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THE INTRAMOLECULAR DIELS-ALDER REACTION AS A ROUTE TO SYNTHETIC LIGNAN LACTONES

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Abstract—Methoxy- and methylenedioxy substituted, unsaturated, open-chain esters of the phenylpropargyl phenylpropiolate, *trans*-cinnamyl phenylpropiolate, and *trans*-cinnamyl *cis*-cinnamate types were cyclized in refluxing acetic anhydride to form lignan lactones containing the 1-phenylnaphthalene nucleus, as well as its 3,4-dihydro and 1,2,3,4-tetrahydro analogs, respectively. By this intramolecular Diels-Alder reaction the derived natural products dehydroanhydropicropodophyllin, dehydrodimethylconidendrin, *rac*-γ-apopicropodophyllin, and *rac*-isodesoxypicropodophyllin were readily synthesized. Although the *trans*-cinnamyl moiety functions only as a diene in these cyclizations, the phenylpropargyl group may serve either as a "diene" or as a dienophile. Structures of products formed were assigned on the bases of spectral characteristics and/or direct comparisons with authentic specimens.

LIGNANS are natural plant products which can be considered dimers of the basic unit Ar–C–C–C (where Ar represents a phenyl group bearing one or more hydroxy, methoxy, and/or methylenedioxy substituents), bonded together at the β-carbons of the side chains.[1] Amongst the various structural patterns of lignans which occur we are here concerned only with the 4-aryltetrahydronaphthalene lactone (or cyclolignan lactone)[2] type and the dehydro analogs thereof. Thanks especially to the efforts of groups led by Haworth,[1] Hartwell and Schrecker,[1,3] Gensler,[4] and Schreier[5] many of these compounds have been synthesized by multistep procedures and their stereochemistries have been elucidated. We wish to report here the adaptation of a novel, simplified synthetic procedure which leads in one step (that of an intramolecular Diels-Alder reaction) directly from open-chain unsaturated esters to a variety of lignan lactones of this type. Two examples of this approach were presented in a preliminary communication[6] and the syntheses of a variety of open-chain unsaturated esters (some of which undergo this cyclization) have been reported.[7] More recently, cyclizations of the parent, unsubstituted molecules *trans*-cinnamyl phenylpropiolate (Ia) and phenylpropargyl phenylpropiolate (VIa),[8] as well as the thiophene analogs of Ia—*trans*-3-(2- and 3-thienyl)allyl phenylpropiolates[9]—have been effected. In this

[1] W. M. Hearon and W. S. MacGregor, *Chem. Rev.* **55**, 957 (1955); M. S. Adjangba, *Bull. Soc. Chim. Fr.* 2344 (1963).
[2] K. Freudenberg and K. Weinges, *Tetrahedron* **15**, 115 (1961).
[3] A. W. Schrecker and J. L. Hartwell, *J. Org. Chem.* **21**, 381 (1956).
[4] W. J. Gensler, C. M. Samour, S. Y. Wang and F. Johnson, *J. Amer. Chem. Soc.* **82**, 1714 (1960); W. J. Gensler and C. D. Gatsonis, *Ibid.* **84**, 1748 (1962); W. J. Gensler and F. Johnson, *Ibid.* **85**, 3670 (1963).
[5] E. Schreier, *Helv. Chim. Acta* **46**, 75, 2940 (1963); **47**, 1529 (1964).
[6] L. H. Klemn and K. W. Gopinath, *Tetrahedron Letters* No. 19, 1243 (1963).
[7] L. H. Klemn, K. W. Gopinath, G. C. Karaboyas, G. L. Capp and D. Hsu Lee, *Tetrahedron* **20**, 871 (1964).
[8] L. H. Klemm, K. W. Gopinath, D. Hsu Lee and C. E. Klopfenstein, submitted for publication.
[9] L. H. Klemm and K. W. Gopinath, *J. Heterocyclic Chem.* **2**, 225 (1965).

paper we report cyclizations of methoxy- and/or methylenedioxy substituted unsaturated esters of structures I (*trans*-enynic), IV (*trans, cis*-dienic) and VI (diynic). The rationale for this approach is based on the concept that joining two ArC_3 units through the γ-carbons should facilitate approach of the β-carbons, between which the desired bond needs to be formed.

In general, cyclizations were conducted by refluxing the unsaturated ester in acetic anhydride for 5 or 6 hr, a period selected because it was sufficiently long to cause the complete disappearance of the C≡C stretching band from the IR spectrum of Ib, taken directly on the reaction mixture. In most runs the concentration of ester was rather high (>10% by wt). Especially in cases Ib and Ic, where the open-chain esters were available in pure form, this use of concentrated solutions facilitated the isolation of cyclized products, which crystallized (in total yields of 53% and 43%, respectively) directly from the cooled reaction mixtures. A preliminary test on the cyclization of Ib at considerably lower concentration indicated the production (in solution) of a higher yield of cyclized compound, with little or no attendant color formation (such as occurred at higher concentration). Hence, those esters of type I (Id, Ie, If) which were available only as crude liquids were cyclized (in 22–43% overall yields) at low concentrations (0·5–1% by wt), although such methodology does introduce the problem of removal of excess solvent.[10] In a few cases of I and IV cyclization was effected by evaporative distillation of the open-chain ester, but yields were usually lower than from the acetic anhydride procedure due to extensive charring of the residue.

Cyclization of Ib gave two crystalline products, Y (m.p. 248°, 43% yield) and Z (m.p. 202°, 10% yield). Y proved to be identical with an authentic sample of *rac*-γ-apopicropodophyllin (IIb) kindly supplied from the stock of Schrecker and Hartwell. γ- Apopicropodophyllin was originally synthesized by Haworth and Richardson[11] by a multiple-step procedure, which was investigated further by Schrecker and Hartwell.[12] The latter workers also isolated this compound as a secondary degradation product resulting from dehydration of the naturally occurring tumor-necrotizing compound podophyllotoxin.[13]

