The chemistry of thujone. X.[1] Thujone as a chiral synthon for the preparation of sesquiterpenes. Synthesis of (+)-α-eudesmol and (−)-α-selinene

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Efficient synthetic routes to the chiral sesquiterpenes (+)-α-eudesmol (**7**) and (−)-α-selinene (**9**) from a thujone-derived intermediate (**2**) are described.

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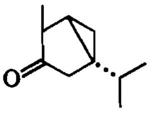
On décrit des méthodes efficaces de synthèse des sesquiterpènes chiraux (+)-α-eudesmol (**7**) et (−)-α-selinène (**9**) à partir de l'intermédiaire (**2**) dérivé de la thujone.

[Traduit par le journal]

In a recent series of papers (2–4) we have described the preparation of the natural chiral sesquiterpenes (+)-β-cyperone (2), (+)-carissone (3), and β-elemol (4) of the eudesmane series by appropriate transformations of the chiral synthon thujone (**1**)[2] as the starting material.



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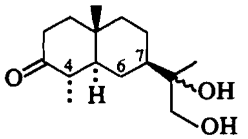

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In these studies the thujone derived keto-diols (general structure **2**) became important intermediates, as for example, in the syntheses of β-elemol (4) and (+)-carissone (3). On the basis of these successful conversions it was possible to assign the absolute configuration in **2** at the chiral centres C-7, C-5, and C-10, as shown, thereby allowing these intermediates to be utilized in further syntheses of naturally occurring sesquiterpenes. In this publication we wish to describe a highly stereoselective synthesis of (+)-α-eudesmol (**7**) and (−)-α-selinene (**9**), proceeding through the intermediate **2**.

The synthetic route to (+)-α-eudesmol (**7**) is outlined in Scheme 1 and our experiments with respect to this study are discussed first.

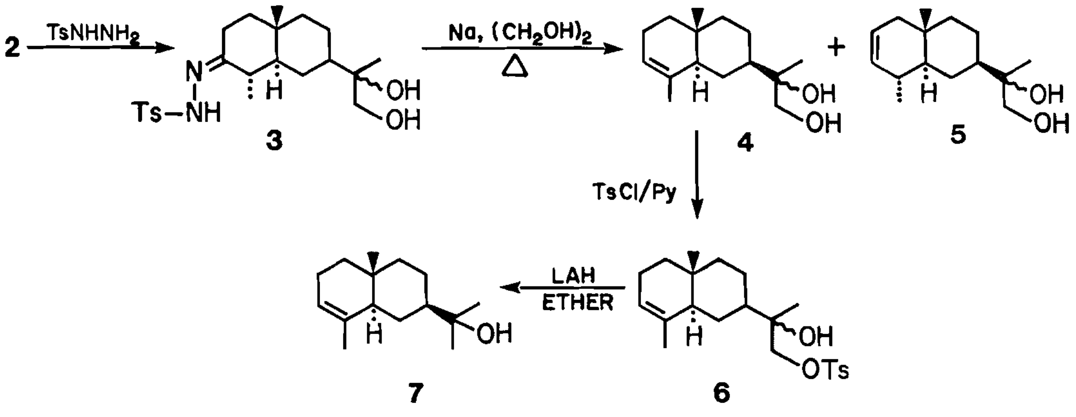
The mixture of known ketodiols **2**, prepared as previously described (4), was converted quantitatively into an inseparable mixture of isomeric tosylhydrazones **3** by treatment with tosylhydrazine and BF_3 in benzene. Since the subsequent steps in the synthesis eliminate the chirality at C-11, separation into the pure isomers was not essential at this time.

The hydrazones **3** were then converted to the corresponding isomeric hydroxyalkenes **4** and **5** using the Bamford–Stevens procedure (for a review of this reaction, see ref. 5). The major components were readily separated by chromatography over silver nitrate impregnated silica gel and it was thus shown that **4** constitutes 70% of the original mixture while **5** is present in 30%.

Treatment of **4** with tosylchloride in pyridine afforded **6**, which was readily reduced by LAH in ether to (+)-α-eudesmol (**7**). The latter compound proved to be identical in every respect with the natural (+)-α-eudesmol (6) (see Experimental).

On the other hand, oxidation of **4** with $NaIO_4$ in aqueous methanol provided the chiral ketone **8** (Scheme 2) in 79% yield. This intermediate could be considered for the synthesis of (−)-α-selinene (**9**) as summarized in Scheme 2.

