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Progress toward a Biomimetic Synthesis of Phomoidride B

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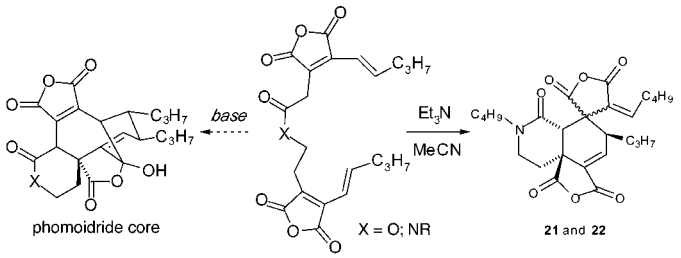
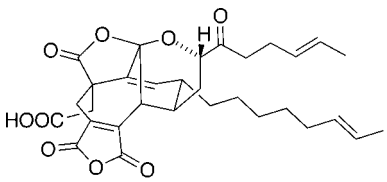
ABSTRACT



An intramolecular cyclization strategy for effecting a biomimetic synthesis of the core structure of the fungal secondary metabolites phomoidrides A and B is described. The cyclization substrate 20 is prepared in eight steps from dibromide 10. Treatment of 20 with triethylamine in acetonitrile results in a rapid cyclization to give 21 and 22 in good yield.

In 1997 workers at Pfizer described the isolation and structure elucidation of CP-225,917 and CP-263,114 (**1**), later given the names phomoidride A and B, respectively.[1] These fungal secondary metabolites were classified as belonging to the nonadride group of natural products, and their structures were assigned by careful NMR analysis. Phomoidride A and phomoidride B were reported to be modest inhibitors of ras farnesyl transferase and squalene synthase. The combination of unique structure and potentially useful biological activity of the phomoidrides generated considerable interest in their total synthesis, with efforts of four groups culminating in total syntheses.[2]



phomoidride B (CP-263,114; **1**)

The unusual core structure of the phomoidrides relative to previously identified nonadrides led us to study their biosynthesis.[3,4] From these investigations we concluded that

(1) (a) Dabrah, T. T.; Harwood, H. J.; Huang, L. H.; Jankovich, N. D.; Kaneko, T.; Li, J. C.; Lindsey, S.; Moshier, P. M.; Subashi, T. A.; Therrien, M.; Watts, P. C. *J. Antibiot.* **1997**, *50*, 1−7. (b) Dabrah, T. T.; Kaneko, T.; Massefski, W.; Whipple, E. B. *J. Am. Chem. Soc.* **1997**, *119*, 1594−1598. (c) Hepworth, D. *Chem. Ind. (London)* **2000**, *2*, 59−65.

(2) (a) Chen, C.; Layton, M. E.; Sheehan, S. M.; Shair, M. D. *J. Am. Chem. Soc.* **2000**, *122*, 7424−7425. (b) 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*, 1669−1675. (c) 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*, 1676−1678. (d) Nicolaou, K. C.; Jung, J. K.; Yoon, W. H.; He, Y.; Zhong, Y. L.; Baran, P. S. *Angew. Chem., Int. Ed.* **2000**, *39*, 1829−1832. (e) Waizumi, N.; Itoh, T.; Fukuyama, T. *J. Am. Chem. Soc.* **2000**, *122*, 7825−7826. (f) Meng, D.; Danishefsky, S. J. *Angew. Chem., Int. Ed. Engl.* **1999**, *38*, 1485−1488. (g) Meng, D.; Tan, Q.; Danishefsky, S. J. *Angew. Chem., Int. Ed.* **1999**, *38*, 3197−3201. (h) Tan, Q.; Danishefsky, S. J. *Angew. Chem., Int. Ed.* **2000**, *39*, 4509−4511.

