

A Convenient Synthesis of *trans*-Sabinene Hydrate from (–)-3-Thujol via a Highly Selective Ene Reaction of Singlet Oxygen

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Abstract—*trans*-Sabinene hydrate (**1**), was synthesized from (–)-3-thujol (**2**) in four steps. The key step was the selective formation of *trans*-2-hydroxy-3-thujene (**6**) by photooxygenation of a 3:1 mixture of 2- and 3-thujenes (**4** and **5**) obtained from (–)-3-thujol mesylate (**3**). Hydrogenation of **6** gave compound **1** in 46% overall yield. Copyright © 1996 Elsevier Science Ltd

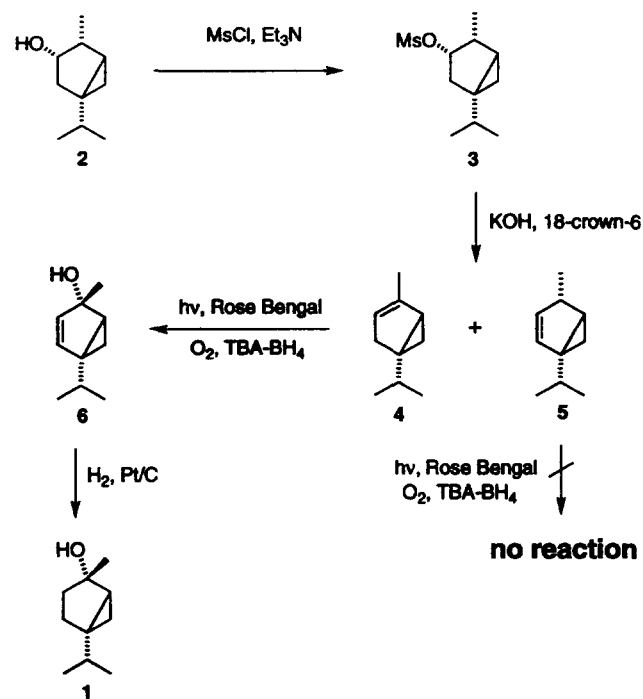
Introduction

The thujane derivative (1*R*,2*S*,5*R*)-2-methyl-5-(methyl-ethyl)bicyclo[3.1.0]hexan-2-ol (*trans*-sabinene hydrate, **1**) has been reported^{1,2} as a component of the odor bouquet emitted by several bark beetle species, as well as the Tunisian desert isopod *Hemilepistus reaumuri*.³ It has also been identified in sunflower aroma as one of the components stimulating the honeybee workers antennal receptors.⁴ Since the exact role of **1** in these chemical communication systems is yet to be investigated, we sought for a synthesis of **1** that would make it possible to produce quantities on the gram scale required for extensive behavioral tests.

Several methods have been developed for the synthesis of **1**. A total-synthesis approach⁵ and a method starting from photooxygenation of sabinene⁶ are both reported with overall yields lower than 15%. Other routes include photooxygenation of 2-thujene (**4**) as a common step,^{7,8} which constitutes a problem. Pure **4** is neither readily available from natural sources nor by synthetic methods. Described procedures, i.e. Birch reduction of sabinol,⁹ pyrolytic or base-promoted decomposition of thujol derivatives,¹⁰ base-catalyzed isomerization of sabinene^{11,12} and Bamford–Stevens rearrangement of thujone *p*-toluenesulfonyl hydrazone,¹³ suffer from serious drawbacks. Repeating the base-catalyzed isomerization of sabinene¹¹ gave an 85:15 equilibrium mixture of 2-thujene and sabinene together with ca. 30% of unidentified hydrocarbons. Decomposition of the *p*-toluenesulfonyl hydrazone gave a 1.5:1 ratio of 2- and 3-thujene (**4** and **5**), but the required hydrazone could only be obtained in 28% yield (lit.¹³ 32%).

Results and Discussion

We now report a convenient synthesis of **1**, outlined in Scheme 1, starting from enantiomerically pure (–)-3-thujol (**2**) which is accessible as such from natural sources,¹⁴ or by reduction⁹ of readily available 3-thujene.¹⁵ The method provides significant improve-



Scheme 1.

ments of the known methods in that it makes possible the use of a mixture of **4** and **5** in the photooxygenation step since the disubstituted double bond of **5** is resistant towards singlet oxygen.

The elimination of mesylate from compound **3** with powdered KOH in toluene, using 18-crown-6 as a catalyst,¹⁶ yields a 3:1 mixture of **4** and **5** in 80% yield. When this mixture was photooxygenated by the method of simultaneous oxidation and reduction,¹⁷ i.e. in the presence of tetrabutylammonium (TBA) borohydride, using TBA-solubilized Rose Bengal as the sensitizer and chloroform as the solvent, a clean formation of *trans*-2-hydroxy-3-thujene (**6**) was observed at a total conversion of compound **4**. Compound **5** remained intact and could be isolated in pure form.

