In 85% dioxane we suggest that interconversion of ion pairs is rate limiting (k_2, Scheme I) in the presence of perchlorate ion. Thus, we might formulate the transition state for this process as Figure 1.

However, in the absence of perchlorate salts or in the presence of common-ion salts, we imagine the rate-limiting step to involve capture of solvent-separated ion pair (k_s^{III}, Scheme I). This is shown schematically in Figure 2.

Assuming that the fractionation factor for chloride ion is $(0.72)^{1/4} = 0.921$ per fully developed lone pair, we estimate ϕ^*_1 for k_2 rate limiting as in eq 2. Here, X represents the degree

$$\phi_1^* = 0.921^3 0.921^X \quad (2)$$

of separation of chloride ion from the carbonium ion in the transition state.

Assuming ϕ^R is unity and the transition state resembles[19] the tight ion pair ($X = 0$), we have

$$k_{H_2O}/k_{D_2O} = 1/0.921^3 = 1.28 \quad (3)$$

The agreement between our estimate and the experimental results is gratifying on the one hand and somewhat surprising on the other. For example, this fractionation factor refers to a wholly aqueous solvent although the experimental results refer to 85% dioxane–15% H_2O. The similarity of the SIE for **1** and **2** suggest that the SIE has its origin primarily in changes of the chloride ion fractionation factor between ground and transition state.

For the transition state resembling nucleophilic capture of the solvent-separated ion pair, we estimate the transition-state fractionation factor from eq 4 where X is the amount of oxygen–carbon bond making in the transition state.

$$\phi_2^* = \phi_{Cl^-}{}^4\, \phi_{OL^+}{}^{2X} = 0.921^4\, \phi_{OL^+}{}^{2X} \quad (4)$$

The average SIE for **1** and **2** in 75% and 85% dioxane–water in the presence and absence of chloride ion salts is 1.47 ± 0.03. Assuming this "exploded"[20] transition state is ion-pair like, we have

$$k_{H_2O}/k_{D_2O} = (1/0.921^4)1/0.69^{2X} \quad (5)$$

$$k_{H_2O}/k_{D_2O} = 1/0.921^4 = 1.39 \quad (6)$$

Treating X as an adjustable parameter furnishes a substantially identical transition state involving very little carbon–oxygen bond making, i.e., $X \approx 0.1$.

Experimental Section

1 was made available from a previous investigation.[2] **2** was made available from Aldrich Chemical Co. and distilled prior to use.

Reaction rates were obtained by monitoring the appearance of *p*-methoxy benzaldehyde (275 nm) or benzophenone (250 nm) for **1** and **2**, respectively, in the thermostated cell compartment of a Gilford Model 2400 spectrophotometer. The rate constant was obtained by a nonlinear least-squares regression analysis of the absorbance–time data. The standard deviation of each individual rate constant was <0.5%. The standard deviation of the isotope effect is based on two–five runs which involved two (one) H_2O runs and one (two) D_2O runs determined concurrently and is listed following the isotope effect in the tables, i.e., 1.302 (9) = 1.302 ± 0.009.

Reaction rates were initiated by adding 1–2 μL of a dioxane solution of **1** or **2** to a solution of a given salt in 75% or 85% dioxane–H_2O (D_2O) made by adding 25 (15) mL of H_2O (D_2O) to 75 (85) mL of purified dioxane.

All salts were the highest purity commercially available samples.

Acknowledgment. We thank the National Institues of Health for support of this work (Grant No. GM-21933).

(19) G. S. Hammond, *J. Am. Chem. Soc.*, **77**, 334 (1955).

(20) W. P. Jencks, *Acc. Chem. Res.*, **13**, 161 (1980).

Total Synthesis of Isopavine and Intermediates for the Preparation of Substituted Amitriptyline Analogues: Facile Routes to Substituted Dibenzocyclooctatrienes and Dibenzocycloheptatrienes

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Contribution from the Department of Chemistry, University of California, Los Angeles, California 90024. *Received August 4, 1980*

Abstract: We report the total synthesis of isopavine (**1**) and a key intermediate for the synthesis of analogues of antidepressant agents such as amitriptyline in only four steps, each in excellent overall yields. The double ortho Friedel–Crafts alkylation of homoveratraldehyde (**11**), promoted by trimethylsilyl iodide, afforded an excellent yield of the dibenzocyclooctadienyl ether **12**. This cyclic ether, although stable to acid, could be readily opened with *n*-butyllithium to produce the dibenzocyclooctatrienol **13**. From this alcohol (available from **11** in 92% yield), either of the synthetic targets could be prepared in two steps in nearly 60% yield. Several rearrangements of dibenzocyclooctatrienyl systems to substituted methyldibenzocycloheptatrienyl systems are reported in high yields. The mechanisms of these processes are discussed in detail. In addition, a novel oxidative cleavage of the *exo*-methylenedibenzocycloheptatriene (**23**) is described and its likely mechanism discussed. Finally, several approaches for the total synthesis of the pavine alkaloids are also presented which indicate the peculiarities of the chemistry of these dibenzocycloalkadiene and -triene systems.

Recently in a study of the addition reactions of trimethylsilyl iodide[2] with aldehydes, we reported a new method for the simple preparation of dibenzocyclooctadienes in good yields.[3] This involved a double ortho Friedel–Crafts alkylation of phenylacetaldehyde promoted by trimethylsilyl iodide. Since a large number of natural alkaloids possess a dibenzocyclooctadiene or dibenzocycloheptadiene ring system, e.g., isopavine (**1**),[4] thalisopavine (**2**),[5] pavine (**3**),[4] and argemonine (**4**),[6] we thought this

(1) Camille and Henry Dreyfus Teacher-Scholar, 1978–1983. Fellow of the Alfred P. Sloan Foundation, 1979–1981.

(2) For the preparation of this reagent for use in chlorinated hydrocarbon solvents, see: Jung, M. E.; Lyster, M. A. *Org. Synth.* **1979**, *59*, 35 and references therein.

(3) Jung, M. E.; Mossman, A. B.; Lyster, M. A. *J. Org. Chem.* **1978**, *43*, 3781.

(4) Neither isopavine nor pavine have yet been isolated from natural sources, but each is the parent compound of a group of natural alkaloids: Dyke, S. F. "Rodd's Chemistry of Carbon Compounds"; Coffey, S. Ed.; Elsevier: New York, 1978, Vol. 4H, p 1.

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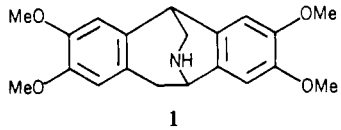

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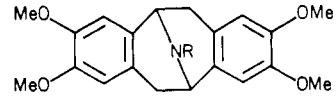
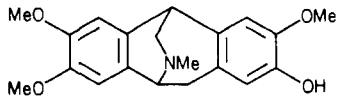


3, R = H
4, R = Me



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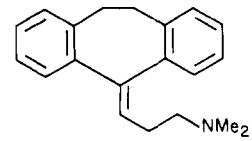

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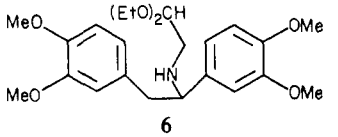
new construction of dibenzocycloalkadienes should be applicable for certain natural product total synthesis. In addition, there are many very active antidepressant agents containing a tricyclic aromatic structure, the most well-known being amitriptyline **5**.[7] Many derivatives of this basic structure have shown potent and varied biological activity.[8] However, compounds with significant modifications in both aromatic rings are rare. Therefore, we began a program aimed at the facile construction of tricyclic aromatic alkaloids, e.g., isopavine (**1**) and pavine (**3**), and of synthetic intermediates for the preparation of substituted amitriptyline analogues. We now report the successful achievement of two of these goals, namely, the preparation of isopavine (**1**) and the ketone **24** from homoveratraldehyde (**11**), each in four steps in overall yield of 53% and 55%, respectively.

Background. Isopavine (**1**) was first prepared by Guthrie et al.[9] by the action of concentrated sulfuric acid on the acetal **6**,



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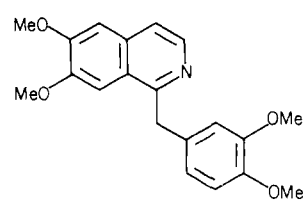

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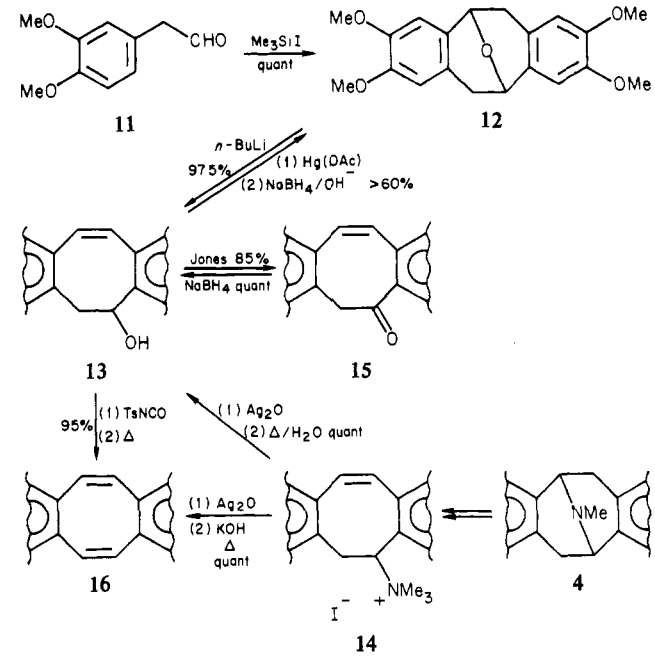
although they misassigned the structure of the product. Later the groups of Waldmann[10] and Battersby[11] repeated this preparation and correctly assigned the structure, with Battersby proposing the name isopavine for compound **1**. Several syntheses of the isopavine alkaloids have been accomplished.[12,13] Most of these have followed the original route to the base,[12] although a few have utilized other schemes.[13] However, until now no synthetic approaches have utilized a functionalized dibenzocyclooctadiene as a precursor to the isopavine alkaloids.

