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Lipase-Catalyzed Kinetic Resolution of Cyclic *trans*-1,2-Diols Bearing a Diester Moiety: Synthetic Application to Chiral Seven-Membered-Ring α,α-Disubstituted α-Amino Acid

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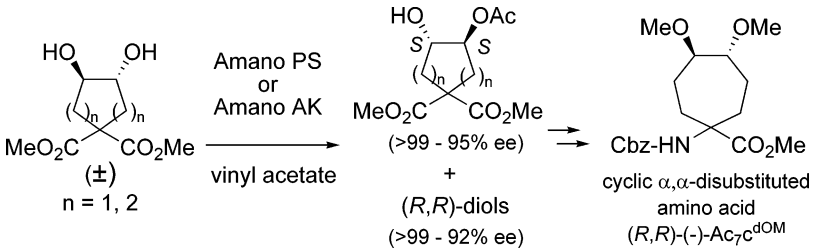
Received June 20, 2007



Chiral cycloalkane-*trans*-1,2-diols (±)-**3** and (±)-**8** having a diester moiety have been prepared from dimethyl dialkenylmalonate using olefin metathesis by Grubbs catalyst, followed by epoxidation and acidic hydrolysis. Kinetic resolution of racemic cyclopentane-*trans*-1,2-diol (±)-**3** by lipase-catalyzed transesterification afforded an optically active monoacetate (−)-**5** of 95% ee in 46% yield and the recovered diol (−)-**3** of 92% ee in 51% yield, and that of cycloheptane-*trans*-1,2-diol (±)-**8** gave a monoacetate (+)-**10** of 95% ee in 51% yield and the diol (−)-**8** of >99% ee in 43% yield, respectively. The enantiomer selectivity of racemic cyclic *trans*-1,2-diols bearing a diester moiety by lipases (Amano PS and Amano AK) was opposite to that of the reported simple racemic cycloalkane-*trans*-1,2-diols. To explain the lipase-catalyzed enantiomer selectivity, computer modeling of lipase−substrate complexes was performed. Furthermore, the optically active diester (−)-**8** could be efficiently converted into an optically active seven-membered-ring α,α-disubstituted amino acid (4*R*,5*R*)-(−)-**15**.

Introduction

Chiral C_2-symmetrical 1,2-diols have widely been used as chiral auxiliaries and chiral ligands for many asymmetric reactions.[1] For instance, we focused our previous studies on asymmetric syntheses using chiral cyclic 1,2-diols of the C_2-axis, especially optically active cycloalkane-1,2-diols, and revealed that the cyclic 1,2-diols, i.e., cyclohexane-*trans*-1,2-diol and cycloheptane-*trans*-1,2-diol, are very useful as a chiral auxiliary for asymmetric reactions.[2] Furthermore, we reported that a combination of optically active cyclic 1,2-diols and Lewis acid can be applied to asymmetric ring transformation reactions and asymmetric ring cleavage reactions. The optically active cyclic *trans*-1,2-diols could be easily prepared by lipase-catalyzed kinetic resolution of the racemic diols, or the corresponding racemic diacetates.[3]

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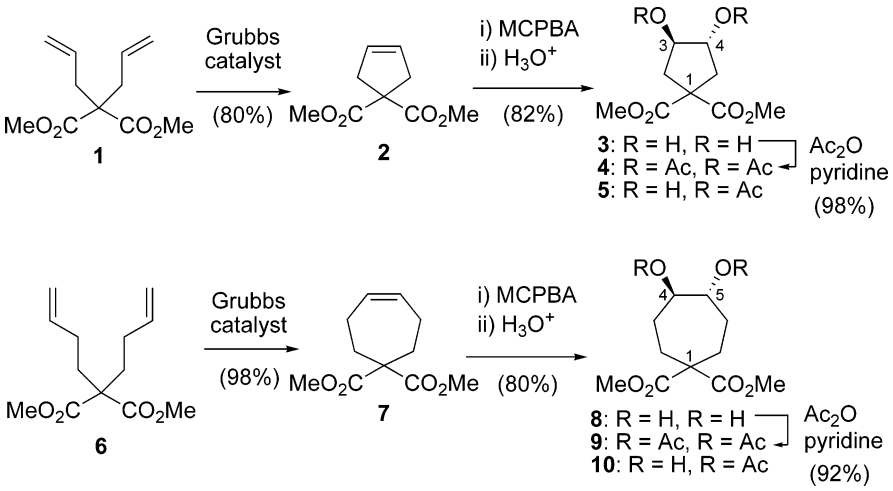
10.1021/jo701317d CCC: $37.00
Published on Web 08/22/2007

SCHEME 1

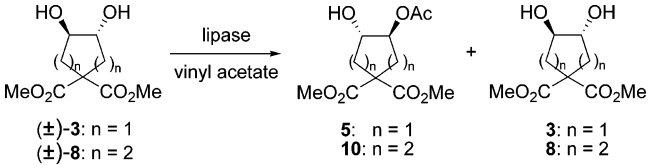


Here we describe a concise synthesis of optically active cyclic 1,2-diols having a diester moiety by using olefin metathesis and lipase-catalyzed kinetic resolution, and insight into the enantiomer selectivity of lipase Amano PS using computer modeling. As an application of the optically active diol having a diester, we designed and synthesized a chiral seven-membered-ring α,α-disubstituted α-amino acid:[4] (4*R*,5*R*)-1-amino-4,5-di(methoxy)-cycloheptanecarboxylic acid {(4*R*,5*R*)-Ac_7c^{dOM}}, in which the α-carbon atom is not a chiral center but asymmetric centers exist at the side-chain cycloheptane.[5−7]

