Highly Effective Resolution of 1,3-Dibenzyl-6-hydroxy-3,3a,6,6a-tetrahydro-1*H*-furo[3,4-*d*]imidazole-2,4-dione, an Intermediate for Biotin, with Optically Active Amines and Reutilization of the Unwanted Epimer

Masaru SENUMA,*[,a] Takehiko FUJII,[b] Masahiko SETO,[b] Kimio OKAMURA,[c] Tadamasa DATE,[c] and Akio KINUMAKI[c]

Research Laboratory of Applied Biochemistry[a] and Osaka Factory,[b] Tanabe Seiyaku Co., Ltd., 3-16-89, Kashima, Yodogawa-ku, Osaka 532, Japan and Organic Chemistry Research Laboratory,[c] Tanabe Seiyaku Co., Ltd., Kawagishi, Toda, Saitama 335, Japan. *Received August 29, 1989*

The direct resolution of (3a*RS*,6*SR*,6a*SR*)-1,3-dibenzyl-6-hydroxy-3,3a,6,6a-tetrahydro-1*H*-furo[3,4-*d*]imidazole-2,4-dione [(±)-9], a key intermediate for biotin, with optically active amines was examined. Reaction of (±)-9 with cinchonidine readily gave the cinchonidine salt of the (4*S*,5*R*)-aldehyde-carboxylic acid (12), acidification of which gave (3a*S*,6*R*,6a*R*)-9, convertible to biotin. *N*-alkyl-D-glucamines (14) were also found to be effective resolving agents for (±)-9 applicable for industrial use. Reutilization of the unwanted epimer [(3a*R*,6*S*,6a*S*)-9] was effected by facile oxidation to the *meso*-diacid (3) with sodium chlorite.

Keywords biotin; (3a*RS*,6*SR*,6a*SR*)-1,3-dibenzyl-6-hydroxy-3,3a,6,6a-tetrahydro-1*H*-furo[3,4-*d*]imidazole-2,4-dione; optical resolution; *N*-alkyl-D-glucamine; unwanted epimer reutilization; oxidation; sodium chlorite

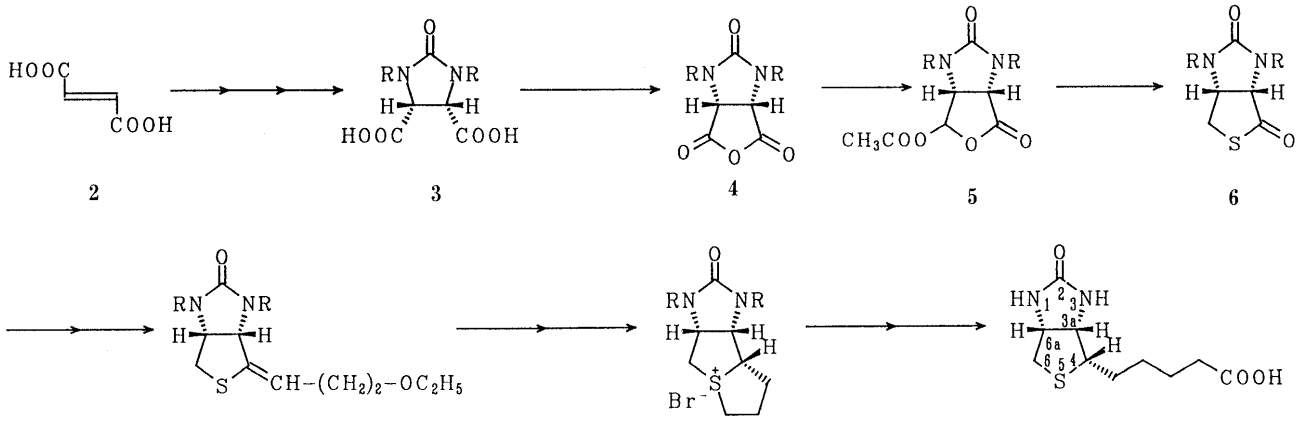
Biotin, (3a*S*,4*S*,6a*R*)-2,3,3a,4,6,6a-hexahydro-2-oxo-1*H*-thieno[3,4-*d*]imidazole-4-pentanoic acid (**1**), is an important growth factor and has been widely used not only as a pharmaceutical drug but also as an additive in cosmetics and feed. The most practical synthesis of biotin, reported by Goldberg and Sternbach[1] has been used for industrial-scale production[2,3] (Chart 1). The synthesis, however, was carried out mostly through racemic modifications, and the separation of enantiomers was achieved at the stage of the thiophanium salt (**8**). This constitutes a major flaw of this method, since **8** is an intermediate in a rather late stage of the sequence of reactions, and the reutilization of the unwanted epimer of **8** is impossible.

