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STEREOSPECIFIC 1,3 AND 1,4 DEHYDRATION REACTIONS IN THE MASS SPECTRA OF PODOCARPAN-12- AND -14-OLS[†]

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Abstract—Specific deuterium labelling revealed that podocarpan- 12α - and -14α -ol, representing conformationally well defined cyclohexanols, eliminate water mainly by stereospecific 1,3 reactions involving *cis* tertiary hydrogens on electron-impact. Dehydration of podocarpan- 12β -ol, which also involves a *cis* tertiary hydrogen, occurs almost exclusively by a 1,4 reaction. Subsequent decomposition of the various $[M - 18]^{+}$ ions was found to lead to different products, thus explaining some of the intensity differences encountered in the lower parts of the spectra of the epimeric podocarpan-12-ols and -14-ols.

INTRODUCTION

IN OUR previous study of mass spectra of various epimeric diterpene alcohols we found a good correlation between the relative magnitudes of the intensities of the $[M-18]^+$ peaks and the availability of tertiary hydrogens in the *cis* 1,3 as well as the *cis* 1,4 positions.¹ These results do not fully concur with those obtained in studies of mass spectra of simpler molecules. Thus, the predominant dehydration reaction in cyclohexanol is a stereospecific 1,4 *cis* elimination, while the 1,3 (or 1,5) process, accounting for the remaining $[M - 18]^+$ ions, is nonstereoselective and is considered to be preceded by carbon-carbon bond cleavage.² The difference in stereospecificity between the 1,4 and 1,3 eliminations has been ascribed to the smaller minimum internuclear distance which can be achieved between the hydroxyl oxygen, and the *cis*-4-hydrogen (1.7 Å) on the one hand and the *cis*-3-hydrogen (2.3 Å) on the other. On the basis of these and other observations a maximum distance for bond formation of 1.8 Å has been proposed.²

Although this maximum distance should be valid when a hydrogen on a secondary non-activated carbon is involved, as in cyclohexanol, it is reasonable to assume that somewhat greater distances may be allowed in cases where the abstracted hydrogen has a lower dissociation energy, e.g. a tertiary hydrogen.

Support for this hypothesis has been given by Karliner *et al.*, who have demonstrated by deuterium labelling that the $[M - 15]^+$ ion derived from cholestan-3 α -o1 undergoes a stereospecific 1,3 dehydration reaction.³

Similarly, Akhtar *et al.*, employing photoionisation, have found that loss of water occurs mainly by a 1,3 process in *trans*-3-methylcyclohexanol but by a 1,4 mechanism in the corresponding *cis* derivative.⁴ To our knowledge, however, there is no conclusive evidence to date for the existence of a transannular 1,3 loss of water involving a tertiary hydrogen from the molecular ion of compound incorporating a cyclohexanol system. In view of this and as an extension to our previous study of mass spectra of diterpene epimers,¹ we found it desirable to firmly establish the presence of such reactions in compounds having a common tricyclic diterpene skeleton.

[†] Part 9 in the series 'Mass Spectra of Diterpenes.' For Part 8, see Ref. 1.

We have therefore examined the mass spectra of epimeric podocarpan-12- and -14-ols (IX, X and XXVIII, XXIX), as well as the spectra of the corresponding derivatives selectively labelled at C-9 (XIII, XIV and XXXIV, XXXV). Since it was also of interest to evaluate the relative importance of the *cis* 1,4 dehydration reactions, the podocarpan-12-ols labelled at C-8 (XVII, XVIII), were synthesised and studied, while attempts failed to prepare the complementary podocarpan-14-ols labelled at C-11. In order to exclude the possibility of thermal dehydration prior to ionisation the podocarpan-11,11,13,13- d_4 -12-ols (XXII, XXIII) and the podocarpan-8 β ,13,13- d_3 -14-ols (XXXVII, XXXVIII) were also examined. The labelled compounds were all prepared from podocarpic acid (I) via podocarp-9(11)-en-12-one (VII) and a series of other derivatives (I to XXXVIII) by standard procedures. The site selectivity of the deuterium labelling as well as the homogeneity of most of these compounds (I to XXXVIII) were confirmed by c.m.r. spectroscopy.



RESULTS

As evidenced by Table 1 and the mass spectra (reproduced in Figs. 1 and 2), podocarpan-12 β -ol (X) gives rise to a stronger $[M - 18]^{+}$ peak than the corresponding α -epimer (IX). This is in agreement with our expectations, since, although both the 1,3 elimination in the α -epimer and the 1,4 elimination in the β -epimer involve tertiary hydrogens, the 1,4 process should be the more favoured reaction.

Table 1. Intensity intervals at a 95% confidence level expressed as a percentage of the total ion intensities \sum_{α} I for selected peaks in the spectra of podocarpan-12 α -ol and-12 β -ol

	70	eV	10	eV
	(IX)	(X)	(IX)	(X)
I _M	2.89-2.99	1.89–1.93	5.57-5.66	3.13-3.36
J _[M-18]	3.55-3.72	4.94-5.06	7.38-7.54	9.00-9.71
I_{217}	3.32-3.47	4.13-4.30	6.34-6.48	6.83-7.46
I ₁₆₁	1.30-1.36	1.16-1.19	1.80-1.87	1.58-1.80
I ₁₄₈	1.74-1.83	1.30-1.38	2.89-2.99	2.02-2.12
I ₁₄₇	3.05-3.18	2.35-2.43	4.14-4.25	2.87-3.08
I ₁₃₅	2.47-2.53	1.74-1.82	3.39-3.50	2.20-2.40
I ₁₂₃	3.32-3.53	5.63-5.87	4.46-4.58	7.39-8.05
I ₁₂₁	2.45-2.54	2.24-2.30	2.78-2.85	2.34-2.40
ΣΪ	2690-2790	1705-1777	1326-1355	1030-1115

^a On average ten spectra of each compound were recorded at both 10 and 70 eV.

