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Concise asymmetric synthesis of dysidiolide

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Abstract

The cdc25A protein phosphatase inhibitor dysidiolide (**1**) has been synthesized via intermolecular Diels–Alder reaction of the triene **4** with crotonaldehyde and construction of a quaternary carbon center by methylation of the exocyclic enolate.

Keywords: terpene; anti-cancer agent; asymmetric synthesis; Diels–Alder reaction; alkylation.

Dysidiolide (**1**), a novel sesterterpene from the Caribbean marine sponge *Dysidea etheria de Laubenfels*,[1] inhibits the protein phosphatase cdc25A (IC_{50}=9.4 μM) that promotes the G1/S transition of the cell cycle by dephosphorylation of the cyclin–cyclin dependent kinase complex.[2] Dysidiolide inhibits the growth of human lung carcinoma cells and murine leukemia cells, probably due to inhibition of cdc25A, which is known to be oncogenic and overexpressed in a number of tumor cell lines.[3] Therefore, the cdc25A-specific inhibitor dysidiolide is regarded as a novel candidate agent for the treatment of cancer and other proliferative diseases.

Although three groups have already reported total syntheses of natural,[4] unnatural[5] and racemic[6] dysidiolide, a synthetic approach to its structure–activity relationship has not been reported yet. Therefore, we planned to develop an efficient synthetic route to dysidiolide and its analogs in order to investigate the structure–activity relationship and to create novel potentially useful compounds with higher activities. Our synthetic strategy described below should afford dysidiolide and a variety of analogs having different configurations and functionalities.

The retrosynthetic analysis is shown in Scheme 1. The decalin framework, the core structure of dysidiolide, could be constructed by intermolecular Diels–Alder reaction of the chiral triene **4** with crotonaldehyde. Subsequently, the quaternary center at C-6 could be created by methylation of the exocyclic enolate generated from the aldehyde **3**. The γ-hydroxybutenolide residue, regarded as a surrogate phosphate, could be created by 1,2-addition of 3-furyllithium[7] to the aldehyde **2** and subsequent photochemical oxidation of the furan ring.[7,8]

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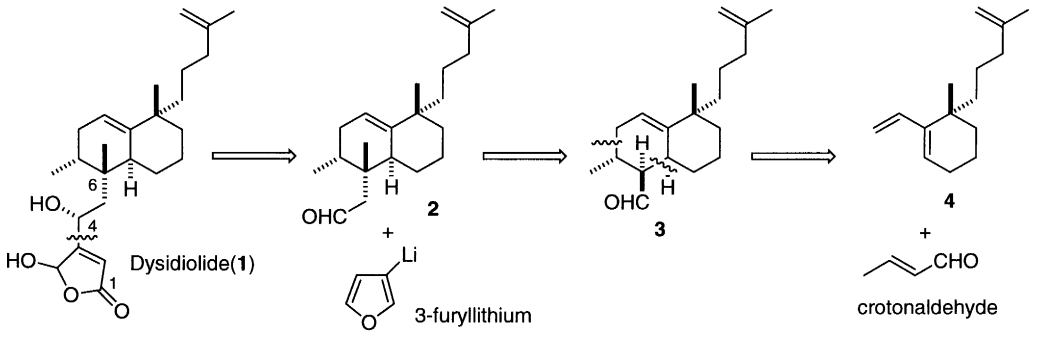
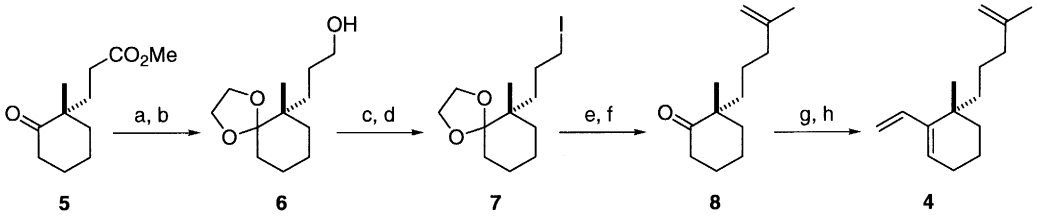


Scheme 1.