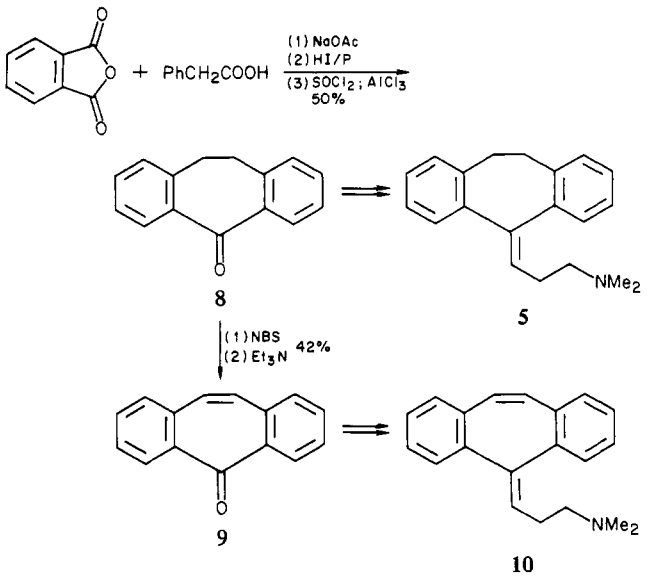
Scheme I



Compound **3** was first prepared by the tin/hydrochloric acid reduction of papaverine (**7**) by Goldschmiedt in 1886[14] and later by Pyman,[15] who named it pavine. The structure of pavine remained ambiguous until 1955 when Battersby again proved it to be as shown in **3**,[16] a structure first suggested along with **1** by Schöpf,[17] who could not distinguish between the two. The syntheses of other pavine alkaloids such as argemonine **4** have involved, almost without exception, a similar acid-catalyzed cyclization of the appropriate 1-benzyl-1,2-dihydroisoquinoline.[18] There are no reports of a synthetic approach to the pavine alkaloids which utilizes a dimerizative cyclization to prepare the dibenzocyclooctadiene ring system.

The very potent antidepressant amitriptyline **5** is generally prepared by several different routes[7] from dibenzocycloheptadienone (**8**), which is available in three steps from phthalic anhydride and phenylacetic acid.[19] Other amitriptyline analogues such as the unsaturated derivative cyclobenzaprine (**10**) are prepared from the dibenzocycloheptatrienone **9**,[20] which is accessible from **8** in 42% yield via two steps (bromination–dehydrobromination).[19] Many derivatives of **5** and **10** have been

(5) Kupchan, S. M.; Yoshitake, A. *J. Org. Chem.* **1969**, *34*, 1062.
(6) (a) Soine, T. O.; Et. al. *J. Am. Pharm. Assoc., Sci. Ed.* **1960**, *49*, 187; *Ibid.* **1951**, *40*, 19; *Ibid.* **1962**, *51*, 1196. (b) Stermitz, F. R.; Lwo, S.-Y.; Kallos, G. *J. Am. Chem. Soc.* **1963**, *85*, 1551. (c) Martell, M. J.; Soine, T. O.; Kier, L. B. *Ibid.* **1963**, *85*, 1022. See also ref 4.
(7) Hoffsommer, R. D.; Taub, D.; Wendler, N. L. *J. Org. Chem.* **1962**, *27*, 4134; *Ibid.* **1963**, *28*, 1751; *J. Med. Chem.* **1965**, *8*, 555 and references therein.
(8) (a) Lacefield, W. B. *J. Med. Chem.* **1971**, *14*, 82. (b) Monkovic, I.; Perron, Y. G.; Martel, R.; Simpson, W. J.; Gylys, J. A. *Ibid.* **1973**, *16*, 403. (c) Coyne, W. E.; Cusic, J. W. *Ibid.* **1974**, *17*, 72. (d) Eichstadt, K. E.; Reepmeyer, J. C.; Cook, R. B.; Riley, P. G.; Davis, D. P.; Wiley, R. A. *Ibid.* **1976**, *19*, 47. (e) Grisar, J. M.; Claxton, G. P.; Wiech, N. L.; Lucas, R. W.; MacKenzie, R. D.; Goldstein, S. *Ibid.* **1973**, *16*, 885. (f) Lippman, W.; Pugsley, T.; Merker, J. *Life Sci.* **1974**, *16*, 213. (g) Boissier, J.-R.; Dumont, C.; Ratouis, R. *Ther. Ggw.* **1971**, *26*, 459. (h) Roszkowski, A. P.; Schuler, M. E.; Marx, M.; Edwards, J. A. *Experientia* **1975**, *31*, 960. (i) Atkinson, J.; Ladinsky, H. *Br. J. Pharmacol.* **1972**, *45*, 519. (j) Lipshitz, W. L.; Hadidian, Z.; Kerpcsar, A. *J. Pharmacol. Exp. Ther.* **1943**, *79*, 97. (k) Funcke, A. B. H.; Zandberg, P. *Arzneim.-Forsch.* **1970**, *20*, 1896. (l) Molina-Negro, P.; Illingworth, R. A. *Union Med. Can.* **1971**, *100*, 1947. (m) For recent work on the efficacy of substituted analogues, see: Randall, W. C.; Anderson, P. S.; Gresson, E. L.; Hunt, C. A.; Lyon, T. F.; Rittle, K. E.; Remy, D. C.; Springer, J. P.; Hirschfield, J. M.; Hoogsteen, K.; Williams, M.; Risley, E. A.; Totaro, J. A. *J. Med. Chem.* **1979**, *22*, 1222 and references therein. (n) Share, N. N.; McFarlane, C. S. *Neuropharmacology* **1975**, *14*, 675.
(9) Guthrie, D. A.; Frank, A. W.; Purves, C. B. *Can. J. Chem.* **1955**, *33*, 729.
(10) Waldmann, E.; Chwala, C. *Justus Liebigs Ann. Chem.* **1957**, *609*, 125.
(11) Battersby, A. R.; Yeowell, D. A. *J. Chem. Soc.* **1958**, 1988.
(12) (a) Dyke, S. F.; Ellis, A. C. *Tetrahedron* **1971**, *27*, 3803; *Ibid.* **1972**, *28*, 3999. (b) Dyke, S. F.; Ellis, A. C.; Kinsman, R. G.; White, A. W. C. *Ibid.* **1974**, *30*, 1193. (c) Hoshino, O.; Taga, M.; Umezawa, B. *Heterocycles* **1973**, *1*, 223.
(13) (a) Kametani, T.; Ogasawara, K. *Chem. Pharm. Bull.* **1973**, *21*, 893. (b) Elliott, Jr., I. W. *J. Org. Chem.* **1979**, *44*, 1162.
(14) Goldschmiedt, G. *Monatsch. Chem.* **1886**, *7*, 485; *ibid.* **1898**, *19*, 321.
(15) (a) Pyman, F. L. *J. Chem. Soc.* **1909**, *95*, 1610. (b) Pyman, F. L.; Reynolds, W. C. *Ibid.* **1910**, *97*, 1320.
(16) Battersby, A. R.; Binks, R. *J. Chem. Soc.* **1955**, 2888.
(17) Schöpf, C. *Experientia* **1949**, *5*, 201.
(18) (a) Stermitz, F. R.; Williams, D. K. *J. Org. Chem.* **1973**, *38*, 1761. (b) Coombs, R. M.; Falck, J. R.; Williams, D. K.; Stermitz, F. R. *Ibid.* **1973**, 3701 and earlier papers by this group. (c) Walsh, D. A.; Lyle, R. E. *Tetrahedron Lett.* **1973**, 3849. (d) An alternative to this general synthetic scheme was the conversion of tetrahydroberberine into the pavine alkaloids, dimethylmunitagine: Ito, K.; Furukawa, H.; Iida, T.; Lee, K.-H.; Soine, T. O. *J. Chem. Soc., Chem. Commun.* **1974**, 1037.
(19) Cope, A. C.; Fenton, S. W. *J. Am. Chem. Soc.* **1951**, *73*, 1673.
(20) (a) Winthrop, S. O.; Davis, M. A.; Myers, G. S.; Gavin, J. G.; Thomas, R.; Barker, R. *J. Org. Chem.* **1962**, *27*, 230. (b) Villiani, F. J.; Ellis, C. A.; Teichman, C.; Bigos, C. *J. Med. Pharm. Chem.* **1962**, *5*, 373.



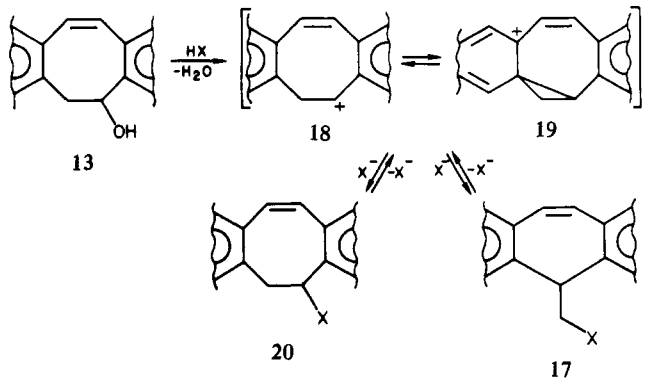
prepared, a large number of which have interesting biological activities.[8] However, there are no synthetic approaches to these compounds in the literature which utilize a ring contraction of a functionalized dibenzocyclooctadiene. Therefore we decided to attempt to prepare derivatives of all three of these groups of compounds by beginning with a double ortho Friedel–Crafts alkylation.

Results and Discussion

Substituted Dibenzocyclooctadienes. Our proposed approach (Scheme I) to these tricyclic aromatic compounds began with the double ortho Friedel–Crafts alkylation of (3,4-dimethoxyphenyl)acetaldehyde (homoveratraldehyde) (**11**). Although we had originally developed trimethylsilyl iodide for the demethylation of aliphatic and aromatic methyl ethers,[21] we reasoned that this dealkylative cleavage would cause no problems in the reaction of **11** with trimethylsilyl iodide for two reasons. First, although catechol dimethyl ethers showed a slight rate enhancement for cleavage when compared to simple anisoles, the dealkylation of aromatic methyl ethers with trimethylsilyl iodide was a relatively slow process (e.g., anisole requires 21 h at 50 °C for demethylation).[21] Secondly, since the rate of the Friedel–Crafts alkylation is very dependent on the electron density of the aromatic ring, the very electron-rich character of **11**, due to the two electron-donating methoxy groups, should cause the Friedel–Crafts reaction to be very rapid. Indeed, this proved to be the case. Addition of trimethylsilyl iodide to a solution of **11** in methylene chloride at −78 °C followed by warming to room temperature and quenching with 1 M aqueous sodium thiosulfate afforded a quantitative yield of the crystalline ether **12**. It should be pointed out that this dibenzylic ether is remarkably stable to acid. It is completely stable both to the trimethylsilyl iodide used for the reaction and to the 2 equiv of hydrogen iodide generated in the double Friedel–Crafts alkylations. This stability is probably due to two factors: the lack of efficient overlap of the carbon–oxygen bond with the π system of the aromatic rings and the fact that backside attack on the protonated ether in an S_N2 reaction is very hindered by the proximate aromatic carbon–hydrogen bond. The ether **12** proved stable to all attempts at opening under acidic conditions, including the following: $BF_3{\cdot}OEt_2$, Ac_2O; $BF_3{\cdot}OEt_2$ then base; $HClO_4$; HOAc, NaOAc; HOAc, H_2SO_4; HCl, $CHCl_3$; CF_3CO_2H, Ac_2O; HCl, EtOH; HN_3, PhH. However, it was clear from inspection of molecular models that one of the vicinal benzylic carbon–hydrogen bonds is almost precisely anti-coplanar to the carbon–oxygen bond of the bridging ether, thereby implying the possibility of an E2 elimination. This was effected by treating the ether **12** with 2 equiv of *n*-butyllithium in dry tetrahydrofuran (THF) for 4 h at 25 °C to produce the dibenzocyclooctatrienol

(21) Jung, M. E.; Lyster, M. A. *J. Org. Chem.* **1977**, *42*, 3761.

