ORGANIC LETTERS

2002
Vol. 4, No. 14
2413−2416

Convergent Enantioselective Synthesis of the Tricyclic Core of Phomactin A

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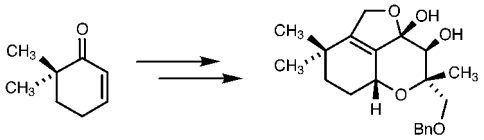
Received May 8, 2002

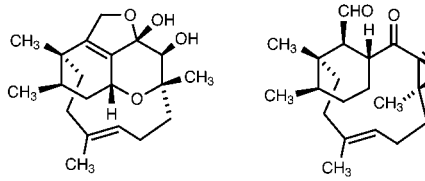
ABSTRACT



22

The tricyclic core of phomactin A was synthesized from 6,6-dimethyl-2-cyclohexen-1-one. Key reactions include the addition of a cyclohexenyllithium reagent to an epoxyaldehyde and a regioselective intramolecular epoxide opening to install the oxadecalin core.

The phomactins are a novel class of platelet activating factor (PAF) antagonists that were isolated from the marine fungus *Phoma* sp. in the early 1990s.[1] Of the seven phomactins isolated, phomactin A (**1**) is the most structurally complex and is the only phomactin to possess a tetracyclic structure and a hydrated furan ring (Figure 1). Although a total



Phomactin A (1) Phomactin D

Figure 1. Structures of representative phomactins.

synthesis of phomactin A has not yet been reported, there have been several reported approaches[2−4] to the oxadecalin core. Recently, several reports[5] have also addressed the construction of the phomactin macrocycle using transition-metal-mediated cyclizations and ring-closing metathesis. A Suzuki macrocyclization has also been employed toward phomactin D,[6] the only phomactin that has been synthesized to date.[7]

This letter describes the synthesis of **22**, a simplified oxadecalin−dihydrofuran system found within phomactin A, starting from 6,6-dimethyl-2-cyclohexen-1-one.[8] The synthetic strategy is outlined in Scheme 1. Starting from enone **2**, conversion to vinyl halide **3** (M = halogen) should be straightforward, and it is anticipated that addition of the corresponding organometallic reagent (M = metal) to epoxyaldehyde **4** can be realized. Intramolecular epoxide

(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. (b) Sugano, M.; Sato, A.; Iijima, Y.; Furuya, K.; Haruyama, H.; Yoda, K.; Hata, T. *J. Org. Chem.* **1994**, *59*, 564. (c) Sugano, M.; Sato, A.; Iijima, Y.; Oshima, T.; Furuya, K.; Kuwano, H.; Hata, T. *J. Antibiot.* **1995**, *48*, 1188.

(2) Foote, K.; Hayes, C.; Pattenden, G. *Tetrahedron Lett.* **1996**, *37*, 275.

(3) (a) Chen, D.; Wang, J.; Totah, N. *J. Org. Chem.* **1999**, *64*, 1776. (b) Seth, P.; Totah, N. *J. Org. Chem.* **1999**, *64*, 8750. (c) Seth, P.; Totah, N. *Org. Lett.* **2000**, *2*, 2507. (d) Seth, P.; Chen, D.; Wang, J.; Gao, X.; Totah, N. *Tetrahedron* **2000**, *56*, 10185.

(4) Chemler, S. R.; Iseloh, U.; Danishefsky, S. J. *Org Lett.* **2001**, *3*, 2949.

(5) (a) Mi, B.; Maleczka, R. *Org. Lett.* **2001**, *3*, 1491. (b) Foote, K.; John, M.; Pattenden, G. *Synlett*. **2001**, 365. (c) Chemler, S.; Danishefsky, S. *Org. Lett.* **2000**, *2*, 2695. (d) Houghton, T. J.; Choi, S.; Rawal, V. H. *Org. Lett.* **2001**, *3*, 3615.

