Pergamon

Tetrahedron 56 (2000) 4691–4700

TETRAHEDRON

Asymmetric α-Alkylation of α-Amino Esters Using Pyridoxal Derivatives Having a Chiral Ansa-Structure and a Chiral Ionophore Function: a Novel Example of Double Asymmetric Induction

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Received 27 March 2000; accepted 8 May 2000

Abstract—Stereoselective alkylation of aldimines, prepared from α-amino esters and a pyridoxal model having a chiral ansa-structure and an ethoxyethoxy group at C-3, proceeded in the presence of Li^+ to give α,α-dialkyl amino esters after acidic hydrolysis. Double asymmetric induction effect was also observed in the alkylation reaction by combination of the chiral ansa-structure and a chiral ionophore side chain at C-3.

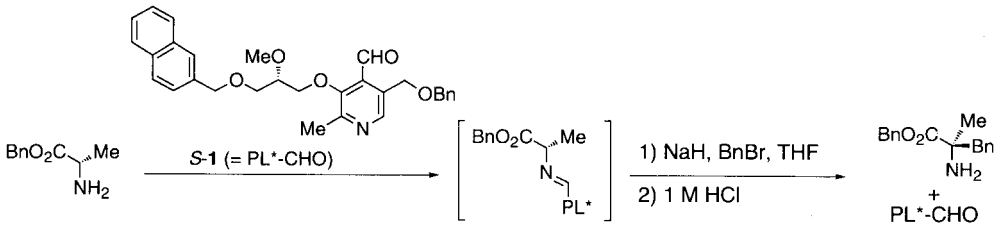
Introduction

α,α-Dialkyl amino acids have been attracting considerable attention from the viewpoints of biological and medicinal chemistry,[1] and extensive synthetic studies, particularly in an enantioselective manner, have been conducted.[2] As a pyridoxal–pyridoxamine system is closely involved in various biosynthetic and metabolic reactions of amino acids in a biological system, we focused on this system as a novel utility for the synthesis of unnatural amino acids in an artificial system. In a previous paper, we described asymmetric α-alkylation of an α-amino ester via aldimine by using pyridoxal model compound *S*-**1** having a chiral ionophore side chain at C-3 as shown in Scheme 1.[3] Among chiral pyridoxal models reported to date,[4] the model compound having a chiral ansa-structure introduced by Kuzuhara and coworkers is known to be very effective.[4a] We were interested in model compounds having a chiral ansa-structure as well as an ionophore side chain at C-3, in particular, those having two chiralities: a chiral ansa-structure and a chiral side chain and their ability as a chiral auxiliary. Here, we describe synthesis of **2A** and **B**, each having achiral and chiral side chains at C-3, and α-alkylation of α-amino esters by using these compounds (Fig. 1).[5]

Results

Syntheses of the pyridoxal derivatives

Syntheses of the pyridoxal derivatives **2A** and **B** were achieved as follows. Racemic pyridoxal **3** was prepared and optically resolved according to the literature[6] with some modification as shown in Scheme 2. The *S*-isomer S_{ansa}-**3** was reportedly obtained by recrystallization of a diastereomeric mixture of aldimine **5** which had been prepared from racemic **3** and aminoglycoside **4** derived from D-glucose. In contrast, the residue obtained from the



Scheme 1.

Keywords: amino acids and derivatives; alkylation; asymmetric reactions; ansa compounds; pyridines.
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PII: S0040-4020(00)00392-6

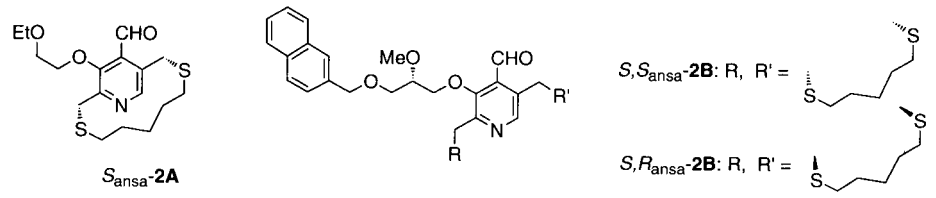
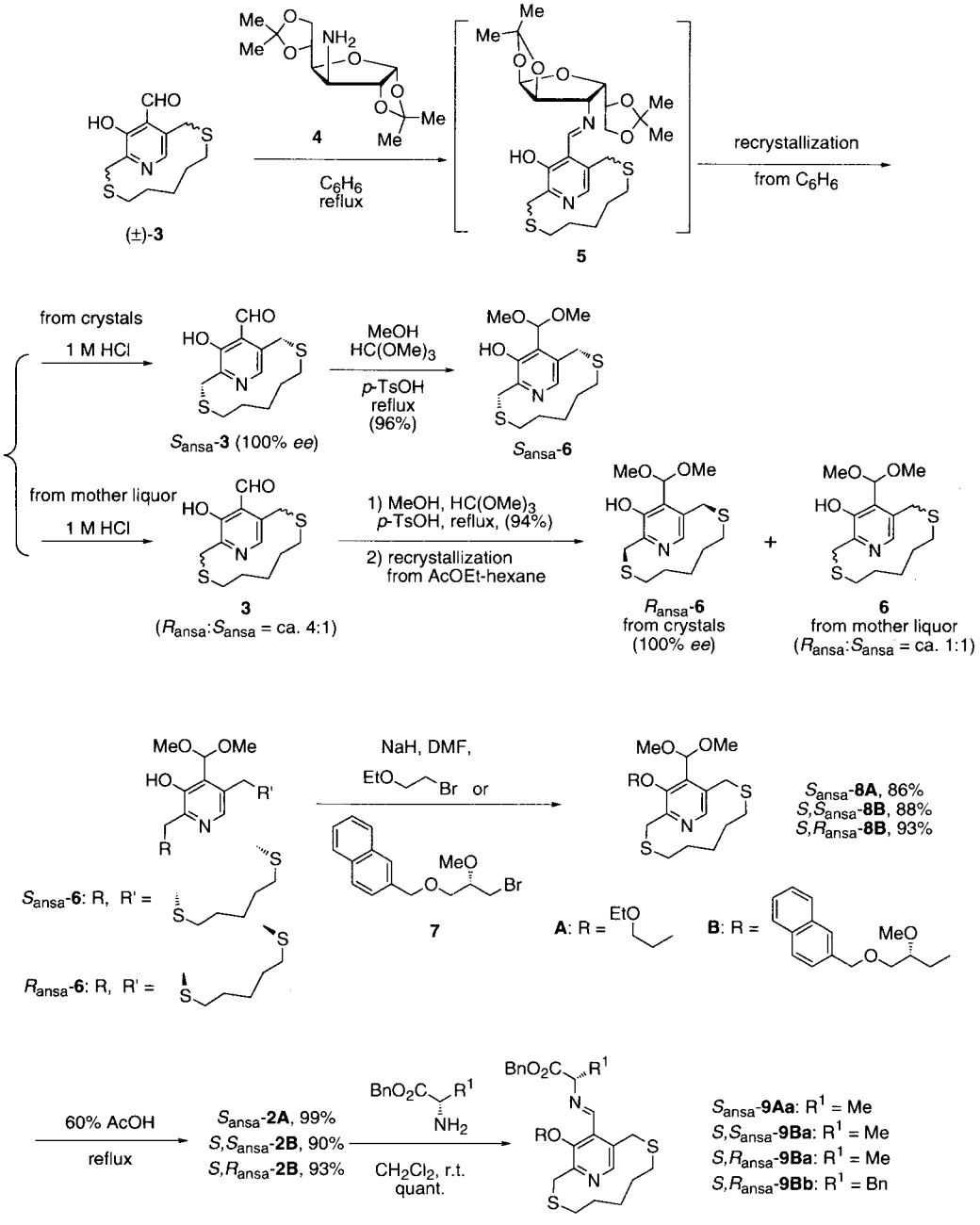


