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# An Efficient Protocol for the Enantioselective Preparation of a Key Polyfunctionalized Cyclohexane. New Access to (*R*)- and (*S*)-4-Hydroxy-2-cyclohexenone and (*R*)- and (*S*)-*trans*-Cyclohex-2-ene-1,4-diol

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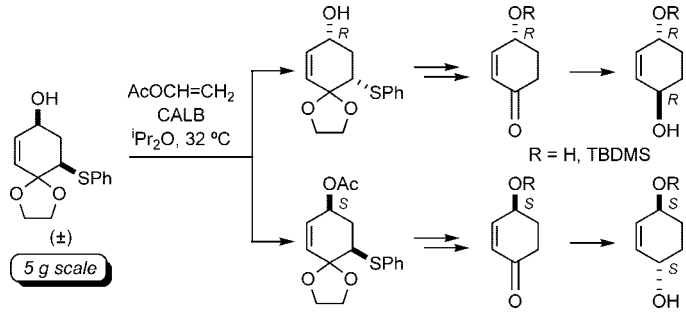


Starting from very accessible raw materials such as *p*-methoxyphenol, ethylene glycol, and thiophenol, a protocol has been developed to prepare multigram quantities of the polyfunctionalized cyclohexane (±)-**7**. A highly efficient resolution of (±)-**7** has been achieved through enantioselective acetylation catalyzed by *Candida antarctica* lipase B. Straightforward and enantioselective syntheses of 4-hydroxy-2-cyclohexenone, **1**, *trans*-cyclohex-2-ene-1,4-diol, **2**, and their *O*-protected derivatives **18** and **19** have been readily accomplished from **7**.

## Introduction

A great number of compounds isolated from natural sources present a cyclohexane core as the main structural feature. Among them, those possessing diverse oxygen-based substituents such as conduritols,[1] conduramines,[2] inositols,[3] cyclohexene epoxides,[4] gabosines,[5] and other carbasugars[6] have deserved the special attention of synthetic chemists because of their diverse biological activities and the challenge of binding oxygen atoms to a carbocycle in a regio- and stereoselective manner. However, in spite of the considerable efforts devoted to this endeavor, much work is still needed in this area. In particular, there is a need for chiral raw materials, sufficiently available in enantiomerically pure form, with the necessary versatility to handle the structural diversity occurring among the pursued polyoxygenated cyclohexanes. In this scenario, the functional motif of α,β-cyclohexenone makes its chiral derivatives very attractive precursors to these targets. In particular, 4-hydroxy-2-cyclohexenone, **1**, has been used as a building block in the synthesis of several bioactive compounds such as the anticholesterol agents compactin and ML-236A,[7] the immunosuppressant FK-506,[8] the marine sesquiterpene 10-isothiocyanatoguaia-6-ene,[9] the structurally related metabolites (+)-epiepoformin, (+)-epiepoxydon, and (+)-bromoxone,[10] the antifungal and antibiotic

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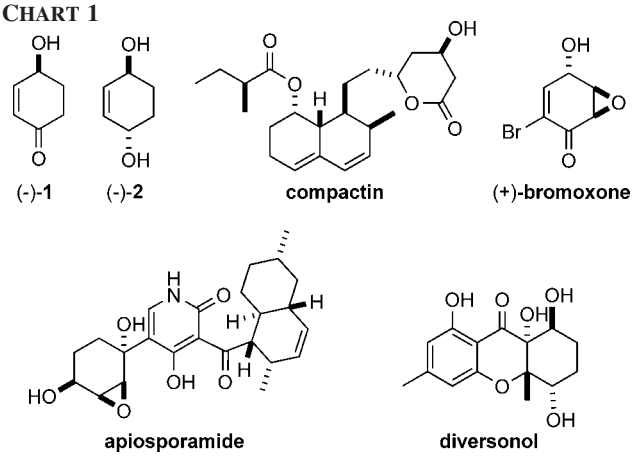
**CHART 1**




(+)-apiosporamide,[11] the fungal metabolite diversonol,[12] and the bacterial DNA primase inhibitor Sch 642305[13] (some of these compounds are depicted in Chart 1). In these syntheses, the relative configuration of the stereogenic centers of the products is induced by the stereogenic center at C-4 of ketone **1**.

In an earlier publication, we reported two alternative preparations of optically active **1**,[14] starting from chiral synthetic equivalents of *p*-benzoquinone previously developed in our laboratories.[15] Other syntheses of (+)- and (−)-**1** (or *O*-protected derivatives of them) have also been described in the literature,[16] many of which involve multistep sequences with low overall yields or poor enantioselectivities. Besides one of our own approaches,[14] only the syntheses described by Demir and Sesenoglu[16k] and by Bräse and co-workers[16o] give access to both (+)- and (−)-**1**, although resolution protocols for racemic **1** have also been described.[16n,17]

