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Synthesis based on cyclohexadienes: Part 26[1] — Total synthesis of some naturally occurring phthalides from *Alternaria species*

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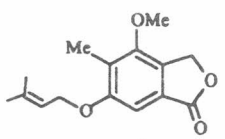
Total synthesis of the naturally occurring phytotoxic phthalides, silvaticol **7**, zinniol **5** and the phthalides **1** and **2**, is reported from the substrate **16** derived from the Alder-Rickert reaction of 1-methoxy-2-methyl-3-trimethylsilyloxycyclohexa-1,3-diene **15** with dimethyl acetylenedicarboxylate.

Several fungi from the genus *Alternaria* cause diseases of commercially important plants and produce a series of chemically related phytotoxins. The fungus *Alternaria porri* (Ellis) Ciferri, the casual fungus of the black spot disease in stone-leek and onion, produces phytotoxins such as the isomeric phthalides **1** and **2**[2,3], silvaticol **7**[4], zinnimidine **6**,[3] porritoxinol **3**,[5] and porritoxin **4**.[6] Zinnolide **10**[7] is obtained from *Alternaria solani*. The pathogenic fungus *Alternaria zinniae* Pape causes leaf and stem blight on zinnia, sunflower and marigold[8]. The tips and margins of infected plants may become chlorotic and then necrotic. From the stationary liquid culture filtrates of this fungus, zinniol **5**[9,10] was isolated as a major metabolite. *Alternaria cichorii* causes foliar blight of Russian knaap-weed, an important pest wed. Examination of the organic extract yielded[11] zinniol **5**, cichorine **8**, zinnimidine **6**, zinndiol **9** and a triol **11**. Compounds **5** and **8** were found [11] to be highly active on knap-weed, corn, oats and soyabeans whereas **9** was active on alfalfa. Silvaticol **7** and cichorine **8** are also produced along with nidulol **12** from *Aspergillus silvaticus*.[11,18] All these compounds possess a novel pentasubstituted aromatic ring. The substituent pattern is similar in many naturally occurring phthalides and hence a general synthetic strategy for these phytotoxins is desired. In a continuing effort[13] towards the synthesis of highly substituted and bioactive fungal metabolites (phthalides), we describe here the total synthesis of the phthalides **1** and **2**,**5** and **7** based on the Alder-Rickert reaction, involving a suitably substituted cyclohexadiene and dimethyl acetylenedicarboxylate (DMAD).



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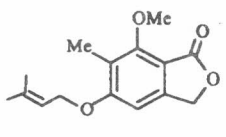

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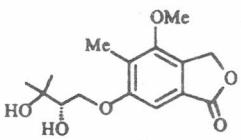

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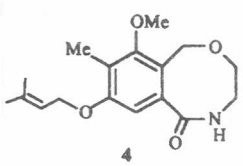

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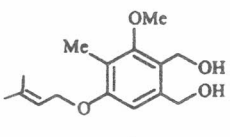

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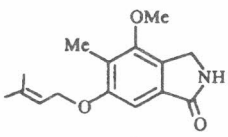

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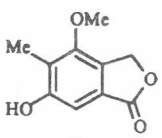

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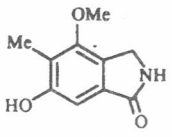

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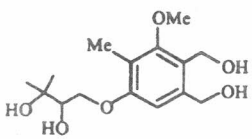

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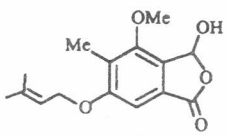

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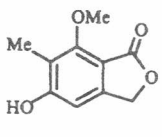

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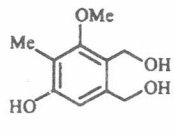

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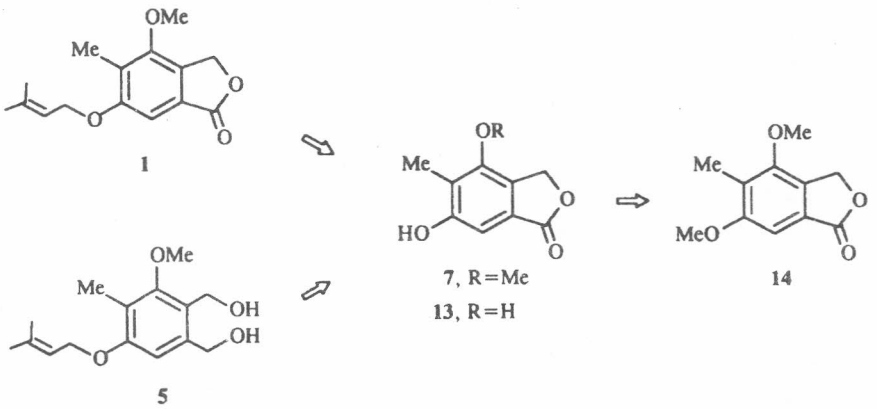
The Alder-Rickert reaction is known to be the most powerful method for constructing the polysubstituted aromatic compounds.

