Pergamon

Tetrahedron 55 (1999) 14623–14634

TETRAHEDRON

Autoxidation of Allohimachalol

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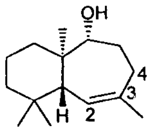
Received 15 July 1999; revised 27 September 1999; accepted 14 October 1999

Abstract: The tri-substituted (2,3)-double bond in allohimachalol (**1**) undergoes autoxidation in the presence of singlet molecular oxygen, resulting in tertiary and secondary allylic hydroperoxides **6** and **7**. These autoxidation products may then participate in complex rearrangement reactions to yield *seco*-allohimachalanes, which have undergone carbon-carbon bond cleavage at the 2,3- or 3,4-positions. The observed autoxidation/rearrangement reactions of **1** *in vitro* would account for the biogenesis of several allohimachalanes recently reported from the medicinal plant *Illicium tsangii* as natural products.

INTRODUCTION

We recently reported the isolation of the rare allohimachalane sesquiterpene **1** from the Chinese medicinal plant *Illicium tsangii*, together with a number of *seco*-allohimachalanes **2**-**5**.[1] The novel skeletons possessed by these compounds were suggestive of formation by rearrangement reactions of secondary and tertiary allylic hydroperoxides[2] produced by autoxidation of the tri-substituted double bond in **1**, in a manner reminiscent of that proposed for formation of the important anti-malarial compound artemisinin (qinghaosu) from *Artemisia annua*.[3] Experimental evidence is now presented that compounds **2**-**5** may indeed be autoxidation products of **1** and for carbon-carbon bond cleavage occurring *via* a mechanism involving a 1,2-shift of the alkene group in the secondary and tertiary allylic hydroperoxide autoxidation products to the internal oxygen atom of the hydroperoxide, accompanied by loss of the terminal oxygen as water (Hock cleavage).[4,5]



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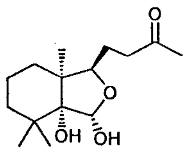

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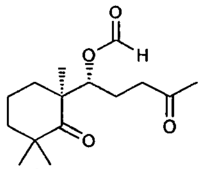

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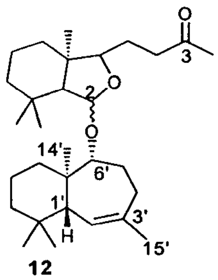

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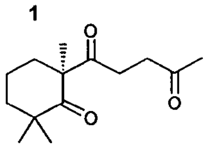

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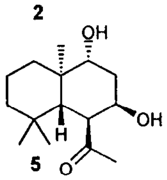

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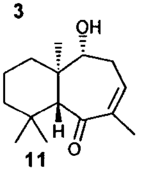

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PII: S0040-4020(99)00938-2

RESULTS AND DISCUSSION

We have recently reported an example of a *seco*-cycloartane triterpenoid containing a tri-substituted double bond[6] which underwent rapid autoxidation in the presence of light and molecular oxygen, but without the requirement for a photosensitizer, to generate secondary and tertiary allylic hydroperoxides in the triterpenoid "side-chain"; these allylic hydroperoxides were then stable over a period of several weeks under the conditions of the reaction (in $CDCl_3$ solution). Against this background, we were interested to discover that a sample of allohimachalol (**1**) which had been left as a solid for one and a half months under conditions of ambient light and temperature had been partially converted into a variety of autoxidation products which were characterized by 2D-NMR (HSQC, HMBC and ^1H-^1H COSY; see Figure 1 and Tables 1 and 2) as known compounds **3** and **8** (previously reported as natural products from *I. tsangii*),[1] novel tertiary and secondary allylic hydroperoxides **6** and **10** and novel allohimachalanes **9**, **11** and **12** (tentative identification only for **12** in the absence of HRMS data for a molecular ion). Complete NMR assignments for novel compounds **6**, **9**, **10** and **11** are reported in Tables 1 and 2.

In the absence of photosensitizer, the autoxidation of **1** was found to be very slow in the solid state under ambient conditions, yielding only a few percent of tertiary allylic hydroperoxide **6** after several days. The reaction in the absence of photosensitizer was more conveniently studied in $CDCl_3$ solution. Resonances which were later assigned as belonging to compounds **6-10** appeared in ^1H NMR spectra within a few days, and there was complete disappearance of starting material within four weeks. However, the complex nature of the various autoxidation and rearrangement reactions which were occuring simultaneously in $CDCl_3$ solution made such a direct study of the autoxidation of **1** unfeasible. Therefore, in order to more easily study the rearrangement chemistry of allylic hydroperoxides, which were thought to be involved in the transformation of **1** to oxidized natural products such as **3** and **8** (see above), we opted to first effect photooxidation of the tri-substituted double bond in the presence of a photosensitizer (in solution). This resulted in clean and rapid transformation of **1** to tertiary allylic hydroperoxide **6** and secondary allylic hydroperoxide **7** without any accompanying rearrangements.

Compounds **6** and **7**, which are two of the three possible products expected from "ene-type" reaction of singlet oxygen with the tri-substituted double bond in **1** (Scheme 1), could be easily separated by HPLC and their rearrangement reactions were studied independently. Rigorous characterization of both hydroperoxides by 2D-NMR (Tables 1 and 2; Figure 1) permitted complete assignment of all resonances, which in turn allowed the relative configuration of the newly introduced hydroperoxide group to be determined by NOESY as β- for both compounds; in the case of compound **6** this configuration is required by the "ene" mechanism for addition of singlet oxygen (H-1β of **1** is involved in this reaction), whereas for **7** it is consistent with addition of molecular oxygen from the less hindered β-face of allohimachalol.