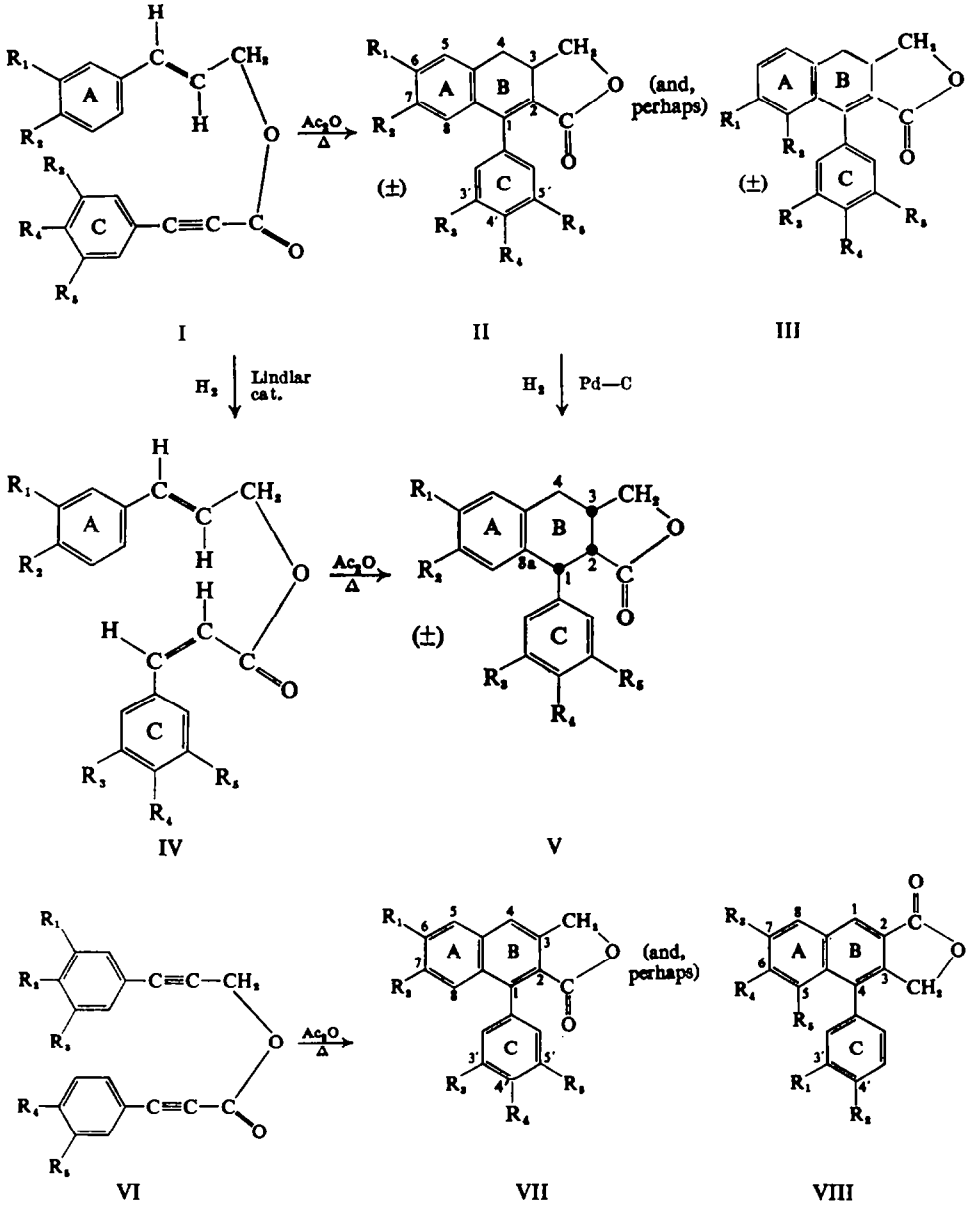
Microanalytical data on Z indicate that it is an isomer of Y. Moreover, the IR spectra of Y and Z are very similar and the NMR spectra in the region of $\delta < 5{\cdot}5$ ppm (where absorptions due to the methoxy and $-CH_2\underset{|}{C}HCH_2-$ groupings in Y occur) are virtually superimposable. At lower fields, however, the NMR spectrum of Z is more complex than that of Y inasmuch as the former contains all of the spectral features of the latter plus two additional ones. Specifically, in this low-field region Y shows singlets at 5·97 (2H, $-OCH_2O-$), 6·54 (3H, aromatic) and 6·78 ppm (1H, aromatic) while Z has a quartet at 5·64 (J = 1·2 c/s, 1·4H) and singlets at 5·94 (0·6H), 6·52 (0·8H), 6·64 (1·4H) and 6·75 (1·8H). On the basis of these data it is proposed that Z is actually a composite (probably a eutectic mixture or a molecular compound) of ca. 30% IIb and 70% IIIb, where IIIb would have NMR absorptions (in the region of $\delta > 5{\cdot}5$ ppm) at 5·64 (quartet, J = 1·2 c/s, 2H—AB-system in $-OCH_AH_BO-$), 6·64 (singlet, 2H-aromatic) and ca. 6·75 (singlet, 2H-aromatic). IIb would arise from

[10] More elaborate studies on the effects of solvent and concentration are planned for the system of unsaturated amides, now under investigation in our laboratory.

[11] R. D. Haworth and T. Richardson, *J. Chem. Soc.* 348 (1936).

[12] A. W. Schrecker and J. L. Hartwell, *J. Amer. Chem. Soc.* **74**, 5672 (1952).

[13] A. W. Schrecker and J. L. Hartwell, *J. Amer. Chem. Soc.* **74**, 5676 (1952).



a: $R_1 = R_2 = R_3 = R_4 = R_5 = H$
b: $R_1R_2 = —OCH_2O—$, $R_3 = R_4 = R_5 = CH_3O$
c: $R_1R_2 = —OCH_2O—$, $R_3 = R_4 = CH_3O$, $R_5 = H$
d: $R_1 = R_2 = R_3 = R_4 = CH_3O$, $R_5 = H$
e: $R_1 = R_3 = CH_3O$, $R_2 = R_4 = R_5 = H$
f: $R_1 = R_2 = R_5 = H$, $R_3 = R_4 = CH_3O$

substitution *para* to one position of attachment of the methylenedioxy group in ring A of Ib and IIIb, from corresponding *ortho* substitution into ring A. The appearance of an upfield-shifted quartet for a methylenedioxy group which occurs in a molecular environment similar to that present in IIIb has been noted in the apomorphine alkaloids dicentrine and bulbocapnine[14] and is more closely exemplified in the cyclolignans (of the tetrahydro type) otobain[15,16] and hydroxyotobain.[17] Spectra of these latter cyclolignans show (for the ring A methylenedioxy group) coupling constants of 1·2–1·5 c/s and upfield shifts (from the 3′,4′-methylenedioxy substituent, present in ring C, taken as a standard) of 0·25–0·30 ppm (note: difference of 0·33 ppm between IIb and IIIb). The spectrum of dehydrootobain,[15,18] on the other hand, shows no splitting of the ring A methylenedioxy signal but does retain the upfield shift (0·27 ppm) thereof.

