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Total Synthesis of Dolabellane Diterpenoid Claenone

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Abstract

Marine dolabellane diterpenoid claenone (**1**) was synthesized from D-mannitol. This synthesis involves the formation of bicyclo[2.2.1]heptane derivative **4a** by sequential Michael reaction, the formation of cyclopentane derivative **9** by retro-aldol reaction and the cyclization of sulfone **19**.

Keywords: antitumour compounds; marine metabolites; Michael reaction; natural products; terpens and terpenoids

Dolabellane diterpenoids, characterized by ordinary *trans*-bicyclo[9.3.0]tetradecane, are obtained primarily from marine sources [1] and in many cases, exhibit antimicrobial, antitumor and antiviral activities [1]. They are also biogenetic and chemical precursors of dolastanes and fusicoccanes [2]. Claenone (**1**), isolated by our group from the Okinawan marine soft coral, *Clavularia* sp., is a dolabellane diterpenoid [3]. Claenone (**1**) was previously found to express potent cytotoxic activity toward human prostate cancer WMF (GI_{50} 2.42 x 10^{-7} M) and RB cells (GI_{50} 3.06 x 10^{-7} M) [4]. The total synthesis of dolabellane diterpenoid has been reported [5,6] though not that of claenone (**1**). The synthesis of claenone (**1**) was conducted here in consideration of its unique structure and biological activity and is reported for the first time in the present communication.

In the course of synthesizing natural products using a bicyclic compound as a chiral building block [7], the present method was applied to the synthesis of claenone. The synthetic strategy involves the diastereoselective formation of bicyclo[2.2.1]heptane derivative **D** by sequential Michael reaction of cyclopentenone **E** and chiral α,β-unsaturated ester **F**, cleavage of the C(14)-C(19) [8] bond in **C** by a retro-aldol reaction to give tetrasubsutituted cyclopentane segment **B** and the cyclization of sulfone **A** (Figure 1).

The sequential Michael reaction of the kinetic enolate of enone **2** with chiral α,β-unsaturated ester **3** [9] prepared from D-mannitol in THF at -78°C afforded bicyclo[2.2.1]heptane derivatives **4a** [10] and **4b** [11] (5.3 : 1) in 82% yield (Scheme 1). Ketone **4a** was converted to

