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A Stereoselective Approach to Functionalized Cyclohexenones

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A catalytic enantioselective approach to 4-hydroxy-6-methylcyclohex-2-enones is presented herein. The stereogenic information is generated through a copper-catalyzed 1,4-addition to *p*-benzoquinone monoketal using a chiral, BINOL-based (BINOL = 1,1′-bi-2-naphthol) phosphane ligand, according to the procedure of Feringa et al. A CBS (Corey–Bakshi–Shibata) reduction of the 1,4-adducts gave the four possible isomers in two steps and 82–97 % *ee* (enantiomeric excess), starting from commercially available 4,4-dimethoxycyclohexa-2,5-dien-1-one (**7**).

Introduction

Substituted cyclohexenones similar to **1** and **2** are valuable building blocks for the synthesis of natural products (see Figure 1). These structural motifs appear in many small molecules such as epoxydine A (**3**),[1] gabosine B (**4**),[2] dihydroepiepoformin,[3] and ampelomin A.[4] These cyclohexenone units are also part of more complex natural products such as blennolide A (**5**) and B,[5,6] secalonic acids A–G,[7] ergochrysin A and B,[8] the phomoxanthones,[9] and leptosphaerin A, B, F (**6**), and G.[10]

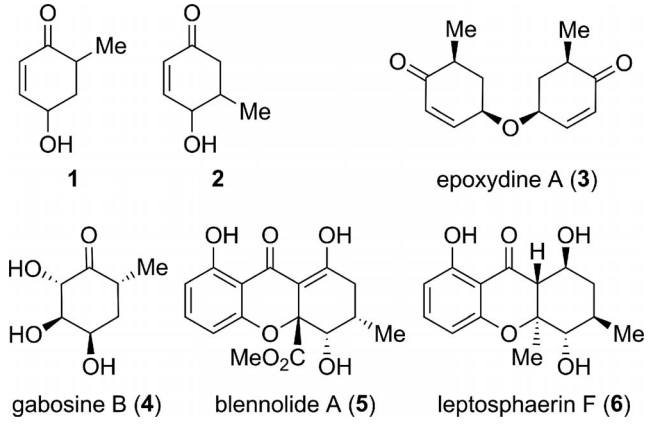

Figure 1. Cyclohexenones **1** and **2** and some of the natural products that contain them.

In the literature, some syntheses of cyclohexenones **1** and **2** have been described. For example, our group recently presented a flexible pathway in only six steps towards both cyclohexenones **1** and **2**.[11] Earlier, an enantioselective seven-step synthesis of the *trans* isomer of **2** was published.[12] Piers and co-workers described an eight-step synthesis towards racemic PMB-protected *cis*-**2** (PMB = *para*-methoxybenzyl).[13] A six-step synthesis of diastereomeric *cis*-**1** and *trans*-**1** was presented by Edwards and co-workers.[14] Carreño et al. described a stereoselective approach in eight steps to both *cis* enantiomers of TBDMS-protected **1** (TBDMS = *tert*-butyldimethylsilyl).[15] By using the chiral pool substance D-quinic acid, Shan and O'Doherty synthesized *trans*-**1** in 10 steps and Boc-protected *cis*-**1** (Boc = *tert*-butyloxycarbonyl) in 9 steps.[16]

Until now, the syntheses of either cyclohexenone **1** or **2** required at least six steps. As they are used as building blocks for natural product synthesis,[3,11] quick access to these compounds will be indubitably advantageous. Herein, we present a two-step synthesis to the four isomers of **1**, which are produced with high enantiomeric excess values (82–97%*ee*).

Results and Discussion

Inspired by the work of Feringa and co-workers,[17] we planned a short and simple approach to both cyclohexenones **1** and **2**. Starting from commercially available benzoquinone monoketal **7**,[18] the enantioselective 1,4-addition of Feringa et al. was realized by using dimethylzinc in the presence of a copper(II) catalyst and the chiral BINOL-based (BINOL = 1,1′-bi-2-naphthol) phosphane ligand (*S*,*R*,*R*)-**9** (see Scheme 1). The 1,4-adduct (*R*)-**8** was obtained in 97%*ee*. We then adapted this procedure by using the enantiomeric ligand (*R*,*S*,*S*)-**9** to give (*S*)-**8**, which was obtained in good yield and 98%*ee*. The enantiomeric excess (*ee*) values of both 1,4-adducts **8** were determined by GC analysis on a chiral modified column.

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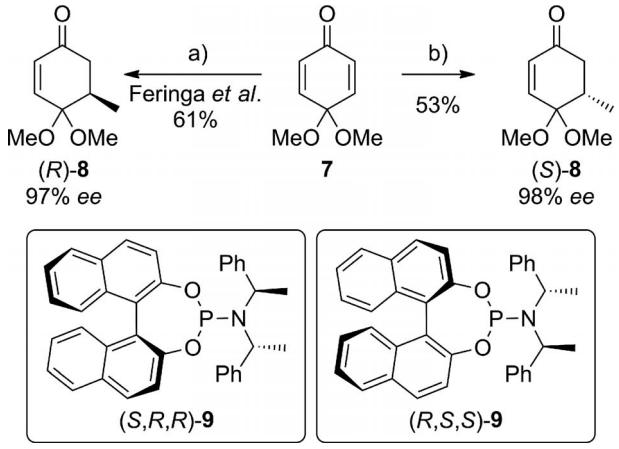
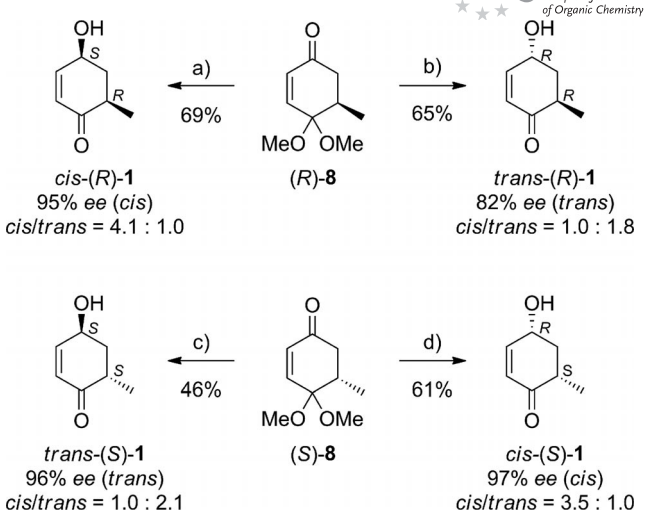


Scheme 1. Synthesis of enantiomeric 1,4-adducts (*R*)- and (*S*)-**8**. Reagents and conditions: (a) $Cu(OTf)_2$, (*S*,*R*,*R*)-**9**, absolute toluene, room temp., 1 h, then –25 °C, **7**, $ZnMe_2$, 12 h, 61%, 97%*ee*;[17] (b) $Cu(OTf)_2$, (*R*,*S*,*S*)-**9**, absolute toluene, room temp., 1 h, then –25 °C, **7**, $ZnMe_2$, 15 h, 53%, 98%*ee*.



