Pergamon

Tetrahedron Letters 40 (1999) 4383–4386

TETRAHEDRON LETTERS

# A Lipase-Mediated Synthesis of Single Enantiomeric *trans*-Epoxides *via* Convergence of Racemic Mixtures

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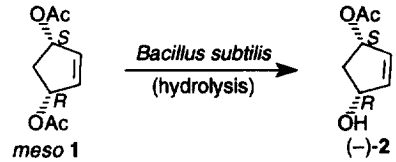
Received 17 March 1999; revised 8 April 1999; accepted 9 April 1999

**Abstract:** A new lipase-mediated methodology has been devised for the preparation of single enantiomeric *trans*-epoxides from unsymmetrical *cis*-olefin precursors *via* enantiomeric convergence of racemic intermediates. 

***Keywords***: asymmetric induction; enzyme and enzyme reactions; epoxides; resolution

Since we first demonstrated[1] the acquisition of a single, optically active compound by enzymatic asymmetric desymmetrization of a *meso* substrate, this *meso* asymmetrization procedure has been used as a standard technology for the construction of single enantiomeric compounds.[2] In our work,[1] the *meso* diacetate **1** was desymmetrized enantiospecificaly to give the enantiomerically active monoacetate **2** by enzymatic hydrolysis in the presence of *Bicillus subtilis* (**Scheme 1**). We envisaged that this enzymatic *meso* asymmetrization technology may be expanded to enantiomeric convergence of diastereomeric mixtures into single enantiomeric products if the racemic mixtures fulfill certain stereochemical requirements. Since in the *meso* asymmetrization an enzyme does not discriminate *meso* symmetry but just the *R/S* chirality, it would be expected that the enzyme discriminates one of the two centers in a racemic diacetate molecule having the opposite relative configurations such as (±)-**3** to give a mixture consisted of the two structurally isomeric chiral monoacetates **4** and **5**. The




**Scheme 1**

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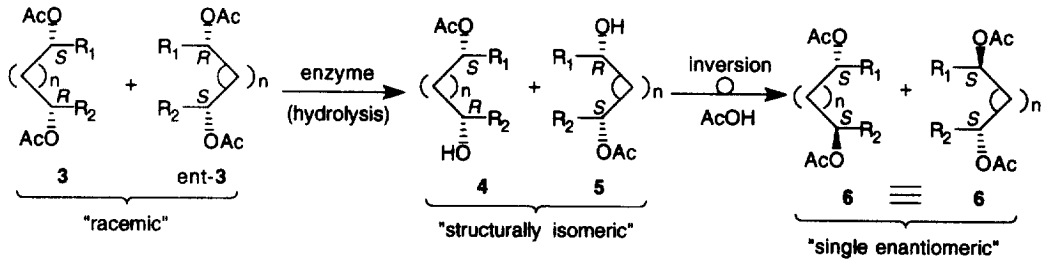
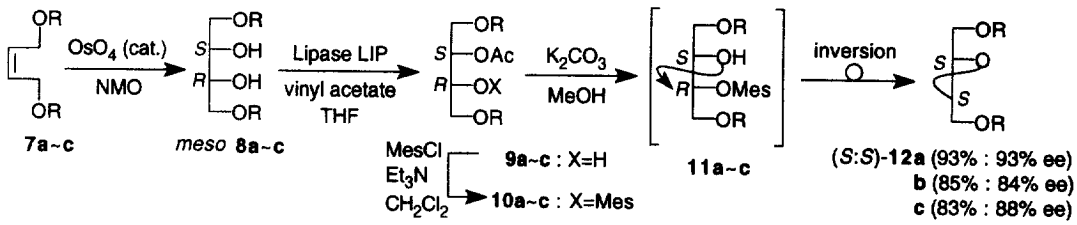
*PII:* S0040-4039(99)00754-6

mixture, however, should furnish convergently the single enantiomeric product **6** if the hydroxy functionality is substituted by an acetoxy group with inversion of the configuration. Quite recently, this concept was realized by the transformation of certain racemic 1,2-diols into single enantiomeric *trans*-epoxides using a chiral oxazaborolidine catalyst (1.2 equiv.)[3] (**Scheme 2**). We report here a much more facile method for the preparation of single enantiomeric *trans*-epoxides from racemic diol precursors *via* sequential lipase-mediated formation of two isomeric monoacetate mixtures and their enantiomeric convergence on the basis of the expanded *meso* asymmetrization concept shown.




