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AN EFFICIENT ASYMMETRIC SYNTHESIS OF 3S, 4S-3-ACYLAMINO-4-HYDROXYMETHYLAZETIDIN-2-ONES

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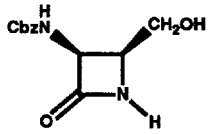
Abstract: An efficient method for the synthesis of azetidinones **1** and **2** from readily available precursors is presented. [2 + 2]-Cycloaddition gives enantiomerically pure azetidinone **5** in 46% isolated yield after a single crystallization. Olefin cleavage and N-1-deprotection afford the desired products in high yield *via* crystalline intermediates.

As part of a larger program in the monocyclic β-lactam field, we required a practical, large-scale synthesis of enantiomerically pure N-protected-3-amino-4-hydroxymethylazetidin-2-ones such as **1** and **2**. The methods available at that time for the synthesis of these β-lactam synthons were limited by requiring labor-intensive classical resolution of racemic mixtures[1] or the use of relatively inaccessible chirons as the source of chirality for asymmetric induction.[2] This letter describes an extremely convenient route to **1** and **2** employing readily available, inexpensive starting materials.



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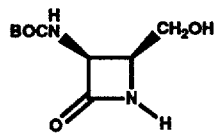

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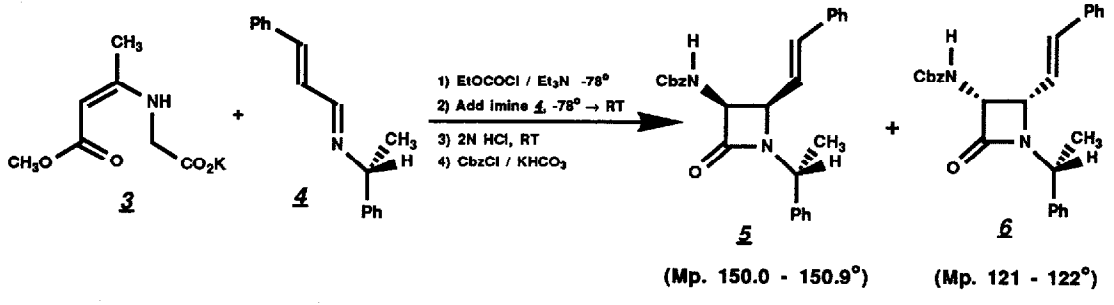
Of the numerous strategies for the synthesis of azetidinones described in the literature, the [2 + 2]-cycloaddition of ketenes with imines appeared to be the most amenable to large-scale synthesis and offered numerous opportunities for asymmetric induction by the incorporation of chiral elements in either the ketene or imine precursor. We recognized two distinct strategies for this approach. The first relies on the design of chiral auxiliaries for optimal asymmetric induction as exemplified by the elegant syntheses of Hubschwerlen,[2] Evans,[3] and Cooper.[4] This approach often entails a lengthy synthesis of the chiral auxiliary and/or problematic removal of this group. The second strategy involves selection of components from the readily available chiral pool, with an eye towards potential ease of separation of diastereomers and refunctionalization to reveal the desired target. We opted for the latter approach since it offered the greatest opportunity for scale-up.

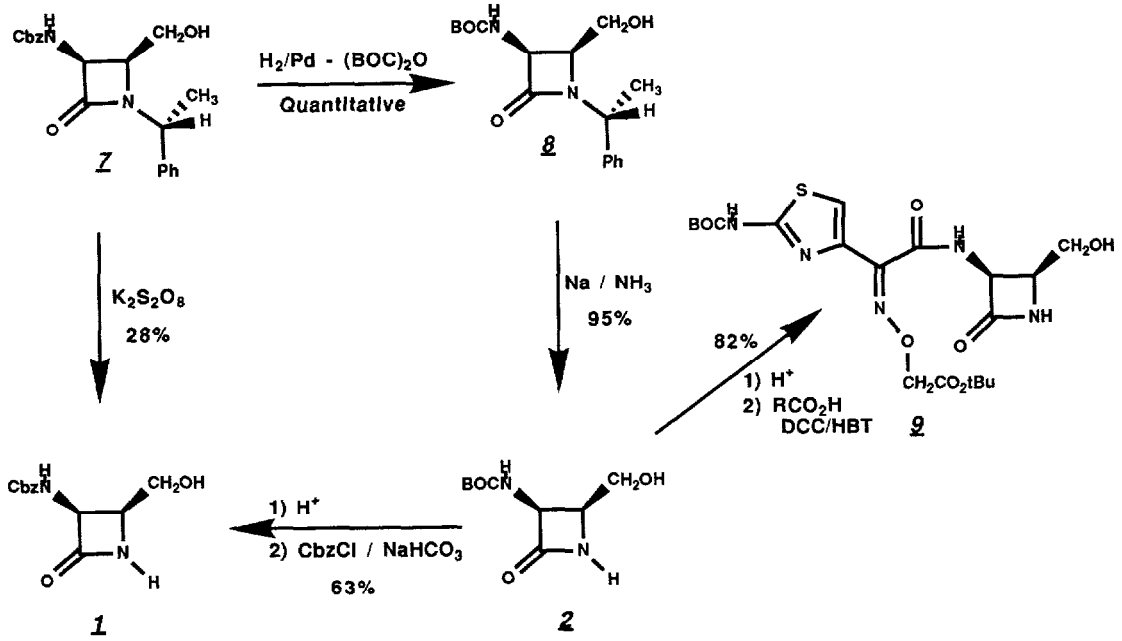
The most readily available chiral component for the condensation is the amine. Prior reports of the use of chiral amines in the [2 + 2]-cycloaddition revealed mixed results ranging from zero to modest asymmetric induction. Our attention was drawn to a paper[5] by the Roussel Uclaf group in which α-methylbenzylamine was employed to generate a C-4-fluoromethylazetidinone with *ca.* 65% diastereomeric excess. The availability of both enantiomers of this relatively inexpensive[6] amine and the anticipation that the aromatic residue would aid in crystallinity of intermediates made this our choice for the source of chirality. Cinnamaldehyde was selected as the aldehyde component for imine formation, again with an eye towards crystallinity and with the knowledge that the resulting C-4-styryl substituent would be an excellent masked hydroxymethyl group. Finally we elected to employ the Dane salt methodology developed by Bose[7] for the cycloaddition since it is high yielding, safe on a large scale, and allows a wide choice of ultimate protecting groups for the C-3 amine, again giving an opportunity to select substituents that would generate crystalline, readily separable diastereomers.

