experiment leads to an agreement factor[18] of 0.02. This compares favorably with the agreement factors (≃0.01) we obtained previously[10] for conformationally restricted adamantane derivatives; other workers have reported agreement factors of 0.04–0.06 for nitriles.[18b] If one recalls that the present results are obtained from the parametrized form of the pseudocontact equation (eq 1) and do not involve a minimization process, the agreement factor of 0.02 for cyclohexanecarbonitrile becomes even more impressive.

The determination of bound shifts and the use of a parametrized form of the pseudocontact equation employing chemically reasonable bond lengths and angles has allowed us to overcome many of the obstacles and uncertainties encountered in previous efforts at utilizing lanthanide-induced shifts for conformational analysis.[5-7,19-21] Consequently, the results reported here further emphasize the value of lanthanide shift reagents for rigorous structure elucidation in the liquid state and demonstrate that structure determination of conformationally mobile systems can be accomplished with a high degree of accuracy.

Experimental Section

Cyclohexanecarbonitrile[22] was prepared by conversion of cyclohexanecarboxylic acid (Aldrich, no. 10,183-4) to the acid chloride and formation of the amide (concentrated aqueous ammonia) followed by dehydration ($POCl_3$). The sample used in this study was purified by preparative gas chromatography (Carbowax 20M).

Tris(1,1,1,2,2,3,3-heptafluoro-7,7-dimethyl-4,6-octadionato)-europium (Aldrich, Resolve-Al EnFOD, no. 16,093-8) was sublimed (160–165 °C, 0.05 Torr) and stored in a vacuum desiccator over P_2O_5 for at least 48 h prior to use.

Nuclear magnetic resonance spectra were obtained using Varian EM-360 and A-60 spectrometers. All spectra were recorded at either 600 (EM-360) or 500 Hz (A-60) sweep widths. Chemical shifts were measured relative to internal Me_4Si and sweep widths were calibrated with an external audio oscillator. When the widths of spectra exceeded the sweep widths, offset spectra were recorded and peak positions were measured relative to a Me_4Si audio sideband.

Shift reagent runs utilized the incremental dilution method[8] in which a CCl_4 solution containing both shift reagent (0.6 M) and the nitrile (0.2 M) was successively diluted with a 0.2 M CCl_4 solution of the nitrile. The precise relative concentrations of shift reagent and nitrile were determined gravimetrically, and spectra were recorded for a total of 25 different concentrations of shift reagent.

Acknowledgments. This work was supported by a grant from the Research Corporation (to M.D.J.) and in part by the donors of the Petroleum Research Fund, administered by the American Chemical Society. We thank Professors K. L. Servis and M. R. Willcott, III, for helpful comments.

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Total Synthesis of (±)-Kadsurin

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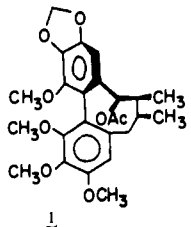
Abstract: The total synthesis of (±)-kadsurin has been achieved in 13 steps starting from 6-bromomyristicinaldehyde (**5**) and 3,4,5-trimethoxybenzyltriphenylphosphonium bromide (**6**). In the key step the 2,2′-bis(bromoacyl)-1,1′-biaryl **16** is cyclized intramolecularly to the diones **17** and **18.** Compound **17** was converted to kadsurin by a series of highly selective steps. Compound **18,** which has the unnatural biaryl configuration, could be also converted to kadsurin by the thermal isomerization of hydroxy ketone **23** to hydroxy ketone **19.**

Kadsurin (**1**) and kadsurarin (**2**) are the constituents of stem extracts from *Kadsura japonica,* used by the Taiwan population as a versatile therapeutic agent.[1] The dibenzocyclooctadiene skeletal structure and the gross substitution pattern classify these compounds as schizandrin-type lignans[2] which are usually characterized by an interesting biological activity related mainly to the central nervous system.[3] Several reports on their pharmacological evaluation are available.[4]



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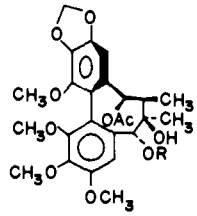


2, R=COC(CH$_3$)=CHCH$_3$

These medicinal properties as well as the interesting structural features have attracted us to the problem of the synthesis of schizandrin-type lignans, a field in which previous efforts had been rather scarce. The syntheses of the structurally related antileukemic lactones, steganacin[5] and its precursor, steganone,[6] have been recently reported. A preliminary report on the first synthesis of desoxyschizandrin has been published.[7]

