Tetrahedron Vol 44, No 17, pp 5333 to 5342, 1988
Printed in Great Britain

0040-4020/88 $3.00+.00
Pergamon Press plc

ASYMMETRIC SYNTHESIS OF α-AMINO ACIDS BY ALKYLATION OF N-[N-BIS-(METHYLTHIO)METHYLENEGLYCYL]-2,5-BIS(METHOXYMETHOXYMETHYL)PYRROLIDINE AND ENANTIOSELECTIVE SYNTHESIS OF PROTECTED (2S,9S)-2-AMINO-8-OXO-9,10-EPOXYDECANOIC ACID

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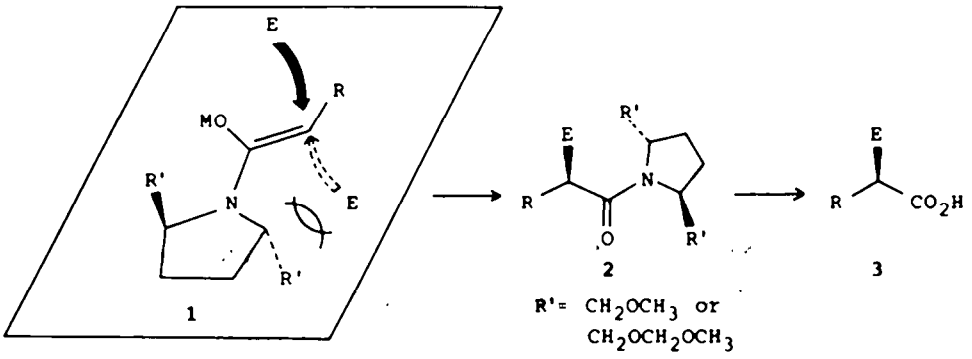
(Received in USA 4 January 1988)

Summary: Highly diastereoselective alkylation (≥96% de) of α-lithiated N-[N-bis(methylthio)methyleneglycyl]-trans-2,5-bis(methoxymethoxymethyl)pyrrolidine and subsequent hydrolysis gave various α-amino acids of high optical purity. An unusual amino acid (2S,9S)-2-amino-8-oxo-9,10-epoxydecanoic acid was also synthesized enantioselectively in its N-protected form by using the alkylation of the above chiral glycine amide and asymmetric epoxidation as means of introducing C2 and C9 asymmetric centers, respectively. Aldol condensation reaction of the same lithiated glycine amide was also examined.

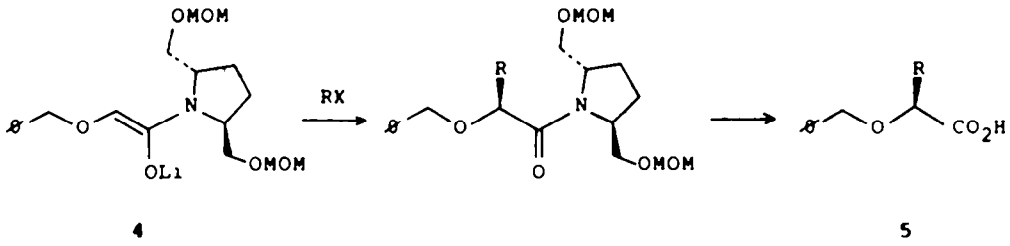
There is a strong demand for the effective methodology for the synthesis of optically pure amino acids because of the growing occurrence of natural rare and biologically active non-proteinogenic amino acids, and various approaches to the asymmetric synthesis of this class of compounds have recently been exploited.[1] Among the conventional methods for the preparation of α-amino acids, the alkylation of glycine derivatives has a particular advantage because a wide variety of α-amino acids can be prepared from a single starting material by the choice of alkylating agents,[2] and several asymmetric versions of this method have also been reported[3,4] where efforts have been directed to the enolates of glycine derivative synthons bearing appropriate chiral auxiliaries. Although the alkylation of some of their enolates was found to proceed with fairly good diastereoselectivity,[4] there still appears to be a demand for the improvement of generality and stereoselectivity.

Recently we found that the amide enolate (1) bearing trans-2,5-disubstituted pyrrolidine as a chiral auxiliary, reacted diastereoselectively with various electrophiles to give α-substituted amides (2), which could be hydrolyzed to give the corresponding α-substituted acids (3) of high enantiomeric purity (≥95% ee, Scheme 1).[5] In this alkylation process, π-facial selectivity of the enolate (1) is not controlled by chelation but principally by steric effect of the C_2-



Scheme 1.

symmetrically placed substituents on the pyrrolidine ring. This suggested that introduction of a heteroatom having lone pair electrons to the α-carbon atom of the amide enolate might not change both degree and sense of asymmetric induction brought about by the auxiliary. Actually, the alkylation of the enolate (4) bearing an oxygen function on its α-carbon atom proved, as expected, to proceed with high diastereoselectivity (≥96% de) and with the same sense of

