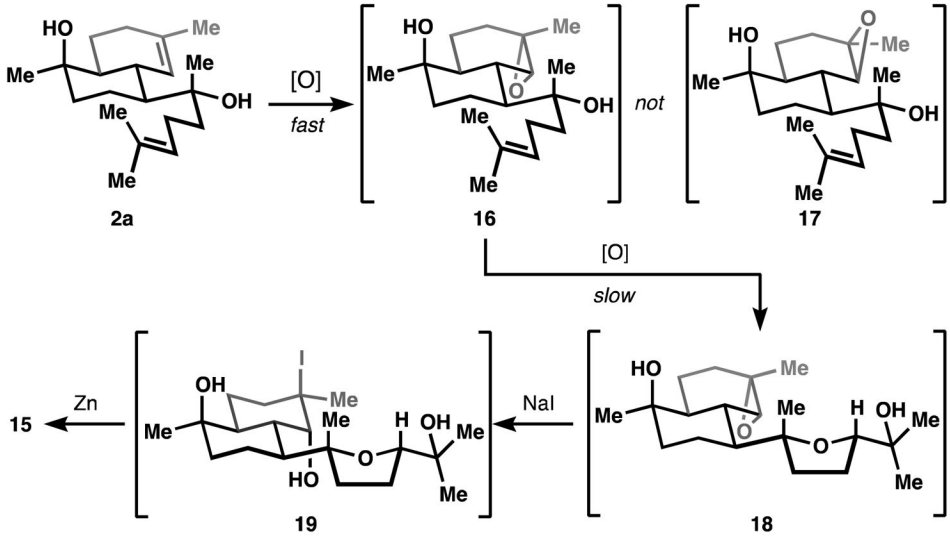


Figure 2.
Stereoselective oxidative cyclization to **15**.

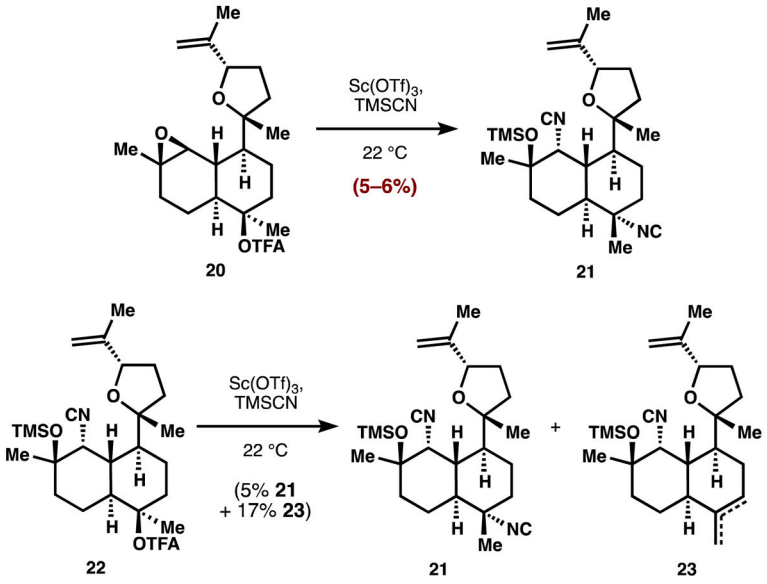
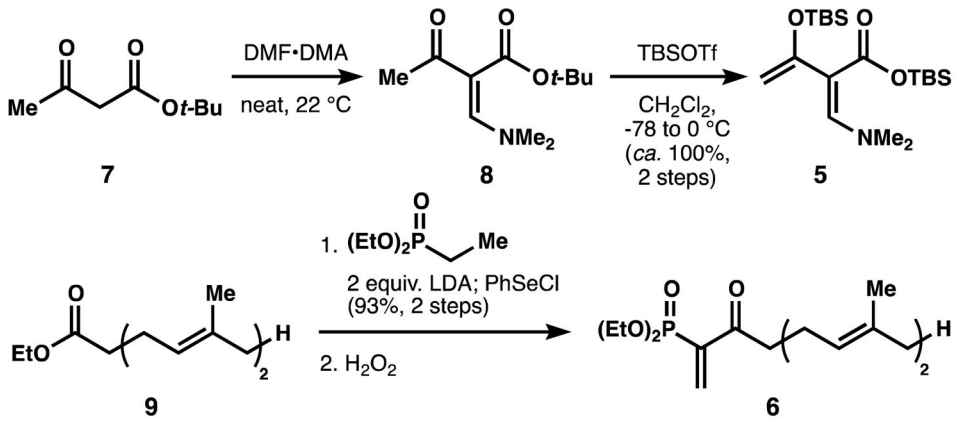
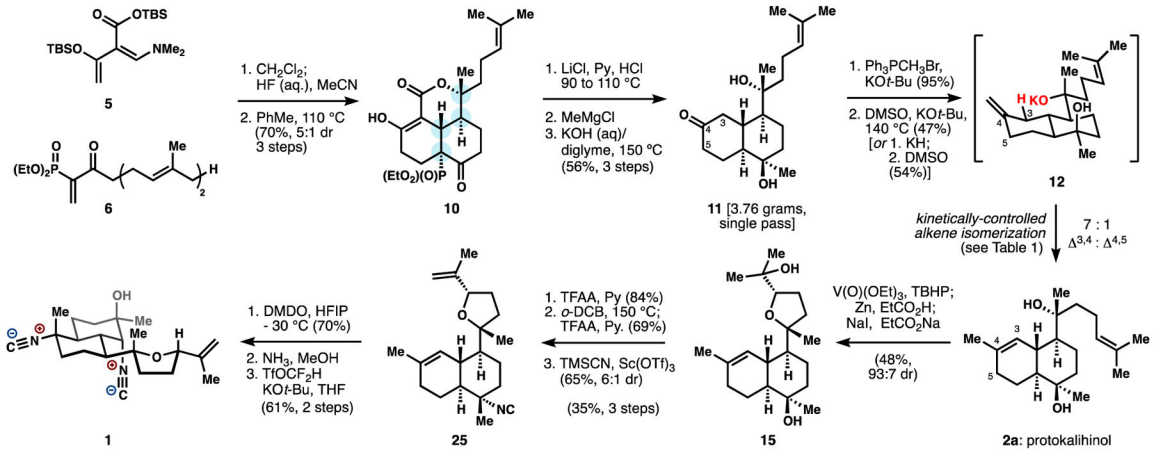


