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Stereocontrolled Regiospecificity of the Water Loss from *trans*-Sobrerol Radical Cation upon Electron Ionization

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Water loss from *trans*-sobrerol upon electron impact ionization selectively involves the tertiary OH group, predominantly occurring by a stereocontrolled H-transfer from C(5) position in a rate-determining step process, as proved by ^{18}O and deuterium labelling. Monomethyl ethers behave accordingly. Ionic structures of the water-loss product or products are investigated by metastable ion and collision activation mass-analysed ion kinetic energy spectroscopy, using model ions generated from some substrates, which are chemically related to *trans*-sobrerol in condensed phase, i.e. α-pinane epoxide, *cis*-sobrerol and pinol. A substantial conversion of *cis*-sobrerol molecular ions to ionized pinol by loss of water has been demonstrated.

INTRODUCTION

The loss of water from alcohols upon electron impact ionization is one of the most thoroughly investigated hydrogen rearrangements in mass spectrometry.[1,2] The mechanism is a stepwise process initiated by hydrogen migration involving preferentially a six-membered ring transition state, although five or seven-membered rings can be allowed.[1-3] Hidden site specificity of the hydrogen migration with a stereochemical bias has been demonstrated for labelled straight-chain[3] and cyclic[2] alcohols. However, the study of this reaction can be complicated by thermal processes of neutrals, on the ionic species by concurrent hydrogen scrambling and, for cyclic substrates, by α-cleavage processes.[2] Moreover, for diols or polyols the hydrogen migration in the loss of water can also take place from a hydroxyl group, provided that the stereochemical requirements are satisfied.[2,4]

The first, and generally 'rate-determining', step of this reaction can be affected by the migratory aptitude of the sterically disposable hydrogens (i.e. tertiary > secondary > primary). On the contrary, for polyols, the chemical nature of the hydroxyls (i.e. primary, secondary, tertiary, allylic, etc.) potentially competing in such a process, should not play an important role in regioselectivity. For instance, ^{18}O labelling of 2-(hydroxymethyl)-cyclohexan-1-ol has shown that the primary hydroxyl function is eliminated as water more easily than the secondary one,[4] while recent results,[5] which are discussed in detail in the present paper, showed for *trans*-sobrerol (**3a**), a widely used mucoregulating drug,[6] a highly selective elimination of the tertiary *v.* the secondary allylic hydroxyl group.

EXPERIMENTAL

Instrumentation

The electron impact (EI) mass spectra were measured with a Hitachi RMU-6D single-focusing mass spectrometer operating at ionizing electron energies, with source and inlet temperatures as indicated in Tables 1 and 2.

The mass-analysed ion kinetic energy (MIKE) spectra have been measured with a VG Micromass ZAB-2F mass spectrometer operating at 70 eV (200 μA), at an accelerating voltage of 8 kV and at ion source temperatures between 100 and 130 °C. Collisional activation experiments were performed with air as target gas at a cell pressure able to reduce the usual ion beam intensity to ~30%.

Differential scanning calorimetry has been performed with a Mettler TA 3000 instrument equipped with a TC-10A processor.

Products

Compound **1** was commercially available (Fluka AG, Switzerland). Compounds **2**, **3a**, **3b**, **3c**, **4**, **5**, **7b** and **8** were synthesized according to Scheme 1 and in particular:

(±)-α-Pinane epoxide (2). A solution of (±)-α-pinene (**1**) [(5 g, 37 mmol) in CH_2Cl_2 (100 cm^3)] was stirred at 0 °C and a slight excess of recrystallized standardized *m*-chloroperbenzoic acid was added portionwise. The reaction mixture was stirred overnight at 22 °C, then diluted with more CH_2Cl_2, washed successively with saturated $NaHCO_3$ solution, brine and dried ($MgSO_4$). Evapor-

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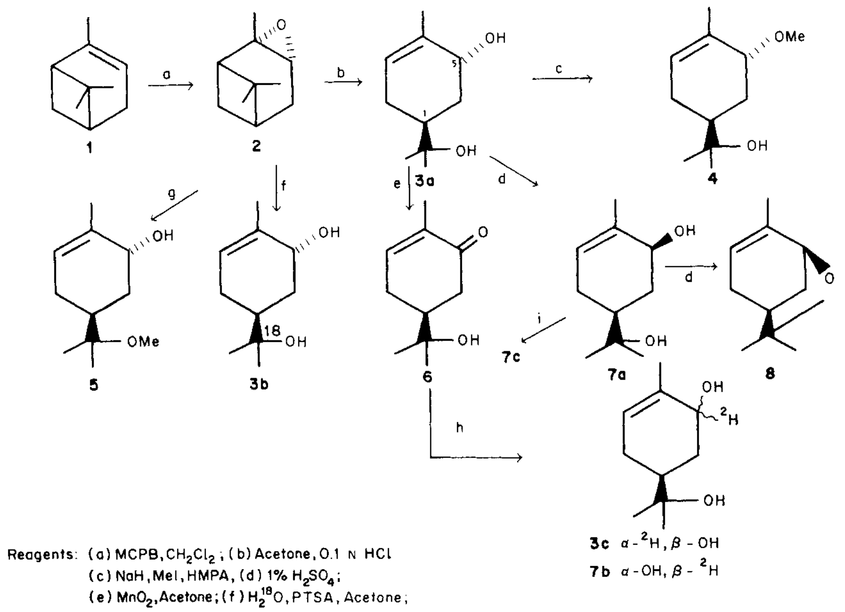


