Tetrahedron. Vol. 28, pp. 3155–3173. Pergamon Press 1972 Printed in Great Britain

CATIONIC REARRANGEMENTS AND CYCLIZATIONS OF DITERPENOID OLEFINS*

S. F. HALL and A. C. OEHLSCHLAGER
Department of Chemistry, Simon Fraser University, Burnaby 2, B.C., Canada

(*Received in the USA* 22 *September* 1971; *Received in the UK for publication* 18 *February* 1972)

Abstract—The biogenesis of tetracarbocyclic diterpenes is considered to involve cyclisation *via* a bicyclic C-13 carbonium ion. This species has been generated *in vitro* from manool and Δ^{13}-manool and found to give, in refluxing acetic acid, a 1:1 mixture of Δ^{13}-manool acetate and olefins. The latter consisted mainly of labdatrienes with smaller amounts of three classes of cyclized products. Ring closure between C-13 and C-17 gave approximately equal amounts of tricyclic α-vinyl isopimaric and β-vinyl pimaric Δ^{7}, Δ^{8} and $\Delta^{8(14)}$ dienes together with products of backbone rearrangement. Each of the dienes was found to be stable under the reaction conditions, indicating backbone rearrangement occurred by transfer of the migrating functions along the backbone of the molecule without participation of the intermediate olefins. The third type of cyclized product was a new cycloocta-1,5-diene which we call 8,13-burnabadiene, generated by cylization between C-15 and C-17.

Under refluxing formic acid, formation of labdatrienes was precluded and yields of the initially cyclized pimaradienes and isopimaradienes, the backbone rearranged products and burnabadiene increased. In this reaction the ratio of Δ^{13}-manool formate to olefins was 1:7. The initial dienes and backbone rearranged products were interconverted by the reaction conditions showing that backbone rearrangement is reversible. A tetracyclic product, hiban-14-α-yl-formate was also isolated and was formed in quantitatively when 8,13-burnabadiene was subjected to the reaction conditions. Deuterium labelling of Δ^{13}-manool at C-14 showed that hiban-14-α-yl-formate was indeed formed *via* such a carbon skeleton.

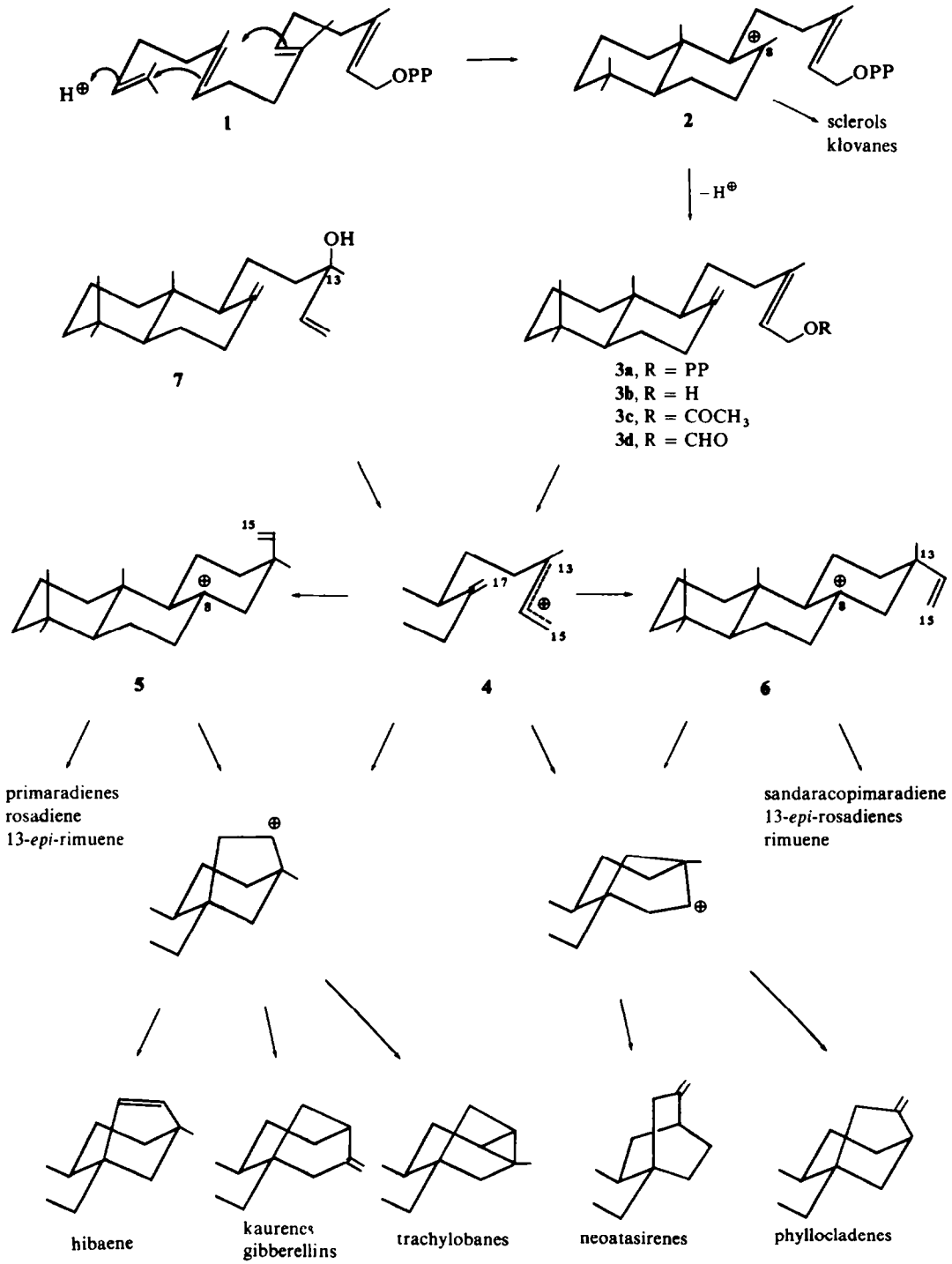
INTRODUCTION

THE BIOGENESIS of terpenes is considered to involve cationic cyclizations of acyclic precursors to give cyclic progenitors. Reasonable cationic rearrangements of these initially formed intermediates can account for the gross carbon structure of most natural terpenoids. A number of the proposed cyclizations and rearrangements have been imitated in the laboratory by generating the appropriate carbonium ions in suitable skeletons.[1–6]

The initial cyclization in the biogenesis of the polycyclic diterpenes is considered to be the proton initiated cyclization of geranylgeranyl pyrophosphate (**1**) to the bicyclic C-8 carbonium ion **2** (Scheme 1). The hydration, neutralization, and rearrangement of **2** is considered to give rise to sclerols, manools and backbone rearranged labdenes. A large number of mineral acid catalysed cyclizations of 1,5-dienes[3, 4, 8–14] portray the essential features of this reaction, *i.e.* concerted cyclizations proceeding to cyclohexyl systems by *trans–anti*-parallel addition to the double bonds. In addition this course of events is supported by the enzymatic transformation of **1** to copalyl-PP (*enantio*-**3a**) by *Gibberella fujikuroi*.[7] This bicyclic compound is considered to be a stabilized intermediate in the biogenesis of the more highly cyclized diterpenes since it is transformed into (−)-kaurene by soluble enzyme preparations from wild cucumber

* For a preliminary communication of a portion of this work see S. F. Hall and A. C. Oehlschlager *Chem. Comm.* 1157 (1969).

SCHEME 1. Biosynthetic routes to diterpenoids



and *G. fujikuroi* and to a mixture of *enantio*-sandaracopimaradiene, hibaene, kaurene and trachylobane in a soluble enzyme fraction from castor bean seedlings. Thus cyclization of **3** *via* **4** is considered to give rise to the pimaradiene diterpenes *via* the biological equivalents of **5** and **6**. Intermediates analogous to **5** and **6** have also been implicated in the biogenesis of backbone rearranged pimaradienes such as the rosadienes and rimuenes. Although **5** and **6** have also often been considered as intermediates in the biogensis of the tetracarbocyclic skeletons[1, 2, 7] direct conversion of **4** to these skeletons is also possible.

