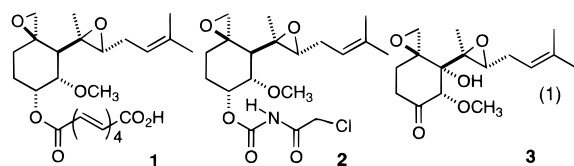# Synthesis of (−)-Fumagillin

Douglass F. Taber,* Thomas E. Christos,
Arnold L. Rheingold,[†] and Ilia A. Guzei[†]

*Department of Chemistry and Biochemistry,
University of Delaware, Newark, Delaware 19716*

Angiogenesis is essential to solid tumor growth.[1a,b] Inhibitors of angiogenesis are therefore under active investigation as antineoplastic agents. Preliminary evidence has recently been put forward that angiogenesis inhibitors also effectively inhibit the growth of atherosclerotic plaque.[1c] Fumagillin **1**, (eq 1) prepared by fermentation, has been a primary lead compound in these investigations. Semisynthetic derivatives such as TNP-470 **2** are currently in clinical trial as antitumor agents.[2,3] Both fumagillin **1**[4] and the related ovalicin **3**[5] have been prepared by total synthesis, and some preliminary structure−activity studies have been reported.[3] The recent discovery that methionine aminopeptidase-2 is the specific enzyme inhibited by fumagillin and ovalicin[2] and the elucidation by X-ray crystallography of the binding mode of **1** to the enzyme[6] make a convincing case for the development of a flexible total synthesis.

Retrosynthetic Analysis. We proposed to prepare fumagillin **1** by conjugate addition to the enantiomerically pure enone **4**, followed by oxygenation of the derived enolate. There were two key questions with this approach: Could an efficient route to

enone **4** be developed, and would the conjugate addition proceed with the requisite high diastereoselectivity?

This approach was particularly compelling because a potentially simple route to the cyclohexenone **4** was available (Scheme 1). Enone **4** could be derived from the cyclopentene **7** by ozonolysis followed by aldol condensation. We had already demonstrated[7] that addition of strong base to a haloalkene such as **9** would lead, via the intermediate alkylidene carbene **10**, to the C−H insertion product and had also confirmed that this process proceeded with retention of absolute configuration at the site of insertion. We thought that it might be possible to extend this reaction to a simple alkene such as **6**. Bromination should give **8** and dehydrobromination would be expected to give **9**, setting the stage for in situ elimination and insertion.

Scheme 1
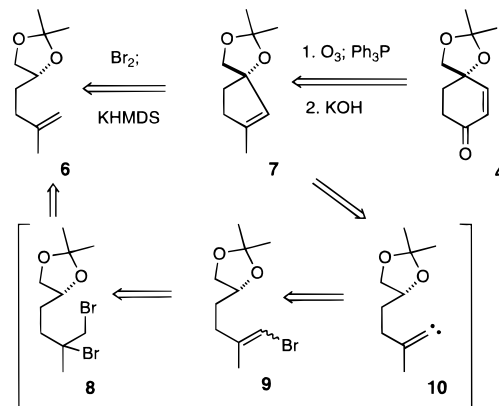
Construction of enone 4. We have prepared **6**[8] from (*S*)-glycidol **11** (Scheme 2) by Grignard opening followed by ketalization. The acetonide **6** was purified on a multigram scale by distillation.

As we had hypothesized, bromination followed by exposure to KHMDS nicely cyclized **6** to **7**. This procedure required some optimization. The ketal tended to participate in the bromination, so it was necessary to effect bromination *in ether* at −78 °C and then immediately add the KHMDS (freshly titrated) before allowing the reaction to come to room temperature. Under these conditions, cyclization proceeded in good yield. Ozonolysis followed by aldol condensation then gave **4**.

Conjugate addition to enone 8. The requisite side chain for the conjugate addition was conveniently prepared in two steps from dihydrofuran **12** (Scheme 3). Following the literature procedure,[9] lithiation of dihydrofuran followed by the addition of tri-

* Corresponding author: (tel.) 302-831-2433; (fax) 302-831-6335; (e-mail) taberdf@udel.edu.

† X-ray crystallography.

