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Enantiomerically enriched bifunctional *sec*-alcohols prepared by *Candida antarctica* lipase B catalysis. Evidence of non-steric interactions

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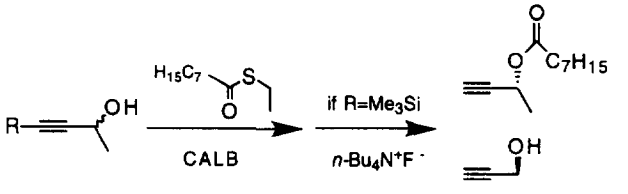
Abstract: Transesterification catalysed by *Candida antarctica* lipase B was used for the preparation of enantiomerically enriched bifunctional *sec*-alcohols. The enantiomeric ratio, *E*, for 3-butyn-2-ol was increased from 1.3 to over 500 by adding an easily removable protecting group. Kinetic resolution of bromohydrins and chlorohydrins bearing a halogen on the large substituent showed high enantioselectivity (E >80). On the other hand, halohydrins with the halogen on the medium group showed low *E*. Large differences in enantioselectivity were found by substituting the halogen atom of 1-halo-2-alkanols by a methyl group. These differences corresponded to more than 2 kcal mol^{-1} and were ascribed to non-steric interactions.

Introduction

Candida antarctica lipase B (CALB) has been used for the resolution of a broad range of substrates in water or non-aqueous media. It has been shown that CALB is particularly suitable for the kinetic resolutions of secondary alcohols[1] and alcohol analogues.[2] Among alcohols, bifunctional secondary alcohols are of special interest as chiral building blocks. Enantiomeric pure halohydrins can easily be transformed to the corresponding epoxide. 1-Alkyn-3-ols can be transformed in a large number of new functional groups.[3] Hence, they have been used in the synthesis of several classes of compounds.[4]

Results

The versatile 3-butyn-2-ol showed low enantioselectivity due to the small difference between medium and large substituents as defined by Kazlauskas *et al.*[5] The considerable steric bulk of an easily removable protecting group, trimethylsilyl, allowed the preparation of enantiomerically pure 3-butyn-2-ol (Scheme 1).This approach was used by Shimizu *et al.* to reverse the enantioselectivity in a lipase catalysed hydrolysis.[6] The enantiomeric ratio, *E*, was increased from 1.3 for the unsilylated alcohol to a value of over 500 for the silylated derivative.



R=	H	Me_3Si
ee_p	9	99
ee_s	9	95

Scheme 1. Strategy for the preparation of pure enantiomers of 3-butyn-2-ol.

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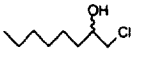
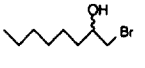
Table 1. Enantioselectivity of CALB toward chlorohydrins and bromohydrins[7]

	Substrate	ee_s	ee_p	c	E^a	f.e.[b]
1		0.41	0.81	0.33	14	*S*-(-)
2		0.56	0.63	0.47	7.6	*S*-(-)
3		0.71	0.97	0.42	160	*R*-(-)
4		0.88	0.98	0.47	370	*R*-(-)
5		0.41	0.96	0.30	81	*R*-(-)

[a] Enantiomeric ratio calculated at several different conversions according to Rakels *et al.*[7]

[b] Fast reacting enantiomer

The results of the kinetic resolutions of halohydrins catalysed by *Candida antarctica* lipase B are shown in Table 1. The substrates, **1** and **2** which have a halo atom situated on the medium size substituent, showed moderate enantioselectivity. On the other hand, all substrates with the halo atom situated on the large substituent (**3** and **4**) displayed high selectivity. Substrate **4** was found to be best resolved.

Within the two different groups of substrates (large and small alcohols) the effect was opposite between the two different halides toward selectivity. Bromo derivatives gave the higher E in short length alcohols relative to the corresponding chloro derivatives. The opposite situation was found with larger alcohols. Here, the bromo-substituted alcohol displayed the lower E compared to the chloro derivative.

Discussion

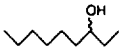
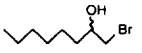
Comparison of enantioselectivity between bromohydrins and the corresponding methyl substituted alcohol are shown in Table 2. Resolution of **6** showed high enantioselectivity compared to **2**. This large difference in enantioselectivity was unexpected, since the size of a bromo substituent is similar to a methyl group.[8] On the other hand, non-steric properties (charge distribution, polarizability *etc.*) of the two groups are different. Consequently, it is reasonable that non-steric interactions between enzyme and substrate play an important role for this substrate. Enantioselectivity for **7** compared to **4** was drastically increased. The value of the difference in $\Delta\Delta G^{\ddagger}$ ($\Delta\Delta\Delta G^{\ddagger}$) is almost the same as between substrates **6** and **2** but with opposite sign. Solvent effects could be ruled out as reactions performed in hexane or dichloromethane for substrate **4** showed no difference in enantioselectivity. One explanation could be repulsive interactions between a part of the active site and the halogenated substituent. According to the empirical rules of Kazlauskas *et al.*,[5] lipase stereoselectivity is mainly set by steric interactions between enzyme and substrate. Additional interactions must occur as the selectivity decreases or increases depending on the position of the halogen. **5** has two substituents of approximately same size therefore $\Delta\Delta G^{\ddagger}$ defines the non-steric contribution to stereoselectivity. Results obtained from **5** and the external comparison of the ethyl and bromomethyl substituents revealed that the non-steric interactions for 1-bromo-2-alkanol contributed with more than 2 kcal mol^{-1}. Same reasoning was applied to 1-chloro-2-alkanol and a similar value was found.