The key positions which the biological equivalents of **4**, **5** and **6** occupy in the biogenetic scheme have prompted several investigations[15–20] into the fate of these species in solution. In general these investigations have been undertaken to give a better understanding of the kinetic and thermodynamic fate of these ions so that enzymatic control during natural processes may be more clearly defined. We have studied the acid catalysed reactions of manool under conditions sufficiently vigorous to consume the manool but not so vigorous as to cause extensive rearrangement of the primary products, which were isolated, identified and reacted further, this process being repeated as often as possible. Thus we have attempted to study the readiness with which each encountered carbonium ion species underwent transformations resembling those proposed for the *in vivo* processes involved in the biosynthesis of the more extensively rearranged and cyclized diterpenes.

RESULTS

Acid catalysed interconversions

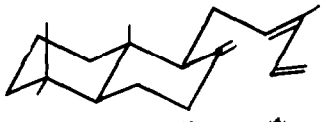
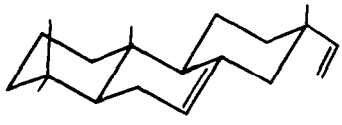
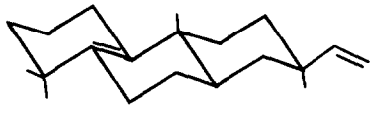
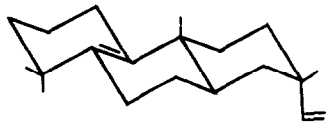
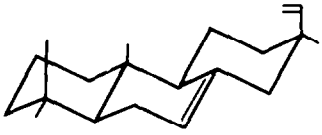
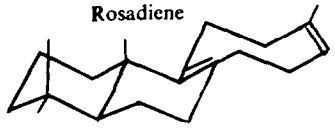
Reaction of manool (**7**) in refluxing AcOH for one hr gave a mixture of unreacted manool, Δ^{13}-manool acetate (**3c**) and olefins. The product distribution (Table 1) was determined by isolation of **7** and **3c** and by VPC analysis of the olefin fraction. Similar reaction of Δ^{13}-manool (**3b**) gave an olefin fraction which exhibited on VPC identical behaviour to that obtained from the manool–AcOH reaction.

After workup and extensive chromatographic separation each of the olefin products was subjected to the original reaction conditions. All except *trans*-biformene were completely stable as determined by VPC analysis. After one hr 70% of *trans*-biformene was consumed. No additional monomeric olefins were observed as products by VPC.

Reaction of manool and Δ^{13}-manool (**3b**) with refluxing HCOOH also gave olefin mixtures with identical chromatograms (Table 2). Representative product distributions produced upon resubjecting tricyclic compounds possessing a 13α-vinyl group to HCOOH and reported in Tables 3 and 4. Results for the epimeric C-13-β-vinyl tricyclic diterpenes are in Tables 5 and 6.

Additional information concerning the pathway by which the bicyclic skeleton of hiban-14α-yl-formate (**23**) was formed was provided by treatment of Δ^{13}-manool (**3b**) (prepared according to Scheme 2) deuterated at C-12, C-14 and C-16 with HCOOH. The extent of deuteration at C-14 was ascertained to be 50% by NMR comparison of the intensity of the pair of signals (τ 5·20, 5·53) due to the C-17 hydrogens with the triplet (τ 4·74) due to those attached to C-14. After chromatography of the mixture, hiban-14α-yl-formate (**23**) was isolated in low yield. Integration of the NMR signal due to the formate hydrogen (τ 1·80) and comparison with that due to the 14β-hydrogen (τ 5·55) in this hiban-14α-yl-formate revealed all of the deuterium originally at C-14 in

TABLE 1. PRODUCT DISTRIBUTION FROM REACTION OF MANOOL WITH AcOH

Compound	Yield (%)	Compound	Yield
Manool (7)	36		
Δ^{13}-Manool acetate (3c)	30		
	15		
trans-Biformene (8)		8,15-Isopimaradiene (14)	2·9
	5·4		
cis-Biformene (9)		Sandaracopimaradiene (15)	0·4
	6·2		
Sclarene (10)		Isopimaradiene (16)	1·2
	3·4		0·2
8,15-Pimaradiene (11)		5(10),15-Rosadiene (17)	
	0·5		0·4
Pimaradiene (12)		13-*epi*-5(10),15-Rosadiene (18)	
	1·1		1·4
7,15-Pimaradiene (13)		8,13-Burnabadiene (19)	
		Total 104·1	

* The experimental error was estimated at ±10% of each value determined, except for yields of less than 1% which were rounded off to the nearest tenth of a percent.

TABLE 2. PRODUCT DISTRIBUTION FROM REACTION OF MANOOL WITH FORMIC ACID

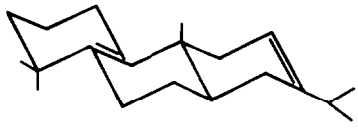
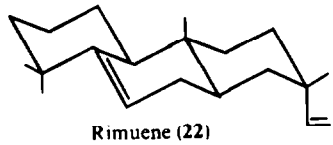
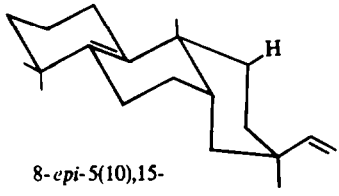
Compound	Yield (%)	Compound	Yield (%)
Δ^{13}-Manool formate (**3d**)	11		
8,15-Pimaradiene (**11**)	24		
Pimaradiene (**12**)	1·5		
7,15-Pimaradiene (**13**	1·8		
8,15-Isopimaradiene (**14**)	19		1·1
Sandaracopimaradiene (**15**)	1·1		
Isopimaradiene (**16**)	1·7	5(10),12-Abietarosadiene (**21**)	
5(10),15-Rosadiene (**17**)	5·0		
13-*epi*-5(10),15-Rosadiene (**18**)	10		
8,13-Burnabadiene (**19**)	2·0		
			1 8
		Rimuene (**22**)	
	1·2		8·0
8-*epi*-5(10),15-Rosadiene (**20**)		Hiban-14α-yl formate (**23**)	
		Unknown (**24**)	1·0
		Total	90·3

TABLE 3. PRODUCT DISTRIBUTION (%) FROM REACTION OF 8,15-ISOPIMARADIENE WITH FORMIC ACID

Product	Reaction time							
	0	2½ min	7½ min	12½ min	30 min	1 hr	3 hr	5 hr
8,15-Isopimaradiene (**11**)	100	87	68	51	30	17	7	5
Sandaracopimaradiene (**15**)		0·4	1·8	2·2	0·6			
Isopimaradiene (**16**)		0·9	3·0	3·5	1·2			
13-*epi*-5(10),15-Rosadiene (**18**)		2·5	14·2	31	46	43	44	37
Rimuene (**22**)			0·8	1·7	2·5	5·9	6·6	5·5
5(10),12-Abietarosadiene (**21**)						0·8	3·4	5·2
Unknown (**24**)			1·3	5·0	8·9	8·8	11	12
Totals	100	90·8	89·1	94·4	89·2	75·5	72·0	64·7

TABLE 4. PRODUCT DISTRIBUTION (%) FROM REACTION OF 13-*epi*-5(10),15-ROSADIENE WITH FORMIC ACID

Product		Reaction time						
		0	10 min	30 min	1 hr	2 hr	4 hr	7 hr
8,15-Isopimaradiene	(**11**)				2·3	3·2	3·6	3·2
13-*epi*-5(10),15-Rosadiene	(**18**	100	69	50	48	47	39	37
Rimuene	(**22**)		3·5	5·4	8·6	11·2	7·6	7·6
5(10),12-Abietarosadiene	(**21**)				1·4	1·8	4·0	6·7
Unknown	(**24**)					2·1	5·3	8·5
Total		100	72·5	55·4	60·3	65·3	59·5	63·0

TABLE 5. PRODUCT DISTRIBUTION (%) FROM REACTION OF PIMARADIENE WITH FORMIC ACID

Product		Reaction time				
		0	5 min	10 min	20 min	1 hr
8,15-Pimaradiene	(**11**)		32	52	54	21
Pimaradiene	(**12**)	100	53	27	9	1·4
7,15-Pimaradiene	(**13**)		3·2	4·1	3·2	1·5
5(10),15-Rosadiene	(**17**)		3·5	5·4	13	23
5(10,12-Abietarosadiene	(**21**)					1·3
8-*epi*-5(10),15-Rosadiene	(**20**)		0·6	2·1	7·4	16
Totals		100	92·3	90·6	86·6	64·2

TABLE 6. PRODUCT DISTRIBUTION (%) FROM REACTION OF 5(10),15-ROSADIENE WITH FORMIC ACID.

