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# α-Alkylation of α-Amino Esters by Using a Pyridoxal Model Compound Having a Li+-Ionophore Character[1]

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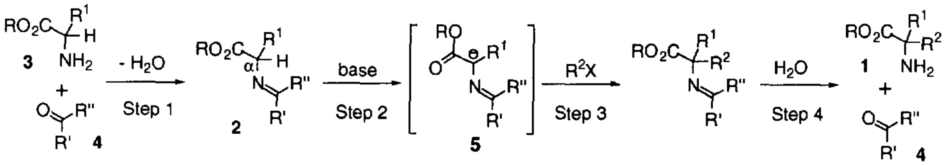
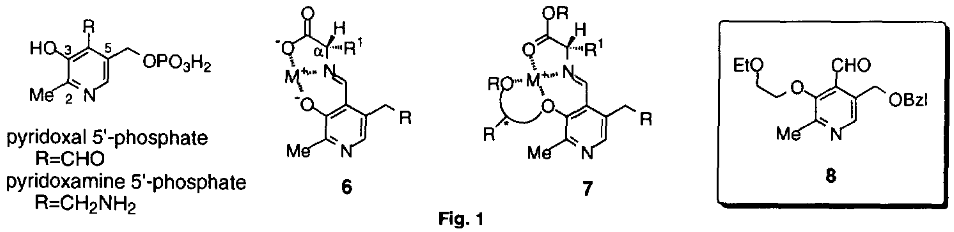
***Abstract:*** Synthesis of α,α-dialkyl-α-amino esters by α-alkylation of aldimines prepared from a novel pyridoxal model compound was studied. The α-alkylation of the aldimines having an ethoxyethoxy group at C-3 proceeded most rapidly when LiOH was employed as a base and gave α,α-dialkyl-α-amino esters after acidic hydrolysis. The chelated structure composed of the aldimine and $Li^+$ was also revealed by $^1$H-NMR analysis. Copyright © 1996 Elsevier Science Ltd

α,α-Dialkyl amino acids **1** (R = H) have been attracting attention from medicinal and biochemical points of view. Some of them are known as an enzyme-inhibitor[2] or a component of biologically active natural products.[3] The conformation of the peptide including particular α,α-dialkyl-α-amino acids is reported to be stereochemically constrained.[4] For the synthesis of these compounds, α-alkylation of the imino-ester **2**, which is easily obtainable from an α-amino ester **3** and a carbonyl compound **4**, has been employed (Scheme 1).[5] We expected that the well-modified pyridoxal could work effectively as a carbonyl part **4** in this method for the following reasons. The α-carbanion **5** generated through the α-alkylation process would be stabilized by the pyridine ring (Step 2). In addition, the electron-withdrawing property of the pyridine moiety is expected to be helpful for both formation and cleavage of the imine bond (Steps 1 and 4). However, in spite of these advantageous properties of the pyridine nucleus and published examples of this type of reaction, α-alkylation by using the pyridoxal model compounds has not, to the best of our knowledge, been reported so far.



**Scheme 1**



pyridoxal 5'-phosphate
R=CHO
pyridoxamine 5'-phosphate
R=CH2NH2

**Fig. 1**

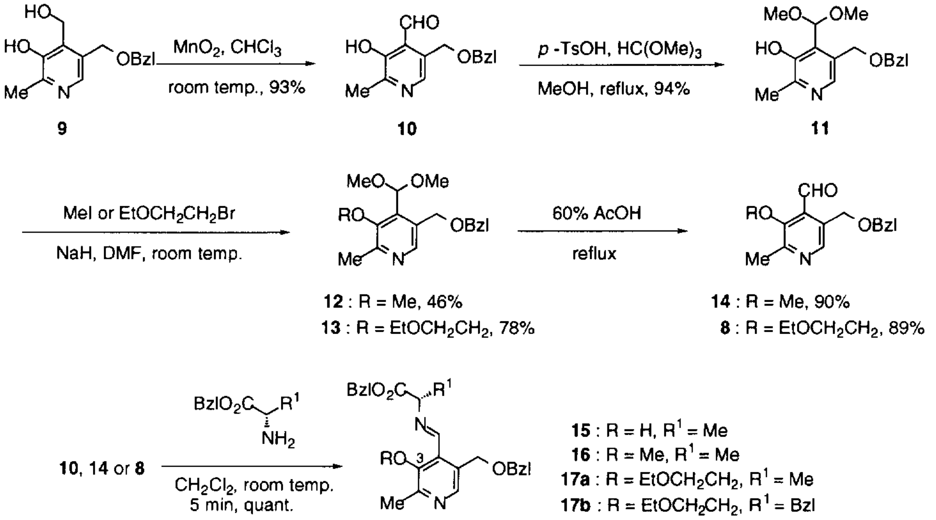
In order to investigate the enzymatic reaction mechanisms or to develop a novel method for syntheses of α-amino acids, artificial models, particularly those with an enantioface differentiation, have attracted much attention.[6] However, all of these models have concentrated on modification of the side-chain at C-5 and/or the methyl group at C-2, neither of which is relevant to the reaction. The successful example of modification of the hydroxyl group at C-3 has not been reported,[7] since this hydroxyl group is known to play an important role in both enzymatic and artificial systems; the conformation of the imino-carboxyl moiety is constrained as shown *via* hydrogen bonding (**6**: $M^+ = H^+$, in enzymatic systems) or by the formation of the chelation structure (**6**: $M^+$ = metal ion, in artificial systems), which consequently positions the $C_\alpha$-H bond perpendicular to the pyridine ring and subsequently stabilizes the carbanion by expanding the conjugation.[8] In particular, this metal complexation in artificial systems is believed to be significant for their reaction rates.[9]

