Lithiation of Polyhydric Compounds. Salicylic Acids

M. Carmen Rotger, Antoni Costa, and José M. Saá*

Departament de Química, Universitat de les Illes Balears, E-07071 Palma de Mallorca, Spain

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Polylithiated derivatives of salicylic and oligosalicylic acids can be generated by means of the halogen-to-metal exchange reaction. Dehydrobromination and other byproducts can be kept to a minimum by working with the preformed lithium salts which are soluble in THF. Even base sensitive salicylic acids such as 6-bromolasalocid acid can be functionalized under these conditions.

Polylithium salts of organic hard acids are likely to be insoluble compounds in organic, nonprotic solvents due to the tendency of lithium compounds to form aggregates of complex nature.[1] Accordingly, the lithiation, i.e., the formation of one or more carbon–lithium bonds either by directed lithiation[2] or halogen-to-lithium exchange,[3] of compounds having several unprotected acid functional groups is, not unfrequently, considered an unfeasible project.[4] Additional problems such as the presence of functional groups not strictly compatible[5] with the organolithium base and/or the existence of base-labile stereogenic centers makes protection unavoidable for most practical cases.

Nevertheless, a survey of the literature reveals that a variety of C-lithiated (O,C; N,C; S,C; O,O,C; O,N,C) compounds derived from mono or dihydric organic acids[4–6] and C,C-dilithiated[7] compounds can be generated in solution. Seebach's remarkable generation of organolithium derivatives of small peptides, phosphono peptides, and cyclopeptides (having up to four additional acidic functional groups) merits special mention as it allows for the direct functionalization (at the sarcosine moiety) of medicinally important cyclosporin A with strict control of stereochemistry (either *R* or *S*) at the newly created stereogenic center.[8] On the other hand, C-lithiated compounds of higher order derived or not from polyhydric organic acids are less commonly used species.[9] Our interest in generating C-lithiated derivatives of polyhydric compounds follows from our recent work on the lithiation of phenols and related compounds.[4b,c,d]

Inasmuch as lithiation of polyacids is related to the solubility of their lithium salts in the common organic solvents used for lithiation, control of their aggregation states is of utmost importance for success. Seebach's approach was to break down aggregates by adding lithium chloride[10] (other lithium salts also work) and a non nucleophilic base to avoid attack on the sensitive functional

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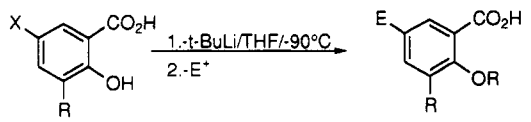
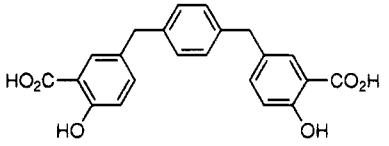
0022-3263/93/1958-4083$04.00/0

Scheme I



1 X = Br, R = H
2 X = R = Br
3 X = I, R = H

4a R = H; E = SMe
4b R = H; E = $CHOHC_6H_5$
4c R = H; E = $CH_2C_6H_5$
4d R = H; E = $COH(C_6H_5)_2$
4e R = H; E = $CH(C_6H_5)_2$
4f R=E = COOEt



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groups (carboxyl and carboxamide) present. The use of excess lithium base has also been shown to have a dramatic effect on solubility presumably because it promotes the formation of mixed aggregates,[11] more soluble in the common solvents used for lithiations. The efficiency of these approaches, either isolated or combined, is often enhanced with the use of ultrasonic irradiation,[12] a valuable aid for promoting reaction in reluctant cases.[4d] Our approach to the problem of lithiation of polyhydric compounds is based on the hypothesis that those compounds having vicinal acid functional groups may give rise to polylithium salts in a lower aggregation state because of their presumed tendency to form "internal aggregates". We report herein that the lithium salts of bromo-substituted salicyclic and oligosalicylic acids, including some having base-sensitive chiral centers, form soluble or partially soluble aggregates of unknown structure which undergo (up to three) halogen–lithium exchange processes under standard conditions (vide infra).

