

141. Synthesis of the Alleged Natural Monoterpenoid α -Santolinenone¹⁾

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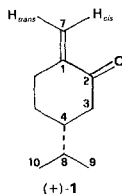
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Summary

Authentic α -santolinenone ($(+)-(4R)$ -1(7)-*p*-menthen-2-one; $(+)$ -**1**) is made available for the first time in 30% overall yield from $(+)-(4R)$ -*p*-menthene ($(+)$ -**2**) via the diastereoisomeric allylic alcohols $(+)$ -**4a**/ $(+)$ -**4b**, which are oxidized to $(+)$ -**1** with $\text{Ag}_2\text{CO}_3/\text{Celite}$. Yields are good, except for the last stage; indeed, only alcohol $(+)$ -**4a**, with equatorial OH-group, undergoes oxidation, and $(+)$ -**1** is partly subtracted via a hetero *Diels-Alder* dimerization giving a mixture of the diastereoisomeric dihydropyrans $(+)$ -**5a**/ $(+)$ -**5b**. When Cr(VI) reagents are used, $(+)$ -**4a**/ $(+)$ -**4b** mainly give phellandral (**6**) and carvotanacetone (**7**). MnO_2 reacts too sluggishly with $(+)$ -**4a**/ $(+)$ -**4b**. A camphor pyrolyzate, previously thought to be **1** must be a different compound, probably **7**.

The structure $(\pm)$ -**1** was proposed seventy years ago for an oily fraction from the steam volatiles of the plant *Santolina chamaecyparissus* and called α -santolinenone [1]. The evidence offered was poor [1], and repeated search for **1** from the same plant species with modern analytical methods has given negative results [2]²⁾. This notwithstanding, α -santolinenone (**1**) has been included, as originally formulated [1], in two authoritative compilations of natural products [4].

We became interested in **1** as a potentially useful chiral synthon for the synthesis of sesquiterpenoids recently isolated in our laboratory from a marine sponge [5]. To the



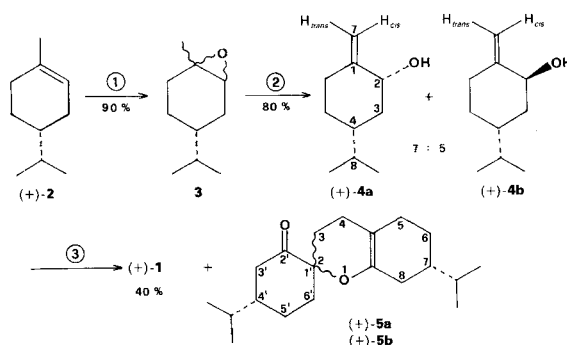
¹⁾ Presented by F.P. as part of a lecture at the University of Innsbruck on March 15th, 1984.

²⁾ Astonishingly, α -santolinenone, as originally formulated $((\pm)$ -**1**) [1], has recently been proposed again as a component of the essential oils of *Santolina virus* and *S. chamaecyparissus* [3], on the basis of much the same earlier evidence [1]. All intervening literature has been ignored.

best of our knowledge, synthetic **1** has only been reported as a product of the flash pyrolysis of camphor [6]. However, the implied [6] high stability of the product, which is surprising for a simple α -methylidene-cyclohexanone [7], and the lack of NMR spectral data, make the structural attribution **1** of dubious value. Also, the extremely poor yield renders the method [6] synthetically unattractive. In fact, it is shown below that the structural attribution **1** for the camphor pyrolyzate [6] has to be revised.

An appraisal of current methods for the synthesis of α -methylidene ketones [8] did not suggest any easy route to enantiomerically pure (+)- or (–)-**1**. Therefore, we chose to synthesize it from (+)-(4*R*)-1-*p*-menthene ((+)-**2**) according to *Scheme 1*. The method involves epoxidation of (+)-**2** followed by base opening of the epoxides **3** to give the alcohols (+)-**4a**/(+)-**4b**³⁾ which are finally oxidized to (+)-(4*R*)-1(7)-*p*-menthen-2-one ((+)-**1**). The yields are good, except for the last stage. Indeed, only (+)-**4a** undergoes oxidation, and (+)-**1** tends to dimerize to give a mixture of diastereoisomeric spiro compounds (+)-**5a**/(+)-**5b**. Though (+)-**1** could be cleanly separated from both (+)-**4b** and (+)-**5a**/(+)-**5b** by HPLC, it was not possible to record spectra of (+)-**1** completely free of the spirocompounds; the latter tend to be reformed even in the cold.

