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Total synthesis of antimalarial diterpenoid (+)-kalihinol A†

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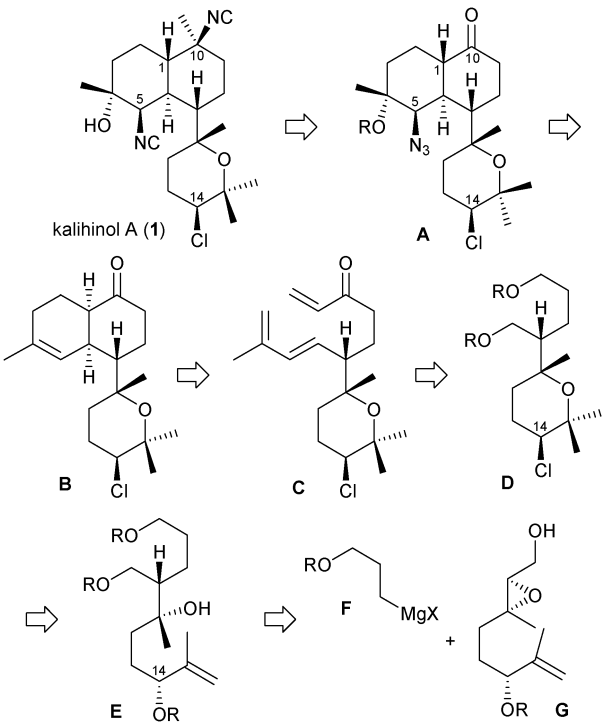
Total synthesis of antimalarial diterpenoid (+)-kalihinol A, isolated from marine sponge *Acanthella* sp., is achieved. This total synthesis involves regioselective alkylation of an epoxide, construction of a tetrahydropyran ring by iodo-etherification, construction of a *cis*-decalin ring by intramolecular Diels–Alder reaction, isomerization of *cis*-decalin to *trans*-decalin, and subsequent functionalization of the *trans*-decalin ring.

Various terpene isocyanides have been isolated from marine invertebrates and many of these are of considerable interest from the standpoint of their respective biological activities.[1] Kalihinol A (**1**), isolated from the marine sponge *Acanthella* sp. by Scheuer and co-workers in 1984, is a richly functional diterpenoid possessing isocyano, hydroxy, tetrahydropyranyl and chlorine moieties. The relative configuration of kalihinol A (**1**) was demonstrated by X-ray analysis.[2] The absolute configuration of **1** was determined using CD exciton chirality methods by the authors.[3] Since kalihinol A was first isolated, more than forty different kalihinane-type diterpenoids, possessing isocyano, isothiocyano and/or formamido moieties, have been isolated and identified from marine sponges.[4a–4i] Kalihinane-type diterpenoids have demonstrated extensive biological activities including antimicrobial,[2,4a,4b,4i] antifungal,[2,4a,4b,4d] cytotoxic,[4d] anthelmintic[4c] and antifouling[4e–4g] activities. Kalihinol A is particularly noted for its antimalarial activity against *Plasmodium falciparum* (EC_{50} 1.2×10^{-9} M) and possesses a remarkable selective index (SI 317), defined as the ratio of FM3A cell cytotoxicity to *P. falciparum*.[4h] The total syntheses of two kalihinane-type diterpenoids were reported. The authors reported the total synthesis of (+)-kalihinene X possessing a *cis*-decalin ring system.[5] Wood and co-workers reported the synthesis of (±)-kalihinol C possessing a tetrahydrofuranyl ring.[6] The authors achieved the first total synthesis of (+)-kalihinol A by construction of a tetrahydropyran ring *via* iodo-etherification and a *cis*-decalin ring *via* an intramolecular Diels–Alder cycloaddition reaction as key steps.

Our synthetic strategy is presented in Scheme 1. (+)-Kalihinol A is synthesized from *trans*-decalin **A** by transduction of methyl and isocyano groups at C-10 and transformation of the azido group at C-5 to an isocyano group. *trans*-Decalin **A** is obtained by diastereoselective introduction of hydroxy and azido groups and isomerization of *cis*-decalin **B** to *trans*-decalin. *cis*-Decalin **B** may likely be formed by intramolecular Diels–Alder reaction of triene **C**, which would be obtained from tetrahydropyran **D** by the construction of diene and dienophile. Tetrahydropyran **D** is obtained from compound **E** by introduction of a chlorine atom with the inversion of stereochemistry at C-14 and formation of the tetrahydropyran ring using iodo-etherification. Compound **E** is obtained by regioselective alkylation of epoxyalcohol **G** using Grignard reagent **F**.



