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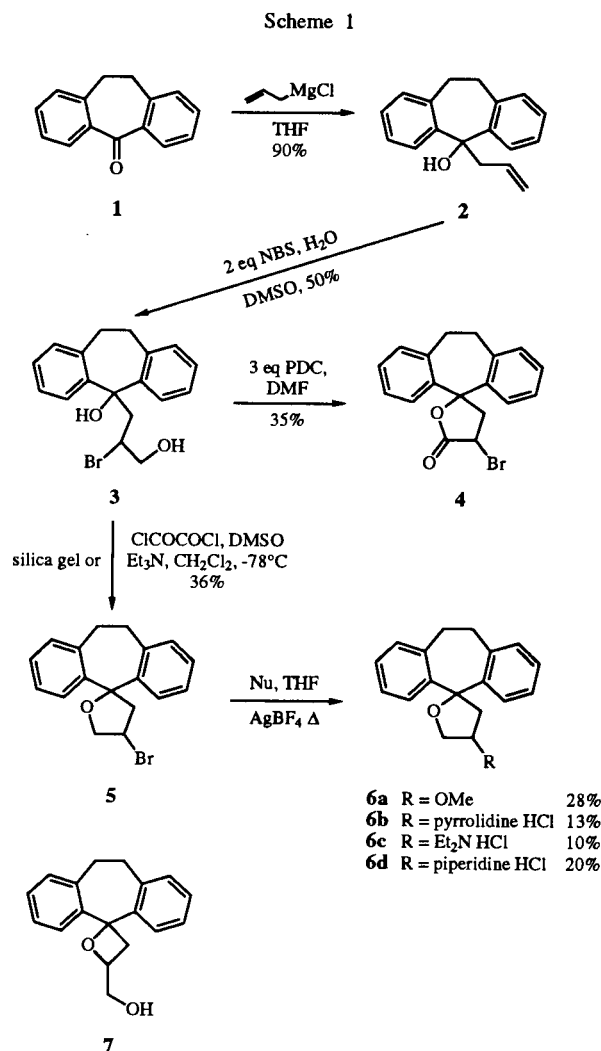
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A synthesis of novel spiro[4',5',10,11-tetrahydro-5*H*-dibenzo[*a,d*]cyclohepten-5-yl-2'(3'*H*)-furans] is described. The key reaction was formation of the tetrahydrofuran ring by cyclization of the diol **3** or the protected diol **10**. These compounds were investigated as potential TNF- α inhibitors.

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As part of our interest in 5,5-disubstituted-10,11-dihydro-5*H*-dibenzo[*a,d*]cycloheptenes as potential cytokine inhibitors, we have synthesized spiro[4',5',10,11-tetrahydro-5*H*-dibenzo[*a,d*]cyclohepten-5-yl-2'(3'*H*)-furans] **6b-d** and tested them as inhibitors of the synthesis or release of tumor necrosis factor (TNF- α). Our goal with these particular compounds was to constrain the spatial relationship between the amino group and the lipophilic dibenzo[*a,d*]cycloheptene ring.

Two different syntheses of these compounds are illustrated in Schemes 1 and 2. Our first approach began with the Grignard addition of allylmagnesium chloride to dibenzosuberone **1** to give the tricyclic benzhydrol **2** in 90% yield [1]. Hydrobromination of the double bond with two equivalents of *N*-bromosuccinimide in aqueous dimethyl sulfoxide [2] provided the unexpected anti-Markovnikov product **3**. The regioselectivity of this reaction is apparently controlled by the steric bulk of the dibenzo[*a,d*]cycloheptene ring, which directs nucleophilic attack by water to the less hindered primary carbocation center of the bromonium intermediate. Bromodiol **3** is very sensitive to silica gel catalyzed 5-exo-tet [3] cyclization. Indeed, the desired bromotetrahydrofuran **5** has been formed in 22% yield by accidental cyclization of **3** on silica gel. This finding indicates that compound **5** can be obtained by deliberate cyclization with prolonged exposure to silica gel as an acidic catalyst. Nonetheless, bromodiol **3** has been successfully purified and isolated in 50% yield by means of flash silica gel chromatography, which was performed so as to minimize residence time on the column. None of the oxetane **7** that would result from a "favored" 4-exo-tet [3] intramolecular displacement of bromine by the tertiary hydroxyl has ever been isolated. Attempted Swern oxidation [4] of bromodiol **3** also resulted in the formation of tetrahydrofuran **5**. Apparently, the Swern sulfonium intermediate activated the primary carbon-oxygen bond to breakage in a 5-exo-tet cyclization in preference to the usual oxidation *via* oxygen-sulfur bond cleavage. However, treatment of bromodiol **3** with pyridinium dichromate successfully oxidized the primary hydroxyl to a carboxylic acid, which cyclized spontaneously to the stable bromolactone **4**. Product **4** served to



further corroborate the unexpected regiochemistry of bromodiol **3**. Treatment of bromide **5** with various nucleophiles and silver tetrafluoroborate produced the desired ether **6a** and target amines **6b-6d**.

