Pergamon

Tetrahedron 55 (1999) 15099–15108

TETRAHEDRON

Synthesis of Amorphane and Cadinane Sesquiterpenes from *Fabiana imbricata*

Koon-Sin Ngo and Geoffrey D. Brown*

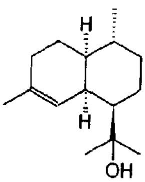
Chemistry Department, The University of Hong Kong, Pokfulam Rd., Hong Kong.

Received 27 July 1999; revised 12 October 1999; accepted 28 October 1999

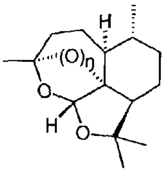
Abstract: The monoterpene (-)-isopulegol (7) has been used as a starting material for the total synthesis in eight/nine steps of two sesquiterpenes which were recently isolated from the medicinal plant *Fabiana imbricata*. Use of this approach has shown that a structure proposed as 3,11-amorphadiene (3) should be revised to that of 4,11-cadinadiene (**18**) and confirmed the structure proposed for the natural product 4-amorphen-11-ol (1).

INTRODUCTION

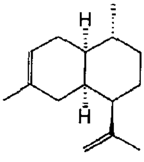
Recent chemical investigations of the Chilean medicinal plant *Fabiana imbricata* (Ruiz. and Pav.)[1] have described a number of amorphane sesquiterpenes and derived compounds[2] including 4-amorphen-11-ol (**1**),[3] the 4,5-*seco*-amorphane, fabianane (**2**)[4] - which was suggested to be derived from **1**, and a sesquiterpene diene for which the structure **3** (3,11-amorphadiene)[5] was proposed. Jung and Youn have recently reported a partial synthesis[6] of **1** from the amorphane sesquiterpene artemisinic acid (**4**) (a non-commercially available natural product isolated from *Artemisia annua*), and were able to confirm that **1** can indeed be converted into **5** (the peroxo analogue of **2**) in the presence of singlet oxygen (*cf.* conversion of artemisinic acid to the anti-malarial natural product artemisinin (**6**) under similar conditions).[7] We now report the first total synthesis of **1** from commercially available (-)-isopulegol (**7**); this synthetic 4-amorphen-11-ol (**1**) is used as substrate for a detailed investigation of the complex mechanism involved in transformation of **1** to **5** in the companion paper. In addition, the synthetic route employed in the total synthesis of **1** has also resulted in the preparation of a series of amorphane and cadinane sesquiterpenes: it is demonstrated that there are consistent and reliable differences in ^{1}H and ^{13}C NMR spectra of these two diastereoisomeric series and this information is used to revise the structure of "3,11-amorphadiene" claimed as a natural product from *F. imbricata*[5] to that of 4,11-cadinadiene obtained by synthesis.



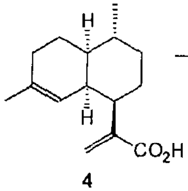
1



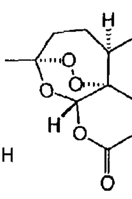
2 n=1
5 n=2



3



4



6

0040-4020/99/$ - see front matter © 1999 Elsevier Science Ltd. All rights reserved.
PII: S0040-4020(99)00985-0

RESULTS AND DISCUSSION

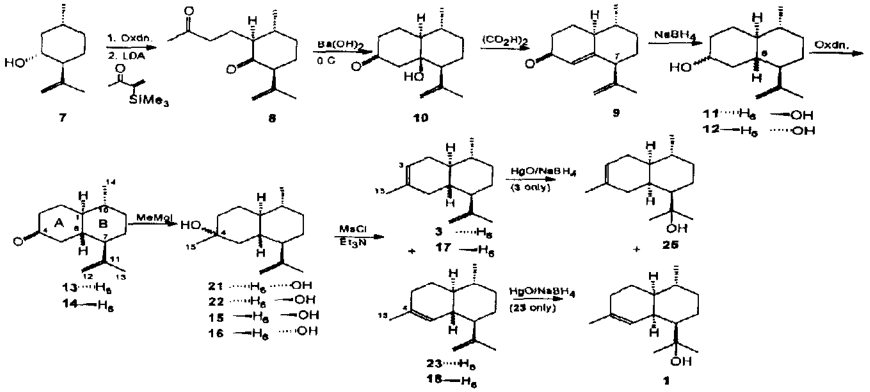
The monoterpene (-)-isopulegol has frequently been employed in the synthesis of cadinane and amorphane sesquiterpenes since it possesses the correct absolute stereochemistry ultimately required in many such natural products at the 7- and 10-positions.[8] In this study, (-)-isopulegol (**7**) was first oxidized to isopulegone, the kinetic enolate of which was used in Michael-type addition to 3-trimethylsilyl-3-buten-2-one[9] to generate the diketone **8**. Robinson annulation of **8** in the presence of $Ba(OH)_2$ at room temperature has been previously reported to result in a poor yield of the desired decalenone product **9** due to both isomerization of the terminal double bond into conjugation with the newly formed α,β-unsaturated ketone group as well as to the occurrence of epimerization at the 7-position.[10] At lower temperature, it was found that the reaction could be stopped at the stage of the tertiary alcohol product **10** which is formed from the initial aldol reaction; compound **10** could then be cleanly converted into the desired α,β-unsaturated ketone **9** by treatment with oxalic acid,[9] without concomitant epimerization or double bond migration.

