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Enantioselective syntheses of decursinol angelate and decursin

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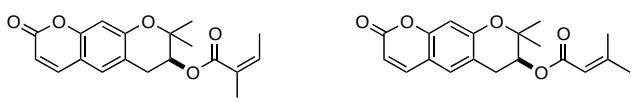
Abstract—The practical enantioselective syntheses of decursinol angelate and decursin were achieved in eight steps from resorcinol. The stereochemistry was addressed using the catalytic asymmetric epoxidation of 7-acetoxy-2,2-dimethylchromene by chiral (salen)Mn complexes as the key step.

Protein kinase C (PKC) is a target of great interest in the development of antitumor agents because of its crucial role in cellular signal transduction and tumor promotion.[1] Decursinol angelate (**1**) and decursin (**2**) are novel cancer chemotherapeutic candidates isolated from *Angelica gigas* Nakai. They have more effective cytotoxic activity against various human cancer cell lines than normal fibroblasts (Fig. 1).[2] Initial studies showed that both decursinol angelate and decursin exhibit PKC activating activity, suggesting that their cytotoxicity may be related to the PKC activation.[2b,c] Recent data indicate that decursinol angelate has stronger activity than decursin in PKC activation.[2d] The combined cytotoxic and PKC activating properties of these pyranocoumarins are similar to those of bryostatins and thus make them attractive targets for total synthesis.[3] Recently, the first asymmetric syntheses of (+)-decursin and its analogues were reported by the Shibasaki group.[4] Here, we report a novel and efficient route to the enantioselective syntheses of decursinol angelate and decursin. Our strategy employed the catalytic asymmetric epoxidation of 7-acetoxy-2,2-dimethylchromene (**7**) as the key step.

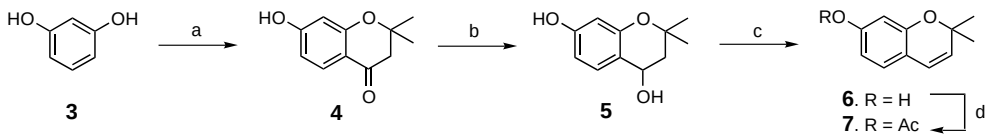


1: (+)-decursinol angelate **2**: (+)-decursin

Figure 1. Structure of decursinol angelate and decursin.

The construction of the requisite epoxidation precursor **7** is illustrated in Scheme 1. Our synthesis began with the condensation of resorcinol **3** and 3-methyl-2-butenoic acid in the presence of methanesulfonic acid and phosphorus pentoxide, providing the chromanone **4** in 96% yield.[5] The subsequent reduction of **4** using $LiAlH_4$ in THF afforded the chroman **5** in 83% yield. The dehydration step was carried out using *p*-TsOH in THF under reflux to give 7-hydroxy-2,2-dimethylchromene (**6**) in 88% yield.[6]

Preliminary attempts to epoxidize the chromene **6** under a variety of standard conditions using *m*-CPBA, NaOCl, *t*-BuOOH or dioxiranes as the oxidant were unsuccessful due to the rapid decomposition of the presumed epoxide.[7] This problem was effectively circumvented via acetylation of the hydroxyl group of **6**.



Scheme 1. *Reagents and conditions*: (a) 3-methyl-2-butenoic acid, $MeSO_3H$, P_2O_5, 70°C, 96%; (b) LAH, THF, Δ, 83%; (c) *p*-TsOH, THF, Δ, 88%; (d) acetic anhydride, pyridine, DMAP, CH_2Cl_2, rt, 98%.

