by hydrolysis of the vinylogous ester (aqueous HCl workup) provided (+)-17[8a] quantitatively. Finally, exposure of (+)-17 to neat, anhydrous trifluoroacetic acid (room temperature, 2.5 h) removed the N-MPM moiety to afford crystalline (+)-hitachimycin (1) in 64% yield after chromatography. Synthetic 1 (mp 236–240 °C dec; mmp 236–240 °C) was identical in all respects including chiroptical properties with an authentic sample kindly provided by Professor Ōmura.

In summary, the first total synthesis of (+)-hitachimycin (1) has been achieved, confirming the assigned structure and absolute stereochemistry. The convergent and moderately effecient route (22 steps, 1.2% yield)[24] exploited a highly stereoselective conjugate addition to (*S*)-(−)-5-methoxycyclopentenone in the critical three-component coupling step.

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**Supplementary Material Available:** Spectroscopic and analytical data for **1**, **2**, **3a,b**, **4a**, **5–8**, **11–17**, and **i** (6 pages). Ordering information is given on any current masthead page.

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(24) This sequence provided 81 mg of (+)-hitachimycin (1).

## Biocatalytic Resolutions of α-Methylene-β-hydroxy Esters and Ketones

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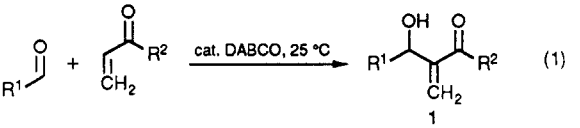
*Summary:* α-Methylene-β-hydroxy esters and ketones are resolved via lipase mediated irreversible acylations;[1] experiments with a range of substrates have been used to identify factors that influence the enantioselection obtained and reaction times required.

α-Methylene-β-hydroxy esters and ketones are suitably functionalized for a multitude of chemical transformations.[2-5] They are easily prepared in racemic form via additions of α,β-unsaturated carbonyl compounds to aldehydes mediated by tertiary amine bases (reaction 1),[6] but their potential in *asymmetric* synthesis has not been exploited since there has been no truly convenient route to monochiral molecules of this type. Unfortunately, these allylic alcohols cannot be resolved via asymmetric Sharpless epoxidation[7-9] because of the deactivating influence of the electron-withdrawing alkene substituent. The most practical route to *optically active* α-methylene-β-hydroxy esters was, before this work, kinetic resolution of racemic samples via hydrogenation in the presence of monochiral transition-metal catalysts.[10-13] The scope of these resolutions with respect to substrate structure has not been reported, but certain limitations are evident; they are, for instance, clearly unsuitable for molecules containing other functionality vulnerable to reduction. Furthermore, manipulations of air-sensitive catalysts under elevated pressures of hydrogen are inconvenient, especially when the reaction must be stopped within a narrow conversion range to ensure good chemical and optical yields. Recent work in our laboratory led us to believe that biocatalytic acylations[14-16] of α-methylene-β-hydroxy carbonyl compounds in organic solvents[17,18] (reaction 2) could be enantioselective, cheap, and experimentally simple; this was confirmed in a preliminary study, the results of which are reported here.




(1)

1

Initial experiments with these resolutions (cf. reaction 2) demonstrated that crude *Pseudomonas AK* preparation (Amano) was slightly superior to *Pseudomonas K-10* (Amano) and these were more promising than any of the other enzymes tested (i.e. those from *Candida cylindracea*, *Geotrichum candidum*, *Rhizopus delemar*, and *Porcine pancreas* {Amano}). Illustrative results for the processes mediated by *Pseudomonas AK* are given in Table I.

Our findings indicate that enantiodiscrimination by the enzyme is high when $R^2$ is a "long chain" but not when this substituent is relatively short. For instance, the ratio of specificity constants (*E* values)[19] for acylation of the butyl ester in entry 1 is much greater than for the methyl ester in entry 4. The acylation is equally effective if $R^2$ is alkoxy or alkyl. Furthermore, aryl, alkyne, alkene, and sulfide entities in the $R^2$ substituent are tolerated by the enzyme without loss of enantioselection (entries 6, 3, 2, and 7, respectively); thus the enzyme can accommodate functional groups that would be destroyed under reductive conditions and others which could poison the transition-metal cata-

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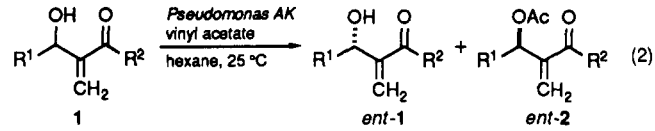
**Table I. Biocatalytic Resolutions of α-Methylene-β-hydroxy Carbonyl Compounds (1)[a]**




