Synthesis of a New Dual Metalloprotease Inhibitor. I. Diastereoselective Alkylation of Protected 6-Oxopipecolic Acid Esters

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Diastereoselective methylation of the enolate generated from various protected 6-oxopipecolic acid esters (3aa—3cd) was studied. The protecting groups on the carboxylic acid and amino groups significantly influenced the *trans*/*cis* selectivity in the methylation reaction. The optimal substrate (3ca), bearing benzhydryl ester and carbobenzyloxy moieties gave a *trans*/*cis* isomer ratio of *ca.* 4:1. Investigation of the reaction conditions revealed that the reaction solvent, alkylating reagent, and base employed to generate the enolate, were decisive factors for diastereoselectivity. Further optimization of reaction conditions, including the amounts of the reagents and their addition sequence enabled maximization of reaction conversion and minimization of by-products to produce the *trans* rich 5-methyl-6-oxopipecolic acid ester (4ca) on a large scale.

Key words atrial natriuretic peptide; angiotensin-converting enzyme; anti-hypertension; practical synthesis; diastereoselective methylation

The recent elucidation of the roles of two enzymes in the cardiovascular system, namely ANP (atrial natriuretic peptide) and ACE (angiotensin-converting enzyme) has suggested that a dual inhibitor against both enzymes might be a promising drug for the treatment of hypertension and congestive heart failure. Based on this concept, extensive efforts to find a potent and well-balanced compound have been published.[1,2] Researchers in our Drug Discovery Division have found that the [5.7]-fused bicyclic lactam ER-40133, depicted in Chart 1, displays excellent *in vitro* and *in vivo* efficacy in preclinical tests.

However, efficient synthesis of this candidate compound is a formidable challenge, since it has six chiral centers and a fused ring system. From a strategic viewpoint, four of the six chiral centers may derive from amino acids, but the other two chiral centers, at the C9-position and the periposition carbon of the bicyclic ring, need to be constructed stereoselectively.

Chart 1 outlines a retrosynthetic analysis of this candidate compound. Commercially available L-α-aminoadipic acid (Aad) was chosen as a starting material, since it could be converted to 6-oxopipecolic acid derivative (V). Introduction of the methyl group onto V in the desired *trans* form was anticipated to be achieved by stereoselective methylation of the enolate to provide (IV). The selective reduction of the methylated imidoketone IV to aminal (III), followed by treatment with L-cysteine should provide linear intermediate (II). Condensation of II was expected to occur by thermodynamically controlled cyclization to give the desired [5.7]-bicyclic key intermediate I for ER-40133. In this report, the chemical transformation of Aad to key 5-methyl-6-oxopipecolic acid esters IV is described.

There is only one previous report on the alkylation of 6-oxopipecolic acid esters.[3] This paper describes the alkylation of *N*-(*tert*-butoxycarbonyl) (Boc)-6-oxopipecolic acid ethyl ester with iodoacetonitrile to provide a 1 : 1 mixture of *trans*/*cis* nitriles. On the other hand, there are several reports on the alkylation of pyroglutamic acid esters,[4,5] which are five-membered ring analogs of V. Baldwin was the first to study the reaction of lithium enolates of *N*-protected pyroglutamic acid esters, generated using lithium bis(trimethylsi-

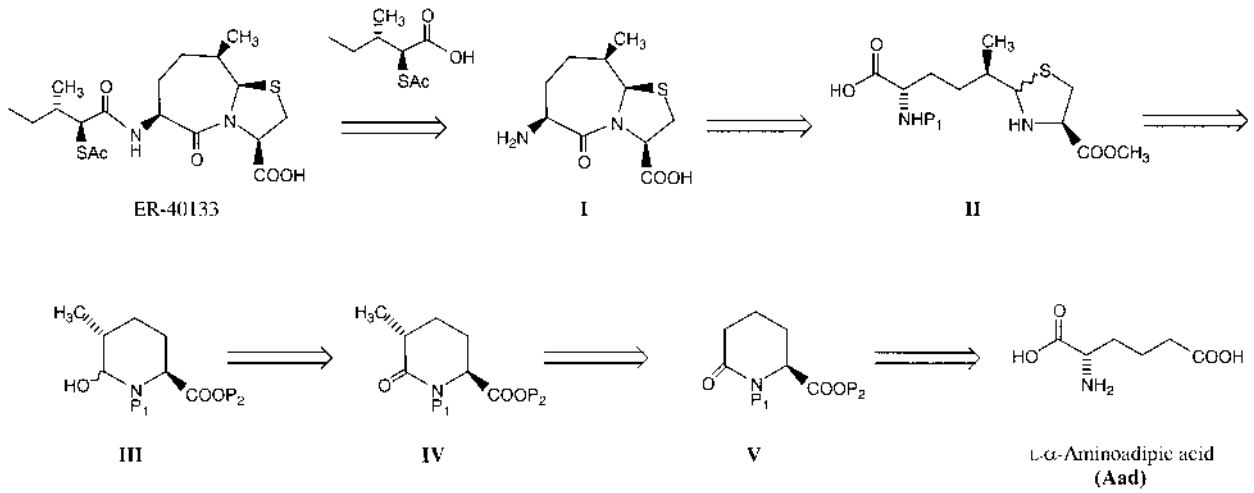

Chart 1. Retrosynthetic Analysis of ER-40133

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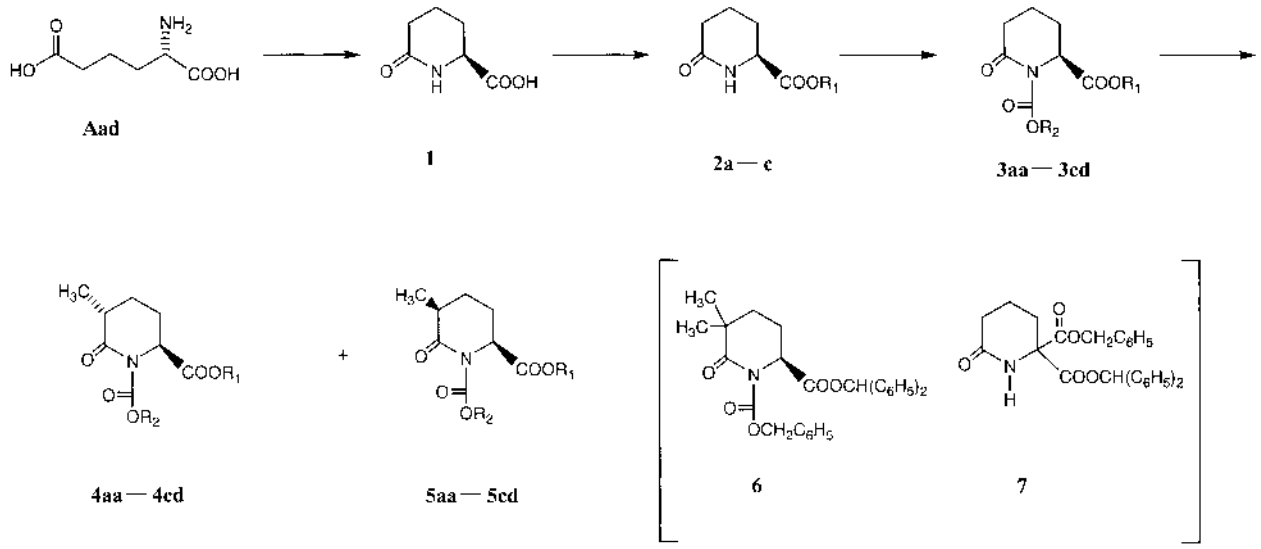


Chart 2

Table 1. Cyclization of **Aad** to 6-Oxopipecolic Acid (**1**) and Esterification with Diphenyldiazomethane

