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Total Synthesis of (±)-Kalihinol C

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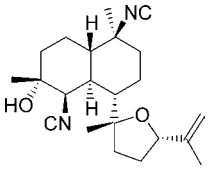
ABSTRACT



kalihinol C

The total synthesis of kalihinol C, a bis-isonitrile marine diterpenoid isolated from *Acanthella* sp., is reported. The decalin framework was established via an intramolecular Diels–Alder cycloaddition and subsequently functionalized through a series of substrate-controlled diastereoselective transformations to install the tertiary isonitrile, *β*-hydroxy isonitrile, and pendant tetrahydrofuranyl ring.

Kalihinol C (**1**), isolated by Scheuer and co-workers in 1984 from the sponge *Acanthella* sp., is a member of a richly functionalized family of marine diterpenoids known as the kalihinanes.[1] This class of natural products includes more than 40 members and is characterized by a highly functionalized tricyclic core containing isonitrile, isothiocyanate, formamide, and/or chlorine moieties. Several kalihinanes have demonstrated anthelmintic,[1,2] antifouling,[1,3] antimicrobial,[1] antifungal,[1,4] and, mostly notably, potent antimalarial activity.[5] While the antimalarial activity of kalihinol C has yet to be determined, the isonitrile-containing kalihinanes that have been tested for in vitro antimalarial activity were found to be nanomolar inhibitors of the malaria parasite, *Plasmodium falciparum*.[5,6]

The initial retrosynthetic analysis of kalihinol C was centered upon three major structural features: the pendant tetrahydrofuran, the isonitriles, and the *trans*-decalin core (Figure 1). On the basis of previous model studies and the

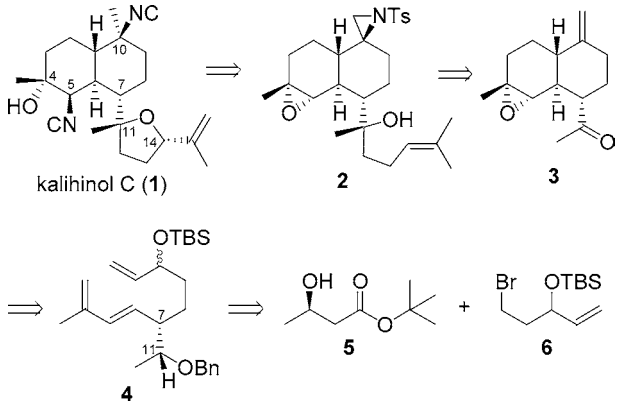


Figure 1. Retrosynthetic analysis.

conformationally rigid nature of *trans*-decalins, the topology enforced by the decalin carbocycle was expected to influence introduction of the remaining functionality through a series of substrate-controlled, diastereoselective reactions.[7] The pendant tetrahydrofuran was envisioned as arising from

(1) (a) 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) Chang, C. W. J.; Patra, A.; Baker, J. A.; Scheuer, P. J. *J. Am. Chem. Soc.* **1987**, *109*, 6119. (c) Shimomura, M.; Miyaoka, H.; Yamada, Y. *Tetrahedron Lett.* **1999**, *40*, 8015. (d) Fusetani, N.; Yasumuro, K.; Kawai, H.; Natori, T.; Brinen, L.; Clardy, J. *Tetrahedron Lett.* **1990**, *31*, 3599. (e) Rodriguez, J.; Nieto, R. M.; Hunter, L. M.; Diaz, M. C.; Crews, P.; Lobkovsky, E.; Clardy, J. *Tetrahedron* **1994**, *50*, 11079. (f) Okino, T.; Yoshimura, E.; Hirota, H.; Fusetani, N. *J. Nat. Prod.* **1996**, *59*, 1081. (g) Patra, A.; Chang, C. W. J.; Scheuer, P. J.; Vanduyne, G. D.; Matsumoto, G. K.; Clardy, J. *J. Am. Chem. Soc.* **1984**, *106*, 7981.

(2) Alvi, K. A.; Tenenbaum, L.; Crews, P. *J. Nat. Prod.* **1991**, *54*, 71.

