

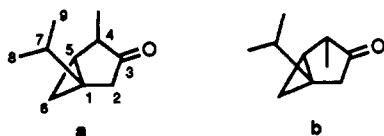
## Chlorination and Base-Induced Dehydrochlorination of (-)-3-Isothujone

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Thujone (1), a natural product which is readily available in vast quantities from the Western red cedar (*Thuja plicata* Don) leaf oil, has been shown to be an effective chiral synthon for the synthesis of various sesquiterpenes.<sup>2</sup> However, despite considerable work carried out on various aspects of its chemistry,<sup>3-5</sup> the overall picture concerning its basic chemistry remained rather fragmented.<sup>5</sup> Except for studies in the 50's on the tribromination of (+)-3-thujone (1b),<sup>6</sup> a later paper on its formylation,<sup>7</sup> and a recent paper on the stereochemistry and mechanism of formation of "tribromothujone",<sup>8</sup> there appears to be no reports on the chlorination of the naturally occurring mixture of thujones, consisting primarily of (-)-3-isothujone (1a).<sup>4-5,9</sup>



The electrophilic halogenation of carbonyl compounds are extensively studied organic reactions,<sup>10</sup> known to be catalyzed by both bases and acids. The  $\alpha$ -halo substitution is the result of the electrophilic attack by the halogenating agent on the initially formed enols through an overall ionic mechanism. The substitution pattern in unsymmetrical ketones, as well as the degree of halogenation, are determined by the relative ease of formation of the structurally isomeric enols. Therefore, the predominant isomer(s) produced is (or are) dependent on the particular reaction conditions, the acid or base used, and the nature of the electrophilic agents employed.

This paper is a short account of our study of the chlorination/dehydrochlorination of the naturally occurring mixture of thujones (i.e. 1), the results of which reflect the enolization patterns and equilibria<sup>10-12</sup> of this intriguing, bicyclic crowded system. Also, we present the first crystal structure of a simple thujone derivative (i.e. 7)

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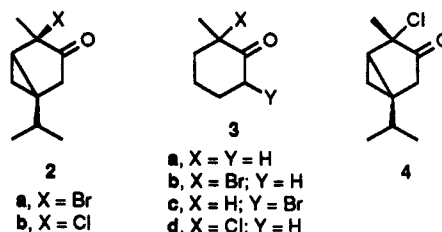
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which sheds light on the predominating five-membered ring conformation as well as on the spatial relationship between the system components in substituted thujones.

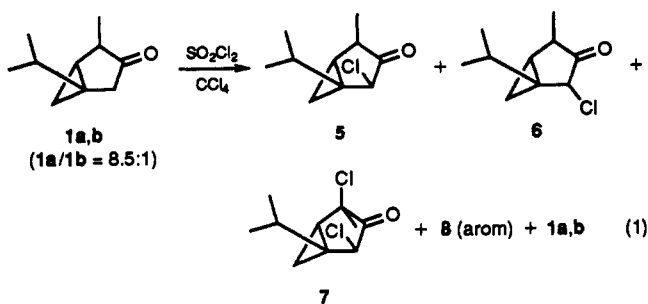
## Results and Discussion

Since (a) both monobromination and monochlorination<sup>8</sup> (with sulfonyl chloride) of (+)-3-thujone (1b) were shown to yield stereospecifically (and almost quantitatively) the corresponding 4-halo-3-thujones 2, the monobrominated product being an unstable compound;<sup>8</sup> (b) bromination of 2-methylcyclohexanone (3a) with bromine gave a mixture of 2-bromo-2-methylcyclohexanone (3b) and 2-methyl-6-bromocyclohexanone (3c) in overall 38% yield, whereas bromiantion with *N*-bromosuccinimide gave the 2-bromo isomer (3b) in 20% yield,<sup>13</sup> and (c) chlorination of 3a with



sulfonyl chloride afforded (exclusively) 2-chloro-2-methylcyclohexanone (3d) in 84% yield,<sup>14</sup> we selected sulfonyl chloride for the chlorination of the naturally occurring mixture of thujones, expecting 4-chloro-3-isothujone (4) to be the dominant product.

