Edelhoch[35] based on optical density measurements performed at 280 and 288 nm. The mass spectra of the peptides were recorded on the spectrometer operating with a FAB ion source, at +8 kV in the positive mode. Mass spectrum data are in accordance with calculated molecular weights (Table I).

(d) Binding Assays. Crude membrane fractions were prepared from brains of male Wistar rats and from cerebellums of guinea pigs as described by Meunier et al.[36] Conditions of equilibrium binding experiment, composition of the coktail of peptidase inhibitors, and determination of nonspecific binding were identical to the assay procedure described by Gairin et al.[10]

K_I values were calculated from the Cheng and Prusoff's equation[37] using 1.6, 1.9, and 0.07 nM for the K_D's of tritiated DAGO, DSLET, and bremazocine, respectively.

(e) Biological Assays. Myenteric plexus–longitudinal muscles of the guinea pig ileum were prepared according to the procedure of Gyang and Kosterlitz,[38] hamster vas deferens preparations were made according to McKnight et al.[27]; and rabbit vas deferens was prepared as described by Oka et al.[28] The tissues were suspended in a 10-mL siliconized organ bath containing Kreb's solution, heated at 37 °C and oxygenated with 95:5 O_2–CO_2. Peptidase inhibitors were added to the bathing solutions according to McKnight et al.[29]

All compounds were tested (i) for agonist activity by application of cumulative concentrations of each peptide (from 10^{-10} to 10^{-5} M) into the bath and (ii) for antagonism by introducing the compound in the bath at least 10 min before testing dynorphin A. In the test for antagonism, the concentration of the peptides used was chosen so that the height of the twitch was depressed by 20–40% as described by Kosterlitz and Watt.[39]

Potencies of the agonists were assessed by measuring IC_{50} values (concentration of the peptide inhibiting 50% of the response). Activities of the antagonists were expressed in terms of K_e (concentration of the peptide that is able to reduce the effect of a double dose of dynorphin A to that of a single dose). Concentrations of dynorphin A and its analogues are expressed in nanomolar.

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Registry No. 1, 79985-34-5; **2**, 94596-26-6; **3**, 102831-32-3; **4**, 102851-34-3; **5**, 102831-31-2; **6**, 102851-33-2; **7**, 102851-32-1; **8**, 102831-30-1.

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Conformation and Activity of Tetrahydrofuran Lignans and Analogues as Specific Platelet Activating Factor Antagonists

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The six (racemic or meso) isomers of 3,4-dimethyl-2,5-bis(3,4-dimethoxyphenyl)tetrahydrofuran and four corresponding desmethyl analogues were prepared and assayed as inhibitors of platelet activating factor (PAF) receptor binding to rabbit platelet plasma membranes. The inhibition by these isomers is stereodependent and varies with the gross shape of the molecules as determined by the molecular mechanics program MM2. The most potent PAF antagonist in this group of compounds is *trans*-2,5-bis(3,4,5-trimethoxyphenyl)tetrahydrofuran (L-652,731, 14) with an IC_{50} of 0.02 μM.

Platelet activating factor (PAF) is a highly potent phospholipid with a chemical structure of 1-*O*-hexadecyl/octadecyl-2-*O*-acetyl-*sn*-glyceryl-3-phosphorylcholine.[1-3] Earlier,[4] an antigen-induced histamine release from rabbit platelets was described. However, the existence of a mediator was not indicated. Platelet activating factor has been linked to various biological activities and pathways, making it one of the important mediators of physiological processes including aggregation and degranulation of platelets[5] and neutrophils, inflammation, and allergic reactions.[6] Platelet activating factor is also reported to be an endogenous hypotensive,[7] chemotactic,[8] and tumor-cytotoxic[9] agent. A specific PAF receptor site in rabbit plasma membranes[10] and human platelets[11] has also been identified and reported.

