Synthesis of 6-Aminoisoproterenol

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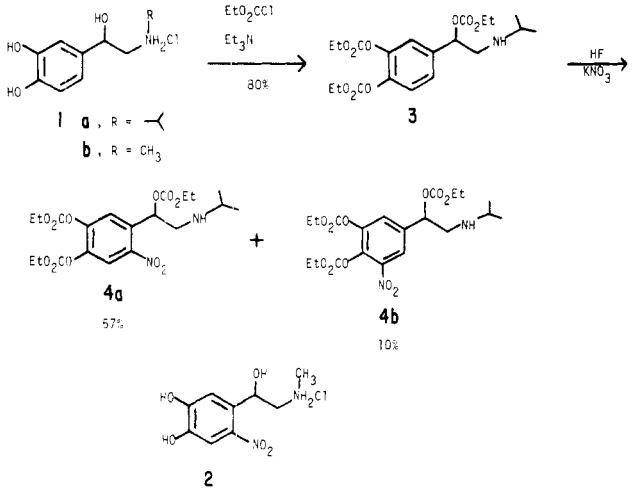
A number of possible approaches to the ring-aminated isoproterenol derivative 4-[1-hydroxy-2-[(1-methylethyl)amino]ethyl]-5-amino-1,2-benzenediol have been attempted. Of these, the total synthesis using the commercially available starting material 6-nitropiperonal proved to be the optimum route. This compound was first converted to 2-nitro-4,5-dihydroxybenzaldehyde and the side chain of the molecule then constructed via conversion to the epoxide with dimethylsulfonium methylide and treatment with isopropylamine. Selective reduction of the aromatic nitro group was achieved by room temperature hydrogenation over platinum at atmospheric pressure. The synthesis of the acetylamino derivative and the extension of this approach to peptide conjugates of this drug are discussed.

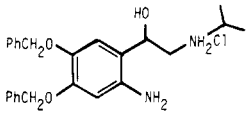
In connection with our studies on novel polymer–drug conjugates, we found it necessary to synthesize ring-aminated analogues of the catecholamine, isoproterenol (**1a**). An examination of the literature revealed that the only derivative of a catecholamine containing a ring nitrogen was 6-nitroepinephrine (**2**), prepared by the action of nitrous acid on epinephrine (**1b**).[1] This reaction failed in our hands with isoproterenol (**1a**) when we either followed conditions exactly or attempted numerous minor variations of the reported reaction parameters. This failure is not surprising, considering the known instability of catecholamines toward oxidation.[2]

In order to circumvent the problem of oxidation, we thought that protection of isoproterenol (**1a**) followed by nitration would yield the desired, ring-derivatized, protected isoproterenol. We found that carboethoxylation of **1a** with ethyl chloroformate and triethylamine in ethyl acetate gave **3** in good yield and also that nitration of **3**



in anhydrous HF with KNO_3 afforded a mixture of ring-nitrated tris(carboethoxy)isoproterenols **4a** and **4b**. Unfortunately we were unable to make use of **4a** either by reduction of the nitro group or by hydroxyl deprotection (an inseparable, complex mixture was obtained in each case). We therefore turned our attention to the total synthesis of the target molecule bis(benzyloxy)-6-aminoisoproterenol hydrochloride (**5**).

A readily available substance which contains the correct ring substitution for the construction of **5** is 6-nitropiperonal (**6**) which can be obtained smoothly by nitration of piperonal.[3] We initiated our synthesis by exchanging the methylenedioxy group of **6** with benzyl ethers before elaboration of the aldehyde function to a vicinal hydroxy amine, since the conditions for the removal of the methylenedioxy groups are quite vigorous. Conversion of piperonal to 3,4-dihydroxybenzaldehyde has been reported to occur with $AlCl_3$ in chlorinated solvents.[4] When this procedure was applied to **6**, an incomplete reaction was observed leading to a nearly quantitative yield of the chloro ether **7**. We were able to cleave the chloro ether **7** to the catechol **8** in 87% yield by treatment of **7** with THF and aqueous HCl (trace of NaI) (see Scheme I).



5

Benzyl ether formation in the case of 3,4-dihydroxybenzaldehyde can be carried out by refluxing the catechol in EtOH with an excess of base and benzyl chloride to give the corresponding bis(benzyloxy)benzaldehyde.[5] This procedure, when applied to 2-nitro-4,5-dihydroxybenzaldehyde (**8**), does not give the expected ether **10** directly. The diethyl acetal **9** is the main product which can be transformed trivially to the bisether **10**.