The nucleophilic character of the free hydroxyl group at C-3 was obviously unfavorable for the α-alkylation reaction shown in Scheme 1, because *O*-alkylation was expected to proceed simultaneously. Therefore, in order to apply pyridoxal models to the α-alkylation reaction, it was necessary to modify the hydroxyl group without losing its desirable contribution described above. For this purpose, we designed the compound **7** possessing an ionophore function at C-3 as a novel pyridoxal model compound. This is expected not only to form a chelation structure like that of model compounds previously reported, but also to enable modification of the 3-side chain with a chiral function as illustrated in **7**. In order to investigate the effect of the ionophore side-chain, we introduced an ethoxyethyl group to the hydroxyl group at C-3 as a first step and studied α-alkylation of the aldimine prepared from this model compound **8** and α-amino ester. In this paper, we report the first successful application of the pyridoxal model compound **8** having an ionophore function to the synthesis of α,α-dialkyl-α-amino esters **1** by the α-alkylation and the structural elucidation of the chelation structure by $^1$H-NMR analysis.

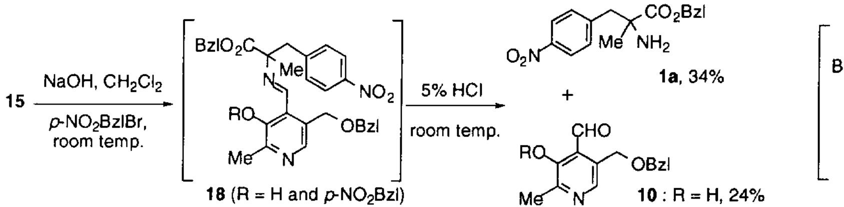
## Synthesis and Application of the Model Compound to the α-Alkylation

Methoxy derivative **14** as well as the ethoxyethoxy derivative **8** was also synthesized as shown in Scheme 2 to investigate the effect of the ethoxyethoxy group. Oxidation of **9**[10] with $MnO_2$ afforded the pyridoxal derivative **10**, which was acetalized according to the usual method to yield the dimetylacetal **11**. Alkylation was achieved by treatment with NaH and then with methyl iodide or 2-bromoethyl ethyl ether to give the corresponding *O*-alkyl derivatives **12** and **13**, respectively. Deacetalization of these compounds by acidic treatment afforded the methoxy and ethoxyethoxy pyridoxal model compounds **14** and **8**. Aldimine-formation by reaction of these compounds **10**, **14** and **8** with α-amino acid benzyl esters proceeded quite easily (at room temperature and within 5 min) to afford the corresponding aldimines **15**, **16**, **17a** and **17b** in almost quantitative yields.

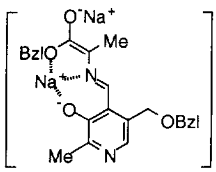
At first, we examined *p*-nitrobenzylation of the 3-hydroxyl derivative **15**. Although LiOH was not effective at all, the reaction of **15** with NaOH proceeded. The alkylated aldimine **18**, without purification, was immediately hydrolyzed by acid to afford the α-nitrobenzyl α-amino ester **1a** and the recovered pyridoxal model **10** accompanied with the *O*-alkylated product **19** as expected (Scheme 3). This suggests that the reaction of **15** would probably proceed *via* formation of the chelated alkoxide **20**, that is a type of chelation usually seen in the pyridoxal model compounds previously reported (cf. **6** in Fig. 1), to induce *O*-alkylation of the pyridoxal moiety as well as *C*-alkylation at the α-position. This result shows that the 3-hydroxyl compound is not suitable for this reaction.



**Scheme 2**



**Scheme 3**

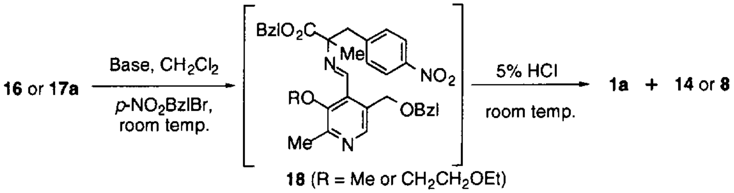


**20**

Next, α-alkylation of the aldimines **16** and **17a** was examined under several different conditions and the results are summarized in Table 1. Although *p*-nitrobenzylation of the methoxy derivative **16** with an alkali hydroxide (LiOH, NaOH or KOH) in dichloromethane did not proceed at all (Runs 1-3), the reaction took place to afford the α-alkyl aldimine **18** only when 0.2 equivalent of a phase-transfer catalyst such as benzyltriethylammonium chloride (BTEACl) or 18-crown-6 was employed as an additive (Runs 4 and 5). In contrast, the reaction of the ethoxyethoxy aldimine **17a** proceeded without a phase-transfer catalyst but was affected by an alkali metal ion of the base (Runs 6-8). Differently from that of **15**, the reaction of **17a** with LiOH proceeded most readily (Run 6), while NaOH was shown to be less effective (Run 7) and the reaction with KOH hardly occurred (Run 8). These results show that the reactivity of the aldimine **17a** depends on the size of the metal ion rather than the basicity of the alkali hydroxide, suggesting that **17a** has an ionophore activity like a crown ether and recognizes $Li^+$ among alkali metal ions. This interesting reactivity of **17a** is obviously attributable to the ethoxyethoxy group at C-3 and, hence, $Li^+$ is most likely to be captured between the imino-ester moiety and the ethoxyethoxy group to form the metal-chelation structure.

