Asymmetric Synthesis of 1,3,4-Trisubstituted and 3,4-Disubstituted 2-Azetidinones: Strategy Based on Use of D-Glucosamine as a Chiral Auxiliary in the Staudinger Reaction.

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An efficient asymmetric approach to the synthesis of trisubstituted azetidin-2-ones is presented. The strategy relies on the use of ketene–imine cycloaddition between ketenes generated from phthalimidoacetic and methoxyacetic acids and a chiral Schiff base (**3**) derived from 3,4;5,6-di-*O*-isopropylidene-D-glucosamine propane dithioacetal (**2**) and cinnamaldehyde; the removal of the chiral auxiliary group by β-elimination is a noteworthy facet of this communication.

Although considerable synthetic progress has been made in the area of mono- and bi-cyclic β-lactam antiobiotics [1] in the last 10 years, the discovery and development of new antibacterial agents with enhanced activity and greater stability towards β-lactamases still remains an important endeavour for medicinal chemists.

In searching for an efficient and versatile approach to the synthesis of the most important types of β-lactams—especially those that are inaccessible from fermentation sources—our strategy has focussed on the ketene–imine cycloaddition process [2–5] (Staudinger reaction) for direct generation of 1,3,4-trisubstituted azetidin-2-ones.

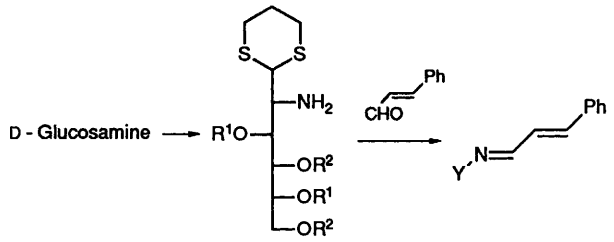
It has been proposed that when the Schiff base is derived from an optically active amine and an achiral aldehyde, the degree of diastereoselectivity in the [2 + 2]-cycloaddition varies.[2]

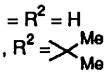
We now describe our own observation on the ketene–imine [2 + 2] cycloaddition for the synthesis of 1,3,4-trisubstituted azetidin-2-ones from activated phthalimidoacetic and methoxyacetic acids and the *chiral* Schiff base (**3**) derived from 3,4;5,6-di-*O*-isopropylidene D-glucosamine propane dithioacetal (**2**) and cinnamaldehyde. The transformation of monobactams (**6**)–(**8**) into the *N*-unsubstituted 3,4-disubstituted azetidin-2-ones (**9**)–(**11**) is also disclosed here.

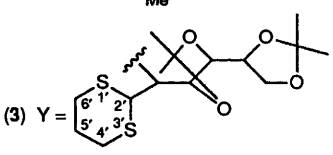
The chiral amine (**2**) required for the preparation of the Schiff base (**3**), was readily obtained from D-glucosamine. Treatment of D-glucosamine with propanedithiol in the presence of concentrated hydrochloric acid over 2 h at 0 °C and then for 12 h at 60 °C afforded a 92% yield of the crystalline D-glucosamine propane dithioacetal (**1**) as its hydrochloric salt {m.p. 79–80 °C, $[\alpha]_D$ +89.4° (*c* 1.3, $CHCl_3$)}. The dithioacetal (**1**) was readily converted into its crystalline 3,4;5,6-di-*O*-isopropylidene derivative (**2**) (dimethoxypropane, *p*-TSOH/H_2SO_4/DMF) in 90% yield {m.p. 79–80 °C, $[\alpha]_D$ +89° (*c* 1.32, $CHCl_3$)}.

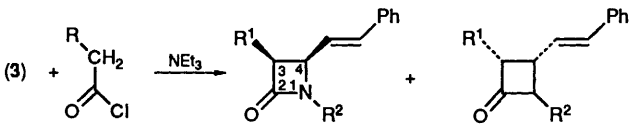
Condensation of the amine (**2**) with cinnamaldehyde provided the Schiff base (**3**). The cycloaddition was accomplished by treatment of (**3**) in the presence of phthalimidoacetyl chloride (**4**) with the addition of triethylamine over 5 min. The crystalline *cis*-β-monobactam (**6**) was isolated exclusively in 92% yield {m.p. 177–178 °C, $[\alpha]_D$ − 79.3° (*c* 1.45, $CHCl_3$)}. The *cis*-orientation of the substituents at C-3 and C-4 was evident from the NMR data ($J_{3,4}$ 6 Hz). Its absolute configuration was assigned on the basis of an X-ray crystal structure determination.

