1-Methyl-3-(phenylsulfonyl)bicyclo[3.3.1]nonan-9-one: obtained as an approximate 1:1 mixture of endo and exo isomers as determined from the NMR spectrum by integration of the two CH_3 singlets at δ 0.98 and 1.00; mp 103–106 °C (benzene–hexane, 5:2), NMR ($CDCl_3$) δ 7.50–8.08 (m, 5), 3.87–4.52 (m, 0.5), 1.40–3.20 (m, 11.5), 0.98 and 1.00 (two s, total 3); mass spectrum, *m/e* (relative intensity) 123 (15), 133 (45), 143 (30), 151 (100), 152 (25), 293 (42).

Anal. Calcd for $C_{16}H_{20}O_3S$: C, 65.74; H, 6.90; S, 10.95. Found: C, 65.64; H, 6.90; S, 10.97.

8-(Phenylsulfonyl)bicyclo[4.3.1]decan-10-one: obtained as an approximate 1:1 mixture of endo and exo isomers by TLC analysis (2% acetone in methylene chloride); mp 127–129 °C (benzene–hexane, 1:1); NMR ($CDCl_3$) δ 7.52–8.04 (m, 5), 3.38–4.00 (m, 1), 2.62–3.07 (m, 2), 1.25–2.30 (m, 12); mass spectrum, *m/e* (relative intensity) 133 (18), 143 (15), 151 (73), 171 (13), 293 (100), 294 (29).

Anal. Calcd for $C_{16}H_{20}O_3S$: C, 65.74; H, 6.90; S, 10.94. Found: C, 65.55; H, 6.92; S, 10.90.

***N*-(Ethoxycarbonyl)-3-aza-7-(phenylsulfonyl)bicyclo[3.3.1]nonan-9-one**: obtained as a 2:1 mixture of endo/exo isomers as determined from the NMR spectrum by integration of the OCH_2 and CH_3 resonances at δ 4.12 and 4.17 (OCH_2) and 1.24 and 1.28 (CH_3); mp 138–144 °C (benzene–hexane, 1:1); NMR ($CDCl_3$) δ 7.50–7.96 (m, 5), 4.40 (br d, 2), [4.12 (q, J = 7 Hz) and 4.17 (q, J = 7 Hz), total 2], 1.82–3.47 (m, 9), [1.24 (t, J = 7 Hz) and 1.28 (t, J = 7 Hz), total 3]; mass spectrum, *m/e* (relative intensity) 210 (100), 306 (50), 352 (70), 353 (13).

Anal. Calcd for $C_{17}H_{21}NO_5S$: C, 58.11; H, 6.02; N, 3.99; S, 9.11. Found: C, 58.04; H, 6.00; N, 3.97; S, 9.08.

Acknowledgment. We thank Dr. Robert Ireland of the California Institute of Technology and Dr. Gary Flynn of the Merrell Dow Research Institute—Cincinnati Center for helpful discussions.

