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Chalcones as Synthetic Intermediates. A Facile Route to (±)-Magnosalicin, an Antiallergy Neolignan

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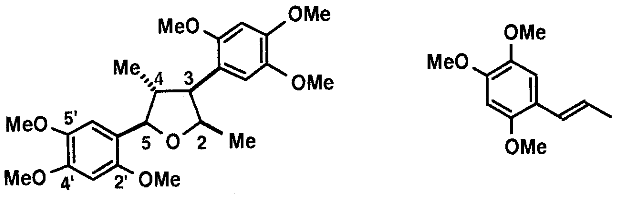
A facile synthetic route was developed to (±)-magnosalicin (1), a new type of neolignan with antiallergy activity isolated from *Magnolia salicifolia*, starting from a chalcone, 1,3-bis(2′,4′,5′-trimethoxyphenyl)prop-2-en-1-one (3).

Keywords synthesis; magnosalicin; chalcone; neolignan; *Magnolia salicifolia*; organoselenium-induced cyclization

Magnosalicin (1) is a new racemic neolignan isolated in 1984 by Sankawa and his co-workers from *Magnolia salicifolia* MAXIM. as an antiallergy compound.[1] Buds of *M. salicifolia* (Japanese name: tamushiba, kamushiba or satoshiba) are used as an oriental medicinal drug, “Shin-i” (Japanese name), to treat nasal allergy and nasal empyema. A biogenetic-type synthesis from asarone (2) has been reported by Mori *et al.*[2]

On the other hand, chalcones, a class of naturally occurring and widely distributed pigments, are versatile starting materials especially for the synthesis of another class of naturally occurring pigments called flavones.[3] Applications to the synthesis of various other types of naturally occurring products have been reported.[4] We also reported the synthesis of some norlignans[5] employing a chalcone as the starting material. In this paper, we present a facile synthesis of (±)-**1** starting from a readily available chalcone, 1,3-bis(2′,4′,5′-trimethoxyphenyl)prop-2-en-1-one (**3**).



magnosalicin(1) asarone (2)

Chart 1

The chalcone (**3**) was obtained by the Claisen–Schmidt reaction of 2,4,5-trimethoxybenzaldehyde with 2,4,5-trimethoxyacetophenone in 82% yield. Conjugate addition of vinylmagnesium bromide to **3** in the presence of cuprous iodide gave 1,3-bis(2′,4′,5′-trimethoxyphenyl)pent-4-en-1-one (**4**) in 78% yield. The conventional alkylation of **4** with methyl iodide gave a 1:1 diastereomeric mixture of 1,3-bis(2′,4′,5′-trimethoxyphenyl)-2-methylpent-4-en-1-one (**5a** and **5b**),[6,7] in 90% yield; the diastereomers were separated from each other by silica gel column chromatography. Lithium aluminum hydride (LAH) reduction of **5a** proceeded diastereoselectively to afford a vinyl alcohol with desired stereochemistry, (1*R**,2*R**,3*S**)-1,3-bis(2′,4′,5′-trimethoxyphenyl)-2-methylpent-4-en-1-ol (**6**),[7] in 93% yield. This remarkably high diastereoselectivity is in accordance