Keywords: decursinol angelate; decursin; decursinol; catalytic asymmetric epoxidation; protein kinase C.
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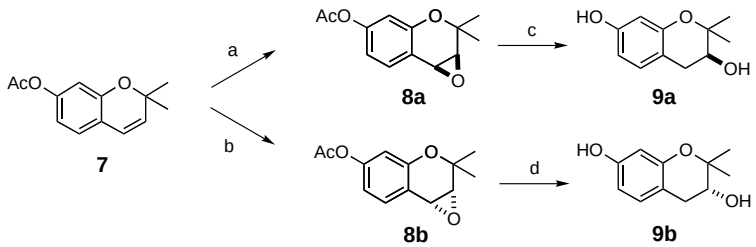
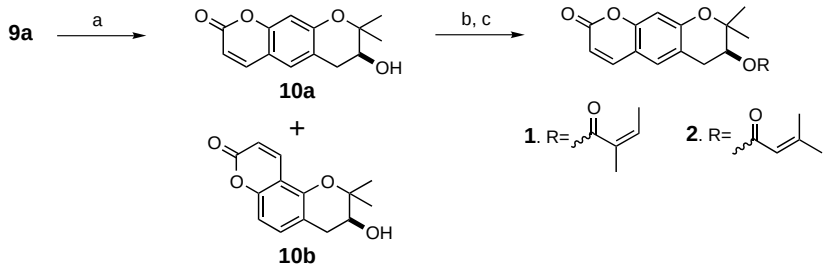


Scheme 2. *Reagents and conditions*: (a) Jacobsen's (*S*,*S*)-salen-Mn(III) catalyst, *n*-Bu_4NHSO_4, buffered solution/CH_3CN, 1,1,1-trifluoroacetone, Oxone®, $NaHCO_3$, 0°C, 83%; (b) Jacobsen's (*R*,*R*)-salen-Mn(III) catalyst, *n*-Bu_4NHSO_4, buffered solution/CH_3CN, 1,1,1-trifluoroacetone, Oxone®, $NaHCO_3$, 0°C, 83%; (c) LAH, THF, 0°C, 81%; (d) identical conditions with (c), 81%.



Scheme 3. *Reagents and conditions*: (a) ethyl propiolate, zinc chloride, 110°C, 40%; (b) angelic acid, DCC, DMAP, CH_2Cl_2, rt, (**1**, 74%); (c) 3,3-dimethylacryloyl chloride, pyridine, CH_2Cl_2, rt, (**2**, 92%).

The chromene **7** was readily epoxidized under buffered neutral reaction conditions (Jacobsen's (*S*,*S*)-(+)- or (*R*,*R*)-(−)-salen-Mn(III) catalysts 4 mol%, 1,1,1-trifluoroacetone, Oxone®, and $NaHCO_3$) to allow the facile production of the epoxide **8a** in good yield (83%) and enantioselectivity (92% ee) (Scheme 2).[8–10] Protection of the hydroxyl group of **6** as *tert*-butyldimethylsilyl ether followed by epoxidation proved to be unsuccessful. Despite its stability to silica gel chromatography, **8a** was immediately reduced without further purification. Reduction of **8a** with $LiAlH_4$ in THF at 0°C proceeded with concomitant removal of the acetyl group to provide the alcohol **9a** (67% yield, two steps from **7**).[11–13] The exclusive regioselectivity of ring opening by $LiAlH_4$ was consistent with that previously found for simple chroman epoxides.[11b] The alcohol **9b** could be prepared by reduction of the epoxide **8b** obtained from **7** using Jacobsen's (*R*,*R*)-salen-Mn(III) catalyst.

(+)-Decursinol (**10a**) was obtained in 40% yield from the condensation of **9a** with ethyl propiolate in the presence of zinc chloride (Scheme 3).[14] This transformation provided a separable mixture (ca. 1:1) of regioisomers **10a** and **10b**. The regioselectivity of the cyclization step was not favorably influenced by employing Pd-catalyzed addition, or $AlCl_3$ as the Lewis acid.[15] Finally, esterification of the hydroxyl group of **10a** with angelic acid or 3,3-dimethylacryloyl chloride provided (+)-decursinol angelate (**1**) and (+)-decursin (**2**) in 74 and 92% yield, respectively.[16]

In conclusion, this study establishes a novel and effective route to the syntheses of (+)-decursinol angelate and (+)-decursin. The synthesis proceeds in eight steps with good overall yield (**1**, 14%; **2**, 17%) and the absolute stereochemistry was established by using Jacobsen's (salen)Mn catalysts. This practical approach should provide access to a series of new analogues that will be useful to elucidate the molecular basis for the role of decursinol angelate and decursin in PKC activation.