3,4-Dimethyl-2,5-bis(3,4-dimethoxyphenyl)tetrahydrofurans belong to a well-recognized subgroup of natural

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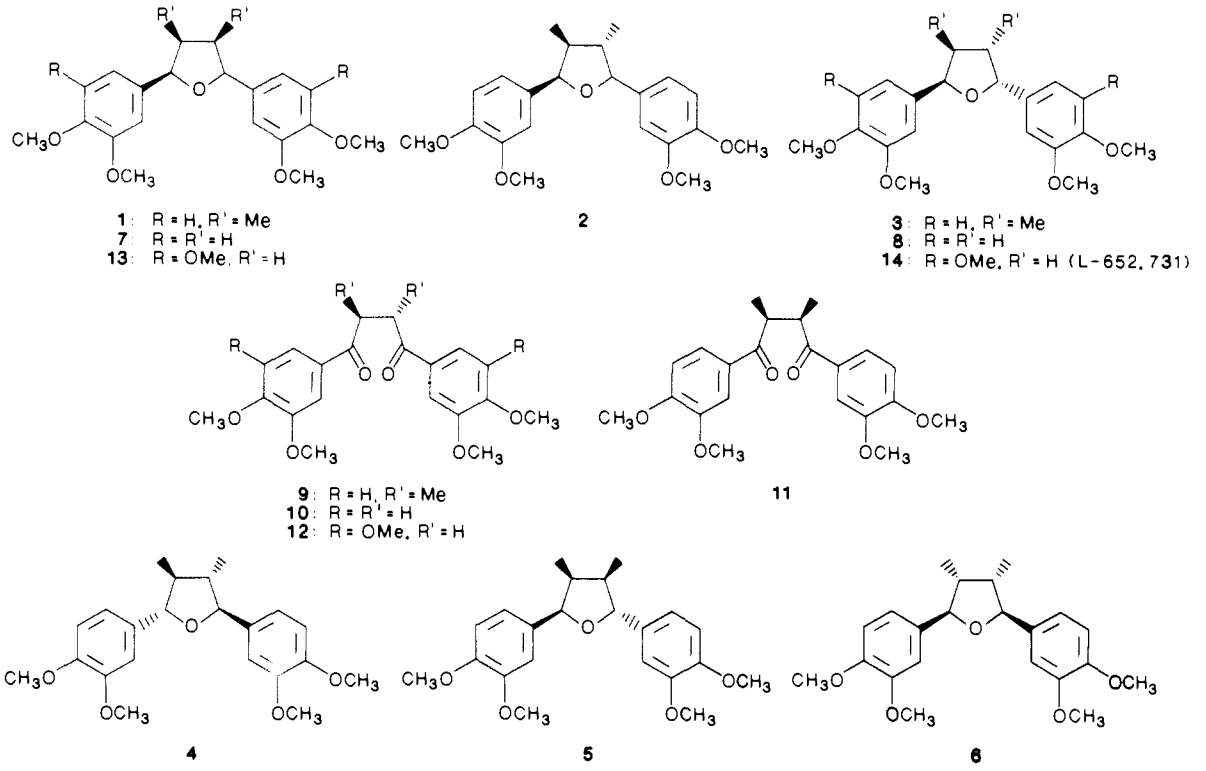
Chart I



products known as lignans. These tetrahydrofuran lignans may exist in six stereoisomeric forms **1–6** (Chart I). These are tetrahydrofuroguaicin B dimethyl ether (**1**),[12-14] veraguensin (**2**),[16-18] saucerneol (**3**),[21] galbelgin (**4**),[18-20] **5** (not reported previously in the literature), and galgravin (**6**).[13-15] Synthetic (±)-veraguensin[18] obtained from the author's previous academic work was found to inhibit PAF binding to platelets. Encouraged by this result, the other five isomers of veraguensin were prepared for further evaluation. In this paper we report the synthesis of these six isomers and the corresponding cis and trans desmethyl analogues **7**, **8**, **13**, and **14**. We also report the conformations of these molecules and their activity as PAF antagonists in rabbit plasma membrane preparations.

Chemistry. The six stereoisomers of 3,4-dimethyl-2,5-bis(3,4-dimethoxyphenyl)tetrahydrofuran **1–6** have been prepared by using new or modified literature procedures.

The dibenzoylbutane intermediates **9** and **11** were made according to previously described methods.[14] The dibenzoylethane derivatives **10** and **12** were made conveniently by the oxidative coupling of 3,4-dimethoxyacetophenone and 3,4,5-trimethoxyacetophenone. Reduction of the 1,4 diketones **9–12** followed by appropriate dehydration gave the tetrahydrofurans **1–8**, **13**, and **14**.

