β-Iodo Ketones by Prévost Reaction of Vinyl Carbinols

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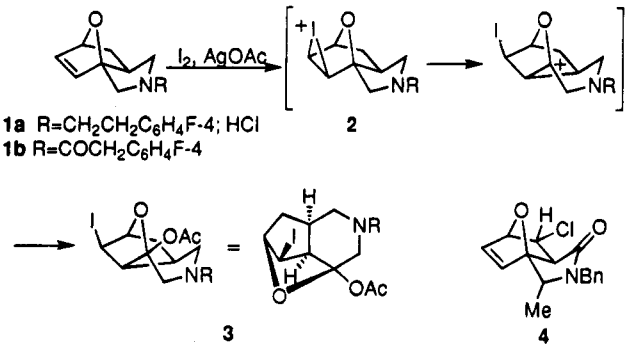
Treatment of α-ethenyl-α-phenylbenzenemethanol with iodine and silver acetate in either acetic acid or benzene gave 1,2-diphenyl-3-iodo-1-propanone (**6**) in 85% yield. Ring enlargements involving similar rearrangements were observed with a number of cyclic vinyl carbinols. In some cases, mixtures of normal Prévost products and rearranged β-iodo ketones were obtained. The exact scope of this apparently novel reaction remains to be elucidated. Treatment of the β-iodo ketones with DBU gave the corresponding α,β-unsaturated ketones from which a number of amino ketones and amino alcohols were prepared by conjugate addition followed by reduction.

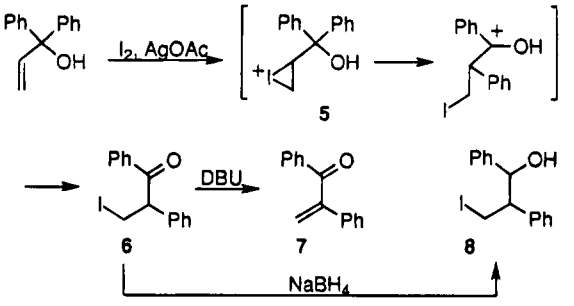
In the course of a project directed at the preparation of σ antagonists as antipsychotics[2] it became necessary to synthesize potential metabolites of the potent and selective σ ligand **1a**.[3] When it was subjected to the conditions of a Prévost reaction[4] in order to prepare the 5,6-dihydroxy derivative, the rearranged iodo acetate **3a** was obtained instead. The structure was established by X-ray crystallography of the free base. The initially formed iodonium ion **2** thus rearranged exclusively or predominantly to the tertiary carbocation even though this placed the positive charge in close proximity to that of the ammonium ion. Amide **1b** similarly gave the correponding rearranged product **3b**. We subsequently discovered that Jung and Street[5] had observed the same skeletal rearrangement in the Prévost reaction of the closely related lactam **4**. Our results confirm their



structure assignment which was made by ^{1}H NMR spectroscopy. These findings led us to investigate the Prévost reaction of vinyl carbinols which should lead to rearranged β-iodo ketones, a reaction that to our knowledge has not been reported before.

Results and Discussion

Treatment of α-ethenyl-α-phenylbenzenemethanol with iodine and silver acetate in either acetic acid or benzene gave the β-iodo ketone **6** in 85% yield, presumably by rearrangement of the initially formed iodonium ion **5**. Because of their instability neither ketone **6** nor any of the other β-iodo ketones preparared in this study were purified. They were characterized by their NMR spectra and their behavior in subsequent reactions. Exposure of ketone **6** to 1,8-diazabicyclo[5.4.0]non-5-ene (DBU) gave the α,β-unsaturated ketone **7** in 77% overall yield; reduction with sodium borohydride produced a single isomer of the iodo alcohol **8** in 49% overall yield from α-ethenyl- α-phenylbenzenemethanol. Since ketones of type **7** are readily available by Mannich reaction of the



corresponding deoxybenzoins,[6] we focused our investigation on systems where the Mannich reaction substrates are not as easily accessible. A further consideration was to prepare intermediates that might lead to products useful as therapeutic agents. Reaction of 10,11-dihydro-5-ethenyl-5*H*-dibenzo[*a*,*d*]cycloheptene-5-ol (**9**) with iodine and silver acetate gave the ring-expanded ketone, 6-(iodomethyl)-5,6,11,12-tetrahydrodibenzo[*a*,*d*]cycloocten-5-

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(2) Abou-Gharbia, M.; Ablordeppey, S. Y.; Glennon, R. A. *Annu. Rep. Med. Chem.* **1993**, *28*, 1.

(3) Ciganek, E. WO Patent 9409006, 1994; *Chem. Abstr.* **1994**, *121*, 83387.

(4) (a) March, J. *Advanced Organic Chemistry*, 4th ed.; Wiley Interscience: New York, 1992; p 823. (b) Haines, A. H. *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Eds.; Pergamon Press: Oxford, 1991; Vol. 7, p 447.

(5) Jung, M. E.; Street, L. J. *Tetrahedron Lett.* **1985**, *26*, 3639. Keay, B. A., Rogers, C., Bontront, J.-L. J. *J. Chem. Soc., Chem. Commun.* **1989**, 1782 and references cited there; cf. also Arjona, O., Fernandez de la Pradilla, R., Garcia, L., Mallo, A., Plumet, J. *J. Chem. Soc., Perkin Trans. 2* **1989**, 1315.

(6) Matti, J.; Laval-Verges, A.; Emod, I. *Bull. Soc. Chim. Fr.* **1963**, 1176. Moffett, R. B.; Strube, R. E.; Skaletzky, L. *J. Med. Chem.* **1971**, *14*, 1088. For a list of reviews of the Mannich reaction see ref 4a, p 900; cf. also Kleinmann, E. F., *Comprehensive Organic Synthesis*, Trost, B. M., Fleming, I., Eds.; Pergamon Press: Oxford, 1991; Vol. 2, p 893.

