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ASYMMETRIC MICHAEL ADDITION OF THIOPHENOL TO MALEIC ACID ESTERS

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(S)-(-)-Diisopropyl phenylthiosuccinate (81% optical purity) is prepared in 95% yield by the asymmetric Michael addition of thiophenol to diisopropyl maleate in the presence of a catalytic amount of cinchonine. The succinate thus prepared is transformed into (R)-(+)-3,4-epoxy-1-butanol without racemization.

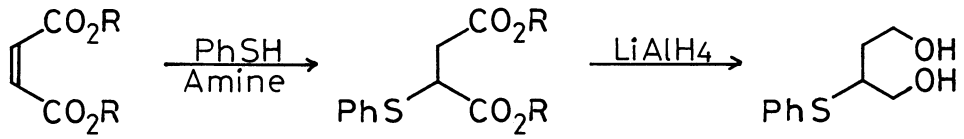
Catalytic asymmetric synthesis is a very attractive method for the synthesis of optically active compounds. Among several successful methods,[1] the asymmetric Michael addition of thiol to α,β-unsaturated carbonyl compound has great advantages in the easy control of reaction conditions and the possible use of stable chiral amines as catalysts. Wynberg et al. obtained (S)-3-(p-t-butylphenylthio)cyclohexanone in 67% e.e.[2] by the use of cinchonine as a base, and the same product was obtained in 88% e.e.[3] by using (2S, 4S)-2-(anilinomethyl)-1-ethyl-4-hydroxypyrrolidine as reported from our laboratory. However, these good optical yields could only be realized in the cases of using cyclohexenone derivatives as the Michael acceptors.[4] In this communication, we wish to report the successful asymmetric Michael addition of thiophenol to maleic acid esters catalyzed by chiral amines such as cinchona and quina alkaloids.

Initially, the reaction was carried out according to the following procedure; a toluene (5 ml) solution of maleic acid ester (1) (4 mmol), thiophenol (4 mmol), and chiral amine (0.04 mmol) was left in the dark at 0 °C for three days. The cooled solution was passed through 20 g of silica-gel column, and eluted by hexane-ethyl acetate (10:1) to give phenylthiosuccinate (2). The isolated yields were over 95% in all cases. 2 was reduced with $LiAlH_4$ to give 2-phenylthio-1,4-butanediol (3) in order to compare the optical purities with the authentic sample. The specific rotations of 2 and 3 are listed in Table 1.

The combination of maleic acid esters of secondary alcohols and cinchonine gave the best results. Then, we examined various reaction conditions by taking the Michael addition of thiophenol to diisopropyl maleate (1a) in the presence of cinchonine as a model reaction. The results are summarized in Table 2. The reaction temperature was sufficient at 0 °C. Lower concentration in less polar solvent gave higher specific rotation and slower reaction rate. These tendencies were almost the same as those already reported in the asymmetric Michael addition.[2,3] Then, the reaction was carried out in toluene (80 ml) at 0 °C for

several days. The specific rotation and the isolated yield of diisopropyl phenylthiosuccinate (2a) are plotted every three days in Fig. 1 (—●—).

Table1. Specific rotations of 2 and 3



1 2 3

Amine	R	Me	Et	i-Pr	t-Bu	⬠	⬡	⬢	Bn
Cinchonine	2[a]	-30.3	-34.9	-31.3	-25.4	-26.5	-34.5	- 9.84	-10.7
	3[b]	- 7.97	-12.5	-13.0	-10.6	-13.0	-13.0	- 3.00	- 8.27
Cinchonidine	2	+26.9	+27.9	+23.7	+15.2	+20.8	+26.0	+ 4.12	+ 9.68
Quinine	2	+18.1	+23.5	+20.8	+ 6.25	+16.5	+19.9	+ 0.99	+ 9.18
Quinidine	2	-29.2	-33.7	-30.9	-13.7	-25.2	-27.5	- 0.29	-13.2
Pyrrolidine der.[c]	2	+ 5.94	+ 6.23	+ 2.17	± 0.0	+ 7.95	+ 4.02	+15.3	+ 4.97

a) $[\alpha]_D^{23}$(c 5.00, CH_2Cl_2). b) $[\alpha]_D^{23}$(c 3.50, MeOH).
c) (2S,4S)-2-(Anilinomethyl)-1-ethyl-4-hydroxypyrrolidine.[3]

