ORGANIC LETTERS

2012
Vol. 14, No. 17
4544–4547

Wharton-Fragmentation-Based Approach to the Carbocyclic Core of the Phomoidrides

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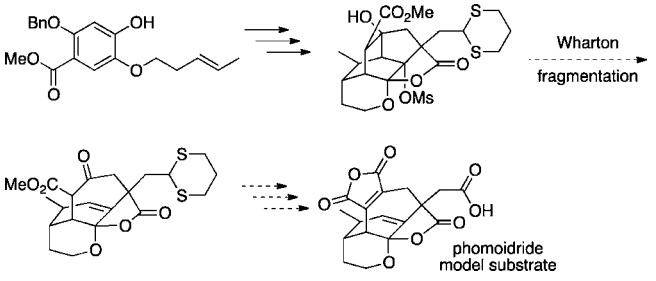
Received July 19, 2012

ABSTRACT



The carbocyclic core of the phomoidrides has been synthesized efficiently and in high yield. Key steps include a phenolic oxidation/intramolecular Diels–Alder sequence, tandem radical cyclization, and a late-stage Wharton fragmentation of a densely functionalized isotwistane skeleton.

In their quest for novel cholesterol-lowering and anticancer agents, researchers at Pfizer reported the isolation and structure elucidation of two novel fungal metabolites, phomoidrides A and B (**1** and **2**, respectively).[1] This report spawned a flurry of activity from synthetic chemists who were intrigued by the molecules' novel structural features.[2] These efforts have not only culminated in several completed syntheses[3] but they have also led to the isolation and structural elucidation of two novel congeners, phomoidrides C and D (**3** and **4**, respectively, Figure 1).[3a,4]

Almost without fail, orchestrating a synthesis of a complex natural product proves to be an arduous road that winds around many obstacles arising from the interplay of densely packed functional groups. Overcoming these obstacles leads to the evolution of a synthetic strategy that is accompanied with, and often guided by, unanticipated discoveries. In previous reports on our efforts in the phomoidride area, we described a synthetic strategy that evolved from an oxy-Cope based approach to one that hinged upon a Wharton-type fragmentation.[5] Efforts to

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(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), 1. (b) Dabrah, T. T.; Kaneko, T.; Massefski, W.; Whipple, E. B. *J. Am. Chem. Soc.* **1997**, *119* (7), 1594.

(2) For a review of early efforts, see (a) Spiegel, D. A.; Njardarson, J. T.; McDonald, I. M.; Wood, J. L. *Chem. Rev.* **2003**, *103* (7), 2691. For subsequent efforts, see (b) Hayashi, Y.; Itoh, T.; Fukuyama, T. *Org. Lett.* **2003**, *5* (13), 2235. (c) Clive, D. L. J.; Cheng, H.; Gangopadhyay, P.; Huang, X.; Prabhudas, B. *Tetrahedron* **2004**, *60* (19), 4205. (d) Yoshimitsu, T.; Sasaki, S.; Arano, Y.; Nagaoka, H. *J. Org. Chem.* **2004**, *69* (26), 9262. (e) Ashenhurst, J. A.; Gleason, J. L. *Tetrahedron Lett.* **2008**, *49* (3), 504. (f) Ashenhurst, J. A.; Isakovic, L.; Gleason, J. L. *Tetrahedron* **2010**, *66* (1), 368.

(3) (a) Meng, D. F.; Tan, Q.; Danishefsky, S. J. *Angew. Chem., Int. Ed.* **1999**, *38* (21), 3197. (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* (11), 1669. (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* (11), 1676. (d) Chen, C.; Layton, M. E.; Sheehan, S. M.; Shair, M. D. *J. Am. Chem. Soc.* **2000**, *122* (30), 7424. (e) Nicolaou, K. C.; Jung, J. K.; Yoon, W. H.; He, Y.; Zhong, Y. L.; Baran, P. S. *Angew. Chem., Int. Ed.* **2000**, *39* (10), 1829. (f) Waizumi, N.; Itoh, T.; Fukuyama, T. *J. Am. Chem. Soc.* **2000**, *122* (32), 7825.

(4) Spencer, P.; Agnelli, F.; Sulikowski, G. A. *Org. Lett.* **2001**, *3* (10), 1443.

(5) Njardarson, J. T.; Wood, J. L. *Org. Lett.* **2001**, *3* (16), 2431.