Scheme 2. Synthesis of cyclohexenones (*R*)- and (*S*)-**1**. Only the main diastereomers are shown. Reagents and conditions: (a) (*R*)-CBS, BH_3·THF, absolute tetrahydrofuran (THF), 0 °C, 1 h, then HCl (1 M), room temp., 30 min, 69%, *cis*/*trans*, 4.1:1.0, 95%*ee* for *cis*, 86%*ee* for *trans*; (b) (*S*)-CBS, BH_3·THF, absolute THF, 0 °C, 1 h, then HCl (1 M), room temp., 30 min, 65%, *cis*/*trans*, 1.0:1.8, 82%*ee* for *trans*, 92%*ee* for *cis*; (c) (*R*)-CBS, BH_3·THF, absolute THF, 0 °C, 1 h, then HCl (1 M), room temp., 30 min, 46%, *cis*/*trans*, 1.0:2.1, 96%*ee* for *trans*, 96%*ee* for *cis*; (d) (*S*)-CBS, BH_3·THF, absolute THF, 0 °C, 1 h, then HCl (1 M), room temp., 20–30 min, 61%, *cis*/*trans*, 3.5:1.0, 97%*ee* for *cis*, 60%*ee* for *trans*.

First, we focused on the synthesis of cyclohexenone **1** (see Scheme 2). The reduction of 1,4-adduct (*R*)-**8** with the (*R*)-CBS ligand (CBS = Corey–Bakshi–Shibata) and a borane–THF complex gave cyclohexenone (*R*)-**1** as a mixture of two inseparable diastereomers with a preference for the *cis* isomer [see Scheme 2, (a)]. The catalyst [(*R*)-CBS] preferentially afforded the (*S*)-configured stereocenter, which in this case is the *cis* diastereomer (catalyst control). In addition, the *cis* diastereomer is also preferred through substrate control, and the attack of the hydride donor mainly occurs on the side opposite to the methyl group, as there is less steric hindrance (kinetic control). Furthermore, the *cis* product is also more stable than the *trans* product, as both substituents on the ring can be in an equatorial position (thermodynamic control). The catalyst and substrate formed a matched pair. The fact that not only the *cis* but also the *trans* product is formed is possibly a result of a fast background reaction without the participation of the CBS ligand. The enantiomeric excess values of the *cis* and the *trans* isomers were obtained by converting them into the corresponding Mosher esters (see Exp. Section) and determined to be 95 and 86%*ee* for the *cis* and *trans* isomer, respectively.

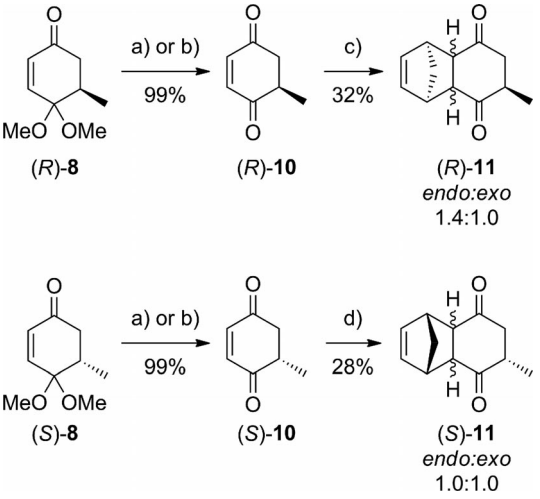
When (*R*)-**8** was treated with the enantiomeric ligand (*S*)-CBS, a preference for the *trans* isomer of **1** was observed, although it was less distinct than that of (*R*)-CBS for the *cis* isomer [see Scheme 2, (b)]. (*S*)-CBS preferentially afforded the (*R*)-configured stereocenter, which in this case is the *trans* diastereomer, although the *cis* diastereomer is preferred through substrate control. The catalyst and substrate formed a mismatched pair, even though catalyst control appears to be stronger than substrate control. These inseparable diastereomers were formed in 82 and 92%*ee* for the *trans* and *cis* isomer, respectively. Interestingly, the *ee* values were very high for the *cis* and lower for *trans* diastereomer in both reactions. As the *ee* value of the substrate [(*R*)-**8**, 97%*ee*] was very high, racemization must take place at the stereocenter with the methyl group. The reduction conditions are very mild, so racemization probably occurs during the acidic deprotection of the ketal. The methyl and hydroxy substituents of the *cis* diastereomer are in equatorial positions, however one substituent in the *trans* diastereomer must be in an axial position. As a result, the *trans* isomer is less stable and probably undergoes racemization easier than the *cis* isomer. Therefore, the *ee* value of *cis* isomer is higher than that of the *trans* isomer.

The same reactions as those with (*R*)-**8** were conducted with 1,4-adduct (*S*)-**8**, Again, the diastereomeric products were inseparable. When (*R*)-CBS was used as the catalyst, there was a minor selectivity for the *trans* isomer, which was the same as that observed with (*R*)-**8** and (*S*)-CBS [mismatched substrate-catalyst pair, see Scheme 2, (c)]. In this case, both diastereomers were produced in 96%*ee*. Nearly no racemization of the *trans* isomer took place, which was probably a result of the slightly shorter stirring time with HCl during workup.

The treatment of (*S*)-**8** with (*S*)-CBS gave the *cis* diastereomer with a high enantiomeric excess value and nearly the same diastereoselectivity as that obtained for the reaction of (*R*)-**8** with (*R*)-CBS [matched substrate-catalyst pair, see Scheme 2, (d)]. The enantioselectivity of the *cis* isomer was 97%*ee* and that of the *trans* isomer was 60%*ee*. This very low *ee* value was probably a result of the longer stirring time with HCl during workup. In summary, we were able to synthesize cyclohexenones (*R*)-**1** and (*S*)-**1** in 29–61%*de* (*de* = diastereomeric excess) and 82–97%*ee* in only two steps from commercially available benzoquinone monoketal **7**.

