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Morpholino Mannich bases of types **5**, **12** react with tetronic acid in aqueous acetic acid to yield uncyclized lactones of types **7**, **13**. Acetylation and methylation of these products yields monoacetylmonomethyl derivatives which can then be cyclized in alkali to give unsaturated lactones of types **8**, **16** and saturated lactones **9b**, **15**. The hydroxylactone **9a** can be synthesized directly by reaction of 3,4,5-trimethoxybenzaldehyde with sesamol and tetronic acid in methanol. With few exceptions the lactones of type **8** and **16** have proven to be active inhibitors of tumor growth in the National Cancer Institute *in vitro* screening program against 60 diverse human cancer cell lines. The lactone **8** is particularly potent, inhibiting *in vitro* growth of some cancers at concentrations as low as 10^{-6}-10^{-7} moles/l.

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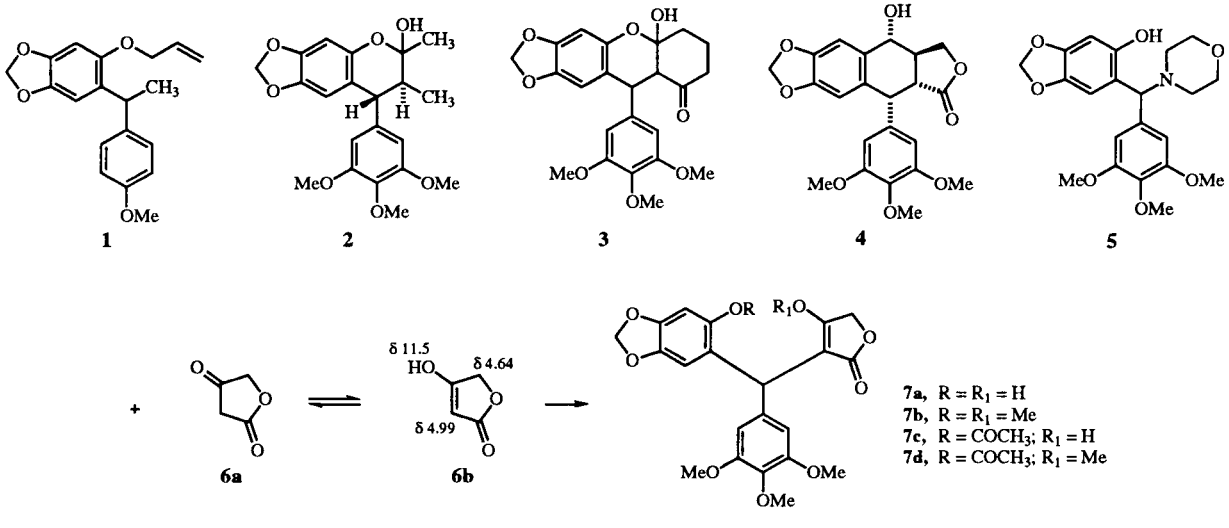
In a recent review of the status of chemotherapeutic agents in cancer treatment Boyd [1] noted that few of the available anti-cancer drugs in the U.S. have any useful clinical activity against most common forms of primary and disseminated cancer. He suggested that major progress in cancer chemotherapy will require the discovery and development of new chemotypes with unprecedented anti-tumor specificities and mechanisms of action. For this purpose, the National Cancer Institute in the late 1980's introduced and made available to researchers a new, extensive *in vitro* screening program which employs a panel of 60 human cancer cell lines of diverse types and produces much statistical information on the effects of a potential drug on cancer growth [2]. Since most randomly selected chemical agents do not inhibit tumor growth, this *in vitro* procedure pinpoints the very small percentage of compounds and lead structures which are active and may prove most likely to be effective in more extensive (and expensive) *in vivo* preclinical evaluation studies against susceptible cancer types. The purpose of this communication is to describe the synthesis and screening of a new class of heterocyclic benzylbenzodioxole lactones. Many of these lactones potently inhibit the *in vitro* growth of human cancers.

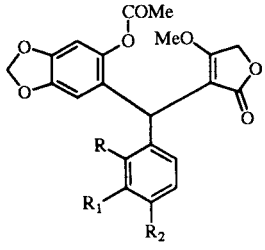
Chemistry.

Many benzyl-1-3-benzodioxoles of types **1**, **2**, and **3** have now been synthesized as potential insect sterilants and growth regulators [3]. These compounds possess some of the structural features found in podophyllotoxin **4**, a plant-derived anti-cancer drug, modifications of which are now in clinical use [4,5]. Like podophyllotoxin, some of the these benzylbenzodioxoles are active against P388 lymphocytic leukemia and other tumors and are potent anti-mitotic agents [6,7].

The benzodioxoles of types **2** and **3** were synthesized by reaction of Mannich bases of types **5**, **12** with ketones and β-diketones such as 2-butanone and cyclohexane-1,3-dione. Since tetronic acid **6** has become commercially available similar methods can now be developed for the synthesis of potentially bioactive, heterocyclic compounds which contain a lactone ring as in podophyllotoxin. Thus, the morpholino compound **5** [8] reacts readily with tetronic acid **6** in aqueous acetic acid at room temperature to give high



yields of a colorless compound, $C_{21}H_{20}O_9$, identified on the basis of its nmr spectra as the uncyclized lactone **7a**. The presence of two free hydroxyl groups in this product was also indicated by its formation of a di-*o*-methyl derivative **7b** on methylation. In its ^1H nmr spectrum methylene and benzylic methine protones appear at δ 4.64 and δ 5.27 respectively, and the protons of the two OH groups appear as broad signals at δ 9.28 and δ 11.64. The ^{13}C nmr spectrum shows signals *inter al.* of a methylene carbon (δ 66.3) and benzylic methine carbon (δ 37.7) as well as two quaternary C signals at δ 174.4 and δ 174.6. These two C signals are assigned to the carbonyl carbon and olefinic C attached to the hydroxyl of the lactone ring. These assignments in the proton and ^{13}C nmr spectra of **7a** (as well as in the related products described later) were readily made by comparison with the spectra of tetronic acid itself in dimethyl sulfoxide. The ^1H spectrum shows that tetronic acid exists as the enol **6b** with signals of CH_2, CH and enolic OH protons appearing at δ 4.64, 4.99 and 11.5 respectively. In the ^{13}C spectrum the two quaternary C carbons appear at δ 175.1 and δ 181.0.



