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Optical Resolution of Asymmetric Amines by Preferential Crystallization as Lasalocid Salts[1]

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Abstract: The ability of the polyether antibiotic lasalocid to transport catecholamines across lipid membranes led to an investigation into the nature of the lasalocid-amine complexes. On finding that the naturally occurring *R* enantiomer of norepinephrine gave a highly crystalline, equimolar salt with lasalocid, the possibility occurred to us that the antibiotic might be able to resolve racemic amines by fractional crystallization as lasalocid salts. As a consequence, several types of amines were successfully resolved, and in one case the resolved complex was analyzed by x-ray crystallography. The results of this analysis provided a possible explanation for the high enantioselectivity displayed by lasalocid on preferential crystallization of salts formed from the antibiotic with racemic amines.

Lasalocid (**1**) is a member of the class of naturally occurring ionophores known as polyether antibiotics.[1] Produced by *Streptomyces lasaliensis*,[2] **1** is both an effective coccidiostat[3] and a cardiotonic agent.[4] Close correlation[5] between the cardiac effects and the ability of a number of derivatives of lasalocid[6] to transport norepinephrine across artificial membranes led to this study of the nature of the interaction between **1** and various organic amines.

In preliminary experiments, three typical catecholamines, dopamine (**2a**), norepinephrine (**2b**), and epinephrine (**2c**), were found to be soluble in a methylene chloride (CH_2Cl_2) solution of the antibiotic **1**. Crystallization of the antibiotic-base salts from these CH_2Cl_2 solutions was attempted by addition of hexane (n-C_6H_{14}) and removal of CH_2Cl_2 by evaporation. Both **2a** and **2b** gave crystalline salts containing equimolar amounts of the amine and antibiotic, but all attempts to crystallize the lasalocid salt of **2c** were unsuccessful. It is interesting to note that permeability coefficients[5] measured in lipid bilayer membranes containing **1** were ten times higher for **2a** and **2b** than for **2c**.

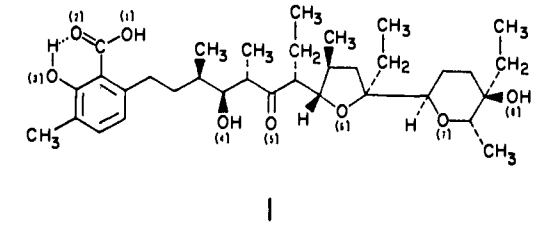
Since norepinephrine (**2b**) has an asymmetric center (*R* configuration), the possibility occurred to us that lasalocid might have the ability to resolve racemic amines. The results of attempts to resolve racemic 1-amino-1-phenylethane (**3a**), 1-amino-1-(4-bromophenyl)ethane (**3b**), 1-dimethylamino-1-phenylethane (**3d**), 1-amino-1-naphthylethane (**4**), 2-aminoheptane (**5**), tetrahydrofurfurylamine (**6**), and 2-amino-1-(3′,4′-dimethoxyphenyl)propane (**7**) by crystallization as a salt of **1** from various solvents are given in Table I.

Each of the first four amines tested (**3a**, **3b**, **4**, **5**) contained an asymmetric carbon atom attached directly to the primary amino group and each gave crystalline salts in which the *R isomer* of the amine predominated to an extent of 6 to 10 times over the *S* isomer when the salt was crystallized from the CH_2Cl_2–C_6H_{14} solvent system. The absolute configuration and optical purity of the amines after each crystallization step were determined by the gas–liquid chromatographic (GLC) analysis of the diastereoisomeric *N*-trifluoracetyl-*S*-prolyl derivatives[8] formed by direct reaction of TPC reagent[9] with 1–5 mg of crystalline salt. This technique has the advantage that the salt can be analyzed without tedious conversion to the amine followed by spectropolarimetry. A number of solvents can thus be rapidly screened for their relative efficiency in preferential crystallization. To further investigate the high enantioselectivity in the formation of crystalline salts of **1** with substituted 2-aminoalkanes, advantage was taken of the heavy atom (Br) in the **3b** salt of **1** to carry out an x-ray crystallographic analysis of the salt, which was shown to have an optical

