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Synthesis of a Chiral α-(Aminooxy)arylacetic Ester. I. A Route through Optical Resolution of a Racemic α-(Phthalimidooxy)arylacetic Acid

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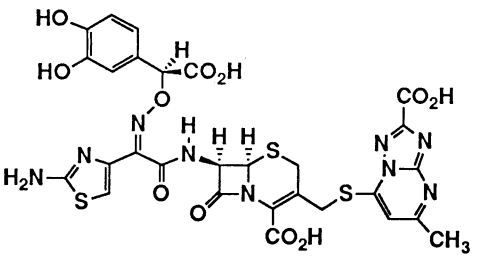
A synthetic route has been developed to the synthesis of a chiral *O*-alkyloxime (*S*)-**16**, which can be a synthetic intermediate for a potent antipsedomonal cephalosporin antibiotic M-14659 (**1**). The oxime moiety in (*S*)-**16** has a chiral center at the carbon atom adjacent to the oxygen atom. We have achieved that (*S*)-**16** can be prepared via *t*-butyl 2-aminooxy-2-[3,4-(isopropylidenedioxy)phenyl]acetate [(*S*)-**15**] from an optically active α-(phthalimidooxy) acid (*S*)-**12a** which is obtained by resolution using quinine. It has been demostrated that M-14659 prepared from (*S*)-**16** is completely free from its (*R*)-diastereomer.

M-14659 (**1**) is a new injectable semisynthetic cephalosporin antibiotic which was discovered by scientists at the Mochida Pharmaceutical Co., Ltd.[1] In vitro and in vivo **1** has a wide spectrum of antibacterial activities against Gram-positive and Gram-negative bacteria. Especially, **1** is more active against *Pseudomonas aeruginosa* including multi-drug resistant strains than ceftizidime which is the most potent agent against *P. aeruginosa*. The structure of **1** contains a 2-(2-amino-4-thiazolyl)-2-[(*Z*)-[(*S*)-carboxy-(3,4-dihydroxyphenyl)methyl]oxyimino]acetamido group at its position 7. In order to synthesize **1** in kilogram quantities we required to establish an efficient synthetic method for optically active *O*-alkyloxime **2**. A cephalosporin derivative which has an *O*-alkyloxime moiety in its side chain at the position 7 and moreover has a chiral center at the carbon atom adjacent to the oxygen atom in *O*-alkyloxime, is already known.[2] Because the alkyl moiety in *O*-alkyloxime **2** has a complex structure, their method in which an optical resolution is conducted in the step of the compound corresponding to **2**, does not seem applicable to this case.[3] Our effort has been focused on developing a more efficient and practical synthetic strategy. In this paper we report some details of synthetic sequences for optically active compound **2**.



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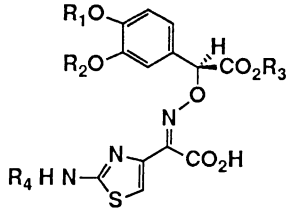

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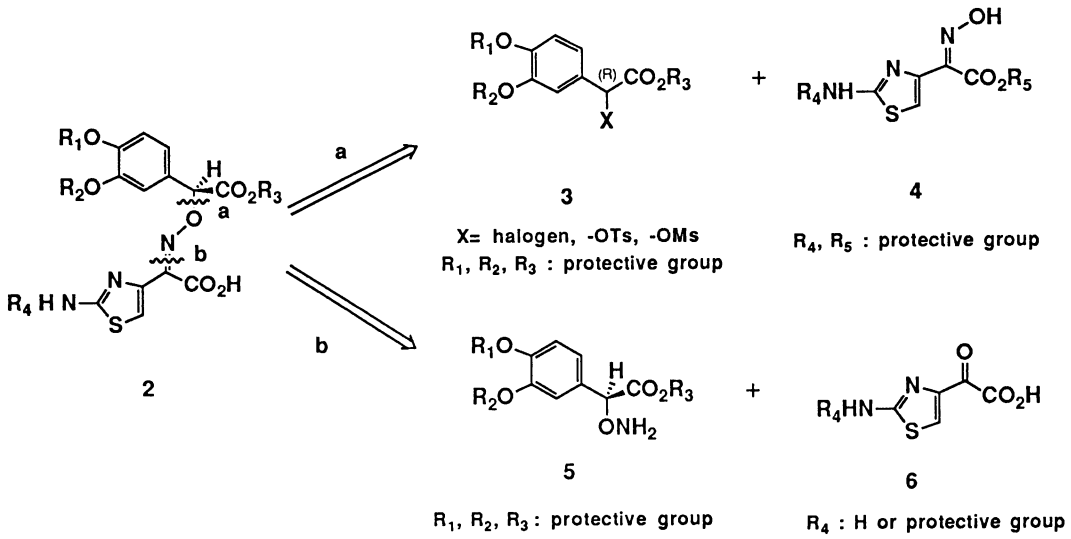
R_1, R_2, R_3, R_4 : protective group

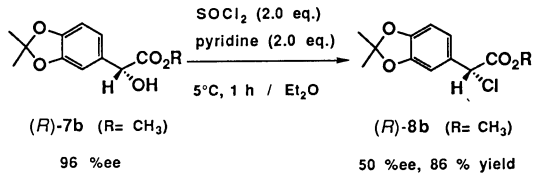
Results and Discussion

It appeared to us that two approaches would be possible for the synthesis of **2** (Scheme 1). The first approach utilizes *O*-alkylation of oxime **4** (Scheme 1.a). However, attempts to obtain an optically active halide (*R*)-**8b** from an optically active alcohol (*R*)-**7b** with complete retention were unsuccessful[4] (Scheme 2). About the attempts utilizing *O*-alkylation of oxime **4** using tosylates, it has been reported that complete racemization occurs during an S_N2 reaction of methyl (*S*)-2-mesyloxy-2-phenylacetate with cesium propionate in DMF.[5] Moreover our attempt to couple α-tosyloxy ester **9** with oxime **10** (*t*-BuOK in THF) was unsuccessful and no desired α-(alkyloxyimino) ester **11** was obtainable (Scheme 3).

We therefore turned our attention to the second approach toward preparation of **2** utilizing oxime formation from optically active α-(aminooxy)phenylacetic acid derivatives **5** and α-keto acid **6** (Scheme 1.b). Having reached our goal by this approach, we needed to develop an efficient synthetic method for optically active **5**. Although various synthetic methods for *O*-alkylhydroxylamines have been reported, only a few of them have a chiral center at the carbon atom adjacent to the oxygen atom.[6] It appeared to us that synthetic sequences containing optically active **3** [for example, 2-chloroacetate (*R*)-**8b**] were not feasible as mentioned above. We therefore have concentrated on developing synthetic routes involving optical resolution after the α-aminooxy group or its equivalent has been incorporated. Protecting groups R_1, R_2, and R_3 in **5** were chosen since they might be easily removed after the

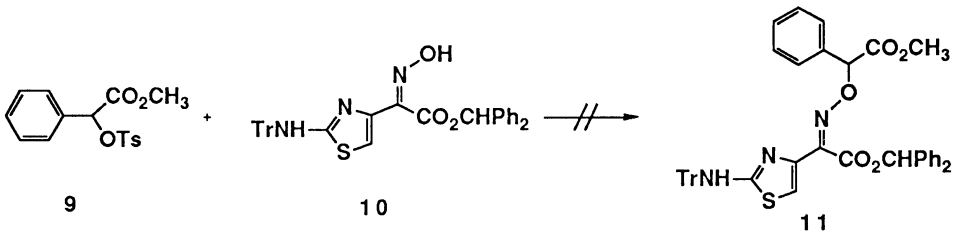


Scheme 1.