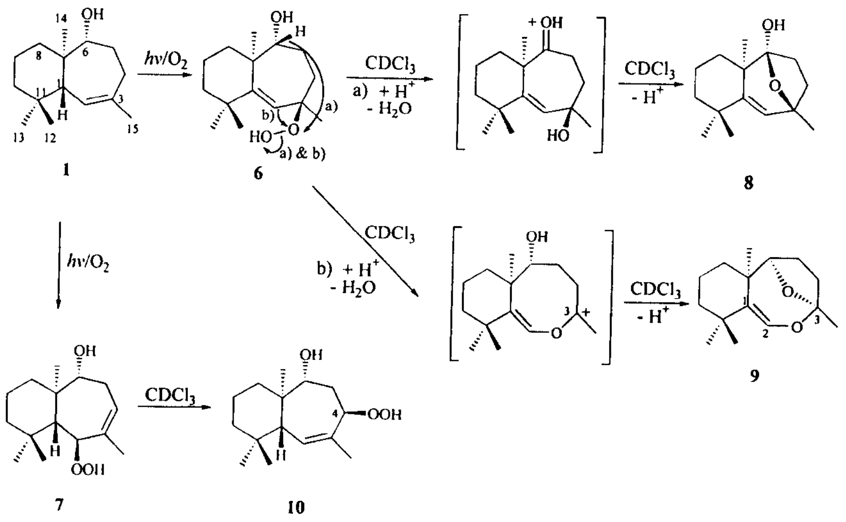
Table 1. ^{13}C NMR data for compounds **6, 7, 9-11** and **13-17** in $CDCl_3$

	Mult.[a]	**6**	**7**	**9**[c]	**10**	**11**	**13**	**14**[b]	**15**[c]	**16**[b]	**17**[b]
1	CH	155.8 (C)	56.3	131.2 (C) [132.5]	47.9	62.9	48.7	46.2	61.5 [61.5]	63.2	60.4
2	CH	127.2	86.5	139.6 [139.2]	132.5	207.7 (C)	50.4	207.2	101.3 [101.3]	99.5	103.3
3	C	84.1	139.7	108.6 [109.1]	134.2	143.0	216.3	212.1	208.7 [211.1]	211.1	212.2
4	CH	31.8 (CH_2)	124.4	36.5 (CH_2) [36.1]	84.2	131.6	66.1	43.7 (CH_2)	41.2 (CH_2) [41.2]	41.2 (CH_2)	41.0 (CH_2)
5	CH_2	30.0	33.6	28.1 [28.0]	33.5	32.4	32.4	18.6	21.3 [21.6]	21.6	21.2
6	CH	77.4	79.4	88.0 [87.9]	78.3	79.6	81.8	36.8	86.1 [86.4]	87.1	89.1
7	C	43.8	41.5	45.1 [44.5]	40.9	43.5	41.2	34.5	43.3 [43.7]	43.8	43.7
8	CH_2	36.7	40.4	35.3 [35.6]	38.3	36.8	36.6	31.8	28.3 [28.2]	28.2	28.0
9	CH_2	17.8	18.2	17.7 [17.9]	18.2	18.1	17.8	17.0	18.2 [18.2]	18.2	17.8
10	CH_2	40.0	43.1	40.5 [40.9]	42.1	42.3	43.0	36.6	36.2 [36.2]	36.1	35.6
11	C	38.1	33.1	33.7 [33.7]	33.4	32.9	34.1	31.2	31.1 [31.6]	31.6	31.2
12	CH_3	32.1	34.0	33.8 [33.1]	33.1	32.6	36.4	29.3	30.4 [30.1]	30.9	29.9
13	CH_3	33.3	23.4	32.2 [32.2]	22.0	22.5	22.7	26.8	28.5 [28.6]	28.6	28.1
14	CH_3	18.3	14.6	25.2 [24.9]	12.7	15.9	13.3	17.5	21.8 [21.8]	21.8	21.5
15	CH_3	27.0	22.7	25.7 [25.3]	25.7	19.0	33.9	30.1	29.9 [30.6]	30.4	30.8

[a] Multiplicity established from DEPT

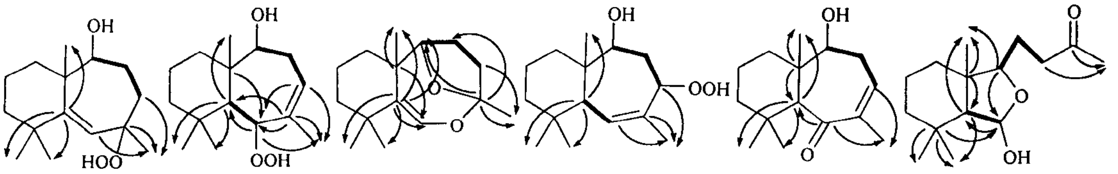
[b] Chemical shifts determined in $CDCl_3$/TFA solution as a mixture by 2D-NMR

[c] Chemical shift values in square brackets determined in $CDCl_3$/TFA solution as a mixture by 2D-NMR (see Experimental)



Scheme 1 Photooxidation of allohimachalol (**1**) yielding tertiary and secondary allylic hydroperoxides **6** and **7** and subsequent rearrangement reactions of these hydroperoxides in $CDCl_3$ solution.

