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The mechanism of formation of 8,8-dimethyl[4.2.1.0³,⁷]nonan-6-yl acetate (fortesyl acetate) during acetolysis of nopyl toluene-p-sulfonate

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Attempts to prepare 2-(2-hydroxyethyl)-6,6-dimethylbicyclo[3.1.1]hept-2-ene (nopol; **1**) labelled with deuterium at C-10 by a process of oxidation of the primary alcohol group of nopol to the aldehyde, followed by H/D exchange and reduction back to alcohol, were unsuccessful because various oxidation procedures, including reaction with *N*-chlorosuccinimide at −78 °C, gave instead a carboxylic acid having an oxygen at C-3. Nopol, labelled at C-11 with deuterium, was obtained through a Prins reaction of β-pinene with deuteriated paraformaldehyde. This labelled nopol was converted into its toluene-p-sulfonate ester, and was solvolysed in acetic acid containing acetate ion to give 8,8-dimethyltricyclo[4.2.1.0³,⁷]nonan-6-yl acetate, which is an earlier reported novel fused ring system (fortesyl acetate; **2** acetate). The position of the label in the product showed that the mechanism of this deep-seated carbon skeletal rearrangement proceeds through the intermediate formation of a cyclobutane ring, followed by shift of a methylene bridge to expand the original cyclobutane ring and then subsequent expansion of the new cyclobutane ring. Calculations of heats of formation of possible ions involved in these shifts confirm the proposed mechanism as the most likely pathway.

Introduction

Acetolysis of the toluene-p-sulfonate ester[1,2] of nopol (2-(2-hydroxyethyl)-6,6-dimethylbicyclo[3.1.1]hept-2-ene; **1**) yields the acetate of fortesol, (8,8-dimethyltricyclo[4.2.1.0³,⁷]nonan-6-ol; **2**). The structure of the 2-phenylpropionate ester of the novel fused ring compound **2** has been determined by X-ray spectroscopy.[3] Two plausible mechanisms for the rearrangement of structure **1** to **2** have been proposed[2] and are summarised in Scheme 1.


1   **2**
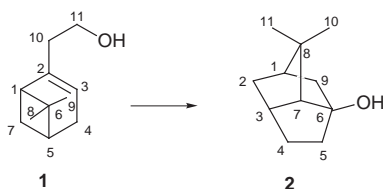
Formation of the parent alkane of **2** has been reported to occur by reaction of the toluene-p-sulfonate **1** with organo-aluminium compounds, from which the alkanes **13,14** (Scheme 2) were isolated.[4] The ethyl derivatives of the alkanes were obtained when the toluene-p-sulfonate was reacted with tri-ethylaluminium. The proposed mechanism, shown in Scheme 2, differs from those (A, B) shown in Scheme 1. A serious objection can be raised to the formation of ion **17** from **16**, which requires a hydride shift that is unprecedented in carbocation chemistry. Any hydride shift would be expected to give ion **18** (Scheme 3), leading to the formation of structure **19**.

