plex. Therefore the extinction coefficient of the benzaldehyde–BF_3 complex (λ_{max} 282 nm) was assumed to be 19 000 M^{-1} cm^{-1}, in analogy with that determined for the benzaldehyde–BF_3 complex in CH_2Cl_2, and in accord with the relative invariance of the extinction coefficient of the mesitaldehyde–BF_3 complex in the three solvents.

***meso*-Tetramesitylporphyrin (6a).** A 2-L three-neck round-bottomed flask fitted with a septum, reflux condenser, and nitrogen inlet port was charged with 1 L of $CHCl_3$ (distilled from K_2CO_3), mesitaldehyde (1.475 mL, 10 mmol, 10^{-2} M), and pyrrole (694 μL, 10 mmol, 10^{-2} M). After the solution was purged with N_2 for 5 min, 1.32 mL of 2.5 M BF_3·OEt_2 (3.3 mmol, 3.3×10^{-3} M) was added via syringe. The room temperature reaction was monitored by removing 50-μL aliquots and oxidizing with excess DDQ, followed by absorption spectrophotometry. At the end of 1 h, *p*-chloranil (1.844 g, 7.5 mmol) was added in powder form and the reaction mixture was gently refluxed (61 °C) for 1 h. The reaction mixture then was cooled to room temperature, 1 equiv of triethylamine (3.3 mmol, 460 μL) was added, and the solution was rotary evaporated to dryness. The crude dry product was scraped from the flask, placed on a filter, and washed with methanol (~75 mL) until the filtrate was clear. The polypyrromethenes and quinone components are highly soluble in methanol and are removed with ease. The final product (576 mg, 29%) was greater than 95% pure as evidenced by TLC, HPLC, and absorption and fluorescence (excitation and emission) spectroscopy. λ_{abs} (log ε): 403 (sh), 418 (5.63, fwhm 10 nm), 480 (2.95), 514 (4.20), 547 (3.57), 590 (3.70), 647 nm (3.48). λ_{em}: 650, 714 nm. The extinction coefficients are the average of three determinations (compare with lit. log ϵ_{Soret} = 5.57,[2] 5.72[3]). ^1H NMR ($CDCl_3$, 300 MHz): δ −2.51 (br s, 2 H, NH), 1.85 (s, 24 H, *o*-CH_3), 2.62 (s, 12 H, *p*-CH_3), 7.27 (s, 8 H, *m*-ArH), 8.61 (s, 8 H, β-pyrrole).

***meso*-Tetrakis(2-ethoxyphenyl)porphyrin (6f).** A 250-mL, three-neck round-bottomed flask fitted with a condenser and nitrogen inlet port was charged with 100 mL of $CHCl_3$ (distilled from K_2CO_3). Samples of 2-ethoxybenzaldehyde (140 μL, 1 mmol, 10^{-2} M) and pyrrole (69 μL, 1 mmol, 10^{-2} M) were added, and the solution was stirred magnetically under a slow steady stream of nitrogen. After 5 min, BF_3·OEt_2 from a 2.5 M stock solution in $CHCl_3$ (132 μL, 3.3 mM) was added and the reaction mixture was allowed to proceed at room temperature. After 1 h, the yield was found to be 25% (assuming $\epsilon_{418} = 5 \times 10^5$ M^{-1} cm^{-1}) upon aliquot removal and oxidation with excess DDQ. At this point, oxidation was initiated by the addition of *p*-chloranil (184 mg, 0.75 mmol, 3 equiv per porphyrinogen), and the reaction vessel was immersed in an oil bath preheated to 65 °C. After a 1-h oxidation period, the reaction mixture was cooled to room temperature and 1 equiv of triethylamine (46 μL, 3.3 mM) was added. The crude reaction mixture was transferred to a 200-mL round-bottomed flask, 750 mg of Florisil was added, and the solvent was removed via rotary evaporation. The resulting dry powder was placed on top of a dry alumina column (1 × 15 cm). The porphyrin eluted quickly with CH_2Cl_2 containing 1–2% ethyl acetate, affording 73 mg (37% yield) of the title compound in greater than 95% purity, as evidenced by TLC (silica, CH_2Cl_2 or CH_2Cl_2/petroleum ether), NMR, absorption and fluorescence (excitation and emission) spectroscopy. ^1H NMR ($CDCl_3$): δ −2.65 (br s, 2 H, NH), 0.61, 0.7 (m, 12 H, CH_3), 3.90, 3.97 (m, 8 H, OCH_2), 7.30, 7.34 (m, 8 H, ArH), 7.69, 7.75 (m, 4 H, ArH), 7.97, 8.03 (m, 4 H, ArH), 8.74 (s, 8 H, β-pyrrole). λ_{abs}: 418, 514, 548, 590, 644 nm. λ_{em}: 650, 712 nm.

Acknowledgment. We thank Dr. Kenneth Suslick and Dr. Mario J. Nappa for generous gifts of 2,4,6-triphenylbenzaldehyde and 2,6-bis(trifluoromethyl)benzaldehyde, respectively. This work was supported by the NIH (GM36238).

