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# Lipase-Catalyzed Resolution of (2*R**,3*S**)- and (2*R**,3*R**)-3-Methyl-3-phenyl-2-aziridinemethanol at Low Temperatures and Determination of the Absolute Configurations of the Four Stereoisomers

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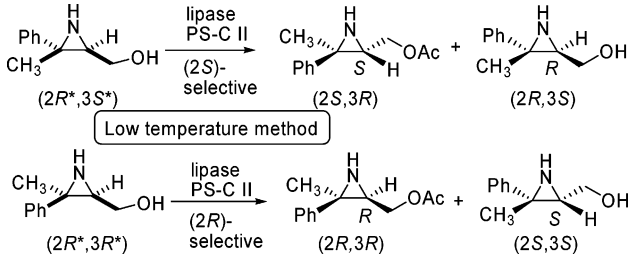


Lipase-catalyzed resolution of (2*R**,3*S**)-3-methyl-3-phenyl-2-aziridinemethanol, (±)-**2**, at low temperatures gave synthetically useful (2*R*,3*S*)-**2** and its acetate (2*S*,3*R*)-**2a** with (2*S*)-selectivity ($E = 55$ at −40 °C), while a similar reaction of (2*R**,3*R**)-3-methyl-3-phenyl-2-aziridinemethanol, (±)-**3**, gave (2*S*,3*S*)-**3** and its acetate (2*R*,3*R*)-**3a** with (2*R*)-selectivity ($E = 73$ at −20 °C). Compound (±)-**2** was prepared conveniently via diastereoselective addition of MeMgBr to *tert*-butyl 3-phenyl-2*H*-azirine-2-carboxylate, (±)-**1a**, which was successfully prepared by the Neber reaction of oxime tosylate of *tert*-butyl benzoyl acetate **7a**. The *tert*-butyl ester was requisite to promote this reaction. For determination of the absolute configuration of (2*S*,3*R*)-**2a**, enantiopure (2*S*,3*R*)-**2** was independently prepared in three steps involving diastereoselective methylation of 3-phenyl-2*H*-azirine-2-methanol, (*S*)-**10**, with MeMgBr. The absolute configuration of (2*S*,3*S*)-**3** was determined by X-ray analysis of the corresponding *N*-(*S*)-2-(6-methoxy-2-naphthyl)propanoyl derivative (*S*,*S*,*S*)-**13**.

## Introduction

Recently, optically active aziridine derivatives have attracted considerable attention because of their versatile synthetic utilities, and a variety of methods for asymmetric syntheses have been reported.[1] Methods for the regio- and stereoselective ring cleavage of the aziridines have been well studied, and are still under active investigation for the syntheses of chiral amines, amino alcohols, amino acids, and so on.[2] Therefore, the development of a convenient synthetic method for optically active aziridine derivatives is an important subject. We have recently reported the "low-temperature method"[3] in the lipase-catalyzed reaction of primary alcohols including azirine derivatives.[3a,e] The method was practically performed with porous ceramic (Toyonite)-immobilized lipase (PS-C II).[3d,e] In this paper, we report (1) new synthetic methods for four stereoisomers of 3-methyl-3-phenyl-2-aziridinemethanol (±)-**2** (2*R**,3*S**) and (±)-**3**

(1) For recent reviews on the synthesis of aziridines, see: (a) Tanner, D. *Angew. Chem., Int. Ed. Engl.* **1994**, *33*, 599−619. (b) Osborn, H. M. I.; Sweeney, J. *Tetrahedron*: *Asymmetry* **1997**, *8*, 1693−1715. (c) Atkinson, R. S. *Tetrahedron* **1999**, *55*, 1519−1559. (d) Rai, K. M. L.; Hassner, A. *Adv. Strained Interesting Org. Mol.* **2000**, *8*, 187−257.

(2) For recent reviews on the reaction of aziridines, see: (a) McCoull, M.; Davis, F. A. *Synthesis* **2000**, 1347−1365. (b) Zwanenburg, B.; ten Holte, P. *Top. Curr. Chem.* **2001**, *216*, 93−124. (c) Cardillo, G.; Gentilucci, L.; Tolomelli, A. *Aldrichim. Acta* **2003**, *36*, 39−50. (d) Hu, X. E. *Tetrahedron* **2004**, *60*, 2701−2743.

(3) (a) Sakai, T.; Kawabata, I.; Kishimoto, T.; Ema, T.; Utaka, M. *J. Org. Chem.* **1997**, *62*, 4906−4907. (b) Sakai, T.; Kishimoto, T.; Tanaka, Y.; Ema, T.; Utaka, M. *Tetrahedron Lett.* **1998**, *39*, 7881−7884. (c) Sakai, T.; Miki, Y.; Tsuboi, M.; Takeuchi, H.; Ema, T.; Uneyama, K.; Utaka, M. *J. Org. Chem.* **2000**, *65*, 2740−2747. (d) Sakai, T.; Hayashi, K.; Yano, F.; Takami, M.; Ino, M.; Korenaga, T.; Ema, T. *Bull. Chem. Soc. Jpn.* **2003**, *76,* 1441−1446. (e) Sakai, T.; Matsuda, A.; Korenaga, T.; Ema, T. *Bull. Chem. Soc. Jpn.* **2003**, *76,* 1819−1821. (f) Sakai, T.; Matsuda, A.; Tanaka, Y.; Korenaga, T.; Ema, T. *Tetrahedron*: *Asymmetry* **2004**, *15*, 1929−1932. (g) Review: Sakai, T. *Tetrahedron*: *Asymmetry* **2004**, *15*, 2749−2756.

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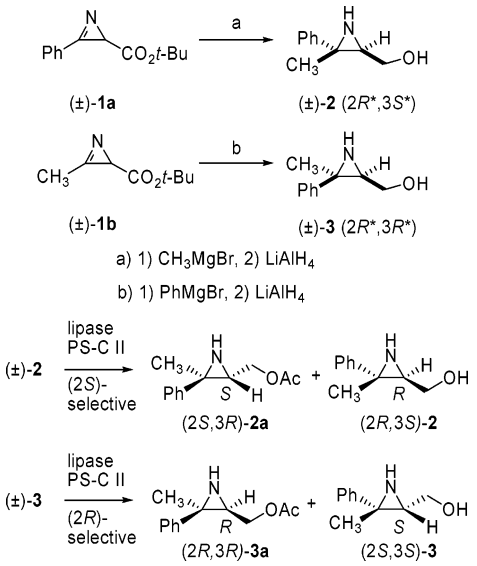
**SCHEME 1. Outline of the Lipase-Catalyzed Resolution of 2-Aziridinemethanols**




(2*R**,3*R**) via the lipase-catalyzed resolution using the low-temperature method and porous ceramic-immobilized lipase PS-C II and (2) an improved method for preparation of *tert*-butyl (±)-3-phenyl-2*H*-azirine-2-carboxylate, (±)-**1a**,[4] an important intermediate for (±)-**2** (Scheme 1). As far as we know, a few examples of the lipase-catalyzed reaction for such 2-aziridinemethanols having two stereogenic centers at $\beta$- and $\gamma$-carbons are known,[5] and none of the reaction with aziridine derivatives without *N*-protection have been reported. Here, we report that the low-temperature method was effective for the resolutions of (±)-**2** and (±)-**3**, and that the lipase showed the opposite stereochemical preferences at the C-2 position of them. The observed temperature effect is also interesting and practically useful for enhancing the enantioselectivity.

