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An efficient and convenient synthesis of enantiopure 4-(*t*-butyldimethylsilyloxy)-cyclohex-2-en-1-one: a formal synthesis of (±)-mesembranol

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Abstract—Inexpensive enantiopure (+)-limonene oxide **1** is converted to 4-(*R*)-(*t*-butyldimethylsilyloxy)-cyclohex-2-en-1-one **2a**. All isolated intermediates can be distilled obviating the need for chromatography. With **2a**,**b** in hand, a formal synthesis of (±)-mesembranol **17** using vinyl triflate methodology is high yielding. © 2001 Elsevier Science Ltd. All rights reserved.

Enantiopure pure 4-(*t*-butyldimethylsilyloxy)-cyclohex-2-en-1-one **2a** is a highly useful chiral building block. Since the first reported synthesis of (*S*)-**2a** from D(−)-quinic acid by Danishefsky in 1989, a number of alternative methods have been published.[1] One report derives its enantiopurity from chiral catalysis; however, the cost of the preparation or purchase of sufficient catalyst to produce multi-gram quantities of **2a** is prohibitive.[2a] Other reports are either low yielding or involve lengthy synthesis or separations.[2] In conjunction with our vinyl triflate projects, an efficient, inexpensive route to **2a** has been developed.[3] Using our chiral vinyl triflate methodology,[4] we also report a formal synthesis of (±)-mesembranol (**17**) based on the total synthesis reported by Ogawa (Fig. 1).[5]

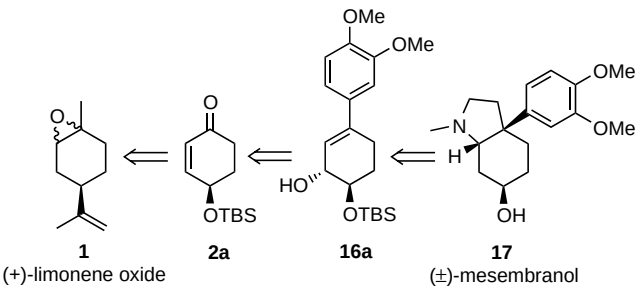
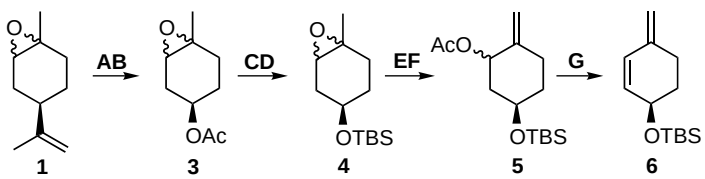


Figure 1.

The key starting material, inexpensive (+)-limonene oxide **1**, is available as a 1:1 mixture of diastereomers. Ozonolysis of the isopropenyl side-chain followed by Baeyer–Villiger oxidation gives acetate **3** following a slight modification of the Cain protocol.[6] Hydrolysis and silylation under standard conditions furnish **4** in 74% yield after distillation (Scheme 1).

Regiospecific conversion of the epoxide mixture **4** to allylic acetates **5** was achieved using diisobutylaluminum-diisopropylamine,[7] followed by acylation of the crude product in 94% yield. Elimination of acetate, facilitated by catalytic palladium[0], yields diene **6** with-



Scheme 1. *Conditions*: **A**: a. O_3, MeOH, CH_2Cl_2, b. Me_2S; **B**: *m*CPBA (2.2 equiv.), CH_2Cl_2 25°C, 48 h; **C**: 10% aq. KOH, MeOH 25°C, 3 h; **D**: TBDMSCl, imidazole, DMF, 25°C, 3 h, distill, 74% from **1**. **E**: $(i\text{-Pr})_2NAl(i\text{-Bu})_2$, benzene, 12 h, 0°C; **F**: Ac_2O, DMAP, Et_3N, 2 h, 0–25°C, 94% crude; **G**: 2.5% $Pd(PPh_3)_4$, Et_3N, dioxane, 5 h, reflux, distill 83%.

