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STUDIES IN 85% H_3PO_4—II

ON THE ROLE OF THE α-TERPINYL CATION IN CYCLIC MONOTERPENE GENESIS

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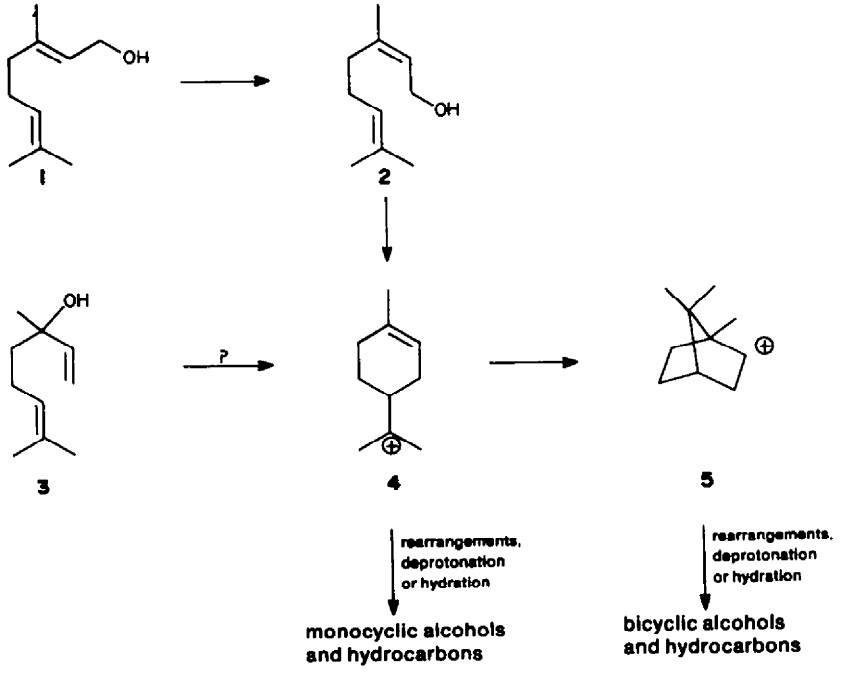
Abstract—The fate of the α-terpinyl cation (4) in 85% phosphoric acid has been examined. In this medium, no products formed by nucleophilic attack by the solvent on the intermediate carbocations were observed. In contrast to all other studies, geraniol (1), nerol (2), linalool (3), and their acetate and phosphate esters all produced cyclized material as the major products; these included limonene (17), isoterpinolene (18), α-terpinene (19), γ-terpinene (20), 3-p-menthene (26), and p-cymene (27), but no terpinolene (16), and no identifiable bicyclic material. Evidence is presented that 17 does not arise from 4, which apparently is not the sole cationic intermediate formed during the cyclization process.

The biogenesis of the cyclic monoterpenes was first brought to conceptual order by Ruzicka's suggestion[1] that they all arise from cyclization of a single, acyclic monoterpene, nerol (2), as outlined in Scheme 1.† Nerol, as the *Z* isomer of geraniol (1), is presumably derived from the latter, and was suggested to be the cyclizing species because it possesses the requisite *Z* double bond geometry. Linalool (3) was suggested as an alternative species which could undergo this type of cationic cyclization.

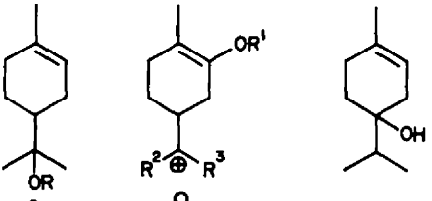
A number of subsequent investigations[2-14] have focused on the examination of possible non-enzymic transformations of this type. The results, obtained using diverse systems and conditions, generally have shown that the neryl systems give monocyclic products in good yield and more rapidly than the geranyl systems, which mostly afford acyclic products. While this is in line with expectations based on Ruzicka's biogenetic scheme, the postulated subsequent cyclization of 4 to the bicyclic level has not been confirmed;[11-13] no bicyclic material has been reported from the cyclization of 1, 2, or 3. Cationic cyclization attempts starting with monocyclic α-terpineol derivatives (6) also apparently never have afforded bicyclic material. It has been shown, however, that enhancement of the nucleophilicity of the double

†It now seems likely that biologically the reacting species are not the alcohols themselves, but rather their pyrophosphate esters.



