extracts were washed with brine, dried, filtered, and concentrated to give a yellow solid (13.2 g), which was recrystallized from Et_2O/hexane to yield a white solid (10.6 g, 70%): ^1H NMR δ 2.25 (d, J = 0.74 Hz, 3 H), 3.35 (s, 2 H), 3.66 (s, 2 H), 5.92 (br s, 1 H). Anal. Calcd for $C_9H_{10}O_5$: C, 54.53; H, 5.09. Found: C, 54.59; H, 5.22. Mp: 133-135 °C.

2,3-Bis(2-hydroxymethyl)-5-methylfuran (5). To an ice-cold solution of 4 (3.4 g, 17.2 mmol) in anhydrous THF (160 mL) was added a 1.0 M Borane-THF complex (86 mL) via syringe. The reaction mixture was allowed to stir in the ice-bath for 20 min and then at room temperature for 2 h. The reaction mixture was carefully poured into ice-cold saturated aqueous $NaHCO_3$; then it was extracted with EtOAc (3 × 200 mL). The combined extracts were washed with saturated $NaHCO_3$ and brine, dried, filtered, and concentrated to give a pale yellow oil. The residue was chromatographed (EtOAc) to yield diol 5 as a colorless oil (2.87 g, 98%): ^1H NMR δ 2.24 (s, 3 H), 2.47-2.60 (m, 1 H), 2.56 (t, J = 6 Hz, 2 H), 2.60-2.73 (m, 1 H), 2.80 (t, J = 6 Hz, 2 H), 3.73 (t, J = 6 Hz, 2 H), 3.82 (t, J = 6 Hz, 2 H), 5.81 (s, 1 H); MS m/e 171 $(M + H)^+$, 188 $(M + NH_4)^+$; exact mass calcd for $C_9H_{14}O_3$ 170.0943, found 170.0942. Anal. Calcd for $C_9H_{14}O_3 \cdot {}^1/_8H_2O$: C, 62.66; H, 8.34. Found: C, 62.86; H, 8.05.

2,3-Bis[2-(*p*-tosyloxy)ethyl]-5-methylfuran (6). A solution of the following composition was allowed to stir at room temperature for 48 h: 5 (2.87 g, 16.8 mmol), *p*-tosyl chloride (12.8 g, 67.1 mmol), triethylamine (9.35 mL, 67.1 mmol), and DMAP (0.10 g, 0.82 mmol) in anhydrous THF (75 mL). The reaction mixture was filtered through a fritted glass funnel (4-8 μm), rinsing the solids with Et_2O. The filtrate was concentrated to a small volume (40-50 mL) and quickly diluted with Et_2O (200 mL). The organic phase was washed with 10% citric acid (100 mL), saturated $NaHCO_3$ (2 × 100 mL), and brine, dried, and concentrtion to give a clear yellow oil (14.3 g). The crude was chromatographed (EtOAc/hexane, 1/10-1/2). The product fractions were concentrated to a volume of approximately 50 mL; then anhydrous dioxane (60 mL) was added. The volume of the solvents was reduced to about 20 mL and the solution was transferred to a flask containing K_2CO_3 (15 g). Assuming a 90% yield,[7] more dioxane (10 mL) was added to achieve a stock solution of 0.5 M concentration, which was stored in the refrigerator under nitrogen. At no time should this product be handled in fully concentrated form, whether crude or purified. The neat compound will decompose within minutes.