In our initial studies with **8** we proceeded to react the latter under normal Wittig reaction conditions, that is, methyl triphenylphosphonium bromide, sodium hydride, and dimethyl sulfoxide (7). Unfortunately the conversion of **8** to **9**, under



SCHEME 1

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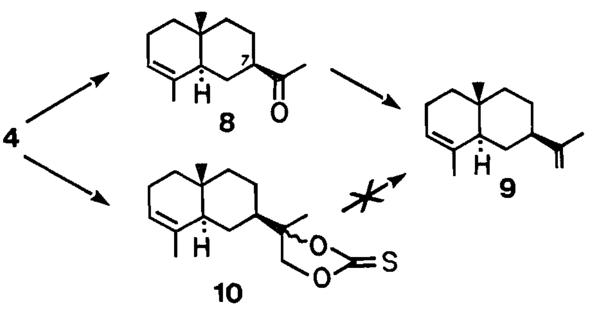
[1] For part IX, see ref. 1.

[2] Thujone is the major component (ca. 80%) of the steam distillate from the slash (waste) of Western red cedar.



SCHEME 2

these conditions, proceeded in only 3% yield. We then turned to the use of a crystalline form of the Wittig reagent as developed by Schlosser and Schaub (8). To our delight a marked improvement was achieved and a 69% yield of **9** was realized.

It is interesting to consider the possibility of epimerization at the chiral centre C-7 in **8** during the basic conditions employed in the Wittig reaction, thereby altering the stereochemistry at this position in the resultant product **9**. Firstly it must be noted that the absolute stereochemistry at C-7, as shown in **8**, is established from our earlier studies relating to the synthesis of (+)-carissone and from nmr spectroscopy (nine-line resonance, tt, $J_{aa} = 12$; $J_{ac} = 4$ Hz centered at 2.40 ppm for the axial C-7 proton). When **8** was treated under the conditions utilized in the Wittig olefination process (NaNH$_2$ in THF, room temperature, 40 min) the starting material was recovered. It is therefore clear that the stereochemical assignment as illustrated for (−)-α-selinene (**9**) is secure.

Finally the alternative pathway 4 → 10 → 9 as outlined in Scheme 2 was also considered. However, although the thiocarbonate **10** could be prepared, its conversion to **9** met with failure and this sequence was therefore abandoned.

In conclusion, it is clear that thujone can indeed serve as an efficient chiral synthon for these types of sesquiterpenes. In a subsequent publication we will demonstrate the further utility of this compound in an efficient synthesis of optically active sesquiterpene lactones.

Experimental

Melting points were determined on a Reichert hot stage apparatus and are uncorrected. Ultraviolet spectra were recorded on a Cary 15 spectrophotometer in methanol solution. Infrared spectra were measured on a Perkin–Elmer 710 spectrophotometer using chloroform as solvent. The ^{1}Hmr spectra were recorded on Bruker WH-400, Bruker WP-80, Varian XL-100, or Nicolet–Oxford H-270 instruments. Deuteriochloroform was used as the solvent with TMS as internal standard. Low resolution mass spectra were determined on either an AEI-MS-902 or an Atlas CH-4B spectrometer. High resolution mass measurements were made on an AEI-MS-50 spectrometer. Optical rotations were recorded on a Perkin–Elmer 141 polarimeter using a cell with a path length of 10 cm. Microanalyses were performed by Mr. P. Borda, Microanalytical Laboratory, University of British Columbia. Column chromatography utilized Merck silica gel 60 (70–230 mesh). Preparative and thin layer chromatography utilized Merck silica gel GF$_{254}$. Petroleum ether refers to the fraction with boiling range 30–60°C.

Hydrazones 3

To a solution of hydroxyketone **2** (369 mg) and *p*-toluene sulfonyl hydrazide (271 mg) in benzene (50 mL) was added a drop of borontrifluoride etherate. The solution was stirred under argon at ambient temperature for 4 h. The resulting mixture was evaporated under reduced pressure, diluted with water (10 mL), extracted with THF–ether (100 mL, 1:1 v/v), and dried (MgSO$_4$). The solvent was removed under reduced pressure giving hydrazones **3** (598 mg, 98%), which were crystallized from ether–THF – pet. ether; mp 98–100°C; ir ν_{max}: 3488, 1600, 1378, 1173 cm^{-1}; uv λ_{max}: 225 (ϵ 13 288), 274 (988) nm; ^{1}Hmr δ: 0.89 (3H, s), 0.93 (1H, m), 0.99, 1.00 (3H, s, two sets), 1.03, 1.13 (3H, d, J = 6 Hz, two sets), 1.16–1.36 (2H, m), 1.38–1.75 (5H, m, including 1.48 (1H, bs, D$_2$O exchangeable)), 1.78–2.38 (6H, m, including 2.07 (1H, bs, D$_2$O exchangeable)), 2.43, 2.44 (3H, s, two sets), 2.56 (1H, m), 3.44 (1H, m), 3.58 (1H, m), 3.75 (1H, bs), 7.30, 7.36 (2H, d, J = 8 Hz, two sets), 7.80, 7.85 (2H, d, J = 8 Hz, two sets); ms *m/e*: 422 (M$^+$), 391, 278, 266. High resolution molecular weight determination, calcd. for $C_{22}H_{34}N_2O_4S$: 422.2239; found: 422.2248. *Anal.* calcd. for $C_{22}H_{34}N_2O_4S$: C 62.56, H 8.06, N 6.63; found: 62.29, H 7.96, N 6.30.

