as a white solid: mp 119–121 °C; IR (KBr) 2980, 2880, 1745, 1345, 1170, 1160, 950, 925, 910, 892, 878 cm^{-1}; ^1H NMR ($CDCl_3$) δ 4.60 (dt, J = 5, 11 Hz, 1 H), 3.61 (d, J = 15 Hz, 1 H), 3.01 (d, J = 15 Hz, 1 H), 0.80–2.54 (m, 31 H).

Cyclohexyl *p*-Toluenesulfinate. Reaction of cyclohexanol (0.21 mL, 2.0 mmol) with *p*-toluenesulfonyl chloride (0.572 g, 3.0 mmol), triethylamine (0.42 mL, 3.0 mmol), and trimethyl phosphite (0.47 mL, 4.0 mmol) under standard conditions afforded, after workup and purification, 0.373 g (78%) of cyclohexyl *p*-toluenesulfinate as a colorless oil: IR (thin film) 3040, 2940, 2865, 1598, 1450, 1138, 945, 850, 763 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.60 (d, J = 8 Hz, 2 H), 7.32 (d, J = 2 Hz, 2 H), 4.33 (tt, J = 4, 9 Hz, 1 H), 2.42 (s, 3 H), 1.13–2.05 (m, 10 H).

1-Decanyl *p*-Toluenesulfinate. A 25-mL two-necked pear-shaped flask was charged with *p*-toluenesulfonyl chloride (0.460 g, 2.4 mmol), triethylamine (0.33 mL, 2.4 mmol), trimethyl phosphite (0.47 mL, 4.0 mmol), and dichloromethane (7 mL) under nitrogen, and the resulting solution was warmed to reflux. After 10 min, 1-decanol (0.323 g, 2.0 mmol) was added via cannula as a solution in 3 mL of dichloromethane. After 6 h at reflux, standard workup afforded 0.61 g of an oil. Purification by flash chromatography (elution with 25% CH_2Cl_2–hexane) afforded 0.481 g (79%) of a mixture of sulfinate and sulfonate esters, in a ratio of 86:14 (as determined by ^1H NMR). An analytical sample of the sulfinate ester was obtained by a second chromatography. Data for 1-decanyl *p*-toluenesulfinate: IR (thin film) 3060, 3030, 2940, 2860, 1600, 1465, 1140, 945 (br), 815, 630 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.59 (d, J = 8 Hz, 2 H), 7.33 (d, J = 8 Hz, 2 H), 3.97–4.06 (m, 1 H), 3.55–3.64 (m, 1 H), 2.43 (s, 3 H), 1.24–1.64 (m, 18 H), 0.88 (t, J = 6.5 Hz, 3 H). Anal. Calcd for $C_{17}H_{28}O_2$: C, 68.87; H, 9.52. Found: C, 69.15; H, 9.80.

1-Decanyl 2,4,5-Triisopropylbenzenesulfinate. Reaction of 2,4,5-triisopropylbenzenesulfonyl chloride (0.731 g, 2.4 mmol), triethylamine (0.33 mL, 2.4 mmol), trimethyl phosphite (0.47 mL, 4.0 mmol), and 1-decanol (0.324 g, 2.0 mmol) for 6 h as described in the preceding paragraph afforded, after workup and purification (chromatography on silica gel, eluting with 5% EtOAc–hexane), 0.637 g (78%) of a colorless oil. ^1H NMR ($CDCl_3$) analysis indicated a 92:8 mixture of sulfinate and sulfonate esters. An analytical sample of the sulfinate ester was obtained by a second chromatography (elution with 20% CH_2Cl_2–hexane). Data for 1-decanyl 2,4,5-triisopropylbenzenesulfinate: IR (thin film) 2965, 2935, 2860, 1600, 1465, 1130 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.08 (s, 2 H), 3.98–4.22 (m, 4 H), 2.88 (heptet, J = 7 Hz, 1 H), 1.18–1.73 (m, 34 H), 0.87 (t, J = 7 Hz, 3 H). Anal. Calcd for $C_{25}H_{44}O_2S$: C, 73.47; H, 10.85. Found: C, 73.22; H, 11.03.

