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TOTAL SYNTHESIS OF PHOMACTIN D

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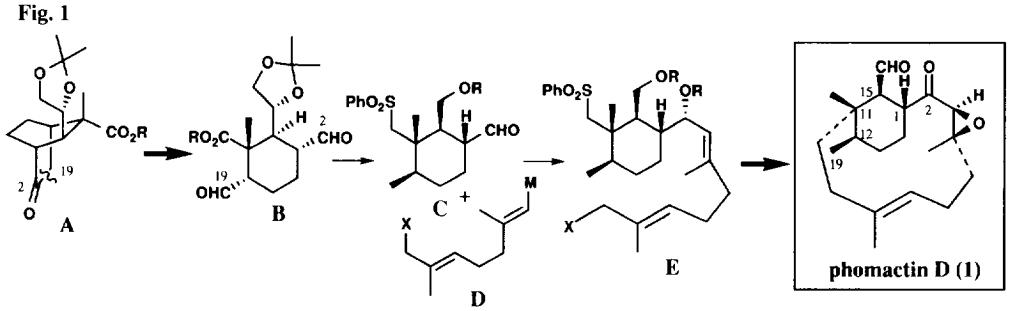
Abstract: The first total synthesis of PAF antagonist marine diterpenoid phomactin D was achieved from L-ascorbic acid. This synthesis involves the formation of bicyclo[2.2.2]octane derivative **3** by the sequential Michael reaction, oxidative cleavage of the double bond of **4** and cyclization of 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, *Chinoecetes 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, B_1 and B_2 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) bond[6] 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).