The spectra of the epimeric podocarpan-14-ols (XXVIII, XXIX Figs. 3 and 4) and the intensity values given in Table 2, demonstrate that loss of water occurs preferentially from the α -epimer (XXVIII). This is consistent with the availability of the tertiary 9α -hydrogen in this epimer; in the corresponding β -epimer (XXIX) there are only secondary hydrogens in appropriate positions for water elimination.

Intensity differences related to the configurational differences are also observed for several other peaks (cf. Tables 1 and 2), but as these are essentially a result of the



FIG. 1. Mass spectrum of podocarpan-12a-ol (IX).



FIG. 2. Mass spectrum of podocarpan- 12β -ol (X).







FIG. 4. Mass spectrum of podocarpan-14 β -ol (XXIX).

	70 e	×٧	10	eV
	(XXVIII)	(XXIX)	(XXVIII)	(XXIX)
I _M	3.11-3.24	3.58-3.70	21.05-22.55	35.02-40.78
I _[M-18]	2.29-2.35	1.02-1.05	10.77-11.17	3.41-4.02
I ₂₁₇	3.72-3.89	2.72-2.79	5.97-6.55	1.23-1.48
I ₁₆₁	2.85-2.96	0.83-0.84	0.44-0.24	0.16-0.21
I ₁₄₈	3.15-3.26	1.37-1.39	1.19–1.36	0.29-0.34
I ₁₄₇	3.14-3.26	2.17-2.21	0.69-0.80	0.38-0.43
I ₁₃₅	2.35-2.42	2.12-2.16	0.91-1.12	0.66-079
I ₁₂₃	2.00-2.04	2.94-3.00	0.65-0.77	0.92-1.08
I ₁₂₁	3.32-3.42	2.69-2.73	0.68-0.82	0.58-0.72
I.11	2.01-2.06	3.32-3.40	0.54-0.66	0.73-0.79
I.98	1.25-1.31	2.35-2.41	1.01-1.09	2.20-2.31
ΣΙ	2568-2688	2706-2776	443-475	247-285

Table 2. Intensity intervals at a 95% confidence level expressed as a percentage of the total on intensities \sum_{α} I for selected peaks in the spectra of podocarpan-14 α -oland -14 β -ol

* On average ten spectra of each compound were recorded at both 10 and 70 eV.

outcome of the $[M]^+ \rightarrow [M - 18]^+$ reactions, we will first discuss the steric course of the elimination of water from the molecular ions of the epimeric podocarpan-12-ols (IX, X) and -14-ols (XXVIII, XXIX) and subsequently the mechanisms for the formation of certain fragments of lower masses.

$[M - 18]^+ \cdot ions$

The labelling results listed in Table 3 confirm that our assumptions regarding the origins of the hydrogens involved in the dehydration reactions of the various podocarpanols are basically correct. Thus, 55% HDO loss is observed in the 70 eV spectrum of podocarpan-9 α -d-12 α -ol (XIII), while the HDO loss in the spectrum of the corresponding 12β -epimer (XIV) is limited to 5%. A similar situation is encountered for podocarpan-9 α -d-14 α -ol (XXXIV): 55% of the total loss of water from the α -epimer at 70 eV occurs as a 1,3 elimination across the 9 and 14 positions, whereas elimination across these positions is of negligeable importance (5%, 70 eV)in the fragmentation of the corresponding 14β -epimer (XXXV). It can be concluded, therefore, that *cis* stereoselective 1,3 eliminations giving ions a and c (cf. Scheme 1) constitute the major dehydration routes in podocarpan-12a-ol (IX) and podocarpan-14a-ol (XXVIII), respectively. These results also imply that transannular reactions involving tertiary hydrogens do take place when the distance between the interacting nuclei is 2.3 Å, a value which slightly exceeds that proposed as the maximum distance for bond formation in cyclohexanol systems. Our findings concur with those recently reported for labelled bicyclo[3,3,1]nonanols by Cable et al., who found evidence for a stereospecific 1,3 dehydration process involving a secondary hydrogen at a distance of 2.5 Å to the hydroxyl oxygen.⁷

In the case of podocarpan-12 β -ol (X) the deuteration data confirm that the 1,4 elimination giving ion b is the predominant reaction. Furthermore, the observed values of 78% and 5% HDO loss from podocarpan-8 β -d-12 β -ol (XVIII) and the

Compound	Position	Position of	70) eV	12	2 eV
No.	of –OH	deuterium	H_2O	HDO	H_2O	HDO
(XIII)	12α	9α	45	55	36	64
(XVII)	12a	8β	95	5	99	1
(XIX)	12α	12β	100	0	100	0
(XXII)	12a	11,11,13,13	100	0	98	2
(XIV)	12β	9a	95	5	99	1
(XVIII)	12β	8β	22	78	18	82
(XX)	12β	12a	100	0	100	0
(XXIII)	12β	11,11,13,13	100	0	99	1
(XXXIV)	14α	9α	45	55	39	61
(XXXVII)	14α	$8\beta, 13, 13$	97	3	97	3
(XXXV)	14β	9α	95	5	98	2
(XXXVIII)	14β	$8\beta, 13, 13$	91	9	88	12

TABLE 3. RELATIVE LOSS OF H_2O and HDO from various labelled podocarpan-12- and -14-ols^a

^a The values are corrected for isotopic inhomogeneity and natural occurrence of ¹³C.

corresponding 12α -epimer (XVII), respectively, suggest that the 1,4 process in X is highly stereospecific.