The synthesis of **1** was completed by a catalytic hydrogenation of compound **6** over a Pt/C catalyst in ether at -20°C . The isolated overall yield of the desired *trans*-sabinene hydrate (**1**) was 46%. Estimation of the enantiomeric purity of (1*R*,2*S*,5*R*)-**1** was checked by measuring the ¹H NMR spectra at 500 MHz in the presence of (S)-(+)-2,2,2-trifluoro-1-(9-anthryl)-ethanol. No splitting of NMR signals characteristic for enantiomeric mixtures was observed. 1-D and 2-D NMR spectra of compounds **1**, **2**, **5** and **6** were recorded and the data are given in Tables 1 and 2.

Our strategy for synthesizing optically pure *trans*-sabinene hydrate (**1**) demonstrates the large selectivity of singlet oxygen towards different types of double bonds. 2-Thujene (**4**) gave the desired compound and 3-thujene (**5**) could be isolated in pure form. The same method can be used to remove undesired isomers from mixtures of olefins. By using the method of simultaneous photooxygenation and reduction, one step is saved compared with conventional methods. Additionally, we find it interesting that the isomeric secondary alcohol with an exocyclic double bond was not observed with our system, i.e. in the presence of chloroform and TBABH₄, although it has been reported to be formed in 10–20% yield when 2-thujene (**4**) is photooxygenated in methanol.^{7,8,18}

Table 1. ¹³C NMR chemical shifts of **1**, **2**, **5** and **6** recorded at 125.7 MHz in CDCl₃

	1 δ	2 δ	5 δ	6 δ
C-1	34.41 d	28.18 d	27.91 d	32.84 d
C-2	80.55 s	37.32 d	42.82 d	82.42 s
C-3	36.64 t	72.56 d	133.78 d	137.43 d
C-4	25.93 t	33.42 t	133.06 d	134.42 d
C-5	34.64 s	31.23 s	41.40 s	40.70 s
C-6	13.35 t	14.34 t	22.24 t	25.71 t
C-7	24.98 q	14.40 q	22.12 q	22.94 q
C-8	32.18 d	33.24 d	30.70 d	29.56 d
C-9	19.93 q	19.58 q	20.88 q	20.35 q
C-10	20.02 q	20.08 q	20.88 q	20.78 q

Experimental

The NMR spectra were recorded in CDCl₃ on a Varian Unity-500 (499.8 MHz for ¹H) spectrometer and are reported in ppm (δ) downfield from the internal TMS standard. ¹H COSY spectra were recorded using the following parameters: spectral width 3100 Hz, acquisition time 0.165 s, number of increments 128, data matrix 1024 × 1024, number of transients 4. For 2-D NMR ¹H–¹³C heterocorrelated spectra of compounds **5** and **6**, the pulse sequence HETCOR was used. The fixed delays correspond to the coupling constant J (¹H, ¹³C) = 140 Hz. Other parameters were as follows: spectral width 18,000 Hz (¹³C axis), 3500 Hz (¹H axis), data matrix 2048 × 512, number of increments 256 and number of transients 64. The ¹³C NMR chemical shifts of **1** and **2** have previously been reported in the literature.¹⁹ Optical rotations were measured on a Perkin–Elmer 241 polarimeter. TLC and preparative liquid chromatography were performed on Merck silica gel 60 (230–400 mesh) using continuous gradient elution (ethyl acetate:hexane) with progressively increased amounts of the polar component, as described in ref 20, GLC: capillary 50 m, Carbowax 1500, 50–200 °C (column A); SE 30, 50–200 °C (column B). Melting points were measured in capillary tubes and are uncorrected.

3-Thujol methanesulfonate (3). A solution of methanesulfonyl chloride (12.6 g, 110 mmol) in dry diethyl

Table 2. ¹H NMR data of **1**, **2**, **5** and **6** recorded at 499.8 MHz in CDCl₃

	1 δ	2 δ	5 δ	6 δ
H-1	1.05 ddd	0.85 dd	1.06 mt	1.45 dd
H-2	—	2.14 m	2.46 m	—
H-3	1.59 dd	3.93 dt	5.53 dt	5.33 dd
H-4	1.84 dddd			
	1.26 ddd	1.55 ddd	5.33 dt	5.33 dd
H-6	1.52 m			
	0.21 dd	0.22 ddd	0.02 t	0.21 t
H-6	0.39 ddd	0.34 dd	0.74 dd	0.86 dd
	0.39 ddd	0.34 dd	0.74 dd	0.86 dd
H-7	1.52 m	0.90 d	0.89 d	1.33 s
H-8	1.43 m	1.22 m	1.42 m	1.53 m
H-9	0.89 d	0.92 d	0.99 d	0.91 d
H-10	0.96 d	0.95 d	1.01 d	0.99 d
	Hz	Hz	Hz	Hz
$J(1,3)$	1.4	0	1.9	1
$J(1,4)$	1.5	1.6	2	1.6
$J(1,6)$	5.2	5	3.5	4.1
$J(1,6')$	8.3	8.2	8	8.3
$J(2,3)$	—	7.1	6.8	—
$J(2,4)$	—	0	2	—
$J(2,7)$	—	7.1	6.8	—
$J(3,4)$	7.9	9.3	5.5	5.5
$J(3,4')$	8.4	7.7	—	—
$J(3',4)$	11.4	—	—	—
$J(4,4')$	14.1	12.1	—	—
$J(6,6')$	3.5	3.8	4.1	4.1
$J(8,9)$	6.8	6.9	6.9	7
$J(8,10)$	7	7.1	6.9	6.9

