# Enantioselective Synthesis of the Enyne A-Ring Synthon of the 1α-Hydroxy Vitamins D

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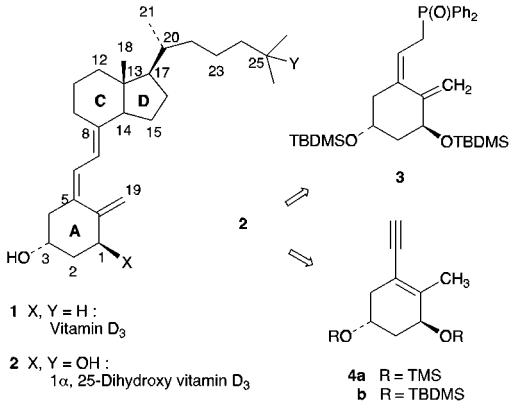
## Introduction

Vitamin $D_3$ (**1**) and its metabolites and analogs exhibit a multitude of biological activities. 1α,25-Dihydroxyvitamin $D_3$ (1α,25-$(OH)_2D_3$ or calcitriol, **2**) is the active hormone in bone homeostasis. Through synthesis, this compound is now available as a prescription drug for the management of hypocalcemia associated with renal failure or with hypoparathyroidism. Other metabolites have demonstrated roles in cell differentiation and immunomodulation, activities which suggest possible clinical applications for these derivatives or for their analogs.[1]

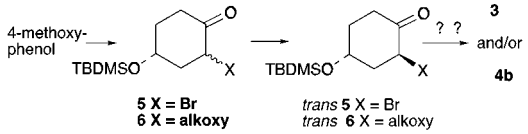



Two general strategies for the synthesis of vitamin D metabolites have emerged. The first of these, initially explored by Windaus and later extended by Barton, is biomimetic and involves the photochemical opening of an appropriately functionalized steroid precursor. The second strategy, pioneered by Lythgoe, entails the coupling of an appropriately fuctionalized A-ring precursor with a *trans*-hydrindane. A number of A-ring equivalents have been developed for this purpose, and the importance of these targets has led to several clever syntheses of intermediates **3** and **4**.[2,3]

## General Approach

The preparation of these functionalized *trans*-1,3-cyclohexanediols is, in fact, not a trivial exercise. Our own long-standing interest in this problem was rekindled by the observation in our labs that a mixture of *cis*- and *trans*-2-bromo-4-(*tert*-butyldimethylsiloxy)cyclohexanone (**5**), readily obtained in three steps from 4-methoxyphenol, rapidly equilibrates to the *trans* isomer (>20:1 *trans*:*cis*).[4] We surmised that a 2,4-dialkoxycyclohexanone (**6**) might also equilibrate to an isomer which was almost exclusively *trans*. This thermodynamic preference could then serve as the basis for the preparation of one or more of the 1α,25-$(OH)_2D_3$ A-ring synthons (Scheme 1). Alternatively, the *trans*-bromo compound **5** might be converted, by two consecutive $S_N2$ reactions, to *trans*-**6**.

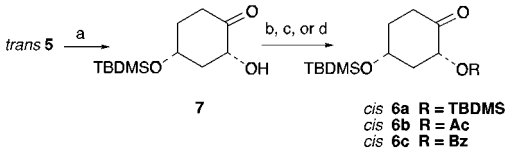
**Scheme 1. General Approach**




## Displacement/Epimerization and Double Displacement Studies

For elaboration to intermediates **3** and/or **4b**, the most attractive candidate **6** was the bis-TBDMS ether *cis*-**6a**. This compound was easily obtained in two steps (Scheme 2). First, bromo ketone *trans*-**5** was treated with NaOH under phase transfer conditions to give *cis*-2-hydroxy-4-(*tert*-butyldimethylsiloxy)cyclohexanone (**7**).[5] Then silylation afforded the desired equilibration substrate *cis*-**6a**.

**Scheme 2. Synthesis of Epimerization Substrates**[a]




[a] (a) NaOH, $BuNHSO_4$, $CH_2Cl_2/H_2O$, 85%; (b) TBDMSOTf, cat. DMAP, Hunig's base, −78 °C, $CH_2Cl_2$, 92%; (c) $Ac_2O$, cat. DMAP, $Et_3N$, $CH_2Cl_2$, 0 °C to rt, 85%; (d) $C_6H_5COCl$, DMAP, $Et_3N$, $CH_2Cl_2$, 0 °C to rt, 80%.

Epimerization of this bis-silyl ether with DBU was sluggish. Hence, alternative substrates were examined.

Hydroxycyclohexanone **7** was derivatized as its acetate (*cis*-**6b**) and as its benzoate (*cis*-**6c**). Unlike the bis-silyl ether **6a**, each of these compounds was easily epimerized with DBU to an equilibrium mixture of stereoisomers. The ratios of *trans*:*cis*-**6b** and -**6c** in several solvents are reported in Table 1. However, in no case was total conversion of *cis*-**6b** or -**6c** to its *trans* isomer observed, and we considered the mixtures which were obtained to be inappropriate for further development.

**Table 1. Equilibrium Ratio of Trans:Cis 6**

| | THF | DMF | $CH_3CN$ | 1:1 DMF/formamide[a] |
|---|---|---|---|---|
| **6b** | 3 | − | 3 | 0.7 |
| **6c** | 4 | 3 | 5 | 1 |

[a] The solvent mixture was chosen for study because the substrate **6** was insoluble in formamide.