Entry	Synthesis of **1**				Synthesis of **2c**		
	Solvent	Temp. (°C)	Time (h)	Isolated Yield of **1** (%)	Solvent	Isolated Yield of **2c** (%)	ee of **2c** (%)
1	AcOH–H_2O (4 : 1)	Reflux	8	80	DMF	61	>99
2	AcOH	Reflux	5	95	DMF	67	>99
3	DMSO	130	3	n.i.	—	76	>99
4	DMF	130	11	n.i.	—	70	0

n.i.; not isolated.

lyl)amide (LiHMDS) or lithium diisopropylamide (LDA) with electrophiles such as alkyl halides and aldehydes to give 4-substituted pyroglutamic acid esters in good yields.[4] However, the 4-substituted pyroglutamic acids obtained were 2 : 1 diastereomeric mixtures except when benzyl bromide was used as the electrophile. Furthermore, the early reports claimed that methyl iodide did not react with the enolate. In spite of this precedent methylation of the enolate generated from 6-oxopipecolic acid derivatives proceeded smoothly and diastereoselectivity was found to be influenced by the ester substituent, *N*-protecting group, and the reaction conditions. Herein we report investigation of diastereoselective alkylation of various protected 6-oxopipecolic acid esters. Some applications of these findings to other analogous molecules are also described.

Results and Discussion

Preparation of Protected 6-Oxopipecolic Acid Esters (3aa—3cd) A series of protected 6-oxopipecolic acid esters (**3aa**—**3cd**) were prepared from Aad, as shown in Chart 2. Aad was converted to 6-oxopipecolic acid (**1**) under acidic conditions, followed by esterification and *N*-carbamate protection to give the protected compounds (**3aa**—**3cd**). Optimization of the preparation of these compounds led to improvements, as described below. In a previous report,[6] Aad was heated in 20% aqueous acetic acid at reflux for 3 h to give **1** in 80% yield together with 20% recovery of starting material (Aad). (Table 1, entry 1). We speculated that water might impede the reaction from reaching completion, therefore the cyclization reaction was carried out in glacial acetic acid. Five hour reflux led to complete reaction to give **1** in 95% yield (Table 1, entry 2). The optical purity of the product, after conversion to benzhydryl ester (**2c**), was determined to be more than 99% by chiral HPLC analysis.

Next, **1** was converted to its esters (**2a**—**2c**). *tert*-Butyl ester (**2a**) was prepared from **1** using 2-methylpropene in the presence of boron trifluoride etherate in only 17% yield, since **1** was easily decomposed to Aad under acidic conditions. Benzyl ester (**2b**) was synthesized through the reaction of **1** with benzyl bromide in the presence of *tert*-BuOK in *N*,*N*-dimethylformamide (DMF) in 49% yield. Diphenylmethyl ester (**2c**) was prepared from **1** and diphenyldiazomethane in DMF at room temperature, followed by work-up and crystallization from AcOBu in 67% yield (Table 1, entry 2). Although the yield of **1** was fairly good, evaporation of the acetic acid used as the solvent for this cyclization was rather impractical on a large scale. Therefore, Aad was treated in dimethyl sulfoxide (DMSO) at 130 °C for 3 h. The obtained crude **1** was readily esterified with diphenyldiazomethane, followed by work-up to provide the target ester **2c** with more than 99% ee in 76% overall yield (Table 1, entry 3). On the other hand, DMF gave completely racemized **2c**, due to the presence of dimethylamine generated from partially decomposed DMF (Table 1, entry 4). Thus, we achieved a one pot procedure for the preparation of **2c**.

These esters (**2a**—**2c**) were converted to *N*-protected 6-ox-

Table 2. Effect of Carboxylic Acid and Amino Protecting Groups on Diastereoselectivity of Enolate Methylation of **3**

Substrate	R_1	R_2	Product	Yield (%)[a]	Ratio (**4** : **5**)[b]
3aa	$C(CH_3)_3$	$CH_2C_6H_5$	**4aa**, **5aa**	85	1.5 : 1
3ac	$C(CH_3)_3$	CH_3	**4ac**, **5ac**	90	2 : 1
3ba	$CH_2C_6H_5$	$CH_2C_6H_5$	**4ba**, **5ba**	62[c]	2 : 1
3ca	$CH(C_6H_5)_2$	$CH_2C_6H_5$	**4ca**, **5ca**	84	4 : 1
3cb	$CH(C_6H_5)_2$	$C(CH_3)_3$	**4cb**, **5cb**	78	3 : 1
3cc	$CH(C_6H_5)_2$	CH_3	**4cc**, **5cc**	82	2.5 : 1
3cd	$CH(C_6H_5)_2$	C_6H_5	**4cd**, **5cd**	64	2 : 1

Reaction conditions; ester **3** (2 mmol) was dissolved in THF (20 vol) and treated with LiHMDS (1.1 eq) at −78 °C, followed by addition of MeI (3 eq). After extraction and chromatographic purification, a mixture of **4** and **5** was isolated. *a*) Isolated yield. *b*) Ratio determined by ^{1}H-NMR. *c*) 1.05 eq of LiHMDS was used.

opipecolic acid esters (**3aa**—**3cd**) in the presence of LiHMDS using appropriate chloroformates or anhydride, such as $C_6H_5CH_2OCOCl$ (Cbz-Cl), C_6H_5OCOCl, CH_3OCOCl or $((CH_3)_3COC)_2O$ ($(Boc)_2O$) at −78 °C in satisfactory yields.

Effect of *N*-Protecting Group and Ester Substituent on Diastereoselectivity The *N*-protected 6-oxopipecolic acid esters (**3aa**—**3cd**) were deprotonated with LiHMDS, followed by treatment with methyl iodide to give a mixture of the corresponding 5-methyl-6-oxopipecolic acid esters (**4aa**—**4cd**, **5aa**—**5cd**). The isomer ratios were determined by ^{1}H-NMR and the configuration of certain products confirmed by ^{1}H-NMR correlation spectroscopy (COSY) analysis. The yields and isomer ratios are summarized in Table 2. The reaction was carried out in a similar manner to that described in the reaction between *N*-protected pyroglutamic acid esters and alkyl halides[4,5] as follows; The substrate (**3aa**—**3cd**) was dissolved in 20 vol of tetrahydrofuran (THF) and cooled at −78 °C, and then 1.2 eq of LiHMDS–THF solution was added dropwise to produce the enolate. After 20 min, 2 eq of MeI in THF solution was added dropwise and the reaction mixture was stirred, followed by quench with AcOH, extractive work-up and column chromatography.

While the yields were independent of the nature of the protecting groups, the isomer ratio depended greatly on the bulkiness of ester and slightly on the *N*-carbamate protecting group. The 6-oxopipecolic acids with a less bulky ester, such as *tert*-butyl ester (**3aa**, **3ac**) and benzyl ester (**3ba**) provided 1.5 : 1—2 : 1 mixtures of *trans*/*cis* isomers (**4**/**5**), showing that the *N*-protecting group only very slightly affected the diastereomer selectivity. Esters (**3ca**—**3cd**) bearing a more bulky diphenylmethyl ester group were found to improve the diastereoselectivity, especially the ester protected with Cbz (**3ca**), which gave a 4 : 1 *trans*/*cis* mixture. The effect of the substituent at the *N*-position on the isomer ratio is shown in Table 2. Less bulky groups like methoxycarbonyl (**3cc**) and *tert*-butoxycarbonyl (**3cb**) gave 2.5 : 1 and 3 : 1 mixtures, respectively, which are slightly lower ratios than that of Cbz compound **3ca**. The phenoxycarbonyl derivatives furnished a lower yield and lower diastereoselectivity (2 : 1). It is speculated that this group partially prevents the enolate from adopting the desired conformation. The effect of the ester group on the diastereoselectivity is explained as follows. Previous literature and ^{1}H-NMR analysis of **3ca** suggested that the enolate generated with LiHMDS might exist as the structure depicted in Fig. 1. The ester was speculated to occupy the axial position, owing to the bulkiness of the protecting