(3) (a) Sutherland, J. K. *Fortschr. Chem. Org. Naturst.* **1967**, *25*, 131−149. (b) Baldwin, J. E.; Barton, D. H. R.; Bloomer, J. L.; Jackman, L. M.; Rodriguez-Hahn, L.; Sutherland, J. K. *Experientia* **1962**, *18*, 345−388. (c) Barton, D. H. R.; Sutherland, J. K. *J. Chem. Soc.* **1965**, 1769−1771. (d) Baldwin, J. E.; Barton, D. H. R.; Sutherland, J. K. *J. Chem. Soc.* **1965**, 1787−1798.

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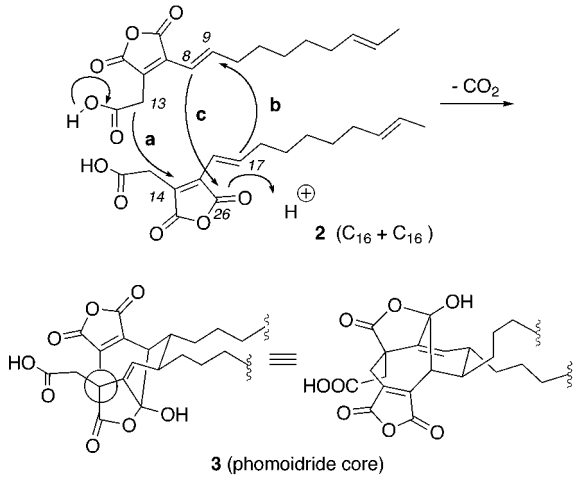
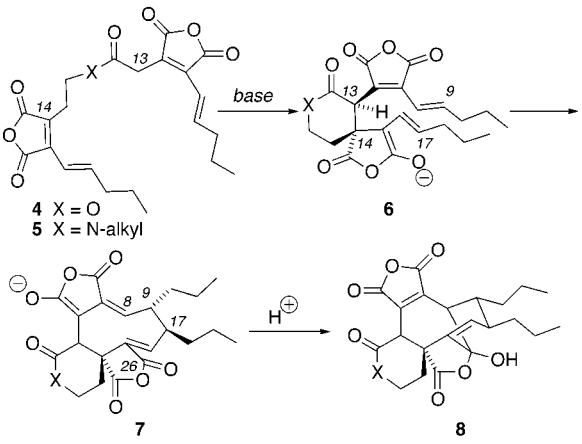
Scheme 1



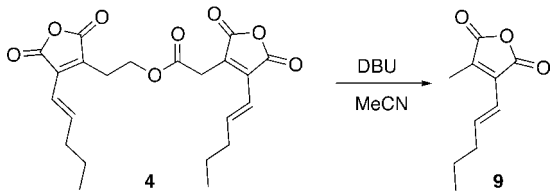
the core structure common to phomoidride A and phomoidride B (**1**) is assembled by the decarboxylative homodimerization of a 16-carbon unsaturated anhydride (Scheme 1). In this remarkable dimerization loss of carbon dioxide is accompanied by the stereoselective formation of three carbon−carbon bonds (a, b, and c). We[5] and others[6] have pursued biomimetic approaches to these compounds based on the homodimerization hypothesis outlined in Scheme 1. In our earlier studies a variety of dimerization products were observed in relatively low chemical yield, but none representing the phomoidride core ring system.[5] In independent studies, Baldwin and co-workers observed dimerizations leading to structures related to the nonadride glaucanic acid in modest chemical yield.[6] The major difficulty encountered in Baldwin's and our own studies was a general lack of regio- and/or stereocontrol. Earlier, we hypothesized that the *intramolecular* cyclization illustrated in Scheme 2 could

Scheme 2



provide the desired regio- and stereocontrol by the pathway shown. Critical to our proposal was the expectation that deprotonation at C(13) would lead to an intramolecular Michael addition at C(14) with an exo approach of the two anhydride units resulting in the formation of δ lactone intermediate **6**. We further hypothesized that good stereocontrol would be observed in a second intramolecular Michael addition (**6** → **7**) due to conformational restrictions imparted by the *first* formed carbon−carbon bond [C(13)−C(14)]. Unfortunately, while deprotonation occurred as predicted at C(13),[7] only fragmentation to give anhydride **9** was observed (Scheme 3). We attribute the reluctance of ester

