A Synthesis of Alibendol, 2-Hydroxy-*N*-(2-hydroxyethyl)-3-methoxy-5-(2-propenyl)benzamide *via m*-CPBA Oxidation of *o*-Vanillin†

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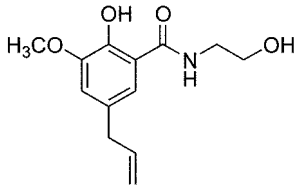
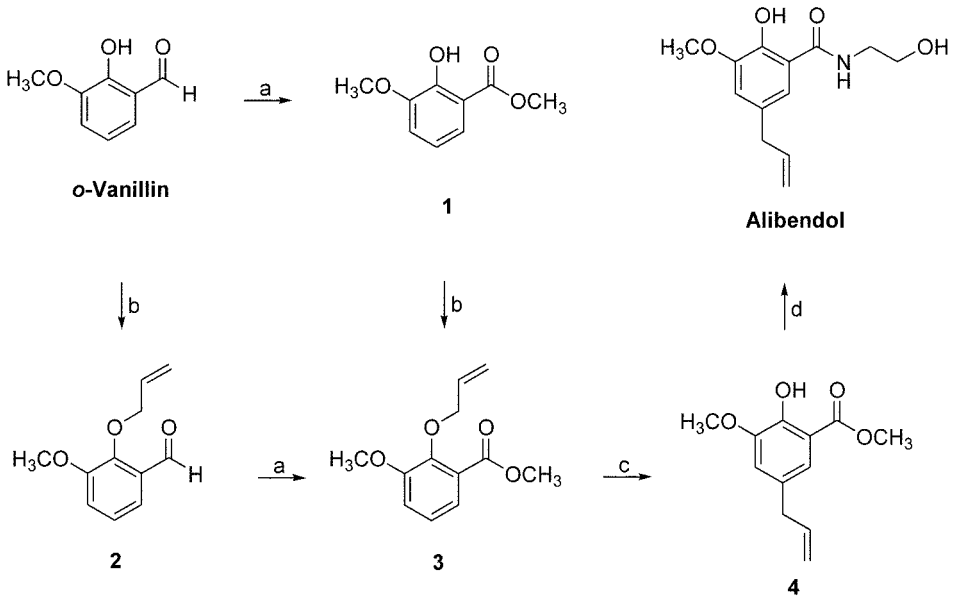
A large number of methods for the conversion of aldehydes to esters have been reported in the literature over the last thirty years.[2] Baeyer-Villiger oxidation of ketones and aldehydes using peracid is frequently chosen due to its easy manipulation and high productivity.[3] However, the reaction of acyclic acetal derived from a ketone (a ketal) with peracid is known to be sluggish and to provide the orthocarbonate as the result of dual Baeyer-Villiger oxidation.[4] Several methods of direct oxidation of acetal to esters with oxidizing agents such as, peracetic acid,[5] chromium trioxide,[6] ozone,[7] *tert*-butylhydroperoxide,[8] PDC/*t*-BuOOH,[9] NBS,[10] peroxymonosulfuric acid,[11] dimethyldioxirane,[12] or hydrogen peroxide[13] have been reported. Recently, we reported a facile procedure for the conversion of aldehydes to the corresponding esters *via* acetal formation from aldehydes and subsequent oxidation by *m*-CPBA with $BF_3{\cdot}OEt_2$.[14] Based on our recent reports, we wish to utilize this methodology for the synthesis of biologically important compounds.

Alibendol, 2-hydroxy-*N*-(2-hydroxyethyl)-3-methoxy-5-(2-propenyl)benzamide is known as antispasmodic, chleretic, and cholekinetic active pharmaceutical ingredient (API) which is useful in treatment of dyspepsia due to biliary insufficiency, alimentary intolerance, urticaria, pruritus, migraine, and constipation of hepatic origin.[15]



Alibendol

To date, only a few patents for the synthesis of Alibendol have been reported.[15] Precedent procedures are started from *o*-vanillic acid, 3-methoxysalicylic acid. *o*-Vanillic acid can be prepared from *o*-vanillin by several methods such as using Pd/C with B_2O_3, Pt/C with $Bi_3(SO_4)_3$, $NaClO_2$ with



