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Synthesis of demethylated nidulol via an intramolecular Michael reaction

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An expeditious synthesis of 5,7-dihydroxy-6-methylphthalide from open-chain precursors is described. The key intermediates, *synthons* **3** and **4**, were readily obtained from accessible materials and were further transformed to a common precursor, a five-membered lactone derivative, via an intramolecular Michael addition. Lactone **2** was aromatised to the phthalide system under basic conditions. The process thus constitutes a formal synthesis of the phthalide framework.

Keywords: phthalides; nidulol; intramolecular aromatisation

1. Introduction

Phthalides (1*H*-2,3-dihydroisobenzofuran-1-ones) constitute the molecular skeleton of many natural products. The 5,6,7-substituted phthalides form a family of natural phytotoxins possessing this heterocyclic unit. They are produced by some lichens of the *Alternaria* genus, which may inflict severe spoilage on commercially important plants. *Alternaria porri* (Hariprakasha & Subba Rao, 1998), for example, causes dark spots on onions and other plants, and *Alternaria zinniae* (Hariprakasha & Subba Rao, 1998; Nozawa, Seyea, Nakajima, Udagawa, & Kawai, 1987) attacks the sunflower stem and leaves. Extracts of *Aleatoria nigricans* (Solberg, 1975) show toxic effects on chicken and mouse embryos. Nidulol (**1a**) and demethylnidulol (**1b**) (Figure 1) were isolated from natural sources (*Aspergillus nidulans* (Aucamp & Holzapfel, 1968) and *Aspergillus duricaulis* (Elix & Joyanthi, 1987)). In a synthetic sequence aimed to elucidate the structure of lichen metabolites, both products were obtained as well (Achenbach, Muehlenfeld, & Brillinger, 1985).

Reported procedures that aimed to synthesise 5,6,7-trisubstituted and 4,5,6,7-tetrasubstituted phthalides are abundant and may be grouped in well-defined strategies. In one approach, a substituted benzene is the starting material on which the construction of the five-membered lactone follows (Kobayashi, Shimizu, Itoh, & Suginome, 1990; Lee, et al., 2001; Makara, Klubek, & Anderson, 1996; Patterson, 1995). Another approach considers the simultaneous formation of the five- and

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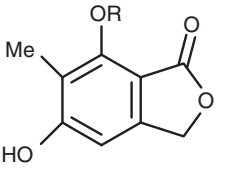
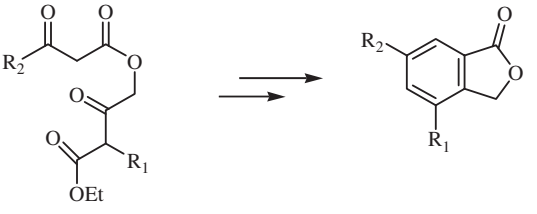


Figure 1. **1a**, $R_1 = Me$, nidulol, **1b**, $R_1 = H$, demethylated nidulol.



Scheme 1. Synthesis of phthalide derivatives via intramolecular condensations.

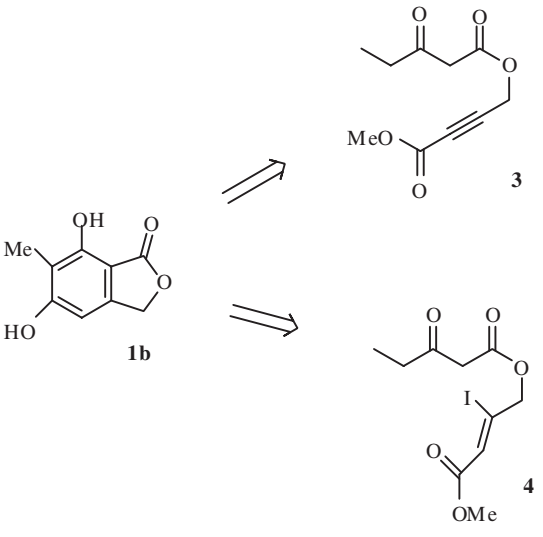
six-membered rings via a Diels–Alder reaction (Cruz, Talamas, Vázquez, & Muchowski, 1997; Watanabe, Tsukazaki, Hamada, Iwao, & Furukawa, 1989) or intramolecular condensations (Covarrubias-Zuñiga et al., 2003, 2005). In the synthetic strategy depicted further (Scheme 1), the five-membered ring is first obtained through an aldol condensation, then the phenyl ring is constructed by a Dieckmann condensation (Auricchio, Ricca, & de Pava, 1983).

