

NOVEL 1,2- AND 1,3-DOUBLE CHIRAL RECOGNITIONS. OPTICAL RESOLUTION
OF α - AND β -HALOACETYLENIC ALCOHOLS BY COMPLEXATION WITH BRUCINE

Fumio TODA,^{*} Koichi TANAKA, and Koji MORI

Department of Industrial Chemistry, Faculty of Engineering,
Ehime University, Matsuyama 790

Optical resolution of α - ($2,3$) and β -haloacetylenic alcohols ($13,14$) which have two chiral carbons at the 1,2- and 1,3-positions, respectively, was performed efficiently by complexation with brucine. By the same method, α,β -dichloroacetylenic alcohols ($8,9$) which have three chiral carbons at the 1,2,3-positions were also resolved.

In a previous paper, we have reported that brucine forms crystalline complex with tertiary acetylenic alcohols, and the alcohols recognize the chirality of brucine and can easily be resolved.¹⁾ It was disclosed further that brucine can recognize not only one chiral center but also two chiral centers of a molecule. This paper reports novel double chiral recognition of the 1,2- and 1,3-carbons of α - ($2,3$) and β -haloacetylenic alcohols ($9,10$), respectively, by the complexation with brucine. By using this 1,2-double chiral recognition method, we also succeeded in obtaining 1,2,3-triply optically active compound.

Reaction of α -chloro ketone (1) and ethynylmagnesium bromide in ether gave in almost quantitative yield a mixture of *parf*- (2)²⁾ and *pref*- α -chloroacetylenic alcohol (3)³⁾ in the ratio shown in Table 1. When a solution of 89:11 mixture of $2a$ and $3a$ (8 g) and brucine (16.2 g) in acetone (150 ml) was kept at room temperature for 12 h, 1:1 brucine complex of (+)- $2a$ (15.3 g) was formed as colorless needles.⁴⁾ Decomposition of the complex with dil HCl gave 16%ee (+)- $2a$ (5.1 g). By repeating the complexation three times more for the partially resolved (+)- $2a$ (5.1 g), 100%ee (+)- $2a$ (1.0 g, 28%,⁵⁾ $[\alpha]_D^{20}$ +6.3⁶⁾) was obtained. By the NMR method, optical purity of the C₁ chiral center can be estimated. Because the finally obtained 100%ee (+)- $2a$ was shown by its ¹H NMR spectrum not to be contaminated by $3a$, both the C₁ and C₂ chiral centers of the (+)- $2a$ should be 100% optically pure. By the same method,