Table 2. Optical purities and chemical yields of 2a in various reaction conditions

Solvent / ml		Temp/°C	O.P./%[a]	Yield/%	Solvent / ml		Temp/°C	O.P./%[a]	Yield/%
Non		0	28.0	98	Toluene	5	0	33.7	97
Benzene	5	10	31.5	97		10	0	45.2	93
Cyclohexane	5	10	33.5	95			20	54.7	92
CCl_4	5	0	33.2	96		20	0	61.5	85
CH_2Cl_2	5	0	25.1	97			-15	60.9	66
EtOEt	5	0	19.3	97		40	0	72.5	68
THF	5	0	11.4	96		80	0	85.4	25
MeOH	5	0	3.54	97		160	0	86.8	7

a) Optical purities are calculated based on the results in Schemes1 and 2. $[\alpha]_D^{23}$ -92.7°(c 5.00, CH_2Cl_2) for optically pure (S)- 2a .

With prolonged reaction time, the chemical yield increased, however, the (-)-specific rotation decreased gradually. It was supposed that the result was due to the formation of diisopropyl fumalate (4), which was measured by liquid chromatography (Fig. 2), or the racemization of 2a in the reaction conditions.

Then, the asymmetric Michael addition of thiophenol to 4 was carried out at the same reaction conditions. As shown in Fig. 1 (—▲—) small and constant (+)-specific rotation was observed, and the reaction rate was slower than that of 1a. Consequently, the decrease of the specific rotation in the case of 1a indicated the competitive addition of thiophenol to 1a and 4 formed by the isomerization of

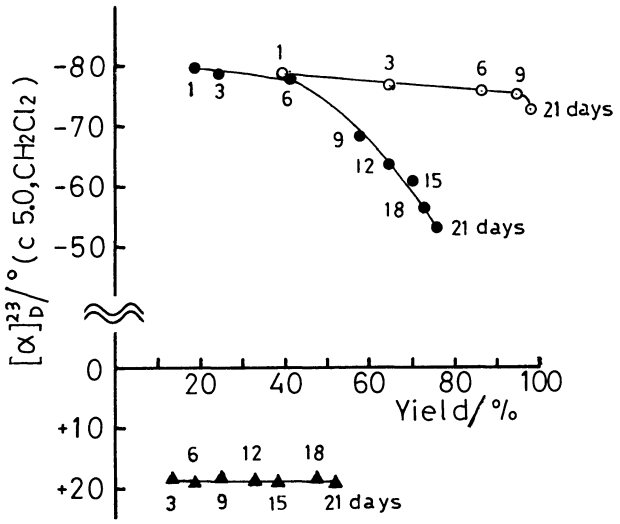


Fig. 1. Time dependence of the specifc rotation and yield of 2a.
(—●—) 1a(4mmol), Thiophenol(4mmol)
(—o—) 1a(4m mol), Thiophenol(2mmol)
(—▲—) 4(4mmol), Thiophenol(4 mmol)

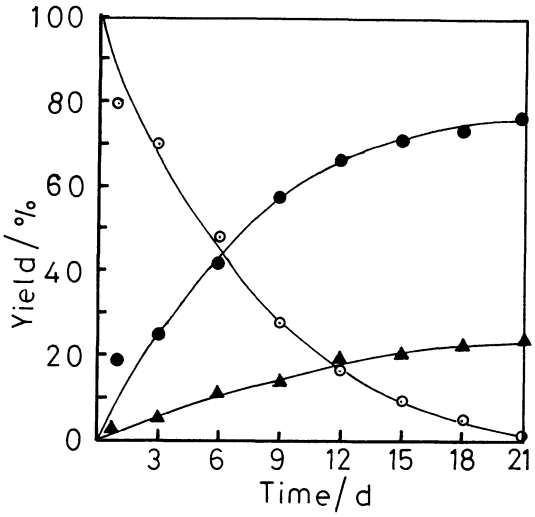
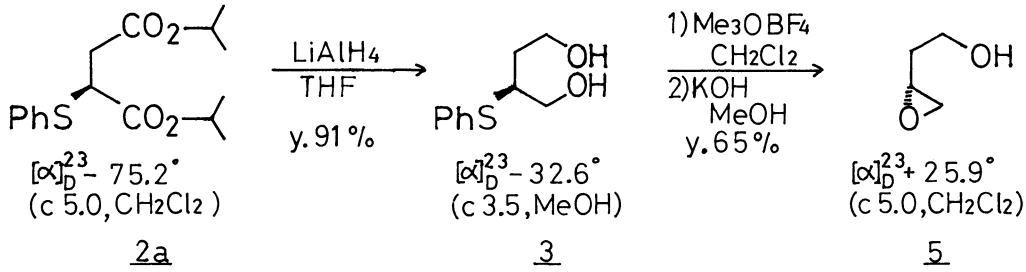