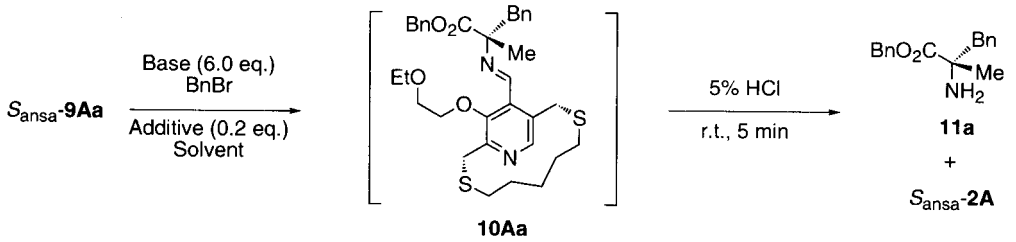
Figure 1. Structures of pyridoxal derivatives **2**.

mother liquor was hydrolyzed and acetalized to give acetal **6**, which was recrystallized to give optically pure *R*-isomer R_{ansa}-**6** as crystals. The aldehyde *S*-**3** obtained by hydrolysis of the recrystallized **5** was also acetalized to give S_{ansa}-**6**. The hydroxyl group of optically resolved acetals S_{ansa}- and R_{ansa}-**6** was alkylated with 2-ethoxyethyl bromide or bromide **7** to give S_{ansa}-**8A**, S,S_{ansa}- and S,R_{ansa}-**8B**. Hydrolysis of these compounds by acidic treatment afforded the pyridoxals S_{ansa}-**2A**, S,S_{ansa}- and S,R_{ansa}-**2B** having a chiral ansa-structure. These compounds were found to be optically



Scheme 2.

Table 1. Benzylation of aldimine S_{ansa}-**9Aa**



Run	Reaction conditions					Amino ester **11a**		
	Base	Additive	Solvent	Temp. (°C)	Time (h)	Isolated yield (%)[a]	ee (%)	Config.
1	LiOH	–	CH_2Cl_2	Room temperature	3	77	76	*S*
2	NaOH	–	CH_2Cl_2	Room temperature	3	29	22	*S*
3	KOH	–	CH_2Cl_2	Room temperature	3	Trace	–	–
4	LiOH	$BnEt_3N^+Cl^-$	CH_2Cl_2	Room temperature	1	46	55	*S*
5	LiOH	12-crown-4	CH_2Cl_2	Room temperature	1.5	59	52	*S*
6	LDA	–	THF	−78	20	Trace	–	–
7	NaH	–	THF	−78	20	39	42	*S*

[a] Yields were based on L-Ala-OBn.

pure by analyzing the ^{1}H NMR spectra of the corresponding aldimines **9Aa** and **9Ba** prepared from L-Ala-OBn.[7]

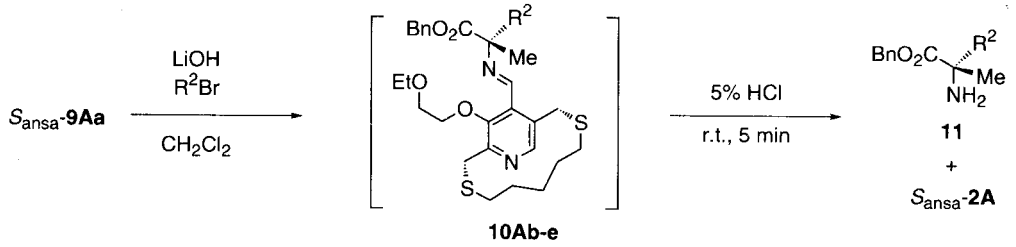
α-Alkylation of aldimines

At first, we examined the stereoselectivity induced by the chiral ansa-structure alone and the results are shown in Table 1. The aldimine S_{ansa}-**9Aa** prepared from S_{ansa}-**2A** having a chiral ansa-structure and an ethoxyethoxy group at C-3 was benzylated under various conditions of a two-phase system (Runs 1–5). In the absence of a phase transfer catalyst (Runs 1–3), the reaction largely depended on the kind of alkali metal hydroxide and that with LiOH afforded the best result in both chemical and optical yields (Run 1),[8] showing that the Li^+ is specifically chelated between the ethoxyethoxy group and the imino ester moiety as expected from our previous result.[9] The reaction proceeded in the presence of a phase transfer catalyst such as a quaternary ammonium salt or a crown ether; however, both chemical and optical yields of the reactions were poor (Runs 4 and 5). Although the reason is not clear, the reaction with NaH or LDA in THF was much less effective (Runs 6 and 7). These results suggest that the stereoselectivity is closely related to the formation of the chelation structure. It was also found that the S_{ansa}-structure prefers *S*-stereoselectivity regardless of the kind of alkali metal ion. Reactions with other alkyl bromides under the conditions of Run 1 in Table 1 also took place to give the products with moderate stereoselectivity as shown in Table 2.

As reported in a previous paper, the compound *S*-**1** having a chiral center at the ionophore side chain had been found to give *R*-stereoselectivity (Scheme 1) in the same reaction.[3] Therefore, it was easily predictable that, if double asymmetric induction is available in this system, a combination of the R_{ansa}(S_{ansa})-structure with the *S*(*R*)-chiral side chain would be a matched pair, while that of S_{ansa}(R_{ansa})-structure with *S*(*R*)-chiral side chain would be mismatched. The results are summarized in Table 3.

As expected, benzylation of *S*,S_{ansa}-**9Ba** proceeded in very poor stereoselectivity (Run 1), while that of *S*,R_{ansa}-**9Ba**

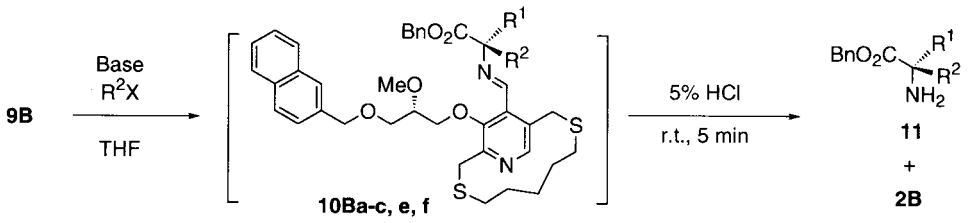
Table 2. Alkylation of aldimine S_{ansa}-**9Aa**



Run	Reaction conditions			Amino ester **11b–e**			
	R^2Br	Temp. (°C)	Time (h)	Product **11**	Isolated yield (%)[a]	ee (%)	Config.
1	4-$O_2NC_6H_4CH_2Br$	0	3	**b**	63	68	*S*
2	CH_2=$CHCH_2Br$	0	3	**c**	66	66	*S*
3	HC≡CCH_2Br	−15	7	**d**	83	66	*S*
4	$BrCH_2CO_2Et$	−15	7	**e**	60	52	*S*

[a] Yields were based on L-Ala-OBn.

