300 mL), and the combined extracts were washed with brine (2 × 50 mL). The organic layer was then dried (K_2CO_3) and concentrated under reduced pressure. The crude oil which resulted was purified by flash chromatography on silica gel (hexane/EtOAc, 1:3) to yield isoreserpine (2) (21 g, 95% yield based on recovered reserpine), accompanied by reserpine (1) (8 g) in a ratio of 2.6:1. The crude isoreserpine was crystallized from methanol to give pure 2 (18 g): mp 150–151 °C [lit.[4d] mp 148–150 °C]; $[\alpha]^{23}_D$ −165.1° (c = 1, $CHCl_3$); [lit.[5] $[\alpha]^{23}_D$ −163° ($CHCl_3$)]; ^1H NMR ($CDCl_3$, 500 MHz) δ 7.75 (s, 1 H), 7.32 (d, J = 8.5 Hz, 1 H), 7.28 (s, 2 H), 6.83 (d, J = 2.0 Hz, 1 H), 6.75 (dd, J = 8.5, 2.0 Hz, 1 H), 5.09 (ddd, J = 12, 8.5, 5 Hz, 1 H), 3.89 (s, 3 H), 3.87 (s, 6 H), 3.84 (s, 3 H), 3.81 (s, 3 H), 3.79 (dd, J = 12, 9 Hz, 1 H), 3.45 (s, 3 H), 3.16 (br d, J = 10 Hz, 1 H), 2.75–3.0 (m, 3 H), 2.80 (dd, J = 11.5, 5 Hz, 1 H), 2.50–2.70 (m, 3 H), 2.32 (dd, J = 11.5, 12.5 Hz, 1 H), 2.31 (m, 1 H), 2.08 (m, 1 H), 1.98 (dddd, J = 12.5, 5, 4 Hz, 1 H), 1.86 (dd, J = 10, 12.5 Hz, 1 H), 1.75 (dd, J = 12.5, 4.0 Hz, 1 H).

The NMR spectrum of 2 was identical in all respects with that of a sample of synthetic 2 kindly provided by Professor Steve Martin. This reaction was run on a 70-g scale with no loss in yield.

Equilibration of Reserpine (1) in MeOH/HCl. Reserpine (1) (500 mg) was dissolved in anhydrous HCl–MeOH (50 g, conc = 1%) and was heated at 68 °C under a nitrogen atmosphere for 12 h. The solvent was removed in vacuo, and the residue was partitioned between dilute aqueous NH_3 and $CHCl_3$ (300 mL). The $CHCl_3$ layer was dried (K_2CO_3), and the solvent was removed in vacuo to provide a solid, which was purified by flash chromatography on silica gel. Elution was carried out with hexane–ethyl acetate (1:3) to provide a crystalline sample of 2 (280 mg, mp 149–150 °C) and reserpine (1) (200 mg, mp 247–252 °C dec) in the approximate ratio of 3:2.

Equilibration of Isoreserpine (2) in MeOH/HCl. Isoreserpine (2) (500 mg) was dissolved in HCl–MeOH (50 g, 1%) and was heated at 68 °C under nitrogen for 12 h. The reaction mixture was worked up as reported in the above experiment. Elution with hexane–EtOAc (1:3) gave pure isoreserpine (2) (435 mg) and reserpine (1) (40 mg) in the approximate ratio of 23:2.