The structures of compounds **3-6** were determined by analysis of ¹H nmr, COSY, and ¹³C nmr spectra. Characteristic ¹H nmr chemical shifts are tabulated in Chart 1. The hydrogens on the five-membered tetrahydrofuran

Scheme 2

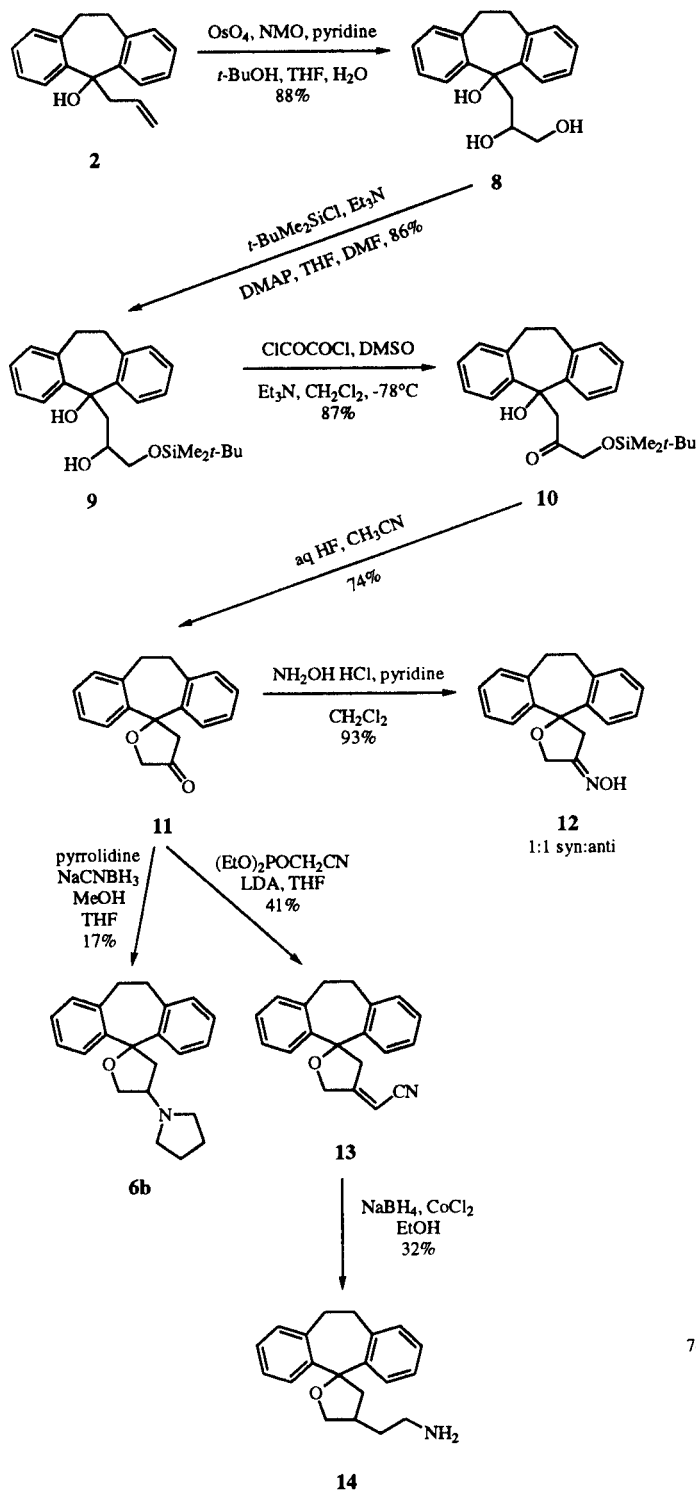


Chart 1

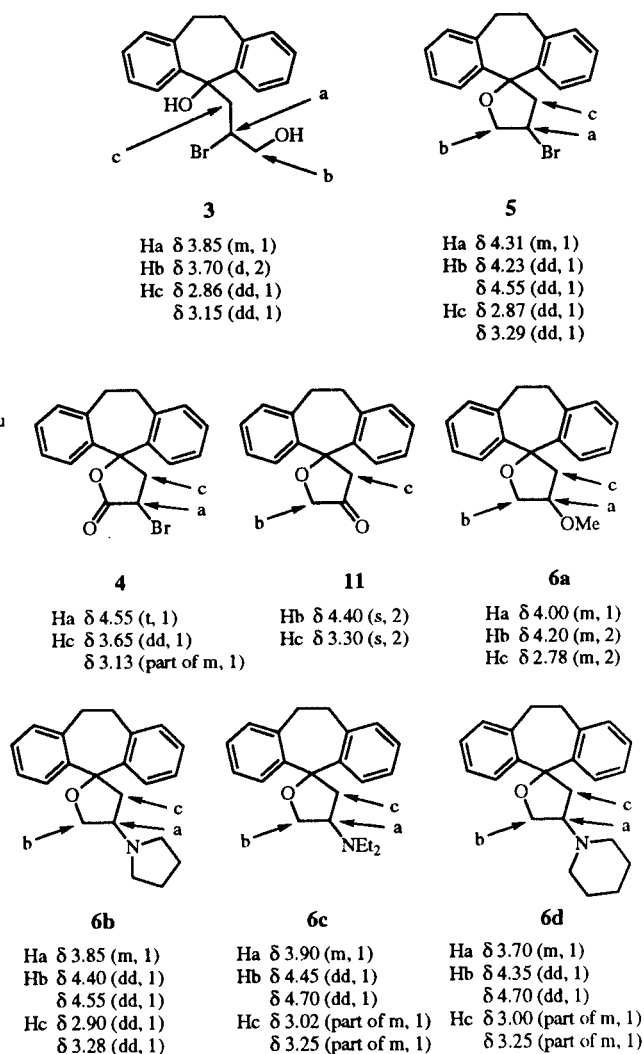
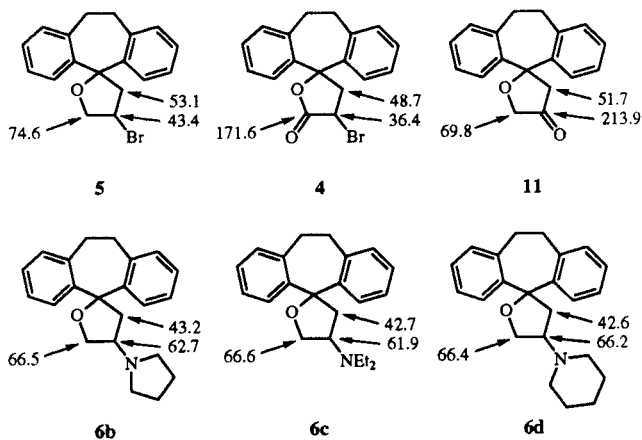
Characteristic ^1H NMR Chemical Shifts