To further extend the use of (*R*)- or (*S*)-**1** as precursors to more sophisticated molecules with multiple stereocenters, we judged convenient to search for a new synthetic approach to the enantiomers of **1**, which was easy to scale, avoiding tedious chromatographic separations that are a severe limitation for multigram availability. Moreover, we also planned to direct the synthesis to a suitably protected derivative of **1**, in order to circumvent some practical problems associated to its isolation, related to its volatility and high solubility in water. In this article we describe a new, more practical preparation of either enantiomer of **1**, as well as a new enantioselective synthesis of *trans*-cyclohexene-1,4-diol, **2**, that improves our previously reported one.[18] A monoprotected derivative of **2** has been used as an intermediate for the synthesis of petasins[16j] and cyclohexane prostanoids.[19]

## Results and Discussion

**Scale-up of the Preparation of the Racemic Starting Material (±)-3.** One of our synthetic sequences previously developed for the preparation of ketones (+)- and (−)-**1** (Scheme 1) was completed in four chemical steps and 54% total yield starting from (−)-and (+)-**3**, respectively. Compound **3** can be visualized as a chiral derivative of *p*-benzoquinone in which one of the carbonyl groups is protected as ethylene ketal and one of the double bonds has been masked by addition of thiophenol.[14] Starting from ketone (−)-**3**, we also synthesized diol (−)-**2** and its monosilyl derivative (−)-**11** in 27% and 35% yield, respectively.[18] The main drawback of these syntheses was that the separated enantiomers of **3** were only available by chromatographic resolution of the racemate on a limited scale of several hundred miligrams.[15b,c] An additional weakness came from the laborious chromatographic separation involved in the isolation protocol of (±)-**3**, which is prepared by conjugate addition of thiophenol to ketal **13** under thermodynamic control, being therefore obtained along with the diaddition products *cis*- and *trans*-**14** and some unreacted **13** (Scheme 2). With the aim of skipping these problems, a thorough reexamination of all the procedures formerly established was undertaken.

Accordingly to literature precedents, we originally prepared the *p*-benzoquinone monoketal **13** from 3,3,6,6-tetramethoxy-1,4-cyclohexadiene by transketalization with ethylene glycol,[20] followed by ketal monohydrolysis.[21] In the present work, we have used a slight modification[22] of the more convenient method recently reported by Wong and co-workers,[23] consisting of the treatment of *p*-methoxyphenol, **12**, with phenyliodonium bis-(trifluoroacetate) (PIFA) and ethylene glycol in dichloromethane. This reaction can be performed on a multigram scale and the product purified by crystallization or filtration through a small path of silica gel. In our previously established procedure, compound (±)-**3** was prepared by reaction of thiophenol with ketal **13** (1.8 equiv) in the presence of lithium hydroxide in chloroform at reflux temperature and isolated from the crude product mixture by column chromatography. This chromatographic purification prevented the scaling up of the process that otherwise could be run with large quantities of reactants without problems. Therefore, we decided to explore the possibility of separating the monoaddition product (±)-**3** from the mixture by fractional crystallization. Thus, the relative solubility of each

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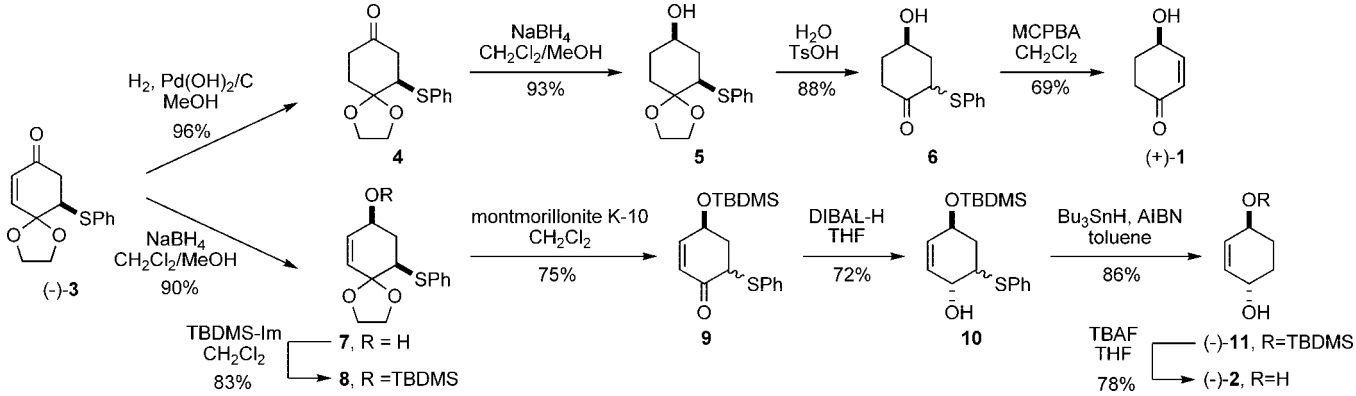
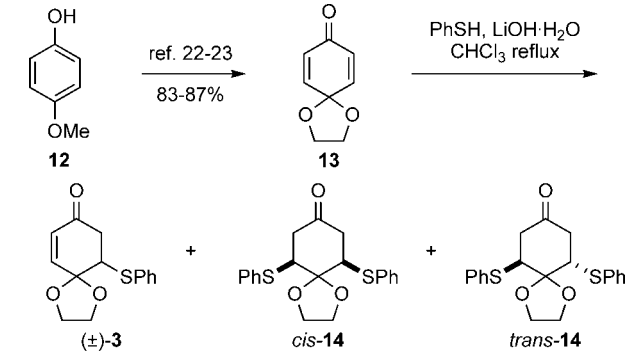
**SCHEME 1. Former Syntheses of Hydroxyenone (+)-1[14] and Enediol (−)-2[18] Starting from (−)-3**