Reduction of Reserpine (1) with Zn/AcOH. Reserpine (1) (1 g) and activated Zn powder (2.2 g) were heated in acetic acid (35 mL) at reflux under N_2 for 12 h. The solution was filtered and evaporated. The residue was partitioned between dilute aqueous NH_3 and $CHCl_3$. The chloroform layer was dried (K_2CO_3), and the solvent was removed in vacuo to provide a gummy solid, which was purified by flash chromatography on silica gel [EtOAc/hexane (3:1)–EtOAc]. This process yielded isoreserpine (2) (695 mg), 2,3-secoreserpine (12) (25 mg),[6b] reserpine (1) (200 mg), and compound 11 (72 mg), mp 236–237 °C (lit.[6a] mp 236–239 °C). The sample of 12 was identical with a sample of authentic material obtained by degradation of reserpine in the presence of formic acid and formamide.[6b]

Reduction of Isoreserpine (2) with Zn/AcOH. Isoreserpine (2) (1 g) and activated Zn powder (2.2 g) were heated in acetic acid (35 mL) at reflux under N_2 for 12 h. The solution was filtered and evaporated. The residue was partitioned between dilute aqueous NH_3 and $CHCl_3$, and the aqueous layer was extracted with chloroform (3 × 100 mL). The combined extracts were washed with brine (1 × 50 mL), dried (K_2CO_3), and concentrated under reduced pressure to furnish a gummy solid, which was purified by flash chromatography on silica gel (EtOAc/hexane (3:1)-EtOAc). This process gave isoreserpine (2) (680 mg), 2,3-secoreserpine (12) (22 mg), reserpine (1) (195 mg), and compound 11 (70 mg), mp 236–237 °C, in a nearly identical ratio with that reported in the previous experiment.

Acknowledgment. We wish to thank the NIH (NS 22287) and NIDA (DA-04963) for financial support. Our thanks go to Professor Steve Martin for a sample of isoreserpine, as well as to Frank Laib for the mass spectra. The 500-MHz NMR was purchased with funds from the NIH (BRSG) and NSF instrument programs. We also wish to acknowledge the helpful comments of Professor John Joule in regard to the present work. Initial support for this work was supplied by the Graduate School (UWM) and BRSG. Keith Krumnow and Liesl Schindler provided excellent technical assistance.

Counteranion Effects on Complexation of Cations

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In the twenty-odd years since Pedersen's first report of the formation of complexes between cyclic polyethers and cations,[2] an astounding number of complexation "hosts" have been designed, synthesized, and studied.[3] The vast majority of these hosts bind cationic "guests", though a rapidly increasing number of accounts report the selective complexation of anions and neutral molecules.[4] In the cationic complexes, the counteranion is generally assumed to be quite separated from the complexed cation. This "sequestration" of cations has been often demonstrated to have dramatic effects on the reactivity of the corresponding "naked" counteranions.[5]

This generalization, however, appears to be somewhat of an oversimplification. In particular, it has been noted in some cases that the binding affinity of a host for a chosen cation may be altered by changing the counteranion.[6] This effect has been most conveniently (and not unreasonably) explained by alteration of crystal lattice energies in the different salts; complexation must "pay the price" for disruption of the solid state of the guest, so solid salts of higher lattice energy disfavor formation of complexes. However, in a scattering of reports, anion effects have been noted even in homogeneous solution. For example, Cram observed[7] that enantiomeric discrimination of amino acid ester salts by a chiral macrocyclic polyether host was influenced by the counteranion, with hexafluorophosphate and perchlorate salts of amino acid esters providing high enantioselection in liquid–liquid extraction experiments, but bromide and picrate salts providing appreciably lower enantioselection.

In the latter example, the amino acid esters were complexed through their protonated amino groups. As structural studies demonstrate in such cases, complexation is effected through formation of three hydrogen bonds from the ammonium group to three oxygens of the polyether host. Such complexation of primary ammonium groups provides a simple and convenient route for the complexation of organic substrates even by very simple hosts such as 18-crown-6. The importance of this type of complexation, coupled with Cram's observation of a counteranion effect on the complexation of ammonium groups by cyclic polyethers, suggested a more detailed study in simple model systems was appropriate. Accordingly, we have examined the complexation of four salts of

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(2) Pedersen, C. J. *J. Am. Chem. Soc.* **1967**, *89*, 2495–2496.