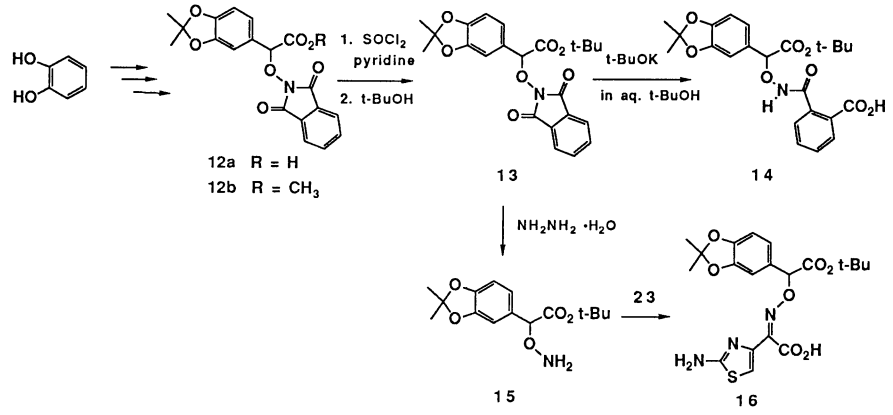


Scheme 2.

side chain moiety **2** was coupled with a cephalosporin derivative. The phthaloyl protection for the aminooxy group in the preparation of **5** was chosen because of the easy deprotection under the conditions that R_1, R_2, and R_3 were stable. Thus, we chose α-(alkyloxyimino) acid **16** as a target molecule and undertook resolution studies on α-(phthalimidooxy) acid **12a**, the substituted benzoic acid **14**, the α-(aminooxy) acid **15**, and **16**, shown in Scheme 4.

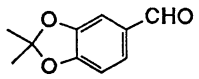


Scheme 3.



Scheme 4.

Preparation of Substrates to Be Optically Resolved. The overall synthetic plan for α-(phthalimidooxy) acid **12a** is outlined in Scheme 5. Catechol was treated with chloral in CH_2Cl_2 in the presence of triethylamine to provide α-(trichloromethyl)benzyl alcohol (**17**) in 63% yield.[7] Isopropylidenation with 2,2-dimethoxypropane in the presence of phosphorus pentaoxide gave 2,2,2-trichloroethanol (**18**) in 86% yield. In the hydrolysis of **18** to α-hydroxy acid **7a**, aldehyde **20** was obtained as a by-product in 25% yield when KOH was used. However, the hydrolysis using LiOH in aqueous dioxane provided **7a** in 70% yield without trace of **20**.[8] Another synthetic sequence to **7a** is illustrated in Scheme 6. Catechol was condensed with glyoxylic acid in aq NaOH provide α-hydroxy acid **21** in 41% yield. Because of the low solubility of **21** in organic solvent, direct protection of phenolic hydroxyl groups by isopropylidenation was unsuccessful. Accordingly, **21** was converted first to 1,3-dioxolan-4-one (**22**) with acetone in the presence of concd H_2SO_4 (84% yield).[9] Isopropylidenation of **22** by using 2,2-dimethoxypropane in the presence of phosphorus pentaoxide followed by hydrolysis in aq KOH gave **7a** in 40—50% yield.[10] α-Hydroxy acid **7a** was converted to α-bromo acid **19** by the treatment with PBr_3 followed by hydrolysis. The *N*-hydroxyphthalimide anion generated initially by NaH was treated with **19** to provide the desired α-(phthalimidooxy) acid **12a** in 86% yield.



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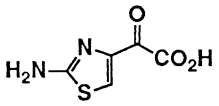

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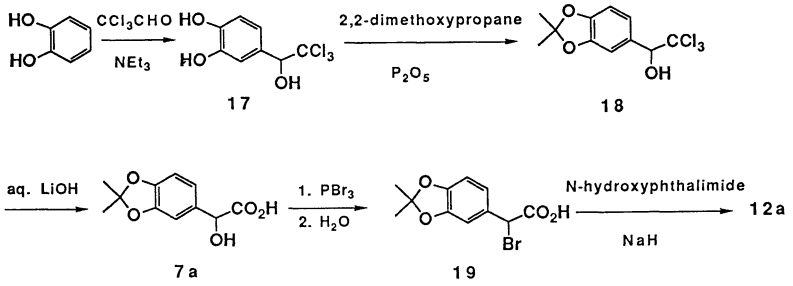
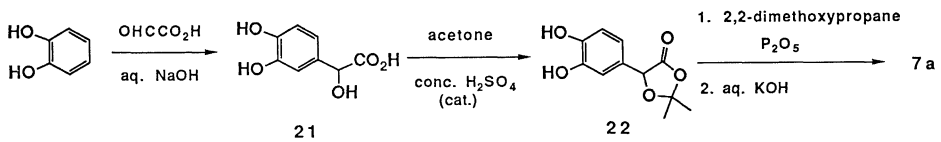
Scheme 4 shows the synthetic route of α-(alkyloxyimino) acid **16**. α-(Phthalimidooxy) acid **12a** was treated with $SOCl_2$–pyridine in toluene and then with *t*-BuOH to give the corresponding *t*-butyl ester **13** in 90% yield. Hydrolysis of **13** to substituted benzoic acid **14** was conducted by using *t*-BuOK in aq *t*-BuOH (78% yield). Removal of the phthaloyl group of *t*-butyl ester **13** with hydrazine hydrate in CH_2Cl_2 afforded α-(aminooxy) ester **15** in 95% yield. Finally α-(alkyloxyimino) acid **16** was prepared by the coupling of **15** with 2-(amino-4-thiazolyl)-2-oxoacetic acid (**23**)[11] in MeOH (80% yield). This coupling gave only syn-form **16**, which was confirmed by ^1H NMR spectrum.[12]

Resolution of Racemic 12a, 14, 15, and 16. Racemic **12a** was resolved through its diastereomeric salts with optically active amines. Because it is known that *N*-alkoxyphthalimides are cleaved by primary amines to ring-opened amides,[14] tertiary amines were mainly tried in search of a suitable basic resolving agent.[15] Racemic compound **12a** and a resolving agent were dissolved in a crystallization solvent at room temperature and the obtained solution was kept at a fixed temperature for crystallization. In the case of a poor solvent for **12a** at room temperature the suspension was heated until clear solution was obtained. The free acid obtained by decomposition of the diastereomeric salts with aq HCl (pH 1.5) followed by extraction with AcOEt, was treated with CH_2N_2 in Et_2O to provide **12b**. The optical purity of resolved **12a** was determined by HPLC analysis of **12b** using an optical isomer separating column. The results are summarized in Table 1.