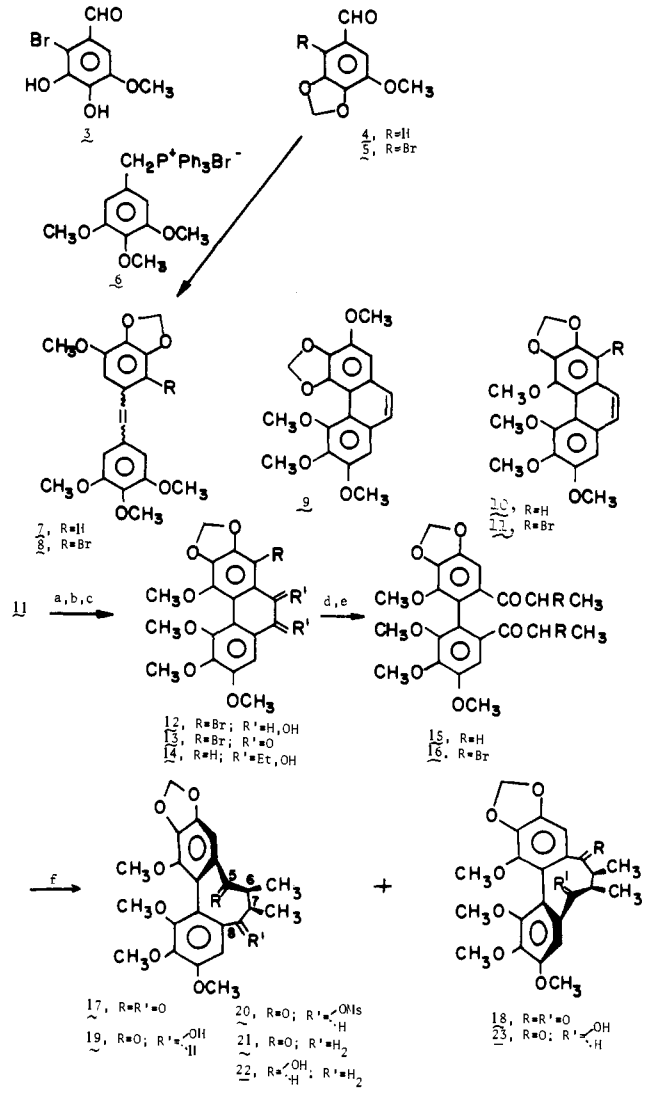
We wish to report now the first total synthesis of (±)-kadsurin and to describe some of the stereochemical features which control the regio- and stereoselective reactivity observed in this system.

Apart from the problems related to the construction of the desired framework, the presence of three chiral carbon atoms in the eight membered ring and of a chiral biaryl axis imposed the search for a selective synthetic approach. Our strategy was based on the synthesis of the biaryl derivative **16** to which the previously described zinc-induced ring closure reaction[8] could be applied. In accordance with our previous observations, this cyclization was expected to afford a dibenzocyclooctadienedione in which the two vicinal methyl groups would have the desired cis stereochemistry. Further synthetic tasks were related to the search of a selective reactivity concerning the two aromatic ketone groups in the eight-membered ring and to the preferential formation of the isomer with the kadsurin-like biaryl configuration.

A Wittig reaction between myristicinaldehyde (**4**) and 3,4,5-trimethoxybenzyltriphenylphosphonium bromide (**6**) was performed, affording a mixture of varying amounts of (*E*)- and (*Z*)-stilbenes **7**, which on photolysis[9] gave the phenanthrenes **9** and **10** (Scheme I) in a 1:1 ratio and in 66% overall yield, in two steps.

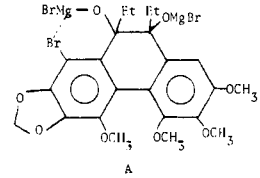
In view of the substantial yield of the undesired isomer **9**, we turned our attention toward a synthetic sequence in which the presence of a blocking bromine substituent in **7** would result in the exclusive formation of the required phenanthrene derivative. The starting material used for this purpose was 5-hydroxyvanillin which was found to undergo bromination in a regiospecific manner affording exclusively the bromoaldehyde **3** (79% yield). The preparation of the methylenedioxy ether (**5**) was then best achieved by means of methylene iodide and cupric oxide in dimethylformamide (in 61% yield).[10] Wittig reaction of the aldehyde **5** with the phosphonium salt **6** and lithium methoxide gave the stilbenes **8** (mixture of *E* and *Z* isomers, 82% yield), which were irradiated in cyclohexane and tetrahydrofuran in the presence of iodine, affording the phenanthrene **11,** mp 172 °C, as the sole product. The photocyclodehydrogenation was found to proceed efficiently (84% yield), in spite of a previous report on unsatisfactory results obtained when substituents which end up in the 3, 4, 5, and 6 positions of the phenanthrene are present.[11] Hydroxylation of the C-9, C-10 bond by means of osmium tetroxide in pyridine produced the cis diol **12,** mp 204 °C, which was further oxidized, using sulfur trioxide–pyridine complex, to the deep red quinone **13,** mp 222–224 °C. The overall yield in these two steps was 74%. A double Grignard reaction with the magnesium derivative of ethyl bromide converted **13** to a mixture of stereoisomeric diols **14** (76%), which unexpectedly was found to be devoid of the aromatic bromine substituent. This unusual debromination can be formulated in terms of coordination of

Scheme I[a]



[a] a, OsO_4, py; b, py-SO_3; c, EtMgBr, C_6H_6; d, $Pb(OAc)_4$, C_6H_6, py; e, Br_2, dioxane–ether; f, Zn–Ag, $MeSO_2$–DME.

the bromine with the neighboring halomagnesium group via a six-membered transition state A as presented, and an ex-



A

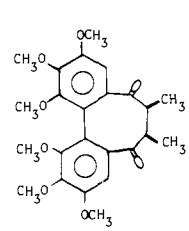
change reaction of the type[12] ArBr + EtMgBr ⇌ ArMgBr + EtBr is thus made easier by the weakening of the C–Br bond.