Chart 2

Characteristic ^{13}C NMR Chemical Shifts

ring are clearly distinguishable. Characteristic ^{13}C nmr chemical shifts are summarized in Chart 2. All compounds were fully characterized with infrared spectral, mass spec-

tral and elemental analysis data (see Experimental).

An alternative synthetic route to compounds **6** and related products is shown in Scheme 2. Osmium tetroxide-catalyzed oxidation [5,6] of the double bond of tricyclic benzhydrol **2** afforded the triol **8** in 88% yield. Selective protection of the primary alcohol moiety as the *t*-butyldimethylsilyl ether [7,8] gave the monoprotected derivative **9**. Swern oxidation [4] of the secondary alcohol cleanly produced the ketone **10** in 87% yield. Removal of the *t*-butyldimethylsilyl group with aqueous hydrofluoric acid [9] and direct cyclization of the intermediate diol formed the key furanone **11**. Reductive amination [10] of ketone **11** with pyrrolidine yielded target amine **6b**, which was shown to be identical with a sample of **6b** derived from bromodiols **3** and thus provided additional substantiation of the sequence shown in Scheme 1. Oxime **12**, a 1:1 mixture of syn and anti isomers, resulted from treatment of ketone **11** with hydroxylamine [11]. Wadsworth-Emmons elaboration of ketone **11** with the cyanomethyl phosphonate reagent [12] yielded the unsaturated nitrile **13**. Reduction of **13** with sodium borohydride-cobalt chloride [13] produced saturated derivative **14**, in which the relative position of the amine substituent has been altered by interpolation of an ethylene bridge between the nitrogen atom and the tetrahydrofuran ring.

All of the target compounds synthesized in this work have been tested in an *in vitro* assay [14] and found to be relatively weak inhibitors of TNF- α synthesis.

EXPERIMENTAL

Melting points were determined on a Thomas-Hoover capillary melting point apparatus and are uncorrected. Infrared spectra were recorded on a Perkin-Elmer 727B, and nuclear magnetic resonance spectra were taken on a Varian XL-200, Varian XL-300, or a Varian XL-400. Chemical shifts are reported in parts per million relative to tetramethylsilane as an internal standard. Mass spectra data were determined on a Finnigan MAT 90 or Hewlett Packard 5989A instrument. All reactions were performed under a nitrogen atmosphere. All solvents used were anhydrous grade. Solvents and starting reagent **1** were purchased from Aldrich and used without further treatment. Solution drying was carried out with anhydrous magnesium sulfate, and solvent removal was accomplished with a rotary evaporator. Flash chromatographic separations were performed using Baker 40-micron silica gel as the solid phase. Elemental analyses were performed by the analytical group at Schering-Plough Research Institute, Kenilworth, New Jersey.

10,11-Dihydro-5-(2-propenyl)-5H-dibenzo[a,d]cyclohepten-5-ol (**2**).

Compound **1** (34.71 g, 0.167 mole) was dissolved in 250 ml of dry tetrahydrofuran and cooled to 0°. Allylmagnesium chloride (100 ml, 0.200 mole, 2.0 M in tetrahydrofuran) was added dropwise *via* an addition funnel. The reaction mixture was warmed to room temperature and stirred for 24 hours. The reac-

tion was recooled to 0°, and 1 N hydrochloric acid was added. The mixture was extracted with ethyl acetate, and the combined organic phase was washed with brine, dried, filtered, and concentrated. The crude product was purified by flash chromatography (5% ethyl acetate-hexane followed by 10% ethyl acetate-hexane) to give 37.50 g (90%) of compound **2** as a yellow oil; ¹H nmr (200 MHz, deuteriochloroform): δ 2.63 (s, 1H, OH), 3.00 (m, 4H, Ar-CH₂-CH₂-Ar), 3.43 (m, 2H, CH₂C=C), 5.08 (m, 2H, C=CH₂), 5.40 (m, 1H, C=CH), 7.18 (m, 6H, ArH), 7.88 (m, 2H, ArH).

β -Bromo-10,11-dihydro-5-hydroxy-5H-dibenzo[a,d]cycloheptene-5-propanol (**3**).

