4,5-Dibenzyloxybenzyne as a Synthon for Diels-Alder Reactions. The Synthesis of 6,7-Dihydroxy-1,4-ethano-1,2,3,4-tetrahydroisoquinolines as Rigid Analogs of Adrenergic Agents. Assignment of Proton and Carbon-13 NMR Parameters Using Homonuclear and Heteronuclear Two-Dimensional Chemical Shift Correlation NMR Spectroscopy

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The synthesis of several rigid analogs of catecholamine type of adrenergic agents is reported. Their synthesis began with a Diels-Alder cycloaddition of 4,5-dibenzyloxybenzyne (generated from 4,5-dibenzyloxyanthranilic acid) to 1-(2-*trans*-phenylvinyl)-2-pyridone and 1-benzyl-3-benzyloxy-2-pyridone. The unsaturated amides so produced were reduced first with hydrogen and palladium and then with lithium aluminum hydride to provide 6,7-dihydroxy-1,4-ethano-1,2,3,4-tetrahydroisoquinolines. Homonuclear and heteronuclear two-dimensional chemical shift correlation nmr spectroscopy confirmed the structure of the bridged tetrahydroisoquinolines and led to the unambiguous assignment of the ^1H and ^{13}C nmr chemical shifts of key compounds.

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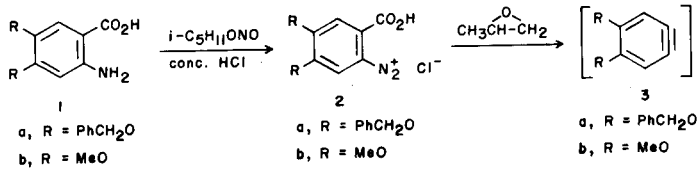
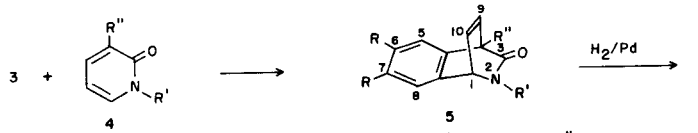
Introduction.

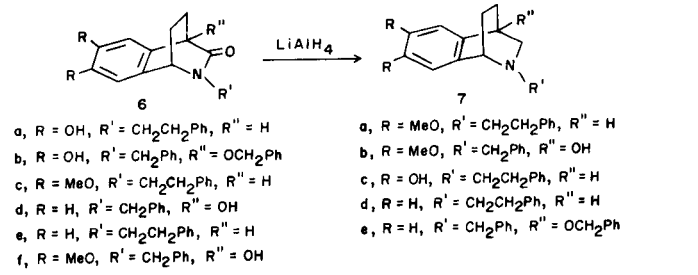
The addition of benzynes to 1-substituted 2-pyridones produces the tricyclic isoquinolone system **5** [2]. Reduction of **5** leads to bridged tetrahydroisoquinolines which can be considered rigid analogs of amphetamine (**7**, R = R'' = H), ephedrine (**7**, R = H, R'' = OH) and dopamine (**7**, R = OH, R'' = H). In a previous paper, we reported the synthesis of **7a** and **7b** [2]. It was planned to remove the ether groups in **7a** to produce a constrained analog of dopamine and in **7b** to obtain an analog of ephedrine. However, attempts to cleave the methoxy groups in **7a** by boiling with 48% hydrobromic acid or by iodotrimethylsilane [3], or by sodium ethylmercaptide in DMF [4] (in **7b**) produced in each instance intractable mixtures. The starting materials had reacted (as judged by thin layer chromatograms) and indeed the methyl ether groups had been removed (from nmr spectra) but pure products could not be isolated even after many chromatographic separations.

In seeking alternative routes to phenolic compounds in the condensed system **7** (R = OH), we sought suitable protective groups from which the phenols could be released under relatively mild conditions at the end of the reaction sequence. The use of benzyl ethers was explored since their hydrogenolysis would release the phenols in the last step.

Therefore, we have investigated the use of 4,5-dibenzyloxybenzyne as the dienophile in the Diels-Alder reaction with 1-substituted 2-pyridones. The starting material was 4,5-dibenzyloxyanthranilic acid (**1a**) which was diazotized to the corresponding carboxy diazonium chloride (**2a**). Removal of the elements of hydrogen chloride by the use of propylene oxide produces the internal salt which, upon gentle heating, lost carbon dioxide and nitrogen in a familiar sequence of events to generate a benzyne, *in situ* [5]. The particular benzyne **3** was expected to add to 1-substituted-2-pyridones in cycloadditions initially developed in our laboratory [6-8] to yield tricyclic amides (**5**). Two representative 2-pyridones (**4**) were chosen for the Diels-Alder additions, namely, 1-(2-*trans*-phenylvinyl)-2-pyridone (**4a**) and 1-benzyl-3-benzyloxy-2-pyridone (**4b**). The first one







was utilized because the electron-attracting *N*-styryl group renders the pyridone more electrophilic (compared to a simple *N*-alkyl substituent) and benzyne additions gave the predictable products [9]. The second pyridone was chosen because the adduct possesses an oxy functional group in the final product **7** (position 4) which would make that compound a rigid analog of ephedrine. The additions of 4,5-dibenzyloxybenzyne to these two pyridones formed the expected unsaturated lactams (**5**). Pure products were isolated after extensive chromatography and were characterized by ^1H and ^{13}C nmr spectra.