Scheme 1 Synthetic strategy for kalihinol A.

cis-Decalin **10** was synthesized from (*E*,*R*)-3,7-dimethylocta-2,7-diene-1,6-diol (**2**)[7] (97% ee) (Scheme 2). The primary hydroxy group in diol **2** was protected as a TBS ether and the secondary hydroxy group was protected as a TBDPS ether. Selective deprotection of the TBS group by treatment with PPTS in MeOH afforded the allylic alcohol in 83% yield (3 steps).

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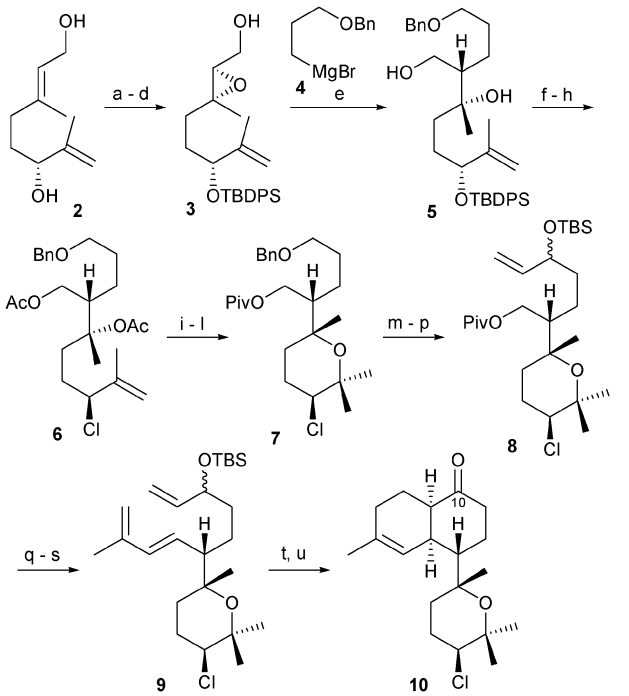


Scheme 2 *Reagents and conditions*: (a) TBSCl; (b) TBDPSCl; (c) PPTS, 83% (3 steps); (d) D-(−)-DET, TBHP, $Ti(OiPr)_4$, 95%; (e) **4**, CuI, 94%; (f) Ac_2O, DMAP, Py, 82%; (g) TBAF, 95%; (h) CCl_3COCCl_3, PPh_3, 90%; (i) DIBAH; (j) PivCl, Py, 78% (2 steps); (k) IDCP; (l) Bu_3SnH, Et_3B, 72% (2 steps); (m) H_2, Pd/C, 99%; (n) Dess–Martin periodinane, 98%; (o) $CH_2{=}CHMgBr$, 99%; (p) TBSCl, 99%; (q) DIBAH, 97%; (r) Dess–Martin periodinane; (s) $CH_2{=}C(CH_3)CH_2P(O)Ph_2$, BuLi, 78% (2 steps); (t) TBAF, 96%; (u) Dess–Martin periodinane, 99%.