Large-Scale Preparation of (*S*)-(−)-Menthyl *p*-Toluenesulfinate. A dry 2-L three-necked round-bottomed flask equipped with a reflux condenser and nitrogen inlet was charged with *l*-menthol (31.25 g, 0.20 mol), *p*-toluenesulfonyl chloride (45.76 g, 0.24 mol), triethylamine (33.5 mL, 0.24 mol), and CH_2Cl_2 (1000 mL). Trimethyl phosphite (35.5 mL, 0.30 mol) was added, and the reaction mixture was heated to reflux. After 10 h the reaction mixture was allowed to cool to room temperature, washed with 1 N HCl (2 × 100 mL), saturated $NaHCO_3$ (100 mL), and saturated NaCl (2 × 100 mL), dried ($MgSO_4$), and concentrated. Kugelrohr distillation (45–50 °C (0.2 mm)) effected removal of trimethyl phosphate and some remaining menthol to afford a yellow oil (61.3 g), which solidified upon standing. This was dissolved in ether–petroleum ether (ca. 1:2, 300 mL) and filtered. *p*-Tolyl disulfone (1.32 g) was collected: mp 215 °C dec (lit.[27] mp 212 °C). The residue after removal of solvent was crystallized from acetone at −20 °C to afford 29.5 g of white crystals in four crops, with concentration after each filtration. HCl(g) was then bubbled through the neat mother liquor for 10 min to effect epimerization at sulfur. A white solid separated out and was recrystallized from acetone to give an additional 12.2 g of product. The combined crops were recrystallized from acetone to yield 39.11 g (66%) of pure (*S*)-(−)-menthyl *p*-toluenesulfinate in two crops: mp 103–105 °C (lit.[28] mp 106–107 °C); $[\alpha]^{25}_D$ −200.2° (*c* 1.23, acetone) (lit.[28] $[\alpha]^{25}_D$ −199° (*c* 2, acetone)).

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Regiospecific Synthesis of β-Thujaplicin (Hinokitiol) from 2-Isopropylphenol

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α-, β-, and γ-thujaplicins (3-, 4-, and 5-isopropyltropolones), isolated from *Chamaecyparis taiwanensis* Masamune et Suzuki[1] and *Thuja plicata* D. Don,[2] were the first naturally occurring monocyclic tropolones, and the unique character of these nonbenzenoid aromatic compounds has attracted considerable synthetic, biogenetic, and theoretical attention.[3] Particularly, their antibacterial and antifungal activities, which evidently confer on the heart-wood its resistance to decay, have aroused interest. A variety of synthetic approaches to these compounds, inter alia to β-thujaplicin (hinokitiol) (1), have been devised so far.[4] In view of the biological significance of 1, however, only the cycloaddition process of 1-isopropylcyclopentadiene with dichloroketene, which was reported from our laboratory,[4f] has been applied practically for industrial purposes.[5]

We now present another expedient synthesis of β-thujaplicin (1) starting from commercially available 2-isopropylphenol (2).[6] The new synthetic process consists of the site-specific ring expansion of 2-isopropylcyclohexanone (3) to 3-isopropylcycloheptanone (5) followed by the regiospecific conversion of the latter into 1 as illustrated in Scheme I.

2-Isopropylcyclohexanone (3)[7] was conveniently prepared from 1 by catalytic hydrogenation on Raney nickel (W-2) followed by sodium hypochlorite oxidation[8] of the resulting cyclohexanols in excellent yield.

Subsequent one-carbon homologation of 3 to the cycloheptanone 5, a key intermediate in this synthesis, was accomplished by the Tiffeneau–Demjanov ring expansion[9] by way of the cyanohydrin isomers 4. For the preparation of cyanohydrins 4, we observed that the reaction of 3 with alcoholic potassium cyanide under the usual conditions was not satisfactory because it proceeded only sluggishly. We found, however, that this transformation was readily performed by exchange with acetone cyanohydrin.[10] Thus the treatment of 3 with acetone cyanohydrin in basic media produced 4 as an isomeric mixture (**4a**/**4b** = 85:15) in 93% yield. The major isomer was assigned as *trans*-**4a** on the basis of application of Julia's method.[11] Although these isomers could be separated by column chromatography, the mixture was, without separation, subjected to the following ring expansion since we assumed that both cyanohydrins 4 would yield predominantly the same cycloheptanone 5 by the Tiffeneau–Demjanov rearrangement.[12]

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Catalytic hydrogenation of 4 over platinum oxide in acetic acid gave a solution of amino alcohols, which was immediately treated with aqueous sodium nitrite to afford a separable mixture of homologous ketones in a ratio of 93:7[13] in 73% overall yield from **3**. Structures of these ketones were unequivocally established as 3-isopropylcycloheptanone (**5**)[4a] and 2-isopropyl congener **6**,[4c] respectively, by spectral data and incorporation of four deuterium atoms into **5** upon treatment with sodium methoxide in methanol-d_1 (Experimental Section). Thus the highly regioselective formation of the desired cycloheptanone **5** was observed as anticipated.

