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FIRST SYNTHESIS OF OPTICALLY PURE α-AMINO AMINE AS ASYMMETRIC AMINO TRANSFER REAGENT AND ITS USE IN ASYMMETRIC MANNICH REACTION

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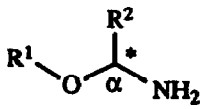
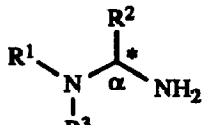
Summary: An optically pure α-amino amine was first synthesized from L-lysine utilizing anodic oxidation as a key step, and its usefulness was exemplified by the asymmetric Mannich reaction to give optically active β-amino acid esters.

Asymmetric transfer of amino group from amines substituted with chiral auxiliary is a convenient synthetic route to new optically active amino compounds[1] but there have been few methods to fulfill some conditions described below which would make this route more convenient. Namely, it is desirable from a synthetic viewpoint that starting optically active amines as sources of amino group are easily available or can be prepared with complete optical purity, the amino transfer reaction takes place efficiently, the removal of chiral auxiliary is easily achievable by simple procedures at the later stage of the transfer reaction sequence, and the chiral auxiliary is recovered after the amino transfer reaction. Such amino transfer reagents recently exploited are α-oxo amines **1** such as O-protected glycosylamines.[2] On view of the successful results using **1**, α-amino amines **2**, N-analogues of **1**, might be expected to be usable in a similar way as **1** or as more efficient amino transfer reagents than **1** because of the possibility of facile structural modification of **2**. There has been, however, no precedent of optically pure **2**. This paper presents a first synthesis of an optically pure α-amino amine which is easily prepared utilizing anodic oxidation and can be regenerated after amino transfer reaction.

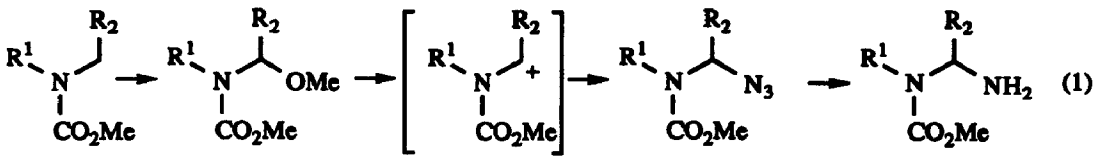


1



2

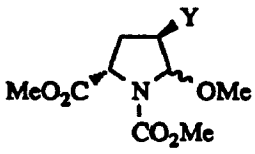
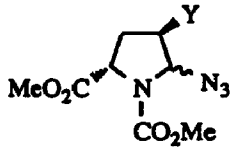
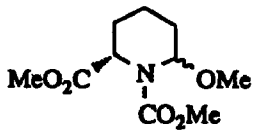
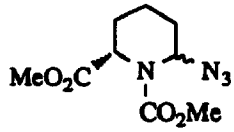
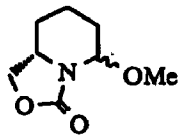
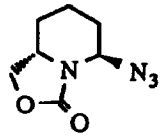
Our approach to prepare optically active **2** uses our previously reported anodic α-methoxylation of carbamates **3** which gives α-methoxylated carbamates **4**.[3] Lewis acid treatment of **4** in the presence of trimethylsilylazide followed by hydrogenation of the products, α-amino azides **6**, gave α-amino amines **7** (eq 1).



3 **4** **5** **6** **7** (1)

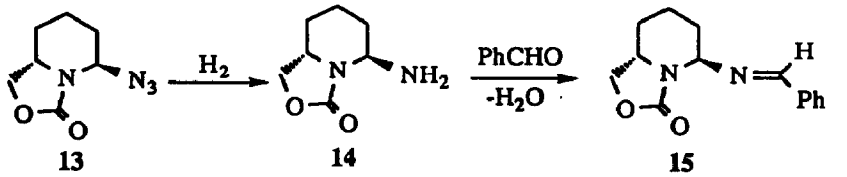
For the preparation of optically active **7**, we first studied the stereoselectivity in the introduction of azide group to acyliminium ions **5** since the stereochemistry of chiral α-carbon of **7** was determined at the stage of the introduction of azide group. The results concerned with anodically prepared α-methoxylated pyrrolidine and piperidine derivatives **8a-d**, **9**, and **10**[4] are shown in Table 1 which indicates that the introduction of azide group to acyliminium ions derived from piperidine ring stereoselectively took place (runs 5, 6), while the introduction to pyrrolidine ring was not stereoselective (runs 1-4).