Based on the results of the alkylation of the aldimines **15**, **16** and **17a** described above, it is assumed that the lower yield of **1a** obtained from the hydroxyl derivative **15** (Scheme 3) than that from **17a** (Table 1, Run 6) is probably due to the competition between the *O*- and *C*-alkylations of **15**. The fact that the reactions of **16** without a phase-transfer catalyst did not proceed at all (Runs 1-3) shows that the firstly *O*-nitrobenzylated aldimine would not undergo *C*-alkylation. This also proves the usefulness of the compound **8** in which the 3-hydroxyl group is protected as an ionophore function.

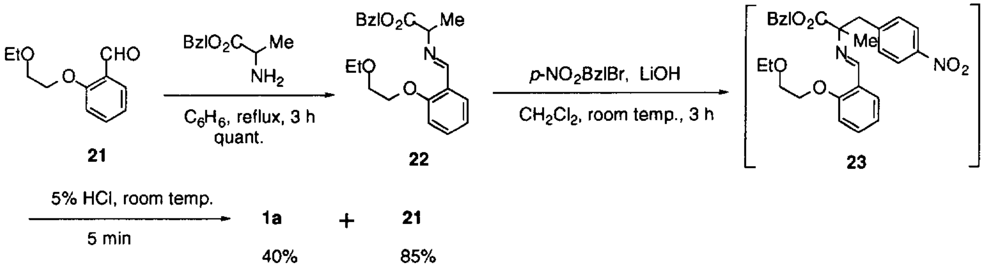
**Table 1** *p*-Nitrobenzylation of the aldimines **16** and **17a**



| Run | Aldimine | R | Base | Additive | Time (min) | Yield of **1a** (%) |
|---|---|---|---|---|---|---|
| 1 | **16** | Me | LiOH | - | 90 | n.r.[a] |
| 2 | **16** | Me | NaOH | - | 90 | n.r.[a] |
| 3 | **16** | Me | KOH | - | 90 | n.r.[a] |
| 4 | **16** | Me | NaOH | BTEACl | 15 | 64 [b] |
| 5 | **16** | Me | KOH | 18-crown-6 | 15 | 58 [b] |
| 6 | **17a** | $(CH_2)_2OEt$ | LiOH | - | 20 | 66 [b] |
| 7 | **17a** | $(CH_2)_2OEt$ | NaOH | - | 90 | 56 [b] |
| 8 | **17a** | $(CH_2)_2OEt$ | KOH | - | 90 | trace |

[a] n.r. means no reaction. [b] The model compound **14** or **8** was recovered in 73-87% yields.

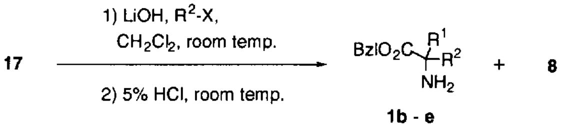
We studied the effect of the pyridine ring on this series of reactions (Steps 1-4, Fig. 1) by employing 2-(2-ethoxyethoxy)benzaldehyde (**21**)[11] as shown in Scheme 4. The α-alkylation of the aldimine **22**, compared with that of the aldimine **17a**, proceeded quite slowly and afforded **1a** in lower yield. Although hydrolysis of the imine bond of **23** proceeded easily (Step 4), the formation of the aldimine **22** (Step 1) required longer reaction time and higher reaction temperature (Scheme 4) than that of the pyridoxal model did (Scheme 2). These results clearly show the usefulness of the pyridine ring for this method as expected.[12]



**Scheme 4**

α-Alkylations of **17a** and **17b** with LiOH and the other alkyl halides were also examined and the results are outlined in Table 2. In every run, the reaction smoothly took place to afford the desired amino esters **1b-e** and the recovered model compound **8** after acidic hydrolysis. Methylation of **17b** (Run 5) also occurred to afford **1d** in the same yield as that of Run 3. These results show that this method would be applicable to the synthesis of various α,α-dialkyl-α-amino esters.

**Table 2** α-Alkylation of the aldimines **17a** and **17b**



| Run | Aldimine 17 | R¹ | R²-X | Time (min) | Product 1 | Yield (%) |
|---|---|---|---|---|---|---|
| 1 | **a** | Me | $CH_2=CHCH_2Br$ | 15 | **b** | 70 |
| 2 | **a** | Me | $CH\equiv CCH_2Br$ | 15 | **c** | 84 |
| 3 | **a** | Me | BzlBr | 30 | **d** | 56 |
| 4 | **a** | Me | $EtO_2CCH_2Br$ | 60 | **e** | 58 |
| 5 | **b** | Bzl | MeI | 30 | **d** | 54 |

