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# Stereochemistry, Part. 62 [1-3] -Acetolysis of Triterpenoid *p*-Toluenesulfonates, Part 2.[4]

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*Abstract* : Synthesis of *p*-toluenesulfonates **8b** and **9b** and of labelled analogs is described and previous assignements of proton NMR signals for quaternary methyl groups are confirmed. Acetolysis of these *p*-toluenesulfonates in the presence of NaOAc gave both substitution and elimination products. Substitution could be accounted for by bimolecular processes (SN2 on carbon, $S_AN$ on sulfur). Kinetics confirmed the intervention of bimolecular processes for **8b**. Elimination products came for a great part from intermediates formed by hydride and/or methyl shifts. All rearranged products could be explained by plain sigmatropic rearrangements or by contact ion pair rearrangements. Attention is drawn to the close resemblance between sigmatropic rearrangements and contact ion pair rearrangements.

## INTRODUCTION AND BACKGROUND

In spite of an enormous amount of work, both experimental and theoretical, the nature of the intermediates involved in the solvolysis of organic compounds R-X ( X being halide, sulfonate, carboxylate, *etc.*) remains obscure. In 1958, in order to interpret the special salt effect,[5] Winstein[6] distinguished intimate (contact) and solvent-separated ion pairs as *intermediates* on the way to the solvolysis products. He did not fully exclude the possibility that what he called intimate ion pairs might be *transition states* in intramolecular rearrangements, but he preferred to speak in terms of *intermediates*, *i.e.* of species in a potential well. All organic chemists followed suit, and the advent of the principle of conservation of orbital symetry in 1963 [7] does not seem to have changed their views on ion pairs. For instance, the rearrangement of an allylic carboxylate may be regarded as an intimate ion pair rearrangement or as a pericyclic sigmatropic rearrangement, and as early as 1955 Braude and Turner[8] had made a good case for what was not yet classified as a (3,3) sigmatropic rearrangement,[9] where an intimate ion pair had involved an allylic cation.

Another matter of discussion obtains, when the cation is actually a pair of equilibrating rearranging plain cations. A great amount of theoretical work has been devoted to calculating the shape and stability of carbenium ions,[10] but this does only apply to the gas phase. What happens in a condensed phase has been largely neglected, but for a few studies.[11] Theoretical calculations tell us what a cation such as cyclohexylium[12] may look like, but we have no assurance that this ion have any existence in a condensed phase, *i.e.* of the influence of the nature and the geometrical position of the anionic partner in a contact ion pair. A few important and recent experimental works imply that:

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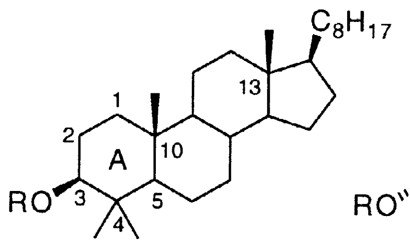

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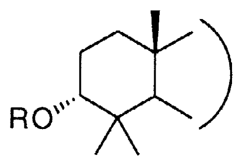

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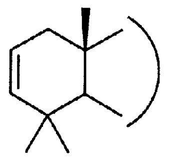

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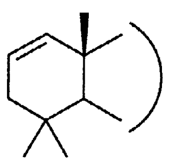

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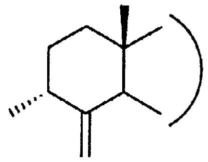

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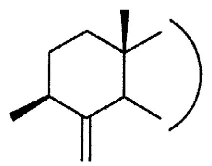

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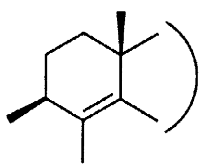

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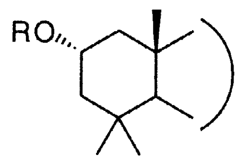

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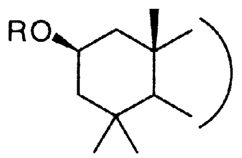
c R=Ac



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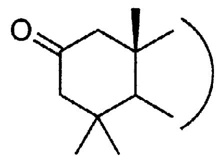

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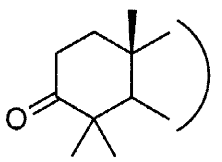

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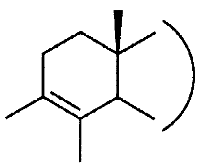

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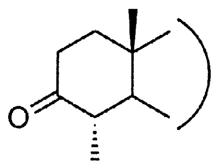

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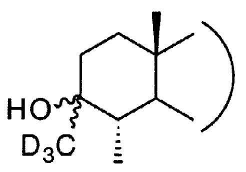


14a αOH
b βOH

a) tertiary aliphatic carbenium ions in solution are equilibrating between two ion pairs, with the anionic partner on one or the other face of the cation, so that the carbocation in solution is different from the carbocation in the gas phase;[13]

b) internal return, involving intimate ion pairs according to Winstein,[6] can play a very important role in the solvolysis of aliphatic secondary tosylates,[14] with no hint as to the true nature of the transformation, *via* ion pair or transition state;

c) a secondary aliphatic carbenium ion pair ($Me_2CH\text{-}CHMe^+$, $ArSO_3^-$) can automerize (by methyl migration) before being trapped by the solvent,[15] a fact which can be interpreted otherwise, *i.e.* automerization takes place through a sigmatropic rearrangement of the starting sulfonate ( see [11]).

It is hoped that the foregoing discussion makes it clear that the option between intimate ion pair or sigmatropic rearrangement is still an open question. Now, work from this laboratory has dealt for many years more or less consciously with this problem, and this paper reports our latest findings.

In previous papers[4,16] was reported a detailed study of the acetolysis of *p*-toluenesulfonates (tosylates) **1b** and **2b**. The conclusions drawn for this study were that each tosylate reacted *stereospecifically* through a sequence of contact ion pairs, with no leak from one sequence to the other. There were however a few points which deserved further examination.

a) Inspection of the deuterium content of the olefin **3** obtained from labelled tosylates **1b** and **2b** led to suspect hydride migrations from C-2 to C-3. This migration was within the limit of the experimental error in the case of labelled **1b**, but was not questionnable in the case of labelled **2b**, *i.e.* a 2β hydride shift to C-3.

b) A visible proof of this hydride migration was the presence of olefin **4** in the solvolysis products from **2b**, a presence which can only be rationalized by an ion pair, where the positive charge is at C-2, provided that olefin **3b** does not isomerize in the reaction medium; this isomerization was conclusively excluded.

c) The only apparent break in the separation of the two sequences of ion pairs was the presence of the olefin **5** in the products arising from **2b**. Whereas **5** is expected, and found indeed, as a 4α methyl migration product from **1b**, it is not expected from **2b**, where a 4β methyl migration is expected to give **6** and **7**, provided there is no solvent separated ion pair nor free carbenium ion. Indeed **6** and **7** are found, but **5** is found too. In order to account for the presence of **5**, it was suggested that **5** might arise from the very ion pair leading to **4**, by a double 3β hydride - 4α methyl migration.

Now it is possible to generate this ion pair by solvolysing tosylate **8b**. This paper reports the results obtained from the study of the acetolyses of tosylate **8b** and of its epimer **9b**, which was undertaken to clarify these points.

## RESULTS

### Synthesis of the starting materials

Alcohols **8a** and **9a** had already been described.[17] Preparation of tosylate **8b** from **8a** and tosyl chloride was straightforward, but this method could not be used with alcohol **9a**, as the reaction is very slow. As for tosylate **2b**[4] it turned out to be necessary to first make the *p*-toluene sulfinates (epimeric at sulfur) and then to oxidize the mixture with *m*-chloroperbenzoic acid to tosylate **9b**.

$LiAlD_4$ reduction of ketone **10** afforded alcohol **9a(2αD)**, that was converted to tosylate **9b(2αD)** as above. Tosylates **8b(3αD)** and **9b(3αD)** could be obtained from alcohols **8a(3αD)** and **9a(3αD)**.[19]

Interest in the fate of the 4α methyl group during acetolysis of tosylates **2b** and **8b** required the stereospecific synthesis of tosylate **8b(4αCD$_3$)**. This was performed by using Stork and Sofia's method[20] to make alcohol **1a**. This method eventually led to alcohol **1a(4αCD$_3$)**, which was transformed through ketones **11(4αCD$_3$)** and **10(4αCD$_3$)**[21] to alcohol **8a(4αCD$_3$)** and then to the tosylate **8b(4αCD$_3$)**. For the same reason it was important to understand the origin of the 3-methyl group in olefin **12**, a major product from **2b**[4]. This can be done by labeling one of the two methyl groups linked to the double bond and by inspecting the proton and $^{13}C$ NMR spectra. Olefin **12(3 CD$_3$)** was synthesized according to Beton, Halsall, Jones and Phillips[22] from ketone **13** and $CD_3MgI$, followed by dehydration of the epimeric alcohols **14**.

The foregoing preparation of compounds containing a fully deuteriated 4α methyl group gave an opportunity to check the assignments of NMR signals for ring A methyl groups proposed in 1966.[23] The correctness of one of these assignments had already been confirmed by Rosenthal.[24] The results from the present study confirm the previous assignments (see experimental section, Table 5).

## Acetolysis study

### Products from **9b**

Acetolysis of 0.047 molar solution of tosylate **9b** in boiling acetic acid containing sodium acetate (0.44 molar) for 2.5 h gave an acetate fraction and an olefin fraction. The percentages of the products can be found in Table 1. Whereas the isolation of acetate **8c** was straightforward, the separation of olefins **3**, **4** and **5**, specially of **4** and **5** was difficult (chromatography over $SiO_2$-$AgNO_3$), but the composition of the various chromatographic fractions could be readily estimated from the proton NMR spectra, by using authentic samples from the previous study.[4]

### Products from **8b**

Under the same conditions, acetolysis for 1.5 h of tosylate **8b** again gave an acetate fraction and an olefin fraction. The olefins were separated as above. The acetates **8c** and **9c** were saponified and the alcohols **8a** and **9a** separated by chromatography. The percentages of the products can be found in Table 1.