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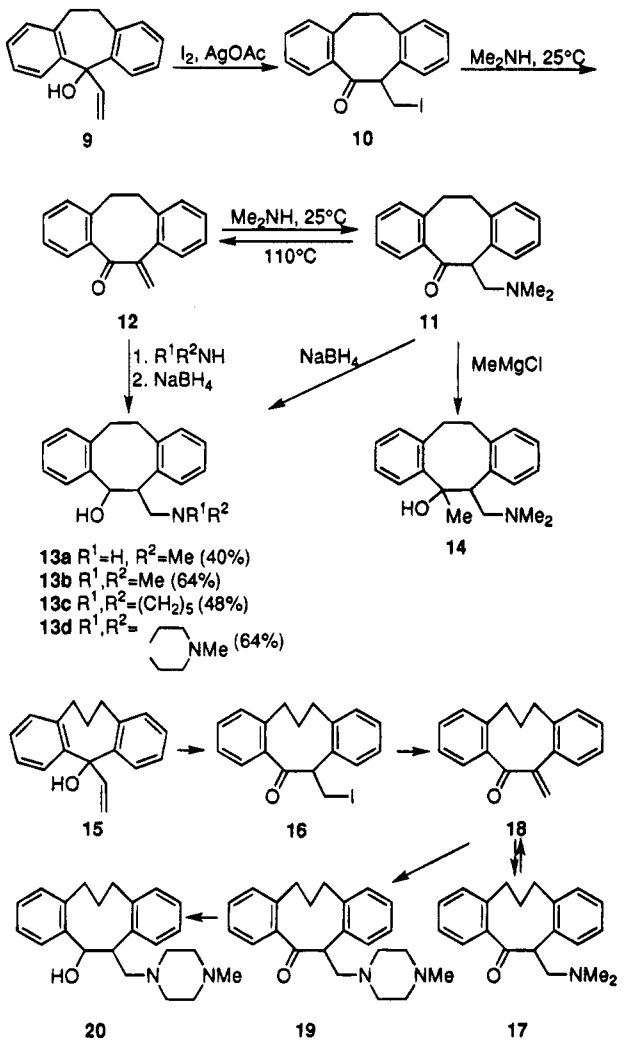
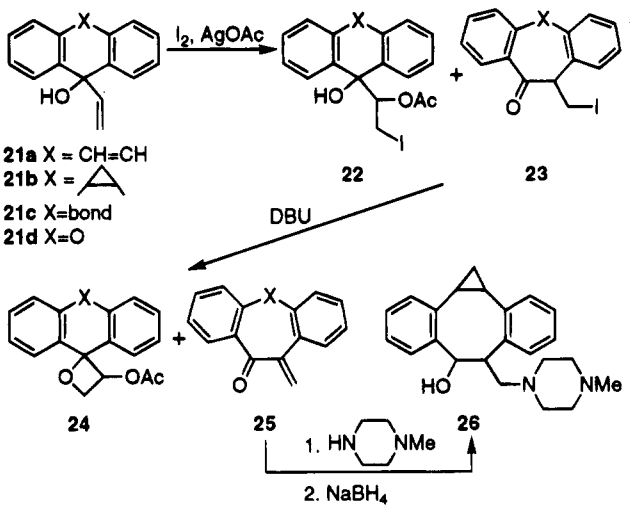
Scheme 1



one (**10**) in almost quantitative yield (Scheme 1). Treatment of the iodo ketone **10** with dimethylamine gave the amine **11** in 73% yield via the α,β-unsaturated ketone **12**. The latter could be regenerated by sublimation of amine **11**, or, in better yield, by heating a solution in toluene to reflux for 1 h. Addition of methylamine, piperidine, or *N*-methylpiperazine to ketone **12** followed by *in situ* reduction with sodium borohydride produced the amino alcohols **13a**, **13c**, and **13d**, respectively, mostly as single isomers. Reduction of amine **11** with sodium borohydride gave the amino alcohol **13b**, whereas addition of methylmagnesium chloride gave the amino alcohol **14**. The homologous vinyl carbinol **15** behaved similarly except that the Mannich base **17** required considerably higher temperatures for conversion into the α,β-unsaturated ketone **18** which on the other hand was more prone to thermal decomposition than the lower homolog **12**. Addition of *N*-methylpiperazine to ketone **18** gave the amino ketone **19** which was reduced to the amino alcohol **20**; in this sequence, only compounds **19** and **20** were fully characterized.

Reaction of 5-ethenyl-5*H*-dibenzo[*a*,*d*]cyclohepten-5-ol (**21a**) with iodine and silver acetate, on the other hand, gave a mixture of the normal Prévost product **22a** and the ring-enlarged iodo ketone **23a** (Scheme 2). Treatment of the mixture **22a**/**23a** with DBU gave a mixture of the spirooxetane **24a** (19% from **21a**) and the unstable

Scheme 2



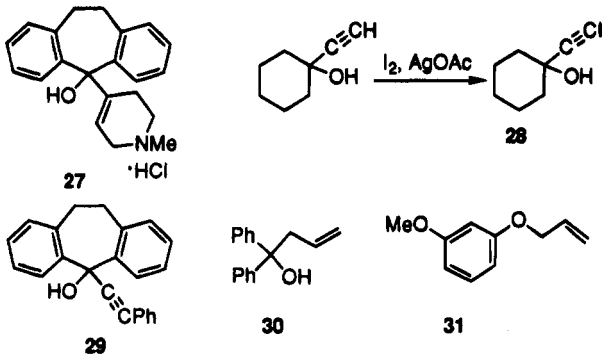
α,β-unsaturated ketone **25a** (31%)[7] which was separated by chromatography. Reaction of 6-ethenyl-1,1a,6,10b-tetrahydrodibenzo[*a*,*e*]cyclopropa[*c*]cyclohepten-6-one with vinylmagnesium bromide gave a single isomer of vinyl carbinol **21b**, presumably the one in which the hydroxyl group and the cyclopropane are *syn*. Treatment of this alcohol with iodine and silver acetate gave a mixture of single isomers of the iodo acetate **22b** (44%) and the iodo ketone **23b** (56%). The two products were separated by chromatography on silica gel which caused most of the iodo ketone **23b** to be converted into the α,β-unsaturated ketone **25b**. Treatment of the iodo acetate **22b** with DBU gave a single isomer of spirooxetane **24b** (96%); similar treatment of iodo ketone **23b** gave the α,β-unsaturated ketone **25b** (85%). Addition of *N*-methylpiperazine to ketone **25b** followed by sodium borohydride reduction gave the amino alcohol **26**.

