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S-Ethyl Thiooctanoate as Acyl Donor in Lipase Catalysed Resolution of Secondary Alcohols

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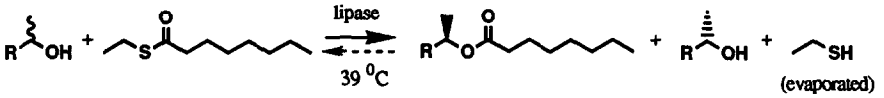
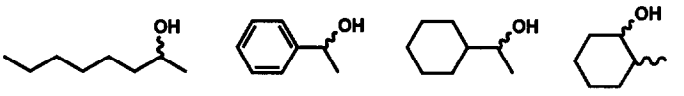
Abstract: The use of S-ethyl thiooctanoate as acyl donor in resolution of secondary alcohols by lipase catalysed transesterification, resulted in an efficient displacement of the equilibrium towards esterification of the alcohol. A lipase (component B) from *Candida antarctica* was used as the catalyst. On a semi-preparative scale, 0.5 g of 2-octanol was resolved in less than one hour, affording an enantiomeric excess of >98% of the remaining alcohol and >97% of the produced ester. Three other alcohols, 1-phenyl ethanol, 1-cyclohexyl ethanol and *trans*-2-methyl cyclohexanol were also resolved with good optical yields. After 50% conversion on a preparative scale, 15 g of alcohol, the (*S*)-enantiomer of 2-octanol could be obtained with an enantiomeric excess of 96%. The (*R*)-enantiomer was isolated with an enantiomeric excess of 97% after hydrolysis of the produced ester.

An unfavourable equilibrium is often a problem in lipase catalysed esterification and transesterification reactions.[1] A number of ways to shift the equilibrium towards product formation in such reactions have been reported.[2] Recently we presented a method in which ethyl octanoate is used as acyl donor. By applying reduced pressure to the reaction mixture, the produced ethanol is evaporated and the reaction can be driven to completion.[3] A similar effect can be achieved at atmospheric pressure by using a thioester as acyl donor. In this investigation, S-ethyl thiooctanoate was used and the produced ethanethiol was evaporated (Scheme 1).



Scheme 1

With S-ethyl thiooctanoate, the equilibrium displacement was more efficient and the optical yields higher, than with ethyl octanoate. The alcohols **1-4** (Scheme 2) were resolved on a semi-preparative scale with an immobilised lipase (component B) from *Candida antarctica* as the catalyst (Table 1).



1 2 3 4 (*trans*)

Scheme 2

Table 1. Resolution of Secondary Alcohols by Transesterification in S-Ethyl Thiooctanoate.

Alcohol	Reaction time (hours)	Conversion (%)	ee_R[a] (%)	ee_S[a] (%)	E[b]
1	0.9	52±2	>97	>98	67±16
2	2.5	51±2	97[c]	98	>200
3	4.4	52±2	95[c]	>98	>130
4	3.1	50±2	97[c]	97	>200

The molar ratio of S-ethyl thiooctanoate to alcohol was 3:1. [a]The enantiomeric excess values are from the produced ester (ee_R) and the remaining alcohol (ee_S). [b]The enantiomeric ratio, E, was calculated with the formula $E=\ln\{(1-c)(1-ee_S)\}/\ln\{(1-c)(1+ee_S)\}$.[4] The calculations were based on the enantiomeric excess of the remaining alcohol at 4-6 different conversions and performed with the program Simfit.[5] [c]The enantiomeric excess of the produced esters of the alcohols (**2-4**), calculated at 50% conversion, using the experimental E-values and the formula $E=\ln\{1-c(1+ee_p)\}/\ln\{1-c(1-ee_p)\}$.[4]

In a preparative scale, 15 g of 2-octanol, dissolved in an equimolar amount of S-ethyl thiooctanoate (21.7 g), was resolved in 3 hours, using 500 mg of immobilised lipase. The enantiomeric excess of the isolated products were 96% for the remaining (*S*)-2-octanol and 97% for the produced ester.

The thioester offers several advantages when used as acyl donor in lipase catalysed resolutions of alcohols. The co-product, ethanethiol, has a low boiling point and is easily removed by evaporation, thus driving the reaction towards the desired ester products. Accordingly high yields and high reaction rates can be achieved. The thioester is a much better substrate than the produced esters, thus racemisation of the products is avoided. As the thiol evaporates, no co-products harmful to the enzyme accumulates and the immobilised enzyme can be reused several times. The work-up of the products is simple. The disagreeable odours of ethanethiol does not cause any problem if the reaction is carried out under sufficient ventilation, such as in a normal hood. The preparation of S-ethyl thiooctanoate is a straight forward, one step synthesis, with a high yield. On a preparative scale, not only alcohols but also amines and thiols should be possible to resolve.

Experimental

^{1}H-NMR spectra were recorded on a Bruker ACF 250 spectrometer. Capillary gas chromatography was performed on Carlo Erba Fractovap 2150 and Perkin-Elmer 8500 instruments. Conversion measurements were done on a J &W DB-1™ column. The optical yields were determined by gas chromatography on an Astec Chiraldex™ B-TA column.

The lipase (component B) derived from *Candida antarctica* is a product from Novo-Nordisk A/S. The enzyme was used as an immobilised preparation on a macroporous polypropylic resin, containing approximately 1% enzyme w/w. The catalytic activity was approximately 20000 LU/g.

Transesterification, general procedure: The racemic alcohol (4 mmol) was dissolved in S-ethyl thiooctanoate (12 mmol). The reaction was started by the addition of the immobilised lipase (50 mg). The reaction was carried out at 39°C with magnetic stirring. Conversion was measured by following the consumption of the secondary alcohol.

(*S*)-2-Octanol and (*R*)-2-octyl octanoate: 2-Octanol, 15 g (0.115 mol) was dissolved in 21.7 g (0.115 mol) of S-ethyl thiooctanoate. The reaction was started by addition of 500 mg of immobilised lipase. The reaction was run at 39°C with magnetic stirring. After 3 hours the conversion of the alcohol had reached 50% and the reaction was stopped by filtering of the immobilised enzyme. The lipase was washed with hexane. The products were distilled at reduced pressure. (*S*)-2-Octanol was distilled at bp_{10}=72-74°C, yield 6.55 g (87%), GC (95% pure), ee 96%. (*R*)-2-Octyl octanoate was distilled at bp_2=91-93°C, yield 11.2 g (76%), GC (99% pure). (*R*)-2-Octanol, ee 97%, was isolated after hydrolysis of the ester with NaOH in methanol.

S-Ethyl thiooctanoate: The thioester was prepared by the general procedure of Renard *et al.*[6] Ethanethiol (49.7 g, 0.8 mol) and pyridine (77.6 ml, 0.96 mol) were dissolved in dry diethyl ether (295 ml). The solution was cooled to 0°C. Octanoyl chloride (65.1 g, 0.4 mol) was dissolved in dietyl ether (95 ml) and added drop-wise to the solution. The temperature was allowed to rise to room temperature. After 24 hours the reaction was completed. The reaction mixture was washed twice with water and dried over $MgSO_4$, followed by distillation, bp_2=65°C, yield 75 g (99%). After chromatography on silica gel 60 (Merck; hexane/ ethyl acetate, 90:10, v/v) 74.4 g of product was isolated (99%), GC (99.5% pure). ^{1}H-NMR ($CDCl_3$) = 0.88 (t,3H), 1.21-1.4 (m,8H), 1.25 (t,3H), 1.59-1.68 (m,2H), 2.49-2.55 (t,2H), 2.72-2.91 (m,2H).

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