**Table 1**

Percentages of products formed in the acetolysis of tosylates **8b** and **9b**

| Substrate | Elimination products | | | | | | Substitution products | |
|---|---|---|---|---|---|---|---|---|
| | **3** | **4** | **5** | **6** | **7** | **12** | **8c** | **9c** |
| 2α-OTs **8b** | 55.6±0.2 | 24.8±0.2 | 1.2±0.2 | 0.5±0.1 | 1.9±0.5 | 2.4±0.5 | 1.8±0.2 | 9.2±0.2 |
| 2β-OTs **9b** | 72.1±0.2 | 12.2±0.1 | 0.6±0.1 | 0.2±0.1 | 1.0±0.2 | | 10.9±0.2 | |

### Products from monodeuteriated tosylates

In order to gain some insight about the stereochemistry of the elimination reaction leading to the olefin **3**, deuteriated analogs **8b(D)** and **9b(D)** of tosylates **8b**-**9b** were acetolysed under the same conditions. The results can be found in Table 2 and come from NMR data based on:

a) a comparison between the areas of the 0.6 ppm peak of the 13β methyl group, which is well separated from the rest of the aliphatic protons, and of the signal of the olefinic protons; this gives the number of olefinic protons;

b) a comparison between the areas of the signal of the H-2 proton at 5.43 ppm and of the signal of the H-3 proton at 5.35 ppm. As shown for tosylate **8b(3αD)**, the NMR data are fairly reproducible (see Table 2).

### Products from trideuteriated tosylate **8b(4αCD$_3$)**

With a view of gaining a knowledge of the extent of 4α methyl group migration, acetolysis of tosylate **8b(4αCD$_3$)** was performed under the same conditions. Olefins **7 and 12(4CD$_3$)**, **3-4(4αCD$_3$)**, **5(3αCD$_3$)** and **6(4CD$_2$)** were obtained and NMR spectra of olefins **12(4CD$_3$)** and **5 and 6 (4CD$_2$)** inspected for the disappearance of signals of $CH_3$ or $CH_2$=C groups. The presence of olefin **5(3αCD$_3$)**, involving a 4α $CD_3$ migration was confirmed (see experimental section). On the other hand olefin **12(4CD$_3$)** within experimental error (proton and $^{13}C$ NMR spectra) was different from olefin **12(3CD$_3$)** synthesized above. This is taken to mean that olefin **12**, formed from tosylate **8b**, is solely formed by 4β methyl migration.

### Kinetics

In order to compare the rates of acetolysis of tosylates **1b**-**2b** and **8b**-**9b**, a kinetic study was undertaken using proton NMR spectroscopy. In 99,99% $CD_3CO_2D$ (0.01 molar in $CD_3CO_2Na$) it is possible to distinguish the aromatic protons *ortho* to $SO_2$ (7.7 to 7.9 ppm), the *meta* protons (7.2 to 7.5 ppm) and the $CH_3$-Ar protons (2.4 to 2.5 ppm) in the tosylate esters from those in sodium tosylate (a similar technique was used by Paradisi and Bunnett[14] in oxygen scrambling experiments run in $CF_3CO_2H$, using only the $CH_3$-Ar proton signal to follow the reaction). By taking advantage of these features, it is possible to run an acetolysis in a NMR tube with only 2 to 3 mg of tosylate ester and to acquire 3 sets of data in a single experiment. The rate constants presented in Table 3 are average values over 3 sets of data.

**Table 2**

Percentages of deuteriated and undeuteriated 4,4-Dimethyl-5α-cholest-2-enes in the acetolysis products of tosylates **8b(3αD)**, **9b(3αD)** and **9b(2αD)**

| Substrate | Percentage (±3)of D in the tosylate | Percentage (±5) of | | | Yield % (±2) |
|---|---|---|---|---|---|
| | | 3 | 3(3D) | 3(2D) | 3+3(3D)+3(2D) |
| 2α-OTs 3αD **8b(3αD)** | 87 | 27 | 53 | 20 | 56.5 |
| | | 28 | 56 | 16 | |
| | | 23 | 57 | 18 | |
| 2β-OTs 3αD **9b(3αD)** | 97 | 15 | 74 | 11 | 71.9 |
| 2β-OTs 2αD **9b(2αD)** | 98 | 08 | | 92 | 72.6 |

In order to calibrate these experiments with the previous ones, followed by acidimetric titration[4], acetolysis of tosylate **1b** was also followed by NMR. Barring solvent isotope effect, it can be seen from Table 3 that there is a good agreement between the previous and the present data.

**Table 3**

Rate constants for the acetolysis of tosylates **1b**, **2b**, **8b** and **9b**

| Substrate | Unimolecular Process $k_1 \times 10^6\ s^{-1}$ | Bimolecular Process $k_2 \times 10^6\ mol.s^{-1}.l^{-1}$ | Temperature °C | Concentration (mMolar) |
|---|---|---|---|---|
| 3β-OTs **1b** | 84.1 ± 8.7 | | 71 | 7.65 |
| | 80.2 ± 0.6 [a] | | 70 | 8.94 |
| 3α-OTs **2b** | 199 ± 7 [a] | | 70 | 1.8 |
| 2α-OTs **8b** | 8.9 ± 0.2 | 55.6 ± 2.2 | 60 | 8.56 |
| | 55 ±1.1 | 346 ± 14 | 71 | 8.74 |
| | 150 ± 3.0 | 917 ± 37 | 80 | 9.23 |
| 2β-OTs **9b** | 1150 ± 150 | | 71 | 7.3 |

a) Ref.4

Acetolysis of tosylate **9b** was beset with two difficulties, poor solubility of the ester in $CD_3CO_2D$ and fast reaction. Assuming that the final part of the reaction is overwhelmingly unimolecular, a rate constant of $1.15\times10^{-3}$ was calculated at 71°C, which certainly is very approximative. In the case of tosylate **8b**, there is definitely a bimolecular reaction superimposed on the unimolecular one. The activation parameters are presented in Table 4. Comparison of the unimolecular processes in tosylates **1b**, **2b**, and **8b** shows that **8b** exhibits higher activation enthalpy and entropy. Undoubtedly intramolecular assistance shows up in the data concerning **1b** and **2b**, but does not in those concerning **8b**.

**Table 4**

Activation parameters for the acetolysis of tosylates **1b**, **2b** and **8b**

| Substrate | Type of Process | $\Delta H^{\pi}$ kJ/mol | $\Delta S^{\pi}$ J/mol.K |
|---|---|---|---|
| 3β-OTs **1b** | Unimolecular [a)] | 113.7 ± 2.5 | 8.4 ± 6.3 |
| 3α-OTs **2b** | Unimolecular [a)] | 110.8 ± 3.8 | 1.3 ± 2.5 |
| 2α-OTs **8b** | Unimolecular | 136.4 ± 3 | 67.4 ± 10 |
| | Bimolecular | 135.3 ± 6 | 79.3 ± 20 |

a) Ref.4

## DISCUSSION

In the following paragraphs, all reactions are depicted by using formulae of covalent tosylates for sake of simplicity, but formulae of intimate ion pairs could be used as well. As expected, acetolysis of **8b** and **9b** shows much more unrearranged products (91.4% and 95.4% respectively) than acetolysis of **1b** and **2b** (8% and 26.5% respectively).[4] What is perhaps unexpected is the sizeable amount of rearranged products arising from tosylates, which would be regarded as "normal", specially in the case of **8b**, the more so if one takes into account the percentage of olefins **3** and **4** formed after hydride shift (see below).

Tosylate **9b**

The case of the tosylate **9b** is simpler and the discussion, which is summarized in Scheme 1, can first begin with it. The NMR signal of the H-2 proton in **9b** is a regular quintet (J=3.7Hz), showing that the predominant conformation of the ring A is the chair **15**, possibly slightly distorded in a symetrical way by the 3 diaxial interactions on the β face.

Olefinic products

Olefin **3** can be formed through *cis* (concerted E1) and/or *trans* (E2) eliminations or through 3α hydride migration to C-2 (and 2β OTs migration to C-3), *i.e.* **15** → **16** or **17**, followed by elimination.

