Synthesis, Resolution, and Renal Vasodilation Activity of Novel DA_1 Agonists: 4-(3,4-Dihydroxyphenyl)-1,2,3,4-tetrahydroisoquinoline Derivatives

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7,8-Dihydroxy-4-(3,4-dihydroxyphenyl)-1,2,3,4-tetrahydroisoquinoline (1) and 4-(3,4-dihydroxyphenyl)-7-hydroxy-8-methyl-1,2,3,4-tetrahydroisoquinoline (2) are potent renal vasodilators which selectively stimulate DA_1 (peripheral dopamine receptor-1) receptors. Especially, (*S*)-(−)-1 is the most potent. Its DA_1 agonist activity is about 10 times stronger than dopamine for increasing renal blood flow in anesthetized dogs. The renal and cardiovascular effects of (*S*)-(−)-1 may be suitable for the treatment of patients with renal insufficiency, heart failure and hypertension.

Keywords DA_1; renal vasodilation; dopamine; optical resolution; 4-phenyltetrahydroisoquinoline

Recently, Massingham *et al.*,[1] through a number of dopamine agonist/antagonist studies, proposed that there exist at least two distinct subtypes of peripheral dopamine receptors. DA_1-dopamine receptors exist postjunctionally in renal and mesenteric arterial beds where their activation leads to direct smooth muscle relaxation. This suggested that this type of activity is useful for renal insufficiency, cardiac failure or hypertension. Thus, we have sought potent and selective DA_1 (peripheral dopamine receptor-1) agonists as therapeutic agents.

Many compounds, *e.g.* benzazepines,[2] octahydrobenzoquinolines,[3] aminotetralines,[4] phenylpiperidines,[5] and tetrahydroisoquinolines,[6] have been synthesized and their DA_1 agonist (or antagonist) activity investigated. On the basis of these studies, we found that (±)-7,8-dihydroxy-4-(3,4-dihydroxyphenyl)-1,2,3,4-tetrahydroisoquinoline (**1**) and (±)-4-(3,4-dihydroxyphenyl)-7-hydroxy-8-methyl-1,2,3,4-tetrahydroisoquinoline (**2**) were potent DA_1 agonists.[7] Therefore we have been interested in the synthesis of the optically active compounds **1** and **2** for evaluating their DA_1 agonist activity.

Compounds **1** and **2** were synthesized by a method shown in Chart 1. Hydroxyamine (**4**), which was derived from veratraldehyde (**3**) *via* cyanohydrin, was reductively condensed with 2,3-dimethoxybenzaldehyde (**5**) to give a secondary amino intermediate (**7**). Compound **7** was cyclized under acid-catalyzed conditions[8] and, following deprotection under the condition of being refluxed in 48% hydrobromic acid or reacted with boron tribromide in dichloromethane at room temperature, gave **1**. Compound **2** was obtained from 3-methoxy-2-methylbenzaldehyde (**6**). The amido intermediate, which was obtained by condensa-