Catalytic reduction of these adducts over palladium on charcoal proceeded in good yield. As expected, in **5a** the benzyl ethers were reduced at the same time as the alkene and provided **6a**. Lithium aluminum hydride reduction of **6a** afforded **7c**. Careful catalytic reduction of **5b** released the phenolic groups but the 4-benzyloxy ether appeared uneffected.

Attempts to reduce **5a** with lithium aluminum hydride in tetrahydrofuran before catalytic reduction gave 2,3-dibenzyloxynaphthalene as the only identifiable product. Apparently, a reverse Diels-Alder reaction with the elimination of PhCH=CHN=C=O had occurred. Such a reaction failed when **5a** was refluxed in tetrahydrofuran. Only after lithium aluminum hydride was added was **5a** converted entirely to 2,3-dibenzyloxynaphthalene. Refluxing **5a** with sodium hydride in tetrahydrofuran also yielded 2,3-dibenzyloxynaphthalene. It would appear that sodium hydride or lithium aluminum hydride acted as strong bases which initiated this elimination.

Structure Proof by NMR.

An analysis of the ^1H 60 MHz nmr spectra of unsaturated amides **5** was in most cases straightforward and substantiated their structures. However, the reduced compounds (**6** and **7**) possessed strongly coupled aliphatic proton systems which could not be analyzed by 60 MHz nmr spectra. Had skeletal rearrangements taken place these could not have been detected unless this complex spin system could be analyzed. With the availability of high field (200 and 360 MHz) proton and carbon spectra, together with two-dimensional (2D) methods [10], nmr parameters were obtained readily to prove the structures of the compounds which we have synthesized.

Homonuclear shift-correlated 2D nmr (COSY) [11] spectra allowed the proton-proton coupling network to be established. In many compounds the assignment of the proton spectra was straightforward. However, when overlap of proton signals prevented an unambiguous assignment, a combination of COSY and heteronuclear shift correlated spectra [12] proved to be sufficient for a complete assignment of both proton and carbon chemical shifts. With the latter type of 2D spectra the assignment of the proton signals is straightforward if the attached carbon have been assigned and *vice versa*. In our system many of the carbon signals were assigned with the aid of off-resonance decoupling, or the more recent APT [13] technique and by comparison with literature assignments from model compounds [14].

Table I

^{13}C-NMR Chemical Shifts [a] of Compounds **5-7** [b]

Compound	C-1	C-3	C-4	C-9	C-10	Others
5a	56.2	169.8	54.5	135.7	137.2	133.2, 133.6 (C-4a and C-8a), 147.0, 147.3 (C-6 and C-7), 128.6, 128.5, 128.4, 127.8, 127.3, 127.2, 126.3, 125.4, 123.9, 112.6, 111.4, 109.1 (CH), 136.3 (CH=CH-Ph, C-*i*), 136.9, 137.0 (2 CH_2Ph, C-*i*), 72.0, 71.5 (2 OCH_2)
5c	56.4	170.0	54.7	135.9	137.4	132.5, 133.0 (C-4a and C-8a), 147.1, 147.2 (C-6 and C-7), 128.7, 126.4, 125.5, 124.0, 109.13, 109.07, 107.6, (CH), 56.32, 56.27 (2 CH_3O), 136.4 (Ph, C-*i*)
5d	57.7	172.6	87.9	139.1	134.5	135.9, 135.2 (C-4a and C-8a), 146.7, 146.5 (C-6 and C-7), 106.1, 106.4 (C-5 and C-8), 128.5, 128.4, 128.3, 127.5, 127.4 (CH), 56.2 (2 CH_3O), 132.5 (NCH_2C), 138.3 (OCH_2C), 49.1 (NCH_2), 69.6 (OCH_2)
6a	56.7	172.9	46.2	27.5	34.0	129.2, 132.0 (C-4a and C-8a), 143.1, 143.8 (C-6 and C-7), 110.0, 111.8 (C-5 and C-8), 45.3 (CH_2CH_2Ph), 22.8 (CH_2CH_2Ph), 128.3, 128.5 (Ph, C-*o* and C-*m*), 138.9 (Ph, C-*i*), 126.0 (Ph, C-*p*)
6c	55.7	127.7	46.6	27.4	34.1	130.8, 133.2 (C-4a and C-8a), 147.0, 147.7 (C-6 and C-7), 106.9, 108.8 (C-5 and C-8), 45.5 (CH_2CH_2Ph), 22.6 (CH_2CH_2Ph), 128.3, 128.8 (Ph, C-*o* and C-*m*), 139.0 (Ph, C-*i*), 126.1 (Ph, C-*p*), 57.1 (2 CH_3O)
6d	56.4	174.2	75.4	30.1	27.5	137.6, 140.5 (C-4a and C-8a), 121.1, 121.0 (C-6 and C-7), 128.6, 128.0, 127.7, 127.5, 126.5, (Ar, CH), 136.0 (Ph, C-*i*), 48.8 (NCH_2)
7d [c]	57.2	54.5	32.3	20.8	22.8	131.5, 135.8 (C-4a and C-8a), 125.5, 124.1 (C-6 and C-7), 57.8 (CH_2CH_2Ph), 30.1 (CH_2CH_2Ph), 139.4 (Ph, C-*i*), 129.7, 128.3, 127.3, 126.6 (Ar, CH)
7e [c]	54.9	55.7	73.8	24.7	23.0	137.7, 141.3 (C-4a and C-8a), 130.2 (OCH_2C), 128.8 (NCH_2C), 66.0 (OCH_2), 59.9 (N-CH_2), 130.9, 130.18, 129.9, 129.3, 128.5, 127.8, 127.0, 125.7, 121.4 (Ar, CH)

