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Total Synthesis of (±)-Phomoidride D

*Joyce C. Leung, Aaron A. Bedermann, Jón T. Njardarson, David A. Spiegel, Graham K. Murphy, Naoto Hama, Barry M. Twenter, Ping Dong, Tatsuya Shirahata, Ivar M. McDonald, Munenori Inoue, Nobuaki Taniguchi, Travis C. McMahon, Christopher M. Schneider, Nancy Tao, Brian M. Stoltz, and John L. Wood**

Dedicated to Professor Amos B. Smith III

Abstract: *Described herein is a synthetic strategy for the total synthesis of (±)-phomoidride D. This highly efficient and stereoselective approach provides rapid assembly of the carbocyclic core by way of a tandem phenolic oxidation/intramolecular Diels–Alder cycloaddition. A subsequent SmI_2-mediated cyclization cascade delivers an isotwistane intermediate poised for a Wharton fragmentation that unveils the requisite bicyclo[4.3.1]decene skeleton and sets the stage for synthesis completion.*

Since the isolation and structural elucidation of the two fungal secondary metabolites, phomoidride A (**1**; CP-225,917) and phomoidride B (**2**; CP-263, 114; Figure 1), by researchers at Pfizer,[1] numerous groups have devoted efforts toward developing new synthetic strategies to construct these natural products.[2] While the cholesterol-lowering and anticancer properties displayed by **1** and **2** certainly motivated synthetic efforts, there is little doubt that the unique and complex architecture inherent to the phomoidrides has served as the primary inspiration to what has proven to be a variety of markedly creative approaches,[2,3] and four completed total syntheses.[4] Studies toward these targets also led to the discovery of two other congeners, phomoidride C and phomoidride D (**3** and **4**, respectively, Figure 1),[4f,5] which differ in the relative stereochemistry at C7. While previous synthetic efforts have been primarily directed toward the densely functionalized carbocyclic phomoidride core, biosynthetic work has focused on biogenesis and congener interconversion.[6] Herein we describe a novel synthetic strategy that employs two cascade sequences en route to a successful synthesis of (±)-phomoidride D (**4**).[7]

As illustrated retrosynthetically in Scheme 1, our plan for accessing **4** called for late-stage introduction of the maleic anhydride moiety, an endgame akin to those reported by the groups of Fukuyama[8] and Shair.[3a] In contrast to the latter efforts, our strategy employs a regioisomeric β-ketoester that derives from the ketone **5**, which was seen as arising from Wharton fragmentation of the isotwistane **6**. Although increasing structural complexity in a retrosynthesis appears counterintuitive from a strategic planning perspective, we envisioned accessing **6** by a ketyl-initiated cascade cyclization wherein an exo-methylene lactone serves as a lynchpin and

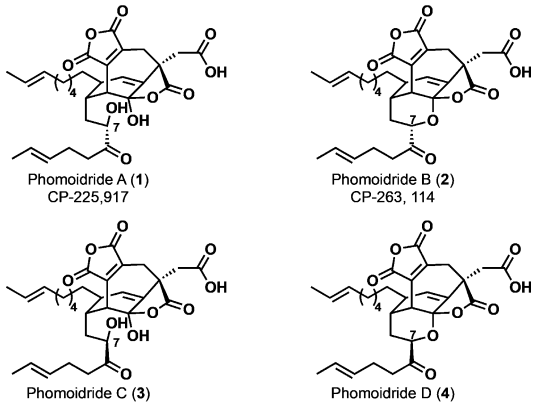
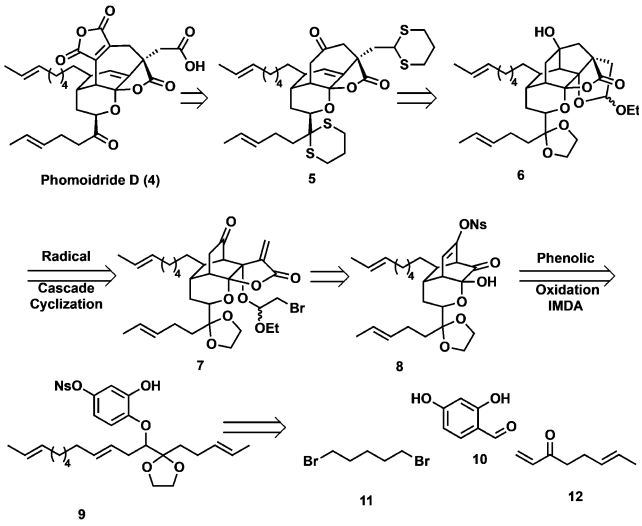


Figure 1. The phomoidride family.