Scheme II



13 in 97.5% yield. The use of excess base (e.g., 2 equiv) in this E2 elimination afforded higher yields of the alcohol, presumably due to the destruction of some of the base by deprotonation of the aromatic protons ortho to the methoxy groups. This alcohol **13** was also prepared by a two-step degradation of argemonine (**4**) via argemonine methine methiodide (**14**) by the method of Battersby.[16,22] In order to prove that a simple E2 reaction had occurred and as a model for a possible internal aminomercuration reaction to generate compounds in the pavine series, the alcohol **13** was treated with mercuric acetate in THF followed by basic sodium borohydride to furnish the ether **12**, the product of an internal oxymercuration reaction, in ~60% yield. That the alcohol **13** was indeed secondary and benzylic was confirmed when Jones oxidation produced the ketone **15**, the IR of which exhibited a carbonyl absorption at 1650 cm^{-1}, typical of a dibenzocyclooctatrienone.[23] The ketone **15** was reconverted into the alcohol **13** by sodium borohydride reduction in order to guarantee that no skeletal rearrangement had occurred under the acidic conditions of the Jones oxidation. As a further confirmation of its structure and so that a potentially useful synthetic intermediate could be produced, the alcohol **13** was dehydrated by thermolysis of the corresponding *N*-*p*-tosylcarbamate formed from **13** and *p*-tosyl isocyanate, to furnish the dibenzocyclooctatetraene **16** in >90% yield. This compound had been previously prepared in poor yield by acid-catalyzed dehydration of the alcohol **13**.[16] In contrast to the report of Battersby,[16] we were able to prepare the tetraene **16** directly from argemonine methine methiodide (**14**) by a normal Hoffmann elimination in essentially quantitative yield. The tetraenes prepared by the two different routes were identical.

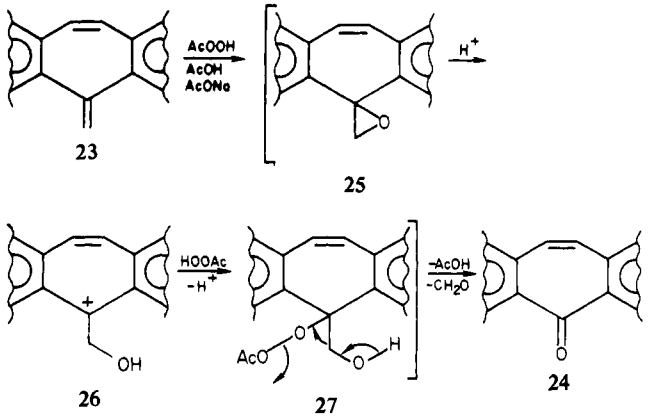
Amitriptyline Analogues. In order to produce intermediates for the preparation of substituted amitriptyline analogues, it was necessary to rearrange the dibenzocyclooctatriene system to a dibenzocycloheptatriene system. This was easily affected by treatment of the alcohol **13** with strong nucleophilic acids (e.g., HCl, HBr, and HI) to give the halides **17a–c** in 91%, 91%, and 97% yield, respectively.[24] This ring contraction presumably occurs by the mechanism shown in Scheme II. Loss of water from the protonated alcohol would give the 8-membered carbonium ion **18** which is in equilibrium with the cyclopropyl carbinyl ion **19** (and all of the numerous resonance contributors possible for this compound). Kinetic trapping of the carbonium ion would probably give the 8-membered product **20**. However, if the group X is a good leaving group, this product **20** could reionize to the mixture of carbonium ions **18** and **19** which could then be converted into the halomethyl 7-membered product **17**. Compound **17** should

(22) Although our material clearly has the structure **13** as shown by both ^{13}C and ^1H NMR, IR, and mass spectroscopy, we could not obtain crystalline material which exhibited the same melting point or solubility characteristics as that reported by Battersby.[16] The reasons for these discrepancies are unknown at this time.

(23) For example, the tetrademethoxy compound dibenzocyclooctatrienone exhibits a carbonyl absorption of 1670 cm^{-1}: Cioranescu, E.; Bucur, A.; Banciu, M.; Nenitzescu, C. D. *Rev. Roum. Chim.* **1965**, *10*, 141.

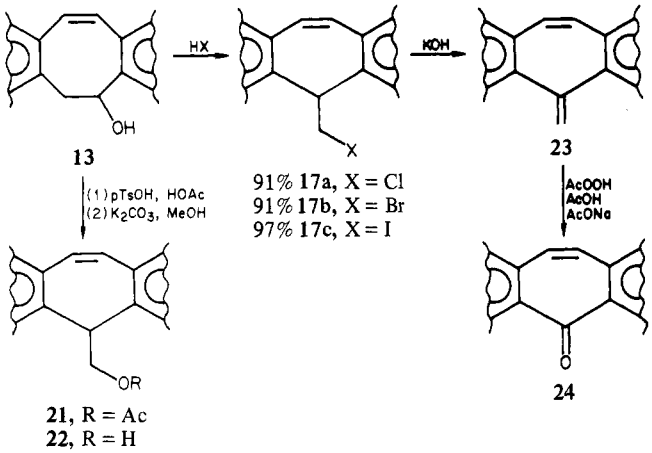
(24) (a) Abdel-Monem, M. M.; Soine, T. O. *J. Pharm. Sci.* **1967**, *56*, 976. (b) Kier, L. B.; Soine, T. O. *Ibid.* **1961**, *50*, 321. (c) Soine, T. O.; Kier, L. B. *Ibid.* **1962**, *51*, 1196. (d) Slavik, J.; Slavikova, L.; Haisova, K. *Collect. Czech. Chem. Comm.* **1967**, *32*, 4420.

Scheme III



be the thermodynamic product since the nonaromatic olefin can achieve a much greater degree of coplanarity and therefore overlap more with the two aromatic rings in the dibenzocycloheptatriene product **17** than in the much more tublike dibenzocyclooctatriene product **20**. As reported later herein, one can obtain just the kinetic 8-membered product **20** by using an acid whose counterion is a good nucleophile but a relatively poor leaving group. There are alternative explanations for this dichotomy of reaction pathways, but this seems the most reasonable one. By using a catalytic amount of *p*-toluenesulfonic acid in acetic acid, one can obtain the rearranged (acetoxymethyl)dibenzocycloheptatriene **21** which was not purified but directly hydrolyzed in base to the alcohol **22**, thus available from **13** in 89% yield.[25]

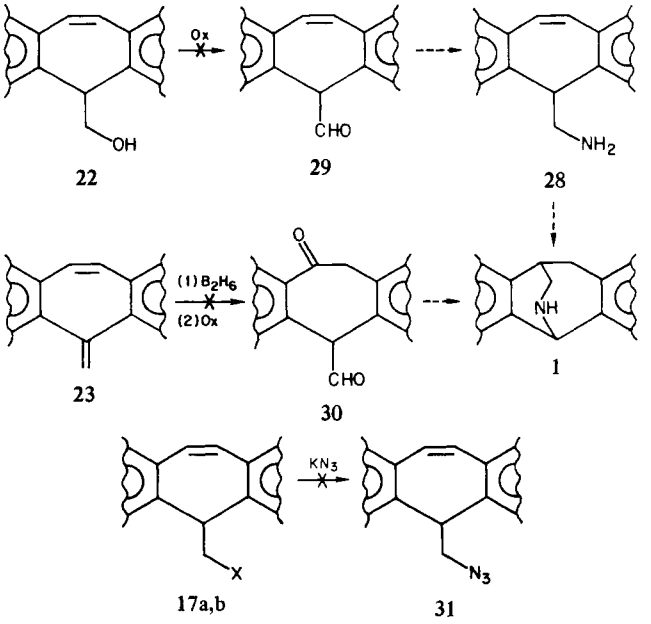
The *exo*-methylenedibenzocycloheptatriene **23** was judged to be an excellent intermediate for the production of amitriptyline analogues. This compound[24a] could be produced in excellent yield from any of the purified halides **17a–c**, but a more convenient



and higher yielding pathway involved the direct production of **23** from the alcohol **13** by way of the chloride **17a** but without isolation of any intermediate. Treatment of the alcohol **13** with ethanolic HCl followed by reaction with 10% ethanolic KOH produced the exo-methylene compound **23** in 95% yield.[26] Since amitriptyline (**5**), cyclobenzaprine (**10**), and their many analogues are all prepared from the dibenzocycloheptadienone **8** and -trienone **9**, all that remained to be accomplished was the conversion of the exo-methylene compound **23** into the cycloheptatrienone **24**. While several methods for this transformation are theoretically possible, we decided to attempt to effect a simple oxidation of the more nucleophilic exocyclic double bond with peracetic acid to produce a diol monoacetate or other similar derivative, which could then be oxidatively cleaved to yield the desired ketone. However, when the exo-methylene compound was treated with peracetic acid, the products were predominantly starting material and the desired ketone **24**. By using an excess of 40% peracetic acid containing sodium acetate, we were able to isolate a 60–65% yield of the desired ketone **24**. Presumably this oxidative cleavage proceeds by the mechanism indicated in Scheme III, namely, an initial epoxidation to give the epoxide **25**. This reactive compound opens to the (hydroxymethyl)dibenzocycloheptatrienyl (dibenzotropylium) cation **26** in acid. Trapping of this cation **26** by the very good nucleophile peracetate would give the hydroxymethyl perester **27**, which by a Baeyer–Villiger type fragmentation would produce the ketone **24**. This process is probably mechanistically similar to the oxidative cleavage of bicyclic enol ethers with peracid to furnish keto lactones reported by Borowitz.[27] This simple production of the dibenzocycloheptatrienone **24** from homoveratraldehyde (**11**) in four steps in 55% overall yield ends our synthetic work on this system. The tetradesmethoxy analogue of **24**, dibenzotropone (**9**), has been transformed (catalytic hydrogenation and subsequent oxidation) into the dibenzocycloheptadienone **8**,[28] which has been converted into amitriptyline (**5**) and its many analogues.[8] Therefore the conversion of the ketone **24** into substituted amitriptyline analogues should be quite straightforward.