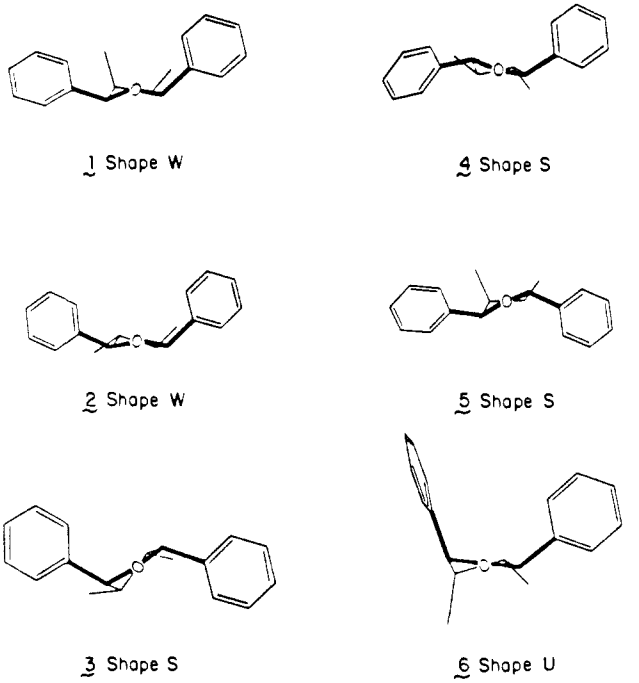


Figure 1. Shapes of MM2-optimized 2,5-diaryltetrahydrofurans.

Conformational Shape. The lowest energy conformations of isomers **1–6** were obtained by using the molecular mechanics program MM2.[22] Several alternative conformations were explored in each case also.

X-ray Crystal Structure Analysis of 7. Suitable crystals of **7** ($C_{20}H_{24}O_5$) for X-ray diffraction studies formed from ether/hexane mixtures with space group

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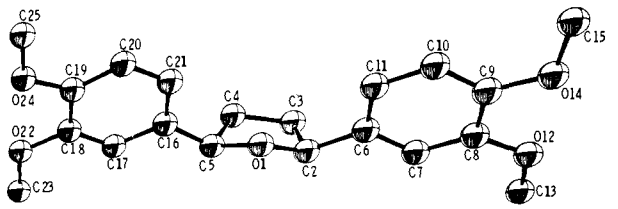

Figure 2.

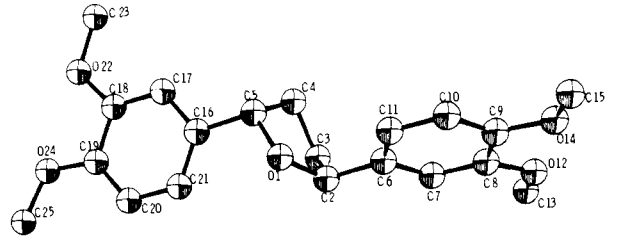

Figure 3.

symmetry of $P2_1/c$ and cell constants of a = 9.603 (2) Å, b = 6.420 (1) Å, c = 30.160 (5) Å, and β = 97.96 (1)° for Z = 4 and a calculated density of 1.242 g/cm^3. Of the 2480 reflections measured with an automatic four-circle diffractometer equipped with Cu radiation, 1975 were observed ($I \geq 3\sigma(I)$). The structure was solved with a multisolution tangent formula approach and difference Fourier analysis and refined with use of full-matrix least-squares techniques.[23] Hydrogens were assigned isotropic temperature factors corresponding to their attached atoms. The function $\sum w(|F_o| - |F_c|)^2$ with $w = 1/(\sigma(F_o))^2$ was minimized to give an unweighted residual of 0.072. No abnormally short intermolecular contacts were noted. Tables II, III, and IV containing the final fractional coordinates, temperature parameters, bond distances, and bond angles are available as supplementary material. Figure 2 is a computer-generated perspective drawing of **7** from the final X-ray coordinates showing its conformation.

