Synthesis of Lignans. I. Nordihydroguaiaretic Acid[1]

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The novel alkylation of the sodium enolate of propioveratrone (4) with α-bromopropioveratrone (5) in liquid ammonia gave the racemic diketone 9. A mechanism for the stereoselectivity of this alkylation is proposed and the structural requirements of the reaction are discussed. Cyclodehydration of 9 to the furan 8 followed by hydrogenation *via* the all-cis tetrahydrofuran 25 afforded nordihydroguaiaretic acid (NDGA) tetramethyl ether (2). A pronounced solvent effect on the hydrogenation was observed. Demethylation of 2 with concentrated hydrobromic acid afforded NDGA (1) in good yield and high purity. An alternate route to 2 *via* the alcohol 28 is also described.

Nordihydroguaiaretic acid (1), more commonly known as NDGA, is a phenolic lignan found in the resinous exudates of many plants, especially *Larrea divaricata*, the creosote bush of the southwestern United States.[2] Its structure was established by synthesis,[3] and there was strong chemical evidence[4] that the naturally occurring optically inactive NDGA was the meso rather than the racemic form.

Several syntheses of NDGA have appeared in the literature[3-8] and in patents,[6,9] but all involve low-yield reactions, lengthy reaction sequences, or expensive starting materials. The creosote bush has remained the only commercial source of NDGA, which has been used as an antioxidant in foods.

This report presents a practical synthetic route to NDGA utilizing a novel and highly stereoselective alkylation reaction to form the lignan carbon skeleton.

In order to obtain an unequivocal confirmation of the configuration[4] of natural NDGA, the tetramethyl ether 2,[5] prepared from commercial NDGA,[10] was brominated, affording the dibromo derivative 3.[5] A
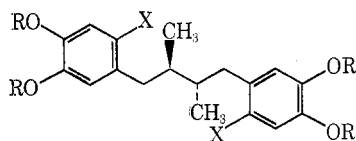

1, R = X = H (NDGA)
2, R = CH₃; X = H
3, R = CH₃; X = Br

single-crystal X-ray analysis[11] confirmed that NDGA (1) has the meso configuration.

Acylation of veratrole with propionyl chloride using chloroform as solvent gave a higher yield (93%) of purer product, 3,4-dimethoxypropiophenone (4), than previously reported methods.[12,13] Bromination of 4

in refluxing chloroform then gave α-bromo-3,4-dimethoxypropiophenone (5), again in considerably better yield (95%) than by the methods previously described.[13]
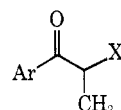

Ar = 3,4-dimethoxyphenyl

4, X = H
5, X = Br
6, X = Cl

Heating 5 with copper powder in refluxing xylene has been reported[14] to give 2,3-diveratroylbutane (7) in 28% yield, but, using a variety of copper powders and solvents, we could obtain the rather insoluble compound 7 in no more than 7% yield. Column chromatography of the mother liquors led to crystalline mixtures containing a second diketone (9) contami-

7 (meso)   **8**   **9 (racemic)**
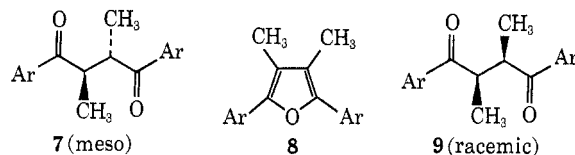
nated with 7. Dehydration of either 7 or 9 afforded the furan 8 in high yields. From the data to be presented, it is clear that 7 and 9 are the expected meso and racemic diketones, respectively.

Support for the assignments of relative configuration to 7 and 9 came from their mass spectra,[15] which showed that a fragment ion at *m/e* 194 was much stronger in the spectrum of 7 than in that of 9. This ion presumably arises by a rearrangement fragmentation,[16] the transition state (10) for which is sterically

10
7, R₁ = H; R₂ = CH₃
9, R₁ = CH₃; R₂ = H

m/e 194
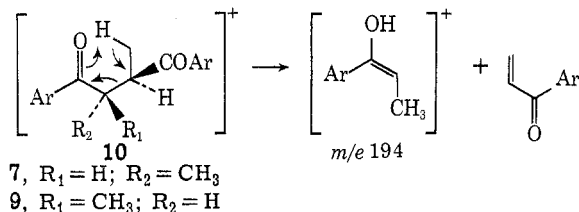
more favorable when R₁ = H and R₂ = CH₃ (7) than when R₁ = CH₃ and R₂ = H (9).

(1) Presented in part at Metrochem 69, New York, N. Y., May 1, 1969, and at the Annual Meeting of the Phytochemical Society of North America, Banff, Alberta, Canada, Aug 20, 1969.

(2) C. W. Waller and O. Gisvold, *J. Amer. Pharm. Ass.*, **34**, 78 (1945).

(3) R. D. Haworth, C. R. Mavin, and G. Sheldrick, *J. Chem. Soc.*, 1423 (1934).

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(8) J. G. Blears and R. D. Haworth, *J. Chem. Soc.*, 1985 (1958).

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(12) T. B. Johnson and W. W. Hodge, *J. Amer. Chem. Soc.*, **35**, 1014 (1913).

(13) R. D. Haworth and D. Woodcock, *J. Chem. Soc.*, 809 (1938).

(14) J. R. Atkinson and R. D. Haworth, *ibid.*, 1681 (1938).

(15) Dr. F. Vane, Hoffmann-La Roche Inc., unpublished results.

(16) F. W. McLafferty, "Interpretation of Mass Spectra," W. A. Benjamin, New York, N. Y., 1966, p 123.

