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Synthesis of 8-Methoxy- and 8-Methoxy-6-methylhomophthalic Anhydrides, Key Intermediates for the Synthesis of Anthracyclinones and *peri*-Hydroxylated Polycyclic Aromatic Compounds

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A novel synthesis of 8-methoxy- (**1a**) and 8-methoxy-6-methylhomophthalic anhydrides (**1b**) is described. Oxidative aromatization of methyl 2-(2-carbomethoxy-3-oxocyclohex-1-enyl)acetate (**2**) using 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) or sublimed sulfur followed by methylation gave methyl (2-carbomethoxy-3-methoxyphenyl)acetate (**4**) (method A). Diels–Alder reaction of 6-methoxy-4-methyl-2-pyrone (**5**) with 1,3-dicarboalkoxyallenes occurred with the loss of carbon dioxide to give alkyl (2-carboalkoxy-3-methoxy-5-methylphenyl)acetates (**6** and **7**) (method B). These esters (**4**, **6**, and **7**) were converted to the corresponding 8-methoxyhomophthalic anhydrides (**1a**, **b**) by a usual alkaline hydrolysis followed by dehydrative cyclization with acetyl chloride in dry acetone.

Keywords——oxidative aromatization; Diels–Alder reaction; 1,3-dicarboalkoxyallene; 8-methoxyhomophthalic anhydride; anthracyclinone precursor; *peri*-hydroxyaromatic compound

8-Methoxyhomophthalic anhydride (**1a**) has recently been shown to be quite useful for the construction of anthracyclinones and *peri*-hydroxylated aromatic compounds.[1] Although several methods are available[2] for the synthesis of some 8-methoxyhomophthalic anhydrides, they still require a long sequence of reactions. The preparation of 8-methoxy-6-methylhomophthalic anhydride (**1b**) has not appeared in the literature despite the obvious potential for the construction of a linear polynuclear phenolic system, a structural feature present in many antibiotics and other natural products.[3] We report here a novel short synthesis of 8-methoxy- (**1a**) and 8-methoxy-6-methylhomophthalic anhydrides (**1b**).

We first investigated a short alternative synthesis of **1a** from a readily available compound. Since direct dehydrogenation of methyl 2-(2-carbomethoxy-3-oxocyclohex-1-enyl)acetate (**2**), easily prepared from methyl acetoacetate by the method of Huckin,[4] seemed to be a short and simple route to methyl (2-carbomethoxy-3-hydroxyphenyl)acetate (**3**), we examined direct oxidative aromatization of **2** by various dehydrogenation methods. Refluxing a benzene solution of **2** in the presence of 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) or manganese dioxide (MnO_2) or heating of **2** with sublimed sulfur gave the dehydrogenated homophthalate (**3**) directly (method A), although the yields are not good enough for preparative purposes. All other attempts to aromatize **2** to **3** by treatment with palladium–charcoal in refluxing xylene, iodine in methanol, *N*-bromosuccinimide (NBS) in refluxing methanol–chloroform, warm acetic anhydride, and NBS-cat. benzoyl peroxide in refluxing carbon tetrachloride were unsuccessful. Methylation of **3** with diazomethane gave the methyl ether (**4**), which was converted into 8-methoxyhomophthalic anhydride (**1a**) by a usual alkaline hydrolysis with 10% KOH followed by dehydrative cyclization with acetyl chloride. 3-Methoxyhomophthalic acid was also obtained from **3** in a one-pot procedure by hydrolytic

methylation with hot dimethyl sulfate in 30% NaOH.

