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Enantioselective syntheses of (+)-decursinol and (+)-*trans*-decursidinol

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Abstract—Selective and practical asymmetric syntheses of (+)-decursinol (**1**) and (+)-*trans*-decursidinol (**2**) have been achieved using naturally occurring umbelliferone, demethylsuberosin, and xanthyletin as the synthetic intermediates. The absolute stereochemistry was established in the late stage of synthesis by employing Jacobsen's enantioselective epoxidation conditions.

(+)-Decursinol (**1**), (+)-*trans*-decursidinol (**2**) and their ester derivatives **3**–**5** (Fig. 1) constitute a class of linear dihydropyranocoumarin natural products.[1] In particular, (+)-decursinol (**1**) and its ester derivatives, such as decursin (**3**) and decursinol angelate (**4**), have received considerable attention because of their diverse range of interesting biological properties including protein kinase related cytotoxicity,[2,3] anti-*helicobacter pylori* activity,[4] and strong analgesic activity.[5] The racemic syntheses of **1** and **3** were reported by Steck in 1971.[6] He constructed the C ring of decursinol by treatment of the *ortho*-prenylated phenols with *m*CPBA under acidic conditions. Recently, the asymmetric synthesis of (+)-decursinol (**1**) and its related natural products were independently achieved by the Shibasaki group[7] and the Han group,[8] who used asymmetric enone epoxidation and Jacobsen's chromene epoxidation, respectively. The racemic synthesis of **2** has been non-selectively achieved from xanthyletin by peracetic acid treatment,[9] but the selective asymmetric synthesis of (+)-*trans*-decursidinol (**2**) has not been reported yet.

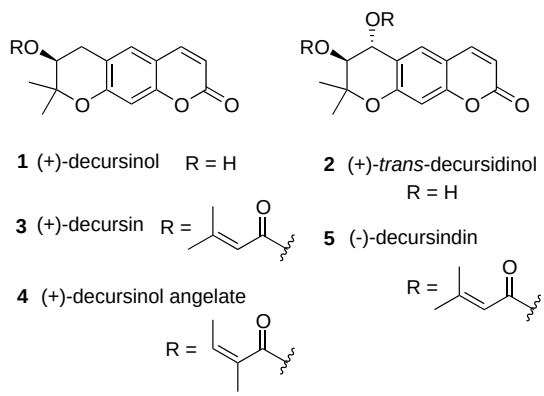

Figure 1. Structures of (+)-decursinol (**1**), (+)-*trans*-decursidinol (**2**) and their ester derivatives **3**–**5**.

In order to investigate the biochemical and pharmaceutical effects of (+)-decursinol (**1**), (+)-*trans*-decursidinol (**2**) and related derivatives, especially for pain relief applications, we needed to synthesize these dihydropyranocoumarins in large quantities. Here, we report an efficient asymmetric synthetic route to (+)-decursinol (**1**) and (+)-*trans*-decursidinol (**2**). In our synthesis, the chirality was introduced in the late stage of synthesis, and several naturally occurring coumarins were employed as intermediates for our presumed biomimetic synthetic approach.

In our retrosynthetic analysis, as summarized in Scheme 1, we envisioned that the desired (+)-decursinol (**1**) and (+)-*trans*-decursidinol (**2**) could be synthesized from the common chiral intermediate **6** by chemo- and regioselective epoxide ring opening reactions. The requisite epoxide **6** could be obtained from naturally occurring xanthyletin (**7**)[1] by employing Jacobsen's enantioselective epoxidation conditions.[10,11] Further analysis indicated demethylsuberosin (**8**)[1] should be an ideal synthetic precursor for **7**.

Keywords: decursinol; decursidinol; Jacobsen's epoxidation; biomimetic synthesis.
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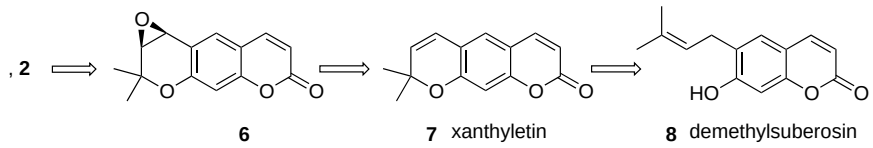


Scheme 1. Retrosynthetic analysis of **1** and **2**.