Table 2 shows that:

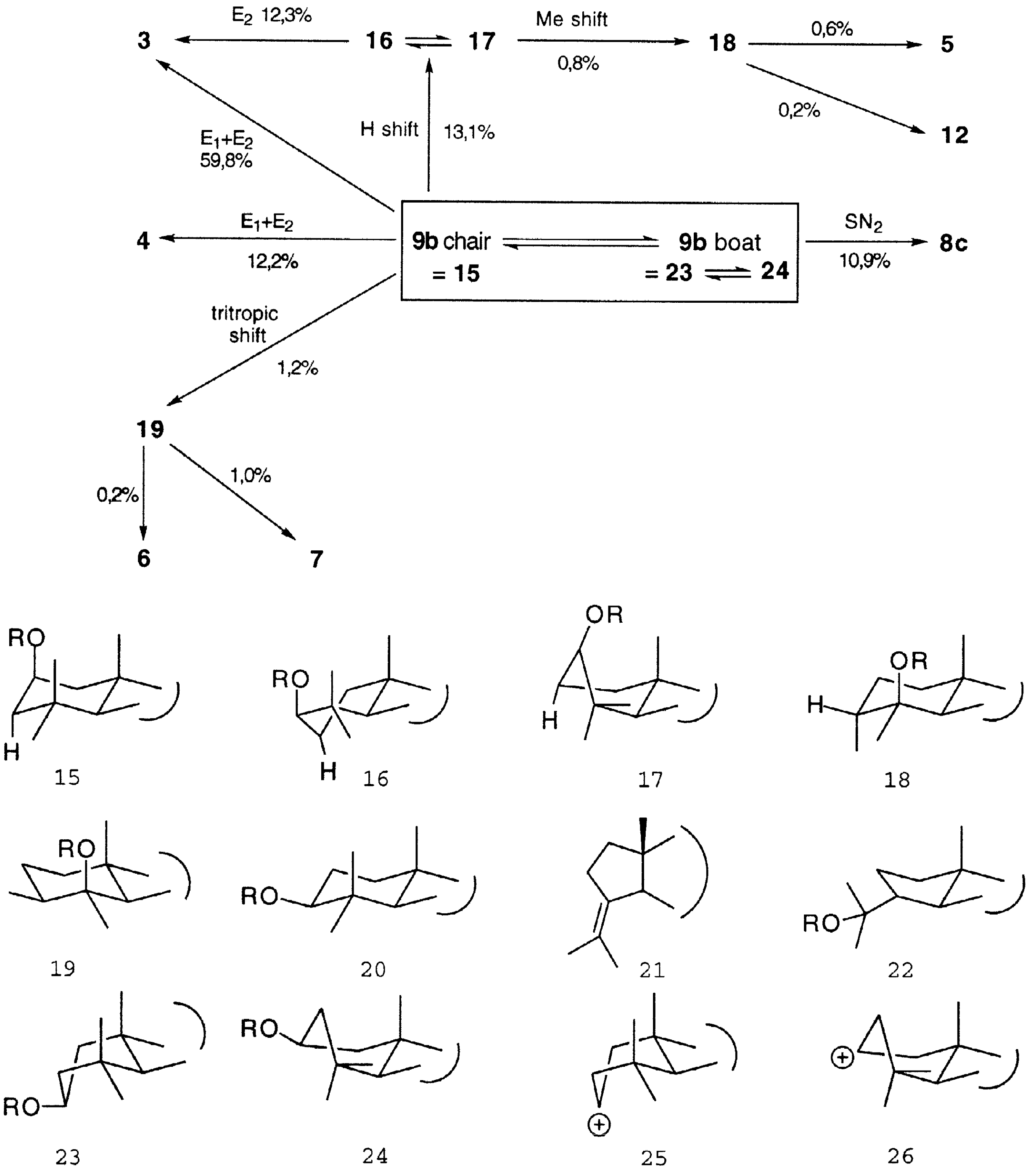
a) **9b(2αD)** gives 1.4% of **3** of undetermined origin (2% x 72.1%), 66.8% of **3(2D)** through *trans* and *cis* eliminations (92% x 72.6%) and 4.4% of **3** through hydride shift from C-3, followed by *trans* elimination (8% x 72.6% - 1.4%);

b) **9b(3αD)** gives 2.2% of **3** of undetermined origin (3% x 72.1%), 8.6% of **3** through *trans* elimination (15% x 71.9% - 2.2%), 53.2% of **3(3D)** through *cis* elimination (74% x 71.9%) and 7.9% of **3(2D)** through deuteride shift from C-3 followed by elimination (11% x 71.9%).

Olefin **4** can be formed in the same way as **3**, except that it is not possible to know the extent of hydride shift from C-1α (see below for the case of **8b**).

Formula **17**, which is **1b** in a boat conformation, explains the small amount of olefin **5**; a 4α methyl-shift to C-3 would afford **18**, which is the precursor of both **5** and **12**, olefins which were found in 10% and 3% yield respectively in acetolysis of **1b**.[4] **12** may have escaped detection (0.2% based on 0.6% of **5**). In this case 0.8% of **18** could be formed from **17** and lead to **5** and **12**, and 12.3% of **15** (7.9% + 4.4%) would lead to **3** and **3(2D)** (barring isotope effects), through **17**; the total amount of **9b** (**15**) undergoing a 3α hydride shift would be 13.1%.

**Scheme 1**



**15-20** and **22-24** R=Ts

Such hydride shifts have long been ignored in solvolysis studies of "normal" sulfonates,[25] but are now taken into account[26] leaving some doubts about the interpretation of published kinetic isotope effects.

There are traces of olefins **6** and **7**, that would not be expected to appear in the solvolysis, unless is called into play a tritropic rearrangement:[27] **15** → **19**; of course **19** is the precursor of **6** and **7**. This tritropic rearrangement has not been detected in the acetolysis of **1b**, but this is no surprise, as it occurs to such a low extent (1.2% from **9b**), and it was shown earlier that **9b** was formed from **1b** to the extent of 1% only.[4]

Finally it must be emphasized that there is no product arising from a rearrangement of **1b** with ring A in the chair conformation, *i.e.* **20**, as there is no trace of ring A contracted products such as **21**, which are characteristic of the solvolysis of **1b** in the chair conformation[4,28] viz. **20** → **22** → **21**, though these products were purposedly looked for.

Substitution products

Although kinetics could not give evidence for the occurence of bimolecular processes (see above), there are certainly some, as shown by the *trans*, assumedly bimolecular, eliminations leading to **3** and **4**. The formation of the acetate **8c** with inversion of configuration, without any detectable trace of epimeric acetate **9c**, also is in favour of a SN2 process. A SN1 process calling into play a free carbenium ion can be dismissed under the present conditions (acetic acid has a dielectric constant as 6.3 at 25°C).[29] A SN1 process, through a solvent-separated ion pair, can be excluded on the following basis.

In the chair conformation **15** of **9b**, for the SN2 reaction as well as for ion pair formation, the axial C-2β-O bond must be tilted towards the 4β and 10β methyl groups. This is most improbable because it increases the non bonded interactions, so that these transformations must occur on boat conformations such as **23** or **24**. The corresponding conformations of the carbenium ion, **25** and **26**, used here to denote the solvent separated ion pair for sake of simplicity, are either accessible from both faces (**26**) or from the β face only (**25**), and should give a mixture of acetates, with **9c** predominating. As only **8c** is obtained, the reaction is SN2 and there is no solvent separated ion pair.[30]

To summarize this part of the discussion, the products of acetolysis of **9b** can be explained by E2 and SN2 processes (**3**, **4**, **8c**), by stereospecific E1 processes (**3**, **4**) and by stereospecific rearrangements, either through contact ion pairs or through pericyclic reactions, dyotropic (**3**, **5**, perhaps **25a**) and tritropic (**6**, **7**). The dyotropic rearrangements only call up the boat conformations **16** or **17** of tosylate **1b** and not the conformation **20**. There is no need to call up tosylates **2b**, **8b** or their transformation products.

Tosylate **8b**

In this case, the discussion is summarized in Scheme 2. The NMR signal of the H-2 proton in **8b** is a regular triplet of triplets ($J_1$=11.4 Hz; $J_2$=4.1 Hz), again showing that the predominant conformation of ring A is a slightly distorded chair **27**.

Olefinic products

Olefin **3** can, as from **9b**, be formed by *cis* (concerted E1) and/or *trans* (E2) eliminations or by hydride shifts followed by elimination.

Table 3 shows that:

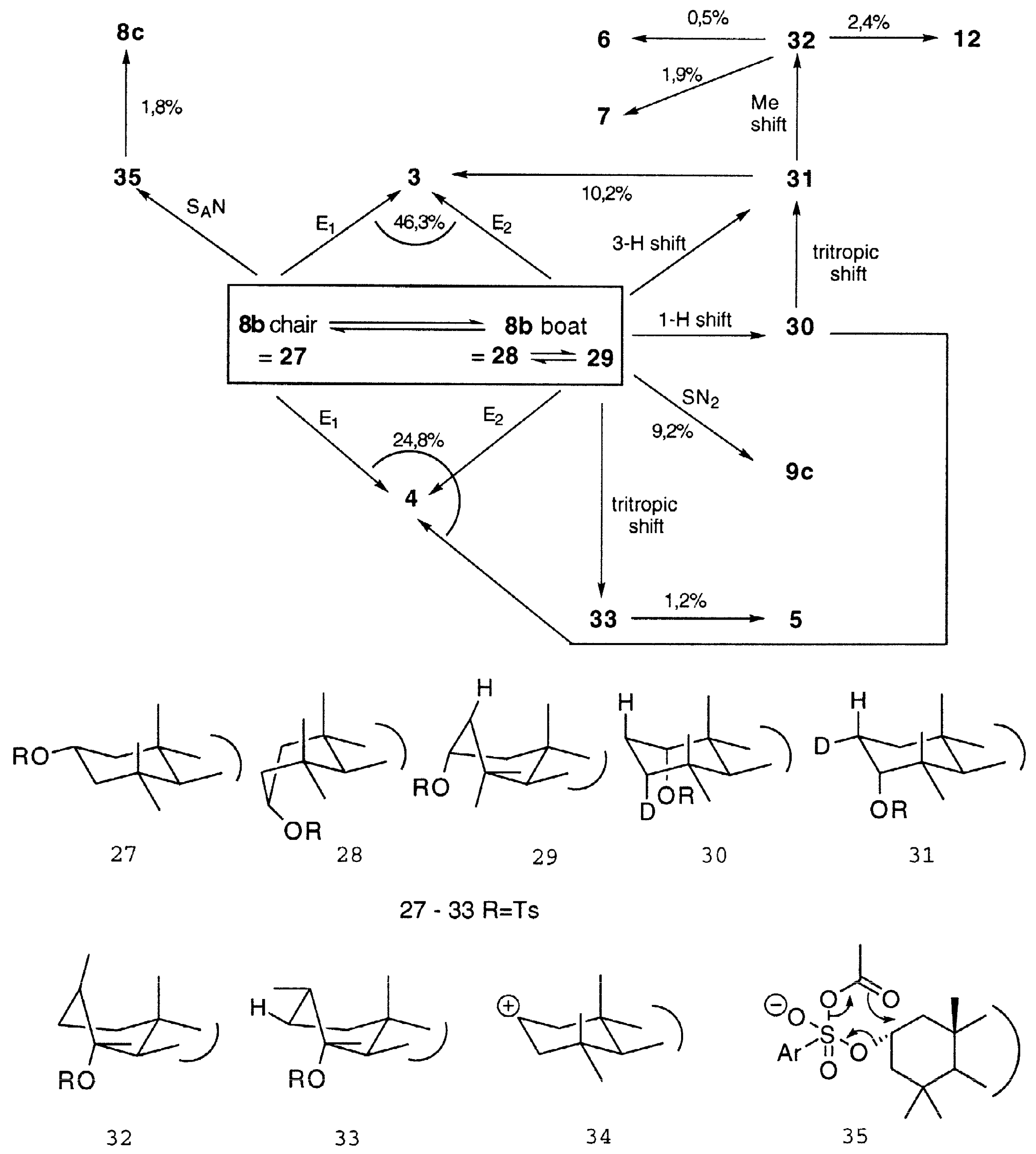
a) **8b(3αD)** gives 7.2% of **3** of undetermined origin (13% x 55.6%), 7.5% of **3** through a *cis* elimination (26% x 56.5% - 7.2%), presumably from the chair conformation **27**, and 31.6% of **3(3D)** through a *trans* elimination (56% x 56.5%), necessarily from the boat conformations **28** or **29**;

