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

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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 (-)- $\alpha$ -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.<sup>1</sup> Phomopsidin shows strong inhibitory activity against assembly of the microtubule proteins purified from porcine brain at an IC<sub>50</sub> of 5.7  $\mu$ M.<sup>1</sup> The relative stereochemistry of phomopsidin was determined on the basis of NMR data,<sup>1,2</sup> and recently, its absolute configuration has been elucidated by the exciton chirality method.<sup>3</sup>

Phomopsidin possesses six stereogenic centers on a cisfused dehydrodecaline ring, which is substituted with hydroxyl, methyl, (1E,2E)-4-carboxy-1,3-butadienyl, and (E)-1-methylpropenyl groups. The biosynthesis of phomopsidin



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Figure 1. (+)-Phomopsidin and the proposed biogenesis.<sup>3</sup>

was proposed to involve an intramolecular Diels–Alder (IMDA) reaction<sup>4</sup> of a linear precursor **1**. The 16Z-isomer of phomopsidin (MK8383) has also been isolated and found to have activity similar to that of phomopsidin.<sup>5</sup> The potent

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<sup>(1)</sup> Namikoshi, M.; Kobayashi, H.; Yoshimoto, T.; Hosoya, T. J. Antibiot. 1997, 50, 890–892.

<sup>(2)</sup> Namikoshi, M.; Kobayashi, H.; Yoshimoto, T.; Meguro, S.; Akano, K. *Chem. Pharm. Bull.* **2000**, *48*, 1452–1457.

<sup>(3)</sup> Kobayashi, H.; Meguro, S.; Yoshimoto, T.; Namikoshi, M. Tetrahedron 2003, 59, 455–459.

<sup>(4)</sup> 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.

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<sup>4,6</sup> to generate the *cis*-dehydrodecaline skeleton of phomopsidin. An intramolecular Horner–Wadsworth–Emmons (HWE) reaction of **5** was expected to provide (E)- $\alpha$ , $\beta$ -unsaturated macrocyclic lactone **4**, which was expected to entropically activate and diastereoselectively control the TADA reaction to form *cis*-dehydrodecaline **3** (Scheme 1).



Suzuki–Miyaura coupling between propargyl ether **10** and ethyl (*Z*)-3-iodo-2-butenoate<sup>7</sup> 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<sub>4</sub> 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  $\delta$ -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 (–)- $\alpha$ -pinene and 9-BBN to afford secondary alcohol **9**.<sup>8,9</sup> The TMS group in **9** was removed



<sup>*a*</sup> Reagents and conditions: (a) Ethylvinyl ether, PPTS, CH<sub>2</sub>Cl<sub>2</sub>, rt. (b) LiAlH<sub>4</sub>, Et<sub>2</sub>O, 0 °C. (c) I<sub>2</sub>, PPh<sub>3</sub>, imidazole, benzene/ CH<sub>3</sub>CN(10/1), rt, 85% (three steps). (d) CH<sub>2</sub>(CO<sub>2</sub>Et)<sub>2</sub>, NaH, THF, reflux. (e) NaCl, H<sub>2</sub>O, DMSO, reflux, 81% (two steps). (f) Me<sub>2</sub>AlCl, MeONHMe–HCl, CH<sub>2</sub>Cl<sub>2</sub>, rt, 78%. (g) Ethylvinyl ether, PPTS, CH<sub>2</sub>Cl<sub>2</sub>, rt, 95%. (h) TMSCCH, *n*-BuLi, THF, 0 °C. (i) (–)- $\alpha$ pinene, 9-BBN, THF, rt. (j) TBAF, THF, rt, 88% (three steps). (k) TIPSOTf, TEA, CH<sub>2</sub>Cl<sub>2</sub>, rt, 76%. (l) (i) 9-BBN, THF, reflux; (ii) PhCHO, rt; (iii) ethyl (*Z*)-3-iodo-2-butenoate, [Pd<sub>2</sub>(dba)<sub>3</sub>]-CHCl<sub>3</sub>, AsPh<sub>3</sub>, K<sub>2</sub>CO<sub>3</sub>, DMF, THF, H<sub>2</sub>O, rt. (m) DIBAL, CH<sub>2</sub>Cl<sub>2</sub>, -78 °C, 76% (two steps). (n) (EtO)<sub>2</sub>P(O)CH<sub>2</sub>CO<sub>2</sub>H, CBr<sub>4</sub>, PPh<sub>3</sub>, Py, CH<sub>2</sub>Cl<sub>2</sub>, rt, 92%. (o) PPTS, EtOH, rt, 98%. (p) Dess–Martin periodinane, CH<sub>2</sub>Cl<sub>2</sub>, rt. (q) K<sub>2</sub>CO<sub>3</sub>, 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<sup>10</sup> 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, 1,1bisboryl adduct, to the desired *trans*-alkenylborane,<sup>10b</sup> and finally reacted with ethyl (Z)-3-iodo-2-butenoate under condition 1 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.

<sup>(5)</sup> 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.

<sup>(6)</sup> Marsault, E.; Toró, A.; Nowak, P.; Deslongchamps, P. *Tetrahedron* **2001**, *57*, 4243–4260.

<sup>(7)</sup> Piers, E.; Wong, T.; Coish, P. D.; Rogers, C. Can. J. Chem. 1994, 72, 1816–1819.

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

<sup>(9)</sup> Another diastereomer could not be observed by 400 MHz NMR.

<sup>(10) (</sup>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 <sup>1</sup>H NMR analysis.



<sup>*a*</sup> 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<sub>2</sub>Cl<sub>2</sub>, rt, 90%; (d) BH<sub>3</sub>–NH<sub>3</sub>, LDA, THF, 0 °C to room temperature, 89%; (e) BPSCl, imidazole, CH<sub>2</sub>Cl<sub>2</sub>, rt, 98%; (f) 1 N HCl, THF, rt, 87%; (g) Dess–Martin periodinane, CH<sub>2</sub>Cl<sub>2</sub>, rt, 78%; (h) CBr<sub>4</sub>, PPh<sub>3</sub>, CH<sub>2</sub>Cl<sub>2</sub>, 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 con-



verted 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** showed significant NOE



Figure 2. Some representative NOE correlations ( $\leftarrow \rightarrow$ ) 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,<sup>11</sup> 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<sub>3</sub>–NH<sub>3</sub> and LDA<sup>12</sup> 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,<sup>13</sup> gave alkyne **2**.

Next we attempted to transform **2** to the trisubstituted iodoalkene **18** (Scheme 5). First, Negishi's carbometalation—iodination protocol was applied,<sup>14</sup> 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,<sup>15</sup> affording **18** in 86% yield. Pd(0)-catalyzed coupling reaction<sup>16</sup> of **18** with dimethylzinc cleanly produced **19** (99%).

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

<sup>(11)</sup> 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.

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

<sup>(13)</sup> Corey, E. J.; Fuchs, P. L. *Tetrahedron Lett.* **1972**, 3769–3772.
(14) Negishi, E. *Pure Appl. Chem.* **1981**, *53*, 2333–2356 and references

<sup>(14)</sup> Negisin, E. *Pure Appl. Chem.* **1961**, 55, 2555–2556 and Ferefences therein.

<sup>(15)</sup> Wipf, P.; Lim, S. Angew. Chem., Int. Ed. Engl. 1993, 32, 1068-1071.

<sup>(16)</sup> 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.



<sup>*a*</sup> 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*)- $\alpha$ , $\beta$ , $\gamma$ , $\delta$ -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 (-)- $\alpha$ -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.

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**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.

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