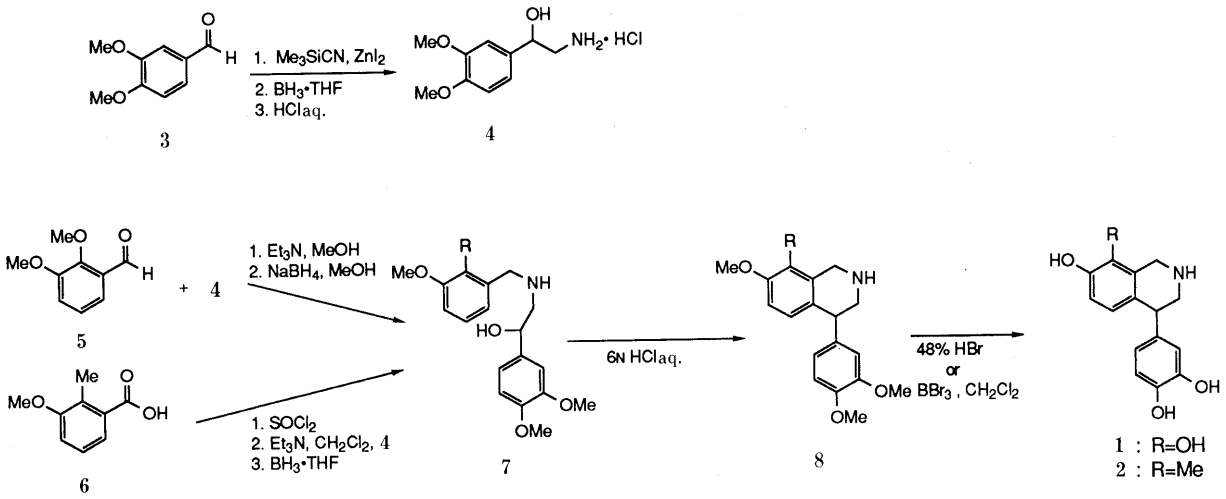


Chart 1

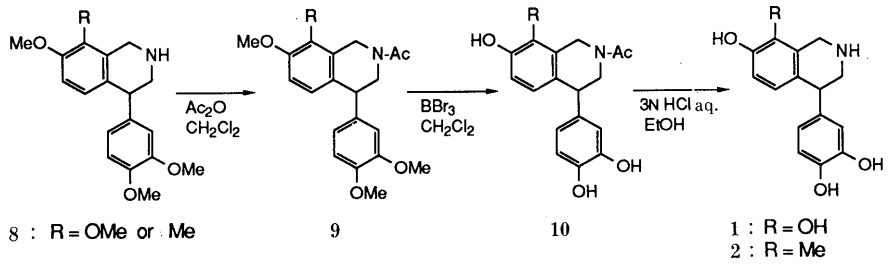
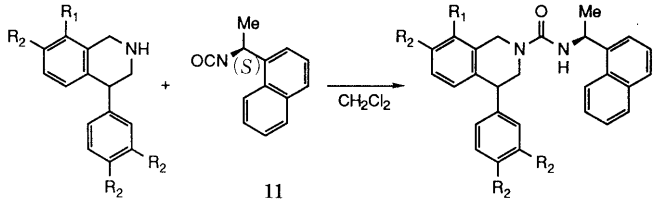


Chart 2



8 : R_1=OMe or Me, R_2=OMe
1 : R_1=R_2=OH
2 : R_1=Me, R_2=OH

Chart 3

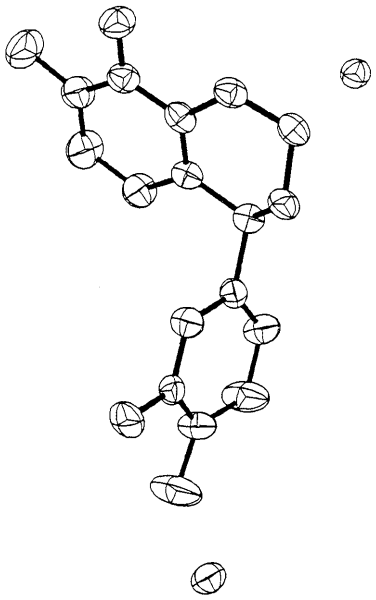


Fig. 1. X-Ray Structure of (−)-**1**·HCl·H_2O

tion of **4** and **6**, was reduced, cyclized, and deprotected to give **2**.

In order to obtain optically active **1** and **2**, a tri- or tetramethoxy precursor (**8**) was resolved, because it was thought that the catecholyl group might be unstable under basic conditions. Compound **8** was recrystallized as diastereomeric hydrogen dibenzoyltartrate,[9] and the salt was treated with aqueous sodium hydroxide to give the free base **8** as crystals. To convert optically active **8** to **1** or **2** with no racemization, and to give **1** or **2** as a hydrochloric acid salt, another route shown in Chart 2 was chosen. After protection of the secondary amine of **8** with an acetyl group, demethylation with boron tribromide and deacetylation with 3 N hydrochloric acid–ethanol produced **1** or **2**. For determination of the optical purities of **1**, **2**, and **8**, each was reacted with (*S*)-1-(1-naphthyl)ethyl isocyanate[10] to form diastereomeric urea derivatives (Chart 3).[11] High performance liquid chromatography (HPLC)[12] determined that **1**, **2**, and **8** were optically pure (at least 99.5% ee, respectively).

The absolute configurations of **1** and **2** were determined by single-crystal X-ray diffraction studies. The structure of (−)-**1** and (−)-**2** are illustrated in Figs. 1 and 2, respectively. As shown in Figs. 1 and 2, the absolute configuration at position 4 of (−)-**1** is *S*, while it is *R* for (−)-**2**. DA_1 agonist activity was evaluated as renal vasodilation which resulted in increased renal blood flow in pentobarbital-anesthetized

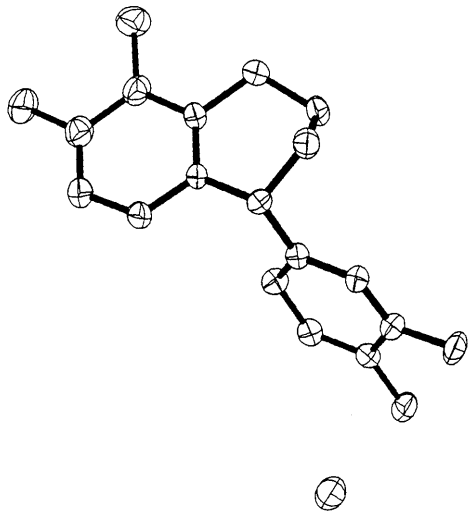


Fig. 2. X-Ray Structure of (−)-**2**·HCl

Table I. ED_{20}s of Optically Active 4-(3,4-Dihydroxyphenyl)-1,2,3,4-tetrahydroisoquinoline Derivatives

