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Tetrahedron 59 (2003) 6889–6897

TETRAHEDRON

Enantioselective total syntheses of (+)-decursin and related natural compounds using catalytic asymmetric epoxidation of an enone

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Received 2 April 2003; revised 27 May 2003; accepted 29 May 2003

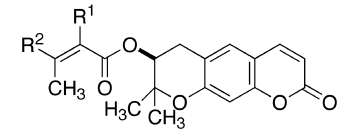
Dedicated to Professor K. C. Nicolaou in recognition of his receipt of the Tetrahedron Prize

Abstract—The enantioselective total syntheses of (+)-decursin (**1**) and related natural dihydropyranocoumarins (−)-prantschimgin (**3**), (+)-decursinol (**4**), and (+)-marmesin (**5**) were achieved for the first time using catalytic asymmetric epoxidation of an enone as the key step. Catalytic asymmetric epoxidation of the enone was effectively promoted by the novel multifunctional asymmetric catalyst generated from La(O-*i*-Pr)$_3$, BINOL, and $Ph_3As{=}O$ in a 1:1:1 ratio to afford epoxide in 94% yield and 96% ee, which was recrystallized to give optically pure epoxide. After conversion to the common key intermediate (−)-peucedanol (**7**), all natural dihydropyranocoumarins were synthesized through palladium-catalyzed intramolecular C–O coupling reactions. A possible reaction mechanism of the catalytic asymmetric epoxidation of enones is also described based on X-ray analysis, laser desorption/ionization time-of-flight mass spectrometry, kinetic studies, and asymmetric amplification studies.

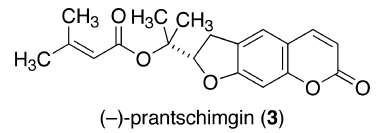
1. Introduction

(+)-Decursin (**1**) is a dihydropyranocoumarin first isolated from *Angelica decursiva* Fr. et Sav[1a] and then from the root of *Angelica gigas* Nakai (Umbelliferae),[1b] which is a traditional medicine for anemia and other disorders in Korea.[2] Other related natural dihydropyranocoumarins (+)-decursinol angelate (**2**), (−)-prantschimgin (**3**), (+)-decursinol (**4**), and (−)-marmesin (**5**), were also identified in *A. gigas* (Fig. 1). Decursin (**1**) and decursinol angelate (**2**) have recently attracted considerable attention due to their remarkable biological activities.[3] They exhibit cytotoxicity against various human cancer cell lines more strongly than against normal fibroblasts.[4] This cytotoxic activity is thought to be related to protein kinase C (PKC) activation. PKC has a major role in intracellular signal transduction cascades and is intimately involved in the regulation of a variety of cellular functions such as gene expression, cellular growth, and differentiation.[5] In addition, PKC activation is thought to be an important step in tumor promotion because PKC is the intracellular receptor of strong tumor promoter phorbol esters. Not all PKC activators are tumor promoters, however, for example, the potent anticancer drugs bryostatins.[6] Recent studies revealed that the cytotoxic and PKC activating properties of **1** were similar to those of bryostatins.[6a,7] Moreover, **1** has a simple structure among the known exogenous PKC activators. These profiles make it an attractive lead compound for drug discovery and as a biological tool for clarification of the PKC activation mechanism.

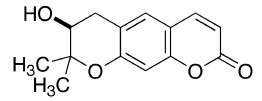
Racemic syntheses of **1** and related dihydropyranocoumarins were reported by Steck using oxidative



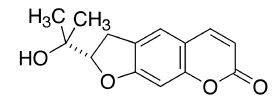
(+)-decursin (**1**): R^1=H, R^2=CH_3
(+)-decursinol angelate (**2**): R^1=CH_3, R^2=H



(−)-prantschimgin (**3**)



(+)-decursinol (**4**)



(+)-marmesin (**5**)

Figure 1. Structure of (+)-decursin (**1**), (+)-decursinol angelate (**2**), (−)-prantschimgin (**3**), (+)-decursinol (**4**), and (+)-marmesin (**5**).

Keywords: asymmetric catalysis; epoxidation of enone; decursin.
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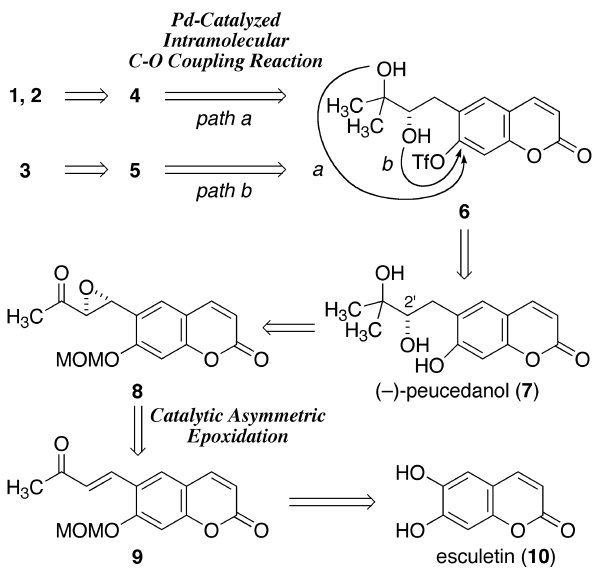
0040–4020/$ - see front matter © 2003 Elsevier Ltd. All rights reserved.
doi:10.1016/S0040-4020(03)00861-5

cyclization[8a] and by Murray et al. using an intramolecular epoxide opening reaction.[8b] In 2000, we achieved enantioselective total syntheses of **1**, **3**, **4**, and **5** using catalytic asymmetric epoxidation of an enone (96% ee) as the key step.[9] Later, enantioselective total syntheses using Jacobsen's epoxidation as the key step were reported independently by Han et al. (92% ee for **1**, **2**, and **4**)[10a] and Kim et al. (97% ee for **1**).[10b] Herein, we present a full account of our efforts towards the enantioselective total syntheses of **1** and related dihydropyranocoumarins including further studies on the catalytic asymmetric epoxidation mechanism.

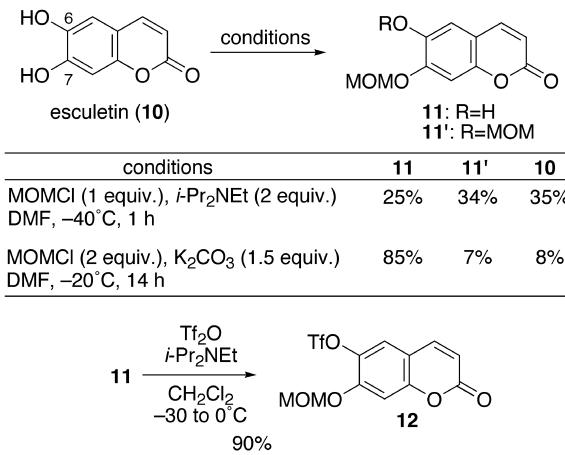
2. Results and discussion

For synthesis, we chose a strategy based on the regioselective palladium-catalyzed intramolecular C–O coupling reaction[11] to construct the dihydropyran ring for **1**, **2**, and **4** (*path a*) and the dihydrofuran ring for **3** and **5** (*path b*) (Scheme 1). This strategy allowed us to synthesize all natural compounds from the same intermediate (−)-peucedanol (**7**). The triol **7** can be synthesized by catalytic asymmetric epoxidation of enone **9** followed by methylation. Although there are many methods for constructing the chiral center at the C-2′ position, this method should be the most effective. For example, Sharpless asymmetric epoxidation of *tert*-allylic alcohol[12] and asymmetric hydrogenation of α-substituted enone[13] do not proceed very well.

