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ASYMMETRIC SYNTHESIS OF α-AMINO ACIDS BY ALKYLATION OF A GLYCINE AMIDE DERIVATIVE BEARING CHIRAL 2,5-DISUBSTITUTED PYRROLIDINE AS AN AMINE COMPONENT

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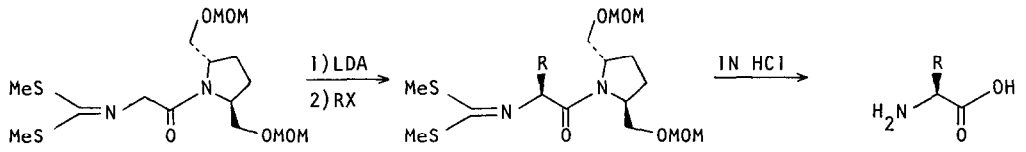
Summary: Highly diastereoselective alkylation (≥96% de) of α-lithiated N-[N'-bis(methylthio)-methyleneglycyl)-trans-2,5-bis(methoxymethoxymethyl)pyrrolidine and subsequent hydrolysis gave α-amino acids of high optical purity. An unusual amino acid (2S,9S)-2-amino-8-oxo-9,10-epoxydecanoic acid was synthesized in its N-protected form as an application of the method.

The alkylation of glycine derivatives has a particular advantage for the synthesis of α-amino acids because a wide variety of α-amino acids can be prepared from a single starting material by the choice of alkylating agents.[1] However, examples of asymmetric synthesis of α-amino acid by this approach in combination with appropriate chiral auxiliaries are not many,[2] and enantiomeric purity attained therein has not been so satisfactory.

Here, we describe a highly effective asymmetric synthesis of α-amino acids by diastereoselective alkylation by using a chiral auxiliary, 2,5-bis(methoxymethoxymethyl)pyrrolidine,[3a] as its N-protected glycine amide (**1**). For the N-protection, bis(methylthio)methylenation[4] gave the best results among others. Results are summarized in Table 1. Alkylation with methyl iodide or benzyl type bromide took place smoothly. The reaction with isopropyl iodide did not proceed, and isobutyl iodide gave only a poor yield (15%). However, the use of the corresponding triflates much improved the yields (entries 3 and 4). All the alkylated products (**2**) were hydrolyzed to the corresponding amino acids (**3**) without appreciable racemization by refluxing them in aqueous 1 mol cm^{-3} HCl for 4h, followed by neutralization of the mixture with $NaHCO_3$ at rt. The (2S,5S)-amide (**1**) invariably gave (S)-amino acids (**3**) indicating the approach of electrophiles on the si-face of the Z-enolate.[3]

Thus, in view of the good overall yield, the high enantiomeric purity, and the predictable stereochemistry of the product, the present method will provide a general and useful means for the synthesis of optically active α-amino acids, especially of those of unusual or unnatural type which are not easily accessible by fermentation procedure.

In a typical experiment, the amide (**1**, 62.5 mg, 0.164 mmol)[5] was lithiated in THF (0.3 ml) by the addition of a solution of lithium diisopropylamide (0.67 mol cm^{-3} in hexane, 270 μl, 1.1 eq) at -78 °C and by keeping the mixture at -20 °C for 5 min. The mixture was cooled to -78 °C, and a solution of isobutyl triflate (0.53 mol cm^{-3} in toluene, 370 μl, 1.2 eq; preparation, reference d in Table 1) was added to this under stirring. The mixture was left to stand for 24 h at -20 °C, and after the addition of aqueous phosphoric acid (5%, 120 μl), the temperature was raised to rt. Extraction (CH_2Cl_2), drying (Na_2SO_4), concentration, and silica gel chromatography (hexane-ethyl acetate, 3:2) gave (2S,5S,2'S)-N-[N'-bis(methylthio)methylene-leucyl]-2,5-bis(methoxymethoxymethyl)pyrrolidine as an oil (48.5 mg, 68%).



