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Communications

A Facile Synthesis of (−)-4-Phenylsulfonyl-2-azetidinone

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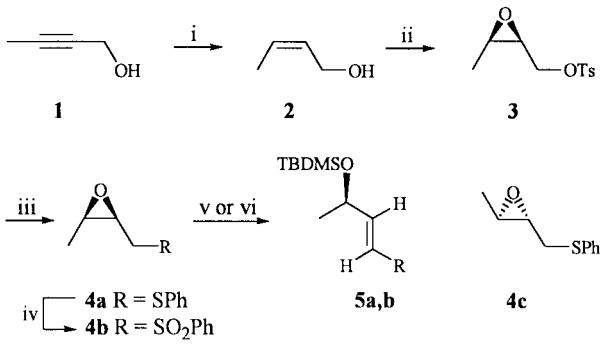
In the late 1970s, scientists at Merck disclosed the potent antibacterial properties and the structure of thienamycin.[1] This nonclassical β-lactam antibiotic is a constitutent of fermentation broths of the soil microorganism, *Streptomyces cattleya*, and it displays activity against *Pseudomonas* and β-lactamase-producing species. Since the discovery of thienamycin, many advances have been made in the chemistry and biology of the carbapenem antibiotics, owing to their structural uniqueness and wide spectrum of antibacterial activities. The efforts have yielded a plethora of potent β-lactam antibiotics, many of which are currently marketed as antibiotics, as exemplified by imipenem[2] and meropenem.[3] It is well known that the most direct access to carbapenem and penem antibiotics is the utilization of 4-acetoxyazetidin-2-one or its synthetic equivalents. Although there are many methods for synthesizing such intermediates, one major difficulty in the construction of azetidinone is the control of the relative and absolute stereochemistry of the three contiguous chiral centres.[4] From existing methods, the isocyanate-alkene approach seems to be the most efficient procedure for the construction of the β-lactam ring.[5] We have now applied this method to a novel stereoselective synthesis of (−)-4-phenylsulfonyl-2-azetidinone **7a**, as a versatile intermediate for carbapenem synthesis.

Cis-crotyl alcohol **2** was prepared from 2-butyn-1-ol **1** by hydrogenation at atmospheric pressure with 5% quinoline-treated Pd/$BaSO_4$.[6] According to Sharpless epoxidation involving *in situ* derivatization, the epoxidation of low molecular weight allylic alcohols is especially facilitated and provides crystalline epoxy alcohol derivatives which were previously difficult to obtain.[7] Thus, the catalytic epoxidation of **2** [$Ti(OPr^i)_4$, (+)-DIPT, cumene hydroperoxide] was employed to afford the chiral epoxy-alcohol. After the excess of hydroperoxide was destroyed with trimethyl phosphite, the chiral glycidol was *in situ* derivatized into the tosylate **3**. $[\alpha]_D^{21}$ −13.7 (*c* 1.2, $CHCl_3$), at the standard conditions (TsCl, DMAP) in 84% yield with >95% ee by ^{1}NMR chiral shift analysis. Nucleophilic substitution of **3** with one equivalent of sodium benzenethiolate in THF gave the epoxy sulfide **4a**, $[\alpha]_D^{22}$ +53.4 (*c* 1.06, $CHCl_3$), in 95% yield. This reaction did not show any epoxide ring opening product. Similarly, *trans*-epoxide **4c**, $[\alpha]_D^{22}$ −2.6 (*c* 1.70, $CHCl_3$), was prepared from the commercially available *trans*-crotyl alcohol. During the preparation of **4c**, (−)-DIPT was used instead of (+)-DIPT in the asymmetric epoxidation step as shown in Scheme 1.



Scheme 1. *Reagents and Conditions:* i, 5% quinoline-treated Pd/$BaSO_4$, H_2, MeOH; ii, $Ti(OPr^i)_4$, (+)-DIPT, cumene hydroperoxide, 3A molecular sieves, CH_2Cl_2, −25 °C; $P(OMe)_3$; TsCl, DMAP, Et_3N; iii, NaH, PhSH, THF, 0 °C; iv, oxone, MeOH-H_2O; v for **5a**, $KOBu^t$, THF, 0 °C; TBDMSCl; vi for **5b**, DBU, THF; TBDMSCl.