Results and Discussion

Preparation of Cyclic C_2-Symmetric 1,2-Diols Having a Diester Moiety. We prepared racemic *trans*-3,4-dihydroxy-1,1-bis(methoxycarbonyl)cyclopentane **3** and *trans*-4,5-dihydroxy-1,1-bis(methoxycarbonyl)cycloheptane **8** starting from dimethyl malonate.[8] That is to say, dialkylation of dimethyl malonate with allyl bromide and 4-bromo-1-butene afforded dienes **1** (98%) and **6** (96%), respectively. Olefin metathesis of **1** with Grubbs catalyst gave cyclopentene **2** in 80% yield.[8] Epoxidation of **2** with MCPBA, followed by hydrolysis with 3% aqueous sulfuric acid afforded cyclic *trans*-1,2-diol (±)-**3** having a diester moiety in 82% yield. Acetylation with Ac_2O in pyridine produced diacetate (±)-**4** in 98% yield. In a similar manner, cycloheptane-*trans*-1,2-diol (±)-**8** and its diacetate (±)-**9** having a diester moiety were also prepared from **6**, as shown in Scheme 1. The spectroscopic data of all compounds supported their structures.

SCHEME 2



Lipase-Catalyzed Kinetic Resolution of Racemic Cyclic 1,2-Diols. At first, we attempted to kinetically resolve racemic diacetates (±)-**4** and (±)-**9** by using lipase-catalyzed hydrolysis in phosphate buffer.[3,9] Unfortunately, neither the diacetate (±)-**4** nor (±)-**9** could be well dissolved in phosphate buffer, even though a small amount of acetone was added as a cosolvent. Thus, the lipase-catalyzed hydrolysis of diacetates (±)-**4** and (±)-**9** did not proceed, and monoacetates could not be detected at all.

Next, we examined the kinetic resolution of diols (±)-**3** and (±)-**8** by using lipase-catalyzed transesterification. The transesterification of racemic (±)-diol (100 mg) was performed by using lipase (100 mg) in vinyl acetate (5 mL) at 40 °C, and after 72 h the reaction was terminated by filtration. The results of kinetic resolutions are summarized in Table 1. As expected, transesterification of the five-membered-ring diol (±)-**3** catalyzed by Amano PS lipase[10] smoothly proceeded to give a monoacetate (−)-**5** of 95% ee in 37% yield and the recovered diol (−)-**3** of 66% ee in 56% yield (entry 1), and the reaction was reproducible on a large scale (entry 2) with better yield for (−)-**5** and better ee for (−)-**3**. The diol (−)-**3** and the monoacetate (−)-**5** products could be well separated by column chromatography on silica gel. Solvolysis of monoacetate (−)-**5** with K_2CO_3 in MeOH afforded (+)-diol **3** in quantitative yield.

(4) (a) Tanaka, M. *J. Synth. Org. Chem., Jpn.* **2002**, *60*, 125−136. (b) Cativiela, C.; Diaz-de-Villegas, M. D. *Tetrahedron*: *Asymmetry* **1998**, *9*, 3517−3599. (c) Cativiela, C.; Diaz-de-Villegas, M. D. *Tetrahedron*: *Asymmetry* **2000**, *11*, 645−732. (d) Vogt, H.; Bräse, S. *Org. Biomol. Chem.* **2007**, *5*, 406−430 and references cited therein.

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(10) Amano PS is a *Burkholderia cepacia* lipase, which was formerly used as *Pseudomonas fluorescens* lipase (PFL) or *P. cepacia* lipase, and Amano AK is now classified as *Pseudomonas fluorescens* lipase.

TABLE 1. Lipase-Catalyzed Kinetic Resolution of Diols (±)-3 and (±)-8 by Transesterification

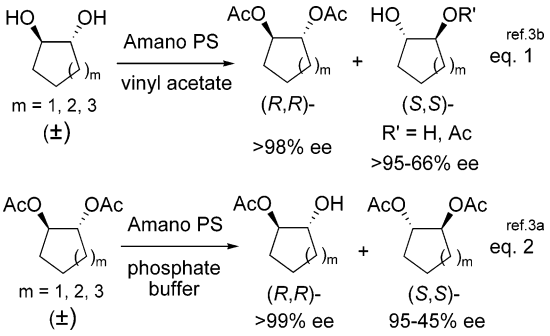
				monoacetate		diol	
entry	substrate	lipase	reaction time (h)	yield	ee	yield	ee
1	(±)-**3**	Amano PS	72[a]	(−)-**5**: 37%	95% ee	(−)-**3**: 56%	66% ee
2	(±)-**3**	Amano PS	72[b]	(−)-**5**: 46%	95% ee	(−)-**3**: 51%	92% ee
3	(±)-**8**	Amano PS	72[a]	(+)-**10**: 11%	>99% ee	(−)-**8**: 87%	10% ee
4	(±)-**8**	Amano AYS	72[a]	(+)-**10**: 2%	40% ee	(−)-**8**: 97%	*d*
5	(±)-**8**	F-AP 15	72[a]	(−)-**10**: 3%	91% ee	(+)-**8**: 96%	*d*
6	(±)-**8**	Amano AS	72[a]	(−)-**10**: 4%	96% ee	(+)-**8**: 95%	*d*
7	(±)-**8**	Amano AK	72[a]	(+)-**10**: 44%	94% ee	(−)-**8**: 51%	84% ee
8	(±)-**8**	Amano AK	24[c]	(+)-**10**: 33%	>99% ee	(−)-**8**: 65%	56% ee
9	(±)-**8**	Amano AK	96[c]	(+)-**10**: 51%	95% ee	(−)-**8**: 43%	>99% ee

[a] A mixture of (±)-diol (100 mg) and lipase (100 mg) in vinyl acetate (5 mL) was stirred at 40 °C. [b] A mixture of (±)-**3** (0.74 g) and Amano PS (2.2 g) in vinyl acetate (50 mL) was stirred at 30 °C. [c] The reaction was performed at 55 °C. [d] Not determined.