6-Benzyl-2-methyl-5,6,7,8-tetrahydro-4*H*-furo[2,3-*d*]azepine (7a). A mixture of K_2CO_3 (5.0 g, 36 mmol) and 6 (0.5 M stock solution, 4.4 mL, 2.2 mmol) was further diluted with anhydrous dioxane (11 mL) and heated to reflux. Benzylamine (0.82 mL, 7.5 mmol) in anhydrous dioxane (10 mL) was added via syringe pump over 2 h and the reaction mixture was heated to reflux overnight. The solids were filtered off and rinsed thoroughly with CH_2Cl_2. Volatiles were removed under reduced pressure to yield a yellow residue, which was chromatographed (EtOAc/hexane, 1/5) to give a clear yellow oil. This free base was treated with oxalic acid to form the salt, a white powder (0.68 g, 93%): ^1H NMR (DMSO-d_6) δ 2.16 (s, 3 H), 2.53-2.62 (m, 2 H), 2.84-2.92 (m, 2 H), 3.02-3.13 (m, 4 H), 4.08 (br s, 2 H), 5.87 (s, 2 H), 7.31-7.50 (m, 5 H); MS m/e 242 $(M + H)^+$. Anal. Calcd for $C_{18}H_{21}NO_5 \cdot 0.4H_2O$: C, 63.86; H, 6.49; N, 4.14. Found: C, 63.97; H, 6.26; N, 4.12. MP 127-129 °C dec.

2-Methyl-5,6,7,8-tetrahydro-4*H*-furo[2,3-*d*]azepine (7b). 1-Chloroethyl chloroformate (1.10 mL, 10.2 mmol) was added dropwise to an ice-cold solution of 7a (0.50 g, 2.1 mmol) in anhydrous 1,2-dichloroethane (14 mL). The reaction mixture was allowed to stir at room temperature for 1 h and then was washed with saturated $NaHCO_3$ (25 mL), and the aqueous phase was back-washed with CH_2Cl_2 (25 mL). The organic extracts were washed with brine, dried, filtered, and concentrated to give a clear brown oil (1.33 g). To the crude carbamate was added anhydrous methanol (14 mL), and the solution was heated to reflux for 1 h. The solvent was removed under reduced pressure and the pink residue was triturated with Et_2O to yield the hydrochloride, a pink powder (0.35 g, 90%): ^1H NMR (DMSO-d_6) δ 2.18 (s, 3 H), 2.70 (t, J = 6 Hz, 2 H), 2.99 (t, J = 6 Hz, 2 H), 3.21 (t, J = 6 Hz, 2 H), 3.22 (t, J = 6 Hz, 2 H), 5.93 (s, 1 H), 9.26 (br s, 1 H); MS m/e 152 $(M + H)^+$. Anal. Calcd for $C_9H_{14}NOCl$: C, 57.73; H, 7.54; N, 7.49. Found: C, 57.57; H, 7.49; N, 7.38. MP 204-206 °C dec.

2-Methyl-6-(5-methylfurfuryl)-5,6,7,8-tetrahydro-4*H*-furo[2,3-*d*]azepine (7c). To a mixture of 7b (100 mg, 0.53 mmol), 5-methylfurfural (80 μL, 0.80 mmol), anhydrous NaOAc (88 mg, 1.07 mmol), and dried, powdered 4A molecular sieves (0.53 g) in anhydrous methanol (2.1 mL) was added sodium cyanoborohydride (67 mg, 1.07 mmole) in one portion. The reaction mixture was allowed to stir overnight at room temperature. To the chilled reaction mixture was added 1.0 N NaOH (10 mL), and the resulting aqueous phase was extracted with Et_2O (3 × 20 mL). The extracts were washed with brine, dried, filtered, and concentrated to give a clear yellow oil. The crude oil was chromatographed (EtOAc/hexane, 1/9-1/5) to yield a clear yellow oil. This free base was treated with oxalic acid to form the salt, an off-white powder (134 mg, 75%): ^1H NMR (CD_3OD) δ 2.19 (s, 3 H), 2.32 (s, 3 H), 2.83 (t, J = 6 Hz, 2 H), 3.10 (t, J = 6 Hz, 2 H), 3.42-3.50 (m, 4 H), 4.45 (s, 2 H), 5.86 (s, 1 H), 6.12 (d, J = 3 Hz, 1 H), 6.60 (d, J = 3 Hz, 1 H); MS m/e 246 $(M + H)^+$. Anal. Calcd for $C_{17}H_{21}NO_6$: C, 60.88; H, 6.32; N, 4.18. Found: C, 60.91; H, 6.34; N, 4.16. Mp 145-147 °C.