In contrast to this complete diastereospecificity, when the same Schiff base (**3**) was treated with methoxyacetyl chloride and triethylamine, a 6.5:3.5 mixture of two *cis*-monobactams (**7**) {m.p. 206–207 °C, $[\alpha]_D$ −101.6° (*c* 1, $CHCl_3$)} and (**8**) {m.p. 156–157 °C, $[\alpha]_D$ +114.7° (*c* 1, $CHCl_3$)} was obtained in 94% yield. The structures of both *cis*-diastereoisomers were rigor-



(1) $R^1 = R^2 = H$
(2) $R^1, R^2 =$ 

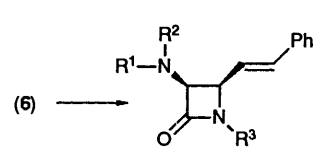




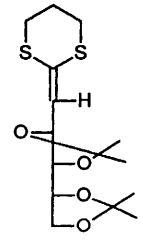
(4) R = Phthalimido
(5) R = OMe

(6) R^1 = Phthalimido, R^2 = Y
(7) R^1 = OMe, R^2 = Y
(9) R^1 = Phthalimido, R^2 = H
(10) R^1 = OMe, R^2 = H

(8) R^1 = OMe, R^2 = Y
(11) R^1 = OMe, R^2 = H



(12) $R^1 = R^2 = H$, R^3 = Y
(13) R^1 = H, R^3 = Y
$R^2 = CO_2Bu^t$
(14) $R^1 = R^3 = H$
$R^2 = CO_2Bu^t$



(15)

ously established on the basis of the NMR results and confirmed by an X-ray crystallographic analysis of the major isomer (**7**). Consequently, the minor *cis*-monobactam (**8**) was assigned the structure depicted.

An important objective of this work was the discovery of an efficient synthetic route to remove the chiral auxiliary and liberate the corresponding *N*-unsubstituted monobactams (**9**)–(**11**). For deprotection, we envisaged to use the β-elimination made possible by the acidic nature of the proton at the 2′-position of the 1′,3′-dithiane ring.

Unfortunately, all attempts to effect the deprotection of the cycloadduct (**6**) by β-elimination were unsuccessful. We therefore decided to transform the phthalimido protecting group in (**6**) into the corresponding t-butoxycarbonyl monobactam (**12**).

Treatment of (**6**) with 2 equiv. of methylhydrazine in dichloromethane and reaction of the derived amine (**12**) with t-butyl oxydiformate in THF–water (1:1) afforded (**13**) [45% overall yield from (**6**)]. Having exchanged the phthalimido group, we were indeed pleased to discover that treatment of (**13**) (400 mg, 0.64 mmol) with BuLi (4 equiv.) in THF (15 ml) at 0 °C under argon for 12 h gave the desired *N*-unsubstituted azetidin-2-one (**14**) {51 mg, 35% yield; $[\alpha]_D$ +6°, (*c* 0.63, $CHCl_3$)} along with the expected β-elimination product ketene-propane dithioacetal (**15**) (176 mg, 85%) {$[\alpha]_D$ +6.8° (*c* 1, $CHCl_3$)}; starting material (**13**) (36 mg) was also recovered.

Likewise, treatment of both 3-methoxy monobactams (**7**) and (**8**) with 2 equiv. of BuLi provided the enantiomeric *N*-unsubstituted azetidin-2-ones (**10**) {m.p. 126–127 °C, $[\alpha]_D$ +10° (*c* 1, $CHCl_3$)} and (**11**) {m.p. 126–127 °C, $[\alpha]_D$ −9.9° (*c* 1, $CHCl_3$)} respectively, in quantitative yield.

The diastereoselectivity of these reactions carried out on relatively simple model compounds, seems to be greatly influenced by the substituents on the imine and ketene precursors.[2] The three substituents of (**6**) acted in synergism and led to 100% diastereoselectivity. However, with the smaller OMe group of (**7**) and (**8**), the three substituents in the transition state do not interact as well, and the diastereoselectivity is hence reduced. These observations indicate that a judicious choice of substituents on both the imine and ketene moieties—especially if D-glucosamine derived chiral auxiliaries are used—should enable us to control the [2 + 2] cycloaddition reaction in terms of asymmetric induction and chemical yield.

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