Compound **2** (15.0 g, 0.0599 mole) was dissolved in 150 ml of dimethyl sulfoxide. Water (2.2 ml, 2.2 g, 0.122 mole) was added, and the reaction mixture cooled to 15°. *N*-Bromosuccinimide (21.33 g, 0.120 mole) was added portionwise while maintaining the internal temperature between 15–20°. The reaction mixture was stirred at room temperature for 1 hour, poured into a 0.5 M sodium bicarbonate solution, and extracted with diethyl ether. The combined organic phase was washed with brine, dried, filtered, and concentrated. The crude product was rapidly purified (approximately one hour or less) by flash chromatography (1:4 ethyl acetate-hexane then 1:3 ethyl acetate-hexane) to give 8.00 g (50%) of compound **3** as a white solid, mp 94–97° dec; ¹H nmr (200 MHz, deuteriochloroform): δ 2.86 (dd, 1H, J = 7.5, 15 Hz, CH-C-Br), 3.00 (m, 2H, CH₂-Ar), 3.15 (dd, 1H, J = 5, 15 Hz, CH-C-Br), 3.40 (m, 2H, CH₂-Ar), 3.70 (d, 2H, J = 5 Hz, CH₂-OH), 3.85 (m, 1H, CH-Br), 7.20 (m, 6H, ArH), 7.85 (m, 1H, ArH), 7.95 (m, 1H, ArH); ir (deuteriochloroform): ν 3650 (OH); ms: (FAB) *m/z* 329 (M⁺ -H₂O), 331 (M⁺ -H₂O).

Anal. Calcd. for C₁₈H₁₉BrO₂: C, 62.25; H, 5.53; Br, 23.01. Found: C, 62.22; H, 4.98; Br, 22.98.

Spiro[4'-bromo-3',4',10,11-tetrahydro-5H-dibenzo[a,d]cycloheptene-5,2'(5'H)-furan-5'-one] (**4**).

Compound **3** (0.500 g, 1.88 mmoles) was dissolved in 10 ml of dimethylformamide. Pyridinium dichromate (1.06 g, 2.82 mmoles) was added, and after 5 hours a second portion of pyridinium dichromate (1.06 g, 2.82 mmoles) was added. The reaction mixture was stirred at room temperature for 16 hours, poured into water, and extracted with diethyl ether. The combined organic phase was washed with brine, dried, filtered, and concentrated. The crude product was purified by flash chromatography (1:4 ethyl acetate-hexane) to give 0.226 g (35% yield) of compound **4** as a white solid, mp 149–150°; ¹H nmr (200 MHz, deuteriochloroform): δ 3.13 (m, 3H, CH₂-Ar, CH-C-Br), 3.48 (m, 2H, CH₂-Ar), 3.65 (dd, 1H, J = 9, 13 Hz, CH-C-Br), 4.55 (t, 1H, J = 9 Hz, CH-Br), 7.25 (m, 6H, ArH), 7.50 (m, 1H, ArH), 7.70 (m, 1H, ArH); ¹³C nmr (75 MHz, deuteriochloroform): δ 32.1 (C-Ar), 36.4 (C-Br), 48.7 (C-C-Br), 87.5 (C-Ar₂), 122.9 (Ar), 123.6 (Ar), 126.1 (Ar), 126.2 (Ar), 128.0 (Ar), 128.1 (Ar), 130.4 (Ar), 131.0 (Ar), 136.0 (Ar), 136.4 (Ar), 139.4 (Ar), 140.1 (Ar), 171.6 (C=O); ir (deuteriochloroform): ν 1790 (C=O); ms: (FAB) *m/z* 343 (M+1), 345 (M+1).

Anal. Calcd. for C₁₈H₁₅BrO₂: C, 62.99; H, 4.41. Found: C, 62.94; H, 4.33.

Spiro[4'-bromo-4',5',10,11-tetrahydro-5H-dibenzo[a,d]cycloheptene-5,2'(3'H)-furan] (**5**).

Oxalyl chloride (6.44 g, 4.4 ml, 50.8 mmoles) was dissolved in 100 ml of dry dichloromethane and cooled to -78° . Dry dimethyl sulfoxide (7.93 g, 7.2 ml, 102 mmoles) dissolved in 25 ml of dry dichloromethane was added dropwise *via* addition funnel over 10 minutes. The reaction mixture was stirred at -78° for 10 minutes, and then compound **3** (11.27 g, 42.3 mmoles), dissolved in 50 ml of dry dichloromethane, was added dropwise *via* an addition funnel over 10 minutes. After stirring the reaction mixture at -78° for 15 minutes, triethylamine (12.84 g, 17.7 ml, 127 mmoles) was added. The reaction mixture was allowed to warm slowly to room temperature, stirred for 3 hours, poured into water, and extracted with dichloromethane. The organic extract was washed successively with 0.25 *N* hydrochloric acid and brine, and was then dried, filtered, and concentrated. The crude product was purified by flash chromatography (1:12 ethyl acetate-hexane) to give 5.02 g (36% yield) of compound **5** as a light yellow solid, mp $145-146^{\circ}$; ^1H nmr (400 MHz, deuteriochloroform): δ 2.87 (dd, 1H, $J = 8, 13$ Hz, CH-C-Ar₂), 2.97 (m, 2H, CH₂-Ar), 3.29 (dd, 1H, $J = 8, 13$ Hz, CH-C-Ar₂), 3.47 (m, 2H, CH₂-Ar), 4.23 (dd, 1H, $J = 7, 9$ Hz, CH-O), 4.31 (m, 1H, CH-Br), 4.55 (dd, 1H, $J = 6, 9$ Hz, CH-O), 7.15 (m, 6H, ArH), 7.70 (m, 1H, ArH); ^{13}C nmr (75 MHz, deuteriochloroform): δ 32.8 (C-Ar), 43.4 (C-Br), 53.1 (C-C-Br), 74.6 (C-O), 86.5 (C-Ar₂), 124.3 (Ar), 124.4 (Ar), 124.5 (Ar), 126.0 (Ar), 126.2 (Ar), 127.4 (Ar), 130.4 (Ar), 130.9 (Ar), 136.9 (Ar), 143.7 (Ar), 144.1 (Ar), 145.1 (Ar); ms: (FAB) m/z 329 (M+1), 331 (M+1).

