ORGANIC LETTERS

2004
Vol. 6, No. 4
553−556

# First Total Synthesis of Antimitotic Compound, (+)-Phomopsidin

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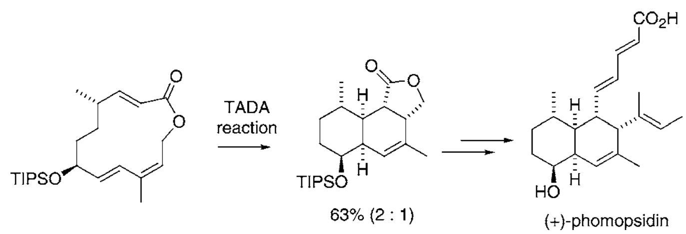
**Received December 1, 2003**

## ABSTRACT




**The first total synthesis of (+)-phomopsidin has been achieved via a diastereoselective transannular Diels–Alder (TADA) reaction. Key steps in the synthesis include diastereoselective ynone reduction with (−)-α-pinene and 9-BBN, macrocyclization by *E*-selective intramolecular Horner–Wadsworth–Emmons (HWE) reaction, as well as carbometalation under Wipf's conditions, followed by HWE reaction at low temperature to selectively construct the (*E*)-1-methylpropenyl and (1*E*,2*E*)-4-carboxy-1,3-butadienyl substituents.**

Phomopsidin (Figure 1) was isolated from marine-derived fungus, *Phomopsis* sp. strain TUF 95F47, collected in Pohnpei as a new inhibitor of microtubule assembly by Namikoshi et al. in 1997.[1] Phomopsidin shows strong inhibitory activity against assembly of the microtubule proteins purified from porcine brain at an $IC_{50}$ of 5.7 $\mu$M.[1] The relative stereochemistry of phomopsidin was determined on the basis of NMR data,[1,2] and recently, its absolute configuration has been elucidated by the exciton chirality method.[3]

Phomopsidin possesses six stereogenic centers on a cis-fused dehydrodecaline ring, which is substituted with hydroxyl, methyl, (1*E*,2*E*)-4-carboxy-1,3-butadienyl, and (*E*)-1-methylpropenyl groups. The biosynthesis of phomopsidin was proposed to involve an intramolecular Diels−Alder (IMDA) reaction[4] of a linear precursor **1**. The 16*Z*-isomer of phomopsidin (MK8383) has also been isolated and found to have activity similar to that of phomopsidin.[5] The potent

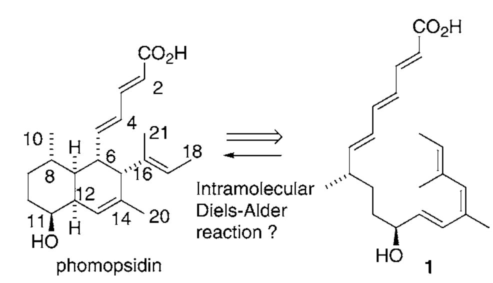



**Figure 1.** (+)-Phomopsidin and the proposed biogenesis.[3]

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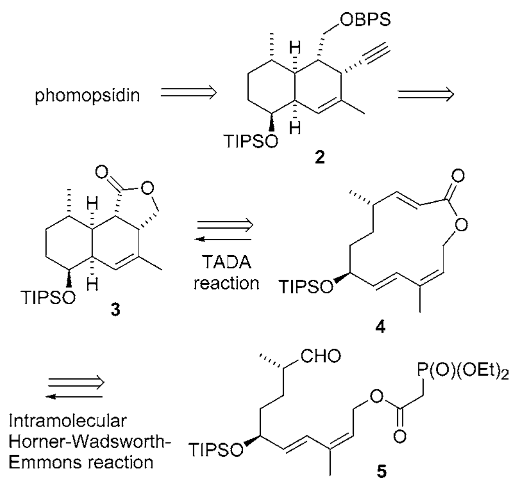
[‡] Tokyo University of Marine Science and Technology.
(1) Namikoshi, M.; Kobayashi, H.; Yoshimoto, T.; Hosoya, T. *J. Antibiot.* **1997**, *50*, 890−892.
(2) Namikoshi, M.; Kobayashi, H.; Yoshimoto, T.; Meguro, S.; Akano, K. *Chem. Pharm. Bull.* **2000**, *48*, 1452−1457.
(3) Kobayashi, H.; Meguro, S.; Yoshimoto, T.; Namikoshi, M. *Tetrahedron* **2003**, *59*, 455−459.
(4) For reviews, see: Roush, W. R. *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Eds.; Pergamon: Oxford, 1991; Vol. 5, pp 513−550 and references therein and in ref 6.