Cyclization of the *trans*-enynic ester Ic gave only one isolable, crystalline product (W, m.p. 223°, 43% yield) which like Z showed both a quartet at 5·67 (J = 1·5, 1·3H) and a singlet at 5·97 ppm (0·7H). As in the case of Z it is again proposed that W is a composite of ca. 30–35% IIc and 65–70% IIIc. In fact, the possibility that each of the products Z and W is a molecular compound of composition III:II = 2:1 seems attractive. An alternative possibility that we have, instead, pure single compounds IIIb and IIIc, respectively, which exist in two NMR-distinguishable conformations was considered. However, the spectra of Z (W not investigated) in dimethylformamide at 25° and at 140° were essentialy identical with respect to the methylenedioxy singlet-quartet region. Thus, this alternative appears to be untenable. On the other hand, limited efforts to separate Z and W by recrystallization and chromatography have not been successful. Hence, the postulation that these products are mixtures must still be deemed tentative.

Cyclizations of the tetramethoxy *trans*-enynic ester Id as well as the corresponding dimethoxy esters Ie and If led to only one crystalline product in each case (assigned structures IId, IIe, and IIf, respectively). Our sample of IId showed a m.p. which compared favorably with that reported by Haworth et al.[19] for this compound synthesized by another method. Additional evidence for the structure of IId was obtained by dehydrogenation of our sample with lead tetraacetate in acetic acid to the known VIId[19–21] (again of melting point comparable to literature values). NMR spectra of our samples showed all methoxy absorption bands in the expected region (ca. 3·6–4·0 ppm) and none shifted further upfield as should occur for IIId and its dehydro derivative as well as for IIIe (cf. VIIIb, *vide infra*). Comparison of the NMR spectra

[14] S. Goodwin, J. N. Shoolery and L. F. Johnson, *Proc. Chem. Soc.* 306 (1958); L. M. Jackman, *Applications of Nuclear Magnetic Resonance Spectroscopy in Organic Chemistry* p. 127. Pergamon Press, Oxford (1959); *NMR Spectra Catalog*, spectra nos. 333 and 342. Varian Associates, Palo Alto (1962).

[15] N. S. Bhacca and R. Stevenson, *J. Org. Chem.* **28,** 1638 (1963).

[16] T. Gilchrist, R. Hodges and A. L. Porte, *J. Chem. Soc.* 1780 (1962).

[17] R. Wallace, A. L. Porte and R. Hodges, *J. Chem. Soc.* 1445 (1963).

[18] D. Brown and R. Stevenson, *J. Org. Chem.* **30,** 1759 (1965); *Tetrahedron Letters* No. 43, 3213 (1964).

[19] R. D. Haworth, W. Kelly and T. Richardson, *J. Chem. Soc.* 725 (1936).

[20] R. D. Haworth and G. Sheldrick, *J. Chem. Soc.* 636 (1935).

[21] M. E. Cisney, W. L. Shilling, W. M. Hearon and D. W. Goheen, *J. Amer. Chem. Soc.* **76,** 5083 (1954).

of these three compounds clearly shows that the methoxy signals in IId (at δ = 3·64—3H, 3·86—3H, and 3·93—6H) are essentially an additive composite of the methoxy signals in IIe (3·58—3H, 3·91—3H) and IIf (3·84—3H, 3·88—3H). The corresponding dehydro compounds VIId (signals for 3H each at 3·76, 3·85, 3·94, 4·01) and VIIf (signals at 3·87 and 3·98) [*vide infra*, VIIe not prepared] show a similar relationship, whereby one of the methoxy substituents in the A-ring (either at C-6 or C-7) corresponds to the signal at highest field (smallest δ-value) and the other substituent on the same ring most likely corresponds to the signal at lowest field. We propose that it is the 7-methoxy group which produces the methoxy signal at the highest field in IId, IIe, and VIId, respectively, as based on the following considerations. Vicinal methoxy groups on a benzene ring cannot be freely rotating (due to steric interference with each other) but would prefer to assume conformations *anti* to one another.[22] For maximal resonance stabilization these groups should favour conformations which are approximately coplanar with the aromatic ring. For the 6-methoxy group the favored location of the methyl moiety should be near C-5, while for the 7-methoxy group it should be near C-8. In fact, when the 7-methoxy group is completely coplanar with ring A the carbon of the methyl group will occupy a position in space close to that of a 7,8-methylenedioxy substituent. The geometry will be such that the methyl moiety of the 7-methoxy group will lie within the inner portion of the induced magnetic field of the non-coplanar (i.e. twisted with respect to ring A) ring C. This situation should result in an upfield shift of the signal for the 7-methoxy group from the signal for the 6-methoxy group, which does not encounter such an environment. Actually the difference of 0·25–0·29 ppm between the signals for the 6- and 7-methoxy protons is nearly equal to the difference (0·33 ppm) between the signals for the methylenedioxy protons (quartet) in IIIb and in IIb (singlet). Unlike the situation for the methylenedioxy case, however, the facile rotation of the methyl group around the O—C bond of the 7-methoxy group makes the protons equivalent. Analogous situations may be found in the otobain series with respect to methylenedioxy groups (*vide supra*) and in the isootobain series[17] (δ-shift = 0·22–0·23 ppm), the dimethylconidendrin series (shift ca. 0·2 ppm),[23] and the isosikkimotoxin series,[24] e.g. X, (shift 0·20–0·24) with respect to the methoxy groups.

Earlier we reported[7] the syntheses of the *trans,cis*-dienic esters IVb and IVc as well as of several analogous *trans,trans*-dienic esters. Efforts to effect cyclization of the *trans,trans* esters (by means of refluxing in acetic anhydride for as long as 72 hr) were of no avail. Starting material was always recovered. In contrast, a period of 24 hr of refluxing in this solvent was sufficient to accomplish cyclization (in 20% and 43% yields, respectively) of the two *trans,cis* esters. In each of these latter cases only one crystalline product, assigned respective *cis*(1:2),*cis*(2:3) structures Vb and Vc (ν_{max} for lactone C=O at 1770 cm^{-1}) was isolated from the reaction mixture. A careful check of the total product by means of column chromatography and IR spectral investigations of the effluent fractions failed to show the presence of any isomeric compounds, particularly ones with a *cis*(1:2),*trans*(2:3) configuration (ν_{max} expected to occur at

[22] L. H. Klemm, E. P. Antoniades and C. D. Lind, *J. Org. Chem.* **27**, 519 (1962).
[23] Y. Kato, *Chem. Pharm. Bull.* **11**, 823 (1963); See compounds XIV and XV.
[24] See first paper in Ref. 5.