Anal. Calcd. for C₁₈H₁₇BrO: C, 65.66; H, 5.21; Br, 24.27. Found: C, 65.70; H, 5.05; Br, 24.34.

Spiro[4',5',10,11-tetrahydro-4'-methoxy-5*H*-dibenzo[*a,d*]cycloheptene-5,2'(3'*H*)-furan] (**6a**).

Compound **5** (0.500 g, 1.76 mmoles) was dissolved in 5 ml of methanol and 5 ml of tetrahydrofuran, and silver tetrafluoroborate (0.410 g, 2.11 mmoles) was added. The reaction mixture was refluxed for 16 hours, cooled to room temperature, and filtered through celite. The isolated silver salts were washed on the filter funnel with ethyl acetate. The filtrate was washed with brine, dried, filtered, and concentrated. The crude product was purified by flash chromatography (5% ethyl acetate-hexane followed by 7% ethyl acetate-hexane) to give 0.145 g (28% yield) of compound **6a** as a light brown oil; ^1H nmr (200 MHz, deuteriochloroform): δ 2.78 (m, 2H, CH₂-C-Ar₂), 2.95 (m, 2H, CH₂-Ar), 3.25 (s, 3H, OMe), 3.50 (m, 2H, CH₂-Ar), 4.03 (m, 1H, CH-OMe), 4.20 (m, 2H, CH₂-O), 7.15 (m, 6H, ArH), 7.70 (m, 1H, ArH), 7.88 (m, 1H, ArH); ms: (EI) m/z 280 (M⁺).

High resolution ms Calcd. for C₁₉H₂₀O₂: 280.1463. Found: 280.1472.

Compounds **6b-d** were synthesized in an analogous manner by using the appropriate amine nucleophile (5-10 equivalents).

Spiro[4',5',10,11-tetrahydro-*N,N*-diethyl-5*H*-dibenzo[*a,d*]cycloheptene-5,2'(3'*H*)-furan-4'-amine] Hydrochloride (**6c**).

This compound had mp $204-207^{\circ}$; ^1H nmr (200 MHz, deuteriochloroform): δ 1.40 (t, 6H, $J = 7.5$ Hz, C-2 of ethyl), 3.02 (m, 6H), 3.25 (m, 2H), 3.50 (m, 2H), 3.90 (m, 1H, CH-N), 4.45 (dd, 1H, $J = 7, 10$ Hz, CH-O), 4.70 (dd, 1H, $J = 6, 10$ Hz, CH-O), 7.13 (m, 6H, ArH), 7.55 (m, 1H, ArH), 7.75 (m, 1H, ArH); ^{13}C nmr (75 MHz, deuteriochloroform): δ 9.20 (C-2 of ethyl), 32.4 (C-Ar), 42.7 (C-C-Ar₂), 45.5 (C-1 of ethyl), 61.9 (C-N), 66.6 (C-O), 86.7 (C-Ar₂), 123.9 (Ar), 126.2 (Ar), 126.5

(Ar), 127.9 (Ar), 130.8 (Ar), 131.6 (Ar), 136.4 (Ar), 136.8 (Ar), 142.1 (Ar), 142.8 (Ar); ms: (FAB) m/z 322 (M+1).

Anal. Calcd. for C₂₂H₂₇NO·HCl·0.25H₂O: C, 72.90; H, 7.94; N, 3.87. Found: C, 72.81; H, 7.94; N, 3.68.

1-Spiro[4',5',10,11-tetrahydro-5*H*-dibenzo[*a,d*]cycloheptene-5,2'(3'*H*)-furan-4'-yl]piperidine Hydrochloride (**6d**).

This compound had mp $255-258^{\circ}$; ^1H nmr (300 MHz, deuteriochloroform): δ 1.80 (m, 4H, piperidine H), 2.32 (m, 2H), 2.53 (q, 1H, $J = 11$ Hz), 2.65 (q, 1H, $J = 11$ Hz), 3.00 (m, 3H, CH₂-Ar and CH-C-Ar₂), 3.25 (m, 2H), 3.50 (m, 3H, CH₂-Ar), 3.70 (m, 1H, CH-N), 4.35 (dd, 1H, $J = 7.5, 11$ Hz, CH-O), 4.70 (dd, 1H, $J = 3.5, 11$ Hz, CH-O), 7.15 (m, 6H, ArH), 7.50 (m, 1H, ArH), 7.72 (m, 1H, ArH); ^{13}C nmr (75 MHz, deuteriochloroform): δ 22.0 (C-4 of piperidine), 22.6 (C-3 of piperidine), 32.3 (C-Ar), 42.6 (C-C-Ar₂), 51.4 (C-2 of piperidine), 66.2 (C-N), 66.4 (C-O), 86.5 (C-Ar₂), 123.5 (Ar), 123.9 (Ar), 126.2 (Ar), 126.4 (Ar), 127.8 (Ar), 131.0 (Ar), 131.6 (Ar), 136.3 (Ar), 136.8 (Ar), 142.3 (Ar), 142.6 (Ar); ms: (FAB) m/z 334 (M+1).