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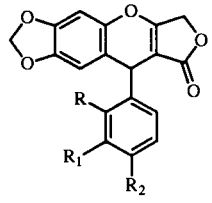

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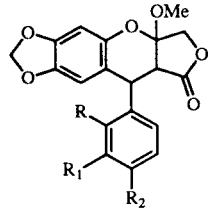

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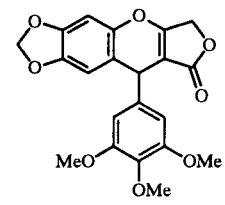
a, R = R_2 = OMe; R_1 = H
b, R = R_1 = OMe; R_2 = H
c, R = H; R_1 = R_2 = OMe
d, R = H; R_1 = R_2 = OCH_2O
e, R = R_1 = H; R_2 = OMe
f, R = R_2 = H; R_1 = OMe
g, R = OMe; R_1 = R_2 = H



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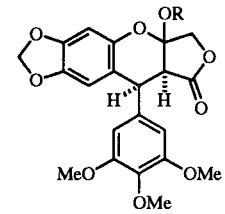
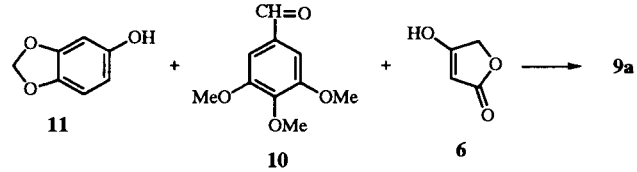
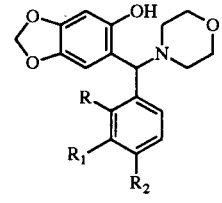


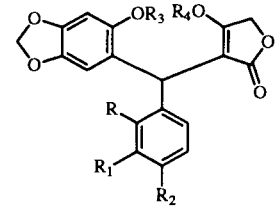
9a, R = H
9b, R = Me



11 **10** **6** **9a**



12a, R = R_2 = OMe; R_1 = H
12b, R = R_1 = OMe; R_2 = H
12c, R = H; R_1 = R_2 = OMe
12d, R = H; R_1 = R_2 = OCH_2O
12e, R = R_1 = H; R_2 = OMe
12f, R = R_2 = H; R_1 = OMe
12g, R = OMe; R_1 = R_2 = H



13a, R = R_2 = OMe; R_1 = R_3 = R_4 = H
13b, R = R_2 = OMe; R_1 = R_4 = H; R_3 = COMe
13c, R = R_2 = OMe; R_1 = H; R_3 = R_4 = COMe
13d, R = R_1 = OMe; R_2 = R_3 = R_4 = H
13e, R = R_3 = R_4 = H; R_1 = R_2 = OMe
13f, R = R_4 = H; R_1 = R_2 = OMe; R_3 = COMe
13g, R = R_3 = R_4 = H; R_1 = R_2 = OCH_2O
13h, R = R_4 = H; R_1 = R_2 = OCH_2O; R_3 = COMe
13i, R = R_1 = R_3 = R_4 = H; R_2 = OMe
13j, R = R_1 = R_4 = H; R_2 = OMe; R_3 = COMe
13k, R = R_2 = R_3 = R_4 = H; R_1 = OMe
13l, R = R_2 = R_4 = H; R_1 = OMe; R_3 = COMe
13m, R = OMe; R_1 = R_2 = R_3 = R_4 = H
13n, R = OMe; R_1 = R_2 = H; R_3 = R_4 = Me
13o, R = OMe; R_1 = R_2 = R_4 = H; R_3 = COMe
13p, R = OMe; R_1 = R_2 = H; R_3 = R_4 = COMe

Attempts to cyclize **7a** in acid solutions to give a hydroxy lactone structurally similar to **3** always gave mixtures of products. However, when **7a** is warmed with acetic anhydride containing sulfuric acid dehydration and cyclization readily occurs to give the unsaturated lactone **8**. Acetylation with acetic anhydride and pyridine, on the other hand, gives a monoacetate **7c** which can be methylated to yield the monoacetyl-monomethyl derivative **7d**. Hydrolysis of **7d** with sodium hydroxide may give two products, depending on reaction conditions. Rapid reaction of **7d** with methanolic sodium hydroxide gives the unsaturated lactone **8** in yields of about 80%. In aqueous methanolic sodium hydroxide, on the other hand, hydrolysis and cyclization of **7c** gives the saturated lactone **9b** in yields of about 50%.

As previously mentioned, attempts to prepare the hydroxy lactone **9a** by acid cyclization of **7a** were unsuccessful. However, it was eventually found that **9a** can be synthesized very easily by warming 3, 4,5-trimethoxybenzaldehyde **10** with sesamol **11** and tetronic acid in methanol. The pure lactone **9a** crystallizes from the reaction solution in yields of about 25%. The trimethoxybenzaldehyde appears to be unique in readily undergoing this reaction. Attempts to use other substituted benzaldehydes to form similar hydroxy lactones have been unsuccessful. In the ^1H nmr spectrum of the lactones **9a** and **9b** the protons of the methylene group are coupled and appear as doublets (J = 8 Hz) at δ 4.28, 4.39 and at δ 4.46, 4.64 respectively. The two CH protons are coupled with J = 2 Hz, indicating the *cis* stereochemistry of these two hydrogens.