10.1021/ol302011b
Published on Web 08/23/2012

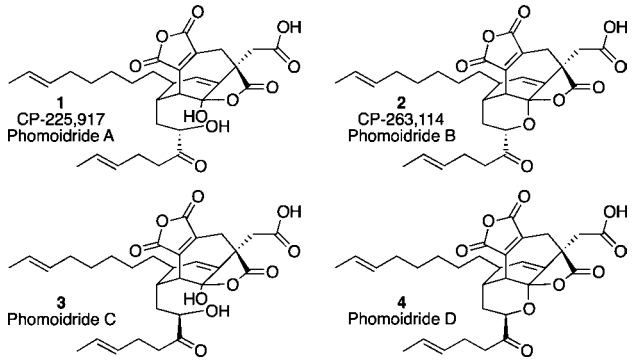
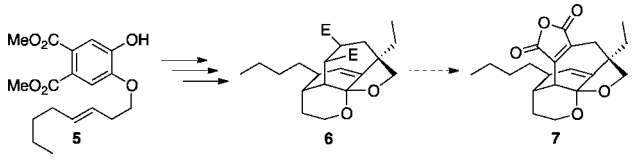


Figure 1. Phomoidrides A–D.

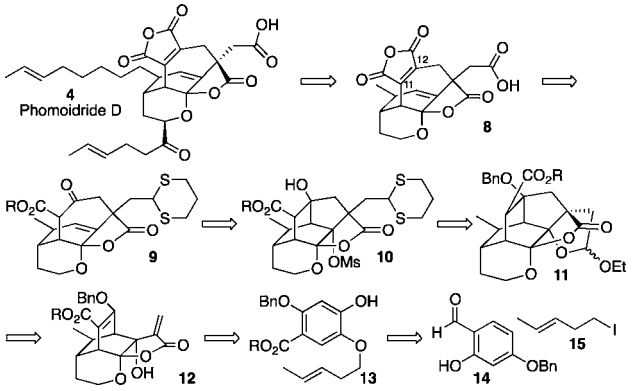
implement the latter approach on substantially functionalized substrates were successful in producing **6**, an intermediate from which access to the complete phomoidride core (**7**) appeared trivially accessible (Scheme 1).[6,7] In yet another affirmation of the axiom that there is no such thing as a trivial reaction, we were unable to advance **6** to the corresponding maleic anhydride, a transformation that also eluded us in efforts to advance substrates possessing the fully functionalized phomoidride core structure.[8]

Scheme 1. Wharton-type Fragmentation Approach to the Phomoidride Core



Given our inability to advance **6**, we considered alternative strategies and eventually turned toward an approach that called for a late-stage carbonylation, a transformation akin to that employed by Shair on a similar but regioisomeric substrate.[9] Thus, as outlined in retrosynthetic fashion (Scheme 2), we envisioned accessing the phomoidride core structure (i.e., **8**) via a sequence that employs keto-ester **9** as the carbonylation substrate. Interestingly, at least from the evolutionary standpoint of this strategy, **9** was seen as arising from a Wharton-type fragmentation reaction of mesylate **10**, which would, in turn, be prepared from mixed acetal **11**.[10] As in our previous studies, assembly of the isotwistane core structure in **11** was seen as proceeding from *exo*-methylene lactone **12** via a radical cyclization cascade that draws upon the pioneering studies of Ueno and Stork.[11] The requisite [2.2.2]-bicycle in lactone **12** would arise by way of a tandem phenolic oxidation/inverse electron-demand Diels–Alder sequence applied to phenol **13**, a compound envisioned available from the etherification of **14** with alkyl iodide **15** followed by further manipulation.

Scheme 2. Retrosynthetic Analysis



In the forward sense, the synthesis began by subjecting phenol **14** (which could be purchased, or prepared from 2,4-dihydroxybenzaldehyde) to a known three-step allylation/Baeyer–Villiger oxidation/formate ester cleavage sequence to give **16** in excellent yield (Scheme 3).[12] Regioselective bromination of **16** with NBS was followed by alkylation with iodide **15** to afford **17** which, upon conversion to the methyl ester and deallylation, furnished phenol **13a**. Phenolic oxidation of **13a**, employing $Pb(OAc)_4$, led to a mixture of bicyclic products **19a** and **20a** via the intermediacy and IMDA reaction of *o*-quinone acetal **18a**, which was also isolated in small quantities. Exposure of **19a** to silica completed the acetate cleavage, and the resulting hemiacetal **20a** was protected employing TMSOTf to give **21a**.