**SCHEME 2. Preparation of (±)-3 from *p*-Methoxyphenol, 12**




**SCHEME 3. Enzymatic Resolution of (±)-7**

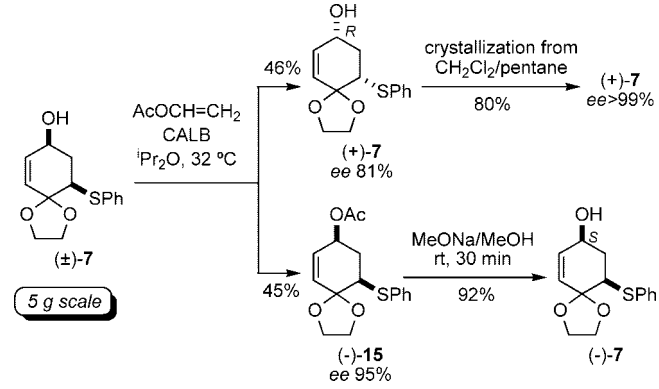



**TABLE 1. Qualitative Solubility of Compounds 3, 13, *cis*-14, and *trans*-14 in Different Solvents at Room and Boiling Temperatures[a]**

| | **3** | | **13** | | ***cis*-14** | | ***trans*-14** | |
|---|---|---|---|---|---|---|---|---|
| solvent | rt | bt | rt | bt | rt | bt | rt | bt |
| pentane | i | i | i | i | i | i | i | i |
| hexane | i | s | i | i[b] | i | i | i | i |
| cyclohexane | i | i[b] | i | i[b] | i | i | i | i[b] |
| $^{i}Pr_2O$ | s | s | s | s | s | s | s | s |
| $^{t}$BuOMe | s | s | s | s | i | i | i | i |
| toluene | s | s | s | s | s | s | s | s |
| $CH_2Cl_2$ | s | s | s | s | s | s | s | s |
| acetonitrile | s | s | s | s | s | s | s | s |
| $^{i}$PrOH | i | s | s | s | i | i | i | i |
| EtOH | i | i[b] | s | s | i | $\delta$ | i | $\delta$ |
| $H_2O$ | $\delta$ | s | $\delta$ | s | i | $\delta$ | i | $\delta$ |
| $^{i}$PrOH/ $H_2O$ | $\delta$ | s | s | s | i | i | $\delta$ | s |
| EtOH/ $H_2O$ | $\delta$ | s | s | s | i | i | $\delta$ | s |
| acetonitrile/ $H_2O$ | $\delta$ | s | s | s | i | i | i | i |

[a] If 25 mg of the pure compound is completely dissolved in 0.25 mL of the solvent at room temperature (rt) or boiling temperature (bt) the experiment is labeled as s (soluble); if dilution up to 0.75 mL leads to total dissolution, the experiment is labeled as $\delta$ (partially soluble); if some solid still remains, the experiment is labeled as i (insoluble). [b] Insoluble oily material is observed.

of the four compounds ((±)-**3**, **13**, *cis*-**14**, and *trans*-**14**) present in the crude reaction product in a series of solvents was qualitatively examined (Table 1).

It was observed that the four compounds show low solubility in apolar solvents and are quite soluble in polar aprotic solvents. Fortunately, a distinct behavior was found in polar protic solvents, where the diaddition compounds *cis*- and *trans*-**14** are poorly soluble compared to **3** and **13**, but the most remarkable observation was that the unreacted ketal **13** is noticeably more soluble than the monoaddition product **3** in 2-propanol at room temperature. Thus, crystallization of the crude reaction material from 2-propanol, followed by one or two recrystallizations from the same solvent, allows the isolation of pure (±)-**3** in 60–70% overall yield from thiophenol. Following this protocol, quantities over 4 g of (±)-**3** have been obtained from a single operation. Since the conjugate addition of thiophenol to ketal **13** is a reversible process, the crystallization residue can be easily recycled.