Scheme 1. Retrosynthetic analysis of phomoidride D. Ns = *o*-nitrobenzenesulfonyl.

[*] Dr. J. C. Leung, Dr. A. A. Bedermann, Prof. J. T. Njardarson, Prof. D. A. Spiegel, Prof. G. K. Murphy, Dr. N. Hama, Dr. B. M. Twenter, Dr. P. Dong, Prof. T. Shirahata, Dr. I. M. McDonald, Dr. M. Inoue, Dr. N. Taniguchi, Dr. T. C. McMahon, Dr. C. M. Schneider, Dr. N. Tao, Prof. B. M. Stoltz, Prof. J. L. Wood
Department of Chemistry and Biochemistry, Baylor University
One Bear Place 97348, Waco, TX 76798 (USA)
E-mail: john_l_wood@baylor.edu

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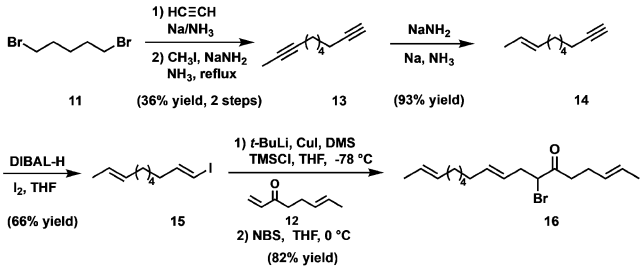
bromide as the nucleofuge. The cyclization cascade precursor (**7**) would arise from the [2.2.2] bicycle **8**, the product of a tandem phenolic oxidation/inverse-electron-demand intramolecular Diels–Alder (IMDA) cycloaddition, wherein the phenol **9** serves as a substrate. This highly efficient combination of two cascade reactions allows global control of the relative stereochemistry and introduces all but five carbon centers present in **4**. The phenol **9** would arise from the readily available precursors **10**, **11**, and **12**.[4e,7d,8,9]

In accord with our synthetic plan, 1,5-dibromopentane (**11**) was homologated to **13** by exposure to sodium acetylide followed by monomethylation of the intermediate diyne (Scheme 2). Deprotonation of **13** at the terminal alkyne

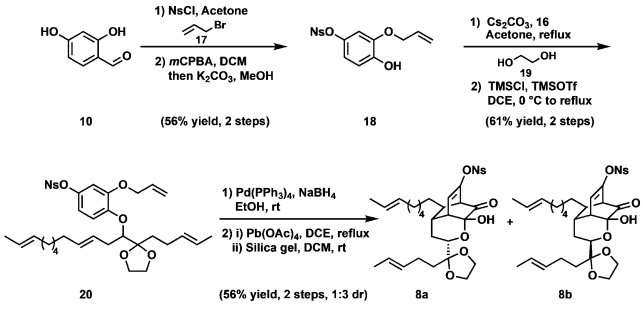


Scheme 2. Synthesis of the α-bromoketone **16**. DIBAL-H = diisobutylalumminum hydride, DMS = dimethylsulfide, NBS = *N*-bromosuccinimide, THF = tetrahydrofuran, TMS = trimethylsilyl.

allowed selective reduction to the enyne **14**. Subsequent hydroalumination/iodination of **14** delivered the vinyl iodide **15**,[10] which, after conversion into the corresponding cuprate was advanced by conjugate addition to the known α,β-unsaturated ketone **12**.[8,9] Under the illustrated TMSCl-accelerated conditions,[11] this latter reaction furnishes an intermediate silyl enol ether which, upon in situ exposure to *N*-bromosuccinimide (NBS), delivers **16**.