In the acetolysis of nopyl toluene-p-sulfonate reported earlier,[1,2] derivatives of the structures **13**, **14** are not found. An acetate at C-3 of structure **13** has been observed as a product of the deamination of nopylamine in acetic acid.[5]
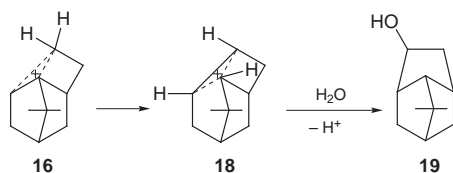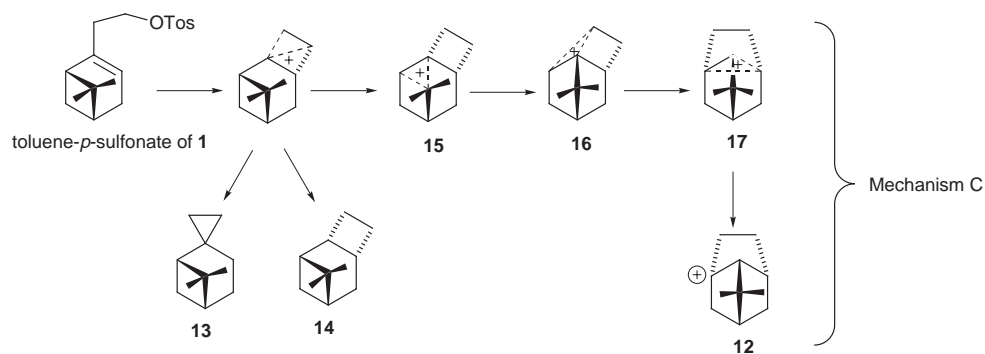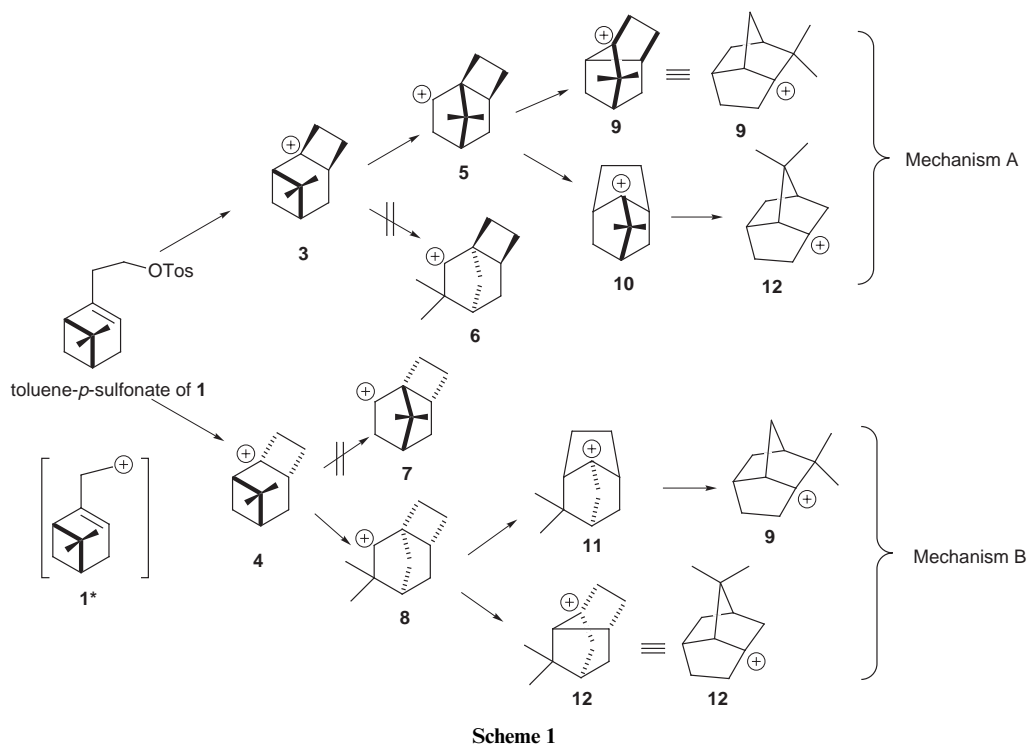
The first step in all three mechanisms (A, B, C; Schemes 1, 2) is formation of a second cyclobutyl ring by cyclisation of the nopyl side-chain during synchronous loss of the toluene-p-sulfonate group. The process is consistent with the similar, well-known cyclisations of toluene-p-sulfonate esters of β,γ-alkenyl alcohols.[6] This cyclisation would be expected to give an ion **4** with the fused ring orientated away from the *gem*-dimethyl bridge. Fused cyclobutane ring derivatives of the pinane system have not been recorded but cyclohexane rings fused to pinane in a similar position are orientated away from the *gem*-dimethyl bridge.[7–10]

The next step in the reaction would be the expansion of the original cyclobutane ring to form bornyl (**5** or **7**) or fenchyl (**6** or **8**) systems. This is the point at which the present proposed mechanisms diverge. Mechanisms A, C require expansion of the *gem*-dimethyl bridge to yield a bornyl system, while mechanism B requires expansion of the methylene bridge to give the fenchyl system. At first sight, this appears to favour the former mechanisms (A, C) because the pinane ring usually expands by shift of the *gem*-dimethyl rather than methylene bridge. However, in this case, the reaction is controlled by strain in the product. If the fused cyclobutane ring in structure **20** involves the *exo*-2 position, molecular models suggest it to be very strained; at the same time, *endo*-2 fusion in structure **21** cannot