**Enzymatic Resolution of (±)-7.** Once a practical methodology for accessing (±)-**3** in substantial amounts had been established, our following challenge was to find an easily scalable mode to resolve its racemate, as an alternative to the previously employed chiral liquid chromatography on cellulose triacetate.[15b,c] Since the enantioselective reduction of ketone (±)-**3** to the alcohol (+)- or (−)-**7** met with failure, we turned out our attention to the resolution of the racemate (±)-**7**, easily prepared from (±)-**3** by reduction with $NaBH_4$.[14]

On the basis of a closely related literature precedent,[17b] we investigated the enzyme-catalyzed enantioselective acetylation of (±)-**7** (Scheme 3). The initial experiments were performed with quantities of around 1 g of racemic substrate following the reported conditions. Accordingly, an 18 mM solution of (±)-**7** in diisopropyl ether was treated with vinyl acetate (6 mol per mol of racemic **7**) in the presence of lipase acrylic resin from *Candida antarctica* (CALB) (2 g per g of racemic **7**) at 32 °C (Scheme 3).[24]

By $^1$H NMR and CHPLC analyses of aliquot samples (Table 2), it was observed that, after 15 min of reaction, almost 50% of the starting racemate was already acetylated and the ee of

(24) A preliminary description of this reaction was included in ref 5b.

**TABLE 2. Evolution of the CALB-Catalyzed Reaction of (±)-7 with Vinyl Acetate in Diisopropyl Ether**

| entry | time | (+)-**7**/(−)-**15**[a] | ee of (+)-**7**[b] (%) | ee of (−)-**15**[b] (%) |
|---|---|---|---|---|
| 1 | 15 min | 1:0.9 | 91 | 95 |
| 2 | 30 min | 1:1.3 | 99 | 93 |
| 3 | 45 min | 1:1.4 | 99 | 91 |
| 4 | 1 h | 1:1.4 | 99 | 89 |
| 5 | 1 h 15 min | 1:1.6 | 99 | 85 |
| 6 | 1 h 30 min | 1:1.7 | 99 | 83 |
| 7 | 2 h 30 min | 1:1.8 | 99 | 71 |
| 8 | 24 h | 1:2.7 | 40 | 13 |

[a] The reaction evolution was monitorized by GC ("cross linked" dimethyl silicone, from 200 to 260 °C, gradient = 6 °C/min), and the product ratio was determined by $^1$H NMR. A GC peak relation of **7**/**15** = 1:1.1 corresponds to an equimolar mixture. [b] The ee's were determined by CHPLC (CHIRACEL OD, 0.7 mL/min, hexane/PrOH 4:1).

**TABLE 3. Evolution of the ee's in the CALB-Catalyzed Enantioselective Acetylation of (±)-7[a]**

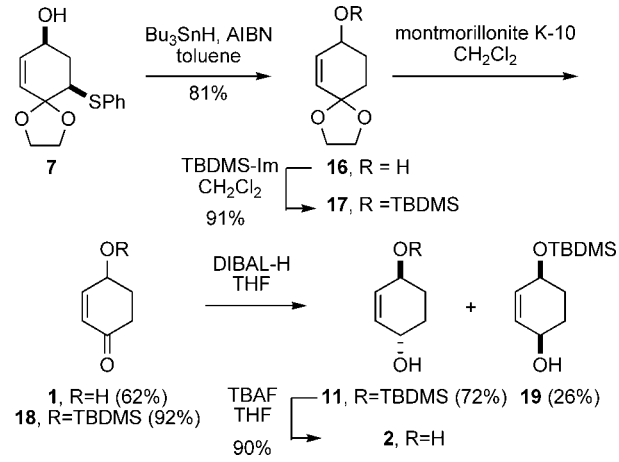
| entry | time (min) | (+)-**7**/(−)-15[b] | ee of (+)-**7**[c] (%) (calcd ee, %)[d] | ee of (−)-**15**[c] (%) |
|---|---|---|---|---|
| 1 | 30 | 1:0.38 | 24 (43) | 100 |
| 2 | 40 | 1:0.57 | 40 (56) | 100 |
| 3 | 50 | 1:0.76 | 56 (75) | 97 |
| 4 | 60 | 1:0.96 | 73 (98) | 95 |
| 5 | 90 | 1:1.15 | 95 | 92 |
| 6 | 105 | 1:1.21 | 93 | 89 |

[a] $[(\pm)\text{-}7]_0$ = 72 mM; weight proportion (±)-**7**/CALB = 1:0.25. [b] Ratio determined by $^1$H NMR. [c] The ee's were determined by CHPLC (CHIRACEL OD, 0.7 mL/min, hexane/$^i$PrOH 4:1). [d] Calculated ee value considering the conversion and assuming that the only process occurring was the acetylation of (−)-**7**.

the remaining alcohol (+)-**7** was 91% (entry 1). Prolonged reaction time increased the ee of (+)-**7** to 99%, with this value being maintained for at least 2.5 h (entries 2–7). During this time, the proportion of acetate (−)-**15** increased slowly and its enantiomeric purity diminished in a percentage consistent with the slower acetylation of the less reactive enantiomer (+)-**7**. It was also observed (entry 8) that, after 1 day under the reaction conditions, the enantiomeric purity of the residual alcohol decreased notably, a fact that we tentatively attributed to an enzyme-catalyzed transesterification process. Since the enantioselective acetylation was quite fast, we investigated the possibility of diminishing the proportion of enzyme and found that a weight ratio of (±)-**7**/CALB = 1:0.25 was enough to complete the process in around 3 h. It was also proved that the enzyme can be reused at least up to four consecutive times without a significant loss of ee's. Next, additional experiments were performed starting from 9, 36, and 72 mM solutions of (±)-**7** and maintaining the same (±)-**7**/vinyl acetate/enzyme ratio. It was observed that the reaction rate increased with the substrate concentration, without any enzyme inhibition being detected. Therefore, the reaction evolution was studied in more detail at an initial substrate concentration of 72 mM (Table 3).