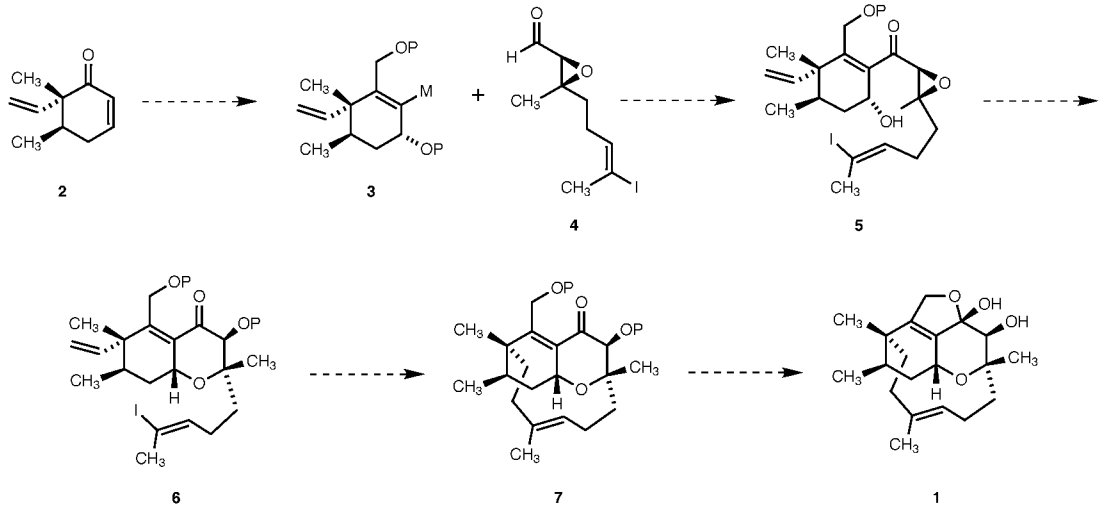
(6) Kallan, N.; Halcomb, R. *Org. Lett.* **2000**, *2*, 2687.

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

(8) Magnusson, G.; Thoren, S. *J. Org. Chem.* **1973**, *38*, 1380.

10.1021/ol026159t CCC: $22.00
Published on Web 06/13/2002

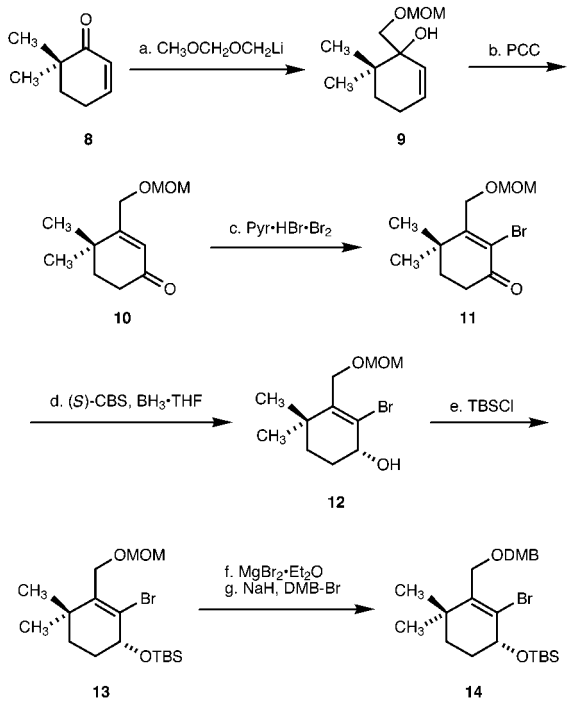
Scheme 1



opening of the addition product **5** would then give the pyran **6**. With the oxadecalin core in place, Suzuki macrocyclization would provide **7**. Global deprotection and hemiketal formation would then generate phomactin A **(1)**.

The synthesis of vinyl bromide **14** (representing the cyclohexenyl unit **3**) is outlined in Scheme 2. Tin−lithium exchange of [(methoxymethoxy)methyl]tributylstannane[9] and addition of the resulting anion to 6,6-dimethylcyclohex-2-en-1-one **8** provided tertiary allylic alcohol **9**. Oxidative rearrangement with PCC[10] gave **10**, which was brominated to provide **11**. This bromination was carried out using pyridinium tribromide, a mild alternative to Br_2. Reaction of **10** with Br_2 led to decomposition, a problem that was previously reported with a similar substrate.[11] An enantioselective reduction[12] was then carried out with the (*S*)-CBS[13] catalyst, and the resulting alcohol **12** was protected as the *tert*-butyldimethylsilyl ether **13**. At this point in the synthesis, the protecting group on the primary alcohol was exchanged. The MOM group introduced early in the synthesis could not be successfully removed at an appropriate later stage. Therefore, it was removed from **13** using magnesium bromide,[14] and the resulting free alcohol was reprotected as a 3,4-dimethoxybenzyl (DMB) ether to give the fully elaborated vinyl bromide **14**. After considerable study, it was determined that the DMB group was stable until the end of the sequence and could also be removed successfully at a suitable point.[15]

Scheme 2[a]