On the other hand, transesterification of the seven-membered-ring diol (±)-**8** by Amano PS in vinyl acetate proceeded sluggishly to yield monoacetate (+)-**10** of >99% ee in 11% chemical yield and the recovered diol (−)-**8** of 10% ee in 87% yield after 72 h (entry 3). The transesterification required a long reaction time, and even after 72 h the yield of monoacetate was not satisfactory. Thus, the Amano PS-catalyzed transesterification reaction is not practical for the kinetic resolution of the diol (±)-**8**. Therefore, we examined several kinds of lipases such as Amano AYS, F-AP 15, and Amano AS. We summarize the results in entries 4−9 of Table 1. The use of Amano AYS, F-Ap 15, and Amano AS did not improve the efficiency of transesterification (entries 4−6). However, it is noteworthy that the transesterification by F-AP 15 or Amano AS afforded the monoacetate (−)-**10** showing the minus sign of specific rotation, albeit the yields of (−)-**10** were very low. These results mean that lipases Amano PS and AS show different enantiomer selectivity. That is to say, Amano PS acylated (+)-**8**, whereas Amano AS acylated the enantiomer (−)-**8**. Finally, we found that the kinetic resolution with Amano AK[10] in vinyl acetate produced the monoacetate (+)-**10** of 94% ee in 44% yield and the diol (−)-**8** of 84% ee in 51% yield (entry 7). Fortunately, in the case of Amano AK-catalyzed transesterification, the shortening of the reaction time (24 h) and the optimized reaction temperature (55 °C) improved the enantiomeric excess of monoacetate (+)-**10** to >99% ee (33% yield), and prolongation of the reaction time (96 h) improved that of diol (−)-**8** to >99% ee (43% yield), (entries 8 and 9). Hydrolysis of acetate in (+)-**10** gave the enantiomeric diol (+)-**8** in quantitative yield. Thus, both enantiomers of the seven-membered-ring diol **8** could be practically synthesized in high enantiomeric excess by using Amano AK-catalyzed transesterification.

Determination of Absolute Configuration of Cyclic 1,2-Diols. It is known that in the case of Amano PS-catalyzed kinetic resolution of simple cyclic (±)-*trans*-1,2-diols, the transesterification by Amano PS preferentially converts (*R*,*R*)-diols into (*R*,*R*)-monoacetates, but (*S*,*S*)-diols remain intact or are less reactive than (*R*,*R*)-diols. In some conditions, the esterification proceeds further, and (*R*,*R*)-diacetates and (*S*,*S*)-monoacetates would be obtained (Scheme 3; eq 1).[3b] On the other hand, in the case of Amano PS-catalyzed hydrolysis of simple cyclic (±)-diacetates, the lipase takes up (*R*,*R*)-diacetates and releases (*R*,*R*)-monoacetates, but (*S*,*S*)-diacetates are not taken up by lipase and remain unchanged (Scheme 3; eq 2).[3] That is to say, the active site of lipase Amano PS exclusively recognizes and takes up (*R*,*R*)-enantiomers, but not (*S*,*S*)-enantiomers. Following this empirical rule, we arbitrarily assumed that the absolute

SCHEME 3



configurations of monoacetates (−)-**5** and (+)-**10** may be *R*,*R* configuration, and that of both unreacted diols (−)-**3** and (−)-**8** may be *S*,*S*.

To determine the absolute configuration of diols **3** and **8**, both enantiomers of the 1,2-diols were converted into the corresponding dibenzoates **11** and **12**, respectively (Scheme 4). The CD spectrum of dibenzoate **11** derived from (−)-**3**, which was not taken up by Amano PS, showed negative first Cotton effect at 238 nm and positive second Cotton effect at 222 nm (negative chirality), and that derived from (+)-**3**, which was prepared from (−)-**5** by solvolysis, showed positive first Cotton effect and negative second Cotton effect (positive chirality). These CD spectra indicate that the configuration of the unreacted (−)-**3** is *R*,*R*, and that of (+)-**3** is *S*,*S*, on the basis of the exciton chirality method.[11] Also, the CD spectrum of **12** derived from (−)-**8**, which was not taken up by either Amano PS or Amano AK, indicated that the first Cotton effect (236 nm) was negative and the second Cotton effect (223 nm) was positive (negative chirality), and that derived from (+)-**10** showed the reverse situation (positive chirality). According to the dibenzoate chirality rule, these CD spectra indicate that the configuration of the unreacted (−)-**8** is *R*,*R*, and that of (+)-**8** is *S*,*S*. The assignment of the absolute configurations is not in accord with that of the reported data, in which the lipase-catalyzed kinetic resolutions of racemic cycloalkane-1,2-diols were described. Thus, we also confirmed the absolute configuration of (−)-**3** by conversion to a known compound, and by the comparison of its specific rotation. The diol function in (−)-**3** was protected as MOM ether, and the specific rotation of **13** showed $[\alpha]^{23}_{D}$ +3.5. Compound **13** was also prepared by us starting from dimethyl L-(+)-tartrate and dimethyl malonate, and the specific