At this higher initial concentration of (±)-**7**, the ee of the residual alcohol (+)-**7** increased more slowly than expected (entries 1–4), indicating that, simultaneously to the enantioselective acetylation, at least another competitive process was occurring that diminished the ee of the residual alcohol. Epimerization of the remaining alcohol (+)-**7** in the reaction medium was discarded because, after submitting a sample of enantiomerically pure (+)-**7** to the reaction conditions for 90 min, the alcohol was recovered without any loss of diastereomeric purity. An analogous reference experiment was performed with a sample of racemic acetate (±)-**15**, and after 90 min, CHPLC analysis of the recovered material showed three peaks, corresponding to the acetate (−)-**15** (27%), the alcohol (−)-**7** (24%), and the acetate (+)-**15** (48%). Consequently, the lower than expected ee of the residual alcohol was attributed to partial hydrolysis of the formed acetate. In an attempt to minimize this undesired hydrolysis reaction, the concentration of enzyme was further reduced to a weight proportion (±)-**7**/CALB = 1:0.06. Reference experiments showed that, at this lower enzyme concentration, the hydrolysis of the acetate (−)-**15** is considerably slower. Under these new conditions, it took 3 h 20 min to complete the enantioselective acetylation, with ee values of 93% for both (+)-**7** and (−)-**15**. The procedure was then scaled up to 5 g of starting substrate and, after 3.5 h of reaction, the residual alcohol (+)-**7** (81% ee) and the acetate (−)-**15** (95% ee) were isolated in 46% and 45% yield, respectively. These compounds are easily separable by a fast column chromatography on silica gel. Methanolysis of the acetate (−)-**15** furnished the corresponding alcohol (−)-**7**. Enantiomerically pure alcohols (+)- or (−)-**7** can be readily obtained by crystallization from dichloromethane/pentane.

**SCHEME 4. Syntheses of 4-Hydroxy-2-cyclohexenone, 1, Its Silyl-Protected Derivative 18, *trans*-Cyclohex-2-ene-1,4-diol, 2, and Its Silyl-Protected Derivative 11**




**Synthesis of 4-Hydroxy-2-cyclohexenone, 1, and *trans*-Cyclohex-2-ene-1,4-diol, 2.** Having a convenient methodology for the supply of both enantiomers of alcohol **7** in substantial amounts, our previous syntheses of hydroxyenone **1** and enediol **2** (Scheme 1) were re-examined. First, our syntheses were continued from this point to the final compounds in racemic fashion. The two transformations required for the conversion of **7** into **1** were ketal hydrolysis and hydrodesulfuration (Scheme 4). The hydrolysis of the ketal in **7** had been previously accomplished, but the reduction of the carbon−sulfur bond on the corresponding ketone was unsuccessful.[14] In former experiments, the desulfurated ketal **16** had been detected as a minor product in reaction mixtures of reduction of **7** with $Bu_3SnH$/AIBN in toluene. Now, we have investigated this reaction in more detail and, after extensive experimentation, we have found that the hydrodesulfuration of **7** can be cleanly accomplished in multigram scale and 81–83% yield if the AIBN is slowly and continuously added to the reaction medium and the $Bu_3SnH$ is added in portions each 30 min to a total amount of 10 equiv. Hydrolysis of the desulfurated ketal **16** by treatment with

montmorillonite K-10 in dichloromethane furnishes the target enone **1** in 62% yield. To avoid losses of material due to the volatility of this ketone, the formation of the TBDMS derivative **17** before ketal hydrolysis results advantageous. This protocol leads to the more convenient protected ketone **18** in 84% total yield from **16**. Treatment of this ketone with DIBAL-H in THF at −78 °C furnished an easily separable mixture of the trans alcohol **11** and the cis isomer **19** in 72% and 26% isolated yield, respectively. Desilylation of **11** was readily accomplished to deliver the corresponding diol **2**. Starting from (−)-**7**, and following identical pathways, the syntheses of (*S*)-**1**,[14] $[\alpha]_D$ = −92 (*c* 0.50, $CHCl_3$), (*S*)-**18**,[10] $[\alpha]_D$ = −100 (*c* 0.16, $CH_2Cl_2$), (1*S*,4*S*)-**11**,[18] $[\alpha]_D$ = −96 (*c* 0.96, $CHCl_3$), and (1*S*,4*S*)-**2**,[18] $[\alpha]_D$ = −112 (*c* 0.25, $CHCl_3$), were also completed without any loss of enantiomeric purity.

