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A Convenient 3-Step Synthesis of (*R*)-7-Hydroxycarvone from (*S*)-α-Pinene

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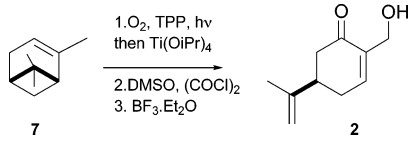

A convenient 3-step synthesis of (*R*)-7-hydroxycarvone (**2**) has been developed starting from (*S*)-α-pinene (**7**), using photooxygenation, oxidation, and fragmentation reactions. An improved synthesis of epoxy alcohol **6** and an unusual $Ti(OiPr)_4$ catalyzed hydroxy epoxide to keto alcohol rearrangement are also described.

For a projected natural product synthesis in our laboratory we required (*R*)-7-hydroxycarvone (**2**) as a starting material (Figure 1). Surprisingly, a literature survey revealed that there were no reports of a practical synthesis of (*R*)-7-hydroxycarvone or any derivatives that might readily be converted to the desired alcohol. Acetate **3** has been prepared in 8% yield from racemic perillyl acetate via CrO_3 oxidation.[1a] Methyl ester **4** has been synthesized in 8 steps from (*R*)-carvone.[1b] Naturally occurring terpenoids are widely employed as chiral pool starting materials.[2] If readily accessible in large quantities, (*R*)-7-hydroxycarvone (**2**) could serve as a versatile starting material for natural product synthesis.

The most direct route to (*R*)-7-hydroxycarvone would be the allylic oxidation of (*R*)-carvone (**1**) itself. However, oxidation of carvone affords products resulting from oxidation of the more electron rich isopropenyl group.[3] Even if the isopropenyl group were somehow masked, regioselective allylic oxidation of the C2 alkyl substituent of 2-alkylcyclohexenones is not well precedented.[4]

We therefore sought to develop a synthesis of (*R*)-7-hydroxycarvone (**2**) starting from readily available and inexpensive (*S*)-α-pinene (**7**) to circumvent the problematic allylic oxidation step. We anticipated that fragmentation of strained epoxide **5** could lead to (*R*)-7-hydroxycarvone (**2**) (Scheme 1). Fragmentation of pinene derivatives has been previously employed in several syntheses.[5] Epoxy ketone **5** could presumably be prepared from oxidation of epoxy alcohol **6**. A convenient synthesis of epoxy alcohol **6** from (*S*)-α-pinene (**7**) has been reported by Adam in a one-pot photooxygenation reaction.[6]

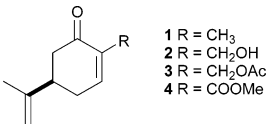

FIGURE 1.

In our hands, however, treatment of α-pinene (**7**) with the Adam conditions (O_2, $Ti(OiPr)_4$ (10 mol %), tetraphenylporphine (TPP), *hν*, CH_2Cl_2, 20 h) gave as the major product not epoxy alcohol **6** but β-hydroxy ketone **8** (Scheme 2).[7]

To gain further insight into this unexpected result, an authentic sample of epoxy alcohol **6** was prepared in 3 steps by known methods (Scheme 3).[8] Exposure of epoxy alcohol **6** to $Ti(OiPr)_4$ at room temperature also afforded rearranged alcohol **8** in 80% yield.

This result suggests that the initially formed epoxy alcohol **6** undergoes a rearrangement involving 1,2-hydride shift to form β-hydroxy ketone **8** (Scheme 4). Adam reported the formation of an enone side product that might have been formed via β-elimination of keto alcohol **8**. The authors alluded to a rearrangement of epoxy alcohol **6** to the enone, but provided no details.[6b] Adam reported one case of formation of a hydroxy ketone via $Ti(OiPr)_4$-catalyzed 1,2-aryl shift in ca. 5% yield.[6] Although a few examples of acid-catalyzed 1,2-hydride shifts of epoxy alcohols have been documented,[9] it is