Both these hydroperoxides were relatively unstable in $CDCl_3$ solution. Thus, tertiary allylic hydroperoxide **6** was converted into two products, cyclic *hemi*-ketal **8** (which was previously reported as the natural product tsangane E from *I. tsangii)*[1] and cyclic enol ether **9**, in less than 72 hours. The rate of transformation for **6** → **9** was slightly faster than that for **6** → **8** (0.0015 min^{-1} and 0.0012 min^{-1} respectively as determined by ^1H NMR -see Experimental). The conversion of **6** to **8** might be explained as a 1,5-shift of the 6β-hydrogen to the internal oxygen of the hydroperoxide group, which accompanies the loss of the terminal oxygen atom of this hydroperoxide as water. Such a reaction would result in a protonated 6-keto intermediate which is then immediately trapped as a *hemi*-ketal by the newly formed 3-hydroxyl group. The formation of **9** can be explained in similar terms as the 1,2-shift of the alkene group in **6** to the internal oxygen atom of the tertiary hydroperoxide group which accompanies loss of the terminal oxygen as water (Hock cleavage).[4,5] Haynes and Vonwiller have proposed just such a mechanism for the rearrangement of the tertiary allylic hydroperoxide produced from autoxidation of dihydroartemisinic acid which is involved in the formation of artemisinin but did not provide direct evidence for the transient carbocation which is expected to be generated by this process.[3] Isolation of compound **9**, in which the 3-carbocation which should be produced by this rearrangement has been trapped as a ketal by the 6-hydroxy group, now provides strong evidence in favour of such a mechanism for Hock cleavage.[7] We are aware of only one other example which appears to involve trapping of such a carbocation intermediate by a hydroxyl group (producing an acyclic enol ether);[8] normally such intermediates are cleaved by water, resulting in two carbonyl groups.[9,10] The relative stereochemistry of the oxygen bridge, which is produced by the trapping reactions, proposed to be involved in the formation of both **8** and **9**, was established by NOESY correlations observed for the protons in the rest of the molecule (interpretation of such correlations relies on complete NMR assignments arising from rigorous 2D-NMR analysis - see Tables 1 and 2; Figure 1) and was consistent with the rearrangement mechanisms suggested.



6 **7** **9** **10** **11** **15**

Figure 1. Critical HMBC correlations (indicated by arrows from ^{13}C to ^1H) and critical ^1H-^1H COSY correlations (indicated by bold lines) used in determining the structures of compounds **6, 7, 9, 10, 11** and **15**

Secondary allylic hydroperoxide **7** was cleanly converted into a single compound **10** in $CDCl_3$ solution at a comparable rate (0.0009 min^{-1} as determined by ^1H NMR - see Experimental) to that observed for the rearrangements of **6**. Rigorous 2D-NMR analysis of **10** unambiguously placed the hydroperoxide group at the 4-position in the rearrangement product (Figure 1) and it was shown by NOESY that the relative stereochemistry of the transposed secondary hydroperoxide group in **10** remained β- (as was the case for **7**). Such rearrangement reactions of allylic hydroperoxides have been infrequently reported, and in all known cases[7,11-14] seem to involve a suprafacial migration of the hydroperoxide group, as has been observed here. It has been postulated that the mechanism involves a cyclic five-membered transition state.[15]

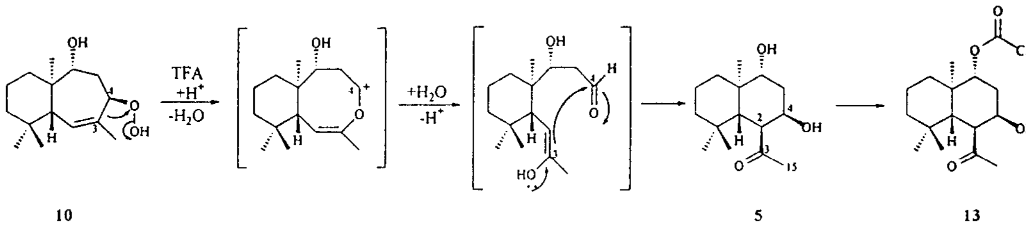
Table 2. ^{1}H NMR data[a] for compounds **6, 7, 9-11** and **13-17** in $CDCl_3$

	6	**7**	**9**[c]	**10**	**11**	**13**	**14**[b]	**15**[c]	**16**[b]	**17**[b]
1	-	1.33	-	2.08 (1H, dd, 4.6, 1.5)	2.54 (1H, s)	2.11	-	1.51 [1.53]	1.50	1.90
2	5.56 (1H, s)	4.58 (1H, d, 4.8)	6.17 (1H, s) [6.19]	5.54 (1H, d, 4.6)	-	2.94 (1H, d, 11.8)	9.75 (1H, s)	5.19 (1H, d, 5.8) [5.18]	5.35 (1H, d, 6.1)	6.18 (1H, d, 6.0)
4α	2.07	5.65 (1H, td, 6.6, 1.5)	1.88 [1.89]	4.38 (1H, d, 5.8)	6.04 (1H, br s)	4.01 (1H, br s)	2.52 (1H, ddd, 19.8, 9.0, 7.8) 2.43 (1H, ddd, 19.8, 7.9, 7.9)	2.62 (1H, ddd, 18.2, 9.2, 5.0) [2.67]	2.73	2.75
4β	1.73		1.98 [2.02]					2.35 (1H, ddd, 18.2, 11.1, 6.6) [2.42]	2.53	2.55
5α	1.77	2.20	2.00 [2.02]	1.71	1.72	1.73	1.97 1.83	1.70 [1.70]	1.75	1.78
5β	2.07	2.60	1.66 [1.68]	2.25	2.72	2.08		1.50 [1.50]	1.55	1.58
6	3.87 (1H, dd, 10.2, 4.5)	3.44 (1H, d, 7.3, 4.9)	3.78 (1H, dd, 8.0, 1.8) [3.87]	3.68 (1H, dd, 11.8, 3.3)	3.51 (1H, br s)	5.24 (1H, dd, 12.0, 4.3)	1.38	3.43 (1H, d, 10.8) [3.44]	3.75 (1H, d, 9.1)	3.73 (1H, d, 10.5)
8α	1.87	1.82	1.29 [1.30]	1.88	1.35	1.60	1.74[d]	1.18 [1.21]	1.21[d]	1.20[d]
8β	1.24	1.03	1.29 [1.30]	1.11	1.26	1.12	1.79[d]	1.24 [1.21]	1.21[d]	1.20[d]
9α	1.74	1.62	1.70 [1.55]	1.55	1.55	1.60	1.55[d]	1.49 [1.49]	1.49[d]	1.53[d]
9β	1.56	1.45	1.53 [1.55]	1.48	1.45	1.48	1.38[d]	1.51 [1.53]	1.58[d]	1.53[d]
10α	1.53	1.43	1.23 [1.25]	1.42	1.38	1.38	1.18[d]	1.24 [1.22]	1.34[d]	1.30[d]
10β	1.36	1.19	1.43 [1.45]	1.13	1.10	1.28	1.30[d]	1.26 [1.26]	1.22[d]	1.20[d]
12	1.12 (3H, s)	1.03 (3H, s)	1.12 (3H, s) [1.13]	0.86 (3H, s)	0.83 (3H, s)	0.73 (3H, s)	1.09 (3H, s)	0.95 (3H, s) [0.93]	0.96 (3H, s)	0.84 (3H, s)
13	1.13 (3H, s)	1.03 (3H, s)	1.15 (3H, s) [1.15]	0.98 (3H, s)	1.33 (3H, s)	1.05 (3H, s)	1.29 (3H, s)	1.04 (3H, s) [1.04]	1.06 (3H, s)	1.08 (3H, s)
14	1.17 (3H, s)	1.08 (3H, s)	1.24 (3H, s) [1.22]	0.81 (3H, s)	1.09 (3H, s)	1.08 (3H, s)	1.28 (3H, s)	1.04 (3H, s) [1.04]	1.07 (3H, s)	1.13 (3H, s)
15	1.36 (3H, s)	1.86 (3H, d, 1.4)	1.59 (3H, s) [1.63]	1.86 (3H, s)	1.85 (3H, s)	2.47 (3H, s)	2.22 (3H, s)	2.12 (3H, s) [2.16]	2.19 (3H, s)	2.22 (3H, s)
OOH	7.58 (1H, s)	7.76 (1H, s)	-	7.90 (1H, s)	-	-	-	-	-	-