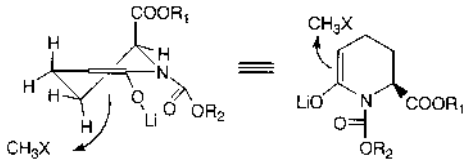


Fig. 1

Table 3. Effect of Solvents, Alkylating Reagents and Bases on Diastereoselectivity

Entry	Base	Reagent	Solvent (vol)	Conversion[a] (%)	Isomer ratio[b] (**4ca** : **5ca**)
1	LiHMDS	CH_3I	THF (35)	96	4 : 1
2			THF–DMF (20–4)	99	4 : 1
3			THF–DMF–DMSO (20–4–0.4)	99	4 : 1
4			THF–C_6H_5Cl (10–20)	99	2 : 1
5			THF–DME (20–10)	30	3 : 1
6			CH_2Cl_2	8	
7	LiHMDS	CH_3Br		No reaction	
8		$CF_3SO_3CH_3$		99	1 : 1
9		$(CH_3O)_2SO_2$		<2	
10	NaHMDS	CH_3I	THF–DMF (20–4)	71	3.5 : 1
11	KHMDS			Multi-components	
12	LDA			Multi-components	

a) Conversion was determined by HPLC analysis. *b*) Isomer ratio was determined by ^{1}H-NMR analysis of the isolated mixture of **4ca** and **5ca**.

group. The carbonyl group of the urethane at the *N*-position is proposed to be coordinated with the Li atom of the enolate. The bulky diphenylmethyl ester hindered the approach of methyl cation from the same side of the ester to result in a *trans* rich mixture. On the other hand, the bulkiness of the *N*-protecting group affected the coordination between Li and carbonyl group to change the selectivity. Thus, among these derivatives, Cbz compound **3ca** gave the best result in terms of diastereoselectivity. Another advantage of **3ca** is that it is a crystalline compound, which is very useful for industrial scale synthesis.

Effect of Solvents, Bases, and Methylating Reagents on Diastereoselectivity Next, the reaction solvent, base, and methylating agent were investigated to improve the diastereoselectivity, and results are summarized in Table 3. At the same time, the extremely poor solubility of crystalline **3ca** in several organic solvents posed another problem. For example, at least 35 volumes of THF were needed to dissolve **3ca** completely at −78 °C, in which the reaction was conducted to give a 4 : 1 mixture of **4a**/**5a** (Table 3, entry 1). However, **3ca** sporadically crystallized, preventing the reaction from proceeding smoothly to completion. Therefore, a better reaction solvent was sought, not only to improve the diastereoselectivity, but also to reduce the volume of solvents. A mixture of THF and DMF (20 vol+4 vol) improved the solubility satisfactorily on a practical scale and gave the same diastereoselectivity (Table 3, entry 2). A mixture of THF, DMF and DMSO (20 vol+4 vol+0.4 vol) also gave the same result (Table 3, entry 3), and was used for optimization of the reac-

Table 4. Optimization of Reaction Conditions

Entry	LiHMDS (eq)	MeI (eq)	Method[a)]	Addition time	Product ratio (%)			Ratio of **4ca**/**5ca**
					3ca	**4ca**+**5ca**	**6**+**7**	
1	1.3	3	A	15 s	1.9	97.1	1.0	4.1 : 1
2	1.3	3	A	1 min	7.2	91.5	1.3	n.d.
3	1.3	3	A	3 min	13.8	84.0	2.2	n.d.
4	1.1	3	B	—	0.4	99.4	0.2	4.2 : 1
5	1.2	3	B	—	0.4	99.1	0.5	4.2 : 1
6	1.3	3	B	—	0.8	98.1	1.1	4.1 : 1
7	1.1	1.5	B	—	4.2	95.4	0.4	n.d.
8	1.1	2	B	—	0.5	99	0.5	4 : 1

a) Method A; LiHMDS was added dropwise to the solution of **3ca** and MeI, Method B; MeI was added dropwise over *ca*. 10 min. Product and isomer ratios were determined by HPLC. n.d.; not determined.

tion conditions (Table 4). A mixture of chlorobenzene and THF (20 vol+10 vol) gave poor diastereoselectivity (2 : 1) (Table 3, entry 4). Addition of dimethoxyethane (DME) worsened the ratio and dichloromethane resulted in no reaction (Table 3, entry 5, 6). Among all solvents tested, THF-DMF or THF–DMF–DMSO was found to be the most practical and adequate solvent system.

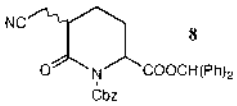
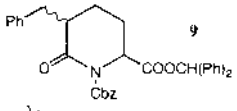
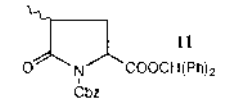
Next, we examined the alkylating reagents, as shown in entries 7—9. As described above, MeI gave a 4 : 1 mixture, however, MeBr did not react with the enolate (Table 3, entry 7). We anticipated that alkyl sulfonates would coordinate with the Li enolate anion to improve the diastereoselectivity. However, the results were disappointing; $CF_3SO_3CH_3$ gave a 1 : 1 mixture in spite of rapid conversion (Table 3, entry 8). The most common methylating reagent, $(CH_3O)_2SO_2$ did not react (Table 3, entry 9). Thus, MeI was found to be the best methylating reagent for this reaction.

Lastly, the base used to generate the enolate was investigated (Table 3, entries 10—12). As mentioned above, all reactions were conducted in THF–DMF (20 vol+4 vol) at −78 °C with MeI using several bases in place of LiHMDS. In the case of sodium bis(trimethylsilyl)amide (NaHMDS), the reaction proceeded very slowly and starting material still remained after 2 h. The reaction was stopped and subjected to extraction and silica gel column purification to give **4a**/**5a** in 71% yield, which was found to be a 3.5 : 1 *trans*/*cis* mixture by ^{1}H-NMR (Table 3, entry 10). The isomer ratio decreased slightly, but the conversion was significantly lower as compared to LiHMDS. Potassium bis(trimethylsilyl)amide (KHMDS) gave **4a**/**5a** together with a number of other components, which deterred us from determining the conversion and isomer ratio (Table 3, entry 11). LDA also gave a very complicated mixture (Table 3, entry 12). Thus, LiHMDS was concluded to be the best base to generate the enolate from **3ca**.

Optimization of Reaction Conditions Finally, detailed reaction conditions such as addition sequence, and amounts of reagents were optimized to minimize the amount of by-products and to obtain a reproducible yield, as we were unable to remove unreacted starting material as well as its transformed derivatives in the latter steps. First, the reagent addition sequence was examined. Entries 1—3 in Table 4 show the results of the LiHMDS addition procedure using 1.3 eq of LiHMDS and 3 eq of MeI. HPLC analysis revealed that reaction conversion depended on the addition period of LiHMDS. Faster addition of LiHMDS led to higher conversion. When the addition time was prolonged, the amount of other impurities increased, which were isolated by silica gel chromatography and identified by ^{1}H-NMR and mass to be the dimethyl compound (**6**) and Cbz transferred compound (**7**). These results indicated that the enolate must be completely formed in the reaction vessel first and then it should be alkylated with MeI. Entries 4—8 show the results of the MeI addition method. As expected, the starting material **3ca** was almost completely consumed to give a 4.2 : 1 mixture of **4ca**/**5ca**, and the amount of other impurities was minimized. Adequate amounts of LiHMDS and MeI were found to be 1.1—1.2 mol eq and 2 mol eq, respectively. Finally, the optical purity of **4ca**/**5ca** was examined by chiral HPLC, and found to be 97—98% ee. This indicates that the chiral center remained intact under these reaction conditions.