The exact scope of the skeletal rearrangement described above remains to be elucidated. The behavior of other electrophiles toward vinyl carbinols probably also merits investigation. However, the observation that mixtures of rearranged and normal Prévost products were obtained in the reaction of the more rigid vinyl carbinols **21a** and **21b** with iodine and silver acetate seems to indicate that certain steric requirements in the intermediate iodonium ions have to be met for rearrangement to occur. This is further corroborated by the fact that 9-ethenyl-9-fluorenol (**21c**) gave a complex mixture on treatment with iodine and silver acetate; ca. 30% of the iodo ketone **23d** were observed in the crude product mixture obtained from the xanthenol **21d**. The trisubstituted vinylcarbinol **27** did not react at all under Prévost conditions in toluene. Only terminal iodination to give the iodoacetylene **28** occurred when 1-ethynylcyclohexanol was treated with iodine and silver acetate; a complex mixture was obtained from carbinol **29**. The normal iodo acetate Prévost products were obtained from the allyl carbinol **30** and the ether **31**.

Experimental Section

General. ^{1}H (300 MHz) and ^{13}C (75 MHz) NMR spectra were determined in $CDCl_3$ unless otherwise specified. Melting points were measured in unsealed capillary tubes and are

(7) This ketone has been prepared previously by a Mannich reaction: Carling, R. W.; Leeson, P. D. *Tetrahedron Lett.* **1988**, *29*, 6985.



uncorrected. Mass spectra were obtained by chemical ionization (NH_3 or CH_4) or by electron ionization.

Materials. Starting materials were obtained from Janssen Chimica or Aldrich Chemical Co. Vinyl carbinols were prepared by the reaction of the appropriate ketone with vinylmagnesium bromide[8] as illustrated below for the synthesis of 12-ethenyl-6,7-dihydrodibenzo[*a*,*d*]cycloocten-12(5*H*)-ol(**15**). The THF used was EM Science anhydrous grade (stored over 4 Å sieves). $MgSO_4$ was used throughout for drying solutions in organic solvents.

(2α,3β,3aβ,4α,7aβ)-6-[2-(4-Fluorophenyl)ethyl]octahydro-3-iodo-2,4-methanofuro[2,3-*c*]pyridin-7a-yl Acetate Hydrochloride (3a). To a mixture of 3.00 g (10 mmol) of 2-[2-(4-fluorophenyl)ethyl]-1,2,3,6,7,7a-hexahydro-3a,6-epoxy-3a*H*-isoindole hydrochloride (**1a**),[3] 3.34 g (20 mmol) of AgOAc, and 25 mL of HOAc was added with stirring 2.67 g (10.5 mmol) of iodine. A mildly exothermic reaction ensued. The mixture was filtered after stirring at rt for 1 h, and the solids were washed with 3 × 30 mL of CH_2Cl_2. The combined filtrates and washings were decolorized with 20% $NaHSO_3$ and made basic with 15% NaOH. Removal of the solvent from the dried organic phase and crystallization of the residue from MeCN gave 2.05 g (45%) of the free base of the title compound in two crops, mp 159–160 °C. The X-ray diffraction structure elucidation was carried out on a crystal grown from MeCN. ^1H NMR δ 7.2 (m, 2 H), 7.0 (m, 2 H), 4.5 (s, 1 H), 3.8 (s, 1 H), 3.3 (d, *J* = 12 Hz, 1 H), 3.2 (d, *J* = 4.5 Hz, 1 H), 2.5–2.8 (m, 6 H), 2.4 (m, 1 H). 2.3 (d, *J* = 11 Hz, 1 H), 2.1 (s, 3 H), 1.7–1.8 (m, 2 H). ^{13}C NMR δ 21.2, 22.5, 32.0, 32.2, 32.7, 48.3, 52.5, 54.8, 58.6, 85.5, 106.8, 114.7, 115.0, 130.0, 130.1, 135.7, 159.6, 162.9, 169.2. Anal. Calcd for $C_{18}H_{21}FINO_3$: C, 48.55; H, 4.75; I, 28.50, N, 3.15. Found: C, 48.61; H, 4.69; I, 29.05; N, 3.11. The hydrochloride **3a** (85% EtOH) had mp 206 °C (dec; mp depended on the rate of heating). Anal. Calcd for $C_{18}H_{22}ClFINO_3$: C, 44.88; H, 4.60; I, 26.34; N, 2.91. Found: C, 45.10; H, 4.49; I, 26.10; N, 2.86.

(2α,3β,3aβ,4α,7aβ)-6-[(4-Fluorophenyl)acetyl]octahydro-3-iodo-2,4-methanofuro[2,3-*c*]pyridin-7a-yl Acetate (3b). 2-[(4-Fluorophenyl)acetyl]-1,2,3,6,7,7a-hexahydro-3a,6-epoxy-3a*H*-isoindole (**1b**)[3] (3.22 g, 11.8 mmol), AgOAc (3.94 g, 23.6 mmol), and HOAc (15 mL) were treated with iodine (3.20 g, 12.6 mmol) as described above to give 4.35 g (80%) of the title compound **3b** in two crops after crystallization from MeCN, mp 164–166 °C (dec, mp depended on rate of heating). The ^1H and ^{13}C NMR spectra were complicated by the presence of two rotamers. Anal. Calcd for $C_{18}H_{19}INO_4$: C, 47.08; H, 4.17; I, 27.63: N, 3.05. Found: C, 47.35; H, 4.09; I, 27.58; N, 3.00.