[a] Integral, multiplicity and coupling constant(s) in Hz indicated in parentheses when resolved in 1D-NMR
[b] Chemical shifts determined in $CDCl_3$/TFA solution as a mixture by 2D-NMR
[c] Chemical shift values in square brackets determined in $CDCl_3$/TFA solution as a mixture by 2D-NMR (see Experimental)
[d] Assignment tentative due to signal overlap; α and β assignments interchangeable

Although both hydroperoxide rearrangement products **9** and **10** were stable over a period of several weeks under the very mildly acidic conditions of a $CDCl_3$ solution, addition of a trace of trifluoroacetic acid (TFA) resulted in further rearrangements. Thus, compound **10** was converted cleanly into tsangane J (**5**) (previously isolated as a natural product from *I. tsangii*)[1] in less than the time required to obtain a ^{1}H NMR spectrum. Consequently, we are unable to offer any hard evidence for the mechanism of this conversion, but suggest that the transformation proceeds *via* a 1,2-shift of the alkene group to the internal oxygen atom of the secondary hydroperoxide group, accompanying loss of the terminal oxygen atom as water (Scheme 2) in a manner similar to that suggested for the carbon-carbon bond cleavage reaction of the tertiary hydroperoxide **6** in

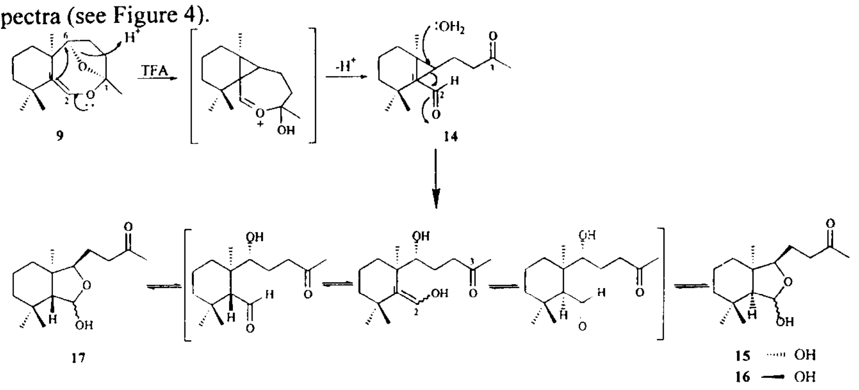
$CDCl_3$ which yields the trapped ketal **9** (Scheme 1). Trapping of the 4-carbocation, which is expected from such rearrangement of **10**, by the 6-hydroxyl group is less favoured than is the case for the 3-carbocation from rearrangement of **6** because this would produce a ketal in a strained four-membered ring; instead, re-addition of water results in a transient 3-enol/4-aldehyde intermediate which immediately undergoes intramolecular aldol reaction to form β-hydroxy ketone **5** (Scheme 2). On standing for several weeks in $CDCl_3$/TFA solution, compound **5** was slowly converted to its trifluoroacetic acid ester **13**, but no other rearrangements or further transformations were noted (the 4-hydroxyl group is involved in hydrogen bonding with the 3-ketone and is presumably therefore less reactive than the 6-hydroxyl group, hence there is only one esterification reaction at the 6-position).



Scheme 2. Proposed mechanism for rearrangement of secondary allylic hydroperoxide **10** to β-hydroxy ketone **5** in $CDCl_3$/TFA.

Fortunately, the rearrangement of **9** in TFA/$CDCl_3$ was a much slower reaction which ultimately yielded *hemi*-ketal **15** after several days. 2D-NMR data sets (HSCQ, HMBC and ^1H-^1H COSY) acquired over the first few hours of the conversion initiated by addition of TFA, indicated **14** as the predominant component (as a mixture with starting material) for which the structure of a cyclopropyl aldehyde was deduced (Tables 1 and 2; Figure 2). 2D-NMR data sets acquired later on in the transformation (after several hours) were used in identifying diastereoisomeric products **15**, **16** and **17** (Tables 1 and 2; Figure 2) which were present as a mixture with each other (a little of **14** was also still present). This kind of analysis of mixtures is possible because the dispersion of the ^1H and ^{13}C NMR resonances for each component of the mixture was sufficiently good to allow identification of sub-sets of connected resonances corresponding to individual components, resulting in structure elucidation for each component, even when present as a mixture. It is the best evidence available for the mechanism of the reaction since compounds **14**, **16** and **17** did not survive attempts at chromatographic separation and HRMS data could therefore not be obtained. Compound **15**, although the most slowly formed of the diastereoismeric *hemi*-ketal products (Figure 3), was ultimately the final product of the reaction after three days, and was the only component of this mixture which could be isolated by HPLC: once isolated, it was stable in $CDCl_3$ solution, suggesting that **15** is the thermodynamically more stable *hemi*-ketal.