Thus, we optimized the reaction conditions to provide the *trans* rich desired mixture (4 : 1) of **4ca**/**5ca** in 99% yield, which was directly used for the next step.

Table 5. Application to Other Substrates

Entry	Product	Yield[a)] (%)	Isomer ratio (*trans* : *cis*)
1	 **8**	93	4 : 1
2	 **9**	90	9 : 1
3	 **11**	Quant.[b)]	1 : 1

a) Isolated yield. *b*) Isolated as a crude mixture.

Application to Other Substrates Since alkylated 6-oxopipecolic acids are useful intermediates in the synthesis of peptide mimetic compounds and total synthesis of natural products, the application of our findings to other substrates could be informative in these areas. First, ICH_2CN was used in place of MeI to give a 4 : 1 mixture of cyanomethyl 6-oxopipecolic acid (**8**) in 93% yield. This was a significant improvement with respect to the procedure using its ethyl ester (the isomer ratio is reported to be 1: 1).[3)] The more reactive and bulkier benzyl bromide gave a 9 : 1 mixture (**9**). Next, we introduced a bulky ester to the pyroglutamic acid system. *N*-

Cbz protected pyroglutamic acid diphenyl ester (**10**) was alkylated in a similar manner to the corresponding 6-oxopipecolic acid to provide a 1 : 1 *trans*/*cis* mixture (**11**) quantitatively, which could be separated by ordinary silica gel column chromatography. Although a previous paper described[4,5] that MeI did not react with the enolate anion generated from *N*-protected pyroglutamic acid esters, the diphenylmethyl ester **10** was found to be methylated using the same reaction conditions as those of 6-oxopipecolic acid. However, the isomer ratio was disappointingly 1 : 1, which means that the conformation of the enolate of the pyroglutamic system is different from that of 6-oxopipecolic acid. In spite of the poor selectivity results, this ester **10** provides a simple method to prepare 4-methyl pyroglutamic acid derivatives.

In conclusion, we succeeded in increasing the diastereoselectivity in the methylation of 6-oxopepecolic acid ester to 4 : 1 by modifying the protecting groups of the carboxylic acid group and *N*-position. The improved isomer ratio was adequate as an intermediate step for the synthesis of our candidate compound, ER-40133, which will be described in our next paper. We also found that the base used to generate the enolate, reaction solvent, and alkylating reagents influenced the diastereoselectivity, which were optimized. In addition, to assess the scope of these findings, we alkylated the 6-oxopipecolic acid with other alkylhalides and also to pyroglutamic acid ester. We are convinced that our findings will not only contribute to our research project but also to research in the fields of peptide and peptide mimetic studies.

Experimental

Melting points were determined on a Yamato MP21 melting points apparatus and are uncorrected. EI-MS and FAB-MS were taken with a JEOL JMS HX100. IR spectra were recorded on a Nicolet 205 FT-IR spectrometer. ^{1}H-NMR and ^{13}C-NMR spectra were measured on a Varian UNITY 400 or JEOL JNM-α600 using tetramethylsilane as an internal standard. Optical rotations were measured with a JASCO DIP-1000 digital polarimeter.

(2*S*)-6-Oxopipecolic Acid (1) A mixture of L-α-aminoadipic acid (50 g, 0.30 mol) in acetic acid (250 ml) was stirred at reflux for 6 h. After cooling, the reaction mixture was concentrated under reduced pressure to give an oily product which was dissolved in EtOH (20 ml) and toluene (100 ml) and evaporated to remove the remaining acetic acid. The residue was suspended in diisopropyl ether (400 ml) to give 40 g of **1** as a white powder (95%). mp 103—104 °C (lit. 101—104 °C).[6] ^{1}H-NMR (DMSO-d_6) δ: 1.55—1.70 (2H, m), 1.70—1.84 (2H, m), 1.90—2.00 (2H, m), 2.08—2.20 (2H, m), 3.94—3.98 (1H, m), 7.24 (1H, s).

***tert*-Butyl 6-Oxopipecolate (2a)** To a solution of **1** (75.5 g, 0.527 mmol) in dichloromethane (2.5 l) cooled in an ice bath was added boron trifluoride etherate (65 ml, 0.53 mol) and 2-methylpropene gas was bubbled through the mixture. When TLC analysis indicated consumption of **1**, excess 2-methylpropene was removed under reduced pressure and the mixture was made alkaline with aqueous 1 M Na_2CO_3 solution (1 l, 1 mol). The organic layer was separated, washed with water (0.5 l), brine (0.5 l), dried over Na_2SO_4, and concentrated under reduced pressure to give crude product (26 g). The residue was purified by silica gel column chromatography (380 g, hexane : AcOEt=1 : 1) to give 21.1 g of **2a** as a white powder (17%). This product was used for the next step without further purification. IR (neat) 1670, 1740 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.48 (9H, s), 1.70—1.82 (2H, m), 1.84—2.20 (2H, m), 2.30—2.45 (2H, m), 3.95—4.00 (1H, m), 6.29 (1H, br s). ^{13}C-NMR ($CDCl_3$) δ: 19.54, 25.52, 27.98, 31.01, 55.28, 82.61, 170.11, 171.52.

Benzyl 6-Oxopipecolate (2b) Potassium *tert*-butoxide (4.31 g, 38.7 mmol) was added to a solution of **1** (5 g, 35 mmol) in DMF (50 ml) and the reaction mixture was stirred for 1 h. Benzyl bromide (8.97 g, 52.5 mmol) was added to the above solution and stirred for 6 d at room temperature. The mixture was diluted with AcOEt (300 ml) and washed with water (3×300 ml), brine (100 ml), then dried over $MgSO_4$ and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (eluent; hexane : AcOEt=4 : 1 to AcOEt : MeOH=19 : 1) to give 4 g of **2b** as a colorless oil (49%). IR (Nujol) 1670, 1750 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.70—1.90 (3H, m), 2.17—2.22 (1H, m), 2.30—2.43 (2H, m), 4.13 (1H, t, J=6 Hz), 5.17 (1H, d, J=12 Hz), 5.22 (1H, d, J=12 Hz), 6.59 (1H, br s), 7.30—7.42 (5H, m). ^{13}C-NMR ($CDCl_3$) δ: 19.38, 25.37, 30.98, 54.79, 67.48, 128.40, 128.66, 128.71, 135.05, 171.03, 171.66. *Anal.* Calcd for $C_{13}H_{15}NO_3\cdot 0.4H_2O$: C, 64.90; H, 6.62; N, 5.82. Found: C, 64.60; H, 6.43; N, 5.79. Mass 234 $(M+H)^+$.