## Conclusions

In summary, we have developed a very convenient protocol for the preparation of multigram quantities of either enantiomer of the polyfunctionalized cyclohexane **7**, starting from very accessible raw materials such as *p*-methoxyphenol, ethylene glycol, and thiophenol. A highly efficient, enantioselective acetylation catalyzed by *C. antarctica* lipase B has been used to perform the key resolution of racemic **7**. Starting from **7**, the syntheses of 4-hydroxy-2-cyclohexenone, **1**, and *trans*-cyclohex-2-ene-1,4-diol, **2**, have been completed in two and five chemical steps and 50% and 44% total yield, respectively. Their corresponding *O*-protected derivatives **18** and **11**, which are more convenient for synthetic purposes, have also been prepared from **7** through three- and four-step sequences and 68% and 49% yields, respectively. Starting from the readily available enantiomers (+)- or (−)-**7**, the same synthetic sequences can be applied to prepare either antipode of the former products, without any loss of enantiomeric purity. Work is in progress to exploit these compounds as precursors to several bioactive polyoxygenated cyclohexanes.

## Experimental Section

**General Procedures.** See the Supporting Information for details.

**Resolution of (±)-7: (8*R*,10*S*)-10-Phenylthio-1,4-dioxaspiro[4.5]dec-6-en-8-ol, (+)-7, and (8*S*,10*R*)-10-Phenylthio-1,4-dioxaspiro[4.5]dec-6-en-8-yl Acetate, (−)-15.** Alcohol (±)-**7** (5.00 g, 18.9 mmol) was placed in a 500 mL reactor provided with mechanical stirrer and dissolved in $^iPr_2O$ (275 mL), and the solution was warmed to 32 °C. Then, lipase acrylic resin from *C. antarctica* (287 mg) and vinyl acetate (10.5 mL, 113.9 mmol) were added. The reaction evolution was monitored by TLC ($CH_2Cl_2/Et_2O$, 9:1) and GC analyses. Enzyme removal was carried out by simple filtration, and the solvents were evaporated under vacuum. Purification of the residue by flash chromatography ($CH_2Cl_2$ to $CH_2Cl_2/Et_2O$, 9:1) furnished (−)-**15**[24] (2.62 g, 8.6 mmol, 45% yield, 95% ee) and (+)-**7**[18,24] (2.32 g, 8.8 mmol, 46% yield, 81% ee). Enantiomerically pure (+)-**7** (1.86 g, 80% yield, >99% ee) was obtained by crystallization from $CH_2Cl_2$/pentane. (−)-**15**: $R_f$ = 0.72 ($CH_2Cl_2/Et_2O$, 9:1); $^1$H NMR (250 MHz, $CDCl_3$) $\delta$ 7.48 (m, 2H), 7.27 (m, 3H), 5.80 (dt, *J* = 10.2, 1.6 Hz, 1H), 5.74 (dd, *J* = 10.2, 1.5 Hz, 1H), 5.31 (ddt, *J* = 10.0, 5.9, 1.5 Hz, 1H), 4.14 (m, 4H), 3.47 (dd, *J* = 13.8, 3.3 Hz, 1H), 2.48 (dddd, *J* = 12.7, 5.9, 3.2, 1.4 Hz, 1H), 2.12 (ddd, *J* = 13.8, 12.7, 10.0 Hz, 1H), 2.01 (s, 3H). (+)-**7**: $R_f$ = 0.30 ($CH_2Cl_2/Et_2O$, 9:1); $^1$H NMR (250 MHz, $CDCl_3$) $\delta$ 7.49 (m, 2H), 7.28 (m, 3H), 5.91 (dt, *J* = 10.1, 1.8 Hz, 1H); 5.66 (dd, *J* = 10.1, 1.9 Hz, 1H); 4.23 (m, 5H); 3.43 (dd, *J* = 12.8, 3.1 Hz, 1H); 2.46 (dddd, *J* = 5.6, 3.1, 2.8, 1.5 Hz, 1H); 2.00 (dt, *J* = 12.8, 9.3 Hz, 1H); 1.68 (dd, *J* = 8.2, 0.6 Hz, 1H). Enantiomeric purities were determined by CHPLC (hexane/2-propanol, 4:1): (−)-**15** (11 min); (−)-**7** (15 min); (+)-**15** (51 min); (+)-**7** (59 min).

**(8*S*,10*R*)-10-Phenylthio-1,4-dioxaspiro[4.5]dec-6-en-8-ol, (−)-7.** To a solution of acetate (−)-**15**(980 mg, 3.2 mmol) in MeOH (11 mL) was added NaMeO (173 mg, 3.2 mmol), and the mixture was stirred at room temperature for 0.5 h. Then, the solvent was removed under reduced pressure, and the residue was diluted in water and slightly acidified with 2% HCl. The aqueous solution was extracted with $CH_2Cl_2$ (3 × 35 mL), the combined organic extracts were dried over anhydrous $MgSO_4$ and the solvent was evaporated under vacuum. Purification of the residue by flash chromatography ($CH_2Cl_2/Et_2O$, 9:1) furnished alcohol (−)-**7** (770 mg, 2.9 mmol, 92% yield, 96% ee) as a white solid, mp 87–88 °C.