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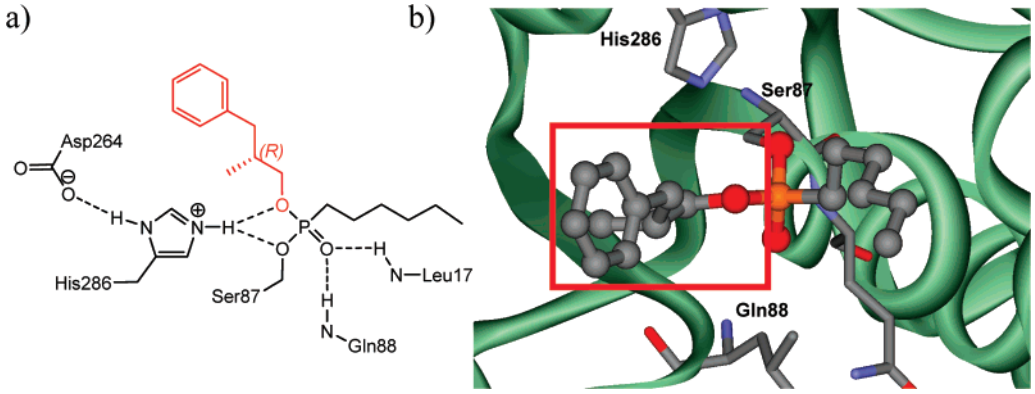
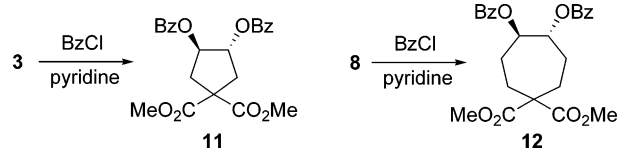
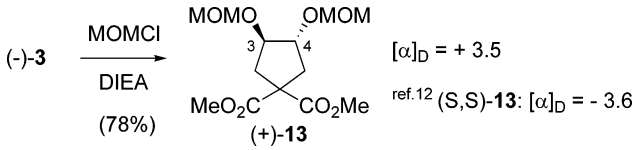


FIGURE 1. X-ray crystallographic analysis of lipase-inhibitor complex reported by Kazlauskas et al.[13d] (a) Hydrogen-bonding pattern of inhibitor and lipase (Amano PS). (b) X-ray structure of inhibitor in the active site. For the calculation, the alcohol part, which is highlighted in the red square, is replaced with 1,2-diol or monoacetate.

SCHEME 4



SCHEME 5



rotation of (*S*,*S*)-**13** showed $[\alpha]^{24}_{D}$ −3.6.[12] Thus, the absolute configuration of (−)-**3** was unambiguously determined to be 3*R*,4*R*. These absolute configurations are opposite to the aforementioned empirical assignments by the Amano PS-chiral recognition.

Insight into Lipase-Catalyzed Enantiomer-Selective Transesterification by Computer Modeling. With regard to the enantiomer recognition of chiral alcohols by Amano PS, several groups reported the structure of lipase and the complex between lipase and chiral alcohols or their phosphate inhibitors based on X-ray crystallographic analysis[13] and also based on modeling.[9a,14] They analyzed the substrate (inhibitor) complex bound to lipase, and proposed several models to explain the enantiomer recognition by Amano PS. The lipase Amano PS is an α/β hydrolase. Its active site consists of catalytic triad residues Asp264, His286, and Ser87, and the amide hydrogens of residues Gln88 and Leu17 (oxyanion hole) also contribute to catalysis by hydrogen bonding to the oxyanion intermediate.

We found experimentally that Amano PS characteristically recognizes enantiomers of the cyclic *trans*-1,2-diols. The Amano PS takes up the simple (*R*,*R*)-cycloalkane-1,2-diols in its active site and converts them into (*R*,*R*)-acetates.[3] In contrast to the *R*,*R* enantiomer recognition of the simple cyclic 1,2-diols, the enzyme took up the (*S*,*S*)-cycloalkane-1,2-diols bearing a diester moiety to produce (*S*,*S*)-monoacetates, whereas the cyclic (*R*,*R*)-diols having a diester remained intact. That is to say, the *R*,*R* and *S*,*S* enantiomer-recognition of cyclic 1,2-diols by Amano PS is opposite between the plain cycloalkane-1,2-diols and the cycloalkane-1,2-diols having a diester moiety. Thus, the diester moiety on the cycloalkane strongly affects the chiral recognition of cyclic 1,2-diols by the enzyme.

We explored the influence of the diester moiety on Amano PS−enantiomer discrimination by using molecular modeling. The enantiomer selectivities observed are probably the result of a complex interplay between Amano PS and the substrate, including structural changes, and therefore we do not intend to quantitatively discuss the detailed lipase−cyclic 1,2-diol intermediates, though exquisite quantitative analyses have already been reported by several groups.[13−15] On the basis of the X-ray crystallographic data of Amano PS−phosphate inhibitor complex (PDB entry 1YS1) reported by Kazlauskas,[13d] the alcohol part of the lipase−inhibitor complex was replaced with chiral five-membered-ring 1,2-diols and their monoacetates. These complexes were assumed to be phosphate analogues of the tetrahedral transition state. A conformational search (Mixed MCMM/Low Mode, AMBER*) with MacroModel produced global minimal energy complexes (Figure 1).