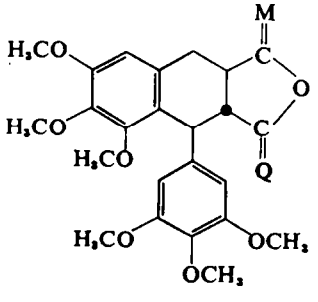
1780–1785 cm^{-1}).[25] The product from IVb was identified as *rac*-isodesoxypicropodophyllin (Vb) by direct comparison with an authentic specimen derived from hydrogenation of *rac*-γ-apopicropodophyllin (IIb). The structure of Vc was assigned on the basis of its IR and NMR spectra. The latter showed methoxy proton signals at 3·69 and 3·77 ppm (consistent with location of the methoxy groups in ring C but not in ring A) and a sharp singlet at 5·99 ppm for the methylenedioxy group (consistent with its location in the 6,7-positions of ring A or the 3′,4′-positions of ring C but not in the 7,8-positions of A).

Although examples of *cis,trans*- and *cis,cis*-dienic esters remain to be studied, it is apparent that the intramolecular Diels-Alder reaction of cinnamyl cinnamates is highly stereo-specific under our reaction conditions. It is to be expected that *cis*-addition will occur to the cinnamate carbon-carbon double bond[26] and lead, thereby (barring possible epimerization at C-2), to a retention in the product (at C-1 : C-2) of the geometric arrangement (*cis* or *trans*) of the hydrogen atoms present in the cinnamate moiety of the open-chain ester. But the stereochemistry of the C-2 : C-3-juncture should be determined by the preferred orientation of the dienic and dienophilic moieties in the transition state. Examination of Stuart-Briegleb molecular models shows that in order to bring dienic (i.e. phenylvinyl—including the A-ring) and dienophilic (i.e. cinnamate C=C) moieties into juxtaposition for intramolecular Diels-Alder reaction one must fold the molecule back onto itself like a hinge, where the alcoholic oxygen atom serves as the pivot point. It appears that the best conformation conducive to reaction which is available in the *trans-cis* esters involves extensive overlapping (in nearly parallel planes) of the approximately coplanar phenylvinyl groups from *both* acid and alcohol moieties. In this conformation one has (a) hydrogens that will appear at C-1, C-2 and C-3 in the product all pointing to the same edge of the hinge (cf. formula V), (b) simultaneous contact of C-2 with C-3 and of C-1 with C-8a, and (c) maximum overlap of the π-systems (*endo* geometry, consistent with the Alder rule).[27,28] Reaction should then result in a *cis*(2:3)-juncture. Also it appears that to attain a *trans*(2:3)-juncture the two aryl moieties must be twisted nearly perpendicular to one another (poor overlap of π-systems) in order to allow proximity of the appropriate carbon atoms. Models of the *trans,trans* esters do not permit both good contact of appropriate atoms and appreciable overlap of π-systems at the same time. It might also be noted that one finds both good contact and fair overlap in models of the reactive *trans*-enynic esters, but neither of these in the non-reactive phenylpropargyl *trans*-cinnamate.[8]

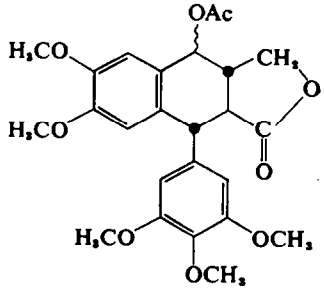
In accordance with general observations on the intermolecular Diels-Alder reaction,[26,27] the alcohol moiety of the *trans*-enynic esters and of the *trans,cis*-dienic esters always functioned as the diene and the acid moiety of these esters functioned as the dienophile in our intramolecular Diels-Alder reaction (i.e. cyclization occurred into the aryl group of the alcohol moiety in every case). For the diynic esters VI, just as for mixed anhydrides of two different arylpropiolic acids,[29] cyclization may occur

[25] A. W. Schrecker and J. L. Hartwell, *J. Amer. Chem. Soc.* **75**, 5916 (1953).
[26] M. C. Kloetzel, *Organic Reactions* (Edited by R. Adams) Vol. IV, Chap. 1. Wiley, New York (1948).
[27] H. L. Holmes, *Organic Reactions* (Edited by R. Adams) Vol. IV, Chap. 2. Wiley, New York (1948).
[28] The *endo* product is probably also thermodynamically more stable than the *exo* product in this case.
[29] F. G. Baddar and L. S. El-Assal, *J. Chem. Soc.* 1844 (1951); F. G. Baddar, L. S. El-Assal and N. A. Doss, *J. Chem. Soc.* 1027 (1959).

into either ring. Thus, the parent unsubstituted ester VIa, gave only one isolable product VIIa from cyclization into the phenyl ring of the alcohol moiety.[8] On the other hand, cyclizations of the substituted esters VIb and VId led to mixtures of isomers of types VII and VIII (the latter from cyclization into the aryl ring of the acid moiety). Needed for syntheses of the substituted diynic esters were the previously unknown 3,4-methylenedioxy- and 3,4-dimethoxyphenylpropargyl alcohols. These were obtained in ca. 70% yields by reduction (at −70° and −40°, respectively) with LAH of the corresponding methyl 3,4-disubstituted-phenylpropiolates. In each case, suitable reaction conditions were devised only as the result of a series of experiments with varying reaction time, temperature, and molar ratio of reducing agent to oxidant. The milder conditions reported[30] for reduction of methyl phenylpropiolate to phenylpropargyl alcohol failed to yield reaction of the substituted methyl esters. The diynic esters were not isolated in pure form since they cyclized to some extent during processing or while standing at room temperature. Infrared examination of the crude diynic esters showed the presence of carbon-carbon triple bond and ester carbonyl functions, both of which disappeared upon treatment of the compounds with acetic anhydride. From VIb there were obtained crystalline isomeric compounds of melting points 203° (13% yield) and 265° (11% yield). The 265°-isomer was identified as dehydroanhydropicropodophyllin (VIIb, no NMR absorption at $\delta > 7{\cdot}7$ ppm) by direct comparison with an authentic sample prepared from podophyllotoxin. The 203°-isomer was assigned the structure of VIIIb on the basis of its NMR spectrum (in CCl_4) which showed a high-field singlet (at 3·40 ppm) for one of the methoxy groups (at C-5) plus two normal singlets (at 3·94 and 4·03) for the other two methoxy groups, a singlet for the methylenedioxy group, and a low-field singlet (at 8·30) for one aromatic proton (at C-1, *ortho* to the lactone carbonyl group). The upfield methoxy signal occurs at a field displaced by ca. −0·2 ppm from that of the 7-methoxy signal found in IId and IIe (measured in $CDCl_3$). As expected, once the position in the naphthalene nucleus *peri* to ring C is occupied by a bulky substituent (R_5 in VIII) the effect of the ring current from C is not transmitted to a methoxy group *ortho* (i.e. at C-6 in VIII) to this substituent. The presence of an exceptionally high-field methoxy signal (at ca. 3·2 ppm) has been noted in the NMR spectra of the cyclolignan lactones resinolide (IXa) and retroresinolide (IXb),[30a] but not in *rac*-O-acetylisosikkimotoxin (X).[24]