Supplementary Material Available: ^1H NMR spectral data and absorption spectral data (λ_{max} values only) of compounds **6b–e** and **6g–o** (3 pages). Ordering information is given on any current masthead page.

Rearrangement of 1-Methyl-2-(substituted-phenyl)piperidinium 1-Methylides in a Neutral Medium

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Reaction of 1-methyl-1-[(trimethylsilyl)methyl]-2-(substituted-phenyl)piperidinium iodides (**3**) with cesium fluoride in DMF gave good yields of 2-methyl-1,3,4,5,6,11a-hexahydro-2*H*-2-benzazonine derivatives (**5**), which are regarded as unstable intermediates in the Sommelet–Hauser rearrangement of ammonium ylides (**4**) to 2-methyl-2,3,4,5,6,7-hexahydro-1*H*-2-benzazonine derivatives (**6**). Compound **5** was converted on heating to two isomers, (*E*)-*N*,*N*-dimethyl-5-(substituted-phenyl)-4-pentenylamines (**8**) and 1-methyl-3-(substituted-phenyl)-perhydroazepines (**9**), and it was aromatized to **6** in the presence of potassium hydroxide. Related reactions are also described.

Introduction

The Sommelet–Hauser rearrangement is well known as a regioselective rearrangement of benzyldialkylammonium *N*-methylides to give ortho-substituted benzylamine derivatives.[1] Hauser et al.[2] reported that this rearrangement is also applicable to a ring expansion reaction giving cyclic amines. For example, 2-methyl-2,3,4,5,6,7-hexahydro-1*H*-2-benzazonine (**6a**) and its analogues (**6b** and **6c**) were prepared in high yields by the ylide reaction of 1,1-dimethyl-2-phenylpiperidinium iodides with sodium amide in liquid ammonia.[2,3]

We previously reported that the fluoride ion assisted desilylation of (substituted-benzyl)dialkyl[(trimethylsilyl)methyl]ammonium halides gave high yields of the Sommelet–Hauser rearrangement products in a nonbasic medium at room temperature.[4] Application of this ylide

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Scheme I

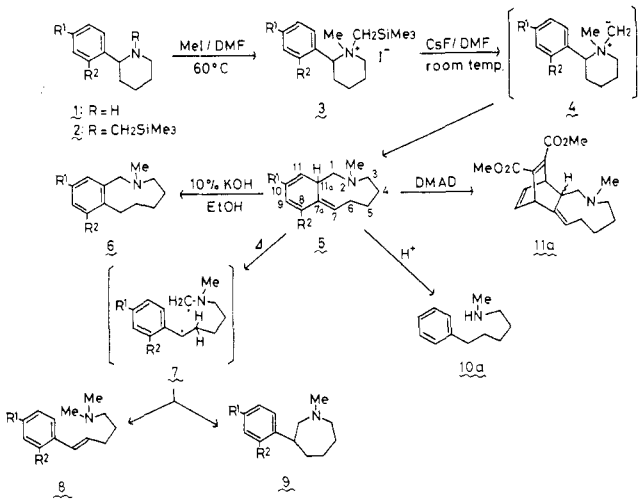


Table I. Reaction of 2-(Substituted-phenyl)-1-[(trimethylsilyl)methyl]piperidine (2a–e) with Methyl Iodide followed by CsF in DMF

entry	2	R^1	R^2	yield of 5[a] %	UV spectra λ_{max}, nm (log ϵ)[b]
1	**a**	H	H	74	318 (3.8)
2	**b**	Me	H	72	317 (3.8)
3	**c**	H	Me	69	319 (3.8)
4	**d**	MeO	H	53	317 (3.7)
5	**e**	H	MeO	58	321 (3.9)

[a] Yield from 2. [b] In *n*-hexane.

formation reaction to the ring expansion reactions should offer a useful synthetic route to potentially bioactive medium ring cyclic amines having various base-sensitive functional groups.

Results and Discussion

Five starting amines, 2-(substituted-phenyl)-1-[(trimethylsilyl)methyl]piperidines (**2a–e**) were prepared from 2-(substituted-phenyl)piperidines (**1a–e**) and (chloromethyl)trimethylsilane. Their characteristic data are listed in Table IV.

Preparation of 1-methyl-2-(substituted-phenyl)-piperidinium *N*-methylide intermediates (**4a–e**) was carried out by treatment of **2** with methyl iodide followed by cesium fluoride at room temperature in *N*,*N*-dimethylformamide (DMF) (Scheme I). Distillation of the reaction product from **2a**, according to Hauser's report,[2] did not give the expected Sommelet–Hauser rearrangement product, 2-methyl-2,3,4,5,6,7-hexahydro-1*H*-2-benzazonine (**6a**) but gave (*E*)-*N*,*N*-dimethyl-5-phenyl-4-pentenylamine (**8a**, 31%) and polymeric oils. The reaction product **5a**, therefore, was purified on a high-performance liquid chromatography (HPLC) column, instead of distillation, to remove a small amount of unreacted starting material. The substituted analogues **2b–e** were also treated in a similar manner. The yields of **5a–e** are shown in Table I.

