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Total synthesis of marine diterpenoid kalihinene X

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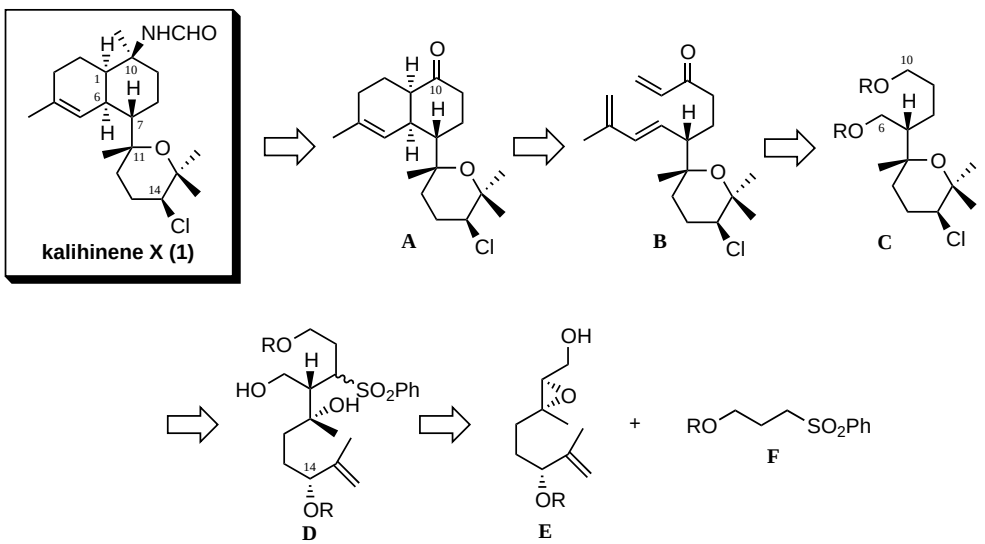
Abstract—Total synthesis of marine diterpenoid kalihinene X was achieved. This total synthesis involves regioselective coupling reaction of carbanion of alkyl sulfone with epoxyalcohol and construction of *cis*-decalin ring by intramolecular Diels–Alder reaction. The absolute configuration of kalihinene X could be determined by this total synthesis. © 2002 Published by Elsevier Science Ltd.

Kalihinane-type diterpenoid possessing *cis*- or *trans*-decalin and tetrahydropyran or tetrahydrofuran as its fundamental skeleton, is a highly functionalized marine diterpenoid, bearing isocyano, isothiocyanato, formamide, hydroxy and/or chlorine groups.[1–15] Most kalihinane-type diterpenoids exhibit antimicrobial,[1–3] antifungal,[1–3,5,7] cytotoxic,[5] anthelmintic,[4,6] antifouling[10–13] and antimalarial[15] activity. Kalihinene X (**1**), isolated from the Japanese marine sponge, *Acanthella cavernosa*, by Fusetani in 1995, is a kalihinane-type diterpene formamide having *cis*-decalin and chlorinated tetrahydropyran moieties.[10] The relative configuration of kalihinene X (**1**) was determined by NOESY though its absolute configuration remains to be elucidated. Kalihinene X (**1**) inhibits the attachment and metamorphosis of cyprid larvae of the barnacle, *Balanus amphitrite* with EC_{50} of 0.49 μg/mL, while no toxicity is found at this concentration. The total synthesis of kalihinane-type diterpenoid has not been reported to date.[16] Consequently, the present study was undertaken to determine the absolute configuration of kalihinene X and establish a method for the total synthesis of kalihinene X. This synthesis was achieved through regio-selective alkylation of alkyl sulfone to epoxide and intramolecular Diels–Alder reaction as key steps, as discussed in the following.



Scheme 1. Synthetic strategy for kalihinene X (**1**).

Keywords: biologically active compounds; marine metabolites; terpenes and terpenoids.