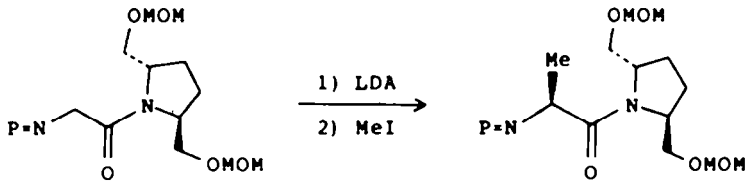


4 5

Scheme 2

asymmetric induction as that in the case of 1, giving optically active O-protected α-hydroxy acids (5) after hydrolysis (Scheme 2).[6] In this paper, we describe another modification of the methodology where the highly effective asymmetric synthesis of α-amino acids has been achieved by the alkylation of the chiral enolate (8) having a nitrogen functionality [R= $(CH_3S)_2C=N-$] at the α-carbon atom.[7]

At first, we investigated the effect of the amino-protecting group upon the diastereoselection in the alkylation of the glycyl amide (6-8) using methyl iodide as an electrophile. As shown in Table 1, bis(methylthio)methylene group[8] was found to be the best in diastereoselectivity and chemical yield. Based on this result, we proceeded to the alkylation of N-[N-bis(methylthio)methylene-glycyl]-trans-2,5-bis(methoxymethoxymethyl)pyrrolidine (8). The results are summarized in Table 2. Alkylation with methyl iodide, propargyl bromide, and benzyl type bromide took place smoothly with high diastereoselectivity (≥96% de) (entries 1, 2, 3, and 4). The reaction with isobutyl bromide proceeded



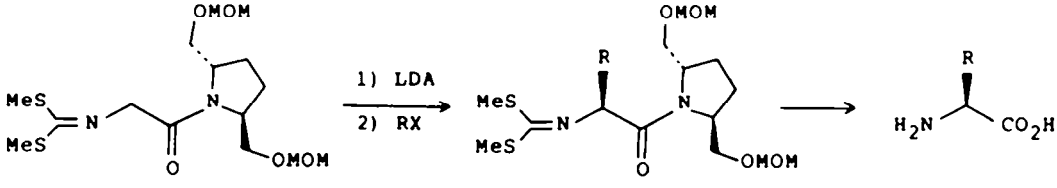
6 P= C_6H_5CH
7 P= o-$(HO)C_6H_4CH$
8 P= $(MeS)_2C$

Table 1. Effect of amino-protecting group upon diastereoselection in alkylation of glycine amides (6-8)[a]

entry	P	Yield (%)	% de
1	C_6H_5CH (6)	66	80
2	o-$(HO)C_6H_4CH$ (7)	-[b]	-
3	$(MeS)_2C$ (8)	84	98

a) To a THF solution of the lithium enolate derived from the corresponding amide was added MeI (1.1 eq) at -78 °C. b) The reaction was quite sluggish.

reluctantly to give a poor yield (15%) even after prolonged reaction time (3 d) and the diastereoselectivity suffered some deterioration (84% de). The reaction of isopropyl iodide did not proceed at all. However, the use of the



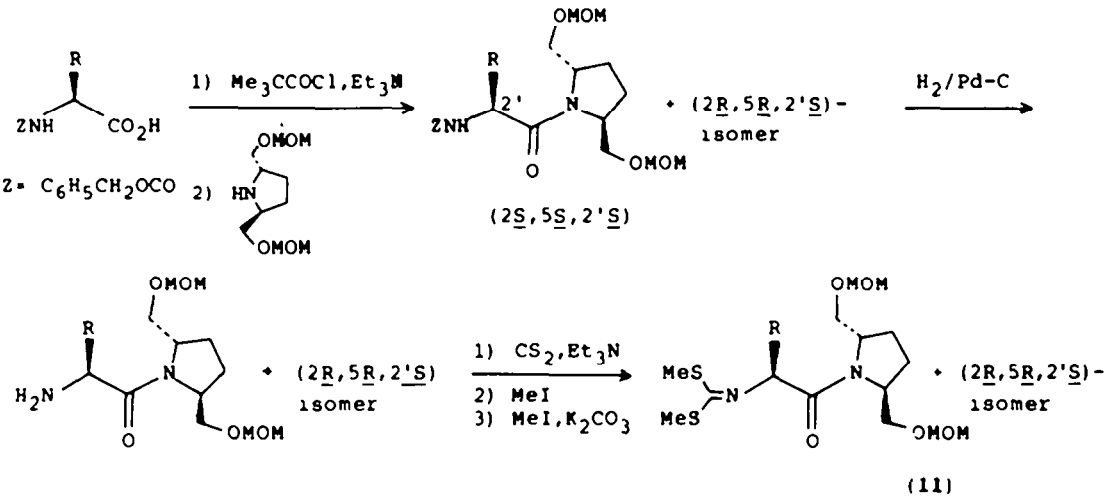
8 9a-f 10a-f

a= Me, b= $PhCH_2$, c= $MeOPhCH_2$
d= $HC{\equiv}CCH_2$, e= Me_2CH, f= Me_2CHCH_2

Table 2. Alkylation of the (2S,5S)-amide (8)

Entry	RX	Alkylated Amide (9a-f) Solvent	Temp (°C)	Yield (%)	% de	α-Amino Acid (10a-f) Yield (%)	% ee	Config.
1	MeI	THF	-78--20	85	98	97	95	S
2	$PhCH_2Br$	THF	-78--20	85	98	92	97	S
3	p-$MeOC_6H_4CH_2Br$	THF	-78--20	91	96	88	95	S
4	$HC{\equiv}CCH_2Br$	THF	-78--20	95	98	51	98[a]	S
5	Me_2CHOTf	THF-pentane	-20	51	98	81	-[b]	S
6	Me_2CHCH_2OTf	THF-toluene	-78--20	68	97	96	97	S