IX a: M = O, Q = H_2
b: M = H_2, Q = O



X

[30] E. B. Bates, E. R. H. Jones and M. C. Whiting, *J. Chem. Soc.* 1854 (1954).
[30a] See Ref. 23, compounds VI and VII.

The tetramethoxydiynic ester VId cyclized to give two crystalline isomeric compounds of melting points 213° (12% yield) and 252° (4·5% yield). The 213°-isomer was identical with an authentic specimen of dehydrodimethylconidendrin (VIIId) prepared from the natural product α-conidendrin by successive steps of methylation and dehydrogenation. The 252°-isomer was identical with our compound VIId, obtained by dehydrogenation of IId as described previously. The identity of the samples of VIId which result from the separate synthetic routes helps to corroborate the structural assignment of this compound. An observation of diagnostic pertinence to the direction of cyclization in these diynic esters is the presence in a compound of structural type VIII (or its absence in a compound of structural type VII) of a low-field singlet at ca. $\delta > 8{\cdot}0$ ppm in the aromatic proton region of the NMR spectrum of the product. This signal is ascribed to the proton at C-1 (in VIII) under the influence of the lactone carbonyl function at C-2. The presence of this signal at 8·30 was noted for VIIIb but was lacking for dehydroanhydropicropodophyllin. Likewise, dehydrodimethylconidendrin shows a well-defined singlet at 8·30 while the 252°-isomer shows no absorption at $\delta > 7{\cdot}8$. In 1-phenylnaphthalene-2,3-dicarboxylic acid anhydride such singlet occurs at 8·66,[8] while in dimethyl 1-(2-bromo-4,5-methylenedioxyphenyl)-5-bromo-7,8-methylenedioxynaphthalene-2,3-dicarboxylate it appears at 8·90 ppm.[18]

EXPERIMENTAL

UV spectra were determined by means of a Cary Model 11 spectrophotometer. IR spectra were obtained in $CHCl_3$ by means of a Beckman IR-7 spectrophotometer. NMR spectra were obtained by means of a Varian A-60 spectrometer using tetramethylsilane as an internal standard and (unless otherwise indicated) $CDCl_3$ as solvent. Elemental analyses were performed by Micro-Tech Laboratories, Skokie, Illinois.

1-*Phenyl*-3,4-*dihydronaphthalene Lignan Lactones*

General spectral observations. Both crude and pure *trans*-I show strong IR absorption bands at 2220–2240 (C≡C) and 1700 ± 10 cm^{-1} (α,β-unsaturated ester C=O) as well as (in most cases) at ca. 970 cm^{-1} (*trans* CH=CH). On cyclization the first and last of these bands disappeared and the middle band was shifted to 1745–1755 cm^{-1} (α,β-unsaturated γ-lactone C=O). In a separate paper[6] the complex NMR spectrum due to the 5-proton system $-CH_2-\underset{|}{CH}-CH_2-$ present in the parent cyclized compound (IIa, IIIa) is presented and analyzed. In the substituted derivatives of II and III considered here, absorption bands due to this same 5-proton system are likewise evident in the spectra, but these absorptions are not reported for the individual compounds. Corrections to the integrated areas for the far more intense sharp methoxy absorptions which overlap part of the same region were made.

Cyclization of trans-3,4-*methylenedioxycinnamyl* 3,4,5-*trimethoxyphenylpropiolate* (Ib)

A solution of Ib[7] (3 g) in Ac_2O (10 ml) was refluxed for 6 hr. The precipitate (1·8 g) which formed on refrigeration overnight of the resultant solution was collected by filtration, dried, and dissolved in hot $CHCl_3$. Dilution with an equal volume of MeOH, concentration of the mixture, and cooling gave crystals, m.p. 245–248°. Recrystallization from the same solvent mixture gave fine colorless needles of IIb, yield 1·3 g (43%), m.p. 252–253°; NMR absorptions at $\delta = 3{\cdot}86$ (singlet, 6H—2MeO at 3′- and 5′-positions), 3·95 (singlet, 3H—MeO at 4′- position), 5·97 (singlet, 2H—OCH_2O), 6·54 (singlet, 3H—aromatic) and 6·78 ppm (singlet, 1H—aromatic). (Found: C, 67·02; H, 5·08. $C_{22}H_{20}O_7$ requires: C, 66·66; H, 5·90%.) This synthetic product was identical in m.p., mixture m.p., IR and UV absorption spectra with a sample of *bona fide rac*-γ-apopicropodophyllin derived from the natural product podophyllotoxin and kindly furnished to us from the stock of Schrecker and Hartwell.[18]

Dilution with MeOH of the mother liquor from crystallization of IIb and then contrancetion to a small volume gave small yellow crystals (0·4 g) which were recrystallized once from the same solvent mixture and twice from MeOH alone to form yellow needles of Z, probably a *molecular compound*

of IIb *and* 1-(3,4,5-*trimethoxyphenyl*)-3-*hydroxymethyl*-7,8-*methylenedioxy*-3,4-*dihydro*-2-*naphthoic acid lactone* (IIIb), yield 0·3 g (10%), m.p. 201–202°; λ_{max} (abs EtOH) in mμ (log ε) 307 (4·00), 350 (3·97); λ_{min} 272 (3·67), 345 (3·88); general IR spectrum very similar to that of IIb; NMR absorptions at δ = 3·81 (singlet, 6H—2MeO at 3′- and 5′-positions), 3·89 (singlet, 3H—MeO at 4′-position), 5·64 (quartet, J_{AB} = 1·2 c/s, δ_{AB} = 4·9 c/s, ca. 1·4H—OCH_AH_BO), 5·94 (singlet, ca. 0·6H—OCH_2O unsplit), and singlets at 6·52 (0·8H), 6·64 (1·4H), and 6·75 ppm (1·8H) for a total of 4 aromatic protons. (Found: C, 66·21; H, 5·40. $C_{22}H_{20}O_7$ requires: C, 66·66; H, 5·09%.)

