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Highly Efficient Synthesis of Enantiomerically Enriched 2-Hydroxymethylaziridines by Enzymatic Desymmetrization

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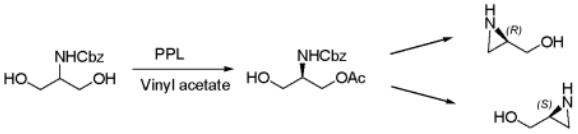
Abstract



Both enantiomers of protected and unprotected 2-hydroxymethylaziridines are efficiently and enantiospecifically synthesized using a combination of enzymatic and synthetic methods. PPL was used for lipase-catalyzed desymmetrization of *N*-protected serinol.

Optically pure aziridines are very useful synthetic precursors and have been used as chiral synthons for chiral amines, amino acids, and amino alcohols. [1] The ring strain of aziridines renders them susceptible to ring opening reactions with various electrophiles and thus they are versatile intermediates in organic synthesis. During the course of our efforts to synthesize biologically active unnatural amino acids and peptidomimetics, we required differentially protected non-racemic 2-hydroxymethylaziridines. There are a number of methods to prepare enantiomerically pure aziridines. One approach is to synthesize them from chiral compounds such as amino acids, carbohydrates, 1, 2-diols, and epoxides.[2] The other is to generate chirality through chiral auxiliaries or by direct enantioselective aziridination of alkene or imine substrates.[3] Even though catalytic aziridination gives a direct approach to these chiral synthons, the synthetic methods have not proven useful for general asymmetric synthesis of aziridines. [4] 2-Hydroxymethylaziridine can be regarded as a nitrogen analogue of 2,3-epoxypropanol (glycidol), which is widely used as a versatile chiral synthon. Although 2-hydroxymethylaziridine is a potentially useful chiral building block, the lack of availability has limited its application compared to glycidol in organic and medicinal chemistry.[5]

Herein we report a novel strategy to synthesize optically pure 2-hydroxymethylaziridines using enzymatic desymmetrization as a key step. There are a few reports using enzymatic methods for aziridine synthesis, but they generally involve resolution of racemic aziridines.[6] We required both enantiomers of a variety of protected 2-hydroxymethylaziridines and recognized the need for a general and efficient method to prepare them from a common chiral intermediate. Thus we envisioned a new synthesis using desymmetrization[7] of meso serinol to generate the monoacetate. As shown in Scheme 1, serinol is prochiral and, if the aziridine ring could be closed selectively, each enantiomer of the corresponding aziridine would be obtained. Once the acetate is obtained stereoselectively, it could be easily transformed to both aziridine enantiomers after a few steps using well-known synthetic methods. Desymmetrization reactions using serinol analogs with PPL (pig pancreatic lipase) have been reported.[8] PPL is

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among the least expensive lipases and can be used in organic solvents. Thus, we decided to use PPL for the desymmetrization reaction.

First, the PPL-catalyzed desymmetrization of N-Ts-protected serinol with vinyl acetate was investigated (Scheme 2). The starting material could be easily prepared from racemic serine or directly from commercially available serinol. The desymmetrization reaction of *N*-Ts-serinol was carried out using PPL (300 mg/mmol substrate) and vinyl acetate (20 ml/mmol substrate) as acetylating agent and solvent at room temperature. Although *N*-Ts-serinol **1a** was only partially soluble in vinyl acetate, it was smoothly consumed in 3 h to give the desired mono-acetate product in good yield (81%) and enantiomeric ratio (90/10). Recrystallization of the product in EtOAc-hexane yields a single enantiomer in 60% yield, which was analyzed by chiral HPLC. The use of THF as a solvent gave a homogeneous reaction solution but did not provide an advantage in terms of reactivity or stereoselectivity.

