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An efficient synthesis of (+)-decursinol from umbelliferone

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Abstract—An efficient, practical and enantioselective total synthesis of (+)-decursinol, which has diverse range of biological properties including anti-cancer, anti-*Helicobacter pylori*, and strong antinociceptive activities, has been achieved in five steps with 41.4% overall yield from umbelliferone. The improved ring construction from coumarin to linear pyranocoumarin has been obtained through quinonemethide intermediate by using phenylboronic acid with propionic acid.

Coumarins have important biological effects including anti-oxidant, anti-inflammatory, anti-allergic, hepatoprotective, antiviral, anticarcinogenic, enzyme inhibitor, and precursor of toxic substances; however, many of them are not suitable for therapeutic use due to their toxic, carcinogenic and mutagenic properties.[1] (+)-Decursinol (**1**) is a linear dihydrocoumarin isolated from the root of *Angelica gigas* Nakai (Umbelliferae)[2] and has known to have cytotoxic activity,[3] anti-*Helicobacter pylori* activity,[4] and strong antinociceptive activity.[5] Several asymmetric total syntheses of **1** were reported by using esculetin,[6] resorcinol,[7] or umbelliferone (**2**)[8] as a starting material with a relatively long step resulting low overall yield. We have focused on the practical and efficient total synthesis of **1**, and reported herein the shortest step and the highest yield of enantioselective total synthesis for (+)-decursinol (Fig. 1).

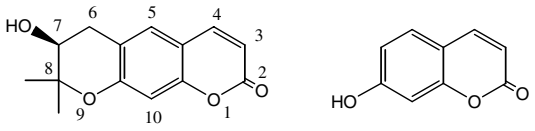
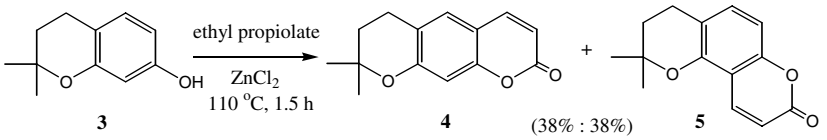


Figure 1.

Our previous total synthesis of (+)-decursinol from resorcinol showed regioisomeric problem during ring construction from chroman (**3**) with ethyl propiolate (1.5 equiv) to give linear pyranochromen (**4**) as shown in Scheme 1.[9] We could not find the regioselective reaction condition to minimize the equimolar amount of by-product (**5**).

Direct ring formation reaction of commercially available umbelliferone (**2**) with 2-methyl-3-butene-2-ol to xanthyletin (**13**) was unsuccessful due to conjugation stability. Umbelliferone was reduced at rt with H_2/Pd–C (10 wt %) for 10 h in 94% yield to produce **6** as shown in Scheme 2, and subsequent ring formation reaction with 2-methyl-3-butene-2-ol (10.5 equiv) afforded pyranochroman **7** (Table 1). The best condition for the ring formation gave 38% yield of **7** by using *p*-TsOH



Scheme 1. Reaction of chroman with ethyl propiolate.

Keywords: Decursinol; Umbelliferone; Coumarin; Quinonemethide; Phenylboronic acid.
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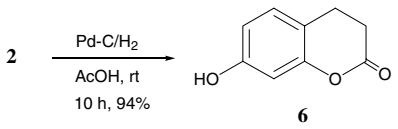
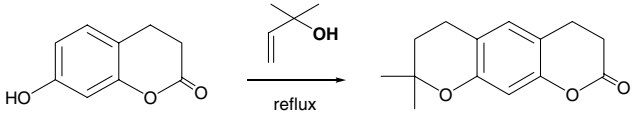


Scheme 2. Reduction of umbelliferone.

(0.2 equiv) in dichloroethane (entry 2), however produced an equimolar amount of regioisomer. Solvent change to dichloromethane in this reaction decreased the yield to 26% (entry 6).

Phenylboronic acid is known as a useful reagent to produce quinonemethide intermediate from phenol with aldehyde.[10] Ring formation reaction of phenol **6** with 3-methyl-2-butenal (1.5 equiv) by using phenylboronic acid (2 equiv) with excess acetic acid produced **8** in 56% yield as shown in Table 2 (entry 2), and no reaction occurred without AcOH (entry 3) or phenylboronic acid

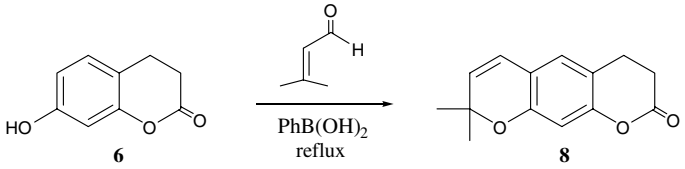
Table 1. Ring formation reaction with 2-methyl-3-butene-2-ol



Entry	Acid	Equivalents	Solvent	Time (h)	Yield[a] (%)
1	*p*-TsOH	0.1	Dichloroethane	8	20
2	*p*-TsOH	0.2	Dichloroethane	8	38
3	*p*-TsOH	0.3	Dichloroethane	4	37
4	*p*-TsOH	0.5	Dichloroethane	4	34
5	*p*-TsOH	1.0	Dichloroethane	8	24
6	*p*-TsOH	0.2	Dichloromethane	8	26
7	H_2SO_4	Cat.	Dichloroethane	2	20
8	$MeSO_3H$	Cat.	Dichloroethane	2	22
9	$MeSO_3H$	Cat.	Benzene	2	19
10	AcOH	Solvent	AcOH	12	5
11	$ZnCl_2$	3.0	Dichloroethane	20	10
12	$ZnCl_2$	3.0	Benzene	8	10
13	$AlCl_3$	1.0	Dichloroethane	20	0
14	$BF_3{\cdot}Et_2O$	1.5	Dichloroethane	16	8
15	$BF_3{\cdot}Et_2O$–TMSOMs	0.5:2.5	Dichloroethane	3	15

