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Efficient Assembly of the Phomactin Core via Two Different Macrocyclization Protocols

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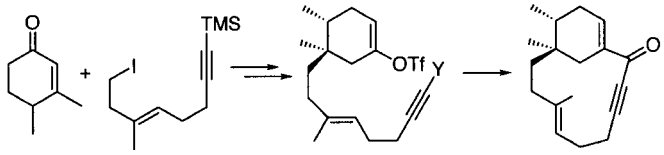
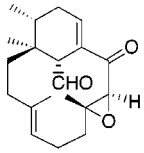
ABSTRACT

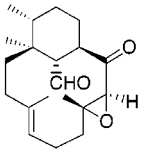


The core structure of phomactins C and D was assembled by an efficient strategy starting from 3,4-dimethylcyclohexen-2-one. Key reactions include (1) a high yielding and highly diastereoselective Michael addition of a mixed cuprate, (2) a carbonylative alkyne–enoltriflate coupling or an intramolecular addition of an acetylide onto an aldehyde to form the macrocycle, (3) chemoselective Michael addition of a cuprate to an enynone, to give the carbon framework of desformyl phomactin C or D, and finally (4) regioselective addition of a thia-nucleophile to the more reactive *β*-position of the resulting dienone.

Phomactins A, C, and D, discovered in the early 1990s, are structurally related platelet activating factor (PAF) antagonists produced by the marine fungus *Phoma* sp.[1] In addition to inducing human platelet aggregation, PAF has been implicated as having a role in causing asthma and other inflammatory diseases.[2] Hence PAF antagonists have definite potential as lead compounds for pharmaceutical drugs. The biological activity and unusual carbon skeleton of the phomactins have prompted much interest among organic chemists but have as yet resulted in only one total synthesis of a phomactin.[3] Several years ago, we began to investigate an efficient and general strategy to these compounds.[4] Recent publications from other groups prompt us to disclose here our strategy and progress towards the total syntheses of phomactins C and D.[5]



1: phomactin C



2: phomactin D

Our synthetic plan[3] for the construction of the phomactins is shown in Scheme 1. The strategy is expected to be quite general and has already led to the synthesis of an advanced intermediate lacking just one carbon of the phomactin

(1) (a) Sugano, M.; Sato, A.; Iijima, Y.; Oshima, T.; Furuya, K.; Kuwano, H.; Hata, T.; Hanzawa, H. *J. Am. Chem. Soc.* **1991**, *113*, 5463−5464. (b) Chu, M.; Patel, M. G.; Gullo, V. P.; Trumees, I.; Puar, M. S.; McPhail, A. T. *J. Org. Chem.* **1992**, *57*, 5817−5818. (c) Chu, M.; Trumees, I.; Gunnarsson, I.; Bishop, W. R.; Kreutner, W.; Horan, A. C.; Patel, M. G.; Gullo, V. P.; Puar, M. S. *J. Antibiot.* **1993**, *46*, 554−563. (d) Sugano, M.; Sato, A.; Iijima, Y.; Furuya, K.; Haruyama, H.; Yoda, K.; Hata, T. *J. Org. Chem.* **1994**, *59*, 564−569. (e) Sugano, M.; Sato, A.; Iijima, Y.; T.; Furuya, K.; Kuwano, H.; Hata, T. *J. Antibiot.* **1995**, *48*, 1188−1190. (f) Sugano, M.; Sato, A.; Saito, K.; Takaishi, S.; Matsushita, Y.; Iijima, Y. *J. Med. Chem.* **1996**, *39*, 5281−5284.

(2) Zhu, X.; Muñoz, N. M.; Kim, K. P.; Sano, H.; Cho, W.; Leff, A. R. *J. Immunol.* **1999**, *163*, 3423−3429.

(3) Miyaoka, H.; Saka, Y.; Miura, S.; Yamada, Y. *Tetrahedron Lett.* **1996**, *37*, 7107−7110.

(4) Choi, S.; Rawal, V. H. Studies Directed Toward the Synthesis of Phomactin D, presented at the 30th Great Lakes Regional Meeting of the American Chemical Society, May 28−30, 1997, Chicago, IL, Abstract 133.