Table I. Yield and Proportion of *R*:*S* Enantiomers[a] in Lasalocid–Amine Salts Crystallized from Three Different Solvents

Amine resolved[b]	No. of crystns	CH_2Cl_2/n-C_6H_{14}		Ethyl acetate		Ethanol	
		% yield[c]	% *R*:*S*	% yield	% *R*:*S*	% yield	% *R*:*S*
R-(+)-**3a**	1	37	89:11	22	84:16	70	56:44
	2	20	*92*:8				
R-(+)-**3b**	1	45	86:14	51	80:20	58	75:25
	2	42	*91*:9	31	90:10	33	*86*:14
	3	32	*100*:0				
S-(−)-**3d**	1	63					
	2	50	10:90[d]				
R-(+)-**4**	1	66	72:28	45	86:14	62	80:20
	2	29	*92*:8	18	*89*:11	38	*87*:13
R-(−)-**5**	1	23	81:19	10	*86*:14	29	*76*:24
	2	8	*86*:14				
S-(+)-**6**	1	55	31:69	0		0	
	2	28	25:*75*				
S-(+)-**7**	1	76	34:66	43	23:77	77	35:65
	2	56	24:*76*	23	15:*85*	28	10:*90*

[a] Determined by the GLC analytical methods described in ref 8. [b] The sign of rotation and absolute configuration (*R* or *S*) are those of the preferred enantiomeric amine isolated as the crystalline lasalocid salt. [c] Any yields above 50% mean poor discrimination between the enantiomers whereas zero yield indicates a failure to crystallize the salt. In all crystallization steps, the percentage yields are based on the weight of starting materials. [d] In the case of **3d**, the optical purity was based solely on the rotation of the resolved amine compared to authentic optically pure material.



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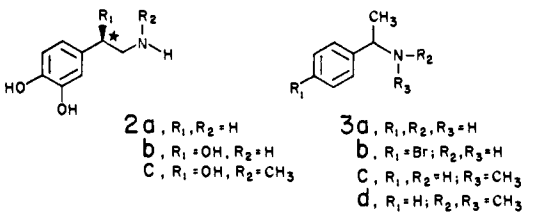
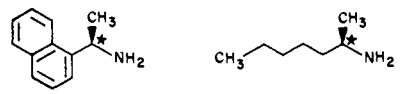


2a, R_1,R_2 = H
b, R_1 = OH, R_2 = H
c, R_1 = OH, R_2 = CH_3

3a, R_1,R_2,R_3 = H
b, R_1 = Br; R_2,R_3 = H
c, R_1,R_2 = H; R_3 = CH_3
d, R_1 = H; R_2,R_3 = CH_3



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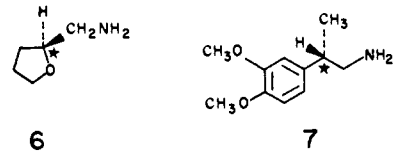

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*The absolute configuration implied in structures 2b and 2c corresponds to that found in the natural products. In the remaining compounds, the absolute configuration of the amine found in excess in the crystalline salt with lasalocid (1) is indicated.

purity of 100% after three crystallizations (Table I).

Unlike all previous complexes of lasalocid analyzed by x ray,[10] the 1-amino-1-(4-bromophenyl)ethane (**3b**) salt of **1** was *monomeric*. Three views of the salt complex are shown stereographically in Figure 1. The hydrogen bonds from the phenethylamine nitrogen to the antibiotic are shown. These three hydrogen bonds together with the phenethylamine N–C bond make the coordination about the nitrogen atom essentially tetrahedral, as can be seen from the bond angles in Table II. The intramolecular hydrogen bonds are listed in Table III. There are no intermolecular hydrogen bonds.

