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Total Syntheses of Microminutin and Other Coumarins Through the Key Intermediate Isomurralonginol.

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Abstract: *A straightforward route to isomurralonginol (1) from umbelliferone (4 steps, 59% yield) is described. Isomurralonginol is used as the key intermediate in the preparation of isomurralonginol acetate (2) (1 step, 94% yield), murralongin (3) (1 step, 75% yield) and microminutin (2 steps and 38% yield). The synthesis of microminutin involves the selenolactonization of α, β–substituted vinyl acetic acid (12) (50% yield) with spontaneous elimination of the selenyl moiety, without oxidation, to the unsaturated lactone.*

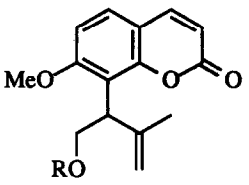
INTRODUCTION

Leaves from species belonging to the family Rutaceae have afforded a wide variety of unique coumarins. Careful examination of recent reports revealed an emerging subclass of coumarins which consist of a 7-methoxy coumarin nucleus alkylated at the 8 position with an isopropenyl moiety containing a 1' substituent. This examination led us to believe that isomurralonginol (**1**) could serve as a precursor for a variety of these recently isolated isopropenyl coumarins, specifically isomurralonginol acetate (**2**)[1] and murralongin (**3**),[2] as well as the cytotoxic γ-butenolide microminutin (**4**), isolated from *Micromelum minutin*.[3] In considering the problems associated with the synthesis of isomurralonginol, two principal facets can be observed: 1) the efficient construction of the side chain, and 2) control of the substitution about the benzene ring. The synthesis of microminutin presents the additional facet in the construction of the butenolide moiety. In a previous synthesis by Wakharkar, *et al.*,[4] the butenolide was introduced in two 2-carbon units following the establishment of regiochemistry through an allylic Claisen rearrangement. Our approach was to attempt to introduce all five carbons as a single unit and to construct the butenolide through a lactonization. Following this concept retrosynthetically, one can see the relationship of microminutin to isomurralonginol (**1**), the acetate of which has been isolated from the leaves of a related plant, *Murraya exotica*.[1]

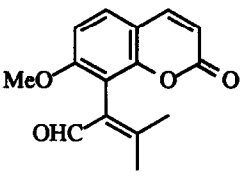
We report herein the preparation of racemic isomurralonginol (**1**) and its subsequent conversion into racemic isomurralonginol acetate (**2**), murralongin (**3**) and microminutin (**4**).

RESULTS AND DISCUSSION

The alkyl appendage in isomurralonginol acetate appeared to be readily available from a Claisen rearrangement of an allyl ether constructed using (*E*)-1-bromo-2-methyl-4-acetoxy-2-butene, a substance easily prepared from isoprene.[5] The aryl component was envisaged as a derivative somewhere along the path from resorcinol to umbelliferone. Although there is precedent for selectivity for the 8 position of the coumarin



1. R = H
2. R = Ac



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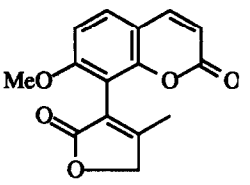

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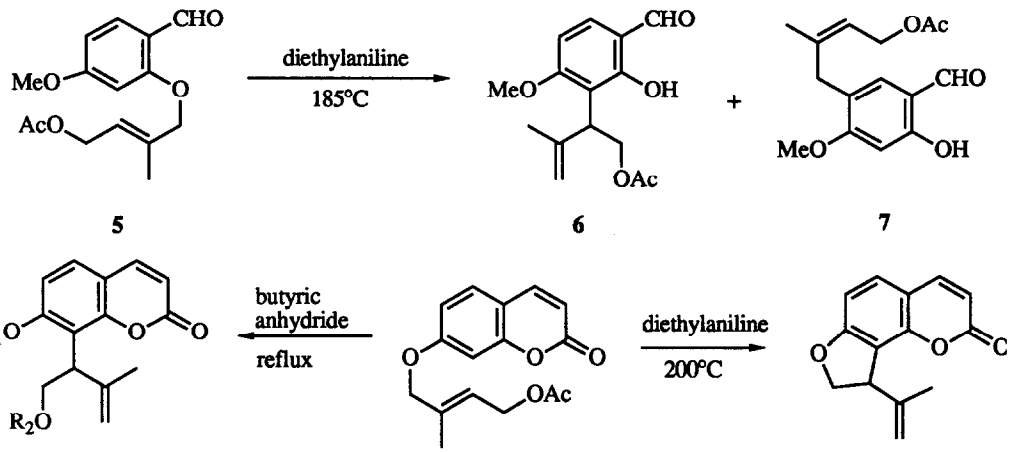
Scheme I

