Organic Process Research & Development **2009**, *13*, 358–361

Large-Scale Preparation of (+)-*p*-Menth-2-ene-1,8-diol, a Key Intermediate in the Synthesis of Δ-9-Tetrahydrocannabinol

John E. Cabaj,* Julie M. Lukesh,† Richard J. Pariza, and Paul M. Zizelman

Process Research and Development, Cedarburg Pharmaceuticals, Inc., 870 Badger Circle, Grafton, Wisconsin 53024, U.S.A.

Abstract:

A manufacturing-scale process for the preparation of *p*-menth-2-ene-1,8-diol, a key intermediate for the preparation of Δ-9-tetrahydrocannabinol (Δ-9-THC), was developed. The process entails a large-scale olefin migration/epoxidation and hydrolytic epoxide opening in organic solvent. The water-soluble product is isolated without the need for exhaustive extraction.

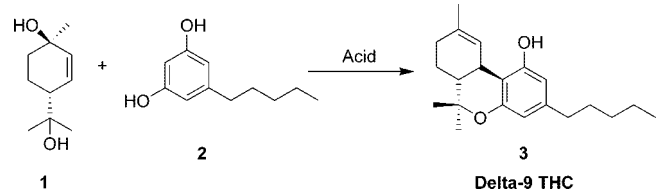
Introduction

The tricyclic diterpene Δ-9-tetrahydrocannabinol (Δ-9-THC, **3** Scheme 1) is the active ingredient in marijuana and is currently being used to reduce nausea in patients who are undergoing chemotherapy. Δ-9-THC has also been shown to have anti-glaucoma as well as analgesic properties. Historically, the source of the chiral portion of the molecule has been obtained through the chiral pool using an appropriately substituted terpene.[1] Although several asymmetric syntheses have been developed, they are, in general, lengthy.[2,3]

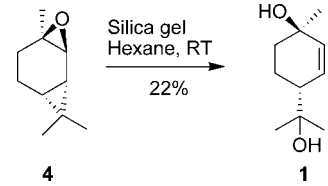
p-Menth-2-ene-1,8-diol (**1**) has been used by several groups as a key intermediate in the synthesis of Δ-9-THC.[4] Typically, **1** is condensed with olivetol (**2**) in the presence of a protic or Lewis acid to give **3** (Scheme 1).

The product is usually purified chromatographically to give **3** as an oil. During our efforts to develop a scalable process for the production of **3**, we needed to produce diol **1** in kilogram quantities. Since we felt that the previous procedures were unsuitable for scale-up, we developed a new process that was successfully implemented in our plant to produce kilogram quantities of **1**. The details of our development work are described herein.[5]

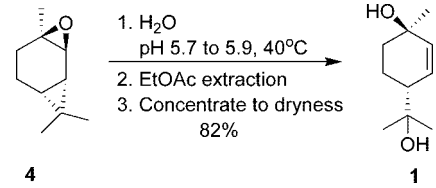
Scheme 1. **Synthesis of THC from (*p*)-menth-2-ene-1, 8-diol**



Scheme 2. **Prasad synthesis of 1**



Scheme 3. **Johnson-Matthey synthesis of 1**



Results and Discussion

Initially, we produced **1** from the known epoxide **4** using the method of Prasad.[6] However, the yields in our hands were low (Scheme 2).

In another method, Bledsoe has reported that treatment of **4** with sulfuric acid in water gives a 50% yield of **1**.[7] More recently, workers at Johnson-Matthey reported an improved procedure for the preparation of **1**.[4d] Their procedure involves stirring **4** in water at a pH of 5.7−5.9 at 40 °C. After exhaustive extraction (seven times) with ethyl acetate followed by concentration to dryness, **1** is isolated in 82% yield (Scheme 3).

We have developed an operationally simple and scalable procedure to produce **1** in a 20 kg batch from a mixture of 2- and 3-carene.

Production of 2-/3-Carene. 3-Carene (**5**, Scheme 4) is an inexpensive raw material. It is available in kilogram quantities for about $62/kg (Aldrich), and some turpentines contain

* To whom correspondence should be addressed. Telephone: (262)-376-1467. Fax: (262)-376-1068. E-mail: john.cabaj@cedarburgpharma.com.