Registry No. **1d**, 90838-29-2; **1e**, 90838-30-5; **6**, 931-59-9; **7**, 107-05-1; **8**, 90838-43-0; **9**, 90838-44-1; **10**, 90838-45-2; **13**, 90838-48-5; **15**, 90838-49-6; PhSH, 108-98-5; 3-(phenylthio)-8-oxobicyclo[3.2.1]oct-2-ene, 90838-31-6; 8-(phenylthio)-10-oxobicyclo[4.3.1]dec-7-ene, 90838-32-7; 1-methyl-3-(phenylthio)-9-oxobicyclo[3.3.1]non-2-ene, 90838-33-8; 1-methyl-3-(phenylthio)-9-oxobicyclo[3.3.1]non-3-ene, 90857-61-7; *N*-(ethoxycarbonyl)-3-aza-7-(phenylthio)-9-oxabicyclo[3.3.1]non-6-ene, 90838-34-9; *endo*-3-(phenylsulfonyl)bicyclo[3.2.1]octan-8-one, 90838-35-0; *exo*-3-(phenylsulfonyl)bicyclo[3.2.1]octan-8-one, 90838-36-1; *endo*-8-(phenylsulfonyl)bicyclo[4.3.1]decan-10-one, 90838-37-2; *exo*-8-(phenylsulfonyl)bicyclo[4.3.1]decan-10-one, 90838-38-3; *endo*-3-(phenylsulfonyl)bicyclo[3.3.1]nonan-9-one, 90838-39-4; *exo*-3-(phenylsulfonyl)bicyclo[3.3.1]nonan-9-one, 90838-40-7; *endo*-*N*-(ethoxycarbonyl)-3-aza-7-(phenylsulfonyl)-bicyclo[3.3.1]nonan-9-one, 90838-41-8; *exo*-*N*-(ethoxycarbonyl)-3-aza-7-(phenylsulfonyl)bicyclo[3.3.1]nonan-9-one, 90838-42-9; *endo*-1-methyl-3-(phenylsulfonyl)bicyclo[3.3.1]nonan-9-one, 90838-46-3; *exo*-1-methyl-3-(phenylsulfonyl)bicyclo-[3.3.1]nonan-9-one, 90838-47-4; 2-[2-(phenylsulfinyl)-2-propenyl]cyclopentanone, 90838-50-9; 2-[2-(phenylsulfinyl)-2-propenyl]cycloheptanone, 90838-51-0; *cis*-2-methyl-6-[2-(phenylsulfinyl)-2-propenyl]cyclohexanone, 90838-52-1; *trans*-2-methyl-6-[2-(phenylsulfinyl)-2-propenyl]cyclohexanone, 90898-46-7; *N*-(ethoxycarbonyl)-3-[2-(phenylsulfinyl)-2-propenyl]-4-piperidone, 90838-53-2; *N*-chlorosuccinimide, 128-09-6; 1-(1-cyclohexenyl)pyrrolidine, 1125-99-1; 1-(1-cyclopentenyl)-pyrrolidine, 7148-07-4; cyclopentanone, 120-92-3; cyclohexanone, 108-94-1; cycloheptanone, 502-42-1; 2-methylcyclohexanone, 583-60-8; ethyl 4-oxopiperidine-1-carboxylate, 29976-53-2.

The Synthesis of Isotopically Labeled β-Adrenergic Agents by Reductive Amination: Unexpected Site of Deuterium Incorporation

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The reduction of imines derived from the condensation of (*R*)-norepinephrine and certain methyl ketones with D_2 over a Pt catalyst leads to the formation of deuterium labeled products in which the deuterium is located exclusively in the methyl substituent. The absence of any detectable label at the methine position argues in favor of a "directed" process in which a methyl proton is the source for the methine CH.

A novel route to potential tissue specific β-adrenergic agonists involves the synthesis of N-substituted norepinephrine derivatives in which the catecholamine moiety is connected through an alkyl spacer arm to a carrier group. Compounds **6** and **7** are examples of such agonists which have been tested in both in vitro and in vivo assays with encouraging results.[1-3] As part of our studies designed to evaluate the pharmacological and metabolic properties of these N-substituted norepinephrine derivatives we required tritium labeled products of high specific activity (10 Ci/mmol). Compounds **6** and **7** have been prepared by $NaCNBH_3$ reduction and catalytic hydrogenation of the corresponding imines **4** and **5** which in turn are derived by condensation of norepinephrine (**1**) and the methyl ketones **2** and **3** (Figure 1).[1] Previous attempts to prepare radiolabeled **7** from commercially available tritium labeled norepinephrine (benzyl label, 5–15 Ci/mmol) were only partly successful in our hands since the yields of the desired amines were low (2–22%) due to the small scale reaction conditions that were required.[4]

In an attempt to overcome these problems, we elected to explore the possibility of introducing the label by catalytic tritiation of the imines **4** and **5**. Before proceeding with reductions with carrier free tritium, well defined reaction conditions had to be established. Additionally, since the final labeled products are to be used in pharmacokinetic and metabolic profiling studies, it was important to determine both the specific activity and the location of the