	(±)-**1**	(+)-**1**	(−)-**1**	(±)-**2**	(+)-**2**	(−)-**2**	Dopamine
Absolute configuration		*R*	*S*		*S*	*R*	
ED_{20}[a] (μg) i.a.	3.0	—[b]	2.0	5.0	2.2	—[b]	18.9

a) Dose for 20% increase in renal blood flow. *b*) No vasodilation activity.

dogs.[4a] Renal blood flow was measured by an electromagnetic flowmeter. The test compounds were injected into the renal artery. The doses (ED_{20}) of the test compounds that caused a 20% increase in renal blood flow were calculated and compared. Furthermore, it was confirmed that the renal vasodilatory effects of the test compounds were antagonized by a selective DA_1 antagonist, SCH23390.[13]

The biological activities (ED_{20} values) are shown in Table I. Under the same conditions, the ED_{20} value of dopamine is 18.9 μg. Comparing optically active **1** or **2**, it is found that only one enantiomer is active and the other one is inactive. From single-crystal X-ray diffraction studies it has been proved that (+)-**1** and (−)-**2** have *R* absolute configurations at position 4 and (−)-**1** and (+)-**2** have *S*. Therefore, only the *S* enantiomers of both **1** and **2** show DA_1 agonist activity. Carl Kaiser *et al.*[6a] proved that (*S*)-3′,4′-dihydroxynomifensine, which also has a 4-phenyl-1,2,3,4-tetrahydroisoquinoline structure, is nearly 20 times more active than the *R* enantiomer.

Compound (−)-**1**, which has the strongest DA_1 agonist activity in this series, was investigated and the results are as follows[14]: receptor binding assays revealed that (−)-**1** had no affinity for D-2, α_1 and α_2 receptors. In open-chest anesthetized dogs, intravenous infusion of a (−)-**1** (0.1—3.0 $\mu g \cdot kg^{-1} \cdot min^{-1}$) dose dependently increased renal blood flow (5—24% from baseline) and cardiac output (0—25%) and decreased mean blood pressure (1—14%), renal (6—30%) and total (1—29%) peripheral resistance with little effect on heart rate or max. *dp/dt*. In anesthetized dogs, intravenous infusion of (−)-**1** (0.1—3.0 $\mu g \cdot kg^{-1} \cdot min^{-1}$) increased the glomerular filtration rate (9—63% over baseline), urine flow rate (19—42%) and urinary sodium excretion (56—444%).

Experimental

Melting points were determined with a Yanaco MP-3 apparatus and were not corrected. Nuclear magnetic resonance (NMR) spectra were recorded on a JEOL FX90Q or FX100 spectrometer using Me_4Si as an internal standard. The following abbreviations are used; s, singlet, d, doublet, t, triplet, m, multiplet, br, broadened. Mass spectra (MS) were determined with a Hitachi M-80 or JEOL JMS-DX300 spectrometer. Elemental analyses are reported by symbols of the elements and the results were within ±0.3% of the calculated values. Optical rotations were determined with a JASCO DIP-370 polarimeter. HPLC was carried out using a Hitachi L-6000 pump, L-4000 UV detector and D-2500 recorder. Silica gel F_{254} (Merck) thin-layer chromatography (TLC) plates were used. For column chromatography, Kieselgel 60 (Merck) was used. All concentrations by evaporation were carried out *in vacuo*. Single-crystal X-ray analyses for (−)-**1**·HCl·H_2O and (−)-**2**·HCl were carried out on a Rigaku AFC-5R diffractometer.

(±)-[[(2,3-Dimethoxybenzyl)-*N*-amino]methyl]-3,4-dimethoxybenzyl Alcohol: (±)-7 (R=OMe) A mixture of 10.0 g of 1-(3,4-dimethoxyphenyl)-2-aminoethanol hydrochloride (**4**),[15] 7.47 g of 2,3-dimethoxybenzaldehyde (**5**), 6.0 ml of triethylamine and 50 ml of MeOH was stirred at room temperature for 1 h, and 1.62 g of sodium borohydride was added portionwise at room temperature. After the reaction was completed, the mixture was concentrated. The residue was dissolved in toluene and H_2O. The organic layer was washed with H_2O and concentrated. The residual solid was recrystallized from toluene–hexane to give 11.1 g of (±)-**7** (R=OMe). mp 96—97 °C. NMR ($CDCl_3$) δ: 2.54 (3H, m), 3.85 (15H, m), 4.66 (1H, dd), 6.70—7.20 (6H, m). Fast atom bombardment mass spectrum (FAB-MS) *m/z*: 348 (M^++H). *Anal.* Calcd for $C_{19}H_{25}NO_5$: C, 65.69; H, 7.25; N, 4.03. Found: C, 65.71; H, 7.27; N, 3.97.