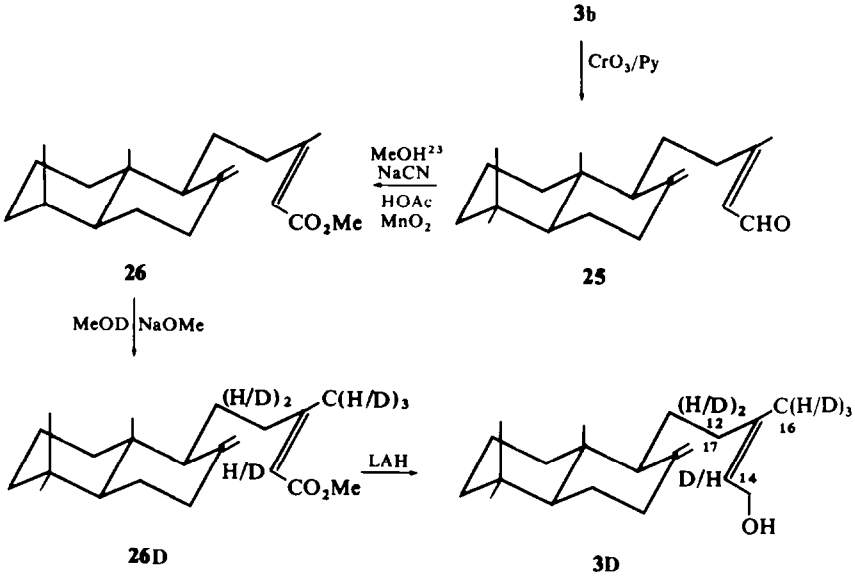
Product		Reaction time					
		0	15 min	30 min	1 hr	2 hr	5 hr
8,15-Pimaradiene	(**11**)		15	20	16	14	10
5(10),15-Rosadiene	(**17**)	100	69	60	48	37	25
5(10),12-Abietarosadiene	(**21**)			1·9	3·0	8·5	14
8-*epi*-5(10),15-Rosadiene	(**20**)			3·6	4·2	13	21
Totals		100	84	85·5	72·0	72·5	70

the starting material to be located at C-14 in this product. Furthermore, the isotope distribution around the parent peak in the mass spectrum of both compounds was the same, indicating that the deuteriums at C-12 and C-16 in the deuterated Δ^{13}-manool (**3d**) were not lost in the reaction.

Structures of the products

Product identification for the acid catalysed reactions was performed on isolated chromatographic fractions shown to be homogeneous by TLC ($SiO_2/AgNO_3$) and,

SCHEME 2. Synthesis of deuterated Δ^{13}-manool



in the case of olefinic products, by VPC analysis on the two capillary columns employed in this study. In the case of the Δ^{13}-manool esters (**3c** and **3d**); *cis* and *trans* biformene (**9** and **8**), sclarene (**10**), 8,15-pimaradiene (**11**), pimaradiene (**12**), 8,15-isopimaradiene (**14**), sandaracopimaradiene (**15**) and isopimaradiene (**16**) direct comparison with authentic samples, generously donated or prepared by known procedures, was possible. In the case of 5(10), 15-rosadiene (**17**), 13-*epi*-5(10), 15-rosadiene (**18**), rimuene (**22**) and hiban-14α-yl formate (**23**) identification was made by comparison of the spectral (NMR, IR, MS) properties with literature values. The structures of 7,15-pimaridiene (**13**), 8-*epi*-5(10), 15-rosadiene (**20**), 5(10),12-abietarosadiene (**21**), and 8,13-burnabdiene (**19**) are suggested on the basis of their spectral properties and chemical interconversions.

Structure of 7,15-*pimaradiene* (**13**)

The tricyclic nature of **13** was indicated by its molecular formula ($C_{20}H_{32}$), mass and NMR spectra. The mass spectrum of **13** exhibited significant fragment ions at *m/e* 272 (P^+), 148, 133, 124 and 109. The fragmentation pattern described in Fig. 1 is supported by metastable ions at *m/e* 119·5 (148 → 109). Increasing the ionization voltage decreased the intensity of the mass 148 ion in relation to its daughter *m/e* 133 an observation reported[24] also for isopimaradiene (**16**). The mass spectra of isopimaradiene (**16**) and **13** are nearly identical, the only significant difference being that the fragment ion *m/e* 148 for the latter is more intense. Since the mass spectra of pimaradiene C-13 epimers (**11** and **14**; **12** and **15**) are nearly identical[24] a C-13 epimeric relationship was suggested between isopimaradiene and **13**. That **13** possessed a C-13β-vinyl group was indicated by its ready acid catalysed interconversion with pimaradiene (**12**) and 8,15-pimaradiene (**11**).

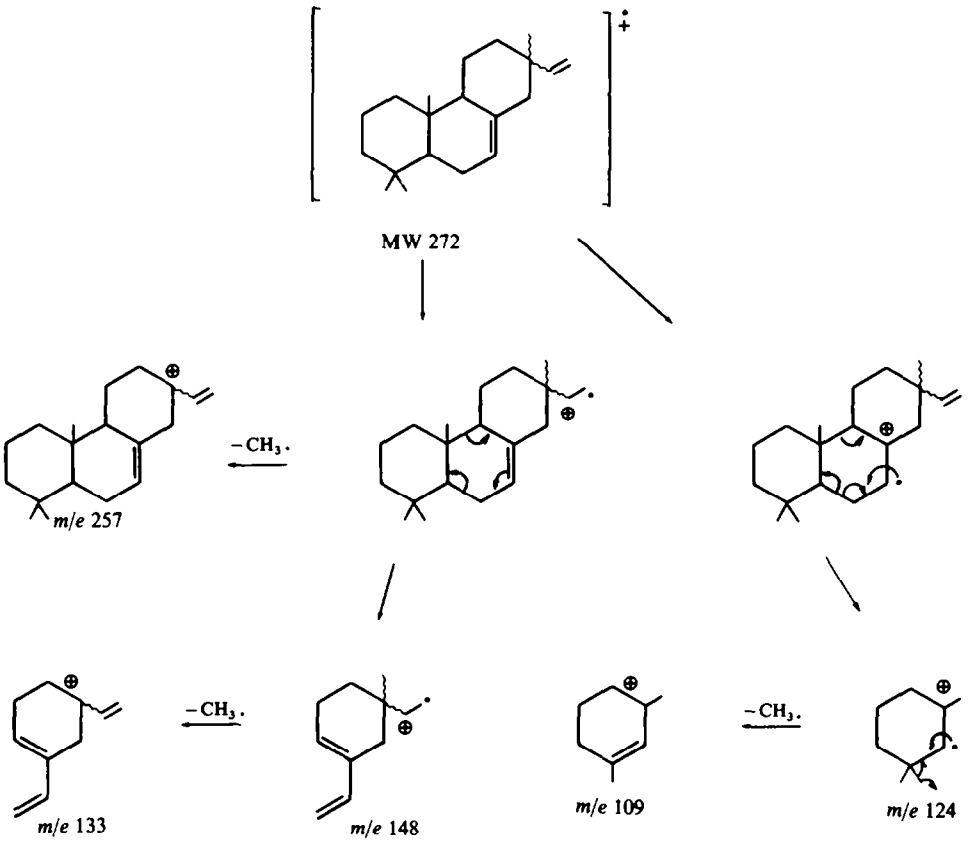


FIG 1. Fragmentation pattern of 7,15-pimaradiene (**13**) and isopimaradiene (**16**)