We then turned our attention to the synthesis of cyclohexenone **2**. Under very mild deprotection conditions (Amberlyst® 15[19] in acetone), (*R*)-**8** afforded the unusual diketone (*R*)-**10** (see Scheme 3) as a slightly yellow oil, which remained stable for several hours at 7 °C without undergoing a tautomerization. Under the same conditions, we also converted (*S*)-**8** into (*S*)-**10**. In both cases, the yields were quantitative. The synthesis of racemic diketone **10** was already known,[20] but the preparation presented herein is the shortest [two steps from commercially available 4,4-dimethoxycyclohexa-2,5-dien-1-one (**7**)] and the only stereoselective one. The preparations of the unsubstituted and the racemic 5-vinyl-substituted dione have also been described in the literature, but through different synthetic pathways.[21] The enantiomeric excess values of (*R*)- and (*S*)-**10** could not be determined by chiral modified GC or HPLC columns, because aromatization occurred during the measurements. Nevertheless, optical rotations of both enantiomers of **10** could be measured, and they were opposite to each other with the same absolute value (see Exp. Section). We then conducted the deprotection step with methanol as the solvent, instead of acetone, which allowed us to react diketone **10** in situ. In this manner, diketones (*R*)- and (*S*)-**10** were subjected to a Diels–Alder reaction with cyclopentadiene to determine their enantiomeric excess values. This conversion has already been described using racemic dione **10**,[20a,20b] and the preparation of the racemic adduct **11** has also been performed through different synthetic routes.[22] Again, the enantiomeric excess values could not be determined, as this time there was a lack of separation on the chiral modified columns (GC and HPLC). However, as the racemization of dione **10** would occur with aromatization, it can be assumed that the enantiomeric excess value of **10** should be equivalent to that of **8**.

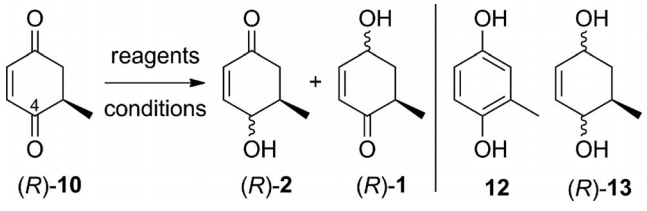
With the assumption that the oxygen at C-4 is more nucleophilic than the one at C-1 because of the presence of the adjacent methyl group, the reduction of diketone (*R*)-**10** under Luche conditions with 1 equiv. of reagent was performed to yield cyclohexenone (*R*)-**2** (see Table 1, Entry 1). Thereby, a mixture of isomers **1** and **2** with a preference for **1** was observed. For **1**, mainly the *cis* diastereomer was formed (92%*de*). No diastereoselectivity was observed for **2**. Next, the same reaction was performed at a lower temperature (see Table 1, Entry 2), which again yielded a mixture of both regioisomers with a slight preference for **1**. Both regioisomers were preferentially formed with the *trans* configuration (29%*de* for **1** and 74%*de* for **2**). We then conducted the reduction without the addition of the cerium(III) reagent. The overall yield was much lower, and no preference between the two regioisomers was observed (see Table 1, Entry 3). Cyclohexenone **1** was formed with a high *de* value (89%*de* for *cis* isomer), whereas the diastereoselectivity of **2** was much lower (43%*de* for *trans* isomer). The treatment of diketone (*R*)-**10** with the milder reducing agent triacetoxyborohydride afforded product in only a very low yield and with no preference observed between the two regioisomers (see Table 1, Entry 4). Here again, the *cis* isomer of **1** was formed in a high *de* (91%). The diastereoselectivity



Scheme 3. Synthesis of diketone **10**. Reagents and conditions: (a) Amberlyst 15®, water (2 drops), acetone, room temp., 10 min, quantitative yield of crude product; (b) Amberlyst 15®, water (2 drops), MeOH, room temp., 10 min, quantitative yield of crude product; (c) cyclopentadiene, MeOH, 0 °C to room temp., 3 d, 32%, *endo*/*exo*, 1.4:1.0; (d) cyclopentadiene, MeOH, 0 °C to room temp., 18 h, 28%, *endo*/*exo*, 1.0:1.0.

of *trans*-**2** was much lower (31%*de*). By using the bulky Alpine-hydride, cyclohexenone **1** was obtained nearly exclusively in good yield, which is probably a result of the steric hindrance from the methyl group (see Table 1, Entry 5). The *cis* isomer of **1** was mainly formed in 77%*de*. The reduction of (*R*)-**10** by treatment with diisobutylaluminium hydride (DIBAL-H) only yielded a small amount of a mixture of both regioisomers **1** and **2**, and again with a preference for **1** (see Table 1, Entry 6). Cyclohexenone **1** mainly had the *cis* configuration, whereas cyclohexenone **2** again was

Table 1. Reaction conditions for reduction of diketone **10**.



Entry	Reagents	Conditions	Yield[a] (%)	**2** (% *de*)/**1** (% *de*)
1	$NaBH_4$, $CeCl_3$	MeOH, 0 °C	44	1.0 (4.8):4.1 (92)
2	$NaBH_4$, $CeCl_3$	MeOH, –78 °C	33	1.0 (74):1.2 (29)
3	$NaBH_4$	MeOH, –10 °C	17	1.0 (43):1.0 (89)
4	$NaBH(OAc)_3$	MeOH, –78 °C	6.7	1.0 (31):1.1 (91)
5	Alpine-hydride[b]	THF, –78 °C	50	1.0 (33):15 (77)
6	DIBAL-H	THF, –78 °C	6.7	1.0 (39):3.8 (71)
7	menthol, $NaBH_4$, DIBAL-H	THF, –78 °C	6.6	1.0 (9.0):8.4 (95)
8	(*R*)-CBS	THF, 0 °C	15	1.0 (4.8):4.4 (93)
9	(*S*)-CBS	THF, 0 °C	46	1.0 (44):1.4 (90)

[a] Yield determined over two steps from cyclohexenone **8**. [b] Alpine-hydride = lithium *B*-isopinocampheyl-9-borabicyclo[3.3.1]-nonyl hydride.

mainly the *trans* isomer. The addition of menthol and sodium borohydride to DIBAL-H gave only low yields, but with a strong preference for cyclohexenone **1** (see Table 1, Entry 7), which also diastereoselectively formed as the *cis* isomer (95%*de*). Finally, the (*R*)- and (*S*)-CBS reagents were applied to the reduction reaction, but, again, mixtures of regioisomers were obtained. In both cases, the formation of **1** was preferred over **2**, although this preference was stronger with (*R*)-CBS (see Table 1, Entry 8). Again, the *cis* diastereomer of **1** was formed with high diastereomeric excess values [93%*de* with (*R*)-CBS and 90%*de* with (*S*)-CBS]. In the formation of **2** with (*R*)-CBS, no diastereoselectivity could be observed. This changed with (*S*)-CBS, where the *trans* diastereomer of **2** was formed in 44%*de*.