Examination of the infrared spectra of these diastereomeric diketones showed some striking differences. The carbonyl absorption frequencies in the infrared spectra of the following compounds were measured in dilute carbon tetrachloride solution: propiophenone (1692 cm^{-1}), *p*-methoxypropiophenone (1685 cm^{-1}), 3,4-dimethoxypropiophenone (4, 1681 cm^{-1}), the racemic diketone (9, 1669 cm^{-1}), and the meso diketone (7, 1662 cm^{-1}). The lowering of the frequency by 11 cm^{-1} from propiophenone to 4 is clearly the result of electron enrichment of the carbonyl group of 4 by the strongly electron-donating methoxyl substituents, but the further lowering of the frequency by 12 cm^{-1} in 9 must be due to strong interaction (and therefore close proximity) between the two aroyl groups of 9. Even stronger aroyl–aroyl interaction must exist in the meso diketone 7. Such aroyl–aroyl interactions can be understood best in terms of the conformations of the diketones shown below (7a and 9a), in which

7a   9a
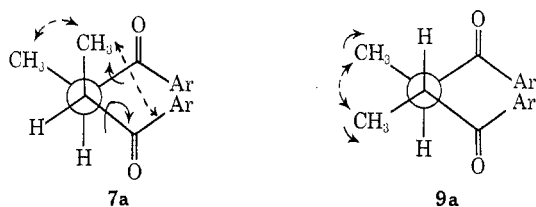
the planar aroyl groups lie in approximately parallel planes and in close proximity.

Inspection of Dreiding models of these molecules also suggests that, in the meso diketone conformer 7a, one of the methyl groups interacts sterically not only with the other methyl group, but also strongly with the ortho hydrogen atom on the nearer aryl group, as indicated by the dotted arrows. Both of these interactions are relieved best by slight rotations of the C–aroyl bonds, as indicated by the solid arrows. Such a conformational adjustment is done at the expense of forcing the aroyl groups into closer proximity, which is compatible with the infrared data. On the other hand, the methyl–methyl interaction in the racemic diketone conformer 9a, shown by the dotted arrow, is easily relieved by slight rotation about the central carbon–carbon bond, and this motion tends to decrease the aroyl–aroyl overlap.[17]

The observed differences in the pmr spectra of these diketones are also understood in terms of such conformations. On the average, the methyl groups of the meso diketone conformer 7a are closer to, and therefore more shielded by, the aroyl groups than are the methyl groups of the racemic diketone conformer 9a. Accordingly, the signals for the methyl protons are found at higher field for 7a than for 9a. Base-catalyzed equilibration of either diketone led to mixtures of 7 and 9, their ratio depending on the solvent as shown in Table I.

A better method of preparing the meso diketone 7 was sought in the reaction of the sodium enolate of 4 with the bromo ketone 5. However, in DMSO the reaction gave the racemic diketone 9 in low yield. When the alkylation reaction was carried out in liquid

TABLE I

Starting material	Solvent	Base	Time, hr	Temp, °C	Ratio, 9:7[a]
7	C$_2$H$_5$OH–CH$_3$OH–C$_6$H$_6$ (4:4:1)	NaOCH$_3$	1	Reflux	1.9
9	C$_2$H$_5$OH–CH$_3$OH–C$_6$H$_6$ (4:4:1)	NaOCH$_3$	1	Reflux	2.2
7	DMSO	KO-*t*-Bu	1	22	3.6
9	DMSO	KO-*t*-Bu	1	22	3.9
7	C$_6$H$_6$	KO-*t*-Bu	1	40	2.8
9	C$_6$H$_6$	KO-*t*-Bu	1	40	2.4

[a] Differences in ratios in the same solvent systems are within experimental error.

ammonia at −33°, the pure racemic diketone 9 was obtained in 90% yield.

As expected from the preceding analysis of the steric interactions in the two diastereomeric diketones, the racemic form 9 was found in each case to be slightly favored over the meso form 7. However, the observed difference in stability does not account for the highly stereoselective alkylation of 4 by 5 to give the racemic diketone almost exclusively.

The novel and highly stereoselective alkylation of 4 by 5 in liquid ammonia seems to have rather specific structural requirements. When the α-chloro ketone 6 was used in place of 5, the major product isolated (*ca.* 15% yield) was the furan 11, perhaps arising *via* cyclization of an intermediate such as 12 resulting from a Darzens-type condensation. When the substituted acetophenones 13 and 14 were condensed under the same conditions, the reaction took yet another course, affording 15 and 16 in low yields along with recovered 13, but none of the expected diketone 17.

11

12

13, X = H
14, X = Br

15   16

17
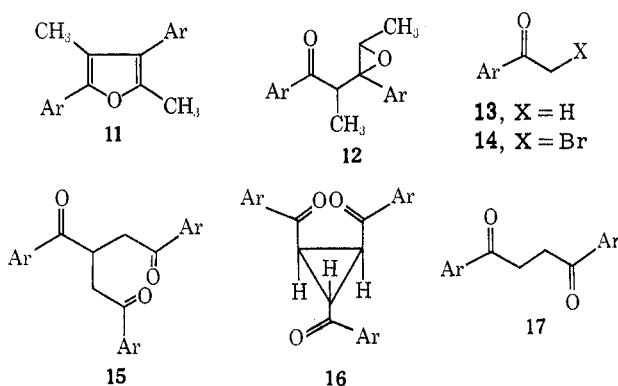
Assignment of structures 15 and 16 was based mainly on elemental analysis, and pmr and mass spectra. The presence of three, rather than two, pmr signals for the methoxy groups of 16 supports the trans configuration assigned.

On the other hand, the condensation proceeded normally with the pairs of propiophenone derivatives 18–19 and 20–21, giving in each case the corresponding racemic diketones, 22 and 23, in good yields. The meso diketones were not detected.

