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

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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-chloroketone (**1**) and ethynylmagnesium bromide in ether gave in almost quantitative yield a mixture of *parf*- (**2**)[2] and *pref*-α-chloroacetylenic alcohol (**3**)[2] in the ratio[3] 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. Decomposition of the complex with dil HCl gave 16%ee[4] (+)-**2a** (5.1 g). By repeating the complexation three times more for the partially resolved (+)-**2a** (5.1 g), 100%ee[4] (+)-**2a** (1.0 g, 28%,[5] $[\alpha]_D$ +6.3°[6]) was obtained. By the NMR method, optical purity of the C_1 chiral center can be estimated. Because the finally obtained 100%ee (+)-**2a** was shown by its ^{1}H NMR spectrum not to be contaminated by **3a**, both the C_1 and C_2 chiral centers of the (+)-**2a** should be 100% optically pure. By the same method,

Scheme 1

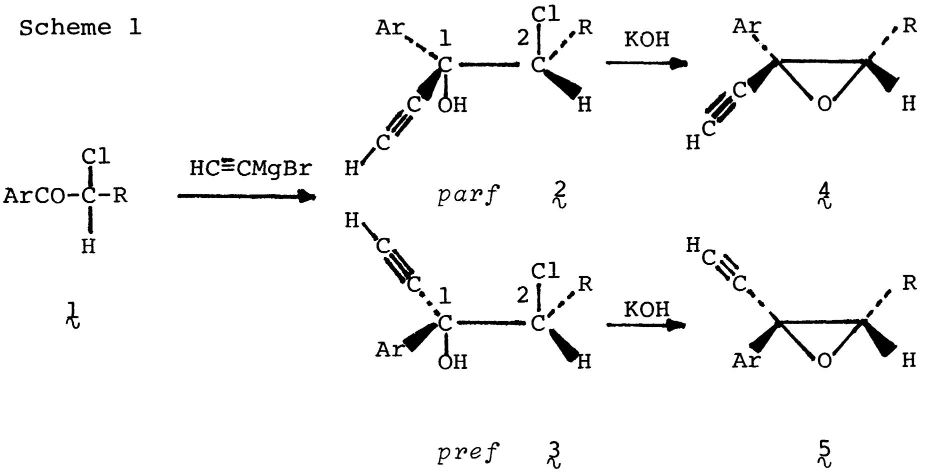
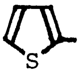


Table 1. 1,2-Double Chiral Recognition

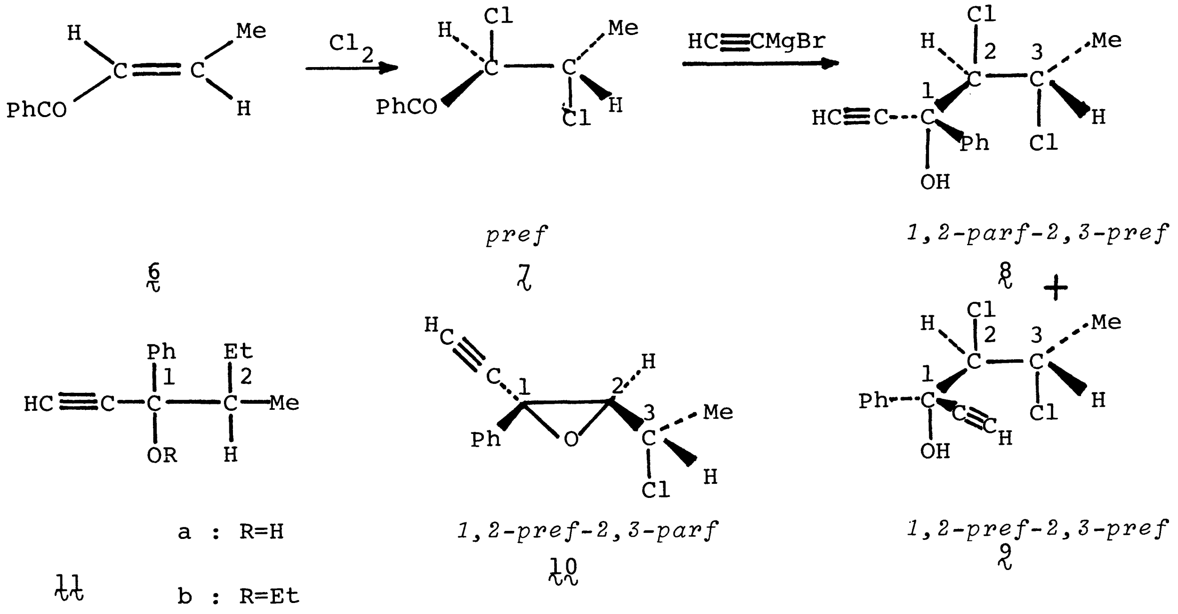
	Ar	R	ratio of 3) **2** : **3**	result of resolution product	 yield (%) 5)	 $[\alpha]_D$ (°) 6)	 %ee 4)
a	Ph	Me	89 : 11	(+)-**2a**	28	+6.3	100
b	Ph	Ph	20 : 80	(+)-**3b**	35	+23.8	100
c		Me	87 : 13	(+)-**2c**	41	+12.2	100