It was not possible to evaluate the importance of the 1,4 process in the fragmentation of the epimeric podocarpan-14-ols (XXVIII, XXIX), since various attempts to prepare derivatives specifically labelled at C-11 failed. However, as evidenced by the data given above, the 1,4 process is apparently less important than the 1,3 dehydration reaction in the α -epimer, (XXVIII). It should also be noted that the rigidity of the cyclic system results in a substantially increased minimum distance between the interacting nuclei across the 11 and 14 positions compared to the corresponding distance in cyclohexanol. This decrease in flexibility is therefore likely to reduce the importance of the 1,4 processes in both epimers.

The results cited above were all based on measurements at 70 eV. As expected, however, the stereospecific dehydration reactions are even more favoured at 12 eV (Table 3). Thus, as judged by the labelling results (XIII, XXXIV) the stereoselective 1,3 processes account for some 60% of the $[M - 18]^+$ ion currents generated by both podocarpan-12 α - and 14 α -ol (IX, XXVIII) at 12 eV. An analogous increase in the relative importance of the *cis* 1,4 dehydration process is observed in the spectrum of podocarpan-8 β -*d*-12 β -ol (XVIII). The correspondingly reduced abundances of dehydrated species generated via other routes indicate that some of them are formed in processes requiring ring cleavage prior to dehydration, since simple bond ruptures usually have considerable higher activation energies than stereospecific dehydration reactions.⁸ According to the labelling data, reactions such as those indicated for the formation of ions *h*, *i* and *j* may be involved (Scheme 2).

We have insufficient labelling data supporting the formulation of the remaining ions contributing to the $[M - 18]^+$ ion currents of these compounds (IX, X, XXVIII, XXIX), but it is clear from the spectra of 11,11,13,13- d_4 -podocarpan-12 α -and -12 β -ols (XXII, XXIII) and 8β ,13,13- d_3 -podocarpan-14 α -ol (XXXVII) that there is no contribution from ions formed by 1,2 dehydration reactions (Table 3). In view of this and since their abundances decrease with decreasing electron energy, it seems highly probable that they are formed in reactions involving ring cleavage.



SCHEME 1. Formation of the major $[M - 18]^{+}$ and $[M - 33]^{+}$ ions derived from IX, X and XXVIII.



SCHEME 2. Minor $[M - 18]^+$ ions formed via ring cleavage reactions from IX, X and XXIX.

Other ions

Studies of the podocarpan-12- and -14-ols labelled at C-9 (XIII, XIV, XXXIV, XXXV) and the podocarpan- 8β -d-12-ols (XVII, XVIII), suggest that the $[M - 33]^+$ ions derived from the podocarpan-12-ols (IX, X) and from podocarpan-14 α -ol (XXVIII) are also formed by highly stereoselective reactions (Table 4). In fact, in the 12 α - and 14 α -alcohols the transfers of hydrogen from C-9 to eliminate water occur to a higher degree in the production of the $[M - 33]^+$ ions than in the generation of the $[M - 18]^+$ ions. Particularly noteworthy is the fact that some 80% of the $[M - 33]^+$ fragments derived from the 14 α -epimer (XXVIII) at 12 eV arise via this *cis* 1,3 dehydration reaction. In contrast, the *cis* 1,4 process, which constitutes the major dehydration route giving rise to the $[M - 18]^+$ ions in the spectrum of podocarpan-12 β -ol (X), is comparatively less effective in the production of the $[M - 33]^+$ species.

One reason for this difference may be that extrusion of the methyl group at C-10 activates elimination of water across the 9 and 12 or the 9 and 14 positions generating ions such as d and f (Scheme 1). Conversely, since metastables demonstrate that the $[M - 15]^+$ as well as the $[M - 18]^{+}$ ions may be precursors, loss of water involving the 9 α -hydrogen should facilitate expulsion of the methyl groups at C-10 giving these ions. Subsequent shifts of allylic hydrogens—a 1,4 migration in d and

169

Compound	Position	Position of	70) eV	12	eV.
No.	of —OH	deuterium	$\rm H_2O + CH_3$	$HDO + CH_3$	$\rm H_{2}O + CH_{3}$	$HDO + CH_3$
(XIII)	12α	9α	41	59	32	68
(XVII)	12α	8β	92	8	94	6
(XIX)	12a	12β	100	0	100	0
(XXII)	12 ¤	11,11,13,13	100	0	99	1
(XIV)	12β	9α	95	5	98	2
(XVIII)	12β	8β	34	66	29	71
(XX)	12β	12a	100	0	100	0
(XXIII)	12β	11,11,13,13	100	0	100	0
(XXXIV)	14α	9α	32	68	19	81
(XXXVII)	14x	$8\beta, 13, 13$	100	0	99	1
(XXXV)	14β	9α	91	9	92	8
(XXXVIII)	14β	8β, 13,13	85	15	86	14

Table 4. Relative loss of $\rm H_{2}O+CH_{3}$ and $\rm HDO+CH_{3}$ from various labelled podo-carpan-12- and 14-ols^4

^a The values are corrected for isotopic inhomogeneity and natural occurrence of ¹³C.

a 1,2 rearrangement in f—would generate the well stabilised ion g, which for reasons discussed below is a probable common intermediate. In the case of podocarpan-12 β -ol (X), however, abstraction of the 8 β -hydrogen only favours elimination of the methyl group at C-10 after a 1,2 hydrogen shift and formation of ion g would require an additional hydrogen shift.