Oxidative cleavage of the C-9,C-10 bond by treatment with lead tetraacetate converted **14** into the diketone **15** (85% yield), which was brominated at the positions α to the two keto groups to give a mixture of isomeric dibromides **16** (93% yield). The presence of more than two stereoisomers of **16** was evidenced by the multiplicity of aromatic proton signals in the NMR spectrum and is explained by the hindered rotation of the diastereomeric dibromides around the biaryl axis. Treatment of the dibromide mixture with zinc–silver couple in dimethyl sulfoxide–dimethoxyethane resulted in ring closure and produced the diketones **17,** mp 161 °C, and **18,** mp 143 °C (in order of increasing polarity), which were formed in 1:1 ratio in 69% total yield. The gross structural assignments for **17** and **18,** as well as the *cis*-dimethyl configuration in both com-

pounds, were strongly supported by their ^{1}H NMR spectra which display two doublets, at δ 0.92 and 1.20 in **17** and δ 0.95 and 1.19 in **18,** for the methyl protons and two double quartets centered at δ 3.34 and 2.51 in **17** and δ 3.22 and 2.49 in **18,** for the adjacent C-6 and C-7 methine protons. This pattern of proton resonances was very similar to that which we found recently for the analogous *cis*-dimethyl diketone **26**[7] and was different from that encountered in trans isomers where the presence of a twofold symmetry axis resulted in identical (or very close[13]) chemical shifts for both methyl groups. We assumed therefore that the isomerism of **17** and **18** could arise from restricted rotation about the biphenyl bond, if two chemically nonequivalent ground states would ensue. While no changes in chemical shifts were observed on the NMR time scale even at 200 °C, prolonged heating at 160 °C under argon (neat) resulted in a slow interconversion of **17** and **18;** after 20 h ~10% of either diketone was converted into its rotamer and after 30 h the extent of isomerization had increased to 25%. Partial decomposition, after longer periods of heating, prevented full equilibration of the diketones.

Insight into the conformational properties of these diketones was provided by their IR spectra: both compounds display two distinct carbonyl absorptions at 1667 and 1704 cm^{-1}, showing that only one of the ketone carbonyls can attain coplanarity with the adjacent aromatic ring. Interestingly, this conformational restriction regarding the carbonyls seems to be specific for cis-6,7-substituted systems[14] and implies that rotation about the biaryl bond would convert the coplanar ketone into a noncoplanar one and vice versa, so that the nonbonded interactions in the system remain unchanged, as could in fact be deduced from the examination of Dreiding models. Hence, each of the nonequivalent aryl rings can be adjacent either to a coplanar or to a noncoplanar ketone and therefore biaryl rotation results in the formation of two distinct isomers. By contrast diketone **26,**[7] with identical aryl rings, interconverts between two enantiomeric conformations. The specific conformational assignments, as shown in the structural formula of **17** and **18,** were provided by the chemical shifts of the aromatic protons in the NMR spectra. These protons should be deshielded if adjacent to a coplanar ketone group or shielded when adjacent to a noncoplanar ketone; besides, they should be slightly more shielded by a vicinal methylenedioxy group than by a methoxy group.[15] Hence, comparison of aromatic proton resonances in **17** (δ 7.18 and 6.41) and **18** (δ 7.03 and 6.51) indicated that the C-5 ketone in **17** and the C-8 ketone in **18** are not coplanar with the adjacent aromatic rings. This assumption was indeed subsequently confirmed.

From the examination of the Dreiding models of these diketones, it became evident that in order to obtain the anisotropic ring shielding of the acetate methyl, which is observed at δ 1.6 in the ^{1}H NMR spectrum of kadsurin,[1] the noncoplanar carbonyl adjacent to the methylenedioxyphenyl ring has to be converted to an acetate group. We anticipated therefore that **17** has the "natural" biaryl configuration and is the precursor of kadsurin. Accordingly, the next phase of the synthesis was concerned with the selective reductive deoxygenation of the C-8 carbonyl group in **17.** We assumed that, of the two ketone groups, the coplanar aromatic ketone would respond more readily to catalytic hydrogenation. Indeed, when **17** was hydrogenated over palladium on carbon in acetic acid, reduction proceeded with complete regiospecificity and the hydroxy ketone **19,** mp 200 °C, was formed as the sole product in almost quantitative yield. The assignment for **19** was supported by the IR spectrum, which exhibited only the nonaromatic carbonyl absorption (1703 cm^{-1}), and by the NMR chemical shifts of the aromatic protons, at δ 6.93 and at 6.34, the shielding of the latter proton being caused by the noncoplanar ketone. All attempts for further reductive deoxygenation of the benzylic hydroxyl group by selective hydrogenolysis under different hydrogenation conditions, or by other methods which were previously used for this purpose,[16] failed completely. Accordingly, the crystalline mesylate **20** (mp 131–132 °C, 80–85%) was prepared and a variety of reducing agents[17] were tried on it, in an attempt to produce an effective reductive demesylation. These attempts resulted at best in low yields of **21** (or **22**). Clearly, the strong steric hindrance at C-8 causes the difficulties encountered at this stage. Thus the reduction with an otherwise effective reagent, lithium triethylborohydride,[18] resulted in a mixture of products consisting of the desired alcohol **22** (25–30%), an oxide **27** (~25%, formed by attack across the ring), and the corresponding 5,8 diol (~30%) obtained from cleavage of the O–S bond in the mesylate. Finally, high efficiency was achieved when **20** was submitted to catalytic hydrogenation over palladium on carbon in methanol solution containing sodium methoxide. The ketone **21,** mp 159 °C, was formed in 88% yield. Hence, this sequence seems to represent a simple and very efficient reductive deoxygenation method of hindered secondary alcohols, when basic conditions are not detrimental.[19] Further reduction of **21** with lithium aluminum hydride afforded stereospecifically the alcohol **22,** mp 143 °C. Acetylation under drastic conditions (acetic anhydride and *p*-toluenesulfonic acid) afforded the desired (±)-kadsurin (**1**), mp 158 °C, in 90% overall yield in the last two steps. The product was found to be identical with a sample of the natural kadsurin by TLC and spectral (NMR, UV, and IR) comparison.[20]



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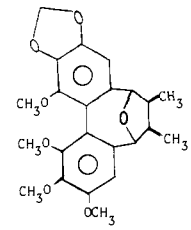