Scheme 1.

bond in an α-terpinyl system by substitution of an alkoxy or acetoxy group on the double bond (7) is sufficient to allow acid-promoted conversion in good yield to bicyclic material at the oxidation level of camphor.[15-16] While these experiments have led to the interesting suggestion that such enol ethers or acetates could be the real biogenetic precursors to the bicyclic monoterpenes,[16] they also serve to refocus attention on the possibility that the α-terpinyl cation 4 plays a central role in monocyclic and bicyclic monoterpene biogenesis.



6 7a: R' = CCH3 b: R' = CH3 8

Significantly, the chemical studies concerning the formation and fate of the cation 4, the hypothetical biological intermediate, all have involved either media of relatively low polarity (e.g. diethyl ether) or the presence of a good nucleophile (e.g. water), conditions which are not particularly conducive to the formation and further intramolecular reaction of carbocations. This presumably was due to the fact that most highly ionizing, nonnucleophilic media also are very acidic, which would give rise to undesired reaction resulting from double bond protonation. The observation[17] that 85% phosphoric acid provides a medium which promotes double bond protonation only slowly compared to ionization of allylic systems suggested that it would be a more appropriate medium for study of the formation and fate of 4.

RESULTS

An initial, qualitative survey of the behavior of 1, 2, 3 and their acetates, and the phosphate esters of 1 and 2, in 85% phosphoric acid revealed the striking observation that all eight of these acyclic monoterpenes provided high proportions of cyclic material. Except for the phosphates and 3, considerable amounts of C-20 compounds and some oligomeric material also were formed; added co-solvents failed to reduce the amounts of these substances. Finally, 1 and its acetate (but not the phosphate) produced some (*ca* 13% of the C-10 material) cyclogeranyl (13) product.

Because the three geranyl systems gave rise to C-10 hydrocarbon mixtures which were virtually identical, as did the three neryl systems, and because of the similar behavior of 3 and geranyl phosphate, the reaction mixtures obtained from treatment of 1, 2 and 3 were selected for careful examination. Parallel sets of experiments, one set using only 85% phosphoric acid and the other using 85% phosphoric acid plus pentane, were carried out. In both cases, the reaction mixtures were heterogeneous. While the results were qualitatively the same, some differences in relative ratios of products were observed, apparently owing to the action of phosphoric acid on the products (e.g. 17; see Table 1). We have focused on the data, summarized in Table 1, which were obtained with pentane present, since they

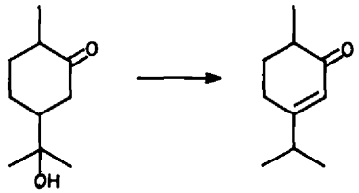
Table 1. Quantitative survey: relative percentages of C-10 hydrocarbons[a,b]

	α-terpinene (19)	γ-terpinene (20)	isoterpinolene (18)	limonene (17)	p-cymene (27)	3-p-menthene (26)	unidentified
Geraniol (1)	19	10	12	11	11	9	28
Nerol (2)	37	11	18	11	8	6	9
Linalool (3)	28	13	18	11	11	9	10
α-Terpineol (6)	43	14	18	0	13	10	2
4-Terpineol (8)	41	15	15	0	10	13	6
Limonene (17)	7	2	3	84	3	1	0

[a] Each mixture analyzed by GC using OV-17 columns.
[b] Reaction carried out at room temperature for 15 minutes using 85% phosphoric acid plus pentane. Qualitatively similar product distributions resulted when pentane was omitted.

reflect more closely the initial product composition. The conclusions drawn from the results, however, are not altered by consideration of the data obtained without pentane present. The products were identified by preparative GC purification and subsequent comparison of their IR and NMR spectra with those reported in the literature, as well as by direct comparison of their GC retention times and mass spectra with authentic samples. The technique described by Thomas[18] for analysis of mass spectra was particularly helpful; the relative abundance *ratios* of the *m/e* 136 (molecular ion) and 93 ion to the total ion current are exceptionally characteristic numbers which permit the differentiation of most acyclic, monocyclic, and bicyclic monoterpene hydrocarbons. The products which were not identified were comprised primarily of mixtures of acyclic compounds (based on NMR) in the geranyl cases, and primarily of reduced material (molecular weight 138) in other cases.