Scheme 1



① *m*-Chloroperbenzoic acid (1 mol-equiv.); NaHCO₃ (2 mol-equiv.) in CH₂Cl₂ at 5–10°, 1 h.

② LDA (2 mol-equiv.) in THF at reflux, 2 h.

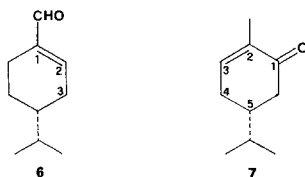
③ Ag₂CO₃/Celite in hexane at reflux, 2 h.

Whereas the formation and opening of **3** are standard and straight-forward⁴⁾, oxidation of the allyl alcohols (+)-**4a**/(+)-**4b** to (+)-**1** proved a very stringent test for the performance of current oxidizing agents for allyl alcohols [10]. In fact, both Cr(VI) and Mn(IV) reagents proved unsatisfactory. Thus, with pyridinium chlorochromate in CH₂Cl₂ [11], (+)-**4a**/(+)-**4b** mainly led to phellandral (**6**) [12]. Pyridinium chlorochromate/NaOAc 1:2 [11] or pyridinium dichromate [13] in CH₂Cl₂ gave a complex

³⁾ Alcohols (+)-**4a** and (+)-**4b** could be separated by *RP-18* reverse-phase chromatography with H₂O/MeOH 7:3, (+)-**4a** being eluted first. The relative configurations are supported by ¹H-NMR spectra which show for H–C(2) of (+)-**4a** a much broader *m* (*w*_{1/2} = 19.0 Hz) than for (+)-**4b** (*w*_{1/2} = 7.1 Hz). This is consistent with a larger diaxial coupling between H–C(2) and H–C(3) in (+)-**4a**.

⁴⁾ A very hindered base has to be used for the epoxide opening, as independently known in the case of limonene epoxides [9a]. Potentially useful alternative routes for **3**→**4** exist [9b].

mixture containing **1** and **6**⁵) in a *ca.* 5:3 ratio, besides some carvotanacetone (**7**)⁵) [14]. Moreover, 4-(dimethylamino)pyridinium chlorochromate [15] gave (+)-**6**⁵) and (+)-**1** in a *ca.* 1:1 ratio, besides traces of **7**⁶). Other Cr(VI) reagents [16] also proved unsatisfactory for similar reasons. Finally, activated MnO₂ [17] reacted as expected too sluggishly, and the products were not investigated. Clearly, in view of the fact that (+)-**1** dimerizes, the oxidizing agent must also be rapid. The oxidizing reagent of choice proved to be Ag₂CO₃ on *Celite*, though, unpredictably [18], only (+)-**4a** underwent oxidation, while (+)-**4b** was recovered unchanged.



The structure of (+)-**1**, which gives UV and IR spectra characteristic of enones, is proved by ¹H-NMR and mass spectra⁷). Thus, CH₂=C(1) appears as 2 broad *s* (further coupled to H–C(6)) at δ 5.82 (H_{cis}) and 5.12 ppm (H_{trans}). (CH₃)₂C(8) give a *d* at 0.90 ppm, while the remaining protons integrate correctly as a series of *m* between 2.5 and 1 ppm. The MS shows the *M*⁺ at 152 with consecutive losses of isopropyl (*m/z* 109) and CO (*m/z* 81), whilst the peak *m/z* 82 is quite weak.

This MS fragmentation pattern for (+)-**1** is different from that reported for the camphor pyrolyzate of *M*⁺ 152, where *m/z* 82 is the base peak whilst *m/z* 81 is quite weak [6c]. In the proposed fragmentation scheme [6c], *m/z* 82 is better accommodated *via* a *retro-Diels-Alder* fragmentation of carvotanacetone (**7**). In fact, both the published [14] and our MS of **7** exactly match the MS reported for the camphor pyrolyzate of *M*⁺ 152, which, therefore, corresponds most probably to carvotanacetone (**7**).

The *Diels-Alder* dimers (+)-**5a**/(+)-**5b** could be nicely separated by HPLC on silica gel. MIKES mass spectra showed them to be diastereoisomers whose structure is sup-

⁵) Both **6** and **7** from the pyridinium chlorochromate/NaOAc oxidation, though pure according to ¹H-NMR spectra, gave only weak optical rotations compared with reported values for the naturally occurring products [12] [14]. This suggests that some migration of the double bond has occurred. In contrast, **6** from the 4-(dimethylamino)pyridinium chlorochromate oxidation gave a higher optical rotation than that reported for the naturally occurring (+)-isomer [12a], but equal in absolute value to that reported for the naturally occurring (–)-isomer [12b].