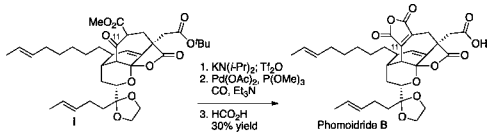
Turning toward installation of the *exo*-methylene lactone, the lynchpin in our planned radical cascade cyclization, ketone **21a** was combined with propionate **22** in a two-step aldol reaction/Cope elimination sequence that furnished enoate **23a** (Scheme 4).[13] Exposure of **23a** to TBAF/AcOH afforded *exo*methylene lactone **12a** which,

(6) Njardarson, J. T.; McDonald, I. M.; Spiegel, D. A.; Inoue, M.; Wood, J. L. *Org. Lett.* **2001**, *3* (16), 2435.

(7) Spiegel, D. A.; Njardarson, J. T.; Wood, J. L. *Tetrahedron* **2002**, *58* (32), 6545.

(8) These efforts will be reported elsewhere.

(9) The late-stage palladium-catalyzed carbonylation reaction at C11 employed by Shair[3d] to install the maleate and complete the total synthesis is illustrated below and differs regiochemically from that illustrated in Scheme 2 for the conversion of **9** to **8**.



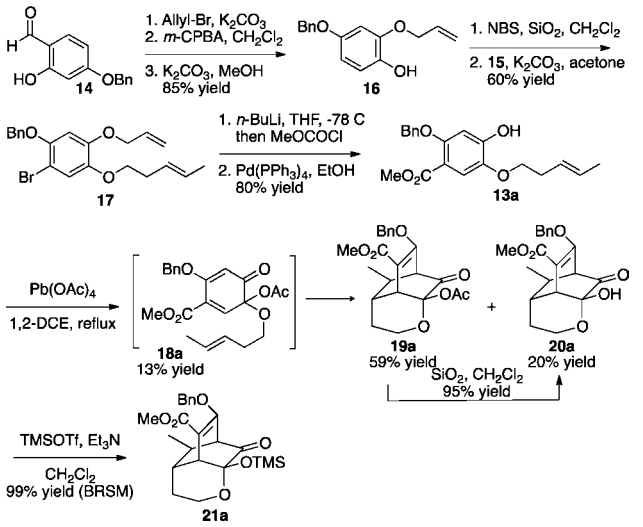
(10) Although in our initial fragmentation studies we had employed a Wharton fragmentation, our ability to rapidly generate advanced intermediates containing both the C11 and C12 esters led us to favor this more convergent approach. Unfortunately, the early introduction of these esters proved to be the Achilles heal of these efforts.

(11) (a) Ueno, Y.; Chino, K.; Watanabe, M.; Moriya, O.; Okawara, M. *J. Am. Chem. Soc.* **1982**, *104*, 5564. (b) Stork, G.; Mook, R.; Biller, S. A.; Rychnovsky, S. D. *J. Am. Chem. Soc.* **1983**, *105* (11), 3741.

(12) Stack, G. P.; Gao, H.; Gildersleeve, E. S. US Patent 6,552,049 B2, Apr. 23, 2003.

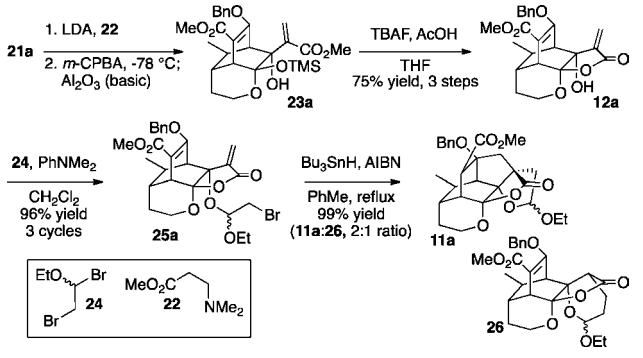
(13) Yu, L. C.; Helquist, P. *J. Org. Chem.* **1981**, *46* (22), 4536.