(5) Synthetic studies: (a) Foote, K. M.; Hayes, C. J.; Pattenden, G. *Tetrahedron Lett.* **1996**, *37*, 275−278. (b) Seth, P. P.; Totah, N. I. *Org. Lett.* **2000**, *2*, 2507−2509. (c) Seth, P. P.; Chen, D.; Wang, J.; Gao, X.; Totah, N. I. *Tetrahedron.* **2000**, *56*, 10185−10195. (d) Kallan, N. C.; Halcomb, R. L. *Org. Lett.* **2000**, *2*, 2687−2690. (e) Chemler, S. R.; Danishefsky, S. J. *Org. Lett.* **2000**, *2*, 2695−2698. (f) Foote, K. M.; John, M.; Pattenden, G. *Synlett* **2001**, 365−368. (g) Mi, B.; Maleczka, R. E., Jr. *Org. Lett.* **2001**, *3*, 1491−1494. (h) Chemler, S. R.; Iserloh, U.; Danishefsky, S. J. *Org. Lett.* **2001**, *3*, 2949−2951 (ref 5h added in proof).

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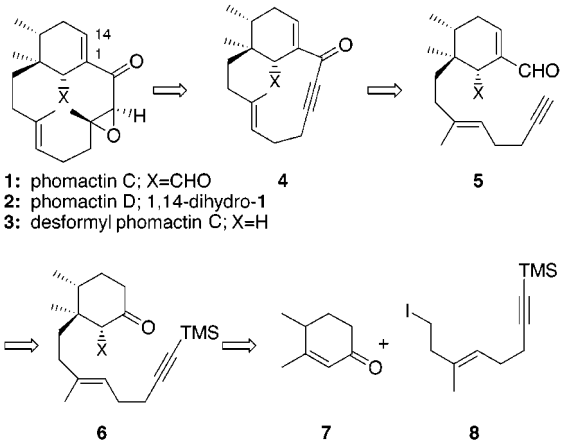
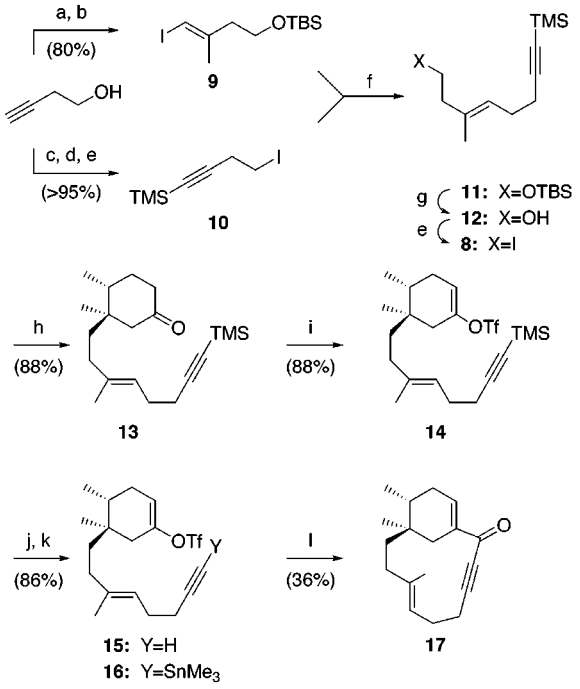
Scheme 1



Scheme 2[a]



[a] (a) $AlMe_3$, Cp_2ZrCl_2, $Cl(C_2H_4)Cl$; then I_2; (b) TBSCl, DMAP, imidazole, CH_2Cl_2; (c) *n*-BuLi, TMSCl, THF; (d) 2M HCl; (e) PPh_3, imidazole, I_2, CH_2Cl_2; (f) **10**, Rieke zinc, THF; **9**, $Pd(PPh_3)_4$; (g) H_2O, AcOH, THF; (h) *t*-BuLi, Et_2O; $Cu(C_5H_7)$, PBu_3; add **7**; (i) LDA, THF; Comins' triflimide; (j) TBAF, THF; (k) *n*-BuLi, Et_2O; Me_3SnCl; (l) $PdCl_2dppf{\cdot}CH_2Cl_2$, LiCl, CO, DMF.