Other morpholino (and piperidino) compounds of type **12**, related to the trimethoxy compound **5**, react similarly with tetronic acid in aqueous acetic acid to yield uncyclized lactones **13**. Acetylation of these with acetic anhydride and pyridine give monoacetates (**13**, $R_3 = COCH_3$, $R_4 = H$) and, in the case of lactones formed from morpholino Mannich bases derived from 2-methoxy- and 2,4-dimethoxybenzaldehydes, diacetates (**13**, $R_3 = R_4 = COCH_3$). Methylation of the mono and diacetates gives monomethylmonoacetyl derivatives **14**. With sodium hydroxide, as previously described, these give the corresponding saturated lactones **15** and/or unsaturated lactones **16**.

EXPERIMENTAL

The nmr spectra were determined in dimethyl sulfoxide with TMS as internal standard on a Nicolet NT-WB 200 FT instrument at 200 MHz (^1H) and at 50 MHz (^{13}C). Analyses were performed in a commercial laboratory. Melting points are uncorrected.

4-Hydroxy-3-[(6-hydroxy-1,3-benzodioxol-5-yl)(3,4,5-trimethoxy-phenyl)methyl]-2(5*H*)-furanone **7a**.

A mixture of the morpholino compound **5**[8] (4 g) and tetronic acid (1.5 g) was suspended in acetic acid (10 ml) and water (10 ml) and stirred to give a clear solution (about 5 minutes). The solution was kept at room temperature for 2 days whereupon the lactone **7a** crystallized as cream-colored, brittle needles, mp 194-195° (4.0 g, 97%); ^1H-nmr: δ 3.61 (OCH), 3.67 (2 OCH_3), 4.64 (CH_2), 5.27 (CH), 5.83 (d, J = 1 Hz) and 5.86 (d, J = 1 Hz) (OCH_2O), 6.39 (ArH), 6.48 (2 ArH), 6.70 (ArH), 9.28 (br s, OH), 11.64 (br s, OH); ^{13}C nmr: δ 37.7 (CH), 55.8 (2 OCH_3), 60.0 (OCH_3) 66.3 (CH_2), 99.4 (CH), 100.4 (CH_2), 101.2 (C), 105.9 (2 CH), 109.3 (CH), 120.4 (C), 135.8 (C), 138.3 (C), 139.2 (C), 145.6 (C), 149.0 (C), 152.4 (2C), 174.4 (C), 174.6 (C). This product is best used without further purification. It can be recrystallized from solvents such as methanol but partial isomerization to the cyclized lactone can occur.

Anal. Calcd. for $C_{21}H_{20}O_9$: C, 60.6; H, 4.8; M^+ = 416.1107. Found: C, 60.5; H, 5.0; M^+ = 416.1094.

Compound **7a** (2 g) was heated on a steam bath with acetic anhydride (10 ml) and pyridine (0.5 ml) for 5 minutes. Water was added and the solid product was recrystallized from acetone-methanol to give the monoacetate **7c** as colorless needles, mp 247-248° (2 g); ^1H-nmr: δ 2.17 ($COCH_3$), 3.64 (OCH_3), 3.69 (2 OCH_3), 4.60 (d, J = 16 Hz) and 4.69 (d, J = 16 Hz) (CH_2), 5.04 (CH), 6.00 (OCH_2O) 6.52 (2 ArH), 6.65 (ArH), 6.73 (ArH).

Anal. Calcd. for $C_{23}H_{22}O_{10}$: C, 60.3; H, 4.8; M^+ = 458.1210. Found: C, 60.0; H, 5.0; M^+ = 458.1227.

The lactone **7a** (0.5 g) was heated under reflux with dimethyl sulfate (0.5 g), anhydrous potassium carbonate (2 g) and acetone (10 ml) for 3 hours. The solvent was removed and the residue was washed with dilute aqueous acetic acid. Recrystallization from acetone-methanol provided the methylated derivative **7b** as colorless needles, mp 193-194° (0.44 g); ^1H-nmr: δ 3.58 (OCH_3), 3.67 (3 OCH_3), 3.83 (OCH_3), 5.01 (CH_2), 5.26 (CH), 5.88 (OCH_2O) 6.42 (2 ArH), 6.63 (ArH), 6.74 (ArH). This same product was obtained by methylation of the cyclized lactone **9a**.

Anal. Calcd. for $C_{23}H_{24}O_9$: C, 62.2; H, 5.4 Found: C, 62.1; H, 5.5.

A mixture of the acetate **7c** (2 g), methyl iodide (5 ml), potassium carbonate (6 g) and acetone (80 ml) was refluxed for 6 hours and filtered. The filtrate was evaporated leaving a solid which was washed with water and recrystallized from acetone-methanol to give **7d** as colorless, glistening plates, mp 178° (1.75 g); ^1H-nmr: δ 2.17 ($COCH_3$), 3.64 (OCH_3), 3.71 (2 OCH_3), 3.90 (OCH_3), 5.01 (d, J = 12 Hz) and 5.09 (d, J = 12 Hz) (CH_2) 5.02 (CH), 6.02 (OCH_2O), 6.47 (2 ArH), 6.61 (ArH), 6.76 (ArH); ^{13}C nmr: δ 20.5 ($COCH_3$), 38.3 (CH), 55.8 (2 OCH_3), 57.9 (OCH_3), 60.0 (OCH_3), 64.8 (CH_2) 101.6 (CH), 102.1 (OCH_2O), 104.1 (CH), 105.8 (2 CH), 108.6 (CH), 128.6, (C), 135.9 (C), 136.2 (C), 142.0 (C), 144.5 (C), 145.9 (C), 152.7 (2C), 169.2 (C), 173.4 (C), 178.2 (C), 197.6 (*C*OCH_3).

Anal. Calcd. for $C_{24}H_{24}O_{10}$: C, 61.0; H, 5.1. Found: C, 61.0; H, 5.3.

6,9-Dihydro-9-(3,4,5-trimethoxyphenyl)-8*H*-1,3-dioxolo[4,5-*g*]-furo[3,4-*b*][1]benzopyran-8-one **8**.