(3) The Nobel Prize lectures given by Pedersen, Lehn, and Cram in 1987 provide a current survey of the state of the field of complexation chemistry: Pedersen, C. J. *Angew. Chem., Int. Ed. Engl.* **1988**, *27*, 1021–1028. Lehn, J.-M. *Ibid.* **1988**, *27*, 89–112. Cram, D. J. *Ibid.* **1988**, *27*, 1009–1020.

(4) See Diederich, F. *Angew. Chem., Int. Ed. Engl.* **1988**, *27*, 362–86 for a recent overview of the complexation of neutral molecules.

(5) Liotta, C. L.; Grisdale, E. E.; Hopkins, H. P. *Tetrahedron Lett.* **1975**, 4205. Liotta, C. L. In *Synthetic Multidentate Macrocyclic Compounds*; Izatt, R. M., Christensen, J. J., Eds.; Academic Press: New York, 1978; pp 111–205.

(6) See, e.g., Pedersen, C. J. *J. Am. Chem. Soc.* **1967**, *89*, 7017–7036. Liotta, C. L., *op. cit.*, pp 114–115.

(7) Kyba, E. P.; Timko, J. M.; Kaplan, L. J.; de Jong, F.; Gokel, G. W.; Cram D. J. *J. Am. Chem. Soc.* **1978**, *100*, 4555–68.

0022-3263/89/1954-4712$01.50/0

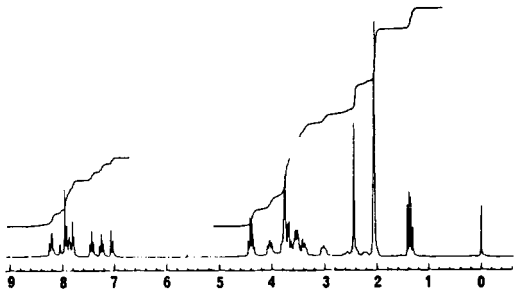
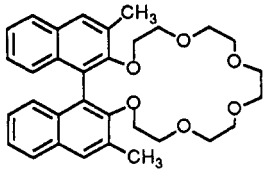
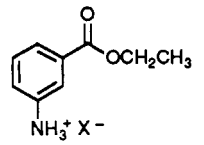


Figure 1. ^{1}H NMR spectrum of 1 and 2 equiv of **2a** in acetone-d_6.

ethyl *m*-aminobenzoate (**2a–d**) by a simple binaphthyl crown ether derivative, 1. (This combination of host and



1



2a, $X^- = ClO_4^-$
2b, $X^- = PF_6^-$
2c, $X^- = Br^-$
2d, $X^- = (NO_2)_3C_6H_2O^-$

guest was chosen to provide convenient NMR probes, in the form of the ethyl group in **2** and the methyl groups of **1**.) We find *dramatic* differences in the complexation of the various salts of **2** by **1** in two very different studies: (1) the solubilization of **2** in $CDCl_3$ by **1** in solid–liquid extraction experiments, and (2) the formation of complexes of **1** and **2** in homogeneous (acetone) solution.

Results

A. Solid–Liquid Extraction. When a $CDCl_3$ solution of racemic host **1** was sonicated with 2 equiv of solid **2a** (the perchlorate salt), some of the **2a** remained undissolved. ^{1}H NMR spectroscopy of the resulting filtered solution demonstrated quantitative solubilization of 1.0 (± 0.05) equiv of **2a**. Identical results were obtained when only a single equivalent of **2a** was used; in this case, all of the **2a** was solubilized. Use of the hexafluorophosphate salt (**2b**) in place of **2a** again gave identical results; a single equivalent of **2b** was solubilized by **1**. These results are perhaps not surprising; host **1** and related hosts have long been known to form 1:1 complexes with alkylammonium ions.[8]

