Asymmetric α-alkylation of α-amino esters using pyridoxal model compounds with a chiral ionophore function; dependence of stereoselectivity on a chelated metal ion

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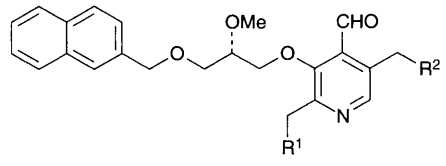
Asymmetric α-alkylation of α-amino esters by use of novel pyridoxal model compounds having a chiral ionophore function is studied; the stereoselectivity is specifically induced by Na^+ and the most effective asymmetric induction occurs with a combination of Na^+ and an additional chiral ansa-structure.

Both natural and unnatural optically active amino acids have increasingly attracted considerable attention from medicinal and biochemical points of view. Since a pyridoxal–pyridoxamine coenzyme plays an important role in the biosyntheses and metabolism of natural amino acids in living systems, artificially well-designed model compounds of this coenzyme are expected to be of great use for the syntheses of various kinds of α-amino acids. Much effort has been paid to these models, particularly ones with enantioface differentiation.[1–3] We designed the novel pyridoxal model compound **1** possessing a chiral and ionophore active side chain. Expecting double asymmetric induction,[4] (*R*)- and (*S*)-**2** having an additional chiral ansa-structure[1] were also designed. Here we describe the synthesis of these compounds and their application to asymmetric α-alkylation of α-amino esters into optically active α,α-dialkyl amino acids,[5] some of which are known to act as an enzyme-inhibitor[6] or to be a component of biologically active natural products.[7] The conformation of the peptide including particular α,α-dialkyl amino acids is reported to be stereochemically constrained.[8]

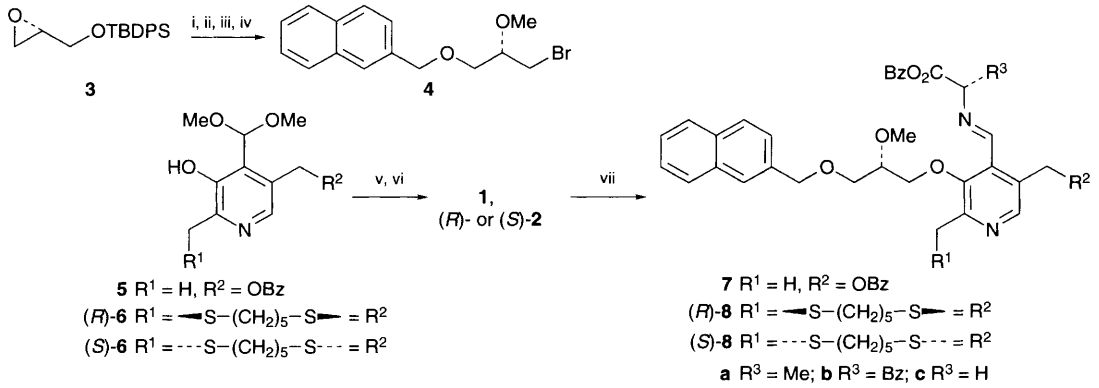
These model compounds were easily synthesized as shown in Scheme 1. Nucleophilic ring opening of the epoxide **3** with naphthalene-2-methanol followed by *O*-methylation, deprotection of the silyl group and bromination gave the sidechain **4**. Etherification of the pyridoxal moieties **5**, (*R*)- and (*S*)-**6** and deacetalization afforded the desired products **1**, (*R*)- and (*S*)-**2**. Treatment of these pyridoxal model compounds with α-amino acid benzyl esters afforded the corresponding aldimines **7**, (*R*)- and (*S*)-**8** respectively in almost quantitative yields.

We examined the α-alkylation of these aldimines **7** and **8** under several different conditions (Table 1).† In the reactions with **7a**, the best optical and chemical yields were obtained when sodium hydride (NaH) was used as a base (run 2), whilst, on treatment with lithium diisopropylamide (LDA) or potassium hydride (KH), both the chemical and optical yields of the alkylation product were much lower (runs 1 and 3). These results indicate that compound **7a** can actually recognize Na^+ among alkali metal ions and, as a consequence, the stereoselectivity has been induced. *p*-Nitrobenzylation also took place in good optical yield to afford **9b** (run 4), whilst **9c** was only obtained in a low optical yield (run 5). Interestingly, the other enantiomer (*S*)-**9a** was obtained in good optical yield by methylation of the aldimine **7b** (run 6). The enhancement of asymmetric induction was observed by combination with the chiral ansa-structure. Introduction of the *R*-bridge ansa-structure to **1** largely increased the optical yield (run 8). The sodium ion is important in this case as well (run 9), indicating that the chiral sidechain plays an important role in this stereoselective reaction. Although no such remarkable effect was observed in