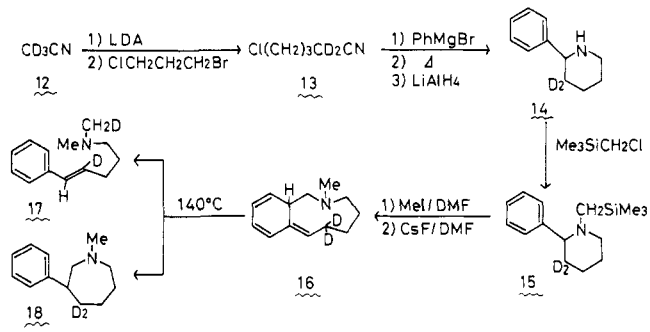
The structures of the products were established as 2-methyl-1,3,4,5,6,11a-hexahydro-2*H*-2-benzazonine (**5a**) and its substituted analogues (**5b–e**), respectively, on the basis of 2D COSY at 400-MHz ^{1}H NMR, ^{13}C NMR, and UV spectroscopies. The UV spectra of **5** (λ_{max} 317–321 nm, log ϵ 3.7–3.9) showed similar maximum values to that of 5-[(dimethylamino)methyl]-1,3,5-trimethyl-6-methylene-1,3-cyclohexadiene[5] (λ_{max} 313 nm, log ϵ 3.8). In the ^{1}H NMR spectrum of **5c**, 7% NOE enhancement at 5.81 ppm (H-7) and 6% NOE at 5.61 ppm (H-9) were observed under irradiation at 1.89 ppm (8-Me).

Table II. Thermal Isomerization of 5 to (*E*)-*N*,*N*-Dimethyl-5-(substituted-phenyl)-4-pentenylamines (8) and 1-Methyl-3-(substituted-phenyl)perhydroazepines (9)

entry	starting compound	reflux in solvent, time (h)	total yield (%) of 8 and 9	ratio 8 to 9
1	**5a**	benzene, 14	90	88:12
2	**5a**	toluene, 2	90	87:13
3	**16**	xylene, 1	94[a]	68:32[a]
4	**5b**	xylene, 1	94	80:20
5	**5d**	xylene, 1	85	77:23
6	**5e**	xylene, 1	62	87:13

[a] Yield and ratio correspond to those of **17** and **18**.

Scheme II



The trienes **5** have been thought to exist only as unstable intermediates in the Sommelet–Hauser rearrangement and to be difficult to isolate because they are easily aromatized by proton transfer. However, they are unexpectedly stable at room temperature and could be stored as hexane solutions without appreciable decomposition for more than a month, although they were slowly polymerized at room temperature as neat oils.

When a diluted solution of **5** in toluene or xylene was heated at reflux, the compounds were converted smoothly into two isomers: (*E*)-*N*,*N*-dimethyl-5-(substituted-phenyl)-4-pentenylamines (**8**) and 1-methyl-3-(substituted-phenyl)perhydroazepines (**9**). The conversion rate was slow at 80 °C (in benzene). The yields and product ratios are listed in Table II.

The formation of **8** and **9** seems to be the result of homolysis of the bond between C-1 and C-11a of **5**, giving a diradical intermediate **7** followed by recombination or hydrogen transfer.

Thus, when 6,6-dideuterium-labeled triene **16** was prepared and heated in xylene according to the route in Scheme II, two deuterated products, **17** and **18**, were obtained. One deuterium atom was rearranged onto the *N*-methyl group in the ring-opened product **17**. The ratio of **17** to **18** differed from that of **8** to **9** (compare entries 2 and 3 in Table II). The decrease in the ratio of **17** to **18** is ascribable to a primary kinetic isotope effect.

Benzylammonium ylides formed under basic conditions are known to be isomerized by two competing pathways: Sommelet–Hauser rearrangement and Stevens rearrangement.[1] However, neither **6** (Sommelet–Hauser rearrangement product) nor **9** (Stevens product) was found in the ylide reaction products from **3**. Furthermore, aromatization from **5** to **6** did not occur in the nonbasic condition

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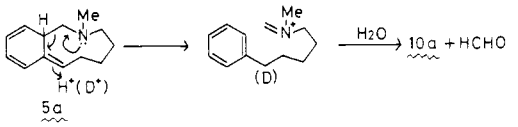
Table III. Isomerization of 5 to 2-Methyl-2,3,4,5,6,7-hexahydro-1*H*-2-benzazonine (6) in 10% KOH-EtOH

	temp, °C	time, h	% yield of 6	bp, °C (mmHg)[a]
a	rt	24	78	165 (24)[b]
b	60	4	65	160 (11)[c]
c	60	4	65	175 (13)[c]
d	60	65	41	170 (12)
e	50	53	58	175 (6)

[a] Oven temperature of Kugelrohr distillation apparatus. [b] Reference 2. [c] Reference 3.

Scheme III



even at the elevated temperature.

The aromatization of **5** proceeded slowly in 10% potassium hydroxide–ethanol solution or during chromatography on an aluminum oxide column. Methoxy-substituted compounds **5d** and **5e** were fairly stable, and a small amount of the starting compounds still remained after over 2 days (Table III). The formation of **6** in ylide reaction brought about by sodium amide in liquid ammonia may be caused by the presence of an excess of base.