A double displacement strategy might also exploit the *trans*-stereochemistry of the 2-halo-4-alkoxycyclohexanones. In order to examine this possibility, we converted hydroxycyclohexanone **7** to the corresponding

(1) Bouillon, R.; Okamura, W.; Norman, A. W. *Endocrine Rev.* **1995**, *16*, 200.
(2) Zhu, G.-D.; Okamura, W. H. *Chem. Rev.* **1995**, *95*, 1877.
(3) For more recent contributions, see: (a) Knolker, H.-J.; Ecker, A.; Struwe, P.; Steinmeyer, A.; Muller, G.; Neef, G. *Tetrahedron* **1997**, *53*, 91. (b) Yokoyama, H.; Miyamoto, K.; Hirai, Y.; Takahashi, T. *Synlett* **1997**, 187. (c) Posner, G. H.; Dai, H.; Bull, D. S.; Lee, J.-K.; Eydoux, F.; Ishihara, U.; Welsh, W.; Pryor, N.; Petr, S., Jr. J. Org. Chem. **1996**, *61*, 671. (d) Achmatowicz, B.; Jankowski, P.; Wicha, J. *Tetrahedron Lett.* **1996**, *37*, 5589.
(4) Parker, K. A.; Kim, H.-J. *J. Org. Chem.* **1992**, *57*, 752.
(5) Alcohol **7** has been isolated from a cis/trans mixture; see Majewski, M; Irvine, N. M.; McKinnon, J. *Tetrahedron Asymmetry* **1995**, *6*, 1837.

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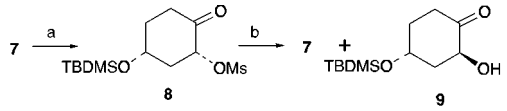
mesylate and attempted $S_N2$ displacement with sodium hydroxide under the phase transfer conditions used above (**5** → **7**). A mixture of α-hydroxy ketones **7** and **9** in a ratio of 1:1.5 was obtained (Scheme 3). A second attempt to effect efficient inversion of the center α to the ketone in substrate **7** by a Mitsunobu procedure resulted in recovery of the starting material.

**Scheme 3. Double Displacement Experiment**[a]




[a] (a) MsCl, cat. DMAP, $Et_3N$, $CH_2Cl_2$, 0 °C, 75%; (b) NaOH, $Bu_4NHSO_4$, $CH_2Cl_2/H_2O$ (1/1), 0 °C to rt, 65%.

### Employing a *cis*-2,4-Dialkoxycyclohexanone

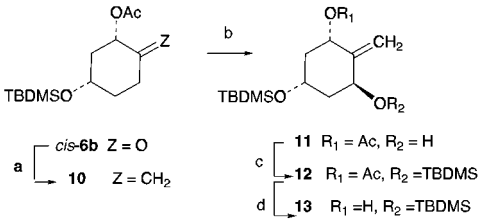
Recognizing the difficulties associated with the clean conversion of substrate **6** or **7** to the desired **9**, we resolved to take advantage of the stereospecific biases inherent in the *cis*-2,4-dialkoxycyclohexanones. We anticipated that these compounds (e.g. **6b**) would undergo Wittig reactions without epimerization and that the resulting exocyclic olefins might be subject to axial hydroxylation at the unsubstituted allylic position (Scheme 4). In this approach, the *trans*-diol arrangement would be established by an indirect but nonetheless stereoselective route, and the previously positioned allylic alkoxy group would remain to provide additional functionality required for the target.

In fact, Wittig olefination of acetoxy ketone **6b** gave olefin **10** which underwent oxidation with $SeO_2$ at the unsubstituted allylic position[6] to afford alcohol **11** as a single stereoisomer. In such $SeO_2$ oxidations, the new stereocenter is derived from the transition state for 2,3-sigmatropic rearrangement of the intermediate allylic selenous acid.[7] In our system and in closely related systems,[8] there is a useful preference for the transition state which leads to introduction of an axial hydroxyl group. Similar trends for axial placement of new functionality have been noted for Claisen and oxy-Cope rearrangements as well as for other (2,3)-sigmatropic rearrangements.[9]

With alcohol **11** in hand, we focussed on the transformations required to convert it to one or both of the A-ring precursors (**3** and/or **4b**). Enone **14** appeared to be a key intermediate in either route and alcohol **13** presented itself as the obvious precursor. Therefore, alcohol **11** was silylated to give the bis-TBDMS ether **12** which was deacylated to give the allylic alcohol **13**. Finally, Dess–Martin oxidation gave ketone **14** (Scheme 5).

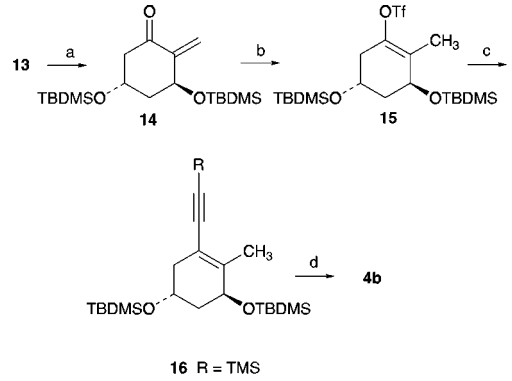
We first attempted to exploit this intermediate by introducing the unsaturated two-carbon side chain of intermediate **3**. When applied to ketone **14**, Horner–Wittig conditions with ethyl dimethylphosphonoacetate (both standard[10] and mild conditions[11]) led to decomposition of the enone.[12] Alternative two-carbon reagents (the lithium enolate of ethyl (trimethylsilyl)acetate, this enolate with cerium chloride additive, and lithium ethoxyacetylide, with or without cerium chloride additive) afforded the enone elimination product in moderate yields.