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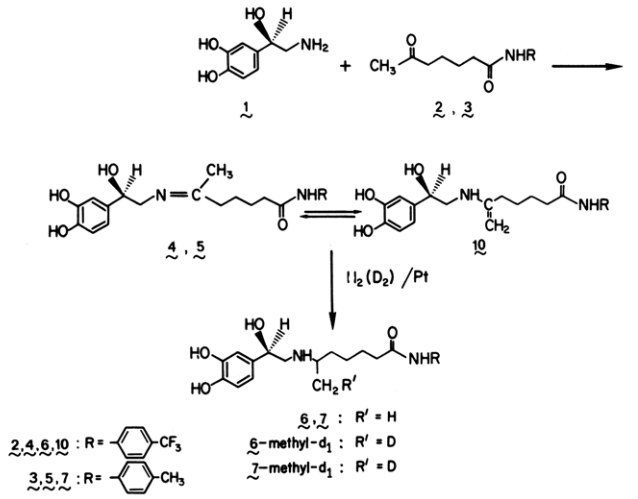


Figure 1. Scheme for the synthesis of norepinephrine derivatives **6** and **7** and the corresponding monodeuterated analogues.

label in the final products. Therefore, we carried out a series of model experiments on imines **4** and **5** employing carrier free deuterium gas.

In order to estimate the percent deuterium incorporation in the final products, we required a sensitive and accurate analytical method that could be applied to these polar and moderately unstable catecholamine derivatives. Although electron-ionization and chemical-ionization mass spectral analyses have been performed on various catecholamines, these methods require multiple derivatization steps and rarely yield intense molecular ions.[5-7] Consequently, we turned our attention to the recently described sputtering-ion mass spectrometric techniques, fast atom bombardment (FAB), and liquid secondary ion (LSI) mass spectrometry (MS).[8,9] Both FABMS (which employs a neutral atom beam such as Xe) and LSIMS (which employs a Cs^+ primary ion beam) have provided excellent mass spectra of a variety of polar molecules.[8,9] The discussion which follows summarizes our mass spectral results obtained with amines **6** and **7**. The spectra obtained under FAB and LSI conditions were essentially identical.

The FAB mass spectrum of the *p*-(trifluoromethyl)-anilide analogue **6** is shown in Figure 2a and the mass fragmentation pattern in Figure 2b. The spectrum was obtained with a 1-μg sample and was readily observed for over 20 min. The assignments were confirmed by the analogous fragmentation pattern observed in the FAB mass spectrum of the corresponding *p*-methylanilide analogue **7** (Figure 2b) and, as discussed later, by the shifts in the masses of the various fragment ions observed with the deuterium labeled products.

In addition to the intense protonated molecular ion, several structurally useful fragment ions are present in the spectrum. Major ions are produced by loss of stable, neutral molecules including water (pathway B), 3,4-dihydroxybenzyl alcohol (pathway C), and norepinephrine (pathway E). The corresponding ions with approximately