Isopavine. As described above, our work on the synthesis of substituted amitriptyline analogues had provided easy access to several functionalized methyltetramethoxydibenzocycloheptatrienes. We initially attempted to use these readily available compounds for the preparation of the structurally quite similar isopavine alkaloids, e.g., isopavine (**1**) itself.

One route to **1** centered about the aminomethyl compound **28**, which we planned to convert to isopavine by an internal aminomercuration–demercuration route. We hoped to prepare this amine **28** by a reductive amination[29] of the aldehyde **29**, seemingly easily accessible from the alcohol **22** which was in hand. However, several attempts (e.g., PCC, Sarett, and Moffatt oxidation) at the simple oxidation of **22** to the desired aldehyde **29** failed completely for undetermined reasons. The double hydroboration–oxidation of the exo-methylene compound **23** to give the keto aldehyde **30** (a potential precursor of **1** via a double reductive amination process) also gave unsatisfactory results. Consequently these approaches were abandoned.



(25) Cioranescu, E.; Bucur, A.; Elian, M.; Nenitzescu, C. D. *Rev. Roum. Chim.* **1965**, *10*, 149.

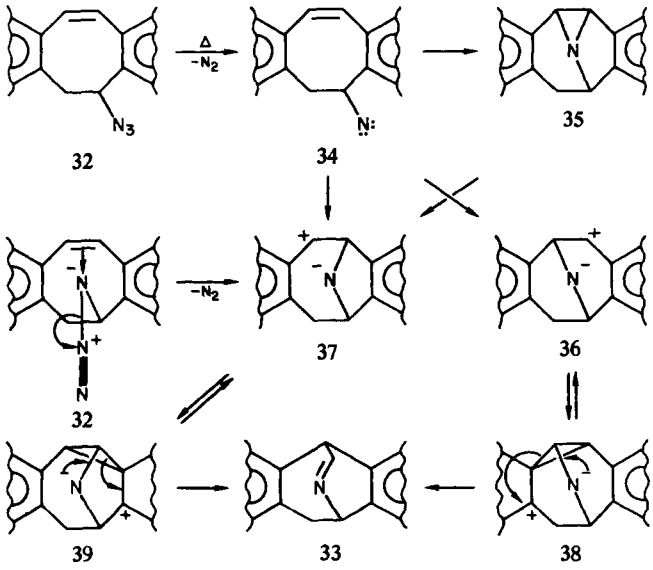
(26) We assume that the report of Slavik et al.[24d] that the iodomethyl compound in the eschscholtzine series (bis(methylenedioxy) analogue of **17c**) afforded the hydroxymethyl compound (bis(methylenedioxy) analogue of **22**) on treatment with boiling methanolic KOH is incorrect. These conditions would presumably yield the *exo*-methylene compound (analogous to **23**).

(27) Borowitz, I. J.; Williams, G. J.; Gross, L.; Rapp, R. *J. Org. Chem.* **1968**, *33*, 2013.

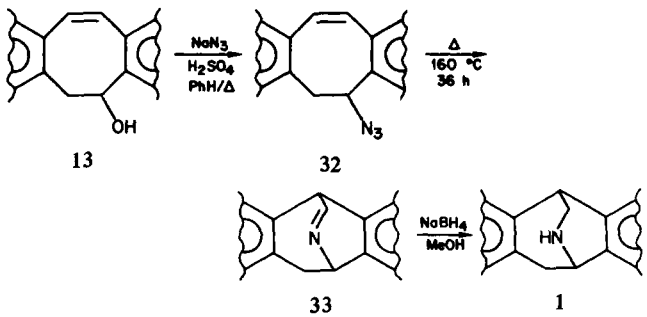
(28) Horning, D. E.; Muchowski, J. M. *Can. J. Chem.* **1968**, *46*, 3665.

(29) Borch, R. F.; Bernstein, M. D.; Durst, H. D. *J. Am. Chem. Soc.* **1971**, *93*, 2897.

Scheme IV

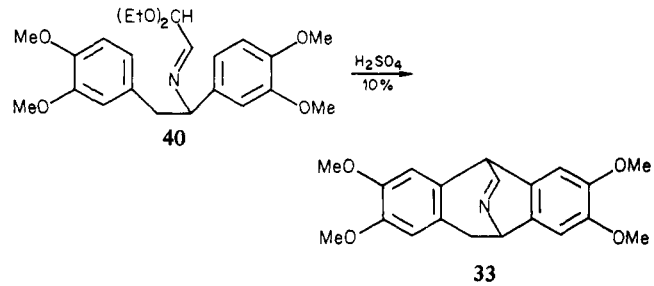


It seemed likely that if the azidomethyl compound **31** could be prepared, any of several reductive methods could convert it to the desired amine **28**. Since the (halomethyl)dibenzocycloheptatrienes **17a–c** were very readily available, the simple substitution of azide for halide was attempted. Under the usual conditions (KN_3, 18-crown-6 ether, CH_3CN, reflux, 24 h), the chloride **17a** gave only recovered starting material, while the more reactive bromide afforded the exo-methylene compound **23** in 90% yield under very similar conditions. Presumably, S_N2 reactions of these primary halides are very slow due to significant steric hindrance of backside attack by the rest of the molecule, especially, the proximate aromatic carbon–hydrogen bonds.



At this point an easy route to isopavine unexpectedly presented itself. When the cyclooctatrienol **13** was treated with hydrazoic acid in benzene, instead of the expected (azidomethyl)cycloheptatriene (**31**), the unrearranged azidocyclooctatriene **32** was obtained in 88% crude yield. As mentioned earlier and shown in Scheme II, the 8-membered product, e.g., **32**, is presumably the kinetic product of trapping of the cyclooctatrienyl cation **18**, whereas the 7-membered product is presumably the thermodynamic product. When the nucleophile is also a good leaving group, e.g., X = Cl, Br, I, etc., only the 7-membered product is obtained, while for a nucleophile that is a poorer leaving group, e.g., X = N_3, only the 8-membered product is obtained. Since our attempts at recrystallization caused decomposition of this azide, it was purified by column chromatography and used as soon as possible after purification. Thermolysis of the purified azide **32**, or better, preparation of the crude azide **32** from the alcohol **13** followed by direct thermolysis (mesitylene, 160 °C, 36 h) afforded the rearranged imine **33** in 63% yield based on the amount of alcohol **13**. This imine **33**, dehydroisopavine, is presumably formed by the mechanism shown in Scheme IV. Thermal loss of nitrogen from the azide would produce the nitrene **34** which may insert into the double bond to give the aziridine **35**. Examination of molecular models indicates that this aziridine is very strained and would very likely not be stable at 160 °C; therefore, if it is ever formed it would probably open very rapidly to the two possible zwitterions **36** and **37**. It is more likely that these zwitterions **36** and **37** are formed either directly from the azide by a concerted attack of the olefin on the azide with concomitant loss of nitrogen or from the nitrene. The zwitterion **36**, having the bicyclo[3.3.1] system, would appear to be more stable than the alternative one **37**, which has the bicyclo[4.2.1] system.[30] However, at 160 °C, it is likely that both are produced. The zwitterions are in equilibrium with the cyclopropyl carbinyl cations, **38** and **39**, respectively, in which the π system of the nonadjacent aromatic ring donates its electron density to stabilize the positive charge. Both of these cyclopropyl carbinyl cations are perfectly set up for an internal cancellation of charge by donation of the negative charge on nitrogen to form an imine with concurrent cleavage of the opposite cyclopropane bond to regenerate the aromaticity of the aromatic ring. From either zwitterion **38** or **39**, this process generates the same product, namely, dehydroisopavine (**33**). This rearrangement process is remarkably similar in all its pertinent features to the rearrangement of the alcohol **13** into the halomethyl compounds **17** (Scheme II).

It is interesting that dehydroisopavine (**33**) had probably been prepared earlier although its structure had not been assigned. Schlittler and Müller[31] isolated a compound in 10% yield by treatment of the imine **40** with 75% H_2SO_4. Since the melting



points of their material and our dehydroisopavine (**33**) match, we assume that they are the same compound. The synthesis of isopavine was completed by reduction with methanolic sodium borohydride to produce isopavine (**1**) in 92% yield. Our synthetic isopavine exhibited spectral properties (NMR, IR, mass spectroscopy) in accord with its structure. More importantly the melting point of both isopavine and the corresponding acetamide derivative matched those in the literature.[9,11] Thus isopavine (**1**) has been synthesized from homoveratraldehyde (**11**) in four steps in over 53% overall yield. The application of this scheme to the synthesis of other isopavine alkaloids should be straightforward.