Reagents: (a) MCPB, CH_2Cl_2; (b) Acetone, 0.1 N HCl
(c) NaH, MeI, HMPA; (d) 1% H_2SO_4;
(e) MnO_2, Acetone; (f) $H_2{}^{18}O$, PTSA, Acetone;
(g) MeOH, PTSA; (h) $CeCl_3.6H_2O$, NaB^2H_4, MeOH; (i) $^2H_2O/C^2H_3O^2H$
MCPBA = *m*-chloroperbenzoic acid
HMPA = hexamethylphosphoramide
PTSA = *p*-toluenesulphonic acid

Scheme 1

ation of the solvent gave the crude epoxide (**2**) (5.5 g, 98% yield).

(±)-*trans*-5-Hydroxy-α,α,4-trimethyl-3-cyclohexen-1-methanol (3a) [(±)-*trans*-sobrerol]. To an ice-cold solution of crude (**2**) (2 g, 13 mmol) in acetone (50 cm^3) 0.1 N HCl (50 cm^3) was quickly added and the solution stirred for 3 h at 22 °C. The reaction mixture was then partitioned between AcOEt and saturated $(NH_4)_2SO_4$ solution. The organic layer was separated, dried ($MgSO_4$) and evaporated *in vacuo*. Flash chromatography of the residue (AcOEt) gave (**3a**) (1 g, 45% yield) as white crystals, m.p. 130–131 °C.[7]

(±)-*trans*-5-Methoxy-α,α,4-trimethyl-3-cyclohexen-1-methanol (4). To a stirred solution of (**3a**) (1.7 g, 10 mmol) in HMPA (50 cm^3), NaH (480 mg, 10 mmol, 50% oil dispersion) was added all at once. When gas evolution ceased, methyl iodide (2.5 cm^3, 45 mmol) was added. The reaction mixture was stirred overnight, then diluted with 0.1 N HCl (100 cm^3) and extracted three times with Et_2O. The combined organic layers were washed with saturated Na_2SO_3 solution, water-dried ($MgSO_4$) and evaporated. Flash chromatography (AcOEt/cyclohexane, 1/1) of the residue yielded (**4**) (400 mg, 20% yield) as colourless oil.

(±)-*trans*-6-Hydroxy-4-(1-methoxy-1-methyletheyl)-1-methylcyclohexene (5). To an ice-cold solution of crude (**2**) (5 g, 33 mmol) in dry methanol (150 cm^3) a few crystals of *p*-toluensulphonic acid were added with vigorous stirring. After 1 h the solvent was removed *in vacuo* and the residue taken up with AcOEt (100 cm^3). The organic phase was washed with water, dried ($MgSO_4$) and evaporated. Flash chromatography of the residue (AcOEt/cyclohexane, 1/1) gave pure (**5**) (2.3 g, 38% yield) as colourless oil.

(±)-*trans*-5-Hydroxy-α,α,4-trimethyl-3-cyclohexen-1-(^{18}O) methanol (3b). To an ice-cold solution of crude (**2**)-(600 mg, 4 mmol) in dry acetone (4 cm^3), $H_2{}^{18}O$ (1 cm^3) and then, under vigorous stirring, a crystal of *p*-

Table 1. Peaks of interest from the 70-eV (80 μA) EI mass spectra of compounds 3a, 3b, 3c, 4, 5 and 7a. Samples introduced with direct inlet probe at ~70 °C into the ion source heated at 130 °C. Intensities are not corrected for the natural isotope contributions

Compound	$M^{+\cdot}$	$[M-H_2O]^{+\cdot}$	$[M-{}^2HOH]^{+\cdot}$	$[M-H_2{}^{18}O]^{+\cdot}$	$[M-CH_3OH]^{+\cdot}$	Base peak
3a	170 (2)	152 (27)	—	—	—	59 (100)
3b[a]	172 (2.1)	154 (0.6)	—	152 (27.7)	—	61 (100)
3c[a,b]	171 (3.1)	153 (23.9)	152 (25.6)	—	—	59 (100)
4	184 (2.5)	166 (39.3)	—	—	152 (5.5)	59 (100)
5	184 (0.2)	166 (0.2)	—	—	152 (14)	73 (100)
7a	170 (0.4)	152 (25)	—	—	—	59 (100)

[a] Values corrected for the contribution of the unlabelled component **3a** (~10%).
[b] Values also corrected for the contribution of the isomer *cis*-sobrerol-5-d_1 **7b** (~8%).