Scheme 3. Phenolic Oxidation/Diels–Alder Sequence



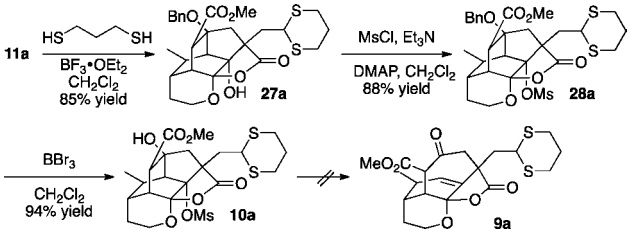
under conditions developed by Stork, was converted to the corresponding bromoacetal **25a**.[11] Although in previous investigations we had only employed electron deficient maleate systems in the radical cascade sequence, we were delighted to find that even the more electron rich vinylogous carbonate moiety in **25a** smoothly undergoes a tandem 5-*exo*/5-*exo* cyclization to give **11a** in 66% yield upon exposure to Bu_3SnH/AIBN. A second product (**26**), resulting from an undesired 6-*endo* cyclization, was also recovered in 33% yield.[14]

Scheme 4. Lactone Formation and Radical Cyclization



Having accessed the isotwistane core, mixed acetal **11a** was converted to thioacetal **27a** which was, in turn, converted to fragmentation precursor **10a** via mesylation of the tertiary alcohol and benzyl-deprotection (Scheme 5).[15] To our surprise, the key Wharton fragmentation reaction of **10a** failed to provide **9a** in all attempts using a host of bases and Lewis acids in various solvents over a wide temperature range.

Scheme 5. Attempted Wharton Fragmentation of an Isotwistane



Confounded by the failure of the Wharton fragmentation, we decided to confirm the integrity of our structural assignments and obtained single crystal X-ray analyses on benzyl ether **28a** and the product of Bn-deprotection, **10a** (Figure 2). Interestingly, these analyses revealed that the stereogenic center adjacent to the methyl ester had epimerized during the deprotection, placing the ester away from the congested polycyclic side of the ring system, giving C11-***epi*-10a** as the major product.

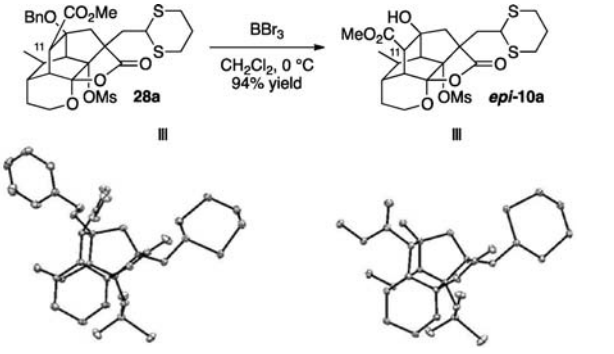


Figure 2. X-ray crystal structures of **28a** and C11-***epi*-10a**.

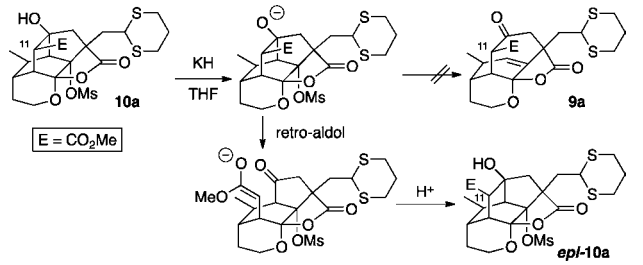
Upon re-examining the deprotection reaction we discovered that the desired product **10a** could be isolated (on occasion) in up to 4% yield, and its exposure to base rapidly induced epimerization to afford C11-***epi*-10a**. At this point we postulated that **10a** and C11-***epi*-10a** were interconverting via a retro-aldol fragmentation (Scheme 6), a reasonable mode of reactivity that would also explain the failed Wharton fragmentation for substrate **10a**.

Suspecting that **10a** was engaging in retro-aldol chemistry instead of the desired fragmentation we considered ways to avert the undesired pathway and decided to target

(14) The intervention of the 6-endo cyclization had been seen in our previous cyclization studies of exomethylene lactone substrates; however with these former maleate containing substrates the 6-endo event was followed by a 4-exo ring closure. Guided by our previous efforts we attempted to circumvent the 6-endo pathway via a top-down cyclization initiated by electron transfer to the vinylogous ester using SmI_2. Although this tranformation furnshed only **11a**, isolated yields were poor. In an effort to neutralize the Michael-acceptor character of the *exo*-methylene moiety in **25a**, we attempted to reduce the lactone to the lactol; however in all cases this was found to proceed via preferential methyl ester reduction.