Diphenylmethyl (2*S*)-6-Oxopipecolate (2c) To a solution of **1** (43 g, 0.30 mol) in DMF (215 ml) cooled in an ice bath was added dropwise a solution of diphenyldiazomethane (61 g, 0.32 mol) in AcOEt (215 ml). After stirring for 18 h at room temperature, the reaction mixture was diluted with AcOEt (0.4 l) and washed with water (3×0.4 l), brine (0.3 l) then dried over $MgSO_4$, and evaporated. The residue was dissolved in AcOBu (50 ml) at reflux and then cooled, followed by addition of diisopropyl ether (150 ml) to provide a white solid. The precipitate was collected by filtration to give 70 g of **2c** as a white powder. mp 100—101 °C, IR (Nujol) 1633, 1721 cm^{-1}. $[\alpha]_D=-10.2$ °C (c=1, temperature=22.4 °C, $CHCl_3$). ^{1}H-NMR ($CDCl_3$) δ: 1.70—1.95 (3H, m), 2.05—2.45 (3H, m), 4.18—4.20 (1H, m), 6.17 (1H, s), 6.94 (1H, s), 7.28—7.40 (10H, m). ^{13}C-NMR ($CDCl_3$) δ: 19.50, 25.51, 31.04, 54.99, 78.30, 126.95, 127.10, 128.29, 128.34, 128.69, 139.35, 171.17. *Anal.* Calcd for $C_{19}H_{19}NO_3$: C, 73.77; H, 6.19; N, 4.53. Found: C, 73.51; H, 6.24; N, 4.60. Mass: 310 $(M+H)^+$. Optical Purity; column, Daicel Chiralcel-OJ; mobile phase, hexane/EtOH=7/3; flow rate, 1 ml/min; detection, UV 210 nm; t_R of (**2c**) and its (2*R*) isomer, 14 min and 22 min, respectively.

Diphenylmethyl (2*R*)-6-oxopipecolate was prepared in a similar manner to that described for **2c** starting from D-α-aminoadipic acid.

Diphenylmethyl (2*S*)-6-Oxopipecolate (2c); One Pot Synthesis A suspension of Aad (50 g, 0.30 mol) in DMSO (200 ml) was stirred at 130 °C for 3 h to obtain a clear solution. The mixture was diluted with AcOEt (50 ml) and stirred with ice-cooling. To the reaction mixture was added dropwise a solution of diphenyldiazomethane (61 g, 0.32 mol) in AcOEt (215 ml). After stirring at room temperature for 18 h, toluene (500 ml) was added and the organic solution was washed with water (3×500 ml), brine (300 ml), then dried over $MgSO_4$, and concentrated under reduced pressure to give crude material. The residue was dissolved in AcOBu (50 ml) at around 100 °C and diisopropyl ether (150 ml) was added. The obtained solution was cooled in an ice bath to give 70 g of **2c** as a white powder (76%).

Diphenylmethyl (2*S*)-*N*-Benzyloxycarbonyl-6-oxopipecolate (3ca) A solution of **2c** (50 g, 162 mmol) in THF (1 l) was cooled to −78 °C in a dry ice methanol bath. 1 M LiHMDS THF solution (170 ml, 170 mmol) was added dropwise over 45 min, and the mixture was stirred at the same temperature for 15 min. A solution of Cbz-Cl (26.6 ml, 185 mmol) in THF (50 ml) was added dropwise over 10 min and the reaction mixture was stirred at −78 °C for 2 h. To the reaction mixture was added a solution of acetic acid (12 ml) in THF (30 ml) and allowed to stand at room temperature. Then, a mixture of AcOEt (1 l) and water (1 l) was added and the organic layer was separated, washed with water (2×1 l), brine (0.5 l) then dried over $MgSO_4$ and concentrated under reduced pressure. The residue was dissolved in AcOEt (0. 4 l) under reflux and diluted with *tert*-butyl methyl ether (TBME) (0.5 l) and allowed to stand at room temperature. The precipitate was collected by filtration to give 62 g of **3ca** as a white powder (87%). mp 140—141 °C. IR (Nujol) 1679, 1752, 1777 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.45—1.72 (2H, m), 1.98—2.10 (1H, m), 2.18—2.28 (1H, m), 2.42—2.58 (2H, m), 4.92—4.96 (1H, m), 5.10 (1H, d, J=12 Hz), 5.24 (1H, d, J=12 Hz), 6.91 (1H, s), 7.25—7.38 (15H, m). ^{13}C-NMR ($CDCl_3$) δ: 18.06, 25.48, 25.78, 34.04, 58.78, 68.81, 78.35, 127.04, 127.08, 127.97, 128.17, 128.21, 128.29, 128.55, 128.62, 135.06, 139.34, 153.86, 170.04, 170.27, $[\alpha]_D=-23.2$ °C (c=1, temperature =22.4 °C, $CHCl_3$). *Anal.* Calcd for $C_{27}H_{25}NO_5\cdot 0.14H_2O$: C, 72.71; H, 5.70; N, 3.14. Found: C, 72.71; H, 5.70; N, 3.06. Mass 444 $(M+H)^+$. Optical Purity; column, Daicel Chiralcel-OD; mobile phase, hexane/EtOH=90/10; flow rate, 1.2 ml/min; detect; UV 254 nm; t_R of **3ca** and its 2*R* isomer were 20 min and 12 min, respectively.

The corresponding *R*-isomer was synthesized from D-α-aminoadipic acid in a similar manner to that described for **3ca**. **3aa**—**3cd** were prepared in a similar manner to that for **3ca**.

tert-Butyl *N*-Benzyloxycarbonyl-6-oxopipecolate (**3aa**): Yield, 78%. Colorless oil. IR (Nujol) 1684, 1728, 1761 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.41 (9H, s), 1.70—1.90 (2H, m), 1.95—2.17 (1H, m), 2.18—2.23 (1H, m), 2.45—2.65 (2H, m), 4.68 (1H, t, J=6 Hz), 5.28 (2H, s), 7.30—7.42 (5H, m). ^{13}C-NMR ($CDCl_3$) δ: 18.23, 25.80, 27.88, 34.48, 59.23, 68.73, 82.47, 128.07, 128.54, 135.24, 154.10, 170.30. *Anal.* Calcd for $C_{18}H_{23}NO_5\cdot 0.2H_2O$: C, 64.16; H, 6.88; N, 4.16. Found: C, 64.04; H, 6.81; N, 4.01. Mass 334

$(M+H)^+$.

tert-Butyl *N*-Methoxycarbonyl-6-oxopipecolate (**3ac**): Yield, 85%. White wax. IR (Nujol) 1700—1750 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.47 (9H, s), 1.72—1.84 (2H, m), 1.96—2.09 (1H, m), 2.17—2.25 (1H, m), 2.45—2.66 (2H, m), 3.86 (3H, s), 4.68 (1H, dd, J=6, 3 Hz). ^{13}C-NMR ($CDCl_3$) δ: 17.41, 23.29, 25.87, 38.04, 54.13, 58.43, 78.28, 120.05, 128.21, 128.61, 139.32, 170.36, 174.04. *Anal.* Calcd for $C_{12}H_{19}NO_5$: C, 56.02; H, 7.44; N, 5.44. Found: C, 56.14; H, 7.44; N, 5.21. Mass 258 $(M+H)^+$.

Benzyl *N*-Benzyloxycarbonyl-6-oxopipecolate (**3ba**): Yield, 74% Colorless oil. IR (Nujol) 1720, 1782 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.60—1.83 (2H, m), 1.98—2.11 (1H, m), 2.16—2.26 (1H, m), 2.45—2.66 (2H, m), 4.83—4.89 (1H, m), 5.18 (2H, ABq, J=12 Hz), 5.25 (2H, ABq, J=12 Hz), 7.25—7.42 (10H, m). ^{13}C-NMR ($CDCl_3$) δ: 18.18, 25.77, 34.48, 58.74, 67.74, 67.42, 68.86, 128.05, 128.29, 128.35, 128.56, 128.66, 135.13, 135.20, 154.03, 170.01, 171.12. *Anal.* Calcd for $C_{21}H_{21}NO_5 \cdot 0.5H_2O$: C, 67.01; H, 5.89; N, 3.72. Found: C, 66.89; H, 5.72; N, 3.77. Mass 368 $(M+H)^+$.