High resolution ms Calcd. for C₂₃H₂₇NO: 333.2093. Found: 333.2077.

1-[(10,11-Dihydro-5-hydroxy-5*H*-dibenzo[*a,d*]cyclohepten-5-yl)methyl]-1,2-ethanediol (**8**).

Compound **2** (16.00 g, 0.0639 mole) was dissolved in 100 ml of *t*-butyl alcohol, 40 ml of tetrahydrofuran, and 20 ml of water. Pyridine (10 ml), osmium tetroxide (2.5 weight % in *t*-butyl alcohol, 4.0 ml, 0.320 mmole), and *N*-methylmorpholine *N*-oxide (8.98 g, 0.0767 mole) were added. The reaction mixture was refluxed for 20 hours and then cooled to room temperature. The solvent was evaporated, and 1 *N* hydrochloric acid and saturated sodium sulfite solution were added. The aqueous phase was extracted with dichloromethane. The organic extract was washed with brine, dried, filtered, and evaporated. The crude product was purified by flash chromatography (1:1 ethyl acetate-hexane followed by 2:1 ethyl acetate-hexane) to give 16.23 g (89% yield) of compound **8** as a colorless oil; ^1H nmr (200 MHz, deuteriochloroform): δ 2.18 (dd, 1H, $J = 10, 15$ Hz, CH-C-Ar₂), 2.55 (dd, 1H, $J = 2, 15$ Hz, CH-C-Ar₂), 2.88 (m, 1H), 3.08 (m, 1H), 3.35 (m, 5H), 7.20 (m, 6H, ArH), 7.95 (dd, 1H, $J = 2, 8$ Hz, ArH), 8.08 (dd, 1H, $J = 2, 8$ Hz, ArH); ir (deuteriochloroform): ν 3650 (OH), 3550 (OH); ms: (FAB) m/z 267 (M⁺ - H₂O).

α -[[[1,1-Dimethylethyl]dimethylsilyl]oxy]methyl]- β -(10,11-dihydro-5-hydroxy-5*H*-dibenzo[*a,d*]cyclohepten-5-yl)-ethanol (**9**).

Compound **8** (15.23 g, 0.0536 mole) was dissolved in 100 ml of dry tetrahydrofuran and 100 ml of dry dimethylformamide, and cooled to 0° . Triethylamine (8.13 g, 11.2 ml, 0.0803 mole), 4-dimethylaminopyridine (0.65 g, 0.00536 mole), and *t*-butyldimethylsilyl chloride (8.88 g, 0.0589 mole) were added. The reaction mixture was warmed up slowly, stirred at room temperature for 5 hours, poured into 0.5 *N* hydrochloric acid, and extracted with ethyl acetate. The organic extract was washed with brine, dried, filtered, and concentrated. The crude product was purified by flash chromatography (1:8 ethyl acetate-hexane followed by 1:4 ethyl acetate-hexane) to give 18.45 g (86% yield) of compound **9** as a colorless oil; ^1H nmr (200 MHz, deuteriochloroform): δ 0.00 (s, 6H, Si-Me₂), 0.85 (s, 9H, Si-*t*-Bu), 2.05 (dd, 1H, $J = 10, 15$ Hz, CH-C-Ar₂), 2.75 (dd, 1H, $J = 2, 15$ Hz, CH-C-Ar₂), 2.90 (m, 1H), 3.13 (m, 1H), 3.40 (m, 5H), 7.20 (m, 6H, ArH), 8.00 (dd, 1H, $J = 2, 8$ Hz, ArH), 8.13 (dd, 1H, $J =$

2, 8 Hz, ArH); ir (deuteriochloroform): δ 3550 (OH); ms: (FAB) m/z 381 ($M^+ - H_2O$).

1-(10,11-Dihydro-5-hydroxy-5*H*-dibenzo[*a,d*]cyclohepten-5-yl)-3-[[1,1-dimethylethyl]dimethylsilyl]oxy]propan-2-one (**10**).

Oxalyl chloride (0.455 g, 0.31 ml, 3.58 mmoles) was dissolved in 5 ml of dry dichloromethane and cooled to -78° . Dry dimethyl sulfoxide (0.560 g, 0.51 ml, 7.16 mmoles) was added dropwise *via* a syringe. The reaction mixture was stirred at -78° for 10 minutes. Compound **9** (1.19 g, 2.99 mmoles), dissolved in 10 ml of dry dichloromethane, was added dropwise *via* addition funnel over 5 minutes. The reaction mixture was stirred at -78° for 15 minutes and was then treated with triethylamine (0.906 g, 1.25 ml, 8.96 mmoles). The reaction mixture was allowed to warm up slowly, poured into water, and extracted with dichloromethane. The combined organic phase was washed with 0.25 *N* hydrochloric acid, brine, dried, filtered, and concentrated. The crude product was purified by flash chromatography (1:8 ethyl acetate-hexane) to give 1.03 g (87% yield) of compound **10** as a colorless oil; 1H nmr (200 MHz, deuteriochloroform): δ 0.00 (s, 6H, Si-Me₂), 0.90 (s, 9H, Si-*t*-Bu), 3.10 (m, 2H, CH₂-Ar), 3.50 (m, 2H, CH₂-Ar), 3.53 (s, 2H, CH₂-C-Ar₂), 3.83 (s, 2H, CH₂-OSi), 5.48 (s, 1H, OH), 7.20 (m, 6H, ArH), 7.95 (m, 2H, ArH); ir (deuteriochloroform): ν 3500 (OH), 1710 (C=O).

