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Autoxidation of 4-amorphen-11-ol and the biogenesis of *nor*- and *seco*-amorphane sesquiterpenes from *Fabiana imbricata*

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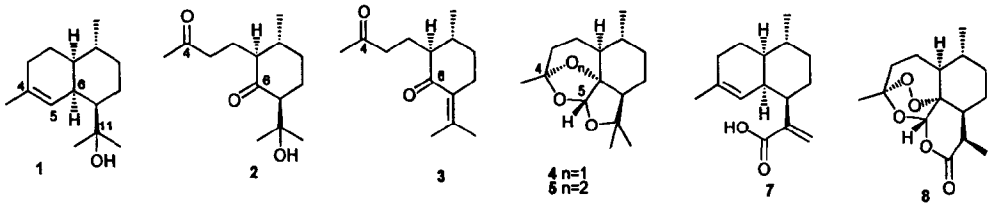
Abstract: Photooxidation of 4-amorphen-11-ol (**1**), recently reported as one of the major sesquiterpene natural products from the medicinal plant *Fabiana imbricata*, results in three allylic hydroperoxides **6**, **9** and **10**, which are expected from the "ene-type" reaction of molecular oxygen with the tri-substituted double bond in **1**. The tertiary allylic hydroperoxide **6** undergoes carbon-carbon bond cleavage and a second autoxidation reaction to yield the more highly oxygenated *seco*-amorphane **11** under very mild conditions. In acid, this compound may then undergo either a second carbon-carbon bond cleavage reaction to yield *nor*-sesquiterpenes **2** and **3** (reported as *bona fide* natural products from *F. imbricata*), or cyclize to the sesquiterpene peroxofabianane (**5**), which is a presumed precursor to the natural product fabianane (**4**). Some mechanistic investigations concerning the two chemical processes: *viz*:- carbon-carbon bond cleavage and autoxidation which would account for the formation of natural products **2**, **3** and **4** from **1** are reported. Tertiary allylic hydroperoxide **32**, which lacks the 11-hydroxyl functional group present in **1** undergoes only C-4/C-5 carbon-carbon bond cleavage under more forcing conditions, suggesting a role for this functional group in assisting the autoxidation reactions of 4-amorphen-11-ol.

INTRODUCTION

The medicinal plant *Fabiana imbricata* (Ruiz. and Pav.), used by the Mapuche indians of central Chile for treating tumours and kidney afflictions,[1-3] has been the subject of several phytochemical investigations this decade,[4-7] resulting in the isolation of over twenty amorphane and muurolane sesquiterpenes. Amongst these are the 11- hydroxy-amorphene **1**,[4] the *nor*-amorphanes **2** and **3**[5] and the 4,5-*seco*-amorphane, fabianane[6] (**4**) – one of only three such sesquiterpenes known from nature (the others are desoxyartemisinin[8] from *Artemisia annua* and macnabin[9] from *Cupressus macnabiana*). Jung and Youn[10] were recently able to demonstrate that peroxofabianane (**5**), the peroxo analogue of fabianane, could be produced from 4-amorphen-11-ol (**1**) (which they obtained by partial synthesis from artemisinic acid - a non-commercially available starting material which can be isolated from *Artemisia annua*)[8,11,12] in low yield (27%) *via* photooxidation to the intermediate tertiary allylic hydroperoxide **6**. The methodology employed by these workers followed closely on that described for the oxidative transformation of artemisinic acid (**7**) to the important anti-malarial sesquiterpene artemisinin (**8**), which has been the subject of detailed mechanistic investigations.[13-16]



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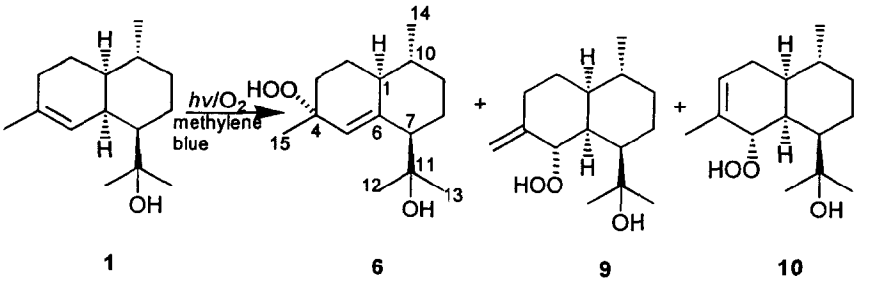
Having recently achieved a total synthesis of 4-amorphen-11-ol from commercially available (-)-isopulegol,[17] we resolved to perform a detailed investigation of this transformation reaction with a view to defining the evidently complex mechanism involved in rearrangement/oxidation of 4-amorphen-11-ol (**1**), improving the yield of peroxofabianane (**5**) (which is of some interest for anti-malarial testing) and also establishing whether the biogenesis of degraded and cleaved sesquiterpene natural products such as **2, 3** and **4** might be simply explained in terms of such autoxidation/rearrangement chemistry.

RESULTS AND DISCUSSION

Photooxidation of 4-amorphen-11-ol (**1**)

As expected, the "ene-type" reaction of the tri-substituted double bond in **1**[17] with singlet oxygen[18] in the presence of a photosensitizer resulted in all three possible oxidation products **6**, **9** and **10** (Scheme 1) with the tertiary allylic hydroperoxide **6** dominating in the mixture. The three hydroperoxides were easily separated by HPLC and complete NMR assignments were made for each isomer by means of 2D-NMR (HSQC, HMBC and ^{1}H-^{1}H COSY) - see Table 1. Knowledge of ^{1}H NMR assignments for each compound was then particularly useful in demonstrating the α-stereochemistry for the new hydroperoxide group of all three compounds by means of correlations observed in NOESY spectroscopy. Complete NMR assignments (Tables 1-5) and relative stereochemistry for all other compounds reported herein were made in the same manner.



Scheme 1. Photooxidation of 4-amorphen-11-ol (**1**) yielding tertiary allylic hydroperoxide **6** and secondary allylic hydroperoxides **9** and **10**.

The rearrangement of 4α-hydroperoxy-5-amorphen-11-ol (6) in the presence of trifluoroacetic acid (TFA)

Compound **6** was treated with TFA in petroleum ether according to a protocol described for a tertiary hydroperoxide derived by reduction and photooxidation of artemisinic acid (**7**), which is reported to result in conversion to artemisinin (**8**) in low yield (30%).[19] In the event, this procedure resulted in a complex mixture containing compounds **2, 5, 11** and **12**. Trioxane ring-containing **5**,[10] which is the 11-oxo analogue of artemisinin (**8**), was isolated in 29% yield, whilst *nor*-sequiterpene **2**, previously reported as a natural product from *F. imbricata*,[5] was obtained as a minor product together with more substantial amounts of its formyl ester,

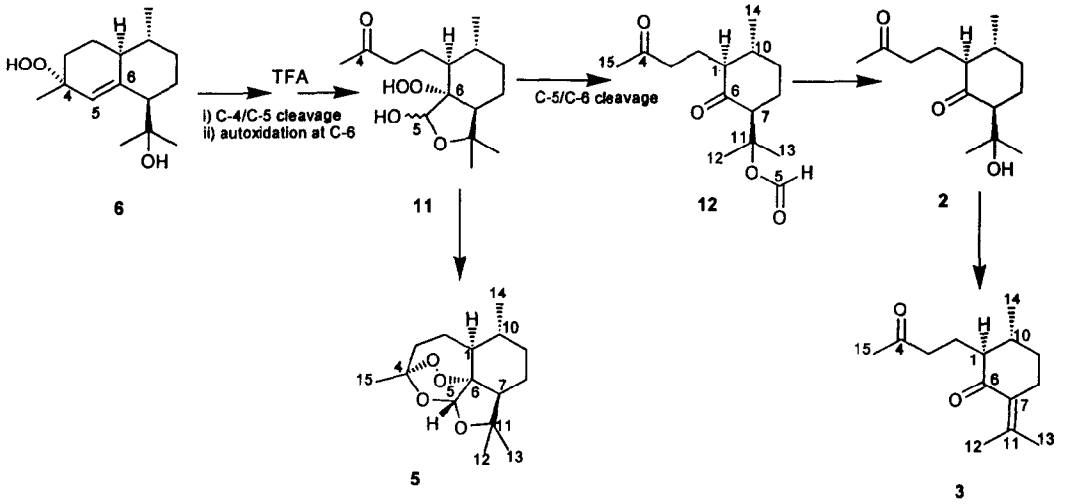
Table 1. NMR assignments for allylic hydroperoxides **6, 9, 10** and **32**