Resolution of **12a** through its (−)-cinchonidine salts crystallized in aq solvent gave optically active **12a** in high optical purities. Unfortunately, the obtained optically pure **12a** had an undesired (*R*)-configuration.



Scheme 5.



Scheme 6.

Table 1. Optical Resolution of α-(Phthalimidooxy) Acid **12a**

Resolving agent[a]	Crystallization of diastereomeric salts[b]		**12a** recovered from salts[c]	
	Solvent	Temperature/°C	Optical purity[d]/%ee	Yield[e]/%
(−)-Cinchonidine	CH_3CN/H_2O (1/1)[f]	Room temperature	100(*R*)	25
(−)-Cinchonidine	Acetone/H_2O (3/1)[f]	Room temperature	98(*R*)	29
(−)-Cinchonidine	AcOEt/$CHCl_3$ (1/1)[f]	Room temperature	76(*R*)	9
(−)-Cinchonidine	AcOEt	Room temperature	4(*R*)	46
(+)-Cinchonine	AcOEt	2	20(*R*)	9
Quinine	EtOH/H_2O (3/1)[f]	Room temperature	68(*S*)	36
Quinine	EtOH	2	42(*S*)	66
Quinine	MeOH	2	58(*S*)	51
Quinine	Acetone	Room temperature	64(*S*)	51
Quinine	AcOEt	2	42(*S*)	62
Quinine	AcOEt/acetone (1/1)[f]	5	58(*S*)	44

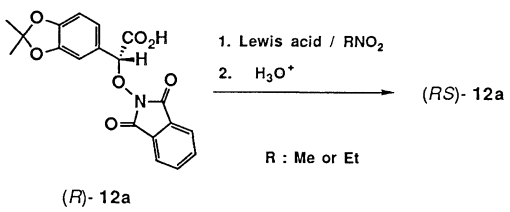
a) An equimolar resolving agent per mol of **12a** was used. b) Crystallization of diastereomeric salts was carried out with stirring. c) Obtained from single crystallization. d) Determined by HPLC analysis using an optical isomer separating column. The details are described in Experimental Section. e) Based on starting racemic **12a**. f) Volume ratio.

Table 2. Racemization of (*R*)-**12a** in the Presence of Lewis Acid

Reagent	Reagent/(*R*)-**12a**[a]	Reaction conditions[b]	Product	
			(*R*)-**12a**/%ee	By-product/%
$AlCl_3$ Et_2O	0.1 0.5	A, 1.5 h	0	—
$AlCl_3$	0.3	B, 6.5 h	4	**8a**(23)[c]
$AlCl_3$	1.0	A, 2 h	0	**8a**(400)[c]
$AlBr_3$	0.3	B, 4.5 h	80	**19**(127)[c]
$BF_3 \cdot Et_2O$ Et_2O	0.1 0.5	A, 15 h	0	—

a) **12a** (1.0 mmole, 100%ee) and the corresponding amounts of Lewis acid and Et_2O. b) A=room temperature in $EtNO_2$; B=0°C in $MeNO_2$. c) Ratio of **8a** or **19** to recovered **12a** in peak area of HPLC analysis.

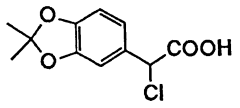
On the other hand, a treatment of racemic **12a** with an equimolar amount of quinine[16] afforded slow precipitation of diastereomeric salts below room temperature. After the decomposition of salts, the desired (*S*)-isomer of **12a** was obtained in moderate optical yields. Especially (*S*)-**12a**, more than 60%ee, was obtained when aq EtOH or acetone was used as a crystallization solvent. However, an undesired reaction of **12a** resulting from the opening of phthalimide ring, was observed when the crystallizations of diastereomeric salts were carried out in aq EtOH. This side reaction was not observed in using acetone for crystallization. Thus, 64%ee (*S*)-**12a** was obtained in 51% yield from racemic **12a** by crystallization in acetone followed by acidic decomposition of diastereomeric salts. Furthermore, we have found that (*S*)-**12a** in 100%ee optical purity was obtainable in 30.5% yield from starting racemic **12a** by recrystallizing



Scheme 7.

64%ee (*S*)-**12a** from acetone/Et_2O.

In a resolution using acetone as a crystallization solvent, (*R*)-isomer-rich **12a** was recovered from the mother liquor. Accordingly, the racemization of **12a** was explored. The racemization of (*R*)-**12a** proceeded smoothly in the presence of Lewis acid (Scheme 7, Table 2). Optically active (*R*)-**12a** was treated with $AlCl_3$ (0.1 equiv) in $EtNO_2$ containing Et_2O for 1.5 h at



8a

room temperature, and racemic **12a** was recovered in 83% yield. The addition of Et_2O was effective for preventing the undesired formation of **8a**[17] when $AlCl_3$ was used. Aluminium tribromide did not promote the racemization effectively and provided **19** as a by-product.[17] The reaction with $BF_3 \cdot Et_2O$ in $EtNO_2$ containing Et_2O for 15 h at room temperature also gave (*RS*)-**12a** in 81% yield.[18] Thus, (*S*)-**12a** was obtained in a 67% total yield based on racemic **12a** in consideration of recovered racemic **12a**.

Resolution of racemic **14** through its diastereomeric salts with optically active amines were also tried. (−)-Cinchonidine, (+)-cinchonine, or quinine did not form any separable salts with racemic **14**. However, (*S*)-(−)-1-phenethylamine gave diaseteromeric salts by crystallization in aq MeOH at room temperature. Treatment with acid followed by extraction with AcOEt gave 27%ee (*S*)-**14**[19] in 35% yield from starting racemic **14**.

O-Alkylhydroxylamines are known to be weak bases ($pK_a \approx 4.5$).[6c,20] Accrodingly, racemic **15** did not form a salt with a weak acid like (*R,R*)-tartaric acid or an N-protected α-amino acid. On the other hand, (+)-10-camphorsulfonic acid gave a clear solution with racemic **15** in Et_2O. Standing it at room temperature gave a precipitation of salt in 77% yield as a mixture of 1:1 diastereomers. All attempts to resolve the mixture by recrystallization were unsuccessful.

Treatment of racemic **16** with equimolar (*R*)-(+)-1-phenethylamine in AcOEt at ambient temperature gave a precipitation of salt in 43% yield. However, this salt liberated only racemic **16**.

