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TOTAL SYNTHESIS OF NOTHOLAENIC ACID[1,2]

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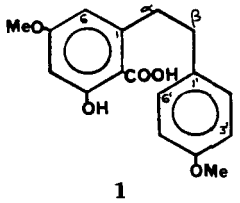
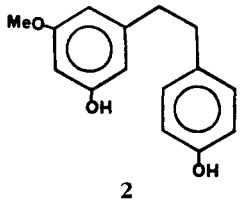
ABSTRACT.—Notholaenic acid (**1**), an inhibitor of photosynthesis isolated from ferns belonging to the genus *Notholaena*, was synthesized from 3-benzyloxy-2-bromo-5-methoxybenzyl alcohol. Oxidation to the analogous aldehyde followed by reaction with the phosphorane prepared from *p*-methoxybenzylbromide provided a mixture of *Z* and *E* stilbenes that was carboxylated by lithium-halogen exchange and treatment with carbon dioxide. Catalytic hydrogenation provided pure notholaenic acid (**1**).

Notholaenic acid (**1**) is an inhibitor of photosynthesis (1) isolated (2) from the ferns *Notholaena dealbata* (Pursh) Kze. and *Notholaena limitanea* Maxon. Its structure was deduced from its chemical and spectroscopic characteristics. As a part of our ongoing program to study the antimicrobial and estrogenic activities of the dihydrostilbenes of *Cannabis*, it was decided to evaluate notholaenic acid (**1**) for similar activities in view of the structural similarities to **2**, a bibenzyl with estrogenic activity isolated (3) from *Cannabis* and to the antimicrobial dihydrostilbenes **3** and **4** isolated (4) from *Amorpha fruticosa*. In order to secure a supply of notholaenic acid (**1**) for this study, we decided to synthesize it starting with readily available material.



1



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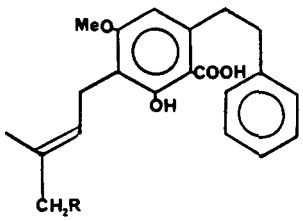
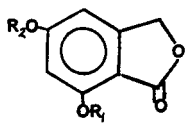


3 R=H
4 R=$CH_2CH=C(CH_3)_2$



8 $R_1=CH_3$, $R_2=CH_2Ph$
9 $R_1=CH_3$, $R_2=OH$
10 $R_1=H$, $R_2=CH_3$
11 $R_1=R_2=CH_3$

The starting material for the synthesis (Figure 1) of (**1**) was 3-benzyloxy-5-methoxybenzyl alcohol (**5**), which could be obtained from commercially available 3,5-dihydroxybenzoic acid using a literature procedure (5). Bromination of **5** using *N*-bromosuccinimide (6) gave two isomeric bromo compounds, **6** and **7**, with structures established by their spectral and chemical behavior. Of the positions available for bromination (2, 4, and 6), position 4 was ruled out on the basis of the ^{13}C-nmr spectra. Carbon 4 was assigned the most upfield signal in the ^{13}C nmr of **5** (δ 100.4) because it is

[1]Taken, in part, from the Ph.D. dissertation of Steve F. Cheatham.

[2]Presented before the MALTO Pharmacognosy-Medicinal Chemistry meeting held in Houston, Texas, May 1983.