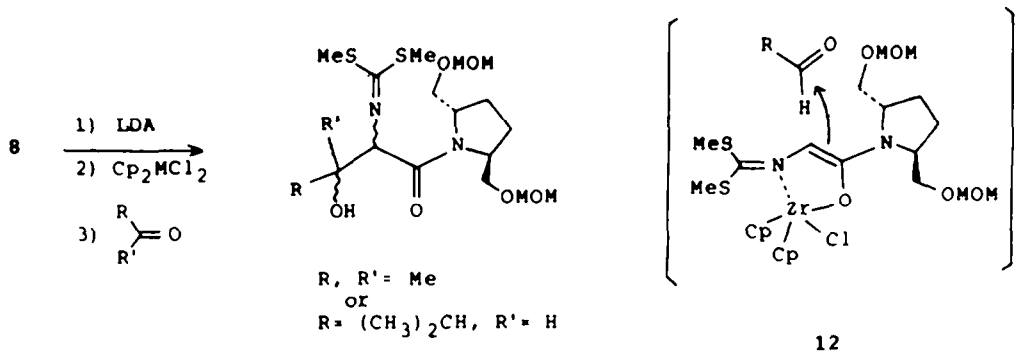
a) The enantiomeric excess was determined by conversion to methyl 2-formylamino-4-pentynoate followed by ^1H NMR (400 MHz) analysis in the presence of $Eu(hfc)_3$. b) The precise value could not be determined either by ^1H NMR or HPLC analysis of the corresponding N-benzyloxycarbonylleucyl dipeptide methyl ester: $[\alpha]_D^{24.8}$ +5.60°, lit. $[\alpha]_D$ +5.63° (J.P.Greenstein and M.Winitz, "Chemistry of Amino Acid," John Wiley & Sons Inc., New York (1961), Vol. 3, p. 2368).



Scheme 3

corresponding triflates improved the yields and diastereoselectivity (entries 5 and 6). Diastereomeric excesses of the products (9) were determined by the comparison of ^{1}H NMR spectra of the products and those of the standard samples containing a mixtures of (2S,5S,2'S)- and (2R,5R,2'S)-amides (11) which were prepared from the corresponding (S)-amino acids and dl-2,5-bis(methoxymethoxymethyl)pyrrolidine by a conventional manner (Scheme 3), wherein the diastereomeric ratios were given by the relative intensities of S-methyl protons in a pair of diastereomers. All the alkylated products (9) were hydrolyzed to the corresponding amino acids (10) in good yields by refluxing them in aqueous 1 mol dm^{-3} HCl for 4 h, followed by neutralization of the mixture with aqueous saturated $NaHCO_3$ at room temperature. The (2S,5S)-amide (8) invariably gave (S)-amino acids (10). This means that the approach of electrophiles occurred on the si-face of Z-enolate and that the sense of asymmetric induction in these reactions is the same as that in the alkylation reaction of 1 (R= alkyl),[5] as expected. In order to determine the optical purity, these amino acids were coupled with an active ester of (S)-N-benzyloxycarbonylleucine by using N-hydroxysuccinimide, and the resulting peptides were converted to the corresponding methyl esters which were analyzed by ^{1}H NMR or HPLC to be ≥95% ee. This confirmed that compounds (9) were hydrolyzed to amino acids (10) without detectable epimerization. The hydrolysis of the amide (9d) gave a 2-amino-4-pentynoic acid which is an unusual amino acid isolated from a mushroom, Amanita pseudoporphria.[9]