There are several reports regarding the enhancement of selectivity and reactivity of the lipase reaction by the use of additives.[9] Triethylamine is the most commomly used additive[9] and generally shows an increase in reaction rate and/or enantioselectivity. When triethylamine was added to the PPL catalysed reaction of *N*-Ts-aziridine **1a**, the reaction rate increased but the selectivity was not changed even when the reaction was run at 0 °C (Run 1–3, Table 1). When the bulkier 2, 4, 6- mesitylsulfonyl protected substrate **1b** was used, the enantioselectivity was decreased (Run 4, Table 1). Similarly, when the trityl protecting group was employed, the reaction was extremely slow and racemic product was obtained (Runs 11–12). The lipase-catalyzed reaction was then investigated using carbamate protecting groups. In all cases (Boc8a, Fmoc and Cbz[8c]), excellent enantioselectivites and high yields were obtained. Changes in the reactant ratios modify the reaction rate but have no effect on enantiomeric excess or yield. To determine the enantiomeric ratio of the monoacetates, authentic samples were prepared for each racemic product and the racemates were characterized by chiral HPLC analysis (Chiralcel OD column). In those cases where the racemic compounds (*rac*-**2d,** *rac*-**2e**) could not be separated by chiral OD column, they were analyzed after esterifying the monoacetate with Mosher's reagent.

Conversion of the monoacetates to the corresponding aziridines was then investigated (Scheme 3). All attempts to convert the *N*-Fmoc protected monoacetate **2c** to aziridine were unsuccessful; deprotection of the Fmoc group under ring closing conditions (PPh_3/DIAD or mesylation followed by NaH) occurred instead. In contrast, both **2d** and **2e** were smoothly converted to the desired aziridines. Compound **2d** was the preferred intermediate because of its chromophore and because of concerns about product stability under the acidic conditions required for Boc deprotection of **2e**.

The monoacetate **2d** was mesylated and treated with NaH to afford protected (*R*)-2-hydroxymethylaziridine **3** in excellent yield (90% over 2 steps). When Mitsunobu conditions were employed, the reaction proceeded smoothly, but purification was a problem because of the DIAD byproduct. On the other hand, the TBS-protected (*S*)-enantiomer **5** was easily prepared under Mitsunobu conditions without purification problems. TBS protected serinol **4** was readily prepared from lipase product **2d** via TBS protection followed by mild acetate hydrolysis.

Attempted acetate deprotection of 2-hydroxymethyl-aziridine **3** led to a surprising result (Schemes 4 and 5). When acetate **3** was treated with K_2CO_3/CH_3OH (1 equiv, rt, 1 h), both Cbz and acetate protecting groups were removed to give (*R*)-2-hydroxymethylaziridine **6** in good yield (75%).[10] This conversion was then carried out in CH_3OH-*d4* and monitored by NMR; the results and tentative resonance assignments are shown in Figure 1, and a mechanism

is proposed in Scheme 4. The acetate group is rapidly deprotected, and the resulting alcohol undergoes intramolecular cyclization to give a transient bicyclic intermediate.

The resonances for this intermediate are identified as peaks f–j in Figure 1. Expulsion of benzyl alcohol is complete within 10 min. Attack at the carbamate carbonyl leads to ring opening and formation of the unsymmetrical carbonate which is ultimately cleaved to give hydroxymethylaziridine **6**. Further support for a neighboring group-assisted mechanism in the hydrolysis of **3** was obtained when TBS-protected aziridine **5** was treated under identical conditions (K_2CO_3, 1 equiv, rt). Hydrolysis of the carbamate required 24 h to proceed to completion in this case. Although normal Cbz amides are quite stable under these conditions, it is known that the acylaziridine amide bond is weaker than normal because of the ring strain of the aziridine.[11] Presumably, this is the reason why the Cbz-aziridine bond is easily and cleanly cleaved under these conditions. Finally, (*S*)-2-hydroxymethylaziridine **6** was obtained from **5** by fluoride cleavage of the silyl protecting group. The best result was obtained by treatment of **5** with CsF in refluxing methanol.[12]

To determine the absolute configuration of the free 2-hydroxymethylaziridines, **6** was converted to Ts-aziridine **8** (Scheme 5), and the optical rotation of **8** ($[\alpha]_D$ +31.6 (c=1.0, EtOAc))8r was compared with the reported value ($[\alpha]_D$ +29.9 (c=9.9, EtOAc)).[13] Compound **8** was also analyzed by chiral column HPLC and showed a single peak. It was concluded that the absolute configuration of the aziridine **6** is (*R*) and that no racemization occurred during transformations subsequent to the lipase reaction.