X-ray Crystal Structure Analysis of 8. Suitable crystals of **8** ($C_{20}H_{24}O_5$) for X-ray diffraction studies formed from methylene chloride with space group symmetry of $P1$ and cell constants of a = 9.911 (1) Å, b = 14.733 (3) Å, c = 6.101 (2) Å, α = 90.65 (2)°, β = 90.14 (1)°, and γ = 81.74 (1)° for Z = 2 and a calculated density of 1.297 g/cm^3. Of the 2379 reflections measured with an automatic four-circle diffractometer equipped with Cu radiation, 2096 were observed ($I \geq 3\sigma(I)$). The structure was solved by the techniques described for **7** and refined to an unweighted residual of 0.042. No abnormally short intermolecular contacts were noted. Tables V–VII containing the final fractional coordinates, temperatue parameters, bond distances, and bond angles are available as supplementary material. Figure 3 is a computer-generated perspective drawing of **8** from the final X-ray coordinates showing its conformation.

Biological Methods

The inhibitory effects of compounds 1–14 on the specific binding of tritiated PAF with its receptor on isolated rabbit platelet plasma membranes were investigated as follows.[24]

Purification of Rabbit Plasma Membranes. Fresh rabbit blood (400–600 mL) was collected from abdominal artery after peritoneal incision or from ear artery into ACD (1.175 g of sodium citrate, 0.685 g of citric acid, and 1.0 g dextrose per 50 mL of water) solution. Platelet-rich plasma was prepared by centrifugation at 270g for 10 min. The plasma was separated from platelets by centrifuging the platelet-rich plasma on ficoll-paque (Pharmacia Fine Chemicals, Piscataway, NY) according to the procedure described by Pinckard et al.[25] The platelets banded between the plasma and ficoll layers were carefully collected and resuspended in 150 mM NaCl, 10 mM Tris, pH 7.5, and 1 mM EDTA. The platelets were sedimented to the bottom of the tube by centrifugation at 1000g at 4 °C for 10 min. The platelet pellets were resuspended in 5 mM $MgCl_2$, 10 mM Tris, pH 7.0, and 2 mM EDTA to a final volume of about 30 mL. The platelet suspension was divided into three portions, 10 mL each, and quickly frozen with liquid nitrogen and thawed slowly at room temperature. The freezing and thawing procedure was repeated at least three times. For isolation of the plasma membrane fraction, the lysed platelet suspension was layered on top of a discontinuous sucrose density gradient of 12% (w/v) and 27% (w/v) sucrose in the three tubes of the SW27 rotor of a Beckman Model L8-70 ultracentrifuge and centrifuged at 63 500g for 5 h. Unbroken platelets, granules, and other debris sedimented to the bottoms of the tubes, while the membrane fractions banding between 12% and 27% were carefully collected and stored at −80 °C. The isolated membranes were used within 2 weeks, and no changes on the PAF binding have been observed.

Inhibition of PAF-Receptor Binding. The tritium-labeled PAF (1-*O*-[1,2-$^3H_2$]alkyl-2-*O*-acetyl-*sn*-glycero-3-phosphocholine) was purchased from New England Nuclear with a specific activity of 45 Ci/mmol. Unlabeled C_{16}-PAF (1-*O*-hexadecyl-2-*O*-acetyl-*sn*-glycero-3-phosphocholine) was obtained from Bachem (Torrance, CA). NMR and mass spectroscopic data indicated that the purity of C_{16}-PAF was higher than 99%, and it was used without further purification. The inhibition of [^{3}H]PAF (purchased from New England Nuclear) binding to rabbit platelet plasma membranes was carried out by a filtration technique using a constant amount of radioactivity (1 pmol per tube) and varying concentrations of compounds 1–14. Platelet plasma membranes (100 μg) were added to a final milliliter of solution containing 1 pmol of [^{3}H]PAF and a known amount of tetrahydrofurans 1–8, 13, and 14 in a medium containing 10 mM $MgCl_2$ and 10 mM Tris 0.25% BSA, pH 7.0 (solution A) at 0 °C. After incubation at 0 °C for 1–2 h, the mixture was filtered through a Whatman GF/C glass fiber filter under vacuum. Each tube was sequentially rapidly washed with a total of 20 mL of ice-cold solution A. No stimulation or inhibition of radiolabeled PAF was found with the addition of 2 mM $CaCl_2$; therefore, Ca^{2+} was not added in the assay even though Ca^{2+} will potentiate the PAF-induced platelet aggregation. No [^{3}H]PAF degradation was found by monitoring radiogram of thin-layer chromatograph of the filter-bound materials even after 1–2-h incubation at 0 °C. The membranes prepared consistently showed greater than 80% specific PAF-receptor binding. The percent inhibition of PAF-receptor binding was expressed as

