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 ($k_4^\text{III}$, 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 $\phi_1^*$ for $k_2$ rate limiting as in eq 2. Here, $X$ represents the degree of separation of chloride ion from the carbonion in the transition state.

Assuming $\phi_2^*$ is unity and the transition state resembles$^{19}$ the tight ion pair ($X = 0$), we have

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

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$_2$O. The similarity of the SIE for 1 and 2 suggests 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.

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


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

$$\frac{k_{H_2O}}{k_{D_2O}} = (1/0.921^4)/1.69^{2X} \quad (5)$$

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

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 $\alpha$-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$_2$O runs and one (two) D$_2$O runs determined concurrently and is listed following the isotope effect in the table, i.e., $1.302 (9) = 1.302 \pm 0.009$.

Reaction rates were initiated by adding 1–2 $\mu$L of a dioxane solution of 1 or 2 to a solution of a given salt in 75% or 85% dioxane–H$_2$O–D$_2$O made by adding 25 (15) mL of H$_2$O (D$_2$O) to 75 (85) mL of purified dioxane.

All salts were the highest purity commercially available samples.

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

Michael E. Jung* and Steven J. Miller

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 dibenzocyclooctatrienyl ether 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 methylidibenzocycloheptatrienyl systems are reported in high yields. The mechanisms of these processes are discussed in detail. In addition, a novel oxidative cleavage of the exo-methylidibenzocycloheptatriene (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 dibenzo[cyclooctadienes 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),$^4$ thalipavine (2),$^5$ pavine (3),$^4$ and argemone (4),$^6$ we thought this

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.
new construction of dibenzo-cycloalkadienes 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.\(^5\)

Many derivatives of this basic structure have shown potent and varied biological activity.\(^6\) However, compounds with significant modifications in both aromatic rings are rare. Therefore, we began a program aimed at the facile construction of tricyclic aromatic analogues. We now report the successful achievement of two of these goals, namely, the preparation of isopavine and the ketone 24 from homoveratraldehyde (11), each in four steps in overall yields 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, although they misassigned the structure of the product. Later the groups of Waldmann\(^10\) and Battersby\(^1\) repeated this preparation.

(15) Pyman, F. L.; Reynolds, W. C. Ibid. 1910, 97, 1320.
(17) Schöpf, C. Experientia 1949, 6, 201.
prepared, a large number of which have interesting biological activities. 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-dimethoxy-phenyl)acetalddehyde (homoveratraldehyde) (Scheme I). 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 dealkylative protonation 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 would make it an ideal substrate for this 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 dibenzyl 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$_{N}2$ 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$_3$OEt$_2$, Ac$_2$O; BF$_3$OEt$_2$ then base; HClO$_4$; H$_2$SO$_4$; HCl, CF$_3$CO$_2$H, Ac$_2$O; HCl, HBr, HI) to give the halides 17a-c with 97% yield, respectively. This ring contraction presumably occurs by the mechanism shown in Scheme II. Loss of water from the protonated alcohol would give the 8-membered product 18 which is in equilibrium with the cyclopropyl carbonyl ion 19 (and all of the numerous resonance contributors possible for this compound). Kinetic trapping of the carbonyl ion would probably give the 8-membered product 18. However, if the group X is a good leaving group, this product 20 could reionize to the mixture of carbonyl ions 18 and 19 which could then be converted into the halomethyl 7-membered product 17. Compound 17 should

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 argemone (4) via argemoneine methine methiodide (14) by the method of Battersby.19,20 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 pavenne 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 dibenzocyclooctatriene.22 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 argemoneine 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 dibenzocyclooctatriene. 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 carbonyl 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

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 compound26 could be produced in excellent yield from any of the purified halides 17a–e, 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), cyclobenprazine (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 monooacetate 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 peracetic acid 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 Borch.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 tetrahydroxy analogue of 24, dibenzo- tropone (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.9 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 amination29 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.