backbone. The epoxide group in the desired targets can be installed at a late stage in the synthesis from the corresponding dienone by taking advantage of peripheral epoxidation to set the relative stereochemistry of this moiety.[6] Examination of molecular models of potential intermediates suggested that of the two enone double bonds the required one would be more reactive to a nucleophilic epoxidizing agent due to its greater degree of conjugation with the ketone carbonyl. Two methods were conceived for the synthesis of the macrocycle. In one case, intramolecular acetylide addition to the unsaturated aldehyde of intermediate **5**,[7] formed regioselectively via the kinetic enolate of ketone **6**, would produce the required 12-membered ring. Conjugate addition of the cuprate of enyne **8**[8] to known enone **7**[9] was predicted to give ketone **6** (X = H) with good diastereoselectivity. For the real system, the expectation was that the enolate formed upon cuprate addition would be intercepted by a suitable electrophile (cf. **6**, X = CH_2OP) to introduce the one-carbon unit required for the natural products.[10] In the second case, ketone **6** would again be a key intermediate, but the ring closure would be achieved by a carbonylative coupling reaction (vide infra). The goal of the initial study[3] was to validate the overall strategy through the synthesis of a compound bearing the desformylphomactin carbon skeleton.

As shown in Scheme 2, iodide **8** was prepared from two butyn-1-ol-derived units using a slight modification of Negishi's method. Upon treatment with Rieke zinc,[11] iodide **10** was converted to the corresponding organozinc, which was coupled with vinyl iodide **9** using Pd catalysis. This coupling protocol has been carried out reliably on a >20 mmol scale in high overall yield. Hydrolysis of the TBS ether followed by conversion of the hydroxyl to an iodide produced **8** in 67% overall yield from **9**. Iodine−lithium exchange followed by addition of a solution of copper pentynylide[12] gave a mixed cuprate that was treated with **7** at −78 °C. The solution was then allowed to warm gradually to −25 °C and upon workup afforded the desired addition product, ketone **13**, in 88% yield as a 13:1 mixture of diastereomers. This reaction is noteworthy in that the cuprate derived from iodide **8** was not used in excess, as is often the case, but was used in a 1:1 ratio with enone **7**. Kinetic deprotonation followed by trapping of the regioselectively formed enolate with Comins' reagent afforded enol triflate **14** (ca. 9:1 ratio), poised for assembling the macrocyclic ring.[13]

A direct route from triflate **14** to the phomactin macrocycle was through a carbonylative cyclization.[14,15] To that end, the trimethylsilyl group was exchanged for a trimethylstannyl under standard conditions.[16] We were gratified to find that stannyl triflate **16** underwent the desired transformation upon heating in a Fischer−Porter bottle under a CO atmosphere in the presence of a Pd catalyst. Although the yield of this reaction must be optimized further, it represents a powerful strategic construct for the phomactin skeleton, accomplishing

(6) This concept was elegantly demonstrated in the synthesis of periplanone B: Still, W. C. *J. Am. Chem. Soc.* **1979**, *101*, 2493−2495.

(7) (a) Danishefsky, S. J.; Mantlo, N. B.; Yamashita, B. S. *J. Am. Chem. Soc.* **1988**, *110*, 6890−6891. (b) Kende, A. S.; Smith, C. A. *Tetrahedron Lett.* **1988**, *34*, 4217−4220.

(8) Rand, C. L.; Van Horn, D. E.; Moore, M. W.; Negishi, E. I. *J. Org. Chem.* **1981**, *46*, 4093−4096.

(9) Compound **7** was prepared according to the general method of Braude et al.: Braude, E. A.; Webb, A. A.; Sultanbawa, M. U. S. *J. Chem. Soc.* **1958**, 3328−3336.

(10) A recent report clearly supports the feasibility of such a transformation: Laval, G.; Audran, G.; Galano, J.-M.; Monti, H. *J. Org. Chem.* **2000**, *65*, 3551−3554.

