

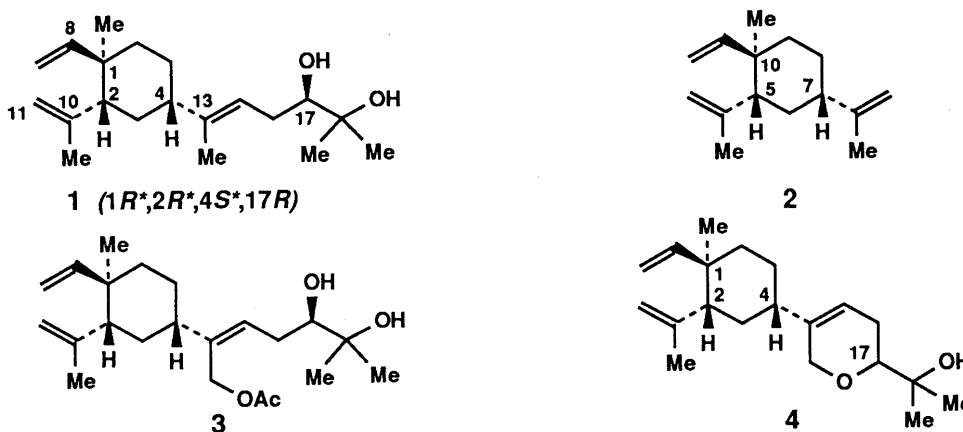
SYNTHESIS OF (1*R*,2*R*,4*S*,17*R*)-LOBA-8,10,13(15)-TRIENE-17,18-DIOL, A MARINE DITERPENE

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Synthesis of marine diterpene **1** (1*R*,2*R*,4*S*,17*R*) has been achieved *via* coupling of ketone **7** and sulfone **6**, leading to the determination of the absolute stereochemistry.

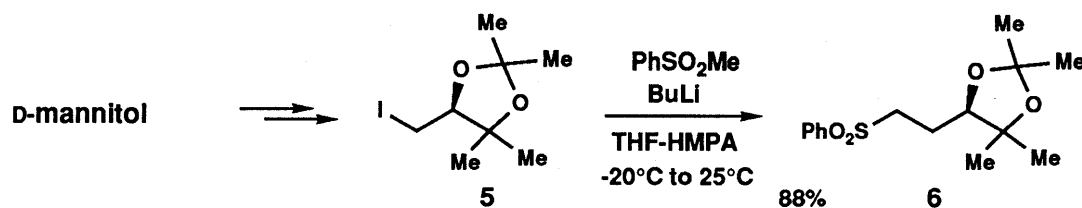
KEYWORDS total synthesis; marine diterpene; (1*R*,2*R*,4*S*,17*R*)-loba-8,10,13(15)-triene-17,18-diol; prenylated elemene skeleton

Loba-8,10,13(15)-triene-17,18-diol (**1**), isolated from a soft coral of the genus *Lobophytum* collected at the Great Barrier Reef by Wells *et al.*, is a structurally unique diterpene having a prenylated elemene skeleton (lobane skeleton) with hydroxyl functionality at C(17).^{1,2)} The relative stereochemistry of the elemene moiety (1*R**, 2*R**, 4*S**) was elucidated based on a comparison of the ¹H-NMR spectrum of **1** with that of β-elemene (**2**). The absolute configuration of C(17) was determined by the Pr(dpm)₃ (dpm=dipivalomethanate) method.^{1,3)} However, the absolute configuration of the elemene moiety has so far not been determined. Several C(17) oxygenated lobane diterpenes such as loba-8,10,13(15)-triene-14,17,18-triol 14-acetate (**3**)¹⁾ and lobatriene (**4**)¹⁾ have been reported, but their stereochemistries were not determined unambiguously.⁴⁾ It was thus considered that the structure of **1** could be determined completely by authentic chemical synthesis *via* coupling of the side chain and the elemene moiety, the stereochemistry of each component was clearly defined. The stereoselective synthesis and complete structure of **1** is presented in the following.