Somewhat surprisingly, conjugate reduction of the endocyclic double bond in **9** was found to occur from both faces of the molecule, resulting in both the 6α-H epimer (**11**) and the 6β-H epimer (**12**) in an approximately 1:1 ratio. Conjugate reduction of very closely related decalenones in which a saturated isopropyl derivative is present as the 7β-substituent has been reported to lead exclusively to the corresponding 6α-H product.[9,10] We propose that the planar 7β-isopropenyl group (sp^2 hybridisation at C-11) in **9** adopts a conformation perpendicular to the plane of the decalenone ring system and therefore does not hinder hydride attack from either face of the molecule; by contrast, all conformations for compounds in which there is a sp^3 hybridised carbon at C-11 of a saturated isopropyl derivative (constituting the 7β-substituent) must lead to some shielding of the β-face of the molecule and thereby favour α-reduction at the 6-position (see also companion paper). Although isomers **11** and **12** were separable by normal phase preparative HPLC, it was more expedient to oxidize the diastereoisomeric mixture **11/12** to the corresponding ketones **13/14**, which were then more conveniently chromatographically separated.

Compounds **13** and **14** (as well as compounds **11** and **12**) were assigned as *cis* and *trans*-decalins respectively on the basis of nuclear Overhauser enhancements observed between protons in NOESY spectra for each compound (Figure 1). In order to be able to interpret such spectra all protons - and carbons - in both compounds were first completely assigned by the use of other 2D-NMR techniques such as HSQC, HMBC and ^1H-^1H COSY - see Tables 1 and 2. Chemical shifts thus established for the bridgehead protons H-1 and H-6 in the *trans* isomer **14** were significantly upfield as compared with the *cis* form **13**, as is expected for axial protons;[11] in addition a large axial-axial coupling constant ($J_{1,6}$ = 11.7 Hz) was evident between these two protons in the 1D-^1H NMR spectrum of **14**. Both observations also held true for all *trans*-decalins (**15**, **16** and **17-20**) derived from **14** (δ_H 0.56-1.07 ppm for H-1 and δ_H 1.00-1.69 ppm for H-6) and all *cis*-decalins (**1**,

3, 21-25) derived from **13** (δ_H 1.16-1.45 ppm for H-1 and δ_H 1.88-2.65 ppm for H-6) (Table 2, all compounds were rigorously assigned by 2D-NMR). Clear differences between the two diastereoisomeric series were also evident in ^{13}C assignments (Table 1) for C-8 (δ_C *cis* 21.5-25.8; δ_C *trans* 31.9-32.6) and C-10 (δ_C *cis* 26.8-28.2; δ_C *trans* 36.5-38.1) for which strong upfield shifts in the B-ring of the *cis* isomers can be ascribed to gauche effects arising from the proximity of H-3β and H-5β in the A-ring. The NMR chemical shift data presented in Tables 1 and 2 thus presents consistent and reliable criteria in ^{1}H and ^{13}C NMR spectra for differentiating amorphane sesquiterpenes, containing a *cis*-decalin system, from cadinane sesquiterpenes, containing a *trans*-decalin ring.

Reaction of the ketone group of **13** with a methyl Grignard reagent resulted in two diastereoisomeric alcohols **21** and **22** which were separable and shown to be epimeric at the 4-position, and for which relative stereochemistry of the new methyl ring-substituent was determined by the same NMR procedures as previously (full assignments given in Tables 1 and 2). Dehydration of such tertiary alcohols is expected to be a facile procedure, and there are several examples in the literature of quite closely related compounds where conversion to the corresponding tri-substituted double bond can be achieved by use of *p*-toluenesulfonic acid.[9] However, in our hands, treatment of compounds **21/22** with this reagent invariably led to complex mixtures in which extensive double bond rearrangement had occurred and ultimately resulted in complete conversion to the ring-B aromatized compound **26**. However, treatment of **21/22** with methanesulfonyl chloride in the presence of base did yield the expected Δ^3- and Δ^4-diene products **3** and **23** (together with a little $\Delta^{4(15)}$ dehydration product **24**). The position of the new tri-substituted double bond in these two regioisomers was unambiguously established by 2D-NMR (Figure 2).



Scheme 1. Synthesis of 4-amorphen-11-ol (**1**), 3,11-amorphadiene (**3**) and 4,11-cadinadiene (**18**) from (-)-isopulegol (**7**).

Table 1. ^{13}C NMR assignments for compounds **1**, **3**, **11-18**, **21-23** and **25** established by 2D-NMR.

		cis-decalins								*trans*-decalins					
Assign-ment	Mult.[a]	1	3	11	13	21	22	23	25	12	14	15	16	17	18
1	CH	42.5	42.5	43.2	42.8	43.4	43.6	41.8	43.2	48.0	47.5	48.3	48.7	43.9	46.2
2	CH_2	25.9	28.0	26.4	27.9	23.6	25.8	26.1	27.8	28.8	30.7	26.0	28.5	31.3	26.7
3	CH_2	26.4	118.7 (CH)	30.2	36.9	33.4	35.1	26.5	118.6 (CH)	35.8	41.4	38.8	40.5	120.2 (CH)	31.0
4	C	134.6	132.6	72.2 (CH)	212.9	70.0	72.0	134.6	132.4	71.0 (CH)	212.1	69.6	71.2	133.4	134.1
5	CH_2	122.2 (CH)	26.8	31.0	38.2	34.0	35.8	120.9 (CH)	28.6	40.5	46.0	43.6	45.4	36.0	123.9 (CH)
6	CH	38.4	34.9	37.8	39.9	33.8	36.8	37.6	34.8	42.4	44.5	38.9	41.7	39.4	42.9
7	CH	51.4	47.3	47.6	47.1	47.5	47.4	47.6	52.1	52.4	53.4	52.5	52.6	53.2	51.3
8	CH_2	22.9	24.7	25.2	24.5	25.1	25.0	25.8	21.5	32.2	31.9	32.3	32.2	31.9	32.6
9	CH_2	36.0	35.9	36.0	35.4	35.9	35.8	35.4	36.2	35.5	35.2	35.6	35.5	35.2	35.8
10	CH	27.8	28.2	27.6	27.4	26.8	27.0	27.9	27.9	37.1	36.9	37.1	37.2	38.1	36.5
11	C	73.1	148.0	147.6	146.4	148.0	147.5	148.0	73.1	148.4	147.1	148.8	148.4	148.7	148.8
12	CH_2	30.6[b]	109.0	109.7	110.2	109.3	109.7	109.8	29.5[b]	111.0	111.7	110.8	111.0	110.6	111.2
13	CH_3	28.0[b]	22.7	22.5	22.3	22.6	22.4	22.6	28.1[b]	18.8	18.5	18.8	18.7	18.7	19.1
14	CH_3	19.8	20.2	19.7	19.6	19.9	19.8	19.8	20.1	20.0	20.1	19.9	20.0	19.9	19.7
15	CH_3	23.9	23.6	-	-	32.0	26.2	23.7	23.7	-	-	31.6	25.9	23.4	23.5