Table 2. Relative intensities of peaks at m/z 152, 153 and 154 due to water loss from molecular ions of compounds 3a, 3b and 3c upon EI at different ionizing electron energies

		Relative intensities of peaks due to water loss from molecular ions				
Compound	m/z	70 eV[a]	20 eV[a]	18 eV[a]	16 eV[a]	15 eV[a]
3a	152	100	100	100	100	100
	153	11.1	11.1	11.1	11.1	11.1
	154	0.7	0.7	0.7	0.7	0.7
3b[b]	152	100	100	—	100	100
	153	12.6	11.4	—	11	11
	154	2.2	2.2	—	2.5	3.3
3c[c]	152	100	100	100	97	92
	153	88.5	89.0	98	100	100
	154	12.5	12.5	16	24	36

[a] Nominal values.
[b] Values corrected for contributions of unlabelled derivative (**3a**).
[c] Values not corrected for contributions from ~10% of **3a** and from ~8% of *cis*-sobrerol-5-d_1 (**7b**).

toluensulphonic acid were added. Stirring was continued for 1 h then the reaction mixture was diluted with EtOAc, washed with saturated $(NH_4)_2SO_4$ solution, dried ($MgSO_4$) and evaporated. Flash chromatography of the residue (AcOEt) gave (**3b**) (250 mg, 37% yield) as white crystals, m.p. 130–131 °C.

The isotopic enrichment measured on the relative intensities of the peaks at m/z 59 and 61, which are due to fragment ions bearing the tertiary hydroxyl group, was 55.5% (70 eV mass spectrum). This enrichment is consistent with that calculated from the ratio of molecular ion intensities, confirming the specific labelling on the tertiary alcoholic function.

(±)-4,7,7-Trimethyl-6-oxabicyclo[3.2.1.]oct-3-ene (8). A mixture of (**3a**) (3.9 g, 23 mmol) and 1% H_2SO_4 (100 cm^3) was refluxed and vigorously stirred for 3 h, then extracted with ethyl ether. The combined organic layers were washed with saturated $(NH_4)_2SO_4$ solution, dried and evaporated, yielding 3.3 g (95% yield) of nearly pure pinol (**8**).

(±)-5-(1-Hydroxy-1-methylethyl)-2-methyl-2-cyclohexen-1-one (6). Compound (**3a**) (1.7 g, 10 mmol) was dissolved in acetone (80 cm^3) and treated with activated MnO_2 (10 g, 0.11 mol). Vigorous stirring was continued for 48 h, then the mixture was filtered through a short pad of celite and the solvent evaporated. Flash chromatography of the residue (AcOEt/cyclohexane, 1/1) gave (**6**) (1.1 g, 65% yield) as colourless oil.

(±)-*cis*- and (±)-*trans*-5-Hydroxy[5^{2}H]-α,α,4-trimethyl-3-cyclohexen-1-methanol (7b), (3c). To a stirred solution of the α, β unsaturated ketone (**6**) (1.7 g, 10 mmol) in methanolic $CeCl_3.6H_2O$ (30 cm^3, 0.4 M) $NaB[^2H]_4$ (420 mg, 10 mmol) was slowly added in portions. The mixture was allowed to react for 30 min, then treated with saturated $(NH_4)_2SO_4$ solution and extracted with AcOEt. The combined organic layers were washed with water, dried ($MgSO_4$) and evaporated. Flash chromatography of the residue (AcOEt) yielded pure (**7b**) (1.5 g, 87% yield) as white crystals melting at 105–106 °C together with 160 mg of a mixture of the pair of diastereoisomers. Careful flash chromatography of the latter (AcOEt: cyclohexane, 1:1) allowed isolation of a small quantity of pure (**3c**) (40 mg, 2% overall yield) as white crystals melting at 130–131 °C.

All the structures of these compounds were confirmed by IR, NMR and mass spectrometric analyses. The *O*-deuterated *cis*-sobrerol (**7c**) was prepared by dissolving the corresponding undeuterated pure compound **7a** in a $^2H_2O/C^2H_3O^2H$ mixture, with removal of the solvent before measurements.

RESULTS AND DISCUSSION

The water loss from *trans*-sobrerol (**3a**) upon electron impact ionization involves with high regioselectivity the tertiary hydroxyl, as shown by its ^{18}O-labelled analogue (**3b**),[5(a)] and in agreement with the largely predominant loss of the tertiary oxygenated function of its monomethyl ethers **4**[5(b)] and **5**, as water or MeOH respectively (see Table 1). These mass spectral results have been obtained with inlet and source temperatures of 70 and 130 °C respectively, i.e. well below the temperature of 180 °C at which thermal dehydration starts, as it was determined for the melted neutral *trans*-sobrerol (**3a**) by differential scanning calorimetry. The regiospecificity of the ionic dehydration reaction, excluding any contributions of thermal processes of neutrals, is clearly demonstrated by metastable molecular ions, which spontaneously dissociate in the second field-free region (2nd FFR) of a reversed geometry double-focusing ZAB-2F mass spectrometer. Figure 1(a) and (b) shows the partial MIKE spectra of unlabelled (**3a**) and ^{18}O-labelled (**3b**) *trans*-sobrerol metastable radical cations, the latter exhibiting practically only the loss of labelled water (m/z 152). Such a high regiospecificity is practically unaffected by the internal energies of dissociating species, as shown in Table 2. This behaviour can be rationalized by the stereochemistry of the neutral substrate. The inspection of the Dreiding models of the four conformers (A–D) of **3a**, indicated in Table 3, with the ring in pseudochair or pseudoboat form and the bulky hydroxyisopropyl group in pseudoequatorial or pseudoaxial position, gives the internuclear distances between the tertiary or the secondary allylic oxygen and those hydrogens, which could migrate to oxygen by a five-, six- or seven-membered ring transition state (5-, 6-, 7-m.r.t.s.). This conformational analysis clearly shows that the tertiary OH meets favourable stereochemical conditions for the abstraction (i) of the pseudoaxial hydrogen at C(5) ($C(5)H_{ax}$), which in conformer B can reach an internuclear distance of ~1.4 Å, by a 6-m.r.t.s., and (ii) of the pseudoaxial or of the pseudoequatorial H at C(6) ($C(6)H_{ax}$ or $C(6)H_{eq}$) both by a 5-m.r.t.s., being the least O ... H internuclear distance of ~1.6 Å for the former in conformation D, and of ~1.7 Å for the latter in conformation C. On the contrary, much less suitable stereochemical conditions can be observed for an H abstraction by the secondary allylic hydroxyl group. The shortest O ... H internuclear distances are shown by C(10)methylic hydrogens (~2.1 and 2.3 Å in conformers C and B respectively), while the H migration could only be forced to occur by a strained 5-m.r.t.s.