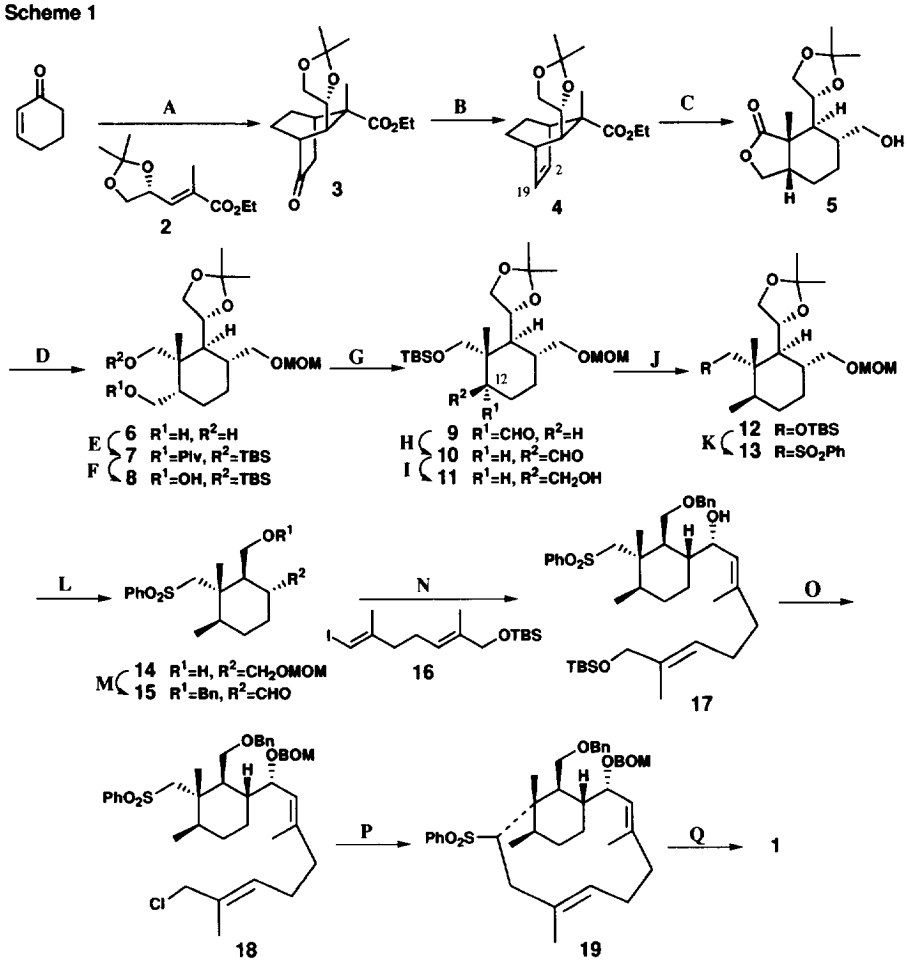
Fig. 1



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° (*c* 1.00, $CHCl_3$), 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° (*c* 1.12, $CHCl_3$), in three steps: 1) $NaBH_4$ 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 achived by ozonolysis in the presence of pyridine in MeOH-CH_2Cl_2 followed by $NaBH_4$ reduction of the aldehyde afforded lactone **5**, $[\alpha]_D$ -62.9° (*c* 1.06, $CHCl_3$). Compound **5** was converted to alcohol **8**, $[\alpha]_D$ -21.1° (*c* 1.45, $CHCl_3$), in five steps: 1) protection of hydroxyl group as MOM ether, 2) $LiAlH_4$ 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 K_2CO_3 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. NH_3 to **12**. The TBS group in **12** was removed with Bu_4NF, whose hydroxyl group was converted to phenyl sulfide whose oxidation by OXONE®[10] gave sulfone **13**, $[\alpha]_D$ -2.4° (*c* 0.25, $CHCl_3$). 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) $NaIO_4$ oxidative cleavage of 1,2-diol, 3) $NaBH_4$ 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 alkenyliodide **16**[11] and ^{t}BuLi, with aldehyde **15** in THF gave alcohol **17**, $[\alpha]_D$ +20.0° (*c* 0.59, $CHCl_3$), 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 Bu_4NF, the hydroxyl group was converted to chloride directly using methanesulfonyl chloride and 4-*N*,*N*-dimethylaminopyridine in CH_2Cl_2 to give allylic chloride **18**. The macrocyclization of sulfone **18** was successfully carried out by treatment with potassium bis(trimethylsilyl)amide (KHMDS) in THF (3.0×10^{-3} M) to afford **19**, $[\alpha]_D$ +5.7° (*c* 0.14, $CHCl_3$). Removal of the phenylsulfonyl group and deprotection of benzyl and BOM ether were carried out by treating **19** with sodium in liq. NH_3 to afford the diol. Epoxidation of the allylic alcohol with ^{t}BuOOH in the presence of vanadyl acetylacetonate[13] 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° (*c* 0.30, $CHCl_3$). ^{1}H-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° (*c* 1.01, $CHCl_3$).[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, $^iPr_2NEt$, CH_2ClCH_2Cl, 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*-phenylthiosucciimide, 50°C, quant., iii) OXONE®, THF-MeOH-H_2O, quant.; **L**. i) 80% AcOH, 50°C, ii) $NaIO_4$, $(NH_4)_2SO_4$, 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**. ^tBuLi, **16**, THF, -78°C~ -10°C, 72%; **O**. i) BOMCl, $^iPr_2NEt$, 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) $VO(acac)_2$, ^tBuOOH, Ph-H, r.t., iii) PDC, 4ÅMS, CH_2Cl_2, r.t., 60% (2 steps).

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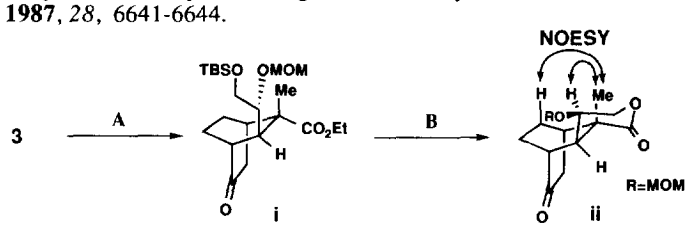
5. a) White, K.B.; Reusch, W. *Tetrahedron*, **1978**, *34*, 2439-2443; b) Nagaoka, H.; Shibuya, K.; Kobayashi, K.; Miura, I.; Muramatsu, M.; Yamada, Y. *Tetrahedron Lett.*, **1993**, *34*, 4039-4042 and references cited therein.

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.

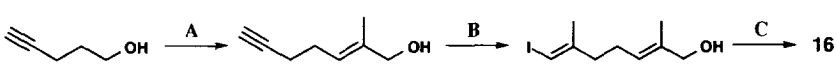


Reagents : A. i) 80% AcOH, 50°C, 97%, ii) TBSCl, imidazole, DMF, r.t., 99%, iii) MOMCl, $^{i}Pr_2NEt$, CH_2ClCH_2Cl, 50°C, 71%; **B**. i) Bu_4NF, THF, r.t., 62%, ii) 1*N* NaOH, DME, r.t., iii) DCC, Py, r.t., 67% (2 steps).

9. The ratio of the diastereomers was determined by ^{1}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) $Ph_3P{=}C(Me)CO_2Et$, 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.

13. Sharpless, K.B.; Michaelson, R.C. *J. Am. Chem. Soc.*, **1973**, *95*, 6136-6137.

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