1,2-Diphenyl-3-iodo-1-propanone (6). General Procedure for the Preparation of β-Iodo Ketones. To a mixture of 1.67 g (10 mmol) of AgOAc, 2.54 g (10 mmol) of iodine, and 20 mL of benzene[9] (**Caution, suspected carcinogen**) was added a solution of 1.80 g (8.6 mmol) of α-ethenyl-α-phenylbenzenemethanol[8] in 4 mL of benzene; the temperature rose to 36 °C and starting material was consumed after 25 min (TLC, silica gel, hexanes/EtOAc 4:1). The mixture was filtered, and the solids were washed twice with benzene. The combined filtrates and washings were stirred with 20 mL of 20% $NaHSO_3$ solution until the color was discharged, and the organic phase was washed with 20 mL of 5% $NaHCO_3$ solution and dried. Removal of the solvent left 2.73 g of the title compound **6** as an oil of at least 90% purity (85% yield) as judged from the ^1H NMR: δ 8.0 (d, *J* = 7 Hz, 2 H), 7.3–7.6 (m, 8 H), 5.1 (d/d, *J* = 9/6 Hz, 1 H), 4.0 (t, *J* = 9 Hz, 1 H), 3.5 (d/d, *J* = 9/6 Hz, 1 H). ^{13}C NMR δ 5.6, 56.6, 127.9, 128.0, 128.4, 128.6, 128.7, 129.3, 133.3, 138.2, 197.4. LRMS 354 [$(M + NH_4)^+$, base peak], 337 [$(M + H)^+$].

1,2-Diphenyl-2-propen-1-one (7). A solution of 0.40 g (1.2 mmol) of unpurified iodo ketone **6** and 0.88 g (5.8 mmol) of DBU in 4 mL of CH_2Cl_2 was allowed to stand at rt for 1 h, ether (20 mL) was added, and the solution was washed with 5% HCl, 5% $NaHCO_3$, and dried. Removal of the solvent left 0.22 g of ketone **7**[6] as an oil of ca. 90% purity (0.20 g, 77% from 1,1-diphenyl-2-propen-1-ol). ^1H NMR δ 8.0 (d, *J* = 7 Hz, 2 H), 7.2–7.6 (m, 8 H), 6.0 (d, *J* = 2 Hz, 1 H), 5.5 (d, *J* = 2 Hz, 1 H). LRMS 226 [$(M + NH_4)^+$, base peak], 209 [$(M + H)^+$].

α-(Iodomethyl)-β-phenylbenzeneethanol (8). A solution of 2.70 g (8.0 mmol) of unpurified iodo ketone **6** in 25 mL of EtOH was cooled to 0 °C and treated with 0.5 g (13 mmol) of $NaBH_4$ in small portions and the mixture was stirred in an ice bath for 1 h. Water (50 mL) was added, and the mixture was extracted with 50 and 2 × 20 mL of CH_2Cl_2. Removal of the solvent from the dried extracts gave 2.43 g of crude product containing ca 75% of iodo alcohol **8**; ca. 5% of a compound having a multiplet at δ 4.9 may have been the other isomer. Crystallization from *n*-BuCl gave 1.40 g of the title product (49% from 1,1-diphenyl-2-propen-1-ol), mp 100–101 °C. ^1H NMR δ 7.1–7.4 (m, 10 H), 5.0 (d/d, *J* = 6.5/3.5 Hz, 1 H), 3.5 (d/d, *J* = 9.5/5.5 Hz, 1 H), 3.1–3.3 (m, 2 H), 2.0 (s, 1 H). ^{13}C NMR δ 8.7, 56.0, 76.5, 126.4, 127.6, 127.9, 128.3, 128.4, 128.6, 139.0, 141.6. Anal. Calcd for $C_{15}H_{15}IO$: C, 53.27; H, 4.47; I, 37.52. Found: C, 53.42; H, 4.50; I, 37.48.

6-(Iodomethyl)-5,6,11,12-tetrahydrodibenzo[*a*,*e*]cycloocten-5-one (10). Yield of crude product (oil): 99%. ^1H NMR δ 7.5 (d, *J* = 7 Hz, 1 H), 7.0–7.5 (m, 7 H), 4.8 (d/d, *J* = 8.5/5.5 Hz, 1 H), 4.3 (d/d, *J* = 10/5.5 Hz, 1 H), 3.6 (d/d, *J* = 10/8.5 Hz, 1 H), 3.1–3.6 (m, 4 H).

6-[(Dimethylamino)methyl]-5,6,11,12-tetrahydrodibenzo[*a*,*e*]cycloocten-5-one (11). A solution of 15.21 g (41.2 mmol) of iodo ketone **10** in 10 mL of EtOH was treated with 20 mL of 33% Me_2NH in EtOH (6.6 g, 147 mmol), and the mixture was allowed to stand at rt for 4 h and at 0 °C for 30 min. The precipitate was collected by filtration, washed with ice-cold EtOH, and dried at rt under high vacuum to give 7.38 g (73%) of the title compound, mp 111–113 °C dec. ^1H NMR δ 7.5 (d/d, *J* = 7.5/1 Hz, 1 H), 7.3 (m, 1 H), 7.0–7.2 (m, 6 H), 4.6 (t, *J* = 6 Hz, 1 H), 3.1–3.6 (m, 5 H), 2.9 (d/d, *J* = 13/6 Hz, 1 H), 2.4 (s, 6 H). ^{13}C NMR δ 33.6, 35.5, 46.4, 55.8, 59,7, 126.9, 127.2, 127.7, 127.7, 128.0, 130.5, 130.9, 131.1, 137.3, 138.0, 139.3, 140.2, 205.8. Anal. Calcd for $C_{19}H_{21}NO$: C, 81.68; H, 7.58; N, 5.01. Found: C, 81.46; H, 7.68; N, 5.06. In $CDCl_3$ at rt, amino ketone **11** was slowly converted into α,β-unsaturated ketone **12** with a half-life of about two weeks.

