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Formal total synthesis of (+)-wortmannin using catalytic asymmetric intramolecular aldol condensation reaction

Hiroki Shigehisa, Takashi Mizutani, Shin-ya Tosaki, Takashi Ohshima* and Masakatsu Shibasaki*

Graduate School of Pharmaceutical Sciences, The University of Tokyo, Hongo, Bunkyo-ku, Tokyo 113-0033, Japan

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Abstract—A catalytic process for the synthesis of optically active C4-substituted tetrahydroindandiones using an asymmetric intramolecular aldol condensation reaction was developed. When 30 mol% of phenylalanine and 50 mol% of pyridinium *p*-toluenesulfonate were used under highly concentrated conditions, a variety of C4-substituted tetrahydroindandiones and octahydronaphthalenediones were obtained in high yield (up to 89% yield) and high enantiomeric excess (up to 94% ee). One of the products was successfully transformed into the key intermediate for the synthesis of the phosphatidylinositol 3-kinase inhibitor wortmannin, achieving formal total synthesis of (+)-wortmannin.

1. Introduction

Phosphatidylinositol 3-kinase (PI 3-kinase) is an important enzyme that functions in signal transduction pathways, and its inhibitors are often used as a biological tool in cell molecular biology.[1] These agents have contributed greatly to studies of intracellular signaling pathways in diabetes and cancer research. Wortmannin (**1**) was isolated from *Penicillium wortmanniii*[2] and *Myrothecium roridium*[3] as an antifungal antibiotic, and later determined to be a potent and specific covalent inhibitor of PI 3-kinase (Fig. 1).[4–6] In addition, it has potent inhibitory activity on smooth muscle light chain kinase,[7] anti-inflammatory activity comparable to that of indomethacin,[8,9] and other biological activities.[10,11]

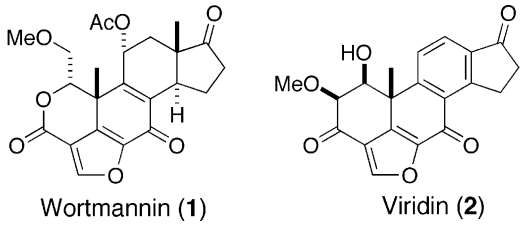
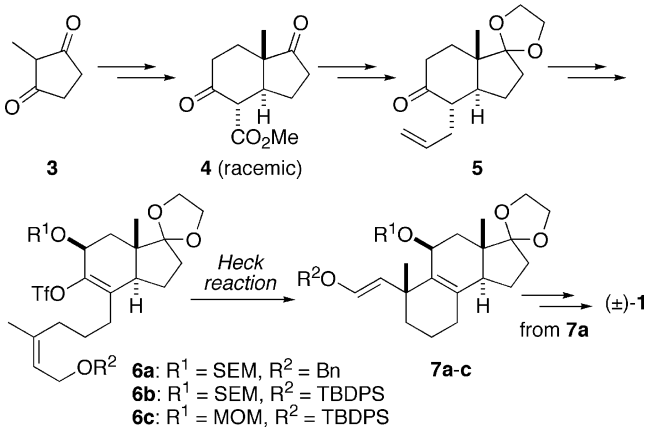


Figure 1. Structures of wortmannin (**1**) and viridin (**2**).

The challenging molecular structure of **1** (a bisallylic quaternary carbon center and a highly reactive furanocyclohexadienone lactone unit on the steroid backbone)[3,12,13] coupled with its exciting biological actions, prompted us to attempt its total synthesis. In 1996, we succeeded in the first chemical synthesis of **1** from hydrocortisone.[14] Later, the first direct total synthesis of (±)-**1** from simple cyclic diketone **3** was also achieved by our group using an intramolecular Heck reaction of **6a** and a diosphenol Claisen rearrangement as key steps (Scheme 1).[15] Recently, Sorensen and co-workers reported a racemic total synthesis of the related natural product viridin (**2**), using rhodium-catalyzed cyclotrimerization, a



Scheme 1.

Keywords: Enantioselective synthesis; (+)-Wortmannin; Intramolecular aldol condensation reaction.
* Corresponding authors. Tel.: +81 3 5684 0651; fax: +81 3 5684 5206; e-mail: mshibasa@mol.f.u-tokyo.ac.jp

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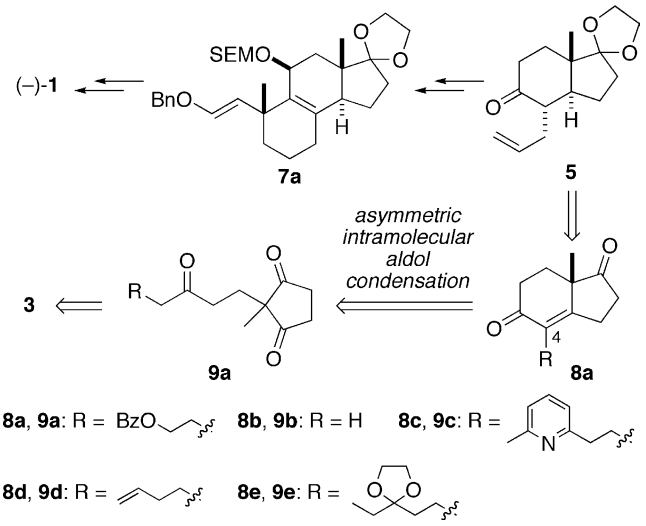
thermal electrocyclic rearrangement, and Donohoe dihydroxylation.[16]

From a medicinal viewpoint, syntheses of optically active wortmannin (**1**) as well as its derivatives, which possess more potent inhibitory activity and have less toxicity, are highly desirable for the development of new antitumor drugs. Other than our chemical transformation from (+)-hydrocortisone, asymmetric synthesis of **1** has not been reported, and a new versatile and direct method for the asymmetric synthesis of **1** is in high demand. To address this issue, we previously examined a kinetic resolution using an asymmetric Heck reaction of **6** with several chiral ligands.[17] All trials of this strategy, unfortunately, resulted in low chemical yield although the enantiomeric excess of **7c** was excellent. These unsatisfactory results[18] led us to search for a more direct route to optically active **7a**, namely an asymmetric intramolecular aldol condensation reaction of triketone **9a** to **8a** (Scheme 2).



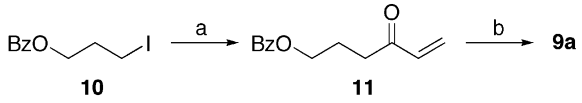
Scheme 2.

The asymmetric intramolecular aldol condensation reaction is one of the most powerful methods to synthesize the tetrahydroindandione skeleton corresponding to the steroidal C-D ring. In the early-to-mid 1970s, Hajos et al.[19] and Wiechart et al.[20] independently developed an asymmetric intramolecular aldol condensation reaction using a catalytic amount of proline to provide C4-unsubstituted tetrahydroindandione **8b** (R=H).[21] Recently, this proline-catalyzed asymmetric reaction was successfully extended to several intermolecular reactions such as the direct aldol reaction.[22] On the other hand, the use of stoichiometric amounts of amino acids is indispensable to construct C4-substituted tetrahydroindandione. Danishefsky et al. reported asymmetric synthesis of C4-substituted tetrahydroindandione **8c**, which was utilized for the total synthesis of estrone and 19-norsteroids, using 1.2 equiv of L-phenylalanine and 0.5 equiv of 1 N $HClO_4$ (82% yield, 86% ee).[23] Tsuji et al. reported similar conditions (1 equiv of L-phenylalanine and 0.4 equiv of 1 N $HClO_4$) for the synthesis of **8d** (85% yield, 76% ee), which was utilized for the total synthesis of (+)-19-nortestosterone.[24] Corey et al. also reported the asymmetric synthesis of the protostenediols synthetic intermediate **8e**, in which 50 mol% of camphorsulfonic acid was used instead of 1 N $HClO_4$ with 1 equiv of L-phenylalanine (77% yield, 95% ee).[25] These stoichiometric reactions prompted us to develop a more atom economical catalytic process for the synthesis of C4-substituted tetrahydroindandione **8**. Herein, we describe the catalytic asymmetric intramolecular aldol reaction of triketone **9** to **8** with broad substrate generality. The concentrations, additive, and sonication were very important to improve the reactivity of the reaction. Moreover, the product **8a** was successfully converted to key intermediates **5** and **7a**, achieving formal total synthesis of (+)-wortmannin.

