Asymmetric Total Synthesis of (+)-Phomalactone, (+)-Acetylphomalactone and (+)-Asperlin Utilizing a Novel Syn-Selective C₄-Oxa-Vinylogous Urethane.

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Abstract: The total synthesis of three natural products isolated from *Nigrospora* sp., *Phoma* sp., and *Aspergillus nidulans*[1] starting from an aldol reaction with a homochiral C₄-oxa-vinylogous urethane is described. Inherent stereoselectivity of the aldol reaction and overall alacrity of molecular construction are discussed. © 1999 Elsevier Science Ltd. All rights reserved.

(+)-Phomalactone **1**, (+)-acetylphomalactone **2**, and (+)-asperlin **3** (Figure 1) share a common 4-oxygenated-4,5-dihydro-1-pyrone structural motif.[2] Additionally, the two stereocenters at C₄ and C₅ which are common to all, are *syn* in orientation. These interesting functional and stereochemical arrangements prompted us to apply some of our recent methodological work toward a total synthesis of all three natural products.

Figure 1.

R= OCH₂CH₂trimethylsilyl

4
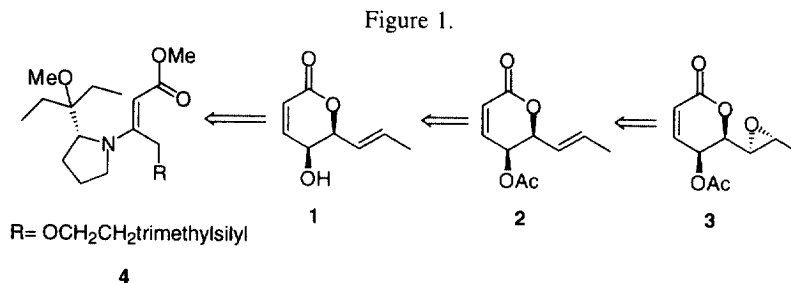
We have recently developed a highly *syn*-selective vinylogous urethane enolate aldol reaction using a protected C₄-hydroxyl vinylogous urethane. The resulting vinylogous urethane lactone **9** possesses vicinal oxa stereocenters that are generated predictably and in high diastereo- and enantiomeric excesses. This work is an extension of our efforts in asymmetric carbon-carbon bond construction utilizing a C₄-methyl (R = Me) substituent.[3] Not only are these C₄-substituted vinylogous urethanes effective in forming C-C bonds asymmetrically, they can also be transformed into 4-substituted-4,5-dihydro-1-pyrones in brief fashion.

The synthesis of vinylogous urethane **4** is accomplished via a Michael addition of Enders' chiral auxiliary **8** derived from D-proline,[4] to alkynyl ester **7** in methanol (Scheme 1).
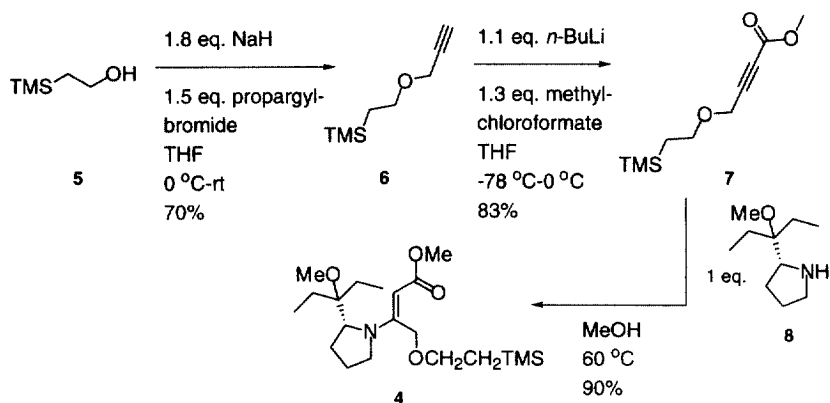
Scheme 1. Synthesis of vinylogous urethane **4**.

The above synthetic sequence can be carried out on multigram scale, and the desired vinylogous urethane **4** is easily purified by vacuum distillation.[5] The lithium enolate of **4**, formed by addition of excess lithium diisopropylamide, when condensed with a variety of aldehydes affords the corresponding vinylogous urethane lactones in good yields, and high diastereo- and enantioselectivity.[5] From related work on our C_4-methyl homochiral vinylogous urethane we postulate that the reason for such high stereoselectivity in these aldol reactions is due in part to the rigid dimeric enolate structure possessed by the lithium anion of **4** in solvents such as THF (Figure 2).[6] These dimeric enolates contain exclusively the Z-(O)-enolate isomer, and are postulated to react via a dipole stabilized "closed" Nolde type transition state with the corresponding aldehyde.[7] In this example, starting with a vinylogous urethane derived from D-proline one obtains the (S,S) aldol product. The resulting *syn*-aldol product lactonizes *in situ*, affording the desired six membered vinylogous urethane lactone **9**.

Figure 2.