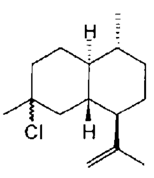
[a] Multiplicity determined from DEPT; [b] Assignments interchangeable within column

Table 2. ^{1}H NMR[a] assignments for compounds **1**, **3**, **11-18**, **21-23** and **25** established by 2D-NMR.

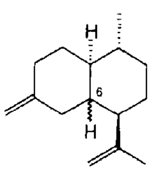
	cis-decalins								*trans*-decalins					
Assign-ment[d]	1	3	11	13	21	22	23	25	12	14	15	16	17	18
1	1.20	1.31	1.21	1.45	1.27	1.24	1.33	1.16	0.58 (1H, dddd, 11.6, 9.8, 9.8, 3.5)	1.07 (1H, dddd, 11.7, 9.8, 9.8, 3.5)	0.56 (1H, dddd, 11.5, 9.9, 9.9, 3.4)	0.61 (1H, dddd, 11.8, 9.9, 9.9, 3.5)	0.88 (1H, dddd, 11.9, 9.8, 9.8, 3.4)	0.75 (1H, dddd, 11.9, 9.8, 9.8, 3.5)
2	1.55 1.90	2.07 2.17	1.32 (α) 1.95 (β)	1.66 (α) 2.22 (β)	1.67 (α) 1.75 (β)	1.38 (α) 1.89 (β)	1.26 1.96	2.08 2.14	2.00 (α) 0.87 (β)	2.30 (α) 1.27 (β)	1.81 (α) 1.19 (β)	1.95 (α) 0.94 (β)	2.28 1.58	2.00 1.15
3	1.90 1.77	5.25 (1H, br s)	1.72 (α) 1.31 (β)	2.20 (α) 2.30 (β)	1.39 1.39	1.48 (α) 1.43 (β)	1.90 1.78	5.26 (1H, d, 5.0)	1.16 (α) 2.00 (β)	2.28 (α) 2.38 (β)	1.31 (α) 1.67 (β)	1.38 (α) 1.73 (β)	5.34 (1H, d, 4.0)	1.98 1.95
4	-	-	3.56 (1H, tt, 11.0, 5.6)	-	-	-	-	-	3.53 (1H, tt, 11.0, 4.2)	-	-	-	-	-
5	5.66 (1H, s)	1.77 1.47	1.47 (α) 1.22 (β)	1.98 (α) 2.22 (β)	1.31 (α) 1.11 (β)	1.40 (α) 1.17 (β)	5.06 (1H, br s)	2.03 1.84	0.78 (α) 1.92 (β)	1.88 (α) 2.35 (β)	0.88 (α) 1.58 (β)	0.96 (α) 1.64 (β)	1.50 1.84	5.25 (1H, s)
6	2.65	2.14	1.88	2.29	2.19	1.92	2.55 (1H, br)	2.19	1.00	1.39	1.35	1.05	1.25	1.69
7	1.31	2.08	2.08	2.17	2.07	2.07	1.99	1.47	1.78	1.88	1.72	1.74	1.75	1.77
8	1.55 1.28	1.64 1.50	1.50 (α) 1.58 (β)	1.55 (α) 1.59 (β)	1.50 1.50	1.51 1.51	1.52 1.52	1.67 1.58	1.57 (α) 1.41 (β)	1.62 (α) 1.39 (β)	1.58 (α) 1.45 (β)	1.58 (α) 1.40 (β)	1.57 1.43	1.60 1.43
9	0.94 1.72	1.02 1.76	1.01 (α) 1.75 (β)	1.14 (α) 1.87 (β)	1.02 (α) 1.75 (β)	1.01 (α) 1.77 (β)	0.97 1.67	1.00 1.77	1.07 (α) 1.69 (β)	1.15 (α) 1.74 (β)	1.08 (α) 1.70 (β)	1.09 (α) 1.69 (β)	1.10 1.69	1.12 1.69
10	1.20	1.38	1.66	1.79	1.57	1.70	1.40	1.43	1.06	1.15	1.14	1.09	1.11	1.17
12	1.29 (3H, s)[b]	4.78 (1H, q, 1.4) 4.62 (1H, s)	4.79 (1H, d, 1.2)[c] 4.59 (1H, s)	4.80 (1H, s)[c] 4.58 (1H, s)	4.78 (1H, s)[c] 4.57 (1H, s)	4.79 (1H, q, 1.4)[c] 4.58 (1H, s)	4.87 (1H, d, 1.2) 4.65 (1H, s)	1.24 (3H, s)	4.70 (1H, d, 1.4)[c] 4.68 (1H, s)	4.73 (1H, s)[c] 4.68 (1H, s)	4.69 (1H, q, 1.5)[c] 4.66 (1H, d, 2.3)	4.69 (1H, q, 1.4)[c] 4.66 (1H, q, 0.5)	4.69 (2H, m)	4.77 (1H, q, 1.5) 4.68 (1H, s)
13	1.26 (3H, s)[b]	1.74 (3H, s)	1.71 (3H, s)	1.69 (3H, s)	1.72 (3H, s)	1.70 (3H, s)	1.74 (3H, s)	1.24 (3H, s)	1.61 (3H, s)	1.60 (3H, s)	1.62 (3H, s)	1.61 (3H, dd, 1.4, 0.5)	1.64 (3H, s)	1.65 (3H, s)
14	0.87 (3H, d, 6.6)	0.84 (3H, d, 6.3)	0.86 (3H, d, 6.4)	0.97 (3H, d, 6.4)	0.86 (3H, d, 6.4)	0.86 (3H, d, 6.4)	0.89 (3H, d, 6.3)	0.82 (3H, d, 6.5)	0.89 (3H, d, 6.0)	0.98 (3H, d, 5.7)	0.89 (3H, d, 6.3)	0.89 (3H, d, 6.0)	0.90 (3H, d, 6.1)	0.91 (3H, d, 6.3)
15	1.63 (3H, s)	1.61 (3H, s)	-	-	1.19 (3H, s)	1.23 (3H, s)	1.61 (3H, s)	1.63 (3H, s)	-	-	1.19 (3H, s)	1.20 (3H, s)	1.61 (3H, s)	1.62 (3H, s)