Table II. Angles about Phenethylamine Nitrogen

C—N···O(1)	103.6°
C—N···O(6)	128.4
C—N···O(8)	115.0
O(1)···N···O(6)	117.3
O(1)···N···O(8)	76.7
O(6)···N···O(8)	104.5

Table III. Hydrogen Bonds

N—H···O(1)	2.81 Å
N—H···O(6)	2.90
N—H···O(8)	2.80
O(3)—H···O(2)	2.45
O(4)—H···O(1)	2.69
O(8)—H···O(2)	2.75

The antibiotic has virtually the same conformation in the **3b** salt as that observed in earlier x-ray analyses[10] of lasalocid complexes with inorganic cations. The reasons for the marked enantioselectivity of this conformation appear to be both steric and electronic. Viewing the molecule from directly above the bond joining the asymmetric carbon (C*) to the amine nitrogen (Figure 1a), the position of the *smallest* substituent (H) attached to C* appears to be dictated by the steric bulk of the carbonyl oxygen (O-5) above the plane of **1**. The *largest* substituent at C*, the 4-bromophenyl group, is situated directly over a depression, or pocket, in the conformation **1** which spans that part of the lasalocid molecule from C-14 to C-23 including the O-6 and O-7 (Figure 1b). This lipophilic pocket apparently provides the best accommodation for the large hydrocarbon side chain in **3b** (also **3a**, **4**, and **5**) leaving the methyl group attached to C* above the hydrogen bond between O-2 and O-8 which link the two ends of **1** together. The view from behind the methyl group looking towards C* is illustrated in figures 1c and 2.