## Results and Discussion

**Preparation of 2-Aziridinemethanols (±)-2 and (±)-3.** First, we required a convenient synthetic method for (±)-**1a**, the precursor for (±)-**2**. The synthetic method for the analogous compound, ethyl (±)-3-methyl-2*H*-azirine-2-carboxylate, had been reported via the Neber reaction of ethyl 3-*N*-hydroxyiminobutanoate.[6] However, the corresponding 3-phenyl-substituted derivative could not be prepared by the method, because the precursor, ethyl 3-phenyl-3-(hydroxyimino)propanoate, is known to

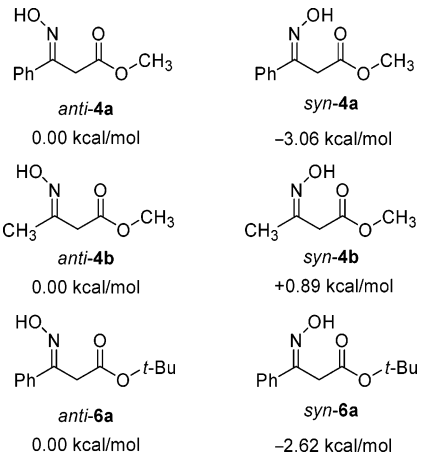



**FIGURE 1.** Calculated relative energy for **4a**, **4b**, and **6a** (syn/anti against ester moiety).

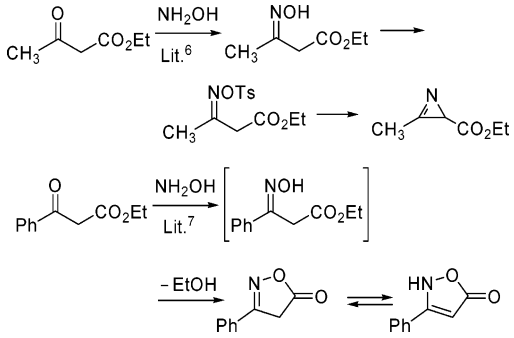
readily cyclize to the corresponding isoxazolone,[7] probably because of the preferential *syn*-hydroxyimino group. In fact, the ab initio calculations at the B3LYP/6-31G*// B3LYP/6-31G* level with ZPE correction by using Gaussian 03W[8,9] performed to study the stability of syn and anti configurations for methyl 3-phenyl-3-(hydroxyimino)-propanoate (**4a**) and methyl 3-(hydroxyimino)butanoate (**4b**) showed that *syn*-**4a** is more stable (3.06 kcal/mol) than *anti*-**4a**, while *anti*-**4b** is more stable (0.89 kcal/mol) than *syn*-**4b** (Figure 1). These results prompted us to reexamine the applicability of the Neber reaction by changing the ester moiety of **4a** to *tert*-butyl ester, which might prevent the intramolecular cyclization. Although

(4) Optically active 3-phenyl-2*H*-azirine-2-carboxylic esters were synthesized by asymmetric syntheses either from *N*-sulfinylaziridine-2-carboxylic ester[4a−c] or from 1*H*-aziridine-2-carboxylic esters:[4d] (a) Davis, F. A.; Liu, H.; Liang, C.-H.; Reddy, G. V.; Zhang, Y.; Fang, T.; Titus, D. D. *J. Org. Chem.* **1999**, *64*, 8929−8935. (b) Davis, F. A.; Liang, C.-H.; Liu, H. *J. Org. Chem.* **1997**, *62*, 3796−3797. (c) Davis, F. A.; Reddy, G. V.; Liu, H. *J. Am. Chem. Soc.* **1995**, *117*, 3651−3652. (d) Gentilucci, L.; Grijzen, Y.; Thijs, L.; Zwanenburg, B. *Tetrahedron Lett.* **1995**, *36*, 4665−4668.

(5) (a) Fuji, K.; Kawabata, T.; Kiryu, Y.; Sugiura, Y. *Tetrahedron Lett.* **1990**, *31*, 6663−6666. (b) Davoli, P.; Prati, F. *Heterocycles* **2000**, *53*, 2379−2389. (c) Davoli, P.; Caselli, E.; Bucciarelli, M.; Forni, A.; Torre, G.; Prati, F. *J. Chem. Soc., Perkin Trans. 1* **2002**, 1948−1953.

(6) Verstappen, M. M. H.; Ariaans, G. J. A.; Zwanenburg, B. *J. Am. Chem. Soc.* **1996**, *118*, 8491−8492.

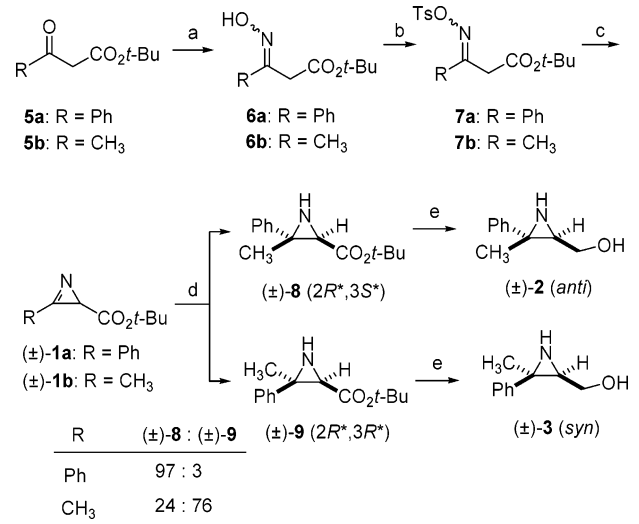
(7) (a) Katritzky, A. R.; Barczynski, P.; Ostercamp, D. L.; Yousaf, T. I. *J. Org. Chem.* **1986**, *51*, 4037−4042. (b) Jacobsen, N.; Kolind-Andersen, H.; Christensen, J. *Can. J. Chem.* **1984**, *62*, 1940−1944.




(8) Frequency calculation performed on optimized structures at the same level produced no imaginary frequencies.

(9) Frisch, M. J.; Trucks, G. W.; Schlegel, H. B.; Scuseria, G. E.; Robb, M. A.; Cheeseman, J. R.; Montgomery, J. A., Jr.; Vreven, T.; Kudin, K. N.; Burant, J. C.; Millam, J. M.; Iyengar, S. S.; Tomasi, J.; Barone, V.; Mennucci, B.; Cossi, M.; Scalmani, G.; Rega, N.; Petersson, G. A.; Nakatsuji, H.; Hada, M.; Ehara, M.; Toyota, K.; Fukuda, R.; Hasegawa, J.; Ishida, M.; Nakajima, T.; Honda, Y.; Kitao, O.; Nakai, H.; Klene, M.; Li, X.; Knox, J. E.; Hratchian, H. P.; Cross, J. B.; Adamo, C.; Jaramillo, J.; Gomperts, R.; Stratmann, R. E.; Yazyev, O.; Austin, A. J.; Cammi, R.; Pomelli, C.; Ochterski, J. W.; Ayala, P. Y.; Morokuma, K.; Voth, G. A.; Salvador, P.; Dannenberg, J. J.; Zakrzewski, V. G.; Dapprich, S.; Daniels, A. D.; Strain, M. C.; Farkas, O.; Malick, D. K.; Rabuck, A. D.; Raghavachari, K.; Foresman, J. B.; Ortiz, J. V.; Cui, Q.; Baboul, A. G.; Clifford, S.; Cioslowski, J.; Stefanov, B. B.; Liu, G.; Liashenko, A.; Piskorz, P.; Komaromi, I.; Martin, R. L.; Fox, D. J.; Keith, T.; Al-Laham, M. A.; Peng, C. Y.; Nanayakkara, A.; Challacombe, M.; Gill, P. M. W.; Johnson, B.; Chen, W.; Wong, M. W.; Gonzalez, C.; Pople, J. A. *Gaussian 03*, Revision B.04; Gaussian, Inc.: Pittsburgh, PA, 2003.