Overall, the methyl group does not appear to bring about a strong difference in the reduction of either of the carbonyl groups. In every case, however, it did effect a preference for cyclohexenone **1** instead of the desired cyclohexenone **2**. In one case (see Table 1, Entry 5), cyclohexenone **1** was obtained in good yield with high regioselectivity. The methyl and the hydroxy groups of **1** are preferentially arranged *cis* to each other. This is probably a consequence of the steric hindrance from the methyl group during the reduction reaction. The reducing agent attacks the carbonyl group on the side opposite to the methyl group. In addition, *cis*-**1** is more stable than *trans*-**1**, as both substituents in *cis*-**1** can be arranged in the equatorial position. For cyclohexenone **2**, the preference changes, and the *trans* diastereomer is mainly formed, although the diastereoselectivities are much lower than that for cyclohexenone **1**. In this case, the steric hindrance from the methyl group does not appear to be that effective. Furthermore, *trans*-**2** is more stable than *cis*-**2**, as both substituents of *trans*-**2** can be in the equatorial position. The yields are moderate to low, as there is a problem with the reactivity of diketone **10** in all these reactions. Under the reaction conditions, the diketone can tautomerize into 2-methylhydroquinone (**12**). This conversion was observed for all the reactions, even in the formation of Diels–Alder adducts **11** (see Scheme 3). Furthermore, the double reduction to diol **13** was also observed, but this was usually produced in low amounts as the reactions were quenched as soon as the double-reduced product was detectable by TLC. The results in Table 1 show that this synthetic pathway is only suitable for the synthesis of cyclohexenone **1** (see Table 1, Entries 5 and 7) and not for cyclohexenone **2**.

Conclusions

We presented the shortest synthetic pathway towards 4-hydroxy-6-methylcyclohex-2-enone (**1**) through an asymmetric Michael addition to benzoquinone monoketal **7**. Both enantiomeric 1,4-adducts **8** were obtained with high enantiomeric excess values (97–98%*ee*). Each enantiomer could then be converted into the corresponding cyclohexenone **1** through reduction by treatment with a CBS reagent. By choosing (*R*)- or (*S*)-CBS, the *trans* or *cis* isomers of cyclohexenones **1** were achieved. They were obtained in 82–97%*ee* and 29–61%*de*. All the reactions could be conducted on a gram-scale and are, therefore, suitable for building block synthesis. In addition, the (*R*)- and (*S*) enantiomers of diketone **10**, suitable reactants for Diels–Alder reactions, were obtained stereoselectively. From diketone **10**, cyclohexenone **1** was also obtained regioselectively by reduction with Alpine-hydride. Under various conditions, regioisomer **2** was obtained as a mixture with **1**.

Experimental Section

General Methods: The NMR spectroscopic data were recorded as solutions with a Bruker Avance 300 or a Bruker AM 400 spectrometer. Chemical shifts are expressed in parts per million (ppm, δ) downfield from tetramethylsilane (TMS) and are referenced to the residual solvent peaks. All coupling constants (J) are absolute values and are expressed in Hertz (Hz). The descriptions of signals include s (singlet), d (doublet), m (multiplet), m_c (centered multiplet), br. s (broad singlet), dd (doublet of doublet), ddd (doublet of doublet of doublet), and so forth. The assignment of different diastereomers or regioisomers was done by COSY experiments and by comparison to the literature (see ref.[11]). The spectra were analyzed according to first order. The signal structure in the ^{13}C NMR spectra was analyzed by DEPT and is described according to + (primary or tertiary C atom, positive DEPT signal), – (secondary C atom, negative DEPT signal), and C_q (quaternary C atom, no DEPT signal). MS [EI (electron impact mass spectrometry)] was performed with a FINNIGAN MAT 90 (70 eV). The mass peak $[M]^+$ and characteristic fragment peaks are given as a mass to charge ratio (m/z), and the intensity of the signals are indicated as a percent that is relative to the intensity of the base signal (100%). IR (infrared spectroscopy) was recorded with a FTIR Bruker alpha, and the intensities of the signals are characterized as vs (very strong, 0–10% transmission), s (strong, 11–30% transmission), m (medium, 31–70% transmission), w (weak, 71–90% transmission), and vw (very weak, 91–100% transmission). Optical rotations were measured with a Perkin–Elmer 241 polarimeter and are given as $[\alpha]_D^{20} = \alpha/(\beta \cdot d)$. The concentration ($c$) is given in g/100 mL, and α is the measured value in degrees (°). β is the concentration in g/mL, and d is the length of the cuvette in dm. Melting points of solid substances were measures with a Mel-Temp II (Laboratory Devices Inc.). Some of the enantiomeric excess values were measured by using a Bruker GC 430 with a chiral modified column (Zebron ZB-5MS), hydrogen as carrier gas, and a flame ionization detector (oxygen). Solvents, reagents, and chemicals were purchased from Aldrich, ABCR, Acros, and Maybridge. All solvents, reagents, and chemicals were used as purchased unless stated otherwise.

1,4-Adduct [(*S*)-8]:[23] A solution of copper(II) triflate (56 mg, 0.156 mmol, 0.0240 equiv.) and (*R*,*S*,*S*)-**9** (168 mg, 0.311 mmol, 0.0480 equiv.) in absolute toluene (30 mL) was stirred at room temp. under argon for 1 h. The mixture was then cooled to –25 °C, and benzoquinone monoketal **7**[24] (1.00 g, 6.49 mmol, 1.00 equiv.) and dimethylzinc (1.2 M in toluene, 8.92 mL, 1.02 g, 10.7 mmol, 1.65 equiv.) were added. After stirring at –25 °C for 15 h, a saturated ammonium chloride solution (16 mL) was added, and the mixture was extracted with ethyl acetate (3 × 120 mL). The combined organic layers were washed with NaOH (1 M solution, 150 mL) and a saturated sodium chloride solution (150 mL) and then dried with sodium sulfate. The solvent was removed under reduced pressure, and the residue was purified by column chromatography (cyclohexane/ethyl acetate, 5:1) to give (*S*)-**8** (580 mg, 3.41 mmol, 53%) as a colorless oil. The enantiomeric excess (98%*ee*) was determined by GC analysis on a chiral modified column. R_f = 0.69 (cyclohexane/ethyl acetate, 1:1). ^1H NMR