	^{13}C				^{1}H			
Atom	**6**	**9**	**10**	**32**	**6**	**9**	**10**	**32**
1	45.5	47.3	46.6	45.1	1.53	1.42	1.37	1.55
2α	23.0	29.4	27.8	23.4	1.97	1.95	2.13	1.97
2β					1.43	1.38	2.13	1.43
3α	28.9	29.7	126.1	29.4	1.48	2.19	5.64	1.53
3β					1.89	2.24		1.88
4	80.6	147.8	131.9	81.3	-	-	-	-
5	122.7	84.4	83.0	119.8	5.71	4.71	4.50	5.26
6	145.2	44.5	36.9	148.5	-	2.08	2.73	-
7	55.4	53.8	53.0	49.8	1.99	1.41	1.55	1.66
8α	30.5	22.1	23.1	28.8	1.94	1.77	1.68	1.84
8β					1.22	1.66	1.53	1.00
9α	35.9	36.8	36.3	35.7	1.21	1.08	1.03	1.15
9β					1.81	1.94	1.80	1.77
10	39.2	29.1	28.9	38.9	1.28	1.78	1.37	1.22
11	73.0	72.2	73.4	27.1	-	-	-	2.01
12[a]	26.7	28.9	30.6	22.3	1.35	1.21	1.40	0.95
13[a]	29.8	28.9	28.1	18.5	1.33	1.24	1.29	0.87
14	20.0	20.0	20.3	20.1	0.93	0.87	0.80	0.93
15	24.5	107.0	19.7	24.5	1.29	5.17	1.80	1.31
						4.94		

[a] Assignments interchangeable within column

seco-floribundione, **12** (previously reported as a natural product from *Liabum floribundum*).[20] The other major product from the reaction was the novel tertiary hydroperoxide *hemi*-acetal **11** which was characterized as a mixture of diastereoisomers. The sequence of reactions involved in conversion of **6** to compounds **2, 5, 11** and **12** was established by treating $CDCl_3$ solutions of each compound in turn with TFA and following the resulting transformations by ^1H NMR spectroscopy. Thus, peroxofabianane (**5**) was stable in $CDCl_3$/TFA over a period of several weeks whilst **12** was slowly converted into **2** and then into conjugated ketone **3** (also previously reported as a natural product from *F. imbricata*).[5] Compound **11** underwent more rapid conversion to both **5** (major product) and **12** (minor product) in $CDCl_3$/TFA. These results are summarized in Scheme 2.

In further studies, it was found that tertiary allylic hydroperoxide **6** could be cleanly converted to intermediate **11** simply by allowing it to stand in $CDCl_3$ solution under ambient conditions, without concomitant production of any of the other products described in Scheme 2. Since, as observed above, a $CDCl_3$ solution of **11** can be converted into **5** in reasonable yield by treatment with TFA, we have therefore been able to achieve a synthesis of peroxofabianane (**5**) from 4-amorphen-11-ol (**1**) *via* the tertiary hydroperoxide **6** in two steps (photooxidation of **1** to **6**; conversion of **6** to **11** in $CDCl_3$ and subsequent addition of TFA to this solution to promote cyclization of **11** to **5**) in a moderate overall yield (49%). 2D-NMR analysis of peroxofabianane (**5**) (Table 2) revealed that several of the ^1H NMR assignments previously reported for this compound were incorrect.[10]



Scheme 2. Proposed relationships between *nor*-sesquiterpenes **2** and **3** and *seco*-sesquiterpenes **5**, **11** and **12** isolated from treatment of **6** with TFA in petroleum ether.

Clearly, conversion of **6** to **11** involves both C-4/C-5 carbon-carbon bond cleavage and a subsequent autoxidation at C-6, whilst further conversion of **11** to **12** involves a second C-5/C-6 carbon-carbon bond cleavage reaction. In the next sections, we set out to further investigate the mechanisms for each of these reactions.

The mechanism of the first carbon-carbon bond cleavage (C-4/C-5) in the conversion of 6 to 11

In order to study the initial C-4/C-5 carbon-carbon bond cleavage reaction independently of the subsequent autoxidation which introduces a hydroperoxyl group at C-6 of compound **11**, a $CDCl_3$ solution of tertiary allylic hydroperoxide **6** was treated with TFA under an atmosphere of nitrogen (see Experimental). Under these conditions, no signals corresponding to any of the compounds **2**, **3**, **5**, **11** or **12** were observed in ^1H NMR spectra: the sole product which could be isolated after several days was α,β-unsaturated ketone **13**. Study of the course of this reaction by acquisition of both 1D- and 2D-NMR spectra at periodic intervals suggested that cyclic enol ether **14** and diastereoisomeric *hemi*-acetals **15a/15b** (Table 3) were formed within a few hours of addition of TFA and were subsequently converted into **13** over the next few days (Scheme 3). However, the structures of intermediates **14** and **15** must remain tentative since 2D-NMR analyses were made of complex mixtures in which several NMR signals overlapped and these compounds could not be isolated by HPLC.

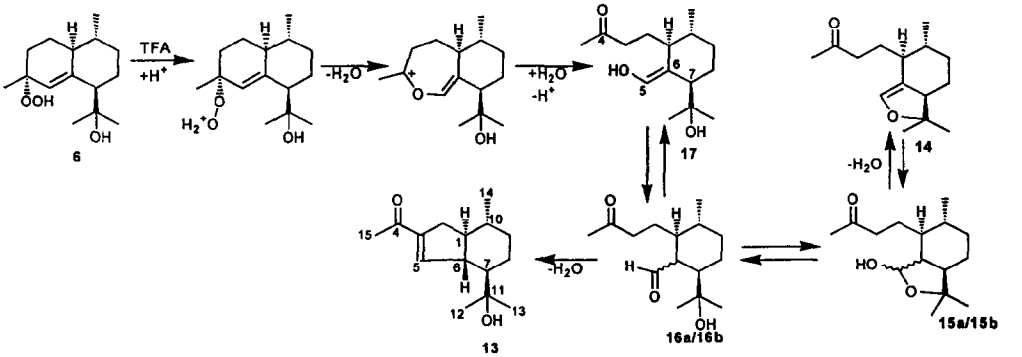
The structure of compound **13** is clearly suggestive of derivation from keto-aldehyde intermediate **16** by an intramolecular aldol reaction as shown in Scheme 3. In turn, compound **16** is the aldehyde tautomer of the enol cleavage product **17** which is the expected product from Hock cleavage[18,21] of tertiary hydroperoxide **6**

Table 2. NMR assignments for **2, 3, 5, 11** and **12** from rearrangement and further autoxidation of allylic hydroperoxide **6** in the presence of TFA.

	^{13}C					^{1}H				
	2	**3**	**5**	**11a/11b**[a]	**12**	**2**	**3**	**5**	**11a/11b**[a]	**12**
1	57.6	57.1	49.2	43.1/42.6	57.5	2.04	1.96	1.49	1.71/1.80	2.06
2	20.0	23.1	24.5	23.5/22.0	20.2	1.78 1.78	1.92 1.76	1.95 (α) 1.38 (β)	2.08/2.33 1.67/1.38	1.76 1.76
3	41.3	41.3	37.4	43.5/43.3	41.4	2.52 2.38	2.53 2.48	2.29 (α) 2.05 (β)	2.80/2.80 2.68/2.68	2.52 2.31
4	208.7	209.2	103.4	214.3/209.6	208.8	-	-	-	-	-
5	-	-	96.4	100.4/99.0	160.4	-	-	5.59	5.07/5.26	7.99
6	216.4	204.3	87.3	97.4/91.3	210.5	-	-	-	-	-
7	59.7	133.0	52.2	45.9/47.4	57.7	2.38	-	1.96	2.32/2.41	3.22
8α 8β	29.3	28.1	26.4	25.6/26.5	28.7	2.13 1.57	2.60 2.35	1.75 1.33	1.75/1.78 1.65/1.31	2.14 1.56
9α 9β	34.5	31.4	32.8	34.0/33.9	34.5	1.54 1.91	1.41 1.81	1.02 1.61	1.01/1.01 1.59/1.59	1.52 1.90
10	40.7	36.1	37.0	35.2/36.2	40.9	1.61	1.73	1.21	1.77/1.29	1.59
11	71.2	140.8	83.8	85.9/83.0	84.6	-	-	-	-	-
12[b]	28.7	22.5	30.2	31.1/30.6	24.9	1.24	1.89	1.58	1.44/1.58	1.63
13[b]	26.1	21.6	25.5	26.7/25.7	23.6	1.20	1.75	1.24	1.29/1.19	1.51
14	20.6	20.6	20.0	21.6/21.4	20.5	1.08	1.04	0.98	0.94/0.99	1.08
15	29.7	30.0	25.5	30.2/29.7	29.2	2.14	2.14	1.44	2.20/2.20	2.12

[a] **11a** = major diastereoisomer; **11b** = minor diastereoisomer

[b] Assignments within column interchangeable



Scheme 3. Postulated mechanism for the C-4/C-5 cleavage reaction of **6** (as observed in $CDCl_3$/TFA under a nitrogen atmosphere).

(involving a 1,2-shift of the alkene group to the internal oxygen atom of this hydroperoxide, which accompanies loss of the terminal oxygen atom as water - see Scheme 3). Enol **17**, the proposed initial cleavage product, was very tentatively identified from a strong peak (δ_H ($CDCl_3$/TFA) 6.30 ppm, s) which rapidly disappeared from ^1H NMR spectra over the first 20 minutes of the reaction. A characteristic aldehyde peak (δ_H 9.75 ppm, d, J = 6.4 Hz) which might be assigned to compound **16** was also evident at a low but constant intensity over several days

in ^{1}H NMR spectra from a $CDCl_3$ solution of **6** left to stand under a normal atmosphere (ultimately yielding **11** as the sole product; see previous section). Thus, we conclude that C-4/C-5 rupture of **6** proceeds by Hock cleavage, producing enol **17** as the initial cleavage product.