Table 1. Diastereoselectivity of Introduction of Azide Group

run	α-Methoxylated Carbamates [a]		Products	Yields (%)	Diastereoselectivity [b] (%)
1		**8a** Y=H		**11a** (96) [c]	57/43
2		**8b** Y=OAc		**11b** (99) [c]	80/20
3		**8c** Y=OPiv		**11c** (76) [c]	81/19
4		**8d** Y=OSiMe$_2$t-Bu		**11d** (83) [c]	83/17
5		**9**		**12** (97) [d]	>95/5
6		**10**		**13** (87) [c]	100/0

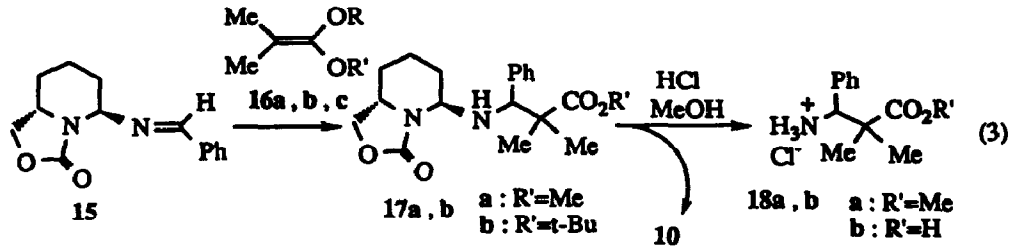
a) The stereochemistry was not determined. b) The ratio of diastereoisomers was determined by GLC or ^{1}H NMR.
c) $SnCl_4$ was used as Lewis acid. d) BF_3•OEt_2 was used.

Since we obtained a single stereoisomer **13**[5] from **10**, we tried the hydrogenation of **13** to get an optically pure α-amino amine **14**[5] (eq 2). The purity and absolute stereochemistry of thus obtained **14** were determined at the stage of the Schiff base **15**[5] which was prepared by condensation with benzaldehyde (eq 2). The result of X-ray analysis of **15** is shown in Fig. 1.[6]



13 **14** **15** (2)

As an application of this optically pure α-amino amine **14** to organic synthesis, we tried the asymmetric Mannich reaction since the reaction might afford pharmaceutically interesting optically active β-amino acid esters. Schiff base **15** derived from **14** smoothly reacted with dimethylketene silylacetal **16** in the presence of Lewis acid to give the coupling products **17** (eq 3). It was noticeable that acid treatment of **17** in methanol quantitatively regenerated **10** without any loss of the optical purity together with β-amino acid esters **18**. The results of the Mannich reaction carried out under a variety of conditions are summarized in Table 2 which shows enough high stereoselectivity (72-88% ee) in the Mannich reaction.



(3)

Table 2. The Mannich Reaction of **15** with **16**

run	Ketene Silylacetal 16	R	R'	Temp. (°C)	Solvent	Lewis Acid	Yield (%) of 17	ee (%) [a] of 18
1	**16a**	Me_3Si	Me	0	CH_2Cl_2	$ZnCl_2$	**17a** (23)	**18a** (72)
2	**16a**			0	Et_2O/CH_2Cl_2 [b]	$ZnCl_2$	**17a** (67)	**18a** (80)
3	**16a**			-78	Et_2O/CH_2Cl_2 [b]	$ZnCl_2$	**17a** (93)	**18a** (88)
4	**16a**			-78	CH_2Cl_2	$TiCl_4$	**17a** (79)	**18a** (80)
5	**16a**			-78	CH_2Cl_2	$BF_3{\cdot}OEt_2$	**17a** (50)	**18a** (85)
6	**16b**	t-$BuMe_2Si$	Me	0	Et_2O/CH_2Cl_2 [b]	$ZnCl_2$	**17a** (35)	**18a** (79)
7	**16c**	Me_3Si	t-Bu	0	Et_2O/CH_2Cl_2 [b]	$ZnCl_2$	**17b** (48)	**18b** (76)

a) The enantiomeric excess was determined by comparison of the optical rotation of the authentic **18a , b** (see ref. 2c).
b) Et_2O/CH_2Cl_2=1/3

On the bases of the absolute stereochemistry of **18** (the predominant isomer; *S* configuration), we can postulate an intermediate in the reaction of **15** with **16** as shown in Fig.2, in which **16** may preferentially approach from the sterically less hindered side, i.e. the *Re* side of the Schiff base which may be coordinated with metal of Lewis acid.

Although the application of amino transfer reaction using **14** to organic synthesis is at present only the Mannich reaction via **15**, the results shown in Table 1 and the reproducibility of **10** suggest that **14** is usable as efficient asymmetric amino transfer reagent. The structural modification of **14** to improve the stereoselectivity of the amino transfer reaction is now under the investigation.