## $^1$H-NMR Analysis of the Chelation Structure

The $^1$H-NMR spectra and the NOE experiments of the aldimines **15**, **16** and **17a** obtained in the absence of $Li^+$ showed that, in the case of **15** a strong hydrogen bond exists between the hydroxyl group at C-3 and the imino-ester moiety (Fig. 2-a), while the imino-ester of **16** and **17a** lies in proximity to the benzyloxymethyl group at C-5 rather than the substituent at C-3. In the presence of $Li^+$, **16** is suggested to exist as an equilibrium mixture of the two chelation structures from the result that, on irradiation of the imino hydrogen (4'-H), the NOE enhancement was observed in both signals of the methoxy group at C-3 and of the benzyloxymethyl group at C-5 (Fig. 2-b). On the other hand, the addition of $Li^+$ to **17a** was shown to induce a drastic conformational change of the imino-ester moiety by the following significant changes in the $^1$H-NMR spectra. i) The shapes of the hydrogens at C-5' and of the benzyl ester were changed as shown in Fig. 3-a and b. ii) The downfield shifts of the chemical shifts for the hydrogens of the ethoxyethoxy group and the imino-ester moiety were observed (Table 3). These results suggest that $Li^+$ is captured between the ethoxyethoxy group and the imino-ester moiety accompanying the rotation of the C4-4' bond to form the chelation structure.[13] This is further confirmed from the NOE experiment of **17a** taken with or without $Li^+$ as shown. Upon irradiation at the 4'-hydrogen, the hydrogens of the side-chain at C-3 were enhanced in the absence of $Li^+$ (Fig. 3-a), while in the presence of $Li^+$, the 5'-hydrogens and the methylene hydrogens of the benzyl ether were enhanced (Fig. 3-b). In addition, weak NOE correlation was also observed between the hydrogens of the benzyl ester and the terminal methyl hydrogens of the ethoxyethoxy group. These results strongly support the chelation structure $Li^+$-**17a** and the phenomenon induced by the addition of $Li^+$. Additionally, this chelation structure is consistent with the stoichiometry of **17a** and $Li^+$ which was successfully disclosed to be 1:1 by Job's continuous variation method[14] as shown in Fig. 4.

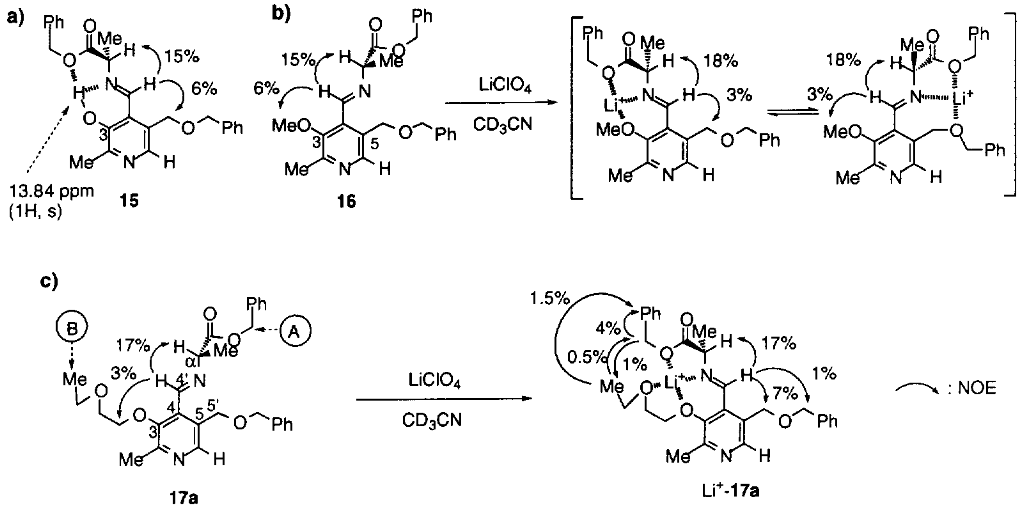


**Fig. 2** Selected $^1$H-NMR data for aldimines **15** (a), **16** (b) and **17a** (c) in the absence and presence of Li$^+$ and possible chelation structures

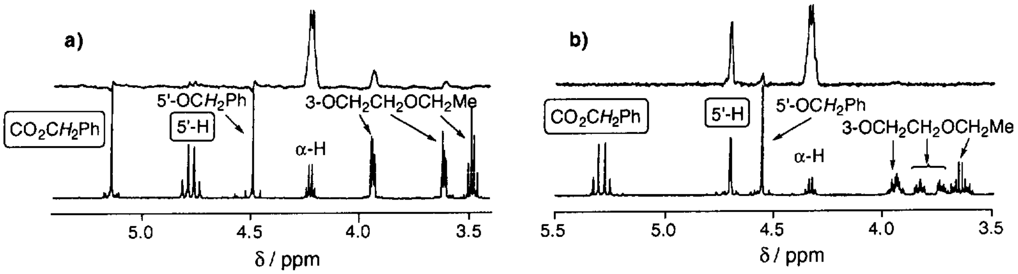


**Fig. 3** $^1$H-NMR and NOE differential spectra of **17a** (a) and Li$^+$-**17a** (b) upon irradiation at 4'-H

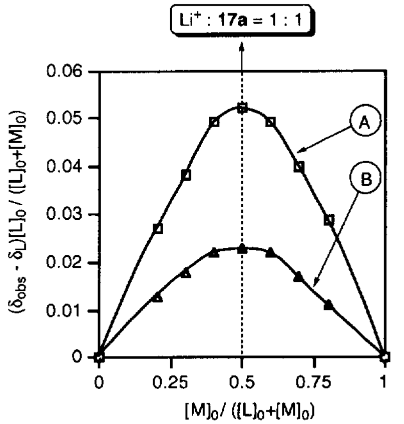


**Fig. 4** Job's plot for complexation of **17a** with Li$^+$ in $CD_3CN$ at total concentration of 0.1 M

$[L]_0$ : concentration of **17a**.