2. Results and discussion

2.1. Catalytic asymmetric intramolecular aldol condensation reaction

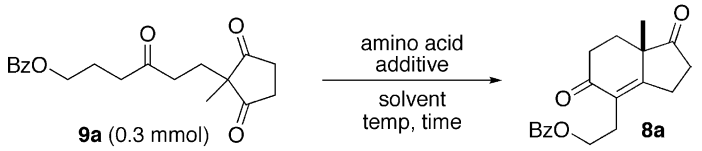
The substrate **9a** for the aldol condensation was synthesized in the following two steps (i) a palladium coupling reaction of the alkylzinc prepared from **10**[26] with acryloyl chloride, and (ii) a Michael reaction of diketone **3** to **10** (53% yield for two steps) (Scheme 3).



Scheme 3. Reagents and conditions: (a) Zn–Cu, THF, reflux, then $Pd(OAc)_2$ (1 mol%), PPh_3 (2.5 mol%), acryloyl chloride, 0 °C to rt; (b) **3**, NEt_3 (30 mol%), DMF, 0 °C to rt, 53% for two steps.

As a preliminary experiment, Danishefsky's condition was first applied to the substrate **9a** and the desired product **8a** was obtained in 47% yield and 58% ee (Table 1, Entry 1). We first screened a variety of natural and synthetic amino acids, including proline (Entry 2), and phenylalanine was best in terms of total efficiency. Next, we investigated additive effects. By changing the additive from $HClO_4$ to pyridinium *p*-toluenesulfonate (PPTS), the reactivity was greatly improved to afford **8a** in 78% yield within 10 h (Entry 3). Enantioselectivity was also improved to 75% ee. The use of other pyridinium salt derivatives of *p*-toluenesulfonic acid, such as salts of picoline, lutidine, collidine, and 2,6-di-*tert*-butyl-4-methylpyridine, did not improve the results. The effects of concentration were then examined. Highly concentrated conditions improved not only the chemical yield but also the enantioselectivity (Entries 4 to 6). The best yield was obtained under solvent free conditions (Entry 6, 90% yield, 83% ee). Although Swaminathan et al. previously reported a solvent-free asymmetric aldol condensation of **9f** (R=Me) using L-phenylalanine and *d*-camphorsulfonic acid, in their case phenylalanine did not work as a catalyst (59% yield and 79% ee using 1 equiv of phenylalanine).[27] Under this solvent free condition, however, there was some difficulty performing the reaction due to the high viscosity of the medium. The addition of 1 equiv of DMSO solved this problem and gave better selectivity (Entry 7). This optimized condition was effective for the catalytic process,

Table 1.



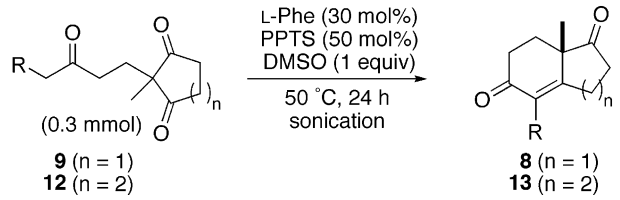
Entry	Amino acid (mol%)	Additive (mol%)	Solvent	Temp (°C)	Time (h)	Yield (%)	ee (%)
1	L-Phe (100)	1 N $HClO_4$ (50)	CH_3CN (0.5 M)	80	168	47	58
2	L-Pro (100)	1 N $HClO_4$ (50)	CH_3CN (0.5 M)	80	168	13	38
3	L-Phe (100)	PPTS (100)	CH_3CN (0.5 M)	80	10	78	75
4	L-Phe (100)	PPTS (100)	CH_3CN (1.0 M)	80	10	80	78
5	L-Phe (100)	PPTS (100)	CH_3CN (2.0 M)	80	10	84	80
6	L-Phe (100)	PPTS (100)	—	80	10	90	83
7	L-Phe (100)	PPTS (100)	DMSO (1 equiv)	80	10	81	85
8	L-Phe (30)	PPTS (50)	DMSO (1 equiv)	60	8	78	86
9	L-Phe (30)	PPTS (50)	DMSO (1 equiv)	50	24	55	94
10[a]	L-Phe (30)	PPTS (50)	DMSO (1 equiv)	50	24	64	94
11[a,b]	L-Phe (30)	PPTS (50)	DMSO (1 equiv)	50	24	73	94

[a] Sonication was used.
[b] 58 mmol scale.

and using 30 mol% of the catalyst, **8a** was obtained in 78% yield and 86% ee (Entry 8). Moreover, the enantiomeric excess was increased to 94% at 50 °C although the chemical yield was moderate (Entry 9). The chemical yield was then improved to 64% using sonication (Entry 10). In addition, the chemical yield of **8a** was improved to 73% in large scale (58 mmol) without loss of enantiomeric excess (Entry 11). The fact that the reaction was performed under highly concentrated conditions with minimal waste makes this process desirable in terms of practicality and environmental consciousness. When L-phenylalanine was used as a catalyst, absolute configuration of the obtained product **8a** was determined to be the *S* configuration, as shown in Scheme 2, by chemical transformation to the known compound.[28]

After determining the optimized conditions, we examined the scope and limitations using a variety of triketones **9** ($n=1$) and **12** ($n=2$) (Table 2). The present catalytic

Table 2.



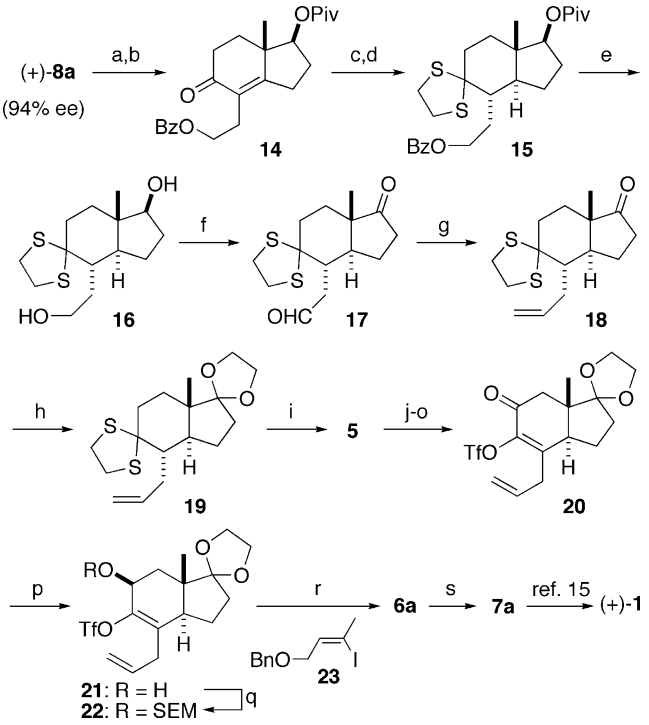
Entry	Substrate	Yield (%)	ee (%)
1	**9f**: R=Me, $n=1$	87	93[a]
2	**12f**: R=Me, $n=2$	83	87[a]
3	**9g**: R=Et, $n=1$	79	91
4	**12g**: R=Et, $n=2$	57	80
5	**9d**: R=$CH_2CH_2CH=CH_2$, $n=1$	69	90[a]
6	**9h**: R=$(CH_2)_3OBz$, $n=1$	65	91
7[b]	**9h**: R=$(CH_2)_3OBz$, $n=1$	89	90
8	**9b**: R=H, $n=1$	73	11[a]
9	**12b**: R=H, $n=2$	75	9[a]

