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Progress toward the Total Synthesis of Kalihinane Diterpenoids

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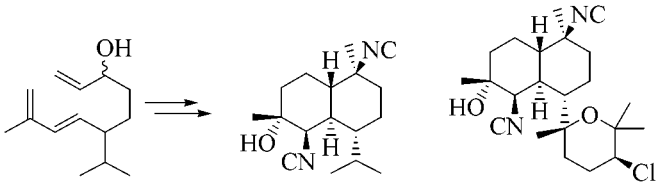
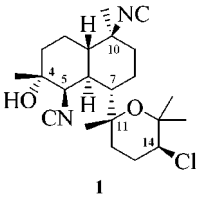
ABSTRACT



2 **11** **kalihinol A**

Studies toward the total synthesis of marine diterpenoids isolated from *Acanthella* sp., e.g., kalihinol A, are described. Efficient construction of the functionalized *trans*-decalin core (11) is achieved through intramolecular Diels−Alder cyclization followed by diastereoselective epoxidation and aziridination.

Kalihinol A (**1**) is one of several structurally related diterpenoids isolated from the marine sponge *Acanthella* (Table 1). Since their discovery in 1984 by Scheuer[1], this class of natural products has grown to include more than 40 members, each characterized by a highly functionalized tricyclic core containing isonitrile, isothiocyanate, formamide, and/or chlorine moieties.



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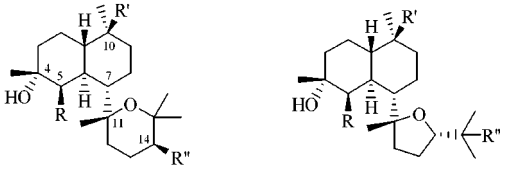
The kalihinane diterpenoids possess an array of important biological activities.[2] In particular, kalihinol A shows potent in vitro inhibition of the malaria parasite, *Plasmodium falciparum* (EC_{50} 1.2×10^{-9} M) with a high selectivity index (SI 317), defined as a ratio of FM3A cell cytotoxicity to *P. falciparum*.[3] Recently, much attention has been given to the growing problem of malaria proliferation due to increased resistance to existing drugs.[4] Considering the antiplasmodial activity of kalihinol A and interesting functionalization of the kalihinane family, a project directed toward their total synthesis was initiated.[5]

Table 1. Representative Kalihinane Diterpenoids



		R	R'	R"
Kalihinol	A	NC	NC	Cl
	E	NC	NC	epi-Cl
	I	NCS	NC	Cl
	X	NC	epi-NCS	Cl
	Z	NC	epi-NC	Cl

		R	R'	R"
Kalihinol	B	NC	NC	Cl
	C	NC	NC	$=CH_2$
	D	Cl	NC	NC
	F	NC	NC	NC
	G	NC	NC	NCS

(1) Chang, C. W. J.; Patra, A.; Roll, D. M.; Scheuer, P. J.; Matsumoto, G. K.; Clardy, J. *J. Am. Chem. Soc.* **1984**, *106*, 4644−4646.

(2) (a) Patra, A.; Chang, C. W. J.; Scheuer, P. J.; Van Duyne, D. G.; Matsumoto, G. K.; Clardy, J. *J. Am. Chem. Soc.* **1984**, *106*, 7981−7983. (b) Chang, C. W. J.; Patra, A.; Baker, J. A.; Scheuer, P. J. *J. Am. Chem. Soc.* **1987**, *109*, 6119−6123. (c) Omar, S.; Albert, C.; Fanni, T.; Crews, P. *J. Org. Chem.* **1988**, *53*, 5971−5972. (d) Fusetani, N.; Yasumura, K.; Kawai, H. Natori, T.; Brinen, L.; Clardy, J. *Tetrahedron Lett.* **1990**, *31*, 3599−3602.

