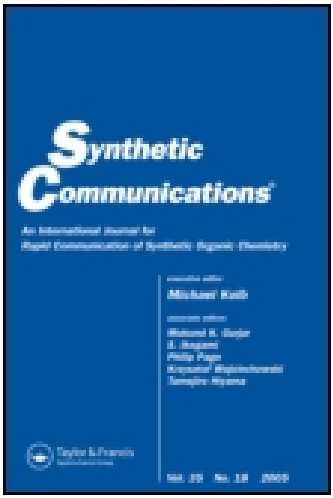

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Convenient Synthesis of 7,8-Dimethoxytetralin-2-one

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Convenient Synthesis of 7,8-Dimethoxytetralin-2-one

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Abstract: 7,8-Dimethoxytetralin-2-one (**1**), an important intermediate for the synthesis of compounds possessing biological activity, was synthesized by simple reaction steps from commercially available starting materials.

Keywords: Cinnamic esters, deethoxycarbonylation, Dieckmann condensation, 2-tetralones

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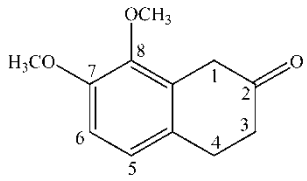
INTRODUCTION

2-Tetralones containing hydroxy and/or methoxy substituent(s) in the aromatic ring are known as important sources of synthetic precursors of a wide range of compounds, including steroids, heterocycles, and pharmaceuticals.[1] The synthesis of 7,8-dimethoxytetralin-2-one (**1**) has been described in the literature,[2] but most of the methods use difficult starting materials and inconvenient reagents.[3] In many cases poor or uncertain yields were reported.[4]



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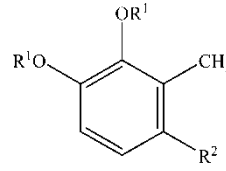


2a; $R^1=R^2=H$
2b; $R^1=CH_3$, $R^2=H$
2c; R^1-CH_3, R^2-CHO

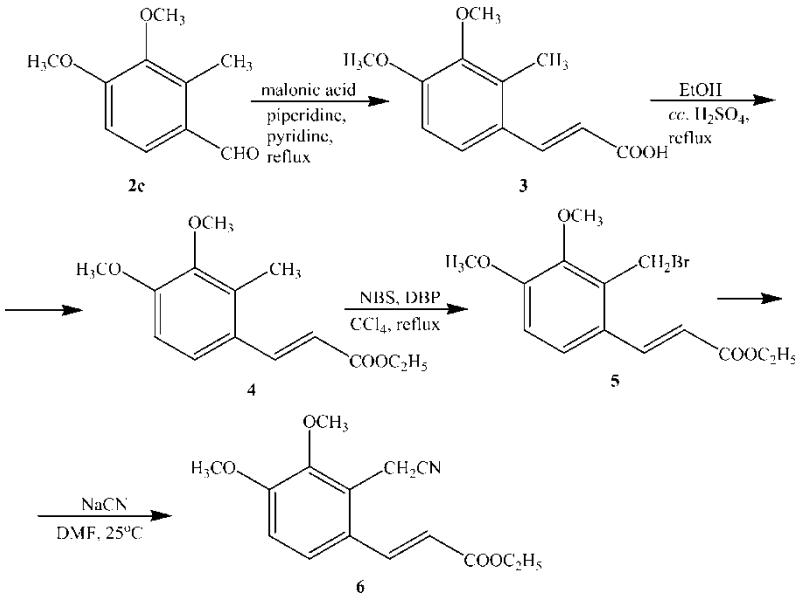
In this article we report an efficient methodology to synthesize the title compound **1** using simple reaction steps and commercially available starting materials and reagents.

RESULTS AND DISCUSSION

The synthesis starts from 3-methylcatechol (**2a**), which could be *O*-methylated to 2,3-dimethoxytoluene (**2b**) with dimethyl sulfate.[5,6] Introduction of the formyl group into the *ortho* position in relation to the methyl substituent (**2c**) could be achieved by using α,α-dichloromethyl methyl ether as formylating reagent in the presence of tin(IV) chloride.[6] Both intermediates **2b** and **2c** are described in the literature and their preparation was successful in high yields: 82.5% and 98%, respectively.