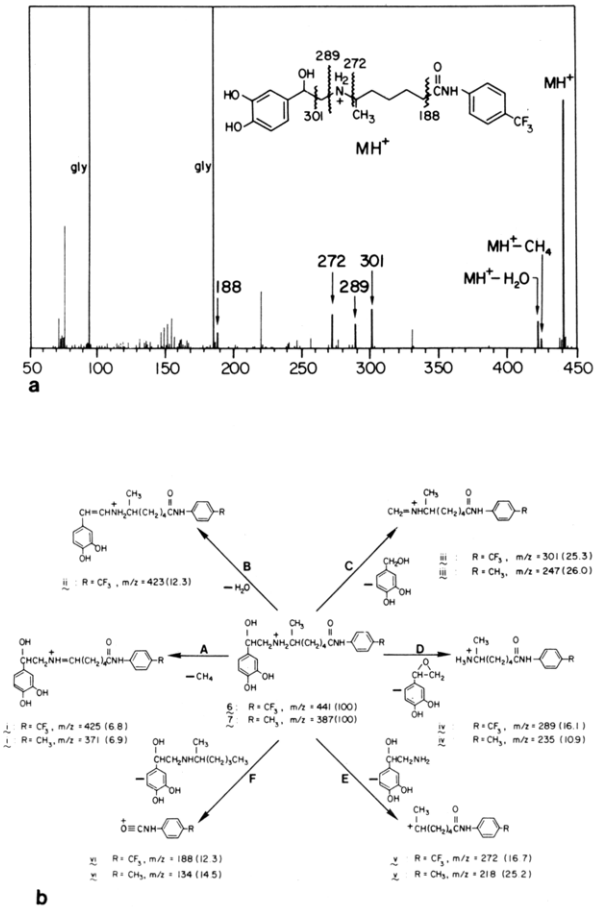
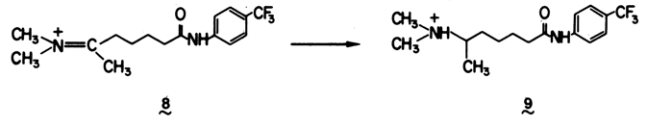


Figure 2. (a) FAB mass spectrum of compound **6**. (b) Fragmentation pattern observed in the FAB mass spectra of compounds **6** and **7**.

equal intensities were obtained in the spectrum of analogue **7**. Particularly informative for analysis of the deuterated products was the ion at *m/z* 425 (pathway A) due to loss of the methyl group as CH_4 (see below).

The reported reaction conditions for the preparation of the unlabeled amines by catalytic hydrogenation of the corresponding imines involved acetic acid as solvent and proved to be not applicable to the synthesis of labeled compounds due to the rapid equilibration of solvent protons with the deuterium gas.[10] In an attempt to avoid this exchange problem we examined the synthesis of **6** in dimethylformamide. Because of instability of the intermediate imine, overall reaction yields were estimated by reversed-phase C-18 HPLC analysis following catalytic hydrogenation.

In addition to the starting ketone and norepinephrine, two major peaks were observed in the HPLC tracing. The compound isolated from the larger of these peaks was shown by retention time and LSIMS to be the desired amine **6**. The second major reaction product was shown by LSIMS and ^1H NMR analysis to correspond to the *N,N*-dimethylamino compound **9** that would result from



8 **9**

catalytic reduction of the iminium intermediate **8**. Prior distillation of the DMF from ninhydrin avoided this com-

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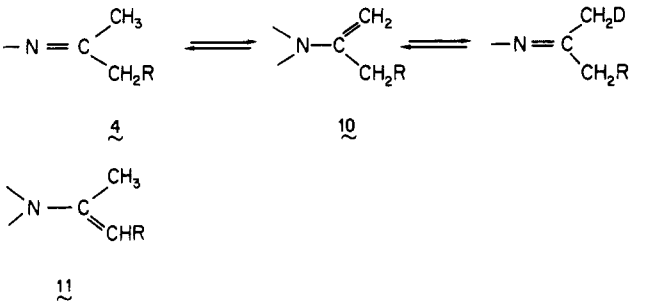
plication. Under the best reaction conditions developed only moderate yields of amines **6** and **7** were realized. Furthermore, catalytic deuteration of imines **4** and **5** provided the corresponding amines bearing on average only 25–30% of one deuterium atom per molecule. We assume that this fractional incorporation of deuterium is due to exchange of the deuterium gas with the labile protons derived from the excess norepinephrine present in the reaction mixture.