$[M]_0$ : concentration of $LiClO_4$.

$\delta_L$ : chemical shifts for hydrogens at A and B of **17a**.

$\delta_{obs}$ : observed chemical shifts for hydrogens at A and B of **17a** in the presence of $LiClO_4$.

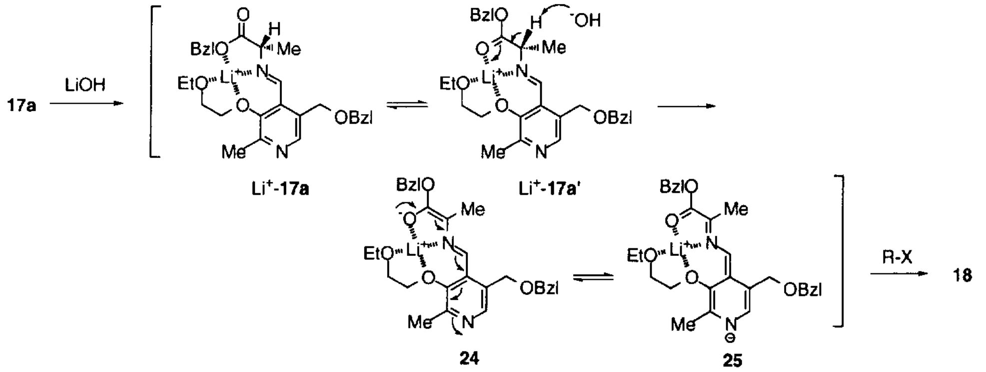
For hydrogens at A and B : see Fig. 2-c

Table 3 $^1$H-NMR data for aldimines **15**, **16** and **17a**

| | **15** | **16** | **17a** | Li$^+$-**16** | Li$^+$-**17a** |
|---|---|---|---|---|---|
| 2-Me | 2.42 (s) | 2.47 (s) | 2.48 (s) | 2.49 (s) | 2.55 (s) |
| 4'-H | 8.79 (s) | 8.64 (s) | 8.72 (s) | 8.63 (s) | 8.62 (s) |
| α-H | 4.31 (q, *J*=6.8) | 4.25 (q, *J*=6.8) | 4.22 (q, *J*=6.8) | 4.33 (q, *J*=6.8) | 4.34 (q, *J*=6.8) |
| α-Me | 1.51 (d, *J*=6.8) | 1.45 (d, *J*=6.8) | 1.45 (d, *J*=6.8) | 1.47 (d, *J*=6.8) | 1.45 (d, *J*=6.8) |
| $CO_2CH_2Ph$ | 5.18 (s) | 5.14 (s) | 5.14 (s) | 5.19-5.27 (AB type) | 5.25-5.33 (AB type) |
| 5'-H | 4.65 (s) | 4.71-4.79 (AB type) | 4.73-4.81 (AB type) | 4.65-4.70 (AB type) | 4.70 (br s) |
| 5'-$OCH_2Ph$ | 4.52 (s) | 4.49 (s) | 4.49 (s) | 4.51-4.58 (AB type) | 4.56 (s) |
| 6-H | 7.93 (s) | 8.42 (s) | 8.42 (s) | 8.34 (s) | 8.37 (s) |
| aromatic H | 7.28-7.93 (m) | 7.27-7.38 (m) | 7.27-7.38 (m) | 7.26-7.40 (m) | 7.29-7.43 (m) |
| 3-substituent | 13.84<br>(1H, s, OH) | 3.68<br>(3H, s, OMe) | 3.94<br>(2H, m, 3-$OCH_2CH_2OEt$)<br>3.61<br>(2H, m, 3-$OCH_2CH_2OEt$)<br>3.48<br>(2H, q, *J*=6.8, $OCH_2Me$)<br>1.14<br>(3H, t, *J*=6.8, $OCH_2Me$) | 3.70<br>(3H, s, OMe) | 3.94<br>(2H, m, 3-$OCH_2CH_2OEt$)<br>3.75, 3.84<br>(each 1H, m, 3-$OCH_2CH_2OEt$)<br>3.60-3.70<br>(2H, m, $OCH_2Me$)<br>1.20<br>(3H, t, *J*=6.8, $OCH_2Me$) |

It is thought the LiOH specific α-alkylation is apparently related to the chelation structure Li$^+$-**17a** (Fig. 2-c) that resembles a metal-crown ether complex. A possible reaction mechanism is proposed in Scheme 5. Naturally, equilibrium can exist between Li$^+$-**17a** and Li$^+$-**17a'**. The ionophore activity induced by formation of these complexes Li$^+$-**17a** and Li$^+$-**17a'** would facilitate deprotonation by HO$^-$ to form the chelated enolate **24**, which should be stabilized by delocalization as shown in **25**. Finally, alkylated aldimine **18** would be afforded by the reaction with alkyl halide at the α-position.

Since pyridoxal 5'-phosphate and pyridoxamine 5'-phosphate are important coenzymes in relation to a number of biosynthetic and metabolic reactions of α-amino acids such as transamination, decarboxylation, aldol reaction, β-substitution reaction, and so on,[15] this interesting feature of our model compound **8** is expected to be of use for other reactions as well.