The peaks at m/e 161, 148, 147, 135 and 121 are more prominent in the spectrum of podocarpan-14 α -ol (XXVIII) than in that of the β -epimer (XXIX) (Table 2). The labelling data confirm that the corresponding fragments comprise ring C and arise via different decomposition reactions in the two epimers (Table 5). Thus, the 9 α -hydrogen is not incorporated in the major m/e 148 ion (75%) originating from the 14 α -epimer (XXVIII). On the other hand, the most abundant m/e 148 fragment (70%) derived from the 14 β -epimer (XXIX) retains this hydrogen. According to accurate mass measurements the ions are hydrocarbons in both cases and the appearance of appropriate metastables verifies that the $[M - 18]^+$ ions are precursors. These results may be accommodated for the 14 α -epimer by the mechanism outlined in Scheme 3, where dehydration involving the 9 α -hydrogen triggers elimination of ring A and subsequent stabilisation is achieved by a 1,2 hydrogen shift. In the case of the 14 β -epimer, where dehydration occurs via alternate routes, loss of ring A is less likely to be a favoured reaction.

A situation similar to that of the m/e 148 ions is prevalent with the fragments of m/e 161, 147, 135 and 121, i.e. the 9 α -hydrogen is retained in the major species formed from the 14 β -epimer (XXVIII), while it is absent in the ions derived from the α -epimer (XXIX). In view of this, and since all these ions are hydrocarbons, it is reasonable to assume that they are formed via dehydration. Although we have no corroborative evidence from appropriate metastable ions, and lack the extensive labelling needed to unambiguously establish the structures of these species, it is worth mentioning that ion $g [M - 33]^+$ is likely to undergo fragmentation reactions analogous to those of the $[M - 15]^+$ ions derived from aromatic diterpenoids and podocarp-8-enes,^{9,10} and leading to the ions of masses 161, 147, 135 and 121, shown in Scheme 3.

	TABLE 5	5. Shifts (%) of	R SELECTED PEA	KS (<i>m</i> / <i>e</i>) IN TI	HE MASS SPECT.	RA OF DEUTER	ATED PODOCAR	PAN-12- AND	-14-olsª	
Compound	Position	Position of				Peaks	(%)			
Ño.	ofOH	deuterium	161	148	147	135	123	121	111	98
(XIII)	12α	9α	161 (50)	148 (50)	147 (55)	135 (70)	123 (90)	121 (60)		
(IIVX)	12α	8β	162 (85)	149 (80)	148 (70)	136 (85)	123 (80)	122 (75)		
(XIX)	12α	12β	162 (95)	149 (100)	148 (100)	136 (85)	123 (100)	122 (80)		
(IIXXI)	12α	11,11,13,13	165 (85)	152 (85)	151 (90)	139 (70)	123 (90)	125 (80)		
(XIV)	12β	9α	162 (80)	149 (75)	148 (65)	136 (65)	123 (95)	122 (70)		
(IIIAX)	12β	8β	161 (55)	148 (50)	147 (60)	135 (65)	123 (70)	121 (70)		
(XX)	12β	12α	162 (100)	149 (100)	148 (100)	136 (95)	123 (100)	122 (90)		
(IIIXX)	12β	11,11,13,13	165 (90)	152 (75)	151 (80)	139 (70)	123 (95)	125 (80)		
(VIXXX)	14α	9α	161 (80)	148 (75)	147 (70)	135 (75)	123 (90)	121 (70)	112 (95)	(06) 66
(IIAXXX)	14α	$8\beta, 13, 13$	164 (100)	151 (90)	150 (85)	138 (70)	123 (90)	124 (80)	113 (90)	101 (85)
(VXXX)	14β	9α	162 (65)	149 (70)	148 (65)	136 (55)	123 (80)	122 (65)	112 (95)	(06) 66
(IIIAXXX)	14β	$8\beta, 13, 13$	164 (80)	151 (70)	150 (65)	138 (50)	123 (90)	224 (70)	113 (90)	101 (85)
				150 (30)	149 (35)	137 (50)				

^a The values are corrected for isotopic inhomogeneity and natural abundance of ¹³C.



SCHEME 3. Fragments formed via decomposition $[M - 18]^+$ and $[M - 33]^+$ ions.

For the same reasons the peaks at m/e 161, 147, 135 and 121 in the spectra of the epimeric podocarpan-12-ols (IX, X), may be ascribed to the same ions, arising via decomposition of the common ion g (Table 5, Scheme 3). Similarly, the labelling results reveal that the m/e 148 fragments essentially arise via two different routes in podocarpan-12 α -ol (IX) and -12 β -ol (X); ions a and b [M - 18]⁺ respectively, being precursors (Scheme 3). The m/e 161, 148, 147, 135 and 121 peaks are all of higher intensity in the spectrum of the 12 α -epimer (IX) than in that of the 12 β -epimer (X), while the reverse is true for the [M - 33]⁺ peak. This may be accounted

for by assuming that the formation of the precursor ion g is slower when generated from the 12β -epimer (X), as an additional hydrogen rearrangement is required and hence less time is available for the subsequent decomposition in the ion source. In agreement with this, the m/e 161, 148, 147, 135 and 121 peaks are also more prominent in the spectrum of the 14α -epimer (XXVIII) than in that of the 14β -epimer (XXIX); the generation of ion g from the latter epimer is less favoured and the intensity of the $[M - 33]^+$ is accordingly lower in this case.

