Direct Synthesis of Dibenzocyclooctadienes via Double Ortho Friedel–Crafts Alkylation by the Use of Aldehyde–Trimethylsilyl Iodide Adducts

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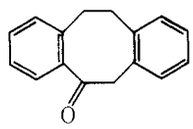
The development of a new, direct method for the preparation of dibenzo[*a*,*e*]cycloocta-1,5-dienes from phenylacetaldehyde by a double ortho Friedel–Crafts alkylation is described. When benzaldehyde (**2b**) is treated with trimethylsilyl iodide (**3**), α,α-diiodotoluene (**6**) is formed in high yield via the intermediacy of α-iodobenzyl trimethylsilyl ether (**4b**). Treatment of phenylacetaldehyde (**2a**) with trimethylsilyl iodide (**3**) under the same conditions gives rise to a different reaction pathway, affording initially the aldehyde iodohydrin trimethylsilyl ether (**4a**), which is transformed on standing into a mixture of three products. The major product of this mixture, isolated in slightly over 50% yield, is the interesting bicyclic ether 3,7-epoxydibenzocycloocta-1,5-diene (**8**); the minor products are 2-phenylnaphthalene (**9**) and 2-iodo-3-phenyltetralin (**10**). The bicyclic ether **8** can be easily transformed by dissolving metal reduction followed by oxidation into the ketone dibenzocycloocta-1,5-dien-3-one (**1**), which has been converted into a large variety of biologically active compounds. A possible mechanism for the reaction is discussed. The reaction of the acetaldehyde–trimethylsilyl iodide adduct (**4c**) with 2-phenylethyl trimethylsilyl ether (**21**) affords 1-methylisochroman (**25**), the expected product of the proposed mechanistic pathway. The potential utility of these α-iodoalkyl trimethylsilyl ethers (**4**) is also discussed.

Many dibenzocycloocta-1,5-diene derivatives have been shown to possess very potent biological activity ranging from antiinflammatory action to psychotropic properties.[1] Nearly all of these compounds are prepared from the aryl ketone dibenzo[*a*,*e*]cycloocta-1,5-dien-3-one (**1**), which is normally



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produced from benzalphthalide by a multistep process utilizing a Friedel–Crafts cyclization to afford the final product.[2] We now report an efficient three-step synthesis of this important intermediate **1** from phenylacetaldehyde (**2**) which involves as the key step a serendipitous double ortho Friedel–Crafts cyclization effected by trimethylsilyl iodide (**3**).[3] These results also indicate the usefulness of aldehyde iodohydrin trimethylsilyl ethers (**4**) in the Friedel–Crafts alkylation of aromatic compounds.

Results

In the course of an investigation of the reactivity of trimethylsilyl iodide (**3**) with various functional groups, it was found that aldehyde iodohydrin trimethylsilyl ethers (**4**) are readily formed from aldehydes **2** by reaction with **3** at room temperature under an inert atmosphere.[4] Although attempted isolation of the iodo silyl ethers (**4**) by distillation or silica gel

$$\underset{\mathbf{2}}{\mathrm{RCHO}} + \underset{\mathbf{3}}{\mathrm{Me_3SiI}} \underset{\Delta \text{ or } \mathrm{SiO_2}}{\overset{25\ ^\circ\mathrm{C}}{\rightleftharpoons}} \underset{\mathbf{4}}{\mathrm{RCH(I)OSiMe_3}}$$

chromatography causes reversion back to the aldehydes, these intermediates are stable indefinitely in solution at room temperature (see Experimental Section). During this study, it was observed that benzaldehyde [**2b** (R = Ph)] afforded α,α-diiodotoluene (**6**) and hexamethyldisiloxane (**7**) via the intermediacy of the iodo ether **4b** in over 50% isolated yield.[5] In this case, the oxygen atom of the iodo silyl ether (**4b**) must silylate a second time to yield a bis(silyl)oxonium iodide (**5**) which is transformed into the diiodide **6** and the disiloxane **7** by an S_N1 mechanism, an S_N2 mechanism, or both. The conversion of **4b** into **6** is faster than the formation of **4b** since