To focus on the possible monocyclic carbocation intermediates, the tertiary alcohols α-terpineol (6, R = H) and 4-terpineol (8) were treated separately with 85% phosphoric acid. Interestingly, neither reaction mixture (see Table 1) contained any limonene (17). Similarly, treatment of the hydroxy ketone 9 resulted in quantitative conversion of 9 into the α,β-unsaturated ketone 10.



9 10

Control experiments indicated (1) that 19 and 20 are unaffected by the reaction conditions, while 17 is transformed only slowly into other monocyclic terpenes (see Table 1), and (2) that all compounds are stable to the GC conditions employed.

DISCUSSION

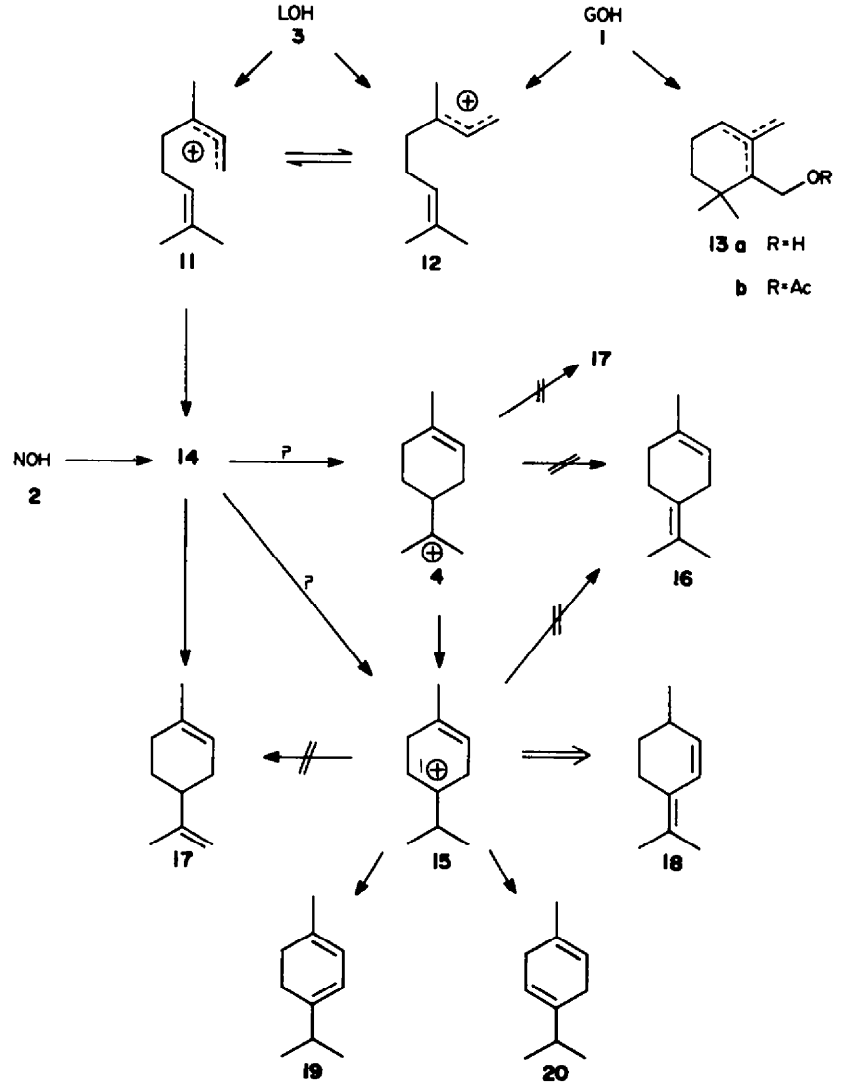
This study was undertaken to investigate possible laboratory parallels to proposed enzymic transfor-