To overcome this problem, Gerecke *et al.*[4] reported the optical resolution of the hydroxylactone [(±)-**9**] *via* the formation of the diastereoisomeric alkoxylactones (**10**) with optically active alcohols (Chart 2). Since the formation of the alkoxylactone (**10**), however, was not stereospecific, troublesome separation of the desired (3a*S*,6a*R*) isomers (**10c,d**) from the four isomers was necessary. The regenerated hydroxylactone (3a*S*,6*R*,6a*R*)-**9** was converted to biotin (**1**) *via* the thiolactone (**6**).

Gerecke *et al.* also reported[4] the optical resolution *via* the half-ester (**11**) (Chart 3). However, the desired diastereoisomer, (4*S*,5*R*)-**11** (R′=cholesteryl), was obtained by the reaction of the anhydride (**4**) with cholesterol in rather low yield (27%). The optical resolution of the racemic cyclohexyl ester (4*RS*,5*SR*)-**11** (R′=cyclohexyl) was effected by the use of ephedrine in 39% yield. Although the unwanted isomer of **11** could radily be converted to the *meso*-diacid (**3**) and reutilized, the use of expensive cholesterol or ephedrine precludes the industrial application of these methods.

In this paper, we report the effective direct resolution of the hydroxylactone [(±)-**9**] with optically active amines and the reutilization of the unwanted epimer of **9** by facile oxidation to the *meso*-diacid (**3**) with sodium chlorite.

Resolution of the Hydroxylactone [(±)-9] with Optically Active Amines Reaction of the racemic hydroxylactone [(±)-**9**] with optically active amines is expected to provide diastereoisomeric salts of the aldehyde-carboxylic acid (**12**) by nucleophilic opening. The feasibility of this approach was preliminarily examined by nuclear magnetic resonance (NMR) measurement. The proton NMR (^{1}H-NMR) spectrum of (±)-**9** in both $CDCl_3$ and CD_3OD showed signals assignable to the hydroxylactone structure. The *trans* relationship of the C_6-H and C_{6a}-H was ascertained, since the signal of the C_6-H appeared as a singlet.[5] When measured in the presence of an equimolar amount of cinchonidine, this signal disappeared with the concomitant appearance of