Diols 4 and 5

The tosyl hydrazones **3** (545 mg) in ethylene glycol (22 mL) containing dissolved sodium metal (568 mg) were heated at 155–165°C in an oil bath for 30 min under argon. The mixture was cooled, diluted with 20 mL water, and extracted with methylene chloride (2 × 100 mL). The organic extracts were dried (MgSO$_4$), concentrated, and the residue was chromatographed on silica gel impregnated with silver nitrate. Elution with petroleum ether – ethyl acetate (1:1 v/v) provided diols **4** (117.8 mg, 38%) and **5** (50.5 mg, 17%) as viscous oils. The physical properties of **4** are as follows: ir ν_{max} (neat): 3338 cm^{-1}; ^{1}Hmr δ: 0.78 (3H, s), 0.96 (1H, m), 1.14, 1.16 (3H, s, two sets), 1.17–1.58 (8H, m, including 1.58 (1H, bs, D$_2$O exchangeable)), 1.60, 1.63 (3H, s, two sets), 1.73 (1H, m), 1.84–1.92 (2H, m, including 1.90 (1H, bs, D$_2$O exchangeable)), 1.97 (1H, m), 2.09 (1H, m), 3.43, 3.45 (1H, d, J = 12 Hz, two sets), 3.58, 3.61 (1H, d, J = 12 Hz, two sets), 5.32 (1H, bs); ms *m/e*: 238 (M$^+$), 220, 205, 207, 189, 163. High resolution molecular weight determination, calcd. for $C_{15}H_{26}O_2$: 238.1923; found: 238.1938. *Anal.* calcd. for $C_{15}H_{26}O_2$: C 75.63, H 10.92; found: C 75.38, H 10.91. And for **5**, ir ν_{max} (neat): 3373 cm^{-1}; ^{1}Hmr δ: 0.83 (3H, s), 0.88 (1H, m), 0.97, 0.99 (3H, d, J = 6 Hz, two sets), 1.13, 1.14 (3H, s, two sets), 1.15–1.42 (2H, m), 1.45–1.60 (4H, m, including 1.55 (1H, s, D$_2$O exchangeable)), 1.64 (1H, dt, J = 12, 6 Hz), 1.68–1.85 (4H, m, including 1.83 (1H, bs, D$_2$O exchangeable)), 1.88 (1H, dt, J = 12, 6 Hz), 3.44, 3.45 (1H, d, J = 12 Hz, two sets), 3.57, 3.60 (1H, d, J = 12 Hz, two sets), 5.43 (1H, m), 5.54 (1H, m); ms *m/e*: 238 (M$^+$), 220, 207, 189. High resolution molecular weight determination, calcd. for $C_{15}H_{26}O_2$: 238.1933; found: 238.1923. *Anal.* calcd. for $C_{15}H_{26}O_2$: C 75.63, H 10.92; found: C 75.39, H 11.17.

Tosylates 6

To a well-stirred solution of diols **4** (45 mg) in 2 mL of pyridine was added, portion-wise, *p*-toluenesulphonyl chloride (108 mg). After 40 h at ambient temperature, the mixture was diluted with water (5 mL) and thoroughly extracted with ether (2 × 50 mL). The combined extracts were washed with water and saturated brine and dried (MgSO$_4$). The crude residue, after evaporation of the solvent *in vacuo*, was chromatographed on silica gel (40 g). Elution with ether – petroleum ether (3:7 v/v) afforded tosylates **6** (63.4 mg, 86%) as a viscous oil; ir ν_{max} (neat): 3512, 1598, 1453, 1353, 1183 cm^{-1}; uv λ_{max}: 222 (ϵ 12 418), 250 (2 179), 272 (871) nm; ^{1}Hmr δ: 0.74 (3H, s), 0.95 (1H, m), 1.12, 1.15 (3H, s, two sets), 1.24–1.53 (7H, m), 1.55, 1.58 (3H, s, two sets), 1.66 (1H, m), 1.79 (1H, s, D$_2$O exchangeable), 1.84 (1H, m), 1.95 (1H, m), 2.08 (1H, m), 2.46 (3H, s), 3.90, 3.91 (1H, d, J = 10 Hz, two sets), 3.97, 4.01 (1H, d, J = 10 Hz, two sets), 5.31 (1H, bs), 7.36 (2H, d, J = 8 Hz), 7.81 (2H, d, J = 8 Hz); ms *m/e*: 392 (M$^+$), 374, 359, 229, 220. High resolution molecular weight determination, calcd. for $C_{22}H_{32}O_4S$: 392.2021; found: 392.2013. *Anal.* calcd. for $C_{22}H_{32}O_4S$: C 67.35, H 8.16; found: C 66.95, H 8.41.