† Current address: The University of Wisconsin-Green Bay, 2420 Nicolet Drive, Green Bay, Wisconsin 54311-7001, U.S.A.

(1) For reviews on THC and other terpenes see: Razdan, R. K. The Total Synthesis of Cannabinoids. In *Chemistry of the Monoterpenes An Encyclopedic Handbook, Part B*; ApSimon, J., Ed.; Wiley: New York, 1981. Erman, W. F. *The Total Synthesis of Natural Products* ; Marcel Dekker, Inc.: New York, 1985; Vol. 4, Chapter 12.

(2) For asymmetric syntheses see: Trost, B. M.; Dogra, K. *Org. Lett.* **2007**, *9*, 861. Evans, D. A.; Barnes, D. M.; Johnson, J. S.; Lectka, T.; von Matt, P.; Miller, S. J.; Murry, J. A.; Norcross, R. D.; Shaughnessy, E. A.; Campos, K. R. *J. Am. Chem. Soc.* **1999**, *121*, 7582.

(3) For a racemic synthesis starting from non-terpenoid starting materials see: Fahrenholtz, K. E.; Lurie, M.; Kierstead, R. W. *J. Am. Chem. Soc.* **1967**, *89*, 5934.

(4) (a) Handrick, G. R.; Uliss, D. B.; Dalzell, H. C.; Razdan, R. K. *Tetrahedron Lett.* **1979**, *20*, 681. (b) Stoss, P.; Merrath, P. *Synlett* **1991**, 553. (c) Stoss, P.; Merrath, P. U.S. Patent 5,227,537, 1993. (d) Casner, M.; Resnick, T. M.; Silverberg, L. J. World Patent Application WO 02/096846, 2002. (e) Silverberg, L. J. World Patent Application WO 02/096899 A1, 2002.

(5) See: Cabaj, J. E.; Pariza, R. J.; Lukesh, J. World Patent Application WO 2005/100333, 2005 for coverage of this work and other methods to produce THC.

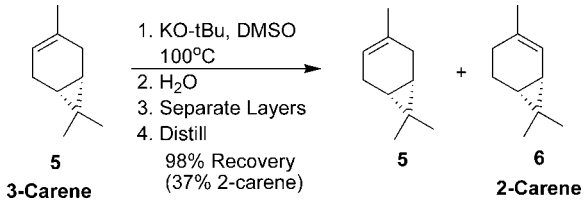
(6) Prasad, R. S.; Dev, S. *Tetrahedron* **1976**, *32*, 1437.

(7) Bledoe, J. O., Jr.; Derfer, J. M.; Johnson, W. E., Jr. U.S. Patent 3,814,733, 1974.

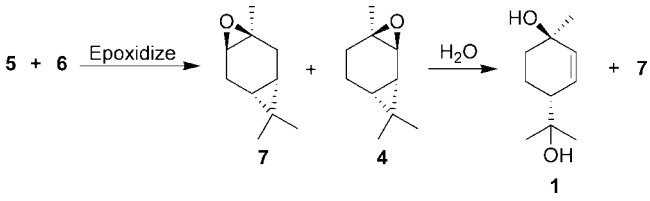
Published on Web 01/05/2009

10.1021/op8002272 CCC: $40.75

Scheme 4. **KO-tBu-mediated equilibration of 3-carene**



Scheme 5. **Diol synthesis from 2-/3-carene mixture**



30−42% 3-carene (The Merck Index). The low cost and availability of this terpene make it an attractive starting material for large-scale **Δ**-9-THC production. 3-Carene is easily equilibrated to an approximate 40/60 mixture of 2-carene (**6**) and 3-carene by heating in DMSO in the presence of KO-tBu. This procedure has been used successfully in our production plant with minor modifications to produce 85 kg of the 2-/3-carene mixture in good yield (98% recovery, Scheme 4).[8]

One modification worthy of note is the elimination of the extraction with petroleum ether. After reaction completion, water was added to dissolve the KO-tBu, and the crude 2-/3-carene product layer was separated from the aqueous layer. The 2-/3-carene mixture was simply distilled on a rotovap or from reactor to reactor to give the 2-/3-carene mixture (37% 2-carene, 60% 3-carene by GC). This minor modification had a large impact on our process throughput and greatly reduced our cycle times.