(300 MHz, $CDCl_3$): δ = 0.97 (d, ^3J = 7.1 Hz, 3 H, CH_3), 2.28 (dd, ^2J = 16.8 Hz, ^3J = 3.1 Hz, 1 H, CH_2), 2.51–2.62 (m, 1 H, C*H*), 2.83 (dd, ^2J = 16.8 Hz, ^3J = 4.8 Hz, 1 H, CH_2), 3.27 (s, 6 H, 2 CH_3O), 6.02 (d, ^3J = 10.4 Hz, 1 H, =C*H*), 6.65 (dd, ^3J = 10.4 Hz, ^4J = 2.0 Hz, 1 H, =C*H*) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 14.88 (+, *C*H$_3$), 35.52 (+, *C*H), 42.24 (–, *C*H$_2$), 47.64 (+, *C*H$_3$O), 49.80 (+, *C*H$_3$O), 99.18 [C_q, *C*(OMe)$_2$], 130.59 (+, =*C*H), 146.53 (+, =*C*H), 198.92 (C_q, *C*O) ppm. IR (KBr): $\tilde{\nu}$ = 2943 (m), 2833 (w), 1685 (m), 1630 (w), 1459 (w), 1413 (w), 1383 (m), 1349 (w), 1293 (w), 1264 (w), 1233 (w), 1203 (m), 1133 (m), 1112 (m), 1069 (m), 1045 (m), 993 (w), 971 (m), 931 (m), 848 (vw), 771 (vw), 706 (vw), 593 (vw) cm^{-1}. MS (FAB): *m*/*z* = 171 [M + H]$^+$, 155 [M – CH$_3$]$^+$, 139 [M – CH$_3$O]$^+$, 137 [$C_9H_{13}O$]$^+$, 136 [$C_8H_9O_2$]$^+$, 123 [$C_7H_7O_2$]$^+$, 107 [C_7H_7O]$^+$. HRMS (FAB): calcd. for $C_9H_{15}O_3$ 171.1021; found 171.1023. $[\alpha]_D^{20}$ = +2.21 (*c* = 0.895, ethyl acetate).

General Procedure for the Synthesis of Cyclohexenones 1: To a solution of CBS reagent (65.1 mg, 235 μmol, 1.00 equiv.) in absolute THF (2 mL) under argon were added 1,4-adduct **8** (40.0 mg, 235 μmol, 1.00 equiv.) in absolute THF (2 mL) at 0 °C, and the reaction mixture was stirred for 5 min. Then, BH$_3$·THF (1 M in THF, 470 μL, 470 μmol, 2.00 equiv.) was added dropwise, and the mixture was stirred at 0 °C for 1 h. After this time, HCl (1 M solution, 2 mL) was added, and the resulting mixture was stirred for 30 min and extracted with ethyl acetate (20 mL). The organic layer was dried with sodium sulfate, and the solvent was removed under reduced pressure. The residue was purified by column chromatography (cyclohexane/ethyl acetate, 1:1). The full analytical data of cyclohexenone **1** have already been reported by the authors (see ref.[11] and Supporting Information).

Cyclohexenone *cis*-(*R*)-1: According to the general procedure, (*R*)-CBS and (*R*)-**8** were used to yield the product (20.4 mg, 162 μmol, 69%) as a colorless oil and as a mixture of two inseparable diastereomers (*cis*-**1**/*trans*-**1**, 4.1:1.0, 95%*ee* for *cis*-**1**, 86%*ee* for *trans*-**1**). ^{1}H NMR (300 MHz, $CDCl_3$, *cis*-**1**): δ = 1.15 (d, ^3J = 6.5 Hz, 3 H, CH_3), 1.74 (m$_c$, 1 H, CH_2), 2.33–2.46 (m, 3 H, O*H*, C*H*CH$_3$, CH_2), 4.64 (m$_c$, 1 H, C*H*OH), 5.95 (d, ^3J = 10.2 Hz, 1 H, =C*H*), 6.88 (m$_c$, 1 H, =C*H*) ppm.

Cyclohexenone *trans*-(*R*)-1: According to the general procedure, (*S*)-CBS and (*R*)-**8** were used to yield the product (19.3 mg, 153 μmol, 65%) as a colorless oil and as a mixture of two inseparable diastereomers (*cis*-**1**/*trans*-**1**, 1.0:1.8, 82%*ee* for *trans*-**1**, 92%*ee* for *cis*-**1**). ^{1}H NMR (300 MHz, $CDCl_3$, *trans*-**1**): δ = 1.16 (d, ^3J = 7.1 Hz, 3 H, CH_3), 2.02–2.23 (m, 3 H, O*H*, CH_2), 2.76 (m$_c$, 1 H, C*H*CH$_3$), 4.55 (m$_c$, 1 H, C*H*OH), 5.95 (d, ^3J = 10.1 Hz, 1 H, =C*H*), 6.87 (m$_c$, 1 H, =C*H*) ppm.

Cyclohexenone *trans*-(*S*)-1: According to the general procedure, (*R*)-CBS and (*S*)-**8** were used to yield the product (13.6 mg, 108 μmol, 46%) as a colorless oil and as a mixture of two inseparable diastereomers (*cis*-**1**/*trans*-**1**, 1.0:2.1, 96%*ee* for *trans*-**1**, 96%*ee* for *cis*-**1**). ^{1}H NMR (300 MHz, $CDCl_3$, *trans*-**1**): δ = 1.16 (d, ^3J = 7.1 Hz, 3 H, CH_3), 2.02–2.18 (m, 2 H, CH_2), 2.76 (m$_c$, 1 H, C*H*CH$_3$), 4.55 (m$_c$, 1 H, C*H*OH), 5.95 (d, ^3J = 10.1 Hz, 1 H, =C*H*), 6.88 (d, ^3J = 10.1 Hz, 1 H, =C*H*) ppm.

Cyclohexenone *cis*-(*S*)-1: According to the general procedure, (*S*)-CBS and (*S*)-**8** were used to yield the product (18.1 mg, 143 μmol, 61%) as a colorless oil and as a mixture of two inseparable diastereomers (*cis*-**1**/*trans*-**1**, 3.5:1.0, 97%*ee* for *cis*-**1**, 60%*ee* for *trans*-**1**). ^{1}H NMR (300 MHz, $CDCl_3$, *cis*-**1**): δ = 1.16 (d, ^3J = 6.2 Hz, 3 H, CH_3), 1.73 (m$_c$, 1 H, CH_2), 1.95 (br. s, 1 H, O*H*), 2.34–2.44 (m, 2 H, C*H*CH$_3$, CH_2), 4.65 (m$_c$, 1 H, C*H*OH), 5.95 (d, ^3J = 10.2 Hz, 1 H, =C*H*), 6.88 (m$_c$, 1 H, =C*H*) ppm.

