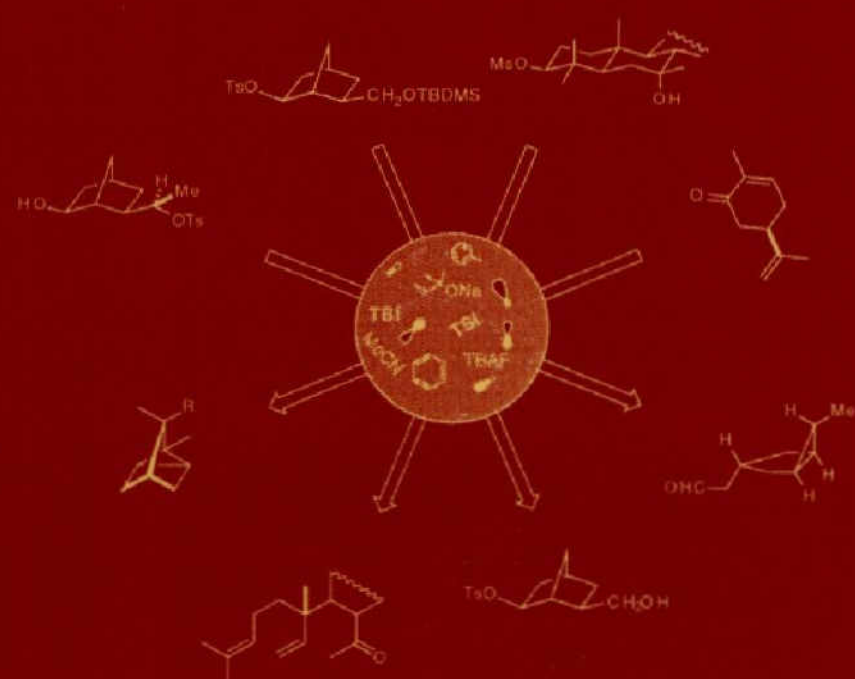


Through-Bond Interactions in Monosulfonated 1,4- and 1,5-Diols and their Application in Natural Product Synthesis



Marc Bastiaansen

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Through-Bond Interactions in Monosulfonated 1,4- and 1,5-Diols and their Application in Natural Product Synthesis

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Aan mijn Vader en Moeder

Voor Joke

Dankwoord

Eindelijk ligt dan het resultaat van vier jaar onderzoeken in de vorm van een boekje voor U. Meer dan honderd pagina's zijn gewijd aan de interacties die aanwezig zijn in en tussen molekulen. Uiteraard zal de lezer geneigd zijn te denken dat deze interacties de belangrijkste zijn die in dit boekje worden besproken. Echter, naar mijn mening is niets minder waar en worden de belangrijkste interacties al op deze en de volgende pagina besproken. Dit boekje draagt dan wel de naam van één auteur maar het moge duidelijk zijn dat vele mensen hier direct of indirect en bewust of onbewust een bijdrage aan hebben geleverd. Deze interacties met en tussen mensen zijn dan ook de belangrijkste ingrediënten van de voedingsbodem waaruit dit boekje heeft kunnen ontspruiten.

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oktober 1996

Marc

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Foreword

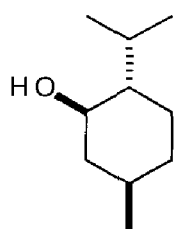
Organic compounds, like sugars, amino acids, fatty acids, and nucleotides, have an essential and well-known function in living organism. In addition to these so-called primary metabolites, most organisms also produce compounds which have a less apparant utility and are generally indicated as secondary metabolites. Some of these secondary metabolites are only produced during particular stages of growth and development, or during periods of stress caused by nutritional limitation or microbial attack. Though, it is not always obvious for which reasons these compounds are produced, they are playing a tremendous role in the well-being of human life. In order to give the reader an indication of their function in today's society, three areas are selected and discussed briefly.

Secondary Metabolites as Food Additives

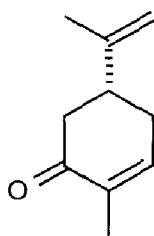
Our food consists mainly of primary metabolites like carbohydrates, lipids (fats), and proteins but it is frequently made more tasty by additives. Most of these additives are organic (flavoring) compounds supplied by nature like linalool, carvone, or thymol which can be added to dishes by adding coriander, spearmint, or thyme, respectively (see Table I for other culinary herbs).

Table I. Culinary Herbs and their Major Oil Components

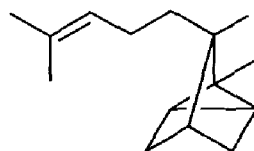
Species	English name	component of the essential oil
<i>Mentha x piperita</i> L.	Peppermint	menthol
<i>Mentha spicata</i> L.	Spearmint	(<i>R</i>)-carvone
<i>Lavendula angustifolia</i>	Lavender	α -santalene
<i>Origanum vulgare</i> L.	Oregano	carvacrol
<i>Thymus vulgaris</i> L.	Thyme	thymol
<i>Corandrum sativum</i> L.	Coriander	(<i>S</i>)-linalool
<i>Pimpinella anisum</i> L.	Anis	anethole
<i>Carum carvi</i> L.	Caraway	(<i>S</i>)-carvone



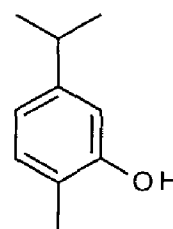
menthol



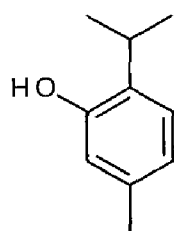
(*R*)-carvone



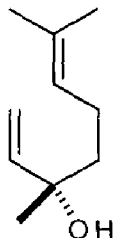
α -santalene



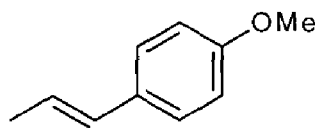
carvacrol



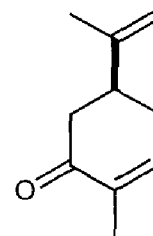
thymol



(S)-linalool



anethole



(S)-carvone

Secondary Metabolites as Medicine

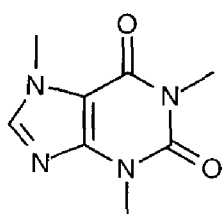
Man has used secondary metabolites, albeit as crude extracts, since the dawn of time as medicines for the relief of pain or alleviation of symptoms of diseases, as effective agents for euthanasia, and as narcotics, hallucinogens, or stimulants to relieve the tedium, or alleviate the fatigue and hunger in his life. Many pharmaceutical compounds used today originate from these ancient recipes (see Table 2 for some examples).

Table 2. The Natural Origin of Some Pharmaceutical Compounds

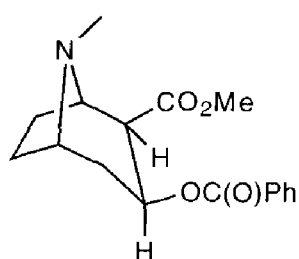
plant species	(derived) pharmaceutical compound
<i>Erythroxylon coca</i>	cocaine
<i>Papaver</i> spp.	morphine
<i>Salicaceae</i> (willow, poplar, etc)	aspirin
<i>Taxus Brevifolia</i>	taxol
<i>Lophophora williamsii</i>	amphetamine
<i>Ephedra vulgaris</i>	ephedrine

It is revealing that some medicines have even found a place on the meal table. A cup of coffee, containing ca. 90 mg of caffeine, is the mildest nervous system stimulant and produces euphoria, a sense of physical and mental well-being, an increased power of mental concentration, and a lowering of the barrier against physical work. These gains are effected at the expense of the body's reserve of physical energie and hence lead to tiredness that is usually eliminated by another dose of the stimulant, and so on. However, drinking too many cups of coffee leads to tremor and insomnia and a still greater excess produces cardiac arrhythmia and delirium. On the other hand, the abrupt cessation of intake usually leads to a headache, experienced often on waking, after two days of abstinence. Much stronger stimulants than caffeine are amphetamine and cocaine, both acting on the cortex of the brain.

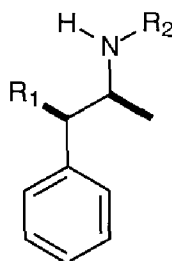
Drugs which depress the central nervous system are not only used as anaesthesia in medicine but sometimes also have recreational use. These analgesics are classed as powerful (morphine) or mild (aspirin and paracetamol).



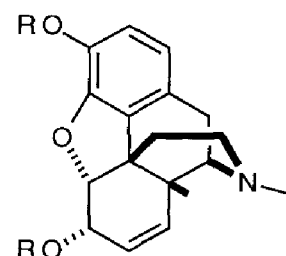
caffeine



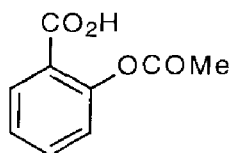
cocaine



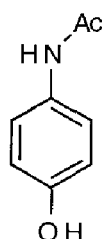
amphetamine: $R_1 = R_2 = H$
 ephedrine: $R_1 = OH$; $R_2 = Me$



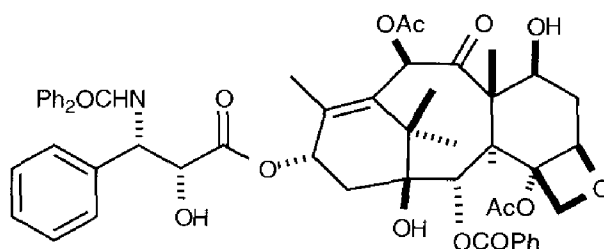
morphine : $R = H$
 heroine : $R = Ac$



aspirin



paracetamol



taxol

Taxol, isolated for the first time from the trunk bark of *Taxus brevifolia* Nutt. (Taxaceae) in 1971, is one of the most promising new drugs studied in the field of cancer chemotherapy. Taxol has shown antitumor activity in several malignant neoplasms and has demonstrated clear efficacy in the treatment of refractory ovarium cancer. Another point of interest is that taxol belongs to a new class of antimitotic agents having an unusual mode of action on the tubulin-microtubulus system.

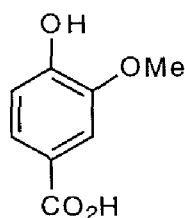
Secondary Metabolites in Chemical Communication

The third function of secondary metabolites discussed in this introduction is their role in communication.

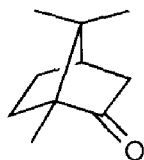
Roundworms (nematodes) are responsible for significant damage to a variety of crops including tobacco, tomato, soybeans, potatoes, and sugarbeets. Extensive studies of pheromones in the soybean cyst nematode *Heterodera glycine* revealed that the female worm emits a pheromone (vanillic acid) that attracts males.

Plants interact with each other not less vigorously than insects, but these interactions are generally nonspecific. Secondary metabolites are released into the environment, above ground from foliage, tree resin, etc., or below the ground via the roots and reduce competition from other species by inhibiting their germination or growth.

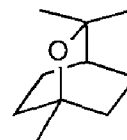
The semi-arid deserts of southern California are dominated by two species of shrub: *Salvia leucophylla* and *Artemesia californica*, the so-called chaparral. Camphor and eucalyptol, which emit from these plants, fall to the earth and are absorbed onto soil particles leading to inhibition of germination of competing plants in the following spring. Those plants which do grow suffer respiratory impairment due to air-borne terpenes. It is only in the wake of a bush fire (a common occurrence in the chaparral where the air is saturated with inflammable compounds) with concomitant destruction of soil- and air-borne monoterpenes, that other species of plants appear in any number. Three comparable examples are juglone which is rain leached from the leaves of walnut trees, and phlorizin and scopoletin which are released from the roots of apple trees and oaks, respectively.



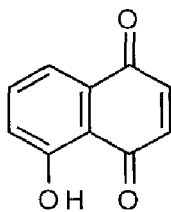
vanillic acid



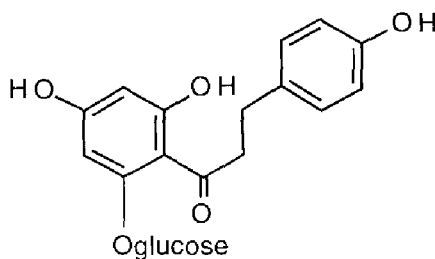
camphor



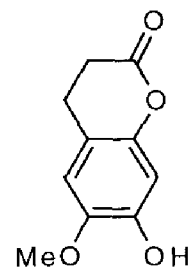
eucalyptol



juglone



phlorizin

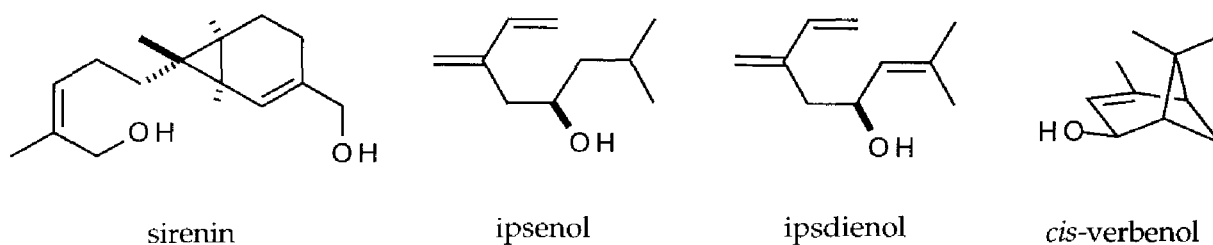


scopoletin

The utilization of so-called gamones by marine plants and fungi resembles a specific intraspecies interaction. A female gamete of water mold (*allomyces*) starts

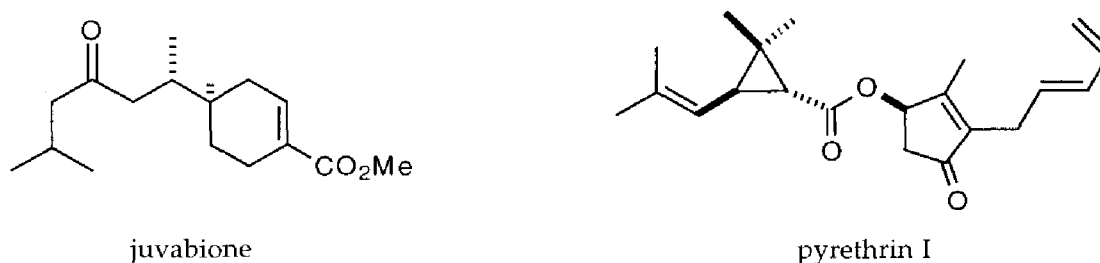
to release a pheromone, known as sirenin, two or three minutes before releasing gametangia, which are small structures filled with gametes. The male gamete that picks up the signal some distance away can sense the differences in concentration of the pheromone and responds to the signal by swimming up the concentration gradient towards the source. Finally, the male and female cells come together in pairs, fuse, and form a zygote, which is the first cell of a new individual.

A mass attack by bark beetles commences with one insect landing on a potential host. If its initial investigation is favorable, this pioneer is soon joined by more and more beetles. The aggregation and breeding of large numbers of beetles can overwhelm and kill a healthy tree. The economic importance of these beetles provided the practical impetus for a careful investigation of the aggregation pheromone. The aggregation pheromone of the California fivespined engraver beetle *Ips paraconfusus* feeding on ponderosa pine exists of a mixture of three synergistically acting compounds: ipsenol, ipsdienol, and *cis*-verbenol.



While natural compounds associated with flowers can play a significant role in attracting pollinators, they are also widely implicated in the defence of plants against herbivores. Juvabione, which occurs in basil (*Ocimum basilicum*), has the ability to arrest the development of some insects leading to imperfect forms or the complete failure to produce adults.

Pyrethrin I, a secondary metabolite of a chrysanthemum species grown in Kenya, has comparable effective insect-killing properties as 1,1,1-trichloro-2,2-bis(4-chlorophenyl)ethane (DDT). Since pyrethrin I is biodegradable and readily metabolized by warm-blooded creatures, it is considered completely safe for household use, and still forms one of the mainstays of domestic fly sprays.

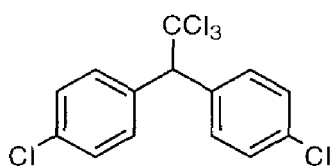


In the early 1960 much anxiety aroused about the persistence of the chlorinated insecticides, like DDT, aldrin, etc., after harvesting. As a consequence, biodegradable insecticides were designed to replace them. In this respect, a well established knowledge of the function that secondary metabolites are playing in chemical communication can certainly be helpful.

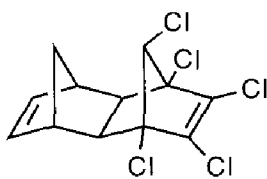
Sex or aggregation pheromones, for example, can be used in traps to monitor, confuse, or kill insects. Such pheromones can also be used to attract the natural predator of a plague. Alarm and spacing pheromones can be used to disperse insects from crops. The benefits of these secondary metabolites are their biodegradability, high selectivity and high biological activity.

Secondary Metabolites as Targets in Organic Syntheses

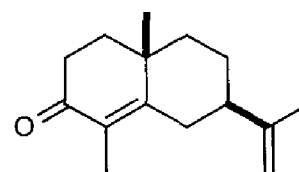
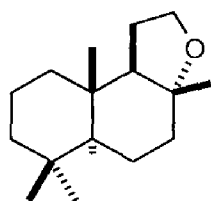
As a consequence of the high biological activity of secondary metabolites, their concentration in plants or animals is mostly very low and/or their isolation from natural sources can be troublesome. For example, the amount of taxol is very limited (0.5 g of taxol from 12 kg of air dried bark (0.004 %)). Similarly, (+)- α -cyperone, exhibiting an activity against malaria parasites, can only be isolated in small amounts from the tubers of *Cyperus rotundus* L.. Ambergris, a highly prized perfumery material having (-)-ambrox as the most important constituent, is a metabolic product of the spermwhale, which is disappearing due to excessive whaling. (+)-(Z)- α -Santalol, another valuable compound in perfumery is available in relatively large amounts from sandelwood oil, but the isolation of this volatile compound from other volatiles in this oil is troublesome.



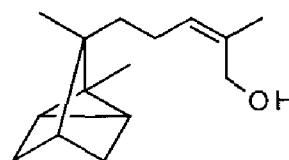
DDT



aldrin

(+) - α -cyperone

(-)-ambrox

(+) - (Z) - α -santalol

For the reasons mentioned above, it is often of (economical) interest to obtain these compounds synthetically. For example, (+)- α -cyperone and (-)-ambrox can both be prepared from the readily available S-(+)-carvone obtained from caraway seeds, whereas camphor can be used as an inexpensive starting material for α -santalol. Obviously, these synthetic compounds do have exactly the same biological activity as the natural ones.

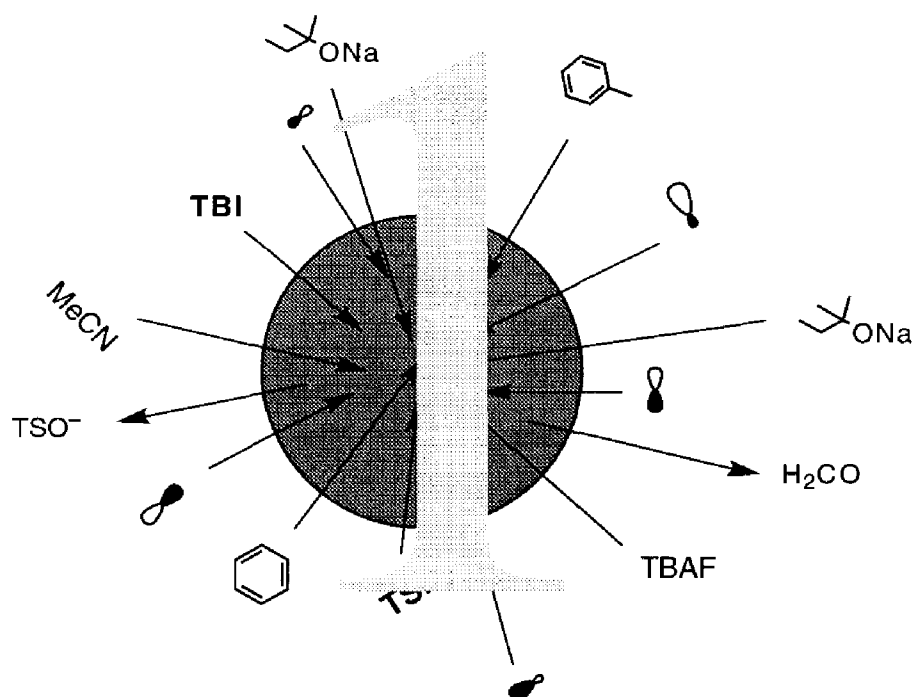
Although a lot of "tricks" already exist in the field of synthetic organic chemistry, the borders are still being expanded in order to find "short cuts" to interesting compounds or to develop routes to (new) compounds which are out of reach. This thesis deals with fundamental investigations toward new types of reactions which might be of value in synthetic organic chemistry.

Suggested Further Reading

- 1 Mann, J. *Secondary Metabolism*; Oxford University Press: Oxford, 1987.
- 2 Mann, J., Davidson, R. S., Hobbs, J. B., Banthorpe, D. V. and Harborne, J. B. *Natural Products their chemistry and biological significance*; Longman Group UK limited: Essex, 1994.
- 3 Albert, A. *Xenobiosis. Foods, drugs and poisons in the human body*; University Press: Cambridge, 1987.
- 4 Albert, A. *Selective Toxicity. The physico-chemical basis of therapy*; University Press: Cambridge, 1985.
- 5 Pedigo, L. P. *Entomology and pest management*; Macmillan Publishing Company: New York, 1991.
- 6 Hay, R. K. M. and Waterman, P. G. *Volatile oil crops: their biology, biochemistry and production*; Longman Group UK limited: Essex, 1993.
- 7 Agosta, W. C. *Chemical communication: the language of pheromones*; Scientific American Library: New York, 1992.
- 8 Verstegen-Haaksma, A. A. PhD-Thesis, Wageningen Agricultural University, 1994.

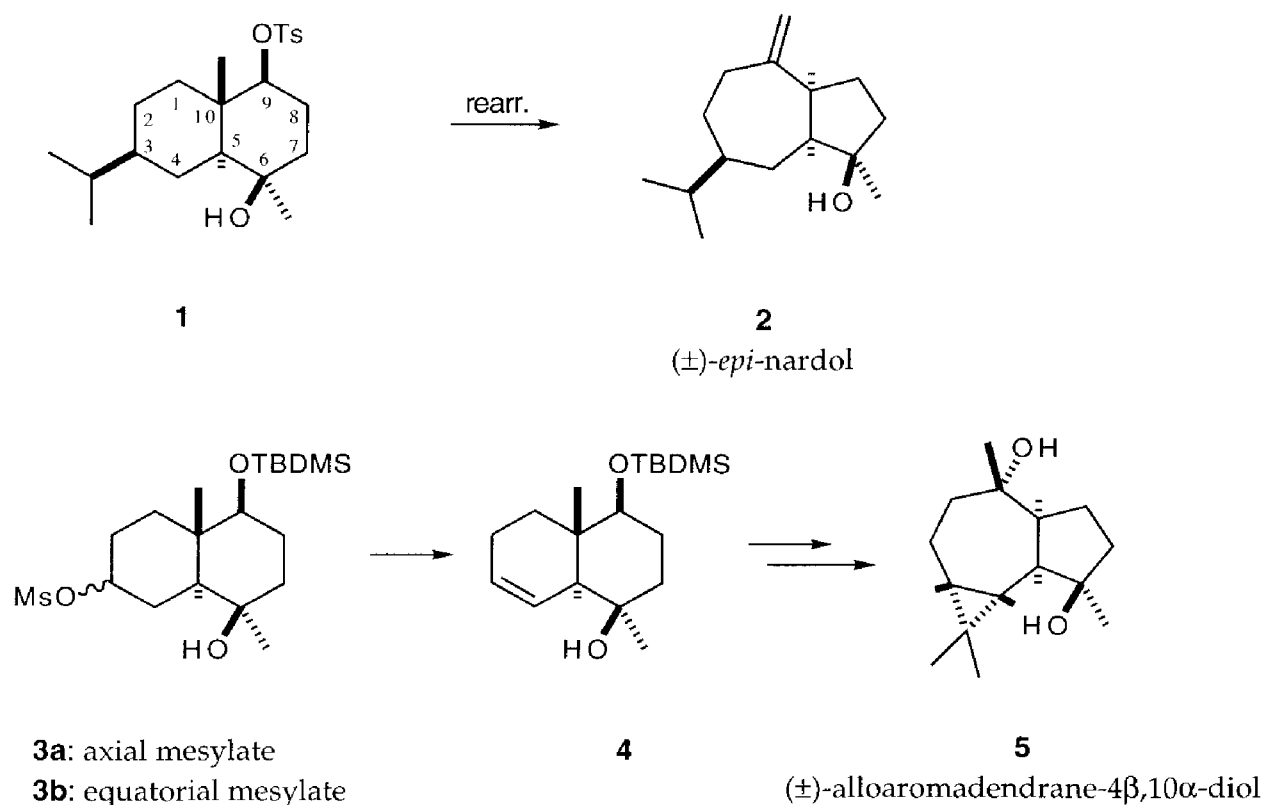
Chapter

General Introduction



1.1 Historical Background

The research described in this thesis originates from the work of Jenniskens et al. on the total synthesis of (\pm)-*epi*-nardol (**2**)¹ and (\pm)-alloaromadendrane-4 β ,10 α -diol (**5**).² The key steps in these total syntheses are the rearrangement and elimination of rigid trans-perhydronaphthalene-1,4-diol monosulfonate esters under the influence of a strong base (Scheme 1.1).



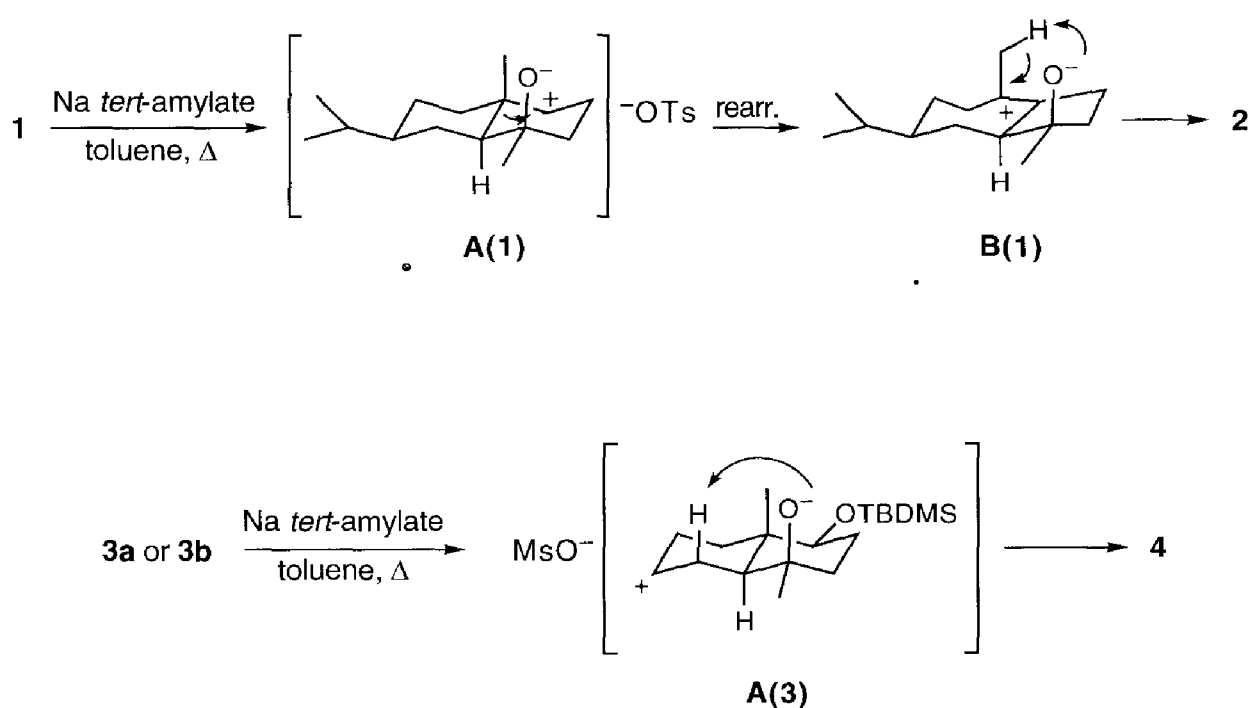
Scheme 1.1

For the synthesis of (\pm)-*epi*-nardol (**2**), the tosylate **1** was treated with sodium *tert*-amylate in refluxing benzene to give **2** in high yield. In contrast to the solvolytic rearrangement,³ this base-induced rearrangement proceeded with high selectivity.⁴ A similar selective rearrangement was also employed in the synthesis of (\pm) alloaromadendrane-4 β ,4 α -diol (**5**).

Another important step in the synthetic route towards **5** was the regioselective elimination of the mesylate group in **3a** and **3b**. Because normally, anti elimination is much faster than syn elimination in fixed six-membered ring

systems, a slow elimination process was expected for the equatorial mesylate **3b**. However, upon treatment with sodium *tert*-amylate in refluxing toluene, it was found that both **3a** and **3b** reacted with practically the same rate to give selectively the olefin **4**.

These results have led to the conclusion that the rearrangement as well as the elimination, probably proceed via an identical mechanism in which the deprotonation of the hydroxyl group is crucial. Related compounds lacking this hydroxyl group at C(6) do not react at all. In refluxing benzene or toluene, deprotonation of the hydroxyl group by sodium *tert*-amylate is thought to be attended with heterolysis of the sulfonate ester bond leading to a dipolar intermediate **A**. (Scheme 1.2). Dependent on the location of the carbocationic center, this intermediate can rearrange to a thermodynamically more stable intermediate which in turn can undergo an intramolecular proton abstraction (**1** → **A(1)** → **B(1)** → **2**) or can give elimination directly, intramolecularly guided by the alkoxide at C(6) (**3a** or **3b** → **A(3)** → **4**).



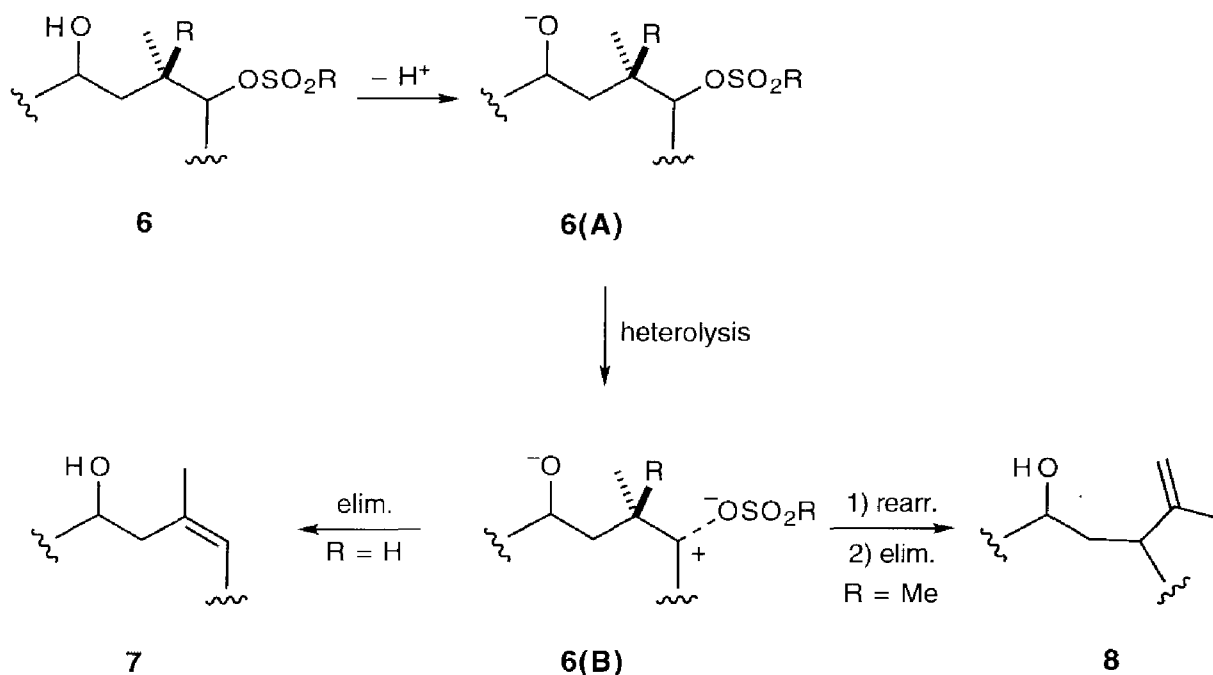
Scheme 1.2

The heterolysis of the sulfonate ester bond, induced by the deprotonated hydroxyl group, can only be rationalized by assuming long-range orbital interactions that couple the alkoxide group to the nucleofugal sulfonate ester group through the intervening C-C single bonds. In Section 1.2, this mechanism

will be explained in more detail and additional experimental support will be given in Section 1.3. Some other reactions in which long-range orbital interactions play a role will be briefly described in Section 1.4.

1.2 The Mechanism of the Base-Induced Heterolysis of 1,4-Diol Monosulfonate Esters

The mechanism proposed for the base-induced elimination and rearrangement of 1,4-diol monosulfonate esters consists of three important steps (Scheme 1.3). The first step is the deprotonation of the hydroxyl group by sodium *tert*-amylate (**6** \rightarrow **6(A)**). The second step involves the intramolecular alkoxide-induced heterolysis of the sulfonate ester bond giving the dipolar intermediate **6(B)**. Since benzene and toluene are used as solvents, it is likely that the sulfonate anion and the carbocation form an ion pair.⁵ The final step in this mechanism is the collapse of the dipolar intermediate through an (intramolecular) elimination or a rearrangement followed by a (selective) deprotonation.



Scheme 1.3

The key step in this mechanism is the facile alkoxide-induced heterolysis of the sulfonate ester bond producing the dipolar intermediate **6(B)**. The alkoxide has a large inductive power since solvation is absent, and this causes an electron delocalization in the σ -bonds between itself and the sulfonate group.

This concept of electron delocalization via saturated bonds, called "Through-Bond Interactions" (TBI), was introduced by Hoffmann et al. in 1968.⁶ Until that time, organic molecules were described as a framework of σ -bonds and on top of that, delocalized π -electron systems and lone pairs were placed, where needed. Hoffmann realized that an interaction between functional groups can originate from a direct interaction –Through-Space Interaction (TSI)– or via the intervening saturated bridge –the σ -relay– between them. This means that the σ -bonds of the molecule are not solely an inert framework, the "backbone" of the molecule, but they interact with the functional groups. These interactions between functional groups were called TBI, and can be described as the mutual coupling of functional group orbitals with σ - and σ^* -orbitals of the intervening saturated bridge. In other words, σ -electrons are delocalized just like π -electrons. The energy effects concomitant with σ -conjugation⁷ are considerably smaller than those in the more familiar π -conjugation.

The most dominant features of TBI –discussed in more detail in Chapter 3– are:

- (1) TBI depend both on the effectiveness of overlap between the orbitals of each interacting functional group with those of the adjoining σ -bonds, and on the overlap of the σ -bridge orbitals with each other.^{8,9} Consequently, the TBI between two functional groups decrease upon changing the geometry of the σ -relay from a "W-", to a "sickle-", and finally, to a "U-shape" (Figure 1.1). This is generally referred to as the "*all-trans rule*".^{10,11}

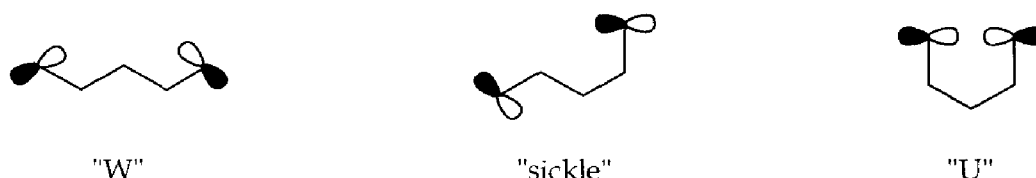


Figure 1.1

- (2) The energy level ordering of the orbitals –symmetrical (S) below anti-symmetrical (A), or the reverse– resulting from TBI depends on the *parity* of the number, n , of the relaying σ -bonds. S being below A for even values of n and A being below S for odd values of n . This level ordering of S and A, known as "the parity rule", predicts that TBI and TSI are "in phase" for even values of n and reinforce each other, but are "out of phase" and oppose each other for odd values of n .¹⁰
- (3) TBI between two functionalities decrease with increasing n , but are still significant if n is eight.¹²

For a careful interpretation of photophysical data –like UV-, CD-, PES-, and ESR-spectra– of organic molecules, the invocation of TBI can be essential.¹³ However, the energy effects concomitant with σ -conjugation are small, and therefore, the localized model normally suits well for chemical thinking, for devising syntheses, and for exploring reaction mechanisms. Though several reactions are influenced significantly by TBI,¹⁴ until now the number of synthetically useful reactions that exploit TBI is limited to the well-studied Grob-^{15,16} and Grob-like^{17,18} fragmentations. As a consequence of their well-defined stereochemical reaction outcome, these fragmentations have been used widely in the syntheses of organic compounds.^{16,19}

1.3 The Base-Induced Heterolysis of 1,4-Diol Monosulfonate Esters

The proposed mechanism of Jenniskens for the TBI-assisted heterolysis of the sulfonate ester bond provided an explanation for the almost similar elimination rates of **3a** and **3b** and the facile rearrangement of **1**. Nevertheless, a more detailed study on rigid monosulfonated *trans*-perhydronaphthalene-1,4-diols was necessary to gain support for this mechanism.

1.3.1 Support for the TBI-Assisted Heterolysis of Sulfonate Esters

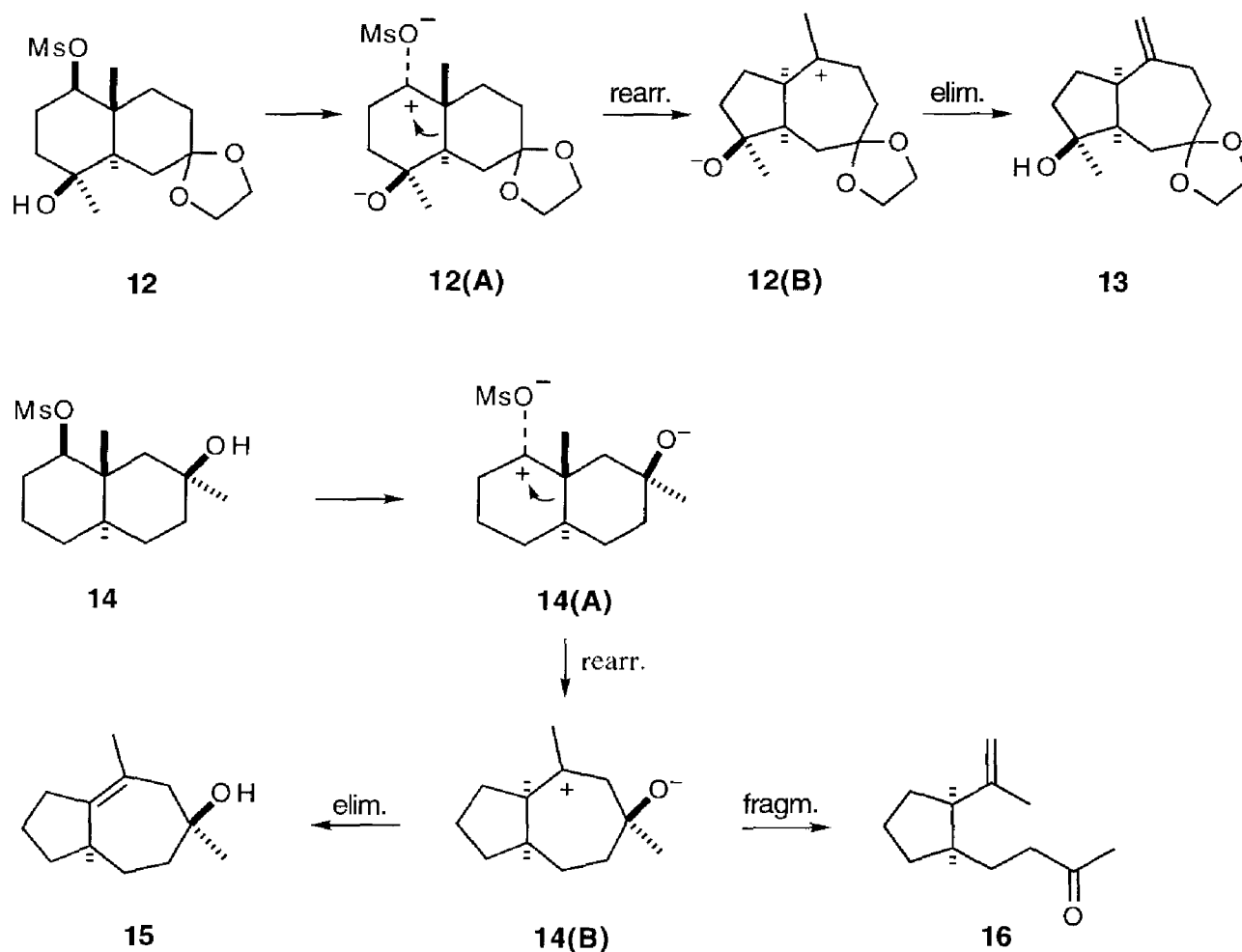
The additional investigations on the base-induced reactions of monosulfonate esters of rigid *trans*-perhydronaphthalene-1,4-diols have afforded further evidence for the proposed TBI-assisted mechanism.²⁰

(1) Quenching of the reaction of the axial mesylate **3a** before it came to completion showed the presence of about 10% of the equatorial mesylate **3b** in the regained mesylate. This indicates that, after the formation of contact ion pair **9**, an internal return of the mesylate group can occur (**9** \rightarrow **10**) with inversion of the configuration at C(3) (Scheme 1.4).

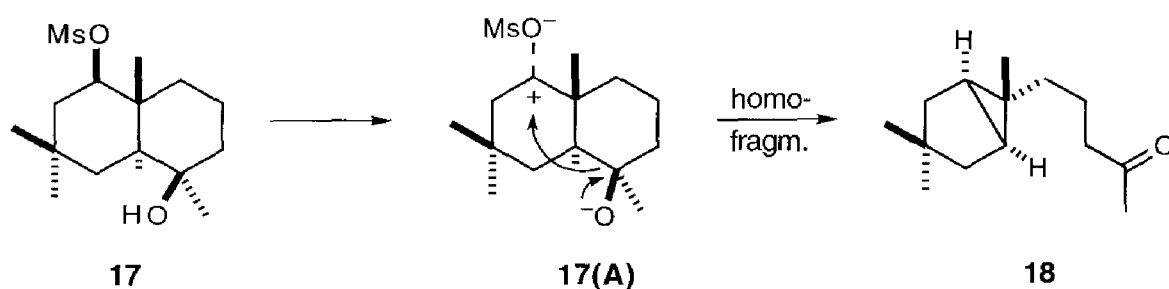


Scheme 1.4

On the other hand, if the arrangement of σ -bonds between the hydroxyl function and the sulfonate ester group describes a W-shape, as is the case for **17**, a relatively fast heterolysis of the sulfonate ester is observed (Scheme 1.6). The geometry not only affects the heterolysis rate but also has a prominent role in determining the reaction course. Whereas the heterolysis of the sulfonate ester bond in **12** and **14** was followed exclusively by a rearrangement, a W arrangement gives selectively homofragmentation to a cyclopropane derivative (**17** \rightarrow **18**).



Scheme 1.5

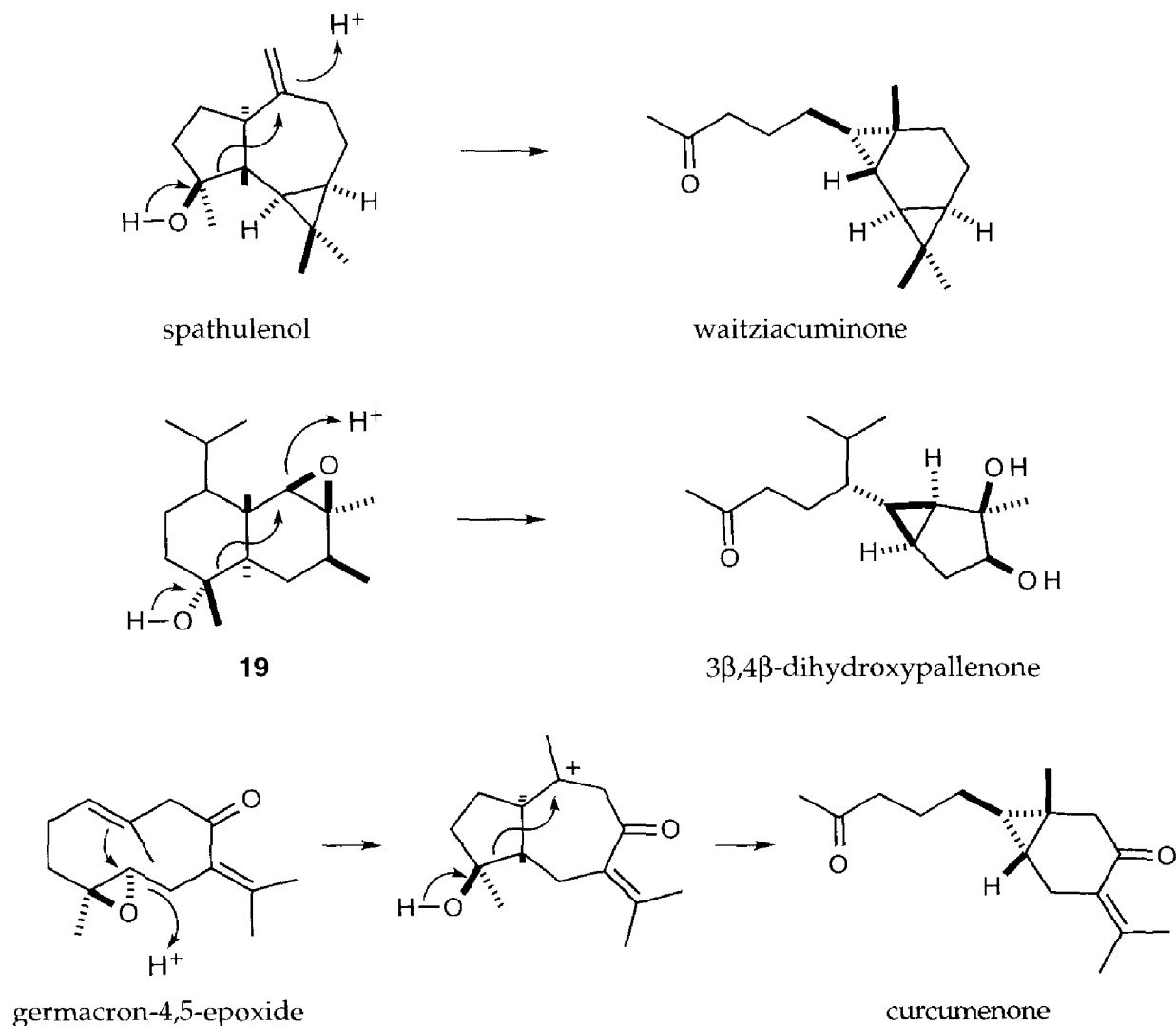


Scheme 1.6

Again, by studying the hydroxyl epimers of **14** and **17**, it was shown that the relative orientation of the hydroxyl group does not affect the reaction rate or the reaction course.

The large difference in reactivity between 1,4-diol monosulfonate esters with a sickle- or W arrangement of the σ -relay between the hydroxyl function and the sulfonate ester can be attributed to differences in transmission of TBI. As stated by the "all-trans rule",^{10,11} these interactions are most efficient when the shape of the σ -relay possesses an all-trans or W arrangement but decrease when the number of gauche interactions increases.

It is interesting to note that the relatively facile homofragmentation, as found in the reaction of **17**, can be a feasible mechanism also in the biosynthesis of natural products like waitziacuminone, 3 β ,4 β -dihdropallenone and curcumenone (Scheme 1.7).



Scheme 1.7

Waitziacuminone is possibly formed via an acid-catalyzed homofragmentation of spathulenol or its biogenetic precursor. Support for this biosynthetic formation of waitziacuminone is obtained from the isolation of both compounds from *Waitzia acuminata*.²⁵ Similarly, the isolation of the cadinane derivative **19** and 3 β ,4 β -dihydroxypallenone from the areal parts of *Pallenis spinosa* suggests the formation of the latter via an acid-catalyzed epoxide opening followed by homofragmentation.²⁶ The biosynthesis of curcumenone may be the result of a homofragmentation of germacron-4,5-epoxide, since both compounds are constituents of the same plant.²⁷ It is also noteworthy that the involvement of enzymes in these proposed biosynthetic homofragmentations may be questioned. These natural product transformations might be due to the intrinsic reactivity of the starting compounds or intermediates, without the involvement of enzymes. Support for this hypothesis is obtained recently from the spontaneous and selective conversion of germacron-4,5-epoxide into curcumenone in water.²⁸

1.3.3 Substituent Effects on the TBI-Assisted Heterolysis of Sulfonates

Solvolysis reactions are affected by the presence and relative position of alkyl substituents.^{29,30,31} Similar effects were supposed to occur in the TBI-assisted heterolysis of 1,4-diol monosulfonate esters.³²

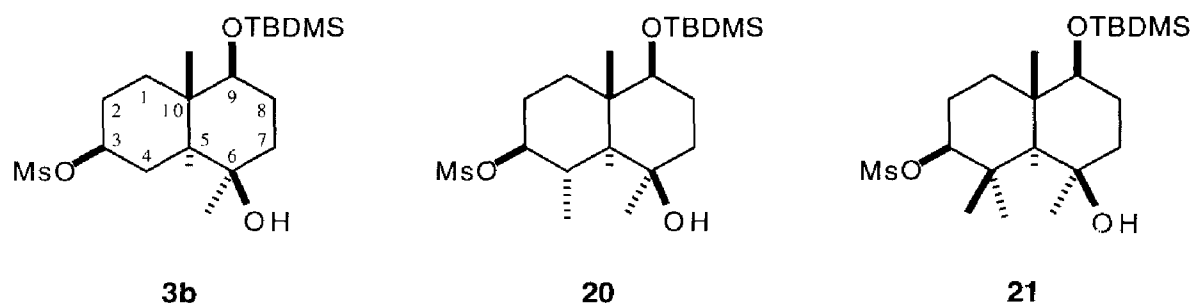


Chart 1.1

In order to confirm this supposition, the reactivity of the mesylates **3b**, **20**, and **21** were compared (Chart 1.1). The C(4)-monomethylated mesylate **20** was indeed much more reactive than the unsubstituted mesylate **3b**. In **20** the developing carbocationic center at C(3) is better stabilized and, therefore, formed faster because the Me group at C(4) allows a stronger σ -participation of the C(4)–C(5) bond.

The introduction of a second Me group at C(4) as in **21**, did not result in extra stabilization of the carbocationic center at C(3). The lack of extra stabilization in **21**

is attributed to the combined action of the 1,3-*peri* effect³³ and the 4,4-dimethyl effect.³⁴ As a result, the C(4)–C(5) bond is no longer antiperiplanar to the developing p orbital of the carbocationic center at C(3) and efficient stabilization of the cationic center is prevented.

Although conformational effects confused the results of the studies on **3b**, **20**, and **21**, it is clear that alkyl substituents α to the sulfonate group do facilitate its heterolysis.

1.4 Other Consequences of TBI

It has been shown extensively that the occurrence of TBI between two functionalities can be reflected in the UV-, CD-, PES-, and ESR-spectra of molecules.¹³ Especially, PES-spectroscopy has proven to be an excellent instrument to analyze these interactions, since the experimental ionization energies can be assigned to the orbital energies of the corresponding compound.³⁵ In contrast to the overwhelming amount of spectroscopic evidence for the occurrence of TBI between two functionalities, relatively few examples are known of the chemical consequences of orbital interactions through three or more σ -bonds.¹⁴ Some examples of the chemical consequences of TBI are presented in the sections 1.4.1 – 1.4.4. The first two examples, the solvolysis of 2-*exo*-norbornyl tosylates and the Cieplak model for diastereoface selection, will illustrate that it is often difficult to determine whether and/or how these interactions are operating.

1.4.1 The Solvolysis of 2-*exo*-Norbornyl Tosylates

Grob et al.³¹ have shown that the solvolysis rate of 2-*exo*-norbornyl tosylates (**22**) depends on the presence of remote substituents (R) (Chart 1.2). The sensitivity of the solvolysis upon the inductive effect of the substituents is expressed in a reaction constant (the ρ_I value). Two different views are given to explain how the inductive effect of a substituent is transmitted through the norbornane skeleton. In Grob's view this transmission can predominantly be ascribed to 1,3-bridging. In structure **23**, which can be considered as a resonance hybrid of the canonical forms **25** – **27**,^{36,37} the degree of 1,3-bridging will be large since the (incipient) carbocationic center at C(2) can be stabilized effectively by the back lobe of the R–C(6) orbital.

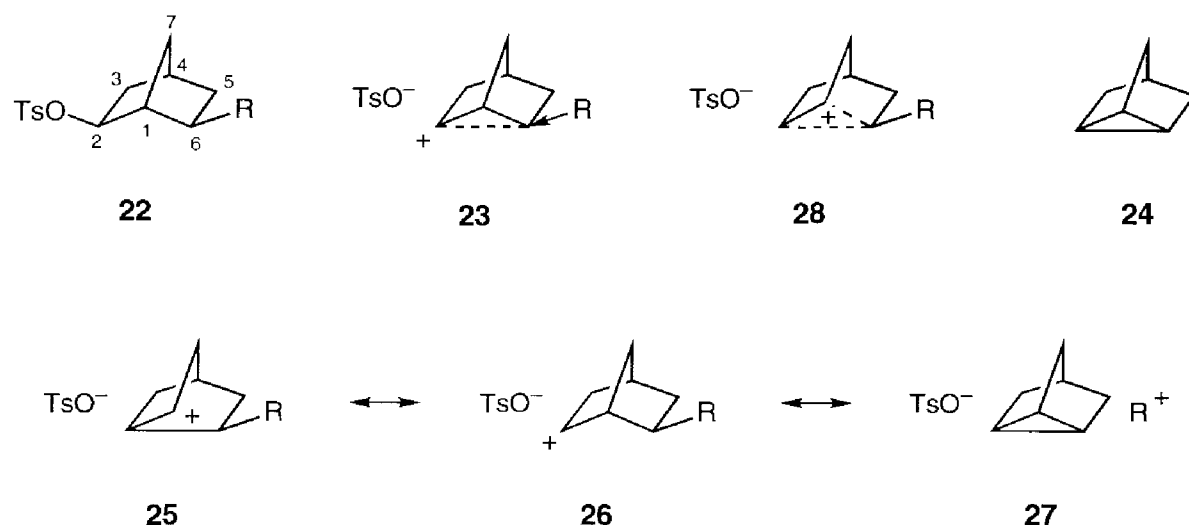


Chart 1.2

To the opinion of Lenoir et al.,³¹ 1,3-bridging plays no role of importance in the stabilization of the carbocationic center at C(2). In their mechanism, the substituent R attenuates inductively the electron density of the C(1)–C(6) bond and its ability to participate in hyperconjugation. The stabilization of the carbocationic center via hyperconjugation of the C(1)–C(6) bond is depicted in structure 28, which is only a resonance hybrid of the canonical forms 25 and 26.

It is noteworthy, that potentially electrofugal groups ($R = \text{CH}_2\text{NH}_2$, CH_2OH , CONH_2 and COO^-) results in a much faster solvolysis of the sulfonate ester at C(2) than can be expected solely on the basis of the inductive effects of these substituents.³⁸ These rate enhancements are attributed to the σ -electron donor ability of these substituents in fragmentation reactions. In fact, upon solvolysis of some of these compounds, small amounts of the homofragmented product 24 were formed.²²

1.4.2 The Cieplak Model for Diastereoface Selection

The 5-substituted 2-adamantanones 29 and their derivatives have served as probes for studying the electronic component involved during face selection in electrophilic addition,³⁹ the capture of carbenes,⁴⁰ radicals,⁴¹ carbocations,⁴² carbanions,⁴³ sulfur oxidation,⁴⁴ thermal⁴⁵ and photo-cycloadditions,⁴⁶ and sigmatropic shifts.⁴⁷ In all these reactions the reagent preferentially attacks that face which is anti to the more electron-rich pairs of vicinal bonds [$\text{C}_1\text{--C}_9$; $\text{C}_3\text{--C}_4$ (30) vs $\text{C}_1\text{--C}_8$; $\text{C}_3\text{--C}_{10}$ (31), see Figure 1.2]. The rational behind this rule is Winstein's σ -participation⁴⁸ in case of cations and Cieplak's transition state hyperconjugation⁴⁹

in case of addition to double bonds. In both models, transition state hyperconjugation, which is TBI, can be performed more efficiently by the more electron-rich vicinal bonds.⁵⁰

Acceptance of this model is widespread,⁵¹ but is certainly not universal. Several other explanations for this face selection are proposed in the literature, among them are pyramidalization of the trigonal carbon,⁵² orbital distortion of the π -bond,⁵³ torsional effects,⁵⁴ chelation,⁵⁵ and electrostatic effects,⁵⁶ all in addition to the Ahn and Felkin models of transition state hyperconjugation.⁵⁷

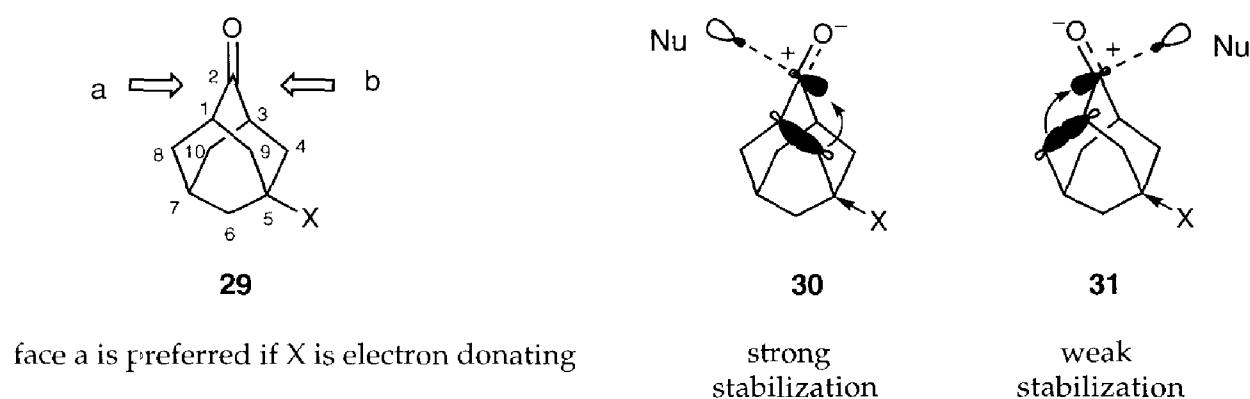


Figure 1.2

1.4.3 The Photochemical Cleavage of Carbon-Chlorine Bonds

Upon photochemical excitation, the cleavage of the C-Cl bonds of *exo*-6-chloro-2-(trimethyl-siloxy)-norbornene **32** and *exo*-2-chlorobenzonorbornene **34** is much faster (8-times and 30-times, respectively) than that of the corresponding *endo* isomers **33** and **35**, respectively (Chart 1.2).⁵⁸ The relative lability of the C-Cl bond in **32** and **34** can be understood in terms of through-space and through-bond interactions between the localized π^* orbitals at C(2) and C(3) and the C-Cl σ^* orbital. These interactions are, for stereoelectronic reasons, nearly absent in the corresponding *endo* isomers.