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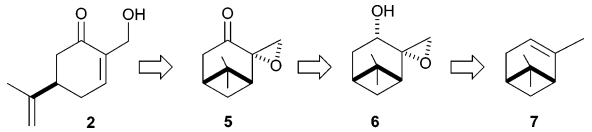
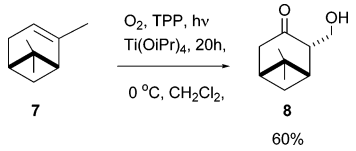
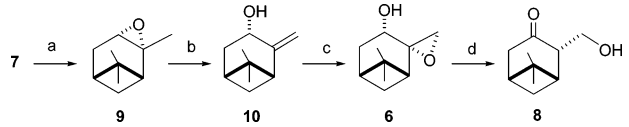
SCHEME 1



SCHEME 2



SCHEME 3 [a]



[a] Reagents and conditions: (a) MCPBA, $NaHCO_3$, CH_2Cl_2, 90%; (b) LDA, ether, −78 °C, 85%; (c) MCPBA, $NaHCO_3$, CH_2Cl_2, 90%; (d) $Ti(OiPr)_4$, CH_2Cl_2, rt, 80%.

surprising that $Ti(OiPr)_4$ is capable of catalyzing the hydride shift. Epoxy alcohols are frequently prepared by $Ti(OiPr)_4$-catalyzed oxidation of allylic alcohols without competing rearrangement.[10] Presumably $Ti(OiPr)_4$ undergoes ligand exchange with epoxy alcohol **6**. The epoxide would be activated toward ring opening upon coordination with the internal Ti alkoxide. Epoxide ring opening would then afford b-hydroxy ketone **8** after hydrolysis of the alkoxide. Alleviation of strain between the carbinol hydrogen and the methyl group on the cyclobutane ring may be responsible for the facility of the rearrangement.

Careful monitoring of the photooxygenation reaction revealed that the rearrangement of epoxy alcohol **6** to ketone **8** occurred before complete consumption of pinene. Adam had noted in one case that a stepwise allylic oxidation/oxygen transfer gave higher yield of the epoxy alcohol than the one-step variant.[6] We were able to both increase the yield and eliminate the undesired rearrangement by employing a stepwise protocol wherein complete photooxygenation of α-pinene (**7**) to hydroperoxide **11** was achieved prior to the introduction of $Ti(OiPr)_4$ (Scheme 5).[11] The progress of the reaction was monitored by ^1H NMR analysis. Addition of a catalytic amount (0.11 equiv) of $Ti(OiPr)_4$ then led to the desired epoxy alcohol **6** within 15 min without competing rearrangement. This one-pot, two-step protocol gave excellent yield of epoxy alcohol **6** accompanied by a few percent of allylic alcohol **10**. On the basis of these results it is clear that the modified Adam procedure could also be used to access hydroxy ketone **8** in a one-pot process in high yields. However, we did not optimize that transformation since the focus of our investigation was the preparation of 7-hydroxycarvone.

Swern oxidation of epoxy alcohol **6** gave epoxy ketone **5** in very good yield (Scheme 6).[12] With the suitably substituted pinene ring system in hand, fragmentation of the strained tricycle was investigated under a variety of conditions. It was not clear at the outset of this study whether the presence of the carbonyl group would inhibit the key fragmentation reaction. Several previously reported fragmentations relied on the formation of a positive or partial positive charge on the carbon adjacent to the cyclobutane ring to initiate the fragmentation reaction.[5a−g] In our case, a positive or partial positive charge would be destabilized by the adjacent carbonyl group. Mineral acids,[5a,b,f] Hg(II) salts,[5c] and bases[5i] have previously been employed in the ring opening of various pinene-derived substrates. We surveyed basic, Bronsted, and Lewis acidic and silylative conditions to effect the fragmentation.

Under basic (tBuOK, LDA, KHMDS) or silylative conditions (TMSOTf, TIPSOTf), only decomposition ensued. Under acidic conditions (Amberlite, AcOH, CF_3CO_2H, H_2SO_4, HCl, $HClO_4$) either decomposition or no reaction was observed except in the case of concentrated $HClO_4$. Treatment of epoxy ketone **5** with concentrated $HClO_4$ afforded (*R*)-7-hydroxycarvone (**2**), albeit in moderate (35%) yield. A survey of Lewis acids catalysts ($LiClO_4$, $Hg(NO_3)_2$, $MgBr_2$, $InCl_3$, $Sm(OAc)_3$, $NaBF_4$, $BF_3{\cdot}Et_2O$) revealed that the optimal conditions for the fragmentation (3 equiv of $BF_3{\cdot}Et_2O$, 0 °C) afforded (*R*)-7-hydroxycarvone (**2**) in 50−55% yield on a multigram scale. In all other cases either no reaction occurred or complex product mixtures were obtained.