Salts **2c** and **2d** provided more unusual results. When 2 equiv of either the bromide salt, **2c**, or the picrate salt, **2d**, were sonicated with a $CDCl_3$ solution of **1**, *all* of the salt dissolved, and ^{1}H NMR spectra confirmed the solubilization of 2.0 (± 0.05) equiv of the salts. In contrast to the spectra of the complexes of **1** with **2a** and **2b**, which displayed a considerable amount of exchange broadening of the host signals, the complexes of **2c** and **2d** displayed very sharp spectra. Titration of a solution of **1** in $CDCl_3$ with increments of picrate salt **2d** gave linear (R = 0.99) changes in the methyl resonance chemical shift up to the addition of 2.0 equiv of the salt. The upfield shift of the methyl resonance is as expected, as the methyl groups of **1** fall into the shielding region of the aromatic ring of complexed salt **2d**.

B. Homogeneous Complexation. Salts **2a–d** are completely insoluble in $CDCl_3$ at room temperature in the absence of host **1**. They are readily soluble in acetone-d_6,

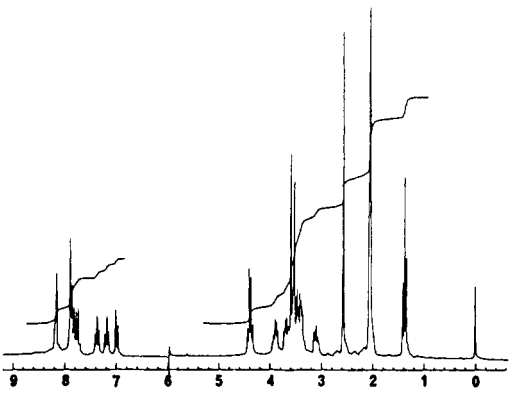


Figure 2. ^{1}H NMR spectrum of **1** and 2 equiv of **2c** in acetone-d_6.

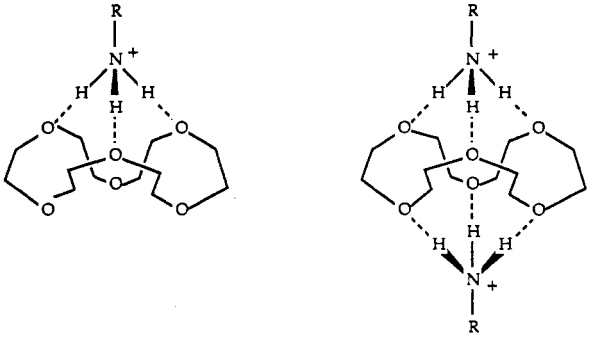


Figure 3. Schematic representation of 1:1 and 2:1 complexes of alkylammonium ions with macrocyclic polyethers.

however. A mixture of **1** and 2.0 equiv of **2a** in acetone-d_6 displayed two overlapping sets of ethyl signals (δ ca. 1.4, 4.4 ppm) with equal intensity in the ^{1}H NMR spectrum (Figure 1); one matches the spectrum of **2a** alone in acetone-d_6, the other presumably represents the complexed salt. A similar mixture of **1** and 2.0 equiv of **2c** in acetone-d_6, on the other hand, displayed only a single ethyl group resonance (Figure 2). In all cases, narrow line widths suggested exchange was either very rapid or very slow in these systems.

Discussion

Polyether host **1** (in $CDCl_3$ solvent) clearly solubilizes 2.0 equiv of the bromide and picrate salts, **2c** and **2d**, but only 1.0 equiv of the perchlorate and hexafluorophosphate salts, **2a** and **2b**. As a simple explanation for such behavior, we suggest that **1** forms complexes of 1:1 stoichiometry with **2a** and **2b**, but complexes of 2:1 stoichiometry with salts **2c** and **2d**. NMR titration data are consistent with 2:1 complex formation with **2d**, with linear response of the methyl resonance (of host **1**) chemical shift up to the addition of 2.0 equiv of salt **2d**. Though any detailed explanation of this effect must be speculative, perhaps tighter ion pairing of the bound ammonium group with the counterion in the case of the picrate and bromide salts eases the positive charge placed into the crown ether, permitting another positively charged guest to approach and be complexed, presumably on the opposite side of the ring (Figure 3). In the extreme limit, the counterion could disrupt the normally expected tripod binding of the ammonium ions, giving an ion-paired dipod arrangement (Figure 4).

