Tetrahedron Letters, Vol.31, No.7, pp 977-980, 1990
Printed in Great Britain

0040-4039/90 $3.00 + .00
Pergamon Press plc

ASYMMETRIC SYNTHESIS WITH CHIRAL β-LACTAMS. HIGHLY STEREOSELECTIVE ALKYLATION AND ALDOL REACTION OF A CHIRAL 3-AMINO-4-STYRYL-β-LACTAM.

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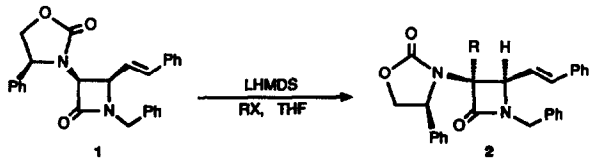
Summary: *Extremely stereoselective alkylation and aldol reaction of enantiomerically pure 3-amino-4-styryl-β-lactams and an application to the asymmetric synthesis of α,β-diamino acid and alcohol are described. Possible mechanisms for these reactions are proposed.*

Significance of non-protein amino acids has recently been recognized in connection with design and synthesis of enzyme inhibitors as potential pharmaceutical drug, and for the study of enzymic reaction mechanisms.[1] These compounds are also important as fragments of peptide hormone analogues, and components of naturally occurring glycosphingolipids and antibiotics.[2] We have been applying our β-lactam - based synthetic method, *"β-Lactam Synthon Method"* to the asymmetric synthesis of various non-protein amino acids and dipeptides containing non-protein amino acid residues.[3] Since the original *"β-Lactam Synthon Method"* is applicable only to the synthesis of *aromatic* amino acids and peptides containing them by using selective N-C^4(Ar) bond cleavage, we started the expansion of this method to the asymmetric synthesis of *non-aromatic* amino acids by using N-C(O) cleavage reactions of β-lactam skeleton after necessary stereoselective modifications. We have also been developing a variety of highly stereoselective reactions by exploiting the sterically and electronically unique structure of β-lactam skeleton. We describe here our preliminary results on extremely stereoselective alkylation and aldol reaction of 3-amino-4-styryl-β-lactams, and an application to the asymmetric synthesis of α,β-diamino acid and alcohol.

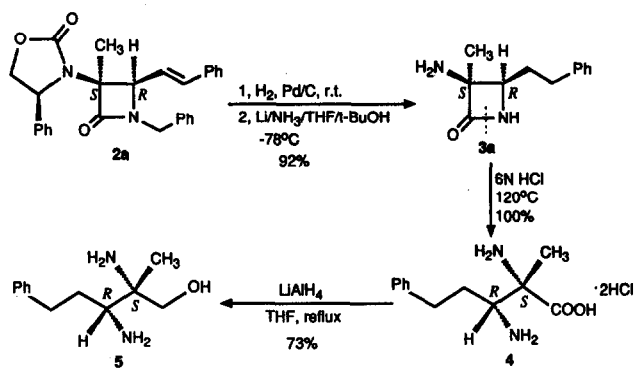
First, we carried out the asymmetric alkylation of *(3S,4R)*-1-benzyl-3-[*(S)*-4-phenyloxazolidinyl]-4-styrylazetidin-2-one (**1**)[4] at C^3 with methyl iodide (at -100°C) and allyl bromide (at -78°C) following the previously reported "Type 1" alkylation of chiral β-lactam enolates[3b,c]. The electrophiles attacked from the backside of 4-styryl group to give the corresponding alkylated β-lactams, *(3S,4R)*-3-methyl-**1** (**2a**) and *(3S,4R)*-3-allyl-**1a** (**2b**), in 95% and 82% yields, respectively (eq. 1).[5] The stereoselectivity of methylation was 98% d.e. at -100°C and that of allylation was >99% d.e. on the basis of ^{1}H NMR analysis. The stereochemistry at C^3 was unambiguously confirmed by NOESY.