(a) A suspension of **7a** (0.5 g) in acetic anhydride (2 ml) containing a drop of concentrated sulfuric acid was warmed briefly on a steam-bath to give a clear solution. Within 3 minutes colorless crystals separated. Water was added and the product was collected. Recrystallized from acetone the unsaturated lactone **8** separated as colorless needles, mp 208-209° (0.42 g); ^1H-nmr: δ 3.62 (OCH_3), 3.78 (2 OCH_3), 4.81 (CH), 5.03 (d, J = 16 Hz) and 5.17 (d, J = 16 Hz) (CH_2) 6.0 (d, J = 1 Hz) and 6.06 (d, J = 1 Hz) (OCH_2O), 6.55 (2 ArH), 6.71 (ArH), 6.96 (ArH); ^{13}C nmr: δ 37.2 (CH), 55.9 (2 OCH_3), 59.7 (OCH_3), 65.7 (CH_2), 98.6 (CH), 101.4 (OCH_2O), 102.0 (C), 105.3 (2 CH), 108.4 (CH), 115.5 (C), 138.4 (C), 139.4 (C), 143.5 (C), 144.9 (C), 147.0 (C), 152.9 (2C), 169.8 (C), 170.7 (C).

Anal. Calcd. for $C_{21}H_{18}O_8$: C, 63.3; H, 4.6; M^+ = 398.1001. Found: C, 63.3; H, 4.8; M^+ = 398.1001.

(b) A drop of 10% aqueous sodium hydroxide was added to a suspension of the acetate **7d** (0.2 g) in boiling methanol (5 ml). Within a couple of seconds a clear solution was obtained. After 10 seconds a second drop of 10% sodium hydroxide was added. Colorless needles rapidly separated. These were collected (0.16 g) and recrystallized from acetone-methanol to give the pure lactone **8**, mp 208-209°.

5a,6,8a,9-Tetrahyrdro-5a-methoxy-9-(3,4,5-trimethyoxyphenyl)-8*H*-1,3-dioxolo[4,5-*g*]furo[3,4-*b*][1]benzopyran-8-one **9b**.

Aqueous sodium hydroxide (10%, 5 ml) was added to a suspension of the acetate **7d** (1.0 g) in boiling methanol (25 ml). The clear solution thus obtained was heated for 10 minutes, diluted with water (50 ml) and acidified with concentrated hydrochloric acid (5 ml). Crystals separated. These were collected and recrystallized from acetone-methanol to give the lactone **9b** as colorless needles, mp 179-180° (0.52 g); ^1H-nmr: δ 3.41 (OCH_3), 3.62 (d, J = 3 Hz, CH), 4.21 (d, J = 3 Hz CH), 4.46 (d, J = 8 Hz) and 4.64 (d, J = 8 Hz) (CH_2), 5.94 (d, J = 1 Hz) and 5.96 (d, J = 1 Hz) (OCH_2O), 6.38 (ArH), 6.68 (ArH), 6.70 (2 ArH).

Anal. Calcd. for $C_{22}H_{22}O_9$: C, 61.4; H, 5.2. Found: C, 61.4; H, 5.2.

5a,6,8a-9-Tetrahydro-5a-hydroxy-9-(3,4,5-trimethoxyphenyl)-8*H*-1,3-dioxolo[4,5-*g*]furo[3,4-*b*][1]benzopyran-8-one **9a**.

A solution of 3,4,5-trimethoxybenzaldehyde (2 g), sesamol (1.4 g) and tetronic acid (1 g) in methanol (20 ml) was heated to boiling under reflux for 2 hours and allowed to cool. Brittle, col-

orless crystals slowly separated. After several days the product was collected, mp 195-196° (1.1 g, 26%). Recrystallized from acetone the lactone separates as colorless brittle needles, mp 197-198°; ^{1}H-nmr: δ 3.47 (d, J = 2 Hz, CH), 3.64 (OCH_3), 3.73 (2, OCH_3) 4.21 (d, J = 2 Hz, CH), 4.28 (d, J = 8 Hz), 4.39 (d, J = 8 Hz) 5.92 (d, J = 1 Hz) and 5.94 (d, J = 1 Hz) (OCH_2O), 6.43 (ArH), 6.54 (ArH), 6.79 (2 ArH), 7.92 (br s, OH). This cyclized product **9a** is unstable. It undergoes ring opening on methylation or acetylation to yield **7b** and **7c** respectively.

Anal. Calcd. for $C_{21}H_{20}O_9$: C, 60.6; H, 4.8. Found: C, 60.8; H, 5.0.

Lactone **13a.**

A solution of the morpholino compound **12a** (10 g) and tetronic acid (6 g) in acetic acid (15 ml) and water (30 ml) was kept at room temperature for 24 hours. The crystalline product was recrystallized from acetone-methanol to yield the lactone **13a** as colorless needles, mp 182-183° (8.7 g, 84%); ^{1}H-nmr: δ 3.66 (OCH_3), 3.72 (OCH_3) 4.57 (CH_2), 5.40 (CH), 5.83 (OCH_2O), 6.35-6.50 (m, 4 ArH), 6.90 (d, J = 9 Hz, ArH), 8.93 (br s, OH), 11.25 (br s, OH).

Anal. Calcd. for $C_{20}H_{18}O_8$: C, 62.2; H, 4.7; M^+ = 386.1001. Found: C, 62.0; H, 4.8; M^+ = 386.1002.

A solution of the lactone **13a** (10 g) in acetic anhydride (20 ml) and pyridine (2 ml) was heated on a steam-bath for 2 minutes and diluted with water. The gummy product crystallized from wet methanol (9.3 g). Recrystallized from acetone-methanol the monoacetate **13b** separated as colorless needles, mp 220-221°; ^{1}H-nmr: δ 2.12 ($COCH_3$), 3.64 (OCH_3) 3.74 (OCH_3), 4.53 (d, J = 16 Hz) and 4.66 (d, J = 16 Hz) (CH_2), 5.31 (CH), 5.97 (OCH_2O), 6.40-6.67 (m, 4 ArH), 7.09 (d, J = 9 Hz, ArH), 11.80 (br s, OH).