**Scheme 4. Introduction of the C-1α Hydroxyl Group**[a]




[a] (a) $Ph_3PCH_3Br$, *tert*-BuOK, THF, 93%; (b) $SeO_2$, pyridine *N*-oxide, dioxane, reflux, 60%; (c) TBDMSOTf, DMAP, (*i*-$Pr_2$)NEt, −78 °C, 95%; (d) $K_2CO_3$, MeOH, 94%.

**Scheme 5. Trapping of Unstable Enolate and Acetylide Coupling**[a]




[a] (a) Dess–Martin, $CH_2Cl_2$, 94%; (b) L-Selectride, $PhNTf_2$, THF, −78 °C to rt, 42%; (c) $(Bu_3Sn)CCTMS$, $Pd(PPh_3)_4$, LiCl, THF, reflux, 90%; (d) $K_2CO_3$, MeOH, 80%.

In light of these experiments, we turned to the conversion of enone **14** to enyne **4b**. This transformation might be the result of a conjugate reduction of the enone system, trapping of the enolate, and coupling of the resulting enol derivative with an acetylene. While a route based on this strategy appears troublesome at first sight, addition of L-Selectride to a THF solution of enone **14** and $PhNTf_2$[13] led to *in situ* trapping of the unstable *β*-alkoxy enolate and isolation of the vinyl triflate **15** in moderate yield. Stille coupling of triflate **15** with (trimethylsilyl)(tributylstannyl)acetylene ($TMSCCSnBu_3$)[14] afforded the fully protected enyne A-ring **16** in 90% yield.

Selective desilylation of the acetylene with $K_2CO_3$ in methanol gave the desired enyne **4b**. The spectroscopic data of this compound were identical with those reported in the literature, and it was further characterized as the known fully desilylated 1,3-diol.

(6) Paulmier, C. *Selenium Reagents and Intermediates in Organic Synthesis*; Pergamon: New York, 1986; p 132.

(7) (a) Sharpless, K. B.; Lauer, R. F. *J. Am. Chem. Soc.* **1973**, *95*, 7917. (b) Sharpless, K. B.; Lauer, R. F. *J. Am. Chem. Soc.* **1972**, *94*, 7154.

(8) (a) Andrews, D. R.; Barton, D. H. R.; Cheng, K. P.; Finet, J.-P.; Hesse, R. H.; Johnson, G.; Pechet, M. M. *J. Org. Chem.* **1986**, *51*, 1637. (b) Kiegiel, J.; Wovkulich, P. M.; Uskokovich, M. R. *Tetrahedron Lett.* **1991**, *32*, 6057.

(9) (a) Ireland, R. E.; Varney, M. D. *J. Org. Chem.* **1983**, *48*, 1829. (b) Paquette, L. A.; Maynard, G. D.; *J. Am. Chem. Soc.* **1992**, *114*, 5018. (c) Hoffmann, R. W.; Gerlach, R.; Goldmann, S. *Tetrahedron Lett.* **1978**, *29*, 2599. (d) Mander, L. N.; Turner, J. V. *Aust. J. Chem.* **1980**, *33*, 1559. (e) van Tamelen, E. E.; Taylor, E. G. *J. Am. Chem. Soc.* **1980**, *102*, 1202. (f) Mori, K.; Mori, H. *Tetrahedron Lett.* **1985**, *41*, 5487.

(10) (a) Wadsworth, W. S.; Emmons, W. D. *J. Am. Chem. Soc.* **1961**, *83*, 1733. (b) Boutagy, J.; Thomas, R. *Chem. Rev.* **1974**, *74*, 8.

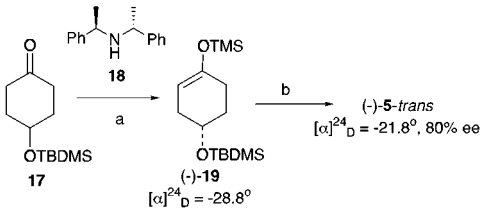
(11) Blanchette, M. A.; Choy, W.; Davis, J. T.; Essenfeld, A. P.; Masamune, S.; Roush, W. R.; Sakai, T. *Tetrahedron Lett.* **1984**, *25*, 2183.

(12) The poor behavior of this substrate in "alkylidenation" had previously been alluded to: see Chen, C.; Crich, D. *Tetrahedron* **1993**, *49*, 7943.

(13) Crisp, G. T.; Scott, W. J. *Synthesis* **1985**, 335.

(14) Logue, M. W.; Teng, K. *J. Org. Chem.* **1982**, *47*, 2549.

**Scheme 6. Preparation of Chiral Starting Material**[a]




[a] (a) (*R,R*)-**18**, BuLi, THF, −95 °C, TMSCl, 93%; (b) 1.2 equiv of NBS, 0.1 equiv of NaOAc, THF/$H_2O$ (1:1), 70%.