[a] The absolute configuration was determined to be *S*.
[b] 3 mmol scale.

asymmetric process was applicable to the synthesis of various C4-substituted tetrahydroindandiones **8** and octahydronaphthalenediones **13** (Entries 1–7). As shown in entry 5, Tsuji's synthetic intermediate **8d** for (+)-19-nortestosterone was obtained in better enantimomeric excess (90% ee using 30 mol% of phenylalanine) compared to the original result (76% ee using 100 mol% of phenylalanine).[24] Furthermore, when **9h** was used as a substrate, scale effects were again observed without loss of enantiomeric excess (Entry 7). In the cases of **9b** and **12b** (R=H), suitable substrates for the proline-catalyzed reaction to provide C4-unsubstituted products **8b** and **13b**,[19,20] very low enantiomeric excess was obtained (Entries 8 and 9).

2.2. Formal total synthesis of (+)-wortmannin

We then focused on the transformation of tetrahydroindandione **8a** to the key intermediate of wortmannin synthesis (Scheme 4). Chemo- and stereoselective reduction of **8a** (94% ee) with $NaBH_4$ at low temperature and the following esterification of the resulting hydroxyl group with pivaloyl chloride gave **14** as a sole product. Next, we examined the conversion of **14** to *trans*-hydrindane.[29] Although Pd–C hydrogenation is a common method for this purpose, in our system the hydrogenation suffered from considerable over-reduction of the carbonyl group to methylene and low reproducibility. These problems were not overcome, even after intensive studies to examine the effects of altering temperature, solvent, and additive. The Ni boride reduction, previously utilized in a similar system by Molander et al., successfully promoted the selective reduction of enone **14** to *trans*-hydrindane in reasonable yield (ca. 50–60%).[28] After conversion of ketone to thioacetal (ca. 70–80%), the mixture of desired **15** and inseparable impurity derived from the Ni boride reduction was further purified by recrystallizaton to provide chemically and optically pure **15** (21% yield from **14**) as a white needle crystalline (mp 114–115 °C, $[\alpha]_D$ +17.9, $CHCl_3$). The reduction of **15** with $LiAlH_4$, Swern oxidation, and Wittig reaction of the resulting aldehyde using NaHMDS led to terminal alkene **18** in



Scheme 4. Reagents and conditions: (a) $NaBH_4$, EtOH, −78 °C, 92%; (b) PivCl, pyridine, DMAP (30 mol%), 0 °C to rt, 90%; (c) $NiCl_2 \cdot 6H_2O$, $NaBH_4$, MeOH, −78 °C; (d) ethanedithiol, $BF_3 \cdot Et_2O$ (30 mol%), CH_2Cl_2, 0 °C to rt, 21% for two steps after recrystallization (>99% ee); (e) $LiAlH_4$, THF, 0 °C to rt, 99%; (f) oxalyl chloride, DMSO, CH_2Cl_2, −78 to −40 °C, 91%; (g) CH_3PPh_3Br, NaHMDS, THF, −78 to 0 °C, 93%; (h) 2-ethyl-2-methyl-1,3-dioxolane, PTSA (10 mol%), rt, 78% (15% of **18** was recovered); (i) $PhI(CF_3CO_2)_2$, CH_3CN–H_2O, rt, 84%; (j) KHMDS, TMSCl, THF, −78 °C; (k) $KHCO_3$, mCPBA, CH_2Cl_2, −20 °C; (l) 1 N NH_4F, MeOH, 0 °C, 42% for three steps; (m) $Cu(OAc)_2$, MeOH, 0 °C to rt; (n) DBU, CH_2Cl_2, 0 °C; (o) Tf_2O, *i*-Pr_2NEt, CH_2Cl_2, −78 °C, 47% for three steps; (p) $NaBH_4$, $CeCl_3 \cdot 7H_2O$, MeOH, 0 °C, 65%; (q) SEMCl, 2,6-lutidine, TBAI (10 mol%), CH_2Cl_2, 40 °C, 87%; (r) 9-BBN, THF, 0 °C then **23**, K_3PO_4, $PdCl_2$(dppf) (3 mol%), THF–DMF, 60 °C, 64%; (s) $Pd(OAc)_2$ (10 mol%), DPPP (20 mol%), K_2CO_3, TBAB, toluene, 100 °C, 65% (α:β=1:18).

excellent yield. When KHMDS or *n*-BuLi was used instead of NaHDMS, the chemical yield was greatly decreased because of dimer formation through the intermolecular aldol reaction. Synthesis of the reported key intermediate **5** in an optically pure manner was completed by acetal formation under mild conditions using 2-ethyl-2-methyl-1,3-dioxolane, followed by transformation of thioacetal to ketone using freshly prepared [bis(trifluoroacetoxy)iodobenzene],[30] resulting in formal total synthesis of (+)-wortmannin (**1**). Compound **5** was further converted to the more advanced intermediate **7a** by following our racemic synthesis. Compound **5** was converted to enol triflate **20** through (i) α-hydroxylation of ketone, (ii) α-keto enol formation by Cu(II) oxidation and DBU treatment, and (iii) triflation of the resulting enol.[14] The subsequent Luche reduction of **20** provided allylic alcohol **21** (α:β=ca. 1:3, 64% yield of isolated β-isomer) and the following SEM-ether formation afforded compound **22**. After hydroboration of **22** with 9-BBN, a Suzuki–Miyaura cross coupling reaction was conducted with alkyl iodide **22** to provide **6a**. Finally, an intramolecular Heck reaction of **6a** gave the optically pure tricyclic intermediate **7a** ($[\alpha]_D$ +28.0, $CHCl_3$).

3. Conclusion

A versatile asymmetric catalysis for the synthesis of C4-substituted tetrahydroindandione **8** using catalytic amounts of L-phenylalanine and PPTS was developed. Furthermore, formal total synthesis of (+)-wortmannin was achieved.

4. Experimental

4.1. General

All reactions were performed under an argon atmosphere with dry solvents, unless otherwise stated. Reagents were purified by the usual methods. Reactions were monitored using thin-layer chromatography with silica gel Merck 60 (230–400 mesh ASTM). 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 ^1H NMR and 125.65 MHz for ^{13}C NMR and calibrated using residual undeuterated solvent as an internal reference. Optical rotation was measured on a JASCO P-1010 polarimeter. ESI mass spectra were measured on a Waters micromass ZQ with a Waters 2695 Separation Module (for LC-MS). HR-MS spectra were measured on a JEOL JMS-MS700V in positive ion mode.