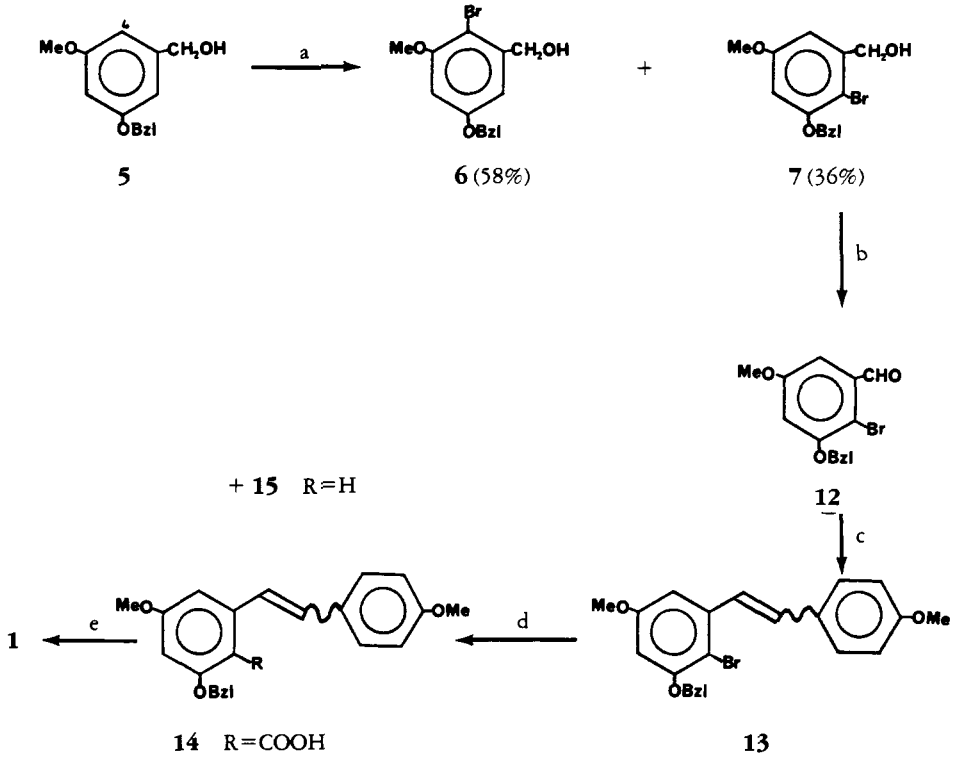


FIGURE 1. a: *N*-bromosuccinimide/CCl_4; b: pyridinium, chlorochromate (79%); c: diethyl-4-methoxybenzyl-phosphonate/NaH (59%); d: *tert*-butyllithium/CO_2 (50%); e: 10% Pd/C (904).

ortho to both the methoxy and benzyloxy groups with carbons 2 and 6 resonating at δ 105.4 and δ 104.9 (assignments interchangeable). In neither of the bromo isomers is this upfield signal significantly changed. In **6**, it occurred at δ 99.7, while in **7**, this signal occurred at δ 100.4. Also, the carbon attached to bromine should undergo an upfield shift due to the heavy halogen effect (7). This took place in both isomers where the brominated carbon came at δ 102.4 in **6** and 102.9 in **7**, an upfield shift of approximately 2 ppm from the position of C-2 and C-6 in **5**. While the position of the methoxy signal should be similar in both **5** and **7**, some shift should be observed in **6**. Examination of the ^{13}C nmr showed that the methoxy carbon resonated at δ 56.3 in **6**, whereas in **7**, it resonated at δ 55.4. Because the position of the methoxy carbon in **5** was at δ 55.2, this helped distinguish between the two compounds. Besides, the yields of the two products, 58% for **6** and 36% for **7**, were consistent with the literature (6) results in brominations of this type.[3]

Still, an ambiguous distinction between **6** and **7** was sought. This was achieved, albeit indirectly, by subjecting **6** to lithium-halogen exchange followed by carboxylation with CO_2 to give the phthalide **8**, which, upon hydrogenolysis, gave the phthalide **9** that was physically and spectroscopically different from the isomeric phthalide **10** prepared by the regiospecific demethylation of **11** using boron tribromide in CH_2Cl_2. Unfortunately, similar treatment of **7**, which should have led directly to **10**, was not successful.