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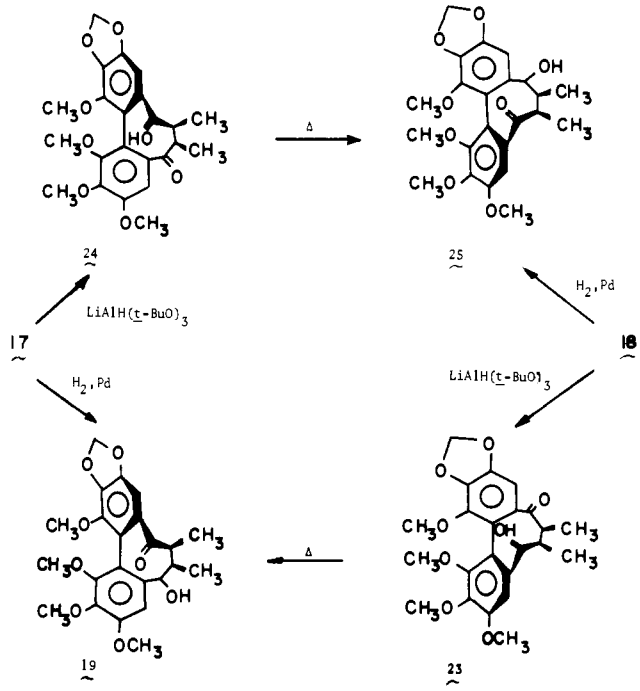
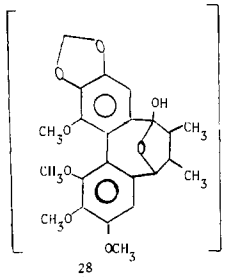
Thermal Isomerizations. The overall yield of (±)-kadsurin could be substantially increased by a remarkable biaryl rotation of the hydroxy ketone **23,** of unnatural configuration, and its conversion to the kadsurin precursor **19** (see Scheme II).

Scheme II



The treatment of the diketone **18** with lithium tri-*tert*-butoxyaluminum hydride in tetrahydrofuran was found to reduce exclusively the noncoplanar ketone group, in contrast to catalytic hydrogenation, but with a similar high degree of specificity. The hydroxy ketone **23** thus obtained (86%), displays in the IR ($CHCl_3$) the aromatic carbonyl absorption at 1667 cm^{-1}. The cis assignment for the hydroxy group, based on the assumption that the hydride attack occurs from the less hindered side, was confirmed in the next step. Heating under argon (160 °C, 30 h) resulted in the conversion of **23** into its rotamer, the hydroxy ketone **19,** as the sole product (91%), which could be further converted into **1.** These results imply that the free-energy barrier for the unusual one-way rotation is lower than that in the interconversion of diketones **17** and **18** described above, although the replacement of a trigonal by a tetragonal carbon atom at C-8 could be expected to lead to opposite results, in view of the assumed increased interaction between the C-5 and C-8 groups in the planar transition state.[21] It has been previously shown, for instance, that the barrier of rotation of analogous 5,8 diketones is lower than that observed in similar systems in which the ketone groups are replaced by methylene groups.[8] A possible explanation for this relatively smooth rotation in a hindered biaryl system may be provided by the intermediacy of a hemiketal (**28**) which could relieve some nonbonded interactions in the planar transition state.[22]



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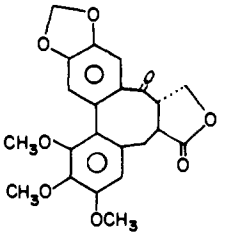

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Supporting evidence on the energetic preference for hydroxy ketones in which the ketone group is not coplanar with the adjacent aromatic ring was provided by the preparation of the two other hydroxy ketones in this series (**24** and **25**), as shown in Scheme II. The reduction of diketone **17** with lithium tri-*tert*-butoxyaluminum hydride and the reduction of **18** by hydrogenation over palladium on carbon proceeded in a stereo- and regiospecific manner, as found previously for **19** and **23.** The thermal conversion of hydroxy ketone **24** into **25** was achieved under conditions identical with those used for **23.**

It might be asked why there should be a preference for the conformation in which the ketone group is prevented from conjugation with the adjacent aromatic ring. The inspection of the Dreiding models of the hydroxy ketones seems to provide an explanation: in the "coplanar ketone" conformation there are eclipsing interactions between the ketone group and the vicinal methyl group as well as between the hydroxy group and its vicinal methyl. These interactions are partly relieved in the "noncoplanar ketone" conformation.

In this context an interesting relationship between the recently published results of Kende et al.[23] and our results should be mentioned. In this latter work, isosteganone **29,** in which the ketone carbonyl is not coplanar with the adjacent aromatic ring, was found to convert thermally into steganone (coplanar ketone); thus the conformational preferences of the ketone carbonyl in the ketolactone system **29** are opposite to those found in our system. It seems therefore that there is a close relationship between the geometry of the C-6 and C-7 substitution and the conformation of the eight-membered ring in this system. This relationship is being further investigated.

Experimental Section

General Procedures. Melting points were determined on a hot stage microscope and are uncorrected. ^1H NMR spectra were recorded in $CDCl_3$ solution on a Varian A-60 (60 MHz) or Bruker 90 (90 MHz) spectrometers, with reference to internal tetramethylsilane. Infrared spectra were recorded on a Perkin-Elmer 237B spectrophotometer. Ultraviolet spectra were measured on a Cary 14 spectrophotometer. Merck silica gel G was used for column chromatography. The compounds were preadsorbed on silica from ether or dichloromethane solution and added to the dry silica column before elution with solvents. Thin layer chromatography (TLC) was carried out on Merck Kieselgel 60 F_{254} precoated aluminum plates. Dimethylformamide (DMF), dimethyl sulfoxide (Me_2SO), and tetrahydrofuran (THF) were distilled from calcium hydride and stored on molecular sieves before use.