Our synthesis started with selective protection of the C-7 phenol of commercially available esculetin (**10**) as the MOM ether.[14] Based on the difference in acidity between C-6 and C-7 phenol, the C-7 phenol can be selectively protected.[15] Although the organic base promoted overprotection to give the diMOM compound **11′** as a major product even at −40°C, selective protection was achieved using an inorganic base. After investigation of inorganic base (Li_2CO_3, Na_2CO_3, and K_2CO_3), the amount of reagents, and reaction temperature, the desired compound



Scheme 1. Retrosynthetic analysis.



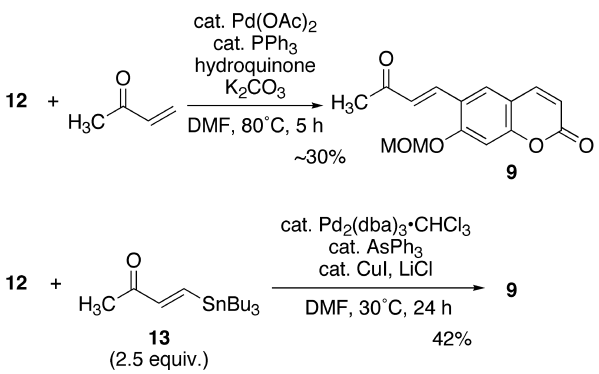
conditions	11	11′	10
MOMCl (1 equiv.), *i*-Pr_2NEt (2 equiv.) DMF, –40°C, 1 h	25%	34%	35%
MOMCl (2 equiv.), K_2CO_3 (1.5 equiv.) DMF, –20°C, 14 h	85%	7%	8%

Scheme 2.

11 was obtained in 85% yield under the conditions described in Scheme 2. Subsequent conversion of the other phenol to the triflate afforded **12**.

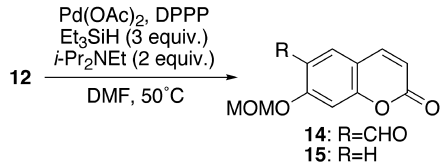
To introduce the enone moiety, we investigated several palladium-catalyzed reactions. First, we performed a Heck reaction of **12** with methyl vinyl ketone. Unfortunately, even after intensive investigation of the reaction conditions the desired enone **9** was obtained in only 30% yield with many by-products. We next performed a Stille coupling reaction of **12** with the tin reagent **13**. Isolated yield of enone **9** was improved to 42%, however, this reaction required 25 mol% of the palladium catalyst and 2.5 equiv. of toxic tin reagent **13** (Scheme 3).

We thus turned our attention to palladium-catalyzed formylation of triflate **12**. In contrast to the absence of a reaction when using the standard reductant Bu_3SnH[16] under CO at atmospheric pressure, Et_3SiH was an efficient reductant (Table 1). Under CO at atmospheric pressure, a mixture of the desired aldehyde **14** (30%) and by-product **15** (68%) were obtained (entry 1). This indicated that insertion of CO was slower than transmetalation at atmospheric pressure. Although slow addition of Et_3SiH did not improve the reaction, high-pressure (15 atm) effectively accelerated CO insertion to afford aldehyde **14** in 82% yield (entry 2). Moreover, catalyst loading was reduced to 5 mol% (entry 4). The Wittig reaction of **14** afforded an 11:1 isomeric mixture of (*E*)- and (*Z*)-enone **9** (94%). These isomers were separated by silica gel column chromatography and (*Z*)-**9**



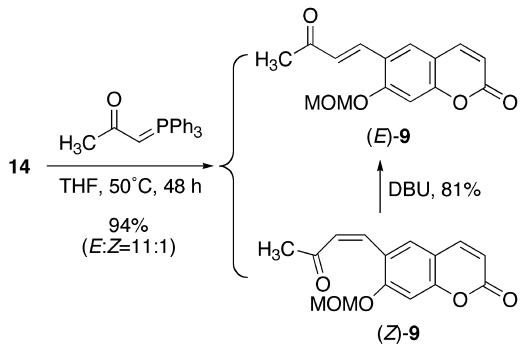
Scheme 3.

Table 1. Palladium-catalyzed formylation



Entry	Amount (mol%)		CO (atm)	Time (h)	Yield (%)	
	$Pd(OAc)_2$	DPPP			**9**	**15**
1[a]	20	30	1	3	30	68
2	20	30	15	2	82	–
3	10	15	15	5	78	–
4	5	7.5	15	5	71	–

[a] 1.5 equiv. of Et_3SiH were used.



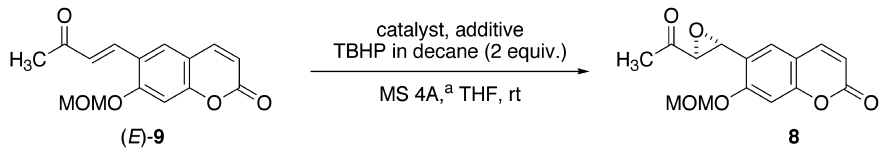
Scheme 4.

was successfully isomerized to the desired (*E*)-**9** by treatment with DBU (81%) (Scheme 4).

With large quantities of pure enone (*E*)-**9**, we then focused on the catalytic asymmetric epoxidation of enone (*E*)-**9**.[17] Preliminary survey 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 4A, provided undesirable results (almost no reaction). Despite the above-mentioned negative factors in epoxidation, we expected that by using the multifunctional asymmetric catalyst developed by our group[18,19] 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 expected, Yb–BINOL (1:1) complex[19] catalyzed the asymmetric epoxidation of (*E*)-**9** to afford epoxyketone **8**[20] (88, 83% ee) (Table 2, entry 3). After optimization of the reaction conditions, the La–BINOL complex with triphenylphosphine oxide[19d] or triphenylarsine oxide[21] were highly effective for catalytic asymmetric epoxidation. In terms of atom economy, the best result was obtained using 1 equiv. of triphenylarsine oxide to La(O-*i*-Pr)$_3$[22]–BINOL (94, 96% ee, entry 12). A single recrystallization of 96% ee epoxide **8** from hexane–acetone afforded epoxide **8** in 76% purified yield with greater than 99% ee.

