Synthesis of sesquiterpene allylic alcohols and sesquiterpene dienes from *Cupressus bakeri* and *Chamaecyparis obtusa*

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Five muurolane (**1**–**5**), one nor-seco-muurolane (**6**) and one nor-muurolane (**7**) sesquiterpene natural products recently reported from *Cupressus bakeri* have been obtained by chemical synthesis together with the unnatural 7-epimeric amorphane analogues of four of these sesquiterpenes (**15**, **16**, **18** and **19**). The conversion of sesquiterpene allylic tertiary alcohols **1**, **2**, **15** and **16** into regioisomeric sesquiterpene dienes **3**–**5** and **17**–**20** was investigated *in vitro* by NMR and the mechanism for such dehydrations and their relevance to the origins of sesquiterpene dienes which have been reported as natural products (such as **3**–**5**) is discussed.

Introduction

In 1994, Cool and co-workers[1] identified the novel sesquiterpene alcohols **1** and **2** from the foliage of *Cupressus bakeri* together with sesquiterpene dienes **3** and **4**, which were suggested to be dehydration products of these alcohols, the known compound epizonarene **5** and two unusual nor-sesquiterpenes **6** and **7** (Fig. 1). Fully assigned ^{13}C NMR data and partial ^{1}H NMR data (in $CDCl_3$ solution) were provided to support the structures of all these natural products with the exception of **4**, which was present in too small amounts to be adequately characterised and for which the proposed structure was only tentative. Two years later, Nagahama and co-workers[2] also reported compounds **1** and **2** (referred to as β-hinokienol and α-hinokienol respectively) as constituents of *Chamaecyparis obtusa* leaf oil. Although fully assigned ^{13}C NMR data and partial ^{1}H NMR data were again provided to support the structures of both diastereoisomers, confirmation of the identity of these natural products by comparison of the NMR data with those in the preceding report is difficult because ^{13}C NMR spectra were acquired in C_6D_6 and no reference was made to the earlier publication. More worryingly, some of the ^{13}C assignments made by the latter authors differed significantly from those in the earlier publication and several are well outside the range of differences expected for solvent-induced shifts (between 5–10 ppm in the case of C-2, C-3 and C-8 for both compounds).

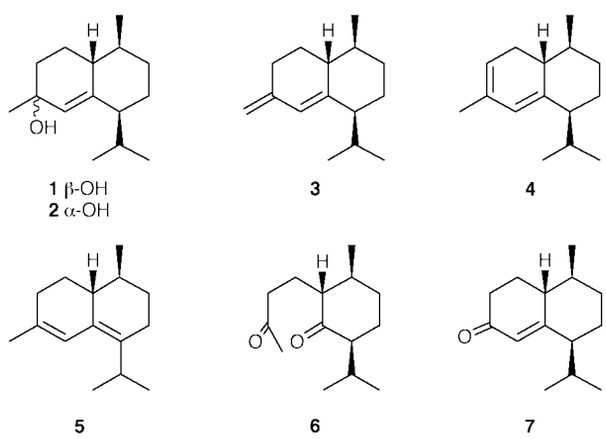


Fig. 1 Sesquiterpenes reported from *C. bakeri*.

Results and discussion

In order to resolve the question of the identity of recently isolated natural products **1** and **2** from *C. bakeri* and *C. obtusa*, we set out to synthesise these compounds from the commercially available menthane monoterpene (+)-menthone (**8**) and also to study their dehydration with a view to confirming the tentative structure proposed for natural product **4**. This synthetic strategy also provided a route to nor-sesquiterpene natural products **6** and **7**, which arise as synthetic intermediates. All compounds reported herein were characterised by 2D-NMR (in both $CDCl_3$ and C_6D_6 in the case of compounds **1**, **2**, **15** and **16**), enabling independent verification of stereochemistry and structure to be made at each step of the synthesis.

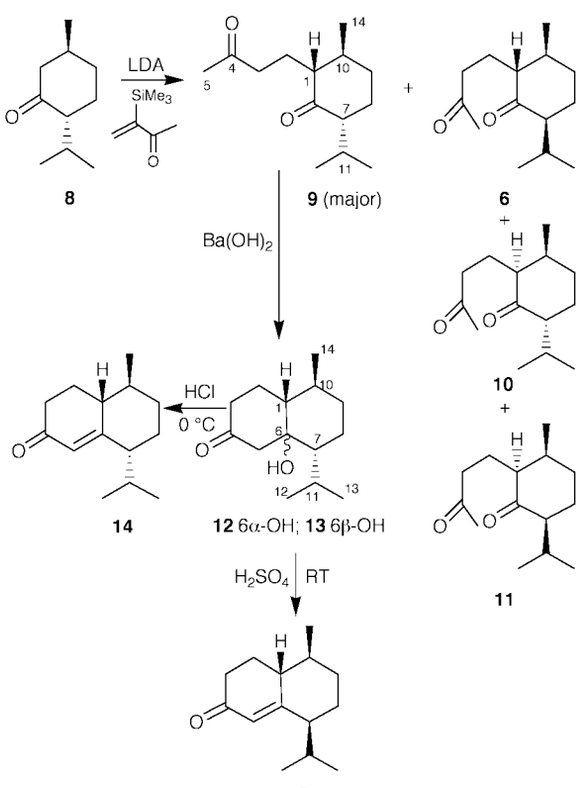
Reaction of (+)-menthone (**8**) with 3-trimethylsilylbut-3-en-2-one yielded the diketone **9** as the major product together with small amounts of diastereoisomeric diketones **6**, **10** and **11** (Scheme 1). ^{13}C NMR data for **6** (Table 1) was almost identical with that reported for the natural product from *C. bakeri* (except that literature assignments for C-13 and C-14 should be interchanged);[1] the relative stereochemistry of diketones **6** and **9**–**11** was determined by NOESY and ^{1}H–^{1}H *J*-resolved spectroscopy. It is clear from the data in Table 1 that there is a strong upfield shift in the ^{13}C resonance of the 14-methyl group in isomers **10** and **11** ($\Delta\delta_C$ 5–7 ppm), for which the newly introduced 1-alkyl ring-substituent is *cis* with respect to the 14-methyl group, as compared to diastereoisomers **6** and **9**; the sizeable upfield shift is the result of a significant *gauche* interaction between these two substituents. The resonances for protons in the 14-methyl group were also shifted upfield in compounds **10** and **11** ($\Delta\delta_H$ 0.2–0.3 ppm) when compared to **6** and **9**, which confirmed the preferred axial conformation of this substituent for these two diastereoisomers (the H-1 proton should therefore be equatorial and indeed was found to be significantly downfield, by approximately 0.4 ppm, in both cases).