$$\% \text{ inhibition} = \frac{\text{total binding} - \text{total binding with drug}}{\text{specific binding}} \times 100\%$$

(23) The following library of crystallographic programs was used: MULTAN 80, P. Main et al., University of York, York, England, 1980; ORTEP-II, C. K. Johnson, Oak Ridge National Laboratory, Oak Ridge, TN 1970; SDP+V1.1, Y. Okaya et al., B. A. Frenz and Associates, College Station, Tx, 1984.

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Table I. PAF Receptor Binding Inhibition of 2,5-Diaryltetrahydrofuran Analogues

no.	formula	mp, °C	anal.	shape of low-energy conformation	PAF receptor inhibn: IC_{50}, μM
1	$C_{22}H_{28}O_5$	130–131	C, H	W	0.2
2	$C_{22}H_{28}O_5$	121–122	C, H	W	1.1
3	$C_{22}H_{28}O_5$		C, H	S	4.5
4	$C_{22}H_{28}O_5$	126–127	C, H	S	4.5
5	$C_{22}H_{28}O_5$		C, H	S	1.1
6	$C_{22}H_{28}O_5$	120–121	C, H	U	4.5
7	$C_{20}H_{24}O_5$	95–96	C, H		>3
8	$C_{20}H_{24}O_5$	114–115	C, H		0.5
13	$C_{22}H_{28}O_7$	129–130	C, H		15.0
14	$C_{22}H_{28}O_7$	140–141	C, H		0.02

where total binding was defined as the total amount of [^{3}H]PAF bound after separation of the free and bound ligands in the absence of compounds 1–14 and unlabeled PAF. Specific binding was total binding minus the nonspecific binding. The nonspecific binding was measured as the total binding of [^{3}H]PAF in the presence of excess unlabeled PAF (1 μM). The nonspecific binding cannot be further displaced with higher concentration of C_{16}-PAF or with additional PAF antagonists 1–14.

Results and Discussion

As shown in Table I, the inhibition of PAF binding to its receptor by the isomers **1–6** is stereodependent.

Geometry-optimized structures of the six isomers **1–6** are shown in Figure 1. The X-ray structures of **7** and **8** are shown in Figures 2 and 3. The spatial arrangements of the Ar–C–O–C–Ar fragment have three distinct shapes that resemble the letters W, S, and U. As the shape changes from W (isomers 1 and **2**) to S (isomers **3–5**) to U (isomer **6**), the activity falls from an IC_{50} of 0.2 μM for 1 to 4.5 μM for **6** (Table I). Despite the cis relationship of the 2,5-diaryl groups in isomers 1 and **6**, there exists a 22.5-fold difference in activity between them. Comparison of the activities of **1**, **2**, and **6** (cis diphenyl compounds with 0, 1, and 2 methyl substituents trans to the phenyl groups) demonstrates that hydrocarbon bulk cannot be tolerated when placed trans to the aryl groups. In addition to the shape variation in structures **1–6**, we believe that the 3,4-dimethyl substituents cause steric interactions that result in loss of activity. The two phenyl groups and the oxygen of the tetrahydrofuran in compounds 1 and **8** were superimposed on the computer and matched well with the low-energy conformation of **1**.