General Procedure for Determination of Enantiomeric Excess Values of Cyclohexenones 1 by Mosher Method:[25] To cyclohexenone **1** (5.0 mg, 39.6 μmol, 1.00 equiv.) in deuterated pyridine (0.5 mL) in a NMR tube was added Mosher chloride (15 μL, 79.2 μmol, 2.00 equiv.). The mixture was shaken for 1 h, and the NMR spectroscopic data were recorded. The enantiomeric excess values were determined by integration of the signals. Full analytical data have already been reported by the authors (see ref.[11]).

General Procedure A for Deprotection of 1,4-Adduct 8: To a solution of 1,4-adduct **8** (20 mg, 118 μmol, 1.00 equiv.) in acetone (1 mL) were added water (2 drops) and then Amberlyst 15® (10 mg). The mixture was stirred at room temp. for 10 min and then diluted with Et_2O (5 mL). The resulting solution was dried with sodium sulfate, and then the solvent was removed under reduced pressure at room temp. to give product **10** (14.6 mg, 118 μmol, quantitative yield) as a yellow oil, which was used without further purification. Note: The product was stable at 7 °C for several hours. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.25 (d, ^3J = 6.6 Hz, 3 H, CH_3), 2.63 (ddd, ^2J = 12.3 Hz, ^3J = 12.3 Hz, ^4J = 3.1 Hz, 1 H, CH_2), 2.94–3.03 (m, 2 H, C*H*CH$_3$, CH_2), 6.70 (dd, ^3J = 10.3 Hz, ^4J = 0.7 Hz, 1 H, =C*H*), 6.74 (d, ^3J = 10.3 Hz, 1 H, =C*H*) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 15.68 (+, *C*H$_3$), 41.98 (+, *C*H), 45.00 (–, *C*H$_2$), 140.68 (+, =*C*H), 140.88 (+, =*C*H), 197.66 (C_q, *C*O), 200.21 (C_q, *C*O) ppm. For [(*R*)-**10**], $[\alpha]_D^{20}$ = –134.68 (*c* = 0.496, acetone) and for [(*S*)-**10**], $[\alpha]_D^{20}$= +130.85 (*c* = 0.496, acetone). No further analytical data were recorded because the molecule was very sensitive to aromatization.

General Procedure B for Deprotection of 1,4-Adduct 8: To a solution of 1,4-adduct **8** (20 mg, 118 μmol, 1.00 equiv.) in MeOH (1 mL) were added water (2 drops) and then Amberlyst 15® (10 mg). The mixture was stirred at room temp. for 10 min, and then it was dried with sodium sulfate and filtered. The filtrate was used directly for the next reaction with the assumption of a quantitative yield for **10**.

Reduction of Diketone 10

(a) Using $NaBH_4$ and $CeCl_3$ at 0 °C: According to general procedure B, (*R*)-**8** was deprotected. The methanolic solution was cooled to 0 °C, and then $CeCl_3$·7H_2O (44.0 mg, 118 μmol, 1.00 equiv.) was added. After stirring for 5 min, $NaBH_4$ (1.1 mg, 29.5 μmol, 0.250 equiv.) was added. The stirring was continued at this temperature for 90 min, and then $NaBH_4$ (1.1 mg, 29.5 μmol, 0.250 equiv.) was added again. After 30 min at this temperature, the mixture was quenched with a saturated ammonium chloride solution (2 mL). The resulting solution was extracted with ethyl acetate (3 × 5 mL), and the combined extracts were dried with sodium sulfate. The solvent was removed under reduced pressure. The residue was purified by column chromatography (cyclohexane/ethyl acetate, 1:1) to give the product as a mixture of (*R*)-**1** (5.2 mg, 41.5 μmol, 35% over 2 steps; *cis*/*trans*, 25.3:1.0) and (*R*)-**2** (1.3 mg, 10.1 μmol, 8.6% over 2 steps; *cis*/*trans*, 1.1:1.0) as a yellow oil.

(b) Using $NaBH_4$ and $CeCl_3$ at –78 °C: According to the general procedure B, (*R*)-**8** was deprotected. The methanolic solution was cooled to –78 °C, and then $CeCl_3$·7H_2O (44.0 mg, 118 μmol, 1.00 equiv.) was added. After stirring for 5 min, $NaBH_4$ (4.5 mg, 118 μmol, 1.00 equiv.) was added. The stirring was continued at this temperature for 60 min, and then the mixture was quenched with a saturated ammonium chloride solution (2 mL). The resulting solution was extracted with ethyl acetate (3 × 5 mL), and the combined extracts were dried with sodium sulfate. The solvent was removed under reduced pressure. The residue was purified by column chromatography (cyclohexane/ethyl acetate, 1:1) to give the product as a mixture of (*R*)-**1** (2.7 mg, 21.2 μmol, 18%; *cis*/*trans*, 1.0:1.8) and (*R*)-**2** (2.2 mg, 17.7 μmol, 15%; *cis*/*trans*, 1.0:6.6) as a yellow oil.

(c) Using $NaBH_4$: According to general procedure B, (*R*)-**8** was deprotected. The methanolic solution was cooled to –10 °C, and then $NaBH_4$ (1.1 mg, 29.5 μmol, 0.250 equiv.) was added. The mixture was stirred at this temperature for 90 min and then quenched with a saturated ammonium chloride solution (2 mL). The resulting mixture was extracted with ethyl acetate (3 × 5 mL), and the combined extracts were dried with sodium sulfate. The solvent was removed under reduced pressure. The residue was purified by column chromatography (cyclohexane/ethyl acetate, 1:1) to give the product as a mixture of (*R*)-**1** (1.3 mg, 9.9 μmol, 8.4%; *cis*/*trans*, 17.1:1.0) and (*R*)-**2** (1.3 mg, 9.9 μmol, 8.4%; *cis*/*trans*, 1.0:2.5) as a yellow oil.

