Synthesis of a Chiral α-(Aminooxy)arylacetic Ester. II.[1] A Route through a Chiral 2-Hydroxy-2-phenylacetic Acid Derivative

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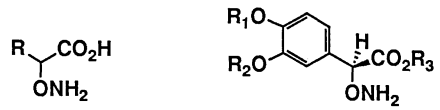
A simple and practical synthetic route has been developed for the synthesis of a chiral α-(aminooxy) ester (*S*)-**16**, which is a synthetic intermediate for a potent antipseudomonal cephalosporin antibiotic M-14659. In this synthetic route, the key intermediate is α-hydroxy acid (*R*)-**7** (100%ee), which is prepared by an asymmetric reduction of α-keto ester with $NaBH_4$-(*R*,*R*)-tartaric acid followed by a hydrolysis and an optical resolution using L-Leu-$NHNH_2$. (*S*)-**16** is obtained stereoselectively through 3 steps from (*R*)-**7**. HPLC analyses and NMR studies have proved that the (*S*)-**16** thus prepared is completely optically pure.

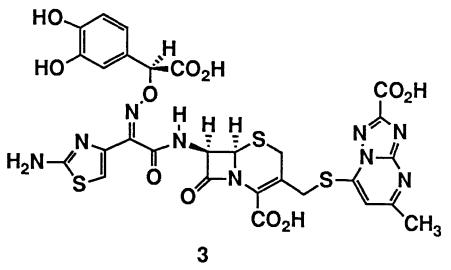
Although α-(aminooxy) acid derivatives **1** are regarded as analogues of α-amino acids, there have been very few studies concerning the synthesis of optically active **1**[2]. α-(Aminooxy) esters of structure **2** were required as synthetic intermediates for M-14659 (**3**),[3] which is a potent antipseudomonal cephalosporin antibiotic. In the preceding report[1] we have shown that optically active α-(aminooxy) ester (*S*)-**4** can be prepared from α-(phthalimidooxy) acid (*S*)-**5** which is obtained by optical resolution.

In search for a simpler and more practical synthetic route to α-(aminooxy) esters of structure **2**, we turned our attention to the following facts found in the course of investigations previously reported:[1] (1) α-hydroxy acid (*R*)-**7** in nearly 100%ee is obtainable by an optical resolution using L-Leu-$NHNH_2$ (Eq. 1), and accordingly, we can use (*R*)-**7** as a chiral starting material; (2) although, as previously described, attempts to obtain optically active 2-halo derivatives (*R*)-**6** were unsuccessful due to the presence of an electron-donating group at the para position, an S_N2 reaction itself at the benzylic position proceeds with virtually complete inversion of configuration (Eq. 2).



1 2

R_1, R_2, R_3: protective group



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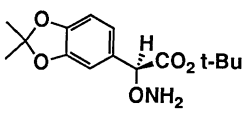
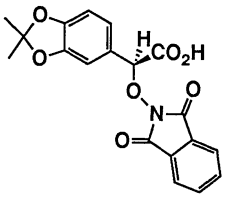
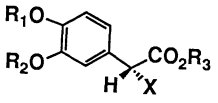


(*S*)-4



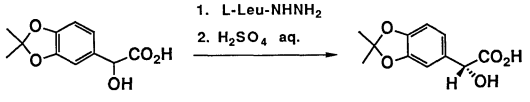
(*S*)-5



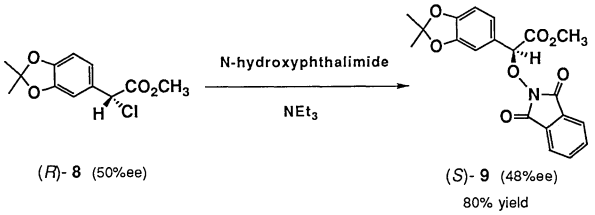
(*R*)-6

X= halogen

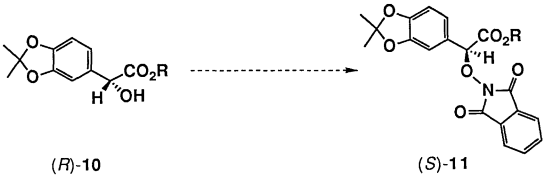
R_1, R_2, R_3 : protective group



7 (*R*)-7 (96%ee) (1)



(*R*)-8 (50%ee) (*S*)-9 (48%ee) 80% yield (2)



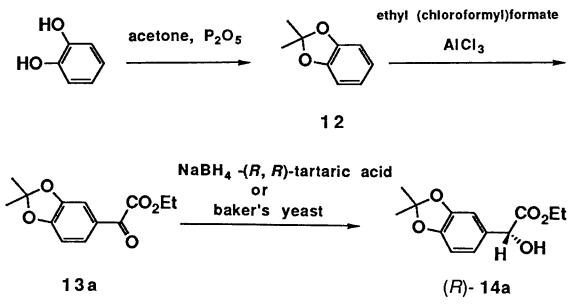
(*R*)-10 (*S*)-11 (3)

R: a protecting group

Namely, it appeared to us that α-(phthalimidooxy) ester (*S*)-**11** could be prepared from α-hydroxy acid (*R*)-**10** with a steric inversion under appropriate conditions (Eq. 3). In addition, tedious operations involved in the recovery of the undesired enantiomer and its racemization might be omitted in this approach. In this paper, we report some details of this synthetic strategy.

