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Synthesis of Optically Pure cis Epoxyalcohols via an Enzymatic Route; An Alternative to the Sharpless Asymmetric Epoxidation.

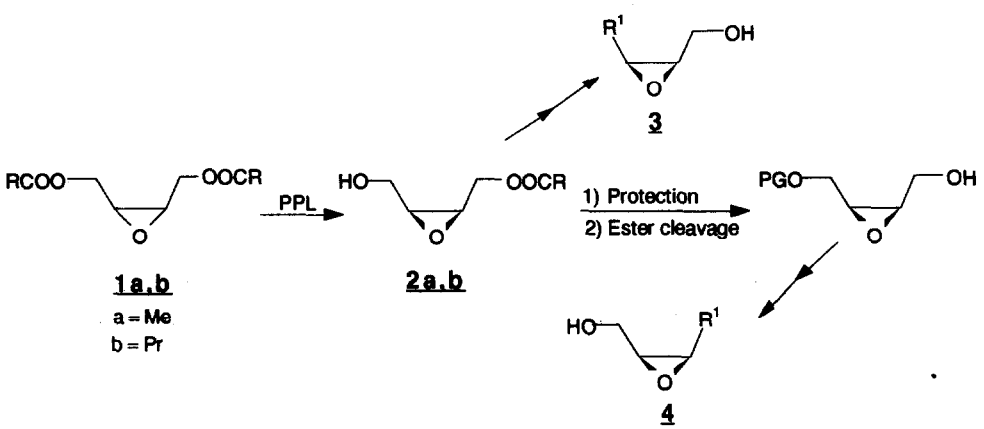
D. GRANDJEAN, P. PALE, J. CHUCHE

Laboratoire de Chimie Organique Physique, associé au CNRS, Université de Reims-Champagne-Ardenne,
BP 347, 51100 Reims, France.

Abstract: Optically pure (2S, 3R)-4-butyryloxy-2,3-epoxybutan-1-ol **2b** and (2R, 3S)-4-tert-butyldiphenylsilyloxy-2,3-epoxybutan-1-ol **5**, starting materials for the synthesis of enantiomeric epoxyalcohols **3** and **4**, were obtained after enzymatic hydrolysis of meso cis-2,3-epoxybutane-1,4-diol diesters **1b**.

In connection with a program devoted to the synthesis of natural products, we required a convenient access to optically pure cis epoxyalcohols. Various methods have been recently developed for the preparation of optically active epoxides, among which the Sharpless asymmetric epoxidation emerges as the most effective.[1-3]

Despite its efficiency and its wide applicability, the Sharpless asymmetric epoxidation suffers from a lower enantioselectivity in the formation of cis epoxyalcohols compared to the trans one.[4] Whitesides and coworkers reported an alternative route to optically active epoxides based on enzymatic resolution of epoxyesters.[5] However only epoxyesters were recovered with a good optical purity and the theoretical maximum yield was limited to 50%. Ee's of the epoxyesters so obtained were highly dependent on the substitution and varied from 60% up to 95%.



Scheme 1

In this communication, we report a new access to optically pure cis epoxyalcohols using enzymatic hydrolysis. Based on the Whitesides's work and on enzymatic hydrolysis of meso compounds,[6] we designed meso epoxyesters **1** which should provide us with epoxyalcohols **2** without yield limitation (scheme 1). The masked symmetric nature of **2** would make both enantiomers readily available via a protection-deprotection

sequence. Each of these enantiomers could be further manipulated by classical chemistry[2,3,7,8] and converted to various optically pure epoxyalcohols, such as **3**,**4** (scheme 1).

The starting diesters **1a**,**b** are conveniently and cheaply prepared from (Z)-2-butene-1,4-diol by epoxidation with magnesium monoperphtalate[9] (MMPP 0.6 equiv., $NaHCO_3$ 1.2 equiv., CH_2Cl_2) and subsequent acylation (RCOCl 2.2 equiv., NEt_3 2.2 equiv., catalytic DMAP, CH_2Cl_2; 88% overall yield).[10]

The cheapest hydrolase, pig pancreatic lipase, PPL, proved to be very efficient with epoxyesters **1a**,**b**, leading to the expected optically active epoxyalcohols **2a**,**b** with excellent chemical yields (80-90%).

