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Asymmetric Syntheses of β-Lactams and Determination of Their Absolute Configuration

Chuansheng Niu and Marvin J. Miller*

Department of Chemistry and Biochemistry
University of Notre Dame
Notre Dame, IN 46556 USA

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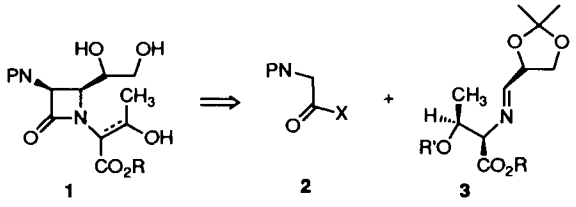
Abstract: Reactions of chiral imines derived from D-glyceraldehyde and threonine derivatives with Oxglycylchloride gave optically active *cis*-substituted β-lactams. The absolute configuration of key intermediates were determined by X-ray analysis and chemical degradation.

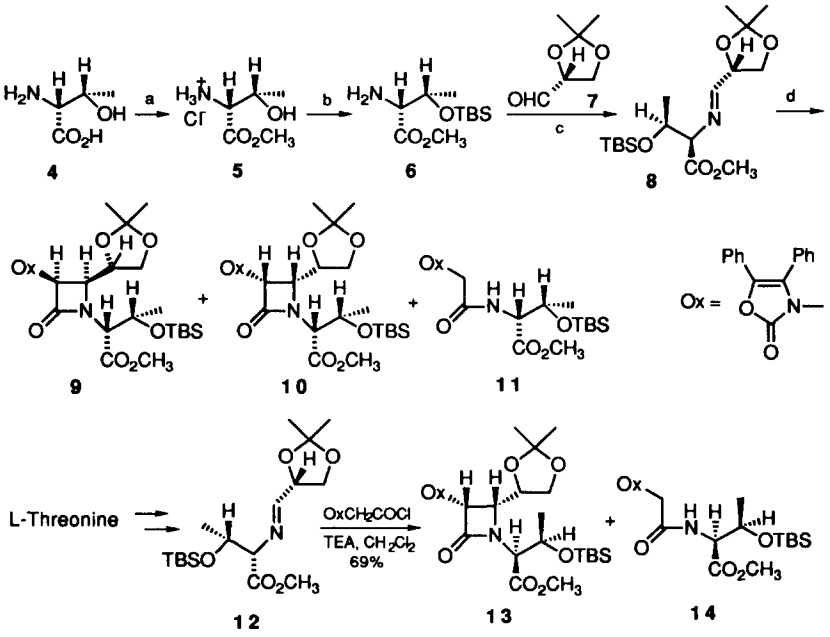
Enantioselective syntheses of β-lactams continues to be of great interest to organic and medicinal chemists[1] because biological activity of β-lactam antibiotics and β-lactamase inhibitors typically is associated with a single enantiomer. In a general program related to the design, syntheses and study of novel β-lactams, we became especially interested in developing a facile synthesis of optically active monocyclic β-lactams containing functionality at both the β-lactam nitrogen and C-4 that could provide versatile intermediates for the syntheses of novel forms of important carbacephalosporins, isooxacephems and other multicyclic β-lactams. If the various functionality in generalized structure **1** could be differentiated, it would be a versatile precursor to many classes of bicyclic β-lactams. A direct approach to **1** might involve a Staudinger (ketene + imine) reaction[2] of a suitably protected glycine **2** and an imine **3**, derived from both protected glyceraldehyde and threonine. Imines separately prepared from glyceraldehyde or from threonine have been utilized frequently in the Staudinger reaction and results from combination of both of these chiral components in a single imine was also of interest. Herein we report the results of studies of the Staudinger reaction of Oxglycine and imines derived from combination of protected glyceraldehyde and threonine derivatives.



