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A New Synthetic Route to Phomoidride B and Its Derivatives

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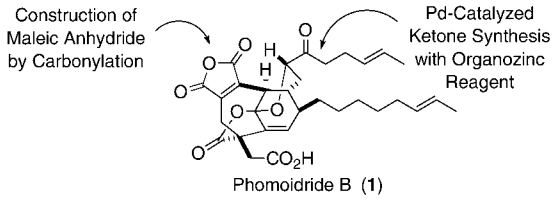
ABSTRACT



We have developed a new synthetic route to phomoidride B, which could also be applied to the synthesis of phomoidride B derivatives using Pd-catalyzed coupling reaction of a thiolester with an organozinc reagent. In addition, direct construction of the maleic anhydride moiety has been achieved by a Pd-catalyzed carbonylation reaction.

Phomoidride B (**1**)[1] was isolated from the culture broth of an unidentified fungus by a Pfizer group and shown to inhibit squalene synthase[2] as well as Ras farnesyl transferase.[3] Because of its attractive biological properties and a unique, complex structure, numerous synthetic approaches to **1** have been reported,[4] and so far, four groups including ours[5] have completed the total synthesis.[6] In our previous total synthesis of phomoidride B, construction of the maleic anhydride moiety has been achieved by a unique formation of a thiobutenoride and oxidation of a siloxythiophene. Herein, we describe another method for constructing the maleic anhydride moiety using a Pd-catalyzed carbonylation which was first reported by Shair and co-workers in their total synthesis of **1**[6d] and a new synthetic route to **1** which could also be applied to the synthesis of phomoidride B derivatives having various substituents at the upper side chain. The two side chains of **1** are highly likely to affect its biological activities. Therefore, the new derivatives of phomoidride B

(1) (a) Dabrah, T. T.; Harwood, H. J., Jr.; Huang, L. H.; Jandovich, N. D.; Kaneko, T.; Li. J.-C.; Lindsey, S.; Mosier, P. M.; Subashi, T. A.; Therrien, M.; Watts, P. C. *J. Antibiot.* **1997**, *50*, 1. (b) Dabrah, T. T.; Kaneko, T.; Massefski, W., Jr.; Whipple, E. B. *J. Am. Chem. Soc.* **1997**, *119*, 1594. For reviews, see: (c) Hepworth, D. *Chem. Ind. (London)* **2000**, 59. (d) Starr, J. T.; Carreira, E. M. *Angew. Chem., Int. Ed.* **2000**, *39*, 1415.

(2) Abe, I.; Tomesch, S. W.; Prestwich, G. D. *Nat. Prod. Rep.* **1994**, *11*. 279.

(3) For a review on Ras farnesyl transferase, see: Leonard, D. M. *J. Med. Chem.* **1997**, *40*, 2971.

