

TOTAL SYNTHESIS OF PHOMACTIN D

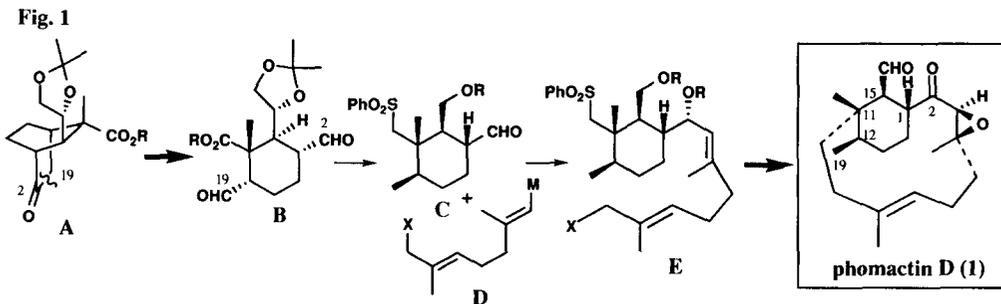
Hiroaki Miyaoka, Yasuhiro Saka, Shotaro Miura and Yasuji Yamada*

School of Pharmacy, Tokyo University of Pharmacy and Life Science,
 Horinouchi, Hachioji, Tokyo 192-03, Japan

Abstract: The first total synthesis of PAF antagonist marine diterpenoid phomactin D was achieved from L-ascorbic acid. This synthesis involves the formation of bicyclo[2.2.2]octane derivative **3** by the sequential Michael reaction, oxidative cleavage of the double bond of **4** and cyclization of sulfone **18**. Copyright © 1996 Elsevier Science Ltd

Phomactins are novel platelet activating factor (PAF) antagonists that have been isolated from the culture filtrate of the marine fungus, *Phoma* sp. (SANK 11486), a parasite on the shell of the crab, *Chionoecetes opilio*.^{1,2} Their structures, containing a rare bicyclo[9.3.1]pentadecane ring system, were determined based on spectroscopic evidences, X-ray crystallography and chemical conversions. The absolute configurations of phomactin A, B, B₁ and B₂ could be clarified while those of phomactin C, D, E, F and G still remain unclear. Phomactin D has the strongest PAF antagonistic activity among phomactins. The synthesis of phomactin D has not been reported.³ Thus, its unique structure and biological activity prompted the authors to undertake the total synthesis of phomactin D. Herein, we wish to report a first total synthesis of phomactin D (**1**).