3,4,5-Trimethoxybenzyltriphenylphosphonium Bromide (6). A solution of 31.5 g of triphenylphosphine (0.12 mol) in dry benzene (120 mL) was added to 26.1 g of 3,4,5-trimethoxybenzyl bromide[5] (0.1 mol) and the mixture was refluxed for 2 h. The precipitated salt was separated by filtration, washed with warm benzene, dissolved in methanol, and crystallized by addition of ether to the methanol solution, affording 48 g of **6** (92%), mp 219–221 °C. Anal. ($C_{28}H_{28}O_3BrP$) C, H.

4,5-Methylenedioxy-3,3′,4′,5′-tetramethoxystilbene (7, Mixture of *E* and *Z* Isomers). Lithium methoxide (12 mmol, prepared from 84 mg of lithium) in absolute methanol (20 mL) was added to a stirred mixture of 5.23 g of **6** (10 mmol) and 1.80 g of myristicinaldehyde[10] (10 mmol) in dry DMF (25 mL) under nitrogen at 90 °C (bath). After 1 h the reaction mixture was cooled and poured into water. The resultant mixture was extracted with 4:1 ether–chloroform and the combined extracts were washed with water. The residue after evaporation of solvents was chromatographed (hexane and 20–30% ethyl acetate) affording a crystalline mixture (TLC) of two isomers: 2.85 g (83%); NMR δ 6.87–6.42 (m, 6), 5.91 (br s, 2), 3.70–3.93 (m, 12). Anal. ($C_{19}H_{20}O_6$) C, H.

3,4-Methylenedioxy-2,5,6,7-tetramethoxyphenanthrene (9) and 2,3-Methylenedioxy-4,5,6,7-tetramethoxyphenanthrene (10). The stilbene **7,** 1.5 g (4.4 mmol, mixture of *E* and *Z* isomers) and 1.27 g of iodine (5 mmol) were dissolved in dry THF (70 mL) and purified cyclohexane (550 ml) and the stirred mixture was irradiated with a 450-W medium-pressure mercury lamp at room temperature under nitrogen. After 7–8 h the conversion was completed (TLC) and the dark red solution was washed with a saturated solution of sodium thiosulfate, dried, and concentrated in vacuo and the solid residue was chromatographed (hexane and 30% ether) affording a crystalline mixture of **10** and **9** (in order of elution), 1.20 g (80% yield). The ratio of **9**:**10**, as determined by NMR integration and TLC, was ~1:1. Compound **10** had mp 125–126 °C, NMR δ 5.96 (s, 2 OCH_2O); the phenanthrene **9** was not separated in pure state, NMR δ 6.09 (s, 2, OCH_2O).

The phenanthrene **10** was also prepared (for identification) by addition of **11** (50 mg, 1.2 mmol) in dry THF (6 mL) to a suspension of 38 mg of $LiAlH_4$ (1 mmol) in THF (6 mL). Reflux for 6 h was followed by quenching with a saturated Na_2SO_4 equeous solution, drying (Na_2SO_4), and filtration. Removal of solvent from filtrate and chromatography (pentane–30% ether) gave 22 mg (52%) of compound identical with **10** (TLC and ^1H NMR). Anal. ($C_{19}H_{18}O_6$) C, H.

3-Methoxy-4,5-dihydroxy-6-bromobenzaldehyde (3). To a stirred solution of 16.8 g of 5-hydroxyvanillin[24] (0.1 mol) in acetic acid (100 mL) was added 16.8 g of bromine (0.105 mol) in acetic acid (20 mL) at room temperature. The formed precipitate was filtered off and the filtrate was concentrated in vacuo. The residue obtained from filtrate was purified by heating with charcoal in ethanol solution followed by filtration and concentration of the filtrate. Dilution with hexane gave an additional crop of crystalline material which was combined with the product from the prior filtration, affording 19.5 g (79%) of **3.** An analytical sample (from pentane–ether) had mp 171–172 °C; NMR (Me_2SO-d_6) δ 9.81 (s, 1), 7.08 (s, 1), 3.85 (s, 3). Anal. ($C_8H_7O_4Br$) C, H.

3-Methoxy-4,5-methylenedioxy-6-bromobenzaldehyde (5). A mixture of 2.97 g of aldehyde **3** (12 mmol), 4 g of CH_2I_2 (15 mmol), CuO (0.25 g), and K_2CO_3 (3.5 g) in dry DMF (25 mL) was stirred at 130 °C (bath) during 4 h. After cooling the reaction mixture was diluted with water and extracted with ether–chloroform (4:1). The combined extracts were washed with aqueous HCl, $NaHCO_3$, and

NaCl solutions. After removal of the solvent the residue was crystallized by addition of methanol and afforded 1.90 g (61%) of **5**. An analytical sample had mp 154 °C (from pentane–ether); NMR δ 9.81 (s, 1), 6.18 (s, 2), 3.92 (s, 3). Anal. ($C_9H_7O_4Br$) C, H.

1-Bromo-2,3-methylenedioxy-4,5,6,7-tetramethoxyphenanthrene (11). The aldehyde **5** (2.60 g, 10 mmol) was reacted with the phosphonium salt **6** in the same manner as described for the preparation of **7**. Chromatographic purification (hexane and 20–30% ethyl acetate) gave 3.48 g (82%) of a crystalline mixture of two compounds (TLC), *E* and *Z* isomers of **8**: NMR δ 7.18–6.45 (m, 5), 6.06 (br s, 2). Without further separation the mixture was irradiated in portions of 1.5 g (3.5 mmol) by the procedure described for **7**. Chromatography (hexane–30% ethyl acetate) afforded **11**, 1.25 g (84%). An analytical sample (from chloroform–hexane) had mp 172 °C; NMR δ 7.87 (d, 1, J = 8 Hz), 7.45 (d, 1, J = 8 Hz), 6.98 (s, 1), 6.16 (s, 2), 3.71–4.16 (m, 12). Anal. ($C_{19}H_{17}O_6Br$) C, H.