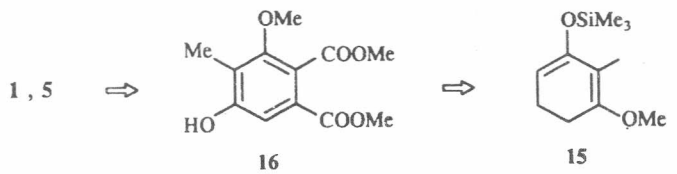
Our synthetic plan is depicted in **Scheme I** Zinniol **5** and the phthalide **1** could be obtained from the phthalide **7** or **13**. Compound **7** was chosen as the key intermediate for further elaboration, since prenylation of the 6-OH group would furnish the phthalide **1** and the reduction of the lactone of **1** would yield zinniol. Compound **7** could, in principle, be obtained from the known[13] phthalide **14**. We anticipated that an equimolar amount of the demethylating reagent should demethylate the less hindered 6-OMe group in **14**.

Dimethoxyphthalide **14**, prepared earlier[13] by the cycloaddition of 1,3-dimethoxy-2-methylcyclohexa-1,3-diene with dimethyl acetylenedicarboxylate (DMAD), was subjected to selective demethylation which failed to yield the monohydroxy compound **7**. Hence, an alternative method involving the hydroxy diester **16** was chosen as the key intermediate for the preparation of the naturally occurring phthalides as shown in **Scheme II.** The key intermediate **16** can easily be prepared from the diene **15** by a Diels-Alder and Alder-Rickert sequence of reactions with DMAD.

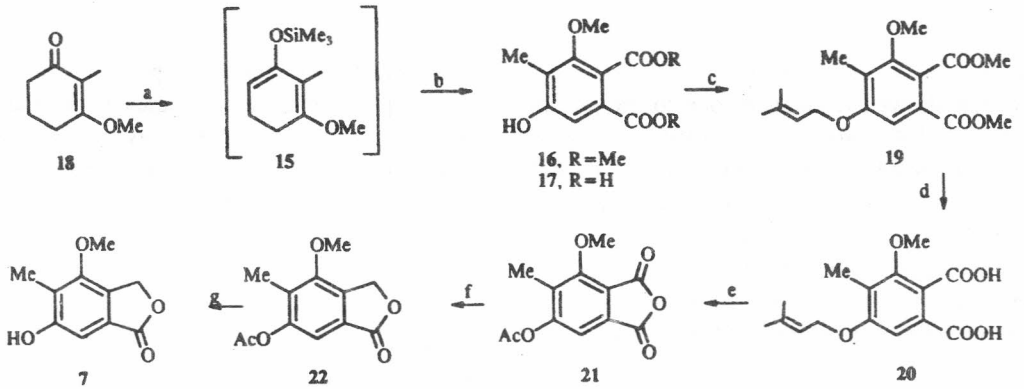
Our synthetic sequence is depicted in **Scheme III**. The known enol ether **18**[15] was treated with LDA in the presence TMSCl[16] at –70 °C to give the enol silyl ether **15** which underwent cycloaddition with DMAD (–20 °C to 70 °C) followed by *in situ* Alder-Rickert[17] reac-tion at 120 °C to yield an adduct. Stirring of the crude reaction mixture with aqueous HCl produced the hydroxyphthalate **16** in 63 % overall yield from the enone **18**. The IR spectrum of **16** showed broad absorptions at 3550-3200 and 1725Cm^{-1} for hydroxyl and ester functionalities. Besides, ^{1}H NMR spectrum showed three singlets at δ 3.77, 3.81 and 3.93 due to the protons of three methoxyl groups. Attempted hydrolysis of the diester **16** using aqueous methanolic alkali did not result in the diacid **17**. Hence, the phenol was converted into its prenyl ether using 1-bromo-3-methyl-2-butene and K_2CO_3 to afford the diester **19** whose ^{1}H NMR spectrum showed a doublet at δ 4.58 and a triplet at δ 5.46 due to allylic methylene and olefinic protons respectively besides six singlets for six methyl groups.