LSI mass spectral analysis of deuterium labeled **6** established the presence of deuterium in fragment ions generated by pathways B, C, D, and E. Consistent with the expected incorporation of deuterium into the N-isoalkyl side chain, the fragment ion resulting from pathway F was deuterium free. We were surprised, however, to observe the absence of a deuterium containing species in the fragment ion involving loss of the isoalkyl methyl group as CH_4 (pathway A). This result indicated that the single atom of deuterium that had been incorporated into the molecule must be present in the methyl substituent instead of the methine position as one would have expected on the basis of deuteration of the imine **4**. The absence of a dideuterated species also ruled out the possibility that the tautomeric enamine **10** had undergone simple addition of D_2 across the double bond. The ^1H NMR spectrum of deuterium labeled **6** displayed a well defined doublet centered at δ 1.29 for the methyl group signal which integrated for less than 3 protons and a 1 proton multiplet at δ 3.39–3.32 assigned to the methine proton. On the basis of these data, we tentatively assigned the structure of the deuterated product as **6**-*methyl-d*. This assignment was confirmed by the ^2H NMR spectrum of deuterated **6**. The spectrum shows a single signal at δ 1.31 corresponding to the proton signal for the methyl group. Similar results were obtained with analogue **7**. The incorporation of one deuterium atom exclusively into the methyl group cannot be rationalized in terms of deuterium addition across the imine or enamine double bond.

These catalytic deuteration reactions were carried out under the conditions required for the preparation of the tritium labeled product (i.e., magnetic stirring and a reservoir of deuterium gas connected to the reaction mixture through an adaptor). Under these conditions the deuterium gas reservoir might not be in equilibrium with the atoms associated with the Pt surface, leading to the selective introduction of protons (generated by local exchange) in the final product. In order to achieve a better exposure of the catalytic surface to the deuterium gas, we repeated the synthesis of deuterium labeled **6** in a Paar shaker apparatus which was charged with deuterium gas. The product isolated from this reaction again displayed incorporation of deuterium exclusively into the methyl group. In this reaction, however, an increase in the % deuterium incorporation was observed (0.6 atoms/molecule vs. 0.3 atoms/molecule in the stirred reaction mixture). Furthermore, 24% of the deuterium labeled product contained two deuterium atoms.

The fact that more than one deuterium atom could be present in the methyl substituent of the labeled product clearly established that the methyl group of the imine intermediate **4** was undergoing exchange with deuterons on the catalyst surface as illustrated below. Such a process requires the fast equilibration of D_2 with labile protons in the reaction mixture[11,12] and the rapid equilibrium of imine **4** with enamine **10**. Presumably, steric restrictions prevent significant involvement of the enamine **11** in these processes.[13]

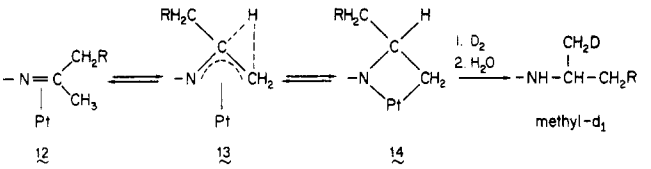


4 **10**

11

The absence of deuterium in the methine position of **6** and **7** is more difficult to explain. The introduction of only hydrogen at the methine position by catalytic reduction of the imine would require extensive exchange of solution protons with the deuterium gas. EI mass spectral analysis of the gas mixture present at the end of the reduction, however, established the deuterium to hydrogen ratio as 1.3 to 1.0. Therefore, one would expect that at least two out of every three molecules formed during the catalytic reduction of the imine (enamine) would bear a deuterium atom at the methine position. The ^2H NMR spectrum, however, clearly rules out such a possibility. The possible influence of a deuterium isotope effect in determining the extent of deuterium incorporation at the methine carbon atoms seems remote since isotope effects recorded in the reduction of double bonds such as ethylene are known to be quite low (about 1.2).[14] Consequently a reaction mechanism involving direct addition of hydrogen to the unsaturated intermediate cannot account for the absence of deuterium at the methine carbon atom of the final product.