2 3 4 5 6

7 (3a*S*, 4*S*, 6a*R*)-8 biotin (**1**) R=benzyl

Chart 1

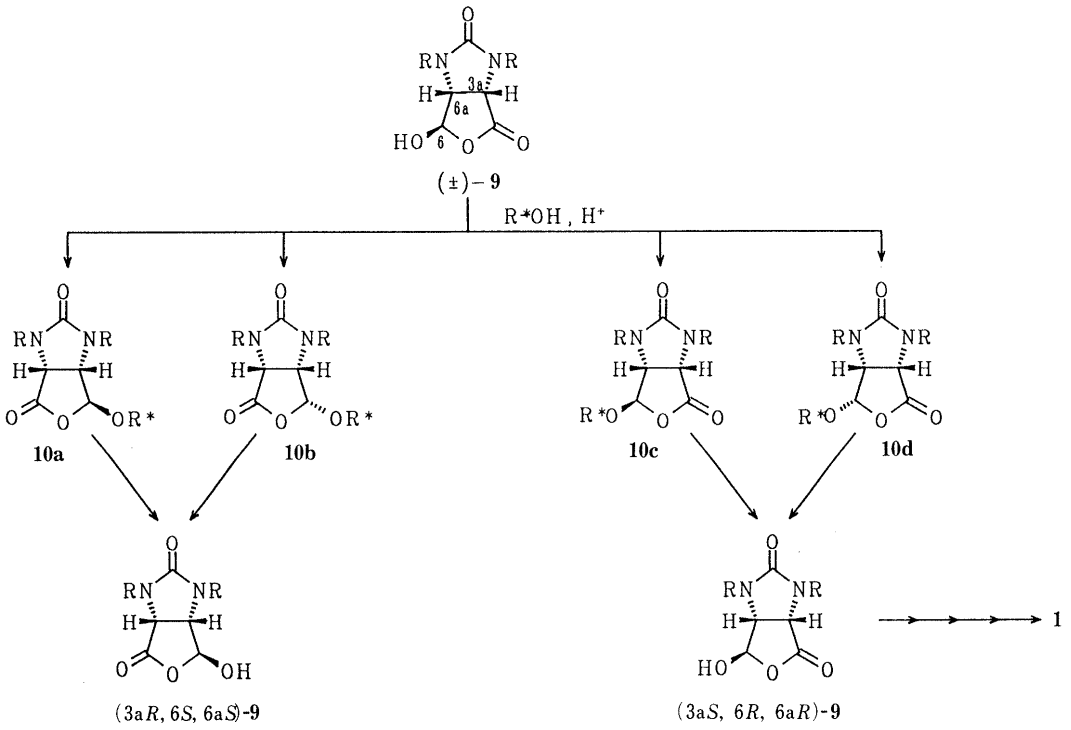


Chart 2

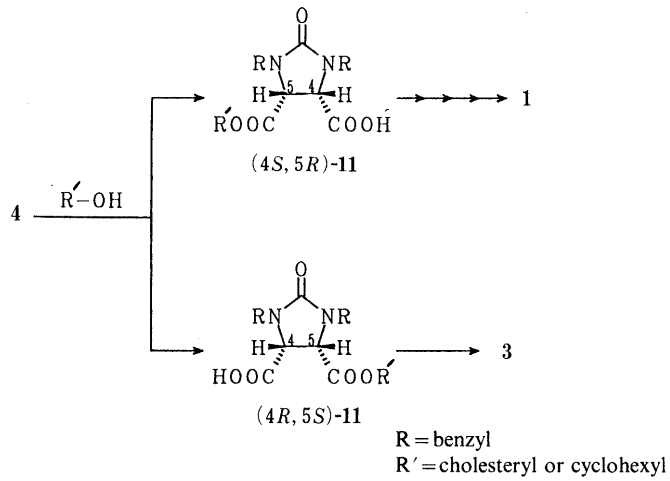


Chart 3

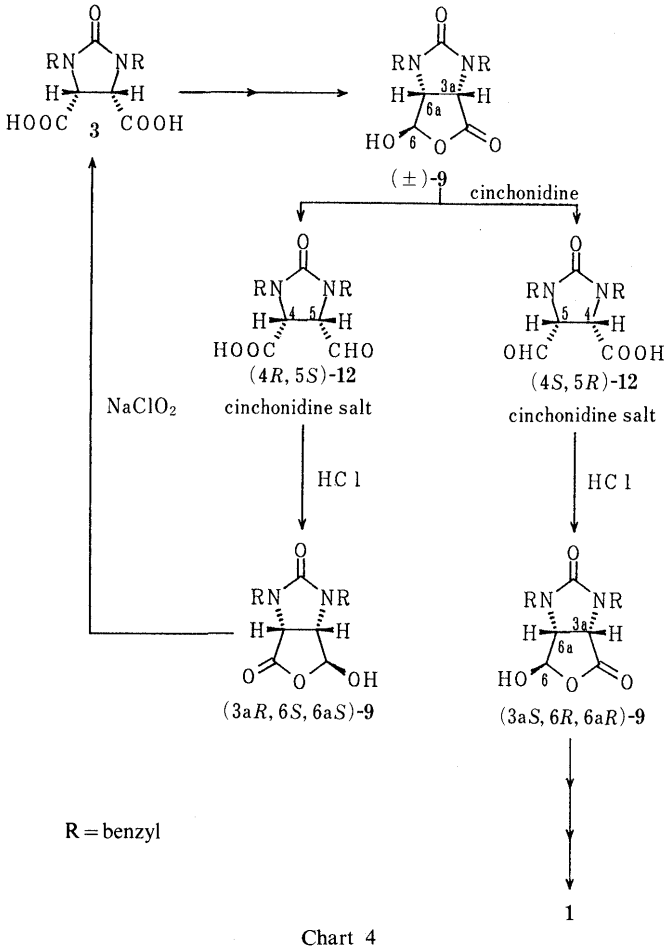


Chart 4

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 [(±)-**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*S*,5*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 (±)-**9**) of desired (3a*S*,6*R*,6a*R*)-**9** (Chart 4). Evaporation of the mother liquor of the salt of (4*S*,5*R*)-**12** gave, after acidification, (3a*R*,6*S*,6a*S*)-**9** in 36.5% yield. The reaction of (±)-**9**