$$\underset{\mathbf{2b}}{\mathrm{PhCHO}} + \underset{\mathbf{3}}{\mathrm{Me_3SiI}} \xrightarrow[25\ ^\circ\mathrm{C},\ 30\ \mathrm{min}]{\mathrm{CHCl_3}} \underset{\mathbf{4b}}{\mathrm{PhCH(I)OSiMe_3}}$$

$$\underset{\mathbf{4b}}{\mathrm{PhCH(I)OSiMe_3}} \xrightarrow{\mathrm{Me_3SiI},\ \mathbf{3}} \underset{\mathbf{5}}{\mathrm{PhCH(I)O^+(SiMe_3)_2\ I^-}} \xrightarrow{S_N1 \text{ or } S_N2} \underset{\mathbf{6}}{\mathrm{PhCHI_2}} + \underset{\mathbf{7}}{\mathrm{(Me_3Si)_2O}}$$

if one employs equimolar amounts of the aldehyde **2b** and the silyl iodide **3** a 1:1 mixture of the starting aldehyde **2b** and the diiodide **6** is produced. In all cases, the crude yield of **6** is always much higher than the isolated yield due to decomposition of this sensitive diiodide upon purification.[5]

In an attempt to extend this reaction to a general synthesis of α,α-diiodoalkanes (or the corresponding vinyl iodides) from aldehydes,[5] a solution of 1 equiv of phenylacetaldehyde (**2a**) and 2.5 equiv of trimethylsilyl iodide (**3**) in chloroform was allowed to stand at room temperature under an inert atmosphere for 15 h. Aqueous workup followed by column chromatography on silica gel afforded an approximately 1:1:1 mixture of three compounds in 90% yield. The most inter-

$$\underset{\mathbf{2a}}{\mathrm{PhCH_2CHO}} + \underset{\mathbf{3}}{\mathrm{Me_3SiI}} \xrightarrow[25\ ^\circ\mathrm{C},\ 10\ \mathrm{min}]{\mathrm{CHCl_3}} \underset{\mathbf{4a}}{\mathrm{PhCH_2CH(I)OSiMe_3}}$$

$$\underset{\mathbf{4a}}{\mathrm{PhCH_2CH(I)OSiMe_3}} \xrightarrow{25\ ^\circ\mathrm{C}} \underset{\mathbf{8}}{\text{epoxide}} + \underset{\mathbf{9}}{\text{2-phenylnaphthalene}} + \underset{\mathbf{10}}{\text{2-iodo-3-phenyltetralin}}$$

esting of these three was identified as the tetracyclic ether **8**, a white crystalline solid (mp 141.5–142.5 °C), by virtue of its spectroscopic data (see Experimental Section). The other byproducts were shown (see below) to be 2-phenylnaphthalene (**9**), a known product of acid treatment of phenylacetaldehyde,[6] and 2-iodo-3-phenyltetralin (**10**). The initial

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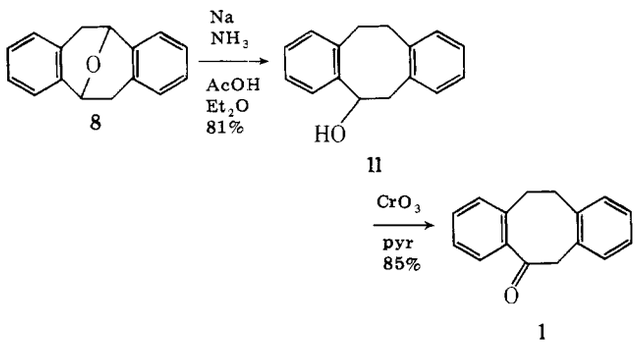
product of the reaction was the expected iodohydrin trimethylsilyl ether (**4a**) as shown by NMR measurements after a short time: ^{1}H NMR ($CDCl_3$) δ 7.29 (5 H, brd s), 6.30 (1 H, t, J = 6 Hz), 3.57 (2 H, d, J = 6 Hz), 0.1 (9 H, s). By conducting the reaction at a lower temperature for a longer period of time, one can isolate **8** in much higher yield. For example, reaction of **2a** and **3** in chloroform at 5 °C in a nitrogen atmosphere for one week afforded a 50% yield of **8**.