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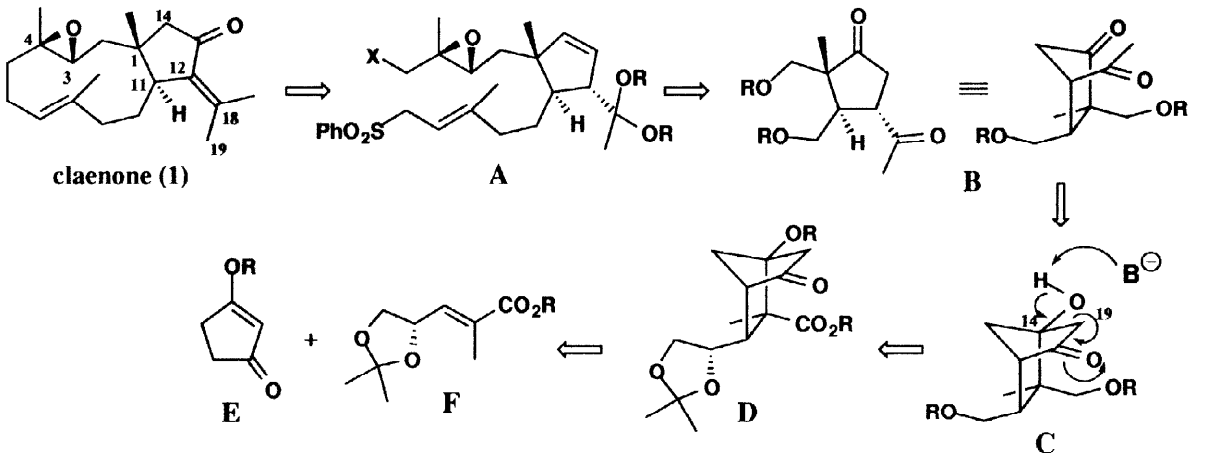
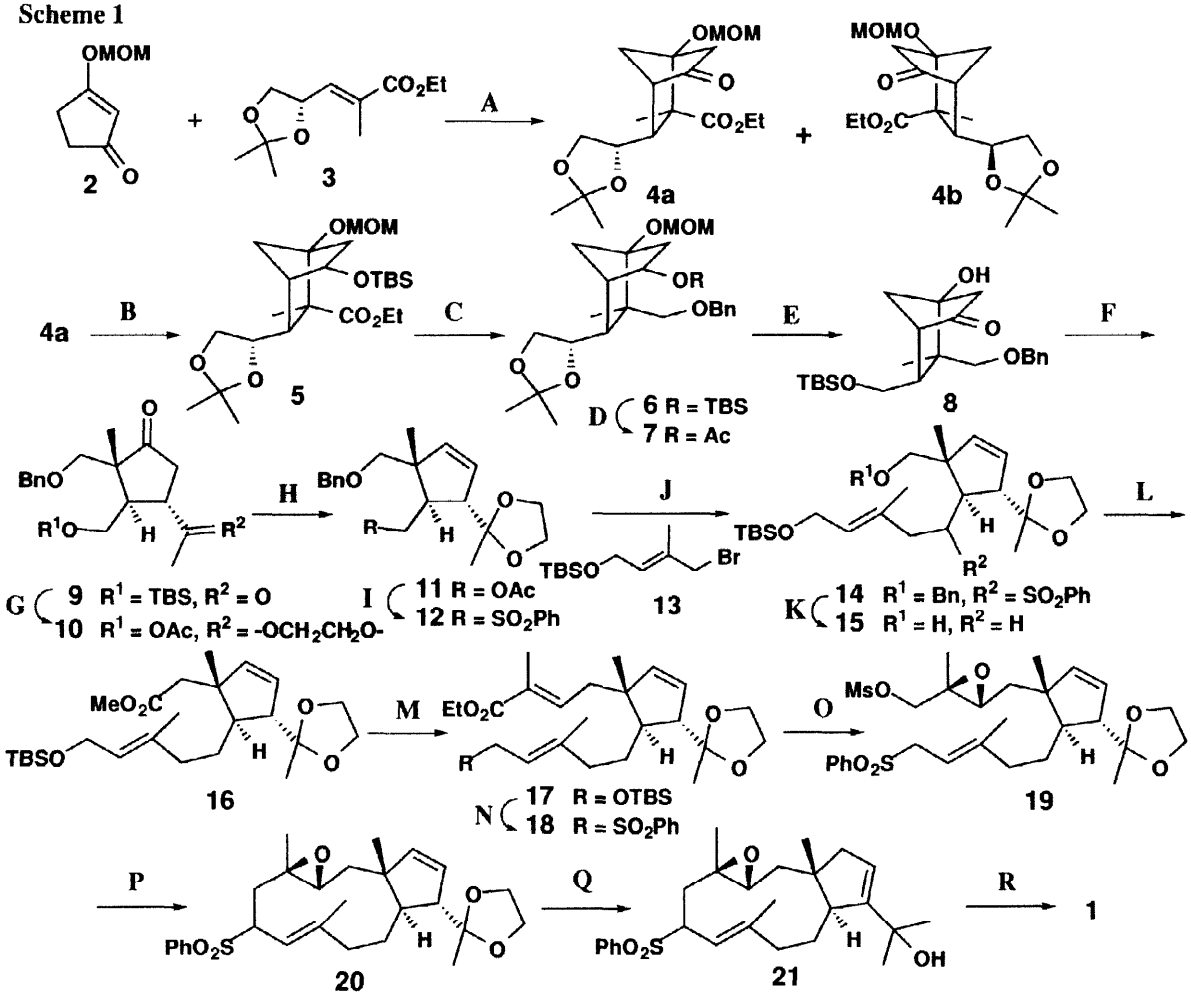
Figure 1