nucleus, these studies utilize rather simple allyl appendages and there are contradictory reports for the degree of selectivity and solvent effects.[6] Although Claisen rearrangement of 7-allyl coumaric acid derivatives have demonstrated selectivity for the eventual 6 position of the coumarin nucleus,[7] there have been no reports, to our knowledge, of Claisen rearrangements of the corresponding 2-allylated resorcinol derivatives. Since we had previously demonstrated the conversion of *ortho*-hydroxy benzaldehyde to coumarin,[8] it was our belief that a Claisen rearrangement of a 2-allylated resorcylaldehyde would be selective for what would ultimately be the 8 position of the coumarin due to the blockage of the competing ortho position by the aldehyde. A preliminary study of compounds **5** and **8** was undertaken to ascertain which precursor would afford the optimal yield of the desired substitution pattern.



5 **6** **7**

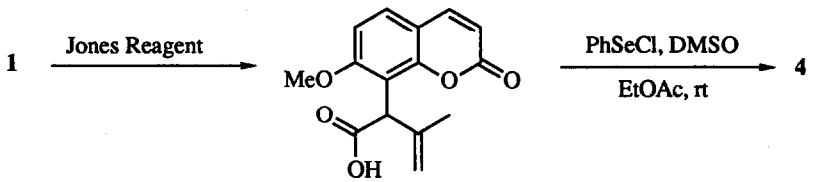
10 $R_1 = CO(CH_2)_2CH_3$; R_2 = Ac
11 $R_1 = R_2 = H$

8 **9**

Scheme II

The 2-allylated derivative of resorcinol (**5**) proved unsatisfactory for our purposes since conditions necessary for rearrangement were also sufficient to cause further Cope rearrangement, thus affording mixtures of substituted resorcinols **6** and **7**. Closure of the coumarin ring before rearrangement proved to be the superior strategy. Allylation of the 7-oxo position of umbelliferone provided the ether (**8**) which undergoes *ortho*-Claisen rearrangement selectively to the 8 position in at least a 7:1 ratio over the 6-position. Initial pyrolysis conditions (200°C, diethylaniline) resulted in the loss of acetic acid and cyclization to form the ether **9**. By conducting the pyrolysis in butyric anhydride,[9] the uncyclized material could be trapped as its butyrate (**10**).Hydrolysis of the diester (**10**) and methylation of the resulting diol (**11**) provided racemic isomurralonginol (**1**). In practice, the sequence of steps for conversion of the allyl ether (**8**) to isomurralonginol (**1**) can be carried out in a single reaction flask in 59% yield. The conversion of isomurralonginol to its acetate with acetyl chloride and triethylamine afforded material identical to the authentic spectra.[1]

Conditions for the oxidation of isomurralonginol are noteworthy. Less vigorous oxidations (Swern or Collins conditions) resulted in the isolation of murralongin[2] (**3**) while the low temperature Jones oxidation provided the ene-acid (**12**). Apparently, the crucial feature for the success of the Jones oxidation is the minimization of the lifetime of the aldehyde, which isomerizes much more readily.