Fig. 2. Isomerization of 1a to 4.
(—o—) 1a
(—●—) 2a
(—▲—) 4

1a, and the racemization of 2a was negligible because of the constant specific rotation in the case of 4.

Considering that both the rates of the formation of 4 and the addition of thiophenol to 4 were slower than the rate of the addition of thiophenol to 1a, half equivalents of thiophenol were used so as to keep excess of 1a throughout the reaction. The results are shown in Fig. 1 (—o—). As expected, only a little decrease of the specific rotation (from -78.3° to -75.2°) was observed with up to 95% chemical yield.

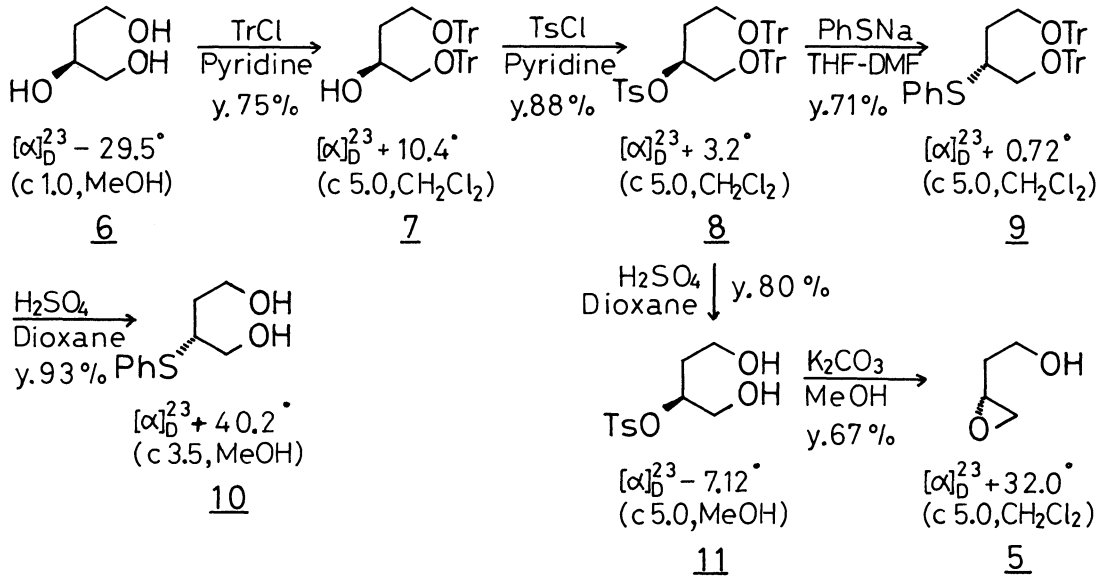
Furthermore, 2a ($[\alpha]_D^{23}$-75.2°) was transformed into (+)-3,4-epoxy-1-butanol (5) ($[\alpha]_D^{23}$+25.9°), a useful chiral building block, by the application of the known method[5] as shown in the following scheme 1.



Scheme 1.

In order to determine the absolute configurations and optical purities of 2a,

3, and 5, we synthesized optically pure 10 and 5[6] from optically pure (S)-(-)-1,2,4-butanetriol (6)[7] by the usual methods as shown in the following scheme 2.



Scheme 2.

Based on the above results, 2a ($[\alpha]_D^{23}$ -75.2°) and 3 ($[\alpha]_D^{23}$ -32.6°) have S-configurations (81% optical purities), and (R)-(+)-5 (81% optical purity) was obtained with complete inversion of the asymmetric center.

It is noted that optically active diisopropyl phenylthiosuccinate was obtained in good optical purity by the Michael addition of thiophenol to diisopropyl maleate, an acyclic Michael acceptor, catalyzed by cinchonine, and is easily transformed into optically active 3,4-epoxy-1-butanol, a useful chiral building block by only two steps without racemization.

References

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