The course of the reaction proposed in Scheme 3 (i.e. the sequence **9** → **14** → **15/16/17**) was confirmed by acquiring ^1H NMR spectra at intervals of several minutes after the addition of TFA, and plotting the percentage composition of the mixture (**9/14/15/16/17**), as determined by integration of characteristic resonances for each species in the ^{1}H NMR spectra, against time (Figure 3; see Experimental). Groups of distinctive resonances, which were previously identified by 2D-NMR as belonging to the same individual component, could be confirmed by comparison of how these integrals increased or decreased between successive spectra (see Figure 4).



Scheme 3. Proposed mechanism for conversion of **9** into **15** and diastereoisomers **16** and **17** *via* cyclopropyl aldehyde intermediate **14** in $CDCl_3$/TFA.

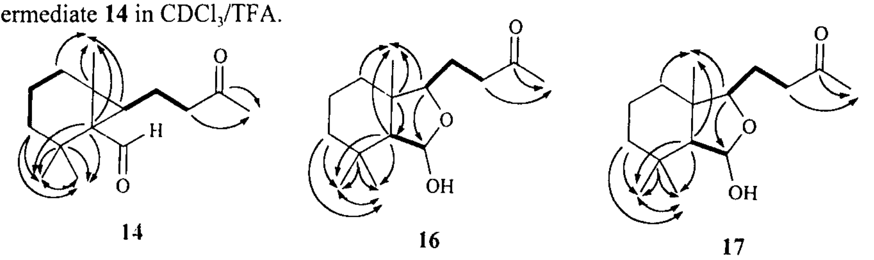


Figure 2. Critical HMBC correlations (indicated by arrows from ^{13}C to ^{1}H) and critical ^{1}H-^{1}H COSY correlations (indicated by bold lines) used in determining the structures of compounds **14**, **16** and **17** from 2D-NMR spectra of mixtures of these compounds with each other in varying proportions (and also with either **9** or **15**) in $CDCl_3$/TFA.

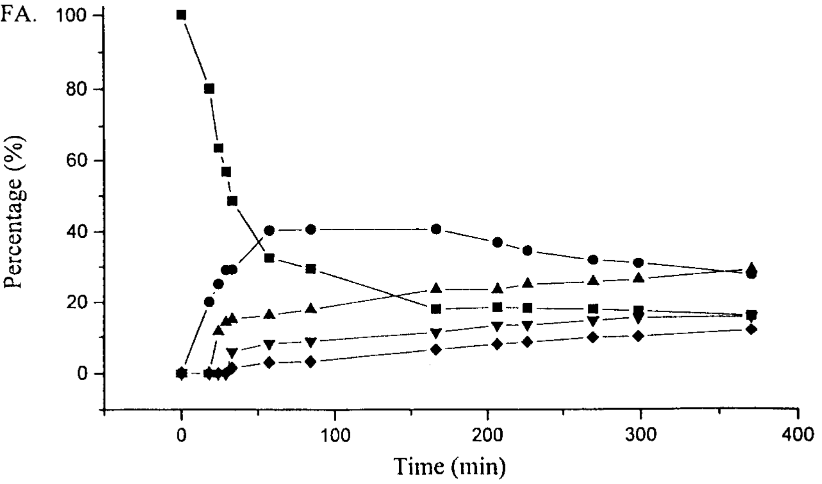


Figure 3. Composition of the reaction mixture (percentage of **9** (■)/**14** (●)/**15** (◆)/**16** (▼) and **17** (▲)) plotted against time for the rearrangement of **9** to **15** in $CDCl_3$/TFA (see Experimental).

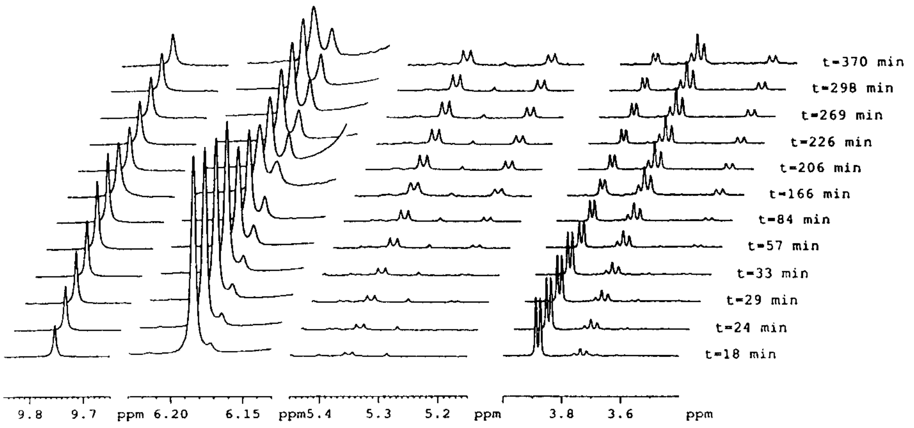
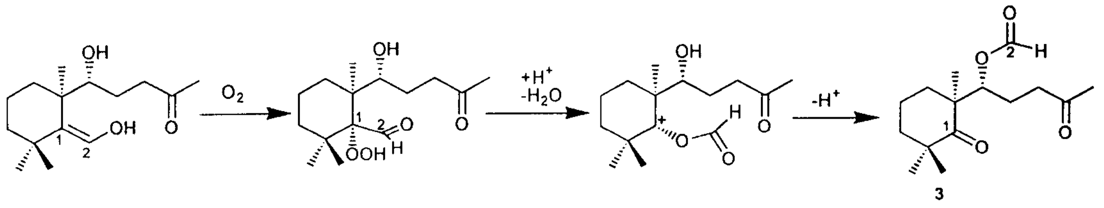