Anal. Calcd. for $C_{22}H_{20}O_9$: C, 61.7; H, 4.71; M^+ = 428.1107. Found: C, 61.4; H, 4.81; M^+ = 428.1121.

A solution of **13a** (2 g) in acetic anhydride (5 ml) and pyridine (1 ml) was stirred at room temperature for 10 minutes. Colorless crystals began to separate. Water was added and the product recrystallized from acetone-methanol to give the diacetate **13c** as colorless glistening prisms, mp 154-155° (2.1 g); ^{1}H-nmr: δ 1.96 ($COCH_3$), 2.07 ($COCH_3$) 3.69 (OCH_3), 3.74 (OCH_3), 5.11 (CH_2), 5.34 (CH), 6.01 (OCH_2O), 6.43-6.57 (m, 3 ArH), 6.76 (ArH), 6.90 (d, J = 9 Hz, ArH).

Anal. Calcd. for $C_{24}H_{22}O_{10}$: C, 61.3; H, 4.7. Found: C, 61.2; H, 4.8.

A mixture of the acetate **13b** (2 g) (or the diacetate, **13c**), methyl iodide (5 ml), potassium carbonate (4 g) and acetone (20 ml) was refluxed, filtered and evaporated to give a gum. This crystallized from wet methanol (1.6 g). Recrystallized from acetone-methanol the acetate **14a** was obtained as colorless needles, mp 181-182°; ^{1}H-nmr: δ 2.11 ($COCH_3$), 3.65 (OCH_3) 3.74 (OCH_3), 3.81 (OCH_3), 4.93 (d, J = 16 Hz) and 5.04 (d, J = 16 Hz) (CH_2), 5.30 (CH), 5.96 (d, J = 1 Hz) and 6.0 (d, J = 1 Hz) (OCH_2O), 6.39 (ArH), 6.42-6.55 (m, 2 ArH), 6.68 (ArH), 7.03 (d, J = 9 Hz, ArH).

Anal. Calcd. for $C_{23}H_{22}O_9$: C, 62.4; H, 5.01. Found: C, 62.4; H, 5.0.

Lactone **16a**.

A suspension of the acetate **14a** (0.2 g) in methanol (2 ml) containing 2 drops of 10% aqueous sodium hydroxide was boiled for one minute. An additional drop of 10% aqueous sodium hydroxide was added causing a product to rapidly crystallize. Water was added and the crystals were collected (0.11 g). Recrystallized, the unsaturated lactone **16a** separated as colorless needles, mp 182-183°; ^{1}H-nmr: δ 3.72 (OCH_3), 3.80 (OCH_3), 5.07 (d, J = 16 Hz) and 5.13 (d, J = 16 Hz) (CH_2), 5.09 (CH), 5.96 (d, J = 1 Hz) and 6.04 (d, J = 1 Hz) (OCH_2O), 6.40-6.59 (m, 3 ArH), 6.90-7.01 (m, 2 ArH).

Anal. Calcd. for $C_{20}H_{16}O_7$: C, 65.2; H, 4.4. Found: C, 65.1; H, 4.5.

The sodium hydroxide reaction filtrate from **16a** gave small amounts of the lactone **15a** upon acidification; mp 178-179°.

Lactone **15a**.

The monoacetate **13b** (1 g) was methylated by refluxing with dimethyl sulfate (0.5 g), potassium carbonate (2.5 g) and acetone (15 ml) for 4 hours. Evaporation of the mixture gave a gum which was washed with water and dissolved in wet methanol containing a drop of acetic acid. On cooling, colorless crystals separated (0.67 g). Recrystallized from acetone-methanol the lactone **15a** was obtained as colorless glistening prisms, mp 178-179°; ^{1}H-nmr: δ 3.26 (OCH_3), 3.42 (d, J = 2.5 Hz, CH), 3.74 (OCH_3), 3.84 (OCH_3), 4.42 (d, J = 9 Hz) and 4.56 (d, J = 9 Hz) (CH_2), 4.61 (d, J = 2.5 Hz, CH), 5.94 (OCH_2O), 6.28 (ArH), 6.46 (dd, J = 2, 9 Hz, ArH), 6.62 (d, J = 2 Hz, ArH), 6.67 (d, J = 2 Hz, ArH), 6.83 (d, J = 9 Hz, ArH).

Anal. Calcd. for $C_{21}H_{20}O_8$: C, 63.0; H, 5.0. Found: C, 63.0; H, 5.1.

Compound **13d**.

Condensation of the morpholino compound **12b** (0.5 g) with tetronic acid (0.4 g) in 50% aqueous acetic acid at room temperature gave compound **13d** (0.42 g) which crystallized from acetone-methanol as brittle, colorless needles, mp 190-191°; ^{1}H-nmr: δ 3.55 (OCH_3), 3.76 (OCH_3), 4.60 (CH_2), 5.64 (CH), 5.85 (OCH_2O), 6.37 (ArH), 6.53 (ArH), 6.67 (dd, J = 2, 8 Hz, ArH), 6.88 (m, 2 ArH), 9.03 (br s, OH), 11.6 (br s, OH).

Anal. Calcd. for $C_{20}H_{18}O_8$: C, 62.2; H, 4.7. Found: C, 62.0; H, 4.8.

