

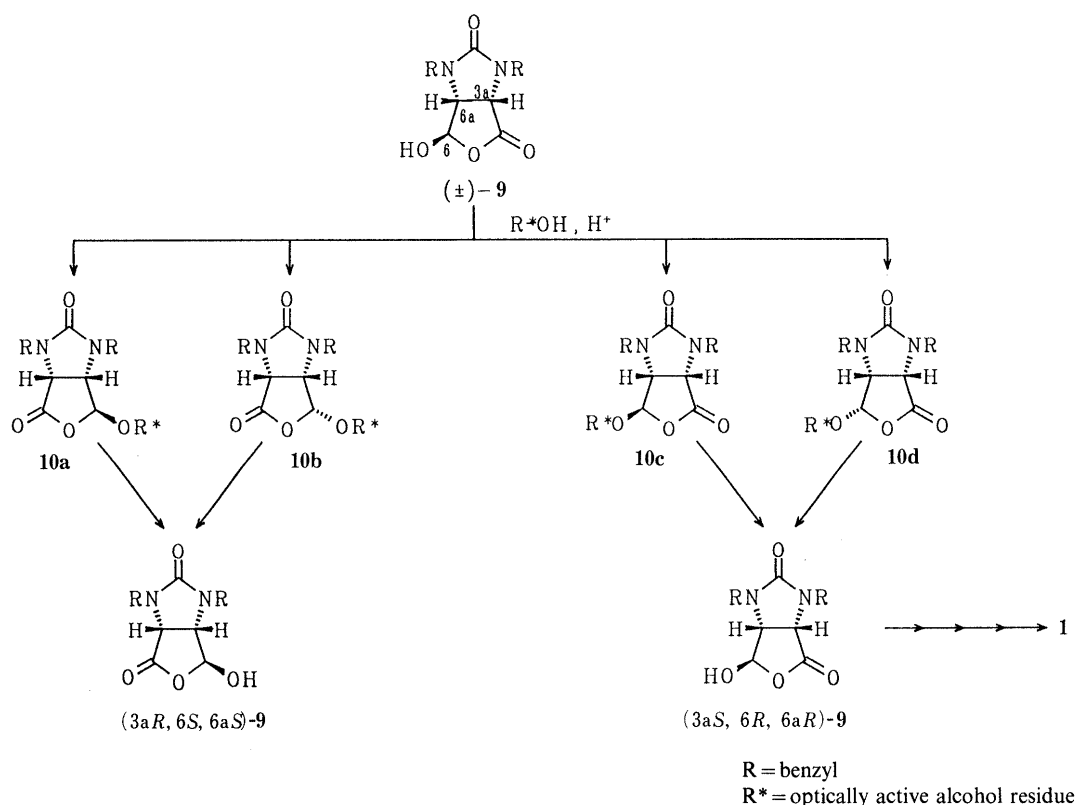


Chart 2

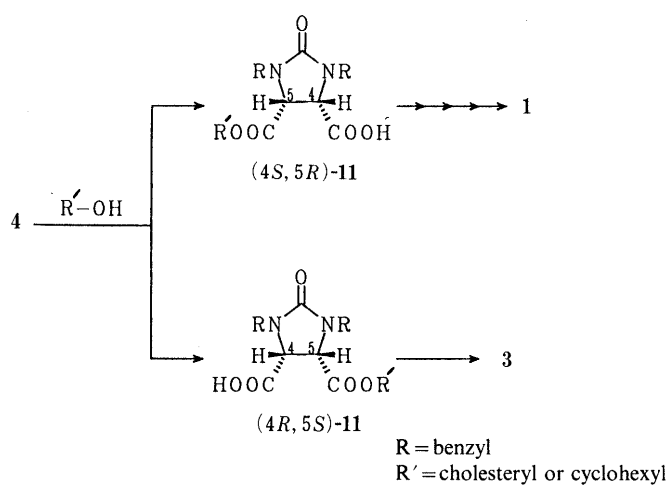


Chart 3

the two peaks at δ 8.97 and 9.03 assignable to aldehyde protons, indicating the formation of the diastereoisomeric salts of the aldehyde-carboxylic acid (**12**). On the basis of this observation, the hydroxylactone [$(\pm)\text{-9}$] was allowed to react with 0.5 eq of cinchonidine in aqueous acetone. The precipitated salt was collected to give the cinchonidine salt of the desired $(4\text{S}, 5\text{R})$ -aldehyde-carboxylic acid (**12**) in 45% yield. The presence of carbonyl absorptions at 1691 cm^{-1} (CHO and imidazolidinone) and 1618 cm^{-1} (carboxylate) and an aldehyde proton resonance at δ 8.97 was consistent with the assigned structure. The optical purity of this salt was assumed to be more than 98%, since no signals assignable to the diastereoisomeric salt were observed in the NMR spectrum.⁶⁾

Upon acidification with aqueous HCl, this salt readily underwent cyclization to give a 42% yield (based on $(\pm)\text{-9}$)