## Chiral Synthesis

Synthetically useful chiral enyne would be available if we could prepare chiral bromo ketone **5**. Therefore, with the intention of brominating the TMS ether **19**, we examined the enantioselective enolization of 4-(*tert*-butyldimethylsiloxy)cyclohexanone (**17**).

Of the two methods we examined,[15] the better asymmetric induction was achieved when the lithium amide of chiral base (*R,R*)-**18** was employed for deprotonation of ketone **17**.[16] The resulting enolate was trapped as the TMS ether (−)-**19** (Scheme 6). Treatment with NBS then gave the desired halo ketone (−)-**5**, which was shown to be of 80% ee.[17]

With bromoketone (−)-**5**, we followed the same reaction sequence that was employed in the racemic series.[18] The optical purity of (−)-enyne **4b** was verified as 80% by integration of the $^1$H NMR spectrum of its bis-(*S*)-Mosher ester derivative. Thus the stereospecific, asymmetric synthesis of the enyne A-ring synthon of 1α-hydroxyvitamin $D_3$ from *trans*-2-bromo-4-(*tert*-butyldimethylsiloxy)-cyclohexanone was completed.

## Experimental Section

**General.** High resolution mass spectra were obtained under EI, CI, or FAB conditions. Thin layer chromatography (TLC) was performed on precoated silica gel 60 F-254 glass-supported plates 0.25 mm thick. Column chromatography was performed with silica gel 60 (230−400 mesh). Ethyl ether, THF, and benzene were distilled from sodium−benzophenone ketyl. DMSO, DMF, pyridine, methylene chloride, methanol, and toluene were distilled from calcium hydride. All reactions were perfomed under argon unless otherwise stated.

***cis*-2-Hydroxy-4-(*tert*-butyldimethylsiloxy)cyclohexanone (7).** To 110 mg (0.3 mmol) of $Bu_4NHSO_4$ and 260 mg (6.6 mmol) of NaOH in a mixture of 20 mL of $CH_2Cl_2$ and 20 mL of $H_2O$ at 0 °C was added 1.0 g (3.3 mmol) of *trans*-2-bromo-4-(*tert*-butyldimethylsiloxy)cyclohexanone. The reaction mixture was allowed to warm to rt over 30 min. After 4 h, the reaction mixture was partitioned, and the aqueous solution was extracted with $CH_2Cl_2$ (4 × 15 mL). The combined organic solution was dried over $Na_2SO_4$ and concentrated to an oily residue. Silica gel chromatography with a 15−40% EtOAc/hexanes gradient afforded 675 mg (85%) of a colorless oil: IR (neat) 3478, 1725 cm$^{-1}$. 250 MHz $^1$H NMR ($CDCl_3$) δ 0.22 (s, 6 H), 0.89 (s, 9 H), 1.60−1.86 (m, 3 H), 2.15 (m, 1 H), 2.38 (ddd, *J* = 13.2, 6.3, 1.2 Hz, 1 H), 2.55 (m, 2 H), 4.13 (m, 2 H). 100.6 MHz $^{13}$C NMR ($CDCl_3$) δ −4.8, 18.0, 25.7, 34.8, 35.3, 44.2, 67.3, 72.2, 210.1.

HRMS (CI) for $C_{12}H_{24}O_3Si$ ($M^+$ + H): calcd, 245.1573; found, 245.1575.

**(−)-*cis*-2-Hydroxy-4-(*tert*-butyldimethylsiloxy)cyclohexanone ((−)-7).** A 1.06 g sample of chiral *trans*-**5** gave 650 mg (77% yield) of material with 80% ee according to the Mosher method. $[\alpha]^{24}_D$ = −5.7° ($CHCl_3$, *c* = 0.47).

**Ketone *cis*-6b.** To a solution of 590 mg (0.24 mmol) of **7**, 1.62 mL (1.23 g, 1.21 mmol) of $Et_3N$, and a catalytic amount of DMAP in 30 mL of $CH_2Cl_2$ was added 0.46 mL of $Ac_2O$ (495 mg, 0.49 mmol) at 0 °C. The reaction mixture was allowed to warm to rt over 30 min. After 2 h, it was poured into $H_2O$, and the resulting mixture was extracted with $CH_2Cl_2$ (4 × 10 mL). The combined organic layer was extracted with several portions of 1% aqueous citric acid (until the aqueous phase showed an acidic pH) and then with aqueous saturated $NaHCO_3$ (2 × 5 mL). The combined organic solution was dried over $Na_2SO_4$ and concentrated to an oily residue. Silica gel chromatography with a 15−40% EtOAc/hexanes gradient gave 590 mg (85%) of a colorless oil: IR (neat) 1754, 1733 cm$^{-1}$. 250 MHz $^1$H NMR δ 0.11 (s, 6 H), 0.90 (s, 9 H), 1.65−1.98 (m, 2 H), 2.13 (broad s, 4 H), 2.42 (m, 3 H), 4.19 (m, 1 H), 5.22 (dd, *J* = 13.2, 6.4 Hz, 1 H). 100.6 MHz $^{13}$C NMR δ −4.8, −4.7, 18.0, 20.6, 25.7, 35.0, 35.8, 40.9, 67.7, 72.9, 169.9, 203.3. HRMS (CI) for $C_{14}H_{26}O_4Si$ for ($M^+$ + H): calcd, 287.1671; found, 287.1646.