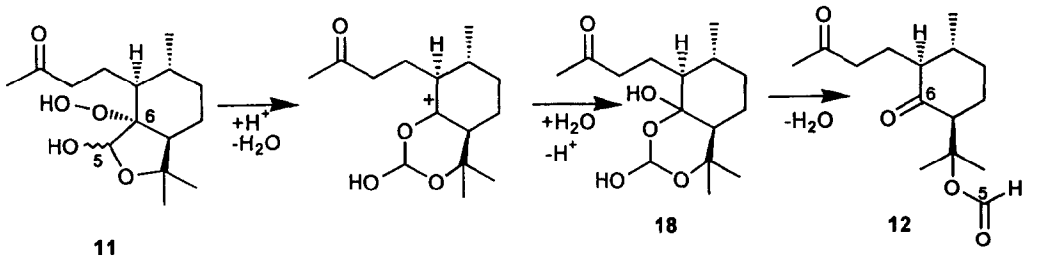
Table 3. NMR assignments for products **13**, **15**, **33** and **34** from rearrangement of allylic hydroperoxides **6** and **32** in $CDCl_3$/TFA in the absence of a second autoxidation reaction.

	^{13}C				^{1}H			
	13	**15a/15b** [a]	**33**	**34**	**13**	**15a/15b** [a]	**33**	**34**
1	55.3	41.3/41.8	46.5	47.1	1.33	1.30/1.22	1.09	1.81
2	33.3	22.8/22.8	24.8	35.2	1.97 (α) 2.66 (β)	1.80/1.75 1.11/1.10	1.94 1.24	2.48 2.48
3	145.4	38.2/39.7	41.0	147.2	-	2.46/2.51 2.40/2.38	2.64 2.34	-
4	197.6	210.8/211.0	208.7	201.1	-	-	-	-
5	150.0	97.4/100.8	207.5	149.2	7.40	5.28/6.32	9.97	6.95
6	53.6	51.6/51.6	51.6	50.1	2.17	1.60/1.60	2.69	3.13
7	52.3	49.9/49.2	47.8	44.8	1.43	1.78/1.61	1.18	1.16
8α 8β	29.8	25.7/25.7	26.4	27.8	1.78 1.07	1.68/1.68 1.11/1.11	1.86 1.48	1.84 0.80
9α 9β	35.6	35.4/35.4	36.3	34.1	1.02 1.81	1.15/1.21 1.80/1.80	1.11 1.91	0.88 1.65
10	36.3	34.0/35.2	33.4	32.2	1.45	1.25/1.25	1.64	1.63
11	74.0	84.4/86.9	30.9	31.3	-	-	1.45	1.61
12[b]	30.9	28.9/29.1	20.8	21.0	1.27	1.29/1.35	0.91	0.94
13[b]	24.0	23.7/23.2	20.6	21.4	1.17	1.03/1.09	0.93	0.99
14	20.1	19.2/19.0	21.2	21.0	0.92	0.93/0.96	0.94	0.87
15	26.2	29.9/29.8	29.9	26.1	2.30	2.18/2.18	2.14	2.39

[a] **15a** = major diastereoisomer, **15b** = minor diastereoisomer; assignments made as a mixture with compounds **13** and **14** in $CDCl_3$/TFA.
[b] Assignments interchangeable within column.

The mechanism of the second carbon-carbon bond cleavage (C-5/C-6) in the conversion of 11 to 12.

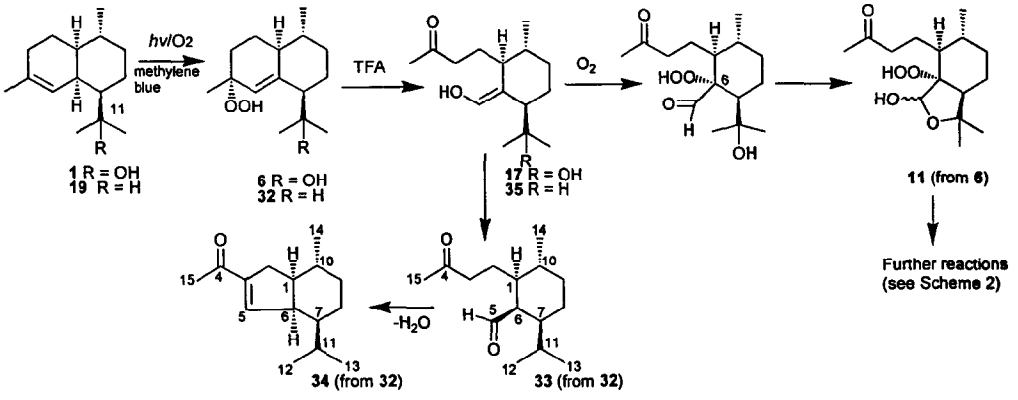
Although the conversion of **11** to **5** (major product) and **12** (minor product) in $CDCl_3$/TFA (Scheme 2) was considerably faster than that of **6** to **13** in $CDCl_3$/TFA (Scheme 3) - occurring over a period of hours rather than days - it was still sufficiently slow to allow the course of the reaction to be charted by recording frequent ^{1}H NMR spectra and also for the structure of proposed intermediate **18** in the second C-5/C-6 cleavage reaction to be tentatively established from such ^{1}H-NMR data (even though compounds **5**, **11** and **12** were also present in the mixture). The proposed mechanism for the conversion of **11** into **12** in the presence of TFA (Scheme 4) involves a 1,2-shift of the *hemi*-acetal group to the internal oxygen atom of the tertiary hydroperoxide group (accompanying loss of the terminal oxygen atom as water) in a manner exactly analogous to that proposed for the 1,2-shift of the alkene which resulted in C-4/C-5 carbon-carbon bond cleavage of **6** (Scheme 3).



Scheme 4. Postulated mechanism for the C-5/C-6 cleavage reaction of **11** in the presence of TFA.

The role of the 11-hydroxy group in assisting the "second" autoxidation reaction at C-6 in the conversion of 6 to 11

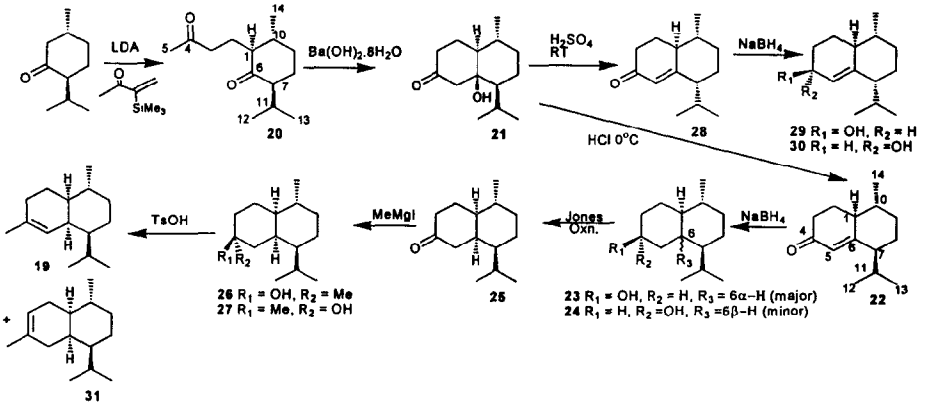
The origin of the tertiary hydroperoxide group in compound **11** can be most simply explained as the result of a "second" "ene-type" addition of molecular oxygen (*c.f.* first section) to the enolic double bond of Hock cleavage product **17** (Scheme 5), which is proposed to be formed during C-4/C-5 cleavage of **6** (Scheme 3). Assuming this mechanism, we were intrigued to note that this reaction seemed to be occuring rapidly in the absence of photosensitizer. Following a recent precedent for the unsensitized photooxidation of a tri-substituted double bond which is assisted by other functional groups in the molecule,[22] we wondered whether the 11-hydroxy group might be assisting this "second" autoxidation reaction in some way. (The alternative possibility that the more highly nucleophilic character of the enolic double bond in **17** might in itself be sufficient to facillitate rapid reaction with electrophilic oxygen in the absence of photosensitizer was also deemed worthy of investigation). In order to determine whether there was a role for the 11-hydroxy group of 4-amorphen-11-ol in promoting this "second" autoxidation reaction, we set out to synthesize 4-amorphene (**19**), in which this functional group is absent, and then subjected it to the same oxidation experiments as have been described for **1**.



Scheme 5. The role of the 11-hydroxy group in assisting the "second" autoxidation which yields compound **11**.