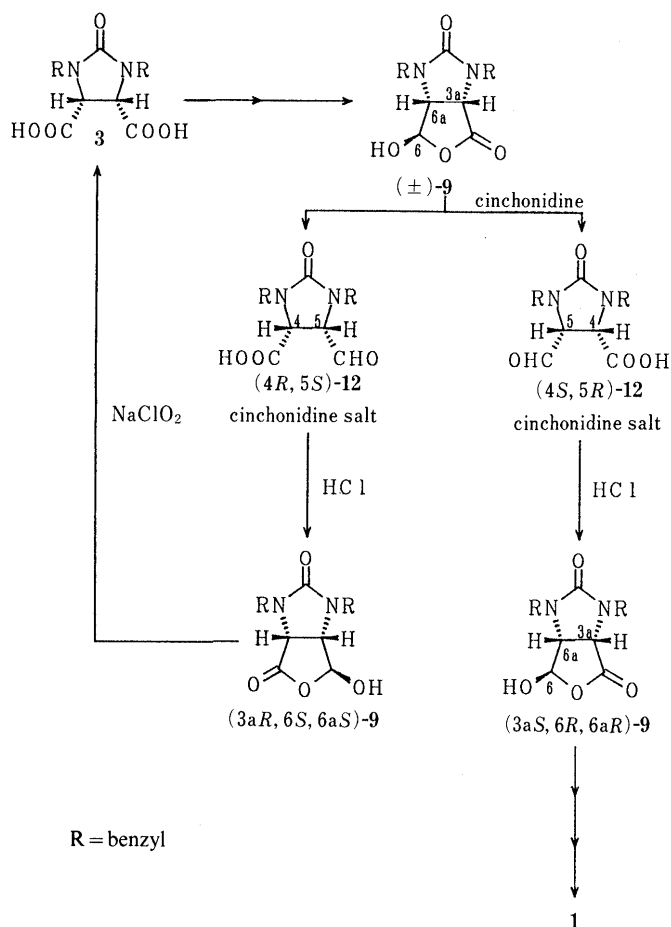


Chart 4

of desired $(3\text{aS}, 6\text{R}, 6\text{aR})\text{-9}$ (Chart 4). Evaporation of the mother liquor of the salt of $(4\text{S}, 5\text{R})\text{-12}$ gave, after acidification, $(3\text{aR}, 6\text{S}, 6\text{aS})\text{-9}$ in 36.5% yield. The reaction of $(\pm)\text{-9}$

with quinine also gave the quinine salt of (4*S*,5*R*)-**12** as a less soluble salt, and (3*aS*,6*R*,6*aR*)-**9** was obtained in 29% yield after acidification with aqueous HCl.

Although cinchonidine was found to be a highly effective resolving agent for (±)-**9**, it is quite expensive and not readily accessible. To find a more practical resolving agent applicable for industrial use, we examined the optical resolution of (±)-**9** with various *N*-alkyl-D-glucamines (**14**). The reaction of D-glucose (**13**) with various amines followed by reduction over Raney nickel readily gave the *N*-alkyl-D-glucamines (**14a–c**) in high yields (Chart 5).^{7,8)}

Reaction of the hydroxylactone [(±)-**9**] with **14a,b,c** readily caused precipitation of the crystalline salts (**15a,b,c**) in 46, 44, and 42% yields, respectively.

Upon acidification with aqueous HCl, these salts (**15a,b,c**) readily regenerated the desired (3*aS*,6*R*,6*aR*)-**9** in nearly quantitative yield, and (3*aR*,6*S*,6*aS*)-**9** was recovered by acidification of the mother liquors of **15a,b,c**.

The structures of **15a,b,c** could not be simply assigned as D-glucamine salts of the aldehyde-carboxylic acid (**12**). In the fast atom bombardment mass spectrum (FAB-MS), the *N*-3-(dimethylamino)propyl-D-glucamine salt (**15b**) showed an [M+H]⁺ ion peak at *m/z* 587, indicating that this

compound was formed by the condensation of the aldehyde-carboxylic acid (**12**) and **14b** with elimination of H₂O. The ¹H-NMR spectrum of **15b** showed a signal at δ 4.63 assignable to a proton in an –O–CH–N< or –O–CH–O– system without a signal attributable to an aldehyde proton. The structure of **15b** having an oxazolidine ring was unequivocally established by X-ray crystallographic analysis (Figs. 1, 2, Table I), the absolute stereochemistry of the imidazolidine group being also determined to be 4*S*,5*R*.

The FAB-MS of **15a,c** showed [M+H]⁺ ion peaks at *m/z*

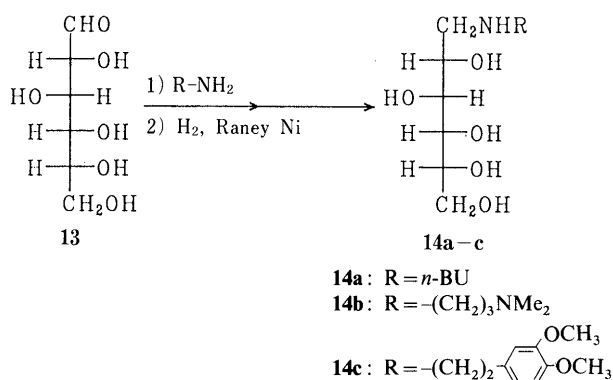


Chart 5

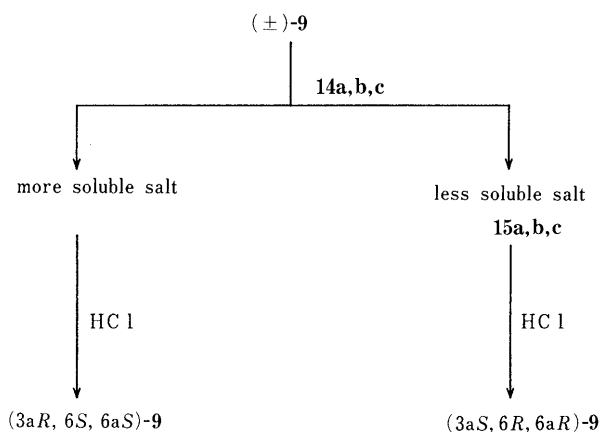
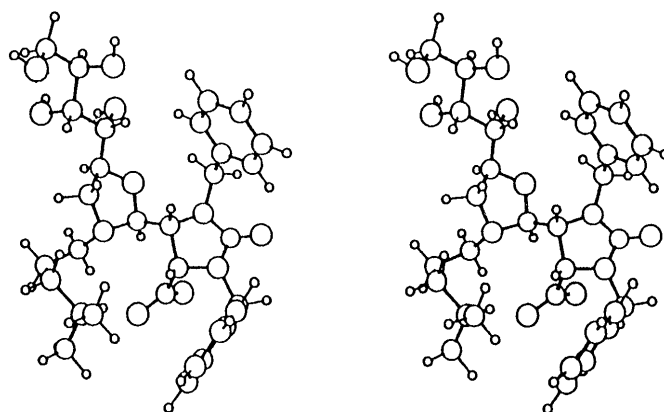
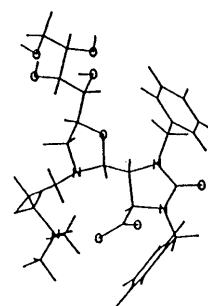
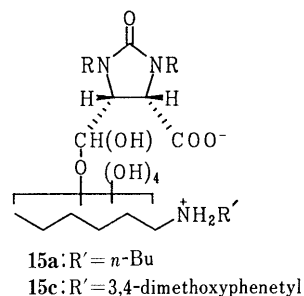
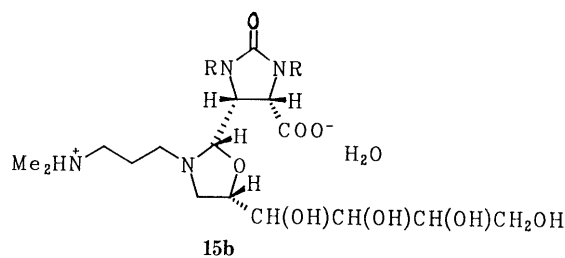