If one carries out the same reaction at ambient temperature, the bisether **10** is obtained directly in about 70% yield. We have speculated that a possible mechanism for the formation of acetal **9** from **8** may be as shown in Scheme II (see Experimental Section for further details). We base this mechanism on the fact that alcohols are known to undergo conjugate addition to systems similar to **8a**.[6]

With the bisether **10** in hand, we were faced with the task of constructing the side chain and then reducing the nitro group. A number of good methods are available for the preparation of catecholamine-type side chains from aryl aldehydes,[5,7] but most of these procedures are laborious. We decided to take advantage of the presence of the ortho nitro substituent in planning our side-chain

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(3) J. Ekeley and M. Klemme, *J. Am. Chem. Soc.*, **50**, 2711 (1928).
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(7) C. M. Sutter, *J. Am. Chem. Soc.*, **66**, 749 (1944); G. Bruckner, *Ber.*, **76B**, 466 (1943); L. Pichat and M. Audinot, *Bull. Soc. Chim. Fr.*, 2255 (1961); D. Howton, J. Mead, and W. Clark, *J. Am. Chem. Soc.*, **77**, 2896 (1955); D. Enders, R. Pieter, B. Renger, and D. Seeback, *Org. Synth.* **58**, 113 (1978); L. Birkofer and H. Dickopp, *Chem. Ber.*, **102**, 14 (1969).

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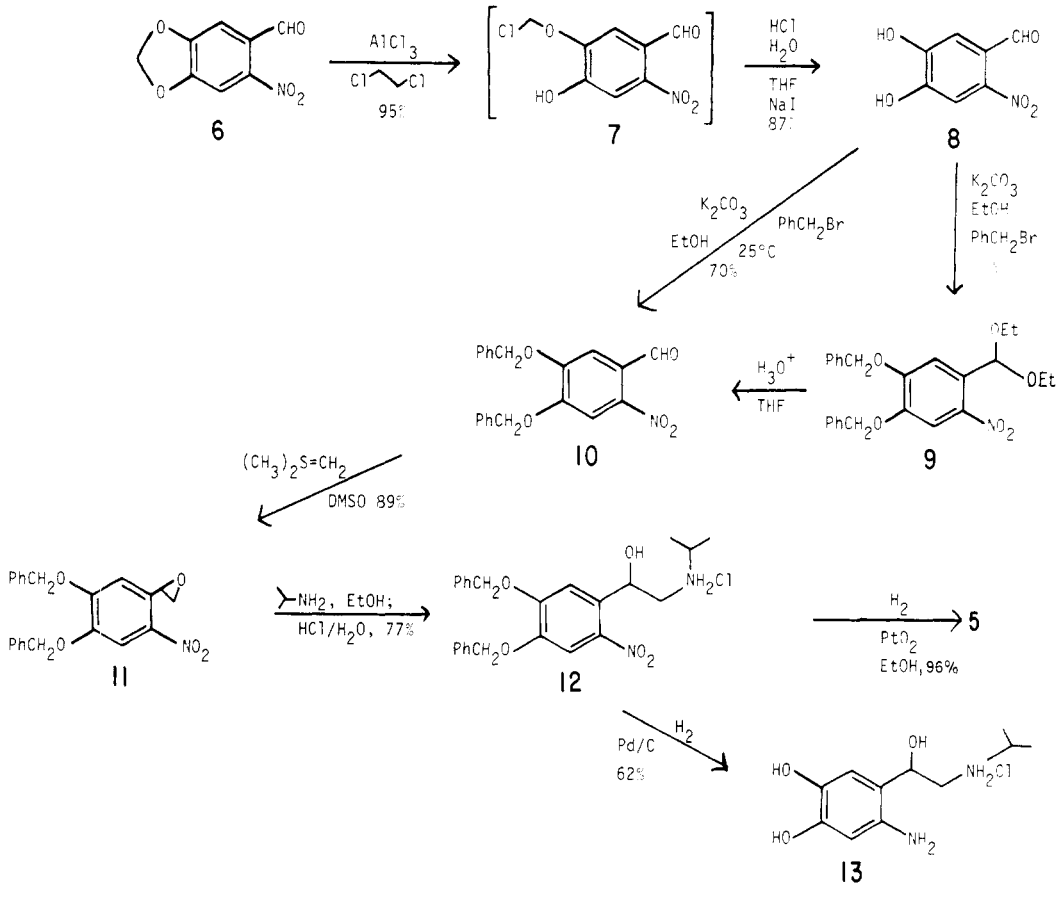
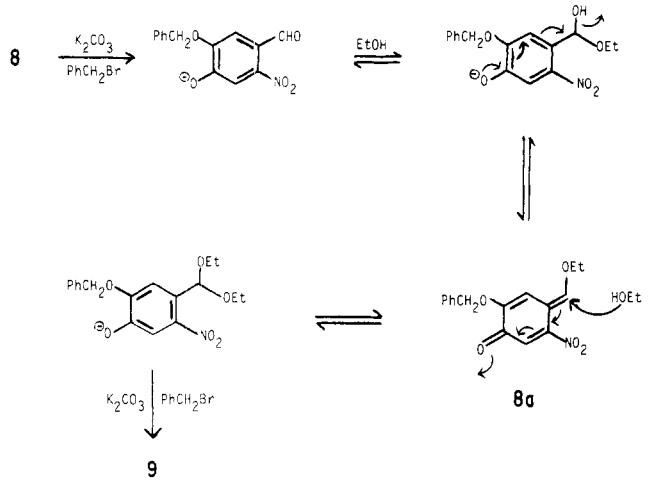
Scheme I