(±)-7,8-Dimethoxy-4-(3,4-dihydroxyphenyl)-1,2,3,4-tetrahydroisoquinoline: (±)-8 (R=OMe) A mixture of 10.5 g of (±)-**7** (R=OMe) and 105 ml of 6 N HCl was stirred at 60 °C for 2 h. After cooling the mixture, the precipitant was extracted with dichloromethane. The combined extracts were washed with 1 N sodium hydroxide and H_2O and concentrated. The residual solid was recrystallized from ethyl acetate–hexane to give 8.14 g of (±)-**8** (R=OMe). mp 109—110 °C. NMR ($CDCl_3$) δ: 1.72 (1H, s), 2.92—3.41 (2H, m), 3.84 (12H, m), 3.98 (1H, t), 4.14 (2H, s), 6.50—6.84 (5H, m). FAB-MS *m/z*: 330 (M^++H). *Anal.* Calcd for $C_{19}H_{23}NO_4$: C, 69.28; H, 7.04; N, 4.25. Found: C, 69.10; H, 7.08; N, 4.29.

(±)-7,8-Dihydroxy-4-(3,4-dihydroxyphenyl)-1,2,3,4-tetrahydroisoquinoline Hydrobromide: (±)-1·HBr A mixture of 10.3 g of (±)-**8** (R=OMe) and 48.1 ml of 48% hydrobromic acid was heated in a 160 °C bath for 2 h. After cooling to 4 °C, 9.19 g of (±)-**1**·HBr was collected as crystals, mp 230 °C (dec.). NMR (DMSO-d_6) δ: 3.24 (1H, m), 3.52 (1H, m), 6.08 (1H, d), 6.48 (1H, dd), 6.58 (1H, s), 6.68 (1H, d). FAB-MS *m/z*: 274 (M^++H). *Anal.* Calcd for $C_{15}H_{16}BrNO_4$: C, 50.87; H, 4.55; Br, 22.56; N, 3.95. Found: C, 51.02; H, 4.33; Br, 22.82; N, 3.96.

(±)-4-(3,4-Dihydroxyphenyl)-7-hydroxy-8-methyl-1,2,3,4-tetrahydroisoquinoline Hydrobromide: (±)-2·HBr A mixture of 50 g of 3-methoxy-2-methylbenzoic acid (**6**) and 66 ml of thionyl chloride was heated under reflux for 40 min. After cooling, the solution was concentrated and azeotroped with toluene. The residue was dissolved in 253 ml of dichloromethane and added dropwise to a solution of 63.2 g of **4** and 83 ml of triethylamine in 316 ml of dichloromethane under ice-bath cooling. After stirring at 3 °C for 1 h, 1 N HCl was added to the reaction mixture. The organic layer was washed with 1 N sodium hydrogen carbonate and brine, dried ($MgSO_4$) and concentrated. The residual solid was recrystallized from ethyl acetate–hexane to give 76.3 g of crystals, mp 105—109 °C.

To a solution of 74.8 g of the crystals in 763 ml of tetrahydrofuran, 796 mg of 1 M borane in tetrahydrofuran was added dropwise at 10 °C and the solution was heated under reflux for 1.5 h. To the reaction mixture was added 96 ml of MeOH at 4 °C and the mixture was refluxed for 30 min, then 66.3 ml of 12 N HCl was added at 4 °C. The precipitants were collected, 760 ml of 1 N sodium hydrogen carbonate added, and the mixture was extracted with $CHCl_3$. The organic layer was dried ($MgSO_4$) and concentrated. The residual solid was recrystallized from $CHCl_3$–hexane to give 43.0 g of (±)-**7** (R=Me), mp 135—136 °C. FAB-MS *m/z*: 332 (M^++H).

The following experimental procedure was the same as for (±)-**1**·HBr. (±)-**2**·HBr, mp 250 °C (dec.). NMR (DMSO-d_6) δ: 2.04 (3H, s), 3.18 (2H, br), 3.48 (2H, br), 4.12 (1H, t), 4.24 (2H, br), 6.52 (1H, s), 6.60 (4H, dd), 9.30 (3H, br). FAB-MS *m/z*: 272 (M^++H). *Anal.* Calcd for $C_{16}H_{18}BrNO_3$: C, 54.56; H, 5.15; Br, 22.69; N, 3.98. Found: C, 54.46; H, 5.17; Br, 22.65; N, 3.91.