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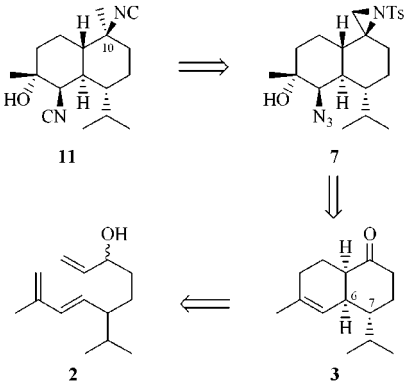
We hoped to access a number of kalihinane congeners and therefore desired an approach to the kalihinane-type carbocycle that would enable maximum flexibility in the introduction of the numerous functional groups present. To this end, retrosynthetic analysis of the decalin core led to an intermediate resembling **3** (Scheme 1), an intermediate in

Scheme 1

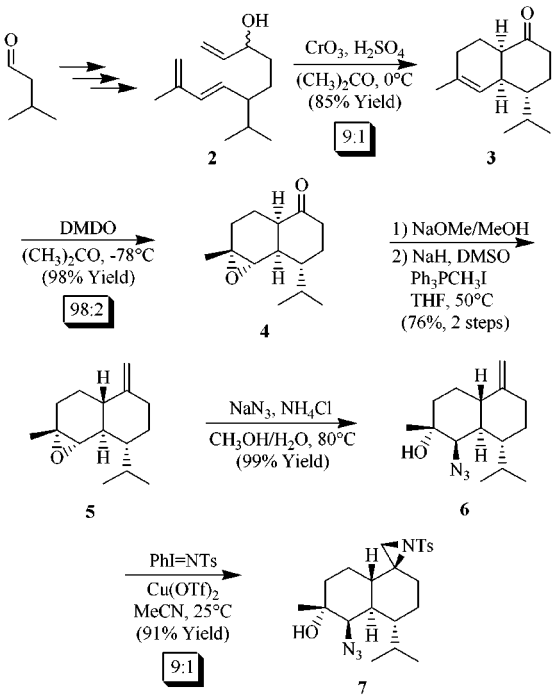


Taber's synthesis of (±)-torreyol.[6] This *cis*-decalin is the intramolecular Diels−Alder cycloadduct resulting from oxidation of triene **2** and possesses the relative stereochemistry between C(6) and C(7) found in the kalihinols. It was thus recognized that **3** could serve as an adequate model scaffold on which to explore construction of the challenging α-hydroxy isonitrile and tertiary isonitrile moieties requisite for the synthesis of kalihinol A and related congeners.

Scheme 1 shows the retrosynthesis of model decalin **11**. It was expected that the topology enforced by *cis*-decalin **3** could be used for stereocontrolled introduction of the α-hydroxy isonitrile, while the *trans*-decalin resulting from epimerization would control the introduction of the equatorial isonitrile at C(10) via aziridine **7**.

Having identified an approach, we commenced work with triene **2** (Scheme 2), which under Jones conditions and in accord with Taber's procedure directly afforded **3** as a 9:1 mixture of decalin diastereomers. As anticipated, epoxidation of **3** with DMDO occurs predominantly from the convex face to provide a 98:2 mixture of epoxide diastereomers favoring **4**.[7] Epimerization of **4** (NaOMe, MeOH) yielded a 7:3 mixture of *trans*- and *cis*-decalins respectively, which could be separated by silica gel chromatography or olefinated directly to give olefin **5** with a slightly improved decalin

Scheme 2



ratio of 78:22. From **5**, azido-alcohol **6** was obtained in near quantitative yield by facile trans-diaxial epoxide opening with ammonium azide.[8]

Installation of the equatorial nitrogen at C(10) was accomplished by copper-catalyzed aziridination with PhI═NTs to give a 9:1 mixture of diastereomers favoring aziridine **7**.[9] Single-crystal X-ray analysis of **7** revealed the correct relative configuration at all six necessary stereocenters (Figure 1).

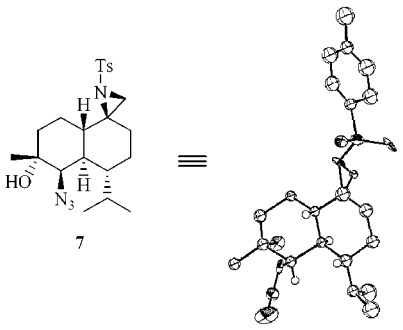


Figure 1. ORTEP plot of aziridine **7**.