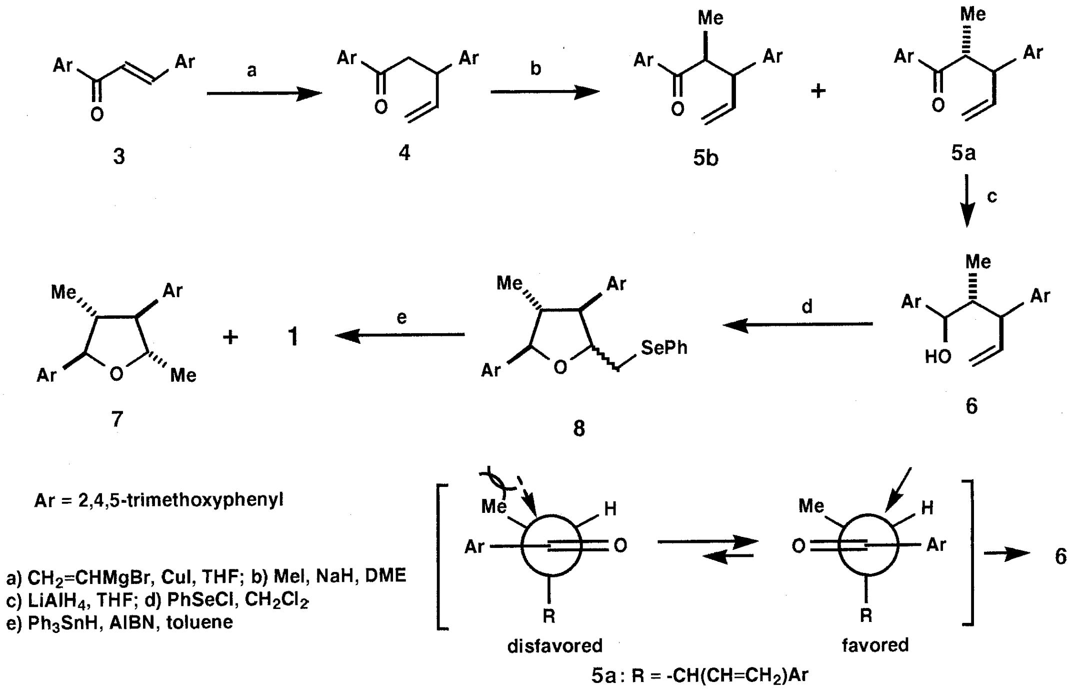


Chart 2

with the prediction of the Felkin–Anh model as shown in Chart 2.

Treatment of **6** with phenylselenenyl chloride at −78 °C followed by radical cleavage with triphenyltin hydride in the presence of a catalytic amount of α,α'-azobisisobutyronitrile (AIBN) gave, although as a minor product, (±)-**1** in 25% yield. The stereoselectivity observed in the reaction of **6** to **1** and its diastereomer, $(2S^*,3S^*,4R^*,5R^*)$-2,4-dimethyl-3,5-bis(2′,4′,5′-trimethoxyphenyl)tetrahydrofuran (**7**), was ascribed to the preferential formation of the sterically favorable *trans*-phenylselenoether (**8**). Attempts to convert **6** into **1** *via* oxymercuration or palladium-mediated cyclization were unsuccessful. The physical and spectral properties of **1** and the major product (**7**) were in good accordance with those reported.1,2)

Experimental

Melting points (mp) are uncorrected. Infrared (IR) spectra were taken with a Shimadzu IR-435 grating spectrometer. ^{1}H-(270 MHz, 500 MHz) and ^{13}C-(67.5, 125 MHz) nuclear magnetic resonance (NMR) spectra were recorded on either a JEOL JNM-GSX270 or a JEOL JNM-GSX500 spectrometer. Coupling constants (J) are given in hertz, and the following abbreviations are used: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, br = broad peak. All the NMR spectra were taken for CDCl$_3$ solutions with tetramethylsilane as an internal standard. Mass (MS) spectra and high-resolution mass (HRMS) spectra were taken on a JEOL JMS-HX100 mass spectrometer. Column chromatography was effected over Kieselgel 60 (Merck Art. 9385, particle size 0.04—0.063 mm) with a pump (FMI model RP). All the organic extracts were dried over anhydrous magnesium sulfate prior to evaporation.