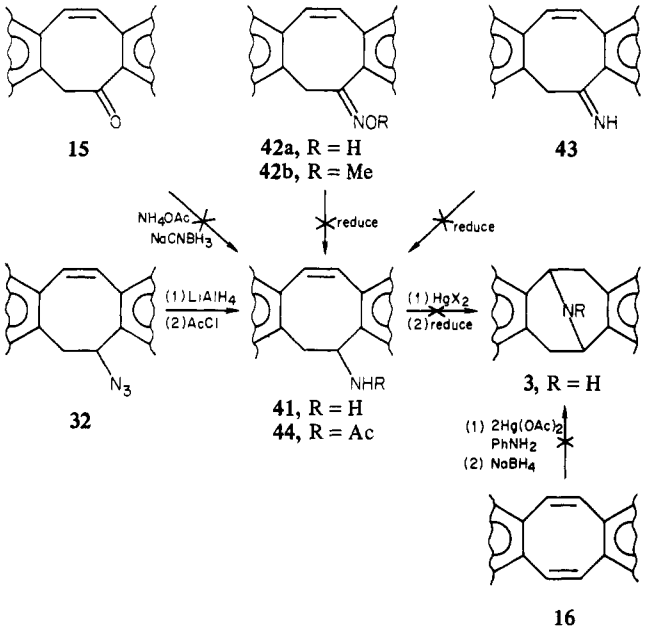
Approach to Pavines. We have also made several attempts to prepare pavine derivatives by this general approach, but thus far all have been unsuccessful. Our initial approach centered about the internal aminomercuration reaction of the aminodibenzocyclooctatriene **41**. It appeared that a simple and well-precedented route to this amine would be the reductive amination of the ketone **15**. However under all attempts—e.g., $HCONH_2$, HCO_2H; and NH_4OAc, $NaCNBH_3$ under various conditions—we were unable to prepare the amine in good yield, mainly obtaining recovered starting ketone. Evidently, the imine or iminium salt is very slow to form, presumably due to the steric hindrance of attack on the tublike ketone. Nor were we able to produce a good yield of the desired amine by hydride reduction of the corresponding oxime **42a** or the methoxime **42b**, each produced from the ketone **15** in 80% and 99% yield, respectively, or the corresponding imine **43**, produced from the oxime **42a** in good to excellent yield. Again an entire array of hydride reducing agents were used for each of these proposed transformations—$NaCNBH_3$, $NaBH_4$, $LiAlH_4$, $NaBH_3OCOCF_3$, DIBAL, AlH_3, B_2H_6, $HSiCl_3$, Na/EtOH, Zn, $SnCl_2$/HCl—all without the desired effect. It is known that

(30) For example, the double aminomercuration of 1,4-cyclooctadiene with aniline and mercuric acetate gave only the [3.3.1] system with none of the [4.2.1] system being produced: Aranda, V. G.; Mur, J. B.; Asensio, G.; Yus, M. *Tetrahedron Lett.* **1972**, 3621.

(31) Schlittler, E.; Müller, J. *Helv. Chim. Acta* **1948**, *31*, 914.

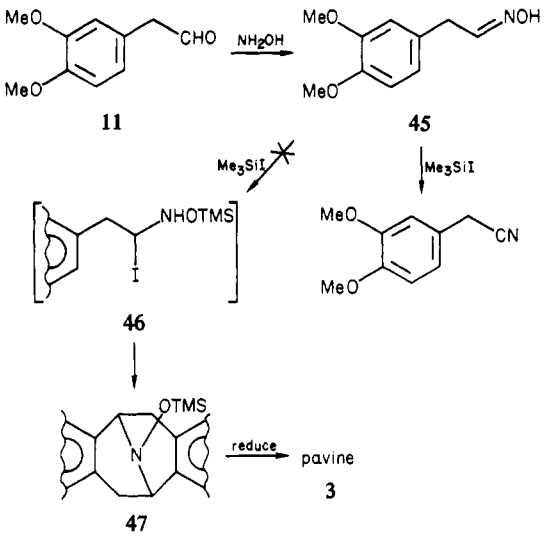
hydride reduction of analogous less-substituted oximes also gives poor yields of the corresponding amines.[32] We also tried unsuccessfully to catalytically hydrogenate the oxime **42a** to the corresponding amine **41**; under all conditions tried, either only starting material was obtained or the olefinic double bond was reduced in preference to the oxime.

The conversion of the alcohol **13** into the 8-membered azide **32** provided an easy route to **41**. Hydride reduction of **32** gave the amine **41** in 94% yield. With this key compound in hand, we attempted the ultimate conversion of **41** into pavine **3** by an internal aminomercuration–demercuration. However, treatment of the amine **41** with several different mercuric salts [$Hg(OAc)_2$, $Hg(NO_3)_2$, $HgCl_2$] followed by reduction (basic $NaBH_4$ or Na_2S) under several sets of conditions completely failed to produce any amounts of pavine **3** or the other possible aminomercuration products. Similar results were obtained by treatment of the corresponding acetamide **44** (formed by acetylation of **41**) with



mercuric acetate or nitrate followed by reduction. All that appears to occur is the slow formation and precipitation of the amine–mercuric salt complex[33] with no involvement of the olefinic double bond. We have no compelling explanation for this difference in behavior between the alcohol **13** and the amine **41** or amide **44** vs. the internal heteromercuration process. Another similar route was also investigated. The tetraene **16** was treated with 2 equiv of mercuric acetate in the presence of aniline followed by excess basic sodium borohydride in an unsuccessful attempt to effect a double aminomercuration reaction.[30] Only starting material was recovered.

An earlier, very simple approach was also investigated. Homoveratraldehyde (**11**) was converted into the aldoxime **45**[34] which was then treated with trimethylsilyl iodide. It was hoped that the oxime would add the silyl iodide to produce the α-iodo hydroxylamine silyl ether **46**[35] and that this compound would then undergo the analogous dimerizative double ortho Friedel–Crafts alkylation to produce the *N*-(trimethylsilyloxy)pavine **47**. However, the only product isolated from **45** upon treatment with

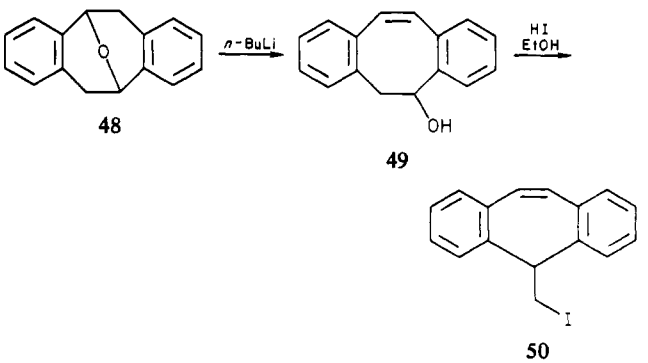


trimethylsilyl iodide was the corresponding nitrile. No evidence for any nitrogen-bridged products such as **47** was obtained. Other approaches of this sort (e.g., via the corresponding imine or imide) also were unsuccessful.

When the routes described above and several other attempts at the synthesis of pavine from the ether **12** failed, we decided to abandon this part of the project.

Conclusion

We have accomplished a direct and high yielding synthesis of functionalized dibenzocyclooctadienes and have developed a route from these compounds to the dibenzocycloheptadiene and -triene systems found in the isopavine alkaloids and in the active medicinal agents such as amitriptyline and cyclobenzaprine. The approaches we have developed should be general enough to permit the production of many derivatives of these compounds. As a test of this generality, we have converted the parent system **48** (formed in



55% yield from phenylacetaldehyde)[3] into the dibenzocyclooctatriene **49**[23] and thence into the (iodomethyl)dibenzocycloheptatriene **50**. The process described above should be quite useful for the synthesis of many compounds of these structural classes.

Experimental Section

General Procedures. Melting points were taken on an Electrothermal melting point apparatus and are uncorrected. Infrared spectra (IR) were recorded on a Perkin-Elmer Model 137B or 710B spectrophotometer in chloroform solution. Proton NMR spectra were measured on a Bruker WP-200 spectrometer in deuterochloroform as solvent and are reported in parts per million downfield from internal tetramethylsilane. Carbon NMR spectra were measured on a Varian CFT-20 spectrometer. Mass spectra were recorded on an AEI MS-9 spectrometer. Ultraviolet spectra were recorded on a Beckman 25 spectrometer; all spectra were run in 95% ethanol solution. For column chromatography, Merck silica gel 60 (70–230 mesh) was used as adsorbent. For preparative layer chromatography, Merck silica gel 60 PF-254 was used. Analyses were performed by Spang Microanalytical Laboratory, Ann Arbor, MI.

2′,3′,2″,3″-Tetramethoxy-2,3:6,7-dibenzo-9-oxabicyclo[3.3.1]nona-2,6-diene (12). To a solution of (3,4-dimethoxyphenyl)acetaldehyde (homoveratraldehyde) (**11**) (3 g, 16.7 mmol) in dry methylene chloride

(32) Cioranescu, E.; Bucur, A.; Banciu, M.; Badea, F.; Elian, M.; Nenitzescu, C. D. *Rev. Roum. Chim.* **1971**, *16*, 1555.

(33) In one case (treatment of **41** with $HgCl_2$), NMR analysis of this precipitate indicates the presence of olefinic absorptions, thus implying that no cyclization had occurred.

(34) Kaufmann, E.; Eliel, E.; Rosenkranz, J. *Ciencia (Mexico City)* **1946**, *7*, 136.

(35) Ojima has successfully added trimethylsilyl cyanide to oximes to produce the α-cyano hydroxylamine trimethylsilyl ethers: Ojima, I.; Inaba, S.-I.; Nakatsugawa, K. *Chem. Lett.* **1975**, 331. We hoped to produce the analogous iodo compound by using trimethylsilyl iodide.

(100 mL) at −78 °C under nitrogen was added slowly with vigorous stirring trimethylsilyl iodide[2] (2.25 mL, 17 mmol). The solution was stirred at −78 °C for 2 h and allowed to warm slowly to room temperature. The reaction was quenched promptly upon reaching room temperature by addition of 100 mL of 1 M aqueous $Na_2S_2O_3$. After the color of iodine had been discharged, the reaction mixture was extracted with 2 × 100 mL of $CHCl_3$ and the combined organic extracts washed with 100 mL of saturated aqueous $NaHCO_3$. The organic phase was dried over Na_2SO_4 and evaporated to give crude ether **12** (3 g, ~100%).

The ether could be purified by recrystallization from MeOH to give the pure ether **12**: mp 163–4 °C; NMR δ 6.58 (2 H, s), 6.49 (2 H, s), 5.21 (2 H, d, J = 5.4 Hz), 3.86 (6 H, s), 3.80 (6 H, s), 3.47 (2 H, dd, J = 15.6, 5.4 Hz), 2.67 (2 H, d, J = 15.6 Hz); IR 1500, 1240, 1110, 1015, 850 cm^{-1}; mass spectroscopy (m/e) 342 (M^+), 328, 327, 314, 313, 311, 299, 283, 190, 152, 151. Anal. Calcd for $C_{20}H_{22}O_5$: C, 70.16; H, 6.48. Found: C, 70.34; H, 6.70. This reaction was also carried out on a large scale. Beginning with 45.3 g of homoveratraldehyde, one isolated 36.7 g of the pure ether **12** after recrystallization from methanol (85.2%).