18, R = X = H
19, R = H; X = Br
20, R = OCH$_3$; X = H
21, R = OCH$_3$; X = Br

22, R = H
23, R = OCH$_3$

(17) No attempt is made to assess the absolute magnitude of aroyl-aroyl (or aryl-aryl) overlap in these compounds, but only the relative overlap as it is affected by these simple conformational adjustments from the ideal completely staggered conformations drawn in the diagrams above.
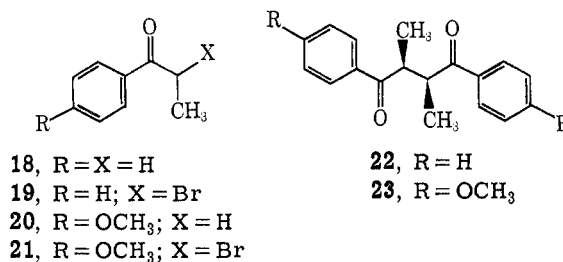
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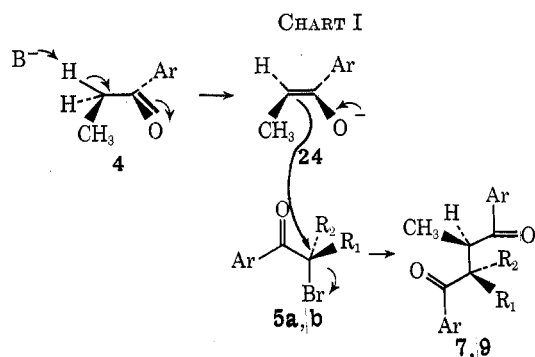
5a, $R_1 = H$; $R_2 = CH_3$ **7**, $R_1 = H$; $R_2 = CH_3$ (meso)
5b, $R_1 = CH_3$; $R_2 = H$ **9**, $R_1 = CH_3$; $R_2 = H$ (racemic)

The stereoselective formation of the racemic diketones in these reactions may be rationalized by the following proposed mechanism. Formation of the enolate from **4** should give predominantly the trans enolate **24**. Reaction of **24** with either enantiomer **5a** or **5b** from either above or below **24** is possible, but it would be sterically more favorable when the aroyl group of **5** is farthest from the aroyl group of **24**, and the methyl group of **5** is toward the oxygen of **24** rather than toward the aryl group. Thus, in the example illustrated in Chart I, reaction would be more likely to occur with **5b** than with **5a**, and displacement of bromide by the enolate with Walden inversion would lead to one enantiomer of the racemic diketone **9**. In like manner, and with equal probability, approach of **5** on the top side of **24** would preferentially form the other enantiomer of **9**, with the net result that the product is predominantly the racemic form.

Catalytic hydrogenation of the furan **8** was reported[8] to give either NDGA tetramethyl ether (**2**) or the all-cis tetrahydrofuran **25** depending on conditions, but no yield was given for the first case, and 70% was reported for the second. During extensive efforts[18] to hydrogenate **8** directly to **2**, an improved procedure for the preparation of **25** in 89% yield was developed, but none of the catalysts or conditions studied gave **2** in significant yields.

25   **26**

27   **28**, R = H
        29, R = COCH$_3$
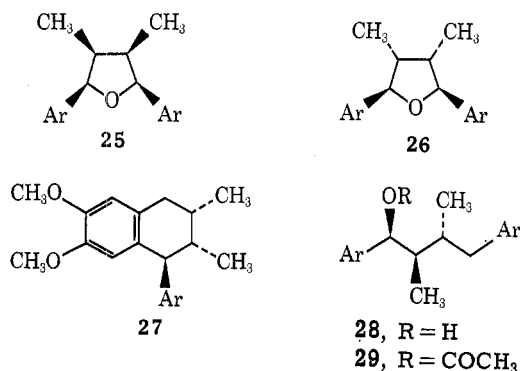
Galgravin (**26**), prepared by acid-catalyzed isomerization of **25**, is reported to be more easily hydrogenated to **2** with palladium oxide than is the furan **8**.[8] A series of similar hydrogenation experiments, summarized in Table II, was conducted on **8** and **25**, and disclosed a remarkable solvent effect on the ratio of

TABLE II

Sub-strate	Cata-lyst	Solvent	Temp, °C	Time, hr	Products, %	
					2	27
8[c]	PdO	AcOH	25	71	28[a]	58[a]
25[c]	PdO	AcOH	25	2	25[a]	75[a]
25	PdO	MeOH	25	20	5[a]	95[a]
25	PdO	EtOAc	25	23	74[a] 56[b]	26[a]
25	PdO	THF	25	45	79[a] 76[b]	21[a]
25	PdO	C$_6$H$_6$	25	24	No reaction	
8	PdO	THF	75 (1500 psig)	0.5	81[a]	18[a]

[a] Determined by gas chromatography.   [b] Isolated crystalline.
[c] Conditions similar to those reported by Blears and Haworth.[8]

the two products formed, **2** and racemic isogalbulin (**27**).[19] The formation of **27** may be the result of desorption of the intermediate alcohol **28** from the catalyst followed by its cyclodehydration in solution. Relatively nonpolar solvents such as THF may cause less desorption of **28**; so relatively more **2** is formed.

As seen from the last entry in Table II, the use of tetrahydrofuran (THF) as a solvent and palladium oxide as a catalyst, along with elevated temperature and pressure, permitted the direct conversion of **8** to **2** in good yield. There seems to be no advantage in the stepwise conversion of **8** to **25** to **2**.

Unfortunately, only fresh palladium oxide, finely powdered, gave good results. A more convenient and reliable catalyst system was sought. Palladium chloride catalyzed the reduction of **8** to **2** but the hydrogen chloride liberated by the reduction of the catalyst caused the formation of 25% of isogalbulin (**27**). The addition of inorganic buffers minimized the formation of **27** and increased the activity of the catalyst, allowing the hydrogenation of **8** to **2** consistently in 65–75% yield. Synthetic **2** was identical with the tetramethyl ether of natural NDGA.

Finally, demethylation of **2** with refluxing concentrated hydrobromic acid afforded, in nearly quantitative yield, NDGA (**1**), identical with a purified sample of the natural product.

An alternative route to **2** involves reductive ring opening[19,20] of **25** by a solution of sodium in liquid ammonia and tetrahydrofuran to give the alcohol **28**, which is probably an intermediate in the hydrogenations of **8** and **25** already described. Cyclization of **28** by a very mild acid treatment[20] gave racemic isogalbulin (**27**) in good yield. Hydrogenolysis of the acetate **29** gave **2**. However, this longer route to **2** seems to have no advantages over the direct hydrogenation of **8**.