**Scheme 2**

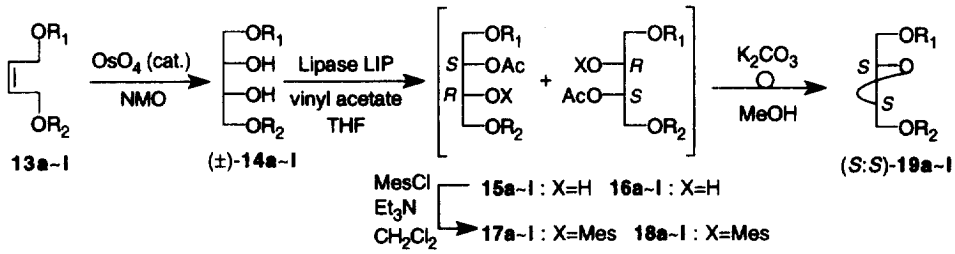
In order to demonstrate our expanded concept, we examined the chiral synthesis of *trans*-epoxides starting from racemic 1,2-glycol precursors. We chose the racemic butane-2,3-diol derivatives having a variety of 1,4-di-*O*-functionalities as substrates, which were readily obtained from the *cis*-2-butene precursors by a catalytic *cis*-dihydroxylation.[4] We first examined the lipase-mediated kinetic ester exchange reaction of the *meso* diols **8a~c** generated from the *cis*-olefins **7a~c** to see whether enzymatic asymmetric monoacylation takes place or not. Among the lipases tested under kinetic transesterification conditions, Lipase LIP (*Pseudomonas* sp., Toyobo) showed the most promising enantiomeric recognition. Thus, when the *meso* **8a** was stirred with vinyl acetate in THF in the presence of Lipase LIP at room temperature, the optically active monoacetate **9a** was generated in excellent yield. The monoacetate **9a** was mesylated under standard conditions to give **10a** which, on methanolysis in the presence of potassium carbonate, afforded the known *trans*-epoxide (*S,S*)-**12a**[5] having 93% ee (determined by hplc using chiral column: CHIRALCEL OD, 10% $^{i}$PrOH-hexane) in 93% overall yield. This indicated that the enzyme reaction occurred at the hydroxy functionality on the *R* stereogenic center of the *meso* substrate **8a**. Virtually the same results were obtained with two analogues, the *bis*-4-methoxybenzyl **8b** and the *bis*-2-naphthylmethyl **8c** ethers, which afforded the corresponding *trans*-epoxides, **12b** and **c**, in 85 and 83% yields having 84 and 88% ee (CHIRALCEL OD, 15% $^{i}$PrOH-hexane), respectively (**Scheme 3**).




**a** series : R=$C_6H_5CH_2$ (Bn), **b** series : R=4-MeO$C_6H_4$ $CH_2$ (MPM)
**c** series : R=2-naphthyl$CH_2$ (NAP)

**Scheme 3**

Having confirmed the enzymatic discrimination of the *meso* 1,2-diol functionalities, we next examined the enzymatic discrimination to the racemic diols (±)-**14a~l** generated from the *cis*-2-butenes **13a~l** having different 1,4-*O*- functionalities by *cis*-dihydroxylation in the presence of the same lipase.[4] Under the same conditions as for the *meso* substrates **8a~c**, all the racemic substrates **14a~l** gave inseparable 1:1 mixtures of the two mono acetates, **15a~l** and **16a~l**, after 24~48 h. The mixtures were immediately mesylated to give mixtures consisted of two isomeric mesylates, **17a~l** and **18a~l**, which, without separation, were then stirred with methanolic potassium carbonate to bring about convergence of the two isomers by concurrent methanolytic removal of the




**Scheme 4**

**Table 1: Formation of the *trans*-Epoxides 19 from the *cis*-Olefins 13**

| Entry | Compounds 13~19 | | | Overall Yield of 19 from 13 (%) | Enantiomeric Purity of 19 (% ee)[a,b] |
|---|---|---|---|---|---|
| | | $R_1$ | $R_2$ | | |
| 1 | **a** | $C_6H_5CH_2$(Bn) | 2-naphthylCH$_2$(NAP) | 81 | 91 |
| 2 | **b** | $C_6H_5CH_2$(Bn) | 4-MeOC$_6$H$_4$(PMP) | 86 | > 99 |
| 3 | **c** | $C_6H_5CH_2$(Bn) | 4-NO$_2$C$_6$H$_4$ | 87 | 86 |
| 4 | **d** | $C_6H_5CH_2$(Bn) | C$_6$H$_4$S | 88 | 10 |
| 5 | **e** | $C_6H_5CH_2$(Bn) | MOM | 74 | 98 |
| 6 | **f** | $C_6H_5CH_2$(Bn) | THP | 83 | 92[c,d] |
| 7 | **g** | $C_6H_5CH_2$(Bn) | Me$_3$CCO | 61 | 55 |
| 8 | **h** | 4-MeOC$_6$H$_4$CH$_2$(MPM) | 2-naphthylCH$_2$(NAP) | 82 | 86 |
| 9 | **i** | 4-MeOC$_6$H$_4$CH$_2$(MPM) | 4-MeOC$_6$H$_4$ | 77 | 87 |
| 10 | **j** | 4-MeOC$_6$H$_4$CH$_2$(MPM) | MOM | 82 | 93 |
| 11 | **k** | 4-MeOC$_6$H$_4$CH$_2$(MPM) | THP | 83 | 87[c,d] |
| 12 | **l** | 2-naphthylCH$_2$(NAP) | THP | 93 | 94[c,d] |

