Tetrahedron Letters, Vol.31, No.30, pp 4289-4292, 1990
Printed in Great Britain

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

ASYMMETRIC SYNTHESIS OF β-LACTAMS BY CHIRAL ESTER ENOLATE - IMINE CONDENSATION

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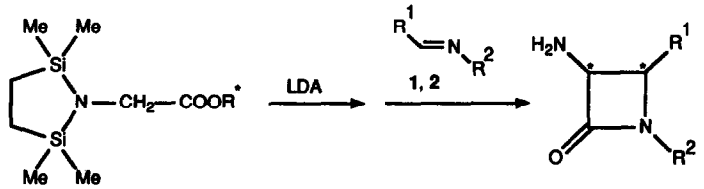
Summary: *Asymmetric cyclocondensation of N,N-bis(silyl)glycinates bearing chiral ester moieties with aldimines is found to proceed with extremely high enantioselectivity to give the corresponding chiral β-lactams in good to high yields. It is found that the E/Z-geometry of the chiral ester-enolate is responsible for cis/trans stereochemistry of the β-lactam formed. Effects of various chiral auxiliaries in the ester-enolates on the enantioselectivity of the reactions are examined.*

We have been applying our "β-Lactam Synthon Method" to the asymmetric synthesis of various non-protein amino acids and dipeptides containing non-protein amino acid residues,[1] which are potential enzyme inhibitors, fragments of peptide hormone analogues, and components of naturally occuring glycosphingolipids and antibiotics.[2] For the asymmetric synthesis of nonprotein amino acids through the "β-Lactam Synthon Method" the development of newer and efficient routes to enantiomerically pure β-lactams are of particular importance. We describe here our preliminary results on the successful application of lithium chiral ester enolate - imine condensation strategy, which has been extensively studied by Hart et al.,[3] to the asymmetric synthesis of 3-amino-β-lactams.

We carried out the reactions of chiral lithium ester enolates (**4**) generated *in situ* from N,N-bis-(silyl)glycinates (**3**) with imines (**1** and **2**), which gave the corresponding chiral β-lactams (**5-11**) in fairly good isolated yields (eq. 1).[4] Results are summarized in Table 1.



(1)

3

5 - 11

3a : R^* = (-) - menthyl
3b : R^* = (+) - neomenthyl
3c : R^* = (-) - bornyl
3d(-) : R^* = (-) - *trans* -2-phenyl-1-cyclohexyl
3d(+) : R^* = (+) - *trans* -2-phenyl-1-cyclohexyl

1a : R^1 = Ph ; R^2 = *p*-MeO-C_6H_4
1b : R^1 = *p*-F-C_6H_4 ; R^2 = *p*-MeO-C_6H_4
1c : R^1 = *p*-CF_3-C_6H_4 ; R^2 = *p*-MeO-C_6H_4
1d : R^1 = *p*-MeO-C_6H_4 ; R^2 = *p*-MeO-C_6H_4
1e : R^1 = 3,4-$(MeO)_2$-C_6H_3 ; R^2 = *p*-MeO-C_6H_4
2a : R^1 = Ph ; R^2 = $SiMe_3$
2b : R^1 = Ph  ; R^2 = $SiMe_3$

Table 1. Asymmetric Synthesis of β-Lactams (**5-11**) through Chiral Ester Enolate - Imine Condensation[a]

Entry	Ester	Imine	Conditions[b]	β-Lactam	Isolated Yield (%)[c]	Product Ratio and Enantioselectivity[d] trans (%)	cis (%)
1	**3a**	**1a**	A	**5a**	65	100 (>99% e.e.; *3R,4R*)	
2	**3b**	**1a**	A	**5a**	65	26 (54% e.e.; *3S,4S*)	
				5b			74 (21% e.e.; *3S,4R*)
3	**3c**	**1a**	A	**5a**	53	37 (5% e.e.; *3R,4R*)	
				5b			63 (2% e.e.; *3R,4S*)
4	**3d(-)**	**1a**	A	**5a**	58	100 (>99% e.e.; *3R,4R*)	
5	**3d(+)**	**1a**	A	**5a**	58	100 (>99% e.e.; *3S,4S*)	
6	**3a**	**2a**	B	**6**	38	100 (68% e.e.; *3R,4R*)	
7	**3a**	**2b**	B	**7**	48		100 (11% e.e.; *3S,4R*)
8	**3d(-)**	**2b**	B	**7**	46		100 (78% e.e.; *3S,4R*)
9	**3a**	**1b**	A	**8**	55	100 (>99% e.e.; *3R,4R*)	
10	**3a**	**1c**	A	**9**	59	100 (>99% e.e.; *3R,4R*)	
11	**3a**	**1d**	A	**10a**	70	89 (>99% e.e.; *3R,4R*)	
				10b			11 (38% e.e.; *3S,4R*)
12	**3a**	**1e**	A	**11a**	54	91 (>99% e.e.; *3R,4R*)	
				11b			9 (27% e.e.; *3S,4R*)