Experimental Section

Microanalyses were performed by Dr. F. Scheidl and associates of the Hoffmann-La Roche Inc. microchemical laboratory. Melting points were determined with a Thomas-Hoover capillary apparatus and are uncorrected. Spectra were recorded on standard instruments by the staff of the Physical Chemistry Department of Hoffmann-La Roche Inc., or on a Perkin-Elmer Model 237B Infracord. Unless otherwise noted, pmr spectra were recorded at 60 MHz. Chemical shifts are expressed as δ values (parts per million downfield from tetramethylsilane as internal reference) and coupling constants (J) are expressed in cycles per

(18) We thank Mr. D. Wagner, Hoffmann-La Roche Inc., for assistance with the high-pressure hydrogenation experiments.

(19) A. J. Birch, B. Milligan, E. Smith, and R. N. Speake, *J. Chem. Soc.*, 4471 (1958).

(20) N. S. Crossley and C. Djerassi, *ibid.*, 1459 (1962).

second. Thin layer chromatograms (tlc) were used routinely for following reactions and separations, and were performed on Brinkmann F254 silica gel plates, which were examined under long- and short-wave ultraviolet light and were then sprayed with a 1:1 mixture of 85% phosphoric acid and concentrated nitric acid and warmed gradually on a hot plate. Gas chromatographic analyses were carried out on a 4 ft × 0.25 in. o.d. copper column packed with 1.1% SE-30 + 0.2% Versamid 900 on AW/DMCS Chromosorb G, 60-80 mesh, installed in an instrument equipped with a thermal conductivity detector, using helium as a carrier and operating at 220-250°.

Purification of NDGA (1).—Commercial NDGA[10] was recrystallized three times from 36% aqueous acetic acid to give tan-colored material, mp 183-184°. This was sublimed at 175-180° (0.03 mm) to afford large white and some yellow crystals. The white crystals were hand picked and ground in a mortar, giving pure NDGA: mp 185-186° (lit.[5] mp 184-185°); optically inactive; ν_{max} (KBr) 3470, 3310, 3200, 1612, 1530, 1520, 790, 755 cm^{-1}; nmr (CD$_3$OD) δ 0.78 (6 H, d, J = 6 Hz), 1.66 (2 H, poorly resolved q, J = 6 Hz), 2.12 (2 H, unsymmetrical q, J = 13, J' = 9 Hz), 2.61 (2 H, unsymmetrical q, J = 12, J' = 6 Hz), 4.98 (4 H, broad s), 6.36-6.75 (6 H, m); λ_{max} (CH$_3$OH) 283, 218 mμ (ϵ 6660, 13,400).

NDGA Tetramethyl Ether (2) from Commercial NDGA.—Addition of potassium hydroxide solution (16 g of KOH in 50 ml of water and 75 ml of methanol) to a solution of NDGA[10] (20.0 g, 0.0663 mol) in methanol (60 ml) at room temperature under nitrogen gave a dark solution to which dimethyl sulfate (67 g, 0.532 mol) was added with stirring over a period of 15 min. The temperature during the addition was maintained at 35-40°, and enough potassium hydroxide solution was introduced periodically to maintain pH 8-9. The reaction mixture was stirred at room temperature for 18 hr and then poured into water. The precipitate was collected by filtration, washed with water, and dried to provide 22.7 g (96%) of tan-colored solid, mp 93-98°. Purification of the product by elution from Florisil with benzene-chloroform (1:1) followed by several recrystallizations from methanol afforded analytically pure product: optically inactive; mp 100-102° (lit.[5] mp 100-101°); ν_{max} (KBr) 1610, 1595, 1525, 1265, 1240, 1160, 1140, 1025 cm^{-1}; nmr (CDCl$_3$) δ 0.85 (6 H, d, J = 6 Hz), 1.50-3.00 (6 H, m), 3.87 (12 H, s), 6.60-6.84 (6 H, m); λ_{max} (CH$_3$OH) 279, 228 mμ (ϵ 6080, 16,400).

Anal. Calcd for C$_{22}$H$_{30}$O$_4$: C, 73.71; H, 8.44. Found: C, 73.77; H, 8.48.

meso-1,4-Bis(2-bromo-4,5-dimethoxyphenyl)-2,3-dimethylbutane (3).—NDGA tetramethyl ether (2, 5.0 g, 14 mmol) was brominated in acetic acid[5] in 91% yield. After several recrystallizations from methanol the product had mp 131-132°. A sample of large, needlelike crystals, obtained by slow evaporation of a saturated methanol solution, was subjected to X-ray crystallographic examination[11] and found to be the meso isomer.

3,4-Dimethoxypropiophenone (4).—To a cooled, well-stirred slurry of anhydrous aluminum chloride (22.0 g, 0.166 mol) in chloroform (80 ml) at 0-5° under an atmosphere of dry nitrogen was added a solution of freshly distilled propionyl chloride (12.0 g, 0.13 mol) in chloroform (10 ml) at such a rate as to maintain a temperature of 0-5°. When the addition was complete (about 15 min), a solution of veratrole (13.8 g, 0.1 mol) in chloroform (10 ml) was added in the same manner over a 30-min period, during which time hydrogen chloride was slowly evolved. The reaction mixture became a nearly clear, yellow-green solution, which was stirred at 0-5° for 1 hr after completion of the addition. With continued stirring and cooling 3 N hydrochloric acid (100 ml) was then added *very* cautiously dropwise, keeping the temperature below 30°. When all the solids were dissolved, the phases were separated, the lower organic phase was washed with 3 N sodium hydroxide solution (50 ml) once, and the two aqueous solutions were back-extracted in succession with chloroform (50 ml). The combined chloroform solution was dried over anhydrous magnesium sulfate, filtered, and evaporated to dryness *in vacuo*, and the residue was crystallized from methanol (25 ml) by chilling overnight in a freezer to afford a first crop, 14.31 g (78.8% yield), mp 58.5-59.5°. A second crop, 3.84 g (20.0% yield), had mp 54-58°. An analytical sample had mp 58-59° (lit.[13] mp 59-60°).