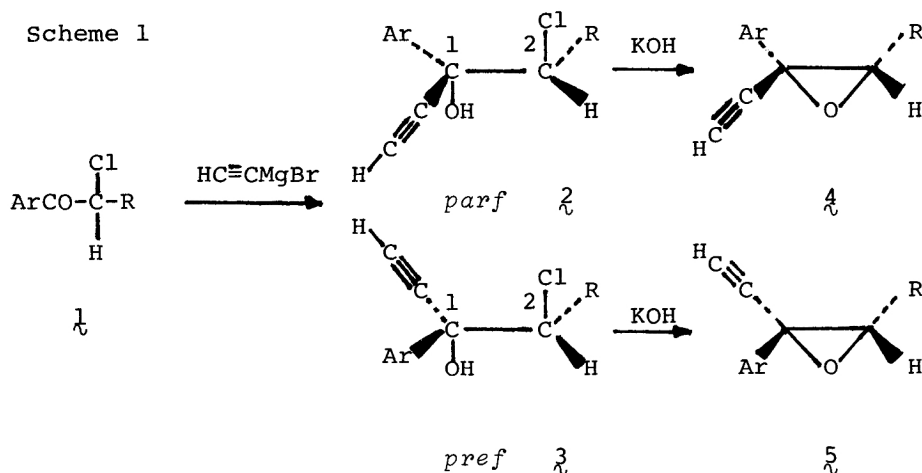



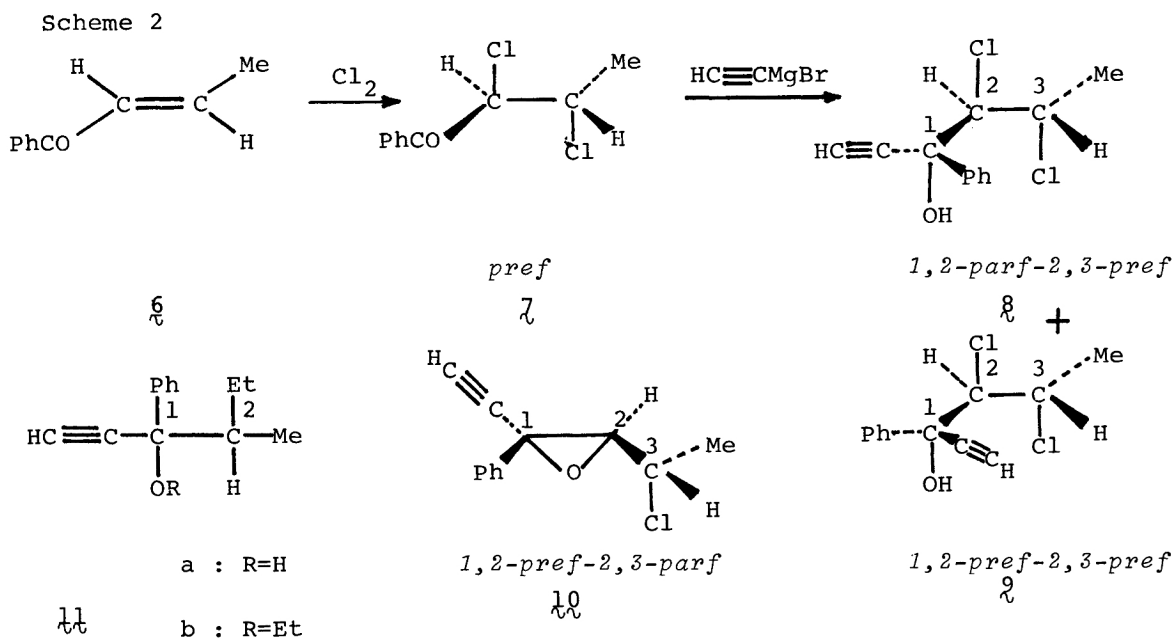
Table 1. 1,2-Double Chiral Recognition

Ar	R	3) ratio of		result of resolution			
		$\overset{2}{\curvearrowright}$	$\overset{3}{\curvearrowleft}$	product	yield (%)	$[\alpha]_D$ (°)	$\%ee$
$\overset{a}{\curvearrowright}$ Ph	Me	89	11	(+)- $\overset{2a}{\curvearrowright}$	28	+6.3	100
$\overset{b}{\curvearrowright}$ Ph	Ph	20	80	(+)- $\overset{3b}{\curvearrowleft}$	35	+23.8	100
$\overset{c}{\curvearrowright}$ 	Me	87	13	(+)- $\overset{2c}{\curvearrowright}$	41	+12.2	100

100%ee (+)- $\overset{3b}{\curvearrowleft}$ and (+)- $\overset{2c}{\curvearrowright}$ were isolated from the corresponding mixture of *parf*- and *pref*-diastereomers (Table 1). These results show that brucine can recognize the both chiralities of C_1 and C_2 at the same time.

The *parf* ($\overset{2}{\curvearrowright}$) and *pref* ($\overset{3}{\curvearrowleft}$) structures were determined by their cyclizations into epoxides 4 and 5, respectively. Treatment of 100%ee (+)- $\overset{2a}{\curvearrowright}$, (+)- $\overset{3b}{\curvearrowleft}$, and (+)- $\overset{2c}{\curvearrowright}$ with KOH gave 100%ee (+)- $\overset{4a}{\curvearrowright}$ (81%, $[\alpha]_D +38.3^\circ$, $^1\text{H NMR } \delta$ 3.60 (q, CH) and 1.05 ppm (d, Me, $J=5.37$ Hz)), (+)- $\overset{5b}{\curvearrowleft}$ (81%, $[\alpha]_D +33.1^\circ$, $^1\text{H NMR } \delta$ 4.05 ppm (s, CH)), and (-)- $\overset{4c}{\curvearrowright}$ (85%, $[\alpha]_D -13.4^\circ$, $^1\text{H NMR } \delta$ 3.61 (q, CH) and 1.24 ppm (d, Me, $J=5.36$ Hz)), respectively. This epoxidation reaction proceeds stereoselectively, and the mixture of $\overset{2}{\curvearrowright}$ and $\overset{3}{\curvearrowleft}$ shown in Table 1 gave 4 and 5 in the same ratio. In the NMR spectrum, epoxide ring proton of 4 appeared at lower field than that of 5 which is shielded by Ar group, and Me of 5 appeared at lower field than that of 4 which is shielded by Ar group.

With combining the 1,2-double chiral recognition and *trans*-addition of Cl_2 to double bond, we succeeded in obtaining 1,2,3-triply optically active compound.



trans-Addition of Cl_2 to *trans*-1-benzoylprop-1-ene (6) gives *pref*-1,2-dichloro-1-benzoylpropane (7). Reaction of 7 and ethynylmagnesium bromide in ether gave 5:3 mixture of 1,2-*parf*-2,3-*pref*- (8) and 1,2-*pref*-2,3-*pref*- α,β -dichloroacetylenic alcohol (9). Three complexations of the mixture with brucine finally gave 100% ee (+)- 8 (61%, $[\alpha]_{\text{D}} +39.0^\circ$) which is not contaminated by 9 . The 1,2-*parf*-2,3-*pref* structure of 8 was identified by converting it to the epoxide 10 (95%, mp 85-87 °C, $[\alpha]_{\text{D}} -98.0^\circ$) which shows epoxide ring proton at lower field (3.57 ppm, d, $J=9.0$ Hz) than that (3.18 ppm, d, $J=9.0$ Hz) of the epoxide derived from 1,2-*pref*-2,3-*pref* isomer (9).