[3]The ^1H-nmr signals for **5**, **6**, and **7** further corroborated this assignment (see Experimental section). Thus, while CH_2OH and CH_3-O in **6** were significantly deshielded relative to their positions in **5**, the OCH_2-ph hardly changed. On the other hand, the CH_2OH and OCH_2-ph of **7** were significantly changed in **7**, while the CH_3O was virtually unchanged.

Oxidation of **7** to **12** was accomplished smoothly in 79% yield using pyridinium chlorochromate. Treatment of **12** with diethyl-4-methoxybenzylphosphonate (8) in the presence of sodium hydride gave the bromostilbene **13** as an *E/Z* mixture in 59% yield. The mixture was subjected to lithium-halogen exchange followed by the addition of solid CO_2 to give the stilbene acids **14** (50%), and stilbenes **15** (21%) presumably derived from hydrogenolyzed **13**. The crude acids (**14**) were subjected to catalytic hydrogenation using 10% palladium on carbon to give notholaenic acid (**1**) in 94% yield. The synthetic material was found to have spectral characteristics and melting point identical to those reported for the natural product (2).

Antimicrobial screening (9) of synthetic notholaenic acid against *Escherichia coli, Staphylococcus aureus, Mycobacterium smegmatis, Saccharomyces cerevisiae,* and *Trichophyton mentagrophytes* revealed only marginal activity that did not warrant any further investigation.[4]

EXPERIMENTAL

GENERAL EXPERIMENTAL PROCEDURES.—Melting points were determined on a Thomas Hoover Uni-melt capillary apparatus and are uncorrected. Infrared (ir) absorption spectra were recorded on KBr pellets or $CHCl_3$ solutions on a Beckman IR-33 spectrophotometer, a Perkin-Elmer 257 spectrophotometer or a Perkin-Elmer 281B spectrophotometer. ^{1}H-nmr spectra were recorded on a Varian Model EM390 nuclear magnetic resonance spectrometer at 90 MHz operating at room temperature with $CDCl_3$ as the solvent unless otherwise stated and TMS as an internal standard with chemical shifts reported as δ values. ^{13}C-nmr (15.03 MHz) spectra were recorded on a JEOL FX-60 instrument with a 45° pulse angle, repetition rates between 5 and 10s, and 8K data points. PND spectra were obtained by broad-band (1 KHz) irradiation. SFORD spectra were conducted by centering the decoupling frequency 1100 Hz downfield from the signal of TMS. Ms were measured on a Finnigan P.T.O. GC-MS 3200 mass spectrometer. Microanalyses were carried out by Scandinavian Microanalytical Laboratories in Herlev, Denmark, or Galbraith Laboratories, Inc. in Knoxville, Tennessee. All reagents and starting compounds were obtained from Aldrich Chemical Company, unless otherwise stated.