10.1021/ol036338q CCC: $27.50 
**Published on Web 01/16/2004**

antimitotic activity, structure, and proposed biosynthesis of phomopsidin all make it an attractive synthetic target. We report herein the first total synthesis of phomopsidin.

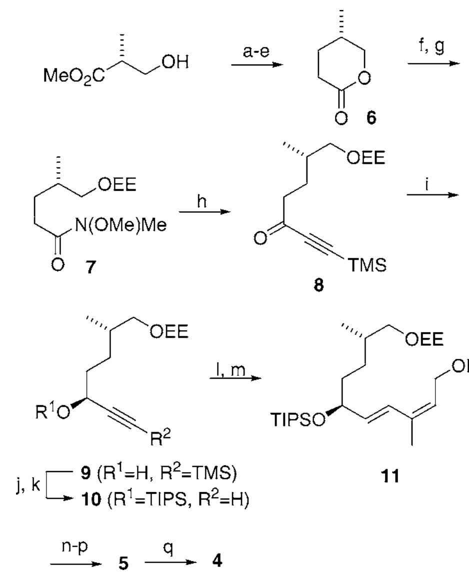
Linear precursor **1** was considered for a synthesis of phomopsidin featuring a biomimetic Diels−Alder reaction (Figure 1); however, this route was not pursued because **1** possesses a sensitive triene, as well as (*E*,*Z*)-dienes that are known to react poorly in Diels−Alder reactions due to the energetically unfavored *s*-cis conformation in the transition state. We decided thus to employ a transannular Diels−Alder (TADA) reaction[4,6] to generate the *cis*-dehydrodecaline skeleton of phomopsidin. An intramolecular Horner−Wadsworth−Emmons (HWE) reaction of **5** was expected to provide (*E*)-α,β-unsaturated macrocyclic lactone **4**, which was expected to entropically activate and diastereoselectively control the TADA reaction to form *cis*-dehydrodecaline **3** (Scheme 1).

**Scheme 1.** Retrosynthetic Analysis of (+)-Phomopsidin




Suzuki−Miyaura coupling between propargyl ether **10** and ethyl (*Z*)-3-iodo-2-butenoate[7] was envisioned to construct the (*E*,*Z*)-diene in **11** (Scheme 2). The synthesis of alkyne **10** began with protection of methyl (*S*)-3-hydroxy-2-methylpropionate as an ethoxyethyl ether, which was reduced with $LiAlH_4$ and transformed to the corresponding iodide (85%, three steps). Coupling of the obtained iodide with diethyl malonate, followed by decarboxylation, which was accompanied with removal of the ethoxyethyl group, afforded δ-lactone **6** (81%, two steps), which was converted into the corresponding Weinreb amide (78%) and then protected as ethoxyethyl ether **7** (95%). Lithium trimethylsilylacetylide reacted with amide **7** to give ynone **8**, which was reduced stereoselectively with (−)-α-pinene and 9-BBN to afford secondary alcohol **9**.[8,9] The TMS group in **9** was removed

**Scheme 2** [a]




[a] Reagents and conditions: (a) Ethylvinyl ether, PPTS, $CH_2Cl_2$, rt. (b) $LiAlH_4$, $Et_2O$, 0 °C. (c) $I_2$, $PPh_3$, imidazole, benzene/$CH_3CN$(10/1), rt, 85% (three steps). (d) $CH_2(CO_2Et)_2$, NaH, THF, reflux. (e) NaCl, $H_2O$, DMSO, reflux, 81% (two steps). (f) $Me_2AlCl$, MeONHMe−HCl, $CH_2Cl_2$, rt, 78%. (g) Ethylvinyl ether, PPTS, $CH_2Cl_2$, rt, 95%. (h) TMSCCH, *n*-BuLi, THF, 0 °C. (i) (−)-α-pinene, 9-BBN, THF, rt. (j) TBAF, THF, rt, 88% (three steps). (k) TIPSOTf, TEA, $CH_2Cl_2$, rt, 76%. (l) (i) 9-BBN, THF, reflux; (ii) PhCHO, rt; (iii) ethyl (*Z*)-3-iodo-2-butenoate, $[Pd_2(dba)_3]$-$CHCl_3$, $AsPh_3$, $K_2CO_3$, DMF, THF, $H_2O$, rt. (m) DIBAL, $CH_2Cl_2$, −78 °C, 76% (two steps). (n) $(EtO)_2P(O)CH_2CO_2H$, $CBr_4$, $PPh_3$, Py, $CH_2Cl_2$, rt, 92%. (o) PPTS, EtOH, rt, 98%. (p) Dess−Martin periodinane, $CH_2Cl_2$, rt. (q) $K_2CO_3$, 18-crown-6, toluene, 0.005 M, rt, 78% (two steps).

