A Convenient Total Synthesis of (+)-Decursinol from Resorcinol

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Received September 27, 2006

Key Words : Decursinol, Resorcinol, Jacobsen's epoxidation, Xanthyletin

(+)-Decursinol (**1**), a class of linear dihydrocoumarin natural product, was isolated from the root of *Angelica gigas* Nakai (Umbelliferae)[1] which is a traditional medicine for anemia in Korea.[2] It has attracted increasing attention due to its prominent biological activities. It exhibits cytotoxic activity related with protein kinase C (PKC) against several human cancer cell line,[3] anti-*helicobacter pylori* activity,[4] and strong antinociceptive activity.[5] The asymmetric total syntheses of **1** were reported by Shibasaki,[6] Han[7] and Kim.[8] The Shibasaki, the Han, and the Kim groups used esculetin (**2**), resorcinol (**3**), and umbelliferone (**4**) respectively as a starting material for (+)-decursinol synthesis. This work focused on the resorcinol as a starting material, since it was cheaper and simpler material, and reported herein is an efficient enantioselective total synthesis of (+)-decursinol in five steps from resorcinol.

The Han group synthesized (+)-decursinol from resorcinol in 7 steps as shown in Scheme 1. The serious problem in their synthesis is the final condensation step which produced equimolar amount of regioisomer (**11**) resulting in a low yield of desired product **1**. Asymmetric epoxidation of **6** to **7**, which requires an expensive Jacobsen's (salen)-Mn catalyst,[9] is the key step for introducing desired chirality on 7-hydroxyl group in product **1**. A condensation reaction of ethyl propiolate with the compounds **5**, **6**, and **7** respectively was done before epoxidation step for economical reason, but it failed. The condensation of phenol derivatives with ethyl propiolate is very sensitive to the functionality (conjugation) of substituents, for instance, **10** reacts but **6** doesn't. Umbelliferone (**4**) also does not react with ethyl propiolate or 3-methyl-2-butenoic acid in this condensation reaction.

This work proposes herein a convenient and practical total synthesis of (+)-decursinol from resorcinol in five steps. The commercially available resorcinol (**3**) is condensed with 2-methyl-3-buten-2-ol using zinc chloride under reflux to give **12** in 70% yield as shown in Scheme 2 (entry 2). Acid catalysts (entries 1, 9) or acid solvents (entries 6, 7) also gave a reasonable yield in this reaction. The subsequent reaction with ethyl propiolate only using zinc chloride produced the 1 : 1 mixture of corresponding lactones **13** and **14**, which is easily separated by column chromatography, in 38% yields respectively (Scheme 3). The formation of regio-

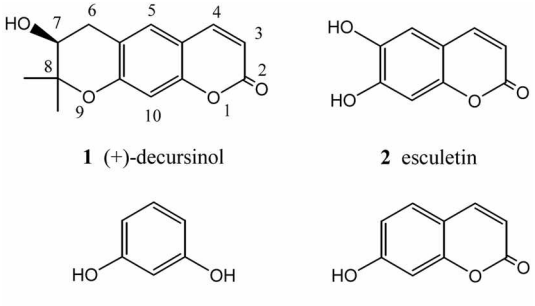
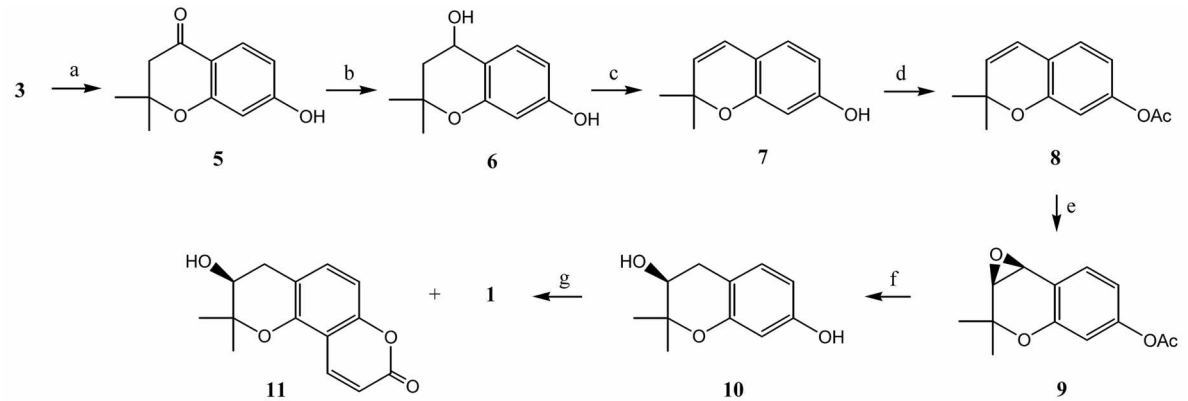
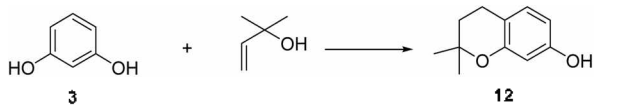