Chart 6

Fig. 1. Stereoscopic View of **15b**

15a: R' = *n*-Bu
15c: R' = 3,4-dimethoxyphenyl

R = benzyl

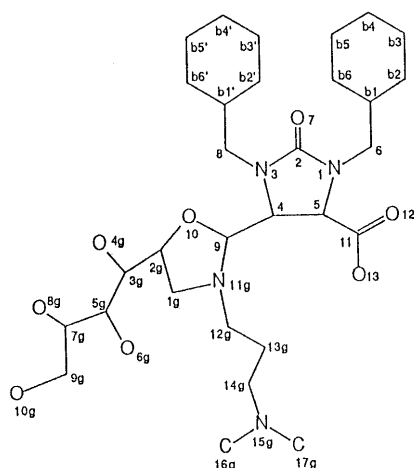


Fig. 2. Nomenclature of Atoms

TABLE I. Final Atomic Coordinates and Equivalent Isotropic or Isotropic Thermal Parameters with Estimated Standard Deviations in Parentheses

No.	Atom	x	y	z	B_{eq} ($\text{\AA}^2$)
1	N 1	0.4905 (3)	0.8470 (3)	0.3826 (7)	4.21 (27)
2	C 2	0.4903 (4)	0.7889 (4)	0.4179 (9)	4.31 (33)
3	N 3	0.5460 (3)	0.8057 (3)	0.4895 (7)	3.83 (25)
4	C 4	0.5860 (4)	0.8811 (3)	0.5063 (7)	3.17 (26)
5	C 5	0.5581 (4)	0.9059 (3)	0.4018 (8)	3.68 (29)
6	C 6	0.4471 (5)	0.8500 (5)	0.2868 (10)	5.58 (42)
7	O 7	0.4471 (3)	0.7302 (3)	0.3898 (8)	6.28 (30)
8	C 8	0.5373 (4)	0.7578 (4)	0.5862 (9)	4.70 (37)
9	C 9	0.6633 (4)	0.9104 (4)	0.4964 (7)	3.10 (26)
10	O 10	0.6865 (3)	0.8784 (3)	0.5831 (5)	4.08 (21)
11	C 11	0.6006 (4)	0.9241 (4)	0.2866 (8)	3.53 (28)
12	O 12	0.5957 (3)	0.8758 (3)	0.2233 (6)	4.78 (24)
13	O 13	0.6387 (3)	0.9870 (3)	0.2609 (6)	4.38 (22)
14	C b1	0.4361 (5)	0.9099 (5)	0.3093 (11)	5.84 (46)
15	C b2	0.3973 (6)	0.9080 (7)	0.4060 (15)	8.02 (66)
16	C b3	0.3920 (7)	0.9673 (9)	0.4317 (18)	11.71 (82)
17	C b4	0.4297 (9)	1.0238 (7)	0.3506 (24)	16.45 (99)
18	C b5	0.4631 (9)	1.0249 (9)	0.2596 (27)	15.94 (95)
19	C b6	0.4677 (6)	0.9663 (7)	0.2375 (15)	8.85 (71)
20	C b1'	0.4973 (4)	0.7607 (4)	0.6969 (9)	4.36 (34)
21	C b2'	0.4293 (5)	0.7405 (5)	0.6854 (11)	5.84 (45)
22	C b3'	0.3923 (5)	0.7406 (6)	0.7847 (12)	6.51 (50)
23	C b4'	0.4225 (5)	0.7598 (5)	0.8962 (11)	5.88 (45)
24	C b5'	0.4912 (6)	0.7794 (5)	0.9069 (10)	6.08 (45)
25	C b6'	0.5275 (5)	0.7788 (5)	0.8069 (11)	5.87 (44)
26	C 1g	0.7177 (4)	0.9874 (4)	0.6525 (8)	3.76 (30)
27	C 2g	0.7320 (4)	0.9293 (4)	0.6682 (7)	3.58 (28)
28	C 3g	0.7184 (4)	0.8988 (4)	0.7906 (8)	4.27 (33)
29	O 4g	0.7343 (4)	0.8452 (3)	0.7901 (7)	6.26 (31)
30	C 5g	0.7545 (4)	0.9508 (4)	0.8912 (8)	4.20 (32)
31	O 6g	0.8271 (3)	0.9874 (4)	0.8710 (7)	6.34 (30)
32	C 7g	0.7370 (5)	0.9195 (5)	1.0144 (8)	4.66 (35)
33	O 8g	0.6650 (4)	0.8802 (3)	1.0222 (7)	6.77 (30)
34	C 9g	0.7686 (5)	0.9717 (5)	1.1161 (9)	4.95 (36)
35	O 10g	0.7477 (3)	1.0220 (3)	1.1130 (6)	4.88 (24)
36	N 11g	0.6990 (3)	0.9844 (3)	0.5232 (6)	3.17 (21)
37	C 12g	0.7597 (4)	1.0233 (4)	0.4473 (8)	4.17 (31)
38	C 13g	0.7914 (5)	1.1011 (4)	0.4643 (10)	5.44 (39)
39	C 14g	0.7437 (7)	1.1236 (5)	0.4886 (13)	7.76 (60)
40	N 15g	0.6847 (4)	1.1031 (3)	0.3888 (8)	5.42 (34)
41	C 16g	0.6330 (7)	1.1087 (6)	0.4511 (17)	9.60 (78)
42	C 17g	0.7172 (9)	1.1481 (7)	0.2874 (16)	10.20 (79)