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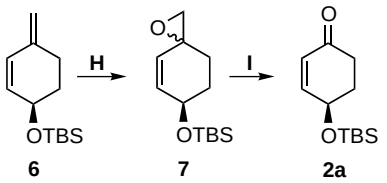
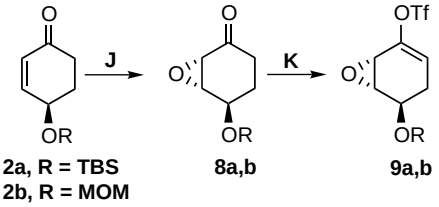
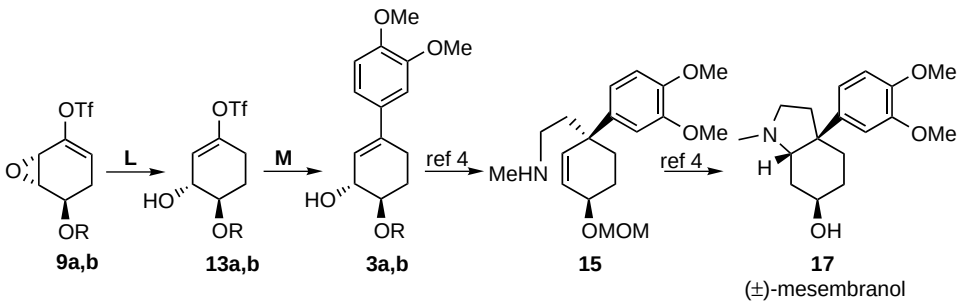


Scheme 2. *Conditions*: **H**: trifluorodimethyldioxirane, generated in situ[9] plus 20% THF, 0°C, 7 h; **I**: 1% solid HIO_4, 1 equiv. $NaIO_4$, 1:1 *t*-BuOH:H_2O, plus 20% THF, 3 h, 25°C, 83%.



Scheme 3. *Conditions*: **J**: TBHP, 2.5% Triton B, benzene, 5°C, 2 h, **8a** 85%, **8b** 83%; **K**: pyr-NTf_2, LDA, THF, −78 to 25°C, 8 h, **9a** 86%, **9b** 55%.



Scheme 4. *Conditions*: **L**: BH_3, THF 0°C 2 h, **13a**,**b** 88%; **M**: Me_3Sn-Ar, 2.5% Pd_2dba_3, $ZnCl_2$, $AsPPh_3$, NMP, 25°C, 1 h, **3a** 83%, Ar-$B(OH)_2$, 2.5% $Pd(PPh_3)_4$, LiCl, 2 M Na_2CO_3, DME, 50°C 45 min, **3b** 86%.

out any competitive aromatization in 83% yield. Filtration through silica is necessary to remove palladium before distillation (Scheme 2).[8]

Regioselective oxidative cleavage is accomplished by first epoxidizing the exo-olefin of **6** to give **7**, followed by treatment with $HIO_4/NaIO_4$ to leave **2a** in 83% yield after silica gel chromatography.[10] These reactions are readily scaled and are regularly performed in our laboratories to give $\geq$20 g of **2a**. Purification of intermediates **4** and **6** is accomplished with distillation, while silica chromatography is normally used to isolate **2a**. The yield over the three isolations is 48%, 97.8% ee (Scheme 3).[11,12]

With **2a**,**b** in hand, a formal synthesis of (±)-mesembranol (**17**) was straightforward. Stereoselective epoxidation of enone **2a**,**b** provides **8a**,**b** with >20:1 selectivity.[13] Trapping the enolate from **8b** as vinyl triflate affords **9b** in only 55% yield; however, **8a** nicely furnishes **8a** in 86% (Scheme 4).[14]

Regioselective 1,5-hydride addition to **9a**,**b** with BH_3 giving **13a**,**b** sets the stage for coupling.[15] Treatment of **13a** with veratrole boronic acid under Suzuki conditions provides **3a** in 86% yield. Similarly, treatment of mono-protected diol **13b** with trimethylstannyl veratrole under Stille conditions affords coupled product **3b**, the Ogawa intermediate, in 83% yield.