Hence, some of the intensity differences encountered in the lower parts of the spectra of these epimeric pairs may be explained by the fact that the abstraction of different hydrogens in the two epimers on dehydration significantly alters subsequent or simultaneous decomposition reactions. However, certain other peaks at lower mass numbers displaying intensity differences, apparently correspond to ions whose formations are only indirectly associated with the dehydration process. Thus, accurate mass measurements and the labelling studies (Table 5) indicate that the peaks at m/e 111 and 98, which are more prominent in the spectrum of podocarpan-14 β -ol (XXIX) than in that of the α -epimer (XXVIII) are due to ions comprising ring C and retaining the hydroxyl group. Plausible mechanisms for their geneses are depicted in Scheme 4.

The reactions are initiated by rupture of the 9,10 bonds-processes which are



SCHEME 4. Ions formed via routes not involving dehydration.

likely to have rate constants of roughly the same magnitudes in the two epimers. In contrast, the rate constants of the competing dehydration reactions are expected to differ considerably in the two epimers.¹ As a consequence, reactions of the former type will be of comparatively greater importance in the less readily dehydrated β -epimer, thus accounting for the observed intensity differences of the corresponding peaks.

Analogous situations are encountered for the m/e 123 peaks, which are more intense in the spectra of the β -epimers X and XXIX than in those of the corresponding α -epimers IX and XXVIII, respectively. The corresponding fragments are assumed to comprise ring A and to arise via ruptures of the 5,6 and 9,10 bonds.

EXPERIMENTAL

Low resolution mass spectra were recorded on the LKB 9000 and 2091 instruments using the direct inlet systems. The temperatures of the inlet systems were kept at 20 °C and those of the ion sources at 270 °C (9000) and 200 °C (2091). The electron energies used were 10, 12 and 70 eV. The two epimeric pairs IX, X and XXVIII, XXIX were subjected to multiple scanning at 10 and 70 eV, and the intensity intervals for total ion currents and selected peaks in these spectra were calculated in a manner described previously.¹

Accurate mass measurements were performed on an Atlas SM-1 instrument using the direct inlet system; ion source temperature 250 °C, electron energy 70 eV. I.r. spectra were recorded on a Perkin-Elmer 257 instrument, n.m.r. spectra on a Varian XL-100 spectrometer using CDCl₃ as a solvent and TMS as an internal standard, and u.v. spectra on a Beckman DK-2A instrument. Melting points were determined on a Leitz Wetzlar instrument and are uncorreced. Analyses were carried out by Centrala Analyslaboratoriet, Uppsala, Sweden and by A. Bernhardt, Elbach über Engelskirchen, West Germany.

Conversion of podocarpic acid (I) to podocarp-9(11)-en-12-one (VII). A solution of 24.8 g of podocarpic acid (I) in 500 ml of ethanol was refluxed with aqueous NaOH (40%) and excess dimethyl-sulphate for 15 h. Dilution with water and extraction with ether gave 27 g of methyl 12-O-methyl podocarpate (II), which on repeated recrystallisation from hexane had m.p. 128.5 to 130 °C (reported 128 °C).¹¹

A solution of 26.2 g of II in 1.2 l of dry ether was refluxed with 5.5 g of LiAlH₄ under N₂ for 7 h Addition of ice water and dilution with aqueous H₂SO₄ (20%) followed by extraction with ether gave 23.6 g of crude 12-O-methylpodocarpol (III), which after recrystallisation from hexane melted at 91 to 92 °C (reported 90 to 91.5 °C).¹¹

To a solution of 22.5 g of III in 1 l of acetone was added with stirring a solution of 11 g of CrO_3 in 250 ml of dilute H_2SO_4 (20%). After 15 min at room temperature the reaction mixture was diluted with water and extracted with ether to give 22 g of 12-O-methylpodocarpal (IV), which on recrystallisation from methanol had m.p. 137 to 139 °C (reported 133 to 135 °C).¹¹

To a solution of 27 g of KOH in 170 ml of diethylene glycol and 12.5 ml of hydrazine hydrate was added 16.5 g of IV. The reaction mixture was refluxed at 145 °C under nitrogen for 2 h. Water and excess hydrazine were removed by distillation at 195 to 215 °C. The reaction mixture was subsequently refluxed for 3 h, now at 210 °C, cooled, diluted with 51 of water, acidified with aqueous H₂SO₄ (50%) and extracted with ether. Chromatography over alumina using a hexane + isopropyl ether gradient furnished two main fractions, the least polar of which consisted of 5 g of 12-O-methylpodo-carpa-8,11,13-triene (V) m.p. 30 to 31 °C. The more polar fraction comprised 5.2 g of podocarpa-8, 11,13-triene (VI), which on recrystallisation from hexane had m.p. 152 to 153 °C. This phenol was converted to an additional 5 g of V using the same method as described above for I \rightarrow II.