**1,4-Dioxaspiro[4.5]dec-6-en-8-ol, 16.** To a boiling solution of alcohol (±)-**7** (1.25 g, 4.7 mmol) in anhydrous toluene (48 mL) under nitrogen were initially added $Bu_3SnH$ (2.5 mL, 9.4 mmol, dropwise addition) and a small quantity of AIBN. Then, a solution of AIBN (2.44 g, 14.8 mmol) in toluene (96 mL) was added continuously during 4 h, and additional portions of $Bu_3SnH$ (1.25 mL, 4.7 mmol) were added every 30 min. After that time, the solvent was evaporated under vacuum and the residue was purified by flash chromatography ($CH_2Cl_2$ to $CH_2Cl_2/Et_2O$, 10:3), providing unreacted (±)-**7** (120 mg, 0.45 mmol, 9.6%) and alcohol (±)-**16**[16l] (595 mg, 3.8 mmol, 81%) as an oil: $R_f$ = 0.14 ($CH_2Cl_2/Et_2O$, 10:3); $^1$H NMR (360 MHz, $CDCl_3$) $\delta$ 5.95 (ddd, *J* = 10.1, 2.8, 1.1 Hz, 1H), 5.63 (dt, *J* = 10.1, 1.5 Hz, 1H), 4.22 (m, 1H), 3.96 (m, 4H), 2.12 (m, 1H), 1.95 (m, 1H), 1.75 (m, 2H). The same reaction starting from (8*S*,10*R*)-**7** furnished (*S*)-**16**, $[\alpha]_D$ = −38 (*c* 1.64, $CHCl_3$) (lit.[10] $[\alpha]_D$ = −40.5 (*c* 1.24, $CHCl_3$)).

**8-*tert*-Butyldimethylsilyloxy-1,4-dioxaspiro[4.5]dec-6-ene, 17.** To a solution of alcohol (±)-**16** (763 mg, 4.9 mmol) in $CH_2Cl_2$ (34 mL) at 0 °C under $N_2$ was added TBDMS-imidazole (1.3 mL, 6.7 mmol) dropwise, and the reaction mixture was heated at the reflux temperature for 20 h. After that time, water (3 mL) was added, and the resulting suspension was acidified with 2 M HCl. The organic layer was separated, the aqueous one extracted with $CH_2Cl_2$ (3 × 10 mL), and the combined organic extracts were dried over anhydrous $MgSO_4$. The solvent was evaporated under reduced pressure, and the residue was purified by flash chromatography ($CH_2Cl_2/Et_2O$, 9:1) to provide silyl ether (±)-**17** (1.20 g, 4.4 mmol, 91% yield) as a colorless oil: $R_f$ = 0.66 ($CH_2Cl_2/Et_2O$, 9:1); $^1$H NMR (360 MHz, $CDCl_3$) $\delta$ 5.84 (ddd, *J* = 10.1, 2.6, 0.9 Hz, 1H), 5.55 (dt, *J* = 10.1, 1.5 Hz, 1H), 4.21 (m, 1H), 3.96 (m, 4H), 1.95 (m, 2H), 1.75 (m, 2H), 0.88 (s, 9H), 0.06 (s, 6H). The same reaction starting from (*S*)-**16** furnished (*S*)-**17**, $[\alpha]_D$ = −47 (*c* 2.40, $CHCl_3$) (lit.[10] $[\alpha]_D$ = −54.9 (*c* 0.70, $CHCl_3$)).

**4-Hydroxy-2-cyclohexenone, 1.** Montmollironite K-10 (383 mg) was added to a solution of acetal (±)-**16** (45 mg, 0.29 mmol) in $CH_2Cl_2$ (3.4 mL), and the mixture was stirred at room temperature for 2 h. Then, it was filtered and the solvent removed under vacuum to furnish an oily residue, which was purified by flash chromatography in Baker silica gel (hexanes/EtOAc, from 7:4 to 1:1) to provide (±)-**1**[14] (20 mg, 0.18 mmol, 62%) as an oil: $R_f$ = 0.4 (EtOAc); $^1$H NMR (360 MHz, $CDCl_3$) $\delta$ 6.93 (ddd, *J* = 10.2, 2.4, 1.6 Hz, 1H), 5.97 (dt, *J* = 10.2, 2.0, 1.0 Hz, 1H), 4.57 (m, 1H), 2.60 (dt, *J* = 17.0, 4.3 Hz, 1H), 2.38 (m, 2H), 1.95 (m, 1H). The same reaction starting from (*S*)-**16** furnished (*S*)-**1**, $[\alpha]_D$ = −92 (*c* 0.50, $CHCl_3$) (lit.[14] $[\alpha]_D$ = −92.3 (*c* 1.30, $CH_2Cl_2$)).