(1)

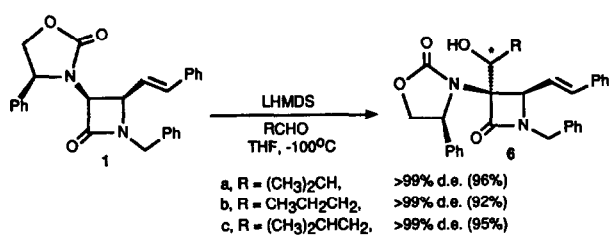
The 3-methyl-β-lactam (**2a**) was further converted to optically pure *(2S,3R)*-2,3-diamino-2-methyl-5-phenylpentanoic acid (**4**) and *(3S,4R)*-2,3-diamino-2-methyl-5-phenyl-1-pentanol (**5**) in high yields, through the optically pure β-lactam **3a** (**Scheme 1**).[6]

Scheme 1



Since a variety of substituents can be introduced to the C^4 position of β-lactams **1** and **2**, these highly stereoselective reactions will provide efficient and convenient routes to various optically pure diamino acids and diamino alcohols, which are useful intermediates for the synthesis of enzyme inhibitors, modified peptides, chiral macrocycles, and chiral ligands or reagents for asymmetric synthesis.

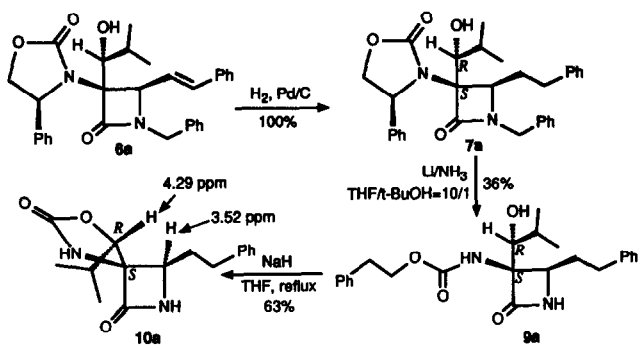
Next, we investigated aldol reaction of **1**, which would create two chiral centers at the C^3 of the β-lactam and at its side chain. The approach of these aldehydes should be from the opposite side of the C^4 styryl group, but the stereochemistry at the side chain and the stereoselectivity of the reaction were not easily predictable. It was found that the reactions of **1** with 2-methylpropanal, butanal, and 3-methylbutanal, proceeded in high chemical yields to give *(3S,4R)*-3-(1'-hydroxyalkyl)-β-lactams (**6**) with >99% d.e. (eq. 2).[7]



(2)

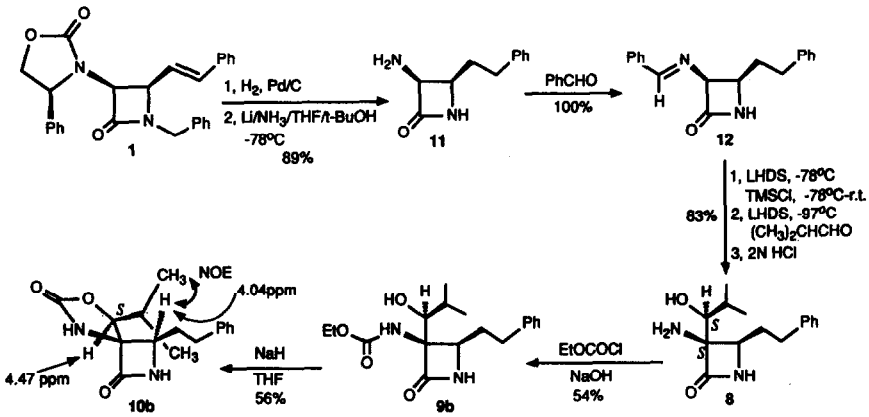
In order to determine the absolute configuration of the newly formed chiral center at the side chain, the β-lactam **6a** (R = i-Pr) was converted to a novel spiro-β-lactam (**10a**)[8] via hydrogenation, modified Birch reduction, and cyclization as shown in **Scheme 2**. The stereochemistry of **10a** was unambiguously determined on the basis of 2D NMR analysis, viz., the NOESY spectrum of **10a** clearly showed that the isopropyl group at $C^{4'}$ of oxazolidinone moiety was in the opposite side of the hydrogen at C^4 (δ 3.52 ppm) of the β-lactam moiety since no appreciable NOE was observed between these two, and an NOE was observed between the $C^{4'}$-hydrogen (δ 4.29 ppm) of oxazolidinone moiety and the C^4-hydrogen of β-lactam moiety. Consequently, the configuration at the newly formed chiral center ($C^{1'}$) at the side chain of **6a** was unambiguously determined to be *R*[12].