Spiro[10,11-dihydro-5*H*-dibenzo[*a,d*]cycloheptene-5,2'(3'*H*)-furan-4'(5'*H*)-one (**11**).

Compound **10** (1.01 g, 2.55 mmoles) was dissolved in 10 ml of acetonitrile, and 1 ml of 48% aqueous hydrofluoric acid was added. The reaction mixture was stirred at room temperature for 1 hour, poured carefully into saturated sodium bicarbonate, and extracted with ethyl acetate. The organic extract was washed with brine, dried, filtered, and concentrated. The crude product was purified by flash chromatography (1:12 ethyl acetate-hexane) to give 0.50 g (74% yield) of compound **11** as a white solid, mp 129-130 $^\circ$; 1H nmr (300 MHz, deuteriochloroform): δ 3.10 (m, 2H, CH₂-Ar), 3.28 (s, 2H, CH₂-C-Ar₂), 3.40 (m, 2H, CH₂-Ar), 4.35 (s, 2H, CH₂-O), 7.18 (m, 6H, ArH), 7.70 (m, 2H, ArH); ^{13}C nmr (75 MHz, deuteriochloroform): δ 31.7 (C-Ar), 51.7 (C-C=O), 69.8 (C-O), 85.2 (C-Ar₂), 123.8 (Ar), 126.0 (Ar), 127.6 (Ar), 130.8 (Ar), 136.6 (Ar), 142.3 (Ar), 213.9 (C=O); ir (deuteriochloroform): ν 1770 (C=O); ms: (EI) m/z 264 (M^+).

Anal. Calcd. for C₁₈H₁₆O₂: C, 81.78; H, 6.11. Found: C, 81.85; H, 6.02.

N-Spiro[4',5',10,11-tetrahydro-5*H*-dibenzo[*a,d*]cycloheptene-5,2'(3'*H*)-furan-4'-ylpyrrolidine] Hydrochloride (**6b**).

Compound **11** (0.92 g, 3.48 mmoles) was dissolved in 6 ml of tetrahydrofuran and 6 ml of methanol. 3A molecular sieves, pyrrolidine (1.48 g, 20.88 mmoles), 19 weight % hydrochloric acid in ethanol (1.7 ml, 6.96 mmoles), and sodium cyanoborohydride (0.146 g, 2.32 mmoles) were added successively. The reaction mixture was stirred at room temperature for 22 hours, poured into 1 *N* sodium hydroxide, and extracted with ethyl acetate. The combined organic phase was extracted with 1 *N* hydrochloric acid. This acidic aqueous solution was made basic with 25 weight % aqueous sodium hydroxide and was extracted with dichloromethane. The combined dichloromethane extracts were dried, filtered, and concentrated. The crude product was purified by flash chromatography (3:1 ethyl acetate-hexane) to give 190 mg (17% yield) of compound **6b** as a colorless foam.

Compound **6b** was dissolved in absolute ethanol, and was acidified with 19 weight % hydrochloric acid in ethanol. Diethyl ether was added to precipitate the hydrochloride salt as a white solid, mp 227-232 $^\circ$; 1H nmr (400 MHz, deuteriochloroform): δ 1.98 (m, 2H, CH₂-C-N), 2.20 (m, 2H, CH₂-C-N), 2.73 (m, 1H, CH-N), 2.84 (m, 1H, CH-N), 2.90 (dd, 1H, *J* = 8, 13 Hz, CH-C-Ar₂), 3.02 (m, 2H, CH₂-Ar), 3.28 (dd, 1H, *J* = 8, 13 Hz, CH-C-Ar₂), 3.48 (m, 2H, CH₂-Ar), 3.56 (m, 1H, CH-N), 3.67 (m, 1H, CH-N), 3.84 (m, 1H, CH-N), 4.42 (dd, 1H, *J* = 7, 10 Hz, CH-O), 4.56 (dd, 1H, *J* = 6, 10 Hz, CH-O), 7.15 (m, 6H, ArH), 7.53 (m, 1H, ArH), 7.75 (m, 1H, ArH); ^{13}C nmr (75 MHz, deuteriochloroform): δ 23.0 (C-C-N), 31.8 (C-Ar), 43.2 (C-C-Ar₂), 51.2 (C-N), 62.7 (C-N), 66.5 (C-O), 86.2 (C-Ar₂), 123.3 (Ar), 125.6 (Ar), 126.0 (Ar), 127.4 (Ar), 130.3 (Ar), 131.1 (Ar), 135.9 (Ar), 136.3 (Ar), 141.6 (Ar), 142.3 (Ar); ms: (EI) m/z 319 (M^+).

Anal. Calcd. for C₂₂H₂₅NO $\cdot$ HCl: C, 74.23; H, 7.38; N, 3.94. Found: C, 74.09; H, 7.29; N, 4.13.

Spiro[10,11-dihydro-5*H*-dibenzo[*a,d*]cycloheptene-5,2'(3'*H*)-furan] 4'(5')-Oxime (**12**).