Diphenylmethyl *N*-*tert*-Butoxycarbonyl-6-oxopipecolate (**3cb**): Yield, 83%. White crystals. mp 114 °C. IR (Nujol) 1685, 1731, 1767 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.39 (9H, s), 1.42—1.58 (1H, m), 1.62—1.75 (1H, m), 1.98—2.10 (1H, m), 2.18—2.25 (1H, m), 2.45—2.55 (2H, m), 4.80—4.82 (1H, m), 6.95 (1H, s), 7.25—7.40 (10H, m). ^{13}C-NMR ($CDCl_3$) δ: 18.13, 25.95, 27.81, 34.44, 58.66, 78.11, 127.00, 127.25, 128.10, 128.19, 128.57, 139.53, 170.34, 170.52. *Anal.* Calcd for $C_{24}H_{27}NO_5$: C, 70.40; H, 6.65; N, 3.42. Found: C, 70.33; H, 6.70; N, 3.35. Mass 410 $(M+H)^+$.

Diphenylmethyl *N*-Methoxycarbonyl-6-oxopipecolate (**3cc**) : Yield, 95%. Colorless oil. IR (Nujol) 1724, 1736 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.50—1.76 (1H, m), 1.65—1.75 (1H, m), 2.00—2.10 (1H, m), 2.20—2.30 (1H, m), 2.42—2.60 (2H, m), 3.76 (3H, s), 4.94 (1H, t, J= 6 Hz), 6.94 (1H, s). ^{13}C-NMR ($CDCl_3$) δ: 18.06, 25.77, 34.37, 54.14, 58.82, 78.32, 127.04, 128.25, 128.61, 139.35, 154.69, 170.09, 170.31. *Anal.* Calcd for $C_{21}H_{21}NO_5 \cdot 0.1H_2O$: C, 68.32; H, 5.73; N, 3.81. Found: C, 68.65; H, 5.76; N, 3.83. Mass 368 $(M+H)^+$.

Diphenylmethyl *N*-Phenoxycarbonyl-6-oxopipecolate (**3cd**): Yield, 75%. White crystals. mp 119 °C. IR (Nujol) 1686, 1728, 1782 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.50—1.70 (1H, m), 1.75—1.85 (1H, m), 2.10—2.20 (1H, m), 2.28—2.37 (1H, m), 2.50—2.66 (2H, m), 5.02—5.08 (1H, m), 6.96 (1H, s) 7.02 (2H, d, J=9 Hz), 7.20—7.36 (13H, m). ^{13}C-NMR ($CDCl_3$) δ: 18.19, 25.83, 34.56, 59.10, 78.52, 121.36, 126.11, 127.08, 127.14, 128.21, 128.25, 128.59, 128.66, 129.25, 139.25, 152.88, 170.06. *Anal.* Calcd for $C_{26}H_{23}NO_5$: C, 72.21; H, 5.40; N, 3.26. Found: C, 72.70; H, 5.39; N, 3.18. Mass 430 $(M+H)^+$.

Diphenylmethyl (2*S*)-*N*-Benzyloxycarbonyl-5-methyl-6-oxopipecolate (4ca, 5ca) A solution of **3ca** (100 g, 0.226 mol) in THF (2 l) and DMF (0.4 l) was stirred in a dry ice MeOH bath under a nitrogen atmosphere. To the mixture was added 1 M LiHMDS THF solution (270 ml, 1.2 eq) dropwise over 25 min and stirred for 15 min, followed by addition of methyl iodide (28 ml, 0.45 mol) over 40 min. After being stirred at the same temperature for 3 h, acetic acid (13.5 ml, 0.226 mol) was added dropwise over 3 min and the mixture was allowed to stand at room temperature. The mixture was diluted with toluene (1.5 l), washed with water (2 l, 1 l), brine (1 l), dried over $MgSO_4$, and concentrated under reduced pressure to give crude material which was purified by silica gel column chromatography (eluent; *n*-hexane : AcOEt=3 : 1) to provide a 4 : 1 mixture of **4ca**/**5ca** as a colorless oil (86 g, 84%). IR (Nujol) 1681, 1733, 1771 cm^{-1}. *Anal.* Calcd for $C_{28}H_{27}NO_5$: C, 73.51; H, 5.95; N, 3.06. Found: C, 73.42; H, 5.98; N, 3.01. Mass 458 $(M+H)^+$.

Each individual isomer was isolated using the following procedure: The mixture (800 mg) obtained above was purified by preparative HPLC (YMC Co., Ltd., SH043-7, eluent; *n*-hexane : AcOEt=12 : 1) to give 570 mg and 140 mg of **4ca** and **5ca**, respectively.

Trans Isomer (**4ca**): White solid. $[\alpha]_D$= 261° ($CHCl_3$, c=1, temperature 30.3 °C). mp 68—70 °C. ^{1}H-NMR (600 MHz, $CDCl_3$) δ: 1.16 (3H, d, J= 7 Hz), 1.37—1.46 (1H, m), 1.76—1.83 (1H, m), 2.11—2.17 (2H, m), 2.29 (1H, ddd, J=7, 7, 8 Hz), 4.98 (1H, dd, J=5, 6 Hz), 5.12 (1H, d, J=12 Hz), 5.24 (1H, d, J=12 Hz), 6.90 (1H, s), 7.20—7.40 (15H, m). ^{13}C-NMR (100 MHz, $CDCl_3$) δ: 17.27, 23,23, 25.79, 37.95, 58.29, 68.76, 78.27, 126.97, 127.02, 127.89, 128.14, 128.21, 128.50, 128.55, 135.13, 139.28, 139.36, 154.01, 170.28, 173.87.

Cis Isomer (**4cb**): White solid. $[\alpha]_D$= 111° ($CHCl_3$, c=1, temperature 30.3 °C). mp 75—76 °C. ^{1}H-NMR (600 MHz, $CDCl_3$) δ: 1.15 (3H, d, J=7 Hz), 1.21—1.33 (1H, m), 1.73—1.80 (1H, m), 2.03—2.13 (1H, m), 2.21—2.27 (1H, m), 2.41—2.51 (1H, m), 4.89 (1H, dd, J=6, 2 Hz), 5.10 (1H, d, J=12 Hz), 5.25 (1H, d, J=12 Hz), 6.92 (1H, s), 7.25—7.34 (15H, m). ^{13}C-NMR (100 MHz, $CDCl_3$) δ: 16.50, 25.88, 27.01, 39.60, 59.64, 68.72, 78.27, 126.96, 127.20, 127.96, 128.09, 128.16, 128.22, 128.54, 135.17, 139.36, 154.43, 170.48, 173.64. HPLC purity: mobile phase, 80% MeOH–0.1% ammonium acetate, flow rate=0.8 ml/min, column J'sphere M80 (250 mm+150 mm) (YMC), UV 254 nm, t_R of **3ca**, **4ca**, **5ca**, **6**+**7**=11.9, 15.5, 16.2, 19.7. Optical purity; mobile phase; *n*-hexane : EtOH, flow rate; 1.2 ml/min, column; Daicel Chiralcel-OD, detection; UV 254 nm, retention time; t_R of (2*R*)-*trans* isomer, (2*R*)-*cis* isomer, **4ca**, **5ca**=6.7/7.5/14.1/15.4, respectively.

Diphenylmethyl *N*-Benzyloxycarbonyl-5,5-dimethyl-6-oxopipecolate (**6**): ^{1}H-NMR ($CDCl_3$) δ: 1.15 (3H, s), 1.26 (3H, s), 1.45—1.60 (2H, m), 2.06—2.30 (2H, m), 4.85—4.89 (1H, m), 5.08 (1H, d, J=12 Hz), 5.26 (1H, d, J= 12 Hz), 6.92 (1H, s), 7.25—7.40 (15H, m).

