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Catalytic Enantioselective Total Synthesis of (−)-Platyphyllide and Its Structural Revision

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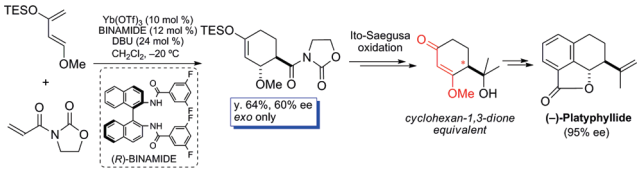
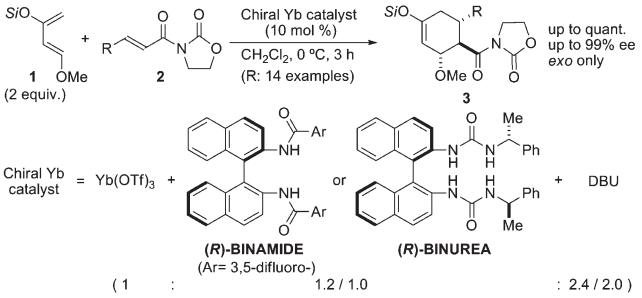


The catalytic asymmetric total synthesis of platyphyllide has been accomplished. A key highly substituted cyclohexene derivative has been obtained by the catalytic asymmetric Diels−Alder reaction of Danishefsky diene with an electron-deficient alkene. The Diels−Alder adduct was converted to a protected cyclohexane-1,3-dione in chiral form by catalytic Ito−Saegusa oxidation. Although the reported structure of platyphyllide was successfully synthesized, the optical rotation was opposite that of the natural compound. The absolute configuration of natural (−)-platyphyllide is revised to be a (6*S*,7*S*)-enantiomer.

The Diels−Alder reaction is widely used in organic synthesis to construct substituted six-membered carbocycles. A catalytic asymmetric version of this reaction has been studied extensively and has been used in the enantioselective synthesis of natural compounds.[1] Danishefsky diene[2] is a well-known substrate for the Diels−Alder reaction to give oxygen-functionalized cyclohexenes and has been recognized as a useful diene in organic synthesis. However, this reactive diene has not been fully utilized due to its instability, which limits the applicable reaction conditions. Thus, the development of a catalytic Diels−Alder reaction of Danishefsky diene has been a difficult problem. Recently, we developed a catalytic asymmetric version of the Diels−Alder reaction of Danishefsky diene with electron-deficient alkenes. We

SCHEME 1. Asymmetric Diels−Alder Reaction Catalyzed by Chiral Yb Complex



chose $Yb(OTf)_3$ as a central metal which is combined with our original axially chiral ligands BINAMIDE or BINUREA and amine.[3] These complexes catalyzed the Diels−Alder reaction in a highly diastereo- and enantioselective manner to give densely functionalized chiral cyclohexenes (Scheme 1).

Although the Diels−Alder reaction using Danishefsky diene often gave a mixture of adduct **3** and corresponding enone, these cyclic silyl enol ethers (**3**) were isolated in a pure form. Since there have been few examples of the direct use of the silyl enol moiety and methoxy group,[4] we studied nonaflation[5] followed by a variety of transition-metal-catalyzed coupling reactions of the silyl enol ethers to expand the utility of Diels−Alder adducts.[3a] In this paper, we report a new synthetic utility of an oxygen functionality of Diels−Alder adducts and its application to a catalytic asymmetric total synthesis of platyphyllide.

(−)-Platyphyllide is a norsesquiterpene lactone that was isolated from *Senecio platyphylloides* in 1977 by Bohlmann et al., who also determined its structure, including the relative configuration.[6]

The asymmetric total synthesis of platyphyllide was accomplished by Kanematsu et al., who proposed the absolute stereochemistry of (−)-platyphyllide as shown in Figure 1. Their synthesis included an asymmetric reduction of the racemic dienone **5** and subsequent separation of the corresponding *trans* and *cis* isomers, as shown in Scheme 2.[7]