Treatment of **9** with barium hydroxide under mild conditions produced the aldol addition product **12** (the *cis*-decalin isomer **13** was also isolated in very small amounts) which could be converted to the nor-amorphane decalenone **14** in moderately acidic conditions at low temperature. More forcing conditions induced epimerisation at the 7-position resulting in the nor-muurolane decalenone **7** (Scheme 1). Synthetic compound **7** gave identical ^{13}C NMR spectra to the natural product reported from *C. bakeri*[1] and is expected to be the thermodynamic product of such Robinson annulation, since the β-isopropyl group can adopt an axial conformation, thereby avoiding $A^{1,3}$ strain with the 5-alkene proton (this unfavourable interaction outweighs the natural tendency for ring substituents to be equatorial).[3] When comparing the fully assigned NMR spectra of these two decalenone products, it can be seen that there is a significant upfield shift (δ_C 4–5 ppm) in the resonances for C-1 and C-9 and a correspondingly large downfield shift at C-5 for nor-muurolane **7** relative to nor-amorphane **14** (Table 1). This is entirely consis-

Table 1 ^{13}C and ^{1}H NMR assignments ($CDCl_3$) for nor-sesquiterpenes **6**, **7** and **9**–**14**

	δ_C								δ_H							
	6	**7**	**9**	**10**	**11**	**12**	**13**	**14**	**6**	**7**	**9**	**10**	**11**	**12**	**13**	**14**
1	54.2	41.1	57.1	52.9	54.4	50.9	50.5	45.9	2.12	1.99	2.03	2.48	2.48	1.29	1.21	1.85
2	21.6	25.9	20.4	20.6	21.6	25.5	22.2	25.3	1.83	1.70 (α)	1.78	1.58	1.39	1.68 (α)	1.97 (α)	1.81 (α)
									1.83	2.21 (β)	1.82	1.89	1.99	2.06 (β)	2.27 (β)	2.17 (β)
3	41.5	35.7	41.5	41.5	41.9	41.1	36.5	34.9	2.36	2.39 (α)	2.34	2.28	2.30	2.44 (α)	2.23 (α)	2.28 (α)
									2.52	2.25 (β)	2.55	2.42	2.53	2.29 (β)	2.28 (β)	2.36 (β)
4	208.7	199.9	208.9	208.4	209.0	211.0	211.4	200.1	—	—	—	—	—	—	—	—
5	29.9	125.5	29.8	29.9	29.8	51.9	45.4	121.9	2.12	5.82	2.12	2.11	2.13	2.74 (α)	2.60 (α)	5.86
														2.22 (β)	2.32 (β)	
6	216.0	169.9	213.3	215.9	213.0	78.1	80.0	170.0	—	—	—	—	—	—	—	—
7	57.3	52.5	57.2	56.0	57.3	50.9	54.6	51.2	2.04	1.91	2.10	2.05	2.06	1.29	1.29	1.88
8α	27.3	28.8	29.6	26.3	25.4	20.4	24.1	29.1	1.72	1.54	1.30	1.65	1.97	1.41	1.19	1.15
8β									1.93	2.00	2.10	1.91	1.57	1.57	1.70	2.00
9α	29.2	29.9	34.9	28.4	32.7	35.4	35.3	35.2	1.68	1.56	1.86	1.88	1.95	1.80	1.86	1.87
9β									1.54	1.40	1.47	1.49	1.71	1.07	1.17	1.25
10	39.2	39.5	40.6	37.5	37.6	32.4	31.3	39.0	1.68	1.42	1.55	2.18	2.36	1.42	1.74	1.52
11	27.2	27.3	26.3	27.1	26.1	25.5	25.1	26.9	2.02	1.89	2.06	2.06	2.10	2.05	2.03	2.01
12[a]	20.9	21.5	21.5	21.0	21.4	23.6	24.7	22.0	0.80	0.77	0.89	0.82	0.89	0.91	0.96	0.96
13[a]	20.0	20.8	18.8	20.0	18.7	18.1	19.3	18.4	0.92	0.97	0.86	0.92	0.86	0.88	0.80	0.88
14	20.5	20.2	20.6	15.6	13.3	20.3	20.1	20.3	1.04	1.03	1.06	0.86	0.73	0.95	1.00	1.04

[a] Assignments interchangeable within column.



Scheme 1 Synthesis of nor-sesquiterpene natural products **6** and **7** from (+)-menthone **8**.

tent with the expectation that the 7β-isopropyl group in **7** adopts an axial conformation,[3] which leads to *gauche* interactions with C-1 and C-9; by contrast, the 7α-isopropyl substituent in **14** is equatorial and is involved in a *gauche* interaction with C-5 (Fig. 2). Inspection of fully assigned NMR data for muurolanes **1**–**4** and **17** and amorphanes **15**, **16** and **18**–**20** (Tables 2 and 3) shows that this effect in the B-ring is also apparent for all five pairs of isomers subsequently obtained by synthesis (C-1: δ_C 39.3–40.7 for muurolanes, δ_C 44.2–45.3 for amorphanes; C-9: δ_C 29.1–30.5 for muurolanes, δ_C 30.3–35.8 for amorphanes), and we suggest that determination of the ^{13}C chemical shift at C-1 and C-9 might provide a general and reliable means for differentiating between muurolane and amorphane sesquiterpenes.

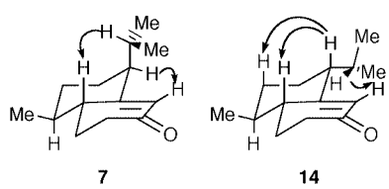


Fig. 2 Solution conformations of nor-muurolane **7** and nor-amorphane **14** as determined by NOESY (critical correlations from ^{1}H to ^{1}H indicated by arrows).

As expected, addition of a methyl Grignard reagent to nor-sesquiterpene **7** yielded muurolane sesquiterpene allylic alcohol natural products **1** and **2**; the corresponding amorphane (7α-isopropyl) alcohols **15** and **16**, which are not known from nature, were obtained from the Grignard reaction of **14** (Scheme 2). Compounds **1**, **2**, **15** and **16** were completely characterised by 2D-NMR in both $CDCl_3$ and C_6D_6. This clearly established that ^{13}C assignments (Table 2) in $CDCl_3$ for the natural products **1** and **2** reported from *C. bakeri* by Cool and co-workers.[1] were correct. Although the actual values of ^{13}C NMR chemical shifts recorded in C_6D_6 reported for natural products **1** and **2** from *C. obtusa*[2] were also correct, over half of the resonances were wrongly assigned in each case, thus explaining the apparent discrepancy in spectral data for the same compounds from two different biological sources. Thus, the identity of the sesquiterpene alcohols **1** and **2** from *C. bakeri* and *C. obtusa* has now been confirmed by total synthesis; ^{13}C assignments reported in the literature for **1** and **2** in C_6D_6 should be revised to those shown in Table 2 in parentheses. The ^{13}C NMR chemical shifts for the C-15 methyl group in alcohols **1** and **15** were slightly upfield (δ_C 1–1.5 ppm) compared with their 4-epimers **2** and **16**, which is consistent with a *pseudo*-axial conformation for this substituent in the half-chair A-ring for these two isomers (see Fig. 5).