In order to check whether a primary amino group is essential

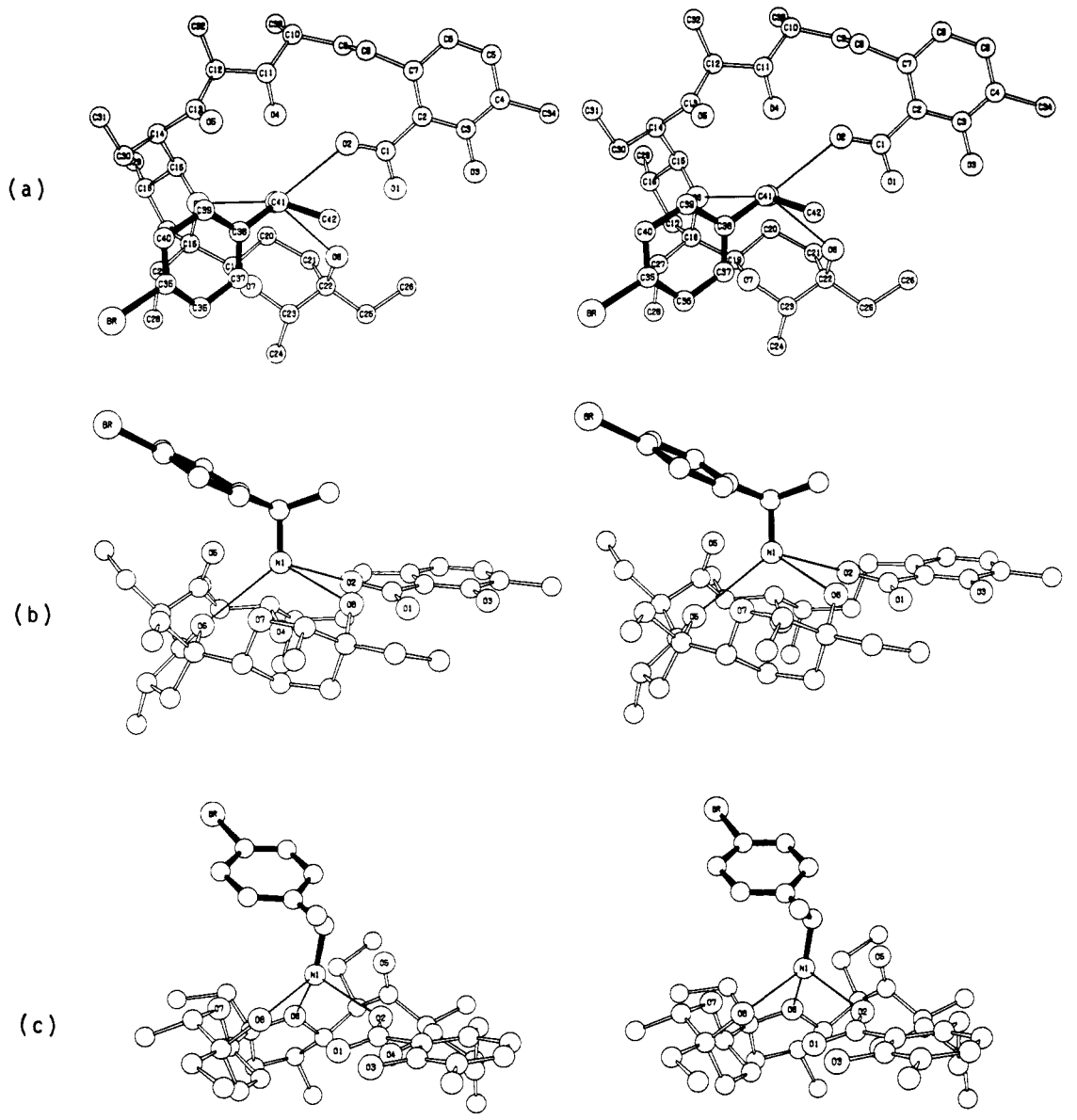

Figure 1. Three stereodrawings of the 4-bromophenethylamine (solid bonds) salt of lasalocid (open bonds). View (a) is down the phenethylamine C–N bond, view (b) is perpendicular to this C–N bond, and view (c) is along an axis which passes through N and is parallel to the plane of O(1), O(6), O(8).

for the formation of crystalline complexes with **1**, attempts were made to resolve the mono- and dimethylated amines **3c** and **3d**. In agreement with the negative result observed with epinephrine (**2c**), all attempts to crystallize either the racemic mixture or the two resolved enantiomeric forms of 1-methylamino-1-phenylethane (**3c**) as salts of **1** were unsuccessful. In contrast to the results with **3c**, crystallizing the 1-dimethylamino-1-phenylethane (**3d**) salt of **1** was unexpectedly easy and clearly must involve a different type of complex than the **3b** salt of **1** as illustrated in Figure 2. This conclusion was confirmed by isolating the amine from the crystalline salt and finding that the enantiomer that was enriched by preferential crystallization had in the case of **3d** the *S* configuration which was *opposite* to the results for **3a**, **3b**, **4**, and **5**.

In the other two amines (**6** and **7**) tested, the asymmetric center is separated by a methylene carbon from the primary amino group and as a result the efficiency of resolution by **1** was less than for the first five amines, where the asymmetric center was attached directly to the amino group. However, both **6** and **7** were resolved by **1** and the enantiomer that was enriched by preferential crystallization had the *S* configuration.

In all cases, the amine can be recovered after resolution by dissolving the crystalline diastereoisomeric complex in a suitable solvent such as CH_2Cl_2 or ethyl acetate and extracting with dilute aqueous mineral acid. The antibiotic is recovered by evaporation or crystallization from the organic solvent. If the more soluble diastereoisomer contains the desired enantiomer of the amine, the same procedure is carried out with the mother liquor from the preferential crystallization.

Similar approaches to the problem of optical resolution have been used by Cram and his co-workers[12] using *synthetic* crown ethers. Depending on the host–guest structural relationship, they obtain amines with optical purities from 20 to 97% by enantiomeric extraction. In the specific case of **3a**, an optical purity of 34% *R* enantiomer was obtained by extracting an aqueous solution of the amine salt with *S,S*-dibinaphthyl crown ether in chloroform.