α-Bromo-3,4-dimethoxypropiophenone (5).—A solution of bromine (65.4 g, 0.408 mol, 2% excess) in chloroform (100 ml) was added as rapidly as possible through an addition funnel to a refluxing solution of 3,4-dimethoxypropiophenone (4, 77.6 g, 0.40 mol) in chloroform (300 ml) with good agitation. The

hydrogen bromide, which was rapidly evolved, was conducted from the top of the reflux condenser to a flowing water scrubber. When the addition was complete the solution was refluxed for 10 min to drive off most of the hydrogen bromide; then the solvent was removed under reduced pressure. Crystallization of the residue from methanol (200 ml) gave a first crop, 101.9 g (93.2% yield), mp 81-82°. A second crop, 2.3 g (2.2% yield), had mp 72-77°, and an analytical sample had mp 82-82.6° (lit.[13] mp 83-84°).

meso-**2,3-Bis(3,4-dimethoxybenzoyl)butane (7). A.**—The procedure described by Atkinson and Haworth[14] was used, except that commercial copper powder was used in place of "freshly precipitated copper"[21] and a small crystal of iodine was added to the reaction mixture. Crystallization of the crude product from methanol afforded white crystals: mp 184.5-187.5° (lit.[14] mp 189-190°); 3.8% yield; nmr (CDCl$_3$) 1.15 (6 H, d, J = 6 Hz), 4.01 (14 H), 6.90-8.0 (6 H, m); m/e (rel intensity) 386 (10), 221 (2), 194 (2), 180 (2), 165 (100), 137 (3), 122 (2).

B.—α-Bromo-3,4-dimethoxypropiophenone (5, 2.73 g, 10 mmol), copper powder (2.73 g, 43 mmol), benzene (20 ml), and diphenyl ether (20 ml) were stirred together under a nitrogen atmosphere and solvent was distilled until the reaction temperature reached 150°. The reaction mixture was stirred at 150° for 18.5 hr; then it was filtered and the filtrate was chromatographed on activity I neutral alumina. Diphenyl ether was eluted with benzene, the crude diketone was eluted with benzene-ether (19:1 through 1:1) and more polar products were eluted with ethyl acetate. Crystallization of the diketone fraction gave fine white needles of 7, mp 186-190° (137 mg, 7.1% yield). Treatment of the mother liquors plus the ethyl acetate eluates with boiling ethanolic hydrochloric acid gave crude crystals of 8, mp 169.5-170.5° (lit.[14] mp 169-170°), 376 mg (20.4% yield).

3,4-Dimethyl-2,5-bis(3,4-dimethoxyphenyl)furan (8). A.—A solution of *meso*-2,3-bis(3,4-dimethoxybenzoyl)butane (7, 24 mg) in 10% ethanolic hydrochloric acid (5 ml) was refluxed for 15 min and cooled to provide colorless crystals of 8, mp 169-170.5° (lit.[14] mp 169-170°), 20 mg (87.4% yield).

B.—To a boiling solution of *rac*-2,3-bis(3,4-dimethoxybenzoyl)butane (9, 38.6 g, 0.10 mol) in dichloromethane (100 ml) was added a 1% solution of hydrogen chloride in methanol (250 ml) slowly with continued boiling. After about 5 min crystals separated, and after the slurry was chilled a first crop was obtained, mp 170-171°, 30.20 g (82% yield). Concentration of the mother liquors afforded a second crop, mp 169.5-170.5°, 4.56 g (12.4% yield), and a third crop, mp 168.2-170.0°, 0.54 g (1.5% yield).

Racemic 2,3-Bis(3,4-dimethoxybenzoyl)butane (9).—To liquid ammonia (approximately 50 ml) was added powdered ferric chloride (50 mg), then small pieces of sodium (0.51 g, 0.022 g-atom, 10% excess) were added and the blue color was allowed to dissipate over about a 20-min period. To the resulting gray suspension of sodamide was added solid 3,4-dimethoxypropiophenone (4, 3.88 g, 0.02 mol) in small portions and the mixture was stirred for about 5 min. Solid α-bromo-3,4-dimethoxypropiophenone (5, 5.46 g, 0.02 mol) was then added in small portions to the gray-green mixture, and the reaction mixture turned deeper green, then reddish, and finally tan colored. After the mixture was stirred for 1 hr, solid ammonium chloride (2.68 g) was added, followed by dichloromethane (50 ml), and the gray mixture was then warmed cautiously to room temperature to evaporate most of the ammonia. The mixture was filtered with suction, the residual solids were extracted twice with dichloromethane, and the combined filtered solutions were concentrated to about 50 ml in volume, diluted with methanol (75 ml), and further concentrated to about 50 ml in volume by boiling. The product crystallized on stirring and cooling, mp 137-141°, 6.96 g (90.3% yield). Recrystallization from methanol provided an analytical sample: mp 145-146°; ν_{max} (KBr) 3080, 1665, 1595, 1585, 1515, 1265, 1245 cm^{-1}; nmr (CDCl$_3$) δ 1.33 (6 H, d, J = 7 Hz), 3.92 (14 H, "d"), 6.9-8.0 (6 H, m); mass spectrum m/e 386 (11), 221 (2), 194 (<1), 180 (<1), 165 (100), 137 (3), 122 (4).

Anal. Calcd for C$_{22}$H$_{26}$O$_6$: C, 68.37; H, 6.78. Found: C, 68.16; H, 6.83.