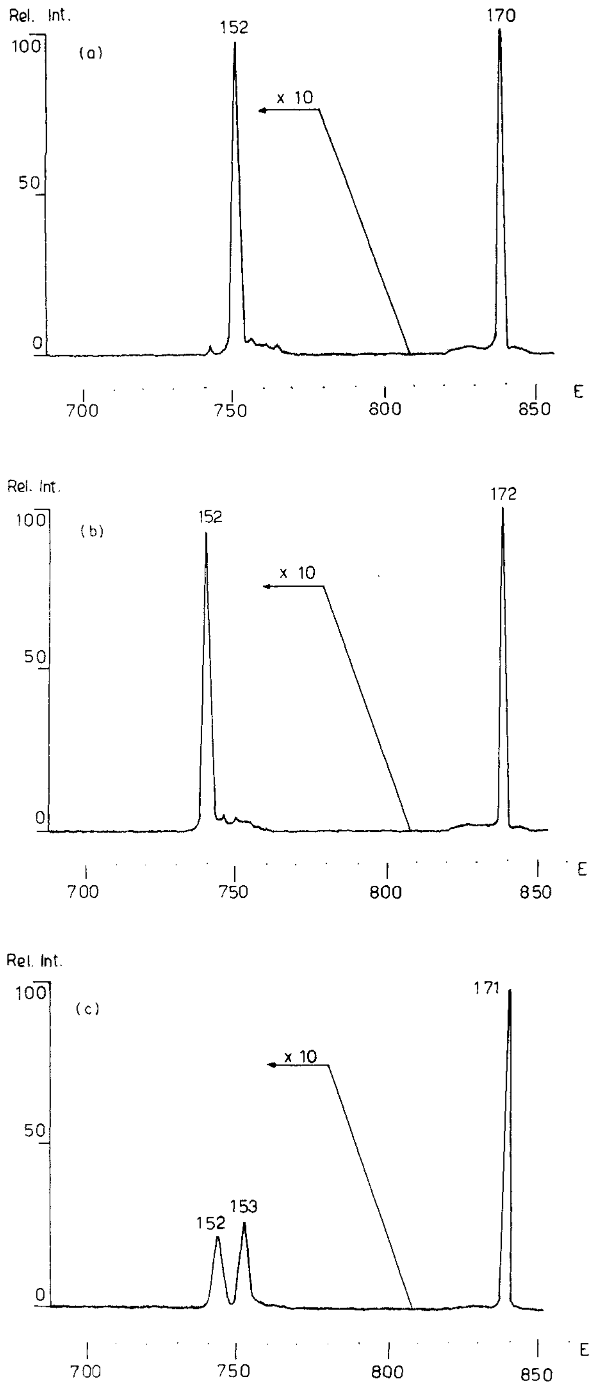


Figure 1. Partial MIKE spectra of metastable molecular ions generated by EI (70 eV) from (a) **3a**, (b) **3b** and (c) **3c**.

