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Enantiodivergent Synthesis of Both Enantiomers of Sulcatol and Matsutake Alcohol from (R)-Epichlorohydrin

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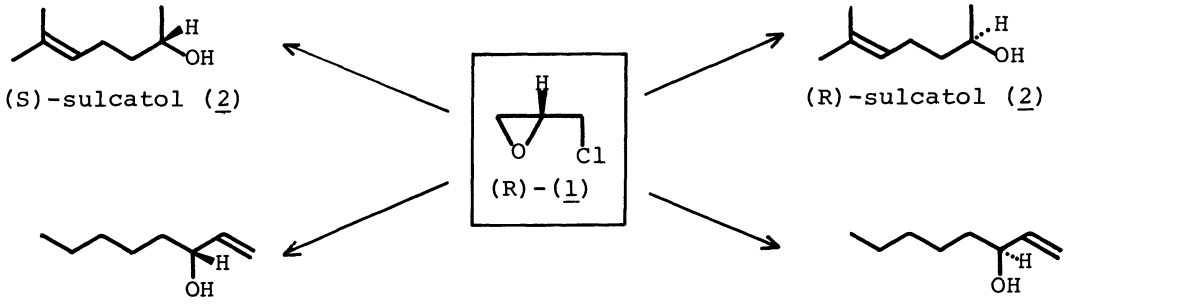
Enantiodivergent synthesis of both enantiomers of sulcatol, an aggregation pheromone of Gnathotrichus sulcatus, and matsutake alcohol, a flavor compound of the mushroom Tricholoma matsutake, has been established using (R)-epichlorohydrin as common chiral precursor.

Since the occurrence of both enantiomers is often encountered in certain groups of natural products, establishment of a selective route to both enantiomers is sometimes very important. We report here a convenient method for the enantiodivergent construction of both enantiomers of natural products carrying secondary hydroxy group using a single optically active starting material, epichlorohydrin **1**, as common precursor. The method is exemplified by an enantiodivergent synthesis of both enantiomers of an insect aggregation pheromone, sulcatol[1] **2**, and a mushroom flavor compound, matsutake alcohol[2] **3**, starting from (R)-epichlorohydrin **1** which is readily available from racemic 2,3-dichloropropanol via microbial resolution.[3]

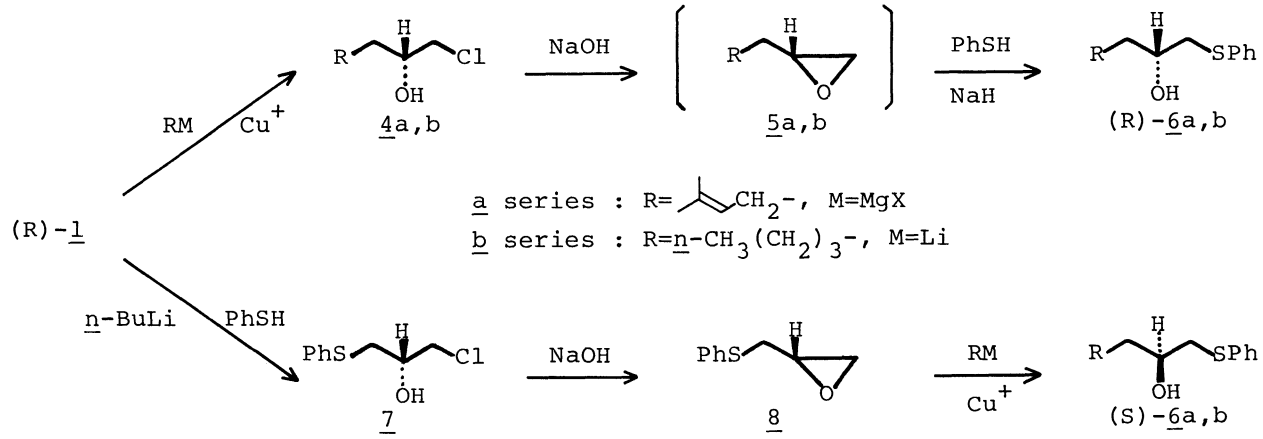


Scheme 1.

