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Synthesis and Potent Antimalarial Activity of Kalihinol B

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Supporting Information

ABSTRACT: Of the 50+ kalihinane diterpenoids reported to date, only five had been tested for antimalarial activity, in spite of the fact that kalihinol A is the most potent among the members of the larger family of antimalarial isocyanoterpenes. We have validated a strategy designed to access many of the kalihinanes with a 12-step enantioselective synthesis of kalihinol B, the tetrahydrofuran isomer of kalihinol A (a tetrahydropyran). Kalihinol B shows similarly high potency against chloroquine-resistant *Plasmodium falciparum*.

Many sponge-derived isocyanoterpenes exhibit potent antimalarial activity.[1] In general, they are as active against drug-resistant *Plasmodium falciparum* (1.2−31 nM for **1**−**4**, Figure 1) as they are against drug-sensitive parasite, and

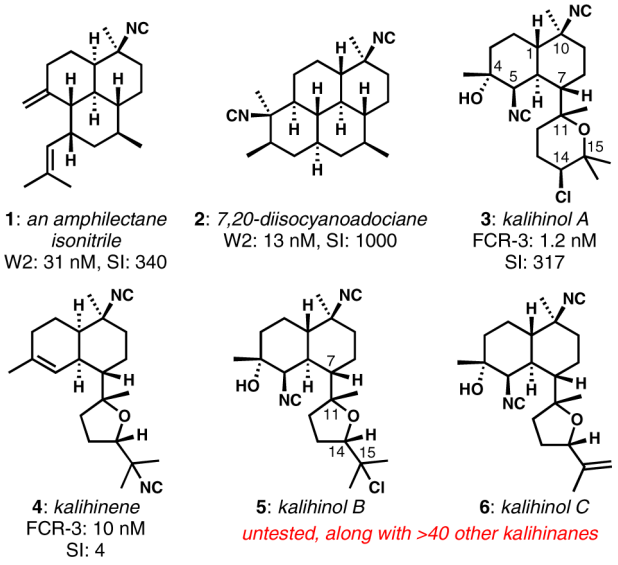

Figure 1. Representative antimalarial isocyanoterpenes (W2 and FCR-3 are drug-resistant strains of *P. falciparum*; SI = selectivity index with respect to mammalian cells).

they typically show high selectivity indices (SIs) for *P. falciparum* over human cells. The kalihinanes (**3**−**6** are representative) are a subgroup of these isocyanoterpenes isolated primarily from sponges of the genus *Acanthella* and characterized by *cis*- or *trans*-decalin cores bearing pendant tetrahydropyrans or tetrahydrofurans and a variable set of isonitrile, isocyanate, isothiocyanate, formamide, hydroxyl, and chloride substituents.[2]

Of the more than 50 kalihinanes reported to date, the antimalarial activities of only five have been reported, and the isonitrile function appears to be critical for high activity.[1] The kalihinanes also demonstrate cytotoxic,[2e,p] antibacterial,[2a−c,f,o] antifungal,[2e] anthelmintic,[2d] and antifouling[2j,k,p] activities. In light of the fact that kalihinol A (**3**) has been known since 1998 to be an extremely potent antiplasmodial agent (EC_{50} = 1.2 nM against the drug-resistant FCR-3 strain, the most potent of all isocyanoterpenes tested to date),[1c] it is surprising that so few kalihinanes have been studied for antimalarial properties. Laboratory syntheses have been reported by Wood (kalihinol C[3]), Yamada (kalihinene X[4]), and Miyaoka (kalihinols A[5a] and Y[5b] and 10-*epi*-kalihinol I[5b]); however, no antimalarial evaluations were undertaken with the synthetic material.[6,7] With the increasing threat from drug-resistant *P. falciparum* strains, including those that do not succumb to artemisinin-based combination therapies,[8] research into any compounds with documented antimalarial activity and selectivity is clearly valuable.

There is a wealth of structural diversity in the kalihinane group,[2] and a synthesis that could address multiple naturally occurring kalihinanes as well as synthetic analogues would permit a thorough evaluation of structure−activity relationships. The relative scarcity of material from natural sources[2] and the length of the reported chemical approaches to the kalihinanes (**3** in ca. 37 steps longest linear sequence (LLS);[5a] and **6** in ca. 24 steps LLS[3b]) likely have been impediments to a systematic evaluation of the biological activity. From the limited set of biological testing reported to date,[1c,6] it is clear that the presence of two isonitriles is correlated with high antiplasmodial activity, but the specific location of the isonitriles is not critical (compare **3** and **4**). To elucidate structure−activity relationships for this family, we aimed to develop a concise strategy that would be applicable to many members of the kalihinane family. As a proof of principle, we report in this preliminary communication a short synthesis (12 steps LLS) of (+)-kalihinol B (**5**) and disclose its potent antimalarial activity.