(d) Using $NaBH(OAc)_3$: According to general procedure B, (*R*)-**8** was deprotected. The methanolic solution was cooled to –78 °C, and then $NaBH(OAc)_3$ (25.0 mg, 118 μmol, 1.00 equiv.) was added. After stirring for 90 min at this temperature, the mixture was quenched with a saturated ammonium chloride solution (2 mL). The resulting mixture was extracted with ethyl acetate (3 × 5 mL), and the combined extracts were dried with sodium sulfate. The solvent was removed under reduced pressure. The residue was purified by column chromatography (cyclohexane/ethyl acetate, 1:1) to give the product as a mixture of (*R*)-**1** (0.52 mg, 4.1 μmol, 3.5%; *cis*/*trans*, 22.4:1.0) and (*R*)-**2** (0.48 mg, 3.8 μmol, 3.2%; *cis*/*trans*, 1.0:1.9) as a yellow oil.

(e) Using Alpine-Hydride: According to general procedure A, (*R*)-**8** was deprotected. The crude **10** was dissolved in absolute THF (2 mL), and the mixture was cooled to –78 °C. Alpine-hydride (0.5 M in THF, 118 μL, 118 μmol, 1.00 equiv.) was then added. After stirring for 60 min at this temperature, the mixture was quenched with a saturated ammonium chloride solution (2 mL), and the resulting solution was extracted with ethyl acetate (3 × 5 mL). The combined extracts were dried with sodium sulfate, and the solvent was removed under reduced pressure. The residue was purified by column chromatography (cyclohexane/ethyl acetate, 1:1) to give the product as a mixture of (*R*)-**1** (7.0 mg, 55.0 μmol, 47%; *cis*/*trans*, 7.6:1.0) and (*R*)-**2** (0.5 mg, 3.7 μmol, 3.1%; *cis*/*trans*, 1.0:2.0) as a yellow oil.

(f) Using DIBAL-H: According to general procedure A, (*R*)-**8** was deprotected. The crude **10** was dissolved in absolute THF (2 mL), and the mixture was cooled to –78 °C. DIBAL-H (1 M in dichloromethane, 118 μL, 118 μmol, 1.00 equiv.) was added. After stirring for 60 min at this temperature, the mixture was quenched with a saturated ammonium chloride solution (2 mL), and the resulting solution was extracted with ethyl acetate (3 × 5 mL). The combined extracts were dried with sodium sulfate, and the solvent was removed under reduced pressure. The residue was purified by column chromatography (cyclohexane/ethyl acetate, 1:1) to give the product as a mixture of (*R*)-**1** (0.8 mg, 6.3 μmol, 5.3% over 2 steps; *cis*/*trans*, 5.9:1.0) and (*R*)-**2** (0.2 mg, 1.7 μmol, 1.4% over 2 steps; *cis*/*trans*, 1.0:2.3) as a yellow oil.

(g) Using (–)-menthol, DIBAL-H, and $NaBH_4$: According to general procedure A, (*R*)-**8** was deprotected. To absolute THF (2 mL) were added (–)-menthol (18.4 mg, 236 μmol, 2.00 equiv.) and DIBAL-H (1 M in dichloromethane, 0.12 mL, 118 μmol, 1.00 equiv.), and the reaction mixture was stirred at room temp. for 1 h. The mixture was cooled to –78 °C. Then, a solution of crude **10** in absolute THF (0.5 mL) and $NaBH_4$ (1.5 mg, 29.5 μmol, 0.250 equiv.) were added to the reaction mixture. The mixture was stirred at –78 °C for 1.5 h and then quenched with a saturated ammonium chloride solution (2 mL). The resulting mixture was extracted with ethyl acetate (3 × 5 mL), and the combined extracts were dried with sodium sulfate. The solvent was removed under reduced pressure. The residue was purified by column chromatography (cyclohexane/ethyl acetate, 1:1) to give the product as a mixture of (*R*)-**1** (0.9 mg, 7.0 μmol, 5.9% over 2 steps; *cis*/*trans*, 41.5:1.0) and (*R*)-**2** (0.1 mg, 0.9 μmol, 0.7% over 2 steps; *cis*/*trans*, 1.0:1.2) as a yellow oil.

(h) Using (*R*)-CBS: According to general procedure A, (*R*)-**8** was deprotected. Crude **10** was dissolved in absolute THF (2 mL), and the mixture was cooled to 0 °C. Then, (*R*)-CBS reagent (32.7 mg, 118 μmol, 1.00 equiv.) was added. After 5 min, BH_3·THF (1 M in THF, 118 μL, 118 μmol, 1.00 equiv.) was added. The mixture was stirred at 0 °C for 1 h and then quenched with HCl (1 M solution, 2 mL). The resulting mixture was extracted with ethyl acetate (3 × 5 mL), and the combined extracts were dried with sodium sulfate. The solvent was removed under reduced pressure. The residue was purified by column chromatography (cyclohexane/ethyl acetate, 1:1) to give the product as a mixture of (*R*)-**1** (1.8 mg, 13.9 μmol, 12% over 2 steps; *cis*/*trans*, 26.0:1.0) and (*R*)-**2** (0.4 mg, 3.2 μmol, 2.7% over 2 steps; *cis*/*trans*, 1.1:1.0) as a yellow oil.

(i) Using (*S*)-CBS: According to general procedure A, (*R*)-**8** was deprotected. Crude **10** was dissolved in absolute THF (2 mL), and the mixture was cooled to 0 °C. Then, (*S*)-CBS reagent (32.7 mg, 118 μmol, 1.00 equiv.) was added. After 5 min, BH_3·THF (1 M in THF, 118 μL, 118 μmol, 1.00 equiv.) was added. The mixture was stirred for 1 h at 0 °C and then quenched with HCl (1 M solution, 2 mL). The resulting mixture was extracted with ethyl acetate (3 × 5 mL), and the combined extracts were dried with sodium sulfate. The solvent was removed under reduced pressure. The residue was purified by column chromatography (cyclohexane/ethyl acetate, 1:1) to give the product as a mixture of (*R*)-**1** (4.0 mg, 31.7 μmol, 27% over 2 steps; *cis*/*trans*, 19.1:1.0) and (*R*)-**2** (2.9 mg, 23.0 μmol, 19% over 2 steps; *cis*/*trans*, 1.0:2.6) as a yellow oil. The full analytical data of cyclohexenone **2** have already been reported by the authors (see ref.[11] and Supporting Information).