1-Bromo-2,3-methylenedioxy-4,5,6,7-tetramethoxy-9,10-dihydro-9,10-phenanthrenediol (12). A solution of 3.5 g of phenanthrene **11** (8.3 mmol) in dry pyridine (25 ml) was added to a solution of 2.8 g of OsO_4 (11 mmol) in pyridine (25 mL) and the reaction mixture was stored in the dark at room temperature. After 96 h a solution of $NaHSO_3$ (9.5 g) in water (75 mL) was added and the resulting mixture was stirred at ambient temperature for 3 h, diluted with water, and extracted with chloroform. The extracts were washed with diluted HCl, $NaHCO_3$, and saturated NaCl solutions. Solvent removal gave a residue which on chromatography (elution with chloroform) afforded 3.21 g (85%) of **12**: mp 202–204 °C (from chloroform–hexane); NMR (in Me_2SO-d_6) δ 6.88 (s, 1), 6.08 (d, 2). Anal. ($C_{19}H_{19}O_8Br$) C, H.

A red substance which eluted from the column prior to **12** was identified as **13** (128 mg).

1-Bromo-2,3-methylenedioxy-4,5,6,7-tetramethoxyphenanthrenequinone (13). To a solution of **12** (4.55 g, 10 mmol) in dry Me_2SO (70 mL) and dry triethylamine (70 ml) was added pyridine–sulfur trioxide complex[25] in excess (23.8 g, 150 mmol) in 70 mL of dry Me_2SO. After stirring for 1 h at room temperature the reaction mixture was diluted with water and extracted with chloroform. The combined extracts were washed with HCl, $NaHCO_3$, and NaCl solutions. Chromatography (methylene chloride–chloroform) afforded the deep red quinone **13**: 3.9 g (87%); mp 222–224 °C; NMR δ 7.13 (s, 1), 6.18 (s, 2); IR ($CHCl_3$) 1680 cm^{-1}. Anal. ($C_{19}H_{15}O_8Br$) C, H.

2,3-Methylenedioxy-4,5,6,7-tetramethoxy-9,10-diethyl-9,10-phenanthrenediol (14, Mixture of Cis and Trans Isomers). A solution of 1.62 g of **13** (3.6 mmol) in dry benzene (80 mL) was added to a Grignard reagent prepared from 0.96 g of magnesium (40 mg-atoms) and excess ethyl bromide in dry ether (70 mL). After the removal of ether by nitrogen flow, the reaction mixture was refluxed for 2 h (90 °C bath), quenched with saturated NH_4Cl, and extracted with ether–chloroform (4:1). The combined extracts were washed with a saturated NaCl solution and chromatographed (methylene chloride–chloroform). The crystalline mixture of isomers, 1.18 g (76%), was homogeneous on TLC and had mp 65–72 °C; NMR δ 6.89 (br s, 1), 6.80 (br s, 1), 5.82–6.02 (br, 2). Anal. ($C_{23}H_{28}O_8$) C, H.

2,2′-Dipropionyl-4,5-methylenedioxy-4′,5′,6,6′-tetramethoxy-1,1′-biphenyl (15). To a solution of 1.3 g of **14** (3 mmol) in dry benzene (75 mL) and dry pyridine (75 mL) was added 3.1 g (7 mmol) of lead tetraacetate, and the reaction mixture was stirred for 1 h at room temperature, diluted with 500 mL of cold water, and extracted with 4:1 ether–chloroform. The combined extracts were washed with aqueous solutions of HCl, $NaHCO_3$, and NaCl. Removal of solvent and chromatography (hexane–30% ether) afforded 1.1 g of diketone **15** (85%). An analytical sample had mp 90–92 °C (from pentane–ether); NMR δ 7.01 (s, 1), 6.91 (s, 1), 6.07 (s, 2), 3.94 (br s, 6), 3.83 (s, 3), 3.62 (s, 3), 2.60 (q, 4, J = 7 Hz), 0.98 (t, 6, J = 7 Hz); IR ($CHCl_3$) 1676 cm^{-1}. Anal. ($C_{23}H_{26}O_8$) C, H.

2,2′-Bis(α-bromopropionyl)-4,5-methylenedioxy-4′,5′,6,6′-tetramethoxy-1,1′-biphenyl (16). To a stirred solution of 1 g of **15** (2.3 mmol) in dioxane–ether (2:1, 36 mL) was added 820 mg of bromine (5.1 mmol, 10% excess) in dioxane (5 mL) and the mixture was stirred at room temperature for 30 min. After dilution with water the reaction mixture was extracted (4:1 ether–chloroform) and the combined extracts were washed with $NaHCO_3$ and NaCl solutions. The residue was chromatographed (hexane–25% ether) affording 1.26 g (93%) of a crystallizable isomeric mixture (several close spots on TLC): NMR δ 7.25–6.92 (m, 2), 6.06 (br s, 2), 4.58–5.16 (m, 2), 3.55–4.10 (m, 12), 1.50–1.80 (br, 6); IR ($CHCl_3$) 1678 cm^{-1}. Anal. ($C_{23}H_{24}O_8Br_2$) C, H.