1,3-Bis(2′,4′,5′-trimethoxyphenyl)prop-2-en-1-one (3) According to the procedure described by Wattanasin and Murphy,8) a mixture of 2,4,5-trimethoxyacetophenone9) (6.0 g, 28.6 mmol), 2,4,5-trimethoxybenzaldehyde (6.16 g, 31.4 mmol), sodium hydroxide (1.5 g) and absolute ethanol (100 ml) was stirred vigorously at room temperature overnight. The deposited yellow solid was collected by filtration, washed with cold ethanol and then with water, and dried to give 9.1 g (82%) of a pale yellow solid, mp 159—160 °C (pale yellow leaflets from ethanol). IR (CHCl$_3$): 2920, 1655, 1605, 1502, 1463, 1400, 1270, 1160, 1030 cm^{-1}. ^{1}H-NMR δ: 3.88 (6H, s), 3.90 (3H, s), 3.91 (3H, s), 3.94 (3H, s), 3.96 (3H, s), 6.52 (1H, s), 6.56 (1H, s), 7.12 (1H, s), 7.36 (1H, s), 7.52 (1H, d, J=16.0), 8.00 (1H, d, J=16.0). ^{13}C-NMR δ: 55.86 (q), 55.94 (q), 56.15 (q), 56.19 (q), 56.3 (q), 55.7 (q), 96.8 (d), 97.2 (d), 111.1 (d), 113.1 (d), 115.9 (s), 120.9 (s), 125.1 (d), 137.3 (d), 143.0 (s), 143.1 (s), 151.9 (s), 152.9 (s), 154.19 (s), 154.22 (s), 190.3 (s). MS *m/z* (%): 388 (M$^+$, 21), 357 (100), 327 (8), 195 (10). HRMS *m/z* Calcd for $C_{21}H_{24}O_7$ (M$^+$): 388.1522. Found: 388.1507.

1,3-Bis(2′,4′,5′-trimethoxyphenyl)pent-4-en-1-one (4) A mixture of vinylmagnesium bromide (16 ml, 1.0 mol solution in tetrahydrofuran (THF)), cuprous iodide (140 mg) and dry THF (10 ml) was added to a suspension of **3** (3.0 g, 7.7 mmol) in dry THF (30 ml) at 0 °C, and the mixture was stirred for 6 h. A solution of 10% aqueous NH$_4$Cl was added, and the mixture was extracted with benzene. The combined extracts were washed with a saturated sodium bicarbonate solution, and evaporated to give 3.4 g of a waxy solid, which, on trituration with ether, gave 2.5 g (78%) of a colorless solid, mp 79—81 °C (colorless needles from ethanol). IR (CHCl$_3$): 2952, 1650, 1604, 1508, 1464, 1401, 1271, 1141, 1030 cm^{-1}. ^{1}H-NMR δ:3.33 (1H, dd, J=16.2, 6.5), 3.46 (1H, dd, J=16.2, 7.0), 3.76 (3H, s), 3.81 (3H, s), 3.84 (3H, s), 3.86 (3H, s), 3.89 (3H, s), 3.95 (3H, s), 4.36 (1H, ddddd, J=7.0, 6.5, 6.5, 1.5, 1.5), 4.96 (1H, ddd, J=17.0, 1.5, 1.5), 5.01 (1H, ddd, J=10.5, 1.5, 1.5), 6.05 (1H, ddd, J=17.0, 10.5, 6.5), 6.49 (1H, s), 6.50 (1H, s), 6.72 (1H, s), 7.30 (1H, s). ^{13}C-NMR δ: 38.3 (t), 48.0 (d), 55.8 (q), 55.9 (q), 55.95 (q), 56.02 (q), 56.3 (q), 56.5 (q), 96.3 (d), 98.1 (d), 112.7 (d), 112.8 (d), 113.5 (t), 119.3 (s), 123.4 (s), 140.8 (d), 142.81 (s), 142.84 (s), 147.8 (s), 151.1 (s), 153.4 (s), 154.6 (s), 198.3 (s). MS *m/z* (%): 416 (M$^+$, 24), 207 (14), 195 (100), 176 (12), 161 (5). HRMS *m/z* Calcd for $C_{23}H_{28}O_7$ (M$^+$): 416.1835. Found: 416.1837.