Cyclialkylation Studies. 1. A Practical Synthetic Approach to the 2,3:6,7-Dibenzobicyclo[3.2.2]nona-2,6-diene System

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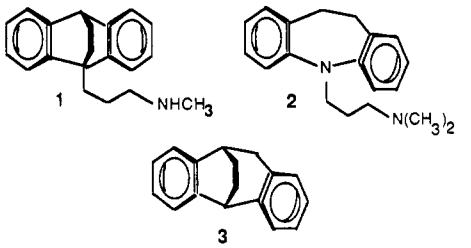
One of the useful antidepressant drugs, maprotiline (1), has a dibenzobicycloalkadiene structure, and another, imipramine (2), has a dibenzoazacycloheptadiene structure. We thought it might be interesting to synthesize molecules incorporating a structure related to both of these compounds, such as amino derivatives of 2,3:6,7-dibenzobicyclo[3.2.2]nona-2,6-diene (3).



Two very different syntheses of the tetracyclic hydrocarbon 3 have been published.[1,2] The earlier synthesis[1] affords 3 in low yield in seven steps from an expensive starting material. The later report[2] came from this laboratory as part of a study of acid-catalyzed cyclidehydrations; the formation of 3 in good yield was an unexpected observation in this study. In order to achieve a practical synthesis of derivatives of 3 with potential valuable medicinal properties, we have reexamined some of the steps in the synthesis of 3.

We now report an efficient and practical synthesis from readily available starting materials, beginning with lactone 4 (Scheme I).[3] The reduction of lactone 4 was a bottleneck for a practical synthesis. Catalytic hydrogenation was sensitive to trace impurities in the lactone and variations of Clemmensen-type reduction were attempted with little

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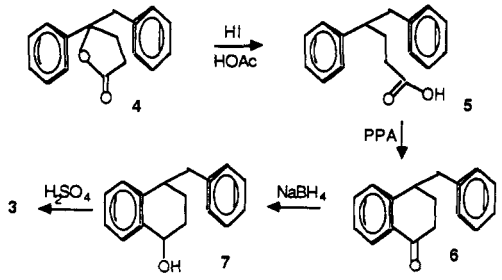
Scheme I



success: yields were no more than 30%, even under forcing conditions. However, use of hydrogen iodide in acetic acid[4] was found to be an excellent method for reducing large quantities of the lactone to the acid.

The yield in the next step, cycliacylation of the acid **5** to product 4-benzyl-1-tetralone (**6**), was improved by efficient stirring and by using polyphosphoric acid (PPA) with xylene as a cosolvent.[5] Yields in this step were found to be more reproducible when the PPA was prepared just before its use by mixing equal weights of 85% phosphoric acid and phosphorus pentoxide. The reduction of tetralone **6** to tetralol **7** was the one step that required careful purification of the starting material (in this case, **6**). A 65% yield of *trans*-4-benzyl-1-tetralol (**7**) was obtained in this way, and it was discovered that the filtrate from the crystalline material contained the cis isomer. According to ^{13}C NMR analysis, the mother liquor contained a 4:1 ratio of the cis and trans isomers, respectively. A combined yield of 91–94% of *cis*- and *trans*-**7** could thus be obtained. The cis isomer was also cyclized to the tetracyclic hydrocarbon **3**.

The best conditions for the cyclidehydration of **7** involved certain modifications to the procedure described in our first report of this reaction.[2] Obtaining reproducible high yields of **3** from cyclidehydration of **7** depends upon use of concentrated (96–98%) sulfuric acid, the addition of **7** in small portions to the acid catalyst, and vigorous stirring of the reaction mixture throughout the course of the reaction. Under these conditions, the only major side reaction is the simple dehydration of **7** to afford 1-benzyl-1,2-dihydronaphthalene. This impurity was best removed by crystallization of the crude product from a minimal amount of hexane.