Epoxidation of 2-/3-Carene. The high cost of pure 2-carene make its use in THC synthesis undesirable. The 2-/3-carene mixture is a cost-effective alternative since the 3-carene epoxide produced after oxidation (**7**, Scheme 5) does not react with H_2O, while the 2-carene epoxide (**4**) gives the solid diol (**1**).

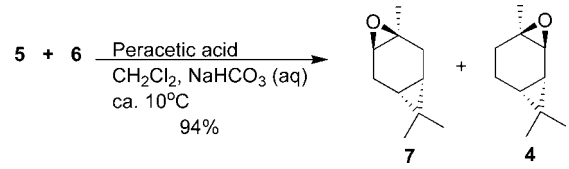
Unreacted **7** and process impurities can be removed by washing the product with solvent. Thus, the low cost of this process makes separation of the two regioisomers unnecessary.

We initially produced the 2-/3-carene epoxide mixture using MCPBA in a biphasic mixture of CH_2Cl_2/aqueous $NaHCO_3$ and obtained a 93% yield of **7** and **4**. The portionwise addition of the solid MCPBA to the biphasic mixture containing **5** and **6** made this procedure unsuitable for reactor-scale production. Peracetic acid was a logical alternative since it exists in liquid form and therefore can be charged through liquid transfer lines. The fact that peracetic acid is approximately one-third the cost of MCPBA was also an advantage.[9] Slow addition of peracetic acid to **5**/**6** as in the MCPBA procedure gave a 94% yield of **7** and **4** (58% **7**, 41% **4** by GC, Scheme 6).

Epoxidation with the peroxyimidic acid prepared using H_2O_2/CH_3CN/$KHCO_3$/MeOH, resulted in incomplete conversion,

(8) Acharya, S. P.; Brown, H. C. *J. Am. Chem. Soc.* **1967**, *89*, 1925.
(9) The cost per mole of oxidant for peracetic acid is $34/mol, whereas the cost for MCPBA is $93/mol (2007−2008 Aldrich catalog pricing).

Scheme 6. **Epoxidation of 2/3-carene mixture with peracetic acid**



whereas the solid byproduct produced using the more reactive trichloromethyl version complicated the isolation.[10,11]

Other bases such as NaOH, NaOAc, Na_3PO_4, and K_2HPO_4 that do not liberate CO_2 when protonated with the liberated acetic acid were also examined. However, $NaHCO_3$ consistently gave the best results.

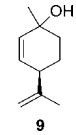
In an attempt to streamline the process to avoid a concentration step, the reaction was run in heptane (the solvent initially used in the epoxide opening step, *vide infra*). However, the reaction was prohibitively slow (~20 h to reach completion), presumably due to the insolubility of the peracid in heptane. In the interest of time, the peracetic acid oxidation in CH_2Cl_2/aqueous $NaHCO_3$ (Scheme 6) was used for scale-up. The CO_2 off gassing was controlled by the addition rate. The process was used to produce enough epoxide to produce 20 kg of **1** in a single batch.

Preparation of Diol 1. Diol **1** is water soluble, making extractive isolations between water and organic solvent inefficient. In addition, due to the known instability of **1**, we sought to develop a process with a minimal number of operations.[12] Given the large difference in polarity of the polar diol and the starting material and impurities we hoped to find a reaction solvent in which the diol would precipitate as it was formed.[13] Remaining starting material, unreacted **7**, and process impurities would then simply be washed out with solvent. Such a process would also protect the diol from further reaction with the reaction media and be operationally simple on reactor scale.[14]

We initially performed this reaction using 3 equiv of water and acetic acid as the catalyst in heptane, since the starting epoxide mixture was readily soluble in this solvent and the product diol had a very low solubility of approximately 2 g/L. The process was quickly optimized in the laboratory and transferred to the plant to produce 3.4 kg of **1** in 53% yield based on the amount of contained **7** (Scheme 7).