Table 3. Alkylation of aldimine **9B**



Run	Aldimine	R^1	R^2X	Base	Amino ester **11**			
					Product **11**	Isolated yield (%)[a]	ee (%)	Config.
1	S,S_{ansa}-**9Ba**	Me	BnBR	NaH	**a**	40	8	*R*
2	S,R_{ansa}-**9Ba**	Me	BnBR	NaH	**a**	41	96	*R*
3	S,R_{ansa}-**9Ba**	Me	BnBR	LDA	**a**	32	55	*R*
4	S,R_{ansa}-**9Ba**	Me	$4\text{-}O_2NC_6H_4CH_2Br$	NaH	**b**	52	84	*R*
5	S,R_{ansa}-**9Ba**	Me	$CH_2{=}CHCH_2Br$	NaH	**c**	39	82	*R*
6	S,R_{ansa}-**9Ba**	Me	$BrCH_2CO_2Et$	NaH	**e**	70	30	*R*
7	S,R_{ansa}-**9Ba**	Me	$Me_2C{=}CHCH_2Br$	NaH	**f**	40	90	*R*
8	S,R_{ansa}-**9Bb**	Bn	MeI	NaH	**a**	33	90	*S*

[a] Yields were based on L-Ala-OBn (runs 1–7) and L-Phe-OBn (run 8).

gave good stereoselectivity (Run 2). It was also shown that combination of the metal ion with the chiral side chain, not the ansa-structure, forms a significant chiral element and is important for stereoselectivity (Run 2 vs. 3). Alkylation of S,R_{ansa}-**9Ba** with other alkyl bromides also took place in a similar stereoselective manner (Runs 4–7), but the stereoselectivity of the reaction with ethyl bromoacetate was unexpectedly low (Run 6). Methylation of S,R_{ansa}-**9Bb** also proceeded to give an enantiomeric **11a** with a slightly lower stereoselectivity compared with that of Run 2.

Discussion

Double asymmetric induction includes two possibilities: (i) a substrate and a reagent each bear one asymmetric element; (ii) a single partner, a substrate or a reagent, bears two asymmetric elements. Although a number of examples corresponding to the former possibility are known, the reported examples clearly demonstrating the latter possibility are much fewer. This apparently can be explained as follows. For instance, when the diastereofaces of I and II are differentiated similarly by the respective chiral elements, A^* and B^*, as shown in Fig. 2, it would be easily understood that the diastereoface of III having two chiral elements A^* and B^* in proximity to each other is not anticipated to be differentiated more effectively. This is because, in the case of III, two close chiral elements A^* and B^* would interact each other and, consequently, could have caused a conformational change. Therefore, such a simple system like III, a combination of I and II, cannot be a double asymmetric induction system, which is critically different from the former possibility and making the latter case ambiguous and difficult to predict. Indeed, a number of stereoselective reactions which involve a substrate or a reagent having more than two stereogenic centers are known, but the relation of each stereogenic center with the stereoselectivity has not been verified, and only a few examples clearly showing that two different asymmetric elements in a substrate or a reagent cooperatively increase the stereoselectivity have been reported to date. To the best of our knowledge, the most general double asymmetric induction corresponding to the latter case was observed in the compounds having a C_2-symmetrical structure as a common feature (IV in Fig. 2).[10]

In the present case, it is quite unique that our model compounds have a central chirality and a planar chirality.

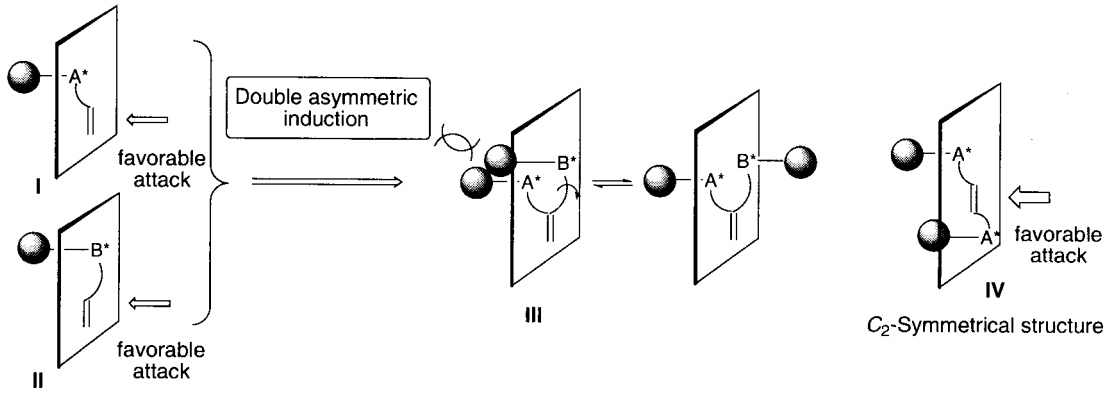


Figure 2. Schematic representation of double asymmetric induction.

Table 4. Selected stereoselectivities (ee % and Config.) for alkylations with the pyridoxal derivations **1** and **2**

R-X	Pyridoxal derivations			
	S-**1**	S_{ansa}-**2A**	S,S_{ansa}-**2B**	S,R_{ansa}-**2B**
BnBr	86 (*R*)	76 (*R*)	8 (*R*)	96 (*R*)
$CH_2{=}CHCH_2Br$	17 (*R*)	66 (*R*)	-	82 (*R*)
$BrCH_2CO_2Et$	78 (*R*)	52 (*S*)	-	30 (*R*)

For comparison, some typical results obtained by using these compounds having a chiral side chain and/or a chiral ansa-structure are summarized in Table 4. It is, as expected, shown that a combination of the *S*-chiral side chain and the R_{ansa}-structure is a matched pair, while that of the *S*-chiral side chain and the S_{ansa}-structure is a mismatched pair. This phenomenon is remarkable, particularly in the reactions with allyl bromide. In contrast, the reaction with ethyl bromoacetate was an exceptional example, in which the stereoselectivity obtained by S,R_{ansa}-**3** was much less than those obtained by *S*-**1** and S_{ansa}-**2**. Although the reason is not clear, this could be attributable to the fact that coordination of the ester function with Na^+ could change the chiral environment produced by the chiral side chain and Na^+.

A possible reaction mechanism is proposed in Fig. 3. The fact that the conformation of the imino ester moiety is