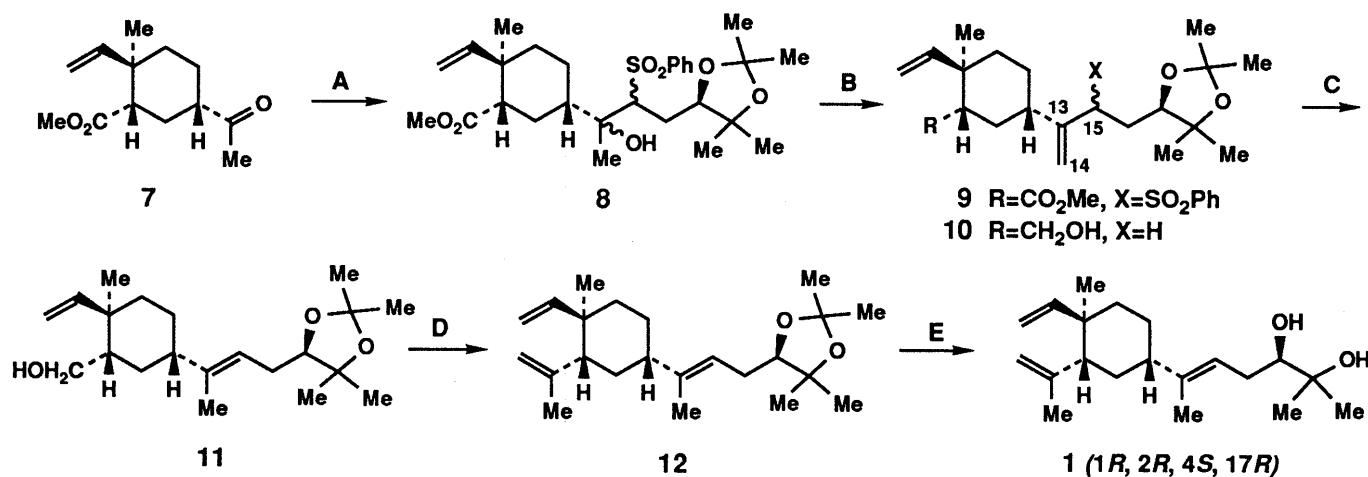
Compound **1** (1*R*,2*R*,4*S*,17*R*) was chosen as the target molecule, since β-elemene (**2**) isolated from the same soft coral has 5*R*, 7*S*, 10*R* configurations.¹⁾ Compound (**7**), whose synthetic method from D-mannitol was developed at this laboratory during the synthesis of fuscol, was used as the elemene moiety.⁵⁾ The requisite side chain precursor (**6**)⁷⁾ was obtained by reaction of iodide (**5**)⁸⁾ with the carbanion generated from methyl phenyl sulfone and butyllithium (Chart 1). The reaction of keto ester (**7**) with the carbanion generated from **6** and butyllithium in the presence of boron trifluoride etherate (BF₃·OEt₂) in THF at -78°C gave **8** as a

Chart 1



mixture of three diastereomeric isomers. In the absence of $\text{BF}_3\cdot\text{OEt}_2$, aldol reaction proceeded sluggishly, resulting in poor yields ($\sim 10\%$). Hydroxy sulfone (8) was converted to the olefin (11) via 9. Dehydration of 8 with thionyl chloride in pyridine gave 9 (1:1 mixture of epimers at C-15), which on treatment with lithium-ammonia produced the desired 13(15)-*E* olefin (11)⁹ as the major product along with a regioisomeric olefin

Chart 2



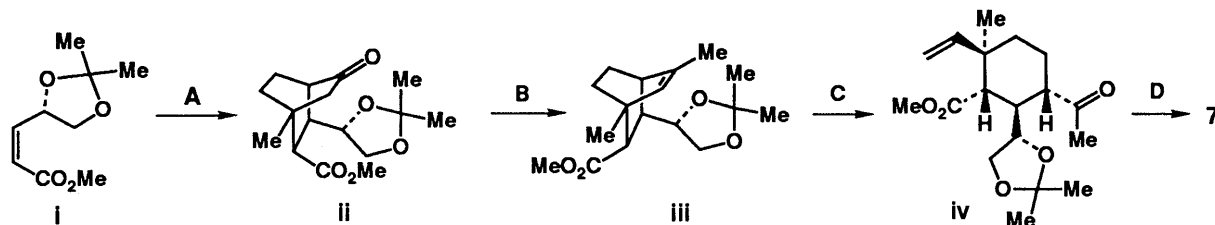
Reagents: (A): 6, BuLi, $\text{BF}_3\cdot\text{OEt}_2$, THF, -78°C , 20 min; (B) SOCl_2 , pyridine, 0°C , 5 min, 70% (from 7); (C) Li, liq $\text{NH}_3\text{-EtOH}$, -78°C , 20 min, 11 (76%), 10 (19%); (D) i) PDC, 4Å MS, CH_2Cl_2 , 24°C , 88%; ii) MeLi, Et_2O , -70°C , 5 min, 98%; iii) PDC, 4Å MS, CH_2Cl_2 , 24°C , 30 min, 95%; iv) $\text{CH}_2\text{Br}_2\text{-Zn-TiCl}_4$, THF- CH_2Cl_2 , 23°C , 1 h, 84%; (E) $\text{AcOH-H}_2\text{O}$ (4:1), 40°C , 1 h, 93%.