Chlorination of the naturally occurring mixture, containing >85% of 1a and <10% of 1b<sup>4,5</sup> with sulfonyl chloride (1:1 molar ratio in CCl<sub>4</sub>) at room temperature, afforded after workup and very long, tedious column chromatography the two monochlorinated products 2 $\alpha$ - and 2 $\beta$ -2-chloro-3-isothujones 5 and 6, the dichlorinated product 2,4-dichloro-3-thujone (7), a not fully identified aromatic compound 8 (most probably carvacrol (12)), and the recovered unreacted thujone (essentially 1a) in 20, 13, 4, 6, and 49% yields, respectively (eq 1). The balance



consisted of polymeric material and tar. No optimization of the reaction conditions for improving the yield(s) have been attempted.

Since the monochlorinated products 5 and 6 predominate and the monochlorination of (+)-3-thujone (1b) with sulfonyl chloride under similar reaction conditions was shown to yield the 4 $\beta$ -Cl-3-thujone (2b) exclusively (and almost quantitatively),<sup>8</sup> the precursor of the former two

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is **1a** whereas that of **7** is most probably **2b**. The yield of **7** (4%) which corresponds to the percentage of **1b** in the starting mixture **1** as well as to the availability of excess sulfonyl chloride to the easily formed **2b** (see Experimental Section), further corroborates this conclusion. Epimerization (prior to chlorination) of **1a** to **1b**, under the mild reaction conditions employed, is highly unlikely. It is quite interesting to note that the major monochlorinated product is **5** in which the chlorination took place at the 2-position on what appears to be the more sterically hindered face of the thujone's five-membered ring. Apparently, the steric hindrance exerted by the *endo*-6-hydrogen atom of the three-membered ring can account, at least partially, for this result. As one can conclude, based on examination of models, the planarity, or almost planarity, of the five-membered ring conformation in thujones<sup>5</sup> should also contribute to the results obtained.

The observed latent period of about 20 min or so within which no chlorination of **1** occurred, suggests an ionic mechanism involving electrophilic attack of the chlorine on the enol after sufficient concentration of hydrochloric acid has been accumulated in the reaction mixture.<sup>10</sup> However, the selectivity of the chlorination, which is in accord with Cocker results in bromination of **1b**,<sup>8</sup> may seem to be *in contrast* with the expected,<sup>14</sup> based on previous studies:<sup>15</sup> The position taken by the entering halogen was shown to be determined by the relative ease of formation of the structurally isomeric enols which, in turn, is enhanced by the enol-stabilizing  $\alpha$ -alkyl substituents. Consequently, the predominant isomer produced should be the one in which the halogen atom has entered the more highly substituted  $\alpha$ -position;<sup>10</sup> that is, the preferred substitution is methine > methylene > methyl.<sup>15,16</sup> In contrast to this well-established pattern,<sup>10,14-16</sup> the  $\alpha$ -chlorination of the less-substituted position of (-)-3-isothujone is the dominant pathway leading to **5** and **6**. That **7** rather than the 2,2-dichloro-3-isothujone is formed, is in accord with the expected, since the presence of an  $\alpha$ -chlorine substituent retards the rate of enol formation in **6**, and the origin of **7** is **2b**. Examination of models suggests that the predominance of **5** over **6** (~3:2 molar ratio) can be rationalized in terms of the better continuous overlap of the p-orbitals in the transition states for removal of the 2- $\beta$  proton to form the enol and for addition of the chlorine atom (while the five-membered ring maintains planarity), compared with the overlap possible if the 2- $\alpha$  proton is removed. Steric effects must also be involved in the halogenation of such a crowded system. In fact, our results combined with those of other studies<sup>8</sup> suggest that no epimerization at C<sub>4</sub> occurs on halogenation of thujone in aprotic solvents under mild acidic conditions.

The structural assignments in the chlorinated products **5-7** are based on spectroscopic data, mainly 300- and 400-MHz NMR spectra (see Experimental Section) in relation to the chemical shifts and coupling constants of the parent thujone, the comparison of these data with that obtained in previous related studies,<sup>5,7,8</sup> and the X-ray crystal structure and data of **7** given below in Figure 1 and Tables I and II, respectively.