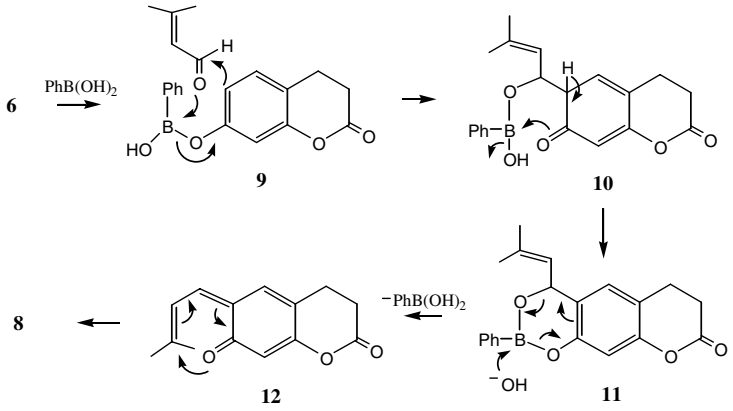
[a] Isolated yield.

Table 2. Ring formation reaction with 3-methyl-2-butenal using phenylboronic acid

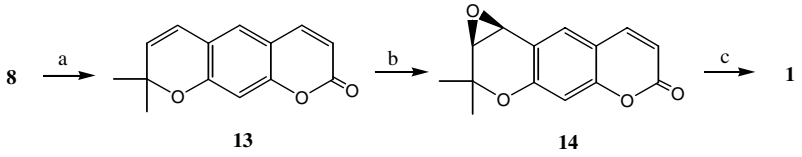


Entry	$PhB(OH)_2$ (equiv)	Acid (equiv)	Solvent	Time (h)	Yield[a] (%)
1	1.0	AcOH (88)	Toluene	24	42
2	2.0	AcOH (88)	Toluene	24	56
3	1.0	None	Toluene	24	0
4	0	AcOH (88)	Toluene	24	0
5	1.5	Propionic acid (110)	Benzene	36	50
6	1.5	Propionic acid (45)	Toluene	36	57
7	1.5	Propionic acid (110)	Toluene	36	62
8	1.5	Propionic acid (cat.)	Toluene	36	15
9	1.0	Formic acid (88)	Benzene	24	0
10	1.5	Butyric acid (110)	Toluene	36	47
11	1.5	Valeric acid (110)	Benzene	36	41
12	1.5	Benzoic acid (2)	Toluene	36	32
13	1.5	Phenyl acetic acid (2)	Toluene	36	45
14	1.0	H_2SO_4 (cat.)	Benzene	24	0
15	1.0	$MeSO_3H$ (cat.)	Benzene	24	0
16	1.0	*p*-TsOH (1)	Benzene	24	0

[a] Isolated yield.



Scheme 3. Ring formation mechanism with phenylboronic acid.



Scheme 4. Reagents and conditions: (a) DDQ (2 equiv), PhH, reflux, 8 h, 92%; (b) Jacobsen's (*S*,*S*)-salen-Mn(III) catalyst (4 mol %), *n*-Bu_4NHSO_4, buffered solution/CH_3CN, 1,1,1-trifluoroacetone, Oxone®, $NaHCO_3$, 0 °C, 1.5 h, 83%; (c) $NaBH_3CN$ (1 equiv), $BF_3{\cdot}OEt_2$, THF, rt, 0.5 h, 93%.

(entry 4). Propionic acid (1.5 equiv) instead of acetic acid using in the reaction with phenylboronic acid increased the product to 62% yield (entry 7);[11] however, the other acids (entries 9–16) showed no advantage. Phenylboronic acid adduct **9** was reacted with aldehyde to form benzodioxaborine **11**, which rearranged to produce quinonemethide intermediate **12** as shown in Scheme 3. Intramolecular hetero electrocyclization of the *exo*-quinonemethide **12** gave the desired product **8** without forming a regioisomer.

Lactone **8** is dehydrogenated by DDQ (2 equiv) in refluxing benzene to give xanthyletin (**13**) in 92% yield within 8 h (Scheme 4),[12] however, the dehydrogenation reaction of **7** required excess amount of DDQ (5 equiv) with longer reaction time (36 h) to give only 82% yield of **13**. Xanthyletin has been isolated from the tissues of *Citrus* infected by *Phytophthora* spp. and known as an efficient growth inhibitor of *Phytophthora citrophthora*.[12] The epoxidation of xanthyletin **13** to the chiral epoxide **14** was proceeded by a known method using Jacobsen's (*S*,*S*)-(+)-salen-Mn(III) catalyst (4 mol %) at 0 °C for 1.5 h in 83% yield (95% ee).[7,8] The absolute configuration of the epoxide **14** was determined by its transformation to the authentic natural (+)-decursinol **1**. The regio- and stereoselective reduction of **14** with $NaBH_3CN$ (1 equiv) at rt for 0.5 h gave (+)-decursinol in 93% yield.[13]

In conclusion, an efficient, practical and enantioselective total synthesis of (+)-decursinol has been achieved from commercially available umbelliferone in five steps with 41.4% overall yield including reduction (94%), condensation (62%), oxidation (92%), asymmetric epoxidation (83%), and reduction (93%). This methodology resolved a previous regioisomer problem, and gave the highest yield and the shortest total synthesis of (+)-decursinol.

Acknowledgements

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13. Compound **1**: 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.[14] $[\alpha]_D^{26}$ +10.8); ^1H 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).
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