[a] Integral, multiplicity and coupling constant when resolved in 1D-NMR indicated in parentheses.

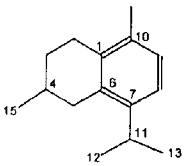
[b] Assignments interchangeable within column; [c] H-12 *cis* to 13-Me group assigned by NOESY spectroscopy; [d] α or β assignments made on the basis of correlations observed in NOESY spectroscopy



20

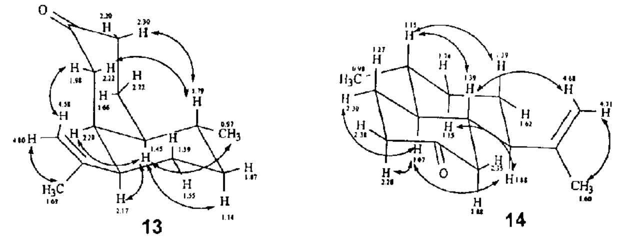


24 ·····H$_6$
19 —H$_6$



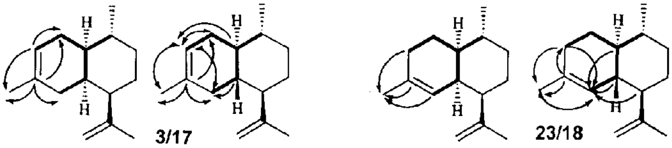
26

Full NMR assignments for compound **3** obtained from total synthesis were significantly different from those claimed for 3,11-amorphadiene which was isolated as a natural product from *F. imbricata*,[5] and the structure of the latter must therefore be in error. However, ^{1}H NMR data for the Δ^4-regioisomer **23** gave reasonable agreement with a natural product of the same structure and stereochemistry - incorrectly referred to as cadina-4,11-diene - previously reported from *Viguiera oblongifolia*.[12] Regioselective hydration of the terminal bond in **23** in the presence of mercuric oxide resulted in compound **1**, which was identical in all respects with the natural product 4-amorphen-11-ol from *F. Imbricata*,[5] thereby confirming the amorphane stereochemistry deduced for intermediates **3**, **11**, **13** and **21-23**. The alkene proton in **21** is significantly downfield-shifted (δ_H 5.66 ppm) when compared to that of its Δ^3-isomer **25** (δ_H 5.26 ppm) which is consistent with the proximity of the 7β-isopropoxyl group to the Δ^4-double bond in the former regioisomer.



13 **14**

Figure 1. Critical NOESY correlations used in defining the *cis* and *trans*-ring junctions for **13** and **14** (indicated by arrows from ^{1}H to ^{1}H).



3/17 **23/18**

Figure 2. Critical HMBC correlations (indicated by arrows from ^{13}C to ^{1}H) and ^{1}H-^{1}H COSY correlations (indicated by bold lines) used in defining the location of the Δ^3- and Δ^4-double bond in regioisomers **3/17** and **23/18**.

Comparison of all ^{1}H and ^{13}C NMR chemical shifts reported in the literature for "3,11-amorphadiene" as a natural product from *F. imbricata*[5] with the full assignments established for *cis*- and *trans*-decalins **3**, **11-16** and **21-23** obtained by synthesis which are reported in Tables 1 and 2 suggested that this compound might more correctly be formulated as containing a *trans*-decalin rather than a *cis*-decalin ring. In particular, chemical shifts reported for H-1 (δ_H 0.75 ppm), H-6 (δ_H 1.65 ppm), C-8 (δ_C 32.6 ppm) and C-10 (δ_C 36.5 ppm) in the natural product "3,11-amorphadiene" are well outside the typical ranges noted earlier for amorphane sesqiuiterpenes (*cis*-decalin) but nicely within the ranges expected for cadinane sesquiterpenes (*trans*-decalin). In order to confirm this, the *trans*-decalin ketone **14** was subjected to the same series of transformations as for **13**, resulting in the pair of *trans*-decalin diene Δ^3- and Δ^4-regioisomers **17** and **18** as the major products (critical HMBC and ^{1}H-^{1}H COSY correlations used to distinguish these regioisomers are shown in Figure 2; full NMR assignments are given in Tables 1 and 2) together with a little of terminal diene **19** and hydrogen chloride addition product **20** (probably arising *via* trapping of the tertiary carbonium ion derived from alcohols **15/16** by chloride ion) . Indeed, NMR data for the Δ^4-*trans*-decalin diene **18** gave an excellent match with that reported in the literature for this natural product and in consequence we suggest that "3,11-amorphadiene" obtained from *F. imbricata* should be reformulated as 4,11-cadinadiene (**18**).