Table 2. Characteristic mass spectral data for selected monoterpene hydrocarbons[a]

Compound	m/e 136/Σ ions	m/e 93/Σ ions	other ions[b]
α-terpinene (19)	9.6	19.6	121(100)
γ-terpinene (20)	7.4	27.7	———
isoterpinolene (18)	8.8	16.6	121(100)
limonene (17)	5.3	12.8	68(100)
3-p-menthene (26)	—	—	138(27), 95(100)
p-cymene (27)	—	—	134(28), 119(100)
terpinolene (16)	13.7	16.9	121(100)

[a]Data obtained at 70 eV.
[b]Ions (*m/e*) which are particularly characteristic. Relative abundances are given in parentheses.

mations, assumed to occur owing to an environment in which nucleophilic attack and deprotonation of the intermediate carbocations are precluded until intramolecular processes are complete. The key postulate of this work was that 85% phosphoric acid would provide an appropriate environment to mimic these enzymic properties. This appears to be the case: carbocation formation is apparently rapid and initiates all observed transformations; intramolecular cyclization is the major fate of all acyclic cations (e.g. 11 and 12) formed, *even for the geranyl systems*, in contrast to all previously reported investigations; and no C-10 product is observed which results from nucleophilic attack on a cation. Of course, nucleophilic attack by the medium on



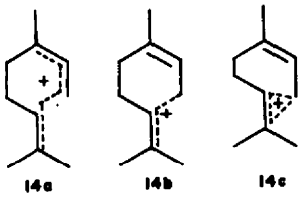
Scheme 2.

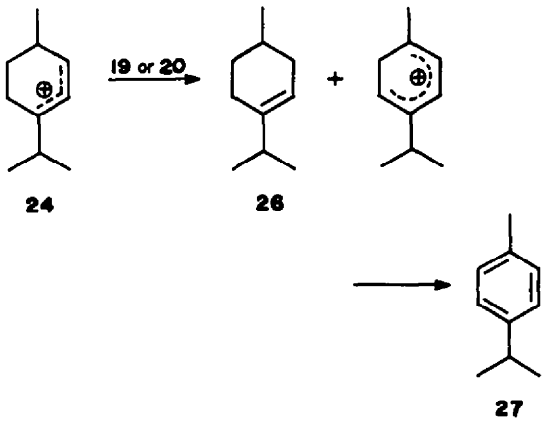
intermediate cations, to form alcohols or phosphates which rapidly re-ionize, is possible. Examination of reaction mixtures at shorter times provided no evidence for the formation of alcohols or phosphate esters; thus, if such compounds are intermediates, their concentration does not build up to a level which permits detection by our methods of analysis. Double bond protonation, an undesirable side reaction, is observed only when 1 or its acetate (but not the phosphate) is the starting material, and this mode of reaction is never a major pathway. Importantly, the products of the transformations all are relatively stable to the acidity of the medium. It therefore appears that 85% phosphoric acid is an appropriate choice for investigation of the intramolecular processes open to the monocyclic cation 4.

A second, most interesting observation regarding the results, summarized in Scheme 2, is the formation of limonene (17) in *ca* 10% yield from all three acyclic alcohols, while α-terpineol (6, R = H) gives rise to no 17 under the same conditions. Apparently, cation 4 is not a precursor to 17. In keeping with this observation, Scheme 2 depicts some other intermediate 14 as the species directly formed from protonated 2 and from 11 (both of which could also give rise to 4 directly). These results do not provide sufficient evidence to permit assignment of a structure to cation 14,† but do suggest further consideration be given to previous cyclization studies, and perhaps to the classical biogenesis scheme as well.

Other groups have devoted considerable effort in attempts to convert 4, generated from acyclic or monocyclic precursors, into bicyclic material; no such transformation could be confirmed.[12] The same conclusion must be drawn from the present experiments. This result is particularly significant because, for the first time, experimental conditions were employed in which *neither* deprotonation of 4 nor nucleophilic attack on 4 accounts for measurable amounts of products (16 or 17 and 6, respectively), although the latter process may occur if the products rapidly re-ionize and react further. In verification, neither α-terpineol (6, R = H) nor 4-terpineol (8) gives rise to 17 (Table 1). The rapid transformation of 4 into 15 (Scheme 2) is in keeping with observed (*vide supra*) quantitative conversion of 9 into 10, which may proceed by way of a similar 1,2-hydride shift (although a dehydration-enolization pathway also would be reasonable). It therefore appears that, thermodynamic considerations[19] notwithstanding, transformation of 4 into 15 is much more rapid than the cyclization of 4 to afford bicyclic material.