Removal of the product from the reactor was difficult during this run since the diol stuck to the walls of the vessel. In order

(10) Bach, R. D.; Knight, J. W. *Org. Synth.* **1981**, *60*, 63.
(11) Arias, L. A.; Adkins, S.; Nagel, C. J.; Bach, R. D. *J. Org. Chem.* **1983**, *48*, 888.
(12) The main decomposition product formed from **1** upon continued exposure to acid is 1-methyl-4-(1-methylvinyl) cyclohex-2-ene-1-ol 9.



9

(13) The R_f difference between **7**/**4** and **1** is approximately 0.6 using 1:1 EtOAc/heptanes as the eluent.
(14) Other examples of this approach were kindly brought to our attention by a reviewer. Chen, C.-K.; Singh, A. K. *Org Process Res. Dev.* **2001**, *5*, 508. Chang, J. H.; Hyunik, S. *Org. Process Res. Dev.* **2008**, *12*, 291.

Scheme 7. **Initial production process for epoxide opening**

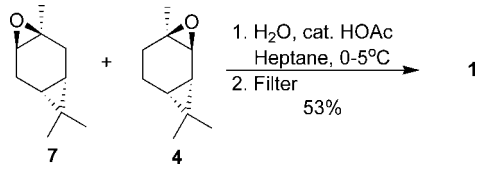


Table 1. **Solvent screening for epoxide opening**

entry	reaction solvent[a]	percent yield[b]
1	heptanes	87
2	cyclohexane	53
3	toluene	65
4	MTBE	68
5	CH_2Cl_2	52
6	$CHCl_3$	29
7	MTBE/heptanes (1/3 by volume)	33
8	CH_2Cl_2/heptanes (1/1 by volume)	48
9	isopropyl acetate/heptane (1/10 by volume)	61

[a] 9 mL/g **7**/**4** mixture. [b] Isolated yield based on the amount of **4** in the **7**/**4** mixture.

Scheme 8. **Final production process for epoxide opening**

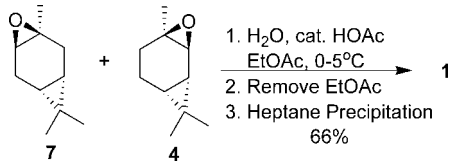


Table 2. **Catalyst screening for epoxide opening**

entry	catalyst[a]	percent yield[b]
1	acetic acid	87
2	formic acid	66
3	benzoic acid	71
4	trifluoroacetic acid	18

[a] All reactions were carried in heptanes at 0−5 °C with 0.1 equiv of catalyst relative to moles of **7**/**4** mixture and 3 equiv of water. [b] Isolated yield.

to alleviate this problem, other solvents were examined for the epoxide-opening reaction. The results are summarized in Table 1.

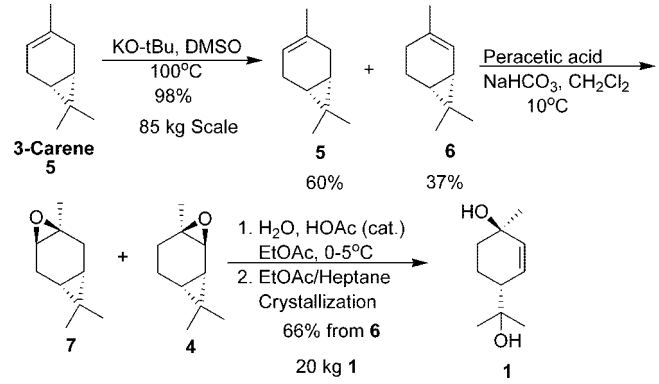
The results indicate that use of other solvents led to diminished yields relative to heptanes on laboratory scale. Use of mixed solvent systems (entries 7−9) did result in an easier transfer of the product, but at the expense of yield.

We routinely purified **1** by recrystallization from ethyl acetate/heptane if necessary. Therefore, we ran the reaction itself in ethyl acetate. After reaction completion, a portion of ethyl acetate was removed to reduce the volume and azeotropically remove water; further precipitation with heptanes gave **1** in 61% yield as a granular solid (97% pure by area % HPLC). When the process was run in this fashion on reactor scale, the diol was easy to remove from the reactor, and a 66% yield (from **6**) of **1** was realized (20 kg batch, 96 area % purity, Scheme 8).

Other acid catalysts were briefly screened. The results are summarized in Table 2.