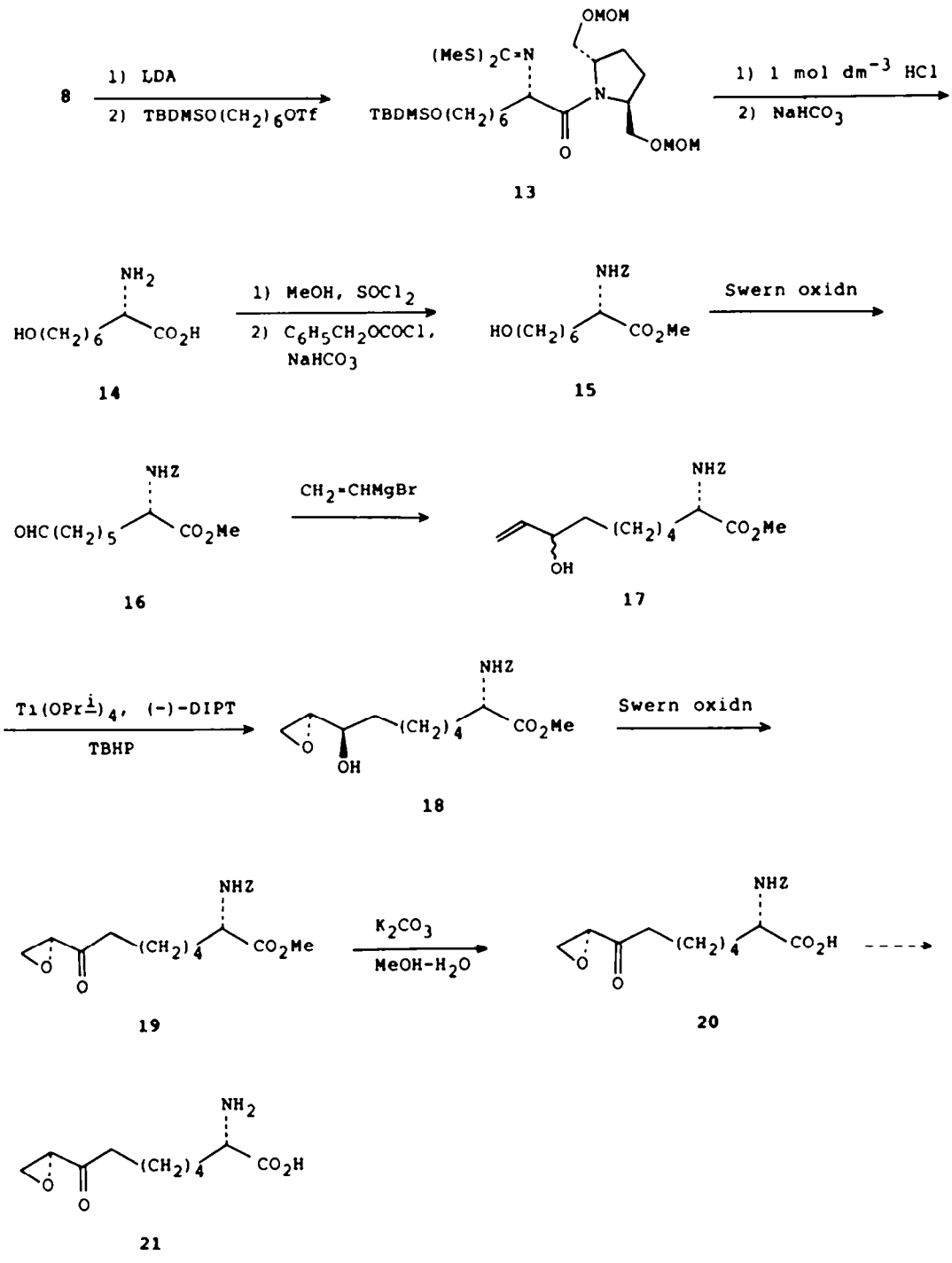
In order to obtain β-hydroxy-α-amino acids, the reaction of the glycine amide (8) with carbonyl compounds was next examined (Scheme 4). The reaction of the lithium enolate with acetone proceeded with moderate diastereoselectivity (71% de), though the yield was not so good (30%). However, the reaction of the



Scheme 4

same enolate with 2-methylpropanal afforded three diastereomeric products in a ratio of 2.4:1:1. The addition of Cp_2TiCl_2 or Cp_2ZrCl_2 to a solution of the lithium enolate prior to the reaction, did not improve the diastereoselectivity. In the aldol reaction of the enolate (1, R= alkyl, M= Li) which did not carry the nitrogen function on its α-carbon atom, high syn-selectivity was secured by the addition of Cp_2ZrCl_2.[10] In the case of the present enolate (12), however, the zirconium ion is coordinatively saturated by the chelation of the azomethine nitrogen so that the reaction proceeds through non-cyclic transition state resulting in the poor stereoselectivity.[11]

As an application of the present method, synthesis of (2S,9S)-2-amino-8-oxo-9,10-epoxydecanoic acid (Aoe, 21) was carried out in its N-protected form (20). Aoe is an unusual amino acid found in several physiologically active peptides[12] as one of the components. Though it has not been isolated in the form of free amino acid, its structure including absolute configuration was established by an X-ray study of a cyclic tetrapeptide, chramydocin,[12b] and the synthesis of dl-[13] or an unnatural diastereomer, (2S,9R)-Aoe[14] has been reported in protected form. Our synthesis (Scheme 5) started with the asymmetric alkylation of 8 with 6-t-butyldimethylsiloxy-1-hexyl triflate which was prepared from the corresponding alkoxide by treatment with trifluoromethanesulfonic anhydride in toluene.[15] The amide (13) was hydrolyzed to the hydroxy amino acid (14) according to the procedure described above. The optical purity of 14 was determined to be 98% ee after its conversion to the dipeptide.[16] The compound (14) was converted to the N-benzyloxycarbonyl methyl ester (15) by successive treatment with thionyl chloride in methanol and with benzyloxycarbonyl chloride in an aqueous $NaHCO_3$ solution. Swern oxidation[17] of 15, followed by treatment of the resulting aldehyde (16) with vinylmagnesium bromide gave a diastereomeric mixture of allylic alcohols (17). The mixture was subjected to the kinetic resolution using a system of titanium tetraisopropoxide, (-)-diisopropyl tartrate, and t-butyl hydroperoxide (TBHP) developed by Sharpless and one of the authors (T.K.),[18] to afford the epoxy alcohol (18) having the desired 9R-



Scheme 5

configuration.[19] The epoxy alcohol (18) was converted to the epoxy ketone (19) by Swern oxidation. The compound (19) was smoothly hydrolyzed by treatment with aqueous K_2CO_3 to give N-benzyloxycarbonyl Aoe (20). But the deprotection (H_2/Pd-C or $RuCl_3$-$NaIO_4$/H_2O-CH_3CN-CCl_4[20]) to the free amino acid (21) was unsuccessful because of the lability of the epoxy ketone structure under the conditions.