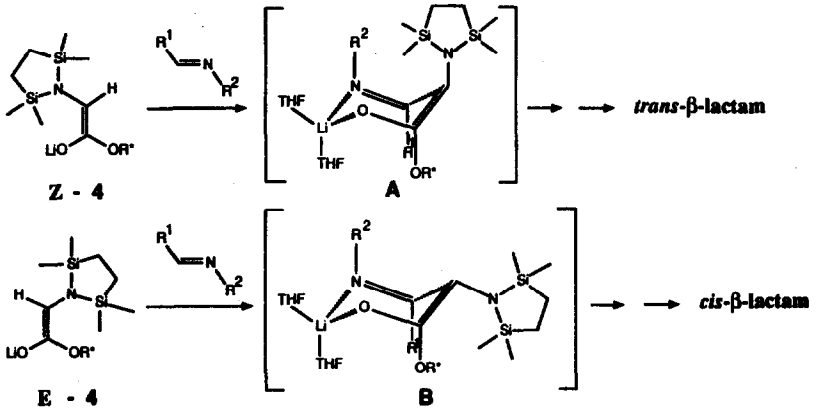
[a]All reactions were run with 2.0 mmole of **3**, 2.20 mmole of LDA, and 2.0 mmole of **1** or **2** in 6 ml of THF. After the mixture was stirred at -78°C and/or -50°C for a given period of time, the reaction mixture was allowed to warm gradually to ambient temperature. The reaction was quenched with 0.1*N* HCl. [b]Condition A, at -78°C for 4h; Condition B, at -78°C for 4 h and at -50°C for 72 h. [c]Yield of β-lactam(s) after passing crude reaction mixture through a short column (15 cm, 10 g of silica gel) to eliminate unreacted starting materials, i.e., chiral auxiliary, aldehyde, and amine. [d]Enantiomeric purity was determined by the Mosher's MTPA method[5] on ^{1}H NMR and/or ^{19}F NMR. Absolute configurations were determined based on chemical correlation (specific rotation) with authentic samples (for 4-aryl-β-lactams, their conversion to the corresponding α-amino acid amides by hydrogenolysis[1] was used), and also based on the NMR chemical shift correlation of 3-MTPA-amino-β-lactams.

As Table 1 shows, the reactions of **3a** (R* = (-)-menthyl) and **3d** (R* = (-)- or (+)-*trans*-2-phenyl-1-cyclohexyl[6]) with **1a-c** give exclusively the corresponding *trans*-β-lactams (**5a**, **8**, and **9**) in fairly good yields with extremely high enantiomeric purity (entries, 1, 4, 5, 9 and 10). The reactions of **3a** with **1d** and **1e** also give *trans*-β-lactams (**10a** and **11a**) as the predominant products with >99% e.e. accompanied by a small amount of *cis*-β-lactams (**10b** and **11b**) (Entries 11 and 12). When (+)-neomenthyl group is used as the chiral auxiliary, the reaction gives a 1:3 mixture of *trans:cis* isomers (**5a** and **5b**) with *S* configuration at the C-3 positions (Entry 2), which is opposite to that of **5a** obtained by using (-)-menthyl group as the chiral auxiliary (Entry 1). A mixture of *trans*- and *cis*-β-lactams (**5a** and **5b**) is also obtained on using (+)-bornyl group as the chiral auxiliary, in which *3R*-isomers are formed with very low enantiomeric purity (Entry 3). *Accordingly, it is obvious that the use of (-)- and (+)-trans-2-phenyl-1-cyclohexyl as well as (-)-menthyl groups as the chiral auxiliaries is the most efficient.* The substituent on the imine nitrogen also exerts a marked influence on

asymmetric induction, viz., 4-methoxylphenyl gives >99% e.e. for **5a** (Entry 1) whereas trimethylsilyl (TMS) induces only 68% e.e. for **6a** (Entry 6). In contrast with the cases of arylimines (**1**), the reactions of **3a** and **3d** with N-silylcinnamaldimine (**2b**) give *cis*-β-lactam (**7**; *3S,4R*) exclusively (Entries 7 and 8), and **3d** gives much higher asymmetric induction (78% e.e.) than **3a**.

The formation of *trans*- and *cis*-β-lactams can be explained by taking into account the stereochemistry of the lithium enolates (*Z*- and *E*-**4**) and transition states, **A** and **B**, as shown in Scheme 1.[3,4c,7]