576 and 684, respectively, indicating that they are the condensation products of **12** and **14a,c** with a covalent bond. The lack of an aldehyde proton resonance and the

presence of a signal at around δ 4.7 in their $^1\text{H-NMR}$ spectra suggested the hemi-acetal formation of the aldehyde groups of **12** with one of the hydroxyl groups of a glucamine moiety. Since we have not yet been able to prepare crystals of **15a,c** suitable for X-ray analysis, the precise structures remain uncertain.⁹⁾

In any case, *N*-alkyl-D-glucamines (**14a,b,c**) were thus found to be effective resolving agents for ($\pm$)-**9**. Among them, the *N*-*n*-butyl derivative (**14a**) proved to be most suitable for industrial use because it gave the highest yield of the desired isomer and because of its ready accessibility by the reaction of D-glucose with *n*-butylamine.

Reutilization of the Unwanted Hydroxylactone [(3*aR*,6*S*,6*aS*)-9**]** Gerecke *et al.*⁴⁾ reported the reutilization of the unwanted hydroxylactone [(3*aR*,6*S*,6*aS*)-**9**] by oxidative conversion to the *meso*-diacid (**3**) with CrO_3 . However, the reaction proceeded rather slowly, and **3** was obtained in only 49% yield after 60 h. Moreover, CrO_3 is not applicable for industrial use because of the problem of pollution. Several attempts were, therefore, made to find other oxidizing agents. Silver nitrate oxidation of (3*aR*,6*S*,6*aS*)-**9** in aqueous EtOH in the presence of 1 N NaOH gave, after treatment with acetic anhydride, the anhydride (**4**) in 58.5% yield. Further, (3*aR*,6*S*,6*aS*)-**9** could be oxidized by bromine to the *meso*-diacid (**3**) in 82% yield under stirring in aqueous Na_2CO_3 and ethyl acetate. These oxidations apparently proceeded after opening of the hydroxylactone (**9**) to the aldehyde-carboxylic acid (**12**) under alkaline conditions. Recently, an aldehyde group was reported to be readily oxidized to a carboxylic acid group by sodium chlorite.¹⁰⁾ The most practical oxidation of (3*aR*,6*S*,6*aS*)-**9** was, therefore, achieved by the use of sodium chlorite under stirring in aqueous Na_2CO_3 and ethyl acetate, readily giving the *meso*-diacid (**3**) in 87% yield.

Thus, the highly effective resolution of the hydroxylactone [($\pm$)-**9**] and the facile reutilization of its unwanted isomer, applicable for industrial production of biotin, were achieved.

Experimental

All melting points are uncorrected. Infrared (IR) spectra were obtained on a Shimadzu IR-420 infrared spectrometer. $^1\text{H-NMR}$ spectra were recorded on a Hitachi R-90H spectrometer or on a JEOL JNM-GSX-400 with tetramethylsilane (TMS) as an internal reference. The following abbreviations are used: s=singlet, d=doublet, dd=doublet of doublets, t=triplet, q=quartet, m=multiplet, and br=broad. Optical rotations were determined for solutions of methanol or benzene on a Perkin-Elmer 243 polarimeter. FAB-MS were recorded with a JEOL JMS-HX-100 mass spectrometer.

(3*aRS*,6*SR*,6*aSR*)-1,3-Dibenzyl-6-hydroxy-3,3*a*,6,6*a*-tetrahydro-1*H*-furo[3,4-*d'*]imidazole-2,4-dione (9**)** A solution of the acetoxy lactone (**5**)⁴⁾ (50 g, 0.13 mol) in concentrated HCl (50 ml) and dioxane (150 ml) was stirred at room temperature for 2.5 h. The mixture was diluted with H_2O (500 ml) and extracted with AcOEt. The organic layer was washed with H_2O and brine, dried and evaporated to give an oil (43.6 g). Crystallization from $\text{Me}_2\text{CO-Et}_2\text{O}$ -petroleum ether gave 37.4 g (84%) of (3*aRS*,6*SR*,6*aSR*)-**9**. mp 113–116 °C. (lit.⁴⁾ mp 110–113 °C). IR $\nu_{\text{max}}^{\text{Nujol}}$ cm^{-1} : 3205, 1795, 1660, 1230, 1110, 915, 700. $^1\text{H-NMR}$ (CDCl_3) δ : 3.87 (1H, d, $J=8.6$ Hz, $\text{C}_{6a}\text{-H}$), 4.04 (1H, d, $J=8.6$ Hz, $\text{C}_{3a}\text{-H}$), 4.29 (1H, d, $J=14.8$ Hz, 3-N- CH_2), 4.37 (1H, d, $J=15.2$ Hz, 1-N- CH_2), 4.51 (1H, d, $J=15.2$ Hz, 1-N- CH_2), 4.94 (1H, d, $J=14.8$ Hz, 3-N- CH_2), 5.1 (1H, brs, $\text{C}_6\text{-OH}$), 5.47 (1H, s, $\text{C}_6\text{-H}$), 7.2–7.4 (10H, m, aromatic protons).

When measured in the presence of an equimolar amount of cinchonidine, two broad singlets were observed at δ 8.97 and 9.03 with disappearance of the signal of $\text{C}_6\text{-H}$.