In regard to an ongoing project aimed at preparing analogs of the anti-HIV agent aurintricarboxylic acid (ATA),[13] we decided to search for a straightforward way of functionalizing salicylic and oligosalicylic acids on the aromatic ring.[14] After some experimentation we found that treatment of 5-bromosalicylic acid (**1**) with *tert*-butyllithium (*t*-BuLi) at low temperature yields a solution of the corresponding *O,O,C*-trilithio derivative which can be successfully quenched with several electrophiles such as dimethyl disulfide, benzaldehyde, benzophenone, or ethyl chloroformate, leading to the desired compounds **4a**, **4c** (after hydrogenolysis), **4e** (after hydrogenolysis), and **4f** in moderate to good yields (Scheme I). In all cases the expected compounds derived from attack on the carboxyl group[15] as well as some debrominated material (salicylic acid) were found as minor byproducts when using method A. By modifying the experimental conditions, the formation of some of these minor byproducts could be minimized. Thus, the debromination reaction was almost completely eliminated by treatment of the pregenerated dilithium salt [MeOLi/THF, followed by thorough drying in vacuo (0.5 mmHg, 60 °C, 2 h)] with *t*-BuLi under the otherwise standard conditions in THF (method B).[15] Curiously enough, whereas the dilithium salt of salicylic acid (and related analogs) is soluble in THF, that of benzoic acid is almost insoluble, thus suggesting that the former exists in solution as aggregates of lower order.

Quenching the above O,O,C-trilithated derivative of **1** (method B) with terephthaldehyde, followed by hydrogenolysis (H_2, Pd/C) of the crude product, provided the bis-salicylic acid derivative **5** in moderate yield.

Lithiation of 5-iodosalicylic acids (**3**) under the conditions of method A led exclusively to the deiodinated compound, presumably as the result of a rapid intermolecular protonation of the trilithiated species, as demonstrated recently by Beak and Gallagher for closely related substances.[16]

In an attempt to investigate whether or not regioselective lithiation of polyhalogenated compounds would be possible, 3,5-dibromosalicylic acid (**2**) was submitted to the above reaction conditions. Unfortunately, we found that lithiation occurred almost indiscriminately on both bromine atoms.[17] Pregeneration of the disodium salt[18] did not provide significant regioselection, either.

The soluble (O,O,O,O,C,C) hexalithio derivative of **6** was analogously generated by treatment of **6** with *t*-BuLi in THF as above (method A). Subsequent trapping with dimethyl disulfide led to **7a** in 33% isolated yield. Interestingly, initial attempts at preparing the (O,O,O, O,O,O,C,C,C) nonalithio derivative of tris-salicylic acid **8** were frustrated by the insolubility of the pregenerated hexalithium salt (method B). Lithiation occurred, however, when using method A under slightly modified conditions of operation (large excess of *t*-BuLi and high dilution). Thus, quenching with dimethyl disulfide led to an unseparable mixture which, on the average, appears to have an equal number of thiomethylated, dehydrobrominated,[19] and untouched (brominated) rings (shown in Scheme II as **9**), as suggested by careful NMR analysis of the aromatic region. A singlet at $\delta = 2.54$ ppm on the ^1H NMR spectrum and another one at $\delta = 31.0$ ppm on the ^{13}C NMR are supportive pieces of evidence for the presence of the methylthio group, thus proving that polylithiation had indeed occurred.

In passing it is worth mentioning that compound **8** was obtained by trimerization[20] of easily available 5-acetyl-

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(15) Jorgenson, M. J. *Org. React.* **1970**, *18*, 1.

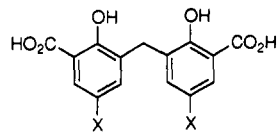
(16) For a recent discussion of the mechanism of lithiation (halogen–lithium exchange) on highly acidic polyfunctional molecules, see; (a) Gallagher, D.; Beak, P. *J. Am. Chem. Soc.* **1991**, *113*, 7984. (b) Narasimhan, N. S.; Sunder, N. M.; Ammanamanchi, R.; Bonde, B. D. *J. Am. Chem. Soc.* **1990**, *112*, 4431. (c) Beak, P.; Musick, T. J.; Chen, C. W. *J. Am. Chem. Soc.* **1988**, *110*, 3538. (d) Beak, P.; Chen, C. W. *Tetrahedron Lett.* **1985**, *26*, 4979.