Results and Discussion

We have already shown two synthetic sequences to racemic **7** starting from catechol[1] and, as described above, (*R*)-**7** is obtainable by optical resolution of racemic **7**.[1] On the other hand, however, one of the most convenient methods for the preparation of optically active α-hydroxy esters is asymmetric reduction of their corresponding α-keto esters. Consequently, an asymmetric reduction of α-keto ester **13a** was first explored in order to obtain ethyl (*R*)-2-(3,4-isopropylidenedioxyphenyl)-2-hydroxyacetate [(*R*)-**14a**] (Scheme 1). Starting material **13a** was prepared by the method shown in Scheme 1.

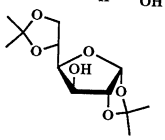
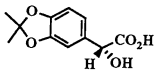


Scheme 1.

An isopropylidenation of catechol in toluene by using acetone in the presence of phosphorus pentaoxide gave 1,2-isopropylidenedioxybenzene (**12**) in 70% yield. α-Keto ester **13a** was prepared by the Friedel–Crafts acylation[4] of **12** with ethyl (chloroformyl)formate in 86% yield without cleavage of isopropylidene protection.[5]

Asymmetric reduction of α-keto esters has been widely studied. One of them utilizes chiral reducing agents[6] and another is a catalytic hydrogenation in the presence of chiral ligands.[7] Although high optical purities are obtained in these cases, neither the chiral reducing agents nor hydrogenation catalysts are necessarily easily accessible. Also, diastereoselective reductions of chiral α-keto amides or α-keto esters with metal hydrides have been well documented.[8] However, because these methods are of multi-step process, they do not fill our requirements for the practical preparation of (*R*)-**14a**. On the other hand, asymmetric reductions of prochiral ketones and cyclic imines with chiral $NaBH_4$ derived systems which are prepared by a reaction of $NaBH_4$ with a monosaccharide[9] or with an α-amino acid derivative (especially L-Pro derivative),[10] have been investigated actively. Although these methods result in moderate optical purities, their simple systems seem applicable to our needs which aim at a more efficient and economical synthetic method for (*R*)-**14a**. Accordingly, we focused

Table 1. Asymmetric Reduction of **13a** with Modified Reagents Prepared from $NaBH_4$ and Various Chiral Compounds[a]

Run	Chiral compound	**14a** Chemical yield/%	**14a** Optical yield/%ee[d]
1	L-Pro	80	53 (*R*)
2	(*R*,*R*)-Tartaric acid	96	70 (*R*)
3	Benzyloxycarbonyl-L-Pro	75	17 (*R*)
4		c)	29 (*R*)
5	 +$ZnCl_2$[b]	c)	9 (*S*)
6		c)	8 (*R*)
7	(*S*)-Mandelic acid	c)	5 (*R*)
8	(*S*)-Malic acid	c)	0
9	*O*,*O*-Dibenzoyl-(*R*,*R*)-tartaric acid	c)	0
10	(*R*,*R*)-Diethyl tartarate	c)	0

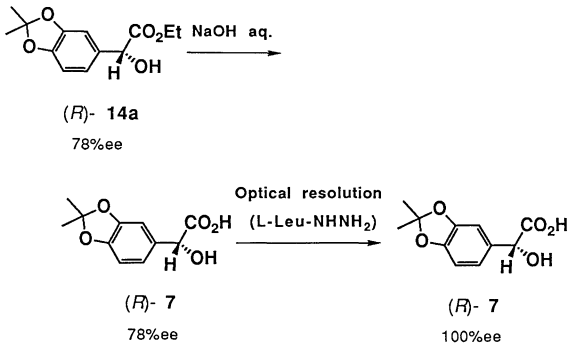
a) Reaction conditions: A solution of **13a** (1.0 mmol) in THF (5 ml) was added at 0 °C to a stirred suspension of chiral reducing agent prepared from $NaBH_4$ (1.0 mmol) and a chiral compound (1.0 mmol) in THF (5 ml) at room temperature for 3 h; the whole was then stirred at 0 °C for 1 d. b) See Ref. 10(e). c) Not estimated. d) Assayed by HPLC analysis using a chiral column. See Experimental Section.

on the asymmetric reduction of **13a** by using chiral $NaBH_4$ derived systems prepared in situ. Reductions of **13a** with reagents prepared in situ from $NaBH_4$ (1.0 equiv) and various chiral compounds (1.0 equiv) were carried out in THF at 0 °C (Table 1).