†It is noteworthy that other workers, employing very different reaction media, also have suggested the possible involvement of non-classical cationic intermediates, such as 14a,[9] 14b,[5,8] and 14c.[5] Of course, direct comparisons with the present work are precluded by the significant differences in the reaction media, in which the structures *and fates* of intervening cationic intermediates may well be different.





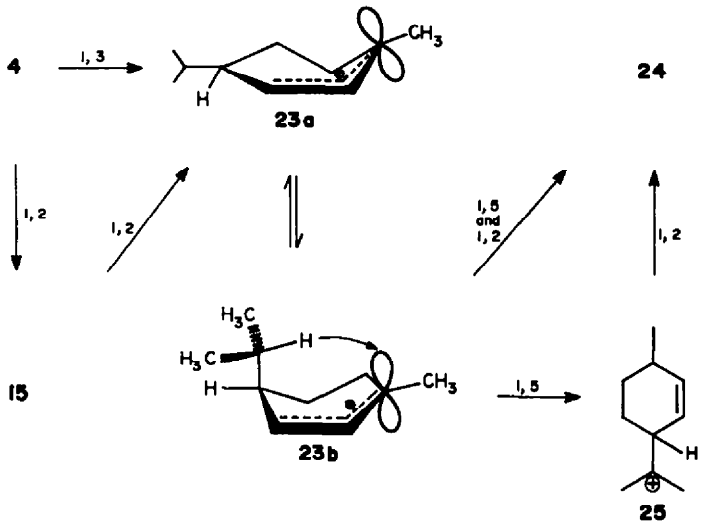
Scheme 3.

The relatively slow rate of deprotonation of carbocations in this medium permits the formation of products resulting from extensive intramolecular rearrangements. Two such products, which account for 20–30% of the starting acyclic or monocyclic alcohols, are isoterpinolene (18) and 3-*p*-menthene (26), shown in Scheme 3. These two products apparently arise from cation 24, the formation of which can be rationalized as depicted in Scheme 4. Inspection of Dreiding models indicates that the migrating hydrogen in 23b can approach the allylic π-system without its severe distortion from planarity, thus permitting the 1,5-hydride migration indicated. This hydride shift could be accompanied by a 1,2 shift of the geometrically well disposed C-4 hydrogen to give the allylic cation 24 directly; alternatively, these events could be consecutive, with ion 25 then being an intermediate. It should be noted that, in the absence of additional evidence, a series of intermolecular hydride transfers to form 24 can not be excluded. Cation 24 then either undergoes deprotonation, forming 18, or intermolecular hydride abstraction. The latter event, a possible example of which is shown in Scheme 3, gives rise to *p*-cymene (27) along with 26.

The initial ionization leading to the described reactions also is of some interest, although details of such ionizations often are obscure. In the present study, it is interesting to note that ionization apparently precedes product composition determination, since the latter is not sensitive to which leaving group is used (in contrast to some other systems).[8] The rate of ionization of 1 or its acetate (but not the phosphate) is slow enough that direct protonation of the isopropylidene double bond is a competitive process (*ca* 13% of 13 is formed). Since double bond protonation of 2 or its acetate cannot compete with ionization, some rate acceleration of the ionization is apparently operating, presumably owing to π-participation of the type described by other groups.[4,8]

Conclusions

The above results show 85% phosphoric acid to be a medium particularly well suited for the examination of carbocationic processes initiated by ionization. In contrast to other such media,[13] the acidity is such that direct double bond protonation is relatively slow. The fate of cations generated under these conditions from 1, 2, 3, and 6 (R = H), indicate that (1) 4 does not give rise to 17, (2) even when formed in an environment where *products* resulting from deprotonation and nucleophilic attack are not observed, 4 suffers rearrangement at the monocyclic



Scheme 4.

level rather than conversion to bicyclic material, and (3) some cation other than 4 is formed from protonated 2 and the acyclic ion 11.