4.2. Substrate synthesis for catalytic asymmetric intramolecular aldol condensation reaction

4.2.1. Synthesis of 9a. A suspension of **10** (50 g, 0.172 mol) and Zn–Cu (17 g, 0.259 mol) in THF (170 mL) was stirred under reflux conditions for 90 min, affording alkylzinc reagent. After cooling the reaction mixture to 0 °C, PPh_3 (386 mg, 4.31 mmol) and $Pd(OAc)_2$ (1.13 g, 1.72 mmol) were added. Acryloyl chloride (15.4 mL, 0.190 mol) was then slowly added to the mixture while maintaining the reaction temperature below 10 °C. After stirring for 90 min at room temperature, the reaction was quenched by the addition of saturated aqueous NH_4Cl solution, concentrated under reduced pressure, and extracted with AcOEt. The organic extract was washed with saturated aqueous $NaHCO_3$ and brine, dried over Na_2SO_4, and concentrated to give crude enone **11**. The slow addition of 2-methyl-1,3-cyclopentanedione (**3**) (13 g, 0.172 mol) to a stirred solution of the crude enone **11** and NEt_3 (7.2 mL, 51.7 mmol) in DMF (180 mL) maintained the reaction temperature below 10 °C (rapid addition of **3** promoted intramolecular aldol reaction to afford racemic **9a**). After stirring for 24 h at room temperature, the reaction was quenched by the slow addition of water while maintaining the temperature below 10 °C (rapid addition of water promoted the intramolecular aldol reaction). The mixture was then extracted with AcOEt and the organic extract was washed with water and brine, dried over Na_2SO_4, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (AcOEt–Hexane=1:3) to give **9a** (30.4 g, 53% for 2 steps) as a pale yellow oil. FT-IR (neat) ν_{max} 2962, 1718, 1681, 1616, 1601, 1584, 1452, 1402, 1315, 1274, 1176, 1115, 1070, 1026, 983, 916, 712, 687, 674 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 1.10 (s, 3H), 1.90 (t, 2H, J=7.1 Hz), 1.98–2.04 (m, 2H), 2.45 (t, 2H, J=7.1 Hz), 2.53 (t,

2H, J=7.1 Hz), 2.71–2.87 (m, 4H), 4.30 (t, 2H, J=6.2 Hz), 7.44 (t, 2H, J=7.6 Hz), 7.56 (br-dt, 1H), 8.01 (br-d, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 19.1, 22.7, 27.8, 34.7, 36.7, 39.1, 55.1, 64.0, 128.4, 130.2, 133.0, 166.5, 208.9, 215.7; MS [ESI(+)] m/z 353 ($M+Na^+$); HR-MS [FAB(+)] Calcd for $C_{19}H_{23}O_5^+$ ($M+H^+$): 331.1540; Found 331.1544.

4.2.2. Synthesis of 9g. Triketone **9g** was synthesized in 65% yield by an intermolecular Michael addition of **3** to 1-hexene-3-one, similar to **9a**. Pale yellow oil; FT-IR (neat) ν_{max} 2963, 2933, 1721, 1455, 1418, 1372, 1299, 1126, 1061, 993 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.83 (t, 3H, J=7.2 Hz), 1.05 (s, 3H), 1.45–1.53 (m, 2H), 1.83 (t, 2H, J=7.2 Hz), 2.28 (t, 2H, J=7.2 Hz), 2.37 (t, 2H, J=7.2 Hz), 2.64–2.86 (m, 4H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 13.5, 17.0, 19.0, 27.8, 34.6, 36.3, 44.7, 55.1, 210.2, 215.7; MS [ESI(+)] m/z 232 ($M+Na^+$); HR-MS [FAB(+)] Calcd for $C_{12}H_{19}O_3^+$ ($M+H^+$): 211.1329; Found 211.1331.

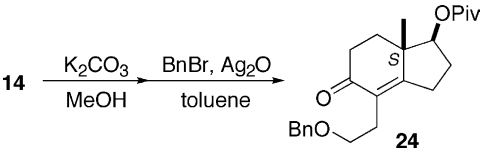
4.2.3. Synthesis of 12g. Triketone **12g** was synthesized in 73% yield by an intermolecular Michael addition of 2-methyl-1,3-cyclohexanedione to 1-hexene-3-one, similar to **9a**. Pale yellow oil; FT-IR (neat) ν_{max} 2962, 1694, 1457, 1024 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.77–0.82 (m, 3H), 1.14–1.15 (m, 3H), 1.43–1.51 (m, 2H), 1.77–2.00 (m, 4H), 2.20–2.28 (m, 4H), 2.51–2.69 (m, 4H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 13.5, 17.0, 17.4, 19.6, 29.5, 37.2, 37.6, 44.5, 64.2, 209.6, 209.9; MS [ESI(+)] m/z 247 ($M+Na^+$); HR-MS [FAB(+)] Calcd for $C_{13}H_{21}O_3^+$ ($M+H^+$): 225.1485; Found 225.1495.

4.2.4. Synthesis of 9h. Triketone **9h** was synthesized similar to **9a**. Starting from 4-iodobutyl benzoate,[31] an I/Zn exchange reaction followed by a palladium-catalyzed coupling reaction with acryloyl chloride afforded the corresponding enone in 52% yield as a colorless oil. FT-IR (neat) ν_{max} 2954, 1717, 1682, 1276, 1116, 713 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.76–1.79 (m, 4H), 2.53–2.56 (m, 2H), 4.30–4.34 (m, 2H), 5.82 (d, 1H, J=10.4 Hz), 6.22 (d, 1H, J=17.7 Hz), 6.35 (dd, 1H, J=10.4, 17.7 Hz), 7.43 (t, 2H, J=7.4 Hz), 7.55 (t, 1H, J=7.4 Hz), 8.03 (d, 2H, J=7.4 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 20.3, 28.2, 38.9, 64.5, 128.1, 128.3, 129.5, 130.3, 132.8, 136.4, 166.6, 200.2; MS [ESI(+)] m/z 255($M+Na^+$). Then, intermolecular Michael addition of **3** to the enone gave **9h** in 80% yield as a white powder. Mp 58–59 °C; FT-IR (neat) ν_{max} 2931, 1718, 1282, 710 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.10 (s, 3H), 1.65–1.77 (m, 4H), 1.90 (t, 2H, J=7.2 Hz), 2.39–2.46 (q, 4H, J=7.3 Hz), 2.71–2.89 (m, 4H), 4.31 (t, 2H, J=6.3 Hz), 7.44 (t, 2H, J=7.4 Hz), 7.56 (t, 1H, J=7.4 Hz), 8.03 (d, 2H, J=7.4 Hz); ^{13}C NMR (125 MHz, $CDCl_3$)) δ 19.2, 20.0, 27.8, 28.1, 34.7, 36.5, 42.2, 55.1, 64.5, 128.3, 129.5, 130.3, 132.8, 166.6, 209.6, 215.8; MS [ESI(+)] m/z 367 ($M+Na^+$); HR-MS [FAB(+)] Calcd for $C_{20}H_{25}O_5^+$ ($M+H^+$): 345.1702; Found 345.1711.

Triketones **9b**,[32] **12b**,[32] **9f**,[33] **12f**,[34] and **9b**[24] are other known compounds.

