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Synthesis of marine sesterterpenoid dysidiolide

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Abstract

Dysidiolide, a novel sesterterpenoid isolated from the Caribbean sponge *Dysidia etheria* de Laubenfels, has been shown an inhibitor of protein phosphatase cdc25A. The authors established a stereocontrolled total synthesis of (±)-dysidiolide using an intramolecular Diels–Alder reaction as the key step.

Keywords: marine metabolites; natural products; terpenes; terpenoids; antitumour compounds.

Dysidiolide (**1**), isolated in 1996 from the Caribbean sponge, *Dysidia etheria* de Laubenfels by Gunasekera and Clardy et al. is a marine sesterterpenoid, possessing a novel carbon skeleton with unique structural features.[1,2] Dysidiolide is the first naturally derived inhibitor of protein phosphatase cdc25A (IC_{50} 9.4 μM). Dysidiolide was noted to inhibit the growth of A-549 human lung carcinoma and P388 murine leukemia cell lines at IC_{50} 4.7 and 1.5 μM, respectively. The relative configuration of dysidiolide was determined based on single-crystal X-ray results and the absolute configuration was determined by enantioselective total synthesis.[3,4] Three total syntheses[3–5] of and two synthetic studies[6,7] on dysidiolide have been reported. The biological activity and rare structural features of dysidiolide prompted the authors to undertake its total synthesis. A stereocontrolled total synthesis of (±)-dysidiolide was established using an intramolecular Diels–Alder reaction as the key step.

Cyclohexenone **2**[8] was converted to α,β,γ,δ-unsaturated ketone **4** in three steps: (i) alkylation of **2** with LDA and 3-iodo-1-(*tert*-butyldimethylsilyl)oxypropane; (ii) further alkylation with LDA and iodomethane to give enone **3**; and (iii) vinylation of **3** with vinylmagnesium bromide followed by treatment with silica gel to form α,β,γ,δ-unsaturated ketone **4** (Scheme 1). α,β,γ,δ-Unsaturated ketone **4** was treated with thiophenol in the presence of Et_3N to produce α,β-unsaturated ketone, which was subsequently reduced with DIBAL-H to give a mixture of β-alcohol **5a** and α-alcohol **5b** (**5a**:**5b**=1.6:1).[9,10] Following separation of these compounds, oxidation of sulfide in β-alcohol **5a** with mCPBA and then acylation with propiolic acid, DCC and DMAP in toluene provided sulfoxide ester **7**. Sulfoxide ester **7** was also obtained from α-alcohol **5b** by the oxidation of sulfide in **5b** with mCPBA followed by Mitsunobu inversion[11] with propiolic acid. Sulfoxide ester **7** was refluxed in toluene in

