Tetrahedron Letters No. 20, pp 1799 - 1802, 1974. Pergamon Press. Printed in Great Britain.

ASYMMETRIC SYNTHESIS OF PEPTIDES I.
ASYMMETRIC SYNTHESIS OF L-PROLYL-D-AMINO ACIDS

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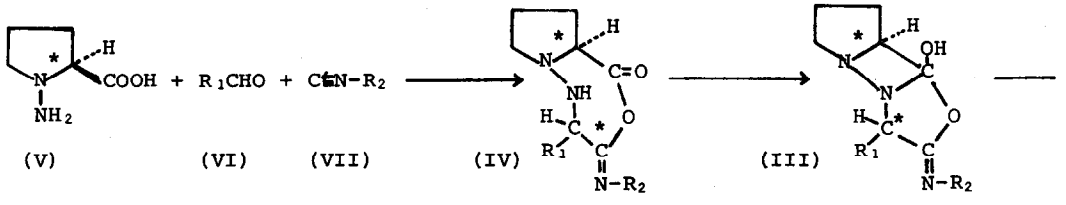
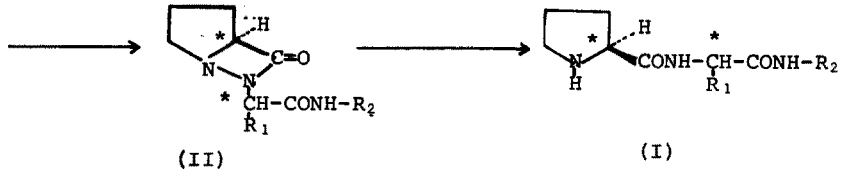
(Received in Japan 30 March 1974; received in UK for publication 8 April 1974)

Di- and tripeptides have recently attracted much attention mainly because some of them have been found to have the physiological activity[1] and these oligopeptides also have served as starting units for synthesis of polypeptides by the fragment condensation method.[2]

We therefore aimed at the asymmetric syntheses[3,4] of these peptides in such a manner that a L-amino acid acted as a chiral reagent and also constituted a part of the product. Our methodology depends on the principles that i) ring intermediates that involve the chiral centers (old and new) are preferred and ii) the protective group which does not form any part of the final product should be avoided. In order to apply these principles to the syntheses of L-prolyl-α-L-amino-acylglycinamide (I; $R_2=CH_2CONH_2$)[e.g. L-prolyl-L-leucyl-glycinamide][5] from L-proline as a chiral starting material, the asymmetric syntheses of L-prolyl-α-amino acid derivatives were examined initially and described in this paper.

For ring formation, the N-N bonded intermediates (II, III, IV) were chosen as depicted below.



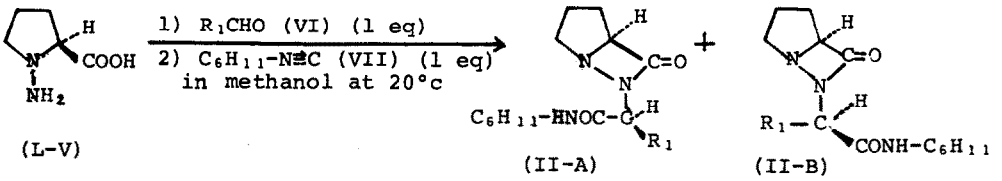


(II) (I)

The reactions of N-amino-L-proline, which was easily obtainable from L-proline, with cyclohexylisonitrile (R_2=cyclohexyl in VII) and an aldehyde (VI) (acetaldehyde, phenylacetaldehyde, isobutyroaldehyde or isovaleroaldehyde) were carried out.[6] Thus a mixture of equivalent amount of reagents in methanol was stirred at 20° or 60° until disappearance of the starting material and after removal of the solvent, the products were purified by preparative chromatography with silicagel and benzene-ethyl acetate (2:1) as an eluting solvent.

The chemical yields, optical rotations and optical yields of these products (IIa-d) thus obtained were listed in Table I.

Table I



(L-V) (II-A) (II-B)

		II		
R_1	Time (hr)	Chem. Yield (%)[a]	$[\alpha]_D^{20}$ (MeOH)	L-D (II-B)[b,d] Optical Yield (%)
IIa $(CH_3)_2CH-CH_2-$	136 (42)[c]	66 (75)	+96.7° (+95°)	32 (26)
IIb $(CH_3)_2CH-$	136 (23)	74 (80)	+116° (+114°)	35 (29)
IIc $\phi-CH_2-$	144 (23)	55 (62)	+134° (+131°)	27 (26)
IId CH_3-	215 (23)	41 (34)	+123° (+118°)	22 (18)

a) Isolated yield. b) Measured by nmr analysis. c) Numbers in parentheses were the results obtained at 60°. d) [(L-D)-(L-L)/(L-D)+(L-L)] x 100.

The asymmetric inductions were observed in 22-35% optical yield when reacted at 20°. It is of practical interest that in the nuclear magnetic resonance (nmr) spectra of these products (IIa-d) two doublet signals referred to L-L and L-D isomeric amide hydrogens are observed.