**SCHEME 2. Synthetic Pathways for (±)-2 and (±)-3**[a]




[a] Reagents: (a) $NH_2OH$; (b) TsCl, pyridine; (c) $Et_3N$; (d) MeMgBr or PhMgBr; (e) $LiAlH_4$.

the calculations for the *tert*-butyl esters *anti*-**6a** and *syn*-**6a** also showed the preference for *syn*-**6a**, compound **6a** was actually converted to tosylate **7a** (Scheme 2). These results suggest that the bulkiness of the *tert*-butyl group in **6a** retarded the cyclization as expected.

A reaction of *tert*-butyl benzoyl acetate (**5a**) with 2 equiv of $NH_2OH{\cdot}HCl$ and pyridine gave ketoxime **6a**, which was immediately tosylated (TsCl in pyridine) to afford oxime tosylate **7a** as a single isomer (Scheme 2). The results were quite different from the case with the corresponding ethyl ester.[7] Subsequent treatment of **7a** with 1.1 equiv of $Et_3N$ gave azirine ester (±)-**1a** successfully. The sequential reactions can be carried out in a one-pot procedure in 70% overall yield from **5a**. This is a convenient pathway for the synthesis of (±)-**1a**, which can accept a variety of nucleophiles to its C=N double bond.

We initially intended to perform the enzymatic resolution of **1a**; however, all attempts for its chemical and enzymatic hydrolysis failed. Therefore, (±)-**1a** was transformed into (±)-**2** by diastereoselective methylation[4b] (MeMgBr, ≥94% de) followed by reduction with $LiAlH_4$ in 75% yield, without affecting the aziridine ring. The relative stereochemistry of (±)-**2** was determined by $^{13}C$ NMR. Diastereomeric compound (±)-**3** was prepared from **5b** through **7b** (a syn/anti (32:68) mixture), (±)-**1b**,[6] and (±)-**9** in a similar way (overall 18% yield). However, the step for addition of PhMgBr to (±)-**1b** gave reduced selectivity (76:24) as shown in Scheme 2.

**Lipase-Catalyzed Resolution of (±)-2 and (±)-3.** We next examined the lipase-catalyzed resolution of (±)-**2** and (±)-**3** without the *N*-protecting group, which is usually essential. For example, the resolution of *cis*-3-phenyl-2-aziridinemethanol with lipase PS (vinyl acetate, at 37 °C) was reported to give only racemic acetate and alcohol, while the resolution of its *N*-benzyl-protected derivative gave high enantioselectivity ($E$ > 200) in a shorter reaction time.[5c] On the other hand, *trans*-*N*-benzyl-3-phenyl-2-aziridinemethanol gave an $E$ value of less than 2.[5c] These results suggested that both the cis/trans stereochemistry and the *N*-substituent moiety on the aziridine ring highly influence the resolution efficiency.

We first examined the resolution of (±)-**2** with lipase PS (immobilized on Celite) and vinyl acetate (1 equiv) in ether at 30 °C; however, the $E$ value[10] was only 7.2, and it took as long as 3 h to reach 26% conversion. The slow reaction rate suggested that further lowering the temperature seemed to be impractical. We then examined lipase PS-C II [lipase PS immobilized on a porous ceramic support (Toyonite)], whose high acceleration ability has been demonstrated by our recent studies.[3c−e,11] Results for the resolution of (±)-**2** are summarized in Table 1 and Figure 2. The reaction with lipase PS-C II at 25 °C in ether (entry 2) gave a higher conversion of 0.52 in only 0.4 h together with a slightly increased $E$ value of 9.3 as compared with those obtained with lipase PS on Celite (entry 1). To further improve the $E$ value in ether, temperature modulation was then attempted. The results in Table 1 show that the $E$ value was found to increase up to 19 by lowering the temperature to −20 °C (entry 4). However, further lowering the temperature rather decreased it to 7.3 (entry 6). Figure 2 shows that a linear correlation was observed between ln $E$ vs $1/T$, obeying Eyring's equation.[12] The temperature (−20 °C) is called the inversion temperature ($T_{inv}$), at which the two lines intersect.[13] The reaction in acetone gave higher enantioselectivity, and the best result ($E$ = 55) was obtained at −40 °C (entry 9). However, further lowering the temperature to −50 °C did not increase the $E$ value. Replacing the acylating agent with vinyl butyrate was not effective to improve the $E$ value (entry 10), although the enantioselectivity for 3-phenyl-2*H*-azirine-2-methanol[3e] had been improved by changing the acylating agent (vinyl butyrate). In contrast, the temperature modulation in THF increased the $E$ value continuously to −60 °C (entries 12−15). These results show that lipase PS-C II made it possible to carry out the low-temperature reaction practically for obtaining high enantioselectivity.

The resolution of compound (±)-**3** was carried out in a similar way in acetone, the best solvent for (±)-**2**. As shown in Table 2, the resolution was first examined with lipase PS (immobilized on Celite) and vinyl acetate at 30 °C and gave the $E$ value of 9.4 (entry 1) with a slow reaction rate (24 h for 11% conversion). The enantioselectivity was also optimized by using lipase PS-C II and lowering the reaction temperature. The plot of ln $E$ vs $1/T$ for this reaction is shown in Figure 3. The $E$ value was increased up to 73 by lowering the temperature to −20 °C, which is the $T_{inv}$ value. Noteworthy is that the (2*R*)-enantiomer for compound **3** reacted faster than the (2*S*)-**3**, while the (2*R*)-enantiomer for compound **2** reacted slower than the (2*S*)-**2**. In general, the stereopreference

(10) Chen, C.-S.; Fujimoto, Y.; Girdaukas, G.; Sih, C. J. *J. Am. Chem. Soc.* **1982**, *104*, 7294−7299.

(11) We have recently reported that lipase PS-C II is also usable at high temperature up to 120 °C and that it is effectively applicable to a bulky substrate: Ema, T.; Kageyama, M.; Korenaga, T.; Sakai, T. *Tetrahedron*: *Asymmetry* **2003**, *14*, 3943−3947.

(12) Phillips, R. S. *Trends Biotechnol.* **1996**, *14*, 13−16.

(13) Cainelli, G.; de Mattesis, V.; Galleti, P.; Giacomini, D. *Chem. Commun.* **2000**, 2351−2352.