It is interesting that **9** is a thermal rearrangement product of **5** but nevertheless has been regarded as a Stevens rearrangement product of **4** via [1,2]-rearrangement process.

The triene **5a** reacted rapidly with hydrochloric acid at room temperature to form *N*-methyl-5-phenylpentylamine (**10a**) in a 76% yield. When deuteriochloric acid was used, a deuterium atom was found at the benzyl position of **10a**. Thus, the process of formation of **10a** from **5a** involves addition of a proton and ring opening followed by hydrolysis of an iminium salt as indicated in Scheme III.

Reaction of **5a** with dimethyl acetylenedicarboxylate (DMAD) gave the Diels–Alder adduct **11a** in a 63% yield. Thus, triene **5** is a useful synthetic intermediate. Further synthetic applications are in progress in our laboratory.

Experimental Section

All reactions were carried out under a nitrogen atmosphere. Dimethylformamide (DMF) was dried over BaO and distilled under reduced pressure. Cesium fluoride was dried over P_2O_5 at 180 °C under reduced pressure. ^1H and ^{13}C NMR spectra were recorded on a JEOL JNM-GSX-400 spectrometer with use of Me_4Si as internal standard. IR spectra were recorded on a JASCO IRA-2 spectrometer. Mass spectra were measured on a JEOL JMS-DX-300 GC–MS system (70 eV) with use of a 5% PEG-20M on Uniport HP, 2-m column. Preparative HPLC analyses were carried out on a TOSOH CCP 8000 system. UV spectra were recorded on a Shimadzu UV-240 spectrophotometer. Melting points and boiling points are uncorrected.

2-(Substituted-phenyl)-1-[(trimethylsilyl)methyl]-piperidine (2). 2-(Substituted-phenyl)-3,4,5,6-tetrahydropyridines were prepared from the corresponding substituted bromobenzenes with 5-chlorovaleronitrile according to the reported method.[6] They were treated with $LiAlH_4$ to give the following amines: 2-phenylpiperidine (**1a**, 58%),[7] 2-(4′-methylphenyl)piperidine (**1b**, 52%),[6] 2-(2′-methylphenyl)piperidine (**1c**, 64%),[8] 2-(4′-methoxyphenyl)piperidine (**1d**, 23%),[9] 2-(2′-methoxyphenyl)piperidine (**1e**, 32%).[10]

A mixture of **1** (80 mmol) and (chloromethyl)trimethylsilane (40 mmol) in dimethyl sulfoxide (DMSO, 30 mL) was stirred at 100 °C for 18 h. The reaction mixture was poured into water and extracted with diethyl ether (about 45% of **1** was recovered from the aqueous layer). The ethereal extract was washed with 1% Na_2CO_3, dried over $MgSO_4$, and concentrated under reduced pressure. Acetic anhydride (3 mL) was added to the residue at room temperature, in order to remove unreacted secondary amines, and the mixture was stirred overnight. Then the mixture was added to 10% HCl and extracted with ether. The acid layer was made basic with NaOH and extracted with ether. The ethereal extract was dried ($MgSO_4$) and concentrated under reduced pressure. The residue was distilled on a Kugelrohr distillation apparatus. The yields and characteristic data are listed in Table IV.

2-Methyl-1,3,4,5,6,11a-hexahydro-2*H*-2-benzazonine (5a) and Substituted Analogues (5b–e) (General Procedure). A mixture of **2** (3 mmol) and iodomethane (30 mmol) in DMF (15 mL) was stirred at 60 °C for a few hours in a 30-mL flask (**2a**, 2 h; **2b**, 3 h; **2c**, 6 h; **2d**, 2 h; **2e**, 4 h). Then about 5 mL of the DMF was distilled away under reduced pressure in order to remove the excess iodomethane. Cesium fluoride (2.0 g, 13 mmol) was added, and the mixture was stirred at room temperature for 20 h. The reaction mixture was poured into 1.5% Na_2CO_3 (200 mL) and was extracted with ether (100 mL × 4). The extract was washed with 1.5% Na_2CO_3 (100 mL × 2), dried ($MgSO_4$), and concentrated under reduced pressure to give **5**.

The yields and UV spectral data are shown in Table I. A part of **5** was purified on a Merck Hibar LiChrosorb NH_2 HPLC column (250 × 10 mm) eluted with a mixture of ether and *n*-hexane at a flow rate of 5 mL/min.

5a: ^1H NMR ($CDCl_3$) δ 1.27 (1 H, m, H-4), 1.50–1.65 (3 H, m, H-4 and H-5), 2.08 (1 H, m, H-6), 2.10 (1 H, dd, J = 13.8 and 1.8 Hz, H-1), 2.35 (3 H, s, NMe), 2.44 (2 H, m, H-3), 2.49 (1 H, dd, J = 13.8 and 8.4 Hz, H-1), 2.92 (1 H, m, H-6), 3.45 (1 H, br s, H-11a), 5.60–5.67 (3 H, m, H-7, H-9, and H-11), 5.87 (1 H, dd, J = 9.5 and 5.5 Hz, H-10), 6.00 (1 H, d, J = 9.5 Hz, H-8); ^{13}C NMR ($CDCl_3$) δ 138.4 (s), 134.3 (d), 130.5 (d), 130.2 (d), 122.3 (d), 119.7 (d), 61.5 (t), 56.5 (t), 45.9 (q), 40.0 (d), 27.4 (t), 27.2 (t), 24.7 (t). (See paragraph at the end of paper about supplementary material.)