(1) For recent examples within 2009, see: (a) Shimizu, Y; Shi, S. -L.; Usuda, H.; Kanai, M.; Shibasaki, M. *Angew. Chem., Int. Ed.* **2010**, *49*, 1103. (b) Dunn, T. B.; Ellis, J. M.; Kofink, C. C.; Manning, J. R.; Overman, L. E. *Org. Lett.* **2009**, *11*, 5658. (c) Nicolaou, K. C.; Tria, G. S.; Edmonds, D. J.; Kar, M. *J. Am. Chem. Soc.* **2009**, *131*, 15909. (d) Yamatsugu, K.; Yin, L.; Kamijo, S.; Kimura, Y.; Kanai, M.; Shibasaki, M. *Angew. Chem., Int. Ed.* **2009**, *48*, 1070. (e) Jones, S. B.; Simmons, B.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2009**, *131*, 13606. (f) Tang, Y.; Cole, K. P.; Buchanan, G. S.; Li, G.; Hsung, R. P. *Org. Lett.* **2009**, *11*, 1591 See also references cited therein.

(2) Danishefsky, S.; Kitahara, T. *J. Am. Chem. Soc.* **1974**, *96*, 7807.

(3) (a) Sudo, Y.; Shirasaki, D.; Harada, S.; Nishida, A. *J. Am. Chem. Soc.* **2008**, *130*, 12588. (b) Harada, S.; Toudou, N.; Hiraoka, S.; Nishida, A. *Tetrahedron Lett.* **2009**, *50*, 5652.

(4) For examples of natural product syntheses or synthetic studies without elimination of the alkoxy group of Danishefsky-type diene, see: (a) Yamamoto, N.; Isobe, M. *Tetrahedron* **1993**, *49*, 6581. (b) Fariña, F.; Noheda, P.; Paredes, M. C. *J. Org. Chem.* **1993**, *58*, 7406. (c) Asenjo, P.; Fariña, F.; Martín, M. V.; Paredes, M. C.; Soto, J. J. *Tetrahedron Lett.* **1995**, *36*, 8319. (d) Asenjo, P.; Fariña, F.; Martín, M. V.; Paredes, M. C.; Soto, J. J. *Tetrahedron* **1997**, *53*, 1823. (e) Trotter, N. S.; Larsen, D. S.; Stoodley, R. J.; Brooker, S. *Tetrahedron Lett.* **2000**, *41*, 8957. (f) Kotha, S.; Stoodley, R. J. *Bioorg. Med. Chem.* **2002**, *10*, 621. (g) Bourghli, L. M. S.; Stoodley, R. J. *Bioorg. Med. Chem.* **2004**, *12*, 2863.

(5) Lyapkolo, I. M.; Webel, M.; Reibig, H.-U. *Eur. J. Org. Chem.* **2002**, *67*, 1015.

(6) (a) Bohlmann, F.; Knoll, K.-H.; Zdero, C.; Mahanta, P. K.; Grenz, M.; Suwita, A.; Ehlers, D.; Le Van, N.; Abraham, W.-R.; Natu, A. A. *Phytochemistry* **1977**, *16*, 965. (b) Bohlmann, F.; Eickeler, E. *Chem. Ber.* **1979**, *112*, 2811.

(7) Nagashima, S.; Ontsuka, H.; Shiro, M.; Kanematsu, K. *Heterocycles* **1995**, *41*, 245.

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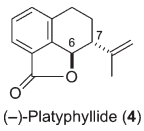


FIGURE 1. Proposed structure of (−)-platyphyllide.

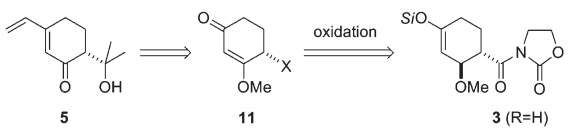
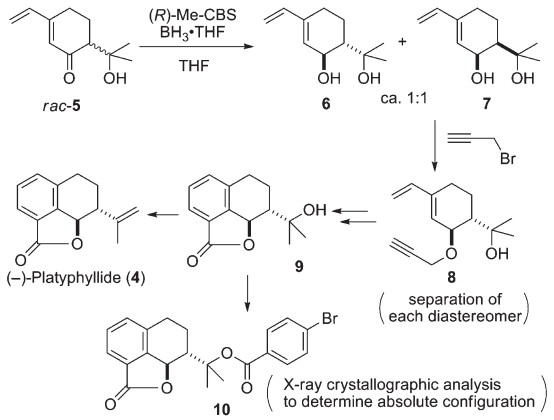
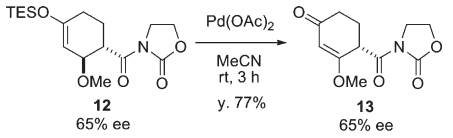


FIGURE 2. Retrosynthetic analysis of dienone **5**.