Scheme 3



4 to adopt the required *s-cis* conformation to be responsible for the observed absence of any cyclized products (vis-à-vis **8**). Similar dipole effects have been proposed to account for the lack of reactivity of esters in intramolecular Diels−Alder reactions.[8] In contrast, intramolecular Diels−Alder cycloadditions of dienes and dienophiles interconnected by *tertiary amides* are comparably facile relative to their ester counterparts.[8d,9] We therefore turned our attention toward examining the cyclization of tertiary amide **5**. The results of this study are the subject of this letter.

The synthesis of tertiary amide **20** began with a malonate anion addition to the crystalline mucobromic acid derivative **10** to give *tert*-butyl malonate **11** (Scheme 4).[3] Acid-catalyzed removal of the *tert*-butyl groups then led to spontaneous decarboxylation and isolation of monocarboxylic acid **12**. The latter was reduced with BH_3·THF to afford alcohol **13** in 31−49% overall yield from **10**. Next, Suzuki−Miyaura cross-coupling of **13** and vinyl boronate **14** afforded diene **15** in 54−61% yield.[10] The primary hydroxyl group of **15** was transformed into secondary amine **16** by *n*-

(4) (a) Sulikowski, G. A.; Agnelli, F.; Spencer, P.; Koomen, J. M.; Russell, D. H. *Org. Lett.* **2002**, *4*, 1447−1450. (b) Spencer, P.; Agnelli, F.; Williams, H. J.; Keller, N. P.; Sulikowski, G. A. *J. Am. Chem. Soc.* **2000**, *122*, 420−421.

(5) Sulikowski, G. A.; Agnelli, F.; Corbett, R. M. *J. Org. Chem.* **2000**, *65*, 337−342.

(6) (a) Baldwin, J. E.; Beyeler, A.; Cox, R. J.; Keats, C.; Pritchard, G. J.; Adlington, R. M.; Watkin, D. J. *Tetrahedron* **1999**, *55*, 7363−7374. (b) Baldwin, J. E.; Adlington, R. M.; Roussi, F.; Bulger, P. G.; Marquez, R.; Mayweg, A. V. W. *Tetrahedron* **2001**, *57*, 7409−7416.

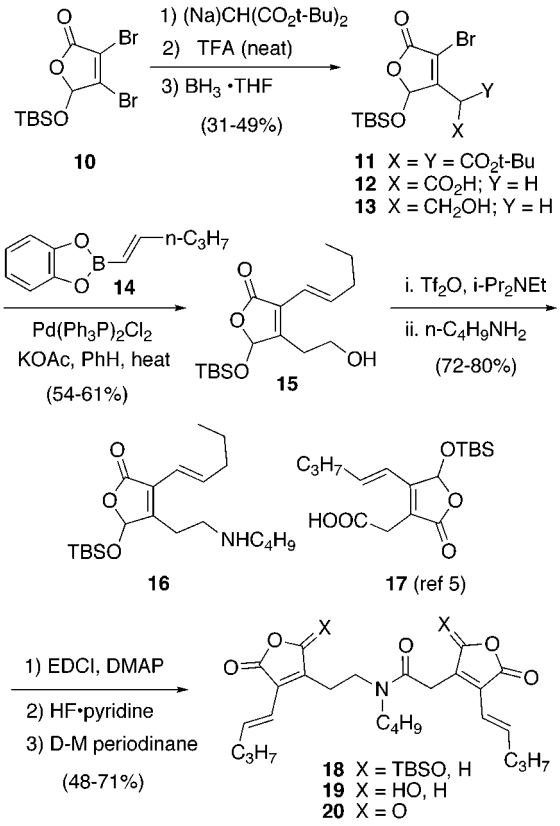
(7) Enolate quenches using D_2O under thermodynamic or kinetic conditions led to deuterium incorporation at C(13); cf: Corbett, R. M. Ph.D. Thesis, Texas A&M University, May 1999.