Next, we turned our attention to the preparation of 8-methoxy-6-methylhomophthalic anhydride (**1b**). Method A, however, is not applicable for the synthesis of **1b**, since the starting 5-methyl substituted enone was obtained only in extremely low yields by a modification of the preparation of **2** using the dianion of methyl acetoacetate. Recent preparations of methyl (2-carbomethoxy-3-hydroxy-5-methylphenyl)acetate, which is expected to be a good precursor to **1b**, have been reported by using 1,3-bis(trimethylsiloxy)-1-methoxy-1,3-butadiene as an active diene in a Diels-Alder reaction. Thus, methyl (2-carbomethoxy-3-hydroxy-5-methylphenyl)acetate was prepared by the reaction of 1,3-bis(trimethylsiloxy)-1-methoxy-1,3-butadiene with acetyl chloride or trimethyl orthoacetate in the presence of titanium tetrachloride.[5,6] In our hands, the above-mentioned methods gave variable yields, probably because of the extremely moisture- and acid-sensitive nature of the bis(trimethylsiloxy)-butadiene and the difficulty of finding adequate reaction conditions. Therefore, attempts were made to prepare these derivatives alternatively by using a more stable diene system. Since the readily available and more stable 2-pyrone derivatives are active enough to react with various dienophiles regioselectively,[7-9] we examined a Diels–Alder reaction of 6-methoxy-4-methyl-2-pyrone (**5**) with 1,3-dicarboalkoxyallene, which is known to be a highly reactive dienophile.[10] The reaction of **5** and 1,3-dicarbomethoxyallene was carried out at 150—160 °C for 3 d in a sealed tube. The pyrone **5** reacted with the allene *via* its rigid "*S-cis*" form, thereby affording an intermediate of type A, which immediately suffered loss of carbon dioxide to give a 55% yield of methyl (2-carbomethoxy-3-methoxy-5-methylphenyl)-acetate (**6**) directly. Similarly, **5** was treated with 1,3-dicarboethoxyallene under similar conditions to give a 61% yield of ethyl (2-carboethoxy-3-methoxy-5-methylphenyl)acetate (**7**). These esters (**6** and **7**) were hydrolyzed with 10% KOH to give the diacid, which was cyclized with acetyl chloride in acetone to give 8-methoxy-6-methylhomophthalic anhydride (**1b**).

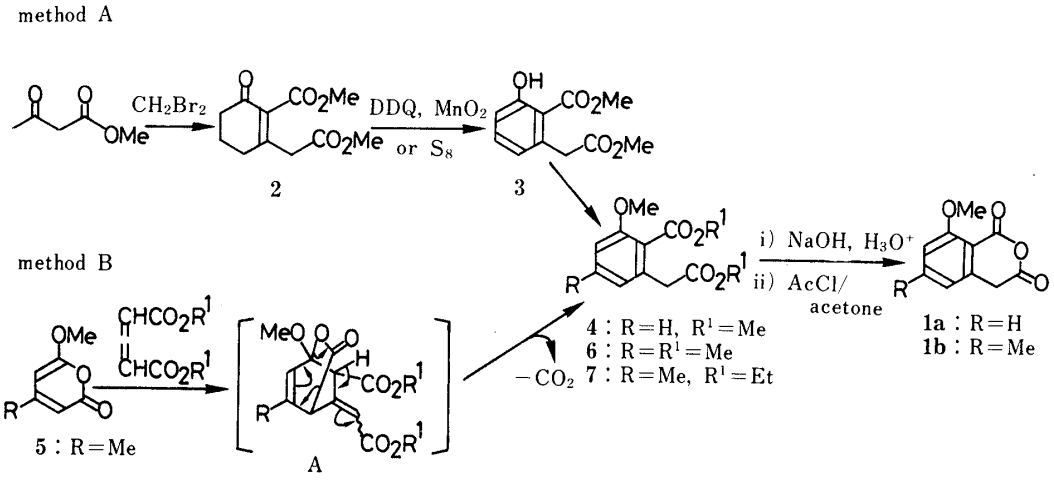

Chart 1

Experimental

All melting points are uncorrected. The infrared (IR) absorption spectra were recorded on a JASCO HPIR-102 spectrometer, and proton nuclear magnetic resonance (^{1}H-NMR) spectra on a Hitachi R-20A (60 MHz) or a Hitachi R-22 (90 MHz) spectrometer (with tetramethylsilane as an internal standard). Low- and high-resolution mass spectra (MS) were obtained with a JEOL JMS D-300 instrument with a direct-inlet system at 70 eV. Column chromatography was carried out on Merck Silica-gel 60.