In conclusion, a convenient synthesis of (*R*)-7-hydroxycarvone (**2**) has been achieved in 3 steps in an overall yield of 45% starting from inexpensive (*S*)-α-pinene on a multigram scale. A modification of the Adam photooxygenation of α-pinene gave higher yield and fewer side products and reduced the reaction time from 20 to 4.5 h.

Experimental Section

As complete ^1H and ^{13}C NMR data for compounds **5** and **6** have not previously been published, we provide full data below.

Hydroxyketone 8[7] **(from epoxy alcohol 6).** $Ti(OiPr)_4$ (0.13 mL, 0.19 g, 0.67 mmol) was added to a solution of epoxy alcohol **6** (1.0 g, 5.95 mmol) in CH_2Cl_2 (20 mL) at 0 °C. The reaction mixture was allowed to warm to room temperature, stirred for 1 h, then quenched by the addition of water (100 mL). The mixture was filtered through a short Celite column, and the organic layer was separated, dried over anhydrous $MgSO_4$, and concentrated in vacuo. The crude material was purified by flash column chromatography on silica gel with 10/90 ethyl acetate/hexanes to give hydroxy ketone **8** as a pale yellow oil (0.79 g, 80%). Proton and ^{13}C NMR data were fully consistent with published data.[7]

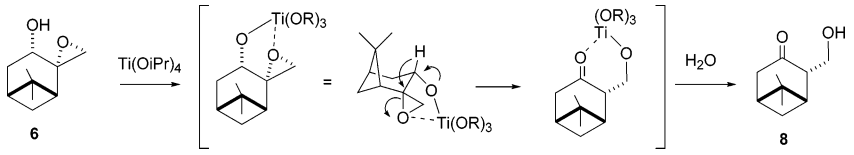
Epoxy Alcohol 6.[6] Oxygen was bubbled into a solution of *S*-(α)-pinene (**7**) (5.0 g, 36.7 mmol) and tetraphenylporphine (TPP) (62 mg, 5×10^{-4} M) in CH_2Cl_2 (200 mL) in a photoreactor at 0 °C under irradiation with a halogen lamp for 4 h. Irradiation was discontinued and $Ti(OiPr)_4$ (1.09 mL, 1.05 g, 3.7 mmol) was introduced at 0 °C. Stirring was continued for 15 min before quenching of the reaction mixture by the addition of water. The solution was filtered through a short Celite column, and the organic layer separated, dried over anhydrous $MgSO_4$, and

(10) See, for example: Paquette, L. A.; Belmont, D. T.; Hsu, Y.-L. *J. Org. Chem.* **1985**, *50*, 4667−4672. For a review, see: Katsuki, T.; Martin, V. S. *Org. React*. **1996**, *48*, 1−299.

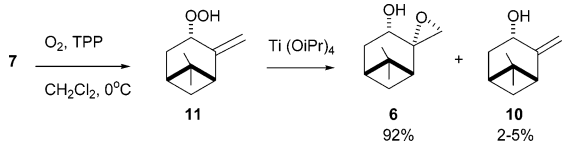
(11) Hydroperoxide **11** has previously been prepared and isolated: Schenck, G, O.; Eggert, H.; Denk, E. *Liebigs Ann. Chem.* **1964**, *19,* 675.

(12) Epoxy ketone **5** has previously been prepared in 16% yield as a mixture of diastereomers via epoxidation of the corresponding enone: Meklati, B.; Bessiere-Chretien, Y. *Bull. Soc. Chim. Fr.* **1971**, *8*, 3133−3137.