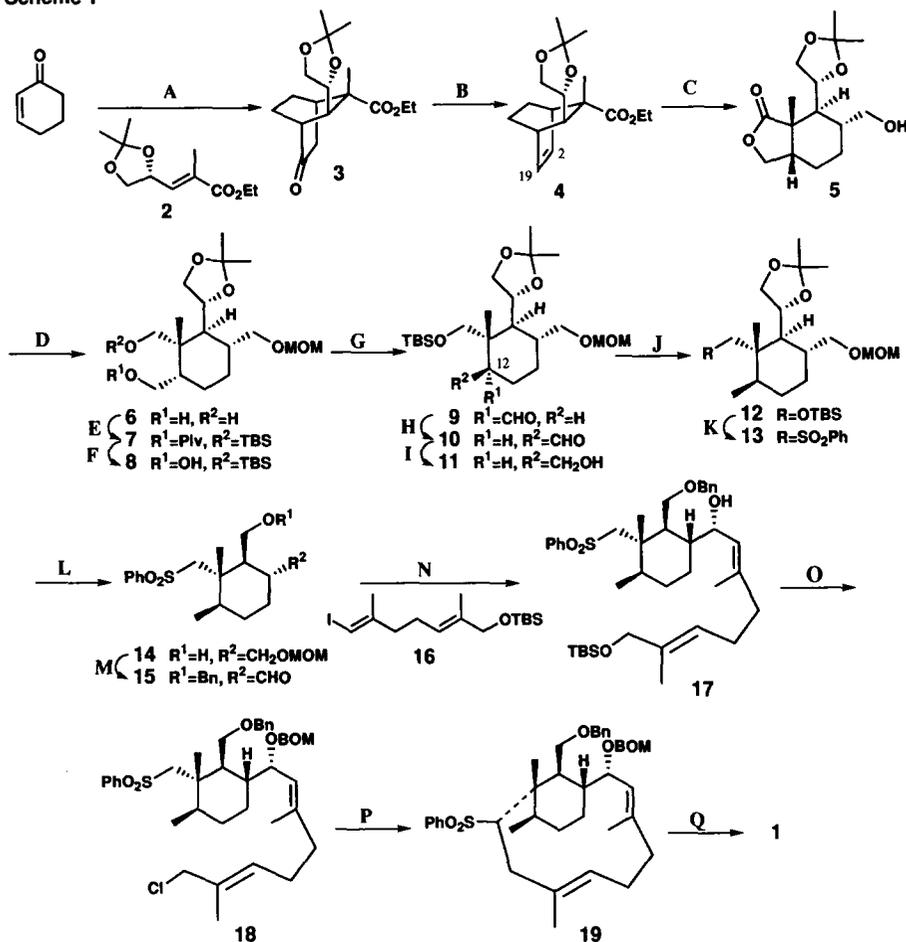
In the course of synthesizing natural products using bicyclo[2.2.2]octane derivatives as chiral building blocks,⁴ the present method was applied to the synthesis of structural unique phomactin D. The synthetic strategy involves the formation of bicyclo[2.2.2]octane derivative **A** by diastereoselective sequential Michael reaction,⁵ oxidative cleavage of the C(2)-C(19) bond⁶ in **A** to give pentasubstituted cyclohexane segment **C** via compound **B** and the cyclization of sulfone **E** obtained by coupling **C** with the sidechain segment **D**, as key steps (Figure 1).



The sequential Michael reaction of the kinetic enolate of 2-cyclohexen-1-one with ethyl (*E, R*)-3-(2,2-dimethyl-1,3-dioxolan-4-yl)-2-methyl-2-propenoate (**2**),⁷ prepared from L-ascorbic acid, in THF -78°C afforded bicyclo[2.2.2]octane derivative **3**,⁸ mp 78-80°C, $[\alpha]_D -21.8^\circ$ (*c* 1.00, CHCl₃), corresponding to **A** in synthetic strategy, as the sole product in 74% yield (Scheme 1). Ketone **3** was converted to olefin **4**, $[\alpha]_D -22.8^\circ$ (*c* 1.12, CHCl₃), in three steps: 1) NaBH₄ reduction to the alcohol, 2) tosylation of the hydroxyl group and 3) elimination of the tosylate by DBU. Oxidative cleavage of the C(2)-C(19) double bond in **4** was achieved by ozonolysis in the presence of pyridine in MeOH-CH₂Cl₂ followed by NaBH₄ reduction of the aldehyde afforded lactone **5**, $[\alpha]_D -62.9^\circ$ (*c* 1.06, CHCl₃). Compound **5** was converted to alcohol **8**, $[\alpha]_D -21.1^\circ$ (*c* 1.45, CHCl₃), in five steps: 1) protection of hydroxyl group as MOM ether, 2) LiAlH₄ reduction of lactone to diol **6**, 3) selective protection of the less hindered primary hydroxyl group as pivalate, 4) protection of another hydroxyl group as TBS ether to silyl ether **7** and 5) reductive deprotection of pivalate by DIBAL-H to alcohol **8**. Oxidation of the primary hydroxyl group in **8** with PDC gave aldehyde **9**. Epimerization of the C-12 position in **9** was carried out by treatment with K₂CO₃ in MeOH to give a mixture of aldehyde **9** and the thermodynamically stable epimer **10**, bearing desired chiral centers at C-1, C-11, C-12 and C-15 corresponding to phomactin D, (**9** : **10** = 1 : 4).⁹ Following reduction of the mixture of **9** and **10**, alcohols **8** and **11** were obtained and separated by silica gel column chromatography. The hydroxyl group in **11** was converted to a methyl group in two steps: 1) conversion of the hydroxyl group to phenyl sulfide and 2) lithium metal reduction of phenyl sulfide in liq. NH₃ to **12**. The TBS group in **12** was removed with Bu₄NF, whose hydroxyl group was converted to phenyl sulfide whose oxidation by OXONE®¹⁰ gave sulfone **13**, $[\alpha]_D -2.4^\circ$ (*c* 0.25, CHCl₃). Sulfone **13** was converted to aldehyde **15**, corresponding to cyclohexane segment C, via alcohol **14** in the following six steps: 1) hydrolysis of acetonide, 2) NaIO₄ oxidative cleavage of 1,2-diol, 3) NaBH₄ reduction of aldehyde to alcohol **14**, 4) protection of hydroxyl group as benzyl ether, 5) deprotection of MOM ether and 6) oxidation of the hydroxyl group to aldehyde **15**.