4.3. Catalytic asymmetric intramolecular aldol condensation reaction

4.3.1. General procedure. A mixture of **9a** (19.0 g, 57.5 mmol), L-phenylalanine (2.84 g, 17.2 mmol), PPTS (7.2 g, 28.8 mmol), and DMSO (4.4 mL, 57.5 mmol) was stirred at room temperature for 1 min and then sonicated at 50 °C for 24 h. The reaction mixture was diluted with AcOEt, poured into saturated aqueous $NaHCO_3$ solution, and extracted with AcOEt. The organic extract was washed with brine, dried over Na_2SO_4, and concentrated under reduced pressure. The residue was purified by flash silica gel column chromatography (AcOEt–hexane=1:3) to give **8a** (11.6 g, 73%, 94% ee) as a pale yellow oil. $[\alpha]_D^{25}$ +180.8 (c 0.52, $CHCl_3$, 94% ee) FT-IR (neat) ν_{max} 2963, 1744, 1716, 1664, 1600, 1451, 1354, 1314, 1273, 1174, 1114, 1070, 1025, 713 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.23 (s, 3H), 1.83 (td, 1H, J=6.0, 13.4 Hz), 2.06 (ddd, 1H, J=2, 5, 13.4 Hz), 2.15–2.23 (m, 1H), 2.49–2.57 (m, 2H), 2.60–2.69 (m, 1H), 2.71–2.81 (m, 3H), 2.99 (ddd, 1H, J=2, 13, 17.2 Hz), 4.38–4.45 (m, 2H), 7.43 (t, 2H, J=7.6 Hz), 7.56 (br-dt, 1H), 7.97 (br-dd, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 21.1, 24.6, 25.4, 28.7, 32.8, 35.5, 49.0, 63.1, 128.5, 129.4, 130.0, 130.1, 133.1, 165.2, 166.4, 197.1, 217.0; MS [ESI(+)] m/z 335 ($M+Na^+$); HR-MS [FAB(+)] Calcd for $C_{19}H_{21}O_4^+$ ($M+H^+$): 313.1434; Found 313.1448. The enantiomeric excess was determined by chiral stationary-phase HPLC analysis [DAICEL CHIRALPAK AD-H, i-PrOH/Hexane 1/9, flow rate 1.0 mL/min, t_R 16.0 min for (R)-isomer and t_R 18.5 min for (S)-isomer, detected at 254 nm]. The absolute configuration of **8a** was determined to be S by transformation to the known compound **24**[28] via **14**, as shown below. $[\alpha]_D^{25}$ +11.4 (c 1.02, $CHCl_3$, 94% ee); Reported data: $[\alpha]_D^{25}$ −11.6 (c 1.03, $CHCl_3$, >99% ee) for the R isomer.



4.3.2. Data for 8g.[35] White powder; $[\alpha]_D^{23}$ +135.1 (c 1.96, $CHCl_3$, 86% ee) FT-IR (neat) ν_{max} 2963, 2672, 1711, 1666, 1606, 1460, 1422, 1358, 1336, 1306, 1262, 1239, 1202, 1161, 1143, 1114, 1065, 1015, 945, 884, 859, 832, 729 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.95 (t, 3H, J=7.4 Hz), 1.28 (s, 3H), 1.82 (dt, 1H, J=5.8, 13.7 Hz), 2.04–2.07 (m, 1H), 2.27 (q, 2H, J=7.4 Hz), 2.37–2.84 (m, 3H), 2.88–2.95 (m, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 13.5, 18.5, 21.2, 24.0, 28.7, 32.9, 35.5, 48.7, 135.9, 162.1, 197.3, 217.7; MS [ESI(+)] m/z 215 ($M+Na^+$); HR-MS [FAB(+)] Calcd for $C_{12}H_{17}O_2^+$ ($M+H^+$): 193.1229; Found 193.1232. The enantiomeric excess was determined by chiral stationary-phase HPLC analysis [DAICEL CHIRALPAK OJ-H, i-PrOH/Hexane 1:9, flow rate 1.0 mL/min, t_R 12.8 min for minor isomer and t_R 14.3 min for major isomer, detected at 254 nm].

4.3.3. Data for 13g. White powder; $[\alpha]_D^{23}$ +58.8 (c 1.15, $CHCl_3$, 75% ee) FT-IR (neat) ν_{max} 2966, 2932, 2872, 1744, 1664, 1448, 1371, 1354, 1311, 1260, 1173, 1120, 1058, 1009, 902, 853, 748 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.90–0.94 (dt, 3H), 1.43 (s, 3H), 1.58 (d, 1H, J=2 Hz), 1.69–1.76 (m, 1H), 2.02–2.19 (m, 3H), 2.34 (m, 2H), 2.41–2.53 (m, 3H), 2.65–2.72 (m, 1H), 2.90 (br-dt, 1H); ^{13}C NMR

(125 MHz, $CDCl_3$) δ 14.0, 18.8, 22.3, 23.5, 26.6, 29.5, 33.6, 37.3, 50.8, 136.9, 158.0, 197.3, 212.1; MS [ESI(+)] *m/z* 229 ($M+Na^+$); HR-MS [FAB(+)] Calcd for $C_{13}H_{19}O_2^+$ ($M+H^+$): 207.1385; Found 207.1384. The enantiomeric excess was determined by chiral stationary-phase HPLC analysis [DAICEL CHIRALPAK OJ-H, *i*-PrOH/Hexane 1:9, flow rate 1.0 mL/min, t_R 10.4 min for minor isomer and t_R 11.5 min for major isomer, detected at 254 nm].

4.3.4. Data for 8h. Pale yellow oil; $[\alpha]_D^{23}$ +153 (*c* 1.10, $CHCl_3$, 86% ee) FT-IR (KBr) ν_{max} 2960, 1745, 1716, 1664, 1275, 1116, 715 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 1.27 (s, 3H), 1.81 (dd, 1H, *J*=5.8, 13.8 Hz), 1.84–1.91 (m, 2H), 2.07 (ddd, 1H, *J*=2.1, 5.2, 13.4 Hz), 2.34–2.60 (m, 5H), 2.72 (dd, 1H, *J*=2.8, 10.8 Hz), 2.77–2.84 (m, 1H), 2.94 (dd, 1H, *J*=2.8, 17.1 Hz), 4.29 (t, 2H, *J*=7.4 Hz), 7.45 (t, 2H, *J*=7.4 Hz), 7.57 (t, 1H, *J*=7.4 Hz), 8.04 (d, 2H, *J*=7.4 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 21.2, 21.9, 24.3, 27.7, 28.9, 32.9, 35.5, 48.9, 64.3, 128.4, 129.5, 130.2, 132.9, 133.1, 163.6, 166.5, 197.3, 217.2; MS [ESI(+)] *m/z* 335 ($M+Na^+$); HR-MS [FAB(+)] Calcd for $C_{20}H_{23}O_4^+$ ($M+H^+$): 327.1597; Found 327.1583. The enantiomeric excess was determined by chiral stationary-phase HPLC analysis [DAICEL CHIRALPAK AD-H, *i*-PrOH/Hexane 1:9, flow rate 1.0 mL/min, t_R 20.1 min for major isomer and t_R 22.8 min for minor isomer, detected at 254 nm].

Other products shown in Table 2 are known compounds and the absolute configuration of those compounds was determined to be *S* by comparison of optical rotation.[27]

4.3.5. HPLC analysis of 8b, 13b, 8f, 13f, and 8d. *Compound* **8b**. The enantiomeric excess was determined by chiral stationary-phase HPLC analysis [DAICEL CHIRALPAK AD-H, *i*-PrOH/Hexane 1:50, flow rate 1.0 mL/min, t_R 30.0 min for (*R*)-isomer and t_R 34.9 min for (*S*)-isomer, detected at 254 nm].

Compound **13b**. The enantiomeric excess was determined by chiral stationary-phase HPLC analysis [DAICEL CHIRALPAK OD-H, *i*-PrOH/Hexane 1:50, flow rate 1.0 mL/min, t_R 25.8 min for (*R*)-isomer and t_R 28.6 min for (*S*)-isomer, detected at 254 nm].

Compound **8f**. The enantiomeric excess was determined by chiral stationary-phase HPLC analysis [DAICEL CHIRALPAK AS-H, *i*-PrOH/Hexane 1:9, flow rate 1.0 mL/min, t_R 20.0 min for (*R*)-isomer and t_R 28.8 min (*S*)-isomer), detected at 254 nm].