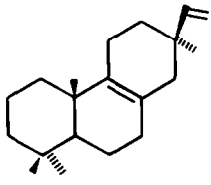
TABLE 7. CHEMICAL SHIFTS OF Me GROUPS OF TRICYCLIC DITERPENES

Compound		C-4	C-10	C-13
8,15-Pimaradiene	(**11**)	9·12, 9·15	9·04	9·07
Pimaradiene	(**12**)	9·13, 9·15	9·27	9·02
7,15-Pimaradiene	(**13**)	9·13, 9·20	9·09	9·04
8,15-Isopimaradiene	(**14**)	9·12, 9·15	9·04	9·04
Sandaracopimaradiene	(**15**)	9·13,	9·20	8·96
Isopimaradiene	(**16**)	9·13, 9·13	9·13	9·08
5(10),15-Rosadiene	(**17**)	9·03, 9·15	9·03	8·96
13-*epi*-5(10),15-Rosadiene	(**18**)	9·07, 9·16	9·07	9·07
Rimuene	(**22**)	9·00, 9·05	9·33	8·95
8-*epi*-5(10),15-Rosadiene	(**20**)	9·05, 9·10	9·05	9·01

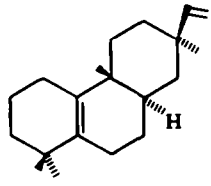
As expected of a pimaradiene, the NMR spectrum of **13** exhibited four quaternary Me resonances, a vinyl (ABX) resonance and a resonance due to a single vinyl hydrogen (τ 4·57), coupled to adjacent hydrogens (Table 7). Inspection of the chemical shifts of the quarternary Me resonances in the NMR spectra of the pimaradienes (**11**,[16] **12**[16]) the isopimaradienes (**14**,[16] **15**,[16] **16**[16]), 5(10), 15-rosadiene (**17**[22]), 13-*epi*-5(10), 15-rosadiene (**18**[17]) and rimuene (**22**[21]) (Table 7) reveals that shifting the endocyclic double bond from the $\Delta^{8(14)}$ position to either the $\Delta^{8(9)}$ or the $\Delta^{7(8)}$ position causes an upfield shift of the C-13 Me resonance in the C-13α-vinyl series. Shifting the double bond from the $\Delta^{8(9)}$ to the $\Delta^{7(8)}$ or $\Delta^{8(14)}$ position results in an upfield shift of the signal due to the C-10 Me. The signals due to the Me groups at C-4 are relatively unaffected by these changes. In the C-13β-vinyl series similar changes in the C-10 Me signal position are observed upon shifting the endocyclic double bond from the $\Delta^{8(9)}$ to the $\Delta^{8(14)}$ position. If **13** possesses a $\Delta^{7(8)}$ double bond, the C-10 and C-13 Me resonances should be at a higher field than that of the $\Delta^{8(9)}$ isomer (**11**). Since this was observed we formulate **13** as 7,15-pimaradiene.

Structure of 8-epi-5(10),15-*rosadiene* (**20**)

The NMR spectrum of **20** and an observed MW of 272 suggested that the compound was tricyclic and possessed both a vinyl group and an additional double bond which was fully substituted by groups other than Me. The exclusive formation of **20** from 8,15-pimaradiene (**11**) further suggested the vinyl group was in a C-13β-position. On the basis of spectral data two attractive structural formulas for **20** are **27** and **28**. Since the mass spectrum of **20** was nearly identical with that of 5(10),15-rosadiene (**17**) it was construed that **20** and **17** contained similar skeletons (**28**) and might be epimeric.



27



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Finally, inspection of molecular models of the C-8 epimers of **28** revealed the 8β-H isomer possessed fewer 1,3-diaxial interactions and thence would be expected to be the more stable toward acid catalysed backbone rearrangement (since increases in steric interactions occurring in this process are much more severe in this isomer.) In accord with the formulation of **20** as 8-*epi*-5(10),15-rosadiene this compound is completely stable to refluxing HCOOH.

Structure of 5(10),12-*abietarosadiene* (**21**)

Formation of **21** (MW 272) from the tricyclic pimaradienes and their backbone rearranged counterparts in both C-13 epimeric series is suggestive of migration of the C-13 Me to C-15 analogous to the transformation of pimaric and isopimaric acid to abietic acid and abietic lactones.[1] The presence of an abietadiene skeleton in **21** was further indicated by its NMR spectrum which revealed four sharp singlets at τ 8·97, 9·02, 9·07, and 9·22 with a total integration corresponding to fifteen hydrogens

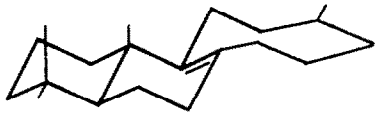
indicating five Me groups. The appearance of a broad vinyl hydrogen signal (τ 4·67) due to a single hydrogen as well as the observation that the UV spectrum was transparent above 200 mμ enabled the elimination of structures possessing conjugated diene systems as well as homoconjugated diene systems which would easily rearrange[2] to conjugated systems.

Tables 3 to 6 reveal that production of **21** from 5(10),15-rosadiene (**17**) and 13-*epi*-5(10),15-rosadiene (**18**) is significantly more efficient than from any of the normal pimaradienes (**11**–**14**) suggesting the presence of a backbone rearranged skeleton in **21**. The structure proposed for **21** exhibits all of the features required by the foregoing discussion.

Structure of 8,13-*burnabadiene* (**19**)

Compound **19** possessed a MW of 272 and must therefore be bicyclic with three double bonds, tricyclic with two double bonds or tetracyclic with one double bond. Since the UV spectrum of **19** was transparent above 200 mμ no conjugated double bonds were present. Significantly the NMR spectrum of **19** revealed the presence of three quarternary Me groups (τ 8·45) coupled (J = 2 Hz) to one more highly coupled vinyl hydrogen (τ 4·60) and ten allylic hydrogens (τ 7·50–8·25).

The presence of at least two double bonds was proven by partial hydrogenation. Thus **19** absorbed one mole of H_2 to give a product (**29**) (MW 274) which gave a positive tetranitromethane test. The NMR spectrum of **29** revealed the vinyl methyl and vinyl hydrogen resonances had disappeared and only six allylic hydrogens remained.



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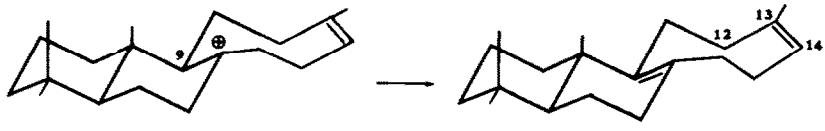
The demonstration *via* labelling (described above) that the formation of hiban-14α-yl formate (**23**), isolated from the reaction of manool with HCOOH, may be visualized as proceeding *via* the tricyclic intermediate **30** coupled with the formation of 8,15-pimaradiene (**11**) and 8,15-isopimaradiene (**14**) from their presumed C-8 cationic precursors further suggested structure **19** as a logical product of the manool cyclization.



30 **19**

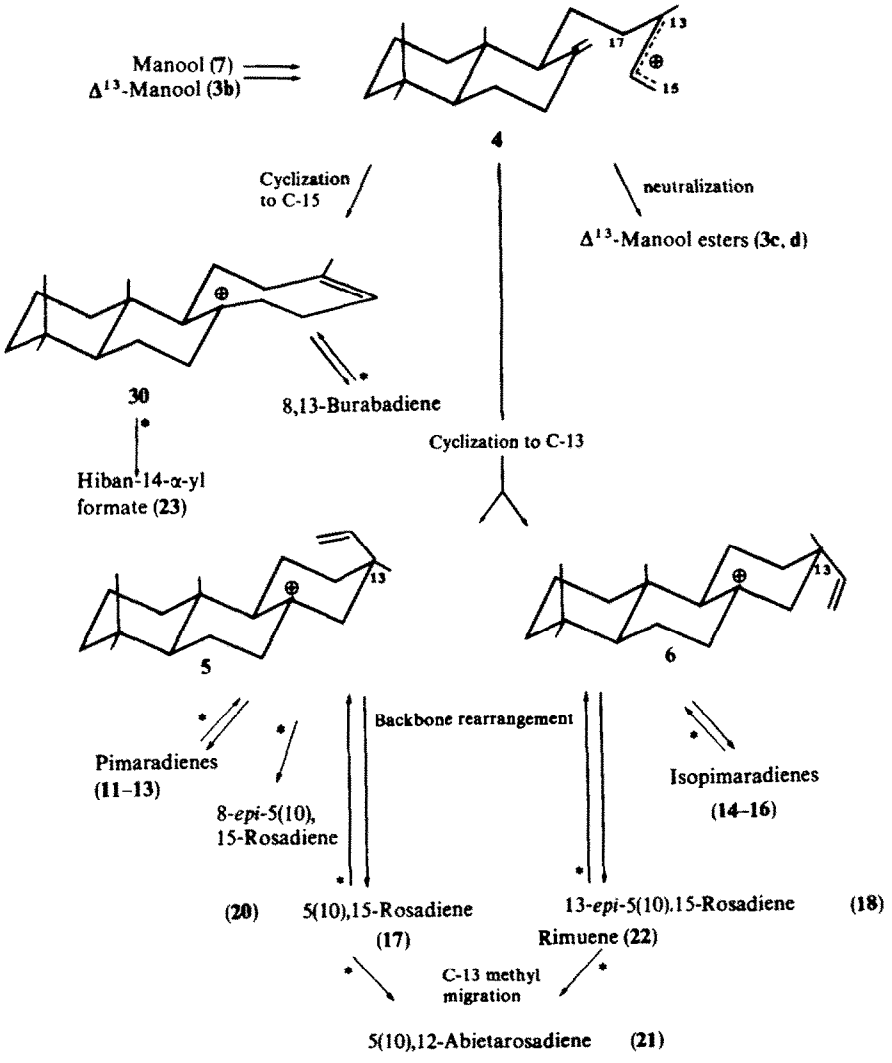
One would expect that upon treatment of **19** with acid that if reprotonation occurred at C-9 to generate **30** then hiban-14α-yl formate would be one of the products. Indeed, although **19** was stable in refluxing AcOH, refluxing with HCOOH resulted in quantitative conversion to hiban-14α-yl formate.