As can be seen in Table 1, the system derived from $NaBH_4$ and (*R*,*R*)-tartaric acid provided (*R*)-**14a** with an enantiomeric excess as high as 70% (Run 2, Table 1). The optical purity in this system was enhanced to 78%ee by using 1.5 equiv of (*R*,*R*)-tartaric acid and lowering the reaction temperature to −20 °C.[11] The chiral reducing agents derived from L-Pro (Run 1, Table 1) and its derivatives (Runs 3 and 4, Table 1) were found to be less effective. The asymmetric reduction of propiophenone with the reagent prepared from $NaBH_4$ and (*S*,*S*)-tartaric acid has already been reported, which, however, gives (*S*)-1-phenyl-1-propanol in only 10% optical yield.[12] Interestingly, the systems using other chiral α-hydroxy acids were found to be much less effective (Runs 6, 7, and 8, Table 1). Also, in the case where either a hydroxyl group or a carboxyl group of (*R*,*R*)-tartaric acid was protected, the stereoselectivities were completely out of operation (Runs 9 and 10, Table 1). Presumably, the steric configuration in the chelation between $NaBH_4$ and bidentate (*R*,*R*)-tartaric acid exerts and effect on the course of the hydride-transfer step in the transition state.

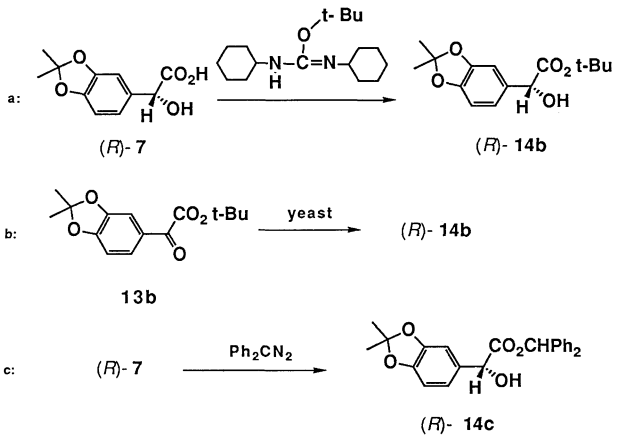
Asymmetric reductions of keto esters to hydroxy esters by microbial transformation have also been widely studied.[13] Consequently, we undertook a study aiming at an asymmetric reduction of **13a** by using a yeast. A reduction of **13a** with baker's yeast in water containing sucrose gave (*R*)-**14a** in 94%ee optical yield (65% chemical yield). The absolute configuration of the product obtained by reduction of a carbonyl group containing a large group and a small group to an alcohol is known to be determined by application of Prelog's rule.[14] Because 3,4-isopropylidenedioxyphenyl group is larger than ethoxycarbonyl group in bulkiness, the absolute configuration of **14a** obtained by yeast reduction is expected to be an (*R*)-configuration. Furthermore, **14a** obtained by yeast reduction showed a Cotton effect $[\theta]_{241}=-14900$ ($c=2.64\times10^{-4}$ M, 17 °C) (1 M=1 mol dm^{-3}). It has been reported that the sign of Cotton effect in the low-wavelength region is negative for the aromatic chromophere of (*R*)-mandelic acid esters.[15] Therefore, it is concluded that **14a** obtained by yeast reduction has an (*R*)-configuration. The absolute configuration of the products in Table 1 was determined by a comparison with (*R*)-**14a** obtained by yeast reduction in HPLC analysis using a chiral column.

A treatment of (*R*)-**14a** (78%ee) with NaOH in aq MeOH gave (*R*)-**7** quantitatively (Scheme 2). The optical purity of the obtained (*R*)-**7** proved that none of (*R*)-**7** racemized in the course of the alkaline hydrolysis. The obtained (*R*)-**7** was treated with L-Leu-$NHNH_2$ in aq MeOH and subjected to a pH adjustment with H_2SO_4 aq to give a diastereomer salt, which was recrystallized by pH adjustment to afford a purified diastereomer salt [100%ee as (*R*)-**7**]. Subsequently acidification of the diastereomer salt followed by crystallization gave (*R*)-**7** (100%ee) in 75% chemical yield from (*R*)-**14a** (Scheme 2).[16] The optical purity of (*R*)-**7** was confirmed by HPLC analysis of a diastereomer prepared from (*R*)-**7** and L-Leu-OMe. Thus, (*R*)-**7** was coupled with L-Leu-OMe by using 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (WSC·HCl) and 1-hydroxybenzotriazole (HOBt) to give *N*-[2-(3,4-isopropylidenedioxyphenyl)-2-hydroxyacetyl]-L-Leu-OMe. The optical purity determined by the diastereomer was in accord with that determined by the assay of the enantiomer.



Scheme 2.