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

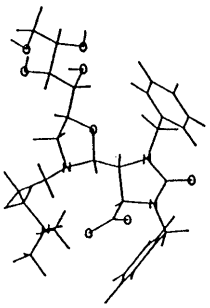
Although cinchonidine was found to be a highly effective resolving agent for (±)-**9**, it is quite expensive and not readily accessible. To find a more practical resolving agent applicable for industrial use, we examined the optical resolution of (±)-**9** with various *N*-alkyl-D-glucamines (**14**). 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 (3a*S*,6*R*,6a*R*)-**9** in nearly quantitative yield, and (3a*R*,6*S*,6a*S*)-**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 H_2O. The ^{1}H-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*



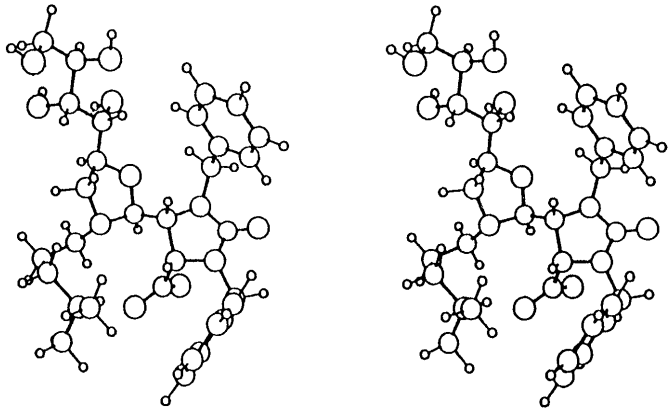


Fig. 1. Stereoscopic View of **15b**

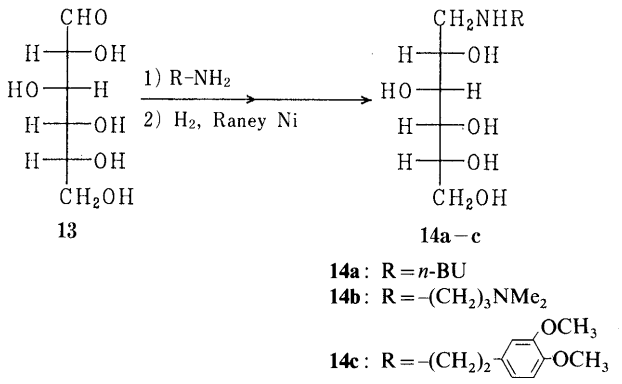
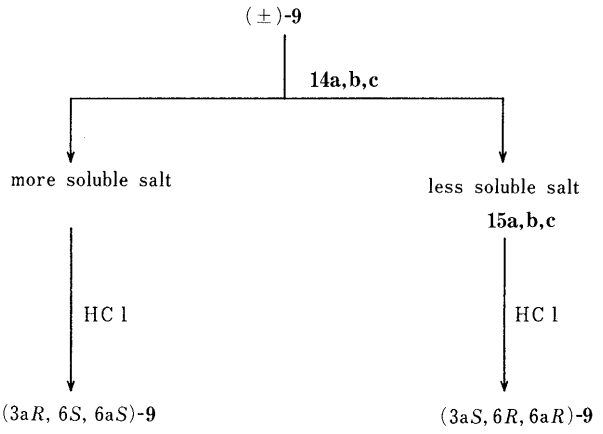
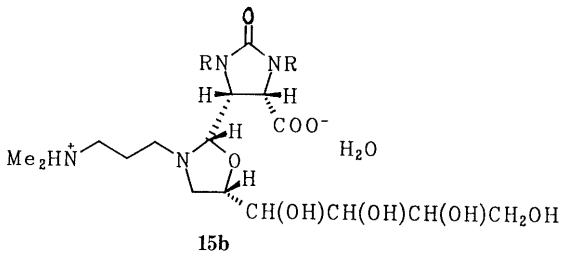
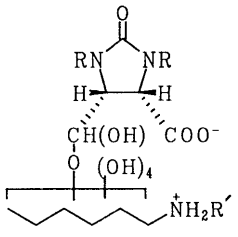