Scheme 1. **a**. (i) trimethyl orthoformate, Amberlyst® 15 (wet), $CHCl_3$, reflux, 3 h; (ii) *m*-CPBA, $BF_3{\cdot}OEt_2$, rt, 1 h, 83% (*o*-vanillin → **1**), 93% (**2** → **3**). **b**. allyl bromide, K_2CO_3, acetone, reflux, 5 h, 99%. **c**. neat, 200-210 °C, 2 h, 90%. **d**. ethanolamine, $CHCl_3$, 120 °C, 1 h, 82%.

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H_2O_2, and Ag_2O.[16] Except the method using $NaClO_2$ with H_2O_2, other methods are carried out in harsh reaction condition. Since we accomplished a simple one-pot procedure for the conversion of aldehydes to methyl esters and *o*-vanillin is a much cheaper chemical than *o*-vanillic acid, a method that could directly oxidize *o*-vanillin to methyl 2-hydroxy-3-methoxybenzoate would be of great value for the synthesis of Alibendol in economic point of view. Thus, we contemplated a facile synthesis of Alibendol from *o*-vanillin.

We speculated that the preparation of methyl 3-methyoxy-2-(2-propenyloxy)benzoate (**3**) would be undoubtedly achieved since the one-pot oxidation of salicyl aldehyde to methyl salicylate has been successfully carried out by *m*-CPBA with $BF_3{\cdot}OEt_2$.[14c] The preparation of methyl 3-methyoxy-2-(2-propenyloxy)benzoate (**3**) has been tried by two routes (Scheme 1). *o*-Vanillin was treated with trimethyl orthoformate and Amberlyst® 15 (wet) to provide *in situ* dimethyl acetal intermediate, and the subsequent oxidation by *m*-CPBA with $BF_3{\cdot}OEt_2$ in chloroform afforded methyl 2-hydroxy-3-methoxybenzoate (**1**) in 83% yield. The hydroxyl group of methyl 2-hydroxy-3-methoxybenzoate (**1**) was quantitatively allylated with allyl bromide and K_2CO_3 to give methyl 3-methyoxy-2-(2-propenyloxy)benzoate (**3**). On the other hand, *o*-vanillin was allylated in same manner as above mentioned method. Then, *O*-allyl *o*-vanillin (**2**) was converted to methyl 3-methyoxy-2-(2-propenyloxy)benzoate (**3**) in 93% yield by the same *in situ* procedure. The Claisen rearrangement of allyl vinyl ether has been well established.[17] Various reaction solvents such as DMF, TFA, *p*-xylene, and toluene have been used for the Claisen rearrangement of methyl 3-methyoxy-2-(2-propenyloxy)-benzoate (**3**). However, most reactions were sluggish and not completed even longer reaction time. Thus, we carried out the Claisen rearrangement in neat reaction condition as in the case of the precedent procedure.[17c] The last step of synthesis of Alibendol was straight forward formation of the amide by the reaction of methyl ester **4** with ethanolamine at 120 °C.

In summary, we accomplished a facile synthesis of Alibendol from *o*-vanillin *via in situ* formation of dimethyl acetal intermediate and the subsequent oxidation by *m*-CPBA with $BF_3{\cdot}OEt_2$, and the *para* Claisen rearrangement in five steps and 68% (through *o*-vanillin to **2**) or 61% (through *o*-vanillin to **1**) overall yield.

Experimental Section

General. All reactions were carried out under an inert atmosphere of argon. Chloroform was freshly distilled from phosphorus pentoxide prior to use. Liquid reagents and solvents used were reagent grade and purified prior to use, if necessary, by methods reported in the literature.[18] Analytical thin layer chromatography was performed on pre-coated Merck silica gel 60 F254 TLC plate. Flash column chromatography was performed using Merck silica gel 60 (230-400 mesh) under positive pressure of air according to the procedure of Still.[19] Uncorrected melting points were determined with a Gallenkamp melting point apparatus. ^1H NMR and ^{13}C NMR spectral data were obtained on a Varian Gemini 300 (300 MHz) spectrometer. Infrared spectra were recorded using a BioRad FT-IR spectrophotometer with internal calibration. Mass spectra were recorded on a Varian WS 1200 mass spectrometer.