BROMINATION OF 3-BENZYLOXY-5-METHOXYBENZYL ALCOHOL (**5**) TO **6** AND **7**.—3-Benzyloxy-5-methoxybenzyl alcohol (**5**) (5.0 g) was dissolved in CCl_4 (50 ml) and 3.74 g of *N*-bromosuccinimide was added. The mixture was refluxed for 40 min, then worked up to give 8.1 g of an oily residue consisting of two components Rf values 0.30 and 0.40 as shown by analysis on silica gel G plates using 15% EtOAc in C_6H_6 as the solvent system. Flash chromotography (10) on SiO_2 using 10% EtOAc in C_6H_6 as solvent provided: a) 3.56 g of **6** (58%) that crystallized from Et_2O, mp 101-103°; ir ($CHCl_3$) ν max 3584 and 3400 cm^{-1} (OH) and 1588 cm^{-1} (Ar); ^{1}H nmr ($CDCl_3$) δ 2.58 (brs, 1H, exchangeable, O*H*), δ 3.77 (s, 3H, O*CH*$_3$), δ 4.64 (brs, 2H, *CH*$_2$OH), 4.98 (s, 2H, O*CH*$_2$Ph), δ 6.43 (d, 1H, *J*=3.0 Hz, H-2 or H-4), δ 6.73 (d, 1H, *J*=3.0 Hz, H-2 or H-4), and δ 7.36 (brs, 5H, OCH$_2$*Ph*); ^{13}C nmr ($CDCl_3$) see Table 1; ms M^+ at *m/z* 322 (1%), M+1 at *m/z* 324 with the base peak at *m/z* 91; Anal. calcd. for $C_{15}H_{15}O_3Br$: C, 55.75; H, 4.68; Br, 24.72; found: C, 55.51; H, 4.79; Br, 24.49; b) 2.2 g of the bromo alcohol **7** which crystallized from Et_2O as shiny plates, mp 99-100°; ir ($CHCl_3$) ν max at 3590 and 3410 cm^{-1} (OH), 1584 cm^{-1} (Ar); ^{1}H nmr ($CDCl_3$) δ 2.82 (brs, 1H, exchangeable, O*H*), δ 3.68 (s, 3H, OCH_3), δ 4.63 (brs, 2H, *CH*$_2$OH); δ 5.01 (s, 2H, O*CH*$_2$Ph), δ 6.40 (d, 1H, *J*=3.0 Hz, H-4 or H-6), δ 6.67 (d, 1H, *J*=3.0 Hz, H-4 or H-6), and δ 7.33 (m, 5H, OCH$_2$*Ph*); ^{13}C nmr ($CDCl_3$) see Table 1; ms M^+ at *m/z* 322 (2%), M+2 at *m/z* 324 (2%) with the base peak at *m/z* 91. *Anal.* calcd. for $C_{15}H_{15}O_3Br$: C, 55.75; H, 4.68, Br, 24.72. Found: C, 55.93; H, 4.82; Br, 24.99.

OXIDATION OF BROMO ALCOHOL **7** TO BROMO ALDEHYDE **12**.—Pyridinium chlorochromate (PCC) (2.33 g) was suspended in 29 ml of CH_2Cl_2 and a solution of 2.9 g of **7** in 29 ml of CH_2Cl_2 was slowly added. The mixture was stirred for 3 h, then diluted out with Et_2O. The mixture was filtered over SiO_2 to remove tarry material and evaporated to give a dark oil that was dissolved in $CHCl_3$ and refiltered over SiO_2 to give upon evaporation of $CHCl_3$ 2.27 g of a crystalline residue (79%). Crystallization from MeOH gave shiny plates, mp 99-100°; ir ($CHCl_3$) ν max at 1682 cm^{-1} (-CHO) and 1581 cm^{-1} (Ar); ^{1}H nmr ($CDCl_3$) δ 3.76 (s, 3H, OCH_3), δ 5.09 (s, 2H, O*CH*$_2$Ph), δ 6.70 (d, 1H, *J*=3.0 Hz, H-4), δ 7.00 (d, 1H, *J*=3.0 Hz, H-6), δ 7.40 (m, 5H, OCH$_2$*Ph*), and δ 10.38 (s, 1H, *CH*O); ^{13}C nmr ($CDCl_3$) δ 191.8 (d, *C*HO) with other signals at δ 159.8 (s), 155.2 (s), 135.7 (s), 134.9 (s), 128.6 (d), 128.2 (d), 127.0 (d),

[4]Results of evaluating notholaenic acid (**1**) for estrogenic and other *Cannabis* activities will be reported elsewhere.

TABLE 1. ^{13}C-nmr Assignments of **5**, **6** and **7**

Carbon	Compounds		
	5	**6**	**7**
1	143.7s	141.9s	141.9s
2	105.4d[a]	105.6d	102.9s
3	160.9s[b]	156.6s[c]	155.5s[c]
4	100.4d	99.7d	100.4d
5	160.1s[b]	159.2s[c]	159.8s
6	104.9d[a]	102.4s	105.2d
7	64.8t	65.1t	65.0t
OCH_3	55.1q	56.3q	55.4q
1′	137.0s	136.6s	136.4s
2′	127.5d	127.6d[a]	127.0d[a]
3′	128.5d	128.6d[a]	128.5d[a]
4′	127.9d	128.1d	127.9d
5′	128.5d	128.6d[a]	128.5d[a]
6′	127.5d	127.6d[a]	127.0d[a]
7′	70.0t	70.4t	70.8t

[a,b]Interchangeable within the same column.