1,3-Bis(2′,4′,5′-trimethoxyphenyl)-2-methylpent-4-en-1-one (5) A solution of **4** (2.0 g, 4.8 mmol) in dry dimethoxyethane (DME, 40 ml) was added dropwise to a suspension of sodium hydride (384 mg, 60% in liquid paraffin, washed twice with dry DME) in dry DME (15 ml) at 0°C, and the mixture was stirred at 70°C for 30 min. The solution was cooled, and a solution of methyl iodide (390 µl, 6.3 mmol) in dry DME (1 ml) was added. The mixture was stirred for 6 h, then methyl iodide (90 µl, 1.4 mmol) was added, and stirring was continued for another 6 h. The reaction was quenched with brine, and the resulting mixture was extracted with benzene. The combined extracts were washed with a saturated sodium bicarbonate solution, and then with brine. Removal of the solvent gave 2.04 g of a pale yellow oil, which, on column chromatography (hexane–ether 1 : 3, v/v), gave 937 mg (46%) of $(2R^*,3S^*)$-1,3-bis(2′,4′,5′-trimethoxyphenyl)-2-methylpent-4-en-1-one (**5a**) and 923 mg (45%) of $(2S^*,3S^*)$-1,3-bis (2′,4′,5′-trimethoxyphenyl)-2-methylpent-4-en-1-one (**5b**), each as a colorless solid.

5a: Colorless prisms (from hexane–ether), mp 91.5—93 °C. IR (CHCl$_3$): 2920, 2832, 1650, 1604, 1508, 1464, 1400, 1268, 1134, 1031 cm^{-1}. ^{1}H NMR δ: 0.95 (3H, d, J=6.0), 3.77 (3H, s), 3.84 (3H, s), 3.87 (3H, s), 3.88 (3H, s), 3.92 (3H, s), 3.96 (3H, s), 4.05–4.22 (2H, m), 4.91 (1H, d-like, J=10.5), 4.98 (1H, d-like, J=17.0), 6.01 (1H, ddd, J=17.0, 10.5, 7.2), 6.51 (1H, s), 6.52 (1H, s), 6.71 (1H, s), 7.29 (1H, s). ^{13}C-NMR δ: 15.8 (q), 46.5 (d), 48.1 (d), 55.9 (q), 56.1 (q), 56.4 (q), 56.6 (q), 96.6 (d), 98.1 (d), 113.1 (d), 113.5 (d), 114.6 (t), 120.4 (s), 122.1 (s), 140.0 (d), 142.9 (s), 142.99 (s), 147.9 (s), 151.7 (s), 153.2 (s), 154.4 (s), 204.4 (s). MS *m/z* (%): 430 (M$^+$, 17), 207 (100), 195 (37), 176 (27), 161 (5). HRMS *m/z* Calcd for $C_{24}H_{30}O_7$ (M$^+$): 430.1991. Found: 430.1992.

5b: Colorless prisms (from hexane–ether), mp 109—111 °C. IR (CHCl$_3$): 2951, 1664, 1605, 1508, 1464, 1400, 1269, 1145, 1031 cm^{-1}. ^{1}H-NMR δ: 1.25 (3H, d, J=6.5), 3.63 (3H, s), 3.66 (3H, s), 3.68 (3H, s), 3.74 (1H, dd-like, J=10.5, 9.0), 3.77 (3H, s), 3.88 (3H, s), 3.90 (3H, s), 4.14 (1H, dq, J=10.5, 6.5), 5.03 (1H, dd, J=10.0, 2.0), 5.08 (1H, ddd, J=17.0, 2.0, 1.0), 6.03 (1H, ddd, J=17.0, 10.0, 9.0), 6.30 (1H, s), 6.43 (1H, s), 6.61 (1H, s), 6.62 (1H, s). ^{13}C-NMR δ: 16.0 (q), 47.4 (d), 49.6 (d), 55.98 (q), 56.04 (q), 56.2 (q), 56.35 (q), 56.43 (q), 96.4 (d), 98.0 (d), 112.4 (d), 113.6 (d), 115.6 (t), 121.7 (s), 122.8 (s), 139.4 (d), 142.7 (s), 142.9 (s), 147.8 (s), 151.3 (s), 152.6 (s), 153.5 (s), 205.7 (s). MS *m/z* (%): 430 (M$^+$, 27), 207 (100), 195 (47), 176 (27), 161 (5). HRMS *m/z* Calcd for $C_{24}H_{30}O_7$ (M$^+$): 430.1992. Found: 430.1995.