Chart 5







15a: R′ = *n*-Bu
15c: R′ = 3,4-dimethoxyphenetyl

R = benzyl

Chart 6

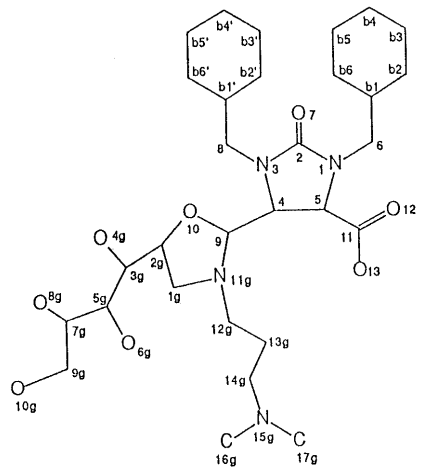


Fig. 2. Nomenclature of Atoms

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

No.	Atom	x	y	z	B_{eq} (Å^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}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 (±)-**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 [(3a*R*,-6*S*,6a*S*)-9] Gerecke *et al.*[4] reported the reutilization of the unwanted hydroxylactone [(3a*R*,6*S*,6a*S*)-**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 (3a*R*,6*S*,6a*S*)-**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, (3a*R*,6*S*,6a*S*)-**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 (3a*R*,6*S*,-6a*S*)-**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 [(±)-**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}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.

(3a*RS*,6*SR*,6a*SR*)-1,3-Dibenzyl-6-hydroxy-3,3a,6,6a-tetrahydro-1*H*-furo[3,4-*d*]imidazole-2,4-dione (9) A solution of the acetoxylactone (**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 Me_2CO–Et_2O–petroleum ether gave 37.4 g (84%) of (3a*RS*,6*SR*,6a*SR*)-**9**. mp 113—116 °C. (lit.[4] mp 110—113 °C). IR ν_{max}^{Nujol} cm^{-1}: 3205, 1795, 1660, 1230, 1110, 915, 700. ^{1}H-NMR ($CDCl_3$) δ: 3.87 (1H, d, J=8.6 Hz, C_{6a}-H), 4.04 (1H, d, J=8.6 Hz, C_{3a}-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, br s, C_6-OH), 5.47 (1H, s, C_6-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 C_6-H.

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

added to a solution of (3a*RS*,6*SR*,6a*SR*)-**9** (43.6 g, 0.13 mol) in Me_2CO (193 ml). The precipitated crystals were collected and washed with Me_2CO 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° (*c*=0.5, MeOH). *Anal.* Calcd for $C_{38}H_{40}N_4O_5 \cdot H_2O$: 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 ν_{max}^{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**]. ^{1}H-NMR ($CDCl_3$) *δ*: 3.91 (1H, dd, *J*=9.7 and 2.5 Hz, C_5-H, changed to d (*J*=9.7 Hz by irr. at *δ* 8.97), 4.15 (1H, d, *J*=9.7 Hz, C_4-H), 4.21 (1H, d, *J*=14.9 Hz, 3-N-CH_2), 4.29 (1H, d, *J*=14.9 Hz, 1-N-CH_2), 4.8 (overlapped with H_2O, 1-N-CH_2), 5.01 (1H, d, *J*=14.9 Hz, 3-N-CH_2), 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 H_2O, dried, and evaporated. Recrystallization of the residue from Me_2CO–Et_2O–petroleum ether gave 17.9 g (42% based on (3a*RS*,6*SR*,6a*SR*)-**9**) of (3a*S*,6*R*,6a*R*)-**9**. mp 129—130 °C. (lit.[4] mp 130—131 °C). $[\alpha]_D^{25}$ +28.1° (*c*=1, benzene). (lit.[4] $[\alpha]_D^{25}$ +28.0 (*c*=1, benzene)). The NMR spectrum of this compound was identical to that of the racemate (**9**) described agbove.