**(−)-Ketone *cis*-6b.** A 621 mg sample of chiral *cis*-**7** gave 641 mg (88% yield) of material with $[\alpha]^{24}_D$ = −33.2° ($CHCl_3$, *c* = 0.37).

**Olefin 10.** To a slurry of 360 mg (0.32 mmol) of *tert*-BuOK and 1.08 g (0.32 mmol) of $Ph_3PCH_3Br$ in 15 mL of THF under Ar at 0 °C was added 430 mg (0.12 mmol) of ketone *cis*-**6b** in THF (5 mL). After 5 min at 0 °C and 3 h at rt, the reaction mixture was poured in $H_2O$, and the resulting mixture was extracted with $Et_2O$ (5 × 10 mL). The combined organic solution was dried over $Na_2SO_4$ and concentrated to an oily residue. Silica gel chromatography with 5% EtOAc/hexanes afforded 568 mg (93%) of a colorless oil: IR (neat) 3100, 1743, 1658 cm$^{-1}$. 400 MHz $^1$H NMR ($CDCl_3$) δ 0.08 (s , 6 H), 0.89 (s, 9 H), 1.37 (m, 1 H), 1.49 (dt, *J* = 11.5, 10.5 Hz, 1 H), 1.91 (m, 1 H), 2.03 (m, 1 H), 2.12 (s, 3 H), 2.19 (m, 1 H), 2.39 (ddd, *J* = 13.9, 7.7, 3.7 Hz, 1 H), 3.83 (m, 1 H), 4.78 (t, *J* = 1.6 Hz, 2H), 5.18 (ddd, *J* = 11.6, 4.6, 2.3 Hz, 1 H). 100.6 MHz $^{13}$C NMR ($CDCl_3$) δ −4.7, −4.6, 18.1, 21.1, 25.8, 30.0, 36.3, 42.3, 68.9, 71.2, 105.9, 145.0, 170.1. HRMS (CI) for $C_{15}H_{28}O_3Si$ ($M^+$ + H): calcd, 285.1878; found, 285.1899.

**(+)-Olefin 10.** From 641 mg of chiral *cis*-**6b** was recovered 521 mg (82% yield) of olefin with $[\alpha]^{24}_D$ = +8.0° ($CHCl_3$, *c* = 0.80), 84% ee.[18]

**Allylic Alcohol 11.** To a solution of 524 mg (1.84 mmol) of **10** and 700 mg (7.36 mmol) of pyridine *N*-oxide in 15 mL of dioxane was added 247 mg (2.21 mmol) of $SeO_2$. The reaction mixture was stirred at 90 °C under argon for 2 h, cooled, and poured into $H_2O$. The aqueous layer was extracted with 5 × 10 mL of EtOAc, and the combined organic solution was washed with saturated aqueous $NaHCO_3$ (1 × 5 mL), dried over $Na_2SO_4$, and concentrated to a dark yellow-brown residue. Silica gel chromatography with a 15−40% EtOAc/hexanes gradient afforded 332 mg (60%) of a light yellow oil: IR ($CHCl_3$) 3446, 1734, 1653 cm$^{-1}$. 250 MHz $^1$H NMR ($CDCl_3$) δ 0.06 (s, 3 H), 0.09 (s, 3 H), 0.89 (s, 9 H), 1.62 (m, 3 H), 2.08 (m, 1 H), 2.13 (s, 3 H), 2.18 (m, 1H), 4.29 (m, 1 H), 4.56 (t, *J* = 3.7 Hz, 1 H), 4.94 (t, *J* = 1.5 Hz, 1 H), 5.02 (s, 1 H), 5.61 (m, 1 H). 100.6 MHz MHz $^{13}$C NMR ($CDCl_3$) −4.8, −4.7, 18.0, 21.1, 25.8, 41.7, 42.8, 65.4, 69.8, 71.5, 108.6, 147.3, 170.1. HRMS (CI) for $C_{15}H_{28}O_4Si$ ($M^+$-OH): calcd, 283.1722; found, 283.1723.

(15) The asymmetrization of ketone **17** was initially attempted by means of Yamamoto's TRIBAL-mediated opening of its (2*R*,4*R*)-2,4-pentanediol acetal. The resulting enol ether was converted to α-hydroxy ketone **7** (by way of the bromo ketone *trans*-**5**), the Mosher ester of which indicated an optical purity that ranged from 38 to 44% ee. See (a) Yamamoto, H.; Naruse, Y. *Tetrahedron Lett.* **1986**, *27*, 1363. (b) Naruse, Y.; Yamamoto, H. *Tetrahedron* **1988**, *44*, 6029.

(16) Subsequent to the completion of our work, Majewski described the enantioselective deprotonation of ketone **17** with a series of chiral bases, obtaining the maximum ee of 90% with the chiral lithium amide **18** and LiCl as an additive; see ref 4 and also Majewski, M.; McKinnon, J. *Can. J. Chem.* **1994**, *72*, 1699.

(17) Haloketone (−)-**5** was converted to the α-hydroxy ketone (−)-**7** by the procedure described above. Integration of the NMR spectrum of the Mosher ester of (−)-**7** indicated the enantiomeric excess.