None of the other known polyether antibiotics tested in the author's laboratory have shown any inclination to form crystalline complexes with asymmetric amines. Consequently, results discussed here represent a unique feature of the complexing properties of lasalocid which should provide a very useful tool for the resolution of racemic amines.

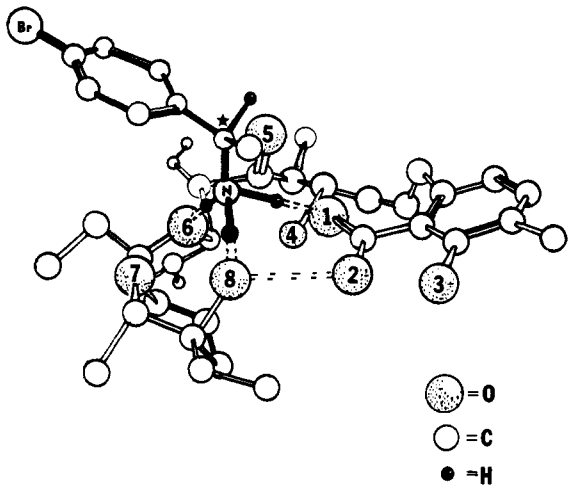

Figure 2. Model of the 4-bromophenethylamine salt of lasalocid (open bonds) constructed from the x-ray analytical data to show the tetrahedron formed between the asymmetric carbon (★) and oxygens O-1, O-6, and O-8.

Experimental Section

Melting points were determined on a Thomas-Hoover capillary melting point apparatus and are uncorrected. Optical rotations were measured with a Perkin-Elmer polarimeter Model 141 at 25 °C. The ORD and CD spectra were obtained using a Jasco J-20 automatic recording spectropolarimeter. GLC analyses were carried out on a Hewlett-Packard HP 7610A gas chromatograph equipped with an electronic integrator (HP 3370B) and fitted with a 2-m glass column, 3 mm i.d., packed with 5% DC-LSX on silanized Chromosorb W 60–80 mesh (column A) and a second column of the same dimensions packed with 10% OV-17 on Gas-Chrom Q 100–120 mesh (column B). The operating conditions were injector temperature 295 °C, FID detectors temperature 270 °C and nitrogen flow 30 mL/min.

Materials. Lasalocid, 6-[7(*R*)-[5(*S*)-ethyl-5-(5(*R*)-ethyltetrahydro-5-hydroxy-6(*S*)-methyl-2*H*-pyran-2(*R*)-yl)tetrahydro-3(*S*)-methyl-2(*S*)-furyl]-4(*S*)-hydroxy-3(*R*),5(*S*)-dimethyl-6-oxononyl]-2,3-cresotic acid (**1**), was isolated from cultures of *S. lasaliensis* as described earlier.[2] All the amines are commercially available (Aldrich Chemical Co., Roche Chemical Division, Hoffmann-La Roche Inc., and Norse Laboratories) with the exception of 2-aminol-(3′,4′-dimethoxyphenyl)propane (**7**), which was synthesized as a racemate by Dr. S. Teitel of Hoffmann-La Roche. The *N*-trifluoracetyl-L-(*S*)-prolyl chloride (TPC) reagent was obtained from Regis Chemical Co. as a 0.1 M solution in $CHCl_3$.