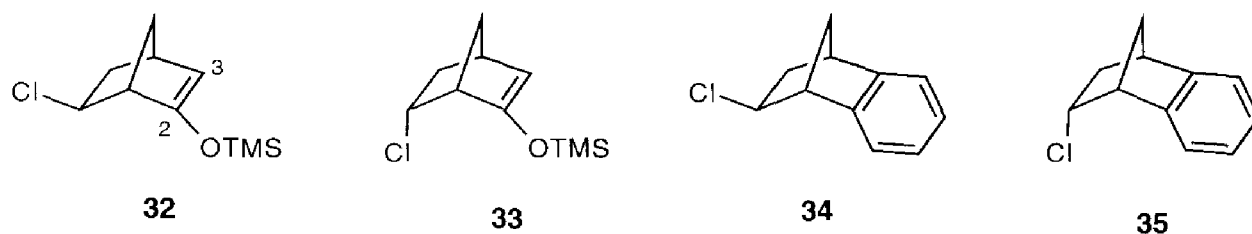
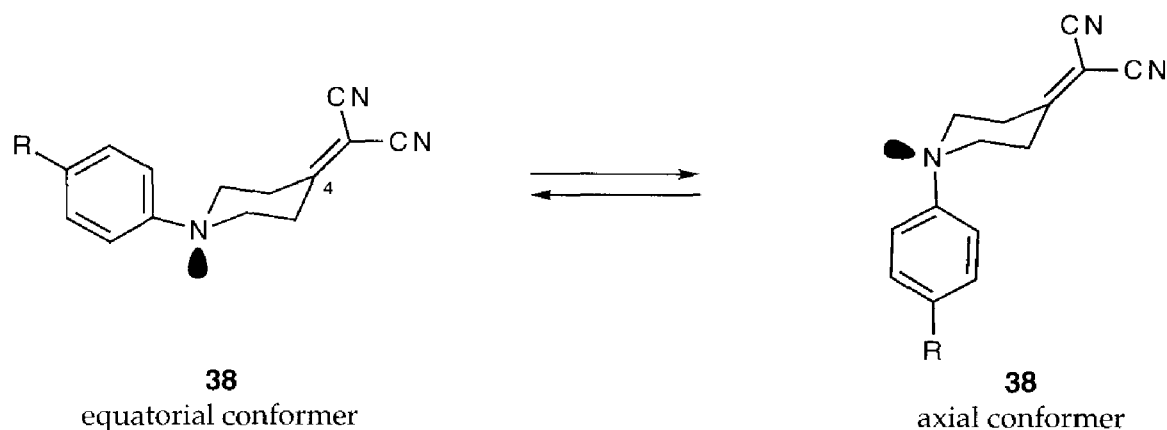


Chart 2.2

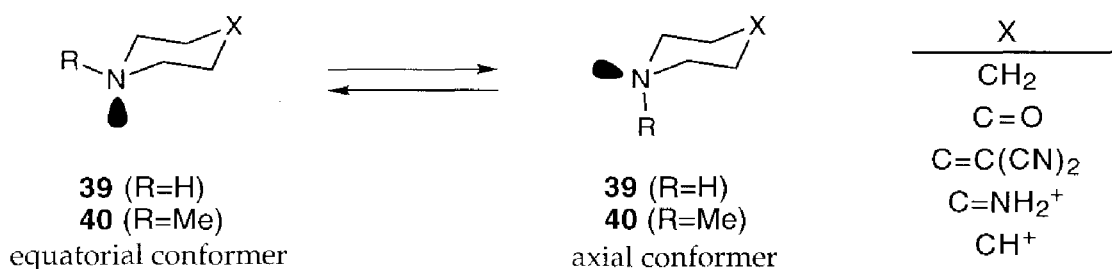
1.4.4 The Influence of TBI on Conformation Equilibria

Almost 25 years ago, Gleiter et al.^{16a} predicted that TBI should lead to pyramidalization of the π -acceptor at C(4) and to an increase in the length of the central C–C bonds (C(2)–C(3) and C(5)–C(6)) in the 4-piperidyl carbocation ion **39** ($X = CH^+$). Recently, such geometric effects have indeed been observed in the crystal structures of the 1-phenylpiperidone derivatives **38** (Scheme 1.8).^{13c}



Scheme 1.8

Equilibrium studies on **38** and extensive calculations on 4-substituted piperidine **39** and N-methylpiperidine derivatives **40** (Scheme 1.9) have confirmed that sterically disfavored conformers with an axial N-substituent are better stabilized by TBI than the equatorial conformers.⁵⁹ As a result of a stronger electron donor–acceptor interaction, the stabilization of the axial conformer of **39** and **40** increases if the strength of the acceptor increases in these systems. These stabilizing effects are even more dominant in the transition state for N inversion since then the donor–acceptor energy gap is smaller.



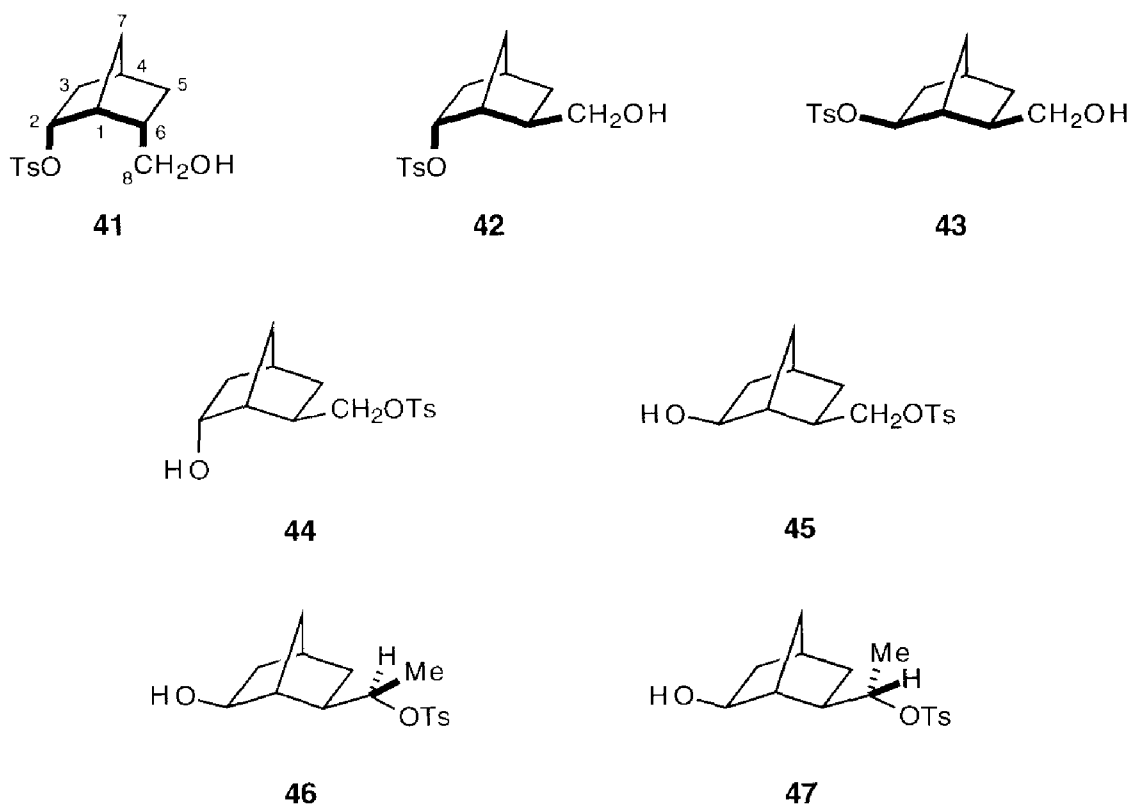
Scheme 1.9

Furthermore, in the axial conformations and in the transition state for N inversion the central C–C bonds are always longer than those in the equatorial

conformation in which no noticeable effect of TBI is observed. In the axial conformations the trend can be observed that stronger TBI go together with an elongation of the central C–C bonds. This holds when different acceptors X are compared and also when N–H is replaced by N-methyl.

1.5 Scope of this Thesis

The results discussed in section 1.3 strongly suggest that rigid *trans*-perhydronaphthalenes-1,4-diol monosulfonate esters react by heterolysis of the sulfonate ester bond induced by long-range orbital interactions with an alkoxide. Whether these long-range orbital interactions also occur in other rigid 1,4-diol monosulfonates will be explored in Chapter 2. For this purpose, seven monotosylated norbornane-1,4-diols (**41–47**; Scheme 1.10) have been designed to investigate the influence of the σ -relay (U-, sickle-, or W-shaped) between the donor and acceptor end of the system, to check whether primary carbocationic ion pairs can act as intermediates, and to study conformational influences on the reactivity and product formation.

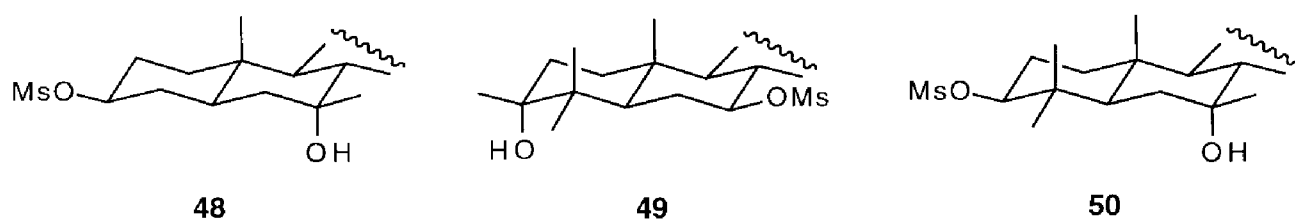


Scheme 1.10

A Molecular Orbital (MO) description of the heterolysis of 1,4-diol monosulfonate esters will be presented in Chapter 3. This description is able to account for several important features observed for the reactions described in Chapter 2.

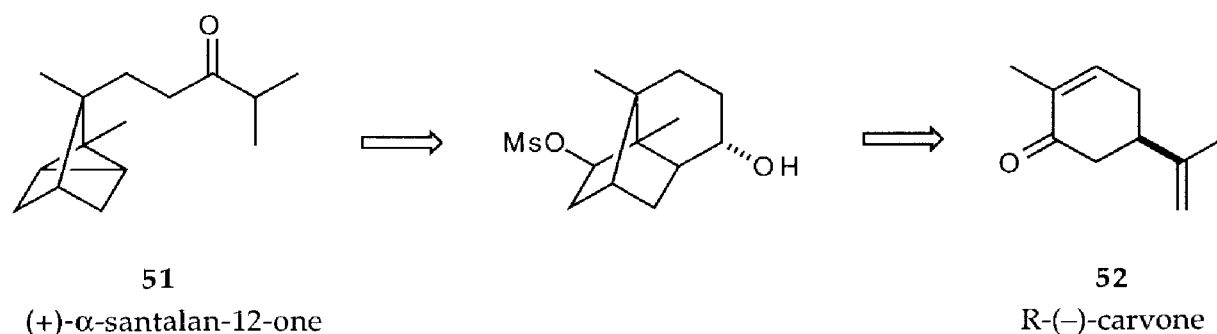
As has been found in Chapter 2, the silyl ether bond of tosylate **43** is remarkably unstable. It is assumed that the remote tosylate group facilitates the cleavage of the Si–O bond, probably by a similar TBI-controlled mechanism which is responsible for the heterolysis of the sulfonate ester bond. In order to find out whether this is a generally occurring interaction, the rate of desilylation of the silyl ethers of the sulfonates **41–47** is studied (Chapter 4).

Whether long-range orbital interactions are still operative in rigid 1,5-diol monosulfonate esters will be studied in Chapter 5. The easily accessible cholestane-3,7-diol monomesylates **48–50** (Scheme 1.11), having an ideal all-trans geometry of the σ -relay, have been selected as 1,5-diol monosulfonate esters. The main goal of this research will be to probe the possibility of a seven-center fragmentation.



Scheme 1.11

Chapter 6 will describe the total synthesis of chiral α -santalan-12-one (**51**) from *R*-(-)-carvone **52** (Scheme 1.12). In the synthetic route towards **51**, the selective homofragmentation described in Chapter 2 will be used as the key step.



Scheme 1.12

1.6 References and Notes

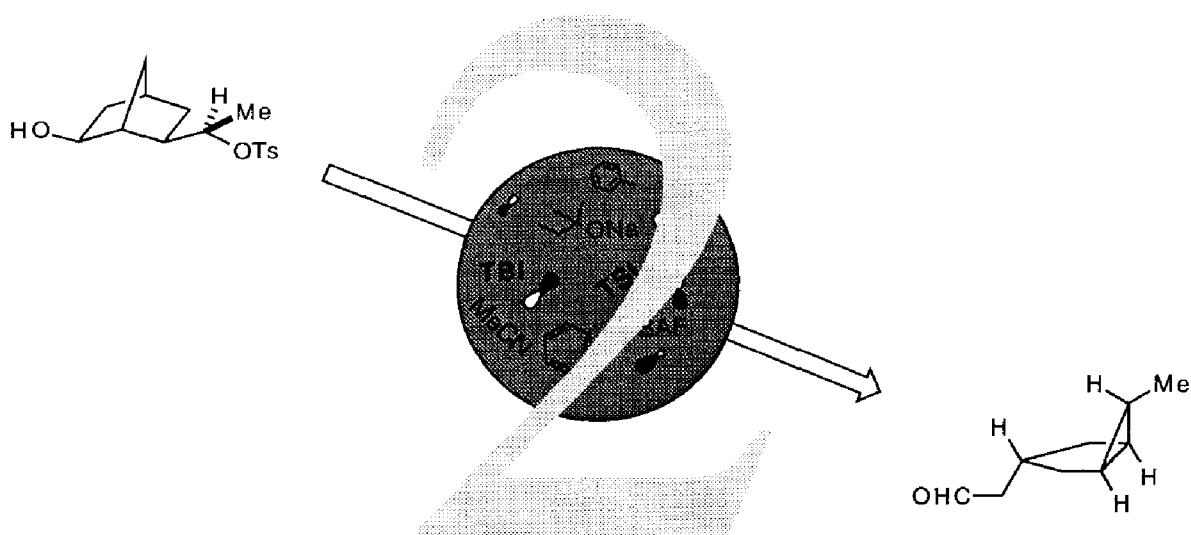
- 1 Wijnberg, J. B. P. A.; Jenniskens, L. H. D.; Brunekreef, G. A.; de Groot, A. *J. Org. Chem.* **1990**, *55*, 941.
- 2 Jenniskens, L. H. D.; Wijnberg, J. B. P. A.; de Groot, A. *J. Org. Chem.* **1991**, *56*, 6585.
- 3 For example see: Ando, M.; Akahane, A.; Yamaoka, H.; Takase, K. *J. Org. Chem.* **1982**, *47*, 3909.
- 4 Other base/solvent combinations than sodium *tert*-amylate/benzene or toluene showed less selectivity. See: L.H.D. Jenniskens; Ph.D. Thesis, Wageningen Agricultural University, 1992.
- 5 (a) Bartsch, R. A. *Acc. Chem. Res.* **1975**, *8*, 239. (b) Sneen, R. A. *Acc. Chem. Res.* **1973**, *6*, 46.
- 6 (a) Hoffmann, R.; Imamura, A.; Hehre, W. J. *J. Am. Chem. Soc.* **1968**, *90*, 1499. (b) Hoffmann, R. *Acc. Chem. Res.* **1971**, *4*, 1.
- 7 Dewar, M. J. S. *J. Am. Chem. Soc.* **1984**, *106*, 669.
- 8 Paddon-Row M. N.; Jordan, K. D.; *J. Am. Chem. Soc.* **1993**, *115*, 2952.
- 9 Paulson, B. P.; Curtiss, L. A.; Bal, B.; Closs, G. L.; Miller, J. R. *J. Am. Chem. Soc.* **1996**, *118*, 378 and references cited therein.
- 10 Paddon-Row, M. N. *Acc. Chem. Res.* **1982**, *15*, 245.
- 11 Jordan K. D.; Paddon-Row, M. N. *Chem. Rev.* **1992**, *92*, 395 and references cited therein.
- 12 Paddon-Row, M. N.; Verhoeven, J. W. *New J. Chem.* **1991**, *15*, 107.
- 13 For example, see: (a) Kovac, B.; Novak, I.; Mlinaric-Majerski, K.; Vinkovic, M.; Kaselj, M. *J. Org. Chem.* **1994**, *59*, 3033. (b) Kroon, J.; Oliver, A. M.; Paddon-Row, M. N.; Verhoeven, J. W. *J. Am. Chem. Soc.* **1990**, *112*, 4868. (c) Krijnen, B.; Beverloo, H. B.; Verhoeven, J. W.; Reiss, C. A.; Goubitz, K.; Heijdenrijk, D. *J. Am. Chem. Soc.* **1989**, *111*, 4433. (d) Schneider, H.-J.; Weigand, E. F.; Becker, N. *J. Org. Chem.* **1988**, *53*, 3361. (e) Closs, G. L.; Calcaterra, L. T.; Green, N. J.; Penfield, K. W.; Miller, J. R. *J. Phys. Chem.* **1986**, *90*, 3673. (f) Snow, L. D.; Williams, F. J. *Chem. Soc., Chem. Commun.* **1983**, 1090. (g) Martin, H.-D.; Mayer, B. *Angew. Chem.* **1983**, *95*, 281. (h) Pasman, P.; Rob, F.; Verhoeven, J. W. *J. Am. Chem. Soc.* **1982**, *104*, 5127. (i) Bartetzko, R.; Gleiter, R.; Muthard, J. L.; Paquette, L. A. *J. Am. Chem. Soc.* **1978**, *100*, 5589.
- 14 For a recent review on this subject, see: Orrü, R. V. A. Ph.D. Thesis, Wageningen Agricultural University, 1993 and references cited therein.
- 15 Grob, C. A. *Angew. Chem., Int. Ed. Engl.* **1969**, *8*, 535 and references cited therein.
- 16 (a) Gleiter, R.; Stohrer, W.-D.; Hoffmann, R. *Helv. Chim. Acta* **1972**, *55*, 893. (b) Gleiter, R. *Angew. Chem., Int. Ed. Engl.* **1974**, *13*, 696.
- 17 The Retro-Claisen, Retro-Mannich and Retro-Dieckmann reactions, probably occur via a similar mechanism as the Grob fragmentation. For an extensive review on these fragmentation reactions, see reference 18.
- 18 Ho, T.-L. In *Heterolytic Fragmentation of Organic Molecules*; Wiley-Interscience New York, **1993**.
- 19 Caine, D. *Org. Prep. Proced. Int.* **1988**, *20*, 1.
- 20 Orrü, R. V. A.; Wijnberg, J. B. P. A.; Jenniskens, L. H. D.; de Groot, A. *J. Org. Chem.* **1993**, *58*, 1199.

- 21 Throughout the text of this paper, the same definitions for TBI and TSI are used as those used by Paddon-Row.⁸ Consequently, 1,3-bridging is defined as TBI unless it involves the orbitals of the functional groups having a direct interaction.
- 22 Fischer, W.; Grob, C. A.; Hanreich, R.; von Sprecher, G.; Waldner, A. *Helv. Chim. Acta* **1981**, *64*, 2298.
- 23 The Li⁺-O⁻ bond has more covalent character than the Na⁺-O⁻ bond. Consequently, the lithium as the counter ion of the alkoxide group confines the negative charge to the alkoxide in a greater extent than sodium and reduces 1,3-bridging. See: Paquette, L. A.; Gilday, J. P. *J. Org. Chem.* **1988**, *53*, 4972.
- 24 Orrū, R. V. A.; Wijnberg, J. B. P. A.; Bouwman, C. T.; de Groot, A. *J. Org. Chem.* **1994**, *59*, 374.
- 25 Jakupovic, J.; Schuster, A.; Bohlmann, F.; King, R. M.; Haegi, L. *Phytochemistry* **1989**, *28*, 1943.
- 26 Ahmed, A. A.; Jakupovic, J.; Bohlmann, F. *Phytochemistry*, **1990**, *29*, 3355.
- 27 Sakui, N.; Kuroyanagi, M.; Ishitobi, Y.; Sato, M.; Ueno, A. *Phytochemistry*, **1992**, *31*, 143.
- 28 Piet, D. P.; Schrijvers, R.; Franssen, M. C. R.; de Groot, A. *Tetrahedron*, **1995**, *51*, 6303.
- 29 (a) Hartman, G. D.; Traylor, T. G. *J. Am. Chem. Soc.* **1975**, *97*, 6147. (b) Martinez, A. G.; Barcina, J. O.; Herrero, M. E. R.; Dios, M. I.; Vilar, E. T.; Subramanian, L. R. *Tetrahedron Lett.* **1994**, *11*, 1793 and references therein cited.
- 30 (a) Grob, C. A. *Angew. Chem.* **1982**, *94*, 87. (b) Grob, C. A. *Acc. Chem. Res.* **1983**, *16*, 426 and references therein cited.
- 31 Lenoir, D.; Apeloig, Y.; Arad, D.; Schleyer, P. v. R. *J. Org. Chem.* **1988**, *53*, 661.
- 32 Orrū, R. V. A.; Wijnberg, J. B. P. A.; de Groot, A. *J. Org. Chem.* **1995**, *60*, 4233.
- 33 Shibata, T.; Ohkura, T.; Shimizu, N.; Inayama, S. *Heterocycles* **1986**, *24*, 893.
- 34 It is known from CD measurements that ring A of 4,4-dimethyl-3-keto steroids adopts a (twist)boat conformation: Tsuda, Y.; Kiuchi, F. *Chem. Pharm. Bull.* **1984**, *32*, 4806 and references cited therein.
- 35 Albert, B.; Elsässer, D.; Heckel, D.; Kopmeier, S.; Martin, H.-D.; Mayer, B.; Chow, T. J.; Wu, T.-K.; Yeh, S.-K. *Chem. Ber.* **1991**, *124*, 803.
- 36 (a) Grob, C. A.; Günther, B.; Hanreich, R. *Helv. Chim. Acta* **1981**, *64*, 2312. (b) Grob, C. A.; Günther, B.; Hanreich, R.; Waldner, A. *Tetrahedron Lett.* **1981**, *22*, 835. (c) Grob, C. A.; Hanreich, R.; Waldner, A. *Tetrahedron Lett.* **1981**, *22*, 3231.
- 37 Brown, H. C. *The Nonclassical Ion Problem* (with comments by P. v. R. Schleyer); Plenum Press, New York, London, **1977**, chapter 6.
- 38 Grob, C. A.; Schaub B. *Helv. Chim. Acta* **1982**, *65*, 1720.
- 39 Srivastava, S.; le Noble, W. J. *J. Am. Chem. Soc.* **1987**, *109*, 5874.
- 40 le Noble, W. J.; Chiou, D.-M.; Okaya, Y. *J. Am. Chem. Soc.* **1979**, *101*, 3244.
- 41 Bodepudi, V. R.; le Noble, W. J. *J. Org. Chem.* **1991**, *56*, 2001.
- 42 (a) Xie, M.; le Noble, W. J. *J. Org. Chem.* **1989**, *54*, 3839. (b) Adcock, W.; Coope, J.; Shiner, V. J.; Trout, N. A. *J. Org. Chem.* **1990**, *55*, 1411.
- 43 Bodepudi, V. R.; le Noble, W. J. *J. Org. Chem.* **1994**, *59*, 3265.
- 44 Mukherjee, A. K.; le Noble, W. J. *J. Org. Chem.* **1993**, *58*, 7955.
- 45 Li, H.; Silver, J. E.; Watson, W. H.; Kashyap, R. P.; le Noble, W. J. *J. Org. Chem.* **1991**, *56*, 5932.
- 46 Chung, W.-S.; Turro, N. J.; Srivastava, S.; le Noble, W. J. *J. Org. Chem.* **1991**, *56*, 5020.
- 47 Mukherjee, A. K.; Wu, Q.; le Noble, W. J. *J. Org. Chem.* **1994**, *59*, 3270.
- 48 Winstein, S.; Trifan, D. *J. Am. Chem. Soc.* **1952**, *74*, 1147.

- 49 (a) Cieplak, A. S. *J. Am. Chem. Soc.* **1981**, *103*, 4540. (b) Cieplak, A. S.; Tait, B. D.; Johnson, C. R. *J. Am. Chem. Soc.* **1989**, *111*, 8447.
- 50 Li, H.; le Noble, W. J. *Recl. Trav. Chim. Pays-Bas* **1992**, *111*, 199.
- 51 For some recent examples, see: (a) Leanna, M. R.; Martinelli, M. J.; Varie, D. L.; Kress, T. *J. Tetrahedron Lett.* **1989**, *30*, 3935. (b) Coxon, J. M.; McDonald, D. Q. *Tetrahedron Lett.* **1992**, *33*, 651. (c) Senda, Y.; Nakano, S.; Kunii, H.; Itoh, H. *J. Chem. Soc., Perkin Trans. 2* **1993**, 1009. (d) Mehta, G.; Khan, F. A. *J. Chem. Soc. Perkin Trans. 1* **1993**, 1727. (e) Gung, B. W.; Francis, M. B. *Tetrahedron Lett.* **1995**, *36*, 2579.
- 52 (a) Rondan, N. G.; Paddon-Row, M. N.; Caramella, P.; Houk, K. N. *J. Am. Chem. Soc.* **1981**, *103*, 2436. (b) Seebach, D.; Maetzke, T.; Petter, W.; Klötzer, B.; Pattner, D. A. *J. Am. Chem. Soc.* **1991**, *113*, 1781.
- 53 (a) Paquette, L. A.; Gugelchuk, M. J. *Org. Chem.* **1988**, *53*, 1835. (b) Ohwada, T.; Okamoto, I.; Haga, N.; Shudo, K. *J. Org. Chem.* **1994**, *59*, 3975.
- 54 (a) Wu, Y.-D.; Tucker, J. A.; Houk, K. N. *J. Am. Chem. Soc.* **1991**, *113*, 5018. (b) Damm, W.; Giese, B.; Hartung, J.; Hasskerl, T.; Houk, K. N.; Hüter, O.; Zipse, H. *J. Am. Chem. Soc.* **1992**, *114*, 4067. (c) Coxon, J. M.; Houk, K. N.; Luibrand, R. T. *J. Org. Chem.* **1995**, *60*, 418.
- 55 (a) Reetz, M. T.; Harms, K.; Rief, W. *Tetrahedron Lett.* **1988**, *29*, 5881. (b) Chen, X.; Hortelano, E. R.; Eliel, E. L.; Frye, S. V. *J. Am. Chem. Soc.* **1992**, *114*, 1778.
- 56 (a) Wong, S. S.; Paddon-Row, M. N. *J. Chem. Soc., Chem. Commun.* **1991**, 327. (b) Paddon-Row, M. N.; Wu, Y.-D.; Houk, K. N. *J. Am. Chem. Soc.* **1992**, *114*, 10638. (c) Ganguly, B.; Chandrasekhar, J.; Khan, F. A.; Mehta, G. *J. Org. Chem.* **1993**, *58*, 1734.
- 57 For a discussion of all three hyperconjugation models, see reference 50.
- 58 (a) Maxwell, B. D.; Nash, J. J.; Morrison, H. A.; Falcetta, M. L.; Jordan, K. D. *J. Am. Chem. Soc.* **1989**, *111*, 7914. (b) Nash, J. J.; Carlson, D. V.; Kasper, A. M.; Love, D. E.; Jordan, K. D.; Morrison, H. J. *J. Am. Chem. Soc.* **1993**, *115*, 8969. (c) Post, A. J.; Nash, J. J.; Love, D. E.; Jordan, K. D.; Morrison, H. J. *J. Am. Chem. Soc.* **1995**, *117*, 4930.
- 59 Brouwer, A. M.; Krijnen, B. *J. Org. Chem.* **1995**, *60*, 32 and references cited therein.

Chapter 2

Chemical Consequences of Through-Bond Interactions in Monotosylated Norbornane-1,4-Diols



Abstract. Seven monotosylated 1,4-diols with the rigid norbornane skeleton were treated with a strong base in refluxing benzene to find out whether these compounds react by initial heterolysis of the tosylate ester bond induced by long-range orbital interactions. The tosylates **1–7** were designed to investigate the influence of the σ -relay (U-, sickle-, or W-shaped) between the donor and acceptor end of the system, to check whether primary carbocationic ion pairs could act as intermediates, and to study conformational influences on reactivity and product formation. Tosylate **1** with an U-like arrangement of the σ -relay reacted relatively slowly and followed reaction pathways in which no long-range orbital interactions are involved. The reaction outcome of tosylate **2** which possesses a sickle-like arrangement of the σ -relay indicates two competitive processes with and without the involvement of long-range orbital interactions. The secondary tosylates **3**, **6**, and **7** which all possess a W-like arrangement reacted relatively fast and showed predominantly homofragmentation. Although an ideal W-like arrangement is present in the primary tosylates **4** and **5**, no reactions in which long-range orbital interactions are involved were observed. The tosylates **6** and **7** in which the tosylate group is conformationally mobile can give rise to mixtures of products. The ratio in which these products are formed can be rationalized by using the Curtin-Hammett principle.

2.1 Introduction

From previous work on the total synthesis of sesquiterpenes^{1,2} (see also Chapter 1, Section 1.1), it is known that monosulfonate esters of rigid *trans*-perhydronaphthalene-1,4-diols react smoothly upon treatment with sodium *tert*-amylate in refluxing apolar solvents like benzene or toluene. Long-range orbital interactions are thought to play an important role in these reactions (see Chapter 1, Section 1.2). The theoretical basis for these orbital interactions through bonds (TBI) and through space (TSI), first described by Hoffmann,³ is nowadays well-established by theoretical and experimental studies.⁴

More detailed investigations on rigid *trans*-perhydronaphthalene-1,4-diol monosulfonate esters under strongly basic conditions indicated that the reactivity of these compounds depends on (i) the orientation and position of the sulfonate ester group^{5,6} and (ii) the position of the hydroxyl function relative to the sulfonate ester group.⁶ The orientation of the hydroxyl group has little or no influence on the reactivity. The extent of the orbital interactions as well as the product composition is determined by the geometry of the relaying σ -bonds between the electron donor (alcoholate) and the electron acceptor (sulfonate ester bond). Homofragmentation, β -elimination, and rearrangement are the main processes observed.

These findings needed confirmation for *other* rigid 1,4-diol monosulfonate esters. Therefore, it was decided to examine the 1,4-diol monotosylate esters **1–7** all with a rigid norbornane skeleton (Chart 2.1). Compared with other rigid systems, these compounds have several advantages: (i) they possess a well-defined geometry of the relaying σ -bonds between the electron donor and electron acceptor, (ii) their synthesis is not very complicated, and (iii) C(6) substituted 2-norbornyl sulfonate esters⁷ have been extensively studied by Grob et al.,⁸ so the spectral and physical data of their products might facilitate the structural assignments of the products found in this study.

As indicated in Chart 2.1 by the bold bonds, the tosylates **1–3** all have a different geometry of the σ -relay: the U-, the sickle-, and the W-like arrangement, respectively. From the reactions of **1–3** with sodium *tert*-amylate in refluxing benzene, we expect to obtain information about the influence of these different geometries on the transmission of orbital interactions in these compounds and on the chemical consequences of these interactions. The reactions of the tosylates **4** and **5** were performed to determine whether the alkoxide function is capable of

inducing heterolysis of a primary sulfonate ester group through three intervening C–C bonds. In addition to **4** and **5**, the corresponding secondary tosylates **6** and **7** were also investigated for obvious reasons (primary vs secondary sulfonate esters). Furthermore, the tosylate group of the compounds **4–7** can rotate freely about the C(6)–C(8) bond. Therefore, from the experiments with **4–7**, we also expect to gather information about the chemical consequences of rotational freedom in these processes.

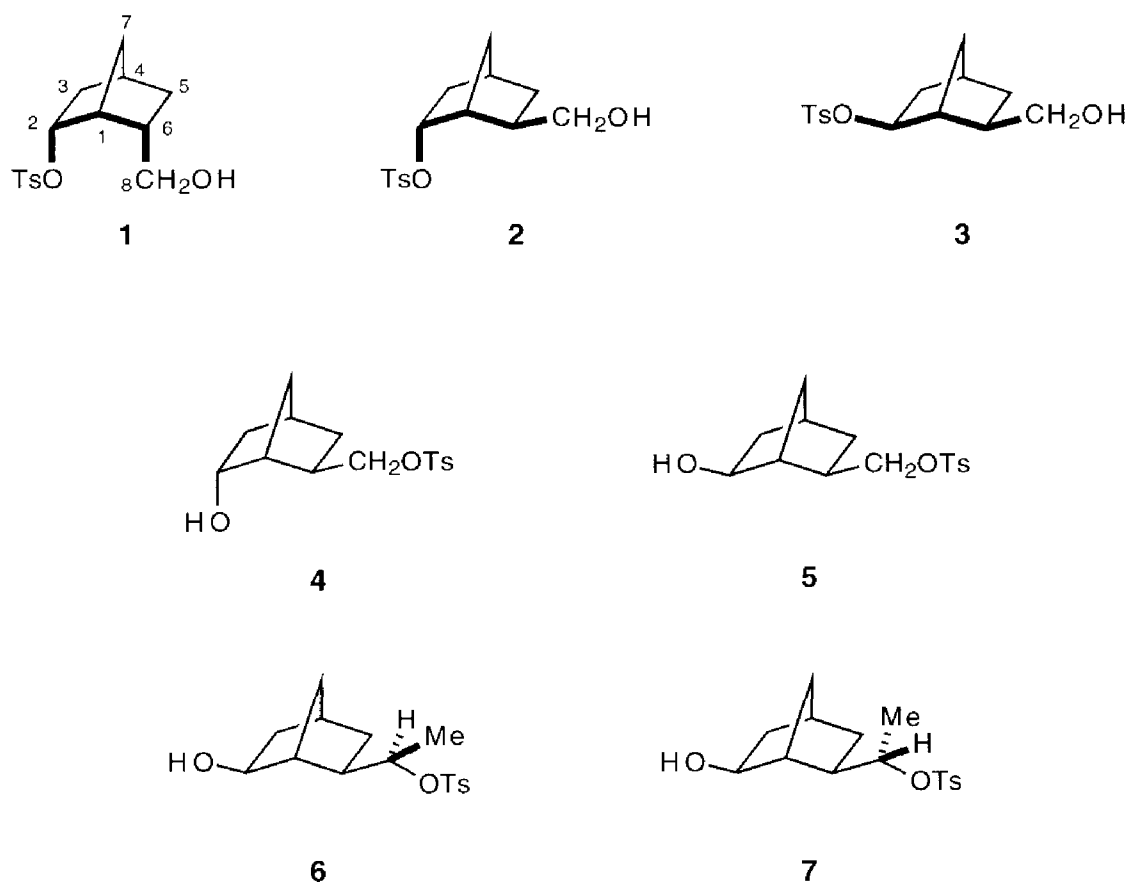
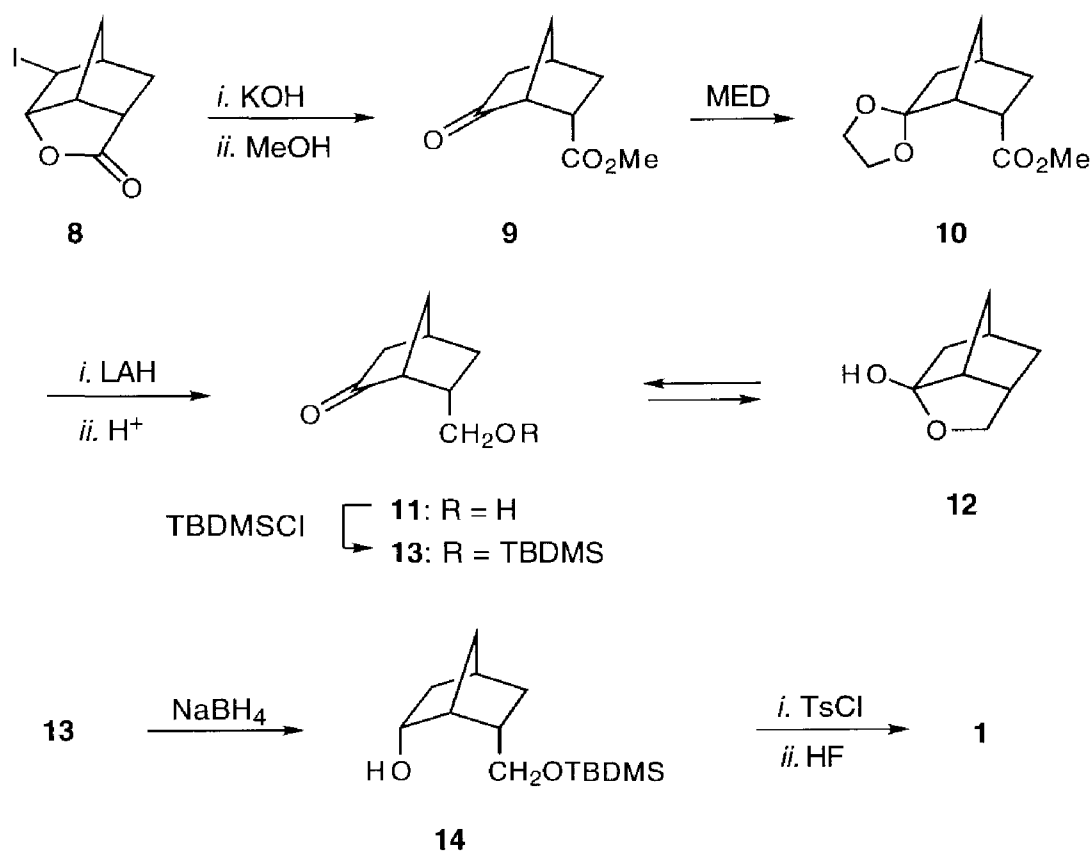


Chart 2.1

2.2 Results and Discussion

The tosylate **1** was prepared from the readily available iodo lactone **8**. Via a modified version of a known procedure, **8** was converted into the keto ester **9**⁹ (Scheme 2.1). Protection of the keto group as its ethylene acetal (**9** → **10**) was successively followed by reduction and hydrolysis to give the keto alcohol **11**. The

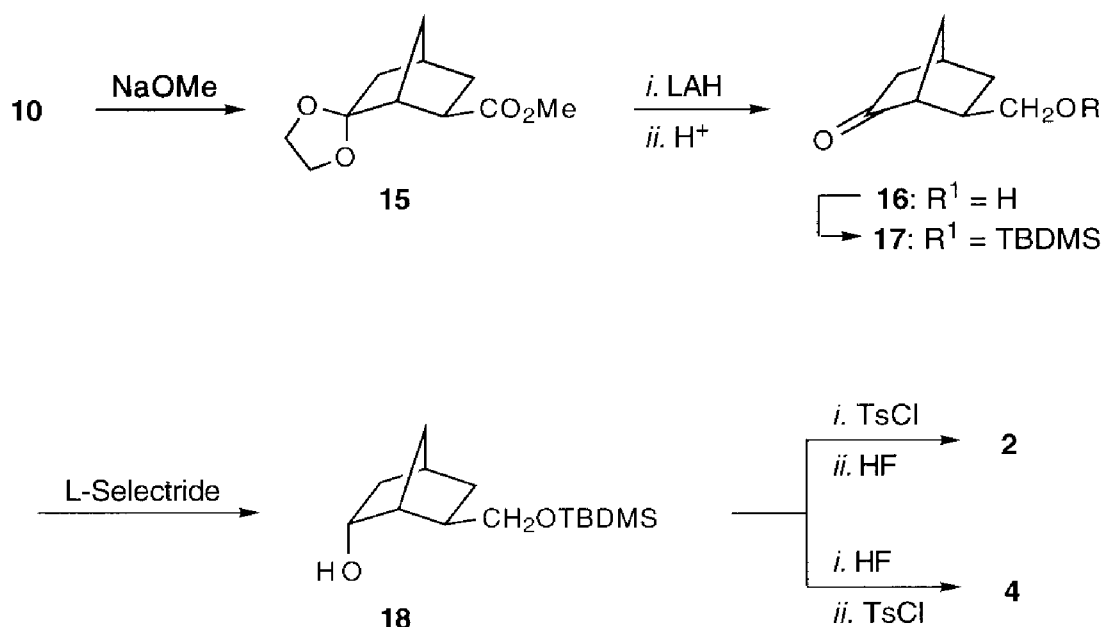
^{13}C NMR spectral data of **11** show the presence of lactol **12** in about 40%. Probably, the keto alcohol **11** exists in equilibrium with its cyclic hemiacetal form **12**. Treatment of this equilibrium mixture with TMSCl in pyridine at 0 °C afforded a mixture of the corresponding silyl ethers. On the other hand, the use of the more bulky TBDMSCl in combination with imidazole in DMF at room temperature afforded selectively the silyl ether **13**. Apparently, TBDMSCl reacts only with the primary hydroxyl group of **11** and not with the tertiary one of **12**. Reduction of **13** with NaBH_4 gave the endo alcohol **14** as the sole product. Further transformation of **14** to tosylate **1** was performed according to standard procedures. In this respect, it should be mentioned that the tosylation of **14** required an elevated temperature (80 °C). With iodo lactone **8** as starting material, the overall yield of **1** amounted to 16 %.



Scheme 2.1

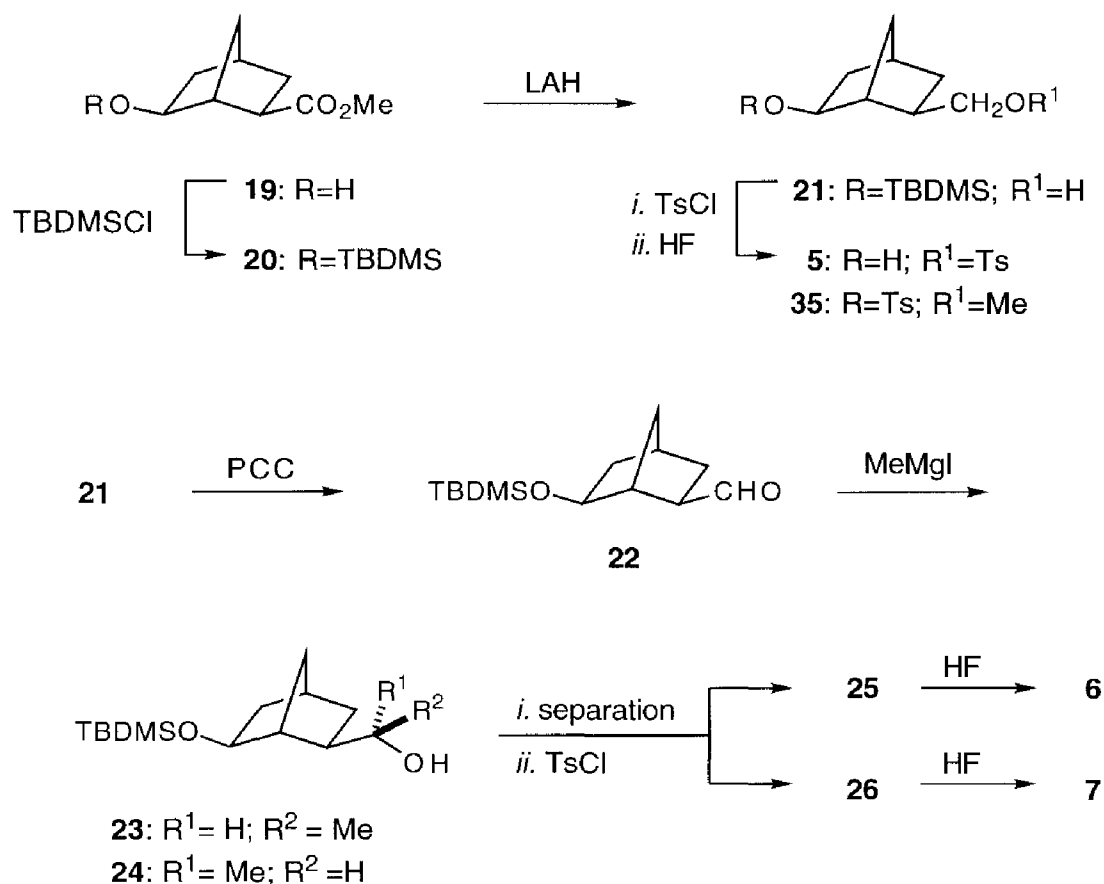
The ethylene acetal **10** was also used in the synthesis of the known tosylate **2**.¹⁰ Epimerization of the endo ester group in **10** to the exo position was achieved with NaOMe in dry MeOH to give the exo ester **15** in 62 % yield (Scheme 2.2).

In an analogous fashion as outlined above, i.e., $15 \rightarrow 16 \rightarrow 17 \rightarrow 18 \rightarrow 2$, the exo ester **15** gave the tosylate **2** in an overall yield of 53 %. In this reaction sequence, L-Selectride was used instead of NaBH_4 because the reduction of **17** with NaBH_4 produced an inseparable mixture of the endo and exo alcohol. The endo alcohol **18** was also converted into the known tosylate **4**¹¹ according to standard procedures (overall yield 41 %).



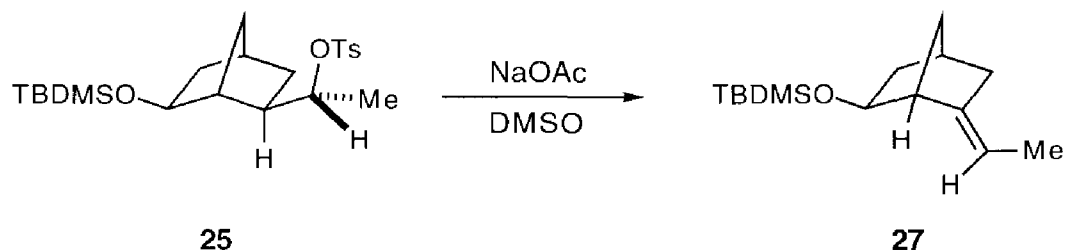
Scheme 2.2

The tosylate **3** was synthesized according to a known procedure.¹² An intermediate in this synthesis, i.e., hydroxy ester **19**, was used as starting material in the preparation of the tosylates **5–7** (Scheme 2.3). After protection of the hydroxyl group of **19**, reduction of the resulting silyl ether **20** gave the primary alcohol **21** in high yield. Tosylation and desilylation of **21** afforded the tosylate **5** in 68 % overall yield from **19**. Oxidation of the primary alcohol function in **21** with PCC produced the aldehyde **22**. Treatment of this aldehyde with an excess of MeMgI in dry ether at 0°C afforded a 1:1 mixture of the diastereoisomeric secondary alcohols **23** and **24**. After separation by column chromatography, both alcohols were tosylated to give the compounds **25** and **26**. Finally, desilylation of the latter two compounds provided the tosylates **6** and **7** in overall yields of 31 and 33 %, respectively, from **19**.



Scheme 2.3

The *R*- and *S*-configuration of **6** and **7**, respectively, followed from a thermodynamically controlled elimination experiment in which the protected tosylate **25** was treated with NaOAc in DMSO^{13,14} (Scheme 2.4). The geometry of the elimination product **27** was ascertained by ¹H NOE difference spectroscopy. Irradiation of the multiplet for the olefinic H at δ 5.36 gives a strong NOE with H-1 at δ 2.48; no NOE was observed between the methyl group and H-1. These data are consistent with the structural assignment for **27**. Since this elimination is assumed to proceed in an anti fashion, tosylate **6** must have the *R*-configuration at C(8), and consequently, tosylate **7** will have the *S*-configuration.



Scheme 2.4

In order to obtain comparable data about the reactivity of the tosylates 1–7, all these compounds were subjected to standard reaction conditions. The reactions were run in benzene at reflux temperature with ca. 5 equiv of sodium *tert*-amylate. Depending on the reaction rate, a reaction time of 1 or 10 min was maintained. By comparing the quantities of recovered starting material, a rough estimate of the relative reaction rates could be obtained. The results of these studies are collected in Table 1.

The reactions of the tosylates 1–3 were performed to investigate the influence of the geometry of the relaying σ -bonds between the hydroxyl and tosylate group on the reaction rate and product composition.

The tosylate 1 gave a mixture of three compounds: diol 28 (22 %), ditosylate 29 (22 %), and lactol 30 (12 %) (entry 1). The quantity of regained starting material after 10 min reaction time amounted to 15 %.

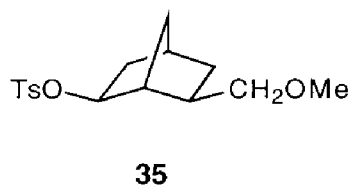
Table 1. Reactions of the Tosylates 1–7 with Sodium *tert*-Amylate^a

entry	tosylate	reaction time ^b	products ^c (%)	recovery ^d
1	1	10	28 (22) + 29 (22) + 30 (12)	15
2	2	10	31 (19) + 32 (4)	21
3	3	1	31 (78) ^e + 33 (3) ^e	0
4	4	10	36 (28) ^e	4
5	5	10	<i>f</i>	48
6	5	1	16 (5) + 37 (5) + 38 (3)	72
7	6	1	39 (51) ^g	0
8	7	1	40, 41, and 42 ^h (42) ^g + 43 (6)	24
9	7	1	40 (53) + 43 (11)	12

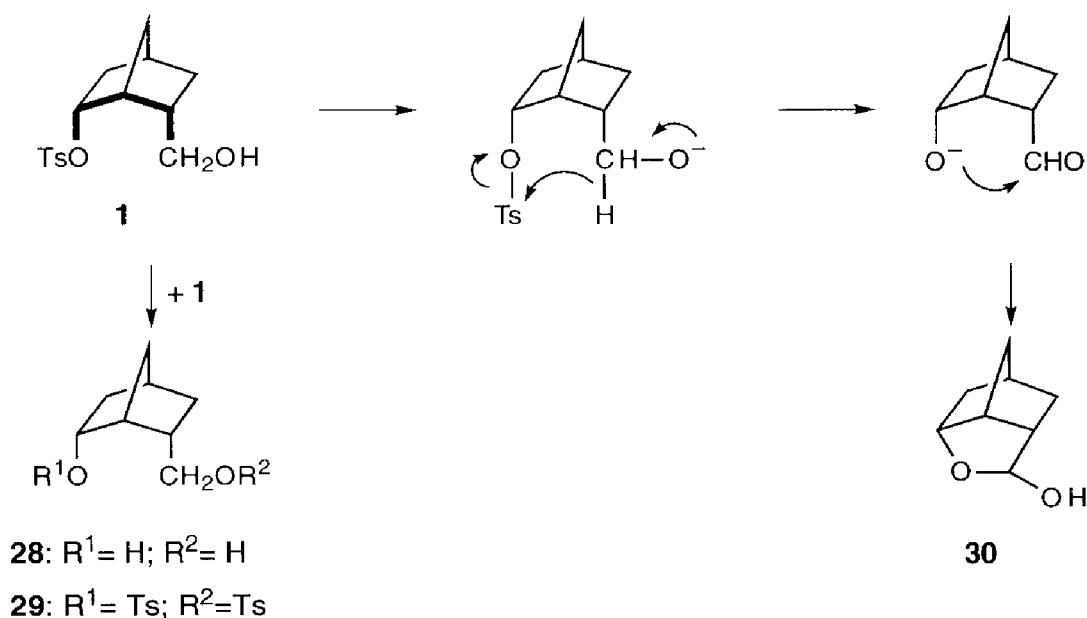
^a All reactions were performed in refluxing benzene with ca. 5 equiv of sodium *tert*-amylate, except for entry 9 in which ca. 5 equiv of sodium *tert*-amylate and 1 equiv 15-crown-5 were used. ^b Reaction time in min. ^c Isolated yield in parentheses. ^d Percentage of recovered starting material. ^e Yield was determined with capillary GC using ethylbenzene as an internal standard. ^f Complex product mixture. ^g Yield is somewhat diminished due to aldol condensations under the influence of sodium *tert*-amylate. ^h These compounds were obtained in a ratio of 15:4:1, respectively.

Treatment (10 min) of the tosylate 2 afforded nortricyclene 31 (19 %), together with a small amount of the ditosylate 32 (4 %) and recovered 2 (21 %) (entry 2). Because of the high volatility of nortricyclene, the isolation of this compound from the reaction mixture was troublesome. Therefore, the yield and identity of nortricyclene was determined in the crude extract by means of capillary GC using ethylbenzene as internal standard and GC/MS analysis, respectively. For that purpose, an authentic sample of nortricyclene was prepared according to a known procedure.¹⁵

No starting tosylate **3** was recovered from the reaction even in 1 minute runs (entry 3). On the basis of GC analysis, the major product was nortricyclene (**31**) (78 %). A small amount (3 %) of the known cyclic ether **33**¹⁶ was also formed. It should be noted that tosylate **3** entirely reacted at room temperature within 10 min to **31** (55 %) and **33** (6 %). On the other hand, the reactivity of the methyl ether **35**¹⁷ of tosylate **3** was extremely low. Under the standard conditions, this compound did not give any detectable reaction product and was regained almost quantitatively. This proves again that the presence of a free hydroxyl group is crucial in these reactions. It is also noteworthy that all attempts to obtain the TBDMS ether of tosylate **3** in pure form via column chromatography on silica gel failed because its silyl ether bond appeared to be very sensitive to hydrolysis. The silyl ether bonds in other TBDMS ethers, for instance in the TBDMS ether of tosylate **2**, were much more stable to hydrolysis.¹⁸



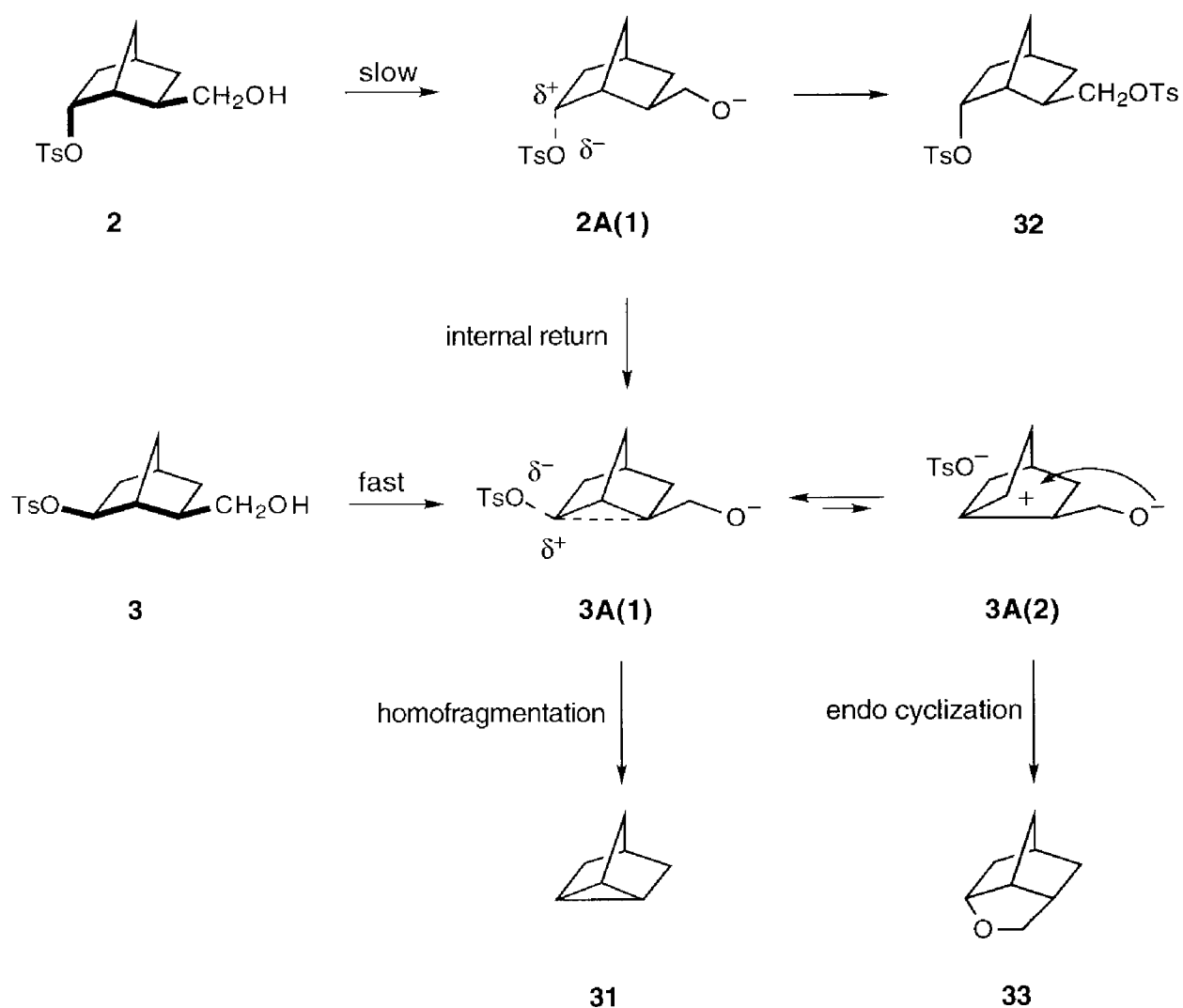
These results clearly show that the reaction rate of the tosylates **1–3** strongly depends on the geometry of their σ -relays. The tosylates **1** and **2** with an U- and sickle-like arrangement, respectively, react very slowly compared with tosylate **3** which possesses a W-like arrangement. The question arises, however, whether the tosylates **1–3** all react according to a mechanism in which orbital interactions control their reactivity and product composition. Especially in case of tosylate **1**, everything points to ordinary intra- and intermolecular substitution reactions without any participation of TBI or other long-range orbital interactions (Scheme 2.5).