6-Methylene-5,6,11,12-tetrahydrodibenzo[*a*,*e*]cycloocten-5-one (12). Ketone **11** (0.75 g) was placed in a short-path still and heated in a 150 °C oil bath under 0.005 mm pressure until distillation was complete to give 0.61 g (97%) of essentially pure ketone **12**. An analytical sample (cyclohexane) had mp 68–69 °C. To obtain the same yield on a larger scale, 10% solutions of ketone **11** in toluene were heated under reflux for 1 h. ^1H NMR δ 7.1–7.4 (m, 8 H), 6.5 (d, *J* = 1.8 Hz, 1 H), 5.7 (d, *J* = 1.8 Hz, 1 H), 3.4 (m, 2 H), 3.3 (m, 2 H). ^{13}C NMR δ 32.7, 33.6, 124.0, 126.2, 126.4, 127.1, 128.4, 129.3, 129.7, 130.7, 137.2, 137.4, 137.7, 139.5, 152.0, 199.2. IR (KBr) 1672 (vs), 1598 (s) cm^{-1}. UV λ_{max} (ε) in EtOH: 261 (5717), 250 (6603), 226 (10,346); in cyclohexane: 248 (6465), 224 (11,240). Anal. Calcd for $C_{17}H_{14}O$: C, 87.15; H, 6.02. Found: C, 87.02; H, 5.89.

6-[(Methylamino)methyl]-5,6,11,12-tetrahydrodibenzo[*a*,*e*]cycloocten-5-ol (13a). To 1.15 g (4.9 mmol) of ketone **12** in 10 mL of EtOH was added 5 mL of 33% $MeNH_2$ in EtOH (1.65 g, 55 mmol), and the mixture was allowed to stand at rt for 24 h and cooled to 0 °C. $NaBH_4$ (1 g, 26 mmol) was added in small portions and the mixture was stirred at 0 °C for 1 h

(8) Eisch, J. J.; Merkley, J. H. *J. Am. Chem. Soc.* **1979**, *101*, 1148.
(9) Toluene may also be used.

and at rt for 17 h. Aqueous NaOH (15%, 10 mL) was added, and the mixture was extracted with CH_2Cl_2 to give 1.20 g of product containing 18% of unreacted ketone **12**. The crude product was dissolved in toluene and treated with HCl in ether, and the precipitate was crystallized from 90% *n*-PrOH to give 0.59 g (40%) of the HCl salt of the title compound, mp 230–232 °C. Anal. Calcd for $C_{18}H_{22}ClNO$: C, 71.16; H, 7.30; N, 4.61. Found: C, 70.99; H, 7.32; N, 4.60. The ^1H NMR of the free base showed the presence of >95% of a single isomer: δ 7.3 (d, J = 7 Hz, 1 H), 6.9–7.0 (m, 7 H), 5.4 (d, J = 6.5 Hz, 1 H), 3.7 (m, 1 H), 3.4 (t, J = 11 Hz, 1 H), 2.9–3.2 (m, 7 H), 2.6 (s, 3 H).

6-[(Dimethylamino)methyl]-5,6,11,12-tetrahydrodibenzo[*a,e*]cycloocten-5-ol (13b). To a solution of 1.00 g (3.6 mmol) of amino ketone **11** in 20 mL of dry THF was added at 0 °C 5 mL of 2 M $LiBH_4$ in THF (10 mmol), and the mixture was stirred in an ice bath for 4 h. Concentrated NaCl (1 mL) was added, and the mixture was filtered after stirring in an ice bath for 15 min. Removal of the solvent from the dried filtrates and short-path distillation of the residue at 190 °C bath temperature/0.002 mm gave 0.98 g (97%) of essentially pure amino alcohol **13b**. The ^1H NMR showed only a single isomer: δ 7.3 (br m, 1 H), 6.8–7.0 (m, 7 H), 5.5 (d, J = 6.5 Hz, 1 H), 3.8 (br m, 1 H), 3.0–3.5 (br m, 5 H), 2.4 (s+m, 7 H). The hydrochloride (0.73 g, 64% from **11**) had mp 237–239 °C (80% EtOH). Anal. Calcd for $C_{19}H_{24}ClNO$: C, 71.80; H, 7.61; N, 4.41. Found: C, 71.72; H, 7.65; N, 4.42.

6-(1-Piperidinylmethyl)-5,6,11,12-tetrahydrodibenzo[*a,e*]cycloocten-5-ol (13c) was prepared as described for the methylamino alcohol **13a** except that piperidine was sustituted for methylamine. The hydrochloride of **13c** was obtained in 48% yield, mp 238–258 °C (95% EtOH). Anal. Calcd for $C_{22}H_{28}ClNO$: C, 73.83; H, 7.89; N, 3.91. Found: C, 73.72; H, 7.85; N, 3.95. Despite the melting point range of the hydrochloride, the ^1H NMR of the free base showed >95% of a single isomer: δ 7.3 (br m, 1 H), 6.8–7.2 (m, 7 H), 5.4 (d, J = 7 Hz, 1 H), 3.8 (br m, 1 H), 2.7–3.3 (br m, 7 H), 2.4–2.6 (m, 3 H), 1.6–1.8 (m, 4 H), 1.5–1.6 (m, 2 H).

