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

Koon-Sin Ngo and Geoffrey D. Brown*

Chemistry Department, The University of Hong Kong, Pokfulam Rd., Hong Kong.

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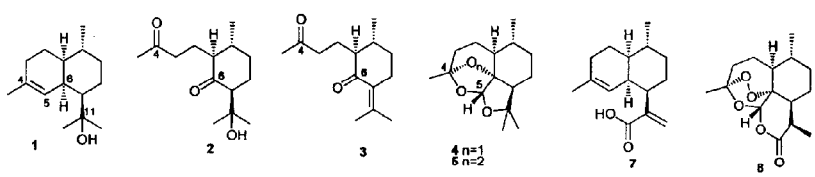
Abstract: Photooxidation of 4-amorphen-11-ol (**1**), recently reported as one of the major sesquiterpene natural products from the medicinal plant *Fabiana imbricata*, results in three allylic hydroperoxides **6**, **9** and **10**, which are expected from the "ene-type" reaction of molecular oxygen 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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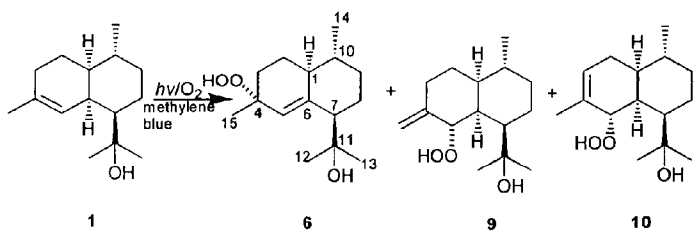
Having recently achieved a total synthesis of 4-amorphen-11-ol from commercially available (-)-isopulegol,[17] we resolved to perform a detailed investigation of this transformation reaction with a view to defining the evidently complex mechanism involved in rearrangement/oxidation of 4-amorphen-11-ol (**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.



1 **6** **9** **10**

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,

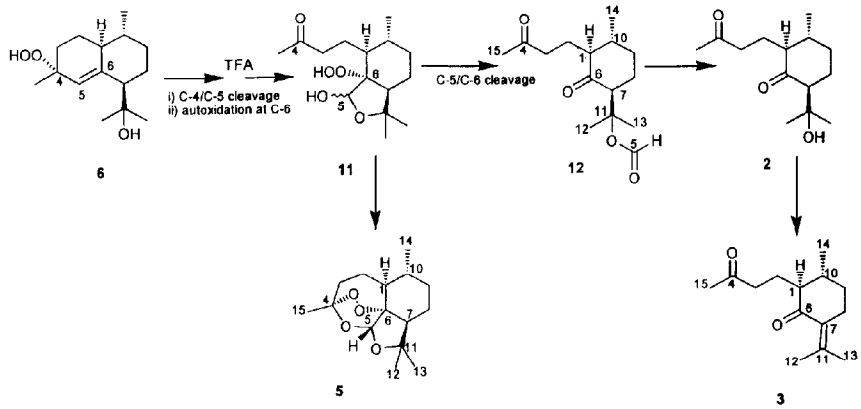
Table 1. NMR assignments for allylic hydroperoxides **6**, **9**, **10** and **32**

	^{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.

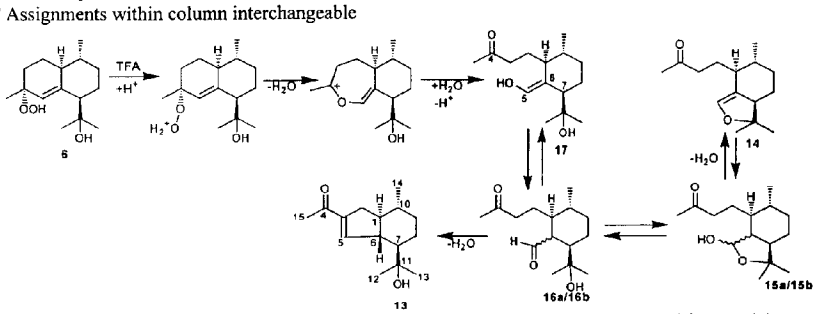
The structure of compound **13** is clearly suggestive of derivation from keto-aldehyde intermediate **16** by an intramolecular aldol reaction as shown in Scheme 3. In turn, compound **16** is the aldehyde tautomer of the enol cleavage product **17** which is the expected product from Hock cleavage[18,21]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