20   **21**
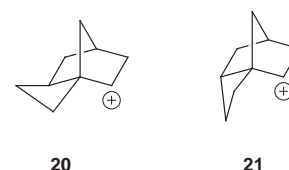
be reconstructed with models because carbon atoms C-1 and C-6 are too far apart to be joined by a normal C–C bond. Thus, structure **3** forms **5** and not **6** (Scheme 1) and **4** forms **8** and not **7**. Mechanism B then requires only a simple bond shift in ion **8** to give the ion **12** and hence the observed product. Mechanism A, proceeding from ion **4** involves formation of a bridgehead carbocation **10**, which would be expected to be relatively

Mechanism A

toluene-*p*-sulfonate of **1**

3

5

9 ≡ **9**

6

10 → **12**

Mechanism B

1*

4

7

8

11 → **9**

12 ≡ **12**

Scheme 1

toluene-*p*-sulfonate of **1**

15 → **16** → **17**

13

14

12

Mechanism C

Scheme 2

**16** → **18** $\xrightarrow[-H^+]{H_2O}$ **19**

Scheme 3

unstable, rearranging to ion **12** and its mirror image. Mechanism C avoids the problem of the bridgehead ion by delocalisation but presents the problem that rearrangement to ion **17** would have to proceed through the bridgehead ion **10**, so there is a barrier to reaction.

To distinguish between the mechanisms, use is made of the symmetry in the system. Mechanism B does not involve a symmetrical intermediate and should give an optically active product starting from optically active nopol; any isotopic label put at C-10 in the optically active starting material should be found at C-5 in the product. Mechanisms A and C both involve the symmetrical ion **10** and should form a racemic product; an isotopic label placed at C-10 in the starting material should appear distributed between C-4 and C-5 in the product. Since the reaction is carried out in acetic acid, in which ion pairing is often important, it may be considered that the observed retention of optical activity is insufficient basis alone for selecting mechanism B as being the correct one.

Results and discussion

A commercial sample of nopol **1** ($[\alpha]^{24}$ −37°; neat) was converted into its toluene-*p*-sulfonate and then solvolysed in acetic acid to give the acetate of fortesol **2**, which was reduced to fortesol ($[\alpha]^{20}_D$ −48°; $c = 5$, EtOH).

In a first attempt to label the side-chain of nopol, the alcohol was reacted with pyridine dichromate[11] so as to form the corresponding aldehyde. The resulting colourless crystals were examined by X-ray diffraction,[12] which showed that a keto alkenoic acid had been formed (structure **22**). Accordingly, the oxidation was attempted with the milder oxidant, *N*-chlorosuccinimide, at −78 °C.[13] Again a white crystalline material was isolated, which was shown by X-ray diffraction[12] to have structure **23**. This was still an alkenoic acid but, com-

22

23
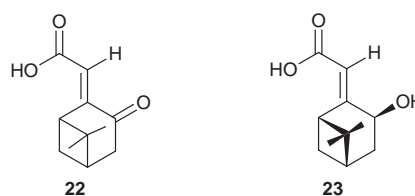
pared with compound **22**, it had been oxidised only to the hydroxy stage rather than to the ketone. It appears never to have been reported that oxidation with *N*-chlorosuccinimide gives a

carboxylic acid. It is not clear whether the oxidation follows an unusual pathway or whether the initial aldehyde product is unusually susceptible to further oxidation.

The next attempts involved Oppenauer oxidation,[14] which gave a mixture of products and finally manganese dioxide,[15] which did not oxidise nopol.