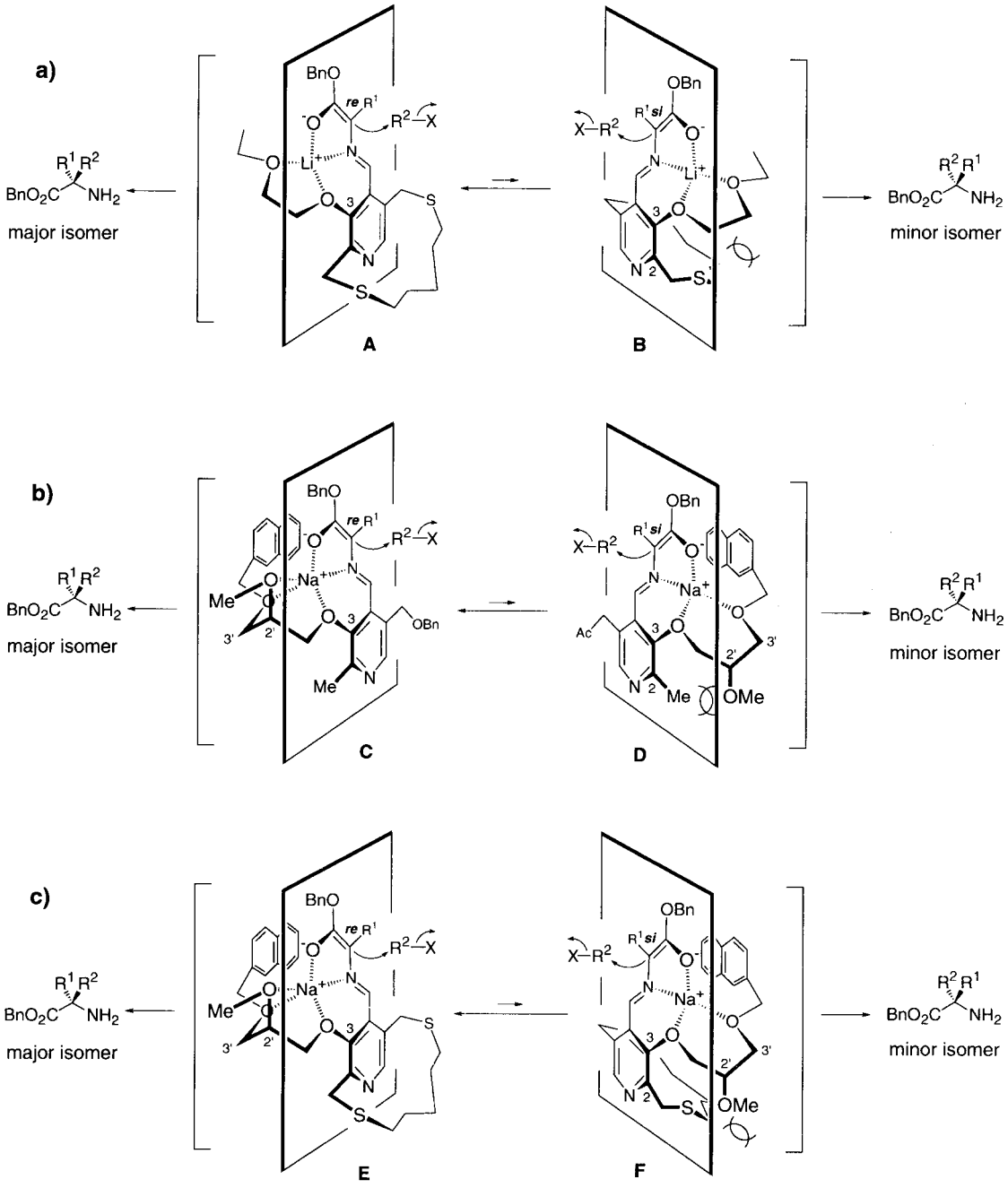


Figure 3. Possible transition states for asymmetric α-alkylation with R_{ansa}-**2A**, *S*-**1** and S,R_{ansa}-**2B**.

fixed in the direction of the ethoxyethoxy group at C-3 to chelate Li^+ and that *S*-stereoselectivity was obtained by using a compound having an S_{ansa}-structure suggests that the alkylation proceeds from the side of the ansa-chain.[11] It has been reported that a tetra-coordinated Li^+ favors a tetrahedral structure rather than a planar square structure,[12] which suggests that the ansa-chain works as a steric barrier not for an alkylating agent but for the chelation with the ethoxyethoxy group and, consequently, would allow the chelation structure to form in another side of the ansa-chain.[13] Taking these factors into account, a mechanism for this stereoselective alkylation with the R_{ansa}-isomer could be proposed as shown in Fig. 3a.[14] In the transition state **A**, the terminal ethyl group of the ethoxyethoxy group would appear to be responsible for the stereoselectivity, preventing the electrophile from approaching from the other side of the ansa-chain. Concerning the stereoselective alkylation with the compound having a chiral side chain in the presence of Na^+, we proposed the mechanism shown in Fig. 3b, as reported in a previous paper.[3] In this reaction, the chiral environment is specifically constructed by formation of the chelation structure with the chiral side chain and Na^+, not Li^+: the methoxy group at C-2′ apparently plays a crucial role and, eventually, the terminal naphtyl group is thought to block the *si*-face as shown.

It would be easily noted that these transition states **A**–**D** shown in Fig. 3a and b clearly explain the double asymmetric induction observed by employing the model compound *S*,R_{ansa}-**2B** having both chiral elements. In the transition state **E**, the two chiral elements, the R_{ansa}-structure and the *S*-chiral center in the ionophore side chain, are a matched pair and would cooperatively stabilize the formation of the chelation structure at the other side of the ansa-loop, which consequently would block the *si*-face more effectively than does each chiral element as represented by the transition states **A** and **B**, respectively.

In conclusion, we have demonstrated asymmetric α-alkylation of α-amino esters by using chiral pyridoxal model compounds, which is a clear example of double asymmetric induction caused by a substrate having two chiral elements. The present example has a characteristic feature in that one chiral element is a stereogenic center (chiral side chain) which forms a chiral environment by chelating a specific metal ion (Na^+), and the other is a molecular asymmetry (ansa-structure). This methodology would be of great use for designing and developing a novel chiral auxiliary not only in the present pyridoxal system but also in other systems.[15]

Experimental

General

Melting points (mps) were taken on a Yanagimoto micro-melting point apparatus and are uncorrected. Infrared spectra were measured on a JASCO FT/IR-200 Fourier-transfer infrared spectrometer. ^{1}H NMR spectra were measured on a JEOL GX-500 (500 MHz) or a Varian VXR-200 (200 MHz) spectrometer and tetramethylsilane (TMS) was used as an internal standard. ^{13}C NMR spectra were measured on a Varian VXR-200 (50.3 MHz) with $CDCl_3$ as an internal standard (77.0 ppm). Low and high resolution mass spectra (EI-MS and HR-MS) were obtained by use of a JEOL D-300 mass spectrometer; $[\alpha]_D$ values were obtained on a JASCO DIP-370 polarimeter. For silica gel and aminopropylsilica gel column chromatography, E. Merck Kieselgel 60 (0.063–0.200 mm) and Fuji Silysia Chemical Ltd. NH-DM1020 (100–200 mesh) were used, respectively.

(S_{ansa})- and (R_{ansa})-14-Hydroxy-15-dimethoxymethyl-2,5-dithian[9]-(2,5)pyridinophane (S_{ansa}- and R_{ansa}-6). A mixture of (±)-**3** (5.57 g, 19.7 mmol) and amino sugar **4** (6.12 g, 23.6 mmol) in benzene (495 ml) was refluxed with a Dean–Stark trap for 2 h and the reaction mixture was cooled at ambient temperature. The crystalline precipitate was collected by filtration and washed with a small portion of benzene to give a diastereomerically pure S_{ansa}-**5** (3.92 g, 38%) as colorless crystals, mp 250–251°C (lit.[6] 249–251°C). The filtrate was concentrated under reduced pressure and the resultant residue was dissolve in dioxane (240 ml) and 1 M HCl (50 ml). After being stirred at room temperature for 4 h, the reaction mixture was diluted with water, neutralized to pH 4 with saturated $NaHCO_3$ solution, and extracted with $CHCl_3$. The organic layer was dried and concentrated to give crude aldehyde S_{ansa}-**3**, which was treated with trimethyl orthoformate (60 ml) and *p*-TsOH·H_2O (449 mg, 2.4 mmol) under reflux for 20 h. The reaction mixture was concentrated, chromatographed with silica gel (ethyl acetate/hexane=1:2) to give dimethyl acetal (*R*:*S*=ca. 4:1), which was recrystallized with ethyl acetate-hexane to give enantiomerically pure dimethyl acetal R_{ansa}-**6** as colorless needles.

The aldimine S_{ansa}-**5** obtained above was hydrolyzed according to the same procedure as described above to give the aldehyde S_{ansa}-**3**. A solution of compound S_{ansa}-**3** (2.25 g, 7.95 mmol) and a catalytic amount of *p*-TsOH·H_2O in MeOH (50 ml) and trimethyl orthoformate (10 ml) was refluxed for 12 h. After concentration under reduced pressure, the residue was neutralized with saturated $NaHCO_3$ solution and extracted with ethyl acetate. The organic phase was washed with H_2O and saturated NaCl solution, dried over $MgSO_4$, and concentrated under reduced pressure. The resultant residue was purified by silica gel column chromatography (ethyl acetate/hexane=1:2) to afford the acetal S_{ansa}-**6** (2.52 g, 96%) as colorless crystals.