Acknowledgement—We thank Firmenich, SA, for generously providing comparison samples of monoterpene alcohols and hydrocarbons.

EXPERIMENTAL

For GC separations, columns utilized High Performance Chromasorb G as the support unless otherwise noted; temp programming was from 50 to 200° at 10°/min unless otherwise noted; a variety of conditions was used: A, 1/8 in × 6 ft 4% OV-101 column at 80°; B, the same column as A, with temp programming; C, 1/8 in × 6 ft 4% OV-17 column at 100°; D, the same column as C, with temp programming from 100 to 200° at 4°/min; E = 1/8 in × 6 ft 5% carbowax 20M column with temp programming; F = 1/4 in × 6 ft 4% DC-550, at 70°; G = 1/8 in × 6 ft 7% Ucon polar on Chromasorb W column with temp programming; GC-mass spectral (GC-MS) analysis utilized a 1/8 in × 4 ft 3% SE-30 on Varapack No. 30 column interfaced to a DuPont 491 mass spectrometer. For TLC analysis, plates made using Merck $HF_{254/366}$ silica gel were used; compounds were visualized with I_2. NMR spectra were obtained using a Varian A-60, with TMS as an internal standard. Spinning band distillation was carried out using a Nester-Faust NFT-50 teflon band still. Elemental analyses were performed by Galbraith Laboratories. Geraniol (1, *ca* 95%) was obtained from a commercial (MCB) mixture using the $CaCl_2$ method;[20] nerol (2, *ca* 97%) was used as obtained from Fluka; linalool (3, *ca* 99%) was used as obtained from Aldrich. Purity was ascertained by GC method B: retention time (min): 3, 14.5; 2, 17; 1, 18. The 85% H_3PO_4 used was Mallinckrodt AR grade.

Treatment of geraniol (1), *nerol* (2), *linalool* (3), *α-terpineol* (6), *and 4-terpineol* (8) *with* 85% H_3PO_4. To a 25 ml round bottom flask containing 9 ml of 85% H_3PO_4, 1 ml pentane, and a 3/4 in teflon-coated stir bar was added with maximum possible stirring under N_2 *ca* 150 mg (0.98 mmol) of monoterpene alcohol. The mixture was stirred for 15 min, was poured into 90 ml of H_2O, and the products were extracted (2 × 20 ml of pentane).

The combined organic portions were washed (1 × 30 ml of sat $NaHCO_3$ aq 1 × 30 ml of sat NaCl aq), dried ($MgSO_4$) and concentrated to a volume of 0.5 ml. The samples were stored under N_2 in a freezer until they could be analyzed by GC (Methods A and C). The results are summarized in Table 1. GC retention times (min) for the products are: (method A) **26**, 21; **19**, 26; **27**, 26; **17**, 28.5; **20**, 34.5; **18**, 41.5; and (method C) **26**, 4.5; **19**, 6.0; **27**, 7.5; **17**, 6.5; **20**, 8.5; **18**, 10.5. The use of 2 or 3 afforded no **13a**; 1 gave **13a** in a yield of *ca* 13%.

Small scale treatment of linalool (3) *with* 85% H_3PO_4 *to determine yield of* C-10 *hydrocarbon.* To 1 ml of 85% H_3PO_4 was added with stirring 150 mg (0.97 mmol) of 3. The mixture was stirred for 15 min and was worked up as above. After evaporation (*ca* 0.1 Torr), there remained 33 mg of nonvolatile material which was not monoterpenoid, indicating a yield of volatile, C-10 hydrocarbons of 78%.