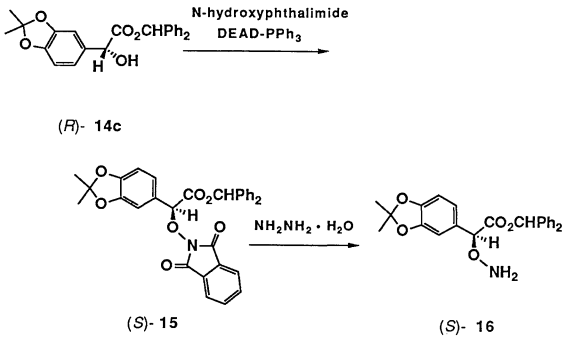
As previously described, the protective group R_3 in a compound of structure **2** should be removable under conditions in which β-lactam ring is stable. Although *t*-butyl group seemed to be suitable for R_3, attempts to obtain α-hydroxy *t*-butyl ester (*R*)-**14b** in both chemically and optically high yield were unsuccessful. Namely, an initial attempt to treat (*R*)-**7** with *O*-*t*-butyl-*N*,*N*′-dicyclohexylisourea[17] gave (*R*)-**14b** in 72% yield even in using 5.0 equiv of the alkylating agent (Scheme 3a). Also, an asymmetric reduction of *t*-butyl



Scheme 3.

ester of α-keto acid **13b** by using baker's yeast gave (*R*)-**14b** in 87%ee (Scheme 3b).[18] Consequently, we chose a diphenylmethyl group as the protective group R_3. A treatment of (*R*)-**7** with Ph_2CN_2 in AcOEt gave diphenylmethyl ester of α-hydroxy acid (*R*)-**14c** quantitatively (Scheme 3c). No decrease in optical purity was observed in this esterification.

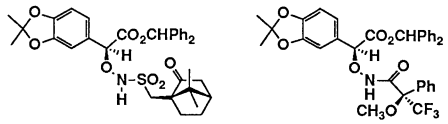
The Mitsunobu reaction has proven to be a useful and practical method for conversion of alcohols to various derivatives.[19] Especially it is known that the reaction proceeds with virtually complete inversion of configuration.[20] Accordingly, we made a study on an application of the Mitsunobu reaction to the conversion of (*R*)-**14c** into α-(phthalimidooxy) ester (*S*)-**15**. The reaction of alcohols with *N*-hydroxyphthalimide under the Mitsunobu conditions has been known.[21] An initial attempt to obtain (*S*)-**15** from (*R*)-**14c** (100%ee) by the treatment with *N*-hydroxyphthalimide in the presence of triphenylphosphine and diethyl azodicarboxylate in AcOEt at room temperature, gave (*S*)-**15** in only 30%ee optical purity and in 46% chemical yield. However, both the optical purity and chemical yield were enhanced to 99.4%ee and 95%, respectively, by carrying out the reaction at −20 °C and by minimizing the H_2O content in the reaction solution (Scheme 4). Because the pK_a value of *N*-hydroxyphthalimide is 6.91 in aqueous medium,[22] the rate-determining step of the whole Mitsunobu process may be the S_N2 step rather than the alcohol activation step.[20d] Actually the reaction followed the S_N2 kinetics, being first order in each of (*R*)-**14c** and *N*-hydroxyphthalimide. Attempts to detect phosphorus-containing intermediates, phosphoranes[23] or alkoxyphosphonium salts,[20d,24] by using HPLC analyses or ^{31}P NMR studies were unsuccessful.[25] A recrystallization of (*S*)-**15** (99.4%ee) from MeOH gave (*S*)-**15** (100%ee) as white crystals (isolated yield 86% from (*R*)-**14c**). It is important to run the Mitsunobu reaction under controlled conditions in order to obtain (*S*)-**15** (100%ee).



(*R*)- **14c** (*S*)- **15** (*S*)- **16**

Scheme 4.

Finally, the removal of the phthalimido group by using hydrazine hydrate in CH_2Cl_2 gave (*S*)-**16** (100%ee) in 97% chemical yield (Scheme 4). Furthermore, it was confirmed by an HPLC analysis of the diastereomer prepared from (*S*)-**16** and (+)-10-camphorsulfonyl chloride. Thus, the obtained (*S*)-**16** was treated with (+)-10-camphorsulfonyl chloride in CH_3CN containing NEt_3 to give sulfoneamide (*S*)-**17**. The optical purity of the diastereomer was in accord with the enantiomer. It was also reconfirmed by ^1H NMR spectra of (*S*)-**17** and (+)-3,3,3-trifluoro-2-methoxy-2-phenylpropionamide[26] ((*S*)-**18**) that the obtained (*S*)-**16** was completely free from (*R*)-enantiomer. The signals of the methylene proton at position 10 in (*S*)-**17** and the methyl proton of methoxyl group in (*S*)-**18** were usable to detect the (*R*)-enantiomer.



(*S*)-17 (*S*)-18

In conclusion, a simpler and more practical synthetic route for the chiral α-(aminooxy) ester (*S*)-**16** (100%ee) has been established. In this synthetic route, (*S*)-**16** was prepared through 3 steps from α-hydroxy acid (*R*)-**7** (100%ee), which was obtained by the asymmetric reduction of α-keto ester **13a** with $NaBH_4$-(*R*,*R*)-tartaric acid followed by a hydrolysis and an optical resolution using L-Leu–$NHNH_2$. The procedures described here have been used to prepare multikilogram batches of (*S*)-**16**, which is in turn converted to M-14659, a potent antipseudomonal cephalosporin antibiotic.