S_{ansa}-6. Mp 112–113°C (ethyl acetate/hexane). $[\alpha]_D^{24}$=−252.4 (*c* 1.00, MeOH). IR ν (KBr): 3298, 2925, 2843 cm^{-1}. ^{1}H NMR ($CDCl_3$) δ: 0.55 (1H, m, ansa-chain H), 0.7–1.0 (4H, m, ansa-chain H), 1.05 (1H, m, ansa-chain H), 2.0–2.2 (2H, m, ansa-chain H), 2.4–2.6 (2H, m, ansa-chain H), 3.24, 3.66 (each 3H, s, OMe), 3.58, 4.39 (each 1H, d, *J*=12.3 Hz, benzylic H), 3.62, 3.92 (each 1H, d, *J*=13.5 Hz, benzylic H), 6.12 (1H, s, $CH(OMe)_2$), 8.01 (1H, s, 6-H), 9.08 (1H, s, OH). ^{13}C NMR ($CDCl_3$) δ: 24.8, 27.9, 28.5, 29.9, 31.1, 31.8, 51.0, 55.9, 102.2, 125.4, 130.5, 142.4, 147.8, 151.1. EI-MS *m*/*z* (%): 329 (M^+, 18), 164 (100). Anal. Calcd for $C_{15}H_{23}NO_3S_2$: C, 54.68; H, 7.04; N, 4.25; S 19.46. Found: C, 54.63; H, 6.84; N, 4.20; S, 19.27.

R_{ansa}-6. Mp 112–113°C (ethyl acetate/hexane). $[\alpha]_D^{21}$=253.1 (*c* 1.00, MeOH).

O-Alkylation of the compound 6

To a stirred DMF (10 ml) suspension of NaH (60% in oil, 349 mg, 8.73 mmol), which had been washed with pentane three times and dried under vacuum before use, was added a solution of **6** (2.52 g, 7.94 mmol) in DMF (20 ml) at room temperature, then the whole was stirred at the same temperature for 1 h. Subsequent to the addition of a solution of 2-ethoxyethyl bromide (1.06 ml, 9.53 mmol) or bromide **7**[3] (2.94 g, 9.53 mmol) in DMF (10 ml), the reaction mixture was stirred at 80°C for 4 h, then extracted with ether and water. The combined ethereal layer was washed with 1 M NaOH solution and worked up as usual. The residue was purified by silica gel column chromatography (ethyl acetate/hexane=1:1) to give **8**.

(S_{ansa})-14-(2-Ethoxyethoxy)-15-dimethoxymethyl-2,5-dithian[9]-(2,5)pyridinophane (S_{ansa}-8A). 86% Yield, a colorless oil, $[\alpha]_D^{22}=-215.9$ (*c* 1.03, MeOH). IR ν (KBr): 2967, 2925, 2865 cm^{-1}. ^1H NMR ($CDCl_3$) δ: −0.34 (1H, m, ansa-chain H), 0.8–1.0 (2H, m, ansa-chain H), 1.0–1.2 (3H, m, ansa-chain H), 1.28 (3H, t, *J*=6.9 Hz, OCH_2CH_3), 2.01 (1H, m, ansa-chain H), 2.3–2.5 (2H, m, ansa-chain H), 2.6–2.8 (1H, m, ansa-chain H), 3.37, 3.54 (each 3H, s, OMe), 3.52, 4.51 (each 1H, d, *J*=13.9 Hz, benzylic H), 3.63 (2H, q, *J*=6.9 Hz, OCH_2CH_3), 3.82, 4.20 (each 1H, d, *J*=12.2 Hz, benzylic H), 3.7–3.9 (2H, m, OCH_2CH_2OEt), 4.03, 4.40 (each 1H, m, OCH_2CH_2OEt), 5.79 (1H, s, $CH(OMe)_2$), 8.61 (1H, s, 6-H). ^{13}C NMR ($CDCl_3$) δ: 15.0, 23.9, 25.7, 28.1, 28.3, 29.3, 30.6, 32.9, 55.4, 56.1, 66.4, 69.1, 75.4, 100.8, 134.7, 138.5, 148.9, 149.21, 149.7. EI-MS *m/z* (%): 401 (M^+, 4.9), 59 (100). High-resolution MS Calcd for $C_{19}H_{31}NO_4S_2$: 401.1690, Found: 401.1691.

(S,S_{ansa})-14-[2-methoxy-3-(2-naphthylmethoxy)propoxy]-15-dimethoxymethyl-2,5-dithian[9]-(2,5)pyridinophane (S,S_{ansa}-8B). 88% Yield, a colorless oil, $[\alpha]_D^{28}=-147.2$ (*c* 1.00, MeOH). IR ν (KBr): 2924, 1602, 1554, 1509 cm^{-1}. ^1H NMR ($CDCl_3$) δ: −0.35 (1H, m, ansa-chain H), 0.85 (2H, m, ansa-chain H), 1.0–1.2 (3H, m, ansa-chain H), 1.99 (1H, m, ansa-chain H), 2.3–2.5 (2H, m, ansa-chain H), 2.68 (1H, m, ansa-chain H), 3.31, 3.46, 3.55 (each 3H, s, OMe), 3.52, 4.48 (each 1H, d, *J*=14.1 Hz, benzylic H), 3.7–3.8 (3H, m, side chain 2-H, side chain 3-H), 3.78, 4.12 (each 1H, d, *J*=12.0 Hz, benzylic H), 4.04 (1H, dd, *J*=3.9, 9.8 Hz, side chain 1-H), 4.30 (1H, dd, *J*=5.5, 9.8 Hz, side chain 1-H), 4.77 (2H, s, benzylic H), 5.67 (1H, s, $CH(OMe)_2$), 7.42–7.52 (3H, m, aromatic H), 7.76–7.88 (4H, m, aromatic H), 8.60 (1H, s, 6-H). ^{13}C NMR ($CDCl_3$) δ: 24.0, 26.0, 28.4, 28.5, 29.5, 30.7, 33.1, 55.5, 56.2, 57.9, 68.3, 73.5, 75.0, 78.9, 101.0, 125.5, 125.7, 125.9, 126.3, 127.4, 127.6, 128.0, 132.8, 133.0, 134.8, 135.1, 138.6, 149.1, 149.3, 149.8. EI-MS *m/z* (%): 557 (M^+, 9.4), 141 ($NaphCH_2^+$, 100). High-resolution MS Calcd for $C_{30}H_{39}NO_5S_2$: 557.2270, Found: 557.2270.