[a] All spectra were obtained in deuteriochloroform except for **6a** (in DMSO-d_6) at 90.8 MHz. Chemical shifts are in ppm (δ) downfield from tetramethylsilane; multiplicity of carbon signals were determined by off-resonance decoupling or the APT [13] technique. [b] The synthesis of **5a** and **6a** is described in this work, that of other compounds has been previously reported by us [2]. [c] Assignments were confirmed by heteronuclear ^{13}C-^1H shift correlation experiments [12].

As an example, the detailed analysis of the nmr spectra of **7e** is presented below. The COSY spectrum of the aliphatic protons of **7e** is shown in Figure 1. The AB quartet (J = 11.3 Hz) at 4.86 and 4.78 ppm is attributed to the OCH_2 group. The broad singlet at 4.41 was assigned to H_1 which in turn led to the assignment of H_{10anti} and H_{10syn} at 3.09 and 1.64 ppm respectively, as evidenced by the cross peaks indicating coupling between these protons. The *syn* proton is expected to be upfield compared to the *anti* counterpart being shielded by the anisotropic effect of the fused benzene ring. The doublet (J = 10.7 Hz) at 4.30 ppm is shown to be coupled to the signal at 2.43 ppm and these signals were assigned to the H_{3exo} and H_{3endo}, respectively. The *endo* proton is really situated above the plane of the benzene ring (not unlike the *syn* 9 and 10 protons) and hence is expected to be upfield. The AX system at 3.52 and 4.00 ppm (J = 13.0 Hz) was assigned to the CH_2N protons. The assignment of the remaining two protons H_{9anti} and H_{9syn} was straightforward taking into consideration the overlap of H_{9syn} and H_{10syn} at 1.64 ppm.

Previous assignments were substantiated by the heteronuclear shift correlated spectrum (Figure 2) which established the carbon-proton connectivity and the unambiguous assignment of the carbon spectrum. In Figure 2, the quaternary carbon C-4 at 73.8 ppm shows no corresponding proton signals as expected. The carbon signal at 66.0 ppm was correlated with the AB quartet arising from the OCH_2 group. The carbon signal at 55.7 ppm is associated with the *endo* and *exo* proton at C-3. The 59.9 ppm carbon resonance is associated with the benzyl NCH_2 protons which appear also as an AX pattern. The signal of 54.9 was assigned to C-1 unambiguously from the APT [13] spectrum since it is the only CH in the aliphatic region of the spectrum. Hence, the assignment of H_1 was substantiated. The assignment of most of the upfield signals, C-9 and C-10 at 24.7 and 23.0 ppm, was based on the prior assignment of the corresponding proton chemical shifts from the COSY spectrum. This technique permitted extrapolation to assign all of the aliphatic shifts carbon and proton resonances of key compounds in this series and these are compiled in Tables I and II.