Large scale treatment of linalool (3) *with* 85% H_3PO_4. To 250 ml of 85% H_3PO_4 and 80 ml pentane was added with rapid stirring by a mechanical stirrer under N_2 *ca* 20 g of 3. The mixture was stirred for 15 min and was poured into 2.25l. H_2O; 50 ml pentane was added, and the organic portion was separated. The aqueous portion was extracted (3 × 50 ml of pentane) and the combined organic portions were washed (3 × 50 ml of sat $NaHCO_3$ aq, 1 × 50 ml sat NaCl aq), and dried ($MgSO_4$). The reaction was repeated until a total of 161.4 g (1.05 mol) of 3 was used. The organic solns were combined, the pentane was removed by distillation, and the volatile products were distilled at room temp under reduced pressure (0.08 Torr). The weight of the clear, colorless liquid obtained was 35.39 g (25%). The pot contained a thick yellow liquid which distilled at 150° (0.7 Torr) to give 45.367g of material which was believed to be dimeric and was not further analyzed. The monoterpene mixture was distilled at 65° (31 Torr) using a teflon spinning band apparatus.

A total of 22 fractions weighing 4.05g were obtained, leaving 31.26g of material in the pot. GC (Method B) analysis showed the fractions mostly contained some of the components present in smaller amounts in the crude cyclization mixture, plus **27**. The material left in the pot was mainly **19**, **27**, **20**, and **18**.

Each of these latter four compounds was purified by preparative GC (Method F) in greater than 95% purity. A pure sample of **27** was obtained from one of the fractions of the spinning band distillation. All IR spectra were identical to those reported in the literature.[21] NMR and mass spectral data (see Table 2) were identical to authentic samples as well as literature data.[22]

Co-injection GC analysis showed that the isolated compounds possessed retention times (min) identical to authentic samples, as indicated below: (Method B) **27**, 10.8; **19**, 10.75; **20**, 11.25; (method E) **19**, 3.5; **20**, 4.25. With method B, **18** had a retention time of 11.75 min. GC analysis by method D allowed separation of **27** and **19** (retention times, 10 and 9 min, respectively). Co-injection GC analysis (method B) showed that **18**, **27**, **19** and **20** all corresponded to the expected peaks in the crude mixture. NMR analysis of the crude mixture showed that it contained all the signals found in the spectra of the isolated compounds.

Isolation of 3-p-*menthene* (**26**). To 250 ml of 85% H_3PO_4 was added with stirring 20.38g (0.135 mol) of **6** (R = H). The mixture was stirred for 15 min, was poured into 2l. H_2O and was worked up as described above. Spinning band distillation of the clear,

colourless monoterpenes (5.68g, 31%), followed by preparative GC (Method F) afforded a sample of **26** shown to be 90% pure by GC analysis (Method B) (retention time: 10 min); IR (CCl_4) corresponded to that in literature; NMR (CCl_4)δ 5.34 ppm (broad s, 1, C=CH), 1.5–2.3 (m, 8, CH_2CH_2, $(CH_3)_2CH$, and CH_3CHCH_2), and 0.98 (d, 9, J=6 Hz, CH_3CH and $(CH_3)_2CH$); mass spectrum (70 eV) *m/e* (rel intensity) 138(35), 123(31), 95(100), 82(18), 81(59), 67(29), 55(17), 43(6), 41(18).

Isolation of limonene (**17**). To 25 ml of 85% H_3PO_4 was added with stirring 2.047g (0.0132 mol) of **2**. The mixture was stirred for 15 min, was poured into 250 ml H_2O, and was worked up as described above. Preparative GC (Method F) of the monoterpene mixture so obtained afforded a purified sample of **17**. GC (Method B) retention time: 11 min; NMR[22] and mass spectral (Table 2) data identical to that in the literature and of authentic material.

Treatment of α-terpinene (**19**) *and γ-terpinene* (**20**) *with* 85% H_3PO_4. To 5 ml of 85% H_3PO_4 was added with stirring either 436 mg (3.2 mmol) of **19** or 428 mg (3.15 mmol) of **20**. The mixtures were stirred for 15 min and worked up as above. Examination of the resulting mixtures (GC, NMR) showed only unchanged starting material.