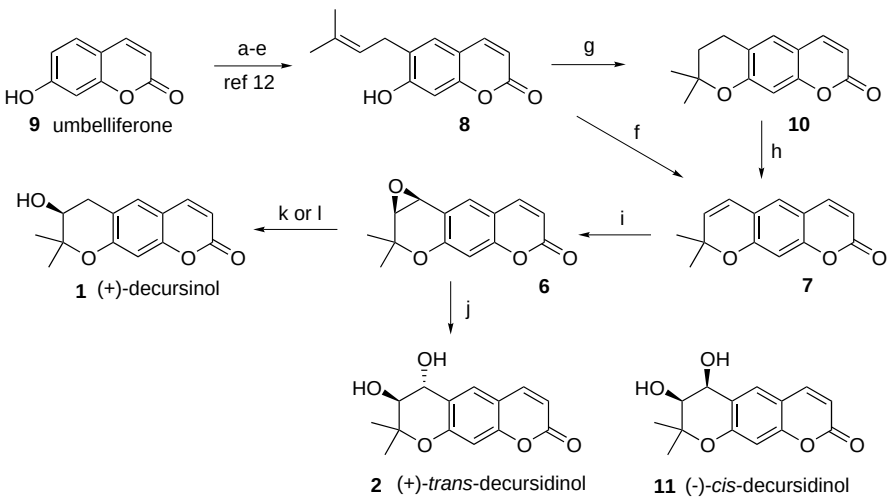
The synthesis began from commercially available umbelliferone (**9**), which was transformed into the desired demethylsuberosin (**8**) in five steps according to the previously established procedure of Harwood and co-workers[12] (Scheme 2). It was felt that these transformations offer the advantage of being able to selectively generate the desired linear coumarin **8** on a multigram scale without undertaking column chromatographic purifications. Demethylsuberosin (**8**) was oxidized with DDQ in refluxing benzene to give xanthyletin (**7**) in 60% yield.[6] Unfortunately, in larger scale reactions (>5 g), the oxidation of **8** with DDQ yielded a significant amount of chromane **10** (20–30%) along with chromene **7** (40–50%). Therefore, we have developed an alternate route to obtain **7**. Our synthetic sequence involves a formic acid-catalyzed conversion of **8** to chromane **10** (98%), which was then oxidized with NBS/AIBN in refluxing CCl_4 to yield chromene **7** in 70% yield.

With multigram quantities of xanthyletin (**7**) in hand, we next investigated the regioselective asymmetric epoxidation of **7**. Treatment of **7** with a basic NaOCl solution in the presence of Jacobsen's (*S*,*S*)-(+)-salen–Mn(III) catalyst (1.9 mol%) provided the desired epoxide **6** with very high enantioselectivity (97% ee) in 78% yield.[11,13,14] It was found that recrystallization of the obtained 97% ee epoxide **6** from hexane:ethyl acetate improved the enantiomeric purity to >99% ee.

Treatment of epoxide **6** with $HClO_4$ or $HClO_4/NaClO_4$ in aqueous THF[15] gave the diol (90%) as a 5:1 mixture of *trans*-diol **2** and *cis*-diol **11** that were inseparable. However, exposure of **6** to Ti(O-*i*Pr)$_4$ and H_2O in THF provided the desired (+)-*trans*-decursidinol (**2**) as the only identifiable product in 93% yield.[16] The improvement of stereoselectivity in opening the epoxide **6** could be understood by considering that the coordination of the epoxy-pyran with the metal center occurred in a bidentate manner, similar to that of Sharpless's selective epoxy alcohol openings.[17]

Attempted hydrogenolysis of the epoxide **6** with Pd/C for the transformation to (+)-decursinol (**1**) was nonselective providing a mixture of product **1** and overreduced compound. However, reaction with Lindlar catalyst under a hydrogen atmosphere cleanly reduced epoxide **6** providing (+)-decursinol (**1**) in 95% yield. The chemo- and regioselective reduction of epoxide **6** was also achieved by using $NaBH_3CN$ and $BF_3{\cdot}Et_2O$ in THF in 92% yield.[18]

In conclusion, the selective and practical asymmetric syntheses of the linear dihydropyranocoumarin natural products (+)-decursinol (**1**) and (+)-*trans*-decursidinol (**2**) have been achieved using naturally occurring umbelliferone, demethylsuberosin, and xanthyletin as the synthetic intermediates. The absolute stereochemistry was introduced by employing Jacobsen's enantioselective epoxidation conditions. The method presented here should allow access to the entire family of linear dihydropyranocoumarins including decursin and decursidin from our key intermediate epoxide **6**.