Konig and co-workers[4] have reported that sesquiterpene dienes such as bicyclosesquiphellandrene, cadina-3,5-diene and zonarene, which are diastereoisomeric with natural products **3**, **4** and **5** at the 10-position can be interconverted simply by exposure to the trace acid naturally present in $CDCl_3$. Accordingly, we set out to study *in vitro* the mechanism by which **1** and **2** undergo dehydration to dienes such as **3**–**5** and the subsequent isomerisation of these dienes by NMR spectroscopic analysis of $CDCl_3$ solutions of these compounds. Allylic tertiary alcohol **1** underwent complete dehydration in $CDCl_3$ in less than

Table 2 ^{13}C NMR assignments ($CDCl_3$)[a] for sesquiterpenes **1**–**5** and **15**–**20**

	1	2	3	4	5	15	16	17	18	19	20
1	40.0 (40.2)	40.5 (40.7)	40.7	39.3	43.2	44.9 (45.1)	44.7 (44.9)	133.3	45.3	44.2	133.4
2	24.6 (25.1)	24.7 (25.0)	28.0	28.3	28.2	24.2 (24.7)	24.6 (24.9)	29.7	27.8	28.6	27.3
3	36.6 (37.0)	36.8 (37.1)	29.5	116.9	31.2	35.9 (36.3)	36.1 (36.5)	27.7	28.4	116.9	28.8
4	69.5 (68.7)	68.5 (67.5)	147.4	130.9	135.3	69.2 (68.7)	68.3 (67.7)	132.5	144.4	131.0	132.2
5	128.7 (130.0)	128.2 (129.5)	124.5	122.5	120.5	124.6 (125.9)	124.5 (125.6)	121.8	119.8	181.6	122.7
6	144.2 (143.2)	145.4 (144.4)	144.5	128.9	127.9	144.3 (143.1)	145.1 (144.1)	128.9	144.6	135.8	126.8
7	51.7 (51.9)	51.4 (51.8)	51.8	51.0	135.0	49.4 (49.5)	48.7 (48.8)	42.7	49.4	49.8	42.7
8	29.0 (29.3)	28.4 (28.8)	28.8	29.0	23.9	28.5 (28.7)	27.9 (27.5)	18.7	28.5	27.2	20.7
9	30.5 (30.8)	30.1 (30.4)	30.4	30.5	31.9	35.8 (36.0)	35.6 (35.8)	29.1	35.8	35.5	30.3
10	39.3 (39.7)	40.3 (40.5)	39.7	40.2	34.6	39.0 (39.2)	40.1 (40.1)	33.1	39.0	39.2	33.6
11	26.4 (26.6)	26.7 (26.9)	26.9	26.7	28.1	27.0 (27.2)	26.9 (27.2)	28.9	27.0	26.9	29.7
12[b]	21.6 (21.9)	21.5 (21.8)	21.8	21.8	21.0	22.3 (22.5)	22.3 (22.4)	20.9	22.3	22.0	21.2
13[b]	20.9 (21.0)	20.9 (21.0)	21.0	20.9	20.4	18.4 (18.5)	18.0 (18.2)	16.8	18.3	18.4	17.5
14	20.1 (20.2)	20.3 (20.4)	20.3	20.3	20.5	20.1 (20.3)	20.4 (20.5)	20.0	20.3	20.4	19.1
15	28.7 (29.2)	30.2 (30.7)	107.8	21.5	24.1	29.1 (29.5)	30.1 (30.5)	23.2	108.3	21.6	23.1

[a] Values in parentheses were obtained in C_6D_6. [b] Values interchangeable within column.

Table 3 ^{1}H NMR assignments ($CDCl_3$)[a] for sesquiterpenes **1**–**5** and **15**–**20**

	1	2	3	4	5	15	16	17	18	19	20
1	1.63 (1.45)	1.56 (1.36)	1.75	1.85	1.58	1.50 (1.33)	1.45 (1.28)	—	1.62	1.70	—
2α	1.35 (1.19)	1.39 (1.34)	1.33	2.00	1.12	1.42 (1.28)	1.43 (1.42)	1.94	1.50	2.01	2.00
2β	1.93 (1.79)	1.92 (1.74)	2.03	2.42	2.08	1.91 (1.79)	1.90 (1.74)	1.94	1.95	2.40	2.08
3α	1.72 (1.61)	1.75 (1.73)	2.31	5.25	2.12	1.69 (1.60)	1.72 (1.71)	2.15	2.32	5.29	2.10
3β	1.51 (1.46)	1.39 (1.27)	2.12		2.00	1.52 (1.50)	1.43 (1.34)	2.03	2.15		2.07
5	5.32 (5.32)	5.35 (5.32)	5.90	5.42	6.22	5.29 (5.34)	5.35 (5.39)	5.61	5.90	5.47	5.61
7	1.62 (1.55)	1.61 (1.55)	1.71	1.73	—	1.62 (1.52)	1.62 (1.52)	1.98	1.60	1.74	1.95
8α	1.40 (1.35)	1.43 (1.42)	1.48	1.48	1.99	0.99 (0.92)	1.05 (0.97)	1.47	1.08	1.12	1.38
8β	1.87 (1.81)	1.87 (1.83)	1.91	1.91	2.03	1.81 (1.71)	1.78 (1.66)	1.47	1.85	2.00	1.61
9α	1.47 (1.32)	1.48 (1.33)	1.46	1.48	1.70	1.79 (1.62)	1.78 (1.62)	1.98	1.72	1.75	1.82
9β	1.29 (1.15)	1.26 (1.17)	1.26	1.30	1.17	1.13 (1.00)	1.14 (0.97)	1.28	1.12	1.20	1.33
10	1.18 (1.01)	1.16 (1.03)	1.23	1.36	1.18	1.19 (1.03)	1.17 (1.03)	2.03	1.30	1.35	2.18
11	1.79 (1.65)	1.74 (1.61)	1.81	1.75	3.03	2.01 (1.99)	2.06 (2.02)	1.99	2.00	2.10	1.95
12[b]	0.77 (0.81)	0.71 (0.72)	0.77	0.80	0.96	0.95 (0.96)	0.95 (0.92)	0.93	0.99	0.97	0.92
13[b]	0.90 (0.85)	0.89 (0.86)	0.92	0.91	0.95	0.86 (0.86)	0.86 (0.87)	0.68	0.86	0.88	0.70
14	0.92 (0.82)	0.96 (0.87)	0.95	0.90	0.97	0.92 (0.83)	0.96 (0.86)	1.02	0.95	0.92	0.96
15	1.26 (1.26)	1.27 (1.28)	4.68	1.68	1.77	1.28 (1.28)	1.29 (1.30)	1.78	4.72	1.71	1.79
			4.62						4.66		

[a] Values in parentheses were obtained in C_6D_6. [b] Assignments interchangeable within column.