A solution of 7.7 g of V in 150 ml of dry tetrahydrofuran was added to 500 ml of liquid ammonia kept in a three-necked round-bottomed flask fitted with a Dry-Ice condensor. Small and dry pieces of lithium, altogether 7.5 g, were added over a period of 20 min, then ethanol until the blue colour disappeared and, finally, 55 g of solid ammonium chloride. The bulk of the ammonia was slowly distilled off. The reaction mixture was acidified with 400 ml of aqueous acetic acid (80%), diluted with water and extracted with ether. The entire product of 7.5 g was dissolved in 200 ml of methanol containing 25 ml of conc. hydrochloride acid and 15 ml of water, and the reaction mixture was

refluxed for 30 min.⁵ Work up and chromatography over silica gel afforded 4.6 g of podocarpa-9(11)en-12-one (VII), m.p. 50 to 52 °C; (Found: C, 83.0; H, 10.5. $C_{17}H_{26}O$ requires C, 82.9; H, 10.6); u.v. absorption at 238 nm, $\varepsilon \sim 14900$ (EtOH); i.r. bands at 1675 and 1605 cm⁻¹; n.m.r. peaks at 0.90 (6H,s), 1.05 (3H,s) and 5.82 (1H,d,J ~ 2) ppm; m/e (%, composition): 246 ([M]⁺,68, $C_{17}H_{26}O$), 231 (26, $C_{16}H_{25}O$), 218 (13, $C_{15}H_{22}O$), 190 (8, $C_{14}H_{22}$, $C_{13}H_{18}O$), 163 (14, $C_{11}H_{15}O$), 136 (29, $C_{10}H_{16}$, $C_{9}H_{12}O$), 123 (100, $C_{9}H_{15}$, $C_{8}H_{11}O$), 110 (37), 109 (39) and 55 (32).

Conversion of VII to podocarpan-12 α -ol (IX) and podocarpan-12 β -ol (X). A solution of 265 mg of VII in 10 ml of ethanol was stirred with 50 mg of 10% Pd/C in a hydrogen atmosphere for 5 h, filtered and evaporated. The residue was chromatographed over silica gel to give 137 mg of *podocarpan*-12-one (VIII), m.p. 43 to 47 °C; (Found: C, 82-4; H, 11·1; C₁₇H₂₈O requires C, 82-2; H, 11·4) i.r. band at 1715 cm⁻¹; n.m.r. peaks at 0·87 (6H,s) and 0·90 (3H,s) ppm; *m/e* (%, composition): 248 ([M]⁺,100,C₁₇H₂₈O), 233 (64,C₁₆H₂₅O), 215 (12,C₁₆H₂₃), 192 (3,C₁₃H₂₀O), 191 (2,C₁₃H₁₉O), 190 (3,C₁₄H₂₂), 163 (34,C₁₁H₁₅O, C₁₂H₁₉), 123 (67,C₈H₁₁O, C₉H₁₅), 109 (46,C₇H₉O, C₈H₁₃), 69 (40), 55 (57) and 41 (60).

To a solution of 97 mg of VIII in 15 ml of methanol was added with stirring 100 mg of NaBH₄ at 0 °C. After 1 h at 0 °C the reaction mixture was acidified with aqueous H_2SO_4 (20%), diluted with water and extracted with ether. Chromatography over silica gel furnished 24 mg of *podocarpan-12α-ol* (IX), m.p. 50 to 55 °C; (Found: C,81·6; H,12·0; [M]^{+.} 250.2301; C₁₇H₃₀O requires C,81·5; H,12·1; [M]^{+.}250·2297), i.r. band at 3360 cm⁻¹, n.m.r. peaks 0·81 (3H,s), 0·83 (3H,s), 0·85(3H,s) and 4·14 (1H,m,W_{1/2} ~ 7) ppm, and 46 mg of *podocarpan-12β-ol* (X) m.p. 94 to 96 °C; (Found: C,81·7; H,11·9; [M]^{+.}250.2305.C₁₇H₃₀O requires C,81·5; H,12·1; [M]^{+.}250·2297); i.r. band at 3360 cm⁻¹, n.m.r. peaks at 0·84 (9H,s) and 3·52 (1H,m, broad) ppm.

Conversion of (VII) to podocarpan-9 α -d-12 α -ol (XIII) and podocarpan-9 α -d-12 β -ol (XIV). A solution of 226 mg of VII in 10 ml of ethanol was stirred with 50 mg of 10% Pd/C in a deuterium atmosphere for 5 h. The reaction mixture was diluted with water and extracted with pentane. Chromatography over silica gel afforded 106 mg of podocarpan-9 α ,11 α -d₂-12-one (XI), mol. wt-m.s. 250.

A solution of 106 mg of XI in 5 ml of ethanol and 0.5 ml of aqueous KOH (45%) was refluxed for 3 h under nitrogen. Dilution with water, acidification, extraction with ether and chromatography over silica gel gave 68 mg of podocarpan-9 α -d-12-one (XII); r.f. value on a t.l.c. plate identical to that of VIII. Isotopic composition: $11\% d_0$, 88% d_1 and $1\% d_2$.

A solution of 68 mg of XII in 12 ml of ethanol was stirred with 80 mg of NaBH₄ at 0 °C for 1 h. Work up and chromatography over silica gel furnished 13 mg of podocarpan-9 α -d-12 α -ol (XIII) and 27 mg of podocarpan-9 α -d-12 β -ol (XIV); r.f. values identical to those of IX and X, respectively. Isotopic compositions: XIII and XIV: 11% d_0 , 88% d_1 and 1% d_2 ;

Conversion of VII to podocarpan-8 β -d-12 α -ol (XVII) and podocarpan-8 β -d-12 β -ol (XVIII). A solution obtained by addition of 100 mg of sodium to 1 ml of O-deuteroethanol and 1.5 ml of deuterium oxide was refluxed with 480 mg of VII under nitrogen for 24 h. After removal of most of the solvents, 2 ml of O-deuteroethanol and 0.1 ml of deuterium oxide was added and the reaction mixture was refluxed for 48 h. Dilution with deuterium oxide, acidification with D₂SO₄, extraction with ether and chromatography over silica gel afforded 377 mg of podocarp-8 β ,11,13,13-d₄-9(11)-en-12-one (XV); r.f. value on a t.l.c. plate identical to that of VII. Isotopic composition: 16% d₃, 82% d₄ and 2% d₅.

