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# A Lipase Mediated Asymmetric Hydrolysis of 3-Acyloxy-1-octynes and 3-(*E*)-Acyloxy-1-octenes

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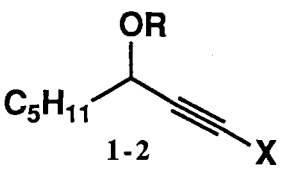
Optical resolution of 3-propionyloxy-1-trimethylsilyl-1-octyne or 3-(*E*)-propionyloxy-1-octene via lipase-mediated hydrolysis gave optically pure (*S*)-1-trimethylsilyl-1-octyn-3-ol and (*R*)-(*E*)-1-iodo-1-octen-3-ol, respectively, in which a reversal of enantio-selectivity for hydrolysis was observed between 3-propionyloxy-1-octyn and its 1-trimethylsilylated derivative, and the effect of the acyl groups on the enantio-discrimination was also investigated.

One of the most useful transformations of organic compounds is reduction of ketones to optically pure secondary alcohols. To this end chemical and biological methods have been developed, where bakers' yeast has offered a ready procedure for optically pure alcohols.[1] Optically pure unsaturated alcohols, however, have not been readily prepared via reduction of unsaturated ketones with microorganism or enzymes due to the substrate specificity of such reductions and/or preferable reduction of C-C unsaturations,[2] although a number of chiral unsaturated alcohols constitute an important class of chiral synthons. Recently the biocatalytic resolution of alcohols mediated by lipases has emerged as convenient procedure for optically active alcohols[3] owing to the following features; operationally simple procedures including non-rigorous reaction conditions such as at room temperatures and under ordinary atmosphere; easy workup by filtering off the catalysts; facile separation of enantiomers by simple chromatography; ready extension to a large scale experiment; ready accessibility of the catalysts at low cost. Especially recent examples show that lipase-catalyzed resolution of unsaturated alcohols in organic media[3, 4] well complements the chemical methods involving the kinetic resolution by asymmetric epoxidation[5, 6b] which is one of the most efficient methods for the resolution of allylic alcohols. Among chiral unsaturated alcohols, of particular importance are chiral 1-octyn-3-ol (**1-2**) and 1-octen-3-ol (**3-5**) derivatives,[6] because facile addition of organocuprate derived from these alcohols to cyclopentenone provides an efficient procedure for the introduction of PG ω chains.[7] However, considerable difficulties have been encountered in the resolution of the particular substrates, 1-octyn-3-ol and 1-octen-3-ol derivatives mediated by lipases in organic solvents. The former substrate was reported to be resolved poorly (23% ee).[4a] As to the latter the attempted resolution with lipases in organic solvents gave disappointing results. Therefore, there still remain important problems of molecular design of the substrates as well as that of reaction media for enantio-discrimination with lipases.



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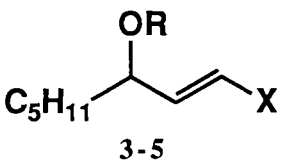

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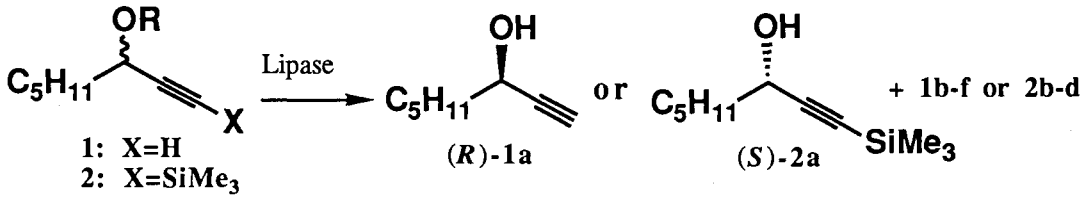