Synthesis of 1 from (*S*)-12a via (*S*)-16. Compound (*S*)-**16** was prepared from 100%ee (*S*)-**12a** via the route shown in Scheme 4. Thus, the treatment of (*S*)-**12a** with $SOCl_2$ in toluene in the presence of pyridine followed by reaction with *t*-BuOH provided (*S*)-**13** in 88% yield. Removal of the phthaloyl group with hydrazine hydrate in CH_2Cl_2 gave (*S*)-**15**, which was coupled with **23** in MeOH to afford (*S*)-**16** in 76% yield from (*S*)-**13**. To demonstrate the availability of (*S*)-**16** prepared by this route, the obtained (*S*)-**16** was converted to compound **1** as illustrated in Scheme 8.

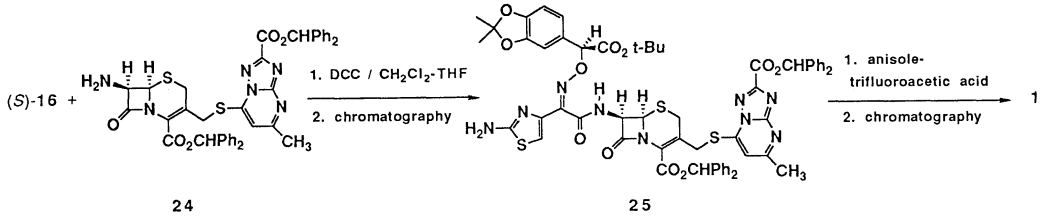
Coupling of (*S*)-**16** with compound **24**[21] by DCC in CH_2Cl_2/THF followed by chromatographic separation on silica gel gave **25** in 39% yield.[1a] Removal of the isopropylidene, *t*-butyl, and benzhydryl groups with anisole and trifluoroacetic acid followed by chromatographic purification provided compound **1** in 39% yield. All of the spectroscopic data were in accord with that reported for compound **1**.[1a] Furthermore, it was confirmed by HPLC analysis that the obtained sample **1** before purification did not contain any trace of the diastereomer derived from (*R*)-**12a**.

A synthetic scheme has been developed in which a chiral 2-aminooxy-2-arylacetic ester (*S*)-**15** (100%ee) is prepared effectively through (*S*)-**12a** obtained by optical resolution. *t*-Butyl ester (*S*)-**15** was converted smoothly to *O*-alkyloxime (*S*)-**16**. The ester (*S*)-**16** is demonstrated to be a synthetic intermediate for **1**, which is a potent antipseudomonal cephalosporin antibiotic.

Experimental

General. All reactions were carried out under nitrogen atmosphere. Unless otherwise noted, materials were obtained from commercial suppliers and used without further purification. Solvents were generally purified and dried by standard methods[22] before use. Melting points determined using a Büchi 510 apparatus and are uncorrected. Proton nuclear magnetic resonance (^1H NMR) spectra were obtained on a Varian EM-390 (90 MHz) or a Varian VXR-300 (300 MHz) spectrometer; chemical shifts are expressed in ppm downfield from internal tetramethylsilane or sodium 3-trimethylsilyl-1-propanesulfonate. ^1H NMR data are tabulated in the order: multiplicity (s, singlet; d, doublet; q, quartet; m, multiplet), the number of protons, coupling constant(s) in hertz. Infrared (IR) spectra were obtained on a JASCO IR-800 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 $60F_{254}$ glass-backed plates. Column chromatography was done using Merck silica gel 60 (70—230 mesh).

2-(3,4-*O*-Isopropylidenedioxyphenyl)-2-hydroxyacetic Acid (7a). Method A: 1-(3,4-Dihydroxyphenyl)-2,2,2-trichloroeth-



Scheme 8.

anol (17). Catechol (33.0 g, 300 mmol) and chloral (70.6 g, 480 mmol) were suspended in 30 ml of AcOEt. To the suspension was added NEt_3 (6.0 g, 59 mmol) at 0 °C over 20 min under nitrogen atmosphere. After the addition the mixture was stirred at 50 °C for 3 h. To the reaction mixture cooled in an ice bath were added 120 ml of 0.5 M (1 M=1 mol dm^{-3}) HCl and 100 ml of AcOEt. The organic layer (the lower) was separated, washed (H_2O) and concentrated in vacuo to give an oil, which was dissolved in 60 ml of toluene. Stirring of the toluene solution at 5 °C for 15 h gave slow precipitation of **17** as a yellowish powder: yield 48.7 g (63%); mp 123—125 °C (decomp); ^1H NMR (acetone-d_6) δ=5.02 (d, 1H, J=7.5 Hz), 5.62 (d, 1H, J=7.5 Hz), 6.67 (d, 1H, J=9.6 Hz), 6.85 (d, 1H, J=9.6 Hz), 7.05 (s, 1H), 7.7 (bs, 1H), and 7.8 (bs, 1H).

1-(3,4-*O*-Isopropylidenedioxyphenyl)-2,2,2-trichloroethanol (18). Compound **17** (50.0 g, 194 mmol), 2,2-dimethoxypropane (24.5 g, 236 mmol), and P_2O_5 (0.03 g, 2.2 mmol) were suspended in toluene (500 ml). The mixture was heated under reflux with a Soxhlet's extractor containing $CaCl_2$ (75 g) to remove MeOH. Additional 2,2-dimethoxypropane (5.72 g, 55 mmol) was added to the reaction mixture at 2 h after the reaction had been started. For further 3 h the reaction mixture was heated under reflux. After cooling, the reaction mixture was washed 1 M Na_2CO_3, then with brine, dried ($MgSO_4$) and filtered. Silica gel (25 g) was added to the solution, which was stirred for 10 min at room temperature. After filteration the solvent was removed in vacuo to afford **18** as an oil: yield 49.5 g (86%); ^1H NMR ($CDCl_3$) δ=1.66 (s, 6H), 3.61 (d, 1H, J=5.1 Hz), 4.98 (d, 1H, J=5.1 Hz), and 6.5—6.8 (m, 3H); IR (film) 3460, 2990, 1500, 1450, 1380, 1260, and 820 cm^{-1}.

Method B: 2-(3,4-Dihydroxyphenyl)-2-hydroxyacetic Acid (21). This was prepared from catechol and glyoxylic acid in 30% NaOH by using the literature procedure[23] (41% yield) as a yellowish solid: ^1H NMR (Me_2SO-d_6) δ=4.72 (s, 1H), and 6.3—6.8 (m, 3H).