(4) Recent synthetic studies: (a) Devaux, J.-F.; O'Neil, S. V.; Guillo, N.; Paquatte, L. A. *Collect. Czech. Chem. Commun.* **2000**, *65*, 490. (b) Clive, D. L. J.; Sun, S.; Gagliardini, V.; Sano, M. K. *Tetrahedron Lett.* **2000**, *41*, 6259. (c) Davies, H. M. L.; Calvo, R. L.; Townsend, R. J.; Ren, P.; Churchill, R. M. *J. Org. Chem.* **2000**, *65*, 4261. (d) Bio, M. M.; Leigton, J. L. *Org. Lett.* **2000**, *2*, 2905. (e) Yoshimitsu, T.; Yanagisawa, S.; Nagaoka, H. *Org. Lett.* **2000**, *2*, 3751. (f) Davies, H. M. L.; Ren, P. *Tetrahedron Lett.* **2000**, *41*, 9021. (g) Njardarson, J. T.; Wood, J. L. *Org. Lett.* **2001**, *3*, 2431. (h) Njardarson, J. T.; McDonald, I. M.; Spiegel, D. A.; Inoue, M.; Wood, J. L. *Org. Lett.* **2001**, *3*, 2435. (i) Ohmori, N. *Chem. Commun.* **2001**, 1552. (j) Baldwin, J. E.; Adlington, R. M.; Roussi, F.; Bulger, P. G.; Marquez, R.; Mayweg, A. V. W. *Tetrahedron* **2001**, *57*, 7409. (k) Banwell, M. G.; McRae, K. J.; Willis, A. C. *J. Chem. Soc., Perkin Trans. 1* **2001**, 2194. (l) Isakovic, L.; Ashenhurst, J. A.; Gleason, J. L. *Org. Lett.* **2001**, *3*, 4189. (m) Ohmori, N. *J. Chem. Soc., Perkin Trans. 1* **2002**, 755. (n) Sulikowski, G. A.; Agnelli, F.; Spencer, P.; Koomen, J. M.; Russell, D. H. *Org. Lett.* **2002**, *4*, 1447. (o) Matsushita, T.; Ashida, H.; Kimachi, T.; Takemoto, Y. *Chem. Commun.* **2002**, 814. (p) Armstrong, A.; Critchley, T. J.; Gourdel-Matin. M.-E.; Kelsey, R. D.; Mortlock, A. A. *J. Chem. Soc., Perkin Trans. 1* **2002**, 1344. (q) Armstrong, A.; Critchley, T. J.; Gourdel-Martin, M.-E.; Kelsey, R. D.; Mortlock, A. A. *Tetrahedron Lett.* **2002**, *43*, 6027. (r) Spiegel, D. A.; Njardarson, J. T.; Wood, J. L. *Tetrahedron* **2002**, *58*, 6545. (s) Bio, M. M.; Leighton. J. L. *J. Org. Chem.* **2003**, *68*, 1693.

(5) Waizumi, N.; Itoh, T.; Fukuyama, T. *J. Am. Chem. Soc.* **2000**, *122*, 7825.

(6) (a) Nicolaou, K. C.; Baran, P. S.; Zhong, Y.-L.; Choi, H.-S.; Yoon, W. H.; He, Y.; Fong, K. C. *Angew. Chem., Int. Ed.* **1999**, *38*, 1669. (b) Nicolaou, K. C.; Baran, P. S.; Zhong, Y.-L.; Fong, K. C.; He, Y.; Yoon, W. H.; Choi, H.-S.; *Angew. Chem., Int. Ed.* **1999**, *38*, 1676. (c) Nicolaou, K. C.; Jung, J.-K.; Yoon, W. H.; He, Y.; Zhong, Y.-L.; Baran, P. S. *Angew. Chem., Int. Ed.* **2000**, *39*, 1829. (d) Chuo, C.; Layton, M. E.; Sheehan, S. M.; Shair, M. D. *J. Am. Chem. Soc.* **2000**, *122*, 7424. (e) Tan, Q.; Danishefsky, S. J. *Angew. Chem., Int. Ed.* **2000**, *39*, 4509.

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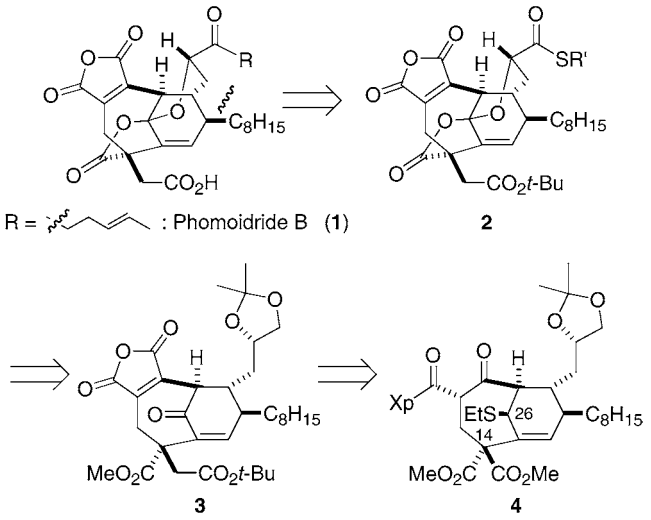
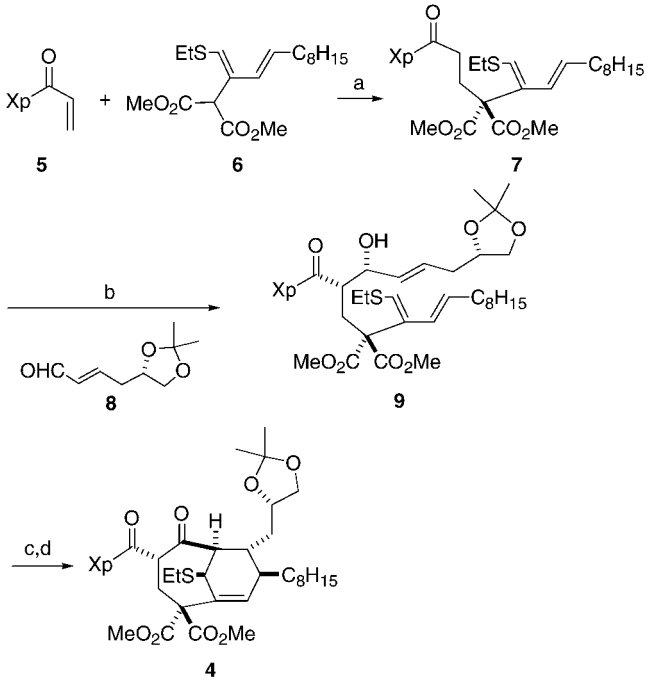
Scheme 1. Retrosynthetic Analysis