Thermal Isomerization of 5 to (*E*)-*N*,*N*-Dimethyl-5-(substituted-phenyl)-4-pentenylamines (8) and 1-Methyl-3-(substituted-phenyl)perhydroazepines (9). A solution of **5** (0.15 mmol) in benzene, toluene, or xylene (5 mL) was heated at reflux (the solvent used and reaction time are listed in Table II). The solution was extracted with 0.5 N HCl (20 mL). The acid extract was washed with ether, made basic with NaOH, and then extracted with ether. The ethereal extracts were dried over $MgSO_4$ and concentrated under reduced pressure to give a mixture of **8** and **9**. The mixture was separated on a HPLC column (Merck LiChrosorb NH_2, eluted with a mixture of ether and hexane). The yields are summarized in Table II.

8a,[11] **8b**,[12] **8d**,[13] and **8e**: ^1H NMR ($CDCl_3$) δ 1.65 (2 H, m), 2.23 (6 H, s, NMe), 2.25 (2 H, m), 2.31 (2 H, t, J = 7.5 Hz), 3.84 (3 H, s, OMe), 6.21 (1 H, dt, J = 15.9 and 6.7 Hz), 6.72 (1 H, d, J = 15.9 Hz), 6.85 (1 H, d, J = 8.2 Hz), 6.90 (1 H, m), 7.18 (1 H, m), 7.41 (1 H, dd, J = 1.7 and 7.7 Hz); mass spectrum, m/z 219.1641 (M^+, calcd for $C_{14}H_{21}NO$ 219.1622). **9a**: ^1H NMR ($CDCl_3$) δ 1.65–1.98 (6 H, m), 2.39 (3 H, s, NMe), 2.55 (1 H, m), 2.65 (1 H, dd, J = 9.7 and 13.0 Hz), 2.79 (2 H, m), 2.94 (1 H, m), 7.15–7.30 (5 H, m); mass spectrum, m/z 189.1526 (M^+, calcd for $C_{13}H_{19}N$ 189.1517). **9b**: ^1H NMR ($CDCl_3$) δ 1.65–1.95 (6 H, m), 2.31 (3 H, s, PhMe), 2.38 (3 H, s, NMe), 2.54 (1 H, m), 2.63 (1 H, dd, J = 10.0 and 13.0 Hz), 2.78 (2 H, m), 2.92 (1 H, m), 7.09 (4 H, s); mass spectrum, m/z 203.1656 (M^+, calcd for $C_{14}H_{21}N$ 203.1673). **9d**: ^1H NMR ($CDCl_3$) δ 1.65–1.95 (6 H, m), 2.38 (3 H, s, NMe), 2.53 (1 H, m), 2.60 (1 H, dd, J = 9.9 and 13.0 Hz), 2.77 (2 H, m), 2.90 (1 H, m), 3.78 (3 H, s, OMe), 6.82 (2 H, d, J

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Table IV. 1-[(Trimethylsilyl)methyl]-2-(substituted-phenyl)piperidines (2)[a]

	% yield	bp, °C (mmHg)[b]	^{1}H NMR ($CDCl_3$) δ SiMe	$SiCH_2N$	H-2
2a	81	165 (20)	−0.04	1.30, 1.99 (AB q, J = 14.3 Hz)	2.80 (dd, J = 11.0, 2.9 Hz)
2b	52	190 (20)	−0.04	1.29, 2.01 (AB q, J = 14.5 Hz)	2.76 (dd, J = 11.0, 2.7 Hz)
2c	50	160 (6)	−0.04	1.26, 1.99 (AB q, J = 14.4 Hz)	3.07 (br d, J = 13.4 Hz)
2d	67	170 (8)	−0.05	1.27, 1.99 (AB q, J = 14.5 Hz)	2.74 (dd, J = 11.0, 2.2 Hz)
2e	71	150 (7)	−0.03	1.31, 2.05 (AB q, J = 14.5 Hz)	3.38 (dd, J = 10.3, 2.2 Hz)

[a] Satisfactory analytical data (±0.4% for C, H, and N) were submitted for review. [b] Oven temperature of Kugelrohr distillation apparatus.

= 8.6 Hz), 7.13 (2 H, d, J = 8.6 Hz); mass spectrum, m/z 219.1629 (M^+, calcd for $C_{14}H_{21}NO$ 219.1622). **9e**: ^{1}H NMR ($CDCl_3$) δ 1.65–1.92 (6 H, m), 2.39 (3 H, s, NMe), 2.56 (1 H, m), 2.64 (1 H, dd, J = 9.6 and 12.8 Hz), 2.78 (2 H, m), 3.40 (1 H, m), 3.82 (3 H, s, OMe), 6.84 (1 H, d, J = 8.1 Hz), 6.90 (1 H, m), 7.16 (1 H, m), 7.19 (1 H, dd, J = 1.6 and 7.3 Hz); mass spectrum, m/z 219.1641 (M^+, calcd for $C_{14}H_{21}NO$ 219.1622).