Of these four catalysts, acetic acid gave the best results. The low yield obtained with the stronger acid trifluoroacetic acid is presumably due to acid-catalyzed decomposition of the diol.

Scheme 9. **Overall plant process to produce 1**



A summary of the overall process to produce **1** is shown in Scheme 9.

The diol produced using the described procedure was used to produce kilogram quantities of crude **Δ**-9-THC.

Summary and Conclusion

A reactor-scale process for the production of (+)-*p*-menth-2-ene-1,8-diol from commercially available 3-carene was developed. Keys to the process were a high throughput rearrangement followed by epoxidation and an operationally simple epoxide opening with water in organic solvent. Diol **1** was produced in a 20 kg batch using this process. The diol **1** produced was used to produce crude **Δ**-9-THC, which can be purified chromatographically or by other means.

Experimental Section

General. All raw materials were used as supplied by vendors. All reactions were performed under nitrogen in glassware or glass-lined reactors as described below. The conversion of **5** to **5**/**6** and **5**/**6** to **7**/**4** was monitored by GC using a Phenomenex ZB-5 capillary column (30 m × 0.32 mm × 0.25 μm). The conversion of **7**/**4** to **1** was monitored by quantitative TLC using 9/1 (by volume) heptanes/MTBE as the eluent (5% phosphomolybdic acid in MeOH to visualize). The purity of **1** was determined by reverse phase HPLC (1 mL/min flow rate) using a Waters Xterra RP 18 column (4.6 mm × 150 mm, 3.5 μm particle size) and a UV detector (210 nm). NMR data were obtained using a Varian 400 MHz instrument. Chemical shifts are reported in ppm. IR data were obtained using a Bruker Vector 22 FTIR. Mass spectral data were obtained using a HP 5972 series Mass Selective Detector interfaced with a HP 6890 GC instrument. The melting point of **1** was determined using a Hoover Unimelt capillary melting point apparatus and is uncorrected.

Preparation of 5/6 Mixture. To a nitrogen-purged, 50-gallon, glass-lined reactor was charged 87.0 kg (639 mol) of 3-carene. To a separate 100-gal reactor was added 31.7 kg of KO-tBu (283 mol) and 80.9 kg of DMSO. The contents of the 100-gal reactor were stirred for 10 min at room temperature. The 3-carene was then transferred to the 100-gal reactor. The contents of the 100-gal reactor were then heated to a temperature of 95−105 °C and held at this temperature for 12 h at which point the reaction was determined to be complete by GC analysis (42% **6**). The reaction was cooled to 25 °C, and 80.1

kg of water was added over 10 min. The layers were separated, and the organic layer was washed with 79.9 kg of water. After removal of an approximately 6 kg forecut by distillation from one reactor to another, the organic layer was bulb-to-bulb distilled on a rotovap at a bath temperature of 65−75 °C at a pressure of approximately 10−20 Torr to give 84.6 kg of **5**/**6** (98% recovery 60% **5**, 37% **6** by GC). On another production run at the same scale, the product was distilled from reactor to reactor to give a 76% recovery of **5**/**6**.