12

Scheme III

Lactonization of the acid (**12**) to microminutin was not well precedented. Work by Liotta suggested that phenylselenolactonization of β,γ-unsaturated carboxylic acids possessing β substituents led to decarboxylation rather than cyclization.[10] Rather than resort to a multistep conversion, a study of conditions for lactonization was conducted. It was found that treatment of **12** with 3 equivalents of PhSeCl in DMSO and ethyl acetate resulted in the lactonization with the concomitant elimination of the phenylselenyl moiety to provide the introduction of the α,β-unsaturation in the butenolide without oxidation, a rare but precedented occurrence.[11]

EXPERIMENTAL

Melting points were obtained on a Thomas Hoover capillary melting point apparatus and are uncorrected. Analytical thin-layer chromatography (TLC) was performed on precoated silica gel 60 F_{254} plates from EM Reagents and visualization was accomplished with 254-nm UV light or ethanolic 12-molybdophosphoric acid solution. Flash chromatography was performed in the manner of Still[12] with EM Reagents silica gel 60 (230-440 mesh). IR spectra were recorded on a BIORAD FTS-7 spectrophotometer. ^{13}C NMR spectra were recorded on Bruker WH 90 spectrometer and ^{1}H NMR spectra were recorded on Bruker 90 MHz and 250 MHz spectrometers. High resolution mass spectra were obtained on a Bruker CMS-476 Fourier transform ion

cyclotron resonance mass spectrometer. Elemental analyses were performed by Galbraith Laboratories, Inc. Where elemental analyses were not performed, ^{1}H NMR spectra indicated purity in excess of 95%. Anhydrous reactions were carried out under nitrogen atmosphere in oven dried glassware using solvents purified according to Riddick, *et al.*[13] All other reagents were purchased from commercial sources and purified by standard procedures.

Preparation of allyl ether 5. A solution of 4-methoxy-2-hydroxybenzaldehyde (3.1817 g, 20.9 mmol) in 20 ml DMF was slowly added to a stirred suspension of NaH (598.6 mg, 24.9 mmol) in DMF (25 ml) under N_2 atmosphere until no evidence of gas evolution remained (within 3 hrs). A solution of (*E*)-1-bromo-2-methyl-4-acetoxy-2-butene[5] (4.9000 g, 23.7 mmol) in 10 ml DMF was added dropwise and the reaction mixture was stirred at room temperature for 40 hrs. The reaction was then quenched with H_2O, diluted with EtOAc (60 ml) and extracted with H_2O (4 X 50 ml). Flash chromatography provided 2.45 g of allyl ether **5** (42% yield) as a white solid. mp= 71.5-73.5°C. IR ν_{max} (CH_2Cl_2) 3059, 2945, 2862, 1734, 1676, 1601 cm^{-1}. ^{1}H NMR ($CDCl_3$) δ 10.37 (s, 1H), 7.83 (d, J=8.4 Hz, 1H), 6.55 (dd, J=8.1, 2.2 Hz, 1H), 6.42 (d, J=2.2 Hz, 1H), 5.78 (t, J=6.2 Hz, 1H) 4.61 (m, 4H), 3.87 (s, 3H), 2.08 (s, 3H), 1.84 (s, br, 3H) ppm. ^{13}C ($CDCl_3$) δ 188.1, 170.9, 166.1, 162.7, 135.8, 130.5, 122.0, 119.3, 106.3, 99.0, 72.9, 60.5, 55.6, 20.8, 14.0 ppm. Anal. Calcd for $C_{15}H_{18}O_5$: C, 64.74%; H, 6.52%. Found: C, 64.80%; H, 6.70%.

Claisen Rearrangement of allyl ether 5. The allyl ether **5** (1.7664 g, 6.35 mmol) was dissolved in 30 ml diethylaniline and heated to 185°C under N_2 for 35 hrs. The crude reaction mixture was concentrated *in vacuo* and the residue was purified by flash chromatography to obtain **6** (777.1 mg, 2.79 mmol)(48% yield) and **7** (418.8 mg, 1.51 mmol)(26.3% yield) (Yields corrected for recovered **5** (165.7 mg, 9.55%)).

Ortho product 6. IR ν_{max} (CH_2Cl_2) 3083, 2968, 2843, 1736, 1650, 1620, 1250 cm^{-1}. ^{1}H NMR ($CDCl_3$) δ 11.68 (s, 1H), 9.72 (s, 1H), 7.45 (d, J=8.8 Hz, 1H), 6.58 (d, J=8.4 Hz, 1H), 4.54 (m, 5H), 3.89 (s, 3H), 1.98 (s, 3H), 1.70 (s, 3H) ppm. ^{13}C NMR ($CDCl_3$) δ 194.7, 171.0, 164.8, 161.8, 143.3, 134.7, 115.6, 115.4, 110.9, 103.7, 64.4, 55.4, 40.1, 21.9, 20.8 ppm.

