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PREPARATION OF (4S)-4-HYDROXY-3-METHYL-2-(2'-PROPYNYL)-2-CYCLOPENTENONE BY COMBINATION OF ENZYMATIC HYDROLYSIS AND CHEMICAL TRANSFORMATION

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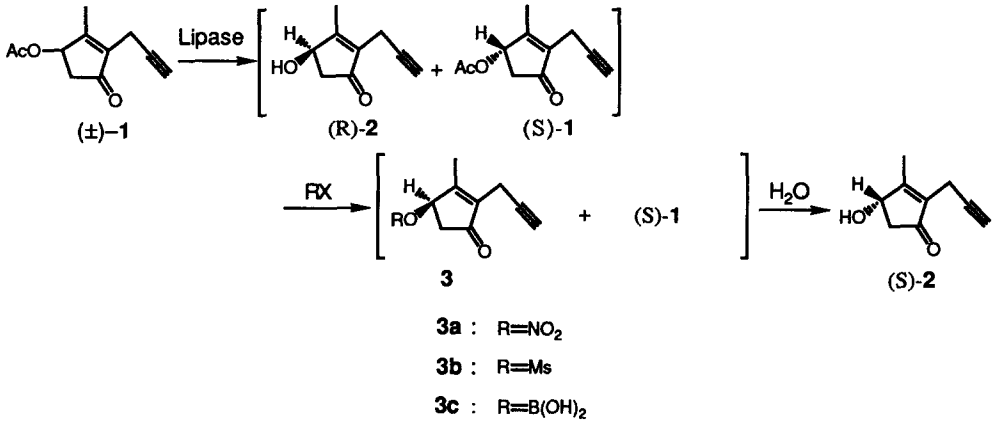
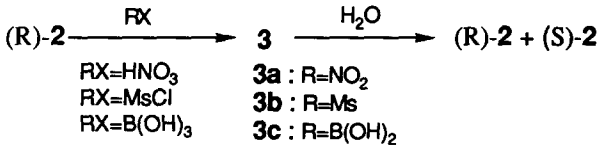
Abstract : (4S)-4-Hydroxy-3-methyl-2-(2'-propynyl)-2-cyclopentenone ((S)-**2**), which is an important alcohol moiety of optically active pyrethroid insecticides, was prepared from the corresponding racemic acetate ((±)-**1**) by the combination of enzymatic hydrolysis and chemical transformation in high chemical and optical yields.

(4S)-4-Hydroxy-3-methyl-2-(2'-propynyl)-2-cyclopentenone ((S)-**2**) is an important alcohol moiety of optically active pyrethroid insecticides.[1,2] We recently reported the preliminary strategy to prepare the optically active (S)-**2** from the corresponding racemic acetate ((±)-**1**) (Scheme 1), in which enzymatic hydrolysis of (±)-**1** was discussed in detail.[3,4] As a part of our ongoing program, we have investigated the sequential chemical transformation of (R)-alcohol ((R)-**2**) and (S)-acetate ((S)-**1**) obtained by the enzymatic hydrolysis, and accomplished the route to prepare (S)-alcohol ((S)-**2**) in high chemical and optical yields, starting from the racemic acetate ((±)-**1**). The result is described herein.

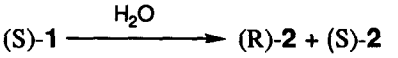


Scheme 1

The racemic acetate ((±)-**1**) was hydrolyzed by using *Arthrobacter* lipase.[3,4] The crude product was purified by column chromatography on silica gel (30% EtOAc in hexane) to give optically pure (R)-alcohol ((R)-**2**) as pale yellow crystals (46%),[5] and optically pure (S)-acetate ((S)-**1**) was recovered as white crystals (46%).[6]