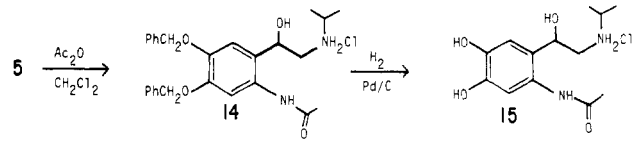
Scheme II



construction. Corey's method of epoxide formation utilizing dimethylsulfonium methylide[8] was applied to **10**, and the epoxide **11** was isolated in 89% yield. Opening of the epoxide of **11** with isopropylamine in ethanol[9] followed by acidification of the reaction mixture gave a 77% yield of bis(benzyloxy)-6-nitroisoproterenol hydrochloride (**12**). Normally styrene epoxides react with alkylamines by an S_N2 process (attack at the secondary epoxide carbon) as well as by an S_N1 process[10] (attack at the benzylic carbon after solvolysis). In our case no product derived from an S_N1 reaction was observed. This is probably due to the effect of the ortho nitro substituent on cation formation at the benzylic position.

We then investigated the selective reduction of the nitro group of **12** in the presence of the benzyl ethers with the goal of preparing **5**. Treatment of **12** with $FeSO_4$ and NH_4OH[11] gave the free base derived from **5** in fair (47%) yield. We were not satisfied with this result and decided to explore reduction of **12** by hydrogenation. Treatment of **12** with H_2 over 10% Pd/C at standard temperature and pressure gave a mixture of compounds composed, in part, of **5**. Exhaustive treatment of **12** under the same conditions afforded 6-aminoisoproterenol hydrochloride (**13**) in 62% yield. However, careful hydrogenation of **12** over Pt at standard temperature and pressure gave **5** cleanly (96% yield). We are currently examining the generality of selective reductions of aryl nitro groups in the presence of aryl benzyl ethers with Pt/H_2.

We have found that acylation of **5** with Ac_2O (no base) in CH_2Cl_2 gave the amide **14** in 84% yield and that hydrogenation of **14** gave 6-(acetylamino)isoproterenol hydrochloride (**15**). We have prepared a series of acyl derivatives of 6-aminoisoproterenol hydrochloride from **5** and have found significant biological activity in vitro (these results will be disclosed elsewhere). We are currently extending the above results to the synthesis of peptide



(8) E. J. Corey and M. Chaykovsky, *J. Am. Chem. Soc.*, **87**, 1353 (1965).
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conjugates of 6-aminoisoproterenol hydrochloride (13) in which the peptide–drug linkage is an acyl bond to the 6-amino group of the drug. There is evidence which indicates that these conjugates will have pronounced biological activity[12-15] and perhaps unique medicinal value.