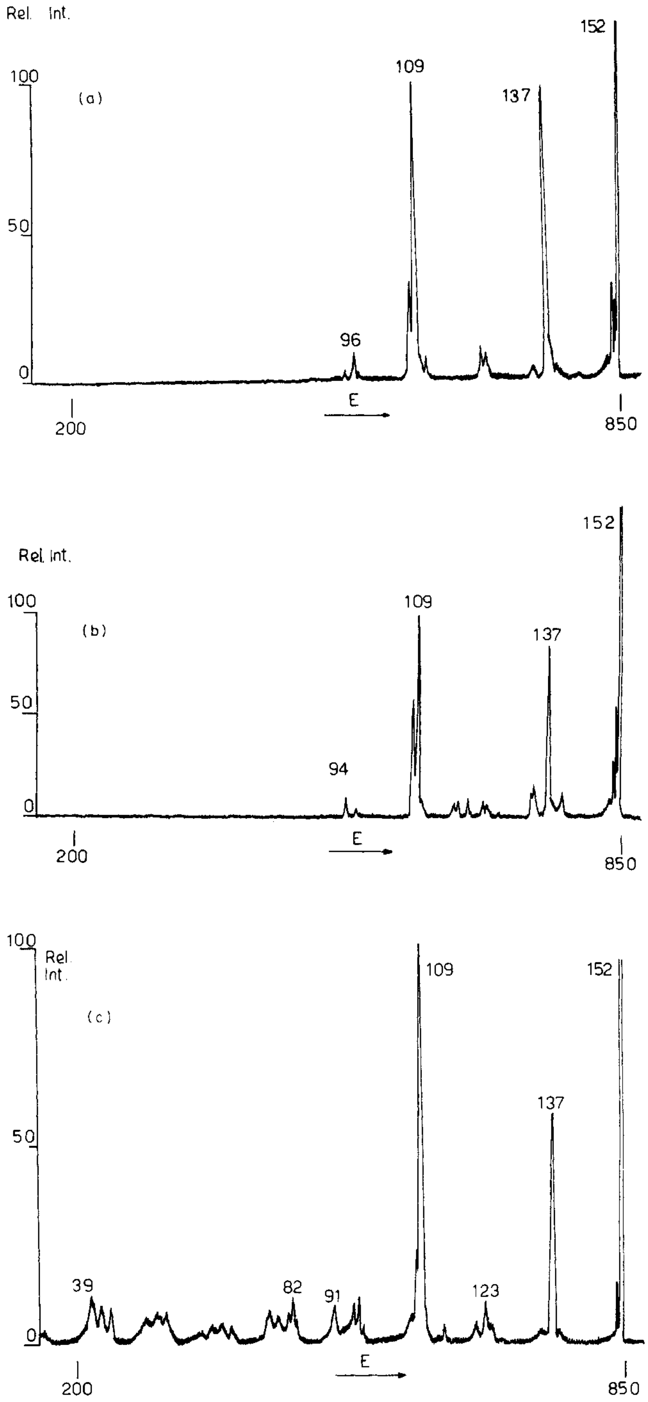
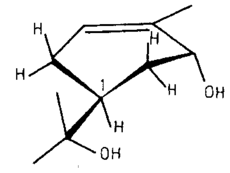
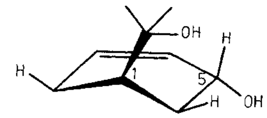
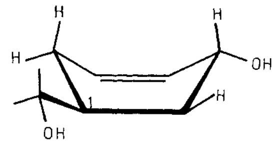
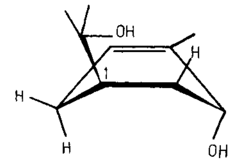


Figure 2. (a) MIKE spectrum of metastable m/z 152 ions generated by EI (70 eV) from **3a**, **3b** or **3c** and (b) from **5**; (c) from **3a**, **3b**, **3c** or **5** by collisional activation.

The above considerations, made on the model of **3a**, give an explanation on stereochemical grounds for the selective elimination of the tertiary OH as water from the corresponding radical cation ($[\mathbf{3a}]^{+\cdot}$) in gas-phase, and can even suggest for the migrating hydrogen(s) a hidden stereoselectivity, which could be uncovered by suitable deuteriated derivative(s). Deuteriation at C(5) (**3c**) has been chosen, since this hydrogen can *a priori* be expected to be preferentially abstracted by the tertiary OH, involving a favourable 6-m.r.t.s. Moreover, the intrinsic migratory aptitude of this secondary allylic hydrogen at α-position to a hydroxyl group can be expected to be high. $C(5)H_{ax}$ could reach to within a very short internuclear distance from the tertiary alcoholic oxygen (1.4 Å), if the same conformation B of **3a** is assumed for $[\mathbf{3a}]^{+\cdot}$. Conformation A, which is the most stable for neutral **3a** in solution,[8] would *not* give important contributions in the water-loss reaction for $[\mathbf{3a}]^{+\cdot}$, as it could allow larger least internuclear distance ($\geq$2.3 Å) of hydrogens at C(2) or at C(6) from the tertiary alcoholic oxygen, to which they could only migrate by a strained 5-m.r.t.s.

Table 3. Indicative values of O...H distances measured on Dreiding models and schematic structures[a] of 3a conformers (A–D)

Conformer	Structure	Alcoholic function	Distances (Å)[b] of hydrogens[c,d] at				
			C(1)	C(2)	C(5)	C(6)	C(10)
A		Tertiary		H_{ax} 2.3 H_{eq} 2.5		H_{ax} 2.6 H_{eq} 2.4	
		Secondary allylic	H_{ax} 2.6				$H(CH_3)$ 3.1
B		Tertiary		H_{eq} 2.2	H_{ax}1.4	H_{eq} 2.6	
		Secondary allylic[e]					$H(CH_3)$ 2.3
C		Tertiary		H_{ax} 2.2 H_{eq} 2.6	H_{ax} 3.1	H_{eq} 1.7	
		Secondary allylic					$H(CH_3)$ 2.1
D		Tertiary		H_{eq} 2.1		H_{ax} 1.6	
		Secondary allylic		H_{ax} 2.5			$H(CH_3)$ 3.4

[a] Only the hydrogens are drawn for which the O...H distances are given. To avoid overcrowding, C(10)-(CH_3) is not drawn for the structures B and C.
[b] Only values < 3.5 Å are given.
[c] H_{ax}=H pseudoaxial; H_{eq}=H pseudoequatorial.
[d] Only relative O...H positions 1,5, 1,6 and 1,7 are considered.
[e] The interactions with the methylic hydrogens of the hydroxyisopropylic group are hindered by C(5) H_{ax}.