Acknowledgements

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10. On a larger scale, **2a** can be distilled (>90% purity by GC). Danishefsky, S. J.; Simoneau, B. *J. Am. Chem. Soc.* **1989**, *111*, 2599.
11. Compound **4**: 52.6 g of (+)-limonene oxide **1** was submitted to the conditions in Ref. 5 and used crude. Crude **3** was added to 700 mL of methanol/water (10:1). 50% w/v aq. KOH (5 mL) was added dropwise to the stirred solution cooled in a 25°C water bath. After 3 h, the volume was reduced by half. Brine was added and the mixture was extracted with CH_2Cl_2. The aqueous layer was continuously extracted into CH_2Cl_2 for 24 h. The combined organic layers were dried with $MgSO_4$ and concentrated. The residue was added to 200 mL of dry DMF and 2.5 equiv. imidazole (59 g, 0.85 mol). TBSCl (0.5 equiv.) was added to a stirred solution cooled in a 25°C water bath. The reaction was allowed to stir for 2 h after which more TBSCl, in 5% increments, was added until TLC indicated the reaction complete. The reaction was partitioned between ether and water. The organic layer was washed with water, sat. LiCl (to remove trace DMF) dried with $MgSO_4$ and concentrated. The clear liquid was fractionally distilled under aspirator pressure; fractions between 110 and 126°C, which were collected and combined yielding 61.4 g, 74%, averaging 93% each step of the operation. ^{1}H NMR ($CDCl_3$): two diastereomers δ 3.85 (m, 1H), 3.58 (m, 1H), 2.98 (d, J=4.11 Hz, 1H), 2.89 (d, J=5.34 Hz, 1H), 2.5–1.9 (m, 4H), 1.90–1.65 (m, 4H), 1.65–1.38 (m, 4H), 1.34 (s, 3H), 1.32 (s, 3H), 0.9 (18H), 0.06 (12H).

   Compound **5**: Neat (i-Bu)$_2$AlCl (87.3 mL, 0.447 mol) was slowly added over 1 h at −78°C to freshly prepared LDA (0.447 mol) in benzene, followed by stirring for 4 additional hours at 0°C. Epoxide **4** (27.1 g, 0.112 mol) dissolved in 30 mL anhydrous benzene was added via cannula over 1 h. After 12 h at 25°C, the reaction was carefully poured into an ice/5% HCl solution and diluted with CH_2Cl_2. The organic layer was separated and dried with $MgSO_4$. Et_3N (17.0 g, 0.168 mol) and DMAP (cat.) (0.5 g) are added to the 0°C organic solution. Ac_2O (11.4 g, 0.112 mol) was added dropwise over 2 min. The cold bath was removed and the reaction was stirred for 5 h. The reaction was poured into water and washed with 5% HCl, brine, and dried with $MgSO_4$. The solvent was removed leaving 29.9 g (94%) of a pale yellow oil that was directly used in the next step. ^{1}H NMR ($CDCl_3$): two diastereomers: δ 5.53 (dd, J=4.42 Hz, 8.24 Hz, 1H), 5.19 (m, 1H), 4.80–4.82 (d, 4H), 4.16 (m, 1H), 3.85 (m, 1H), 2.55–2.16 (m, 4H), 2.13 (s, 3H), 2.09 (s, 3H), 2.09–1.30 (m, 8H), 0.9 (18H), 0.06 (12H).