Experimental Section

Melting points were taken on a Thomas-Hoover capillary melting-point apparatus; they are uncorrected. IR spectra were recorded on a Perkin-Elmer 180 spectrophotometer. High-resolution ^1H NMR spectra were obtained in the Fourier transform mode by using a Varian HR-220 spectrometer at the University of California, San Diego. All chemical shifts are reported in parts per million downfield from Me_4Si. Mass spectra were determined on an LKB-9000A mass spectrometer. All elemental analyses were performed by Galbraith Laboratories, Knoxville, TN.

Tris(carboethoxy)isoproterenol (3). To a dry 100-mL round-bottomed flask equipped with magnetic stirring, a 50-mL addition funnel, and a nitrogen inlet were added isoproterenol hydrochloride (1.0 g, 4 mmol), ethyl chloroformate (3 mL, 30 mmol), and dry EtOAc (25 mL). The addition funnel was charged with dry EtOAc (25 mL) and dry TEA (3 mL, 25 mmol). The TEA solution was added dropwise over a 1-h period at room temperature under N_2. The mixture was stirred for 29 h at room temperature and then added to 100 mL of saturated $NaHCO_3$ (aqueous). EtOAc (100 mL) was added. The aqueous phase was extracted with EtOAc (2 × 50 mL), the organic phases were combined and washed with H_2O (3 × 75 mL), dried over $MgSO_4$, filtered, and rotary evaporated, giving a thick oil which was placed under high vacuum overnight. Chromatography on 70 g of silica gel with 25% EtOAc/hexane gave **3** as a clear glass (1.1 g, 64% yield): IR (film) 3450, 1785, 1700 cm^{-1}; NMR (CCl_4) δ 7.24 (s, 1 H), 7.19 (AB, 2 H, J = 8 Hz), 4.76 (s, 1 H), 4.26 (AB, 6 H, J = 6 Hz), 4.13 (m, 2 H), 3.26 (m, 1 H), 1.42 (t, 6 H, J = 6 Hz), 1.30 (t, 3 H, J = 6 Hz), 1.10 (dd, 6 H, J = 7 Hz); mass spectrum, m/e 427 (M^+), 409, 381, 337, 311.

Tris(carboethoxy)-6-nitroisoproterenol (4a) and Tris(carboethoxy)-5-nitroisoproterenol (4b). In a Teflon reaction vessel equipped with a Teflon stirring bar were placed tris(carboethoxy)isoproterenol (3) (220 mg, 0.515 mmol) and KNO_3 (220 mg, 2.18 mmol). Anhydrous HF was distilled into the reaction vessel at liquid N_2 temperature. The reaction vessel was allowed to warm to 0 °C and was stirred for 90 min. The HF was evaporated, leaving a yellowish mass. EtOAc (100 mL) and saturated $NaHCO_3$ (aqueous) (100 mL) were added. The aqueous phase was extracted with EtOAc (2 × 40 mL), and the organic phases were combined and washed with 100 mL of saturated NaCl (aqueous). The organic phase was dried over $MgSO_4$ and filtered, and the solvent was removed by rotary evaporation. The resulting yellow oil was chromatographed on a preparative TLC plate with 1:1 EtOAc–hexanes. Two products were obtained; the higher R_f material, tris(carboethoxy)-6-nitroisoproterenol (**4a**), weighed 137 mg (56% yield) and was a light yellow oil: IR (film) 770, 840, 1540, 1650, 1700, 1775, 3450 cm^{-1}; NMR (CCl_4) δ 8.21 (s, 1 H), 7.72 (s, 1 H), 6.82 (t, 1 H, J = 7 Hz), 4.23 (m, 7 H), 3.72 (d, 2 H, J = 6 Hz), 1.2 (m, 15 H); mass spectrum, m/e 472 (M^+), 456, 427, 411, 397, 382.

The lower R_f material, tris(carboethoxy)-5-nitroisoproterenol (**4b**), weighed 26 mg (10% yield): IR (film) 1540, 1650, 1700, 1775, 3450 cm^{-1}; NMR (CCl_4) δ 8.03 (s, 1 H), 7.90 (s, 1 H), 5.5 (t, 1 H, J = 7 Hz), 4.3 (m, 7 H), 3.60 (d, 2 H, J = 6 Hz), 1.25 (m, 15 H); mass spectrum, m/e 472 (M^+), 456, 409, 391.