EXPERIMENTAL

Chemical shifts are expressed in ppm (δ) relative to TMS as internal standard. All NMR experiments were run on a Bruker DRX 500 instrument. HSQC and HMBC spectra were recorded with 1024 data points in F_2 and 256 data points in F_1. High-resolution MS were recorded in EI mode at 70 e.v. on a Finnigan-MAT 95 MS spectrometer. IR spectra were recorded in $CHCl_3$ on a Shimadzu FT-IR-8201 PC instrument. Column chromatography was performed using silica gel 60-200 μm (Merck). HPLC separations were performed using a Varaian chromatograph equipped with RI star 9040 and UV 9050 detectors and a normal phase Intersil PREP-SIL 20 mm x 25 cm column, flow rate 8 mL/min.

Conversion of (-)-isopulegol (7) to **8** - see reference 10 for procedure and physical data for **8**.

Aldol reaction of 1β-(butan-3-one)-isopulegol (**8**). To a solution of **8** (3.00 g) in EtOH (90 ml) was added $Ba(OH)_2.8H_2O$ (4.26 g) and the solution was stirred at ice-bath temperature for 1.5 h. The solution was then neutralized with HCl (10%) and concentrated under reduced pressure. The residue was extracted with CH_2Cl_2 (3 x 150 ml) and the organic extract was washed with water, dried ($MgSO_4$) and rotary evaporated. The crude product **10** (2.51 g, 84 % yield) was used in the next step without any need for purification. $[\alpha]_D$ -16.3 (*c* 0.6, $CHCl_3$); IR υ_{max} 3553, 2959, 2930, 1713, 1450, 1371, 1217 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.93 (1H, t, *J* = 1.5 Hz, H-12), 4.75 (1H, s, H-12), 2.41 (1H, m, H-3β), 2.38 (1H, d, *J* = 14.0 Hz, H-5α), 2.34 (1H, d, *J* = 14.0 Hz, H-5β), 2.30 (1H, m, H-3α), 2.09 (1H, m, H-2α), 2.07 (1H, dd, *J* = 11.4, 3.3 Hz, H-7), 1.81 (1H, m, H-8α), 1.78 (3H, s, H-13), 1.75 (1H, m, H-9β), 1.72 (1H, m, H-2β), 1.53 (1H, m, H-10), 1.48 (1H, m. H-8β), 1.34 (1H, m, H-1) ,1.11 (1H, dddd, *J* = 12.3, 12.3, 12.3, 3.3 Hz, H-9α) ,0.95 (3H, d, *J* = 6.4 Hz, H-14); ^{13}C NMR (125 MHz, $CDCl_3$) δ 211.0 C (C-4), 146.7 C (C-11), 113.1 CH_2 (C-12), 75.8 C (C-6), 54.7 CH (C-7), 53.1 CH_2

(C-5), 49.9 CH (C-1), 41.1 CH_2 (C-3), 35.3 CH_2 (C-9), 31.8 CH (C-10), 27.3 CH_2 (C-8), 25.7 CH_2 (C-2), 24.7 CH_3 (C-13), 20.1 CH_3 (C-10); MS (EI) *m/z* (rel. intensity) 222 (100), 204 (60), 164 (20), 139 (100), 110 (85); HRMS calcd. for $[M^+]$ $C_{14}H_{22}O_2$ 222.1620, found 222.1617.

Dehydration of 4-keto-6β-hydroxy-15-nor-amorph-11-ene (**10**). Compound **10** (2.35 g) was stirred with oxalic acid in EtOH (100 ml; 2.5% soln.) for 6 days. The solution was neutralized with $NaHCO_3$ (5%) and concentrated under reduced pressure. The residue was extracted with CH_2Cl_2 (3 x 100 ml), and the combined organic extracts were washed with water (2 x 100 ml) and brine (100 ml), then dried and rotary evaporated to give the α,β-unsaturated ketone **9** (1.73 g, 80 % yield) without need for further purification. $[\alpha]_D$ -22.8 (*c* 2.96, $CHCl_3$); IR υ_{max} 3011, 2959, 2932, 2872, 1713, 1663, 1450, 1379, 1217 cm^{-1} - other physical data for **9** identical with reference 10.

Reduction of 4-keto-15-nor-amorph-5,11-diene (9) to 15-nor-amorph-11-en-4β-ol (11) and 15-nor-cadin-11-en-4α-ol (12). To a solution of $NaBH_4$ in pyridine (1.67 g, 15 ml) was added a solution of α,β-unsaturated ketone **9** in pyridine (1.5 g, 15 ml). The reaction mixture was stirred at room temperature for 6 h, then water (10 ml) was added and stirring continued for a further 3 h. The reaction mixture was diluted with Et_2O (250 ml) and acidified with HCl (10%). The ethereal layer was then separated and washed successively with HCl (10%, 4 x 40 ml), Na_2SO_3 (2 x 40 ml) and water (40 ml) and the extract was dried and concentrated to give an oil, shown by NMR spectroscopy to consist of diastereoisomers **11** and **12** in an approximately 1:1 ratio (911 mg, 60% yield) which were separable with difficulty by HPLC (15% EtOAc/hexane): **11** (R_f 27.5 min), **12** (R_f 27.7 min). (**11**): Oil. $[\alpha]_D$ -21.3 (*c* 0.2, $CHCl_3$); IR υ_{max} 3429 (br), 3007, 2930, 2870, 1467, 1379 cm^{-1}. ^1H and ^{13}C NMR, see Tables 1 and 2; MS (EI) *m/z* (rel. intensity) 208 (30), 190 (100), 175 (30), 148 (60), 107 (35), 105 (40); HRMS calcd. for $[M^+]$ $C_{14}H_{24}O$ 208.1827, found 208.1824. (**12**): Oil. $[\alpha]_D$ -12.4 (*c* 0.6, $CHCl_3$); IR υ_{max} 3427 (br), 3009, 2970, 2924, 2860, 1645, 1447 1377, 1211 cm^{-1}. ^1H and ^{13}C NMR, see Tables 1 and 2; MS (EI) *m/z* (rel. intensity) 208 (40), 190 (90), 175 (20), 147 (40), 123 (100), 105 (70); HRMS calcd. for $[M^+]$ $C_{14}H_{24}O$ 208.1827, found 208.1828.