1 R^1 = H, R^2 = OBz
(*R*)-**2** R^1 = ⁓S–$(CH_2)_5$–S⁓ = R^2
(*S*)-**2** R^1 = ---S–$(CH_2)_5$–S--- = R^2

Fig. 1 Pyridoxal model compounds



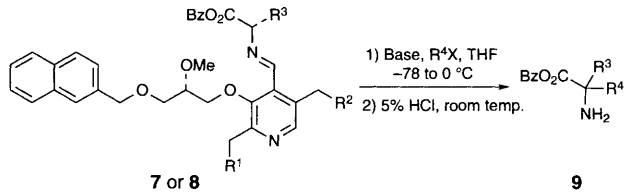
5 R^1 = H, R^2 = OBz
(*R*)-**6** R^1 = ⁓S–$(CH_2)_5$–S⁓ = R^2
(*S*)-**6** R^1 = ---S–$(CH_2)_5$–S--- = R^2

7 R^1 = H, R^2 = OBz
(*R*)-**8** R^1 = ⁓S–$(CH_2)_5$–S⁓ = R^2
(*S*)-**8** R^1 = ---S–$(CH_2)_5$–S--- = R^2
a R^3 = Me; **b** R^3 = Bz; **c** R^3 = H

Scheme 1 *Reagents and conditions*: i, naphthalene-2-methanol, tropylium tetrafluoroborate, $CHCl_3$, 70 °C, (74%); ii, NaH, MeI, THF, room temp., (97%); iii, $Bu_4N^+F^-$, THF, room temp. (99%); iv, NBS, PPh_3, CH_2Cl_2, room temp., (76%); v, NaH, **4**, DMF, 80 °C [72% from **5**, 93% from (*R*)-**6**, 88% from (*S*)-**6**]; vi, 60% AcOH, reflux [**1**: 87%, (*R*)-**2**: 93%, (*S*)-**2**: 90%]; vii, **a**: L-alanine benzyl ester, **b**: L-phenylalanine benzyl ester or **c**: glycine benzyl ester, CH_2Cl_2, room temp., (quant.)

p-nitrobenzylation (*cf.* runs 4 and 10), similar enhancement was gained in allylation and methylation of (*R*)-**8** (runs 11 and 12).

The CD spectra of the aldimine **7c** measured in the absence and presence of metal ions is shown in Fig. 2. Although there is no absorption of **7c** in the absence of metal ions, a remarkable spectral change was observed by addition of metal ions. This finding shows that the chiral environment accompanying the drastic conformational change was actually induced by the addition of metal ions. It is also evident from these spectra that the respective shapes of the metal-chelation structures of **7c** formed with Li^+ and Na^+ are quite different, which is probably attributable to the difference of their ion radii and/or coordination numbers. The metal ion is most likely to be captured between the imino ester moiety and the side chain at C-3 to give the metal enolate.[9]



7 or **8** **9**

Table 1 α-Alkylation of aldimines **7** and **8**

Run	Aldimine	R^3	Base	R^4X	**9**	Yield[a] (%)	ee[b] (%)	Config.[c]
1	**7a**	Me	LDA	BzBr	**a**	34	26	*R*
2	**7a**	Me	NaH	BzBr	**a**	58	86	*R*
3	**7a**	Me	KH	BzBr	**a**	28	7	*R*
4	**7a**	Me	NaH	*p*-NO_2BzBr	**b**	61	83	*R*
5	**7a**	Me	NaH	Allyl Br	**c**	48	17	*R*
6	**7b**	Bz	NaH	MeI	**a**	51	82	*S*
7	(*S*)-**8a**	Me	NaH	BzBr	**a**	40	8	*R*
8	(*R*)-**8a**	Me	NaH	BzBr	**a**	41	96	*R*
9	(*R*)-**8a**	Me	LDA	BzBr	**a**	32	55	*R*
10	(*R*)-**8a**	Me	NaH	*p*-NO_2BzBr	**b**	52	84	*R*
11	(*R*)-**8a**	Me	NaH	Allyl Br	**c**	39	82	*R*
12	(*R*)-**8b**	Bz	NaH	MeI	**a**	33	90	*S*

[a] Isolated yield of **9** from **7** or **8**. [b] The ee values were obtained from the ^{19}F or ^1H NMR spectra of the corresponding (*S*)-MTPA amide. [c] The stereochemistry of **9a** was determined by comparison of the optical rotation of the corresponding amino acid obtained by hydrolysis with that of the authentic sample (S. Terashima, K. Achiwa and S. Yamada, *Chem. Pharm. Bull.*, 1966, **14**, 1138). The stereochemistries of **9b** and **c** were assigned as indicated, respectively, by comparison of the ^{19}F and ^1H NMR spectra of the corresponding (*S*)-MTPA amide with those of the (*S*)-MTPA amide of **9a**.