(S,R_{ansa})-14-[2-methoxy-3-(2-naphthylmethoxy)propoxy]-15-dimethoxymethyl-2,5-dithian[9]-(2,5)pyridinophane (S,R_{ansa}-8B). 93% Yield, colorless crystals, mp 71–72°C (ethyl acetate/hexane). $[\alpha]_D^{27}=+170.4$ (*c* 1.00, MeOH). IR ν (KBr): 2925, 1602, 1550, 1509 cm^{-1}. ^1H NMR ($CDCl_3$) δ: −0.36 (1H, m, ansa-chain H), 0.85 (2H, m, ansa-chain H), 1.0–1.2 (3H, m, ansa-chain H), 1.98 (1H, m, ansa-chain H), 2.3–2.5 (2H, m, ansa-chain H), 2.67 (1H, m, ansa-chain H), 3.37, 3.45, 3.57 (each 3H, s, OMe), 3.52, 4.99 (each 1H, d, *J*=13.7 Hz, benzylic H), 3.7–3.8 (3H, m, side chain 2-H, side chain 3-H), 3.81, 4.19 (each 1H, d, *J*=12.0 Hz, benzylic H), 3.98 (1H, dd, *J*=6.0, 10.3 Hz, side chain 1-H), 4.42 (1H, dd, *J*=3.4, 10.3 Hz, side chain 1-H), 4.75, 4.76 (2H, AB q, *J*=10.5 Hz, benzylic H), 5.68 (1H, s, $CH(OMe)_2$), 7.42–7.50 (3H, m, aromatic H), 7.76–7.85 (4H, m, aromatic H), 8.60 (1H, s, 6-H). ^{13}C NMR ($CDCl_3$) δ: 24.2, 26.2, 28.7, 29.8, 31.0, 33.4, 55.6, 56.4, 58.4, 68.5, 73.7, 75.8, 79.3, 101.2, 125.7, 126.0, 126.2, 126.6, 127.7, 127.8, 128.2, 133.0, 133.2, 135.0, 135.3, 138.8, 149.4, 149.6, 150.2. EI-MS *m/z* (%): 557 (M^+, 11), 141 ($NaphCH_2^+$, 100). Anal. Calcd for $C_{30}H_{39}NO_5S_2$: C, 64.60; H, 7.05; N, 2.51; S, 11.50. Found: C, 64.45; H, 7.03; N, 2.50; S, 11.42.

(*S*)-14-Ethoxyethoxy-2,5-dithian[9]-(2,5)pyridinophane-15-carbaldehyde (S_{ansa}-2A). A solution of S_{ansa}-**8A** (2.66 g, 6.35 mmol) in acetic acid/water (3:2, 16 ml) was stirred at 100°C for 12 h. Subsequent to the neutralization with a saturated $NaHCO_3$ solution, the reaction mixture was extracted with ethyl acetate. The ethyl acetate layer was worked up as usual and the resultant residue was purified by silica gel column chromatography (ethyl acetate/hexane=1:1) to give S_{ansa}-**2A** (2.25 g, 99%) as colorless crystals, mp 67–68°C (ether/hexane). $[\alpha]_D^{22}=-25.1$ (*c* 1.01, $CHCl_3$). IR ν (KBr): 2972, 2924, 2868, 1697 cm^{-1}. ^1H NMR ($CDCl_3$) δ: 0.5–0.9 (5H, m, ansa-chain H), 1.07 (1H, m, ansa-chain H), 1.21 (3H, t, *J*=7.3 Hz, OCH_2CH_3), 2.0–2.3 (2H, m, ansa-chain H), 2.35 (1H, m, ansa-chain H), 2.5–2.6 (1H, m, ansa-chain H), 3.50, 4.37 (each 1H, d, *J*=13.0 Hz, benzylic H), 3.54 (2H, q, *J*=7.3 Hz, OCH_2CH_3), 3.71, 4.63 (each 1H, d, *J*=12.8 Hz, benzylic H), 3.7–3.8 (2H, m, OCH_2CH_2OEt), 4.1–4.2 (2H, m, OCH_2CH_2OEt), 8.43 (1H, s. 6-H), 10.43 (1H, s, CHO). ^{13}C NMR ($CDCl_3$) δ: 15.0, 24.4, 28.5, 28.6, 29.5, 29.9, 30.5, 32.6, 66.7, 69.0, 76.7, 133.5, 135.0, 147.6, 153.6, 155.5, 192.1. EI-MS *m/z* (%): 355 (M^+, 62), 182 (100). Anal. Calcd for $C_{17}H_{25}NO_3S_2$: C, 57.43; H, 7.09; N, 3.94; S, 18.04. Found: C, 57.26; H, 7.00; N, 3.97; S, 17.81.

The aldehydes S,S_{ansa}- and S,R_{ansa}-**2B** were obtained similarly.

(S,S_{ansa})-14-[2-methoxy-3-(2-naphthylmethoxy)propoxy]-2,5-dithian[9]-(2,5)pyridinophane-15-carbaldehyde (S,S_{ansa}-2B). 90% Yield, colorless crystals, mp 68–69°C (ethyl acetate/hexane). $[\alpha]_D^{26}=+0.96$ (*c* 1.00, $CHCl_3$). IR ν (KBr): 2924, 1700, 1602, 1546, 1507 cm^{-1}. ^1H NMR ($CDCl_3$) δ: 0.62 (2H, m, ansa-chain H), 0.7–0.9 (3H, m, ansa-chain H), 1.09 (1H, m, ansa-chain H), 2.11 (1H, m, ansa-chain H), 2.22 (1H, m, ansa-chain H), 2.39 (1H, m, ansa-chain H), 2.54 (1H, m, ansa-chain H), 3.45 (3H, s, OMe), 3.48, 4.60 (each 1H, d, *J*=13.7 Hz, benzylic H), 3.6–3.8 (3H, m, side chain 2-H, side chain 3-H), 3.69, 4.29 (each 1H, d, *J*=12.8 Hz, benzylic H), 4.09, 4.18 (each 1H, m, side chain 1-H), 4.73 (2H, s, benzylic H) 7.43–7.53 (3H, m, aromatic H), 7.77–7.89 (4H, m, aromatic H), 8.41 (1H, s, 6-H), 10.61 (1H, s, CHO). ^{13}C NMR ($CDCl_3$) δ: 24.3, 28.3, 28.5, 29.4, 29.8, 30.5, 32.6, 57.7, 67.7, 73.6, 76.7, 78.9, 125.6, 125.9, 126.1, 126.5, 127.6, 127.7, 128.2, 132.9, 133.1, 133.2, 134.0, 135.0, 147.5, 153.3, 155.5, 191.8. EI-MS *m/z* (%): 511 (M^+, 7.1), 141 ($NaphCH_2^+$, 100). Anal.

Calcd for $C_{28}H_{33}NO_4S_2$: C, 65.72; H, 6.50; N, 2.74; S, 12.53. Found: C, 65.58; H, 6.50; N, 2.64; S, 12.57.

(S,R_{ansa})-14-[2-methoxy-3-(2-naphthylmethoxy)propoxy]-2,5-dithian[9]-(2,5)pyridinophane-15-carbaldehyde (S,R_{ansa}-2B). 93% Yield, colorless crystals, mp 82–83°C (ethyl acetate/hexane). $[\alpha]_D^{27}=+23.9$ (c 1.00, $CHCl_3$). IR ν (KBr): 2927, 1700, 1602, 1546, 1508 cm^{-1}. ^1H NMR ($CDCl_3$) δ: 0.5–0.7 (2H, m, ansa-chain H), 0.7–0.9 (3H, m, ansa-chain H), 1.05 (1H, m, ansa-chain H), 2.10–2.24 (2H, m, ansa-chain H), 2.34 (1H, m, ansa-chain H), 2.53 (1H, m, ansa-chain H), 3.47, 4.36 (each 1H, d, J=12.2 Hz, benzylic H), 3.49 (3H, s, OMe), 3.6–3.8 (3H, m, side chain 2-H, side chain 3-H), 3.68, 4.59 (each 1H, d, J=13.4 Hz, benzylic H), 4.09 (1H, dd, J=4.9, 9.8 Hz, side chain 1-H), 4.19 (1H, dd, J=2.5, 9.8 Hz, side chain 1-H), 4.71, 4.74 (2H, AB q, J=12.2 Hz, benzylic H) 7.41–7.52 (3H, m, aromatic H), 7.73–7.88 (4H, m, aromatic H), 8.41 (1H, s, 6-H), 10.60 (1H, s, CHO). ^{13}C NMR ($CDCl_3$) δ: 24.3, 28.4, 28.5, 29.4, 29.8, 30.4, 32.5, 58.0, 67.8, 73.6, 77.0, 78.7, 125.6, 125.9, 126.1, 126.6, 127.6, 127.8, 128.2, 132.9, 133.1, 133.3, 134.0, 135.0, 147.6, 153.6, 155.2, 191.8. EI-MS m/z (%): 511 (M^+, 7.4), 141 ($NaphCH_2^+$, 100). Anal. Calcd for $C_{28}H_{33}NO_4S_2$: C, 65.72; H, 6.50; N, 2.74; S, 12.53. Found: C, 65.75; H, 6.48; N, 2.70; S, 12.45.