5-(Chloromethoxy)-4-hydroxy-2-nitrobenzaldehyde (7). A dry 25-mL round-bottomed flask equipped with a magnetic stirring bar and nitrogen inlet was weighed and placed in a glove box. $AlCl_3$ was placed in the flask (2.25 g, 0.0168 mol). The flask was placed under N_2 in the hood and dry 1,2-dichloroethane was added (15 mL). 6-Nitropiperonal (obtained from Aldrich; 1 g, 0.005 mol) was then added in 1,2-dichloroethane (7 mL) to the $AlCl_3$ suspension. A dark red color formed immediately. The mixture was stirred for an additional 2 h at 25 °C and then added to cold water (100 mL). The mixture was extracted with EtOAc (3 × 50 mL), and the combined organics were washed with saturated NaCl (aqueous) (3 × 50 mL), dried over Na_2SO_4, filtered, and rotary evaporated. The resulting dark solid was recrystallized from EtOAc–hexanes to give 1.10 g (93.2% yield) of green yellow crystals: mp 159–161 °C; NMR (Me_2SO-d_6) δ 6.34 (s, 2 H), 7.68 (s, 1 H), 7.82 (s, 1 H), 10.32 (s, 1 H); mass spectrum, m/e 231 (M^+), 229, 163.

4,5-Dihydroxy-2-nitrobenzaldehyde (8). The crude chloro ether **7** from above was taken into THF (35 mL) and added to a 100-mL round-bottomed flask equipped with magnetic stirring, a reflux condenser, and a N_2 inlet. Aqueous HCl (6 N, 10 mL) was added, followed by powdered KI (50 mg). The mixture was refluxed until reaction was complete by TLC (approximately 6 h) and was then added to water (150 mL). The mixture was extracted with EtOAc (4 × 50 mL). The combined organic phase was washed with H_2O (2 × 70 mL) and then with saturated NaCl (aqueous) (2 × 70 mL). The organic phase was dried over molecular sieves and filtered, and the solvent was removed by rotary evaporation. The resulting dark solid was recrystallized from ether to give 0.68 g of yellow crystals, mp 199–202 °C (72% yield). The mother liquors were chromatographed quickly on silica gel and the product was recrystallized from ether to give an additional 149 mg. The overall yield was 87.9%, based on 6-nitropiperonal: IR (Nujol) 750, 910, 1060, 1170, 1200, 1325, 1350, 1450, 1540, 1590, 1620, 1680, 3450 cm^{-1}; NMR (Me_2SO-d_6) δ 7.2 (s, 1 H), 7.5 (s, 1 H), 10.18 (s, 1 H), 10.6 (br s, 2 H); mass spectrum, m/e 183 (M^+), 182, 153, 152, 138, 135, 106. Anal. Calcd: C, 45.90; H, 2.73; N, 7.65. Found: C, 45.91; H, 3.00; N, 7.55.

4,5-Bis(benzyloxy)-2-nitrobenzaldehyde Diethyl Acetal (9). In order to substantiate our speculated mechanism for the formation of the diethyl acetal **9** from 2-nitro-4,5-dihydroxybenzaldehyde (8), a small-scale reaction was carried out to isolate, purify, and characterize this intermediate. To a 25-mL round-bottomed flask equipped with magnetic stirring, a reflux condenser, and a N_2 inlet were added the catechol 8 (140 mg, 0.76 mmol), pulverized anhydrous K_2CO_3 (320 mg, 2.3 mmol), benzyl bromide (0.28 g, 2,36 mmol), NaI (~5 mg), and ethanol (2 mL). The mixture was refluxed for 6.5 h, stirred overnight at 25 °C, then added to water, and extracted with ether (3 × 5 mL). The ether extract was dried over $MgSO_4$, filtered, and rotary evaporated. The product was chromatographed on a preparative TLC plate (9:1 hexanes–EtOAc) and the major band with the highest R_f eluted to give an oil (100 mg, 30% yield): IR (KBr) 1059, 1109, 1158, 1169, 1215, 1276, 1336, 1454, 1524, 1579 cm^{-1}; NMR ($CDCl_3$) δ 1.15 (t, 6 H), 3.44 (q, 2 H), 3.57 (q, 2 H), 5.13 (s, 2 H), 5.21 (s, 2 H), 5.93 (s, 1 H), 7.32 (m, 11 H), 7.49 (s, 1 H); mass spectrum, m/e 437 (M^+), 422, 421, 392, 346, 107, 103, 91, 45; exact mass calcd for $C_{25}H_{27}NO_6$ 437.1838, found 437.1818. A small amount of sample was placed in an NMR tube and dissolved in CD_3CN, an NMR spectrum was recorded, and then an excess of DCl (from a 1 M solution of DCl in D_2O) was added and allowed to react for 30 min. A new peak appeared at 10.2 ppm, indicating the presence of the aldehyde, and the two distinct methylene quartets of the diethyl acetal collapsed. Careful integration showed that 2 mol of ethanol had formed.