The location of the $\Delta^{8(9)}$ double bond in **19** appears clear from the absence of vinyl hydrogens in the NMR spectrum of **29**, however, it could be argued that the $\Delta^{13(14)}$ double bond could perhaps be at the $\Delta^{12(13)}$ position. The latter can be ruled out since the deuterium labelling studies established that deprotonation–reprotonation processes do not occur at C-12 or C-14 during the conversion of manool to hiban-14α-yl formate.

DISCUSSION

The reactions of manool (**7**) and Δ^{13} manool (**3b**) with AcOH and HCOOH are formulated in Scheme 3.

SCHEME 3. Reactions of manools in acids



* These reactions only proceed in HCOOH.

That the bicyclic species undergoing cyclization is best represented by **4** is indicated by the identical product distribution from both manool (**7**) and Δ^{13}-manool (**3b**).

In AcOH neutralization at C-15 and deprotonation to *trans*-biformene (**8**), *cis*-biformene (**9**) and sclarene (**10**) were the predominant fates of **4**.[19] The stability of the labdatrienes in this medium demonstrated that the cyclized products were formed directly from **4** without participation of bicyclic triene intermediates.

In HCOOH no triene products were detected and the compounds derived from **4** were derived *via* cyclization to C-17. Since trienes **8–10** when subjected individually to the reaction conditions gave VP chromatograms that possessed peaks at shorter retention times than those of the earliest peaks observed in the chromatogram of the manool reaction it seems likely that once the bicyclic ion (**4**) was formed it underwent cyclization at a rate which precluded deprotonation by formate to a labdatriene. Since in both mediums manool or its Δ^{13} isomer were the only precursors of **4** these reactions closely parallel events considered to occur *in vivo* for the conversion of **3** to the primaradiene type diterpenes. Thus in the only comprehensive study of the enzymatic cyclizations leading to the more highly cyclized diterpenes West[7c] reported no labdatrienes in the hydrocarbon mixture derived from the transformation of *enantio*-**3a** (or **1**) to *enantio*-sandaracopimaradiene, (−)-kaurene, (+)-stachene ((+)-hibaene) and trachylobane by soluble enzyme preparations from seedlings of castor beans (*Ricinus communis*).

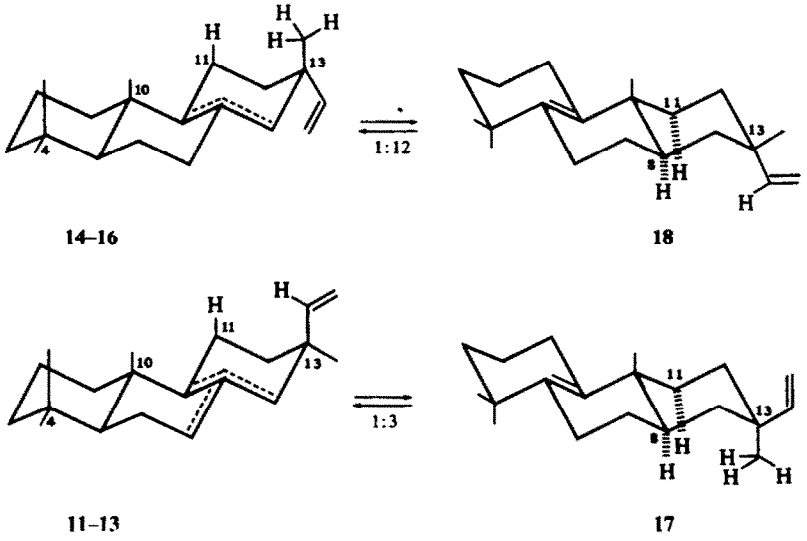
Since *in vitro* cyclization of **4** to **5** and **6** is modestly efficient and shows no bias significant toward the generation of a particular tricyclic C-13 epimeric series one might reasonably inquire into the point of enzymatic control in this step, especially since tricyclic diterpenes of both C-13 epimeric series often co-occur. West[7c] was able to fractionally separate enzymatic activity for the cyclization of *enantio*-**3a** to *enantio*-sandaracopimaradiene (C-13-α-vinyl) from that for cyclization of *enantio*-**3a** to hibaene, kaurene and trachylobane (C-13, β-vinyl). The production of C-13 epimeric series *in vivo* may thus be *via* two stereospecific enzyme systems.

In both AcOH and HCOOH cyclization of **4** between C-13 and C-17 gave the tricyclic pimaradienes (**11–13**) and isopimaradienes (**14–16**) as well as the corresponding backbone rearranged products (**17**, **18**) previously reported.[16–18] We observed that the tricyclic diterpene olefins (**11–16**) were stable to AcOH but that treatment of the pimaradienes of either C-13 epimeric series with HCOOH lead initially to isomerization around C-8, then to backbone rearrangement, and eventually to the pimaradiene–abietadiene rearrangement. At equilibrium the composition of the Δ^8 pimaradiene mixtures was $1(\Delta^7):1(\Delta^{8(14)}):25(\Delta^8)$. In AcOH where interconversion of the Δ^8 isomers did not occur the distribution was $2–3(\Delta^7):1(\Delta^{8(14)}):6–7(\Delta^8)$. If one regards the latter mixtures as those derived from kinetically controlled deprotonation of **5** and **6** it is apparent that the enzymatic conversion of copalyl-PP (*enantio*-**3a**) to *enantio*-sandaracopimaradiene[7c] represents preferential loss of the C-14 hydrogen of **6**.

The observation that each of the tricyclic products (**11–16**) was stable to refluxing AcOH requires the backbone rearranged products, **17** and **18**, formed in the AcOH reaction to come directly from the initially formed carbonium ions **5** and **6** without the participation of olefinic intermediates. This observation parallels the reports of *in vivo*[25–28] backbone rearrangements which proceed without intervention of olefinic intermediates. In most studies of acid catalysed backbone rearrangements[29] investigators have inferred such concerted mechanisms from the stereochemical outcome.

As can be seen from the reactions in HCOOH the cross stereochemical features of the backbone rearrangements in this medium are the same as in AcOH even though olefinic intermediates are undoubtedly involved in HCOOH. Data comparison (Tables 1 to 6) indicates that the increased yield of backbone rearranged products in the initial HCOOH reaction is attributable. at least in part, to an increase in the competitiveness of backbone rearrangement of the initially formed tricyclic ions (**5** and **6**) in this medium.

Prolonged HCOOH treatment of the pimaradienes (**11–13**), isopimaradienes (**14–16**), or the epimeric rosadienes (**17** and **18**) resulted in equilibrium mixtures of regular and backbone rearranged skeletons in which the latter predominated (Tables 3 to 6). Preponderance of backbone rearranged products is due to the absence of 1,3-diaxial interaction between the C_4 and C_{10} methyls in these products. Furthermore it can be seen that 1,3-diaxial interaction in the backbone rearranged skeletons between the C-13α group and the α (axial) protons at C-8 and C-11 will be greater when the axial α group at C-13 is Me rather than vinyl. Similarly, the loss of steric interaction between the C-13β group and the C-11β-proton is greater for rearrangement in the isopimarane series (**14–16**). These effects indicate that loss of steric interaction on formation of **18** is greater than on formation of **17** in agreement with the observed product ratios.