Preparation of aldimines 9

Aldimines **9** were prepared from pyridoxal model compounds **2** (0.20 mmol) and amino esters (0.20 mmol) according to the same procedure as reported previously.[3] ^1H NMR analysis of aldimines **9a** showed that **9a** were pure enough and the reaction had proceeded in almost quantitative yields. ^1H NMR data for **9** measured in $CDCl_3$ are as follows: S_{ansa}-**9Aa** δ: 0.39 (1H, m, ansa-chain H), 0.64–0.91 (5H, m, ansa-chain H), 1.17 (3H, t, J=7.5 Hz, CH_3CH_2O), 1.52 (3H, d, J=7.5 Hz, α-Me), 2.09–2.18 (2H, m, ansa-chain H), 2.36 (1H, m, ansa-chain H), 2.46 (1H, m, ansa-chain H), 3.52 (2H, q, J=7.5 Hz, CH_3CH_2O), 3.58 (1H, d, J=13.0 Hz, ansa-chain H), 3.66 (1H, d, J=13.0 Hz, ansa-chain H), 3.65–3.68 (2H, m, OCH_2CH_2OEt), 4.01–4.05 (2H, m, OCH_2CH_2OEt), 4.12 (1H, q, J=7.5 Hz, α-H), 4.32 (1H, d, J=13.0 Hz, ansa-chain H), 4.66 (1H, d, J=13.0 Hz, ansa-chain H), 5.10 (2H, s, CO_2CH_2Ph), 7.31–7.37 (5H, m, aromatic H), 8.35 (1H, s, 6-H), 8.85 (1H, s, imine H); S,S_{ansa}-**9Ba** δ: 0.40–0.52 (2H, m, ansa-chain H), 0.62–0.88 (3H, m, ansa-chain H), 1.05 (1H, m, ansa-chain H), 1.44 (3H, d, J=7.5 Hz, α-Me), 1.97, 2.12, 2.40, and 2.55 (each 1H, m, ansa-chain H), 3.45 (3H, s, OMe), 3.66 (1H, d, J=14.0 Hz, ansa-chain H), 3.65–3.74 (3H, m, side chain 2- and 3-H), 3.67 (1H, d, J=13.0 Hz, ansa-chain H), 4.08–4.15 (2H, m, side chain 1-H), 4.18 (1H, q, J=7.5 Hz, α-H), 4.29 (1H, d, J=13.0 Hz, ansa-chain H), 4.58 (1H, d, J=14.0 Hz, ansa-chain H), 4.74 (2H, s, OCH_2Naph), 5.08–5.13 (2H, AB type, CO_2CH_2Ph), 7.25–7.53 and 7.76–7.88 (total 12H, m, aromatic H), 8.35 (1H, s, 6-H), 8.68 (1H, s, imine H); S,R_{ansa}-**9Ba** δ: 0.37 (1H, m, ansa-chain H), 0.68–0.96 (5H, m, ansa-chain H), 1.50 (3H, d, J=7.5 Hz, α-Me), 2.00–2.11 (2H, m, ansa-chain H), 2.39 and 2.55 (each 1H, m, ansa-chain H), 3.51 (3H, s, OMe), 3.64 (1H, d, J=13.0 Hz, ansa-chain H), 3.66 (1H, d, J=13.0 Hz, ansa-chain H), 3.68–3.76 (3H, m, side chain 2- and 3-H), 3.92–3.98 (2H, m, side chain 1-H), 4.09 (1H, q, J=7.5 Hz, α-H), 4.35 (1H, d, J=13.0 Hz, ansa-chain H), 4.69 (2H, s, OCH_2Naph), 4.72 (1H, d, J=13.0 Hz, ansa-chain H), 5.11 (2H, s, CO_2CH_2Ph), 7.33–7.56 and 7.70–7.83 (total 12H, m, aromatic H), 8.35 (1H, s, 6-H), 8.82 (1H, s, imine H); S,R_{ansa}-**9Bb** δ: 0.35 (1H, m, ansa-chain H), 0.70–0.96 (5H, m, ansa-chain H), 2.02, 2.22, 2.38, and 2.58 (each 1H, m, ansa-chain H), 3.03–3.38 (2H, AB in ABX, α-CH_2Ph), 3.50 (3H, s, OMe), 3.64 (1H, d, J=13.0 Hz, ansa-chain H), 3.66 (1H, d, J=12.5 Hz, ansa-chain H), 3.66–3.74 (3H, m, side chain 2- and 3-H), 4.00–4.08 (2H, m, side chain 1-H), 4.16 (1H, dd, J=5.0, 9.0 Hz, α-H), 4.32 (1H, d, J=13.0 Hz, ansa-chain H), 4.73 (1H, d, J=12.5 Hz, ansa-chain H), 4.71–4.74 (2H, AB type, OCH_2Naph), 5.13 (2H, s, CO_2CH_2Ph), 7.23–7.38, 7.40–7.53, and 7.76–7.88 (total 17H, m, aromatic H), 8.37 (1H, s, 6-H), 8.81 (1H, s, imine H). The aldimines **9** were immediately used for alkylation without purification.

General procedure for alkylation with alkali metal hydroxides as a base

A powdered alkali hydroxide (2.33 mmol) was added to the solution of the aldimine S_{ansa}-**9Aa**, prepared as described above, in CH_2Cl_2 (2.0 ml) at room temperature, and the reaction mixture was stirred at the same temperature for 5 min. Alkyl halide (0.428 mmol) was then added to this reaction mixture at room temperature and the whole was stirred at the temperature and for the period indicated in Tables 1 and 2. The reaction mixture was filtered and the filtrate was concentrated under reduced pressure. The residue was diluted with ethyl acetate (10 ml) and stirred with 5% HCl (2 ml) at room temperature for 5 min. After dilution with H_2O (10 ml), the organic phase was separated and the aqueous phase was extracted with ethyl acetate. The combined organic layer was washed with H_2O and saturated NaCl solution, dried over $MgSO_4$, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (ethyl acetate/hexane=1:1) to afford the pyridoxal model compound. The aqueous layer was basified with saturated $NaHCO_3$ solution, and extracted with CH_2Cl_2. The CH_2Cl_2 layer was washed with saturated NaCl solution, dried over Na_2SO_4, and concentrated under reduced pressure. The residue was purified by aminopropyl-silica gel column chromatography (ethyl acetate/hexane=2:1) to afford the α,α-dialkyl amino esters **11a**–**e**.