In summary, a highly efficient and novel synthesis of enantiopure 2-hydroxymethylaziridines has been developed using lipase desymmetizaion followed by aziridine ring formation reactions. These aziridines should be versatile chiral synthons, and further conversion to phosphoserine peptidomimetics is currently under investigation.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgements

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References

1. For reviews on the synthesis and reactions of chiral aziridines, see: a) Sweeney JB. Chem Soc Rev 2002;31:247. [PubMed: 12357722] b) McCoull W, Davis FA. Synthesis 2000:1347. c) Tanner D. Angew Chem 1994;106:625.Angew Chem Int Ed Engl 1994;33:599. d) Müller P, Fruit C. Chem Rev 2003;103:2905. [PubMed: 12914485]and references therein
2. Kim SK, Jacobsen EN. Angew Chem Int Ed Engl 2004;43:3952. [PubMed: 15274223]
3. Gillespie KM, Sanders CJ. J Org Chem 2002;67:3450. [PubMed: 12003558]
4. A few direct aziridinations of styrene have been reported: a) Nishikori H, Katsuki T. Tetrahedron Lett 1996;37:9245. b) Li Z, Conser KR, Jacobsen EN. J Am Chem Soc 1993;115:5326. c) Evans DA, Faul MM, Bilodeau MT, Anderson BA, Barnes DM. J Am Chem Soc 1993;115:5328.
5. Asymmetirc synthesis of 2-hydroxymethylazirine has been briefly reported from chiral amino acid without isolation and characterization: Xu J. Tetrahedron: Asymmetry 2002;13:1129.
6. (a) Sakai T, Liu Y, Ohta H, Korenaga T, Ema T. J Org Chem 2005;70:1369. [PubMed: 15704972] b Sampath Kumar HM, Shesha Lao M, Pawan Chakravarthy P, Yadav JS. Tetrahedron: Asymmetry

2004;15:127. c Renold P, Tamm C. Tetrahedron; Asymmetry 1993;4:2295. d Fuji K, Kawabata T, Kiryu Y, Sugiura Y. Tetrahedron Lett 1990;31:6663.

7. For a review of enantioselective enzymatic desymmetrizations in organic synthesis, see Garcia-Urdiales E, Alfonso I, Gotor V. Chem Rev 2005;105:313. [PubMed: 15720156]
8. (a) Neri C, Williams JMJ. Adv Synth Catal 2003;345:835. b Terradas F, Teston-Henry M, Fitzpatrick PA, Klibanov AM. J Am Chem Soc 1993;115:390. c Wang YF, Lalonde JJ, Momongan M, Bergbreiter DE, Wong CH. J Am Chem Soc 1998;110:7200.
9. For a review of enhancement of selectivity and reactivity of lipase by additives, see Theil F. Tetrahedron 2000;56:2905.
10. Free 2-hydroxymethylaziridine 6 was dimerized or oligomerized under acidic conditions or at temperature higher than *ca.* 50 °C. Therefore, it was purified by chromatography on basic alumina.
11. (a) Bennet AJ, Wang Q-P, Slebocka-Tilk H, Somayaji V, Brown RS. J Am Chem Soc 1990;112:6383. b) Shustov GV, Kadorkina GK, Varlamov SV, Kachanov AV, Kostyanovsky RG, Rauk A. J Am Chem Soc 1992;114:1616.
12. All attempts to get and isolate *N*-Cbz-2-hydroxymethylaziridine from 5 failed, which include the use of TBAF, HF-Pyridine and HF-Et_3N. Benzyl alcohol was rapidly produced at −10 °C, which is a byproduct from Cbz deprotection.
13. Bergmeier SC, Seth PP. J Org Chem 1997;62:2671. [PubMed: 11671621]

