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Enantioselective total syntheses of novel PKC activator (+)-decursin and its derivatives using catalytic asymmetric epoxidation of an enone†

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Abstract

The catalytic asymmetric total syntheses of (+)-decursin and three related natural products, (+)-decursinol, (−)-prantschimgin and (+)-marmesin, were achieved for the first time using catalytic asymmetric epoxidation of an enone as the key step. The catalytic asymmetric epoxidation of enone was found to be promoted effectively by novel multifunctional asymmetric catalyst generated from $La(O\text{-}i\text{-}Pr)_3$, BINOL and $O{=}AsPh_3$ in a 1:1:1 ratio to afford epoxide in 94% yield and 96% ee, which was recrystallized to give the optically pure epoxide.

Keywords: catalytic asymmetric synthesis; (+)-decursin; asymmetric catalyst; epoxidation of enone.

Protein kinase C (PKC) is thought to play principal roles in cellular signal transductions and has been focused on as a target of anticancer drug screening.[1] Recently, it was shown that (+)-decursin (**1**)[2,3] (a dihydropyranocoumarin originally isolated from *Angelica decursiva* Fr. et Sav.[2a]) exhibits cytotoxicity against several human cancer cell lines and relatively low cytotoxicity against normal fibroblasts.[2c,d] The cytotoxic activity of **1** was found to be related to the mechanism of PKC activation.[2c,d] However, this has not yet been clarified. Moreover, **1** has a simple structure among the exogenous PKC activators reported so far. These profiles have made **1** quite attractive as a lead compound for drug discovery and a biological tool for clarification of the mechanism of PKC activation. Herein we report the first catalytic asymmetric total syntheses of (+)-decursin (**1**) and three related natural products **2**, **3** and **4** using catalytic asymmetric epoxidation of an enone as the key step (Fig. 1).

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† This paper is dedicated to Professor Harry Wasserman on the occasion of his 80th birthday.

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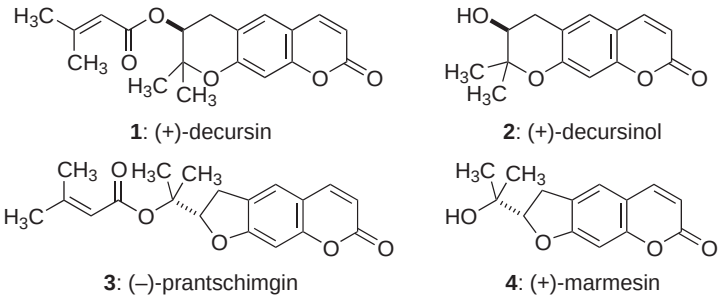
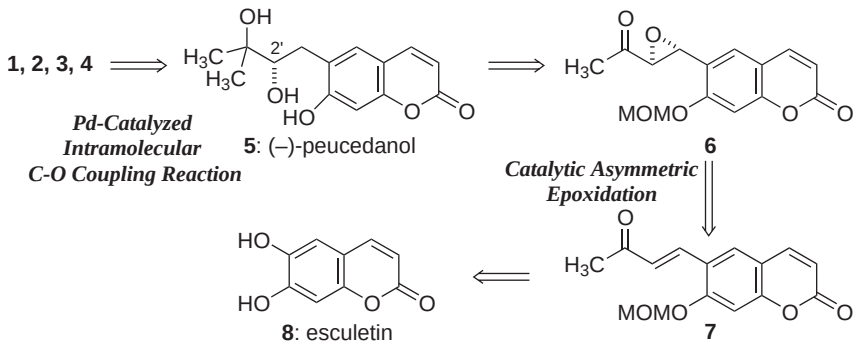


Figure 1. Structures of (+)-decursin (**1**), (+)-decursinol (**2**), (–)-prantschimgin (**3**) and (+)-marmesin (**4**)