Figure 4. ^{1}H NMR spectra (500 MHz; selected regions in the range δ 3.4-10.0 ppm) showing the signals for starting material **9** (δ_H 6.19, 1H, s, H-2; 3.87, 1H, dd, *J*=8.0, 1.8 Hz, H-6), intermediate **14** (δ_H 9.75, 1H, s, H-2) and diastereoisomeric products **15** (δ_H 5.18, 1H, d, *J* = 5.8 Hz, H-2; 3.44, 1H, dd, *J*=10.8 Hz, H-6), **16** (δ_H 5.35, 1H, d, *J*=6.1 Hz, H-2; 3.75, 1H, d, *J*=9.1 Hz, H-6) and **17** (δ_H 6.18, 1H, d, *J*=6.0 Hz, H-2; 3.73, 1H, d, *J* = 10.5 Hz, H-6) at various times following treatment of **9** with TFA in $CDCl_3$.

Cyclopropyl aldehyde **14**, the initial product of the rearrangement, can be envisaged as arising from rapid intramolecular nucleophilic attack of the cyclic enol ether at the 6-position of the oxygen bridge, which functions as a good leaving group when protonated. It is proposed that further rearrangement of **14** to a transient keto-enol intermediate then occurs at a slower rate over a period of several hours; this reaction can be rationalized as occurring *via* hydrolytic cleavage of the aldehyde-substituted cyclopropyl group in intermediate **14** in a "Michael"-type process, in which the strained cyclopropyl σ-bond assumes the role of the π-bond of the α,β-unsaturated carbonyl group in a conventional Michael reaction . No evidence for this keto-enol intermediate was ever observed in ^{1}H NMR spectra, but the overall conversion of **14** to *hemi*-ketal products such as **15, 16** and **17** *via* intramolecular cyclization of its aldehyde tautomers with the 6-hydroxyl group provides good evidence that such a species must be transiently formed.

We have previously proposed[1] that the keto-enol intermediate discussed above should be produced from the autoxidation/rearrangement reactions of **1** in order to account for the presence of 1,2-*seco*-allohimachalane natural products such as **3** and **4** from *I. tsangii* (Scheme 4). The rationale for this prediction was that a second autoxidation reaction at the highly nucleophilic 1,2-enol double bond of this intermediate would produce a 1-hydroperoxy-2-aldehyde which could then undergo Hock cleavage (this time involving a 1,2-shift of the aldehyde double bond to the internal oxygen atom of the 1-hydroperoxy group) thereby yielding **3**, in the same manner that has now been demonstrated for the carbon-carbon bond cleavage reactions of **6** and **10** (*c.f.* also the mechanism proposed for the second autoxidation/rearrangement in the biogenesis of aremisinin).[3] Although no products of further autoxidation were observed under the conditions used to transform **9** to **15** (i.e. $CDCl_3$/TFA) the isolation of **15** is encouraging, as it suggests that it might be possible to find alternative conditions which would account for formation of 1,2-*seco*-allohimachalane natural products (such as **3** and **4**) from *I. tsangii* solely in terms of such further autoxidation/rearrangement reactions.



Scheme 4. Proposed further autoxidation/rearrangement reaction of the keto-enol intermediate from C-2/C-3 cleavage which would account for biogenesis of *seco*-allohimachalane natural product **3**.

In conclusion, our initial observation that a sample of allohimachalol (**1**) left on the bench for one and a half months had been partially converted into a complex mixture of compounds, containing seven isolable products appears to be explicable in terms of the autoxidation/rearrangement chemistry which has now been explicitly demonstrated for this compound. Thus, the tertiary allylic hydroperoxide **6** was clearly a product formed directly by autoxidation, whilst secondary allylic hydroperoxide **10** was formed by rearrangement of the secondary allylic hydroperoxide **7** from such autoxidation, and *hemi*-ketal **8** and ketal **9** were formed by further rearrangement of **6**. Compounds **3**, **11** and **12** were not obtained as products from further rearrangement reactions of **6** and **7** under the conditions employed in this study, but it is now clear, at least in principle, how they may have arisen. Thus, **3** is expected as a product of further autoxidation/rearrangement of the keto-enol intermediate obtained from opening of the cyclopropyl group in **14**; **11** may be formed by dehydration of **7**; and the dimer **12** may result from trapping of one of the aldehyde intermediates proposed in the rearrangement of **14**, by another molecule of allohimachalol (**1**). The autoxidation/rearrangement chemistry now described for the sesquiterpene allohimachalol seems to confirm previous biogenetic speculation concerning the origins of several allohimachalane natural products recently reported from *I. tsangii*.[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. HSQC and HMBC spectra were recorded with 1024 data points in F_2 and 256 data points in F_1. High-resolution MS were recorded in EI mode at 70 e.v. on a Finnigan-MAT 95 MS spectrometer. IR spectra were recorded in $CHCl_3$ on a Shimadzu FT-IR-8201 PC instrument. Column chromatography was performed using silica gel 60-200 μm (Merck). HPLC separations were performed using a

Varian chromatograph equipped with RI star 9040 and UV 9050 detectors and a normal phase Intersil PREP-SIL 20 mm x 25 cm column, flow rate 8 ml/min.