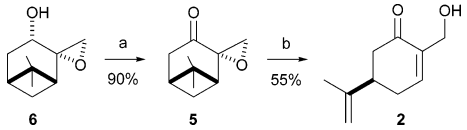
SCHEME 4



SCHEME 5



SCHEME 6 [a]



[a] Reagents and conditions: (a) DMSO, $(COCl)_2$, NEt_3, −78 °C; (b) $BF_3{\cdot}OEt_2$, CH_2Cl_2, 0 °C.

concentrated in vacuo. The crude material was purified by flash column chromatography on silica gel with 10/90 ethyl acetate/hexane to give epoxy alcohol **6** (4.9 g, 92%) as a dark oil: $[\alpha]^{23}_D$ +4.05 (*c* 1.48, $CHCl_3$); IR (film) 3506 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) δ 0.81 (s, 3H), 1.3 (s, 3H), 1.5 (t, J = 5.4 Hz, 1H), 1.9 (d, J = 10.1 Hz, 1H), 1.96 (m, 2H), 2.15−2.35 (m, 2H), 2.5 (s, 1H), 2.8 (d, J = 4.7 Hz, 1H), 2.95 (d, J = 4.7 Hz, 1H), 3.9 (d, J = 7.4 Hz, 1H); ^{13}C NMR (67 MHz, $CDCl_3$) δ 21.4, 25.7, 25.9, 33.3, 39.8, 41.3, 47.7, 57.0, 64.5, 66.1.

Epoxy Ketone 5.[12] A solution of DMSO (5.9 mL, 6.5 g, 83.2 mmol) in CH_2Cl_2 (10 mL) was added to a solution of oxalyl chloride (3.1 mL, 4.5 g, 35.5 mmol) in CH_2Cl_2 (100 mL) at −78 °C. After 5 min epoxy alcohol **6** (2.0 g, 11.9 mmol) in CH_2Cl_2 (10 mL) was added dropwise followed after 10 min by NEt_3 (14.8 mL, 10.8 g, 107.1 mmol). The reaction mixture was allowed to warm to room temperature and concentrated in vacuo. The residue was dissolved in water and extracted with hexanes (3 × 50 mL). The combined organic extracts were washed with water, dried over anhydrous $MgSO_4$, and concentrated in vacuo. The crude material was purified by flash column chromatography on silica gel with 10/90 ethyl acetate/hexanes to give epoxy ketone **5** (1.7 g, 86%) as a pale yellow liquid: $[\alpha]^{23}_D$ +79.5 (*c* 1.71, $CHCl_3$); IR (film) 1731 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) δ 0.94 (s, 3H), 1.36 (s, 3H), 1.54 (d,1H), 1.81 (t,1H), 2.25 (m, 1H), 2.5−2.8 (m, 4H), 3.25 (d, 1H); ^{13}C NMR (67 MHz, $CDCl_3$) δ 20.8, 26.0, 30.0, 38.5, 41.1, 42.6, 44.9, 53.9, 62.3, 208.2.

***(R)*-7-Hydroxycarvone (2).** $BF_3{\cdot}Et_2O$ (5.7 mL, 45 mmol) was added dropwise to a solution of epoxy ketone **5** (2.5 g, 15 mmol) in CH_2Cl_2 at 0 °C and stirred for 4 h at room temperature. The reaction mixture was quenched by the addition of saturated $NaHCO_3$ solution. The organic layer was separated and the aqueous layer was extracted with CH_2Cl_2 (3 × 30 mL). The combined organic phases were dried, concentrated, and purified by flash chromatography on silica gel with CH_2Cl_2, followed by 5/95 methanol/CH_2Cl_2, to obtain (*R*)-7-hydroxycarvone (**2**) (1.4 g, 55%) as a yellow liquid: $[\alpha]^{23}_D$ +36.9 (*c* 1.90, $CHCl_3$); IR (film) 3464,1655 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) δ 1.74 (s, 3H), 2.3−2.8 (m, 5H), 4.25 (d, J = 3.0 Hz, 2H), 4.76 (s, 1H), 4.82 (s, 1H), 6.93 (m, 1H); ^{13}C NMR (67 MHz, $CDCl_3$) δ 20.4, 30.9, 42.1, 43.1, 61.8, 110.8, 138.1, 145.8, 146.2, 200.3.

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Supporting Information Available: The ^1H and ^{13}C NMR spectra of compounds **2**, **5**, **6**, and **8**. This material is available free of charge via the Internet at http://pubs.acs.org.

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