Diels–Alder Adduct (*S*)-11: To a solution of 1,4-adduct (*S*)-**8** (50.0 mg, 295 μmol, 1.00 equiv.) in acetone (2 mL) were added water (2 drops) and then Amberlyst 15® (10 mg). The mixture was stirred at room temp. for 10 min then diluted with Et_2O (10 mL). The resulting solution was dried with sodium sulfate, and the solvent was removed under reduced pressure at room temp. to give (*S*)-**10** as a yellow oil (14.6 mg, 118 μmol, quantitative yield). The product was dissolved in methanol (5 mL), and the solution was cooled to 0 °C. Freshly distilled cyclopentadiene (25 mg, 378 μmol, 1.28 equiv.) was added. The mixture was stirred at room temp. for 18 h, and then the solvent was removed under reduced pressure. The residue was purified by column chromatography (cyclohexane/ethyl acetate, 20:1). One fraction of pure *endo*-(*S*)-**11** (5.4 mg, 28.4 μmol, 10%) and a mixed fraction of *endo*- and *exo*-(*S*)-**11** (10.4 mg, 54.7 μmol, 19%; *endo*/*exo*, 1.0:4.2) were obtained. Data for *endo*-(*S*)-**11**: R_f = 0.53 (cyclohexane/ethyl acetate, 2:1); m.p. 76 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.10 (d, ^3J = 6.7 Hz, 3 H, CH_3), 1.38 (d, ^2J = 8.7 Hz, 1 H CH_2), 1.50 (ddd, ^2J = 8.6 Hz, ^3J = 1.7 Hz, ^3J = 1.7 Hz, 1 H, CH_2), 2.26–2.52 (m, 3 H, CHCH$_3$, CH_2), 3.18 (dd, ^3J = 9.8 Hz, ^3J = 3.8 Hz, 1 H, CH), 3.25 (dd, ^3J = 9.8 Hz, ^3J = 3.9 Hz, 1 H, CH), 3.42 (m_c, 1 H, CH), 3.48 (m_c, 1 H, CH), 6.12 (dd, ^3J = 5.6 Hz, ^3J = 2.9 Hz, 1 H, =CH), 6.25 (dd, ^3J = 5.6 Hz, ^3J = 2.9 Hz, 1 H, =CH) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 15.34 (+, *C*H$_3$), 41.97 (+, *C*HCH$_3$), 46.00 (–, *C*H$_2$), 47.00 (+, *C*H), 48.52 (+, *C*H), 49.24 (–, *C*H$_2$), 50.66 (+, *C*H), 52.64 (+, *C*H), 135.74 (+, =*C*H), 137.37 (+, =*C*H), 208.94 (C_q, *C*O), 212.05 (C_q, *C*O) ppm. Data for *exo*-(*S*)-**11**: R_f = 0.47 (cyclohexane/ethyl acetate, 2:1); m.p. 89 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.00 (d, ^3J = 6.5 Hz, 3 H, CH_3), 1.35 (d, ^2J = 8.7 Hz, 1 H CH_2), 1.58 (ddd, ^2J = 8.9 Hz, ^3J = 1.7 Hz, ^3J = 1.7 Hz, 1 H, CH_2), 1.95

(dd, ^2J = 16.9 Hz, ^3J = 14.4 Hz, 1 H, CH_2), 2.55 (ddd, ^2J = 16.9 Hz, ^3J = 5.4 Hz, ^4J = 1.5 Hz, 1 H, CH_2), 2.73–2.83 (m, 1 H, CHCH$_3$), 3.17 (dd, ^3J = 10.1 Hz, ^3J = 3.8 Hz, 1 H, CH), 3.32 (ddd, ^3J = 10.0 Hz, ^3J = 3.9 Hz, ^4J = 1.3 Hz, 1 H, CH), 3.40 (m_c, 1 H, CH), 3.50 (m_c, 1 H, CH), 6.04 (dd, ^3J = 5.6 Hz, ^3J = 2.8 Hz, 1 H, =CH), 6.25 (dd, ^3J = 5.6 Hz, ^3J = 2.9 Hz, 1 H, =CH) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 13.75 (+, CH_3), 41.49 (+, $CHCH_3$), 45.45 (+, CH), 45.67 (–, CH_2), 48.47 (+, CH), 48.56 (–, CH_2), 52.20 (+, CH), 52.55 (+, CH), 135.07 (+, =CH), 138.26 (+, =CH), 210.11 (C_q, CO), 210.30 (C_q, CO) ppm. IR [attenuated total reflectance (ATR) platinium, mixture of diastereomers]: $\tilde{\nu}$ = 2972 (vw), 2946 (vw), 1695 (w), 1458 (vw), 1412 (vw), 1373 (vw), 1339 (vw), 1299 (vw), 1261 (vw), 1244 (vw), 1223 (vw), 1181 (vw), 1157 (vw), 1104 (vw), 1057 (vw), 991 (vw), 910 (vw), 860 (vw), 781 (vw), 751 (vw), 729 (vw), 613 (vw), 576 (vw), 501 (vw) cm^{-1}. MS (EI, 70 eV, mixture of diastereomers): *m*/*z* (%) = 190 (44) $[M]^+$, 91 (19) $[C_7H_7]^+$, 66 (100) $[C_5H_6]^+$. HRMS (EI, mixture of diastereomers): calcd. for $C_{12}H_{14}O_2$ 190.0994; found 190.0995.

Diels–Alder Adduct (*R*)-11: To a solution of 1,4-adduct (*R*)-**8** (50.0 mg, 295 µmol, 1.00 equiv.) in acetone (2 mL) were added water (2 drops) and then Amberlyst 15® (10 mg). The mixture was stirred at room temp. for 10 min and then diluted with of Et_2O (10 mL). The resulting mixture was dried with sodium sulfate, and then the solvent was removed under reduced pressure at room temp. to give (*R*)-**10** (14.6 mg, 118 µmol, quantitative yield) as a yellow oil. The product was dissolved in methanol (5 mL), and the solution was cooled to 0 °C. Freshly distilled cyclopentadiene (25 mg, 378 µmol, 1.28 equiv.) was added. The mixture was stirred at room temp. for 18 h, and then the solvent was removed under reduced pressure. The residue was purified by column chromatography (cyclohexane/ethyl acetate, 10:1). One fraction of pure *endo*-(*S*)-**11** (5.7 mg, 30.0 µmol, 10%) and a mixed fraction of *endo*- and *exo*-(*S*)-**11** (12.0 mg, 63.1 µmol, 21%; *endo*/*exo*, 1.0:1.6) were obtained. The analytical data of *endo*-(*R*)-**11** corresponds with *endo*-(*S*)-**11**, and the data for *exo*-(*R*)-**11** corresponds with *exo*-(*S*)-**11**. Therefore, they are not listed.

Supporting Information (see footnote on the first page of this article): Further experimental and analytical data as well as ^{1}H and ^{13}C NMR spectra are presented.

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