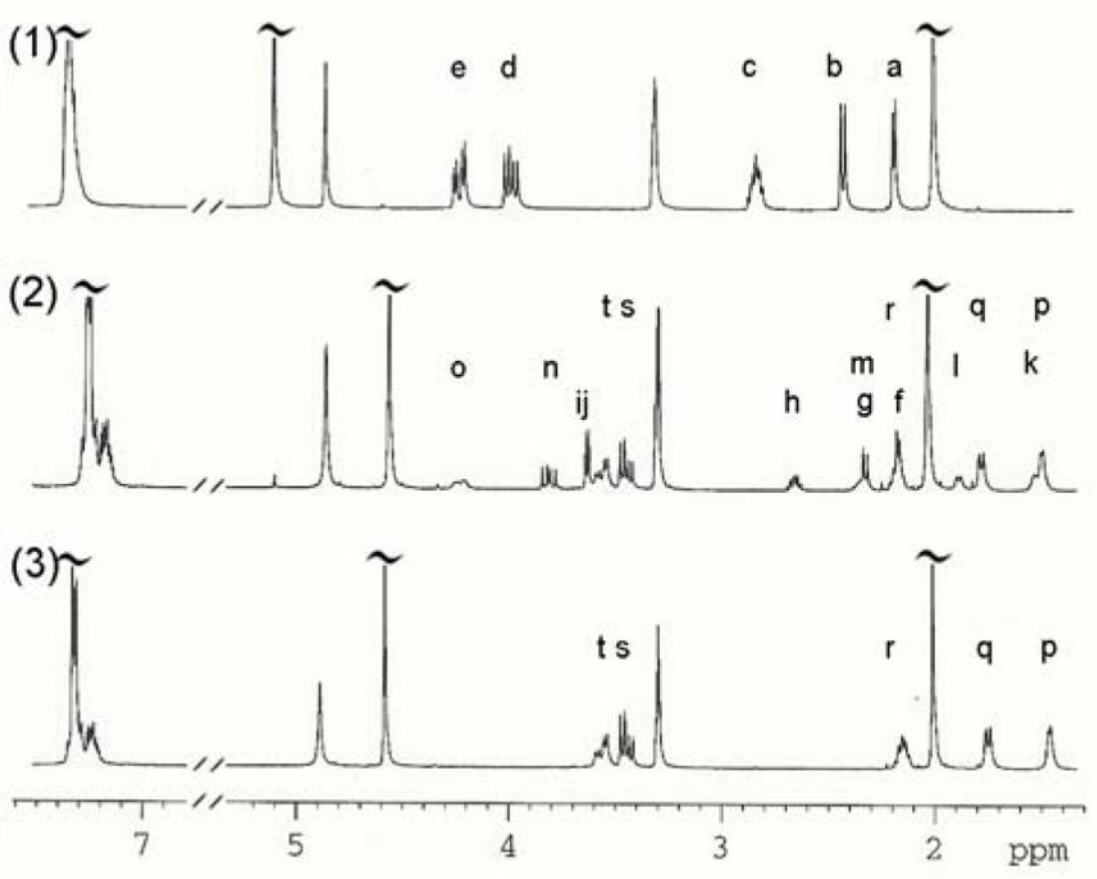
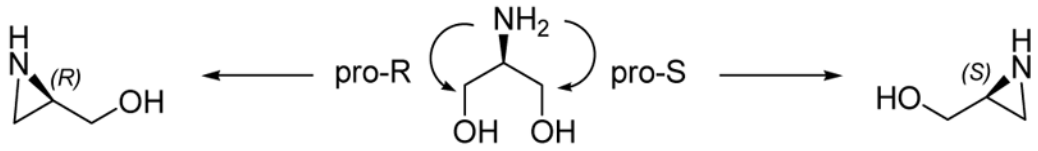
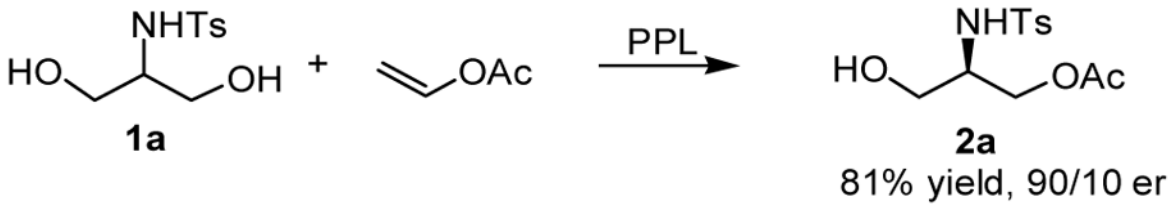


Figure 1.