Scheme 2



Scheme 3

In order to convert (R)-**2** to (S)-**2**, several kinds of esters (**3a** : nitrate, **3b** : mesylate, **3c** : borate) of (R)-**2** were prepared,[7-9] and their hydrolysis under acidic or neutral conditions was examined (Scheme 2). The results are summarized in Table 1. The esters (**3a-c**) were prepared by using 10 mmol of (R)-**2**. The hydrolysis of **3a-c** was carried out in 30 mL of water in the presence of CaCO3 at 85°C for 4h. After neutralization with aq. $NaHCO_3$ and extraction with EtOAc, the organic phase was concentrated *in vacuo*. The yields of the resulting alcohols ((R)-**2** + (S)-**2**) and the ratios ((R)-**2** : (S)-**2**) were determined by HPLC, using LiChrosorb RP-8 and an optically active stationary phase, Sumipax OA-4100. Borate (**3c**) preferentially gave (R)-alcohol ((R)-**2**) with retention, which may be due to preferential C-O bond fission rather than B-O bond in this case (entry 7). On the other hand, the hydrolysis of nitrate (**3a**) and mesylate (**3b**) under neutral or acidic conditions was followed by inversion to give (S)-alcohol ((S)-**2**) preferentially. For example, the rate of inversion was 86% for **3a** and 94% for **3b** under the presence of 1 eq of $CaCO_3$ (entries 1 and 4). As the amount of $CaCO_3$ was decreased, the rate of inversion was decreased. In the absence of $CaCO_3$, the rate of inversion was 72% for **3a** and 91% for **3b** (entries 3 and 6). This tendency may be due that the contribution of SN1 reaction is getting larger as the reaction mixture becomes acidic. Thus, it was found that the esters of (R)-**2**, nitrate (**3a**) and mesylate (**3b**), are hydrolyzed under neutral or acidic conditions to give (S)-alcohol ((S)-**2**) preferentially as a result of inversion of (R)-alcohol ((R)-**2**).

Next, the hydrolysis of (S)-acetate ((S)-**1**) under acidic conditions was investigated (Scheme 3). The hydrolysis of (S)-**1** was carried out on a 10 mmol scale in 30 mL of aqueous acid at 80°C. The resulting products were treated in the same manner as described above. The results are summarized in Table 2. Both aqueous H_2SO_4 and HNO_3 gave (S)-alcohol ((S)-**2**) quantitatively with retention. The rate of retention was over 99% in both cases. Thus, it was also found that (S)-acetate ((S)-**1**) are hydrolyzed under acidic conditions to afford (S)-alcohol ((S)-**2**) with retention.

Finally, our strategy to prepare (S)-alcohol ((S)-**2**) from the corresponding racemic acetate ((±)-**1**) was proved to be realized as follows. The racemic acetate ((±)-**1**) was hydrolyzed by *Arthrobacter* lipase, and the crude mixture of (R)-alcohol ((R)-**2**) and (S)-acetate ((S)-**1**) was esterified with fuming HNO_3 (Method A) or MsCl (Method B) to afford the mixture of the corresponding nitrate (**3a**) or mesylate (**3b**) and (S)-acetate ((S)-**1**). The (S)-acetate ((S)-**1**) was unaffected by the esterification conditions. The resultant mixture of **3a** and (S)-**1** or **3b** and (S)-**1** was hydrolyzed in the presence of 0.2 eq of $CaCO_3$. Method A afforded (S)-alcohol ((S)-**2**) of 82 %ee in 74 % yield.[10] Similarly, Method B gave (S)-**2** of 90 %ee in 82 % yield.[10] Thus, the racemic acetate ((±)-**1**) was converted with maximum efficiency to the desired (S)-alcohol ((S)-**2**) in high chemical and optical yields without separation or purification of any intermediates.

A further study on generalization of this methodology is in progress.

Table 1. Hydrolysis of Esters (**3a–c**) [a]

Entry	Substrate	$CaCO_3$ for Neutralization (eq.)	Yield of ((R)-**2** + (S)-**2**)[b] (%)	Isomer Ratio [c] (R)-**2** : (S)-**2**
1	**3a**	1	85	14 : 86
2		0.2	84	19 : 81
3		—	90	28 : 72
4	**3b**	1	92	6 : 94
5		0.2	95	7 : 93
6		—	90	9 : 91
7	**3c**	0.2	99	98 : 2

a) The reaction conditions are described in the text. b) Determined by HPLC (LiChrosorb RP-8). c) Determined by HPLC (Sumipax OA-4100).

Table 2. Hydrolysis of (S)-Acetate ((S)-**1**) [a]

Entry	Aq. Acid	Temp. (°C)	Time (h)	Yield of ((R)-**2** + (S)-**2**) [b] (%)	Isomer Ratio [c] (R)-**2** : (S)-**2**
1	2.5%H_2SO_4	80	3	96	0.7 : 99.3
2	2.5%HNO_3	80	1.5	100	0.8 : 99.2

a) The hydrolysis was carried out on a 10 mmol scale in 30 mL of aqueous acid. b) Determined by HPLC (LiChrosorb PR-8). c) Determined by HPLC (Sumipax OA-4100).

