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A SHORT ROUTE TO β-LACTAMS: USE OF CYCLIC SULFITES FROM SYN-2,3-DIHYDROXY ESTERS

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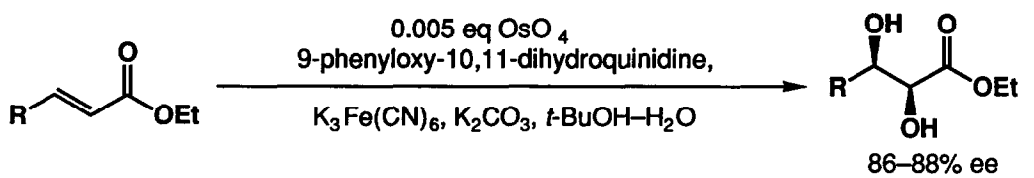
Summary: A convenient synthetic route has been developed to prepare homochiral β-lactams in a highly stereospecific manner through the use of cyclic sulfites prepared from vicinal diols produced by catalytic asymmetric dihydroxylation (ADH).

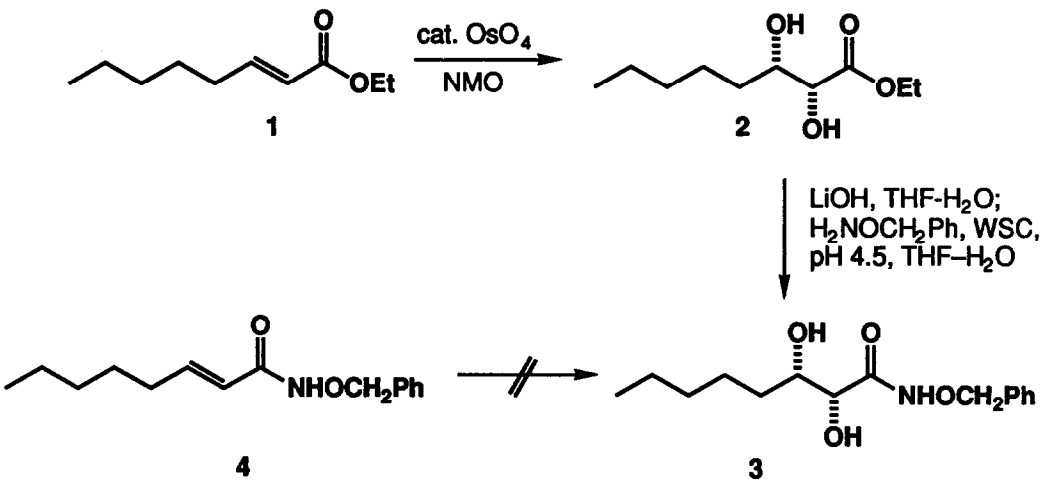
Recently we reported a very efficient asymmetric dihydroxylation utilizing a catalytic amount of OsO_4 and cinchona alkaloid derivatives.[1] In our continuing effort to improve the scope of this new process, we found a highly selective ligand-type for the case of alkyl- or carboalkoxy-substituted olefins. With the use of 9-aryl substituted dihydroquinidine derivatives, 2,3-syn-dihydroxy esters can be obtained from α,β-unsaturated esters in a highly enantioselective manner (upto 90% ee).[2] It was also found that very high asymmetric induction could be achieved in *t*-BuOH–H_2O (1:1) with $K_3Fe(CN)_6$ as the secondary oxidant.[3,1e] Since 2,3-dihydroxy esters of high enantiomeric purity are now easily obtainable, we wish to report a short synthetic route to β-lactam cores starting from 2,3-dihydroxy esters and proceeding through the corresponding diol cyclic sulfite intermediates.



We have shown that vicinal diol cyclic sulfates are versatile chiral synthons when made via the ADH process.[4] However, since the corresponding cyclic sulfites are known to exhibit low reactivity towards nucleophiles, they have not seen much use as synthetic intermediates.[5]