Experimental

General. All reactions except optical resolution were carried out under nitrogen atmosphere. Unless otherwise noted, materials were obtained from commercial suppliers and used without further purification. Melting points were determined using a Büchi 510 apparatus and are uncorrected. ^1H NMR spectra were obtained on a Varian VXR-300 (300 MHz) spectrometer with tetramethylsilane as the internal standard. IR spectra were obtained on a JASCO IR-800

Table 2. HPLC Analyses of the Synthetic Intermediates[a]

Compound	Retention time/min
12	11.3
13a	12.1
14a	7.1
7	3.2
14c	15.6
15	35.4
16	17.6

a) HPLC conditions: column NUCLEOSIL-ODS (5 μm) 6 mm×200 mm, eluent CH_3CN–H_2O (6:4, v/v), flow 1.0 ml min^{-1}, 50 °C, and λ 290 nm.

Table 3. HPLC Analyses of the Optical Isomers

Compound	Column	Eluent	Flow	Column temperature	UV detection	Retention time/min	
			ml min^{-1}	°C	nm	(*R*)-	(*S*)-
14a	Daicel CHIRALPAK OT(+) 4.6 mm×250 mm	MeOH	0.50	−2	290	8.2	13.0
7	Daicel CHIRALPAK WH 6.4 mm×250 mm	0.25 M $CuSO_4$ aq	1.0	50	238	31	25
7-L-Leu-OMe	NUCLEOSIL-5NH_2 6 mm×200 mm	Hexane–*i*-PrOH (92.5:7.5)[a]	1.0	20	288	29.6	22.7
14c	Daicel CHIRALPAK OT(+) 4.6 mm×250 mm	MeOH–H_2O (92:8)[a]	0.50	−2	290	18.5	22.5
15	Daicel CHIRALCEL OA 4.6 mm×250 mm	Hexane–EtOH–*i*-PrOH–H_2O (100:10:5:0.5)[a]	0.50	20	290	32.1	37.1
16	Daicel CHIRALCEL OD 4.6 mm×250 mm	Hexane–EtOH–*i*-PrOH (100:10:10)[a]	0.50	20	290	18.3	23.1
17	NUCLEOSIL 7.2 mm×250 mm	CH_3CN–H_2O (6:4)[a]	1.0	20	290	47	40

a) Volume ratio.

or a Perkin–Elmer 1640 spectrometer in the indicated phase. Mass spectra were measured on a JEOL DX-300 mass spectrometer. Optical rotations were recorded on a JEOL DIP-140 polarimeter. Analytical thin-layer chromatography (TLC) was performed on Merck silica gel 60 F_{254} glass-backed plates. Column chromatography was done using Merck silica gel 60 (70—230 mesh). Chemical purities of the synthetic intermediates (accordingly, yields in each step) were determined by HPLC analysis. All compounds were assayed under the same conditions. The HPLC conditions and the retention times of all intermediates were tabulated in Table 2. Optical purities of enantiomeric intermediates were also determined by HPLC analysis using a chiral column. Some of optically active intermediates were converted to diastereomers whose optical purities were determined. The conditions were summarized in Table 3.

1,2-Isopropylidenedioxybenzene (12). A mixture of catechol (110 g, 1.0 mol) and P_2O_5 (28.4 g, 0.20 mol) in toluene (500 ml) was heated at 75 °C. To the suspension was added dropwise acetone (147 ml, 2.0 mol) over 3 h. After the addition had been started, four portions of P_2O_5 (28.4 g, 0.20 mol) were added to the reaction mixture every 30 min. Totally 142 g of P_2O_5 was used. After the addition of acetone, the mixture was stirred at 75 °C for further 1 h. After removing the oily compound (the lower layer), 150 ml of 25% NaOH was added. The organic layer was separated, washed with H_2O and concentrated in vacuo to give an oil, from which **12** was obtained by distillation as a colorless liquid: Yield 105 g (70%); bp 75—78 °C/23.5 mmHg (1 mmHg=133.322 Pa); ^1H NMR ($CDCl_3$) δ=1.65 (s, 6H) and 6.7—6.8 (m, 4H).