References and notes

(1) T. Matsuo, T. Nishioka, M. Hirano, Y. Suzuki, K. Tsushima, N. Itaya, and H. Yoshioka, *Pestic. Sci.*, **11**, 202 (1980).

(2) K. Aketa, N. Ohno, and H. Yoshioka, *Agric. Biol. Chem.*, **42**, 895 (1978).

(3) S.Mitsuda, T. Umemura, and H. Hirohara, *Appl. Microbiol. Biotech.*, **29**, 310 (1988).

(4) T.Umemura, and H. Hirohara, *ACS Symposium Series*, No. 389, 371 (1989).

(5) The absolute configuration has already been determined.[1,2] (R)-**2** : mp 43~5°C ; $[\alpha]_D^{25}$ -21.6° (c 1.47, $CHCl_3$) ; IR (nujol) 3350, 3270, 2900, 1690, 1640, 1460, 1375 cm^{-1} ; ^1H NMR (60 MHz, $CDCl_3$) δ=1.98 (t, J=3Hz, 1H), 2.20 (S, 3H), 2.25 (dd, J=3, 18Hz, 1H), 2.85 (dd, J=6, 18Hz, 1H), 3.07 (d, J=3Hz, 2H), 3.72 (br.s, 1H), 4.72 (br.d, J=5Hz, 1H) ; ^{13}C NMR (67.5 MHz, $CDCl_3$) δ=12.17, 13.85, 43.80, 68.80, 71.15, 79.51, 135.97, 172.00, 204.30.

(6) The absolute configuration has already been determined.[1-3] (S)-**1** : mp 45~6°C ; $[\alpha]_D^{23}$ +39.4° (c 1.25, $CHCl_3$) ; IR (nujol) 3250, 2900, 1710, 1660, 1460, 1375, 1240 cm^{-1} ; ^1H NMR (60 MHz, $CDCl_3$) δ=1.99 (t, J=3Hz, 1H), 2.09 (S, 3H), 2.14 (S, 3H), 2.21 (dd, J=3, 18Hz, 1H), 2.90 (dd, J=6, 18Hz, 1H), 3.14 (d, J=3Hz, 2H), 5.65 (br.s, J=6Hz, 1H) ^{13}C NMR (67.5 MHz, $CDCl_3$) δ=12.23, 13.93, 20.66, 41.17, 68.92, 72.65, 79.14, 138.17, 166.51, 170.44, 202.02.

(7) **3 a** was obtained as a pale yellow oil (97%) by column chromatography on silica gel (30% EtOAc in hexane) for analysis : $[\alpha]_D^{23}$ -103.1° (c 1.41, $CHCl_3$) ; IR (neat) 3290, 2120, 1715, 1650, 1630, 1280 cm^{-1} ; ^1H NMR (60 MHz, CDCl3) δ=2.04 (t, J=3Hz, 1H), 2.26 (s, 3H), 2.48 (dd, J=2, 18Hz, 1H), 3.06 (dd, J=6, 18Hz, 1H), 3.19 (d, J=3Hz, 2H), 5.90 (br.d, J=6Hz, 1H).

(8) **3b** was obtained as yellow crystals (97%) by column chromatography on silica gel (50% EtOAc in hexane) for analysis : mp 75~6°C ; $[\alpha]_D^{23}$ -18.6° (c 1.25, $CHCl_3$) ; IR (nujol) 3280, 2120, 1700, 1650, 1350, 1170 cm^{-1} ; ^1H NMR (60 MHz, $CDCl_3$) δ=2.03 (t, J=3Hz, 1H), 2.26 (s, 3H), 2.54 (dd, J=6, 18Hz, 1H), 2.99 (dd, J=6, 18Hz, 1H), 3.11 (s, 3H), 3.17 (d, J=3Hz, 2H), 5.60 (br.d, J=6Hz, 1H).

(9) **3 c** was obtained in a quantitative yield by azeotropic distillation in benzene.

(10) A small part of the crude products was purified by column chromatography on silica gel (30% EtOAc in hexane) for analysis. The IR, ^1H NMR and ^{13}C NMR spectra of the products were identical with those of (S)-alcohol ((S)-**2**). Method A : $[\alpha]_D^{23}$ +17.7° (c 1.25, $CHCl_3$), Method B : $[\alpha]_D^{23}$ +19.2° (c 1.14, $CHCl_3$).

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