**TABLE 1. Lipase PS-C II-Catalyzed Resolution of 2-Aziridinemethanol (±)-2 at Low Temperatures**

| entry[a] | solvent (5 mL) | lipase (mg) | vinyl acetate[b] | temp (°C) | alcohol % ee[c] | ester % ee[c] | time (h) | conv[d,e] | $E$[e] |
|---|---|---|---|---|---|---|---|---|---|
| 1 | $Et_2O$ | 50[f] | 1 | 30 | 25 | 70 | 3.0 | 0.26 | 7.2 |
| 2 | $Et_2O$ | 50 | 1 | 25 | 70 | 66 | 0.4 | 0.52 | 9.3 |
| 3 | $Et_2O$ | 50 | 1 | 0 | 72 | 72 | 0.8 | 0.50 | 13 |
| 4 | $Et_2O$ | 50 | 1 | −20 | 55 | 84 | 2.5 | 0.40 | 19 |
| 5 | $Et_2O$ | 50 | 1 | −30 | 25 | 78 | 3.5 | 0.24 | 10 |
| 6 | $Et_2O$ | 200 | 2 | −40 | 49 | 64 | 5.0 | 0.43 | 7.3 |
| 7 | acetone | 50 | 1 | 0 | 70 | 83 | 3.0 | 0.46 | 22 |
| 8 | acetone | 200 | 2 | −20 | 84 | 85 | 3.5 | 0.50 | 32 |
| 9 | acetone | 300 | 2 | −40 | 77 | 92 | 15 | 0.46 | 55 |
| 10 | acetone | 300 | 2[g] | −40 | 87[h] | 90[i] | 17 | 0.49 | 53 |
| 11 | acetone | 300 | 2 | −50 | 53 | 94 | 17 | 0.36 | 54 |
| 12 | THF | 50 | 1 | 0 | 69 | 82 | 2.0 | 0.46 | 20 |
| 13 | THF | 50 | 1 | −20 | 89 | 77 | 7.8 | 0.54 | 22 |
| 14 | THF | 300 | 2 | −40 | 85 | 83 | 5.0 | 0.51 | 28 |
| 15 | THF | 300 | 2 | −60 | 78 | 87 | 24 | 0.47 | 33 |

[a] In all entries, (±)-**2** (50 mg, 0.31 mmol) was used. [b] Molar equivalent. [c] Determined by GC analysis. [d] Conversion calculated from $c$ = ee (substrate)/(ee (product) + ee (substrate)). [e] Reference 10. [f] Lipase PS on Celite. [g] Vinyl butyrate. [h] $[\alpha]^{21}_D$ −31.3 ($c$ 0.75, $CHCl_3$). [i] Butanoate (2*S*,3*R*)-**2b**.

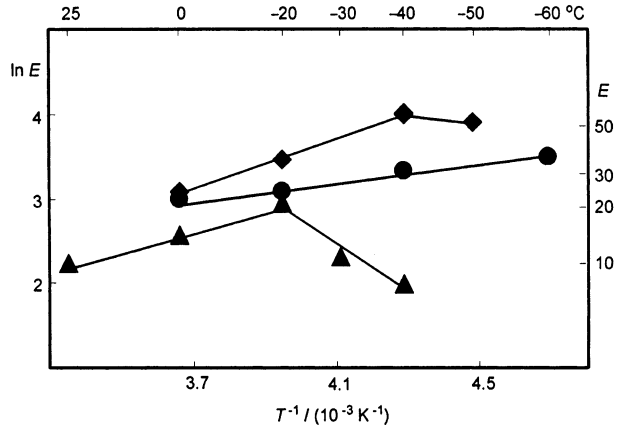



**FIGURE 2.** Temperature effect in the lipase-catalyzed resolution of (±)-**2**: ◆, in acetone; ●, in THF; ▲, in $Et_2O$.

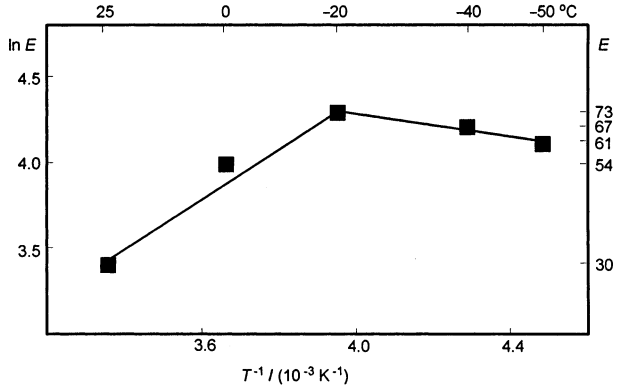



**FIGURE 3.** Temperature effect in the lipase-catalyzed resolution of (±)-**3** in acetone.

**TABLE 2. Lipase PS-C II-Catalyzed Resolution of 2-Aziridinemethanol (±)-3 in Acetone**

| entry[a] | lipase (mg) | vinyl acetate[b] | temp (°C) | alcohol % ee[c] | ester % ee[d] | time (h) | conv[e,f] | $E$[f] |
|---|---|---|---|---|---|---|---|---|
| 1 | 50[g] | 1 | 30 | 10 | 79 | 24 | 0.11 | 9.4 |
| 2 | 50 | 1 | 25 | 38 | 91 | 3.0 | 0.29 | 30 |
| 3 | 50 | 1 | 0 | 65 | 93 | 12 | 0.41 | 54 |
| 4 | 50 | 1 | −20 | 41 | 96 | 29 | 0.30 | 73 |
| 5 | 300 | 5 | −40 | 54 | 95 | 15 | 0.36 | 67 |
| 6 | 300 | 5 | −50 | 23 | 96 | 24 | 0.19 | 61 |

[a] In all entries, (±)-**3** (50 mg, 0.31 mmol) was used. [b] Molar equivalent. [c] Determined by HPLC analysis. [d] Determined by GC analysis. [e] Conversion calculated from $c$ = ee (substrate)/(ee (product) + ee (substrate)). [f] Reference 10. [g] Lipase PS on Celite.

in the lipase-catalyzed resolution of primary alcohols[3,14] is not clear in contrast with that for secondary ones.[15] The present results suggest that the C-3 position (3*R*) has the priority in the stereorecognition, whereas the C-2 stereogenic center is not critical. Similar results are reported in the resolution of (2-fluoro-2-phenylcyclopropyl)methanol,[16] in which (2*S*)-enantiomers reacted faster than (2*R*)-ones, while the C-1 stereogenic center, adjacent to the alcohol moiety, does not affect the enantiopreference. Accumulation of these examples would be useful for prediction of the enantioselectivity.

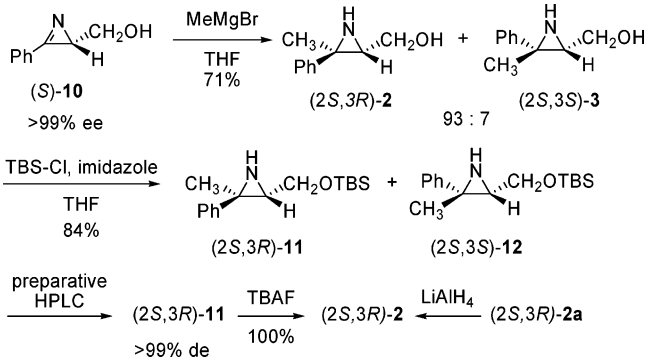
**Absolute Configurations of (2*S*,3*R*)-2a and (2*S*,3*S*)-3.** Compound (2*S*,3*R*)-**2a** in Scheme 1 was converted to the corresponding alcohol (2*S*,3*R*)-**2**, the absolute configuration of which was determined by comparison of its specific rotation [$[\alpha]^{26}_D$ +49.9 ($c$ 1.1, $CHCl_3$)] with that prepared from optically pure azirine-2-methanol (*S*)-**10**[3a] as shown in Scheme 3. The starting compound (*S*)-**10** was prepared by the previous method in five steps from cinnamyl alcohol involving the lipase-catalyzed resolution at low temperatures (−40 °C) in the final step.[3a,e] Addition of MeMgBr to (*S*)-**10** at room temperature in THF gave a 93:7 inseparable mixture of (2*S*,3*R*)-**2** and (2*S*,3*S*)-**3** as a result of coordination control. The minor compound (2*S*,3*S*)-**3** could not be removed at this stage. The diastereoselectivity was much improved here by the temper-

(14) For recent examples: (a) Itoh, T.; Kawai, K.; Hayase, S.; Ohara, H. *Tetrahedron Lett.* **2003**, *44*, 4081−4084. (b) Kurokawa, M.; Shindo, T.; Suzuki, M.; Nakajima, N.; Ishihara, K.; Sugai, T. *Tetrahedron*: *Asymmetry* **2003**, *14*, 1323−1333. (c) Murakami, M.; Kamaya, H.; Kaneko, C.; Sato, M. *Tetrahedron*: *Asymmetry* **2003**, *14*, 201−215. (d) de Gonzalo, G.; Brieva, R.; Sánchez, V. M.; Bayod, M.; Gotor, V. *J. Org. Chem.* **2003**, *68*, 3333−3336.

