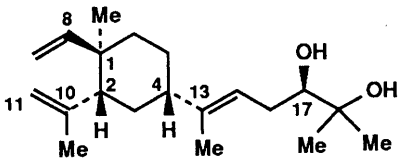
SYNTHESIS OF (1*R*,2*R*,4*S*,17*R*)-LOBA-8,10,13(15)-TRIENE-17,18-DIOL, A MARINE DITERPENE

Hiroto NAGAOKA,* Makoto IWASHIMA, Masayoshi MIYAHARA, and Yasuji YAMADA*
Tokyo College of Pharmacy, Horinouchi, Hachioji, Tokyo 192-03, Japan

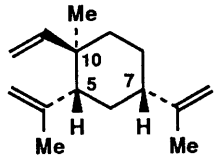
Synthesis of marine diterpene **1** (1*R*,2*R*,4*S*,17*R*) has been achieved *via* coupling of ketone **7** and sulfone **6**, leading to the determination of the absolute stereochemistry.

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

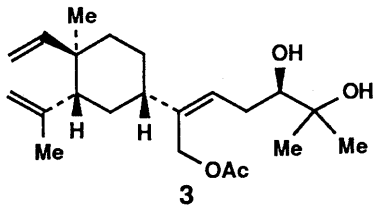
Loba-8,10,13(15)-triene-17,18-diol (**1**), isolated from a soft coral of the genus *Lobophytum* collected at the Great Barrier Reef by Wells *et al.*, is a structurally unique diterpene having a prenylated elemane skeleton (lobane skeleton) with hydroxyl functionality at C(17).[1,2] The relative stereochemistry of the elemane moiety (1*R**, 2*R**, 4*S**) was elucidated based on a comparison of the ^{1}H-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 elemane 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 elemane moiety, the stereochemistry of each component was clearly defined. The stereoselective synthesis and complete structure of **1** is presented in the following.



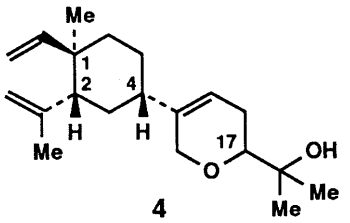
1 *(1R*,2R*,4S*,17R)*



2



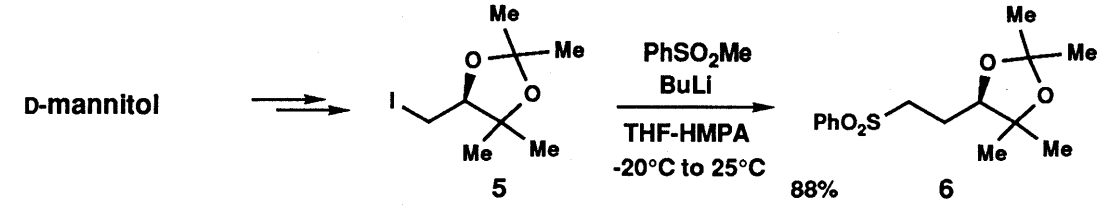
3



4

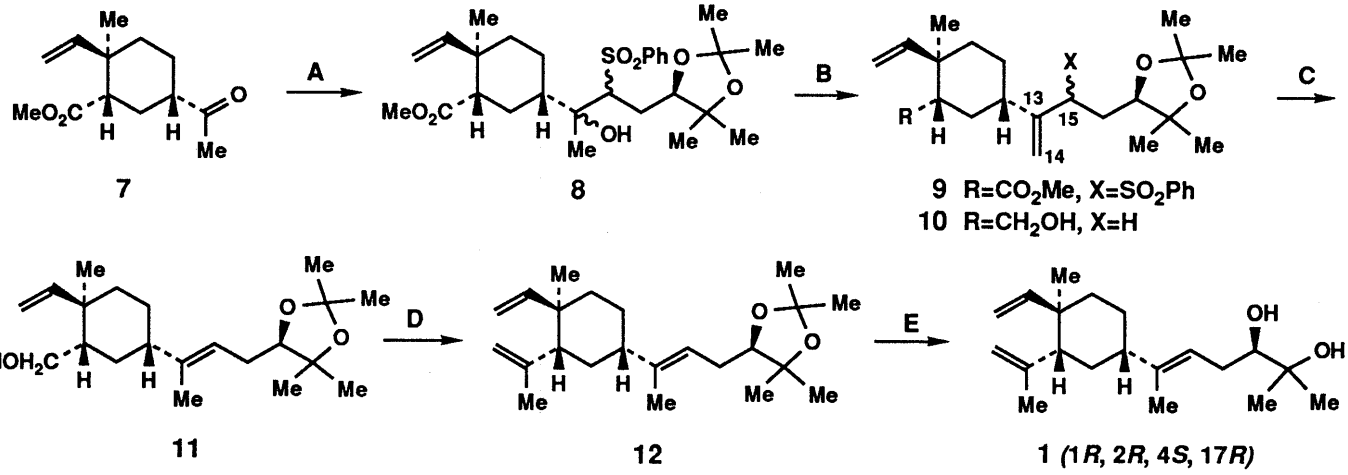
Compound **1** (1*R*,2*R*,4*S*,17*R*) was chosen as the target molecule, since β-elemene (**2**) isolated from the same soft coral has 5*R*, 7*S*, 10*R* configurations.[1] Compound (**7**), whose synthetic method from D-mannitol was developed at this laboratory during the synthesis of fuscol, was used as the elemane 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 (BF_3·OEt_2) in THF at -78°C gave **8** as a