Optical Resolution of the Hydroxylactone [(3*aRS*,6*SR*,6*aSR*)-9**] with Cinchonidine** Cinchonidine (19.5 g, 0.066 mol) and H_2O (64.4 ml) were

added to a solution of (3*aRS*,6*SR*,6*aSR*)-**9** (43.6 g, 0.13 mol) in Me₂CO (193 ml). The precipitated crystals were collected and washed with Me₂CO to give 36.7 g (45%) of the cinchonidine salt of (4*S*,5*R*)-1,3-dibenzyl-5-formyl-2-oxo-4-imidazolidine carboxylic acid (**12**). mp 138.5–142.5 °C. $[\alpha]_D^{24} -55.8^\circ$ ($c=0.5$, MeOH). *Anal.* Calcd for C₃₈H₄₀N₄O₅·H₂O: C, 70.13; H, 6.51; N, 8.61; O, 14.75. Found: C, 70.07; H, 6.65; N, 8.56; O, 14.97. IR $\nu_{\text{max}}^{\text{Nujol}}$ cm⁻¹: 3080, 2715, 1691, 1618, 1585, 1220, 1065, 1047, 704. FAB-MS m/z : 295 [(M+H)⁺ for cinchonidine], 339 [(M+H)⁺ for **12**]. ¹H-NMR (CDCl₃) δ : 3.91 (1H, dd, $J=9.7$ and 2.5 Hz, C₅-H, changed to d ($J=9.7$ Hz by irr. at δ 8.97), 4.15 (1H, d, $J=9.7$ Hz, C₄-H), 4.21 (1H, d, $J=14.9$ Hz, 3-N-CH₂), 4.29 (1H, d, $J=14.9$ Hz, 1-N-CH₂), 4.8 (overlapped with H₂O, 1-N-CH₂), 5.01 (1H, d, $J=14.9$ Hz, 3-N-CH₂), 8.97 (1H, br s, CHO), 7.26 (10H, m, aromatic protons). δ (H numbers) of cinchonidine moiety: 1.28 (1H), 1.76 (1H), 2.03 (3H), 2.60 (1H), 2.97 (1H), 3.11 (1H), 3.34 (2H), 4.99 (1H), 5.02 (1H), 5.55 (1H), 6.23 (1H), 7.58 (1H), 7.71 (1H), 8.02 (1H), 8.13 (1H), 8.90 (1H).

The cinchonidine salt of (4*S*,5*R*)-**12** (36 g, 0.057 mol) was dissolved in 6.25% aqueous HCl, and the liberated oil was extracted with AcOEt. The extract was washed with H₂O, dried, and evaporated. Recrystallization of the residue from Me₂CO–Et₂O–petroleum ether gave 17.9 g (42% based on (3*aRS*,6*SR*,6*aSR*)-**9**) of (3*aS*,6*R*,6*aR*)-**9**. mp 129–130 °C. (lit.⁴) mp 130–131 °C. $[\alpha]_D^{25} +28.1^\circ$ ($c=1$, benzene). (lit.⁴) $[\alpha]_D^{25} +28.0^\circ$ ($c=1$, benzene)). The NMR spectrum of this compound was identical to that of the racemate (**9**) described above.

The mother liquor from the salt of (4*S*,5*R*)-**12** was evaporated and 10% aqueous HCl (25 ml) was added to the residue. The mixture was extracted with AcOEt. Evaporation of the AcOEt extracts gave, after washing with H₂O and drying, an oil. Crystallization from Me₂CO–Et₂O–petroleum ether gave 15.9 g (36.5% based on (3*aRS*,6*SR*,6*aSR*)-**9**) of (3*aR*,6*S*,6*aS*)-**9**. mp 129–130 °C. $[\alpha]_D^{25} -27.8^\circ$ ($c=1$, benzene).

Optical Resolution of (3*aRS*,6*SR*,6*aSR*)-9** with Quinine** Quinine (3.24 g, 0.01 mol) and (3*aRS*,6*SR*,6*aSR*)-**9** (3.38 g, 0.01 mol) were added to a solution of H₂O (2 ml) and methyl ethyl ketone (22 ml) at room temperature. The precipitated crystals were collected and washed with a solution of methyl ethyl ketone (4 ml) and petroleum ether (2 ml) to afford 2.23 g (33.6%) of the quinine salt of (4*S*,5*R*)-**12**. mp 94–97 °C. $[\alpha]_D^{25} -86.4^\circ$ ($c=1$, MeOH). The quinine salt of (4*S*,5*R*)-**12** (2 g, 3 mmol) was treated in a similar manner as above to give, after drying, 0.88 g (29%) of (3*aS*,6*R*,6*aR*)-**9**. mp 128–129 °C. $[\alpha]_D^{25} +27.9^\circ$ ($c=1$, benzene).

***N*-*n*-Butyl-D-glucamine (**14a**)** A mixture of D-glucose (54 g, 0.3 mol), *n*-butylamine (21.9 g, 0.3 mol), and MeOH (120 ml) was refluxed for 1 h. After addition of H₂O (7.5 ml), the mixture was hydrogenated over Raney-Ni (W-5, 10.8 g) at 60 °C at 10 atm. The catalyst was filtered off and the filtrate was evaporated to give, after recrystallization with EtOH, 49.8 g (70%) of *N*-*n*-butyl-D-glucamine. mp 130–133 °C (lit.⁷) mp 129–131 °C. $[\alpha]_D^{25} -15.3^\circ$ ($c=1$, H₂O). (lit.⁷) $[\alpha]_D^{25} -14.3^\circ$ ($c=1$, H₂O)).