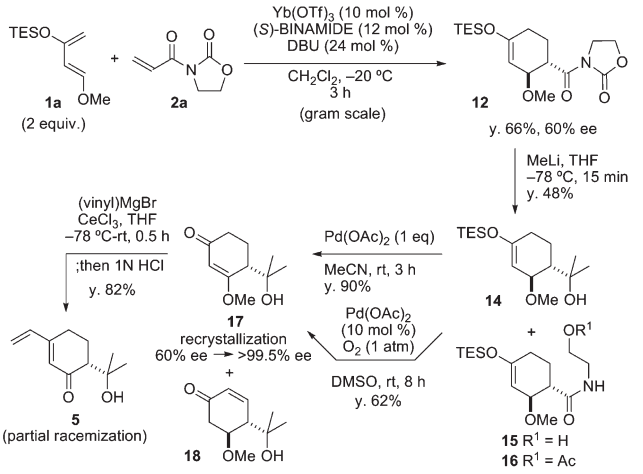
SCHEME 2. Synthetic Pathway and Determination of the Absolute Configuration Reported by Kanematsu



SCHEME 3. Ito−Saegusa Oxidation of 3-Methoxy-1-silyloxycyclohexenone 12



SCHEME 4. Synthesis of Intermediate 5



However, the enantiopurity of their compounds was not reported at any stage in their synthetic pathway.

The absolute configuration was determined to be (6*R*,7*R*) by X-ray analysis of *p*-bromobenzoyl derivative **10** of their intermediate **9**. This is the only chemical synthesis of chiral platyphyllide to date.[8]

In the retrosynthesis of Kanematsu's intermediate, our Diels−Alder adduct **3** should be recognized as a starting material (Figure 2).

Key *β*-methoxycyclohexenone **11** would be obtained by the oxidation of Diels−Alder adduct **3**. It is well-known that the oxidation of silyl enol ethers to enones is promoted by $Pd(OAc)_2$ (Ito−Saegusa oxidation)[9] or IBX-MPO.[10] Although no example of oxidation of a silyl enol ether like **3** has been reported,[11] a model study using chiral substrate **12** proceeded cleanly to give *β*-methoxyenone in 77% yield without racemization by Ito−Saegusa oxidation (Scheme 3).

Sequential Diels−Alder reaction/oxidation of Danishefsky diene derivatives is a new method for obtaining selectively protected chiral cyclohexane-1,3-diones.[12] Encouraged by this preliminary result, we began the total synthesis of optically active platyphyllide (**4**), as shown in Scheme 4.

The asymmetric Diels−Alder reaction of TES-protected diene **1a** and dienophile **2a** catalyzed by $Yb(OTf)_3$/(*S*)-BINAMIDE complex gave the adduct **12** (60% ee) in gram scale.[3a] The nucleophilic attack of methyllithium to the oxazolidinone group suffered from undesired ring-opening of the oxazolidone unit to give a 1:1 mixture of the desired tertiary alcohol **14** and byproducts. All efforts to transform these byproducts to desired **14** were unsuccessful. Oxidation of **14** to key intermediate **17** was achieved by Ito−Saegusa oxidation in 90% yield. Moreover, the catalytic conditions of this reaction reported by Larock et al.[13] were also applicable to give **17** in 63% yield using 10 mol % of $Pd(OAc)_2$.[14] Recrystallization of **17** gave optically pure **17** from the filtrate after the removal of racemic crystals. *β*-Methoxyenone **17** was then converted into reported dienone **5** by the addition of Grignard reagent and subsequent acid treatment, which achieved the formal synthesis of platyphyllide. However, compound **17** was unstable against racemization under basic conditions and the enantiopurity of product **5** dropped to 54% ee (ee was determined after conversion to **8** by HPLC

(8) For racemic syntheses of platyphyllide, see: (a) Hayakawa, K.; Ohsuki, S.; Kanematsu, K. *Tetrahedron Lett*. **1986**, *27*, 947. (b) Ho, T. -L.; Ho, M. -F. *J. Chem. Soc., Perkin Trans. 1* **1999**, 1823.