Scheme I

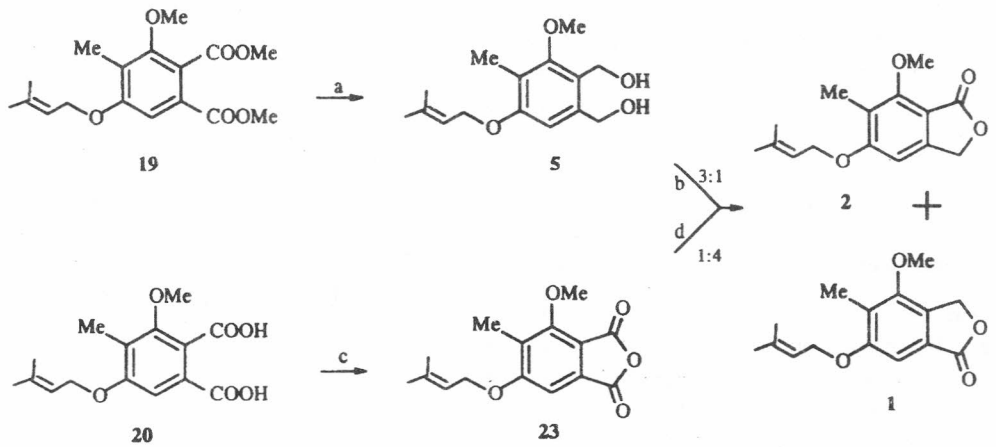


Scheme II



a) LDA, TMSCl,THF; b)(i) DMAD, -23 to 70°C; (ii) 120°C; c) K_2CO_3,1-bromo-3-methylbut-2-ene,DMF,85°C; d) KOH,EtOH,Δ; e) Ac_2O,Δ; f) $NaBH_4$,DMF,0°C; g) K_2CO_3, MeOH,Δ.

Scheme III



a) DIABAL-H, THF, -70°C; b) PCC, CH_2Cl_2; c) DCC, THF; d) $NaBH_4$, DMF,0°C

Scheme IV

Further, the IR spectrum of **19** showed the absence of a hydroxyl group. Hydrolysis of the diester **19** with KOH in refluxing EtOH smoothly produced the diacid **20**. Reaction of **20** with acetic anhydride under reflux gave the anhydride which showed an extra band in its IR spectrum at 1740cm^{-1}, apart from the absorptions due to anhydride function. The ^{1}H NMR spectrum showed the absence of a prenyl group, instead a singlet appeared at δ 2.43. Based on these observations, struc-ture **21** for the anhydride was proposed wherein the prenyl group at C-5 is replaced by the acetyl func-tionality. The structure of **21** was conclusively established by converting **21** to the known phthalide **22**[10] with $NaBH_4$. Hydrolysis of the acetate in **22** using K_2CO_3 in MeOH afforded silvaticol **7** in an excellent yield. The spectral data of the synthetic silvaticol was comparable with the reported data for the natural silvaticol[4,18].

The diester **19** on reduction with excess of diisobutyl-aluminium hydride produced zinniol **5**[19] in a quantitative yield (**Scheme IV**), the spectral characteristics are indistinguishable from that of the natural zinniol[10,11]. Oxid;ation of zinniol with PCC gave a mixture of phthalides **1** and **2** in a 1:3 ratio respectively which could be easily separated by column chromato-graphy. n order to obtain the phthalide **1** exclusively, the diacid **20** was transformed to the anhydride **23** under neutral conditions, using DCC, in quantitative yield (**Scheme IV**). The prenyl group was intact during this

transformation as evidenc;ed from its ^1H NMR spectrum which showed resonances due to the olefinic proton (triplet, δ 5.44) and allylic methylene protons (doublet, δ 4.64) besides other signals. The anhydride **23**, on regioselective reduction[14] using $NaBH_4$ in dry DMF, afforded a 4:1 mixture of the phthalides **1** and **2** respectively in a good yield. These two phthalides were readily separated by column chromatography. Their structures as phthalides were deduced from the spectral data which are in excellent agreement with those reported for the natural phthalaides.[2,3] In the ^1H NMR spectra of **1** and **2**, the signals due to aromatic proton appeared at different positions (δ 7.08 for **1** and δ 6.61 for **2**) which indicated the carbonyl group to be adjacent to the proton in **1** away from the proton in **2**.