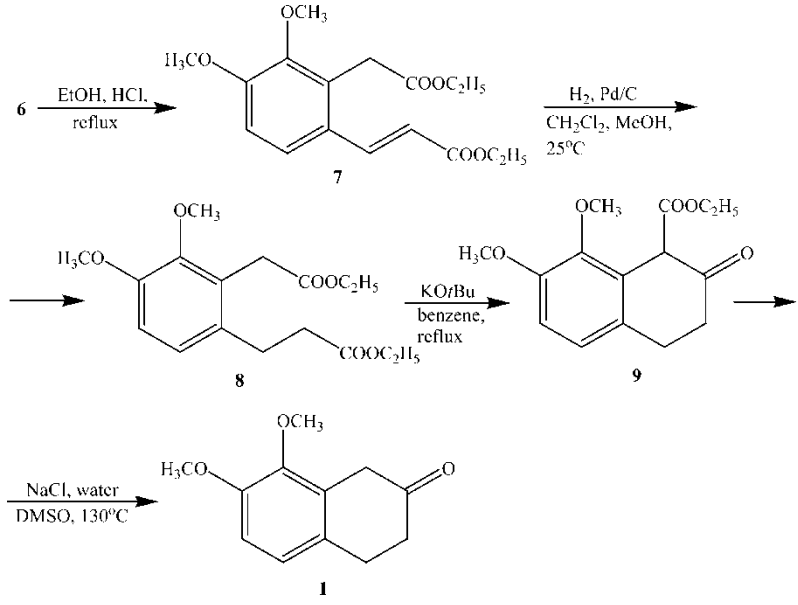
In the next reaction step aldehyde **2c** was treated with malonic acid in refluxing pyridine in the presence of piperidine. In the course of the Knoevenagel condensation cinnamic acid derivative **3** was obtained in 92.7% yield (Scheme 1) that was subsequently esterified with ethanol to yield ethyl 3,4-dimethoxy-2-methylcinnamate (**4**) (93%). To build an ester function into the methyl group, compound **4** was subjected to *N*-bromosuccinimide under the usual reaction conditions with catalytic amount of benzoyl peroxide in carbon tetrachloride at reflux temperature. The corresponding bromomethyl derivative **5** was obtained in 65% yield.

The conversion of the bromo atom of the cinnamic ester **5** into the cyano group was carried out by sodium cyanide in DMF solution at room temperature, resulting in nitrile **6** in 90% yield. The Pinner reaction



2c 3 4 5 6

Scheme 1.



7 8 9 1

Scheme 2.

of nitrile (**6**) was performed in refluxing ethanol in the presence of dry hydrochloric acid, resulting in diester **7** in 92.8% yield (Scheme 2). The compound **7** was subjected to catalytic hydrogenation in dichloromethane–methanol 1 : 1 mixture at room temperature and at atmospheric pressure using palladium on charcoal catalyst to give the saturated derivative **8** in 94% yield. The saturated diester **8** proved to be the appropriate intermediate for the next Dieckmann condensation reaction to form the 2-tetralone ring via the corresponding β-ketoester **9**. The diester **8** was treated with potassium *tert*-butoxide in benzene under reflux and the expected β-ketoester **9** was obtained in 55% yield. Deethoxycarbonylation for removal of ethoxycarbonyl group from position 1 proved to be more effective than hydrolysis and decarboxylation. Thus, the preparation of the title compound **1** was successful using sodium chloride and water in DMF solution at 150°C (73%).

We may conclude that the synthesis of 7,8-dimethoxytetralin-2-one (**1**) is favored starting from the commercially available 3-methylcatechol (**2a**) and using the simple reaction steps presented. Investigation of the scope and limitations of the procedure as well as its utilization in the synthesis of biologically active compounds are in progress.

EXPERIMENTAL

General

Melting points are uncorrected. IR spectra were recorded on Zeiss IR 75 and 80 instruments. ^{1}H and ^{13}C NMR spectra were recorded on a Varian INOVA 300 spectrometer. High-resolution MS measurements were carried out on a Finnigan MAT 95XP mass spectrometer; perfluorotributylamine was used as a reference compound (EI, 70 eV). TLC was carried out using Kieselgel $60F_{254}$ (Merck) glass plates. 3-Methylcatechol (**2a**) was purchased from Aldrich. 2,3-Dimethoxytoluene (**2b**) and 3,4-dimethoxy-2-methylbenzaldehyde (**2c**) were obtained according to procedures described in the literature.[5,6]

3-(3,4-Dimethoxy-2-methylphenyl)-2-propenoic Acid (3)