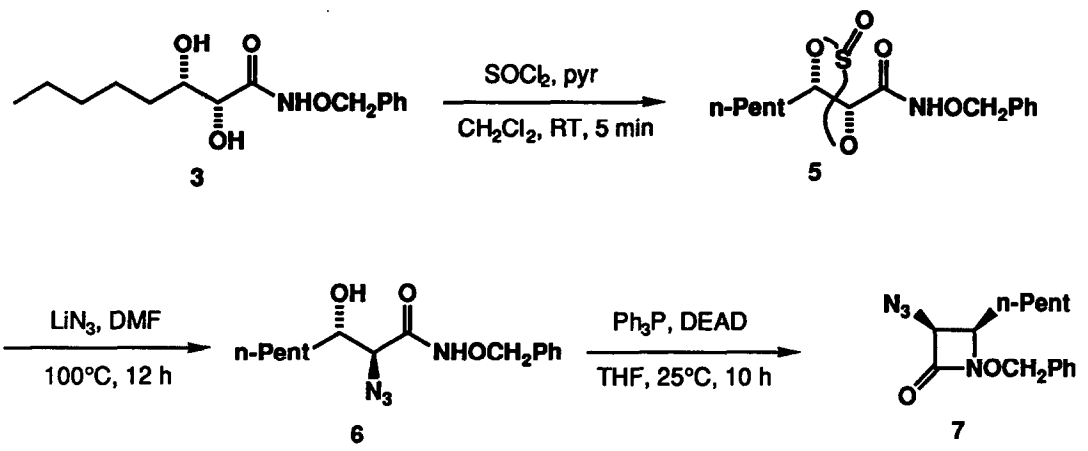
As shown in Scheme 1, the racemic diol ester **2** was prepared by catalytic dihydroxylation.[6] One pot synthesis of the diol hydroxamate **3** was accomplished by hydrolysis of **2** followed by coupling at pH 4.5 with *O*-benzylhydroxyamine effected by a water soluble carbodiimide (WSC), 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride in 85% yield from **1** after crystallization from EtOAc–hexane.[7,8] Initial attempts to prepare **3** directly from the corresponding α,β-unsaturated hydroxamate were unsuccessful due to the inactivation of the osmium catalyst by the hydroxamate functionality (Scheme 1).

Scheme 1.



The formation of diol cyclic sulfite **5** was effected smoothly by the treatment of **3** with $SOCl_2$ (1.5 eq) in the presence of pyridine (2.0 mol eq) in dichloromethane at room temperature (Scheme 2). A 2.8:1 diastereomeric mixture of cyclic sulfites was formed in 92-95% yield. Since catalytic oxidation of the cyclic sulfite to the sulfate using a ruthenium catalyst was blocked again by the nature of the substrate, we decided to attempt opening of the cyclic sulfite ring directly, since it should be activated by the α-carboalkoxy group.[9] Opening of **5** with lithium azide in DMF at 100°C afforded azido alcohol **6** in 76% yield. The azido alcohol **6** can serve as a useful intermediate for the synthesis of various amino alcohol derivatives. Cyclization of the crude **6** under Mitsunobu conditions provided the desired β-lactam core **7** in 53% yield from **5**.

Scheme 2.



Since β-lactam 7 was found to be a single diastereomer by examination of both ^{1}H and ^{13}C NMR spectra,[10] this method when coupled with catalytic ADH constitutes a very efficient route to β-lactam derivatives of high enantiomeric purity. It is noteworthy that this strategy should allow the synthesis of other classes of β-lactam derivatives from functionalized α,β-unsaturated esters.

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7. For the hydroxamate approach to the synthesis of β-lactams, see Miller, M. J. *Acc. Chem. Res.* **1986**, *19*, 49 and references therein.

8. Physical data of **3**: mp 134-135 °C; ^{1}H NMR (DMSO-d_6, 250 MHz) 0.85 (3H, t, *J*=6.7 Hz), 1.22-1.34 (8H, m), 3.33-3.60 (1H, m), 3.67 (1H, dd, *J*=3.8, 6.4 Hz), 4.44 (1H, -O*H*, d, *J*=6.5 Hz), 4.78 (2H, s), 5.15 (-O*H*, d, *J*=6.5 Hz), 7.32-7.49 (5H, m), 10.95 (N*H*, s); ^{13}C NMR (DMSO-d_6, 75.4 MHz) 13.97, 22.15, 25.07, 31.34, 32.67, 71.37, 73.65, 76.83, 128.17, 128.25, 128.69, 136.02, 169.56; IR (KBr, cm^{-1}) 3372 (br), 2955, 2860, 2115, 1681, 1497, 1455, 1264, 989; Anal. calcd C:64.00, H:8.14, N:5.01, obsd C: 64.04, H:8.24, N:4.90.

9. Utilization of the cyclic sulfite instead of the sulfate has also been necessary in cases where the corresponding cyclic sulfate was extremely unstable. B. M. Kim, B. B. Lohray and K. B. Sharpless, unpublished results.

10 .Physical data of **7**: ^{1}H NMR ($CDCl_3$, 300 MHz) 0.90 (3H, t, *J*=6.8 Hz), 1.20-1.33 (6H, m), 1.43-1.51 (2H, m), 3.59 (1H, m), 4.40 (1H, d, *J*=4.7 Hz), 4.96 (1H, d, J_{AB}=11.3 Hz), 5.01 (1H, d, J_{AB}=10.4 Hz), 7.4 (5H, m); ^{13}C NMR ($CDCl_3$, 75.4 MHz) 13.86, 22.31, 25.33, 28.09, 31.54, 62.36, 63.56, 78.43, 128.68, 129.25, 129.46, 134.66, 160.48: IR (film, cm^{-1}) 2932, 2106, 1782, 1455, 1264, 1059; MS (EI) 260 (M^+–28), 202, 153, 149, 139, 111, 91.

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