In the case of plain cyclopentane-*trans*-1,2-diols, no large energy difference was observed between the global minimum-energy structures of *R*,*R* and *S*,*S* enantiomers. On the other hand, calculations for the Amamo PS complexes with their monoacetates showed that the (*R*,*R*)-monoacetate complex was more stable than the (*S*,*S*)-enantiomer complex by 5.4 kcal/mol (Figure 2a,b). These calculations are in good accord with the experimental findings that both (*R*,*R*)- and (*S*,*S*)-diols were monoacylated by Amano PS, and the enantiomer discrimination was attained by the kinetic resolution of the corresponding monoacetate to (*R*,*R*)-diacetate (Scheme 3, eq 1). In the case of cyclopentane-1,2-diols **3** having a diester moiety, the global minimum-energy calculation estimated that the Amano PS

(12) Synthesis of (*S*,*S*)-**13** from dimethyl L-(+)-tartrate has already been presented. See: Demizu, Y.; Tanaka, M.; Kurihara, M.; Suemune, H. *Peptide Science 2002*; Proceedings of the 39th Japanese Peptide Symposium; Japanese Peptide Society: Minoh, Osaka, Japan, 2003; pp 321−322.

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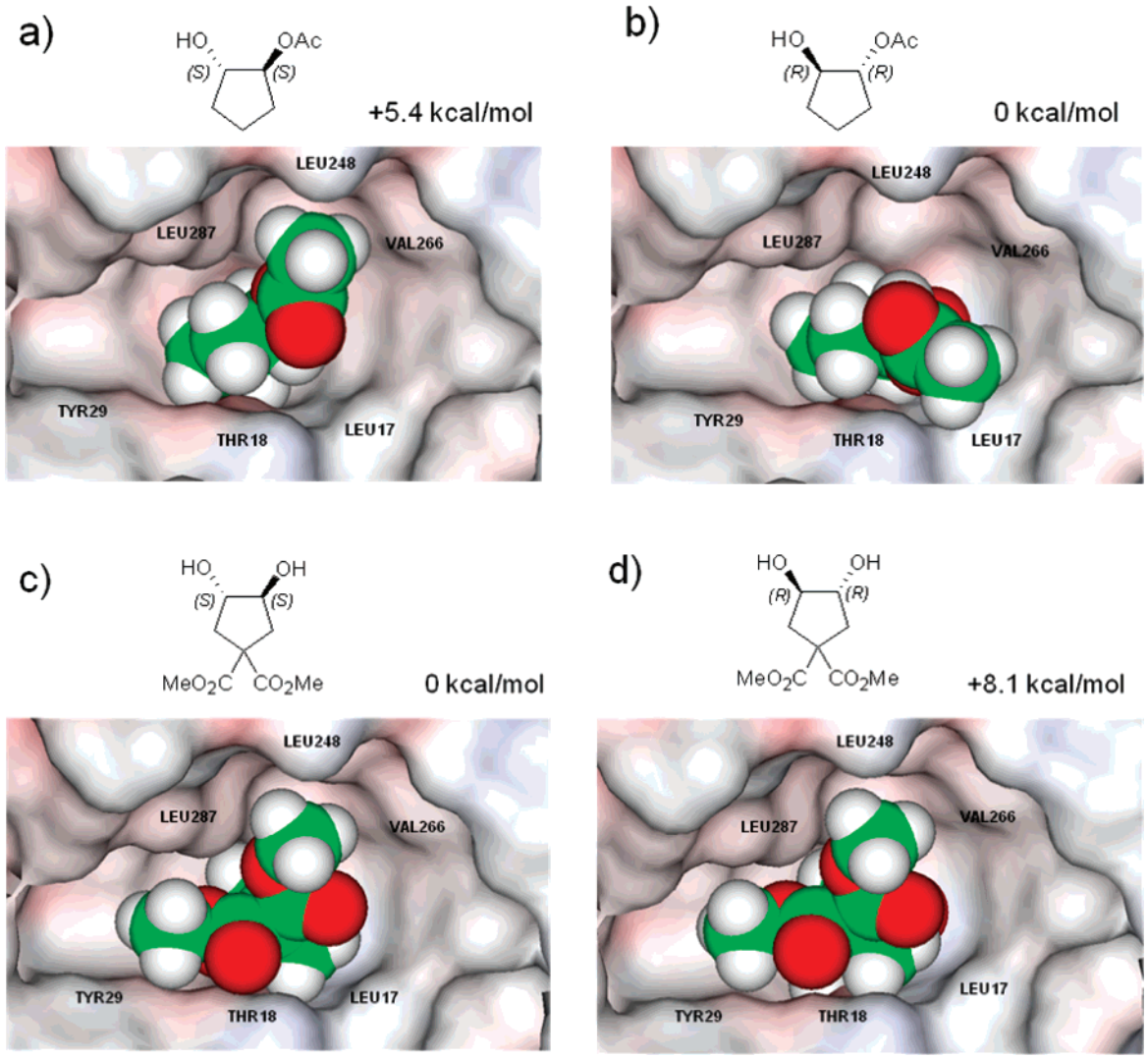