(10)¹⁰ (11:10=4:1). The mixture was separated by AgNO_3 -impregnated silica gel. The hydroxymethyl group of 11 was converted to isopropenyl group in four steps: 1) PDC oxidation to the corresponding aldehyde; 2) methylation with methyllithium; 3) PDC oxidation and 4) methylenation with Nozaki-Lombardo reagent¹¹ to afford triene (12). The acetonide group was then removed by acid treatment to give 1 (1*R*, 2*R*, 4*S*, 17*R*), $[\alpha]_{\text{D}}^{25} +34.3^\circ$ (c 0.25, CHCl_3), as a colorless oil. The ^1H - and ^{13}C -NMR spectra and the sign of optical rotation of the synthesized 1 were identical to those of a natural sample, $[\alpha]_{\text{D}}^{25} +25.9^\circ$ (c 0.34, CHCl_3). This synthesis clearly indicates the complete structure of loba-8,10,13(15)-triene-17,18-diol to be 1 (1*R*, 2*R*, 4*S*, 17*R*).

REFERENCES AND NOTES

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- 5) The keto ester (**7**) was synthesized from D-mannitol *via* sequential Michael reaction of α,β -unsaturated ester **i**⁶⁾ with lithium enolate of 3-methyl-2-cyclohexenone to give **ii**, ozonolysis of **iii**, methylenation, epimerization of methyl ketone, and the removal of 1,3-dioxolane moiety in **iv**. M. Iwashima, H. Nagaoka, K. Kobayashi, and Y. Yamada, *Tetrahedron Lett.*, in press.



Reagents: (A) 3-methyl-2-cyclohexenone, LDA, 93%; (B) i) LDA then (EtO)₂POCl, 98%; ii) MeMgI, Ni(acac)₂, 73%; iii) *t*-BuOK, 99%; (C) i) O₃ then Me₂S, 96%; ii) CH₂I₂, Zn, Me₃Al, 79%; iii) MeONa, 83%; (D) i) 80% AcOH; ii) NaIO₄, 78% (2 steps); iii) NaClO₂, 78%; iv) (COCl)₂, pyridine; v) N-hydroxypyridine-2-thione sodium salt, DMAP then Bu₃SnH, AIBN, 71% (2 steps).

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- 7) Structural assignments were made for all stable synthetic intermediates by ¹H-NMR (400 MHz), IR, high resolution mass spectroscopy and/or combustion analysis.
- 8) R. Dumont and H. Pfander., *Helv. Chem. Acta*, **66**, 814 (1983); M. Ohmori, Y. Takano, S. Yamada, and H. Takayama, *Tetrahedron Lett.*, **27**, 71 (1986).
- 9) **11**: ¹H-NMR (400 MHz) (CDCl₃) δ : 0.96 (3H, s), 1.19 (3H, s), 1.25 (3H, s), 1.35 (3H, s), 1.43 (3H, s), 1.35-1.60 (3H, m), 1.65 (3H, s), 1.75 (1H, dddd, J=13.1, 7.6, 5.1, 3.5 Hz), 1.94 (1H, tt, J=11.8, 3.2 Hz), 2.20 (1H, ddd, J=15.1, 7.3, 6.8 Hz), 2.32 (1H, ddd, 15.1, 6.8, 6.5 Hz), 3.27 (1H, dd, J=10.8, 7.6 Hz), 3.68 (1H, dd, J=10.8, 5.1 Hz), 3.74 (1H, dd, J=7.3, 6.5 Hz), 5.01 (1H, dd, J=10.8, 1.1 Hz), 5.03 (1H, dd, J=17.5, 1.1 Hz), 5.21 (1H, brt, J=6.8 Hz), 5.84 (1H, dd, J=17.5, 10.8 Hz).
- 10) **10**: ¹H-NMR (400 MHz) (CDCl₃) δ : 0.97 (3H, s), 1.11 (3H, s), 1.25 (3H, s), 1.33 (3H, s), 1.42 (3H, s), 1.34-1.74 (6H, m), 1.83 (1H, dddd, J=13.2, 7.7, 5.1, 3.6 Hz), 1.94 (1H, tt, J=12.0, 3.2 Hz), 2.07 (1H, ddd, J=15.2, 10.3, 6.1 Hz), 2.31 (1H, ddd, 15.2, 10.8, 4.7 Hz), 3.27 (1H, dd, J=10.8, 7.7 Hz), 3.69 (1H, dd, J=10.8, 5.1 Hz), 3.69 (1H, dd, J=7.5, 6.5 Hz), 4.77 (1H, d, J=1.3 Hz), 4.82 (1H, brs), 5.01 (1H, dd, J=10.8, 1.2 Hz), 5.02 (1H, dd, J=17.5, 1.2 Hz), 5.84 (1H, dd, J=17.5, 10.8 Hz).
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(Received December 13, 1991)