The starting ketone **5** was prepared from racemic 2-methylcyclohexanone by d'Angelo's procedure.[9] Optically pure **5** was obtained by recrystallization of corresponding semicarbazone followed by regeneration of the original ketone ($[\alpha]_D^{29}$ −35.9 (*c* 2.93, EtOH), lit. $[\alpha]_D^{29}$ −33.8 (*c* 2.95, EtOH)[9]). Protection of the ketone as the ethylene acetal followed by reduction afforded the corresponding alcohol **6**, which was converted to the iodide **7** via the tosylate, followed by cross-coupling with 2-propenylmagnesium bromide in the presence of a catalytic amount of CuI. Removal of the ketal with pyridinium *p*-toluenesulfonate gave the ketone **8**. Then, 1,2-addition of vinylcerium reagent to the carbonyl group of **8** and dehydration of the corresponding carbinol with anhydrous $CuSO_4$[5] afforded the desired triene **4** along with 10% of the alkenyl side chain isomer. These products were readily separated by $AgNO_3$-coated silica gel column chromatography (Scheme 2).

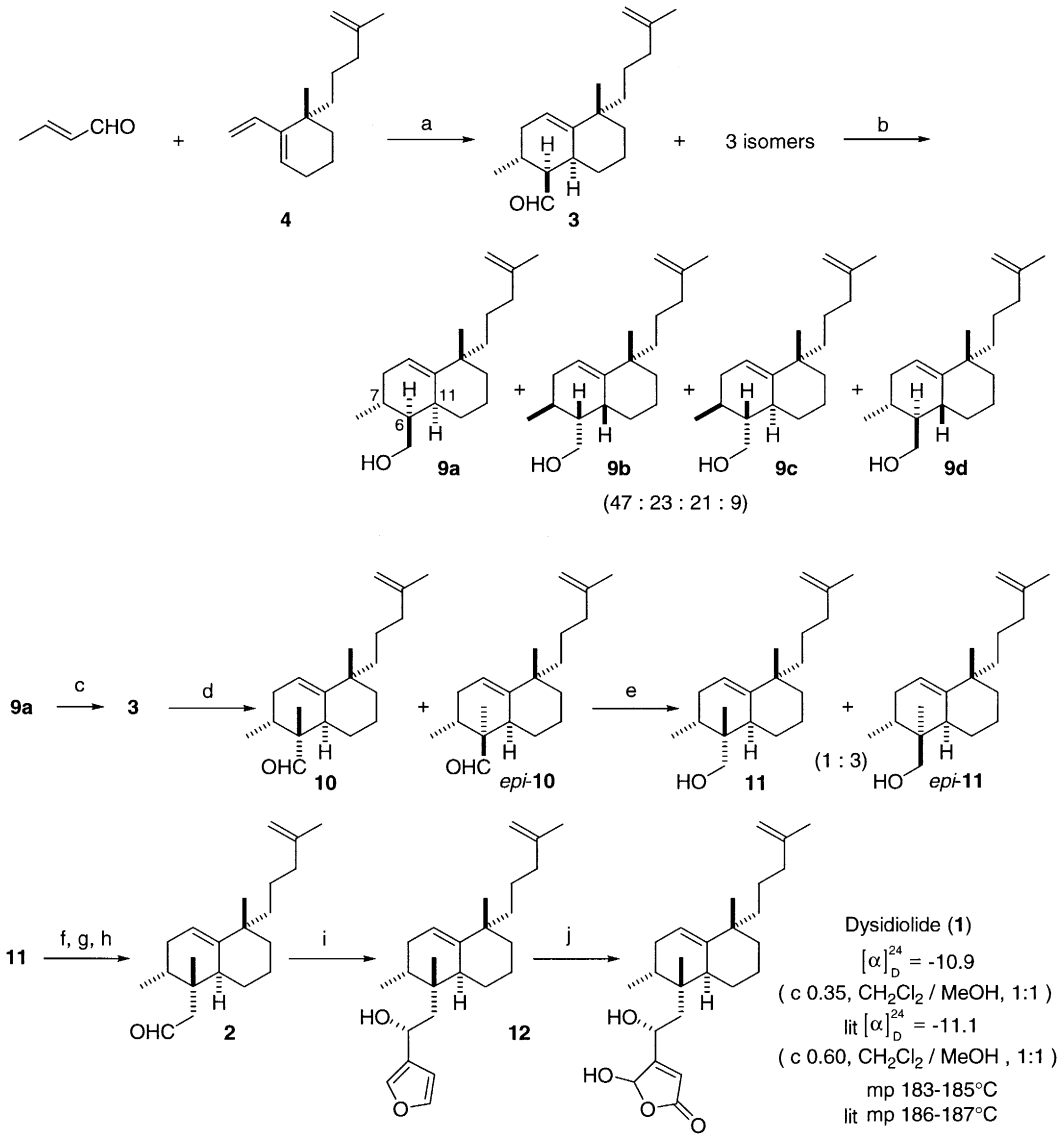


Scheme 2. Reagents and conditions. (a) Ethylene glycol, benzene, reflux (96%); (b) $LiAlH_4$, THF, 0°C (90%); (c) TsCl, pyridine, 0°C (92%); (d) NaI, acetone, reflux (90%); (e) 2-propenylmagnesium bromide, CuI, THF, −30°C→0°C (92%); (f) pyridinium *p*-toluenesulfonate, acetone, reflux (94%); (g) vinylmagnesium bromide, anhydrous $CeCl_3$, THF, rt (89%); (h) anhydrous $CuSO_4$, benzene, reflux (89%)

Intermolecular Diels–Alder reaction of the triene **4** and crotonaldehyde proceeded smoothly at −30 to 0°C, catalyzed by $EtAlCl_2 \cdot THF$, to give an inseparable adduct mixture of four isomers in 83% yield.[10] Reduction of the mixture with AlH_3 provided a mixture of four alcohols **9a**–**9d** (**9a** (*endo*-6*S*,7*R*,11*R*):**9b** (*endo*-6*R*,7*S*,11*S*):**9c** (*exo*-6*R*,7*S*,11*R*):**9d** (*exo*-6*S*,7*R*,11*S*)=47:23:21:9), and the pure alcohol **9a** derived from the *endo* major isomer **3** was obtained.