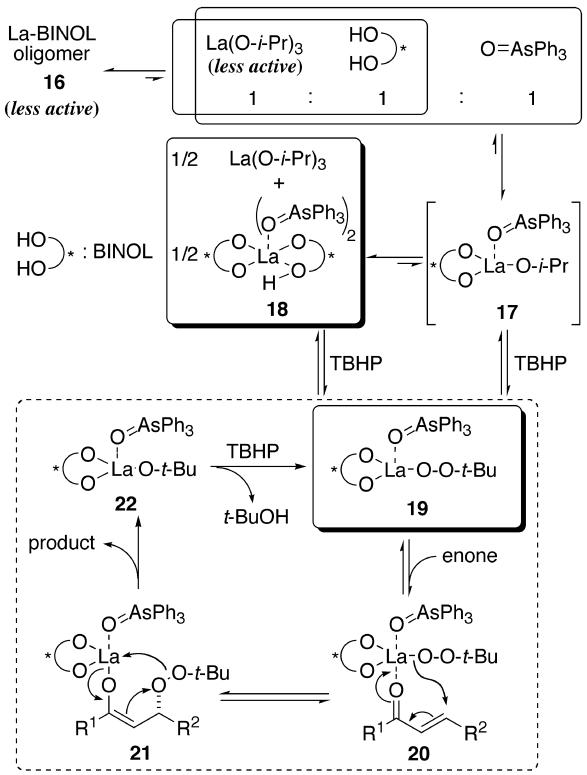
The asymmetric catalyst Ln–BINOL–$Ph_3As{=}O$ complex generated in a ratio of 1:1:1 was quite effective for catalytic asymmetric epoxidation of not only enone[21] but also α,β-unsaturated imidazolide[23] and α.β-unsaturated amide[24] with high substrate generality. The structure of the active catalyst and reaction mechanism was clarified by X-ray analysis, laser desorption/ionization time-of-flight mass spectrometry, kinetic studies, and asymmetric amplification studies.[21] The proposed mechanism of the epoxidation is shown in Scheme 5. Our observation suggests that alkali-metal free Ln–BINOL complex **16** exists as an oligomer and oxygen-containing ligands such as $Ph_3As{=}O$ make it a monomeric complex. In the complex solution generated from La(O-*i*-Pr)$_3$, BINOL, and $Ph_3As{=}O$ in the best ratio (1:1:1), the monomeric La–BINOL–$Ph_3As{=}O$ (1:2:2) complex **18** is formed as the major complex with 1 equiv. of excess La(O-*i*-Pr)$_3$. The excess La(O-*i*-Pr)$_3$ reacts with TBHP and also **18** to afford the most active and effective catalyst La–BINOL–$Ph_3As{=}O$ (1:1:1) **19**. Excess La(O-*i*-Pr)$_3$ might facilitate the transformation of **18** to **19**.[25]

Table 2. Catalytic asymmetric epoxidation of enone (*E*)-**9** using Ln–BINOL complexes[a]

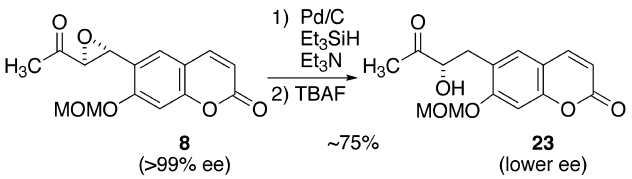


Entry	Catalyst (mol%)	Additives (mol%)	Time (h)	Yield (%)	ee (%)
1	La(O-*i*-Pr)$_3$ (10)	–	24	Trace	–
2	La(O-*i*-Pr)$_3$ (10)	$Ph_3As{=}O$ (10)	18	Trace	–
3[b]	Yb–(*R*)-BINOL (1:1) (25)	–	15	88	83
4	La–(*R*)-BINOL (1:1) (25)	–	25	28	20
5	La–(*R*)-BINOL (1:1) (25)	$Ph_3P{=}O$ (100)	2.5	98	97
6	La–(*R*)-BINOL (1:1) (25)	$Ph_3P{=}O$ (75)	4	91	97
7	La–(*R*)-BINOL (1:1) (25)	$Ph_3P{=}O$ (50)	4	82	93
8	La–(*R*)-BINOL (1:1) (25)	$Ph_3P{=}O$ (25)	4	89	91
9	La–(*R*)-BINOL (1:1) (25)	$Ph_3As{=}O$ (100)	25	55	75
10	La–(*R*)-BINOL (1:1) (25)	$Ph_3As{=}O$ (75)	12	56	91
11	La–(*R*)-BINOL (1:1) (25)	$Ph_3As{=}O$ (50)	6	88	95
12	La–(*R*)-BINOL (1:1) (25)	$Ph_3As{=}O$ (25)	2	94	96
13	La–(*R*)-BINOL (1:1) (10)	$Ph_3As{=}O$ (10)	5	90	93

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

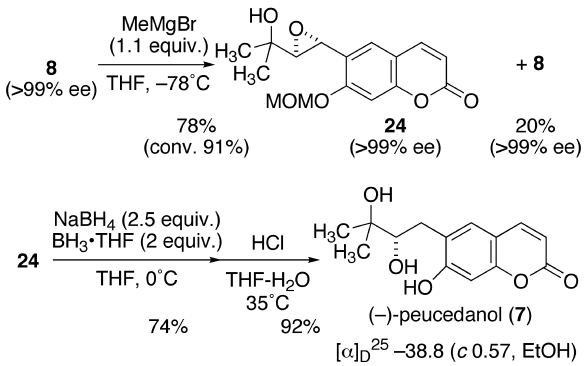


Scheme 5.



Scheme 6.

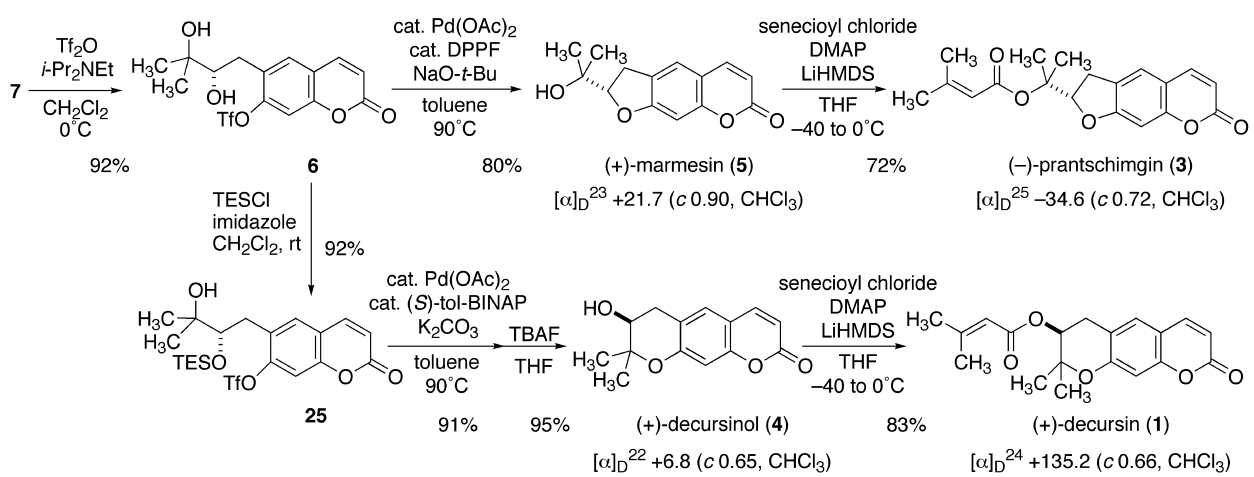
To convert epoxide **8** to (−)-peucedanol (**7**), we first examined the reductive epoxide opening reaction and the following methylation of ketone. Due to the chemoselective problems with the aluminum hydride reagent, we chose palladium-catalyzed reductive epoxide opening reactions. Under a H_2 atmosphere, reduction of both the epoxide and C-3–C-4 double bond proceeded. In contrast, Et_3SiH was a good hydride source and, after several examinations of palladium catalyst, solvent, and additive, the desired reduction proceeded smoothly with catalytic amounts of Pd–C, Et_3SiH, and Et_3N in CH_2Cl_2. Partial racemization occurred under the reaction conditions (Scheme 6).