Herein, an approach for the synthesis of metabolite **1b** (5,7-dihydroxy-6-methylisobenzofuran-2-one), similar to the aforementioned synthetic strategy, is described.

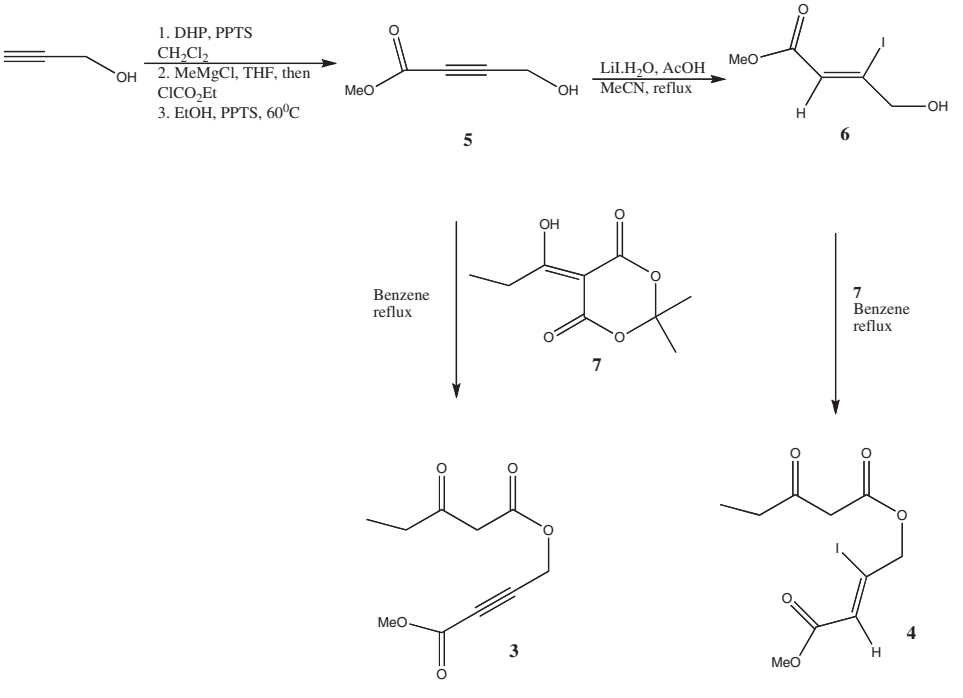
2. Results and discussion

We viewed the possibility of accessing the target molecule **1b** from either a propargyl derivative, *synthon* **3**, or from an iodoalkene, *synthon* **4**, in accordance with the retrosynthetic analysis outlined in Scheme 2.

The synthetic sequence employed to obtain *synthons* **3** and **4** is depicted in Scheme 3. The synthesis began with propargylic alcohol, which was the common starting material for the preparation of intermediates **5** and **6**. Thus, in accordance with well-established procedures, the corresponding tetrahydropyranyl (THP) derivative was obtained in 71% yield, as a liquid (85–87°C/19 mm) (Henbest, Jones, & Walls, 1950; 47–50°C/3.5–5 mm), which on treatment with methylmagnesium chloride, followed by the addition of methyl chloroformate, gave the corresponding ester (80% yield), which was purified by low-pressure distillation, b.p. 114°C/5, 0 mm (Earl & Townsend, 1981; Henbest et al., 1950; Jung & Hagenah, 1987; 145–148°C/32 mm). Removal of the protective group (Miyashita, Yoshikoshi, & Grieco, 1977) provided compound **5**, which was treated with monohydrated lithium iodide in glacial acetic acid and dry acetonitrile without further purification (Ma, Lu, & Li, 1992) to afford diastereoselectively allylic alcohol **6**, in 54% yield. The spectroscopic information obtained from **6** was similar to that reported in the literature (Shinada & Yoshihara, 1996).