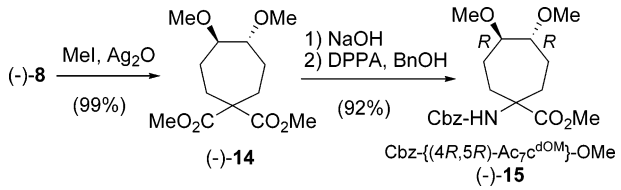
FIGURE 2. Computer modeling of transition state analogue−Amano PS complexes. (a, b) Modeling of the transition state analogue of plain (*S*,*S*)- and (*R*,*R*)-monoacetate in the active site of Amano PS. The (*R*,*R*)-enantiomer was more stable than the (*S*,*S*)-enantiomer by 5.4 kcal/mol. (c, d) Modeling of the transition state analogue of (*S*,*S*)- and (*R*,*R*)-diol **3** having a diester moiety in the active site. A hydrogen bond between the diester moiety and Thr18 is observed. The (*S*,*S*)-enantiomer was more stable than the (*R*,*R*)-enantiomer by 8.1 kcal/mol.

complex with (*S*,*S*)-cyclopentane-1,2-diol (+)-**3** was more favorable than that with (*R*,*R*)-diol (−)-**3** by + 8.1 kcal/mol (Figure 2c,d). In the calculated structures of both the (*R*,*R*)- and (*S*,*S*)-diol complexes, a hydrogen bond between the carbonyl function of the diester (substrate) and the hydroxyl function of the amino acid residue (Thr 18) was observed. The hydrogen bond may be crucial for the reversal of the enantiomeric selectivity. Although it is known that the calculated energies of lipase−small molecule complexes are not a reliable basis to judge whether a conformation is catalytically relevant,[15] in our cases, comparison of the calculated energies matched the experimental finding that (*S*,*S*)-cyclopentane-1,2-diol (+)-**3** was preferentially acylated. The phosphates used here correspond to the heptanoyl ester, not the acetyl group, and the enantiomer discrimination is determined by the kinetic constant (k_{cat}/K_m; reaction rate k_{cat} and binding constant K_m). Moreover, a stable nonproductive binding complex that would not lead to acylation may exist in the case of the slow reactive enantiomer. Regardless of the exact mechanisms and the aforementioned issues, this simple calculation can be applied to predict the enantiopreference of Amano PS toward the cyclic 1,2-diols, and the reversal of enantiomer selectivity can be well explained.

Synthesis of Optically Active Seven-Membered-Ring α,α-Disubstituted Amino Acid. We have already reported chiral cyclic α,α-disubstituted α-amino acids in which the α-carbon atom is not a chiral center but chiral centers existing at the side chain cyclopentane.[5] By using these α,α-disubstituted amino acids, we controlled the helical-screw direction of their peptide foldamers without a chiral center on the peptide backbone.

As an application for an optically active cyclic 1,2-diol, we synthesized a new chiral cyclic α,α-disubstituted α-amino acid having a seven-membered ring: (4*R*,5*R*)-1-amino-4,5-di-(methoxy)cycloheptanecarboxylic acid {**15**: (4*R*,5*R*)-Ac$_7$c^{dOM}}, which is an analogue of the five-membered-ring one.[5a] That is to say, methylation of the diol function in (−)-**8** with MeI and Ag_2O gave a dimethoxy compound (−)-**14** in 99% yield. Partial hydrolysis of the diester under basic conditions, followed by Curtius rearrangement[16] and workup with benzyl alcohol produced the cyclic amino acid Cbz-{(4*R*,5*R*)-Ac$_7$c^{dOM}}-OMe (−)-**15** in 92% yield without any problem.

SCHEME 6



Conclusion

We synthesized the cycloalkane-*trans*-1,2-diols **3** and **8** bearing a diester moiety by using olefin metathesis with Grubbs catalyst, followed by epoxidation and acidic hydrolysis. The Amano PS-catalyzed kinetic resolution of racemic diol (±)-**3** by transesterification afforded the enantiomerically enriched monoaceate (*S*,*S*)-(−)-**5** (95% ee) in 46% yield and the diol (*R*,*R*)-(−)-**3** (92% ee) in 51% yield. Furthermore, the Amano AK-catalyzed transesterification of the seven-membered-ring (±)-**8** gave the highly enantiomerically enriched monoacetate (*S*,*S*)-(+)-**10** (>99% ee) and the diol (*R*,*R*)-(−)-**8** (>99% ee), by tuning the reaction conditions. It is noteworthy that the lipases Amano PS and Amano AK took up the (*S*,*S*)-diols **3** and **8** in their active site, but not the (*R*,*R*)-enantiomers. In the case of the reported simple cycloalkane-1,2-diols, the active site of Amano PS took up and acylated the opposite (*R*,*R*)-enantiomers. To explain the influence of the diester moiety on the enantiomer selectivity, we performed calculations for the lipase−substrate complexes by using computer modeling. The calculation showed that in the case of simple cyclopentane-1,2-diol, the (*R*,*R*)-monoacetate−lipase complex was more stable than the (*S*,*S*) complex, and in the case of cyclopentane-1,2-diol **3** having a diester, the (*S*,*S*)-diol−lipase complex was more stable than the (*R*,*R*) complex. These calculated results are in good agreement with the experimental results. As an application of the optically active 1,2-diol, we efficiently synthesized the chiral cyclic α,α-disubstituted amino acid (4*R*,5*R*)-Ac_7c^{dOM} (−)-**15**, in which the α-carbon atom is not an asymmetric center.