Experimental

^{1}H NMR spectra were recorded with JEOL FX90Q in $CDCL_3$ using TMS as the internal standard unless otherwise mentioned. MS spectra were recorded on JEOL DX-300.

(2S,5S)-N-[N-Bis(methylthio)methyleneglycyl]-2,5-bis(methoxymethoxymethyl)pyrrolidine (8)

LiOH (69.2 mg, 2.5 eq) was added to a solution of N-[bis(methylthio)methylene]glycine methyl ester (290 mg, 2.3 eq)[8] in methanol (3.0 ml) and the mixture was stirred at room temperature for 16 h. The solution was concentrated in vacuo to dryness and the residue was suspended in dichloromethane (2 ml). To this was added pivaloyl chloride (185 µl, 2.3 eq) and the mixture was stirred for 8 h at room temperature. To the mixture was added a solution of (2S,5S)-bis(methoxymethoxymethyl)pyrrolidine (140.8 mg, 0.643 mmol) and triethylamine (269 µl, 3 eq) in dichloromethane (1 ml). After 12 h, the mixture was concentrated and chromatographed on silica gel with hexane-ethyl acetate (1:1) to give **8** (208.6 mg, 84.5%) as an oil; $[\alpha]_D^{23.6}$-59.49° (c= 4.13, MeOH); ^{1}H NMR δ 1.64-2.20(m, 4H), 2.32(s, 3H), 2.48(s, 3H), 3.26(s, 6H), 3.63-3.70(m, 4H), 4.14(m, 2H), 4.22(s, 2H), 4.51(s, 4H). Found: C, 47.33; H, 7.36, N, 7.36%. Calcd for $C_{15}H_{28}N_2O_5S_2$: C, 47.35; H, 7.42, N, 7.36%.

(2S,5S)-N-[(S)-N-Bis(methylthio)methylenealanyl]-2,5-bis(methoxymethoxymethyl)pyrrolidine (9a)

A THF solution of LDA (0.631 mol dm^{-3}, 211 µl, 1.05 eq) was added to a solution of the amide (**8**, 48.4 mg) in THF (0.6 ml) at -78 °C and the temperature was raised to -20 °C. After 5 min, the mixture was again cooled to -78 °C and methyl iodide (9.5 µl, 1.2 eq) was added to this under stirring. The mixture was kept at -20 °C for 24h and quenched with aqueous phosphoric acid (5%, 150 µl) at the same temperature. The mixture was allowed to warm to room temperature and extracted with dichloromethane. The organic layer was dried over Na_2SO_4 and concentrated under reduced pressure. The residue was chromatographed on silica gel with hexane-ethyl acetate (3:2) to give **9a** (83.7 mg, 85.5 %) as an oil; $[\alpha]_D^{25.6}$-44.6° (c=3.38, MeOH); ^{1}H NMR δ 1.35(d, J=6.4 Hz, 3H), 1.84-2.12(m, 4H), 2.43(s, 3H), 2.56(s, 3H), 3.34(s, 6H), 3.34-3.72(m, 4H), 3.96-4.36(m, 2H) 4.58(s, 4H), 4.49-4.78(m, 1H). Found: C, 48.64; H, 7.66; N, 7.08%. Calcd for $C_{16}H_{30}N_2O_5S_2$: C, 48.71; H, 7.66; N, 7.10%.

(2S,5S)-N-[(S)-N-Bis(methylthio)methylenephenylalanyl]-2,5-bis(methoxymethoxymethyl)pyrrolidine (9b)

The compound was prepared in a similar manner to that described for **9a**. An oil; $[\alpha]_D^{24.4}$-67.6° (c=2.88, MeOH); ^{1}H NMR δ 1.80-2.08(m, 4H), 2.36(s, 3H), 2.48(s, 3H), 2.64-3.84(m, 6H), 3.23(s, 3H), 3.31(s, 3H), 4.04-4.32(m, 2H), 4.37(d, 2H), 4.56(s, 2H), 4.64-4.88(m, 1H), 7.10-7.36(m, 5H). Found: C, 55.88; H, 7.32; N, 5.91%. Calcd for $C_{22}H_{34}N_2O_5S_2$: C, 56.14; H, 7.28; N, 5.95%.

(2S,5S)-N-[(S)-N-Bis(methylthio)methylene-O-methylthyrosyl]-2,5-bis(methoxymethoxymethyl)pyrrolidine (9c)

The compound was prepared in a similar manner to that described for **9a**. An oil; $[\alpha]_D^{26.8}$-72.5° (c=3.66, MeOH); ^{1}H NMR δ 1.67-1.96(m, 4H), 2.44(s, 3H), 2.54(s, 3H), 2.68-3.76(m, 6H), 3.30(s, 3H), 3.33(s, 3H), 3.76(s, 3H), 4.04-4.36(m, 2H), 4.52(s, 2H), 4.54(s, 2H), 4.54-4.84(m, 1H), 6.78(d, J=11.3 Hz, 2H), 7.17(d, J=11.3 Hz, 2H). Found: C, 55.00; H, 7.23; N, 5.58%. Calcd for $C_{23}H_{36}N_2O_6S_2$: C, 55.18; H, 7.25; N,5.60%.