Evaporative distillation of Ib (200 mg) at 235–240° (0·3 mm) for 24 hr gave a crude sublimate, m.p. 175–215°. Three crystallizations from AcOEt–MeOH gave pale brown crystals (21 mg, m.p. 242–244°), believed to consist largely of IIb.

Cyclization of trans-3,4-*methylenedioxycinnamyl* 3,4-*dimethoxyphenylpropiolate* (Ic)

Refluxing Ic[7] (0·6 g) in Ac_2O (4 ml) for 6 hr and then refrigerating the mixture gave crystals which were washed with cold, fresh Ac_2O (yield 0·26 g, 43%, m.p. 220–222°) and recrystallized first from $CHCl_3$–EtOH and then from AcOEt to form yellow-green prisms of W, m.p. 222–223°, probably a *molecular compound of* 1-(3,4-*dimethoxyphenyl*)-3-*hydroxymethyl*-6,7-*methylenedioxy*-3,4-*dihydro*-2-*naphthoic acid lactone* (IIc) *and* 1-(3,4-*dimethoxyphenyl*)-3-*hydroxymethyl*-7,8-*methylenedioxy*-3,4-*dihydro*-2-*naphthoic acid lactone* (IIIc); λ_{max} ($CHCl_3$) in mμ (log ε) 292 (4·09), 303 shoulder (4·08), 347 (4·05); λ_{min} 275 (3·99), 330 (4·02); NMR absorptions at δ = 3·86 and 3·93 (two sharp singlets, 3H each—$2CH_3O$), 5·67 (quartet, J_{AB} = 1·5 c/s, δ_{AB} = 3·7 c/s, ca. 1·3H—OCH_AH_BO), 5·97 (singlet, ca. 0·7H—OCH_2O unsplit), 6·51 (singlet, 0·5H—aromatic), and 6·7–7·0 ppm (complex, 4·5 H—aromatic). (Found: C, 68·74; H, 4·97. $C_{21}H_{18}O_6$ requires: C, 68·84; H, 4·95%.)

1-(3,4-*Dimethoxyphenyl*)-3-*hydroxymethyl*-6,7-*dimethoxy*-3,4-*dihydro*-2-*naphthoic acid lactone* (IId)

A mixture of 3,4-dimethoxyphenylpropiolic acid (5·8 g, 0·028 mole), fresh reagent-grade thionyl chloride (4·5 ml, 0·062 mole), and anhydrous benzene (30 ml) was refluxed for 1·5 hr. To the residue from evaporation of the mixture was added benzene (40 ml) and a solution of *trans*-3,4-dimethoxycinnamyl alcohol (5·5 g, 0·028 mole) in anhydrous pyridine (5 ml). This mixture was refluxed for 5 hr, cooled, and washed successively with 2N HClaq, 10% $NaHCO_3$aq, and water. Evaporation of the dried benzene layer gave 7·8 g of crude trans-3,4-*dimethoxycinnamyl* 3,4-*dimethoxyphenylpropiolate* (Id).

A solution of crude Id (3 g) in Ac_2O (500 ml) was refluxed for 6 hr and poured slowly into water (500 ml). The mixture was evaporated *in vacuo*. A $CHCl_3$-solution of the residue was washed with 10% $NaHCO_3$aq and then water, dried, and evaporated. Chromatography of the dark residue on neutral alumina using a binary eluent which varied from pure benzene to pure AcOEt gave intermediate fractions of yellow effluent that contained 2·1 g of solid. Crystallization from MeOH gave yellow plates of IId (1·3 g, 32% overall from dimethoxyphenylpropiolic acid), m.p. 221–222°, lit.[19] 216–217°; NMR absorptions at δ = 3·64 (singlet, 3H—CH_3O at 7-position), 3·86 (singlet, 3H—CH_3O at 3′- or 4′-position), 3·93 (singlet, 6H—$2CH_3O$, at 6- and at 4′- or 3′-positions), 6·58 (1H at 8-position), 6·79 (doublet, J = 1 c/s, 1H at 5-position), 6·93 (>2H, including ones at 2′- and 5′-positions), and 7·26 ppm (<1H—aromatic). (Found: C, 68·85; H, 5·77. $C_{22}H_{22}O_6$ requires: C, 69·10; H, 5·80%.)

1-*Phenyl*-3-*hydroxymethyl*-6,7-*dimethoxy*-3,4-*dihydro*-2-*naphthoic acid lactone* (IIe)

This was prepared from phenylpropiolic acid (Aldrich Chemical Co.) and *trans*-3,4-dimethoxycinnamyl alcohol in the same manner as used for the synthesis of IId. The intermediate enynic ester, trans-3,4-*dimethoxycinnamyl phenylpropiolate* (Ie), was obtained as a crude, dark liquid. Chromatography and crystallization of the cyclized product gave cream-colored needles of IIe, m.p. 180–181° (22% overall yield); NMR absorptions at δ = 3·58 (singlet, 3H—CH_3O at 7-position), 3·91 (singlet, 3H—CH_3O at 6-position), 6·44 (singlet, 1H at 8-position), 6·75 (broad singlet, 1H at 5-position), and 6·9–7·5 ppm (complex, 5H—phenyl group). (Found: C, 74·79; H, 5·79. $C_{20}H_{16}O_4$ requires: C, 74·52; H, 5·63%.)

1-(3,4-*Dimethoxyphenyl*)-3-*hydroxymethyl*-3,4-*dihydro*-2-*naphthoic acid lactone* (IIf)

This was prepared from 3,4-dimethoxyphenylpropiolic acid and *trans*-cinnamyl alcohol in the same manner as used for the synthesis of IId, except that chromatography was omitted as part of the

purification process. The intermediate enynic ester, trans-*cinnamyl* 3,4-*dimethoxyphenylpropiolate* (If), was obtained as a red liquid. IIf formed tan needles, m.p. 188–189° (43% overall yield); NMR absorptions at δ = 3·84 and 3·88 (two singlets, 3H each—$2CH_3O$), 6·86 (>2H, including ones at 2′- and 5′-positions), and 6·9–7·3 ppm (complex, ca. 5H—aromatic). (Found: C, 74·29; H, 5·79. $C_{20}H_{18}O_4$ requires: C, 74·52; H, 5·63%.)