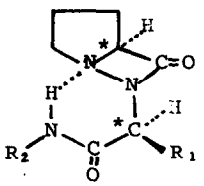
Characteristic NMR Spectra of Products (IIa-d)[a,b]

R_1 in II	Amide NH in $CDCl_3$		Amide NH in CCl_4	
	Signal 1 (δ)	Signal 2 (δ)	Signal 1 (δ)	Signal 2 (δ)
$(CH_3)_2CH-CH_2-$ (IIa)	6.68	7.58	6.74	7.14
$(CH_3)_2CH-$ (IIb)	6.42	7.41	6.94	7.19
$\phi-CH_2-$ (IIc)	6.56	7.52	6.70	(~7.14)[c]
CH_3- (IId)	6.72	7.52	7.04	7.23

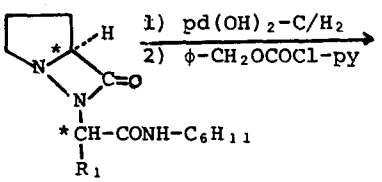
a) Measured at the concentration of 30 mg of II in 0.3 ml of solvent. b) Recorded on 100 MHz spectrometer using TMS as an internal reference. c) Aromatic protons appeared at the same position.

We assigned the lower nmr signals (δ 7.41-7.58 in $CDCl_3$) to the amide hydrogen of L-L isomers (IIa-d-A), since these structures were more suitable for intramolecular hydrogen bonding formation between -CONH- and ➔N as shown in Fig. I. To confirm this consideration, the chemical correlation of the newly formed chiral center was carried out as follows. Repeated purification of IIa by preparative TLC with silicagel and benzene-ethyl acetate (2:1) as an eluting solvent gave two compounds (IIa-A[7,8] and IIa-B[7,9]) that showed the doublet signals of the amide hydrogen centered at δ 7.58 and 6.68 in $CDCl_3$ respectively. Infrared spectrum of IIa-A also indicated the presence of the strong intramolecular hydrogen bonding. Subsequent catalytic hydrogenation of IIa-A and IIa-B followed by benzyloxycarbonylation with benzyloxycarbonyl chloride and pyridine gave in high yields N-cyclohexyl-L-prolyl-L-leucylamide (Ia-A[7,10]) and N-cyclohexyl-L-prolyl-D-leucylamide (Ia-B[7,11]) respectively, which were identified with each authentic sample synthesized from L-proline and L-leucine or D-leucine derivatives.

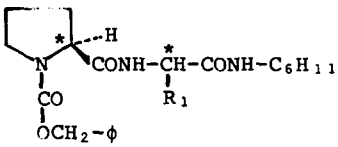
Fig. I



(IIa-d-A)



(IIa-A) (L-L)
(IIa-B) (L-D)
(IIa-d)



(Ia-A) (L-L)
(Ia-B) (L-D)
(Ia-d)

Direct conversion of IIa-d into Ia-d also showed the predominant formation of L-D isomers in these asymmetric syntheses.

Although further improvements for optical yield were needed, this asymmetric synthesis offered a new synthetic method for L-D-dipeptides and also for determination of the absolute configuration of new α-amino acids involved in peptides.

Some applications along this line are under active investigation.

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1) a) R. Geiger; Angew. Chem. Internat. Edit. 10, 152 (1971). b) K. Folkers, N-G. Johansson, F. Hooper, B. Currie, H. Sievertsson, J-K. Chang and C.Y. Bowers, Angew. Chem. Internat. Edit. 12, 255 (1973).

2) E. Schröder and K. Lübke; "The Peptides", Akademic Press, New York 1965/66.

3) Although some asymmetric syntheses[4] of di- or tripeptides using α-amino acid as a chiral reagent were reported previously, but no work on synthesis of peptides via the ring intermediate have been published.

4) a) R.G. Hiskey and R.C. Northrop; J. Am. Chem. Soc., 87, 1753 (1965). b) K. Harada and K. Matsumoto; J. Org. Chem., 32, 1794 (1967). c) K. Harada and K. Matsumoto; Bull. Chem. Soc. Japan, 44, 1068 (1971). d) M. Nakayama, G. Maeda, T. Kaneko and H. Katsura; Bull. Chem. Soc. Japan, 44, 1150 (1971). e) D. Elad and J. Sperling; Chem. Comm., 1969, 234. f) S. Winter and H. Pracejus; Ber., 99, 151 (1966). g) F. Weygand, W. Steglich and X.B. de Lama, Tetrahedron Supplement, 8, 9 (1966).

5) Melanocyte release inhibitory hormone and also an important fragment used for oxytocin.

6) Reaction of β-amino acid with aldehyde and isonitrile has been reported. Cf. I. Ugi; "Isonitrile Chemistry" Academic Press (1971) p. 145.

7) Satisfactory a) analytical and b) spectroscopic data were obtained for this substance.

8) M.p. 85-87°, $[\alpha]_D^{20}$+78.1° (c=1.426; MeOH).

9) Oil, $[\alpha]_D^{20}$+105°, (c=1.042, MeOH).

10) M.p. 130-132°, $[\alpha]_D^{20}$-81.2°(c=4.17, MeOH).

11) M.p. 143-145°, $[\alpha]_D^{20}$+16.9° (c=2.134, MeOH).