

SYNTHESIS OF OPTICALLY ACTIVE SELENOXIDE

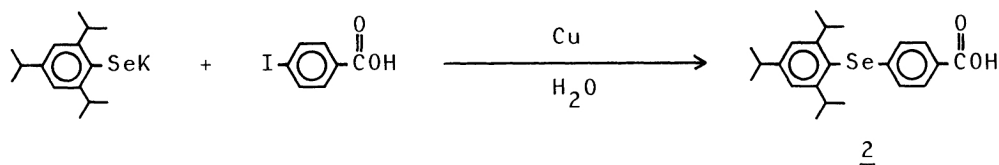
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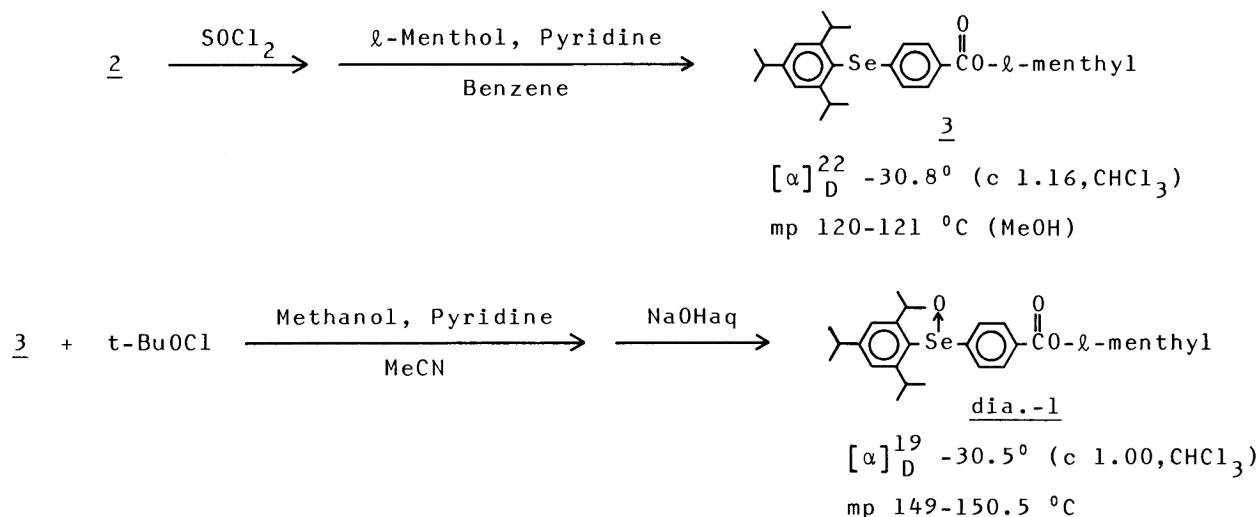
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Fractional recrystallization of diastereomeric 2,4,6-triisopropylphenyl 4'-(ℓ -menthyloxycarbonyl)phenyl selenoxide gave optically pure (-)-selenoxide. Transesterification of this diastereomerically pure (-)-selenoxide with methanol gave enantiomeric (-)-2,4,6-triisopropylphenyl 4'-(methoxycarbonyl)-phenyl selenoxide in 88.1% optical purity.

Since optically active sulfoxides were resolved for the first time in 1926¹⁾ many optically active sulfoxides had been isolated up to the present. On the contrary, despite of the repeated attempts,²⁾ there had been no example of the optically active selenoxide for a long time. Difficulty of optical resolution of selenoxide is attributed the facile racemization due to the formation of achiral hydrates.^{2,3)} In 1970, two optically active diastereomeric steroidal selenoxides were isolated for the first time.⁴⁾ Recently partially active enantiomeric selenoxides were prepared by using bulky substituents to prevent racemization via achiral hydrate by Davis et al.⁵⁾ However their optical purities were only 5-11%. We report here the synthesis of diastereomeric optically pure selenoxide and enantiomeric selenoxide with high optical activity.