Activation of Dane salt **3** (EtOCOCl / Et_3N, -78°) followed by addition of the preformed cinnamaldehyde - (R)-(+)-α-methylbenzylamine derived imine **4** (-78°→ RT) gave the desired cycloaddition. The crude product was isolated without purification of intermediates by hydrolysis of the vinylogous amide (2N HCl, RT) followed by direct conversion to the diastereomeric benzyloxycarbonyl derivatives **5** and **6** (CbzCl / $KHCO_3$, aqueous acetone). The ratio of **5** to **6** was approximately 3:1, as determined by ^1H and ^{13}C NMR spectra. The sense of asymmetric induction observed in the present instance is the same as that reported by the Roussel Uclaf group, i.e. the R-amine gives rise to the 3S,4R-**5** as the major diastereomer. The importance of the proper selection of functionality at each position on the β-lactam ring was underscored at this point by the observation that *a single recrystallization of the crude product from acetone/hexane gave chemically and enantiomerically pure* **5** *(mp 150.0 - 150.9°, $[\alpha]_D$ -64° (c, 0.78, $CHCl_3$))in 46% isolated yield* (unoptimized, average yield). Analysis of the mother liquors revealed additional **5** as well as **6** which were readily separable by chromatography, with no indication of any *trans*-isomers. *Thus, in a single step optically pure* β*-lactam* **5** *was synthesized in good yield from readily available, inexpensive precursors.*



Ozonolysis ($CHCl_3$ / 0°) with a reductive workup (addition of ethanolic $NaBH_4$) served to cleave the styryl group giving crystalline alcohol **7** (mp 84.5 - 85.9°, $[\alpha]_D$ -41° (c, 0.8165, $CHCl_3$)) in 86% yield. We were now faced with the difficult task of removing the α-methylbenzyl substituent. In a manner similar to that employed to remove N-1 dimethoxybenzyl groups from β-lactams, **5** was treated with excess potassium persulfate in aqueous acetonitrile. The lower reactivity of the α-methylbenzyl group was apparent and the desired lactam **1** was isolated in only 28% yield (based on recovery of 50% of the starting material). *In spite of the low yield for the final step, this still represents a very efficient three step route to enantiomerically pure azetidinone* ***1****.*

A variety of other oxidative methods for cleaving the N-1 substituent were explored without success. Attention then turned to reductive techniques based on analogy to the successful cleavage of an N-1 methoxy substituent by dissolving metal reduction as reported by Floyd.[8] This route required an exchange of protecting groups which was accomplished in one pot (H_2 / Pd black / $[BOC]_2O$) giving **8** (mp 134.1-135.5°, $[\alpha]_D$ -16° (c, 0.86, $CHCl_3$)) in quantitative yield. Whereas **8** was inert to a variety of catalytic hydrogenolysis conditions, dissolving metal reduction (Na / NH_3 / THF) gave the desired product **2** (mp 167.0-167.5° $[\alpha]_D$ +21° (c, 0.5185, $CHCl_3$)) in 95% isolated yield.[9] No products of overreduction or ring cleavage were observed in the crude material. The isolated yield of **2** is only limited by its water solubility which necessitates exhaustive extraction during the workup.



The optical purity of **2** was established by conversion to the corresponding (+)-α-methoxy-α-(trifluoromethyl)phenylacetic acid ester. Comparison of the high field proton NMR spectrum of the ester to that of an authentic diastereomeric mixture prepared from racemic **2** proved that, within the limits of the NMR experiment, the azetidinone prepared by the above procedure was a single enantiomer. The utility of **2** for synthesis was established by its facile conversion to the Cbz-protected derivative **1** (mp 127-128°, $[\alpha]_D$ +9° (c, 0.9305, $CHCl_3$); lit.[3] mp 128.5-129.5°, $[\alpha]_D$ +8.6° (c, 0.9, $CHCl_3$)) and the aminothiazolyloximinoacetyl derivative **9** in 63% and 82% yield respectively.

The synthetic scheme described in this letter allows the synthesis of enantiomerically pure C-4-hydroxymethyl azetidinone **2** in four steps utilizing inexpensive, readily available starting materials and reagents. The yields in all steps are high, although no attempt has been made to optimize the reaction conditions, isolation methods or the recrystallizations. All of the reactions are amenable to large-scale synthesis and all intermediates are highly crystalline solids. This is the shortest, highest yielding method for the synthesis of these valuable β-lactam synthons.

References and Notes

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