Synthesis of (*R*)-(−)-Muscone *via* Enzymatic Resolution of 3-Methylcyclopentadecan-1-ol

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(*R*)-(−)-Muscone was synthesized efficiently by oxidation of 3-(*R*)-methylcyclopentadecan-1-(*RS*)-ol, which was obtained by lipase-catalyzed resolution of its diastereomeric mixture.

Key words lipase; resolution; transesterification; isopropenyl acetate; muscone

Since (*R*)-(−)-muscone (***R*-1**) was found about 90 years ago to be a valuable perfume compound in the male deer *Moschus moschiferus*,[1] synthetic approaches for obtaining optically pure muscone have been reported.[2] However, there is no report, to our knowledge, on its efficient enzymatic synthesis, although lipase-catalyzed reaction in an organic solvent has been recently recognized as a useful synthetic method for various optically active compounds.[3] In this paper we describe a convenient method for the synthesis of (*R*)-(−)-muscone (***R*-1**) *via* lipase-catalyzed transesterification of 3-methylcyclopentadecan-1-ol (**2**) with isopropenyl acetate.

A few years ago, Takabe and co-workers reported a synthetic method for ***R*-1** *via* lipase-catalyzed resolution of 3-methylcyclopentadecan-1-ol (**2**), with which they obtained ***R*-1** with high optical purity but in low chemical yield (Chart 1).[4] Because the substrate **2** includes four stereoisomers, it seemed impossible to increase the chemical yield up to the theoretical yield of 50%. However, when screening tests of the transesterification of **2** with isopropenyl acetate using various lipases were examined, it was found that the resolution of two pairs of enantiomers in **2** occurred simultaneously with lipase QL (*Alcaligenes* sp.),[5] resulting in ***R*-1** with high optical purity in near 50% yield. This result encouraged us to investigate in detail the characteristic selectivity of lipase QL.

We carried out the transesterification of **2**, prepared from (±)-muscone, with isopropenyl acetate in isopropyl ether (IPE) using several lipases (entries 1—5 in Table 1). Although lipase AK (*Pseudomonas* sp.) gave the most optically pure muscone (entry 1), the low chemical yield suggests that only one enantiomer among the four isomers is esterificated. However, it is obvious that lipase QL works both diastereo- and enantioselectively on the basis of the chemical yield and optical purity (entry 5). This phenomenon was also confirmed by gas-liquid chromatography (GLC) analysis in the

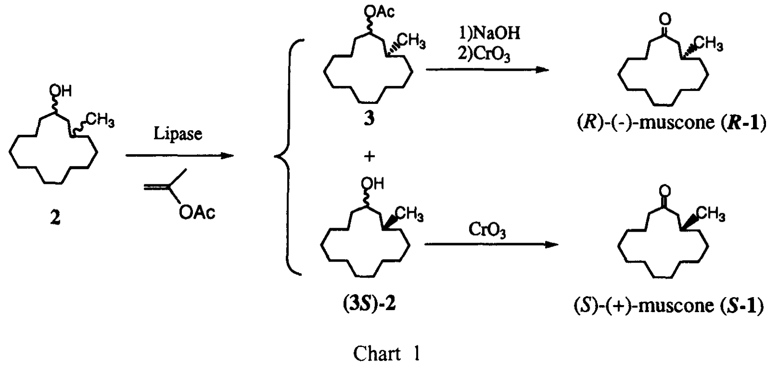

Chart 1

Table 1. Lipase-Catalyzed Transesterification of 3-Methylcyclopentadecan-1-ol (**2**) with Isopropenyl Acetate

Entry	Lipase	Solvent	Time (d)	Conv. (%) **3**[a)]	$[\alpha]_D^{22}$ (c=1.0, MeOH)			
					***R*-1**	%ee[b)]	***S*-1**	%ee[b)]
1	AK	IPE	1.3	23	−11.6	91.3	2.3	18.1
2	AL	IPE	8	26	−0.6	4.7	1.3	10.2
3	AH	IPE	14	50	−8.1	63.8	7.7	60.6
4	LIP	IPE	7.3	50	−0.1	0.8	0.5	3.9
5	QL	IPE	3	51	−10.8	85.0	11.2	88.2
6	QL	*t*-BME[c)]	1.3	46	−11.3	89.0	9.2	72.4
7	QL	Cyclohexane	6	51	−11.5	90.6	11.3	89.0
8	QL	Hexane	3.8	49	−11.0	86.6	10.0	78.7
9	QL	Toluene	3.7	47	−9.6	75.6	9.0	70.9

a) Determined by GLC analysis. *b*) Based on the specific rotation of optically prure (*R*)-(−)-muscone, $[\alpha]_D^{22}$ −12.7° (c=1.0, MeOH). *c*) *tert*-Butyl methyl ether.