Scheme 2. Retrosynthetic analysis of **1b** from either *synthon* **3** or **4**.



Scheme 3. Synthesis of *synthons* **3** and **4**.

The propanoyl Meldrum's acid derivative (**7**), required for the next step, was obtained by the condensation of Meldrum's acid with propanoic acid in the presence of dicyclohexylcarbodiimide (DCC) and dimethylaminopyridine (DMAP) (Tabuchi, Hamamoto, Miki, Tejima, & Ichihara, 1994). Alcohol **5** was dissolved in dry benzene

and heated with derivative (**7**) at 80°C for 20 h, in an adaptation of a related protocol (Oikawa, Sugano, & Yonemitsu, 1978). After the work-up procedure, the crude mixture was purified by column chromatography to deliver **3** as colourless oil, in 60% yield. In the IR spectrum, **3** showed the enol tautomer at 3425, the triple bond at 2252 and the carbonyls at 1757.8 and 1721.1 cm^{-1}. On the one hand, the ^1H NMR spectrum of **3** showed the methylene protons adjacent to the oxygen and the triple bond as a singlet at δ 4.86, as well as the methoxy group as a singlet at δ 3.79. On the other hand, the methylene protons amidst both carbonyls gave a singlet at δ 3.52. The ethyl group gave a quartet at δ 2.59 ($J = 7.24$ Hz) and a triplet at δ 1.09 ($J = 7.25$ Hz). Likewise, compound **4** was obtained from the reaction of **6** with Meldrum's acid derivative (**7**) and was isolated as a semisolid in 90% yield. In the IR spectrum, compound **4** showed three distinctive carbonyl bands at 1747, 1730 and 1704 cm^{-1}. In the ^1H NMR spectrum, product **4** showed the vinylic proton as a triplet at δ 6.71 ($J = 1.76$ Hz) due to the interaction with the methylene protons (CH_2-1), which gave a doublet at δ 4.91 ($J = 1.76$ Hz), thus confirming the double bond *Z* stereochemistry. The methoxy group resonated as a singlet at δ 3.79 and the methylene protons amidst both carbonyls gave a singlet at δ 3.56. The ethyl group gave a quartet at δ 2.61 ($J = 7.30$ Hz) and a triplet at δ 1.11 ($J = 7.20$ Hz).

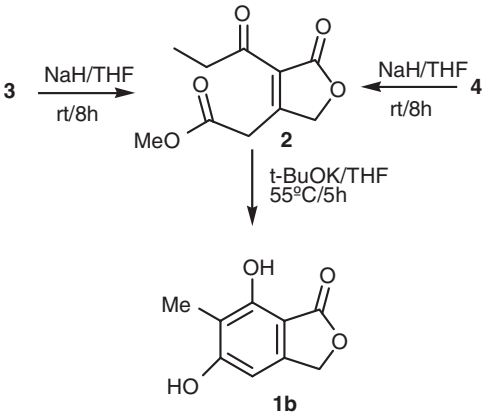
On the treatment of tricarbonyl intermediate **3** with sodium hydride in dry THF at low temperature (0–5°C) for a period of 8 h, a product was isolated, for which compound **2** (98% crude yield) was proposed based on spectroscopic data. In the IR spectrum, a lactone carbonyl band was absorbed at 1781 cm^{-1}, while the ester and ketone absorptions were superimposed to give an intense, slightly broad absorption at 1743 cm^{-1}. In the ^1H NMR spectrum, the lactone methylene protons were found as a singlet at 5 ppm, the methoxy group was observed as a singlet at 3.75, while the methylene protons adjacent to the ester were shown at 3.99 ppm. Lactone **2** was obtained in excellent yield from **4** as well, via an intramolecular condensation reaction promoted by sodium hydride in dry THF at room temperature.