*a*. Enantiomeric purity of **19** was determined by hplc using a chiral column (CHIRALCEL OD): **a** (10% $^i$PrOH-hexane); **b** (15% $^i$PrOH-hexane); **c** (15% $^i$PrOH-hexane); **d** (15% $^i$PrOH-hexane); **e** (0.5% $^i$PrOH-hexane); **g** (1% $^i$PrOH-hexane); **h** (20% $^i$PrOH-hexane); **i** (15% $^i$PrOH-hexane); **j** (1% $^i$PrOH-hexane).

*b*. Specific rotations of **19** in $CHCl_3$: **a** $[\alpha]_D^{26}$ –7.4 (*c* 1.7); **b** $[\alpha]_D^{24}$ –14.9 (*c* 1.2); **c** $[\alpha]_D^{26}$ –14.2 (*c* 1.6); **d** $[\alpha]_D^{25}$ –0.7 (*c* 1.7); **e** $[\alpha]_D^{25}$ –14.4 (*c* 1.3); **g** $[\alpha]_D^{29}$ –15.6 (*c* 0.9); **h** $[\alpha]_D^{29}$ –5.1 (*c* 1.4); **i** $[\alpha]_D^{27}$ –12.0 (*c* 1.5); **j** $[\alpha]_D^{26}$ –8.8 (*c* 1.0).

*c*. Determined by hplc using chiral column (CHIRALCEL OD) after removal of THP group: **f** (10% $^i$PrOH-hexane); **k** (20% $^i$PrOH-hexane); **l** (20% $^i$PrOH-hexane).

*d*. Specific rotations were measured after removal of THP group: **f** $[\alpha]_D^{27}$ –19.0 (*c* 1.2) {lit.[6]: $[\alpha]_D^{24}$ –22.0 (*c* 1.07)}; **k** $[\alpha]_D^{25}$ –15.6 (*c* 0.44); **l** $[\alpha]_D^{28}$ –14.7 (*c* 0.48).

acetyl functionality and internal $S_N2$ substitution to give rise to the single enantiomeric epoxides **19a~l** in good to excellent overall yields having high enantiomeric excess, except for the sulfide **19d** and the pivalate **19g**. Although the absolute configurations of all of the epoxides **19** were not determined unambiguously, it was presumed that they all have 2*S*, 3*S* configuration based on the enzymatic discrimination exhibited by the *meso* substrates **8** above as well as the fact that both the products **13b** and **13f** afforded the same (–)-(2*S*:3*S*)-4-benzyloxy-2,3-epoxy-1-butanol[6] by removal of 4-methoxyphenyl (from **13b**) with ceric ammonium nitrate (CAN) in aqueous acetonitrile (1:1)[7] and THP (from **13f**) with Montmorillonite K 10 in methanol[8,9] (**Scheme 4**: **Table 1**).

The following describes a typical experimental procedure involving a new procedure for the removal of the THP protecting group without touching the epoxide functionality. Thus, the diol **14f** (4.1 g, 14 mmol) was stirred with Lipase LIP (4.1 g) in THF (80 ml) containing vinyl acetate (12.7 ml, 138 mmol) at room temperature for 38 h. After filtration, the solution was evaporated under reduced pressure to leave a mixture of the two monoacetates, **15f** and **16f**, which was treated with methanesulfonyl chloride (MesCl) (1.3 ml, 17 mmol) in dichloromethane (60 ml) containing triethylamine (2.5 ml, 18 mmol) at room temperature for 10 min to give a mixture of two mesylates, **17f** and **18f**. The mixture was then stirred with $K_2CO_3$ (1.9 g, 14 mmol) in MeOH (50 ml) at room temperature for 10 min to afford the single epoxide **19f** (3.1 g, 81% overall) after silica gel column chromatography. Although the removal of the THP group was difficult under standard conditions,[8] it could be accomplished by stirring with Montmorillonite K10 in MeOH at room temperature. Thus, when **19f** (3.1 g, 11 mmol) was stirred with Montmorillonite K10 (1.5 g) in methanol (60 ml) at room temperature for 3 h, (–)-(2*S*:3*S*)-4-benzyloxy-2,3-epoxy-1-butanol[6] (1.54 g, 70%) was obtained after silica gel column chromatography.

In summary, we have devised a new lipase-mediated methodology for the preparation of single enantiomeric *trans*-epoxides from racemic 1,2-diol precursors on the basis of the expanded *meso* asymmetrization concept. Further application of the present technology is currently under investigation.

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