1 2 3

Table 1. Alkylation of the (2S,5S)-Amide (1)

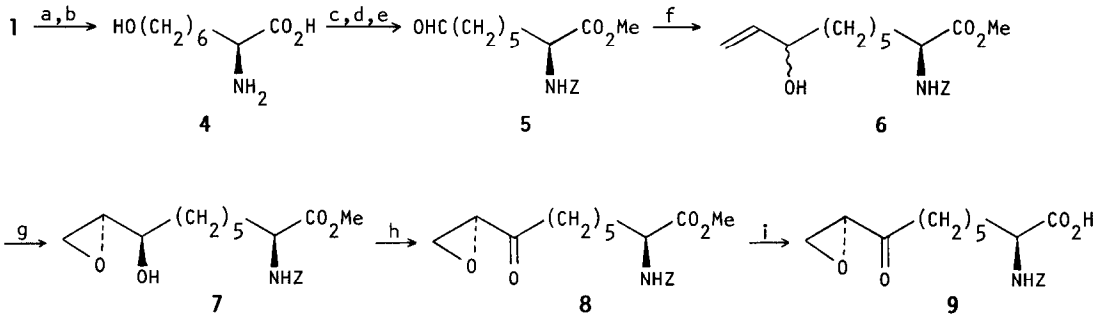
Entry	Alkylation			Alkylated Amide (2)			α-Amino Acid (3)		
	RX	Solvent	Temp (°C)	Yield (%)	% de[a]	$[\alpha]_D$ (MeOH)	Yield (%)	% ee	Confn.[b]
1	MeI	THF	-78~-20	84	98	-44.6°	97	95[e]	S
2	$PhCH_2Br$	THF	-78~-20	85	98	-67.6°	92	97[f]	S
3	Me_2CHOTf[c]	THF-pentane	-20	51	98	-34.0°	81	-[g]	S
4	Me_2CHCH_2OTf[d]	THF-Toluene	-78~-20	68	97	-27.4°	96	97[h]	S
5	p-$MeOC_6H_4CH_2Br$	THF	-78~-20	91	96	-72.5°	88	95[f]	S

a) Diastereomeric ratios were determined from intensities of relevant ^1H NMR(90 MHz) signals. b) Configuration was determined from the sign of optical rotation of the amino acid. c) The triflate was prepared from the corresponding alcohol and $(CF_3SO_2)_2O$ in pentane in the presence of pyridine according to the reported procedure [C.D.Beard, K.Baum, and V.Grakauskas, J. Org. Chem., **38**, 3673 (1973)]. d) The triflate was prepared from the corresponding Li alkoxide (n-BuLi) and $(CF_3SO_2)_2O$ in toluene [W.G. Dauben and J.W.Vinson, J. Org. Chem., **40**, 3756 (1975)]. e) The amino acid was coupled with an active ester of N-(benzyloxycarbonyl)-L-leucine (Z-leucine) with N-hydroxysuccinimide [G.W.Anderson, J.E.Zimmerman, and F.M.Callahan, J. Am. Chem. Soc., **86**, 1839 (1964); Y.Shimohigashi, S.Lee, and N.Izumiya, Bull. Chem. Soc. Jpn., **49**, 3280 (1976)] and the dipeptide obtained was converted to the corresponding methyl ester (CH_2N_2). Enantiomeric excess was determined from the intensity of the ^1H NMR signal (alanine methyl). f) Determined from the intensity of ^1H NMR signal (ester methyl) of the Z-leucyl dipeptide methyl ester (see reference e). g) Precise value could not be obtained either by ^1H NMR or HPLC analysis of the Z-leucyl dipeptide methyl ester. $[\alpha]_D^{26.5}$+5.38°, lit. $[\alpha]_D^{25}$+5.63° (J.P.Greenstein and M.Winitz, "Chemistry of the Amino Acid," John Wiley & Sons, Inc., New York, 1961, Vol. 3, p. 2368). h) Determined after the separation of the Z-leucyl dipeptide methyl ester by HPLC.

The alkylated amide thus obtained was refluxed in aqueous HCl (1 mol cm^{-3}, 1.1 ml) for 4 h. The mixture was neutralized with saturated aqueous $NaHCO_3$, and ion-exchange chromatography [Dowex 1 (OH-form) and 50W (H-form)] gave (S)-leucine [14.6 mg, 96%, $[\alpha]_D^{26}$-10.9° (H_2O, c=0.52), lit.[6] $[\alpha]_D^{25}$-11.0° (H_2O, c=2)].