[2,2-$^2H_2$]-5-Chlorovaleronitrile (13). A solution of *n*-BuLi in hexane (10 w/v%, 77 mL, 123 mmol) was added to a solution of diisopropylamine (12.5 g, 123 mmol) in tetrahydrofuran (THF, 150 mL) at 0 °C with additional stirring for 0.5 h. To the resulting LDA solution was added dropwise a solution of CD_3CN (99% D, 5.786 g, 131 mmol) in THF (10 mL) at −78 °C. After 1 h of stirring, the mixture was added dropwise by syringe to a solution of 1-bromo-3-chloropropane (20.539 g, 130.5 mmol) in THF (130 mL) at −78 °C, and stirring was continued for 1.5 h. The reaction mixture was poured into a 5% citric acid solution (500 mL) and extracted with ether (200 mL × 3). The ethereal extract was washed with saturated aqueous NaCl, dried ($MgSO_4$), and concentrated under reduced pressure. Distillation of the residue gave 12.326 g (84%) of **13**, bp 113 °C (21 mmHg): ^{1}H NMR ($CDCl_3$, 100 MHz) δ 1.70–2.10 (4 H, m), 3.62 (2 H, t, J = 6 Hz); IR (film) 2250 (CN), 2200–2100 (C–D) cm^{-1}; mass spectrum, m/z 84.0748 (M^+ − Cl, calcd for $C_5H_6D_2N$ 84.0782).

[3,3-$^2H_2$]-2-Phenylpiperidine (14). A solution of **13** (8.533 g, 71.4 mmol) in ether (15 mL) was added dropwise to a solution of PhMgBr (74 mmol) in ether (65 mL) at room temperature. The reaction mixture was refluxed for 2 h. The ether was removed by distillation, the volume in the flask being kept constant by the addition of dry xylene. Heating just sufficient to reflux the xylene was continued for 1 h. The precipitate was filtered off and washed with anhydrous ether (60 mL). The filtrate and washing were added into a suspension of $LiAlH_4$ (3 g, 79 mmol) in ether (80 mL) at room temperature with additional stirring for 1 h. The reaction was quenched with a saturated aqueous solution of potassium sodium tartrate, and the mixture was extracted with ether. The ethereal phase was extracted with 0.5 N HCl. The aqueous extract was made basic with NaOH and extracted with ether. The ethereal extract was dried ($MgSO_4$) and concentrated. Distillation of the residue gave **14** (1.967 g, 17%): bp 150 °C (15 mmHg, oven temperature of Kugelrohr distillation apparatus); ^{1}H NMR ($CDCl_3$) δ 1.44–1.70 (3 H, m), 1.88 (1 H, br d, J = 10.3 Hz, H-4), 2.78 (1 H, m, H-6), 3.19 (1 H, br d, J = 12.8 Hz, H-6), 3.57 (1 H, s, H-2), 7.20–7.38 (5 H, m); IR (film) 2200–2050 (C–D) cm^{-1}; mass spectrum, m/z 163.1314 (M^+, calcd for $C_{11}H_{13}D_2N$ 163.1329).

[3,3-$^2H_2$]-2-Phenyl-1-[(trimethylsilyl)methyl]piperidine (15). In a manner similar to that described for **2**, **14** (2.224 g, 13.6 mmol) was treated with (chloromethyl)trimethylsilane (0.917 g, 7.5 mmol) to give **15** (1.113 g, 65%): bp 160 °C (15 mmHg, Kugelrohr); ^{1}H NMR ($CDCl_3$) δ −0.04 (9 H, s, SiMe), 1.30 and 1.97 (2 H, AB q, J = 14.3 Hz), 1.31 (1 H, m, H-4), 1.60–1.76 (3 H, m, H-4 and H-5), 1.96 (1 H, m, H-6), 2.78 (1 H, s, H-2), 3.06 (1 H, br d, J = 12.8 Hz, H-6), 7.18 (1 H, m), 7.25–7.30 (4 H, m); IR (film) 2200, 2100 (C–D) cm^{-1}; mass spectrum, m/z 249.1872 (M^+, calcd for $C_{15}H_{23}D_2NSi$ 249.1881).

[6,6-$^2H_2$]-2-Methyl-1,3,4,5,6,11a-hexahydro-2*H*-2-benzazonine (16). According to the general procedure for **5a**, **15** (784 mg, 3.14 mmol) was treated to give **16** (451 mg, 75%): ^{1}H NMR ($CDCl_3$) δ 1.27 (1 H, m, H-4), 1.50–1.65 (3 H, m, H-4 and H-5), 2.10 (1 H, dd, J = 1.8 and 13.8 Hz, H-1), 2.35 (3 H, s, NMe), 2.44 (2 H, m, H-3), 2.49 (1 H, dd, J = 8.4 and 13.8 Hz, H-1), 3.45 (1 H, br s, H-11a), 5.60–5.68 (3 H, m, H-7, H-9 and H-11), 5.87 (1 H, dd, J = 5.5 and 9.5 Hz, H-10), 6.00 (1 H, d, J = 9.5 Hz, H-8), signals of H-6 (2.08 and 2.92 ppm in the spectrum of **5a**) were not observed in this spectrum.