prepared by the present route might help understand the structure/activity relationships of the phomoidrides.

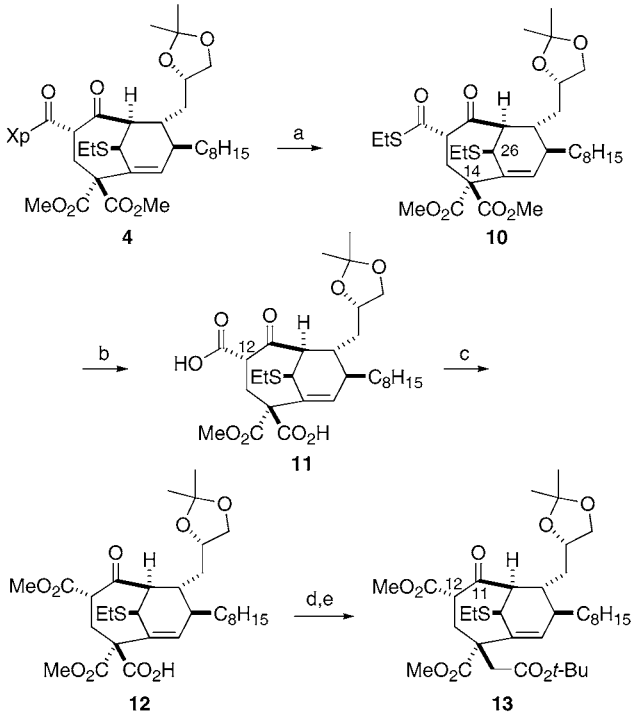
Our retrosynthetic analysis of **1** and its derivatives as shown in Scheme 1 is based on the intermediacy of the thiolester **2** as a key intermediate, which could be coupled with a variety of organozinc reagents by means of a Pd-catalyzed reaction developed in our laboratory.[7] Since this coupling reaction proceeds under very mild conditions, selective conversion of thiolester to the corresponding ketone is possible in the presence of esters, aldehydes, and ethers. Hence, we fully anticipated that preparation of a range of ketones would be possible from such highly oxy-functionalized compound **2** at the very last stage of the synthesis. We envisioned that thiolester **2** would arise from the ketone intermediate **3** via the formation of the γ-lactone-acetal. The intermediate **3** in turn could be obtained from the bicyclic compound **4** by a four-step sequence involving removal of the Evans' chiral auxiliary (Xp), one-carbon homologation of the β-side methyl ester at C-14, conversion of the ethythio group at C-26 to the ketone, and construction of the maleic anhydride moiety.