Para product 7. IR.(CH_2Cl_2) ν_{max} 3054, 2983, 2842, 1725, 1640, 1240 cm^{-1}. ^{1}H NMR ($CDCl_3$) δ 9.69 (s, 1H), 7.21 (s, 1H), 6.42 (s, 1H), 5.32 (t, J=6.6 Hz, 1H), 4.65 (m, 3H), 3.86 (s, 3H), 3.27 (s, br, 2H), 2.05 (s, 3H), 1.69 (s, br, 3H) ppm. ^{13}C NMR ($CDCl_3$) δ 194.4, 171.0, 164.9, 163.5, 140.1, 134.6, 120.4, 120.2, 114.5, 98.8, 61.2, 55.8, 38.0, 20.9, 16.5 ppm

Preparation of allyl ether 8. Umbelliferone (111.0 g, 0.686 mol), acetone (820 ml), K_2CO_3 (94.6 g, 0.686 mol) and (*E*)-1-bromo-2-methyl-4-acetoxy-2-butene (141.9 g, 0.685 mol) were combined and the mixture was heated at reflux overnight with mechanical stirring. The reaction mixture was cooled, filtered and concentrated *in vacuo*. The crude reaction mixture was slowly poured into rapidly stirred hexanes which resulted in a precipitate that was isolated by vacuum filtration. The filtrate was concentrated *in vacuo* and the procedure was repeated. The solid precipitates were combined and recrystallized from ethanol providing 62.7 g of allyl ether **8** (32% yield). mp 108-110°C. IR (CH_2Cl_2) ν_{max} 3054, 1733, 1614, 1268, 1131, 840 cm^{-1}. ^{1}H NMR ($CDCl_3$) δ 7.66 (d, J=9.2 Hz, 1H), 7.40 (d, J=7.7 Hz, 1H), 6.86 (d, J=7.7 Hz, 1H), 6.81 (s, 1H), 6.26 (d, J=9.2 Hz, 1H), 5.76 (t, J=7.0 Hz, 1H), 4.72 (s, 1H), 4.64 (s, 1H), 4.50 (s, 2H), 2.08 (s, 3H), 1.83 (s, 3H) ppm. ^{13}C NMR ($CDCl_3$) δ 170.8, 161.7, 161.0, 155.8, 143.3, 135.6, 128.7, 122.2, 113.2, 113.0, 112.7, 101.7, 72.9, 60.4, 20.7, 13.8 ppm. Anal. Calcd for $C_{16}H_{16}O_5$: C,66.66%; H, 5.59%. Found: C, 66.69%; H, 5.62%.

Preparation of dihydrofuran 9. A solution of the allyl ether **8** (12.0 g, 43.5 mmol) in 200 ml of diethyl aniline was heated at reflux for 6 hrs, concentrated *in vacuo* and the residue was purified by flash chromatography which provided a yellow solid that was recrystallized from pentane/diethyl ether (3:1) to provide dihydrofuran **9** as white needles (2.85 g, 12.5 mmol)(29% yield). mp 93-94°C. IR ν_{max} (CH_2Cl_2) 3020, 2950, 1725, 1605, 1110, 1055 cm^{-1}. ^{1}H NMR ($CDCl_3$) δ 7.88 (d, J=9.5 Hz, 1H), 7.50 (d, J=8.4 Hz, 1H), 6.80 (d, J=8.1 Hz, 1H), 6.17 (d, J=9.5 Hz, 1H), 4.62 (m, 5H), 1.71 (s, br, 3H) ppm. ^{13}C NMR ($CDCl_3$) δ 164.5, 160.8, 152.0, 143.9, 142.8, 129.5, 115.5, 113.3, 113.2, 112.4, 107.2, 77.9, 47.3, 19.5 ppm. Anal. Calcd for $C_{14}H_{12}O_3$: C, 73.67%; H, 5.30%. Found: C, 73.82%; H, 5.40%.