Since the completion of the work described in this manuscript, Kagan and Watson have reported the synthesis of this heretofore unknown ether **8** from phenylacetaldehyde (**2a**) using fluorosulfonic acid in carbon tetrachloride in just over 50% crude yield.[7] The structure of **8** was conclusively assigned by X-ray structural analysis. The remaining 50% of the reaction mixture, however, was not accounted for.

The conversion of the tetracyclic ether **8** into the desired ketone **1** was accomplished in two steps in high yield. Reduction of the benzylic ether was effected by addition of compound **8** and acetic acid in a solution of diethyl ether to a solution of sodium in liquid ammonia at −78 °C, thus affording the alcohol **11** in 81% yield. The use of acetic acid is crucial to the success of the reaction since in the absence of a proton donor no reduction is observed, and the use of other simple proton donors such as ethanol or water gives only complex mixtures in which the aromatic rings have suffered partial reduction. Furthermore, catalytic hydrogenation of the ether **8** in ethanol/acetic acid over a 10% Pd/C catalyst failed to effect any hydrogenolysis of the benzylic ether function. Oxidation of the alcohol **11** by the method of Nenitzescu[8] furnished the desired ketone **1** in 85% yield. Thus, the important ketone **1** is available from phenylacetaldehyde (**2a**) in three steps in an unoptimized, isolated yield of 34%. Its conversion into tricyclic aromatic derivatives which possess significant biological activity has already been described.[1]



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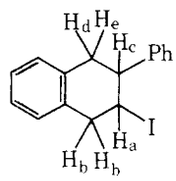
The structure of **9** was easily assigned by comparison of its spectral data (IR, NMR, and mass spectra) with those published for 2-phenylnaphthalene.[9] The assignment of structure



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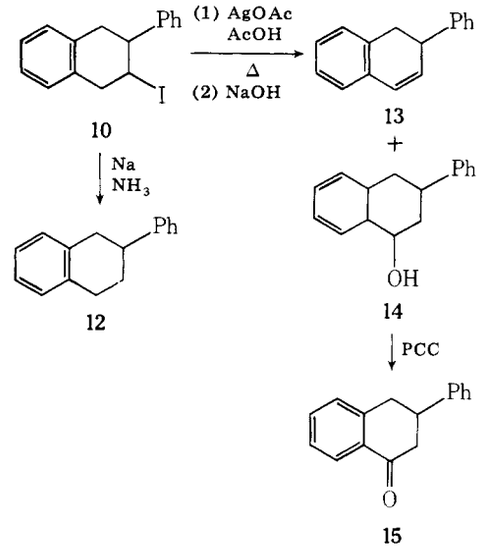
10 to the second byproduct of this reaction was made on the basis of spectroscopic and chemical evidence. The major spectroscopic evidence (in addition to consistent IR, ^{13}C NMR, and mass spectra) was the highly expanded 251 MHz ^{1}H NMR spectrum. ^{1}H NMR ($CDCl_3$): δ 7.33 (9 H, m, aromatic H), 4.58 [1 H, d (J = 6.0 Hz) of t (J = 4.5 Hz), H_a], 3.61 (2 H, d, J = 4.5 Hz, H_b), 3.34 [1 H, d (J = 3.4 Hz) of t (J = 6.0 Hz), H_c], 3.21 [1 H, d (J = 10.5 Hz) of d (J = 3.4 Hz), H_d], 3.02 [1 H, d (J = 10.5 Hz) of d (J = 6.0 Hz), H_e]. The 2 protons giving rise to the signals for H_b are in fact a strongly coupled AB pattern, which, due to "deceptive simplicity",[10] affords identical splitting with H_a. The relative stereochemistry cannot be assigned at present. The chemical evidence is derived from both reductive and oxidative conversions. Reduction of **10** with sodium in ammonia afforded an 82% yield of 2-phenyltetralin (**12**), identified by comparison (^{1}H NMR, IR, MS, and gas chromatography) with an authentic sample prepared by reduction of 2-phenylnaphthalene (**9**).[11] Reaction