Scheme 2.5

The formation of diol **28** and ditosylate **29** can easily be explained by an intermolecular nucleophilic reaction between two molecules of **1** via an attack of the primary alkoxide of one molecule on the tosylate sulfur atom of the other.¹⁹ The formation of lactol **30** probably proceeds via an intramolecular hydride transfer from C(8) bearing the alkoxide function to the sulfur atom of the tosylate group.²⁰ This results in the cleavage of the S–O bond to give an intermediate oxygen anion which then cyclizes to lactol **30**.

The reaction outcome of tosylate **2** indicates two competitive processes (Scheme 2.6). One involves the intramolecularly induced heterolysis of the tosylate group to form nortricyclene (**31**); the other, leading to ditosylate **32**, must proceed intermolecularly in a similar way as described above for the formation of **29** from tosylate **1**.



Scheme 2.6

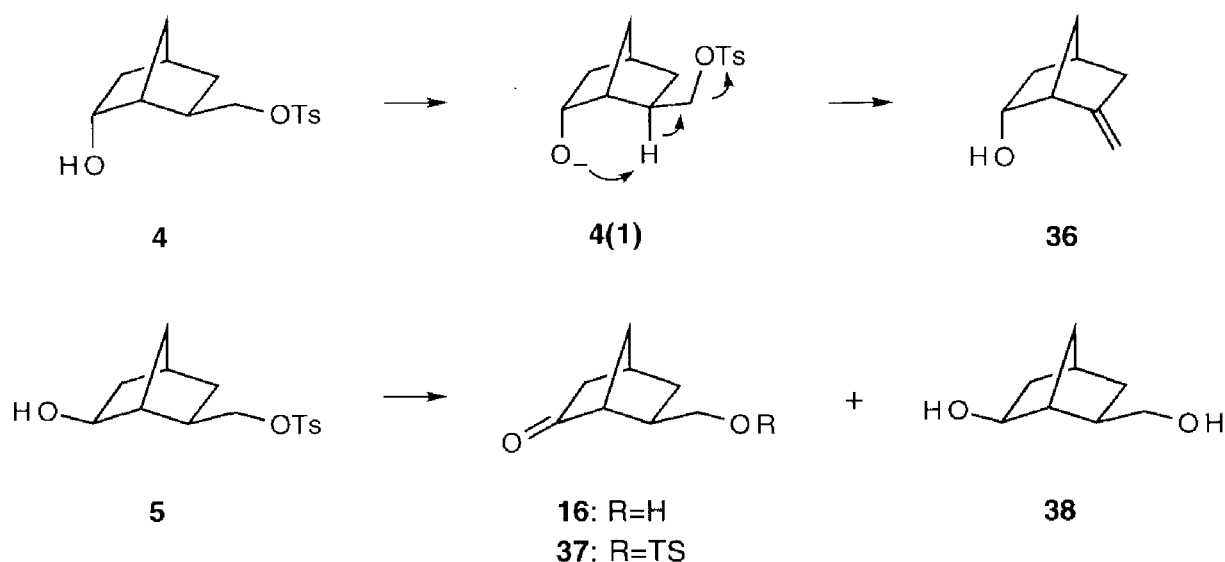
In the heterolysis step of **2**, σ -participation is not very likely because no C–C bond is antiperiplanar to the tosylate ester bond.²¹ A similar stereochemical requirement (no C–H bond antiperiplanar to the C–OTs bond) prevents σ -(C–H) participation. As a consequence, the heterolysis of tosylate **2** induced by orbital interactions will be relatively slow and intermolecular processes in which no long-range orbital interactions are involved can compete successfully with the homofragmentation pathway leading to **31**. The formation of **31** from **2** probably proceeds via an internal return with inversion of the stereochemistry of the tosylate group at C(2).⁵ Because all reactions are performed in benzene, contact ion pairs are most likely involved in the intramolecularly induced departure of the tosylate group. In the contact ion pair **2A(1)**, 1,3-bridging is inhibited by the tosylate anion that is located on the endo side.²² Internal return can lead to the more stable bridged intermediate **3A(1)** which subsequently homofragments into **31** and formaldehyde. Unfortunately, it is not possible to demonstrate this internal return (**2** \rightarrow **2A(1)** \rightarrow **3A(1)** \rightarrow **3**), because tosylate **3** reacts extremely fast under the influence of sodium *tert*-amylate (vide infra).

The high reactivity of tosylate **3** and the highly selective formation of nortricyclene **31** observed for the reaction of **3** can be attributed to the fast formation of intermediate **3A(1)** as a result of a combined action of TBI, σ -participation, and 1,3-bridging.⁶ The formation of a small amount of cyclic ether **33** in this reaction suggests that, when **3A(1)** is formed, some of it rearranges to give **3A(2)** before it can collapse to **31**. Endo cyclization²³ of the unbridged intermediate **3A(2)** will give **33**. The simultaneous occurrence of homofragmentation and rearrangement in this reaction also suggests that homohyperconjugation^{24,25} in these norbornane systems is somewhat less effective than in the corresponding *trans*-perhydronaphthalene derivatives.²⁶

In order to determine whether an alcoholate function can intramolecularly induce the heterolysis of a primary sulfonate ester group through three intervening C–C bonds, the tosylates **4** and **5** were treated with sodium *tert*-amylate in refluxing benzene for 10 min. After reaction of tosylate **4**, the known olefinic alcohol **36**¹¹ (28 %) was the only detectable product. A small amount (4 %) of starting material **4** was recovered (entry 4). The determination of the yield and identity of the relatively volatile **36** was performed in a manner identical to that of nortricyclene. A complex mixture of (decomposition) products and a relatively large amount (48 %) of unreacted starting material was obtained from the reaction with tosylate **5** (entry 5). A reaction time of 1 min provided more information about the course of this reaction. After workup, small amounts of the carbonyl

compounds **16** (5 %) and **37** (5 %) and the diol **38** (3 %) could be isolated in addition to 72 % of starting material (entry 6).²⁷

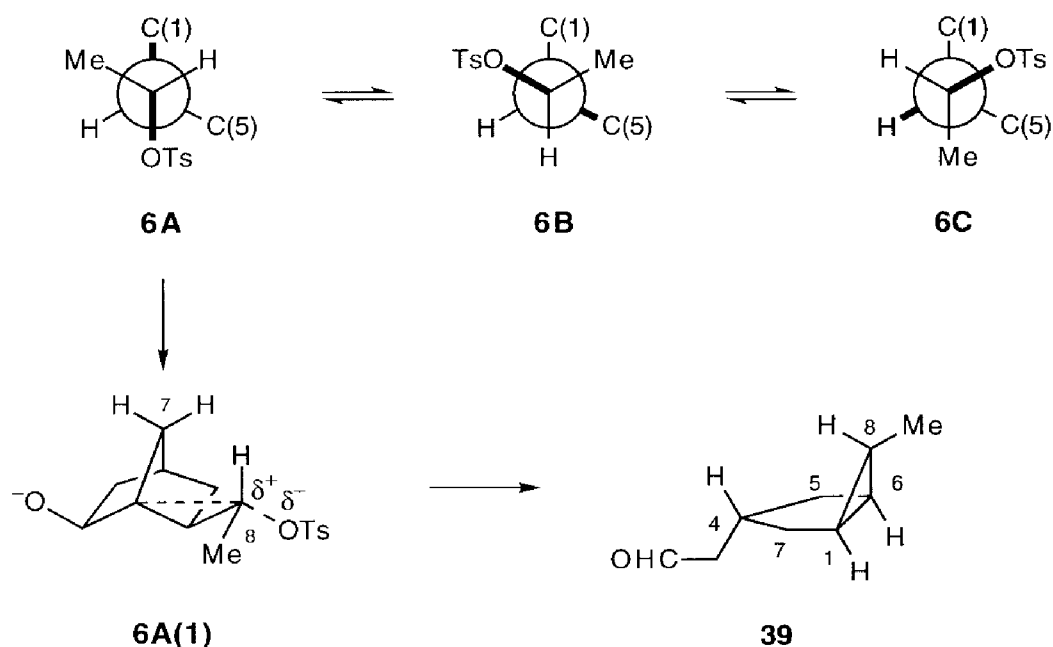
The formation of olefinic alcohol **36** from tosylate **4** is most likely the result of an anti E2 mechanism in which the 2-*endo*-alcoholate acts as an intramolecular catalyst¹¹ as depicted by structure **4(1)** (Scheme 2.7). In tosylate **5** with the hydroxyl group in the *exo* position, such an intramolecular catalysis is not possible and, therefore, **5** will react slower than **4** (entries 4 and 5). It is very much open to question whether orbital interactions through the intervening C–C bonds participate in the reactions of **4** and **5** because none of the products which resulted from the 1 min reaction of tosylate **5** (entry 6) can be explained with initial heterolysis of the sulfonate ester bond. The formation of the ketones **16** and **37** must be attributed to an alkoxide-induced intermolecular hydride shift,²⁸ while S–O bond cleavage by either a hydride or an alkoxide attack on the sulfur atom of the tosylate group in **5** accounts for the formation of diol **38**. Since **4** and **5** have the same geometry of the σ -relay, it is therefore justified to conclude that orbital interactions only play a secondary role in the reactivity of both compounds. Possibly in combination with a restraining effect of free rotation about the C(6)–C(8) bond, the formation of an unstable primary carbocation at C(8) probably impedes the heterolysis of the sulfonate ester bond induced by orbital interactions in these compounds.²⁹



Scheme 2.7

The reactions of the secondary tosylates **6** and **7** were performed to find out whether the presence of the primary sulfonate ester group in the tosylates **4** and **5**

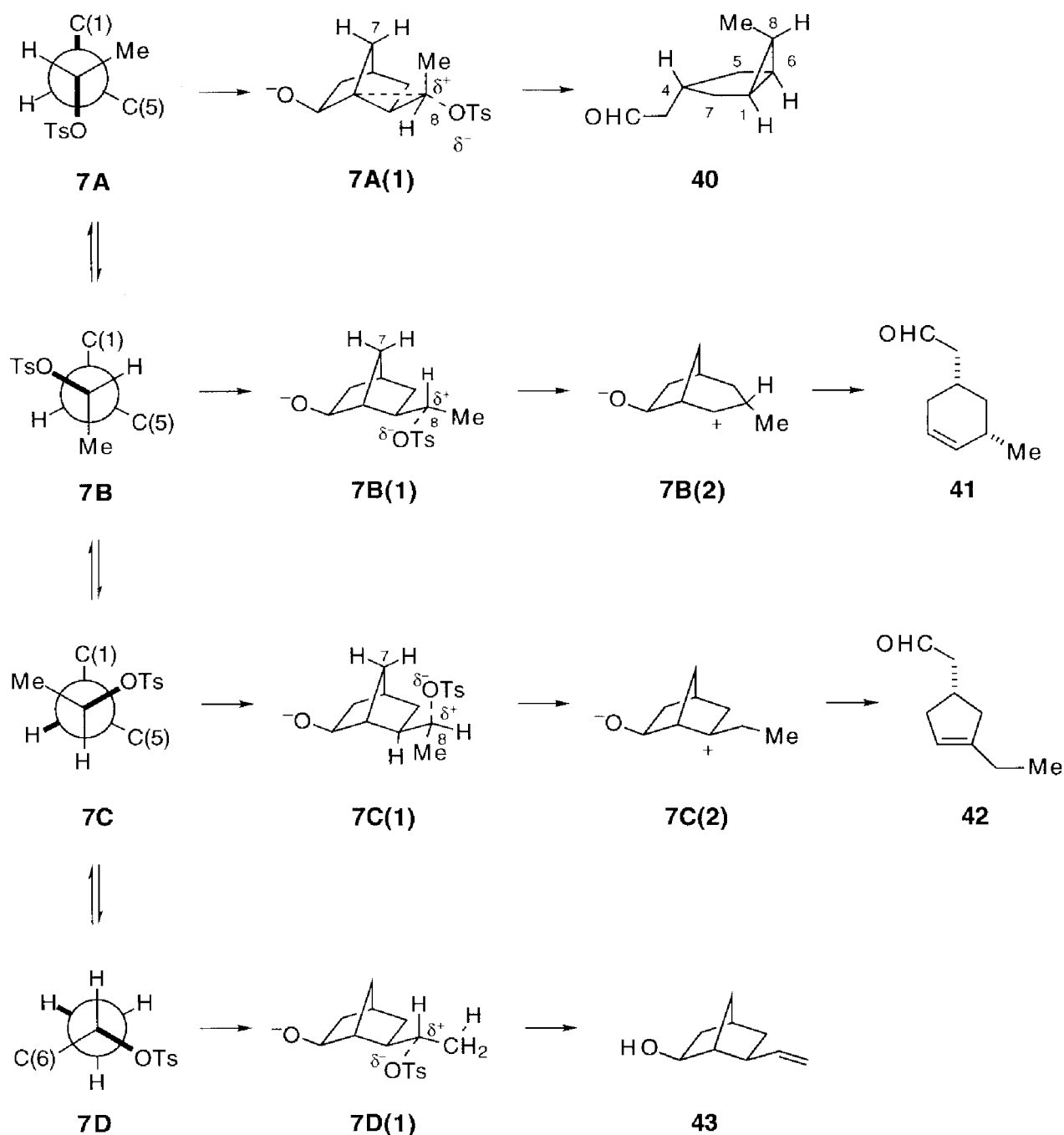
constitutes the major obstacle for effective transmission of TBI in these compounds. A short treatment (1 min) of tosylate **6** afforded the cyclopropane derivative **39** in 51 % yield as the sole product (entry 7, Scheme 2.8). No starting material could be detected. It should be noted that longer reaction times diminished the yield of **39** by aldol condensation reactions.³⁰ The presence of a cyclopropane ring in **39** was concluded from the proton-coupled ^{13}C NMR spectrum. The signals of the tertiary cyclopropane carbon atoms appear at δ 14.01 (d, $J_{\text{CH}} = 158.6$ Hz) and 25.14 (2d, $J_{\text{CH}} = 165.0$ Hz). The stereochemistry of **39** was established by NOE-difference and 2D ^1H - ^{13}C chemical shift correlation measurements. Irradiation of H-8 at δ 0.58 gives a NOE with the three-proton signal at δ 1.80–2.07. One of these protons proves to be H-4 the other two are β -H-5 and β -H-7. According to molecular mechanics calculations using the MM2(87) force field program,³¹ the NOE signal probably originates from an interaction between H-4 and H-8. However, it still remains uncertain from which signal the NOE arises. Notwithstanding, these data unequivocally confirm our structural assignments for **39**.



Scheme 2.8

Tosylate **7** reacted more slowly than **6**. After a reaction time of 1 min, the quantity of regained **7** amounted to 24 %. As products, a 15:4:1 mixture (42 %) of the three aldehydes **40**, **41**, and **42**, respectively, and the olefin **43** (6 %) were obtained (entry 8, Scheme 2.9). Because it was not possible to separate the mixture of aldehydes by column chromatography, analytical samples of **40**, **41**, and **42** were

produced by preparative GC. In the ^{13}C NMR spectrum of **40**, the signals due to the tertiary cyclopropane carbon atoms appear at δ 13.93 (d, $J_{\text{CH}} = 151.8$ Hz) and 25.14 (2d, $J_{\text{CH}} = 165.4$ Hz). The orientation of H-8 was established by a NOE signal between this proton and the other cyclopropane protons at C(1) and C(6). Furthermore, no NOE was observed between H-8 and H-4 or between H-8 and the β protons at C(5) and C(7). Consequently, this compound possesses the stereochemistry as shown in structure **40**.



Scheme 2.9

More selectivity was observed when **7** was treated with a mixture of sodium *tert*-amylate and 15-crown-5 (entry 9). This reaction gave, next to recovered **7** (12 %), the aldehyde **40** (53 %) and the olefin **43** (11 %). The other two aldehydes **41** and **42** could not be detected in the product mixture.

The results of these studies on **4–7** clearly show that the presence of a secondary sulfonate ester is a prerequisite for effective transmission of orbital interactions in these systems. Furthermore, it turns out from the fast reaction of **6** that the free rotation about the C(6)–C(8) bond has no significant influence on the reactivity.

The formation of the homofragmentation product **39** from tosylate **6** requires an all-trans arrangement of the participating σ -bonds.^{6,32} This means that the C(8)–OTs bond in **6** must adopt an orientation antiperiplanar to the C(6)–C(8) bond as indicated by the Newman projection formula **6A** along the C(6)–C(8) bond (Scheme 2.8). Deprotonation of **6A** will lead to the bridged intermediate **6A(1)** which can homofragment to give the aldehyde **39**.

The formation of the main aldehyde **40** from tosylate **7** proceeds analogously with that of **39** and must originate from conformation **7A** (Scheme 2.9). In conformation **7B**, the C(5)–C(6) bond and the C(8)–OTs bond are properly aligned (antiperiplanar) for skeletal rearrangement. The initially formed dipolar intermediate **7B(1)** rearranges to **7B(2)** which can undergo a Grob fragmentation to give the aldehyde **41**. The formation of aldehyde **42** from conformation **7C** proceeds in a similar way, i.e., via **7C(1)** and **7C(2)**, but now a 1,2-H shift (C(6) \rightarrow C(8)) precedes the Grob fragmentation. The olefin **43** is probably formed by an intermolecularly base-assisted anti elimination from the conformations **7A–7C** as the reaction path **7D** \rightarrow **7D(1)** \rightarrow **43** shows.^{33,34}

Although these mechanisms provide a good explanation for the formation of these different products from **6** and **7**, no answer is given why the diastereomeric compounds **6** and **7** show differences in selectivity and reactivity. As depicted in Schemes 2.8 and 2.9, the products **39** and **40–42** must be derived from the staggered conformations **6A** and **7A–7C**, respectively, and can therefore be considered as the chemical consequences of conformational isomerism.

In order to explain the different chemical behavior of **6** and **7**, the Curtin-Hammett (C-H) principle is very useful.³⁵ The reaction of **6** to form **39** through conformation **6A**³⁶ in which the σ -relay has adopted the W-like arrangement is the only product-forming route. Consequently, the lowest-energy transition state must be the one leading to the bridged intermediate **6A(1)**, assuming that heterolysis (or ion pair formation) is the rate-determining step.¹ This is consistent with the trans rule, which predicts that the extent of orbital interactions through σ -bonds is

maximized for an all-trans (W-like) arrangement of the σ -bonds,³² and is supported by our earlier findings.⁶

The reaction outcome of tosylate **7** is more complicated to explain. Of the three staggered conformations of **7** leading to products, conformation **7B**³⁶ must have the lowest energy. If the product ratio was directly equated to the ground state conformational preferences,³⁷ one would expect aldehyde **41** as the main product and not, as found in this reaction, **40**. The 15:4:1 ratio of the products **40**, **41**, and **42**, respectively, must therefore be controlled by the differences in free energy of the three transition states leading to the respective intermediates **7A(1)**, **7B(1)**, and **7C(1)**. The lower energy of the transition state leading to the bridged intermediate **7A(1)** and the higher energies of the other two transition states can be attributed to the W-like arrangement of the σ -relay in conformation **7A** and the sickle-like arrangements of the σ -relay in the conformations **7B** and **7C**. The difference in steric repulsion between syn H-7 and H-8 (more favorable) in the transition state to **7B(1)** and between syn H-7 and the tosylate group (less favorable) in the transition state to **7C(1)** can explain the different formation rate of the aldehydes **41** and **42**.

The same steric effects which give rise to the formation of three different products in the reaction of **7** can also explain the selectivity in the reaction of **6**. The adverse steric repulsion between syn H-7 and C(8)-Me, which is present in the transition state to the bridged intermediate **7A(1)**, is absent in the transition state to **6A(1)**. As a result, 1,3-bridging in the transition state to **6A(1)** will be lower in energy than in the case of the reaction of **7A** to **7A(1)**. On the other hand, the transition state derived from conformation **6B** (see Scheme 2.8) is assumed to be higher in energy (more steric repulsion) than the transition state in the reaction of **7B** to **7B(1)**, while the transition state originated from **6C** will lie close in energy to the one involved in the reaction of **7C** to **7C(1)** (about the same steric repulsion). As a consequence, the absolute differences in free energies of the three transition states will be smaller in the reaction of **7** than they are assumed to be in the reaction of **6**. In other words, homofragmentation is the preferred (and only) pathway by which **6** reacts, while in the case of **7**, different product-forming reactions (homofragmentation, rearrangement, and 1,2-H shift) can take place at the same time.

The relative energies of transition states are also used to explain the more selective reaction of **7** upon treatment with sodium *tert*-amylate in combination with 15-crown-5. Since the use of 15-crown-5 leads to a "naked" alkoxide³⁹ which is a better electron donor, 1,3-bridging will be strengthened, and this may be the principal factor in the increased stabilization of the transition state to **7A(1)**

compared with two other transition states, leading to **7B(1)** and **7C(1)**, in which no 1,3-bridging can occur.³⁷

2.3 Concluding Remarks

As these and earlier experiments^{5,6} show, the reactivity of rigid 1,4-diol monosulfonate esters under strongly basic conditions is directly related to the geometry of the relaying C–C bonds (trans rule), irrespective of the structural features of the substrate. It also appears that the reactivity of these compounds depends on whether the sulfonate ester group is primary or secondary (the energy gap between primary and secondary carbocations is ~ 20 kcal/mol).⁴⁰ Primary monosulfonate esters of rigid 1,4-diols probably react via processes in which orbital interactions only play a minor role,⁴¹ whereas the corresponding secondary monosulfonate esters can show typical reactions in which orbital interactions are involved. Secondary monosulfonate esters which possess a W-like arrangement of the σ -relay react relatively fast and show predominantly the TBI controlled homofragmentation. If a sickle-like arrangement is present, then reactions with and without the involvement of long-range orbital interactions are observed. Compounds with a U-like arrangement of the σ -relay follow reaction pathways in which no long-range orbital interactions are involved.

Secondary monosulfonate esters in which the sulfonate ester group is conformationally mobile can give rise to mixtures of different products. The ratio in which these products are formed can be very well-analyzed with the C–H principle. Conformations in which the σ -relay has the W-like arrangement are (much) more reactive than conformations with a sickle-like arrangement, just as the trans rule predicts.

2.4 Experimental Section

General. Melting points are uncorrected. NMR spectra are recorded in CDCl₃ unless otherwise noted. Chemical shifts are relative to TMS (δ 0.00) with CHCl₃ as internal standard (δ 7.23 (¹H) and δ 76.90 (¹³C)). ¹³C NMR multiplicities were determined by using a DEPT pulse sequence. ¹H–¹³C heteronuclear shift correlation spectra were performed at 200 MHz, using delay times in the pulse sequence of 3.3 and 2.2 ms. ¹H NOE difference experiments were done at 200 MHz, using a τ_m of 2 s. MS data were determined at 70 eV on either an AEI MS 902 spectrometer or a Hewlett Packard 5970B series Mass Selective Detector, coupled with a DB-17 fused silica capillary column, 30 m X 0.25 mm i.d., film thickness 0.25 μ m. GC analyses were carried out with FID and a DB-17 fused silica capillary column, 30 m X 0.25

mm i.d., film thickness 0.25 μm , and H_2 as carrier gas. Peak areas were integrated electronically. Flash chromatography was performed on Merck silica gel 60 (230–400 mesh). Column chromatography was performed using Merck silica gel 60 (70–230 mesh) and ICN alumina B-Super I (activity grade II).

Solvents were dried and freshly distilled by common practice. For all dry reactions, flasks were dried at 150 $^\circ\text{C}$ and flushed with dry N_2 , just before use, and reactions were carried out under N_2 unless otherwise reported. Product solutions were dried over MgSO_4 , unless otherwise noted, and then the solvent was evaporated under reduced pressure.

Materials. All reagents were purchased from Aldrich or Janssen and were used without further purification unless otherwise stated. A stock solution of sodium *tert*-amylate (3.2 M in toluene) was prepared by the procedure of Conia⁴² and stored under an Ar atmosphere in a refrigerator. The tosylate **3**¹² and the starting materials **8**⁹ and **19**¹² were prepared following previously described procedures. The compounds **4**,¹¹ **9**,¹¹ **20**,¹² **29**,⁹ **31**¹⁵ and **36**¹¹ have been characterized before.

(endo)-6-(Carbomethoxy)bicyclo[2.2.1]heptan-2-one (9). To a solution of 84 g KOH (1.49 mol) in 150 mL of MeOH and 600 mL of H_2O was added 137.68 g (0.522 mol) of iodolactone **8**. The solution was stirred at rt for 72 h, acidified with concd HCl, and extracted with five 200-mL portions of EtOAc. The combined organic layers were washed with 100 mL of brine and dried. After evaporation under reduced pressure, the remaining residue was dissolved in 800 mL of dry MeOH and 200 mL (1.576 mol) of TMSCl was added. The mixture was stirred at rt for 4 h, and then carefully neutralized with 4N aqueous NaOH. After removal of MeOH under reduced pressure, the remaining aqueous solution was extracted with three 150-mL portions of EtOAc. The combined organic layers were washed successively with 100 mL of saturated aqueous NaHCO_3 and 100 mL of brine, and dried. After evaporation, the resulting product was purified via flash chromatography on silica gel (3:1 petroleum ether (bp 40–60 $^\circ\text{C}$)/EtOAc) to yield 65.86 g (75 %) of **9**. The spectroscopic data for **9** were identical with those reported in the literature.¹¹

(endo)-6'-(Carbomethoxy)spiro[1,3-dioxolane-2,2'-bicyclo[2.2.1]heptane] (10). To a solution of 57.56 g (0.343 mol) of **9** in a mixture of 525 mL of CH_2Cl_2 and 340 mL (2.745 mol) of MED were added catalytic amounts of ethylene glycol and $\text{TsOH}\cdot\text{H}_2\text{O}$. The reaction mixture was stirred at rt for 65 h, after which time 7 mL of Et_3N was added. The reaction mixture was then diluted with 500 mL of CH_2Cl_2 and washed with 300 mL of brine. The organic layer was dried and evaporated, and the crude dioxolane was chromatographed on basic alumina (activity II) (3:1 petroleum ether (bp 40–60 $^\circ\text{C}$)/EtOAc) to afford 58.68 g (81 %) of **10**: ^1H NMR δ 1.38 (m, 1 H), 1.51–1.92 (m, 5 H), 2.27 (m, 1 H), 2.57–2.73 (m, 2 H), 3.63 (s, 3 H), 3.67–3.92 (m, 4H); ^{13}C NMR δ 29.43 (t), 34.96 (d), 39.06 (t), 42.05 (d), 43.26 (t), 46.95 (d), 51.11 (q), 63.72 (t), 64.57 (t), 115.10 (s), 174.45 (s); MS m/z (relative intensity) 212(M^+ , 59), 181 (15), 153 (100), 127 (38), 126 (32), 114 (12), 100 (23), 87 (12), 82 (13), 74 (20); calcd for $\text{C}_{11}\text{H}_{16}\text{O}_4$ (M^+) m/z 212.1048, found m/z 212.1047. Anal. Calcd for $\text{C}_{11}\text{H}_{16}\text{O}_4$: C, 62.25; H, 7.60. Found: C, 61.95; H, 7.52.

(endo)-6-(Hydroxymethyl)bicyclo[2.2.1]heptan-2-one (11). A solution of 23.11 g (0.109 mol) of **10** in 100 mL of dry THF was added dropwise to a stirred solution of 4.96 g of LAH (0.131 mol) in 50 mL of dry THF at -78 $^\circ\text{C}$. The reaction mixture was stirred at -78 $^\circ\text{C}$ for 1 h, allowed to come to rt, and stirring was continued for an additional 16 h. The excess LAH

was carefully quenched with a small amount of saturated aqueous Na_2SO_4 . After the addition of 200 mL of EtOAc, the reaction mixture was dried and evaporated to yield 18.71 g (93 %) of a crude hydroxy ethylene acetal. This product was dissolved in 50 mL of acetone and 350 mL of 1N HCl was added. The reaction mixture was stirred at rt for 72 h and then neutralized with 4 N aqueous NaOH. After concentration under reduced pressure, the residue was taken up in 100 mL of H_2O and extracted with five 100-mL portions of CH_2Cl_2 . The combined organic layers were dried and evaporated. The resulting product was flash chromatographed (1:1 petroleum ether (bp 40–60 °C)/EtOAc) to give 12.73 g (83 %) of **11**: MS m/z (relative intensity) 140 (M^+ , 40), 122 (15), 111 (30), 110 (17), 97 (18), 96 (23), 82 (70), 81 (100), 80 (47), 67 (60); calcd for $\text{C}_8\text{H}_{12}\text{O}_2$ (M^+) m/z 140.0837, found m/z 140.0836. The ^{13}C NMR spectrum of **11** revealed the presence of its cyclic hemiacetal **12** in about 40 %.

11: ^{13}C NMR (main peaks) δ 30.32 (t), 40.64 (d), 45.76 (t), 52.36 (d), 64.14 (t), 217.98 (s).

12: ^{13}C NMR (main peaks) δ 38.19 (d), 46.64 (t), 50.20 (d), 70.65 (t), 112.21 (s).

(endo)-6-[[[(1,1-Dimethylethyl)dimethylsilyl]oxy]methyl]bicyclo[2.2.1]-heptan-2-one

(13). To a solution of 5.08 g (36.2 mmol) of **11** in 50 mL of DMF were added 4.41 g (64.8 mmol) of imidazole and 5.48 g (36.3 mmol) of TBDMSCl. The reaction mixture was stirred at rt for 24 h, poured into 80 mL of H_2O , and then extracted with five 50-mL portions of CH_2Cl_2 . The combined organic layers were washed with 50 mL of brine, dried, and evaporated. The resulting product was flash chromatographed (20:1 petroleum ether (bp 40–60 °C)/EtOAc) to yield 8.20 g (89 %) of **13** as a clear oil: ^1H NMR δ –0.02 (s, 3 H), –0.01 (s, 3 H), 0.83 (s, 9 H), 1.12 (m, 1 H), 1.58–2.08 (m, 5 H), 2.29 (m, 1 H), 2.52–2.62 (m, 2 H), 3.43 (dd, J = 6.2, 10.1 Hz, 1 H), 3.46 (dd, J = 6.8, 10.1 Hz, 1 H); ^{13}C NMR δ –5.78 (2q), 18.03 (s), 25.63 (3q), 30.53 (t), 34.66 (d), 38.35 (t), 40.84 (d), 45.33 (t), 52.66 (d), 64.49 (t), 216.08 (s); MS m/z (relative intensity) 239 ($\text{M}^+ - 15$, 3.8), 199 (5), 198 (17), 197 (100), 106 (9), 92 (5), 90 (5), 80 (7), 67 (23), 74 (10), 60 (4); calcd for $\text{C}_{13}\text{H}_{23}\text{O}_2\text{Si}$ ($\text{M}^+ - 15$, 3.8) m/z 239.1467, found m/z 239.1467.

(endo,endo)-6-[[[(1,1-Dimethylethyl)dimethylsilyl]oxy]methyl]bicyclo[2.2.1]heptan-2-ol

(14). To a stirred solution of 2.71 g (10.7 mmol) of **13** in 75 mL of EtOH was added 0.60 g (15.9 mmol) of NaBH_4 . The reaction mixture was stirred at 50 °C for 90 min and then quenched with an excess of saturated aqueous NH_4Cl . After concentration under reduced pressure, the resulting residue was taken up in 30 mL of H_2O and extracted with four 25-mL portions of EtOAc. The combined organic layers were washed with 25 mL of brine, dried, and evaporated. The remaining product was flash chromatographed (20:1 petroleum ether (bp 40–60 °C)/EtOAc) to give 2.62 g of **14** (96 %) as a clear oil: ^1H NMR δ 0.07 (s, 6 H), 0.83 (m, 1 H), 0.89 (s, 9 H), 1.18–1.42 (m, 3 H), 1.65 (m, 1 H), 1.92–2.24 (m, 4 H), 3.78 (dd, J = 2.4, 10.9 Hz, 1 H), 3.90 (dd, J = 5.3, 10.9 Hz, 1 H), 4.09 (m, 1 H), 4.88 (d, J = 10.2 Hz, OH); ^{13}C NMR δ –5.84 (q), –5.76 (q), 18.05 (s), 25.57 (3q), 31.19 (t), 36.98 (d), 38.78 (d), 39.12 (t), 41.22 (d), 46.66 (d), 63.30 (t), 73.95 (d); MS m/z (relative intensity) 241 ($\text{M}^+ - 15$, 1.9), 199 (55), 32 (19), 108 (74), 106 (19), 92 (10), 82 (22), 81 (29), 80 (68), 76 (100); calcd for $\text{C}_{13}\text{H}_{25}\text{O}_2\text{Si}$ ($\text{M}^+ - 15$) m/z 241.1624, found m/z 241.1624.

(endo,endo)-6-[(4-Methylphenyl)sulfonyl]oxy]bicyclo[2.2.1]heptan-2-methanol (1). To a stirred solution of 1.24 g (4.8 mmol) of alcohol **14** in 25 mL of dry pyridine were added 1.715 g (9.0 mmol) of TsCl and 2.01 g (16.5 mmol) of DMAP. The reaction mixture was stirred at 80 °C for 52 h and then concentrated under reduced pressure. The resulting mixture was taken up

in 100 mL of EtOAc and washed successively with two 25-mL portions of saturated aqueous NaHCO_3 and one 25-mL portion of brine. The organic layer was dried and evaporated, and the crude product was flash chromatographed (50:1 petroleum ether (bp 40–60 °C)/EtOAc) to give 0.858 g (44 %) of pure (*endo,endo*)-6-[[[(1,1-dimethylethyl)dimethylsilyl]oxy]-methyl]bicyclo[2.2.1]heptan-2-ol 4-methylbenzenesulfonate: ^1H NMR δ 0.05 (s, 6 H), 0.91 (s, 9 H), 1.04 (m, 1 H), 1.18 (m, 1 H), 1.27–1.46 (m, 2 H), 1.86–2.30 (m, 4 H), 2.39–2.50 (m, 1 H), 2.46 (s, 3 H), 3.74 (dd, $J = 8.5, 10.2$ Hz, 1 H), 3.83 (dd, $J = 6.0, 10.2$ Hz, 1 H), 4.84 (dddd, $J = 1.7, 4.3, 4.3, 10.2$ Hz, 1 H), 7.35 (d, $J = 8.2$ Hz, 2 H), 7.80 (d, $J = 8.2$ Hz, 2 H); ^{13}C NMR δ –5.46 (2q), 18.20 (s), 21.37 (q), 25.74 (3q), 34.89 (t), 36.33 (d), 36.73 (t), 37.78 (t), 43.17 (d), 43.34 (d), 66.10 (t), 83.23 (d), 127.46 (2d), 129.49 (2d), 134.01 (s), 144.23 (s); MS m/z (relative intensity) ($M^+ - 57$, 0.3), 231 (8), 230 (14), 229 (100), 149 (4), 107 (19), 91 (9), 79 (6), 75 (4), 73 (6); calcd for $\text{C}_{17}\text{H}_{25}\text{O}_4\text{SSi}$ ($M^+ - 57$) m/z 353.1243; found m/z 353.1248. To a solution of 0.680 g (1.49 mmol) of this TBDMS ether in 10 mL of acetonitrile was added 10 drops of 40 % aqueous HF. The reaction mixture was stirred at rt for 30 min and then poured into 50 mL of saturated aqueous NaHCO_3 . The aqueous layer was extracted with three 25-mL portions of EtOAc, after which the combined organic layers were dried and evaporated. The crude product was flash chromatographed (5:1 petroleum ether (bp 40–60 °C)/EtOAc) afforded 0.457 g (92 %) of **1** as an oil: ^1H NMR δ 0.99 (m, 1 H), 1.16 (m, 1 H), 1.32–1.65 (m, 2 H), 1.83–2.12 (m, 2 H), 2.21–2.53 (m, 3 H), 2.47 (s, 3 H), 2.63 (m, 1 H), 3.75 (dd, $J = 7.4, 11.1$ Hz, 1 H), 3.91 (dd, $J = 8.5, 11.1$ Hz, 1 H), 4.92 (m, 1 H), 7.37 (d, $J = 8.2$ Hz, 2 H), 7.82 (d, $J = 8.2$ Hz, 2 H); ^{13}C NMR δ 21.41 (q), 33.53 (t), 36.22 (d), 36.28 (t), 37.82 (t), 42.74 (2d), 64.99 (t), 83.56 (d), 127.49 (2d), 129.66 (2d), 133.24 (s), 144.65 (s); MS m/z (relative intensity) 266 ($M^+ - 30$, 5), 125 (59), 107 (25), 96 (38), 95 (100), 92 (91), 82 (28), 81 (74), 80 (55), 68 (38), 67 (38); calcd for $\text{C}_{14}\text{H}_{18}\text{O}_3\text{S}$ ($M^+ - 30$) m/z 266.0977; found m/z 266.0974. Anal. Calcd for $\text{C}_{15}\text{H}_{20}\text{O}_4\text{S}$: C, 60.78; H, 6.80. Found: C, 60.57; H, 6.86.

(*exo*)-6'-(Carbomethoxy)spiro[1,3-dioxolane-2,2'-bicyclo[2.2.1]heptane] (**15**). To a solution of 18.75 g (88.44 mmol) of dioxolane **10** in 175 mL of dry MeOH was added 100 mL of 0.45 M NaOMe in dry MeOH. The solution was refluxed under a N_2 atmosphere for 68 h, allowed to come to rt, and then poured into 400 mL of ice-water and 150 mL of brine. The aqueous layer was extracted with three 200-mL portions of EtOAc. The combined organic layers were washed with 150 mL of brine, dried, and evaporated. The resulting oil was flash chromatographed (3:1 petroleum ether (bp 40–60 °C)/EtOAc) to give 11.61 g (62 %) of **15** as a clear oil: ^1H NMR δ 1.37–1.63 (m, 4 H), 1.71–1.93 (m, 2 H), 2.27 (m, 1 H), 2.37 (m, 1 H), 2.87 (dd, $J = 5.1, 9.8$ Hz, 1 H), 3.62 (s, 3 H), 3.77–4.00 (m, 4 H); ^{13}C NMR δ 32.65 (t), 35.10 (d), 35.53 (t), 39.05 (d), 42.44 (t), 47.51 (d), 51.51 (q), 63.76 (t), 64.34 (t), 115.14 (s), 176.09 (s); MS m/z (relative intensity) 212 (M^+ , 35), 154 (9), 153 (100), 127 (33), 126 (15), 114 (8), 100 (19), 82 (10), 74 (16), 28 (33); calcd for $\text{C}_{11}\text{H}_{16}\text{O}_4$ (M^+) m/z 212.1048, found m/z 212.1047. Anal. Calcd for $\text{C}_{11}\text{H}_{16}\text{O}_4$: C, 62.25; H, 7.60. Found: C, 61.97; H, 7.68.

(*exo*)-6-(Hydroxymethyl)bicyclo[2.2.1]heptan-2-one (**16**). The keto alcohol **16** was prepared from **15** (8.59 g, 40.49 mmol) as described for the synthesis of **11**. Workup and flash chromatography (3:1 petroleum ether (bp 40–60 °C)/EtOAc) afforded 4.82 g (85 %) of pure **16**: ^1H NMR δ 1.28 (m, 1 H), 1.50–2.09 (m, 6 H), 2.55 (m, 1 H), 2.60 (m, 1 H), 2.90 (br s, OH), 3.34–3.53 (m, 2 H); ^{13}C NMR δ 31.52 (t), 34.11 (t), 35.00 (d), 38.85 (d), 44.52 (t), 51.70 (d), 64.60 (t), 217.87 (s); MS m/z (relative intensity) 140 (M^+ , 78), 109 (49), 96 (100), 82 (89), 81

(35), 80 (69), 79 (42), 68 (61), 42 (30), 28 (75); calcd for $C_8H_{12}O_2$ (M^+) m/z 140.0839, found m/z 140.0838.

(*exo*)-6-[[[(1,1-Dimethylethyl)dimethylsilyl]oxy]methyl]bicyclo[2.2.1]-heptan-2-one (17).

The silyl ether **17** was prepared from **16** (3.00 g, 21.43 mmol) as described for the silylation of **11**. Workup and flash chromatography (20:1 petroleum ether (bp 40–60 °C)/EtOAc) afforded 5.30 g (97 %) of **17**: 1H NMR δ 0.01 (s, 6 H), 0.86 (s, 9 H), 1.33 (m, 1 H), 1.50–2.12 (m, 6 H), 2.56 (m, 1 H), 2.63 (m, 1 H), 3.38–3.54 (m, 2 H); ^{13}C NMR δ –5.58 (2q), 18.04 (s), 25.65 (3q), 31.34 (t), 34.13 (t), 35.07 (d), 38.57 (d), 44.54 (t), 51.99 (d), 65.02 (t), 217.35 (s); MS m/z (relative intensity) 239 ($M^+ - 15$, 3.4), 198 (17), 197 (100), 132 (6), 118 (8), 106 (21), 90 (6), 80 (24), 76 (41), 74 (12); calcd for $C_{13}H_{24}O_2Si$ ($M^+ - 15$) m/z 239.1467, found m/z 239.1467.

(2-*endo*,6-*exo*)-6-[[[(1,1-Dimethylethyl)dimethylsilyl]oxy]methyl]bicyclo[2.2.1]-heptan-2-ol (18).

To 10.8 mL of 1 M L-selectride in THF was slowly added dropwise a solution of 2.50 g (9.84 mmol) of **17** in 100 mL of dry THF at –78 °C. The solution was stirred at –78 °C for 15 min, allowed to come to rt, and stirring was continued for 16 h. Then a mixture of 12.5 mL of H_2O and 37.5 mL of EtOH was carefully added to the reaction mixture. Stirring was continued at rt for 20 min, after which time a mixture of 12.5 mL of 4 M aqueous NaOH and 25 mL of 30 % H_2O_2 was added. Stirring was continued for 5 h and then the reaction mixture was concentrated under reduced pressure. To the remaining residue was added 100 mL of H_2O , and the aqueous layer was extracted with four 75-mL portions of EtOAc. The combined organic layers were dried and evaporated, and the crude product was flash chromatographed (20:1 petroleum ether (bp 40–60 °C)/EtOAc) to yield 2.24 g (89 %) of **18** as a clear oil: 1H NMR δ 0.03 (s, 6 H), 0.83 (m, 1 H), 0.88 (s, 9 H), 1.00–1.52 (m, 4 H), 1.61 (br s, OH), 1.95 (m, 1 H), 2.10–2.22 (m, 2 H), 2.34 (m, 1 H), 3.37 (dd, J = 8.6, 10.0 Hz, 1 H), 3.42 (dd, J = 6.8, 10.0 Hz, 1 H), 4.22 (m, 1 H); ^{13}C NMR δ –5.28 (2q), 18.36 (s), 25.96 (3q), 33.90 (d), 34.09 (t), 34.49 (t), 37.12 (d), 38.71 (t), 44.64 (d), 66.47 (t), 72.70 (d); MS m/z (relative intensity) 241 ($M^+ - 15$, 1.3), 199 (37), 132 (21), 108 (72), 106 (21), 82 (14), 80 (75), 78 (9), 76 (100), 28 (37); calcd for $C_{13}H_{25}O_2Si$ ($M^+ - 15$) m/z 241.1624, found m/z 241.1624.

(2-*exo*,6-*endo*)-6-[[[(4-Methylphenyl)sulfonyl]oxy]bicyclo[2.2.1]heptan-2-methanol (2).

The alcohol **18** (0.508 g, 1.98 mmol) was treated with TsCl for 8 h as described for the tosylation of **14**. After workup, the crude product was purified by flash chromatography (20:1 petroleum ether (bp 40–60 °C)/EtOAc) to afford 0.643 g (79 %) of (2-*endo*,6-*exo*)-6-[[[(1,1-dimethylethyl)dimethyl-silyl]oxy]methyl]bicyclo-[2.2.1]heptan-2-ol 4-methylbenzene-sulfonate: 1H NMR δ –0.03 (s, 6 H), 0.82 (s, 9 H), 0.99–1.19 (m, 3 H), 1.29–1.46 (m, 2 H), 1.84 (m, 1 H), 2.06–2.30 (m, 3 H), 2.38 (s, 3 H), 3.26 (d, J = 6.9 Hz, 2 H), 4.71 (ddd, J = 4.0, 4.0, 10.3 Hz, 1 H), 7.27 (d, J = 8.2 Hz, 2 H), 7.73 (d, J = 8.2 Hz, 2 H); ^{13}C NMR δ –5.57 (2q), 18.01 (s), 21.36 (q), 25.67 (3q), 33.30 (t), 33.77 (t), 34.07 (d), 35.79 (t), 36.11 (d), 43.01 (d), 65.65 (t), 82.10 (d), 127.50 (2d), 129.49 (2d), 134.03 (s), 144.16 (s); MS m/z (relative intensity) 353 ($M^+ - 57$, 0.2), 131 (9), 130 (16), 129 (100), 181 (9), 108 (17), 92 (9), 80 (17), 76 (12), 74 (8); calcd for $C_{17}H_{25}O_4SSi$ ($M^+ - 57$) m/z 353.1242, found m/z 353.1238. A sample of this TBDMS ether (0.613 g, 1.50 mmol) was desilylated with HF as described for the synthesis of **1**. Workup and flash chromatography (2:1 petroleum ether (bp 40–60 °C)/EtOAc) afforded 0.408 g (92 %) of **2**: 1H NMR δ 1.04–1.57 (m, 5 H), 1.89 (m, 1 H), 2.09–2.38 (m, 4 H), 2.43 (s, 3 H), 3.27 (dd, J = 8.3, 10.5 Hz, 1 H), 3.35 (dd, J = 6.9, 10.5 Hz, 1 H),

4.78 (ddd, $J = 4.2, 4.2, 10.3$ Hz, 1 H), 7.34 (d, $J = 8.2$ Hz, 2 H), 7.79 (d, $J = 8.2$ Hz, 2 H); ^{13}C NMR δ 21.30 (q), 33.54 (t), 33.63 (t), 34.44 (d), 35.68 (t), 35.94 (d), 42.75 (d), 65.22 (t), 82.28 (d), 127.50 (2d), 129.64 (2d), 133.54 (s), 144.60 (s); MS m/z (relative intensity) 296 (M^+ , 1.6), 173 (26), 155 (36), 125 (100), 107 (60), 96 (45), 94 (23), 92 (80), 81 (58), 80 (40); calcd for $\text{C}_{15}\text{H}_{20}\text{O}_4\text{S}$ (M^+) m/z 296.1082, found m/z 296.1081.

(2-*exo*,6-*endo*)-6-Hydroxybicyclo[2.2.1]heptane-2-methanol α -(4-Methylbenzenesulfonate) (4). The silyl ether **18** (1.00 g, 3.91 mmol) was desilylated with HF as described for the synthesis of **1**. The crude diol was dissolved in 20 mL of dry pyridine, cooled to 0 °C, and then 0.780 g (4.09 mmol) of TsCl was added. The reaction mixture was stirred at 0 °C for 1 h, allowed to come to rt, and stirring was continued for 100 h. An additional portion of 0.475 g (3.910 mmol) of TsCl was added and stirring was continued for 16 h. After concentration under reduced pressure, the workup and flash chromatography (3:1 petroleum ether (bp 40–60 °C)/EtOAc) afforded 0.51 g (29 %) of (2-*exo*,6-*endo*)-6-[[4-methylphenylsulfonyl]oxy]bicyclo[2.2.1]heptane-2-methanol 4-methylbenzenesulfonate (**32**) as white crystals; mp 98–99 °C (from hexane); ^1H NMR δ 0.92–1.24 (m, 4 H), 1.38 (m, 1 H), 1.82 (m, 1 H), 2.00–2.13 (m, 2 H), 2.22–2.45 (m, 1 H), 2.36 (s, 6 H), 3.60 (d, $J = 7.4$ Hz, 2 H), 4.65 (ddd, $J = 4.0, 4.0, 10.4$ Hz, 1 H), 7.26 (d, $J = 8.0$ Hz, 4 H), 7.60–7.71 (2d, $J = 8.0$ Hz, 4 H); ^{13}C NMR δ 21.41 (2q), 31.31 (d), 33.23 (t), 33.78 (t), 35.46 (t), 35.93 (d), 42.71 (d), 72.12 (t), 81.20 (d), 127.54 (4d), 129.70 (4d), 132.92 (s), 133.81 (s), 144.61 (2s); MS m/z (relative intensity) 450 (M^+ , 0.3), 253 (23), 197 (26), 155 (20), 149 (21), 108 (36), 102 (56), 92 (38), 89 (23), 44 (100); calcd for $\text{C}_{22}\text{H}_{26}\text{O}_6\text{S}_2$ (M^+) m/z 450.1170, found m/z 450.1170. Anal. Calcd for $\text{C}_{22}\text{H}_{26}\text{O}_6\text{S}_2$: C, 58.64; H, 5.82. Found: C, 58.45; H, 5.75. Further elution afforded 0.650 g (56 %) of hydroxy tosylate **4**. The spectroscopic data for **4** were identical with those reported in the literature.¹¹

(*exo*,*exo*)-2-[[4-Methylphenylsulfonyl]oxy]bicyclo[2.2.1]heptane-2-methanol (3). The tosylate **3** was prepared as described previously.¹² The spectroscopic data for **3** are as follows: ^1H NMR δ 0.92 (m, 1 H), 1.10–1.28 (m, 2 H), 1.36–1.67 (m, 4 H), 2.03 (br s, OH), 2.24 (m, 1 H), 2.31 (m, 1 H), 2.42 (s, 3 H), 3.34 (d, $J = 7.5$ Hz, 2 H), 4.43 (m, 1 H), 7.31 (d, $J = 8.2$ Hz, 2 H), 7.75 (d, $J = 8.2$ Hz, 2 H); ^{13}C NMR δ 21.40 (q), 32.00 (t), 32.18 (t), 34.89 (d), 38.96 (t), 39.29 (d), 43.94 (d), 65.32 (t), 84.74 (d), 127.43 (2d), 129.56 (2d), 134.20 (s), 144.28 (s); MS m/z (relative intensity) 124 ($\text{M}^+ - 172$, 9.1), 173 (98), 125 (61), 108 (38), 96 (65), 92 (100), 83 (42), 82 (44), 81 (84), 80 (45), 70 (32), 68 (42); calcd for $\text{C}_8\text{H}_{12}\text{O}$ ($\text{M}^+ - 172$) m/z 124.0888, found m/z 124.0888.

(*exo*,*exo*)-2-(carbomethoxy)-6-[[1,1-Dimethylethyl]dimethylsilyl]oxy]bicyclo[2.2.1]heptane (20). The hydroxy ester **19**¹² (12.64 g, 74.3 mmol) was treated with TBDMSCl for 90 min as described for the silylation of **11**. Workup and flash chromatography (50:1 petroleum ether (bp 40–60 °C)/EtOAc) gave 20.21 g (96 %) of **20** as a clear oil: ^1H NMR δ 0.00 (s, 3 H), 0.01 (s, 3 H), 0.83 (s, 9 H), 1.22–1.38 (m, 3 H), 1.48–1.78 (m, 3 H), 2.08 (dd, $J = 5.6, 9.0$ Hz, 1 H), 2.25 (m, 1 H), 2.30 (m, 1 H), 3.63 (s, 3 H), 3.68 (m, 1 H); ^{13}C NMR δ -4.97 (q), -4.92 (q), 17.73 (s), 25.56 (3q), 32.59 (t), 33.11 (t), 34.69 (d), 41.64 (d), 42.03 (t), 48.38 (d), 51.44 (q), 74.19 (d), 175.83 (s); MS m/z (relative intensity) 284 (M^+ , 0.3), 227 (46), 189 (33), 150 (9), 149 (16), 148 (100), 134 (14), 122 (14), 94 (10), 76 (18), 74 (17); calcd for $\text{C}_{15}\text{H}_{28}\text{O}_3\text{Si}$ (M^+) m/z 284.1807, found m/z 284.1807.

(*exo,exo*)-6-[(1,1-Dimethylethyl)dimethylsilyl]oxy]bicyclo[2.2.1]heptane-2-methanol

(21). The ester **20** (20.21 g, 71.2 mmol) was treated with LAH at -78°C for 4 h as described for the synthesis of alcohol **11**. Workup and flash chromatography (10:1 petroleum ether (bp $40\text{--}60^{\circ}\text{C}$)/EtOAc) gave 18.14 g (99 %) of **21** as a clear oil: ^1H NMR δ 0.02 (s, 6 H), 0.84 (s, 9 H), 0.92 (m, 1 H), 1.05–1.66 (m, 7 H), 2.00 (m, 1 H), 2.20 (m, 1 H), 3.29–3.48 (m, 2 H), 3.66 (m, 1 H); ^{13}C NMR δ -4.82 (2q), 17.81 (s), 25.65 (3q), 31.54 (t), 32.78 (t), 34.83 (d), 39.87 (d), 42.34 (t), 46.30 (d), 66.10 (t), 74.84 (d); MS m/z (relative intensity) 256 (M^+ , 0.3), 219 (13), 200 (15), 199 (100), 131 (10), 119 (40), 108 (50), 80 (90), 74 (18), 70 (17); calcd for $\text{C}_{15}\text{H}_{28}\text{O}_2\text{Si}$ (M^+) m/z 256.1858, found m/z 256.1858.

(*exo,exo*)-6-Hydroxybicyclo[2.2.1]heptane-2-methanol α -(4-Methylbenzene-sulfonate)

(5). The silyl ether **21** (0.363 g, 1.42 mmol) was treated with TsCl as described for the synthesis of **4**. Workup and flash chromatography (250:1 petroleum ether (bp $40\text{--}60^{\circ}\text{C}$)/EtOAc) afforded 0.430 g (75 %) of (*exo,exo*)-6-[(1,1-dimethylethyl)dimethylsilyl]oxy]bicyclo[2.2.1]heptane-2-methanol α -(4-methylbenzenesulfonate): ^1H NMR δ -0.01 (s, 6 H), 0.80–1.00 (m, 2 H), 0.83 (s, 9 H), 1.11–1.37 (m, 2 H), 1.42–1.67 (m, 3 H), 1.90 (m, 1 H), 2.16 (m, 1 H), 2.43 (s, 3 H), 3.60 (m, 1 H), 3.78 (d, $J = 7.7$ Hz, 2 H), 7.33 (d, $J = 8.2$ Hz, 2 H), 7.77 (d, $J = 8.2$ Hz, 2 H); ^{13}C NMR δ -4.72 (q), -4.66 (q), 17.94 (s), 21.60 (q), 25.80 (3q), 31.69 (t), 32.72 (t), 35.00 (d), 36.48 (d), 42.24 (t), 46.40 (d), 72.88 (t), 74.48 (d), 127.79 (2d), 129.78 (2d), 133.19 (s), 144.61 (s). A sample of this silyl ether (0.394 g, 0.96 mmol) was desilylated with HF as described for the synthesis of **1**. Workup and flash chromatography (2:1 petroleum ether (bp $40\text{--}60^{\circ}\text{C}$)/EtOAc) afforded 0.272 g (96 %) of **5**: ^1H NMR δ 0.84 (m, 1 H), 1.03 (m, 1 H), 1.11–1.35 (m, 2 H), 1.40–1.68 (m, 3 H), 2.02 (m, 1 H), 2.07 (br s, OH), 2.19 (m, 1 H), 2.41 (s, 3 H), 3.65–3.82 (m, 3 H), 7.31 (d, $J = 8.2$ Hz, 2 H), 7.74 (d, $J = 8.2$ Hz, 2 H); ^{13}C NMR δ 21.60 (q), 31.50 (t), 32.27 (t), 35.12 (d), 36.49 (d), 41.11 (t), 46.19 (d), 72.62 (t), 74.06 (d), 127.78 (2d), 129.85 (2d), 132.94 (s), 144.77 (s); MS m/z (relative intensity) 124 ($\text{M}^+ - 172$, 63), 106 (20), 95 (16), 91 (35), 81 (28), 80 (100), 79 (17), 67 (13); calcd for $\text{C}_8\text{H}_{12}\text{O}$ ($\text{M}^+ - 172$) m/z 124.0888, found m/z 124.0887.