b) **8b(3αD)** gives 10.2% of **3(2D)** (18% x 56.5%) by a deuteride shift to C-2, but **3(2D)** cannot arise from a plain dyotropic shift, as D and OTs are *cis* to each other in **8b(3αD)**. Nevertheless the presence of **3(2D)** can be explained in the following way:

i) a 1β hydride shift to C-2 (and migration of 2α OTs to C-1) from **28(3αD)** to afford **30**;
ii) a tritropic rearrangement from **30** to **31**, with a deuteride shift from 3α to 2α;
iii) a trans elimination to **3(2D)**.

This explanation implies that some of the olefin **4** may come from **30**, and not directly from **27** or **28**. There is no reason why a 1-2 shift should only take place toward C-3 and not toward C-1. This experiment tends to prove that 1-2 shifts also take place toward C-1.

**Scheme 2**



Olefin **4** can be formed through *cis* and *trans* eliminations, not only from **28**, but also from **30** after a hydride shift.

The boat conformations **28** and **29** are also well suited for a 3β hydride shift to C-2 giving **31(2αH)**, *i.e.* **2b** in the chair conformation. Acetolysis of **2b** is known to afford 7%, 15% and 46.5% of **6**, **7** and **12** respectively through **32**.[4] These proportions are approximately reproduced in the values of Table 1, taking into account the necessarily higher errors made on such small values.

The presence of olefin **5** in the reaction products confirms the earlier suggestion[4] that, in the acetolysis of **2b**, the 1% of **5** come indeed from **8b**, since **8b** generates 1.2% of **5**. Again this can be explained by a tritropic rearrangement **29** → **33**. Of course **33** is the precursor of **5** but not of **12**, as experiments with **8b(4αCD$_3$)** reported above exclude this possibility.

Substitution products

Table 2 shows that **8b** leads to 1.8% of **8c** (retention of configuration) and to 9.2% of **9c** (inversion). If the reaction takes place through a solvent separated ion pair (again denoted by the carbenium ion for the sake of simplicity), there is no reason to call up boat conformations such as **25** and **26**. The chair conformation **34** shows that attack on the α face is easier (because of the 4β and the 10β methyl groups) and one expects more **8c** and less **9c**. It is obviously not the case and this disposes of the solvent-separated ion pair.

Since the kinetic study shows that there are bimolecular processes, it is reasonnable to assume that formation of acetate **9c** is one of these, another being the previous mentionned *trans* elimination, the SN2 process taking place on **28** or **29**.[30] Finally there remains to be explained the 1.8% formation of acetate **8c** with retention of configuration.

It seems appropriate to suggest here two possible bimolecular processes, which could account for the formation of **8c** from **8b**. Both begin with attack of $ROSO_2Ar$ by $AcO^-$ on sulphur. This bimolecular process has ben encountered several times with alkaline alkoxides[31] and might become visible here because the Walden inversion on C-2 is hampered by the presence of the 4β and 10β methyl groups of **27**. In the present case, this process would generate **35**. This could then undergo a pericyclic rearrangement to **8c** and $TsO^-$ as shown, or a fragmentation to $RO^-$ and TsOAc, which would further react to **8c** and $TsO^-$ . On thermodynamic grounds, the first process seems much more likely.[32]

To summarize this part of the discussion, the products of acetolysis of **8b** can be explained by bimolecular processes (E2, SN2, $S_AN$ on sulphur, for **3**, **4**, **9c**, **8c** respectively), by stereospecific rearrangements, either through contact ion pairs or through pericyclic reactions, dyotropic (**4**, **6**, **7**, **12**) and tritropic (**3**, **5**). The rearrangements invoked to explain the acetolysis products of **2b** are confirmed, namely the intermediacy of tosylate **8b** or of the corresponding contact ion pair. There is no need to call upon tosylates **1b**, **9b** or their transformation products.

## CONCLUDING REMARKS

The experiments described in the present and the two preceeding papers[4,16] show that acetolysis of secondary tosylates *in a buffered, if not basic, medium (excess sodium acetate)* proceeds along a wide variety of reactions. If one is prepared to accept the intermediacy of **35**, then there are bimolecular processes (SN2, $S_AN$ on sulphur, E2) and stereospecific unimolecular ones (concerted 6-centers elimination, dyotropic and tritropic rearrangements), even with a tosylate as "normal" as **8b**. Isomeric tosylates, in which the C-O bonds are on the same face of the molecular skeleton, *i.e.* **1b** and **9b** or **2b** and **8b**, share some reactions in common; isomeric tosylates, in which the C-O bonds are on different faces of the molecular skeleton, *i.e.* **1b** and **2b** or **8b** and **9b**, have no reaction in common. These facts are hard to reconcile with solvent separated ion pairs. A decision as to the nature of the pathways followed in the rearrangements cannot be reached from the present data. It should only be emphasized that:

a) these rearrangements exhibit both stereospecificity and unimolecularity (linked with concertedness), which are both criteria of sigmatropic reactions;

b) the decision amounts to distinguishing between a transition state between two isomeric tosylates and a transition state between two isomeric contact ion pairs i.e. to assessing the extent of ionic character of the C-O bond in a solvated tosylate and in a solvated contact ion pair. The extent of ionic character probably varies with substrate and solvent, and there may be a continuum of possible transition states, but the likelihood of sigmatropic reactions cannot be underestimated. This would rationalize the automerization of 3-methyl-2-butyl arenesulfonates[15] mentioned in the introduction.

## EXPERIMENTAL SECTION

The usual work up and the presentation of most spectroscopic data are outlined in ref.[16] All rotations are recorded in $CHCl_3$ solution. Further particulars for NMR are qua for quartet, qui for quintet, all spectra recorded in $CDCl_3$ ($CHCl_3$ for deuterium) at 200 MHz for proton, at 50.29 MHz for carbon and 61.4 MHz for deuterium. Microanalyses were performed by the Central Analytical Service of CNRS and the Microanalytical Service of P. et M. Curie University.

### Starting materials

#### Tosylate 8b

To a solution of alcohol **8a**[17] (0.7g; 1.7 mmol) in pyridine (10 ml) was added dropwise at 0°C a solution of *p*-toluenesulfonyl chloride (1.5g; 7 mmol) in pyridine (5 ml). After 24h the mixture was worked up to afford a crude product (0.89g; 93%), which was purified by thin layer chromatography, mp 94-95°C, Found C, 75.78; H, 10.12; S, 5.78%; $C_{36}H_{58}O_3S$ requires C, 75.74; H, 10.24; S, 5.62%; $\delta_H$ 2.40 (s., 3H, *para* $CH_3$), 4.69 (tt, $J_1$=11.4, $J_2$=4.1 Hz, 2-**H**), 7.32 (d., J=8.0 Hz, 2**H** *meta*), 7.78(d., J=8.0 Hz, 2**H** *ortho*), $\delta_C$ 79.3 (2-C), 33.32 (4α-$CH_3$).

#### Tosylate 9b

To a solution of alcohol **9a**[18] (1.3g; 3.1 mmol) and pyridine (0.5 ml) in anhydrous ether (20 ml) was added dropwise at 0°C *p*-toluenesulfinyl chloride (1.3 ml) and the mixture was stirred for 2 h at room temperature. Usual work up gave a crude product, which was flash chromatographed over $SiO_2$. The mixture of epimeric *p*-toluene sulphinates was separated as an oil (1.39g; 80%), $\delta_H$ 2.5 (s., 3H, *para* $CH_3$), 4.7 (qui., J=3.8 Hz, 2-**H**), 7.3 (d., J=8.0 Hz, 2**H** *meta*), 7.6 (d., J=8.0 Hz, 2**H** *ortho*).