Oxidation of 11/12 to 15-nor-amorph-11-en-4-one (13) and 15-nor-cadin-11-en-4-one (14). To a mixture of **11** and **12** in acetone (911 mg, 10 ml) was added freshly-prepared Jones reagent (6 ml) and the mixture was stirred for 2 h at ice-bath temperature. The mixture was then extracted by pet. ether (bp 40-60°C, 3 x 40 ml) and the combined organic extracts were washed with water (2 x 20 ml) and brine (2 x 20 ml), dried and rotary evaporated to give saturated ketones **13** and **14** (626 mg, 69% yield) as a mixture of diastereoisomers, which were separated by preparative normal phase HPLC (5% EtOAc/hexane): **13** (190 mg R_f 24.1 min), **14** (220 mg R_f 23.1 min). (**13**): Oil. $[\alpha]_D$ -28.2 (*c* 0.3, $CHCl_3$); IR υ_{max} 3011, 2957, 2928, 2874, 2853, 1703, 1452, 1209 cm^{-1}; ^1H and ^{13}C NMR, see Tables 1 and 2; MS (EI) *m/z* (rel. intensity) 206 (100), 191 (15), 164 (28), 148 (40), 123 (58), 121 (43); HRMS calcd. for $[M^+]$ $C_{14}H_{22}O$ 206.1671, found 206.1665. (**14**): Oil. $[\alpha]_D$ -20.8 (*c* 0.6, $CHCl_3$); IR υ_{max} 3011, 2957, 2924, 2872, 1707 1645, 1454, 1209 cm^{-1}; ^1H and ^{13}C NMR, see Tables 1 and

2; MS (EI) *m/z* (rel. intensity) 206 (100), 191 (10), 163 (15), 150 (12), 123 (30), 107 (20); HRMS calcd. for [M$^+$] $C_{14}H_{22}O$ 206.1671, found 206.1663.

Conversion of 13 to amorph-11-en-4α-ol (21) and amorph-11-en-4β-ol (22). To a Grignard reagent freshly-prepared from Mg (319 mg), CH_3I (2.07 g) and Et_2O (30 ml) was added a solution of the saturated ketone **13** in Et_2O (180 mg, 30 ml). The reaction mixture was refluxed for 1 h and Et_2O (100 ml) was added upon completion. The ethereal layer was washed with water (2 x 30 ml), dried ($MgSO_4$) and rotary evaporated to give an oily product consisting of diastereoisomers **21** and **22** (138 mg, 71% yield) which were separable by preparative normal phase HPLC (14% EtOAC/hexane): **21** (R_t 17.5 min), **22** R_t (26.2 min). (**21**): Oil. $[\alpha]_D$ -2.4 (*c* 0.6, $CHCl_3$) ; IR υ_{max} 3435 (br), 3007, 2927, 2851, 2870, 1643, 1375 cm^{-1}; ^{1}H and ^{13}C NMR, see Tables 1 and 2; MS (EI) *m/z* (rel. intensity) 222 (20), 207 (30), 204 (50), 189 (25), 162 (100), 122 (35); HRMS calcd. for [M$^+$] $C_{15}H_{26}O$ 222.1984, found 222.1978. (**22**): Oil. $[\alpha]_D$ +2.3 (*c* 0.3, $CHCl_3$); IR υ_{max} 3429 (br), 3009, 2928, 2870, 2855, 1643, 1454, 1379 cm^{-1}; ^{1}H and ^{13}C NMR, see Tables 1 and 2; MS (EI) *m/z* (rel. intensity) 222 (30), 207 (50), 204 (100), 189 (50), 161 (55), 148 (100), 122 (80), 119 (85), 109 (60); HRMS calcd. for [M$^+$] $C_{15}H_{26}O$ 222.1984, found 222.1982.

Conversion of 14 to cadin-11-en-4β-ol (15) and cadin-11-en-4α-ol (16). To a Grignard reagent freshly-prepared from Mg (330 mg), CH_3I (2.07 g) and Et_2O (30 ml) was added a solution of the saturated ketone **14** in Et_2O (200 mg, 30 ml). The reaction mixture was refluxed for 1 h and Et_2O (100ml) was added upon completion. The organic layer was washed with water (2 x 30 ml), dried ($MgSO_4$) and rotary evaporated under reduced pressure to give an oily product consisting of diastereoisomers **15** and **16** (163 mg; 76 % yield) which were separable by preparative normal phase HPLC (14% EtOAc/hexane): **15** (R_t 17.0 min), **16** (R_t 27.0 min). (**15**): Oil. $[\alpha]_D$ -21.2 (*c* 0.5, $CHCl_3$); IR υ_{max} 3443 (br), 3007, 2970, 2924, 2858, 1643, 1453, 1375 cm^{-1} ; ^{1}H and ^{13}C NMR, see Tables 1 and 2; MS (EI) *m/z* (rel. intensity) 222 (50), 207 (95), 204 (100), 189 (45), 161 (60), 122 (70), 109 (80), 95 (70); HRMS calcd. for [M$^+$] $C_{15}H_{26}O$ 222.1984, found 222.1980. (**16**): Oil. $[\alpha]_D$ –25.9 (*c* 0.3, $CHCl_3$); IR υ_{max} 3393 (br), 3007, 2970, 2874, 2856, 1647, 1454, 1379 cm^{-1}; ^{1}H and ^{13}C NMR, see Tables 1 and 2; MS (EI) *m/z* (rel. intensity) 222 (30), 207 (50), 204 (100), 189 (30), 161 (35), 148 (20), 122 (30), 119 (55); HRMS calcd. for [M$^+$] $C_{15}H_{26}O$ 222.1984, found 222.1977.