Figure 1. Structure of (+)-decursinol, esculetin, resorcinol and umbelliferone.



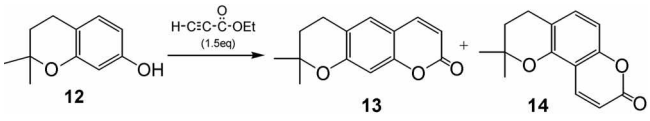
Scheme 1. Han's synthesis: (a) 3-methyl-2-butenoic acid, $MeSO_3H$, P_2O_5, 70 °C, 96%; (b) LAH, THF, reflux, 83%; (c) *p*-TsOH, THF, reflux, 88%; (d) acetic anhydride, pyridine, DMAP, CH_2Cl_2, rt, 98%; (e) Jacobsen's (*S,S*)-salen-Mn(III) catalyst, *n*-Bu_4NHSO_4, buffered solution/CH_3CN, 1,1,1-trifluoroacetone, Oxone®, $NaHCO_3$, 0 °C, 83%; (f) LAH, THF, 0 °C, 81%; (g) ethyl propiolate, zinc chloride, 110 °C, 40%.



entry	acid	eq (mol)	solvent	time(h)	Yield(%)*
1	p-TsOH	0.1	dichloromethane	6	65
2	$ZnCl_2$	1	dichloromethane	7	70
3	H_2SO_4	Cat.	dichloromethane	4	37
4	$AlCl_3$	1	dichloromethane	7	-
5	BF_3Et_2O/TMSOMS	0.1/0.5	dichloromethane	7	20
6	HCO_2H	solvent		4	64
7	AcOH	solvent		4	63
8	$MeSO_3H$	solvent		7	-
9	$MeSO_3H$	Cat	dichloromethane	6	58

* isolated yield

Scheme 2. Condensation reaction of resorcinol with 2-methyl-3-butene-2-ol.



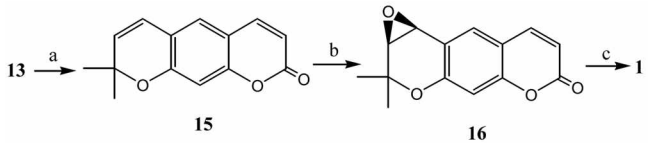
entry	acid	eq(mol)	solvent	time(h)	**yeild(%)	
					13	14
1	$ZnCl_2$	1eq	neat*	1.5h	38	38
2	$ZnCl_2$	1eq	PhH	8h	-	-
3	$ZnCl_2$	4eq	PhH	8h	-	-
4	$ZnCl_2$	1eq	toluene	8h	-	-
5	$ZnCl_2$	1eq	EtOH	8h	-	-
6	$AlCl_3$	1eq	neat*	1.5h	-	-
7	$Ca(OH)_2$	1.5eq	dioxane	8h	-	-
8	H_2SO_4	cat.	EtOH	8h	-	-
9	H_2SO_4	cat.	PhH	8h	-	-

*reaction temp.(110°C) ** isolated yield

Scheme 3. Condensation reaction of **12** with ethyl propiolate.

isomer **14** could not be minimized in several different reaction conditions. Despite the low yield of desired lactone **13**, the Han's problem[7] could be overcome by introducing this troublous step at an early stage before chiral epoxidation rather than at a final stage.