Interestingly, there is a substantial increase in the length of the C<sub>(3)</sub>-C<sub>(4)</sub> bond and a decrease in that of the C<sub>(4)</sub>-C<sub>(5)</sub>

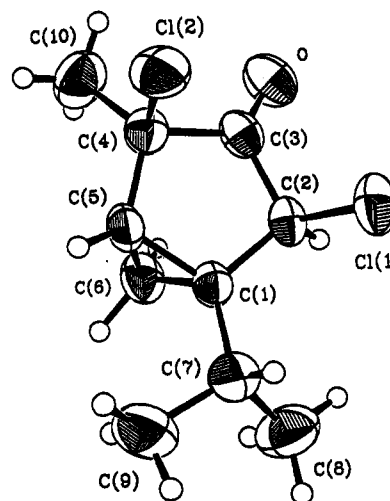


Figure 1. X-ray structure of compound **7**.

Table I. Bond Lengths (Å) (with estimated standard deviations in parentheses)

bond	length	bond	length
Cl(1)-C(2)	1.797(2)	C(2)-C(3)	1.532(4)
Cl(2)-C(4)	1.826(3)	C(3)-C(4)	1.546(3)
O-C(3)	1.197(3)	C(4)-C(5)	1.496(3)
Cl(1)-C(2)	1.514(3)	C(4)-C(10)	1.511(4)
Cl(1)-C(5)	1.521(3)	C(5)-C(6)	1.500(4)
Cl(1)-C(6)	1.506(4)	C(7)-C(8)	1.527(5)
Cl(1)-C(7)	1.520(3)	C(7)-C(9)	1.531(5)

Table II. Bond Angles (deg) (with estimated standard deviations in parentheses)

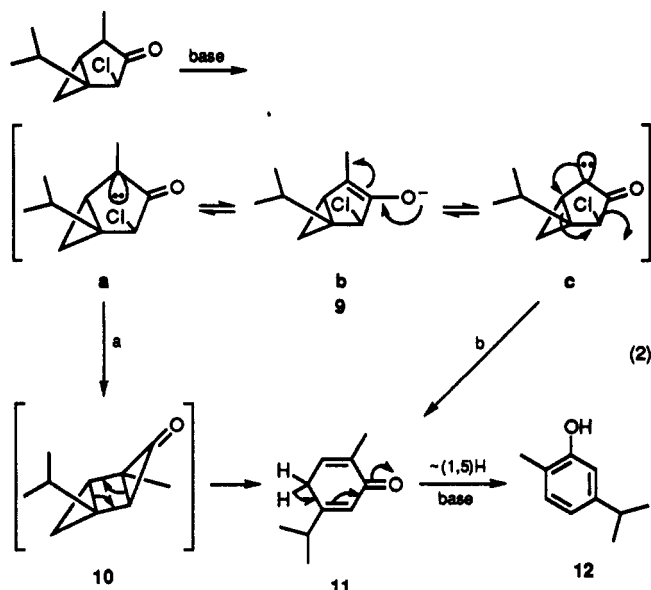
bonds	angle	bonds	angle
C(2)-C(1)-C(5)	107.5(2)	Cl(2)-C(4)-C(5)	108.6(2)
C(2)-C(1)-C(6)	110.2(2)	Cl(2)-C(4)-C(10)	108.2(3)
C(2)-C(1)-C(7)	119.4(2)	C(3)-C(4)-C(5)	103.2(2)
C(5)-C(1)-C(6)	59.4(2)	C(3)-C(4)-C(10)	114.3(2)
C(5)-C(1)-C(7)	125.4(2)	C(5)-C(4)-C(10)	117.1(3)
C(6)-C(1)-C(7)	120.8(2)	C(1)-C(5)-C(4)	110.8(2)
Cl(2)-C(2)-C(1)	113.8(2)	C(1)-C(5)-C(6)	59.8(2)
Cl(1)-C(2)-C(3)	106.9(2)	C(4)-C(5)-C(6)	113.5(2)
C(1)-C(2)-C(3)	105.0(2)	C(1)-C(6)-C(5)	60.8(2)
O-C(3)-C(2)	125.1(2)	C(1)-C(7)-C(8)	109.3(3)
O-C(3)-C(4)	125.5(3)	C(1)-C(7)-C(9)	113.7(3)
C(2)-C(3)-C(4)	109.3(2)	C(8)-C(7)-C(9)	111.4(3)
Cl(2)-C(4)-C(3)	104.6(2)		