3-Hydroxy-2′,3′,2″,3″-tetramethoxy-1,2:5,6-dibenzocycloocta-1,5,7-triene (13). To a solution of the ether **12** (10 g, 29.2 mmol) in dry THF (300 mL) at room temperature under nitrogen was added slowly *n*-butyllithium (24.6 mL, 2.44 M, 60 mmol). The reaction mixture was stirred at room temperature under nitrogen for 4 h. The reaction was quenched by careful addition of water and extracted with 2 × 200 mL $CHCl_3$. The combined organic phases were washed with 150 mL of brine, dried over Na_2SO_4, and evaporated to give 9.8 g crude alcohol. This was purified by column chromatography on silica gel, eluting first with $CHCl_3$ to remove impurities and followed by EtOAc to give 9.75 g (28.5 mmol, 97.5%) of pure alcohol **13** as a glass: mp ≃ 90–110 °C (lit.[16] mp 145–146 °C[22]); ^1H NMR δ 7.00 (1 H, s), 6.76 (1 H, s), 6.71 (1 H, s), 6.70 (1 H, s), 6.62 (1 H, s), 6.59 (1 H, s), 5.20 (1 H, m), 3.88 (6 H, s), 3.84 (3 H, s), 3.81 (3 H, s), 3.3 (2 H, m); ^{13}C NMR δ 148.1 (2 C, s), 147.4 (s), 147.0 (s), 133.9 (s), 130.3 (2 C, d), 129.0 (2 C, s), 126.9 (s), 112.7 (d), 112.2 (d), 111.8 (d), 111.6 (d), 73.8 (d), 55.6 (4 C, q), 42.3 (t); IR 3500, 1600, 1500, 1240 cm^{-1}; mass spectroscopy (m/e) 342 (M^+), 324 ($M - H_2O$), 311, 309, 293; UV λ_{max} 290 (log ε = 4.0), 220 (4.48), λ_{min} 266 (3.88) [lit.[16] λ_{max} 292.5 (4.06), λ_{min} 267 (3.94), lit.[24a] λ_{max} 292 (4.05), 220 (4.49), λ_{min} 267.5 (3.97)].

Formation of 12 from 13 by Internal Oxymercuration. The alcohol **13** (200 mg, 0.59 mmol) was dissolved in THF (15 mL), and mercuric acetate (187 mg, 0.59 mmol) was added. The mixture was stirred at reflux under nitrogen for 4 h. After the mixture was cooled to room temperature, 1 mL of 10% aqueous NaOH was added, followed by 50 mg of sodium borohydride in 2 mL of 10% aqueous NaOH. Stirring was continued for 30 min at room temperature. The mixture was diluted with 20 mL of water and extracted with 2 × 30 mL $CHCl_3$. The combined organic extracts were dried over Na_2SO_4 and evaporated to leave 216.5 mg of crude product, the NMR of which indicated the presence of the ether **12**.

Column chromatography of the crude product on silica gel and eluting with $CHCl_3$ gave a fraction containing 135 mg, which was shown by NMR to be very predominantly the ether **12**. No attempts were made to purify the ether further or to optimize the reaction conditions.

2′,3′,2″,3″-Tetramethoxy-1,2:5,6-dibenzocycloocta-1,5,7-trien-3-one (15). To a solution of the alcohol **13** (1 g, 2.92 mmol) in acetone (50 mL) at 0 °C was added slowly Jones reagent (1 mL, 3 mmol). Stirring was continued at 0 °C for 20 min after the addition was complete and excess reagent consumed by addition of isopropyl alcohol. The mixture was diluted with 50 mL of water and extracted with 2 × 100 mL $CHCl_3$. The combined organic phases were washed with 50 mL of saturated aqueous $NaHCO_3$, dried over Na_2SO_4, and evaporated to give 847.6 mg crude ketone **15** (2.49 mmol; 85.4%).

The ketone could be recrystallized from MeOH to give pure ketone **15**: mp 176–178 °C; NMR δ 7.87 (1 H, s), 6.96 (1 H, s), 6.94 (1 H, s), 6.88 (1 H, s), 6.82 (1 H, s), 6.72 (1 H, s), 3.96 (3 H, s), 3.94 (3 H, s), 3.91 (3 H, s), 3.88 (2 H, s), 3.84 (3 H, s); IR 1650, 1600, 1500, 1360, 1250, 1090 cm^{-1}; mass spectroscopy (m/e): 340 (M^+), 325, 309, 298, 281, 170, 165, 136; UV λ_{max} 259 (log ε = 4.54), inflection at 298. Anal. Calcd for $C_{20}H_{20}O_5$: C, 70.58; H, 5.92. Found: C, 70.82; H, 6.25.

Formation of 13 from 15 by Reduction. A solution of sodium borohydride (11 mg, 0.294 mmol) in 10 mL of ethanol was added to a solution of the ketone **15** (100 mg, 0.295 mmol) in 10 mL of ethanol and stirred at room temperature under nitrogen for 2 h. The mixture was diluted with 10 mL of 10% aqueous NaOH and stirred at room temperature for 1 h. Extraction with $CHCl_3$ gave a crude yield of 104.2 mg of alcohol **13** identical by NMR with that obtained earlier.

2′,3′,2″,3″-Tetramethoxy-1,2:5,6-dibenzocyclooctatetraene (16). To a solution of the alcohol **13** (100 mg, 0.292 mmol) in dry diglyme (5 mL) was added *p*-tosyl isocyanate (69 mg, 0.35 mmol). After 1 h of stirring at room temperature under nitrogen, the mixture was stirred at reflux for 16 h, followed by evaporation of the solvent. Column chromatography of the residue on silica gel eluting with $CHCl_3$ gave 98.4 mg of semipure tetraene **16**. NMR showed three singlets identical with those of tetraene **16** obtained by degradation, but the material was still orange and showed some contamination in the NMR. No further attempts were made to purify the product.

Preparation of 13 and 16 from Argemonine 4 via Argemonine Methine Methiodide (14). Argemonine methine methiodide (**14**) was prepared from argemonine **4** by using the method of Battersby.[16]

Tetraene 16. The methiodide **14** (477.2 mg, 0.93 mmol) was suspended in 30 mL of water and stirred with Ag_2O (174 mg, 0.75 mmol) at room temperature for 2 h; after which it was filtered, and the filtrate was washed with 5 mL of water. Potassium hydroxide (35 g) was added, and the mixture was heated at reflux for 5 h. After being cooled to room temperature, the mixture was diluted with 30 mL of water and extracted with 150 mL of $CHCl_3$. The organic phase was dried over Na_2SO_4 and evaporated to give 2′,3′,2″,3″-tetramethoxy-1,2:5,6-dibenzocyclooctatetraene (**16**) (306.6 mg, 0.95 mmol, 100%). This could be recrystallized from benzene to give pure tetraene **16**: mp 184–185 °C (lit. 159–164 °C[16]); NMR δ 6.63 (4 H, s), 6.54 (4 H, s), 3.84 (12 H, s); IR 1600, 1500, 1460, 1350, 1245, 1075, 870 cm^{-1}; mass spectroscopy (m/e) 324 (M^+), 309, 293.

Alcohol 13. The methiodide **14** (203.3 mg, 0.4 mmol) was suspended in 18 mL of water and stirred with silver oxide (51 mg, 0.22 mmol) at room temperature for 2 h; after which it was filtered and stirred at reflux for 12 h. After being cooled to room temperature, this was diluted with 15 mL of water and extracted with 50 mL of $CHCl_3$. The organic layer was dried over Na_2SO_4 and evaporated to give the alcohol **13** (153.9 mg, ~100%) identical in every respect with that obtained synthetically.

3-(Chloromethyl)-2′,3′,2″,3″-tetramethoxy-1,2:4,5-dibenzocyclohepta-1,4,6-triene (17a). A solution of the alcohol **13** (1 g, 2.92 mmol) in EtOH (40 mL) and concentrated HCl (20 mL) was stirred at reflux under nitrogen for 2 h. After the mixture was cooled to room temperature, it was diluted with 50 mL of water and extracted with 100 mL of $CHCl_3$. The organic phase was washed with 50 mL of saturated aqueous $NaHCO_3$, dried over Na_2SO_4, and evaporated to give the chloride **17a** (951.1 mg, 90.74%). This could be recrystallized from glacial acetic acid to give pure chloride **17a**: mp 220–222 °C (lit. 219–220 °C[24a]); NMR δ 6.82 (4 H, s), 6.78 (2 H, s), 4.14 (1 H, t, J = 8 Hz), 3.95 (6 H, s), 3.89 (6 H, s), 3.74 (2 H, d, J = 8 Hz); IR 1600, 1500, 1460, 1350, 1260, 1095, 870 cm^{-1}; mass spectroscopy (m/e): 360 (M^+), 311 ($M - CH_2Cl$).

3-(Bromomethyl)-2′,3′,2″,3″-tetramethoxy-1,2:4,5-dibenzocyclohepta-1,4,6-triene (17b). Treatment of the alcohol **13** (100 mg, 0.292 mmol) with concentrated HBr (5 mL) in EtOH (10 mL) under the same conditions as for the chloride gave the bromide **17b** (107.5 mg, 90.9%). This could be recrystallized from MeOH to give pure bromide **17b**: mp 206–208 °C dec; NMR δ 6.82 (2 H, s), 6.80 (2 H, s), 6.76 (2 H, s), 4.15 (1 H, t, J = 8.3 Hz), 3.95 (6 H, s), 3.88 (6 H, s), 3.63 (2 H, d, J = 8.3 Hz); IR 1600, 1500, 1460, 1350, 1260, 1095, 870 cm^{-1}; mass spectroscopy (m/e) 406, 404 (M^+), 311 ($M - CH_2Br$).

3-(Iodomethyl)-2′,3′,2″,3″-tetramethoxy-1,2:4,5-dibenzocyclohepta-1,4,6-triene (17c). Treatment of the alcohol **13** (1 g, 2.92 mmol) with concentrated HI (10 mL) in EtOH (20 mL) under the above conditions gave the iodide **17c** (1.28 g, 97%). This could be recrystallized from EtOH to give pure iodide **17c**: mp 188–190 °C dec; NMR δ 6.83 (2 H, s), 6.77 (4 H, s), 4.13 (1 H, t, J = 7.8 Hz), 3.95 (6 H, s), 3.89 (6 H, s), 3.49 (2 H, d, J = 7.8 Hz); IR 1600, 1500, 1470, 1360, 1260, 1095, 870 cm^{-1}; mass spectroscopy (m/e): 452 (M^+), 311 ($M - CH_2I$).