Resolution of (±)-7,8-Dimethoxy-4-(3,4-dimethoxyphenyl)-1,2,3,4-tetrahydroisoquinoline: (+)- and (−)-8 (R=OMe) To a mixture of 100 g of (±)-**8** (R=OMe) and 300 ml of ethanol was added dropwise a solution of 114 g of (−)-dibenzoyl-L-tartaric acid monohydrate in 400 ml of ethanol. After the mixture was stirred at room temperature for 1 h, 139 g of crystals were collected. Recrystallization from ethanol–H_2O (3:1, v/v) gave 79.4 g of **8** (R=OMe) hydrogen dibenzoyl-L-tartrate, mp 181 °C (dec.). $[\alpha]_D^{20}$ −23° (*c*=1, DMF). *Anal.* Calcd for $C_{19}H_{23}NO_4 \cdot C_{18}H_{14}O_8$: C, 64.62; H, 5.42; N, 2.04. Found: C, 64.43; H, 5.48; N, 2.05. 78.9 g of the crystals were added to 390 ml of 1 N sodium hydroxide, and the resulting mixture was extracted with dichloromethane. The extracts were washed with H_2O, dried ($MgSO_4$) and concentrated. The residual solid was recrystallized from ethyl acetate–hexane to give 33.2 g of (+)-**8** (R=OMe), mp 98 °C. $[\alpha]_D^{20}$ +14° (*c*=1, $CHCl_3$). *Anal.* Calcd for $C_{19}H_{23}NO_4$: C, 69.28; H, 7.04; N, 4.25. Found: C, 69.04; H, 7.06; N, 4.18.

All mother liquors from the previous isolations were combined and concentrated. The residue was added to 640 ml of 1 N sodium hydroxide and the mixture was extracted with dichlormethane. The extracts were washed with H_2O, dried ($MgSO_4$), and concentrated. The residue was treated with an equivalent of (+)- dibenzoyl-D-tartaric acid monohydrate as described for (+)-**8** (R=OMe). After recrystallization, 74.9 g of **8** (R=OMe) hydrogen dibenzoyl-D-tartrate was obtained, mp 181 °C (dec.). $[\alpha]_D^{20}$ +25° (*c*=1, DMF). Then 29.9 g of (−)-**8** (R=OMe) was obtained, mp 98 °C. $[\alpha]_D^{20}$ −14° (*c*=1, $CHCl_3$). *Anal.* Calcd for $C_{19}H_{23}NO_4$: C, 69.28; H, 7.04; N, 4.25. Found: C, 69.07; H, 7.03; N, 4.12.

(*S*)-(−)-7,8-Dihydroxy-4-(3,4-dihydroxyphenyl)-1,2,3,4-tetrahydroisoquinoline Hydrochloride Hydrate: (*S*)-(−)-1·HCl·H_2O To a solution of 29.7 g of (−)-**8** (R=OMe) in 150 ml of dichloromethane was added dropwise 12.7 ml of acetic anhydride at room temperature. After being stirred at room temperature for 10 min, the solution was concentrated and azeotroped with toluene. The residual solid was added to 300 ml of 1 N sodium hydroxide, and the mixture was extracted with dichloromethane. The extracts were washed with H_2O, dried ($MgSO_4$) and concentrated. The residual solid was recrystallized from ethyl acetate–hexane to give 31.9 g of (+)-**9** (R=OMe), mp 128 °C. $[\alpha]_D^{20}$ +39° (*c*=1, $CHCl_3$). *Anal.* Calcd for $C_{21}H_{25}NO_5$: C, 67.91; H, 6.78; N, 3.77. Found: C, 67.81; H, 6.82; N, 3.72.

To a solution of 31.8 g of (+)-**9** (R=OMe) in 160 ml of dichloromethane was added dropwise 428 ml of 1 M boron tribromide in dichloromethane at −30 °C. After stirring at room temperature for 90 min, the solution was added to 78 ml of MeOH at −30 °C and warmed to room temperature. The solution was concentrated and azeotroped with MeOH. The residue was added to 318 ml of 0.1 N HCl at room temperature. After cooling to 4 °C, 25.2 g of (+)-**10** (R=OH) was collected as crystals, mp 225 °C (dec.). $[\alpha]_D^{20}$ +85° (*c*=1, MeOH). *Anal.* Calcd for: $C_{17}H_{17}NO_5 \cdot 1/4H_2O$: C, 63.84; H, 5.52; N, 4.38. Found: C, 63.87; H, 5.52; N, 4.31.

A mixture of 87.9 g of (+)-**10** (R=OH), 703 ml of 3 N HCl and 703 ml of ethanol was heated under reflux for 43 h. The reaction mixture was concentrated to about 870 ml. After cooling to 4 °C, 75.4 g of (*S*)-(−)-**1**·HCl·H_2O was collected as crystals. $[\alpha]_D^{20}$ −14° (*c*=1, MeOH). *Anal.* Calcd for $C_{15}H_{15}NO_4 \cdot HCl \cdot H_2O$: C, 54.97; H, 5.54; Cl, 10.82; N, 4.27. Found: C, 54.70; H, 5.42; Cl, 10.98; N, 4.34.

