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LIPASE-MEDIATED RESOLUTIONS OF SPAC REACTION PRODUCTS

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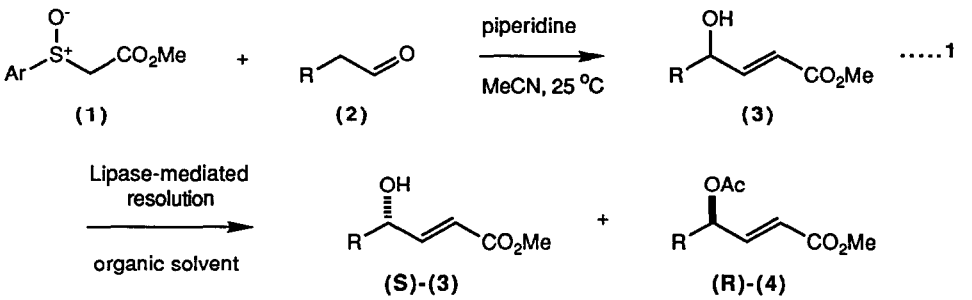
Abstract: γ-Hydroxy-α,β-unsaturated compounds (3) (SPAC reaction products) are resolved via irreversible biocatalytic acylations; this process can be used in series with asymmetric SPAC reactions to improve optical purities.

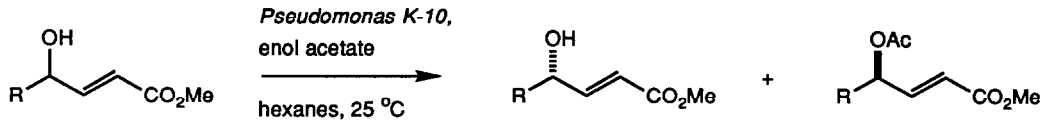
γ-Hydroxy-α,β-unsaturated compounds (3) are easily produced via the SPAC (Sulfoxide Piperidine And Carbonyl) transformation (reaction 1). They have an array of functionality which can be used in many different ways; however, applications of these materials as *chirons* have been hampered because access to homochiral materials has been difficult. Recently, we have shown the sulfinyl acetates (1) used in the SPAC process can be resolved via hydrolyses mediated by the crude lipase preparation *Pseudomonas-K10*,[1] and induction in the SPAC reaction is enhanced by matching the sulfoxide chirality with stereodirecting auxiliaries.[2] This paper describes biocatalytic resolutions of γ-hydroxy-α,β-unsaturated compounds, transformations which are particularly useful when coupled with asymmetric variants of the SPAC reaction.



Screening experiments with racemic E-methyl 4-hydroxyhept-2-enoate {(3): R = n-Pr} indicated that one mass equivalent (i.e. equal masses of the substrate and the enzyme preparation) of the crude lipase preparations *Candida Cylindracea* (Amano) and *Porcine Pancreatic Lipase* (Sigma) did not catalyze acylation of this substrate by *iso*-propenyl acetate at a reasonable rate (1.0 M in hexanes, at 25 °C over 48 h); *Pseudomonas-AK* (Amano)

was a catalyst under the same conditions but gave low enantioselectivity. Crude *Pseudomonas K-10* (Amano), however, mediated acylations of E-methyl 4-hydroxyhept-2-enoate at a convenient rate and the **(R)**-enantiomer of this substrate reacted significantly faster than its optical antipode. Results for resolutions of this substrate and simple homologues (R = Me and Et) are given in Table 1; optically active alcohols **(3)** (R = Me, n-Pr) are known[3,4] hence the absolute configurations of these products were assigned via polarimetry. Enantiodiscrimination in each of these reactions is high as indicated by the E values (ratios of specificity constants)[5] obtained.