Scheme 7.

Thus, we examined methylation of ketone prior to the reductive epoxide opening reaction. MeLi and MeLi–$CeCl_3$ gave unsatisfactory results (half conversion and no reaction, respectively). On the other hand, methylation using MeMgBr proceeded very cleanly to afford tertiary alcohol **24** in 78% yield (91% yield based on the recovery of starting material **8**) without loss of optical purity.[26] Subsequent regioselective reduction was achieved with $NaBH_4$ in the presence of BH_3·THF[27] in 74% yield rather than palladium-catalyzed reduction (less reactive). Finally, removal of the MOM group provided the common intermediate (−)-peucedanol (**7**) in 92% yield (Scheme 7).

Completion of the total syntheses was now possible (Scheme 8). Selective transformation of the phenolic hydroxyl group to the triflate provided substrate **6**. With the use of 10 mol% of $Pd(OAc)_2$, 20 mol% of DPPF, and NaO–*t*-Bu, the 5-membered ring product (+)-marmesin (**5**) was obtained exclusively in 80% yield. We then examined the Pd-catalyzed direct 6-membered ring formation using diol **6** under a variety of reaction conditions. In all cases, however, only the 5-membered ring product **5** was obtained. Thus, the secondary hydroxyl group was first protected with a TES group. Cyclization of the mono-protected substrate



Scheme 8.

25 proceeded in 91% yield using 10 mol% of $Pd(OAc)_2$, 12 mol% of (*S*)-tol-BINAP, and K_2CO_3 ((*R*)-tol-BINAP had lower reactivity). After removal of the TES group, (+)-decursinol (**4**) was obtained. Finally, esterification of (+)-marmesin (**5**) and (+)-decursinol (**4**) resulted in the first asymmetric total syntheses of (−)-prantschimgin (**3**) and (+)-decursin (**1**), respectively.[28] The enantiomeric excesses of **4** and **25** were confirmed using chiral stationary phase HPLC analysis.

3. Conclusions

Enantioselective total syntheses of natural dihydropyranocoumarins (+)-decursin (**1**), (−)-prantschimgin (**3**), (+)-decursinol (**4**), and (+)-marmesin (**5**) were achieved from the same intermediate (−)-peucedanol (**7**). **7** was synthesized in an optically pure form by catalytic asymmetric epoxidation of enone **9** using La(O-*i*-Pr)$_3$, BINOL, and $Ph_3As{=}O$ in the best ratio (1:1:1). Although there are several methodologies for catalytic asymmetric epoxidation of enones,[17,29] only a few applications for total synthesis have been reported.[30] There are no published examples of the use of an enolizable enone as a substrate.

4. Experimental

4.1. General

Infrared (IR) spectra were recorded on a JASCO FT/IR 410 Fourier transform infrared spectrophotometer. NMR spectra were recorded on a JEOL JNM-LA500 spectrometer, operating at 500 MHz for ^{1}H NMR and 125.65 MHz for ^{13}C NMR. Chemical shifts in $CDCl_3$ were reported downfield from TMS (=0 ppm) for ^{1}H NMR. For ^{13}C NMR, chemical shifts were reported downfield from TMS (=0 ppm) or on the scale relative to $CHCl_3$ (77.00 ppm for ^{13}C NMR) as an internal reference. Chemical shifts in DMSO-d_6 were reported on the scale relative to DMSO (2.50 ppm for ^{1}H NMR and 39.5 ppm for ^{13}C NMR). Chemical shifts in acetone-d_6 were reported on the scale relative to acetone (2.04 ppm for ^{1}H NMR and 206.0 ppm for ^{13}C NMR). Optical rotations were measured on a JASCO P-1010 polarimeter. EI mass spectra were measured on a JEOL JMS-DX303 or JMS-BU20 GCmate. LDI TOF mass spectra were measured on a Shimadzu MALDI IV. Column chromatography was performed with silica gel Merck 60 (230–400 mesh ASTM). The enantiomeric excess (ee) was determined by HPLC analysis. HPLC was performed on JASCO HPLC systems consisting of the following: pump, 880-PU or PU-980; detector, 875-UV or UV-970, measured at 254 or 280 nm; column, DAICEL CHIRALPAK AD, DAICELCHIRALCEL OD, DAICEL CHIRALPAK AS; mobile phase, hexane–2-propanol or EtOH–2-propanol; flow rate, 0.30–1.25 mL/min. Reactions were performed in dry solvents under an argon atmosphere, unless otherwise stated. Tetrahydrofuran (THF) was distilled from sodium benzophenone ketyl. La(O-*i*-Pr)$_3$ and Yb(O-*i*-Pr)$_3$ were purchased from Kojundo Chemical Laboratory Co., LTD. Other reagents were purified by the usual methods.

4.1.1. 6-Hydroxy-7-(methoxymethoxy)chromen-2-one (11).

Methoxymethyl chloride (0.443 mL, 5.84 mmol) was added to a stirred suspension of esculetin (**10**) (520.5 mg, 2.92 mmol) and potassium carbonate (605 mg, 4.38 mmol) in DMF (14.6 mL) at −20°C. After stirring for 13 h at the same temperature, the reaction mixture was diluted with water (10 mL) and then 1N aqueous HCl was added at 0°C until the yellow solution turned clear. The resulting solution was extracted with ethyl acetate (3×20 mL) and washed successively with water. The combined aqueous layers were extracted with ether (2×30 mL). The combined organic layers were then washed with brine (20 mL), dried over Na_2SO_4, and evaporated in vacuo. The residue was purified by flash column chromatography (SiO_2, hexane–ethyl acetate 9:2 to 2:1) to give MOM ether **11** (555.3 mg 85%) as a yellow solid. IR (KBr) ν 3157, 1686, 1558, 1287, 1142 cm^{-1}; ^{1}H NMR (DMSO-d_6) δ 3.41 (s, 3H), 5.28 (s, 2H), 6.27 (d, J=9.5 Hz, 1H), 7.05 (s, 1H), 7.06 (s, 1H), 7.91 (d, J=9.5 Hz, 1H), 9.49 (s, 1H); ^{13}C NMR (DMSO-d_6) δ 56.0, 94.6, 103.5, 112.7, 112.7, 113.3, 144.1, 144.3, 147.7, 148.5, 160.5; MS *m*/*z* 222 [M$^+$]; HRMS (M$^+$) calcd for $C_{11}H_{10}O_5$: 222.0528. Found 222.0532.

4.1.2. 7-(Methoxymethoxy)-6-(trifluoromethanesulfonyl)chromen-2-one (12).