(*exo,exo*)-6-[(1,1-dimethylethyl)dimethylsilyl]oxy]bicyclo[2.2.1]heptane-2-carboxaldehyde (**22**). To a suspension of 6.76 g (31.4 mmol) of PCC and 1.19 g (14.5 mmol) of NaOAc in 50 mL of dry CH_2Cl_2 was added a solution of 5.13 g (20.0 mmol) of alcohol **21** in 50 mL of dry CH_2Cl_2 at rt. The suspension was stirred at rt for 210 min and, after dilution with 100 mL of ether, filtered through Celite. The filter cake was washed with three 100-mL portions of ether, and the combined filtrates were concentrated to 100 mL. The concentrate was washed with 25 mL of saturated aqueous NaHCO_3 and 50 mL of brine. After drying and evaporation, flash chromatography (50:1 petroleum ether (bp $40\text{--}60^{\circ}\text{C}$)/EtOAc) gave 3.82 g (75 %) of pure aldehyde **22** as a colorless oil: ^1H NMR δ 0.02 (s, 3 H), 0.03 (s, 3 H), 0.85 (s, 9 H), 1.01 (m, 1 H), 1.16 (ddd, $J = 2.7, 9.2, 9.2$ Hz, 1 H), 1.33 (m, 1 H), 1.52–1.84 (m, 3H), 2.10 (m, 1 H), 2.30 (m, 1 H), 2.35 (m, 1 H), 3.76 (m, 1 H), 9.62 (d, $J = 1.6$ Hz, 1 H); ^{13}C NMR δ -4.94 (2q), 17.74 (s), 25.56 (3q), 29.18 (t), 32.32 (t), 34.81 (d), 42.58 (t), 45.70 (d), 50.01 (d), 74.41 (d), 202.10 (d); MS m/z (relative intensity) 254 (M^+ , 1.1), 200 (5), 198 (15), 197 (100), 169 (12), 132 (19), 106 (11), 80 (9), 76 (46), 74 (16); calcd for $\text{C}_{14}\text{H}_{26}\text{O}_2\text{Si}$ (M^+) m/z 254.1702, found m/z 254.1706.

($\alpha\text{R},\text{exo,exo}$)- and ($\alpha\text{S},\text{exo,exo}$)- α -Methyl-6-[(1,1-dimethylethyl)dimethylsilyl]oxy]bicyclo[2.2.1]heptane-2-methanol (**23** and **24**). To 50 mL of 0.9 M MeMgI in dry ether

was added dropwise a solution of 3.82 g (15.0 mmol) of aldehyde **22** in 50 mL of dry ether at 0 °C. The reaction mixture was stirred at 0 °C for 30 min, after which time the excess of MeMgI was cautiously destroyed with saturated aqueous NH₄Cl. After dilution with H₂O, the two phase mixture was separated and the aqueous layer was extracted with four 150-mL portions of ether. The combined organic layers were washed with 100 mL of brine, dried, and evaporated. The remaining mixture of diastereoisomers was chromatographed (20:1 petroleum ether (bp 40–60 °C)/EtOAc) to give 1.92 g (47 %) of **24** as a white solid: mp 78–79 °C (from hexane); ¹H NMR δ 0.02 (s, 3 H), 0.03 (s, 3 H), 0.86 (s, 9 H), 0.90 (m, 1 H), 1.02–1.64 (m, 7 H), 1.10 (d, *J* = 6.2 Hz, 3 H), 2.13–2.24 (m, 2 H), 3.38 (m, 1 H), 3.67 (m, 1 H); ¹³C NMR δ –4.89 (q), –4.80 (q), 17.78 (s), 20.82 (q), 25.64 (3q), 31.68 (t), 33.35 (t), 35.23 (d), 41.99 (t), 45.92 (2d), 70.26 (d), 75.07 (d); MS *m/z* (relative intensity) 255 (*M*⁺ – 15, 3.2), 214 (16), 213 (100), 122 (49), 96 (11), 94 (49), 80 (35), 76 (74), 74 (27), 45 (15); calcd for C₁₄H₂₇O₂Si (*M*⁺ – 15) *m/z* 255.1780, found *m/z* 255.1781. Anal. Calcd for C₁₅H₃₀O₂Si: C, 66.63; H, 11.18. Found: C, 66.95; H, 11.46. Further elution provided 1.95 g (48 %) of **23** as an oil: ¹H NMR δ –0.01 (s, 6 H), 0.83 (s, 9 H), 1.00–1.36 (m, 5 H), 1.17 (d, *J* = 6.1 Hz, 3 H), 1.42–1.59 (m, 2 H), 1.77–1.89 (m, 2 H), 2.21 (m, 1 H), 3.46 (m, 1 H), 3.62 (m, 1 H); ¹³C NMR δ –4.95 (q), –4.84 (q), 17.80 (s), 22.27 (q), 25.64 (3q), 32.35 (t), 33.07 (t), 35.20 (d), 41.88 (t), 45.63 (d), 47.48 (d), 70.88 (d), 75.23 (d); MS *m/z* (relative intensity) 255 (*M*⁺ – 15, 3.6), 214 (18), 213 (100), 122 (75), 96 (17), 94 (57), 80 (38), 76 (92), 74 (37), 68 (9); calcd for C₁₄H₂₇O₂Si (*M*⁺ – 15) *m/z* 255.1780, found *m/z* 255.1776. Anal. Calcd for C₁₅H₃₀O₂Si: C, 66.63; H, 11.18. Found: C, 66.73; H, 11.31.

(*αR,exo,exo*)-*α*-Methyl-6-[(1,1-dimethylethyl)dimethylsilyl]oxy]bicyclo[2.2.1]-heptane-2-methanol *α*-(4-Methylbenzenesulfonate) (**25**). The method of Kabalka et al.⁴³ was employed. To a stirred solution of 1.903 g (7.05 mmol) of alcohol **23** in 10 mL of CHCl₃ was added 1.10 g (13.90 mmol) of dry pyridine followed by 1.99 g (10.42 mmol) of TsCl in small portions at 0 °C. The reaction mixture was stirred at rt for 24 h and then concentrated under reduced pressure. The resulting residue was taken up in 100 mL of EtOAc and washed successively with two 10-mL portions of saturated aqueous NaHCO₃ and one 10-mL portion of brine. The organic layer was dried and evaporated, and the remaining oil was flash chromatographed (50:1 petroleum ether (bp 40–60 °C)/EtOAc) to afford 2.618 g (88 %) of **25** as white crystals: mp 56–57 °C (from hexane); ¹H NMR δ –0.02 (s, 6 H), 0.83 (s, 9 H), 1.05–1.56 (m, 7 H), 1.26 (d, *J* = 6.2 Hz, 3 H), 1.70 (m, 1 H), 2.16 (m, 1 H), 2.42 (s, 3 H), 3.57 (m, 1 H), 4.46 (m, 1 H), 7.31 (d, *J* = 8.2 Hz, 2 H), 7.77 (d, *J* = 8.2 Hz, 2 H); ¹³C NMR δ –4.90 (2q), 17.77 (s), 19.84 (q), 21.38 (q), 25.59 (3q), 32.32 (t), 32.70 (t), 34.88 (d), 41.68 (t), 43.32 (d), 47.18 (d), 74.92 (d), 83.34 (d), 127.45 (2d), 129.43 (2d), 134.36 (s), 144.17 (s); MS *m/z* (relative intensity) (*M*⁺ – 57, 2.3), 231 (9), 230 (15), 229 (100), 195 (6), 121 (46), 93 (10), 91 (13), 79 (8), 75 (18), 73 (13); calcd for C₁₈H₂₇O₄SSi (*M*⁺ – 57) *m/z* 367.1399, found *m/z* 367.1398. Anal. Calcd for C₂₂H₃₆O₄SSi: C, 62.23; H, 8.55. Found: C, 61.98; H, 8.54.

(*αS,exo,exo*)-*α*-Methyl-6-[(1,1-dimethylethyl)dimethylsilyl]oxy]bicyclo[2.2.1]-heptane-2-methanol *α*-(4-Methylbenzenesulfonate) (**26**). The alcohol **24** (1.863 g, 6.90 mmol) was treated with TsCl as described for the tosylation of **23**. Workup and flash chromatography (50:1 petroleum ether (bp 40–60 °C)/EtOAc) gave 2.742 g (94 %) of tosylate **26** as white crystals: mp 75–77 °C (from hexane); ¹H NMR δ –0.04 (s, 6 H), 0.82 (s, 9 H), 0.88 (m, 1 H), 1.09–1.54 (m, 6 H), 1.23 (d, *J* = 6.1 Hz, 3 H), 1.79 (m, 1 H), 2.14 (m, 1 H), 2.42 (s, 3 H), 3.52

(m, 1 H), 4.25 (m, 1 H), 7.31 (d, $J = 8.3$ Hz, 2 H), 7.78 (d, $J = 8.3$ Hz, 2 H); ^{13}C NMR δ -5.03 (q), -4.90 (q), 17.73 (s), 18.83 (q), 21.33 (q), 25.58 (3q), 31.51 (t), 33.18 (t), 35.12 (d), 41.66 (t), 43.35 (d), 46.03 (d), 74.44 (d), 82.08 (d), 127.45 (2d), 129.46 (2d), 134.28 (s), 144.17 (s); MS m/z (relative intensity) ($M^+ - 57$, 1.4), 231 (10), 230 (16), 229 (100), 195 (32), 121 (34), 93 (9), 91 (15), 75 (29), 73 (14); calcd for $\text{C}_{18}\text{H}_{27}\text{O}_4\text{SSi}$ ($M^+ - 57$) m/z 367.1399, found m/z 367.1396. Anal. Calcd for $\text{C}_{22}\text{H}_{36}\text{O}_4\text{SSi}$: C, 62.23; H, 8.55. Found: C, 62.27; H, 8.72

($\alpha R,exo,exo$)- α -Methyl-6-hydroxybicyclo[2.2.1]heptane-2-methanol α -(4-Methylbenzenesulfonate) (6). The silyl ether **25** (2.41 g, 5.68 mmol) was desilylated with HF as described for the synthesis of **1**. Workup and flash chromatography (2:1 petroleum ether (bp 40–60 °C)/EtOAc) afforded 1.73 g (98 %) of **6**: ^1H NMR δ 1.10–1.63 (m, 7 H), 1.20 (d, $J = 6.1$ Hz, 3 H), 1.87 (m, 1 H), 1.97 (br s, OH), 2.18 (m, 1 H), 2.40 (s, 3 H), 3.67 (m, 1 H), 4.44 (m, 1 H), 7.29 (d, $J = 8.2$ Hz, 2 H), 7.73 (d, $J = 8.2$ Hz, 2 H); ^{13}C NMR δ 19.93 (q), 21.57 (q), 32.39 (t), 32.70 (t), 35.21 (d), 41.02 (t), 43.50 (d), 47.00 (d), 74.65 (d), 83.57 (d), 127.57 (2d), 129.70 (2d), 134.46 (s), 144.53 (s); MS m/z (relative intensity) ($M^+ - 155$, 24), 138 (60), 109 (11), 95 (20), 94 (100), 93 (10), 91 (29), 79 (19), 67 (13); calcd for $\text{C}_9\text{H}_{15}\text{O}_2$ ($M^+ - 155$) m/z 155.1072, found m/z 155.1086.

($\alpha S,exo,exo$)- α -Methyl-6-hydroxybicyclo[2.2.1]heptane-2-methanol α -(4-Methylbenzenesulfonate) (7). The silyl ether **26** (2.54 g, 5.99 mmol) was desilylated with HF as described for the synthesis of **1**. Workup and flash chromatography (2:1 petroleum ether (bp 40–60 °C)/EtOAc) afforded 1.84 g (99 %) of **7**: ^1H NMR δ 0.77–1.02 (m, 2 H), 1.11–1.86 (m, 6 H), 1.15 (d, $J = 6.1$ Hz, 3 H), 2.06 (m, 1 H), 2.20 (m, 1 H), 2.42 (s, 3 H), 3.68 (m, 1 H), 4.24 (m, 1 H), 7.32 (d, $J = 8.2$ Hz, 2 H), 7.78 (d, $J = 8.2$ Hz, 2 H); ^{13}C NMR δ 18.50 (q), 21.37 (q), 31.40 (t), 32.87 (t), 35.27 (d), 40.60 (t), 43.48 (d), 46.02 (d), 74.13 (d), 81.91 (d), 127.50 (2d), 129.52 (2d), 134.13 (s), 144.34 (s); MS m/z (relative intensity) (M^+ , 0.1), 155 (18), 138 (54), 109 (13), 95 (23), 94 (100), 93 (10), 91 (30), 79 (19), 67 (14); calcd for $\text{C}_{16}\text{H}_{22}\text{O}_4\text{S}$ (M^+) m/z 310.1239, found m/z 310.1234.

(exo)-6-ethylidenebicyclo[2.2.1]heptan-2-ol (27). A solution of 0.116 g (0.273 mmol) of tosylate **25** and 0.056 g (0.68 mmol) of NaOAc in 2 mL of dry DMSO was stirred at 50 °C for 24 h and at 70 °C for an additional 30 h. The reaction mixture was allowed to come to rt and poured into 50 mL of H_2O . The aqueous layer was extracted with five 25-mL portions of ether. The combined organic layers were washed with 25 mL of brine, dried, and evaporated. The remaining residue was flash chromatographed (250:1 pentane/ether) to give 0.036 g (52%) of a 19:1 mixture of **27** and the TBDMS ether of **43**,⁴⁴ respectively. The spectroscopic data of **27** and the TBDMS ether of **43** are shown below.

27: ^1H NMR δ 0.02 (s, 3 H), 0.04 (s, 3 H), 0.88 (s, 9 H), 1.15–1.78 (m, 8 H), 1.97 (m, 1 H), 2.37 (m, 1 H), 2.48 (m, 1 H), 3.72 (m, 1 H), 5.36 (m, 1 H); ^{13}C NMR δ -4.72 (q), -4.58 (q), 14.13 (q), 18.25 (s), 25.93 (3q), 34.92 (t), 35.41 (t), 35.72 (d), 42.44 (t), 53.93 (d), 74.79 (d), 114.43 (d), 142.38 (s); MS m/z (relative intensity) 252 (M^+ , <0.1), 196 (16), 195 (100), 122 (12), 121 (19), 120 (11), 106 (7), 94 (8), 76 (34), 74 (15); calcd for $\text{C}_{15}\text{H}_{28}\text{OSi}$ (M^+) m/z 252.1909, found m/z 252.1910.

TBDMS ether of 43: ^1H NMR δ 0.02 (s, 6 H), 0.86 (s, 9 H), 1.10–1.38 (m, 4 H), 1.47–1.73 (m, 2 H), 1.81–1.76 (m, 2 H), 2.23 (m, 1 H), 3.70 (m, 1 H), 4.81–4.98 (m, 2 H), 5.69 (m, 1 H); ^{13}C NMR δ -4.83 (2q), 18.93 (s), 25.65 (3q), 31.90 (t), 35.33 (d), 36.07 (t), 40.81 (d), 42.40 (t), 50.18 (d), 74.77 (d), 111.63 (t), 143.07 (d); MS m/z (relative intensity) 252 (M^+ , 0.8), 197

(5), 196 (17), 195 (100), 120 (6), 92 (5), 80 (4), 78 (5), 77 (6), 76 (72), 74 (14); calcd for $C_{15}H_{28}OSi$ (M^+) m/z 252.1909, found m/z 252.1905.

(*exo,exo*)-2-(methoxymethyl)-6-[[1,1-Dimethylethyl]dimethylsilyl]oxy]bicyclo[2.2.1]-heptane (34). To a solution of 0.304 g (1.19 mmol) of **21** in a mixture of 10 mL of MeI and 10 mL of dry DMF was added 0.150 g (6.25 mmol) of NaH. The reaction mixture was refluxed for 2 h, allowed to come to rt, and then carefully quenched by the addition of an excess of saturated aqueous NH_4Cl , followed by 20 mL of H_2O . The aqueous mixture was extracted with three 25-mL portions of EtOAc. The combined organic layers were washed with 10 mL of brine, dried, and evaporated. The resulting oil was flash chromatographed (100:1 petroleum ether (bp 40–60 °C)/EtOAc) to afford 0.253 g (79 %) of **34**: 1H NMR δ 0.00 (s, 3 H), 0.01 (s, 3 H), 0.84 (s, 9 H), 0.86 (m, 1 H), 1.03–1.37 (m, 3 H), 1.41–1.60 (m, 3 H), 1.98 (m, 1 H), 2.17 (m, 1 H), 3.03–3.23 (m, 2 H), 3.29 (s, 3 H), 3.66 (m, 1 H); ^{13}C NMR δ –4.90 (2q), 17.75 (s), 25.62 (3q), 31.58 (t), 33.14 (t), 34.83 (d), 36.88 (d), 42.32 (t), 46.62 (d), 58.35 (q), 74.79 (d), 76.12 (t); MS m/z (relative intensity) 213 ($M^+ - 57$, 100), 214 (19), 140 (35), 108 (65), 92 (8), 90 (27), 82 (6), 80 (46), 76 (44), 74 (23); calcd for $C_{11}H_{21}O_2Si$ ($M^+ - 57$) m/z 213.1311, found m/z 213.1308.

(*exo,exo*)-6-(Methoxymethyl)bicyclo[2.2.1]heptan-2-ol 4-Methylbenzenesulfonate (35). The silyl ether **34** (0.220 g, 0.81 mmol) was desilylated with HF as described for the synthesis of **1**. Workup afforded 0.121 g of a clear oil. This crude oil was treated with TsCl for 8 h as described for the tosylation of **14**. Workup and flash chromatography (10:1 petroleum ether (bp 40–60 °C)/EtOAc) afforded 0.180 g (71 %) of pure **35** as an oil: 1H NMR δ 0.93 (m, 1 H), 1.10–1.29 (m, 2 H), 1.41–1.63 (m, 4 H), 2.16–2.28 (m, 2 H), 2.41 (s, 3 H), 2.99–3.18 (m, 2 H), 3.24 (s, 3 H), 4.42 (m, 1 H), 7.30 (d, $J = 8.2$ Hz, 2 H), 7.74 (d, $J = 8.2$ Hz, 2 H); ^{13}C NMR δ 21.35 (q), 32.07 (t), 32.45 (t), 34.91 (d), 36.46 (d), 38.98 (t), 44.23 (d), 58.37 (q), 75.34 (t), 84.75 (d), 127.42 (2d), 129.51 (2d), 134.29 (s), 144.16 (s); MS m/z (relative intensity) 139 ($M^+ - 171$, 64), 155 (48), 139 (64), 138 (36), 109 (46), 108 (44), 92 (100), 80 (58), 67 (43), 46 (37); calcd for $C_9H_{15}O$ ($M^+ - 171$) m/z 139.1126, found m/z 139.1126.

Reactions of Tosylates 1–7 and 35 with Sodium *tert*-Amylate. Procedure A. All reactions were carried out at a concentration of ca. 0.1 M tosylate in dry benzene. The solutions were degassed and refluxed under an Ar atmosphere. Ca. 5 equiv of sodium *tert*-amylate (3.2 M in toluene) was added at once, via syringe, to the refluxing solution of the tosylate. The reaction mixture was heated at reflux temperature for 1 or 10 min, quenched with precooled saturated aqueous NH_4Cl , and then quickly cooled to 0 °C. The mixture was vigorously stirred for 20 min, followed by extraction with five 10-mL portions of ether. The combined organic layers were dried and carefully evaporated under reduced pressure to afford the crude reaction products. Product ratios, yields, and pure compounds were obtained by chromatographical techniques.

Procedure B. The procedure A was employed by using a mixture of the tosylate and 1.0 equiv of an internal standard (ethylbenzene). After workup, quantitative GC analysis of the combined organic layers (prior to evaporation) were performed with the use of authentic compounds and the internal standard. A response factor was used for analysis in a standard way. Mass spectra, for identification of products, were measured with GCMS. Evaporation and flash chromatography afforded the non-volatile products.

a. Procedure A was employed by using 0.199 g (0.67 mmol) of **1**. The reaction time was 10 min. Workup and flash chromatography (pentane to ether) afforded, in order of elution, 0.065 g (22 %) of the ditosylated compound **29**, 0.011 g (12 %) of lactol **30**, 0.030 g (15 %) of unreacted **1**, and 0.021 g (22 %) of diol **28**. The spectroscopic data of **28–30** are shown below.

(*endo,endo*)-6-Hydroxybicyclo[2.2.1]heptane-2-methanol (**28**): ^1H NMR δ 0.87 (ddd, $J = 3.1, 4.7, 12.7$ Hz, 1 H), 1.14–1.40 (m, 3 H), 1.63 (m, 1 H), 1.93 (m, 1 H), 2.03–2.23 (m, 3 H), 3.58–3.79 (m, 2 H), 4.13 (m, 1 H), 5.60 (br s, 2 OH); ^{13}C NMR δ 31.34 (t), 36.92 (d), 38.20 (t), 38.60 (t), 41.33 (d), 45.90 (d), 62.16 (t), 73.38 (d); MS m/z (relative intensity) 124 ($\text{M}^+ - 18$, 14), 106 (16), 96 (15), 95 (15), 82 (27), 81 (100), 80 (33), 68 (35), 67 (18), 56 (15), 42 (17); calcd for $\text{C}_8\text{H}_{12}\text{O}$ ($\text{M}^+ - 18$) m/z 124.0888, found m/z 124.0891.

(*endo,endo*)-6-[(4-Methylphenyl)sulfonyl]oxy]bicyclo[2.2.1]heptane-2-methanol 4-Methylbenzenesulfonate (**29**): ^1H NMR δ 0.89–1.48 (m, 4 H), 1.81–2.07 (m, 2 H), 2.16–2.47 (m, 3 H), 2.44 (s, 6 H), 4.22 (d, $J = 7.3$ Hz, 2 H), 4.78 (m, 1 H), 7.27–7.40 (2d, 4 H), 7.68–7.80 (2d, 4 H); ^{13}C NMR δ 21.42 (2q), 34.35 (t), 36.23 (d), 36.47 (t), 37.65 (t), 39.26 (d), 43.33 (d), 73.88 (t), 82.51 (d), 127.50 (2d), 127.67 (2d), 129.59 (4d), 132.89 (s), 133.64 (s), 144.32 (s), 144.57 (s); MS m/z (relative intensity) 450 (M^+ , 0.2), 172 (29), 155 (61), 124 (34), 108 (68), 107 (23), 96 (17), 92 (100), 81 (21), 80 (39); calcd for $\text{C}_{22}\text{H}_{26}\text{O}_6\text{S}_2$ (M^+) m/z 450.1171, found m/z 450.1170.

2-Oxatricyclo[4.2.1.0^{4,8}]nonan-3-ol (**30**): ^1H NMR δ 1.14–1.93 (m, 6 H), 2.15–2.42 (m, 2 H), 2.80–3.05 (m, 2 H), 4.52 (m, 1 H), 5.25 (m, 1 H); ^{13}C NMR δ 32.88 (t), 34.58 (d), 37.47 (t), 40.67 (t), 43.83 (d), 45.39 (d), 79.95 (d), 102.47 (d); MS m/z (relative intensity) 123 ($\text{M}^+ - 17$, 43), 119 (100), 117 (98), 97 (35), 95 (42), 85 (18), 83 (17), 80 (32), 67 (22), 28 (65); calcd for $\text{C}_8\text{H}_{11}\text{O}$ ($\text{M}^+ - 17$) m/z 123.0810, found m/z 123.0812.

b. Procedure B was employed by using 0.120 g (0.40 mmol) of **2**. The reaction time was 10 min. According to GC(MS) analysis, 0.007 g (19 %) of **31**¹⁵ was formed. Further workup and flash chromatography (pentane to ether) afforded, in order of elution, 0.008 g (4%) of **32** and 0.021 g (21%) of unreacted **2**.

c. Procedure B was employed by using 0.076 g (0.26 mmol) of **3**, except that the reaction was stirred at rt for 10 min. According to GC(MS) analysis, 0.013 g (55 %) of **31** and 0.002 g (6 %) of **33**¹⁶ were formed.

d. Procedure B was employed by using 0.050 g (0.17 mmol) of **3**, except that the solution of **3** was added to the refluxing solution of sodium *tert*-amylate. The reaction time was 1 min. According to GC(MS) analysis, 78 % of **31** and 3 % of **33** were formed.⁴⁵

e. Procedure B was employed by using 0.532 g (1.80 mmol) of **4**. The reaction time was 10 min. According to GC(MS) analysis, 0.062 g (28 %) of **36**¹¹ was formed. Further workup and flash chromatography (pentane to ether) afforded 0.021 g (4 %) of unreacted **4**.

f. Procedure A was employed by using 0.164 g (0.55 mmol) of **5**. The reaction time was 10 min. After workup, a complex mixture was obtained from which only unreacted **5** (48 %) could be isolated.

g. The same as above, except that the reaction mixture was heated at reflux for 1 min. Starting from 0.250 g (0.85 mmol) of **5**, workup and flash chromatography (pentane to ether) afforded, in order of elution, 0.012 g (5 %) of **37**, 0.180 g (72 %) of unreacted **5**, 0.006 g (5 %) of **16**, and 0.004 g (3 %) of **38**. The spectroscopic data of **37** and **38** are shown below.

(*exo*)-6-[(4-Methylphenyl)sulfonyl]oxy]bicyclo[2.2.1]heptane-2-one (**37**): ^1H NMR δ 1.37 (m, 1 H), 1.55–1.73 (m, 3 H), 1.83 (m, 1 H), 1.97–2.20 (m, 2 H), 2.44 (s, 3 H), 2.47 (m, 1 H),

2.67 (m, 1 H), 3.90 (d, $J = 7.4$ Hz, 2 H), 7.34 (d, $J = 8.2$ Hz, 2 H), 7.77 (d, $J = 8.2$ Hz, 2 H); ^{13}C NMR δ 21.68 (q), 31.76 (t), 34.50 (t), 35.29 (d), 35.62 (d), 44.44 (t), 51.76 (d), 71.15 (t), 127.89 (2d), 129.95 (2d), 133.12 (s), 145.02 (s), 215.52 (s); MS m/z (relative intensity) 294 (M^+ , 27), 122 (100), 94 (49), 93 (33), 91 (80), 81 (37), 80 (60), 79 (88), 78 (94); calcd for $\text{C}_{15}\text{H}_{18}\text{O}_4\text{S}$ (M^+) m/z 294.0926, found m/z 294.0926.

(*exo,exo*)-6-Hydroxybicyclo[2.2.1]heptane-2-methanol (38): ^1H NMR δ 0.86 (m, 1 H), 1.07–1.70 (m, 6 H), 2.14 (m, 1 H), 2.23 (m, 1 H), 2.70 (br s, 2 OH), 3.24–3.48 (m, 2 H), 3.76 (m, 1 H); ^{13}C NMR δ 31.46 (t), 32.43 (t), 35.12 (d), 39.97 (d), 41.41 (t), 46.20 (d), 65.77 (t), 74.60 (d); MS m/z (relative intensity) 124 ($\text{M}^+ - 18$, 11), 106 (53), 93 (36), 91 (35), 81 (31), 80 (100), 79 (41), 67 (72), 55 (22), 41 (25); calcd for $\text{C}_8\text{H}_{12}\text{O}$ ($\text{M}^+ - 18$) m/z 124.0888, found m/z 124.0881.

h. Procedure A was employed by using 0.396 g (1.28 mmol) of **6**. The reaction time was 1 min. Workup and flash chromatography (pentane to 2:1 pentane/ether) afforded 0.098 g (51 %) of [(1' α ,3' α ,5' α ,6' α)-6'-methyl-bicyclo[3.1.0]-hexan-3'-yl]acetaldehyde (**39**) as the sole product: ^1H NMR δ 0.58 (m, 1 H), 0.82–0.98 (m, 2 H), 0.89 (d, $J = 5.9$ Hz, 3H), 1.20–1.42 (m, 2 H), 1.80–2.07 (m, 3 H), 2.31–2.43 (m, 2 H), 9.66 (t, $J = 2.1$ Hz, 1 H); ^{13}C NMR δ 14.01 (d, $J = 158.6$ Hz), 17.32 (q), 25.14 (2d, $J = 165.0$ Hz), 29.88 (d), 34.36 (2t), 49.45 (t), 202.23 (d); MS m/z (relative intensity) 138 (M^+ , 0.8), 95 (25), 94 (100), 93 (13), 79 (63), 77 (11), 67 (16), 55 (27), 41 (14); calcd for $\text{C}_9\text{H}_{14}\text{O}$ (M^+) m/z 138.1045, found m/z 138.1046.

i. Procedure A was employed by using 0.215 g (0.69 mmol) of **7**. The reaction time was 1 min. Workup and flash chromatography (pentane to ether) afforded, in order of elution, 0.040 g (42 %) of an inseparable 15:4:1 mixture of **40**, **41**, and **42**, respectively, 0.006 g (6 %) of **43**, and 0.051 g (24 %) of unreacted **7**. Analytical samples of the aldehydes **40–42** were obtained by preparative GC. The spectroscopic data of **40–43** are shown below.

[(1' α ,3' α ,5' α ,6' β)-6'-Methylbicyclo[3.1.0]hexan-3'-yl]acetaldehyde (40): ^1H NMR δ 0.76 (m, 1 H), 0.92 (d, $J = 6.2$ Hz, 3 H), 1.19–1.32 (m, 2 H), 1.40–1.56 (m, 2 H), 1.87 (dd, $J = 8.2$, 13.2 Hz, 2 H), 2.11 (m, 1 H), 2.42 (dd, $J = 2.1$, 7.0 Hz, 2 H), 9.68 (t, $J = 2.1$ Hz, 1 H); ^{13}C NMR δ 7.91 (q), 13.93 (d, $J = 151.8$ Hz), 21.20 (2d, $J = 165.4$ Hz), 31.88 (2t), 34.80 (d), 51.95 (t), 202.35 (d); MS m/z (relative intensity) 138 (M^+ , 56), 109 (23), 95 (32), 94 (100), 91 (36), 79 (26), 71 (30), 57 (43), 55 (31); calcd for $\text{C}_9\text{H}_{14}\text{O}$ (M^+) m/z 138.1045, found m/z 138.1043.

[(3' α ,5' α)-3'-Methylcyclohexen-5'-yl]acetaldehyde (41): ^1H NMR δ 0.96 (d, $J = 7.1$ Hz, 3 H), 1.50–1.85 (m, 3 H), 2.02–2.43 (m, 5 H), 5.45–5.66 (m, 2 H), 9.78 (t, $J = 2.2$ Hz, 1 H); MS m/z (relative intensity) 138 (M^+ , 49), 121 (32), 95 (15), 94 (100), 93 (14), 91 (36), 79 (26), 75 (14), 67 (12); calcd for $\text{C}_9\text{H}_{14}\text{O}$ (M^+) m/z 138.1045, found m/z 138.1043.

(1'-Ethyl-cyclopenten-4'-yl)acetaldehyde (42): ^1H NMR δ 1.02 (dd, $J = 7.4$, 7.4 Hz, 3H), 1.84–2.13 (m, 4 H), 2.43–2.82 (m, 5 H), 5.25 (m, 1 H), 9.75 (t, $J = 1.9$ Hz, 1 H); MS m/z (relative intensity) 138 (M^+ , 49), 97 (17), 95 (22), 94 (100), 91 (36), 79 (29), 57 (30), 43 (24), 41 (19); calcd for $\text{C}_9\text{H}_{14}\text{O}$ (M^+) m/z 138.1045, found m/z 138.1043.

(2-*exo,6-exo*)-2-Hydroxy-6-ethenylbicyclo[2.2.1]heptane (43): ^1H NMR δ 1.14–1.74 (m, 7 H), 1.87–2.08 (m, 2 H), 2.28 (m, 1 H), 3.82 (m, 1 H), 4.83–4.99 (m, 2 H), 5.74 (ddd, $J = 7.4$, 10.0, 17.1 Hz, 1 H); ^{13}C NMR δ 31.78 (t), 35.47 (d), 35.59 (t), 40.76 (d), 41.52 (t), 50.06 (d), 74.49 (d), 112.02 (t), 142.62 (d); MS m/z (relative intensity) 138 (M^+ , 11), 120 (83), 105 (57), 95 (90), 94 (60), 93 (96), 92 (46), 84 (42), 80 (100), 78 (41); calcd for $\text{C}_9\text{H}_{14}\text{O}$ (M^+) m/z 138.1045, found m/z 138.1045.

j. The same as above, except that in addition to sodium *tert*-amylate 1 equiv 15-crown-5 was used. After workup, flash chromatography (pentane to ether) gave, in order of elution, 0.042 g (53 %) of **40**, 0.009 g (11 %) of **43**, and 0.021 g (12 %) of unreacted **8**.

k. Procedure A was employed by using 0.105 g (0.34 mmol) of **35**. The reaction time was 10 min. After workup, 87 % of unreacted **35** was recovered. No reaction products could be isolated.

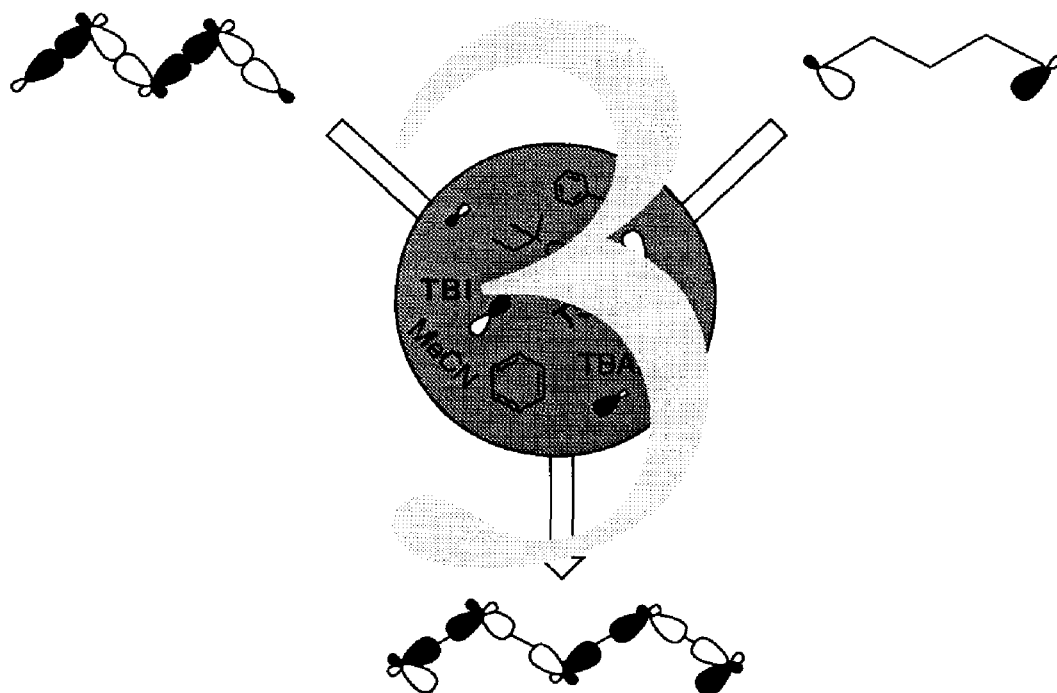
2.5 References and Notes

- 1 Wijnberg, J. B. P. A.; Jenniskens, L. H. D.; Brunekreef, G. A.; de Groot, A. J. *Org. Chem.* **1990**, 55, 941.
- 2 Jenniskens, L. H. D.; Wijnberg, J. B. P. A.; de Groot, A. J. *Org. Chem.* **1991**, 56, 6585.
- 3 Hoffmann, R.; Imamura, A.; Hehre, W. J. *J. Am. Chem. Soc.*, **1968**, 90, 1499.
- 4 For example, see: (a) Hoffmann, R. *Acc. Chem. Res.* **1971**, 4, 1. (b) Gleiter, R. *Angew. Chem., Int. Ed. Engl.* **1974**, 13, 696. (c) Martin, H. D.; Mayer, B. *Angew. Chem., Int. Ed. Engl.* **1983**, 22, 283. (d) Paddon-Row, M. N.; Jordan, K. D. In *Modern Models of Bonding and Delocalization*; Liebman, J. F., Greenberg, A., Eds.; VCH Publishers: New York, 1988, Chapter 3.
- 5 Orrū, R. V. A.; Wijnberg, J. B. P. A.; Jenniskens, L. H. D.; de Groot, A. J. *Org. Chem.* **1993**, 58, 1199.
- 6 Orrū, R. V. A.; Wijnberg, J. B. P. A.; Bouwman, C. T.; de Groot, A. J. *Org. Chem.* **1994**, 59, 374.
- 7 The numbering system as given in structure **1** will be followed throughout the text of this chapter.
- 8 For example, see: Grob, C. A. *Angew. Chem.* **1982**, 94, 87 and references cited therein.
- 9 Nakazaki, M.; Naemura, K.; Kondo, Y. *J. Org. Chem.* **1976**, 41, 1229.
- 10 Fischer, W.; Grob, C. A.; von Sprecher, G.; Waldner, A. *Helv. Chim. Acta* **1980**, 63, 816.
- 11 Menger, F. M.; Chow, J. F.; Kaiserman, H.; Vasquez, P. C. *J. Am. Chem. Soc.* **1983**, 105, 4996.
- 12 Fischer, W.; Grob, C. A.; von Sprecher, G. *Helv. Chim. Acta* **1980**, 63, 806.
- 13 Bartsch, R. A.; Read, R. A.; Larsen, D. T.; Roberts, D. K.; Scott, K. J.; Rae Cho, B. B. A. *J. Am. Chem. Soc.* **1979**, 101, 1176.
- 14 The ¹H NMR data and GC analysis of olefin **27** revealed the presence of the TBDMS ether of **43** (ca. 5%).
- 15 Roberts, J. D.; Trumbell, E. R.; Bennet, W.; Armstrong, R. J. *Am. Chem. Soc.* **1950**, 72, 3116.
- 16 An authentic sample of the cyclic ether **33** was prepared following a previously described procedure.⁹
- 17 The O-methylated tosylate **35** was obtained by treatment of the primary alcohol **21** with NaH and MeI in dry DMF to give the corresponding methyl ether **34**, followed by cleavage of the silyl ether bond and tosylation (see Experimental Section).
- 18 We assume that orbital interactions are responsible for the remarkable instability of the silyl ether bond in the TBDMS ether of tosylate **3**.
- 19 Competing S–O bond scission often occurs upon treatment of tosylate esters with O-nucleophiles. For example, see: Netscher, T. *Tetrahedron Lett.* **1988**, 29, 455.
- 20 It is also possible that S–O bond scission occurs by an intermolecular alkoxide attack¹⁹ instead of an intramolecular hydride attack.
- 21 Fischer, W.; Grob, C. A.; von Sprecher, G.; Waldner, A. *Tetrahedron Lett.* **1979**, 21, 1905.

- 22 Grob, C. A. *Acc. Chem. Res.* **1983**, *16*, 426.
- 23 Fischer, W.; Grob, C. A.; Hanreich, R.; von Sprecher, G.; Waldner, A. *Helv. Chim. Acta* **1981**, *64*, 2298.
- 24 Adcock, W.; Kok, G.B. *J. Org. Chem.* **1987**, *52*, 356.
- 25 Grob, C. A.; Gründel, M.; Sawlewitz, P. *Helv. Chim. Acta* **1988**, *71*, 1502.
- 26 *trans*-Perhydronaphthalene-1,4-diol monosulfonate esters possessing the ideal W-like arrangement only show homofragmentation.⁶
- 27 Similar (side) reactions can also occur with the other tosylates.
- 28 Oxidation of secondary alcohols by hydride transfer under the influence of alkali-metal alkoxides in benzene has been reported in the literature. For example, see: Warnhoff, E. W.; Reynolds-Warnhoff, P. *J. Org. Chem.* **1963**, *28*, 1431.
- 29 Menger¹¹ also came to the conclusion that in the base-induced formation of **36** from (2-*endo*,6-*exo*)-6-bromomethylbicyclo[2.2.1]heptan-2-ol, "long-distance catalysis appears unlikely". The remark that "through-bond inductive effects are, in any event, attenuated by three intervening carbons" to support this conclusion is not really essential in this respect as follows from our work presented here.
- 30 See ref 5 and references cited therein.
- 31 (a) Allinger, N. L. *J. Am. Chem. Soc.* **1977**, *99*, 8127. (b) The QCPE MM2(87) program was used.
- 32 Paddon-Row, M. N. *Acc. Chem. Res.* **1982**, *15*, 245.
- 33 The Newman projection formula **7D** is viewed along the C(8)–CH₃ bond.
- 34 A minor statistical factor should also be considered as there are three equivalent conformations **7D** which may be interconverted by 120° rotation about the C(8)–CH₃ bond.
- 35 Seeman, J. I. *Chem. Rev.* **1983**, *83*, 83.
- 36 Because of the relatively small steric repulsion between syn H-7 and H-8 this staggered conformation is probably the most stable one.
- 37 It might be possible that stereoelectronic effects also influences the conformational equilibrium position of the deprotonated conformations of **7**,³⁸ but this has **no influence** on the product ratio as long as the rate of interconversion remains much **faster than** the rate of product formation.
- 38 The possible influence of orbital interactions on the relative energies of conformations was suggested by Hoffmann et al., see: Gleiter, R.; Stohrer, W.-D.; Hoffmann, R. *Helv. Chim. Acta* **1972**, *55*, 893. The first experimental verification of this effect was reported in 1989, see: Krijnen, B.; Beverloo, H. B.; Verhoeven, J. W.; Reiss, C. A.; Goubitz, K.; Heijdenrijk, D. *J. Am. Chem. Soc.* **1989**, *111*, 4433.
- 39 Bartsch, R. A. *Acc. Chem. Res.* **1975**, *8*, 239.
- 40 Schultz, J. C.; Houle, F. A.; Beauchamp, J. L. *J. Am. Chem. Soc.* **1984**, *106*, 3917.
- 41 In the related Wharton reaction a few primary sulfonate esters give products which can only be explained as the result of the chemical consequences of orbital interactions, see: Caine, D. *Org. Prep. Proced. Int.* **1988**, *20*, 1.
- 42 Conia, M. J.-M. *Bull. Soc. Chim. Fr.* **1950**, *17*, 537.
- 43 Kabalka, G. W.; Varma, M.; Varma, R. S. *J. Org. Chem.* **1986**, *51*, 2386.
- 44 Treatment of **25** with sodium *tert*-amylate (procedure A, reaction time 10 min) gave this compound as the sole product in a slow reaction.
- 45 This reaction is another example of the highly selective formation of nortricyclene in norbornyl reactions, see: Shine, H. J.; Yueh, W. *J. Org. Chem.* **1994**, *59*, 3553.

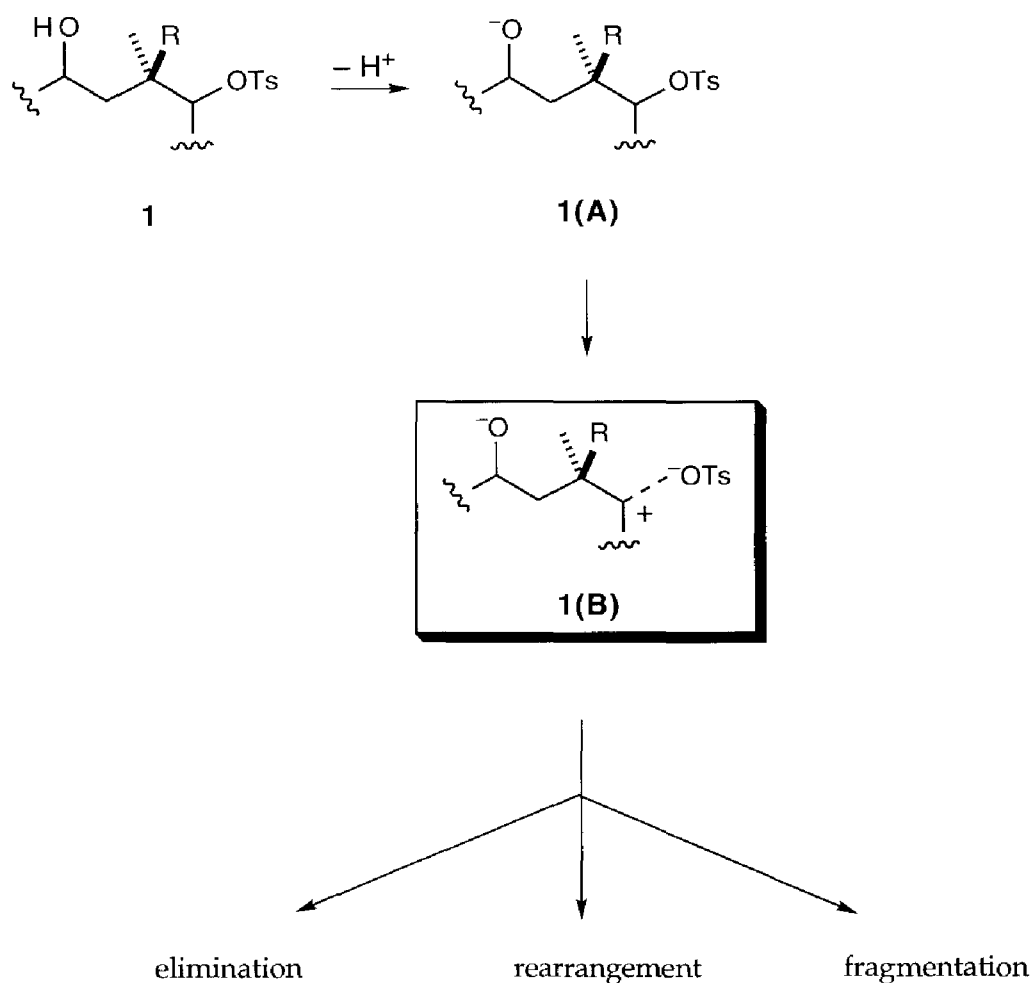
Chapter 3

Theory of Through-Bond Interactions in Monosulfonated 1,4-Diols



3.1 Introduction

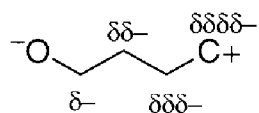
The 1,4-diol monosulfonates of rigid *trans*-perhydronaphthalenes¹ and norbornanes² show a similar reaction behavior upon basic treatment. After initial deprotonation of the hydroxyl group (formation of intermediate **1(A)**), a very fast or relatively fast heterolysis of the sulfonate ester can be observed. This relatively facile heterolysis, giving a dipolar intermediate **1(B)**, may be followed by three different processes, *viz.* elimination, rearrangement, and/or fragmentation to neutralise both charges (Scheme 3.1). Since in these reactions an apolar solvent is used, it is most likely that an ion pair is formed between the sulfonate anion and the carbocation.³



Scheme 3.1

The key step, and certainly also the most striking feature under these non-solvolytic conditions, is the smooth heterolysis of the sulfonate ester. The generation of an alkoxide group prior to, or simultaneously with this heterolysis is essential. Sodium *tert*-amylate, which is used as the base, is non-nucleophilic and, consequently, will *not* participate *directly* in the heterolysis of the sulfonate group. Furthermore, since stabilization via solvation is negligible, the alkoxide is strongly electron-donating and in one way or another induces the departure of the sulfonate ester intramolecularly. Clearly, the remote carbocation and/or its formation is stabilized intramolecularly by the alkoxide. To account for this stabilization, several factors may be invoked.

(i) **σ -Inductive effects.** The stability of the dipolar intermediate can be explained by the polarity of the C–O[−] bond as propagated to the carbocation center by successive polarization of the intervening σ -bonds.^{4,5} However, this mechanism is generally viewed as a short-range effect^{6,7} and it should be regarded as relatively unimportant beyond the range of two bonds.^{8,9} According to calculations, the fall-off in polarization in saturated systems ranges between 0.2 and 0.7.⁴ Applying the smallest decay factor of 0.7 to the 1,5-dipolar intermediates, it can be concluded that



the stabilization by successive polarization is a rather small effect. Further, and more important, such σ -inductive effects can not explain the observed geometry dependence of the heterolysis of 1,4-diol monosulfonate esters.^{1d}

(ii) **Field effects.** Although the field effect is a long-range effect, it can hardly be the only factor controlling the heterolysis. This can be concluded by comparing the rates of heterolysis of **2** and **3** (Chart 3.1).^{1d}

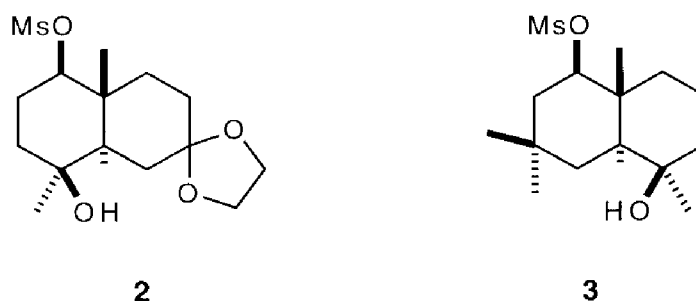


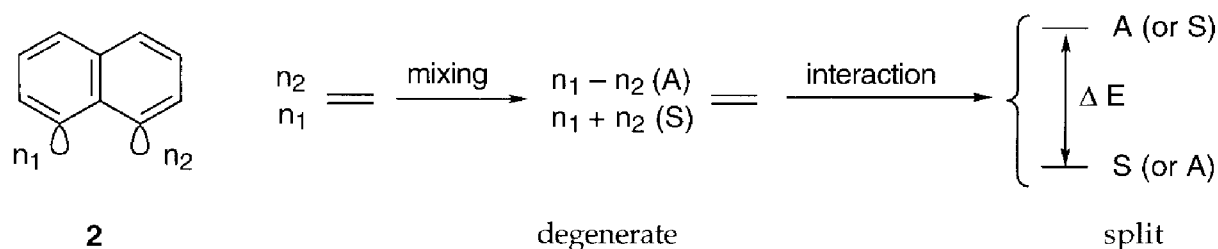
Chart 3.1

Since field effects are transmitted through space a relatively fast heterolysis of the sulfonate ester of **2** should have been observed in view of the relatively small spatial separation between the alkoxide and the (incipient) carbocation in the dipolar intermediate of this compound. Actually, experimental evidence rules against these field effects since the heterolysis of the sulfonate ester occurs much faster in **3** than in **2**, despite the large distance between the negative and positive charges present in the dipolar intermediate of **3**.

(iii) Through-bond interactions (TBI). Up to this point the reactivities and reactions encountered in the base-induced heterolysis of 1,4-diol monosulfonate esters were explained successfully in terms of through-bond interactions (TBI) between the alkoxide and the (incipient) carbocation. The theoretical basis for TBI was published by Hoffmann et al. as early as 1968.¹⁰ Hoffmann converted the traditional and generally very useful localized bond model of organic molecules into a delocalized molecular orbital (MO) model by applying perturbation theory¹¹ to the former. In view of the importance of TBI in the base-induced heterolysis of diol monosulfonate esters, a closer inspection of this description is justified, and will be provided in the next section. After an introduction, those features of the TBI model that can account for the most important observables met in the heterolysis of monosulfonated diols (and many other reactions) are discussed. For example, (a) why is an interaction between two functionalities most efficient when the arrangement of σ -bonds connecting them possesses an "all-trans" or "W" shape? (b) why is it easier to generate a carbocation when a remote alkoxide group is present in the same molecule? and (c) how does an indirect transfer of negative charge from an alkoxide to a carbocation take place? The description of TBI offered here is of a qualitative nature, and is not able to account for subtle differences in reactivity. Its main benefit lies in its simplicity, and for a graphical description "on the back of an envelope" no sophisticated computational methods have to be invoked.

3.2 An Introduction to TBI

In organic chemistry the concepts of TBI and TSI nicely account for the interaction of localized sets of orbitals, chromophores, or functional groups in organic molecules. Originally, the concept of TBI was based on the results of extended Hückel calculations¹² on a variety of diradicals. Computationally, these radicals were generated by the removal of two hydrogen atoms from an aromatic molecule (**2**) (figure 3.2).



Scheme 3.2

Since rotation about a twofold axis interchanges the remaining sp^2 -type σ orbitals (n_1 and n_2), two symmetry-adapted combinations can be formed: the symmetrical combination $S (= n_1 + n_2)$ and the anti-symmetrical combination $A (= n_1 - n_2)$. These two orbitals (S and A) are degenerate if n_1 and n_2 have no mutual interaction. However, simple calculations (such as extended Hückel) already show a splitting of S and A , indicating an interaction between n_1 and n_2 . Further, this lifting of the degeneracy turned out to be independent of any specific molecule since comparable results were obtained in model molecules too. Actually, it proved to be the arrangement of the σ -bonds connecting the radical lobes that constitutes the main influence on the magnitude of the splitting. The interaction responsible for the splitting could be partitioned into a direct (through-space; TSI) and an indirect (through-bond; TBI) contribution.¹³ The basis of both effects is to be found in two powerful conclusions from the application of perturbation theory: (i) upon interaction of two orbitals (wave functions), the *lower* level is *stabilized* while the *upper* level is *destabilized* (the orbitals repel each other) and (ii) the *lower* energy orbital is stabilized because the higher energy orbital is mixed into it by the perturbation (i.e. the interaction) in a *bonding* way, whereas the lower energy orbital is mixed into the *higher* energy orbital in an *antibonding* way, resulting in destabilization of the latter. To be more precise: when two wave functions ϕ_1 and ϕ_2 interact, two new wave functions ψ_1 and ψ_2 are formed. Perturbation theory predicts that, as long as the coupling is modest, ψ_1 may be considered to consist mainly of ϕ_1 with a bit of ϕ_2 mixed in, while ψ_2 is built up from ϕ_2 with a small amount of ϕ_1 included. For the energy levels, perturbation theory predicts that, as the interaction grows larger, the splitting increases. Whether the mixing produces a decrease or an increase in the energies of ψ_1 and ψ_2 , respectively, depends on the sign of the interaction (perturbation) term in the equations (and thus on the specifics of the interaction). This matter will be seen to return in the following sections.

An increase in the energy difference between the two interacting levels thus implies a weaker interaction. In figure 3.3, MO correlation diagrams representing the formation of a C–O and of a C–C σ -bond are given as an illustration of the principles discussed above.

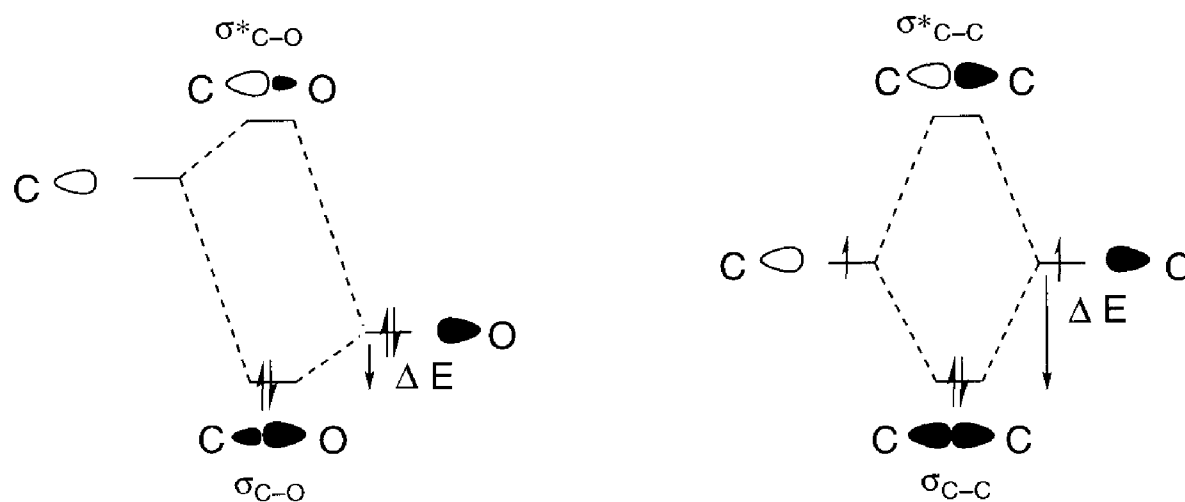


Figure 3.3

The through-space contribution to the splitting of A and S originates from a direct spatial overlap of n_1 and n_2 . In figure 3.4 it can be seen that n_1 and n_2 mix to form the two orbitals S ($= n_1 + n_2$) and A ($= n_1 - n_2$). As should be expected, the lower energy orbital S does not have a nodal plane, while the higher energy orbital A has one. The sign of the through-space interaction is such that, if TSI were the only interaction operative in the system, S would always have a lower energy than A.

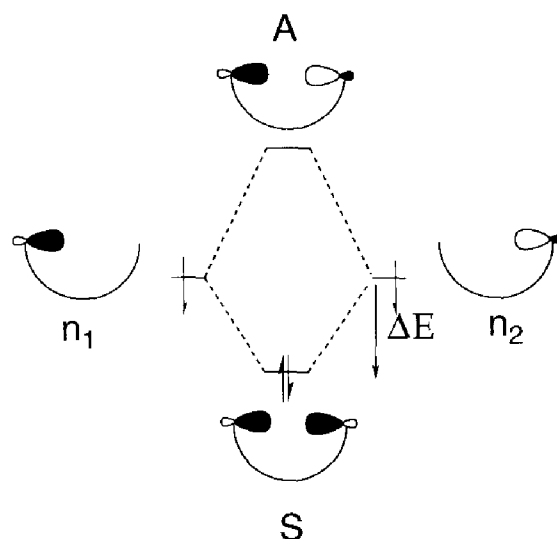


Figure 3.4

In practice, the energy order of S and A may found to be reversed. This is due to the second mode of interaction, TBI. Hoffmann described these through-bond interactions in a case where n_1 and n_2 are separated by a relay of three σ -bonds (Figure 3.5).