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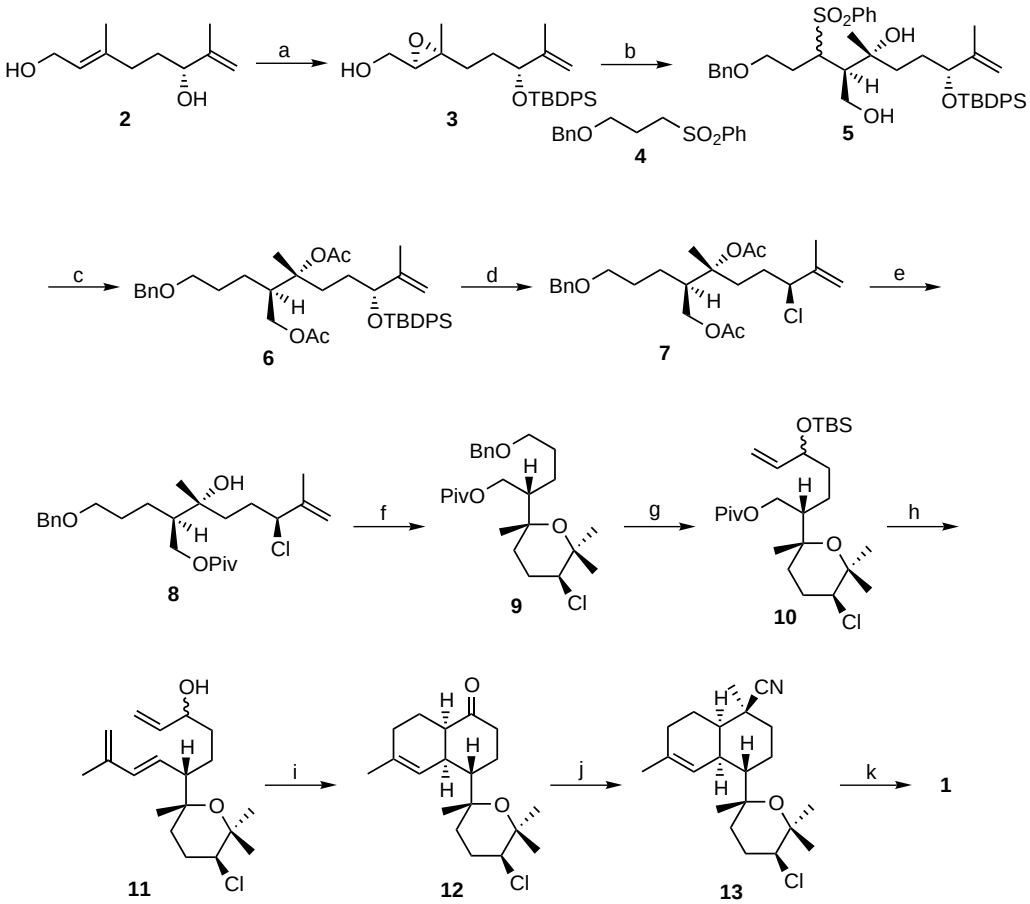
Our synthetic strategy is presented in Scheme 1. We decided to utilize the key intermediate **A**, capable of being transformed into kalihinene X (**1**) via diastereoselective introduction of methyl and formamido groups at C-10 position. *cis*-Decalin **A** may likely be formed by intramolecular Diels–Alder reaction of trienone **B** which would be obtainable from compound **C** in the construction of enone and dienen. It was considered that compound **C** could be produced from compound **D** by removal of phenylsulfonyl group, chlorination at C-14 and construction of tetrahydropyran moiety and that compound **D** could be synthesized by a regioselective epoxide-opening reaction of carbanion of sulfone **F** with epoxide **E**.

The synthesis of kalihinene X (**1**) was conducted starting from known (*E*,*R*)-3,7-dimethylocta-2,7-diene-1,6-diol[17] (**2**) (97% ee) (Scheme 2). The primary hydroxy group in diol **2** was protected as TBS ether and the secondary hydroxy group, as TBDPS ether. Selective methanolysis of TBS ether afforded allylic alcohol. Epoxidation of the allylic alcohol according to Sharpless procedure[18] gave epoxide **3** as a diastereomeric mixture (10:1).[19] Regioselective coupling reaction of an anion of sulfone **4**[20] with epoxyalcohol **3** was effectively carried out to produce coupling product **5**.[21] The phenylsulfonyl group of **5** was removed by treatment with Na–Hg in MeOH and two hydroxy groups were protected as acetate to give diacetate **6**, $[\alpha]_D^{22}$ –17.4° (*c* 0.81, $CHCl_3$).[22] The TBDPS group in **6** was removed by treatment with TBAF to give allylic alcohol. A solution of the allylic alcohol in CCl_4 was refluxed in the presence of Ph_3P to afford allylic chloride **7** as the sole product. Reductive removal of acetate was carried out by treatment with DIBAL-H to give diol, the selective protection of whose primary hydroxy group as pivalate gave alcohol **8**. Alcohol **8** was subsequently treated with $Hg(OAc)_2$ in THF–H_2O (3:1) and then reductively