Dehydration of 21/22 to 3,11-amorphadiene (3) and 4,11-amorphadiene (23). To a stirred solution of **21** and **22** in $CHCl_3$ (79 mg, 15 ml) was added triethylamine (0.42 ml). The mixture was cooled to 0°C and methanesulfonyl chloride (0.23 ml) was added dropwise. The reaction mixture was stirred for 1 h at room temperature, then water (10 ml) was added and the mixture was stirred overnight, extracted with $CHCl_3$ (3 x 20 ml), dried and rotary evaporated to give an oil (41 mg, 57%), consisting of regioisomers **3** and **23** together with a small amount of 4(15),11-amorphadiene (**24**), which was separated chromatographically. (**3**): IR υ_{max} 2932, 2855, 1597, 1458 cm^{-1}; ^{1}H and ^{13}C NMR, see Tables 1 and 2. (**23**): Oil. $[\alpha]_D$ –14.0 (*c* 0.4, $CHCl_3$); IR υ_{max} 2924, 2868, 1450, 1375 cm^{-1}; ^{1}H and ^{13}C NMR, see Tables 1 and 2; MS (EI) *m/z* (rel. intensity) 204 (8), 189 (20), 155

(25), 139 (10), 119 (20), 99 (100); HRMS calcd. for $[M^+]$ $C_{15}H_{24}$ 204.1878, found 204.1864. (**24**): ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.79 (1H, q, J = 1.2 Hz, H-12), 4.59 (1H, s, H-12), 4.57 (1H, s, H-15), 4.55 (1H, s, H-15), 1.72 (3H, s, H-13), 0.90 (3H, d, J = 6.3 Hz, H-14); ^{13}C NMR (125 MHz, $CDCl_3$) δ 150.5 C (C-4), 147.9 C (C-11), 109.4 CH_2 (C-12), 106.6 CH_2 (C-15), 47.8 CH (C-7), 43.9 CH (C-1), 40.6 CH, 36.0 CH_2 (C-9), 30.5 CH_2, 29.9 CH_2, 29.8 CH_2, 27.3 CH (C-10), 24.9 CH_2, 22.6 CH_3 (C-13), 19.8 CH_3 (C-14).

Dehydration of 15/16 to 3,11-cadinadiene (17) and 4,11-cadinadiene (18). To a stirred solution of **15** and **16** in $CHCl_3$ (71 mg, 15 ml) was added triethylamine (0.42 ml). The mixture was cooled to 0°C and methanesulfonyl chloride (0.23 ml) was added dropwise. The reaction mixture was stirred for 1 h at room temperature, then water was added (10 ml) and the mixture was stirred overnight, extracted with $CHCl_3$ (3 x 20 ml), dried and rotary evaporated to give an oily product (34 mg, 53%) consisting of regioisomers **17** and **18**, together with a small amount of 4(15),11-cadinadiene (**19**) and 4ξ-chloro-cadin-11-ene (**20**), which were separated chromatographically. (**17**): Oil. IR υ_{max} 2924, 2862, 1643, 1450, 1373 cm^{-1}; ^{1}H and ^{13}C NMR, see Tables 1 and 2; MS (EI) *m/z* (rel. intensity) 204 (36), 189 (9), 161 (13), 147 (7), 133 (11), 119 (100), 93 (17); HRMS calcd. for $[M^+]$ $C_{15}H_{24}$ 204.1878, found 204.1848. (**18**): Oil. IR υ_{max} 2927, 2864, 1645, 1452, 1378 cm^{-1}; ^{1}H and ^{13}C NMR, see Tables 1 and 2; MS (EI) *m/z* (rel. intensity) 204 (35), 189 (10), 163 (40), 147 (20), 119 (100), 93 (60); HRMS calcd. for $[M^+]$ $C_{15}H_{24}$ 204.1878, found 204.1874. (**19**): ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.69 (2H, s, H-12), 4.57 (1H, s, H-15), 4.55 (1H, s, H-15), 1.62 (3H, s, H-13), 0.90 (3H, d, J = 6.3 Hz, H-14), 0.75 (1H, dddd, J = 11.9, 9.8, 9.8, 3.4 Hz, H-1); ^{13}C NMR (125 MHz, $CDCl_3$) δ 149.8 C (C-4), 148.6 C (C-11), 110.8 CH_2 (C-12), 106.3 CH_2 (C-15), 52.9 CH (C-7), 48.4 CH (C-1), 45.4 CH, 39.7 CH_2, 37.2 CH (C-10), 35.5 CH_2, 35.0 CH_2, 32.1 CH_2, 32.0 CH_2, 19.9 CH_3 (C-14), 18.7 CH_3 (C-13). (**20**): Oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.69 (1H, s, H-12), 4.67 (1H, s, H-12), 1.63 (3H, s, H-13), 1.58 (3H, s, H-15), 0.90 (3H, d, J = 6.4 Hz, H-14), 0.58 (1H, dddd, J = 11.9, 9.7, 9.7, 3.2 Hz, H-1); ^{13}C NMR (125 MHz, $CDCl_3$) δ 148.7 C (C-11), 111.0 CH_2 (C-12), 72.8 C (C-4), 52.0 CH (C-7), 48.0 CH (C-1), 45.8 CH_2 (C-5), 41.4 CH_2 (C-3), 39.1 CH (C-6), 36.8 CH (C-10), 35.4 CH_2 (C-9), 34.4 CH_3 (C-15), 32.0 CH_2 (C-8), 26.5 CH_2 (C-2), 19.9 CH_3 (C-14), 18.4 CH_3 (C-13); MS (EI) 242(6)/240 (18), 205 (24), 197 (11), 163 (100), 147 (19), 121 (37), 119 (33); HRMS calcd. for $[M^+]$ $C_{15}H_{25}Cl$ 240.1645, found 240.1644.