Compound **11** (0.500 g, 1.89 mmoles) was dissolved in 10 ml of dichloromethane, and 3A sieves, pyridine (0.299 g, 0.31 ml, 3.78 mmoles), and hydroxylamine hydrochloride (0.197 g, 2.84 mmoles) were added successively. The reaction mixture was stirred at room temperature for 16 hours, poured into 0.5 *N* hydrochloric acid, and extracted with dichloromethane. The combined organic phase was washed with brine, dried, filtered, and concentrated. The crude product was purified by flash chromatography (1:3 ethyl acetate-hexane) to give 0.49 g (93% yield) of compound **12** as a white solid, mp 151-153 $^\circ$; 1H nmr (300 MHz, deuteriochloroform): δ 3.08 (m, 2H, CH₂-Ar), 3.45 (m, 2H, CH₂-Ar), 3.45 and 3.50 (s, 2H, CH₂-C-Ar₂, 1:1 isomer), 4.75 and 4.85 (s, 2H, CH₂-O, 1:1 isomer), 7.15 (m, 6H, ArH), 7.55 and 7.60 (s, 1H, OH), 7.65 (m, 2H, ArH); ^{13}C nmr (75 MHz, deuteriochloroform): δ 32.5 (C-Ar), 43.2 and 44.6 (C-C=N), 65.6 and 67.1 (C-O), 86.8 and 87.1 (C-Ar₂), 124.2 (Ar), 124.4 (Ar), 126.3 (Ar), 127.7 (2 Ar), 131.0 (Ar), 137.0 (Ar), 142.7 (Ar), 143.2 (Ar), 162.0 and 163.4 (C=N); ms: (FAB) m/z 280 ($M+1$).

Anal. Calcd. for C₁₈H₁₇NO₂: C, 77.38; H, 6.15; N, 5.02. Found: C, 77.18; H, 6.08; N, 5.07.

Spiro[4',5',10,11-tetrahydro-5*H*-dibenzo[*a,d*]cycloheptene-5,2'(3'*H*)-furan-4'-ylidene-acetonitrile (**13**).

Diisopropylamine (0.65 g, 0.90 ml, 6.43 mmoles) was dissolved in 15 ml of dry tetrahydrofuran, and the resulting solution cooled to 0 $^\circ$. *n*-Butyllithium (2.5 *M* in hexane, 2.4 ml, 6.05 mmoles) was added dropwise *via* a syringe. The reaction mixture was stirred at 0 $^\circ$ for 5 minutes, then cooled to -45° . Diethyl cyanomethylphosphonate (1.14 g, 1.04 ml, 6.43 mmoles) was added dropwise *via* a syringe. Stirring at -45° was continued for 1 hour, and then compound **12** (1.00 g, 3.78 mmoles) was added. The reaction mixture was warmed slowly to room temperature, heated at 45 $^\circ$ for 16 hours, poured into saturated ammonium chloride, and extracted with ethyl acetate. The combined organic phase was washed with brine, dried, filtered, and concentrated. The crude product was purified by flash chromatography (1:9 ethyl acetate:hexane) to give 0.45 g (41% yield) of compound **13** as a colorless foam; 1H nmr (200 MHz, deuteriochloroform): δ 3.10 (m, 2H, CH₂-Ar), 3.45 (m, 2H, CH₂-Ar), 3.55 and 3.70 (s, 2H, CH₂-C-Ar₂, 1:1 isomer), 4.85 and 5.03 (s, 2H, CH₂-O,

1:1 isomer), 5.25 (s, 1H, C=CH), 7.20 (m, 6H, ArH), 7.65 (m, 2H, ArH).

Spiro[4',5',10,11-tetrahydro-5H-dibenzo[*a,d*]cycloheptene-5,2'(3'*H*)-furan-4'-ethanamine] Hydrochloride (14).

Compound 13 (0.44 g, 1.53 mmoles) was dissolved in 25 ml of absolute ethanol, and sodium borohydride (0.347 g, 9.18 mmoles) was added. The reaction mixture was stirred at room temperature for 10 minutes before adding cobalt chloride hexahydrate (0.364 g, 1.53 mmoles). Stirring was continued for 30 minutes, then additional sodium borohydride (0.347 g, 9.18 mmoles) was added. The reaction mixture was stirred for 4.5 hours, poured into 2 *N* hydrochloric acid, and washed with ethyl acetate. The aqueous phase was made basic with 25 weight % sodium hydroxide and extracted with dichloromethane. The organic extract was washed with brine, dried, filtered, and concentrated. The crude product was dissolved in absolute ethanol and was acidified with 19 weight % hydrochloric acid in ethanol. Addition of diethyl ether resulted in the precipitation of the hydrochloride salt of compound 14 [0.163 g (32%)] as a light green solid, mp 135-140° (foams); ¹H nmr (300 MHz, deuteriochloroform): δ 1.75 (m, 2H, CH₂-C-N), 2.25 (m, 2H, CH₂-N), 2.85 (m, 5H), 3.45 (m, 2H), 3.65 (t, 1H, J = 7.5 Hz, CH-O), 4.35 (t, 1H, J = 7.5 Hz, CH-O), 7.13 (m, 6H, ArH), 7.73 (m, 2H, ArH), 8.15 (broad s, 2H, NH₂); ms: (FAB) *m/z* 294 (M+1).

Anal. Calcd. for C₂₀H₂₃NO•HCl•1/2H₂O•1/4C₄H₇O₂: C, 69.88; H, 7.56; N, 3.88. Found: C, 69.97; H, 7.23; N, 4.07.

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