The direct oxidation approach to give an aldehyde, which could have been exchanged to incorporate deuterium on C-10 was abandoned and, instead, nopol labelled on C-11 was synthesised directly from β-pinene by utilising a Prins reaction[16] with perdeuterioparaformaldehyde. To minimise any potential loss of the deuterium label by exchange with a Brønsted acid, Lewis acid catalysis was used. Experiments with the two most popular catalysts, zinc(II) chloride[17] and tin(IV) chloride[18] showed that the first gave a higher yield of nopol. Reaction of perdeuterioparaformaldehyde with β-pinene catalysed by zinc chloride gave nopol labelled with two deuterium atoms at C-11 (structure **24**). Both ^{1}H and ^{13}C NMR spectroscopy showed that the hydrogen at C-11 had been replaced completely by deuterium. The C-11-labelled nopol was converted into its toluene-*p*-sulfonate ester with no loss of label as shown by ^{1}H and ^{13}C NMR spectroscopy. Mass spectrometry also showed an increase in molecular mass to 322, compared with 320 in the unlabelled nopyl toluene-*p*-sulfonate. Finally, the toluene-*p*-sulfonate was solvolysed in acetic acid in the normal way to give the fortesyl acetate product (Scheme 4).
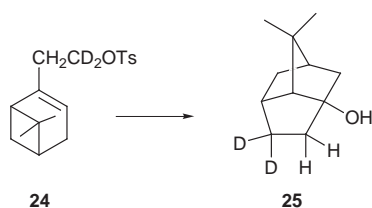
Scheme 4

Examination of the resulting labelled acetate by MS showed that the molecular mass of the labelled acetate at 210 was two mass units greater than that of the corresponding unlabelled fortesyl acetate. ^{13}C NMR spectroscopy revealed that the C-4 signal at δ 28.5, which is present in unlabelled fortesyl acetate, had disappeared because of the deuterium attached to this carbon. Substitution of hydrogen by deuterium causes a large increase in the relaxation time of the carbon spin states compared with their short relaxation times when hydrogen is attached. In keeping with the expected absence of deuterium at C-5, its signal at δ 37.9 remained unaffected in the labelled molecule. As a further check, the acetate was reduced to fortesol with lithium tetrahydroaluminate. MS on this alcohol gave a molecular ion peak at *m/z* 168; there were no peaks at *m/z* 166 or 167, which might have corresponded with unlabelled or partially labelled nopol. The ^{13}C NMR spectrum of the labelled fortesol showed that the C-4 signal of unlabelled fortesol at δ 27.2 had disappeared but the C-5 signal at δ 41.4 remained. The ^{1}H NMR spectrum of the labelled fortesol product revealed that the signal at δ 1.88 for the original axial proton attached to C-4 in the unlabelled alcohol was absent. The signal from the equatorial proton at δ 1.35 closely overlapped the axial proton signal on C-9 at δ 1.40, so that the product spectrum only indicates that the pattern of peaks is different from that in unlabelled fortesol in this small region.

It is clear from these results that the overall rearrangement proceeds as shown in Scheme 4. The deuterium label remains intact during the solvolysis, yielding structure **25**, and it is not spread over two carbons as required by mechanisms A, C. From these data, together with the optical activity results, it is concluded that the mechanism outlined in mechanism B is correct.

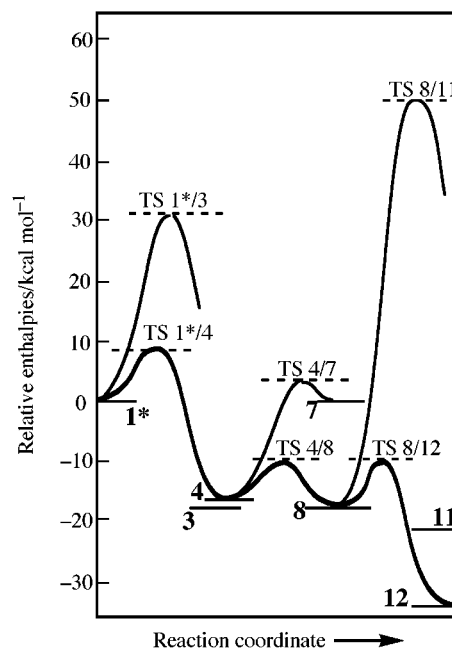The stereoselectivity of this rearrangement of nopol to

Fig. 1 A diagrammatic representation of the relative enthalpies of formation and transition state energies for the ions shown in Scheme 1. The structure numbers of the ions are shown in bold. Calculated transition state energies are shown for example as TS 1*/4 to represent the saddle point during rearrangement of ion **1*** to ion **4**. The energies are relative to the calculated enthalpy of formation for ion **1*** of 236 kcal mol^{−1}. To facilitate understanding, where the mechanisms diverge along two pathways, only the lower energy path is pursued along the reaction coordinate. The thick continuous curve reveals the lowest energy route from the nopol skeleton to that of fortesol *via* mechanism B of Scheme 1.