**Scheme 5**

## Experimental

*General.* All 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 Fourie-Transfer infrared spectrometer. $^1$H-NMR spectra were measured on a JEOL GX-500 (500 MHz), Hitachi R-250HT (250 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. 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. The starting material **9**[10] and 2-(2-ethoxyethoxy)benzaldehyde (**21**)[11] were prepared according to the respective literatures.

**5-(Benzyloxymethyl)-3-hydroxy-2-methylpyridine-4-carbaldehyde (10)** $MnO_2$ (936 mg, 10.8 mmol) was added to a stirred solution of compound **9** (698 mg, 2.69 mmol) in $CHCl_3$ (5 ml). After being stirred at room temperature for 20 h, the reaction mixture was filtered through a Celite short pad, and the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography (AcOEt : hexane, 2:1) to afford the aldehyde **10** (643 mg, 93%) as light yellow crystals, mp 39-40 °C. IR ν (KBr): 3040, 1662, 1603, 1496 cm$^{-1}$. $^1$H-NMR ($CDCl_3$) δ: 2.54 (3H, s, 2-Me), 4.58, 4.74 (each 2H, s, benzylic H and 5-$CH_2$), 7.21-7.46 (5H, m, aromatic H), 8.20 (1H, s, 6-H), 10.40 (1H, s, CHO), 11.46 (1H, s, OH). $^{13}$C-NMR ($CDCl_3$) δ: 18.73, 66.43, 72.48, 120.28, 127.84, 128.00, 128.47, 129.55, 136.95, 139.58, 152.56, 153.86, 197.12. EI-MS *m/z*: 257 ($M^+$, 5.6), 91 ($Bzl^+$, 100). HR-MS Calcd for $C_{15}H_{15}NO_3$: 257.1050, Found : 257.1050.

**5-(Benzyloxymethyl)-3-hydroxy-2-methylpyridine-4-carbaldehyde Dimethyl Acetal (11)** A solution of compound **10** (19.0 g, 73.9 mmol) and a catalytic amount of *p*-toluenesulfonic acid hydrate in MeOH (70 ml) and trimethyl orthoformate (70 ml) was heated at reflux for 12 h. After concentration under reduced pressure, the residue was neutralized with saturated $NaHCO_3$ solution and extracted with AcOEt. 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 (AcOEt) to afford the acetal **11** (21.0 g, 94%) as a colorless oil, IR ν (film): 3321, 1600, 1497 cm$^{-1}$. $^1$H-NMR ($CDCl_3$) δ: 2.44 (3H, s, 2-Me), 3.30 (6H, s, OMe), 4.22, 4.48 (each 2H, s, benzylic H and 5-$CH_2$) , 5.78 (1H, s, $CH(OMe)_2$), 7.23-7.40 (5H, m, aromatic H), 7.82 (1H, s, 6-H). $^{13}$C-NMR ($CDCl_3$) δ: 18.99, 53.77, 67.04, 71.81, 102.59, 125.21, 127.59, 127.72, 128.19, 128.28, 137.45, 140.44, 149.25, 150.16. EI-MS *m/z*: 303 ($M^+$, 0.8), 91 ($Bzl^+$, 100). HR-MS Calcd for $C_{17}H_{21}NO_4$: 303.1468, Found: 303.1460.

**5-(Benzyloxymethyl)-3-methoxy-2-methylpyridine-4-carbaldehyde Dimethyl Acetal (12)** Under a nitrogen atmosphere, a solution of compound **11** (6.00 g, 19.8 mmol) in DMF (30 ml) was added dropwise to a stirred suspension of NaH (60% in oil, 872 mg, 21.8 mmol) in DMF (10 ml) at room temperature, and the reaction mixture was stirred at the same temperature for 1 h. Methyl iodide (1.48 ml, 23.8 mmol) was then added to this reaction mixture at 0 °C, and the whole was stirred at room temperature for 10 h. The reaction mixture was quenched by addition of $H_2O$, and extracted with ether. The organic phase was washed with 1N NaOH, $H_2O$ and saturated NaCl solution, dried over $MgSO_4$, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (AcOEt : hexane, 2:1) to afford the title compound **12** (2.89 g, 46%) as a colorless oil, IR ν (film): 1590, 1497 cm$^{-1}$. $^1$H-NMR ($CDCl_3$) δ: 2.52 (3H, s, 2-Me), 3.40 (6H, s, $CH(OMe)_2$), 3.74 (3H, s, 3-OMe), 4.60, 4.82 (each 2H, s, benzylic H and 5-$CH_2$), 5.56 (1H, s, $CH(OMe)_2$), 7.40-7.47 (5H, m, aromatic H), 8.52 (1H, s, 6-H). $^{13}$C-NMR ($CDCl_3$) δ: 19.20, 55.83, 61.70, 66.99, 72.48, 101.75, 127.47, 127.65, 128.26, 131.17, 136.65, 138.30, 145.29, 151.89, 151.97. EI-MS *m/z*: 318 ($M^+$+H, 0.1), 194 (100). HR-MS Calcd for $C_{18}H_{24}NO_4$ ($M^+$+H): 318.1705, Found: 318.1705.