(2S,5S)-N-[(2S)-2-Bis(methylthio)methyleneamino-4-pentynoyl]-2,5-bis(methoxymethoxymethyl)pyrrolidine (9d)

The compound was prepared in a similar manner to that described for **9a**. An oil; $[\alpha]_D^{26.0}$-71.2° (c=3.58, MeOH); ^{1}H NMR (400 MHz) δ 1.92-2.26(m, 6H), 1.97(t, J= 2.4 Hz, 1H), 2.41(s, 3H), 2.48(ddd, J=16.1, 4.9, 2.4 Hz, 1H), 2.58(s, 3H), 2.79(ddd, J=16.1, 9.3, 2.4 Hz, 1H), 3.30-3.43(m, 2H), 3.33(s,3H), 3.35(s, 3H), 3.47(dd, J=9.7, 7.4 Hz, 1H), 3.85(dd, J=9.7, 2.9 Hz, 1H), 4.11(m, 1H), 4.34(m, 1H), 4.57(ABq, J=6.4 Hz, 2H), 4.62(ABq, J=6.4 Hz, 2H), 4.79(dd, J=9.3, 4.9 Hz, 1H). Found: C, 51.36; H, 7.17; N, 6.52%. Calcd for $C_{18}H_{30}N_2O_5S_2$: C, 51.65; H, 7.22; N, 6.69%.

(2S,5S)-N-[(S)-N-Bis(methylthio)methylenevalyl]-2,5-bis(methoxymethoxymethyl)pyrrolidine (9e)

The compound was prepared in the same manner as described for **9a** except that isopropyl triflate was used as the alkylating agent. The triflate was prepared

from the corresponding alcohol and trifluoromethanesulfonic anhydride in pentane in the presence of pyridine according to the reported procedure.[21] An oil; $[\alpha]_D^{24.0}$ -34.0° (c=2.61, MeOH); ^{1}H NMR δ 0.94(d, J=6.4 Hz, 3H), 0.96(d, J=6.4 Hz, 3H), 1.80-2.36(m, 5H), 2.44(s, 3H), 2.55(s, 3H), 3.34(s, 6H), 3.34-3.86(m, 4H), 4.00-4.44(m, 3H), 4.59(s, 4H). Found: C, 51.19; H, 8.16; N, 6.56%. Calcd for $C_{18}H_{34}N_2O_5S_2$: C, 51.16; H, 8.11; N, 6.63%.

(2S,5S)-N-[(S)-N-Bis(methylthio)methyleneleucyl]-2,5-bis(methoxymethoxymethyl)pyrrolidine (9f)

The compound was prepared in a similar manner to that described for **9e**. The triflate was prepared from the corresponding lithium alkoxide and trifluoromethanesulfonic anhydride according to the reported procedure.[15] An oil; $[\alpha]_D^{23.6}$ -27.4° (c=1.89, MeOH); ^{1}H NMR δ 0.76-1.08(m, 6H), 1.50-1.74(m, 3H), 1.80-2.24(m, 4H), 2.42(s, 3H), 2.57(s, 3H), 3.34(s, 6H), 3.34-3.82(m, 4H), (3.96-4.40(m, 2H), 4.59(s, 4H), 4.46-4.72(m, 1H). Found: C, 52.12; H, 8.20; N, 6.42%. Calcd for $C_{19}H_{36}N_2O_5S_2$: C, 52.27; H, 8.31; N, 6.42%.

Hydrolysis of the Amide (9f) to (S)-Leucine

The amide (**9f**, 48.5 mg) was refluxed in 1 mol dm^{-3} hydrochloric acid (1 ml) for 4 h and cooled to room temperature. The mixture was neutralized with saturated aqueous $NaHCO_3$. Then, the solution was added to an anion exchange column [Dowex 1 (OH-form)]. The column was washed with water until the effluent was neutral and the product was eluted with 1 mol dm^{-3} hydrochloric acid. Ninhydrin-positive fractions were collected and concentrated. The residue was further added to a cation exchange resin [Dowex 50W (H-form)]. The column was washed with water and the product was eluted with 1 mol dm^{-3} NH_4OH solution. Ninhydrin-positive fractions were collected and concentrated to give (S)-leucine (14.6 mg) in 96% yield. $[\alpha]_D^{25}$ -10.9° (c=0.52, H_2O); lit.[22] $[\alpha]_D^{25}$ -11.0° (c=2, H_2O).

For the determination of the optical purity, the leucine thus obtained was converted to methyl benzyloxycarbonyl-(S)-leucylleucinate.

