

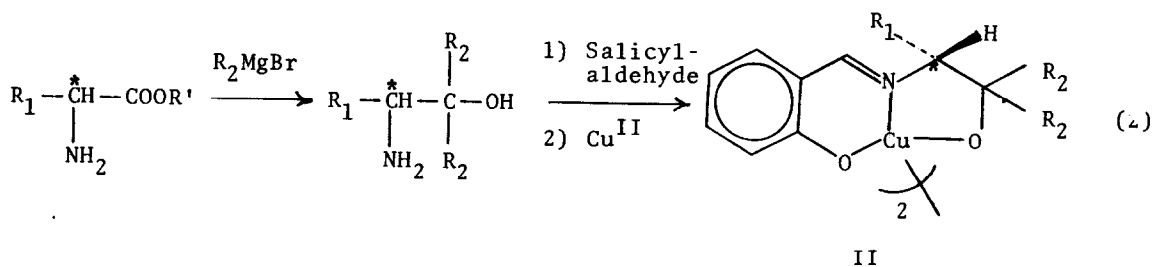
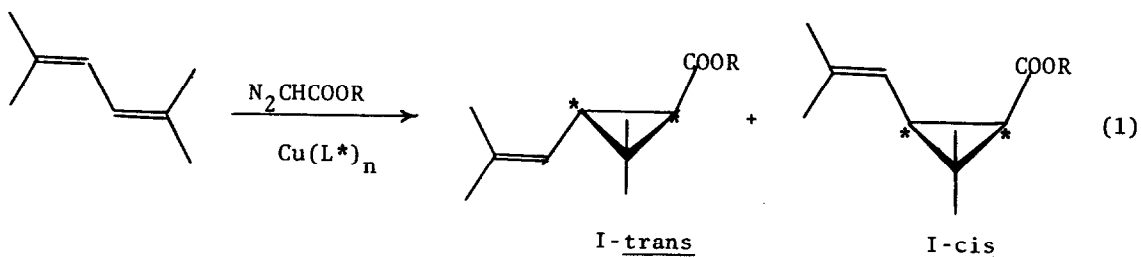
ASYMMETRIC SYNTHESIS OF CHRYSANTHEMIC ACID.
AN APPLICATION OF COPPER CARBENOID REACTION

T. Aratani,* Y. Yoneyoshi and T. Nagase
Central Research Laboratory, Sumitomo Chemical Co., Ltd.
Takatsuki, Osaka 569, Japan

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Chrysanthemic acid (I, R = H) constitutes an acidic component of the pyrethroid,¹ which is effective as an insecticide. Among its four optical isomers, the naturally occurring d-trans isomer has the highest activity.

The decomposition of diazoalkanes in the presence of certain chiral copper complexes gives rise to optically active products.² We have applied this chiral copper carbenoid reaction to the synthesis of alkyl chrysanthemate (Eq. 1). An extensive search has been carried out for both a catalyst and a diazo compound to achieve an enantiomeric excess (e.e.) of 90%.



An e.e. of 60-70% has been attained with the use of a novel copper catalyst (II) and ethyl diazoacetate.³ The chiral copper complex II was conveniently prepared from an optically active α -amino acid according to Eq. 2. This paper is concerned with the effects of alkyl diazoacetate on the asymmetric synthesis.

A procedure for preparing alkyl diazoacetate is illustrated as follows. l-Menthyl chloroacetate was treated (20°, 8 hr) with ammonia in aqueous dimethylformamide to give glycine l-menthyl ester.⁴ This ester was diazotized⁵ with isoamyl nitrite in chloroform in the presence of a catalytic amount of acetic acid to produce l-menthyl diazoacetate,⁶ mp. 48-49°, $[\alpha]_D -86.8^\circ$ (c 1.00, chloroform) in 81% overall yield after chromatography on silica gel.

l-Menthyl diazoacetate was added (20°, 7 hr)⁷ to a solution of the copper catalyst (R)-IIa (R_1 = methyl, R_2 = 5-t-butyl-2-octyloxyphenyl) (0.005 equiv.) in 2,5-dimethyl-2,4-hexadiene (10 equiv.) to give a diastereomeric mixture of l-menthyl chrysanthemate (I, R = l-menthyl), bp. 100°/0.2 mm, $\alpha_D -41.5^\circ$ (neat, 1 dm) in 72% yield. Gas chromatographic (GC) analysis of the ester revealed the composition of chrysanthemic acid to be d-trans 89.9%, l-trans 2.7% and cis (not completely resolved) 7.4%. The e.e. was calculated to be 94% for the trans isomer. Complete resolution of the optical isomer was carried out on the d-2-octyl ester.⁸ Alkaline hydrolysis of the l-menthyl ester followed by esterification with d-2-octanol gave the d-2-octyl ester. GC analysis established the composition to be d-trans 90.4%, l-trans 4.7%, d-cis 3.6% and l-cis 1.3%. The e.e. was calculated to be 90% for the trans isomer and 47% for the cis isomer.