Chart 1



mixture of three diastereomeric isomers. In the absence of $BF_3 \cdot OEt_2$, aldol reaction proceeded sluggishly, resulting in poor yields (~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, $BF_3 \cdot OEt_2$, THF, -78°C, 20 min; (**B**) $SOCl_2$, pyridine, 0°C, 5 min, 70% (from **7**); (**C**) Li, liq NH_3-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) CH_2Br_2-Zn-$TiCl_4$, THF-CH_2Cl_2, 23°C, 1 h, 84%; (**E**) AcOH-H_2O (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 reagent[11] to afford triene (**12**). The acetonide group was then removed by acid treatment to give **1** (1*R*, 2*R*, 4*S*, 17*R*), $[\alpha]_D^{25}$ +34.3° (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, $[\alpha]_D^{25}$ +25.9° (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

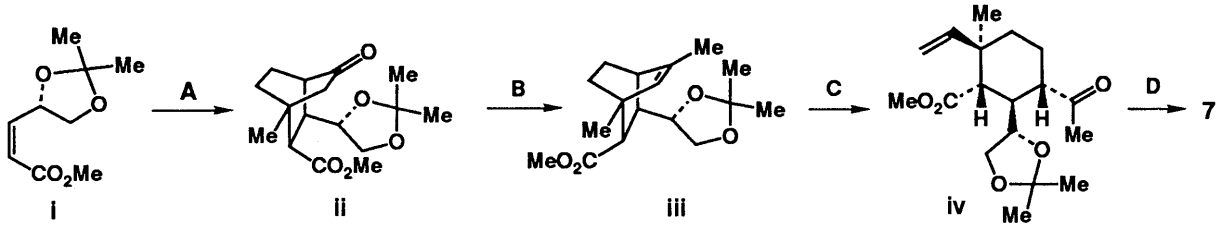
1) R. W. Dunlop and R. J. Wells, *Aust. J. Chem.*, **32**, 1345 (1979).

2) In lobane diterpenes, fuscoside B has been of particular interest owing to its potent topical antiinflammatory property and selective inhibitory effects on leukotriene production. J. Shin and W. Fenical, *J. Org. Chem.*, **56**, 3153 (1991).

3) J. Dillon and K. Nakanishi, *J. Am. Chem. Soc.*, **97**, 5417 (1975).

4) Recently Kakisawa *et al.* elucidated the complete structure of lobatriene (**4**) (1*R*,2*R*,4*S*,17*R*) by use of the modified Mosher's method. *Symp. Pap.-Chem. Nat. Prod., 33th*, 456 (1991).

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) O_3 then Me_2S, 96%; ii) CH_2I_2, Zn, Me_3Al, 79%; iii) MeONa, 83%; (**D**) i) 80% AcOH; ii) $NaIO_4$, 78% (2 steps); iii) $NaClO_2$, 78%; iv) $(COCl)_2$, pyridine; v) N-hydroxypyridine-2-thione sodium salt, DMAP then Bu_3SnH, AIBN, 71% (2 steps).

6) N. Minami, S. S. Ko and Y. Kishi, *J. Am. Chem. Soc.*, **104**, 1109 (1982); H. Matsunaga, T. Sakamaki, H. Nagaoka, and Y. Yamada, *Tetrahedron Lett.*, **24**, 3009 (1983).

7) Structural assignments were made for all stable synthetic intermediates by ^{1}H-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**: ^{1}H-NMR (400 MHz) ($CDCl_3$) 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**: ^{1}H-NMR (400 MHz) ($CDCl_3$) 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).

11) K. Takai, Y. Hotta, K. Oshima, and H. Nozaki, *Tetrahedron Lett.*, 2417 (1978); L. Lombardo, *Tetrahedron Lett.*, **23**, 4293 (1982).

(Received December 13, 1991)