SHORT PAPER

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Autoxidation of α-santalene†

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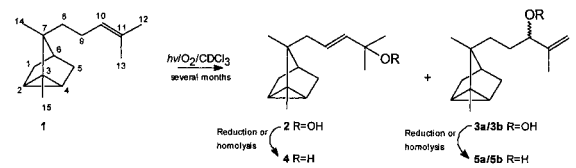
Fifteen compounds (**2** – **11**) have been isolated from the spontaneous slow autoxidation of the tri-substituted double bond in the side-chain of the tricyclic sesquiterpene α-santalene; most of these compounds have also been reported as natural products.

α-Santalane sesquiterpenes are amongst the characteristic components of East Indian sandalwood (*Santalum album*) oil[1,2] and lavender (*Lavandula officinalis*) oil,[3] two important essential oils in perfumery. α-Santalene (**1**), the parent of this class of natural products, is itself an important olefactory chemical and has been the target of numerous syntheses.[4] Extensive chemical studies of sandalwood oil have shown the presence of almost 20 santalanes in which the C–8 – C–13 side-chain of α-santalene has apparently been modified by oxidation and/or cleavage reactions, whilst the tricyclic ring system remains intact.[1,5,6] Lavender oil is also reported to contain some 10 sesquiterpenes apparently derived from oxidation and cleavage reactions in the side-chain.[3,7]

We became interested in studying the autoxidation chemistry of the tri-substituted double bond in the α-santalene side-chain following a phytochemical investigation of the Chinese medicinal plant *Illicium tsangii*,[8] from which we isolated large amounts of (-)-α-santalene (**1**), together with several other santalane sesquiterpenes, including the tertiary and secondary allylic hydroperoxides **2** and **3** – which have structures clearly suggestive of formation by the 'ene'-type reaction of singlet oxygen with the tri-substituted double bond in **1**.[8] In fact, it has been explicitly shown by others that photosantalols A (**4**) and B (**5**), which are the hydroxy analogues of compounds **2** and **3**, can be isolated by reduction of the mixture arising from photooxidation of α-santalene[7] in the presence of photosensitizer.

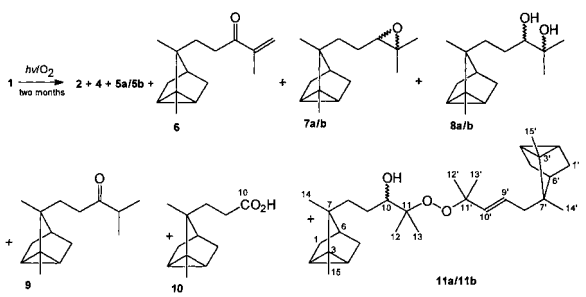
In an attempt to verify whether natural products such as **2** and **3** might be formed from **1** by spontaneous autoxidation occurring either in the plant or during the extraction process, dilute solutions of **1** (1mg/0.6 ml in $CDCl_3$) were left under conditions of natural light and temperature. This did indeed result in conversion to hydroperoxides **2** and **3**, but the reaction was very slow in the absence of photosensitizer, requiring several months to attain completion (Scheme 1). Thus hydroperoxides **2** and **3** would seem unlikely to be artifacts from the extraction procedure used for *I. tsangii* (which typically required just a few days), although it is still possible that they are formed by autoxidation reactions occurring during storage in the plant cell over a more prolonged period of time, which are possibly assisted by the presence of pigments such as chlorophyll, which can function as a photosensitizer.



Scheme 1 Very slow formation of allylic hydroperoxides **2** and **3** by non-photosensitized autoxidation of α-santalene (1) in CDCl3 solution.

In a separate experiment, it was found that pure (-)-α-santalene when left in the form of a oil under ambient conditions for two months was converted into a complex mixture of products from which compounds **2** and **4–11** were isolated by chromatography (Scheme 2). The structures of all these compounds were elucidated primarily by 2D-NMR (HSQC, HMBC, ^1H-^1H COSY and NOESY); complete NMR assignments for **7–11** are reported for the first time in Tables 1 and 2 (for complete NMR assignments of the other autoxidation products see ref. 8). The structures of dimers **11a** and **11b** are only tentative because no molecular ion was observed in mass spectroscopy and there are too many bonds involved in the peroxide linkage to confirm this connection between the two halves of the molecule on the basis of ^{13}C-^1H correlations observed in HMBC spectra. It is interesting to note that, with the exception of compounds **11a/11b**, all other eleven products obtained from autoxidation of α-santalene as an oil have been reported previously as natural products from one source or another: thus, we ourselves previously identified compounds **2–6** from *I. tsangii*,[8] compounds **4–6** and **9** have been reported from *L. officinalis*,[3,7] **4–7** and **9** are present in *Severinia buxifolia*,[9] **8** has been isolated from *Porella subobtusa*[10] and *P. caespitans*[11] and **10** is known from *S. album*.[1,5]