Acknowledgements

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9. (3*S*,4*S*)-7-Acetoxy-3,4-epoxy-2,2-dimethylchroman (**8a**): To a solution of **7** (360 mg, 1.65 mmol), (*S*,*S*)-(+)-*N*,*N*′-bis(3,5-di-*tert*-butylsalicylidene)-1,2-cyclohexanediaminomanganese(III) chloride (Jacobsen's (*S*,*S*)-salen-Mn(III) catalyst, 43 mg, 0.068 mmol) and n-Bu_4NHSO_4 (20 mg, 0.059 mmol) in CH_3CN (18 mL) was added a buffer solution of 50 mM $Na_2B_4O_7{\cdot}10H_2O$ in 0.4 mM aqueous Na_2EDTA (12 mL), and the reaction mixture was cooled to 0°C. 1,1,1-Trifluoroacetone (0.2 mL) was added, followed by portionwise addition of two solutions of Oxone® (3.8 g, 6.2 mmol) in 0.4 mM aqueous Na_2EDTA (18 mL) and $NaHCO_3$ (1.2 g, 14.3 mmol) in H_2O (18 mL) with stirring over the reaction period (1.5 h). The reaction mixture was then treated with water and extracted with diethyl ether. The combined organic layers were dried over $MgSO_4$, filtered, and concentrated in vacuo. The residue was purified by flash chromatography (EtOAc:hexane = 1:2) to give **8a** as a yellow oil (0.32 g, 83%). TLC (EtOAc:hexane = 1:1): $R_f = 0.57$; ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.32 (d, $J = 8.1$ Hz, 1H), 6.67 (dd, $J = 8.0$, 2.6, 1H), 6.57 (d, $J = 2.4$, 1H), 3.90 (d, $J = 4.2$, 1H), 3.48 (d, $J = 5.1$, 1H), 2.26 (s, 3H), 1.26 (s, 6H).
10. The absolute configuration of the epoxide **8a** was determined by its transformation to (+)-decursinol. See: Ref. 4.
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12. (3*S*)-3,7-Dihydroxy-2,2-dimethylchroman (**9a**): To a suspension of lithium aluminium hydride (167 mg, 4.40 mmol) in dry THF (15 mL) under nitrogen at 0°C was added dropwise a solution of **8a** (345 mg, 1.47 mmol) in THF (25 mL). After the addition was completed the reaction mixture was stirred for 2 h at 0°C. The reaction was quenched with water at 0°C and extracted with ethyl acetate. The combined organic layers were washed with brine, dried over $MgSO_4$, and concentrated in vacuo. The residue was purified by flash chromatography (EtOAc:hexane = 1:2) to afford **9a** (0.23 g, 81%) as a white solid. TLC (EtOAc:hexane = 1:1): $R_f = 0.41$; ^{1}H NMR (300 MHz, $CDCl_3$): δ 6.91 (d, $J = 8.4$ Hz, 1H), 6.39 (dd, $J = 8.1$, 2.7, 1H), 6.32 (d, $J = 2.7$, 1H), 4.80 (brs, 1H), 3.78 (dd, $J = 10.8$, 5.4, 1H), 3.00 (dd, $J = 16.2$, 4.8, 1H), 2.70 (dd, $J = 16.5$, 5.4, 1H), 1.75 (d, $J = 7.5$, 1H), 1.35 (s, 3H), 1.30 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 155.27, 153.16, 130.58, 110.39, 108.56, 103.73, 76.81, 69.79, 30.48, 24.71, 22.36; HRMS (FAB) calcd for $C_{11}H_{14}O_3$ (M^+): 194.0943. Found: 194.0947; $[\alpha]_D^{23} = +11.5$ (c 1.03, $CHCl_3$).
13. The ee values of products were determined by analytical HPLC on a chiral column (Chiralpak AD, 4.6×250 mm, Daicel) under isocratic conditions (2-propanol:hexane = 15:85, 1 mL min^{-1} flow rate, $\lambda = 254$ nm). Retention time: **9a**, 12.50 min; **9b**, 14.88 min.
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16. (a) Nelson, T. D.; Meyers, A. I. *J. Org. Chem*. **1994**, *59*, 2577–2580; (b) Compound **1**: $[\alpha]_D^{26} = +73.6$ (c 1.42, $CHCl_3$). Compound **2**: $[\alpha]_D^{26} = +121.3$ (c 1.08, $CHCl_3$).