In the event, the most successful strategy for the synthesis of 4-amorphene (**19**) turned out to be by employing (-)-menthone as starting material in a synthetic route (Scheme 6) which was closely related to that reported for the synthesis of 4-amorphen-11-ol (**1**) from (-)-isopulegol in the companion paper.[17] It will not therefore be elaborated upon in detail here, except to point out two notable differences in the syntheses of **1** and **19**, which are presumed to be due to the presence of an isopropyl group rather than an isopropenyl group in (-)-menthone which was used as starting material in the synthesis of **19**. Firstly, the kinetic product of Robinson annulation, α,β-unsaturated ketone **22**, preferentially undergoes 6α-conjugate reduction. This is presumably the result of steric hindrance to the β-face of the molecule by the bulky 7β-isopropyl group in which C-11 is sp^3 hybridized. By contrast, the planar 7β-isopropenyl group (in which C-11 is sp^2-hybridized) of the analogue of **22** employed in the synthesis of **1** (i.e. compound **9** in the companion paper) underwent smooth conjugate reduction equally from both the α- and β-faces of the molecule, perhaps as a result of this substituent being able to adopt a conformation perpendicular to the plane of the decalenone ring which does not hinder attack from either face of the molecule.[17] Interestingly, the thermodynamic annulation product[23] **28** in which the 7α-isopropyl group is axial, did not undergo conjugate reduction at all under the same conditions – only products of direct reduction of the carbonyl group (**29** and **30**) were observed, which might again be ascribed to increased steric hindrance by this substituent. Secondly, dehydration of the tertiary alcohol group in Grignard addition product **26/27** was readily affected by *p*-toluenesulfonic acid resulting in the desired alkene **19** (together with its regioisomer **31**) - by contrast, treatment of the 7β-isopropenyl analogues of **26/27** (i.e. compounds **22/21** in the companion paper) with *p*-toluenesulfonic acid[17] resulted in extensive double bond migrations and eventual aromatization, requiring that an alternative dehydration procedure (conversion of the tertiary alcohol to a mesylate, followed by base-catalysed elimination) be adopted in the synthesis of **1**.

As expected, 4-amorphene (**19**) could be readily converted into the corresponding tertiary allylic hydroperoxide (**32**) (Table 1) by treatment with singlet molecular oxygen (Scheme 5). However, unlike its 11-



Scheme 6. Synthesis of 4-amorphene (**19**) from (-)-menthone.

hydroxy analogue **6**, compound **32** was stable in $CDCl_3$ solution over a period of several weeks under ambient conditions. Carbon-carbon bond cleavage of **32** could only be affected under more forcing conditions (by addition of TFA to the $CDCl_3$ solution) resulting in slow conversion into aldol condensation product **34** *via* aldehyde **33** (Table 3) over the period of one week. No other products of further autoxidation reactions were detectable even on prolonged TFA treatment of **32**. These findings contrast sharply with the complex autoxidation/rearrangement chemistry observed for tertiary allylic hydroperoxide **6** in the presence of TFA (Scheme 2). In order to obtain the corresponding intramolecular aldol addition product **13** from the C-4/C-5 cleavage reaction of **6**, it was neccessary to rigorously exclude oxygen from solution (Scheme 3). Since the only difference between the enol cleavage products **35** and **17** (both arising by Hock cleavage of the corresponding hydroperoxides), is the absence of the 11-hydroxyl group in the former, it can be inferred that this group does indeed assist the "second" autoxidation reaction of **17** involved in the transformation of **6** to **11**.

Table 4. ^{13}C NMR assignments for intermediates in the synthesis of **19**.

	19	**20**	**21**	**22**	**23**	**24**	**25**	**26**	**27**	**28**	**29**	**30**	**31**
1	42.2	57.1	50.9	45.9	43.4	48.4	43.1	43.9	43.6	41.1	40.4	40.2	42.8
2	26.0	20.4	25.5	25.3	26.4	28.9	28.0	25.9	23.8	25.9	22.9	25.2	28.0
3	26.7	41.5	41.1	34.9	30.6	35.7	37.1	35.4	33.7	35.7	30.3	31.7	119.0
4	134.7	208.9	211.0	200.1	72.2	71.3	213.0	72.2	70.1	199.9	65.4	67.4	132.6
5	121.2	29.8	51.9	121.9	30.6	39.2	38.1	35.4	33.6	125.5	123.5	125.6	26.8
6	38.0	213.3	78.1	170.0	37.7	42.6	40.1	36.7	33.8	169.9	147.5	145.4	34.9
7	48.8	57.2	50.9	51.2	48.4	47.7	48.1	48.4	48.4	52.5	51.7	51.4	48.5
8	26.5	29.6	20.4	29.1	25.4	24.2	24.7	25.3	25.3	28.8	28.7	28.8	25.0
9	36.0	34.9	35.4	35.2	36.4	35.7	35.8	36.3	36.3	29.9	30.2	30.3	36.3
10	27.7	40.6	32.4	39.0	27.4	37.4	27.2	26.8	26.5	39.5	39.8	40.1	27.9
11	28.8	26.3	25.5	26.9	29.1	26.3	28.9	29.0	28.9	27.3	26.5	26.3	29.2
12[a]	21.7	21.5	23.6	22.0	21.5	21.5	21.3	21.5	21.5	21.5	21.6	21.7	21.4
13[a]	20.7	18.8	18.1	18.4	20.7	15.0	20.5	20.5	20.7	20.8	20.9	20.9	20.9
14	19.9	20.6	20.3	20.3	19.7	20.3	19.7	19.8	19.9	20.2	20.4	19.9	20.2
15	23.7	-	-	-	-	-	-	26.3	32.0	-	-	-	23.6

[a] Assignments interchangeable within column

It should be noted that the aldehyde group in C-4/C-5 cleavage product **33** was clearly shown to be β- by NOESY spectroscopy and to assume an axial conformation with respect to the cyclohexane ring - this may be because, in this conformation, steric interaction with the neighbouring equatorial 1- and 7-substituents on the ring is minimized, making this the thermodynamically more stable configuration. This configuration is also observed in aldol condensation product **34**, for which H-6 was shown to be α- by NOESY. By contrast, H-6 in aldol condensation product **13** (Scheme 3) has a β-configuration, which requires that the aldehyde group in the presumed precursor **16** be α-orientated. Although compound **16** was never isolated, this would seem to be a

reasonable proposition because an equatorial conformation for such an aldehyde ring-substituent would allow for the possibility of intramolecular hydrogen bonding with the 11-hydroxy group, perhaps outweighing the unfavourable steric interactions which force aldehyde **33** to adopt the opposite configuration at C-6.

Table 5. ^{1}H NMR assignments for intermediates in the synthesis of **19**.

	19	**20**	**21**	**22**	**23**	**24**	**25**	**26**	**27**	**28**	**29**	**30**	**31**
1	1.18	2.03	1.29	1.85	1.07	0.56	0.94	1.10	1.11	1.99	1.59	1.65	1.14
2α	1.54	1.82[b]	2.06	2.17	1.31	2.00	1.65	1.35	1.62	2.21	1.81	1.94	2.01
2β	1.92	1.78[b]	1.68	1.81	1.93	0.88	2.20	1.86	1.75	1.70	1.46	1.16	2.13
3α	1.91	2.34[b]	2.29	2.28	1.82	1.18	2.22	1.45	1.45	2.25	1.68	1.99	5.26
3β	1.79	2.55[b]	2.44	2.36	1.65	1.99	2.32	1.54	1.37	2.39	1.57	1.27	
4	-	-	-	-	3.59	3.57	-	-	-	-	4.16	4.14	-
5α	5.23	2.12	2.22	5.86	1.72	0.78	2.34	1.43	1.42	5.82	5.50	5.40	1.88
5β			2.74		1.30	2.17	2.14	1.36	1.29				1.62
6	2.51	-	-	-	1.84	0.91	2.26	1.87	2.12	-	-	-	2.08
7	0.91	2.10	1.29	1.88	0.99	0.99	1.11	0.99	0.99	1.91	1.65	1.65	1.02
8α	1.65	2.10	1.57	2.00	1.65	1.62	1.76	1.65	1.64	2.00	1.90	1.90	1.69
8β	0.91	1.30	1.41	1.15	1.08	0.99	1.13	1.08	1.04	1.54	1.42	1.42	1.19
9α	0.90	1.47	1.07	1.25	0.95	0.99	1.04	0.92	0.94	1.40	1.26	1.29	0.94
9β	1.62	1.86	1.80	1.87	1.73	1.70	1.85	1.72	1.70	1.56	1.45	1.46	1.64
10	1.41	1.55	1.42	1.52	1.65	0.99	1.80	1.69	1.58	1.42	1.23	1.11	1.37
11	1.56	2.06	2.05	2.01	1.39	1.98	1.29	1.36	1.36	1.89	1.77	1.77	1.39
12[a]	0.91	0.89	0.91	0.96	0.88	0.88	0.88	0.88	0.87	0.77	0.73	0.79	0.88
13[a]	0.89	0.86	0.88	0.88	0.86	0.70	0.86	0.85	0.88	0.97	0.90	0.90	0.89
14	0.86	1.06	0.95	1.04	0.83	0.87	0.94	0.82	0.83	1.03	0.96	0.92	0.81
15	1.62	-	-	-	-	-	-	1.27	1.21	-	-	-	1.62

[a] Assignments interchangeable within column
[b] Assignment as α or β not applicable