To a solution of 10.16 g (56.4 mmol) of 3,4-dimethoxy-2-methylbenzaldehyde (**2c**) in pyridine (28 ml), 14.7 g (0.141 mol) of malonic acid and 1.1 ml of piperidine were added and the reaction mixture was heated with stirring in an oil bath at 100–110°C for 1.5 h and then at 130–140°C for 30 min. After cooling the mixture was poured into 300 ml of a 2M hydrochloric acid solution, and the precipitate was filtered off and dried at rt. Carboxylic acid (**3**) (11.6 g, 92.7%) was obtained, which was suitable for the next esterification reaction without any purification. Mp 189–191°C (ethanol). TLC (ethyl

acetate–hexane 10 : 1) R_f 0.7. IR (KBr) 3430, 2950, 1700, 1640, 1595, 1495, 1270, 1085, 800 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) 2.30 (s, 3H, CH_3), 3.71 (s, 3H, OCH_3), 3.82 (s, 3H, OCH_3), 6.2 (d, $J = 15.9$ Hz, 1H, =CH–), 6.73 (d, $J = 8.7$ Hz, 1H, ArH), 7.35 (d, $J = 8.7$ Hz, 1H, ArH), 7.94 (d, $J = 15.9$ Hz, 1H, –CH=) ppm. Anal. calcd. for $C_{12}H_{14}O_4$: C, 64.85; H, 6.35: Found C, 64.64; H, 6.31.

Ethyl 3-(3,4-Dimethoxy-2-methylphenyl)-2-propenoate (4)

Carboxylic acid (**3**) (10.37 g, 46.7 mmol) was dissolved in ethanol (155 ml) and 1.5 ml of *cc.* H_2SO_4 was added. The reaction mixture was refluxed for 2 h, solvent was evaporated to dryness under reduced pressure, and the residue was shared between saturated aqueous sodium hydrogencarbonate solution (70 ml) and dichloromethane (100 ml). The aqueous layer was extracted with dichloromethane (100 ml), the combined organic layers were washed with water (3 × 100 ml), and after drying ($MgSO_4$) was evaporated to dryness under vacuum. Product (**4**) (10.86 g, 93%) was obtained as a crystallizable oil, used in the next bromination step without any purification. TLC (benzene–MeOH 14 : 3) R_f 0.8. IR (KBr) 2990, 2940, 1720, 1640, 1600, 1500, 1260, 1180, 1080, 870, 820 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) 1.33 (t, $J = 7.0$ Hz, 3H, $OCH_2C\underline{H}_3$), 2.36 (s, 3H, CH_3), 3.78 (s, 3H, OCH_3), 3.87 (s, 3H, OCH_3), 4.25 (q, $J = 7.0$ Hz, 2H, $OC\underline{H}_2CH_3$), 6.25 (d, $J = 15.6$ Hz, 1H, =CH–), 6.77 (d, $J = 8.7$ Hz, 1H, ArH), 7.33 (d, $J = 8.7$ Hz, 1H, ArH), 7.92 (d, $J = 15.6$ Hz, 1H, –CH=) ppm. HRMS: calcd. 250.1200, found 250.1201 (delta: 0.7 ppm).

Ethyl 3-(2-Bromomethyl-3,4-dimethoxyphenyl)-2-propenoate (5)

To a solution of ester (**4**) (7.27 g, 29.1 mmol) in carbon tetrachloride (180 ml), 200 mg of benzoyl peroxide and 7.87 g (44.2 mmol) of *N*-bromosuccinimide was added. After refluxing the reaction mixture for 8 h with stirring, precipitate was filtered off and the filtrate was evaporated to dryness under reduced pressure. The residue was recrystallized from ethanol, and from the ethanolic mother liquor another part of product was isolated by column chromatography on silica gel (dichloromethane) and by preparative layer chromatography (silica, dichloromethane). Yield: 6.22 g (65%). Mp 93–94°C. TLC (dichloromethane) R_f 0.65. IR (KBr) 2990, 2936, 1720, 1640, 1600, 1500, 1280, 1190, 1090, 1040, 820 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) 1.35 (t, $J = 7.2$ Hz, 3H, $OCH_2C\underline{H}_3$), 3.90 (s, 3H, OCH_3), 3.96 (s, 3H, OCH_3), 4.27 (q, $J = 7.2$ Hz, 2H, $OC\underline{H}_2CH_3$), 4.71 (s, 2H, CH_2Br), 6.35 (d, $J = 15.6$ Hz, 1H, =CH–), 6.90 (d, $J = 8.7$ Hz, 1H, ArH), 7.35 (d, $J = 8.7$ Hz, 1H, ArH), 7.95 (d, $J = 15.6$ Hz, 1H, –CH=) ppm. Anal. calcd. for $C_{14}H_{17}BrO_4$: Br, 24.27. Found: Br, 24.20.