100%ee (+)-**3b** and (+)-**2c** 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* (**2**) and *pref* (**3**) structures were determined by their cyclizations into epoxides **4** and **5**, respectively. Treatment of 100%ee (+)-**2a**, (+)-**3b**, and (+)-**2c** with KOH gave 100%ee (+)-**4a** (81%, $[\alpha]_D$ +38.3°, ^{1}H NMR δ 3.60 (q, CH) and 1.05 ppm (d, Me, J=5.37 Hz)), (+)-**5b** (81%, $[\alpha]_D$ +331°, ^{1}H NMR δ 4.05 ppm (s, CH)), and (-)-**4c** (85%, $[\alpha]_D$ -13.4°, ^{1}H NMR δ 3.61 (q, CH) and 1.24 ppm (d, Me, J=5.36 Hz)), respectively. This epoxidation reaction proceeds stereoselectively, and the mixture of **2** and **3** 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 combineing 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.

Scheme 2

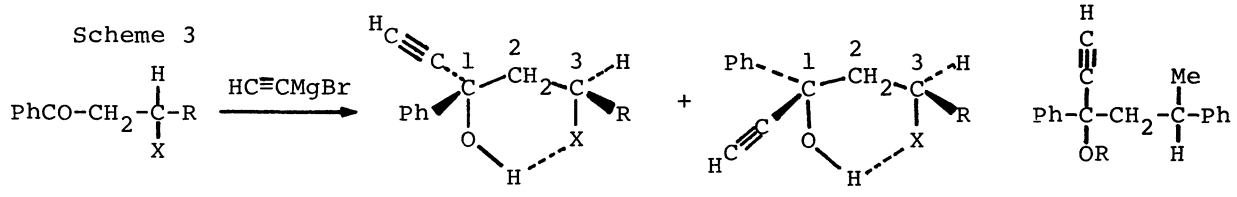


trans-Addition of Cl_2 to *trans*-1-benzoylprop-1-ene (6) gives *pref*-1,2-dichloro-1-benzoylpropane (7). Reaction of 7 and ethynylmagnesium bromide in ether gave 5:3 mixture of 1,2-*parf*-2,3-*pref*- (8) and 1,2-*pref*-2,3-*pref*-α,β-dichloroacetylenic alcohol (9). Three complexations of the mixture with brucine finally gave 100%ee (+)-8 (61%, $[\alpha]_D$ +39.0°) 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, $[\alpha]_D$ -98.0°) 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 ($[\alpha]_D$ -8.9°) 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-haloketone (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

Scheme 3



12 *pref* **13** *parf* **14** **15** a : R=H b : R=Et

Table 2. 1,3-Double Chiral Recognition

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

two diastereomers ([α]$_D$ -17.2°) which on acid-catalyzed ethanolysis afforded optically inactive **15b**. These results show an atom which has lone pair of electrons should be present on the C_3 of acetylenic alcohol for the 1,3-double chiral recognition. Of *pref* (**13**) and *parf* structure (**14**), 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 (**13**,**14**) formed by intramolecular hydrogen bond, R of **13** and H of **14** are shielded by Ph group. For example, CH signal of **14a** (5.18 ppm) appears at higher field than that of **13a** (5.40). Me Signals of **13b** (1.74) and **13c** (1.05) appear at higher field than those of **14b** (1.80) and **14c** (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 ^{1}H 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 [α]$_D$ values were measured in MeOH (*c* 0.01) with a 1-dm cell at 25 °C.

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