The Ox group is a versatile and convenient protecting group.[3] Because it fluoresces, it is easily detected even on TLC analysis and facilitates reaction monitoring processes. It can be removed by reductive, oxidative or photolytic processes and we have shown previously[4] that, upon reaction with select imines in a Staudinger reaction, *cis*-β-lactams are obtained. Thus, Oxglycylchloride was chosen as the "ketene" component in our studies. Use of glyceraldehyde acetonide-based imines in Staudinger reactions also generally induces formation of *cis*-β-lactams with

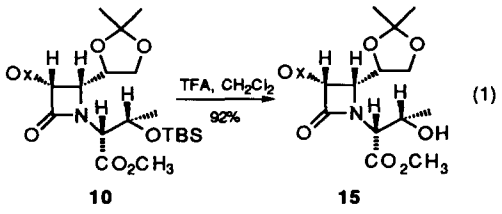
good diastereoselectivity.[5] Imines derived from threonine derivatives also react to give mostly *cis*- products in the Staudinger reaction and increasing the size of the protecting group on the threonine hydroxyl group reportedly favors increased diastereoselectivity.[6] Thus, reaction of an imine derived from combination of D-glyceraldehyde acetonide and O-TBDMS protected threonine esters with Oxglycyl chloride was anticipated to provide optically active, highly functionalized *cis*-β-lactams.

Syntheses: As shown in Scheme 1, esterification[7] and silylation[8] of D-threonine followed by reaction with D-glyceraldehyde acetonide **7**[9] in the presence of magnesium sulfate afforded desired imine **8**. Reaction of imine **8** with the acid chloride derived from Oxglycine[10] produced a 1:2.9 mixture of diastereomeric β-lactams **9** and **10** in 61% yield along with a byproduct, amide **11** in 21% yield. Assignment of the *cis* relationship of the β-lactam ring substituents of each diastereomer was based on the coupling constants of 5.4 Hz for the C_3-C_4 protons in the NMR spectra. Interestingly, substitution of L-threonine-derived imine **12** for that derived from D-threonine (**8**) in the overall procedure resulted in formation of a single *cis*-β-lactam **13** in 69% yield from the Staudinger reaction suggesting a matched-mismatched combination (D-glyceraldehyde, L-threonine vs. D-glyceraldehyde, D-threonine) in the imine can affect diastereoselectivity. The only other product was amide **14.**



Scheme 1. a) 3N HCl, CH_3OH, reflux, 100%. b) TBDMSCl, DMF, imidazole, 94%. c) $MgSO_4$, CH_2Cl_2. d) $OxCH_2COCl$, TEA, CH_2Cl_2, 61% of **9** & **10**.

Determination of the absolute configuration of the Staudinger products: Desilylation of β-lactam **10** provided **15** (Eq 1) in crystalline form suitable for X-ray crystallographic analysis which confirmed the 3(*R*), 4(*R*) configuration of both **15** and initially formed β-lactam **10**.



(1)

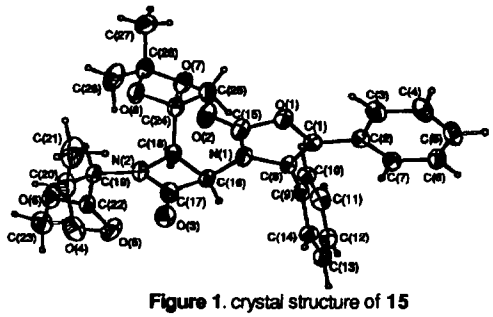
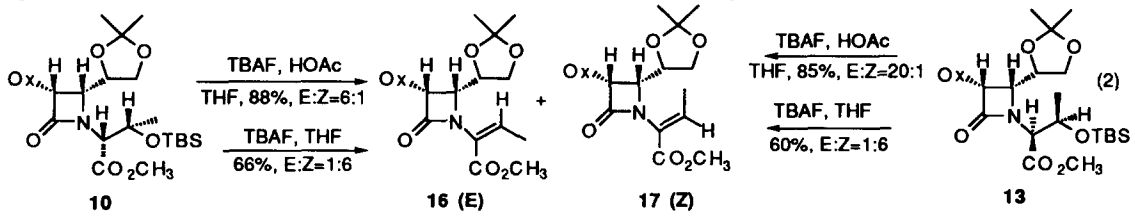