6(*RS*),7(*SR*)-6,7-Dihydro-6,7-dimethyl-2,3-methylenedioxy-1,10,11,12-tetramethoxydibenzo[*a*,*c*]cyclooctene-5,8-dione, *RS*-biar (17) and *SR*-biar (18).[26] To a stirred mixture of 588 mg of dibromide **16** (1 mmol), 300 mg of NaI (2 mmol), 336 mg of $NaHCO_3$ (4 mmol), and Zn–Ag couple[27] (3.90 g, 60 mmol) was added dry Me_2SO (150 mL) and dimethoxyethane (50 mL) through a dropping funnel, after evacuation of air and flushing with nitrogen of the oven-dried reaction flask. The stopped flask was efficiently stirred for 40 min at 60 °C (bath). Dilution with cold NH_4Cl solution and extraction (4:1 ether–chloroform) gave, after solvent removal, a residue which consisted mainly of two compounds (TLC). Chromatography (20–30% ether and pentane) resulted in separation of **17** (146 mg) from **18** (149 mg), in order of elution (69% total yield). Recrystallization of **17** (ether–pentane) gave an analytical sample: mp 161 °C; NMR δ 7.18 (s, 1), 6.41 (s, 1), 6.05 (s, 2), 3.48–3.94 (m, 12), 3.34 (dq, 1, J = 7 Hz), 2.51 (dq, 1, J = 7 Hz), 1.20 (d, 3, J = 7 Hz), 0.92 (d, 3, J = 7 Hz); IR ($CHCl_3$) 1704 and 1667 cm^{-1}. Anal. ($C_{23}H_{24}O_8$) C, H.

Diketone **18** had mp 143 °C; NMR δ 7.03 (s, 1), 6.51 (s, 1), 6.03 (s, 2), 3.65–3.92 (m, 12), 3.22 (dq, 1, J = 7 Hz), 2.49 (dq, 1 J = 7 Hz), 1.19 (d, 3, J = 7 Hz), 0.95 (d, 3, J = 7 Hz); IR ($CHCl_3$) 1703, 1668 cm^{-1}. Anal. ($C_{23}H_{24}O_8$) C, H.

6(*RS*),7(*SR*),8(*SR*)-6,7-Dimethyl-6,7,8-trihydro-8-hydroxy-2,3-methylenedioxy-1,10,11,12-tetramethoxydibenzo[*a*,*c*]cyclooct-en-5-one, *RS*-biar (19). To a solution of 100 mg of diketone **17** (0.23 mmol) in acetic acid (15 ml) was added 300 mg of 10% palladium on carbon and the mixture was hydrogenated overnight in a Parr apparatus, at 45–60 psi. The reaction mixture was then filtered, the catalyst washed several times with hot chloroform, and the filtrate neutralized with a 10% NaOH solution and extracted with chloroform. The combined extracts were washed with saturated NaCl solution and evaporated to dryness. Crystallization gave 96 mg (95.5%) of **19**. An analytical sample (from chloroform–hexane) had mp 198–200 °C; NMR δ 6.93 (s, 1), 6.34 (s, 1), 6.01 (s, 2), 3.57–3.90 (m, 12), 1.12 (d, 3, J = 7 Hz), 0.70 (d, 3, J = 7 Hz); IR ($CHCl_3$) 1703 cm^{-1}. Anal. ($C_{23}H_{26}O_8$) C, H.

Preparation of Mesylate 20. To a cooled solution of 50 mg of **19** (0.12 mmol) in 1.5 mL of dry pyridine (ice bath) was added 230 mg of methanesulfonyl chloride (2 mmol). After 3 h at 5–10 °C the reaction mixture was diluted with cold water and extracted (4:1 ether–chloroform). The combined extracts were washed with aqueous solutions of HCl and NaHCO and a saturated solution of NaCl. Removal of solvent at reduced pressure without excessive heating, gave a residue which crystallized by addition of pentane and ether (49 mg, 83%). An analytical sample had mp 131–132 °C; NMR δ 6.75 (s, 1), 6.37 (s, 1), 6.05 (s, 2), 5.61 (br s, 1). Anal. ($C_{24}H_{28}O_{10}S$) C, H.

Preparation of Ketone 21. To a solution of 50 mg of mesylate **20** (0.1 mmol) in absolute methanol (10 mL) was added NaOMe (100 mg) and palladium on carbon (200 mg) and the mixture was stirred under hydrogen at atmospheric pressure. After 3 h the conversion was usually completed (TLC),[28] the catalyst was filtered, and the filtrate was diluted with water and extracted ether–chloroform (4:1). The organic layer was washed with NaCl solution, dried, and concentrated to dryness affording a crystalline residue (36 mg, 88%). An analytical sample (from pentane–ether) had mp 159 °C; NMR δ 6.45 (s, 1), 6.36 (s, 1), 6.03 (s, 2), 1.07 (d, 3, J = 7 Hz), 0.84 (d, 3, J = 7 Hz); IR ($CHCl_3$) 1704 cm^{-1}. Anal. ($C_{23}H_{26}O_7$) C, H.

Preparation of Alcohol 22. A solution of 20 mg (0.05 mmol) of ketone **21** in dry THF (3 ml) was added to a suspension of $LiAlH_4$ in excess (20 mg) in THF (3 mL) and the mixture was stirred for 1 h at room temperature. Usual workup gave, after chromatographic purification (pentane and 25% ether), the alcohol **22** (19 mg, 95%). An analytical sample had mp 143 °C; NMR δ 6.60 (s, 1), 6.36 (s, 1), 6.00 (br s, 2), 4.62 (br, 1), 2.66 (d, 2, J = 4 Hz), 1.81–2.14 (br, 2), 1.17 (d, 3, J = 7 Hz), 0.96 (d, 3, J = 7 Hz). Anal. ($C_{23}H_{28}O_7$) C, H.