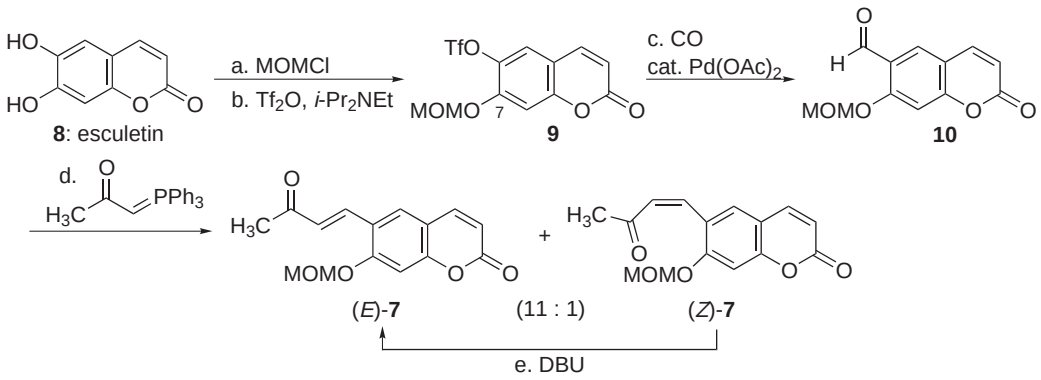
From a synthetic point of view, we chose the strategy based on the palladium-catalyzed intramolecular C–O coupling reaction[4] to construct the dihydropyran ring for (+)-decursin (**1**) and the dihydrofuran ring for (–)-prantschimgin (**3**), respectively (Scheme 1). This strategy allowed us to synthesize all natural compounds from the same intermediate (–)-peucedanol (**5**). Although there are many different ways of constructing the chiral center at the C-2′ position, catalytic asymmetric epoxidation of enone **7** followed by methylation should be the most effective method. It is well known that Sharpless asymmetric epoxidation of *tert*-allylic alcohol[5] and asymmetric hydrogenation of α-substituted enone[6] do not proceed so well.



Scheme 1. Retrosynthetic analysis of **1**, **2**, **3** and **4**

Scheme 2 summarizes the construction of the required epoxidation precursor **7**. Our synthesis started with commercially available esculetin (**8**). Selective protection of the C-7 hydroxyl group as MOM ether[7] followed by conversion of the other hydroxyl group to the triflate afforded **9**. To introduce the enone moiety,[8] we carried out palladium-catalyzed formylation of triflate **9** in the presence of triethylsilane[9] under a CO atmosphere (82%) followed by Wittig reaction to afford a 11:1 isomeric mixture of (*E*)- and (*Z*)-enone **7** (94%). These isomers were separated by silica gel column chromatography and (*Z*)-**7** was successfully isomerized to the desired (*E*)-**7** isomer by treatment with DBU (81%).

Having pure (*E*)-**7** in large quantities, we then focused on the catalytic asymmetric epoxidation of (*E*)-**7**. Preliminary experiments using several general conditions, such as TBHP–Triton B, H_2O_2–NaOH and even TBHP–La(O-*i*-Pr)$_3$ with or without MS 4 Å, provided undesired results. Semiempirical molecular orbital calculation (AM1) of (*E*)-**7** suggested that the LUMO at the β-position of (*E*)-**7** would be much smaller than that of the 3,4-dihydro version of (*E*)-**7**.[10]



Scheme 2. Reagents and conditions: (a) MOMCl, K_2CO_3, DMF, −20°C, 85%. (b) Tf_2O, *i*-Pr_2NEt, CH_2Cl_2, −30 to 0°C, 90%. (c) $Pd(OAc)_2$, DPPP, $HSiEt_3$, *i*-Pr_2NEt, CO (15 atm), DMF, 60°C, 82%. (d) Wittig reagent, THF, 60°C, 94% (*E*/*Z* = 11:1). (e) DBU, CH_2Cl_2, 40°C, 81%

Despite the above-mentioned negative factors in epoxidation, we expected that by using the multifunctional asymmetric catalyst developed in our group[11,12] we could overcome these problems. The unique feature of the catalyst is believed to be a result of a synergistic cooperation of metals and ligands. As we expected, Yb–BINOL (1:1) complex[12] catalyzed the asymmetric epoxidation of (*E*)-**7** to afford epoxyketone **6**[13] (88%, 83% ee) (Table 1, entry 1). After optimization of the reaction conditions, we finally found that a La–BINOL complex with

Table 1
Catalytic asymmetric epoxidation of enone (*E*)-**7** to epoxyketone **6** using Ln–BINOL complexes