Conclusion

Conversion of 4α-hydroperoxy-5-amorphen-11-ol (**6**) into the highly-oxygenated *seco*-sesquiterpene **11**, involving Hock cleavage of the allylic hydroperoxide group and a "second" "ene-type" reaction of the enolic tri-substituted double bond of the cleavage product with molecular oxygen, is a facile process in $CDCl_3$ soution and occurs without the requirement for a photosensitizer. In addition, it can be shown that 4-amorphen-11-ol (**1**) itself will also undergo conversion to **11** over a period of several weeks, as the result of a spontaneous "first" autoxidation reaction of the tri-substituted double bond **1** in $CDCl_3$ solution, which also occurs in the absence of photosensitizer, albeit very much more slowly than the "second" autoxidation reaction described above. Compound **11** was then found to be a precursor of both natural product *nor*-amorphanes **2** and **3** and the *seco*-amorphane **5** – itself a presumed precursor of natural product **4**, all of which have been recently described from *F. imbricata*. Since 4-amorphen-11-ol is one of the major sesquiterpenes present in *F. imbricata*, there exists the strong possibility that the latter stages of the biogenesis of each of compounds **2-4** might be explained simply in terms of the autoxidation/rearrangement chemistry of **1** that has now been described, occurring either within the

plant or during the extraction process, without the need to postulate any enzymic processes at all. Further, the 11-hydroxyl group has been shown to be a necessary structural feature required for inducing some of these spontaneous reactions of the Δ^4-double bond in **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 with $CDCl_3$ as solvent. Proton chemical shifts, multiplicities and integrals reported in this section are those which are clearly resolved in ^{1}H 1D-NMR spectra without recourse to 2D-NMR analysis (see Tables in text for 2D-NMR). HSQC and HMBC experiments were recorded with 2048 data points in F_2 and 128 data points in F_1. HREIMS were recorded at 70 eV on a Finnigan-MAT 95 MS spectrometer. FTIR spectra were recorded in $CHCl_3$ on a Shimadzu FTIR-8201 PC instrument. 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 x 25 cm column, flow rate 8 ml/min.

Photooxidation of 4-amorphen-11-ol (1). Methylene blue (3.8 mg) was added to a solution of 4-amorphen-11-ol (**1**) in acetone (35 mg/70 ml) and the mixture cooled in an ice-bath while irradiating with a tungsten lamp (500 W). The starting material had completely disappeared after 1 h (by TLC) and the solvent was removed on a rotary evaporator. The residue was taken up in Et_2O (80 ml) and filtered to remove most of the dye, after which solvent was removed to yield a crude product (36 mg, 90 %), which was subjected to preparative HPLC (35% EtOAc/hexane): **6** (30 mg, 75 %, R_f 25.4 min); **9** (3.3 mg, 8 %, R_f 13.1 min); **10** (1.2 mg, 3%, R_f 11.7 min). *4α-Hydroperoxy-5-amorphen-11-ol (6):* Oil. $[\alpha]_D$ +2.7 (*c* 0.5, $CHCl_3$); IR ν_{max} 3364 (br), 2932, 2870, 1456, 1373 cm^{-1}; ^{13}C NMR (125 MHz) see Table 1; ^{1}H NMR (500 MHz) δ 0.93 (3H, d, *J* = 6.2 Hz), 1.29 (3H, s), 1.33 (3H, s), 1.35 (3H, s), 2.17 (1H, br s, -OH), 5.71 (1H, s), 8.29 (1H, br s, -OOH); MS (EI) *m/z* (rel. intensity) 236 (M^+ - H_2O) (5), 205 (2), 178 (35), 163 (100), 162 (50), 147 (10), 107 (25); HRMS calcd. for (M^+ - H_2O) $C_{15}H_{24}O_2$ 236.1776, found 236.1771. *5α-Hydroperoxy-4(15)-amorphen-11-ol (9)*: Oil. $[\alpha]_D$ -140.5 (*c* 0.2, $CHCl_3$); IR ν_{max} 3414 (br), 3209 (br), 2937, 2872, 1456, 1225 cm^{-1}; ^{13}C NMR (125 MHz) see Table 1; ^{1}H NMR (500 MHz) δ 0.87 (3H, d, *J* = 6.3 Hz), 1.21 (3H, s), 1.24 (3H, s), 4.17 (1H, br s, -OH), 4.71 (1H, d, *J* = 11.2 Hz), 4.94 (1H, s), 5.17 (1H, s), 11.03 (1H, s, -OOH); MS (EI) *m/z* (rel. intensity) 236 (M^+ - H_2O) (2), 220 (15), 203 (65), 178 (50), 163 (100), 162 (85), 147 (70), 108 (55); HRMS calcd. for (M^+ - H_2O) $C_{15}H_{24}O_2$ 236.1776, found 236.1773. *5α-Hydroperoxy-3-amorphen-11-ol (10):* Oil. $[\alpha]_D$ +20.4 (*c* 0.08, $CHCl_3$); IR ν_{max} 3339 (br), 2930, 2855, 1460 cm^{-1}; ^{13}C NMR (125 MHz) see Table 1; ^{1}H NMR (500 MHz) δ 0.80 (3H, d, *J* = 5.6 Hz), 1.29 (3H, s), 1.40 (3H, s), 1.80 (3H, s), 2.13 (2H, s), 2.60 (1H, br s, -OH), 2.73 (1H, d, *J* = 9.5 Hz), 4.50 (1H, d, *J* = 9.5 Hz), 5.64 (1H, s), 8.90 (1H, br s, -OOH); MS (EI) *m/z* (rel. intensity) 236 (M^+ - H_2O) (3), 221 (15), 203 (70), 178 (40), 163 (100), 162 (75), 147 (25), 119 (20), 106 (38); HRMS calcd. for (M^+ - H_2O) $C_{15}H_{24}O_2$ 236.1776, found 236.1775.

Rearrangement/oxidation of 4α-hydroperoxy-5-amorphen-11-ol (6) in petroleum ether/trifluoroacetic acid (TFA). 4α-Hydroperoxy-5-amorphen-11-ol (**6**) (22 mg) was dissolved in petroleum ether (bp. 40-60°C, 25 ml) containing 2 drops of TFA and the mixture stirred (36 h) at room temperature. Solvent was removed by rotary evaporation and the semi-solid residue extracted with Et_2O (2 x 25 ml). The combined organic extracts were washed with water (20 ml), dried ($MgSO_4$) and rotary evaporated to give a crude product (15 mg) which was purified by HPLC (45% EtOAc/hexane): **5** (4.4 mg, 29%, R_t 9.0 min), **12** (3.3 mg, 22%, R_t 11.3 min); **11** (2.4 mg, 16%, R_t 20.7 min); **2** (0.8 mg, 5%, R_t 23.2 min). (**2**): physical data identical with reference 5; ^{13}C NMR (125 MHz) see Table 2; ^1H NMR (500 MHz) δ 1.08 (3H, d, J = 6.1 Hz), 1.20 (3H, s), 1.24 (3H, s), 2.14 (3H, s), 2.38 (2H, m), 2.52 (1H, m), 3.81 (1H, s, -OH). (**3**): Oil. $[\alpha]_D$ +56.4 (*c* 0.1, $CHCl_3$); IR ν_{max} 3009, 2930, 2856, 1713, 1677, 1450, 1371, 1288 cm^{-1}; ^{13}C NMR (125 MHz) see Table 2; ^1H NMR (500 MHz) δ 1.04 (3H, d, J = 6.6 Hz), 1.75 (3H, s), 1.89 (3H, s), 2.14 (3H, s); MS (EI) *m/z* (rel. intensity) 222 (90), 207 (30), 189 (10), 164 (100), 137 (70), 121 (35); HRMS calcd. for (M^+) $C_{14}H_{22}O_2$ 222.1620, found 222.1621. *Peroxofabianane (5):* physical data identical with reference 10. ^{13}C NMR (125 MHz) see Table 2; ^1H NMR (500 MHz) 0.98 (3H, d, J = 6.5 Hz), 1.24 (3H, s), 1.44 (3H, s), 1.58 (3H, s), 2.05 (1H, ddd, J = 14.6, 3.8, 3.8 Hz), 2.29 (1H, ddd, J = 14.6, 12.9, 4.0 Hz), 5.59 (1H, s); MS (EI) *m/z* (rel. intensity) 236 (50), 221 (3), 192 (22), 178 (100), 165 (10); HRMS calcd. for (M^+ - O_2) $C_{15}H_{24}O_2$ 236.1776, found 236.1769. *Tertiary hydroperoxide hemi-acetal diastereoisomers 11a/11b:* Oil (inseparable mixture). MS (EI) *m/z* (rel. intensity) 254 (1), 236 (75), 223 (58), 207 (30), 178 (100), 149 (70), 109 (40). HRMS calcd. for (M^+ - O_2) $C_{15}H_{26}O_3$ 254.1882, found 254.1883; HRMS calcd. for (M^+ - O_2 – H_2O) $C_{15}H_{24}O_2$ 236.1776, found 236.1771. MS (CI) *m/z* (rel. intensity) 269 (6) [M+1 – H_2O], 251 (15) [M+1 – $2H_2O$], 235 (27), 223 (100). ^{13}C NMR (125 MHz) see Table 2; *major diastereoisomer 11a*: ^1H NMR (500 MHz) δ 0.94 (3H, d, J = 6.3 Hz), 1.29 (3H, s), 1.44 (3H, s), 2.20 (3H, s), 2.32 (1H, dd, J=13.2, 6.7 Hz), 2.46 (1H, s, -OH), 2.68 (1H, m), 2.80 (1H, m), 5.07 (1H, s), 9.82 (1H, s, -OOH). ^1H NMR (500 MHz) *minor diastereoisomer 11b*: ^1H NMR (500 MHz) δ 0.99 (3H, d, J = 6.4 Hz), 1.19 (3H, s), 1.58 (3H, s), 2.20 (3H, s), 2.41 (1H, dd, J=13.2, 6.4 Hz), 2.68 (1H, m), 2.80 (1H, m), 3.03 (1H, d, J = 12.4 Hz, -OH), 5.26 (1H, d, J = 12.4 Hz), 10.44 (1H, s, -OOH). *seco-Floribundione (12):* Oil. $[\alpha]_D$ -47.9 (*c* 0.2, $CHCl_3$); IR ν_{max} 3018, 2932, 2874, 1715, 1370, 1200 cm^{-1}; ^{13}C NMR (125 MHz) see Table 2; ^1H NMR (500 MHz) δ 1.08 (3H, d, J = 6.1 Hz), 1.51 (3H, s), 1.63 (3H, s), 2.12 (3H, s), 2.31 (1H, ddd, J = 15.5, 9.0, 6.3 Hz), 2.52 (1H, ddd, J = 15.5, 9.1, 5.5 Hz), 3.22 (1H, dd, J = 12.0, 4.0 Hz), 7.99 (1H, s); MS (EI) *m/z* (rel. intensity) 222 (100), 207 (50), 194 (30), 164 (90), 152 (40), 134 (15), 109 (30), 99 (100); HRMS calcd. for (M^+ - HCOOH) $C_{14}H_{22}O_2$ 222.1620, found 222.1623.