A solution of N-hydroxysuccinimide ester of (S)-N-benzyloxycarbonylleucine (26 mg, 2 eq) in dioxane (1 ml) was added to a solution of the leucine obtained (6.3 mg), triethylamine (6.7 μl, 1 eq) in dioxane (1 ml) and water (1 ml) at 0 °C and the mixture was stirred for 14 h at room temperature. The mixture was concentrated in vaccuo and diluted with ether. Diazomethane was bubbled through the solution until it turned yellow. The solution was filtered through silica gel column and concentrated. The residue was analyzed by HPLC using Unisil Q (purchased from Gasukuro Kogyo Co. Ltd.) and hexane-ether(7:3) as an eluent, and diastereomeric purity of the product was determined to be 97% de.

Other amide (**9a, 9b, 9c, 9d, and 9e**) were also converted to the respective amino acids in the same manner.

(2S,5S)-N-[(2S)-8-t-Butyldimethylsiloxy-2-bis(methylthio)methyleneamino-octanoyl]-2,5-bis(methoxymethoxymetyl)pyrrolidine (13)

A solution of n-butyl lithium in hexane (1.60 mol dm^{-3}, 1.49 ml, 1.05 eq) was added to a solution of 6-t-butyldimethylsiloxy-1-hexanol (527 mg, 2.27 mmol) at 0 °C. After 1 min, trifluoromethanesulfonic anhydride (382 μl, 1 eq) was added and the whole mixture was submitted to centrifugal filtration at the same temperature. To a THF solution (1.3 ml) of the lithium enolate (0.802 mmol) prepared from **8** (308 mg) in the same manner as described for preparation of **9a**, was added dropwise the above filtrate (4.2 ml) containing the triflate (0.963 mmol, 1.2 eq) at -78 °C. The mixture was then kept at -20 °C for 24 h and, after the addition of aqueous phosphoric acid (5%, 560 μl), allowed to warm to room temperature. After the usual workup, chromatography on silica gel with hexane-ethyl acetate (3:2) gave **13** (446.2 mg) in 93% yield as an oil; $[\alpha]_D^{24.8}$ -30.22° (c=0.72, MeOH); ^{1}H NMR δ 0.04(s, 6H), 0.89(s, 9H), 1.13-1.61(m, 10H), 1.64-2.20(m, 4H), 2.42(s, 3H), 2.56(s, 3H), 3.33(s, 6H), 3.40-3.81(m, 6H), 4.0-4.37(m, 3H), 4.58(s, 4H). MS(EI), m/z 594(M^+, 0.4%), 563(10), 547(78), 537(43), 471(51), 348(100). HRMS calcd for $C_{27}H_{51}N_2O_6S_2Si$ 594.31894, found m/z 594.31920.

(2S)-2-Amino-8-hydroxyoctanoic Acid (14)

The compound was prepared from **13** in 94.3% yield in a similar manner to that described for the hydrolysis of **9f**.
Crystals; m.p. 236 °C(decomp); $[\alpha]_D^{24.4}$ +4.6° (c= 2.63, H_2O); ^{1}H NMR (D_2O) δ 1.1-1.9(m, 10H), 3.52(m, 3H). The compound (**14**) was used for the next reaction without further purifcation.

Methyl (2S)-2-Benzyloxycarbonylamino-8-hydroxyoctanoate (15)

Thionyl chloride (3 ml) was added dropwise to a solution of the amino acid

(14, 193.7 mg) in methanol (10 ml) at -10 °C. Then, the mixture was refluxed for 4 h, cooled to room temperature, and concentrated. The residue was dissolved in water (2 ml) and, after the addition of ether (0.4 ml), $NaHCO_3$ (330 mg, 3.6 eq) and benzyloxycarbonyl chloride (128 µl, 0.65 eq) were added to this under stirring. After 2 h, a further amount of $NaHCO_3$ (170 mg) and benzyloxycarbonyl chloride (128 µl, 0.65 eq) was added and stirring was continued for another 3 h. The mixture was extracted with dichloromethane. The organic layer was dried over Na_2SO_4 and concentrated in vacuo. The residue was chromatographed on silica gel with hexane-ethyl acetate (3:2) to give **15** (281.9 mg, 79.5%) as an oil; $[\alpha]_D^{26.8}$ -16.25° (c= 1.44, MeOH); ^{1}H NMR δ 1.0-2.0(m, 11H), 3.64(t, J=6.0 Hz, 2H), 3.72(s, 3H), 4.32(m, 1H), 5.10(s, 2H), 5.28(m, 1H), 7.32(br s, 5H). Found: C, 63.18; H, 7.79; N, 4.36%. Calcd for $C_{17}H_{25}NO_5$: C, 63.14; H,7.79; N, 4.33%.

Methyl (2S)-2-Benzyloxycarbonylamino-8-oxooctanoate (16)

Dimethylsulfoxide (77 µl, 2.2 eq) was added to a solution of oxalyl chloride (46 µl, 1.1 eq) in dichloromethane (12.5 ml) at -60 °C and stirred for 2 min. To this solution was added at the same temperature, a solution of the N-benzyloxycarbonyl methyl ester (**15**, 158.5 mg, 0.49 mmol) in dichloromethane (0.5 ml). After 5 min, triethylamine (342 µl, 5 eq) was added and the mixture was allowed to warm to room temperature. The mixture was filtered through Celite and concentrated in vacuo. The residue was chromatographed on silica gel with hexane-ethyl acetate (7:3) to give **16** (138.7 mg, 88%) as an oil; ^{1}H NMR δ 1.0-2.0(m, 8H), 2.41(t, J=6 Hz, 2H), 3.72(s, 3H), 4.32(m, 1H), 5.10(s, 2H), 5.28(m, 1H), 7.32(br s, 5H).