As demonstrated by Whitesides and coworkers,[5] the chain length of the ester influenced the optical purity of the isolated cis-2,3-epoxybutane-1,4-diol monoesters **2a**,**b** (Scheme 1, R = Me or Pr). The optical purity of these epoxyalcohols was also dramatically influenced by experimental conditions (Table 1).

Table 1. PPL Catalyzed Hydrolysis of cis 2,3-epoxybutane-1,4-diol diesters **1a**,**b**.

entry	substrate	pH	enzyme ratio[a]	T (°C)	time (h)	conversion[b]	ee[c]
1	**1a**	7.5	260	24	2.0	71	54
2		7.0	280	"	3.5	74	68
3		6.5	260	"	4.3	75	78
4		"	270	-5	26.0	54	90
5		6.0	270	24	8.3	62	68
6	**1b**	7.0	230	"	0.5	89	66
7		"	14	"	2.5	90	80
8		"	35	3	1.5	90	85
9		6.5	110	24	0.5	98	82
10		"	16	"	1.5	68	88
11		"	30	3	1.5	90	95
12		6.0	17	24	3.5	90	89

a) mg of crude PPL/ g of substrate; b) calculated from the delivered amount of NaOH relative to the theoretical amount required to neutralize 1 equiv. of butyric acid liberated; c) calculated from ^1H NMR of the acetate derivative **6** in the presence of $Eu(hfc)_3$.

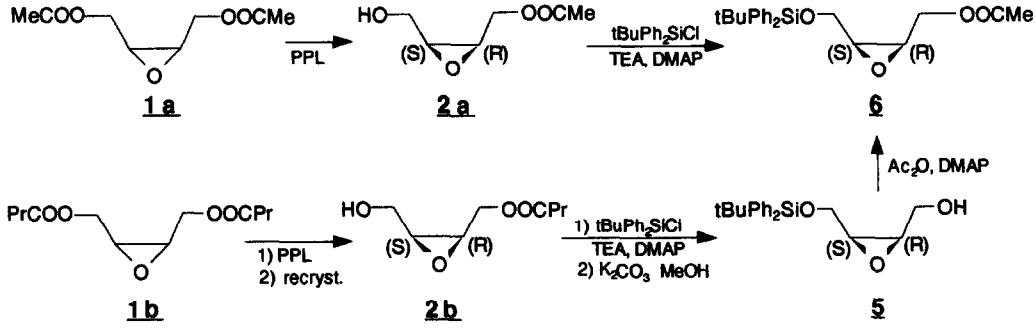
With epoxyacetate **1a** as substrate, the PPL enantiomeric discrimination was very sensitive to pH variations at 25° C. Highest ee was obtained at pH 6.5 (Table 1, entry 3 vs 1,2,5). At this pH, lowering the temperature further increased the optical purity (Table 1, entry 4 vs 3).

Enzymatic hydrolysis of the epoxybutyrate **1b** proved to be less sensitive to pH and temperature factors. Nevertheless, ee were significantly higher at pH 6-6.5 (80 to 90%, Table 1, entries 9-12) than at pH 7.0 (70 to 85%, Table 1, entries 6-8). A slight temperature effect was observed (Table 1, entries 7 vs 8 and 10 vs 11).

In the best conditions we found, (2S, 3R)-4-butyryloxy-2,3-epoxybutan-1-ol **2b** was obtained in 90% yield with 95% ee (Table 1, entry 11). Despite considerable experimentation, we were unable to observe experimental trends which could allow further increase of optical purity. We eventually found that epoxyalcohol **2b** can be recrystallized at -20° from a mixture of pentane and methylene chloride (v/v = 1/1). After a single

crystallization, optically pure **2b** was obtained from samples having ee ranging around 90%. This process has been successfully scale up to 50g.[11]

The ee was best determined by ^1H NMR in the presence of $Eu(hfc)_3$ after derivatization to the (2R, 3S)-1-acetoxy-4-tert-butyldiphenylsilyloxy-2,3-epoxybutane **6** (scheme 2). Absolute configuration was secured by comparison with results obtained through Sharpless asymmetric epoxidation.[12] The deprotection-protection sequence, used in the derivatization of **2b** to **6**, provided a convenient access to **5** which can be considered, regardless of the protecting group, as the enantiomer of **2b** (scheme 2).