(8) (a) Parker, K. A.; Adamchuk, M. R. *Tetrahedron Lett.* **1978**, 1689−1692. (b) Boeckman, R. K., Jr.; Demko, D. M. *J. Org. Chem.* **1982**, *47*, 1789−1792. (c) Voyle, M.; Kyler, K. S.; Arseniyadis, S.; Dunlap, N. K.; Watt, D. S. *J. Org. Chem.* **1983**, *48*, 470−476. (d) Martin, S. F.; Williamson, S. A.; Gist, R. P.; Smith, K. M. *J. Org. Chem.* **1983**, *48*, 5170−5180.

(9) Jung, M. E.; Gervay, J. *J. Am. Chem. Soc.* **1989**, *111*, 5469−5470.

(10) (a) Miyaura, N.; Suzuki, A. *Chem. Rev.* **1995**, *95*, 2457−2483. (b) Suzuki, A. *J. Organomet. Chem.* **1999**, *576*, 147−168.

Scheme 4



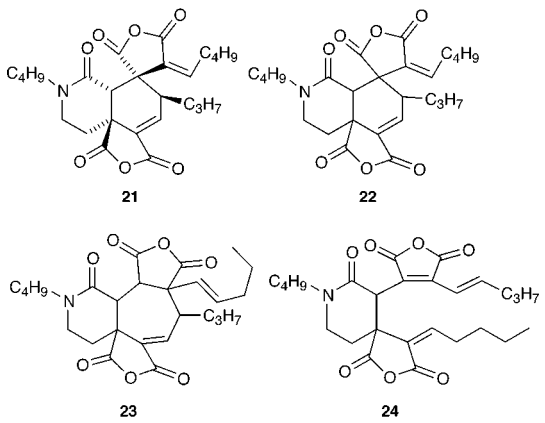
butylamine displacement of the in situ derived triflate. Coupling of amine **16** and carboxylic acid **17** using EDCI-DMAP provided amide **18**. Removal of the TBS groups was accomplished using HF•pyridine, and the resultant bisacetal was oxidized using Dess−Martin periodinane[11] to afford bisanhydride **20** (48−71%, three steps).

Next, we examined the base-catalyzed cyclization of tertiary amide **20**. Toward this end, amide **20** was added to an acetonitrile solution containing 0.3 equiv of triethylamine, resulting in an immediate appearance of a deep-red color, indicative of enolate formation as was observed for ester **4**. However, in contrast to **4** this color immediately dispersed to return a colorless solution. Analysis of the reaction mixture by TLC indicated complete consumption of starting material within 10 min. Purification by flash chromatography led to the isolation of two polycyclization products that were assigned the structures **21** (49%) and **22** (31%) on the basis of NMR analysis. The former compound was crystallized from acetonitrile to give white needles that were subjected to single-crystal X-ray analysis that allowed full stereochemical assignment of **21**. Spectral data (1D NOESY) suggests **22** differs from **21** in stereochemistry at the spirocyclic carbon, but this assignment is not absolute. When the reaction solvent was changed from acetonitrile to dichloromethane, a much slower cyclization occurred (48 h) this time to give cycloheptane **23** (18%) and monocyclized product **24** (54%).

(11) (a) Dess, D. B.; Martin, J. C. *J. Am. Chem. Soc.* **1991**, *113*, 7277−7287. (b) Meyer, S.; Schreiber, S. L. *J. Org. Chem.* **1994**, *59*, 7549−7552.

The structures of **23** and **24** were assigned primarily on the basis of ^{1}H and ^{13}C NMR analysis. The stereochemistry of **23** and **24** was not assigned.