**5-(Benzyloxymethyl)-3-(2-ethoxyethoxy)-2-methylpyridine-4-carbaldehyde Dimethyl Acetal (13)** Ethoxyethoxy derivative **13** was obtained as a colorless oil in 78% yield by using 2-bromoethyl ethyl ether instead of methyl iodide according to the similar procedure described for **12**. IR ν (film): 1591, 1497 cm$^{-1}$. $^1$H-NMR ($CDCl_3$) δ: 1.28 (3H, t, *J*=6.6 Hz, $OCH_2$*Me*), 2.52 (3H, s, 2-Me), 3.40 (6H, s, $CH(OMe)_2$), 3.62 (2H, q, *J*=6.6 Hz, O*CH$_2$*Me), 3.78, 3.96 (each 2H, t, *J*=4.6 Hz, $OCH_2CH_2OEt$), 4.60, 4.86 (each 2H, s, benzylic H and 5-$CH_2$) , 5.74 (1H, s, $CH(OMe)_2$), 7.22-7.62 (5H, m, aromatic H), 8.54 (1H, s, 6-H). $^{13}$C-NMR ($CDCl_3$) δ: 15.08, 19.08, 55.68, 66.63, 66.87, 69.22, 72.37, 73.82, 101.34, 127.29, 127.49, 128.11, 131.36, 136.78, 138.27, 145.11, 150.49, 151.57. EI-MS *m/z*: 376 ($M^+$+H, 0.4), 91 ($Bzl^+$, 100). HR-MS Calcd for $C_{21}H_{30}NO_5$ ($M^+$+H): 376.2124, Found: 376.2141.

**5-(Benzyloxymethyl)-3-methoxy-2-methylpyridine-4-carbaldehyde (14)** A solution of **12** (2.11 g, 6.66 mmol) in AcOH-$H_2O$ (3:2, 10 ml) was heated at reflux for 20 h. The reaction mixture was neutralized with saturated $NaHCO_3$ solution and extracted with AcOEt. The organic phase was washed with saturated $NaHCO_3$ solution, $H_2O$ and saturated NaCl solution, dried over $MgSO_4$, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (AcOEt : hexane, 1:1) to afford the aldehyde **14** (1.62 g, 90%) as a colorless oil. IR ν (film): 1700, 1585, 1497 cm$^{-1}$. $^1$H-NMR ($CDCl_3$) δ: 2.56 (3H, s, 2-Me), 3.84 (3H, s, 3-OMe), 4.62, 4.82 (each 2H, s, benzylic H and 5-$CH_2$), 7.17-7.43 (5H, m, aromatic H), 8.60 (1H, s, 6-H), 10.52 (1H, s, CHO). $^{13}$C-NMR ($CDCl_3$) δ: 18.70, 62.84, 67.11, 72.84, 127.44, 127.49, 128.16, 131.13, 131.66, 137.54, 144.22, 153.88, 155.18, 191.58. EI-MS *m/z*: 271 ($M^+$, 0.7), 180 ($M^+$-Bzl, 100). HR-MS Calcd for $C_{16}H_{17}NO_3$: 271.1209, Found: 271.1209.

**5-(Benzyloxymethyl)-3-(2-ethoxyethoxy)-2-methylpyridine-4-carbaldehyde (8)** The ethoxyethoxy derivative **8** was obtained from **13** as colorless crystals in 89% yield according to the similar procedure described for **14**. mp 32-33 °C (hexane-ether). IR ν (KBr): 1700, 1585, 1497 cm$^{-1}$. $^1$H-NMR ($CDCl_3$) δ: 1.20 (3H, t, *J*=7.3 Hz, $OCH_2$*Me*), 2.60 (3H, s, 2-Me) 3.54 (2H, q, *J*=7.3 Hz, O*CH$_2$*Me), 3.76, 4.10 (each 2H, t, *J*=4.3 Hz, $OCH_2CH_2OEt$), 4.64, 4.86 (each 2H, s, benzylic H and 5-$CH_2$), 7.28-7.42 (5H, m, aromatic H), 8.64 (1H, s, 6-H), 10.60 (1H, s, CHO). $^{13}$C-NMR ($CDCl_3$) δ: 14.90, 19.19, 66.63, 67.34, 69.10, 72.97, 74.82, 127.56, 127.58, 128.28, 131.14, 131.83, 137.73, 144.34, 153.92, 154.41, 192.54. EI-MS *m/z*: 329 ($M^+$, 0.5), 91 ($Bzl^+$, 100). *Anal.* Calcd for $C_{19}H_{23}NO_4$: C, 69.28; H, 7.04; N, 4.25. Found: C, 69.19; H, 6.99; N, 4.27.

**General Procedure for Preparation and α-Alkylation of the Aldimine** A $CH_2Cl_2$ (2.0 ml) solution of L-amino acid benzyl ester (0.389 mmol) was added to a stirred $CH_2Cl_2$ (2.0 ml) solution of the pyridoxal model compound **10**, **14**, and **8** (0.389 mmol). After being stirred for 5 min at room temperature, the reaction mixture was concentrated under reduced pressure and the residue was dried up by azeotropic evaporation with benzene to afford the aldimine **15**, **16**, and **17** in quantitative yield, which was pure enough for the next reaction and was used immediately without purification. A powdered alkali hydroxide (2.33 mmol) was then added to the solution of the aldimine 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 same temperature 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 AcOEt (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 AcOEt. 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 (AcOEt : 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 aminopropylsilica gel column chromatography (AcOEt : hexane, 2:1) to afford the α,α-dialkyl amino esters **1a-e**. Yields are shown in Tables 1 and 2. $^1H$-NMR data and NOE experiments for aldimines **15**, **16** and **17a** (40 mM in $CD_3CN$) in the absence and presence of $LiClO_4$ (6 eq.) were obtained at 500 MHz and are summarized in Table 3 and Figs. 2 and 3. Physical properties of α,α-dialkyl amino esters **1a-e** are as follows.