In Table 2 are given the relative intensities of the peaks of molecular ions and of their water-loss products in EI mass spectra at 70 eV and at lower ionizing electron energies of C(5) deuteriated derivative (**3c**), which contains ~10% of **3a** and ~8% of *cis*-sobrerol-5-d_1 (**7b**). The peak intensities are not corrected for the contributions of these components. As expected, these data clearly show the preferential loss of deuterium as ^{2}HOH leading to *m/z* 152 ions. The selectivity of the reaction, however, slightly decreases by lowering ionizing electron energy. This may be due to: (i) intramolecular H/^{2}H exchange before dissociation, or (ii) concurrent elimination of unlabelled water, i.e. rearrangements proceeding through tight transition states, which are kinetically favoured for reacting ions of lower internal energies. Furthermore, primary kinetic isotope effects ($K_H/K_{^2H} > 1$), which can increase in magnitude for the ions of lower internal energies (metastables included), could be also important, provided that the H/^{2}H intramolecular transfers were rate-determining steps. The MIKE spectrum of metastable $[\mathbf{3c}]^{+\cdot}$(*m/z* 171) (see Fig. 1(c)) shows an abundance ratio for the products of labelled (*m/z* 152) and unlabelled (*m/z* 153) water losses of 0.85, which is somewhat lower than the figure of 1.21 resulting from the normal 70-eV abundances (Table 1), after correction for the natural isotope contributions. This difference is consistent with the trend observed in the normal EI spectra after reducing the ionizing energy (Table 2). The sum of the relative abundances, referred to molecular species, of the water-loss products (*m/z* 152 and *m/z* 153) of **3c** (~0.05) is about one half of that (~0.1) observed for the *m/z* 152 water-loss product(s) of unlabelled **3a** (Fig. 1(a)). This denotes significant kinetic isotope effects, which support a rate-determining step for the C(5)-labelled hydrogen migration to the tertiary hydroxyl group, as expected.

For investigating the structure(s) of the water-loss product(s) of *trans*-sobrerol, analyses by MIKE spectroscopy of spontaneous (MI) and collisional activated (CA) dissociations of *m/z* 152 ions from compounds **3a**, **3b**, **3c** and **5** have been made. The MIKE MI spectra of *m/z* 152 from **3a**, **3b**, and **3c** are practically superimposable (Fig. 2(a)), while few differences are observed in that of **5** (Fig. 2b). Such differences completely disappear in the CA spectra (Fig. 2(c)). Reasonable models for the structure(s) of *m/z* 152 water-loss products of *trans*-sobrerol have been selected from among compounds related to its condensed-phase chemistry such as epoxide **2**, *cis*-sobrerol (**7a** and **7c**) and pinol (**8**) (see Scheme 1). MIKE MI and CA spectra of $[\mathbf{2}]^{+\cdot}$ (Fig. 3(a) and (b)), of water-loss product(s) *m/z* 152 of $[\mathbf{7a}]^{+\cdot}$ (Fig. 4(a) and (b)) and of $[\mathbf{8}]^{+\cdot}$ (Fig. 5(a) and (b)) are markedly different from those of water-loss product(s) of $[\mathbf{3a}]^{+\cdot}$. This excludes an epimerization of $[\mathbf{3a}]^{+\cdot}$ to $[\mathbf{7a}]^{+\cdot}$ as well as a retrograde water-loss reaction to $[\mathbf{2}]^{+\cdot}$. However, both epimerization of **3a** to **7a** and hydration