(17) For the regioselective lithiation of polyhalophenols, see ref 4d and 4g.

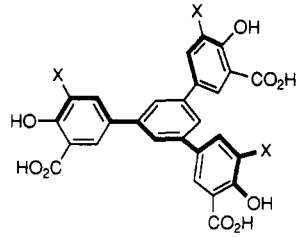
(18) Horne, S.; Weeratunga, G.; Rodrigo, R. *J. Chem. Soc. Chem. Commun.* **1990**, 39.

(19) Selective hydrodebromination has been recently achieved on a tetrabromo cavitand by short (1 min) treatment with excess BuLi. See, Timmerman, P.; van Mook, M. G. A.; Verbom, W.; van Hummel, G. J.; Harkema, S.; Reindhoudt, D. V. *Tetrahedron Lett.* **1992**, *33*, 3377.

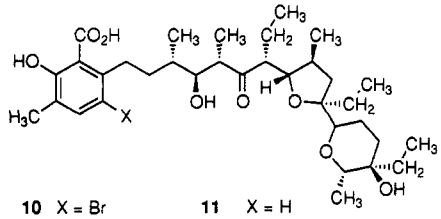
Scheme II



6 X = Br
7a X = SMe



8 X = Br
9 X = SMe, Br, H



10 X = Br

11 X = H
11a X = SMe
11g X = D

3-bromo-2-hydroxybenzoic acid by using an slightly modified version of the reported trimerization procedure.[21]

Finally, in an effort to learn on the synthetic utility of the above halogen–lithium exchange methodology we have briefly examined the functionalization of a base-sensitive salicylic acid, namely 6-bromolasalocid, sodium salt (**10**),[22] straightforwardly prepared from commercial (Aldrich) lasalocid sodium salt (**11**).[23] Lasalocid is a well-known naturally occurring salicylic acid-based ionophore which possesses a carbonyl group (C-13), two extra hydroxy groupings, and two highly sensitive chiral centers (C-12 and C-14) α to the carbonyl group at C-13. In spite of its lability towards acids and bases[24] we found that treatment of **10** with *t*-BuLi/THF at −90 °C as above (method A), led to the formation of a yellowish solution which, on quenching with deuterated methanol led to ca. 50% deuteration as revealed by ^{1}H NMR. Even more remarkable is the fact that the ^{13}C NMR spectra[25] revealed the complete stereochemical integrity of all chiral centers! Only the expected deuterium shifts were observed in the ^{13}C NMR spectra of the ca. 1:1 mixture of **11** and **11g** for C-4, C-7, and C-5[22] (+0.02, +0.08, and +0.10 ppm, respectively),[26] thus proving the presence of deuterium in C-6, only.

Table I. Selected ^{13}C NMR Data for 1-HH, 1-HLi, and 1-LiLi[a]

compd	*T* (K)	$-CO_2-$[b]	C-2[b]	C-5[b]	concn,[c] M
1-H,H	298	173.0	163.5	112.1	0.5
1-H,H	183	173.4	163.4	112.2	0.5
1-H,Li	298	174.5	163.4	111.2	0.2
1-H,Li	183	174.1	163.4	111.2	0.2
1-Li,Li	298	176.8	172.0	103.5	0.2
1-Li,Li	298	177.0	171.9	103.7	0.5
1-Li,Li	183	175.4	172.0	102.6	0.2
		177.7	172.0	103.3	0.5
1-Li,Li	183	175.5		102.6	
		175.2			

[a] The terms 1-H,H; 1-H,Li, and 1-Li,Li refer to compound **1**, its monolithium salt, and dilithium salts, respectively. [b] Chemical shifts are given in ppm relative to TMS. [c] In THF-d_8.

Presumably, hydrogen atoms α to the carbonyl centers are not accessible to the bulky base, possibly because this part of the molecule lies buried in the interior of the complex.[27] Quenching with dimethyl disulfide yielded a 1:2 unseparable mixture of **11a**:**11**, as suggested by the presence of two singlets at δ = 7.18 ppm (aromatic proton) and δ = 2.36 ppm (methylthio group) in the ^{1}H NMR spectrum of the mixture and two signals at *m*/*e* = 681 (M + Na$^+$) and 659 (M) in the FAB mass spectrum.