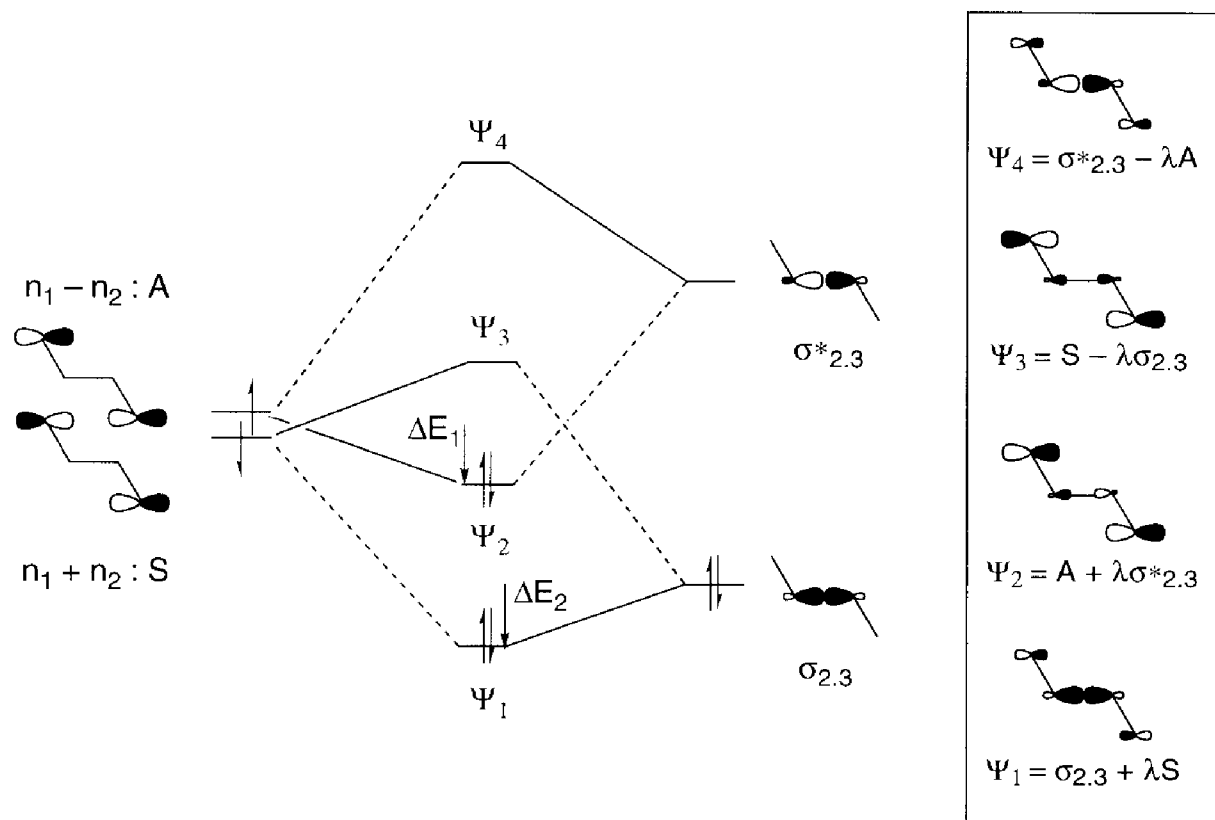


Figure 3.5

With respect to the twofold axis intersecting the central $\sigma_{2,3}$ -bond (C_2 symmetry), this bond and $S (= n_1 + n_2)$ are symmetric whereas the $\sigma_{2,3}^*$ -bond and $A (= n_1 - n_2)$ are antisymmetric. It should be noted that in the Hoffmann description the bonds $\sigma_{1,2}$ and $\sigma_{3,4}$ are not decomposed into their constituent orbitals because $\sigma_{1,2}$ and $\sigma_{3,4}$ always enter in the shape of symmetry-adapted pairs. In the ensuing symmetry-prescribed interaction of orbitals, the bonding (symmetrical) $\sigma_{2,3}$ combination lowers its energy by mixing in a bonding way with the symmetrical, higher energy orbital S to produce a new orbital Ψ_1 . At the same time though, this mixing leads to a higher energy of the symmetrical combination S since the latter mixes in an antibonding fashion with the symmetrical $\sigma_{2,3}$ combination to give Ψ_3 . In other words, here again we encounter the well-known conclusion that (the energy levels of) "orbitals of the same symmetry repel". Analogously, mixing of A and the anti-symmetrical $\sigma_{2,3}^*$ -bond (yielding the new orbitals Ψ_2 and Ψ_4) leads to a lowering of A and a raising of the energy of the

antibonding $\sigma^*_{2,3}$ combination. Thus it is seen that here the TSI and TBI interaction terms have different signs.

In the equations given in the right half of figure 3.5 the mixing in of e.g. S in $\sigma_{2,3}$ to produce Ψ_1 is indicated by the (small) multiplication factor λ (yielding, of course, an expression in which Ψ_1 formally is not normalized).

It might be argued that the $C_{1,2}$ and $C_{3,4}$ bonds should be included in this picture. One should realize, though, that due to the fact that S then must be mixed with both symmetrical combinations ($\sigma_{1,2} + \sigma_{3,4}$) and ($\sigma^*_{1,2} + \sigma^*_{3,4}$), the net effect is zero. The same goes for the result of combining A with ($\sigma_{1,2} - \sigma_{3,4}$) and ($\sigma^*_{1,2} - \sigma^*_{3,4}$), respectively.¹⁴ Consequently, as far as their influence on S and A is concerned, $C_{1,2}$ and $C_{3,4}$ can be left out of the picture.

Although the delocalized bond model of Hoffmann offered a very plausible explanation for the fact that, for an odd number of intervening σ -bonds, A (Ψ_2 in figure 3.4) was found to have an energy lower than S (Ψ_3), the experimentally observed¹⁵ level ordering of S below A for an even number of σ -bonds remained a puzzle. Fortunately, the correct level ordering, regardless of the number of intervening σ -bonds, can be obtained via the revised TBI model of Verhoeven et al.¹⁶ The essential difference between the TBI models of Verhoeven and Hoffmann, respectively, is the use of all σ -bonds connecting n_1 and n_2 (instead of the central C–C bond only) in describing the interaction by the former. Consequently, the Verhoeven model gives a description in terms of fully delocalized σ MO's. The symmetries and coefficients of these σ MO's can easily be obtained via the so-called "C-approximation" of Sandorfy and Daudel¹⁷ (a Hückel-MO scheme for σ -electrons) in which sp^3 hybrid orbitals are the basis atomic orbitals and MO's are formed by combining the former into linear combinations (Figure 3.6)¹⁸ (cf. the formation of orbitals by linear combination of $2p_z$ -AO's in the Hückel-MO method). Consequently, the symmetries, nodal properties, and relative level ordering of such σ -MO's are identical to those of π MO's resulting from a topologically equivalent array of $2p_z$ -AO's. It should be noted that, in applying the C-approximation, one has the choice of either including the C–H σ -bonds and C–C σ -bonds that are not immediately relevant to the matter at hand, or not. Usually, the choice is made for the latter in order to focus on the essentials of the problems, and because it simplifies the calculations by reducing the size of the Hückel matrix. Thus, viewed in this way, propane and hexatriene are identical systems (each built up from six localized AOs, combining into six delocalized MO's). The same applies to cyclopropane and benzene.

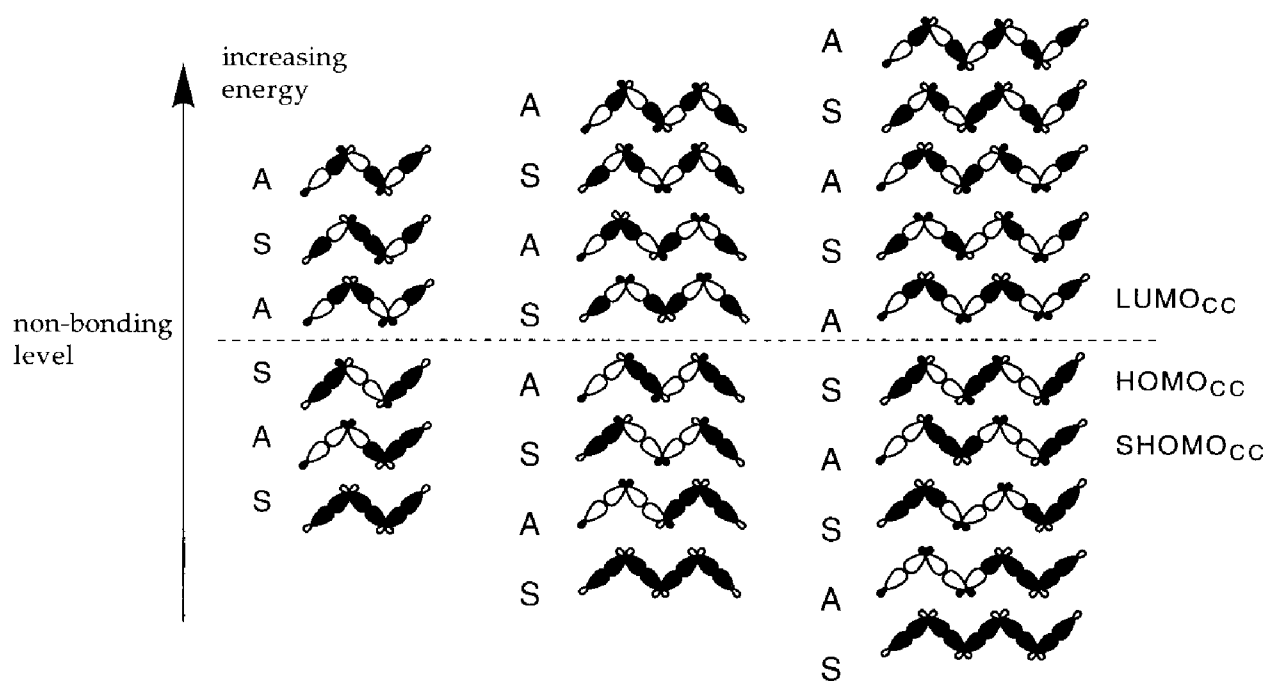


Figure 3.6

Although in principle every σ -MO of the C–C framework can interact with either S or A, the only important contributions stem from the interactions of the latter with the so-called frontier orbitals – the Highest Occupied Molecular Orbital (HOMO_{CC}), Lowest Unoccupied Molecular Orbital (LUMO_{CC}) and Second Highest Occupied Molecular Orbital (SHOMO_{CC}).^{19,20} The interaction of the other MO's with S or A is negligible due to the fact that the energy difference between these MO's and both A and S is large, the energy effects ensuing from their interaction are quite small (generally, when two one-electron systems interact, the splitting of their energy levels is maximal when the levels originally were degenerate).

From inspection of the frontier orbitals in figure 3.6 it can be seen that the symmetry of the HOMO_{CC} , LUMO_{CC} , and SHOMO_{CC} is determined by the number of intervening C–C bonds (N) of the σ -relay. When $N = \text{odd}$, the HOMO_{CC} is always symmetric; when $N = \text{even}$, it is antisymmetric. Of course, the reverse holds for the LUMO_{CC} and SHOMO_{CC} . Consequently, S and A will always be able to interact with the frontier orbitals of the σ -relay.

In two examples, one with $N = \text{even}$ and one with $N = \text{odd}$, it will be shown how the level ordering of A and S upon interaction with the HOMO_{CC} and LUMO_{CC} is obtained (for the sake of clarity, the interaction of S or A with the SHOMO_{CC} is omitted).

For odd N the symmetric HOMO_{CC} will mix with S (Figure 3.7). Since S has a higher energy than the HOMO_{CC} , it mixes with the HOMO_{CC} in an antibonding manner. As a consequence, the energy of S is raised, whereas the energy of the HOMO_{CC} is lowered (as it mixes with S in a bonding fashion). A similar interaction takes place between A and the antisymmetrical LUMO_{CC} , this time resulting in a lowering of A (and a raising of the LUMO_{CC}). Thus, the energy level of A ends up below that of S .

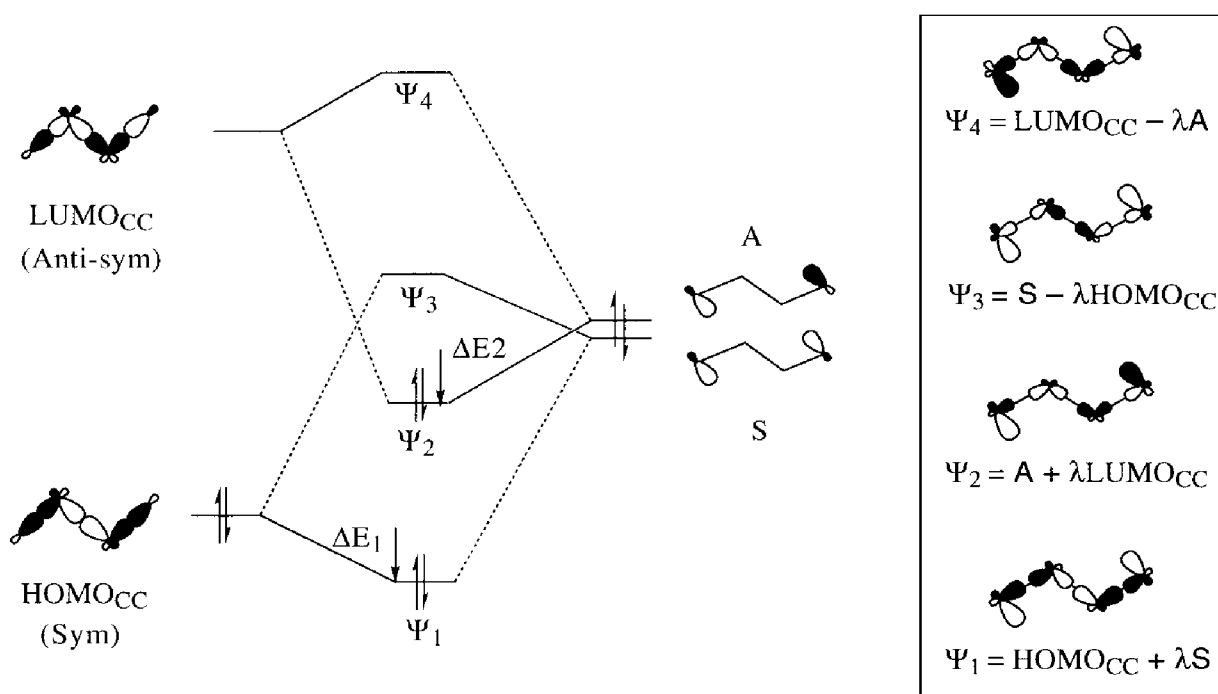


Figure 3.7

For even N , on the other hand, the symmetries of the HOMO_{CC} and LUMO_{CC} are reversed. Consequently, the HOMO_{CC} now interacts with A , while the LUMO_{CC} interacts with S (Figure 3.8). The same line of reasoning as given for $N = \text{odd}$ shows that now the energy of S is lowered while the energy of A is raised: in the end S is found to lie below A .

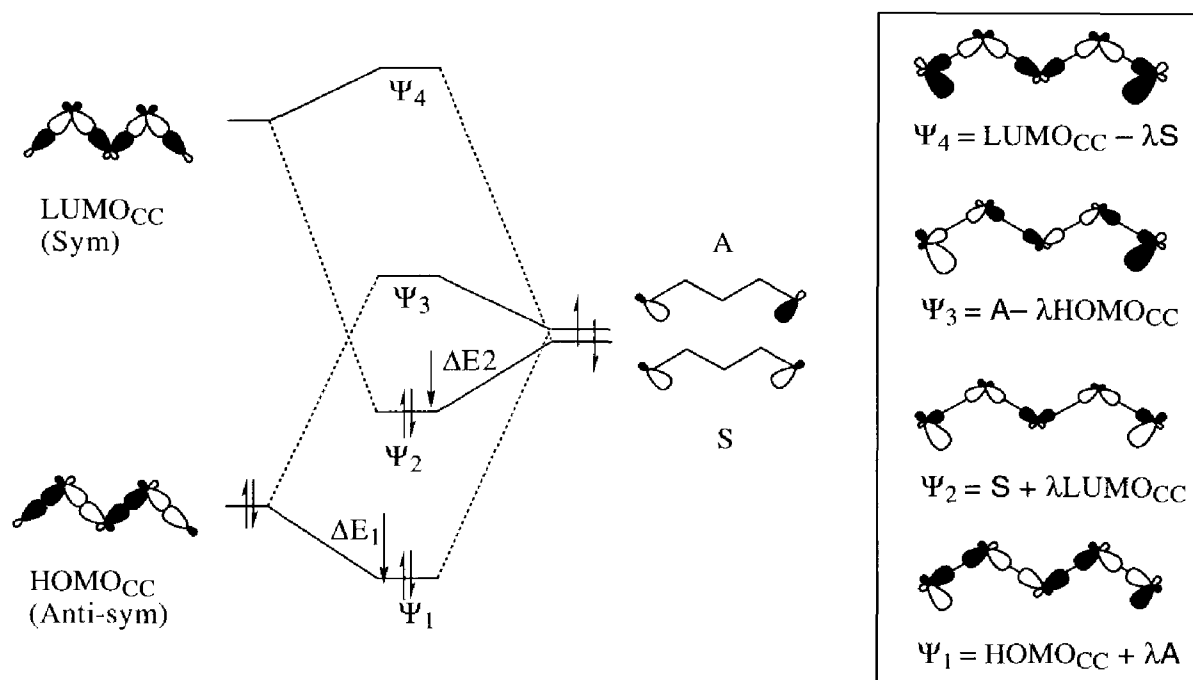


Figure 3.8

Calculation of the interaction energies of S and A with the frontier orbitals of the σ -relay always agrees with the level ordering observed experimentally. The level ordering of S below A for even values of N, and A below S for odd N has become known as the "*parity rule*".²¹ In fact, predicted level orderings not only can be observed spectroscopically,²² but prove to have chemical consequences as well. For example, it appears to be operative when a distinction must be made between a (Grob) fragmentation or a cyclization of acyclic γ -amino sulfonates. Also, the preferred odd instead of even membered transition state in radical cyclizations originates in the TBI-imposed level ordering of S below A.²³

3.3 TBI in the Heterolysis of 1,4-diol Monosulfonate esters

Up to this point, only completely symmetrical σ -relays and symmetrical combinations of n_1 and n_2 were dealt with. The presence of TBI, though, is not restricted to molecules possessing formal symmetry, but can also be applied to molecules in which a symmetry element is only approximate.^{24,25} For example, when the σ -relay is changed from the W arrangement to the sickle-arrangement,

formally the σ -relay is no longer symmetrical. However, to a good approximation the system retains its symmetry properties (so one might speak of pseudo-symmetry). To be specific: qualitatively the behaviour of the *nodes* in the respective wave functions (MO's) does not change, as a consequence of which the concept of orbital symmetry retains its usefulness. This allows us to keep on classifying the σ MO's of the C-C framework as symmetric or antisymmetric. The only essential differences between a system with or without formal symmetry are (a) a less straight forward classification (in group-theoretical terms) of the symmetry properties of the MO's, and (b) the change in overlap of the orbitals.

In describing the base-induced heterolysis of 1,4-diol monosulfonate esters in terms of molecular orbital interactions, a comparison with the MO-description of the Grob fragmentation² suggests itself. Of course, there is no formal symmetry element correlating the nitrogen lone pair and the C-OTs σ^* -orbital in γ -amino tosylates. Consequently, instead of the "pure" configurations A_2 or S_2 , the true wave function will be a mixture of the two configurations $c_1A_2 + c_2S_2$ ($c_1 \neq c_2$, $c_1^2 + c_2^2 = 1$); as a result of this unequal configurational mixing in the ground state the levels of the pseudo-symmetrical set "S" and of the pseudo-antisymmetrical set "A" will be split. Furthermore, "S" (or "A", depending on the specifics of the connecting σ relay) will predominantly display the characteristics of the C-OTs σ^* -orbital whereas "A" (or "S") will predominantly represent the nitrogen lone pair. Ultimately, this ground-state configurational mixing leads to a more pronounced bond alternation and to a pronounced specificity of concerted reactions.²⁶ In strict analogy with this MO description of the Grob fragmentation, in the base induced heterolysis of 1,4-diol monosulfonates the "A" and "S" combinations can be obtained by an (unequal) configurational mixing of the C-OTs σ^* -orbital and an oxygen lone pair.

3.3.1 *The Stabilization of, an (Incipient) Carbocation by Interaction with a Remote Alkoxide Group*

As stated in the introduction, an alkoxide is able to stabilize an (incipient) carbocation within the same molecule by an indirect transfer of electron density to this carbocationic center. TBI between an oxygen lone pair and the C-OTs σ^* -orbital, as depicted in figure 3.9, can be used to explain and visualize this indirect transfer of charge density.

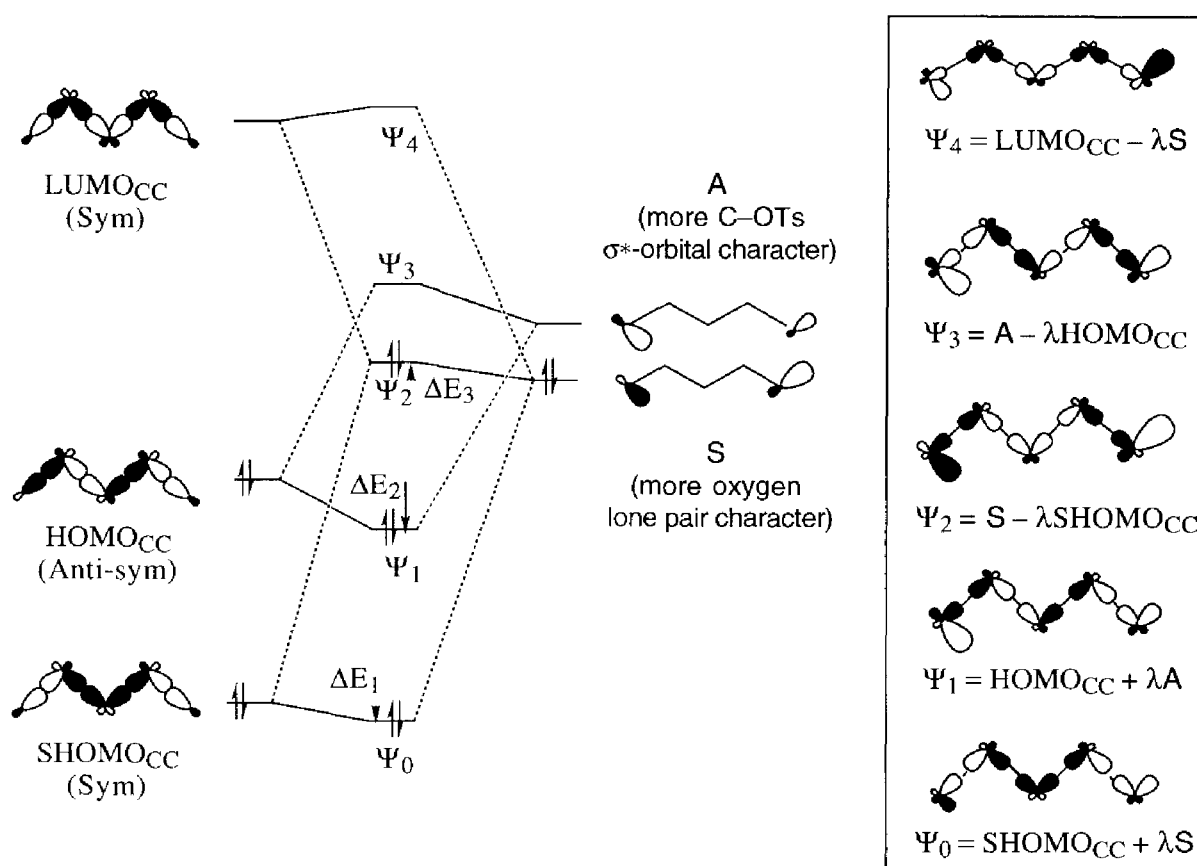


Figure 3.9

The oxygen lone pair and the C-OTs σ^* -orbital mix to a (pseudo-)symmetric and a (pseudo-)antisymmetric combination. No formal symmetry element being present, unequal ground-state configurational mixing will take place between these orbitals. Consequently, the lower-lying (and thus filled) symmetrical set will predominantly have an oxygen lone pair character. The unoccupied antisymmetrical set will merely have the character of the C-OTs σ^* -orbital. The (pseudo-)symmetrical set (S) still has the right symmetry (i.e. nodal-plane behavior) to interact with the symmetrical SHOMO_{CC} and the symmetrical LUMO_{CC} . The interaction of the SHOMO_{CC} with S is bonding and therefore the SHOMO_{CC} is lowered in energy by an amount E_3 , while the energy of S is raised by a slightly larger amount. Although the specific energy of S also depends on its stabilization by mixing with the LUMO_{CC} , both E_3 and E_1 will be small as the energy gap between S and both the SHOMO_{CC} and the LUMO_{CC} is relatively large.²⁷ On the other hand, the energy difference between the empty (pseudo-)

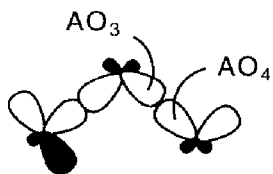
antisymmetrical set (A) – composed of the oxygen lone pair and the C–OTs σ^* -orbital – and the symmetrical HOMO_{CC} is relatively small, consequently giving rise to an extensive interaction between these orbitals. This interaction significantly lowers the energy of the HOMO_{CC} (transforming it into Ψ_1) and raises the energy of A (giving Ψ_3). As the HOMO_{CC} is doubly occupied and A is empty, this interaction will result in an energy gain of $2E_2$. – Incidentally, this is the reason why TBI are much more important in two-electron than in one-electron cases. – Starting from the fair assumption that E_3 and E_1 cancel, the orbital interactions described here will result in a net lowering of the energy of the deprotonated 1,4-diol monosulfonates with approximately $2E_2$.²⁸

Within this MO representation, electron transfer to the (incipient) carbocation center is achieved in the following way. Before mixing takes place, the HOMO_{CC} is occupied by two electrons. After interaction, this orbital still contains two electrons, but now the characteristics of this orbital have changed in such a way as to make it considerably more delocalized, and impart it with a finite electron density at the carbon atom containing the sulfonate ester.

3.3.2 The Influence of the Geometry of the σ -Relay on the Stabilization of 1,4-Dipolar Intermediates

In discussing the influence of the geometry of the σ -relay, TBI over four σ -bonds will be used as an example. Here, it can be shown that the largest amount of stabilization of 1,4-dipolar intermediates is due to the mixing of the HOMO_{CC} with A, giving a wave function $\text{HOMO}_{\text{CC}} + \lambda A$ (Ψ_1) (figure 3.8). However, changes in the geometry of the σ -relay have a drastic influence on this stabilization. To clarify this point, the effect of W- vs sickle- vs U-shape on the stabilization of 1,4-dipolar intermediates will be discussed *via* its specific influence on the $\text{HOMO}_{\text{CC}} + \lambda A$ orbital.²⁹

In the W-shaped arrangement of the σ -relay, the relatively low energy of the mixed orbital $\text{HOMO}_{\text{CC}} + \lambda A$ (or Ψ_1) results from a strong interaction of the C–OTs σ^* -orbital with AO_3 (a). A strong interaction can safely be inferred on the basis of the relatively large coefficient of the C–OTs σ^* -orbital (or incipient carbocation) in the MO, and on its stereochemical relationship with AO_3 . In addition to this interaction, for similar reasons there will be a significant homoallylic bonding overlap (b) between the C–OTs σ^* -orbital and AO_5 as well (figure 3.10).³⁰



On the other hand, in a gauche orientation between the C–OTs bond and the vicinal C–C bond (as present in a sickle-arrangement of the σ -relay) there is relatively little stabilization of the HOMO_{CC} . This can be traced back to the stereochemical relationship between the σ^* -orbital of the C–OTs bond, AO_3 , and AO_5 that produces a poor bonding allylic and homoallylic overlap of the C–OTs σ^* -orbital with AO_3 (**d**) and AO_5 (**e**). However, it should be noted that in the sickle-shape geometry the allylic stabilization (**e**) becomes more important when the σ^* -orbital of the C–OTs bond is converted to a carbocationic center in the course of the heterolysis. In other words, as the reaction proceeds, the TBI-induced stabilization becomes significantly larger. Provided the sulfonate anion is at a far enough distance, the stabilization of the "final product" (the free carbocation) is exactly the same for the sulfonate ester with a sickle-shape or W-shape geometry of the σ -relay.³¹

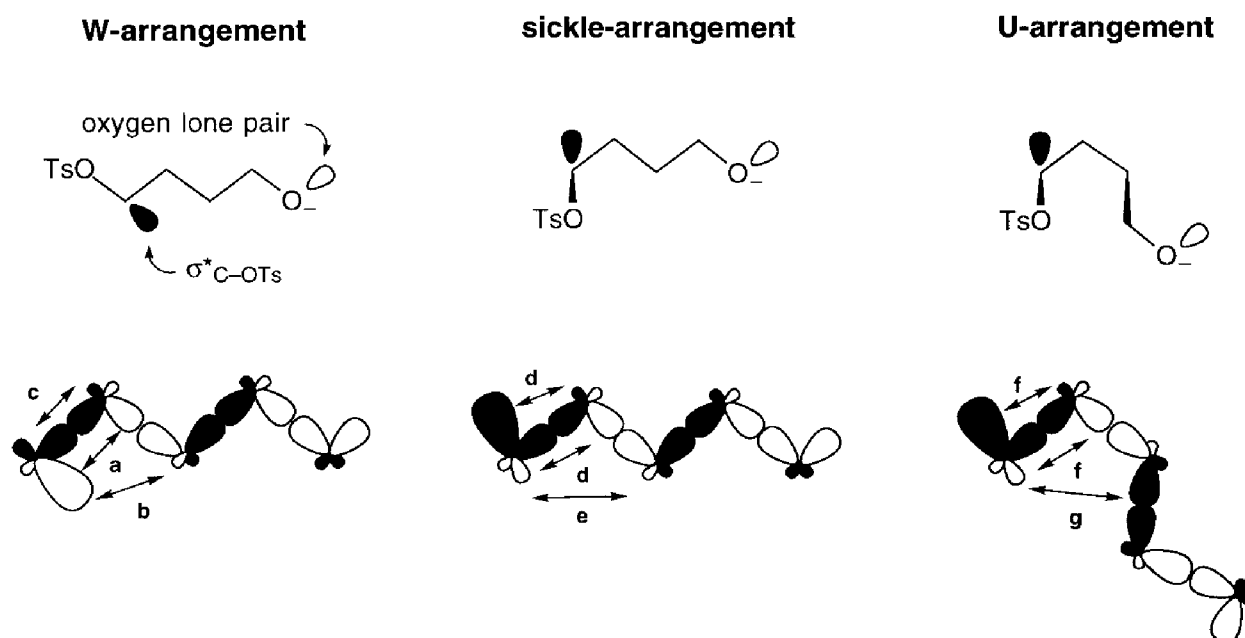


Figure 3.10

Finally, in the U-arrangement the energy of $\text{HOMO}_{\text{CC}} + \lambda A$ is higher than it is in the corresponding sulfonate ester with a sickle-like arrangement of the σ -relay. This additional destabilization in the U-arrangement originates in the conversion of a bonding homoallylic interaction into an antibonding one (**e** vs **g**, respectively). As, in such a sulfonate ester, the heterolysis proceeds, TBI stabilization can increase, but the same amount of stabilization as found in W- or sickle-shaped sulfonate esters will never be reached.

3.4 Concluding Remarks

As stated in the introduction of this chapter, the reaction behavior of base-treated rigid 1,4-diol monosulfonate esters can be explained most satisfactorily by the involvement of TBI. The interaction between the alkoxide group and sulfonate ester *via* the intervening σ -bonds offers a solid explanation for the favored all-trans arrangement of the σ -relay, the relatively facile formation of a 1,4-dipolar intermediate, and the through-bond transfer of electron density from the alkoxide to the (incipient) carbocation positioned four σ -bonds away.

3.5 References and Notes

- 1 (a) Jenniskens, L. H. D.; Wijnberg, J. B. P. A.; de Groot, A. *J. Org. Chem.* **1991**, *56*, 6585. (b) Wijnberg, J. B. P. A.; Jenniskens, L. H. D.; Brunekreef, G. A.; de Groot, A. *J. Org. Chem.* **1990**, *55*, 941. (c) Orrū, R. V. A.; Wijnberg, J. B. P. A.; Jenniskens, L. H. D.; de Groot, A. *J. Org. Chem.* **1993**, *58*, 1199. (d) Orrū, R. V. A.; Wijnberg, J. B. P. A.; Bouwman, C. T.; de Groot, A. *J. Org. Chem.* **1994**, *59*, 374. (e) Orrū, R. V. A.; Wijnberg, J. B. P. A.; de Groot, A. *J. Org. Chem.* **1995**, *60*, 4233.
- 2 Bastiaansen, P. M. F. M.; Wijnberg, J. B. P. A.; de Groot, A. *J. Org. Chem.* **1995**, *60*, 4240.
- 3 (a) Bartsch, R. A. *Acc. Chem. Res.* **1975**, *8*, 239. (b) Seen, R. A. *Acc. Chem. Res.* **1973**, *6*, 46.
- 4 Reynolds, W. F. *J. Chem. Soc., Perkin Trans. 2* **1980**, 985.
- 5 Topsom, R. D. *Prog. Phys. Org. Chem.* **1976**, *12*, 1.
- 6 Davidson, R. B.; Williams, C. R. *J. Am. Chem. Soc.* **1978**, *100*, 2017.
- 7 Topsom, R. D. *J. Am. Chem. Soc.* **1981**, *103*, 39.
- 8 Adcock, W.; Abeywickrema, A. N. *J. Org. Chem.* **1982**, *47*, 2957.
- 9 Recently, ^{19}F -NMR spectroscopic results were presented indicating that a four-bond pathway (of which six were available) represents the longest distance over which the σ -inductive effect has been observed to operate; Della, E. W.; Head, N. J. *J. Org. Chem.* **1995**, *60*, 5303.
- 10 (a) Hoffmann, R.; Imamura, A.; Hehre, W. J. *J. Am. Chem. Soc.* **1968**, *90*, 1499. (b) Hoffmann, R. *Acc. Chem. Res.* **1971**, *4*, 1.
- 11 The basics of perturbation theory can be found in any quantum mechanics (introductory) textbook.
- 12 Hoffmann, R. *J. Chem. Phys.* **1963**, *39*, 1397.
- 13 Although generally TSI and TBI are described as separate mechanisms, there is no distinction in the physical mechanism operative in these two cases.
- 14 Hoffmann pointed out that the analysis (given in this paper) of orbital interactions via three σ bonds (viz. by focusing on the central $\text{C}_{2,3}$ σ -bond) was not intended to imply that, for a system consisting of a large odd number of intervening σ -bonds between two interacting orbitals, it is the central σ -bond that causes the splitting of S and A.

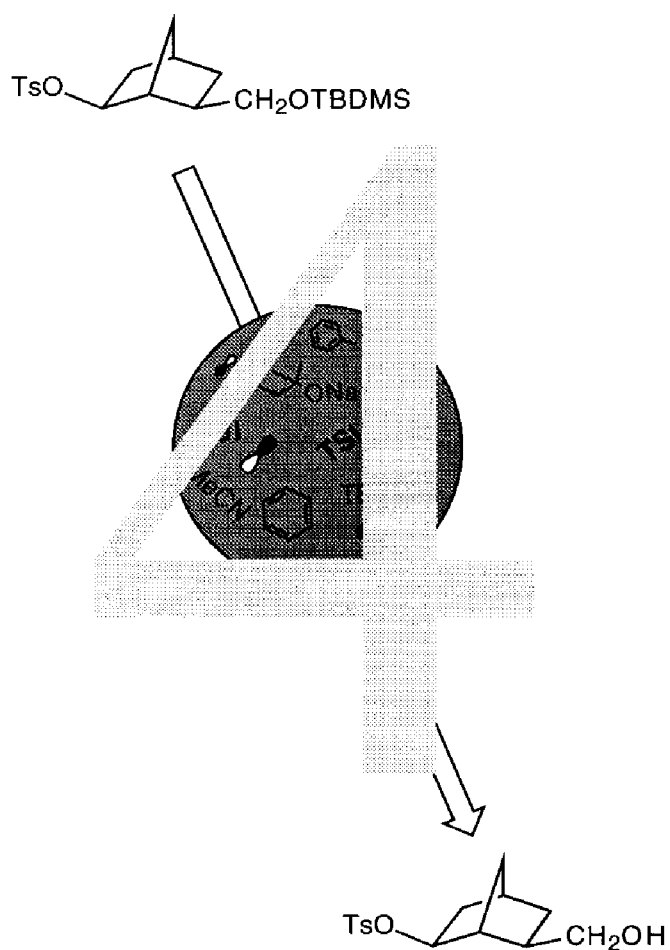
- 15 See: Paddon-Row, M. N.; Jordan, K. D. In *Modern Models of Bonding and Delocalization*; J. F. Liebman and A. Greenberg, Ed.; VCH publishers: New York, **1988**: chapter 3 and references cited therein.
- 16 (a) Verhoeven, J. W. *Recl. Trav. Chim. Pays-Bas* **1980**, 99, 143 (b) Verhoeven, J. W.; Pasman, P. *tetrahedron* **1981**, 37, 943.
- 17 (a) Sandorfy, C.; Daudel, R. *Compt. Rend.* **1954**, 238, 93. (b) Sandorfy, C. *Can. J. Chem.* **1955**, 33, 1337. (c) Herndon, W. C. *Prog. Phys. Org. Chem.* **1972**, 9, 99. (d) Dewar, M. J. S. *Bull. Soc. Chim. Belg.* **1979**, 88, 957.
- 18 No allowance is made for the different coefficients of the AO's.
- 19 The involvement of the LUMO_{CC} in these TBI effects has been questioned.^{19a} The large contribution of fragmentation reactions,^{19b} as well as TBI effects exerted in the conformational equilibrium and geometrical distortions of 1-phenylpiperidone derivatives^{19c} are all in favor of the incorporation of the LUMO_{CC} in TBI. Obviously, the extent of these interactions depends on the energy levels of the orbitals. Consequently, different results may be obtained for the sp³ orbitals of dianions or p orbitals in carbon diradicals or carbocations. (a) Brunck, T. K.; Weinhold, F. *J. Am. Chem. Soc.* **1976**, 98, 4392. (b) Ho, T.-L. In *Heterolytic Fragmentation of Organic Molecules*; Wiley-Interscience New York, **1993**. (c) Krijnen, B.; Beverloo, H. B.; Verhoeven, J. W.; Reiss, C. A.; Goubitz, K.; Heijdenrijk, D. *J. Am. Chem. Soc.* **1989**, 111, 4433.
- 20 Interactions with the SHOMO_{CC} (and HOMO_{CC}) are more important than interactions with the SLUMO_{CC} (and LUMO_{CC}), even though the magnitudes of the energy differences with S or A are comparable, since AO₃ and AO₄ are of the same phase in the SHOMO_{CC} (and HOMO_{CC}) but are of opposite phase in the SLUMO_{CC} (and LUMO_{CC}). Consequently, the net overlap of A or S with the SHOMO_{CC} (and HOMO_{CC}) is larger than the net overlap with the SLUMO_{CC} (and LUMO_{CC}).
- 21 Paddon-Row, M. N. *Acc. Chem. Res.* **1982**, 15, 245.
- 22 (a) Heilbronner, E.; Maier, J. P. *J. Am. Chem. Soc.* **1970**, 92, 3818. (b) Heilbronner, E.; Maier, J. P. *Helv. Chim. Acta* **1974**, 57, 151.
- 23 For other examples of the chemical consequences of the relative sign of TBI and TSI see reference 16b.
- 24 See: Woodward, R. B.; Hoffmann, R. In *The Conservation of Orbital Symmetry*; Verlag Chemie, Academic Press: Weinheim, **1970**.
- 25 Gleiter, R.; Stohrer, W.; Hoffmann, R. *Helv. Chim. Acta* **1972**, 55, 893.
- 26 (a) Salem, L. *Chem Comm.* **1970**, 981. (b) Hayes, E. F.; Siu, A. K. *Q. J. Am. Chem. Soc.* **1971**, 93, 2090. (c) Siu, A. K. Q.; St. John, W. M.; Hayes, E. F. *J. Am. Chem. Soc.* **1970**, 92, 7249.
- 27 Whether S is stabilized or destabilized depends on the absolute size of its interaction with the SHOMO_{CC} and LUMO_{CC}. Apart from the energy difference between S and the SHOMO_{CC}, this interaction will be small too since AO₃ of the SHOMO_{CC} is small. The interaction of the oxygen lone pair and the C-OTs σ*-orbital with the σ-relay occurs principally via the allylic CC bond and then largely through the overlap with AO₃: see Paddon-Row, M. N.; Patney, H. K.; Brown, R. S.; Houk, K. N. *J. Am. Chem. Soc.* **1981**, 103, 5577.
- 28 Without deprotonation of the hydroxyl group the energies of S and the HOMO_{CC} (fig. 3.9) will be considerably lower thereby reducing the degree of interaction of S with the LUMO_{CC} and that of A with the HOMO_{CC}. As a result, E₃ will not completely cancel

E_1 and the stabilization of the HOMO_{CC} will be less since its separation with A is enhanced.

- 29 Incorporation of the interaction of S with the SHOMO_{CC} and LUMO_{CC} will only increase the differences between the geometries of the σ -relay.
- 30 The vicinal interaction c (fig. 3.10) will be very small due to poor orbital overlap.
- 31 The orbital overlap of the C-OTs σ^* -orbital and AO_5 that, for stereochemical reasons, is unfavorable will become more favorable if the C-OTs σ^* -orbital is converted into a p-type orbital.

Chapter 4

Effects of Through-Bond Interactions on the Desilylation Rate of Silyl Ethers



Abstract. The kinetics of the desilylation reactions of a range of sulfonated and methoxylated norbornyl silyl ethers **1–10** were investigated to establish the quantitative correlation between the geometry of the σ -relay and the rate of desilylation. These desilylation rates generally decrease in the order W > sickle-like > U arrangement of the σ -relay. The methoxylated silyl ethers show a decreased reactivity in comparison with the corresponding sulfonated silyl ethers. The orientation of the silyloxy group does not affect the reaction rate. Conformational mobility of the σ -relay also is of influence on the rate of desilylation.

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4.1 Introduction.

In previous publications and in Chapter 2 the attention was primarily focused on the reaction behavior of 1,4-diol monotosylates under strongly basic conditions in apolar non-nucleophilic solvents.¹ Long-range orbital interactions through the four σ -bonds between the alcoholate anion (electron donor) and the sulfonate ester group (electron acceptor) are considered to be responsible for the heterolysis of the sulfonate ester bond. As discussed in detail in Chapter 3, the extent of these through-bond interactions (TBI)² depends on the geometry of the σ -relay. A W arrangement of the σ -relay is the most favorable geometry for transmission of TBI (trans rule)³ and can result, as a chemical consequence, in a selective homofragmentation.^{1e} The introduction of a gauche interaction in the σ -relay leads to a sickle-like arrangement and makes transmission of TBI more difficult, thereby reducing the reactivity of the compound involved. Compounds in which two gauche interactions are present (U arrangement) do not react via TBI-induced heterolysis of the sulfonate ester bond. Although a rough estimate of the relative reaction rates could be obtained from comparison of the quantities of recovered starting material after a limited reaction time, accurate kinetic measurements on these compounds are problematic.⁴

As described in Chapter 2, it was noticed that the silyl ether bond of tosylate **1** is remarkably unstable. It was assumed that the remote tosylate group facilitates the cleavage of the Si–O bond, probably by a similar TBI-controlled mechanism that induces heterolysis of the sulfonate ester bond. If this assumption is correct, the stability of the Si–O bond should also depend on the geometry of the σ -relay. Therefore, in order to provide more detailed insight into this interaction, the kinetics of desilylation reactions of a number of norbornyl silyl ethers at appropriate temperatures are studied and the results are described in this chapter.

The sulfonated norbornyl silyl ethers **1–3** (Chart 4.1) were investigated to establish the quantitative correlation between the geometry of the σ -relay and the rate of desilylation.

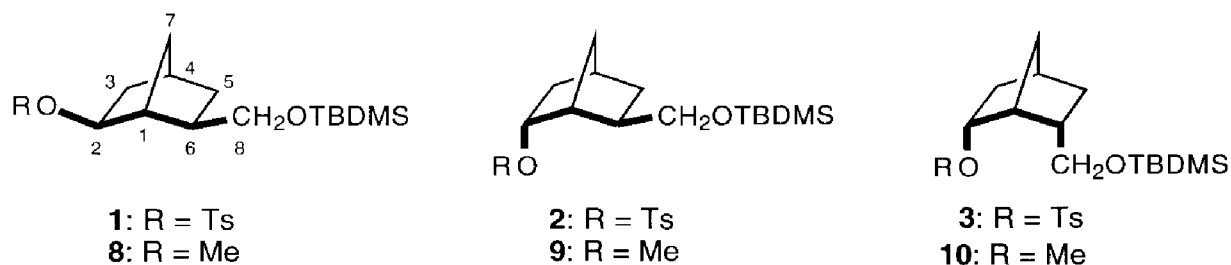


Chart 4.1

As indicated in Chart 4.1 by the bold bonds, the silyl ethers **1**, **2**, and **3** have the W, sickle-like, and U arrangement of the σ -relay, respectively.

The silyl ethers **4** and **5** were studied to find out whether the orientation of the silyl ether function has any influence on the rate of desilylation. Information about the effect of a primary vs secondary sulfonate ester group on the desilylation rate was obtained from the silyl ethers **5–7** (Chart 4.2). If the rate of desilylation is indeed affected by a remote sulfonate ester group, then this rate will change when the sulfonate ester group is replaced by a less strongly electron-withdrawing group, e.g., a methoxy group. In order to confirm this hypothesis, the silyl ethers **8–10** were investigated.

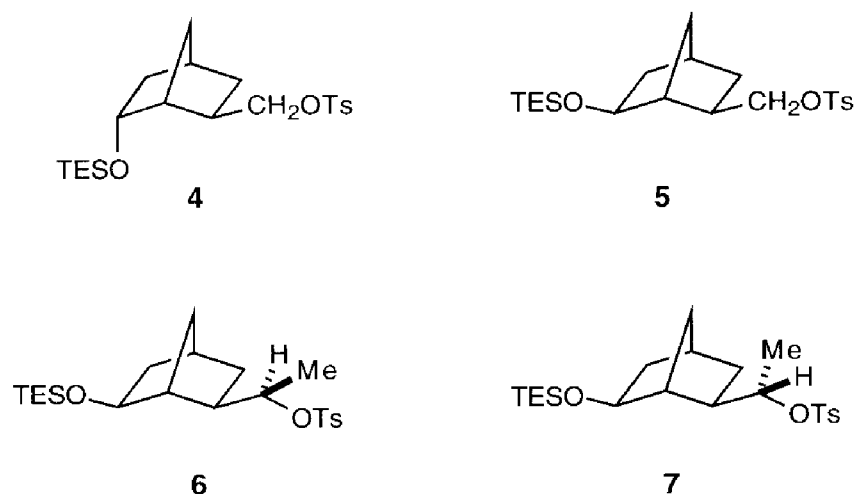


Chart 4.2

4.2 Results and Discussion.

The tosylated silyl ether **1** was obtained upon treatment of the corresponding alcohol^{1e} with TBDMSCl in CHCl_3 and could only be isolated in pure form after reversed-phase chromatography. The tosylated silyl ethers **2–7** were prepared according to standard procedures (see Experimental Section). The known carboxylic acid **11**⁵ was used as starting material for the synthesis of the silylated methyl ether **8** (Scheme 4.1). For the preparation of **9** and **10**, the corresponding monosilylated 1,4-diols^{1e} were treated with *t*-BuOK and MeI in THF at 0 °C.⁶



Scheme 4.1

The desilylation reactions were performed under standardized conditions using dry acetonitrile as the solvent and commercial tetrabutylammonium fluoride (TBAF) as desilylating reagent.⁷ The reactions were studied under pseudo-first-order conditions and resulted in the generation of the corresponding alcohols.⁸ The extent of reaction was followed by HPLC, monitoring the change in concentration of the silyl ether with time.⁹ In this way, linear plots were obtained from which the pseudo-first-order rate constants (k_{obs}) could easily be determined. For practical reasons,¹⁰ the use of TBDMS ethers derived from primary alcohols was preferred. In case of secondary and tertiary alcohols the corresponding triethylsilyl (TES)¹¹ and TMS ethers, respectively, were employed. The kinetic data obtained from these experiments are collected in Tables 1 and 2.

The tosylated silyl ethers **1**, **2**, and **3** show distinct differences in their rate of desilylation (Table 1, entries 1–3). A decrease in k_{obs} is noticed in the order **1** > **2** > **3** which corresponds with a reactivity order W > sickle-like > U arrangement of the σ -relay, respectively.

Table 1. Pseudo-First-Order Rate Constants (k_{obs}) for Desilylation of TBDMS Ethers with TBAF in MeCN at 25 °C^a

entry	substrate	$k_{\text{obs}} \times 10^{-3} \text{ min}^{-1}$	r^b
1	1	15.4	0.999
2	2	4.3	0.996
3	3	1.3	0.996
4	8	5.6	0.999
5	9	2.3	0.995
6	10	0.4	0.993

^a The pseudo-first-order rate constants (k_{obs}) were determined in triplicate with an excess of TBAF (10 equiv) and were reproducible to within $\pm 5\%$. Temperature control was within ± 0.1 °C. ^b Correlation coefficient at worst.

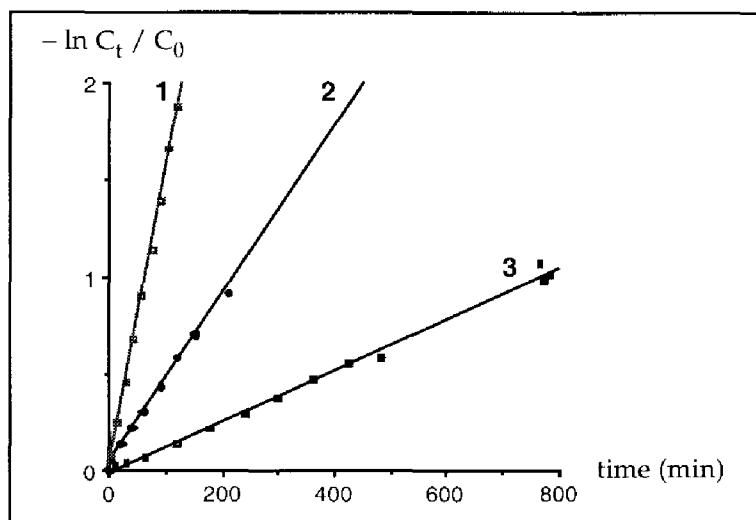


Figure 4.1 Plots of $-\ln C_t/C_0$ against time for the desilylation of the silyl ethers 1–3 with TBAF in acetonitrile at 25 °C.

A similar tendency is observed for the methylated silyl ethers 8, 9, and 10, on the understanding that each Me compound reacts more slowly than its tosyl analog upon treatment with TBAF (Table 1, entries 4–6).

One could argue that a relief in *endo*-crowding¹² might affect the desilylation rate of compounds in which an U arrangement of the σ -relay is present (3 and 10). However, this argument is not valid for explaining the differences in reaction rate between 1 and 8 and between 2 and 9, because in each pair the TBDMS group is free of steric hindrance. It is assumed that the differences in reaction rate are directly related to the differences in the leaving-group ability of the alcohol function.¹³ If the breaking of the Si–O bond occurs by a one-step concerted reaction (S_N2 –Si mechanism),¹⁴ partial negative charge will be built up on oxygen in the transition state (Chart 4.3). Stabilization of this partial negative charge by the remote sulfonate ester group via an electronic coupling through the intervening C–C bonds will lower the energy of the transition state, and consequently, the rate of desilylation will increase. As the k_{obs} values in Table 1 clearly show, the sulfonate ester group is, in this respect, more effective than the less strongly electron-withdrawing methoxy group.

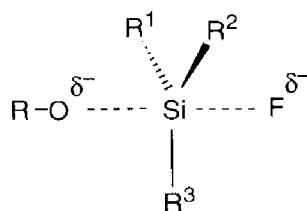


Chart 4.3

The relatively fast desilylation rate of the compounds **1** and **8** in the tosyl and Me series, respectively, is consistent with the trans rule (Table 1, entries 1 and 4). According to this rule, the W arrangement of the σ -relay in **1** and **8** ensures a proper alignment of the orbitals involved through which transmission of TBI is more efficient and, as a result, a relatively fast reaction can occur. In the corresponding reactions of compounds in which one (**2** and **9**) or two (**3** and **10**) gauche interactions are present, transmission of TBI will be more difficult, thereby reducing the reactivity of these compounds.

Table 2. Pseudo-First-Order Rate Constants (k_{obs}) for Desilylation of TES Ethers with TBAF in Acetonitrile at 0 °C^a

entry	substrate	$k_{\text{obs}} \times 10^{-2} \text{ min}^{-1}$	r^b
1	4	5.1	0.991
2	5	4.6	0.991
3	6	4.8	0.983
4	7	1.9	0.997

^a The pseudo-first-order rate constants (k_{obs}) were determined in triplicate with an excess of TBAF (10 equiv) and were reproducible to within ± 5 %. Temperature control was within ± 0.1 °C. ^b Correlation coefficient at worst.

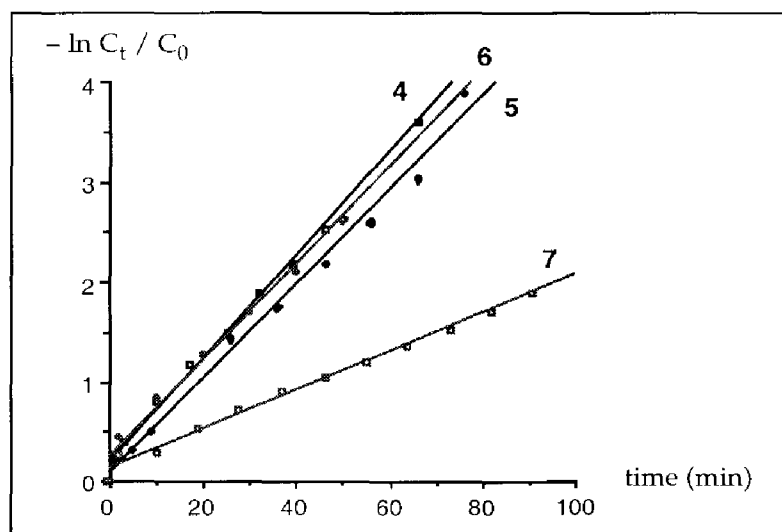


Figure 4.2 Plots of $-\ln C_t/C_0$ against time for the desilylation of the silyl ethers **4–7** with TBAF in acetonitrile at 0 °C.

The reactions of the TES ethers **4** and **5** show no significant difference in the rate of desilylation (Table 2, entries 1 and 2). Apparently, the orientation of the silyl ether group has little influence on the transmission of TBI. This phenomenon has also been observed in the base-induced heterolysis of 1,4-diol monosulfonate esters.^{1c}

By the interpretation of the k_{obs} values determined for the reactions of **5–7** (Table 2, entries 2–4), one has to keep in mind that these compounds will adopt the minimum-energy geometry that is available by rotation about the C(6)–C(8) bond.¹⁵ From the Newman projections of the three staggered ground state conformations of **5–7** around the C(6)–C(8) bond, it is clear that the lowest-energy conformations will be **5A** or **5B**, **6A**, and **7B**, respectively (Chart 4.4).

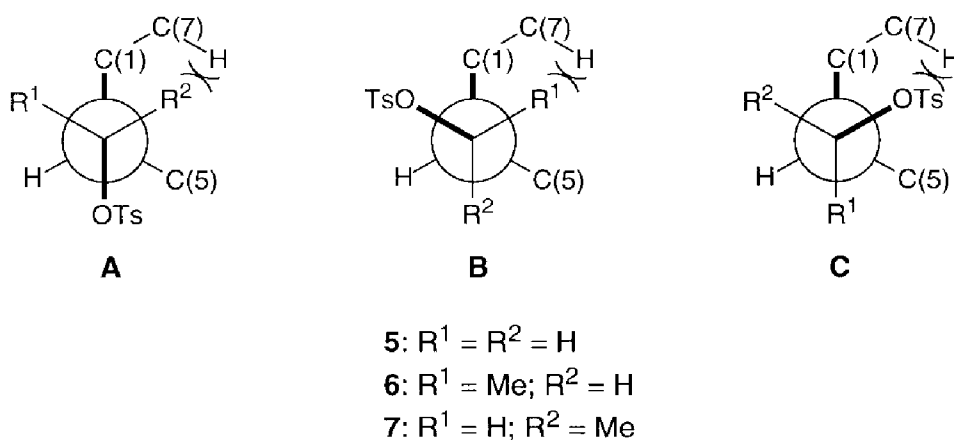


Chart 4.4

In these conformations only a small steric repulsion between syn H-7 and H-8 will exist. The other staggered conformations are assumed to be higher in energy because of more steric repulsion between syn H-7 and, in these cases, the larger C(8) substituents (Me in **6B** and **7A**; tosylate in **5C**, **6C**, and **7C**). The Newman projections of the lowest-energy conformations of **5–7** also point to differences in the σ -relay of these conformations. The anti relationship between the C(1)–C(6) bond and the C(8)–OTos bond in **5A** and **6A** corresponds with a W arrangement of the σ -relay, while in **5B** and **7B** the gauche relationship between these two bonds represents a sickle-like arrangement. In line with this reasoning and with the knowledge that conformations in which a W arrangement of the σ -relay is present are more reactive than those with a sickle-like arrangement,^{1e} the differences in k_{obs} found for the reactions of **5–7** can be better understood. With the use of the Winstein–Holness (W–H) principle,¹⁶ it follows that **6** will react more rapidly than

7 (Table 2, entries 3 and 4) and that the reaction rate of 5 and 6 will be broadly the same (Table 2, entries 2 and 3), assuming that the contribution of conformation **5B** to the overall rate constant of 5 is only modest.¹⁷ The approximately equal k_{obs} values determined for 5 and 6 also suggest that the nature of the sulfonate ester group (primary or secondary) has little influence on the desilylation rate. In this respect, it should be mentioned that in the base-induced reactions of the corresponding 1,4-diol monosulfonate esters large differences in reactivity between primary and secondary compounds are observed.^{1e}

4.3 Concluding Remarks

These kinetic experiments clearly show that the rate of desilylation of the compounds studied is directly related to the geometry of the σ -relay and generally decreases in the order $W > \text{sickle-like} > U$ arrangement. These findings confirm, once again, the validity of the trans rule in TBI-controlled processes. Replacing of the sulfonate ester group by the less electron-accepting methoxy group leads to a decrease of reactivity.¹⁸ The orientation of the silyloxy group does not affect the rate of desilylation. The differences in k_{obs} found for the conformationally mobile silyl ethers are easily understood with the W-H principle.