An alternate pathway that appears to be consistent with these data is summarized below. Complexation of the imine **4** with Pt leads to an intermediate **12** which undergoes rearrangement via **13** to the cyclic species **14**. This process is accompanied by migration of a hydrogen atom from the methyl group to the methine position. Subsequent reductive cleavage of the carbon–platinum bond generates the final deuterated product. The platinum-catalyzed asymmetric incorporation of deuterium into compounds such as methyl vinyl ketone has been reported previously.[15] Additionally, this proposal is supported by the known propensity of platinum to promote analogous rearrangements via metallocyclobutane intermediates such as **14**.[16]



12 **13** **14**

Employing the reaction conditions developed for the synthesis of **6**-*methyl-d*, we subjected the preformed imine **4** to catalytic tritiation with carrier free tritium gas. The purification of the radiolabeled product was carried out on an analytical RP-18 HPLC column. The specific activity of the purified material was found to be 10.0 Ci/mmol. This value corresponds to the incorporation of 0.33

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tritium atoms per molecule of **6** and is very similar to the percent incorporation of deuterium in **6-*methyl-d***. On the basis of these results, we have concluded that the structure of tritium labeled **6** is **6-*methyl-t***.

Experimental Section

The ^1H and ^2H NMR spectra were obtained on a home-built wide-bore 240-MHz spectrometer. Chemical shifts are reported in parts per million (ppm) downfield from tetramethylsilane (Me_4Si). LSI and FAB mass spectra were obtained on a Kratos MS-50S mass spectrometer with either a xenon (FABMS) or a Cs^+ ion gun (LSIMS).[8] The HPLC employed for analytical separations consisted of the following: Altex Model 110A pump, Altex Model 210 injector, Altex/Hitachi variable wavelength UV–vis detector set at 254 nm. The EI mass spectra of the gas molecules above the reaction mixture were analyzed by using a UTI Model 100C quadrupole mass spectrometer. A sample of the gas mixture was leaked via a reservoir into the ionization chamber maintained at a base pressure of 4×10^{-9} torr. During the actual analysis the base pressure rose to 1.4×10^{-8} torr. The mass spectrometer was calibrated with known amounts of H_2 and D_2. The preparation of unlabeled **6** and **7** was accomplished by the reported literature methods.[1]

Mixture of 5-[(*R*)-*N*-(2-(3,4-Dihydroxyphenyl)-2-hydroxyethyl)amino]heptanoic-*7-d* Acid *p*-(Trifluoromethyl)anilide (6-*methyl-d*) and Unlabeled 6. (*R*)-Norepinephrine free base[1] **1**, 0.3 g, 1.77 mmol), 6-oxoheptanoic acid p-(trifluoromethyl)anilide[1] (**2**, 0.05 g, 0.177 mmol), and 3 pieces of Linde 3A molecular sieves were added to 5 mL of freshly distilled dimethylformamide in a 10-mL round-bottom flask. The reaction mixture was stirred under argon for 24 h at 75 °C. After the reaction had cooled to room temperature, PtO_2 (30 mg, 0.13 mmol) was added and the flask was charged 3 times with D_2 (97%). A 300-mL balloon reservoir of D_2 was maintained above the stirred reaction mixture during the 2-h reduction period. The reaction mixture was then transferred to a 10-mL centrifuge tube and, following a brief centrifugation, the supernatant was removed and treated with 0.1 N HCl to adjust the pH to 1–2. Analysis of the crude reaction mixture by HPLC [Lichrosorb C_{18} 10 μ (Altex)–mobile phase: 30% THF, 20 mM sodium phosphate, 30 mM citric acid, 10 mM trimethylnonylammonium bromide, pH 3.5, retention volume 16.6 mL] indicated a yield of 38% of **6** and **6-*methyl-d***. The product was purified by preparative HPLC employing a Whatman Partisil ODS-3 column with 40% THF, 20 mM sodium phosphate, and 30 mM citric acid (pH 4.2) as the eluent, retention volume 44–48 mL. The appropriate fractions were collected and lyophilized. In order to remove the salts from the mobile phase, the residue was dissolved in 1 mL of water and passed through a Sep Pak C_{18} cartridge. After washing the cartridge with 2 mL of water, the product was eluted with 2 mL of methanol. The HPLC retention time of this product was identical with that of standard **6**: 240 MHz ^1H NMR (D_2O) δ 7.67, 7.58 (AB quartet, J = 7.1 Hz, 4 H, $F_3CC_6H_4$), 6.90–6.79 [m, 3 H, $(OH)_2C_6H_3$], 3.39–3.32 (m, 1 H, NCH), 3.21 (d, J = 6.4 Hz, 2 H, CH_2N), 2.45 (t, J = 6.3 Hz, 2 H, CH_2CO), 1.79–1.25 (m, including d at 1.29, J = 6.4 Hz, 8 H); ^2H NMR (H_2O) δ 1.31 (s, CH_2D).