A brief study of the solution structure of the lithiated species derived from simple salicylic acids was undertaken with the aid of ^{7}Li and ^{13}C NMR spectra. The ^{7}Li spectra[28] at 298 K of a 0.2 M solution (in THF-d_8) of the dilithium salt of **1** showed a broad signal at 2.09 ppm (2.17 ppm for the dilithium salt of salicylic acid itself) which suggested the existence of rapidly equilibrating processes for the lithium atoms of phenolate and carboxylate moieties. The spectra recorded at 183 K showed signals at 2.70, 2.64, and 2.56 ppm and at 1.64, 1.56, and 1.48 ppm corresponding to the lithium phenolate and carboxylate moieties, respectively, thus actually proving that at least three differently aggregated species exist at this temperature. A further minor signal at 2.01 ppm is tentatively assigned to an additional monomeric species having a plane of symmetry (or a pair of very rapidly equilibrating species). The above assignments are in accordance with the results of a titration experiment in which a solution of **1** was portionwise added to a solution of the corresponding dilithium salt, at 183 K (Figure 1). Disappearance of the low-field signals (lithium phenolate) was observed together with collapse of the remaining ones and the upsurge of a new wide singlet at 1.54 ppm (the ^{7}Li spectra of the highly insoluble lithium benzoate shows a singlet at 1.62 ppm). Analysis of the ^{13}C NMR spectra of **1** and those of the monolithium and dilithium salts of **1** also leads to analogous conclusions (Table I shows the most significant data). Thus, at least three complex signals (177.7, 175.5, and 175.2 ppm) can be observed for the carboxylate carbon on the dilithium salt solution of **1** (0.5 M in THF-d_8), at 183 K. On dilution, that at 177.7 ppm disappears, thus suggesting that it could be assigned to the most aggregated species.

In summary, polylithiated salicylic acids can be generated and functionalized by means of the halogen-to-lithium exchange methodology. Lithium salts of salicylic

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(24) Westley, J. W.; Evans, R.H.; Berger, J.; Pruess, D. L.; Stempel, A. *J. Chem. Soc. Chem. Commun.* **1970**, 71. See also ref 22.
(25) Gueco, R. C. R.; Everett, G. W. *Tetrahedron* **1985**, *41*, 4437.
(26) Forsyth, D. A. In *Isotopes in Organic Chemistry* Buncel, E., Lee, C. C., Eds.; Elsevier Science Publishers B. V.: Amsterdam, 1984; Vol. 6.
(27) Bissell, E. C.; Paul, I. C. *J. Chem. Soc. Chem. Commun.* **1972**, 967. Hilgenfeld, R.; Saenger, W. In *Host Guest Complex Chemistry Macrocycles: Synthesis, Structures, Applications*; Vögtle, F., Weber, E., Eds.; Springer Verlag: Heidelberg, 1985; p 45.
(28) LiCl in D_2O was used as external reference.