Optical Analysis of Amines by the GLC Analysis of Diastereoisomers. The absolute configuration and optical purity of the asymmetric amines (as their crystalline lasalocid salts) were determined by the GLC analysis of their TPC derivatives.[8]

A 1–5-mg sample of the amine salt was dissolved in CH_2Cl_2 and an aliquot (0.05 mmol) treated with an equimolar aliquot of TPC reagent and 3 drops of triethylamine. After shaking for 1 min, 1 μL was injected into the gas chromatograph. All the TPC derivatives of the amines were analyzed on column A with the exception of **7** (column B). The column operating temperatures and retention time in minutes of the *SR* and *SS* diastereoisomers respectively follow: **3a** (185 °C), 16, 20; **3b** (205 °C), 19, 24; **4** (230 °C), 13, 16.5; **5** (175 °C), 12, 13.7; **6** (185 °C), 14, 15; **7** (230 °C), 39, 42.

Preparation of the Dopamine (2a) Salt of Lasalocid. To a solution of lasalocid sodium salt (1.24 g, 2 mmol) in methanol (40 mL) was added dopamine hydrochloride (380 mg, 2 mmol) in methanol (10 mL) and the solution evaporated under reduced pressure to an oil. The residue was partitioned in equal volumes (25 mL) of CH_2Cl_2–H_2O, the organic phase separated, and the **2a** salt crystallized by simultaneous addition of 25 mL of n-C_6H_{14} and evaporation of CH_2Cl_2 on the steam bath. The resulting crystals (1.327 g, 89%) melted at 220 °C, $[\alpha]_D$ −24° (*c* 1.0, $CHCl_3$).

Anal. Calcd for $C_{42}H_{65}NO_{10}$ (743.9): C, 67.81; H, 8.81; N, 1.88. Found: C, 67.59; H, 8.82; N, 1.82.

The **norepinephrine (2b)** salt of lasalocid was prepared in the same way as described above for the **2a** salt to yield 81% of the crystalline salt, mp 189–191 °C, $[\alpha]_D$ −60° (*c* 1.0, $CHCl_3$).

Table IV. Interatomic O-O Contacts <3.6 Å Not Involving Hydrogen Bonding

O(1)···O(2)	2.22 Å
O(1)···O(8)	3.48
O(4)···O(5)	3.18
O(4)···O(6)	3.61
O(5)···O(6)	3.19
O(6)···O(7)	3.02
O(7)···O(8)	2.74

Anal. Calcd for $C_{42}H_{65}NO_{11}$ (759.9): C, 66.38; H, 8.62; N, 1.84. Found: C, 66.20; H, 8.51; N, 1.77.

Optical Resolution of Racemic 1-Amino-1-phenylethane (3a) as a Lasalocid Salt. To a solution of lasalocid (1.18 g, 2 mmol) in CH_2Cl_2 (4 mL) was added 2 mmol (242 mg) of **3a** in 2 mL of CH_2Cl_2. To this mixture was added 24 mL of n-C_6H_{14} and the resulting solution allowed to concentrate by evaporation overnight at room temperature. The resulting crystals were isolated by filtration and checked by GLC analysis for optical purity. (All yields are listed in Table I.)

The crystals were redissolved in CH_2Cl_2, 24 mL of n-C_6H_{14} added, and the solution again left overnight. This recrystallized lasalocid salt of *R*-(+)-**3a** melted at 198–199 °C, $[\alpha]_D$ −77° (*c* 1.0, $CHCl_3$).

Anal. Calcd for $C_{42}H_{65}NO_8$ (711.9): C, 70.85; H, 9.20; N, 1.97. Found: C, 71.12; H, 9.28; N, 1.97.

1-Amino-1-(4-bromophenyl)ethane (3b) was resolved in an identical manner with that described above for **3a** to yield crystals of the *R*-(+)-**3b** salt of lasalocid, mp 205–207 °C, $[\alpha]_D$ −71° (*c* 1.0, $CHCl_3$).

Anal. Calcd for $C_{42}H_{64}BrNO_8$ (790.9): C, 63.78; H, 8.16; Br, 10.11; N, 1.77. Found: C, 63.91; H, 8.36; Br, 10.19; N, 1.64.

Crystals of the **3b** salt of **1** were analyzed by x-ray analysis and the most significant bond angles and interatomic distances are summarized in Tables II–IV.