Although synthesis of thujaplicins from isopropylcycloheptanones via selenium dioxide oxidation followed by bromination and dehydrobromination is well-known,[4a,14] this approach to β-thujaplicin has seriously suffered from poor yield of the product (less than 10%), probably owing to drastic reaction conditions reported. We eliminated such drawbacks and achieved an efficient synthesis of **1** from **5** as described below.

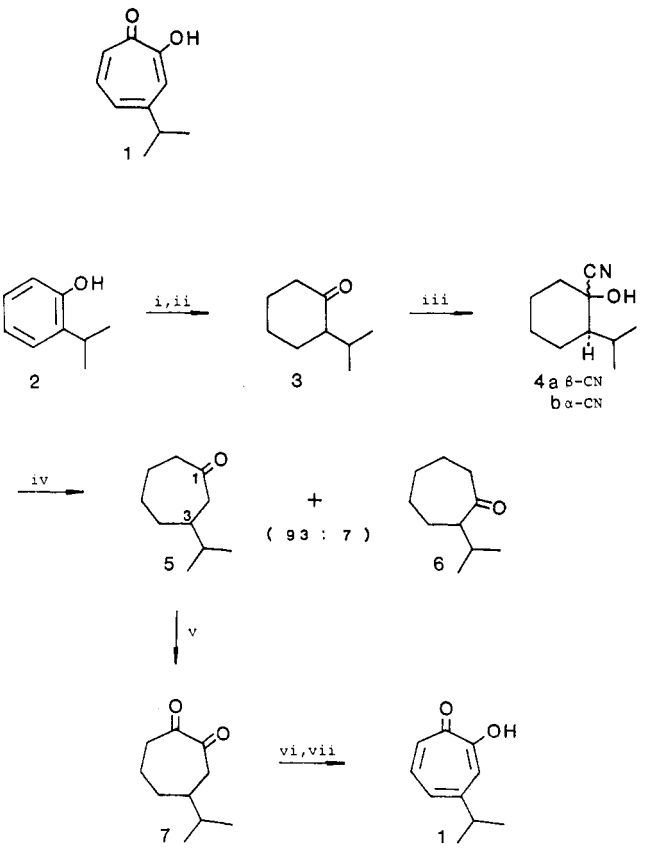
Treatment of the cycloheptanone **5** with 2 equiv of selenium dioxide in ethanol at 90 °C gave the expected α-dione **7**[15] as a tautomeric mixture. Bromination of the crude dione **7** with 2.5 equiv of phenyltrimethylammonium tribromide[16] in THF at room temperature followed by dehydrobromination with LiCl–Li_2CO_3–DMF at 120 °C produced β-thujaplicin (**1**) as the exclusive tropolonic product (61% overall yield from **5**).[17] Control of reaction conditions in both the oxidation and subsequent bromination steps was found to be crucial.

Synthetic β-thujaplicin showed a single spot on H_3PO_4-impregnated paper chromatography at the same R_f value as that of the authentic specimen, and its spectral data were also superimposable with those of an authentic sample. These results clearly indicate that the oxidation of **5** with selenium (IV) dioxide occurred regiospecifically at C_7, owing to a pronounced steric effect by an isopropyl substituent, as was the precedent by Nozoe et al.[15]

We also observed that the crude cycloheptanone which consists of 93:7 mixture of **5** and **6** (vide supra) gave quite similar results by the same reaction sequence, although a trace of α-thujaplicin was detected in this case.

Thus we have established a straightforward synthesis of β-thujaplicin (**1**) starting from 2-isopropylphenol (**2**). The present approach may also be applicable to the regiospecific conversion of 2-substituted cyclohexanones to specific 4-substituted tropolones.

Scheme I[a]



[a] (i) H_2, Raney Ni (W-2), EtOH; (ii) 10% aqueous NaOCl, AcOH; (iii) $(CH_3)_2C(OH)CN$, K_2CO_3, EtOH; (iv) H_2, PtO_2, AcOH, and then 10% aqueous $NaNO_2$; (v) SeO_2, 95% EtOH; (vi) $C_6H_5N^+(CH_3)_3Br^-\cdot Br_2$, THF; (vii) LiCl, $LiCO_3$, DMF.