2,2-Dimethyl-5-(3,4-dihydroxyphenyl)-1,3-dioxolan-4-one (22). To a solution of **21** (0.5 g, 2.71 mmol) in 1.5 ml of acetone cooled at −10 °C was added dropwise over 1 min concd H_2SO_4 (0.15 ml, 5.4 mmol). After the addition had been completed, the mixture was stirred at −10 °C for a further 10 min. The reaction was quenched with 5.37 M Na_2CO_3 (1.0 ml). The reaction mixture was extracted with AcOEt, washed (brine), dried ($MgSO_4$), filtered and separated chromatographically by using silica gel (20 g, hexane/AcOEt, 3:1) to give **22** as a yellowish solid: yield 0.51 g (84%); ^1H NMR ($CDCl_3$) δ=1.61 (s, 3H), 1.68 (s, 3H), 5.15 (s, 1H), 6.2 (b, 2H), and 6.4—6.8 (m, 3H).

2-(3,4-*O*-Isopropylidenedioxyphenyl)-2-hydroxyacetic Acid (7a): From 18. To a solution of $LiOH \cdot H_2O$ (108 g, 90% purity, 2.32 mol) in 370 ml of H_2O cooled in an ice bath was added a solution of **18** (184 g, 0.62 mol) in 370 ml of dioxane. The resulting suspension was stirred for 3 d at ambient temperature. The solvent was removed in vacuo to afford a brownish solid, which was recrystallized from aq soltion at pH 2.8 after decolorization with activated carbon to give **7a** as a yellowish powder: yield 97.0 g (70%); mp 178—180 °C; ^1H NMR (Me_2SO-d_6) δ=1.61 (s, 6H), 4.85 (s, 1H), and 6.6—6.8 (m, 3H); IR (KBr) 1702 cm^{-1} (C=O); HPLC analysis (column YMC-PACK(ODS) A303 200 mm×6 mm, eluent phosphate buffer (pH 3.8)/CH_3CN (84:16), flow 1.0 ml min^{-1}, 50 °C, λ 286 nm, and retention time 11.6 min).

From 22. A mixture containing **22** (2.50 g, 11.1 mmol), 2,2-dimethoxypropane (3.38 g, 32.5 mmol), and P_2O_5 (0.015 g, 0.105 mmol) in 35 ml of benzene was heated under reflux with a Dean-Stark apparatus to remove MeOH using Molecular Sieve 4A for 40 h. After cooling, the reaction mixture was diluted with 50 ml of Et_2O, washed (aq Na_2CO_3 and then brine), dried ($MgSO_4$), filtered and concentrated to give a yellowish oil, which was subsequently dissolved in a mixture of 1 M NaOH (20 ml) and EtOH (20 ml). The mixture was stirred at 50 °C for 30 min, neutralized with 1 M HCl, extracted with AcOEt, washed (brine), dried ($MgSO_4$) and concentrated in vacuo to give a yellowish solid. Recrystallization from AcOEt/hexane gave **7a** as a yellowish powder: yield 1.10 g (44%). The IR and NMR spectra were identical with those of **7a** prepared by method A.

(*R*)-2-(3,4-*O*-Isopropylidenedioxyphenyl)-2-hydroxyacetic Acid [(*R*)-7a]. Racemic **7a** (28.2 g, 127 mmol) wad dissolved in a mixture of MeOH (86 ml) and 48% NaOH (9 ml). To the solution was added L-Leu·$NHNH_2$[24] (18.3 g, 127 mmol) in MeOH (91 ml). After the pH of the solution was adjusted to 6.8 with 98% H_2SO_4, the solution was stirred at 28 °C for 2 h to give a diastereomeric salt (51.2 g). The isolated salt was suspended in H_2O (102 ml) and crystallization at pH 2.0 provided (*R*)-**7a** as a white powder: yield 10.5 g (optical purity 96%ee, 37% from racemic **7a**); mp 132—133 °C; $[\alpha]_D^{24}$ −88.7° (*c* 1.36, MeOH); HPLC analysis for optical isomers (column Daicel CHIRALPAC WH 250 mm×6.4 mm, eluent 0.25 M aq $CuSO_4$, flow 1.0 ml min^{-1}, 50 °C, λ 238 nm, retention time 31 min for (*R*)-**7a**, and 25 min for (*S*)-**7a**). The IR and NMR spectra were identical with those of racemic **7a**. The absolute configuration of the **7a** prepared by this resolution, was in accord with that of the **7a** obtained from ethyl 2-(3,4-*O*-isopropyridenedioxyphenyl)-2-oxoacetate by yeast reduction followed by hydrolysis, in an HPLC analysis using an optical isomer separating column. Therefore, we concluded that the optically active **7a** prepared by resolution has an (*R*)-configuration.[25]

Methyl (*R*)-2-(3,4-*O*-Isopropylidenedioxyphenyl)-2-hydroxyacetate [(*R*)-7b]. To a solution of (*R*)-**7a** (1.80 g, 8.04 mmol) in 20 ml of THF was added a solution of CH_2N_2, prepared from 1-methyl-3-nitro-1-nitrosoguanidine (1.47 g, 10.0 mmol), in 30 ml of Et_2O and the reaction mixture was stirred at room temperature for 15 h. After AcOH (0.2 ml) was added, the reaction mixture was washed with satd. $NaHCO_3$, dried ($MgSO_4$) and concentrated in vacuo to give (*R*)-**7b** quantitatively as a clear yellowish oil; ^1H NMR ($CDCl_3$) δ=1.63 (s, 6H), 3.30 (bs, 1H), 3.70 (s, 3H), 5.02 (s, 1H), 6.68 (d, 1H, J=7.6 Hz), and 6.75—6.9 (m, 2H); $[\alpha]_D^{22}$ −39.4° (*c* 1.15, $CHCl_3$); IR (film) 1734 cm^{-1} (C=O).

Reaction of (*R*)-7b with $SOCl_2$-Pyridine to Form Methyl (*R*)-2-Chloro-2-(3,4-*O*-isopropylidenedioxyphenyl)acetate [(*R*)-8b]. To a solution of $SOCl_2$ (0.146 ml, 2.0 mmol) in 5.0 ml of Et_2O was added at 0 °C a mixture of (*R*)-**7b** (96%ee, 0.238 g, 1.0 mmol) and pyridine (0.162 ml, 2.0 mmol) in Et_2O (3.0 ml). The reaction was stirred at 0 °C for 1 h. Ice (2 g) was added to the reaction mixture, which was extracted with AcOEt, washed (satd. $NaHCO_3$, 1 M HCl and brine, in order), dried (Na_2SO_4) and concentrated to give a clear oil. Chromatographic separation on silica gel (10 g, AcOEt/hexane, 1:1) gave (*R*)-**8b** as a colorless oil: yield 0.220 g (50%ee, 86%); ^1H NMR ($CDCl_3$) δ=1.65 (s, 6H), 3.68 (s, 3H),

5.03 (s, 1H), and 6.4—6.8 (m, 3H); IR (film) 1740 cm^{-1} (C=O); HPLC analysis for chemical yield (column YMCPACK (ODS) A303 200 mm×6 mm, eluent MeOH, flow 1.0 ml min^{-1}, 0 °C, λ 254 nm, retention time 7.4 min) and for an optical isomer (column Daicel CHIRALPAC OT(+) 200 mm×5 mm, eluent MeOH, flow 0.2 ml min^{-1}, −2 °C, λ 210 nm, retention time 27 min for (*R*)-**8b** and 29 min for (*S*)-**8b**).