In conclusion, we demonstrated the utility of 4,5-dibenzyloxybenzyne for the synthesis of rigid analogs of catecholamine-type adrenergic agents. Furthermore, we have as-

Table II

High-Field (360 and 200 MHz) ^{1}H-NMR Parameters [a] of Compounds **5-7** [b]

Compound	Frequency MHz	H_1	H_3	H_4	H_9 and H_{10}	Aromatic	Others
5e [c]	200	4.89 (dd) $J_{1,9}$ = 1.7 Hz, $J_{1,10}$ = 5.7 Hz	—	—	7.06 (m, H_9) 6.73 (dd, H_{10}, $J_{9,10}$ = 7.7 Hz, $J_{1,10}$ = 5.7 Hz)	6.91-7.69 (m)	4.36, 4.62 (ABq, 2H, NCH_2, J = 15.1 Hz) 5.07, 5.54 (ABq, 2H, OCH_2, J = 12.3 Hz)
6a	200	4.62 (m)	—	3.71 (m)	1.40 (m, H_{9syn} and H_{10syn}) 1.79 (m, H_{9anti} and H_{10anti})	6.68 (s, 1H, H_5) 6.70 (s, 1H, H_8) 7.15-7.25 (m, 5H, Ph)	2.69 (m, 2H, CH_2Ph) 3.40-3.49 (m, 2H, NCH_2) 8.76 (bd, 2H, 2OH)
6c	360	4.30 (m)	—	3.77 (m)	1.32-2.02 (m)	6.54 (s, 1H, H_5) 6.82 (s, 1H, H_8) 7.11-7.26 (m, 5H, Ph)	2.79 (t, 2H, CH_2Ph) 3.72, 3.53 (2dt, 2H, NCH_2, J_{gem} = 13.9 Hz, J_{vic} = 7.2 Hz) 3.87 (s, 3H, MeO), 3.85 (s, 3H, MeO)
6d	200	4.47 (m)	—	—	1.42-2.05 (m)	7.00-7.58 (m)	4.52, 4.67 (ABq, 2H, NCH_2, J = 15.0 Hz) 4.33 (s, 1H, OH)
6e [c]	200	4.42 (m)	—	3.83 (m)	1.51 (m, H_{10syn} and H_{9syn}) 1.96 (m, H_{10anti} and H_{9anti})	6.57-7.74 (m)	2.78 (t, 2H, CH_2Ph) 3.68, 3.56 (2dt, 2H, NCH_2, J_{gem} = 13.8 Hz, J_{vic} = 7.3 Hz)
7d [c,d]	360	4.62 (m)	4.08 (m, H_{3exo}) 2.47 (m, H_{3endo})	3.39 (m)	2.15 (m, H_{9anti}), 3.12 (m, H_{10anti}), 1.51 (m, H_{9syn}), 1.60 (m, H_{10syn})	7.18-7.45 (m)	2.93, 2.65 (m, 2H, NCH_2) 3.12, 3.40 (m, 2H, CH_2Ph)
7e [c,d]	360	4.41 (m)	2.43 (m, H_{3endo}) 4.30 (d, H_{3exo}) J = 10.7 Hz	—	1.64 (m, H_{10syn} and H_{9syn}) 3.09 (m, H_{10anti}), 2.50 (m, H_{9anti})	7.23-7.77 (m)	3.52, 4.00 (AX, 2H, NCH_2Ph, J = 13.0 Hz) 4.86, 4.78 (ABq, 2H, OCH_2, J = 11.3 Hz)

[a] All spectra were obtained in deuteriochloroform, except for **6a** (in DMSO-d_6); chemical shifts are in ppm (δ) downfield from tetramethylsilane; for abbreviations, see Experimental Section. [b] The synthesis of **6a** is described in this work; that of the other compounds has been previously reported by us [2]. [c] Assignments were confirmed by a COSY [11] experiment. [d] Assignment was confirmed by a heteronuclear ^{13}C-^{1}H shift correlation experiment [12].

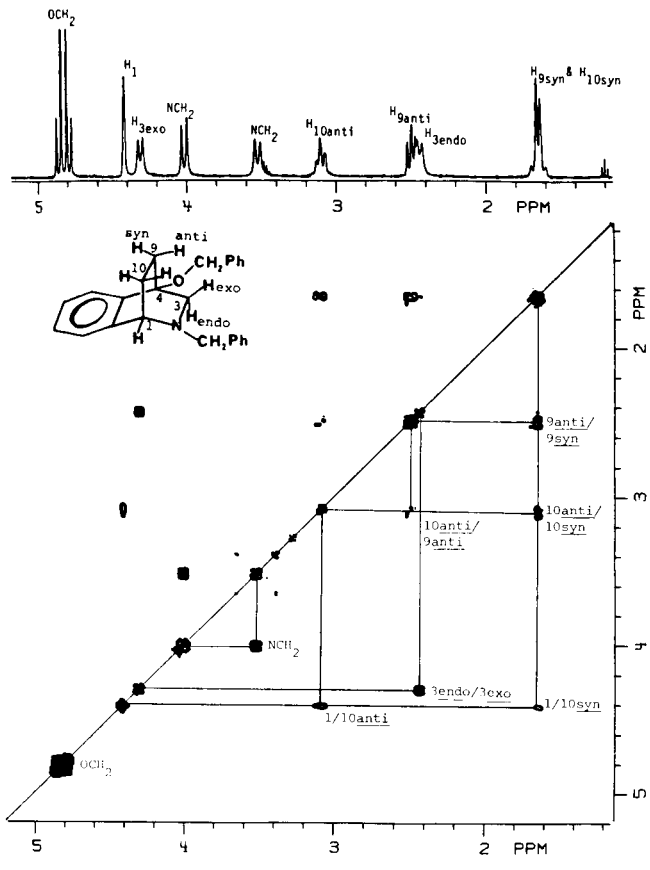


Figure 1. Two-dimensional (360 MHz) homonuclear shift-correlated (COSY) spectrum of **7e** (upfield resonances only).