ether (200 mL) was added dropwise to a stirred solution of (-)-3-thujol (**2**) (14.9 g, 97 mmol, $[\alpha]_D^{25} - 22.0/\text{EtOH}$, lit.¹⁴ $-22.5/\text{EtOH}$) and triethylamine (11.1 g, 110 mmol) in diethyl ether (150 mL) at 0 °C. After 3 h, a 2:1 mixture of diethyl ether and water (600 mL) was added. The organic layer was separated, washed with brine (200 mL) and dried (MgSO_4). Solvent removal in vacuo gave essentially pure (TLC, GLC, column A) sulfonate **3** (21.4 g, 95%, $[\alpha]_D^{25} - 22.5/\text{EtOH}$), which was used in the next step without purification.

Mixture of 2-thujene (4) and 3-thujene (5). Powdered KOH (8.4 g) and 18-crown-6 (158 mg) were added to a solution of sulfonate **3** (11.0 g, 47.4 mmol) in toluene (150 mL). The mixture was stirred vigorously at 100 °C for 4 h. After cooling, hexane (250 mL) was added and the organic layer was washed consecutively with water, 3% HCl solution, satd NaHCO_3 solution and brine (100 mL of each). Drying (MgSO_4) and solvent removal in vacuo gave a yellow oil (6.0 g), which was chromatographed on silica gel (2.5 cm i.d. \times 30 cm column, gradient EtOAc in hexane). This gave a 3:1 mixture (GLC, column B) of 2- and 3-thujenes (**4** and **5**) (5.16 g, 80%), 3-thujol (**2**) (10%) and unreacted starting material (**3**) (5%). No attempts to optimize the reaction conditions were made.

***trans*-2-Hydroxy-3-thujene (6).** The 3:1 mixture of the isomeric thujenes **4** and **5** (4.1 g, 30.1 mmol) was dissolved in a stock solution of TBA solubilized Rose Bengal¹⁷ in chloroform (300 mL) and irradiated, with a constant flow of oxygen bubbling through the solution, using an Osram 400 W sodium lamp in an immersion well apparatus (ACE glass). At 0, 15, 30 and 45 min of irradiation, portions of 4.2, 2.1, 1.1 and 1.1 g TBA borohydride were added (total 8.5 g, 35 mmol). After 60 min of irradiation, the chloroform was evaporated under reduced pressure. Diethyl ether (70 mL) and potassium iodide (6 g), dissolved in a minimum of water, were added with stirring to precipitate TBA iodide. After 30 min, the solids were filtered and washed with diethyl ether. The ether layer was dried (MgSO_4) and the solvent was removed in vacuo. The residue was chromatographed on silica gel (2.5 cm i.d. \times 30 cm column, gradient EtOAc in hexane), giving unreacted 3-thujene (**5**) (1.2 g, 93%, $[\alpha]_D^{25} + 168.0/\text{EtOH}$; lit.⁸ $+172.8/\text{MeOH}$) and *trans*-2-hydroxy-3-thujene (**6**) (3.9 g, 90%, $[\alpha]_D^{25} + 103.0/\text{EtOH}$, lit.⁸ $+136.0$, solvent not reported).

***trans*-Sabinene hydrate (1).** PtO_2 (0.3 g) and activated carbon (Darco 0.6 g) were suspended in dry diethyl ether (10 mL) and hydrogenated with stirring at 25 °C to form the catalyst (Pt/C). After 30 min, the suspension was cooled to -20 °C in a bath using a slush of solid carbon dioxide and CCl_4 , and alcohol **6**, dissolved in diethyl ether, was added dropwise. The hydrogenation was monitored using a gas burette and was

completed after 120 min. The catalyst was removed by filtration and washed with diethyl ether. Removal of the solvent in vacuo followed by sublimation of the crystalline residue, afforded *trans*-sabinene hydrate (**1**) (2.0 g, 89%) as white needles, mp 58–59 °C (lit.¹⁹ 60–61 °C); $[\alpha]_D^{25} + 32.5/\text{EtOH}$ (lit.¹⁹ $+32.2/\text{EtOH}$).

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