Figure 3.
Tandem isonitrile formation is very low yielding.



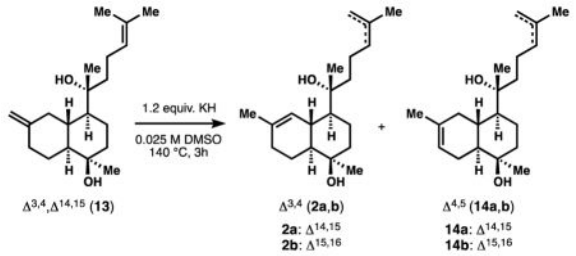
Scheme 1.
Routes to building blocks.



Scheme 2.
Synthesis of kalihinol C.

Table 1

Alkoxide-directed alkene isomerization.



Entry	Variations (& % 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

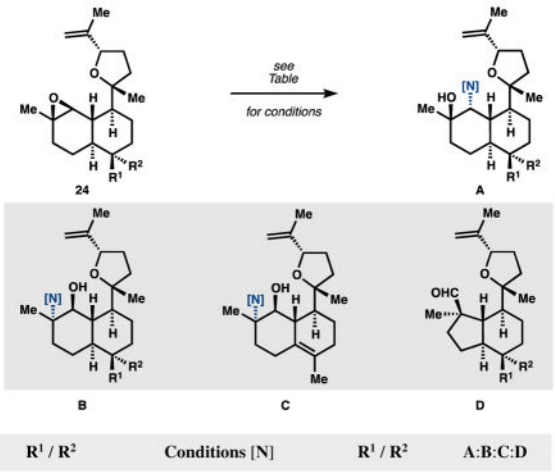
[a] ^{1}H NMR;

[b] GCMS;

[c] Co(Sal*t*-Bu,*t*-Bu)Cl•H_2O

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.