Preparation of butyrate 10. The allyl ether **8** (470 mg, 1.63 mmol) was dissolved in 15 ml of butyric anhydride and heated to 200°C for 12 hrs. The reaction mixture was concentrated *in vacuo* and the residue was purified by flash chromatography to provide butyrate **10** (334.2 mg, 0.93 mmol)(57% yield). IR ν_{max} (CH_2Cl_2) 2970, 2877, 1736, 1602, 1240 cm^{-1}. ^{1}H NMR ($CDCl_3$) δ 7.72 (d, J=9.9 Hz, 1H), 7.44 (d, J=8.4

Hz, 1H), 7.00 (d, J=8.4 Hz, 1H), 6.41 (d, J=9.5 Hz, 1H), 4.73 (m, 5H), 2.55 (t, J=7.0 Hz, 2H), 1.93 (s, 3H), 1.81 (m, 2H), 1.65 (s, 3H), 0.96 (t, J=7.0 Hz, 3H) ppm. ^{13}C NMR ($CDCl_3$) δ 171.3, 170.8, 159.8, 153.5, 152.3, 143.4, 142.0, 126.9, 120.7, 119.8, 116.6, 115.7, 111.7, 64.0, 40.8, 35.9, 22.3, 20.7, 18.0, 13.5 ppm. Anal. Calcd for $C_{20}H_{22}O_6$: C, 67.03%; H, 6.19%. Found: C, 66.88%; H, 6.11%.

Preparation of diol 11. A solution of diester **10** (81.1 mg, 0.23 mmol) and 500 mg K_2CO_3 in 5 ml MeOH was stirred at room temperature overnight. The MeOH was removed *in vacuo* and the residue was purified by flash chromatography to provide diol **11** (50.4 mg, 0.21 mmol)(91% yield). IR ν_{max} (nujol) 3329, 2924, 2854, 1695, 1457 cm^{-1}. ^1H NMR (d_6 acetone) δ 7.87 (d, J=9.5 Hz, 1H), 7.43 (d, J=8.8 Hz, 1H), 6.86 (d, J=8.4 Hz, 1H), 6.17 (d, J=9.5 Hz, 1H), 4.90 (m, 1H),4.78 (m, 1H), 4.26 (m, 3H), 1.82 (s, br, 3H) ppm. ^{13}C NMR (d_6 acetone) δ 160.5, 160.4, 154.1, 144.7, 143.0, 128.0, 115.6, 114.1, 112.0, 111.4, 62.4, 43.7, 21.6 ppm.

Preparation of isomurralonginol (1). A solution of diol **11** (46.2 mg, 0.188 mmol), 100 mg K_2CO_3 and 100 µl MeI in 10 ml acetone was heated at reflux overnight. The crude reaction mixture was diluted with 20 ml EtOAc, water washed and the organics were dried over $MgSO_4$. Flash chromatography provided **2** (37.6 mg, 0.144 mmol)(77% yield). IR ν_{max} (CH_2Cl_2) 3600, 2970, 2915, 1604, 1283, cm^{-1}. (250 MHz) ^1H NMR ($CDCl_3$) δ 7.62 (d, J=9.7 Hz, 1H,), 7.39 (d, J=8.6 Hz, 1H), 6.88 (d, J=8.6 Hz, 1H), 6.24 (d, J=9.7 Hz, 1H,), 5.03 (S, 1H), 4.96 (s, 1H) 4.87 (s, 1H), 3.89 (S, 3H), 1.88 (S, 3H) ppm. ^{13}C NMR ($CDCl_3$) δ 161.1, 160.8, 153.7, 143.9, 143.1, 127.4, 116.7, 113.1, 112.9, 114.4, 107.9, 62.6, 56.0, 44.5, 22.0 ppm. HRMS (EI) exact mass calcd for $C_{15}H_{14}O_3$ (m-CH_2O), 230.0936; observed 230.0938 (parent-CH_2O; parent peak not observed).