Sharpless asymmetric epoxidation of the aforementioned allylic alcohol afforded epoxyalcohol **3** in 95% yield (87% de). Regioselective nucleophilic alkylation of epoxyalcohol **3** with Grignard reagent **4**[8] in the presence of CuI afforded diol **5** in 94% yield as a sole product. The two hydroxy groups in **5** were acetylated with Ac_2O and DMAP in pyridine to give the diacetate in 82% yield. The TBDPS group was deprotected by treatment with TBAF in the presence of AcOH to afford the allylic alcohol in 95% yield. The allylic alcohol was treated with CCl_3COCCl_3 and Ph_3P to give allylic chloride **6** in 90% yield with concomitant inversion of the stereochemical configuration at C-14.[9] Although the allylic alcohol was converted into allylic chloride **6** by treatment with Ph_3P in CCl_4 under reflux, the reproducibility of the reaction was invariably poor. The two acetyl groups in **6** were removed with DIBAH to give the diol, the primary hydroxy group of which was protected to give the mono pivalate in 78% yield (2 steps). Intramolecular iodoetherification of the mono pivalate was achieved by treatment with iodonium di-*sym*-collidine perchlorate (IDCP)[10] to give iodotetrahydropyran, which was dehalogenated by Bu_3SnH and Et_3B to afford tetrahydropyran **7** in 72% yield (2 steps). Although tetrahydropyran **7** was also obtained by intramolecular alkoxymercuration (1. $Hg(OAc)_2$, THF–H_2O, 2. $NaBH_4$, MeOH–KOH aq.), the chemical yield was low (41% yield). The Bn group in tetrahydropyran **5** was removed by hydrogenolysis to give the primary alcohol in 99% yield, oxidized using Dess–Martin periodinane[11] to give the aldehyde in 98% yield, vinylated using vinyl magnesium bromide to the secondary alcohol as a diastereomeric mixture (1 : 1) in 99% yield, and subsequent protection of the hydroxy group using TBSCl to give TBS ether **8** in 99% yield. The pivaloyl group in **8** was removed using DIBAH to give the primary alcohol in 97% yield, oxidized using Dess–Martin periodinane to give the aldehyde, and subsequently treated with $CH_2{=}C(CH_3)CH_2P(O)Ph_2$ with BuLi in the presence of HMPA to afford triene **9** in 78% yield (2 steps).[12] Deprotection of the TBS group in triene **9** gave the allylic alcohol in 96% yield, which was then oxidized with Dess–Martin periodinane to facilitate, *via endo*-selective intramolecular Diels–Alder reaction, in the spontaneous formation of *cis*-decalin **10** as a sole product in 99% yield.[13]

Epoxidation of ketone **10** using *m*CPBA in the presence of Na_2HPO_4 generated a mixture of desired α-epoxide **11a** and its diastereomer β-epoxide **11b** (**11a** : **11b** = 1 : 3) in 95% yield (Fig. 1). Furthermore, when other epoxidation reagents (magnesium monoperoxyphthalate, DMDO) were used, the desired α-epoxide **11a** was obtained as a minor product. The relative configuration of α-epoxide in **11a** was confirmed by X-ray crystallographic analysis. In an effort to obtain α-epoxide as a major product, the oxygenated functional group at C-10 in **10** was used.

Ketone **10** was reduced with $NaBH_4$ to afford the β-alcohol as a major product in 95% yield (β-OH : α-OH = 5 : 1) (Scheme 3). The hydroxy group in the β-alcohol was protected as a TBS ether in quantitative yield. Epoxidation of the TBS ether was achieved using *m*CPBA in the presence of Na_2HPO_4 to give the desired α-epoxide **12** as a sole product in 99% yield. Deprotection of the TBS group in α-epoxide **12** was achieved by treatment with TBAF to afford the secondary alcohol in 93% yield, which was then oxidized using 2-iodoxybenzoic acid (IBX) in THF–DMSO to give the ketone in 95% yield.[14] The ketone was treated with NaN_3 in the presence of NH_4Cl to give *trans*-decalin **13** and *cis*-decalin **14** (**13** : **14** = 2 : 1) in 95% yield. Following separation of these compounds, *cis*-decalin **14** was treated with ^{t}BuOK in EtOH to afford a mixture of *trans*-decalin **13** and *cis*-decalin **14** (**13** : **14** = 3 : 2) in 99% yield.

trans-Decalin **13** was treated with 2-(methylsulfonyl)benzothiazole[15] and LiHMDS to give *exo*-olefine **15** in 88% yield (Scheme 4). When using the Wittig reagent ($Ph_3P^+CH_3I^-$ and BuLi), *exo*-olefine **15** (24% yield) and the epoxide (24% yield) were obtained, and *trans*-decalin **13** (22%) was recovered.