Diisopropylethylamine (0.261 mL, 1.5 mmol) was added to an ice-cold suspension of MOM ether **11** (114.4 mg, 0.497 mmol) in CH_2Cl_2 (5 mL) and the mixture was stirred for 10 min at 0°C. After the solution was cooled to −30°C, trifluoromethansulfonic anhydride (0.126 mL, 0.75 mmol) was added dropwise. The reaction mixture was stirred for 2 h at 0°C and then saturated aqueous sodium hydrogencarbonate (10 mL) was added. The aqueous layer was extracted with CH_2Cl_2 (2×10 mL). The combined organic layers were washed with brine and dried over Na_2SO_4. After concentration in vacuo, the residue was purified by flash column chromatography (SiO_2, hexane–ethyl acetate 8:1) to give **12** (158 mg, 90%) as a white solid. IR (KBr) ν 1743, 1624, 1426, 1214, 1131, 937 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 3.54 (s, 3H), 5.33 (s, 2H), 6.38 (d, J=9.5 Hz, 1H), 7.27 (s, 1H), 7.37 (s, 1H), 7.63 (d, J=9.5 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 56.9, 95.4, 104.7, 112.6, 115.5, 118.7 (q, 320 Hz), 120.8, 135.5, 142.0, 151.9, 154.3, 159.8; MS *m*/*z* 354 [M$^+$]. Anal. calcd for $C_{12}H_9F_3O_7S$: C, 40.68; H, 2.56. Found: C, 40.84; H, 2.78.

4.1.3. 6-Formyl-7-(methoxymethyl)chromen-2-one (14).

A solution of **12** (70.8 mg, 0.2 mmol), $Pd(OAc)_2$ (4.5 mg, 0.02 mmol), DPPP (12.4 mg, 0.03 mmol), and triethylsilane (0.096 mL, 0.6 mmol) in DMF (2 mL) was stirred for 5 h at 60°C under a CO atmosphere (15 atm). The reaction mixture was poured into water (10 mL) and extracted with ethyl acetate (2×20 mL). The combined organic layers were washed with water (4×10 mL) and brine (10 mL), then dried over Na_2SO_4 and evaporated in vacuo. The residue was purified by flash column chromatography (SiO_2, hexane–ethyl acetate 5:1) to give **14** (36.5 mg, 78%) as a white solid. Moreover, **14** was obtained in 82% yield when 20 mol% of $Pd(OAc)_2$ was used. IR (KBr) ν 1734, 1672, 1608, 1377, 1128, 1077, 971 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 3.55 (s, 3H), 3.57 (s, 2H), 6.35 (d, J=9.5 Hz, 1H), 7.16 (s, 1H), 7.69 (d, J=9.5 Hz, 1H), 8.01 (s, 1H), 10.45 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 56.9, 95.0, 103.1, 113.4, 115.1, 122.6, 128.8, 143.2, 159.2, 159.7, 161.8, 187.8; MS *m*/*z* 234 [M$^+$]; HRMS (M$^+$) calcd for $C_{12}H_{10}O_5$ 234.0528. Found 234.0532.

4.1.4. 7-(Methoxymethoxy)-6-[(*E*)-3-oxo-1-butenyl]-chromen-2-one ((*E*)-9). A solution of **14** (106.4 mg, 0.454 mmol) and 1-triphenylphosphoranylidene-2-propanone (180.8 mg, 0.568 mmol) in THF (4.5 mL) was stirred for 50 h at 60°C. After the reaction mixture was cooled to room temperature, water (10 mL) was added, and the solution was extracted with ethyl acetate (3×15 mL), 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 2.5:1) to give enone **9** (116.6 mg, 94%) as a mixture of *E* and *Z* isomers (11:1). The *E* isomer (11.3 mg, 0.0412 mmol) was separated by flash column chromatography (SiO_2, hexane–ethyl acetate 4:1) and isomerized by treating with DBU (0.3 mL) in CH_2Cl_2 (2.7 mL) at 40°C for 2 days. After the reaction was quenched by the addition of saturated aqueous ammonium chloride (10 mL), the aqueous layer was extracted with CH_2Cl_2 (2×5 mL), the combined organic layers were washed with brine (5 mL), dried over Na_2SO_4, and evaporated in vacuo. The residue was purified by flash column chromatography (SiO_2, hexane–ethyl acetate 4:1) to give (*E*)-**9** (9.2 mg, 81%) as a yellow solid. IR (KBr) ν 1739, 1665, 1618, 1384, 1168, 1134, 959 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.40 (s, 3H), 3.52 (s, 3H), 5.33 (s, 2H), 6.32 (d, *J*=9.5 Hz, 1H), 6.77 (d, *J*=16.5 Hz, 1H), 7.14 (s, 1H), 7.65 (d, *J*=9.5 Hz, 1H), 7.66 (s, 1H), 7.83 (d, *J*=16.5 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 27.6, 56.7, 94.9, 102.9, 113.4, 114.7, 121.4, 127.2, 128.3, 136.6, 142.9, 156.6, 158.6, 160.3, 198.3; MS *m*/*z* 274 [M^+]. Anal. calcd for $C_{15}H_{14}O_5$: C, 65.69; H, 5.15. Found: C, 65.42; H, 5.22.

4.1.5. 6-[(1*R*,2*S*)-1,2-Epoxy-3-oxobutyl]-7-(methoxymethyl)chromen-2-one (8). La(O-*i*-Pr)$_3$ (0.125 mL, 0.025 mmol, 0.2 M solution in THF) was added to a mixture of (*R*)-BINOL (7.2 mg, 0.025 mmol), triphenylarsine oxide (8.1 mg, 0.025 mmol) and MS 4A (250 mg; MS 4A was not dried (1000 mg/mmol of starting material)) in dry THF (3.4 mL) at room temperature and the mixture was stirred for 1 h, and then TBHP (0.1 mL, 0.5 mmol, 5 M solution in decane) was added. After stirring for 30 min, enone (*E*)-**9** (68.5 mg, 0.25 mmol) was added directly and the mixture was stirred at room temperature. After 5 h, the reaction was quenched by the addition of 2.5% aqueous citric 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 with Na_2SO_4. After concentration in vacuo, the residue was purified by flash column chromatography (SiO_2, hexane–ethyl acetate 4:1) to give epoxy ketone **8** (65.0 mg, 90%, 93% ee) as a white solid. The enantiomeric excess of this product was determined by chiral stationary-phase HPLC analysis (DAICEL CHIRALCEL AD, *i*-PrOH–hexane 1:9, flow rate 1.0 mL/min, t_R 28.4 min (1*S*,2*R*)-isomer and 36.0 min (1*R*,2*S*)-isomer, detection at 254 nm). The enantiomeric excess of epoxy ketone was increased by recrystallization. Acetone was added to a suspension of **8** (148 mg, 93% ee) in hexane (12 mL) at 50°C until **8** was completely dissolved into the solvent. The solution was cooled slowly and maintained at room temperature. A total of 6 mL of hexane was added. After 24 h, optically pure **8** was obtained as a needle-like crystal (113 mg, 76%, >99% ee). IR (KBr) ν 1736, 1716, 1625, 1379, 1132, 961 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.22 (s, 3H), 3.38 (d, *J*=1.8 Hz, 1H), 3.50 (s, 3H), 4.33 (d, *J*=1.8 Hz, 1H), 5.28 (d, *J*=8.0 Hz, 1H), 5.29 (d, *J*=8.0 Hz, 1H), 6.30 (d, *J*=9.5 Hz, 1H), 7.10 (s, 1H), 7.28 (s, 1H), 7.61 (d, *J*=9.5 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 24.8, 53.1, 56.5, 62.8, 94.7, 102.2, 113.1, 114.2, 121.7, 124.4, 142.9, 155.4, 158.2, 160.4, 203.8; MS *m*/*z* 290 [M^+]; $[\alpha]_D^{22}$=+1.9 (*c* 1.0 $CHCl_3$(>99% ee)). Anal. calcd for $C_{15}H_{14}O_6$: C, 62.07; H, 4.86. Found: C, 61.94; H, 4.98.