In conclusion, a simple and efficient total synthesis of the naturally occurring phthalides from *Alternaria species* is reported from readily available cyclohexadienes. A key intermediate, the hydroxy diester **16**, derived from the Alder-Ricket reaction of enol silyl ether **15** with DMAD, was elaborated to the natural products.

Experimental Section

General. Mps are uncorrected and were recorded on a Mettler FP1 instrument. IR spectra were recorded as liquid films, solutions in chloroform or Nujol mulls on a Perkin-Elmer model 781. ^1H NMR and ^{13}C NMR spectra were recorded on JEOL FX-90Q, Bruker AMX-400 spectrometers in $CDCl_3$ (unless otherwise stated) with $SiMe_4$ as internal standard (chemical shifts in δ, ppm and *J* values in Hz). Mass spectra were recorded on a JEOL MS-DX 303 with a built-in direct inlet system. Microanalyses were carried out using a Carlo Erba 1106 analyser. All anhydrous solvents were prepared by standard procedures. Analytical TLC was performed on glass plates coated with Acme's silica gel G (containing 13 % calcium sulphate as the binder) and Acme's silica gel (60-120 mesh) was used for column chromatography. All reactions involving air and moisture sensitive reagents were performed under a blanket of argon filled-in balloons. Hexane refers to petroleum ether fraction of boiling range 60-80 °C.

Dimethyl 5-hydroxy-3-methoxy-4-methylphthalate 16. A solution of LDA was prepared by the addition of *n*-butyllithium (31 mL, 0.98 *M* in *n*-hexane) to diisopropylamine (4.8 mL, 34 mmoles)in dry THF (25 mL) for 10 min. Thereafter, a solution of the enone 18 (4.25 g, 30.3 mmoles) in 20 mL of THF was added over 20 min. and the reaction mixture stirred for 45 min. at –70 °C. Triethylamine (10 mL) was then added to the reaction mixture and poured into ice-water. The resulting solution was extracted with ether (3×20 mL) and the combined organic layers were washed with water, brine and dried over anhydrous K_2CO_3. Evaporation of the solvent gave the silyloxydiene which was used immediately in the next step.

The above silyloxydiene in xylene (15 mL) was cooled to –23 °C and DMAD (4 mL) Added to it dropwise over 5 min. The resulting solution was stirred at room temperature for 2 hr and then heated to 70 °C for 2 hr. The temperature was raised to 120 °C and left for 3 hr. The organic layer was separated and the aqueous layer extracted with ethyl acetate. The combined organic extracts were washed with water, $NaHCO_3$ solution, water and brine and dried over anhydrous Na_2SO_4. Evaporation of the solvent gave a gum, which was chromatographed over silica gel using ethyl acetate hexane (1:3) to afford **16** as a solid which was recrystallized from rthyl acetate (4.86 g, 63 % overall from the enone **18**), mp 115 °C. Anal. Calcd for $C_{12}H_{14}O_6$: C, 56.69; H, 5.55. Found: C, 56.66; H, 5.53%; IR(Nujol): 3550-3200, 1725, 1600 cm^{-1}; ^1H NMR (200 MHz; $CDCl_3$): 2.17 (3H, s, ArMe), 3.77 (3H, s, OMe), 3.81 (3H, s, OMe), 3.93 (3H, s, OMe), 7.1 (1H, br s, D_2O exchangeable, OH) and 7.2 (1H, s, ArH); ^{13}C NMR (22.5 MHz; $CDCl_3$):9.06 (q), 52.29 (q), 52.72 (q), 61.93 (q), 112.3 (d), 121.63 (s), 124.12 (s), 125.75 (s), 156.41 (2s), 166.83 (s) and 169.41 (s).