[c]Assigned by inspection of the coupled spectrum in which carbon 5 appears as a quartet due to three bond coupling to the methoxy protons.

109.7 (s), 107.4 (d), 104.1 (d), 71.2 (t), 55.7 (q); ms M^+ at *m/z* 320 (16%), M+2 at *m/z* 322 (13%) with the base peak at *m/z* 91. *Anal.* calcd. for $C_{15}H_{13}O_3Br$: C, 56.10; H, 4.08; Br, 24.88. Found: C, 56.32; H, 4.21; Br, 24.78.

PREPARATION OF BROMOSTILBENES **13**.—Diethyl-4-methoxybenzylphosphonate (2 g) (8) was added to 5 ml of dry DMF containing 186.6 mg of NaH. After gas evolution ceased (30 min), 2.27 g of **12** in 7 ml of dry DMF was added and the mixture kept at 40-50° for 8 h. Regular workup using C_6H_6 as solvent provided 3.2 g of a dark oil that was filtered over a bed of SiO_2 using 10% EtOAc in C_6H_6 as solvent. The yellowish oil thus obtained was crystallized from hexane to give 1.42 g of a single isomer (*E* or *Z*); mp 93-94°; ir ($CHCl_3$) ν max at 1581 and 1508 cm^{-1} (Ar); ^{1}H nmr ($CDCl_3$) δ 3.76 (s, 6H, 2 OCH_3), 5.07 (s, 2H, OCH_2Ph), 6.40 (d, 1H, J=2.5 Hz), and a complex series of signals between δ 6.73-7.60 (12H); ^{13}C nmr ($CDCl_3$) three oxygenated aromatic singlets at δ 159.8, 159.5, and 156.0; ms M^+ at *m/z* 424 (9%), M+2 at *m/z* 426 (9%) with the base peak at *m/z* 91.

A further 0.34 g of **13** was obtained by chromatographing the mother liquor on SiO_2 using 20% hexane in C_6H_6 as solvent, but it resisted crystallization as it was a mixture of the *E* and *Z* isomers based on its ^{1}H-nmr spectrum (two OCH_3 signals at δ 3.47 and 3.70 and two two-proton doublets at δ 6.69 and 7.12, J=8.0 Hz, together with signals from the other isomer, see above); ms *m/z* 424 (14%), M+2 at *m/z* 426 (17%) with base peak at *m/z* 91. *Anal.* calcd. for $C_{23}H_{21}O_3Br$: C, 64.95; H, 4.98; Br, 18.79. Found: C, 64.82; H, 4.79, Br, 18.70.

CARBOXYLATION OF BROMOSTILBENES **13** TO **14**.—The bromostilbene mixture **13** (1.6 g) was dissolved in THF (16 ml) and the solution cooled to −78°. To the stirred solution, 2.6 ml of 1.6 M *n*-butyllithium in hexane was added and stirring of the now darkened solution continued for 0.75 h. Excess solid CO_2 was then added, and upon normal workup using $CHCl_3$ as extraction solvent, 1.57 g of a dark red oil was obtained. Flash chromatography (10) of this oil afforded 730 mg of **14** as a foam; ir ($CHCl_3$) 3500-2400 cm^{-1} (CO*OH*) and 1717 cm^{-1} (*C*OOH); ^{1}H nmr ($CDCl_3$) 4 OCH_3 at δ 3.54, 3.72, 3.79, and 3.84 indicating that the material was a mixture of isomers; ms M^+ at *m/z* 390 (3%), a peak at *m/z* 346 (3%, M-CO_2) and the base peak at *m/z* 91. This material was used in the next step without further purification.