Conversion of 6 to 11 in $CDCl_3$. 4α-Hydroperoxy-5-amorphen-11-ol (**6**) (5 mg) was dissolved in $CDCl_3$ (0.6 ml). After 1 week under ambient conditions, **6** had been converted into compounds **11a/11b** (3.5 mg, 70%). ^1H NMR spectra acquired at intervals throughout the course of the transformation consistently revealed the presence of a low intensity peak (δ_H 9.75, d, J=6.4 Hz), tentatively identified as belonging to 4-keto/5-aldehyde **16**.

*Conversion of tertiary allylic hydroperoxide **6** to aldol condensation product **13** in TFA/$CDCl_3$ under an atmosphere of nitrogen.* 4α-Hydroperoxy-5-amorphen-11-ol (**6**) (5 mg) was dissolved in $CDCl_3$ (0.6 ml) in a Schlenck NMR tube and the $CDCl_3$ solution degassed of oxygen by repeatedly freezing in liquid nitrogen, allowing the solution to thaw under vacuum and then introducing a nitrogen atmosphere via the teflon valve of the Schlenck tube. TFA (2μl) was added, the solution degassed once more and the NMR tube sealed under a nitrogen atmosphere. Compound **6** was converted into α,β-unsaturated ketone **13** (3 mg, 60%) after five days under ambient conditions. (**13**): Oil. IR ν_{max} 3382 (br), 3013, 2961, 2928, 2873, 1709, 1655, 1485, 1375, 1275, 1169 cm^{-1}; ^{13}C NMR (125 MHz) see Table 3; ^1H NMR (500 MHz) δ 0.92 (3H, d, J = 6.4 Hz), 1.17 (3H, s), 1.27 (3H, s), 2.17 (1H, t, J = 10.3 Hz), 2.30 (3H, s), 2.66 (1H, dd, J = 14.9, 6.8 Hz), 7.40 (1H, s); MS (EI) *m/z* (rel. intensity) 236 (10), 218 (95), 203 (40), 175 (30), 155 (20), 135 (60), 99 (100); HRMS calcd. for (M^+) $C_{15}H_{24}O_2$ 236.1776, found 236.1782. 1D- and 2D-NMR spectra acquired at intervals over the course of the conversion (5 days) suggested the formation of intermediates **14** and **15a/15b**, which were tentatively identified, but not isolated, from the reaction mixture. (**14**): ^1H NMR (500 MHz; $CDCl_3$/TFA) δ 0.96 (3H, d, J = 5.5 Hz, H-14), 1.23 (3H, s, H-12/13), 1.32 (3H, s, H-12/13), 2.17 (3H, s, H-15), 2.22 (1H, m, H-7), 5.81 (1H, s, H-5). ^{13}C NMR (125 MHz; $CDCl_3$/TFA) 19.1 (C-14), 23.2 (C-12/13), 28.3 (C-12/13), 29.9 (C-15), 42.8 (C-3), 54.4 (C-7), 85.5 (C-11), 113.6 (C-6), 133.4 (C-5), 211.3 (C-4). (**15a**): ^{13}C NMR (125 MHz) see Table 3; ^1H NMR (500 MHz; $CDCl_3$/TFA) δ 0.93 (3H, d, J = 6.4 Hz), 1.03 (3H, s), 1.29 (3H, s), 2.18 (3H, s), 5.28 (1H, d, J = 4.1 Hz); (**15b**): ^{13}C NMR (125 MHz) see Table 3; ^1H NMR (500 MHz; $CDCl_3$/TFA) δ 0.96 (3H, d, J = 5.8 Hz), 1.09 (3H, s), 1.35 (3H, s), 2.18 (3H, s), 6.32 (1H, d, J = 2.9 Hz).

*Conversion of **11** to **5** and **12** in $CDCl_3$/TFA.* Tertiary hydroperoxy *hemi*-acetal intermediate (**11**) (2 mg) was dissolved in $CDCl_3$ (0.6 ml). TFA (2μl) was added and the sample monitored by ^1H NMR spectroscopy at regular time intervals for 140 mins, after which time it had been converted to *seco*-floribundione (**12**) (0.4 mg, 20%) and peroxofabianane (**5**) (1.3 mg, 65%). The structure of intermediate **18** (not isolated) was tentatively determined by 1D-NMR spectra acquired during the transformation. ^1H NMR chemical shifts for each of these compounds determined as a mixture in the presence of TFA are given below. (**5**): ^1H NMR (500 MHz; $CDCl_3$/TFA) δ 0.98 (3H, d, J = 6.4 Hz), 1.30 (3H, s), 1.42 (3H, s), 1.63 (3H, s), 5.69 (1H, s). (**11**): ^1H NMR (500 MHz; $CDCl_3$/TFA)*δ 0.95 (3H, br d, H-14), 1.25 (3H, s, H-12/13), 1.36 (3H, s, H-12/13), 2.25 (3H, s, H-15), 5.29 (1H, br s, H-5). *A single broadened resonance was observed for each of H-5, H-12, H-13, H-14 and H-15 of **11a/11b** in TFA solution, most probably as the result of rapid interconversion of these two diastereoisomers on the NMR time-scale. (**12**): ^1H NMR (500 MHz; $CDCl_3$/TFA) δ 1.08 (3H, d, J = 6.9 Hz), 1.25 (3H, s), 1.53 (3H, s), 2.23 (3H, s), 8.08 (1H, s). (**18**) ^1H NMR (500 MHz; $CDCl_3$/TFA) δ 1.09 (3H, d, J = 6.1 Hz, H-14), 1.28 (3H, s, H-12/13), 1.31 (3H, s, H-12/13), 2.29 (3H, s, H-15), 5.98 (1H, s, H-5).

*Preparation of 1β-(butan-3-one)-menthone (**20**) from (-)-menthone.* To a cooled solution (-78°C) of lithium diisopropylamide (LDA) in THF (prepared from BuLi (1.6 M; 3.96 ml), diisopropylamine (0.89 ml) and

THF (12 ml)) was added dropwise a solution of (-)-menthone (722 mg) in THF (1.2 ml). After stirring for 30 min, 3-trimethylsilylbut-3-en-2-one (1.0 g) in THF (2 ml) was added dropwise and stirring continued at -78°C for 1 h. The mixture was warmed to 0°C and stirring continued for 2.5 h, before quenching with HCl (10%), neutralization by $NaHCO_3$ (5%) and extraction with EtOAc (3 x 20 ml). The combined organic extracts were washed with water (2 x 20 ml), dried ($MgSO_4$) and rotary evaporated to give a crude product consisting predominantly of **20**, which was purified by HPLC in 8% EtOAc/hexane (335 mg, 32 %, R_f 24.8 min). (**20**): Oil. $[\alpha]_D$ –46.1 (*c* 1.5, $CHCl_3$); IR ν_{max} 3024, 2961, 2932, 2874, 1705, 1445, 1367, 1217 cm^{-1}; ^{13}C NMR (125 MHz) see Table 4; ^1H NMR (500 MHz) δ 0.86 (3H, d, *J* = 6.4 Hz), 0.89 (3H, d, *J* = 6.4 Hz), 1.06 (3H, d, *J* = 6.2 Hz), 2.12 (3H, s), 2.34 (1H, ddd, *J* = 17.1, 8.1, 4.0 Hz), 2.55 (1H, ddd, *J* = 17.1, 8.8, 5.7 Hz); MS (EI) *m/z* (rel. intensity) 224 (95), 209 (100), 182 (20), 167 (25), 149 (30), 111 (25); HRMS calcd. for (M^+) $C_{14}H_{24}O_2$ 224.1776, found 224.1775.

