

ASYMMETRIC SYNTHESIS OF β -AMINO- α , α -DIMETHYL-
PROPIONIC ACID

Mitsuru Furukawa^{*}, Tadashi Okawara, Hideyoshi Noguchi,
and Yuriko Terawaki

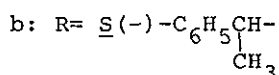
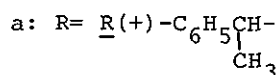
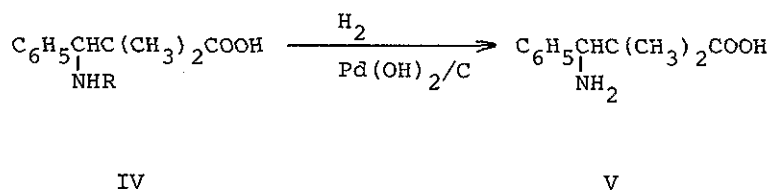
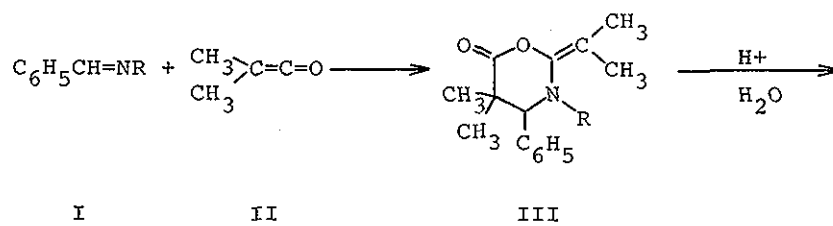
Faculty of Pharmaceutical Sciences, Kumamoto University,
5-1, Oe-hon-machi, Kumamoto, 862, Japan

Asymmetric synthesis of optically active β -amino- α , α -dimethyl- β -phenylpropionic acid (V) was achieved by the reaction of the chiral Schiff bases with dimethylketene and with the Reformatsky reagent. The specific rotation and the configuration of V were determined by the correlation with authentically prepared R(+)- β -benzoylamino- α , α -dimethyl- β -phenylethanol (X).

Several naturally occurring β -amino acids having an asymmetric carbon atom have been isolated,¹⁾ and have attracted attention in the field of biochemistry. A few papers^{2a-c)} have hitherto been reported on the asymmetric synthesis of β -amino acids, in which the addition of chiral amines to carbon-carbon double bond compounds^{2a,b)} and the reaction of chiral Schiff bases with chiral and achiral Reformatsky reagents^{2c)} were involved.

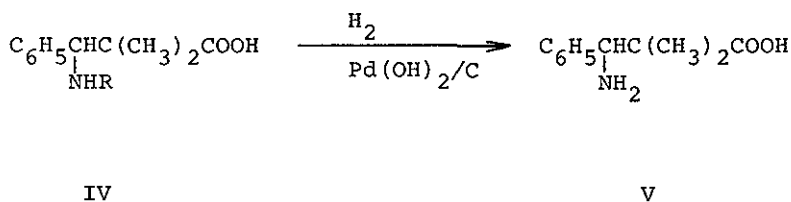
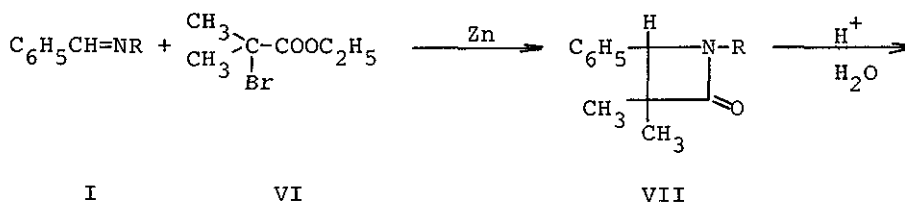
Another possible route to β -amino acids is the process through the cycloaddition of Schiff bases to ketene, and this reaction

has been investigated using achiral substrates.³⁾ We now wish to report the asymmetric synthesis of β -amino- α,α -dimethyl- β -phenylpropionic acid by the use of chiral Schiff bases and dimethylketene in this synthesis. In addition, the reaction of chiral Schiff bases with the corresponding Reformatsky reagent was also examined.



The cycloaddition of chiral Schiff bases (I) containing $\underline{\text{R}}$ (+)- α -methylbenzylimino or $\underline{\text{S}}$ (-)- α -methylbenzylimino moiety to dimethylketene (II), which was prepared from isobutyryl chloride and triethylamine in solution in situ, was successfully carried out by treating in acetonitrile at $-30 \sim -40^\circ$ for 0.5 hr to afford the corresponding oxazinones (III) in 56-68 % yields. Without being

isolated from the reaction mixture, the compound III was hydrolyzed with 6N hydrochloric acid under boiling conditions and then treated with IR 120 (H⁺ form) to give β-benzylamino acids (IV), followed by hydrogenolysis over 10 % palladium hydroxide on charcoal to yield R(+)-V and S(-)-V in the optical purities of 47 and 53 %, respectively.



The asymmetric synthesis of V through the formation of β-lactam using Reformatsky reagent, prepared in solution in situ, was also achieved in about 35 % overall yields. The reaction smoothly proceeded by adding ethyl α-bromoisobutyrate (VI) into the boiling solution of I in dry benzene containing an excess of zinc powder to give 1-benzyl-3,3-dimethyl-4-oxo-2-phenylazetidines (VII)

in fairly good yields of 73-76 %. The compound VII was hydrolyzed and then hydrogenolyzed, without being isolated from the reaction mixture, to give R(+)-V and S(-)-V in the optical purities of 36 and 33 %, respectively. The specific rotations, configurations, optical purities, and overall yields of V are listed in Table.