(11) Zhu, L.; Wehmeyer, R. M.; Rieke, R. D. *J. Org. Chem.* **1991**, *56*, 1445−1453.

(12) Corey, E. J.; Beames, D. J. *J. Am. Chem. Soc.* **1972**, *94*, 7210−7211.

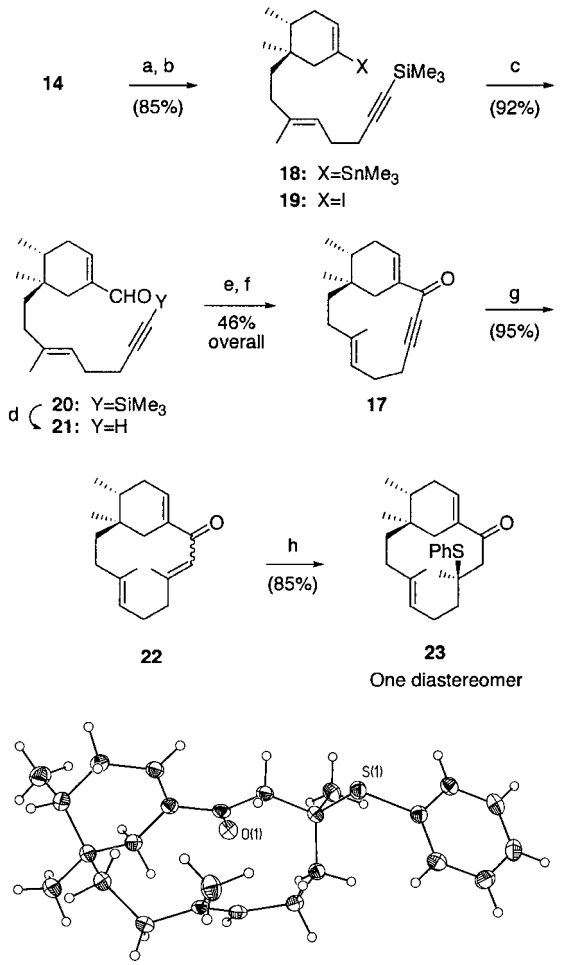
(13) Comins, D. L.; Dehghani, A. *Tetrahedron Lett.* **1992**, *33*, 6299−6302.

(14) (a) Crisp, G. T.; Scott, W. J.; Stille, J. K. *J. Am. Chem. Soc.* **1984**, *106*, 7500−7506. (b) Gyorkos, A. C.; Stille, J. K.; Hegedus, L. S. *J. Am. Chem. Soc.* **1990**, *112*, 8465−8472.

not only the necessary one carbon homologation and two C−C bonds but also the attendant macrocyclization. The longest linear sequence to **17** by this route is only 11 steps from butyn-1-ol.

An alternate route to the critical large ring was via a ring-forming acetylide addition to an aldehyde (Scheme 3).[17] The

Scheme 3[a]



[a] (a) $Pd(PPh_3)_4$, $(SnMe_3)_2$, Li_2CO_3, LiCl, THF; (b) I_2, CH_2Cl_2; (c) *n*-BuLi, Et_2O; DMF; NH_4Cl; (d) $KF{\cdot}2H_2O$, EtOH; (e) NaHMDS, THF; (f) MnO_2, CH_2Cl_2; (g) $LiCuMe_2$, THF; (h) LiSPh, THF.

Wulff reaction[18] converted triflate **14** to the corresponding trimethylstannane (**18**), a compound that was prone to proto-destannylation during chromatographic purification. As such, the crude reaction product was treated with a solution of iodine to yield alkenyl iodide **19** in 85% overall yield. Iodine−lithium exchange followed by quenching with DMF and acidic workup produced aldehyde **20**, a potential macrocyclization precursor.[19] As the CsF-mediated direct desilation/cyclization protocol proved unsuccessful for this substrate, the silyl group was first removed in 91% yield using $KF{\cdot}2H_2O$. A THF solution of the alkyne−aldehyde (**21**) was added by syringe pump over ca. 100 min to a 0.036 M THF solution of NaHMDS at −10 °C, which triggered the desired macrocyclization to afford, upon workup, a mixture of diastereomeric alcohols in 54% yield. Treatment of the alcohols with manganese dioxide provided the alkynyl enone **17**, identical to that obtained by the carbonylative cyclization procedure.