To a solution of the epimeric sulphinates (1.4g; 2.5 mmol) in $CH_2Cl_2$ (22.5 ml) was added at 0°C a solution of m.chloroperbenzoic acid (1.0g; 5.8 mmol) in $CH_2Cl_2$ (22.5 ml). After stirring for 24 h, the usual work up gave a product (1.37g; 95%) purified by thin layer chromatography, mp 104-107°C, Found C, 75.70;

H, 10.17; S, 5.48%; $C_{36}H_{58}O_3S$ requires C, 75.74; H, 10.24; S, 5.62%; $\delta_H$ 2.40 (s., 3H,*para* $CH_3$), 4.80 (qui., J=3.7 Hz, 2-**H**), 7.31 (d., J=8.0 Hz, **2H** *meta*), 7.61(d., J=8.0 Hz, **2H** *ortho*), $\delta_C$ 81.82 (2-**C**).

### 2α-Deuterio-4,4-dimethyl-5α-cholestan-2β-ol 9a(2αD)

A solution of ketone **10** (1.8g; 4.3 mmol) in anhydrous ether (450 ml) was refluxed for 3h with $LiAlD_4$ (0.7g; 16.7 mmol). After usual work up, the crude product was chromatographed over $SiO_2$ to afford alcohol **9a(2αD)** (1.66g; 92%), mp 140-141 °C, $[\alpha]_D$ +36 (*c* 0.34) lit.[18] mp 140-141°C, $[\alpha]_D$ +37; $\delta_H$: the signal at 4.13 vanished, $\delta_C$ 67.7 (t., J=20 Hz, 2-**C**).

**Tosylate 9b(2αD)** mp 105-107°C; $\delta_H$: the signal at 4.70 vanished.

### Mono- and dideuterio-4,4-dimethyl-5α-cholestan-2β-ols 9a(3αD) (or $d_1$) and 9a(2α,3αD2) (or $d_2$)

Reduction of 2,3β-epoxy-4,4-dimethyl-5α-cholestane according to ref.[18] gave a mixture of alcohols **9a(3αD)** and **9a(2α,3α$D_2$)** (along with deuteriated alcohol **1a**), mp 138-140°C (lit.[18] mp 140-141°C), $\delta_H$ 4.12 (qua., J=5Hz, 2-**H**, 49% $\mathbf{d_1}$, 51% $\mathbf{d_2}$), $\delta_D$ 1.37 (3-**D**), 4.06 (2-**D**, 48% $\mathbf{d_1}$, 52% $\mathbf{d_2}$), $\delta_C$ 68.08 (s., 2-**C** of $\mathbf{d_1}$), 67.62 (t., J=20Hz, 2-**C** of $\mathbf{d_2}$), 46,63 (t., J=18Hz, 3-**C** of $\mathbf{d_1}$), 46.50 (t., J=20Hz, 3-**C** of $\mathbf{d_2}$).

### 3α-Deuterio-4,4-dimethyl-5α-cholestan-2-one 10(3αD)

A solution of alcohols **9a(3αD)** and **9a(2α,3α$D_2$)** (0.72g; 1.7 mmol) in acetone (10 ml) was treated at 0°C for 15 mn with Jones's reagent[33]. Usual work up gave ketone **10(3αD)** (0.66g; 92%), mp 129-131°C (lit.[18] mp 124-125°C), $\delta_H$ 2.10 (s., 3-**H**), $\delta_C$ 212 (2-**C**).

### 3α-Deuterio-4,4-dimethyl-5α-cholestan-2β-ol 9a(3αD)

To a solution of ketone **10(3αD)** (1.2g; 2.9 mmol) in anhydrous THF (12 ml) was added at -75°C *L-Selectride* ($LiBH(s\text{-}Bu)_3$, 3.6 ml; 16 mmol). After 2h the reaction mixture was neutralized by 5% HCl. Usual work up gave a crude product, chromatographed over $SiO_2$ to afford alcohol **9a(3αD)** (1.15g; 95%), mp 138-140°C, $[\alpha]_D$ +33 (*c* 0.85) (lit.[18] mp 140-141°C, $[\alpha]_D$ +34; $\delta_H$ 4.18 (qua., J=5.0Hz, 2-**H**)), $\delta_C$ 68.15 (2-**C**).

**Tosylate 9b(3αD)** mp 105-107°C; $\delta_H$ 4.80 (qua., J=3.7Hz, 2-**H**), $\delta_C$ 81.15 (2-**C**).

### 3α-Deuterio-4,4-dimethyl-5α-cholestan-2α-ol 8a(3αD)

To anhydrous liquid $NH_3$ (65 ml) were added simultaneously a solution of ketone **10(3αD)** (195mg; 0.47 mmol) in a mixture of EtOH (1 ml), t-BuOH (1 ml) and THF (8 ml) and sodium pellets (0.11g; 4.7 mmol). The mixture was stirred for another 30 mn and worked up to afford a crude product, which was chromatographed over $SiO_2$. Along with some epimeric alcohol **9a(3αD)** alcohol **8a(3αD)** was obtained (98mg; 50 %) mp 123-125°C (lit.[17] mp 124-127°C), $\delta_H$ 3.80 (dt., $J_1$=10.8, $J_2$=4.0Hz, 2-**H**), $\delta_C$ 65.58 (2-**C**), 52 (t., J=19Hz, 3-**C**).

**Tosylate 8b(3αD)** mp 93-95°C, $\delta_H$ 4.62(dt., $J_1$=11.0, $J_2$=4.2Hz, 2-**H**), $\delta_C$ 79.25 (2-**C**).

### 4α-Trideuteriomethyl-4β-methyl-5α-cholestan-3β-ol 1a(4α$CD_3$)

Treatment, according to Julia and Lavaux [34], of cholest-4-ene-3-one (6.5g; 17 mmol) and $CD_3I$(3.0g; 20.7 mmol) gave **4α-trideuteriomethyl-cholest-4-ene-3-one** (4.34g; 64%), mp 97-99°C (lit.[34] mp 101-102°C), $[\alpha]_D$ +85 (*c* 0.98), Found C, 83.43; H, 11.43%, $C_{28}H_{43}D_3O$ requires C, 83.72; H, 11.54%, $\delta_C$ 199 (3-**C**), 164.0 (5-**C**), 127.8 (4-**C**).

A solution of this ketone (4.74g; 11.8 mmol) in anhydrous ether (190 ml) was added to a solution of $LiAlH_4$ (1.9g; 4.50 mmol) in anhydrous ether (150 ml) and stirred for 1h at room temperature. Usual work up and chromatography over $SiO_2$ gave, along with the epimeric alcohol, **4α-trideuteriomethyl-cholest-4-ene-3β-ol** (3.67 g; 77 %), mp 149°C (lit.[34] mp 151-152°C), $[\alpha]_D$ +54 (*c* 2.01), Found C, 83.37; H, 11.68 %, $C_{28}H_{45}D_3O$ requires C, 83.30; H, 11.98; $\delta_H$ 3.98 (t., J=6.5Hz, 3-**H**), $\delta_C$ 141.5 (5-**C**), 125.8 (4-**C**), 71.4 (3-**C**).

To a solution of this alcohol (0.3g; 0.74 mmol) in $CH_2Cl_2$ (5 ml) were added first a solution of $Et_3N$ (0.5 ml) and of 4-dimethylamino-pyridine (3mg) in $CH_2Cl_2$ (4.5 ml), then after 10 mn a solution of $Me_2SiCl$-$CH_2Br$ (0.14g; 0.75 mmol) in $CH_2Cl_2$ (5 ml). The mixture was stirred for 1h and worked up as usual to afford, after filtration over $SiO_2$, the **silyl ether** (0.4g; 93 %), mp 87-89°C, $[\alpha]_D$ +36 (*c* 1.48). Found C, 66.92; H, 10.13 %, $C_{31}H_{52}D_3OSiBr$ requires C, 67.11; H, 10.05, $\delta_H$ 0.30 (6H, s., **Me**$_2$Si), 2.50 (2H, s., SiC**H**$_2$Br), 4.12 (t., J=7Hz, 3-**H**), $\delta_C$ 2.30 (**Me**$_2$Si), 73.0 (3-**C**), 15.8 (4-**C**), 141.0 (5-**C**).

A solution of this silyl ether (0.9g; 1.6 mmol), of $NaBH_3CN$ (0.2g; 3.2 mmol), of azobis isobutyronitrile (26mg; 0.16 mmol) and $ClSnBu_3$ (0.52g; 3.2 mmol) in t-BuOH (80 ml) was refluxed for 6 h. Usual work up and chromatography over $SiO_2$ gave the **cyclic silyl ether** (0.46g; 60%), mp 135-137°C, $[\alpha]_D$ +22 (*c* 4.29), Found C, 77.94; H, 11.74%, $C_{31}H_{53}D_3OSi$ requires C, 78.04; H, 11.86, $\delta_H$ 0.21 (s., 6H, **Me**$_2$Si), 3.17 (dd., $J_1$=11.5, $J_2$=5.5Hz, 3-**H**), $\delta_C$ 1.30 and 2.90 (**Me**Si), 13.9 (**C**H$_2$Si), 85.3 (3-**C**).

To a solution of this cyclic silyl ether (0.92g; 1.9 mmol) in anhydrous $HCONMe_2$ (75 ml) was added at room temperature a 1 M solution of $Bu_4NF$ in THF (5.0 g; 19.4 mmol). The mixture was stirred for 5 h at 70°C and worked up as usual. The crude product was chromatographed over $SiO_2$ to afford alcohol **1a(4αCD$_3$)** (0.67g ; 83 %), mp 156-157°C (lit.[28] 155-156°C), $[\alpha]_D$ +13 (*c* 2.76) (lit.[18] $[\alpha]_D$ +12), Found C, 82.66; H, 12.42%; $C_{29}H_{49}D_3O$ requires C, 82.98; H, 12.49, $\delta_C$ 79.10 (3-**C**).