Experimental Section

Kinetic Resolution of (±)-3 by Transesterification. A mixture of diol (±)-**3** (100 mg, 0.459 mmol) and Amamo PS (100 mg) in vinyl acetate (5 mL) was vigorously stirred at 40 °C for 72 h. The lipase was filtered off, and the filtrate was evaporated in vacuo to afford a residue, which was purified by column chromatography on silica gel. The fraction eluted with 30% EtOAc in hexane afforded monoacetate (−)-**5** (44 mg, 37%, 95% ee), and that eluted with EtOAc gave diol (−)-**3** (56 mg, 56%, 66% ee). (−)-**5**: 95% ee; a colorless oil; $[\alpha]^{24}_D$ −14.0 (*c* 1.00, $CHCl_3$); IR (neat) 3507 (br), 1736 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 4.93 (m, 1H), 4.21 (m, 1H), 3.76 (s, 3H), 3.75 (s, 3H), 2.82 (dd, J = 6.7, 15.0 Hz, 1H), 2.76 (br, 1H), 2.68 (dd, J = 6.4, 14.4 Hz, 1H), 2.38 (dd, J = 4.5, 15.0 Hz, 1H), 2.78 (dd, J = 4.3, 14.4 Hz, 1H), 2.04 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.6, 171.7, 171.1, 81.1, 76.2, 57.6, 53.1, 52.9, 39.9, 37.4, 20.9; FAB(+)HRMS calcd for $C_{11}H_{17}O_7$ (M^+ + H) 261.0974, found 261.1024. (*R*,*R*)-(−)-**3**: 92% ee (entry 2); colorless crystals; mp 72−74 °C; $[\alpha]^{24}_D$ −11.2 (*c* 1.00, $CHCl_3$). Enantiomeric excess of diols **3** was determined by HPLC [column, DAICEL-CHIRALPAK AD; eluent, 10% *i*-PrOH in hexane; flow rate, 1.0 mL; detection, RI; retention time (t_R): (±)-**3**: t_R = 16 and 18 min, (*R*,*R*)-(−)-**3**: t_R = 18 min].

(*S*,*S*)-(+)-3,4-Dihydroxy-1,1-bis(methoxycarbonyl)cyclopentane (3). Solvolysis of (−)-**5** by treatment with K_2CO_3 in MeOH afforded (*S*,*S*)-(+)-**3** in quantitative yield. (*S*,*S*)-(+)-**3**: colorless crystals; $[\alpha]^{31}_D$ +12.0 (*c* 1.00, $CHCl_3$).

Kinetic Resolution of (±)-8. Amano AK-catalyzed transesterification of (±)-**8** afforded monoacetate (+)-**10** (51%, 95% ee) and the diol (−)-**8** (43%, >99% ee). (+)-**10**: a colorless oil; $[\alpha]^{26}_D$ +16.0 (*c* 1.04, $CHCl_3$); IR (neat) 3468 (br), 1728 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 4.64 (m, 1H), 3.73 (s, 3H), 3.72 (s, 3H), 3.68 (m, 1H), 2.40 (br, 1H), 2.25−2.42 (m, 2H), 2.08 (s, 3H), 1.72−2.05 (m, 4H), 1.64−1.76 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.5, 172.3, 171.1, 80.3, 74.8, 56.2, 52.6, 52.5, 27.9, 27.3, 27.1, 25.3, 21.2; FAB(+)HRMS calcd for $C_{13}H_{21}O_7$ (M^+ + H) 289.1287, found 289.1294. Enantiomeric excess of monoacetate **10** was determined by HPLC [column, DAICEL-CHIRALPAK AD; eluent, 10% *i*-PrOH in hexane; flow rate, 1.0 mL; detection, RI; retention time: (±)-**10**: t_R = 16 and 17 min, (+)-**10**: t_R = 17 min]. (*R*,*R*)-(−)-**8**: colorless crystals; mp 59−61 °C; $[\alpha]^{26}_D$ −16.7 (*c* 1.01, $CHCl_3$). Enantiomeric excess of diol **8** was determined by HPLC [column, TOSOH-BP developing column; eluent, 10% *i*-PrOH in hexane; flow rate, 1.0 mL; detection, RI; retention time: (±)-**8**: t_R = 7 and 8 min, (−)-**8**: t_R = 8 min].

(*S*,*S*)-(+)-4,5-Dihydroxy-1,1-bis(methoxycarbonyl)cycloheptane (8). Solvolysis of (+)-**10** by treatment with K_2CO_3 in MeOH afforded (*S*,*S*)-(+)-**8** (quantitative). Colorless crystals; $[\alpha]^{31}_D$ +15.4 (*c* 1.05, $CHCl_3$).

(4*R*,5*R*)-(−)-4,5-Dimethoxy-1,1-bis(methoxycarbonyl)cycloheptane {(−)-14}. A suspension of (−)-**8** (1.30 g, 5.28 mmol) and Ag_2O (24.5 g, 105 mmol) in MeI (30 mL) was vigorously stirred and refluxed under an Ar atmosphere. After being stirred for 10 days, the Ag_2O was filtered off, and the filtrate was concentrated in vacuo to leave a solid, which was purified by column chromatography on silica gel. The fraction eluted with 20% EtOAc in hexane afforded (−)-**14** (1.43 g, 99%) as colorless crystals. Mp 51−53 °C (from $CHCl_3$/hexane); $[\alpha]^{24}_D$ −2.90 (*c* 1.23, $CHCl_3$); IR (KBr) 2952, 2823, 1733 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 3.71 (s, 6H), 3.35 (s, 6H), 3.26 (m, 2H), 2.20 (m, 2H), 1.99 (m, 2H), 1.70−1.80 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.7, 82.7, 56.6, 56.5, 52.4, 25.9, 23.5; FAB(+)MS *m*/*z* 275 (M^+ + H). Anal. Calcd for $C_{13}H_{22}O_6$: C, 56.92; H, 8.08. Found: C, 56.55; H, 7.92.

