ASYMMETRIC SYNTHESIS WITH AMINO ACID I

ASYMMETRIC INDUCTION IN THE ALKYLATION OF KETO-ENAMINE

Shun-ichi Yamada, Kunio Hiroi and Kazuo Achiwa

Faculty of Pharmaceutical Sciences

University of Tokyo, Bunkyo-ku, Tokyo, Japan

Optically active α-alkylcarbonyl compounds are key intermediates for the total synthesis of optically active natural products such as terpenes, steroids and alkaloids. In general, resolution of racemic carbonyl compounds is tedious and difficult[1] and optically active α-alkyl carbonyl compounds have not been easily obtained until now.

This paper deals with asymmetric synthesis of optically active α-alkyl-cyclohexanone derivatives by way of enamine alkylation. Pyrrolidine has been widely used for the formation of enamines with various carbonyl compounds[2]. To form cyclohexanone enamine, we used L-proline esters I which are now readily available, as the amine components of enamine. On alkylation of this enamine II we succeeded in obtaining optically active α-substituted cyclohexanones, III and IV, induced by I.

I	R
a	CH₃
b	C₂H₅
c	t-Bu

	X
III	CN
IV	COOCH₃
V	COOH
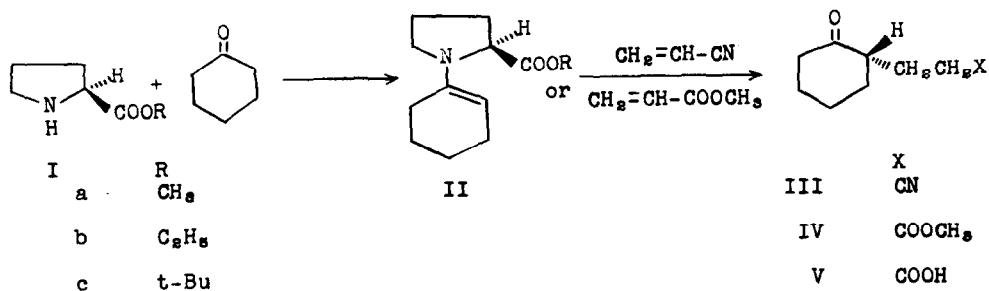
Enamine II is easily formed by the reflux of I with cyclohexanone in benzene in the presence of molecular sieves 4A. Alkylation of II with electro-philic olefins such as methyl acrylate and acrylonitrile was investigated under

several conditions. Optically active III and IV were obtained by the usual hydrolysis.

The degree of asymmetric synthesis upon alkylation in alcohol was enhanced with the increasing bulkiness of the ester moiety of proline esters, Ia, Ib and Ic. Optical rotations and product yields are summaried in Table I. Both products, III and IV, show a negative maximum[a] in their CD curves at 290 mμ in methanol, hence they are proven to have the same (S)-configuration on the basis of the octant rule[4].

Table I Effects of Ester Moiety of L-Proline Esters on Asymmetric Induction

Alkylating Conditions	Ester Part of Proline(R)	CH_3	C_2H_5	t-Bu
CH_2=CH-COOCH$_3$ 3 hrs. reflux in CH_3OH	Yield (%)[a]	32	38	33
	Optical Yield (%)[b]	15	21	43
	$[\alpha]_{460}$	-1.7° at 23°C (4.11, CH_3OH)	-2.3° at 28°C (4.35, CH_3OH)	-4.8° at 14.5°C (2.51, CH_3OH)
	Mol. Ellipticity $[\theta]_{290}$	-332 at 30.5°C (CH_3OH)	-406 at 24°C (CH_3OH)	-915 at 13°C (CH_3OH)
CH_2=CH-CN 3 hrs. reflux in C_2H_5OH	Yield (%)[a]	34	36	41
	$[\alpha]_D$	+1.2° at 21°C (3.05, CH_3OH)	+1.2° at 26.5°C (3.37, CH_3OH)	+2.6° at 12°C (3.06, CH_3OH)
	$[\theta]_{290}$	-160 at 21°C (CH_3OH)	-218 at 29°C (CH_3OH)	-348 at 11°C (CH_3OH)

a) Based on L-proline ester.

b) Calculated from the value of IV, $[\alpha]_{460}^{18}$ -11.2° (CH_3OH), obtained by the resolution of V ethylene ketal, followed by esterification with diazomethane and deketalization.

Solvent effects on enamine alkylation are summarized in Table II. After the reflux of Ib with cyclohexanone in benzene with molecular sieves 4A, benzene was removed under reduced pressure and the solvent was replaced with CH_3OH, C_2H_5OH, CH_3CN, or dioxane. In each solvent, alkylation of IIb with acrylo-

Table II Effects of Solvents on Alkylation of Enamine IIb with Acrylonitrile

Solvents	Dioxane	Benzene	CH_3CN	CH_3OH	C_2H_5OH
Yield (%)	9	8	18	48	55
$[\theta]_{290}$ in CH_3OH	-546 (25°C)	-528 (21.5°C)	-297 (19°C)	-248 (28°C)	-214 (27.5°C)

nitrile was carried out under reflux for 8 hours.