Differential solubility and/or lattice energies of salts **2a–d** could conceivably have played a role in generating these results. However, the complexation studies in homogeneous solution appear to rule out such effects. Even when presented with 2 equiv of **2a** in solution, host **1** appears to complex only 1 equiv. This stands in sharp

(8) For representative discussions, see: Stoddart, J. F. *Chem. Soc. Rev.* **1979**, *7*, 85. Hayward, R. C. *Ibid.* **1983**, *12*, 285. Sutherland, I. O. *Ibid.* **1986**, *15*, 63. Cram, D. J.; Cram J. M. *Acc. Chem. Res.* **1978**, *11*, 8.

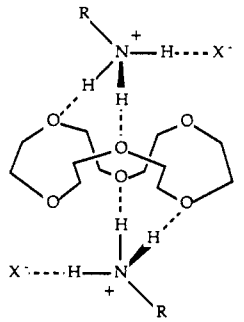


Figure 4. Extreme depiction of proposed interaction of counteranions with complexed alkylammonium ions–dipodal binding.

contrast to the behavior of 1 with **2c**, where 2 equiv appear to be complexed under both heterogeneous and homogeneous conditions.

It may prove possible to explain the results in homogeneous acetone solution without postulating the formation of discrete 2:1 complexes. If free **2c** exchanged rapidly on the NMR time scale with complexed **2c**, a single resonance for **2c**, as observed, would result. Conversely, very slow exchange of free **2a** with complexed **2a** would explain the two resonances observed. Thus, essentially an anion-assisted labilization of complexed ammonium ions, with bromide more effective than perchlorate, could account for the observations in homogeneous solution.

There do appear to be some counteranion effects on exchange rates. We feel we have never observed the slow exchange limit in these systems, in that 1:1 complexes of ammonium salts with 1 should give inequivalent host methyl groups, and we have always observed only a single resonance for these groups. The bromide and picrate salts, **2c** and **2d**, appear to give very rapid exchange in both $CDCl_3$ and deuterioacetone; even with limited amounts of salt present, the methyl groups of 1 appear as a single, sharp resonance. The perchlorate and hexafluorophosphate salts, **2a** and **2b**, do indeed appear to give somewhat slower exchange in $CDCl_3$, with a considerable broadening of the methyl resonance of 1 evident. The exchange rates of these salts in deuterioacetone, however, appear comparable to those of **2c** and **2d**; in this solvent, only a single sharp resonance for the methyl groups is again observed. Given these observations, it appears likely that anion-assisted labilization *may* play some role in this chemistry. However, the *dominant* factor at work here does appear to be 2:1 complex formation with salts **2c** and **2d**. Exchange rates, especially in acetone solvent, simply do not have the proper relative magnitudes (vide supra) to explain the homogeneous complexation results. In addition, simple exchange arguments do not easily reconcile with the heterogeneous extraction and titration experiments discussed earlier.

Conclusions

A dramatic anion effect has been observed for the complexation of ammonium ions by a simple macrocyclic polyether. Bromide and picrate salts appear to form complexes of 2:1 stoichiometry, while perchlorate and hexafluorophosphate salts form 1:1 complexes, under either heterogeneous (solid–liquid extraction) or homogeneous (acetone solution) conditions. Tighter ion pairing of bromide and picrate with the bound ammonium ion may lift the ion partially away from the binding pocket, easing the local positive charge and facilitating the approach of a second positively charged guest.