bond compared with that of the other C-C bonds in the five-membered ring of the molecule. The C<sub>(3)</sub>-C<sub>(4)</sub>-C<sub>(5)</sub> angle is the smallest in the five-membered ring of the thujone. Nevertheless, it is fair to conclude that the planar conformation of this ring predominates in the crystal form of **7** and most probably of **1**, too. The fact that the two chlorine substituents are on the same side of the ring plane (i.e.  $\beta$ ) may reflect both the initial release of strain via enolization and the steric hindrance of the 6-*endo*-hydrogen atom which "blocks" the electrophilic chlorine atom from approaching the enolic C<sub>(4)</sub> atom from the  $\alpha$ -face.

The treatment of **5** with an equimolar amount of NaH afforded 2-methyl-5-isopropylphenol (carvacrol (**12**)) in essentially quantitative yield, most probably via a Favorskii-type intermediate **10** (path *a*) as depicted below (eq 2). Although enolization and formation of **9c** is required, in order for the appropriate relative steric orientation of the enolic lone pair orbital and the chlorine atom in **9c** to facilitate the elimination of the latter as a chloride anion via a 6-electron p-trans- $\sigma$ -trans- $\sigma$ -trans process, this mechanism (path *b*) cannot be excluded.

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Since there is a kinetic preference for abstracting a proton by a base from the less highly substituted  $\alpha$ -carbon atom, this kinetically-controlled generation of enolate anions will usually lead to mixtures of the latter in which the less highly substituted enolate predominates. Rapid equilibrium of the enolate anions formed is achieved in the presence of protic solvents.<sup>10,17</sup> In our case, however (aprotic conditions), the preferred formation and relative stabilization of the  $\alpha$ -methyl-substituted carbanion together with the "leaving group effect" of the  $\alpha$ -chloro substituent are responsible for the ultimate formation of carvacrol (12), most probably via path a.

In summary, although many unsymmetrical cyclic ketones yield mixtures containing substantial amounts of both structurally isomeric enolates, appropriate procedures can be applied to affect the electrophilic  $\alpha$ -substitution in the desired direction even in the case of the uniquely crowded thujone system. Specifically, the chlorination of (-)-3-isothujone with sulfuryl chloride does not follow the pattern observed in "ordinary" unsymmetrical cyclic ketones due to the unique steric and electronic effects of the thujone system.

### Experimental Section

**General.** Reagents and solvents were purified and dried by standard procedures. The <sup>1</sup>H NMR spectra were recorded on Bruker WH-400 and Varian XL-300 spectrometers using CDCl<sub>3</sub> as solvent unless otherwise specified. The chemical shifts are reported in ppm relative to tetramethylsilane. The IR spectra were recorded on Perkin-Elmer 710B and 1710 spectrometers. The mass spectra were recorded on AE1-MS-9.

**Chlorination of Thujone.** To a stirred solution of 5.264 g (5.6 mL, 32.8 mmol) of freshly distilled 1 (containing 90% of 1a and 5% of 1b by GC; the balance: unidentified "inert" material) in dried CCl<sub>4</sub> (15 mL) at room temperature was added dropwise

4.721 g (2.81 mL, 35 mmol) of SO<sub>2</sub>Cl<sub>2</sub> over a period of 20 min. No gas evolution (HCl, SO<sub>2</sub>) could be observed during the addition period. The reaction mixture was stirred for an additional 4 h while maintaining the temperature at 24–27 °C (water bath). The reaction mixture was then washed with water (3 × 7.5 mL) and saturated NaHCO<sub>3</sub> and NaCl (7.5 mL each), and dried (MgSO<sub>4</sub>), and the solvent was removed under reduced pressure to give a yellow oil (6.33 g). Column chromatography of the oil (2.25 g, silica gel, benzene) gave 8 (0.130 g, ~6%), 7 (0.092 g, 3.8%), 5 (0.420 g, 20.4%), 6 (0.260 g, 12.6%), and unreacted thujone (0.870 g, 49%) (essentially 1a) successively (total, 91.8% based on the starting 1).

Samples for analysis were prepared via rechromatography of the separated chlorinated products on silica gel using CH<sub>2</sub>Cl<sub>2</sub> as an eluant.