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 H_2O and drying, an oil. Crystallization from Me_2CO–Et_2O–petroleum ether gave 15.9 g (36.5% based on (3a*RS*,6*SR*,6a*SR*)-**9**) of (3a*R*,6*S*,6a*S*)-**9**. mp 129—130 °C. $[\alpha]_D^{25}$ −27.8° (*c*=1, benzene).

Optical Resolution of (3a*RS*,6*SR*,6a*SR*)-9 with Quinine Quinine (3.24 g, 0.01 mol) and (3a*RS*,6*SR*,6a*SR*)-**9** (3.38 g, 0.01 mol) were added to a solution of H_2O (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° (*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 (3a*S*,6*R*,6a*R*)-**9**. mp 128—129 °C. $[\alpha]_D^{25}$ +27.9° (*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 H_2O (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° (*c*=1, H_2O). (lit.[7] $[\alpha]_D^{25}$ −14.3° (*c*=1, H_2O)).

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° *c*=1, MeOH). *Anal.* Calcd for $C_{11}H_{26}N_2O_5$: C, 49.61; H, 9.84; N, 10.52. Found: C, 48.95; H, 9.87; N, 9.77. IR ν_{max}^{Nujol} cm^{-1}: 3310, 3240, 1090, 1050, 1015. ^{1}H-NMR (DMSO-d_6) *δ*: 1.55 (2H, m, NH-CH_2C$\underline{H}_2$), 2.10 (6H, s, NMe_2), 2.2 (2H, t, *J*=7 Hz, C$\underline{H}_2$-NMe_2), 2.5 (2H, m, NH-C$\underline{H}_2$$CH_2$), 2.59 (2H, m, NH-C$\underline{H}_2$CH), 3.3—3.4 (3H, m, C$\underline{H}OH, C\underline{H}_2$OH), 3.48 (1H, m, C$\underline{H}$OH), 3.59 (1H, dd, *J*=10.8 and 3.5 Hz, C$\underline{H}$OH), 3.64 (1H, m, C$\underline{H}$OH).

N-(3,4-Dimethoxyphenethyl)-D-glucamine (**14c**) was similarly obtained in 63.7% yield. mp 134—135 °C. $[\alpha]_D^{25}$ −8.3° (*c*=1, MeOH). *Anal.* Calcd for $C_{11}H_{26}N_2O_5$: C, 55.64; H, 7.88; N, 4.06. Found: C, 55.73; H, 7.96; N, 3.96. IR ν_{max}^{Nujol} cm^{-1}: 3340, 3240, 1590, 1520, 1265, 1050. ^{1}H-NMR (DMSO-d_6) *δ*: 2.63 (2H, m, NHC$\underline{H}_2$CH), 2.7 (4H, m, NH-CH_2-CH_2), 3.35 (2H, m, C$\underline{H}_2$OH), 3.4 (1H, br d, *J*=8.5 Hz, C$\underline{H}$OH), 3.48 (1H, m, C$\underline{H}$OH), 3.58 (1H, m, C$\underline{H}$OH), 3.65 (1H, m, C$\underline{H}$OH), 3.71 (3H, s, OCH_3), 3.73 (3H, s, OCH_3), 6.70 (1H, dd, *J*=8.1 and 1.8 Hz, aromatic proton), 6.80 (1H, d, *J*=1.8 Hz, aromatc proton), 6.84 (1H, d, *J*=8.1 Hz, aromatic proton).