4,5-Bis(benzyloxy)-2-nitrobenzaldehyde (10). To a 250-mL round-bottomed flask equipped with magnetic stirring, a reflux condenser, and a N_2 inlet were added the catechol 8 (1.83 g, 0.01 mol), pulverized anhydrous K_2CO_3 (4.2 g, 0.03 mol), benzyl bromide (8.55 g, 0.05 mol), and ethanol (100 mL). The mixture was refluxed until reaction was complete by TLC (approximately 5–6 h) and then cooled to ambient temperature. An equal volume of aqueous HCl (6 N, 100 mL) was carefully added to the reaction mixture and the resulting suspension stirred at room temperature for 30 min. The crystals were collected by filtration and placed under high vacuum overnight. The solid was then recrystallized from EtOAc–hexanes to give yellow crystals (2.5 g, 70% yield): mp 137.5–138.5 °C; IR (Nujol) 700, 740, 980, 1060, 1180, 1230, 1310, 1390, 1540, 1580, 1610, 1705 cm^{-1}; NMR ($CDCl_3$) δ 5.25 (s,

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4 H), 7.45 (br s, 11 H), 7.64 (s, 1 H), 10.34 (s, 1 H); mass spectrum m/e 363 (M^+), 333, 272, 256, 242, 181. Anal. Calcd: C, 69.42; H, 4.68; N, 3.86. Found: C, 69.28; H, 4.86; N, 3.75.

4,5-Bis(benzyloxy)-2-nitroepoxystyrene (11). To a dry 250-mL round-bottomed 3-necked flask equipped with magnetic stirring, a stopper, septum, and argon inlet was added NaH (0.60 g of a 50% oil dispersion, 12.3 mmol). The oil was removed with dry hexanes. Dry, distilled Me_2SO was added (70 mL) via syringe and the suspension was heated at 60 °C for 1 h. The resulting greenish solution was diluted with dry THF (80 mL) added via syringe. The above solution was cooled to 0 °C and Me_3SI (2.7 g, 12.3 mmol) in dry Me_2SO (50 mL) was added slowly via syringe over a 15-min period. After a few minutes, a solution of the aldehyde **10** (4.5 g, 12.4 mmol) in dry THF (40 mL) was added, at a fast drip rate, to the sulfur ylide. The dark purple mixture was stirred until reaction was complete by TLC (approximately 15 min at 0 °C) and then added to water (1 L). The mixture was extracted with ether (3 × 200 mL), and the organic layers were combined, washed with H_2O (5 × 100 mL), dried over $MgSO_4$, and filtered, and the solvent was removed by rotary evaporation. The resulting oil was quickly passed through a pad of silica gel with ether, the solvent was removed, and the solid was purified by preparative high-performance LC (25% EtOAc–hexanes). The product (yellow crystals), mp 87.5–89 °C, weighed 4.18 g (90% yield): IR (Nujol) 750, 795, 880, 910, 1010, 1060, 1080, 1220, 1290, 1340, 1395, 1420, 1460, 1530, 1590, 1620, 2940, 3075 cm^{-1}; NMR (CCl_4) δ 7.64 (s, 1 H), 7.30 (br s, 10 H), 6.95 (s, 1 H), 5.09 (d, 4 H), 4.31 (t, 1 H, X part of ABX), 3.10 (t, 1 H, B part of ABX), 2.40 (q, 1 H, A part of ABX); mass spectrum, m/e 377 (M^+), 361, 360, 333, 287, 270, 256, 242. Anal. Calcd: C, 70.02; H, 5.07; N, 3.71. Found: C, 70.00; H, 5.18; N, 3.73.