3-(Acetoxymethyl)-2′,3′,2″,3″-tetramethoxy-1,2:4,5-dibenzocyclohepta-1,4,6-triene (21). To a solution of the alcohol **13** (500 mg, 1.46 mmol) in glacial acetic acid (10 mL) was added *p*-toluenesulfonic acid (5 mg), and the mixture was stirred at reflux under nitrogen for 14 h. It was allowed to cool to room temperature and then was poured into 50 mL of saturated aqueous Na_2CO_3 solution. The aqueous layer was extracted with 3 × 30 mL $CHCl_3$; the organic layer was then dried and evaporated. The dark brown residue was filtered through a short column of silica gel eluting with $CHCl_3$. The crude acetate **21** thus obtained could be recrystallized from EtOH to give the pure acetate **21**: mp 158.5–160 °C; NMR δ 6.81 (2 H, s), 6.78 (2 H, s), 6.76 (2 H, s), 4.26 (3 H, m), 3.93 (6 H, s), 3.88 (6 H, s), 1.87 (3 H, s); IR 1740, 1610, 1520, 1470, 1360, 1265, 1100, 870 cm^{-1}; mass spectroscopy (m/e): 384 (M^+), 311 ($M^+ - CH_2OAc$).

3-(Hydroxymethyl)-2′,3′,2″,3″-tetramethoxy-1,2:4,5-dibenzocyclohepta-1,4,6-triene (22). The crude acetate **21** was taken up in MeOH (25 mL), and K_2CO_3 (100 mg) was added. The mixture was stirred at room temperature for 1 h, diluted with 50 mL of water, and extracted with 3 × 40 mL of $CHCl_3$. The combined organic phases were dried and evaporated to give 443 mg (1.295 mmol, 88.7%) of crude alcohol **22**, containing some of the cyclooctatetraene **16** as the major impurity. This could be recrystallized from EtOH to give the pure alcohol **22**: mp

188–189 °C; NMR δ 6.83 (2 H, s), 6.81 (2 H, s), 6.71 (2 H, s), 4.03 (1 H, t, J = 8.5 Hz), 3.94 (6 H, s), 3.88 (6 H, s), 3.79 (2 H, dd, J = 8.5, 6.5 Hz), 1.04 (1 H, t, J = 6.5 Hz); IR 3550 (w), 1610, 1520, 1470, 1360, 1265, 1100, 870 cm^{-1}; mass spectroscopy (m/e) 342 (M^+), 311 ($M^+ - CH_2OH$); high resolution mass spectroscopy (m/e) 342.1445, calcd for $C_{20}H_{22}O_5$ 342.1467; 311.1289, calcd for $C_{19}H_{19}O_4$ 311.1283.

3-Methylene-2′,3′,2″,3″-tetramethoxy-1,2:4,5-dibenzocyclohepta-1,4,6-triene (23). To a solution of the alcohol **13** (500 mg, 1.46 mmol) in EtOH (20 mL) was added concentrated HCl (10 mL), and the mixture was stirred at reflux for 2 h. The mixture was allowed to cool to room temperature and was diluted with 50 mL of water and extracted with 3 × 60 mL of $CHCl_3$. The combined organic extracts were washed with 25 mL of saturated aqueous $NaHCO_3$, dried, and evaporated. To the crude residue was added 10% ethanolic KOH (50 mL). The mixture was stirred at reflux for 4 h and then allowed to cool to room temperature. The mixture was diluted with 60 mL of water and extracted with 3 × 60 mL of $CHCl_3$. The combined extracts were dried and evaporated to leave 450.8 g (1.39 mmol, 95.3%) the crude alkene **23**. This could be recrystallized from EtOH to give the pure alkene **23**: mp 230–231 °C (lit.[24a] mp 234–236 °C); NMR δ 6.93 (2 H, s), 6.75 (2 H, s), 6.68 (2 H, s), 5.23 (2 H, s), 3.96 (6 H, s), 3.90 (6 H, s); IR 1600, 1505, 1460, 1385, 1340, 1260, 1240, 1075, 870 cm^{-1}; mass spectroscopy (m/e) 324 (M^+), 311, 309, 293; UV λ_{max} 322 (log ε = 4.04), 246 (4.66), λ_{min} 290 (3.82).

2′,3′,2″,3″-Tetramethoxy-1,2:4,5-dibenzocyclohepta-1,4,6-trien-3-one (24). To a solution of the alkene **23** (100 mg, 0.309 mmol) in methylene chloride (10 mL) was added sodium acetate (25 mg) and commercially available 40% peracetic acid in acetic acid (0.37 mL), and the mixture was stirred under nitrogen at room temperature for 48 h. The mixture was diluted with 30 mL of $CHCl_3$, washed with 15 mL of water and 15 mL of saturated aqueous $NaHCO_3$, dried over Na_2SO_4 and evaporated to give 117.1 mg of crude ketone **24**. Sublimation at 165 °C (0.02 torr) gave 69 mg of pale yellow ketone **24** still showing a slight impurity in the NMR spectra.

Recrystallization of the sublimed ketone from MeOH gave the pure ketone **24**: mp 220–221 °C; NMR δ 8.06 (2 H, s), 7.00 (2 H, s), 6.99 (2 H, s), 4.06 (6 H, s), 4.03 (6 H, s); IR 1601 (sh), 1580, 1520, 1470, 1400, 1280, 1080 cm^{-1}; mass spectroscopy (m/e) 326 (M^+) 311, 255, 240; UV λ_{max} 290 (log ε = 4.79), 242 (4.25), λ_{min} 257 (4.11). Anal. Calcd for $C_{19}H_{18}O_5$: C, 69.93; H, 5.56. Found: C, 69.83; H, 5.38.

3-Azido-2′,3′,2″,3″-tetramethoxy-1,2:5,6-dibenzocycloocta-1,5,7-triene (32). A solution of hydrazoic acid in benzene was prepared by adding benzene (36 mL) to a paste of NaN_3 (3.9 g, 60 mmol) in warm water (3.6 mL) and cooling to 0 °C. Concentrated sulfuric acid (1.64 mL, 30 mmol) was added slowly to the vigorously stirred mixture which was cooled in an ice bath. After the addition was complete, the mixture was stirred at 0 °C for 10 min. The benzene solution of hydrazoic acid was then decanted into a round-bottom flask charged with the alcohol **13** (1 g, 2.92 mmol) and stirred at reflux under nitrogen for 1 h. After it was cooled to room temperature, the mixture was diluted with 50 mL of saturated aqueous $NaHCO_3$ and extracted with 2 × 100 mL of $CHCl_3$. The combined organic phases were dried over Na_2SO_4 and evaporated to give the crude azide **32** (943.1 g, 88%). This could be purified by column chromatography on silica gel, eluting with $CHCl_3$, to give the pure azide **32**: mp 58 °C dec; NMR δ 6.78 and 6.68 (2 H, AB quartet, J = 12.2 Hz), 6.76 (1 H, s), 6.73 (1 H, s), 6.61 (2 H, s), 4.85 (1 H, dd, J = 12.2, 6.3 Hz), 3.87 (6 H, s), 3.84 (3 H, s), 3.80 (3 H, s), 3.43 (1 H, d, J = 12.2 Hz), 3.18 (1 H, dd, J = 12.2, 6.3 Hz); IR 2100, 1610, 1515, 1470, 1250, 870 cm^{-1}; mass spectroscopy (m/e) 367 (M^+), 339, 324, 312.

2′,3′,2″,3″-Tetramethoxy-2,3:8,9-dibenzo-6-aza-bicyclo[3.2.2]nona-2,6,8-triene (Dehydroisopavine) (33). The azide **32** was prepared in the usual manner from 100 mg (0.292 mmol) of the alcohol **13** by treatment with hydrazoic acid in benzene. The crude azide obtained upon workup was taken up directly in mesitylene (10 mL) and stirred at 160 °C under nitrogen for 36 h. After this period, the mixture was allowed to cool to room temperature, diluted with 10 mL of $CHCl_3$, and extracted with 2 × 20 mL of dilute HCl. The aqueous layer was washed with 10 mL of $CHCl_3$ and the pH adjusted to >12 with NaOH. This was extracted with 3 × 15 mL of $CHCl_3$, dried, and evaporated to leave 62.4 mg (0.184 mmol, 63.04%) of crude imine **33**. The imine could be recrystallized from benzene/petroleum ether to give pure imine **33**: mp 218–220 °C (lit.[31] mp 222–223 °C); ^1H NMR δ 8.55 (1 H, d, J = 3.9 Hz), 6.89 (1 H, s), 6.76 (1 H, s), 6.70 (1 H, s), 6.43 (1 H, s), 5.23 (1 H, t, J = 3.4 Hz), 4.35 (1 H, d, J = 3.9 Hz), 3.90 (3 H, s), 3.88 (3 H, s), 3.87 (3 H, s), 3.76 (3 H, s), 3.25 (1 H, dd, J = 17.4, 3.4 Hz), 3.0 (1 H, dd, J = 17.4, 3.4 Hz); ^{13}C NMR δ 158 (d), 138.6 (s), 138.4 (s), 138 (s), 137.1 (s), 119.9 (s), 119.8 (s), 117.8 (s), 117.1 (s), 105.2 (d), 101.6 (d), 99.3 (d), 98.2 (d), 51.7 (d), 46.3 (q), 29.8 (d), 22 (t); IR 1640, 1616, 1516, 1465, 1260, 1115 cm^{-1}; mass spectroscopy (m/e): 339 (M^+), 324, 312 ($M - HCN$). Anal. Calcd for $C_{20}H_{21}NO_4$: C, 70.78; H, 6.24. Found: C, 70.40; H, 6.40.

Isopavine (1). To a solution of the imine **33** (100 mg, 0.295 mmol) in MeOH (10 mL) was added sodium borohydride (10 mg) and the mixture stirred at room temperature under nitrogen for 1 h. The mixture was quenched by addition of 10% aqueous NaOH, diluted with 10 mL of water, and extracted with 2 × 15 mL of $CHCl_3$. The organic layer was dried and evaporated to leave 93 mg (0.273 mmol, 92.45%) of isopavine (**1**). This was recrystallized from EtOH to give 81 mg of pure isopavine **1**: mp 149–150 °C (lit.[11] mp 149–151 °C); NMR δ 6.77 (1 H, s), 6.76 (1 H, s), 6.69 (1 H, s), 6.53 (1 H, s), 4.26 (1 H, dd, J = 3.90, 3.42 Hz), 3.89 (3 H, s), 3.88 (3 H, s), 3.87 (3 H, s), 3.79 (3 H, s), 3.9–3.0 (5 H, complex multiplet), 1.70 (1 H, very br s); IR 1615, 1510, 1470, 1240, 1110 cm^{-1}; mass spectroscopy (m/e) 341 (M^+), 340, 312 ($M - CH_2NH$).