Scheme 2



We also looked at the participation of the chiral 4-phenyloxazolidinone moiety in asymmetric induction. Thus, β-lactam **1** was converted to 3-amino-β-lactam **11** through hydrogenation and modified Birch reduction, and then to 3-imino-β-lactam **12**. The aldol reaction of **12** with 3-methylpropanal in a manner similar to that for the formation of **6**, gave the *(3S,4R,1'S)*-3-(1'-hydroxy-2'-methyl)propyl-β-lactam **8b** in 83% yield with 90% d.e. (**Scheme 3**).[9] The stereochemistry at $C^{1'}$ was determined by converting **8b** to the spirobicyclic β-lactam **10b**[10] followed by the NOESY analysis of **10b**, viz., very strong NOE was observed between one of the methyls of the isopropyl group at $C^{4'}$ of oxazolidinone moiety and the C^4-hydrogen (δ 4.04 ppm) of β-lactam moiety, and no appreciable NOE was detected between the $C^{4'}$-hydrogen and the C^4-hydrogen, which clearly indicated that the newly formed chiral center ($C^{1'}$) of **8b** was *S*.

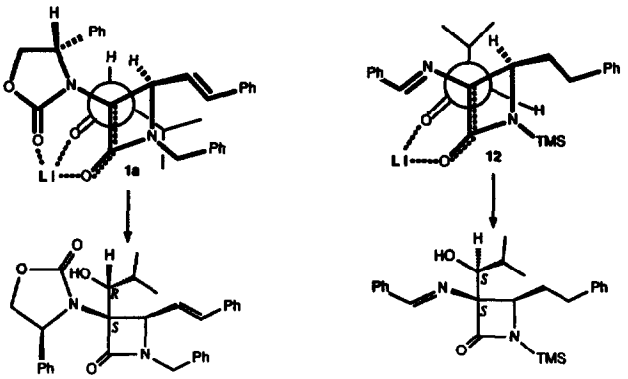
Scheme 3



Accordingly, it is found that (i) the β-lactams, **1** and **12**, give opposite configurations at the newly formed chiral centers ($C^{1'}$) at the side chain, and (ii) simple β-lactam skeleton such as **12** possesses relatively high stereogenecity (90% d.e.) in this aldol reaction. Possible mechanisms which can accommodate these findings are proposed in **Scheme 4**. In the Newman projections of the cyclic transition states for the aldol reaction of 2-methylpropanal with lithium β-lactam enolates, the top position is the least hindered in the case of **12**, and thus bulky isopropyl group takes this position to give *S* configuration , whereas the top position is very crowded in the case of **1** because of the 4-phenyl group of oxazolidinone moiety directing toward this top position, and thus the isopropyl group can no longer occupy this position to give *R* configuration.

Further studies on the applications of these highly stereoselective alkylation and aldol reaction to the asymmetric synthesis of a variety of non-protein amino acids as well as amino-sugars are actively in progress.

Scheme 4



Acknowledgment. This research was supported by grants from National Institute of Health (NIGMS) and the Center for Biotechnology, SUNY at Stony Brook, which is sponsored by the New York Science & Technology Foundation. Generous support from Ajinomoto Co., Inc. is also gratefully acknowledged.