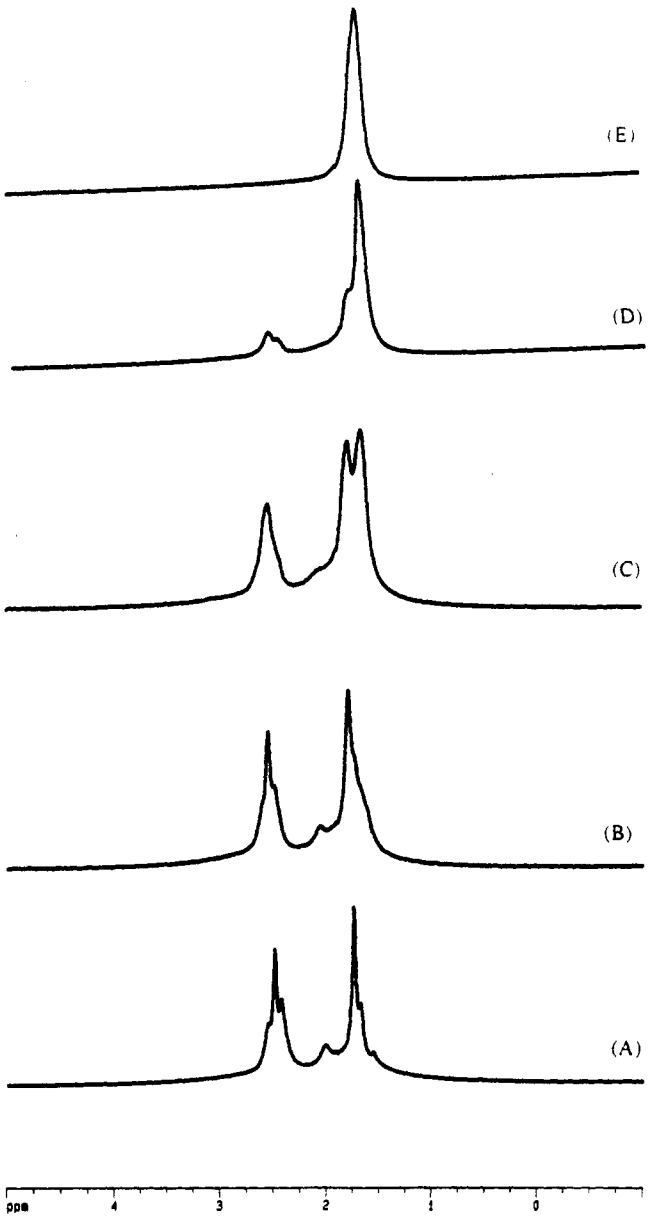

Figure 1. ^{7}Li NMR spectra at 183 K of a mixture of 1 (free acid) and 1 (dilithium salt) at different molar ratios: (A) 0:1; (B) 0.1:1; (C) 0.25:1; (D) 0.50:1; (E) 1:1.

and oligosalicylic acids are sufficiently soluble in THF for the halogen-to-metal exchange reaction to occur in an efficient manner. In most cases the dehydrobromination byproducts can be kept to a minimum by working at low temperature directly with the preformed salts of the salicylic (and oligosalicylic) acids. Presumably, this methodology can also be applied to closely related compounds having acid functional groups in the vicinity of each other thus avoiding the need to use protecting groups.

Experimental Section

General. All melting points are uncorrected and were taken on a capillary melting point apparatus. The boiling points given refer to those observed on bulb-to-bulb distillation. Proton NMR spectra were obtained on a 300-MHz spectrometer in $CDCl_3$ (unless otherwise noted). Electron impact mass spectra were recorded at 70 eV ionizing energy. Column chromatography was performed on silica gel Merck (Kieselgel 40). Solvents used for lithiation were dried as shown previously.[4b,c,d] The purity of all compounds for which no elemental analysis is provided was judged to be >95% by ^{13}C and ^{1}H NMR (see supplementary material).

General Procedure for Lithiation of Bromosalicylic Acids. Method A. An oven-dried three-necked flask sealed with septa was charged with bromosalicylic acid (10 mmol) and anhydrous THF (25 mL), under argon, and cooled to −90 °C. *t*-BuLi (33 mmol) in pentane was slowly (ca. 30 min) added via syringe. After addition the mixture was allowed to warm to −40 °C. The appropriate electrophile (12 mmol) was then added dropwise over a 10-min period. After stirring for 1 h the bath was removed and the mixture allowed to stand at room temperature overnight. The standard workup involved addition of water (10 mL) and solvent evaporation under vacuo. The resulting mixture was partitioned between water (40 mL) and ether (30 mL). The water layer was acidified to pH = 1 and the resulting suspension extracted with ether (3 × 20 mL). Crude salicylic acids were converted, in most cases, to the corresponding methyl esters with the aid of diazomethane and then purified by column chromatography on silica gel using 2–5% ethyl acetate in the hexane as eluant and eventually crystallized or bulb-to-bulb distilled. The yields given below refer to nonoptimized conditions.