Experimental Section

All NMR spectra were obtained in $CDCl_3$ solution. A Varian EM-390 instrument was used to obtain ^1H NMR spectra; ^{13}C NMR spectra were obtained at 20 MHz on a Varian FT-80A instrument. A Finnegan MAT instrument 4023 equipped with a T & W Scientific 50-m DBI bonded phase capillary column (0.25-mm film thickness) was used for all GC/MS analyses. All temperatures are uncorrected.

4,5-Diphenylpentanoic Acid (5).[6] A solution of nearly anhydrous hydriodic acid in acetic acid was prepared by adding a solution of 290 mL of 47% aqueous hydriodic acid in 100 mL of glacial acetic acid dropwise to a well-stirred solution prepared from 1.03 L (1.13 kg, 11 mol) of acetic anhydride[7] and 100 mL of glacial acetic acid. Addition took about 1 h; the solution was kept cool with a water bath. The solution was allowed to stir for 30 min after the addition was complete. Solid **4**[3] (100.8 g, 399 mmol) was rinsed into the reaction vessel with 100 mL of glacial acetic acid. The mixture was heated at reflux in close proximity to an unfrosted 150-W incandescent lamp for 12 h. The jet-black solution was then allowed to cool to about 50 °C and was poured over 500 g of ice in a 4-L Erlenmeyer flask. Granular zinc (20 mesh; ca. 25 g) was added to the mixture; 100 mL of dichloromethane was added to reduce the viscosity of the organic layer. The mixture was stirred mechanically until the aqueous layer remained clear and colorless. The layers were separated. The aqueous layer was extracted with two 100-mL portions of dichloromethane. The combined organic layers were filtered through cotton and stripped of solvent to afford 100.4 g (98.8% of the theoretical yield) of crude **5** as a clear, light yellow oil. ^1H NMR: δ 10.4 (s, 1 H), 7.05 (br m, 10 H), 2.74 (br s, 3 H), 2.05 (br s, 4 H) ppm. ^{13}C NMR: δ 179.9, 143.6, 140.0, 129.1, 128.4, 128.1, 127.7, 126.5, 125.9, 47.2, 43.6, 42.2, 30.2 ppm. IR: 3500–2500 (br, m, COO–H str), 3050 (m, sp^2 C–H str), 2950 (m, sp^3 C–H str), 1720 (vs, C=O str), 1510 and 1470 (m, arom C–C str), 1275 (br m, C–O str), 762 (s, arom bend) cm^{-1}. MS [*m/e* (relative intensity)]: 254 (M^+, <1), 163 (100), 117 (85), 91 (41).

4-Benzyl-1-tetralone (6).[5] Polyphosphoric acid was prepared by mixing 173.8 g of 85% H_3PO_4 with 175.2 g of P_2O_5 at 120 °C until nearly all of the solid had dissolved into the water-white, freely stirring solution. (The P_2O_5 was added in small portions over a 10-min period; about 1 h later, the solution was homogeneous.) A solution of 100.4 g of **4** in 100 mL of xylene was added to the polyphosphoric acid. The mixture was heated at 120 °C and was stirred for 2 h. The reddish brown mixture was then poured over about 500 g of ice; that mixture was stirred (mechanically) for 4 h to ensure complete hydrolysis of the PPA. The layers were separated. The aqueous layer was washed once with 100 mL of diethyl ether. The combined organic layers were washed once with water, once with 50 mL of saturated sodium bicarbonate solution, and again with 50 mL of water. After being dried over sodium sulfate, the organic solution was stripped of solvent at reduced pressure to afford 94.4 g (100% of the theoretical yield) of crude 4-benzyl-1-tetralone as a clear red oil. A 65-g portion of the crude product was distilled at reduced pressure to afford 50.6 g (77% of the theoretical recovery) of pure **6** (bp 177–8 °C, 0.65 mmHg). ^{13}C NMR: δ 197.8, 147.3, 139.7, 133.3, 131.9, 128.9, 128.4, 128.3, 127.3, 126.8, 126.3, 41.2, 39.8, 34.7, 26.0 ppm. IR: 3080 (m, sp^2 C–H str), 2900 (m, sp^3 C–H str), 1695 (vs, C=O str), 1602 (s, arom C–C str), 1340 (s), 1295 (s). HRMS: calcd for $C_{17}H_{16}O$ 236.1201, obsd 236.1197. MS [*m/e* (relative intensity)]: 236 (M^+, 20), 145 (100), 144 (73), 117 (40), 115 (37), 91 (72).