**4-*tert*-Butyldimethylsilyloxy-2-cyclohexenone, 18.** Montmollironite K-10 (5.81 g) was added to a solution of acetal (±)-**17** (1.18 g, 4.4 mmol) in $CH_2Cl_2$ (50 mL), and the mixture was stirred at room temperature for 1 h. Then, it was filtered and the solvent removed under vacuum to furnish an oily residue, which was purified by flash chromatography in Baker silica gel ($CH_2Cl_2/Et_2O$, 10:3) to provide (±)-**18** (905 mg, 4.0 mmol, 92%) as an oil: $R_f$ = 0.66 ($CH_2Cl_2/Et_2O$, 10:3); $^1$H NMR (360 MHz, $CDCl_3$) $\delta$ 6.83 (ddd, *J* = 10.2, 2.4, 1.7 Hz, 1H), 5.92 (ddd, *J* = 10.2, 2.0, 1.1 Hz, 1H), 4.53 (ddt, *J* = 9.0, 4.5, 2.4 Hz, 1H), 2.57 (dtd, *J* = 17.1, 4.5, 1.1

Hz, 1H), 2.35 (ddd, $J$ = 17.1, 12.8, 4.5 Hz, 1H), 2.21 (m, 1H), 2.02 (ddd, $J$ = 12.8, 9.1, 4.5 Hz, 1H), 0.92 (s, 9H), 0.12 (s, 6H). The same reaction starting from (*S*)-**17** furnished (*S*)-**18**, $[\alpha]_D$ = −100 (*c* 0.16, $CH_2Cl_2$) (lit.[16n] $[\alpha]_D$ = −109.6 (*c* 1.46, $CH_2Cl_2$)).

***trans*-4-*tert*-Butyldimethylsilyloxy-2-cyclohexenol, 11.** To a solution of (±)-**18** (505 mg, 2.2 mmol) in THF (30 mL) at −78 °C was added DIBAL-H (1 M THF, 9 mL, 9.0 mmol) dropwise, and the mixture was stirred for 50 min, quenched with MeOH (30 mL), and allowed to warm to room temperature. After 1 h of additional stirring, the mixture was filtered through a Celite pad and the solvent was evaporated. The residue so obtained was purified by flash chromatography (hexanes/EtOAc, from 20:1 to 12:1) to provide (±)-**11**[7] (365 mg, 1.6 mmol, 72%) and (±)-**19**[25] (135 mg, 0.6 mmol, 26%). (±)-**11**: oil; $R_f$ = 0.38 (hexanes/EtOAc, 7:3); $^1$HNMR (360 MHz, $CDCl_3$) $\delta$ 5.71 (m, 2H), 4.26 (m, 2H), 2.12 (m, 1H), 2.00 (m, 1H), 1.54 (m, 1H), 1.46 (m, 1H), 0.89 (s, 9H), 0.08 (s, 3H), 0.07 (s, 3H). (±)-**19**: oil; $R_f$ = 0.44 (hexanes/EtOAc, 7:3); $^1$H NMR (250 MHz, $CDCl_3$) $\delta$ 5.75 (m, 2H), 4.12 (m, 1H), 4.08 (m, 1H), 1.72 (m, 2H), 1.47 (d, $J$ = 7.6 Hz, 1H), 1.29 (m, 2H), 0.89 (s, 9H), 0.08 (s, 3H), 0.07 (s, 3H). The same reaction starting from (*S*)-**18** furnished (1*S*,4*S*)-**11**, $[\alpha]_D$ = −96 (*c* 0.96, $CHCl_3$) (lit.[18] $[\alpha]_D$ = −95 (*c* 0.95, $CHCl_3$)) and (1*R*,4*S*)-**19**, $[\alpha]_D$ = −30 (*c* 0.40, EtOH) (lit.[25] for the enantiomer $[\alpha]_D$ = +34 (*c* 1.58, EtOH)).

***trans*-Cyclohex-2-ene-1,4-diol, 2.** To a solution of silyl ether (±)-**11** (334 mg, 1.5 mmol) in THF (2.9 mL) at room temperature was added TBAF (1 M in THF, 2.9 mL, 2.9 mmol), and the mixture was stirred for 14 h. Then, the solvent was evaporated under reduced pressure and the residue was purified by flash chromatography ($CHCl_3$/MeOH, 30:1) to provide (±)-**2**[18,26] (151 mg, 1.3 mmol, 90%) as a white solid: $R_f$ = 0.30 (EtOAc); $^1$H NMR (360 MHz, $CDCl_3$) $\delta$ 5.81 (s, 2H), 4.27 (bt, 2H), 2.14 (m, 2H), 1.50 (m, 2H). The same reaction starting from (1*S*,4*S*)-**11** furnished (1*S*,4*S*)-**2**, $[\alpha]_D$ = −112 (*c* 0.25, $CHCl_3$) (lit.[27] for the enantiomer $[\alpha]_D$ = +144.7 (*c* 0.15, $CHCl_3$)).

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**Supporting Information Available:** General experimental procedures, preparation of compounds **13**, (±)-**3**, and (±)-**7**, $^1$H NMR spectra of compounds **1**−**3**, **7**, **11**, **13**, (−)-**15**, and **16**−**19**, CHPLC of **2**, **7**, **11**, and **15**, and CGC of compound **1**. This material is available free of charge via the Internet at http://pubs.acs.org.

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