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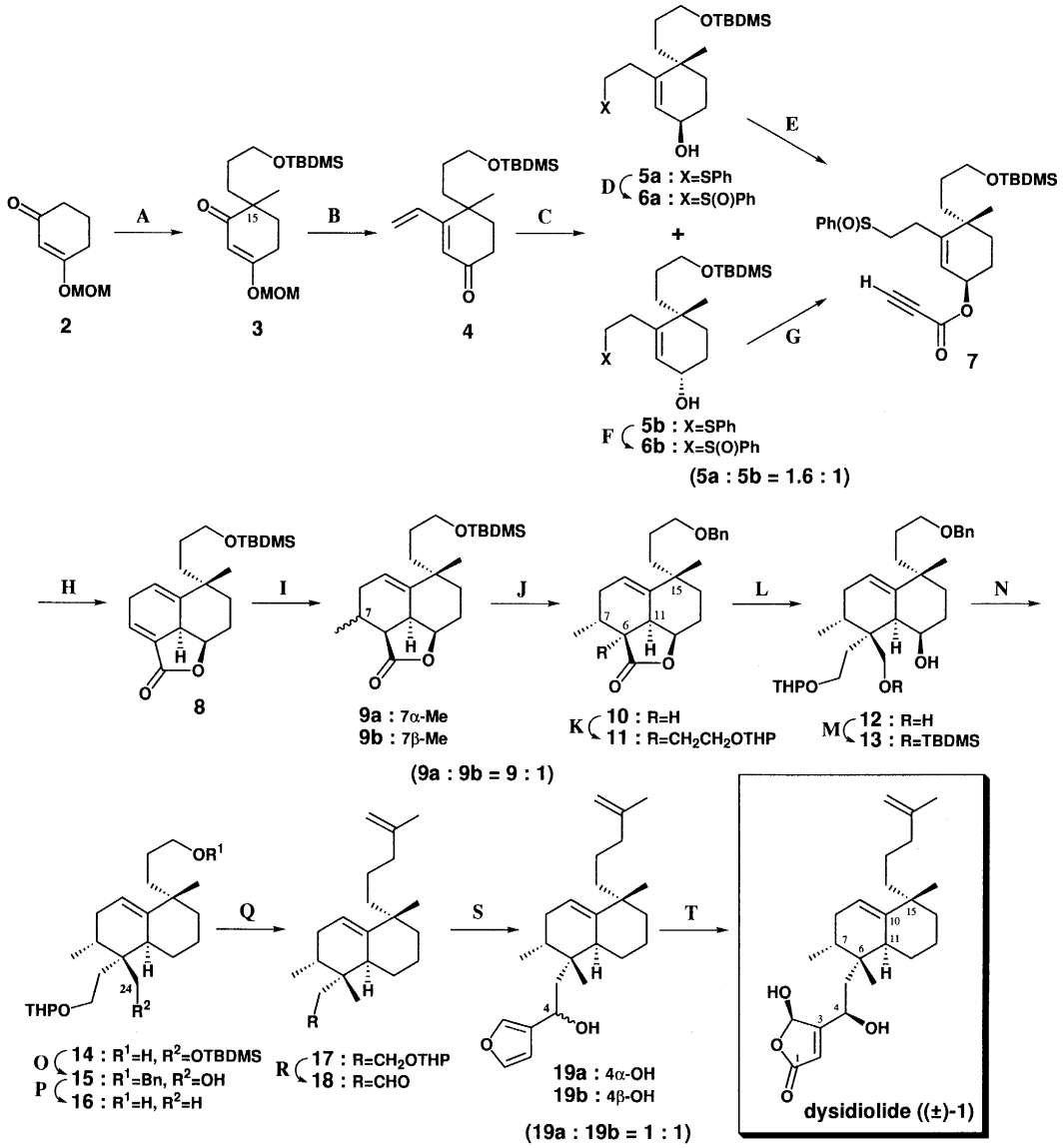

Scheme 1. *Reagents and conditions*: **A**: (i) LDA, HMPA, $TBDMSOCH_2CH_2CH_2I$, THF, −78°C–rt, 76%; (ii) LDA, MeI, THF, 96%; **B**: vinyl magnesium bromide, THF, 0°C, then silica gel, 92%; **C**: (i) PhSH, Et_3N, benzene, rt, 90%, (ii) DIBAL-H, toluene, −78°C, quant.; **D**: mCPBA, CH_2Cl_2, −78°C, 99%; **E**: propiolic acid, DCC, DMAP, toluene, rt, quant.; **F**: mCPBA, CH_2Cl_2, −78°C, 96%; **G**: propiolic acid, DEAD, Ph_3P, THF, rt, 97%; **H**: pyridine, toluene, reflux, 78%; **I**: Me_2CuLi, Et_2O, −15°C, 91%; **J**: (i) TBAF, THF, rt, 90%, (ii) Bn-Br, NaH, THF:DMF (4:1), rt, 87%; **K**: LDA, $THPOCH_2CH_2I$, THF, 92%; **L**: (i) DIBAL-H, toluene, −78°C, (ii) $LiBH_4$, MeOH–THF, 0°C, 90% (two steps); **M**: TBDMS-Cl, imidazole, DMF, rt, 97%; **N**: (i) PON-Cl, MeLi, TMEDA, THF, 0°C–rt, 87%, (ii) Li, $EtNH_2$, ^{t}BuOH, 0°C–rt, 94%; **O**: (i) Bn-Br, NaH, THF–DMF, quant., (ii) TBAF, THF, reflux, quant.; **P**: (i) PON-Cl, MeLi, TMEDA, THF, 0°C–rt, 87%, (ii) Li, $EtNH_2$, ^{t}BuOH, 0°C, 72%; **Q**: (i) I_2, Ph_3P, imidazole, 2-methyl-2-butene, CH_2Cl_2, rt, 96%, (ii) 2-bromopropene, ^{t}BuLi, CuI, Et_2O, rt, 80%; **R**: (i) AcOH:H_2O (4:1), rt, 95%, (ii) TPAP, NMO, CH_2Cl_2, rt, 86%; **S**: 3-bromofuran, ^{n}BuLi, THF, −78°C, 93%; **T**: O_2, hν, Rose Bengal, $^i Pr_2NEt$, CH_2Cl_2, −78°C, 88%