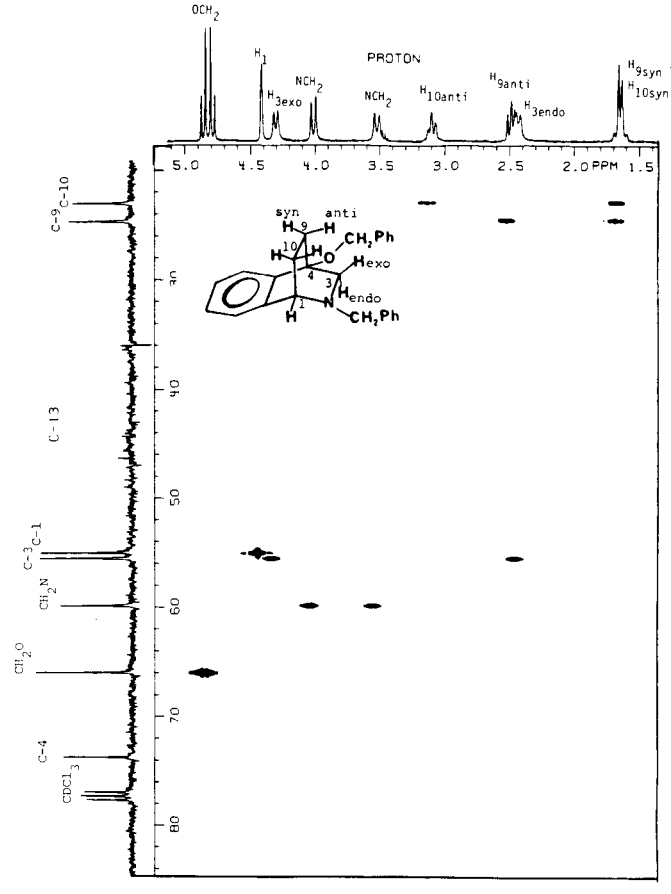


Figure 2. Two-dimensional heteronuclear shift-correlated spectrum of **7e** [360 (^{1}H) and 90.8 (^{13}C) MHz] in deuteriochloroform. Only the aliphatic region is shown.

signed chemical shifts for aliphatic protons and carbons in this cyclic system.

EXPERIMENTAL

Melting points were determined on a Mel-Temp block and are uncorrected. Elemental analyses were performed by Micro-Tech Laboratories, Skokie, Illinois. All solvents were reagent grade and distilled prior to use. Petroleum ether is the fraction of petroleum that boils between 35-60°. Removal of solvents "*in vacuo*" implies distillation of those solvents in a flash evaporator at a temperature of 95° (steam bath) or less using a water aspirator (20-30 Torr).

Proton nuclear magnetic resonance (^{1}H nmr) spectra were obtained on a Varian T-60 A spectrometer equipped with a Nicolet Instrument Corp. TT-7 Fourier transform accessory operating at 60 MHz. Nicolet NIC-200 and NIC-360 spectrometers were used to obtain 200 and 360 MHz ^{1}H nmr spectra. Carbon-13 nmr spectra were obtained on the NIC-360 instrument operating at 90.8 MHz for carbon using a 5 mm probe unless otherwise stated. Chemical shifts are reported in parts per million (δ) downfield from tetramethylsilane as internal standard. The following abbreviations were used: s, singlet; b, broad; d, doublet; t, triplet; q, quartet; and m, complex, overlapping or unresolved multiplet. For the homonuclear ^{1}H nmr two-dimensional chemical-shift correlation experiments (COSY) [11] an initial data matrix (256 × 512 points) was zero-filled to 512 × 1024 points. Quadrature phase detection was used in both dimensions and 4 transients were acquired for each t_1 increment with a preparation delay of 1 second. Sine-bell resolution enhancement function was used in both dimensions. The spectrum showed is in the absolute value mode and was symmetrized [15]. The heteronuclear ^{1}H-^{13}C shift correlated spectra [12] were obtained using a 12 mm probe. The 90° pulse lengths for carbon and proton were 22 and 85 μs respectively. The latter was callibrated as described by Bax [16] using a benzene sample doped with Cr(acac)$_3$. The phase cycle employed consisted of the 4-step cycle described by Bax [12d] plus simultaneous inversion of the first proton and the 180° carbon pulses. The coherence transfer anti-echo was detected. The mixing delays Δ_1 and Δ_2 were 3.8 and 2.4 ms and the preparation period was 1 second. The initial data matrix (256 × 2K) was zero-filled in F_1. Shifted sine-bell function was used for resolution enhancement and the spectra were displayed in the absolute value mode. Mass spectra were obtained by Mr. Richard Dvorak from a Varian MAT 112S mass spectrometer or a Hitachi Perkin-Elmer RMU-6D mass spectrometer. In general, relative abundances are reported for fragments over 10% of the base peak.