Compound **2** was poised for an intramolecular Claisen-type condensation. Accordingly, after lactone **2** was generated *in situ*, potassium tert-butoxide (3 molar equivalents) was added and the reaction was kept for 5 h at reflux temperature (THF). After work up of the reaction mixture, phthalide **1b** was isolated in 32% yield (Scheme 4). The ^1H NMR spectrum showed compound **1b** as a singlet at δ 6.41 ppm (Ar–H), the methylene protons as a singlet at δ 5.18 ppm and the methyl group as a singlet at δ 2.12. On the other hand, the exchangeable signal with D_2O at δ 2.43 was assigned to the hydroxyl groups at C-5 and C-7. These data are in agreement with those reported by Solberg (1975).

3. Experimental

3.1. *General*

IR spectra were recorded on a Nicolet spectrometer. ^1H- and ^{13}C-NMR spectra were recorded with a Jeol Delta-GSX-270 spectrometer. ^1H-NMR spectra were recorded at 270.05 MHz (spectral width 2700 Hz, acquisition time 1.52 s, pulse width 45°, 32 scans, recycle delay 2 s). ^{13}C NMR spectra were recorded at 67.80 MHz (spectral width 12224.9 Hz acquisition time 1.34 s, pulse width 30°, 128 scans, recycle delay 0.8 s). The chemical shifts are referenced to internal $(CH_3)_4Si$



Scheme 4. Synthesis of **1b** from lactone **2**.

($\delta^1H = 0$, $\delta^{13}C = 0$). The HRMS were recorded using a Hewlett–Packard HP-5998A spectrometer.

3.1.1. *3′-Carbomethoxypropyn-2-yl-3-oxo-pentanoate (**3**)*

Propanoyl Meldrum's acid derivative (**7**, 200 mg (1.0 mmol)) and hydroxymethyl propargylic methyl ester (**5**, 216 mg (1.5 mmol)) were dissolved in anhydrous benzene and heated at reflux temperature for 20 h, under a nitrogen atmosphere. The reaction mixture was cooled to room temperature, the solvent was removed under vacuum and the residue was purified by column chromatography. The title compound was isolated as oil in 60% yield. IR (film), (cm^{-2}) 3425, 2252, 1757.8, 1721.1, 1434.7. ^1H NMR ($CDCl_3$), δ 4.86 (s, 2H, $\underline{H}_2C$–O), 3.79 (s, 3H, $\underline{H}_3C$–O), 3.52 (s, 2H, $\underline{H}_2C(CO)_2$), 2.60 (q, 2H, $J = 7.24$ Hz, $\underline{H}_2C$–CO), 1.09 (t, 3H, $J = 7.25$ Hz, $\underline{H}_3C$). ^{13}C NMR ($CDCl_3$), δ (ppm). 202.3, 166.2, 153.1, 80.5, 78.0, 52.8, 51.9, 48.3, 36.3, 7.4. HRMS Calcd for $C_{10}H_{12}O_5$: 212.0785; found: 212.0780.

3.1.2. *(Z) 3-Carbomethoxy-2-iodopropen-2-yl-3-oxo-pentanoate (**4**)*

The title compound was isolated as a semisolid in 90% yield after column chromatography purification, following the same procedure described for the preparation of **3**. IR (film), (cm^{-2}) 3044.2, 2932.4, 1747.5, 1730.4, 1704.5, 1658.9, 1640.8, 1434.1, 1407.2, 1362.2, 1318.7,1173.3. ^1H NMR ($CDCl_3$), δ 6.72 (t, 1H, $J = 1.76$ Hz, $\underline{H}C{=}C$), 4.91 (d, 2H, $J = 1.76$ Hz, $\underline{H}_2C$–O), 3.79 (s, 3H, $\underline{H}_3C$–O), 3.56 (s, 2H, $\underline{H}_2C(CO)_2$), 2.61 (q, 2H, $J = 7.3$ Hz, $\underline{H}_2C$–CO), 1.11 (t, 3H, $J = 7.3$ Hz, $\underline{H}_3C$). ^{13}C NMR ($CDCl_3$) δ 202.5, 165.7, 164.4, 124.7, 110.8, 72.4, 51.8, 48.4, 36.5, 7.5. HRMS Calcd for $C_{10}H_{13}IO_5$: 339.9916; found: 339.9908.