Next, the alcohol **9a** was reoxidized to the previous aldehyde **3**, which was methylated with *t*-BuOK–MeI to give an inseparable mixture of **10** and *epi*-**10** in 80% yield with moderate α-selectivity. The course of stereoselectivity is understood that the β-methyl group at the quaternary carbon center blocked β-face of exocyclic enolate by model analysis. The absolute configuration of **10** and *epi*-**10** was established as Diels–Alder reaction of triene **4** with tiglic aldehyde (*trans*-2-methyl-2-butenal) gave *epi*-**10**.[10] Reduction of the mixture of **10** and *epi*-**10** with $NaBH_4$ provided the easily separable alcohols **11** and *epi*-**11** in yields of 16% and 45% from **3**, respectively. Although *epi*-**11** has the wrong stereochemistry for the synthesis of **1**, this is still a valuable intermediate to synthesize novel stereoisomers of dysidiolide. Next, compound **11** was converted to the tosylate, which was displaced by cyanide ion in HMPA solvent.[11] Subsequently, DIBAL reduction of the nitrile gave the known synthetic

intermediate (**2**) of dysidiolide.[4–6] Treatment of **2** with excess 3-furyllithium[7] provided **12** and *epi*-**12**, which were separated by silica gel chromatography. Finally, photochemical oxidation[7,8] of **12** afforded dysidiolide **1** as colorless crystals (Scheme 3). The ^{1}H NMR and MS/HRMASS spectra, optical rotation and melting point of synthetic **1** were identical to those reported.[1]



Scheme 3. Reagents and conditions: (a) $EtAlCl_2 \cdot THF$ (1:1), CH_2Cl_2, −30°C→0°C (83%); (b) AlH_3, THF, 0°C and separation (25% from **4**); (c) TPAP, NMO, MS4 Å, rt (90%); (d) CH_3I, *t*-BuOK, THF, rt (80%); (e) $NaBH_4$, MeOH, 0°C, **11** (16% from **3**) and *epi*-**11** (45% from **3**); (f) TsCl, pyridine, 0°C (89%); (g) NaCN, HMPA, 90°C (90%); (h) DIBAL-H, CH_2Cl_2, −78°C (72%); (i) 3-bromofuran, *n*-BuLi, THF, −78°C (88% 1:1, **12**:*epi*-**12**); (j) O_2, hν, Rose Bengal, *i*-Pr_2EtN, CH_2Cl_2, −78°C (85%)

This synthetic approach provided a facile route to dysidiolide and could be applicable for preparing a wide range of novel derivatives. Synthesis of such analogs and studies of the structure–activity relationships are in progress.

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