4.1.6. 6-[(1*R*,2*S*)-1,2-Epoxy-3-hydroxy-3-methylbutyl]-7-(methoxymethoxy)chromen-2-one (24). MeMgBr (0.893 mL, 0.757 mmol, 0.848 M solution in THF) was added to a stirred solution of dry **8** (200 mg, 0.689 mmol, >99% ee) in THF (13.8 mL) over 5 min at −78°C. The reaction mixture was stirred for 15 min and then quenched by the addition of saturated aqueous ammonium chloride (10 mL). The mixture was extracted with ethyl acetate (2×15 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 2:1) to give **24** (160.5 mg, 76%) as a colorless oil and the recovered starting material (40.7 mg, 20%). The enantiomeric excess of the product was determined by chiral stationary-phase HPLC analysis (DAICEL CHIRALCEL AD, *i*-PrOH–hexane 1:9, flow rate 0.5 mL/min, t_R 13.5 min (1*R*,2*S*)-isomer and 16.6 min (1*S*,2*R*)-isomer) after conversion of the hydroxyl group into trimethylsilyl ether. IR (neat) ν 3460, 2973, 1730, 1623, 1376, 1274, 1155, 1130, 1073, 973 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.35 (s, 3H), 1.40 (s, 3H), 1.90 (s, 1H), 2.86 (d, *J*=2.1 Hz, 1H), 3.50 (s, 3H), 4.26 (d, *J*=2.1 Hz, 1H), 5.28 (d, *J*=10.7 Hz, 1H), 5.30 (d, *J*=10.7 Hz, 1H), 6.28 (d, *J*=9.5 Hz, 1H), 7.07 (s, 1H), 7.31 (s, 1H), 7.61 (d, *J*=9.5 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 24.9, 27.7, 51.0, 56.4, 67.9, 68.5, 94.5, 101.9, 113.1, 114.1, 123.9, 124.4, 143.1, 155.1, 157.9, 160.8; MS *m*/*z* 306 [M^+]; $[\alpha]_D^{22}$=−31.3 (*c* 0.83 $CHCl_3$(>99% ee)); HRMS (M^+) calcd for $C_{16}H_{18}O_6$ 306.1103. Found 306.1115.

4.1.7. 6-[(2*S*)-2,3-Dihydroxy-3-methylbutyl]-7-(methoxymethoxy)chromen-2-one. BH_3·THF complex (0.216 mL, 0.234 mmol, 1.08 M solution in THF) was added to a stirred suspension of sodium borohydride (11 mg, 0.293 mmol) in THF (4 mL) at 0°C. The resulting mixture was stirred for 10 min and then a THF solution of **24** (36 mg, 0.117 mmol, 1.2 mL) was added to the reaction mixture at the same temperature. After stirring for 1 h, the reaction mixture was diluted with ethyl acetate (5 mL) and then saturated aqueous ammonium chloride (5 mL) was added. The aqueous layer was extracted with ethyl acetate (10 mL×2), and the combined organic layers were washed with brine (5 mL) and dried over Na_2SO_4. After concentration in vacuo, the residue was purified by flash column chromatography (SiO_2, hexane–ethyl acetate 4:5) to give diol (26.8 mg, 74%) as a white solid. IR (KBr) ν 3267, 2979, 1730, 1619, 1165, 1132, 1090, 1064, 976 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.29 (s, 3H), 1.33 (s, 3H), 2.08 (s, 1H), 2.28 (d, *J*=4.0 Hz, 1H), 2.57 (dd, *J*=10.4, 14.1 Hz, 1H), 3.03 (dd, *J*=1.9, 14.1 Hz, 1H), 3.50 (s, 3H), 3.65 (ddd, *J*=1.9, 10.4, 14.1 Hz, 1H), 5.27 (s, 2H), 6.26 (d, *J*=9.5 Hz, 1H), 7.07 (s, 1H), 7.34 (s, 1H), 7.62 (d, *J*=9.5 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 23.6, 26.4, 32.7, 56.5, 72.9, 77.8, 94.7, 102.1, 113.0, 113.8, 125.4, 129.7, 143.2, 154.5, 158.1, 161.1; MS *m*/*z* 308 [M^+]; $[\alpha]_D^{22}$=−55.1 (*c*

0.76 $CHCl_3$). Anal. calcd for $C_{16}H_{20}O_6$: C, 62.33; H, 6.54. Found: C, 62.10; H, 6.55.

4.1.8. (−)-Peucedanol (7). Concentrated HCl (0.5 mL) was added to a stirred solution of the diol (27.2 mg, 0.088 mmol) in THF (2.2 mL) and water (1.7 mL) at 35°C and the reaction mixture was stirred for 17 h at the same temperature. After cooling to room temperature, the resulting mixture was extracted with CH_2Cl_2 (5 mL×2), washed with brine (5 mL), and dried over Na_2SO_4. After concentration in vacuo, the residue was purified by flash column chromatography (SiO_2, MeOH–CH_2Cl_2 1:40) to give (−)-peucedanol (**7**) (21.4 mg, 92%) as a white solid. IR (KBr) ν 3385, 2976, 1708, 1628, 1577, 1387, 1147 cm^{-1}; ^1H NMR (acetone-d_6) δ 1.24 (s 3H), 1.25 (s, 3H), 2.68 (dd, J=10.1, 14.4 Hz, 1H), 2.79 (s(b), 2H), 3.02 (dd, J=1.8, 14.4 Hz, 1H), 3.65 (dd, J=1.8, 10.1 Hz, 1H), 6.13 (d, J=9.5 Hz, 1H), 6.71 (s, 1H), 7.41 (s, 1H), 7.81 (d, J=9.5 Hz, 1H) (phenolic proton was not observed in acetone-d_6); ^{13}C NMR (acetone-d_6) δ 25.5, 25.6, 33.9, 72.8, 80.4, 103.9, 112.8, 113.0, 125.9, 131.4, 144.7, 155.7, 160.9, 161.3; MS m/z 264 [M^+]; $[\alpha]_D^{25}$=−38.8 (c 0.57 EtOH). Anal. calcd for $C_{14}H_{16}O_5$: C, 63.63; H, 6.10. Found: C, 63.70; H, 6.31.