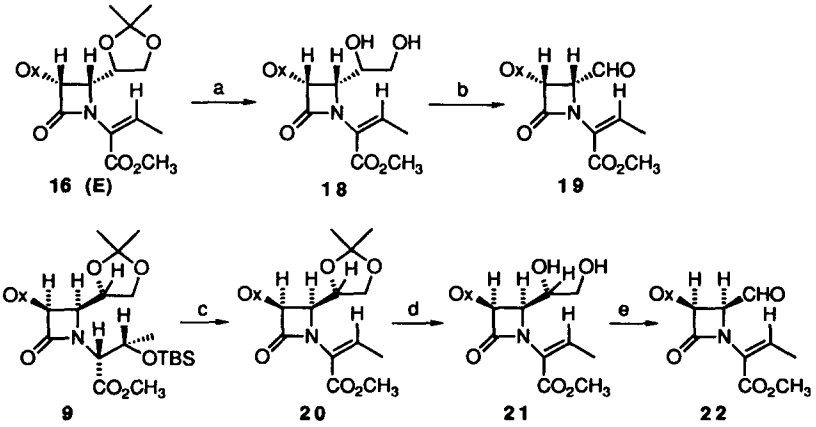
Figure 1. crystal structure of **15**

Treatment of **10** with tetrabutylammonium fluoride (TBAF) and glacial acetic acid gave a 6:1 ratio of *E*- and *Z*-alkenes **16** and **17** in 88% yield. Use of excess TBAF in THF without the addition of acetic acid resulted in a reversal of the ratio of **16** (*E*) and **17** (*Z*) to 1:6 (Eq 2). The assignment of the *E* and *Z* isomers was based on comparison to reported NMR data of related dehydrothreonines.[11] Similar reaction of **13** with TBAF afforded the corresponding *E* and *Z* isomers which were identical with **16** and **17** based on comparison of mp, R_f, IR, NMR and optical rotation data. Therefore, the 3(*R*), 4(*R*) configuration was also assigned to β-lactam **13**.



(2)

The absolute configuration of β-lactam **9** could now be determined by chemical degradation as shown in Scheme 2. Deprotection of **16** (*E*) with HCl in THF gave diol **18** and subsequent oxidation with $NaIO_4$ afforded aldehyde **19**. Treatment of **9** with TBAF and glacial acetic acid gave *E*-alkene **20**. Deprotection and periodate oxidation of **20** gave **22**. β-Lactams **19** and **22** had identical chemical and physical properties except for optical rotations which were of the same value, but of opposite sign. Thus, the 3(*S*), 4(*S*) configuration could be assigned to **9**.[12]



Scheme 2. a) THF, HCl, rt, 90%. b) 10% $NaIO_4$ on silica gel, CH_2Cl_2, 70%. c) TBAF, HOAc, THF, 83%. d) THF, HCl, rt, 88%. e) 10% $NaIO_4$ on silica gel, CH_2Cl_2, 67%.

Studies demonstrating the utility of the described optically active β-lactams for the syntheses of fused bicyclic and multicyclic β-lactams are in progress.