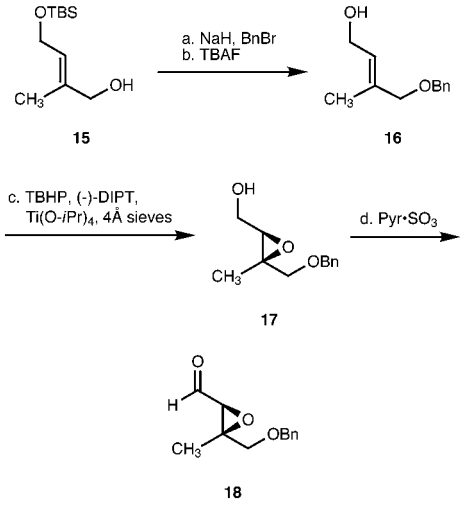


[a] Reagents and conditions: (a) *n*-BuLi, $Bu_3SnCH_2OCH_2OCH_3$, THF, −78 °C (78%); (b) PCC, CH_2Cl_2, rt (90%); (c) pyridinium tribromide, pyridine, CH_2Cl_2, rt to 40 °C (60%); (d) (S)-CBS, BH_3·THF, THF, rt (92%, 80%ee); (e) TBS-Cl, imidazole, DMF, rt (85%); (f) $MgBr_2$·Et_2O, BuSH, Et_2O, rt (70%); (g) NaH, DMB-Br, THF, rt (95%).

The synthesis of epoxyaldehyde **18** (representing **4**) is outlined in Scheme 3. Alcohol **15**[16] was protected as the benzyl ether, and subsequent desilylation gave allylic alco-

(9) Johnson, C.; Medich, J. *J. Org. Chem.* **1988**, *53*, 4131.
(10) Dauben, W.; Michno, D. *J. Org. Chem.* **1977**, *42*, 682.
(11) Dauben, W.; Warshawsky, A. *Synth. Commun.* **1988**, *18*, 1323.
(12) The enantiomeric excess and absolute configuration of compound **12** were determined according to the method of Mosher: Dale, J. A.; Mosher, H. S. *J. Am. Chem. Soc.* **1973**, *95*, 512.
(13) Corey, E. J.; Bakshi, R.; Shibata, S. *J. Am. Chem. Soc.* **1987**, *109*, 7925.
(14) Kim, S.; Kee, I.; Park, Y.; Park, J. *Synlett* **1991**, 183.
(15) While a PMB ether was stable until the end of the sequence, it could not be removed under standard deprotection conditions (DDQ or CAN) to generate the desired dihydrofuran. Oxidation of the deprotected primary allylic alcohol to the corresponding aldehyde was observed in both cases.
(16) Watanabe, H.; Hatakeyyama, S.; Tazumi, K.; Takano, S.; Masuda, S.; Okano, T.; Kobayashi, T.; Kubodera, N. *Chem. Pharm. Bull.* **1996**, *44*, 2281.

Scheme 3[a]



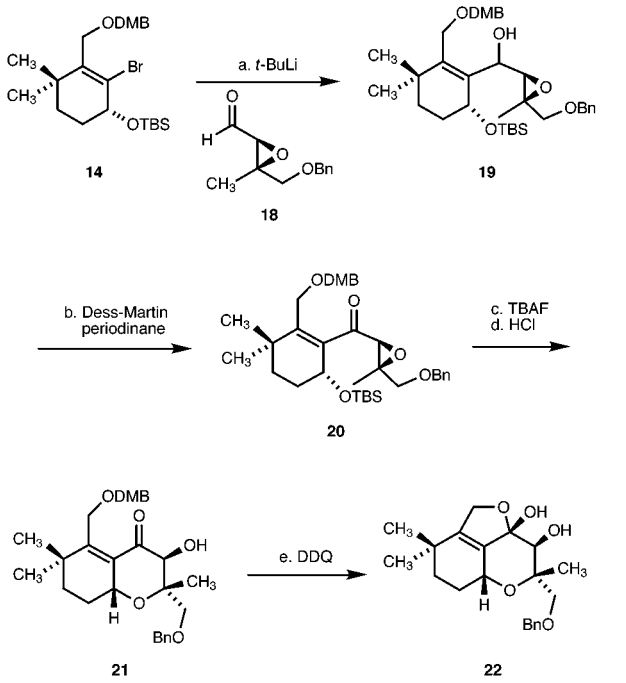
[a] Reagents and conditions: (a) NaH, BnBr, THF, rt (95%); (b) TBAF, THF, rt (90%); (c) TBHP, (−)-DIPT, Ti(O-*i*-Pr)$_4$, 4 Å sieves, CH_2Cl_2, −18 °C (92%, 84% ee); (d) Pyr·SO_3, Et_3N, DMSO, CH_2Cl_2, 0 °C (75%).

hol **16**. A Sharpless asymmetric epoxidation[17,18] provided epoxide **17**, which was oxidized[19] to give epoxyaldehyde **18**.