Compound **13f**. The enantiomeric excess was determined by chiral stationary-phase HPLC analysis [DAICEL CHIRALPAK AS-H, *i*-PrOH/Hexane 1:9, flow rate 1.0 mL/min, t_R 17.4 min for (*R*)-isomer and t_R 20.4 min for (*S*)-isomer, detected at 254 nm]. $[\alpha]_D^{23}$ +120.7 (*c* 0.49, $CHCl_3$, 80% ee).

Compound **8d**. The enantiomeric excess was determined by chiral stationary-phase HPLC analysis [DAICEL CHIRALPAK AS-H, *i*-PrOH/Hexane 1:9, flow rate 1.0 mL/min, t_R 15.7 min (*R*)-isomer] and t_R 22.1 min (*S*)-isomer), detected at 254 nm]. $[\alpha]_D^{23}$ +219.3 (*c* 1.67, $CHCl_3$, 90% ee).

4.4. Formal total synthesis of (+)-wortmannin

4.4.1. Synthesis of 14. $NaBH_4$ (1.00 g, 26.3 mmol) was added over 30 min to a stirred solution of **8a** (31.4 g, 0.101 mol, 94% ee) in absolute EtOH (500 mL) at −78 °C. After stirring for 1 h at the same temperature, the reaction mixture was poured into saturated aqueous NH_4Cl solution, concentrated under reduced pressure, and extracted with AcOEt. The organic extract was washed with brine, dried over Na_2SO_4, and concentrated to give crude β-alcohol. DMAP (3.70 g, 30.3 mmol) and pivaloyl chloride (25 mL, 0.202 mol) were added to a stirred solution of the crude β-alcohol in pyridine (200 mL) at 0 °C. After stirring for 48 h at room temperature, the reaction mixture was poured into water and extracted with AcOEt. The organic extract was washed with water, 1 N aqueous solution of HCl and brine, dried over Na_2SO_4, and concentrated. The residue was purified by flash silica gel column chromatography (AcOEt–hexane=1:3) to afford pivaloyl ester **14** (33.0 g, 82% for 2 steps) as a pale yellow oil. $[\alpha]_D^{28}$ +17.0 (*c* 2.0, $CHCl_3$, 94% ee) FT-IR (neat) ν_{max} 2973, 1722, 1665, 1601, 1479, 1453, 1420, 1396, 1375, 1355, 1314, 1274, 1154, 1114, 1069, 1027, 1008, 937, 891, 769 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 1.07 (s, 3H), 1.14 (s, 9H), 1.66–1.90 (m, 3H), 2.09–2.15 (m, 1H), 2.33–2.37 (m, 1H), 2.45–2.64 (m, 5H), 4.25–4.33 (m, 2H), 4.64 (dd, 1H, *J*=7.6, 10.3 Hz), 7.36 (t, 2H, *J*=7.6 Hz), 7.48 (t, 1H, *J*=7.3 Hz), 7.91 (d, 2H, *J*=7.6 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 16.5, 25.4, 25.5, 26.2, 27.0, 32.9, 33.7, 38.7, 44.7, 62.7, 80.4, 128.2, 129.2, 130.0, 132.7, 166.1, 168.3, 177.7, 197.2; MS [ESI(+)] *m/z* 421 ($M+Na^+$); Anal. Calcd for $C_{24}H_{30}O_5$: C 72.34, H 7.59; Found C 72.05, H 7.61.

4.4.2. Synthesis of 15. $NiCl_2\cdot 6H_2O$ (2.15 g, 9.03 mmol) was added to a stirred solution of **14** (720 mg, 1.81 mmol) in MeOH (18 mL) at room temperature. After $NiCl_2\cdot 6H_2O$ was dissolved in MeOH, $NaBH_4$ (682 mg, 18.1 mmol) was added over 30 min at −78 °C. After stirring for 20 min at room temperature, silica gel was added to the reaction mixture, which was then filtered and concentrated under reduced pressure. The residue was purified by flash silica gel column chromatography (AcOEt–hexane=1:9) to afford *trans*-hydrindane compound with inseparable byproducts. Ethanedithiol (0.10 mL, 1.21 mmol) was added to a stirred solution of the residue in CH_2Cl_2 (3.6 mL), followed by the addition of $BF_3\cdot Et_2O$ (0.076 mL, 0.606 mmol) at 0 °C. After stirring for 18 h at room temperature, the reaction mixture was poured into saturated aqueous $NaHCO_3$ solution and extracted with AcOEt. The organic extract was washed with brine, dried over Na_2SO_4, and concentrated. The residue was purified by flash silica gel column chromatography (AcOEt–hexane=1:20) to give **15** with inseparable byproducts, which was then further purified by recrystallization (ether–hexane) to give chemically and optically pure **15** (180 mg, 21% from **14**, >99% ee) as a white needle crystalline. Mp 114–115 °C; $[\alpha]_D^{28}$ +11.4 (*c* 2.6, $CHCl_3$, >99% ee) FT-IR (KBr) ν_{max} 3421, 2970, 2921, 2851, 1723, 1654, 1601, 1583, 1478, 1455, 1421, 1395, 1364, 1334, 1314, 1282, 1164, 1123, 1071, 1024, 991, 972, 936, 898 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 0.89 (s, 3H), 1.19 (s, 9H), 1.39–1.66 (m, 5H), 1.69–1.76 (m, 1H), 1.80–1.85 (m, 1H), 1.92–1.97 (m, 1H), 2.11 (td, 1H *J*=3.4, 14.4 Hz), 2.17–2.25 (m, 2H), 2.33–2.39 (m, 1H), 3.18–3.33

(m, 4H), 4.25–4.30 (m, 1H), 4.39–4.44 (m, 1H), 4.61 (dd, 1H, J=7.7, 9.5 Hz), 7.44 (t, 2H, J=7.7 Hz), 7.54–7.57 (m, 1H), 8.06–8.08 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 12.0, 24.9, 27.2, 27.4, 30.6, 36.0, 38.7, 38.8, 39.0, 42.2, 42.5, 42.9, 51.1, 64.9, 75.5, 81.5, 128.3, 129.6, 130.4, 132.8, 166.6, 178.4; MS [ESI(+)] m/z 499 ($M+Na^+$); Anal. Calcd for $C_{26}H_{36}O_4S_2$: C 65.51, H 7.61; Found C 65.23, H 7.52. The enantiomeric excess was determined by chiral stationary-phase HPLC analysis [DAICEL CHIRALPAK AD-H, i-PrOH/Hexane 1:9, flow rate 1.0 mL/min, t_R 8.1 min for major isomer and t_R 9.6 min for minor isomer, detected at 254 nm].

4.4.3. Synthesis of 16. Compound **15** (1.04 g, 2.19 mmol) was added to a stirred suspension of $LiAlH_4$ (311 mg, 6.56 mmol) in THF (10 mL) at 0 °C. After stirring for 90 min at room temperature, the reaction mixture was quenched by the addition of water (0.3 mL) at 0 °C, followed by 4 N aqueous solution of NaOH (0.3 mL) and water (0.9 mL), which was then filtered and concentrated. The residue was purified by flash silica gel column chromatography (AcOEt–hexane=1:1) to afford **16** (689 mg, 99%) as a white powder. $[\alpha]_D^{28}$ +29.4 (c 0.36, $CHCl_3$, >99% ee) FT-IR (KBr) ν_{max} 3292, 2920, 2876, 1637, 1445, 1428, 1383, 1353, 1278, 1241, 1205, 1160, 1135, 1033, 1018 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.57 (s, 3H), 1.24–1.30 (m, 1H), 1.38–1.59 (m, 8H), 1.92 (ddd, 1H, J=2.3, 6.6, 11.8 Hz), 2.03–2.24 (m, 4H), 3.15–3.35 (m, 4H), 3.51–3.57 (m, 1H), 3.66–3.73 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 10.9, 24.5, 30.1, 34.6, 35.7, 38.7, 38.8, 42.3, 42.4, 43.0, 51.4, 62.5, 75.9, 80.9; MS [ESI(+)] m/z 311 ($M+Na^+$); HR-MS [EI(+)] Calcd for $C_{14}H_{24}O_2S_2$ (M^+): 288.1218; Found 288.1230.