Table 1. Biocatalytic Resolutions of Simple γ-Hydroxy-α,β-unsaturated Methyl Esters



	R	time[a] h	unreacted alcohols ee %[b] (config.)	yield %[c]	product acetates ee %[b] (config.)	yield %[c]	E
1	Me	49	>95 (S)	37[d]	91 (R)	39[d]	>30
2	Et	50	>95 (S)	44	>95 (R)	45	>150
3	n-Pr	400	>95 (S)	42	74 (R)	54	>20

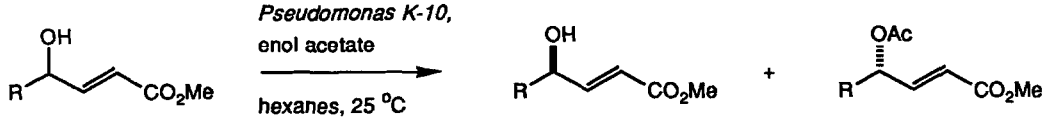
[a] All the reactions were performed on a 1-2 mmol scale using two mass equivalents of the enzyme preparation, 1.0 M in heptane presaturated with pH 7.5 phosphate buffer, at 25 °C with 10 equivalents of *iso*-propenyl acetate; reaction rates could be increased by using more enzyme. [b] Enantiomeric excesses were determined by ^{1}H NMR using Eu(hfc)3. [c] Isolated yields after flash chromatography. [d] Some material was lost in the isolation procedure because this compound is slightly volatile.

More substrates were examined to explore the scope of resolutions mediated by *Pseudomonas K-10* and the results are depicted in Table 2. Assignments of absolute configurations for these experiments are based upon: (i) correlations with samples formed via SPAC reactions of homochiral sulfinate ester **(1)** (where the **(R)**-reagent gives predominantly the **(R)**-enantiomer of the product in all cases studied so far)[6,3,2]; and, (ii) ^{1}H NMR shift experiments in which the downfield resonances for the CO_2CH_3 protons in the perturbed spectra of the recovered starting material are most intense for these resolutions whereas the opposite is true for the experiments depicted in Table 1.

The data presented in Table 2 is somewhat surprizing. We conclude that *when the substituent R contains "branched chain" functionalities the enantioselectivity of the enzyme is reversed.* It is known that small changes in substrate structure can alter the course of enzyme mediated reactions[7] but this is a particularly striking example. Enantioselection by the enzyme is poor when R is i-Pr or i-PrCH_2 (entries 1 and 2); these substrates apparently have structural features that reverse the enzyme selectivities relative to those observed in the first experiments (Table 1) but not to the extent that discrimination is large in the opposite sense. Better enantioselection is observed for the substrate in which R is CyCH_2 (Cy = cyclohexyl; entry 3) and even more

for the dimethylthexylsilyl ether depicted in entry 4. The latter observation is particularly important because desilylation of the resolved product and further manipulation of the deblocked primary alcohol functionality could be used to elaborate this side chain for a range of synthetic applications.

Table 2. Biocatalytic Resolutions of "Branched Chain" γ-Hydroxy-α,β-unsaturated Esters



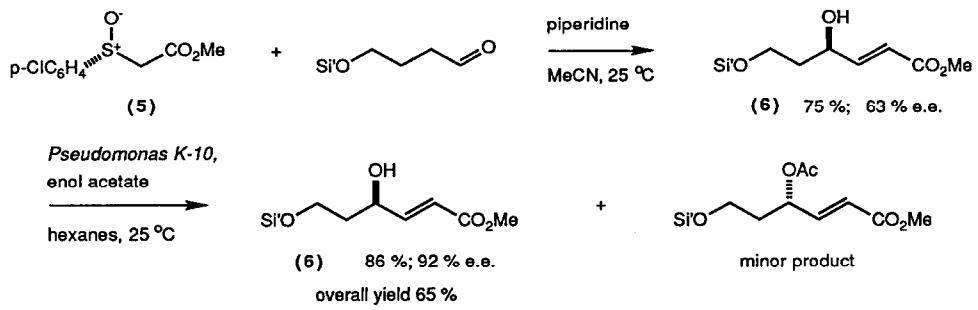
	R	time[a] days	unreacted alcohols ee %[b] (config.)	yield %[c]	product acetates ee %[b] (config.)	yield %[c]	E
1	i-Pr	6	14 (R)	46	19 (S)	43	1.6
2	i-PrCH$_2$	7	37 (R)	40	28 (S)	55	2.5
3	CyCH$_2$	6.5	54 (R)	51	77 (S)	36	13
4	Si'O(CH$_2$)$_2$[d]	7	72 (R)	57	>95 (S)	35	>150