A variety of alkyl diazoacetates and different forms of the chiral catalyst II were subjected to the asymmetric synthesis. The results are summarized in Table I. The catalyst of R configuration tends to produce dextrorotatory chrysanthemic acid rather than levorotatory chrysanthemic acid both in cis and trans isomers.¹⁰ This preference is not affected by the chirality of alkyl diazoacetate.¹¹ Table I shows that the bulkier the alkyl group of the diazo compound is, the higher the trans/cis ratio of the product and the e.e. of trans isomer become.

Table I. Asymmetric Synthesis of Chrysanthemic Acid

Alkyl Diazoacetate		Catalyst ^b	Ester	% e.e. of Acid ^d		
R	Method of Preparation ^a			Yield,%	<u>trans/cis</u> ^c	<u>trans</u>
<u>d</u> -Menthyl ^e	A	(<u>R</u>)-IIa	64	72/28	90	59
<u>dl</u> -Menthyl	A	(<u>R</u>)-IIa	67	81/19	90	75
<u>l</u> -Menthyl	A	(<u>R</u>)-IIb	67	89/11	87	25
<u>l</u> -Menthyl	A	(<u>R</u>)-IIc	42	91/9	86	22
<u>l</u> -Menthyl	A	Cu powder ^g	69	76/24	0.7	0
<u>d</u> -Neomenthyl	A	(<u>R</u>)-IIa	77	89/11	87	<u>h</u>
1-Adamantyl	A	(<u>R</u>)-IIa	82	84/16	85	46
Cyclohexyl	B	(<u>R</u>)-IIa	71	58/42	70	58
2,3,4-Trimethyl-3-pentyl	B	(<u>R</u>)-IIa	64	92/8	88	<u>h</u>
2,3-Dimethyl-2-butyl	B	(<u>R</u>)-IIa	71	78/22	85	43
<u>t</u> -Butyl	B	(<u>R</u>)-IIa	74	75/25	75	46
α,α -Dimethylbenzyl	B	(<u>R</u>)-IIa	60	56/44	71	<u>h</u>
Ethyl ^f	A	(<u>R</u>)-IIa	54	51/49	68	62

^a Method A, diazotization of the corresponding glycine ester.

Method B, application of Regitz's method (Ref. 9).

^b The catalyst has the following substituents. For IIa, see the text.

For IIb, R₁ = methyl and R₂ = 2-butoxy-5-t-butylphenyl.

For IIc, R₁ = benzyl and R₂ = 5-t-butyl-2-heptyloxyphenyl.

^c Determined by GC of the alkyl chrysanthemate.

^d Determined by GC of d-2-octyl chrysanthemate.

^e The experiment was carried out with the use of l-menthyl diazoacetate and the catalyst IIa of S configuration to give levorotatory chrysanthemic acid.

^f Taken from Ref. 3.

^g The reaction temperature was 123°.

^h Not determined.

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References and Notes

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2. H. Nozaki, H. Takaya, S. Moriuti and R. Noyori, Tetrahedron, 24, 3655 (1968).
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4. Although the product was contaminated with a 12% yield of di-l-menthyl iminodiacetate, it was diazotized without further purification. A pure sample was obtained by column chromatography on silica gel. The reaction of glycine with l-menthol in the presence of p-toluenesulfonic acid gave only a 23% yield of glycine l-menthyl ester. Cf. K. Harada and T. Hayakawa, Bull. Chem. Soc. Japan, 37, 191 (1964).
5. N. Takamura, T. Mizoguchi, K. Koga and S. Yamada, Tetrahedron, 31, 227 (1975).
6. This compound has been reported by P. E. Krieger in his Ph. D. Dissertation, Univ. of Kansas (1974). His preparation was based on House's method. Cf. Org. Syntheses, Coll. Vol. 5, 258 (1973).
7. The diazo ester was added as a solution in 2,5-dimethyl-2,4-hexadiene. In the early stages of the addition, the reaction mixture was warmed to 75° to promote the evolution of nitrogen gas.
8. A. Murano, Agric. Biol. Chem. 36, 2203 (1972).
9. For the preparation of t-butyl diazoacetate, see Org. Syntheses, Coll. Vol. 5, 179 (1973).
10. The absolute configuration of chrysanthemoid acid has been established. d-trans Isomer has (1R,3R) configuration and d-cis isomer has (1R,3S) configuration.
11. A double asymmetric induction was observed in the hydrosilylation of l-menthyl benzoylformate in the presence of a chiral rhodium complex. Cf. I. Ojima and Y. Nagai, Chem. Letters, 191 (1975).