A solution of 370 mg of XV in 5 ml of ethanol was stirred with 50 mg of 10% Pd/C in a hydrogen atmosphere for 5 h, diluted with water and extracted with ether. The residue was refluxed with 15 ml of ethanol and 0.5 ml aqueous KOH (45%) under nitrogen for 3 h. The reaction mixture was subsequently diluted with water, acidified, extracted with ether and chromatographed over silica gel to give 145 mg of podocarpan-8 β -d-12-one (XVI); r.f. value on a t.l.c. plate indistinguishable from that of VIII.

A solution of 140 mg of XV in 5 ml of methanol was stirred with 150 mg of NaBH₄ at 0 °C for 1 h. Work up in the usual manner and chromatography over silica gel furnished 26 mg of podocarpan-8 β d-12 α -ol (XVII) and 82 mg of podocarpan-8 β -d-12 β -ol (XVIII), r.f values on a t.l.c. plate identical to those of IX and X, respectively. Isotopic compositions: XVII and XVIII: 4% d_0 , 91% d_1 and 5% d_2 .

Conversion of VIII to podocarpan- 12β -d- 12α -ol (XIX) and podocarpan- 12α -d- 12β -ol (XX). A solution of 140 mg of VIII in 10 ml of ether was stirred with excess LiAlD₄ at room temperature for

1 h. Work up and chromatography over silica gel gave 25 mg of podocarpan- 12β -d- 12α -ol (XIX) and 78 mg of podocarpan- 12α -d- 12β -ol (XX). Isotopic compositions: XIX and XX: $100\% d_1$.

Conversion of VIII to podocarpan-11,11,13,13-d₄-12 α -ol (XXII) and podocarpan-11,11,13,13-d₄-12 β -ol (XXIII). A solution obtained by addition of 200 mg of sodium to 2 ml of O-deuteroethanol and 3 ml of deuterium oxide was refluxed with 250 mg of VIII for 5 h. Work up and chromatography over silica gel gave 109 mg of podocarpan-11,11,13,13-d₄-12-one (XXI). On reduction using NaBH₄ this deuterated ketone was converted to a mixture of podocarpan-11,11,13,13-d₄-12 α -ol (XXII) and podocarpan-11,11,13,13-d₄-12 β -ol (XXIII), which was separated by chromatography over silica gel. Isotopic compositions: XXII and XXIII: 2% d₂, 12% d₃ and 86% d₄.

Conversion of VIII to podocarpan-14 α -ol (XXVIII) and podocarpan-14 β -ol (XXIX). To a solution of 2.6 g of VIII in 150 ml of ethyl acetate + chloroform 9:1 was added 4 g of CuBr₂. The mixture was stirred at room temperature under a slightly reduced pressure for 6 h and filtered. The filtrate was diluted with ethyl acetate, washed with water and evaporated. The residue was dissolved in 110 ml of *N*,*N*-dimethylacetamide and refluxed with 14 g of CaCO₃ for 45 min. The reaction mixture was filtered, acidified with aqueous H₂SO₄ (20%) and extracted with ether. Chromatography over SiO₂ gave 1.9 g of *podocarp*-13-*en*-12-*one* (XXIV), m.p. 104 to 105 °C; (Found: [M]⁺.246.1980.C₁₇H₂₆O requires 246.1984); u.v. absorption (EtOH) at 228 nm, $\varepsilon = 8700$; n.m.r. peaks at 0.88 (6H,s), 0.92 (3H,s), 5.95 (1H,*dd*,J = 10 and 3), 6.70 (1H, broadened *d*,J = 10 and 2) ppm; m.s. (%, elemental composition): 246 ([M]⁺,74,C₁₇H₂₆O), 231 (28,C₁₆H₂₃O), 218 (9,C₁₆H₂₆), 203 (13,C₁₄H₁₉O), 190 (9,C₁₃H₁₈O), 176 (15,C₁₃H₂₀), 161 (35,C₁₁H₁₃O), 149 (15,C₁₁H₁₇ and C₁₉H₁₃O), 133 (35,C₉H₉O and C₁₀H₁₃), 123 (77,C₉H₁₅ and C₈H₁₁O), 122 (54,C₈H₁₀O and C₉H₁₄), 109 (100,C₇H₉O and C₈H₁₃), 108 (28), 107 (59,C₇H₇O and C₈H₁₁), 95 (50,C₇H₁₁ and C₆H₇O), 81 (57), 69 (60) and 55 (54).

