Synthesis of (−)-Fumagillin

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Angiogenesis is essential to solid tumor growth.1,2 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 forward that angiogenesis inhibitors are therefore under active investigation as antineoplastic agents. Preliminary evidence has recently been put

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 demonstrated7 that addition of strong base to a haloalkane 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.

Construction of enone 4. We have prepared 6′ from (S)-glycidol 11 (Scheme 2) by Grignard opening followed by ketalization. The acetone 6 was purified on a multigram scale by distillation.

As we had hypothesized, bromination followed by exposure to KHMS 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 KHMS (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,7 lithiation of dihydrofuran followed by the addition of tri-
butylstannylithium 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\(^\text{10}\) 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\(^\text{11}\) 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\(_4\)Cl, a reagent combination recently developed in our laboratory,\(^\text{12}\) 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\(^\text{13}\) sulfoxonium ylide. We had been concerned that the intermediate \(\beta,\gamma\)-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,\(^\text{4}\) 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 \(\beta,\gamma\)-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 indetical by TLC, \(^1\)H NMR, and \(^{13}\)C NMR. 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, m.p. 193-195° (lit.\(^\text{3}\) m.p. = 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 \([\alpha]_D = -27.0^\circ\) (lit.\(^\text{3}\) \([\alpha]_D = -26.2^\circ\)).

**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.

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**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.

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