Scheme 2. *Reagents and conditions*: (a) (1) TBS–Cl, Et_3N, DMAP, CH_2ClCH_2Cl, rt, (2) TBDPS–Cl, imidazole, DMF, rt, (3) PPTS, MeOH, rt, 83% (three steps), (4) *t*BuOOH, (–)-DIPT, $Ti(OiPr)_4$, 4 Å MS, CH_2Cl_2, –20°C, 95%; (b) **4**, *n*BuLi, THF, –78°C to rt; (c) (1) Na–Hg, Na_2HPO_4, MeOH, rt, 89% (two steps), (2) Ac_2O, pyridine, DMAP, 60°C, 82%; (d) (1) TBAF, AcOH–THF, 60°C, quant., (2) CCl_4, Ph_3P, reflux, 86%; (e) (1) DIBAL-H, toluene, –78°C, (2) Piv–Cl, pyridine, rt, 78% (two steps); (f) (1) $Hg(OAc)_2$, THF/H_2O (3:1), rt, (2) $NaBH_4$, MeOH–KOH aq., 41% (two steps); (g) (1) H_2, Pd–C, EtOH, 94%, (2) Dess–Martin periodinane, CH_2Cl_2, rt, 93%, (3) vinyl magnesium bromide, THF, 0°C, 89%, (4) TBS–Cl, imidazole, DMF, rt, 96%; (h) (1) DIBAL-H, toluene, –78°C, 90%, (2) Dess–Martin periodinane, CH_2Cl_2, rt, (3) $CH_2{=}C(CH_3)CH_2P(O)Ph_2$, *n*BuLi, HMPA, THF, –78°C to rt, (4) TBAF, THF, rt, 75% (three steps); (i) Dess–Martin periodinane, CH_2Cl_2, rt, 93%; (j) (1) $TsCH_2NC$, *t*BuOK, DME/*t*BuOH (5:1), 0°C to rt, 96%, (2) KHMDS, MeI, toluene, rt, 83%; (k) (1) DIBAL-H, toluene, –78°C, 91%, (2) $NaClO_2$, 2-methyl-2-butene, NaH_2PO_4, *t*BuOH/H_2O (4:1), (3) DPPA, Et_3N, toluene, rt to 100°C, (4) DIBAL-H, toluene, –78°C, 63% (three steps).

demercurated with $NaBH_4$,[23] giving tetrahydropyran **9**, $[\alpha]_D^{22}$ –13.4° (*c* 0.71, $CHCl_3$). Compound **9** was converted to TBS ether **10** in four steps: (1) removal of Bn group by hydrogenolysis to give primary alcohol, (2) oxidation of the hydroxy group with Dess–Martin periodinane[24] to give aldehyde, (3) vinylation with vinyl magnesium bromide to give a secondary alcohol as a diastereomeric mixture (1:1) and (4) protection of the hydroxy group as TBS ester. TBS ether **10** was converted to allylic alcohol **11** as follows: (1) reductive removal of pivaloyl group with DIBAL-H to give primary alcohol, (2) oxidation of the hydroxy group with Dess–Martin periodinane[24] to produce aldehyde, (3) reaction of 2-methyl-2-propenyldiphenylphosphine oxide[25] with ^{n}BuLi in the presence of HMPA to selectively provide *E*-diene and (4) deprotection of TBS group with TBAF.

Oxidation of allylic alcohol **11** with Dess–Martin periodinane[24] in CH_2Cl_2 resulted, via intramolecular Diels–Alder reaction, in the spontaneous formation of *cis*-decalin **12**, $[\alpha]_D^{23}$ –82.5° (*c* 0.48, $CHCl_3$), as the sole product.[26] Ketone **12** was treated with tosylmethyl isocyanide ($TsCH_2NC$)[27] and ^{t}BuOK in DME–^{t}BuOH (5:1) to produce nitrile as a diastereomeric mixture (1:1) at the cyano group. Without separation of the diastereomers, methylation at C-10 was conducted with KHMDS then CH_3I to afford compound **13** along with its diastereomer (6:1). The reduction of nitrile **13** with DIBAL-H gave aldehyde and subsequent oxidation with $NaClO_2$ in the presence of NaH_2PO_4, carboxylic acid. Treatment of this carboxylic acid with diphenylphosphoryl azide (DPPA)[28] and Et_3N afforded isocyanate and reduction with DIBAL-H led to kalihinene X (**1**), $[\alpha]_D^{27}$ +24.4° (*c* 0.34, $CHCl_3$). Spectral data and sign of optical rotation of synthetic kalihinene X (**1**) were identical with those of natural kalihinene X, $[\alpha]_D^{23}$ +26.7° (*c* 0.31, $CHCl_3$).[10] The absolute configuration of kalihinene X was clearly shown to be **1** from the present synthesis.

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