The coupling of the two components (**14** + **18**) is outlined in Scheme 4. Lithium−halogen exchange of **14** was performed in ether at −78 °C, and the addition of the resulting vinyllithium reagent to aldehyde **18** was carried out in the presence of TMEDA. In the absence of TMEDA, the yield of addition product **19** was 15−20% lower. The resulting alcohol **19** was isolated as a 10:1 mixture of diastereomers at the newly formed carbinol center. This mixture was then simultaneously oxidized[20] without separation to give enone **20** as a single diastereomer. The silyl group was then removed with fluoride, and the resulting alcohol underwent an intramolecular epoxide opening under acidic conditions to give bicyclic compound **21**. None of the product of 5-exo epoxide opening was observed.[5a,21] With the oxadecalin core now in place, the relative stereochemistry was confirmed using coupling constant analysis and NOE studies.[22]

The final conversion of **21** to **22** was carried out with DDQ to successfully remove the DMB group and spontaneously form the dihydrofuran, completing the synthesis of the tricyclic core of phomactin A. This efficient deprotection

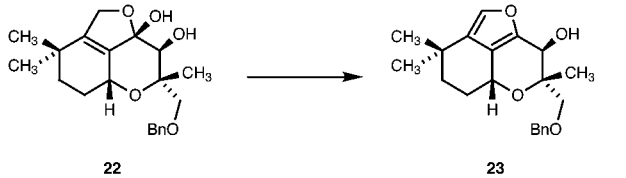
Scheme 4[a]



[a] Reagents and conditions: (a) *t*-BuLi, Et_2O, −78 °C, then TMEDA, **18** (60%); (b) Dess−Martin periodinane, $NaHCO_3$, CH_2Cl_2, rt (90%); (c) TBAF, THF, 0 °C (90%); (d) 1% HCl, *i*-PrOH, 0 °C to rt (77%); (e) DDQ, 20:1 CH_2Cl_2/H_2O, 0 °C to rt (60%).

was carried out in only 20 min at room temperature. Longer reaction times led to the formation of other products, primarily compound **23** (Scheme 5). The desired dihydro-

Scheme 5. Furan Formation



furan **22** was extremely unstable, even after purification, and dehydrated readily[1a,2,23] to provide the more stable furan **23**. Short reaction times and immediate purification of **22** were both necessary to isolate the tricyclic core of phomactin A in high yield.

In summary, the tricyclic core of phomactin A was synthesized. Key reactions include the addition of a cyclohexenyllithium reagent to an epoxyaldehyde and an intramolecular epoxide opening. The strategy employed here is currently being adapted to an enantioselective total synthesis of phomactin A.

(17) Gao, Y.; Hanson, R.; Klunder, J.; Ko, S.; Masamune, H.; Sharpless, K. B. *J. Am. Chem. Soc.* **1987**, *109*, 5765.
(18) Enantiomeric excess determined by the method of Mosher (see ref 12). For a Sharpless asymmetric epoxidation on a similar compound, see: Evans, D. A.; Williams, J. M. *Tetrahedron Lett.* **1988**, *29*, 5065.
(19) Escudier, J.; Baltas, M.; Gorrichon, L. *Tetrahedron* **1993**, *49*, 5253.
(20) Dess, B.; Martin, J. *J. Am. Chem. Soc.* **1991**, *113*, 7277.
(21) Urano, M.; Kagawa, H.; Hrigaya, Y.; Li, S.; Onda, M. *J. Heterocycl. Chem.* **1991**, *28*, 1845.
(22) See the Supporting Information for important NOE enhancements on compound **21**.
(23) Compound **22** was quantitatively converted to furan **23** on standing in $CDCl_3$ for 1 h. NMR analysis in C_6D_6 allowed for characterization of **22**; however, the desired dihydrofuran still dehydrated within 24 h.

Acknowledgment. This research was supported by the NIH (GM53496), Pfizer, and Novartis. R.L.H. also thanks the National Science Foundation (Career Award) and the Camille and Henry Dreyfus Foundation (Camille Dreyfus Teacher−Scholar Award) for support. This work was greatly facilitated by a 500 MHz NMR spectrometer that was purchased partly with funds from an NSF Shared Instrumentation Grant (CHE-9523034). Bob Barkley (University of Colorado) is thanked for obtaining mass spectra.

Supporting Information Available: Experimental procedures and full characterization for compounds **9**−**14** and **16**−**23**. This information is available free of charge via the Internet at http://pubs.acs.org.

OL026159T