The lactone **13** is dehydrogenated by DDQ in refluxing benzene to give xanthyletin (**15**) in 82% yield (Scheme 4).[10] The alternative use of NBS/AIBN in refluxing CCl_4 produced a low yield of **15**. Xanthyletin have been isolated from tissues of Citrus infected by *Phytophthora* spp. and known as an efficient growth inhibitor of *Phytophthora citrophthora*.[11] The xanthyletin **15** was converted to the desired chiral epoxide **16** in 83% yield (95% ee) in the presence of Jacobsen's (*S,S*)-(+)-salen-Mn(III) catalyst with Oxone® using the procedure developed by Han.[7-9] The absolute configuration of the epoxide **16** was determined by its transformation to the authentic natural (+)-decursinol **1**. The



Scheme 4. Reagents and conditions: (a) DDQ, PhH, reflux, 82%; (b) Jacobsen's (*S,S*)-salen-Mn(III) catalyst, *n*-Bu_4NHSO_4, buffered solution/CH_3CN, 1,1,1-trifluoroacetone, Oxone®, $NaHCO_3$, 0 °C, 83%; (c) $NaBH_3CN$, $BF_3{\cdot}OEt_2$, THF, rt, 93%.

regio- and stereoselective reduction of **16** by using $NaBH_3CN$ with $BF_3{\cdot}OEt_2$ in THF at rt gave (+)-decursinol in 93% yield.[8]

In conclusion, the enantioselective and convenient synthesis of (+)-decursinol has been achieved from resorcinol in five steps with 16.8% overall yield including double condensation, oxidation, chiral epoxidation, and reduction. The introduction of ethyl propiolate condensation step, which produced equimolar amount of regioisomer resulting in low yield of **1**, at an early stage lead to a practical and economical synthesis of (+)-decursinol.

Experimental Section

All chemicals used were purchased from commercial sources and used as received unless otherwise stated. NMR spectra were recorded at Varian Gemini-300 MHz FT-NMR for ^1H and 75.5 MHz for ^{13}C, with the chemical shifts (δ) reported in parts per million (ppm) relative to TMS and the coupling constants (J) quoted in Hz. $CDCl_3$ was used as a solvent and an internal standard. Flash chromatography was carried out using silica gel Merck 60 (230-400 mesh). Thin-layer chromatography (TLC) was performed on DC-Plastikfolien 60, F_{254} (Merck, layer thickness 0.2 mm) plastic-backed silica gel plates with visualization by UV light (254 nm) or by treatment with *p*-anisaldehyde. Optical rotation was determined on a Rudolph Research AUTOPOL®III polarimeter with 10 cm tube. Melting points were measured on a MEL-TEMP II apparatus and were uncorrected.

7-Hydroxy-2,2-dimethylchroman (12). To a solution of resorcinol **3** (1.00 g, 9.08 mmol) in dichloromethane (20 mL) was added zinc chloride (0.62 g, 4.54 mmol) followed by 2-methyl-3-buten-2-ol (0.48 mL, 4.54 mmol) and stirred for 2 h at rt. The reaction mixture was heated to reflux for 7 h. After being cooled, the mixture was neutralized with saturated $NaHCO_3$ and extracted with diethyl ether. Concentration and column chromatography (EtOAc : Hexane = 1 : 9) gave the white solid **8** (0.55 g, 70%). R_f 0.60 (EtOAc : Hexane = 1 : 2); mp 62-64 °C; ^1H NMR (300 MHz, $CDCl_3$) δ 1.31 (6H, s, C2-methyls), 1.77 (2H, t, J = 6.6 Hz, C3-H), 2.68 (2H, t, J = 6.6 Hz, C4-H), 4.97 (1H, s, OH), 6.27 (1H, br s, C8-H), 6.32 (1H, br d, J = 8.1 Hz, C6-H), 6.88 (1H, d, J = 8.1 Hz, C5-H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 22.1 (C3), 27.2 (2Me), 33.3 (C4), 74.6 (C2), 104.0 (C8), 107.5 (C6), 113.5 (C4a), 130.2 (C5), 154.9 (C7), 155.0 (C8a).