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1. e.g., (a) Saari, W. S.; Halczenko, W.; Cochran, D. W.; Dobrinska, M. R.; Vincek, W. C.; Titus, D. G.; Gaul, S. L.; Sweet, C. S. *J. Med. Chem.*, **1984**, *27*, 713. (b) Ramalingam, K.; Woodard, R. W. *Tetrahedron Lett.*, **1985**, *26*, 1135. (c) Walsh, J. J.; Metzler, D. E.; Powell, D.; Jacobson, R. A. *J. Am. Chem. Soc.*, **1980**, *102*, 7136. (d) Paul, P. K. C.; Sukumar, M.; Bardi, R.; Piazzesi, A. M.; Valle, G.; Toniolo, C.; Balaram, P. *J. Am. Chem. Soc.*, **1986**, *108*, 6363 and references cited therein. (e) Schöllkopf, U. *Pure & Appl. Chem.*, **1983**, *55*, 1799. (f) Polt, R.; Seebach, D. *J. Am. Chem. Soc.*, **1989**, *111*, 2622. (g) Sinclair, P. J.; Zhai, D.; Reibenspies, J.; Williams, R. M. *J. Am. Chem. Soc.*, **1986**, *108*, 1103. (h) Georg, G. I.; Guan, X.; Kant, J. *Tetrahedron Lett.*, **1988**, *29*, 403.
2. e.g., Jung, M. J. In *"Chemistry and Biochemistry of Amino Acids"*, Barrett, G. C. Ed.; Chapman and Hall, New York, **1985**, 227.
3. e.g., (a) Ojima, I.; Qiu, X. *J. Am. Chem. Soc.*, **1987**, *109*, 6537. (b) Ojima, I.; Chen, H.-J. C.; Nakahashi, K. *J. Am. Chem. Soc.*, **1988**, *110*, 278. (c) Ojima, I.; Chen, H.-J. C.; Qiu, X. *Tetrahedron*, **1988**, *44*, 5307. (d) Ojima, I.; Komata, T.; Qiu, X. *ibid*, **1989**, *111*, in press. (e) Ojima, I. In *"Asymmetric Reactions and Processes in Chemistry"*, Eliel, E. L.; Otsuka, S. Eds.; *Am. Chem. Soc., Symp. Series*, **1982**, *185*, 109.
4. Chiral β-lactam **1** was prepared by the literature method: see Evans, D. A.; Sjogren, E. B. *Tetrahedron Lett.*, **1985**, *26*, 3783.
5. **2a**: $[\alpha]_D^{20}$ -152° (c 2.00, $CHCl_3$).[11] **2b**: $[\alpha]_D^{20}$ -157° (c 3.00, $CHCl_3$).[11]
6. **3a**: $[\alpha]_D^{20}$ +16.5° (c 2.00, $CHCl_3$).[11] **4**: $[\alpha]_D^{20}$ +22.2° (c 1.00, $CHCl_3$).[11] **5**: $[\alpha]_D^{20}$ +27.4° (c 1.00, $CHCl_3$).[11]
7. Typical procedure for asymmetric aldol reaction is as follows. To a solution of **1** (1.00 mmol) in THF (30 ml) at -100°C is added dropwise a solution of LHMDS (2.0 eq.) in THF (ml). After stirring the mixturte for 15 min an aldehyde (1.50 mmol) is added, and the mixture is kept at -100°C with stirring for 10 hr. The reaction is quenched with water and the mixture is allowed to warm to room temperature. After usual workup and purification on a short silica gel column, pure aldol product (**6**) is obtained in high yield. **6a**: $[\alpha]_D^{20}$ -41° (c 3.00, $CHCl_3$).[11] **6b**: $[\alpha]_D^{20}$ -11.7° (c 3.00, $CHCl_3$).[11] **6c**: $[\alpha]_D^{20}$ +2.0° (c 3.00, $CHCl_3$).[12]
8. **10a**: $[\alpha]_D^{20}$ +33.3° (c 0.30, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 0.99(d, J=6.6Hz, 3H), 1.07(d, J=6.5Hz, 3H), 1.90(m, 1H), 2.05(m, 1H), 2.25(m, 1H), 2.65(m, 1H), 2.80(m, 1H), 3.52(dd, J=5.7, 7.7Hz, 1H), 4.29(d, J=7.7Hz, 1H), 5.95(b, 1H), 7.30(m, 5H).[11]
9. **8b**: $[\alpha]_D^{20}$ 15.0° (c 0.45, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 0.84(d, J=6.9Hz, 3H), 1.06(d, J=6.6Hz, 3H), 1.75-2.20(m, 5H), 2.78(m, 2H), 3.47(d, J=8.0Hz, 1H), 3.58(dd, J=2.4, 10.0Hz, 1H), 5.90(b, 1H), 7.30(m, 5H).[11]
10. **10b**: $[\alpha]_D^{20}$ -13.6° (c 0.27, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 0.95(d, J=6.5Hz, 3H), 1.00(d, J=6.7Hz, 3H), 1.96(m, 3H), 2.70(t, J=7.4Hz, 2H), 3.92(dd, J=4.9, 8.7Hz, 1H), 4.49(d, J=6.2Hz, 1H), 6.65(b, 1H), 7.35(m, 5H).[11]
11. Satisfactory spectral and microanalyses data were obtained for all new compounds.
12. This absolute configuration was also confirmed by X-ray crystallography for the N-(*p*-bromophenyl) derivative. Results will be published elsewhere.

(Received in USA 20 November 1989)