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(17) Both the yield and purity of β-thujaplicin do depend upon the oxidation step with selenium dioxide because prolonged reaction time or higher temperature gave a lower yield of **1**.

Experimental Section

IR spectra were recorded on a JASCO A-3 spectrophotometer. ^{1}H NMR spectra were recorded on a JEOL JNM-FX 90 Q (90 MHz) spectrometer in $CDCl_3$, and chemical shifts are expressed in δ values relation to Me_4Si as internal standard. Coupling constants (J) are given in hertz. Mass spectra were obtained on a JEOL JMS-DX 300 instrument. GLPC analyses were performed on a JEOL JGC-20K instrument with a 10% SE-30 column (1 m × 3 mm). Microanalyses were performed by the Microanalytical Laboratory in this institute.

2-Isopropylcyclohexanone (3).[7] A mixture of 2-isopropylphenol (**2**) (3.0 g, 22 mmol) and Raney nickel (W-2, 0.5 mL, 300 mg)[18] in ethanol (15 mL) was hydrogenated (initial pressure of H_2 at 20 °C, 110 lb) in an externally heated stainless-steel autoclave at 100 °C for 4 h. The catalyst was removed by filtration through a pad of Celite, and the filtrate was diluted with ether and washed successively with 5% aqueous NaOH, water, and saturated brine. Evaporation of the solvent left an oil, an epimeric mixture of 2-isopropylcyclohexanols, which was submitted to the following oxidation without purification.

To a cold solution of the crude cyclohexanols in acetic acid (23 mL) was added a 10% aqueous sodium hypochlorite solution[8] (19.8 mL, 26.5 mmol) in an ice bath and the mixture was further stirred for 1.5 h in the cold. The reaction mixture was poured into cold water and extracted with ether. The ether extract was successively washed with aqueous $NaHCO_3$, aqueous $NaHSO_3$, water, and saturated brine. Removal of the solvent gave an oil, which was distilled under reduced pressure to give 3.01 g (97%) of **3**: bp 82 °C (12 mmHg) [lit.[7e] bp 90–98 °C (30 mmHg)]; IR (neat) 1708, 1370 cm^{-1}; ^{1}H NMR 0.89 (d, 6 H, J = 7), 1.2–2.4 (m, 10 H).

1-Hydroxy-*c*-2-isopropyl-*r*-1-cyclohexanecarbonitrile and Its 2-Epimer (4a and 4b). To a solution of **3** (362 mg, 2.58 mmol) in ethanol (3.6 mL) was added at 0 °C acetone cyanohydrin (1.65 mL, 18.2 mmol) and K_2CO_3 (107 mg, 0.77 mmol), and the mixture was further stirred at 0–10 °C for 18 h. The mixture was diluted with ether and washed with water and saturated brine. Removal of the solvent gave **4** as an isomeric mixture, which in general was submitted to the following ring expansion without separation. For characterization, however, these compounds were separated by flash column chromatography [silica gel, hexane–ethyl acetate (8:1) as solvent] to give 60 mg (14%) of **4b** and 340 mg (79%) of **4a** as an oil, respectively. **4a:** IR (neat) 3440, 2245, 1455, 1100, 1080, 1070 cm^{-1}; ^{1}H NMR 1.01 (d, 6 H, J = 7), 1.10–2.68 (m, 10 H), 2.9 (br s, 1 H, OH). **4b:** IR (neat) 3430, 2240, 1455, 1158, 978 cm^{-1}; ^{1}H NMR 1.01 (d, 6 H, J = 7), 1.05–2.45 (m, 10 H), 3.08 (s, 1 H, OH). Anal. Calcd for $C_{10}H_{17}NO$: C, 71.81; H, 10.25; N, 8.38. Found: C, 71.57; H, 9.95; N, 8.68.