Scheme 2

In conclusion, we have developed an efficient large scale enzymatic access to optically pure (2S, 3R)-4-butyryloxy-2,3-epoxybutan-1-ol **2b** and to its formal enantiomer (2R, 3S)-4-tert-butyldiphenylsilyloxy-2,3-epoxybutan-1-ol **5**. These optically pure cis epoxyalcohols are new chiral tools for synthesis. Optically active monoprotected cis-2,3-epoxybutane-1,4-diols, obtained by asymmetric epoxidation, have already been applied in synthesis.[12-16]

This method, complementary to the Whitesides's procedure, can be a mild and convenient alternative to the Sharpless asymmetric epoxidation for the synthesis of both enantiomers of optically pure cis epoxyalcohols.

Total syntheses of natural products using these chiral synthons are now underway in our group.

Experimental part: Enzymatic hydrolysis: a suspension of 2,3-epoxybutane-1,4-diol diester **1b** (50g, 205 mmol) in desionized water (971 ml) was adjusted at room temperature to the required pH (6) by adding a NaOH solution. Under vigorous magnetic stirring, PPL (Sigma, type II, 855 mg) was added. The pH of the mixture was kept constant by continuous addition of a NaOH solution through a pH-controller. When 0.9 equiv of NaOH was added, the reaction was stopped by pouring it into ether (500 ml) and quickly decanting the organic layer. The aqueous layer was further extracted twice with ether (500 ml) and then 5 times with ether (300 ml). After drying, solvent evaporation, and flash chromatography (eluted with a gradient 8-2 to 5-5 petroleum ether-ethyl acetate), the (2S, 3R)-4-butyryloxy-2,3-epoxybutan-1-ol was isolated as an oil (28.8g-90% yield). After storage overnight in a freezer, **2b** crystallized as white sheets (m.p. 20 ± 3°) from a 1 to 1 mixture of pentane (or petroleum ether) and methylene chloride. The solid was collected in a cooled double wall filtering flask and rinsed with cold (-20°) pentane (or petroleum ether).

Recrystallization of crude **2b** gave optically pure **2b** , $[\alpha]_D^{24}$ = + 17.9 (c 0.81, CH_2Cl_2).

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10. The reverse sequence, acylation followed by epoxidation, was ineffective in our hands: epoxidation of diesters of (Z)-2-buten-1,4-diol with various peracids invariably proceeded with very low conversion.
11. For convenience, such large scale experiments were run at room temperature. **2b** so obtained usually had an optical purity around 90%. A single recrystallization afforded optically pure **2b** (see experimental part).
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    In this paper, (Z)-4-tert-butyldiphenylsilyloxy-2-buten-1-ol was epoxidized with the Sharpless catalyst, (+)-DET, $Ti(OiPr)_4$, tBuOOH. The absolute stereochemistry (2S, 3R) of the resulting 4-tert-butyldiphenylsilyloxy-2,3-epoxybutan-1-ol **5** was confirmed by its conversion to a thienamycin precursor.
    Unfortunately, no optical rotation was reported for **5**. We therefore repeated this asymmetric epoxidation and we obtained the epoxyalcohol **5** which exhibited in our hands a negative optical rotation (-)-**5** : $[\alpha]_D^{24} = -4.4$ (c 0.8, CH_2Cl_2) for a 75 % ee, determined by ^1H NMR on its acetate **6**. 4-butyryloxy-2,3-epoxybutan-1-ol **2b**, having after recrystallizations a constant optical rotation, was derivatized by silylation followed by ester cleavage to the same alcohol (+)-**5** which showed a positive optical rotation: $[\alpha]_D^{24} = +6.1$ (c 0.8, CH_2Cl_2) for a 100% ee. Therefore **2b** had the same absolute configuration as the Sharpless product we have obtained.
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