Acetylation of compound **13c** gave a monoacetate, mp 123-124°; ^{1}H-nmr: δ 2.14 ($COCH_3$), 3.78 (2 OCH_3), 4.57 (d, J = 16 Hz) and 4.63 (d, J = 16 Hz) (CH_2), 5.46 (CH), 5.96 (d, J = 1 Hz) and 5.98 (d, J = 1 Hz) (OCH_2O), 6.53 (ArH), 6.72, (ArH), 6.84-7.04 (m, 3 ArH). Methylation of this acetate with methyl iodide, potassium carbonate and acetone as described above gave the monoacetyl-monomethyl derivative **14b** which crystallized from acetone-methanol as colorless needles, mp 173-174°; ^{1}H-nmr: δ 2.14 ($COCH_3$), 3.46 (OCH_3), 3.78 (OCH_3), 3.83 (OCH_3), 4.98 (d, J = 16 Hz) and 5.05 (d, J = 16 Hz) (CH_2), 5.45 (CH), 5.98 (d, J = 1 Hz) and 6.02 (d, J = 1 Hz) (OCH_2O), 6.49 (ArH), 6.74 (ArH), 6.83 (dd, J = 1, 9 Hz, ArH), 6.96-7.02 (m, 2 ArH).

Anal. Calcd. for $C_{23}H_{22}O_9$: C, 62.4; H, 5.0. Found: C, 62.5; H, 5.3.

A suspension of **14b** (1 g) in boiling methanol (16 ml) was slowly treated with 10% aqueous sodium hydroxide (4 ml) during 2 minutes. Crystals separated. Water (30 ml) was added and the product was collected and recrystallized from acetone-methanol to give the unsaturated lactone **16b** as colorless needles, mp 230-231° (1.1 g); ^{1}H-nmr: δ 3.68 (OCH_3), 3.80 (OCH_3), 5.04 (d, J = 16 Hz) and 5.12 (d, J = 16 Hz) (CH_2), 5.10 (CH), 5.98 (d, J = 1 Hz, ArH) and 6.04 (d, J = 1 Hz) (OCH_2O), 6.45 (ArH), 6.71 (dd, J = 2, 8 Hz, ArH), 6.92-7.03 (m, 3 ArH).

Compound **13e**.

The morpholino compound **12c** (5.5 g) reacted with tetronic acid (5 g) in aqueous acetic acid (20 ml, 50%) to give the compound **13e** (5.8 g). This was recrystallized from methanol to give solvated needles, mp 182-183°; ^{1}H-nmr: δ 3.61 (OCH_3), 3.68 (OCH_3), 4.56 (CH_2), 5.29 (CH), 5.80 (OCH_2O), 6.39 (ArH), 6.52-6.85 (m, 4 ArH).

Anal. Calcd. for $C_{20}H_{18}O_8$•CH_3OH: C, 60.3; H, 5.3. Found: C, 60.5; H, 5.1.

Acetylation of **13e** in acetic anhydride and pyridine gave the acetate **13f** which crystallized from acetone-methanol as colorless needles, mp 245-246°; δ 2.11 ($COCH_3$), 3.60 (OCH_3), 3.67 (OCH_3), 4.57 (CH_2), 5.04 (CH), 5.98 (OCH_2O), 6.51-6.90 (m, 5 ArH).

Anal. Calcd. for $C_{22}H_{20}O_9$: C, 61.7; H, 4.7. Found: C, 61.8; H, 4.8.

Methylation of **13f** in the usual way with methyl iodide gave the monoacetyl-monomethyl derivative **14c**. This crystallized from methanol as solvated colorless needles, mp 81-82°; δ 2.18 ($COCH_3$), 3.67 (OCH_3), 3.74 (OCH_3), 3.88 (OCH_3), 5.01 (d, J = 16 Hz) and 5.07 (d, J = 16.0 Hz) (CH_2), 5.02 (CH), 5.99 (d, J = 1.0 Hz) and 6.10 (d, J = 1.0 Hz) (OCH_2O), 6.57 (ArH), 6.65-6.88 (m, 4 ArH).

Anal. Calcd. for $C_{23}H_{22}O_9$: C, 62.4; H, 5.0. Found: C, 62.7; H, 5.3.

Addition of 10% aqueous sodium hydroxide (2 ml) to a suspension of **14c** (2.7 g) in boiling methanol (15 ml) gave a clear solution which was heated until crystals began to separate (3 minutes). Water was added. The product was collected and recrystallized from acetone-methanol to give the unsaturated lactone **16c** as colorless needles, mp 224-225° (1.9 g); ^{1}H-nmr: δ 3.72 (OCH_3), 3.76 (OCH_3), 4.70 (CH), 5.03 (d, J = 16 Hz) and 5.13 (d, J = 16 Hz) (CH_2), 5.98 (d, J = 1.0 Hz) and 6.04 (d, J = 1 Hz) (OCH_2O), 6.64 (ArH), 6.69 (dd, J = 2, 8 Hz, ArH), 6.85-6.96 (3 ArH).

Anal. Calcd. for $C_{20}H_{16}O_7$: C, 65.2; H, 4.4. Found: C, 65.1; H, 4.4.

Compound **13g**.

The morpholino compound **12d** (10 g) reacted in 50% aqueous acetic acid (40 ml) with tetronic acid (10 g) to yield the compound **13g** (10.2 g). Recrystallized from acetone-methanol, **13g** was obtained as colorless needles, mp 191-192°; ^{1}H-nmr: δ 4.65 (CH_2), 5.27 (CH), 5.86 (OCH_2O), 5.94 (OCH_2O), 6.40 (ArH), 6.52-6.80 (m, 4 ArH), 9.13 (br s, OH), 11.89 (br s, OH).

Anal. Calcd. for $C_{19}H_{14}O_8$: C, 61.6; H, 3.8: M^+ = 370.0688. Found: C, 61.7; H, 3.9; M^+ = 370.0648.

The acetate of **13g**, prepared with acetic anhydride and pyridine at room temperature, crystallized from acetone-methanol. The acetate **13h** was obtained as colorless needles, mp 232-233°; ^{1}H-nmr: δ 2.15 ($COCH_3$), 4.63 (CH_2), 5.02 (CH), 5.96 (OCH_2O), 5.97 (OCH_2O), 6.60-6.84 (m, 5 ArH).

Anal. Calcd. for $C_{21}H_{16}O_9$: C, 61.2; H, 3.9: M^+ = 412.0794. Found: C, 61.4; H, 4.0; M^+ = 412.0790.

Lactone **16d**.