$(1R^*,2R^*,3S^*)$-1,3-Bis(2′,4′,5′-trimethoxyphenyl)-2-methylpent-4-en-1-ol (6) A solution of **5a** (400 mg, 0.93 mmol) in dry THF (10 ml) was added dropwise to a suspension of LAH (72 mg, 1.89 mmol) in dry THF (5 ml) at 10 °C. After 6 h of stirring at room temperature, the reaction was quenched with ethyl acetate. A 10% aqueous sodium hydroxide solution was added, and the mixture was extracted with benzene. The combined extracts were washed with brine, and evaporated to give 399 mg of a pale yellow solid, which, on recrystallization from isopropyl ether, gave 374 mg (93%) of **6** as colorless needles, mp 102—104 °C. IR (CHCl$_3$): 3475, 2920, 1611, 1509, 1464, 1398, 1315, 1178, 1110, 1031 cm^{-1}. ^{1}H-NMR δ: 0.57 (3H, d, J=7.0), 2.31 (1H, dqd, J=9.5, 7.0, 5.0), 3.69 (3H, s), 3.84 (3H, s), 3.86 (6H, s), 3.87 (3H, s), 3.91 (3H, s), 4.01 (1H, d, J=4.5, exchangeable with D$_2$O), 4.27 (1H, ddt, J=7.0, 5.0, 1.5), 4.44 (1H, dd, J=9.0, 4.5), 5.13 (1H, dt, J=10.0, 1.5), 5.17 (1H, d-like, J=17.0), 6.22 (1H, ddd, J=17.0, 10.0, 7.0), 6.46 (1H, s), 6.59 (1H, s), 6.74 (1H, s), 6.92 (1H, s). ^{13}C-NMR δ: 12.0 (q), 41.9 (d), 45.7 (d), 56.0 (q), 56.3 (q), 56.4 (q), 56.6 (q), 57.1 (q), 70.9 (d), 97.4 (d), 98.0 (d), 111.2 (d), 114.3 (d), 114.9 (t), 120.7 (s), 122.8 (s), 141.5 (d), 143.1 (s), 143.3 (s), 147.9 (s), 148.5 (s), 151.0 (s), 151.2 (s). MS *m/z* (%): 432 (M$^+$, 22), 414 (18), 383 (6), 207 (44), 197 (100), 176 (16). HRMS *m/z* Calcd for $C_{24}H_{32}O_7$ (M$^+$): 432.2148. Found: 432.2178.

Magnosalicin (1) Phenylselenenyl chloride (145 mg, 0.76 mmol) was added to a solution of **6** (300 mg, 0.69 mmol) in dry CH$_2$Cl$_2$ (10 ml) at −78 °C, and stirring was continued at the same temperature for 2 h. The mixture was allowed to warm to room temperature, and evaporated to give 437 mg of a pale yellow oil, which was dissolved in dry toluene (5 ml). To this solution, triphenyltin hydride (485 mg, 1.38 mmol) and AIBN (12 mg, 7.3 mmol) were added. The mixture was heated under reflux for 4 h. Removal of the solvent gave 926 mg of a pale yellow oil, which, on column chromatography (hexane–ether 2 : 1, v/v), gave 75 mg (25%) of (±)-**1** as a colorless solid and 149 mg (50%) of its diastereomeric isomer, $(2S^*,3S^*,4R^*,5R^*)$-2,4-dimethyl-3,5-bis(2′,4′,5′-trimethoxyphenyl)tetrahydrofuran (**7**),2) as a pale yellow solid.

(±)-**1**: Colorless prisms, mp 133—134 °C (ethanol), lit.,1) mp 134.5—135 °C, lit.,2) mp 133—134 °C. IR (CHCl$_3$): 2950, 1612, 1510, 1464, 1399, 1179, 1035 cm^{-1}. ^{1}H-NMR δ: 0.90 (3H, d, J=6.5), 1.04 (3H, d, J=6.5), 2.31 (1H, ddq, J=10.5, 9.0, 6.5), 3.60 (1H, dd, J=10.5, 8.5), 3.79 (3H, s), 3.81 (3H, s), 3.82 (3H, s), 3.87 (3H, s), 3.90 (3H, s), 3.91 (3H, s), 4.60 (1H, dq, J=8.5, 6.5), 4.97 (1H, d, J=9.0), 6.535 (1H, s), 6.540 (1H, s), 6.69 (1H, s), 7.14 (1H, s). ^{13}C-NMR δ: 14.9 (q), 18.3 (q), 44.5 (d), 49.4 (d), 56.1 (q), 56.3 (q), 56.5 (q), 56.7 (q), 57.0 (q), 58.3 (q), 75.9 (d), 80.6 (d), 97.5 (d), 97.8 (d), 111.4 (d), 113.1 (d), 119.6 (s), 121.6 (s), 142.8 (s), 143.4 (s), 148.1 (s), 148.9 (s), 151.8 (s), 152.3 (s). MS *m*/*z* (%): 432 (M^+, 45), 388 (100), 220, (24), 205 (35), 181 (14), 165 (6), 151 (6). HRMS *m*/*z*: Calcd for $C_{24}H_{32}O_7$ (M^+): 432.2148. Found: 432.2175.

