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# Lipase Catalyzed Resolutions of Some $\alpha,\alpha$-Disubstituted 1,2-Diols in Organic Solvents; Near Absolute Regio and Chiral Recognition.

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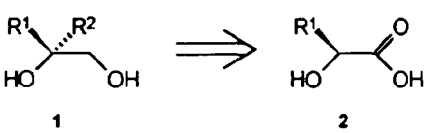
**Abstract:** Several racemic 1,2-diols bearing a tertiary benzylic alcohol stereogenic center can be esterified regioselectively by vinyl acetate using lipases and esterases in organic media. With the correct choice of enzyme and if the non-phenyl substituent at the tertiary center is unsaturated, E values of >250 can be achieved.

Enantiomerically pure vicinal diols can be used for a broad variety of synthetic applications; examples are the preparation of enantiomerically pure amino alcohols and aziridines[1] or the direct use of the diols as ligands in metal catalyzed reactions.[2] Although the value of such compounds is clear, there is a problem of access. An especially troublesome class to obtain enantiomerically pure are those diols bearing a tertiary stereogenic center adjacent to (generally) a primary center (**1** in eq. 1).



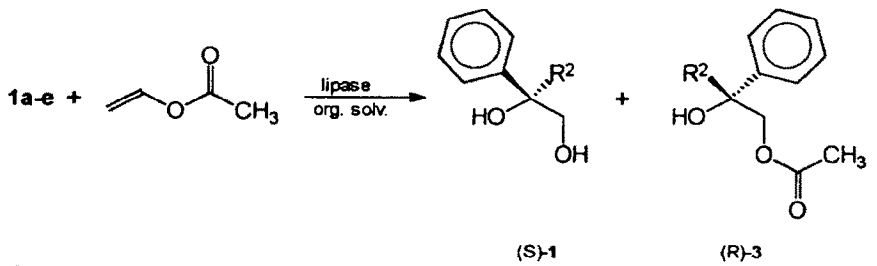

a) $R^1=C_6H_5$; $R^2=C_2H_5$
b) $R^1=C_6H_5$; $R^2=n\text{-}C_3H_7$
c) $R^1=C_6H_5$; $R^2=CH_2CHCH_2$
d) $R^1=C_6H_5$; $R^2=CH_2CHCHCH_3$
e) $R^1=C_6H_5$; $R^2=CH_2C_6H_5$
f) $R^1=C_6H_5$; $R^2=H$

Eq. 1

A good example is **1e**, used as a building block for the synthesis of biologically active azole derivatives, which have strong fungicide and growth regulating activities.[3] The most trustworthy route currently employed to such derivatives appears to be the Seebach approach,[4] which entails conformational locking of an enantiomerically pure acid **2** followed by diastereoselective alkylation to introduce $R^2$, followed by deprotection. Recently other routes to optically pure diols **1** have been reported which, however, make use of expensive chiral auxiliaries and/or laborious procedures.[5] Therefore, a more direct route would have clear advantages.

It has been reported recently that diols bearing adjacent secondary (stereogenic) and primary alcohol centers are acylated by lipases in organic solvents at both hydroxyl groups[6] and that

enantioselectivity is associated only with acylation of the hydroxyl group at the stereogenic center itself.[7] Although we were concerned by this report as well as the possibility of complete repression of reaction owing to steric hindrance, diols **1a-e**[8] were observed to be acylated smoothly by various lipases in organic solvents (Eq. 2). Di-isopropyl ether was chosen as the standard solvent. A survey of various lipases (lipase A, AKG, AY, CE, D, G, GC, L, M, N, PS, and R from Amano as well as *hog pancreatine* and *Candida Cylindracae* from Sigma and *Candida Antarctica* from NOVO were tested) revealed that in all cases acylation of **1** proceeded readily despite the presence of a hindered tert-alcohol. Within the limits of experimental detection acylation was regioselective and provided only **3**,[9] the product of acylation at the least hindered group.