Scheme 2[a]



[a] Reagents and conditions: (a) Cs_2CO_3, CH_3CN, 50 °C, 73%; (b) Bu_2BOTf, −78 °C; Et_3N, −78 to 0 °C; **8**, CH_2Cl_2, 0 °C, 71%; (c) SO_3·Py, DMSO−*i*-Pr_2NEt, 73%; (d) $ZnCl_2$·OEt_2, Py, CH_2Cl_2, 88%.

Scheme 3[a]



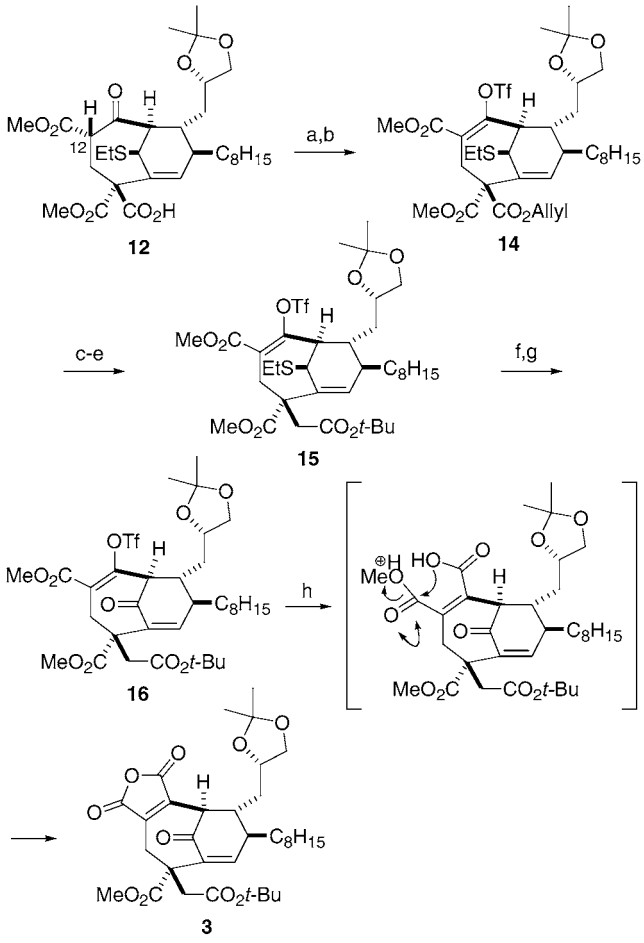
[a] Reagents and conditions: (a) LiSEt, THF, 0 °C, 75%; (b) $Ba(OH)_2$·$8H_2O$, MeOH; (c) $ClCO_2Me$, Et_3N, CH_3CN; aq $NaHCO_3$; (d) $(COCl)_2$, cat. DMF, CH_2Cl_2; CH_2N_2, Et_2O, −20 °C, 41% (three steps); (e) $PhCO_2Ag$, *t*-BuOH, 50 °C, 36%.

The bicyclic compound **4** was synthesized according to our procedure reported earlier (Scheme 2). Assembly of the three fragments (1,3-diene unit **6**, *N*-acryloyl-(*S*)-4-benzyl-oxazolidinone **5**, and enantiopure α,β-unsaturated aldehyde **8** which was prepared from L-malic acid[8]) was effected successively by Michael reaction, Evans' aldol reaction,[9] and the intramolecular Diels−Alder reaction to give **4** in good yield.

The Evans' chiral auxiliary was removed by treatment with lithium ethylthiolate to afford the thiolester **10** (Scheme 3).[9] To carry out a one-carbon homologation of the β-side methyl ester at C-14, selective conversion to the corresponding