Methyl (2S,8RS)-2-Benzyloxycarbonylamino-8-hydroxy-9-decenoate (17)

To a solution of the aldehyde (**16**, 33.2 mg, 0.103 mmol) in THF (0.5 ml) was added a THF solution of vinylmagnesium bromide (0.888 mol dm^{-3}, 0.24 ml) at -78 °C. The mixture was stirred for 1 h at the same temperature and quenched with saturated aqueous NH_4Cl. The mixture was filtered through Celite and concentrated in vacuo. The residue was chromatographed on silica gel with hexane-ethyl acetate (7:3) to give **17** (19.4 mg, 53.7%) as an oil; $[\alpha]_D^{24.8}$-12.89° (c=2.61, MeOH); ^{1}H NMR δ 1.1-2.0(m, 10H), 3.72(s, 3H), 4.07(m, 1H), 4.37(m, 1H), 5.08(m, 2H), 5.10(s, 2H), 5.28, (m, 2H), 7.32(br s, 5H). Found: C, 65.57; H, 7.66; N, 4.09%. Calcd for $C_{19}H_{27}NO_5$: C, 65.30; H, 7.79; N, 4.01%.

Methyl (2S,8R,9R)-2-Benzyloxycarbonylamino-9,10-epoxy-8-hydroxydecanoate (18)

(-)-Diisopropyl tartrate (32.6 mg, 1.3 eq) was added at -20 °C to a solution of $Ti(OPr^i)_4$ (31.4 µl, 1 eq) in dichloromethane (0.5 ml). After 5 min, a solution of the allylic alcohol (**17**, 37.5 mg, 0.107 mmol) in dichloromethane and a solution of TBHP (6.11 mol dm^{-3}, 34 µl, 2eq) in dichloroethane were added successively at the same temperature, and the mixture was left to stand for 4 days in a refrigerator (-22 °C). The mixture was quenched with acetone (1 ml) and water (10 µl), and allowed to warm to room temperature. The solution was filtered through Celite and concentrated. Chromatography on silica gel with hexane-ethyl acetate (3:2) gave **18** (13.0 mg, 33.2%) as an oil; $[\alpha]_D^{27.2}$-15.83° (c=0.39, MeOH); ^{1}H NMR δ 1.0-2.0(m, 10H), 2.75(m, 2H), 2.98(m, 1H), 3.72(s, 3H), 3.80(m, 1H), 4.37(m, 1H), 5.10(s, 2H), 5.22(m, 1H), 7.32(s, 5H). Diastereomeric purity of the product was determined to be >94% by comparison of ^{1}H NMR spectra of its α-methoxy-α-trifluoromethylphenylacetate (MTPA)[23] with that of the corresponding MTPA ester derived from the epoxidation product of **17** with $VO(acac)_2$-TBHP system[24].

Methyl (2S,9S)-2-Benzyloxycarbonylamino-8-oxo-9,10-epoxydecanoate (19)

The compound (**18**) was oxidized to **19** in a similar manner to that described for **16**. Yield, 76.1%. An oil; $[\alpha]_D^{25.6}$-32.29° (c=0.35, MeOH); ^{1}H NMR δ 1.1-2.0(m, 8H), 2.29(m, 2H), 2.88(m, 2H), 3.41(m, 1H), 3.72(s, 3H), 4.32(m, 1H), 5.10(s, 2H), 5.22(m, 1H), 7.32(br s, 5H). MS (FAB), m/z 364(MH^+, 13%), 320(22), 91(100). HRMS calcd for $C_{19}H_{25}NO_6$ 363.16822, found m/z 363.16832.

(2S,9S)-2-Benzyloxycarbonylamino-8-oxo-9,10-epoxydecanoic Acid (20)

A mixture of K_2CO_3 (0.136 mol dm^{-3}, 0.91 ml) and the compound (**19**, 15 mg) in water and methanol (1:1) was stirred at room temperature for 8 h. The solution was adjusted to pH 4 by the addition of aqueous phosphoric acid (5%) and the mixture was extracted with dichloromethane. The organic layer was dried over Na_2SO_4 and concentrated in vacuo. Reversed phase chromatography on Merk silica gel 60 silanised (70-230 mesh) with hexane-ethyl acetate (1:1) gave **20** (12.2 mg, 84.5%) as an oil; $[\alpha]_D^{24.4}$-17.81° (c=0.26, MeOH); ^{1}H NMR δ 1.1-2.0(m, 8H), 2.29(m, 2H), 2.88(m, 2H), 3.41(m, 1H), 4.32(m, 1H), 5.10(s, 2H), 5.22(m, 1H), 7.32(s,

5H). MS (FD) m/z 350(MH^+, 100%), 304(12), 91(27).

The authors thank Dr. Michinori Waki, Department of Chemistry, Kyushu University, for helpful discussions. Support by the Grant-in-Aid for Scientific Research (No. 59470020) from the Ministry of Education, Science, and Culture, Japan, is also gratefully acknowledged.

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