General Procedure for Lithiation of Bromosalicylic Acids. Method B. A solution of LiMeO (4 mmol) in anhydrous THF (5 mL), at 0 °C, under argon, was added to a THF solution (10 mL) of bromosalicylic acid (2 mmol). The mixture was evaporated to dryness under reduced pressure. The residue was then carefully dried under vacuo (1 mmHg) at 60 °C for 2 h. The resulting pale yellow solid was dissolved in anhydrous THF (10 mL) at −90 °C and then treated with a 1.3 M pentane solution of *t*-BuLi (2.2 mmol) was added dropwise via syringe. Workup was carried out as in method A above. The yields given below refer to nonoptimized conditions.

Methyl 5-(Methylthio)salicylate. Methyl Ester of 4a. White crystalline (hexane) solid, mp 52–3 °C isolated in 60% overall yield (method A): ^{1}H NMR ($CDCl_3$) δ 10.67 (s, 1H), 7.81 (d, J = 2.4 Hz, 1H), 7.46 (dd, J = 8.7 and 2.4 Hz, 1H), 6.95 (d, J = 2.4 Hz, 1H), 3.96 (s, 3H), 2.46 (s, 3H) ppm; IR (KBr) ν 3100, 1685, 1350, 1300, 1050 cm^{-1}; MS m/e 198 (99, M$^+$), 166 (100), 138 (88), 123 (10), 105 (14), 96 (60), 77 (4). Anal. Calcd for $C_9H_{10}SO_3$: C, 54.53; H, 5.08. Found: C, 54.69; H, 5.07.

[4-Hydroxy-3-(methoxycarbonyl)phenyl]phenylmethane. Methyl Ester of 4c. Obtained in 49% overall yield (method A, followed by hydrogenolysis) as a clear oil: bp 150 °C (5 × 10^{-3} mmHg), which slowly solidifies on cooling, mp 74–5 °C; ^{1}H NMR ($CDCl_3$) δ 10.69 (s 1H), 7.73 (d, J = 2.4 Hz, 1H), 7.35–7.21 (m, 6H), 6.99 (d, J = 8.7 Hz, 1H), 3.98 (s, 5H) ppm; IR (KBr) ν 3100, 1685, 1450, 1220 cm^{-1}; MS m/e 242 (57, M$^+$), 210 (100), 181 (39), 153 (24), 133 (8), 105 (12), 77 (11). Anal. Calcd for $C_{15}H_{14}O_3$: C, 74.36; H, 5.82. Found: C, 74.20; H, 5.88.

(3-Carboxy-4-hydroxyphenyl)diphenylmethane (4e). White crystalline solid (hexane/chloroform), mp 150–1 °C, obtained (method A, followed by hydrogenolysis) in 12% overall yield: ^{1}H NMR ($CDCL_3$) δ 10.33 (s 1H), 7.63 (d, J = 2.4 Hz, 1H), 7.23–7.33 (m, 10H), 7.12 (d, J= 8.7 Hz, 1H), 6.95 (d, J = 8.7 Hz, 1H), 5.50 (s, 1H) ppm; ^{13}C NMR ($CDCl_3$) δ 175.4, 161.5, 144.1, 138.9, 136.0, 131.7, 130.0, 130.2, 127.2, 118.9, 111.5, 56.4 ppm; IR (KBr) ν 3150, 1715, 1340, 1240 cm^{-1}; MS m/e 304 (70, M$^+$), 286 (94), 257 (27), 209 (66), 181 (32), 165 (58), 153 (48), 152 (98), 151 (31), 149 (100); HREIMS calcd for $C_{20}H_{16}O_3$ 304.1099, found 304.1099.