Completion of the desformyl-phomactin skeleton necessitated the introduction of a methyl group to enynone **17**. This process required not only that a conjugate addition be chemoselective—to the alkyne rather than the alkene—but also that it be stereoselective. In the event, treatment of the ketone with excess lithium dimethylcuprate gave exclusively products resulting from the expected conjugate addition to the alkyne, albeit as a ∼2.5:1 mixture of *Z* and *E* isomers, favoring the undesired *Z* compound (by GOESY NMR experiments).[20] Photoequilibration of the mixture[21] failed to increase the proportion of the *E* isomer. Treatment of **22** with a large excess of lithium thiophenolate produced in high yield a single crystalline product. It had been anticipated that addition to the cyclohexenyl double bond would be favored for steric reasons and that the remaining enone double bond might be isomerized via addition−elimination.[22] X-ray crystallography, however, firmly established the product to be **23**, wherein the thiophenyl group had added to the double bond in the macrocycle. This result supports our initial assertion that the macrocyclic enone should be more electrophilic than the cyclohexenyl enone.

Compound **23** bears the full carbon skeleton of desformyl phomactin C. It and several other compounds shown in Scheme 3 are currently undergoing preliminary biological testing to evaluate their PAF antagonist properties. Further developments on the synthesis of the phomactins will be reported in due course.

Acknowledgment. Partial financial support from Pfizer Inc. is gratefully acknowledged. We thank Dr. Ian M. Steele for the X-ray structure determination.

Supporting Information Available: ^1H and ^{13}C spectra of all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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(15) The optimum route to the desired macrocycle was through the carbonylative coupling of alkynyl-enoltriflate **15**, a process that has precedence in the work of Ortar and co-workers: Ciattini, P. G.; Morera, E.; Ortar, G. *Tetrahedron Lett.* **1991**, *32*, 6449−6452. Unfortunately, the direct macrocyclization of alkyne **15** proved unsuccessful.

(16) Stille, J. K.; Simpson, J. H. *J. Am. Chem. Soc.* **1987**, *109*, 2138−2152.

(17) For use of this type of ring closure on intermediates containing an enolizable aldehyde, see: (a) Tius, M. A.; Cullingham, J. M. *Tetrahedron Lett.* **1989**, *29*, 3749−3752. (b) Kobayashi, S.; Reddy, R. S.; Sugiura, Y.; Sasaki, D.; Miyagawa, N.; Hirama, M. *J. Am. Chem. Soc.* **2001**, *123*, 2887−2888.

(18) Wulff, W. D.; Peterson, G. A.; Bauta, W. E.; Chan, K.-S.; Faron, K. L.; Gilbertson, S. R.; Kaesler, R. W.; Yang, D. C.; Murray, C. K. *J. Org. Chem.* **1986**, *51*, 279−280.

(19) (a) Wender, P. A.; Beckham, S.; Mohler, D. L. *Tetrahedron Lett.* **1995**, *36*, 209−212. (b) Mastalerz, H.; Doyle, T.; Kadow, J.; Leung, K.; Vyas, D. *Tetrahedron Lett.* **1995**, *36*, 4927−4930.

(20) Please see Supporting Information for NMR spectra.

(21) Photoequilibration of a conjugated alkene proved very useful in syntheses of hydroxyjatrophones A and B: Smith, A. B., III; Lupo, A. T., Jr.; Ohba, M.; Chen, K. *J. Am. Chem. Soc.* **1989**, *111*, 6648−6656.

(22) (a) Marshall, J. A.; Crooks, S. L.; DeHoff, B. S. *J. Org. Chem.* **1988**, *53*, 1616−1623. (b) Marshall, J. A.; Andersen, M. W. *J. Org. Chem.* **1992**, *57*, 2766−2768.