A mixture of the above acetate **13h** (2 g), potassium carbonate (15 g), methyl iodide (3 ml) (or dimethyl sulfate) and acetone (15 ml) was refluxed for 7 hours, filtered and evaporated. The oily residue was dissolved in boiling methanol (10 ml) and 10% aqueous sodium hydroxide (0.5 ml) was slowly added. Within a few minutes colorless crystals separated. Water was added, the crystalline product (1.15 g) was collected, and recrystallized from acetone-methanol. The unsaturated lactone **16d** was obtained as colorless needles, mp 229-230°; ^{1}H-nmr: δ 4.78 (CH), 5.04 (CH_2), 6.00 (2 OCH_2O), 6.60-6.95 (m, 5 ArH).

Anal. Calcd. for $C_{19}H_{12}O_7$: C, 64.8; H, 3.4. Found: C, 64.8; H, 3.6.

Compound **13i**.

The morpholino compound **12e** (2 g), and tetronic acid (2 g) in 50% aqueous acetic acid (10 ml) at room temperature for two days gave compound **13i**. It crystallized (1.9 g) from acetone-methanol as colorless needles, mp 163-164°; ^{1}H-nmr: δ 3.70 (OCH_3), 4.64 (CH_2), 5.30 (CH), 5.85 (OCH_2O), 6.39 (ArH), 6.67 (ArH), 6.79 (d, J = 8 Hz, 2 ArH), 7.02 (d, J = 8 Hz, 2 ArH), 9.13 (br s, OH), 11.80 (br s, OH).

Anal. Calcd. for $C_{19}H_{16}O_7$: C, 64.0; H, 4.5. Found: C, 64.1; H, 4.5.

With acetic anhydride and pyridine the above product formed a monoacetate **13j**. This crystallized from acetone-methanol as colorless needles, mp 185-186°; ^{1}H-nmr: δ 2.17 ($COCH_3$), 3.72 (OCH_3), 4.64 (CH_2), 5.07 (CH), 5.99 (OCH_2O), 6.60 (ArH), 6.72 (ArH), 6.86 (d, J = 8 Hz, 2 ArH), 7.07 (d, J = 8 Hz, 2 ArH), 12.07 (br s, OH).

Anal. Calcd. for $C_{21}H_{18}O_8$: C, 63.3; H, 4.6. Found: C, 63.2; H, 4.7.

Lactone **16e**.

(a) A solution of compound **13i** (0.36 g) in acetic anhydride (2 ml) containing a drop of concentrated sulfuric acid was heated on a steam-bath for 5 minutes and diluted with water. The gummy product crystallized from wet methanol (0.28 g). Recrystallized from acetone-methanol, the unsaturated lactone **16e** was obtained as glistening, colorless prisms, mp 194-195°; ^{1}H-nmr: δ 3.71 (OCH_3), 4.83 (CH), 5.01 (d, J = 12 Hz), and 5.12 (d, J = 12 Hz) (CH_2), 5.98 (d, J = 1 Hz) and 6.06 (d, J = 1 Hz) (OCH_2O), 6.58 (ArH), 6.87 (d, J = 9 Hz, 2 ArH), 6.94 (ArH), 7.17 (d, J = 9 Hz, 2 ArH).

Anal. Calcd. for $C_{19}H_{14}O_6$: C, 67.5; H, 4.2. Found: C, 67.6; H, 4.4.

This same lactone was also prepared by methylation of the acetate **13j** and without further purification hydrolysis of the product with methanolic sodium hydroxide.

Compound **13k**.

This compound was prepared in the usual way from **12f** and tetronic acid. Compound **13k** crystallized from methanol as colorless needles, mp 172-173°; ^{1}H-nmr: δ 3.67 (OCH_3), 4.66 (CH_2), 5.34 (CH), 5.85 (OCH_2O), 6.41 (ArH), 6.60-7.20 (m, 5 ArH), 9.15 (br s, OH), 11.95 (br s, OH).

Anal. Calcd. for $C_{19}H_{16}O_7$: C, 64.0; H, 4.5. Found: C, 63.7; H, 4.4.

With acetic anhydride and pyridine the monoacetate **13l** was obtained. It crystallized from acetone-methanol as colorless needles, mp 236-237°; ^{1}H-nmr: δ 2.17 ($COCH_3$), 3.70 (OCH_3), 4.64 (CH_2), 5.08 (CH), 6.01 (OCH_2O), 6.63 (ArH), 6.70-6.84 (m, 4 ArH), 7.22 (dd, J = 8, 8 Hz, ArH).

Lactone **16f**.

Methylation of acetate **13l** with methyl iodide in the usual way gave the monomethyl derivative **14f**. This product crystallized from acetone-methanol as colorless, glistening plates, mp 167°; ^{1}H-nmr: δ 2.17 ($COCH_3$), 3.70 (OCH_3), 3.87 (OCH_3),

5.04 (CH_2), 5.08 (CH), 6.01 (OCH_2O), 6.60-7.30 (m, 6 ArH).

Anal. Calcd. for $C_{22}H_{20}O_8$: C, 64.1; H, 4.9. Found: C, 64.1; H, 4.9.

Aqueous sodium hydroxide (10%, 2 ml) added to a suspension of **14f** (1.8 g) in boiling methanol gave a clear solution which after a few seconds began to deposit crystals. Water was added and the product was collected (1.4 g). Recrystallized from acetone-methanol, the unsaturated lactone **16f** separated as colorless needles, mp 200-201°; ^{1}H-nmr: δ 3.72 (OCH_3), 4.82 (CH), 5.08 (CH_2), 6.20 (OCH_2O), 6.62 (ArH), 6.73-7.00 (m, 5 ArH).

Anal. Calcd. for $C_{19}H_{14}O_6$: C, 67.5; H, 4.2. Found: C, 67.6; H, 4.3.

Compound **13m**.