⁶) Only alcohol (+)-**4b** with axial OH-group was oxidized to (+)-**1**, whilst (+)-**4a** was recovered unchanged.

⁷) Because of the spontaneous dimerization of (+)-**1**, its specific rotation could not be obtained directly. However, as (+)-**5a** and (+)-**5b** have not too dissimilar specific rotations, we simply evaluated the concentration ratio of (+)-**1**/(+)-**5a, b** by ¹H-NMR spectroscopy for a mixture of known total concentration in order to deduce $[\alpha]_D^{20} \approx +98^\circ$ (*c* = 0.24, CHCl₃) for (+)-**1**.

ported by ^{13}C -NMR spectra⁸). However, superimposition of ^1H -NMR signals did not allow to assign unambiguously which is which⁹).

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Experimental Part

1. *General Remarks.* Silica-gel HPLC and reverse-phase HPLC were carried out with, respectively, *Merck LiChrosorb Si-60* (7 μm , 25 $\times$ 1 cm) and *LiChrosorb RP-18* (7 μm , 25 $\times$ 1 cm) columns. NMR spectra were obtained with *Varian CFT20*, modified for ^1H and equipped with a capillary probe for ^{13}C , and *Bruker WP 200* spectrometers. Multiplicities in ^{13}C -NMR are from off-resonance decoupling. Chemical shifts are given in δ with respect to TMS and J are given in Hz. Electron impact mass spectra were taken with either a home-made computerized spectrometer, based on the *ELFS 4-162-8 Extranuclear* quadrupole and a *VG ZAB2F* spectrometer. IR and UV spectra were recorded with *Perkin-Elmer 337* and *Beckman DB-4* spectrometers, resp. Polarimetric data are from a *JASCO DIP-181* polarimeter.

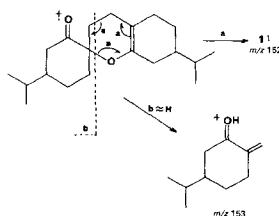
2. (+)-(2R,4R)-1(7)-p-Menthen-2-ol ((+)-**4a**) and (+)-(2S,4R)-1(7)-p-menthen-2-ol ((+)-**4b**). Standard epoxidation of (+)-p-menthene ((+)-**2**; *Fluka*; stated $[\alpha]_D^{20} = +107.2^\circ$ ($c = 11.1$, CHCl_3)), followed by lithium diisopropylamid treatment of the diastereoisomeric mixture of epoxides **3**, gave a 7:5 mixture (+)-**4a**/(+)-**4b** in 72% overall yield. Reverse-phase HPLC with $\text{MeOH}/\text{H}_2\text{O}$ 7:3 gave pure (+)-**4a** followed by pure (+)-**4b**. Data of (+)-**4a**: Colourless liquid, $[\alpha]_D^{20} = +23.1^\circ$ ($c = 0.55$, CHCl_3). IR (film): 3350s, 1660m, 1115m, 1090s, 1065s, 1032m, 1010w. ^1H -NMR (80 MHz, CDCl_3): 4.88 (br. s, further coupled to 2H-C(6), as shown by irradiation at 2.6, 1H, H_{cis} -C(7)); 4.73 (br. s, further coupled to 2H-C(6), 1H, H_{trans} -C(7)); 4.15 (m, $w_{1/2} = 19.0$, 1H, H-C(2)); 2.6–1.0 (series of m, 9H); 0.85 (d, $J = 6.0$, 6H, 2CH_3 -C(8)); on irradiation at 2.6 (H_{eq} -C(6) as X of ABX), s at 4.88 and 4.73 sharpened (ABX changed into AB with $J_{AB} = 2.2$). MS: 154 (4, M^+), 136 (24, $\text{M}^+ - \text{H}_2\text{O}$), 111 (16, $\text{M}^+ - \text{C}_3\text{H}_7$), 93 (100, 111 $-\text{H}_2\text{O}$).

Data of (+)-**4b**: Colourless liquid, $[\alpha]_D^{20} = +29.8^\circ$ ($c = 1.1$, CHCl_3). IR (film): 3350s, 1660m, 1075m, 1048m, 1030s, 980m. ^1H -NMR (80 MHz, CDCl_3): 4.78 (br. s, 1H, H_{cis} -C(7)); 4.72 (br. s, 1H, H_{trans} -C(7), $J_{\text{cis/trans}} = 2.2$); 4.30 (m, $w_{1/2} = 7.1$, 1H, H-C(2)); 2.6–1.0 (series of m, 9H, X at 2.6); 0.84 (d, $J = 5.5$, 6H, 2CH_3 -C(8)). MS: superimposable to that of **4a**.