6-[(4-Methyl-1-piperazinyl)methyl]-5,6,11,12-tetrahydrodibenzo[*a,e*]cycloocten-5-ol (13d) was prepared as described for the methylamino alcohol **13a** except that 1-methylpiperazine was sustituted for methylamine, and the product was isolated in 64% yield as the free base, mp 176–178 °C (toluene). ^1H NMR δ 7.2 (br m, 1 H), 6.8–7.0 (m, 7 H), 5.4 (d, J = 7 Hz, 1 H), 3.8 (br m, 1 H), 2.3–3.4 (mostly br m, 15 H), 2.3 (s, 3 H); there was ca. 12% of a second product which is most likely the other isomer: δ 5.1 (d, J = 4 Hz, 1 H), 2.2 (s, 3 H). Anal. Calcd for $C_{22}H_{28}N_2O$: C, 78.53; H, 8.39; N, 8.33. Found: C, 78.40; H, 8.46; N, 8,03.

6-[(Dimethylamino)methyl]-5-methyl-5,6,11,12-tetrahydrodibenzo[*a,e*]cycloocten-5-ol (14). To 0.4 g (1.4 mmol) of amino ketone **11** in 5 mL of THF was added with cooling l mL of 3 M MeMgCl in THF (3 mmol), and the mixture was stirred in an ice bath for 4 h. Addition of 10 mL of 20% NH_4Cl and extraction with EtOAc gave a single isomer of alcohol **14**. ^1H NMR δ 7.4 (m, 1 H), 7.2 (d, J = 8 Hz, 1 H), 6.9–7.1 (m, 5 H), 6.8 (d, J = 7 Hz, 1 H), 4.0 (t, J = 6 Hz, 1 H), 3.4–3.6 (m, 2 H), 2.8–3.1 (m, 4 H), 2.2 (s, 6 H), 1.7 (s, 3 H). LRMS 296 [(M + H)$^+$]. The hydrochloride crystallized from 99% EtOH as the hydrate (0.34 g, 68%), mp 283°C dec. Anal. Calcd for $C_{20}H_{28}ClNO_2$: C, 68.65; H, 8.07; N, 4.00. Found: C, 68.98; H, 8.09; N, 3.96.

12-Ethenyl-6,7-dihydrodibenzo[*a,d*]cycloocten-12(5*H*)-ol (15). Vinylmagnesium bromide (30 mL of 1 M solution in THF, 30 mmol) was added with cooling to 4.44 g (20 mmol) of 6,7-dihydrodibenzo[*a,d*]cycloocten-12(5*H*)-one[10] in 30 mL of THF, the mixture was stirred at 0 °C for 1 h and rt for 5 h, and 30 mL of 20% NH_4Cl was added. Extraction with EtOAc followed by short-path distillation (130–165 °C bath temperature, 0.002 mm) gave 4.72 g (94%) of essentially pure vinyl carbinol **15** which was used without further purification. An analytical sample (0.55 g, 78%) was prepared by crystallization of 0.66 g from EtOH, mp 106–107 °C. ^1H NMR δ 7.8 (br s, 2 H), 7.2 (m, 4 H), 7.0 (m, 2 H), 6.2 (d/d, J = 16/10 Hz, 1 H), 5.5 (d/d, J = 16/1 Hz, 1 H), 5.1 (d/d, J = 10/1 Hz, 1 H), 2.4–2.8 (br m, 4 H), 2.0 (s, 1 H), 1.6 (m, 2 H). Anal. Calcd for $C_{18}H_{18}O$: C, 86.38; H, 7.25. Found: C, 86.38; H, 7.20.

Using the procedures described for the preparation of compounds **10**, **11**, and **12**, the following products were obtained sequentially from alcohol **15**:

6-(Iodomethyl)-6,11,12,13-tetrahydro-5*H*-dibenzo[*a,e*]cyclononen-5-one (16). Yield of crude product (oil): quantitative. ^1H NMR δ 7.1–7.4 (m, 8 H), 4.9 (broadened t, 1 H), 4.2 (d/d, J = 10/8 Hz, 1 H), 3.4 (d/d, J = 10/7 Hz, 1 H), 2.6–3.0 (m, 4 H), 2.2 (m, 2 H). LRMS 377 [(M + H)$^+$], 394 [(M + NH_4)$^+$].

6-[(Dimethylamino)methyl]-6,11,12,13-tetrahydro-5*H*-dibenzo[*a,e*]cyclononen-5-one (17). Yield of crude product (solid): 95%. ^1H NMR δ 7.1–7.3 (m, 8 H), 4.7 (d/d, J = 12/3 Hz, 1 H), 3.7 (t, J = 12 Hz, 1 H), 2.4–2.8 (m, 5 H), 2.4 (s, 6 H), 2.0 (m, 2 H). The solid could be dried at 70 °C without decomposition.

6-Methylene-6,11,12,13-tetrahydro-5*H*-dibenzo[*a,e*]cyclononen-5-one (18). Sublimation of **17** at 100–180 °C bath temperature (0.002 mm) gave the title compounds in 57% yield of ca. 90% purity still containing some unreacted amino ketone **17**. Resublimation resulted in further loss due to decomposition without improving the purity. ^1H NMR δ 7.0–7.3 (m, 8 H), 6.2 (s, 1 H), 5.5 (s, 1 H), 2.9 (m, 2 H), 2.8 (m, 2 H), 2.0 (m, 2 H).

6-[(4-Methyl-1-piperazinyl)methyl]-6,11,12,13-tetrahydro-5*H*-dibenzo[*a,e*]cyclononen-5-one (19). A mixture of 0.65 g of ketone **18** of 90% purity (0.58 g, 2.4 mmol), 0.43 g (4.3 mmol) of *N*-methylpiperazine, and 1.5 mL of EtOH was allowed to stand at rt for 5 h, cooled, and filtered, and the solids were washed once with cold EtOH and dried to give 0.63 g (77%) of the title compound, mp 151–152 °C. ^1H NMR δ 7.5 (d, J = 7 Hz, 1 H), 7.2–7.4 (m, 7 H), 4.7 (d/d, J = 12/3 Hz, 1 H), 3.8 (t, J = 12 Hz, 1 H), 2.4–2.8 (m, 11 H), 2.3 (s, 3 H), 1.8–2.2 (m, 4 H). Anal. Calcd for $C_{23}H_{28}N_2O$: C, 79.27; H, 8.10; N, 8.04. Found: C, 79.56; H, 8.10; N, 7.85.