Preparation of 1. To a nitrogen-purged, 300-gal, glass-lined reactor was charged 299.7 kg of water and 110.7 kg of $NaHCO_3$. The mixture was cooled to a set point of 7−16 °C while stirring. Methylene chloride (110.7 kg) was then added to the reactor followed by 60.1 kg (441 mol) of a ca. 60/40 mixture of **5**/**6**. **Safety note: The 5/6 mixture can create a significant static discharge. Use only in inert environments with proper grounding techniques.** To the biphasic mixture at 7−16 °C was added 114.9 kg (483 mol) of 32% peracetic acid over ∼15 h. The rate of CO_2 evolution was controlled by the addition rate. The reaction was stirred for an additional 1 h at 7−16 °C after the addition was complete. The reaction was determined to be complete at this point by GC analysis. To the reaction mixture was added 112.1 kg of an aqueous solution of sodium thiosulfate pentahydrate (10 kg sodium thiosulfate pentahydrate/69 kg water) at a temperature of <15 °C over ∼5 h (KI test negative). The layers were then separated, and the aqueous layer was extracted with 380.0 kg of methylene chloride. The combined organic extracts were washed with 219 kg of a mixture of 22.3 kg of $NaHCO_3$ in 306 kg of water, and twice with 240 kg of water. The organic layer was concentrated to a final volume of 50−70 gal containing a mixture **7** and **4**. NMR data for **7** ^{1}H NMR ($CDCl_3$): δ 2.85 (t, J = 2.0 Hz, 1 H), 2.32 (ddd, J = 2.0, 9.0, 16.4 Hz, 1 H), 2.16 (ddd, J = 1.1, 9.1, 16.3 Hz, 1 H), 1.67 (dt, J = 2.2, 17.5 Hz, 1 H), 1.51 (dd, J = 2.3, 16.3 Hz, 1 H), 1.27 (s, 3 H), 1.02 (s, 3 H), 0.75 (s, 3 H), 0.55 (dt, J = 2.2, 9.1 Hz, 1 H), 0.47 (dt, J = 2.0, 9.2 Hz, 1 H). ^{13}C NMR ($CDCl_3$): δ 58.2, 55.9, 27.8, 23.4, 23.1, 19.2, 16.1, 16.0, 14.6, 13.9 ppm. NMR data for **4** ^{1}H NMR ($CDCl_3$): δ 3.03 (d, J = 2.0 Hz, 1 H), 1.97−1.87 (m, 1 H), 1.72−1.67 (m, 2 H), 1.60−1.54 (m, 1 H), 1.27 (s, 3 H), 1.10−1.06 (m, 1 H), 1.09 (s, 3 H), 1.08 (s, 3 H), 0.68 (dddd, J = 0.6, 2.9, 6.1, 9.1 Hz, 1 H). ^{13}C NMR ($CDCl_3$): δ 58.1, 57.9, 28.9, 27.1, 23.7, 21.9, 21.0, 20.7, 16.5, 16.4 ppm. IR (**7**/**4** mixture, neat): 2922, 1451, 1377, 1065, 866, 840 cm^{-1}. MS (**7**/**4** mixture, EI): *m*/*e* 152 (M^+).

To the CH_2Cl_2 solution of **7** and **4** was added 540 kg of ethyl acetate. The CH_2Cl_2 was displaced by concentrating to a volume of 70−90 gal. The ethyl acetate solution of **7** and **4** was cooled to ≤10 °C, and a solution of 2.5 kg (42 mol) of acetic acid in 19.9 kg (1.11 kmol) of water was added over ∼45 min while maintaining a temperature of 5−10 °C. The mixture was stirred vigorously at 5−10 °C for 8 h at which point the reaction was determined to be complete by TLC analysis. The reaction mixture was concentrated to a volume of 50−70 gal at a temperature of ≤45 °C. Ethyl acetate (320.0 kg) was then added, and the reaction mixture was concentrated to a volume of 40−60 gal at a temperature of ≤45 °C. Heptane (290.0 kg) was then added over ∼4 h at a temperature of ≤30 °C to further precipitate the product. The slurry was cooled to ≤10 °C and held at this temperature for ∼2 h. The slurry was filtered on a Cogeim filter, washed with a cold (≤10 °C) mixture of 50 kg of heptane/15 kg of ethyl acetate (two equal portions), and dried in the filter at a temperature of 25−30 °C to give 19.9 kg of **1** (66% from contained **6** in **5**/**6** mixture, 96% area % purity, 6.3% water present). Mp 111−113 °C (lit. 115 °C) ^{1}H NMR ($CDCl_3$): δ 5.7 (AB_q, J = 11 Hz, 2 H), 2.2 (m, 1H), 1.9 (m, 2 H), 1.7 (m, 1 H), 1.3−1.5 (m, 3 H), 1.3 (s, 3 H), 1.2 (s, 3 H), 1.1 (s, 3 H). ^{13}C NMR ($CDCl_3$): δ 136.6, 127.8, 72.6, 69.4, 47.0, 38.3, 28.3, 27.9, 26.2, 23.0. IR (KBr): 3250, 1375, 1125, 900 cm^{-1}. MS (EI): 152 ($M^+ - H_2O$).

Acknowledgment

We thank Steve Guntz and the entire Cedarburg production staff for their guidance in transferring the laboratory procedures to the plant and the Cedarburg analytical group for assay development.

Received for review September 14, 2008.

OP8002272