four days (Fig. 3); the diene **3** was the most rapidly formed product, accounting for 50% of the mixture at this point in time (Fig. 3). ^{13}C NMR data for compound **3** agreed well with that reported for the natural product[1] (with the exception that assignments reported in the literature for C-3–C-9 and C-4–C-6 should be reversed within each pair). Over the next week, peaks due to **3** were seen to disappear from the ^{1}H NMR spectrum at a rate roughly equivalent to that at which peaks for **17** (not yet reported as a natural product) appeared in the mixture; isomerisation of **3** to **17** involves conversion of an exocyclic double bond to a thermodynamically more stable endocyclic double bond. In Fig. 3 it can also be seen that diene **4** is also formed in the early phases of the dehydration of **1** at a slower rate than for **3**. As for all compounds reported herein, the structure of **4** was unambiguously established by 2D-NMR (Tables 2 and 3) thereby rigorously establishing the identity of this natural product, which was previously only tentatively identified on mass spectral evidence alone.[1] Diene **4** reaches its maximum concentration after around three days in $CDCl_3$ solution (Fig. 4), after which the signal for this isomer disappears from the ^{1}H NMR spectrum at a rate roughly equivalent to that for the appearance of regioisomeric diene **5** (Fig. 3), which is the known compound epizonarene. The course of the reaction followed by tertiary alcohol **2** (epimeric at the 4-position) was similar to that described for **1**, although the rate of dehydration was slower in the case of epimer **2**. On the basis of the foregoing results we suggest that diene natural products **3** and **4** were produced directly from the

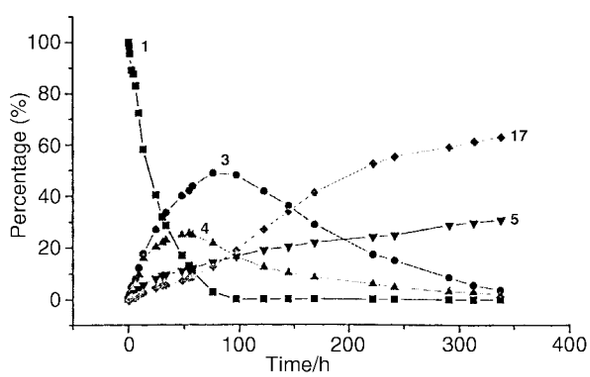


Fig. 3 Dehydration of muurolane allylic tertiary alcohol **1** to sesquiterpene dienes **3**–**5** and **17** as studied by ^{1}H NMR spectroscopy in $CDCl_3$ solution.

dehydration of allylic alcohols **1** and/or **2**, either as a result of chemical processes occurring in the plant cell or during the extraction procedure for *C. bakeri*, and that natural product **5** was then formed principally by subsequent isomerisation of diene **4** (Scheme 2).

In vitro study of the course of dehydration of the unnatural amorphane tetiary alcohol **15** in $CDCl_3$ by ^{1}H NMR showed that this compound underwent *direct* dehydration to the 4,6-diene **5** (epizonarene) at a rate which was appreciably faster than that for the alternative route yielding the 4(15),5-diene **18**

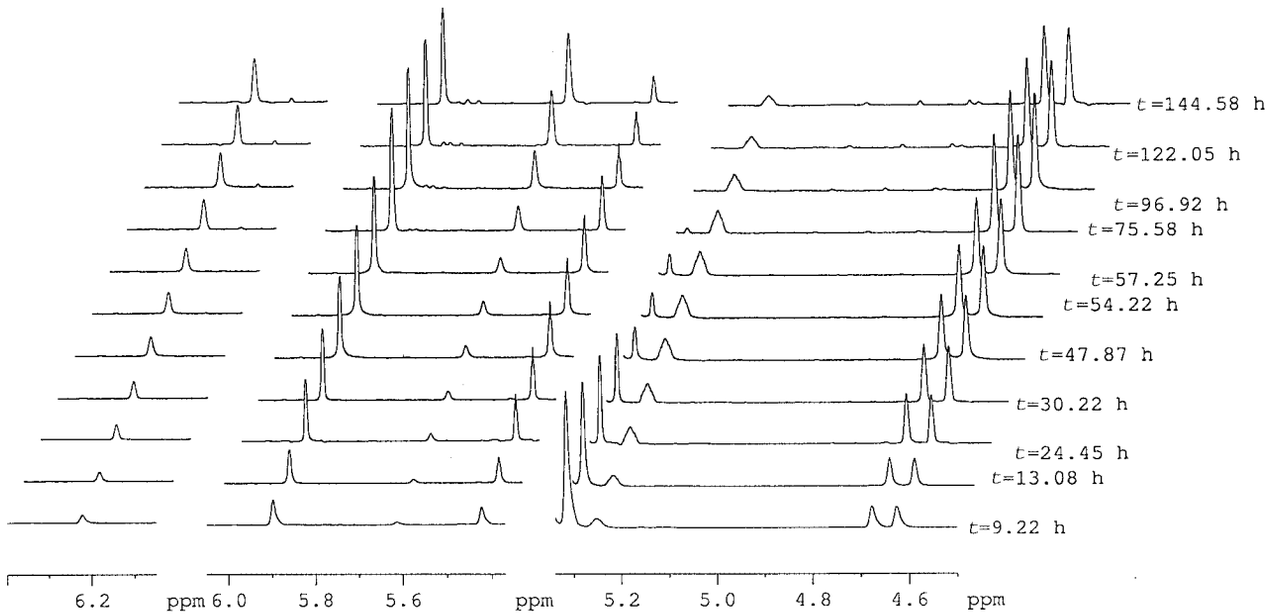
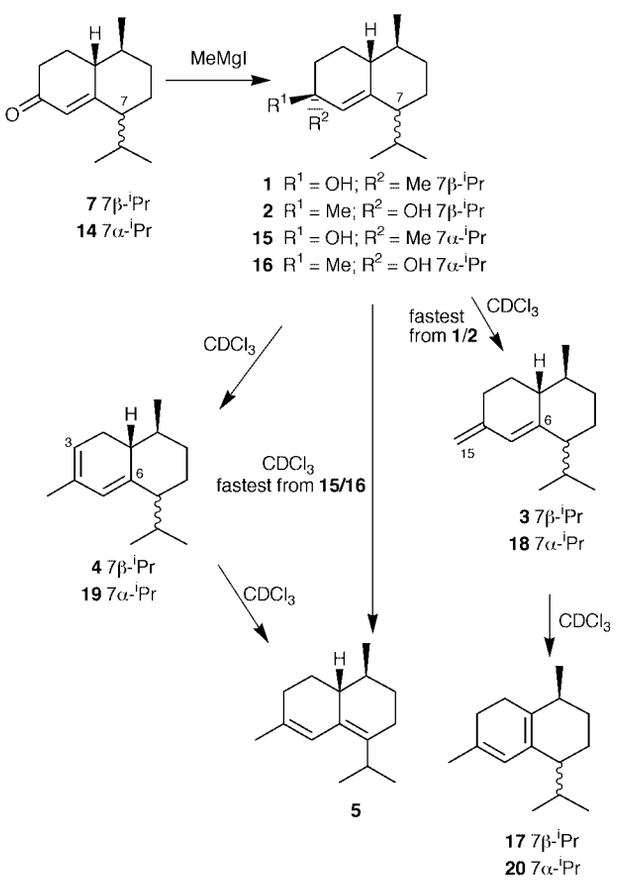


Fig. 4 Selected ^{1}H NMR spectra (expansion of alkene region) showing the variation in intensity for signals corresponding to compounds **1** (δ_H 5.32, H-5), **3** (δ_H 5.90, H-5; 4.68 and 4.62, H-15), **4** (δ_H 5.42, H-5, 5.25 (br), H-3), **5** (δ_H 6.22, H-5) and **17** (δ_H 5.61, H-5) against time, used in calculating the product distribution in Fig. 3.



