HETEROCYCLES, Vol. 6, Nos. 9, 10, 1977

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

Mitsuru Furukawa*, Tadashi Okawara, Hideyoshi Noguchi, and Yuriko Terawaki

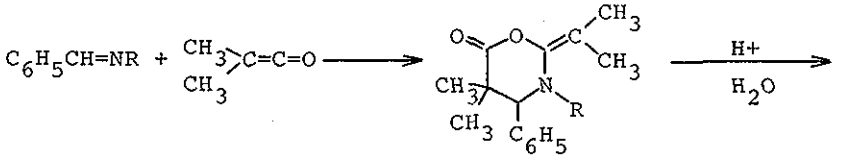
Faculty of Pharmaceutical Sciences, Kumamoto University, 5-1, Oe-hon-machi, Kumamoto, 862, Japan

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).

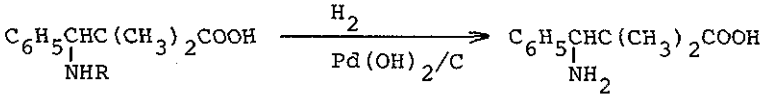
Several naturally occurring β-amino acids having an asymmetric carbon atom have been isolated,[1] and have attracted attention in the field of biochemistry. A few papers[2a-c] have hitherto been reported on the asymmetric synthesis of β-amino acids, in which the addition of chiral amines to carbon-carbon 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.



I II III

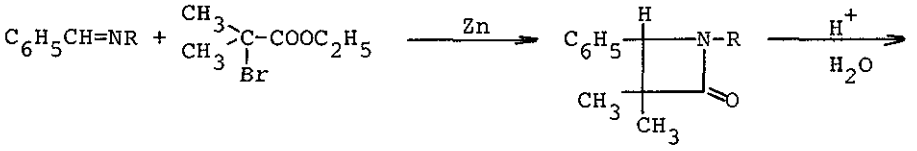


IV V

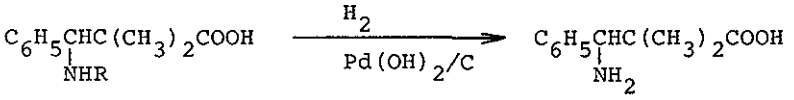
a: R= R(+)-C_6H_5CH(CH$_3$)- b: R= S(-)-C_6H_5CH(CH$_3$)-

The cycloaddition of chiral Schiff bases (I) containing R(+)-α-methylbenzylimino or 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 ~-40° 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.



I VI VII



IV V

a: R= R(+)-C_6H_5CH(CH$_3$)- b: R= S(-)-C_6H_5CH(CH$_3$)-

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 fairely 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	R(+)-$C_6H_5CH(CH_3)$-	+14.5° (c=0.8) [a]	R	47	21
	S(-)-$C_6H_5CH(CH_3)$-	-16.3° (c=1.5) [a]	S	53	28
B	R(+)-$C_6H_5CH(CH_3)$-	-11.0° (c=1.9) [a]	S	36 (30) [b]	35
	S(-)-$C_6H_5CH(CH_3)$-	+10.0° (c=2.2) [a]	R	33 (28) [b]	36

A The process through reaction of I with dimethylketene

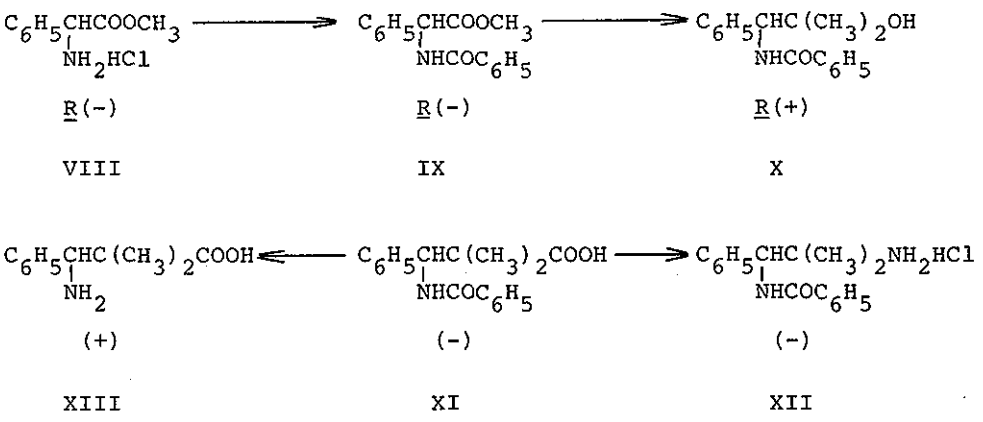
B The process through Reformatsky reaction of I

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

b) These optical purities were calculated from the integration of ^{1}H-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 R(+)-β-benzoylamino-α,α-dimethyl-β-phenylethanol (X) ($[\alpha]_D^{15}$ +12.5°, c=2.5, EtOH), prepared authentically from methyl 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°, 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°, 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°; c=1.5, 1N HCl). Therefore, it is reasonable to conclude that the configuration of

(+)-V is R.

ACKNOWLEGMENT 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