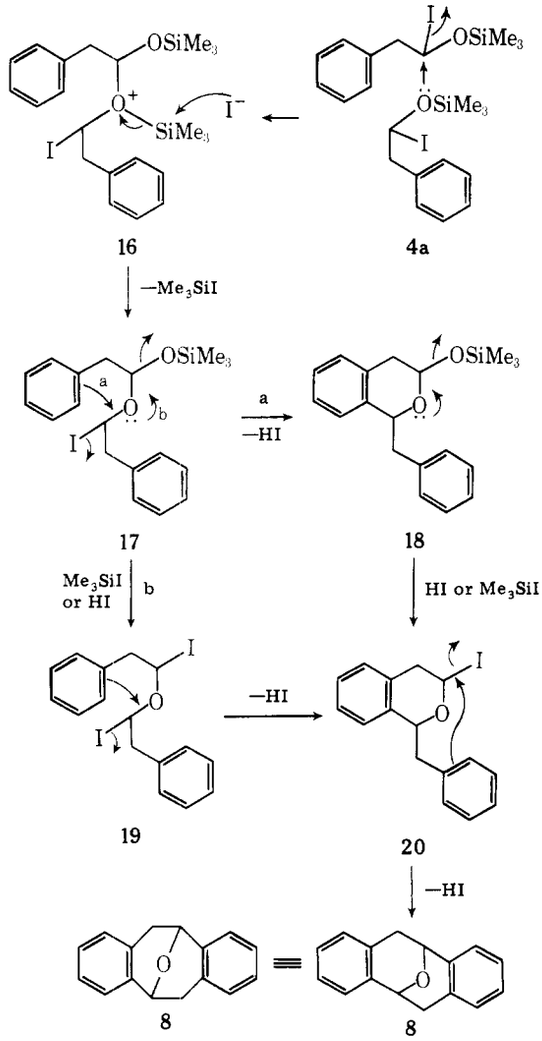
of the iodide **10** with silver acetate in boiling acetic acid followed by basic hydrolysis furnished a mixture of products which could be separated on thick-layer chromatography into an olefin and an alcohol. The olefin was assigned structure **13** on the basis of its NMR spectrum. The alcohol was assumed to have the structure **14** since on Collins oxidation it was converted into 3-phenyl-1-tetralone (**15**), identified by ^{1}H NMR, IR, and the melting point of its semicarbazone.[12]

Mechanistic Discussion

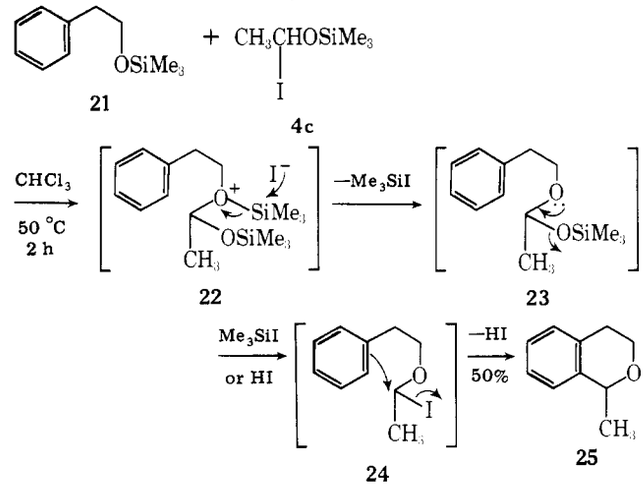
A probable mechanism for this unusual cyclization is shown in Scheme I. Displacement of iodine from one molecule of **4a** by the oxygen atom of a second molecule would lead to the silylated oxonium iodide **16**, which upon loss of trimethylsilyl iodide would afford the iodo acetal **17**. This compound would then be converted into the iodo ether **20** by either of two pathways: (a) initial Friedel–Crafts cyclization with loss of hydrogen iodide to give the acetal **18** which would then be converted into the iodo ether **20** by hydrogen iodide or trimethylsilyl iodide; or (b) initial conversion of the acetal function to the symmetrical diiodo ether **19** followed by Friedel–Crafts cyclization. The iodo ether **20** would then be transformed into **8** by a simple internal ortho Friedel–Crafts cyclization.[13] There are two major reasons for favoring this mechanism.