[a] All the reactions were performed on a 1-2 mmol scale using 5 mass equivalents of enzyme and 10 molar equivalents of vinyl acetate relative to substrate; 0.005 M in heptane presaturated with pH 7.5 phosphate buffer, at 25 °C. These reaction rates could be increased by using more enzyme. [b] Enantiomeric excesses were determined by ^{1}H NMR using Eu(hfc)$_3$. [c] Isolated yields after flash chromatography. [d] Si' = Me$_2$ThexSi.

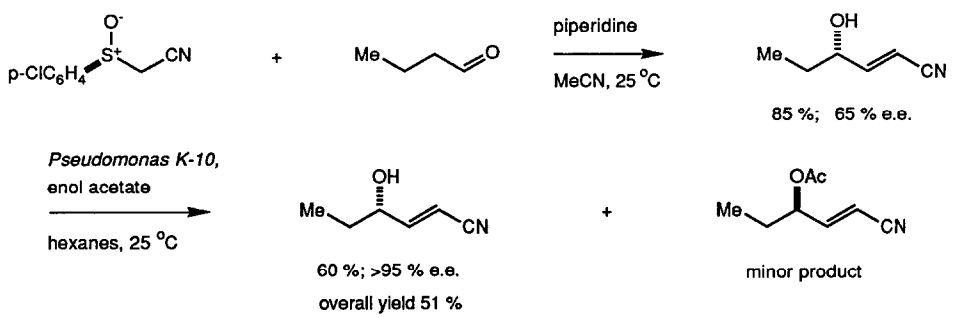
Kinetic resolutions of *racemic* samples are intrinsically wasteful because the maximum yield of desired optically pure material is 50 % (unless the enantiomers of the starting material can be equilibrated, or both product and recovered starting material are useful). Conversely, kinetic resolutions of *optically active* materials can give high yields of homochiral products. For instance, if a sample of 60 % e.e. is subjected to a kinetic resolution then the maximum chemical yield of recovered homochiral starting material is 80 %. Consequently, poor asymmetric induction processes can be coupled with efficient kinetic resolutions to give products which approach optical purity in good chemical yields; in our laboratory we refer to such systems as "asymmetric amplifiers".[8] This approach to asymmetric synthesis has been somewhat neglected in comparison with other methods.[9]

Combinations of SPAC reactions with biocatalytic resolutions illustrate "asymmetric amplification" admirably and Schemes 1 and 2 depict two examples of this. Reactions of optically pure sulfoxide reagents {e.g. (**5**)} with aldehydes generally give γ-hydroxy-α,β-unsaturated compounds {e.g. (**6**)} in around 65 % e.e.. Substrates formed in this way can be subjected to kinetic resolutions of the type outlined above to give good chemical yields of products with high optical purities. The sequence in Scheme 1 underlines the flexibility and potential of crude lipase preparations: *Pseudomonas-K10* was used to resolve sulfinyl acetate (**5**) for the SPAC reaction, and it was also employed to amplify the enantiomeric purity of the SPAC reaction product (**6**). Scheme 2 demonstrates that the resolutions described above are not confined to γ-hydroxy-α,β-unsaturated esters, they can also be used for the corresponding *nitriles*.

Scheme 1. Asymmetric Amplification in a Synthesis of an α,β-Unsaturated Ester



Scheme 2. Asymmetric Amplification in a Synthesis of an α,β-Unsaturated Nitrile



SPAC reaction products cannot be resolved via Sharpless' epoxidations[10] because of the deactivating influence of the electron withdrawing alkene-substituent. We are now accumulating evidence that biocatalytic resolutions can be applied to many more unsaturated alcohol substrates that cannot be resolved via asymmetric epoxidation methodology.[11,12]

References and Notes

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