Conversion of (*R*)-8b to Methyl (*S*)-2-(3,4-*O*-isopropylidenedioxyphenyl)-2-(phthalimidooxy)acetate [(*S*)-12b]. (*R*)-**8b** (50%ee, 0.172 g, 0.670 mmol) was dissolved in CH_3CN (3.0 ml) and to the obtained solution cooled in an ice bath were added *N*-hydroxyphthalimide (0.109 g, 0.670 mmol) and NEt_3 (0.186 ml, 0.134 mmol). The reaction mixture was stirred at room temperature for 15 h. After removing the solvent in vacuo, chromatographic separation on silica gel (10 g, AcOEt/hexane 1:2) gave (*S*)-**12b** as a colorless oil: yield 0.205 g (80%, 48%ee); ^1H NMR ($CDCl_3$) δ=1.66 (s, 6H), 3.73 (s, 3H), 5.70 (s, 1H), 6.55—6.95 (m, 3H), and 7.5—7.8 (m, 4H); HPLC analysis for an optical isomer (column YMCPACK (ODS) A303 200 mm×6 mm+Daicel CHIRALPAC OT(+) 200 mm×5 mm connected in series, eluent MeOH, flow 1.0 ml min^{-1}, 0 °C, λ 254 nm, retention time 10.6 min for (*S*)-**12b** and 14.6 min for (*R*)-**12b**).

2-Bromo-2-(3,4-*O*-isopropylidenedioxyphenyl)acetic Acid (19). To a suspension of **7a** (10.0 g, 44.6 mmol) in anhydrous benzene (75 ml) was added dropwise PBr_3 (15.1 g, 55.9 mmol) over 1 h. After the addition had been completed, the mixture was stirred under reflux for 5 h. After cooling, to the reaction mixture was added slowly a mixture of ice (100 g) and Et_2O (100 ml). The organic layer was separated, washed (H_2O and then brine), dried ($MgSO_4$) and concentrated in vacuo to give a yellowish powder, which was recrystallized from AcOEt/hexane to afford **19** as a white powder: yield 11.0 g (86%); ^1H NMR (Me_2SO-d_6) δ=1.63 (s, 6H), 5.43 (s, 1H), 6.52 (d, 1H, *J*=8.4 Hz), and 6.8—6.9 (m, 2H); TLC ($CHCl_3$/MeOH, 3:1) R_f=0.61.

2-(3,4-*O*-Isopropylidenedioxyphenyl)-2-(phthalimidooxy)-acetic Acid (12a). *N*-Hydroxyphthalimide (6.10 g, 37.4 mmol) was suspended in 80 ml of THF and to the suspension cooled to 0 °C was added slowly NaH (3.00 g, 75 mmol, 60% dispersion in mineral oil, used after washed with hexane). The resulting suspension was stirred at room temperature for 30 min. To a solution of **19** (10.8 g, 37.6 mmol) in 80 ml of THF was added dropwise over 2 h the above solution of *N*-hydroxyphthalimide at 0 °C. After the addition had been completed, the reaction was stirred at 0 °C for 2 h and then at ambient temperature for 15 h. A mixture of ice (150 g), 37% HCl (7.9 ml), and AcOEt (150 ml) was added to the reaction mixture. The organic layer was separated, washed (H_2O and then brine), dried ($MgSO_4$) and concentrated in vacuo to give a white powder, which was recrystallized from AcOEt to give **12a** as a white powder: yield 11.9 g (86%); mp 166—168 °C; ^1H NMR (Me_2SO-d_6) δ=1.63 (s, 4H), 5.50 (s, 1H), 6.62 (d, 1H, *J*=9.0 Hz), 6.8—6.9 (m, 2H), and 7.65 (s, 4H); IR (KBr) 1800, 1752, and 1730 cm^{-1} (C=O); MS (FD) *m/z* 369 (M^+); TLC ($CHCl_3$/MeOH, 3:1) R_f=0.52. Found: C, 61.68; H, 4.01; N, 3.62%. Calcd for $C_{19}H_{15}NO_7$: C, 61.79; H, 4.09; N, 3.79%.

Optical Resolution of Racemic 12a to Form (*R*)-12a and (*S*)-12a. (*R*)-12a. Racemic **12a** (36.9 g, 0.10 mol) was suspended in 550 ml of CH_3CN and to the suspension was added (−)-cinchonidine (29.44 g, 0.10 mol) in 550 ml of H_2O. The resulting suspension was heated to 60 °C with stirring to give a clear solution, which was allowed to cool to room temperature and left at room temperature for 1 d. The crystals were isolated by filtration and dissolved in 100 ml of 1 M HCl and the mixture was extracted with AcOEt (100 ml×2). The combined extracts were washed (H_2O and then brine), dried ($MgSO_4$) and concentrated in vacuo to give (*R*)-**12a** as a white powder: yield 9.23 g (25%, 100%ee); $[\alpha]_D^{22}$ −255° (*c* 0.48, acetone). The IR and NMR spectra of (*R*)-**12a** were identical with those of racemic **12a**. A portion of the obtained (*R*)-**12a** was dissolved in 4 ml of AcOEt and treated with CH_2N_2 in Et_2O to give (*R*)-**12b**. The optical purity of the obtained (*R*)-**12a** was determined by an HPLC analysis of the prepared (*R*)-**12b** under conditions shown above.

(*S*)-12a. To a solution of racemic **12a** (30.0 g, 81.3 mmol) in 150 ml of acetone was added at room temperature quinine (26.4 g, 81.3 mmol) and the obtained clear solution was stirred at room temperature for 18 h. The resulting crystals were isolated by filtration and washed with 30 ml of acetone. The washings were combined with the filtrate. From the filtrate (*R*)-**12a** (13.2 g, 66%ee) was recovered after acidification followed by extraction. The obtained crystals were suspended in a mixture of AcOEt (225 ml) and H_2O (150 ml) and pH was adjusted to 1.5 by 1 M HCl. The organic layer was separated, washed (brine), dried ($MgSO_4$) and concentrated in vacuo to give (*S*)-**12a** as a white powder: yield 15.3 g (64%ee). A solution of the obtained (*S*)-**12a** in 75 ml of acetone was stirred for 15 h at room temperature. Racemic **12a** (4.59 g) was obtained as crystals after isolated by filtration. The filtrate was evaporated in vacuo to leave a white powder, which was recrystallized from a mixture of acetone (15 ml) and Et_2O (60 ml) to give (*S*)-**12a** (yield 8.43 g, 100%ee) after isolation by filtration. From the filtrate, further crystallization from acetone/Et_2O gave (*S*)-**12a** (0.72 g, 100%ee) as crystals and racemic **12a** (0.66 g) from the filtrate. Totally this resolution process gave (*S*)-**12a** (9.15 g, 100%ee), (*R*)-**12a** (13.2 g, 66%ee), and racemic **12a** (5.25 g). (*S*)-**12a**: $[\alpha]_D^{22}$ +265° (*c* 0.50, acetone); mp 168—170 °C; The IR and NMR spectra were identical with those of racemic **12a**.