(9) Ito, Y.; Hirao, T.; Saegusa, T. *J. Org. Chem*. **1978**, *43*, 1011.

(10) Nicolaou, K. C.; Gray, D. L. F.; Montagnon, T.; Harrison, S. T. *Angew. Chem., Int. Ed*. **2002**, *41*, 996.

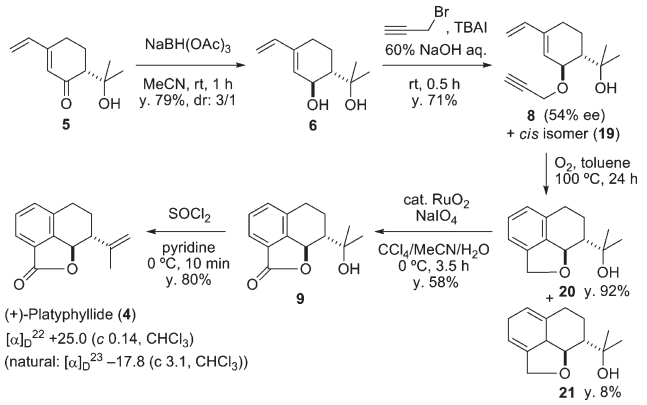
(11) Successful examples of Ito−Saegusa or other oxidations with a *β*-ethereal group have been limited to hydropyran- or hydrofuran-type compounds; see: (a) Danishefsky, S. J.; Pearson, W. H. *J. Org. Chem*. **1983**, *48*, 3865. (b) Danishefsky, S. J.; Uang, B. J.; Quallich, G. *J. Am. Chem. Soc*. **1985**, *107*, 1285. (c) Herrinton, P. M.; Klotz, K. L.; Hartley, W. M. *J. Org. Chem*. **1993**, *58*, 678. (d) Evans, P. A.; Nelson, J. D. *J. Org. Chem*. **1996**, *43*, 7600. (e) Orellana, A.; Rovis, T. *Chem. Commun*. **2008**, 730.

(12) This versatile building block has been constructed by the Diels−Alder reaction of 1,1-dimethoxy-3-siloxy-1,3-butadiene or its derivatives with alkenes. The Diels−Alder reaction of such dienes with alkyne or quinone was also a very powerful method for synthesizing resorcinols. However, they require several steps for preparation. For preparation, see: (a) Banville, J.; Brassard, P. *J. Chem. Soc. Perkin Trans. 1* **1976**, 1852. For various conversions of the Diels−Alder adduct derived from the diene, see: (b) Danishefsky, S.; Singh, R. K.; Gammill, R. B. *J. Org. Chem*. **1978**, *43*, 379.

(13) Larock, R. C.; Hightower, T.; Kraus, G. A.; Hahn, P.; Zheng, D. *Tetrahedron Lett*. **1995**, *36*, 2423.

(14) The isomerized product **18** was obtained in 22% yield (containing trace inseparable compound) at this step. So far, we do not have any information about the mechanism of this isomerization. Further screenings of the conditions to selectively give **18** and a mechanistic study are in progress.

SCHEME 5. Unexpected Total Synthesis of (+)-*ent*-Platyphyllide



analysis). The slow addition of vinyl magnesium bromide at −78 °C might cause racemization of the tertiary alkoxide intermediate before the addition of Grignard reagent to carbonyl.