In addition to **14**, the by-product **15** (500 mg) was obtained as an oily residue; ir ($CHCl_3$) no CO bands; ms M^+ at *m/z* 346 (38%) with base peak at *m/z* 91. Since **15** was a mixture of *Z* and *E* isomers, it was further characterized as its dihydroderivative prepared by hydrogenating it (250 mg) for 12 h at 20 psi in 10 ml of EtOH using 50 mg of 10% Pd/C as catalyst. Upon workup and further purification of the crude product by chromatography on SiO_2 using 3% EtOAc in C_6H_6, the dihydro derivative was obtained (134 mg) as a colorless oil, homogeneous on tlc; ir ($CHCl_3$) ν max at 3580, 3328, 1608, and 1595 cm^{-1}; ^{1}H nmr ($CDCl_3$) δ 2.89 (s, 4H, 2 CH_2), 3.70 (s, 3H, OCH_3), 3.76 (s, 3H, OCH_3), 5.47 (brs, 1H, exchangeable, OH), 6.27 (m, 3H, ring A), 6.81 (d, 2H, J=8.5 Hz), and 7.10 (d, 2H, J=8.5 Hz) (AA′BB′

system of ring B); ^{13}C nmr ($CDCl_3$) δ 160.8 (s), 157.8 (s), and 156.8 (s, three oxygenated aromatic carbons) with two methylene signals at δ 38.1 and 36.6. *Anal.* calcd. for $C_{16}H_{18}O_3$: C, 74.40; H, 7.02. Found: C, 74.37; H, 7.12.

HYDROGENATION OF **14** TO NOTHOLAENIC ACID (**1**).—The crude acid **14** (500 mg) in EtOH (7 ml) was added to 10 ml of EtOH containing 100 mg of 10% Pd/C presaturated with hydrogen. Hydrogenation under atmospheric pressure for 5.5 h and then usual workup provided 494 mg of notholaenic acid **1**◊, which crystallized from C_6H_6 to give 296 mg of silky needles, mp 149-150° [lit. (2) 148-149°]; ir ($CHCl_3$) ν max at 3500-2400, 1630, and 1610 cm^{-1}; ^{1}H nmr (CD_3OH) δ 2.80 (m, 2H, CH_2), 3.13 (m, 2H, CH_2), 3.73 (s, 6H, 2 OCH_3), 6.22 and 6.32 (each d, 1H, J=2.5 Hz, arom. H of ring A), 6.80 and 7.10 (each d, 2H, J=8.5 Hz, AA'BB' system of ring B); ^{13}C nmr (CD_3OH) δ 148.2 (s, C-1), 105.5 (s, C-2), 158.7 (s, C-3), 99.7 (d, C-4), 166.7 (s, C-5 or C-4'), 110.9 (d, C-6), 39.6 and 38.9 (both t, C-α or C-β), 134.9 (s, -C-1'), 130.0 (d, C-2' or C-6'), 114.4 (d, C-3' or C-5'), 164.8 (s, C-4'), 173.9 (s, *C*OOH), and 55.6 and 55.4 (both *q*, 20 Me); ms M^+ at *m/z* 302 (12%) with the base peak at *m/z* 121. These spectral data were consistent with those reported (2) for notholaenic acid (**1**).