by TBAF (88%, three steps), and the hydroxyl group was protected as TIPS ether **10** (76%).

With alkyne **10** in hand, Suzuki−Miyaura coupling[10] of **10** and ethyl (*Z*)-3-iodo-2-butenoate was carried out. Thus, alkyne **10** was reacted with 9-BBN first, followed by treatment with benzaldehyde to convert the byproduct, 1,1-bisboryl adduct, to the desired *trans*-alkenylborane,[10b] and finally reacted with ethyl (*Z*)-3-iodo-2-butenoate under condition l in Scheme 2. The coupling reaction proceeded successfully; however, concomitant impurities were also produced. Therefore, the crude product was used for the next step without purification. The crude product was reduced by DIBAL-H, and to our delight, pure **11** was obtained by silica gel chromatography (76%, two steps). Alcohol **11** was condensed with diethylphosphonoacetic acid (92%), followed by treatment with PPTS in ethanol to deprotect the ethoxyethyl group (98%). Oxidation of the resultant alcohol with Dess−Martin periodinane furnished **5**, the substrate for the intramolecular HWE reaction.

(5) Wakui, F.; Harimaya, K.; Iwata, M.; Sashita, R.; Chiba, N.; Mikawa, T. *Jpn. Kokai Tokkyo Koho* JP 07,126,211, May 16, 1995, Appl. Oct. 29, 1993; *Chem. Abstr.* **1995**, *123*, 105272b.

(6) Marsault, E.; Toró, A.; Nowak, P.; Deslongchamps, P. *Tetrahedron* **2001**, *57*, 4243−4260.

(7) Piers, E.; Wong, T.; Coish, P. D.; Rogers, C. *Can. J. Chem.* **1994**, *72*, 1816−1819.

(8) Midland, M. M.; McDowell, D. C.; Hatch, R. L.; Tramontano, A. *J. Am. Chem. Soc.* **1980**, *102*, 867−869.

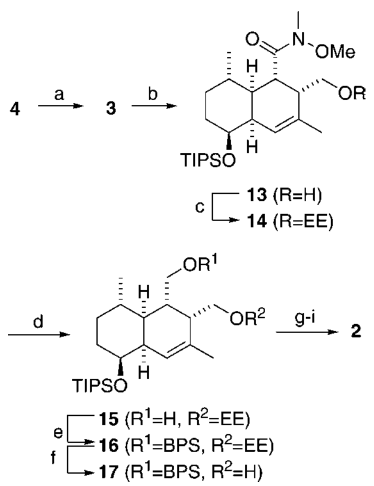
(9) Another diastereomer could not be observed by 400 MHz NMR.

(10) (a) Miyaura, N.; Suzuki, A. *Chem. Rev.* **1995**, *95*, 2457−2483 and references therein. (b) Colberg, J. C.; Rane, A.; Vaquer, J.; Soderquist, J. A. *J. Am. Chem. Soc.* **1993**, *115*, 6065−6071.

The intramolecular HWE reaction of **5** was examined under various conditions, and it was found that the desired ($E$)-$\alpha,\beta$-unsaturated macrocyclic lactone **4** was successfully generated in 78% yield (two steps) under the highly diluted (0.005 M) condition (q) in Scheme 2. The concentration was found to be crucial, that is, the macrolactonization afforded a dimer under the more concentrated reaction condition.