Dimethyl 3-methoxy-4-methyl-5-(3-methyl-2-butenyloxy)phthalate 19. A mixture of the hydroxydiester **16** (4.4 g, 17.3 mmoles), anhydrous K_2CO_3 (4.78 g, 34.65 mmoles) and prenyl bromide (4 mL) in dry DMF (40 mL) was heated at 85 °C. After a time interval of 12 hr and 24 hr, additional amounts of prenyl bromide (2 mL) and K_2CO_3 (2.5 g) each were added and the mixture was stirred for 48 hr, cooled, diluted with water and extracted with ethyl acetate. The combined organic extracts were washed with water, aqueous $Na_2S_2O_3$, brine and dried over anhydrous Na_2SO_4. Removal of the solvent gave a solid which was crystallized from ethyl acetate to give colourless crystals of **19** (4.96 g, 89 %), mp 62.1 °C. Anal. Calcd for $C_{17}H_{22}O_6$: C, 63.34; H, 6.88. Found: C, 63.36; H, 6.9 %; IR ($CHCl_3$): 1730, 1720, 1595 cm^{-1}; ^1H NMR (200 MHz; $CDCl_3$): 1.76 (3H, s, Me), 1.8 (3H, s, Me), 2.19 (3H, s, ArMe), 3.78 (3H, s, OMe), 3.87 (3H, s, OMe), 3.92 (3H, s, OMe), 4.58 (2H, d, J = 6.6 Hz, OCH_2), 5.46 (1H, t, J = 6.6 Hz, olefinic) and 7.25 (1H, s, ArH);^{13}C NMR (22.5 MHz; $CDCl_3$): 8.56 (q), 17.27 (q), 24.82 (q), 51.48 (2q), 61.23 (q), 64.74 (t), 107.4 (d), 118.85

(d), 122.62 (s), 125.1 (s), 125.48 (s), 137.19 (s), 157.48 (s), 164.76 (s) and 167.1 (s).

3-Methoxy- 4-methyl-5-(3-methyl-2-butenyloxy)-phthalic acid 20. A mixture of the diester **19** (2 g, 6.2 mmoles) and15 % KOH solution in EtOH (10 mL) was refluxed for 12 hr. EtOH was removed *in vacou* and the concentrate acidified with dil. HCl. The precipitate was filtered, dried and recrystallized from ethyl acetate to give colourless needles of **20** (1.7 g, 93 %), mp 140.2 °C. Anal. Calcd for $C_{15}H_{18}O_6$: C, 61.22; H, 6.16. Found: C, 61.13; H, 6.14; IR Nujol): 3200-2500, 1710, 1685, 1590 cm^{-1}; 1H NMR (90 MHz; $CDCl_3$): 1.69 (6H, s, 2×Me), 2.08 (3H, s, ArMe), 3.66 (3H, s, OMe), 4.56 (2H, d, J = 8.1 Hz, OCH2), 5.39 (1H, t, J = 8.1 Hz, =CH–) and 7.2 (1H, s, ArH); ^{13}C NMR (22.5 MHz; DMSO-d_6): 9.95 (q), 18.58 (q) 25.99 (q), 62.36 (q), 65.79 (t), 108.91 (d), 120.18 (d), 125.2 (2s), 129.59 (s), 138.31 (s), 156.11 (s), 157.77 (s), 167.28 (s) and 169.16 (s).

5-Acetoxy-3-methoxy-4-methylphthalic anhydride 21. The above phthalic acid **20** (1 g, 3.4 mmoles) was refluxed with AC_2O (6 mL) for 3 hr. Acetic anhydride and acetic acid were removed under vacuum and the residue was crystallized from ethyl acetate to afford **21** (0.749 g, 88 %). Anal. Calcd for $C_{12}H_{10}O_6$: C, 57.61; H, 4.03. Found: C, 57.63; H, 4.02 %; IR (Nujol): 1840, 1775, 1740, 1610 cm^{-1} ; ^1H NMR (90 MHz; DMSO-d_6): 2.2 (3H, s, $ArCH_3$), 2.43 (3H, s, $COCH_3$), 4.19 (3H, s, OMe) and 7.73 (1H, s, ArH).

6-Acetoxy-4-methoxy-5-methylphthalide 22. T a stirred solution of the anhydride **21** (0.65 g, 2.59 mmoles) in dry DMF (10 mL) at 0 °C was added $NaBH_4$ (0.1 g, 2.63 mmoles) in two portions. After stirring for 4 hr, water was added followed by the addition of a few drops of dil. HCI and the resulting precipitate filtered. Recrystallization of the crude product from ethanol gave the phthalide **22** (0.594 g, 96 %) mp 134.7 °C (lit.[10] mp 134-135 °C). Anal. Calcd for $C_{12}H_{12}O_5$: C, 61.01; H, 5.12. Found: C, 61.02; H, 5.16 %; IR ($CHCl_3$): 1750 (br), 1365 cm^{-1}; ^1H NMR (90 MHz; $CDCl_3$): 2.15 (3H, s, $ArCH_3$), 2.35 (3H, s, $COCH_3$) 3.91 (3H, s, OMe), 5.42 (2H, s, CH_2O) and7.3 (1H, s, ArH); 13C NMR (22.5 MHz; $CDCl_3$): 10.39 (q), 20.67 (q), 59.15 (q), 68.33 (t), 113.32 (d), 125.26 (s), 128.91 (s), 131.68 (s), 151.02 (s), 153.35 (s), 168.92 (s), 169.93 (s).