Base-Catalyzed Equilibration of Diketones 7 and 9.—A mixture of 7 (50 mg), methanol (20 ml), benzene (5 ml), ethanol (20 ml), and sodium methoxide (62 mg) was boiled gently for about 1 hr and then stored at room temperature overnight. The solution

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(21) In one experiment "freshly precipitated copper" was used, but only traces of 7 could be detected in the product.

was boiled down to a volume of 15 ml, powdered magnesium sulfate (100 mg) was added to neutralize base, the mixture was filtered, and the filtrate was reduced to dryness under reduced pressure. Extraction of the residue twice with chloroform and removal of the solvent left a residue (48 mg) which was analyzed by nmr spectrometry (100 MHz), using the signals at δ 1.15 ppm (compound 7) and 1.33 ppm (compound 9) to determine the ratio of 9:7, which was 1.87.

Similarly, 9 (50 mg) gave a mixture (48 mg) with a ratio of 9:7 = 2.17.

α-Chloro-3,4-dimethoxypropiophenone (6).—A solution of α-chloropropionyl chloride (50.1 g, 0.39 mol) in chloroform (50 ml) was added to a stirred slurry of anhydrous aluminum chloride (66.5 g, 0.50 mol) in chloroform (300 ml), while the temperature of the mixture was maintained at −5 to 0°. A solution of veratrole (41.4 g, 0.30 mol) in chloroform (40 ml) was then added dropwise while the same temperature was maintained. The dark solution was stirred for 4 hr at 0–5°, then for 1 hr at room temperature. Hydrochloric acid (3 N, 300 ml) was added very cautiously with ice-bath cooling, and the mixture was extracted and washed as described for compound 4 to afford 55 g of dark brown liquid. Column chromatography over activity I neutral alumina (600 g) afforded a fraction (6.47 g, eluted with hexane–benzene and benzene–chloroform mixtures) which solidified. Crystallization from hexane–benzene gave colorless needles (6.4 g, mp 57–60°). An analytical sample had mp 58.5–60.5°, ν_{max} (KBr) 1692 cm^{-1}.

Anal. Calcd for $C_{11}H_{13}ClO_3$: C, 57.78; H, 5.73; Cl, 15.50. Found: C, 57.80; H, 5.47; Cl, 15.41.

2,4-Dimethyl-3,5-bis(3,4-dimethoxyphenyl)furan (11).—A solution of the enolate of 4 (3.88 g, 0.02 mol) was prepared in 75 ml of liquid ammonia as described above. The chloro compound 6 (4.57 g, 0.02 mol) was added rapidly and the reaction mixture was stirred for 5 hr. After addition of solid ammonium chloride (1.2 g) and dichloromethane (50 ml), the ammonia was allowed to evaporate. Extraction with dichloromethane gave a green, viscous liquid (8.7 g), the hexane-insoluble fraction of which was triturated with methanol to give a solid (0.935 g, mp 154–157°). Recrystallization from methanol afforded an analytical sample: mp 158–160°; λ_{max} (MeOH) 290 nm (ε 26,830), inflection 233 (18,950); nmr (CDCl$_3$) δ 2.17 (3 H, s), 2.35 (3 H, s), 3.90 and 3.95 (6 H, 2 s), 7.0 (6 H, m).

Anal. Calcd for $C_{22}H_{24}O_5$: C, 71.72; H, 6.57. Found: C, 71.87; H, 6.54.

3,4-Dimethoxyacetophenone (13).—By the same procedure used for the preparation of 4, veratrole was acetylated to 13 in 82% yield, mp 48–50° (from benzene–hexane) (lit.[22] mp 48°).

α-Bromo-3,4-dimethoxyacetophenone (14).—Treatment of 13 (18.0 g, 0.10 mol) in chloroform (75 ml) with a solution of bromine (16.3 g, 0.102 mol) in chloroform (25 ml) at 25° gave 16.5 g (64% yield) of crude 14. An analytical sample recrystallized from benzene–hexane had mp 80–81° (lit.[23] mp 80–81°).

1,2,3-Tris(3,4-dimethoxybenzoyl)propane (15).—A suspension of sodamide in liquid ammonia (50 ml) was prepared from sodium (0.51 g, 0.022 mol), and 13 (3.60 g, 0.02 mol) was added in small portions, followed by 14 (5.18 g, 0.02 mol). The mixture was stirred at −33° for 3 hr and worked up in the usual manner to afford 10 g of dark, viscous liquid, which was chromatographed over 250 g of neutral alumina. Several fractions solidified and were combined and crystallized from benzene–hexane to afford 1 g of 15: mp 174–175°; ν_{max} (KBr) 1680 cm^{-1} (broad); λ_{max} (CH$_3$OH) 229, 276, 306 nm (ε 49,000, 33,520, 27,310); nmr (CDCl$_3$) 3.39 (4 H, q, J = 7, J' = 3 Hz), 3.88 and 3.93 (18 H, 2 s), 4.75 (1 H, t, J = 7 Hz), 6.8–8.0 (9 H, m); mass spectrum m/e 165 (base peak), 370 (M − ArCO, H), 536 (M$^+$).

Anal. Calcd for $C_{30}H_{32}O_9$: C, 67.15; H, 6.01. Found: C, 67.11; H, 6.01.

***trans*-1,2,3-Tris(3,4-dimethoxybenzoyl)cyclopropane (16).**—Fractional crystallization from the mother liquors of 15 afforded 150 mg of a second compound, 16: mp 202–204°; ν_{max} (KBr) 1660 cm^{-1} (broad); λ_{max} (CH$_3$OH) 230, 280, 312 nm (ε 33,400, 24,530, 23,940); nmr (CDCl$_3$) δ 3.7–4.3 (21 H, m, with three strong singlets for –OCH$_3$), 6.8–8.1 (9 H, m); mass spectrum m/e 165 (base peak), 369 (M − ArCO), 534 (M$^+$).

Anal. Calcd for $C_{30}H_{30}O_9$: C, 67.40; H, 5.66. Found: C, 67.51; H, 5.61.