Regioselective hydration of the terminal double bond in 3 and 23 to 4-amorphen-11-ol (1) and 3-amorphen-11-ol (25). To a stirred solution of **3** and **23** in THF/H_2O (14mg, 2 ml (1:1 v/v)) was added mercuric oxide (14 mg) and trifluoroacetic acid (10.3 μl). The mixture was sonicated until the colour of the mercuric oxide had completely disappeared. NaOH (10%; 133μl) was then added followed by $NaBH_4$ in NaOH (2.5 mg, 133μl (5%)) and the suspension was stirred for 1 h. After decantation, the filtrate was then extracted with Et_2O (2 x 10 ml), dried and rotary evaporated to yield a crude oily product consisting of regioisomers **1** and **25** which were separable by preparative HPLC (15% EtOAc/hexane): **1** (2 mg, R_t 14.2 min), **25** (7 mg, R_t 17.1 min). (**1**): Oil. $[\alpha]_D$ –3.9 (c 1.0, $CHCl_3$); IR υ_{max} 3387 (br), 2923, 2847, 1605, 1458, 1288 cm^{-1}; ^{1}H and ^{13}C NMR, see

Tables 1 and 2; MS (EI) *m/z* (rel. intensity) 204 (80), 189 (40), 161 (98), 149 (100); HRMS calcd. for [M^+-H_2O] $C_{15}H_{24}$ 204.1878, found 204.1868. **(25)**: Oil. $[\alpha]_D$ +52.7 (*c* 0.3, $CHCl_3$); IR υ_{max} 3402 (br), 2932, 2878, 1597, 1458, 1373 cm^{-1}; ^1H and ^{13}C NMR, see Tables 1 and 2; MS (EI) *m/z* (rel. intensity) 222 (1), 204 (40), 189 (5), 161 (50), 149 (10), 119 (100); HRMS calcd. for [M^+] $C_{15}H_{26}O$ 222.1984, found 222.1966; calcd. for [M^+-H_2O] $C_{15}H_{24}$ 204.1878, found 204.1877.

Ring-B aromatized cadalene (26). A solution of tosic acid in THF (440 mg/1 ml) was added to a solution of **21**/**22** (440 mg) in benzene (440mg/40 ml). The reaction mixture was refluxed for 1 h to remove water (employing a Dean-Stark head) then rotary evaporated to give a complex mixture of compounds (315 mg) from which only **26** (38 mg) could be identified following column chromatography. ^1H NMR (500 MHz, $CDCl_3$) δ 7.03 (1H, d, *J* = 8.1 Hz, H-8), 6.99 (1H, d, *J* = 8.1 Hz, H-9), 3.15 (1H, sept, *J* = 6.6 Hz, H-11), 2.91 (1H, dd, *J* = 15.0, 8.3 Hz, H-5), 2.75 (1H, m, H-2), 2.63 (1H, m, H-2), 2.19 (3H, s, H-14), 1.21 (3H, d, *J* = 6.6 Hz, H-12/13), 1.19 (3H, d, *J* = 6.6 Hz, H-12/13), 1.09 (3H, d, *J* = 6.5 Hz, H-15); ^{13}C NMR (125 MHz, $CDCl_3$) δ 144.5 C (C-7), 134.5 C (C-10), 127.1 CH (C-9), 121.8 CH (C-8), 35.1 CH_2 (C-5), 31.1 CH_2 (C-3), 29.0 CH (C-4), 27.7 CH_2 (C-2), 23.7 CH_3 (C-12/13), 23.4 CH_3 (C-12/13), 22.4 CH_3 (C-15), 19.7 CH_3 (C-14); MS (EI) *m/z* (rel. intensity) 202 (36), 187 (100), 159 (47); HRMS calcd. for [M^+] $C_{15}H_{22}$ 202.1722, found 202.1705.

ACKNOWLEDGMENTS

We thank the CRCG for funding this research.

REFERENCES

1. Houghton, P. J.; Marby, J. *J. Ethnopharm.* **1985**, *13*, 89. San Martin, J. *Econ. Bot.* **1983**, *37*, 216.
2. Schmeda-Hirschmann, G.; Papastergiou, F. *Phytochemistry* **1994**, *36*, 1439.
3. Brown, G. D. *Phytochemistry* **1994**, *35*, 425.
4. Brown, G. D. *J. Nat. Prod.* **1994**, *57*, 328.
5. Brown, G. D.; Shill, J. *Planta Med.* **1994**, *60*, 495.
6. Jung, M.; Youn, B. H. *Heterocycles* **1996**, *43*, 1587.
7. Nowak, D. M.; Lansbury, P. T. *Tetrahedron* **1998**, *54*, 319.
8. Ho, T.-L. *Enantioselective synthesis: natural products from chiral terpenes,* Wiley, New York, 1992, p. 99. Ho, T.-L. *Carbocyclic construction in terpene synthesis,* VCH, Weinheim, 1988,p 3-46.
9. Xu, X.-X.; Zhu, J.; Huang, D.-Z.; Zhou, W.-S. *Tetrahedron* **1986**, *42*, 819.
10. Hui, S.-M.; Ngo, K.-S.; Brown, G. D. *J. Chem. Soc. Perkin Trans I* **1997**, 3435.
11. Pretsch, E.; Seibl, J.; Simon, W.; Clerc, T. *Spectral data for structure determination of organic compounds*, Springer-Verlag, Berlin, 1989, H195.
12. Bohlmann, F.; Gerke, T.; Jakupovic, J.; King, R. M.; Robinson, H. *Phytochemistry* **1984**, *23*, 1183.