General procedure for the preparation of methyl ester 1 and 3. To a solution of aldehyde (10 mmol) in dried $CHCl_3$ (30 mL) were added Amberlyst® 15 (wet) ion exchange resin (0.5 g) and triethyl orthoformate (4.4 mL, 40 mmol) under the argon atmosphere at ambient temperature. The mixture was stirred at reflux condition. After being stirred for 3 h, a small amount of $BF_3{\cdot}OEt_2$ (0.38 mL, 3 mmol) and *m*-CPBA (72%, 2.40 g, 10 mmol) were added. The resulting reaction mixture was stirred for 1 h at ambient temperature. The reaction mixture was diluted with ethyl acetate (15 mL) and quenched with 0.5 N NaOH solution (30 mL). The resulting solution was treated with 0.5 N HCl solution (30 mL). The aqueous layer was extracted with ethyl acetate (15 mL × 3) and the combined organic layer was dried over anhydrous sodium sulfate. The desired methyl esters were purified by SiO_2 gel flash column chromatography.

Methyl 2-hydroxy-3-methoxybenzoate (1).[17c] 1.51 g, 83%, a white solid (R_f = 0.45, EtOAc/*n*-Hexane = 1 : 4, v/v). ^1H NMR (300 MHz, $CDCl_3$) δ 11.01 (s, 1H), 7.42 (dd, J = 8.2, 1.4 Hz, 1H), 7.04 (d, J = 8.0 Hz, 1H), 6.82 (t, J = 8.1 Hz, 1H), 3.95 (s, 3H), 3.90 (s, 3H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 171.0, 152.3, 148.7, 121.8, 118.9, 116.8, 112.9, 56.5, 52.5; MS (EI) *m/z* 182 (M^+), 151, 150, 149, 122, 121, 120, 107, 92.

Methyl 3-methyoxy-2-(2-propenyloxy)benzoate (3).[17c] 2.06 g, 93%, a yellow liquid (R_f = 0.65, EtOAc/*n*-Hexane = 1 : 4, v/v). ^1H NMR (300 MHz, $CDCl_3$) δ 7.32 (dd, J = 7.2, 2.4 Hz, 1H), 7.08 (t, J = 8.4 Hz, 1H), 7.04 (dd, J = 8.1, 2.1 Hz, 1H), 6.13 (ddt, J = 17.1, 10.5, 5.9 Hz, 1H), 5.40 (dq, J = 17.3, 1.7 Hz, 1H), 5.23 (dq, J = 10.2, 1.5 Hz, 1H), 4.57 (dt, J = 6.0, 1.3 Hz, 2H), 3.89 (s, 3H), 3.86 (s, 3H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 166.8, 153.5, 147.7, 134.1, 126.3, 123.8, 122.1, 117.5, 115.6, 74.7, 56.0, 52.1; MS (EI) *m/z* 222 (M^+), 191, 181, 149, 135, 122, 107, 97, 83, 69, 55.

General procedure for the allylation of *o*-vanillin and compound 1. To a solution of *o*-vanillin or methyl 2-hydroxy-3-methoxybenzoate (**1**) (1.0 equiv.) in acetone (~1.5 M) were added allyl bromide (2.4 equiv.) and potassium carbonate (2.2 equiv.). The mixture was stirred at 80 °C (external) for 5 h, then cooled to 20 °C. The reaction solution was diluted with diethyl ether (30-40 mL), filtered, and then concentrated to dryness. The desired allylated products were purified by SiO_2 gel flash column chromatography.