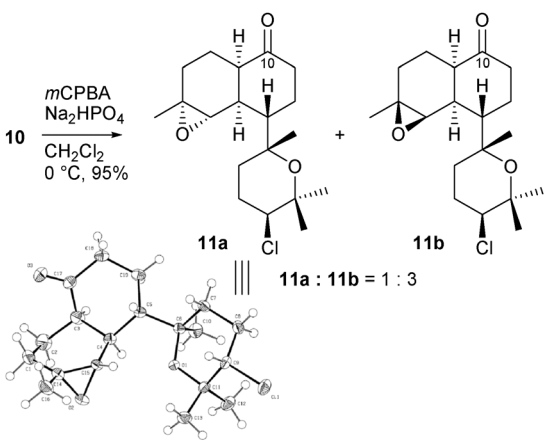
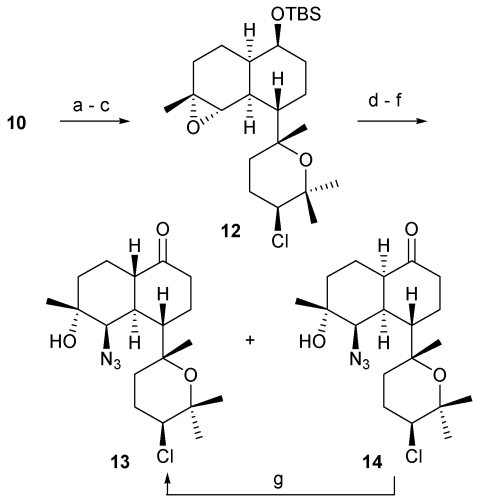
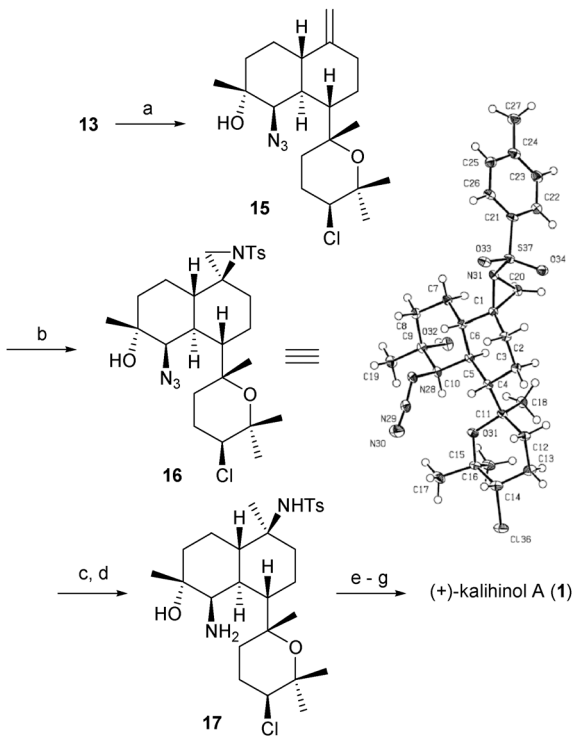


Fig. 1 Epoxidation of *cis*-decalin **10** and ORTEP drawing of epoxide **11a**.



Scheme 3 *Reagents and conditions*: (a) $NaBH_4$, 95%; (b) TBSCl, quant.; (c) *m*CPBA, 99%; (d) TBAF, 93%; (e) IBX, 95%; (f) NaN_3, 95%; (g) ^tBuOK, 99%.

Diastereoselective aziridination of *exo*-olefine **15** using PhI=NTs and $Cu(OTf)_2$ resulted in the formation of desired aziridine **16** as a sole product in 46% yield.[16] The relative configuration of aziridine **16** was confirmed by X-ray crystallographic analysis. Azide **16** was reduced with $NaBH_4$ in the presence of $NiCl_2 \cdot 6H_2O$[17] to give the amine (84% yield), which was then treated with $LiBHEt_3$ to afford tosylamide **17** in 83% yield. Deprotection of the tosyl group with lithium naphthalenide[18] in **17** afforded the diamine, which upon formylation with acetic formic anhydride and subsequent dehydration with TsCl and pyridine[19] gave (+)-kalihinol A (**1**) in 74% yield (3 steps). The spectral data and sign of the optical rotation of synthetic (+)-kalihinol A, $[\alpha]_D^{25}$ +12.4 (*c* 0.64, $CHCl_3$), were identical with those of natural kalihinol A, $[\alpha]_D$ +16.0 (*c* 1.0, $CHCl_3$).[2] Hence, the first total synthesis of (+)-kalihinol A was achieved.



Scheme 4 *Reagents and conditions*: (a) 2-(methylsulfonyl)benzothiazole, LiHMDS, 88%; (b) PhI=NTs, $Cu(OTf)_2$, 46%; (c) $NaBH_4$, $NiCl_2 \cdot 6H_2O$, 84%; (d) $LiBHEt_3$, 83%; (e) Li, naphthalene; (f) acetic formic anhydride; (g) TsCl, Py, 74% (3 steps).

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