The most potent compound among the 10 compounds tested is *trans*-2,5-bis(3,4,5-trimethoxyphenyl)tetrahydrofuran (**14**) with an IC_{50} of 0.02 μM. At a cellular level, *trans*-2,5-bis(3,4,5-trimethoxyphenyl)tetrahydrofuran (**14**) inhibited PAF (10^{-9} M) induced aggregation of gel-filtered rabbit platelets[10] with an IC_{50} of 1.1×10^{-7} M. The corresponding cis isomer **13** was completely inactive at this level. The aggregation was monitored by turbidity changes with a Model 400 Chrono-Log-Aggregometer (Havertown, PA). No significant inhibition (0–4%) by compound **14** (2.9–29 μM) was detected on the binding of [^{3}H]leukotriene D_4 to leukotriene D_4 receptors[26] on guinea pig lung membrane preparation, [^{3}H]pyrilamine to H_1 receptors[27] on guinea pig brain membranes, [^{3}H]diazepam to rat cerebral cortex membranes,[28] and [^{3}H]nitredipine to calcium channel membrane preparations[29] from bovine ventricles.

The receptor binding activity and the cellular and tissue responses of several analogues of **14** will be discussed in a separate paper.

Experimental Section

Melting points were determined on a Thomas-Hoover melting point apparatus and are uncorrected. The NMR spectra were taken on a Varian XL-100 or T-60 spectrophotometer, using tetramethylsilane as the internal reference. Mass spectra were obtained on a Finnigan Model 731 spectrophotometer. X-ray diffraction data were collected on an Enraf-Nonius CAD-4 diffractometer. Elemental analyses were performed by Research and Development Labs of Merck & Co., Inc., Rahway, NJ.

***all-cis*-3,4-Dimethyl-2,5-bis(3,4-dimethoxyphenyl)tetrahydrofuran (1).** One gram of the racemic diketone **9** dissolved in 4 mL of methylene chloride was refluxed with 5 mL of 5% HCl in methanol for 15 min. The mixture was cooled, and the crystalline crop of 3,4-dimethyl-2,5-bis(3,4-dimethoxyphenyl)furan was recovered by filtration: mp 169–170 °C; yield 0.75 g. This furan (0.3 g) in 20 mL of acetic acid and 3 g of 10% Pd/C was stirred over H_2 until 2 equiv of hydrogen was taken up, and workup followed by crystallization from ether–chloroform (few drops) gave 0.22 g of the *all-cis*-3,4-dimethyl-2,5-bis(3,4-dimethoxyphenyl)tetrahydrofuran: mp 130–131 °C; NMR ($CDCl_3$) δ 0.62 (d, 6 H, C-3 and C-4 Me, J = 7 Hz), 3.88 and 3.90 (s, 6 H each, Ar OMe), 5.15 (d, 2 H, H-2 and H-5, J = 7 Hz), 7.0–7.17 (m, 6 H, Ar H).

Veraguensin (2). Seven grams of racemic diketone **9** was dissolved in 200 mL of acetic acid, treated with 1.5 g of 10% Pd/C, and hydrogenated at 40 psi overnight. An additional 1.5 g of 10% Pd/C was then added, and shaking under H_2 was continued for 4 h. Filtration, evaporation, and chromatography on silica gel gave 2.8 g of crystalline **2** when eluted with ethyl acetate/hexane (40:60): mp 121–122 °C; NMR ($CDCl_3$) δ 0.67 (d, 3 H, 4-Me, J = 6.6 Hz), 1.07 (d, 3 H, 3-Me, J = 6.2 Hz), 1.6–2.5 (m, 2 H, 3-H, 4-H), 3.85, 3.87, 3.88, and 3.90 (s, each 3 H, OMe), 4.44 (d, 1 H, 2-H, J = 8.6 Hz), 5.13 (d, 1 H, 5-H, J = 8.1 Hz), 6.87–7.11 (m, 6 H, Ar H).

Saucerneol (3). The racemic diketone **9** was reduced with lithium aluminum hydride, and 1 g of the resulting diol and 0.35 g of triethylamine in 20 mL of methylene chloride were treated with 0.8 g of methanesulfonyl chloride. After 3 h of stirring, the mixture was treated with 100 mL of ether, and the organic layer was washed with 1 N HCl, 5% NaOH, and distilled water. Drying (Na_2SO_4) and evaporation gave 0.4 g of a mixture from which component **3** was recovered by HPLC: NMR ($CDCl_3$) δ 1.05 (d, 6 H, 2 × CH_3, J = 7.1 Hz), 2–2.5 (m, 2 H, 3-H, 4-H), 3.86 (s, 12 H, 4 × OCH_3), 5.47 (d, 2 H, 2-H, 5-H, J = 8.2 Hz), 6.8 (s, 6 H, Ar H).