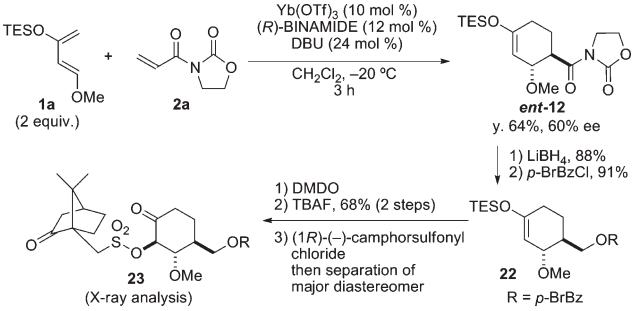
Subsequent steps to platyphyllide are shown in Scheme 5.

First, the carbonyl group of dienone **5** was reduced stereoselectively directed by the neighboring hydroxyl group by sodium triacetoxyborohydride[15] to give the desired *trans* product in 3:1 selectivity, while Luche reduction predominantly gave the *cis* isomer (dr: 1/14). At this stage, both the absolute and relative configurations of the two stereocenters in platyphyllide were successfully controlled. Next, we tried to shorten the steps to platyphyllide from **6**, which required eight steps in Kanematsu's pathway.[7] We introduced a propargyl unit as reported by Kanematsu. Compound **8** and its diastereomer **19** were separated at this stage, and the ee of **8** was confirmed at this stage by chiral HPLC. The intramolecular Diels−Alder reaction proceeded quickly under thermal conditions, and we also found aromatized product **20** in the mixture of products. The Diels−Alder reaction of **8** under an oxygen atmosphere gave **20** in 92% yield with a one-pot process. The oxidation of benzyl ether by ruthenium oxide[16] gave the reported compound **9** in moderate yield. Finally, a known elimination method gave platyphyllide, and the total synthesis of platyphyllide was achieved in four simple steps from **6**.

All of the spectral features (^{1}H NMR, ^{13}C NMR, IR, and MS) of synthetic platyphyllide were indistinguishable from those of natural platyphyllide, except that the optical rotation was *positive*, which is opposite that of natural (−)-platyphyllide. Furthermore, signs of optical rotation of other intermediates **8** and **9** were also opposite to the reported data.[7]

Therefore, we decided to reexamine the absolute configuration of the Diels−Alder adduct by X-ray crystallographic analysis after condensation with a suitable chiral auxiliary,

SCHEME 6. Confirm the Absolute Configuration of Our Diels−Alder Adduct



as shown Scheme 6.[17,18] The asymmetric Diels−Alder reaction using (*R*)-BINAMIDE gave the adduct ***ent*-12**, which should have the correct absolute configuration for the synthesis of (−)-platyphyllide (***ent*-4**), in 60% ee. The side chain of ***ent*-12** was reduced and protected by *p*-bromobenzoyl group to give **22**. Oxidation with DMDO and sequential desilylation gave the secondary alcohol as a single diastereomer, and then (1*R*)-camphorsulfonyl group was introduced to the alcohol and the major diastereomer **23** was separated. X-ray crystallographic analysis of **23** proved that the absolute configuration of **23** was as shown in Scheme 6,[19] which is consistent with reported assignment of the Diels−Alder adducts previously.

Based on those studies, we revised the absolute configuration of natural (−)-platyphyllide to be (6*S*,7*S*). Moreover, we reconsidered Kanematsu's procedure for determining the absolute configuration (Scheme 2). They used CBS reduction to obtain chiral diol **6** (ee: not reported) from racemic dienone, and the absolute configuration was determined later by X-ray analysis of *p*-bromobenzoyl derivative **10**. However, the reported optical rotation of propargyl intermediate **8** (really ***ent*-8**) was $[\alpha]^{26}_{D}$ −24.3 (*c* 0.7, $CHCl_3$),[7] which is much lower than that of **8** in our synthesis; $[\alpha]^{24}_{D}$ +76.3 (*c* 1.3, $CHCl_3$, 54% ee). Thus, their compounds were estimated to be 10−20% ee, and this may be associated with the recrystallization of **10**, such as undesired resolution or contamination of the crystal derived from the minor enantiomer.