(3) (a) Hirota, H.; Tomono, Y.; Fusetani, N. *Tetrahedron* **1996**, *52*, 2359. (b) Fusetani, N. *J. Nat. Toxins* **1996**, *5*, 249.

(4) Trimurtulu, G.; Faulkner, D. J. *J. Nat. Prod.* **1994**, *57*, 501.

(5) Miyaoka, H.; Shimomura, M.; Kimura, H.; Yamada, Y.; Kim, H. S.; Wataya, Y. *Tetrahedron* **1998**, *54*, 13467.

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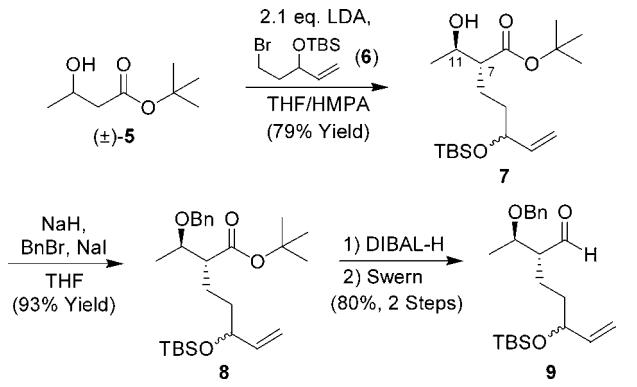
addition to a methyl ketone (**3**) and subsequent 5-*exo* cyclization of bishomoallylic alcohol **2**. The C(4)/C(5) functionality would derive from a trans diaxial opening of an epoxide with a nucleophilic nitrogen source. The equatorial nitrogen at C(10) would be installed by aziridination of *exo*-methylene **3**. An intramolecular Diels−Alder cycloaddition was expected to deliver the decalin core, and triene **4** could be derived from the coupling of β-hydroxy ester **5** and alkyl bromide **6**.

To set the relative stereochemistry between C(7) and C(11), β-hydroxy ester (±)-**5** was treated with lithium diisopropylamide followed by alkyl bromide **6** (Scheme 1).[8,9]

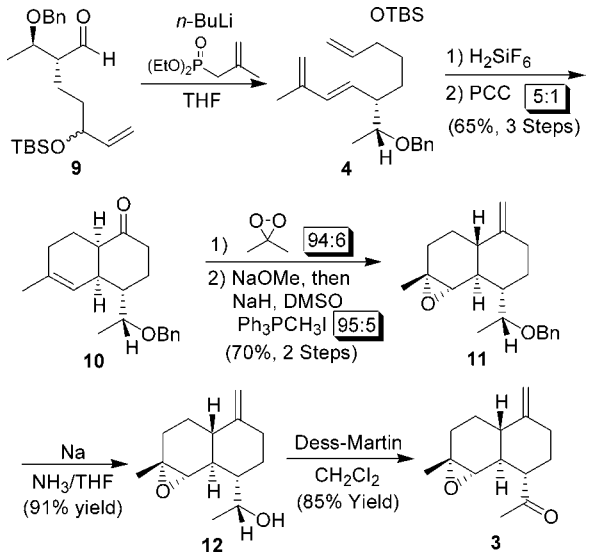
Scheme 1



Alcohol mixture **7** was obtained in 79% yield, diastereomeric only at the silyl ether (vide infra). The free alcohol was protected as its benzyl ether **8**, and the substrate was subjected to diisobutylaluminum hydride reduction and Swern oxidation to provide aldehyde **9**.