This interaction of the bound ammonium group with the counteranion may help account for the decrease in enantioselection observed by Cram on switching from perchlorate or hexafluorophosphate salts of amino acid esters to the corresponding bromide or thiocyanate salts. Chiral discrimination in these systems appears to depend largely on formation of a well-ordered complex, maximizing the discriminatory interactions responsible for enantioselection. If the counteranion disrupts the complex through tight ion pairing (as proposed above to account for the bromide and picrate salt studies), these discriminating interactions may well be appreciably reduced, lowering the enantioselectivity of complexation.

Experimental Section

Host 1 was prepared as described.[9] Ethyl *m*-aminobenzoate is commercially available (Aldrich Chemical Co.).

Ethyl *m*-Aminobenzoate Perchloric Acid Salt (2a). Ethyl *m*-aminobenzoate (0.5 g, 3.03 mmol) was dissolved in 10 mL of methanol. To this solution was added 71% aqueous picric acid (0.428 g, 3.03 mmol). The solvent was removed on a rotary evaporator, and the residue was dried by azeotropic distillation (Dean–Stark trap) with benzene. The resulting suspension was cooled and filtered, affording an off-white powder, 0.774 g (96%), which was recrystallized from $CHCl_3$/hexanes: mp 215.3–217.7 °C dec; IR (KBr) 3100 (s, br, NH_3), 2950 (s, br, CH and NH_3), 1685 (s, C=O), 1300 (vs), 1100 (vs, br, ClO_4^-) cm^{-1}; NMR (acetone-d_6) δ 1.39 (t, 3 H, J = 7.2 Hz, CH_3), 4.40 (q, 2 H, J = 7.2 Hz, CH_2), 7.79–7.89 (m, 2 H, ArH), 8.20–8.26 (m, 2 H, ArH). Anal. Calcd for $C_9H_{12}ClNO_6$: C, 40.69; H, 4.55. Found: C, 40.72; H, 4.56.

Ethyl *m*-Aminobenzoate Hexafluorophosphoric Acid Salt (2b). Hexafluorophosphoric acid etherate (1.332 g, 6.05 mmol) was added to a solution of ethyl *m*-aminobenzoate (1.0 g, 6.05 mmol) in 10 mL of CH_2Cl_2. An aliquot was removed and triturated with ether and petroleum ether, affording a tan solid. The reaction mixture was seeded with this solid and placed in a freezer at −20 °C. After ca. 1 h, the small white crystals which had formed were isolated by filtration and washed with petroleum ether, 0.70 g (37%): mp 135.0–137.5 °C dec; IR (KBr) 3225 and 2800–2900 (m, br, NH_3 and CH), 1685 (s, C=O), 1300 (s, br), 840 (vvs, br, PF_6^-) cm^{-1}; NMR (acetone-d_6) δ 1.38 (t, 3 H, J = 7.2 Hz, CH_3), 4.40 (q, 2 H, J = 7.2 Hz, CH_2), 7.80–7.85 (m, 2 H, ArH), 8.17–8.30 (m, 2 H, ArH). Samples decomposed rather quickly, apparently generating HF, precluding satisfactory elemental analysis.

Ethyl *m*-Aminobenzoate Hydrogen Bromide Salt (2c). A solution of ethyl *m*-aminobenzoate (1.0 g, 6.05 mmol) in 100 mL of Et_2O was bubbled with dry HBr gas until precipitation appeared complete. The salt was isolated by filtration, washed with Et_2O, air-dried, and then recrystallized from $CHCl_3$/hexanes. The yield of white crystalline product was 1.346 g (90%): mp 193.9–195.0 °C dec; IR (KBr) 2750–3150 (s, br, NH_3 and CH), 1685 (s, C=O), 1300 (vs) cm^{-1}; NMR (acetone-d_6) δ 1.38 (t, 3 H, J = 6.8 Hz, CH_3), 4.40 (q, 2 H, J = 6.8 Hz, CH_2), 7.71–7.84 (m, 2 H, ArH), 8.16–8.20 (m, 2 H, ArH). Anal. Calcd for $C_9H_{12}BrNO_2$: C, 43.92; H, 4.91. Found: C, 44.01; H, 5.04.