Diastereomeric 2,4,6-triisopropylphenyl 4'-(ℓ -menthyloxycarbonyl)phenyl selenoxide (dia.-1) was prepared by the following scheme. Reaction of potassium 2,4,6-triisopropylbenzeneselenolate with 4-iodobenzoic acid in water in the





presence of copper powder gave 2,4,6-triisopropylphenyl 4'-carboxyphenyl selenide (2) in 47% yield after a day of reflux.⁶⁾ 2,4,6-Triisopropylphenyl 4'-(l-menthyloxycarbonyl)phenyl selenide (3) was prepared in 84% yield via acid chloride from 2. Oxidation of selenide 3 was achieved with t-butyl hypochlorite in the presence of methanol and pyridine in 91% yield.⁷⁾ The $[\alpha]_D$ of resulting selenoxide 1 was -30.5° in chloroform. No asymmetric oxidation of selenide group was observed by HPLC using optically active column.⁸⁾ Therefore, this optical rotation must be due to l-menthyl moiety. Fractional recrystallization was repeated from methanol. Optically pure diastereomeric selenoxide (-)-1⁹⁾ (1.00 g) was obtained after five recrystallization from 7.30 g of the diastereomeric selenoxide pair dia.-1 (Table 1). The CD spectrum of (-)-1 shows the negative Cotton effect at 290 nm in methanol. Furthermore, 1.45 g of (+)-selenoxide (+)-1

Table 1. Fractional recrystallization of dia.-1

	(-) crystal	(+) from mother liquid
Optical purity ^{a)}	100%	75.3%
$[\alpha]_D$ (CDCl ₃) ^{b)}	-99.0°	$+17.7^\circ$
CD $[\theta]_{290}$ (MeOH)	-2.80×10^4	$+1.86 \times 10^4$
Mp $\theta\text{m}/^\circ\text{C}$	186.5-187.5	147-151

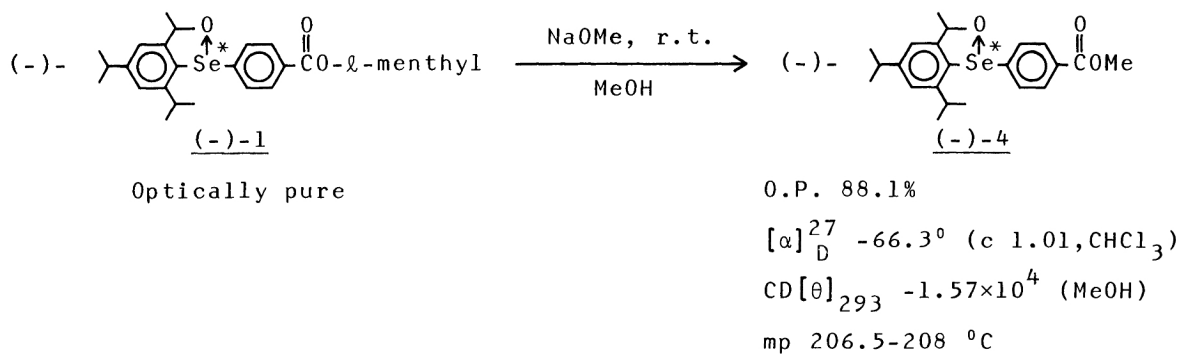
a) Optical purities were determined by HPLC using optically active column.⁸⁾

b) Optical rotations were taken in chloroform at 26°C ((-)-1) and 19°C ((+)-1).

was obtained from mother liquid in 75.3% optical purity. This selenoxide (+)-1 has the positive Cotton effect.