### 4α–Trideuteriomethyl-4β-methyl-5α-cholestan-3-one 11(4αCD$_3$)

It was prepared by oxidizing alcohol **1a(4αCD$_3$)** (5.2g; 12.4 mmol) with Jones's reagent.[33] Usual work up gave **ketone 11(4αCD$_3$)** (4.92g; 95%), m.p. 104-105°C, $[\alpha]_D$ +2 (*c* 0.79) (lit.[22] mp. 100-102°C, $[\alpha]_D$ +4) Found C, 83.09; H, 12.08%, $C_{29}H_{47}D_3O$ requires C, 83.39; H, 12.06%, $\delta_C$ 217.4 (3-**C**).

### 4α-Trideuteriomethyl-4β-methyl-5α-cholestan-2-one 10(4αCD$_3$)

To a solution of ketone **11(4αCD$_3$)** (4.0g; 9.7 mmol) in AcOH (275 ml) containing 5 drops of conc. HBr and 5 drops of $Ac_2O$ was added dropwise over 8h at 15°C under vigorous stirring a solution of bromine (1.52g; 9.5 mmoles) in AcOH (12 ml). After usual workup, the crude product was chromatographed over $SiO_2$, to afford the **2-bromoketone** (4.62g, 97%), mp 73-74°C, $[\alpha]_D$ -6 (*c* 1.3), (lit.[35] mp 70-71°C, $[\alpha]_D$ -8).

A solution of the 2-bromoketone (1.8g; 3.65 mmol) and of anhydrous KOAc (7.3g; 74.5 mmol) in AcOH (36 ml) was refluxed for 35h. After usual workup the crude product was chromatographed over $SiO_2$ to afford a mixture of **acetoxyketones** (1.36g; 79%). To a solution of calcium (2.7g; 67.5 mmoles) in anhydrous liquid $NH_3$ (650 ml) was added dropwise under stirring over 40 mn a solution of the mixture of acetoxyketones (3.6g; 7.6 mmol) in toluene (170 ml), and stirring was continued for 20 mn. The blue colour was discharged by adding a 1:1 mixture of toluene and methanol and, after usual workup, the crude product was chromatographed over $SiO_2$, affording **ketone 10a(4CD$_3$)** (1.96g; 62%), mp 129-130°C (lit.[18] mp 124-125°C), $\delta_C$ 211.8 (2-**C**), 33.4 (4α$CH_3$), along with ketone **11a(4αCD$_3$)** (379mg; 12%), **alcohol 1a(4αCD$_3$)** (507mg; 16%) and **alcohol 8a(4αCD$_3$)** (135mg; 4%).

### 4α-Trideuteriomethyl-4β-methyl-5α-cholestan-2α-ol 8a(4αCD$_3$)

It was prepared from ketone **10(4αCD$_3$)**, in a 75% yield (along with some epimeric alcohol **9a(4αCD$_3$)** as decribed for alcohol **8a(3αD)** from ketone **10(3αD)**, mp 125-126°C, $[\alpha]_D$ +14 (*c* 1.27) (lit.[17] mp 124-

126°C, $[\alpha]_D$ +13), Found C, 82.68; H, 12.55, $C_{29}H_{49}D_3O$ requires C, 82.98; H, 12.49, $\delta_H$ 3.86 (tt., $J_1$=11.5, $J_2$=4.1Hz, 2-**H**), $\delta_C$ 65.62 (2-**C**); the signal at 33.66 (4α$CH_3$) vanished.

**Tosylate 8b(4α$CD_3$)**, mp 93-95°C, $[\alpha]_D$ -24 (*c* 2.6), $\delta_H$ 4.69 (tt., $J_1$=11.8, $J_2$=4.1Hz, 2-**H**), $\delta_C$: the signal at 33.32 (4α$CH_3$) vanished.

### 3β-Trideuteriomethyl-4α-methyl-5α-cholestan-3α-ol 14a

To a solution of $CD_3MgI$ made frome $CD_3I$ (0.1 ml) and Mg turnings (0.2g) in anhydrous ether (3 ml) was added a solution of 4α-methyl-5α-cholestan-3-one [22] (80mg; 0.20 mmol) in anhydrous ether (10 ml). The mixture was stirred for 24 h and worked up as usual. The crude product was chromatographed over $SiO_2$ and gave, along with some of the epimer **14b**, **alcohol 14a** (62mg; 74%), mp 132-134°C, $[\alpha]_D$ +10.5 (*c* 0.85) (lit.[22] mp 133-134°C, $[\alpha]_D$ +13.5, $\delta_H$: the signal at 1.17 (s., 3β$CH_3$) vanished, $\delta_C$: the 25.98 signal (3β$CH_3$) vanished.

### 3-Trideuteriomethyl-4-methyl-5α-cholest-3-ene 25c 12(3$CD_3$)

Dehydration of alcohol **14a** (35mg) with $POCl_3$ (3.5 ml) in anhydrous pyridine (15 ml) and usual work up gave, after chromatography **olefin 12(3$CD_3$)** (20mg ; 59%), mp 109-110°C (lit.[22] mp 110-112°C), $\delta_H$: the 1.58 signal (s., 3-$CH_3$) vanished, $\delta_C$ 127.2 and 124.4 (3-**C** and 4-**C**), the signal at 19.5 (3-$CH_3$) vanished.

## Acetolysis

**Acetolysis of tosylate 8b:** Tosylate **8b** (1.5g ; 2.6 mmol) in anhydrous AcOH (55 ml) containing NaOAc (2.0g; 24.4 mmol) was refluxed for 1.5h. After usual work up the crude product (1.1g) was chromatographed over $SiO_2$. Petroleum ether eluted the hydrocarbon fraction (0.93g); petroleum ether-$Et_2O$ (96:4) eluted the acetate fraction (0.135g). The acetate fraction in MeOH (5 ml) containing KOH (20mg) was refluxed for 1 h. After usual work up, the crude product was chromatographed over $SiO_2$, affording successively **4,4-dimethyl-5α–cholestan-2β-ol 9a** (101mg, 9.2%), mp 140-141°C (lit.[18] mp 140-141°C, $\delta_H$ 4.14 (qui., J=11.4Hz, 2-**H**), $\delta_C$ 68.15 (2-**C**), then **4,4-Dimethyl-5α-cholestan-2α-ol 8a** (19.6mg; 1,8%), mp 125-126°C (lit.[21] mp 124-126°C), $\delta_H$ 3.85 (tt., $J_1$=11.4, $J_2$=4Hz, 2-**H**), $\delta_C$ 65.6 (2-**C**). The hydrocarbon fraction was chromatographed over $AgNO_3$-$SiO_2$ (10:90). Petroleum ether eluted successively a mixture of **7** and **12** (45mg, 4.3%) which was analyzed by proton NMR spectroscopy into **3β,4-Dimethyl-cholest-4-ene 7** (1.9%), $\delta_H$ 0.67 (3H, s., 13β-**Me**), 1.00 (3H, d., J=7Hz, 3β-**Me**), 1.58 (3H, s., 4-**Me**), $\delta_C$ 138.1 and 127.6 (4-**C** and 5-**C**), and **3,4-Dimethyl-5α-cholest-3-ene 12** (2.4%), $\delta_H$ 0.65 (3H, s., 13β-**Me**), 1.54 (3H, s., 4-**Me**), 1.58 (3H, s., 3-**Me**), then **4,4-Dimethyl-5α-cholest-2-ene 3** (582mg, 55,6%), mp 88-90°C, $[\alpha]_D$ +38 (*c* 3.6) (lit.[18] mp 89-90°C, $[\alpha]_D$ +38), $\delta_H$ 5.35 (dd., $J_1$=10.1, $J_2$=2.1Hz, 3-**H**), 5.43 (ddd., $J_1$=10.1, $J_2$=5.7, $J_3$=1.6Hz, 2-**H**), $\delta_C$ 138.1 and 128.1 (2-**C** and 3-**C**), m/z = 398 (100%), 397 (0.8), 399 (30.8), 400 (2.5), then a mixture of **4,5** and **6** (278mg, 26,5%) which was analyzed by proton NMR spectroscopy into **4,4-Dimethyl-5α-cholest-1-ene 4** (24.8%), $\delta_H$ 5.46 (ddd., $J_1$=10.0, $J_2$=5.0, $J_3$=2.5Hz, 2-**H**) 5.78 (br. d., J=10Hz, 1-**H**), $\delta_C$ 135.9 and 123.1 (1-**C** and 2-**C**), **3α-Methyl-4-methylene-5α-cholestane 5** (1.2%), $\delta_H$ 1.08 (3H, d., J=7Hz, 3α**Me**), 4.40 and 4.74 (2H, two br. s., C=$CH_2$), $\delta_C$ 155.8 and 105.6 (C=$CH_2$), and **3β-Methyl-4-methylene-5α-cholestane 6** (0.5%), $\delta_H$ 4.50 and 4.68 (2H, two d., J=0.8Hz, C=$CH_2$), $\delta_C$ 155.6 and 103.0 (C=$CH_2$).

**Acetolysis of Tosylate 9b:** Tosylate **9b** (1.5 g; 2.6 mmol) was treated in anhydrous AcOH, NaOAc as described for tosylate **8b**. The acetate fraction (0.13g) was pure **2α–Acetoxy-4,4-dimethyl-5α-**

**cholestane 8c** (10.9%), mp 66-67°C, $[\alpha]_D$ -12 (*c* 0.48) (lit.[17] mp 65-67°C, $[\alpha]_D$ -6)[36], $\delta_H$ 2.00 (3H, s., **MeCO**), 5.00 (tt., $J_1$=11.8, $J_2$=4.1Hz, 2-**H**), $\delta_C$ 170.8 (**CO**) 69.5 (2-**C**).