Dimeric enolate   Closed TS   9
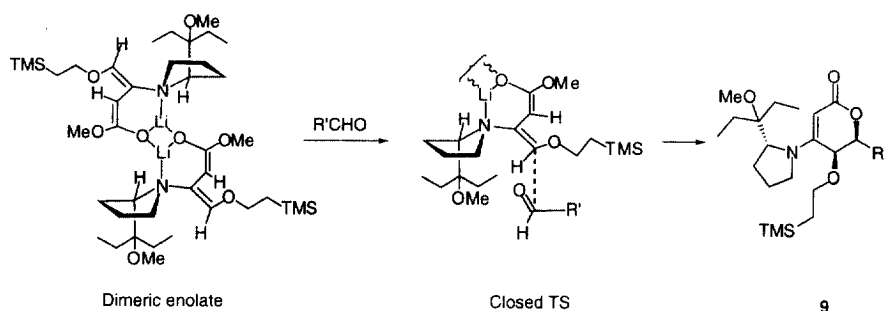
Due to the predictable nature and generality of these aldol reactions we decided to extend this methodology toward the total syntheses of three structurally interesting natural products. The synthesis of (+)-phomalactone **1**, (+)-acetylphomalactone **2**, and (+)-asperlin **3** was initiated by condensing the lithium enolate of **4** with crotonaldehyde, affording the desired vinylogous urethane lactone **10** in 51% yield. Chiral HPLC analysis

confirmed that **10** had been synthesized with a *syn/anti* ratio of >99/1 and in 99% enantiomeric excess. This first synthetic step sets both stereocenters present in the 4,5-dihydro-1-pyrone ring. Removal of the chiral auxiliary was accomplished via a two step Borch reduction[8]/Cope elimination[9] sequence, producing the α,β-unsaturated-δ-lactone **11** in 71% overall yield. The absolute configuration of both stereocenters were determined to be (S,S) *vide infra* (Scheme 2).
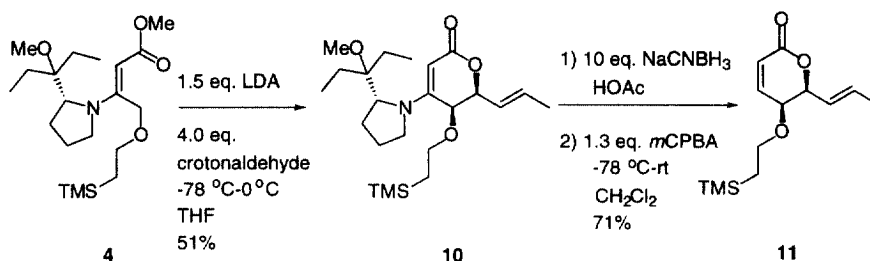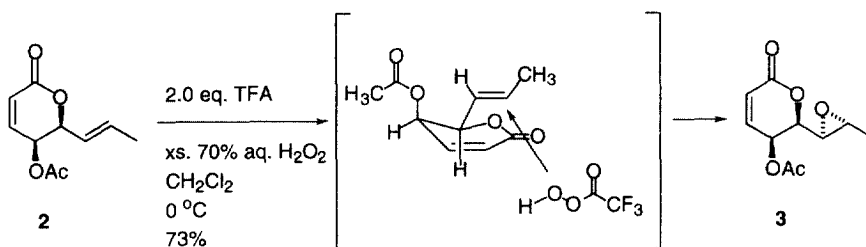

Scheme 2.

Deprotection of lactone **11** with excess trifluoroacetic acid in dichloromethane afforded (+)-phomalactone **1** in 79% yield $[\alpha]_{D25}$ =+99.81 (c=0.70, CH_2Cl_2). The sign and magnitude of optical rotation for synthetic **1** was identical to that of the natural product,[10] thereby unambiguously proving the absolute configuration of both stereocenters set in the initial aldol reaction. Acetylation of the C_4 hydroxyl group of **1** under standard conditions produced (+)-acetylphomalactone $[\alpha]_{D25}$ =+275 (c=1.08, CH_2Cl_2) **2** in 81% yield. As before, the sign and magnitude of rotation was identical to that possessed by the natural product (Scheme 3).[11]
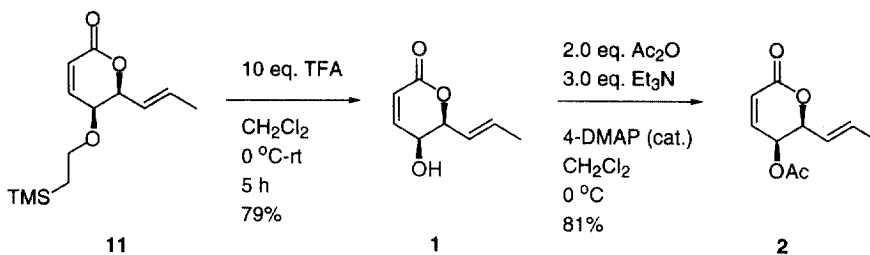
Scheme 3.

Conformational analysis based on NMR coupling constants of the α,β-unsaturated lactone **2** indicated that the C_4 substituent is pseudo-axially disposed. This axial substituent hinders the approach of an epoxidizing reagent from the β-face of the molecule. Additionally, semi-empirical MM2 calculations indicated an energetic bias toward the acyclic double bond lying in a *syn*-periplanar orientation to the lactone oxygen. These two factors lead us to believe that we could stereoselectively epoxidize the double bond, favoring the relative configuration to

that present in the natural product (+)-asperlin **3**. Indeed, when we subjected lactone **2** to trifluoroperacetic acid[12] we obtained the desired α-epoxide **3** (79%yield) in a 4.3:1 ratio over the β-epoxide (Scheme 4).

Scheme 4.

In summary, (+)-asperlin **3**, (+)-phomalactone **2**, and (+)-acetylphomalactone **1** were synthesized in an efficient manner starting from a homochiral C_4-oxa-vinylogous urethane **4**. This demonstrates the alacrity in which starting with **4**, one can generate vicinal oxa-stereocenters *de novo* and further elaborate to synthesize interesting and ubiquitous carbon scaffolds.

† Dedicated to the memory of Richard H. Schlessinger. ‡ Current address: Bristol-Myers Squibb 5 Research Parkway PO Box 5100,Wallingford CT 06492-7660. E-mail address: gillmank@bms.com

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