Now the stage was set for the TADA reaction of **4**. The substrates with ($E$,$E$)-dienes are particularly reactive in the TADA reaction, and their reactions are known to proceed even at room temperature because they can reach the prerequisite *s-cis* conformation easily. However, since **4** possesses ($E$,$Z$)-diene, the TADA reaction of **4** proceeded slowly at the reflux temperature of toluene. Actually, the TADA reaction of **4** took 1 day to complete. The products **3** were found to be an inseparable mixture of two diastereomers (63%, a 2:1 ratio, Scheme 3) by $^1$H NMR analysis.

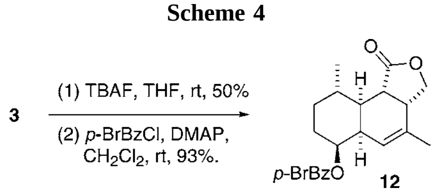
**Scheme 3** [a]




[a] Reagents and conditions: (a) BHT, toluene, reflux, 1 day, 63% (2:1); (b) MeONHMe−HCl, *i*-PrMgCl, THF, 0 °C, 68%; (c) ethylvinyl ether, PPTS, $CH_2Cl_2$, rt, 90%; (d) $BH_3-NH_3$, LDA, THF, 0 °C to room temperature, 89%; (e) BPSCl, imidazole, $CH_2Cl_2$, rt, 98%; (f) 1 N HCl, THF, rt, 87%; (g) Dess−Martin periodinane, $CH_2Cl_2$, rt, 78%; (h) $CBr_4$, $PPh_3$, $CH_2Cl_2$, rt, 93%; (i) *n*-BuLi, THF, −78 to 0 °C, 73%.

The relative stereochemistry of the major product was elucidated as follows. The products **3** were treated with TBAF to remove the TIPS group, giving the corresponding alcohols (50%), which were separated easily by silica gel chromatography (Scheme 4). The major alcohol was converted to *p*-bromobenzoate **12** (93%), but this *p*-bromobenzoate did not afford a crystal suitable for single-crystal X-ray analysis. Then, a NOE experiment was carried out on **12**. As shown in Figure 2, compound **12 s**howed significant NOE

**Scheme 4**




12

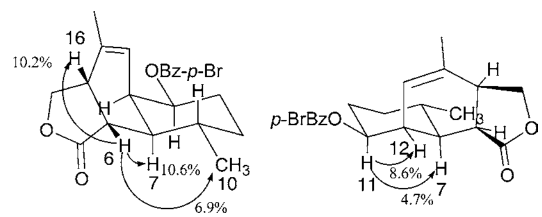



**Figure 2.** Some representative NOE correlations (← →) for **12**.

correlations between [H-16-H-6-H-7 and -H-10] and [H-7-H-11-H-12] (Figure 2). The result of the NOE experiment with **12** suggested that the major product obtained by the TADA reaction of **4** has the desired configuration.

A diastereomeric mixture **3** was converted to Weinreb amide **13** (68%) under Williams conditions,[11] and this was found to be separated from the minor component by silica gel chromatography. Weinreb amide **13** was prone to recyclize under acidic or basic conditions to generate **3**. Accordingly, the Weinreb amide **13** was immediately converted to ethoxyethyl ether **14** (90%), and **14** was reduced with $BH_3-NH_3$ and LDA[12] to give alcohol **15** successfully (89%). Alcohol **15** was converted to BPS ether **16** (98%), followed by careful removal of the ethoxyethyl group under acidic conditions to afford **17** (87%). Dess−Martin oxidation of **17** (78%), followed by the Corey−Fuchs protocol,[13] gave alkyne **2**.

Next we attempted to transform **2** to the trisubstituted iodoalkene **18** (Scheme 5). First, Negishi's carbometalation−iodination protocol was applied,[14] but the yield was low under the conditions reported by Negishi et al. After several attempts, the carbometalation of **2** was found to accelerate dramatically under Wipf's conditions,[15] affording **18** in 86% yield. Pd(0)-catalyzed coupling reaction[16] of **18** with dimethylzinc cleanly produced **19** (99%).

A problem remaining with this synthesis was the construction of the (1$E$,2$E$)-4-carboxy-1,3-butadienyl substituent of phomopsidin. Hence, conversion of **19** to aldehyde **21** for the planned HWE reaction was examined. Selective depro-

(11) Williams, J. M.; Jobson, R. B.; Yasuda, N.; Marchesini, G.; Dolling, U.-H.; Grabowski, E. J. J. *Tetrahedron Lett.* **1995**, *36*, 5461−5464. Other methods resulted in low yield because Weinreb amide **13** readily recyclized to afford lactone **3** as mentioned in the text.