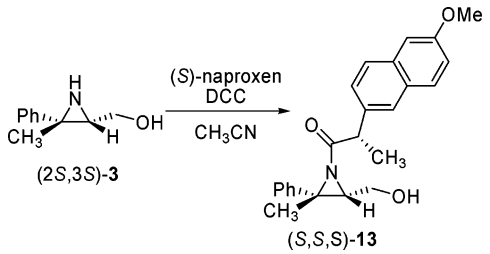
(15) Review: Ema, T. *Curr. Org. Chem.* **2004**, *8*, 1009−1025.

(16) Rosen, T. C.; Haufe, G. *Tetrahedron*: *Asymmetry* **2002**, *13*, 1397−1405.

**SCHEME 3. Preparation of 2-Aziridinemethanol (2*S*,3*R*)-2 as Reference**




**SCHEME 4. Preparation of (*S*,*S*,*S*)-13**




ature control and choice of solvent as compared with the results reported by Laurent et al.,[17] who observed a low diastereoselectivity of 56:44 in 70% yield in a similar reaction but at a reflux temperature in toluene. The mixture of (2*S*,3*R*)-**2** and (2*S*,3*S*)-**3** was once transformed into the corresponding TBS ethers (2*S*,3*R*)-**11** and (2*S*,3*S*)-**12**, which were separated by a preparative HPLC, and deprotected (TBAF) to give pure (2*S*,3*R*)-**2** [$[\alpha]^{21}_{D}$ +49.7 (*c* 1.86, $CHCl_3$)]. The absolute configuration of (2*S*,3*R*)-**2a** was thus determined by comparison of the specific rotation after conversion to (2*S*,3*R*)-**2**.

On the other hand, the absolute configuration of (2*S*,3*S*)-**3** was determined by X-ray analysis[18] of the corresponding *N*-(*S*)-2-(6-methoxy-2-naphthyl)propanoyl derivative (*S*,*S*,*S*)-**13**, which was prepared by the reaction of (2*S*,3*S*)-**3** with (*S*)-2-(6-methoxy-2-naphthyl)propanoic acid in the presence of DCC (Scheme 4). X-ray structure shows that the reaction occurred exclusively at the aziridine nitrogen atom, while the hydroxyl group and the aziridine three-membered ring remained intact. The bulky naphthyl moiety is fixed anti to the phenyl and methyl groups on the aziridine ring. The hydroxyl group is weakly hydrogen bonded with the oxygen atom of the carbonyl group of the adjacent **13** intermolecularly.

## Conclusions

We obtained and assigned the absolute configurations of four stereoisomers of 3-methyl-3-phenyl-2-aziridinemethanol, which were prepared by the Neber reaction followed by the lipase-catalyzed resolution at low temperatures. Use of lipase PS-C II enabled us to carry out the acylation reaction of the aziridine derivatives without *N*-protection. The low-temperature method in the lipase-catalyzed reaction was proved to be effective for primary aziridine alcohols **2** and **3**. Although (2*S*,3*R*)-**2** was prepared independently from (*S*)-**10** for assignment of the absolute configuration, the method via the Neber reaction is a shorter and more convenient synthetic pathway with high diastereoselectivity. The regio- and stereoselective cleavage of the aziridine skeleton is also under investigation.

## Experimental Section

***tert*-Butyl 3-Phenyl-2*H*-azirine-2-carboxylate [(±)-1a].** To a solution of $NH_2OH{\cdot}HCl$ (0.28 g, 4.0 mmol) in pyridine (2 mL) was added *tert*-butyl benzoyl acetate (**5a**) (0.44 g, 2.0 mmol) dropwise. After the solution was stirred for 14 h, a usual workup gave *tert*-butyl 3-phenyl-3-(hydroxyimino)propanoate (**6a**) as a crude product, to which was added TsCl (0.45 g, 2.4 mmol) and pyridine (2 mL). After the solution was stirred for 3 h, toluene was added, and the mixture was filtered under nitrogen atmosphere to give oxime tosylate **7a** as a single isomer: colorless solid, mp 80−81 °C. IR (KBr) 1724 (C=O), 1303, 1120 (S=O) $cm^{-1}$. $^1H$ NMR ($CDCl_3$) $\delta$ 7.93−7.89 (d, 2H, $J$ = 8.2 Hz), 7.56−7.52 (m, 2H), 7.43−7.32 (m, 5H), 3.76 (s, 2H), 2.43 (s, 3H), 1.35 (s, 9H). $^{13}C$ NMR ($CDCl_3$) $\delta$ 165.9, 159.9, 145.0, 132.9, 132.4, 130.9, 129.5, 128.8, 128.6, 127.0, 82.3, 35.6, 27.7, 21.7. Anal. Calcd for $C_{20}H_{23}NO_5S$: C, 61.68; H, 5.95; N, 3.60. Found: C, 61.44; H, 6.02; N, 3.21. To the obtained **7a** was added $Et_3N$ (0.40 g, 4.0 mmol) dropwise at 0 °C, and the mixture was stirred at room temperature for 6.5 h. The usual workup gave a crude product (±)-**1a**, which was purified by column chromatography (hexane/EtOAc = 4/1) to afford 0.31 g of **1a** (70% yield from keto ester **5a**): colorless solid, mp 71−72 °C. IR (KBr) 1770 (C=N), 1724 (C=O) $cm^{-1}$. $^1H$ NMR ($CDCl_3$) $\delta$ 7.90−7.85 (m, 2H), 7.63−7.56 (m, 3H), 2.75 (s, 1H), 1.46 (s, 9H). $^{13}C$ NMR ($CDCl_3$) $\delta$ 170.8, 158.8, 133.6, 130.2, 129.4, 129.2, 122.5, 81.6, 30.6, 28.1. These spectral data are consistent with those reported.[4b]

***tert*-Butyl 3-Methyl-3-phenylaziridine-2-carboxylate** [(±)-**8**] was prepared by the diastereoselective methylation of azirine-2-carboxylate **1a** with MeMgBr in a similar way to the reported procedure.[4b] A solution of azirine ester (±)-**1a** (0.22 g, 1.0 mmol) in THF (5 mL) was cooled to −78 °C and MeMgBr (3.8 mL, 3.45 mmol, 0.93 M in THF) was added dropwise. The mixture was stirred at −78 °C for 1.5 h, warmed to −15 °C, and then stirred for an additional 20 min. The reaction was quenched with $H_2O$ (1 mL) at −78 °C, diluted with EtOAc (50 mL), warmed to room temperature, and then filtered. The filtrate was evaporated under reduced pressure to give a crude product, which was purified by column chromatography (hexane/EtOAc = 4/1) to give 0.15 g of (±)-**8** (65%). The percent de value was determined to be higher than 94% by the $^1H$ NMR analysis of the aziridine ring proton. Compound (±)-**8**: IR (film) 3274 (N−H), 1720 (C=O), 1602 (N−H) $cm^{-1}$. $^1H$ NMR ($CDCl_3$) $\delta$ 7.46−7.28 (m, 5H), 2.59 (s, 1H), 1.69 (s, 3H), 1.53 (s, 9H). $^{13}C$ NMR ($CDCl_3$) $\delta$ 169.3, 142.9, 128.2, 127.0, 126.0, 82.0, 45.0, 43.1, 28.2, 18.4.