Finally, we started the asymmetric total synthesis of natural (−)-platyphyllide. The Diels−Alder adduct ***ent*-12** was converted into ***ent*-17** as described above. After the enantiopurity of ***ent*-17** was enriched to be 94% ee by recrystallization (Scheme 7), vinyl Grignard reagent was added in one portion to suppress racemization based on our hypothesis vide supra, to give ***ent*-5** in 90% ee. Diastereoselective reduction using borane-THF complex gave the trans product selectively in 7:1 ratio. Recrystallization of ***ent*-6** gave racemic crystal, and almost pure ***ent*-6** (95% ee) was obtained from the mother liquor. Using the procedure described above, we achieved the catalytic enantioselective total synthesis of natural (−)-platyphyllide (***ent*-4**).

In conclusion, we have discovered a method for the efficient conversion of the alkoxy silyl enol moiety in Diels−Alder adduct using Danishefsky diene to a chiral cyclohexane-1,3-dione equivalent by Ito−Saegusa oxidation. This method was successfully applied to the catalytic

(15) Evans, D. A.; Chapman, K. T.; Carreira, E. M. *J. Am. Chem. Soc.* **1988**, *110*, 3560.

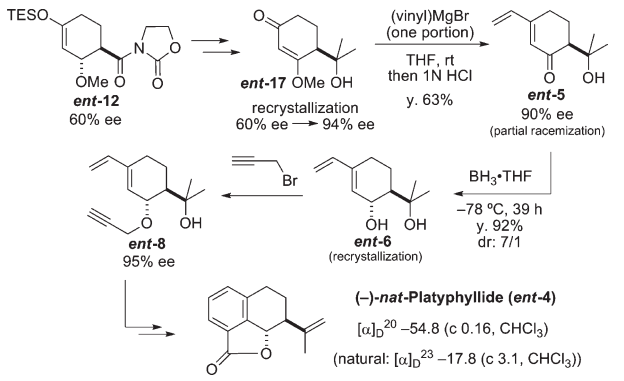
(16) Schuda, P. F.; Cichowicz, M. B.; Heimann, M. R. *Tetrahedron Lett.* **1983**, *24*, 3829.

(17) We have previously determined the absolute configuration of Diels−Alder adducts of our asymmetric reaction using (*S*)-BINAMIDE by conversion to a known compound.[3a] For details, see the Supporting Information.

(18) The absolute configuration of synthetic (+)-platyphyllide was also estimated by Mosher's method. For details, see the Supporting Information.

(19) CCDC 773055 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

SCHEME 7. Total Synthesis of Natural (−)-Platyphyllide



asymmetric total synthesis of (+)- and (−)-platyphyllide. The absolute configuration of natural (−)-platyphyllide was revised to be (6*S*,7*S*) by our asymmetric total synthesis. The absolute stereochemistry of the key intermediate obtained by asymmetric Diels−Alder reaction using Danishefsky diene was unambiguously determined by X-ray crystallographic analysis.

Experimental Section

3-((1*S*,2*S*)-2-Methoxy-4-(triethylsilyloxy)cyclohex-3-enecarbonyl)oxazolidin-2-one (12). Asymmetric Diels−Alder Reaction of 1a and 2a. A mixture of $Yb(OTf)_3$ (535 mg, 0.863 mmol) and (*S*)-BINAMIDE (584 mg, 1.04 mmol) in a flask with a stirring bar was dried at 90 °C under reduced pressure (< 0.1 mmHg) for 0.5 h with stirring. After the mixture was allowed to cool to room temperature, the flask was charged with dry argon. CH_2Cl_2 (28.8 mL) and DBU (316 μL, 2.07 mmol) were successively added, and the mixture was stirred for 2 h at room temperature. Dienophile **2a** (1.22 g, 8.64 mmol) in CH_2Cl_2 (14.4 mL) was added at 0 °C. The mixture was immediately cooled to −20 °C, diene **1a** (4.15 mL, 17.2 mmol) was added dropwise, and the mixture was stirred for 3 h at the same temperature. Water (10 mL) was then added to quench the reaction, and the insoluble materials were filtered through a pad of Celite. The water layer was extracted three times with CH_2Cl_2, and the combined organic layers were washed with brine and dried over Na_2SO_4. After the volatile material was removed under reduced pressure, the resulting residue was purified by column chromatography (SiO_2, hexane/AcOEt = 5/1) to give **12** (2.04 g, yield 66%) as a colorless oil. The enantiomeric excess was determined to be 60% ee by HPLC analysis after conversion to enone by TFA (Daicel Chiralcel OJ-H, hexane/*i*PrOH = 60/40, flow: 0.75 mL/min, 254 nm, t_R: 35.1 min (major) and 36.6 min (minor)): ^{1}H NMR ($CDCl_3$, 400 MHz) δ 0.69 (6H, q, J = 8.0 Hz), 0.98 (9H, t, J = 8.0 Hz), 1.65−1.74 (1H, m), 2.00−2.04 (2H, m), 2.29−2.37 (1H, m), 3.30 (3H, s), 3.81 (1H, ddd, J = 3.0, 8.8 11.6 Hz), 3.98−4.12 (2H, m), 4.37−4.44 (2H, m), 4.70 (1H, d, J = 8.8 Hz), 5.00 (1H, s); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 5.3, 7.0, 24.9, 29.5, 43.1, 44.0, 55.6, 62.2, 76.6, 103.2, 153.3, 153.4, 174.9; IR (neat) 1775, 1696, 1660 cm^{-1}; LRMS(FAB) m/z 356 $[M + H]^+$; HRMS-(FAB) calcd for $C_{17}H_{30}NO_5Si$ 356.1893, found 356.1879; $[\alpha]^{25}_D$ +45.8 (*c* 1.0, $CHCl_3$, 60% ee). For the enantiomer ***ent*-12** in Scheme 7, $[\alpha]^{24}_D$ −61.9 (*c* 0.24, $CHCl_3$, 60% ee).