1-*Phenyl*-1,2,3,4-*tetrahydronaphthalene Lignan Lactones*

rac-*Isodesoxypicropodophyllin* (Vb)

(a) *By cyclization.* A mixture of IVb[7] (0·6 g) and Ac_2O (9 ml) was refluxed for 24 hr. The residue from removal of the solvent (using repetitive evaporation *in vacuo* with MeOH) was chromatographed on a column of neutral alumina using AcOEt (15–30%)–benzene as eluent. The solid (0·19 g) from one fraction of effluent formed needles from MeOH, yield 0·12 g (20%), m.p. 203–204°; ν_{max} at 1770 cm^{-1}; lit[25] needles, m.p. 203–204°; ν_{max} at 1765 cm^{-1}. (Found: C, 66·17; H, 5·71. $C_{22}H_{22}O_7$ requires: C, 66·32; H, 5·57%.)

Sublimation of IVb (190 mg) at 180–190° (0·2 mm) for 24 hr and crystallization of the sublimate from MeOH gave Vb (28 mg; 15%), identical with product from cyclization using Ac_2O.

(b) *By hydrogenation.* A solution of IIb (280 mg) in glacial AcOH was agitated for 2 hr with 10% Pd–C (260 mg) at 75° and in the presence of H_2 gas at 1·2 atm press. The residue from evaporation of the filtered solution was treated with MeOH. The methanolic extract was filtered (to remove unreacted IIb) and concentrated to give crystals (42 mg) of Vb, identical with product from part (a) as based on m.p., mixture m.p., and IR spectrum.

cis(1:2),cis(2:3)-1-(3,4-*Dimethoxyphenyl*)-3-*hydroxymethyl*-6,7-*methylenedioxy*-1,2,3,4-*tetrahydro*-2-*naphthoic acid lactone* (Vc)

Compound IVc[7] was cyclized by means of refluxing Ac_2O and processed in the manner used for the preparation of Vb. The product (m.p. 171–174°, 43% yield) was recrystallized from MeOH and then from MeOH–ethyl acetate to give prisms, m.p. 175–176°; ν_{max} at 1770 cm^{-1}; NMR absorptions at δ = 3·04 (broad, 4H), 3·69 and 3·77 (2 singlets, 3H each—$2CH_3O$) superimposed on 3·5–4·6 (complex, 3H), 5·99 (singlet, 2H—OCH_2O), 6·38 (singlet, 1H on 8-position), and 6·5–7·0 ppm (complex, 4H—aromatic). (Found: C, 68·65; H, 5·28. $C_{21}H_{20}O_6$ requires: C, 68·47; H, 5·47%.)

1-*Phenylnaphthalene Lignan Lactones*

3,4-*Dimethoxyphenylpropargyl alcohol*

To a cold (−40°), stirred suspension of LAH (1·5 g, 0·039 mole) in 50 ml dry ether was added dropwise a solution of 5 g (0·023 mole) methyl 3,4-dimethoxyphenylpropiolate[31] in 125 ml ether. The mixture was stirred 2·3 hr longer. Water was then added slowly and the mixture was allowed to warm to room temp. From the dried organic layer and ether extracts of the aqueous phase was obtained (on distillation) 3 g (68%) of light yellow liquid, b.p. 152–160° (0·2 mm), which crystallized on standing, m.p. 44–47°. Recrystallizations from benzene–petrol (60–90°) and then from petrol alone gave colorless prisms, m.p. 55–55·5°; ν_{max} at 3600 (medium, OH), 3520–3420 (weak, OH) and 2220 cm^{-1} (weak, C≡C); NMR absorptions at δ = 3·76, 3·79 (6H—$2CH_3O$), 4·11 (broad singlet, 1H—OH), 4·50 (broad singlet, 2H—methylene), and 6·6–7·2 ppm (multiplet, 3H—aromatic). (Found: C, 68·62; H, 6·63. $C_{11}H_{12}O_3$ requires: C, 68·73; H, 6·29%.)

The 3,5-*dinitrobenzoate* formed yellow needles from MeOH, m.p. 129·5–130°; ν_{max} at 2240 (weak, C≡C), 1740 (strong, C=O), 1515 and 1345 cm^{-1} (strong, NO_2). (Found: C, 55·96; H, 3·76; N, 7·52. $C_{18}H_{14}N_2O_8$ requires: C, 55·96; H, 3·65; N, 7·25%.)

3,4-*Methylenedioxyphenylpropargyl alcohol*

To a cold (−70°), stirred suspension of LAH (280 mg, 7·4 mmoles) in 30 ml of dry ether was added over a period of several seconds a solution of 2 g (9·8 mmoles) of methyl 3,4-methylenedioxyphenylpropiolate[7] (prepared in a manner analogous to that used for methyl 3,4-dimethoxyphenylpropiolate) in 28 ml of ether. After a reaction time of 1 hr water was added and the product was

[31] K. Freudenberg and G. Wilke, *Chem. Ber.* **85**, 78 (1952).

extracted as before. Evaporation of the ether left a liquid which gave yellow crystals (1·3 g, 76%) from benzene–petrol (30–60°), m.p. 72–75°, raised to 75–76° on recrystallizations from the same solvent mixture and then from CCl_4; ν_{max} at 3600 (sharp, OH), 3450 (broad, OH), and 2220 cm^{-1} (C≡C); NMR absorptions (CCl_4) at δ = 2·98 (broad singlet, 1H—OH), 4·38 (singlet, 2H—$OCH_2C{\equiv}$C), 5·90 (sharp singlet, 2H—OCH_2O), and 6·5–7·0 ppm (multiplet, 3H—aromatic). (Found: C, 67·74; H, 4·58. $C_{10}H_8O_3$ requires: C, 68·18; H, 4·58%.)

3-*Hydroxymethyl*-4-(3,4-*dimethoxyphenyl*)-6,7-*dimethoxy*-2-*naphthoic acid lactone* (VIIId)

Dimethyl-α-conidendrin (prepared by methylation of α-conidendrin)[23] was dehydrogenated by means of N-bromosuccinimide according to a published procedure.[21] The product (VIIId) was obtained as colorless crystals, m.p. 215·5–217°; lit[21] 209–211°, lit[20,23] 215–216°; ν_{max} at 1755 cm^{-1} (strong, five-membered lactone C=O); NMR absorptions at 3·82, 3·88, 3·99, 4·04 (12H—4 CH_3O), 5·22 (singlet, 2H—methylene), 6·8–7·4 (complex, 5H—aromatic), and 8·30 ppm (singlet, 1H at 1-position).