Ethyl 2-(3,4-Isopropylidenedioxyphenyl)-2-oxoacetate (13a). To a suspension of $AlCl_3$ (5.0 g, 37.5 mmol) in CH_2Cl_2 (30 ml) cooled to 5 °C was added slowly ethyl (chloroformyl)formate (3.41 g, 25.0 mmol) and the resulting solution was stirred for 15 min at 5 °C. To the solution was added **12** (3.75 g, 25.0 mmol) over 5 min. After the addition the mixture was stirred at room temperature for 1 h. The reaction mixture cooled to 5 °C was poured slowly into 25 ml of H_2O cooled to 5 °C. The organic layer was separated, washed (satd. $NaHCO_3$ and then H_2O), dried ($MgSO_4$), filtered and concentrated in vacuo to give a wine-red liquid, from which **13a** was obtained by distillation as a yellowish liquid: Yield 5.38 g (86%); bp 129—131 °C/0.65 mmHg; ^1H NMR ($CDCl_3$) δ=1.40 (t, 3H), 1.68 (s, 6H), 4.42 (q, 2H), 6.69 (d, 1H, *J*=11), 7.38 (d, 1H, *J*=2.5), and 7.55 (dd, 1H, *J*=11, 2.5); MS (FD) *m/z* 250 (M^+).

Ethyl (*R*)-2-(3,4-Isopropylidenedioxyphenyl)-2-hydroxyacetate [(*R*)-14a]. Reduction by $NaBH_4$-(*R*, *R*)-Tartaric Acid. $NaBH_4$ (1.26 g, purity 90%, 30.0 mmol) and (*R*,*R*)-tartaric acid (4.50 g, 30.0 mmol) were suspended in THF (100 ml) and the resulting suspension was heated at 70 °C for 4 h. The suspension cooled to −20 °C was added dropwise **13a** (5.0 g, 20.0 mmol) in 10 ml of THF over 5 min. After the addition, the reaction mixture was stirred at −20 °C for 15 h. To the mixture were added 50 ml of AcOEt and 25 ml of 1M (1 M=1 mol dm^{-3}) HCl at −20 °C. The organic layer was separated, washed (satd. $NaHCO_3$), dried ($MgSO_4$), filtered and concentrated in vacuo to give a pale yellow oil. Chromatographic separation on silica gel (30 g, hexane–AcOEt, 6:1 v/v) gave **14a** as an oil: Yield 4.74 g (94%, optical purity 78%ee); ^1H NMR ($CDCl_3$) δ=1.25 (t, 3H), 1.65 (s, 6H), 3.25 (b, 1H), 4.22 (m, 2H), 5.03 (s, 1H), 6.68 (d, 1H, *J*=10), 6.79 (d, 1H, *J*=2.5), and 6.82 (dd, 1H, *J*=10, 2.5); MS (FD) *m/z* 252 (M^+).

Reduction by $NaBH_4$-L-Pro. $NaBH_4$ (5.04 g, 90% purity, 120 mmol) and L-Pro (13.8 g, 120 mmol) were suspended in 240 ml of THF and the resulting suspension was stirred at room temperature for 3.5 h. To the resulting clear solution cooled to 0 °C was added **13a** (30.0 g, 120 mmol) in 30 ml of THF over 10 min and the mixture was stirred at 0 °C for 17.5 h. The solvent of the reaction mixture was removed in vacuo. The obtained oil was dissolved in toluene (120 ml) and H_2O (120 ml). The organic layer was separated, washed (H_2O), dried ($MgSO_4$), filtered and concentrated in vacuo to give **14a** as an oil: Yield 29.5 g (86% chemical purity, 84% yield, 52%ee). The NMR spectra were identical with those of **14a** prepared above.

Reduction by Yeast. A mixture of sucrose (15 g) and baker's yeast[27] (14 g) in 100 ml of distilled water was stirred

at 30 °C for 1 h. To the mixture was added **13a** (7.84 g, 31.4 mmol) and the fermenting suspension was stirred at 30 °C for another 22 h. The mixture was worked up by adding 3 g of Celite and filtering. The Celite was washed with 50 ml of AcOEt and then with 50 ml of H_2O. The washings were combined with the filtrate. The organic layer was separated and the aquesous layer was washed with AcOEt (30 ml×3). The combined AcOEt extracts were washed (brine), dried ($MgSO_4$), filtered and concentrated in vacuo to give an oil. Chlomatographic separation on silica gel (30 g, hexane–AcOEt, 6:1 v/v) gave **14a** as a pale yellow oil: Yield 5.14 g (65%, 94%ee). The NMR spectra were identical with those of **14a** prepared above.

(*R*)-2-(3,4-Isopropylidenedioxyphenyl)-2-hydroxyacetic Acid [(*R*)-7]. α-Hydroxy ester **14a** [56.3 g, chemical purity 88%, optical purity 76%ee, 173 mmol as (*R*)-**14a**] was dissolved in a mixture of MeOH (150 ml) and 48% NaOH (17 ml). The mixture was stirred at 30 °C for 1.5 h. To the mixture was added L-Leu–$NHNH_2$ (28.6 g, 197 mmol) in 150 ml of MeOH. An adjustment of pH to 6.8 with 95% H_2SO_4 followed by a crystallization with stirring at 28 °C for 2 h gave white crystals, which were recrystallized by a pH adjustment to give a diastereomer salt [58.7 g, 100%ee, 92% from (*R*)-**14a**]. The obtained salt was suspended in 300 ml of H_2O and the pH of the mixture was adjusted to 2.0 with 95% H_2SO_4. A crystallization with stirring at 33 °C for 3.5 h gave (*R*)-**7** as a white powder: Yield 30.7 g [optical purity 100%ee, 79% from (*R*)-**14a**]; mp 132—133 °C; $[\alpha]_D^{24}$ −88.7° (*c*=1.36, MeOH); ^1H NMR (Me_2SO-d_6) δ=1.61 (s, 6H), 3.3 (b, 1H), 4.85 (s, 1H), and 6.73—6.88 (m, 3H); IR(KBr) 1702 cm^{-1} (C=O). Found: C, 58.80; H, 5.63%. Calcd for $C_{11}H_{12}O_5$: C, 58.92; H, 5.40%.