14–16 **18**

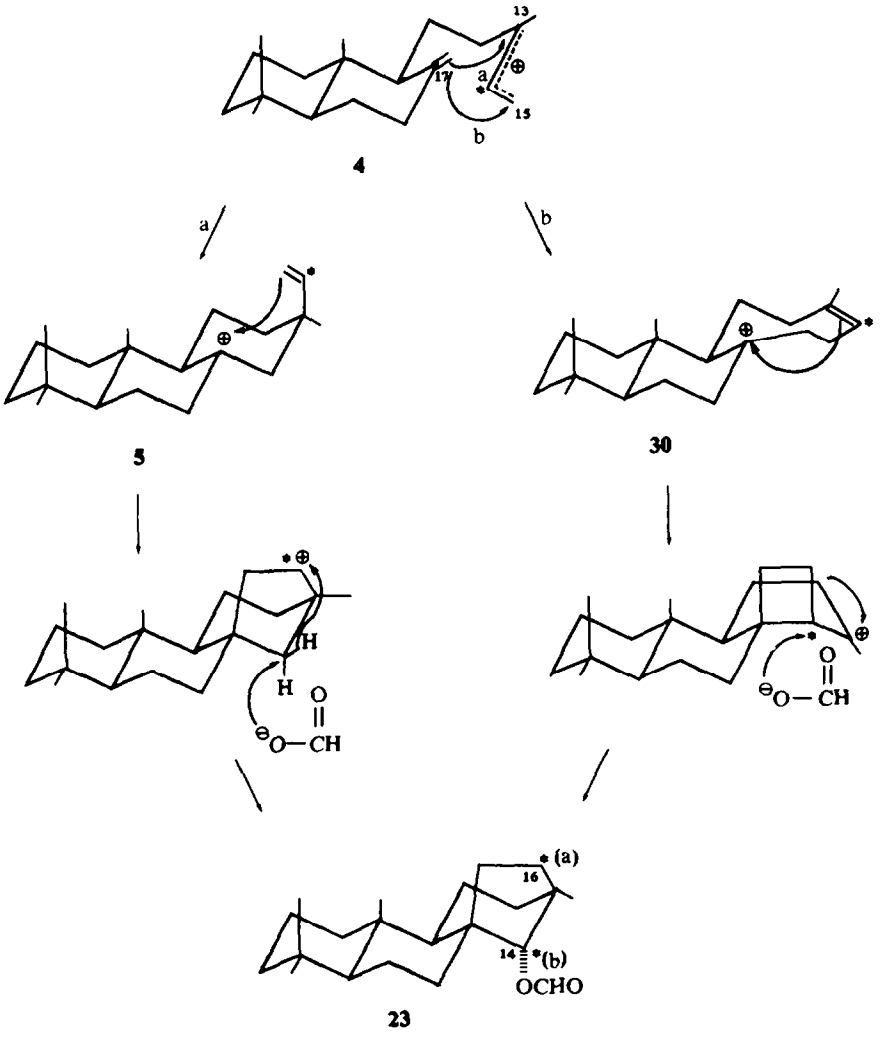
11–13 **17**

Tables 3 to 6 reveal that the compound assigned the 5(10),12-abietarosadiene (**21**) structure was formed much faster from 5(10),15-rosadiene (**17**) than from the pimaradienes (**11–13**), or 13-*epi*-5(10),15-rosadiene (**18**) and it is in this latter compound that the migrating C-13 Me group is in the least stable configuration. These observations suggest that in the formation of **21** initial backbone rearrangement is followed by C-13 → C-15 Me migration and deprotonation.[17] This is in agreement with the expectation that backbone rearrangement would precede faster than Me shift since protonation to give a tertiary carbonium ion is usually faster than protonation

to give a secondary carbonium ion, the requisite intermediates for the two transformations.

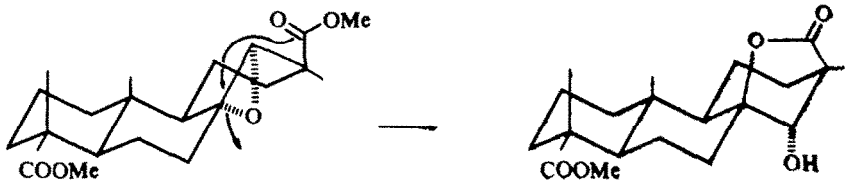
Since the cyclization of **4** between C-17 and C-13 (path **a**) leads easily to cation **5** which is the precursor of the pimaradienes (**11–13**) further ring closure between C-15 and C-17 followed by a hydride shift and neutralization might be expected to be the route by which tetracarbocyclic product **23** is formed (Scheme 5). This is the pathway by which the tetracyclic and pentacyclic diterpenoids have long been considered to be synthesized *in vivo*.[30] The observation that deuterium at C-14 of the bicyclic precursor **4** is located at C-14 in **23** not only rules out this attractive route but confirms

SCHEME 5



path **b** as the route by which **4** is transformed to **23**. Parallel labelling experiments by Edwards[16] and Wenkert[20] have also demonstrated the manool→**23** conversion is *via* path **b**. Consistent with these demonstrations was the isolation of the compound formulated as 8,13-burnabadiene (**19**) which was quantitatively converted to **23** in HCOOH.

It is intriguing that the tetracyclic hibane skeleton is formed from the bicyclic labdane skeleton by a route (path **a**) *in vivo*[7,31] which is quite different from the pathway (path **b**) to the same skeleton followed in *vitro*. While the absence of detectable amounts of tetracyclic products formed by closure between C-15 and C-8 of pimaradiene products in the laboratory reaction is surprising this mode of closure would not be expected to be a predominant fate of **5** or **6** since the vinyl groups in these ions would be expected to have preferred orientations away from the Δ^8 linkages. These ring closures could thus easily be envisioned to be sufficiently slow to allow other processes such as backbone and pimaradiene → abietadiene rearrangements to occur. Recent report[33] of ring closure of α-epoxide **32** to hydroxy-γ-lactone **33** supports this view.



32 **33**

In **32** the bulk of the —OMe group results in the preferential orientation of the carbonyl group over the developing carbonium site facilitating cyclization. Since production the tetracarbocyclic diterpenes occurs in Nature *via* path **a** and we and others[17] were unable to detect cyclization of **5** and **6** to these skeletons significant enzymatic control must be exerted in the *in vivo* conversion of the bicyclic precursor (**3a**) to tetracarbocyclic derivatives. Two limiting mechanisms can be envisioned for the conversion of **3a** to tetracarbocycles; one involving conversion to **5** and **6** (which are stabilized) and thence to tetracycles or direct conversion of **3** to **4** which is directly cyclized to tetracarbocyclic products. Stabilization of **5** or **6** would be expected to yield the 8,15-pimaradienes isomeric about C-8 and C-13. It is significant that attempts to gain evidence to indicate the obligatory intermediacy of these dienes in the conversion of **3a** to tetracarbocyclic derivatives have failed. Thus, specifically labelled *enantio*-8,14(15)-pimaradiene was not incorporated into gibberellic acid by *G. fujikuroi* to a significant extent.[32] The amounts and patterns of labelling observed in metabolites after feeding 4(R)-[4-^{3}H, 2-^{14}C] mevalonate and [2^3H_2, 2-^{14}C]-mevalonate to this organism also rule out *enantio*-8,15-pimaradiene and *enantio*-7,15-pimaradiene as precursors of (−)-kaurene and gibberellic acid.[32c] Fractionated enzyme preparations which convert *enantio*-**3a** to hibaene, kaurene and trachylobane do not produce tricyclic dienes.[7c] These observations coupled with the rarity of 8-hydroxy-15-pimarenes in Nature suggest the biogenesis of the tetracarbocyclic diterpenes proceeds directly from **4**.