3.1.3. *(5H)-3-Propionyl-4-methoxycarbonylmethylfuran-2-one (**2**)*

Sodium hydride (2 molar equivalents) was placed in a flask and washed with dry hexane (3×5 mL) under argon atmosphere. Freshly distilled dry THF was added

and the suspension was cooled to 0–2°C. Compound **3** (1 molar equivalent) dissolved in dry THF was slowly added to the previous suspension for a period of 15 min. Stirring was continued until the starting material disappeared (8 h, determined by TLC, EtOAc : Hexane, 4 : 6). Then, 20% aqueous HCl was added until pH was equal to 1. The solvent was removed under vacuum and the residue was taken in EtOAc, and then washed with brine (3×10 mL). The organic extract was dried (Na_2SO_4) and the solvent was distilled under reduced pressure to yield the title compound as a semisolid in 98% yield. IR (film) (cm^{-2}) 1782, 1743, 1697, 1655. ^{1}H NMR ($CDCl_3$) δ 5.0 (s, 2H, $\underline{H}_2C$–O), 3.98 (s, 2H, $\underline{H}_2C$–CO_2Me), 3.75 (s, 3H, $\underline{H}_3C$–O), 3.03(q, 2H, $J = 7.12$ Hz, $\underline{H}_2C$–CO), 1.08(t, 3H, $J = 7.12$ Hz, $\underline{H}_3C$–CH_2). HRMS Calcd for $C_{10}H_{12}O_5$: 212.0785; found: 212.0778.

3.1.4. *5,7-Dihydroxy-6-methylphthalide (**1b**)*

Under an inert, argon atmosphere, 2 molar equivalents of sodium hydride (previously washed with dry hexane) was suspended in dry THF. The suspension was cooled to 2°C and then a dry solution of **3** (1 molar equivalent) in THF was added for 15 min. Stirring at the same temperature was continued and after 8 h, TLC (EtOAc : Hexano, 4 : 6) indicated the presence of lactone **2**. At this point, freshly prepared potassium tert-butoxide (3 molar equivalents) in dry THF was slowly added for 15 min. Then the reaction mixture was refluxed for 5 h. The reaction was cooled to room temperature and the pH was adjusted to 1 by the addition of 20% HCl. The solvent was removed under vacuum and the residue was extracted with ethyl acetate (3×20 mL). The organic extracts were combined, washed with brine and dried (Na_2SO_4). The solvent was removed under pressure and the residue was purified by column chromatography, followed by preparative thin layer chromatography, to give **1b** in 31.2% yield. ^{1}H NMR ($CDCl_3$–CD_3OD) δ 6.41 (s, 1H, $\underline{H}$–Ar), 5.18 (s, 2H, $\underline{H}_2C$–O), 2.12 (s, 3H, $\underline{H}_3C$–Ar), 2.43 (bs, $\underline{H}$O–Ar, D_2O) (lit.[3] ^{1}H NMR 100 MHz (CD_3CN-d_3) 6.50, 5.16 and 2.04). ^{13}C NMR ($CDCl_3$), δ 164.9, 147.7, 112.4, 103.7, 101.1, 71.1, 7.9.

4. Conclusion

The key intermediate for the synthesis of dihydroxy-6-methylphthalide (**1b**) was compound **2**, a 3,4-disubstituted lactone, which in turn became easily accessible from triple and double bond intermediates, *synthons* **3** and **4**, respectively. The synthetic approach described here represents the first synthesis of 5,7-dihydroxy-6-methylphthalide.

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