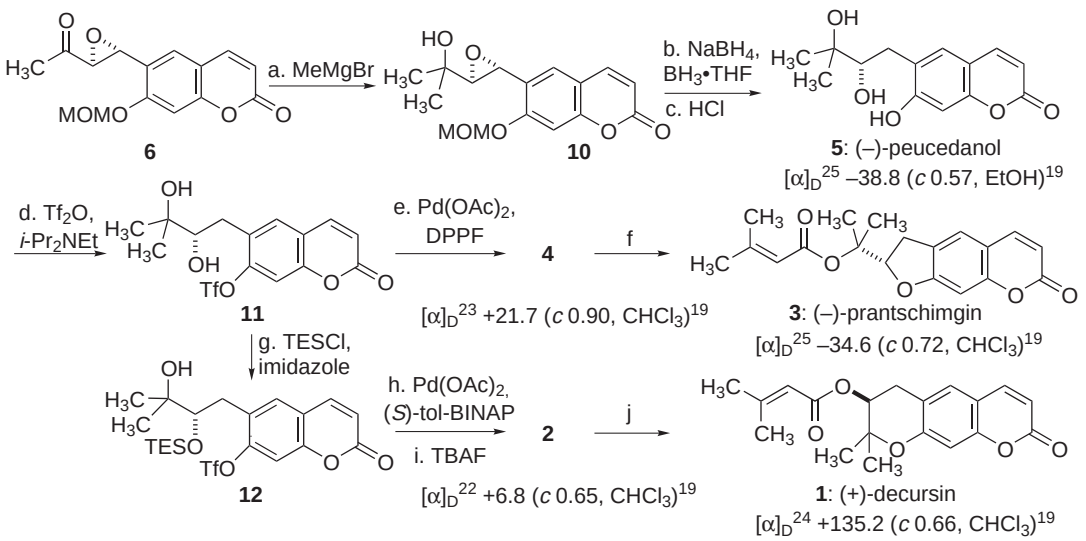
7 + TBHP in decane (2 equiv.) —catalyst, additive; MS 4 Å,[a] THF, rt→ **6**

Entry	Catalyst (mol %)	Additives (mol %)	Time (h)	Yield (%)	Ee (%)
1[b]	Yb–(*R*)-BINOL (1:1) (25)	–	15	88	83
2	La–(*R*)-BINOL (1:1) (25)	–	25	28	20
3	La–(*R*)-BINOL (1:1) (25)	O=PPh_3 (100)	2.5	98	97
4	La–(*R*)-BINOL (1:1) (25)	O=PPh_3 (25)	4	89	91
5	La–(*R*)-BINOL (1:1) (25)	O=$AsPh_3$ (100)	25	55	75
6	La–(*R*)-BINOL (1:1) (25)	O=$AsPh_3$ (75)	12	56	91
7	La–(*R*)-BINOL (1:1) (25)	O=$AsPh_3$ (50)	6	88	95
8	La–(*R*)-BINOL (1:1) (25)	O=$AsPh_3$ (25)	2	94	96
9	La–(*R*)-BINOL (1:1) (10)	O=$AsPh_3$ (10)	5	90	93
10	La(O-*i*-Pr)$_3$ (10)	O=$AsPh_3$ (10)	18	Trace	–
11	La(O-*i*-Pr)$_3$ (10)	–	24	Trace	–

[a] MS 4 Å was not dried (1000 mg/mmol).
[b] MS 4 Å was dried for 3 h at 180°C under reduced pressure before use (200 mg/mmol) and TBHP in toluene was used.

triphenylphosphine oxide[12d] or triphenylarsine oxide was highly effective for the catalytic asymmetric epoxidation. In terms of atom economy, the best result was obtained using 1 equiv. of triphenylarsine oxide to La(O-*i*-Pr)$_3$[14]–BINOL (94%, 96% ee, entry 8).[15] A single recrystallization of 96% ee epoxide **6** from hexane–acetone affords >99% ee epoxide **6** in 76% purified yield. Although several methodologies for catalytic asymmetric epoxidation of enones have been developed,[16] only a few applications to total syntheses have been reported.[17] No examples using an enolizable enone as a substrate could be found. To the best of our knowledge, this is the first application of this chemistry.

With the nearly optically pure advanced intermediate **6** in hand, the stage was set for completion of the total synthesis (Scheme 3). Methylation of epoxyketone **6** afforded epoxyalcohol **10** (76%, conv. 91%), and subsequent regioselective reduction[18] (74%) followed by removal of the MOM group (92%) provided common intermediate (–)-peucedanol (**5**). Selective transformation of the phenolic hydroxyl group to the triflate provided substrate **11**. With the use of 10 mol% Pd(OAc)$_2$, 20 mol% DPPF, and NaO-*t*-Bu, the five-membered ring product (+)-marmesin (**4**) was obtained exclusively. We next examined the Pd-catalyzed direct six-membered ring formation using diol **11** under a variety of reaction conditions. However, in all cases we obtained only the five-membered ring product. Thus, the secondary hydroxyl group was first protected with a TES group. Cyclization of the mono-protected substrate **12** proceeded in 91% yield using 10 mol% Pd(OAc)$_2$, 12 mol% (*S*)-tol-BINAP, and K_2CO_3. After removal of the TES group (+)-decursinol (**2**) was obtained. Finally, esterification of (+)-marmesin (**4**) and (+)-decursinol (**2**) resulted in the first asymmetric total syntheses of (–)-prantschimgin (**3**) and (+)-decursin (**1**), respectively.[19]