4-[1-Hydroxy-2-[(1-methylethyl)amino]ethyl]-5-nitro-1,2-bis(benzyloxy)benzene Hydrochloride (12). To a 100-mL round-bottomed flask equipped with magnetic stirring, a reflux condenser, and an argon inlet were added the epoxide **11** (1 g, 2.64 mmol) and ethanol (40 mL). Isopropylamine was then added (10 mL) and the mixture heated at 80 °C until reaction was complete by TLC (approximately 8 h). The solvent was removed by rotary evaporation and the product recrystallized from EtOAc–hexanes, giving light yellow crystals of 4-[1-hydroxy-2-[(1-methylethyl)amino]ethyl]-5-nitro-1,2-bis(benzyloxy)benzene: mp 177–178 °C; 0.85 g; 73.5% yield; IR ($CHCl_3$) 725, 760, 940, 1110, 1250, 1310, 1370, 1555, 1615, 1650 cm^{-1}; NMR ($CDCl_3$) δ 1.05 (d, 6 H, J = 6 Hz), 2.0–3.3 (m, 3 H), 4.0 (br s, 2 H, washed out with D_2O), 5.11 (s, 2 H), 5.17 (1 H), 5.23 (s, 2 H), 7.35 (m, 11 H), 7.65 (s, 1 H); mass spectrum (chemical ionization), m/e 437 (M^+), 438 (M + 1), 403, 401, 390, 347, 334, 295, 234. Anal. Calcd: C, 68.79; H, 6.46; N, 6.42. Found: C, 68.67; H, 6.34; N, 6.30.

Alternatively the crude material obtained above (after rotary evaporation) was redissolved in ethanol (20 mL) and treated with aqueous HCl (6 N, 20 mL). A flocculent precipitate formed which was filtered and placed under high vacuum. The solid was recrystallized from ethanol to give crystals of **12**: mp 193–195 °C; 0.96 g; 77% yield; NMR (Me_2SO-d_6) δ 1.26 (d, 6 H, J = 6 Hz), 2.1–3.5 (m, 5 H), 5.27 (br s, 4 H), 5.5 (sh, 1 H), 7.30 (br s, 11 H), 7.70 (s, 1 H).

4-[1-Hydroxy-2-[(1-methylethyl)amino]ethyl]-5-amino-1,2-bis(benzyloxy)benzene Hydrochloride (5). To a 50-mL round-bottomed flask equipped with magnetic stirring were added PtO_2 (100 mg) and pure ethanol (25 mL). Hydrogenation of the mixture gave a black suspension to which was added the nitro compound **12** (0.80 g, 1.69 mmol). The suspension of **12** was stirred under 1 atm of H_2 at ambient temperature until the theoretical amount of H_2 was taken up (approximately 4 h, 130 mL). Filtration and slow removal of the solvent under vacuum resulted in the formation of crystals. Alternatively the filtrate can be treated directly with ether and the resulting crystals of **5** collected in two crops, giving 0.72 g (96% yield): mp 150–151 °C; NMR (Me_2SO-d_6) δ 1.24 (d, 6 H, J = 6 Hz), 2.2–3.6 (m, 7 H), 4.94 (s, 2 H), 5.01 (s, 2 H), 5.05 (sh, 1 H), 6.43 (s, 1 H), 6.90 (s, 1 H), 7.35 (br s, 10 H); mass spectrum, m/e 406 (M^+ – HCl), 334, 329, 273, 238, 210. Anal. Calcd: C, 67.78; H, 7.05; N, 6.32. Found: C, 67.76; H, 7.01; N, 6.27.

The free base derived from **5** by neutralization had the following: NMR ($CDCl_3$) δ 1.05 (d, 6 H, J = 6 Hz), 2.82 (m, 2 H), 3.48 (septet, 1 H, J = 6 Hz), 4.53 (t, 1 H, J = 7 Hz), 5.01 (s, 2 H), 5.07 (s, 2 H), 6.27 (s, 1 H), 6.72 (s, 1 H), 7.35 (m, 10 H); mass spectrum, m/e 406 (M^+), 388, 374, 360, 346, 334, 329.