   Compound **6**: **5** (29.9 g, 0.105 mol) was dissolved in 150 mL of anhydrous, degassed, 1,4-dioxane in a flame dried flask equipped with a reflux condenser. Et_3N (13.5 g, 0.133 mol) and $Pd(PPh_3)_4$ (3 g, 2.6 mmol, 2.4%) was added. Under positive pressure of argon, the reaction was heated to reflux for 6 h. The condenser was replaced with a short path distillation apparatus and the volume was reduced by half. The remaining volume was filtered through a short plug of silica to remove the catalyst. The diene was then fractionally distilled through a 15 cm vigreux column, 48°C at 0.03 torr. 19.1 g (81%); $[\alpha]_D$ (c 0.10, $CHCl_3$)=+98.80; ^{1}H NMR ($CDCl_3$): δ 6.19 (dd, J=0.9 Hz, 10 Hz, 1H), 5.76 (d, J=10 Hz, 1H), 4.85 (s, 2H), 4.38 (m, 1H), 2.52 (dt, J=5 Hz, 15 Hz, 1H), 2.32 (m, 1H), 1.93 (m, 1H), 1.79 (m, 1H), 0.94 (s, 9H), 0.132 (s, 3H) 0.126 (s, 3H).

   Compound **2a**: Diene **6** (12.3 g, 54.8 mmol) was dissolved in 110 mL of MeCN/THF (8:2). Aqueous EDTA (90 mL 4×10^{-4} M) was added. $NaHCO_3$ (23 g, 0.273 mol) was added and a −78°C dry ice condenser affixed. The solution was cooled to 0°C and 3 mL CH_3COCF_3 (Aldrich, used as received) was added. Oxone (16.8 g, 27.3 mmol) was added in small portions to the stirring solution over 20 min. After 1 h, a second 3 mL portion of CH_3COCF_3 was added. After 6 h, water was added and the solution was extracted into CH_2Cl_2. The solvent was removed and the residue dissolved in t-BuOH/H_2O/THF (45:45:10). $NaIO_4$ (12.0 g, 56.3 mol) was added and the reaction was stirred at 25°C with a water bath. HIO_4 (100 mg) was added. After 3 h, water was added and the solution extracted into ether. The organic layer was washed with brine, dried with $MgSO_4$, and concentrated. Flash chromatography (4:1 hex–EtOAc) afforded 10.4 g (83%) of a clear colorless oil. Enone **2a** can also be distilled. Bp 120–122°C (5 mmHg); HPLC Chiracel OD (97:3 hexane:i-PrOH) 97.8% ee; $[\alpha]_D$ (c 0.04, $CHCl_3$)=+103.76; ^{1}H NMR ($CDCl_3$): δ 6.84 (dm, J=10.2, 1H), 5.93 (dm, J=10.2 Hz, 1H), 4.54 (m, 1H), 2.59 (dt, J=4.7 Hz, 16.8 Hz, 1H), 2.36 (dq, J=4.7 Hz, 12.8 Hz, 16.8 Hz, 1H), 2.23 (m, 1H), 2.01 (m, 1H), 0.94 (s, 9H), 0.148 (s, 3H) 0.139 (s, 3H). More detailed experiments as well as ^{13}C data and mass spectra are available from the author.
12. Racemic **2a** was synthesized as a standard for HPLC analysis. The ee was determined by HPLC: ChiralCel OD 25 cm with 5 cm guard column (97:3, hexane:i-PrOH, 1 mL/min), (S)-enantiomer 6.1 min, (R)-enantiomer 6.7 min. (R)-Limonene oxide, purchased from Aldrich is reported as 98.5% ee.
13. Enone **2b** was used in racemic form.
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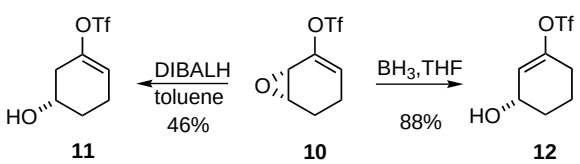
15. Hydride addition to epoxyvinyl triflates can be completely regiospecifically controlled. Addition of DIBAL-H to compound **10** regiospecifically yields the 1,3-reduction product **11**. BH_3 in contrast yields the complimentary 1,5-reduction adduct **12**.



11 **10** **12**