EXPERIMENTAL

IR spectra were recorded on a Perkin–Elmer 457 Spectrophotometer. NMR spectra were obtained on a Varian A 56/60 Spectrophotometer in $CDCl_3$ with TMS as internal standard. UV spectra were obtained on a Cary 14 Recording Spectrophotometer in abs. EtOH. Optical rotations were determined on a Perkin–Elmer P22 Spectropolarimeter in hexane. Mass spectra were obtained on a Hitachi Perkin–Elmer RMU-6E Mass Spectrometer using an inlet temperature of 80° and an ionization voltage of 80 eV. VPC analysis was performed on a Varian Series 1200 Gas Chromatograph equipped with flame ionization detector while preparative separations were performed on a Varian Autoprep 700 equipped with cathrometer detector. Column A was a 150 ft × 0·02 in. wall coated DEGS; Col. B a 150 ft × 0·02 in. wall coated Ucon oil LB-550-X; Col. C a 20 ft × ⅜ in., 30% DEGS on HMDS treated Chrom. W; Col. D a 5 ft × ¼ in., 20% DEGS on HMDS treated Chrom. W; Col. E a 6 ft × ½ in., 20% XF 1150 on HMDS treated Chrom. W; Col. F a 5 ft × ⅛ in., 5% DEGS on HMDS treated Chrom W; and Col. G a 6 ft × ⅛ in., 20% DEGS on HMDS treated Chrom. W.

Purification of manool (7). Manool (20 g) (Koch-Light) was purified by chromatography on silica gel impregnated with 10% $AgNO_3$ (500 g). Unidentified impurities were eluted by petroleum ether through 60% benzene in petroleum ether and pure manool (13·5 g) was eluted by benzene.

Reaction of manool with acetic acid. Manool (12·5 g) in glacial AcOH (125 ml) was heated under reflux for 1 hr. The mixture was poured into water (400 ml), neutralized with $NaHCO_3$ and extracted with ether. The ether extractes were combined, washed with water, dried ($MgSO_4$) and evaporated to give a brown oil (11·3 g) which was chromatographed on Act. I neutral alumina (300 g): petroleum ether eluted a mixture of hydrocarbons (3·50 g); 10% benzene in petroleum ether eluted Δ^{13}-manool acetate (**3c**; 3·23 g)[3,4] 60% benzene in petroleum ether eluted unreacted manool (2·76 g).

The mixture of hydrocarbons was chromatographed on silica gel impregnated with 10% $AgNO_3$ (200 g): 10% benzene in petroleum ether eluted 8,13-burnabadiene (**19**; 109 mg $[\alpha]_D$ +17° (c = 0·84); for spectral data see text) and mixture A (840 mg); 15% benzene through 20% benzene in petroleum ether eluted mixture B (1·263 g); benzene eluted *cis*-biformene (**9**; 532 mg), $[\alpha]_D$ +42·5° (c = 0·61); 3% $CHCl_3$ through 20% $CHCl_3$ in benzene eluted *trans*-biformene (**8**; 517 mg) $[\alpha]_D$ +34° (c = 0·90).[19,34,35] Repetition using larger amounts of materials; 40% benzene in petroleum ether eluted 7,15-pimaradiene (**13**; 255 mg) $[\alpha]_D$ −22·8° (c = 0·86). (spectral data see text).

Mixture A was re-chromatographed on silica gel impregnated with 10% $AgNO_3$ (25 g): petroleum ether eluted 8,13-burnabadiene (**19**; 70 mg) and 8,15-pimaradiene, (**11**; 500 mg) $[\alpha]_D$ +57·9° (c = 0·59). The latter was identical on columns A and B (150°) with an authentic sample supplied by Dr. O. E. Edwards.[16] In a repeat, 4% benzene in petroleum ether eluted mixture C (630 mg) which was separated by prep. VPC on column C at 183° into 8,15-pimaradiene (**11**; 188 mg) and mixture D (106 mg). Mixture D was purified by prep. VPC on column D at 150° to give isopimaradiene (**16**; 50 mg). The latter was identical with a sample supplied by Dr. L. Westfelt on Columns A and B (150°).

Mixture B was separated by prep. VPC on column E at 130° to give 8,15-isopimaradiene (**14**; 125 mg); $[\alpha]_D$ +107·7° (c = 0·80); m.p. 50–51° (lit.[16] m.p. 51–52·5°), identical on columns A and B with an authentic sample supplied by Dr. Edwards,[16] and sclarene; $[\alpha]_D$ +33·5° (c = 0·37).

Diels–Alder adduct of sclarene with tetracyanoethylene. A soln of sclarene (**10**); (100 mg; 0·37 moles) and TCNE (47 mg; 0·37 mmoles) in EtOAc (10 ml) was refluxed for 24 hr. The soln was evaporated and the solid recrystallised from EtOH–H_2O to give white needles (80 mg) m.p. 138–139° (lit.[35] m.p. 115°).

Reaction of manool with formic acid. Manool (14 g) in 97% HCOOH (140 ml) was refluxed for 1 hr, poured into water (450 ml), neutralised with K_2CO_3 and ether extracted. The extracts were combined, washed with water, dried ($MgSO_4$) and evaporated to give a brown oil (11·7 g) 10·7 g of which was chromatographed on silica gel (500 g). Pet. ether eluted a mixture of hydrocarbons (7·26 g); $CHCl_3$ eluted mixture A (2·287 g) ν_{max} 1730s, 1170s cm^{-1}; no O–H.

The mixture of hydrocarbons was chromatographed on silica gel impregnated with 10% $AgNO_3$ (350 g); pet ether through 10% benzene in pet. ether eluted unidentified mixtures (799 mg); 10% benzene in pet. ether eluted mixture B (1·316 g); 10% benzene in pet. ether through 40% benzene in petroleum ether eluted a mixture of 8,15-pimaradiene (**11**) and 8,15-isopimaradiene (**14**; 1:1, 4·623 g); $CHCl_3$ eluted 7,15-pimaradiene (**13**; 100 mg).

A soln of mixture A in dry ether (100 ml) was added dropwise with stirring to LAH (0·5 g) in dry ether (200 ml) during 30 min. and the mixture refluxed for 30 min. Excess reagent was destroyed with water, the soln filtered, dried ($MgSO_4$) and evaporated to give a yellow oil (1·79 g) ν_{max} 3450 cm^{-1}, no C=O, which

was chromatographed on silica gel (50 g): 20% benzene in petroleum ether eluted hiban-14α-ol (400 mg) m.p. 110·5–1 12" (lit.[16] m.p. 114–115°).

Mixture B was separated by prep. VPC on column C at 186" to give 13-*epi*-5(10),15-rosadiene (18; 211 mg) $[\alpha]_D - 68·7°$ (c = 0.62).

In addition 8,13-burnabadiene (19; 112 mg), rimuene (22;[21,26] 25 mg) and 8-*epi*-5(10),15-rosadiene (20; 35 mg) $[\alpha]_D - 112°$ (c = 0·76) (P)' = 272, were isolated.

Hiban-14α-yl acetate. Hiban-14α-ol (100 mg) was dissolved in pyridine (3 drops), Ac_2O (5 drops) added and maintained at 100" for 28 hr Standing over P_2O_5 and NaOH in a vacuum dessicator for 20 hr. gave hiban-14α-yl acetate crystals (100 mg) m.p. 84-85" (lit.[16] m.p. 85-86").

Hiban-14α-yl formate from hiban-14α-ol. Hiban-14α-ol (100 mg) was dissolved in HCl (4 mg of 38% soln.) and HCOOH (270 mg of 97% soln). The mixture was placed in a sealed tube at 90° for 18 hr then added to water and ether extracted. The extracts were combined, washed with NaHCO,aq and water, dried (MgSO,) and evaporated to give a colourless oil which showed one spot on TLC and a single peak on VPC column F at 190° ν_{max} 1730 s, 1175 s cm^{-1}; NMR (r): 1·80 (s, formyl H), 5.55 (s, 1H, H-C--O--), 9·07, 9·13, 9.17, 9·20 (4 singlets, 4Me). (P)' 318.

Hiban-14α-yl formate from 8,13-burnabadiene. 8,13-Burnabadiene (19; 50 mg) was refluxed with HCOOH (1 ml) for 1 hr. The mixture was neutralized with 10% Na_2CO_3 aq and ether extracted. The extracts were combined, water washed, dried ($MgSO_4$) and evaporated to give hiban-14α-yl formate (23; 50 mg)—m.p. and NMR identical with those of the sample prepared above.