Thermal Isomerization of 16. A solution of **16** (51 mg, 0.27 mmol) in xylene (4 mL) was heated at reflux for 1 h. The mixture was worked up in a manner as described for the thermal isomerization of **5**. The result is shown in Table II.

17: ^{1}H NMR ($CDCl_3$) δ 1.64 (2 H, m), 2.23 (5 H, s, CH_3 and CH_2D), 2.23 (2 H, m), 2.30 (2 H, t, J = 7.5 Hz), 6.38 (1 H, s), 7.18 (1 H, m), 7.25–7.35 (4 H, m); mass spectrum, m/z (relative intensity) 191 (M^+, 9), 85 (21), 59 (100) (189 was not observed); mass spectrum, m/z 191.1641 (M^+, calcd for $C_{13}H_{17}D_2N$ 191.1642), 59.0722 (calcd for C_3H_7DN 59.0719). **18**: ^{1}H NMR ($CDCl_3$) δ 1.66–1.74 (2 H, m), 1.78–1.90 (2 H, m), 2.39 (3 H, s, NMe), 2.55 (1 H, m), 2.65 (1 H, dd, J = 9.7 and 13.0 Hz, H-2), 2.79 (2 H, m), 2.92 (1 H, br d, J = 9.7 Hz, H-3), 7.15–7.30 (5 H, m); mass spectrum, m/z (relative intensity) 191 (M^+, 40), 100 (40), 84 (100), (189 was not observed); mass spectrum, m/z 191.1648 (M^+, calcd for $C_{13}H_{17}D_2N$ 191.1642).

Base-Assisted Isomerization of 5 to 2-Methyl-2,3,4,5,6,7-hexahydro-1*H*-2-benzazonine (6a) and Substituted Analogues (6b–e). In a 10% KOH ethanol solution (6 mL) was dissolved **5** (2 mmol), and the mixture was stirred under the condition listed in Table III. After the addition of saturated aqueous NaCl solution (50 mL), the mixture was extracted with ether (20 mL × 4). The extract was washed with saturated aqueous NaCl (10 mL × 2), dried ($MgSO_4$), and concentrated under reduced pressure. The residue was distilled to give **6**. The yields are listed in Table III.

6d: ^{1}H NMR ($CDCl_3$) δ 1.39 (4 H, m), 1.75 (2 H, m), 2.40 (3 H, s, NMe), 2.44 (2 H, m, H-3), 2.89 (2 H, t, J = 6.3 Hz, H-7), 3.65 (2 H, s, H-1), 3.79 (3 H, s, OMe), 6.67 (1 H, d, J = 2.8 Hz, H-11), 6.75 (1 H, dd, J = 2.8 and 8.2 Hz, H-9), 7.02 (1 H, d, J = 8.2 Hz, H-8); mass spectrum, m/z 219.1612 (M^+, calcd for $C_{14}H_{21}NO$ 219.1622). **6e**: ^{1}H NMR ($CDCl_3$) δ 1.36 (4 H, m), 1.77 (2 H, m), 2.39 (3 H, s, NMe), 2.43 (2 H, t, J = 5.6 Hz, H-3), 2.99 (2 H, t, J = 6.3 Hz, H-7), 3.69 (2 H, s, H-1), 3.80 (3 H, s, OMe), 6.74 (1 H, d, J = 7.5 Hz, H-9), 6.78 (1 H, d, J = 8.1 Hz, H-11), 7.08 (1 H, dd, J = 7.7 and 7.9 Hz, H-10). Anal. Calcd for $C_{14}H_{21}NO$: C, 76.67; H, 9.65; N, 6.39. Found: C, 76.70; H, 9.56; N, 6.39.

***N*-Methyl-5-phenylpentylamine (10a).** A solution of **5a** (52 mg, 0.28 mmol) in 2 N HCl (6 mL) was stirred for 2 h at room temperature. The mixture was made alkaline with NaOH and extracted with ether (10 mL × 4). The extract was washed with saturated aqueous NaCl, dried ($MgSO_4$), and concentrated under reduced pressure. The residue was chromatographed on an NH_2 HPLC column (eluted with a mixture of MeOH and dichloromethane) to give **10a**[14] (37 mg, 76%).

A similar treatment of **5a** in 2 N DCl in D_2O (99% D) gave *N*-methyl-5-phenyl-5-deuteriopentylamine: ^{1}H NMR ($CDCl_3$) δ 1.36 (2 H, m), 1.52 (2 H, m), 1.63 (2 H, q, J = 7.7 Hz, H-4), 1.95 (1 H, s, NH), 2.42 (3 H, s, NMe), 2.54–2.62 (3 H, m, H-1 and H-5), 7.15–7.18 (3 H, m), 7.24–7.28 (2 H, m); mass spectrum, m/z

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(relative intensity) 178 (M^+, 24), 177 (2), 92 (11), 44 (100); mass spectrum, m/z 178.1578 (M^+, calcd for $C_{12}H_{18}DN$ 178.1579).