(18) The allylic alcohol derived from the deacylation of (+)-**10** as well as compound (+)-**13** were converted to their Mosher esters. Integration of the NMR spectra of these derivatives showed enantiomeric excesses of 82 ± 2%.

**(+)-Allylic Alcohol 11.** A 512 mg sample of chiral **10** gave 306 mg (57% yield) of material with $[\alpha]^{24}_D = +32.4°$ ($CHCl_3$, $c = 0.51$).

**Bis(silyloxy) Olefin 12.** To a solution of 384 mg (1.28 mmol) of alcohol **11**, 0.90 mL (660 mg, 5.12 mmol) of diisopropylethylamine, and a catalytic amount of DMAP in 15 mL of $CH_2Cl_2$ at −78 °C, was added 500 μL (575 mg, 2.17 mmol) of TBDMSOTf. After 40 min the reaction mixture was poured into $H_2O$ and was extracted with $CHCl_3$ (5 × 10 mL). The combined organic solution was washed with 1% aqueous citric acid and aqueous saturated $NaHCO_3$, dried over $Na_2SO_4$, and concentrated to an oily residue. Silica gel chromatography with 5% EtOAc/hexanes yielded 504 mg (95%) of a colorless oil: IR (neat) 3091, 1745, 1661 $cm^{-1}$. 250 MHz $^1H$ NMR ($CDCl_3$) δ 0.04 (s, 3 H), 0.08 (s, 9 H), 0.86 (s, 18 H), 1.53 (m, 2H), 1.97 (m, 1 H), 2.09 (s, 3 H), 2.19 (m, 1 H), 4.28 (m, 1 H), 4.49 (m, 1 H), 4.88 (t, $J = 1.6$ Hz, 1 H), 4.91 (s, 1 H), 5.57 (dd, $J = 10.6$, 4.9 Hz, 1 H). 100.6 MHz $^{13}C$ NMR ($CDCl_3$) δ −5.3, −4.9, −4.8, −4.8, 18.0, 18.1, 21.1, 25.7, 25.8, 41.8, 44.5, 65.6, 69.9, 72.0, 107.1, 147.9, 169.8. HRMS (EI) for $C_{21}H_{42}O_4Si_2$ ($M^+ - C(CH_3)_3$): calcd, 357.1917; found, 357.1908.

**(+)-Bis(silyloxy) Olefin 12.** A 295 mg sample of chiral **11** gave 373 mg (91% yield) of material with $[\alpha]^{24}_D = +37.5°$ ($CHCl_3$, $c = 0.69$).

**Alcohol 13.** To a solution of 271 mg (0.65 mmol) of olefin **12** in 15 mL of MeOH was added 90 mg (1.31 mmol) of $K_2CO_3$. After 2 h the reaction mixture was poured into $H_2O$, and the resulting reaction mixture was extracted with EtOAc (6 × 10 mL). The organic solution was dried over $Na_2SO_4$ and concentrated to an oily residue. Silica gel chromatography with 5% EtOAc/hexanes afforded 230 mg (94%) of a white solid: mp 69−71 °C. IR ($CHCl_3$) 3480, 3015, 1256, 1218 $cm^{-1}$. 250 MHz $^1H$ NMR ($CDCl_3$) δ 0.08 (s, 6 H), 0.12 (s, 6 H), 0.92 (s, 18 H), 1.64 (m, 1 H), 1.81 (distorted dt, $J = 13.7$, 3.3 Hz, 1 H), 1.98 (m, 2 H), 3.72 (d, $J = 8.7$ Hz, 1 H), 4.36 (broad m, 1 H), 4.42 (m, 1 H), 4.80 (dd, $J = 9.7$, 4.2 Hz, 1 H), 4.98 (s, 1 H), 5.04 (t, $J = 1.6$ Hz, 1 H). 100.6 MHz $^{13}C$ NMR ($CDCl_3$) −5.2, −5.1, −5.0, −4.9, 17.9, 18.2, 25.7, 25.8, 40.9, 44.6, 67.3, 69.4, 72.9, 107.0, 152.2. HRMS (CI) for $C_{19}H_{40}O_3Si_2$ ($M^+ - H_2O$): calcd, 355.2478; found, 355.2489.

**(+)-Alcohol 13.** A 373 mg sample of chiral **12** gave 320 mg (95% yield) of material with $[\alpha]^{24}_D = +33.9°$ ($CHCl_3$, $c = 0.51$), 82% ee.[18]

**Enone 14.** To a solution of 309 mg (0.83 mmol) of alcohol **13** in 15 mL of $CH_2Cl_2$ was added 936 mg (2.21 mmol) of Dess−Martin reagent. After 1−1.5 h the reaction was quenched with saturated aqueous $NaHCO_3$. The aqueous phase was washed with $CH_2Cl_2$ (3 × 15 mL), and the combined organic solution was dried over $Na_2SO_4$ and concentrated to a milky residue. Silica gel chromatography with a 5−15% EtOAc/hexanes gradient gave 286 mg (94%) of product: IR (neat) 3018, 1697, 1624 $cm^{-1}$. 250 MHz $^1H$ NMR ($CDCl_3$) δ 0.07 (s, 3 H), 0.09 (s, 6 H), 0.12 (s, 3 H), 0.88 (s, 9 H), 0.92 (s, 9 H), 1.92 (ddd, $J =$ 12.5, 9.4, 2.4 Hz, 1H), 2.14 (m, 1 H), 2.55 (m, 2 H), 4.41 (broad m, 1 H), 4.83 (m, 1 H), 5.42 (t, $J = 1.9$ Hz, 1 H), 5.84 (t, $J =$ 1.9 Hz, 1 H). 100.6 MHz $^{13}C$ NMR ($CDCl_3$) δ −5.0, −4.9, −4.9, −4.8, 18.1, 25.7, 25.8, 42.0, 49.0, 65.8, 68.9, 118.7, 149.8, 200.6. HRMS (EI) for $C_{19}H_{38}O_3Si_2$ ($M^+ - C(CH_3)_3$): calcd, 313.1647; found, 313.1676.