Most importantly, the lack of any products resulting from attack of the electrophilic aldehyde component at the normally favored para position of the second aromatic ring argues strongly for an intramolecular reaction in the initial Friedel–Crafts cyclization. For this reason, the mechanism presented by Kagan and Watson[7] for the cyclization process they observed, namely, an initial Friedel–Crafts reaction before any complexation of the aldehyde components, cannot be correct in our case since if it were one would expect a large proportion of para substitution. Therefore, there must be some complexation or association of the two aldehyde components before the initial Friedel–Crafts alkylation. We propose that this complexation involves the formation of either the iodo acetal **17** or the diiodo ether **19**. Both of these compounds would now be expected to give only ortho substitution because of the internal delivery of the electrophile to only the ortho position. Secondly, if the mechanism shown in Scheme I were correct,

Scheme I



Scheme II



one would expect that other similar systems should undergo analogous reactions. This is the case. Reaction of 2-phenylethyl trimethylsilyl ether (**21**) with the trimethylsilyl iodide adduct (**4c**) of acetaldehyde at 50 °C in chloroform for 2 h affords a 50% yield of 1-methylisochroman (**25**)[14] (Scheme II). We assume that the reaction proceeds via the intermediates **22–24**, which are analogous to those proposed in Scheme I for the formation of **8**. Again no products arising from para substitution of the aromatic ring are observed. The clean formation of **25** from **21** and **4c** offers evidence for the mechanism proposed in Scheme I. However, in both of these cases since hydrogen iodide is produced in the Friedel–Crafts alkylation or cyclization steps, this strong protic acid may complicate the detailed mechanistic picture.[15,16]

Conclusion

The α-iodo ethers **4**, which are now readily available from aldehydes, have good synthetic potential. Since they can be formed in quantitative yield even from aldehydes with very reactive α hydrogens (e.g., acetaldehyde, propanal, etc.), one might be able to use them as electrophilic aldehyde equivalents in various reactions, such as nucleophilic additions and Friedel–Crafts alkylations. Such possibilities are currently being investigated in our laboratories, as well as extensions of this double ortho Friedel–Crafts alkylation process to the preparation of other tricyclic aromatic compounds of biological interest.

Experimental Section

General. Melting points were taken on a Büchi melting point apparatus and are uncorrected. Infrared spectra were obtained on a Perkin-Elmer 137B spectrophotometer. Proton NMR spectra were measured on a Varian T-60 spectrometer and are reported in parts per million downfield from internal tetramethylsilane, except for the spectrum of **10** which was measured at 251 MHz. Carbon NMR spectra were measured on a Varian CFT-20 spectrometer. Mass spectra were recorded on an MS-9 instrument. Analyses were performed by Spang Microanalytical Laboratory, Ann Arbor, Mich.

Formation of Aldehyde Iodohydrin Trimethylsilyl Ethers (4). In general, to a solution of the aldehyde **2** in a chlorinated hydrocarbon solvent (CCl_4, $CHCl_3$, CH_2Cl_2, or $CDCl_3$) under a nitrogen atmosphere was added via syringe 1 equiv of trimethylsilyl iodide (**3**) at room temperature or slightly below. The solution was allowed stand for 15–30 min at room temperature. (Usually the exothermic reaction was complete after only a few minutes.) Proton NMR analysis indicated the complete disappearance of the peaks due to the aldehyde **2** and the appearance of the peaks due to the iodo ether **4**. Attempted distillation or chromatography on silica gel afforded the starting aldehyde. ^1H NMR for **4** [RCH(OSiMe$_3$)I]: **4a** (R = CH_2Ph) ($CDCl_3$) δ 7.29 (5 H, brd s), 6.30 (1 H, t, J = 6 Hz), 3.57 (2 H, d, J = 6 Hz), 0.02 (9 H, s); **4b** (R = Ph) (CH_2Cl_2) δ 8.00–7.60 (6 H, m); **4c** (R = CH_3) ($CDCl_3$) δ 6.08 (1 H, q, J = 7 Hz), 2.18 (3 H, d, J = 6 Hz), 0.02 (9 H, s); **4d** (R = CH_3CH_2) ($CDCl_3$) δ 6.13 (1 H, t, J = 5 Hz), 2.12 [2 H, d (J = 5 Hz) of q (J = 7 Hz)], 0.97 (3 H, t, J = 7 Hz), 0.02 (9 H, s); **4e** (R = $CH_3CH_2CH_2$) ($CDCl_3$) δ 6.23 (1 H, t, J = 6 Hz), 2.48–2.02 (2 H, m), 1.92–1.35 (2 H, m), 0.98 (3 H, t, J = 6 Hz), 0.07 (9 H, s); **4f** (R = $(CH_3)_2CH$) ($CDCl_3$) δ 6.20 (1 H, d, J = 4 Hz), 2.2–1.5 (1 H, m), 1.05 (6 H, d, J = 6 Hz), 0.07 (9 H, s); **4g** (R = $CH_3(CH_2)_4$) ($CDCl_3$) δ 6.25 (1 H, t, J = 5 Hz), 2.53–2.03 (2 H, m), 1.95–1.03 (6 H, m), 0.93 (3 H, t), 0.07 (9 H, s); **4h** (R = $CH_3(CH_2)_5$) (CH_2Cl_2) δ 6.19 (1 H, t, J = 5 Hz), 2.27 (2 H, m), 1.38 (8 H, m), 0.95 (3 H, t, J = 7 Hz), 0.1 (9 H, s).