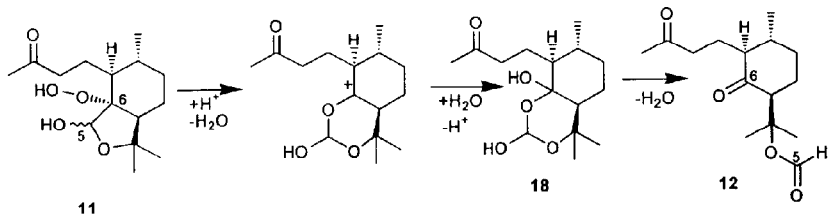
Table 3. NMR assignments for products **13**, **15**, **33** and **34** from rearrangement of allylic hydroperoxides **6** and **32** in $CDCl_3$/TFA in the absence of a second autoxidation reaction.

	^{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.

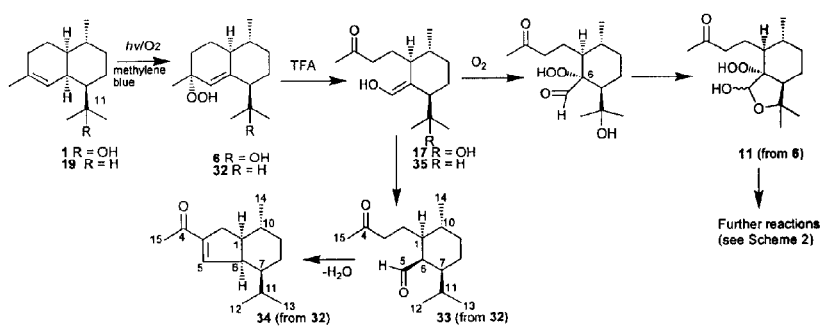
Although the conversion of **11** to **5** (major product) and **12** (minor product) in $CDCl_3$/TFA (Scheme 2) was considerably faster than that of **6** to **13** in $CDCl_3$/TFA (Scheme 3) - occurring over a period of hours rather than days - it was still sufficiently slow to allow the course of 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

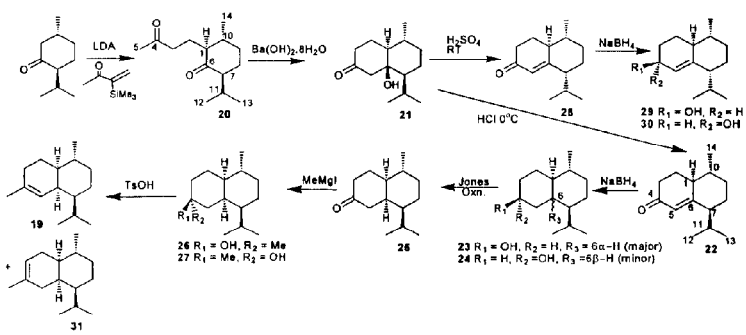
The origin of the tertiary hydroperoxide group in compound **11** can be most simply explained as the result of a "second" "ene-type" addition of molecular oxygen (*c.f.* first section) to the enolic double bond of Hock cleavage product **17** (Scheme 5), which is proposed to be formed during C-4/C-5 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_t 25.4 min); 9 (3.3 mg, 8 %, R_t 13.1 min); **10** (1.2 mg, 3%, R_t 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_f 9.0 min), **12** (3.3 mg, 22%, R_f 11.3 min); **11** (2.4 mg, 16%, R_f 20.7 min); **2** (0.8 mg, 5%, R_f 23.2 min). (**2**): physical data identical with reference 5; ^{13}C NMR (125 MHz) see Table 2; ^{1}H 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; ^{1}H 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; ^{1}H 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*: ^{1}H 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). ^{1}H NMR (500 MHz) *minor diastereoisomer 11b*: ^{1}H 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; ^{1}H 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%). ^{1}H 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_t 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_t 16.4 min), dehydration product **22** (24 mg, 7 %, R_t 17.6 min) and decalone alcohol **21** (120 mg, 51 %, R_t 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_t 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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