acetate **7** *via* silyl ether **5** and benzyl ether **6** in the following six steps: 1) $NaBH_4$ reduction to the alcohol, 2) protection of the hydroxy group to give TBS ether **5**, 3) reduction of the ester, 4) protection of the hydroxy group to give benzyl ether **6**, 5) deprotection of TBS ether by treatment with TBAF, and 6) acetylation of the hydroxy group. Acetate **7** was converted to β-hydroxyketone **8** in five steps: 1) acid hydrolysis of acetonide and MOM ether, 2) $NaIO_4$ oxidation followed by $NaBH_4$ reduction, 3) protection of the hydroxy group as TBS ether, 4) methanolysis of acetate, and 5) PCC oxidation of the hydroxy group. Cleavage of the C(14)-C(19) bond in **8** was achieved by a retro-aldol reaction in the presence of NaH and 15-crown-5 in toluene to afford cyclopentane derivative **9**, possessing the desired chiral centers at C-1 and C-11 corresponding to claenone. Selective protection of the less hindered ketone in **9** was achieved in the following three steps: 1) deprotection of TBS ether, 2) acetylation of the hydroxy group, and 3) treatment with 1,2-bis(trimethylsilyloxy)ethane in the presence of TMSOTf [12] to give monoketal **10**. Ketone **10** was converted to cyclopentene **11** in two steps: 1) $NaBH_4$ reduction of ketone 2) dehydration by treatment with *N*-phenylthiosuccinimide and *n*-Bu_3P in pyridine. The acetyl group in **11** was removed by K_2CO_3 in MeOH, whose hydroxy group was converted to phenyl sulfide; the oxidation of sulfide by OXONE® [13] gave sulfone **12**. Reaction of the lithio derivative of sulfone **12** with allylic bromide **13** [14] at -78°C to -30°C gave the coupling product **14** and sulfone **14** was treated with Na in liq. NH_3 to provide alcohol **15**. The hydroxy group in **15** was oxidized by PDC to give the aldehyde, which was reacted with Wittig reagent to produce methyl enol ether, which was oxidized by PCC-Al_2O_3 [15] directly to give methyl ester **16**. DIBAL-H reduction of ester **16** gave the aldehyde, which was reacted with Horner-Emons reagent to give α,β-unsaturated ester **17** as the sole product. The TBS group in **17** was removed with TBAF, whose hydroxy group was converted to phenyl sulfide which was oxidized by OXONE® to obtain sulfone **18**. Compound **18** was converted to epoxy mesylate **19** in three steps: 1) DIBAL-H reduction to the allylic alcohol, 2) Sharpless epoxidation [16] and 3) mesylation of the hydroxy group. Regio-selective macrocyclization of **19** was carried out by treatment with KHMDS in THF to give **20** as a sole product. Compound **20** was converted to allylic alcohol **21** in three steps: 1) hydrolysis of acetal, 2) isomerization of

olefin to the enone and 3) methylation by MeLi. The phenyl sulfonyl group was removed by treatment with Na-Hg and oxidation of the tertiary allylic alcohol with PCC [17] afforded claenone (**1**), $[\alpha]_D$ -49.2° (*c* 0.42, $CHCl_3$). Spectral data and the sign of optical rotation of synthetic **1** were identical to those of natural claenone, $[\alpha]_D$ -50.9° (*c*1.25, $CHCl_3$) [3].

Scheme 1



Reagents and conditions: A. LDA, THF, -78 °C, then **3**, 82%; **B**. i) $NaBH_4$, MeOH, 0 °C, quant., ii) TBSCl, imidazole, DMF, r.t., quant.; **C**. i) $LiAlH_4$, Et_2O, 0 °C, 99%, ii) BnBr, NaH, DMF, r.t., 94%; **D**. i) TBAF, THF, r.t., quant., ii) Ac_2O, Py, r.t., 99%; **E**. i) AcOH-H_2O (4:1), 65 °C, 85% at 85% conversion, ii) $NaIO_4$, $(NH_4)_2SO_4$, MeOH-H_2O (1:1), 0 °C, then $NaBH_4$, 0 °C, 88%, iii) TBSCl, imidazole, DMF, r.t., 96%, iv) K_2CO_3, MeOH, r.t., quant., v) PCC, 4 Å MS, CH_2Cl_2, r.t., 90%; **F**. NaH, 15-crown-5, toluene, r.t., 86%; **G**. i) AcOH-H_2O (4:1), r.t., 97%, ii) Ac_2O, Py, r.t., quant., iii) 1,2-bis(trimethylsilyloxy)ethane, TMSOTf, CH_2Cl_2, -40 °C, 90%; **H**. i) $NaBH_4$, MeOH, 0 °C, 98%, ii) *N*-phenylthiosuccinimide, *n*-Bu_3P, Py, 60 °C, 93%, **I**. i) K_2CO_3, MeOH, r.t., quant., ii) PhSSPh, *n*-Bu_3P, Py, 60 °C, iii) OXONE®, THF-MeOH-H_2O (2:2:3), 0 °C, 85% (2 steps); **J**. *n*-BuLi, THF, -78 °C, then **13**, -78 to -30 °C, **K**. Na, liq. NH_3, THF, -78 °C, 68% (2 steps); **L**. i) PDC, 4 Å MS, CH_2Cl_2, r.t., ii) Ph_3P=CHOMe, THF, 0 °C, 84% (2 steps), iii) PCC-Al_2O_3, benzene, 40 °C, 85%; **M**. i) DIBAL-H, toluene, -78 °C, ii) $(EtO)_2P(O)CH(Me)CO_2Et$, NaH, THF, 0°C, 80% (2 steps); **N**. i) *n*-Bu_4NF, THF, r.t., quant., ii) PhSSPh, *n*-Bu_3P, Py, 60 °C, 92%, iii) OXONE®, THF-MeOH-H_2O (1:1:1), 0 °C, 90%; **O**. i) DIBAL-H, toluene, -78 °C, 98%, ii) *t*-BuOOH, (-)-DET, Ti(O-*i*-Pr), 4 Å MS, CH_2Cl_2, -20 °C, 95%, iii) MsCl, DMAP, CH_2Cl_2, r.t., 97%; **P**. KHMDS, THF, 45 °C, 60% at 75% conversion; **Q**. i) AcOH-H_2O (4:1), 45 °C, 93%, ii) K_2CO_3, MeOH, r.t., quant., iii) MeLi, THF, -78°C, 86%; **R**. i) Na(Hg), Na_2HPO_4, MeOH-THF (1:1), 0 °C, 83%, ii) PCC, 4 Å MS, CH_2Cl_2, r.t., 63%.