Preparation of 4-Keto-6β-hydroxy-15-nor-amorphane (21) by Aldol reaction of 20. To a solution of 1,5-diketone **20** in EtOH (243 mg, 15 ml) was added $BaOH.8H_2O$ (342 mg). The solution was stirred at ice-bath temperature for 3 h, then neutralized with HCl (10%) and concentrated under reduced pressure. The residue was extracted with $CHCl_3$ (3 x 20 ml) and the combined organic extracts were washed with water (2 x 20 ml), dried ($MgSO_4$) and rotary evaporated to yield a crude product (238 mg, 98 %) consisting predominantly of decalone alcohol **21**. HPLC separation (15% EtOAc/hexane) yielded unreacted starting material **20** (59 mg, 25%, R_f 16.4 min), dehydration product **22** (24 mg, 7 %, R_f 17.6 min) and decalone alcohol **21** (120 mg, 51 %, R_f 24.8 min) in addition to small amounts of other diastereoisomeric 1,5-diketones. (**21**): Oil. $[\alpha]_D$ –51.4 (*c* 2.5, $CHCl_3$); IR ν_{max} 3614, 3422 (br), 3026, 3011, 2961, 2932, 1709, 1464, 1450, 1379, 1376 cm^{-1}; ^{13}C NMR (125 MHz) see Table 4; ^1H NMR (500 MHz) δ 0.88 (3H, d, *J* = 6.9 Hz), 0.91 (3H, d, *J* = 6.9 Hz), 0.95 (3H, d, *J* = 6.4 Hz), 2.44 (1H, dddd, *J* = 14.3, 7.1, 4.6, 2.3 Hz), 2.74 (1H, dd, *J* = 14.1, 2.4 Hz); MS (EI) *m/z* (rel. intensity) 224 (30), 209 (20), 164 (15), 139 (100), 111 (20); HRMS calcd. for (M^+) $C_{14}H_{24}O_2$ 224.1776, found 224.1775.

Preparation of 4-keto-15-nor-amorph-5-ene (22) by dehydration of 21. A solution of tertiary alcohol **21** in EtOH (116 mg, 30 ml) was stirred with HCl (6 M, 30 ml) for 5 h in an ice-bath. The reaction was neutralized with $NaHCO_3$ (5%) and concentrated under reduced pressure. The residue was extracted with $CHCl_3$ (3 x 15 ml) and the combined organic extracts were washed with water (2 x 10 ml) and brine (20 ml), dried and rotary evaporated to give a crude product (109 mg) from which **22** was obtained by HPLC in 15% EtOAc/hexane (55 mg, 52 %, R_f 17.5 min). Oil. $[\alpha]_D$ –3.2 (*c* 2.8, $CHCl_3$); IR ν_{max} 2961, 2932, 2874, 1663 cm^{-1}; ^{13}C NMR (125 MHz) see Table 4; ^1H NMR (500 MHz) δ 0.88 (3H, d, *J* = 6.7 Hz), 0.96 (3H, d, *J* = 6.7 Hz), 1.04 (3H, d, *J* = 6.4 Hz), 2.17 (1H, m), 2.28 (1H, ddd, *J* = 17.0, 14.0, 5.0 Hz), 2.36 (1H, ddd, *J* = 17.0, 9.3, 4.6 Hz). 5.86 (1H, s); MS (EI) *m/z* (rel. intensity) 206 (50), 191 (8), 164 (100), 149 (18), 122 (18); HRMS calcd. for (M^+) $C_{14}H_{22}O$ 206.1671, found 206.1672.

Preparation of 15-nor-amorphan-4β-ol (23) and 15-nor-cadinan-4α-ol (24) by conjugate reduction of 22. To a solution of $NaBH_4$ in pyridine (234 mg, 3 ml) was added a solution of α,β-unsaturated ketone **22** in pyridine (212 mg, 3 ml). The reaction mixture was stirred at room temperature for 6 h, then water (2 ml) was added and stirring continued for a further 3 h. The reaction mixture was diluted with Et_2O (50 ml) and acidified with HCl (10%). The ethereal layer was then separated and washed successively with HCl (10%, 4 x 15 ml), Na_2SO_3 (2 x 15 ml) and water (20 ml) and the extract was dried and concentrated to give an oil (141 mg, 65 %) consisting predominantly of **23** with a small amount of **24**. These components were purified by HPLC (18% EtOAc/hexane): **23** (108 mg, 46%, R_f 22.4 min), **24** (12 mg, 5 %, R_f 23.5 min). (**23**): Oil. $[\alpha]_D$ +7.8 (*c* 0.7, $CHCl_3$); IR ν_{max} 3600, 3421 (br), 3007, 2941, 2868, 1472, 1447, 1379, 1376 cm^{-1}; ^{13}C NMR (125 MHz) see Table 4; ^1H NMR (500 MHz) δ 0.83 (3H, d, *J* = 6.4 Hz), 0.86 (3H, d, *J* = 6.7 Hz), 0.88 (3H, d, *J* = 6.6 Hz), 3.59 (1H, tt, *J* = 11.0, 5.5 Hz); MS (EI) *m/z* (rel. intensity) 210 (2), 192 (100), 177 (5), 149 (100), 121 (10), 107 (18); 93 (20); HRMS calcd. for M^+ $C_{14}H_{26}O$ 210.1984, found 210.1985. (**24**): ^{13}C NMR (125 MHz) see Table 4; ^1H NMR (500 MHz) δ 0.56 (1H, dddd, *J* = 10.2, 10.2, 10.2, 3.0 Hz), 0.70 (3H, d, *J* = 6.8 Hz), 0.87 (3H, d, *J* = 5.7 Hz), 0.88 (3H, d, *J* = 7.0 Hz), 3.57 (1H, m).

Preparation of 4-keto-15-nor-amorphane (25) by oxidation of 23. To a solution of **23** in acetone (105 mg, 5 ml) was added freshly-prepared Jones reagent (0.6 ml) and the mixture was stirred for 2 h at ice-bath temperature. The mixture was extracted by petroleum ether (bp. 40-60°C, 3 x 15 ml) and the combined organic extracts were washed with water (2 x 10 ml) and brine (20 ml), dried and rotary evaporated to give saturated ketone **25** (80 mg, 77%) without any need for further purification. Oil. $[\alpha]_D$ +16.0 (*c* 0.28, $CHCl_3$); IR ν_{max} 2961, 2920, 2874, 1701, 1472, 1452, 1209 cm^{-1}; ^{13}C NMR (125 MHz) see Table 4; ^1H NMR (500 MHz) δ 0.86 (3H, d, *J* = 6.6 Hz), 0.88 (3H, d, *J* = 6.7 Hz), 0.94 (3H, d, *J* = 6.3 Hz); MS (EI) *m/z* (rel. intensity) 208 (100), 193 (10), 165 (20), 147 (50), 123 (60), 107 (40); HRMS calcd. for (M^+) $C_{14}H_{24}O$ 208.1827, found 208.1820.

Preparation of amorphan-4β-ol (26) and amorphane-4α-ol (27) by Grignard reaction of 25. To a Grignard reagent freshly prepared from Mg (85 mg), CH_3I (546 mg) and Et_2O (25 ml) was added a solution of the saturated ketone **25** in Et_2O (72 mg, 5 ml). The reaction mixture was refluxed for 1 h and Et_2O (40 ml) was added upon completion. The ethereal layer was washed with water (2 x 10 ml), dried and rotary evaporated to give an oily crude product (57 mg, 73%) consisting of sesquiterpenes **26** and **27** in an approximately 1:1 ratio. The two diastereoisomers were separated by HPLC (14% EtOAc/hexane: **26** (23 mg, 29%, R_f 27.7 min), **27** (24 mg, 31 %, R_f 15.5 min). (**26**): Oil. $[\alpha]_D$ +25.2 (*c* 0.2, $CHCl_3$); IR ν_{max} 3600, 2928, 2870, 1472, 1454, 1379, 1367, 1219 cm^{-1}; ^{13}C NMR (125 MHz) see Table 4; ^1H NMR (500 MHz) δ 0.82 (3H, d, *J* = 6.2 Hz), 0.85 (3H, d, *J* = 6.6 Hz), 0.88 (3H, d, *J* = 6.5 Hz), 1.27 (3H, s); MS (EI) *m/z* (rel. intensity) 224 (20), 209 (20), 206 (16), 191 (15), 181 (20), 163 (100), 139 (10), 123 (35); HRMS calcd. for M^+ $C_{15}H_{28}O$ 224.2140, found 224.2135. (**27**): Oil. $[\alpha]_D$ +4.0 (*c* 0.26, $CHCl_3$); ^{13}C NMR (125 MHz) see Table 4; ^1H NMR (500 MHz) δ 0.83 (3H, d, *J* = 6.5 Hz), 0.87 (3H, d, *J* = 6.6 Hz), 0.88 (3H, d, *J* = 6.5 Hz), 1.21 (3H, s); MS (EI) *m/z* (rel. intensity) 224 (40), 209

(100), 206 (50), 191 (15), 163 (90), 150 (88); HRMS calcd. for (M^+) $C_{15}H_{28}O$ 224.2140, found 224.2133.