Scheme 2 Synthesis of sesquiterpene allylic tertiary alcohols **1**, **2**, **15** and **16** and conversion into sesquiterpene dienes **3**–**5** and **17**–**20**.

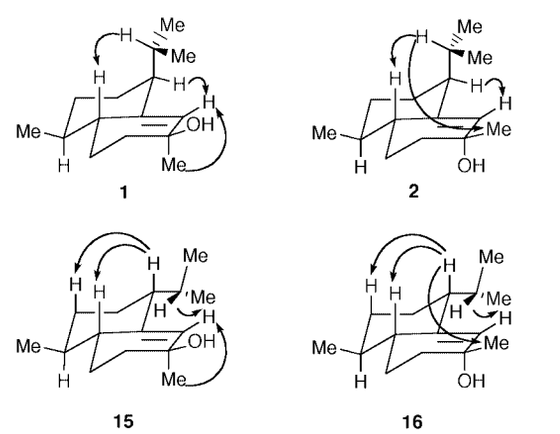


Fig. 5 Preferred conformations of muurolane allylic alcohols **1** and **2** and amorphane allylic alcohols **15** and **16** as demonstrated by NOESY (critical correlations from ^{1}H to ^{1}H indicated by arrows).

(which is the amorphane analogue of **3**). Compound **18** was in turn formed more rapidly than the 3,5-diene **19** (which is the amorphane analogue of **4**, Scheme 2). The same observations held true for the tertiary alcohol 4-epimer **16**, which underwent dehydration more slowly than **15** (*cf.* slower rate of dehydration of **2** as compared with **1**) but gave a qualitatively similar pattern of products. On completion of the dehydration/rearrangement reactions of both **15** and **16** in $CDCl_3$ solution, the reaction mixture consisted predominantly of epizonarene **5**, with only small amounts of the 1(6),4-diene **20**, which is formed by further isomerisation of **18**; by contrast, the final product from dehydration/rearrangement of muurolanes **1** and **2** consisted predominantly of the 1(6),4-diene **17** with smaller amounts of **5**.

Clearly, the main difference between the dehydration of amorphane allylic tertiary alcohols **15** and **16** and muurolane allylic alcohols **1** and **2** in $CDCl_3$ solution is the direct formation of epizonarene **5** in the former case, involving elimination of H-7. The preference for this elimination in the amorphane allylic alcohols can be explained as a consequence of the axial conformation of H-7 in **15** and **16** as compared with the equatorial conformation of H-7 in **1** and **2**. Such conformational preferences have been noted before for muurolane and amorphane sesquiterpenes [3] and were explicitly demonstrated in this study by analysing NOESY spectra for all four isomeric alcohols (Fig. 5). Assuming an E_1 mechanism, direct formation of diene **5** should involve the initial generation of a C-4–C-6 allylic cation by elimination of water, followed by elimination of H-7. The latter process is more favoured when this proton is axial (as is the case for the amorphanes) because there is a better orbital overlap between the $\sigma(C_7–H_7)$ bond and the π-system of the allylic cation in the intermediate (Fig. 6) than is the case when H-7 is equatorial (as is found for muurolane sesquiterpenes **1** and **2**, Fig. 5).

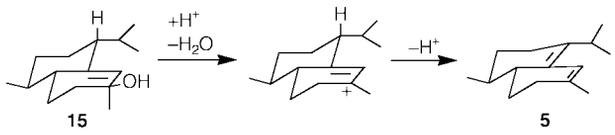


Fig. 6 Dehydration of amorphane allylic tertiary alcohol **15** to epizonarene (**5**) favoured by the axial nature of H-7.

Experimental

General methods

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 (C_6D_6 was also used for compounds **1**, **2**, **15** and **16**). 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 × 25 cm column, flow rate 8 ml min^{-1}. Optical rotations were recorded on a Perkin-Elmer 343 polarimeter at 20 °C and $[\alpha]_D$ has units of 10^{-1} deg cm^2 g^{-1}.