Importantly, the orthogonally masked amines present in aziridine **7** allow for a selective reduction protocol that

(3) (a) Miyaoka, H.; Shimomura, M.; Kimura, H.; Yamada, Y.;. Kim, H.; Wataya, Y. *Tetrahedron*. **1998**, *54*, 13467−13474. (b) König, G. M.; Wright, A. D.; Angerhofer, C. K. *J. Org. Chem*. **1996**, *61*, 3259−3267. (c) Wright, A. D.; König, G. M.; Angerhofer, C. K.; Greenidge, P.; Linden, A.; Desqueyroux-Faundez, R. *J. Nat. Prod*. **1996**, *59*, 710−716.

(4) Kim, H.; Certa, U.; Dobeli, H.; Jakob, P.; Hol, G. J. *Biochemistry* **1998**, *37*, 4388−4396.

(5) The absolute stereochemistry of kalihinol A has recently been reported, see: Shimomura, M.; Miyaoka, H.; Yamada, Y. *Tetrahedron Lett.* **1999**, *40*, 8015−8017.

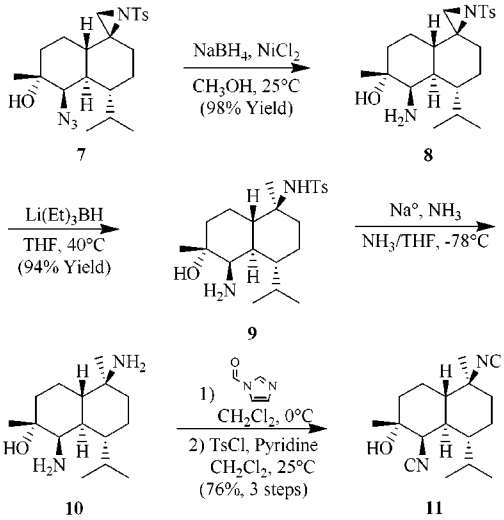
(6) Taber, D. F.; Gunn, B. P. *J. Am. Chem. Soc*. **1979**, *101*, 14, 3992−3993.

(7) Interestingly, *m*-CPBA offered no diastereoselectivity.

(8) Behrens, C. H.; Sharpless, K. B. *J. Org. Chem*. **1985**, *50*, 5696−5704.

(9) (a) Evans, D. A.; Faul, M. M.; Bilodeau, M. T. *J. Am. Chem. Soc*. **1994**, *116*, 2742−2753. (b) Tanner, D. *Angew. Chem., Int. Ed. Engl*. **1994**, *33*, 599−619.

Scheme 3



enables derivatization of each free amine according to the functional groups required in each of the kalihinols (e.g., −NCS, −NCO, −NC). Thus, reduction of the azide with nickel boride, generated in situ from nickel chloride and sodium borohydride, gave amine **8** in excellent yield (Scheme 3).[10] This was followed by aziridine opening with lithium triethylborohydride and detosylation with sodium/ammonia to furnish diamine **10**. Finally, bisformylation of **10** using *N*-formyl imidazole followed by dehydration gave bisisonitrile **11**.[11]

In summary, we have developed an efficient approach to the functionalized decalin core of kalihinol A and related congeners. This approach employs an intramolecular Diels−Alder cycloaddition and highly diastereoselective epoxidation and aziridination procedures to install the appropriate functionality in 25% overall yield and 11 steps from **2**. Further efforts directed toward the asymmetric total synthesis of the kalihinane diterpenoids, in particular, kalihinol A, are currently underway and will be reported in due course.

Acknowledgment. We are pleased to acknowledge the support of this investigation by Bristol-Myers Squibb, Yamanouchi, Pfizer, Merck, and the Camille and Henry Dreyfus Foundation for a Teacher-Scholar Award. J.L.W. is a fellow of the Alfred P. Sloan Foundation.

Supporting Information Available: Experimental and spectral data for compounds **4**−**9** and **11**. This material is available free of charge via the Internet at http://pubs.acs.org.

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(10) (a) These conditions were chosen only after considerable experimentation using standard hydrogenolysis conditions (e.g., Pd/C, Pt Black, Rh/Al_2O_3, PtO_2, or $Pd(OH)_2$ and H_2), which principally gave the epoxide as the major product. (b) Back, T. G.; Baron, D. L.; Yang, K. *J. Org. Chem.* **1993**, *58*, 2407−2413.

(11) Kitagawa, T.; Ito, J.; Tsutsui, C. *Chem. Pharm. Bull.* **1994**, *42*, 9, 1931−1934.