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Synthesis of Both Enantiomers of C_2 Symmetric *trans*-2,5-Bis(hydroxymethyl)pyrrolidine. Lipase Mediated Sequential Kinetic Resolutions

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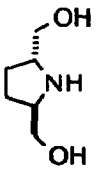
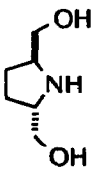
Summary: Lipase mediated sequential kinetic resolution has been employed to give both enantiomers of *trans*-2,5-bis(hydroxymethyl)pyrrolidine in optically pure form. The effect of different parameters on the ee and yields in these resolutions are also reported.

Compounds with C_2 symmetry are useful chiral auxiliaries in asymmetric synthesis,[1] since stereoselectivities of reactions employing them are very high. Pioneering work of Katsuki has shown that O-protected derivatives of *trans*-2,5-bis(hydroxymethyl)pyrrolidine are very useful chiral auxiliaries.[1b] Since the original report of Katsuki[2] on the preparation of these auxiliaries by a resolution, other more efficient approaches to the syntheses of these compounds have not been reported in the literature. A pig liver esterase (PLE) mediated resolution of *meso*-2,5-pyrrolidine dimethylesters has been reported by Boutelje.[3] Synthesis of (R,R)-2,5-bis(hydroxymethyl)pyrrolidine from D-mannitol,[4] and by cyclization of dibromoadipates using optically pure phenylethylamine,[5] has also been recently reported. This paper reports an enzymatic method for the preparation of both enantiomers of *trans*-2,5-bis(hydroxymethyl)pyrrolidines **1** and **2** in excellent optical purity.



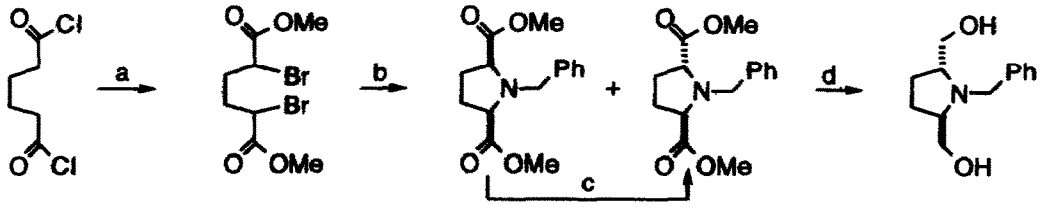
1 (R,R)



2 (S,S)

Our synthetic approach to the two enantiomers **1** and **2** was a sequential kinetic resolution[6] using enzymes. The initial task was preparation of the substrate. This was achieved using a modified literature procedure[7] in four steps (overall yield 68%) (Scheme 1). The utility of lipases in organic solvents for a variety of organic transformations has been well documented.[8] The enzyme of choice for our sequential resolution experiments was lipase PS.[9] This was selected based on literature precedents wherein the successful application of lipase PS in the kinetic resolution of primary alcohols,[10] sequential resolutions of diols,[11] and for other applications[12] have been reported.

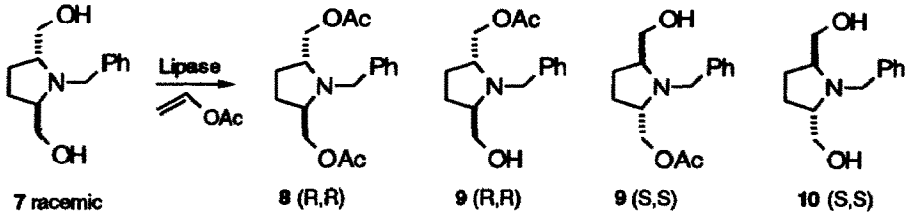
Scheme 1



Key: [a] Br_2, reflux, cool to rt, then MeOH, 98% (dl:meso=1:1)[13]; [b] dl 4, $PhCH_2NH_2$, PhH, reflux, 77% (5:6 = 1:3)[14]; [c] NaOMe, MeOH, reflux, 95%[14]; [d] 6, LAH, THF, rt, 95%.

At the outset, several parameters were optimized with respect to conversion to the acetates and %ee of the products. These included solvent, acyl donor, ratio of acyl donor to substrate, and ratio of enzyme to substrate (Table). Four acyl donors (vinyl acetate, isopropenyl acetate, ethyl acetate, and cyclohexyl acetate) were evaluated; of these, vinyl acetate gave the best results. The ratio of acyl donor to substrate had a great impact on conversion and enantioselectivity. The optimal molar ratio of acyl donor to substrate was 2:1; however, a large excess of the acyl donor resulted in lower selectivity and slower rate. For example, using vinyl acetate as both the solvent as well as acyl donor furnished 24% of **8** (78%ee) and 24% of **10** (53%ee) (entry 5). On the other hand, an acyl donor to substrate ratio of 2:1 gave 50% of **8** (88%ee) and 29% of **10** (>99%ee) (entry 3). Use of less than a molar equivalent of the acyl donor gave inferior resolution (entry 9). The absolute configuration for the products was established by hydrolysis of the diacetate and the monoacetate to diol **7** and further conversion to the known dibenzylethers.[15] The effect of the substrate to lipase ratio on enantioselectivity was also examined. These data indicate higher ratios of substrate to enzyme provides higher ee's for the diacetate (compare entries 1-4).