Methyl (4*R*,5*R*)-(−)-1-Benzyloxycarbonylamino-4,5-(dimethoxy)cycloheptanecarboxylate [Cbz-{(*R*,*R*)-Ac_7c^{dOM}}-OMe; 15]. A solution of (−)-**14** (1.26 g, 4.60 mmol) in MeOH (50 mL) and 0.1 N aqueous NaOH solution (70 mL) was stirred overnight from at 0 °C to room temperature. The solution was acidified with 10% aqueous HCl to pH 3−4, and then MeOH was evaporated. The aqueous solution was extracted with EtOAc and dried over Na_2SO_4. Removal of the solvent afforded a crude monocarboxylic acid that was used for the next reaction without purification. A solution of the crude carboxylic acid, Et_3N (700 mg, 6.90 mmol), and diphenylphosphoryl azide (DPPA; 1.90 g, 6.90 mmol) in toluene (20 mL) was refluxed for 1.5 h under an Ar atmosphere. Then, benzyl alcohol (0.7 mL, 6.9 mmol) was added to the solution, and the whole was refluxed for 3 days. After being cooled to room temperature, the solution was diluted with EtOAc, washed with 2% aqueous HCl, 5% aqueous $NaHCO_3$, and brine, and dried over $MgSO_4$. After removal of the solvent, the residue was purified by column chromatography on silica gel (60% EtOAc in hexane) to give (−)-**15** (1.54 g, 92%) as a colorless oil. $[\alpha]^{24}_D$ −8.32 (*c* 1.04, $CHCl_3$); IR (neat) 3346, 2936, 2823, 1732, 1520 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.31−7.38 (m, 5H), 5.08 (s, 2H), 5.04 (s, 1H), 3.68 (br s, 3H), 3.35 (s, 6H), 3.17−3.30 (m, 2H), 2.32 (m, 1H), 2.03 (m, 2H), 1.60−1.90 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 174.7, 155.2, 136.2, 128.4, 128.0, 127.9, 82.8, 82.0, 66.6,

(16) (a) Shioiri, T.; Ninomiya, K.; Yamada, S. *J. Am. Chem. Soc.* **1972**, *94*, 6203−6205. (b) Ninomiya, K.; Shioiri, T.; Yamada, S. *Tetrahedron* **1974**, *30*, 2151−2157. (c) Evans, D. A.; Wu, L. D.; Wiener, J. J. M.; Johnson, J. S.; Ripin, D. H. B.; Tedrow, J. S. *J. Org. Chem.* **1999**, *64*, 6411−6417. (d) Ghosh, A. K.; Fidanze, S. *J. Org. Chem.* **1998**, *63*, 6146−6152. (e) Spino, C.; Godbout, C. *J. Am. Chem. Soc.* **2003**, *125*, 12106−12107.

61.7, 56.6, 56.4, 52.4, 29.7, 27.7, 22.8, 21.8; FAB(+)HRMS calcd for $C_{19}H_{28}NO_6$ ($M^+ + H$) 366.1917, found 366.2014.

Computer Modeling of Transition State Analogues−Amamo PS Complex. All molecular modelings and calculations were performed with MacroModel version 8.1 (Schrodinger, LLC), using the Mixed MCMM/Low Mode procedure and AMBER* force field. For modeling, the X-ray crystal structure of *Burkholderia cepacia* lipase (Amano PS) complexed with hexylphosphonic acid (*R*)-2-methyl-3-phenylpropyl ester, which is a covalently docked tetrahedron transition state mimic, was obtained from the Protein Data Bank (PDB entry, 1YS1). The water molecules were removed and hydrogen atoms were added with use of the MacroModel protocol. Initial structures were manually built by replacing the alcohol part (indicated in the red square, Figure 1) of hexylphosphonic acid ester in the 1YS1 structure with the enantiomers of cyclic 1,2-diols and their monoacetates. To determine the global minimum-energy structures of these complexes, a systematic conformational search protocol (Mixed MCMM/Low Mode) was employed. AMBER* was used as a Force Field. More than 1000 conformers were energy minimized for each model. The backbone conformation and side-chain conformation of lipase and part of hexylphosphonic acid were fixed during the conformational search.

Acknowledgment. This work was in part supported by a Grant-in-Aid for Scientific Research (B) from the Japan Society for the Promotion of Science, by a Grant-in-Aid for Scientific Research on Priority Areas (No. 19028052, Chemistry of Concerto Catalysis), and from the Ministry of Education, Culture, Sports, Science and Technology, Japan, and was also supported by a grant from the NOVARTIS Foundation (Japan) for the Promotion of Science.

Supporting Information Available: Preparation of (±)-**3**, **5**, **8**, and **10**, and their benzoate derivatives, spectroscopic data, and copies of ^{1}H NMR or ^{13}C NMR spectra of all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

JO701317D