Treatment of isopavine **1** with acetyl chloride in pyridine gave the acetamide, which was recrystallized from EtOH; mp 206–207 °C (lit.[9] 203.5–204 °C).

2′,3′,2″,3″-Tetramethoxy-1,2:5,6-dibenzocycloocta-1,5,7-trien-3-one Oxime (42a). A solution of the ketone **15** (847.6 mg, 2.49 mmol) and hydroxylamine hydrochloride (870 mg, 12.5 mmol) in pyridine (5 mL) and absolute ethanol (5 mL) was stirred under reflux for 2 h. This was cooled to room temperature, diluted with 100 mL of 10% aqueous HCl, and extracted with 3 × 150 mL of $CHCl_3$. The combined organic phases were washed with 100 mL of saturated aqueous $NaHCO_3$, dried over Na_2SO_4, and evaporated to give the crude oxime **42a**, which was purified by column chromatography on silica gel, eluting with EtOH to give the oxime **42a** (663.7 mg, 1.98 mmol, 79.6%). This could be recrystallized from aqueous EtOH to give oxime **42a**: mp 164–165 °C; NMR δ 7.31 (1 H, s), 6.99 (1 H, s), 6.72 (2 H, s), 6.66 (1 H, s), 6.65 (1 H, s), 4.03 (2 H, s), 3.89 (3 H, s); 3.88 (6 H, s), 3.83 (3 H, s) (the hydroxyl proton was not observed); IR 3500 (br), 1600, 1500, 1250, 1045 cm^{-1}; mass spectroscopy (m/e) 355 (M^+), 339, 338, 337, 327, 324, 322, 312, 169.

2′,3′,2″,3″-Tetramethoxy-1,2:5,6-dibenzocycloocta-1,5,7-trien-3-one Oxime Methyl Ether (42b). A solution of the ketone **15** (250 mg, 0.74 mmol) and methoxylamine hydrochloride in pyridine (2 mL) and absolute ethanol (2 mL) was stirred under reflux for 2 h, after which time the solvents were removed in vacuo. Purification by column chromatography on silica gel eluting with $CHCl_3$ gave oxime methyl ether **42b** (270 mg, 0.731 mmol, 98.9%): NMR δ 7.34 (1 H, s), 6.93 (1 H, s), 6.70 (2 H, s), 6.65 (1 H, s), 6.64 (1 H, s), 4.02 (3 H, s), 3.96 (2 H, s), 3.94 (3 H, s), 3.90 (3 H, s), 3.88 (3 H, s), 3.83 (3 H, s).

2′,3′,2″,3″-Tetramethoxy-1,2:5,6-dibenzocycloocta-1,5,7-trien-3-imine (43). To a solution of the oxime **42a** (100 mg, 0.28 mmol) and ammonium acetate (280 mg, 3.6 mmol) in dioxane (0.6 mL) was added 1:1 (v:v) acetic acid in water (0.11 mL), followed by aqueous $TiCl_3$ (20% aqueous solution, 0.52 mL). This was stirred at room temperature for 1 h, diluted with 20 mL of saturated aqueous $NaHCO_3$, and then extracted with 2 × 30 mL of $CHCl_3$. The combined organic phases were dried over Na_2SO_4 and evaporated to give the crude imine **43**. The yield fluctuated from ~60–100%, due to difficulties in isolation from the TiO_2 formed in the reaction; NMR δ 7.72 (1 H, s), 6.8 (2 H, s), 6.79 (1 H, s), 6.70 (2 H, s), 3.91 (5 H, s), 3.89 (3 H, s), 3.88 (3 H, s), 3.82 (3 H, s). The imine proton was not observed.

3-Amino-2′,3′,2″,3″-tetramethoxy-1,2:5,6-dibenzocycloocta-1,5,7-triene (41). To a solution of the freshly prepared azide **32** (862.7 mg, 2.35 mmol) in dry THF (30 mL) was added lithium aluminum hydride (134 mg, 3.5 mmol), and the mixture was stirred at reflux under nitrogen for 1 h. After the mixture was cooled to room temperature, the reaction was quenched by careful addition of water followed by 10% aqueous NaOH and stirred at room temperature for 1 h. This was diluted with water and extracted three times with $CHCl_3$. The combined organic layers were dried over Na_2SO_4 and evaporated to give the crude amine **41** (771.2 mg). This was taken up in EtOH and precipitated as the HCl salt by addition of gaseous HCl to give 825 mg (2.185 mmol, 93.6%) of crude amine hydrochloride. The amine hydrochloride could be recrystallized from EtOH to give pure amine hydrochloride: mp 253–254 °C dec.

The amine **41** regenerated from the pure hydrochloride salt with aqueous NaOH showed the following spectral properties: NMR δ 6.84 (1 H, s), 6.74 and 6.65 (2 H, AB quartet, J = 12.2), 6.72 (1 H, s), 6.60 (1 H, s), 6.56 (1 H, s), 4.45 (1 H, dd, J = 9.3, 7.8 Hz), 3.86 (6 H, s), 3.82 (3 H, s), 3.80 (3 H, s), 3.14 (1 H, d, J = 9.3 Hz), 3.14 (1 H, d, J = 7.8 Hz), 1.54 (2 H, br s); IR 1610, 1515, 1470, 1250, 1090, 870 cm^{-1}; mass spectroscopy (m/e) 341 (M^+), 339, 326, 324, 309, 293.

3-Acetamido-2′,3′,2″,3″-tetramethoxy-1,2:5,6-dibenzocycloocta-1,5,7-triene (44). Acetyl chloride (0.1 mL, 1.3 mmol) was added to a solution of the amine **41** (320 mg, 0.85 mmol) and triethylamine (0.5 mL, 3.4 mmol) in THF (10 mL) at 0 °C under nitrogen. The mixture was stirred at 0 °C for 1 h, diluted with $CHCl_3$, washed with dilute HCl and saturated aqueous $NaHCO_3$, and evaporated to give the crude amide **44**. Recrystallization from benzene/petroleum ether gave 316.6 mg (0.83 mmol, 97%) of amide **44**: mp 111–112 °C; mass spectroscopy (m/e) 383

(M^+), 324 ($M^+ - CH_3CONH_2$), 309, 293; high resolution mass spectroscopy (*m/e*) 383.1745, calcd for $C_{22}H_{25}NO_5$ 383.1733; 324.1365, calcd for $C_{20}H_{20}O_4$ 324.1362.

(3,4-Dimethoxyphenyl)acetaldoxime (45). This compound was prepared from the aldehyde via its bisulfite addition complex by the known method.[34]

Reaction of 45 with Trimethylsilyl Iodide. The oxime **45** (97.5 mg, 0.5 mmol) in $CHCl_3$ was treated with 1 equiv of trimethylsilyl iodide at room temperature for 2 h. After workup and preparative TLC (solvent $CHCl_3$), 40 mg of the corresponding nitrile, (3,4-dimethoxyphenyl)-acetonitrile, were isolated.

3-Hydroxy-1,2:5,6-dibenzocycloocta-1,5,7-triene (49). Treatment of the ether **48**[3] (100 mg, 0.45 mmol) with 2 equiv of *n*-butyllithium, under the identical conditions as described above for the preparation of **13** from **12**, gave after preparative TLC (solvent $CHCl_3$) 83.5 mg of alcohol **49** (83.5%): mp 119–120 °C (lit.[25] mp 120–121 °C).

3-(Iodomethyl)-1,2:4,5-dibenzocyclohepta-1,4,6-triene (50). Treatment of the alcohol **49** (50 mg, 0.225 mmol) in EtOH (4 mL) with concentrated HI (2 mL) under the conditions described above for preparation of **17c** from **13** gave 87.1 mg of crude iodide **50**. The iodide could be recrystallized from ethanol. Identity was established by comparison of the NMR with that of the tetramethoxy case: NMR δ 7.2–7.4 (8 H, m), 6.95 (2 H, s), 4.34 (1 H, t, J = 8.3 Hz), 3.56 (2 H, d, J = 8.3 Hz).

Acknowledgment. We thank the National Cancer Institute and the National Science Foundation for their generous support of our synthetic program. The Bruker 200-MHz NMR instrument was purchased with funds provided by a major instrument grant from the National Science Foundation.

Simple *o*-Quinodimethane Route to (±)-4-Demethoxydaunomycinone

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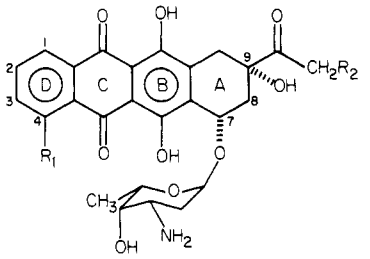
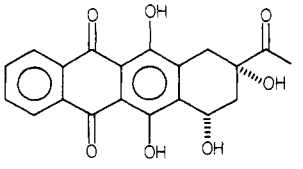
Abstract: The anthracycline antibiotics daunorubicin and adriamycin are important clinically useful drugs in the treatment of a number of human cancers. The structurally simplified synthetic analogues 4-demethoxydaunorubicin and 4-demethoxyadriamycin show much clinical promise. The synthesis of the corresponding aglycone (±)-4-demethoxydaunomycinone from the inexpensive dye intermediate quinizarin, utilizing *o*-quinodimethane intermediates, is discussed.

The anthracycline antibiotics daunorubicin (**1**) and adriamycin (**2**) are of great current interest in view of their activity against various experimental tumors, as well as their clinical effectiveness in the treatment of many types of human cancer.[1]



1, $R_1 = OCH_3$; $R_2 = H$
2, $R_1 = OCH_3$; $R_2 = OH$
3, $R_1 = R_2 = H$



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The antineoplastic acitivity of these compounds can be improved by structural modification, as shown by the recent report that the totally synthetic analogue 4-demethoxydaunorubicin (**3**) is 4–8 times more active than daunorubicin itself.[2] Although several syntheses of the corresponding aglycone 4-demethoxydaunomycinone (**4**) have been described,[3] a simple and practical route for a larger scale preparation of **4** has yet to be devised. The work reported in this paper represents our initial efforts toward the attainment of this goal.[4]

Results and Discussion

About 2 decades ago, studies in our laboratory,[5,6] as well as those of Jensen[7] and Alder,[8] showed that unstable *o*-quinodimethane intermediates could be trapped by suitable dienophiles: these early observations have since formed the basis for a powerful new technique for the synthesis of a variety of natural products from benzocyclobutene precursors.[9]

Our present synthetic strategy has centered upon the concept of constructing ring A of an anthracyclinone system by the

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