We viewed the "attached ring motif"[9]—in this case the oxygen heterocycle attached to the decalin with its attendant vicinal C7/C11 stereogenic centers—as a significant challenge that could arguably be viewed as the cause of the length of previous kalihinane syntheses. These earlier successes took

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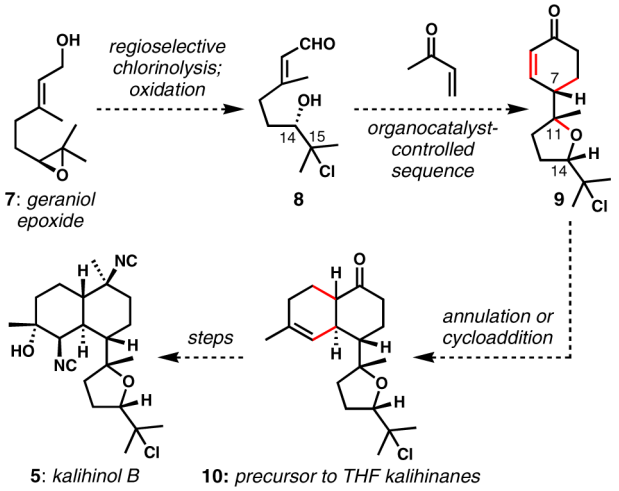
advantage of a biosynthetically relevant C14(C15)−O bond formation to generate the heterocycle. We viewed the C11−O bond as a strategic disconnection in our plan to address the attached ring problem (Scheme 1). α,β-Unsaturated aldehyde

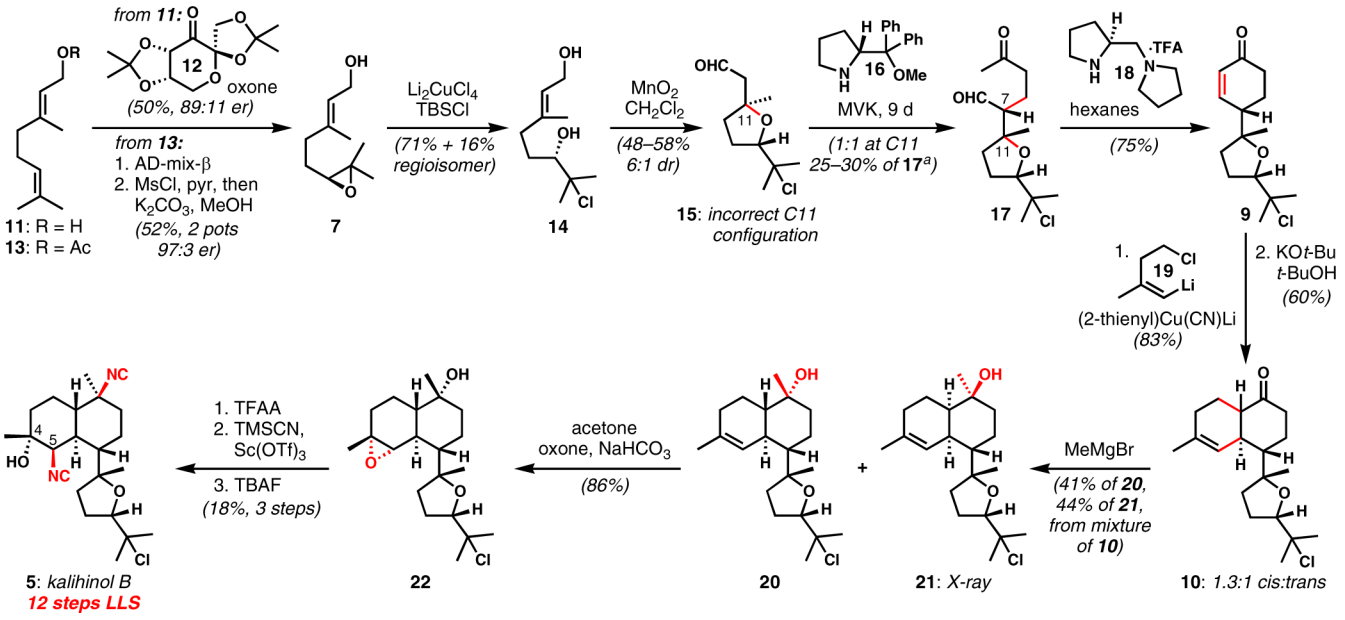
Scheme 1. Strategy To Access the THF Kalihinanes



8, accessed by regioselective chlorinolysis and oxidation of geraniol epoxide (**7**), will engage in an oxa-Michael−Robinson annulation sequence to generate cyclohexenone **9** with the vicinal C7−C11 stereogenic centers. Precedent suggested that pyrrolidine-based secondary amine catalysts of the same enantiomeric series could be used to control the C11 center in the course of the oxa-Michael addition[10] as well as the C7 center in the Michael addition step of the Robinson annulation,[11] thereby presenting the possibility of using a single catalyst for this sequence. Either annulation or cycloaddition processes would permit access to the decalin in key intermediate **10**, which should be readily elaborated to kalihinane natural products, including kalihinol B (**5**).[2c] A key aspect of the endgame involved the installation of both isonitriles in one step. For this finish, we aimed to take advantage of the recent critical advance from the Shenvi laboratory in the stereoinvertive displacement of tertiary trifluoroacetates by TMSCN,[12] a method developed in the context of their exceptional synthesis of amphilectane **1**.[13]