**(-)-(1S,2S,4R,5R)-2-Chloro-3-isothujone (5):** colorless oil, pleasant odor; IR (liquid film) 2960, 2875, 1753, 1472, 1174, 1108, 1022, 997, 801, 782 cm<sup>-1</sup>; <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>)  $\delta$  4.02 [s, H(2- $\alpha$ )], 2.53 [m, H(7)], 2.38 [q, H(4)], 1.52 [dd, H(5)], 1.40 [d, Me(10)], 1.04 [d, Me(8)], 0.97 [d, H(6-exo)], 0.73 [d, Me(9)], -0.05 [m, H(6-endo)]; MS, *m/e* 188 and 186 (M<sup>+</sup>), 169, 158, 151 (M - Cl), 135 (base), 123, 115, 107, 103, 95, 91, 81, 67, 55, 41, 31.

**(-)-(1S,2R,4R,5R)-2-Chloro-3-isothujone (6):** colorless solid; IR (CDCl<sub>3</sub>) 2970, 2955, 2875, 1758, 1457, 1167, 1014 cm<sup>-1</sup>; <sup>1</sup>H NMR  $\delta$  4.80 [s, H(2- $\beta$ )], 2.44 [q, H(4)], 1.57 [m, H(7)], 1.35 [dd, H(5)], 1.22 [d, Me(10)], 1.13 [d, Me(8)], 1.07 [d, Me(9)], 0.93 [m, H(6-exo)], 0.51 [m, H(6-endo)]; MS, *m/e* 186 (M<sup>+</sup>), 151 (M - Cl, base), 135, 123, 115, 107, 91, 81, 67, 55, 40.

**(-)-(1S,2R,4R,5S)-2,4-Dichloro-3-isothujone (7):** colorless solid; IR (CDCl<sub>3</sub>) 2970, 2935, 1762, 1471, 1382, 1074, 993, 820 cm<sup>-1</sup>; <sup>1</sup>H NMR  $\delta$  4.08 [s, H(2- $\alpha$ )], 2.58 [m, H(7)], 2.15 [dd, H(5)], 1.62 [s, Me(10)], 1.09 [d, H(6-exo)], 1.04 [d, Me(8)], 0.77 [d, Me(9)], and -0.13 [m, H(6-endo)]; MS, *m/e* 220 (M<sup>+</sup>), 185 (M - Cl), 177, 169, 157, 150 (M - 2Cl), 143, 135, 121, 115, 107, 103, 91, 82, 77, 67, 53, 43.

A single crystal for X-ray crystallography was obtained by a very slow evaporation of the solvent from the solution of 7 in CDCl<sub>3</sub> in the NMR tube.<sup>18</sup>

**Dehydrochlorination of (-)-(1S,2S,4R,5R)-2-Chloro-3-isothujone (5).** To a stirred solution of 8 (140 mg, 0.75 mmol) in dry ether (2.5 mL) was added 18 mg (0.075 mmol) of NaH (80% dispersion in oil). The stirring was continued for 24 h at room temperature. Filtration gave an off-white solid (NaCl, 48 mg). Removal of the ether from the filtrate gave 131 mg of a yellow oil which was chromatographed (silica gel, CH<sub>2</sub>Cl<sub>2</sub>) to yield 12 quantitatively (114 mg) as a colorless oil: IR (liquid film) 3380, 2955, 2855, 1597, 1522, 1462, 1422, 1367, 1306, 1260, 1180, 1121, 872, 818, 641 cm<sup>-1</sup>; <sup>1</sup>H NMR  $\delta$  7.12 [d, 1H, arom], 6.80 [d, 1H, arom], 6.72 [s, 1H, arom], 2.88 [m, 1H, arom], 2.29 [s, Me], 1.28 [d, 2Me]; MS, *m/e* 150 (M<sup>+</sup>), 135 (base), 115, 107, 91, 77.

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**Supplementary Material Available:** Copies of the <sup>1</sup>H NMR spectra of 5–7 and 12 (7 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.

(18) The author has deposited atomic coordinates for this structure with the Cambridge Crystallographic Data Centre. The coordinates can be obtained, on request, from the Director, Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge, CB2 1EZ, UK.

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