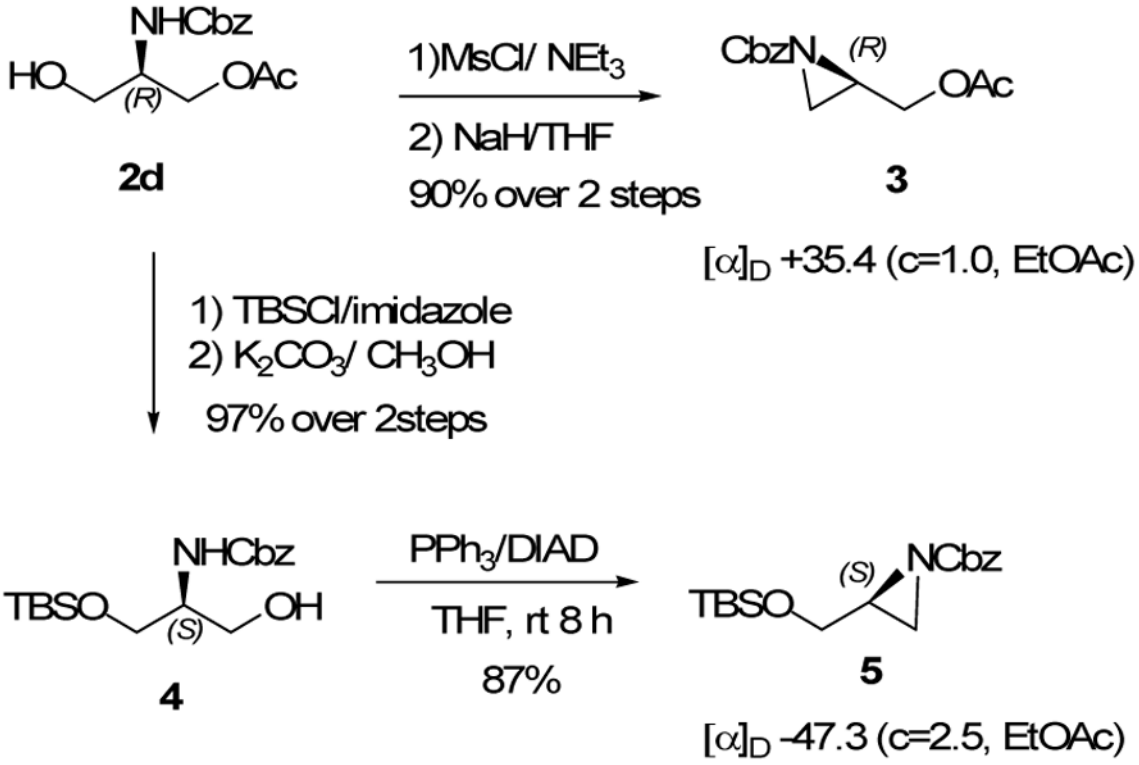
^{1}H NMR experiment: Reaction of **3** with K_2CO_3 in CD_3OD. (1) starting material **3**; (2) 10 min reaction, **3** + cyclic intermediate + acyclic intermediate + benzyl alcohol + product **6**; (3) 50 min reaction, product **6** + benzyl alcohol. See Scheme 4 for resonance letter assignments.