Our strategy was executed as illustrated in Scheme 2. Shi epoxidation of geraniol (**11**) afforded 6,7-epoxygeraniol (**7**) with moderate enantioselectivity.[14] Alternatively, a two-pot procedure using Sharpless dihydroxylation of geranyl acetate (**13**) provided **7** in 97:3 er.[15] Regioselective epoxide chlorinolysis using dilithium tetrachlorocuprate in the presence of *tert*-butyldimethylchlorosilane[16] afforded desired chlorohydrin **14** in 71% yield along with a 16% yield of its regioisomer (not shown). Allylic oxidation of **14** triggered spontaneous stereoselective cyclization of the secondary alcohol, affording tetrahydrofuran **15** with predominantly the incorrect C11 configuration. However, exposure of **15** to the Gellman prolinol catalyst **16**[11] induced the desired intermolecular Michael reaction, resulting in a 1:1 mixture of Michael adducts epimeric at C11, from which a ca. 30% yield of the desired stereoisomer **17** could be isolated. The catalyst effectively controlled the configuration at C7 and facilitated a partial correction of the C11 center, clearly indicating that the oxa-Michael reaction is reversible under these reaction conditions.[10,17] *This partial stereochemical correction is a noteworthy victory* and suggests that conditions might eventually be found to favor isomer **17**. Complete Robinson annulation could not be accomplished in one step because of decomposition; aldol condensation of **17** was catalyzed with diamine **18**[18,19] to afford enone **9**. Keto aldehyde **17** proved sensitive to basic conditions, and more typical aldol condensation conditions with hydroxide/alkoxide bases[20] were less reliable.[21,22] A Piers-type annulation[23] onto enone **9** was accomplished via fully diastereoselective conjugate addition of the cuprate derived from **19** and subsequent intramolecular alkylation using potassium *tert*-butoxide, delivering *trans*-decalin **10** as the minor component of a 1:1.3 mixture

Scheme 2. Enantioselective Synthesis of Kalihinol B[a]



[a]The yield range shown was obtained when material of 97:3 er was used; when material of 89:11 er was used, the yield of **17** was 23−25%.

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that is not easily resolved.[24] Although this stereochemical outcome is not ideal, the *cis*-decalin is, in principle, useful for the synthesis of the kalihinenes (see **4**).

trans-Decalin **20** and its cis isomer **21** can be accessed in pure form after high-yielding, stereoselective nucleophilic methylation of the mixture of isomers of **10**. While *trans*-decalin **20** failed to crystallize, X-ray crystal structure analysis of *cis*-decalin **21** indicated that the stereochemistry of the attached ring motif matched that found in the natural product targets. Epoxidation of *trans*-decalin **20** using dimethyldioxirane (DMDO) yielded the desired α-epoxide **22** as a single diastereomer. At this stage, we looked to Shenvi's conditions for invertive tertiary trifluoroacetate displacement by trimethylsilyl cyanide for the installation of the isonitriles.[12,13] Conversion of the tertiary alcohol of **22** to a trifluoroacetate preceded exposure to scandium(III) triflate and trimethylsilyl cyanide, which effected rapid isocyanosilylation of the epoxide and much slower invertive displacement of the trifluoroacetate. Desilylation of the tertiary TMS ether gave kalihinol B (**5**). The isonitrile introduction result is noteworthy for the two aspects of regiocontrol in the epoxide isocyanolysis. While the Fürst–Plattner principle predicts trans-diaxial nucleophilic opening of the epoxide at the least hindered C5 position, it was not clear whether the isonitrile or nitrile isomer would predominate.[25] Success in this reaction, even with the relatively low overall yield (due largely to competitive elimination of the axial tertiary trifluoroacetate), eliminates a significant number of steps and is critical to the short overall sequence, in which the natural product is obtained in 12 or 13 steps from geraniol.

Synthetic (+)-kalihinol B was subjected to the SYBR Green parasite proliferation assay[26] to test for antiplasmodial activity against wild-type *P. falciparum* (3D7 strain) and the chloroquine-resistant parasite (Dd2 strain). It exhibited potent antimalarial activity against each strain (IC_{50} = 8.4 nM for 3D7 and 4.6 nM for Dd2).

We have developed a concise, enantioselective synthesis of (+)-kalihinol B and shown that it is potently toxic toward a strain of drug-resistant malaria parasite. Our synthesis also proves the feasibility of our approach to this family of complex isocyanoterpenes. In principle, this design also permits access to the tetrahydropyran-containing kalihinanes (such as kalihinol A) via the regioisomer of chlorohydrin **14**, a possibility that we are actively investigating. While some transformations in our current synthesis would benefit from improved selectivity, even in its current form our achievement is the most concise synthesis of any of the kalihinanes because nearly all of the steps generate key C–O, C–Cl, C–C, or C–N bonds. We are currently optimizing the unselective reactions and implementing our strategy in the synthesis of other members of the family and unnatural analogues in order to gain greater insights into the structural requirements for antiplasmodial activity.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

Experimental procedures and characterization data for all new compounds, X-ray crystallographic structure and information for **21** (CIF), and complete ref 8b. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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