Diphenylmethyl 2-Benzyloxycarbonyl-5-methyl-6-oxopipecolate (**7**): ^{1}H-NMR ($CDCl_3$) δ: 1.10 (1.5H, d, J=7 Hz), 1.25 (1.5H, d, J=7 Hz), 1.50—1.90 (2H, m), 2.30—2.70 (3H, m), 4.98—5.08 (2H, m), 6.03 (0.5H, br s), 6.15 (0.5H, br s), 6.83 (0.5H, s), 6.85 (0.5H, s), 7.10—7.40 (15H, m).

Methylation of 3ca with Other Methylating Reagents Methylation of **3ca** with other methylating reagents was carried out in a similar manner to that described with MeI. Generally, **3ca** (1 mmol) was dissolved in a mixture of THF and DMF (20 vol and 4 vol, respectively) and the solution was cooled in a dry ice MeOH bath. To the solution was added 1.2 eq of 1 M LiHMDS THF solution and 20 min later a solution of the methylating reagent (2—4 mmol) in THF was added and stirred for a certain period. After AcOH quench, the organic solution was treated as described above and purified by column chromatography to give a mixture of **4ca**/**5ca.** The *cis*/*trans* ratio was determined by ^{1}H-NMR analysis.

Methylation of 3ca in Various Solvents Methylation of **3ca** in various solvents was carried out in a similar manner to that described above. Fundamentally, **3ca** (1 mmol) was dissolved in each solvent (20 vol) and reacted with MeI in the presence of LiHMDS at −78 °C. After extraction and purification, a mixture of **4ca/5ca** was obtained and the isomer ratio was determined by ^{1}H-NMR.

Methylation of 3aa—3cd Methylation of the other substrates was carried out in a similar manner to that described above except for solvent. Ester **3aa**—**3cd** (1 mmol) was dissolved in THF (20 vol) and the mixture was stirred in a dry ice MeOH bath. To the solution above was added 1.05 eq of 1 M LiHMDS THF solution dropwise, followed by MeI (3 mmol). After being stirred for 3 h, the mixture was diluted with a solution of AcOH (1 mmol) in THF and allowed to stand at room temperature. The organic solution was washed with water, brine, dried over $MgSO_4$ and concentrated under reduced pressure. The residue was purified by silica gel column chromatography to give a mixture of the corresponding methylated compounds (**4aa**—**4cd**/**5aa**—**5cd**). The *cis*/*trans* ratio was determined by ^{1}H-NMR analysis.

tert-Butyl *N*-Benzyloxycarbonyl-5-methyl-6-oxopipecolate (**4aa**, **5aa**): The compound was isolated as an inseparable 3 : 2 mixture of **4aa** and **5aa**. The isomer ratio was determined by integration of the C-2 proton signals. White wax. IR (Nujol) 1725, 1781 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.26 (3H, d, J=7 Hz), 1.41 (9H, s), 1.50—1.62 (2H, m), 1.90—2.25 (2H, m), 2.44—2.53 (1H×2/5, m), 2.54—2.64 (1H×3/5, m), 4.62—4.66 (1H×2/5, m), 4.72 (1H×3/5, t, J=7 Hz), 5.27 (2H, ABq, J=13 Hz), 7.28—7.44 (5H, m). *Anal.* Calcd for $C_{19}H_{25}NO_5$: C, 65.59; H, 7.25; N, 4.03. Found: C, 65.32; H, 7.22; N, 4.03. Mass 348 $(M+H)^+$.

tert-Butyl *N*-Methoxycarbonyl-5-methyl-6-oxopipecolate (**4ac**, **5ac**): This compound was isolated as an inseparable 2 : 1 mixture of **4ac** and **5ac**. The isomer ratio was determined by integration of the C-2 proton signals. Colorless oil. IR (Nujol) 1730, 1784 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.26 (3H, d, J=7 Hz), 1.47 (9H, s), 1.40—1.65 (1H, m), 1.90—2.30 (3H, m), 2.45—2.55 (1H×1/3, m), 2.50—2.63 (1H×2/3, m), 3.85 (3H, s), 4.63 (1H×1/3, d, J=6 Hz), 4.70 (1H×2/3, t, J=7 Hz). HR-MS *m/z*: 272.1505 (Calcd for $C_{13}H_{22}NO_5$: 272.1498). Mass 272 $(M+H)^+$.

Benzyl *N*-Benzyloxycarbonyl-5-methyl-6-oxopipecolate (**4ba**, **5ba**): Isolated as an inseparable 2 : 1 mixture of **4ba** and **5ba**. Colorless oil. IR (Nujol) 1717, 17497, 1782 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.23 (3H, d, J=7 Hz), 1.36—1.48 (1H×1/3, m), 1.46—1.55 (1H×2/3, m), 1.82—1.92 (1H×1/3, m), 1.86—1.97 (1H×2/3, m), 2.05—2.25 (2H, m), 2.45—2.55 (1H, m), 4.02 (1H×1/3, d, J=7 Hz), 4.92 (1H×2/3, t, J=7 Hz), 5.15 (2H×2/3, s), 5.10—5.18 (2H×1/3, m), 5.18—5.28 (2H×1/3, m), 5.24 (2H×2/3, s), 7.30—7.40 (10H, m). *Anal.* Calcd for $C_{22}H_{23}NO_5 \cdot 0.2H_2O$: C, 68.63, H, 6.13, N, 3.64. Found C, 68.53, H, 6.07, N, 3.68. Mass 382 $(M+H)^+$.

Diphenylmethyl *N*-*tert*-Butoxycarbonyl-5-methyl-6-oxopipecolate (**4cb**, **5cb**): Isolated as an inseparable 3 : 1 mixture of **4cb** and **5cb**. Colorless oil. IR (Nujol) 1714, 1727, 1777 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.13 (3H×1/4, d, J=7 Hz), 1.17 (3H×3/4, d, J=7 Hz), 1.41 (9H, s), 1.35—1.50 (2H×1/4, m), 1.70—1.85 (2H×3/4, m), 2.10—2.25 (2H, m), 2.42—2.50 (1H×1/4, m),

2.50—2.58 (1H×3/4, m), 4.77 (1H×1/4, d, J=6 Hz), 4.90 (1H×3/4, t, J=6 Hz), 6.93 (1H×3/4, s), 6.96 (1H×1/4, s), 7.25—7.40 (10H, m). HR-MS *m/z*: 424.2148 (Calcd for $C_{25}H_{30}NO_5$: 424.2124). Mass 424 $(M+H)^+$.

Diphenylmethyl *N*-Methoxycarbonyl-5-methyl-6-oxopipecolate (**4cc**, **5cc**): Isolated as an inseparable 2.5 : 1 mixture of **4cc** and **5cc**. Colorless oil. IR (Nujol) 1730, 1785 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.19 (3H×5/7, d, J=6 Hz), 1.16 (3H×2/7, d, J=6 Hz), 1.22—1.35 (1H×2/7, m), 1.40—1.52 (1H×5/7, m), 1.75—1.88 (1H×2/7, m), 2.05—2.30 (3H×2/7, m), 2.10—2.30 (2H×5/7, m), 2.35—2.44 (1H×5/7), 3.76 (3H×2/7), 3.78 (3H×5/7), 4.91 (1H×2/7, d, J=6 Hz), 4.98 (1H×5/7, t, J=6 Hz), 6.92 (1H×2/7, s), 6.95 (1H×5/7, s), 7.24—7.38 (10H, m). HR-MS *m/z*: 382.1645 (Calcd for $C_{22}H_{24}NO_5$: 382.1654). Mass 382 $(M+H)^+$.