11,12-Bis(methoxycarbonyl)-3-azatricyclo[7.4.0.2^{10,13}]pentadeca-8,11,14-triene (11a). A solution of **5a** (380 mg, 2 mmol) and dimethyl acetylenedicarboxylate (570 mg, 4 mmol) in benzene (7 mL) was stirred at 50 °C for 20 h. The mixture was concentrated under reduced pressure. The residue was chromatographed on an alumina column (ether/benzene, 5:95) to give **11a** (417 mg, 63%): mp 118–119 °C; ^{1}H NMR ($CDCl_3$) δ 1.14 (1 H, m), 1.36–1.52 (3 H, m), 1.91 (1 H, m), 2.16 (2 H, m), 2.31 (1 H, m), 2.33 (3 H, s, NMe), 2.44 (2 H, m), 3.13 (1 H, m), 3.78 (6 H, s, COOMe), 3.89 (1 H, m), 4.32 (1 H, dd, J = 1.7 and 6.0 Hz), 5.45 (1 H, dd, J = 6.4 and 11.5 Hz), 6.32 (1 H, m), 6.43 (1 H, m); IR (Nujol) 1705, 1630, 1280, 1070 cm^{-1}; mass spectrum, m/z (relative intensity) 331 (M^+, 37), 300 (15), 272 (45), 137 (82), 136 (79), 84 (85), 57 (100). Anal. Calcd for $C_{19}H_{25}NO_4$: C, 68.85; H, 7.62; N, 4.23. Found: C, 68.75; H, 7.68; N, 4.19.

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Supplementary Material Available: A figure of the H–H COSY for **5a** and full NMR data for **5b–e** (3 pages). Ordering information is given on any current masthead page.

An Efficient Synthesis of the Highly Tumorigenic *anti*-Diol Epoxide Derivative of Benzo[*c*]phenanthrene

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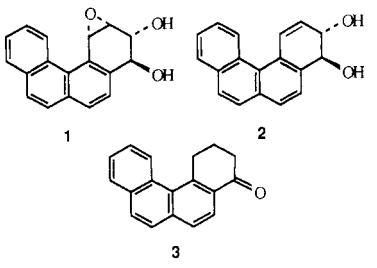
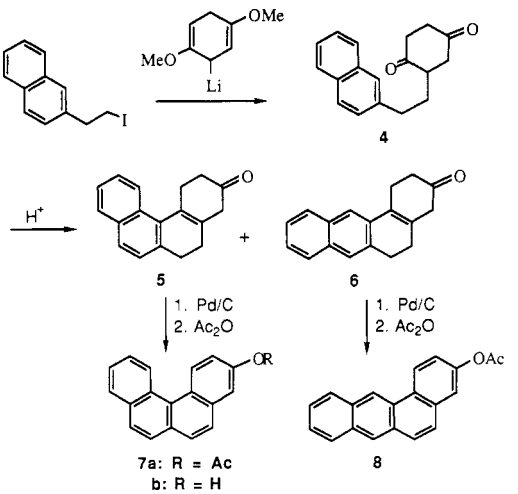
Synthesis of the potent tumorigen *trans*-3,4-dihydroxy-*anti*-1,2-epoxy-1,2,3,4-tetrahydrobenzo[*c*]phenanthrene (**1**) in relatively few steps and superior overall yield is described. The method entails synthesis of the key intermediate 3-hydroxybenzo[*c*]phenanthrene (**7b**) via reaction of the 6-lithio salt of 1,4-dimethoxycyclohexadiene with 2-(2-naphthyl)ethyl iodide followed by cyclodehydration and dehydrogenation. 3-Hydroxybenz[*a*]anthracene is obtained as a minor product of this synthesis. Oxidation of **7b** with $(KSO_3)_2NO$ followed by reduction of the resulting quinone with $NaBH_4$ and peracid oxidation affords **1**. This method is applicable in principle to the synthesis of the substituted derivatives of benzo[*c*]phenanthrene and their oxidized metabolites. Alternative synthetic routes involving $TiCl_4$-catalyzed aldol condensation of the trimethylsilyl enol ethers of cyclohexanone and 6-methoxytetralone with 2-arylacetaldehydes were also examined and shown to afford substantially higher ratios of benz[*a*]anthracene products.

Diol epoxide metabolites are implicated as the active forms of carcinogenic polycyclic aromatic hydrocarbons.[1,2] These intermediates bind covalently to DNA in vivo, leading initially to mutation, and ultimately to tumor induction. The bay region diol epoxide derivative of benzo[*c*]phenanthrene, *trans*-3,4-dihydroxy-*anti*-1,2-epoxy-1,2,3,4-tetrahydrobenzo[*c*]phenanthrene (**1**), is of particular interest because it is reported to exhibit the highest tumor-initiating activity of all the hydrocarbon diol epoxides tested to date.[3] This compound is also distinguished by its exceptionally high level of covalent binding to DNA in vitro and the relatively high ratio of deoxyadenosine–deoxyguanosine adducts it affords.[4,5]



1 2 3

Scheme I



In order to obtain **1** in sufficient quantity for investigations of its mechanism of DNA interaction and other pertinent studies, we required a practical synthetic route to this compound. Although synthesis of the 3,4-di-

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