α,α-Diiodotoluene (6). Freshly distilled benzaldehyde (**2b**) (2.1 g, 19.8 mmol) was dissolved in 10 mL of methylene chloride (dried over molecular sieves) in a 25 mL round-bottom flask. The flask was flushed with nitrogen, sealed with a rubber septum, and cooled to 0 °C in an ice bath. Trimethylsilyl iodide (**3**) (5.8 mL, 8.7 g, 43.5 mmol) was added over 3 min via syringe. The mixture was warmed to 25 °C and allowed to stand for 0.5 h. The solution was then washed with sodium thiosulfate (1 M, 10 mL) and 5 mL of saturated sodium bicarbonate and dried (sodium sulfate). The solvent was evaporated in vacuo and the residue sublimed at 55 °C and 0.02 mm of pressure, using dry ice to cool the collector, to yield 3.5 g (51.4%) of **6** as a white solid: ^1H NMR ($CDCl_3$) δ 7.1–7.7 (5 H, m), 6.2 (1 H, s); MS m/e 334 (M^+), 217, 204, 90. This white solid turns light brown rapidly on exposure to light and/or heat.

2,3:6,7-Dibenzo-9-oxabicyclo[3.3.1]nona-2,6-diene (8). A 50 mL Erlenmeyer flask was charged with phenylacetaldehyde (**2a**) (1.2 g, 10 mmol) and 5 mL of freshly distilled chloroform. The flask was stoppered under a nitrogen atmosphere with a serum cap and cooled in an ice bath. To this solution was added freshly distilled trimethylsilyl iodide (**3**) (1.6 mL, 2.4 g, 12 mmol), and the reaction was allowed to stand at 5 °C for 7 days. Sodium thiosulfate (1 M, 10 mL) and methylene chloride (10 mL) were added, and the mixture was stirred until the iodine color was discharged. The organic phase was separated, dried (sodium sulfate), and concentrated in vacuo. NMR analysis of this crude reaction mixture indicated the presence of 54% of the ether **8**, 25% of 2-phenylnaphthalene (**9**), and 20% of the iodide **10**. Chromatography on 35 g of silica gel eluting with either carbon tetrachloride or chloroform yielded 562 mg of the crystalline ether **8** (50%). Elution with carbon tetrachloride permits the separation of **9** and **10**.

Compound 8: mp 141.5–142.5 °C; ^{1}H NMR ($CDCl_3$) δ 7.1 (8 H, m), 5.25 (2 H, d, J = 6 Hz), 3.55 (2 H, dd, J = 6 and 16 Hz), 2.70 (2 H, d, J = 16 Hz); ^{13}C NMR ($CDCl_3$) δ 137.78 (s), 131.58 (s), 129.08 (d), 126.83 (d), 125.96 (d), 125.14 (d), 69.56 (d), 36.12 (t); IR (liquid film) 3.25, 3.37, 6.68, 6.87, 9.22, 12.75, 12.90, 14.35, 14.65 μm; MS m/e 222 (M^+), 204, 203, 179, 178. Anal. Calcd for $C_{16}H_{14}O$: C, 86.45; H, 6.35. Found: C, 86.58; H, 6.24.