(1*S*,2*R*,4*R*)-1-Methyl-2-(3-oxobutyl)-3-oxo-4-(1-methylethyl)-cyclohexane 9

To a solution of lithium diisopropylamide (LDA) in THF (freshly prepared from BuLi (1.6 M; 3.96 ml), diisopropylamine (0.89 ml) and THF (12 ml)) was added dropwise a solution of (+)-menthone (**8**) in THF (722 mg, 1.2 ml) under cooling (−78 °C). After stirring for 30 min, 3-trimethylsilylbut-3-en-2-one[5] in THF (1.0 g, 2 ml) was added dropwise and stirring continued at −78 °C for 1 h, then the solution was warmed to 0 °C and stirring continued for 2.5 h. The reaction was quenched by acidification with HCl (10%), neutralised with $NaHCO_3$ (5%) and extracted into EtOAc (3 × 20 ml). The organic extract was dried and rotary evaporated to give a crude product which consisted predominantly of diketone **9**, which was purified by preparative HPLC (8% EtOAc–hexane). *(1S,2R,4R)-1-Methyl-2-(3-oxobutyl)-3-oxo-4-(1-methylethyl)cyclohexane* ***9***: oil (335 mg, 32%; R_t 24.8 min); $[\alpha]_D$ +46.1 (*c* 1.5, $CHCl_3$); ν_{max}/cm^{-1} 3024, 3011, 2961, 2932, 2874, 1705, 1445, 1367; δ_H 2.55 (1H, ddd, *J* 17.1, 8.8, 5.7 Hz), 2.34 (1H, ddd, *J* 17.1, 8.1, 4.0 Hz), 2.12 (3H, s), 1.06 (3H, d, *J* 6.2 Hz), 0.89 (3H, d, *J* 6.4 Hz), 0.86 (3H, d, *J* 6.4 Hz); ^{13}C NMR—see Table 1; *m/z* (rel. int.) 224.1775 (M^+, calc. 224.1776 for $C_{14}H_{24}O_2$) (95), 209 (100), 182 (20), 167 (25), 149 (30), 111 (25), 95 (30). *(1S,2R,4S)-1-Methyl-2-(3-oxobutyl)-3-oxo-4-(1-methylethyl)cyclohexane* ***6***: oil (40 mg, 4%; R_t 36.0 min); $[\alpha]_D$ −62.3 (*c* 1.1, $CHCl_3$); ν_{max}/cm^{-1} 3024, 3011, 2961, 2932, 2872, 1705, 1458, 1371; δ_H 2.52 (1H, ddd, *J* 17.4, 8.2, 6.3 Hz), 2.36 (1H, ddd, *J* 17.4, 8.1, 7.9 Hz), 2.12 (3H, s), 1.04 (3H, d, *J* 6.4 Hz), 0.92 (3H, d, *J* 6.3 Hz), 0.80 (3H, d, *J* 6.3 Hz); ^{13}C NMR—see Table 1; *m/z* (rel. int.) 224.1782 (M^+, calc. 224.1776 for $C_{14}H_{24}O_2$) (100), 209 (95), 182 (20), 166 (60), 139 (70), 111 (70), 95 (75). *(1S,2S,4R)-1-Methyl-2-(3-oxobutyl)-3-oxo-4-(1-methylethyl)cyclohexane* ***10***: oil (15 mg, 1.5%; R_t 37.9 min); $[\alpha]_D$ +60.1 (*c* 0.5, $CHCl_3$); ν_{max}/cm^{-1} 3024, 2963, 2932, 2874, 1701, 1458, 1369; δ_H 2.11 (3H, s), 0.92 (3H, d, *J* 6.4 Hz), 0.86 (3H, d, *J* 7.1 Hz), 0.82 (3H, d, *J* 6.4 Hz); ^{13}C NMR—see Table 1; *m/z* (rel. int.) 224.1780 (M^+, calc. 224.1776 for $C_{14}H_{24}O_2$) (95), 209 (100), 181 (17), 166 (62), 153 (65), 124 (70), 111 (80), 95 (55). *(1S,2S,4S)-1-Methyl-2-(3-oxobutyl)-3-oxo-4-(1-methylethyl)cyclohexane* ***11***: oil (5 mg, 0.5%; R_t 36.5 min); $[\alpha]_D$ −5.4 (*c* 0.3, $CHCl_3$); ν_{max}/cm^{-1} 2955, 2876, 1705; δ_H 2.13 (3H, s), 0.89 (3H, d, *J* 6.5 Hz), 0.86 (3H, d, *J* 6.5 Hz), 0.73 (3H, d, *J* 7.2 Hz); ^{13}C NMR—see Table 1; *m/z* (rel. int.) 224.1779 (M^+, calc. 224.1776 for $C_{14}H_{24}O_2$) (90), 209 (100), 181 (15), 167 (55), 153 (60), 139 (45), 124 (50), 95 (50).

(1*R*,6*S*,7*R*,10*S*)-6-Hydroxy-7-(1-methylethyl)-10-methylbicyclo-[4.4.0]decan-4-one 12

To a solution of **9** in EtOH (243 mg, 15 ml) was added $Ba(OH)_2 \cdot 8H_2O$ (342 mg) and the solution was stirred for 3 h at 0 °C. The reaction was neutralised with HCl (10%), concentrated under reduced pressure and extracted with $CHCl_3$ (3 × 20 ml). The organic extract was washed with water (2 × 20 ml), dried and rotary evaporated to yield a crude product (238 mg, 98%) which was shown to consist predominantly of decalone alcohol **12** by preparative HPLC (15% EtOAC–hexane). *(1R,6S,7R,10S)-6-Hydroxy-7-(1-methylethyl)-10-methylbicyclo[4.4.0]decan-4-one* ***12***: oil (120 mg, 51%; R_t 24.8 min); $[\alpha]_D$ +51.4 (*c* 2.6, $CHCl_3$); ν_{max}/cm^{-1} 3614, 3422 (br), 3026, 3011, 2961, 2932, 1709, 1466, 1452; δ_H 2.74 (1H, dd, *J* 14.1, 2.4 Hz), 2.44 (1H, dddd, *J* 14.3, 7.1, 4.6, 2.4 Hz), 2.29 (1H, ddd, *J* 14.3, 14.2, 6.8 Hz), 2.22 (1H, d, *J* 14.1 Hz), 0.95 (3H, d, *J* 6.4 Hz), 0.91 (3H, d, *J* 6.9 Hz), 0.88 (3H, d, *J* 6.9 Hz); ^{13}C NMR—see Table 1; *m/z* (rel. int.) 224.1775 (M^+, calc. 224.1776 for $C_{14}H_{24}O_2$) (30), 209 (20), 164 (15), 139 (100), 111 (20). *(1R,6R,7R,10S)-6-Hydroxy-7-(1-methylethyl)-10-methylbicyclo[4.4.0]decan-4-one* ***13***: oil (3 mg, 1%; R_t 60.4 min); $[\alpha]_D$ +36.2 (*c* 0.1, $CHCl_3$); ν_{max}/cm^{-1} 3595, 3414 (br), 3022, 2961, 2928, 2872, 1707, 1468, 1450; δ_H 2.60 (1H, d, *J* 16.6 Hz), 1.00 (3H, d, *J* 6.5 Hz), 0.96 (3H, d, *J* 6.9 Hz), 0.80 (3H, d, *J* 6.9 Hz); ^{13}C NMR—see Table 1; *m/z* (rel. int.) 224.1784 (M^+, calc. 224.1776 for $C_{14}H_{24}O_2$) (20), 209 (8), 206 (8), 164 (10), 139 (100), 120 (20), 112 (20).

(1*R*,7*S*,10*S*)-7-(1-Methylethyl)-10-methylbicyclo[4.4.0]dec-5-en-4-one 7

A solution of tertiary alcohol **12** in EtOH (70 mg, 15 ml) was stirred in conc. H_2SO_4 (15 ml) at room temperature for 3 h. The reaction was neutralised with $NaHCO_3$ (5%), concentrated under reduced pressure and extracted with $CHCl_3$ (3 × 15 ml). The combined organic extracts were washed with water (2 × 10 ml) and brine (20 ml), dried and rotary evaporated to give a crude product consisting predominantly of decalenone **7** which was purified by preparative HPLC (5% EtOAc–hexane): oil (38 mg, 59%; R_t 55.5 min); $[\alpha]_D$ +49.5 (*c* 0.4, $CHCl_3$); ν_{max}/cm^{-1} 2961, 2930, 2870, 1663; δ_H 5.82 (1H, d, *J* 1.7 Hz), 1.03 (3H, d, *J* 6.0 Hz), 0.97 (3H, d, *J* 6.2 Hz), 0.77 (3H, d, *J* 6.2 Hz); ^{13}C NMR—see Table 1; *m/z* (rel. int.) 206.1672 (M^+, calc. 206.1671 for $C_{14}H_{22}O$) (45), 191 (8), 164 (100), 149 (26), 122 (22).