**Benzyl 2-Amino-2-methyl-3-(4-nitrophenyl)propanoate (1a)**, light yellow crystals, mp 62-63 °C (AcOEt-hexane). IR ν (KBr): 3386, 3323, 1722, 1596, 1515, 1498, 1341 $cm^{-1}$. $^1H$-NMR ($CDCl_3$) δ: 1.43 (3H, s, 2-Me), 1.58 (2H, br s, $NH_2$), 2.89, 3.18 (2H, AB q, *J*=13.0 Hz, 3-H), 5.13, 5.15 (2H, AB q, *J*=12.1 Hz, benzylic H), 7.25-7.42 (7H, m, aromatic H), 7.95-8.07 (2H, m, aromatic H). $^{13}C$-NMR ($CDCl_3$) δ: 26.56, 46.40, 58.63, 67.08, 123.21, 128.58, 128.61, 130.81, 135.30, 144.20 (2C), 146.89, 176.14. EI-MS *m/z*: 315 ($M^+$+H, 0.1), 91 ($Bzl^+$, 100). *Anal.* Calcd for $C_{17}H_{18}N_2O_4$: C, 64.96; H, 5.77; N, 8.91. Found: C, 64.76; H, 5.66; N, 8.85.

**Benzyl 2-Amino-2-methyl-4-pentenoate (1b)**, a colorless oil, IR ν (film): 3377, 3310, 1731, 1640, 1603, 1498 $cm^{-1}$. $^1H$-NMR ($CDCl_3$) δ: 1.34 (3H, s, 2-Me), 1.76 (2H, br s, $NH_2$), 2.28 (1H, dd, *J*=13.7, 7.7 Hz, 3-H), 2.53 (1H, dd, *J*=13.7, 7.7 Hz, 3-$CH_2$), 5.06-5.18 (2H, m, CH=C*H*$_2$), 5.14 (2H, s, benzylic H), 5.63-5.72 (1H, m, C*H*=$CH_2$), 7.30-7.40 (5H, m, aromatic H). $^{13}C$-NMR ($CDCl_3$) δ: 26.12, 45.06, 57.50, 66.76, 119.34, 128.08, 128.23, 128.50, 132.67. 135.77, 176.96. EI-MS *m/z*: 220 ($M^+$+H, 0.1), 91 ($Bzl^+$, 100). HR-MS Calcd for $C_{13}H_{18}NO_2$ ($M^+$+H): 220.1337, Found: 220.1337.

**Benzyl 2-Amino-2-methyl-4-pentynoate (1c)**, a colorless oil, IR ν (film): 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: 25.75, 30.80, 57.42, 67.05, 71.39, 79.62, 128.02, 128.25, 128.49, 135.62, 175.81. EI-MS *m/z*: 218 ($M^+$+H, 0.1), 82 ($M^+$-$CO_2$Bzl, 100). HR-MS Calcd for $C_{13}H_{16}NO_2$ ($M^+$+H): 218.1178, Found: 218.1177.

**Benzyl 2-Amino-2-methyl-3-phenylpropanoate (1d)**, colorless crystals, mp 45-46 °C (AcOEt-hexane). IR ν (KBr): 3374, 3314, 1723, 1593, 1496 $cm^{-1}$. $^1H$-NMR ($CDCl_3$) δ: 1.41 (3H, s, 2-Me), 1.63

(2H, br s, $NH_2$), 2.80, 3.14 (2H, AB q, *J*=13.1 Hz, 3-H), 5.12 (2H, s, benzylic H), 7.02-7.42 (10H, m, aromatic H). $^{13}$C-NMR ($CDCl_3$) δ: 26.62, 46.77, 58.79. 66.82, 126.84, 128.26, 128.29, 128.32, 128.53, 129.91, 135.60, 136.38, 176.82. EI-MS *m/z*: 270 ($M^+$+H, 0.1), 91 ($Bzl^+$, 100). HR-MS Calcd for $C_{17}H_{20}NO_2$ ($M^+$+H): 270.1495, Found: 270.1495.

**Benzyl 2-Amino-3-ethoxycarbonyl-2-methylpropanoate (1e)**, a colorless oil, IR ν (film): 3383, 3313, 1735, 1604, 1499 $cm^{-1}$. $^1$H-NMR ($CDCl_3$) δ: 1.20 (3H, t, *J*=7.1 Hz, $CH_2$*Me*), 1.34 (3H, s, 2-Me), 2.09 (2H, br s, $NH_2$), 2.55, 2.97 (2H, AB q, *J*=16.9 Hz, $CH_2CO_2Et$), 4.07 (2H, q, *J*=7.1 Hz, $CH_2$Me), 5.14, 5.16 (2H, AB q, *J*=12.3 Hz, benzylic H), 7.27-7.42 (5H, m, aromatic H). $^{13}$C-NMR ($CDCl_3$) δ: 14.03, 27.01, 44.26, 55.90, 60.54, 66.98, 128.05, 128.20, 128.47, 135.72, 171.27, 176.75. EI-MS *m/z*: 266 ($M^+$+H, 0.3), 130 ($M^+$-$CO_2$Bzl, 100). HR-MS Calcd for $C_{14}H_{20}NO_4$ ($M^+$+H): 266.1392, Found: 266.1397.

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