(1) (a) Folkman, J. in *Cancer: Principles and Practices of Oncology*, 5ᵗʰ Ed., DeVita, V. T., Jr., Hellman, S., Rosenberg, S. A., Eds.; Lippincott-Raven: Philadelphia, 1997; Vol. 2, pp 3075−3085. (b) Fan, T.-P.; Jaggar, R.; Bicknell, R. *Trends Pharmacol Sci.* **1995** (February), 57. (c) Moulton, K. S.; Heller, E.; Konerding, M. A.; Flynn, E.; Palinski, W.; Folkman, J. *Circulation* **1999**, *99*, 1726.

(2) (a) Hasuike, T.; Hino, M.; Yamane, T.; Nishizawa, Y.; Morii, H.; Tatsumi, N. *Eur. J. Hemaet.* **1997**, *58*, 293. (b) Dzube, B. J.; Vonroenn, J. H.; Holdenwiltse, J.; Remick, S.; Cooley, T. P.; Cheung, T. W.; Sommodossi, J. P.; Shriver, S. L.; Suckow, C. W.; Gills, P. S. *Retrovirology* **1997**, *14*, 78. (c) Sin, N.; Meng, L.; Wang, M. Q. W.; Wen, J. J.; Bornmann, W. G.; Crews, C. M. *Proc. Natl. Acad. Sci.* **1997**, *94*, 6099. (d) Griffith, E. C.; Su, Z.; Turk, B. E.; Chen, S.; Chang, Y. H.; Wu, Z.; Biemann, K.; Liu, J. O. *Chem. Biol.* **1997**, *4*, 461.
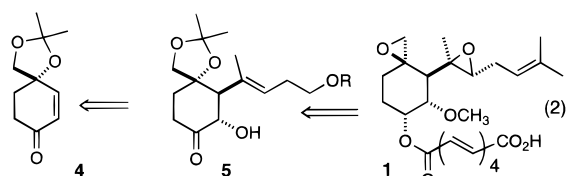
(3) For leading references both to the isolation of fumagillin and to the use of semisynthetic derivatives as antiangiogenic agents, see the following: (a) Hanson, T. E. *Antibiot. Chemother. (Washington, D.C.)* **1951**, *1*, 54. (b) Marui, S.; Itoh, Y.; Kosai, Y.; Sudo, K.; Kishimoto, S. *Chem. Pharm. Bull.* **1992**, *40*, 96. (c) Marui, S.; Kishimoto, S. *Chem. Pharm. Bull.* **1992**, *40*, 575. (d) Marui, S.; Yamamoto, T.; Sudo, K.; Akimoto, H.; Kishimoto, S. *Chem. Pharm. Bull.* **1995**, *43*, 588. (e) Dorey, G.; Leon, P.; Sciberras, S.; Leonce, S.; Guilbaud, N.; Pierre, A.; Atassi, G.; Billington, D. C. *Bioorg. Med. Chem. Lett.* **1996**, *6*, 3045. (e) Griffith, E. C.; Su, Z.; Niwayama, S.; Ramsay, C. A.; Chang, Y.-H.; Liu, J. O. *Proc. Natl. Acad. Sci. U.S.A.* **1998**, *95*, 15183.

(4) For synthetic approaches to fumagillin, see the following: (a) Corey, E. J.; Snider, B. B. *J. Am. Chem. Soc.* **1972**, *94*, 2549. (b) Kim, D.; Ahn, S. K.; Bae, H.; Choi, W. J.; Kim, H. S. *Tetrahedron Lett.* **1997**, *38*, 4437.

(5) For syntheses of ovalicin, see the following: (a) Corey, E. J.; Dittami, J. P. *J. Am. Chem. Soc.* **1985**, *107*, 256. (b) Bath, S.; Billington, D. C.; Gero, S. D.; Quiclet-Sire, B.; Samadi, M. *J. Chem. Soc., Chem. Commun.* **1994**, 1495. (c) Corey, E. J.; Guzman-Perez, A.; Noe, M. *J Am. Chem. Soc.* **1994**, *116*, 12109. (d) For a synthesis of FR65814, see the following: Amano, S.; Ogawa, N.; Ohtsuka, M.; Chida, N. *Tetrahedron* **1999**, *55*, 2205.