Although the expected secondary hydroperoxide product **3** was not isolated from autoxidation of **1** when performed as an oil, the secondary hydroxide **5** is almost certainly derived from this autoxidation product by homolysis of the oxygen-oxygen linkage, which is expected to occur by a radical process (tertiary alcohol **4** is likewise probably derived from tertiary allylic hydroperoxide **2**).[12] The more complex product mixture obtained from the slow non-photosensitized autoxidation of α-santalene as an oil, as compared with that from the very slow autoxidation occurring in $CDCl_3$ solution might be ascribed to further more extensive radical reactions of the hydroperoxide products occurring in the oil, resulting in cleavage,[12] dehydration[12] and epoxide formation[12] in the santalene side-chain. Subsequent hydrolytic cleavage of diastereoisomeric epoxides **7a/7b** would lead to the vicinal diols **8a/8b** whereas nucleophilic attack at **7a/7b** by a second molecule of **2** would account for the formation of the epoxide ring-opened dimers tentatively assigned as structures **11a** and **11b**.



Scheme 2 Products obtained from the slow autoxidation of α-santalene (**1**) as an oil.

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† This is a Short Paper, there is therefore no corresponding material in *J Chem. Research (M).*

Table 1 ^{13}C NMR assignments for α-santalanes **7–11**.

Assignment	Multiplicity[a]	**7a/7b**	**8a/8b**	**9**	**10**	**11a**	Assignment	Multiplicity[a]	**11a**
1	CH_2	31.49	31.67	31.5	31.5	31.5	1′	CH_2	31.3
2	CH	19.64/19.58	19.67/19.58	19.6	19.7	19.67	2′	CH_2	19.67
3	C	27.38/27.35	27.50/27.40	27.4	27.4	27.5	3′	C	27.0
4	CH	19.51/19.47	19.53/19.50	19.5	19.5	19.69	4′	CH_2	19.58
5	CH_2	30.96/30.99	31.02	31.0	31.0	31.0	5′	CH_2	31.1
6	CH	38.21/38.17	38.21/38.23	38.3	38.1	38.3	6′	CH	38.6
7	C	45.71/45.69	45.85/45.73	45.5	45.6	45.7	7′	C	46.4
8	CH_2	30.78/30.61	31.48/31.46	28.4	29.4	31.8	8′	CH^2	37.4
9	CH_2	24.35/24.32	26.78/26.76	36.0	29.7	26.5	9′	CH_2	127.3
10	CH	64.97/64.92	79.76/79.59	215.4 (C)	178.4 (C)	76.4	10′	CH	136.0
11	C	58.38/58.33	73.23	40.9 (CH)	–	83.6	11′	C	80.3
12[b]	CH_3	24.97	23.37/23.28	18.4	–	18.9	12′	CH_3	24.9
13[b]	CH_3	18.62	26.61/26.60	18.4	–	22.1	13′	CH_3	25.1
14	CH_3	17.40/17.53	17.57/17.46	17.3	17.2	17.5	14′	CH_3	17.4
15	CH_3	10.63/10.66	10.69	10.6	10.6	10.7	15′	CH_3	10.7

[a] Multiplicity established from DEPT.
[b] Assignments interchangeable within column.

Table 2 ^1H NMR assignments[a] for α-santalanes **7–11**.