Ethyl *m*-Aminobenzoate Picric Acid Salt (2d). Addition of a solution of ethyl *m*-aminobenzoate (0.5 g, 3.03 mmol) in 10 mL of $CHCl_3$ to a solution of picric acid (0.77 g of 90% picric acid, 3.03 mmol) in 30 mL of $CHCl_3$ gave a dense yellow precipitate. The crude product (0.96 g, 80%) was isolated by filtration and air-dried. Recrystallization from $CHCl_3$ provided the pure salt as bright yellow crystals: mp 165.4–169.7 °C; IR (KBr) 3230 (m, NH_3), 2500–3000 (ms, br, CH and NH_3), 1690 (s, C=O), 1610 (s, br), 1570 (s), 1520 and 1340 (s, NO_2), 1280 (s) cm^{-1}; NMR (acetone-d_6) δ 1.37 (t, 3 H, J = 7.2 Hz, CH_3), 4.38 (q, 2 H, J = 7.2 Hz, CH_2), 7.74–7.76 (m, 2 H, ArH), 8.08–8.20 (m, 2 H, ArH), 8.77 (s, 2 H, picrate ArH). Anal. Calcd for $C_{15}H_{14}N_4O_9$: C, 45.69; H, 3.58. Found: C, 45.62; H, 3.61.

Solid–Liquid Extraction. A test tube was charged with 10 mg of macrocycle 1, an excess of the desired solid salt of ethyl *m*-aminobenzoate, and 1.0 mL of $CDCl_3$. The mixture was so-

(9) Helgeson, R. C.; Weisman, G. R.; Toner, J. L.; Tarnowski, T. L.; Chao, Y.; Mayer J. M.; Cram, D. J. *J. Am. Chem. Soc.* **1979**, *101*, 4928–4941.

nicated for 3 min in a standard low-power laboratory ultrasonicator and then filtered through glass wool into a 5-mm NMR tube for analysis. As control experiments, each of the salts **2a–d** was treated in the same way in the absence of **1**. In each case, no detectable amounts of the salts were solubilized.

Homogeneous Complexation A mixture of 5.0 mg of macrocycle **1** (9.7 μmol) and 5.15 mg of perchlorate salt **2a** (19.4 μmol) in 0.5 mL of acetone-d_6 in a 5-mm NMR tube was sonicated to give a homogeneous solution and then analyzed by NMR spectroscopy. A similar mixture was made up from 5.0 mg of **1** and 4.81 mg of bromide salt **2c**. For comparison acetone-d_6 solutions of salts **2a** and **2c** were also prepared in the absence of **1**.

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Synthesis of (+)-Lasalocid Aldehyde

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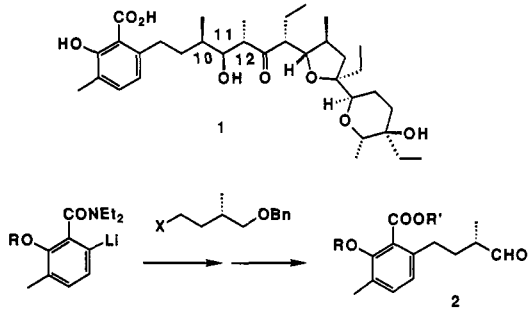
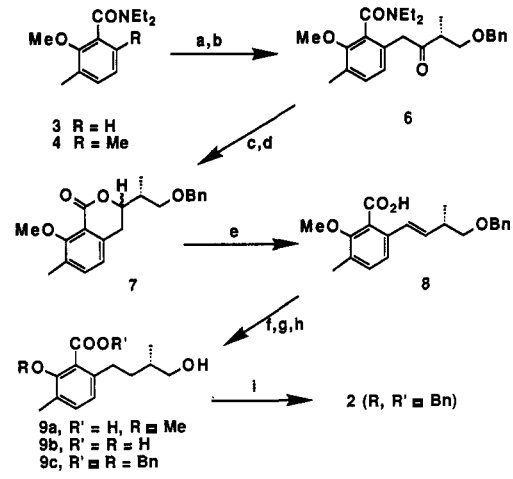
In connection with our studies of the effect of stereochemistry and substitution on the ionophoric properties of the polyether antibiotics, we recently suggested that the diastereomer of lasalocid A (**1**)[1] which is epimeric at C10, C11, and C12 is as well preorganized for binding cations as lasalocid A itself.[2] In preparation for synthesizing that diastereomer, we needed a source of the aldehydic lasalocid precursor (**2**), which is enantiomeric with the natural series. While the enantiomers of **2** have been prepared previously,[3] we felt that a more practical route to **2** might be available using the metalated salicylic acid derivative shown below.