6-[(4-Methyl-1-piperazinyl)methyl]-6,11,12,13-tetrahydro-5*H*-dibenzo[*a,e*]cyclononen-5-ol (20). Reduction of ketone **19** with $NaBH_4$ in EtOH at rt for 5 h and crystallization of the crude product from DMF gave the title compound in 70% yield as a 2:1 mixture of two isomers, mp 201–203 °C. In the ^1H NMR the major isomer had a broadened singlet at δ 5.5 (1 H) for the proton on the OH-bearing carbon; the corresponding signal in the minor isomer was a singlet at δ 5.3. Anal. Calcd for $C_{23}H_{30}N_2O$: C, 78.82; H, 8.63; N, 7.99. Found: C, 78.46; H, 8.54; N, 8.02.

Spiro[dibenzo[*a,d*]cycloheptene-5,2′-oxetanyl] Acetate (24a) and 5,6-Dihydro-6-methylenedibenzo[*a,e*]cycloocten-5-one (25a). Vinyl carbinol **21a** (2.34 g, 10 mmol) was treated with AgOAc (3.48 g, 20 mmol) and iodine (2.70 g, 10.6 mmol) in acetic acid (15 mL) for 45 min as described in the General Procedure. The crude mixture of acetate **22a** and iodo ketone **23a** (3.47 g) was dissolved in 15 mL of CH_2Cl_2 and treated with 3 mL of DBU. Toluene (100 mL) was added after 1 h at rt, and the solution was washed sequentially with 5% HCl, 10% Na_2CO_3, and brine and dried. Chromatography of the crude product (2.78 g) on silica gel gave 0.73 g (31%) of the oily ketone **25a**,[7] eluted with 98/2 hexanes/EtOAc, and 0.55 g (19%) of spiroacetate **24a**, eluted with 9/1 hexanes/EtOAc and obtained in ca. 80–90% purity as an oil.

Spiroacetate 24a: ^1H NMR δ 7.6 (d, J = 8 Hz, 2 H), 7.3–7.4 (m, 6 H), 7.0 (s, 2 H), 4.0 (d/d, J = 12/3 Hz, 1 H), 3.5 (d/d, J = 12/7 Hz, 1 H), 3.1 (d/d, J = 7/3 Hz, 1 H), 2.0 (s, 3 H). IR (neat) no OH, 1744 cm^{-1} (vs). HRMS calcd for $C_{19}H_{16}O_3$ 292.109945, found 292.108135.

Ketone 25a: ^1H NMR δ 7.4 (d, J = 8 Hz, 1 H), 7.0–7.3 (m, 7 H), 6.7 and 6.9 (ABq, J = 12 Hz, 2 H), 6.4 (d, J = 1.8 Hz, 1 H), 5.4 (d, J = 1.8 Hz, 1 H). ^{13}C NMR δ 126.8, 127.3, 127.4, 127.4, 127.7, 128.2, 128.3, 129.2, 130.0, 130.2, 131.3, 134.3, 135.7, 137.8, 139.5, 149.9, 197.1. HRMS calcd for $C_{17}H_{13}O$ [(M + H)$^+$] 233.096640, found 233.096115. Ketone **25a** polymerized fairly rapidly at rt; only 60% was remaining after 3 days.

6-Ethenyl-1,1a,6,10b-tetrahydrodibenzo[*a,e*]cyclopropa[*c*]cyclohepten-6-ol (21b). Yield of distilled (190–210 °C

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bath temperature, 0.002 mm) product from 1,1a,6,10b-tetrahydrodibenzo[*a,e*]cyclopropa[*c*]cyclohepten-6-one:[11] 87% of a single isomer. An analytical sample (cyclohexane) had mp 81–82 °C. ^{1}H NMR δ 7.8 (d, J = 7 Hz, split further, 2 H), 7.3 (d, J = 7 Hz, split further, 2 H), 7.1–7.2 (m, 4 H), 6.8 (d/d, J = 17/10 Hz, 1 H), 5.3 (d/d, J = 10/1 Hz, 1 H), 5.2 (d/d, J = 17/1 Hz, 1 H), 2.2 (m, 2 H), 2.0 (s, 1 H), 1.6 (m, 1 H), 0.7 (s, 1 H). Anal. Calcd for $C_{18}H_{16}O$: C, 87.06; H, 6.49. Found: C, 86.82; H, 6.39.

[2-Iodo-1-(1,1a,6,10b-tetrahydro-6-hydroxydibenzo[*a,e*]cyclopropa[*c*]cyclohepten-6-yl)ethyl] Acetate (22b) and 7-(Iodomethyl)-1a,6,7,11b-tetrahydrodibenzo[*a,e*]cyclopropa[*c*]cycloocten-6-one (23b). Vinyl carbinol **21b** (2.03 g, 8.3 mmol) was treated with AgOAc (1.67 g, 10 mmol) and iodine (2.54 g, 10 mmol) in toluene (10 mL) for 1 h as described in the General Procedure to give 3.24 g of a 1:1 mixture of the title compounds, both as single isomers. Chromatography of 1.86 g of the crude product on silica gel gave 0.69 g (56%) of a 83:17 mixture of α,β-unsaturated ketone **25b** and iodo ketone **23b**, eluted with 98/2 hexanes/EtOAc, and 0.90 g (44%) of iodo acetate **22b** (9/1 hexanes/EtOAc).