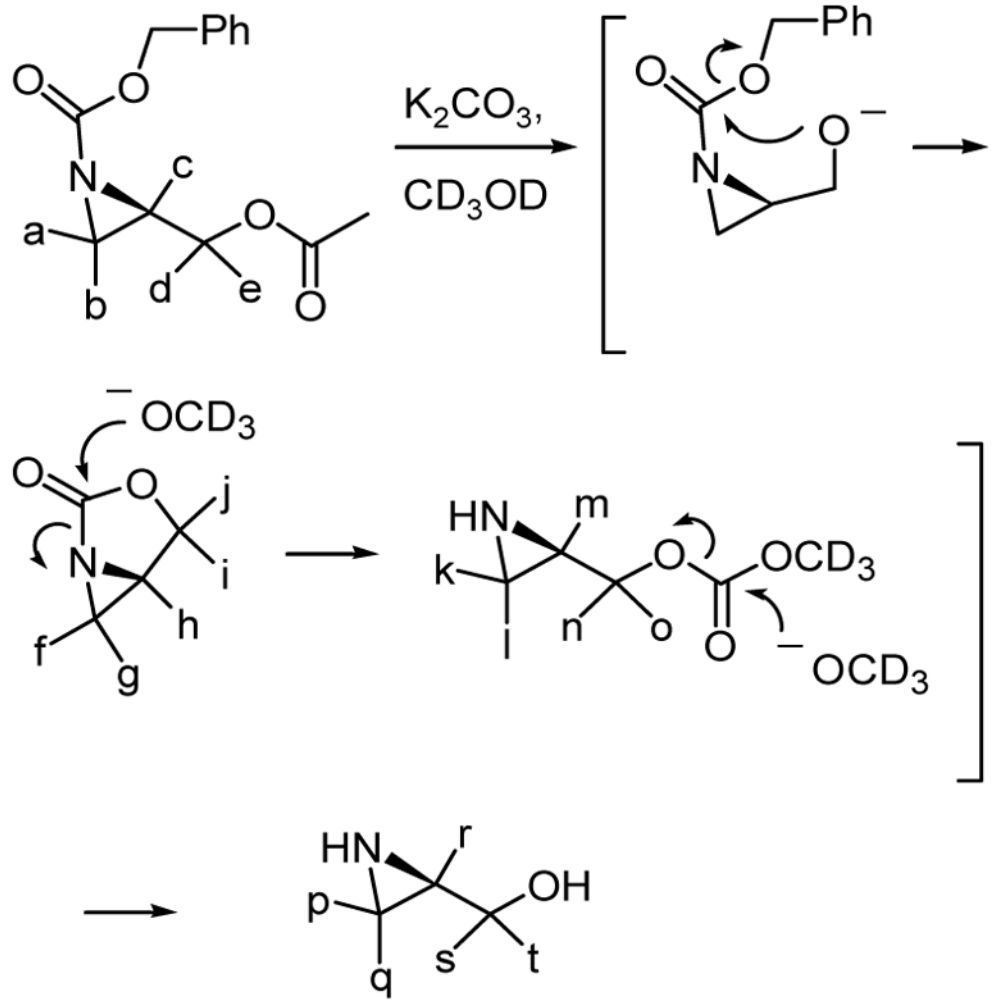
Scheme 1.
Prochirality of Serinol and transformation to aziridine



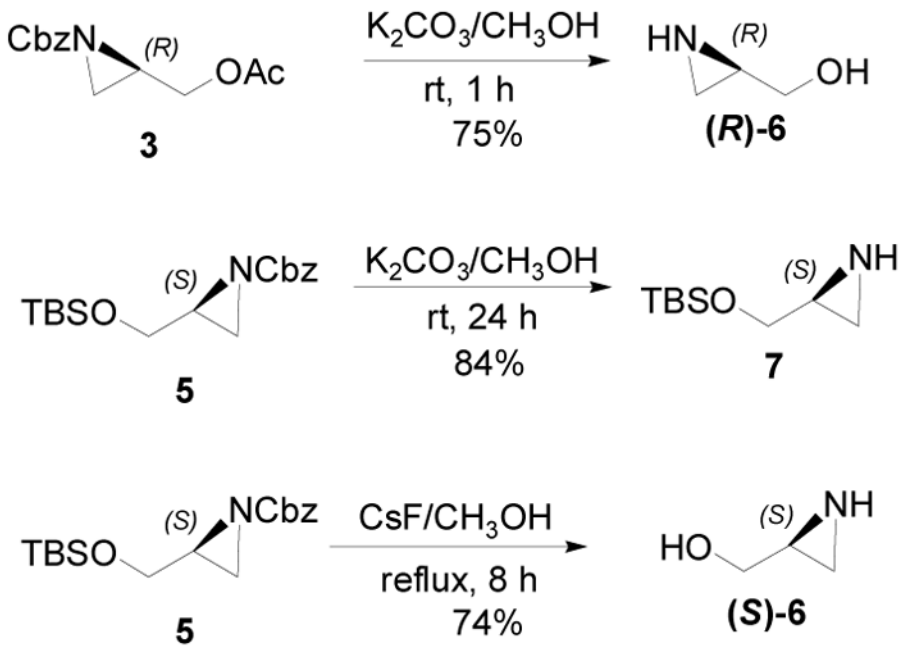
Scheme 2.
Desymmetrization of N-Ts-serinol 1a with PPL.