As an application of the present method, synthesis of (2S,9S)-2-amino-8-oxo-9,10-epoxydecanoic acid (Aoe) was carried out in its N-protected form (**9**). Aoe is an unusual amino acid

found in several physiologically active peptides[7] as a component. Though it has not been isolated as a free amino acid, its structure including absolute configuration was established by an X-ray study of a cyclic tetrapeptide, chlamydocin,[7b] and the synthesis of dl-[8] or unnatural (2S,9R)[9] Aoe has been reported in protected form. Our synthesis (Scheme 1) started with the asymmetric alkylation of **1** with 6-t-butyldimethylsiloxy-1-hexyl triflate[10] followed by acid hydrolysis according to the procedure described above. The hydroxy amino acid (**4**)[11] thus obtained was converted into an aldehyde (**5**)[12] and then into a diastereomeric mixture of



a) LDA, $TfO(CH_2)_6OTBDMS$ (-78~-20 °C, 86%) b) 1 mol cm^{-3} HCl reflux (91.2%) c) $SOCl_2$, MeOH d) $ClCOOCH_2C_6H_5$, $NaHCO_3$ (79.5% from 4) e) $(COCl)_2$, DMSO, Et_3N, CH_2Cl_2 (88%) f) vinylmagnesium bromide, THF (52%) g) $Ti(O^iPr)_4$, D-(-)-diisopropyl tartrate, $(CH_3)_3COOH$ CH_2Cl_2 (32%) h) the same reagents as e (75%) i) K_2CO_3, MeOH-H_2O (1:1) (84.5%)

Scheme 1

allyl alcohols (**6**)[13] by conventional transformations. The corresponding N-(t-butoxycarbonyl) compound was the intermediate of the synthesis by Jacquier et al.[9] and the next kinetic resolution by asymmetric epoxidation[14] to **7**[15] was carried out in a similar way. The Swern oxidation of **7** gave the ketone (**8**).[16] **8** was smoothly hydrolyzed to N-benzyloxycarbonyl Aoe (**9**)[17] but the deprotection to the free amino acid was unsuccessful because of the lability of **9** under the conditions.

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References and Notes

1) For example: M.J. O'Donnell and J. Falmagne, Tetrahedron Lett., **26**, 699 (1985); A. Shanzer, L. Somekh, and D. Butina, J. Org. Chem., **44**, 3967 (1979); G. Stork, A.Y.W. Leong, and A.M. Touzin, ibid., **41**, 3491 (1976); A.P. Krapcho and E.A. Dundulis, Tetrahedron Lett., **17**, 2205 (1976); D. Hoppe, Angew. Chem., Int. Ed. Engl., **14**, 426 (1975); V. Schöllkopf, D. Hoppe, and R. Jentsch, ibid., **10**, 331 (1971); S. Ohdan, T. Ichikawa, Y. Araki, and Y. Ishido, Bull. Chem. Soc. Jpn., **47**, 1295 (1974). 2) S. Yamada, T. Oguri, and T. Shioiri, J. Chem. Soc., Chem.