Assignment	**7a/7b**	**8a/8b**	**9**	**10**	**11a**	Assignment	**11a**
1α	1.07	1.06	1.08	1.09	1.06	1α′	1.06
1β	1.61	1.61	1.61	1.62	1.60	1β′	1.60
2	0.85	0.85	0.83	0.86	0.85	2′	0.85
4	0.85	0.85	0.83	0.86	0.85	4′	0.85
5α	1.04	1.04	1.04	1.06	1.06	5α′	1.03
5β	1.55	1.55	1.56	1.59	1.63	5β′	1.61
6	1.54	1.55	1.50	1.52	1.54	6′	1.52
8	1.41/1.33	1.48/1.25	1.50	1.56	1.12	8′	1.96
	1.27/1.17	1.20/1.12	1.43	1.56	1.07		1.86
9	1.56/1.51	1.46/1.40	2.36	2.29	1.35	9′	5.54 (1H, *m*)
	1.41/1.34	1.24/1.16	2.36	2.25	1.20		
10	2.68 (1H, *t*, 6.1)	3.28 (1H, *dt*, 10.0, 2.0)	–	–	3.63 (1H, *d*, 9.9)	10′	5.54 (1H, *m*)
11	–	–	2.63 (1H, *sept*, 7.0)	–	–	11′	–
12[b]	1.31 (3H, *s*)	1.16 (3H, *s*)	1.09 (3H, *d*, 7.0)	–	1.05 (3H, *s*)	12′[b]	1.31 (3H, *s*)
13[b]	1.27 (3H, *s*)	1.22/1.21 (3H, *s*)	1.09 (3H, *d*, 7.0)	–	1.21 (3H, *s*)	13′[b]	1.29 (3H, *s*)
14	0.83/0.82 (3H, *s*)	0.82 (3H, *s*)	0.81 (3H, *s*)	0.83 (3H, *s*)	0.81 (3H, *s*)	14′	0.80 (3H, *s*)
15	1.02 (3H, *s*)	1.02 (3H, *s*)	1.02 (3H, *s*)	1.03 (3H, *s*)	1.01 (3H, *s*)	15′	1.01 (3H, *s*)

[a] Integrals, multiplicity and coupling constants (in Hz) indicated in parentheses when resolved in 1D-NMR spectra.
[b] Assignments interchangeable within column.

Lower terpenes, such as α-santalene, are normally stored as components of an essential oil in the trichomes or equivalent storage structures located on the epidermis of higher plants.[13] It is thus possible that compounds such as **2–10**, which have been reported previously as *bona fide* natural products – but which have now been obtained from the spontaneous autoxidation of **1** (either in solution or as an oil), might in reality be formed by (non-enzymic) singlet oxygen autoxidation reactions of α-santalene and subsequent rearrangement reactions of the allylic hydroperoxide products occurring *in vivo* at the site of storage on the plant surface. In addition, the precise course and rate of such autoxidation reactions might be further modified by the presence of other components in the essential oil and/or by the photosensitizing effects of plant pigments:[14] it would be interesting to investigate how many more of the large number of side-chain oxidized and cleaved santalanes known from *S. album*, *L. officinalis* and other natural sources might also be produced by varying the conditions associated with the spontaneous *in vitro* autoxidation of **1**.

Experimental

Chemical shifts are expressed in ppm (δ) relative to TMS as internal standard. All NMR experiments were run on a Bruker DRX 500 instrument. Two-dimensional spectra were recorded with 1024 data points in F_2 and 256 data points in F_1. MS were recorded in e.i. mode at 70 e.v. on a Finnigan-MAT 95 MS spectrometer. IR spectra were recorded in solution on a Shimadzu FTIR-8201 PC-7 spectrometer. TLC plates were developed using *p*-anisaldehyde. Column chromatography was performed using silica gel 60–200 μm (Merck). HPLC separations were performed using a PREP-SIL 20 mm × 25 cm column, flow rate 8 ml/min.