One pot procedure for isomurralonginol (1). The allyl ether **8** (24.0 g, 83.3 mmol) was dissolved in butyric anhydride and heated at reflux overnight. The solvent was removed *in vacuo* and replaced with pentane and heated at reflux for 10 min then decanted. The pot residue was dissolved in MeOH (250 ml) and K_2CO_3 (20 g, 147 mmol) were added and the reaction stirred overnight. The MeOH was removed *in vacuo* and replaced with acetone (200 ml) and MeI (34 g, 241 mmol); the reaction was heated at reflux overnight. Removal of the solvent and flash chromatography provided isomurralonginol (**1**)(12.74 g, 59% yield).

Preparation of ene-acid 12. A solution of isomurralonginol (**1**) (1.924 g, 7.39 mmol) in 150 ml acetone was cooled to 0°C and Jones reagent (267 g CrO_3 and 230 ml H_2SO_4 diluted to 1.0 l with H_2O) was added dropwise over 10 hrs. The reaction mixture was decanted from the precipitate and concentrated *in vacuo*. The residue was diluted with Et_2O (100 ml) and water washed (2 X 40 ml), the organic layer was then extracted with 1 N NaOH (2 X 30 ml). The basic aqueous layer was acidified with 1 N HCl and extracted with Et_2O (2 X 75 ml) and the combined organic layers were dried over $MgSO_4$. The solvent was removed *in vacuo* to provide acid **12** (1.3194 g, 4.81 mmol)(65% yield). IR ν_{max} (CH_2Cl_2) 3082, 2845, 1734, 1715, 1607, 1120 cm^{-1}. 250 MHz ^1H NMR ($CDCl_3$) δ 7.62 (d, J=9.7 Hz, 1H), 7.39 (d, J=8.6 Hz, 1H), 6.88 (d, J=8.6 Hz, 1H), 6.24 (d, J=9.7 Hz, 1H), 5.03 (s, 1H), 4.96 (s, 1H), 4.87 (s, 1H), 3.89 (s, 3H), 1.88 (s, 3H) ppm. ^{13}C NMR (d_6DMSO) δ 172.0, 159.8, 159.7, 152.3, 144.7, 141.4, 128.4, 114.6, 114.4, 112.8, 112.3, 108.6, 56.3, 46.9, 21.3 ppm. HRMS (EI) exact mass calcd for $C_{15}H_{14}O_5$, 274.0836; found 274.0836.

Preparation of microminutin (4). A soln of the ene-acid (**12**) (44.4 mg, 0.16 mmol) and DMSO (60 µl, 0.84 mmol) in 2.0 ml EtOAc was added dropwise to a stirred solution of PhSeCl (41.0 mg, 0.21 mmol) in 2.0 ml EtOAc. The solution slowly turned from red to yellow within 15 min. PhSeCl (53.8 mg, 0.28 mmol) was added as a solid after 36 hrs. Following continuous stirring for an additional week, the solvent was removed *in vacuo* and flash chromatography provided microminutin (22.8 mg, 0.08 mmol) (50.0% yield). The spectral data were identical with literature reports.[3]

Preparation of isomurralonginol acetate (2). Isomurralonginol (**1**) (42.4 mg, 0.16 mmol) and Et_3N (34 ml, 0.24 mmol) was dissolved in THF (5.0 ml). To this solution was added acetyl chloride (17.0 ml, 0.24 mmol). The reaction was stirred at room temperature for 14 hrs. The crude mixture was diluted with Et_2O (5 ml) and extracted with H_2O (2 ml), saturated aq $NaHCO_3$ (2 ml), H_2O (2 ml). The combined organic layers were dried over $MgSO_4$ and purified by flash chromatography which provided isomurralonginol acetate (**2**) (45.6 mg, 94 % yield). The spectral data were identical with literature reports.[1]

Preparation of murralongin (3). Murralongin was prepared by oxidation according to Swern[14] using isomurralonginol (2) (110.0 mg, 0.423 mmol), 60 µl oxalyl chloride, 100 µl DMSO and 400 µl triethylamine. The usual workup and flash chromatography provided 81.8 mg (75 % yield) of a white solid whose spectral data was identical with literature reports.[8]

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