We began by metalating[4] the methyl ether of *N,N*-diethyl-3-methylsalicylamide[5] (**3**) using *sec*-butyllithium (THF/TMEDA, −78 °C). A variety of electrophiles including alkyl bromides and carbonyl compounds added smoothly to the resulting aryllithium. However, in the case of alkylation, the resulting highly hindered amide could not be hydrolyzed. With aldehyde electrophiles, the amide was readily cleaved using the internal alcohol nucleophile to give an intermediate γ-lactone,[6] but reduction of the benzylic lactone oxygen was problematic. Catalytic hydrogenolysis with Raney Ni, Pd, or Pt gave only the starting lactone, and Birch reduction resulted when dissolving metal conditions were used. While a neighboring benzylic alcohol group facilitated hydrolysis of our amide, the more remote terminal hydroxyl (as in **9**) did not provide the necessary assistance.

Scheme I[a]



[a] (a) (i) *s*-BuLi, TMEDA; (ii) CH_3I; (b) (i) *n*-BuLi; (ii) (*R*)-methyl 3-(benzyloxy)-2-methylpropionate (**5**); (c) $NaBH_4$; (d) CSA; (e) DBU (f) H_2, 30% Pd/C; (g) BBr_3; (h) K_2CO_3, BnBr; (i) $(COCl)_2$, DMSO.

To allow amide hydrolysis and formation of a fully reduced side chain, we chose an alternative pathway via a homobenzylic alcohol which could assist in the amide hydrolysis and then be removed by a subsequent elimination. Therefore, we alkylated the above aryllithium with methyl iodide to give **4** (96%). A second deprotonation using *n*-BuLi (THF, −78 °C) followed by acylation with 1 equiv of the benzyl ether of commercial methyl (*R*)-3-hydroxy-2-methylpropionate (**5**) then gave adduct **6** in 46% yield (81% based on consumed **4**).[7] The highly acidic nature of the benzyl ketone substructure of **6** was important for several reasons. In particular, the strongly basic conditions employed immediately deprotonated **6** upon its formation, thus suppressing elimination of the terminal benzyloxy group and epimerization of the chiral methine. However, the anion of starting **4** also functioned as the base in deprotonating **6**, and thus only a 50% conversion of **4** could be achieved. We were unable to improve the conversion using additional quantities of *n*-BuLi or other bases. An alternative scheme using the aldehydic analogue of **5** avoided a subsequent reduction step but provided lower yields of the coupled product. We therefore proceeded using **6** (Scheme I).

Conversion of the keto amide **6** to an intermediate δ-lactone (**7**) with loss of diethylamine was effected in 72% yield by reduction ($NaBH_4$, MeOH) and acidic lactonization (camphorsulfonic acid, $PhCH_3$). The ~1:1 mixture of diastereomeric lactones was subjected to elimination conditions by heating overnight at 135 °C with DBU in butyronitrile to give styrene **8**. Catalytic hydrogenation (30% Pd/C, EtOH) removed the benzylic ether and saturated the olefin to provide **9a**. Demethylation (BBr_3, CH_2Cl_2) then gave the free salicylic acid derivative **9b**.

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