Scheme 5

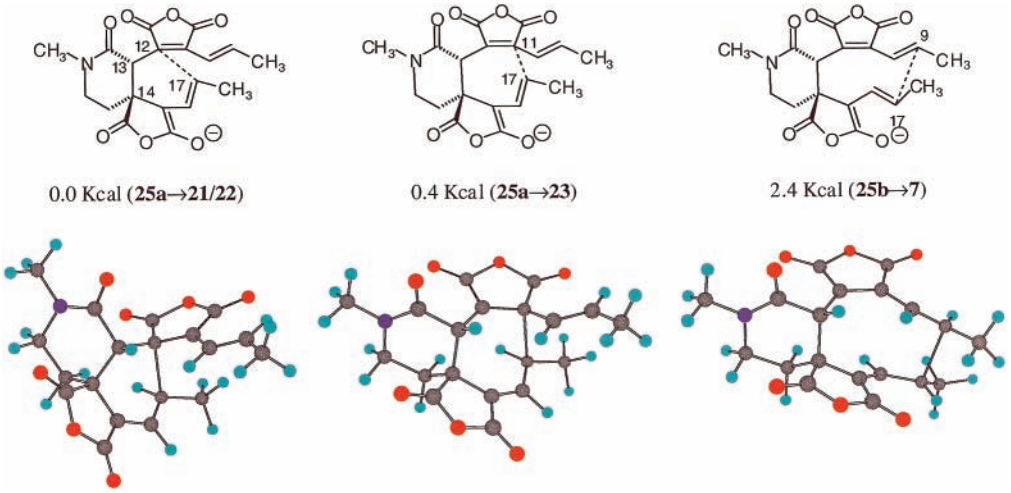


A rationale to explain the observed production of cyclization products **21**−**24** is presented in Scheme 6 starting from intermediate dienolate **25**, the product of the intramolecular Michael addition of the C(13) derived enolate to the C(14) Michael acceptor. Notably, this first Michael cyclization occurred with the anticipated stereoselectivity through an exo approach of the two anhydride units. The second intramolecular Michael addition of the intermediate *s-cis* dienolate **25b** was proposed to give the phomoidride core structure via *trans*,*trans*-cyclononadiene **7** in accord with the rationalization outlined in the introduction of this letter (Scheme 2). Unfortunately, a second set of intramolecular Michael cyclizations effectively competed with the desired reaction pathway via the *s-trans* dienolate (**25a**), leading to spiro compounds **21**/**22** and bicycle **23**. The fourth observed cyclization product **24** is accounted for by simple protonation of dienolate **25**. To estimate the difference in energy between the transition states leading to the six-, seven-, and nine-membered carbocycles, a series of semiempirical calculations were performed. In each case the distance between the Michael donor and acceptor carbons was restricted to 2.3 Å and then optimized to the transition state using semi-empirical calculations (MOPAC). The results of these calculations indicate that the desired cyclization pathway is higher in energy by approximately 2.0−2.4 Kcal relative to the observed cyclization pathways (Scheme 6). The transition structure leading to cycloheptane **23** is approximately 0.4 Kcals higher in energy than the estimated transition state structure leading to **21**/**22**. Current efforts are directed toward examining substrates that will conform the intermediate dienolate to an *s-cis* conformation (**25b**).

Acknowledgment. We gratefully acknowledge support by the National Institutes of Health (CA 75471) and the

(12) (a) Bernardi, A.; Capelli, A. M.; Comotti, A.; Gennari, C.; Scolastico, C. *Tetrahedron Lett.* **1991**, *32*, 823−826. (b) Bernardi, A.; Capelli, A. M.; Cassinari, A.; Comotti, A.; Gennari, C.; Scolastico, C. *J. Org. Chem.* **1992**, *57*, 7029−7034.

Scheme 6



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Supporting Information Available: Full characterization data of all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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