The hydrocarbon fraction (0.95g) was chromatographed over $AgNO_3$-$SiO_2$ (10:90). Petroleum ether eluted successively **3β,4-Dimethyl-cholest-4-ene 7** (10mg, 1%), mp 90.5-91°C (lit.[22] mp 90°C), $\delta_H$ 0.67 (3H, s., 13β-**Me**), 1.00 (3H, d., J=7Hz, 3β-**Me**, 1.58 (3H, s.,4-**Me**), then **4,4-Dimethyl-5α-cholest-2-ene 3** (755mg, 72.1%), mp 90°C, $[\alpha]_D$ +35 (*c* 0.60) (lit.[18] mp 89-90°C, $[\alpha]_D$ +38), $\delta_H$ 5.35 (dd., $J_1$=10.1, $J_2$=2.1Hz, 3-**H**), 5.43 (ddd., $J_1$=10.1, $J_2$=5.7, $J_3$=1.6Hz, 2-**H**), $\delta_C$ 138.1 and 121.7 (3-**C** and 2-**C**) then a mixture of **4**, **5** and **6** (195mg, 13%) which was analyzed by proton NMR spectroscopy into **4,4-Dimethyl-5α-cholest-1-ene 4** (12.2%), $\delta_H$ 5.46 (d., J=10Hz, 1-**H**), 5.78 (ddd., $J_1$=10, $J_2$=5, $J_3$=2.5Hz, 2-**H**), $\delta_C$ 135.9 (1-**C**), 123.1 (2-**C**), **3α–Methyl-4-methylene-5α-cholestane 5** (0.6%), $\delta_H$ 1.08 (3H, d., J=7Hz, 3α-**Me**), 4.40 and 4.75 ( 2H, two br. s.,**C=CH$_2$**), $\delta_C$ 155.8 and 105.6 (**C=CH$_2$**), and **3β-Methyl-4-methylene-5α-cholestane 6** (0.2%), $\delta_H$ 4.50 and 4.68 (2H, two d., J=0.8Hz, C=**CH$_2$**).

**Acetolysis of tosylate 8b(3αD):** Tosylate **8b(3αD)** containing 0.87 ± 0.03 D atom/molec. (600mg, 1.05 mmol) was treated as for tosylate **8b**, giving an acetate fraction and a hydrocarbon fraction. From the hydrocarbon fraction, among other olefins, was isolated a mixture of **4,4-Dimethyl-5α-cholest-2-enes 3, 3(3D)** and **3(2D)** (241mg, 56.5%) mp 89-91°C (lit.[18] mp 89-90°C), m/z 399 (100%), 398 (77.5), 400 (28.5), 401 (3.8). The ratios of NMR proton intensities are (2-H+3-H/13-Me) = 1.27/3, 1.28/3 and 1.23/3 and (2-H/3-H) = 63/37, 66/34 and 67/33 (three different spectra of the same product).

**Acetolysis of tosylate 9b(2αD):** Tosylate **9b(2αD)** containing 0.98 ± 0.03 D atom/molec. (760mg, 1.30 mmol) was treated as for tosylate **9b**, giving an acetate fraction and hydrocarbon fraction. From the hydrocarbon fraction, among other olefins, was isolated a mixture of **4,4-Dimethyl-5α-cholest-2-enes 3 and 3(2D)**, (385mg, 72.6%), mp 89-90°C (lit.[18] mp 89-90°C) m/z 399 (100%), 398 (2.5), 400 (30.2), 401 (3.1). The ratios of NMR proton intensities are (2-H+3-H/13-Me) = 1.08/3 and (2-H/3-H)= 8/92.

**Acetolysis of tosylate 9b(3αD):** Tosylate **9b(3αD)** containing 0.97 ± 0.03 D atom/molec. (300mg, 0.525 mmol) was treated as for tosylate **9b**, giving an acetate fraction and a hydrocarbon fraction. From the hydrocarbon fraction, among other olefins, was isolated a mixture of **4,4-Dimethyl-5α-cholest-2-enes 3(3D) and 3(2D)** (151mg, 71.9%), mp 89-91°C (lit.[18] mp 89-90°C) m/z 399 (100%), 398 (31.2), 400 (28.1), 401 (9.3). The ratio of NMR proton intensities are (2-H+3-H/13-Me) = 1.15/3 and (2-H/3-H) = 77/23.

**Acetolysis of tosylate 8b(4αCD$_3$):** Tosylate **8b(4αCD3)** (1.4g, 2.44 mmol) was treated as for tosylate **8b**, giving an acetate fraction and a hydrocarbon fraction. From the hydrocarbon fraction were isolated successively a mixture of **7(4CD$_3$)** and **12(4CD$_3$)**, (53mg 5.4%), which was analyzed by proton NMR spectroscopy into **3β-Methyl-4-trideuteriomethyl-cholest-4-ene 7(4CD$_3$)** (2.2%), $\delta_H$ 0.67 (3H, s., 13β-**Me**), 0.99 (3H, d., J=7Hz, 3β-**Me**), $\delta_D$ 1.59 (3D, s., 4-$CD_3$) and **3-Methyl-4-trideuteriomethyl-5α-cholest-3-ene 12(4CD$_3$)** (3.2%), $\delta_H$ 1.58 (3H, s., 3-**Me**), $\delta_D$ 1.55 (3D, s., 4 $CD_3$), then **4α-Trideuteriomethyl-4β-methyl-5α-cholest-2-ene 3(4αCD$_3$)** (539mg, 55%), mp 89-90°C (lit.[18] mp 89-90°C), $\delta_H$ 5.35 and 5.43 (2H,m., 2-**H** and 3-**H**), see acetolysis of **8b**, $\delta_D$ 0.92 (3D, s., 4α$CD_3$), then a mixture of **4(4αCD$_3$)**, **5(3αCD$_3$)** and possibly **6(4CD$_2$)** (255mg, 27.0%), which was analyzed by proton NMR spectroscopy into **4α-Trideuteriomethyl-4β-methyl-5α-cholest-1-ene 4(4αCD$_3$)** (25.9%), $\delta_H$ 5.45 and 5.77 (2H, m., 1-**H** and 2-**H**, see acetolysis of **8b**), $\delta_D$ 0.87 (3D, s., 4α-$CD_3$), **3α-Trideuteriomethyl-4-methylene-5α-cholestane 5(3αCD$_3$)** (1.1%), $\delta_H$ 4.40 and 4.74 (2H, two br. s., C=**CH$_2$**), $\delta_D$ 1.07 (3D, broad s., 3α-$CD_3$),and **3β-Methyl-4-dideuteriomethylene-5α-cholestane 6(4$CD_2$)** (traces ?) $\delta_H$: No doublets at 4.50 and 4.68.

**Table 5**

Proton NMR signals of methyl groups at C-4 and C-10
in some 4,4-dimethyl-5α-cholestane derivatives (200 Mhz in $CDCl_3$)

| Formula | Functional group | Undeuterated compounds | | | 4α-Trideuteriomethylated compounds | |
|---|---|---|---|---|---|---|
| | | 10β | 4α | 4β | 10β | 4β |
| **11a** | 3 one | 1.02 | 1.03 | 1.02 | 1.02 | 1.02 |
| **2a** | 3α OH | 0.86 | 0.92 | 0.86 | 0.86 | 0.86 |
| **1a** | 3β OH | 0.86 | 0.94 | 0.77 | 0.86 | 0.765 |
| **10a** | 2 one | 0.86 | 1.02 | 0.86 | 0.855 | 0.855 |
| **8a** | 2α OH | 0.89 | 0.88 | 0.86 | 0.90 | 0.86 |
| **8c** | 2α OAc | 0.93 | 0.89 | 0.86 | 0.93 | 0.86 |
| **9a** | 2β OH | 1.09 | 0.86 | 1.01 | 1.09 | 1.01 |
| **9c** | 2β OAc | 1.04 | 0.86 | 0.98 | 1.04 | 0.97 |
| **3** | 2 ene | 0.87 | 0.93 | 0.87 | 0.875 | 0.875 |
| **4** | 1 ene | 0.96 | 0.87 | 0.87 | 0.96 | 0.87 |

## Kinetics

All experiments were run in NMR tubes using 0.5 ml of $CD_3CO_2D$ (99.99%), 0.01M in $CD_3CO_2Na$. The tubes were sealed and kept in liquid nitrogen before the beginning of the experiment. Time zero was taken as the time when the sealed tube was dipped into a beaker containing water at the temperature chosen for the experiment; the tube was then transferred after 10 mn into the NMR instrument (Bruker 500 Mhz).

The weighed masses were

for **1b**: 2.18 mg at 71°C : 0.00765 molar solution
for **9b**: 2.08 mg at 71°C : 0.0073 molar solution
for **8b**: 2.41 mg at 60°C : 0.00846 molar solution
2.49 mg at 71°C : 0.00874 molar solution
2.63 mg at 80°C : 0.00923 molar solution

The dissolution of the solid tosylate into the solvent was usually very fast, except for **9b**, whose dissolution was only achieved at the end of the 10 mn period of dipping in water.

## Evaluation of the percentage of labelled compounds

Proton NMR spectral evaluation of olefins **3(3D)** and **3(2D)** produced from acetolysis of tosylates **8(3αD)**, **9(3αD)** and **9(2αD)**:

Let a be the molar fraction of **3**, b that of **3(3D)** and c that of **3(2D)**. In the acetolysis of **9b(3αD)**, one can write: $a+b+c = 1$, $2a+b+c = 1.15$ and $(a+b)/(a+b) = 77/23$. Hence $a = 0.15$, $b= 0.74$, $c = 0.11$.