(±)-Kadsurin (1). The alcohol **22** (15 mg) was dissolved in acetic anhydride (1 mL) to which a few crystals of *p*-toluenesulfonic acid were added. After 3 h at room temperature the solution was diluted with cold water and extracted with chloroform. The organic layer was washed with $NaHCO_3$ and NaCl solutions. Removal of solvent gave the crude product (15 mg, 95%), which was crystallized from pentane–ether. An analytical sample had mp 158 °C; NMR, IR, UV, and mass spectra were identical with those for natural kadsurin.[1,20]

The Reaction of Mesylate 20 with Lithium Triethylborohydride. To a stirred solution of 30 mg of **20** (0.06 mmol) in dry THF (3 mL) under argon, was added 0.2 mL of a 1 M solutiom of lithium trieth-

ylborohydride in THF, via a rubber septum. After the mixture was stirred for 45 min at room temperature, 1 mL of water was added and stirring was continued for 10 min. A mixture of 1 mL of 3 N NaOH and 1 mL of 30% H_2O_2 was then added and the reaction mixture was stirred for an additional hour. Dilution with water was followed by extraction (4:1 ether–chloroform) and washing of the organic layer with saturated NaCl solution. Removal of solvents gave a residue (several spots in TLC) which was chromatographed (pentane and 20–50% ether). From the less polar fraction (13 mg) the alcohol **22** and an additional compound which has the assumed structure **27**, mp 171–172 °C, could be separated: NMR δ 6.45 (s, 1), 6.35 (s, 1), 5.98 (s, 2), 4.97 (s, 1), 4.33 (br, 1), 1.10 (s, 3), 1.02 (s, 3); mass spectrum *m/e* 414 (M^+). The gross structure of **27** was proven by hydrogenation in a Parr apparatus (50 psi) of 8 mg of **27** in 6 mL of acetic acid to which a few crystals of *p*-toluenesulfonic acid and 50 mg of 10% palladium on carbon were added. The crude product, which exhibited acetate groups, was treated with $LiAlH_4$ in THF at room temperature (1 h). Workup in the usual manner gave a polar product which was oxidized without purification with the Jones reagent[29] in acetone solution (5 mL). Dilution with water, extraction with ether, and removal of solvent gave a mixture of **17** and **18** (TLC and ^1H NMR).

The last polar chromatographic fraction (7 mg) was not entirely purified; mass spectrum *m/e* 432 (M^+) agrees with the structure of a 5,8-diol. Jones oxidation[29] converted this product to **17.**

6(*RS*),7(*SR*),8(*SR*)-6,7-Dimethyl-6,7,8-trihydro-8-hydroxy-2,3-methylenedioxy-1,10,11,12-tetramethoxydibenzo[*a*,*c*]cyclooctene-5-one, *SR*-biar (23).[26] To a cooled solution of 600 mg of $LiAlH(t\text{-}BuO)_3$ (2.3 mmol) in dry THF (6 mL) was added 100 mg of the diketone **18** (0.23 mmol) in THF (6 mL). After stirring for 2 h at 0 °C, the excess reagent was decomposed with a saturated solution of Na_2SO_4, dry Na_2SO_4 was added, and the mixture was filtered. Removal of solvent and chromatography (pentane and 40% ether) gave an amorphous product, homogeneous on TLC (86 mg); NMR δ 7.48 (s, 1), 6.46 (s, 1), 6.05 (s, 2), 3.91 (s, 6), 3.78 (s, 3), 3.57 (s, 3), 1.02 (d, 3, J = 7 Hz), 0.93 (d, 3, J = 7 Hz); IR ($CHCl_3$) 1667 cm^{-1}. Anal. ($C_{23}H_{26}O_8$) C, H.

Preparation of Hydroxy Ketone 24. The diketone **17** (50 mg) in 4 mL of dry THF was reduced with $LiAlH(t\text{-}BuO)_3$ and worked up under the same conditions as those used for the preparation of **23.** Compound **24** (42 mg, 85%) had mp 184–185 °C (from pentane–ether); NMR δ 7.62 (s, 1), 6.39 (s, 1), 6.04 (s, 2), 4.78 (br, 1), 3.52–3.96 (m, 12), 1.03 (d, 3, J = 7 Hz), 0.93 (d, 3, J = 7 Hz); IR ($CHCl_3$) 1668 cm^{-1}. Anal. ($C_{23}H_{26}O_8$) C, H.

Preparation of Hydroxy Ketone 25. The diketone **18** (40 mg) was hydrogenated over palladium on carbon in acetic acid solution overnight and worked up under the same conditions as those used for the preparation of **19.** The compound **25** (38 mg, 95%) had mp 180–181 °C (from chloroform–hexane); NMR δ 6.83 (s, 1), 6.38 (s, 1), 5.97 (s, 2), 4.83 (br s, 1), 3.34–3.91 (m, 12), 1.25 (d, 3, J = 7 Hz), 1.17 (d, 3, J = 7 Hz); IR ($CHCl_3$) 1703 cm^{-1}. Anal. ($C_{23}H_{26}O_8$) C, H.

Thermal Isomerizations. Pure diketones **17** and **18** (10–20 mg) were submitted separately to heating at 160 °C (constant-temperature oil bath) under argon. The amount of conversion from **17** to **18** and from **18** to **17,** after 20 and 30 h, was determined by ^1H NMR integration of signals. Darkening and partial decomposition was observed when the diketones were heated for periods longer than 30 h. Similar amounts of pure hydroxy ketones **23** and **24** were heated in the same manner. After 30 h the products (**19** and **25**, respectively) were obtained by crystallization on trituration with pentane, after cooling (90–95% recovery).

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