Optical Resolution of (3a*RS*,6*SR*,6a*SR*)-9 with 14a (3a*RS*,6*SR*,6a*SR*)-**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 (3a*RS*,6*SR*,6a*SR*)-**9**) of the salt (**15a**). mp 84—87 °C. $[\alpha]_D^{25}$ −14.0° (*c*=1, DMF). *Anal.* Calcd for $C_{29}H_{41}N_3O_9$: 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 ν_{max}^{Nujol} cm^{-1}: 3280, 3030—3080, 1672, 1627, 1245, 1050. ^{1}H-NMR (CD_3OD: DMSO-d_6=10:1) *δ*: 4.38 and 4.40 (1H, d, *J*=15 Hz, 1-N-CH_2), 4.67 and 4.82 (1H, d, *J*=15 Hz, 1-N-CH_2), 3.95 and 4.01 (1H, d, *J*=15 Hz, 3-N-CH_2), 4.94 (1H, d, *J*=15 Hz, 3-N-CH_2), 3.78 (1H, d, *J*=*ca.* 10 Hz, C_4-H), 3.50 and 3.51 (1H, dd, *J*=*ca.* 10 and 2.5 Hz, C_5-H), 4.65 and 4.76 (1H, d, *J*=2.5 Hz, O-C$\underline{H}$OH), 7.26 (10H, m, aromatic proton). *δ* (H numbers) of *N*-*n*-butyl-D-glucamine moiety: 0.96 (3H, -CH_3), 1.40 (2H, CH_2-C$\underline{H}_2$-CH_3), 1.67 (2H, -CH_2-C$\underline{H}_2$-CH_2), 2.99 (2H, N^+H_2-C$\underline{H}_2$-CH_2), 3.12 and 3.16 (2H, CH-C$\underline{H}_2$-N^+H_2), 4.04 (1H, C$\underline{H}$-CH_2), 3.81 (1H, C$\underline{H}$OH), 3.25 (1H, C$\underline{H}$OH), 3.66 (1H, CH_2-C$\underline{H}$OH), 3.63 (2H, -C$\underline{H}_2$OH). ^{13}C-NMR δ_c: 96.0 and 97.8 (O-CHOH).

This salt (**15a**) (24 g, 0.04 mol) was added to a mixture of H_2O (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 Me_2CO–Et_2O–petroleum ether gave 13.7 g (44.7% based on (3a*RS*,6*SR*,6a*SR*)-**9**) of (3a*S*,6*R*,6a*R*)-**9**. mp 129—130 °C. $[\alpha]_D^{25}$ +27.9° (*c*=1, benzene). The NMR spectrum of this compound was identical to that of (3a*RS*,6*SR*,6a*SR*)-**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 H_2O and drying, an oil. Crystallization from Me_2CO–Et_2O–petroleum ether gave 13 g (41.5%) of (3a*R*,6*S*,6a*S*)-**9**. mp 128—130 °C. $[\alpha]_D^{25}$ −27.8° (*c*=1, benzene).

Optical Resolution of (3a*RS*,6*SR*,6a*SR*)-9 with 14b (3a*RS*,6*SR*,6a*SR*)-**9** (10 g, 0.03 mol) and **14b** (7.9 g, 0.03 mol) were added to a solution of EtOH (20 ml) and Me_2CO (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° (*c*=1, MeOH). *Anal.* Calcd for $C_{30}H_{42}N_4O_8 \cdot H_2O$: 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 H_2O was ascertained by thermogravimetric and differential thermal analyses. FAB-MS *m/z*: 587 [M+H]$^+$. IR ν_{max}^{Nujol} cm^{-1}: 3420, 3240, 1697, 1612, 1220, 1025. ^{1}H-NMR (DMSO-d_6) *δ*: 4.55 (1H, d, *J*=15.6 Hz, 1-N-CH_2), 4.71 (1H, d, *J*=15.6 Hz, 1-N-CH_2), 3.77 (1H, d, *J*=14.8 Hz, 3-N-CH_2), 4.74 (1H, d, *J*=14.8 Hz, 3-N-CH_2), 3.46 (1H, d, *J*=8 Hz, C_4-H), 3.13 (1H, br t, *J*=8 Hz, C_5-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, CH_2-C$\underline{H}_2$-CH_2), 2.39 and 2.95 (1H×2, CH-C$\underline{H}_2$-N), 2.58 (2H, N-C$\underline{H}_2$-CH_2), 2.62 (6H, NMe_2), 2.65 (2H, C$\underline{H}_2$OH), 3.33 (1H, C$\underline{H}$OH), 3.36 (2H, C$\underline{H}_2$-NMe_2), 3.5 (1H, C$\underline{H}$OH), 3.54 (1H, C$\underline{H}$OH), 3.97 (1H, -O-C$\underline{H}$-CH_2).