Table 1 Enthalpies of formation and transition state energies (kcal mol^{−1}) for ions shown in Fig. 1[a]

Ion X[+]	Ion Y[+]	X[+]→Y[+]
1* (0)	**3** (−18)	**1**→**3** (+30)
	4 (−17)	**1**→**4** (+7)
4 (−17)	**7** (−1)	**4**→**7** (+1)
		4→**8** (+6)
8 (−18)	**11** (−22)	**8**→**11** (+50)
	12 (−34)	**8**→**12** (−12)

[a] Columns 1, 2 give in parentheses the calculated enthalpies of formation for the ions as numbered and shown in Scheme 1. These enthalpies are relative to ion **1***, for which the calculated enthalpy of formation was 236 kcal mol^{−1}; the enthalpy of formation for the gegen ion (acetate) has not been included. The third column gives the calculated transition state energies in parentheses for transitions between the ions indicated, again relative to the enthalpy of formation of ion **1***.

fortesol is unexpected in a scheme as complex as that outlined in Scheme 1. To help resolve the complexity, the MOPAC PM3 method[19] was used to calculate enthalpies of formation for the various ions depicted in Scheme 1 and to calculate various transition state energies (saddle points) along the different reaction pathways. The calculations began with ion **1*** (Scheme 1), a primary carbocation formed by removal of the toluene-*p*-sulfonate group from the ester 1 (Scheme 1), although acetolysis of the toluene-*p*-sulfonate **1** probably proceeds through concerted departure of the toluene-*p*-sulfonate anion as the electrons of the double bond approach C-11 on the opposite side to the departing sulfonate. However, calculation of the enthalpies of formation of the ions **3**, **4** (Table 1) shows that they are very similar, but the transition state energy in proceeding from ion **1*** to **3** is much greater than that in going from **1*** to **4**. Thus, kinetically, mechanism B is preferred from the outset of reaction. Proceeding along the path of mechanism B, the next

possible divergence of ion **4** to either **7** or **8** is again controlled mostly by transition state energies in favour of the rearrangement of **4** to **8** (the rearrangement of **4** to **7** is also disfavoured in being endothermic). Completion of mechanism B requires only a small transition state energy in rearranging ion **8** into ion **12** (the product ion isolated in the solvolysis as its acetate). The outline of the salient energy changes is given in Fig. 1. Although the calculations are certainly subject to some error, the differences in both the transition state energies and the enthalpies of formation revealed for the two mechanisms A, B are so large as to give confidence in their significance.

The other product observed during acetolysis of nopyl toluene-*p*-sulfonate is 1-ethyl-4-(2-propyl)benzene (**26**), probably arising as a result of breaking the *gem*-dimethyl bridge.[1] This contrasts with the observation[20,21] that the parent hydrocarbon of **2** (brendane, **27**) can be converted easily into noradamantane **28**. Calculation of the enthalpies of formation

26

27   →   **28**
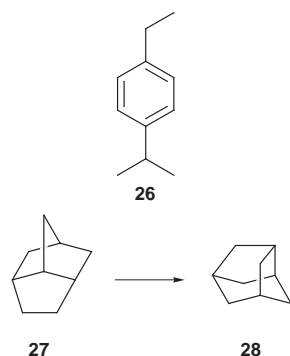
of these molecules confirms that such rearrangement is energetically favourable.[22] Therefore, an attempt was made to convert fortesyl acetate into dimethylnoradamantane or possibly methyladamantane by refluxing it in acetic acid containing 1 M H$_2$SO$_4$ at 118 °C for 24 hours. The small amount of decomposition of fortesyl acetate that occurred gave only black tar. The *gem*-dimethyl bridge is probably a weak link in the structure of both nopol and fortesol. It has been observed already that nopyl toluene-*p*-sulfonate can cleave at this centre, offering a ring-opening reaction as an alternative to formation of fortesol. Should any of the methylene bridges of brendane **27** open, the reaction would have to give a primary carbocation, whereas opening of the *gem*-dimethyl bridge of fortesol gives a much more stable tertiary carbocation. Accordingly, brendane reacts by rearrangement to the thermodynamically more favourable structure **28**.