Methyl (2-Carbomethoxy-3-hydroxyphenyl)acetate (3)——i) DDQ Treatment: A mixture of methyl 2-(2-

carbomethoxy-3-oxocyclohex-1-enyl)acetate (**2**, 160 mg, 0.71 mmol)[5] and DDQ (161 mg, 0.71 mmol) in dry benzene (3 ml) was heated at 100 °C for 9 h. The solvent was removed under reduced pressure, and the residue was subjected to column chromatography on silica gel (with benzene : ether = 20 : 1 as the eluting solvent) to give a 21% yield (34 mg) of **3**, which was purified by column chromatography on silica gel with CH_2Cl_2 as the eluting solvent to give a pure sample as colorless needles, mp 53—55 °C (lit.[4,6] 53—55 °C).

ii) MnO_2 Treatment: A mixture of **2** (0.5 g, 2.2 mmol) and MnO_2 (3.9 g, 44 mmol) in dry chloroform (30 ml) was heated at 80 °C for 6 h. The reaction mixture was passed through a Celite column and the filtrate was concentrated under reduced pressure. The residue was subjected to column chromatography on silica gel to give a 10% yield (51 mg) of **3**, which was identical with an authentic sample obtained above.

iii) Sublimed Sulfur Treatment: A mixture of **2** (226 mg, 1 mmol) and sublimed sulfur (32 mg, 1 mmol) in decalin was heated at 200 °C for 27 h. The reaction mixture was subjected to column chromatography on silica gel to give a 24% yield (52.5 mg) of **3**, which was identical with an authentic sample obtained in i).

Methyl (2-Carbomethoxy-3-methoxyphenyl)acetate (4)——A solution of a large excess of CH_2N_2 in ether (3 ml) was added to a solution of methyl (2-carbomethoxy-3-hydroxyphenyl)acetate (**3**, 500 mg, 2.23 mmol) in ether (5 ml). The reaction mixture was allowed to stand at room temperature overnight and concentrated under reduced pressure. The residual syrup was distilled to give an 84% yield of **4**, bp 110 °C/2 mmHg (lit.[11] 117—124/0.3 mmHg). ^{1}H-NMR (10% solution in $CDCl_3$) δ: 3.62 (2H, s, CH_2CO_2Me), 3.64 (3H, m, CO_2Me), 3.80 (3H, s, OMe), 3.87 (3H, s, CO_2Me), 6.7—7.4 (3H, m, ArH).

Methyl (2-Carbomethoxy-3-methoxy-5-methylphenyl)acetate (6)——A solution of 6-methoxy-4-methyl-2-pyrone[7] (**5**, 1.50 g, 10.7 mmol), 1,3-dicarbomethoxyallene (2.80 g, 17.9 mmol) and *ortho*-dichlorobenzene (30 ml) in a sealed tube was heated at 150—160 °C for 3 d. The reaction mixture was subjected to column chromatography (with benzene : ether = 1 : 1 as the eluting solvent) to give a 55% yield (1.48 g) of **6** as a liquid. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1740, 1725, 1615. ^{1}H-NMR (10% solution in $CDCl_3$) δ: 2.33 (3H, s, $ArCH_3$), 3.61 (2H, s, $ArCH_2CO_2CH_3$), 3.67 (3H, s, $CH_2CO_2CH_3$), 3.80 (3H, s, $ArCO_2CH_3$), 3.87 (3H, s, OCH_3), 6.66 (2H, s, ArH). Exact mass calcd. for $C_{13}H_{16}O_5$: 252.0995. Found: 252.0987.

Ethyl (2-Carboethoxy-3-methoxy-5-methylphenyl)acetate (7)——A solution of 6-methoxy-4-methyl-2-pyrone (**5**, 140 mg, 1.0 mmol), 1,3-dicarboethoxyallene (313 mg, 1.7 mmol), and *ortho*-dichlorobenzene (4 ml) in a sealed tube was heated at 150—160 °C for 3 d. The reaction mixture was subjected to column chromatography on silica gel (with benzene : ether = 10 : 1 as the eluting solvent) to give a 61% yield (172 mg) of **7** as a colorless liquid. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1720, 1610, 1580. ^{1}H-NMR (10% solution in $CDCl_3$) δ: 1.21 (3H, t, J = 7 Hz, $CH_2CO_2CH_2CH_3$), 1.32 (3H, t, J = 7 Hz, $CO_2CH_2CH_3$), 2.29 (3H, s, $ArCH_3$), 3.58 (2H, s, CH_2CO_2Et), 3.74 (3H, s, $ArOCH_3$), 4.09 (2H, q, J = 7 Hz, $CH_2CO_2CH_2CH_3$), 4.31 (2H, q, J = 7 Hz, $CO_2CH_2CH_3$), 6.60 (1H, s, ArH), 6.63 (1H, s, ArH). *Anal.* Calcd for $C_{15}H_{20}O_5$: C, 64.27; H, 7.19. Found: C, 63.96; H, 7.21.