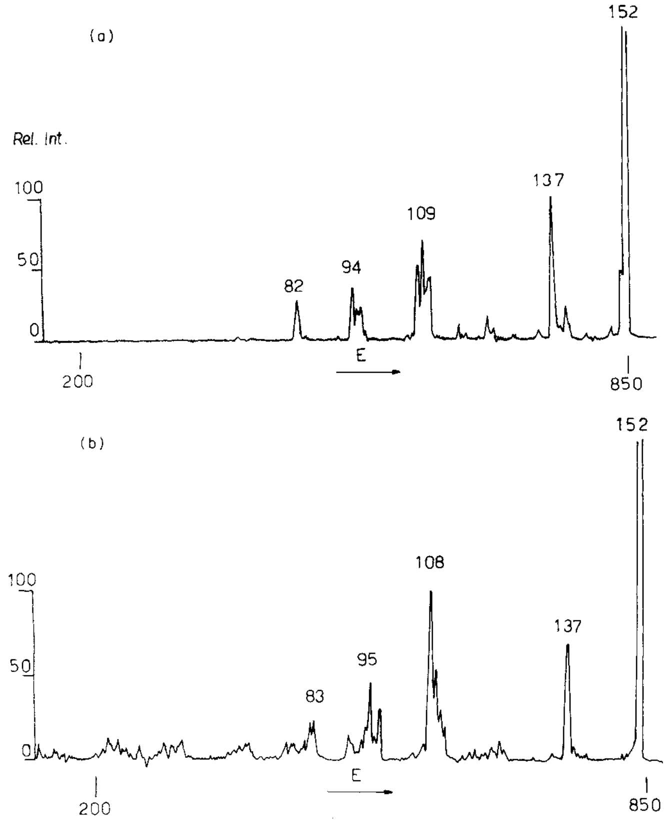


Figure 3. (a) Metastable ion and (b) collisional activation MIKE spectra of [**2**]$^{+\cdot}$ generated by EI (70 eV).

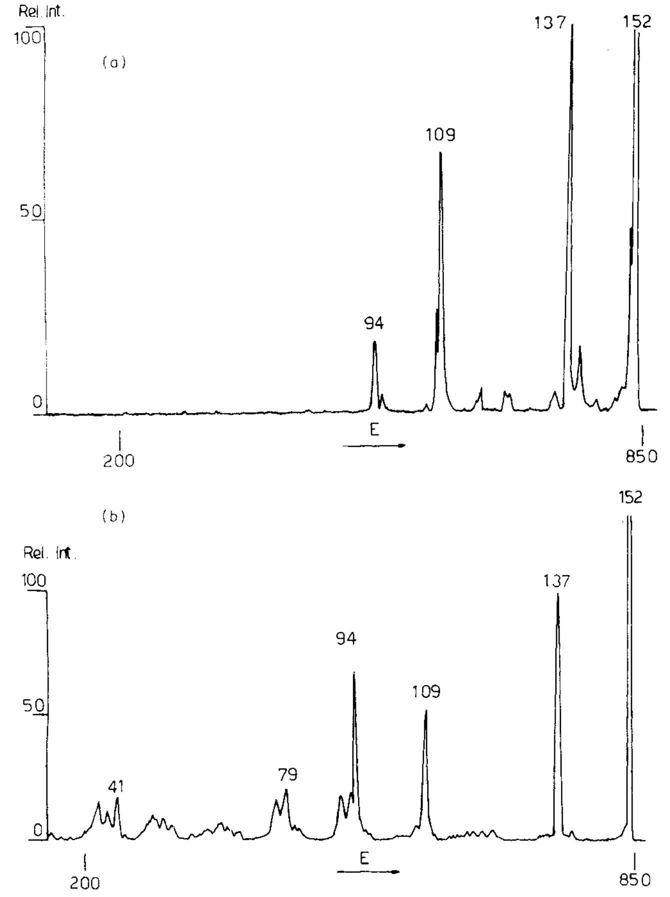


Figure 4. (a) Metastable ion and (b) collisional activation MIKE spectra of *m/z* 152 ions generated from *cis*-sobrerol (**7a**) by EI (70 eV).

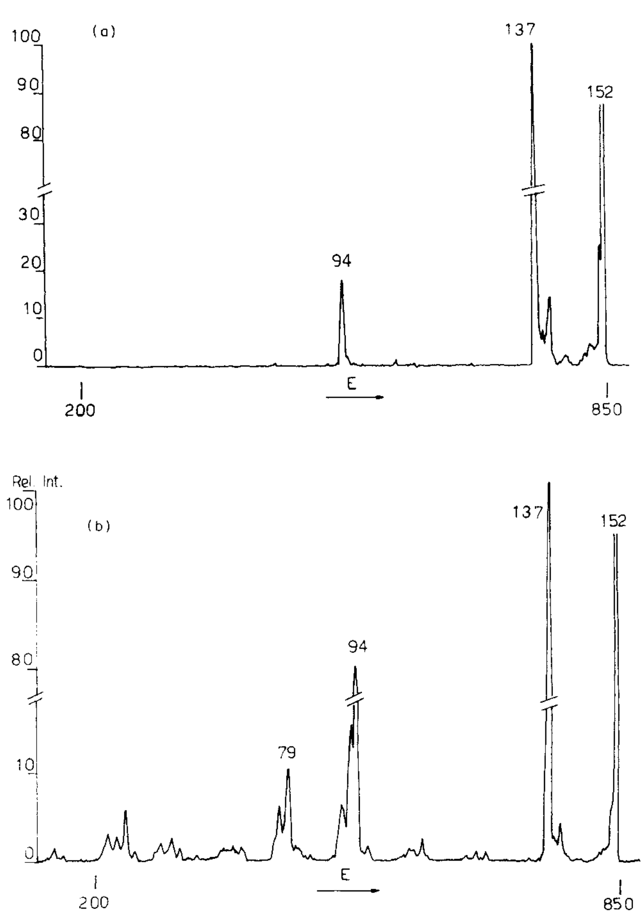


Figure 5. (a) Metastable ion and (b) collisional activation MIKE spectra of [**8**]$^{+\cdot}$ generated by EI (70 eV).