Similar effects on the reactivity have been found for 1,4-diol monosulfonate esters in the base-induced heterolysis reactions (see Chapter 2).^{1d,e} From this similarity, one may conclude that in the desilylation reaction as well as in the heterolysis reaction the same through-bond orbital interactions are involved.

In conclusion, it appears that long-range through-bond orbital interactions do affect the rate of desilylation in a predictable manner and that the desilylation reaction offers a simple method for exploring the extent of such interactions. The results of this study may also be helpful for explaining unexpected features of polyfunctional systems, as for example the remarkable instability of the Si-O bond of compound **1**.

4.4 Experimental Section

General.¹⁹

The monotosylated 1,4-diols used in the synthesis of **1** and **4-7** and the monosilylated 1,4-diols used in the synthesis of **9** and **10** were prepared following previously described

procedures.^{1e} Compounds **2** and **3** have been synthesized and fully characterized before (see Chapter 2). The carboxylic acid **11** was prepared as described previously.⁵

exo,exo-6-[[[(1,1-Dimethylethyl)dimethylsilyl]oxy]methyl]bicyclo[2.2.1]heptane-2-ol 4-methylbenzenesulfonate (1). This compound was prepared upon treatment of a solution of 0.203 g (0.68 mmol) of the corresponding monotosylated 1,4-diol in 10 mL of dry CHCl₃ with 0.077 g (1.13 mmol) of imidazole and 0.143 g (0.95 mmol) of TBDMSCl. The solution was stirred at rt for 7 h, after which time another portion of TBDMSCl (0.070 g, 0.47 mmol) was added. Stirring was continued for 16 h and then five drops of MeOH were added. The solution was stirred for an additional 15 min and poured into 25 mL of ether. The organic layer was washed with H₂O and brine, dried, and evaporated. The remaining oil was chromatographed on a SPE column filled with reversed phase C₁₈ particle size 40 μm (3:1 H₂O/CH₃CN to CH₃CN) to give 0.102 g (37 %) of **1**: ¹H NMR δ -0.02 (s, 6 H), 0.82 (s, 9 H), 0.89 (m, 1 H), 1.06–1.27 (m, 2 H), 1.30–1.51 (m, 2 H), 1.55–1.64 (m, 2 H), 2.22 (m, 1 H), 2.26 (br s, 1 H), 2.41 (s, 3 H), 3.19–3.40 (m, 2 H), 4.41 (m, 1 H), 7.30 (d, *J* = 8.2 Hz, 2 H), 7.75 (d, *J* = 8.2 Hz, 2 H); ¹³C NMR δ -5.40 (2 q), 18.20 (s), 21.58 (q), 25.85 (3 q), 32.06 (2 t), 35.12 (d), 39.31 (t), 39.39 (d), 44.09 (d), 65.50 (t), 85.33 (d), 127.59 (2 d), 129.73 (2 d), 134.62 (s), 144.28 (s); MS *m/z* (relative intensity) 353 (*M*⁺ - 57, 5), 230 (14), 229 (100), 149 (4), 107 (20), 91 (8), 79 (7), 75 (5), 73 (7); HRMS calcd for C₁₇H₂₅O₄SSi (*M*⁺ - 57) 353.1243, found 353.1249.

General Procedure for the Preparation of TES Ethers 4–7. To a solution (0.074–0.104 M) of the corresponding monotosylated 1,4-diol in dry DMF were added imidazole (ca. 2 equiv) and TESCl (ca. 1.5 equiv). The reaction mixture was stirred at rt and the reaction progress was monitored by TLC. At completion, the mixture was poured into 25 mL of H₂O and extracted with four 10 mL portions of ether. The combined organic layers were washed with brine, dried, and evaporated. The resulting product was purified by flash chromatography (50:1 petroleum ether (bp 40–60 °C)/EtOAc).

(2-endo,6-exo)-6-[(Triethylsilyl)oxy]bicyclo[2.2.1]heptane-2-methanol α-(4-Methylbenzenesulfonate (4): yield 99 %; ¹H NMR δ 0.44 (q, *J* = 7.8 Hz, 2 H), 0.45 (q, *J* = 7.8 Hz, 4 H), 0.67–1.10 (m, 4 H), 0.94 (t, *J* = 7.8 Hz, 9 H), 1.39 (m, 1 H), 1.77 (m, 1 H), 1.94 (m, 1 H), 2.05 (m, 1 H), 2.37 (s, 3 H), 2.53 (m, 1 H), 3.68–3.84 (m, 2 H), 4.02 (m, 1 H), 7.26 (d, *J* = 8.2 Hz, 2 H), 7.71 (d, *J* = 8.2 Hz, 2 H); ¹³C NMR δ 4.72 (3 t), 6.76 (3 q), 21.60 (q), 31.00 (d), 34.10 (t), 34.26 (t), 37.03 (d), 39.02 (t), 45.10 (d), 72.09 (d), 73.52 (t), 127.83 (2 d), 129.74 (2 d), 133.53 (s), 144.51 (s); MS *m/z* (relative intensity) 381 (*M*⁺ - 29, 0.8), 257 (100), 107 (42), 79 (18), 71 (18), 69 (21), 57 (26), 55 (19), 43 (19); HRMS calcd for C₁₉H₂₉O₄SSi (*M*⁺ - 29) 381.1556, found 381.1550.

exo,exo-6-[(Triethylsilyl)oxy]bicyclo[2.2.1]heptane-2-methanol α-(4-Methylbenzenesulfonate (5): yield 93 %; ¹H NMR δ 0.52 (q, *J* = 7.8 Hz, 2 H), 0.53 (q, *J* = 7.8 Hz, 4 H), 0.78–1.03 (m, 2 H), 0.91 (t, *J* = 7.8 Hz, 9 H), 1.10–1.37 (m, 2 H), 1.43–1.68 (m, 3 H), 1.92 (m, 1 H), 2.17 (m, 1 H), 2.43 (s, 3 H), 3.61 (m, 1 H), 3.78 (d, *J* = 7.7 Hz, 2 H), 7.33 (d, *J* = 8.2 Hz, 2 H), 7.77 (d, *J* = 8.2 Hz, 2 H); ¹³C NMR δ 4.79 (3 t), 6.77 (3 q), 21.58 (q), 31.75 (t), 32.69 (t), 35.00 (d), 36.59 (d), 42.30 (t), 46.48 (d), 72.80 (t), 74.34 (d), 127.78 (2 d), 129.76 (2 d), 133.21 (s), 144.61 (s); MS *m/z* (relative intensity) 381 (*M*⁺ - 29, 1.0), 259 (10), 258 (18), 257

(100), 107 (23), 79 (8), 69 (6), 57 (8); HRMS calcd for $C_{19}H_{29}O_4SSi$ ($M^+ - 29$) 381.1556, found 381.1555.

($\alpha R,exo,exo$)- α -Methyl-6-[(triethylsilyl)oxy]bicyclo[2.2.1]heptane-2-methanol α -(4-Methylbenzenesulfonate) (6): yield 91 %; 1H NMR δ 0.51 (q, $J = 7.8$ Hz, 2 H), 0.52 (q, $J = 7.8$ Hz, 4 H), 0.90 (t, $J = 7.8$ Hz, 9 H), 1.05–1.36 (m, 8 H), 1.42–1.56 (m, 2 H), 1.74 (m, 1 H), 2.16 (m, 1 H), 2.42 (s, 3 H), 3.58 (m, 1 H), 4.45 (m, 1 H), 7.31 (d, $J = 8.2$ Hz, 2 H), 7.76 (d, $J = 8.2$ Hz, 2 H); ^{13}C NMR δ 4.77 (3 t), 6.74 (3 q), 20.05 (q), 21.56 (q), 32.58 (t), 33.00 (t), 35.10 (d), 41.98 (t), 43.67 (d), 47.43 (d), 74.97 (d), 83.57 (d), 127.64 (2 d), 129.63 (2 d), 134.60 (s), 144.37 (s); MS m/z (relative intensity) 395 ($M^+ - 29$, 2.4), 258 (18), 257 (100), 121 (39), 99 (22), 57 (20), 55 (16); HRMS calcd for $C_{20}H_{31}O_4SSi$ ($M^+ - 29$) 395.1712, found 395.1710.

($\alpha S,exo,exo$)- α -Methyl-6-[(triethylsilyl)oxy]bicyclo[2.2.1]heptane-2-methanol α -(4-Methylbenzenesulfonate) (7): yield 88 %; 1H NMR δ 0.50 (q, $J = 7.8$ Hz, 2 H), 0.51 (q, $J = 7.8$ Hz, 4 H), 0.89 (t, $J = 7.8$ Hz, 9 H), 0.77–0.98 (m, 2 H), 1.09–1.57 (m, 8 H), 1.87 (m, 1 H), 2.15 (m, 1 H), 2.42 (s, 3 H), 3.53 (m, 1 H), 4.27 (m, 1 H), 7.30 (d, $J = 8.2$ Hz, 2 H), 7.78 (d, $J = 8.2$ Hz, 2 H); ^{13}C NMR δ 4.77 (3 t), 6.77 (3 q), 18.99 (q), 21.54 (q), 31.80 (t), 33.37 (t), 35.32 (d), 41.98 (t), 43.71 (d), 46.32 (d), 74.51 (d), 82.18 (d), 127.66 (2 d), 129.64 (2 d), 134.50 (s), 144.37 (s); MS m/z (relative intensity) 395 ($M^+ - 29$, 1.2), 258 (17), 257 (100), 121 (55), 93 (16), 91 (17), 87 (12), 75 (11); HRMS calcd for $C_{20}H_{31}O_4SSi$ ($M^+ - 29$) 395.1712, found 395.1710.

***exo,exo*-2-Carbomethoxy-6-methoxybicyclo[2.2.1]heptane (12).** To a stirred solution of 0.202 g (1.29 mmol) of carboxylic acid **11** in 10 mL of dry DMF were added successively 10 mL of MeI and 0.150 g (6.25 mmol) of NaH. The reaction mixture was refluxed for 7 h and, after being cooled to rt, quenched with a small amount of saturated aqueous NH_4Cl . After addition of 20 mL of H_2O , the aqueous solution was extracted with five 25 mL portions of EtOAc. The combined organic layers were washed with brine, dried, and evaporated. The resulting oil was dissolved in 50 mL of dry MeOH and 1 mL (7.88 mmol) of TMSCl was added. The solution was stirred at rt for 3 h, and then carefully neutralized by the addition of 1 N aqueous NaOH. The solution was concentrated under reduced pressure and the remaining residue was taken up into 20 mL of EtOAc. The organic layer was washed with saturated aqueous $NaHCO_3$ and brine, dried, and evaporated. The resulting oil was flash chromatographed (10:1 petroleum ether (bp 40–60 °C)/EtOAc) to give 0.158 g (66 %) of **12** as a clear oil: 1H NMR δ 1.24–1.60 (m, 5 H), 1.73 (m, 1 H), 2.09 (m, 1 H), 2.26 (m, 1 H), 2.58 (m, 1 H), 3.19–3.28 (m, 4 H), 3.63 (s, 3 H); ^{13}C NMR δ 33.01 (t), 33.38 (t), 34.81 (d), 38.64 (t), 42.03 (d), 43.98 (d), 51.76 (q), 56.16 (q), 83.37 (d), 175.94 (s); MS m/z (relative intensity) 184 (M^+ , 7), 153 (24), 152 (100), 125 (21), 124 (38), 120 (18), 93 (74), 92 (25), 67 (22); HRMS calcd for $C_{10}H_{16}O_3$ (M^+) 184.1099, found 184.1099.

***exo,exo*-6-Methoxy-2-[[[(1,1-dimethylethyl)dimethylsilyl]oxy]methyl]bicyclo[2.2.1]heptane (8).** To a solution of 0.136 g (0.74 mmol) of **12** in 15 mL of dry THF was added 0.028 g (0.74 mmol) of LAH at 0 °C. The reaction mixture was stirred at this temperature for 1 h and the excess of LAH was destroyed by careful addition of a small amount of saturated aqueous Na_2SO_4 . After addition of 20 mL of EtOAc, the mixture was dried and evaporated. The resulting oil was dissolved in 5 mL of dry DMF and imidazole (0.070 g, 1.03 mmol) and TBDMSCl (0.110 g, 0.83 mmol) were added. The solution was

stirred at rt for 16 h and then diluted with 15 mL of H₂O. After extraction with three 10 mL portions of EtOAc, the combined organic layers were washed with brine, dried, and evaporated. The resulting oil was flash chromatographed (50:1 petroleum ether (bp 40–60 °C)/EtOAc) to give 0.120 g (76 %) of **8** as a clear oil: ¹H NMR δ 0.02 (s, 6 H), 0.81–0.98 (m, 1 H), 0.88 (s, 9 H), 1.08–1.60 (m, 6 H), 2.20 (m, 1 H), 2.33 (m, 1 H), 3.20–3.45 (m, 6 H); ¹³C NMR δ –5.30 (2 q), 18.30 (s), 25.90 (3 q), 31.70 (t), 32.70 (t), 34.97 (d), 38.85 (t), 40.11 (d), 41.83 (d), 55.81 (q), 66.14 (t), 84.15 (d); MS *m/z* (relative intensity) 213 (*M*⁺ – 57, 65), 119 (30), 107 (100), 89 (66), 79 (63), 75 (39), 73 (21), 91 (16); HRMS calcd for C₁₁H₂₁O₂Si (*M*⁺ – 57) 213.1311, found 213.1313.

Preparation of the Silylated Methyl Ethers 9 and 10. A stirred solution (0.015–0.020 M) of the corresponding monosilylated 1,4-diol in dry THF was cooled to 0 °C and then *t*-BuOK (ca. 10 equiv) was added, immediately followed by addition of MeI (ca. 40 equiv). The reaction mixture was stirred at 0 °C for 30 min and then diluted with 25 mL of ether. The organic layer was washed with brine, dried, and evaporated. The resulting residue was flash chromatographed (30:1 petroleum ether (bp 40–60 °C)/EtOAc) to give the pure product.

(2-*endo*,6-*exo*)-6-[[[(1,1-Dimethylethyl)dimethylsilyl]oxy]methyl]-2-methoxybicyclo[2.2.1]heptane (9): yield 85 %; ¹H NMR δ 0.03 (s, 6 H), 0.80–1.47 (m, 5 H), 0.88 (s, 9 H), 1.88 (m, 1 H), 2.09–2.27 (m, 2 H), 2.41 (m, 1 H), 3.24 (s, 3 H), 3.27–3.46 (m, 2 H), 3.71 (m, 1 H); ¹³C NMR δ –5.33 (2 q), 18.40 (s), 25.89 (3 q), 33.75 (2 t), 33.94 (d), 36.45 (d), 36.55 (t), 40.76 (d), 56.35 (q), 66.16 (t), 81.43 (d); MS *m/z* (relative intensity) 213 (*M*⁺ – 57, 26), 133 (13), 107 (70), 91 (13), 89 (100), 79 (79), 75 (28), 73 (24), 59 (13); HRMS calcd for C₁₁H₂₁O₂Si (*M*⁺ – 57) 213.1311, found 213.1314.

***endo,endo*-6-[[[(1,1-Dimethylethyl)dimethylsilyl]oxy]methyl]-2-methoxybicyclo[2.2.1]heptane (10):** yield 87 %; ¹H NMR δ 0.03 (s, 6 H), 0.83–1.01 (m, 2 H), 0.88 (s, 9 H), 1.30–1.36 (m, 2 H), 1.78–2.25 (m, 4 H), 2.46 (m, 1 H), 3.28 (s, 3 H), 3.70–3.99 (m, 3 H); ¹³C NMR δ –5.23 (2 q), 18.30 (s), 25.96 (3 q), 35.12 (t), 36.68 (d), 37.33 (t), 38.41 (t), 41.06 (d), 44.06 (d), 57.23 (q), 65.93 (t), 84.54 (d); MS *m/z* (rel intensity) 213 (*M*⁺ – 57, 76), 107 (77), 91 (14), 89 (100), 79 (80), 75 (24), 73 (27), 59 (14); HRMS calcd for C₁₁H₂₁O₂Si (*M*⁺ – 57) 213.1311, found 213.1308.

Kinetic Studies on the Silyl Ethers 1–10. The reactions were studied under pseudo-first-order conditions at which [TBAF] >> [silyl ether]. The disappearance of the silyl ether was monitored by HPLC. The following procedure was adopted: 70 μL of 1.1 M TBAF in THF was added at once, via syringe, to 1.0 mL of 0.0075 M silyl ether in dry acetonitrile in a sealed ampule. The solution was stirred continuously, and the extent of reaction was followed at the indicated temperature until at least 60 % of the silyl ether was disappeared.

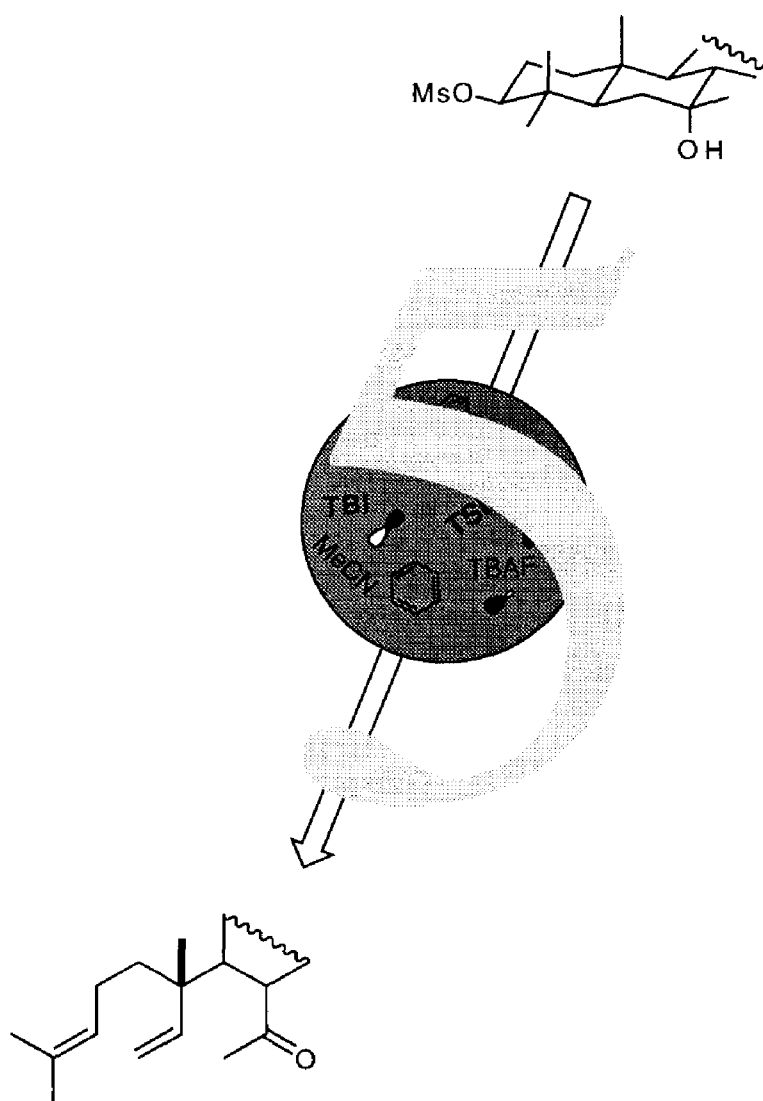
High Performance Liquid Chromatography. The HPLC equipment was a high precision pump, and a refractive index and UV (262 nm) detector assembled with a 10 μL loop injection valve. The chromatography column (25 x 1/4 m) was packed with 10 μm SPHERISORB ODS 2. Results were obtained by eluting with acetonitrile/H₂O (isocratic, 80 or 95 % v/v) at a column temperature of 26 °C. The solvent mixture was degassed prior to elution (flow rate = 1 mL/min).

4.5 References and Notes

- 1 (a)Wijnberg, J. B. P. A.; Jenniskens, L. H. D.; Brunekreef, G. A.; de Groot, A. *J. Org. Chem.* **1990**, *55*, 941. (b) Jenniskens, L. H. D.; Wijnberg, J. B. P. A.; de Groot, A. *J. Org. Chem.* **1991**, *56*, 6585. (c) Orrū, R. V. A.; Wijnberg, J. B. P. A.; Jenniskens, L. H. D.; de Groot, A. *J. Org. Chem.* **1993**, *58*, 1199. (d) Orrū, R. V. A.; Wijnberg, J. B. P. A.; Bouwman, C. T.; de Groot, A. *J. Org. Chem.* **1994**, *59*, 374. (e) Bastiaansen, P. M. F. M.; Wijnberg, J. B. P. A.; de Groot, A. *J. Org. Chem.* **1995**, *60*, 4240. (f) Orrū, R. V. A.; Wijnberg, J. B. P. A.; de Groot, A. *J. Org. Chem.* **1995**, *60*, 4233.
- 2 Paddon-Row, M. N.; Jordan, K. D. In *Modern Models of Bonding and Delocalization*; Liebman, J. F., Greenberg, A., Eds.; VCH Publishers: New York, 1988, Chapter 3 and references cited therein.
- 3 Paddon-Row M. N. *Acc. Chem. Res.* **1982**, *15*, 245.
- 4 The vigorous conditions (excess of strong base, refluxing benzene) at which the heterolysis of 1,4-diol monosulfonate esters proceeds, do not allow for easy kinetic measurements.
- 5 Fischer, W.; Grob, C. A.; von Sprecher, G.; Waldner, A. *Helv. Chim. Acta* **1980**, *63*, 816.
- 6 Green, T. W.; Wuts, P. G. M. In *Protective Groups in Organic Synthesis*; Wiley-Interscience: New York, 1991, p 15.
- 7 TBAF is available commercially as a 1 M solution in THF, containing 4.5–5 % H₂O. This amount of H₂O can serve as proton donor in the desilylation reactions.
- 8 Corey, E. J.; Venkateswarlu, A. *J. Am. Chem. Soc.* **1972**, *94*, 6190.
- 9 Bently, T. W.; Gream, G. E. *J. Org. Chem.* **1985**, *50*, 1776.
- 10 When TMS or TES ethers derived from primary alcohols were desilylated at room temperature or 0 °C, the reaction proceeded so fast that accurate kinetic measurements were not possible. Likewise, the TBDMS ethers (too slow) and TMS ethers (too fast) of secondary alcohols were not suitable for these measurements.
- 11 The kinetic measurements on TES ethers were performed at 0 °C.
- 12 Grob, C. A.; Günther, B.; Hanreich, R. *Helv. Chim. Acta* **1982**, *65*, 2110.
- 13 Colvin, E. In *Silicon in Organic Synthesis*; Butterworths: London, 1981, Chapter 15.
- 14 The exact mechanism for Si–O bond breaking is still a point of discussion. For example, see: Dietze, P. E. *J. Org. Chem.* **1993**, *58*, 5653.
- 15 The numbering system as given in structure 1 (Chart 4.1) will be followed throughout the text of this chapter.
- 16 According to the W–H principle, the overall rate constant (k_{obs}) is the average of the specific rate constants of the individual conformers weighted by their mole fractions: Seeman, J. I. *Chem. Rev.*, **1983**, *83*, 83.
- 17 It might be possible that the conformational equilibrium position of ground state conformations is affected by TBI. This possibility was suggested by Hoffmann et al.: Gleiter, R.; Stohrer, W.-D.; Hoffmann, R. *Helv. Chim. Acta* **1972**, *55*, 893. The first experimental verification of this effect was reported in 1989: Krijnen, B.; Beverloo, H. B.; Verhoeven, J. W.; Reiss, C. A.; Goubitz, K.; Heijdenrijk, D. J. *J. Am. Chem. Soc.* **1989**, *111*, 4433.
- 18 Modifications in the electron donor–acceptor system can affect the extent of TBI. See ref 17: Krijnen et al.
- 19 For a general description of the experimental procedures reported in this chapter, see chapter 2.

Chapter 5

Chemical Consequences of Through-Bond Interactions in Monomesylated Cholestane-3,7-Diols. A Seven-Center Fragmentation



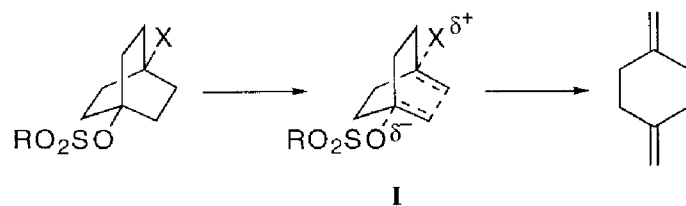
Abstract. The manifestation of through-five-bond interactions in the reactions of the rigid 1,5-diol monosulfonate esters (**1–3**), having an ideal all-trans geometry of the σ -relay, with sodium *tert*-amylate is investigated. It has been shown that the deprotonation of the alcohol group in **2** and **3**, which results in an increased electrofugal ability of this group, finds expression in a seven-center fragmentation. This fragmentation also illustrates that effective through-five-bond interactions exists between the alcoholate group and the carbocationic center which is generated during the heterolysis. The reaction outcome of mesylate **1** does not indicate effective through-bond interactions, and only elimination is observed. This difference can be attributed to the alkyl substituents on the γ - and α -positions to the mesylate group in **2** and **3**, respectively, which stimulate the seven-center fragmentation. Though a reasonable amount of fragmentation product is obtained from **3**, the through-five-bond interaction is not strong enough to dominate the reaction course completely and typical E1-like processes, i.e., elimination and rearrangement, are competitive. As expected, only a 1,2 Me-shift is observed in the reaction of the axial mesylate **4** where a gauche interaction is present in the geometry of the σ -relay. The presence of through-bond interactions in the reactions of **3** and **4** becomes apparent by comparison of the reactivity of **3** and **4** with their O-silylated analogs **5** and **6**.

5.1 Introduction

The best-known example of participation of the σ -framework in an intramolecular chemical reaction is the heterolytic Grob fragmentation,¹ which is almost certainly the result of orbital interactions through three σ -bonds.² The base-induced fragmentation of cyclic 1,3-diol monosulfonate esters, known as the Wharton reaction, is a typical example of the Grob fragmentation and finds widespread application in organic synthesis.³

The synthetic value of reactions in which orbital interactions through four σ -bonds are supposed to be operative is best illustrated with the intramolecular base-induced rearrangement and elimination reactions of trans-fused perhydronaphthalene-1,4-diol monosulfonate esters.^{4,5} More detailed studies revealed that when these compounds possess an all-trans arrangement of the σ -bonds homofragmentation is the characteristic reaction pathway^{6a-c} and that a more substituted σ -framework results in a higher reactivity of these compounds (see also Chapter 2, Section 1.3).^{6d}

Reports on the chemical consequences of orbital interactions through more than four σ -bonds are scarce. Paddon-Row et al.⁷ used the Birch reduction as a tool for exploring the chemical consequences of long-range orbital interactions through five and six σ -bonds and came to the conclusion that any chemical consequences arising from such interactions should be small. Grob et al.⁸ examined the solvolysis of a number of 4-substituted (X) bicyclo[2.2.2]octylsulfonate esters (X = COO⁻, CONH₂, CH₂OH, and CH₂NH₂) to find out whether these saturated compounds are capable of undergoing seven-center fragmentation in which five σ -bonds are involved.⁹ However, careful scrutiny of the reaction products revealed that only substitution and no seven-center fragmentation to 1,4-dimethylenecyclohexane had occurred (Scheme 5.1). Grob concluded that for the weakly electron-donating substituents X mentioned above double hyperconjugation, as illustrated in structure I, does not progress to the point where fragmentation occurs and an energetically more favorable substitution reaction takes place.



Scheme 5.1

More recently, Adcock et al.¹⁰ reported the fragmentation to 1,4-dimethyldene-cyclohexane in the reaction with the strongly electron-donating trimethylstannyl group as the substituent X. This and other related results¹¹ supported Grob's view that fragmentation can occur only when the group X is a sufficiently active electrofuge.¹²

In order to test this hypothesis, an investigation into the reaction behavior of 1,5-diol monosulfonate esters under strongly basic nonsolvolytic conditions was undertaken.⁶ Because deprotonation of the hydroxyl group in these sulfonate esters would lead to a strongly increased electrofugal ability of the carbinol function, the seven-center fragmentation Grob had in mind might be feasible.¹³ Furthermore, it is known that structural features such as (1) an all-trans (zigzag) σ -relay,¹⁴ (2) a tertiary alcohol function,¹⁵ and (3) a higher degree of substitution of the σ -relay¹⁶ all may favor fragmentation reactions. Therefore, as 1,5-diol monosulfonate esters, the easily accessible cholestane-3,7-diol monomesylates **1**–**4**¹⁷ (Chart 5.1) were investigated. Especially, the mesylates **2** and **3** possess all the favorable structural features for the occurrence of seven-center fragmentation.

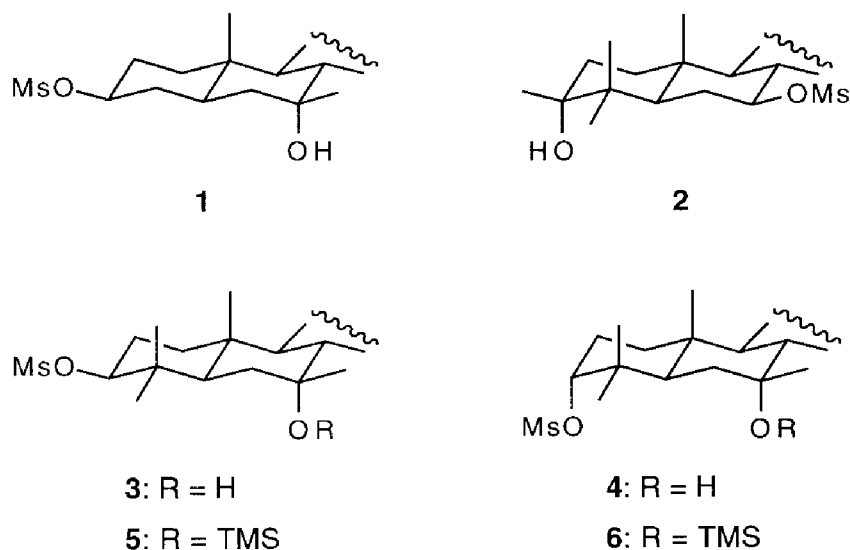


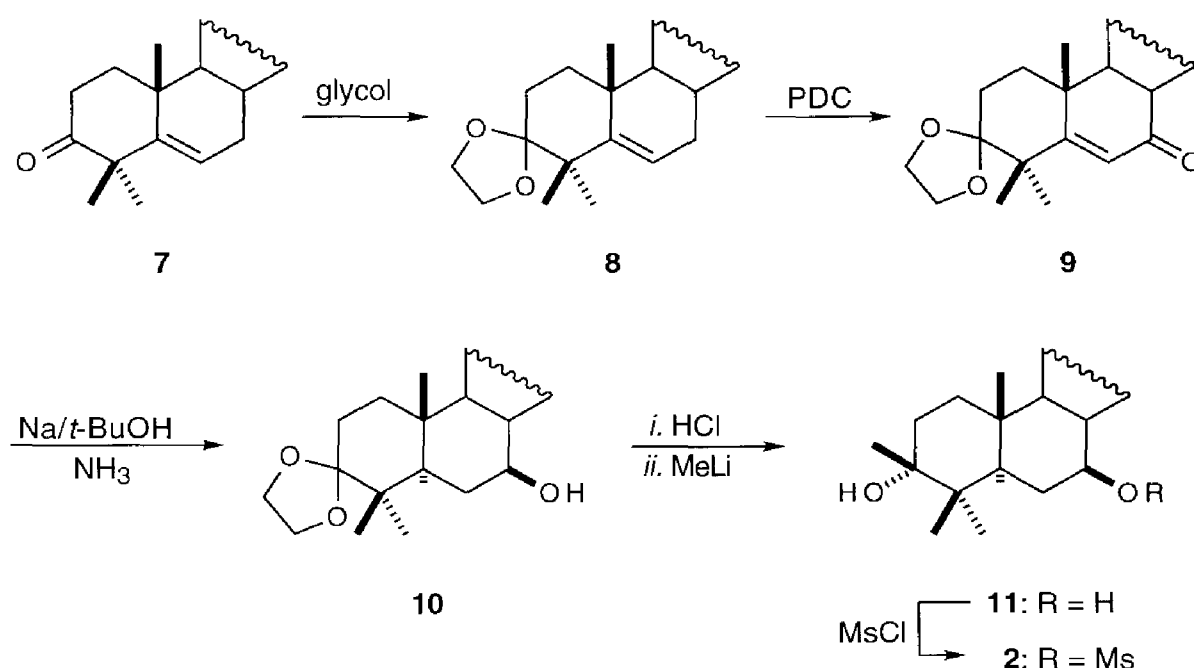
Chart 5.1

There were two other reasons for selecting these particular cholestane derivatives for study. First, from the reactions of the mesylates **1**–**3**, having different alkyl substitution patterns, it was expected that further evidence for the accelerating effect of alkyl substituents in these processes would be obtained.^{6d} Second, from the reaction of the axial mesylate **4**, it was expected to get information on whether through-bond interactions (TBI) over five σ -bonds would still be significant for the product composition and reactivity of compounds having a nonzigzag σ -relay.

Additionally, the O-silylated mesylates **5** and **6** were subjected to the same strongly basic conditions as well to demonstrate again that the generation of an alcoholate function is crucial for the reactivity of these compounds. In this chapter the results of this study are reported.

5.2 Results and Discussion

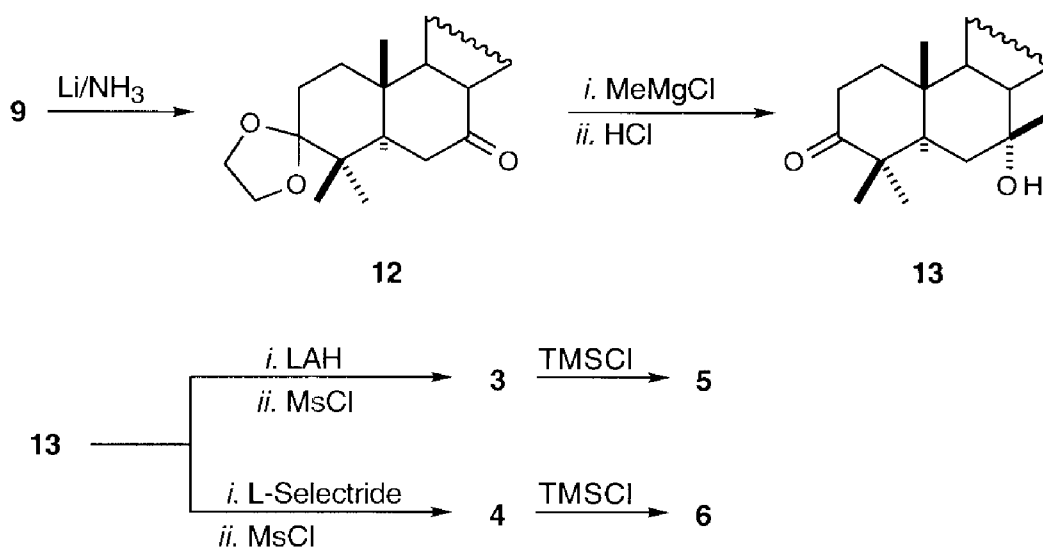
The mesylate **1** was prepared from the known 3β -hydroxy- 5α -cholestan-7-one¹⁸ by mesylation and successive treatment with MeMgI at 0 °C.¹⁹ The synthesis of mesylate **2** started with the readily available dimethylated ketone **7**.²⁰ Protection of the carbonyl group of **7** as its ethylene acetal **8** was followed by an allylic oxidation with PDC in refluxing pyridine²¹ to give the enone **9** (Scheme 5.2). Treatment of **9** with Na in liquid NH₃ in the presence of *t*-BuOH (3 equiv) gave the 7β -hydroxy compound **10** as the sole product. Hydrolysis of the acetal function of **10** and subsequent treatment with MeLi afforded the diol **11**.²² Finally, the secondary alcohol group of **11** was converted into a mesylate group to afford compound **2** in 34% overall yield from **7**.



Scheme 5.2

For the synthesis of the mesylates **3** and **4**, the double bond of **9** was reduced with Li in liquid NH₃ at reflux temperature (Scheme 5.3). The resulting ketone **12** was treated with an excess of MeMgI and then with HCl to afford predominantly the

keto alcohol **13**. The stereochemistry of the hydroxyl group at C(7) in **13** was confirmed by X-ray crystallography.²³ After reduction of **13** with LAH and subsequent treatment with MsCl, the mesylate **3** was obtained in 66% overall yield from **9**. Reduction of **13** with L-Selectride and mesylation of the resulting diol gave the mesylate **4** in 61% overall yield from **9**. Treatment of **3** and **4** with TMSCl and HMDS afforded the corresponding O-silylated mesylates **5** and **6**, respectively, in high yields.



Scheme 5.3

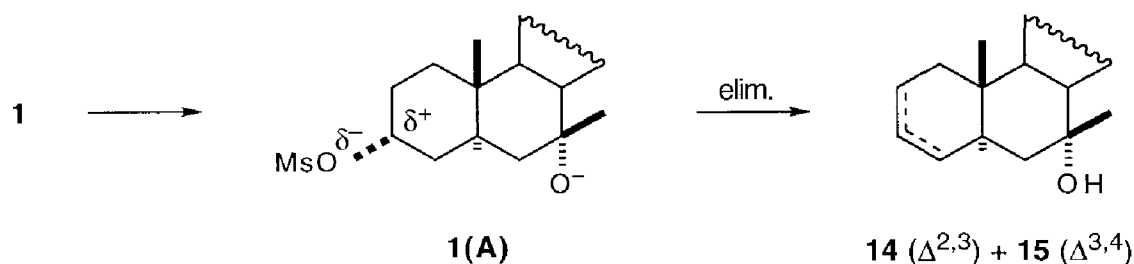
In order to obtain comparable data about the reactivity of the mesylates **1–6**, all reactions were run in refluxing toluene²⁴ with ca. 5 equiv of sodium *tert*-amylate for 10 min. Comparison of the quantities of recovered starting material gave a rough estimate of the relative reaction rates.²⁵ The results of these studies are collected in Table 1.

Table 1. Reactions of the Mesylates **1–6** with Sodium *tert*-Amylate^a

entry	mesylate	products (%) ^b	recovery ^c
1	1	14 (4) ^d + 15 (3) ^d	75
2	2	16 (3) + 17 (6) ^d + 18 (32) ^d	51
3	3	19 (20) + 20 (13) + 21 (22) + 22 (6)	17
4	4	23 (6) ^d + 24 (48) + 25 (21) ^d	2
5	5	-- (17) ^e	66
6	6	26 (13) ^d + 27 (14) ^d	58

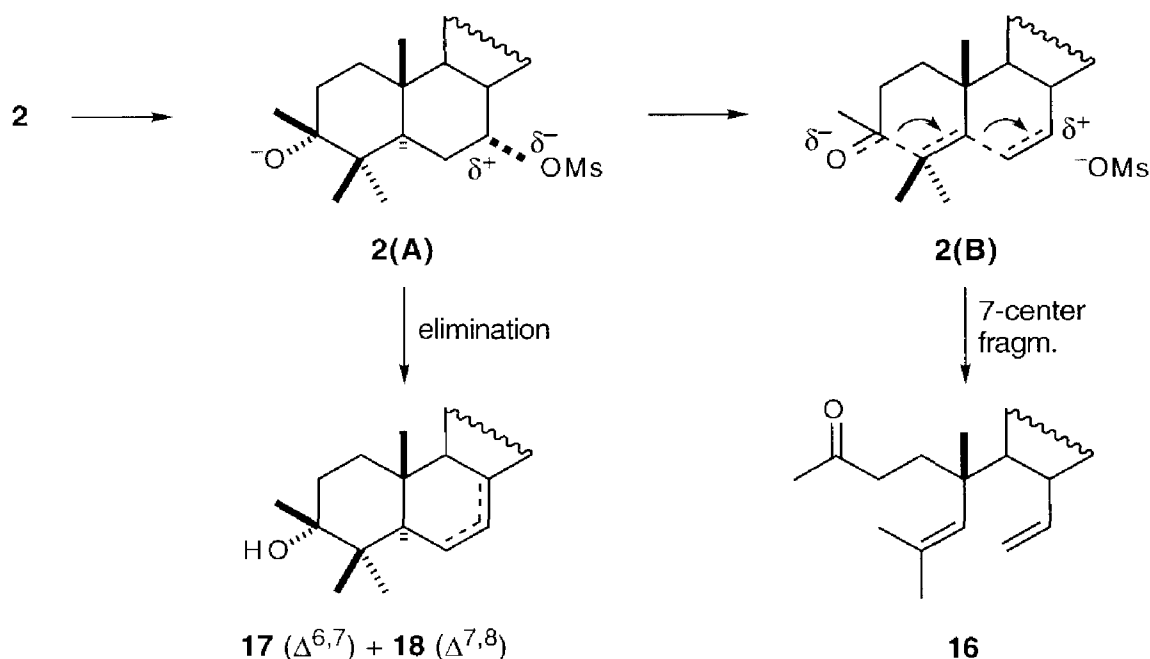
^a All reactions were performed in refluxing toluene with ca. 5 equiv of sodium *tert*-amylate for 10 min. ^b Yield in parentheses. ^c Percentage of recovered starting material. ^d The yield of this product is based on NMR analysis. ^e Inseparable mixture of five probably olefinic compounds.

The reaction of the mesylate **1**²⁶ gave a small amount (7%) of an inseparable ca. 3:2 mixture of the olefins **14** and **15**, respectively, together with 75% of recovered starting material (entry 1, Scheme 5.4). In the ¹H NMR spectrum of the mixture, the olefinic signals of the major olefin **14** appear as a broad singlet ($W_{1/2} \approx 5$ Hz) at δ 5.59, while the corresponding signals of the minor olefin **15** resonance at δ 5.20 (br dd, $J = 2.2, 10.0$ Hz, 1H) and 5.56 (m, 1 H). Similar differences in splitting pattern and chemical shift have been reported for the signals of the olefinic protons of 5 α -cholest-2-ene and 5 α -cholest-3-ene.²⁷



Scheme 5.4

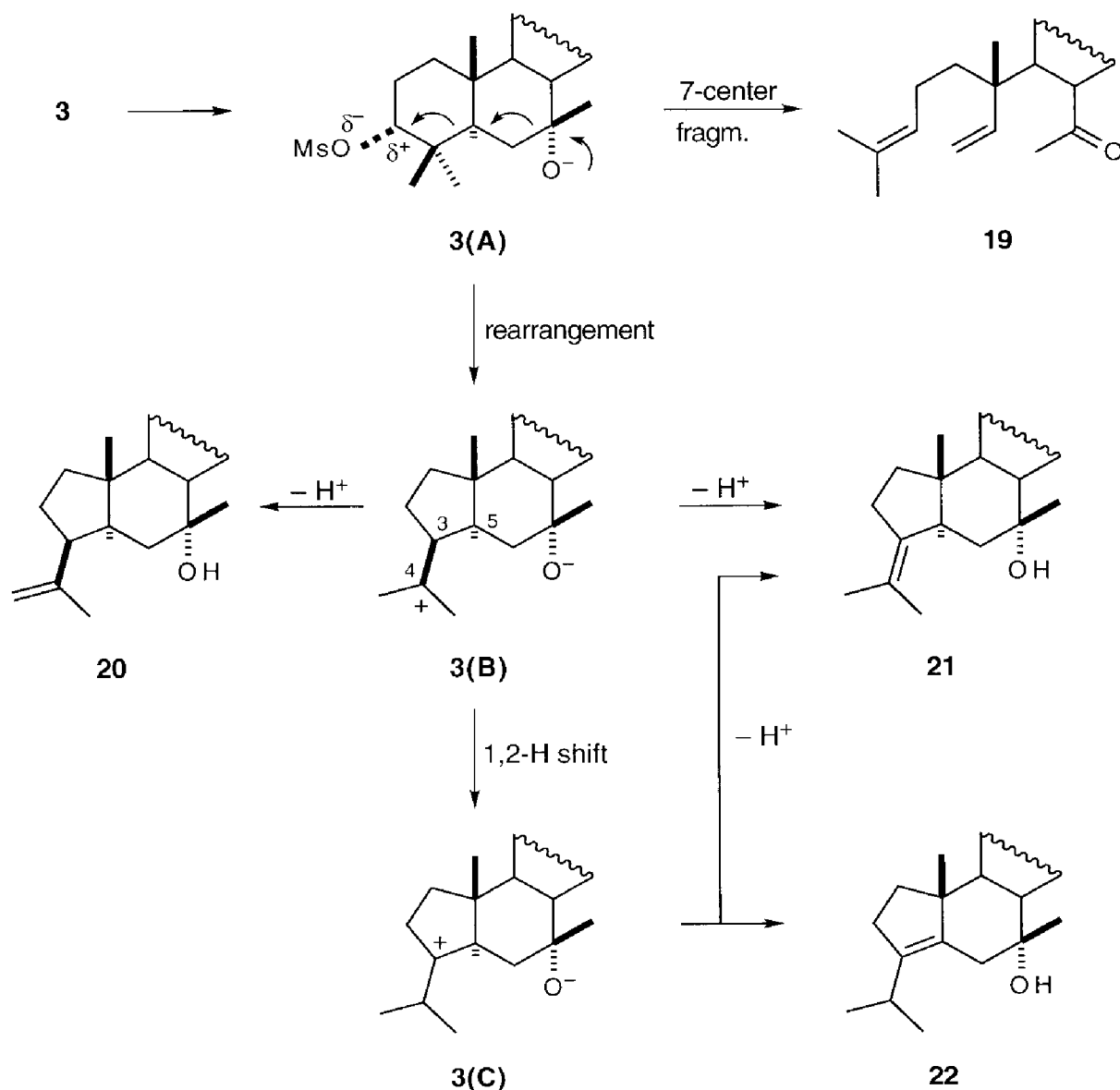
The mesylate **2** reacted slightly faster than **1**, as follows from the lesser amount (51%) of recovered starting material, and afforded a small quantity (3%) of the fragmentation product **16**²⁸ together with an inseparable ca. 1:5 mixture (38%) of the olefins **17** and **18**, respectively (entry 2, Scheme 5.5).



Scheme 5.5

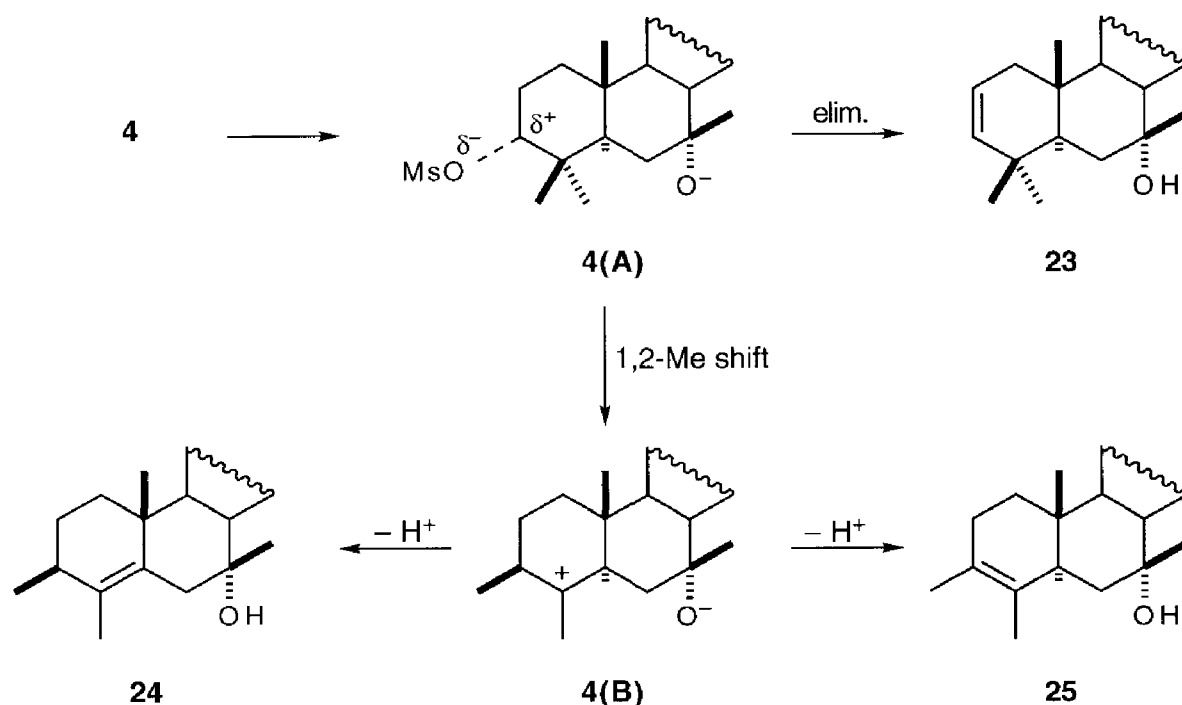
The NMR spectral data of **16** are fully consistent with the structure given in Scheme 5.5. Although the reaction pathway to **16** is only a minor side reaction, it is, to the best of the author's knowledge, the first example of a seven-center fragmentation over five single bonds in unstrained compounds.

The mesylate **3** reacted considerably faster than the mesylates **1** and **2** (17% of **3** was regained) (entry 3, Scheme 5.6). Four compounds were formed in this reaction: the seven-center fragmentation product **19** (20%)²⁸ and the olefins **20**, **21**, and **22** in 13, 22, and 6% yields, respectively. Also, in this case the NMR spectral data of the seven-center fragmentation product **19** are fully consistent with the assigned structure.



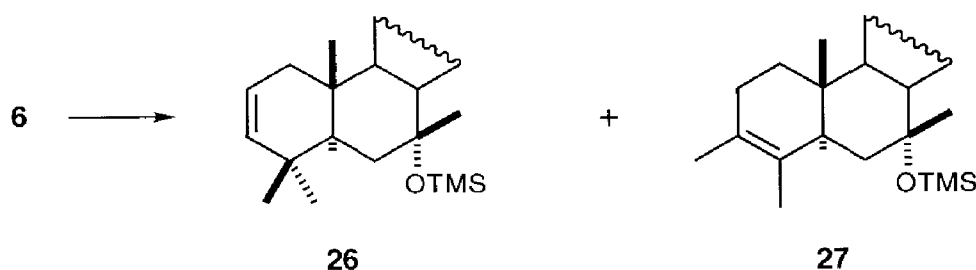
Scheme 5.6

The mesylate **4** reacted the fastest of all the compounds studied. After the standard treatment, only a small amount of starting material (2%) could be regained (entry 4, Scheme 5.7). As products, the three olefins **23**, **24**, and **25** in a ratio of 1:8:3.5, respectively, were obtained. Column chromatography gave pure **24** (48%) and an inseparable mixture (27%) of **23** and **25**.



Scheme 5.7

Compared with the mesylates **3** and **4**, the corresponding O-silylated mesylates **5** and **6** reacted more slowly (entries 5 and 6). The quantities of recovered starting material (66 and 58%, respectively) suggest that **6** reacts slightly faster than **5**. On the other hand, the product compositions are noticeably different. Whereas **5** produced a complex mixture (ca. 17%) of at least five olefinic compounds, **6** only gave two products: the $\Delta^{2,3}$ olefin **26** (13%) and the rearranged olefin **27** (14%) (Scheme 5.8).



Scheme 5.8

The results collected in Table 1 clearly show that Me substitution at C(4) leads to an increase in reaction rate (entries 1–3). The occurrence of different product-forming pathways in the reactions of **1**–**3** can be connected with the presence (or absence) of Me substituents as well. Furthermore, it is evident that alkoxide formation is also important for the reactivity of these compounds as can be concluded from the differences in reaction rate between **3** and **5** and between **4** and **6** (entries 3–6). These observations have led to the assumption that the mesylates **1**–**4** react by a mechanism which is comparable with that proposed for the 1,4-diol monosulfonate esters.⁶ This means that the mesylates **1**–**4** will react via dipolar intermediates with intramolecular alkoxide-induced heterolysis of the mesylate bond as the rate-determining step. The dipolar intermediates in turn may undergo typical cationic reactions such as elimination, rearrangement, 1,2-Me shift, and/or fragmentation. The product compositions and reaction rates found for **1**–**4** are easily understood on this basis.

The equatorial mesylate **1**, which is supposed to react via the intermediate **1(A)**, undergoes a 1,2-elimination as the sole product-forming pathway (Scheme 5.4). The relatively slow formation of the olefins **14** and **15** suggests that intermediate **1(A)** is not very effectively stabilized by TBI.

The enhanced reactivity of mesylate **2**, compared with that of **1**, indicates that in intermediate **2(A)** the carbocationic center on C(7) is better stabilized than the one on C(3) in **1(A)** (Scheme 5.5). The higher degree of stabilization of **2(A)** can be attributed to enhanced σ -participation^{6d,29} as result of the presence of the C(8)–C(14) bond next to the carbocationic center on C(7). It might be possible that the electron-donating Me substituents at C(4) also participate in the stabilization of **2(A)** by enlargement of the electron density of the σ -relay. Combined with the enhanced stability of the carbocation, this inductive donation will favor the reaction pathway leading to fragmentation via the double hyperconjugatively stabilized intermediate (or transition state) **2(B)**.³⁰ The formation of a small amount of fragmentation product **16** in the reaction of **2** can be attributed to this effect. Elimination leading to **17** and **18**, however, remains the main reaction pathway as the elimination:fragmentation ratio (ca. 13:1 in favor of elimination) indicates.

The difference in reaction rate found for the mesylates **2** and **3** can be explained similarly (Scheme 5.6). Stabilization by σ -participation will be more effective in **3(A)** than in **2(A)** because the C(4) atom adjacent to the carbocationic center in **3(A)** bears *two* alkyl substituents (Me groups), whereas in **2(A)** only *one* alkyl substituent, i.e., the C(8)–C(14) bond, is present next to the carbocationic center. In addition, cationic carbon atoms are better stabilized by alkyl substituents located at

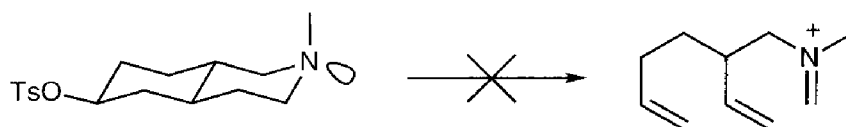
the α -position (as in **3(A)**) than by alkyl substituents at the γ -position (as in **2(A)**).³¹ Consequently, TBI will be more effective in **3(A)** than in **2(A)**, which finds expression in the reactivity order $3 > 2$ and the relatively high yield (20%) of the seven-center fragmentation product **19**.

The other compounds (**20**, **21**, and **22**) found in the reaction of **3** must be formed via rearrangement of the initially formed intermediate **3(A)** to the thermodynamically more stable intermediate **3(B)**. This tertiary carbocationic intermediate can undergo proton loss to give the olefins **20** and **21**, but can also react further by way of a 1,2-H shift ($C(3) \rightarrow C(4)$) to afford another tertiary intermediate (**3(C)**), which in turn can give additional **21** and the olefin **22**, the latter probably as the result of an intramolecularly assisted deprotonation.³² The formation of **22** can only proceed stepwise, because a concerted mechanism starting from **3(B)** is not allowed for stereochemical reasons (both H-3 and H-5 have the α -orientation). It might be possible that **3(C)** is somewhat better stabilized than **3(B)**, because in **3(C)** the number of σ -bonds between the alcoholate function and the carbocationic center is reduced by one.³³

The main reason for examining mesylate **4** was to find out to what extent an axially positioned leaving group influences the rate and course of these TBI-induced reactions. Seven-center fragmentation was not expected in this reaction because the required antiperiplanar relationship between the leaving group and the C(4)–C(5) bond is lacking.^{11b} Instead, it was expected that a 1,2-Me shift would be the main reaction pathway since both the leaving mesylate group and the β -Me group at C(4) are axially positioned. The formation of the rearranged olefins **24** and **25** in which the intermediates **4(A)** and **4(B)** should be involved corresponds with this expectation (Scheme 5.7). Again, intramolecular deprotonation (48% of **24**) is preferred over intermolecular deprotonation (21% of **25**). An intermolecular anti-elimination explains the formation of olefin **23** from **4(A)**.