CARBOXYLATION OF **6** TO PHTHALIDE **8**.—Bromoalcohol **6** (2.0 g) was dissolved in 20 ml of dry THF and cooled to −78° in a dry ice-acetone bath. *n*-BuLi (8.5 ml of 1.6 M in *n*-hexane) was slowly added and the mixture stirred for 0.25 h with excess dry ice (CO_2). The cloudy solution was allowed to return to room temperature, then diluted out with H_2O (20 ml) and worked up using EtOAc as extraction solvent. The crude phthalide **8** was crystallized from Et_2O-Me_2CO to give 654 mg of colorless needles, mp 163-164°; ir ($CHCl_3$) ν max at 1745 and 1600 cm^{-1}; ^{1}H nmr ($CDCl_3$) δ 3.88 (s, 3H, OCH_3), 5.09 (s, 2H, OCH_2Ph), 5.12 (s, 2H, OCH_2Ar), 6.50 (brs, 1H), 6.54 (brs, 1H), 7.41 (br, 5H); ^{13}C nmr ($CDCl_3$) 168.9 (s), 165.9 (s), 159.7 (s), 151.7 (s), 135.8 (s), 128.7 (d), 128.4 (d), 127.5 (d), 106.6 (s), 99.5 (d), 98.6 (d), 70.7 (t), 68.5 (t), 55.9 (q); ms M^+ at *m/z* 270 (19%) with the base peak at *m/z* 91. *Anal.* calcd. for $C_{16}H_{14}O_4$: C, 71.10; H, 5.22. Found: C, 71.07; H, 5.20.

HYDROGENOLYSIS OF **8** TO **9**.—The phthalide **8** (150 mg) was dissolved in 20 ml of 1:1 EtOAc-EtOH and hydrogenated under atmospheric pressure in the presence of 40 mg of 10% Pd/C as catalyst. After usual workup, **9** (126 mg) crystallized from MeOH to give bright shiny needles, mp 240°; Rf value 0.23 on SiO_2 plates using 34% EtOAc in *n*-hexane (distinction from **10** which showed an Rf value of 0.51); ir (KBr) ν max at 3250 (br) and 1720 cm^{-1}; ^{1}H nmr (DMSO-d_6) δ 3.86 (s, 1H), 5.18 (s, 2H), 6.42 (bs, 1H), 6.48 (bs, 1H), 10.51 (bs, exchangeable); ^{13}C nmr (DMSO-d_6) δ 168.1 (s), 165.0 (s), 159.4 (s), 152.0 (s), 103.8 (s), 100.6 (d), 98.9 (d), 68.2 (t), 55.5 (q); ms M^+ at *m/z* 180 (35%) with base peak at *m/z* 134. *Anal.* calcd. for $C_9H_8O_4$: C, 60.00; H, 4.48. Found: C, 60.22; H, 4.19.

REGIOSPECIFIC DEMETHYLATION OF **11** TO **10**.—5,7-Dimethoxyphthalide (**11**) (2.0 g) (11) was dissolved in CH_2Cl_2 and the solution cooled in a dry ice/acetone bath for 0.25 h; then, 30 ml of a 1M BBr_3 solution in CH_2Cl_2 was added. Stirring was then continued for 1 h, then the mixture was worked up using EtOAc as solvent to give 1.95 g of a crystalline solid that was recrystallized from MeOH to give colorless needles, mp 180-182°; ir ($CHCl_3$ saturated solution) ν max at 3445 unchanged upon dilution, 1728 (hydrogen bonded CO; distinction from the CO absorption of **9**, which occurred at 1740 cm^{-1}), and 1626 cm^{-1}; ^{1}H nmr (DMSO-d_6) δ 3.73 (s, 3H), 5.17 (s, 2H), 6.41 (d, 1H J=1.5 Hz), 6.58 (d, 1H J=1.5 Hz), 10.6 (br, 1H exchangeable); ^{13}C nmr (DMSO-d_6) δ 168.9 (s), 166.0 (s), 157.8 (s), 151.5)s), 104.3 (s), 101.4 (d), 98.6 (d), 68.6 (t), 55.7 (q); ms M^+ at *m/z* 180 (41%) with the base peak at *m/z* 151. *Anal.* calcd. for $C_9H_8O_4$: C, 60.00: H, 4.48. Found: C, 59.91; H, 4.60.

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