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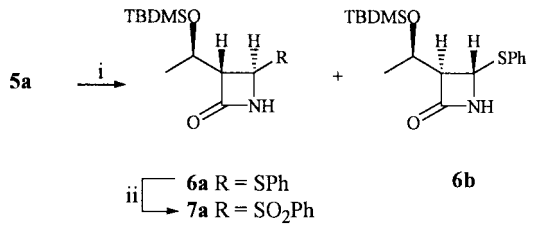
The *cis*-epoxide **4a** was then subjected to the key elimination step promoted by KOBu^t to afford the ring-opened species, which were immediately trapped by treatment with TBDMSCl to give *E*-alkenyl phenyl sulfide **5a** and sulfone **5b**, respectively, in 95% yield. The *E*-geometry was determined by the coupling constants for vinyl protons of **5a**: δ 5.82 (dd, 1H, J = 14.9, 5.2 Hz) and 6.26 (dd, 1H, J = 15.0, 1.2 Hz). The epoxy-sulfone **4b**, prepared from **4a** by the sulfur oxidation with oxone,[8] was also readily converted to the *E*-vinyl sulfone **5b** by the treatment of organic bases such as Et_3N and DBU. It is noteworthy that an optically active γ-hydroxy-α,β-unsaturated sulfone has been utilized in stereocontrolled cycloadditions and conjugated additions.[9] Whereas, the ring-opening of the *trans*-epoxide **4c** showed the mixture of *E*- (**5a**) and the corresponding *Z*-alkenyl sulfides in 1.4 : 1 ratio from NMR spectrum. The stereochemical outcome of the eliminative ring-opening of β-epoxy derivatives is in agreement with the observation reported by Takano.[10]

The cycloaddition of an alkene across the C=N bond of an isocyanate is a useful method for the synthesis of β-lactams. It is also reported that the excellent stereoselectivity is obtained in the cyclization of *N*-chlorosulfonylisocyanate (CSI) with the optically active enol ether.[11] Thus the known *E*-vinyl sulfide **5a** was treated in ethyl ether at 25 °C with CSI to give a 2.5 : 1 diastereomeric mixture of phenylthioazetidinones[12] (**6a** and **6b**), after the reductive removal of the *N*-chlorosulfonyl group of the adduct. This crude mixture was cleanly separated by simple washing with *n*-hexane to afford optically pure **6a**, $[\alpha]_D^{22}$ +83.3 (*c* 0.12, $CHCl_3$), in 40% yield. Finally, sulfur oxidation of the sulfide **6a** with oxone in MeOH-H_2O afforded the known (−)-4-phenylsulfonyl-2-azetidinone[13] **7a** in 80% yield (Scheme 2).

One possible explanation of the facial selectivity in the [2 + 2] cycloaddition is that the preferred product arises from the conformational preference of allylic groups in transition structure. The diastereofacial preference of **6a** for the *E*-isomer **5a** can be explained by a predominant conformer arising from the contribution of the two existing allylic strains as depicted in Figure 1-a, where the largest group (TBDMSO-group) is *anti* to the approaching CSI. This staggered conformation model is well suitable to the predominant conformer obtained by a conformational search using MM2 energy calculations.[12] An attempted synthesis of the sulfone **7a** from **5b** failed, presumably, due to the destabilization of a first stepwise-adduct by the electron-withdrawing benzenesulfonyl group (Figure 1-b). This observation strongly suggested that the activation of alkene by electron-releasing substituents is favorable in this reaction.



Scheme 2. *Reagents and Conditions:* i, CSI, Et_2O; AcSH, pyridine; ii, oxone, MeOH-H_2O.

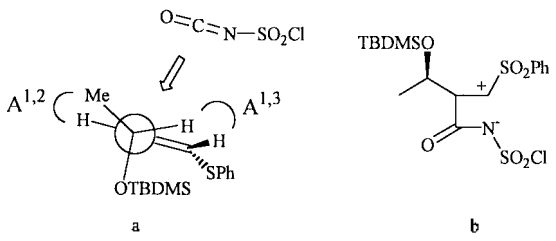


Figure 1.

This communication has demonstrated that *cis*-epoxy sulfide can be efficiently transformed into *E*-alkenyl sulfide in a highly stereoselective manner. Optically active alkenyl phenyl sulfide has been proved as a useful building block in the enantioselective synthesis of azetidin-2-one. Further studies are in progress to improve the diastereoselection in [2 + 2]cyclization and the construction of carbapenem skeleton.

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