(6) Liu, S.; Widom, J.; Kemp, C. K.; Crews, C. M.; Clardy, J. *Science (Washington, D.C.)* **1998**, *282*, 1324.

(7) For the efficient cyclization of haloalkenes, see (a) Taber, D. F.; Sahli, A.; Yu, H.; Meagley, R. P. *J. Org. Chem.* **1995**, *60*, 6571. For earlier references to the generation of alkylidene carbenes from haloalkenes, see the following: (b) Erickson, K. L.; Wolinsky, J. *J. Am. Chem. Soc.* **1965**, *87*, 1143. (c) Wolinsky, J.; Clark, G. W. *J. Org. Chem.* **1976**, *41*, 745. (d) Fisher, R. H.; Baumann, M.; Koebrich, G. *Tetrahedron Lett.* **1974**, 1207.
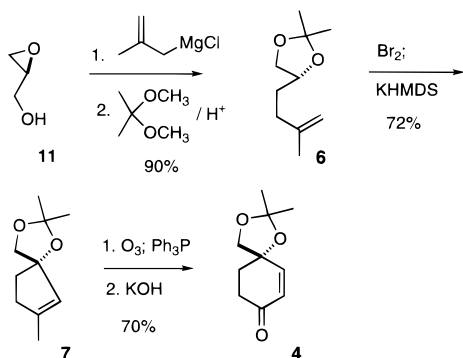
(8) Acetonide **7** was previously reported by Ohira: (a) Ohira, S.; Ishii, S.; Shinohara, K.; Nozaki, H. *Tetrahedron Lett.* **1990**, *31*, 1039. (b) Ohira, S.; Okai, K.; Moritani, T. *J. Chem. Soc., Chem. Commun.* **1992**, 721.

(9) Le Menez, P.; Fargeas, V.; Poisson, J.; Ardisson, J.; Lallemand, J.-Y.; Pancrazi, A. *Tetrahedron Lett.* **1994**, *35*, 7767.

Scheme 3
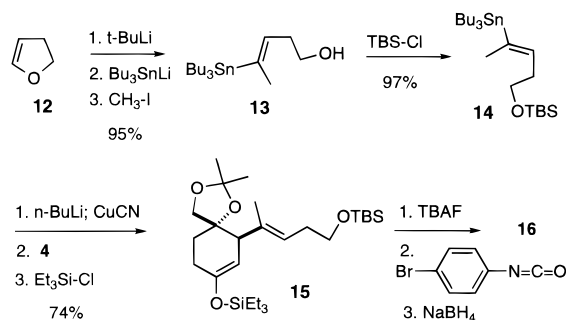
Scheme 2

Scheme 4

butylstannyllithium gave an intermediate that was quenched with methyl iodide to give the alcohol **13**. Silylation then gave **14**.

With the side chain in hand, we were ready to attempt conjugate addition to the enone **4**. There was some literature precedent[10] for conjugate addition taking place anti to the oxygen of the spirocyclic ether. In the event, conjugate addition/enolate trapping proceeded smoothly to give **15** and its easily separated diastereomer in a 96:4 ratio.

Rubottom oxidation[11] of the silyl enol ether **15** (Scheme 4) suffered somewhat from competing epoxidation of the double bond. The most serious difficulty with this procedure for enolate hydroxylation, however, was the removal of the secondary OTES group in the presence of the primary OTBS group. We finally found that TBAF/THF buffered with solid NH_4Cl, a reagent combination recently developed in our laboratory,[12] effected the selective desilylation. Methylation of **17** followed by reduction of the ketone provided **18** as a single diastereomer. Benzoylation of **18** followed by hydrolysis then gave the triol **19**.

At this point, we needed to convert the triol to the epoxide **20**. This transformation could proceed by inversion of the quaternary center. While this might be possible, we elected instead to cleave the diol to the ketone, then establish the epoxide using the equatorial-selective[13] sulfoxonium ylide. We had been concerned that the intermediate β,γ-unsaturated ketone, from periodate cleavage of diol **19**, would be unstable. As it turned out, this ketone could be handled without difficulty. Addition of the ylide to this ketone led to epoxide **20** as a single diastereomer.