**a: R=H, b: R=CHO, c: $COCH_3$, d: R=$COC_2H_5$, e: R=$COC_3H_7$, f: R=$COC_4H_9$**

Table 1. Hydrolysis of 3-Acyloxy-1-octyne or 3-Acyloxy-1-trimethylsilyl-1-octyne[a)]

| Entry | Substrate | Time/h | Product | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | Alcohol | Yield/%[b)] | ee/%[c)] | Config | Ester | Yield/%[b)] | ee/%[e)] | Config | E[d)] |
| 1 | **1b** | 1 | **1a** | 39 | 17 | R[f)] | **1b** | 36 | 7 | S | 1.5 |
| 2 | **1c** | 23 | **1a** | 21 | 62 | R | **1c** | 44 | 11 | S | 5.5 |
| 3 | **1d** | 12 | **1a** | 29 | 80 | R | **1d** | 49 | 27 | S | 12 |
| 4 | **1e** | 10 | **1a** | 35 | 33 | R | **1e** | 45 | 10 | S | 2.2 |
| 5 | **1f** | 10 | **1a** | 28 | 27 | R | **1f** | 53 | 9 | S | 1.9 |
| 6 | **2b** | 72 | **2a** | 30 | 52 | S[g)] | **2b** | 50 | 26 | R | 4.1 |
| 7 | **2c** | 168 | **2a** | 39 | 62 | S | **2c** | 44 | 23 | R | 5.3 |
| 8 | **2d** | 144 | **2a** | 34 | 80 | S | **2d** | 49 | 35 | R | 13 |
| 9 | **2d**[h)] | 70 | **2a** | 35 | >95 | S | **2d** | 39 | 49 | R | 63 |

a) Unless otherwise stated the reaction was carried out with PPL according to the typical experimental procedure. b) Isolated yield. c) Determined by $^{19}F$ NMR analysis of the corresponding MTPA esters. d) See Ref. 8. e) Determined by $^{19}F$ NMR analysis of the corresponding MTPA esters of the alcohols obtained by the reduction of the ester with LAH. f) See Ref. 9. g) Absolute configuration was assigned after conversion into 1-octyn-3-ol[9)] by desilylation with n-$Bn_4NF$. h)Lipase Amano PS was used in THF/buffer.

It has been found that a lipase-mediated hydrolysis of 3-acyloxy-1-octyn (**1**-**2**) and 3-acyloxy-1-octene (**3**-**5**) derivatives provides the hydrolyzed alcohols in good to excellent optical purity. Initial examination into the hydrolysis of propargyl esters (**1**) with PPL(Porcine Pancreatic Lipase) indicates that the propionate (**1d**) appears to be a derivative of choice, in which (*R*)-**1a** was obtained in 80% ee (entry 3), whereas the formate (**1b**), acetate (**1c**), butyrate (**1e**), and pentanoate (**1f**) did not show satisfactory selectivity. With this particular substrate (**1d**) lipase Amano PS did not resolve the enantiomers, and almost racemic alcohol and ester were obtained. An intriguing reversal of preference for hydrolysis was observed with the trimethylsilylated analogues (**2**), where (*S*)-alcohol (**2a**) was selectively formed. Recently reversal of enantioselectivity by large substituents in lipase mediated acylation has been reported,[10)] and in our case large trimethylsilyl group was considered to effect the observed reversal of the enantioselectivity. As to the cases with trimethylsilylated derivatives (**2**), a combination of propionate (**2d**) with lipase Amano PS gave the best result, and (*S*)-**2a** was obtained in optically pure form (entry 9), making a contrast to the silyl-free substrate (**1**). In this instance the efficiency of lipase Amano PS should be noted as compared with PPL with respect to the reaction times and optical purity. Furthermore, desilylation was readily carried out with tetra-*n*-butylammonium fluoride in THF at room temperature to give (*S*)-1-octyn-3-ol (**1a**) without racemization in quantitative yield.

Next, the esters derived from γ-halo allylic alcohols were examined, and Table 2 shows the results. Propionates of chloro (**3d**, entry 13) and bromo (**4d**, entry 17) derivatives met with moderate success, whereas

iodo analogue (**5d**) recorded excellent selectivity, providing (***R***)-**5a** in optically pure form (entry 20). Here again the ability for the enantiomeric recognition was less effective on the acetates and formates. In contrast to

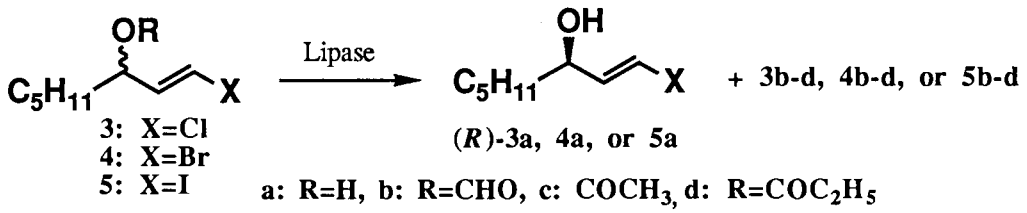


Table 2. Hydrolysis of 3-Acyloxy-1-halo-1-octene[a)]