(12) Myers, A. G.; Yang, B. H.; Chen, H.; McKinstry, L.; Kopecky, D. J.; Gleason, J. L. *J. Am. Chem. Soc.* **1997**, *119*, 6496−6511.

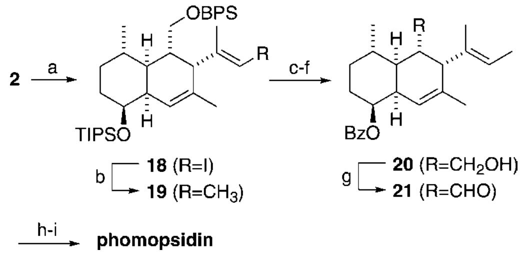
(13) Corey, E. J.; Fuchs, P. L. *Tetrahedron Lett.* **1972**, 3769−3772.

(14) Negishi, E. *Pure Appl. Chem.* **1981**, *53*, 2333−2356 and references therein.

(15) Wipf, P.; Lim, S. *Angew. Chem., Int. Ed. Engl.* **1993**, *32*, 1068−1071.

(16) For reviews, see: (a) Roush. W. R. *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Eds.; Pergamon: Oxford, 1991; Vol. 3, pp 435−480 and references therein. (b) Knochel, P.; Singer, R. D. *Chem. Rev.* **1993**, *93* (6), 2117−2188.

**Scheme 5** [a]




[a] Reagents and conditions: (a) $Cp_2ZrCl_2$, $Me_3Al$, $H_2O$, $CH_2Cl_2$, −20 to 0 °C; then $I_2$, THF, 0 °C, 86%. (b) $Me_2Zn$, $PdCl_2(PPh_3)_2$, THF, rt, 99%. (c) TBAF, THF, reflux, 95%. (d) TBSCl, imidazole, $CH_2Cl_2$, rt, 86%. (e) $Bz_2O$, DMAP, $CH_2Cl_2$, 0 °C to room temperature, 93%. (f) TBAF, THF, rt, 89%. (g) Dess−Martin periodinane, $CH_2Cl_2$, rt, 76%. (h) $(EtO)_2P(O)CH_2CH{=}CHCO_2Et$ (**22**), LHMDS, THF, −78 to −20 °C, quant. (i) LiOH, EtOH, $H_2O$, 93%.

tection of the BPS group in **19** failed under all conditions, so both silyl groups were removed simultaneously with TBAF (95%). The resultant primary hydroxyl group was protected selectively as the TBS ether (86%), followed by benzoylation of the secondary hydroxyl group (93%), deprotection of the TBS group (89%), and Dess−Martin oxidation to afford aldehyde **21** (76%).

The HWE reaction of **21** with phosphonate **22** at −20 °C gave (*E*,*E*)-α,$\beta$,$\gamma$,$\delta$-unsaturated ester stereoselectively and quantitatively. The obtained ester was treated with LiOH to accomplish the total synthesis of (+)-phomopsidin (93%), which proved to be identical in all respects to an authentic sample.

In summary, the first total synthesis of (+)-phomopsidin via the TADA reaction has been achieved. The key steps include highly diastereoselective reduction of ynone **8** with (−)-α-pinene and 9-BBN, Suzuki−Miyaura coupling, and a highly *E*-selective intramolecular Horner−Wadsworth−Emmons (HWE) reaction to synthesize the substrate of the TADA reaction. Carbometalation under Wipf's coditions and HWE reaction at low temperature were crucial to the stereoselective construction of the (*E*)-1-methylpropenyl and (1*E*,2*E*)-4-carboxy-1,3-butadienyl substituents. Optimization of the low-yielding reaction conditions as well as reduction in the number of steps is now underway, and our efforts are directed toward studies of the structure−activity relationships of (+)-phomopsidin.

**Acknowledgment.** We are grateful to Dr. Hisayoshi Kobayashi, Department of Structural Biology, Institute of Molecular and Cellular Biosciences, The University of Tokyo, for the supply of natural (+)-phomopsidin. This work was financially supported in part by 21COE "Practical Nano-Chemistry".

**Supporting Information Available:** Spectral data for key intermediates and synthetic (+)-phomopsidin. This material is available free of charge via the Internet at http://pubs.acs.org.

OL036338Q