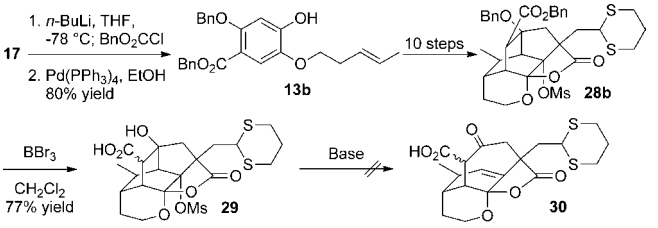
(15) In rare cases where the dithiane was also removed, re-exposure of the crude product mixture to the dithiane formation conditions resulted in regeneration of **10a**.

Scheme 6. Conversion of **10a** to C11-*epi*-**10a** by a Retro-aldol Process



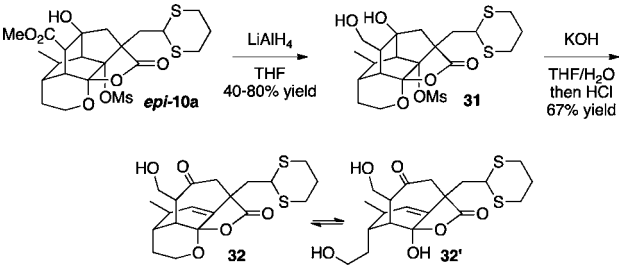
β-hydroxyacid **29** as a fragmentation substrate, presuming that formation of an intermediate carboxylate dianion via retro-aldol would be less favored than the desired Wharton fragmentation. Unfortunately all attempts to convert **28a** to **29** failed and we had to resort to its de novo preparation. As illustrated in Scheme 7, we simply altered the alkylation of **17** so as to deliver benzyl ester **13b** and then followed the same route that had been employed for the methyl ester series.[16] Deprotection of **28b** with BBr_3 afforded an inseparable 2:1 mixture of β-hydroxyacid epimers **29** in excellent yield.[17] Upon treating the derived acids with a variety of bases, none of the desired fragmentation product **30** was observed. The reactions afforded either recovered starting material or decomposition products.

Scheme 7. Attempt at Wharton Fragmentation on **29**



Although initial attempts to eliminate the undesired fragmentation pathway had failed, we eventually decided to reduce the methyl ester to the corresponding alcohol and attempt to fragment the resulting diol. To this end, we were delighted to find that $LiAlH_4$ reduces the methyl ester in deference to the lactone, and furnishes diol **31** in good, though variable yield (Scheme 8). Diol **31** was found to fragment upon exposure to several bases (e.g., NaH, *t*-BuOK, KHMDS) and with KOH in THF/H_2O affords the desired product **32** in 67% yield. Single crystal X-ray analysis confirmed the identity of the fragmentation product **32**, which was found to also exist as the hydrated hemiketal isomer **32′**.

Scheme 8. Wharton Fragmentation of Diol **31**



Having established that an appropriately functionalized isotwistane core is capable of undergoing Wharton fragmentation to the phomoidride ring system, we have initiated efforts to advance fully functionalized material suited for conversion to the natural products. Clearly, efforts to minimize the late stage oxidation state changes that have been required for the successful preparation of **32** will be incorporated in our efforts to develop a streamlined approach to the phomoidrides. These latter efforts are underway and will be reported in due course.

Acknowledgment. J.L.W. thanks Amgen for financial support. G.K.M. and N.H. acknowledge NSERC of Canada and the Uehara Foundation, respectively, for postdoctoral fellowships. Dr. Chris Incarvito (Yale), Dr. Chris Rithner (CSU), Don Heyse (CSU) and Don Dick (CSU) are acknowledged for their assistance in obtaining crystallographic and spectroscopic data.

Supporting Information Available. Spectroscopic and experimental data for all numbered compounds and isolated intermediates. Single crystal X-ray analysis data for indicated compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

The authors declare no competing financial interest.

(16) Yields, reactivities, and product distributions were comparable to the methyl ester series throughout the conversion of **17** to **29**. See the Supporting Information for details.

(17) Though these were not characterized, exposing them to ethereal CH_2N_2 afforded epimers **10a** in quantitative yield.