Silvaticol 7. A mixture of the acetoxyphthalide **22** (0.1 g, 0.42 mmoles), anhydrous K_2CO_3 (0.12 g, 0.87 mmoles) in MeOH (6 mL) was refluxed for 10 hr.The solvent was removed, and the residue diluted with water and acidified with dil. HCl. The resulting precipitate was collected under suction, dried and recrystallized from MeOH to furnish silvaticol **7** (0.078 g, 96 %), mp 233.2 °C (lit.[4,10] 233-235 °C).Anal. Calcd for $C_{10}H_{10}O_4$: C, 61.85; H, 5.19. Found: C, 61.91; H, 5.18; IR (Nujol): 3320, 1732 cm^{-1}; ^1H NMR (400 MHz; acetone-d_6): 2.14 (3H, s, Me), 3.91 (3H, s, OMe), 5.48 (2H, s, CH_2) and 6.99 (1H, s, ArH); ^{13}C NMR (100 MHz; acetone-d_6): 9.81 (q), 59.35 (q), 69.24 (t), 105 05 (d(, 123.58 (s), 125.74 (s), 127 (s), 154.31 (s), 158.66 (s) and 171.62 (s).

Zinniol 5. DIBAL-H (18 mL, 1*M* solution in *n*-hexane) was added dropwise to a solution of the diester **19** (1.284 g, 4 mmoles) in dry THF (50 mL) under Ar atmosphere at –70 °C and stirred foı 2 hr at the same temperature. Drops of methanol were added slowly to destroy the excess DIBAL-H. Saturated potassium tartrate solution eas added and extracted with ether. The combined ethereal layers were washed with brine and dried over anhydrous Na_2SO_4. Evaporation of the solvent followed by chromatograohy over silica gel using ethyl acetate-hexane (1:2) gave **5** as a viscous liquid (1.064 g, quantitative yield); IR (Neat); 3520-3100, 1600 cm^{-1}; ^1H NMR (200 MHz; $CDCl_3$): 1.74 (3H, s, Me), 1.80 (3H, s, Me), 2.16 (3H, s, ArMe), 2.94 (2H, br s, 2×OH), 3.77 (3H, s, OMe), 4.53 (2H, d, J = 6.5 Hz, $ArOH_2$–), 4.70 and 4.78 (2×2H, 2s, $2×CH_2OH$), 5.49 (1H, t, J = 6.5 Hz, olefinic) and 6.68 (1H, s, ArH); ^{13}C NMR (225 MHz; $CDCl_3$): 8.67 (q), 17.62 (q), 25.2 (q), 55.54 (t), 61.17 (q), 62.9 (t), 64.75 (t), 108.09 (d), 118.7 (s), 119.68 (d), 123.69 (s), 136.69 (s), 138.75 (s), 156.95 (s) and 157.38 (s); MS: m/z 266 (M^+, 15 %), 249 (16), 198 (100), 180 (87), 163 (32) and 69 (25).Anal. Calcd for $C_{15}H_{22}O_4$: M^+, 266.1518. Found: M^+, 266.1519.