(*R*)-(+)-**1**·HCl·H_2O, (*S*)-(+)-**2**·HCl, and (*R*)-(−)-**2**·HCl were obtained as already described.

(*R*)-(+)-**1**·HCl·H_2O; $[\alpha]_D^{20}$ +15° (*c*=1, MeOH). (*S*)-(+)-**2**·HCl: $[\alpha]_D^{25}$ +3.8° (*c*=2, MeOH). (*R*)-(−)-**2**·HCl: $[\alpha]_D^{25}$ −3.7° (*c*=2, MeOH).

Single-Crystal X-Ray Analysis of (−)-1·HCl·H_2O Suitable crystals of (−)-**1**·HCl·H_2O for an X-ray diffraction study were grown from a MeOH–H_2O solution. A crystal of approximate dimensions, 0.4×0.2×0.15 mm, was used for data collection. Diffraction measurements were carried out on a Rigaku AFC-5R diffractometer using graphite-monochromated Cu$K\alpha$ radiation (λ=1.54184 Å). The unit cell dimensions were obtained by least squares of 20 high angle reflections. The crystal data are as follows: $C_{15}H_{18}NO_5Cl$, M_r=327.77, orthorhombic, space group $P2_12_12_1$, a=11.164(2) Å, b=26.054(3) Å, c=5.364(1) Å, Z=4, D_c=1.395 g/cm^3. Intensities were measured in the θ–2θ scan mode with a scanning speed of 8°(2θ)/min. Of 1487 independent reflections with 2θ<125°, 20 weak reflections below the background were considered to be zero reflections. Corrections were made for Lorentz and polarization factors but not for absorption.

The structure was solved by the direct method using the program SHELXS86,[16] and the atomic parameters were refined by the block-diagonal least-squares method. The refinements were performed first isotropically and then anisotropically for non-hydrogen atoms. H atoms attached to O and N atoms were not included in the refinements, but a

TABLE II. Fractional Coordinates and Isotropic Temperature Factors of (−)-**1**·HCl·H_2O

Atom	x	y	z	B(Å^2)
Cl	0.4556 (7)	0.3419 (3)	0.752 (2)	3.5⟨9⟩
N2	0.4702 (6)	0.3995 (3)	0.770 (1)	3.4⟨8⟩
C3	0.3539 (8)	0.4266 (3)	0.797 (2)	3.4⟨8⟩
C4	0.2638 (7)	0.4068 (3)	0.620 (2)	3.0⟨9⟩
C5	0.1590 (8)	0.4358 (3)	0.590 (2)	3.2⟨5⟩
O5	0.1460 (5)	0.4784 (2)	0.736 (1)	4.1⟨11⟩
C6	0.0783 (8)	0.4240 (3)	0.406 (2)	3.8⟨9⟩
O6	−0.0191 (6)	0.4562 (3)	0.383 (2)	5.5⟨24⟩
C7	0.0921 (9)	0.3805 (4)	0.263 (2)	4.7⟨21⟩
C8	0.1927 (8)	0.3498 (3)	0.301 (2)	3.8⟨11⟩
C9	0.2783 (7)	0.3625 (3)	0.477 (2)	2.9⟨4⟩
C10	0.3921 (7)	0.3301 (3)	0.505 (2)	3.0⟨4⟩
C11	0.3672 (7)	0.2722 (3)	0.484 (2)	3.0⟨4⟩
C12	0.2844 (8)	0.2488 (3)	0.645 (2)	3.3⟨6⟩
C13	0.2589 (6)	0.1967 (3)	0.611 (2)	2.9⟨7⟩
O13	0.1786 (6)	0.1734 (2)	0.774 (1)	4.7⟨20⟩
C14	0.3065 (9)	0.1699 (3)	0.428 (2)	3.8⟨13⟩
O14	0.2707 (8)	0.1203 (2)	0.396 (2)	6.5⟨44⟩
C15	0.394 (1)	0.1928 (4)	0.273 (2)	5.7⟨38⟩
C16	0.4206 (9)	0.2448 (3)	0.301 (2)	3.8⟨14⟩
Cl	0.5796 (2)	0.44374 (7)	1.2622 (4)	2.99⟨33⟩
OW	0.3321 (6)	0.0535 (2)	0.018 (1)	4.0⟨9⟩

The B values accompanied with ⟨ ⟩ are the equivalent isotropic temperature factors calculated from anisotropic thermal parameters using the equation $B=8\pi^2(U_1+U_2+U_3)/3$, where U_1, U_2, and U_3 are principal components of the mean square displacement matrix U. Values in ⟨ ⟩ are anisotropicity defined by $(\Sigma(B-8\pi^2U_i)^2/3)^{1/2}$ and those in ( ) are e.s.d.'s; they refer to last decimal places.