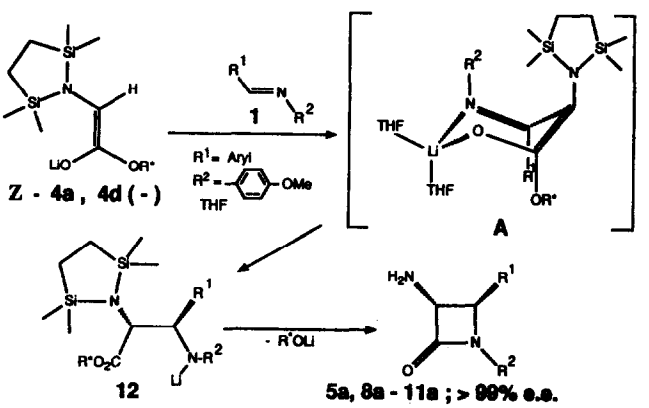
Scheme 1



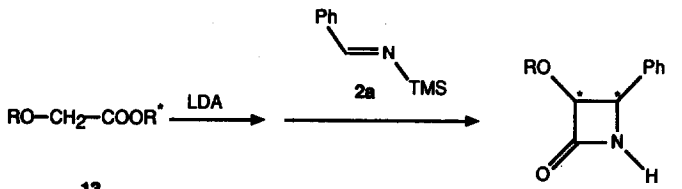
As Scheme 1 shows, the reaction of *Z*-enolate proceeds through the transition state **A** to give *trans*-β-lactams, while the reaction of *E*-enolate gives *cis*-β-lactams via the transition state **B**.[3,4c,7] When (-)-menthyl and (-)- or (+)-2-phenyl-1-cyclohexyl groups are used as the chiral auxiliaries, *trans*-β-lactams are formed predominantly or exclusively, which strongly suggests that *Z*-enolates (*Z*-**4a,d**) react much faster than *E*-enolates (*E*-**4a,d**) and thus the reactions proceed through the transition state **A**. It is also indicated that the imines (**1a-e**) approach exclusively from the *re*-face of *Z*-**4a** and *Z*-**4d(-)** (*si*-face of *Z*-**4d(+)**) to give N-lithiated-β-amino esters (**12a**), which then cyclize to afford the corresponding *trans*-β-lactams (**5a, 8a-11a**) with >99% e.e. (Scheme 2).

On the other hand, the fact that the reactions of **4a** and **4d(-)** with **2b** (R^1 = *trans*-styryl, R^2 = TMS) exclusively give *cis*-β-lactam **7b**, strongly suggests that these reactions proceed through the transition state **B**, i.e., the *E*-enolates (*E*-**4a,d**) react with **2b** exclusively.

Scheme 2



We also looked at the reactions of the lithium enolates of (-)-N-methylephedrinyl and (-)-menthyl O-protected hydroxyacetates (**13a-c**) with **2a** (eq. 2).[8] The reactions gave exclusively the corresponding *cis*-β-lactams, **14** and **15**: **14** from **13a**, 20% yield, 67% e.e. (*3R,4S*); **14** from **13b**, 15% yield, 18% e.e. (*3S,4R*); **15** from **13c**, 25%, 20% e.e. (*3R,4S*).



(2)

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13a : R = $PhCH_2$; R* = (-) - N-methylephedrinyl
13b : R = $PhCH_2$; R* = (-) - menthyl
13c : R = Ph ; R* = (-) - N -methylephedrinyl

14 - 15

14 : R = $PhCH_2$
15 : R = Ph

Further studies on the mechanisms and applications of the chiral enolate - imine condensation are actively in progress.

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. The authors are grateful to Dr. Alan Schwartz, Hoffmann-La Roche, Inc., for his generous gift of (-)-trans-2-phenyl-1-cyclohexanol and (+)-trans-2-phenyl-1-cyclohexyl chloroacetate. Also, the author (I.O.) would like to thank Drs. Wayne Luke and Christina C. Bodurow, Lilly Research Laboratories for useful discussions.

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1. 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*, 770. (e) Ojima, I. In *"Asymmetric Reactions and Processes in Chemistry"*, Eliel, E. L.; Otsuka, S. Eds.; *Am. Chem. Soc., Symp. Series*, **1982**, *185*,109.

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4. The reactions of the corresponding zinc enolates have been extensively studied by van Koten et al., e.g., (a) van der Steen, F. H.; Kleijn, H.; Jastrzebski, J. T. B. H.; van Koten, G. *Tetrahedron Lett.*, **1989**, *30*, 765; (b) van der Steen, F. H.; Jastrzebski, J. T. B. H.; van Koten, G. *ibid*, **1988**, *29*, 2467; (c) Jastrzebski, J. T. B. H.; van der Steen, F. H.; van Koten, G. *Rec. Trav. Chim. Pays-Bas*, **1987**, *106*, 516. However, the best enantioselectivity so far attained in the zinc enolate - imine condensation process is 50% e.e. (Ref. 3c).

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7. For similar discussion in aldol reactions, see (b) Evans, D.A.; Sjogren, E.B.; Weber, A.E.; Conn, R.E. *Tetrahedron Lett.*, **1987**, *28*, 39; (c) Evans, D.A.; Nelson, J.V.; Taber, T.R. In *"Topics in Sterochemistry"*, Vol. 13, *"Stereoselective Aldol Condensations"*, ed. by Allinger, N.L.; Eliel, E.L.; Wilen, S.H. Wiley, New York (1982).

8. The reactions were carried out in a manner similar to those shown in Table 1 except the fact that the reaction mixture was stirred at -78°C for 4 h and then at -50°C for 48 h.

(Received in USA 19 April 1990; accepted 6 June 1990)