***N*-[3-(Dimethylamino)propyl]-D-glucamine (**14b**)** was prepared in a similar manner in 68.4% yield from *N*,*N*-dimethyl-1,3-propanediamine. mp 110–112 °C. $[\alpha]_D^{25} -18.7^\circ$ ($c=1$, MeOH). *Anal.* Calcd for C₁₁H₂₆N₂O₅: C, 49.61; H, 9.84; N, 10.52. Found: C, 48.95; H, 9.87; N, 9.77. IR $\nu_{\text{max}}^{\text{Nujol}}$ cm⁻¹: 3310, 3240, 1090, 1050, 1015. ¹H-NMR (DMSO-*d*₆) δ : 1.55 (2H, m, NH-CH₂CH₂), 2.10 (6H, s, NMe₂), 2.2 (2H, t, $J=7$ Hz, CH₂-NMe₂), 2.5 (2H, m, NH-CH₂CH₂), 2.59 (2H, m, NH-CH₂CH), 3.3–3.4 (3H, m, CHOH, CH₂OH), 3.48 (1H, m, CHOH), 3.59 (1H, dd, $J=10.8$ and 3.5 Hz, CHOH), 3.64 (1H, m, CHOH).

***N*-(3,4-Dimethoxyphenethyl)-D-glucamine (**14c**)** was similarly obtained in 63.7% yield. mp 134–135 °C. $[\alpha]_D^{25} -8.3^\circ$ ($c=1$, MeOH). *Anal.* Calcd for C₁₁H₂₆N₂O₇: C, 55.64; H, 7.88; N, 4.06. Found: C, 55.73; H, 7.96; N, 3.96. IR $\nu_{\text{max}}^{\text{Nujol}}$ cm⁻¹: 3340, 3240, 1590, 1520, 1265, 1050. ¹H-NMR (DMSO-*d*₆) δ : 2.63 (2H, m, NHCH₂CH), 2.7 (4H, m, NH-CH₂-CH₂), 3.35 (2H, m, CH₂OH), 3.4 (1H, br d, $J=8.5$ Hz, CHOH), 3.48 (1H, m, CHOH), 3.58 (1H, m, CHOH), 3.65 (1H, m, CHOH), 3.71 (3H, s, OCH₃), 3.73 (3H, s, OCH₃), 6.70 (1H, dd, $J=8.1$ and 1.8 Hz, aromatic proton), 6.80 (1H, d, $J=1.8$ Hz, aromatic proton), 6.84 (1H, d, $J=8.1$ Hz, aromatic proton).

Optical Resolution of (3*aRS*,6*SR*,6*aSR*)-9** with **14a**** (3*aRS*,6*SR*,6*aSR*)-**9** (31.5 g, 0.09 mol) and **14a** (11.0 g, 0.046 mol) were added to 7% aqueous acetonitrile (189 ml). The mixture was stirred at 10–25 °C for 24 h, and the precipitated crystals were collected and washed with aqueous acetonitrile to give 24.65 g (46% based on (3*aRS*,6*SR*,6*aSR*)-**9**) of the salt (**15a**). mp 84–87 °C. $[\alpha]_D^{25} -14.0^\circ$ ($c=1$, DMF). *Anal.* Calcd for C₂₉H₄₄N₃O₉: C, 60.51; H, 7.30; N, 7.18. Found: C, 59.67; H, 7.21; N, 7.11. FAB-MS m/z : 576 [M+H]⁺. IR $\nu_{\text{max}}^{\text{Nujol}}$ cm⁻¹: 3280, 3030–3080, 1672, 1627, 1245, 1050. ¹H-NMR (CD₃OD: DMSO-*d*₆ = 10:1) δ : 4.38 and 4.40 (1H, d, $J=15$ Hz, 1-N-CH₂), 4.67 and 4.82 (1H, d, $J=15$ Hz, 1-N-CH₂), 3.95 and 4.01 (1H, d, $J=15$ Hz, 3-N-CH₂), 4.94 (1H, d, $J=15$ Hz, 3-N-CH₂), 3.78 (1H, d, $J=$

$ca.$ 10 Hz, C₄-H), 3.50 and 3.51 (1H, dd, $J=ca.$ 10 and 2.5 Hz, C₅-H), 4.65 and 4.76 (1H, d, $J=2.5$ Hz, O-CHOH), 7.26 (10H, m, aromatic proton). δ (H numbers) of *N*-*n*-butyl-D-glucamine moiety: 0.96 (3H, -CH₃), 1.40 (2H, CH₂-CH₂-CH₃), 1.67 (2H, -CH₂-CH₂-CH₃), 2.99 (2H, N⁺H₂-CH₂-CH₂), 3.12 and 3.16 (2H, CH-CH₂-N⁺H₂), 4.04 (1H, CH-CH₂), 3.81 (1H, CHOH), 3.25 (1H, CHOH), 3.66 (1H, CH₂-CHOH), 3.63 (2H, -CH₂OH). ¹³C-NMR δ_c : 96.0 and 97.8 (O-CHOH).

This salt (**15a**) (24 g, 0.04 mol) was added to a mixture of H₂O (300 ml) and AcOEt (300 ml). After addition of 10% aqueous HCl (50 ml), the organic layer was separated, washed with water and evaporated. Recrystallization of the residue from Me₂CO–Et₂O–petroleum ether gave 13.7 g (44.7% based on (3*aRS*,6*SR*,6*aSR*)-**9**) of (3*aS*,6*R*,6*aR*)-**9**. mp 129–130 °C. $[\alpha]_D^{25} +27.9^\circ$ ($c=1$, benzene). The NMR spectrum of this compound was identical to that of (3*aRS*,6*SR*,6*aSR*)-**9**.

The mother liquor from the salt (**15a**) was evaporated and 10% aqueous HCl (25 ml) was added to the residue. The mixture was extracted with AcOEt. Evaporation of the extracts gave, after washing with H₂O and drying, an oil. Crystallization from Me₂CO–Et₂O–petroleum ether gave 13 g (41.5%) of (3*aR*,6*S*,6*aS*)-**9**. mp 128–130 °C. $[\alpha]_D^{25} -27.8^\circ$ ($c=1$, benzene).