Diphenylmethyl *N*-Phenoxycarbonyl-5-methyl-6-oxopipecolate (**4cd**, **5cd**): Isolated as an inseparable 2 : 1 mixture of **4cd** and **5cd**. Colorless oil. IR (Nujol) 1714, 1755, 1779 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.20 (3H×1/3, d, J=7 Hz), 1.24 (3H×2/3, d, J=7 Hz), 1.25—1.40 (1H×1/3, m), 1.50—1.60 (1H×3/2, m), 1.80—1.95 (1H, m), 2.15—2.35 (2H, m), 2.40—2.52 (1H×2/3, m), 2.50—2.63 (1H×1/3, m), 5.00 (1H×1/3, d, J=4 Hz), 5.10 (1H×2/3, t, J=5 Hz), 6.94 (1H×1/3, s), 6.96 (1H×2/3, s), 7.00—7.40 (15H, m). HR-MS *m/z*: 444.1814 (Calcd $C_{27}H_{26}NO_5$: 444.1811). Mass 444 $(M+H)^+$.

Diphenylmethyl *N*-Benzyloxycarbonyl-5-cyanomethyl-6-oxopipecolate (8) The Li enolate from **3ca** (1 g, 2.26 mmol) was reacted with iodoacetonitrile (0.33 ml, 4.5 mmol) in a mixture of THF (20 ml) and DMF (4 ml) at −78 °C to provide a 4 : 1 *trans*/*cis* mixture of **8** (1.0 g, 93%). mp 100—101 °C, IR (Nujol) 1743, 1782, 2600, 2662 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.30—1.40 (1H×1/4, m), 1.65—1.75 (1H×3/4, m), 2.05—2.15 (2H×1/4, m), 2.20—2.30 (2H×3/4, m), 2.50—2.80 (4H, m), 4.91 (1H×1/4, d, J=5 Hz), 5.11 (1H×3/4, t, J= 5 Hz), 5.17 (1H, d, J=12 Hz), 5.26 (1H, d, J=12 Hz), 6.91 (1H×3/4, s), 6.92 (1H×1/4, m), 7.25—7.40 (15H, m). *Anal.* Calcd for $C_{29}H_{26}N_2O_5$: C, 71.19; H, 5.43; N, 5.81. Found: C, 71.94; H, 5.42; N, 6.03. Mass 483 $(M+H)^+$.

Diphenylmethyl *N*-Benzyloxycarbonyl-5-benzylmethyl-6-oxopipecolate (9) The Li enolate from **3ca** (5 g, 11.3 mmol) was reacted with benzyl bromide (2.69 ml, 22.6 mmol) in a mixture of THF (100 ml) and DMF (20 ml) at −78 °C to provide a 9 : 1 *trans*/*cis* mixture of **9** (5.4 g, 90%). An analytical sample was prepared by crystallization from AcOEt–diisopropyl ether. mp 94 °C. IR (Nujol) 1670, 1748, 1777 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.08—1.20 (1H×1/10, m), 1.38—1.49 (1H×9/10, m), 1.53—1.68 (1H×9/10, m), 1.90—2.10 (2H×1/10, m), 1.98—2.22 (2H×9/10, m), 2.53—2.70 (2H, m), 3.22—3.30 (1H×9/10, m), 3.52—3.58 (1H×1/10, m), 4.91 (1H×1/10, t, J=6 Hz), 4.96 (1H×9/10, t, J=6 Hz), 5.16 (1H, d, J=12 Hz), 5.28 (1H, d, J=12 Hz), 6.89 (1H×9/10, s), 6.93 (1H×1/10, s), 7.00—7.40 (20H, m). *Anal.* Calcd for $C_{34}H_{31}NO_5$: C, 76.53; H, 5.86; N, 2.62, Found: C, 76.41; H, 5.91; N, 2.63. Mass 534 $(M+H)^+$.

Diphenymethyl *N*-Carbobenzyloxylpyroglutamate (10) Diphenyldiazomethane (120 g, 0.1 mmol) was added to a solution of *N*-benzyloxycarbonyl-pyroglutamic acid (26.3 g, 0.1 mol) in THF (500 ml) and the mixture was stirred for 16 h at room temperature. After AcOEt (500 ml) was added, the precipitate was collected by filtration to provide 33 g of **10** as white crystals (77%). White crystals. mp 169—170 °C. IR (Nujol) 1746, 1782 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.98—2.04 (1H, m), 2.30—2.40 (1H, m), 2.45—2.62 (2H, m), 4.78 (1H, d, J=6 Hz), 5.01 (1H, d, J=12 Hz), 5.21 (1H, d, J=12 Hz), 6.92 (1H, s), 7.22—7.37 (15H, m). ^{13}C-NMR ($CDCl_3$) δ: 21.72, 30.99, 58.92, 68.35, 78.28, 126.95, 127.13, 128.11, 128.44, 128.66, 128.71, 134.85, 139.20, 150.72, 170.00, 174.97. *Anal.* Calcd for $C_{26}H_{23}NO_5$: C, 72.56; H, 5.44; N, 3.00. Found: C, 72.71; H, 5.40; N, 3.26. Mass 430 $(M+H)^+$.

Diphenymethyl *N*-Benzyloxycarbonyl-4-methylpyroglutamate (11) A solution of LiHMDS (1 M solution, 13.4 ml, 13.4 mmol) in THF was added dropwise over 10 min to a solution of **10** (5 g, 11.7 mmol) in a mixture of THF–DMF (100 ml/50 ml) at −78 °C under nitrogen atmosphere. After 10 min, methyl iodide (1.5 ml, 24.1 mmol) was added dropwise over 45 min and the mixture was stirred for 3 h at the same temperature. The mixture was then poured into a mixture of AcOEt (200 ml) and water (200 ml) and the organic layer was separated, washed with water (3×200 ml), brine (100 ml), dried over $MgSO_4$ and concentrated under reduced pressure to give a crude product. The isomer ratio was determined by ^{1}H-NMR analysis for this mixture. The crude material was charged on a silica gel column and eluted with a mixture of *n*-hexane/AcOEt (7/3) to provide 1 g of *trans* isomer of **11** followed 1 g of *cis* isomer of **11**.

Trans Isomer: White crystals. mp 108 °C. IR (Nujol) 1739, 1790 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.19 (3H, d, J=7 Hz), 1.95 (1H, dd, J=12, 19 Hz), 2.27 (1H, dd, J=8, 12 Hz), 2.57—2.68 (1H, m), 4.74 (1H, d, J= 8 Hz), 5.05 (1H, d, J=12 Hz), 5.24 (1H, d, J=12 Hz), 6.91 (1H, s), 7.20—7.38 (15H, m). ^{13}C-NMR ($CDCl_3$) δ: 15.15, 30.64, 36.48, 57.04, 68.32, 78.30, 120.35, 126.93, 127.13, 128.01, 128.22, 128.35, 128.38, 128.58, 128.66, 128.71, 134.91, 139.24, 142.96, 170.00, 175.38. *Anal.* Calcd for $C_{27}H_{25}NO_5$: C, 73.12; H, 5.68; N, 3.16. Found: C, 73.10; H, 5.66; N, 3.20. Mass 444 $(M+H)^+$.

Cis Isomer: White crystals. mp 109 °C. IR (Nujol) 1739, 1790 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.16 (3H, d, J=7 Hz), 1.57—1.64 (1H, m), 2.53—2.68 (2H, m), 4.68—4.72 (1H, m), 5.00 (1H, d, J=12 Hz), 5.20 (1H, d, J=12 Hz), 6.92 (1H, s), 7.25—7.35 (15H, m). ^{13}C-NMR ($CDCl_3$) δ: 16.19, 29.55, 37.37, 57.38, 68.35, 78.13, 127.12, 127.23, 128.09, 128.22, 128.32, 128.40, 128.56, 128.60, 128.65, 134.86, 139.25, 150.92, 170.17, 175.46. *Anal.* Calcd for $C_{27}H_{25}NO_5$: C, 73.12; H, 5.68; N, 3.16. Found: C, 73.22; H, 5.75; N, 3.22. Mass 444 $(M+H)^+$.

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