General procedure for alkylation with LDA or NaH as a base

To a stirred solution of LDA (0.24 mmol) or a suspension of NaH (60% in oil, 12 mg, 0.30 mmol) in THF (0.5 ml) was added a THF solution (0.5 ml) of the aldimine **9B**, prepared as described above, at −78°C and the whole was stirred at −45°C for 5 min. Alkyl halide (0.24 mmol) was added to the reaction mixture at −78°C and stirring was continued at the same temperature for 10 h. The reaction mixture was gradually warmed to 0°C, diluted with ethyl acetate (10 ml) and vigorously stirred with 5% HCl at room temperature for 5 min. The organic layer was separated and the aqueous phase was extracted with ethyl acetate. The combined organic layers were worked up as usual and the resultant residue was purified by silica gel column chromatography (ethyl acetate/hexane=1:2) to give the

pyridoxal model compound **10**. The aqueous phase was neutralized with $NaHCO_3$ and extracted with CH_2Cl_2. The organic layer was washed with saturated NaCl solution, dried over Na_2SO_4 and concentrated under reduced pressure. The residue was purified by aminopropylsilica gel column chromatography (ethyl acetate/hexane=1:2) to afford α-alkylated amino ester **11**. The results are shown in Table 3. The structures and stereochemistries of amino esters **11a–c**, **e** were determined by comparison of their spectral properties with those reported previously.[3] The optical purities of **11** were determined by derivatizing with (*R*)-MTPACl to the corresponding MTPA amides, similarly to those reported previously.[3] Spectral properties of amino esters **11d** and **f** are as follows.

Benzyl (*S*)-2-Amino-2-methyl-4-pentynoate (11d). A colorless oil. 66% ee, $[\alpha]_D^{22}=-23.1$ (*c* 0.99, $CHCl_3$). IR ν (KBr): 3377, 3292, 2119, 1733, 1588, 1498 cm^{-1}. ^1H NMR ($CDCl_3$) δ: 1.40 (3H, s, 2-Me), 1.89 (2H, br s, NH_2), 2.04 (1H, t, *J*=2.6 Hz, 5-H), 2.47 (1H, dd, *J*=16.5, 2.6 Hz, 3-H), 2.57 (1H, dd, *J*=16.5, 2.6 Hz, 3-H), 5.17 (2H, s, benzylic H), 7.31–7.40 (5H, m, aromatic H). ^{13}C NMR ($CDCl_3$) δ: 25.8, 30.8, 57.4, 67.1, 71.4, 79.6, 128.0, 128.3, 128.5, 135.6, 175.8. EI-MS *m/z* (%): 218 (M^++H, 0.1), 82 (M^+-CO_2Bn, 100). High-resolution MS Calcd for $C_{13}H_{16}NO_2$ (M^++H): 218.1178, Found: 218.1177.

Benzyl (*R*)-2-Amino-2,5-dimethyl-4-hexenoate (11f). A colorless oil. 90% ee, $[\alpha]_D^{21}=+21.4$ (*c* 0.68, $CHCl_3$). IR ν (KBr): 3377, 3315, 1731, 1587, 1497 cm^{-1}. ^1H NMR ($CDCl_3$) δ: 1.34, 1.59, 1.67 (each 3H, s, Me), 1.67 (2H, br s, NH_2), 2.31 (1H, dd, *J*=14.1, 8.4 Hz, 3-H), 2.47 (1H, dd, *J*=14.1, 6.8 Hz, 3-H), 4.93–5.07 (1H, m, CH=CMe_2), 5.14 (2H, s, benzylic H), 7.25–7.38 (5H, m, aromatic H). ^{13}C NMR ($CDCl_3$) δ: 18.0, 26.0, 26.2, 33.3, 58.2, 66.7, 118.3, 128.1, 128.2, 128.3, 128.5, 136.0, 177.4. EI-MS *m/z* (%): 248 (M^++H, 0.1), 91 (Bzl+, 100). High-resolution MS Calcd for $C_{15}H_{22}NO_2$ (M^++H): 248.1651, Found: 248.1653.

Acknowledgements

This work was supported by Grant-in-Aid for Scientific Research (C), no. 09672282, from the Japanese Society for the Promotion of Science.

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7. The *O*-alkylated products, *S*,S_{ansa}- and *S*,R_{ansa}-**8B**, were also obtained as a single diastereomer, showing that these compounds are optically pure and no racemization takes place under the conditions of the transformation reactions. A homologue of this type of the compound, which has a six methylene unit at the ansa-loop, was reported to undergo racemization at room temperature.[6] See also: Eliel, E. L. *Stereochemistry of Carbon Compounds*; McGraw-Hill: New York, 1962; p 175.

8. In this reaction, S_{ansa}-**2A** was recovered in 81% yield without loosing its optical purity.

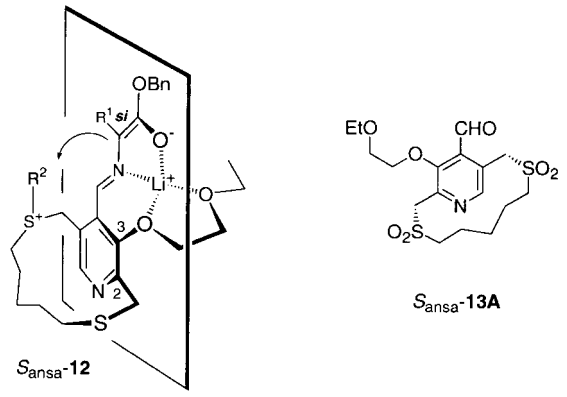
9. Miyashita, K.; Miyabe, H.; Kurozumi, C.; Imanishi, T. *Chem. Lett.* **1995**, 487–488; Miyashita, K.; Miyabe, H.; Kurozumi, C.; Tai, K.; Imanishi, T. *Tetrahedron* **1996**, *52*, 12125–12136.

10. Seyden-Penne, J. *Chiral Auxiliaries and Ligands in Asymmetric Synthesis*; Wiley: New York, 1995; pp 36–41; Tolbert, L. M., Ali, M. B. *J. Am. Chem. Soc.* **1984**, *106*, 3806–3810.

11. A similar hypothesis was proposed by Kuzuhara and coworkers as well: Kuzuhara, H.; Watanabe, N.; Ando, M. *J. Chem. Soc., Chem. Commun.* **1987**, 95–96.

12. For review about coordination chemistry of Li^+: Olsher, U.; Izatt, R. M.; Bradshaw, J. S.; Dalley, N. K. *Chem. Rev.* **1991**, *91*, 137–164.

13. Participation of the neighboring sulfur atom via formation of sulfonium salt S_{ansa}-12 might also explain the diastereoface selective alkylation from the ansa-chain as shown in Fig. 4. However,



S_{ansa}-**12** S_{ansa}-**13A**

Figure 4. Structures of S_{ansa}-**12** and S_{ansa}-**13A**.

this possibility would be ruled out by the experimental result that the reaction with bis-sulfone derivative S_{ansa}-**13A** also proceeded with a similar stereoselectivity to that with the sulfide derivative S_{ansa}-**2A**, giving *S*-**11a** in 75% ee and 74% chemical yield.

14. Although we employed S_{ansa}-**2A** in the actual experiments as shown in Tables 1 and 2, the mechanism for the reaction with its enantiomer R_{ansa}-**2A** is illustrated in Fig. 3 in order to clarify the effect of double asymmetric induction.

15. Asymmetric catalysts bearing a combination of a central chirality and an axial chirality have been already reported, but the double asymmetric induction effect is ambiguous. For example: Sasaki, H.; Irie, R.; Hamada, T.; Suzuki, K.; Katsuki, T. *Tetrahedron* **1994**, *50*, 11827–11838; Ito, Y. N.; Katsuki, T. *Bull. Chem. Soc. Jpn.* **1999**, *72*, 603–619; Ducry, L.; Diederich, F. *Helv. Chim. Acta* **1999**, *82*, 981–1004.