Homologation of **9** under Horner−Wadsworth−Emmons conditions produced the desired triene (**4**) as a single olefin isomer (Scheme 2). With the intramolecular Diels−Alder precursor in hand, initial efforts were focused upon a one-step deprotection−oxidation−cyclization sequence to obtain *cis*-decalin **10** via the anticipated *endo*-boat transition state.[10] Indeed, treatment of **4** with Jones reagent gave **10** as the major stereoisomer. However, due to the delicate nature of **4**, the optimized yield of this reaction was only 30%. Less acidic conditions were explored, and it was found that deprotection of **4** with catalytic fluorosilicic acid[11] followed

Scheme 2



by oxidation with pyridinium chlorochromate afforded *cis*-decalin **10** in 65% overall yield from **9** with 5:1 diastereoselectivity.[12] In the course of screening oxidants, a clear correlation was observed between the Lewis acidity of the reagent and diastereoselectivity of the reaction.[13]

Epoxidation of *cis*-decalin **10** with dimethyl dioxirane proceeded with 94:6 diastereoselectivity. Subsequent epimerization afforded a 3:2 mixture of decalins favoring the *trans*-decalin, which, upon Wittig methylenation, gave almost exclusively *trans*-decalin **11**.[14] Benzyl deprotection of **11** with sodium metal afforded alcohol **12**, which was oxidized using Dess−Martin periodinane to provide the corresponding methyl ketone **3**.[15]

With the ketone at C(11) serving as a handle for incorporation of the tetrahydrofuran, selectivity of nucleophilic addition to ketone **3** was examined (Scheme 3). Reduction of **3** with sodium borohydride provided a mixture of alcohols with 91:9 diastereoselectivity. The stereochemistry of the major product differed from that of **12**, as observed by ^{1}H NMR (see Scheme 2), and thus was assigned as its C(11) epimer (**13**). If a homoprenyl carbon nucleophile added with the same facial selectivity as hydride, the desired C(11) epimer would be obtained. Interestingly, the desired stereoisomer corresponds to the anti-Felkin product.[16,17]

In an effort to obtain alcohol **14**, methyl ketone **3** was exposed to homoprenylmagnesium bromide (**15**) under a

(6) For antimalarial activity of other isonitrile-containing compounds, see: (a) Wright, A. D.; Konig, G. M.; Angerhofer, C. K.; Greenidge, P.; Linden, A.; Desqueyroux-Faundez, R. *J. Nat. Prod.* **1996**, *59*, 710. (b) 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. (c) Schwartz, O.; Brun, R.; Bats, J. W.; Schmalz, H. *Tetrahedron Lett.* **2002**, *43*, 1009.

(7) White, R. D.; Wood, J. L. *Org. Lett.* **2001**, *3*, 1825.

(8) ±)-**5** was prepared from reduction of *tert*-butyl acetoacetate with sodium borohydride; see: Mohrig, J. R.; Rosenberg, R. E.; Apostol, J. W. et al. *J. Am. Chem. Soc.* **1997**, *119*, 479. Alternatively, (−)-**5** can be accessed by Noyori hydrogenation of *tert*-butyl acetoacetate. For preparation of alkyl bromide **6**, see Supporting Information.

(9) Frater, G.; Wulf, G.; Mueller, U. *Helv. Chim. Acta* **1989**, *72*, 1846.

(10) Taber, D. F.; Gunn, B. P. *J. Am. Chem. Soc.* **1979**, *101*, 3992.

(11) Pilcher, A. S.; Hill, D. K.; Shimshock, S. J.; Waltermire, R. E.; DeShong, P. *J. Org. Chem.* **1992**, *57*, 2492.

(12) Minor component in this ratio represents the combined yield of the three undesired decalin stereoisomers as determined by GC.

(13) See Supporting Information.

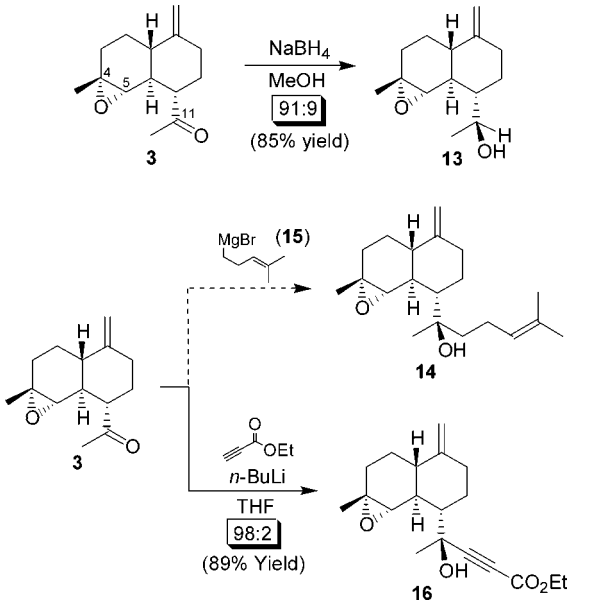
(14) Direct methylenation of the pure *cis*-decalin led to a variable ratio of *trans*- to *cis*-decalin olefinated product.