Optical Purity Determination of (*R*)-7 by HPLC Analysis of a Diastereomer Prepared from (*R*)-7 and L-Leu-OMe. A sample of (*R*)-**7** (0.224 g, 1.0 mmol) and L-Leu-OMe·HCl (0.272 g, 1.50 mmol) were suspended in 7 ml of CH_3CN containing NEt_3 (0.21 ml, 1.50 mmol). To the obtained clear solution cooled to 0 °C were added 1-hydroxybenzotriazole (0.177 g, 1.0 mmol) and 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (0.211 g, 1.10 mmol) and the reaction mixture was stirred at room temperature for another 2 h. Et_2O (15 ml) was added to the reaction mixture. The organic layer was separated and washed with 1 M HCl and then with saturated $NaHCO_3$. After dilution with an eluent, the organic layer was analyzed by HPLC under the conditions which are shown in Table 3.

Diphenylmethyl (*R*)-2-(3,4-Isopropylidenedioxyphenyl)-2-hydroxyacetate [(*R*)-14c]. α-Hydroxy acid (*R*)-**7** (22.4 g, 100 mmol, 100%ee) was suspended in 120 ml of AcOEt and to the suspension was added dropwise Ph_2CN_2 (20.4 g, 105 mmol) in 15 ml of CH_2Cl_2 over 1 h. During the addition the inner temperature was kept below 35 °C. After the addition, the reaction was stirred for another 1 h. After quenching the excess Ph_2CN_2 with AcOH, the reaction mixture was washed with saturated $NaHCO_3$. The organic layer was separated and concentrated in vacuo to give a white powder, which was recrystallized from EtOH to give (*R*)-**14c** as a white powder: Yield 35.9 g (92%, 100%ee); mp 136—136.5 °C; $[\alpha]_D^{22}$ −34.7° (*c*=0.944, $CHCl_3$); ^1H NMR ($CDCl_3$) δ=1.65 (s, 6H), 5.15 (s, 1H), 6.84 (d, 1H, *J*=10), 6.88 (d, 1H, *J*=2.4), 6.92 (dd, 1H, *J*=10, 2.4), 6.94 (s, 1H), 6.99 (m, 2H), and 7.15—7.4 (m, 8H); IR(KBr) 1731 cm^{-1} (C=O); MS (FD) *m/z* 390 (M^+). Found: C, 73.79; H, 5.74%. Calcd for $C_{24}H_{22}O_5$: C, 73.83; H, 5.68%.

Diphenylmethyl (*S*)-2-(3,4-Isopropylidenedioxyphenyl)-2-(phthalimidooxy)acetate [(*S*)-15]. To a solution of (*R*)-**14c** (19.5 g, 50.0 mmol, 100%ee) in 200 ml of AcOEt were added triphenylphosphine (17.6 g, 67.0 mmol) and *N*-hydroxyphthalimide (9.79 g, 60.0 mmol). To the obtained suspension cooled to −20 °C was added diethyl azodicarboxylate (11.7 g, 67.0 mmol) in one mass. The reaction mixture was stirred at −20 °C for 1 h. The solvent was removed in vacuo. A recrystallization from 160 ml of MeOH at 5 °C gave (*S*)-**15a** as white crystals: Yield 23.0 g (86%, 100%ee); mp 117.5—118 °C; $[\alpha]_D^{22}$ +116.7° (*c*=1.30, $CHCl_3$); ^1H NMR ($CDCl_3$) δ=1.65 (s, 6H), 5.29 (s, 1H), 6.66 (d, 1H, *J*=10), 6.92 (d, 1H, *J*=2.4), 6.97 (dd, 1H, *J*=10, 2.4), 6.99 (s, 1H), 7.1—7.35 (m, 10H), and 7.65—7.8 (m, 4H); IR(KBr) 1793, 1752, and 1734 cm^{-1} (C=O). Found: C, 71.49; H, 4.94; N, 2.51%. Calcd for $C_{32}H_{25}NO_7$: C, 71.76; H, 4.71; N, 2.62%.