Chromatography.

Extensive chromatography was required to obtain the adducts from the initial reaction mixtures. Purification of the adducts is hindered by the fact that on warming, the adducts undergo retro-Diels-Alder reactions, producing an isocyanate and a 2,3-disubstituted-naphthalene. Care

must be taken to remove solvents used in chromatography without heat.

Silica gel (230-400 mesh) was purchased from Merck. "Baker Analyzed" reagent Silica Gel (60-200 mesh) purchased from J. T. Baker Chemical Company was used for flash column chromatography [17]. Thin layer chromatograms (tlc) were obtained on 6 × 6 cm strips of Eastman Chromagram silica gel sheets (No. 13181) mixed with a fluorescent indicator. Developing solvents were chloroform (solvent A), 10% petroleum ether-ethyl acetate (solvent B), ethyl acetate (solvent C), ethylene chloride (solvent D), 20% ethanol/chloroform (solvent E), 10% methanol/chloroform (solvent F), methanol (solvent G), and 10% ethanol/methylene chloride (solvent H).

4,5-Dibenzyloxyanthranilic Acid (**1a**).

3,4-Dihydroxybenzaldehyde was alkylated with benzyl chloride [18] to produce 3,4-dibenzyloxybenzaldehyde, mp 85-86°, lit [18] mp 87.5-89°, tlc, R_f = 0.79 (solvent A); ^{1}H nmr (60 MHz, deuteriochloroform): δ 5.21 (s, OCH_2), 5.25 (s, OCH_2), 6.50-7.93 (m, aromatic), 9.81 (s, CHO); ms: m/e 318 (M^+, 17), 227 (21), 181 (10), 91 (100), 65 (11). Nitration of 3,4-dibenzyloxybenzaldehyde with nitric acid [19] at 20° gave 4,5-dibenzyloxy-2-nitrobenzaldehyde, mp 138-140°, lit [19] mp 139-141°, tlc, R_f = 0.93 (solvent A); ^{1}H nmr (60 MHz, deuteriochloroform): δ 5.28 (s, 2 OCH_2), 6.51-7.86 (m, aromatic), 10.40 (s, CHO); ms: m/e 363 (M^+, 2), 273 (8), 181 (7), 91 (100), 65 (9). Oxidation using potassium permanganate, in boiling acetone [19] provided 4,5-dibenzyloxybenzoic acid, mp 169-172°, lit [19] mp 173-174°, tlc, R_f = 0.20 (solvent E); ^{1}H nmr (60 MHz, deuteriochloroform): δ 5.24 (s, 2 OCH_2), 6.92-7.93 (m, aromatic); ms: m/e 379 (M^+, 3), 181 (5), 91 (100), 65 (7). Reduction with ferrous sulfate and concentrated ammonium hydroxide yielded 4,5-dibenzyloxyanthranilic acid [19], mp 168-169°, lit [19] mp 182-183° dec, tlc, R_f = 0.25 (solvent E); ^{1}H nmr (60 MHz, DMSO-d_6): δ 4.97 (s, OCH_2), 5.12 (s, OCH_2), 6.47-7.43 (m, aromatic); ms: m/e 349 (M^+, 11), 258 (31), 214 (10), 91 (100).

2-Carboxy-4,5-dibenzyloxybenzenediazonium Chloride (**2a**).

To a suspension of 4,5-dibenzyloxyanthranilic acid (11.5 g, 0.033 mole) in 418 ml of absolute ethanol, at 10° was added 3.4 ml of concentrated hydrochloric acid. The suspension was mechanically stirred and the temperature was kept below 10° throughout the experiment. To this suspension was added isoamyl nitrite (5.0 ml, 0.038 mole) and the mixture was stirred for 30 minutes. At this point 180 ml of anhydrous ether was added and the mixture was stirred for an additional 30 minutes. The light beige solid was collected and washed with anhydrous ether to yield 11.12 g of the diazonium chloride in 85.1% yield; ^{1}H nmr (60 MHz, DMSO-d_6): δ 5.35 (s, OCH_2), 5.59 (s, OCH_2), 7.02-8.86 (m, aromatic). This diazonium chloride can be restored at 25° in a vacuum desicator and was used in the Diels-Alder reaction within 24 hours.