4-[1-Hydroxy-2-[(1-methylethyl)amino]ethyl]-5-amino-1,2-benzenediol Hydrochloride *d*-Tartarate Ethanolate (13). To a 100-mL round-bottomed flask equipped with magnetic stirring were added the nitro compound **5** (0.5 g, 1.06 mmol) and degassed ethanol (40 mL). Pd/C (10%) was then added (50 mg) and the mixture hydrogenated at 25 °C under 1 atm of H_2 for 48 h. Absolutely all manipulations were carried out under argon. The mixture was filtered under Ar through Celite into a 100-mL flask equipped with magnetic stirring. *d*-Tartaric acid was added (150 mg, 1.06 mmol) and the mixture stirred for 4 h. The solvent was reduced slowly under vacuum to $^1/_3$ the initial volume. A pink crystalline solid separated and was collected by filtration under argon and dried under high vacuum to give 300 mg (62% yield): mp 75–80 °C (desolvation); NMR (Me_2SO-d_6) δ 6.92 (br s, 7 H), 6.65 (s, 1 H), 6.18 (s, 1 H), 4.95 (d, 1 H), 4.28 (s, 2 H), 3.45 (q, 2 H, J = 7.5 Hz), 3.32 (septet, 1 H, J = 6.2 Hz), 2.93 (m, 2 H), 1.21 (t, 6 H, J = 6.2 Hz), 1.06 (t, 3 H, J = 7.5 Hz). Anal. Calcd: C, 44.50; H, 6.81; N, 6.10; Cl, 7.73. Found: C, 44.34; H, 6.80; N, 6.10; Cl, 7.60.

4-[1-Hydroxy-2-[(1-methylethyl)amino]ethyl]-5-(acetylamino)-1,2-bis(benzyloxy)benzene Hydrochloride (14). To a 50-mL round-bottomed flask equipped with magnetic stirring and a nitrogen inlet were added the alcohol amine **5** (300 mg, 0.678 mmol), CH_2Cl_2 (8 mL), and $CHCl_3$ (2 mL). The mixture was cooled to 0 °C and Ac_2O (0.075 mL, 0.78 mmol) was added. The mixture was stirred for 1 h at 0 °C, 3 h at 25 °C, and then –20 °C overnight. The solvent was removed by rotary evaporation. The resulting solid was then chromatographed on two preparative TLC plates with a mixture of $CHCl_3$ (95%), CH_3OH (5%), and concentrated HCl (0.1%), giving 277 mg of solid (84.4% yield): NMR ($CDCl_3$) δ 9.25 (br s, 1 H), 8.89 (s, 1 H), 8.37 (br s, 1 H), 7.31 (m, 10 H), 7.18 (s, 1 H), 7.06 (s, 1 H), 5.75 (br s, 1 H), 5.39 (d, 1 H, J = 8.8 Hz), 5.04 (s, 2 H), 5.02 (s, 2 H), 3.23 (septet, 1 H, J = 6 Hz), 2.96 (sextet, 2 H, J = 8.8 Hz), 2.19 (s, 3 H), 1.29 (d, 6 H, J = 6 Hz). Peaks at δ 9.25, 8.89, 8.37, and 5.75 disappeared on addition of D_2O.

4-[1-Hydroxy-2-[(1-methylethyl)amino]ethyl]-5-(acetylamino)-1,2-benzenediol Hydrochloride Ethanolate (15). The procedure for the preparation of **13** was followed exactly, utilizing 277 mg of **14** (0.57 mmol), ethanol (25 mL), and 10% Pd/C (20 mg). The resulting light pink solid weighed 124 mg, (71%) yield): mp 70–75 °C (softening); NMR (Me_2SO-d_6) δ 7.75 (s, 1 H), 6.95 (s, 2 H), 5.16 (d, 1 H, J = 8.8 Hz), 3.58 (q, 2 H, J = 7 Hz), 3.35 (septet, 1 H, J = 6 Hz), 3.03 (sextet, 2 H, J = 8.8 Hz), 2.18 (s, 3 H), 1.35 (d, 6 H, J = 6 Hz), 1.18 (t, 3 H, J = 7 Hz). Anal. Calcd: C, 48.30; H, 7.20. Found: C, 48.7; H, 7.60.

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Registry No. 1a, 51-30-9; **3**, 73635-69-5; **4a**, 73635-70-8; **4b**, 73635-71-9; **5**, 73635-72-0; **5** (free base), 73635-73-1; **6**, 712-97-0; **7**, 73635-74-2; **8**, 73635-75-3; **9**, 73635-76-4; **10**, 18002-41-0; **11**, 73635-77-5; **12**, 73635-78-6; **12** (free base), 73635-79-7; **13**, 73651-33-9; **14**, 73635-80-0; **15**, 73635-81-1; isopropylamine, 75-31-0; $Me_2S{=}CH_2$, 40651-06-7.