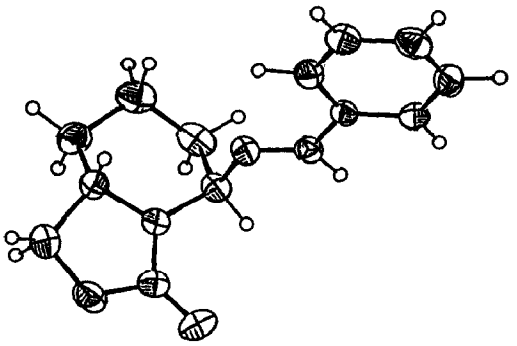


Fig.1 ORTEP Drawing of **15**

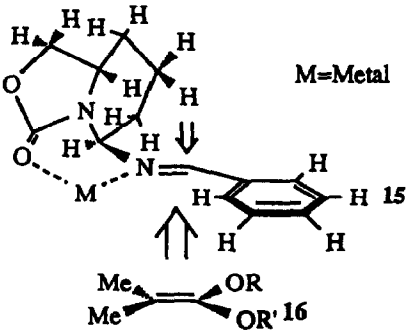


Fig.2 Plausible Intermediate in the Mannich Reaction

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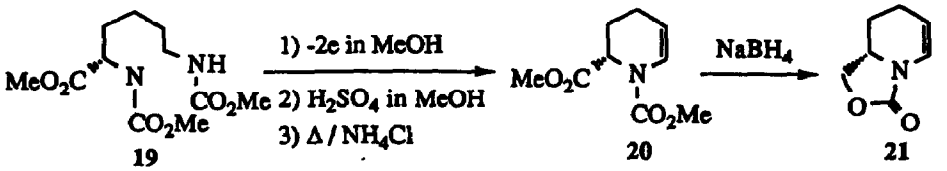
References and Notes

1.(a) Harada, K.; Matsumoto, K. *J.Org.Chem.*, **1968**, *33*, 4467. b) Frahm, Q.W.; Knupp, G. *Tetrahedron Lett.*, **1981**, *22*, 2633. c) Knupp, G.; Frahm, A.W. *Chem.Ber.*, **1984**, *117*, 2076. d) Shono, T.; Matsumura, Y.; Tsubata, K.; Sugihara, Y. *Nippon Kagaku Kaishi*, **1984**, 1782. e) Négrádi, M. "Stereoselective Synthesis" VCH, 1986, New York, Chap.2, pp 100-103.

2.(a) Kunz, H.; Sager, W. *Angew.Chem.Int.Ed.Engl.*, **1987**, *26*, 557. (b) Kunz, H.; Pfrengle, W. *Angew.Chem.Int.Ed.Engl.*, **1989**, *28*, 1068. (c) Kunz, H.; Rück, K. *Angew.Chem.Int.Ed.Eng.*, **1993**, *32*, 336. (d) Georg, G.I.; Akgün, E.; Mashava, P.M.; Milstead, M.; Ping, H.; Wu, Z.; Velde, D.V. *Tetrahedron Lett.*, **1991**, *33*, 2111.

3. (a) Shono, T.; Hamaguchi, H.; Matsumura, Y. *J.Am.Chem.Soc.*, **1975**, *97*, 4264. (b) Shono, T.; Matsumura, Y.; Tsubata, K. *Org. Synth.* **1984**, *63*, 206.

4. **8a** was prepared by a procedure described in the literature.[3b] **8b,c,d** were prepared by conventional methods (b; 90% by acetyl chloride with pyridine, c; 100% by pivaloyl chloride with 4-dimethylaminopyridine, d; 65% by *t*-butyldimethylsilyl chloride with imidazole) from methyl 4-hydroxy-1-methoxycarbonyl-5-methoxy-2-pyrrolidinecarboxylate which was anodically prepared from methyl 4-hydroxy-1-methoxycarbonyl-2-pyrrolidinecarboxylate (70%). The preparation of **9** and **10** from L-lysine derivative **19** was carried out as follows; anodic oxidation of **19** in methanol, acid treatment of the oxidation product in methanol, and heating the product, successively, gave enecarbamates **20** (40% overall yield). Addition of methanol to **20** (MeOH/*p*-TsOH) afforded **9** (80%), while the reduction of **20** with $NaBH_4$ in methanol followed by acid catalyzed addition of methanol to the reduction product **21** gave **10** (86%).



5. **13**; $[\alpha]_D^{20}$+48.10 (c=1.45 in MeOH), **14**; $[\alpha]_D^{20}$-5.36 (c=1.05 in MeOH), **15**; $[\alpha]_D^{20}$+8.40 (c=1.41 in $CHCl_3$).

6. Crystal data for **15**; mp 184°C; *M*=244.0, Orthorhombic, space group $P2_12_12_1$, *a*=10.382(2), *b*=11.871(3), *c*=10.362(3)Å, *V*=1277.1(5)Å^3, *Z*=4, *Dc*=1.27g/cm^3, and μ=0.50cm^{-1}. Atomic co-ordinates, bond lengths and angles, and thermal parameters have been deposited at the Cambridge Crystallographic Data Centre.

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