(15) Dess, D. B.; Martin, J. C. *J. Am. Chem. Soc.* **1991**, *113*, 7277.

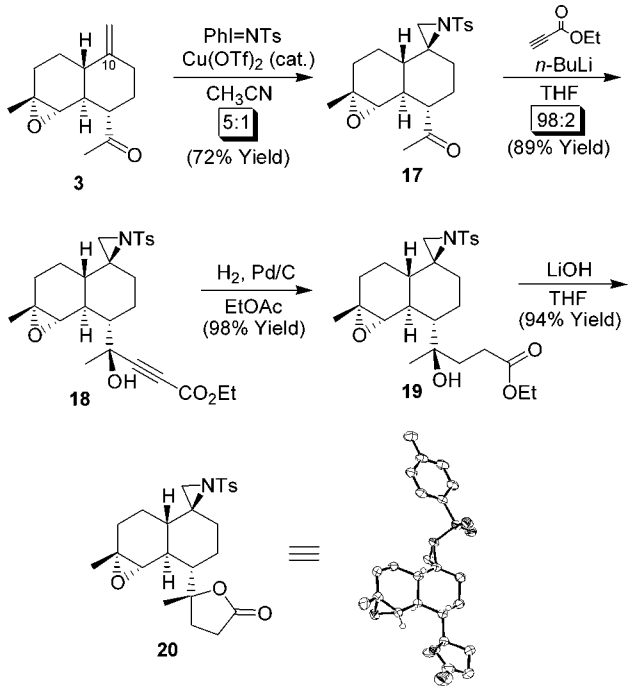
(16) (a) Fieser, L. F.; Huang, W. Y.; Goto, T. *J. Am. Chem. Soc.* **1960**, *82*, 1688. (b) Anh, N. T.; Eisenstein, O. *Nouv. J. Chim.* **1977**, *1*, 61. (c) Cherest, M.; Felkin, H.; Prudent, N. *Tetrahedron Lett.* **1968**, 2199. (d) Eliel, E. L.; Wilen, S. H.; Mander, L. N. *Stereochemistry of Organic Compounds*; Wiley & Sons: New York, 1994.

(17) Methine is the "large" group, the methylene is the "medium" group, and the hydrogen is the "small" group, as defined by ref 16a. The anti-Felkin selectivity of hydride addition was also observed in related substrates with varying functionality at C(4) and C(5).

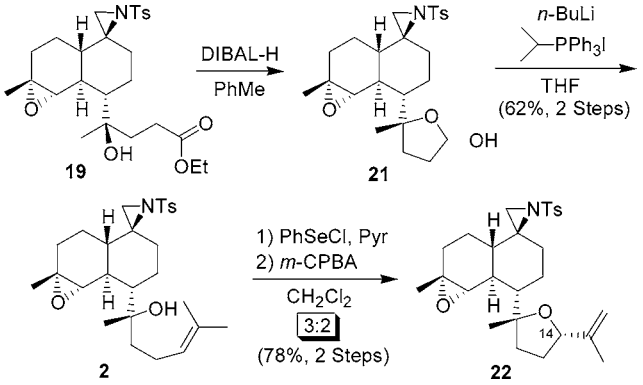
Scheme 3



Scheme 4



Scheme 5



variety of conditions. However, addition was not observed. Furthermore, a range of sp^3- and sp^2-hybridized nucleophiles, including Grignard reagents, dithianes, sulfones, alkyllithium reagents, and enolates, failed to undergo addition to **3**. Deuterium-quenching experiments revealed that enolization of the methyl ketone was occurring under the reaction conditions. Attempts to modulate the nucleophile basicity by transmetalation did not promote addition. Ultimately, less basic and less sterically demanding sp-hybridized nucleophiles were examined. It was found that the lithium anion of ethyl propiolate efficiently added to **3**, affording propargyl alcohol **16** with excellent diastereoselectivity (98:2).