Scheme 2. *Reagents and conditions:* (a) BnBr, K_2CO_3, acetone, reflux, 5 h, 99%; (b) NaOMe, MeOH, reflux, 6 h, 90%; (c) prenyl bromide, K_2CO_3, acetone, reflux, 5 h, 90%; (d) $PhNEt_2$, reflux, 16 h, 80%; (e) BCl_3, CH_2Cl_2, 0°C, 2 h, 85%; (f) DDQ, benzene, reflux, 3 h, 60%; (g) formic acid, reflux, 1 h, 98%; (h) NBS, AIBN, CCl_4, reflux, 8 h, 70%; (i) Jacobsen's (*S*,*S*)-(+)-salen–Mn(III) cat., Clorox®, Na_2HPO_4, NaOH, CH_2Cl_2, 0°C, 6 h, 78%; (j) Ti(O-*i*Pr)$_4$, H_2O, THF, rt, 4 h, 93%; (k) Lindlar cat., H_2, EtOAc, rt, 2 days, 90%; (l) $NaBH_3CN$, $BF_3{\cdot}Et_2O$, THF, rt, 0.5 h, 92%.

Acknowledgements

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13. The procedure for the catalytic asymmetric epoxidation of **7** was as follows. 14.3 ml of commercial household bleach (Clorox®) was diluted with 5.7 ml of a 0.05 M Na_2HPO_4 solution, and the pH of the resulting solution was adjusted to pH 11.3 by addition of a 1N NaOH solution. To this solution was added a solution of (*S*,*S*)-(+) - *N*,*N* - bis(3,5 - di - *tert* - butylsalicylidene) - 1,2 - cyclohexanediaminomanganese(III) chloride (72.5 mg, 0.11 mmol) and **7** (1.3 g, 5.7 mmol) in 6 ml of CH_2Cl_2. The two-phase mixture was stirred at 0°C. After 6 h, 10 ml of CH_2Cl_2 was added to the reaction mixture and the brown organic phase was separated, washed with 50 ml of water and then 50 ml of brine, and dried over $MgSO_4$. After solvent removal, the residue was purified by silica gel column chromatography (hexane/EtOAc = 3/2) to give 1.08 g (78%) of the desired chiral epoxide **6** as a white solid. ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.31 (3H, s), 1.61 (3H, s), 3.54 (1H, d, J = 4.4 Hz), 3.96 (1H, d, J = 4.4 Hz), 6.27 (1H, d, J = 9.5 Hz), 6.77 (1H, s), 7.46 (1H, s), 7.63 (1H, d, J = 9.5 Hz); $[\alpha]_D^{24} = -274.7$ (*c* 0.7, $CHCl_3$).
14. The absolute configuration of epoxide **6** was re-confirmed by transformation to the authentic natural compounds (+)-**1** and (+)-**2**. The enantiomeric excess of **6** was determined by chiral stationary phase HPLC analysis (CHIRALPAK AD-H, hexane/2-propanol (4:1, v/v), flow rate: 1.0 ml/min, retention time: 11.91 min (*R*,*R*)-isomer and 25.88 min (*S*,*S*)-isomer, detected at 254 nm).
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18. The enantiomeric excess of **1** was determined by chiral stationary phase HPLC analysis (CHIRALPAK AD-H, hexane/2-propanol (4:1, v/v), flow rate: 1.0 ml/min, retention time: 8.32 min (*S*)-isomer and 9.92 min (*R*)-isomer, detected at 254 nm). ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.30 (3H, s), 1.33 (3H, s), 2.76 (1H, dd, J = 5.7, 16.8 Hz), 3.04 (1H, dd, J = 5.7, 16.8 Hz), 3.80 (2H, t, J = 5.7 Hz), 6.16 (1H, d, J = 9.6 Hz), 6.72 (1H, s), 7.11 (1H, s), 7.51 (1H, d, J = 9.6 Hz); $[\alpha]_D^{24} = +10.5$ (*c* 1.0, $CHCl_3$).