**3-Methyl-3-phenyl-2-aziridinemethanol [(±)-2].** A solution of *tert*-butyl ester of aziridine carboxylate (±)-**8** (0.93 g, 4.0 mmol) in $Et_2O$ (10 mL) was added dropwise to a suspension of $LiAlH_4$ (0.30 g, 8.0 mmol) in $Et_2O$ (5 mL) at 0 °C. The mixture was stirred at 0 °C for 0.5 h and then at room temperature for 9 h. The usual workup gave a crude product, which was purified by recrystallization from $Et_2O$ to give 0.49 g of (±)-**2** as a white solid in 75% yield. The percent de value was higher than 99% as determined by $^1H$ NMR analysis. The relative stereochemistry was determined by

(17) Laurent, A.; Marsura, A.; Pierre, J.-L. *J. Heterocycl. Chem.* **1980**, *17*, 1009−1017.

(18) The single-crystal growth for (*S*,*S*,*S*)-**13** was carried out in *i*-$Pr_2O$ at room temperature. $C_{24}H_{25}NO_3$, Fw = 375.47, orthorhombic, space group $P2_12_12_1$, $a$ = 6.102(2) Å, $b$ = 9.911(4) Å, $c$ = 30.75(1) Å, $V$ = 1859(1) Å$^3$, $T$ = 150.2 K, $Z$ = 4, $D_{calc}$ = 1.341 g $cm^{-3}$, $R$ = 0.069 for 2615 observed reflections [$I > 2.00\sigma(I)$] and 329 variable parameters. All measurements were made on a Rigaku RAXIS-IV imaging plate area detector with Mo Kα radiation. Crystallographic data for the structure reported in this paper have been deposited with the Cambridge Crystallographic Data Center as supplementary publication no. CCDC-255492.

comparison of the $^{13}C$ NMR data with those reported.[17] (2*R**,3*S**)-(±)-**2**: mp 72−73 °C (lit.[17] mp 74−76 °C). IR (KBr) 3240 (N−H), 2818 (O−H) $cm^{-1}$. $^1H$ NMR ($CDCl_3$) $\delta$ 7.34−7.24 (m, 5H), 3.92 (dd, 1H, $J$ = 5.5, 11.7 Hz), 3.74 (dd, 1H, $J$ = 6.6, 11.7 Hz), 2.52 (dd, 1H, $J$ = 5.5, 6.6 Hz), 1.85 (br s, 2H), 1.54 (s, 3H). $^{13}C$ NMR ($CDCl_3$) $\delta$ 144.5, 128.5, 127.1, 125.9, 61.3, 44.0, 42.3, 20.1.

***tert*-Butyl 3-Methyl-2*H*-azirine-2-carboxylate** [(±)-**1b**] was prepared from *tert*-butyl acetoacetate (**5b**) in a similar way to the reported procedure.[6] β-Keto ester **5b** (3.16 g, 20 mmol) was added to a solution of $NH_2OH{\cdot}HCl$ (1.53 g, 22 mmol) and $NaHCO_3$ (1.85 g, 22 mmol) in aqueous MeOH. After the mixture was stirred at room temperature for 1 h, a usual workup gave an oily crude product **6b**, which was dissolved in $CH_2Cl_2$ (10 mL). A solution of TsCl (3.81 g, 20 mmol) and pyridine (1.58 g, 20 mmol) in $CH_2Cl_2$ (10 mL) was added, and the mixture was stirred for 3 h. Usual workup and purification by column chromatography (EtOAc/hexane = 4/1) gave **7b** (5.06 g, 77%) as a mixture of syn/anti isomers (32/68 by NMR). The stereochemistry of syn and anti isomers was not assigned spectroscopically.[6] The major isomer was isolated by recrystallization from $Et_2O$ for analysis. Oxime tosylate **7b**: major, white solid, mp 93−95 °C. IR (KBr) 1720 (C=O), 1355, 1157 (S=O) $cm^{-1}$. $^1H$ NMR ($CDCl_3$) $\delta$ 7.84 (d, 2H, $J$ = 8.2 Hz), 7.32 (d, $J$ = 8.2 Hz), 3.16 (s, 2H), 2.43 (s, 3H), 2.03 (s, 3H), 1.39 (s, 9H). $^{13}C$ NMR ($CDCl_3$) $\delta$ 166.7, 162.0, 144.8, 132.4, 129.4, 128.5, 82.0, 41.8, 27.7, 21.5, 15.8. Minor: $^1H$ NMR ($CDCl_3$) $\delta$ 7.84 (d, 2H, $J$ = 8.2 Hz), 7.32 (d, $J$ = 8.2 Hz), 3.34 (s, 2H), 2.43 (s, 3H), 2.00 (s, 3H), 1.43 (s, 9H).

To a solution of tosylate **7b** (2.94 g, 8.98 mmol) in $CH_2Cl_2$ (20 mL) was added $Et_3N$ (1.00 g, 9.87 mmol) dropwise with ice cooling. After the mixture was stirred at room temperature for 6.5 h, the usual workup gave an oily crude product, which was purified by bulb-to-bulb distillation (100−110 °C (4 mmHg); lit.[6] 110 °C (0.5 mmHg)) to give 0.92 g (66%) of (±)-**1b** as a colorless oil. Azirine ester **1b**: IR (film): 1801 (C=N), 1732 (C=O) $cm^{-1}$. $^1H$ NMR ($CDCl_3$) $\delta$ 2.50 (s, 3H), 2.34 (s, 1H), 1.45 (s, 9H). $^{13}C$ NMR ($CDCl_3$) $\delta$ 171.1, 159.3, 81.4, 29.7, 28.1, 12.6.

***tert*-Butyl (2*R**,3*R**)-3-Methyl-3-phenylaziridine-2-carboxylate [(±)-9].** A solution of azirine ester **1b** (1.29 g, 8.31 mmol) in THF (30 mL) was cooled to −80 °C, and a THF solution of PhMgBr [magnesium turning (0.81 g, 33.25 mmol), bromobenzene (5.22 g, 33.25 mmol), and 50 mL of THF] was added dropwise through a dropping funnel. After the mixture was stirred at −80 °C for 1 h, the reaction was quenched with $H_2O$ (2 mL) at −80 °C. A usual workup gave crude products (isomeric ratio of 76/24 by $^1H$ NMR), which were separated by column chromatography (hexane/EtOAc = 4/1) to give the major (0.93 g, 48%) and minor products (0.32 g, 17%).

Major product: (±)-**9**, colorless oil, $R_f$ 0.30 (hexane/EtOAc = 2/1). IR (film) 3240 (N−H), 1716 (C=O), 1610 (N−H) $cm^{-1}$. $^1H$ NMR ($CDCl_3$) $\delta$ 7.32−7.23 (m, 5H), 2.67 (s, 1H), 1.70 (br s, 1H), 1.56 (s, 3H), 1.19 (s, 9H). $^{13}C$ NMR ($CDCl_3$) $\delta$ 167.7, 139.5, 127.6, 126.8, 126.7, 80.9, 45.5, 43.2, 27.2, 27.0. Anal. Calcd for $C_{14}H_{19}NO_2$: C, 72.07; H, 8.21; N, 6.00. Found: C, 72.35; H, 8.12; N, 6.11.