4-Benzyl-1-tetralol (7). Solid sodium borohydride (7.3 g, 193 mmol) was added through the top of a condenser, as rapidly as foaming would permit, to a solution of 4-benzyl-1-tetralone (37.1 g, 157 mmol) in 300 mL of refluxing methanol. The solution was heated under reflux for 1 h. The methanol was removed under reduced pressure to leave a yellow solid, to which 300 mL of water was added, and the pH was lowered to 7 by the dropwise addition of concentrated hydrochloric acid. More finely divided solid precipitated. The mixture was transferred to a separatory funnel and extracted with three 200-mL portions of diethyl ether. The combined ether layers were washed with 100 mL of saturated sodium bicarbonate solution, 100 mL of water, and 50 mL of saturated sodium chloride solution. The ether solution was dried over 4-Å molecular sieves overnight. Removal of solvent gave a mass of colorless crystals, which, on recrystallization from hexane, afforded 24.7 g (66%) of *trans*-4-benzyl-1-tetralol, mp 98–100 °C.[2,8] The mother liquor was concentrated to yield an oil, which could not be induced to crystallize. Analysis of this oil by ^{13}C NMR showed it to be a 4:1 mixture of *cis*- and *trans*-4-benzyl-1-tetralol. This material (which comprised 25% of the theoretical yield of 4-benzyl-1-tetralol), as well as the pure trans form, was suitable for use in the preparation of **3**; thus, the total yield of 4-benzyl-1-tetralol (cis + trans) was 91% of the theoretical amount. Spectral data for trans isomer. ^1H NMR: δ 7.49 (m, 1 H), 7.24 (br m, 8 H), 4.75 (br t, 1 H), 3.20 (dd, J_1 = 3.5 Hz, J_2 = 13 Hz,

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1 H), 3.04 (sextet, J = 4.5 Hz, 1 H), 2.75 (dd, J_1 = 10 Hz, J_2 = 13.5 Hz, 1 H), 2.17 (s, 1 H), 1.91 (comp mult, 2 H), 1.72 (comp mult, 3 H) ppm. ^{13}C NMR: δ 140.6, 140.4, 139.2, 129.2, 128.4, 128.3, 128.1, 127.6, 126.4, 126.1, 68.9, 43.0, 39.4, 29.3, 23.4 ppm. ^{13}C NMR of the cis isomer: δ 140.5, 140.2, 138.6, 129.0, 128.9, 128.5, 128.2, 127.4, 126.2, 126.0, 67.5, 42.7, 39.2, 28.3, 21.8 ppm.