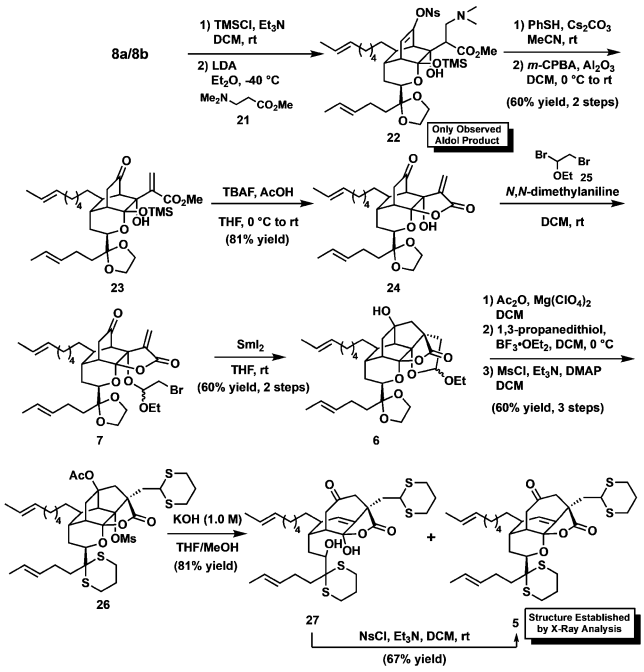
Having developed an efficient five-step sequence to the α-bromoketone **16**, we next focused on the aromatic coupling partner. It is worth noting that a considerable number of experiments over many years indicated that the planned IMDA would likely be successful if the diene component were sufficiently electron poor. In efforts to satisfy this electronic requirement, the *o*-nitrobenzenesulfonyl (nosyl) moiety was discovered to be sufficiently electron withdrawing and stable to subsequent synthetic steps. Thus, as illustrated in Scheme 3, commercially available 1,2-dihydroxybenzaldehyde (**10**) was sequentially nosylated, allylated, and exposed to Dakin oxidation conditions to furnish **18**. Alkylation of **18** with **16** furnished an intermediate ketone that was protected under modified Noyori conditions.[12] Exposure of the derived acetal (**20**) to palladium-mediated allyl removal and a subsequent $Pb(OAc)_4$-induced tandem aryl oxidation cycloaddition sequence, provided the α-hydroxy ketones **8a** and **8b** as an inseparable 1:3 mixture of diastereoisomers.[13]

Interestingly, treating the derived mixture with TMSCl followed by the lithium enolate of methyl 3-(dimethylamino)propionate results in conversion of only the major diastereomer (**8b**) into the corresponding aldol product **22** (Scheme 4).[14] Subsequent nosyl removal, Cope elimination,



Scheme 3. Tandem phenolic oxidation/Diels–Alder cascade. DCE = 1,2-dichloroethane, DCM = dichloromethane.

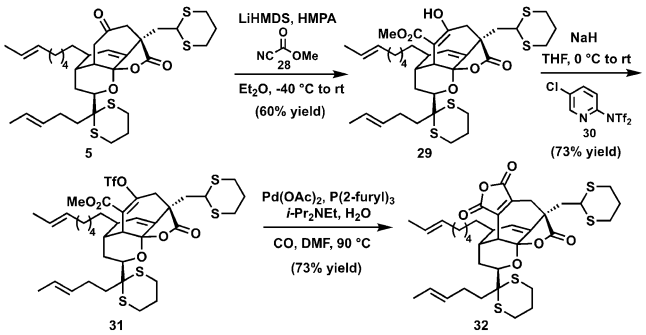
and desilylation provides an intermediate (**24**) containing an exo-methylene lactone poised to serve as a lynchpin in the second cascade reaction. Effecting this latter event begins by condensing **24** with the dibromide **25** to afford the Stork/Ueno bromoacetal **7**.[15] Exposure of **7** to freshly prepared SmI_2 promotes a smooth 5-*exo*-trig/5-*exo*-tet cyclization cascade[16] that delivers the key **6** in excellent yield. Importantly, this sequential C–C bond-forming event sets stereochemistry at the imbedded quaternary center and positions the core structure for fragmentation to the bicyclo[4.3.1]decene. To this end, we first converted **6** into the corresponding acetate and then unveiled the latent tertiary alcohol by transacetalization with 1,3-propanedithiol. Introduction of the requisite nucleofuge was accomplished by mesylation of the derived alcohol to provide the fragmentation substrate **26**. To our delight, exposure of **26** to KOH in a THF/MeOH solvent mixture resulted in Wharton fragmentation and installation of