Scheme 2



Solvent plays a crucial role in the resolution experiment.[16] The non-polar solvent, hexanes, provides optimal resolution as compared to the more polar solvents CH_2Cl_2, THF, and t-butylmethylether (TBME), which showed lower selectivities (compare entry 3 with 10, 11, and 12). However, the reaction in hexanes is triphasic since the diol has very poor solubility. In order to monitor the reaction more accurately and enhance the enantioselectivity, we examined several combinations of solvents (hexanes-THF, hexanes-TBME, and hexanes-CH_2Cl_2). Of these combinations, the 1:1 mixture of hexanes-CH_2Cl_2 provided the optimal resolution. Under this condition, both the diacetate and the diol could be obtained in excellent optical purity

and good chemical yields (entries 14 and 15). The reactions can be carried out in gram scales conveniently.[17] Compound **10** was quantitatively debenzylated [$Pd(OH)_2/C$, MeOH, H_2] to provide **2**. Similarly, deacetylation of **8** [K_2CO_3/MeOH/H_2O(90:10), 98%] followed by catalytic debenzylation furnished **1**.

Table. Resolution of **7** using Lipase PS.[a,b]

Entry	Solvent	PS:Diol (wt)	Vinyl Ace.:Diol (mol)	Yield, **8** (% ee, RR)	Yield, **9** (% ee)	Yield, **10** (%ee, SS)
1	Hexane	1:30	2:1	36 (90)	25 (18, SS)	39 (69)
2	Hexane	1:15	2:1	44 (91)	26 (56, SS)	30 (85)
3	**Hexane**	**1:10**	**2:1**	**50 (88)**	**21 (78, SS)**	**29 (>99)**
4	Hexane	1:5	2:1	54 (78)	20 (81, SS)	26 (89)
5	None	1:10	20:1	24 (78)	52 (16, SS)	24 (53)
6	Hexane	1:10	10:1	39 (82)	41 (38, SS)	20 (83)
7	Hexane	1:10	6:1	48 (80)	32 (61, SS)	20 (92)
8	Hexane	1:10	4:1	54 (79)	27 (76, SS)	19 (>99)
9	Hexane	1:10	1.5:1	41 (89)	22 (35, SS)	37 (76)
10	TBME	1:10	2:1	41 (86)	30 (39, SS)	29 (85)
11	THF	1:10	2:1	20 (91)	37 (15, RR)	43 (56)
12	CH_2Cl_2	1:10	2:1	18 (95)	41 (38, RR)	41 (83)
13	Hexane:CH_2Cl_2 (1/3)[c]	1:10	2:1	27 (94)	35 (20, RR)	38 (90)
14	**Hexane:CH_2Cl_2 (1/1)[c]**	**1:10**	**2:1**	**35 (96)**	**30 (1, SS)**	**35 (>99)**
15	**Hexane:CH_2Cl_2 (3/1)[c]**	**1:10**	**2:1**	**42 (95)**	**28 (34, SS)**	**30 (>99)**

[a] All reactions were carried out on 0.5 mmol scale at room temperature for 24 hours. [b] %ee and relative yields were determined by HPLC using a Chiracel OD column. These results were confirmed by isolating the pure compounds by column chromatography and further NMR or HPLC analysis (see reference 17). [c] By volume.

In conclusion, we have shown that lipase mediated sequential kinetic resolutions can be effectively applied to the synthesis of useful chiral auxiliaries. The effect of different parameters on the kinetic resolutions reported here provides qualitative guidelines for the manipulation of ee and yields in lipase resolutions. The extension of this methodology to the resolution of other aminoalcohols is currently underway in our laboratory.

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13. The meso isomer was converted to the dl isomer using the procedures reported in refs. 5 and 7.

14. The cyclization starting with pure dl isomer **4** provides a mixture of dl (**6**) and meso (**5**) products (dl:meso=3:1). The meso compound **5** was epimerized under basic conditions (NaOMe/MeOH) to the dl product **6** (equilibrium ratio of dl:meso = 3:1) (see ref. 7d).

15. Ref. 4 and references cited therein. All new compounds prepared showed physical, spectral (IR, NMR, and MS), and analytical data consistent with their structure. Rotation values: (R,R)-**8** $[\alpha]^{25}_{D}$= +67.9° (c = 1.0, CH_2Cl_2); (R,R)-**9** $[\alpha]^{25}_{D}$ = +69.6° (c = 1.0, CH_2Cl_2); (S,S)-**10** $[\alpha]^{25}_{D}$ = -70.3° (c = 0.5, MeOH). The optical purities of the diacetate and the monoacetate were established by chiral HPLC and by hydrolysis to the diol and subsequent NMR analysis of the corresponding Mosher esters. Similarly, the optical purity of the diol was established by chiral HPLC and Mosher ester analysis. The literature (ref. 4a) rotation value for (R,R)-**10** is $[\alpha]^{25}_{D}$ = +49.2° (c = 0.5, MeOH). We believe that this rotation is erroneous.

16. For other examples of solvent effect on resolutions see: Bornscheuer, U.; Herar, A.; Kreye, L.; Wendel, V.; Capewell, A.; Meyer, H. H.; Scheper, T.; Kolisis, F. *Tetrahedron: Asymmetry* **1993**, *4*, 1007. Hirose, Y.; Kariya, K.; Sasaki, I.; Kurono, Y.; Ebiike, H.; Achiwa, K. *Tetrahedron Lett.* **1992**, *33*, 7157.

17. A typical resolution experiment: To a solution of **7** (1.01 g, 4.75 mmol) in 10 mL of solvent (hexane:CH_2Cl_2=3:2) was added vinylacetate (0.84 mL, 9.11 mmol) and 100 mg of Lipase PS. The reaction was stirred at rt and was monitored by HPLC. The reaction was stopped when the desired conversion was obtained. The reaction mixture was filtered through celite, the solids washed with CH_2Cl_2, and the filtrate concentrated. The crude product was purified by flash chromatography using silica gel to give **8**, 0.46 g (33%, 95%ee); **9**, 0.41 g (34%, 2%ee); **10**, 0.26 g (26%, >99%ee).

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