This salt (7.7 g, 0.013 mol) was added to H_2O (100 ml). After addition of 10% aqueous HCl (17 ml), the liberated oil was extracted with AcOEt. The extract was washed with H_2O and evaporated. Recrystallization of the rsidue from Me_2CO–Et_2O–petroleum ether gave 4.1 g (42%) of (3a*S*,6*R*,6a*R*)-**9**. mp 128—129 °C. $[\alpha]_D^{25}$ +28.1° (*c*=1, benzene).

Optical Resolution of (3a*RS*,6*SR*,6a*SR*)-9 with 14c (3a*RS*,6*SR*,6a*SR*)-**9** (8.46 g, 0.025 mol) and **14c** (4.32 g, 0.0125 mol) were added to a solution of Me_2CO (50 ml) and H_2O (6 ml). The mixture was stirred at 25 °C for 48 h, and the precipitated crystals were collected and washed with aqueous Me_2CO to give 7.44 g (43.5%) of the salt (**15c**). mp 109—111 °C. $[\alpha]_D^{25}$ −2.7° (*c*=1, MeOH). *Anal.* Calcd for $C_{35}H_{45}N_3O_{11}$: 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 ν_{max}^{Nujol} cm^{-1}: 3280, 1671, 1631, 1615, 1520, 1240, 1055, 1035. ^{1}H-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-CH_2), 4.75 (1H, 1-N-CH_2), 4.3 (1H, 3-N-CH_2), 4.8 (1H, 3-N-CH_2), 4.2 (1H, d, *J*=9 Hz, C_4-H), 3.9 (1H, C_5-H), 4.7 (1H, -O-C$\underline{H}$OH), 7.3 (10H, m, aromatic). *δ* (H numbers) of *N*-(3,4-dimethoxyphenethyl)-D-glucamine moiety: 2.6 (2H, CH_2-C$\underline{H}_2$-Ar), 2.8 (2H, N^+H_2-C$\underline{H}_2$-CH_2), 2.95 and 3.15 (2H, N^+H_2-C$\underline{H}_2$-CH), 3.9 (1H, C$\underline{H}$OH), 3.9 (1H, C$\underline{H}$OH), 3.3—3.6 (4H, C$\underline{H}$OH×2, C$\underline{H}_2$OH).

This salt (7.0 g) was treated with aqueous 10% HCl and the separated oil was extracted with AcOEt. The extract was washed with H_2O and evaporated. The residue was recrystallized from Me_2CO–Et_2O–petroleum ether to give 3.35 g (42.1%) of (3a*S*,6*R*,6a*R*)-**9**. mp 129.5—131 °C. $[\alpha]_D^{25}$ +28.0° (*c*=1, benzene).

***meso*-1,3-Dibenzyl-1,3,3a,6a-tetrahydro-2*H*-furo[3,4-*d*]imidazole-2,4,6-trione (4) from (3a*R*,6*S*,6a*S*)-9** A solution of silver nitrate (44.8 g, 0.26 mol) in H_2O (100 ml) was added to a solution of (3a*R*,6*S*,6a*S*)-**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 H_2O, 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.[1] mp 236—237 °C.)

***meso*-1,3-Dibenzyl-2-oxo-imidazolidine-4,5-dicarboxylic Acid (3) from (3a*R*,6*S*,6a*S*)-9** a) Oxidation with Bromine: Bromine (5.67 g, 0.035 mol) was added dropwise to a mixture of Na_2CO_3 (11.5 g, H_2O (44 ml), (3a*R*,6*S*,6a*S*)-**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 H_2O, dried, and evaporated. After addition of Et_2O 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.[1] mp 167 °C).

b) Oxidation with Sodium Chlorite: A solution of sodium chlorite (16.1 g, 0.178 mol) in H_2O (127 ml) was added dropwise to a stirred mixture of Na_2CO_3 (23.3 g), H_2O (132 ml), (3a*R*,6*S*,6a*S*)-**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 H_2O and aqueous sodium thiosulfate, dried, and evaporated. After addition of Et_2O 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 $0.4 \times 0.3 \times 0.2$ mm was chose 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) Å, hexagonal, space group $P6_5$, $Z=6$, $D_x=1.204$ g/cm^3, $F(000)=1884$, μ(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 $|F_O| \geqq 2.67\,\delta\,(F)$ were judged significant. The structure was solved by the direct method using SIR85[11] 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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