(±)-7: Pale yellow prisms, mp 72—73.5 °C (ether–isopropyl ether). IR ($CHCl_3$): 2950, 1611, 1510, 1463, 1400, 1375, 1317, 1178, 1121, 1032 cm^{-1}. ^1H-NMR δ: 0.90 (3H, d, $J=6.5$), 1.27 (3H, d, $J=6.0$), 2.43 (1H, ddq, $J=11.0$, 9.0, 6.5), 3.12 (1H, dd, $J=11.0$, 9.5), 3.81 (3H, s), 3.82 (3H, s), 3.84 (3H, s), 3.89 (3H, s), 3.896 (3H, s), 3.90 (3H, s), 4.34 (1H, dq, $J=9.5$, 6.0), 5.02 (1H, d, $J=9.0$), 6.54 (1H, s), 6.56 (1H, s), 6.76 (1H, s), 7.08 (1H, s). ^{13}C-NMR δ: 14.5 (q), 20.2 (q), 49.4 (d), 54.4 (d), 55.98 (q), 56.03 (q), 56.4 (q), 56.68 (q), 56.74 (q), 56.8 (q), 80.7 (d), 81.4 (d), 97.8 (d), 98.3 (d), 111.6 (d), 112.2 (d), 119.4 (s), 122.2 (s), 143.2 (s), 143.3 (s), 148.2 (s), 148.8 (s), 151.6 (s), 152.6 (s). MS *m*/*z* (%): 432 (M^+, 84), 388 (100), 220 (25), 205 (41), 181 (18), 165 (8), 151 (7). HRMS *m*/*z*: Calcd for $C_{24}H_{32}O_7$ (M^+): 432.2148. Found: 432.2168.

References and Notes

1) T. Tsuruga, Y. Ebizuka, J. Nakajima, Y.-T. Chun, H. Noguchi, Y. Iitaka, U. Sankawa and H. Seto, *Tetrahedron Lett.*, **25**, 4129 (1984).
2) K. Mori, M. Komatsu, M. Kido and K. Nakagawa, *Tetrahedron*, **42**, 523 (1986).
3) D. N. Dhar, "The Chemistry of Chalcones and Related Compounds," John Wiley and Sons, Inc., New York, 1981, pp. 96—106.
4) Z. Horii, C. Iwata, T. Tanaka and T. Momose, *Heterocycles*, **6**, 697 (1977); Z. Horii, A. Go, T. Momose and C. Iwata, *Chem. Pharm. Bull.*, **19**, 2212 (1971).
5) O. Muraoka, N. Fujiwara, G. Tanabe and T. Momose, *Tetrahedron Assym.*, **2**, 357 (1991).
6) An intensive study on the diastereoselectivity of the reaction in a similar system has been reported; I. Fleming and J. J. Lewis, *J. Chem. Soc., Chem. Commun.*, **1985**, 149.
7) The relative stereochemistry of **5a**, **6** and **5b** was deduced from that of **1** and its diastereomeric isomers.[2]
8) S. Wattanasin and W. S. Murphy, *Synthesis*, **1980**, 647.
9) K. Maruyama and T. Kozuka, *Bull. Chem. Soc. Jpn.*, **51**, 3586 (1978); L. Quijano, J. S. Calderon, F. Gémez G., I. E. Soria and T. Ríos, *Phytochemistry*, **19**, 2439 (1980).