1,4-Etheno-2-(2-*trans*-phenylvinyl)-6,7-dibenzyloxy-3-oxo-1,2,3,4-tetrahydroisoquinoline (**5a**).

To a boiling solution of 1-(2-*trans*-phenylvinyl)-2-pyridone [20] (2.76 g, 0.014 mole) in 1,2-dichloroethane (125 ml) was added 2-carboxy-4,5-dibenzyloxybenzenediazonium chloride in six portions (total 5.56 g, 0.014 mole) and propylene oxide in six portions (total 3 ml, 0.044 mole) at 15 minute intervals. After 1.5 hours an additional portion of propylene oxide (2 ml, 0.030 mole) was added. The black solution was then refluxed for 2 additional hours. Solvents were removed *in vacuo* keeping the bath temperature below 30°. This precaution was exercised to minimize any potential retro-Diels-Alder reaction. It had been observed that pure samples of these types of adducts decomposed above their melting points, so the evaporation was conducted at low temperature. In order to remove other volatile products, the residue was mixed with toluene and evaporated azeotropically several times. This procedure yielded 10.87 g of oil which was then adsorbed onto two times its weight of silica gel (22 g of 230-400 mesh). This solid mixture was then divided into two and each half was subjected to flash chromatography [17] using a 600 ml flash column for each half of the mixture. The column was packed with 110 g of silica gel, followed by the addition of 10% ethyl acetate/petroleum ether. An initial impurity (R_f = 0.84) was removed by the elution with 1 liter of 10% ethyl acetate/petroleum ether, followed by 500 ml of 15% and then 500 ml of 20%. This impurity was later shown to be 2,3-dibenzyloxynaphthalene by tlc and ^{1}H nmr. This compound was shown to be identical with that produced by the decomposition of **5a** when refluxed with lithium aluminum hydride or sodium hydride. The desired adduct eluted with 1 liter of 25% ethyl acetate/petroleum ether to yield **5a** (0.25 g, 7.3%), mp 170-172°, tlc, R_f = 0.62 (solvent A); ^{1}H nmr (60 MHz, deuteriochloroform): δ 4.59 (m, H_4), 5.11 (s, 2 CH_2O), 5.67 (m, H_1), 6.14 (d, CHC_6H_5, J = 15.0 Hz), 6.92-7.72 (m, aromatic, H_9, H_{10}, NHC=C); ^{13}C nmr: see Table I; ms: m/e 485 (M^+, 6), 341 (14), 340 (49), 250 (14), 249 (67), 221 (17), 181 (29), 102 (10), 91 (100), 65 (15).

Anal. Calcd. for $C_{33}H_{27}NO_3$: C, 81.63; H, 5.60; N, 2.88. Found: C, 81.24; H, 5.69; N, 2.78.

1,4-Etheno-2-benzyl-3-oxo-4,6,7-tribenzyloxy-1,2,3,4-tetrahydroisoquinoline (**5b**).

To a refluxing solution of 1-benzyl-3-benzyloxy-2-pyridone [21] (5.95 g, 0.02 mole) in 215 ml of 1,2-dichloroethane was added 2-carboxy-4,5-dibenzyloxybenzenediazonium chloride (8.11 g, 0.02 mole) and propylene oxide (9 ml, 0.13 mole), each in 6 divided portions at 15 minute intervals. Upon completion of the additions the black solution was refluxed for an additional 2.5 hours. The reaction was then worked up as **5a** to provide **5b** (2.00 g, 17%), mp 39-44°, tlc, R_f = 0.5 (solvent A); ^{1}H nmr (60 MHz, deuteriochloroform): δ 4.01-5.62 (m, NCH_2, 3 OCH_2, H_1), 6.50-7.83 (m, H_9, H_{10}, aromatic); ms: m/e 488 (M^+-$CH_2C_6H_5$, 1), 446 (M^+-$OCHCH_2C_6H_5$, 4), 133 (17), 92 (20), 91 (100), 57 (11), 43 (25), 42 (13), 41 (17), 39 (10), 18 (13).

Anal. Calcd. for $C_{39}H_{33}NO_4$: C, 80.81; H, 5.74; N, 2.42. Found: C, 80.60; H, 5.92; N, 2.31.

1,4-Ethano-2-(2-phenylethyl)-3-oxo-6,7-dihydroxy-1,2,3,4-tetrahydroisoquinoline (**6a**).

A solution of **5a** (0.24 g, 0.494 mmole) in glacial acetic acid (100 ml) was hydrogenated over 10% palladium on activated carbon (0.2 g) for 17 hours at 35 psi. Filtration, removal of the solvent *in vacuo* and recrystallization from aqueous acetic acid provided **6a** (0.08 g, 52%), mp 215-217°, tlc R_f = 0.67 (solvent F); ^{1}H nmr: see Table II; ^{13}C nmr: see Table I; ms: m/e 309 (M^+, 14), 218 (47), 177 (36), 162 (46), 161 (100), 149 (12), 116 (13), 115 (19), 105 (12), 91 (14), 85 (13), 83 (19), 77 (14), 60 (30), 45 (51), 43 (62), 30 (53), 28 (16), 18 (25).