Crystals of the **3b** salt of **1** are orthorhombic, space group $P2_12_12_1$, with a = 14.098 (1), b = 16.573 (6), c = 20.373 (8) Å, and d_{calcd} = 1.103 g cm^{-3} for Z = 4 ($C_{42}H_{64}BrNO_8$, mol wt 790.88). The intensity data were measured on a Hilger-Watts four-circle diffractometer (Ni-filtered Cu Kα radiation, θ–2θ scans) from a crystal which was approximately 0.30 × 0.35 × 0.55 mm in size. The crystal was coated lightly with epoxy cement and mounted in a sealed capillary in order to prevent deterioration. Of 5000 accessible reflections for $\theta < 70°$, 3033 had intensities significantly greater than background and these data were used for the analysis. The data were corrected for absorption (μ 16.6 cm^{-1}).

The structure was solved by Patterson and Fourier techniques. Eight additional carbon atoms were included in order to account for the disordered solvent molecules present in the crystal. The final refinement was carried out by block diagonal least squares in which the matrix was partitioned into three blocks. Anisotropic thermal parameters were used for the heavier atoms and isotropic temperature factors were used for the hydrogen atoms. The hydrogen atoms were included in the structure factor calculations but their parameters were not refined. The final discrepancy indices are R = 0.058 and wR = 0.048 for the 3033 observed data. There are no peaks greater than ±0.4 e A^{-3} on the final difference map.

Resolution of Amines Using Ethyl Acetate and Ethanol as Solvents for Crystallization. The same technique used to resolve **3a** was repeated with replacement of n-C_6H_{14} by first ethyl acetate and in a second set of experiments, ethanol, as the excess solvent used for crystallization of salts of **3a**, **3b**, **4**, **5**, and **7**. In most cases the CH_2Cl_2–C_6H_{14} solvent system gave the best resolution, but the lasalocid salt of amine **7** was resolved most efficiently from ethanol.

The yields and optical purity analyses for all the resolution experiments are summarized in Table I.

Isolation of (*R*)-(+)-1-Amino-1-(4-bromophenyl)ethane (3b) Hydrochloride. The lasalocid salt of **3b** was shown (Table I) to have an optical purity of 100% after three crystallizations from CH_2Cl_2–C_6H_{14}.

A portion of the optically pure salt (1.58 g, 2 mmol) used for the x-ray analysis (Figure 1) was dissolved in 25 mL of ethyl acetate and extracted twice with 1 volume of 1 N HCl. The aqueous extracts were pooled and lyophilized to yield 436 mg (92%) of *R*-(+)-**3b** HCl, $[\alpha]_D$ +2.6° (*c* 1, H_2O). The hydrochloride was shown to be optically pure

by the GLC analysis of the TPC derivative.

Anal. Calcd for $C_9H_{10}ClN$: C, 40.62; H, 4.69; Cl, 14.99; N, 5.92. Found: C, 40.24; H, 4.76; Cl, 14.74; N, 5.87.

The antibiotic was recovered quantitatively by evaporation of the ethyl acetate phase under reduced pressure.

***N,N,α*-Trimethylbenzylamine (3d).** To a solution of lasalocid (5.9 g, 10 mmol) in CH_2Cl_2 (25 mL) was added 10 mmol (1.49 g) of **3d** in 25 mL of CH_2Cl_2. To this mixture was added 100 mL of *n*-C_6H_{14} and the resulting solution allowed to evaporate overnight at room temperature. The crystalline solid was separated by filtration (4.67 g, 63.1% yield) and recrystallized from the same solvent pair to yield 3.7 g (50%) of the lasalocid salt, mp 121–122.5 °C, $[\alpha]_D$ −30° (*c* 1.0, $CHCl_3$).

Anal. Calcd for $C_{44}H_{69}NO_8$ (740.0): C, 71.41; H, 9.40; N, 1.89. Found: C, 71.58; H, 9.65; N, 1.77.