General Procedures for the Conversion of Alkyl (2-Carboalkoxy-3-methoxyphenyl)acetates (4, 6, and 7) into 8-Methoxyhomophthalic Anhydrides (1a, b)——A solution of alkyl (2-carboalkoxy-3-methoxyphenyl)acetate (**4**, **6**, or **7**, 2 mmol) and KOH (1.2 g) in water (6 ml) and methanol (4 ml) was heated at 90 °C for 2 h. The methanol was removed by evaporation under reduced pressure. The residual aqueous solution was diluted with water (4 ml), washed with ether (10 ml), acidified to pH 1 with 10% HCl, and extracted with ether (3 × 30 ml). The combined extract was dried over $MgSO_4$ and concentrated to give the corresponding homophthalic acid, which was used for the next reaction without purification. The acid (1.5 mmol) was added portionwise to a solution of acetyl chloride (0.4 ml) in dry acetone (1.2 ml) at room temperature and the reaction mixture was stirred for 1 h under the same conditions. Concentration of the reaction mixture under reduced pressure below 50 °C gave the corresponding anhydride. No purification was necessary before further reaction.

8-Methoxyhomophthalic Anhydride (1a)——i) From 3-Methoxyhomophthalic Acid (**4**): The acid **4** (180 mg, 0.86 mmol) was treated with acetyl chloride in acetone under the conditions described in the general procedure to give a 73% yield (713 mg) of **1a**, mp 133—138 °C. Recrystallization from benzene gave pure **1a**, mp 137—140 °C (lit.,[12] no experimental section). IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1800, 1750. ^{1}H-NMR (10% solution in $CDCl_3$) δ: 3.99 (3H, s, OCH_3), 4.01 (2H, s, CH_2), 6.8—7.65 (3H, m, ArH). Exact mass calcd. for $C_{10}H_8O_4$: 192.0423. Found: 192.0446.

ii) From Methyl (2-Carbomethoxy-3-hydroxyphenyl)acetate (**3**): Dimethyl sulfate (2.8 ml) was added dropwise to a stirred suspension of **3** (1.5 g, 7.7 mmol) in 30% NaOH (5.3 ml) over 10 min at room temperature. Additional 30% NaOH (5.3 ml) was added, then the mixture was heated at 100 °C for 3 h, and concentrated under reduced pressure. The residue was washed with ether (3 ml), dissolved in water, and acidified with 10% HCl to give 3-methoxyhomophthalic acid (mp 154—158 °C), which was treated with acetyl chloride without purification to give **1a**. This was identical with an authentic sample obtained above. The overall yield of **1a** from **3** is 48%.

8-Methoxy-6-methylhomophthalic Anhydride (1b)——The homophthalate (**6** or **7**, 2 mmol) was treated with KOH in water and methanol under the conditions described in the general procedure to give 80—85% yields of 3-methoxy-5-methylhomophthalic acid. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1720, 1680. ^{1}H-NMR (10% solution in acetone-d_6) δ: 2.32 (3H, s, $ArCH_3$), 3.70 (2H, s, $ArCH_2$), 3.97 (3H, s, OMe), 6.75 (1H, br s, ArH), 6.82 (1H, br s, ArH). The acid (336 mg) was treated with acetyl chloride in acetone to give a 91% yield (281 mg) of **1b**, mp 170—172 °C. Recrystallization from acetone–*n*-hexane gave pure **1b**, mp 171—173 °C. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1795, 1755, 1615, 1585. ^{1}H-NMR (10% solution in

$CDCl_3$) δ: 2.42 (3H, s, $ArCH_3$), 3.97 (5H, s, $ArOCH_3$ and $ArCH_2$), 6.64 (1H, d, J=2 Hz, ArH), 6.74 (1H, br s, ArH). *Anal.* Calcd for $C_{11}H_{10}O_4$: C, 64.07; H, 4.89. Found: C, 64.14; H, 4.79.

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