A second peak eluting from the preparative column was collected (retention volume 34–38 mL) and further purified by passage through a Sep Pak cartridge. This product proved to be a mixture of unlabeled and monodeuterated 6-(*N*,*N*-dimethylamino)heptanoic acid *p*-(trifluoromethyl)anilide (**10** and **10-*d***): LSIMS, *m*/*z* (relative intensity) MH 318 (85%) and 317 (100), 290 (45), 289 (64), 273 (61), 272 (75), and 188 (100); 240 MHz ^1H NMR (D_2O) δ 7.70, 7.60, (AB quartet, J = 8.5 Hz, 4 H, $CF_3C_6H_4$), 3.41–3.30 (m, 0.9 H, NCH), 2.78, 2.74 [s, $N(CH_3)_2$, partially obscured by an impurity], 2.46 (t, J = 7.1 Hz, 2 H, CH_2CO), 1.82–1.31 (m, 6 H, $CH(CH_2)$, 1.26 (d, J = 6.2 Hz, 2.5 H, $CHCH_3$).

Mixture of 5-[(*R*)-*N*-(2-(3,4-Dihydroxyphenyl)-2-hydroxyethyl)amino]heptanoic-*7-d* Acid *p*-Methylanilide (7-*methyl-d*) and Unlabeled 7. This product was prepared in the same fashion as described above for the corresponding *p*-(trifluoromethyl)anilide system. Analytical HPLC [Lichrosorb C_{18} 10μ (Altex)–mobile phase: 10% THF, 20 mM sodium phosphate, 30 mM citric acid, 10 mM trimethylnonylammonium bromide, pH 3.4, retention volume 18.8 mL] indicated a yield of 30%. Preparative HPLC was carried out on a Whatman Partisil ODS-3 column employing 20% THF, 20 mM sodium phosphate and 30 mM citric acid (pH 3.5) as the eluent. The product was freed from salts by rechromatographing on the Whatman column employing 40% THF, 5% acetic acid, and 55% water (pH 2.9): LSIMS, *m*/*z* (relative intensity) MH^+ 388 (47%) and 387 (82), 370 (42), 369 (76), 263 (4), 262 (11), 248 (9), 247 (21), 219 (42), 218 (100), 134 (43); 240 MHz ^1H NMR (D_2O) δ 7.29–7.20 (m, 4 H, $CH_3C_6H_4$), 6.90–6.75 [m, 3 H, $(HO)_2C_6H_3$], 3.39–3.29 (m, 1 H, NCH), 3.20 (d, J = 6.9 Hz, 2 H, CH_2), 2.45 (t, J = 7.1 Hz, 2 H, CH_2CO), 2.75 (s, 3 H, $PhCH_3$), 1.84–1.27 (m, 8.8 H including d, J = 6.4 Hz, at 1.28); ^2H NMR (H_2O) δ 1.23 (s, CH_2D).

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Registry No. **1**, 51-41-2; **2**, 84417-40-3; **3**, 83086-06-0; **4**, 90900-17-7; **5**, 90900-18-8; **6**, 83086-14-0; **6-d_1**, 90900-19-9; **7**, 83086-04-8; **7-d_1**, 90900-20-2.