Racemization of (*R*)-12a to Racemic 12a. To a solution of $AlCl_3$ (0.48 g, 3.60 mmol) in 60 ml of $EtNO_2$ containing Et_2O (1.89 ml, 18.0 mmol) was added (*R*)-**12a** (13.2 g, 36.0 mmol, 66%ee) at room temperature with stirring. The reaction mixture was stirred at room temperature for 1.5 h, had 240 ml of AcOEt added, and washed with 1 M HCl and then with brine. The organic layer was separated, dried ($MgSO_4$) and concentrated in vacuo to give a white powder, which was recrystallized from AcOEt to afford racemic **12a**: yield 11.0 g (83%). The disappearance of the enantiomer excess was confirmed by HPLC analysis after conversion to **12b**.

***t*-Butyl (*S*)-2-(3,4-*O*-Isopropylidenedioxyphenyl)-2-(phthalimidooxy)acetate [(*S*)-13].** To a solution of (*S*)-**12a** (2.0 g, 5.42 mmol) and pyridine (0.88 ml, 10.84 mmol) in 20 ml of the toluene cooled to 0 °C was added dropwise over 5 min a solution $SOCl_2$ (0.79 ml, 10.84 mmol) in 10 ml of toluene. After the addition had been completed, the mixture was stirred at room temperature for further 45 min. The solvent was removed in vacuo to give an oil, which was dissolved in 10 ml of toluene containing pyridine (0.88 ml, 10.84 mmol).

To the solution cooled to 0 °C was added dropwise over 5 min a solution of *t*-BuOH (1.0 ml, 10.84 mmol) in 5 ml of toluene. After stirring for 10 min at room temperature, the reaction mixture was poured into an ice water (30 ml) and extracted with 30 ml of AcOEt. The extracts were washed (1 M HCl, satd. aq $NaHCO_3$, and brine, in order), dried ($MgSO_4$) and concentrated in vacuo to give a yellowish solid. Chromatographic separation on silica gel (60 g, AcOEt/hexane, 1:4) gave (*S*)-**13** as a yellowish powder: yield 2.03 g (88%); $[\alpha]_D^{24}$ +154° (*c* 0.20, $CHCl_3$); mp 100—104 °C; ^1H NMR ($CDCl_3$) δ=1.46 (s, 9H), 1.66 (s, 6H), 5.06 (s, 1H), 6.70 (d, 1H, *J*=8.5 Hz), 6.9—7.0 (m, 2H), and 7.6—7.8 (m, 4H); IR (KBr) 1795, 1753, and 1738 cm^{-1} (C=O). Found: C, 65.21; H, 5.43; N, 3.01%. Calcd for $C_{23}H_{23}NO_7$: C, 64.93; H, 5.45; N, 3.29%.

[[*t*-Butoxycarbonyl(3,4-*O*-isopropylidenedioxyphenyl)-methoxy]aminocarbonyl]benzoic Acid (14). A solution of racemic **13** (6.0 g, 14.1 mmol), prepared from racemic **12a** by the method given above, and *t*-BuOK (1.98 g, 17.6 mmol) in a mixture of *t*-BuOH (10 ml) and H_2O (10 ml) was heated at 50 °C for 3 h. After cooling to room temperature, the reaction mixture was acidified to pH 2.0 with 1 M HCl and extracted with AcOEt. The extracts were washed (brine), dried ($MgSO_4$) and concentrated in vacuo to give an oil, which was recrystallized from Et_2O to provide **14** as a white powder: yield 4.90 g (78%); ^1H NMR ($CDCl_3$) δ=1.40 (s, 9H), 1.65 (s, 3H), 5.4 (b, 1H), 6.4—6.8 (m, 3H), 7.8—8.0 (m, 2H), and 9.1 (b, 2H).

***t*-Butyl (*S*)-2-Aminooxy-2-(3,4-*O*-isopropylidenedioxyphenyl)acetate [(*S*)-15].** To a solution of (*S*)-**13** (1.90 g, 4.47 mmol) in 30 ml of CH_2Cl_2 cooled to 0 °C was added $NH_2NH_2 \cdot H_2O$ (0.45 g, 8.94 mmol). The reaction mixture was stirred at 0 °C for 1 h. After filtration, the filtrate was concentrated in vacuo to give an oil, which was treated by chromatographic separation (silica gel 50 g, AcOEt/hexane, 1:4) to give (*S*)-**15** as a white powder: yield 1.23 g (93%); $[\alpha]_D^{24}$ +35.0° (*c* 0.20, $CHCl_3$); mp 49—52 °C; ^1H NMR ($CDCl_3$) δ=1.46 (s, 9H), 1.65 (s, 6H), 4.79 (s, 1H), 5.66 (b, 2H), and 6.5—6.8 (m, 3H); IR (KBr) 3320, 2990, 2970, 1734, 1502, and 1260 cm^{-1}. Found: C, 61.21; H, 7.25; N, 4.60%. Calcd for $C_{15}H_{21}NO_5$: C, 61.00; H, 7.17; N, 4.74%.

2-(2-Amino-4-thiazolyl)-2-[(*Z*)-[(*S*) *t*-butoxycarbonyl(3,4-*O*-isopropylidenedioxyphenyl)methyl]oxyimino]acetic Acid [(*S*)-16]. To a solution of (*S*)-**15** (1.00 g, 3.39 mmol) in 10 ml of MeOH was added **23** (0.729 g, 4.24 mmol) and the reaction mixture was stirred at room temperature for 2 h. The insoluble materials were filtered off and the solvent of the filtrate was removed in vacuo. The obtained residue was dissolved in 20 ml of Et_2O and the solution was washed (brine), dried ($MgSO_4$), filtered and concentrated in vacuo to give a yellowish solid, which was treated by column chromatography (silica gel 40 g, $CHCl_3$/MeOH, 30:1) to give (*S*)-**16** as a yellowish powder: yield 1.24 g (82%); $[\alpha]_D^{24}$ +45.0° (*c* 0.20, acetone); mp 111 °C (decomp); ^1H NMR ($CDCl_3$) δ=1.46 (s, 9H), 1.64 (s, 6H), 5.78 (s, 1H), 6.65 (d, 1H, *J*=8.5 Hz), and 6.74—6.85 (m, 3H); IR (KBr) 1738 and 1625 cm^{-1} (C=O); TLC ($CHCl_3$/MeOH, 3:1) R_f=0.33. Found: C, 53.64; H, 5.08; N, 9.51%. Calcd for $C_{20}H_{23}N_3O_7$: C, 53.44; H, 5.16; N, 9.35%.