**(−)-Enone 14.** A 372 mg sample of chiral **13** gave 269 mg (90% yield) of material with $[\alpha]^{24}_D = -6.2°$ ($CHCl_3$, $c = 0.66$).

**Vinyl Triflate 15.** A solution of 143 mg (0.38 mmol) of enone **14** and 120 mg of $Tf_2NPh$ (0.43 mmol) in 12 mL of THF was stirred at −78 °C during the addition of 425 μL (0.43 mmol) of a 1 M solution of L-Selectride in THF. The reaction mixture was allowed to warm to rt overnight and then quenched with brine. The resulting mixture was extracted with $CHCl_3$ (6 × 10 mL) and the combined organic solution was concentrated. Preparative TLC (silica gel, 1000 μm) of the residue with 15% EtOAc/hexanes afforded 80 mg (42%) of a colorless oil: IR ($CH_2Cl_2$) 3054, 1700 (w), 1414 $cm^{-1}$. 250 MHz $^1H$ ($CDCl_3$) δ 0.07 (s, 6 H), 0.11 (s, 6 H), 0.85 (s, 9 H), 0.92 (s, 9 H), 1.79 (broad s, 5 H), 2.32 (dd, $J = 15.4$, 6.0 Hz, 1 H), 2.58 (dd, $J = 17.5$, 4.5 Hz, 1 H), 4.21 (m, 1 H), 4.32 (broad t, $J = 3.9$ Hz, 1 H). 100.6 MHz $^{13}C$ NMR ($CDCl_3$) δ −5.1, −4.9, −4.8, −4.4, 13.8, 17.9, 18.0, 25.5, 25.6, 25.7, 25.7, 25.8, 37.6, 40.5, 64.3, 68.7, (113.6, 116.8, 119.9, 123.1; q, $J = 319.6$ Hz), 128.3, 142.4. HRMS (CI) for $C_{20}H_{39}F_3O_5SSi_2$ ($M^+ + H$): calcd, 505.2087; found, 505.2079.

**(−)-Vinyl Triflate 15.** A 212 mg sample of chiral **14** gave 118 mg (41% yield) of material with $[\alpha]^{24}_D = -22.9°$ ($CHCl_3$, $c = 1.21$).

**Compound 16.** To a solution of 37 mg (0.07 mmol) of vinyl triflate **15**, 16 mg (0.01 mmol) of $Pd(PPh_3)_4$, and 13 mg (0.29 mmol) of LiCl in 7 mL of THF was added 34 mg of (trimethylsilyl)(tributylstannyl)acetylene. The reaction mixture was stirred at reflux for 11 h, cooled, and diluted with hexanes (20 mL). The organic layer was washed with brine, dried over $Na_2SO_4$, and concentrated to a dark yellow-brown residue. Preparative TLC (silica gel, 1000 μm) with 15% EtOAc/hexanes afforded 30 mg (90%) of a light yellow to colorless oil: IR ($CH_2Cl_2$) 3090, 2140, 1260 $cm^{-1}$. 250 MHz $^1H$ NMR ($CDCl_3$) δ 0.06 (s, 6 H), 0.09 (s, 6 H), 0.19 (s, 9 H), 0.88 (s, 18 H), 1.65 (ddd, $J = 14.6$, 10.4, 4.2 Hz, 1 H), 1.83 (m, 1 H), 1.92 (broad s, 3 H), 2.07 (m, 1 H), 2.40 (dd, $J = 16.8$, 4.4 Hz, 1 H), 4.08 (m, 1 H), 4.17 (t, $J = 3.8$ Hz, 1 H). 100.6 MHz $^{13}C$ NMR ($CDCl_3$) δ −4.8, −4.7, −4.6, −4.3, 0.1, 18.0, 18.1, 19.1, 25.8, 25.8, 25.9, 39.4, 41.2, 64.1, 69.8, 96.5, 105.4, 115.1, 143.1. HRMS (CI) for $C_{24}H_{48}O_2Si_3$ ($M^+ + H$): calcd, 453.3040; found, 453.3040.

**(−)-Compound 16.** A 70 mg-sample of chiral **15** gave 55 mg (87% yield) of material with $[\alpha]^{24}_D = -48.9$ ($CHCl_3$, $c =$ 0.64).