Galbelgin (4). One gram of the diol obtained by LAH reduction of **9** and 0.4 g of 10% Pd/C in 40 mL of acetic acid was stirred over 40 psi of hydrogen. Workup followed by crystallization from hexane/ether gave 320 mg of **4**: mp 126–127 °C; NMR ($CDCl_3$) δ 1.05 (d, 6 H, 2 × CH_3, J = 6.3 Hz), 1.80 (m, 2 H, 3-H, 4-H), 3.87 and 3.90 (each s, 6 H, 2 × OMe), 4.67 (d, 2 H, 2-H, 5-H, J = 9.3 Hz), 6.90–7.03 (m, 6 H, Ar H).

Tetrahydrofuran 5. Hydrogenation of 150 mg of racemic 2,3-bis(3,4-dimethoxyphenyl)-1,4-butanediol prepared from LAH reduction of the meso diketone **11** and subsequent separation by HPLC (Waters Partisil-10 column eluted with ethyl acetate/hexane 25:75) gave tetrahydrofuran **5** as a colorless viscous oil:

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NMR ($CDCl_3$) δ 0.64 (d, 3 H, CH_3, J = 7.0 Hz), 1.03 (d, 3 H, CH_3, J = 6.0 Hz), 2.36–2.56 (m, 2 H, 3-H and 4-H), 3.92 (s, 6 H, 2 × OCH_3), 3.93 and 3.94 (s, 3 H each, OCH_3), 6.49 (d, 1 H, 2-H, J = 8.8), 5.49 (d, 1 H, 5-H, J = 4.0), 6.8–7.0 (6 H, Ar H).

Galgravin (6). The meso diketone 11 was reduced with lithium aluminum hydride and cyclized with methanesulfonyl chloride as shown in the previous cases to give 38 mg of the major component **6** by crystallization from hexane: mp 120–121 °C; NMR ($CDCl_3$) δ 1.02 (d, 6 H, J = 6.4 Hz, 2 × CH_3), 3.90 (s, 12 H, 4 × OCH_3), 4.52 (d, 2 H, 2-H, 5-H, J = 6.0 Hz).

1,2-Bis(3,4-dimethoxybenzoyl)ethane (10). In a 500-mL flask equipped with a stirrer and N_2, lithium diisopropylamide (LDA) was prepared from 20 mL of THF, 10.1 g of diisopropylamine, and 62 mL of 1.7 M n-butyllithium at −10 °C. The temperature was dropped to −40 °C, and then 18 g of 3,4-dimethoxyacetophenone in 40 mL of THF was added. After 1 h, 13 g of anhydrous $CuCl_2$ in 150 mL of DMF was added, and stirring was continued overnight.

Hydrochloric acid (500 mL, 1 N) was added, and the resulting precipitate was collected by filtration. The precipitate was dissolved in methylene chloride and filtered through a bed of silica gel. Evaporation followed by crystallization from ethyl acetate gave 4.5 g of 1,2-bis(3,4-dimethoxybenzoyl)ethane (**10**): mp 181–182 °C; NMR ($CDCl_3$) δ 3.40 (s, 4 H, CCH_2CH_2C), 3.92 (s, 12 H, 4 × OCH_3), 6.8–7.74 (6 H, Ar H).