4β-Hydroxymuurol-5-ene 1 and 4α-hydroxymuurol-5-ene 2 †

To a Grignard reagent freshly prepared from Mg (43 mg), CH_3I (273 mg) and Et_2O (15 ml) was added a solution of the α,β-unsaturated ketone **7** in Et_2O (36 mg, 3 ml). The reaction mixture was refluxed (1 h) and Et_2O (20 ml) was added upon completion. The ethereal layer was washed with water (2 × 5 ml), dried and rotary evaporated to give an oily crude product consisting of sesquiterpene diastereoisomers **1** and **2** in an approximately 1:1 ratio which were separated by preparative HPLC (10% EtOAc–hexane). *4β-Hydroxymuurol-5-ene* ***1***: crystal, mp 75–77 °C (11 mg, 29%; R_t 23.9 min); $[\alpha]_D$ +33.3 (*c* 0.1, $CHCl_3$); ν_{max}/cm^{-1} 3429 (br), 2957, 2928, 2868, 1454, 1367; δ_H ($CDCl_3$) 5.32 (1H, s), 1.26 (3H, s), 0.92 (3H, d, *J* 6.4 Hz), 0.90 (3H, d, *J* 6.6 Hz), 0.77 (3H, d, *J* 6.6 Hz); δ_H (C_6D_6) 5.32 (1H, s), 1.26 (3H, s), 0.85 (3H, d, *J* 6.6 Hz), 0.82 (3H, d, *J* 6.5 Hz), 0.81 (3H, d, *J* 6.6 Hz); ^{13}C NMR—see Table 2; *m/z* (rel. int.) 222.1983 (M^+, calc. 222.1984 for $C_{15}H_{26}O$) (10), 207 (100), 204 (25), 179 (10), 161 (95), 105 (30). *4α-Hydroxymuurol-5-ene* ***2***: oil (11 mg, 29%; R_t 25.5 min); $[\alpha]_D$ +91.4 (*c* 0.1, $CHCl_3$); ν_{max}/cm^{-1} 3442 (br), 2928, 2856; δ_H ($CDCl_3$) 5.35 (1H, s), 1.27 (3H, s), 0.96 (3H, d, *J* 6.4 Hz), 0.89 (3H, d, *J* 6.6 Hz), 0.71 (3H,

† IUPAC names for **1** and **2** are (1*R*,4*S*,7*S*,10*S*)- and (1*R*,4*R*,7*S*,10*S*)-4-hydroxy-7-(1-methylethyl)-4,10-dimethylbicyclo[4.4.0]dec-5-ene, respectively.

d, *J* 6.6 Hz); δ_H (C_6D_6) 5.32 (1H, s), 1.28 (3H, s), 0.87 (3H, d, *J* 6.4 Hz), 0.86 (3H, d, *J* 6.4 Hz), 0.72 (3H, d, *J* 6.4 Hz); ^{13}C NMR—see Table 2; *m*/*z* (rel. int.) 222.1980 (M^+, calc. 222.1984 for $C_{15}H_{26}O$) (5), 207 (100), 204 (15), 161 (30).

(1*R*,7*R*,10*S*)-7-(1-Methylethyl)-10-methylbicyclo[4.4.0]dec-5-en-4-one 14

A solution of tertiary alcohol **12** in EtOH (116 mg, 30 ml) was stirred with HCl (6 M, 30 ml) for 5 h at 0 °C. The reaction was neutralised with $NaHCO_3$ (5%), concentrated under reduced pressure and extracted with $CHCl_3$ (3 × 15 ml). The combined organic extracts were washed with water (2 × 10 ml) and brine (20 ml), dried and rotary evaporated to give a crude product consisting predominantly of decalenone **14** which was purified by HPLC (15% EtOAc–hexane): oil (55 mg, 52%; R_t 17.5 min); $[\alpha]_D$ +3.2 (*c* 0.4, $CHCl_3$); ν_{max}/cm^{-1} 2961, 2932, 2874, 1663; δ_H 5.86 (1H, s), 2.36 (1H, ddd, *J* 17.0, 9.3, 4.6 Hz), 2.28 (1H, ddd, *J* 17.0, 14.0, 5.0 Hz), 2.17 (1H, m), 1.04 (3H, d, *J* 6.4 Hz), 0.96 (3H, d, *J* 6.7 Hz), 0.88 (3H, d, *J* 6.7 Hz); ^{13}C NMR—see Table 1; *m*/*z* (rel. int.) 206.1672 (M^+, calc. 206.1671 for $C_{14}H_{22}O$) (50), 191 (8), 164 (100), 149 (18), 122 (18).

4β-Hydroxyamorph-5-ene 15 and 4α-hydroxyamorph-5-ene 16‡

To a Grignard reagent freshly prepared from Mg (43 mg), CH_3I (273 mg) and Et_2O (15 ml) was added a solution of the α,β-unsaturated ketone **14** in Et_2O (36 mg, 3 ml). The reaction mixture was refluxed (1 h) and Et_2O (20 ml) was added upon completion. The ethereal layer was washed with water (2 × 5 ml), dried and rotary evaporated to give an oily crude product consisting of sesquiterpene diastereoisomers **15** and **16** in an approximately 3:2 ratio which were separated by preparative HPLC (10% EtOAc–hexane). *4β-Hydroxyamorph-5-ene* ***15***: crystal, mp 46–47 °C (15 mg, 38%; R_t 25.5 min); $[\alpha]_D$ +37.2 (*c* 0.3, $CHCl_3$); ν_{max}/cm^{-1} 3599, 3420 (br), 3007, 2959, 2930, 2872, 1452, 1371, 1215; δ_H ($CDCl_3$) 5.29 (1H, s), 1.28 (3H, s), 0.95 (3H, d, *J* 6.7 Hz), 0.92 (3H, d, *J* 6.2 Hz), 0.86 (3H, d, *J* 6.7 Hz); δ_H (C_6D_6) 5.34 (1H, s), 1.28 (3H, s), 0.96 (3H, d, *J* 6.7 Hz), 0.86 (3H, d, *J* 6.7 Hz), 0.83 (3H, d, *J* 6.0 Hz); ^{13}C NMR—see Table 2; *m*/*z* (rel. int.) 222.1984 (M^+, calc. 222.1984 for $C_{15}H_{26}O$) (5), 207 (100), 202 (50), 189 (10), 179 (7), 161 (50). *4α-Hydroxyamorph-5-ene* ***16***: oil (10 mg, 27%; R_t 22.6 min); $[\alpha]_D$ +69.2 (*c* 0.4, $CHCl_3$); ν_{max}/cm^{-1} 3599, 3429 (br), 3007, 2959, 2930, 2872, 1452, 1375; δ_H ($CDCl_3$) 5.35 (1H, s), 1.29 (3H, s), 0.96 (3H, d, *J* 6.2 Hz), 0.95 (3H, d, *J* 6.7 Hz), 0.86 (3H, d, *J* 6.7 Hz); δ_H (C_6D_6) 5.39 (1H, s), 1.30 (3H, s), 0.92 (3H, d, *J* 6.7 Hz), 0.87 (3H, d, *J* 6.7 Hz), 0.86 (3H, d, *J* 6.1 Hz); ^{13}C NMR—see Table 2; *m*/*z* (rel. int.) 222.1978 (M^+, calc. 222.1984 for $C_{15}H_{26}O$) (10), 207 (100), 204 (10), 179 (18), 161 (70).