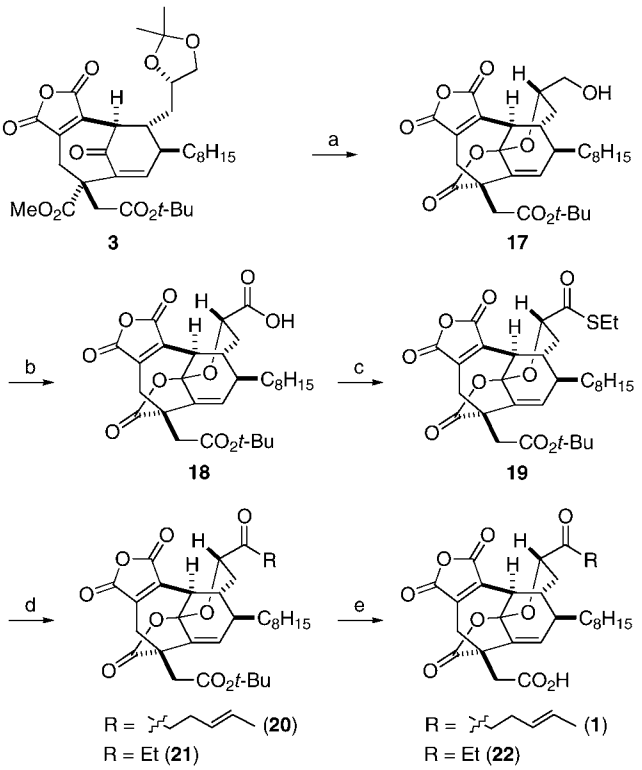
(7) Tokuyama, H.; Yokoshima, S.; Yamashita, T.; Fukuyama, T. *Tetrahedron Lett.* **1998**, *39*, 3189.

Scheme 4[a]



[a] Reagents and conditions: (a) allyl bromide, K_2CO_3, DMF; (b) NaH; *p*-$O_2NC_6H_4NTf_2$, THF, 71% (four steps from thiolester **10**); (c) cat. $Pd(PPh_3)_4$, HCO_2H, Et_3N, CH_2Cl_2; (d) $(COCl)_2$, cat. DMF, CH_2Cl_2; CH_2N_2, Et_2O, −20 °C, 64% (two steps); (e) $PhCO_2Ag$, Et_3N, *t*-BuOH, 50 °C, 86%; (f) *m*-CPBA, CH_2Cl_2, −20 °C; (g) TFAA, *i*-Pr_2NEt, Et_2O, 92% (two steps); (h) cat. $Pd(OAc)_2$, P(2-furyl)$_3$, *i*-Pr_2NEt, H_2O, CO (1 atm), DMF, 90 °C, 10 min; H^+.

Scheme 5[a]



[a] Reagents and conditions: (a) 80% aq AcOH, 70 °C, 34% (two steps from **16**); (b) Jones oxidn; (c) $(COCl)_2$, cat. DMF, CH_2Cl_2; EtSH, imidazole, CH_2Cl_2, 63% (two steps); (d) cat. $PdCl_2(PPh_3)_4$, RZnI−THF solution; pump up; toluene, 0.5−1 h, 78% (**20**), 65% (**21**); (e) HCO_2H, quant.

monocarboxylic acid was required. Hydrolysis of **10** with barium hydroxide proceeded selectively at the thiolester and the β-side methyl ester to give dicarboxylic acid **11**. The successful differentiation of the two methyl esters might be attributable to the steric hindrance of the ethylthio group at C-26 near the α-side methyl ester. Successive treatment of **11** with methyl chloroformate,[10] triethylamine, and aqueous sodium bicarbonate caused selective esterification of the carboxylic acid at C-12, yielding the desired monocarboxylic acid **12** as the sole product. Conversion of **12** to the diazoketone and the subsequent Wolff rearrangement provided homologated *tert*-butyl ester **13** in disappointingly low yield (36%). We reasoned that the unexpected C−H insertion of the carbene into the C-12 position and successive decomposition of the resulting β-keto ester moiety might be responsible for the poor result.

Fortunately, we found that this homologation reaction could be improved by introducing a double bond between C-11 and C-12. Thus, the free carboxylic acid of **12** was protected as the allyl ester (Scheme 4). While extraction of the proton at C-12, which was situated at the concave side of the bicyclic system, was quite difficult when a large base such as LHMDS was used. Deprotonation proceeded smoothly using a small base like sodium hydride. Subsequent treatment with *p*-$O_2NC_6H_4NTf_2$[11] gave the enol triflate **14** without incident. After removal of the allyl group, the resulting carboxylic acid was subjected to Arndt-Eistert reaction to afford the corresponding *tert*-butyl ester **15** in good yield (86%). We next attempted construction of the maleic anhydride moiety. Despite attempts under a variety of conditions, Pd-catalyzed carbonylation of **15** was unsuccessful presumably due to the steric hindrance by the ethylthio group. To decrease the steric effect, **15** was converted to the ketone **16** by Pummerer reaction. Gratifyingly, carbo-

(8) A detailed procedure for the preparation of aldehyde **8** is described in the Supporting Information.