3. Oxidation of the 7:5 Mixture (+)-**4a**/(+)-**4b**. 3.1. With $\text{Ag}_2\text{CO}_3/\text{Celite}$. The mixture (+)-**4a**/(+)-**4b** (0.15 g, 1.0 mmol) and 5 mmol of the *Fetizon* reagent [18] in 35 ml of hexane were refluxed under N_2 for 2 h, then filtered, evaporated, and the residue was subjected to silica-gel HPLC with hexane (i-Pr) $_2\text{O}$ 9:1. The mixture

⁸) The MS reveals (*Scheme 2*) peaks of both protonated α -santolinenone and α -santolinenone radical cation. In fact, the spectrum of both (+)-**5a** and (+)-**5b** exactly matches that of α -santolinenone from m/z 152 downwards.

Scheme 2



⁹) Either the use of higher fields, or of shift reagents at 200 MHz, would allow to assign the ^1H -NMR spectra.

(+)-**5a**/(+)-**5b** was eluted first, followed by (+)-(*4R*)-1(*7*)-*p*-menthen-2-one ((+)-**1**), then by **6** in traces, and, finally, by a 95:5 mixture (+)-**4b**/(+)-**4a**. Preparatively, (+)-**1** could be best isolated from the mixture by flash chromatography. Data of ((+)-**1**)¹⁰: Colourless liquid, $[\alpha]_D^{20} \approx +98^\circ$ ($c = 0.24$, CHCl_3). UV (95.5 hexane/(i-Pr)₂O; 233. IR (film): 1680, 1620. ¹H-NMR (80 MHz, CDCl_3): 5.82 (br. *s*, further coupled to $\text{H}_{\text{eq}}\text{-C}(6)$), as shown by irradiation at 2.8, 1H, $\text{H}_{\text{eq}}\text{-C}(7)$); 5.12 (br. *s*, further coupled to $\text{H}_{\text{eq}}\text{-C}(6)$), 1H, $\text{H}_{\text{trans}}\text{-C}(7)$, $J_{\text{cis,trans}} = 2.2$); 2.8 (*m*, 2H, $\text{H}_{\text{eq}}\text{-C}(6)$, $\text{H}_{\text{eq}}\text{-C}(3)$); 2.5–1.0 (series of *m*, 6H); 0.90 (*d*, $J = 6.0$, 6H, $2\text{CH}_3\text{-C}(8)$). MS: 152 (1, M^+), 109 (23, $M^+ - \text{C}_3\text{H}_7$), 82 (24), 81 (100, 109 $-\text{CO}$), 69 (60), 41 (64).

3.2. With Pyridinium Chlorochromate (PCC). Standard conditions [11] with $[\text{PCC}]/[\mathbf{4}] = 1.5$ in CH_2Cl_2 at r.t. for 2 h gave a mixture containing (¹H-NMR and HPLC) mainly **6**, together with some **1**, **5**, and **7**.

3.3. With Pyridinium Chlorochromate/NaOAc 1:2 (PCC/NaOAc) or Pyridinium Dichromate (PDC). Standard conditions with PCC/NaOAc 1:2 [13] using $[\text{PCC}]/[\mathbf{4}] = 1.5$ in CH_2Cl_2 at r.t. for 2 h gave a mixture containing (¹H-NMR and HPLC) **1**, **6** and **7** in 5:3:2 relative ratios, besides some **5**. The relative amounts of **1** and **5** were found to depend on the time elapsed from the mixing of the reagents. Much the same results were obtained with PDC under standard conditions [14] with $[\text{PDC}]/[\mathbf{4}] = 0.8$ in CH_2Cl_2 at r.t. for 6 h. HPLC purification on silica gel as above led to **6** and **7**. (+)-(*4R*)-1-*p*-Menthen-7-al (**6**): $[\alpha]_D^{20} = +33.0^\circ$ ($c = 0.7$, CHCl_3). ¹H-NMR (80 MHz, C_6D_6): 9.33 (*s*, 1H, CHO); 6.05 (*m*, 1H, $\text{H-C}(2)$); 2.2–1.0 (series of *m*, 8H); 0.70 (*d*, $J = 5.8$, 6H, $(\text{CH}_3)_2\text{CH}$). MS: 151 (1, $M^+ - 1$), 123 (5, $M^+ - 29$), 109 (70, $M^+ - \text{C}_3\text{H}_7$), 81 (75), 43 (100). (–)-(*5R*)-5-Isopropyl-2-methyl-2-cyclohexen-1-one (**7**): $[\alpha]_D^{20} = -22.0^\circ$ ($c = 0.51$, CHCl_3). ¹H-NMR (80 MHz, C_6D_6): 6.14 (*m*, 1H, $\text{H-C}(3)$); 2.5–1.0 (series of *m*, 6H); 1.8 (*s*, 3H, $\text{CH}_3\text{-C}(2)$); 0.67 (*d*, $J = 6.2$, 6H, $(\text{CH}_3)_2\text{CH}$) [14c]. MS: superimposable to reported spectra [14a].