Commun., **1976**, 136; P. Duhamel, J. Eddine, and J. Valnot, Tetrahedron Lett., **25**, 2355 (1984). 3) a) Asymmetric alkylations: Y. Kawanami, Y. Ito, T. Kitagawa, Y. Taniguchi, T. Katsuki, and M. Yamaguchi, Tetrahedron Lett., **25**, 857 (1984); M. Enomoto, Y. Ito, T. Katsuki, and M. Yamaguchi, ibid., **26**, 1343 (1985). b) Other asymmetric reactions: Y. Ito, T. Katsuki, and M. Yamaguchi ibid., **25**, 6015 (1984); T. Katsuki and M. Yamaguchi, ibid., **26**, 5807 (1985). 4) D. Hoppe and L. Beckmann, Justus Liebigs Ann. Chem., **1979**, 2066. 5) The amide (1) was prepared by stirring (2S,5S)-bis(methoxymethoxymethyl)pyrrolidine (1 mmol) and mixed [bis(methylthio)-methylene]glycyl pivalic anhydride (2.3 mmol) in CH_2Cl_2 in the presence of Et_3N (3 mmol) and dimethylaminopyridine (0.1 mmol) at rt. Yield 84.5%. An oil; $[\alpha]_D^{23.6}$-59.49° (MeOH, c=4.13); ^1H NMR($CDCl_3$), δ 1.64~2.20 (m, 4H), 2.32 (s, 3H), 2.48 (s, 3H), 3.26 (s, 6H), 3.36~3.70 (m, 4H), 4.14 (m, 2H), 4.22 (s, 2H), 4.51 (s, 4H). 6) J.P. Greenstein and M. Winitz, "Chemistry of the Amino Acids," John Wiley & Sons, Inc., New York, 1961, Vol. 3, p. 2075. 7) a) A. Hirota, A. Suzuki, K. Aizawa, and S. Tamura, Agric. Biol. Chem., **37**, 953 (1973); J.M. Liesch, C.C. Sweeley, G.D. Staffeld, M.S. Anderson, D.J. Weber, and R.P. Scheffer, Tetrahedron, **38**, 45 (1982); A. Closse and R. Huguenin, Helv. Chim. Acta, **57**, 533 (1974). b) J.L. Flippen and I.L. Karle, Biopolymers, **15**, 1081 (1976). 8) D.H. Rich, J. Singh, and J.H. Gardner, J. Org. Chem., **48**, 432 (1983). 9) R. Jacquier, R. Razaro, H. Ranirisehenо, and R. Viallefont, Tetrahedron Lett., **25**, 5525 (1984). 10) 6-t-Butyldimethylsiloxy-1-hexanol prepared by partial silylation of hexane-1,6-diol was converted to the triflate by the method quoted in reference d of Table 1. 11) $[\alpha]_D^{24.4}$+4.6° (H_2O, c=2.63). Enantiomeric purity (98% ee) was determined after HPLC separation of a Z-leucyl dipeptide methyl ester (reference e, Table 1). ^1H NMR (D_2O): δ 1.1~1.9 (m, 10H), 3.52 (m, 3H). 12) ^1H NMR ($CDCl_3$): δ1.0~2.0 (m, 8H), 2.41 (t, J=6Hz, 2H), 3.72 (s, 3H), 4.32 (m, 1H), 5.10 (s, 2H), 5.28 (m, 1H). 13) $[\alpha]_D^{24.8}$-12.89° (MeOH, c=2.61). ^1H NMR ($CDCl_3$): δ1.1~2.0 (m, 10H), 3.72 (s, 3H), 4.07 (m, 1H), 4.37 (m, 1H), 5.08 (m, 2H), 5.10 (m, 2H), 5.28 (m, 1H), 5.82 (m, 2H), 7.32 (s, 5H). 14) V.S. Martin, S.S. Woodard, T. Katsuki, Y. Yamada, M. Ikeda, and K.B. Sharpless, J. Am. Chem. Soc., **103**, 6237 (1981). 15) $[\alpha]_D^{27.2}$ -15.83° (MeOH, c=0.39). Diastereomeric excess (94% de) was determined by ^1H NMR of its α-methoxy-α-trifluoromethylphenylacetate. ^1H NMR ($CDCl_3$): δ1.0~2.0 (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). 16) $[\alpha]_D^{25.6}$-32.29° (MeOH, c=0.35). Mass (FAB): MH^+=364 $(C_{19}H_{25}NO_6+H)^+$. ^1H NMR ($CDCl_3$): δ1.1~2.0 (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 (s, 5H). 17) $[\alpha]_D^{24.4}$-17.81° (MeOH, c=0.26). Mass (FD), MH^+=350 $(C_{18}H_{23}NO_6+H)^+$. ^1H NMR ($CDCl_3$): δ1.1~2.0 (m, 8H), 2.29 (m, 8H), 2.88 (m, 2H), 3.41 (m, 1H), 4.32 (m, 1H), 5.10 (s, 2H), 5.22 (m, 1H), 7.32 (s, 5H).

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