4.1.9. 6-[(2*S*)-2,3-Dihydroxy-3-methylbutyl]-7-(trifluoromethanesulfonyl)chromen-2-one (6). Trifluoromethansulfonic anhydride (0.05 mL, 0.297 mmol) was added dropwise to an ice-cold solution of **7** (70.5 mg, 0.267 mmol) and diisopropylethylamine (0.116 mL, 0.667 mmol) in CH_2Cl_2 (7.5 mL) and the mixture was stirred for 10 min at the same temperature. After the reaction was quenched by the addition of saturated aqueous sodium hydrogen carbonate (5 mL), the aqueous layer was extracted with CH_2Cl_2 (2×5 mL), and the combined organic layers were washed with brine (5 mL), dried over Na_2SO_4, and evaporated in vacuo. The residue was purified by flash column chromatography (SiO_2, hexane–ethyl acetate 1:1) to give **6** (97.5 mg, 92%) as a white solid. IR (KBr) ν 3497, 3402, 1698, 1426, 1248, 1223, 1137, 887 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.30 (s, 3H), 1.35 (s, 3H), 1.80 (s, 1H), 2.29 (d, J=4.6 Hz, 1H), 2.70 (dd, J=11.0, 14.3 Hz, 1H), 3.05 (dd, J=1.6, 14.3 Hz, 1H), 3.65 (ddd, J=1.6, 4.6, 11.0 Hz, 1H), 6.47 (d, J=9.5 Hz, 1H), 7.29 (s, 1H), 7.62 (s, 1H), 7.68 (d, J=9.5 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 23.5, 26.6, 31.9, 73.0, 77.4, 110.2, 117.8, 118.5 (q, 320 Hz), 118.6, 129.0, 131.4, 142.3, 149.5, 153.0, 159.5; MS m/z 396 [M^+]; $[\alpha]_D^{23}$=−17.3 (c 0.53 $CHCl_3$). Anal. calcd for $C_{15}H_{15}F_3O_7S$: C, 45.46; H, 3.81. Found: C, 45.21; H, 3.79.

4.1.10. (+)-Marmesin (5). Na(O-*t*-Bu) (0.415 mL, 0.196 mmol, 0.427 M solution in THF) was added to a stirred solution of **6** (51.7 mg, 0.1305 mmol), $Pd(OAc)_2$ (2.94 mg, 0.01 31 mmol), and DPPF (14.5 mg, 0.0262 mmol) in toluene (3 mL) at room temperature. After stirring for 1 h at 90°C, the reaction mixture was then poured into water (5 mL), the aqueous layer was extracted with ethyl acetate (2×10 mL), and the combined organic layers were washed with brine (10 mL), dried over Na_2SO_4, and evaporated in vacuo. The residue was purified by flash column chromatography (SiO_2, hexane–ethyl acetate 2:1) to give (+)-marmesin (**5**) (25.6 mg, 80%) as a white solid. IR (KBr) ν 3480, 2979, 1704, 1631, 1572, 1269, 1138, 962, 948 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.24 (s, 3H), 1.37 (s, 3H), 1.83 (s, 1H), 3.19 (dd, J=9.5, 15.9 Hz, 1H), 3.25 (dd, J=8.3, 15.9 Hz, 1H), 4.74 (dd, J=8.3, 9.5 Hz, 1H), 6.21 (d, J=9.5 Hz, 1H), 6.73 (s, 1H), 7.22 (s, 1H), 7.59 (d, J=9.5 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 24.3, 26.1, 29.5, 71.6, 91.1, 97.9, 112.2, 112.7, 123.4, 125.1, 143.7, 155.6, 161.4, 163.1; MS m/z 246 [M^+]; $[\alpha]_D^{23}$=+21.7 (c 0.9 $CHCl_3$) (lit.[20b] ($[\alpha]_D^{23}$=+20.3). Anal. calcd for $C_{14}H_{14}O_4$: C, 68.28; H, 5.73. Found: C, 68.01; H, 5.89.

4.1.11. (−)-Prantschimgin (3). LiHMDS (0.05 mL, 0.05 mmol, 1 M solution in THF) was added to a stirred solution of **5** (9.9 mg, 0.04 mmol), and DMAP (12.2 mg, 0.1 mmol) in THF (1 mL) at −40°C. After the reaction mixture was stirred for 15 min at the same temperature, senecioyl chloride (0.022 mL, 0.2 mmol) was added. The stirred solution was warmed to room temperature for 2 h and then quenched by the addition of saturated aqueous sodium hydrogen carbonate (1 mL). After dilution with ethyl acetate (2 mL), the aqueous layer was extracted with ethyl acetate (2×4 mL), and the combined organic layers were washed with brine (4 mL) and dried over Na_2SO_4. After concentration in vacuo, the residue was purified by flash column chromatography (SiO_2, hexane–ethyl acetate 5:1 to 2:1) to give (−)-prantschimgin (**3**) (9.5 mg, 72%) as a white solid. IR (KBr) ν 2922, 1717, 1706, 1626, 1267, 1228, 1123 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.53 (s, 3H), 1.60 (s, 3H), 1.85 (d, J=1.2 Hz, 3H), 2.10 (d, J=1.2 Hz, 3H), 3.23 (m, 2H), 5.14 (dd, J=8.0, 9.5 Hz, 1H), 5.55 (t, J=1.2 Hz, 1H), 6.21 (d, J=9.5 Hz, 1H), 6.74 (s, 1H), 7.21 (s, 1H), 7.59 (d, J=9.5 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 20.1, 21.3, 22.3, 27.4, 29.6, 81.3, 88.7, 98.0, 112.3, 112.7, 117.0, 123.2, 124.6, 143.6, 155.8, 156.6, 161.4, 163.5, 165.8; MS m/z 328 [M^+]; $[\alpha]_D^{25}$=−34.6 (c 0.72 $CHCl_3$); HRMS (M^+) calcd for $C_{19}H_{20}O_5$ 328.1311. Found 328.1315.

4.1.12. 6-[(2*S*)-3-Hydroxy-3-methyl-2-(triethylsilyloxy)-butyl]-7-(trifluoromethanesulfonyl)chromen-2-one (25). Chlorotriethylsilane (0.017 mL, 0.102 mmol) was added to an ice-cold solution of **6** (13.5 mg, 0.034 mmol) and imidazole (9.3 mg, 0.136 mmol) in CH_2Cl_2 (1.2 mL). The reaction mixture was stirred for 12 h at room temperature and then saturated aqueous sodium hydrogen carbonate (2 mL) was added. The aqueous layer was extracted with CH_2Cl_2 (2×4 mL), the combined organic layers were washed with brine (4 mL) and dried over Na_2SO_4. After concentration in vacuo, the residue was purified by flash column chromatography (SiO_2, hexane–ethyl acetate 5:1) to give **25** (15.9 mg, 92%) as a colorless oil. The enantiomeric excess of this product was determined by chiral stationary-phase HPLC analysis (DAICEL CHIRALCEL OD, *i*-PrOH–hexane 2:98, flow rate 0.3 mL/min, t_R 25.0 min (2*R*)-isomer and 26.9 min (2*S*)-isomer). IR (KBr) ν 3495, 2958, 2879, 1748, 1425, 1218, 1140, 1101, 1065, 880 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.19–0.35 (m, 6H), 0.79 (t, J=7.9 Hz, 9H), 1.25 (s, 3H), 1.26 (s, 3H), 1.90 (s, 1H), 2.69 (dd, J=10.1, 14.0 Hz, 1H), 3.11 (dd, J=2.5, 14.0 Hz, 1H), 3.80 (dd, J=2.5, 10.1 Hz, 1H), 6.49 (d, J=9.5 Hz, 1H), 7.31 (s, 1H), 7.47 (s, 1H), 7.67 (d, J=9.5 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 5.0 (×3), 6.8 (×3), 24.3, 26.3, 33.7, 73.0, 79.3, 110.1, 118.0, 118.3, 118.6 (J=320 Hz), 129.2, 132.1, 141.8, 149.7, 153.0, 159.4; MS m/z 481 [$M^+-CH_2CH_3$]; $[\alpha]_D^{22}$=−18.2 (c 0.79

$CHCl_3$(>99% ee)). Anal. calcd for $C_{15}H_{15}F_3O_7S$: C, 45.46; H, 3.81. Found: C, 45.21; H, 3.79.