As shown in Table II, non-polar aprotic solvents such as dioxane and benzene, produced III in poor yields but in good optical yields. In polar protic solvents the results were reversed.

Table III   Effects of Reaction Temperatures on Asymmetric Induction of
Enamine IIc with Methyl Acrylate

Reaction[a] Conditions	Yield (%)	$(\alpha)_{460}$	$(\theta)_{290}$	Optical Yield (%)[b]
20°C, 5 hrs.	17	-6.7° at 22°C (2.30, CH_3OH)	-1241 at 22°C (CH_3OH)	59
40°C, 3 hrs.	22	-6.0° at 20°C (3.45, CH_3OH)	-1145 at 22°C (CH_3OH)	53
Reflux, 3 hrs.	33	-4.8° at 14.5°C (2.51, CH_3OH)	-915 at 13°C (CH_3OH)	43

a) L-Proline t-Butyl ester enamine IIc was alkylated with methyl acrylate in
   CH_3OH at the temperatures and reaction times shown in the Table.

b) Calculated as in Table I.

VII

VIII

IX

X.
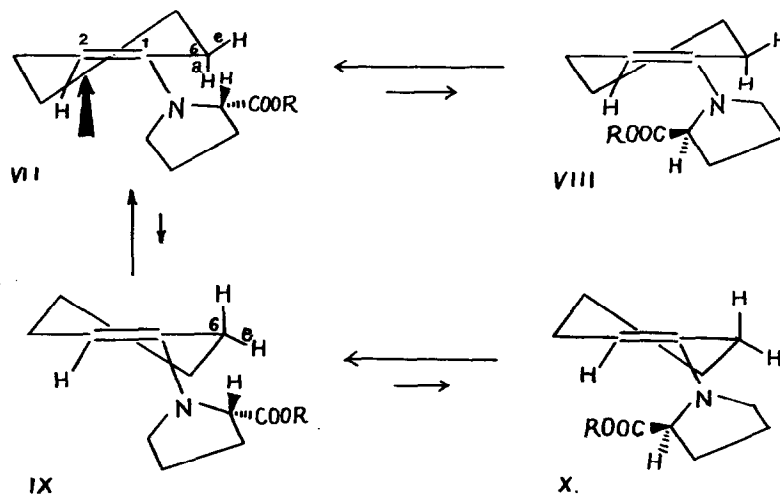
As shown in Table III, IV was obtained in considerably higher optical yield at room temperature, and at higher temperatures optical yield slightly decreased and yield increased.

As (S)-α-alkylcyclohexanone derivatives are obtained from all L-proline esters employed here, the above mechanism now seems available to account for the observed stereospecificity.

Conformers VII and IX seem to be prefered to VIII and X. The trivalency of nitrogen probably causes the ester group of proline to interfere with a hydrogen attached to the double bond in VIII and X, if overlap is to be maintained between nitrogen unshared electrons and the double bond. In VII and IX, quasi-equatorial hydrogen at C_6 in IX interferes with ester group sterically larger than quasi-axial hydrogen at C_6 in VII.[5] Hence, VII is the most preferable conformation. Axial attack of an entering alkyl group at C_2 in VII results in (S)-α-alkylcyclohexanone.

We believe that this synthesis of optically active α-alkylcyclohexanone is the first example of asymmetric induction at the α-carbon atom of carbonyl compounds. This method is advantageous as it employs optically active α-amino acids which are easily obtainable.

Investigations are underway on the scope of this new type of asymmetric synthesis and on increasing yield and optical yield.

References

1) W.R. Adams, O.L. Chapman, J.B. Sieja, and W.J. Welstead, Jr., _J. Am. Chem. Soc._, _88_, 162 (1966), and cited therein.

2) G. Stork, A. Brizzolara, H. Landesman, J. Szmuszkovicz, and R. Terrell, _Ibid._, _85_, 207 (1963).

3) C. Djerassi, _Proc. Chem. Soc._, _1963_, 299.

4) J.C. Tai, and N.L. Allinger, _J. Am. Chem. Soc._, _88_, 2179 (1966).

5) a) W.R.N. Williamson, _Tetrahedron_, _3_, 314 (1958). b) F. Johnson, and A. Whitehead, _Tetrahedron Letters_, _1964_, 3825. c) H.J. Schaeffer, and V.K. Jain, _J. Org. Chem._, _29_, 2595 (1963). d) F. Johnson, and S.K. Malhotra, _J. Am. Chem. Soc._, _87_, 5492, 5493 (1965).