Experimental

Preparation and purification of the starting materials

(±)-4-Trimethylsilyl-3-butyn-2-ol was prepared according to the procedure of Fleming *et al.*[10]

Table 2. Comparison of CALB enantioselectivity toward aliphatic alcohols and bromohydrins[9]

	Substrate	E^a	$\Delta\Delta G^{\ddagger b}$ (kcal mol^{-1})	$\Delta\Delta\Delta G^{\ddagger c}$ (kcal mol^{-1})
6		340	3.6	
				2.4
2		7.6	1.2	
7		9	1.4	
				-2.1
4		370	3.5	
5		81	2.6	

[a] Enantiomeric ratio calculated at several different conversions according to Rakels *et al.*[7] [b] Difference in free energy of activation between the two enantiomers calculated according to Norin *et al.*[9] [c] Difference between $\Delta\Delta G^{\ddagger}$ of aliphatic alcohol and $\Delta\Delta G^{\ddagger}$ of the methyl bromide derivative.

(±)-1-Chloro-2-octanol **1** was synthesised according to Damin *et al.*[11] The crude product mixture, 1-chloro-2-octanol (75%) and 2-chloro-1-octanol (25%) was purified using column chromatography, yielding 5.14 g (62%) of **1**.

(±)-1-Bromo-2-octanol **2**. Under nitrogen, 1-octene (120 mmol, 13.4 g) and water (240 mmol, 4.3 ml) in DMSO (200 ml) were treated with *N*-bromosuccinimide (240 mmol, 42.7 g). The mixture was stirred for 15 minutes and then the reaction was quenched by adding water. The product was extracted with diethyl ether, the solution was dried and solvent evaporated. The product was purified by column chromatography yielding 4.70 g (20%) of **2**.

(±)-1-Chloro-2-propanol **3** was purchased from Lancaster Synthesis Ltd (Lancashire, UK). The bottle contained 25% of 2-chloro-1-propanol. Difference in nucleophilicity was used during the purification step. In a round-bottom flask crude **3** (20 mmol, 1.89 g), *t*-butyldiphenylchlorosilane (8 mmol, 2.19 g), triethylamine (8 mmol, 0.81 g) and dimethyl-4-aminopyridine (0.24 mmol, 0.029 g) in dichloromethane were stirred under nitrogen for 24 hours. Product and remaining alcohol were separated by column chromatography.

(±)-1-Bromo-2-propanol **4** was purchased from Lancaster Synthesis Ltd (Lancashire, UK) and was purified as described for substrate **3**.

(±)-1-Bromo-2-butanol **5** was purchased from TCI Co. (Tokyo, Japan). A colourless solution was prepared by distillation of the initial mixture. The 1-bromo-2-butanol was separated from 2-bromo-1-butanol by column chromatography.

(±)-3-Nonanol **6** was prepared through the Grignard reaction as described by Orrenius *et al.*[12]

Transesterification: general procedures

In a sealed round flask, a mixture of alcohol (1 eq., 1 M), vinyl butyrate (1 eq., 1 M) and tridecane (0.3 eq., 0.3 M) in hexane (**1**, **2**, **4**, **5**, **6** and **7**) or dichloromethane (**3** and **4**) was incubated for one hour at 23°C to check spontanous reaction. The reaction was then started by the addition of 5 to 25 mg of Novozym® per mmol of alcohol. The reaction was quenched by filtering off the enzyme. Product and substrate were separated by column chromatography.

3-Butyn-2-ol or 4-trimethylsilyl-3-butyn-2-ol. In a open flask, an equimolar amount of alcohol and *S*-ethyl thiooctanoate were stirred at 39°C in presence of Novozym®. Work-up was carried out as described above.

Absolute configuration

Assignment of absolute configuration for substrates **1**, **2**, **3**, **4**, **5**, **6** and **7** was done on the basis of their specific rotation values (Perkin Elmer 241 Polarimeter) and literature data comparisons.

Analysis

Reactions were monitored by chiral GC using a Chrompack CP-chirasil-DEX CB (25 m±0.32 mm) or a Astec Chiraldex G-TA (10 m±0.25 mm). 4-Trimethylsilyl-3-butyn-2-ol and product ester were desilylated with n-$Bu_4N^+F^-$ in dichloromethane before analysis. E was calculated using the Simfit program.[13]

Acknowledgements

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