Compound 10: ^{1}H NMR ($CDCl_3$) δ 7.33 (9 H, m, aromatic H), 4.58 [1 H, d (J = 6.0 Hz) of t (J = 4.5 Hz), H_a], 3.61 (2 H, d, J = 4.5 Hz, H_b), 3.34 [1 H, d (J = 3.4 Hz) of t (J = 6.0 Hz), H_c], 3.21 [1 H, d (J = 10.5 Hz) of d (J = 3.4 Hz), H_d], 3.02 (1 H, d (J = 10.5 Hz) of d (J = 6.0 Hz), H_e]; IR (liquid film) 3.33, 3.48, 6.25, 6.38, 6.71, 6.90, 7.00, 8.83, 9.72, 14.32 μm; MS m/e 334 (M^+), 207.

1,2:5,6-Dibenzocycloocta-1,5-dien-3-ol (11). Ammonia (15 mL) was distilled from sodium into a 100 mL three-neck round-bottom flask equipped with a Dewar condenser under a nitrogen atmosphere. This flask was maintained at −78 °C while the ether 8 (111 mg, 0.5 mmol) and acetic acid (44 μL) in 5 mL of anhydrous diethyl ether was added. Sodium metal (61.5 mg, 2.8 mmol) was added, and the mixture was allowed to reflux for 40 min. At this time, ammonium chloride (0.5 g) was added and the ammonia was removed in a stream of nitrogen. Hydrochloric acid (1 N, 35 mL) was added, and the mixture was extracted with 2 × 20 mL of carbon tetrachloride. The organic layer was dried (sodium sulfate) and concentrated to an oil. Chromatography on silica gel, eluting with methylene chloride, yielded 91.3 mg (81.5%) of the crystalline alcohol **11** (R_f 0.3). Crystals from chloroform had mp 109–110 °C (lit.[8] mp 113–114 °C); ^{1}H NMR ($CDCl_3$) δ 7.33–7.0 (8 H, m), 5.26 (1 H, t, J = 8 Hz), 3.77–3.0 (7 H, m); MS m/e 224 (M^+), 2.06.

The conversion of **11** into **1** was carried out by a method of Nenitzescu.[8] Crystals of the ketone **1** showed mp 94.5–95.5 °C (lit.[8] mp 95 °C); 2,4-DNP, mp 195–197 °C (lit.[8] mp 198–200 °C).

2-Phenyltetralin (12). A solution of the iodide **10** (334 mg, 1 mmol) in 5 mL of diethyl ether was added to a cooled (−78 °C) flask containing 20 mL of distilled ammonia under a nitrogen atmosphere. Sodium metal (49 mg, 2 mmol) was added and the reaction stirred at −33 °C for 30 min. Ammonium chloride (0.5 g) was added, and the solvents were evaporated. Water (50 mL) was added and the aqueous mixture extracted with 2 × 30 mL of methylene chloride. The combined organic layers were dried (sodium sulfate) and concentrated in vacuo. Bulb to bulb distillation of the residue yielded 184 mg (82%) of 2-phenyltetralin (**12**): ^{1}H NMR ($CDCl_3$) δ 7.25 (5 H, s), 7.10 (4 H, s), 2.90 (4 H, m), 2.1 (2 H, m); IR (liquid film) 3.34, 3.46, 6.25, 6.33, 6.70, 6.87, 6.98, 13.16, 13.42, 14.33 μm; MS m/e 208 (M^+). This reduction product was shown to be identical with 2-phenyltetralin (**12**) by comparison (NMR, IR, MS, and gas chromatography) with an authentic sample.[11]