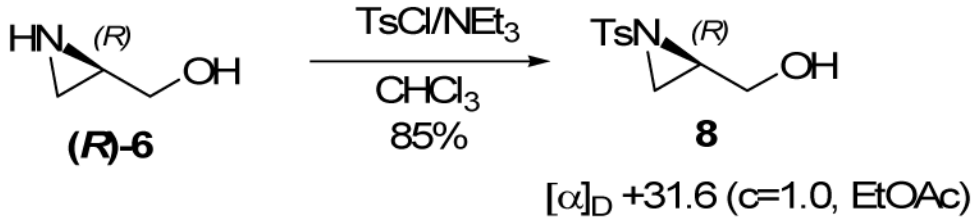
Scheme 3.
Aziridine synthesis from lipase product **2d**.



Scheme 4.
Mechanism of deprotection for Aziridine **3**.



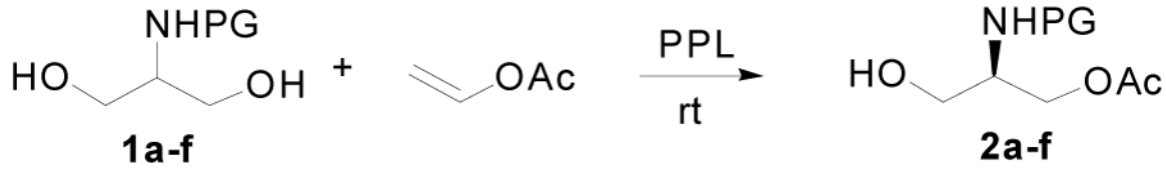
Scheme 5.
Deprotection reactions of Aziridine **3** and **5**.



Scheme 6.
Determination of Absolute Configuration

Table 1

PPL-Catalyzed Desymmetrizations of *N*-Protected Serinol [a]



1a-f **2a-f**

run	PG	VA (mL/mmol)	PPL (mg/mmol)	time (h)	yield (%)[a]	er[b]
1	Ts **1a**	20	300	3	81	90/10
2[d]	Ts **1a**	20	300	1.5	83	91/09
3,[cd]	Ts **1a**	20	300	4.5	80	89/11
4	Mesityl-SO_2 **1b**	20	300	5	75	70/30
5	Fmoc **1c**	20	300	3.5	90	99/01
6	Fmoc **1c**	20	100	8	91	99/01
7	Fmoc **1c**	10	100	9.5	90	99/01
8	Cbz **1d**	20	300	1.5	85	99/01[e]
9	Cbz **1d**	10	100	3	86	99/01[e]
10	Boc **1e**	10	300	1.5	83	99/01[e]
11	Tr **1f**	20	300	11 d	55	50/50
12[d]	Tr **1f**	20	300	6 d	73	50/50

[a] Isolated Yield.

[b] Enatiomeric ratios were determined by chiral HPLC analysis (Chiralcel OD) of the monoacetate.

[c] The reaction was run at 0 °C.

[d] 1 equiv of NEt_3 was used.

[e] Analyzed by chiral HPLC after reacting Mosher reagent with the corresponding monoacetates