TABLE III. Bond Distances (Å) and Angles (°) of (−)-**1**·HCl·H_2O

Bond distance (Å)					
Cl–N2	1.51 (1)	C1–C10	1.53 (1)	N2–C3	1.48 (1)
C3–C4	1.48 (1)	C4–C5	1.40 (1)	C4–C9	1.40 (1)
C5–O5	1.37 (1)	C5–C6	1.37 (1)	C6–O6	1.38 (1)
C6–C7	1.38 (1)	C7–C8	1.39 (1)	C8–C9	1.38 (1)
C9–C10	1.53 (1)	C10–C11	1.54 (1)	C11–C12	1.40 (1)
C11–C16	1.35 (1)	C12–C13	1.40 (1)	C13–O13	1.39 (1)
C13–C14	1.32 (1)	C14–O14	1.36 (1)	C14–C15	1.41 (1)
C15–C16	1.40 (1)				
Bond angle (°)					
N2–C1–C10	107.7 (7)		C1–N2–C3	112.5 (6)	
N2–C3–C4	111.5 (7)		C3–C4–C5	117.1 (7)	
C3–C4–C9	124.3 (7)		C5–C4–C9	118.6 (7)	
C4–C5–O5	117.3 (7)		C4–C5–C6	120.8 (8)	
O5–C5–C6	121.7 (8)		C5–C6–O6	116.4 (8)	
C5–C6–C7	120.7 (9)		O6–C6–C7	122.8 (9)	
C6–C7–C8	118.7 (9)		C7–C8–C9	121.3 (8)	
C4–C9–C8	119.5 (7)		C4–C9–C10	119.8 (7)	
C8–C9–C10	120.6 (7)		C1–C10–C9	111.1 (7)	
C1–C10–C11	110.1 (7)		C9–C10–C11	112.5 (6)	
C10–C11–C12	119.9 (7)		C10–C11–C16	119.4 (7)	
C12–C11–C16	120.5 (8)		C11–C12–C13	118.4 (7)	
C12–C13–O13	118.2 (7)		C12–C13–C14	122.0 (8)	
O13–C13–C14	119.7 (7)		C13–C14–O14	118.6 (8)	
C13–C14–C15	119.4 (9)		O14–C14–C15	121.9 (9)	
C14–C15–C16	120 (1)		C11–C16–C15	119.6 (9)	

rigid model with idealized geometry was employed for H atom refinement. The final R factor was 0.101 for the reflections with $|F_o|>3\sigma|F_o|$. Eight Bijvoet pairs which exhibited the greatest effect of anomalous scattering from the Cl atom were selected. The ratios of $|F_c(hkl)|/|F_c(\bar{h}\bar{k}\bar{l})|$ for the enantiomer shown in Fig. 1 were in agreement with the observed values. Consequently, the absolute configuration of (−)-**1**·HCl·H_2O was determined to be *S*.

The final values of positional parameters, bond distances and bond angles are available as supplementary material (Tables II and III).

Single-Crystal X-Ray Analysis of (−)-2·HCl Suitable crystals of (−)-**2**·HCl for an X-ray diffraction study were grown from a MeOH solution. A crystal of approximate dimensions, 0.3×0.2×0.1 mm, was used for data collection. The crystal data is as follows: $C_{16}H_{18}NO_3Cl$, $M_r=307.78$, monoclinic, space group $P2_1$, $a=8.304(5)$ Å, $b=12.803(3)$ Å, $c=7.468(4)$ Å, $\beta=116.04(5)°$, $Z=2$, $D_c=1.433$ g/cm^3. Of 1117 independent reflections with $2\theta<120°$, 5 weak reflections below the background were considered to be zero reflections.

The structure was solved by the direct method. A rigid model with idealized geometry was employed for H atom refinement. The final R factor was 0.050 for the reflections with $|F_o|>3\sigma|F_o|$. Other details of the experiment and refinement are as for the (−)-**1**·HCl·H_2O.

TABLE IV. Fractional Coordinates and Isotropic Temperature Factors of (−)-**2**·HCl