| Entry | Substrate | Time/h | Product | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | Alcohol | Yield/%[b)] | ee/%[c)] | Config | Ester | Yield/%[b)] | ee/%[e)] | Config | E[d)] |
| 10 | **3b** | 2 | **3a** | 26 | 58 | R[f] | **3b** | 61 | 38 | S | 5.4 |
| 11 | **3c** | 10 | **3a** | 34 | 24 | R | **3c** | 51 | 10 | S | 1.8 |
| 12 | **3c**[g)] | 2 | **3a** | 34 | 49 | R | **3c** | 58 | 15 | S | 3.4 |
| 13 | **3d** | 11 | **3a** | 24 | 70 | R | **3d** | 69 | 30 | S | 7.6 |
| 14 | **3d**[g)] | 4 | **3a** | 34 | 34 | R | **3d** | 52 | 21 | S | 2.4 |
| 15 | **4b** | 3 | **4a** | 29 | 55 | R[h)] | **4b** | 54 | 38 | S | 4.9 |
| 16 | **4c** | 10 | **4a** | 28 | 50 | R | **4c** | 53 | 12 | S | 3.4 |
| 17 | **4d** | 11 | **4a** | 32 | 71 | R | **4d** | 50 | 31 | S | 7.9 |
| 18 | **5b** | 4 | **5a** | 54 | 53 | R | **5b** | 31 | 50 | S | 5.2 |
| 19 | **5c** | 7 | **5a** | 34 | 57 | R[h)] | **5c** | 52 | 18 | S | 4.3 |
| 20 | **5d** | 10 | **5a** | 28 | >95 | R | **5d** | 58 | 29 | S | 52 |
| 21 | **5d**[g)] | 11 | **5a** | 39 | 81 | R | **5d** | 31 | 49 | S | 15 |

a) Unless otherwise stated the reaction was carried out with PPL according to the typical experimental procedure. b) Isolated yield. c) Determined by $^{19}F$ NMR of the corresponding MTPA esters. d) See Ref. 8. e) Determined by $^{19}F$ NMR examination of the corresponding MTPA esters of the alcohols obtained by reduction with LAH. f) Determined by conversion to 1-octyn-3-ol with LDA. See Refs. 9 and 12. g) Lipase Amano PS was used. h) See Ref. 12.

1-trimethylsilyl-1-octyn-3-ol derivatives, the resolving ability of PPL was superior to that of lipase Amano PS with this substrate.

Although for preparing optically active 1-octyn-3-ol or 1-octen-3-ol derivatives, kinetic resolution of alcohols with chiral amines,[6a)] resolution via asymmetric epoxidation,[6b)] resolution mediated by biocatalysts,[4a, 6c)] reduction of unsaturated ketones with microorganism,[6d)] and reduction with chiral reducing agent[6e)] have been reported, many of those approaches suffer from several drawbacks such as the need for expensive reagents, low chemical yield, low optical purity, severe reaction conditions, unavailability of both enantiomers, and so on. The enzymatic resolution mediated by lipases examined here provides a new ready access to valuable optically pure chiral synthons for the construction of biologically important molecules. With a suitable choice of the acyl groups, optically pure alcohols were obtained, and in the case with 1-octyn-3-ol, the modification of the substrate with a trimethylsilyl group realized the reversal of preferred enantiomer for selective hydrolysis.

The hydrolysis of (*E*)-1-iodo-3-propionyloxy-1-octene[13] represents a typical experimental procedure: A solution of (*E*)-1-iodo-propionyloxy-1-octene (191 mg, 0.64 mmol) in phosphate buffer (pH 7, 2.9 ml) and acetone (0.3 ml) was stirred at room temperature for 10 min. To it was added PPL (Tokyo Kasei, 50 mg), and the entire mixture was stirred at room temperature for 10 days. After normal work up, the resultant crude oil was purified on preparative silica gel TLC (eluent: hexane/ethyl acetate=6/1) to give (*R*)-(*E*)-1-iodo-1-octene-3-ol (45 mg, 28%; $[\alpha]_D^{23}$ -9.97 (c 0.90, MeOH) ) and (*S*)-(*E*)-1-iodo-3-propionyloxy-1-octene (115 mg, 58%; $[\alpha]_D^{23}$ -34.8 (c 2.30, MeOH) ).

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