Reaction of alkenyllithium reagent, corresponding to side chain segment D, prepared from alkenyllithide **16**¹¹ and ^tBuLi, with aldehyde **15** in THF gave alcohol **17**, $[\alpha]_D +20.0^\circ$ (*c* 0.59, CHCl₃), as the sole product in 72% yield.¹² The hydroxyl group in **17** was protected as benzyloxymethyl (BOM) ether; by deprotection of TBS ether using Bu₄NF, the hydroxyl group was converted to chloride directly using methanesulfonyl chloride and 4-*N,N*-dimethylaminopyridine in CH₂Cl₂ to give allylic chloride **18**. The macrocyclization of sulfone **18** was successfully carried out by treatment with potassium bis(trimethylsilyl)amide (KHMDs) in THF (3.0 x 10⁻³ M) to afford **19**, $[\alpha]_D +5.7^\circ$ (*c* 0.14, CHCl₃). Removal of the phenylsulfonyl group and deprotection of benzyl and BOM ether were carried out by treating **19** with sodium in liq. NH₃ to afford the diol. Epoxidation of the allylic alcohol with ^tBuOOH in the presence of vanadyl acetylacetonate¹³ gave epoxide as the sole product. Finally, PDC oxidation of the primary and secondary hydroxyl groups completed the synthesis phomactin D (**1**), mp 96-97°C, $[\alpha]_D +103.0^\circ$ (*c* 0.30, CHCl₃). ¹H-NMR (400 MHz) spectra and the sign of optical rotation of synthetic **1** were identical to those of natural phomactin D, mp 97-98°C, $[\alpha]_D +114.3^\circ$ (*c* 1.01, CHCl₃).^{1b} The absolute configuration of phomactin D is thus shown to be **1**.