Anal. Calcd. for $C_{19}H_{19}NO_3$: C, 73.77; H, 6.19; N, 4.53. Found: C, 73.65; H, 6.43; N, 4.51.

1,4-Ethano-2-benzyl-3-oxo-4-benzyloxy-6,7-dihydroxy-1,2,3,4-tetrahydroisoquinoline (**6b**).

Catalytic hydrogenation (40 psi) of **5b** (0.67 g, 1.16 mmoles) in 35 ml glacial acetic acid, using palladium (10%) on activated carbon (0.4 g) provided **6b** (0.30 g, 62%), mp 247-249°, tlc R_f = 0.68 (solvent G); ^{1}H nmr (60 MHz, DMSO-d_6): δ 1.16-2.28 (m, CH_2CH_2), 4.37-5.13 (m, NCH_2, OCH_2), 6.60 (s, H_8), 6.90 (s, H_5), 7.07-7.83 (m, aromatic), 8.73 (s, OH), 8.93 (s, OH); ms: m/e 401 (M^+, 1), 268 (10), 178 (25), 177 (100), 149 (17), 131 (12), 103 (13), 91 (95), 65 (17), 28 (13), 18 (12).

Anal. Calcd. for $C_{25}H_{23}NO_4 \cdot \frac{3}{4}H_2O$: C, 72.36; H, 5.95; N, 3.38. Found: C, 72.68; H, 5.70; N, 3.51.

1,4-Ethano-2-(2-phenylethyl)-6,7-dihydroxy-1,2,3,4-tetrahydroisoquinoline Hydrochloride (**7c**).

To a solution of **6a** (0.18 g, 0.595 mmole) in tetrahydrofuran (20 ml) was added lithium aluminum hydride (0.18 g, 4.76 mmoles) and this mixture was refluxed for 21 hours. The reaction was quenched with the addition of 10 ml of ethyl acetate. Solvents were distilled off *in vacuo* to yield a white residue to which was added 25 ml of 5% aqueous sodium bicarbonate solution. The mixture was transferred to a separatory funnel with the aid of an additional 25 ml of ethyl acetate and 25 ml of 5% sodium bicarbonate solution. Extraction with ethyl acetate (2 × 50 ml), followed by removal of solvent yielded an oil which was dissolved in ether (100 ml). The hydrochloride was prepared by bubbling hydrogen chloride gas into this solution, producing **7c** (0.053 g, 27%), crystal structure change at

121°, melts at 163-164°, tlc R_f = 0.34 (solvent F); ^{1}H nmr (60 MHz, DMSO-d_6): δ 1.22-4.70 (a series of complex multiplets, H_1, H_4, $2CH_2CH_2$, H_{3a}, H_{3s}), 6.80 (s, H_4), 6.90 (s, H_1), 7.34 (s, aromatic), 8.99 (s, OH), 9.19 (s, OH), 11.24 (m, NH); ms: m/e 295 (M^+-hydrochloric acid, 3), 204 (15), 135 (16), 134 (100), 105 (84), 79 (11), 77 (12), 44 (82), 43 (15), 42 (16), 36 (22), 30 (21), 28 (16), 18 (19).

Anal. Calcd. for $C_{19}H_{21}NO_2 \cdot \frac{1}{2}H_2O$: C, 66.95; H, 6.80; N, 4.11. Found: C, 67.22; H, 6.66; N, 4.39.

2,3-Dibenzyloxynaphthalene.

To a solution of 1,4-etheno-2-(2-*trans*-phenylvinyl)-6,7-dibenzyloxy-3-oxo-1,2,3,4-tetrahydroisoquinoline (**5a**) (0.25 g, 0.52 mmole) in THF (50 ml) was added lithium aluminum hydride (60 mg, 1.6 mmoles). This mixture was refluxed for 15 hours, cooled, and the excess hydride was then decomposed by the dropwise addition, in this order, of water (0.6 ml), 15% sodium hydroxide solution (0.6 ml), and water (1.8 ml). This mixture was then stirred for 0.5 hour and then filtered with suction, and the precipitate washed with THF. The combined THF solutions were evaporated yielding a yellow oil, which was subjected to flash chromatography to produce 2,3-dibenzyloxynaphthalene (60 mg, 34%), mp 131-133°, lit [22] mp 135-136°, tlc R_f = 0.92 (solvent A); ^{1}H nmr (60 MHz, deuteriochloroform): δ 5.28 (s, $2OCH_2$, 4H), 7.22-7.72 (m, aromatic, 16H); ms: m/e 340 (M^+, 4), 249 (9), 181 (6), 92 (7), 91 (100), 65 (7).

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