2,3:6,7-Dibenzobicyclo[3.2.2]nona-2,6-diene (3).[1,2] Crystalline *trans*-4-benzyl-1-tetralol (14.05 g) was added slowly and in small portions to 150 mL of well-stirred concentrated H_2SO_4 at room temperature (ca. 25 °C). The crystals appeared to liquefy in the reaction mixture, which turned red, and tan solid material formed at the top of the stirred mixture. After all of the 4-benzyl-1-tetralol had been added (during about 30 min), the mixture was stirred an additional 10 min. Hexane (75 mL) was added; the solid dissolved in it. The mixture was transferred to a separatory funnel and the layers were separated. The acid layer was extracted with two 25-mL portions of hexane, which were then added to the other hexane layer. The hexane solution was washed with saturated sodium bicarbonate solution, dried over 4 Å molecular sieves, and stripped of solvent under reduced pressure at room temperature. The white solid residue, 12.53 g, amounted to 96% of the theoretical amount of slightly impure 2,3:6,7-dibenzobicyclo[3.2.2]-nona-2,6-diene (3), mp 60–68 °C. This product was dissolved in hexane and passed through a column of silica gel. The hexane was removed and the residual solid was recrystallized from methanol to afford 11.17 g (86%) of pure material, mp 75–77 °C.[1,2] Repeated crystallization of a small amount of this material from hexane afforded an X-ray-quality crystal; the X-ray analysis of this compound will be reported separately.[9] ^{1}H NMR: δ 7.09 (m, 8 H), 3.73 (br d, 1 H), 3.13 (br s, 3 H), 2.1 (br mult, 4 H) ppm. ^{13}C NMR: δ 143.9, 143.3, 141.2, 135.9, 131.3, 128.0, 126.6, 126.3, 125.7, 125.4, 47.4, 41.1, 37.5, 30.9, 26.3 ppm. MS [*m/e* (relative intensity)]: 220 (M^+, 100), 205 (22), 192 (84), 128 (21), 105 (23).

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Chemical Synthesis of Stereospecifically Labeled Pyridoxamine 5′-Phosphate

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The vitamin B_6 phosphate dependent enzymes are an important class of enzymes that catalyze a wide variety of biological transformations involved in the metabolism of amino acids and amines, such as transamination, decarboxylation, racemization, β- and γ-elimination, and substitution.[1] Although the catalytic roles of vitamin B_6 phosphate are amazingly versatile, its catalytic functions rely primarily on the ability of this cofactor to act as an electron sink, temporarily storing the electrons that are later used for the cleavage and/or formation of covalent bonds. While the aldehyde form of this cofactor, pyridoxal 5′-phosphate (PLP), is the most common form for vitamin B_6 dependent enzymes, the amine form of this coenzyme, pyridoxamine 5′-phosphate (PMP), has also been shown to play an important role in the reactions mediated by transaminases.[2] Since transaminases act by a ping-pong mechanism, the oscillation of the coenzyme between the aldehyde and amine forms occurs simultaneously with the substrate's alternation between an amino and a keto acid. Although both PLP and PMP are now perceived as the standard coenzymes for the metabolism of amino acids, they have also been demonstrated to be involved in glycogen phosphorylation[3] and a sugar deoxygenation process,[4] respectively. Studies of the catalysis of vitamin B_6 phosphate linked enzymes have shown a remarkable stereochemical uniformity in which the bond cleavage and/or formation, with a few exceptions, always take places at the *si* face of C-4′ in the substrate–cofactor complex.[5] Such stereochemical consistency is expected to be maintained by an enzyme that adheres to the well-established vitamin B_6 phosphate cofactor chemistry. Thus, a study directed at elucidating the stereochemical course of the reaction catalyzed by this class of enzymes may provide unique mechanistic insights that are not available from other experimental approaches.

Crucial to this stereochemical analysis is the availability of the (4′*S*)- and (4′*R*)-[4′-$^3H_1$]PMP coenzymes. While the 4′*S*-labeled pyridoxamine can be obtained by incubating pyridoxal and glutamate with apoaspartate aminotransferase in tritiated buffer and the 4′*R*-labeled epimer can be prepared from [4′-$^3H_1$]pyridoxal by an identical procedure,[6] this enzymatic method is laborious and is limited to microscale preparation. Although an asymmetric reduction of an L-threonine–pridoxal–metal complex with sodium borohydride to make chirally labeled pyridoxamine is also known,[7] this chemical method leads to products of low enantiomeric purity. In order to circumvent these problems, we have developed a reaction sequence producing the requisite stereospecifically labeled PMP with high chiral purity and satisfactory chemical yield. The detailed pathway and a full account of the experimental procedures involved are described in this paper.

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