(+)-α-Eudesmol 7

A solution of tosylates **6** (100 mg) in ether (5 mL) was added to a stirred suspension of lithium aluminium hydride (50 mg) in dry ether (10 mL) and the mixture refluxed for 2 h. The cooled mixture was decomposed with ice water, extracted with ether, and dried ($MgSO_4$). The solvent was distilled under reduced pressure to give an oil which solidified on standing. Recrystallization from petroleum ether afforded (+)-α-eudesmol **7** (49.5 mg, 86%); mp 74–75°C; $[\alpha]_D$ +28.6° (*c* 1.05, $CHCl_3$) (lit. (6) mp 74–75°C, $[\alpha]_D$ +28.5° (*c* 1.2, $CHCl_3$)); ir ν_{max}: 3575 cm^{-1}; ^{1}Hmr δ: 0.78 (3H, s), 0.98 (1H, m), 1.04–1.20 (2H, m), 1.21 (3H, s), 1.22 (3H, s), 1.26–1.51 (6H, m), 1.53 (1H, bs, D_2O exchangeable), 1.63 (3H, s), 1.88 (1H, dd, J = 10, 2Hz), 1.96 (1H, m), 2.10 (1H, m), 5.33 (1H, bs); ms *m/e*: 222 (M^+), 204, 189. High resolution molecular weight determination, calcd. for $C_{15}H_{26}O$: 222.1984; found: 222.1974. *Anal.* calcd. for $C_{15}H_{26}O$: C 81.08, H 11.71; found: C 81.16, H 11.56.

Ketone 8

To a solution of diols **7** (80 mg) in methanol (3.5 mL) and water (0.7 mL) was added $NaIO_4$ (233 mg). The resulting mixture was stirred at room temperature for 30 min. After the successive addition of a saturated solution of NaCl (7 mL) and sodium thiosulphate (7 mL), the product was extracted with ether–THF (100 mL, 1 : 1 v/v) and dried over $MgSO_4$. Solvent was removed and the residue chromatographed on silica gel (15 g), then eluted with ether – petroleum ether (0.3 : 9.7, v/v) to give as an oil **8** (55 mg, 79%); $[\alpha]_D$ −19.1° (*c* 0.44, $CHCl_3$); ir ν_{max} (neat): 1708 cm^{-1}; ^{1}Hmr δ: 0.81 (3H, s), 1.17–1.38 (4H, m), 1.52 (1H, dt, J = 12, 4 Hz), 1.63 (3H, s), 1.64–1.78 (2H, m), 1.88–1.96 (2H, m), 2.00 (1H, m), 2.09 (1H, m), 2.17 (3H, s), 2.40 (1H, tt, J = 12, 4 Hz, 9 lines), 5.35 (1H, bs); ms *m/e*: 206 (M^+), 191, 163. High resolution molecular weight determination, calcd. for $C_{14}H_{22}O$: 206.1671; found: 206.1662. *Anal.* calcd. for $C_{14}H_{22}O$: C 81.55, H 10.68; found: C 81.47, H 10.79.

(−)-α-Selinene 9

Ketone **8** (30 mg) in THF (2 mL) was added to a mixture of methyl triphenylphosphonium bromide (1 g) and THF (8 mL) which had been stirred for 40 min at room temperature. After the mixture had been stirred for an additional 40 min, the excess of reagent decomposes with cold water. The reaction mixture was extracted with petroleum ether and dried over $MgSO_4$. Evaporation of the solvent and purification by preparative layer chromatography with petroleum ether gave pure **9** as an oil, yield 20.6 mg (69%): $[\alpha]_D$ −12.9° (*c* 0.21, $CHCl_3$) (lit. (9) $[\alpha]_D$ −14.5° ($CHCl_3$, 1%)); ir ν_{max} (neat): 1641, 1440, 1375, 890 cm^{-1}; ^{1}Hmr δ: 0.81 (3H, s), 1.12–1.27 (2H, m), 1.30–1.38 (2H, m), 1.46 (1H, dt, J = 12, 4 Hz), 1.51–1.59 (2H, m), 1.61 (3H, s), 1.75 (3H, s), 1.78 (1H, m), 1.88–2.01 (3H, m), 2.10 (1H, m), 4.69 (1H, s), 4.72 (1H, s), 5.81 (1H, bs); ms *m/e*: 204 (M^+), 189, 175. High resolution molecular weight determination, calcd. for $C_{15}H_{24}$: 204.1878; found: 204.1878. *Anal.* calcd. for $C_{15}H_{24}$: C 88.24, H 11.76; found: C 88.25, H 11.88.

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