Racemic 2,3-Dimethyl-1,4-diphenyl-1,4-butanedione (22).—Propiophenone (13.8 g, 0.1 mol) was added to a suspension of sodamide (0.13 mol) in liquid ammonia (200 ml) and stirred for 15 min before addition of α-bromopropiophenone (21.3 g, 0.1 mol). The reaction mixture was stirred for 30 min and the ammonia was replaced with methylene chloride. Extraction with methylene chloride gave 26 g of dark-colored liquid which was chromatographed over 100 g of Florisil. Elution with hexane–benzene mixtures gave a solid which after recrystallization from hexane weighed 10.0 g: mp 86–87°;[24] ν_{max} (KBr) 1680 cm^{-1}; nmr (CDCl$_3$) δ 1.27 (6 H, d, J = 6 Hz), 3.75 (2 H, m), 7.2–8.0 (10 H, m); mass spectrum m/e 266 (M$^+$).

Anal. Calcd for $C_{18}H_{18}O_2$: C, 81.17; H, 6.81. Found: C, 80.90; H, 6.89.

Boiling 22 in methanolic hydrogen chloride for a few minutes converted it to 2,5-diphenyl-3,4-dimethylfuran, mp 114–115° (lit.[25] mp 116°), in good yield.

α-Bromo-*p*-methoxypropiophenone (21).—Bromination of *p*-methoxypropiophenone in refluxing chloroform provided 21 in 86% yield, mp 66–69° (from methanol) [lit.[26] mp 68.5° (petroleum ether, bp 30–60°)].

Racemic 2,3-Bis(*p*-methoxybenzoyl)butane (23).—The condensation of *p*-methoxypropiophenone (16.4 g, 0.10 mol) with 21 (24.3 g, 0.10 mol) was carried out as described for compound 22 above. The product was crystallized from methanol to afford a cream-colored solid (22.1 g, 67% yield), mp 116–121°. An analytical sample melted at 124–127°: ν_{max} (KBr) 1660 cm^{-1}; nmr (CDCl$_3$) δ 1.30 (6 H, d, J = 6 Hz), 3.9 (8 H, strong s over m), 7.0 and 8.1 (8 H, aromatic AA'BB' pattern); mass spectrum m/e 135 (base peak), 326 (M$^+$).

Anal. Calcd for $C_{20}H_{22}O_4$: C, 73.60; H, 6.79. Found: C, 73.80; H, 6.64.

***all-cis*-3,4-Dimethyl-2,5-bis(3,4-dimethoxyphenyl)tetrahydrofuran (25).**—Hydrogenation of the furan 8 (36.8 g, 0.1 mol) over 10% palladium on calcium carbonate catalyst (5.0 g) in ethanol (1000 ml) at 125° under 1500 psig hydrogen for 3 hr, followed by filtration and removal of solvents, gave a white solid (35 g) which on recrystallization from methylene chloride–methanol gave a first crop, mp 127.5–130.0° (29.86 g, 80.4% yield). Concentration of the mother liquors gave a second crop, mp 125.5–128.0° (2.54 g, 6.8% yield), and a third crop, mp 124.5–127.5° (0.47 g, 1.3% yield). An analytical sample had mp 131–132° (lit.[8] mp 132–133°); nmr (CDCl$_3$) δ 0.62 (6 H, d, J = 7 Hz), 2.70 (2 H, m), 3.94 (12 H, s), 5.19 (2 H, d, J = 6.5 Hz), 7.0–7.17 (6 H, m).

Hydrogenations of 8 and 25. General Procedure.—A mixture of the compound to be reduced (0.2–3.68 g), catalyst (usually 0.2 g), and solvent (50 ml) was stirred magnetically under an atmosphere of hydrogen at the desired temperature. After filtration of the spent catalyst, the filtrate was examined by gas chromatographic analysis. For isolation of crude NDGA tetramethyl ether (2), the solvents were removed and the residue was crystallized from 10–20 times its weight of hexane.

NDGA Tetramethyl Ether (2). A. From 8.—The furan 8 (33.3 g, 90.5 mmol) in THF (500 ml) was hydrogenated over powdered palladium oxide (2.0 g) at 50° (1500 psig) for about 10 hr. Gas chromatographic analysis indicated 77.8% of 2 in the crude filtrate. Removal of solvent and crystallization of the residue (33.7 g) from hexane (550 ml) gave crude 2, mp 91.5–95° (25.4 g, 78% yield).

B. From 25.—Compound 25 (745 mg, 2 mmol) in THF (50 ml) was hydrogenated over powdered palladium oxide (200 mg) at 25° (1 atm) for 46 hr. Gas chromatographic analysis indicated 78.5% of 2 in the crude filtrate. Removal of solvent and crystallization of the residue (848 mg) from hexane gave crystalline 2, mp 93–95° (543 mg, 76% yield).

C. From 8, Using Palladium Chloride.—The furan 8 (4.00 g), palladium chloride (0.40 g), and sodium acetate (0.46 g) in tetrahydrofuran (100 ml) were shaken in a rocking autoclave at 75° under hydrogen at 50 psig for 10 hr. Gas chromatography indicated a yield of 79% of 2, 85% of which could be isolated as described above.

NDGA (1) from 2.—Concentrated hydrobromic acid (860 g) was added under nitrogen to 2 (71.56 g, 0.201 mol) and the mixture was stirred and refluxed for 9 hr and allowed to cool to room

(22) H. Stephen and C. Weizmann, *J. Chem. Soc.*, **105**, 1046 (1914).
(23) C. Mannich and F. L. Hahn, *Ber.*, **44**, 1542 (1911).

(24) The meso isomer melts at 67°: A. Wolf, German Patent 876,237 (May 11, 1953); *Chem. Abstr.*, **52**, 9227b (1958).
(25) R. E. Lutz and R. J. Taylor, *J. Amer. Chem. Soc.*, **55**, 1593 (1933).
(26) C. Hell and A. Hollenberg, *Ber.*, **682** (1896).

temperature overnight with continued stirring. The dark-colored solid product, collected by filtration, washed with water, and dried, had mp 174–182° (59.27 g, 97.5% yield). Recrystallization from about 1600 ml of 20% aqueous acetic acid with charcoal treatment gave a much lighter colored, but still gray-brown, crystalline product, mp 184–186° (45.74 g) (77% recovery, 75% yield). A second recrystallization with charcoal gave light tan crystals, mp 184–185.3° (91% recovery). After a third recrystallization the cream-colored crystals (95% recovery) had mp 184.5–186°, identical in all respects with purified natural NDGA, mmp 184–186°.