Optical Resolution of (3*aRS*,6*SR*,6*aSR*)-9** with **14b**** (3*aRS*,6*SR*,6*aSR*)-**9** (10 g, 0.03 mol) and **14b** (7.9 g, 0.03 mol) were added to a solution of EtOH (20 ml) and Me₂CO (20 ml). After being stirred at 55 °C for 30 min, the reaction mixture was allowed to stand for 24 h at 25 °C. The precipitated crystals were collected to give 7.9 g (44.2%) of the salt (**15b**). mp 148–149 °C. $[\alpha]_D^{25} -60.6^\circ$ ($c=1$, MeOH). *Anal.* Calcd for C₃₀H₄₂N₄O₈·H₂O: C, 59.59; H, 7.33; N, 9.27; O, 23.81. Found: C, 59.88; H, 7.37; N, 9.01; O, 23.66. The presence of 1 mol of solvated H₂O was ascertained by thermogravimetric and differential thermal analyses. FAB-MS m/z : 587 [M+H]⁺. IR $\nu_{\text{max}}^{\text{Nujol}}$ cm⁻¹: 3420, 3240, 1697, 1612, 1220, 1025. ¹H-NMR (DMSO-*d*₆) δ : 4.55 (1H, d, $J=15.6$ Hz, 1-N-CH₂), 4.71 (1H, d, $J=15.6$ Hz, 1-N-CH₂), 3.77 (1H, d, $J=14.8$ Hz, 3-N-CH₂), 4.74 (1H, d, $J=14.8$ Hz, 3-N-CH₂), 3.46 (1H, d, $J=8$ Hz, C₄-H), 3.13 (1H, br t, $J=8$ Hz, C₅-H), 4.63 (1H, d, $J=9$ Hz, -O-CH-N), 7.2–7.4 (10H, m, aromatic proton). δ (H numbers) of *N*-[3-(dimethylamino)propyl]-D-glucamine moiety: 1.72 (2H, CH₂-CH₂-CH₂), 2.39 and 2.95 (1H × 2, CH-CH₂-N), 2.58 (2H, N-CH₂-CH₂), 2.62 (6H, NMe₂), 2.65 (2H, CH₂OH), 3.33 (1H, CHOH), 3.36 (2H, CH₂-NMe₂), 3.5 (1H, CHOH), 3.54 (1H, CHOH), 3.97 (1H, -O-CH-CH₂).

This salt (7.7 g, 0.013 mol) was added to H₂O (100 ml). After addition of 10% aqueous HCl (17 ml), the liberated oil was extracted with AcOEt. The extract was washed with H₂O and evaporated. Recrystallization of the residue from Me₂CO–Et₂O–petroleum ether gave 4.1 g (42%) of (3*aS*,6*R*,6*aR*)-**9**. mp 128–129 °C. $[\alpha]_D^{25} +28.1^\circ$ ($c=1$, benzene).

Optical Resolution of (3*aRS*,6*SR*,6*aSR*)-9** with **14c**** (3*aRS*,6*SR*,6*aSR*)-**9** (8.46 g, 0.025 mol) and **14c** (4.32 g, 0.0125 mol) were added to a solution of Me₂CO (50 ml) and H₂O (6 ml). The mixture was stirred at 25 °C for 48 h, and the precipitated crystals were collected and washed with aqueous Me₂CO to give 7.44 g (43.5%) of the salt (**15c**). mp 109–111 °C. $[\alpha]_D^{25} -2.7^\circ$ ($c=1$, MeOH). *Anal.* Calcd for C₃₅H₄₅N₃O₁₁: C, 61.48; H, 6.63; N, 6.15; O, 25.74. Found: C, 61.39; H, 6.81; N, 6.07; O, 25.75. FAB-MS m/z : 684 [M+H]⁺. IR $\nu_{\text{max}}^{\text{Nujol}}$ cm⁻¹: 3280, 1671, 1631, 1615, 1520, 1240, 1055, 1035. ¹H-NMR (DMSO-*d*₆). The spectrum suggested the presence of several isomeric components. The following data represent the approximate positions of the center of several peaks. δ : 4.6 (1H, 1-N-CH₂), 4.75 (1H, 1-N-CH₂), 4.3 (1H, 3-N-CH₂), 4.8 (1H, 3-N-CH₂), 4.2 (1H, d, $J=9$ Hz, C₄-H), 3.9 (1H, C₅-H), 4.7 (1H, -O-CHOH), 7.3 (10H, m, aromatic). δ (H numbers) of *N*-(3,4-dimethoxyphenethyl)-D-glucamine moiety: 2.6 (2H, CH₂-CH₂-Ar), 2.8 (2H, N⁺H₂-CH₂-CH₂), 2.95 and 3.15 (2H, N⁺H₂-CH₂-CH), 3.9 (1H, CHOH), 3.9 (1H, CHOH), 3.3–3.6 (4H, CHOH × 2, CH₂OH).

This salt (7.0 g) was treated with aqueous 10% HCl and the separated oil was extracted with AcOEt. The extract was washed with H₂O and evaporated. The residue was recrystallized from Me₂CO–Et₂O–petroleum ether to give 3.35 g (42.1%) of (3*aS*,6*R*,6*aR*)-**9**. mp 129.5–131 °C. $[\alpha]_D^{25} +28.0^\circ$ ($c=1$, benzene).

meso*-1,3-Dibenzyl-1,3,3*a*,6*a*-tetrahydro-2*H*-furo[3,4-*d*]imidazole-2,4,6-trione (**4**) from (3*aR*,6*S*,6*aS*)-**9* A solution of silver nitrate (44.8 g, 0.26 mol) in H₂O (100 ml) was added to a solution of (3*aR*,6*S*,6*aS*)-**9** (40.6 g, 0.12 mol) and EtOH (400 ml). After addition of 1 *N* NaOH (600 ml) at room temperature, the mixture was stirred at the same temperature for 5 h, and allowed to stand overnight. Insoluble material was filtered off, and the filtrate was made acidic with 10% aqueous HCl and extracted with AcOEt. The organic layer was washed with H₂O, dried, and evaporated. Acetic anhydride (60 ml) was added to the residue and the whole was

refluxed for 5 min. Precipitated crystals, after cooling, were collected and dried to give 23.6 g (58.5%) of the anhydride (4). mp 233–234 °C. (lit.¹¹ mp 236–237 °C.)