(*R*)-4-(2-Hydroxypropan-2-yl)-3-methoxycyclohex-2-enone (17). Ito−Saegusa Oxidation of 14. A solution of **14** (248 mg, 0.825 mmol) and $Pd(OAc)_2$ (18.5 mg, 82.5 μmol) in DMSO (16.5 mL) was stirred under O_2 for 8 h. The solvent was distilled under reduced pressure (0.1 mmHg) at 55 °C. The resulting residue was purified by column chromatography (SiO_2, AcOEt) to give **17** (94.3 mg, yield 62%) as a colorless solid and **18** (34.2 mg, containing trace inseparable compound, yield < 22%) as a colorless oil.

Compound **17** (149 mg) was recrystallized from hexane/AcOEt to give racemic **17** (53.4 mg, yield 36%) as a colorless crystal and chiral **17** (93.8 mg, yield 63%) from the mother liquor as a colorless oil. The enantiomeric excess was determined to be > 99.5% ee by HPLC analysis (Daicel Chiralpak IA, hexane/*i*PrOH = 97/3, flow: 1.0 mL/min, 254 nm, t_R: 48.7 min (minor) and 50.5 min (major)). For the enantiomer ***ent*-17** (Daicel Chiralpak AD-H, hexane/iPrOH = 97/3, flow: 1.0 mL/min, 254 nm, t_R: 46.2 min (minor) and 48.3 min (major)): ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.25 (3H, s), 1.28 (3H, s), 1.79−1.88 (1H, m), 2.09−2.17 (1H, m), 2.26−2.39 (1H, m), 2.50−2.57 (1H, m), 2.64 (1H, dd, J = 5.8, 8.6 Hz), 3.08 (1H, s), 3.77 (3H, s), 5.50 (1H, s); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 24.1, 26.1, 28.8, 35.4, 48.7, 55.8, 73.2, 104.6, 178.3, 199.2; IR(neat) 3391, 1590 cm^{-1}; LRMS(FAB) m/z 185 $[M + H]^+$; HRMS(FAB) calcd for $C_{10}H_{17}O_3$ 185.1178, found 185.1170; $[\alpha]^{23}_D$ −1.17 (*c* 1.0, $CHCl_3$, > 99.5% ee). For the enantiomer ***ent*-17** in Scheme 7, $[\alpha]^{20}_D$ +1.67 (*c* 0.95, $CHCl_3$, 94% ee); mp 92.5−93.0 °C.

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Supporting Information Available: Experimental procedures, spectral data, copies of ^{1}H and ^{13}C NMR spectra, HPLC chart, and CIF (**23**). This material is available free of charge via the Internet at http://pubs.acs.org.