Treatment of limonene (**17**) *with* 85% H_3PO_4. The treatment of **17** with 85% H_3PO_4 was carried out in the same manner as for the reactions of the alcohols, using 139 mg (1.02 mmol) of **17**. Products were examined by GC (Methods A and C). The results are shown in Table 1.

cis- *and* trans- p-*Menth*-2-*on*-8-*ol* (**9**).[23] To 19.67g (0.062 mol) of mercuric acetate in 60 ml H_2O was added 60 ml of THF, resulting in a yellow suspension. To this was added with stirring 9.39g (0.062 mol) of *cis*- and *trans*-*p*-menth-8-en-2-one (prepared from carvone as described[16]) with immediate loss of color. After 5 min, 60 ml of 3M NaOH aq was added, followed by 120 ml of 0.5M $NaBH_4$ in 3M NaOH aq. The mixture was stirred for 2 hr and was poured into a separatory funnel with exclusion of the mercury metal. The aqueous phase was saturated (K_2CO_3) and the organic layer was separated. The aqueous layer was extracted (2 × 50 ml of THF) and the combined organic portions were dried (K_2CO_3), filtered and concentrated. The viscous liquid was taken up in benzene, treated with activated charcoal, and filtered (Celite). Crystallization from the benzene gave 5.04g (47.5%) of a mixture of *cis*- and *trans*- **28**, as white crystals, m.p. 100–120°. Further concentration gave 4.73g (44.5%) of additional material, m.p. 70-110°;† TLC (10% ethyl acetate/hexane)R_f: 0.15, 0.20 and 0.28; NMR ($CDCl_3$)δ 3.11 ppm (s, 2, OH) and 0.9–1.5 (broad m, 18, CH_3, CH_2, CH).

To a suspension of 9.49g (0.044 mol) of pyridinium chlorochromate[24] and 482 mg (5.87 mmol) of NaOAc in 25 ml of anhyd CH_2Cl_2 was added with stirring 5.043g (0.0293 mol) of diols(**28**) in 50 ml of CH_2Cl_2. The mixture was stirred for 3 hr, 40 ml of diethyl ether was added and the liquid was decanted from the black tar. The tar was extracted (3 × 10 ml of diethyl ether) and the combined organic portions were passed through a 3 × 29 cm column of Florisil (prepared as a diethyl ether slurry). Removal of the solvent gave 5.00g of crude **9**. Distillation (83°, 0.5 mm) afforded 4.07g (82%) of pure **9**: TLC (10% ethyl acetate/hexane) R_f: 0.47; GC (Method B) retention time: 15.5 min; IR (neat) 3450 (OH) and 1710 cm^{-1} (C=O); NMR ($CDCl_3$) δ 3.42 ppm (broad s, 1,OH), 1.3–2.5 (m, 7, CH and CH_2), 1.16 (s, 6, $(CH_3)_2COH$), and 0.94 (d, 3, J=6 Hz, CH_3CH). The ring stereochemistry was not determined.

Treatment of p-*menth*-2-*on*-8-*ol* (**9**) *with* 85% H_3PO_4 *to give* 3-p-*menthen*-2-*one* (**10**). To a 25 ml flask containing 9 ml of 85% H_3PO_4 (Mallinckrodt, AR) and a 3/4 in teflon-coated stir bar was added with highest possible stirring under N_2 161 mg (0.95 mMol) of **9**. The mixture was stirred at room temp for 15 min, was poured into 90 ml H_2O, and the resulting mixture was extracted (4 × 20 ml of diethyl ether); the combined organic portions were worked up as described above, to give 113 mg (78.5%) of the known ketone, **10**, a clear, colorless oil;[16] TLC (5% ethyl acetate/hexane) R_f: 0.19; GC (Method B) retention time: 13.4 min; UV max (95% ethanol) 235 nm (ϵ = 11,800); IR (neat) 1675 (conjugated C=O) and 1620 cm^{-1} (C=C); NMR (CCl_4) δ 5.74 ppm (s, 1, C=CHC=O), 1.4–2.6 (m, 6, $CHCH_2CH_2$ and $(CH_3)_2CH$), 1.11 (d, 6, J=7 Hz, $(CH_3)_2CH$); and 1.05 (d, 3, J=6.5 Hz, CH_3CH); mass spectrum (70 eV) *m/e* (rel intensity) 152(14), 110(100), 95(78), 67(33), 41(18), 39(16).

†The large m.p. ranges are due to mixtures of diastereomers.

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