A solution of the morpholino compound **12g** (6 g) and tetronic acid (4.5 g) in acetic acid (15 ml) and water (30 ml) was heated on a steam-bath for 20 minutes. Colorless crystals separated. After cooling, the product was collected and recrystallized from acetone-methanol to give **13m** as colorless, solvated needles, mp 132-133° (5.8 g). Crystallized from benzene the unsolvated **13m** separates as colorless needles, mp 176-177°; ^{1}H-nmr: δ 3.68 (OCH_3), 4.59 (CH_2), 5.49 (CH), 5.84 (OCH_2O), 6.36 (ArH), 6.45 (ArH), 6.77-7.21 (m, 4 ArH), 9.00 (br s, OH), 11.42 (br s, OH).

Anal. Calcd. for $C_{19}H_{16}O_7$•CH_3OH: C, 61.8; H, 5.2. Found: C, 61.6; H, 5.1.

Anal. Calcd. for $C_{19}H_{16}O_7$: C, 64.0; H, 4.5. Found (from benzene): C, 64.3; H, 4.8.

Methylation of **13m** in the usual way gave the di-*o*-methyl derivative **13n**. This crystallized from acetone-methanol as colorless needles, mp 174-175°; ^{1}H-nmr: δ 3.61 (OCH_3), 3.67 (OCH_3), 3.76 (OCH_3), 4.98 (CH_2), 5.55 (CH), 5.92 (OCH_2O), 6.46 (ArH), 6.72 (ArH), 6.80-7.00 (m, 3 ArH), 7.13-7.24 (m, ArH).

Anal. Calcd. for $C_{21}H_{20}O_7$: C, 65.6; H, 5.2. Found: C, 65.4; H, 5.4.

Compound **13m** was warmed with acetic anhydride (5 ml) and pyridine (1 ml) for 3 minutes and diluted with water. The solid product was crystallized from wet acetone-methanol. Colorless crystals of the diacetate **13p** (see below) first separated (0.68 g, mp 134-135°). The filtrate was concentrated and cooled. A monoacetate then separated (1.20 g). Recrystallized from acetone-methanol the monoacetate **13o** separated as brittle, colorless needles, mp 182-183°; ^{1}H-nmr: δ 2.10 ($COCH_3$), 3.65 (OCH_3), 4.56 (d, J = 16 Hz) and 4.67 (d, J = 16 Hz) (CH_2), 5.42 (CH), 5.98 (OCH_2O), 6.41 (ArH), 6.69 (ArH), 6.98 (m, 2 ArH), 7.24 (m, 2 ArH), 11.80 (br s, OH).

Anal. Calcd. for $C_{21}H_{18}O_8$: C, 63.3; H, 4.55. Found: C, 63.3; H, 4.6.

The diacetate **13p** obtained as a minor product in the above reaction was prepared as the primary product by warming **13m** with acetic anhydride (5 ml) and pyridine (4 drops) for 2 minutes. The solid obtained on adding water was crystallized from methanol to give the diacetate **13p** as colorless needles, mp 134-135° (0.9 g); ^{1}H-nmr: δ 1.93 ($COCH_3$), 2.04 ($COCH_3$), 3.71 (OCH_3), 5.11 (CH_2), 5.42 (CH), 6.02 (OCH_2O), 6.55 (ArH), 6.77 (ArH), 6.83-7.04 (m, 3 ArH), 7.18-7.33 (m, ArH).

Anal. Calcd. for $C_{23}H_{20}O_9$: C, 62.7; H, 4.6. Found: C, 62.6; H, 4.7.

Lactones **15g** and **16g**.

The diacetate **13p** (2 g) was refluxed with methyl iodide (5 ml), potassium carbonate (10 g) and acetone (20 ml) for 6 hours, filtered and evaporated. The residues were washed with water and crystallized from acetone-methanol to give the monomethyl-monoacetyl derivative as colorless prisms, mp 200-201° (1.27 g); ^{1}H-nmr: δ 2.10 ($COCH_3$), 3.66 (OCH_3), 3.83 (OCH_3), 4.94 (d, J = 16 Hz) and 5.04 (d, J = 16 Hz) (CH_2), 5.41 (CH), 5.98 (d, J = 1 Hz) and 6.01 (d, J = 1 Hz) (OCH_2O), 6.50 (ArH), 6.72 (ArH), 6.85-6.97 (2 ArH), 7.12-7.29 (2, ArH).

Without further purification the above product (1.0 g) was suspended in boiling methanol (25 ml) and diluted with 10% aqueous sodium hydroxide (10 ml). The solution was boiled for 10 minutes with further additions of methanol (25 ml) and water (30 ml). On cooling, colorless crystals separated. Recrystallized from acetone-methanol the unsaturated lactone **16g** was obtained as colorless, felted needles, mp 221-222° (0.13 g); ^{1}H-nmr: δ 3.82 (OCH_3), 5.0 (d, J = 16 Hz) and 5.14 (d, J = 16 Hz) (CH_2), 5.20 (CH), 5.96 (d, J = 1 Hz) and 6.03 (d, J = 1 Hz) (OCH_2O), 6.57 (ArH), 6.82-7.28 (m, 5 ArH).

Anal. Calcd. for $C_{19}H_{14}O_6$: C, 67.4; H, 4.2. Found: C, 67.4; H, 4.2.

The sodium hydroxide reaction filtrate from **16g** was acidified with concentrated hydrochloric acid (10 ml). Colorless crystals separated on standing. Recrystallized from acetone-methanol the lactone **15g** was obtained as colorless prisms, mp 162-163° (0.6 g); ^{1}H-nmr: δ 3.27 (OCH_3), 3.86 (OCH_3), 4.42 (d, J = 16 Hz) and 4.57 (d, J = 16 Hz) (CH_2), 4.72 (CH), 5.96 (OCH_2O), 6.30 (ArH), 6.68 (ArH), 6.82-7.30 (m, 4 ArH).

Anal. Calcd. for $C_{20}H_{18}O_7$: C, 64.9; H, 4.9. Found: C, 64.9; H, 5.1.

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