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12. ^1H NMR spectral data: **9** ($CDCl_3$) δ 0.05 (s, 3H), 0.11 (s, 3H), 0.87 (s, 9H), 1.26 (s, 3H), 1.40 (d, 3H, J = 7.5 Hz), 1.42 (s, 3H), 3.73 (s, 3H), 3.95 (dd, 1H, J = 8.8 & 6.0 Hz), 4.24 (dd, 1H, J = 8.8 & 6.0 Hz), 4.48 (dd, 1H, J = 9.3 & 5.4 Hz), 4.53 (m, 2H), 4.71 (m, 2H), 7.2-7.6 (m, 10H). **10** ($CDCl_3$) δ 0.00 (s, 3H), 0.06 (s, 3H), 0.81 (s, 9H), 1.29 (s, 3H), 1.31 (d, 3H, J = 6.3 Hz), 1.34 (s, 3H), 3.64 (dd, 1H, J = 8.3 & 6.7 Hz), 3.71 (s, 3H), 3.85 (dd, 1H, J = 8.5 & 5.5 Hz), 3.96 (dd, 1H, J = 8.3 & 6.8 Hz), 4.30 (d, 1H, J = 5.2 Hz), 4.51 (m, 1H), 4.67 (d, 1H, J = 5.4 Hz), 4.79 (m, 1H), 7.2-7.6 (m, 10H). **13** ($CDCl_3$) δ 0.01 (s, 3H), 0.07 (s, 3H), 0.82 (s, 9H), 1.23 (d, 3H, J = 6.3 Hz), 1.31 (s, 3H), 1.37 (s, 3H), 3.76 (s, 3H), 3.99 (m, 2H), 4.12 (dd, 1H, J = 7.5 & 5.5 Hz), 4.17 (d, 1H, J = 5.8 Hz), 4.59 (m, 1H), 4.68 (d, 1H, J = 5.5 Hz), 4.89 (m, 1H), 7.2-7.6 (m, 10H). **15** ($CDCl_3$) δ 1.32 (s, 3H), 1.37 (s, 3H), 1.49 (d, 3H, J = 6.3 Hz), 3.51 (dd, 1H, J = 8.2 & 6.4 Hz), 3.72 (dd, 1H, J = 9.4 & 5.4 Hz), 3.77 (s, 3H), 3.99 (dd, 1H, J = 8.2 & 6.5 Hz), 4.32 (d, 1H, J = 3.0 Hz), 4.45 (m, 1H), 4.74 (m, 1H), 4.80 (d, 1H, J = 5.3 Hz), 7.2-7.65 (m, 10H). **16** ($CDCl_3$) δ 1.28 (s, 3H), 1.32 (s, 3H), 2.14 (d, 3H, J = 7.2 Hz), 3.58 (dd, 1H, J = 8.4 & 5.1 Hz), 3.73 (s, 3H), 4.01 (dd, 1H, J = 8.4 & 6.5 Hz), 4.29 (dd, 1H, J = 9.4 & 5.6 Hz), 4.76 (m, 1H), 4.78 (d, 1H, J = 5.6 Hz), 6.93 (q, 1H, J = 7.2 Hz), 7.2-7.65 (m, 10H). **17** ($CDCl_3$) δ 1.25 (s, 3H), 1.28 (s, 3H), 1.89 (d, 3H, J = 7.2 Hz), 3.55 (dd, 1H, J = 8.7 & 6.6 Hz), 3.74 (s, 3H), 3.89 (dd, 1H, J = 8.7 & 6.4 Hz), 4.16 (m, 1H), 4.71 (m, 2H), 6.86 (q, 1H, J = 7.2 Hz), 7.2-7.6 (m, 10H). **19** ($CDCl_3$) δ 2.21 (d, 3H, J = 7.3 Hz), 3.77 (s, 3H), 4.84 (dd, 1H, J = 6.4 & 2.0 Hz), 4.94 (d, 1H, J = 6.4 Hz), 7.09 (q, 1H, J = 7.3 Hz), 7.2-7.6 (m, 10H), 9.89 (d, 1H, J = 2.0 Hz); $[\alpha]^{23}_D$=-23.6° (c 0.5, $CHCl_3$). **22** ($CDCl_3$) δ 2.21 (d, 3H, J = 7.3 Hz), 3.77 (s, 3H), 4.84 (dd, 1H, J = 6.4 & 2.0 Hz), 4.94 (d, 1H, J = 6.4 Hz), 7.09 (q, 1H, J = 7.3 Hz), 7.2-7.6 (m, 10H), 9.89 (d, 1H, J = 2.0 Hz); $[\alpha]^{23}_D$=+24.6° (c 0.5, $CHCl_3$).

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