(9) (a) Evans, D. A.; Bartroli, J.; Shih, T. L. *J. Am. Chem. Soc.* **1981**, *103*, 2127. (b) Evans, D. A.; Ripin, D. H. B.; Johnson, J. S.; Shaughnessy, E. A. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 2119.

(10) Kim, S.; Kim, Y. C.; Lee, J. I. *Tetrahedron Lett.* **1983**, *24*, 3365.

(11) (a) This reagent seems to be as highly reactive as Comins' reagent[11b] and is particularly effective for construction of enol triflates from the β-keto ester: Fukuyama, T. et al. Unpublished results. (b) Comins, D. L.; Dehghani, A. D.; Foti, C. J.; Joseph, S. P. *Org. Synth.* **1997**, *74*, 77.

nylation of **16** was in turn successful upon treatment with a catalytic amount of $Pd(OAc)_2$, $P(furyl)_3$, and *i*-Pr_2NEt under an atmosphere of CO (1 atm) in DMF containing water at 90 °C, giving the desired maleic anhydride **3** in a quantitative yield after acidic workup. On the other hand, use of methanol instead of water resulted in the formation of dimethyl maleate, which could not be converted to the maleic anhydride **3**. While Shair and co-workers reported earlier a construction of the maleic anhydride moiety by Pd-mediated carbonylation, it required rather drastic reaction conditions (5.0 equiv of $Pd(OAc)_2$, 12.5 equiv of $P(OMe)_3$, and CO (500 psi) in THF−CH_3CN).[6d] Nicolaou and co-workers have attempted the similar Pd-mediated transformation without success.[12]

At the last stage of the total synthesis, **3** was converted to the key intermediate thiolester **19** (Scheme 5). When **3** was heated with 80% aqueous acetic acid, removal of the acetonide and the cyclization occurred concomitantly to provide the γ-lactone-acetal **17**. The resulting primary alcohol of **17** was oxidized with Jones reagent to give the carboxylic acid **18**. Conversion of **18** to the acid chloride followed by treatment with ethanethiol furnished the thiolester **19**.[13] With the thiolester in hand, the critical Pd-catalyzed coupling reaction was next attempted. Initial attempts at coupling **19** with (*E*)-3-pentenylzinc iodide (1.0 M THF solution) in toluene were unsuccessful, recovering only the starting material. The model studies revealed that the Pd-catalyzed coupling reaction proceeds more slowly in THF than in toluene.[14] Indeed, when THF was removed under reduced pressure before adding toluene, the reaction proceeded smoothly to give the desired ketone **20** in 78% yield without affecting the other delicate functional groups. Finally, deprotection of the *tert*-butyl ester with formic acid gave phomoidride B (**1**). Similarly, the ethyl ketone analogue (**22**) was synthesized.

In conclusion, we have successfully developed a new synthetic route featuring Pd-catalyzed carbonylation reaction and Pd-catalyzed coupling reaction of thiolester with organozinc reagents, which could be applied to the synthesis of phomoidride B and its derivatives. Because the introduction of the upper side chains are performed at the last stage of the synthesis, it is easy to prepare a variety of the side-chain analogues of phomoidride B. Hopefully, the present synthetic route would help understand the structure/activity relationships of phomoidrides.

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Supporting Information Available: Experimental details and spectroscopic data. This material is available free of charge via the Internet at http://pubs.acs.org.

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(12) Nicolaou, K. C.; Baran, P. S.; Zhong, Y.-L.; Fong, K. C.; Choi, H.-S. *J. Am. Chem. Soc.* **2002**, *124*, 2190.

(13) It was difficult to condense **18** with ethanethiol using DCC, BOPCl, or WSCD or via mixed anhydride due to the extreme steric hindrance around the carboxylic acid.

(14) Fukuyama, T. et al. Unpublished results.