**3,5-Bis(*tert*-butyldimethylsiloxy)-1-ethynyl-2-methylcyclohexene (4b).** To a solution of 52 mg (0.11 mmol) of **16** in 3 mL of MeOH was added 33 mg (0.24 mmol) of $K_2CO_3$. After 6 h the solvent was evaporated in vacuo at rt. The addition of hexanes (10 mL) provided a slurry from which solids were removed by filtration. The hexane solution was concentrated to an oil which was subjected to preparative TLC (silica gel, 1000 microns) with 15% EtOAc/hexanes to afford 34 mg (80%) of a light yellow oil: IR ($CHCl_3$) 3312, 2145 (w), 1472 $cm^{-1}$. 250 MHz $^1H$ NMR ($CDCl_3$) δ 0.08 (s, 6 H), 0.11 (s, 6 H), 0.87 (s, 9H), 0.93 (s, 9 H), 1.68 (ddd, $J = 14.4$, 10.0, 4.4 Hz, 1 H), 1.83 (m, 1 H), 1.93 (broad s, 3 H), 2.08 (dd, $J = 16.9$, 8.2 Hz, 1 H), 2.43 (dd, $J = 17.1$, 4.2 Hz, 1 H), 3.06 (s, 1 H), 4.10 (m, 1 H), 4.21 (broad t, $J = 3.9$ Hz, 1 H). 100.6 MHz $^{13}C$ NMR ($CDCl_3$) δ −4.8, −4.7, −4.7, −4.3, 18.0, 18.1, 18.9, 25.8, 25.8, 25.9, 39.4, 41.1, 64.1, 69.7, 79.5, 83.8, 114.1, 143.5. HRMS (CI) for $C_{21}H_{40}O_2Si_2$ ($M^+ + H$): calcd, 381.2645; found 381.2646.

**(−)-(3*S*,5*R*)-Bis(*tert*-butyldimethylsiloxy)-1-ethynyl-2-methylcyclohexene (4b).** A 30 mg sample of chiral **16** gave 19 mg (74% yield) of material with $[\alpha]^{24}_D = -52.4°$ ($CHCl_3$, $c =$ 0.36).

**Silyl Enol Ether (−)-19.** To a solution of 1.54 g (6.83 mmol, 1.61 mL) of chiral amine **18** in 180 mL of anhydrous THF at −95 °C was added 4.30 mL (6.83 mmol) of a 1.6 M solution of BuLi in hexanes. The solution was allowed to warm slowly to rt and then recooled to −95 °C. To this cold solution was added 3.40 mL (2.91 g, 2.67 mmol) of TMSCl (previously neutralized with $Et_3N$). After 2−3 min, 1.30 mL (1.20 g, 5.26 mmol) of ketone **17** was added dropwise over a period of 40 min. After an additional 30−40 min, 15 mL of $Et_3N$ was added, and the reaction mixture was poured into aqueous saturated $NaHCO_3$. The resulting mixture was extracted with hexanes (5 × 60 mL), and the combined organic solution was dried over $Na_2SO_4$ and concentrated to a light yellow liquid. Silica gel chromatography with 5% EtOAc/hexanes and Kugelrohr distillation (160−164 °C, 0.8 mmHg) afforded 1.47 g (93%) of a colorless liquid: IR (neat) 3054, 3020, 1670 $cm^{-1}$. 250 MHz $^1H$ NMR ($CDCl_3$) δ 0.06 (s, 6 H), 0.18 (s, 9 H), 0.89 (s, 9 H), 1.74 (m, 2 H), 2.08 (m, 3H), 2.19 (m, 1H), 3.89 (m, 1 H), 4.71 (ddd, $J = 4.7$, 3.2, 1.7 Hz, 1 H). 100.6 MHz $^{13}C$ NMR ($CDCl_3$) δ −4.7, −4.6, 18.1, 25.9, 28.1, 31.7, 33.3, 67.3, 101.3, 149.7. HRMS (CI) for $C_{15}H_{32}O_2Si_2$ ($M^+ + H$): calcd, 301.2019; found 301.2010. $[\alpha]^{24}_D = -28.8°$ ($CHCl_3$, $c = 0.25$).

**(−)-5-*trans* from (−)-19.** To a solution of 1.05 g (5.89 mmol) of NBS and 41 mg (0.49 mmol) of NaOAc in 60 mL of THF and $H_2O$ (50:50) at 0 °C was added dropwise 1.48 g (4.92

mmol) of enol ether (−)-**19**. The reaction mixture was allowed slowly to warm to rt over 30 min. After stirring for 2−3 h at rt, the reaction mixture was quenched with $H_2O$, and the resulting mixture was extracted with hexanes (5 × 15 mL). The combined organic solution was dried over $Na_2SO_4$ and concentrated. The residue was chromatographed on a silica gel column with 5% EtOAc/hexanes to give 1.06 g (70%) of 80% ee product (see text). $[\alpha]^{24}_D = -21.8^o$ ($CHCl_3$, $c = 0.60$).

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**Supporting Information Available:** Experimental procedures for the preparation of ketones *cis*-**6a**, *cis*-**6c**, **8**, and **17**, the deprotection of silyl ethers **16** and **4b** to *trans*-5-ethynyl-4-methylcyclohexene-1,3-diol; $^1$H NMR, $^{13}$C NMR, and IR spectra for compounds **4b**, **6**−**17** and (−)-**19**; $^1$H spectra for the bis-(*S*)-Mosher ester of (−)-*trans*-5-ethynyl-4-methylcyclohexene-1,3-diol, the (*S*)-Mosher ester derivatives of (−)-**7** and (+)-**13**, and the mixtures **6b** (*cis* and *trans*), **6c** (*cis* and *trans*), and **7** and **9** (55 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

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