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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 <u>Gnathotrichus sulcatus</u>, and matsutake alcohol, a flavor compound of the mushroom <u>Tricholoma</u> <u>matsutake</u>, 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, sulcatol¹⁾ 2, and a mushroom flavor compound, matsutake $alcohol^{2)}$ 3, starting from (R)-epichlorohydrin 1 which is readily available from racemic 2,3-dichloropropanol <u>via</u> microbial resolution.³⁾



(R)-matsutake alcohol (3)

(S)-matsutake alcohol (3)

Scheme 1.

Reaction of (R)-epichlorohydrin 1 with prenylmagnesium chloride (1.5 equiv., THF, -30 °C-rt) in the presence of copper (I) iodide⁴⁾ (0.15 equiv.) gave the chlorohydrin 4a, $[\alpha]_D^{25}$ +1.8° (c 3.37, CHCl₃), 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 <u>in situ</u> 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, CHCl₃) (>95% ee), ⁵⁾ (35.5% overall yield from 1) for identification. Similarly, (R)-1 was sequentially treated with <u>n</u>-

butyllithium (2.4 equiv.) in the presence of copper (I) cyanide⁶⁾ (1.2 equiv.), and lithium phenyl sulfide (prepared from <u>in situ</u> thiophenol (2.0 equiv.) and <u>n</u>-butyl-lithium (2.0 equiv., THF)) in the same flask to give the (R)-sulfide **6b**, $[\alpha]_D^{25}$ -34.7° (c 1.54, CHCl₃) 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, $\left[\alpha\right]_{D}^{27}$ +8.7° (c 1.56, CHCl₃) (>94% ee),⁵) in 95% yield. The resulting 7 was readily converted into the known glycidyl sulfide⁷ 8, $\left[\alpha\right]_{D}^{28}$ -29.8° (c 1.57, CHCl₃) (lit.⁷) $\left[\alpha\right]_{D}^{23}$ -34.1° (c 1.54, CHCl₃)), 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) iodide⁴ 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 <u>n</u>-butyllithium (1.3 equiv., -78 °C-rt) in THF in the presence of copper (I) cyanide⁶ (2.6 equiv.) in the same flask, afforded the (S)-sulfide 6b, $\left[\alpha\right]_{D}^{25}$ +34.8° (c 1.52, CHCl₃), in 68% overall yield.



Both enantiomers of sulcatol 2, isolated from <u>Gnathotrichus sulcatus</u> 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. NH₃) 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 phenyl-thiomethylene 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 <u>Tricholoma</u> <u>matsutake</u> 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 <u>m</u>-chloroperbenzoic acid (1.0 equiv.) gave the sulfoxide **9b** quantitatively. Upon treatment with <u>n</u>-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 ((3, 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, CHCl₃) (>94% ee),⁵⁾ in 65% yield and (S)-**6b** gave unnatural (S)-**3**, $[\alpha]_D^{26}$ +8.1° (c 1.46, CHCl₃) (>94% ee),⁵⁾ in 57% yield, respectively.



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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- 9) Spectral data: IR (neat) cm⁻¹; 90 MHz ¹H-NMR (CDCl₂). Compound 6a: v 3425; & 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: v 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: v 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: v 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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