Ethyl 3-(2-Cyanomethyl-3,4-dimethoxyphenyl)-2-propenoate (6)

Bromomethyl derivative (**5**) (5.7 g, 17.3 mmol) was dissolved in DMF (52 ml), 5.13 g (0.105 mol) of sodium cyanide was added, and it was stirred at room temperature for 1.5 h. The reaction mixture was poured into water (100 ml), extracted with dichloromethane (3 × 100 ml), and the combined organic layers were washed with water (3 × 150 ml). After drying ($MgSO_4$) the solvent was evaporated to dryness in vacuum and the product (**6**) was isolated by column chromatography on silica (hexane–ethyl acetate 3 : 1) to give 4.3 g (90%) of nitrile **6**. Mp 82–83°C. TLC (hexane–ethyl acetate 3 : 1) R_f 0.25. IR (KBr) 2990, 2950, 2245, 1705, 1640, 1600, 1505, 1290, 1270, 1240, 1180, 1080, 1040, 810 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) 1.34 (t, $J = 7.2$ Hz, 3H, $OCH_2\underline{CH_3}$), 3.84 (s, 2H, CH_2CN), 3.91 (s, 3H, OCH_3), 3.95 (s, 3H, OCH_3), 4.27 (q, $J = 7.2$ Hz, 2H, $OC\underline{H_2}CH_3$), 6.30 (d, $J = 15.6$ Hz, 1H, =CH–), 6.93 (d, $J = 8.7$ Hz, 1H, ArH), 7.35 (d, $J = 8.7$ Hz, 1H, ArH), 7.81 (d, $J = 15.6$ Hz, 1H, –CH=) ppm. Anal. calcd. for $C_{15}H_{17}NO_4$: C, 65.44; H, 6.22; N, 5.09. Found: C, 65.39; H, 6.24; N, 5.11.

Ethyl 3-(3,4-Dimethoxy-2-ethoxycarbonylmethylphenyl)-2-propenoate (7)

Dry hydrochloric acid was introduced for 1 h into a suspension of 2.4 g (8.8 mmol) of nitrile (**6**) in ethanol (68 ml). Then, the reaction mixture was refluxed for 1 h and evaporated to dryness under reduced pressure, and the residue was shared between saturated aqueous sodium hydrogencarbonate solution (150 ml) and dichloromethane (200 ml). The water phase was extracted with dichloromethane (100 ml) and the combined organic layers were washed with water (100 ml), dried ($MgSO_4$), and evaporated to dryness in vacuum. The residue was purified by column chromatography on silica gel (hexane–ethyl acetate 3 : 1) to give 2.63 g (92.8%) of diester (**7**) as a crystallizable oil. Mp 39–40°C. TLC (hexane–ethyl acetate 2 : 1) R_f 0.6. IR (KBr) 1735, 1710, 1630, 1585, 1280, 1260, 1180, 1080, 1030, 800 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) 1.26 (t, $J = 7.2$ Hz, 3H, $OCH_2\underline{CH_3}$), 1.32 (t, $J = 7.2$ Hz, 3H, $OCH_2\underline{CH_3}$), 3.83 (s, 3H, OCH_3), 3.86 (s, 2H, CH_2CO), 3.89 (s, 3H, OCH_3), 4.16 (q, $J = 7.2$ Hz, 2H, $OC\underline{H_2}CH_3$), 4.25 (q, $J = 7.2$ Hz, 2H, $OC\underline{H_2}CH_3$), 6.25 (d, $J = 15.6$ Hz, 1H, =CH–), 6.87 (d, $J = 8.7$ Hz, 1H, ArH), 7.36 (d, $J = 8.7$ Hz, 1H, ArH), 7.83 (d, $J = 15.6$ Hz, 1H, –CH=) ppm. Anal. calcd. for $C_{17}H_{22}O_6$: C, 63.34; H, 6.88. Found: C, 63.42, H, 7.08.