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time course of the reactions. Two GLC peaks due to *syn*- and *anti*-isomers of **2**6) were observed to diminish simultaneously as the reaction proceeded, in spite of the fact that a decrease of only one peak was observed in entry 1. Furthermore, the reaction with lipase QL was carried out in several solvents for optimization (entries 6—9).

The general procedure is as follows: A mixture of 3-methylcyclopentadecan-1-ol **2** (4 mmol), isopropenyl acetate (4 mmol), and lipase QL (500 mg) in an organic solvent (10 ml) was stirred at room temperature. After consumption of half the amount of **2** had been confirmed by GLC analysis, the lipase was removed by filtration and washed with ether. The combined organic layer was concentrated to afford an oily residue, which was chromatographed on a silica-gel column with an AcOEt-hexane system to give the corresponding ester **3**7) and unreacted **(3*S*)-2**. The isolated **3** and **(3*S*)-2** were converted to muscone (Chart 1) and their specific rotations were measured.

It is noteworthy that the specific rotation ($[\alpha]_{\mathrm{D}}^{22}$ -11.5° in MeOH) of (*R*)-($-$)-muscone obtained *via* the reaction in cyclohexane (entry 7) showed a value near that of natural muscone.8) However, in a recent paper, the $[\alpha]_{\mathrm{D}}$ of optically pure (*R*)-($-$)-muscone was reported to be -12.6°.2c) In order to clarify the purity, the 2,4-dinitrophenylhydrazones of both racemic muscone9) and (*R*)-($-$)-muscone obtained were prepared and checked by HPLC analysis using a chiral column (Chiralcel OD). The racemic 2,4-dinitrophenylhydrazone showed four peaks, indicating the presence of geometric isomers. However, that of the synthetic (*R*)-($-$)-muscone showed two large peaks and two very small peaks. The purity calculated from the peak areas was estimated to be 91%ee (entry 7), recrystallization of which gave optically pure 2,4-dinitrophenylhydrazone of (*R*)-($-$)-muscone. Then it was converted to (*R*)-($-$)-muscone, $[\alpha]_{\mathrm{D}}^{22}$ -12.7° (c=1.0, MeOH).

Thus the high enantioselective reaction with lipase QL has been achieved for the diastereomeric mixture. We believe that such stereoselectivity of lipase is rarely found. Recently, lipase QL has been reported to have a very hydrophobic binding site,10) which seems to be one of the reasons why it is well suited for substrates like muscone derivatives.

References and Notes

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5) Obtained from Meito Sangyo Co., Ltd.

6) The ratios of diastereomers, in **2**, **3**, and **(3*S*)-2** were estimated to be 29 : 71 by GLC analysis, although it is unknown which isomer, *syn* or *anti*, is greater in amount.

7) A mixture of diastereomers, colorless oil. FAB-MS *m/z*: 283 (MH)$^+$. IR (liq.): 1740 cm^{-1} (CO). ^{1}H-NMR (CDCl$_3$, 500 MHz) δ: 0.83 (d, J=4.5 Hz), 0.84 (d, J=5 Hz), 1.09—1.71 (m), 1.955 (s), 1.959 (s), 4.86—4.93 (m). ^{13}C-NMR (CDCl$_3$, 125 MHz) δ: 20.6, 21.1, 21.4, 22.8, 23.6, 24.1, 25.2, 26.4, 26.5, 26.60, 26.64, 26.69, 26.7, 26.8, 27.0, 27.1, 27.3, 28.5, 28.6, 31.8, 32.8, 34.4, 35.5, 39.9, 41.2, 72.5, 73.0, 170.66, 170.69.

8) Bramca Q., Fischli A., *Helv. Chim. Acta*, **60**, 925—944 (1977).

9) A mixture of geometric isomers, orange needles (EtOH). mp 114—116 °C. FAB-MS *m/z*: 419 (MH)$^+$. IR (KBr): 3310 cm^{-1} (NH). ^{1}H-NMR (CDCl$_3$, 500 MHz) δ: 0.94 (d, J=7.0 Hz), 1.05 (d, J=6.5 Hz), 1.23—2.51 (m), 7.97 (d, J=9.5 Hz), 8.29 (dd, J=3, 9.5 Hz), 9.13 (d, J=3 Hz). ^{13}C-NMR (CDCl$_3$, 125 MHz) δ: 20.3, 20.9, 23.8, 24.7, 24.8, 25.0, 26.02, 26.06, 26.09, 26.24, 26.25, 26.28, 26.59, 26.65, 26.69, 27.0, 27.3, 28.0, 29.2, 29.3, 30.4, 35.3, 35.7, 36.8, 37.7, 44.9, 116.4, 123.6, 128.8, 128.9, 129.9, 130.0, 137.5, 145.2, 154.3, 161.99, 162.04.

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