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## Bibliographic references

1. Part 61, Agami, C.; Puchot, C. *Tetrahedron* **1986**, *42*, 2037-2042.
2. Part 60, Agami, C.; Rizk, T. *Tetrahedron* **1985**, *41*, 537-540.
3. Part 59, Audouin, M.; Levisalles, J. *Bull. Soc. Chim. Fr.* **1985**, 1280-1284.
4. Part 1, Abad, A.; Levisalles, J. *Bull. Soc. Chim. Fr.* **1972**, 1135-1147.
5. Fainberg, A. H.; Winstein, S. *J. Amer. Chem. Soc.* **1956**, *78*, 2767-2770.
6. Robinson, G. C.; Winstein, S. *J. Amer. Chem. Soc.* **1958**, *80*, 169-181.
7. Hofmann, R.; Woodward, R. B. *Acc. Chem. Res.* **1968**, *1*, 17-22. Fukui, K. *Bull. Chem. Soc. Japan* **1966**, *39*, 498-503. Longuet-Higgins, H. C.; Abrahamson, E. W. *J. Amer. Chem. Soc.* **1965**, *87*, 2045-2046. Zimmerman, H. E. *Acc. Chem. Res.* **1971**, *4*, 271-280. Dewar, M. J. S. *Angew. Chem., Int. Ed. Engl.* **1971**, *10*, 761-776.
8. Braude, E. A.; Turner, D. W. *Chem. Ind. (London)* **1955**, 1223-1224.
9. For a theoretical treatment see Pascal, Y. L.; Levisalles, J.; Normant, J. M. *Tetrahedron* **1993**, *49*, 7679-7690.
10. For a recent review see Saunders, M.; Jimenez-Vasquez, H. A. *Chem. Rev.* **1991**, *91*, 375-397.
11. Hamon, L.; Levisalles, J.; Pascal, Y. L. *Tetrahedron* **1989**, *45*, 1711-1722; **1994**, *50*, 161-170, report an *ab initio* calculation on the automerization of ethyl formate,

$$H_a-\underset{1}{CH_2}-\underset{2}{CH_2}-\underset{3}{O}-\underset{4}{CH=O} \rightleftharpoons \underset{4}{O=CH}-\underset{3}{O}-\underset{1}{CH_2}-\underset{2}{CH_2}-H_a$$

    treated as a 6 center sigmatropic rearrangement. *In the transition state* the charge on the formate moiety is 0.741 electron; it would most probably be closer to 1 electron if the formate were replaced by a sulfonate. This is taken to mean that the transition state is a *quasi* contact ion pair.
12. Dannenberg, J. J.; Abrams C.; Decoret, C.; Rayez J. C.; Metras F. *J. Org. Chem.* **1983**, *48*, 3315; Mueller P.; Mareda J. *Helv. Chim. Acta* **1985**, *68*, 119.
13. Kirchen, R. P.; Ranganayukulu, K.; Sorensen, T. S. *J. Amer. Chem. Soc.* **1987**, *109*, 7811-7816. Finnes, E. S.; Gunn, J. R. jr; Sorensen, T. S. *J. Amer. Chem. Soc.* **1987**, *109*, 7816-7823; for a recent theoretical explanation see Rauk, A.; Sorensen, T. S.; Maerker, C.; De Carneiro, J. W.; Sieber, S.; Schleyer, P. von R. *J. Amer. Chem. Soc.* **1996**, *118*, 3761-3762.
14. Paradisi, C.; Bunnett, J. F. *J. Amer. Chem. Soc.* **1981**, *103*, 946-948; **1985**, *107*, 8223-8233, see also Chang, S.; Le Noble, W. J. *J. Amer. Chem. Soc.* **1983**, *105*, 3708-3709; Dietze, P. E.; Wojciechowski M. W. *J. Amer. Chem. Soc.* **1990**, *112*, 5240.
15. Farcasiu, D.; Marino, G.; Harris, J. M.; Hovanes, B. A.; Hsu, C. S. *J. Org. Chem.* **1994**, *59*, 154-162.
16. Abad, A.; Allard, M.; Levisalles, J. *Bull. Soc. Chim. Fr.* **1969**, 1236-1244.
17. Lablache-Combier, A.; Levisalles, J. *Bull. Soc. Chim. Fr.* **1964**, 2236-2244.
18. Lablache-Combier, A.; Levisalles, J.; Pete, J. P.; Rudler, H. *Bull. Soc. Chim. Fr.* **1963**, 1689-1701.
19. Inspection of the NMR spectrum of **9a(3αD)** prepared according to ref.17 revealed that this alcohol was a 1:1 mixture of **9a(3αD)** and of **9a(2α,3αD$_2$)**, so that it became necessary to oxidize the mixture to ketone

**10(3αD)**, whose reduction under appropriate conditions led to alcohols **8a(3αD)** and **9a(3αD)**. A similar case was encountered in the reduction of 4 t-butyl cyclohexene oxide by Rickborn, B.; Quartucci, J. *J. Org. Chem.* **1964**, *29*, 3185-3188.

20. Stork, G.; Sofia, M. J. *J. Amer. Chem. Soc.* **1986**, *108*, 6826-6828.
21. Lablache-Combier, A.; Lacoume, B.; Levisalles, J. *Bull. Soc. Chim. Fr.* **1966**, 897-905.
22. Beton, J. L.; Halsall, T. G.; Jones, E. R. H.; Phillips, P. C. *J. Chem. Soc.* **1957**, 753-765.
23. Hemmert, F.; Lablache-Combier, A.; Lacoume, B.; Levisalles, J. *Bull. Soc. Chim. Fr.* **1966**, 982-987.
24. Rosenthal, D. *J. Org. Chem.* **1967**, *32*, 4084-4086.
25. For example see Humski, K.; Sendijarevic, V.; Shiner, V. J. jr *J. Amer. Chem. Soc.* **1973**, *95*, 7722-7728. Imhoff, M. A.; Shiner, V. J. jr *J. Amer. Chem. Soc.* **1985**, *107*, 2121-2124.
26. Lambert, J. B.; Putz, G. J. *J. Amer. Chem. Soc.* **1973**, *95*, 6313-6319. Sorensen, T. S.; Witworth, S. M. *J. Amer. Chem. Soc.* **1990**, *112*, 6647-6651. Schneider, H. J.; Bisch, R. *J. Org. Chem.* **1982**, *47*, 1766-1769. Imhoff, M. A.; Ragain, R. M.; Moore, K.; Shiner, V. J. jr *J. Org. Chem.* **1991**, *56*, 3542-3549.
27. Hamon, L.; Levisalles, J. *Bull. Soc. Chim. Fr.* **1990**, 807-812.
28. Biellmann, J. F.; Ourisson, G. *Bull. Soc. Chim. Fr.* **1962**, 331-336. Levisalles, J.; Pete, J. P. *Bull. Soc. Chim. Fr.* **1967**, 3747-3752. Kohen, F.; Stevenson, R. *J. Org. Chem.* **1965**, *30*, 2268-2272.
29. Both calculations and experiment (infra-red evidence) concur to show that the 2-butyl cation is, at least partly, a H-bridged *trans* $C_2$ cation in a superacidic medium (see Sieber S.; Buzek P.; Schleyer P.v.R.; Koch W.; Walkimar de M.Carneiro J. *J. Amer. Chem. Soc.* **1993**, *115*, 259). However the experimental conditions are so different from acetolysis that it does not sound advisable to extend these results to the present case.
30. It must be emphasized that SN2 here does not distinguish between SN2 (one stage) and SN2 (intermediate) (see Bentley T.W.; Bowen C.T.; Morten D.H.; Schleyer P.v.R. *J. Amer. Chem. Soc.* **1981**, *103*, 5466 and references cited). Although a SN2 (intermediate) would be more acceptable for AcOH itself, the presence of sizable amounts of AcONa probably also implies a SN2 (one stage) mechanism.
31. Bunton, C. A.; Frei, Y. F. *J. Chem. Soc.* **1951**, 1872-1873. Chang, F. C. *Tetrahedron Lett.* **1964**, 305-309. Eades E. D.; Ball, D. H.; Long, L. *J. Amer. Chem. Soc.* **1964**, *86*, 3579-3580. *J. Org. Chem.* **1966**, *31*, 1159-1162. Christmann, A. R.; Oae, S. *Chem. Ind. (London)*, **1959**, 1251-1252. Levisalles, J.; Pete, J. P. *Bull. Soc. Chim. Fr.* **1968**, 2912-2915. Formation of **35** implies a $S_AN$ and not a SN2 mechanism; see Gordon, I. M.; Maskill, H.; Ruasse, M. F. *Chem. Soc. Rev.* **1989**, *18*, 123-151.
32 A referee suggested that the formation of **8c** might occur on the solvant separated ion pair. If so, there must be two simultaneous processes, SN1 (giving more **8c**) and SN2 (giving **9c** only) to account for the ratio **9c/8c**. We cannot exclude this possibility. Unfortunately kinetics do not help and an experiment with AcOH $^{18}O$ would not distinguish between SN1 and $S_AN$ on sulphur + pericyclic rearrangement of **35**.
33. Bowden, K.; Heilbronn, I. M.; Jones, E. R. H.; Weedon, B. C. L. *J. Chem. Soc.* **1946**, 39-45.
34. Julia, S.; Lavaux, J. P. *Bull. Soc. Chim. Fr.* **1963**, 1231-1237.
35. Chaudhry, G. R.; Halsall, T. G.; Jones, E. R. H. *J. Chem. Soc.* **1961**, 2725-2732.
36. The difference between $[\alpha]_D$ of the present sample and that of the reference sample[16] arises from the difference in purification. The present sample was chromatographed and crystallized, whereas the reference sample was made from a sample of alcohol **8a** prepared by reduction of ketone **10a** and not chromatographed. In this case **8a** may have contained some epimeric **9a**, and the corresponding acetate **8c**, the reference sample, some acetate **9c** which would shift $[\alpha]_D$ toward more positive values; **9c** has $[\alpha]_D$ +23[17].