Iodo acetate 22b: mp 145–146 °C (MeCN). ^{1}H NMR δ 7.8 (d/d, J = 8/1.2 Hz, 1 H), 7.5 (d/d, J = 7.5/1.2 Hz, 1 H), 7.4 (m. 2 H), 7.1–7.3 (m, 4 H), 6.8 (d/d, J = 7.5/6 Hz, 1 H), 4.4 (d/d, J = 12/7.5 Hz, 1 H), 4.3 (d/d, J = 12/6 Hz, 1 H), 3.0 (s, 1 H), 2.6 (m, 2 H), 1.9 (s, 3 H), 1.7 (m, 1 H), 0.7 (m, 1 H). ^{13}C NMR δ 16.5, 20.0, 21.0, 21.1, 46.2, 67.5, 78.4, 123.8, 125.1, 126.8, 127.4, 128.5, 128.6, 133.8, 133.9, 135.2, 135.7, 140.6, 148.2, 170.9. Anal. Calcd for $C_{20}H_{19}IO_3$: C, 55.32; H, 4.41. Found: C, 55.24; H, 4.37.

Iodo ketone 23b (oil): ^{1}H NMR δ 7.6 (d/d, J = 8/0.7 Hz, 1 H), 7.0–7.3 (m, 7 H), 5.7 (d/d, J = 10/6 Hz, 1 H), 4.2 (d/d, J = 10/6 Hz, 1 H) 3.6 (t, J =10 Hz, 1 H), 2.5–2.7 (m, 2 H), 1.7–1.8 (m, 1 H), 1.2–1.3 (m, 1 H).

1a,10b-Dihydrospiro[dibenzo[*a,e*]cyclopropa[*c*]cycloheptene-6(1*H*),2′-oxetan-3′-yl] Acetate (24b). To 0.90 g (2.1 mmol) of iodo acetate **22b** in 5 mL of CH_2Cl_2 was added 0.9 g (6 mmol) of DBU; after 30 min, 30 mL of toluene was added and the solution was washed sequentially with 10% HCl, water, and 10% Na_2CO_3, dried, and concentrated. Short-path distillation of the residue (160–190 °C bath temperature, 0.002 mm) gave 0.61 g (96%) of the title compound as an oil. ^{1}H NMR δ 7.5 (m, 4 H), 7.2–7.4 (m, 4 H), 4.5 (d/d, J = 12/3 Hz, 1 H), 3.9 (d/d, J = 12/7 Hz, 1 H), 3.7 (m, 1 H), 2.6 (m, 2 H), 2.2 (s, 3 H), 1.6 (m, 1 H), 0.8 (m, 1 H). ^{13}C NMR δ 12.9, 19.0, 21.2, 62.7, 64.3, 65.0, 123.9, 125.4, 127.1, 127.2, 128.6, 128.8, 132.2, 132.3, 136.6, 136.7, 138.9, 141.8, 171.2. HRMS calcd for $C_{20}H_{18}O_3$: 307.13342, found 307.13213.

7-Methylene-1a,6,7,11b-tetrahydrodibenzo[*a,e*]cyclopropa[*c*]cycloocten-6-one (25b). Treating an 83/17 mixture of α,β-unsaturated ketone **25b** and iodo ketone **23b**, obtained as described above, with DBU as described for the synthesis of spiro compound **24b** gave the title compound as a solid in 85% yield. An analytical sample (cyclohexane) has mp 118–119 °C. ^{1}H NMR δ 7.0–7.2 (m, 8 H), 6.0 (d, J = 1.8 Hz, 1 H), 5.6 (d, J = 1.8 Hz, 1 H), 2.2–2.8 (m, 2 H), 1.5 (m, 1 H), 1.4 (m, 1 H). ^{13}C NMR δ 11.1, 20.4, 22.0, 126.3, 126.8, 126.9, 127.0, 128.3, 129.1, 129.2, 130.1, 135.5, 137.6, 140.4, 142,3, 148.5, 198.0. Anal. Calcd for $C_{18}H_{14}O$: C, 87.78; H, 5.73. Found: C, 87.32; H, 5.70.

7-[(4-Methyl-1-piperazinyl)methyl]-1a,6,7,11b-tetrahydrodibenzo[*a,e*]cyclopropa[*c*]cycloocten-6-ol (26). Ketone **25b** (0.32 g) was treated as described for the methylamino alcohol **13a** except that 1-methylpiperazine was sustituted for methylamine, and the crude product was isolated as the free base and mostly as a single isomer in quantitative yield. Crystallization from toluene gave a single isomer of the title compound (0.15 g, 33%), mp 203–204 °C. ^{1}H NMR δ 7.4 (δ, J = 8 Hz, 1 H), 6.8–7.0 (m, 7 H), 5.8 (d, J = 8 Hz, 1 H), 4.6 (m, 1 H), 3.6 (t, J = 12 Hz, 1 H), 2.3–3.2 (m+s, 15 H), 1.4 (m, 1 H), 1.3 (m, 1 H). Anal. Calcd for $C_{23}H_{28}N_2O$: C, 79.27; H, 8.10; N, 8.04. Found: C, 79.11; H, 8.17; N, 7.68.

1-(2-Iodoethynyl)-1-cyclohexanol (28). To a mixture of 1.24 g (10 mmol) of 1-ethynyl-1-cyclohexanol, 1.89 g (11.3 mmol) of AgOAc, and 6 mL of HOAc was added 2.61 g (10.3 mmol) of iodine, the mixture was stirred at rt for 2 h, and the product was isolated as described for the preparation of iodo acetate **3a** to give 2.40 g (96%) of essentially pure title compound[12] as an oil that slowly crystallized. ^{13}H NMR δ 0.3, 23.1, 25.0, 39.8, 70.4, 98.3. LRMS 233 $[M + H - H_2O]^+$.

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Supporting Information Available: ^{1}H and/or ^{13}C NMR spectra of new compounds **6**, **10**, **16**, **24a**, and **24b**, and previously described compounds **25a** and **28**, for which elemental analyses were not obtained (9 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be obtained from the ACS; see any current masthead page for ordering information.

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