The 1,2-double chiral recognition was not applicable to chlorine free acetylenic alcohols. Several complexations of a mixture of *pref*- and *parf*- 11a gave a mixture of two diastereomers ($[\alpha]_{\text{D}} -8.9^\circ$) which on acid-catalyzed ethanolysis afforded optically inactive 11b . This shows that only the C_1 of 11a can be resolved by the complexation with brucine.

The resolution method could also be applied to β -haloacetylenic alcohol. The reaction of β -halo ketone (12) with ethynylmagnesium bromide in ether gave *pref*- (13) and *parf*- β -haloacetylenic alcohol (14) in the ratio shown in Table 2. Three complexations of the mixture with brucine gave 100% ee enantiomer which is not contaminated by diastereomer (Table 2). This method was applicable to β -methoxyacetylenic alcohol (Table 2). However, only the C_1 of 15a was resolved by this method. Several complexations of a mixture of *parf*- and *pref*- 15a with brucine gave a mixture of

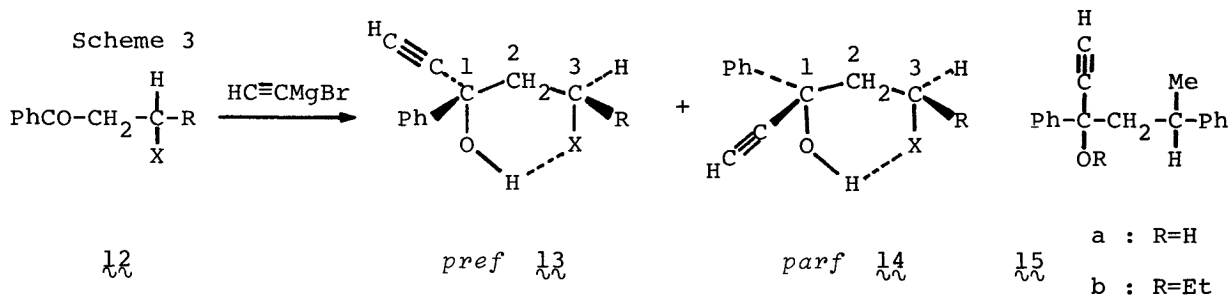


Table 2. 1,3-Double Chiral Recognition

R	X	ratio ³⁾ of		product	result of resolution ⁵⁾		
		$\overset{13}{\sim\sim}$: $\overset{14}{\sim\sim}$	yield (%)		$[\alpha]_D$ (°) ⁶⁾	%ee ⁴⁾	
$\overset{a}{\sim}$	Ph	Cl	50 : 50	(+)- $\overset{13a}{\sim\sim}$	44	+11.6	100
$\overset{b}{\sim}$	Me	Br	50 : 50	(-)- $\overset{14b}{\sim\sim}$	50	-3.0	100
$\overset{c}{\sim}$	Me	OMe	40 : 60	(+)- $\overset{13c}{\sim\sim}$	42	+1.6	100

two diastereomers ($[\alpha]_D -17.2^\circ$) which on acid-catalyzed ethanolysis afforded optically inactive $\overset{15b}{\sim\sim}$. These results show an atom which has lone pair of electrons should be present on the C₃ of acetylenic alcohol for the 1,3-double chiral recognition. Of *pref* ($\overset{13}{\sim\sim}$) and *parf* structure ($\overset{14}{\sim\sim}$), the former was tentatively assigned to the diastereomer which shows R and H NMR signals at relatively higher and lower fields, respectively, than those of the other diastereomer. In the cyclic structure ($\overset{13,14}{\sim\sim}$) formed by intramolecular hydrogen bond, R of $\overset{13}{\sim\sim}$ and H of $\overset{14}{\sim\sim}$ are shielded by Ph group. For example, CH signal of $\overset{14a}{\sim\sim}$ (5.18 ppm) appears at higher field than that of $\overset{13a}{\sim\sim}$ (5.40). Me signals of $\overset{13b}{\sim\sim}$ (1.74) and $\overset{13c}{\sim\sim}$ (1.05) appear at higher field than those of $\overset{14b}{\sim\sim}$ (1.80) and $\overset{14c}{\sim\sim}$ (1.15), respectively.

References

- 1) F. Toda, K. Tanaka, and H. Ueda, *Tetrahedron Lett.*, **22**, 4669 (1981).
- 2) Relative configuration was specified according to the recent proposal. F. A. Carey and M. E. Kuehne, *J. Org. Chem.*, **47**, 3811 (1982).
- 3) Ratio of diastereomers of acetylenic alcohols were determined by ¹H NMR spectra. Recently, it was reported that addition of acetylenic Grignard reagent to α-chloroketone proceeds stereoselectively. C. Santelli-Rouvier and M. Santelli, *Tetrahedron Lett.*, **23**, 4945 (1982).
- 4) Enantiomeric excess (ee) was determined by the same method as has been reported.¹⁾
- 5) Yield of optical resolution was calculated based on the theoretical amount of the optical isomer contained.
- 6) All the $[\alpha]_D$ values were measured in MeOH (c 0.01) with a 1-dm cell at 25 °C.

(Received March 14, 1983)