Minor product: (±)-**8**,[4b] $R_f$ 0.60 (hexane/EtOAc = 2/1).

**3-Methyl-3-phenyl-2-aziridinemethanol** [(±)-**3**] was prepared in 72% yield and >99% de ($^1H$ NMR) by a similar procedure to that for (±)-**2**. (±)-**3**: mp 102−103 °C. IR (KBr) 3251 (N−H), 2821 (O−H), 1603 (N−H) $cm^{-1}$. $^1H$ NMR ($CDCl_3$) $\delta$ 7.42−7.23 (m, 5H), 3.38 (dd, 1H, $J$ = 5.6, 11.7 Hz), 3.11 (1H, dd, $J$ = 7.0, 11.7 Hz), 2.47 (dd, $J$ = 5.6, 7.0 Hz), 1.64 (s, 3H), 1.47 (br s, 2H). $^{13}C$ NMR ($CDCl_3$) $\delta$ 140.4, 128.2, 127.4, 126.9, 62.5, 44.6, 43.0, 28.0. The $^{13}C$ NMR spectral data are consistent with those reported.[17]

**General Procedure for the Lipase-Catalyzed Resolution of (±)-2.** To a mixture of (±)-**2** (50 mg, 0.30 mmol) and lipase PS or PS-C II in an organic solvent (5 mL) was added vinyl acetate at the temperature indicated in Table 1. The suspension was vigorously stirred, and the reaction progress was monitored by TLC. The lipase was removed by filtration through Celite pad quickly, and the filtrate was concentrated under reduced pressure. The products were separated by column chromatography (EtOAc), and the enantiomeric purities of both **2** and **2a** were determined by capillary GC, using a CP-cyclodextrin-β-2,3,6-M-19 column (Chrompack, Φ 0.25 mm × 25 m, oven temperature 130 °C): retention time = 56.9 min for (2*S*,3*R*)-**2**, 59.1 min for (2*R*,3*S*)-**2**, 61.3 min for (2*R*,3*S*)-**2a**, and 63.8 min for (2*S*,3*R*)-**2a**.

(2*S*,3*R*)-**2a**: colorless oil. IR (film) 3295 (N−H), 1731 (C=O), 1603 (N−H) $cm^{-1}$. $^1H$ NMR ($CDCl_3$) $\delta$ 7.33−7.24 (m, 5H), 4.26 (d, 2H, $J$ = 6.6 Hz), 2.48 (t, 1H, $J$ = 6.6 Hz), 2.11 (s, 3H), 1.55 (s, 3H). $^{13}C$ NMR ($CDCl_3$) $\delta$ 170.9, 144.3, 128.5, 127.1, 125.9, 64.5, 41.6, 40.7, 20.9, 20.3. $[\alpha]^{29}_D$ +23.8 (*c* 0.33, $CHCl_3$), 70% ee. Anal. Calcd for $C_{12}H_{15}NO_2$: C, 70.22; H, 7.37; N, 6.82. Found: C, 70.08; H, 7.36; N, 7.08.

(2*R*,3*S*)-**2**: colorless oil. $[\alpha]^{21}_D$ −31.3 (*c* 0.75, $CHCl_3$), 87% ee.

**Butanoate of 3-Methyl-3-phenyl-2-aziridinemethanol (2*S*,3*R*)-2b (Table 1, entry 10):** colorless oil. IR (film) 3242 (N−H), 1735 (C=O), 1602 (N−H) $cm^{-1}$. $^1H$ NMR ($CDCl_3$) $\delta$ 7.34−7.22 (m, 5H), 4.32 (dd, 1H, $J$ = 6.6, 11.8 Hz), 4.24 (dd, 1H, $J$ = 6.6, 11.8 Hz), 3.47 (br s, 1H), 2.50 (t, 1H, $J$ = 6.6 Hz), 2.36 (t, 2H, $J$ = 7.4 Hz), 1.78−1.60 (m, 2H), 1.56 (s, 3H), 0.93 (t, 3H, $J$ = 7.4 Hz). $^{13}C$ NMR ($CDCl_3$) $\delta$ 173.6, 144.4, 128.5, 127.1, 126.0, 64.3, 41.7, 40.8, 36.2, 20.4, 18.5, 13.7. Anal. Calcd for $C_{14}H_{19}NO_2$: C, 72.07; H, 8.21; N, 6.00. Found: C, 72.32; H, 8.26; N, 5.65. GC analysis (oven temperature 150 °C, retention time of the butanoate: 69.2 min for (2*R*,3*S*) and 71.3 min for (2*S*,3*R*). $[\alpha]^{21}_D$ +31.8 (*c* 0.75, $CHCl_3$), 90% ee.

**General Procedure for the Lipase-Catalyzed Resolution of (±)-3.** To a mixture of (±)-**3** (50 mg, 0.30 mmol) and lipase PS or PS-C II in acetone (5 mL) was added vinyl acetate at the temperature indicated in Table 2. The resulting suspension was vigorously stirred, and the reaction progress was monitored by TLC. After workup in a usual manner, the percent ee value of (2*R*,3*R*)-**3a** was determined by capillary GC using a CP-cyclodextrin-β-2,3,6-M-19 column (Chrompack, Φ 0.25 mm × 25 m, oven temperature 130 °C): retention time = 47.6 min for (2*S*,3*S*)-**3a** and 49.4 min for (2*R*,3*R*)-**3a**. The enantiomeric purity of (2*S*,3*S*)-**3** was determined by HPLC using a Chiralpak AD-H column (hexane/*i*-PrOH = 9/1, flow rate 1.0 mL/min, detection 254 nm), 8.3 min for (2*S*,3*S*)-**3** and 9.7 min for (2*R*,3*R*)-**3**).

(2*S*,3*S*)-**3**: white solid, mp 107−108 °C. $[\alpha]^{26}_D$ +89.8 (*c* 1.10, $CHCl_3$), 99% ee.

(2*R*,3*R*)-**3a**: colorless oil. IR (film) 3305 (N−H), 1732 (C=O), 1604 (N−H) $cm^{-1}$. $^1H$ NMR ($CDCl_3$) $\delta$ 7.41−7.23 (m, 5H), 3.86 (dd, 1H, $J$ = 5.4, 11.8 Hz), 3.49 (dd, 1H, $J$ = 7.4, 11.8 Hz), 2.49 (dd, 1H, $J$ = 5.4, 7.4 Hz), 2.03 (s, 3H), 1.64 (s, 3H). $^{13}C$ NMR ($CDCl_3$) $\delta$ 170.9, 140.1, 128.3, 127.5, 127.1, 65.4, 42.5, 41.0, 28.0, 20.9. Anal. Calcd for $C_{12}H_{15}NO_2$: C, 70.22; H, 7.37; N, 6.82. Found: C, 70.06; H, 7.51; N, 6.82. $[\alpha]^{26}_D$ −31.5 (*c* 0.98, $CHCl_3$), 94% ee.