1-(3,4-*Dimethoxyphenyl*)-3-*hydroxymethyl*-6,7-*dimethoxy*-2-*naphthoic acid lactone* (VIId)

A sample of the foregoing lactone IId was dehydrogenated by means of lead tetraacetate in glacial AcOH at 80° according to published directions.[19] The product, VIId, was obtained as slightly yellow crystals from $CHCl_3$–MeOH, m.p. 251·5–253°; lit[19,20] colorless prisms, m.p. 254–255°; lit[21] yellow crystals, m.p. 245–249°; ν_{max} at 1755 cm^{-1}; NMR absorptions at δ = 3·76, 3·85, 3·94, 4·01 (12H—4CH_3O), 5·32 (sharp singlet, 2H—methylene), 6·8–7·4 (complex, 5H—aromatic), and 7·76 ppm (singlet, 1H—aromatic).

Cyclization of 3,4-*dimethoxyphenylpropargyl* 3,4-*dimethoxyphenylpropiolate* (VId)

A benzene solution (50 ml) of the acid chloride prepared from 3,4-dimethoxyphenylpropiolic acid[24] (4 g, 0·019 mole) was added to a mixture of 3,4-dimethoxyphenylpropargyl alcohol (4 g, 0·021 mole) in anhydrous pyridine (4 ml, 0·05 mole). The mixture was refluxed for 6 hr and processed as in the isolation of Id. The brown, oily product (7·1 g) was assigned the structure of VId; ν_{max} at 2240 (C≡C) and 1710 cm^{-1} (α,β-unsaturated ester C=O). Crude VId was refluxed with Ac_2O (20 ml) for 6 hr and processed further in the manner used for the preparation of IId. Treatment of the crude product with MeOH gave crystals which were recrystallized from $CHCl_3$–MeOH and identified as VIIId (m.p. 212–213°, undepressed on admixture with the previously described sample of VIIId obtained by dehydrogenation of dimethyl-α-conidendrin and identical with that sample in IR spectrum). Chromatography of the residue from the crystallization mother liquors gave first a liquid ester (discarded), then more VIIId, and finally a fraction of m.p. 249·5–252° (after recrystallizations), identified as VIId by direct comparison with the previously described sample thereof; overall yields 0·85 g (12%) of VIIId and 0·32 g (4·5%) of VIId.

Dehydroanhydropicropodophyllin (VIIb)

Essentially according to the procedure of Späth *et al.*[25] an intimate mixture of podophyllotoxin (1 g, m.p. 116–118°, isolated[26] from Merck Podophyllin N.F.) and 30% Pd–C (0·3 g) was sublimed at 275° (0·15 mm) for 8 hr. Crystallization of the sublimate (45 mg) from MeOH and then from AcOEt gave VIIb, m.p. 266·5–267·5°; lit[11] 267–268°; ν_{max} at 1760 cm^{-1}; NMR absorptions at δ = 3·83 (sharp singlet, 6H—2CH_3O at 3′- and 5′-positions), 3·96 (sharp singlet, 3H—CH_3O at 4′-position), 5·35 (broad singlet, 2H—lactone methylene), 6·05 (sharp singlet, 2H—OCH_2O), 6·54 (sharp singlet, 2H—aromatic), and 7·1–7·7 (complex, ca. 3H—aromatic).

Cyclization of 3,4-*methylenedioxyphenylpropargyl* 3,4,5-*trimethoxyphenylpropiolate* (VIb)

This was prepared and cyclized in a manner analogous to that used for VId. The crystals which deposited from the cooled Ac_2O cyclization mixture were separated and washed with MeOH, m.p.

[23] B. Holmberg and M. Sjöberg, *Ber. Dtsch. Chem. Ges.* **54**, 2406 (1921).
[24] R. D. Haworth, T. Richardson and G. Sheldrick, *J. Chem. Soc.* 1576 (1935).
[25] J. D. Fulton and R. Robinson, *J. Chem. Soc.* 1463 (1933).
[26] E. Späth, F. Wessely and L. Kornfield, *Ber. Dtsch. Chem. Ges.* **65**, 1536 (1932).
[26] J. L. Hartwell and W. E. Detty, *J. Amer. Chem. Soc.* **72**, 246 (1950).

263–265° (11% overall yield), identified as VIIb by direct comparison (mixture m.p. and IR spectrum) with the preceding sample thereof obtained from podophyllotoxin.

Admixture of the Ac_2O filtrate and the methanolic wash solution caused precipitation of a second crop of crystals. These were collected and washed with MeOH, m.p. 187–189° (13% overall yield). Recrystallizations from AcOEt and then from MeOH gave needles, m.p. 201·5–203°, of *3-hydroxymethyl-4-(3,4-methylenedioxyphenyl)-5,6,7-trimethoxy-2-naphthoic acid lactone* (VIIIb); ν_{max} at 1755 cm^{-1}; NMR absorptions (CCl_4) at δ = 3·40 (singlet, 3H—CH_3O at 5-position), 3·94 and 4·03 (two singlets, 6H—CH_3O groups at 6- and 7-positions), 5·08 (singlet, 2H—lactone methylene), 6·05 (singlet, 2H—OCH_2O), 6·7–7·3 (complex, 4H—aromatic), and 8·30 ppm (singlet, 1H—aromatic at 1-position). (Found: C, 66·91; H, 4·39. $C_{22}H_{18}O_7$ requires: C, 67·00; H, 4·60%.)

1-(3,4-Dimethoxyphenyl)-3-hydroxymethyl-2-naphthoic acid lactone (VIIf)

A mixture of IIf (1 g), 30% Pd–C (0·5 g) and *p*-cymene (40 ml) was stirred and refluxed for 44 hr. The catalyst was removed by filtration and the filtrate was evaporated. The residue crystallized from MeOH as light tan needles (0·7 g, 70%), m.p. 208·5–209·5°; ν_{max} at 1765 cm^{-1}; NMR absorptions at δ = 3·87 and 3·98 (two singlets, 3H each—$2CH_3O$), 5·43 (doublet, J = 1·2 c/s, 2H—methylene), 6·8–8·1 ppm (complex, 8H—aromatic). (Found: C, 74·78; H, 4·93. $C_{20}H_{16}O_4$ requires: C, 74·98; H, 5·04%.)

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