Table Optically active β -Amino- α,α -dimethyl- β -phenylpropionic Acid (V) through the intermediates (III and VII)

Method	R in III and VII	$[\alpha]_D^{25}$ (1N HCl)	Config. of V	Optical Purity (%)	Overall Yield (%)
A	<u>R</u> (+)-C ₆ H ₅ CH- CH ₃	+14.5° (c=0.8) ^{a)}	R	47	21
	<u>S</u> (-)-C ₆ H ₅ CH- CH ₃	-16.3° (c=1.5) ^{a)}	S	53	28
B	<u>R</u> (+)-C ₆ H ₅ CH- CH ₃	-11.0° (c=1.9) ^{a)}	S	36 (30) ^{b)}	35
	<u>S</u> (-)-C ₆ H ₅ CH- CH ₃	+10.0° (c=2.2) ^{a)}	R	33 (28) ^{b)}	36

A The process through reaction of I with dimethylketene

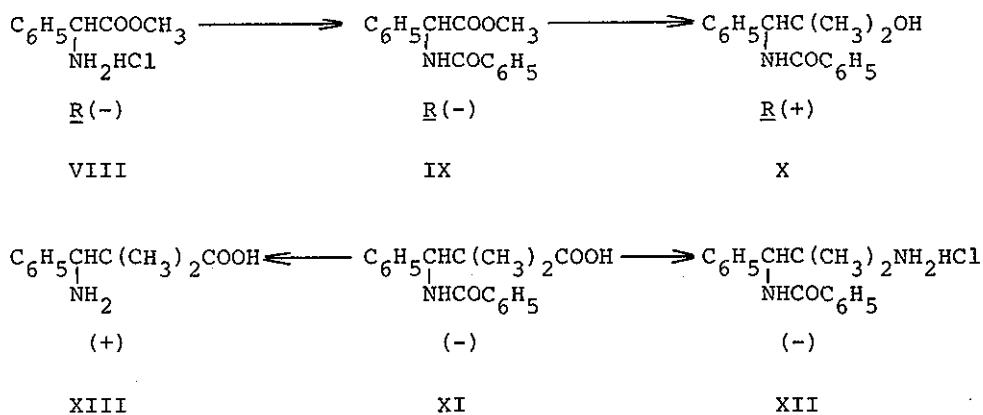
B The process through Reformatsky reaction of I

a) Defined as $([\alpha]_D \text{ obs.}/[\alpha]_D \text{ pure}) \times 100$. R(+)-V showed $[\alpha]_D^{15} +30.6^\circ$ (c=1.5, 1N HCl).

b) These optical purities were calculated from the integration of ¹H-NMR spectra of β -lactam(VII).

As can be seen in the Table, it is of interest that these two methods formed V of reverse direction of the specific rotation. The determinations of specific rotation and the configuration of V

were performed by the stereochemical correlation of $\underline{R}(+)$ - β -benzoylamino- α, α -dimethyl- β -phenylethanol (X) ($[\alpha]_D^{15} +12.5^\circ$, $c=2.5$, EtOH), prepared authentically from methyl $\underline{R}(-)$ -aminophenylacetate (VIII) through the Grignard reaction of the N-benzoyl intermediate (IX), with that derived from the racemic compound of V through three steps.



The racemic V was converted into the N-benzoyl, followed by resolution with cinchonine to give optically active N-benzoyl derivative V (XI) ($[\alpha]_D^{15} -24.1^\circ$, $c=2.0$, EtOH). The Schmidt reaction of XI with sodium azide in chloroform in the presence of sulfuric acid afforded the corresponding amino derivative (XII), followed by diazotization to give X ($[\alpha]_D^{25} +9.8^\circ$, $c=0.6$, EtOH). On the other hand, the hydrolysis of XI with 6N hydrochloric acid gave the optically active V (XIII) ($[\alpha]_D^{25} +30.6^\circ$; $c=1.5$, 1N HCl). Therefore, it is reasonable to conclude that the configuration of

(+)-V is R.

ACKNOWLEDGMENT We are indebted to Mrs.K.Shiraki for elemental analyses and to Mr.K.Takeda for nmr and mass spectral measurements.

REFERENCES

- 1 (a) H.R.Crumpler,C.E.Dent,H.Harris, and R.G.Westall, Nature, 1951, 167, 307; (b) N.Otake,S.Takeuchi,T.Endo, and H.Yonehara, Agr. Biol.Chem. (Tokyo), 1966, 30, 132; (c) M.Sato and T.Tatsuno, Chem. Pharm.Bull. (Tokyo), 1968, 16, 2182; (d) S.Kondo,S.Shibahara,S.Takahashi,K.Maeda,H.Umezawa, and M.Ohno, J.Am.Chem.Soc., 1971, 93, 6305; (e) T.Wakamiya,T.Shiba, and T.Kaneko, Bull.Chem.Soc.Japan, 1972, 45, 3668.
- 2 (a) A.P.Terentev,R.A.Gracheva, and T.F.Dendeko, Dolk.Akad.Nauk. SSSR, 1965, 163, 674; (b) M.Furukawa,T.Okawara, and Y.Terawaki, Chem. Pharm.Bull. (Tokyo), in press; (c) M.Furukawa,T.Okawara, and Y.Terawaki, submitted.
- 3 (a) J.C.Martin,V.A.Hoyle,Jr., and K.C.Brannock, Tetrahedron Letters, 1965, 3589; (b) J.C.Martin,K.C.Brannock,R.D.Burpitt,P.G.Gott, and V.A.Hoyle,Jr., J.Org.Chem., 1971, 36, 2211.

Received, 11th June, 1977