Following the literature precedent,[4] peracid oxidation of **20** led to **21**, again as the only detected diastereomer. At this point we were once again concerned about the stability of an intermediate,
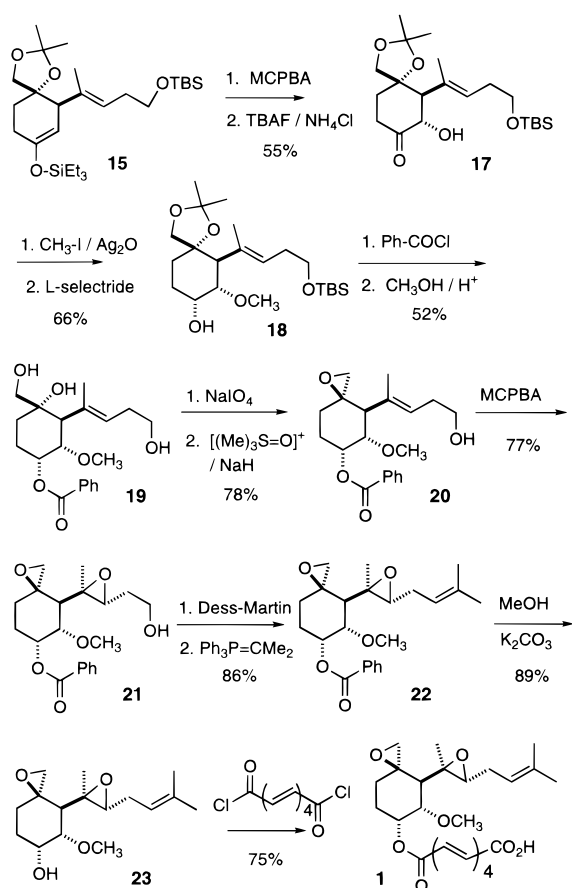
in this case the β,γ-epoxy aldehyde from oxidation of **21**. These fears proved to be well-founded, as the aldehyde was indeed very unstable. Direct homologation of the crude aldehyde, however, delivered the desired alkene **22** in acceptable overall yield.

At this point, debenzoylation allowed us to compare our synthetic (−)-fumagillol **23** with authentic material prepared from natural fumagillin. The two were indentical by TLC, ^{1}H NMR, and ^{13}C NMR. The synthetic material had $[\alpha]_D = -68.8°$ (lit.[3] $[\alpha]_D = -67.7°$). Conversion of the C-10 diacid (prepared from natural fumagillin) to the acid chloride[4a] followed by acylation of the synthetic **23** led to synthetic **1**, mp = 193−195° (lit.[3] mp = 194−195° for natural material). This substance was identical to natural fumagillin in all respects (TLC, ^{1}H NMR, ^{13}C NMR). The synthetic material had $[\alpha]_D = -27.0°$ (lit.[3] $[\alpha]_D = -26.2°$).

Conclusion

The in situ bromination/dehydrobromination protocol introduced here offers a potentially very flexible route from 1,1-disubstituted alkenes to cyclopentenes. As (*S*)-glycidol is inexpensive on a commercial scale ($18/mole), and since the ketone **4** is nicely crystalline, we expect that **4** and its enantiomer will become valuable chirons for natural product synthesis.

Supporting Information Available: Experimental details, full characterization data, and figure of the X-ray structure of a derivative of **16** (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

JA990784K

(10) Corey, E. J.; Boaz, N. W. *Tetrahedron Lett.* **1985**, *26*, 6015.
(11) This now-classic reaction was originated simultaneously by three research groups: (a) Rubottom, G. M.; Vazquez, M. A.; Pellagrina, D. R. *Tetrahedron Lett.* **1974**, 4319. (b) Hassner, A.; Reuss, R. H.; Pinnick, H. W. *J. Org. Chem.* **1975**, *40*, 3427. (c) Brook, A. G.; Macrae, D. M. *J. Organomet. Chem.* **1974**, *77*, C19.
(12) Taber, D. F.; Kanai, K. *Tetrahedron* **1998**, *54*, 11767.
(13) Cook, C. E.; Corley, R. C.; Wall, M. E. *Tetrahedron Lett.* **1965**, 891.