4.4.4. Synthesis of 17. A solution of DMSO (0.74 mL, 10.4 mmol) in CH_2Cl_2 (4.3 mL) was added to a stirred solution of oxalyl chloride (0.45 mL, 5.21 mmol) in CH_2Cl_2 (4.3 mL) at −78 °C. After stirring for 20 min at the same temperature, a solution of **16** (500 mg, 1.74 mmol) in CH_2Cl_2 (9 mL) was added to the mixture. After stirring for 1 h at −40 °C, triethylamine (2.4 mL) was added and the reaction mixture was stirred for 20 min at the same temperature. The reaction mixture was poured into saturated aqueous NH_4Cl and extracted with CH_2Cl_2. The organic extract was washed with brine, dried over Na_2SO_4, and concentrated under reduced pressure. The residue was purified by flash silica gel column chromatography (AcOEt–hexane=1:4) to give **17** (449 mg, 91%) as a white powder. $[\alpha]_D^{28}$ +109.8 (c 1.3, $CHCl_3$, >99% ee) FT-IR (KBr) ν_{max} 3443, 3416, 2997, 2919, 2883, 2858, 2841, 2716, 1710, 1473, 1462, 1427, 1398, 1377, 1351, 1336, 1305, 1281, 1262, 1243, 1225, 1206, 1161, 1130,1119, 1088, 1071, 1053, 1031, 1013 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.97 (s, 3H), 1.53–1.62 (m, 3H), 1.72–1.80 (m, 2H), 2.05–2.12 (m, 1H), 2.16–2.27 (m, 2H), 2.41–2.54 (m, 2H), 2.71–2.76 (m, 1H), 2.96 (ddd, 1H, J=1.9, 5, 17.4 Hz), 3.10–3.28 (m, 4H), 9.83 (t, 1H, J=1.9 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 13.5, 22.9, 30.7, 35.5, 38.9, 39.0, 41.2, 41.4, 44.9, 47.6, 50.1, 74.1, 200.3, 219.7; MS [ESI(+)] m/z 307 ($M+Na^+$); HR-MS [FAB(+)] Calcd for $C_{14}H_{21}O_2S_2^+$ ($M+H^+$): 285.0977; Found 285.0990.

4.4.5. Synthesis of 18. A 1.0 M THF solution of NaHMDS (2.3 mL, 2.28 mmol) was added to a stirred suspension of Ph_3PCH_3Br (1.08 g, 3.04 mmol, dried at 100 °C for 1 h under reduced pressure prior to use) in THF (10 mL) at 0 °C. After stirring for 30 min at the same temperature, a solution of **17** (431 mg, 1.52 mmol) in THF (10 mL) was added at −78 °C, which was gradually warmed to 0 °C within 4 h. The reaction mixture was then quenched by the addition of saturated aqueous NH_4Cl at −78 °C and extracted with AcOEt. The organic extract was washed with brine, dried over Na_2SO_4, and concentrated. The residue was purified by flash silica gel column chromatography (AcOEt–hexane=1:20) to give **18** (400 mg, 93%) as a white powder. $[\alpha]_D^{28}$ +111.5 (c 2.1, $CHCl_3$, >99% ee) FT-IR (KBr) ν_{max} 3454, 3071, 2962, 2924, 2857, 1732, 1637, 1473, 1457, 1431, 1407, 1378, 1282, 1251, 1089, 1039, 1011, 994, 923 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.93 (s, 3H), 1.57–1.65 (m, 3H), 1.69–1.73 (m, 1H), 1.99–2.12 (m, 3H), 2.15–2.25 (m, 3H), 2.37–2.44 (m, 1H), 2.75–2.79 (m, 1H), 3.15–3.34 (m, 4H), 4.95–5.08 (m, 2H), 5.84–5.92 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 13.6, 23.7, 30.9, 35.3, 35.8, 39.0, 39.1, 41.9, 46.2, 47.8, 51.7, 75.1, 115.2, 138.9, 219.6; MS [ESI(+)] m/z 305 ($M+Na^+$); HR-MS [FAB(+)] Calcd for $C_{15}H_{23}OS_2^+$ ($M+H^+$): 283.1185; Found 283.1179.

4.4.6. Synthesis of 19. p-Toluenesulfonic acid (181 mg, 0.954 mmol) was added to a stirred solution of **18** (2.70 g, 9.54 mmol) in 2-ethyl-2-methyl-1,3-dioxolane at room temperature. After stirring for 48 h at the same temperature, the reaction mixture was poured into saturated aqueous $NaHCO_3$ solution and extracted with AcOEt. The organic extract was washed with brine, dried over Na_2SO_4, and concentrated. The residue was purified by flash silica gel column chromatography (AcOEt–hexane=1:20) to give **19** (2.43 g, 78%) as a colorless oil with recovery of **18** (398 mg, 15%). $[\alpha]_D^{21}$ +4.6 (c 0.70, $CHCl_3$, >99% ee) FT-IR (neat) ν_{max} 3071, 2972, 2945, 2878, 1637, 1457, 1435, 1380, 1309, 1279, 1228, 1187, 1163, 1103, 1035, 995, 957, 907, 855 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.91 (s, 3H), 1.25–1.40 (m, 2H), 1.71–1.97 (m, 6H), 2.07–2.21 (m, 3H), 2.54 (brdd, 1H), 3.14–3.33 (m, 4H), 3.80–3.96 (m, 4H), 4.90 (d, 1H, J=10.1 Hz), 5.01 (d, 1H, J=17.1 Hz), 5.83–5.91 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 14.1, 24.3, 30.0, 34.2, 36.0, 38.9, 39.0, 42.2, 46.2, 46.7, 51.0, 64.7, 65.2, 75.6, 114.5, 118.4, 139.6; MS [ESI(+)] m/z 349 ($M+Na^+$); HR-MS [FAB(+)] Calcd for $C_{17}H_{27}O_2S_2^+$ ($M+H^+$): 327.1447; Found 327.1449.

4.4.7. Synthesis of 5. Freshly prepared $PhI(OCOCF_3)_2$ (79 mg, 0.184 mmol) was added to a stirred solution of **19** (30.0 mg, 0.0920 mmol) in CH_3CN (0.8 mL) and H_2O (0.1 mL) at room temperature. After stirring for 1 min at the same temperature, the reaction mixture was quenched by the addition of saturated aqueous $NaHCO_3$ solution and extracted with AcOEt. The organic extract was washed with brine, dried over Na_2SO_4, and concentrated. The residue was purified by flash silica gel column chromatography (AcOEt–hexane=1:9) to give **5** (19.3 mg, 84%) as a colorless oil. $[\alpha]_D^{22}$ +17.9 (c 1.96, $CHCl_3$, >99% ee) FT-IR (neat) ν_{max} 3078, 2975, 2878, 1708, 1434, 1308, 1177 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.13 (s, 3H), 1.37–1.45 (m, 1H), 1.52–1.56 (m, 1H), 1.73–1.80 (m, 1H), 1.83–1.89 (m, 1H), 1.92–2.02 (m, 2H), 2.03–2.09 (m, 1H), 2.21–2.44 (m, 5H), 3.81–3.92 (m, 4H), 4.93–5.02 (m, 2H), 5.80 (ddt, 1H);

^{13}C NMR (125 MHz, $CDCl_3$) δ 13.9, 23.2, 28.9, 30.9, 34.4, 37.4, 45.8, 48.2, 50.7, 64.5, 65.3, 116.1, 117.7, 136.5, 211.3; MS [EI(+)] *m/z* 250 (M^+); HR-MS [EI(+)] Calcd for $C_{15}H_{22}O_3^+$ (M^+): 250.1569; Found 250.1571.