Experimental

^{1}H NMR spectra were recorded in CDCl$_3$ on a Varian Gemini spectrometer at 300 MHz and ^{13}C spectra on the same spectrometer at 75 MHz with Me$_4$Si as internal standard. Infrared spectra were recorded on a Perkin-Elmer 1320 instrument, solid samples in Nujol and liquid samples as neat films. Reaction mixtures were monitored by GC with OV351 or FFAP capillary columns on a Dani 3800 chromatograph with flame ionisation detection. Mass spectra were measured on a Fisons Trio 1000 spectrometer, using electron ionisation at 70 volts.

Preparation of materials

Unlabelled nopol, $[a]^{24}$ −37°, was obtained commercially (Aldrich) and was used without further purification. It was converted into its toluene-*p*-sulfonate ester by conventional methods[1] and was subjected to acetolysis in acetic acid as described earlier.[1] The product was distilled to yield fortesyl

acetate, bp 70–74 °C/0.5 Torr† (lit.[1] bp 116 °C/12 Torr), which was pure by GC on an OV351 column. Reduction with lithium tetrahydroaluminate gave fortesol **2**, mp 72–75 °C (from diethyl ether; lit.[1] 75–77 °C), $[a]^{20}_D$ −48 °C (*c* = 5; EtOH).

[11,11-[2]H$_2$]-2-(2-Hydroxyethyl)-6,6-dimethylbicyclo[3.1.1]-hept-2-ene. Deuteriated nopol was prepared by using a known synthesis of nopol,[17] but in which paraformaldehyde was replaced by perdeuterioformaldehyde (99 atom%; Aldrich). The product had δ_H 5.34 (1H, s), 2.38 (1H, m), 2.25 (4H, m), 2.02 (2H, br d), 2.02 (1H, br s), 1.34 (3H, s), 1.15 (1H, d, J = 8.5 Hz), 0.85 (3H, s); the peak at δ 3.61 (2H, br t, J = 5.5 Hz) in the unlabelled nopol was absent. δ_C (CDCl$_3$) 144.9 (s, C-2), 119.0 (d, C-3), 45.7 (t, C-10), 40.8 (d, C-5)†, 40.0 (d, C-1)†, 37.8 (s, C-6), 31.6 (t, C-4)*, 31.3 (t, C-7)*, 26.2 (q, C-8) and 21.1 (q, C-9). The peak at δ 60.1 (t, C-11) in the unlabelled material is missing. Assignment of peaks marked † or * may be interchanged without affecting the labelling results.

[11,11-[2]H$_2$]-2-(6,6-Dimethylbicyclo[3.1.1]hept-2-en-2-yl)ethyl toluene-*p*-sulfonate 24. This was prepared as for the unlabelled ester by reaction of the unlabelled alcohol with toluene-*p*-sulfonyl chloride in pyridine.[1] MS, *m/z* 322 [M$^+$ + [2]H$_2$] (0.10%), 150 (27), 135 (28), 120 (28) 107 (100), 105 (29), 91 (48), 41 (24); δ_H (CDCl$_3$) 7.80 (2H, d, J = 8.0 Hz), 7.34 (2H, d, J = 8.0 Hz), 5.22 (1H, br s), 2.45 (3H, s), 2.33 (3H, m), 2.20 (1H, m), 2.07 (1H, m), 1.95 (1H, m), 0.76 (3H, s); the peak at δ 4.03 (2H, t, J = 7.1 Hz) in the unlabelled compound was absent; δ_C (CDCl$_3$) 144.7 (s, C-2), [142.7 (s), 133.5 (s), 129.8 (d), 127.9 (d) all toluene-*p*-sulfonate group], 119.7 (d, C-3), 45.6 (d, C-1), 40.7 (d, C-5), 38.0 (s, C-6), 35.9 (d, C-10), 31.5 (t, C-4)*, 31.3 (t, C-7)*, 26.1 (q, C-8), 21.6 (q, OTs), 21.0 (q, C-9). Assignments marked with an asterix could be interchanged.