Scheme 4. Synthesis of the [4.3.1]-bicyclic core by radical cyclization cascade and a Wharton fragmentation. DMAP = 4-(*N*,*N*-dimethylamino)pyridine, LDA = lithium diisopropylamide, *m*-CPBA = *m*-chloroperbenzoic acid, Ms = methanesulfonyl, TBAF = tetra-*n*-butylammonium fluoride.

the bridgehead olefin to furnish **5**. Unsurprisingly, the reaction conditions required for fragmentation also resulted in varying amounts of a diol (**27**) derived from ring opening of the spiroacetal, an unwanted side-reaction that could be reversed by treating the reaction mixture with nosyl chloride and triethylamine. The illustrated stereochemical outcome of the two cascade sequences was firmly established by single-crystal X-ray analysis.

With ready access to the bicyclic carbon framework, we turned attention to constructing the maleic anhydride moiety and began exploring conditions for the regio- and chemoselective acylation of **5**. After some experimentation, we were gratified to discover that Mander's reagent (**28**),[17] employed with Et_2O as the solvent under thermodynamic deprotonation conditions, not only minimized O acylation but led to predominately the desired regioisomer **29** as a mixture of keto–enol tautomers, favoring the latter.[18] Subsequent transformation of **29** into the corresponding enol triflate **31**, using Comins' reagent (**30**),[19] enabled maleic anhydride installation by a palladium-mediated carbonylation (Scheme 5). At

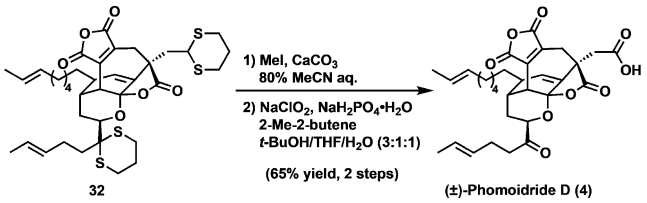


Scheme 5. Preparation of the maleic anhydride by palladium-mediated carbonylation. DMF = *N*,*N*-dimethylformamide, HMDS = hexamethyldisilazide, HMPA = hexamethylphosphoramide.

this point, all that was required to complete **4** was deprotection of **32** followed by oxidation of the derived aldehyde.

In the latter events, numerous methods to remove the dithiane moieties, including both alkylation and oxidation processes, were attempted but often led to the formation of complex mixtures instead of the desired keto-aldehyde. Eventually, we found that exposing **32** to excess iodomethane (80 equiv) in the presence of calcium carbonate ($CaCO_3$) resulted in clean conversion into an intermediate keto-aldehyde which, upon Pinnick oxidation using sodium chlorite ($NaClO_2$), sodium dihydrogenphosphate monohydrate ($NaH_2PO_4{\cdot}H_2O$) as buffer, and 2-methyl-2-butene as hypochlorous acid scavenger, furnished (±)-phomoidride D (**4**) in excellent yield (Scheme 6).

In conclusion, a total synthesis of (±)-phomoidride D has been achieved by employing a novel strategy that requires 26 steps in its longest linear sequence. From the outset, the primary motivation for pursuing a synthesis of this intriguing molecule was the challenge of developing a non-obvious yet efficient approach, an endeavor that invariably advances the forefront of strategies and tactics in the science of synthesis.



Scheme 6. Completion of the total synthesis of (±)-phomoidride D.

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Conflict of interest

The authors declare no conflict of interest.

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