2,5-Bis(3,4-dimethoxyphenyl)tetrahydrofurans 7 and 8. 1,2-Bis(3,4-dimethoxybenzoyl)ethane (3.0 g) was reduced with 350 mg of lithium aluminum hydride in 50 mL of THF at 0 °C for 1 h and ambient temperature for 3 h. After the usual workup, 2.8 g of the white solid diol was recovered and dissolved in 50 mL of methylene chloride. The solution at 0 °C was treated with 1.2 g of triethylamine followed by 1.2 g of methanesulfonyl chloride and stirred under N_2 until the starting diol disappeared as indicated by TLC. At this point, 200 mL of ether was added and the organic layer was washed with water, 3 N HCl, 10% NaOH, and water and dried over anhydrous sodium sulfate. The residue obtained by evaporation was chromatographed to recover the major spot (silica gel, ethyl acetate/hexane 30:70). Crystallization from 50 mL of methylene chloride and 100 mL of hexane evaporated to a final volume of 100 mL gave 0.6 g of *trans*-2,5-bis(3,4-dimethoxyphenyl)tetrahydrofuran (**8**): mp 114–115 °C; NMR ($CDCl_3$) δ 1.9–2.5 (m, 4 H, 3-H, 4-H), 3.85 and 3.90 (each s, 6 H, 2 × OCH_3), 5.24 (t, 2 H, 2-H, 5-H, J = 6.6 Hz), 6.8–7.0 (m, 6 H, Ar H). The second and third crops gave 1.1 g of crystalline product that contained a mixture of cis and trans isomers. Separation of the isomers was made on a Partisil-10 HPLC column using hexane (80%)/ethyl acetate (20%) as eluting solvent, to yield 0.8 g of the cis isomer **7**: mp 92–96 °C; NMR ($CDCl_3$) δ 1.9–2.5 (m, 4 H, 3-H, 4-H), 3.88 and 3.83 (each s, 6 H, 2 × OCH_3), 5.04 (t, 2 H, J 6.7 Hz, 2-H, 5-H), 6.8–7.0 (m, 6 H, Ar H). The separation also yielded 0.3 g of the trans isomer.

1,2-Bis(3,4,5-trimethoxybenzoyl)ethane (12). In a 2-L flask equipped with a stirrer and nitrogen, LDA was prepared from 60 mL of tetrahydrofuran, 30.3 g of diisopropylamine, and 115 mL of 2.1 M n-butyllithium at −10 °C. The temperature was dropped to −70 °C, and then 63 g of 3,4,5-trimethoxyacetophenone in 170 mL of tetrahydrofuran was added. After 2 h, 39 g of anhydrous cupric chloride in 450 mL of dimethyl formamide was added, and stirring was continued for two more hours.

To the reaction mixture was added 1500 mL of 1 N hydrochloric acid, and the precipitate formed was collected by filtration. The precipitate was then washed successively with water, methanol, and ether to give 31 g of the diketone **12** as off white solid, mp 189–190 °C.

***trans*- and *cis*-2,5-Bis(3,4,5-trimethoxyphenyl)tetrahydrofurans 14 and 13.** The above diketone **12** (5.0 g) was reduced in 50 mL of THF with 0.9 g of lithium aluminum hydride at 0 °C. To work up, 4 mL of ethyl acetate followed by 50 mL of methylene chloride and 10 mL of 5% sodium hydroxide solution was added. The slurry was stirred at room temperature for 30 min and filtered. The filtrate was washed with water, dried (sodium sulfate), mixed with an equal volume of hexane, and evaporated to half its volume to yield 4.2 g of the 1,4-diol (mp 127–130 °C).

This diol was dissolved in 40 mL of chloroform and treated with 40 mL of 10% (v/v) trifluoroacetic acid in chloroform at room temperature. After 0.5 h, the organic layer was washed with 5% sodium hydroxide, dried (anhydrous sodium sulfate), and evaporated. The residue was chromatographed (as shown for **7** and **8**) to yield the front-running trans isomer (2.1 g; mp 140–141 °C; NMR ($CDCl_3$) δ 1.8–2.5 (m, 4 H, 3-H and 4-H), 3.85 (s, 12 H, 4 × OCH_3), 3.90 (s, 6 H, 2 × OCH_3), 5.22 (t, 2 H, 2-H, 5-H, J = 6.7 Hz), 6.66 (s, 4 H, Ar H)) and the cis isomer (0.9 g; mp 129–130 °C; NMR ($CDCl_3$) δ 1.85–2.6 (m, 4 H, 3-H and 4-H), 3.85 (s, 12 H, 4 × OCH_3), 3.90 (s, 6 H, 2 × OCH_3), 5.04 (t, 2 H, 2-H and 5-H, J = 6.8 Hz), 6.68 (s, 4 H, Ar H)).

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Supplementary Material Available: Tables II–VII containing the final fractional coordinates, temperature parameters, bond distances, and bond angles of structures **7** and **8** are available as supplementary material (8 pages). Ordering information is given on any current masthead page.