Diphenylmethyl (*S*)-2-(3,4-Isopropylidenedioxyphenyl)-2-(aminooxy)acetate [(*S*)-16]. To a solution of (*S*)-**15** (16.1 g, 30.0 mmol, 100%ee) in 60 ml of CH_2Cl_2 was added NH_2NH_2·H_2O (3.60 g, 72.0 mmol). The mixture was stirred at room temperature for 1 h. H_2O (150 ml) was added to the reaction mixture and the resulting precipitates were removed by filtration. The organic layer of the filtrate was separated, washed (H_2O), dried ($MgSO_4$), filtered and concentrated in vacuo to give a white solid. A recrystallization from MeOH gave (*S*)-**16** as a white powder: Yield 11.8 g (97%, 100%ee); mp 96—97 °C; $[\alpha]_D^{24}$ +24.5° (*c*=0.669, $CHCl_3$); ^1H NMR ($CDCl_3$) δ=1.66 (s, 6H), 5.22 (s, 1H), 6.66 (d, 1H, *J*=10), 6.75 (d, 1H, *J*=2.4), 6.81 (dd, 1H, *J*=10, 2.4), 6.92 (s, 1H), 7.07—7.11 (m, 2H), and 7.20—7.32 (m, 10H); IR(KBr) 1730 cm^{-1} (C=O); Found: C, 70.89; H, 5.60; N, 3.40%. Calcd for $C_{24}H_{23}NO_5$: C, 71.10; H, 5.72; N, 3.45%.

Diphenylmethyl (*S*)-2-(3,4-Isopropylidenedioxyphenyl)-2-[[(+)-10-camphorsulfonyl]aminooxy]acetate [(*S*)-17]. To a solution of (*S*)-**16** (81 mg, 0.20 mmol, 92.0%ee by HPLC analysis using a chiral column) in 2 ml of CH_3CN were added NEt_3 (0.056 ml, 0.40 mmol) and (+)-10-camphorsulfonyl chloride (100 mg, 0.40 mmol). The reaction mixture was stirred at room temperature for 1 h. The solvent was removed in vacuo to give an oil, which was dissolved in 20 ml of AcOEt. After washed with 1 M HCl aq, saturated $NaHCO_3$ and brine in this order, the organic layer was assayed by HPLC under the conditions which are shown in Table 3 to result in 92.3%ee. Racemic **16** was converted to racemic **17** by the method shown above. Each of (*S*)-**17** and (*R*)-**17** was isolated by preparative HPLC under the conditions shown in Table 3. (*S*)-**17**: ^1H NMR ($CDCl_3$) δ=0.94 (s, 3H), 1.00 (s, 3H), 1.67 (s, 3H), 1.68 (s, 3H), 1.87—2.14 (m, 6H), 2.41 (m, 1H), 2.89, 2.94, 3.81, and 3.86 (ABq, 2H, methylene proton at position 10), 5.58 (s, 1H), 6.68 (d, 1H, *J*=10), 6.77 (d, 1H, *J*=2.4), 6.84 (dd, 1H, *J*=10, 2.4), 6.88 (s, 1H), 7.07—7.11 (m, 2H), 7.18—7.30 (m, 8H), and 8.43 (s, 1H). (*R*)-**17**: ^1H NMR ($CDCl_3$) δ=0.90 (s, 3H), 0.95 (s, 3H), 1.665 (s, 3H), 1.662 (s, 3H), 1.90—2.20 (m, 6H), 2.41 (m, 1H), 2.79, 2.84, 3.70, and 3.75 (ABq, 2H, methylene proton at position 10), 5.61 (s, 1H), 6.63 (d, 1H, *J*=10), 6.76(d, 1H, *J*=2.4), 6.80 (dd, 1H, *J*=10, 2.4), 6.95 (s, 1H), 7.13—7.33 (m, 10H), and 9.12 (s, 1H).

Diphenylmethyl (*S*)-2-(3,4-Isopropylidenedioxyphenyl)-2-[[(2*R*)-3,3,3-trifluoro-2-methoxy-2-phenylpropionyl]aminooxy]acetate [(*S*)-18]. To a solution of (*S*)-**16** (203 mg, 0.50 mmol, 100%ee) in 5 ml of CH_3CN containing NEt_3 (0.075 ml, 0.60 mmol) was added (*R*)-(+)-3,3,3-trifluoro-2-methoxy-2-phenylpropionyl chloride[2] (0.150 mg, 0.60 mmol). The reaction mixture was stirred at room temperature for 1 h. The solvent was removed in vacuo and the obtained oil was dissolved in 20 ml of Et_2O. The Et_2O solution was washed with 1 M HCl, saturated $NaHCO_3$ and brine in this order and then concentrated in vacuo to give an oil, which was analyzed by NMR: ^1H NMR ($CDCl_3$) δ=1.66 (s, 6H), 3.25 (s, 3H, methyl proton in methoxyl group), 5.53 (s, 1H), 6.68 (d, 1H, *J*=10), 6.79 (s, 1H, *J*=2.4), 6.82 (dd, 1H, *J*=10, 2.4), 6.88 (s, 1H), 7.03—7.48 (m, 15H), and 9.52 (s, 1H). On the other hand, racemic **18** showed two peaks at δ=3.25 and 3.18 corresponding to methyl proton in methoxyl group.

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