Atom	x	y	z	B(Å^2)
N1	0.8582 (6)	0.8036 (4)	0.7219 (7)	2.9⟨12⟩
C2	0.7331 (8)	0.8497 (4)	0.8019 (9)	3.0⟨10⟩
C3	0.7332 (7)	0.7817 (5)	0.9685 (8)	2.5⟨7⟩
C4	0.6027 (7)	0.8070 (5)	1.0317 (9)	2.9⟨7⟩
C5	0.5897 (7)	0.7406 (5)	1.1786 (9)	3.1⟨8⟩
C6	0.7039 (7)	0.6574 (5)	1.2578 (8)	3.1⟨9⟩
C7	0.8383 (7)	0.6371 (4)	1.1951 (8)	2.8⟨10⟩
C8	0.8527 (7)	0.7005 (4)	1.0496 (8)	2.3⟨7⟩
C9	1.0036 (7)	0.6779 (4)	0.9889 (9)	2.4⟨5⟩
C10	1.0347 (7)	0.7754 (5)	0.8889 (9)	3.0⟨7⟩
C11	0.4815 (8)	0.9006 (5)	0.954 (1)	3.6⟨12⟩
O12	0.4628 (6)	0.7665 (4)	1.2390 (8)	5.3⟨35⟩
C13	0.9672 (7)	0.5833 (4)	0.8472 (8)	2.3⟨4⟩
C14	1.0926 (7)	0.5608 (5)	0.7766 (8)	2.5⟨7⟩
C15	1.0640 (7)	0.4790 (4)	0.6488 (8)	2.6⟨7⟩
C16	0.9173 (7)	0.4134 (5)	0.5993 (8)	2.7⟨10⟩
C17	0.7921 (7)	0.4356 (4)	0.6654 (8)	2.8⟨7⟩
C18	0.8143 (7)	0.5219 (4)	0.7874 (8)	2.6⟨4⟩
O19	1.1803 (5)	0.4583 (3)	0.5617 (6)	3.2⟨13⟩
O20	0.9033 (5)	0.3276 (3)	0.4802 (6)	3.3⟨15⟩
Cl	0.6280 (2)	0.1541 (2)	0.4612 (2)	3.82⟨87⟩

The B values accompanied with ⟨ ⟩ are the equivalent isotropic temperature factors calculated from anisotropic thermal parameters using the equation $B=8\pi^2(U_1+U_2+U_3)/3$, where U_1, U_2, and U_3 are principal components of the mean square displacement matrix U. Values in ⟨ ⟩ are anisotropicity defined by $(\Sigma(B-8\pi^2U_i)^2/3)^{1/2}$ and those in ( ) are e.s.d.'s; they refer to last decimal places.

TABLE V. Bond Distances (Å) and Angles (°) of (−)-**2**·HCl

Bond distance (Å)					
N1–C2	1.526 (8)	N1–C10	1.493 (8)	C2–C3	1.518 (9)
C3–C4	1.397 (9)	C3–C8	1.381 (8)	C4–C5	1.429 (9)
C4–C11	1.507 (9)	C5–C6	1.375 (9)	C5–O12	1.357 (8)
C6–C7	1.412 (9)	C7–C8	1.402 (8)	C8–C9	1.536 (8)
C9–C10	1.533 (9)	C9–C13	1.549 (8)	C13–C14	1.388 (8)
C13–C18	1.390 (8)	C14–C15	1.366 (8)	C15–C16	1.389 (8)
C15–O19	1.407 (7)	C16–C17	1.363 (8)	C16–O20	1.385 (7)
C17–C18	1.391 (8)				
Bond angle (°)					
C2–N1–C10	110.7 (5)		N1–C2–C3	110.1 (5)	
C2–C3–C4	115.0 (5)		C2–C3–C8	122.2 (5)	
C4–C3–C8	122.8 (6)		C3–C4–C5	116.9 (5)	
C3–C4–C11	122.8 (6)		C5–C4–C11	120.3 (5)	
C4–C5–C6	121.5 (6)		C4–C5–O12	116.1 (5)	
C6–C5–O12	122.4 (6)		C5–C6–C7	119.7 (6)	
C6–C7–C8	120.0 (5)		C3–C8–C7	119.1 (5)	
C3–C8–C9	122.3 (5)		C7–C8–C9	118.6 (5)	
C8–C9–C10	108.9 (5)		C8–C9–C13	114.1 (5)	
C10–C9–C13	109.1 (5)		N1–C10–C9	106.9 (5)	
C9–C13–C14	117.9 (5)		C9–C13–C18	122.6 (5)	
C14–C13–C18	119.5 (5)		C13–C14–C15	119.7 (5)	
C14–C15–C16	120.9 (5)		C14–C15–O19	121.5 (5)	
C16–C15–O19	117.6 (5)		C15–C16–C17	119.8 (6)	
C15–C16–O20	117.8 (5)		C17–C16–O20	122.4 (5)	
C16–C17–C18	120.0 (5)		C13–C18–C17	119.9 (5)	

Thirteen Bijvoet pairs which exhibited the greatest effect of anomalous scattering from the Cl atom were selected. The ratios of $|F_C(hkl)|/|F_C(\bar{h}\bar{k}\bar{l})|$ for the enantiomer shown in Fig. 2 were in agreement with the observed values. The absolute configuration of the inactive enantiomer (−)-**2**·HCl was determined to be *R*.

The final values of positional parameters, bond distances and bond angles are available as supplementary material (Tables IV and V).

References and Notes

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