Methyl 2-[(Ethoxycarbonyl)oxy]-5-(ethoxycarbonyl)benzoate. Methyl Ester of 4f. Obtained in 48% yield (method B) as a viscous oil: bp 165 °C (0.5 mmHg); ^{1}H NMR ($CDCl_3$) δ 8.68 (d, J = 2.2 Hz, 1H), 8.24 (dd, J = 8.4, 2.2 Hz, 1H), 7.27 (d, J = 8.5 Hz, 1H), 4.40 (q, J = 7.2 Hz, 2H), 4.35 (q, J = 7.2 Hz, 2H), 3.92 (s, 3H), 1.42 (t, J = 7.2 Hz, 3H), 1.41 (t, J = 7.2 Hz, 3H) ppm; IR (KBr) ν 1770, 1725, 1250 cm^{-1}. MS m/e (M$^+$ − 31) 265 (6), 251 (5), 224 (14), 196 (17), 193 (29), 192 (100), 179 (23), 165 (24), 164 (68), 149 (22), 147 (80), 120 (21). Anal. Calcd for $C_{14}H_{16}O_7$: C, 56.73; H, 5.44. Found: C, 56.99; H, 5.50.

***p*-Xylylenebis[4-hydroxy-3-(methoxycarbonyl)benzene]. Dimethyl Ester of 5.** White crystalline solid (ethyl acetate/hexane), mp 134–5 °C, obtained (method B, followed by hydrogenolysis) in 20% overall yield: ^{1}H NMR ($CDCl_3$) δ 10.6 (s, 2H), 7.66 (d, J = 2.1 Hz, 2H), 7.26 (dd, J = 2.4 and 8.7 Hz, 2H), 7.08 (s, 4H), 6.90 (d, J = 8.4 Hz, 2H), 3.92 (s, 6H), 3.87 (s, 4H) ppm; ^{13}C NMR ($CDCl_3$) δ 171.3, 160.8, 139.7, 137.3, 132.6,

130.5, 129.6, 118.5, 112.8, 53.0, 41.2 ppm; IR (KBr) ν 3250, 1685, 1305, 1210, 1180 cm^{-1}; MS *m/e* 406 (43, M$^+$), 374 (36), 342 (47), 316 (26), 209 (47), 181 (34), 171 (73), 165 (30), 153 (33), 152 (46), 133 (100); HREIMS calcd for $C_{24}H_{22}O_6$ 406.14163, found 406.14180.

Bis[2-hydroxy-3-(methoxycarbonyl)-5-(methylthio)phenyl]methane. Methyl Ester of 7a. White crystalline solid (chloroform/hexane), mp 150–1 °C, obtained in 33% overall yield (method A): ^{1}H NMR ($CDCl_3$) δ 11.0 (s, 2H), 7.69 (d, J = 2.4 Hz, 2H), 7.38 (d, J = 2.4 Hz, 2H), 3.99 (s, 2H), 3.94 (s, 6H), 2.42 (s, 6H) ppm; IR (KBr) ν 3160, 1680, 1450, 1350 cm^{-1}; MS *m/e* 408 (100, M$^+$), 376 (72), 348 (26), 344 (41), 316 (13), 269 (23), 188 (12), 172 (36), 115 (6). Anal. Calcd for $C_{19}H_{20}S_2O_6$: C, 55.87; H, 4.93. Found: C, 55.87; H, 4.93.

1,3,6-Tris[3-bromo-4-hydroxy-5-(methoxycarbonyl)phenyl]benzene. Trimethyl Ester of 8. 3-Bromo-2-hydroxy-5-acetylbenzoic acid (3.0 g, 11.5 mmol) was dissolved in 100 mL of dry ethanol at room temperature. Silicon tetrachloride (20 mL, 8.0 mmol) was added dropwise and the resulting dark solution was stirred at room temperature for 24 h. The reaction was poured onto 300 g of crushed ice and the mixture stirred overnight. The suspension was filtered and the solid dried in the air. The residue was taken up in Et_2O, and the extracts were pooled, dried over Na_2SO_4, filtered, and concentrated. The crude acid was washed with several portions of chloroform, dried, and converted to the trimethyl ester with diazomethane. Recrystallization (Et_2O/hexanes) yielded 1.18 g (40%) of the trimethyl ester of 8 as a yellowish solid: mp >240 °C dec; ^{1}H NMR ($CDCl_3$) δ 11.53 (s, 3H), 8.10 (d, J = 2.1 Hz, 3H), 8.05 (d, J = 2.1 Hz, 3H), 7.58 (s, 3H), 4.03 (s, 9H) ppm; ^{13}C NMR ($CDCl_3$) δ 170.1, 157.9, 140.4, 137.6, 132.8, 127.7, 124.5, 113.6, 112.0, 53.0 ppm; IR (KBr) ν 3130, 1680, 1610, 1440, 1385 cm^{-1}; MS *m/e* 768 (3), 767 (2), 766 (9), 765 (2), 764 (9), 762 (3), 702 (8), 668 (5), 670 (14), 668 (14), 622 (10), 352 (10), 351 (36), 350 (36), 349 (16), 336 (14), 335 (100), 334 (89), 332 (32); HREIMS, calcd for $C_{30}H_{21}O_9{}^{79}Br^{81}Br_2$ 765.8735, found 765.8698.