2-Phenyl-1,2-dihydronaphthalene (13) and 3-Phenyl-1-tetralone (15). A solution of **10** (334 mg, 1 mmol) and silver acetate (184 mg, 1.1 mmol) in 10 mL of acetic acid was refluxed for 40 min. Diethyl ether (100 mL) was added, and the solution was washed several times with saturated aqueous sodium bicarbonate, dried (sodium sulfate), and evaporated in vacuo to afford 235 mg of residue. This mixture was taken up in 15 mL of acetone to which was added 15 mL in 1 N sodium hydroxide, and the solution was allowed stand at 25 °C for 2 h. The acetone was extracted with 2 × 30 mL of ether, and the ethereal solution was dried (sodium sulfate) and concentrated in vacuo. Preparative layer chromatography of the residue on silica gel eluting with carbon tetrachloride afforded two separate bands (R_f 0.8 and 0.05). The upper band (50 mg) was assigned as 2-phenyl-1,2-dihydronaphthalene (**13**) on the basis of its NMR spectrum: ^{1}H NMR (CCl_4) δ 7.27 (5 H, s), 7.13 (4 H, s), 6.60 (1 H, dd, J = 10 and 1.5 Hz), 6.06 (1 H, dd, J = 10 and 2 Hz), 3.70 (1 H, m), 3.00 (2 H, m).

The lower band (170 mg), probably the alcohol **14**, was oxidized with pyridinium chlorochromate to afford 3-phenyl-1-tetralone (**15**) (151 mg). The structure of **15** was assigned on the basis of the compound's NMR and IR spectra and the melting point of its semicarbazone: semicarbazone, mp 209–210 °C (lit.[12] mp 208 °C); ^{1}H NMR (CCl_4) δ 7.95 (1 H, m), 7.37–7.21 (9 H, m), 3.08 (3 H, m), 2.77 (2 H, m); IR (liquid film) 5.95 μm.

1-Methylisochroman (25). A 5 mL round-bottom flask charged with freshly distilled acetaldehyde (311 mg, 7.06 mmol) and 1 mL of chloroform (dried over molecular sieves) was flushed with nitrogen and sealed with a rubber septum. To this was added via syringe trimethylsilyl iodide (**3**) (0.94 mL, 1.412 g, 7.06 mmol), the flask being cooled to keep the reaction mixture at 25 °C. (The reaction of the aldehyde and the silyl iodide is exothermic.) To this solution of **4c** in chloroform was added via syringe 2-phenylethyl trimethylsilyl ether (**21**) (2.11 mL, 9.9 mmol) (prepared by silylation of the corresponding alcohol by the usual method). The reaction mixture was warmed to 50 °C for 2 h and cooled to 25 °C, and 20 mL of diethyl ether was added. The organic solution was washed with 3 × 10 mL of 10% aqueous sodium thiosulfate and 2 × 10 mL of water, dried (sodium sulfate), and evaporated in vacuo. The residue was chromatographed on 80 g of silica gel. Elution with benzene afforded 0.553 g (50%) of the desired isochroman **25:** ^{1}H NMR ($CDCl_3$) δ 6.8–7.2 (4 H, m), 4.75 (1 H, q, J = 7 Hz), 3.5–4.3 [2 H, m (14 line pattern)], 2.4–3.2 (2 H, m), 1.57 (3 H, d, J = 7 Hz); IR (liquid film) 3.3–3.6, 8.93, 13.16, 13.60 μm; MS m/e 148 (M^+).

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Registry No.—**1,** 838-15-3; **2a,** 122-78-1; **2b,** 100-52-7; **2c,** 75-07-0; **2d,** 123-38-6; **2e,** 123-72-8; **2f,** 78-84-2; **2g,** 66-25-1; **2h,** 111-71-7; **3,** 16029-98-4; **4a,** 66858-68-2; **4b,** 66858-69-3; **4c,** 66858-70-6; **4d,** 66858-71-7; **4e,** 66858-72-8; **4f,** 66858-73-9; **4g,** 66858-74-0; **4h,** 66858-75-1; **6,** 28000-59-1; **8,** 66365-45-5; **9,** 612-94-2; **10,** 66858-76-2; **11,** 888-42-6; **12,** 29422-13-7; **13,** 62019-39-0; **14,** 66858-77-3; **15,** 14944-26-4; **21,** 14629-58-4; **25,** 26164-06-7.

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(16) The detailed mechanisms for the formation of **9** and **10** are not known at present. However, the fact that the aldehyde **2a** is not observed by NMR spectroscopy during the reaction leads us to suggest that both **9** and **10** may be formed from the α-iodo silyl ether **4a** by some electrophilic process.