3-Isopropylcycloheptanone (5) and 2-Isopropylcycloheptanone (6). A mixture of **4** (crude oil, 167 mg, 1 mmol) and platinum(IV) oxide (15 mg) in acetic acid (3 mL) was hydrogenated (initial hydrogen pressure, 8 lb) at room temperature until hydrogen uptake ceased (ca. 17 h). The catalyst was filtered off, and the filtrate was diluted with acetic acid (2 mL). A cold 10% aqueous solution of sodium nitrite (10.3 mL, 1.03 g) was added dropwise to the above amino alcohol solution in an ice bath, and the mixture was stirred for 3 h in the cold. Stirring was further continued for an additional 17 h at room temperature. The reaction mixture was partitioned between methylene chloride and water. The organic layer was successively washed with water, aqueous $NaHCO_3$, water, and saturated brine. Evaporation of the solvent left a volatile oil, whose GLPC showed two main peaks in a ratio of 97:3. Flash column chromatography (silica gel, CH_2Cl_2 as solvent) yielded **6**[4c] (8 mg, 5%) and **5** (103 mg, 68%) in 73% overall yield from **3**. **5:** IR (neat) 1700, 1460, 1445, 1368, 1258 cm^{-1}; ^{1}H NMR 0.88 (d, 6 H, J = 7), 1.0–2.2 (m, 8 H), 2.2–2.7 (br m, 4 H); MS, m/e 154 (M^+). Anal. Calcd for $C_{10}H_{18}O$: C, 77.86; H, 11.76. Found: C, 77.58; H, 11.55. **6**:[4c] ^{1}H NMR 0.88 (d, 6 H, J = 6), 1.0–2.7 (m, 12 H); MS, m/e 154 (M^+).

Deuteriation of 5. A solution of **5** (15 mg) in methanol-d_1 (0.5 mL) was added to a sodium methoxide solution prepared from sodium (20 mg) and methanol-d_1 (0.5 mL), and the mixture was refluxed for 1 h under argon. Deuterium oxide (3 drops) was added, and the solvent was removed. The residue was dissolved in ether and dried ($MgSO_4$). Evaporation of the solvent left an oil, which showed m/e 158 (M^+) in its mass spectrum.

4-Isopropylcycloheptane-1,2-dione (7). A mixture of **5** (123 mg, 0.80 mmol) and selenium dioxide (177 mg, 1.6 mmol) in 95% ethanol (0.8 mL) was stirred at 90 °C (bath temperature)[17] for 2 h. Precipitated selenium was filtered off, and the filtrate was diluted with ether (10 mL). The ethereal solution was washed with saturated brine and evaporated in vacuo to give oily **7** as a tautomeric mixture: IR (neat) 3465, 1715, 1065 cm^{-1}; ^{1}H NMR 0.84 and 0.92 (each d, 6 H in total, J = 7), 1.2-3.0 (m, 10 H). This dione was immediately submitted to the following reaction.

***β*-Thujaplicin (Hinokitiol) (1).** A mixture of **7** (the above crude oil, 0.80 mmol) and phenyltrimethylammonium tribromide[16] (752 mg, 2 mmol) in THF (10 mL) was stirred at room temperature for 1.75 h under nitrogen. The reaction mixture was poured into 0.1 M aqueous $Na_2S_2O_3$ and extracted with ether. The ethereal extract was washed with water and saturated brine, and dried ($MgSO_4$). After removal of the solvent, the residue of dibromo dione was dissolved in DMF (4 mL) and heated with dry LiCl (160 mg) and Li_2CO_3 (160 mg) at 120 °C for 45 min. The cooled reaction mixture was partitioned between ether and water, and the organic layer was extracted with 5% aqueous NaOH. The combined aqueous extracts were acidified with 10% HCl, and the acidic product was thoroughly extracted with CH_2Cl_2. The CH_2Cl_2 extract was washed with water and saturated brine. Evaporation of the solvent gave **1** (80 mg, 61% overall yield from **5**). Both H_3PO_4-impregnated paper chromatography (benzene as solvent) and silica gel TLC [ether–hexane (5:1) as solvent] of the crude tropolone showed a single spot (detection by $FeCl_3$) whose R_f value was identical with that of authentic β-thujaplicin. Its spectra were also superimposable with those of the authentic specimen. None of the α-isomer was detected on H_3PO_4-impregnated paper chromatography.

The crude cycloheptanone **5** which contains 5% of **6** gave quite similar results by the same sequence of reactions, although a trace of α-thujaplicin was detected on TLC.

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Hofmann Degradation of β-Hydroxy Ammonium Salts. 2.[1] 4-Hydroxybenzylisoquinolines and 4-Hydroxyaporphines

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Introduction

The in vivo late-stage introduction of oxygen, often accompanying further structural modification in alkaloids, is thought to be involved in their subsequent degradation

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