Ethyl 3-(3,4-Dimethoxy-2-ethoxycarbonylmethylphenyl)-propionate (8)

Unsaturated ester (**7**) (2.04 g, 6.33 mmol) was hydrogenated in a mixture of dichloromethane (14 ml) and ethanol (14 ml) in the presence of 10%

palladium on charcoal (0.6 g) at room temperature under atmospheric pressure. The catalyst was filtered off, the filtrate was evaporated to dryness, and the residue was isolated by column chromatography on silica gel (hexane–ethyl acetate 4 : 1) to give 1.92 g (94%) of saturated diester (**8**). Mp 38–39°C. TLC (hexane–ethyl acetate 2 : 1) R_f 0.65. IR (KBr) 1735, 1710, 1630, 1585, 1280, 1260, 1180, 1080, 1030, 800 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) 1.24 (t, $J = 7.2$ Hz, 3H, $OCH_2C\underline{H}_3$), 1.26 (t, $J = 7.2$ Hz, 3H, $OCH_2C\underline{H}_3$), 2.54 (m, 2H) and 2.86 (m, 2H) [$-CH_2CH_2CO-$], 3.74 (s, 2H, $-CH_2CO-$), 3.81 (s, 3H, OCH_3), 3.84 (s, 3H, OCH_3), 4.15 (q, $J = 7.2$ Hz, 2H, $OC\underline{H}_2CH_3$), 4.16 (q, $J = 7.2$ Hz, 2H, $OC\underline{H}_2CH_3$), 6.80 (d, $J = 8.7$ Hz, 1H, ArH), 7.36 (d, $J = 8.7$ Hz, 1H, ArH) ppm. Anal. calcd. for $C_{17}H_{24}O_6$: C, 62.95; H, 7.46. Found: C 62.81; H, 7.23.

7,8-Dimethoxy-1-ethoxycarbonyl-1,2,3,4-tetrahydro-naphthalene-2-one (9)

To a solution of 200 mg (0.62 mmol) of diester (**8**) in benzene (9 ml), 180 mg (1.6 mmol) of potassium *tert*-butoxide was added. The reaction mixture was refluxed for 30 min and after cooling ca. 0.3 ml of water was added and evaporated to dryness under reduced pressure. The residue was treated with 1 N hydrochloric acid (9 ml), extracted with dichloromethane (3 × 5 ml) and after drying the solvent was evaporated under vacuum. The product was isolated from the residue by preparative layer chromatography on silica gel (hexane–ethyl acetate 2 : 1) as an oil, yield 95 mg (55%). TLC (hexane–ethyl acetate 2 : 1) R_f 0.45. IR (KBr) 3480, 1750, 1730, 1500, 1280, 1240, 810 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) (mainly enolic form) 1.39 (t, $J = 7.0$ Hz, 3H, $OCH_2C\underline{H}_3$), 2.67 (t, $J = 9.0$ Hz, 2H) and 2.97 (t, $J = 9.0$ Hz, 2H) [$-CH_2CH_2-$], 3.83 (s, 3H, OCH_3), 3.87 (s, 3H, OCH_3), 4.37 (q, $J = 7.0$ Hz, 2H, $OC\underline{H}_2CH_3$), 7.02 (s, 2H, ArH) ppm. HRMS: calcd 278.1149, found 278.1143 (delta: −2.0 ppm).

7,8-Dimethoxytetralin-2-one (1)

β-Oxoester (**9**) (380 mg, 1.36 mmol) was dissolved in DMSO (1.5 ml); 106 mg (1.8 mmol) of sodium chloride and 0.1 ml (5.6 mmol) of water were added. The reaction mixture was heated at 150°C for 2.5 h. The mixture after cooling was diluted with 15 ml of dichloromethane, the organic layer was washed with water (3 × 10 ml), and after drying ($MgSO_4$) was evaporated to dryness under reduced pressure. The product (**1**) was isolated by preparative layer chromatography on silica gel (dichloromethane-methanol 100 : 1; R_f 0.6) to give 204 mg (73%) of tetralone (**1**). Mp 73–74°C (hexane) (lit.,[2] 75–76°C). IR (KBr) 2950, 1705, 1495, 1280,1080, 860, 795 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) 2.54 (t, 2H, H_2-4), 3.00 (t, 2H, H_2-3), 3.60 (s, 2H,

H_2 − 1), 3.81 (s, 3H, OCH_3), 3.86 (s, 3H, OCH_3), 6.79 (d, $J = 8.4$ Hz, 1H, ArH), 6.93 (d, $J = 8.4$ Hz, 1H, ArH) ppm.

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