Scheme 1

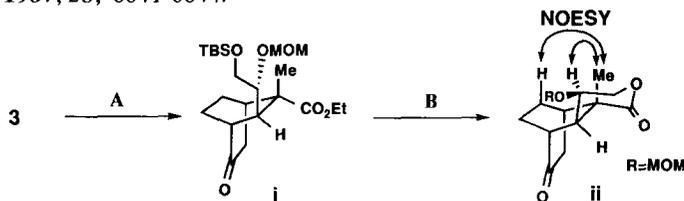


Reagents : A. LDA, THF, -78°C , then **2**, 74%; B. i) NaBH_4 , MeOH, 0°C , ii) TsCl, Py, 0°C , iii) DBU, toluene, 100°C , 53% (3 steps); C. O_3 , Py, CH_2Cl_2 -MeOH, -78°C , Me_2S , then NaBH_4 , 0°C , 96%; D. i) MOMCl, $^i\text{Pr}_2\text{NEt}$, $\text{CH}_2\text{ClCH}_2\text{Cl}$, 50°C , 99%, ii) LiAlH_4 , THF, 0°C , 88%; E. i) PivCl, Py, 0°C , 75%, ii) TBSCl, imidazole, DMF, r.t., quant.; F. DIBAL-H, toluene, -78°C , quant.; G. PDC, 4ÅMS, CH_2Cl_2 , r.t.; H. K_2CO_3 , MeOH, r.t.; I. NaBH_4 , MeOH, 0°C , 88% (3 steps); J. i) PhSSPh, Bu_3P , Py, r.t., 96%, ii) Li, liq. NH_3 , THF, -34°C , 84%; K. i) Bu_4NF , THF, r.t., quant., ii) PhSSPh, Bu_3P , Py, *N*-phenylthiosuccinimide, 50°C , quant., iii) OXONE[®], THF-MeOH- H_2O , quant.; L. i) 80% AcOH, 50°C , ii) NaIO_4 , $(\text{NH}_4)_2\text{SO}_4$, MeOH- H_2O , 0°C , iii) NaBH_4 , MeOH, 0°C , 97% (3 steps); M. i) BnBr, NaH, THF-DMF, r.t., 86%, ii) 6*N* HCl, r.t., 98%, iii) PDC, 4ÅMS, CH_2Cl_2 , r.t., 86%; N. $^t\text{BuLi}$, 16, THF, $-78^\circ\text{C} \sim -10^\circ\text{C}$, 72%; O. i) BOMCl, $^i\text{Pr}_2\text{NEt}$, 50°C , 94%, ii) Bu_4NF , THF, r.t., 73%, iii) MsCl, DMAP, CH_2Cl_2 , r.t.; P. KHMDS, THF, r.t., 39% (2 steps); Q. i) Na, liq. NH_3 , THF, -34°C , 98%, ii) $\text{VO}(\text{acac})_2$, $^t\text{BuOOH}$, Ph-H, r.t., iii) PDC, 4ÅMS, CH_2Cl_2 , r.t., 60% (2 steps).

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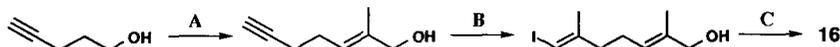
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6. Numbering of compounds is in accordance with that for phomactin D.
7. Leonard, J.; Mohialdin, S.; Swain, P. A. *Synth. Commun.*, **1989**, *19*, 3529-3534.
8. The stereochemistry of **3** was determined by the NOESY spectrum of compound **ii**, which was converted from **3** via compound **i**, as shown below. Similar sequential Michael reaction has been reported by our laboratory. See: Nagaoka, H.; Kobayashi, K.; Okamura, T.; Yamada, Y. *Tetrahedron Lett.*, **1987**, *28*, 6641-6644.



Reagents : A. i) 80% AcOH, 50°C, 97%, ii) TBSCl, imidazole, DMF, r.t., 99%, iii) MOMCl, Pr_2NEt , $\text{CH}_2\text{ClCH}_2\text{Cl}$, 50°C, 71%; B. i) Bu_4NF , THF, r.t., 62%, ii) 1N NaOH, DME, r.t., iii) DCC, Py, r.t., 67% (2 steps).

9. The ratio of the diastereomers was determined by $^1\text{H-NMR}$ analysis.
10. Trost, B.M.; Curran, D.P. *Tetrahedron Lett.*, **1981**, *22*, 1287-1290.
11. Alkenyliodide **16** was synthesized from 4-pentyn-1-ol in the following. cf: Negishi, E.; Van Horn, D.V.; King, A.O.; Okukado N. *Synthesis*, **1979**, 501-502.



Reagents : A. i) PDC, 4ÅMS, CH_2Cl_2 , r.t., ii) $\text{Ph}_3\text{P}=\text{C}(\text{Me})\text{CO}_2\text{Et}$, benzene, r.t., 63% (2 steps), iii) DIBAL-H, toluene, -78°C, 97%; B. Me_3Al , Cp_2ZrCl_2 , CH_2Cl_2 , 0°C~r.t., then I_2 , THF, -30°C, 89%; C. TBSCl, imidazole, DMF, r.t., 83%.

12. Attempt at the direct coupling of aldehyde **15** and alkenyliodide **16** using CrCl_2 in the presence of NiCl_2 was unsuccessful. cf: Takai, K.; Tagashira, M.; Kuroda, T.; Oshima, K.; Utimoto, K.; Nozaki, H. *J. Am. Chem. Soc.*, **1986**, *108*, 6048-6050.
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