To a solution of 1.8 g of XXIV in 40 ml of MeOH, kept at -15 °C, was added 2.3 ml of hydrogen peroxide (30%) followed by 1.7 ml of 6M NaOH. The mixture was stirred for 2 h, diluted with water, acidified, extracted with ether and evaporated. The residue was dissolved in 20 ml of dry methanol and cooled in an ice bath. To this solution was added 1.07 g of hydrazine hydrate and 95 mg of acetic acid.⁶ After 0.5 h at room temperature the reaction mixture was diluted with water, extracted with ether and chromatographed over SiO₂ (light petrol + isopropyl ether 1:0 \rightarrow 9:1) to give 282 mg of *podocorp-12-en-14\alpha-ol* (XXV), m.p. 82 to 84 °C. (Found: [M]+·248.2129. C₁₇H₂₈O requires [M]+·248.2140), i.r. band at 3450 and 1665 cm⁻¹; n.m.r. peaks at 0.86 (9H,s), 3.85 (1H,m, W_{1/2} ~ 8) and 5.85 (2H,m) ppm; m.s. (%), 248 (M,100), 233 (15), 230 (5), 215 (12), 177 (12), 163 (18), 149 (10), 145 (11), 137 (16), 135 (17), 123 (33), 109 (34), 95 (37), 91 (30), 81 (33), 69 (39), 55 (37), and 433 mg of *podocarp-12-en-14β-ol* (XXVI) m.p. 99.5 to 102 °C; (Found: [M]+·248.2154. C₁₇H₂₈O requires [M]+·248.2140), i.r. bands at 3340 and 1665 cm⁻¹, n.m.r. peaks at 0.88 (9H,s), 3.78 (1H,m,W ~ 16) and 5.62 (2H,m) ppm; m.s. (%): 248 ([M]+,100), 233 (14), 230 (4), 215 (10), 177 (15), 163 (14), 149 (11), 145 (8), 137 (18), 135 (16), 123 (36), 109 (33), 95 (45), 91 (24), 81 (36), 69 (40), 55 (38).

On treatment with Jones reagent both XXV and XXVI afforded *podocarp-12-en-14-one* (XXVII), m.p. 113 to 115 °C; (Found: [M]⁺·246. $C_{17}H_{26}O$ requires [M]⁺·246), u.v. absorption at 223 nm, $\varepsilon = 11700$; i.r. band at 1680 cm⁻¹, n.m.r. peaks at 0.88 (6H,s), 0.93 (3H,s) 5.97 (1H, broadened $d, J \sim 10, 1.5$) and 6.93 (H,m,W_{1/2} ~ 20); m.s. (%): 246 ([M]⁺,44), 231 (20), 190 (4), 177 (7), 161 (10), 150 (12), 138 (54), 123 (54), 122 (30), 109 (73), 108 (46), 96 (48), 95 (100), 81 (34), 80 (34), 79 (33), 69 (35), 55 (38) and 41 (47).

A solution of 90 mg of XXV in 10 ml of ethanol was stirred with 20 mg of 5% Pd/C in a hydrogen atmosphere for 2h, filtered and evaporated. Chromatography over SiO₂ gave 85 mg of podocarpan-14 α -ol (XXVIII) m.p. 106 to 108 °C, (reported 99 to 100 °C);¹² (Found: C,81·3; H,11·8; [M]^{+.250}. 2289. Calc. for C₁₇H₃₀O: C,81·5; H,12·1; [M]⁺250.2297), i.r. band at 3480 cm⁻¹; n.m.r. peaks at 0·84 (6H,s), 0·85 (3H,s) and 3·75 (1H,m,W_{1/2} ~ 7) ppm.

Hydrogenation of 160 mg of XXVI, carried out in the same manner as described above for XXV, gave after purification 152 mg of podocarpan-14 β -ol (XXIX), m.p. 110 to 112 °C (reported 118 to 119 °C);¹² (Found: C,81·3; H,11·9; [M]+250.2287 Calc. for C₁₇H₃₀O: C,81·5; H,12·1; [M]+250.2297), i.r. band at 3380 cm⁻¹, n.m.r. peaks at 0.85 (6H,s), 0.86 (3H,s) and 3·3 (1H,m, W_{1/2} ~ 14) ppm.

Both XXVIII and XXIX were transformed to podocarpan-14-one (XXX), m.p. 88 to 91 °C (reported 73 to 73.5 °C,¹³ 67 to 68 °C)¹² on oxidation using Jones reagent. XXX had i.r. bands at 1708, 1148 and 1124 cm⁻¹, which agree with values published before;^{12,13} n.m.r. peaks at 0.83 (3H,s),

0.86 (3H,s) and 0.94 (3H,s); m/e (%): 248 ([M]⁺,74), 233 (35), 230 (14), 215 (24), 192 (8), 177 (7), 164 (14), 163 (14), 150 (46), 138 (78), 135 (40), 124 (48), 123 (100), 109 (42), 95 (64), 82 (48), 81 (60), 69 (58) and 55 (72).

Conversion of XII to podocarpan-9 α -d-14 α -ol (XXXIV) and podocarpan-9 α -d-14 β -ol (XXXV). Using the same sequence of reactions as described above for the preparation of XXVIII and XXIX from VIII, XII (isotopic composition: 16% d_0 , 82% d_1 and 2% d_2) was converted to podocarpan-9 α -d-14 α -ol (XXXIV) and podocarpan-9 α -d-14 β -ol (XXXV) via podocarpan-9 α -d-13-en-12-one (XXXI), and podocarp-9 α -d-12-en-14 α -ol (XXXII) and podocarpan-9 α -d-14 α -ol (XXXII), respectively. The labelled derivatives had r.f. values on t.l.c. plates identical to those of the corresponding nondeuterated derivatives.

Conversion of XXX to podocarpan- 8β , 13, 13-d₃-14 α -ol (XXXVII) and podocarpan- 8β , 13, 13-d₃-14 β -ol (XXXVII). Using the same procedure as described above for the base catalysed exchange of hydrogen for deuterium in VIII, XXX was converted to podocarpan- 8β , 13, 13-d₃-14-one (XXXVI). Reduction of this deuterated ketone with NaBH₄ followed by chromatography of the reaction mixture gave podocarpan- 8β -13, 13-d₃-14 α -ol (XXXVII) and podocarpan- 8β , 13, 13-d₃-14 β -ol (XXXVII) Isotopic compositions: XXXVII and XXXVIII: 7% d₂, 90% d₃ and 3% d₄.

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