8,8-Dimethyl-7,8-dihydro-6*H*-pyrano[3,2-*g*]chromen-2-one (13) and 6,6-dimethyl-6,7-dihydro-8*H*-pyrano[2,3-*f*]-chromen-2-one (14). To a chroman **12** (0.55 g, 3.08 mmol)

was added ethyl propiolate (0.47 mL, 4.62 mmol) with zinc chloride (0.41 g, 3.08 mmol), and heated at 110 °C for 1.5 h. After being cooled, the reaction was quenched with 5% aqueous HCl and extracted with EtOAc. Concentration and column chromatography (EtOAc : Hexane = 1 : 7) gave the white solid **13** (0.27 g, 38%) and **14** (0.27 g, 38%). **13**: R_f 0.68 (EtOAc : Hexane = 1 : 2); mp 102-104 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.36 (6H, s, C8-methyls), 1.84 (2H, t, J = 6.6 Hz, C7-H), 2.82 (2H, t, J = 6.6 Hz, C6-H), 6.18 (1H, d, J = 9.3 Hz, C3-H), 6.70 (1H, s, C10-H), 7.14 (1H, s, C5-H), 7.56 (1H, d, J = 9.3 Hz, C4-H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 22.2 (C7), 27.2 (2Me), 32.7 (C6), 76.0 (C8), 104.8 (C3), 112.4 (C4a), 112.9 (C10), 118.6 (C5a), 128.4 (C5), 143.4 (C4), 154.1 (C10a), 157.8 (C9a), 161.7 (C2). **14**: R_f 0.81 (EtOAc : Hexane = 1 : 2); mp 172-175 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.38 (6H, s, C6-methyls), 1.84 (2H, t, J = 6.6 Hz, C7-H), 2.77 (2H, t, J = 6.6 Hz, C8-H), 6.28 (1H, d, J = 9.6 Hz, C3-H), 6.77 (1H, d, J = 8.5 Hz, C10-H), 7.17 (1H, d, J = 8.5 Hz, C9-H), 8.06 (1H, d, J = 9.6 Hz, C4-H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 22.2 (C7), 27.2 (2Me), 32.7 (C8), 76.1 (C6), 107.8 (C3), 109.5 (C4a), 114.1 (C10), 115.9 (C8a), 132.8 (C9), 139.0 (C4), 150.4 (C10a), 153.7 (C4b), 161.5 (C2).

Xanthyletin (15). To a solution of chromenone **13** (0.16 g, 0.69 mmol) in benzene (30 mL) was added DDQ (0.37 g, 2.06 mmol) and refluxed for 40 h. After being cooled, the reaction was quenched with saturated aqueous $NaHSO_3$ and extracted with diethyl ether. Concentration and column chromatography (EtOAc : Hexane = 1 : 4) gave the pale yellow solid **15** (0.13 g, 82%). R_f 0.73 (EtOAc : Hexane = 1 : 2); mp 88-90 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.47 (6H, s, C8-methyls), 5.68 (2H, d, J = 9.9 Hz, C6-H), 6.21 (1H, d, J = 9.6 Hz, C3-H), 6.33 (1H, d, J = 9.9 Hz, C7-H), 6.71 (1H, s, C10-H), 7.03 (1H, s, C5-H), 7.56 (1H, d, J = 9.3 Hz, C4-H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 28.7 (2Me), 77.9 (C8), 104.6 (C3), 112.9 (C4a), 113.2 (C10), 118.6 (C5a), 120.9 (C6), 124.9 (C7), 131.3 (C5), 143.4 (C4), 155.5 (C10a), 156.9 (C9a), 161.2 (C2).