of **2** to **3a** (see Scheme 1) are actually acid-catalysed processes in condensed phase, and work is in progress for reproducing them under suitable conditions in gas-phase. Interestingly, the water-loss reaction from the molecular ion of *O*-deuterated *cis*-sobrerol (**7c**, *m/z* 172) gives rise to prominent ^{2}HOH elimination (*m/z* 153) as shown by MIKE MI spectrum (Fig. 6), although a considerable loss of ^2H_2O (*m/z* 152) is observed, which clearly involves hydrogen migration from one to the other hydroxyl group. This migration appears to be a stereochemically favourable process on the Dreiding model of neutral **7a**, and the product of the consequent

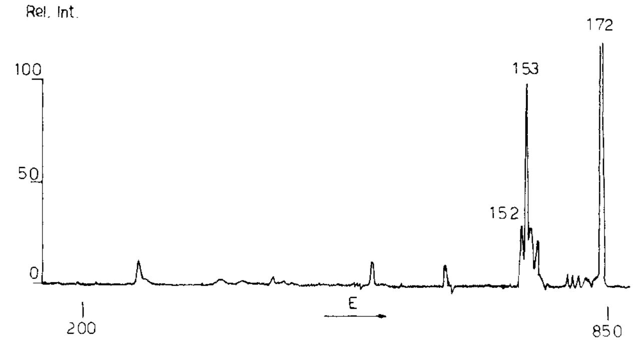


Figure 6. MIKE spectrum of metastable *O*-deuterated *cis*-sobrerol molecular ions [**7c**]$^{+\cdot}$ generated by EI (70 eV).

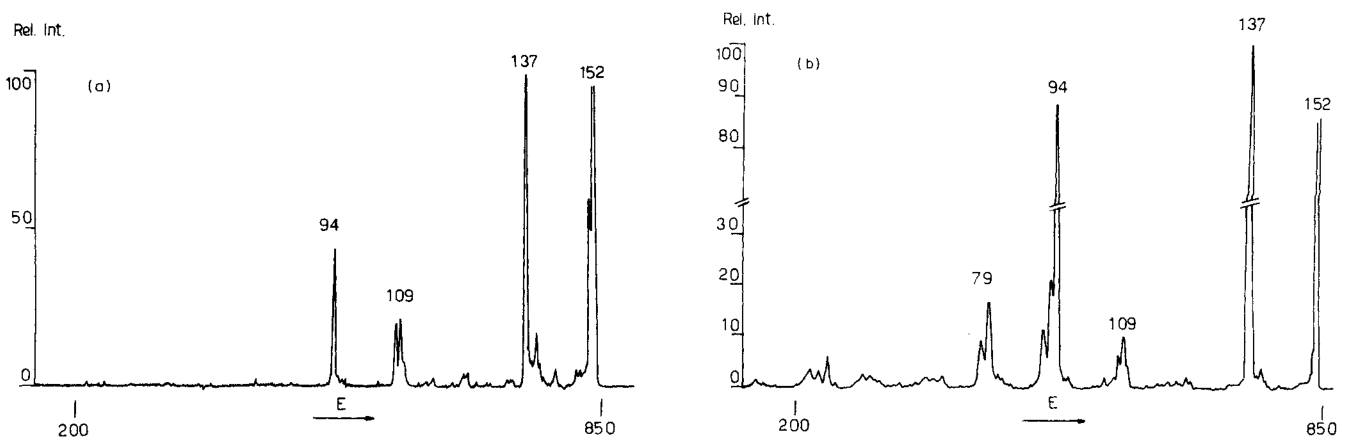


Figure 7. (a) Metastable ion and (b) collisional activation MIKE spectra of *m/z* 152 ions generated from *O*-deuterated *cis*-sobrerol (**7c**) by EI (70 eV).

water-loss reaction can be expected to have the structure of ionized pinol ($[\mathbf{8}]^{+\cdot}$).

While the MIKE MI spectra of $[\mathbf{8}]^{+\cdot}$ (Fig. 5(a)) and of *m/z* 152 from $[\mathbf{7c}]^{+\cdot}$ (Fig. 7(a)) show some differences, the corresponding MIKE CA (Figs 5(b) and 7(b)) become rather similar. This confirms that ionized pinol ($[\mathbf{8}]^{+\cdot}$) can be obtained to a considerable extent from *cis*-sobrerol (**7a** or **7c**) by water-loss upon EI conditions.

Finally, as a conclusive remark it must be pointed out that the high stereocontrolled regiospecificity of the water-loss process from *trans*-sobrerol (**3a**) upon electron impact ionization is consistent with the intact-ring structure of the reacting radical cations ($[\mathbf{3a}]^{+\cdot}$). The same assumption can be made for mono-methyl ether **5**, while the isomer **4**, which shows a lower selectivity for the loss of the tertiary OH as water *v.* the loss of the secondary allylic OCH_3 as CH_3OH (see Table 1), could also involve ring-opened radical cations, generated prior to the elimination reaction by α-cleavage, for instance of the C(5)—C(6) allylic bond. This is in accord with the much easier formation of opened-ring molecular ions from methoxycyclohexane,[9] than from cyclohexanol,[10] and it can be reasonably explained by the lower critical energy[11] of α-cleavage processes for ethers than for the corresponding alcohols.

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