Preparation of 3-amorphene (31) and 4-amorphene (19) by dehydration of 26/27 using p-toluenesulfonic acid (p-TsOH). A solution of p-TsOH in THF (40 mg/1 ml) was added to a solution of the mixture of **26** and **27** in benzene (40 mg, 25 ml). The reaction mixture was refluxed for 1 h using a Dean-Stark head to remove water then subjected to rotary evaporation to give a crude product (42 mg) consisting of compounds **19** and **31** which were separated by column chromatography in pure hexane. (**19**) (12 mg, 30%): Oil. $[\alpha]_D$ –25.8 (*c* 0.1, $CHCl_3$); IR ν_{max} 2924, 2870, 2855, 1448, 1381, 1217 cm^{-1}; ^{13}C NMR (125 MHz) see Table 4; ^1H NMR (500 MHz) δ 0.86 (3H, d, *J* = 6.4 Hz), 0.89 (3H, d, *J* = 6.6 Hz), 0.91 (3H, d, *J* = 6.9 Hz), 1.62 (3H, s), 2.51 (1H, s), 5.23 (1H, s); MS (EI) *m/z* (rel. intensity) 206 (15), 191 (2), 163 (100), 121 (12); HRMS calcd. for M^+ $C_{15}H_{26}$ 206.2035, found 206.2027. (**31**) (18 mg, 45%): IR ν_{max} 2955, 2920, 2866 cm^{-1}; ^{13}C NMR (125 MHz) see Table 4; ^1H NMR (500 MHz) 0.81 (3H, d, *J* = 6.6 Hz), 0.88 (3H, d, *J* = 7.0 Hz), 0.89 (3H, d, *J* = 6.6 Hz), 1.62 (3H, s), 5.26 (1H, br s); MS (EI) *m/z* (rel. intensity) 206 (20), 163 (100), 150 (10), 121 (8); HRMS calcd. for (M^+) $C_{15}H_{26}$ 206.2035, found 206.2022.

Preparation of 4-keto-15-nor-muurol-5-ene (28) by dehydration of 21. A solution of tertiary alcohol **21** in EtOH (70 mg, 15 ml) was stirred with H_2SO_4 (conc., 15 ml) for 3 h at room temperature, then neutralized with $NaHCO_3$ (5%) and concentrated under reduced pressure. The residue was extracted with $CHCl_3$ (3 x 15 ml) and the combined organic extracts washed with water (2 x 10 ml) and brine (20 ml), dried ($MgSO_4$) and rotary evaporated to yield a crude product (62 mg) which was separated by HPLC (5 % EtOAc/hexane): **22** (12 mg, 25%, R_f 58.0 min) and **28** (38 mg, 59%, R_f 55.5 min). (**28**): Oil. $[\alpha]_D$ –49.5 (*c* 0.4, $CHCl_3$); IR ν_{max} 2961, 2930, 2870, 1663, 1616, 1458, 1217 cm^{-1}; ^{13}C NMR (125 MHz) see Table 4; ^1H NMR (500 MHz) δ 0.77 (3H, d, *J* = 6.2 Hz), 0.97 (3H, d, *J* = 6.2 Hz), 1.03 (3H, d, *J* = 6.0 Hz), 5.82 (1H, d, *J* = 1.7 Hz); MS (EI) *m/z* (rel. intensity) 206 (45), 191 (8), 164 (100), 149 (26), 122 (22); HRMS calcd. for (M^+) $C_{14}H_{22}O$ 206.1671, found 206.1672.

Preparation of 15-nor-muurol-5-en-4β-ol (29) and 15-nor-muurol-5-en-4α-ol (30) by reduction of 28. To a solution of $NaBH_4$ in pyridine (50 mg, 1 ml) was added a solution of α,β-unsaturated ketone **28** in pyridine (45 mg, 1 ml). The reaction mixture was stirred at room temperature for 6 h, then water (1 ml) was added and stirring continued for a further 3 h. The reaction mixture was diluted with Et_2O (25 ml) and acidified with HCl (10%). The ethereal layer was then separated and washed successively with HCl (10%, 3 x 5 ml), Na_2SO_3 (2 x 5 ml) and water (10 ml) and the extract was dried and concentrated to give an oil (29 mg, 64 %), consisting predominantly of **29** with a small amount of **30**. These two compounds were separated by HPLC (12% EtOAc/hexane): **29** (12 mg, 27%, R_f 26.5 min), **30** (2 mg, 5%, R_f 23.5 min). (**29**): Oil. $[\alpha]_D$ –42.8 (*c* 0.49, $CHCl_3$); IR ν_{max} 3599, 3420 (br), 3011, 2955, 2928, 2868, 1454, 1383, 1223 cm^{-1}; ^{13}C NMR (125 MHz) see Table 4; ^1H NMR (500 MHz) δ 0.73 (3H, d, *J* = 6.6 Hz), 0.90 (3H, d, *J* = 6.4 Hz), 0.96 (3H, d, *J* = 6.2 Hz), 4.16 (1H, ddd, *J* = 4.0, 4.0, 4.0 Hz), 5.50 (1H, s); MS (EI) *m/z* (rel. intensity) 208 (30), 165 (10), 149 (40), 147 (45), 123 (100); HRMS calcd. for (M^+) $C_{14}H_{24}O$ 208.1827, found 208.1817. (**30**): ^{13}C NMR (125 MHz) see Table 4;

^{1}H NMR (500 MHz) δ 0.79 (3H, d, J = 6.6 Hz), 0.90 (3H, d, J = 6.2 Hz), 0.92 (3H, d, J = 5.6 Hz), 4.14 (1H, m), 5.40 (1H, s).

Photooxidation of 19. Methylene blue (1.3 mg) was added to a solution of 4-amorphene (**19**) in acetone (12 mg, 25 ml) and the mixture was cooled in an ice-bath while irradiating with a tungsten lamp (500 W) for 30 min. The solvent was removed on a rotary evaporator and the residue was taken up in Et_2O (40 ml) and filtered to remove most of the dye, after which solvent was removed to yield a crude product (12 mg, 89 %), which was subjected to preparative HPLC (7% EtOAc/hexane): **32** (6 mg, 45 %, R_f 19.8 min). *4α-Hydroperoxy-5-amorphene (32):* Oil. $[\alpha]_D$ –12.6 (*c* 4.0, $CHCl_3$); IR ν_{max} 3531, 3440 (br), 2957, 2932, 2872, 1655, 1456, 1367 cm^{-1}; ^{13}C NMR (125 MHz) see Table 1; ^{1}H NMR (500 MHz) δ 0.87 (3H, d, J = 6.8 Hz), 0.93 (3H, d, J = 6.2 Hz), 0.95 (3H, d, J = 6.7 Hz), 1.31 (3H, s), 5.26 (1H, s), 7.19 (1H, s, -OOH); MS (EI) *m/z* (rel. intensity) 238 (0.5), 220 (10), 205 (100), 177 (55), 161 (50), 149 (30), 121 (65); HRMS calcd. for (M^+) $C_{15}H_{26}O_2$ 238.1933, found 238.1928; calcd. for (M^+-H_2O) $C_{15}H_{24}O$ 220.1827, found 220.1826.

Transformation of 32 in CDCl3/TFA. 4α-Hydroperoxy-5-amorphene (**32**) (5 mg) was dissolved in $CDCl_3$ (0.6 ml) in an NMR tube. TFA (2μl) was added and the reaction was left under ambient conditions. When solvent was removed after 1 day, aldehyde **33** was found to be the major product. When left for one week, the reaction mixture consisted predominantly of aldol condensation product **34**. Compound **34** was then stable to further transformation in $CDCl_3$/TFA solution over a period of several weeks. (**33**): Oil. $[\alpha]_D$ –34.5 (*c* 0.4, $CHCl_3$); IR ν_{max} 3018, 2959, 2930, 2872, 1709, 1456, 1369, 1215 cm^{-1}; ^{13}C NMR (125 MHz) see Table 3; ^{1}H NMR (500 MHz) δ 0.91 (3H, d, J = 6.6 Hz), 0.93 (3H, d, J = 6.6 Hz), 0.94 (3H, d, J = 6.6 Hz), 2.14 (3H, s), 2.69 (1H, br), 9.97 (1H, d, J = 5.6 Hz); MS (EI) *m/z* (rel. intensity) 238 (12), 220 (18), 195 (50), 177 (26), 149 (53), 95 (100); HRMS calcd. for (M^+), $C_{15}H_{26}O_2$ 238.1933, found 238.1929. (**34**): Oil. $[\alpha]_D$ +20.9° (*c* 0.2, $CHCl_3$); IR ν_{max} 3013, 2961, 2928, 2874, 1709, 1655, 1458, 1375, 1275 cm^{-1}; ^{13}C NMR (125 MHz) see Table 3; ^{1}H NMR (500 MHz) δ 0.87 (3H, d, J = 6.4 Hz), 0.94 (3H, d, J = 6.7 Hz), 0.99 (3H, d, J = 6.3 Hz), 2.39 (3H, s), 3.13 (1H, br s), 6.95 (1H, br s); MS (EI) *m/z* (rel. intensity) 220 (65), 177 (45), 159 (20), 137 (100), 109 (25); HRMS calcd. for (M^+), $C_{15}H_{24}O$ 220.1827, found 220.1826.

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