4.1.13. (*S*)-7,8-Dihydro-8,8-dimethyl-7-triethylsilyloxy-6*H*-pyrano[3,2-*g*]chromen-2-one. A solution of **25** (22.3 mg, 0.0437 mmol), $Pd(OAc)_2$ (1.00 mg, 0.00437 mmol), (*S*)-tol-BINAP (3.56 mg, 0.00524 mmol), and K_2CO_3 (9.0 mg, 0.0655 mmol) in toluene (1.5 mL) was stirred for 16 h at 80°C. After cooling to room temperature, the reaction mixture was poured into H_2O (3 mL), and the aqueous layer was extracted with ethyl acetate (2×5 mL). The combined organic layers were washed with brine (5 mL), dried over Na_2SO_4, and evaporated in vacuo. The residue was purified by flash column chromatography (SiO_2, hexane–ethyl acetate 15:1) to give triethylsilyl ether (14.3 mg, 91%) as a white solid. IR (KBr) ν 3422, 2956, 1737, 1627, 1561, 1458, 1389, 1299, 1116 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.64 (q, J=8.0 Hz, 6H), 0.97 (t, J=8.0 Hz, 9H), 1.24 (s, 3H), 1.40 (s, 3H), 2.75 (dd, J=8.9, 16.2 Hz, 1H), 2.94 (dd, J=5.2, 16.2 Hz, 1H), 3.84 (dd, J=5.2, 8.9 Hz, 1H), 6.20 (d, J=9.5 Hz, 1H), 6.74 (s, 1H), 7.13 (s, 1H), 7.57 (d, J=9.5 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 5.0 (×3), 6.8 (×3), 20.0, 26.2, 31.7, 70.0, 78.6, 104.5, 112.5, 113.0, 117.8, 128.4, 143.2, 154.2, 156.7, 161.4; MS m/z 360 [M^+]; $[\alpha]_D^{22}$=+110.0 (c 1.6 $CHCl_3$). Anal. calcd for $C_{20}H_{28}O_4Si$: C, 66.63; H, 7.83. Found: C, 66.90; H, 7.91.

4.1.14. (+)-Decursinol (4). Tetrabutylammonium fluoride (0.05 mL, 0.05 mmol, 1 M solution in THF) was added to a stirred solution of the triethylsilyl ether (6.3 mg, 0.0175 mmol) in THF (1 mL) at room temperature. After stirring for 10 min, the reaction mixture was quenched by the addition of saturated aqueous ammonium chloride (1 mL). The aqueous layer was extracted with ethyl acetate (3 mL×2), and the combined organic layers were washed with brine (3 mL) and dried over Na_2SO_4. After concentration in vacuo, the residue was purified by flash column chromatography (SiO_2, hexane–ethyl acetate 2:1) to give (+)-decursinol (**4**) (4.1 mg, 95%) as a white solid. The enantiomeric excess of this product was determined by chiral stationary-phase HPLC analysis (DAICEL CHIRALCEL AD, *i*-PrOH–hexane 1:9, flow rate 1.0 mL/min, t_R 26.5 min (*S*)-isomer and 34.9 min (*R*)-isomer). IR (KBr) ν 3452, 1703, 1628, 1562, 1392, 1141, 1072, 821 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.37 (s, 3H), 1.39 (s, 3H), 1.98 (s, 1H), 2.84 (dd, J=5.8, 17.1 Hz, 1H), 3.11 (dd, J=4.6, 17.1 Hz, 1H), 3.87 (dd(b), J=4.6, 5.8 Hz, 1H), 6.22 (d, J=9.5 Hz, 1H), 6.78 (s, 1H), 7.18 (s, 1H), 7.57 (d, J=9.5 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 22.1, 25.0, 30.7, 69.2, 78.2, 104.8, 113.0, 113.3, 116.4, 129.0, 143.1, 154.2, 156.5, 161.3; MS m/z 246 [M^+]; $[\alpha]_D^{22}$=+6.8 (c 0.65 $CHCl_3$(>99% ee)) (lit.[20a] $[\alpha]_D^{26}$=+10.8). Anal. calcd for $C_{14}H_{14}O_4$: C, 68.28; H, 5.73. Found: C, 68.11; H, 6.02.

4.1.15. (+)-Decursin (7). Decursin (**7**) was obtained from (+)-decursinol (**4**) (4.2 mg, 0.017 mmol) and senecioyl chloride in the same manner as (−)-plantschimgin. (+)-Decursin (4.6 mg, 83%) was obtained as a colorless oil. IR (neat) ν 2981, 2933, 1731, 1627, 1565, 1391, 1299, 1281, 1227, 1135 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.36 (s, 3H), 1.38 (s, 3H), 1.88 (d, J=1.0 Hz, 3H), 2.14 (d, J=1.0 Hz, 3H), 2.86 (dd, J=4.9, 17.1 Hz, 1H), 3.19 (dd, J=4.6, 17.1 Hz, 1H), 5.08 (dd, J=4.6, 4.9 Hz, 1H), 5.66 (s(b), 1H), 6.22 (d, J=9.5 Hz, 1H), 6.79 (s, 1H), 7.14 (s, 1H), 7.57 (d, J=9.5 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 20.4, 23.2, 25.0, 27.5, 27.9, 69.2, 76.8, 104.7, 112.8, 113.3, 115.6, 116.0, 128.7, 143.1, 154.2, 156.5, 158.5, 161.3, 165.8; MS m/z 328 [M^+]; $[\alpha]_D^{24}$=+135.2 (c 0.66 $CHCl_3$) (lit.[4a] $[\alpha]_D^{15}$=+172.9); HRMS (M^+) calcd for $C_{19}H_{20}O_5$ 328.1311. Found 328.1317.

Acknowledgements

Financial support was provided by CREST, The Japan Science and Technology Corporation (JST), and RFTF of Japan Society for the Promotion of Science.

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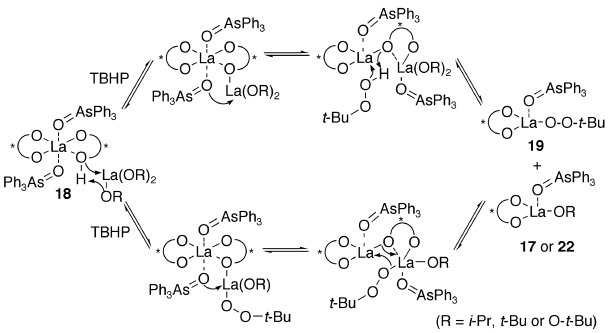

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