**(2*S*,3*R*)-3-Methyl-3-phenyl-2-aziridinemethanol [(2*S*,3*R*)-2] from 3-Phenyl-2*H*-azirine-2-methanol [(*S*)-10].** To a solution of (*S*)-**10**[3a] (150 mg, 1.0 mmol) in THF (15 mL) was added MeMgBr [4.6 mL (4.0 mmol, 0.87 M in THF)] dropwise at room temperature and the mixture was stirred at room temperature for 3 h. A usual workup and purification by column chromatography (EtOAc) gave a 93:7 ($^1H$ NMR) inseparable diastereomeric mixture of (2*S*,3*R*)-**2** and (2*S*,3*S*)-**3** (126 mg, 71% yield). Thus, the mixture (93 mg, 0.57 mmol) was dissolved in THF (3 mL), and a THF (2 mL) solution of imidazole (82 mg, 1.2 mmol) and a THF (3 mL) solution of TBS-Cl (181 mg, 1.2 mmol) were added subsequently. After being stirred at room temperature for 4.5 h, the mixture was treated in a usual manner to give products, which were purified by column chromatography (hexane/EtOAc = 5/1) to afford a mixture of TBS ethers (2*S*,3*R*)-**11** and (2*S*,3*S*)-**12** (132 mg, 84% yield) as oily products. The mixture was separated by preparative HPLC on a YMC-Pack SIL column (Φ 6 mm ×

250 mm, hexane/EtOAc = 3/1) to afford a major product of 95 mg (72%) and a minor product of 5 mg.

Major product: (2*S*,3*R*)-**11**, retention time = 12.0 min, ≥ 99% de. IR (film) 3285 (N−H), 1064 (Si−O) $cm^{-1}$. $^1H$ NMR ($CDCl_3$) $\delta$ 7.34−7.25 (m, 5H), 3.91 (dd, 1H, $J$ = 5.4, 11.2 Hz), 3.76 (dd, 1H, $J$ = 6.6, 11.2 Hz), 2.35 (t, 1H, $J$ = 6.6 Hz), 1.53 (s, 3H), 0.92 (s, 9H), 0.10 (s, 6H). $^{13}C$ NMR ($CDCl_3$) $\delta$ 145.4, 128.5, 126.9, 126.2, 62.8, 44.3, 41.4, 26.0, 20.1, 18.4, −5.1, −5.2. Anal. Calcd for $C_{16}H_{27}NOSi$: C, 69.26; H, 9.81; N, 5.05. Found: C, 69.61; H, 9.91; N, 5.09. $[\alpha]^{26}_D$ +22.7 (*c* 1.40, $CHCl_3$).

Minor product: (2*S*,3*S*)-**12**, retention time = 10.8 min, ≥99% de. IR (film) 3260 (N−H), 1078 (Si−O) $cm^{-1}$. $^1H$ NMR ($CDCl_3$) $\delta$ 7.43−7.21 (m, 5H), 3.40 (dd, 1H, $J$ = 5.4, 10.8 Hz), 3.09 (dd, 1H, $J$ = 7.0, 10.8 Hz), 2.36 (dd, 1H, $J$ = 5.4, 7.0 Hz), 1.61 (s, 3H), 1.37 (br s, 1H), 0.82 (s, 9H), −0.11 (s, 6H). $^{13}C$ NMR ($CDCl_3$) $\delta$ 140.8, 128.0, 127.8, 126.7, 63.5, 44.6, 42.7, 28.2, 25.9, 18.3, −5.5. Anal. Calcd for $C_{16}H_{27}NOSi$: C, 69.26; H, 9.81; N, 5.05. Found: C, 69.46; H, 9.78; N, 5.08. $[\alpha]^{26}_D$ +19.5 (*c* 0.20, $CHCl_3$).

A THF solution of TBAF [0.41 mL, 0.41 mmol (1 M in THF)] was added to a THF (1 mL) solution of (2*S*,3*R*)-**11** (94 mg, 0.34 mmol) at room temperature. After being stirred at room temperature for 2 h, the mixture was treated in a usual manner to give a product, which was purified by column chromatography (EtOAc) to afford (2*S*,3*R*)-**2** quantitatively as a colorless oil. $[\alpha]^{21}_D$ +49.7 (*c* 1.86, $CHCl_3$).

**Transformation of (2*S*,3*R*)-2a to (2*S*,3*R*)-2.** A solution of (2*S*,3*R*)-**2a** [98 mg, 0.48 mmol, 94% ee, obtained by the lipase-catalyzed resolution of (±)-**2**] in $Et_2O$ (5 mL) was added dropwise to a suspension of $LiAlH_4$ (36 mg, 0.95 mmol) in $Et_2O$ (5 mL) at 0 °C. The mixture was stirred at 0 °C for 0.5 h and then at room temperature for 2.5 h. The usual workup gave a crude product which was purified by column chromatography (EtOAc) to afford 45 mg (58%) of (2*S*,3*R*)-**2** as a colorless oil. $[\alpha]^{26}_D$ +49.9 (*c* 1.10, $CHCl_3$), the same sign (+) as that obtained from (*S*)-**10**.

**(2*S*,3*S*)-*N*-[(*S*)-2-(6-Methoxy-2-naphthyl)propionyl]-3-methyl-3-phenyl-2-aziridinemethanol (*S*,*S*,*S*)-13.** A solution of (2*S*,3*S*)-**3** [73 mg, 0.45 mmol, 90% ee, obtained by lipase-catalyzed resolution of (±)-**3**] in $CH_3CN$ (10 mL) was added to a mixture of (*S*)-naproxen (154 mg, 0.67 mmol) and DCC (185 mg, 0.90 mmol) in $CH_3CN$ (10 mL). The mixture was stirred for 3.5 h at room temperature, and a usual workup gave a crude product, which was purified by column chromatography (hexane/$Et_2O$ = 1/5) and then recrystallized from *i*-$Pr_2O$ to give a crystalline product (85 mg, 50%): mp 132−133 °C. IR (KBr) 3327 (O−H), 1651 (C=O) $cm^{-1}$. $^1H$ NMR (600 MHz, acetone-$d_6$) $\delta$ 7.83 (d, 1H, $J$ = 1.8 Hz), 7.82 (d, 1H, $J$ = 9.6 Hz), 7.79 (d, 1H, $J$ = 9.6 Hz), 7.53 (dd, 1H, $J$ = 1.8, 8.4 Hz), 7.35−7.30 (m, 3H), 7.28−7.22 (m, 3H), 7.16 (dd, 1H, $J$ = 3.0, 8.4 Hz), 4.16 (q, 1H, $J$ = 7.2 Hz), 3.16−3.14 (m, 2H), 2.68 (t, 1H, $J$ = 6.0 Hz), 1.52 (s, 3H), 1.51 (d, 3H, $J$ = 7.2 Hz). $^{13}C$ NMR (acetone-$d_6$) $\delta$ 183.9, 158.6, 140.2, 137.4, 134.8, 129.9, 128.8, 128.1, 128.0, 127.2, 119.7, 106.5, 61.5, 55.6, 50.1, 49.4, 48.5, 23.5, 20.2. Anal. Calcd for $C_{24}H_{25}NO_3$: C, 76.77; H, 6.71; N, 3.73. Found: C, 76.52; H, 6.69; N, 3.42. $[\alpha]^{25}_D$ +133.0 (*c* 0.20, $Et_2O$), 99% ee.

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**Supporting Information Available:** Copies of $^1H$ and $^{13}C$ NMR spectra of all new compounds (**2a**, **2b**, **3a**, **7a**, **9**, **11**, **12**, and **13**), computational data for **4a**, **4b**, and **6a**, and X-ray crystallographic analytical data for (*S*,*S*,*S*)-**13** (CIF file). This material is available free of charge via the Internet at http://pubs.acs.org.

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