Autoxidation of allohimachalol (1) as a solid. A vial containing allohimachalol[1] (**1**) (45 mg) was left on the bench for one and a half months under laboratory conditions of ambient light and temperature, after which the sample was re-investigated by ^{1}H NMR (in CDCl$_3$) which revealed several new low intensity peaks in the spectrum. The sample was subjected to gradient column chromatography (pure hexane → 30% EtOAc/hexane) which yielded **1** (from 10% EtOAc/hexane; further purification by HPLC in 10% EtOAc/hexane, R$_f$ 26.2 min, 26 mg), **12** (from 10% EtOAc/hexane; further purification by HPLC in 10% EtOAc/hexane, R$_f$ 21.2 min, 1 mg), **3** (from 20% EtOAc/hexane, 1 mg), **11** (from 20% EtOAc/hexane, 1 mg), **9** (from 30% EtOAc/hexane; further purification by HPLC in 15% EtOAc/hexane, R$_f$ 9.1 min, 0.3 mg), **10** (from 30% EtOAc/hexane; further purification by HPLC in 30% EtOAc/hexane, R$_f$ 21.6 min, 0.6 mg), **8** (from 30% EtOAc/hexane; further purification by HPLC in 15% EtOAc/hexane, R$_f$ 24.0 min, 0.4 mg) and **6** (from 30% EtOAc/hexane; further purification by HPLC in 30% EtOAc/hexane, R$_f$ 32.9 min, 2 mg). *Tsangane H (3)*: see ref. 1 for physical data. *2-Keto-6α-hydroxy-allohimachal-3-ene* (**11**): Oil. IR υ_{max} 3422 (br), 3015, 2957, 2874, 1716, 1661,1458, 1375 cm^{-1}; ^{1}H and ^{13}C NMR, Tables 1 and 2; EIMS (70 eV, *m/z*, %) 236 (10), 221 (10), 178 (10), 163 (35) 149 (40), 99 (100); HRMS 236.1776 calcd for $C_{15}H_{24}O_2$ (M$^+$), found 236.1776. *Allohimachalane dimer* (**12**): Oil. ^{1}H NMR (δ, CDCl$_3$, ppm) 5.25 (1H, d, 5.6, H-2'), 5.14 (1H, d, 8.3, H-2), 3.44 (1H, dd, 9.4, 4.7, H-6), 3.17 (1H, dd, 11.3, 3.2, H-6'), 2.79 (1H, m, H-4a), 2.46 (1H, m, H-4b), 2.15 (3H, s, H-15), 1.77 (3H, s, H-15'), 1.16 (3H, s, H-14), 0.99 (3H, s, H-13'), 0.96 (3H, s, H-13), 0.90 (3H, s, H-12), 0.82 (3H, s, H-12'), 0.77 (3H, s, H-14'); ^{13}C NMR* (δ, CDCl$_3$, ppm) 209.8 (C-3), 138.7 (C-3'), 126.6 (C-2'), 100.3 (C-2), 90.7 (C-6'), 89.0 (C-6), 55.3 (C-1), 49.8 (C-1'), 44.2 (C-7), 42.7 (C-10'), 42.0 (C-10), 40.8 (C-4), 39.6 (C-8'), 33.7 (C-12), 33.7 (C-12'), 33.5 (C-8), 33.0 (C-5'), 31.5 (C-11), 30.5 (C-15), 29.5 (C-4'), 25.7 (C-15'), 23.5 (C-14), 22.7 (C-13'), 22.5 (C-13), 19.5 (C-9), 18.6 (C-9'), 14.5 (C-14') *Several carbons (C-5, C-7' and C-11') not resolved; C-12 and C-12' overlapping.

Photooxidation of allohimachalol (1). Methylene blue (2 mg) was added to a solution of allohimachalol (**1**) in acetone (16 mg/30 ml) and the mixture was irradiated (tungsten lamp, 500 W) for 30 mins with ice-bath cooling. The solvent was removed by rotary evaporation, the residue was resuspended in Et$_2$O (50 ml) and the dye removed by filtration. Removal of solvent by rotary evaporation gave a crude product (15 mg, 86 % yield) which was separated by preparative normal phase HPLC (33% EtOAc/hexane) into **6** (9 mg, 47%, R$_f$ 30.3 min) and **7** (3 mg, 17%, R$_f$ 19.8 min). *3β-Hydroperoxy-6α-hydroxy-allohimachal-1-ene* (**6**): Oil. $[\alpha]_D$ +28.2 (*c* 0.56, CHCl$_3$). IR υ_{max} 3528, 3310 (br), 2934, 2870, 1458, 1370 cm^{-1}; ^{1}H and ^{13}C NMR, Tables 1 and 2; EIMS (70 eV, *m/z*, %) 236 (20), 221 (40), 203 (100), 180 (20), 163 (30), 161 (50), 125 (90), 111 (80); HRMS calcd 236.1776 for $C_{15}H_{24}O_2$ (M$^+$ - H$_2$O), found 236.1777. *2β-Hydroperoxy-6α-hydroxy-allohimachal-3-ene* (**7**): Oil. $[\alpha]_D$ -8.4

(*c* 0.20, $CHCl_3$). IR υ_{max} 3321 (br), 3028, 2932, 2855 cm^{-1}; ^1H and ^{13}C NMR, Tables 1 and 2; EIMS (70 eV, *m/z*, %) 254 (1), 236 (7), 219 (18), 203 (10), 161 (10), 154 (18), 135 (20), 123 (25), 109 (50), 95 (58), 69 (100); HRMS 254.1882 calcd for $C_{15}H_{26}O_3$ (M^+), found 254.1880; 236.1776 calcd for $C_{15}H_{24}O_2$ (M^+ - H_2O), found 236.1776.