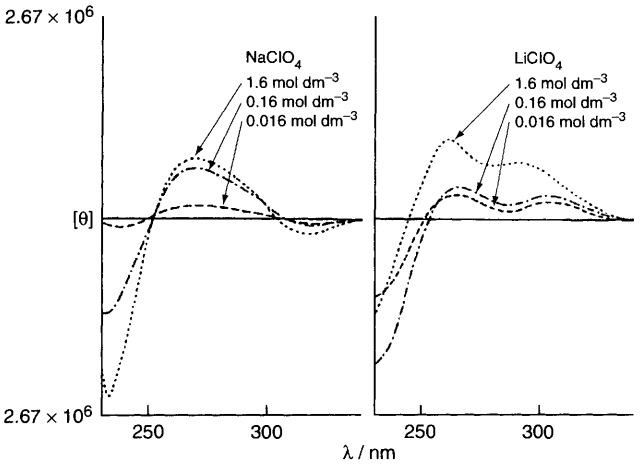


Fig. 2 CD spectra of 7c (0.16 mmol dm^{-3} in MeCN) measured in the presence of Na^+ and Li^+

Footnotes

† We studied the effect of the substituents of the glycerol sidechain on the stereoselectivity. The results will be discussed in the full article.

‡ The benzylation of the aldimine, prepared from **1** and D-alanine benzyl ester, was also examined and was found to afford a similar result to that obtained with the L-isomer.

References

1 For pyridoxal model compounds with an ansa-structure: M. Ando, J. Watanabe and H. Kuzuhara, *Bull. Chem. Soc. Jpn.*, 1990, **63**, 88; M. Ando and H. Kuzuhara, *Bull. Chem. Soc. Jpn.*, 1990, **63**, 1925 and references cited therein.

2 For pyridoxal model compounds with a cyclodextrin-moiety and/or an amino side chain: R. Breslow, J. Chmielewski, D. Foley, B. Johnson, N. Kumabe, M. Varney and R. Mehra, *Tetrahedron*, 1988, **44**, 5515 and references cited therein.

3 For pyridoxal model compounds with a functionalised bilayer vesicle: J. Kikuchi, Z.-Y. Zhang and Y. Murakami, *J. Am. Chem. Soc.*, 1995, **117**, 5383 and references cited therein.

4 For review: S. Masamune, W. Choy, J. S. Petersen and L. R. Sita, *Angew. Chem., Int. Ed. Engl.*, 1985, **24**, 1.

5 Recent review for asymmetric synthesis of α-amino acids by α-alkylation: M. J. O'Donnell, S. Wu and J. C. Huffman, *Tetrahedron*, 1994, **50**, 4507.

6 For example: W. S. Saari, W. Halczenko, D. W. Cochran, M. R. Dobrinska, W. C. Vincek, D. G. Titus, S. L. Gaul and C. S. Sweet, *J. Med. Chem.*, 1984, **27**, 713; W. S. Saari, M. B. Freedman, R. D. Hartman, S. W. King, A. W. Raab, W. C. Randall, E. L. Engelhardt, R. Hirschmann, A. Rosegay, C. T. Ludden and A. Scriabine, *J. Med. Chem.*, 1978, **21**, 746; K. Ramalingam and R. W. Woodard, *Tetrahedron Lett.*, 1985, **26**, 1135; J. J. Walsh, D. E. Metzler, D. Powell and R. A. Jacobson, *J. Am. Chem. Soc.*, 1980, **102**, 7136.

7 J. Shoji, H. Ninoo, T. Kato, K. Nakauchi, S. Matsuura, M. Mayama, Y. Yasuda and Y. Kawamura, *J. Antibiot.*, 1981, **34**, 374; K. Morimoto, N. Shimada, H. Naganawa, T. Takita and H. Umezawa, *J. Antibiot.*, 1981, **34**, 1615; K. Fukushima, T. Arai, Y. Mori, M. Tsuboi and M. Suzuki, *J. Antibiot.*, 1983, **36**, 1613; T. Mori, K. Takahashi, M. Kashiwabara, D. Uemura, C. Katayama, S. Iwadare, Y. Shizuri, R. Mitomo, F. Nakano and A. Matsuzaki, *Tetrahedron Lett.*, 1985, **26**, 1073.

8 P. K. C. Paul, M. Sukumar, R. Bardi, A. M. Piazzesi, G. Valle, C. Toniolo and P. Balaram, *J. Am. Chem. Soc.*, 1986, **108**, 6363 and references cited therein.

9 K. Miyashita, H. Miyabe, C. Kurozumi and T. Imanishi, *Chem. Lett.*, 1995, 487.

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