3.4. With 4-(Dimethylamino)pyridinium Chlorochromate. Standard conditions [15] gave **6** which, after reverse-phase HPLC purification, showed $[\alpha]_D^{20} = +151.7^\circ$ ($c = 0.20$, CHCl_3), besides to (+)-**1**, in equivalent amount, and traces of **7**.

4. (*4'S,7S*)-4',7-Diisopropyl-5,6,7,8-tetrahydro-spiro[chroman-2,1'-cyclohexan]-2'-one ((+)-**5a** and (+)-**5b**). The mixture (+)-**5a**/(+)-**5b**, separated by HPLC from either the mixtures of oxidation of **4** or from α -santoninone on standing (see above), was separated into its components (4:1 molar ratio of (+)-**5a**/(+)-**5b**) by silica gel HPLC (hexane/(i-Pr)₂O 96:4). Data of (+)-**5a** (eluted first): Colourless liquid, $[\alpha]_D^{20} = +36.1^\circ$ ($c = 0.45$, CHCl_3). IR (film): 1725s, 1700m¹¹). ¹H-NMR (200 MHz, C_6D_6): 2.75 (*dd*, $J = 12.0$, 12.0, 1H); 2.4 (br. *m*, 1H); 2.2 (*m*, 3H); 2–1 (series of *m*, 15H); 0.87 (*d*, $J = 7.0$, 6H); 0.76 (*d*, $J = 7.0$, 3H); 0.72 (*d*, $J = 7.0$, 3H). On irradiation at 1.3, both the *d* at 0.87, 0.76, and 0.72 became *s*, whilst the *dd* at 2.75 became a *d*. ¹³C-NMR (20 MHz, C_6D_6): 210.4 (*s*, C=O); 144.7 (*s*, $\text{C}(8a)$); 105.4 (*s*, $\text{C}(4a)$); 79.5 (*s*, $\text{C}(2)$); 20.2, 19.8, 19.8, 19.7 (4*q*); 42.1, 39.3, 31.7, 29.2, 27.9, 26.9, 24.0, 23.2 (8*t*); 48.1, 41.5, 33.1, 32.5 (4*d*). MS: 304 (27, M^+); HR found 304.2382 $\pm$ 0.005; calc. for $\text{C}_{20}\text{H}_{32}\text{O}_2$ 304.2402; 261 (1, $M^+ - \text{C}_3\text{H}_7$); 243 (1, 261 $-\text{CO}$); 153 (100, $M^+ - 151$); HR found 153.1242 $\pm$ 0.005; calc. for $\text{C}_{16}\text{H}_{17}\text{O}$ 153.1279; 152 (29, $M^+ - 152$); 135 (5, 153 $-\text{H}_2\text{O}$); 109 (24, 152 $-\text{C}_3\text{H}_7$); 81 (45, 109 $-\text{CO}$). Linked scans showed the following relationships 261 $\rightarrow$ 243 + 153 + 152; 153 $\rightarrow$ 135.

Data for (+)-**5b** (eluted second): Colourless liquid, $[\alpha]_D^{20} = +54.8^\circ$ ($c = 0.26$, CHCl_3). IR (film): 1725s, 1700m. ¹³C-NMR (20 MHz, C_6D_6): 206.8, 146.0, 102.0, 81.3 (4*s*); 20.1, 20.1, 19.8, 19.8 (4*q*); 41.7, 36.7, 31.5, 29.3, 28.7, 26.9, 25.0, 23.1 (8*t*); 46.0, 41.2, 32.4, 31.5 (4*d*). MS: superimposable to that for (+)-**5a** (also the MIKES spectra).

¹⁰) As the diastereoisomeric (+)-**5a**/(+)-**5b** are rapidly reformed, spectra of (+)-**1** always revealed a little of their mixture; the corresponding signals had to be subtracted from those of (+)-**1**.

¹¹) Two C=O bands have already been observed with α -halogenated monoketo-steroids [19].

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