Reaction of (R)-epichlorohydrin **1** with prenylmagnesium chloride (1.5 equiv., THF, -30 °C-rt) in the presence of copper (I) iodide[4] (0.15 equiv.) gave the chlorohydrin **4a**, $[\alpha]_D^{25}$ +1.8° (c 3.37, $CHCl_3$), which was treated with powdered sodium hydroxide (5.0 equiv.) in ether to give the (R)-epoxide **5a**. Because of its high volatility **5a** was immediately treated with sodium phenyl sulfide (prepared in situ from thiophenol (1.1 equiv.) and sodium hydride (1.2 equiv., THF)) to afford the (R)-sulfide **6a**, $[\alpha]_D^{18}$ -27.2° (c 1.52, $CHCl_3$) (>95% ee),[5] (35.5% overall yield from **1**) for identification. Similarly, (R)-**1** was sequentially treated with n-

butyllithium (2.4 equiv.) in the presence of copper (I) cyanide[6] (1.2 equiv.), and lithium phenyl sulfide (prepared from in situ thiophenol (2.0 equiv.) and n-butyllithium (2.0 equiv., THF)) in the same flask to give the (R)-sulfide **6b**, $[\alpha]_D^{25}$ -34.7° (c 1.54, $CHCl_3$) in 71% overall yield without isolation of the intermediates, the chlorohydrin **4b** and the epoxide **5b**.

On the other hand, the same (R)-epichlorohydrin **1** was first treated with lithium phenyl sulfide (1.1 equiv.) in THF (-30 °C-rt) to give the chlorohydrin **7**, $[\alpha]_D^{27}$ +8.7° (c 1.56, $CHCl_3$) (>94% ee),[5] in 95% yield. The resulting **7** was readily converted into the known glycidyl sulfide[7] **8**, $[\alpha]_D^{28}$ -29.8° (c 1.57, $CHCl_3$) (lit.[7] $[\alpha]_D^{23}$ -34.1° (c 1.54, $CHCl_3$)), in 93% yield on treatment with powdered sodium hydroxide (3 equiv.) in ether. Reaction of **8** with prenylmagnesium chloride (1.9 equiv., THF, -30 °C-rt) in the presence of copper (I) iodide[4] gave (S)-**6a** in 81% yield. Practically, these conversions could be carried out in one flask as shown in the synthesis of (S)-**6b**. Thus, sequential treatment of (R)-**1** with lithium phenyl sulfide (1.2 equiv.) and n-butyllithium (1.3 equiv., -78 °C-rt) in THF in the presence of copper (I) cyanide[6] (2.6 equiv.) in the same flask, afforded the (S)-sulfide **6b**, $[\alpha]_D^{25}$ +34.8° (c 1.52, $CHCl_3$), in 68% overall yield.

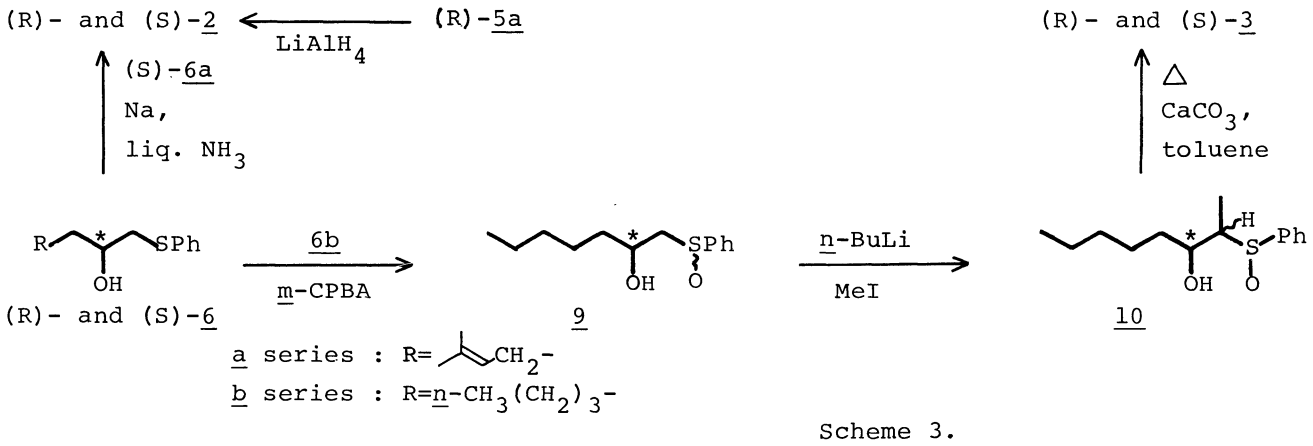


Scheme 2.