![Diagram](image-url)
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)dibenzo[cycloheptatrienes 17a–c were very readily available, the simple substitution of azide for halide was attempted. Under the usual conditions (KN₃, 18-crown-6 ether, CH₃CN, 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, SN₂ 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 cyclooctatrienyl 13 was treated with hydrazoic acid in benzene, instead of the expected (azidomethyl)cyclooctatriene (31), the unarranged 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 = N₃, 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. Thermalysis 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 nitrile 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 nitrone. 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. However, at 160 °C, it is likely that both are produced. These 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 cyclopropene 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 isolated a compound in 10% yield by treatment of the imine 40 with 75% H₂SO₄. 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 spectrosocopy) in accord with its structure. More importantly, the melting point of both isopavine and the corresponding acetamide derivative matched those in the literature. 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 aminocoupling reaction of the aminobenzocyclooctatetraene 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., HCONH₂, HCO₂H, and NH₂OAc, NaCNBH₃ 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—NaCNBH₃, NaBH₄, LiAlH₄, NaBH₄OOCF₃, DIBAL, AlH₃, B₃H₆, HSiCl₃, Na/EtOH, Zn, SnCl₄/HCl—all without the desired effect. It is known that (31) Schlicker, E.; Müllcr, J. Helv. Chim. Acta 1948, 31, 914.
Hydride reduction of analogous less-substituted oximes also gives poor yields of the corresponding amines. 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(NO3)2, HgCl2] followed by reduction (basic NaBH4 or NaS) 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 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 dibenzo[cyclooctadienes] and have developed a route from these compounds to the dibenzo[cycloheptadiene]-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

![Diagram](image-url)

mercuric acetate or nitrate followed by reduction. All that appears to occur is the slow formation and precipitation of the amine-mercuric salt complex 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. Only starting material was recovered.

An earlier, very simple approach was also investigated. Homoveratraldehyde (11) was converted into the aldoxime 45 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 and that this compound would then undergo the analogous dimerization double ortho Friedel–Crafts alkylation to produce the N-trimethylsilyloxy)pavine 47. However, the only product isolated from 45 upon treatment with 55% yield from phenylacetaldehyde into the dibenzo[cyclooctatriene] and then into the (iodomethyl)dibenzo[cycloheptatriene] 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''-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
quenched by careful addition of water and extracted with 2
volumes of ethyl acetate (187 mg, 0.59 mmol) was added. The mixture was stirred at
room temperature under nitrogen for 4 h. The reaction was quenched promptly upon reaching room temper-

ture by addition of 100 mL of 1 M aqueous Na2S2O3. After the mixture was cooled to room temper-

ture for 1 h. Extraction with CHCl3, gave a crude yield of 104.2 mg (97.5%). This could be recryst-

alized from MeOH to give pure tetraene 16: mp 184-185 °C (lit. 159.6-164 °C); NMR δ 6.63 (2 H, s), 6.54 (4 H, s); IR 1600, 1500, 1430, 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 4 h. After being cooled to room temperature, it was diluted with 15 mL of water and extracted with 50 mL of CHCl3. The organic layer was dried over Na2SO4 and evaporated to give 44.3 mg (1.295 mmol, 88.7%) of crude alcohol 13.

(Chloromethyl)-2',2',3',3'-tertamethoxy-1,2,4,5-dibenzocycloheptatrie (17). A solution of sodium borohydride (11 mg, 0.294 mmol) in 10 mL of ethanol was added to a solution of hepta-1,4,6-triene (17c). Formation of 13 from 15 by Reduction.

Preparation of tetraene 16 (477.2 mg, 0.93 mmol) was suspended in 30 mL of water and stirred with Ag2O (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 CHCl3. The organic phase was dried over Na2SO4 and evaporated to give 23.2,3',3'-tetramethoxy-1,2,5,6-dibenzocyclo-

octatetraene (16) (306.6 mg, 0.95 mmol, 100%). This could be recryst-

alized from benzene to give pure tetraene 16: mp 184-185 °C; IR 159.6-164 °C; NMR δ 6.63 (2 H, s), 6.54 (4 H, s); IR 1600, 1500, 1430, 1245, 1075, 870 cm⁻¹; mass spectroscopy (m/e) 324 (M⁺), 309, 293.