Lithiation of 1,3,5-Tris(3-bromo-4-hydroxy-5-carboxyphenyl)benzene (8). The general procedure of method A was employed except for the following two facts: more dilute conditions (0.27 mmol in 10 mL of THF) and excess (1.66 M, 4 mL, 6.6 mmol) *t*-BuLi were used. The standard workup yielded a crude material in 83% yield (based on **9a**) which was treated with diazomethane and repeatedly purified by TLC. The resulting purified material, in spite of its apparent homogeneity (^{1}H and ^{13}C NMR spectra are given as supplementary material) was shown to be an unseparable mixture of compounds which, on the average, contain one H, one Br, and one SMe group per molecule (shown in Scheme II as **9**).

6-Deuterolasalocid Sodium Salt. Sodium Salt of 11g. Lithiation of 6-bromolasalocid sodium salt (**10**)[22] was carried out in THF (2 mL) as described in method A (5.5 equiv of *t*-BuLi added), followed by quenching with excess deuterated methanol. The mixture was then added to ethyl acetate, at 0 °C, followed by 1 N HCl (0.5 mL). The solution was washed with a saturated solution of Na_2CO_3, dried with anhydrous Na_2SO_4, and evaporated to dryness. The oily residue was taken up in CH_2Cl_2 and hexane added. The precipitated sodium salt **11g** (40% yield) was shown to contain ca. 55% deuterium incorporated at C-6: FAB MS (matrix: thioglycerol) 614 (100), 613 (80); ^{1}H NMR ($CDCl_3$) δ 12.34 (s, 1H), 6.95 (d, J = 7.2 Hz, 0.5H), 6.95 (s, 0.5H), 6.45 (d, J = 7.2 Hz, 0.5H), 4.84 (bs, 1H), 4.49 (d, 9.9 Hz, 1H), 3.95 (q, J = 6.3 Hz, 2H), 3.83 (d, J = 6.3 Hz, 1H), 3.45 (d, J = 11.7 Hz, 1H), 2.82 (m, 1H), 2.55 (d, J = 16.2 Hz, 1H), 2.19 (s, 3H), 1.79–0.74 (m, 36H), 0.59 (t, J = 7.2 Hz, 3H) ppm; ^{13}C NMR ($CDCl_3$) δ 219.1, 176.9, 161.3, 143.8, 143.7, 131.9, 131.7, 123.5, 120.1, 118.4, 87.7, 83.2, 71.5, 71.0, 68.7, 56.0, 49.2, 38.2, 38.1, 34.7, 34.3, 33.4, 31.4, 30.0, 29.5, 19.7, 16.8, 16.1, 15.9, 14.0, 13.8, 13.1, 12.8, 10.0, 7.2 ppm; IR (KBr) ν 3250, 1700, 1590, 1450, 1385 cm^{-1}.

6-(Methylthio)lasalocid Sodium Salt. Sodium Salt of 11a. Lithiation of 6-bromolasalocid sodium salt (**10**)[22] as above was followed by quenching with excess dimethyl disulfide. The standard workup provided a 1:2 unseparable mixture of the expected **11a** and dehydrodebrominated **11**, respectively, in 50% yield, as demonstrated by the ^{1}H, ^{13}C, and FABMS spectra (supplementary material).

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Supplementary Material Available: ^{1}H and/or ^{13}C NMR and FABMS spectra for compounds **4e**, **5**, **8**, **9**, **11a**, and **11g** are given together with the ^{7}Li and ^{13}C NMR data for the monolithium and dilithium derivatives of **1** (14 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.