The overall yield of thrice-recrystallized product was 65%. No product of satisfactory quality could be recovered from the mother liquors.

Monoalcohol 28.—Sodium (4.37 g, 0.19 mol) was added to anhydrous liquid ammonia (1.1 l.) and stirred under reflux under a nitrogen atmosphere. After 1 hr a solution of the tetrahydrofuran 25 (18.6 g, 50 mmol) in THF (500 ml) was added. After 2.5 hr of stirring under reflux the ammonia was removed by warming the reaction mixture to room temperature. Addition of methanol (10 ml) and then water (400 ml), followed by extraction with chloroform, washing with water, drying over sodium sulfate, and removal of solvents, gave the crude product (22.0 g), which was crystallized from methanol to afford white crystals of 28, mp 107.5–109° (16.34 g, 43.7 mmol, 87.4% yield). A second crop was collected to give a total of 17.96 g (48 mmol, 96% yield). An analytical sample was recrystallized from benzene–hexane: mp 110–111.3°; ν_{max} (KBr) 3570, 1258, 1238, 1135, 1130, 1025 cm^{-1}; λ_{max} (CH$_3$OH) 229, 269, 285 mμ (ϵ 16,553, 5824, 4883); nmr (CDCl$_3$) δ 0.84 (3 H, d, J = 6 Hz), 1.10 (3 H, d, J = 6 Hz), 1.80 (2 H, m), 1.98 (1 H, broad s, exchangeable with D$_2$O), 2.10 (1 H, q, J_1 = 13, J_2 = 10 Hz), 2.82 (1 H, q, J_1 = 13, J_2 = 3 Hz), 3.70–4.17 (12 H = 4 CH$_3$O), 4.70 (1 H, d, J = 6 Hz), 6.40–7.00 (6 H, m).

Anal. Calcd for C$_{22}$H$_{30}$O$_5$: C, 70.56; H, 8.08. Found: C, 70.74; H, 7.96.

Racemic Isogalbulin 27.—A slurry of 28 (2.52 g, 6.72 mmol) in ethanol (18 ml) was treated with concentrated hydrochloric acid (3 ml) and stirred for 4.5 hr at room temperature. The solution was poured into water and extracted with ether to give a crude product (2.84 g) which was crystallized from methanol with cooling. Recrystallization from hexane provided 1.71 g (4.8 mmol, 72.4%) of 27 as a white solid, mp 66.5–72°. An analytical sample was recrystallized successively from hexane, ethanol, and methanol: mp 70.5–72.5° (lit.[19] mp 86°); ν_{max} (KBr) 1470, 1262, 1250, 1150, 1140, 1109 cm^{-1}; λ_{max} (CH$_3$OH) 204, 232, 282, 287 mμ (ϵ 62,750, 16,500, 7100, 6600); nmr (CDCl$_3$) δ 0.97 (6 H, d, J = 7 Hz), 2.5 (4 H, m), 3.67–4.10 (13 H, m), 6.71 (5 H, m).

Anal. Calcd for C$_{22}$H$_{28}$O$_4$: C, 74.13; H, 7.92. Found: C, 73.86; H, 7.83.

Monoacetate 29.—To an ice-cold mixture of acetic anhydride (10 g) and pyridine (10 g) was added 28 (3.74 g, 10 mmol) and the mixture was stirred for 5 min before being allowed to warm to room temperature. After 2 hr the mixture was poured into water (200 ml), extracted with chloroform, washed with water, dried, and freed of solvent. The crude product (4.59 g) was crystallized from methanol to give 671 mg of starting material. Second and third crops gave a total of 2.75 g (6.62 mmol, 80.6% corrected yield) of 29, mp 77–82°.

An analytical sample was recrystallized from hexane: mp 80–82°; ν_{max} (KBr) 1760, 1270, 1240, 1155, 1135, 1030 cm^{-1}; λ_{max} (CH$_3$OH) 229, 278, 285 mμ (ϵ 14,100, 4850, 3900); nmr (CDCl$_3$) δ 0.80 (3 H, d, J = 6 Hz), 1.07 (3 H, d, J = 6 Hz), 2.07 (3 H, s), 2.50 (4 H, m), 3.78–3.90 (12 H = 4 OCH$_3$), 5.80 (1 H, d, J = 8 Hz), 6.71 (6 H, m).

Anal. Calcd for C$_{24}$H$_{32}$O$_6$: C, 69.21; H, 7.74. Found: C, 69.48; H, 7.82.

All subsequent experiments gave a dimorphic form of 29, mp 100–102°, the solution spectral properties of which were identical with those of the lower melting acetate. The lower melting dimorph was converted to the higher melting one by recrystallization from hexane and seeding with the higher melting solid. However, conversion of the higher melting to the lower melting dimorph could not be achieved.

Hydrogenolysis of 29.—A mixture of 29 (1.045 g, 2.5 mmol), ethyl acetate (50 ml), and powdered palladium oxide (100 mg) was hydrogenated at room temperature and 1 atm for 22 hr. Filtration and removal of solvent gave 1.015 g of oil which was crystallized from hexane to give 0.703 g (1.96 mmol, 79%) of crude 2 as a white solid, mp 93–95.5°. Gas chromatographic analysis of the sample showed that it contained 90.3% 2 and 9.7% 27.

Registry No.—1, 27686-84-6; 2, 24150-24-1; 3, 36287-35-1; 6, 36287-36-2; 7, 36287-37-3; 9, 27686-81-3; 11, 36287-39-5; 15, 36287-40-8; 16, 36287-41-9; 22, 36287-42-0; 23, 36208-08-9; 25, 27686-82-4; 27, 36286-72-3; 28, 36286-73-4; 29, 36286-74-5.