4.4.8. Synthesis of 20. A solution of **5** (135 mg, 0.540 mmol) in THF (2.7 mL) was added dropwise to a stirred solution of potassium hexamethyldisilazide (324 mg, 1.619 mmol) in THF (2.7 mL) at −78 °C. After stirring for 30 min at the same temperature, TMSCl (0.14 mL, 1.08 mmol) was added at −78 °C. After additional stirring for 20 min at the same temperature, the reaction was quenched by the addition of saturated aqueous $NaHCO_3$ solution and extracted twice with Et_2O. The combined organic extracts were washed with brine, dried over Na_2SO_4, and concentrated to give crude enol silyl ether. *m*-Chloroperbenzoic acid (219 mg, 0.756 mmol) was added by portions to a stirred suspension of the residual oil and $KHCO_3$ (270 mg, 2.70 mmol) in CH_2Cl_2 (2.7 mL) at −20 °C. After stirring for 2 h at the same temperature, the reaction mixture was diluted with CH_2Cl_2 and poured into saturated aqueous $NaHCO_3$ solution to give white precipitate. Water was added to dissolve the precipitate and extracted with CH_2Cl_2. The organic extract was washed with saturated aqueous $Na_2S_2O_3$ solution and brine, dried over Na_2SO_4, and concentrated. A mixture of the residual oil and 3 N aqueous solution of NH_4F (0.54 mL) in MeOH (2.7 mL) was stirred at 0 °C for 15 min, and then about half of the MeOH was removed under reduced pressure. The residual mixture was poured into a saturated aqueous $NaHCO_3$ solution, and extracted with EtOAc. The organic extract was washed with brine, dried over Na_2SO_4, and concentrated. The residue was purified by flash silica gel column chromatography (AcOEt–hexane=1:4) to give α-hydroxy ketone (61 mg, 42%) as a colorless oil. $Cu(OAc)_2\cdot H_2O$ (91 mg, 0.456 mmol) was added to a solution of the α-hydroxy ketone in MeOH (1.1 mL) at 0 °C. After stirring for 15 h at room temperature, the reaction mixture was quenched by the addition of water. After additional stirring for 30 min, the mixture was extracted with CH_2Cl_2. The organic extract was successively washed with brine, 10% aqueous citric acid solution and brine, dried over Na_2SO_4, and concentrated. A solution of the residual oil and DBU (0.034 mL, 0.228 mmol) in CH_2Cl_2 (1 mL) was stirred at 0 °C for 10 min, which was then quenched by the addition of saturated aqueous NH_4Cl solution, and extracted with CH_2Cl_2. Organic extract was washed with brine, dried over Na_2SO_4, and concentrated to give crude diosphenol. Diisopropylethylamine (0.048 mL) and Tf_2O (0.038 mL) were added to a solution of the residual oil in CH_2Cl_2 (1 mL) −78 °C. After stirring for 15 min at the same temperature, the reaction mixture was quenched by the addition of saturated aqueous $NaHCO_3$ solution and extracted with AcOEt. The organic extract was washed with brine, dried over Na_2SO_4, and concentrated. The residue was purified by silica gel column chromatography (AcOEt–hexane=1:20) to give **20** (42 mg, 47%) as a colorless oil. $[\alpha]_D^{22}$ +38.8 (*c* 0.17, $CHCl_3$, >99% ee) FT-IR (neat) ν_{max} 1747, 1697, 1418, 1210, 1140, 1017, 865 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.99 (s, 3H), 1.71–1.80 (m, 1H), 1.93–2.12 (m, 3H), 2.45 (d, 1H, *J*=16.5 Hz), 2.75 (d, 1H, *J*=16.5 Hz), 2.96 (dd, 1H, *J*=7.2, 13.5 Hz), 3.22 (dd, 1H, *J*=7.2, 13.5 Hz), 3.32 (dd, 1H, *J*=5.8, 14.3 Hz), 3.82–3.96 (m, 4H), 5.19 (d, 1H, *J*=10.5 Hz), 5.20 (d, 1H, *J*=16.0 Hz), 5.73 (ddt, 1H, *J*=7.2, 10.5, 16.0 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 14.6, 21.2, 33.2, 33.3, 45.0, 45.9, 48.5, 64.6, 65.6, 118.5 (q, coupling with F), 119.3, 131.1, 141.3, 150.6, 190.0; MS [EI(+)] *m/z* 386 (M^+); HR-MS [EI(+)] Calcd for $C_{16}H_{20}O_6F_3S^+$ (M+): 397.0932; Found 397.0939.

4.4.9. Synthesis of 21. $CeCl_3\cdot 7H_2O$ (699 mg) was added to a solution of **20** (620 mg, 1.56 mmol) in MeOH (10 mL) at room temperature and the mixture was stirred at the same temperature until $CeCl_3\cdot 7H_2O$ was dissolved. Then $NaBH_4$ (77 mg, 2.03 mmol) was added to the mixture at 0 °C. After stirring for 1 h at the same temperature, the reaction mixture was quenched by the addition of acetone followed by water, and extracted with AcOEt. The organic extract was washed with brine, dried over Na_2SO_4, and concentrated. The residue was purified by silica gel column chromatography (AcOEt–hexane=5:1) to give **21** (403 mg, 65%) and the diastereomer (about 130 mg) as white solids. $[\alpha]_D^{23}$ +43.8 (*c* 0.16, $CHCl_3$, >99% ee) FT-IR (neat) ν_{max} 3471, 2974, 2889, 1408, 1209, 1141, 1039 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.06 (s, 3H), 1.57–1.66 (m, 1H), 1.81 (d, 1H, *J*=14.1 Hz), 1.83–1.96 (m, 2H), 2.11 (d, 1H, *J*=6.4 Hz), 2.12–2.22 (m, 2H), 2.71–2.80 (m, 2H), 3.16 (dd, 1H, *J*=6.9, 14.6 Hz), 3.84–3.94 (m, 4H), 4.53 (t, 1H, *J*=6.4 Hz), 5.09 (dd, 1H, *J*=1.5, 10.5 Hz), 5.14 (dd, 1H, *J*=1.5, 17.1 Hz), 5.68–5.76 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 15.2, 21.0, 32.1, 34.8, 37.0, 44.2, 46.2, 64.5, 65.4, 65.9, 117.4, 117.6, 132.8, 133.1, 143.3; MS [FAB(+)] *m/z* 381 ($M-H_2O+H^+$); HR-MS [FAB(+)] Calcd for $C_{16}H_{20}O_5F_3S^+$ (M^+): 381.983; Found 381.994.

Spectroscopic data except for optical rotation of **22**, **24**, and **7a** and experimental procedure for the syntheses of those compounds were previously reported.[15]

4.4.10. Optical rotation of 22, 24 and 7a. *Compound* **22**: $[\alpha]_D^{23}$ +83.3 (*c* 0.12, $CHCl_3$, >99% ee).

Compound **24**: $[\alpha]_D^{21}$ +4.6 (*c* 0.70, $CHCl_3$, >99% ee).

Compound **7a**: $[\alpha]_D^{22}$ +28.0 (*c* 0.10, $CHCl_3$, >99% ee, diastreomixture, α:β=1:18).

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tet.2005.03.038

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