Finally, it is of interest to note that **4** reacts somewhat faster than **3**. According to the trans rule, one should expect the reverse order because of the all-trans arrangement of the σ -relay present in **3**.^{14a} In order to explain this discrepancy, the results of the reactions of **3** and **4** are compared with those of the O-silylated mesylates **5** and **6**. These silyl ethers show a similar reactivity order as found for **3** and **4**, i.e., compound **6** with an axial mesylate group reacts slightly faster than **5** in which an equatorial mesylate group is present. It is known that the tosylate esters of 4,4-dimethylcholestan-3 α -ol and the 3 β -epimer both react by an E1-like mechanism upon treatment with sodium *tert*-amylate in refluxing benzene.³⁴ Moreover, the 3 α -epimer reacts two to three times faster than the 3 β -epimer,³⁵ which can be attributed to relief of steric strain. A similar E1-like mechanism may

also be operative in the closely related mesylates **5** and **6** which are supposed to react *without* involvement of long-range orbital interactions.^{6a} In contrast to **5** and **6**, the structurally related O-silylated trans-fused perhydronaphthalene-1,4-diol mesylates (equatorial and axial) lacking the Me groups at C(4) do not react at all under similar reaction conditions.^{6a} Thus, the relatively high reactivity of **5** and **6** and their product composition can be associated with the steric and/or electronic effects of the Me groups at C(4). On the basis of these facts, it is assumed that the mesylates **3** and **4** also react via an E1-like mechanism but now *with* participation of TBI since both **3** and **4** react faster than their respective O-silylated analogs **5** and **6**. The influence of Me groups at C(4) will predominate over TBI in **3** and **4** because of the large distance between the alcoholate group and the mesylate ester.³³ On the other hand, it will be clear that the additional stabilization of the carbocationic intermediates by TBI is somewhat more pronounced in **3(A)** than in **4(A)** (trans rule) which finds expression in the formation of the seven-center fragmentation product **19** in the reaction of **3**.



Scheme 5.9

The results of this study provide a good explanation for the nonoccurrence of fragmentation products in the solvolysis of the ϵ -amino tosylate studied by Grob et al. (Scheme 5.9).⁸ In spite of the proper alignment of the σ -bonds, the absence of two alkyl substituents next to the carbon atom bearing the tosylate group and the presence of a weakly electron-donating alkylated amino group in this *trans*-perhydroisoquinoline system make seven-center fragmentation an unfavorable process, and only substitution will take place as Grob et al. found experimentally.

5.3 Concluding Remarks

These results clearly indicate that an alkoxide function can assist in the formation of a carbocationic center via TBI over *five* σ -bonds. However, the reaction course is not solely determined by these interactions and typical E1-like processes come into play, this in contrast to the previously studied 1,4-diol monosulfonate esters⁶ where TBI over *four* σ -bonds is considered to be the main factor determining the reaction behavior of these compounds. Nevertheless, the

involvement of through-five-bond interactions is reflected by the occurrence of a seven-center fragmentation in the reactions of 1,5-diol monosulfonate esters in which the five σ -bonds are held in the all-trans geometry. The presence of alkyl substituents, especially on the α -position, which results in enhanced σ -participation is also a prerequisite for allowing seven-center fragmentation. The occurrence of seven-center fragmentation also supports Grob's view that the enhanced solvolysis rates of the 4-substituted bicyclo[2.2.2]octylsulfonate esters mentioned in the Introduction may be due to double hyperconjugation.^{8,31} The synthetic value of this fragmentation reaction is limited because other more favorable reaction pathways, i.e., elimination and rearrangement, are preferred.

Though, the occurrence of long-range orbital interactions through five σ -bonds still enhances the reaction rate of 1,5-diol monosulfonate esters in comparison with systems that lack these interactions, a dramatic decrease in reaction rate is found with respect to the 1,4-diol monosulfonate esters. In the author's opinion, the ability of an alcoholate function to induce intramolecularly the heterolysis of a remote sulfonate ester group has reached its limit with the 1,5-diol monosulfonate esters.

5.4 Experimental Section

General.³⁶ (3 β ,5 α)-3-Hydroxycholestan-7-one¹⁸ and 4,4-dimethylcholest-5-en-3-one (7)²⁰ were prepared following previously described procedures.

(3 β ,5 α)-3-Hydroxycholestan-7-one Methanesulfonate. To a stirred solution of 2.80 g (6.95 mmol) of (3 β ,5 α)-3-hydroxycholestan-7-one in 2.8 mL of dry pyridine was added 2.60 g (22.7 mmol) of MsCl. The reaction mixture was stirred at rt for 18 h and then poured into H₂O. The aqueous layer was extracted with CHCl₃ and washed successively with 5% HCl, water, 10% KHCO₃, and brine. After drying and evaporation, crystallization from CHCl₃/ether afforded 1.60 g (45%) of pure (3 β ,5 α)-3-hydroxycholestan-7-one methanesulfonate: mp 167–168 °C; ¹H NMR δ 0.62 (s, 3 H), 0.75–2.43 (m, 29 H), 0.83 (d, J = 6.4 Hz, 6 H), 0.88 (d, J = 6.5 Hz, 3 H), 1.08 (s, 3 H), 2.98 (s, 3 H), 4.56 (m, 1 H); ¹³C NMR δ 11.65 (q), 12.02 (q), 18.74 (q), 21.79 (t), 22.53 (q), 22.78 (q), 23.73 (t), 24.91 (t), 27.94 (d), 28.34 (2t), 34.84 (t), 35.60 (d), 35.65 (s), 35.72 (t), 36.08 (t), 38.58 (t), 38.72 (q), 39.41 (t), 42.44 (s), 45.59 (t), 46.37 (d), 48.79 (d), 49.86 (d), 54.70 (d), 54.95 (d), 80.61 (d), 211.04 (s); MS m/z (relative intensity) 480 (M⁺, 22), 385 (10), 384 (21), 358 (30), 357 (100), 356 (17), 272 (11), 253 (9); HRMS calcd for C₂₈H₄₈O₄S (M⁺) 480.3273, found 480.3273. Anal. Calcd for C₂₈H₄₈O₄S: C, 69.95; H, 10.06. Found: C, 70.02; H, 10.21.

(3 β ,5 α ,7 α)-7-Methylcholestane-3,7-diol 3-(Methanesulfonate) (1). To a stirred solution of 0.230 g (0.48 mmol) of (3 β ,5 α)-3-hydroxycholestan-7-one methanesulfonate in 50 mL of dry ether was added 0.48 mL (0.96 mmol) of MeMgI (2.0 M in ether) at once at 0 °C. The reaction mixture was stirred for 1 min and then carefully quenched with a small amount of saturated

aqueous NH_4Cl . After the addition of 15 mL of H_2O , the two-phase mixture was separated and the organic layer was washed with 10 mL of brine, dried, and evaporated. The remaining residue was flash chromatographed (3:1 petroleum ether (bp 40–60 °C)/EtOAc) to give 0.080 g of unreacted starting material and 0.101 g (42%) of **1**: ^1H NMR δ 0.66 (s, 3 H), 0.77 (s, 3 H), 0.80–2.05 (m, 30 H), 0.85 (d, J = 6.3 Hz, 6 H); 0.83 (d, J = 6.5 Hz, 3 H), 1.23 (s, 3 H); 2.97 (s, 3 H), 4.60 (m, 1 H); ^{13}C NMR δ 11.42 (q), 12.24 (q), 18.81 (q), 21.60 (t), 22.54 (q), 22.78 (q), 23.72 (t), 27.96 (d), 27.96 (t), 28.52 (t), 28.76 (t), 32.08 (q), 34.46 (t), 34.86 (s), 35.64 (d), 36.07 (t), 36.95 (t), 38.40 (d), 38.66 (q), 39.46 (t), 39.76 (t), 44.01 (s), 44.28 (d), 45.04 (t), 49.47 (d), 51.34 (d), 54.98 (d), 72.32 (s), 82.00 (d); MS m/z (relative intensity) 481 ($\text{M}^+ - 15$, 18), 385 (19), 383 (19), 367 (17), 332 (30), 256 (22), 97 (67), 83 (88), 69 (100), 55 (78); HRMS calcd for $\text{C}_{28}\text{H}_{49}\text{O}_4\text{S}$ ($\text{M}^+ - 15$) 481.3352, found 481.3353. Anal. Calcd for $\text{C}_{29}\text{H}_{52}\text{O}_4\text{S}$: C, 70.11; H, 10.55. Found: C, 70.30; H, 10.75.

4',4'-Dimethylspiro[1,3-dioxolane-2,3'-cholest-5'-ene] (8). A solution of 8.00 g (19.4 mmol) of **7**, 0.347 g of camphorsulfonic acid, and 11 mL of ethylene glycol in 300 mL of toluene was refluxed in the flask equipped with a Dean–Stark column packed with 4 Å molecular sieves for 16 h, cooled, and poured into 100 mL of saturated aqueous NaHCO_3 . The two-phase mixture was separated and the aqueous layer was extracted with three 100 mL portions of CH_2Cl_2 . The combined organic layers were dried and evaporated. The remaining residue was flash chromatographed (25:1 petroleum ether (bp 40–60 °C)/EtOAc) to yield 8.14 g (92%) of **8**: ^1H NMR δ 0.66 (s, 3 H), 0.85 (d, J = 6.7 Hz, 6 H), 0.90–2.18 (m, 26 H), 0.91 (d, J = 6.5 Hz, 3 H), 1.03 (s, 3 H), 1.12 (s, 3 H), 1.22 (s, 3 H), 3.87–4.03 (m, 4 H), 5.52 (m, 1 H); ^{13}C NMR δ 11.83 (s), 18.66 (q), 20.53 (t), 21.66 (q), 22.36 (q), 22.53 (q), 22.79 (q), 23.79 (t), 24.16 (t), 26.81 (t), 27.98 (d), 28.25 (t), 29.81 (q), 30.87 (d), 32.31 (t), 35.24 (t), 35.76 (d), 36.16 (t), 36.24 (q), 39.49 (t), 39.71 (t), 42.19 (s), 44.79 (s), 50.55 (d), 55.95 (d), 57.17 (d), 64.84 (t), 65.20 (t), 113.19 (s), 119.90 (d), 149.64 (s); MS m/z (relative intensity) 456 (M^+ , 3), 412 (2), 356 (1), 124 (2), 107 (1), 100 (5), 99 (100), 95 (1), 87 (1), 55 (2); HRMS calcd for $\text{C}_{31}\text{H}_{52}\text{O}_2$ (M^+) 456.3967, found 456.3967. Anal. Calcd for $\text{C}_{31}\text{H}_{52}\text{O}_2$: C, 81.52; H, 11.48. Found: C, 81.69; H, 11.71.

4',4'-Dimethylspiro[1,3-dioxolane-2,3'-cholest-5'-en-7'-one] (9). To a stirred solution of 8.14 g (17.9 mmol) of **8** and 1.00 g of 3 Å molecular sieves in 400 mL of dry pyridine was added 80.0 g of PDC. The reaction mixture was heated at reflux for 2 h, cooled, and then poured into 750 mL of brine. The aqueous layer was extracted with six 250 mL portions of CH_2Cl_2 , and the combined organic layers were dried and evaporated. The remaining residue was flash chromatographed (25:1 petroleum ether (bp 40–60 °C)/EtOAc) to yield 7.29 g (87%) of **9**: ^1H NMR δ 0.67 (s, 3 H), 0.84 (d, J = 6.7 Hz, 6 H), 0.90 (d, J = 6.5 Hz, 3 H), 0.90–2.40 (m, 24 H), 1.06 (s, 3 H), 1.31 (s, 3 H), 1.32 (s, 3 H), 3.87–4.03 (m, 4 H), 5.88 (s, 1 H); ^{13}C NMR δ 11.90 (q), 18.80 (q), 20.13 (q), 20.81 (t), 21.50 (q), 22.51 (q), 22.79 (q), 23.81 (t), 26.39 (t), 26.56 (t), 27.96 (d), 28.32 (q), 28.54 (t), 34.18 (t), 35.76 (d), 36.13 (t), 37.94 (s), 38.82 (t), 39.43 (t), 43.34 (s), 45.21 (d), 45.86 (s), 50.70 (d), 51.56 (d), 54.77 (d), 65.00 (t), 65.30 (t), 112.20 (s), 124.88 (d), 175.78 (s), 202.79 (s); MS m/z (relative intensity) 470 (M^+ , 2), 455 (1), 149 (1), 100 (4), 99 (100), 69 (2), 57 (1), 55 (3), 43 (1); HRMS calcd for $\text{C}_{31}\text{H}_{50}\text{O}_3$ (M^+) 470.3760, found 470.3757. Anal. Calcd for $\text{C}_{31}\text{H}_{50}\text{O}_3$: C, 79.10; H, 10.71. Found: C, 79.29; H, 10.90.

(5' α ,7' β)-4',4'-Dimethylspiro[1,3-dioxolane-2,3'-cholestan-7'-ol] (10). To a stirred solution

of 1.60 g (69.6 mmol) of Na in 200 mL of refluxing liquid NH_3 was added dropwise a solution of 2.18 g (4.64 mmol) of **9** and 1.03 g (13.9 mmol) of *t*-BuOH in 50 mL of THF. After the addition was complete, the reaction mixture was stirred at reflux temperature for 1 h and then 10.0 g of solid NH_4Cl was added. NH_3 was allowed to evaporate overnight and 100 mL of H_2O was cautiously added to the residue. The aqueous phase was extracted with five 100 mL portions of ether. The combined organic layers were dried and evaporated, and the resulting product was flash chromatographed (10:1 petroleum ether (bp 40–60 °C)/EtOAc) to give 1.75 g (80%) of **10**: ^1H NMR δ 0.60–2.03 (m, 28 H), 0.63 (s, 3 H), 0.80 (s, 3 H), 0.81 (s, 3 H), 0.84 (s, 3 H), 0.87 (d, $J = 7.1$ Hz, 3 H), 0.91 (d, $J = 6.7$ Hz, 6 H), 3.32 (m, $W_{1/2} = 15$ Hz, 1 H), 3.80–4.02 (m, 4 H); ^{13}C NMR δ 12.05 (q), 14.29 (q), 18.74 (q), 19.90 (q), 20.77 (t), 22.49 (q), 22.76 (2q), 23.81 (t), 26.90 (t), 27.02 (t), 27.93 (d), 28.68 (t), 31.39 (t), 35.62 (d), 35.64 (s), 35.72 (t), 36.15 (t), 39.45 (t), 39.81 (t), 41.88 (s), 43.02 (d), 43.14 (s), 49.68 (d), 53.84 (d), 55.14 (d), 55.76 (d), 64.72 (t), 64.83 (t), 76.14 (d), 113.08 (s); MS m/z (relative intensity) 474 (M^+ , 2), 431 (2), 109 (1), 100 (9), 99 (100), 95 (2), 81 (2), 69 (2), 55 (2), 43 (1); HRMS calcd for $\text{C}_{31}\text{H}_{54}\text{O}_3$ (M^+) 474.4073, found 474.4070. Anal. Calcd for $\text{C}_{31}\text{H}_{54}\text{O}_3$: C, 78.42; H, 11.47. Found: C, 78.60; H, 11.68.

(3 α ,5 α ,7 β)-3,4,4-Trimethylcholestane-3,7-diol (11). To a stirred solution of 0.867 g (1.84 mmol) of **10** in 200 mL of acetone was added 4 mL of 4 N HCl. The reaction mixture was stirred at rt for 3 h and then neutralized with 10 mL of saturated aqueous NaHCO_3 . After concentration under reduced pressure, the remaining aqueous solution was extracted with 50 mL of CH_2Cl_2 . The organic layer was washed with 15 mL of brine, dried, and evaporated. The so-obtained crude (5 α ,7 β)-7-hydroxy-4,4-dimethylcholestan-3-one (0.777 g, 99%) was dissolved in 30 mL of THF and cooled to -78 °C. After addition of 5.7 mL of 1.6 M MeLi, the reaction mixture was stirred at -78 °C for 10 min and allowed to warm to rt over a 2-h period. The excess of MeLi was then cautiously destroyed with a small amount of saturated aqueous NH_4Cl . After dilution with 25 mL of ether, the organic layer was washed with 10 mL of brine, dried, and evaporated. The remaining residue³⁷ was flash chromatographed (5:1 petroleum ether (bp 40–60 °C)/EtOAc) to give 0.469 g (57%) of pure **11**: ^1H NMR δ 0.64 (s, 3 H), 0.65 (m, 1 H), 0.72–1.92 (m, 27 H), 0.83 (s, 3 H), 0.84 (d, $J = 6.1$ Hz, 6 H), 0.88 (s, 3 H), 0.89 (s, 3 H), 0.89 (d, $J = 6.3$ Hz, 3 H), 1.17 (s, 3 H), 1.98 (m, 1 H), 3.34 (ddd, $J = 5.4, 10.4, 10.4$ Hz, 1 H); ^{13}C NMR δ 12.06 (q), 14.67 (q), 18.75 (q), 18.82 (q), 20.74 (t), 22.50 (q), 22.75 (q), 23.07 (q), 23.83 (t), 24.36 (q), 26.88 (t), 27.95 (d), 28.69 (t), 31.84 (t), 34.20 (t), 35.63 (d), 36.15 (t), 36.30 (s), 36.45 (t), 39.44 (t), 39.79 (t), 40.71 (s), 43.02 (d), 43.44 (s), 49.63 (d), 54.52 (d), 55.20 (d), 55.76 (d), 75.05 (s), 76.33 (d); MS m/z (relative intensity) 446 (M^+ , 2), 428 (5), 375 (18), 374 (28), 358 (38), 357 (100), 149 (19), 123 (13), 122 (10), 95 (12); HRMS calcd for $\text{C}_{30}\text{H}_{54}\text{O}_2$ (M^+) 446.4138, found 446.4127. Anal. Calcd for $\text{C}_{30}\text{H}_{54}\text{O}_2$: C, 80.65; H, 12.18. Found: C, 80.65; H, 11.93.

(3 α ,5 α ,7 β)-3,4,4-Trimethylcholestane-3,7-diol 7-(Methanesulfonate) (2). To a solution of 0.439 g (0.98 mmol) of **11** in 20 mL of dry pyridine was added 0.200 g (1.75 mmol) of MsCl. The reaction mixture was stirred at rt overnight and then concentrated under reduced pressure. The resulting residue was taken up in 50 mL of EtOAc and washed successively with two 15 mL portions of saturated aqueous NaHCO_3 and one 15 mL portion of brine. The organic layer was dried and evaporated, and the remaining residue was flash chromatographed (5:1 petroleum ether (bp 40–60 °C)/EtOAc) to give 0.487 g (94%) of **2**: ^1H

NMR δ 0.63 (s, 3 H), 0.64–1.94 (m, 26 H), 0.82 (s, 3 H), 0.85 (s, 3 H), 0.86 (d, J = 7.7 Hz, 6 H), 0.87 (d, J = 7.7 Hz, 3 H), 0.90 (s, 3 H), 1.23 (s, 3 H), 1.98 (m, 1 H), 2.20 (m, 1 H), 2.99 (s, 3 H), 4.47 (ddd, J = 5.5, 10.6, 10.6 Hz, 1 H); ^{13}C NMR δ 11.98 (q), 14.54 (q), 18.75 (q), 18.89 (q), 20.80 (t), 22.53 (q), 22.78 (q), 23.08 (q), 23.72 (t), 24.26 (q), 25.97 (t), 27.94 (d), 28.50 (t), 29.87 (t), 33.97 (t), 35.52 (d), 35.91 (t), 36.04 (t), 36.18 (s), 39.34 (t), 39.40 (t), 40.00 (q), 40.30 (d), 40.77 (s), 43.43 (s), 49.37 (d), 54.58 (d), 54.77 (d), 55.07 (d), 74.86 (s), 86.54 (d); MS m/z (relative intensity) 428 ($\text{M}^+ - 96$, 47), 411 (30), 410 (71), 395 (27), 358 (54), 357 (100), 274 (22), 149 (26), 135 (21), 95 (25); HRMS calcd for $\text{C}_{30}\text{H}_{52}\text{O}$ ($\text{M}^+ - 96$) 428.4018, found 428.4019. Anal. Calcd for $\text{C}_{31}\text{H}_{56}\text{O}_4\text{S}$: C, 70.94; H, 10.76. Found: C, 70.88; H, 11.18.

(5 α)-4',4'-Dimethylspiro[1,3-dioxolane-2,3'-cholestan-7'-one] (12). A solution of 2.58 g (5.48 mmol) of **9** and 0.425 g (5.74 mmol) of *t*-BuOH in 50 mL of THF was added dropwise to a stirred solution of 0.515 g (74.6 mmol) of Li in 200 mL of liquid NH_3 at reflux temperature. After the addition was complete, stirring was continued for 10 min and 10.0 g of solid NH_4Cl was added. Workup as described for the synthesis of **10** was followed by flash chromatography (10:1 petroleum ether (bp 40–60 °C)/EtOAc) to yield 2.33 g (90%) of **12**: ^1H NMR δ 0.61 (s, 3 H), 0.78 (s, 3 H), 0.80–2.44 (m, 27 H), 0.83 (d, J = 6.5 Hz, 6 H), 0.87 (d, J = 7.7 Hz, 3 H), 0.96 (s, 3 H), 1.12 (s, 3 H), 3.80–3.98 (m, 4 H); ^{13}C NMR δ 11.99 (q), 13.66 (q), 18.75 (q), 19.53 (q), 21.12 (t), 22.51 (q), 22.57 (q), 22.75 (q), 23.72 (t), 25.09 (t), 27.04 (t), 27.94 (d), 28.39 (t), 34.89 (t), 35.61 (d), 36.10 (t), 36.73 (s), 38.57 (t), 39.43 (t), 39.82 (t), 42.36 (s), 42.60 (s), 48.90 (d), 49.56 (d), 53.89 (d), 54.88 (d), 55.66 (d), 64.92 (2t), 112.66 (s), 212.71 (s); MS m/z (relative intensity) 472 (M^+ , 1), 457 (1), 169 (1), 131 (1), 121 (1), 119 (2), 107 (1), 100 (10), 99 (100), 69 (3); HRMS calcd for $\text{C}_{31}\text{H}_{52}\text{O}_3$ (M^+) 472.3916, found 472.3915. Anal. Calcd for $\text{C}_{31}\text{H}_{52}\text{O}_3$: C, 78.76; H, 11.09. Found: C, 78.96; H, 11.32.

(5 α ,7 α)-7-hydroxy-4,4,7-trimethylcholestan-3-one (13). To a stirred solution of 2.31 g (4.89 mmol) of **12** in 50 mL of dry ether was added 7.0 mL (18.2 mmol) of MeMgI (2.6 M in ether) at 0 °C. The reaction mixture was stirred at 0 °C for 1 h and at rt for an additional 1 h. The excess of MeMgI was then cautiously destroyed with saturated aqueous NH_4Cl . After dilution with 100 mL of H_2O , the two-phase mixture was separated and the aqueous layer was extracted with three 100 mL portions of EtOAc. The combined organic layers were washed with 100 mL of brine, dried, and evaporated. The crude product was treated with HCl in acetone as described for the synthesis of **11**. After workup, the crude product was purified by flash chromatography (10:1 petroleum ether (bp 40–60 °C)/EtOAc) to give 1.75 g (81%) of **13**: ^1H NMR δ 0.67 (s, 3 H), 0.84 (d, J = 6.5 Hz, 6 H), 0.91 (d, J = 6.6 Hz, 3 H), 0.95–2.05 (m, 26 H), 1.00 (s, 3 H), 1.02 (s, 3 H), 1.05 (s, 3 H), 1.30 (s, 3 H), 2.31 (m, 1 H), 2.62 (m, 1 H); ^{13}C NMR δ 12.25 (q), 13.16 (q), 18.86 (q), 21.34 (t), 21.72 (q), 22.57 (q), 22.81 (q), 23.70 (t), 25.32 (q), 29.97 (t), 28.01 (d), 28.57 (t), 32.44 (q), 34.75 (t), 35.68 (d), 36.12 (t), 36.26 (s), 38.46 (t), 39.50 (t), 39.58 (t), 39.70 (t), 43.98 (s), 44.00 (d), 47.04 (s), 48.63 (d), 51.11 (d), 51.36 (d), 55.03 (d), 72.46 (s), 216.99 (s); MS m/z (relative intensity) 444 (M^+ , 56), 430 (29), 429 (100), 426 (45), 411 (21), 341 (48), 340 (21), 125 (28), 43 (20); HRMS calcd for $\text{C}_{30}\text{H}_{52}\text{O}_2$ (M^+) 444.3967, found 444.3967. Anal. Calcd for $\text{C}_{30}\text{H}_{52}\text{O}_2$: C, 81.02; H, 11.79. Found: C, 80.88; H, 12.06.

(3 β ,5 α ,7 α)-4,4,7-Trimethylcholestan-3,7-diol 3-(Methanesulfonate) (3). To a stirred solution of 0.645 g (1.45 mmol) of **13** in 50 mL of dry THF was added 0.080 g (2.11 mmol) of LAH at –78 °C. The reaction mixture was stirred at –78 °C for 2 h and at rt for an additional

30 min. The reaction mixture was then carefully quenched with a small amount of saturated aqueous Na_2SO_4 . After addition of 50 mL of CH_2Cl_2 , the organic layer was dried and evaporated. The remaining residue was flash chromatographed (5:1 petroleum ether (bp 40–60 °C)/EtOAc) to give 0.643 g (99%) of a diol [^1H NMR δ 0.63 (s, 3 H), 0.73–2.00 (m, 29 H), 0.76 (s, 3 H), 0.80 (s, 3 H), 0.84 (d, J = 6.5 Hz, 6 H), 0.89 (d, J = 6.5 Hz, 3 H), 0.94 (s, 3 H), 1.26 (s, 3 H), 3.22 (m, 1 H)]. This diol (0.528 g, 1.18 mmol) was treated with MsCl as described for the synthesis of 2. After workup, the crude product was purified by flash chromatography (5:1 petroleum ether (bp 40–60 °C)/EtOAc) to yield 0.566 g (91%) of 3: ^1H NMR (C_6D_6) δ 0.70 (s, 3 H), 0.71 (s, 3 H), 0.76–2.10 (m, 28 H), 0.84 (s, 3 H), 0.95 (d, J = 6.8 Hz, 6 H), 1.03 (s, 3 H), 1.08 (d, J = 6.4 Hz, 3 H), 1.23 (s, 3 H), 2.38 (s, 3 H), 4.36 (dd, J = 4.5, 11.9 Hz, 1 H); ^{13}C NMR (C_6D_6) δ 12.11 (q), 13.16 (q), 16.09 (q), 18.93 (q), 21.02 (t), 22.48 (q), 22.75 (q), 24.05 (t), 25.63 (t), 27.72 (q), 28.00 (t), 28.11 (d), 28.69 (t), 32.21 (q), 35.86 (d), 36.33 (t), 37.12 (s), 37.12 (t), 37.85 (s), 37.94 (q), 38.83 (t), 39.62 (t), 39.90 (t), 43.76 (d), 43.97 (s), 47.64 (d), 51.01 (d), 51.27 (d), 55.26 (d), 71.67 (s), 89.21 (d); MS m/z (relative intensity) 524 (M^+ , 1), 509 (30), 428 (26), 413 (20), 411 (37), 410 (100), 395 (51), 367 (16), 121 (23), 95 (20); HRMS calcd for $\text{C}_{31}\text{H}_{56}\text{O}_4\text{S}$ (M^+) 524.3899, found 524.3899. Anal. Calcd for $\text{C}_{31}\text{H}_{56}\text{O}_4\text{S}$: C, 70.94; H, 10.76. Found: C, 70.98; H, 10.98.

(3 α ,5 α ,7 α)-4,4,7-Trimethylcholestane-3,7-diol 3-(Methanesulfonate) (4). To a solution of 0.608 g (1.37 mmol) of 13 in 25 mL of dry THF was added dropwise 4.1 mL (4.1 mmol) of L-Selectride (1 M in THF) at –78 °C. The solution was stirred at –78 °C for 2 h and allowed to come to rt overnight. The reaction mixture was cooled again to 0 °C, cautiously quenched with 3 mL of EtOH followed by the addition of 3 mL of 4 M NaOH and 3 mL of 35% H_2O_2 , and stirring was continued at rt for 6 h. The reaction mixture was then concentrated under reduced pressure, taken up in 50 mL of H_2O , and extracted with four 25 mL portions of CH_2Cl_2 . The combined organic layers were dried and evaporated. The remaining residue was treated with MsCl as described for the synthesis of 2. After workup, the crude product was purified by flash chromatography (5:1 petroleum ether (bp 40–60 °C)/EtOAc) to yield 0.605 g (84%) of 4: ^1H NMR (C_6D_6) δ 0.70 (s, 6 H), 0.71 (s, 3 H), 0.85–2.06 (m, 28 H), 0.99 (d, J = 6.8 Hz, 6 H), 1.01 (s, 3 H), 1.06 (d, J = 6.6 Hz, 3 H), 1.23 (s, 3 H), 2.36 (s, 3 H), 4.50 (br s, $W_{1/2}$ = 6.3 Hz, 1 H); ^{13}C NMR (C_6D_6) δ 12.12 (q), 13.14 (q), 18.90 (q), 20.86 (t), 21.41 (q), 22.45 (q), 22.69 (q), 24.06 (t), 24.26 (t), 27.99 (t), 28.05 (q), 28.08 (d), 28.61 (t), 32.19 (t), 32.30 (q), 35.81 (d), 36.03 (t), 36.30 (s), 36.62 (s), 37.88 (q), 38.72 (t), 39.61 (t), 39.68 (t), 42.64 (d), 43.71 (s), 44.19 (d), 51.13 (d), 51.25 (d), 55.25 (d), 71.54 (s), 87.09 (d); MS m/z (relative intensity) 524 (M^+ , 0.3), 509 (1), 428 (7), 413 (11), 411 (28), 410 (100), 395 (45), 121 (10), 109 (9), 95 (11); HRMS calcd for $\text{C}_{31}\text{H}_{56}\text{O}_4\text{S}$ (M^+) 524.3899, found 524.3897. Anal. Calcd for $\text{C}_{31}\text{H}_{56}\text{O}_4\text{S}$: C, 70.94; H, 10.76. Found: C, 71.14; H, 11.05.

(3 β ,5 α ,7 α)-4,4,7-Trimethyl-7-[(trimethylsilyl)oxy]cholestan-3-ol 3-(Methane-sulfonate) (5). To stirred solution of 0.217 g (0.41 mmol) of mesylate 3 in 10 mL of dry pyridine were added 0.330 g (2.0 mmol) of hexamethyldisilazane (HMDS) and 0.650 g (6.0 mmol) of TMSCl. The reaction mixture was stirred at 50 °C for 20 h and then neutralized with 10 mL of saturated aqueous NaHCO_3 . The reaction mixture was concentrated under reduced pressure and the concentrate was taken up in 50 mL of EtOAc. The organic layer was washed with 25 mL of brine, dried, and evaporated. The remaining residue was flash chromatographed (10:1 petroleum ether (bp 40–60 °C)/EtOAc) to give 0.233 g (95%) of 5: ^1H NMR δ 0.09 (s, 9 H),

0.60 (s, 3 H), 0.75–2.03 (m, 27 H), 0.83 (s, 6 H), 0.85 (d, $J = 6.5$ Hz, 6 H), 0.89 (d, $J = 6.5$ Hz, 3 H), 0.97 (s, 3 H), 1.30 (s, 3 H), 3.00 (s, 3 H), 4.35 (dd, $J = 5.1, 11.0$ Hz, 1 H); ^{13}C NMR δ 2.68 (3q), 12.26 (q), 13.54 (q), 16.32 (q), 18.90 (q), 20.84 (t), 22.51 (q), 22.80 (q), 23.97 (t), 25.67 (t), 27.74 (t), 27.94 (d), 28.38 (q), 28.50 (t), 31.71 (q), 35.73 (d), 36.06 (s), 36.15 (t), 37.37 (t), 38.06 (s), 38.79 (q), 39.18 (t), 39.47 (t), 39.50 (t), 43.55 (s), 45.68 (d), 47.74 (d), 50.37 (d), 50.98 (d), 55.02 (d), 75.85 (s), 90.78 (d); MS m/z (relative intensity) 596 (M^+ , 9), 500 (35), 485 (13), 419 (32), 418 (100), 410 (69), 395 (17), 210 (12), 143 (34), 73 (18); HRMS calcd for $\text{C}_{34}\text{H}_{64}\text{O}_4\text{SSi}$ (M^+) 596.4295, found 596.4298. Anal. Calcd for $\text{C}_{34}\text{H}_{64}\text{O}_4\text{SSi}$: C, 68.41; H, 10.81. Found: C, 68.14; H, 10.92.

(3 α ,5 α ,7 α)-4,4,7-Trimethyl-7-[(trimethylsilyl)oxy]cholestan-3-ol 3-(Methane-sulfonate) (6). The mesylate **4** (0.300 g, 0.57 mmol) was treated with HMDS and TMSCl for 24 h as described above for the synthesis of **5**. Workup and flash chromatography (10:1 petroleum ether (bp 40–60 °C)/EtOAc) yielded 0.307 g (90%) of **6**: ^1H NMR δ 0.09 (s, 9 H), 0.61 (s, 3 H), 0.80–2.00 (m, 27 H), 0.82 (s, 3 H), 0.84 (d, $J = 6.8$ Hz, 6 H), 0.88 (d, $J = 6.5$ Hz, 3 H), 0.89 (s, 3 H), 0.96 (s, 3 H), 1.29 (s, 3 H), 2.99 (s, 3 H), 4.52 (br s, $W_{1/2} = 4.0$ Hz, 1 H); ^{13}C NMR δ 2.61 (3q), 12.26 (q), 13.54 (q), 18.90 (q), 20.61 (t), 21.79 (q), 22.53 (q), 22.81 (q), 24.00 (t), 24.39 (t), 27.79 (t), 27.94 (d), 28.54 (q), 28.54 (t), 31.84 (q), 32.15 (t), 35.78 (d), 36.06 (s), 36.16 (t), 36.91 (s), 38.63 (q), 38.88 (t), 39.47 (2t), 42.06 (d), 43.49 (s), 45.89 (d), 50.37 (d), 51.16 (d), 55.08 (d), 75.84 (s), 88.17 (d); MS m/z (relative intensity) 596 (M^+ , 5), 500 (11), 485 (10), 419 (33), 418 (100), 410 (64), 395 (28), 210 (8), 143 (17), 73 (10); HRMS calcd for $\text{C}_{34}\text{H}_{64}\text{O}_4\text{SSi}$ (M^+) 596.4295, found 596.4297. Anal. Calcd for $\text{C}_{34}\text{H}_{64}\text{O}_4\text{SSi}$: C, 68.41; H, 10.81. Found: C, 68.38; H, 11.00.

Reactions of Mesylates 1–6 with Sodium *tert*-Amylate. General Procedure. All reactions were carried out at a concentration of ca. 0.1 M mesylate in dry toluene. The solutions were degassed and refluxed under an Ar atmosphere. Ca. 5 equiv of sodium *tert*-amylate (3.2 M in toluene) was added at once, via syringe, to the refluxing solution of the mesylate. The reaction mixture was heated at reflux temperature for 10 min, quenched with precooled saturated aqueous NH_4Cl , and then quickly cooled to 0 °C. The mixture was vigorously stirred for 20 min, followed by extraction with five portions of EtOAc. The combined organic layers were dried and evaporated under reduced pressure to afford the crude reaction products. Unless noted otherwise, product ratios, yields, and pure compounds were obtained by chromatographical techniques.

a. The general procedure was employed by using 0.093 g (0.19 mmol) of **1**. Workup and flash chromatography (100:1 to 2:1 petroleum ether (bp 40–60 °C)/EtOAc) afforded 0.005 g (7%) of an inseparable 3:2 mixture³⁸ of **14** and **15**, respectively, and 0.070 g (75%) of unreacted **1**.

(5 α ,7 α)-7-Methylcholest-2-en-7-ol (14): ^1H NMR (main peak) δ 5.59 (br s, $W_{1/2} \approx 5$ Hz, 2 H); HRMS (3:2 mixture) calcd for $\text{C}_{28}\text{H}_{48}\text{O}$ (M^+) 400.3705, found 400.3703.

(5 α ,7 α)-7-Methylcholest-3-en-7-ol (15): ^1H NMR (main peaks) δ 5.20 (br dd, $J = 2.2, 10.0$ Hz, 1 H), 5.56 (m, 1 H).

b. The general procedure was employed by using 0.336 g (0.64 mmol) of **2**. Workup and flash chromatography (50:1 to 2:1 petroleum ether (bp 40–60 °C)/EtOAc) afforded 0.008 g (3%) of **16**, 0.104 g (38%) of an inseparable 1:5 mixture³⁸ of **17** and **18**, respectively, and 0.172 g (51%) of unreacted **2**. The spectroscopic data of **16**, **17**, and **18** are shown below.

16: ^1H NMR δ 0.67 (s, 3 H), 0.85 (d, J = 6.7 Hz, 6 H), 0.84–2.08 (m, 21 H), 0.88 (d, J = 6.7 Hz, 3 H), 1.00 (s, 3 H), 1.56 (d, J = 1.1 Hz, 3 H), 1.60 (d, J = 1.2 Hz, 3 H), 2.11 (s, 3 H), 2.15–2.50 (m, 3 H), 4.66 (dd, J = 2.3, 9.9 Hz, 1 H), 4.69 (dd, J = 2.3, 16.9 Hz, 1 H), 4.79 (br s, 1 H), 5.36 (dt, J = 9.9, 16.9 Hz, 1 H); ^{13}C NMR δ 11.96 (q), 18.57 (q), 19.26 (q), 21.81 (q), 22.54 (t), 22.71 (q), 22.80 (q), 23.78 (t), 26.08 (t), 27.63 (t), 27.98 (q), 27.98 (d), 30.05 (q), 33.60 (t), 35.84 (d), 36.00 (t), 39.46 (t), 39.72 (t), 39.99 (t), 41.19 (s), 41.96 (s), 45.97 (d), 52.28 (d), 54.13 (d), 56.54 (d), 110.04 (t), 128.96 (s), 135.47 (d), 144.48 (d), 210.24 (s); MS m/z (relative intensity) 428 (M^+ , 6), 357 (35), 354 (7), 301 (7), 179 (9), 153 (100), 149 (25), 135 (85), 95 (43), 43 (37); HRMS calcd for $\text{C}_{30}\text{H}_{52}\text{O}$ (M^+) 428.4018, found 428.4014.

(3 α ,5 α)-3,4,4-Trimethylcholest-6-en-3-ol (17): ^1H NMR (main peaks) δ 0.66 (s, 3 H), 1.19 (s, 3 H), 5.56 (br s, 2 H); ^{13}C NMR (main peaks) δ 12.11 (q), 14.17 (q), 34.25 (t), 34.25 (t), 34.68 (t), 37.00 (d), 53.00 (d), 54.49 (d), 126.88 (d), 130.40 (d); MS m/z (relative intensity) 410 (M^+ – 18, 2), 297 (1), 147 (5), 136 (8), 122 (20), 121 (18), 105 (18), 69 (20), 55 (46), 43 (100); HRMS (1:5 mixture) calcd for $\text{C}_{30}\text{H}_{52}\text{O}$ (M^+) 428.4018, found 428.4017.

(3 α ,5 α)-3,4,4-Trimethylcholest-7-en-3-ol (18): ^1H NMR (main peaks) δ 0.50 (s, 3 H), 0.83 (d, J = 6.7 Hz, 6 H), 0.84 (s, 3 H), 0.85 (s, 3 H), 0.98 (s, 3 H), 0.90 (d, J = 6.3 Hz, 3 H), 1.18 (s, 3 H), 5.20 (m, 1 H); ^{13}C NMR (main peaks) δ 11.77 (q), 15.05 (q), 18.82 (q), 20.96 (t), 23.52 (t), 23.90 (t), 24.41 (q), 27.96 (d), 36.10 (t), 36.18 (d), 48.39 (d), 52.46 (d), 54.86 (d), 56.05 (d), 75.20 (s), 118.18 (d), 138.79 (s); MS m/z (relative intensity) 428 (M^+ , 0.4), 161 (4), 149 (4), 119 (9), 95 (13), 71 (38), 69 (16), 57 (31), 55 (26), 43 (100).

c. The general procedure was employed by using 0.252 g (0.48 mmol) of **3**. Workup and flash chromatography (100:1 to 2:1 petroleum ether (bp 40–60 °C)/EtOAc) afforded 0.040 g (20%) of **19**, 0.026 g (13%) of **20**, 0.045 g (22%) of **21**, 0.012 g (6%) of **22**, and 0.043 g (17%) of unreacted **3**. The spectroscopic data of **19**–**22** are shown below.

19: ^1H NMR δ 0.63 (s, 3 H), 0.84 (d, J = 6.6 Hz, 6 H), 0.80–2.16 (m, 23 H), 0.89 (d, J = 6.5 Hz, 3 H), 0.96 (s, 3 H), 1.54 (br s, 3 H), 1.64 (br s, 3 H), 2.04 (s, 3 H), 2.44 (m, 1 H), 4.86 (br d, J = 10.7 Hz, 1 H), 4.89 (dd, J = 1.5, 17.6 Hz, 1 H); 5.01 (br t, J = 7.0 Hz, 1 H), 5.61 (dd, J = 10.7, 17.6 Hz, 1 H); ^{13}C NMR δ 11.34 (q), 16.60 (q), 17.55 (q), 18.59 (q), 21.52 (t), 22.49 (q), 22.66 (t), 22.74 (q), 23.73 (t), 25.04 (t), 25.63 (q), 27.94 (t), 27.94 (d), 34.61 (q), 35.76 (d), 36.01 (t), 38.97 (t), 39.42 (t), 40.63 (t), 42.14 (s), 43.07 (s), 45.32 (d), 51.42 (d), 53.61 (d), 54.95 (d), 112.09 (t), 124.84 (d), 131.08 (s), 147.66 (d), 213.82 (s); MS m/z (relative intensity) 428 (M^+ , 11), 411 (31), 410 (100), 396 (17), 395 (51), 137 (46), 121 (14), 109 (11), 95 (19), 43 (13); HRMS calcd for $\text{C}_{30}\text{H}_{52}\text{O}$ (M^+) 428.4018, found 428.4014.

20: ^1H NMR δ 0.68 (s, 3 H), 0.72 (s, 3 H), 0.85 (d, J = 6.6 Hz, 6 H), 0.82–2.03 (m, 28 H), 0.91 (d, J = 6.5 Hz, 3 H), 1.27 (s, 3 H), 1.75 (s, 3 H), 2.71 (m, 1 H), 4.82 (d, J = 7.7 Hz, 2 H); ^{13}C NMR δ 12.37 (q), 13.47 (q), 18.90 (q), 22.52 (q), 22.75 (q), 23.76 (2t), 25.24 (q), 27.75 (t), 27.76 (t), 27.96 (d), 28.45 (t), 32.30 (q), 35.64 (d), 36.12 (t), 39.48 (t), 39.82 (s), 39.82 (2t), 41.31 (t), 44.50 (d), 44.50 (s), 46.04 (d), 47.46 (d), 51.28 (d), 51.50 (d), 55.10 (d), 73.71 (s), 110.62 (t), 148.13 (s); MS m/z (relative intensity) 428 (M^+ , 73), 413 (25), 411 (29), 410 (100), 395 (54), 161 (25), 121 (38), 109 (32), 95 (35), 43 (38); HRMS calcd for $\text{C}_{30}\text{H}_{52}\text{O}$ (M^+) 428.4018, found 428.4013.

21: ^1H NMR δ 0.60 (s, 3 H), 0.68 (s, 3 H), 0.80–2.33 (m, 28 H), 0.85 (d, J = 6.9 Hz, 6 H), 0.91 (d, J = 6.4 Hz, 3 H), 1.28 (s, 3 H), 1.58 (br s, 3 H), 1.69 (br s, 3 H); ^{13}C NMR δ 12.35 (q), 13.30 (q), 18.90 (q), 19.84 (q), 22.53 (q), 22.76 (q), 22.91 (q), 23.68 (t), 23.75 (t), 27.74 (t), 27.97 (d), 28.48 (t), 29.22 (t), 32.30 (q), 35.65 (d), 36.12 (t), 37.43 (t), 39.49 (t), 39.86 (t),

43.36 (t), 44.05 (d), 44.27 (s), 44.41 (s), 49.41 (d), 49.79 (d), 51.19 (d), 55.13 (d), 73.33 (s), 121.47 (s), 135.42 (s); MS m/z (relative intensity) 428 (M^+ , 8), 411 (29), 410 (100), 395 (40), 367 (32), 163 (17), 137 (19), 109 (18), 95 (22), 43 (22); HRMS calcd for $C_{30}H_{52}O$ (M^+) 428.4018, found 428.4016.

22: 1H NMR δ 0.68 (s, 3 H), 0.80–2.33 (m, 27 H), 0.85 (d, J = 6.3 Hz, 6 H), 0.89 (s, 3 H), 0.91 (d, J = 6.7 Hz, 3 H), 0.93 (d, J = 6.8 Hz, 3 H), 0.99 (d, J = 6.8 Hz, 3 H), 1.29 (s, 3 H), 2.65 (qq, J = 6.8, 6.8 Hz, 1 H); ^{13}C NMR δ 12.38 (q), 18.10 (q), 18.99 (q), 21.26 (q), 22.21 (q), 22.56 (q), 22.79 (q), 23.34 (t), 23.83 (t), 26.23 (d), 27.82 (t), 28.01 (d), 28.37 (t), 28.57 (t), 30.48 (q), 35.62 (d), 36.17 (t), 37.72 (t), 39.54 (t), 39.82 (t), 40.37 (t), 44.42 (s), 45.63 (d), 49.57 (s), 50.77 (d), 51.39 (d), 55.06 (d), 73.06 (s), 136.14 (s), 140.88 (s); MS m/z (relative intensity) 428 (M^+ , 11), 411 (35), 410 (96), 395 (78), 367 (48), 189 (22), 161 (25), 137 (100), 121 (20), 43 (31); HRMS calcd for $C_{30}H_{52}O$ (M^+) 428.4018, found 428.4017.

d. The general procedure was employed by using 0.213 g (0.41 mmol) of **4**. Workup and flash chromatography (250:1 to 2:1 petroleum ether (bp 40–60 °C)/EtOAc) afforded 0.084 g (48%) of **24**, 0.048 g (27%) of an inseparable 1:3.5 mixture³⁸ of **23** and **25**, respectively, and 0.005 g (2%) of unreacted **4**. The spectroscopic data of **23**,³⁹ **24**, and **25**³⁹ are shown below.

(5 α ,7 α)-4,4,7-Trimethylcholest-2-en-7-ol (23): 1H NMR (main peaks) δ 0.66 (s, 3 H), 0.84 (d, J = 6.5 Hz, 6 H), 1.29 (s, 3 H), 5.33–5.52 (m, 2 H); ^{13}C NMR (main peaks) δ 12.14 (q), 12.91 (q), 31.46 (q), 39.73 (t), 42.55 (t), 44.04 (d), 45.01 (d), 50.04 (d), 51.41 (d), 121.64 (d), 137.64 (d); MS m/z (relative intensity) 410 (M^+ – 18, 5), 395 (5), 161 (15), 147 (14), 137 (63), 121 (74), 119 (43), 109 (50), 107 (61), 69 (100); HRMS (1:3.5 mixture) calcd for $C_{30}H_{52}O$ (M^+) 428.4018, found 428.4020.

(3 β ,7 α)-3,4,7-Trimethylcholest-4-en-7-ol (24): 1H NMR (C_6D_6) δ 0.70 (s, 3 H), 0.80–2.15 (m, 28 H), 0.92 (d, J = 6.1 Hz, 6 H), 0.95 (s, 3 H), 0.95 (d, J = 6.4 Hz, 3 H), 1.00 (d, J = 6.3 Hz, 3 H), 1.32 (s, 3 H), 1.63 (s, 3 H); ^{13}C NMR (C_6D_6) δ 12.35 (q), 16.63 (q), 18.93 (q), 19.91 (2q), 22.29 (t), 22.48 (q), 22.75 (q), 24.08 (t), 27.82 (t), 28.11 (d), 28.79 (2t), 30.61 (q), 35.87 (2d), 36.33 (t), 36.50 (t), 37.71 (s), 39.62 (t), 40.16 (t), 42.90 (t), 43.90 (s), 45.24 (d), 50.48 (d), 51.79 (d), 55.31 (d), 73.18 (s), 131.69 (s), 134.10 (s); MS m/z (relative intensity) 428 (M^+ , 11), 411 (33), 410 (100), 396 (22), 395 (59), 187 (13), 163 (14), 137 (47), 95 (28); HRMS calcd for $C_{30}H_{52}O$ (M^+) 428.4018, found 428.4018.

(5 α ,7 α)-3,4,7-Trimethylcholest-3-en-7-ol (25): 1H NMR (main peaks) δ 0.67 (s, 3 H), 0.84 (d, J = 6.5 Hz, 6 H), 1.27 (s, 3 H), 1.53 (s, 3 H), 1.58 (s, 3 H); ^{13}C NMR (main peaks) δ 11.90 (q), 12.35 (q), 15.45 (q), 18.84 (q), 19.38 (d), 21.54 (t), 22.54 (q), 22.78 (q), 27.98 (d), 29.58 (t), 32.25 (q), 35.72 (d), 36.10 (t), 43.10 (d), 43.76 (d), 49.29 (d), 51.74 (d), 55.07 (d), 72.58 (s), 125.11 (s), 126.08 (s); MS m/z (relative intensity) 410 (M^+ – 18, 2), 395 (2), 135 (7), 121 (10), 119 (6), 109 (14), 107 (10), 95 (21), 57 (31), 43 (100).

e. The general procedure was employed by using 0.168 g (0.28 mmol) of **5**. Workup and flash chromatography (100:1 to 50:1 petroleum ether (bp 40–60 °C)/EtOAc) gave 0.024 g (17%) of a complex mixture of at least five apolar compounds and 0.111 g (66%) of unreacted **5**.

f. The general procedure was employed by using 0.191 g (0.32 mmol) of **6**. Workup and flash chromatography (100:1 to 2:1 petroleum ether (bp 40–60 °C)/EtOAc) afforded 0.044 g (27%) of an inseparable ca. 1:1 mixture³⁸ of **26** and **27** and 0.111 g (58%) of unreacted **6**. The spectroscopic data of **26** and **27** are shown below.⁴⁰

(5 α ,7 α)-4,4,7-Trimethyl-7-[(trimethylsilyl)oxy]cholest-2-ene (26): 1H NMR (main peaks) δ

0.10 (s, 9 H), 0.65 (s, 3 H), 0.86 (d, $J = 6.3$ Hz, 6 H), 0.94 (s, 3 H), 1.32 (s, 3 H), 5.35–5.55 (m, 2 H); ^{13}C NMR (main peaks) δ 2.65 (3q), 18.91 (q), 20.96 (t), 24.00 (t), 28.60 (t), 32.07 (q), 40.19 (t), 40.98 (t), 44.58 (d), 46.01 (d), 49.12 (d), 51.29 (d), 75.70 (s), 121.93 (d), 137.79 (d); MS m/z (relative intensity) 418 ($\text{M}^+ - 82$, 5), 210 (4), 175 (6), 143 (9), 95 (18), 81 (17), 75 (31), 73 (60), 57 (32), 43 (100); HRMS (1:1 mixture) calcd for $\text{C}_{33}\text{H}_{60}\text{OSi}$ (M^+) 500.4414, found 500.4416.

(5 α ,7 α)-3,4,7-Trimethyl-7-[(trimethylsilyl)oxy]cholest-3-ene (27): ^1H NMR (main peaks) δ 0.10 (s, 9 H), 0.63 (s, 3 H), 0.83 (d, $J = 6.5$ Hz, 6 H), 1.26 (s, 3 H), 1.54 (br s, 3 H), 1.60 (br s, 3 H); ^{13}C NMR (main peaks) δ 2.65 (3q), 19.35 (q), 21.48 (t), 27.70 (t), 29.74 (t), 31.80 (q), 45.62 (d), 48.50 (d), 51.72 (d), 75.91 (s), 124.82 (s), 126.63 (s); MS m/z (relative intensity) 410 ($\text{M}^+ - 90$, 22), 396 (30), 201 (21), 179 (16), 161 (17), 109 (51), 75 (69), 73 (79), 57 (100), 43 (75).

5.4 References and Notes

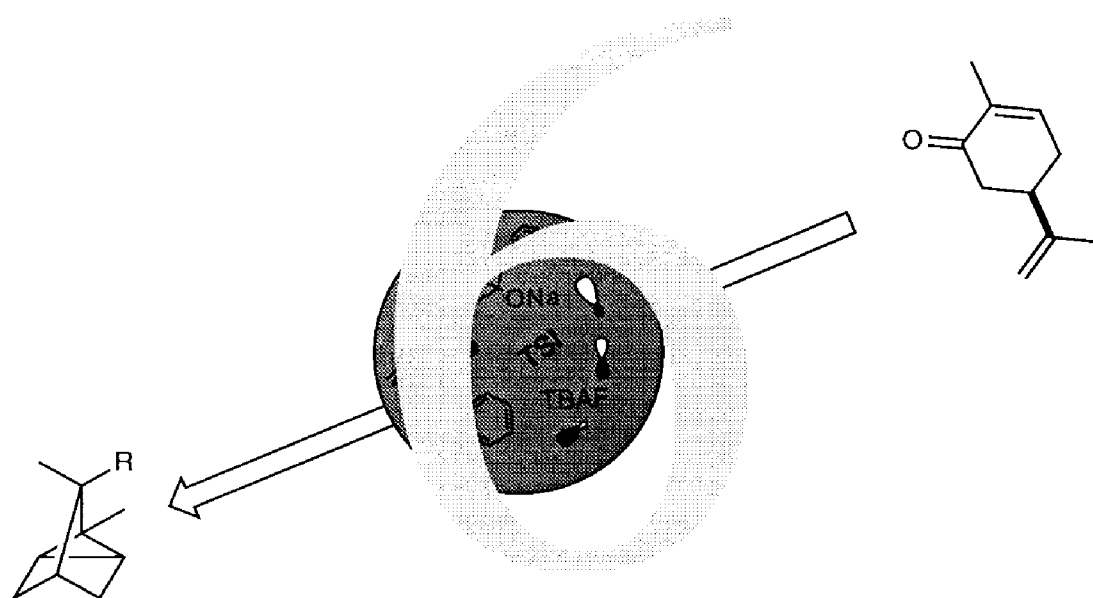
- Grob, C. A. *Angew. Chem.* **1969**, *81*, 543.
- Gleiter, R.; Stohrer, W.-D.; Hoffmann, R. *Helv. Chim. Acta* **1972**, *55*, 893.
- For an extensive review of the Wharton reaction, see: Caine, D. *Org. Prep. Proced. Int.* **1988**, *20*, 1.
- Wijnberg, J. B. P. A.; Jenniskens, L. H. D.; Brunekreef, G. A.; de Groot, A. *J. Org. Chem.* **1990**, *55*, 941.
- Jenniskens, L. H. D.; Wijnberg, J. B. P. A.; de Groot, A. *J. Org. Chem.* **1991**, *56*, 6585.
- (a) Orrü, R. V. A.; Wijnberg, J. B. P. A.; Jenniskens, L. H. D.; de Groot, A. *J. Org. Chem.* **1993**, *58*, 1199. (b) Orrü, R. V. A.; Wijnberg, J. B. P. A.; Bouwman, C. T.; de Groot, A. *J. Org. Chem.* **1994**, *59*, 374. (c) Bastiaansen, P. M. F. M.; Wijnberg, J. B. P. A.; de Groot, A. *J. Org. Chem.* **1995**, *60*, 4240. (d) Orrü, R. V. A.; Wijnberg, J. B. P. A.; de Groot, A. *J. Org. Chem.* **1995**, *60*, 4233.
- Paddon-Row, M. N.; Hartcher, R. *J. Am. Chem. Soc.* **1980**, *102*, 671.
- Grob, C. A.; Rich, R. *Helv. Chim. Acta* **1979**, *62*, 2793 and references cited therein.
- Seven-center Beckmann-type fragmentations are known in the literature: (a) Eisele, W.; Grob, C. A.; Renk, E.; von Tschammer, H. *Helv. Chim. Acta* **1968**, *51*, 817. (b) Ibuka, T.; Mitsui, Y.; Hayashi, K.; Minakata, H.; Inubushi, Y. *Tetrahedron Lett.* **1981**, *22*, 4425. Also, seven-center fragmentations in which double bonds and/or highly strained ring systems are involved have been reported. For example, see: (c) Ho, T.-L. In *Heterolytic Fragmentation of Organic Molecules*; Wiley-Interscience: New York, 1993; Chapter 9 and references cited therein.
- Adcock, W.; Krstic, A. R.; Duggan, P. J.; Shiner, V. J., Jr.; Coope, J.; Ensinger, M. W. *J. Am. Chem. Soc.* **1990**, *112*, 3140.
- (a) Adcock, W.; Coope, J.; Shiner, V. J., Jr.; Trout, N. A. *J. Org. Chem.* **1990**, *55*, 1411. (b) Lambert, J. B.; Salvador, L. A.; So, J.-H. *Organometallics* **1993**, *12*, 697.
- An electrofugal group can act as an electron donor in heterolytic fragmentation and splits off without the bonding electron pair: Grob, C. A. *Angew. Chem., Int. Ed. Engl.* **1969**, *8*, 535.
- It has been demonstrated that an alcoholate group is a very active electrofuge in both the Wharton fragmentation³ and the base-induced homofragmentation of 1,4-diol monosulfonate esters in apolar solvents like benzene or toluene.^{6a-c}

- 14 This structural feature guarantees that (a) the extent of orbital interactions through σ -bonds is maximized and (b) the five σ -bonds involved are properly aligned for fragmentation. See: (a) Jordan, K. D.; Paddon-Row, M. N. *Chem. Rev.* **1992**, 92, 395. (b) Ref 11b.
- 15 In general, fragmentations that lead to ketones occur more readily than those producing aldehydes.³
- 16 Fragmentation products containing more highly substituted olefins are more easily formed than those containing less highly substituted olefins. See: ref 3 and ref 9(c), p 7.
- 17 The numbering system for the cholestane derivatives used in this chapter follows the original steroid numbering.
- 18 Davies, A. R.; Summers, G. H. R. *J. Chem. Soc. (C)* **1967**, 1227.
- 19 The stereochemistry of the hydroxyl group at C(7) could not be established by NMR measurements. Since in the Grignard reaction of **12** the favored attack of the reagent is from the β side (see Scheme 4.3), a similar preferential approach is assumed to occur in the Grignard reaction leading to **1**.
- 20 Woodward, R. B.; Patchett, A. A.; Barton, D. H. R.; Ives, D. A. J.; Kelly, R. B. *J. Chem. Soc.* **1957**, 1131.
- 21 Parish, E. J.; Wei, T.-Y. *Synth. Commun.* **1987**, 17, 1227.
- 22 The stereochemistry of the hydroxyl group at C(3) could not be established by NMR measurements. Since the nucleophilic addition of MeLi to cholestan-3-one and 4a-methyl-*trans*-3-decalone at -78°C proceeds preferentially from the equatorial β side, the stereochemistry at C(3) was tentatively assigned as given in structure **11**. See: Macdonald, T. L.; Clark Still, W. *J. Am. Chem. Soc.* **1975**, 97, 5280 and references cited therein. In this context, it is important to note that the reactivity of 1,4-diol monosulfonate esters upon treatment with sodium *tert*-amylate in refluxing benzene is not affected by the orientation of the hydroxyl group.^{6b}
- 23 Kooijman, H.; Spek, A. L. manuscript in preparation.
- 24 Toluene as solvent was preferred over benzene because it was expected that the reactivity of the mesylates studied would be moderate.
- 25 The percentages of recovered starting material were somewhat lowered (up to 7%) by competing S-O bond scission.
- 26 Treatment of (3 β ,5 α ,7 α)-cholestane-3,7-diol 3-(methanesulfonate) with sodium *tert*-amylate in refluxing toluene afforded a complex mixture of products, probably as a result of alkoxide-induced intermolecular hydride shifts.^{6c}
- 27 Cragg, G. M. L.; Davey, C. W.; Hall, D. N.; Meakins, G. D.; Richards, E. E.; Whateley, T. L. *J. Chem. Soc. (C)* **1966**, 1266.
- 28 It might be possible that the yield of this product was somewhat diminished due to aldol condensations under the influence of sodium *tert*-amylate.^{6a}
- 29 (a) Jensen, F. R.; Smart, B. E. *J. Am. Chem. Soc.* **1969**, 91, 5686. (b) Traylor, T. G.; Hanstein, W.; Berwin, H. J.; Clinton, N. A.; Brown, R. S. *J. Am. Chem. Soc.* **1971**, 93, 5715.
- 30 Enhanced TBI should lead to increased fragmentation.¹⁰
- 31 Biemann, R.; Grob, C. A.; Kury, D.; Wei Yao, G. *Helv. Chim. Acta* **1985**, 68, 2158.
- 32 Since intramolecular alkoxide-assisted elimination is a highly favorable process,^{6a} the formation of **21** from intermediate **3(C)** via an intermolecular proton abstraction will only be a minor reaction pathway.
- 33 Paddon-Row, M. N.; Patney, H. K.; Brown, R. S.; Houk, K. N. *J. Am. Chem. Soc.* **1981**, 103, 5575.
- 34 Levisalles, J.; Pète, J.-P. *Bull. Soc. Chim. Fr.* **1967**, 3747.