Scheme 3. Reagents and conditions: (a) MeMgBr, THF, –78°C, conv. 91%. (b) $NaBH_4$, BH_3·THF, THF, 0°C, 74%. (c) Conc. HCl–H_2O–THF (1:3:4), 40°C, 92%. (d) Tf_2O, *i*-Pr_2NEt, CH_2Cl_2, 0°C, 92%. (e) Pd(OAc)$_2$ (10 mol %), DPPF (20 mol %), NaO-*t*-Bu, toluene, 90°C, 80%. (f) Senecioyl chloride, DMAP, LHMDS, THF, –40 to 0°C, 72%. (g) TESCl, imidazole, CH_2Cl_2, rt, 92%. (h) Pd(OAc)$_2$ (10 mol %), (*S*)-tol-BINAP (12 mol %), K_2CO_3, toluene, 90°C, 91%. (i) TBAF, THF, rt, 95%. (j) Senecioyl chloride, DMAP, LHMDS, THF, –40 to 0°C, 83%

In summary, we have succeeded in catalytic asymmetric total syntheses of natural coumarins (+)-decursin (**1**), (+)-decursinol (**2**), (−)-prantschimgin (**3**), and (+)-marmesin (**4**) from the same intermediate (−)-peucedanol (**5**). **5** was synthesized in an optically pure form by catalytic asymmetric epoxidation of enone **7** using La(O-*i*-Pr)$_3$, BINOL, and O=AsPh$_3$ in the best ratio (1:1:1). Further studies on the mechanism of the catalytic asymmetric epoxidation and the structural determination of the asymmetric catalyst will be described in due course.

Acknowledgements

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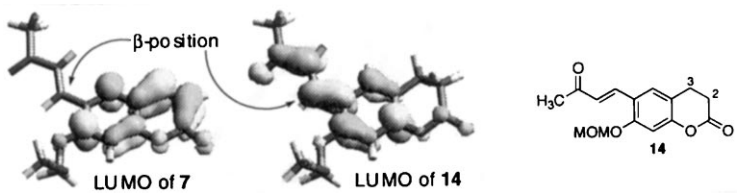
7. Catalytic asymmetric epoxidations using enones protected with other protecting group, such as Bn and PMB, provided worse result due to their low solubility in THF.
8. We at first examined Heck reaction and Stille coupling reaction extensively. However, we could not obtain a satisfactory result.
9. Standard formylation condition using Bu_3SnH as a reductant gave no desired aldehyde **10**.
10. LUMOs of **7** and **14**.



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14. La(O-*i*-Pr)$_3$ can be purchased from Kojundo Chemical Laboratory Co., Ltd., 5-1-28, Chiyoda, Sakado-shi, Saitama 350-0214, Japan (fax: +(81)-492-84-1351).
15. The catalytic asymmetric epoxidation of **7** is as follows. To a mixture of (*R*)-BINOL (7.2 mg, 0.025 mmol), triphenylarsine oxide (8.1 mg, 0.025 mmol) and MS 4 Å (250 mg) in dry THF (3.4 mL) was added a solution of La(O-*i*-Pr)$_3$ (0.125 mL, 0.025 mmol, 0.2 M solution in THF) at room temperature. After being stirred for 1 h at the same temperature, TBHP (0.1 mL, 0.5 mmol, 5 M solution in decane) was added. After being stirred for 30 min, enone **7** (68.5 mg, 0.25 mmol) was added and the mixture was stirred at room temperature. After 5 h, the reaction was quenched by addition of 2.5% aqueous critic acid (5 mL) at 0°C and extracted with ethyl acetate (3 10 mL). The combined organic layers were washed with brine (10 mL) and dried over Na_2SO_4. After concentration in vacuo, the residue was purified by flash column chromatography (SiO_2, hexane/ethyl acetate 4/1) to give epoxyketone **6** (65.0 mg, 90%, 93% ee) as a white solid.
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