| entry | $R^1$ | $R^2$ | mass equiv of enzyme | time, h | convn,[b] % | *ent*-1 yield, %[c] | *ent*-1 ee, %[d] | $E$[e] |
|---|---|---|---|---|---|---|---|---|
| 1 | Me | OBu | 0.5 | 48 | 50 | 41 | >95 | >56 |
| 2 | Me | $OCH_2CHCH_2$ | 1 | 12 | 53 | 43 | >95 | >43 |
| 3 | Me | $OCH_2CCH$ | 1 | 17 | 54 | 43 | >95 | >34 |
| 4 | Me | OMe | 2 | 12 | 64 | 22 | 87 | 8 |
| 5 | Me | Bu | 2 | 12 | 52 | 23 | >95 | >56 |
| 6 | Me | $(CH_2)_2Ph$ | 2 | 12 | 56 | 41 | >95 | >24 |
| 7 | Me | $O(CH_2)_2SPh$ | 1 | 12 | 55 | 39 | >95 | >29 |
| 8 | Pr | OBu | 5 | 60 | 50 | 23 | >95 | >56 |
| 9 | Pr | OMe | 9 | 240 | 46 | 32 | 52 | 7 |
| 10 | Pr | Me | 5 | 24 | 67 | 21 | 72 | 4 |

[a] The substrate at 0.1 M concentration in hexane was stirred with the enzyme and 4 equiv of vinyl acetate for the indicated time at 25 °C, see illustrative procedure. [b] As monitored by capillary GC (corrected by using mixtures of known composition) and by $^1H$ NMR integrals. [c] GC studies show these reactions are very clean, some of the isolated yields expressed here reflect the usual difficulties encountered with separation and purification of volatile compounds. [d] The absolute configuration of the recovered starting material *ent*-1 in entry 4 was elucidated via hydrogenation to give a known compound (see ref 13); the configurations indicated above are tentatively assigned to the other products on the basis of their similar behavior in chiral shift experiments; in all the shifted spectra of optically enriched samples the lower field vinylic protons were most intense. [e] Values determined from the extent of conversion and the enantiomeric excess of the recovered substrate as described in ref 19.

lysts one might otherwise use to resolve these materials.

The substituent $R^1$ seems to govern the rate of the reaction; hence long reaction times are required when $R^1$ is propyl (entries 8–10) relative to those cases where $R^1$ is methyl (entries 1–7). Competition experiments to monitor consumption of the methyl-substituted butyl ester (1) ($R^1$ = Me, $R^2$ = OBu) versus that of the propyl-substituted butyl ester (1) ($R^1$ = Pr, $R^2$ = OBu) during the early stages of the reaction were attempted to obtain quantitative information about relative rates: however, at 10% conversion of the former we were unable to detect any of the acylated, propyl-substituted butyl ester by capilliary GC. The reaction is also prohibitively slow when $R^1$ is phenyl (so much so that we did not complete a resolution of this substrate). However, the *enantioselectivity* can be high for larger substituents at $R^1$ if $R^2$ is also a long chain substituent. For example, it took a relatively long time (6 days) to achieve 50% conversion of the starting material in the experiment corresponding to entry 8 ($R^1$ = *n*-Pr, $R^2$ = OBu) but the product isolated was of >95% ee.

Crude *Pseudomonas AK* preparation is currently available for under $1 per gram so these reactions are extremely economical. The following procedure illustrates the simplicity of the method.

**Preparation of (*S*)-(−)-Butyl 3-Hydroxy-2-methylenebutanoate.** To 2.0 g of dried 4-Å molecular sieves and 4.3 g of crude *Pseudomonas AK* preparation (Amano) were added 8.61 g (100 mmol, 9.2 mL) of distilled vinyl acetate and 8.6 g (50 mmol) of racemic butyl 3-hydroxy-2-methylenebutanoate (1) ($R^1$ = Me, $R^2$ = OBu) in 300 mL of hexanes, under dinitrogen and with stirring. Progress of this reaction was monitored by capilliary GC; hence after 48 h the reaction was stopped at 50% conversion. Thus the solid material was removed from the suspension via filtration and the filtrate was concentrated in vacuo. Flash chromatographic separation with 2–20% acetone in hexanes afforded: (i) 4.67 g (43%) of (*R*)-(+)-butyl 3-acetoxy-2-methylene which had an enantiomeric excess of >95% {$Eu(hfc)_3$ shift experiment in $CDCl_3$}, $R_f$ 0.6 (15% acetone/hexane on silica plates), $[\alpha]_D$ +10.36° ($CHCl_3$, *c* 2.5); and, (ii) 3.55 g (41%) of (*S*)-(−)-butyl 3-hydroxy-2-methylenebutanoate with an enantiomeric excess of >95% {$Eu(hfc)_3$ shift experiment in $CDCl_3$}, $R_f$ 0.3 (15% acetone/hexane on silica plates), $[\alpha]_D$ −11.85° ($CHCl_3$, *c* 2.6).

The approach described here is extremely convenient for syntheses of monochiral compounds (1) ($R^1$ = Me). It is cheap, experimentally simple, and compatible with several functional groups that are not tolerated in transition-metal catalyzed, asymmetric hydrogenations (i.e. unsaturated appendages and sulfide moieties). Further studies indicate that biocatalytic resolutions of this kind may be applicable to other categories of allylic alcohols that are not amenable to asymmetric epoxidation methodology.[20]

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