The ketone 15 was taken up in MeOH (25 mL) and K2CO3 (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 CHCl3. The combined organic phases were dried and evaporated to give 44.3 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

100 mL) at -78 °C under nitrogen was added slowly with vigorous stirring trime-thylsilyl iodide (2.25 mL, 17 mmol). The solution was stirred at -78 °C for 2 h and allowed to warm to room temper-

ture. The reaction was quenched promptly upon reaching room temper-

ture by addition of 100 mL of 1 M aqueous Na2S2O3. After the color of iodide had been discharged, the reaction mixture was extracted with 2 × 100 mL of CHCl3 and the combined organic extracts washed with 100 mL of saturated aqueous NaHCO3. The organic phase was dried over Na2SO4 and evaporated to leave 216.5 mg (85.2%). This could be recryst-

alized from benzene to give pure tetraene 16: mp 184-185 °C; IR 159.6-164 °C; NMR δ 6.63 (2 H, s), 6.54 (4 H, s); IR 1600, 1500, 1430, 1245, 1075, 870 cm⁻¹; mass spectroscopy (m/e) 324 (M⁺), 309, 293.

To a solution of the other ether 12 (10 g, 29.2 mmol) in dry THF (300 mL) at room temperature under nitrogen was added slowly n-butyl-

	lithium (24.6 g, 24.4 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 CHCl3. The combined organic phases were washed with 150 mL of saturated NaHCO3 and evaporated to leave the pure ether 12. This was purified by column chromatography on silica gel, eluting first with CHCl3 to remove impurities and followed by EtOAc to give 97.5 g (28.5 mmol, 97.5%) of pure alcohol 13 (153.9 mg, 100%) identical in every respect with that obtained synthetically.

A solution of sodium borohydride (11 mg, 0.294 mmol) in 10 mL of ethanol and 100 mL of CHCl3 was stirred at room temperature 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 CHCl3. The organic phase was washed with 50 mL of saturated aqueous NaHCO3, dried over Na2SO4 and evaporated to give the free alcohol 13 (97.5 mg, 95.4%). This could be recrystallized from CHCl3 and was identical by NMR with that obtained earlier.
Total Synthesis of Isopavine


Isopavine (1). To a solution of the imine 33 (100 mg, 0.295 mmol) in MeOH (10 mL) was added sodium hydroxide (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 CHCl₃. The organic layer was dried and evaporated to leave 93 mg of crude isopavine (1). This was recrystallized from EtOH to give 81 mg of pure isopavine (1) (mp 149-151 °C; NMR δ 7.31 (1 H, s), 6.76 (1 H, s), 6.69 (1 H, s), 6.53 (1 H, s), 4.26 (1 H, d, J = 3.90, 3.42 Hz), 3.85 (3 H, s), 3.87 (3 H, s), 3.77 (3 H, s), 3.25 (1 H, d, J = 17.4, 3.4 Hz), 3.00 (1 H, dd, J = 17.4, 10.8 Hz) ppm; mass spectroscopy (m/e) 341 (M⁺), 304, 239 (23%).

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

Francis A. J. Kerdesky, Robert J. Ardecky, M. V. Lakshmikantham, and Michael P. Cava*

Contribution from the Department of Chemistry, University of Pennsylvania, Philadelphia, Pennsylvania 19104. Received August 25, 1980

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.

![Chemical Structure](attachment:image.png)

The antineoplastic activity 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. Although several syntheses of the corresponding aglycone 4-demethoxydaunomycinone (4) have been described, 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.

Results and Discussion

About 2 decades ago, studies in our laboratory, as well as those of Jensen and Alder, 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.

Our present synthetic strategy has centered upon the concept of constructing ring A of an anthracyclinone system by the new technique for the synthesis of a variety of natural products.

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