meso-1,3-Dibenzyl-2-oxo-imidazolidine-4,5-dicarboxylic Acid (3) from (3aR,6S,6aS)-9 a) Oxidation with Bromine: Bromine (5.67 g, 0.035 mol) was added dropwise to a mixture of Na₂CO₃ (11.5 g, H₂O (44 ml), (3aR,6S,6aS)-9 (10 g, 0.03 mol), and AcOEt (44 ml) at 25 °C. The mixture was stirred at the same temperature for 4.5 h, then allowed to stand for a short time. The separated upper layer was washed with H₂O, dried, and evaporated. After addition of Et₂O to the residue, precipitated crystals were collected and dried to give 8.58 g (82%) of the dicarboxylic acid (3). mp 163–165 °C. (lit.¹¹ mp 167 °C).

b) Oxidation with Sodium Chlorite: A solution of sodium chlorite (16.1 g, 0.178 mol) in H₂O (127 ml) was added dropwise to a stirred mixture of Na₂CO₃ (23.3 g), H₂O (132 ml), (3aR,6S,6aS)-9 (30 g, 0.089 mol), and AcOEt (132 ml) at 25 °C. Stirring was continued for 6.5 h, and the reaction mixture was made acidic (pH 5.0) with 35% aqueous HCl. The aqueous layer was then separated and adjusted to pH 1.2 with 35% aqueous HCl. The separated oil was extracted with AcOEt, and the extract was washed with H₂O and aqueous sodium thiosulfate, dried, and evaporated. After addition of Et₂O to the residue, crystals were collected to give, after drying, 27.4 g (87%) of the dicarboxylic acid (3). mp 163–164 °C.

X-Ray Analysis of 15b A colorless transparent prism of **15b** with dimensions of 0.4 × 0.3 × 0.2 mm was chosen for the diffraction experiments. The crystal data are as follows: $a = 22.510$ (2), $b = 22.510$ (1), $c = 11.066$ (2) Å, $\alpha = 90.0$ (0), $\beta = 90.00$ (0), $\gamma = 120.0$ (0)°, $U = 4856.1$ (8) Å³, hexagonal, space group $P6_3$, $Z = 6$, $D_x = 1.204$ g/cm³, $F(000) = 1884$, $\mu(\text{Cu K}\alpha) = 7.323$ cm⁻¹. The intensity data were measured on a four-circle diffractometer (AFC-5, Rigaku). Of 2912 unique reflections, 2406 with $|F_o| \geq 2.67 \sigma(F)$ were judged significant. The structure was solved by the direct method using SIR85¹¹ and refined by the block-diagonal least-squares method with anisotropic thermal factors for the non-hydrogen atoms and with isotropic ones for all hydrogen atoms. The final R value was 0.081 ($R_w = 0.103$). The atomic scattering factors were taken from "International Tables for X-Ray Crystallography".¹² The atomic parameters are listed in Table I. The molecular structures are shown in Fig. 1 with a stereoscopic drawing, and the atomic nomenclature is shown in Fig. 2.

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References and Notes

- 1) M. W. Goldberg and L. H. Sternbach, U. S. Patents 2489232 (1951) [*Chem. Abstr.*, **45**, 184b (1951)]; *idem, ibid.*, 2489238 (1951) [*Chem. Abstr.*, **45**, 186a (1951)]; *idem, ibid.*, 2489235 (1951) [*Chem. Abstr.*, **45**, 186g (1951)].
- 2) Elegant total syntheses of biotin starting from D-mannose, D-glucose and L-cystein have been reported. However, several flaws in these methods such as lengthy sequences of reactions and the use of expensive and dangerous reagents preclude their industrial application. See reference 3.
- 3) a) H. Ohrui and S. Emoto, *Tetrahedron Lett.*, **1975**, 2765; b) T. Ogawa, T. Kawano and M. Matsui, *Carbohydr. Res.*, **1977**, C31; c) N. P. Confalone, G. Pizzolato, D. Lollar, E. Baggoiollini and M. Uskokvic, *J. Am. Chem. Soc.*, **99**, 7020 (1977).
- 4) M. Gerecke, S. P. Zimmerman and W. Achwanden, *Helv. Chim. Acta*, **53**, 491 (1970).
- 5) The dihedral angle between C₆-H and C_{6a}-H is about 90° when the protons are *trans*. Gerecke *et al.* did not mention stereochemistry of the hydroxy group of **9**. See reference 4.
- 6) The detection limit for signals in NMR is said to be about 1%.
- 7) P. G. Holton, U. S. Patent 055258 (1979) [*Chem. Abstr.*, **95**, 6907j (1981)].
- 8) F. Kagan, M. A. Rebenstorf and R. V. Heinzelman, *J. Am. Chem. Soc.*, **79**, 3541 (1957).
- 9) The NMR spectra of **15a, c** in CD₃OD–DMSO-*d*₆ showed two sets of signals. See experimental section. In DMSO-*d*₆, the spectra exhibited more complex patterns. These results suggest ready isomerization of the compounds in solution by epimerization at the hemi-acetal carbon or by positional change of the hydroxyl group in the glucamine moiety to form a hemi-acetal.
- 10) a) S. Plaune and D. Heissler, *Tetrahedron Lett.*, **28**, 1401 (1987); b) E. Dalcanele and F. Montanari, *J. Org. Chem.*, **51**, 569 (1986); c) E. J. Corey, M. C. Desai and T. A. Engler, *J. Am. Chem. Soc.*, **107**, 4339 (1985).
- 11) SIR85, A computer program for automatic analysis of phase problems; C. Giacovazzo, G. L. Cascarano, G. Polidori, R. Spagna and D. Viterbo, *Acta Crystallogr., Sect. A*, **38**, 663 (1982); *idem, ibid.*, **43**, 22 (1987).
- 12) "International Tables for X-Ray Crystallography," Vol. IV, Kynoch Press, Birmingham, 1974.