3-Methyoxy-2-(2-propenyloxy)benzaldehyde (2). 1.90 g, 99%, a pale yellow liquid (R_f = 0.70, EtOAc/*n*-Hexane = 1 : 4, v/v). IR (neat) 1731, 1476, 1314, 1265, 1062, 989, 753 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 10.44 (s, 1H), 7.40 (dd, J = 7.1, 2.3 Hz, 1H), 7.15 (dd, J = 8.1, 2.1 Hz, 1H), 7.11 (t, J = 7.5 Hz, 1H), 6.14-6.01 (m, 1H), 5.35 (dq, J = 17.1, 1.4 Hz, 1H), 5.26 (dd, J = 10.5, 1.2 Hz, 1H), 4.66 (dd, J = 6.2, 1.1

Hz, 2H), 3.89 (s, 3H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 190.4, 153.0, 151.2, 133.2, 130.1, 124.2, 119.0, 118.9, 118.0, 75.2, 56.0; MS (EI) *m/z* 192 (M^-), 191, 178, 165, 149, 111, 97, 84, 71, 57.

Methyl 3-methyoxy-2-(2-propenyloxy)benzoate (3). 1.14 g, 99%, a yellow liquid (R_f = 0.65, EtOAc/*n*-Hexane = 1 : 4, v/v).

Methyl 2-hydroxy-3-methoxy-5-(2-propenyl)benzoate (4).[17c] *O*-Allyl ether **3** (10.8 g, 48.6 mmol) was kept at 200-210 °C (external) and stirred for 2 h until no starting material was observed by TLC. The crude product was diluted with chloroform (100 mL), treated with char coal (2 g) for decolorization, and filtered. The product was purified by SiO_2 gel flash column chromatography (R_f = 0.50, chloroform), affording the *para* Claisen rearrangement product **4** (9.72g, 90%) as a white solid, mp 45-46 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 10.86 (s, 1H), 7.25 (d, J = 2.1 Hz, 1H), 6.87 (d, J = 2.1 Hz, 1H), 5.94 (ddt, J = 17.7, 9.3, 6.6 Hz, 1H), 5.09 (dq, J = 10.8, 1.6 Hz, 1H), 5.08 (dq, J = 17.6, 1.6 Hz, 1H), 3.94 (s, 3H), 3.89 (s, 3H), 3.32 (d, J = 6.6 Hz, 2H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 170.8, 150.4, 148.4, 137.1, 130.2, 120.2, 117.3, 116.1, 112.2, 56.1, 52.3, 39.6; MS (EI) *m/z* 222 (M^-), 190, 162, 149, 71, 57, 55.

Alibendol, 2-hydroxy-*N*-(2-hydroxyethyl)-3-methoxy-5-(2-propenyl)benzamide.[15a] Ethanolamine (14.4 mL, 238.6 mmol) was added to a concentrated solution of methyl 2-hydroxy-3-methoxy-5-(2-propenyl)benzoate (**4**) (13.2 g, 59.4 mmol) in chloroform (3 mL) at ambient temperature. The reaction mixture was heated at 120 °C for 1 h. The resulting mixture was extracted with ethyl acetate (40 mL × 3). The organic phases were thoroughly washed with dilute hydrochloric acid. The organic layer was dried over anhydrous sodium sulfate and the organic solvent was evaporated. The product was purified by SiO_2 gel flash column chromatography (R_f = 0.47, methanol/chloroform = 1 : 10, v/v), affording Alibendol, 2-hydroxy-*N*-(2-hydroxyethyl)-3-methoxy-5-(2-propenyl)benzamide (12.2 g, 82%) as a white solid. Recrystallization of the product was carried out with hot methanol and water, mp 95-96 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 11.30 (s, 1H), 7.17 (br s, 1H), 6.94 (d, J = 1.5 Hz, 1H), 6.81 (d, J = 1.5 Hz, 1H), 5.99-5.86 (m, 1H), 5.08 (dq, J = 10.4, 1.5 Hz, 1H), 5.07 (dq, J = 17.6, 1.5 Hz, 1H), 3.89 (s, 3H), 3.86 (t, J = 5.0 Hz, 2H), 3.63 (q, J = 5.1 Hz, 2H), 3.31 (d, J = 6.6 Hz, 2H), 2.58 (br s, 1H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 170.4, 149.1, 149.0, 137.8, 130.5, 118.0, 116.5, 115.8, 115.0, 62.3, 56.0, 42.7, 39.9.

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