Due to functional group incompatibilities encountered while attempting to advance **16**, we turned to a strategy that installed the C(10) nitrogen prior to propiolate addition to the methyl ketone (Scheme 4). Toward this end, aziridination of **3** led to the desired aziridine (**17**) with 5:1 diastereoselectivity. Treatment of **17** with propiolate anion gave **18** in 89% yield and thus demonstrated that the propiolate addition was both highly diastereoselective and chemoselective.

Alkyne reduction using catalytic hydrogenation conditions provided ester **19**. Lactonization with lithium hydroxide gave lactone **20**, a crystalline solid for which an X-ray structure was obtained. X-ray crystallography revealed that **20** possessed the correct C(11) stereochemistry and confirmed that the propiolate addition had indeed occurred in the desired, anti-Felkin mode.

Reduction of ester **19** with diisobutylaluminum hydride provided lactol mixture **21**, which was converted to bishomoallylic alcohol **2** in 62% yield over two steps (Scheme 5). Seleno-etherification of **2** followed by elimination provided exclusively the tetrahydrofuran regioisomer with modest preference (3:2) for the desired C(14) epimer (**22**).[18]

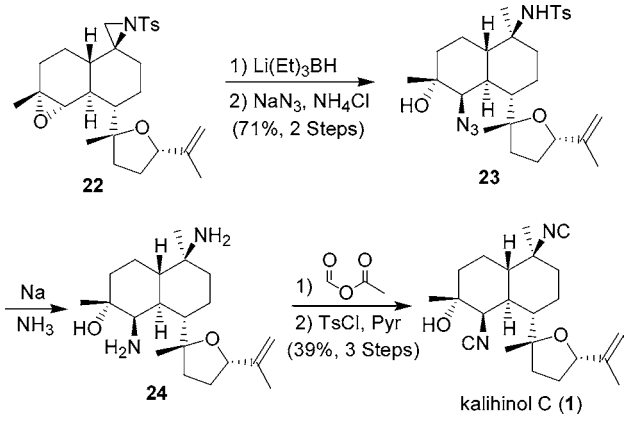
With the *trans*-decalin and tetrahydrofuran in place, the endgame strategy required incorporation of the isonitriles. To this end, it was found that nucleophiles consistently added to the terminal aziridine in preference to the epoxide. As a result, aziridine **22** was treated with Super-Hydride to give the corresponding tertiary amine, which was then exposed to ammonium azide to afford azido-alcohol **23** (Scheme 6).

Tosyl deprotection and simultaneous azide reduction with sodium metal[19] provided bisamine **24**, which upon formylation with acetic formic anhydride and subsequent dehydration afforded kalihinol C (**1**). The spectroscopic and chromatographic properties of **1** were identical to those reported for the natural product.[20]

(18) Stereochemical assignments were based upon the ^{13}C NMR shifts of the C(11) and C(14) ether carbons; see Supporting Information.

(19) An unexpected side product of this reduction was the corresponding bishomoallylic alcohol, resulting from fragmentation of the tetrahydrofuran ring. For a similar example, see: Sakai, K.; Ohtsuka, T.; Misumi, S.; Shirahama, H.; Matsumoto, T. *Chem. Lett.* **1981**, 355.

Scheme 6



In summary, the first total synthesis of the marine diterpenoid kalihinol C has been accomplished. The decalin core is constructed via diastereoselective intramolecular Diels−Alder cycloaddition, and facial bias of this core is utilized throughout the synthesis to direct functionalization with high fidelity. Our continued work toward other members of the kalihinane family will be reported in due course.

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Supporting Information Available: Experimental and spectral data for compounds **1**−**23**. This material is available free of charge via the Internet at http://pubs.acs.org.

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(20) See refs 1a and 1b.