Diphenylmethyl (6*R*,7*R*)-7-[2-(2-Amino-4-thiazolyl)-2-[(*Z*)-[(*S*)-*t*-butoxycarbonyl(3,4-isopropylidenedioxyphenyl)methyl]-oxyimino]acetamido]-3-[[[2-(diphenylmethyl)oxycarbonyl]-5-methyl[1,2,4]triazolo[1,5-a]pyrimidin-7-yl]thiomethyl]-8-oxo-5-thia-1-azabicyclo[4,2,0]oct-2-ene-2-carboxylate (25). To a solution of (*S*)-**16** (260 mg, 0.579 mmol) in 2 ml of THF was added **24** (437 mg, 0.579 mmol) in 6 ml of CH_2Cl_2. To the mixture cooled to 0 °C was added DCC (0.134 g, 0.695 mmol) in 4 ml of THF. The reaction mixture was stirred at 0 °C for 1 h and then at room temperature for 21 h. After filteration, 10 ml of AcOEt was added to the filtrate, which was washed (satd. $NaHCO_3$ and then brine), dried ($MgSO_4$), filtered and concentrated in vacuo to give an oil. Chromatographic separation on silica gel (35 g, AcOEt/hexane, 1:5) gave **25** as an oil: yield 268 mg (39%); ^1H NMR ($CDCl_3$) δ=1.33 (s, 9H), 1.64 (s, 6H), 2.51 (s, 3H), 3.60 (s, 2H), 4.36 (ABq, 2H), 5.10 (d, 1H, *J*=4.8 Hz), 5.67 (s, 1H), 5.94 (m, 1H), 6.69 (d, 1H, *J*=8.5 Hz), 6.83 (s, 1H), 6.9—6.95 (m, 3H), 7.02 (s, 1H), 7.22—7.51 (m, 21H), and 9.08 (bd, 1H); TLC (AcOEt) R_f=0.40.

Trisodium Salt of (6*R*,7*R*)-7-[2-(2-Amino-4-thiazolyl)-2-[(*Z*)-[(*S*)-carboxy(3,4-dihydroxyphenyl)methyl]oxyimino]acetamido]-3-[(2-carboxy-5-methyl[1,2,4]triazolo[1,5-a]pyrimidin-7-yl)thiomethyl]-8-oxo-5-thia-1-azabicyclo[4,2,0]oct-2-ene-2-carboxylic Acid. To a suspension of **25** (250 mg, 0.211 mmol) in 2 ml of anisole cooled to 0 °C was added 4.0 ml of CF_3CO_2H, and the mixture was stirred at room temperature for 4 h. To the reaction mixture were added 12 ml of Et_2O and 6 ml of hexane, and the resulting powder was isolated by filtration. After drying, the powder was dissolved in 5 ml of H_2O with pH adjusted to 6.5 by $NaHCO_3$. The obtained solution was applied to chromatographic separation (Diaion HP-20, column volume 10 ml, eluent H_2O). The fractions containing **1** were collected and lyophilized to give the sodium salt of **1** as an amorphous powder: yield 68 mg (39% as trisodium salt); ^1H NMR (Me_2SO-d_6, D_2O) δ=2.59 (s, 3H), 3.48 (ABq, 2H), 4.50 (ABq, 2H), 5.00 (d, 1H, *J*=4.8 Hz), 5.11 (s, 1H), 5.64 (d, 1H, *J*=4.8 Hz), 6.67 (d, 1H, *J*=8.5 Hz), 6.78 (s, 1H), 6.85—6.9 (m, 2H), and 7.48 (s, 1H). Detection of (*R*)-diastereomer in the crude **1** before chromatographic purification was carried out under the following HPLC conditions: column YMCPAC(ODS) A-313 100 mm×6 mm, eluent 0.01 M phosphate buffer (pH 6.5)/CH_3CN (93:7), flow 1.5 ml min^{-1}, 35 °C, λ 298 nm, and retention times 10.9 min for **1** [(*S*)-diastereomer] and 24.7 min for (*R*)-diastereomer.

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3) As will be described below, we made an optical resolution study on (*RS*)-**16** corresponding to **2**, which however was unsuccessful.

4) It has been reported that preparation of ethyl L-(+)-2-chloro-2-phenylacetate is demonstrated from ethyl D-(−)-2-hydroxy-2-phenylacetate by using $SOCl_2$ in Et_2O in the presence of pyridine. See: a) C. H. Depuy, F. W. Breitbeil, and K. R. Debruin, *J. Am. Chem. Soc.*, **88**, 3347 (1966). b) J. Kenyon, A. G. Lipscomb, and H. Phillips, *J. Chem. Soc.*, **1930**, 415. Thus, it is known that the substitution reaction leads to a steric inversion (S_N2) in chlorination of 2-hydroxy-2-phenyacetic acid esters by $SOCl_2$ in Et_2O in the presence of pyridine. However, though pyridine was present in our case, the reaction proceeded mainly with a steric retention (S_Ni). The presence of electron-donating group at the para position of phenyl ring may also account for this fact.

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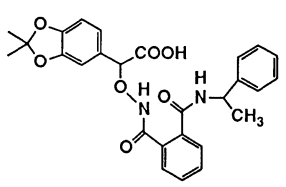
15) Compound **12a** was dissolved in refluxing acetone in the presence of D-(+)-1-phenethylamine and allowed to stand overnight at room temperature to provide crystals. However, NMR studies proved that the product was phthalamide **26**.



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16) The increase in quantity of quinine used for crystallization had no effect on improving either yield or optical purity of **12a** when acetone was used as a crystallization solvent.

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18) Neither $ZnCl_2$ nor $FeCl_3$ in $EtNO_2$ was effective for the racimization of (*R*)-**12a**.

19) The optical purity of the obtained (*S*)-**14** was determined by measurement of optical rotation in reference to 100%ee (*S*)-**15** ($[\alpha]_D^{24}$ +52.0°, *c* 0.25, acetone) prepared from 100%ee (*S*)-**12a** by the same method.

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24) Mp 48—49 °C. Prepared by using the literature procedure. See: a) H. T. Cheung and E. R. Blout, *J. Org. Chem.*, **30**, 315 (1965); b) F. Chillemi, *Gazz. Chim. Ital.*, **96**, 359 (1966).

25) Methyl 2-hydroxy-2-phenylacetate prepared from methyl 2-oxophenylacetate by yeast reduction has (*R*)-configuration. See: B. S. Deol, D. D. Ridley, and G. W. Simpson, *Aust. J. Chem.*, **29**, 2459 (1976). For details about the absolute configuration of the product in yeast reduction of 2-(3,4-*O*-isopropylidenedioxyphenyl)-2-oxoacetic acid esters, see: H. Iwagami, M. Yatagai, M. Nakazawa, H. Orita, Y. Honda, T. Ohnuki, and T. Yukawa, unpublished result, which will be reported in near future.