Dehydration of muurolane allylic alcohols (1 and 2) in $CDCl_3$

Compound **1** (10 mg) was dissolved in $CDCl_3$ (0.6 ml) in an NMR tube wrapped in silver foil (to prevent Diels–Alder type addition reactions of singlet oxygen with endocyclic dienes formed during the reaction) and left at room temperature. ^{1}H NMR spectra were acquired at intervals of several hours during the first few days of the reaction and then once or twice a day until all reaction had ceased. Spectra for around 20–30 time points acquired in this way were then used to create a graph of the percentage composition of each diene product in the mixture against time by calculating the ratio of an integral in ^{1}H NMR for an alkene proton which was clearly resolved for each particular compound (**1**: H-5, δ 5.32 (1H, s); **2**: H-5, δ 5.35 (1H, s); **3**: H-5, δ_H 5.90 (1H, s); **4**: H-3, δ_H 5.25 (1H, br s); **5**: H-5, δ_H 6.22 (1H, s); **17**: H-5, δ_H 5.61 (1H, s)) to the sum of all such integrals. The product distribution for dehydration/rearrangement of compound **2** (10 mg, 0.6 ml, $CDCl_3$) was calculated in the same way. *Muurola-4(15),5-diene* ***3***:§ see ref. 1 for physical data; δ_H 5.90 (1H, s), 4.68 (1H s), 4.62 (1H, s), 0.95 (3H, d, *J* 6.4 Hz), 0.92 (3H, d, *J* 6.6 Hz), 0.77 (3H, d, *J* 6.6 Hz); ^{13}C NMR—see Table 2. *Muurola-3,5-diene* ***4***:§ see ref. 1 for physical data; δ_H 5.42 (1H, s), 5.25 (1H, br s), 1.68 (3H, d, *J* 1.7 Hz), 0.91 (3H, d, *J* 6.3 Hz), 0.90 (3H, d, *J* 6.6 Hz), 0.80 (3H, d, *J* 6.6 Hz); ^{13}C NMR—see Table 2. *Epizonarene (muurola-4,6-diene)* ***5***:§ see ref. 1 for physical data; δ_H 6.22 (1H, s), 3.03 (1H, sept, *J* 6.9 Hz), 1.77 (3H, s), 0.97 (3H, d, *J* 6.8 Hz), 0.96 (3H, d, *J* 6.9 Hz), 0.95 (3H, d, *J* 6.9 Hz); ^{13}C NMR—see Table 2. *Muurola-1(6),4-diene* ***17***:§ oil, δ_H 5.61 (1H, s), 1.78 (3H, s), 1.02 (3H, d, *J* 7.0 Hz), 0.93 (3H, d, *J* 6.6 Hz), 0.68 (3H, d, *J* 6.6 Hz); ^{13}C NMR—see Table 2; *m*/*z* (rel. int.) 204.1868 (M^+, calc. 204.1878 for $C_{15}H_{24}$) (55), 189 (33), 161 (100), 159 (30), 133 (20), 119 (35), 105 (40).

Dehydration of amorphane allylic alcohols (15 and 16) in $CDCl_3$

Compound **15** (10 mg) was dissolved in $CDCl_3$ (0.6 ml) in an NMR tube wrapped in silver foil (to prevent Diels–Alder type addition reactions of singlet oxygen with endocyclic dienes formed during the reaction) and left at room temperature. ^{1}H NMR spectra were acquired at intervals of several hours during the first few days of the reaction and then once or twice a day until all reaction had ceased. Spectra for around 20–30 time points acquired in this way were then used to create a graph of the percentage composition of each diene product in the mixture against time by calculating the ratio of an integral in ^{1}H NMR for an alkene proton which was clearly resolved for each particular compound (**15**: H-5, δ 5.29 (1H, s); **16**: H-5, δ 5.35 (1H, s); **5**: H-5, δ_H 6.22 (1H, s); **18**:¶ H-5, δ_H 5.90 (1H, s); **19**: H-5, δ_H 5.47 (1H, s); **20**: H-5, δ_H 5.61 (1H, s) to the sum of all such integrals. The product distribution for dehydration/rearrangement of compound **16** (10 mg, 0.6 ml, $CDCl_3$) was calculated in the same way. *Epizonarene* ***5***: physical data as in previous section. *Amorpha-4(15),5-diene* ***18***: δ_H ($CDCl_3$) 5.90 (1H, s), 4.72 (1H, s), 4.66 (1H, s), 0.99 (3H, d, *J* 6.4 Hz), 0.95 (3H, d, *J* 6.2 Hz), 0.86 (3H, d, *J* 6.4 Hz); ^{13}C NMR—see Table 2. *Amorpha-3,5-diene* ***19***:¶ δ_H 5.47 (1H, d, *J* 1.4 Hz), 5.29 (1H, br s), 1.71 (3H, d, *J* 1.8 Hz), 0.97 (3H, d, *J* 6.4 Hz), 0.92 (3H, d, *J* 6.2 Hz), 0.88 (3H, d, *J* 6.4 Hz); ^{13}C NMR—see Table 2. *Amorpha-1(6),4-diene* ***20***:¶ δ_H 5.61 (1H, s), 1.79 (3H, s), 0.96 (3H, d, *J* 6.4 Hz), 0.92 (3H, d, *J* 6.7 Hz), 0.70 (3H, d, *J* 6.7 Hz); ^{13}C NMR—see Table 2.

Acknowledgements

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‡ IUPAC names for **15** and **16** are (1*R*,4*S*,7*R*,10*S*)- and (1*R*,4*R*,7*R*,10*S*)-4-hydroxy-7-(1-methylethyl)-4,10-dimethylbicyclo[4.4.0]dec-5-ene, respectively.

§ IUPAC name for **3** is (1*R*,7*S*,10*S*)-4-methylidene-7-(1-methylethyl)-10-methylbicyclo[4.4.0]dec-5-ene. IUPAC name for **4** is (1*R*,7*S*,10*S*)-7-(1-methylethyl)-4,10-dimethylbicyclo[4.4.0]deca-3,5-diene. IUPAC name for **5** is (1*R*,10*S*)-7-(1-methylethyl)-4,10-dimethylbicyclo[4.4.0]-deca-4,6-diene. IUPAC name for **17** is (7*S*,10*S*)-7-(1-methylethyl)-4,10-dimethylbicyclo[4.4.0]deca-1(6),4-diene.

¶ IUPAC name for **18** is (1*R*,7*R*,10*S*)-4-methylidene-7-(1-methylethyl)-10-methylbicyclo[4.4.0]dec-5-ene. IUPAC name for **19** is (1*R*,7*R*,10*S*)-7-(1-methylethyl)-4,10-dimethylbicyclo[4.4.0]deca-3,5-diene. IUPAC name for **20** is (7*R*,10*S*)-7-(1-methylethyl)-4,10-dimethylbicyclo[4.4.0]deca-1(6),4-diene.

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