Autoxidation of (-)-α-santalene (1) as an oil: Compound **1** (80 mg), obtained from the Chinese medicinal plant *I. tsangii* (see ref. 8), was left for two months on the bench in a glass vial under ambient conditions of light and temperature, after which autoxidation products **2**, **4–11** were separated by CC or CC/ HPLC: **2** (2 mg, R_t 26.1 min, 10% EtOAC/hexane); **4** (2 mg, R_f 0.29, 10% EtOAc/hexane); **5a/5b** (2 mg, R_f 0.34, 10% EtOAC/hexane); **6** (12 mg, R_t 10.7 min, 10% EtOAC/hexane); **7a/7b** (18 mg, R_t 13.3 min, 10% EtOAC/hexane); **8a/8b** (5 mg, R_f 0.34, 15% EtOAC/hexane); **9** (3 mg, R_t 13.4 min 2% EtOAC/hexane); **10** (2 mg, R_f 0.24, 20% EtOAC/hexane); **11a** (5mg, R_t 14.1 min, 10% EtOAC/hexane); **11b** (7 mg, R_t 11.4 min, 10% EtOAC/hexane). *10ξ,11ξ-Epoxy-α-santalene (***7a/7b***)*: Oil. (ν / cm^{-1}) 3040, 1230. ^1H and ^{13}C NMR data, Tables 1 and 2. HREIMS *m/z* (intensity %): 220.1824 (M^+, $C_{15}H_{24}O$ requires 220.1827) (8), 138 (30), 121 (65), 93 (100). *10ξ,11ξ-Dihydroxy-α-santalene (***8a/8b***)*: Oil. (ν / cm^{-1}) 3422 (br), 2974, 2951, 2874, 1458, 1375, 1221. ^1H and ^{13}C NMR data, Tables 1 and 2. HREIMS *m/z* (intensity %): 238.1930 (M^+, $C_{15}H_{26}O_2$ requires 238.1933) (8), 220 (4), 205 (4), 180 (6), 123 (60), 121 (100), 93 (95). *Dihydro-α-santalen-10-one* (**9**): Oil. (ν / cm^{-1}) 2947 (br), 2876, 1705, 1454. ^1H and ^{13}C NMR data, Tables 1 and 2. HREIMS *m/z* (intensity %): 220.1822 (M^+, $C_{15}H_{24}O$ requires 220.1827) (95), 205 (10), 177 (60), 149 (48), 121 (95), 93 (100). *Tricycloekasantalic acid (10)*: Oil. (ν / cm^{-1}) 3400–2600 (br), 2930, 2876, 1717, 1458. ^1H and ^{13}C NMR data, Tables 1 and 2. HREIMS *m/z* (intensity %): 194.1307 (M^+, $C_{12}H_{18}O_2$ requires 194.1307) (40), 179 (18), 149 (72), 121 (100), 91 (52). *Santalane dimer 11a*: Oil. (ν / cm^{-1}) 3543 (br), 2978, 2951, 2874, 1456, 1377. ^1H and ^{13}C NMR data, Tables 1 and 2. EIMS *m/z* (intensity %): 203 (22), 121 (100), 93 (21). CIMS *m/z* (intensity %): 219 (40), 203 (100), 121 (40). *Santalane dimer 11b*: Oil. (ν / cm^{-1}) 3551

(br), 2978, 2950, 2874, 1456, 1377. δ_H ($CDCl_3$, 500 MHz): 5.55 (2H, *m*, H-9'/10'), 3.63 (1H, *dt*, *J* 9.0, 2.7 Hz, H-10), 2.62 (1H, *s*, -OH), 1.31 (3H, *s*, H-12'/13'), 1.29 (3H, *s*, H-12'/13'), 1.20 (3H, *s*, H-12/13), 1.06 (3H, *s*, H-12/13), 1.02 (3H, *s*, H-15/15'), 1.01 (3H, *s*, H-15/15'), 0.82 (3H, *s*, H-14/14'), 0.80 (3H, *s*, H-14/14'). δ_C ($CDCl_3$, 125 MHz): 135.9 CH (C-10'), 127.3 CH (C-9'), 83.6 C (C-11), 80.3 C (C-11'), 76.1 CH (C-10), 46.4 C (C-7/7'), 45.8 C (C-7/7'), 38.5 CH (C-6/6'), 38.1 CH (C-6/6'), 37.3 CH_2 (C-8'), 31.6 CH_2, 31.5 CH_2, 31.3 CH_2, 31.02 CH_2, 31.00 CH_2, 27.4 C (C-3/3'), 26.9 C (C-3/3'), 26.4 CH_2 (C-9), 25.2 CH_3 (C-12'/13'), 24.8 CH_3 (C-12'/13'), 22.1 CH_3 (C-12/13), 19.6 CH x 2, 19.5 CH x 2, 18.8 CH_3 (C-12/13), 17.4 CH_3 x 2 (C-14 and 14'), 10.7 CH_3 (C-15 and C-15'). EIMS *m/z* (intensity %): 203 (22), 121 (100), 93 (24). CIMS *m/z* (intensity %): 219 (38), 203 (100), 121 (66).

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