Eq. 2

However, for virtually all the enzymes tested E values were near zero reflecting, we assumed, the fact that acylation was occurring two bonds removed from the stereogenic center. Fortunately this conclusion proved to be unjustified. Lipase AKG (Pseudomonas sp., Amano) proved capable of resolving **1c,d** with workable E values (Table 1). For the important intermediate **1e** an E value of >200 was obtained. Further fine-tuning of the resolutions was obtained by use of other solvents with this optimal enzyme system. With benzene as solvent an E value of >250 could be obtained for the resolution of **1e**; the improvement with **1c,d** was modest; about a 10% increase in E values was obtained (data not included). No improvements were noticed with **1a,b**; E values remained close to zero.

From a preparative scale resolution it was shown that lipase AKG has a preference for acylating the (R) form of diol **1c**. The configuration of the remaining substrate was shown to be (S) by comparison of the optical rotation with literature values.[5b] The rotation of the other diols could unfortunately not be correlated with literature data. This proviso must be attached to the generic character of Eq. 2.

**Table 1**

| entry | alcohol | reaction time | c (%) | e.e. (%) alcohol | e.e. (%) acetate | E |
|---|---|---|---|---|---|---|
| 1 | **1a** | 1d | 13 | 1 | 7 | 1 |
| 2 | **1b** | 1d | 8 | 0 | 0 | 0 |
| 3 | **1c** | 7d | 49 | 76 | 78 | 19 |
| 4 | **1d** | 3d | 59 | 94[a] | 65 | 16 |
| 5 | **1e** | 2d | 52 | >99[b] | 93 | >200 |
| 6 | **1e**[c] | 2d | 50 | >97[b] | >97 | >250 |

a) alcohol 1d was resolved on a 50m WCOT fused silica capillary GC column coated with CP cyclodextrin-B-2,3,6-M-19 (Chrompack No. 7501); the e.e. of the corresponding acetate was calculated from e.e.(acetate)= e.e(alc.)/c-e.e.(alc.).[10] b) alcohol 1e could not be resolved on a Daicel OJ HPLC column but the e.e. was calculated from e.e.(alc)= -c.(e.e.(acetate))/(c-1)[10] instead. c) di-isopropylether was used as solvent in entrys 1-5, benzene in entry 6.

The present work illustrates that a) regio- and enantioselective recognition can be achieved at a reaction site removed from the stereogenic center in a substrate, b) that chiral recognition can be determined only by the subtle effect of a double bond relatively far moved from the reaction site - polar or sterically demanding substituents are usually used to attain such effects -, and c) that a new, straightforward route to a compound (or compounds) of demonstrated industrial interest has been achieved.

**Experimental:** Diol (0.25 mmol) was dissolved in 1 ml solvent that contained 0.3 ml vinyl acetate. Lipase (20 mg) was added and the heterogeneous mixture was stirred at room temperature. The progress of the reaction was monitored by TLC (silica/ether:hexane 1:2). At regular time intervals aliquots of 0.1 ml were taken and were filtered over 0.5 cm celite® in a pasteur pipet. The celite® was washed with 1 ml ether and the filtrate was evaporated. The crude mixture of diol and monoacetate was dissolved in 0.5 ml of i-propanol and was analyzed on a Daicel OJ HPLC column (hexane: i-propanol 9:1 or 8:2) at a flow rate of 1 ml/min at 210 nm.

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8. Diols were prepared by reduction of α-alkylated dioxazolinones derived from mandelic acid (Moorlag, H., Kellogg, R.M., *Tetrahedron:Asymmetry*, **1991**, 2, 705) with $LiAlH_4$ in dry THF (reflux 2 h.). After workup and distillation (1a-1d) or crystallisation (1e) all showed satisfactory NMR-spectra ($^1H$ and $^{13}C$), elemental analyses and exact mass data.

9. The monoacetates and diols can be isolated by column chromatography (silica/ether:hexane 1:2). All monoacetates showed satisfactory NMR-spectra ($^1H$ and $^{13}C$), elemental analyses and exact mass data.

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