the presence of pyridine to afford decalin **8**[12] as the sole product with elimination of sulfoxide and intramolecular Diels–Alder reaction. α,β-Unsaturated lactone **8** was treated with Me_2CuLi to give stereoselectively 7α-methyl lactone **9a** with a small amount of 7α-methyl lactone **9b** (**9a**:**9b**=9:1). Compound **9a** was converted to lactone **11**[13] in three steps: (i) TBAF, THF; (ii) BnBr, NaH, THF–DMF to give lactone **10**; and (iii) alkylation with LDA and 1-iodo-2-(tetahydropyranyl)oxyethane. Lactone **11** was reduced by a two-step sequence: (i) DIBAL-H and (ii) $LiBH_4$ to give diol **12**. Deoxygenation of two hydroxyl groups in diol **12** was successively carried out according to Ireland's phosphoramidate method.[14] The primary hydroxyl group in diol **12** was selectively protected by treatment with TBDMS-Cl and imidazole to give mono-TBDMS ether **13**. Deoxygenation of secondary hydroxyl group in **13** was carried out by treatment with $(Me_2N)_2P(O)Cl$ (PON–Cl) to give phosphoramidate followed by Benkeser reduction ($Li/EtNH_2$) to afford alcohol **14**. The hydroxyl group in **14** was protected as the benzyl ether and the TBDMS protecting group was removed to give alcohol **15**. The primary alcohol **15** was converted to phosphoramidate followed by Benkeser reduction to give alcohol **16**. Iodination[15] of alcohol **16** followed by cross-coupling with 2-lithiopropene, prepared from 2-bromopropene and ^{t}BuLi, in the presence of CuI afforded compound **17**. By cleavage of the THP protecting group in **17** by treatment with acetic acid and subsequent oxidation with TPAP and NMO,[16] aldehyde **18**[2,3,5] was obtained. Finally, the total synthesis of dysidiolide was performed essentially according to Corey's procedure.[3] The addition of 3-lithiofuran, prepared from 3-bromofuran and ^{n}BuLi, to aldehyde **18** gave epimeric alcohols **19a**[3] and **19b** (**19a**:**19b**=1:1). The photochemical oxidation of **19a** furnished (±)-dysidiolide ((±)-**1**). Spectral data (NMR and IR) of synthesized (±)-**1** were identical to those reported.[1,5]

Acknowledgements

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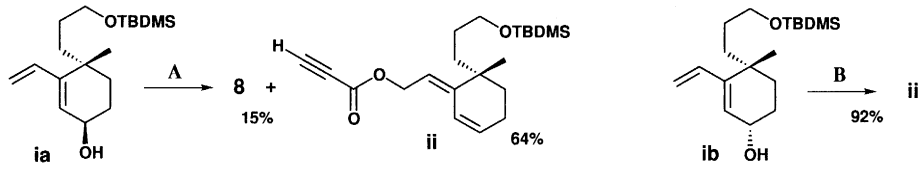
9. β-Alcohol **ia**, prepared from dienone **4** by DIBAL-H reduction, was treated with propiolic acid in the presence of *N*,*N*-bis(2-oxo-3-oxazolidinyl)phosphinic chloride (BOP-Cl) to give decalin **8** (15%) and ester **ii** (64%). α-Alcohol **ib**, also prepared from dienone **4** by DIBAL-H reduction, was treated with propiolic acid in the presence of DEAD and Ph_3P according to the Mitsunobu procedure to give ester **ii** in 92% yield as the sole product. The diene portion of dienone **4** was thus shown to be protected as the phenyl sulfide.



Reagents and conditions : **A**. propiolic acid, BOP-Cl, benzene, r.t.; **B**. propiolic acid, DEAD, Ph_3P, THF, r.t.

10. The relative configuration of alcohols **5a** and **5b** was determined from the NOESY spectrum of decalin **8**, which was derived from **5a** and **5b**, respectively.
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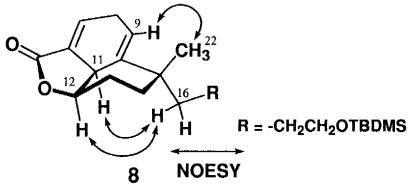
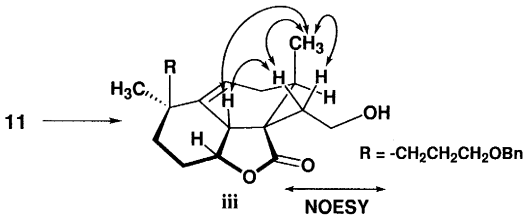
12. The relative configuration of decalin **8** was determined by the NOESY spectrum.



13. The relative configuration of compound **11** was determined by the NOESY spectrum of compound **iii**, which was converted from compound **11**.



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