Thermal stabilities of optically active selenoxide (-)-1 toward racemization were preliminary examined. Optically active selenoxide (-)-1 is stable in crystalline state at room temperature. Its solution in dry methanol showed no loss of optical activity after 3 h at room temperature. In boiling methanol, however, selenoxide (-)-1 was converted slowly to dia.-1. Optical purity of (-)-1 was decreased from 100% to 50% after about 40 h in boiling methanol. No racemization was detected after 3 h by vigorous stirring in dichloromethane-water in the presence of sodium hydroxide. According to Davis et al.,⁵⁾ addition of a trace of p-toluenesulfonic acid monohydrate to (+)-methyl 2,4,6-triisopropylphenyl selenoxide resulted in complete racemization in less than 10 seconds.

Accordingly, we attempted transesterification of (-)-1 under basic conditions, namely with methanol in the presence of sodium methoxide at room temperature.



When reaction was followed by HPLC, transesterification was shown to be completed after 4 d. The product was extracted with dichloromethane after addition of water. Removal of the solvent gave a solid product, which was washed with hexane several times. Enantiomeric selenoxide (-)-4¹⁰⁾ was obtained in 66% chemical yield. The structure and chemical purity were confirmed by ¹H-NMR and HPLC. Optical purity of (-)-4 was estimated to be 88.1% by HPLC using optically active column.⁸⁾ Studies on its absolute configuration are under way.

References

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- 8) Bakerbond chiral phase HPLC column DNBPG/Aminopropylsilica; 25 cm × 4.6 mm; using hexane : 2-propanol = 95 : 5 as eluent.
- 9) Compound (-)-1: Mp 186.5-187.5 °C. $[\alpha]_D^{26} -99.0^\circ$ (c 1.25, CHCl₃). CD[θ]₂₉₀ -2.80×10⁴ (MeOH). IR (KBr) ν = 820(Se=O) and 1710(C=O) cm⁻¹. UV (MeOH) 220 (ε 2.24×10⁴), 240(2.24×10⁴), and 275(1.03×10⁴) nm. ¹H-NMR (60 MHz, CDCl₃) δ = 0.92, 1.24, 1.30 (18H, d, J=6.6 Hz, CH₃ of triisopropylphenyl), 0.6-2.2 (18H, m, *l*-menthyl except O-methine), 2.89 (1H, hep., J=6.6 Hz, methine of para isopropyl), 3.73 (2H, hep., J=6.6 Hz, methine of ortho isopropyl), 4.93 (1H, dt, J=4.2, 9.9 Hz, O-methine), 7.03 (2H, s, aromatic protons of triisopropylphenyl), 7.61 and 8.07 (4H, ABq, J=8.4 Hz, aromatic protons of p-substituted aromatic ring). Mass M⁺ 558(⁸⁰Se). Found: m/e 542.2661 (⁸⁰Se)(lack of one oxygen). Calcd for C₃₂H₄₆O₃⁸⁰Se: 542.2662.
- 10) Compound (-)-4: Mp 206.5-208 °C. $[\alpha]_D^{27} -66.3^\circ$ (c 1.01, CHCl₃). CD[θ]₂₉₃ -1.57×10⁴ (MeOH). IR (KBr) ν = 820(Se=O) and 1720(C=O) cm⁻¹. UV (MeOH) 214 (ε 2.27×10⁴), 237(2.03×10⁴), and 275(9.28×10³) nm. ¹H-NMR (60 MHz, CDCl₃) δ = 0.92, 1.24, 1.30 (18H, d, J=6.6 Hz, CH₃ of triisopropyl), 2.91 (1H, hep., J=6.6Hz, para methine), 3.73 (2H, hep., J=6.6 Hz, ortho methine), 3.91 (3H, s, methoxy), 7.06 (2H, s, aromatic protons of triisopropylphenyl), 7.65 and 8.10 (4H, ABq, J=7.2 Hz, aromatic protons of p-substituted aromatic ring). Found: m/e 434.1390 (⁸⁰Se). Calcd for C₂₃H₃₀O₃⁸⁰Se: 434.1359.

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