Acetolysis of labelled nopyl toluene-*p*-sulfonate

Acetolysis of *[11,11-[2]H$_2$]-2-(6,6-dimethylbicyclo[3.1.1]hept-2-en-2-yl)ethyl toluene-p-sulfonate* **24** was carried out by refluxing the ester (4 g) at 118 °C for 100 h in acetic acid (50 mL), containing sodium acetate (1.3 g).[1] The cooled solution was poured into water (50 mL) and extracted with diethyl ether (3 × 20 mL). The combined extracts were washed with water, aqueous sodium hydrogen carbonate and water again before being dried (MgSO$_4$). Evaporation of the solvent gave a product (0.9 g), which was shown to be 85% pure. Mass and NMR spectra were obtained without further purification. The mass spectrum showed a molecular ion for fortesyl acetate at *m/z* 210; there was a small peak at *m/z* 208 representing some fortesyl acetate with no deuterium label. From the relative abundances of these two peaks, it was estimated that a minimum of 93% of the original deuterium label was still present. MS, *m/z* 210 (0.7%) [M$^+$]$_{labelled}$, 208 (0.05%) [M$^+$]$_{unlabelled}$, 168 (90), 150 (30), 98 (36), 84 (45), 83 (44), 43 (100), 41 (37); δ_C (CDCl$_3$) 170.1 (s, C=O), 92.6 (s, C-6), 59.2 (d, C-7), 49.1 (t, C-9), 48.9 (s, C-8), 45.0 (d, C-1), 37.9 (d, C-5), 37.6 (t, C-2), 37.2 (s, C-3), 23.7 (q, C-10), 22.0 (q, CH$_3$CO) and 21.6 (q, C-11). The signal for C-4 at δ 28.5 in the unlabelled acetate was absent in this labelled product. Reduction of the labelled fortesyl acetate with lithium tetrahydroaluminate gave the corresponding alcohol, for which the mass spectrum showed a molecular ion at *m/z* 168, corresponding to dideuteriated fortesol and there were no peaks at *m/z* 167, 166 corresponding to undeuteriated fortesol; this result supports the estimate of a minimum 93% retention of label during rearrangement. MS, *m/z* 168 (11.9%) [M$^+$], 109 (40), 98 (71), 97 (67), 96 (73), 95 (53), 85 (81), 84 (89), 83 (100), 43 (45), 41 (53); δ_C (CDCl$_3$) 86.0 (s, C-2), 60.2 (d, C-7), 49.6 (t, C-9), 48.9 (s, C-8), 44.9 (d, C-1), 41.4 (d, C-5), 38.8 (t, C-2), 38.3 (d, C-3), 23.5 (q, C-10) and 21.3 (q, C-11). The signal for C-4 at δ 27.7 in

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† 1 Torr = 133.322 Pa.

unlabelled fortesol was absent in this labelled material. The ^{1}H NMR spectrum showed that a multiplet at δ 1.88 corresponding to the equatorial hydrogen on C-4 was absent. The signal for the corresponding axial hydrogen at δ 1.35 was too close to the signal at δ 1.4 to be certain that it had disappeared, though the coupling pattern in this region had changed.

Calculation of enthalpies of formation and transition state energies

The enthalpies of formation for the various ions listed in Table 1 were calculated using the MOPAC semi-empirical quantum chemical approach at the PM3 level, which was developed for the purpose of accurately estimating molecular properties.[19] Similarly, the same programme was used to estimate transition state energies through calculation of 'saddle points', the stationary geometries for which total energy increases when atoms are displaced in any direction except one; at this point, only one of the force constants at the transition state energy is negative. Rather than quote the absolute calculated enthalpies, which are essentially gas phase values, enthalpies relative to that of the ion **1*** are given in Table 1. The enthalpy of formation for the positive ion **1*** was calculated to be 236 kcal mol^{-1}, very similar to typical measured values for such hydrocarbon gas phase ions, for which considerable amount of data is available.[23]

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