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References and Notes

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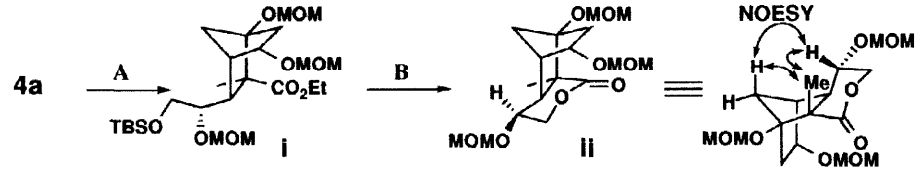
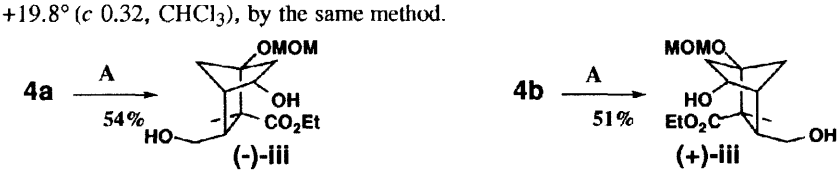
[10] The stereochemistry of **4a** was determined by the NOESY spectrum of compound **i i**, which was converted from **4a** *via* compound **i** as shown below.



Reagents and conditions : A. i) AcOH-H_2O (4:1), 40°C, 60%, ii) TBSCl, imidazole, DMF, r.t., 80%, iii) $NaBH_4$, MeOH, 0°C, 79%, iv) MOMCl, *i*-Pr_2NEt, CH_2ClCH_2Cl, 50°C, 87%; **B**. i) TBAF, THF, r.t., quant., ii) 30% NaOH aq., reflux, 69%, iii) BOPCl, Et_3N, CH_2ClCH_2Cl, r.t., 53%.

[11] The stereochemistry of **4b** was determined based on its chemical correlation with **4a**. Acid hydrolysis of the acetonide group in **4a** followed by $NaIO_4$ oxidation-$NaBH_4$ reduction gave (-)-**i i i**, $[\alpha]_D$ -19.8° (*c* 0.55, $CHCl_3$), whose enantiomer (+)-**i i i** was obtained from **4b**, $[\alpha]_D$ +19.8° (*c* 0.32, $CHCl_3$), by the same method.



Reagents and conditions : A. i) AcOH-H_2O (4:1), 40°C, ii) $NaIO_4$, MeOH-H_2O, 0°C, then $NaBH_4$, 0°C,

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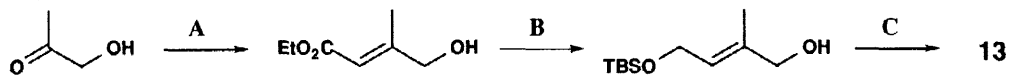
[14] Allylic bromide **13** was synthesized from hydroxyacetone in the following steps:



Reagents and conditions : A. Ph_3P=$CHCO_2Et$, benzene, 70°C, 87%; **B**. i) 2-methoxypropene, PPTS, CH_2Cl_2, r.t., ii) DIBAL-H, toluene, -78°C, iii) TBSCl, imidazole, DMF, r.t., iv) AcOH-THF-H_2O (1:2:2), r.t., 56% (4 steps); **C**. NBS, Ph_3P, CH_2Cl_2, 0°C, 80%.

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