3-Methoxy-4-methyl-5-(3-methyl-2-butenyloxy)-phthalic anhydride 23. A mixture of the phthalic acid **20** (0.62 g, 2.11 mmoles) and DCC (0.435 g, 2.11 mmoles) in dry THF (13 mL) was stirred at room temperature for 6 hr. Water was added to the reaction mixture and extracted with ethyl acetate. The combined organic extracts were washed with brine and dried over anhydrous Na_2SO_4. The residue, thus obtained, was purified by chromatography over silica gel. Elution with ethyl acetate-hexane (1:6) afforded the anhydride **23** (0581 g, 99 %). Anal. Calcd for $C_{15}H_{16}O_5$: C,65.21; H, 5.84. Found: C, 65.18; H, 5.78%; IR (Nujol): 1840, 1775, 1610 cm^{-1}; ^1H NMR (90 MHz; $CDCl_3$); 1.73 (3H, s, Me), 1.79 (3H, s, Me), 2.23 (3H, s, ArMe),4.14 (3H, s, OMe), 4.64 (2H, d, J = 8.36 Hz, $–OCH_2–$), 5.44 (1H, t, J = 8.36 Hz, =CH) and 7.14 (1H, s, ArH); 13C NMR (22.5 MHz; $CDCl_3$): 9.35 (q), 18.05 (q), 25.52 (q), 62.04 (q), 66.37 (t), 102.99 (d), 111.8 (s), 118.27 (d),

128.02 (s), 131.81 (s), 139.29 (s), 157.7 (s), 160.63 (s), 163.12 (s) and 164.42 (s).

4-Methoxy-5-methyl-6-(3-methyl-2-butenyloxy)-phthalide 1 and 7-methoxy-6-methyl-5-(3-methyl-2-butenyl-oxy)phyhalide 2 : (a) From Zinniol. A slurry of Zinniol **5** (0.80 g, 3.02 mmoles), PCC (2.16 g, 10 mmo;es and NaOAc (3 g,) in dry CH_2Cl_2 was stirred for 3 hr.The solvent was removed, ether added and the mixture filtered through a pad of Celite. The residue, obtained after the removal of the solvent, was purified by chromatography over silica gel. Elution with ethyl· acetate-hexane (1:9) initially afforded the phthalide **1** (0.216 g, 27.3 %), mp 84-86 °C (lit.[2,10] 84-85 °C). Anal. Calcd for $C_{15}H_{18}O_4$: C, 68.69; H, 6.92. Found: C, 68.61; H, 6.89 %; IR (Nujol): 1750, 1610 cm–1; ^{1}H NMR(400 MHz; $CDCl_3$): 1.75 (3H, s, Me), 1.80 (3H, s, Me), 2.21 (3H, s, ArMe), 3.88 (3H, s, OMe), 4.57 (2H, d, J = 6.48 Hz, $=CCH_2O$), 5.37 (2H, s, ArCH2O), 5.48 (1H, t, J = 6.48 Hz, =CH) and 7.08 (1H, s, ArH); ^{13}C NMR (100 MHz; $CDCl_3$): 9.76 (q), 18.31 (q), 25.78 (q), 59.28 (q), 65.83 (t), 68.31 (t), 101.82 (d), 119.31 (d), 124.75 (s), 125.65 (s), 127.99 (s), 138.18 (s), 152.91 (s), 159.2 (s) and 171.29(s).

Further elution using the same solvent system furnished the phthalide **2** (0.504 g, 63 %), mp 107.2 °C (lit.[10],mp 106-108 °C). Anal. Calcd for $C_{15}H_{18}O_4$: C, 68.69; H, 6.92. Found: C, 68.73; H, 6.97 %; IR ($CHCl_3$): 1755 cm1; ^{1}H NMR (400 MHz; $CDCl_3$): 1.75 (3H, s, Me), 1.81 (3H, s, Me), 2.14 (3H, s, ArMe), 4.02(3H, s, OMe), 4.59 (2H, d, J = 6.44, $=CCH_2O$), 5.17 (2H, s, $ArCH_2O$), 5.47 (1H, t, J = 6.44, =CH) and 6.61 (1H, s, ArH); ^{13}C NMR (100 MHz; $CDCl_3$): 8.65 (q), 18.27 (q), 25.75 (q), 62 (q), 65.81 (t), 68.8 (t), 99.63 (d), 109.37(s), 119 (d), 120.6 (s), 138.52 (s), 148.23 (s), 157.68 (s), 163.63 (s) and 169.04 (s).

(b) From the anhydride 23. To a stirred solution of the anhydride **23** (0.34 g, 1.23 mmoles) in dry DMF (10 mL) at 0 °C was added $NaBH_4$ (0.05 g, 132 mmoles) in two portions. After stirring for 4 hr, the reaction mixture was diluted with water followed by the addition of a few drops of dil. HCl. The resulting precipitate was collected under suction and purified by chromatography as detailed above to give 97 % yield of the phthalide **1** (0.251 g) and phthalide**2** (0.063 g) in 4:1 ratio.

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