Isolation of (−)-*N,N,α*-Trimethylbenzylamine. A solution of 1.3 g of the lasalocid salt of **3d** in CH_2Cl_2 (20 mL) was extracted three times with 1 N HCl (20 mL). The acid extracts were combined, the pH was adjusted to 11 with NaOH, and the solution was extracted three times with ethyl ether (20 mL). The ether extracts were pooled, dried over anhydrous Na_2CO_3, and concentrated to an oil (232 mg), $[\alpha]_D$ −62.4° (*c* 1, isooctane).

Pure (−)-*N,N,α*-trimethylbenzylamine had $[\alpha]_D$ −70° (*c* 1, isooctane).

Isolation of (*S*)-(+)-1-Amino-2-(3′,4′-dimethoxyphenyl)propane (7) Hydrobromide. The lasalocid salt of **7** with the highest optical purity (80%) was that obtained by recrystallization from ethanol. This recrystallized *S*-(+)-**7** salt of lasalocid melted at 185–190 °C, $[\alpha]_D$ −25° (*c* 1.0, $CHCl_3$).

Anal. Calcd for $C_{45}H_{71}NO_{10}$ (786.02): C, 68.76; H, 9.41; N, 1.78. Found: C, 68.60; H, 9.40; N, 2.01.

Part of the *S*-(+)-**7** salt (770 mg, 0.98 mmol) was dissolved in 10 mL of CH_2Cl_2 and thoroughly mixed with 10 mL of H_2O containing 1 mmol of HBr. The aqueous phase was separated and evaporated under reduced pressure. Crystallization of the residue from ethanol yielded 158 mg (37%) of *S*-(+)-**7** HBr, mp 250 °C, $[\alpha]_D$ +26° (*c* 1, H_2O).

Anal. Calcd for $C_{11}H_{18}BrNO_2$: C, 47.84; H, 6.57; Br, 28.93; N, 5.07. Found: C, 47.78; H, 6.63; Br, 29.13; N, 4.91. The absolute configuration was shown to be *S* and the optical purity of the hydrobromide salt was determined to be 82% by the GLC analysis of the TPC derivative. Assignment of the configuration was confirmed by ORD (H_2O) ($[\Phi]_{285}^{pk}$ +775°, $[\Phi]_{269}^{lr}$ +225°, $[\Phi]_{227}^{pk}$ +3000°, $[\Phi]_{221}^{lr}$ +2250°) and CD (H_2O) ($[\theta]_{278}^{max}$ +320°).

(*R*)-(−)-1-Amino-2-(3′,4′-dimethoxyphenyl)propane Hydrobromide. The *R*-(−)-**7** enantiomer was obtained by evaporation of the mother liquor from the crystallization of the *S*-(+)-**7** lasalocid salt, conversion to the hydrobromide, and recrystallization from ethanol to give 134 mg of the *R*-(−) isomer, mp 250 °C, $[\alpha]_D$ −17.5° (*c* 1, H_2O).

Anal. Calcd for $C_{11}H_{18}BrNO_2$ (276.18): C, 47.84; H, 6.57; Br, 29.93; N, 5.07. Found: C, 48.13; H, 6.75; Br, 29.13; N, 5.10.

GLC analysis of the TPC derivatives showed the optical purity of the (−) enantiomer to be 74% and the absolute configuration as *R*. The latter result was confirmed by ORD in H_2O ($[\Phi]_{288}^{tr}$ −825°, $[\Phi]_{270}^{pk}$ −525°, $[\Phi]_{223}^{tr}$ −3000°, $[\Phi]_{220}^{pk}$ −20000°) and CD also in H_2O ($[\theta]_{275}^{max}$ −560°).

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Supplementary Material Available: Tables of the final positional and thermal parameters for the **3b** salt of **1** (5 pages). Ordering information is given on any current masthead page.

References and Notes

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