Conversion of 6 into 8 and 9 in $CDCl_3$. Compound **6** (5 mg) was dissolved in $CDCl_3$ (0.6 ml) in an NMR tube and left under ambient conditions for 3 days after which it was subjected to HPLC (15 % EtOAc/hexane) resulting in **8** (0.7 mg, R_t 24.0 min) and **9** (2.7 mg R_t 9.1 min). *Tsangane E* (**8**): see ref. 1 for physical data. *Cyclic enol ether* (**9**): Oil. $[\alpha]_D$ +119.7 (*c* 0.09, $CHCl_3$); EIMS (70 eV, *m/z*, %) 236 [M^+] (0.1), 211 (10), 167 (8), 155 (45) 149 (50), 99 (100); ^1H and ^{13}C NMR, Tables 1 and 2; HRMS 236.1776 calcd for $C_{15}H_{24}O_2$ (M^+), found 236.1747; CIMS 237 [M+1] (100), 219 (50), 191 (13), 161 (18), 123 (19). *Calculation of the rate of conversion of 6 into 8 and 9 in* $CDCl_3$ *by* ^1H *NMR.* ^1H NMR spectra were recorded at 12-24 h intervals during the conversion of **6** into **8** and **9** and characteristic integrals were determined for a well-resolved signal (H-2) associated with each compound (**6**, δ_H 5.56, 1H, s; **8**, δ_H 5.40, 1H, s; **9**, δ_H 6.17, 1H, s). The rate of reaction for **6** → **8** was determined by plotting the logarithm of the ratio of the integral for H-2 of starting material **6** to the integral of H-2 for product **8** against time and determining the slope of the resulting line. The rate of reaction for **6** → **9** was determined in similar fashion.

Conversion of 7 into 10 in $CDCl_3$. Compound **7** (2 mg) was dissolved in $CDCl_3$ (0.6 ml) in an NMR tube and left under ambient conditions for 2 days resulting in clean conversion to **10** (2 mg) without any need for further purification. *4β-Hydroperoxy-6α-hydroxy-allohimachal-2-ene* (**10**): Oil. $[\alpha]_D$ +67.9 (*c* 0.16, $CHCl_3$). IR υ_{max} 3530, 3308 (br), 2930, 2872, 2853, 1458, 1369 cm^{-1}; ^1H and ^{13}C NMR, Tables 1 and 2; EIMS (70 eV, *m/z*, %) 254 [M^+] (0.1), 236 [M^+-H_2O] (60), 221 (20), 219 (18), 192 (85), 177 (80), 135 (80), 109 (100); HRMS 254.1882 calcd for $C_{15}H_{26}O_3$ (M^+), found 254.1885; 236.1776 calcd for $C_{15}H_{24}O_2$ (M^+ - H_2O), found 236.1772. *Calculation of the rate of conversion of 7 into 10 in* $CDCl_3$ *by* ^1H *NMR.* ^1H NMR spectra were recorded at approximately 12 h intervals during the conversion of **7** into **10** and characteristic integrals were determined for a well-resolved signal associated with each compound (**7**, δ_H 4.58, 1H, d, J = 4.8 Hz, H-2; **10**, δ_H 4.38, 1H, d J = 5.8 Hz, H-4). The rate of reaction for **7** → **10** was determined by plotting the logarithm of the ratio of H-2 for starting material **7** to the integral of H-4 for product **10** against time and determining the slope of the resulting line.

Conversion of 10 into 5 and 13 in $CDCl_3$*/TFA.* Compound **10** (2 mg) was dissolved in $CDCl_3$ (0.6 ml) in an NMR tube. TFA (2μl) was added to the solution resulting in complete conversion to **5** (as determined by ^1H NMR) within less than 10 min. On standing for 4 weeks in $CDCl_3$/TFA solution, **5** was completely converted to its trifluoroacetic acid ester **13**. *Tsangane J* (**5**): see ref. 1 for physical data. *Tsangane J 6-OH trifluoroacetic acid ester (13)* Oil. ^{1}H and ^{13}C NMR, Tables 1 and 2. EIMS (70 eV; *m/z*; %) 350 (3), 332 (8), 289 (14), 274 (28), 236 (48), 193 (30), 175 (44), 161 (50), 149 (55), 123 (55), 109 (80), 93 (65), 69 (100); HRMS 350.1705 calcd for $C_{17}H_{25}F_3O_4$ (M^+), found 350.1702.

Transformation of 9 in CDCl3/TFA. Compound **9** (5 mg) was dissolved in $CDCl_3$ (0.6 ml) in an NMR tube. TFA (2μl) was added to the solution and the sample left for 3 days after which solvent was removed. HPLC (30 % EtOAc/hexane) of the residue yielded compound **15** (1.6 mg, R_t 13.6 min). (**15**): Oil. IR υ_{max} 3485 (br), 2939, 2872, 1713, 1464, 1367 cm^{-1}; ^{1}H and ^{13}C NMR, Tables 1 and 2. EIMS (70 eV; *m/z*; %) 254 (4), 253 (10), 237 (85), 236 (10), 221 (34), 191 (8), 178 (30) 163 (100), 161 (20); HRMS 254.1882 calcd for $C_{15}H_{26}O_3$ (M^+), found 254.1876; 236.1776 calcd for $C_{15}H_{24}O_2$ (M^+-H_2O), found 236.1773. *Calculation of the percentages of each component as a function of time in the conversion of 9 to 15/16/17 via 14 in CDCl3/TFA by ^{1}H NMR.* ^{1}H NMR spectra were recorded at 5-90 min intervals following treatment of **9** with TFA and integrals were determined for a characteristic signal associated with each compound present in the mixture (**9**, δ_H 3.87, 1H, dd, J = 8.0, 1.8 Hz, H-6); **14**, δ_H 9.75, 1H, s, H-2; **15**, δ_H 5.18, 1H, d, J = 5.8 Hz, H-2; **16**, δ_H 5.35, 1H, d, J = 6.1 Hz, H-2; **17**, δ_H 3.73, 1H, d, J = 10.5 Hz, H-6; see Figure 4). The percentage composition for each of compounds **9**, **14**, **15**, **16** and **17** in the mixture at a given time was then determined by dividing the integral for each species by the sum of such integrals for all compounds; the product distribution data calculated for thirteen time points (including t=0 min before addition of TFA) in this manner is plotted against time in Figure 3 .

ACKNOWLEDGEMENTS

We thank the CRCG for funding this research.

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