Both enantiomers of sulcatol **2**, isolated from Gnathotrichus sulcatus in 65:35 mixture of (S)- and (R)-enantiomers,[1] were prepared as follows; reduction of crude (R)-**5a** with lithium aluminum hydride (THF, reflux) gave (S)-**2**, $[\alpha]_D^{26}$ +14.3° (c 0.88, EtOH) (>94% ee)[5] (lit.[1b] $[\alpha]_D^{23}$ +14.4° (c 0.998, EtOH)), in 75% overall yield from **1**, while dissolving metal reduction (Na, liq. NH_3) of (S)-**6a** gave (R)-**2** (>91% ee),[5] in 30% yield. In the dissolving metal reduction, competing reductive cleavage between the carbon atom carrying secondary hydroxy group and the phenylthiomethylene group took place decreasing yield of the desired **2a** in a considerable extent. Removal of the sulfide moiety was also possible to give **2a** in a much better yield using Raney nickel catalyst (W2) in ethanol, however, it was accompanied by the inseparable dihydrogenated by-product.

Matsutake alcohol **3**, isolated from Tricholoma matsutake as (R)-configuration, and its unnatural (S)-enantiomer were prepared from the corresponding progenitors **6b** by a three-step sequence of reactions. Oxidation of **6b** with m-chloroperbenzoic

acid (1.0 equiv.) gave the sulfoxide **9b** quantitatively. Upon treatment with n-butyllithium (2.3 equiv., THF, -78 °C-rt), followed by methyl iodide (1.1 equiv., -78 °C), **9b** afforded **10b** as a mixture of diastereomers in an excellent yield (≈99%). On thermolysis (toluene, reflux, overnight) in the presence of calcium carbonate (3.0 equiv.) **10b** furnished matsutake alcohol **3** with the corresponding chirality via regioselective elimination; (R)-**6b** gave natural (R)-**3**, $[\alpha]_D^{24}$ -8.8° (c 1.50, $CHCl_3$) (>94% ee),[5] in 65% yield and (S)-**6b** gave unnatural (S)-**3**, $[\alpha]_D^{26}$ +8.1° (c 1.46, $CHCl_3$) (>94% ee),[5] in 57% yield, respectively.



Scheme 3.

The present methodology may be widely applicable to the enantiodivergent synthesis of both enantiomers of a versatile compounds carrying chiral secondary alcohols as well as more complex target molecules starting from a single optically active epichlorohydrin as common precursor.

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References

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4) cf. C. Huynh, F. Derguini-Boumechal, and G. Linstrumelle, Tetrahedron Lett., 1979, 1503 and related papers.

5) Optical purities were determined by comparison of ^{1}H-NMR spectra (500 MHz) of both (R)- and (S)-MTPA esters of the secondary alcohols.

6) cf. B. H. Lipshutz, R. S. Wilhelm, J. A. Kozlowski, and D. Parker, J. Org. Chem., 49, 3928 (1984).

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9) Spectral data: IR (neat) cm^{-1}; 90 MHz ^{1}H-NMR ($CDCl_3$).
Compound **6a:** ν 3425; δ 1.4-1.7 (m, 2H), 1.60 (brs, 3H), 1.67 (brd, J=12 Hz, 3H), 1.95-2.25 (m, 2H), 2.37 (brd, exchangeable, 1H), 2.83 (dd, J=13.7 and 8.7 Hz, 1H), 3.15 (dd, J=13.4 and 3.7 Hz, 1H), 3.5-3.85 (m, 1H), 5.09 (brt, J=7.1 Hz, 1H), 7.15-7.5 (m, 5H).
Compound **6b:** ν 3400; δ 0.88 (m, 3H), 1.21-1.62 (m, 8H), 2.42 (brs, exchangeable), 2.70-3.27 (m, 2H), 3.65 (m, 1H), 7.21-7.41 (m, 5H).
Compound **9:** ν 3375; δ 0.88 (m, 3H), 1.21-1.62 (m, 8H), 2.70-3.27 (m, 2H), 4.18 (m, 2H, 1H exchangeable), 7.50-7.75 (m, 5H).
Compound **10:** ν 3350; δ 0.96 (m, 6H), 1.20-1.62 (m, 8H), 2.34-3.02 (m, 1H), 3.70-4.41 (m, 2H, 1H exchangeable), 7.27-7.82 (m, 5H).
Compound **3:** ν 3370, 1645; δ 0.89 (brt, 3H), 1.15-1.48 (m, 9H, 1H exchangeable), 4.10 (m, 1H), 5.09 (m, 1H), 5.22 (m, 1H), 5.83 (m, 1H).
Compound **4a:** ν 3400; δ 1.4-1.7 (m, 2H), 1.62 (brs, 3H), 1.69 (brs, 3H), 1.9-2.3 (m, 3H, 1H exchangeable), 3.3.-3.6 (m, 2H), 3.65-3.95 (m, 1H), 5.11 (brt, J=7.0 Hz, 1H).

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