Hydrogenation *of 8,13-burnabadiene.* A soln of 8,13-burnabadiene (48 mg) in EtOAc (3 ml) was shaken with Pt/C (30 mg) under 70 p.s.i.g. H_2 for 4 days. The catalyst was removed by centrifugation and the supematant evaporated to give 8-burnabene (32; 46 mg) as white solid $[\alpha]_D + 6°$ (c = 0·5), m.p. 60–62°. This product gave a positive tetranitromethane test and a mass spectrum which possessed no peak at m/e = 272. NMR (τ) 9.27, 9·20, 9·15 (s, 3Me). 9.26 (d, J = 6 Hz, Me). (P)' = 274.

Formic acid *treatment of* 8,15-*pimaradiene.* A soln of 8,15-pimaradiene (880 mg) in 97% HCOOH (10 ml) was refluxed for 6 hr. The mixture was poured into water (100 ml), neutralized with Na_2CO_3 and etha extracted. The extracts were combined, water washed, dried (MgSO,) and evaporated to give brown oil (806 mg), which 680 mg was chromatographed on silica gel impregnated with 10% $AgNO_3$ (40 g): 3% benzene in pet. ether eluted 5(10),12-abietarosadiene (21; 27 mg), $[\alpha]_D - 126°$ (c = 0·38); $(P)^+$ 272, and 8-*epi*-5(10),15-rosadiene (20; 7 mg). Elution with 5% benzene in pet. ether gave a mixture (108 mg) purified by prep. VPC on column D at 150" to give 5(10),15-rosadiene (17; 34 mg) (P)' 272.[22]

Preparation of *sandaracopimaradiene from methyl sandaracopimarate.* Sandaracopimaric acid, supplied by Professor J. W. ApSimon, (130 mg) was converted to methyl sandaracopimarate (103 mg) m.p. 63-64 (lit.[37] m.p. 64–65·5°) with ethereal CH_2N_2 and thence to sandaracopimaradiene"' which possessed spectral characteristics reported for this compound.[16,24] Dr. Edwards kindly supplied a tracing of the vinyl pattern of an authentic sample of sandaracopimaradiene for comparison.

Preparation of pimaradiene from pimaric acid. Pimaric acid (Koch Light) was converted to pimaradiene[16] by the same sequence described for the preparation of sandaracopimarad'ene.

Preparation of deutero Δ^{13}-*manool* (3D) enantio-copoldehyde (25). CrO_3 (3.9 g; 3·9 x 10^{-2} moles) was added with stirring to ice-cold anhyd. pyridine (100 ml) during 10 min. A soln of Δ^{13}-manool[17] (3.868 g) in anhyd. pyridine (20 ml) was added in one portion whereupon the mixture darkened. Stirring at 0° was continued for ½ hour and at r.t. for 15 hr. The mixture was poured into water (11) and ether extracted. The extracts were combined and evaporated to a few ml The residue was dissolved in ether, washed with 2% $NaHSO_4$ aq, water, 2% K_2CO_3 aq, again with water, then dried (MgSO,) and evaporated to give a mixture of *cis* and *trans* enantiocopaldehyde (25; 2995 g) ν_{max} 1678 cm^{-1}. NMR (τ): 0.13 (t, J = 8 Hz, 1H, is actually two superimposed doublets at 007 and 0·222, aldehyde proton, *cis–trans* mixture), 4·20 (d, J = 8 Hz, 1H, C-14 vinyl), 5·18 (s, 1H, C-17 vinyl). 5.55 (s, 1H, C-17 vinyl), 7.87 (d, J = 1 Hz, 1·5 H approx, vinyl Me, *trans*-isomer), 8·05 (d, J = 1 Hz, 1·5 H approx, vinyl Me, cis-isomer), 9·14, 9.21, 9·32, (3s, 3Me).

Enantio-methyl *copalate* (26). A soln of *enantio*-copaldehyde (25) (446 g) NaCN (4.13 g), AcOH (1.52 g) and freshly prepared[38] MnO_2 in MeOH (90 ml) was stirred at r.t. for 12 hr. MnO_2 was removal by centrifugation and the soln evaporated to give an amber solid which was dissolved in water and ether. The aqueous layer was extracted several times with ether and the ether extracts combined, washed with 10% Na_2CO_3 aq and water, dried (MgSO,) and evaporated to give a mixture of *cis* and *trans enantio*-methyl copalate (26) previously described[39] (3.868 g) ν_{max} 1720 cm^{-1}.

Deuterium exchange of enantio-methyl *copalate.* A solution of *enantio*-methyl copalate (2.533 g) and NaOMe (3.7 g) in MeOD (250 ml) was stirred at r.t. for 2½ hr, then evaporated to dryness at 40". The residue

was dissolved in D_2O and dry ether, the D_2O layer was dry ether extracted. the extracts combined. washed with D_2O, dried ($MgSO_4$) and evaporated to give partially deuterated *enantio*-methyl copalate (**26D**; 1·48 g). Integration of C-14 vinyl hydrogen *vs.* ester OMe and C-17 hydrogens indicated 50% deuteration at C-14. Appreciable deuterium exchange also occurred at the vinyl Me.

Deuterated Δ^{13}-manool (**3D**). A soln of deuterated *enantio*-methyl copalate (**26D**; 1·48 g) in dry ether (54 ml) was added dropwise with stirring to LAH (0·4 g) in dry ether (100 ml) and refluxed overnight. Excess reagent was destroyed with water, the soln filtered, dried ($MgSO_4$) and evaporated to give deuterated Δ^{13}-manool. The NMR spectrum again indicated 50% deuteration at C-14 and the singlet at τ 8·37 corresponding to vinyl Me was buried in the background. The doublet (J = 7 Hz) centred at τ 5·95 corresponding to the two C-15 protons had collapsed to a singlet. In the mass spectrum the isotopic distribution around the parent peak was the same as that for the deuterated *enantio*-methyl copalate (**26D**).

Formic acid treatment of deuterated Δ^{13}-manool. A soln of deuterated Δ^{13}-manool (1·3 g) in HCOOH (13 ml) was refluxed for 1 hr, poured into water (50 ml) neutralized with K_2CO_3 and ether extracted. The extracts were combined, water washed, dried ($MgSO_4$) and evaporated to give a yellow oil (1·23 g) which was chromatographed on silica gel (70 g): petroleum ether eluted a mixture of hydrocarbons (542 mg); 10% benzene in petroleum ether eluted a mixture of hiban-14α-yl formate and unidentified impurity A (254 mg); A (76 mg) was also eluted by this solvent. The above mixture was re-chromatographed on silica gel (12·5 g) to give hiban-14α-yl formate contaminated with A and VPC on column F at 170° showed that the tetracyclic ester was 72% pure. Mass spectral analysis showed that the isotopic distribution around the parent peak was the same as that in **3D** (d_0 22%, d_1 6%, d_2 26%, d_3 17%, d_4 16%, d_5 10%, d_6 2%, $d_7 < 1\%$).

Integration of the NMR spectrum of this hiban-14-α-yl formate showed that the peak due to the 14β hydrogen was 50% of that due to the formate hydrogen. The NMR spectrum of impurity A possessed no absorption in these two regions.

Studies of acid catalysed reactions of hydrocarbons. To a known weight (10–70 mg) of pure hydrocarbon was added a known weight of octadecane, a sample of the mixture passed through VPC column A or B and the area of the peak for each component measured. To this mixture was added the appropriate acid (2 ml) and the mixture heated under reflux for the appropriate length of time. The solution was poured into water (20 ml), neutralized with Na_2CO_3 and ether extracted. The extracts were water washed, dried ($MgSO_4$) and evaporated. The components of the residue were identified by peak enhancement from mixed injection on columns A and B at 150°.

Acknowledgements—We wish to thank the National Research Council of Canada for financial support of this work through an operating grant (A.C.O.) and Postgraduate Fellowship (S.F.H.). We also wish to thank Dr. J. W. ApSimon for a sample of sandaracopimaric acid; Dr. O. E. Edwards for samples of 8,15-pimaradiene, 8,15-isopimaradiene and for the n.m.r. spectra of pimaradiene and sandaracopimaradiene and Dr. L. Westfelt for a sample of isopimaradiene.

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