(6*S*,7*R*)-6,7-Epoxy-8,8-dimethyl-7,8-dihydro-6*H*-pyrano-[3,2-*g*]chromen-2-one (16). To a solution of xanthyletin **15** (0.10 g, 0.44 mmol) in CH_3CN (5 mL) at rt was added (*S,S*)-(+)-*N,N'*-bis(3,5-di-*t*-butylsalicylidene)-1,2-cyclohexane-diaminomanganese(III) chloride (Jacobsen's (*S,S*)-salen-Mn(III) catalyst, 5 mg, 0.018 mmol) and *n*-Bu_4NHSO_4 (5.3 mg, 0.015 mmol) with a buffer solution of 50 mM $Na_2B_4O_7 \cdot 10H_2O$ in 0.4 mM aqueous Na_2EDTA (3.5 mL). After the reaction mixture was cooled to 0 °C, 1,1,1-trifluoroacetone (0.05 mL) was added, followed by portionwise addition of two solutions of Oxone® (1.0 g, 1.62 mmol) in 0.4 mM aqueous Na_2EDTA (5 mL) and $NaHCO_3$ (0.3 g, 3.57 mmol) in H_2O (5 mL) with stirring over the reaction period (1.5 h).

The reaction mixture was then treated with water and extracted with diethyl ether. Concentration and column chromatography (EtOAc : hexane = 1 : 2) gave the white solid **16** (85 mg, 83%). R_f 0.35 (EtOAc : Hexane = 1 : 2); mp 135-140 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.31 (3H, s, Me), 1.61 (3H, s, Me), 3.54 (1H, d, J = 4.5 Hz, C7-H), 3.97 (1H, d, J = 4.5 Hz, C6-H), 6.26 (1H, d, J = 9.6 Hz, C3-H), 6.76 (1H, s, C10-H), 7.45 (1H, s, C5-H), 7.62 (1H, d, J = 9.6 Hz, C4-H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 23.5 (Me), 25.8 (Me), 50.5 (C7), 62.3 (C6), 74.8 (C8), 106.3 (C3), 113.3 (C4a), 114.1 (C10), 117.5 (C5a), 129.0 (C5), 143.0 (C4), 156.2 (C9a & C10a), 160.9 (C2).

(+)-Decursinol (1). To a solution of epoxide **16** (0.035 g, 0.143 mmol) in THF (10 mL) was added $NaBH_3CN$ (0.011 g, 0.172 mmol) with $BF_3 \cdot OEt_2$ (0.018 g, 0.143 mmol) at 0 °C and stirred at rt for 0.5 h. The reaction was quenched with saturated aqueous $NaHCO_3$ and extracted with EtOAc. Concentration and column chromatography (EtOAc : Hexane = 1 : 2) gave the white solid **1** (0.033 g, 93%). R_f 0.13 (EtOAc : Hexane = 1 : 2); mp 167-170 °C; $[\alpha]_D^{26}$ = +10.3 (*c* 1.0, $CHCl_3$, 95% ee) (lit.[12] $[\alpha]_D^{26}$ = +10.8); ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.36 (3H, s, Me), 1.39 (3H, s, Me), 2.00 (1H, br s, OH), 2.83 (1H, dd, J = 5.7, 16.5 Hz, C6-H), 3.10 (1H, dd, J = 5.7, 16.5 Hz, C6-H), 3.86 (1H, br t, J = 5.4 Hz, C7-H), 6.19 (1H, d, J = 9.3 Hz, C3-H), 6.76 (1H, s, C10-H), 7.16 (1H, s, C5-H), 7.56 (1H, d, J = 9.3 Hz, C4-H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 22.4 (Me), 25.4 (Me), 31.0 (C6), 69.3 (C7), 78.5 (C8), 104.9 (C3), 113.1 (C4a), 113.3 (C10), 116.8 (C5a), 129.2 (C7), 143.4 (C6), 154.2 (C10a), 156.7 (C9a), 161.6 (C2).

Acknowledgements. This work was supported by grant No. (R01-2005-000-10916-0) from the Basic Research Program of Korea Science & Engineering Foundation, and in part by the Ministry of Commerce, Industry and Energy through the Center for Efficacy Assessment and Development of Functional Foods and Drugs at Hallym University, Korea.

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