- 35 Arad, A.; Levisalles, J. *Bull. Soc. Chim. Fr.* **1972**, 1135.
- 36 For a general description of the experimental procedures employed in this chapter, see Chapter 2. GC analysis was carried out with FID and a DB-5MS fused silica column, 15 m \times 0.25 mm i.d., film thickness 0.10 μ m, and H₂ as carrier gas. For GCMS analysis the same DB-5MS column was used.
- 37 The NMR spectrum of this crude product revealed the presence of unreacted (5 α ,7 β)-7-hydroxy-4,4-dimethylcholestan-3-one (~ 30%) and, probably, the C(3) epimer of **11** (~ 10%).
- 38 This ratio was determined by ¹H NMR analysis.
- 39 The mass spectral data of this compound were obtained by GCMS analysis.
- 40 Careful column chromatography afforded a small sample of a ca.1:2 mixture of **26** and **27**, respectively. With this mixture the structures of **26** and **27** could be established by spectroscopic analysis (¹H and ¹³C NMR, and GCMS).

Chapter 6

A New Enantiospecific Synthesis of α -Santalanes via Homofragmentation



Abstract. The homofragmentation of 1,4-diol monosulfonate esters was applied as a key step in the synthesis of α -santalanes. The enantiospecific synthesis of (+)- α -santalan-12-one (**1d**) was achieved via the tricyclic dione **2** which, in turn, could easily be obtained from (*R*)-(-)-carvone. A 1,2-carbonyl transposition in dione **2** followed by functional group transformations afforded the tricyclic 1,4-diol monomesylate **3**, which could be homofragmented to the tricyclic aldehyde **4** in 76% yield. From this compound the synthesis of several α -santalanes can be achieved; the synthesis of **1d** was accomplished in 11 steps from **2** in 8% overall yield.

This chapter has been published for the greater part: Bastiaansen, P. M. F. M.; Wijnberg, J. B. P. A.; de Groot, A. *J. Org. Chem.* **1996**, *61*, 4955.

6.1 Introduction

The detailed studies on the chemical consequences of long-range orbital interactions in the stereochemically rigid *trans*-perhydronaphthalene- and norbornane-1,4-diol monosulfonate esters have shown that the chief pathways by which these compounds react upon treatment with strong base in nonpolar solvents are rearrangement, β -elimination, and homofragmentation.¹

The synthetic utility of the rearrangement and elimination reaction of *trans*-perhydronaphthalene-1,4-diol monosulfonate esters has been demonstrated in the total syntheses of guaiane² and alloaromadendrane sesquiterpenes³ (see also Chapter 2, Section 1.1). In this chapter the applicability of the homofragmentation reaction of 1,4-diol monosulfonate esters in the synthesis of α -santalane sesquiterpenes having the tricyclic ring system **1** as a common structural feature is described (Chart 6.1).

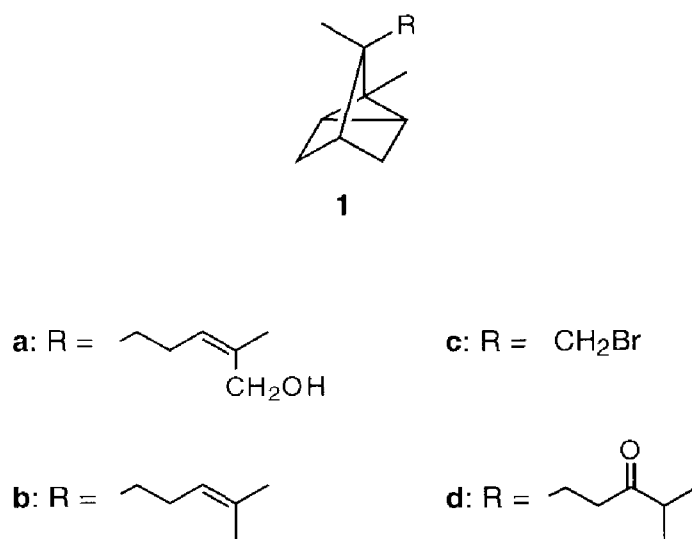
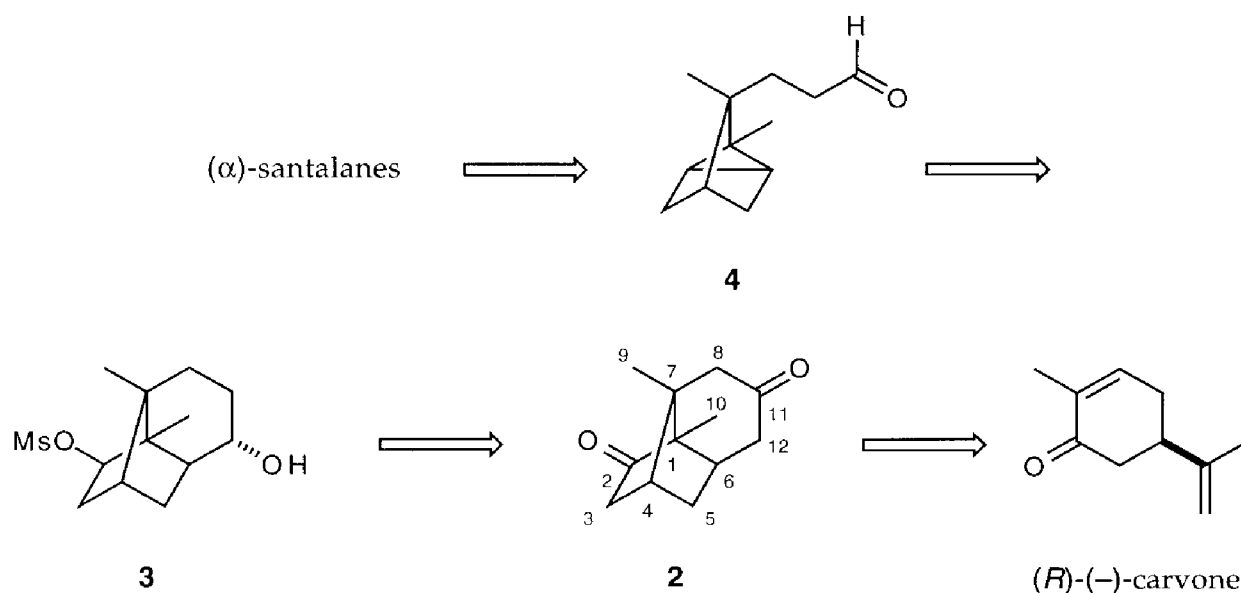


Chart 6.1

α -Santalanes belong to the characteristic components of East Indian sandalwood oil^{4,5} and lavender oil,⁶ two important essential oils in perfumery. From the α -santalanes that are of sensory importance, (+)-(Z)- α -santalol (**1a**) and (+)- α -santalene (**1b**) have received the most synthetic attention.⁷ All enantiospecific syntheses of **1a**, **1b**, and other α -santalanes started with (-)- π -bromotricyclene (**1c**), which can be prepared from (+)-camphor in a four-step reaction sequence.⁸

In the synthetic approach to the α -santalane ring skeleton, the recently described tricyclic dione **2**,⁹ easily prepared from (*R*)-(-)-carvone,¹⁰ was used as the starting material (Scheme 6.1). A 1,2-transposition of the C(11) carbonyl to C(12) was needed to convert **2** into the mesylate **3**.¹¹ The key step in this approach, the transformation of mesylate **3** to aldehyde **4**, involved a base-induced homofragmentation reaction in which the C(2)–C(6) bond formation occurs with simultaneous breaking of the C(6)–C(12) bond.^{1a–c} With aldehyde **4** in hand, further elaboration to α -santalanes is demonstrated by the enantiospecific synthesis of (+)- α -santalane-12-one (**1d**), recently isolated from *Severinia buxifolia*.¹²

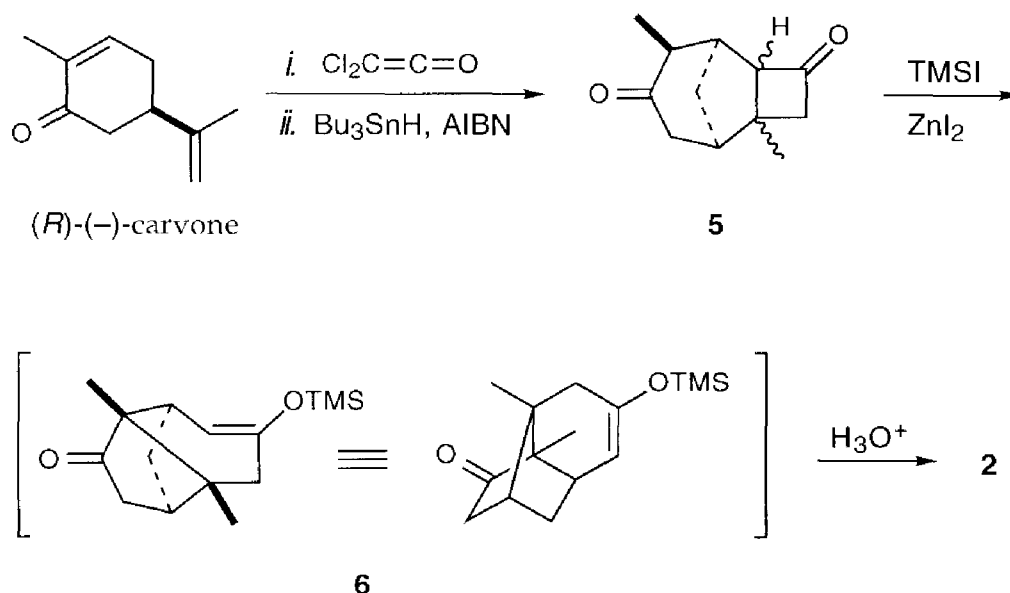


Scheme 6.1

6.2 Results and Discussion

The starting material, the tricyclic dione **2**, was obtained in ca. 30% overall yield from (*R*)-(-)-carvone following the procedure recently described in the literature^{9b} (Scheme 6.2). In order to achieve an oxygen function at C(12), α -hydroxylation of the silyl enol ether **6** seemed to be the easiest way.¹³ As depicted in Scheme 6.2, **6** was postulated as an intermediate in the TMSI-promoted cyclobutane ring opening of **5** and was thought to give the dione **2** only upon hydrolytic workup. With this in mind, it was tried to modify the reaction conditions for cyclobutane ring opening in such a way that isolation of silyl enol ether **6** could be achieved. However, all attempts failed and led only to dione **2**. The preparation of **6** from dione **2** under kinetically as well as thermodynamically controlled conditions also failed; in all cases a strong preference for the formation of the silyl enol ether with the double

bond in the C(8)–C(11) position was observed. These disappointing results forced us to develop an alternative route for introduction of an oxygen function at C(12).



Scheme 6.2

From the enolization experiments with dione **2**, it appeared that the double bond in the C(8)–C(11) position is energetically more favorable than in the C(11)–C(12) position. It was therefore expected that elimination of an axial hydroxyl group at C(11) would result in the selective formation of the C(8)–C(11) double bond. Via allylic oxidation, the planned 1,2-transposition of the carbonyl function (C(11) \rightarrow C(12)) then can be achieved.

The introduction of an axial hydroxyl group at the C(11) position of dione **2** was accomplished with L-Selectride giving the diol **7** as the sole product in 77% yield (Scheme 6.3). The ^1H NMR spectrum of **7** shows a double double double doublet with $J = 2.9, 4.7, 7.8,$ and 7.8 Hz at δ 4.16, which is consistent with an axial hydroxyl group at C(11). The exo orientation of the hydroxyl group at C(2) in **7** was concluded from comparison with camphor, which was stereoselectively reduced to isborneol upon treatment with L-Selectride.¹⁴ Because the hydroxyl group at C(2) and the hydrogen atoms at C(3) in **7** are not properly aligned for an anti elimination, it was expected that selective elimination of the axial hydroxyl group at C(11) would be possible. For that purpose, diol **7** was treated with a catalytic amount of *p*-TsOH in refluxing toluene. After a reaction time of 11 h, the yield of olefin **8** was 66% on the basis of recovered **7**. Products resulting from an acid-catalyzed Wagner-Meerwein rearrangement, often observed with camphor-like systems,¹⁵ were not isolated. The C(8)–C(11) position of the double bond in **8**

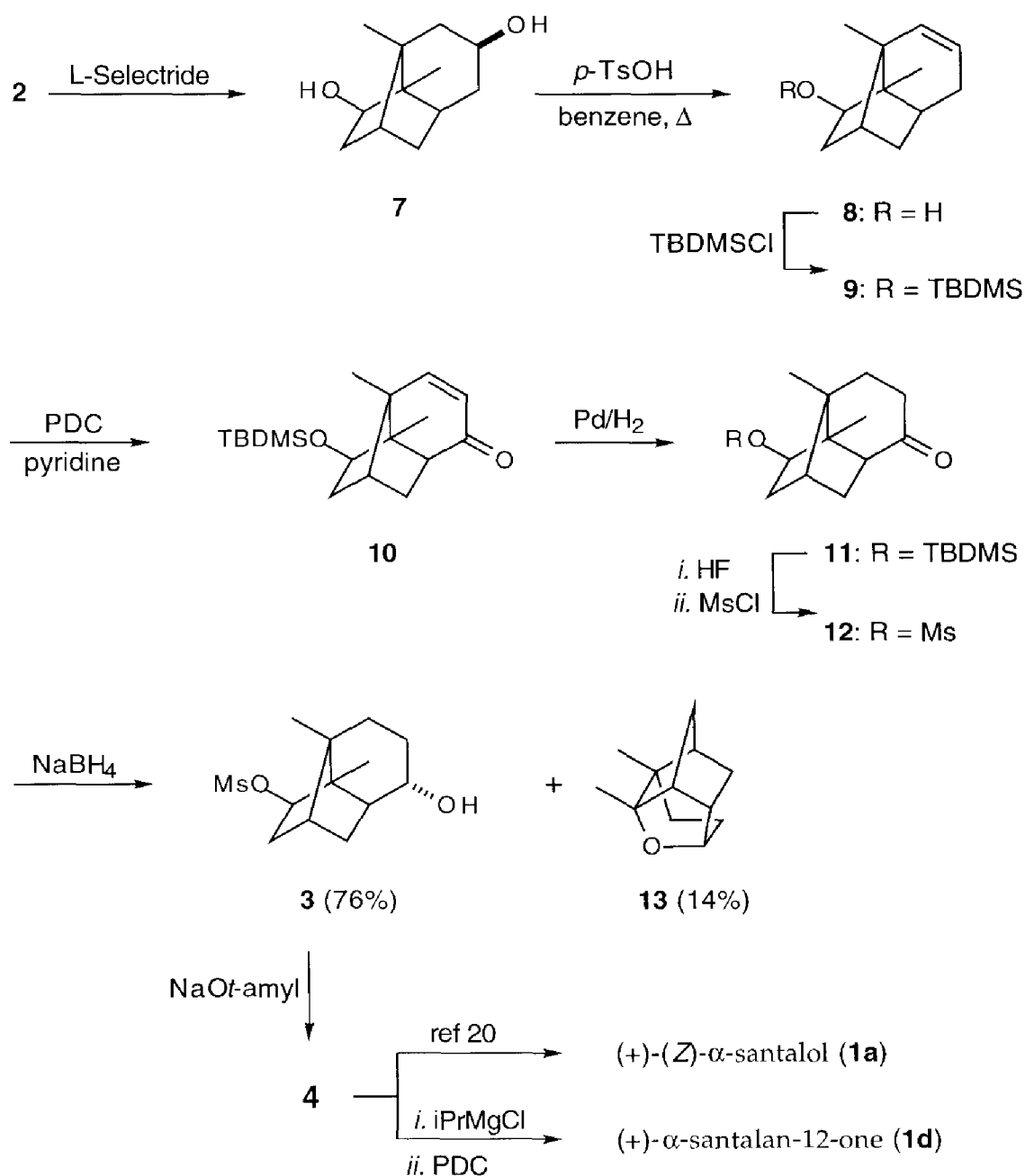
follows from its COSY and ^1H - ^{13}C heteronuclear shift correlation spectrum. After protection of the hydroxyl group at C(2) as its TBDMS ether (**8** \rightarrow **9**), allylic oxidation with excess PDC in refluxing pyridine¹⁶ afforded the enone **10** in ca. 50% overall yield from **8**. The appearance of a one-proton doublet with $J = 9.7$ Hz at δ 6.52 in the ^1H NMR spectrum of **10** is consistent with the C(8)=C(11)-C(12)=O unit. Catalytic reduction of the double bond in **10** produced the saturated ketone **11** in 87% yield.

At this stage, the straightforward conversion of **11** into (+)- α -santalene-12-one (**1d**) was investigated. It was hoped that addition of isopropylmagnesium chloride (iPrMgCl) to the C(12) carbonyl of **11**, followed by conversion of the TBDMS ether group at C(2) into a mesylate group, would give a product that should homofragmentate to **1d** upon heating with sodium *tert*-amylate in benzene.¹ However, treatment of **11** with iPrMgCl or its cerium analog¹⁷ did not give any addition product; only starting material was recovered. Probably due to steric hindrance, nucleophilic addition to the carbonyl group of **11** was hampered, and instead, enolization had taken place.

Confronted with this negative result, the original strategy via the mesylate **3** was followed again (see Scheme 6.1). Thus, cleavage of the TBDMS ether bond in **11** with aqueous HF in MeCN at 55 °C and subsequent treatment of the intermediate keto alcohol with MsCl in the presence of DMAP afforded the mesylated ketone **12** in 85% yield. The reduction of the carbonyl function of **12** was accomplished with NaBH₄ in EtOH at room temperature and gave, along with the desired mesylate **3** (76%), a small amount (14%) of the cyclic ether **13**. The ^1H NMR spectrum of **3** shows a double double doublet with $J = 3.4, 3.4,$ and 6.9 Hz at δ 3.90 indicating an axial hydroxyl group at C(12). The formation of the cyclic ether **13** can be explained by a Wagner-Meerwein rearrangement followed by direct trapping of the positive charge at C(1) by the hydroxyl function at C(12).

The key step in the synthetic plan to α -santalanes, the homofragmentation reaction of **3** into aldehyde **4**, was investigated next. From the previous work on the chemical consequences of long-range orbital interactions,^{1c} it is known that the yield of aldehydes obtained via homofragmentation is considerably lowered by aldol condensation reactions. In order to suppress these yield-lowering reactions as much as possible, a dilute solution of **3** (0.01 M in benzene) was treated with 2 equiv of sodium *tert*-amylate at reflux temperature for 1 min. In this way, the aldehyde **4**, better known as tricycloekasantalal, was obtained in 76% yield.¹⁸ Our synthetic **4** was spectroscopically identical to the natural product isolated from sandalwood oil¹⁹ and can be used to prepare (+)-(*Z*)- α -santalol (**1a**) as previously reported.²⁰

The synthesis of (+)- α -santalol (**1a**) was completed by treatment of **4** with $i\text{PrMgCl}$ in ether followed by oxidation of the adduct with PDC in CH_2Cl_2 , affording **1d** in 73% yield. The spectroscopic data of synthetic **1d** were identical with those reported in the literature.^{6,12} The synthesis of **1d** requires 11 steps from dione **2** and proceeds in ca. 8% overall yield.²¹



Scheme 6.3

In an attempt to develop a more direct approach to **1d**, the mesylate **3** was treated with excess *i*PrMgCl in refluxing benzene. It was hoped that *i*PrMgCl would act first as a base to achieve homofragmentation to **4** and then as a trapping reagent of the resulting aldehyde function. With such a procedure aldol condensation reactions could also be avoided. However, the reaction of **3** with *i*PrMgCl only led to the selective formation of the cyclic ether **13**. Apparently, the electron-donating ability of the alkoxide group with MgCl⁺ as counter ion, produced after deprotonation of **3** by *i*PrMgCl, is not strong enough for the induction of homofragmentation, and consequently, only rearrangement resulting in cyclic ether formation take place.^{1b}

Summarizing these results, we may state that our "carvone" route to α -santalanes represents a nice illustration of the applicability of the homofragmentation reaction in natural product synthesis and presents an attractive alternative for the commonly applied "camphor" route. Like camphor, carvone is an excellent chirogen on account of its commercial availability in both optical isomers and thus allows the enantiospecific synthesis of both enantiomeric forms of the α -santalanes.

6.3 Experimental Section

General.²² The dione **2** was prepared as previously described.^{9b}

(-)-(3*R*,7*R*)-5,6-Dimethyltricyclo[4.4.0.0^{5,9}]decane-3,7-diol (7). To a stirred solution of 2.03 g (10.57 mmol) of **2** in 100 mL of dry THF was slowly added dropwise 29.0 mL of L-Selectride (1 M in THF) at 0 °C. The solution was stirred at 0 °C for 30 min and at rt for 1 h, and then 150 mL of 75% aqueous EtOH was carefully added at 0 °C. After being stirred at rt for 2 h, the reaction mixture was treated with 75 mL of 4 M aqueous NaOH and 225 mL of 30% H₂O₂ at 0 °C. The reaction mixture was stirred at rt for another 16 h and then concentrated under reduced pressure. The remaining residue was mixed with 100 mL of water and extracted with three 100 mL portions of ether. The combined organic layers were dried and evaporated. Purification by flash chromatography (2:1 petroleum ether (bp 40–60 °C)/EtOAc) yielded 1.60 g (77%) of **7**: [α]_D –42.8° (c 0.71); ¹H NMR (400 MHz) δ 0.93 (s, 3 H), 1.00 (s, 3 H), 1.16 (dd, *J* = 8.5, 12.8 Hz, 1 H), 1.35–1.90 (m, 9 H), 2.03 (m, 1 H), 2.16 (ddd, *J* = 3.6, 7.6, 14.5 Hz, 1 H), 3.59 (dd, *J* = 4.5, 7.9 Hz, 1 H), 4.16 (dddd, *J* = 2.9, 4.7, 7.8, 7.8 Hz, 1 H); ¹³C NMR (50 MHz) δ 9.83 (q), 20.33 (q), 34.42 (t), 36.82 (t), 39.73 (d), 41.25 (t), 41.85 (t), 44.52 (d), 45.30 (s), 48.00 (s), 63.77 (d), 78.63 (d); MS *m/z* (relative intensity) 196 (M⁺, <1), 152 (31), 135 (12), 134 (100), 119 (25), 107 (12), 106 (14), 93 (11), 91 (9); HRMS calcd for C₁₂H₂₀O₂ (M⁺) 196.1463, found 196.1459. Anal. Calcd for C₁₂H₂₀O₂: C, 73.43; H, 10.27. Found: C, 73.41; H, 10.42.

(-)-(7*R*)-5,6-Dimethyl-7-hydroxytricyclo[4.4.0.0^{5,9}]dec-3-ene (8). To a solution of 1.06 g (5.46 mmol) of diol **7** in 400 mL of toluene was added 0.075 g of *p*-TsOH. The reaction mixture was refluxed under Dean-Stark conditions for 11 h. During this reflux period, two

additional 0.075 g portions of *p*-TsOH (one after 5 h, the other after 7 h) were added to the reaction mixture. The solution was allowed to come to rt and washed successively with two 100 mL portions of saturated aqueous NaHCO₃ and one 100 mL portion of brine. After drying and evaporation, the remaining residue was flash chromatographed (20:1 to 2:1 petroleum ether (bp 40–60 °C)/EtOAc) to give 0.517 g (54%) of **8**: [α]_D –108.8° (c 0.49); ¹H NMR (400 MHz) δ 0.90 (s, 3 H), 1.04 (s, 3 H), 1.18 (dd, *J* = 8.2, 12.3 Hz, 1 H), 1.32–1.44 (m, 2 H), 1.64 (br s, OH), 1.66–1.86 (m, 2 H), 1.87 dd, (*J* = 7.9, 12.6 Hz, 1 H), 2.04 (t, *J* = 4.4 Hz, 1 H), 2.26 (m, 1 H), 3.60 (dd, *J* = 4.8, 7.2 Hz, 1 H), 5.38 (ddd, *J* = 1.6, 1.6, 9.5 Hz, 1 H), 5.50 (dddd, *J* = 1.6, 1.6, 4.2, 9.5 Hz, 1 H); ¹³C NMR (100 MHz) δ 9.42 (q), 17.69 (q), 33.42 (t), 35.81 (t), 39.51 (d), 41.14 (t), 48.05 (s), 48.60 (s), 48.86 (d), 79.12 (d), 124.08 (d), 136.34 (d); MS *m/z* (relative intensity) 178 (M⁺, 79), 163 (30), 160 (67), 145 (70), 119 (100), 109 (86), 107 (71), 106 (66), 91 (85), 79 (43); HRMS calcd for C₁₂H₁₈O (M⁺) 178.1358, found 178.1356. Anal. Calcd for C₁₂H₁₈O: C, 80.85; H, 10.18. Found: C, 81.14; H, 10.39. Further elution afforded 0.198 g (19%) of unreacted **7**.

(–)-(7R)-5,6-Dimethyl-7-[(1,1-dimethylethyl)dimethylsilyl]oxy]tricyclo[4.4.0.0^{5,9}]-dec-3-ene (9). To a solution of 0.485 g (2.76 mmol) of **8** in 10 mL of DMF were added 0.335 g (4.92 mmol) of imidazole and 0.488 g (3.24 mmol) of TBDMSCl. The reaction mixture was stirred at rt for 22 h and at 60 °C for 3 h. Then an additional 0.488 g portion of TBDMSCl was added, and stirring was continued at 70 °C for 7 h. The reaction mixture was allowed to come to rt, and 0.25 mL of MeOH was added. After being stirred for 10 min, the mixture was poured into 150 mL of water and extracted with five 75 mL portions of ether. The combined organic layers were washed with 100 mL of brine, dried, and evaporated. Purification by flash chromatography (50:1 petroleum ether (bp 40–60 °C)/ether) gave 0.738 g (92%) of **9** as a clear oil: [α]_D –107.1° (c 1.00); ¹H NMR (200 MHz) δ 0.01 (s, 6 H), 0.80 (s, 3 H), 0.88 (s, 9 H), 0.99 (s, 3 H), 1.11 (dd, *J* = 8.1, 12.2 Hz, 1 H), 1.23–1.41 (m, 2 H), 1.55–1.80 (m, 3 H), 1.97 (t, *J* = 4.2 Hz, 1 H), 2.23 (m, 1 H), 3.47 (dd, *J* = 4.4, 7.2 Hz, 1 H), 5.35 (ddd, *J* = 1.6, 1.6, 9.5 Hz, 1 H), 5.46 (dddd, *J* = 1.6, 1.6, 4.2, 9.5 Hz, 1 H); ¹³C NMR (50 MHz) δ –5.14 (q), –4.61 (q), 9.66 (q), 17.05 (q), 17.93 (s), 25.78 (3q), 33.20 (t), 35.51 (t), 39.21 (d), 42.42 (t), 47.91 (s), 48.28 (s), 48.60 (d), 78.47 (d), 123.41 (d), 136.18 (d); MS *m/z* (relative intensity) 292 (M⁺, 6), 237 (5), 236 (20), 235 (100), 161 (12), 159 (13), 119 (10), 105 (7), 75 (61), 73 (10); HRMS calcd for C₁₈H₃₂OSi (M⁺) 292.2222, found 292.2221.

(–)-(7R)-5,6-Dimethyl-7-[(1,1-dimethylethyl)dimethylsilyl]oxy]tricyclo[4.4.0.0^{5,9}]-dec-3-en-2-one (10). To a stirred solution of 0.703 g (2.42 mmol) of **9** and 2.75 g of 4 Å molecular sieves in 120 mL of dry pyridine was added 12.0 g of PDC. The reaction mixture was refluxed for 6 h and, after cooling on an ice-bath, diluted with 1 L of ether. The organic layer was stirred at rt for 2 h, filtered through Celite, and evaporated. The remaining residue was flash chromatographed (50:1 petroleum ether (bp 40–60 °C)/ether) to yield 0.391 g (53%) of **10**: [α]_D –128.8° (c 0.49); ¹H NMR (200 MHz) δ 0.00 (s, 3 H), 0.01 (s, 3 H), 0.85 (s, 3 H), 0.86 (s, 9 H), 1.22 (s, 3 H), 1.41–1.68 (m, 3 H), 1.87 (m, 1 H), 1.98–2.12 (m, 3 H), 3.43 (dd, *J* = 4.4, 7.4 Hz, 1 H), 5.87 (dd, *J* = 1.8, 9.7 Hz, 1 H), 6.52 (d, *J* = 9.7 Hz, 1 H); ¹³C NMR (50 MHz) δ –5.14 (q), –4.63 (q), 9.72 (q), 16.89 (q), 17.89 (s), 25.74 (3q), 32.88 (t), 43.04 (d), 43.30 (t), 51.97 (s), 55.86 (d), 60.36 (s), 77.08 (d), 126.57 (d), 155.78 (d), 203.75 (s); MS *m/z* (relative intensity) 306 (M⁺, 5), 250 (20), 249 (100), 231 (8), 181 (13), 157 (12), 75 (33), 73 (10); HRMS calcd for C₁₈H₃₀O₂Si (M⁺) 306.2015, found 306.2017.

(-)-(7R)-5,6-Dimethyl-7-[(1,1-dimethylethyl)dimethylsilyl]oxy]tricyclo-[4.4.0.0^{5,9}]-decan-2-one (11). A mixture of 0.361 g (1.19 mmol) of **10** and 0.160 g of 10% Pd/C in 60 mL of EtOH was hydrogenated in a Parr hydrogenator under 23 psi of H₂ for 90 min. The reaction mixture was filtered through Celite and evaporated. Purification by flash chromatography (50:1 petroleum ether (bp 40–60 °C)/EtOAc) gave 0.314 g (87%) of **11**: [α]_D –63.1° (c 0.32); ¹H NMR (200 MHz) δ –0.06 (s, 3 H), –0.05 (s, 3 H), 0.79 (s, 9 H), 0.81 (s, 3 H), 0.99 (s, 3 H), 1.24 (br dd, *J* = 8.5, 13.4 Hz, 1 H), 1.52–2.20 (m, 8 H), 2.44 (m, 1 H), 3.44 (dd, *J* = 4.4, 7.4 Hz, 1 H); ¹³C NMR (50 MHz) δ –5.21 (q), –4.72 (q), 10.40 (q), 17.81 (s), 19.66 (q), 25.67 (3q), 30.46 (t), 31.61 (t), 33.88 (t), 43.83 (t), 46.10 (d), 47.13 (s), 53.01 (s), 56.79 (d), 77.96 (d), 214.88 (s); MS *m/z* (relative intensity) 308 (M⁺, 3.5), 253 (6), 252 (32), 251 (100), 159 (17), 157 (48), 107 (13), 75 (36), 73 (7); HRMS calcd for C₁₈H₃₂O₂Si (M⁺) 308.2172, found 308.2166.

(-)-(7R)-5,6-Dimethyl-7-[(methanesulfonyl)oxy]tricyclo[4.4.0.0^{5,9}]decan-2-one (12). To a solution of 0.28 g (0.91 mmol) of **11** in 20 mL of MeCN was added 10 drops of 40% aqueous HF. The reaction mixture was stirred at 55 °C for 5 h, poured into 50 mL of saturated aqueous NaHCO₃, and then extracted with four 25 mL portions of EtOAc. The combined organic layers were washed with 50 mL of brine, dried, and evaporated. The remaining residue was dissolved in 10 mL of CHCl₃, and 0.48 g (3.92 mmol) of DMAP and 0.414 g (3.61 mmol) of MsCl were successively added in small portions at 0 °C. The reaction mixture was stirred at rt for 30 h, concentrated under reduced pressure, and taken up in 80 mL of ether. The solution was washed successively with 20 mL of 10% aqueous H₂SO₄, 20 mL of saturated aqueous NaHCO₃, and 20 mL of brine. The organic layer was dried and evaporated, and the remaining oil was purified by flash chromatography (3:1 petroleum ether (bp 40–60 °C)/EtOAc) to afford 0.209 g (85%) of **12**: [α]_D –43.6° (c 1.60); ¹H NMR (200 MHz) δ 0.92 (s, 3 H), 1.00 (s, 3 H), 1.35 (dd, *J* = 8.4, 13.7 Hz, 1 H), 1.55–1.84 (m, 2 H), 1.90–2.27 (m, 6 H), 2.50 (m, 1 H), 2.94 (s, 3 H), 4.40 (dd, *J* = 3.9, 8.0 Hz, 1 H); ¹³C NMR (50 MHz) δ 10.28 (q), 19.48 (q), 29.68 (t), 31.04 (t), 33.63 (t), 38.26 (q), 41.02 (t), 46.07 (d), 47.58 (s), 52.75 (s), 55.93 (d), 86.57 (d), 212.76 (s); MS *m/z* (relative intensity) 272 (M⁺, 21), 150 (100), 122 (74), 94 (37), 86 (23), 84 (36), 49 (27); HRMS calcd for C₁₃H₂₀O₄S (M⁺) 272.1082, found 272.1082. Anal. Calcd for C₁₃H₂₀O₄S: C, 57.33; H, 7.40. Found: C, 57.07; H, 7.52.

(-)-(2S,7R)-5,6-Dimethyltricyclo[4.4.0.0^{5,9}]decan-2,7-diol 7-Methanesulfonate (3). To a stirred solution of 0.198 g (0.73 mmol) of **12** in 20 mL of EtOH was added 0.180 g (4.74 mmol) of NaBH₄. The reaction mixture was stirred at rt for 90 min, quenched with saturated aqueous NH₄Cl at 0 °C, and, after addition of 50 mL of water, extracted with five 25 mL portions of ether. The combined organic layers were washed with 25 mL of brine, dried, and evaporated. The remaining residue was flash chromatographed (3:1 petroleum ether (bp 40–60 °C)/EtOAc) to give 0.017 g (14%) of 2,7-dimethyl-3-oxatetracyclo[6.2.1.0^{2,7}.0^{4,10}]decane (**13**): [α]_D +8.23° (c 0.51); ¹H NMR (200 MHz) δ 0.83 (s, 3 H), 1.10–1.30 (m, 2 H), 1.24 (s, 3 H), 1.40–2.10 (m, 8 H), 2.53 (m, 1 H), 4.32 (dd, *J* = 5.4, 7.6 Hz, 1 H), ¹³C NMR (50 MHz) δ 18.41 (q), 24.32 (q), 27.50 (t), 29.69 (t), 32.65 (t), 35.57 (t), 39.85 (d), 41.31 (s), 49.29 (d), 54.49 (d), 76.20 (d), 88.21 (s); MS *m/z* (relative intensity) 178 (M⁺, 40), 135 (24), 121 (29), 120 (100), 108 (43), 107 (29), 105 (21), 93 (58), 91 (55), 79 (30); HRMS calcd for C₁₂H₁₈O (M⁺) 178.1358, found 178.1354. Further elution provided 0.151 g (76%) of **3**: [α]_D –49.6° (c 1.16); ¹H NMR (400 MHz) δ 0.98 (s, 3 H), 1.18 (dd, *J* = 8.6, 13.4 Hz, 1 H), 1.28 (s, 3 H), 1.34

(dddd, $J = 2.5, 3.4, 5.2, 13.4$ Hz, 1 H), 1.45–1.72 (m, 5 H), 1.86 (t, $J = 4.5$ Hz, 1 H), 1.91 (dd, $J = 8.6, 13.4$ Hz, 1 H), 1.95–2.07 (m, 2 H), 3.00 (s, 3 H), 3.90 (ddd, $J = 3.4, 3.4, 6.9$ Hz, 1 H), 4.44 (dd, $J = 4.5, 8.0$ Hz, 1 H); ^{13}C NMR (50 MHz) δ 11.02 (q), 20.40 (q), 26.36 (t), 28.61 (t), 32.46 (t), 38.24 (q), 40.82 (t), 44.05 (d), 46.24 (s), 46.51 (d), 48.98 (s), 72.72 (d), 88.48 (d); MS m/z (relative intensity) 274 (M^+ , <0.1), 152 (100), 120 (17), 108 (54), 97 (75), 95 (40), 94 (64), 93 (18), 85 (56), 83 (83); HRMS calcd for $\text{C}_{13}\text{H}_{22}\text{O}_4\text{S}$ (M^+) 274.1239, found 274.1235.

(+)-Tricycloekasantalal (4). A solution of 0.067 g (0.244 mmol) of **3** in 25 mL of dry benzene was degassed and refluxed under an Ar atmosphere. To the refluxing solution was added at once, via syringe, 0.32 mL of sodium *tert*-amylate (1.56 M in toluene). The reaction mixture was refluxed for 1 min, quenched with precooled saturated aqueous NH_4Cl , and then quickly cooled to 0 °C. The mixture was vigorously stirred at rt for 20 min, followed by extraction with five 10 mL portions of ether. The combined organic layers were dried and evaporated. Purification by flash chromatography (100:1 pentane/ether) afforded 0.033 g (76%) of **4**: $[\alpha]_{\text{D}} +15.2^\circ$ (c 1.52); ^{13}C NMR (100 MHz) δ 10.95 (q), 17.71 (q), 19.81 (d, $J = 175.8$ Hz), 20.07 (d, $J = 172.2$ Hz), 26.73 (t), 27.70 (s), 31.33 (t), 31.83 (t), 38.58 (d), 40.31 (t), 46.08 (s), 203.39 (s); MS m/z (relative intensity) 178 (M^+ , 16), 121 (48), 120 (32), 119 (33), 111 (24), 105 (21), 93 (100), 92 (24), 91 (36); HRMS calcd for $\text{C}_{12}\text{H}_{18}\text{O}$ (M^+) 178.1358, found 178.1355. The ^1H NMR data of **4** were identical with those reported in the literature.^{19,20a}

(+)- α -Santalal-12-one (1d). To a solution of 0.016 g (0.087 mmol) of **4** in 2 mL of ether was added 0.3 mL of *i*PrMgCl (1.5 M in ether) at 0 °C. The reaction mixture was stirred at 0 °C for 5 min and then at rt for 30 min. The reaction mixture was quenched with an excess of saturated aqueous NH_4Cl at 0 °C. After being stirred at rt for 15 min and diluted with 25 mL of ether, the two phase-mixture was separated and the organic layer was washed with 10 mL of brine, dried, and evaporated. The remaining residue was dissolved in 3 mL of CH_2Cl_2 and, after addition of 0.071 g of PDC, stirred at rt for 16 h. The suspension was then diluted with 50 mL of ether, and stirring was continued at rt for an additional 1 h. After filtration through Celite, the filtrate was concentrated under reduced pressure. Purification by flash chromatography (25:1 pentane/ether) gave 0.014 g (73%) of **1d**: $[\alpha]_{\text{D}} +17.5^\circ$ (c 0.48) (lit.⁶ $[\alpha]_{\text{D}} +17.8^\circ$) (lit.¹² $[\alpha]_{\text{D}} +3.7^\circ$); ^{13}C NMR (100 MHz) δ 10.98 (q), 17.70 (q), 18.76 (2q), 19.86 (d, $J \approx 160$ Hz), 19.99 (d, $J \approx 160$ Hz), 27.74 (s), 28.70 (t), 31.35 (t), 31.86 (t), 36.40 (t), 38.59 (d), 41.25 (d), 45.88 (s), 215.84 (s). The ^1H NMR and mass spectral data for **1d** were identical with those reported in the literature.^{6,12}

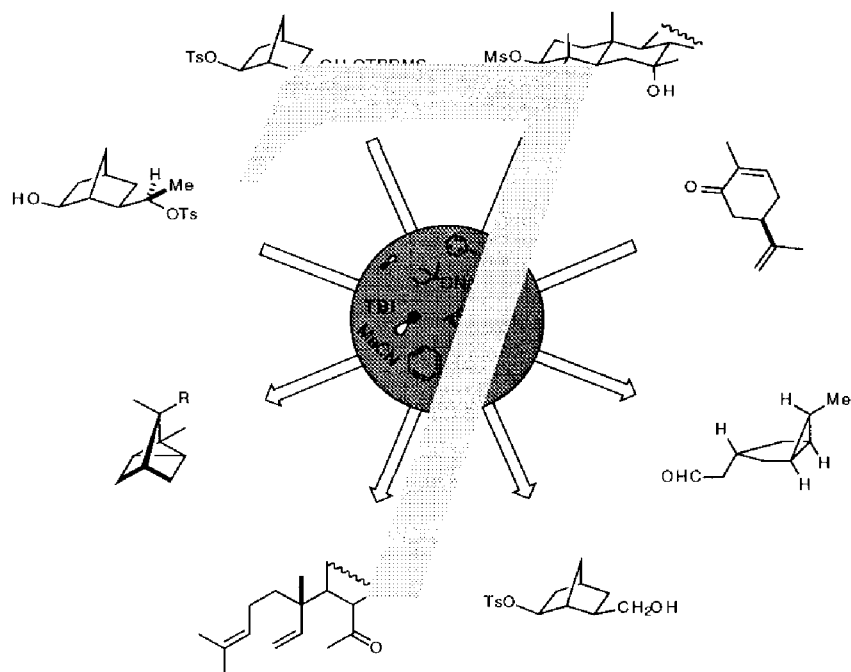
6.4 References and Notes

- (a) Orrū, R. V. A.; Wijnberg, J. B. P. A.; Jenniskens, L. H. D.; de Groot, A. J. *Org. Chem.* **1993**, *58*, 1199. (b) Orrū, R. V. A.; Wijnberg, J. B. P. A.; Bouwman, C. T.; de Groot, A. J. *Org. Chem.* **1994**, *59*, 374. (c) Bastiaansen, P. M. F. M.; Wijnberg, J. B. P. A.; de Groot, A. J. *Org. Chem.* **1995**, *60*, 4240. (d) Orrū, R. V. A.; Wijnberg, J. B. P. A.; de Groot, A. J. *Org. Chem.* **1995**, *60*, 4233.
- Wijnberg, J. B. P. A.; Jenniskens, L. H. D.; Brunekreef, G. A.; de Groot, A. J. *Org. Chem.* **1990**, *55*, 941.
- Jenniskens, L. H. D.; Wijnberg, J. B. P. A.; de Groot, A. J. *Org. Chem.* **1991**, *56*, 6585.

- 4 Demole, E.; Demole, C.; Enggist, P. *Helv. Chim. Acta* **1976**, 59, 737.
- 5 Brunke, E.-J.; Schmaus, G. *Dragoco Rep.* **1995**, 42, 197 and 245 and references cited therein.
- 6 Kaiser, R.; Lamparsky, D. *Helv. Chim. Acta* **1983**, 66, 1835.
- 7 For some representative examples, see: (a) Ho, T.-L. *Enantioselective Synthesis: Natural Products from Chiral Terpenes*; Wiley Interscience: New York, 1992; pp 231–234. (b) Schlosser, M.; Zhong, G. *Tetrahedron Lett.* **1993**, 34, 5441.
- 8 Corey, E. J.; Chow, S. W.; Scherrer, R. A. *J. Am. Chem. Soc.* **1957**, 79, 5773.
- 9 (a) Zhang, W.; Dowd, P. *Tetrahedron Lett.* **1994**, 29, 5161. (b) Dowd, P.; Zhang, W.; Geib, S. J. *Tetrahedron* **1995**, 51, 3435. We are indebted to Professor P. Dowd for sending us the experimental procedure for the synthesis of dione **2** prior to publication.
- 10 Another approach to (α)-santalanes, in which (*R*)-(-)-carvone was used as the starting material, led to complete racemization: Hodgson, G. L.; MacSweeney, D. F.; Money, T. *J. Chem. Soc., Perkin Trans. 1* **1973**, 2113.
- 11 The numbering system as given in structure **2** is based on the system adopted for camphor and will be followed throughout the text of this chapter.
- 12 Wu, T.-S.; Niwa, M.; Furukawa, H. *Phytochemistry* **1984**, 23, 595.
- 13 For example, see: Hassner, A.; Reuss, R. H.; Pinnick, H. W. *J. Org. Chem.* **1975**, 40, 3427.
- 14 Brown, H. C.; Krishnamurthy, S. *J. Am. Chem. Soc.* **1972**, 94, 7159.
- 15 Berson, J. A. In *Molecular Rearrangements*; de Mayo, P., Ed.; Interscience Publishers: New York, 1963; Part 1, Chapter 3.
- 16 Parish, E. J.; Wei, T.-Y. *Synth. Commun.* **1987**, 17, 1227.
- 17 Molander, G. A. *Chem. Rev.* **1992**, 92, 29 and references cited therein.
- 18 Under standard conditions (0.1 M mesylate in benzene, 5 equiv of sodium *tert*-amylate),^{1c} the yield of aldehyde **4** dropped to ca. 50%.
- 19 Kretschmar, H. C.; Barneis, Z. J.; Erman, W. F. *Tetrahedron Lett.* **1970**, 37.
- 20 (a) Lewis, R. G.; Gustafson, D. H.; Erman, W. F. *Tetrahedron Lett.* **1967**, 401. (b) Corey, E. J.; Yamamoto, H. *J. Am. Chem. Soc.* **1970**, 92, 226.
- 21 Except for the homofragmentation reaction (**3** \rightarrow **4**), no attempts have been made to improve the yields.
- 22 For a general description of the experimental procedures reported in this chapter, see Chapter 2. Optical rotations were measured in CHCl₃ solutions.

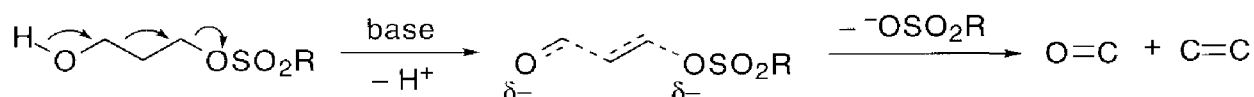
Chapter 7

Concluding Remarks



7.1 Introduction

Almost 30 years have passed since Hoffmann, Imamura, and Hehre reported that *not* all chemical and physical observations of organic molecules could be explained via a localized bond model.¹ Until that time organic molecules were described as a framework of σ -bonds and on top of that framework delocalized π -electron systems and lone pairs were placed, as needed. Hoffmann realized that this supposedly inert σ -framework actually can interact with functional groups. This interaction (TBI) involves a mutual coupling of the functional group orbitals with the σ - and σ^* -orbitals of the intervening saturated bridge. Or in other words, σ -electrons are delocalized just like π -electrons. The energy effects concomitant with σ -conjugation,² however, are considerably smaller than those with the more familiar π -conjugation. Therefore, the localized model developed over the years by organic chemists is normally effective as a guide in their chemical thinking, in devising syntheses, and in exploring reaction mechanisms. However, for a careful interpretation of photophysical data of organic molecules, like UV-, CD-, PES-, and ESR-spectra, the incorporation of TBI can be essential.³ In certain cases the chemical behavior of organic molecules is better understood if TBI are considered (Chapter 2). Synthetically useful reactions that utilize TBI over a fully unstrained arrangement of σ -bonds are limited to the well-studied Grob fragmentation⁴ and the related base-induced Wharton fragmentation of cyclic 1,3-diol monosulfonate esters.⁵ In the Wharton reaction which is almost certainly the result of TBI mediated via three σ -bonds, the compounds involved undergo olefin-forming fragmentation with release of an electrofugal carbonyl fragment (Scheme 7.1).



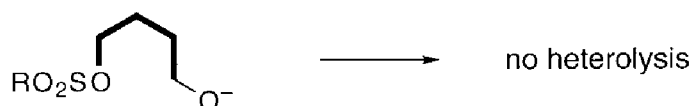
Scheme 7.1

The investigations by Jenniskens and Orr⁶ have shown that TBI also control the reactivity and reaction outcome of rigid *trans*-perhydronaphthalene-1,4-diol monosulfonate esters, in which the hydroxyl group is separated from the nucleofugal sulfonate ester group by one additional carbon atom. Whether TBI

still play an important role when other rigid 1,4-diol monosulfonate esters are treated with base or when the hydroxyl group is separated from the sulfonate ester by two additional carbon atoms was not reported. To fill this gap, the reactions of norbornane-1,4-diol monosulfonate esters and cholestane-1,5-diol monosulfonate esters with sodium *tert*-amylate in apolar solvents (benzene or toluene) were investigated. In the following sections, the main conclusions of these studies and those of the previous investigations by Jenniskens and Orr⁶ are summarized.

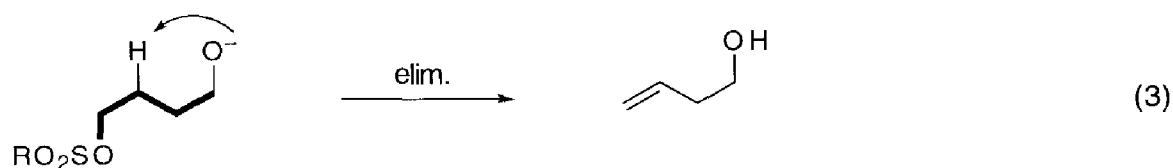
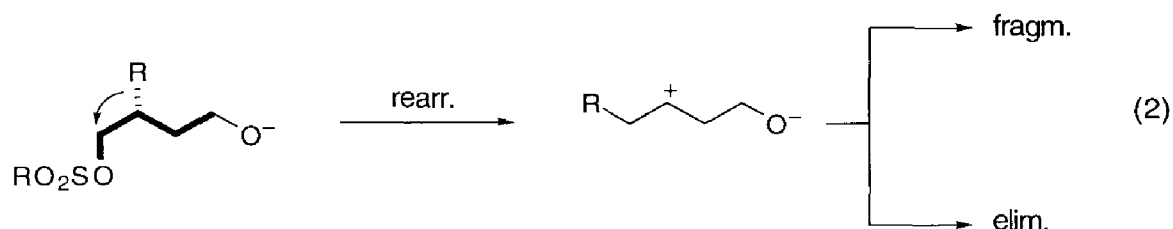
7.2 The Base-Induced Heterolysis of 1,4-Diol Monosulfonate Esters

From the investigations on monosulfonated 1,4-diols in rigid systems described in chapter 2, it is clear that TBI are certainly not always capable to induce heterolysis of the sulfonate ester bond. No reaction via heterolysis of the sulfonate group can be observed if a *U-like geometry* of the σ -relay is present between the sulfonate ester and the alkoxide group (Scheme 7.1).^{6f}



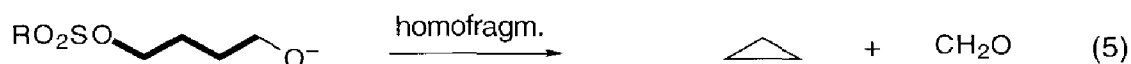
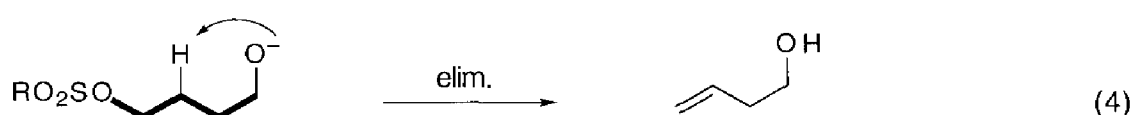
Scheme 7.1

Upon basic treatment of 1,4-diol sulfonate esters with a *sickle-like geometry* of the σ -relay, the generated alkoxide group is capable to induce the heterolysis of the sulfonate group (Scheme 7.2). If the sulfonate anion is removed far enough and a more or less free carbocation has been evolved a homofragmentation can take place (Scheme 7.2). As can be judged from the relatively low reaction rate and low yield, this homofragmentation does not occur readily and other reactions can easily be favored. A quantitatively occurring rearrangement, for example, is much more attractive than a fragmentation if a C–C bond antiperiplanar to the leaving group is present (eq 2).^{6a-c} Homofragmentation is also circumvented if the alkoxide and a proton β to the sulfonate ester group are properly aligned for intramolecular β -elimination (eq 3).^{6d}



Scheme 7.2

In scheme 7.3 the two main reaction pathways for monosulfonated 1,4-diols with an *all-trans* or *W-like geometry* of the σ -relay are given. If the proton β to the sulfonate ester group and the alkoxide group are properly aligned, a β -elimination can take place (eq 4);^{6c} in other cases homofragmentation will be the most likely reaction path (eq 5).^{6d,7} Since these compounds even fragment at room temperature, indicating a low barrier of activation, homofragmentation might be a spontaneous biosynthetic process.⁸



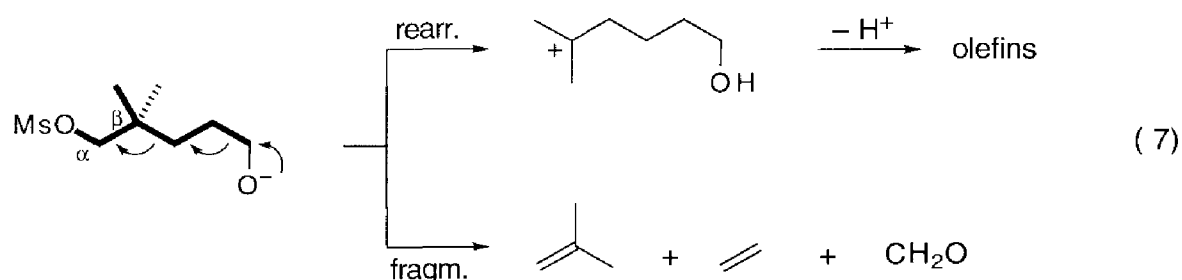
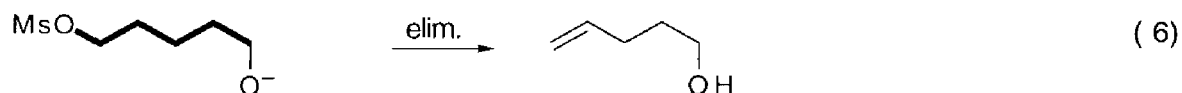
Scheme 7.3

In contrast to the Wharton fragmentation, primary sulfonate esters do not homofragment.⁹ This might be the result of diminished TBI caused by rotation around the $\text{C}_\alpha\text{-C}_\beta$ bond of the primary sulfonate esters. However, secondary sulfonate esters with a similar rotational freedom homofragment smoothly. Most

likely, the primary sulfonate esters resist to fragment since the formation of an intermediate primary carbocation is energetically unfavorable. Such constraints have not been found for the hydroxyl group. The orientation of the hydroxyl group is irrelevant and high yielding homofragmentations are observed with primary, secondary, and tertiary hydroxyl groups. For synthetic purposes, the presence of secondary hydroxyl groups requires special reaction conditions in order to prevent aldol condensation of the susceptible aldehyde function, formed in fragmentation reactions.

7.3 The Base-Induced Heterolysis of 1,5-Diol Monosulfonate Esters

Separation of the sulfonate ester, for practical reasons always a mesylate group,¹⁰ and the alkoxide group by an additional C–C bond results in a dramatic decrease of TBI, also when the σ -relay possesses an ideal all-trans arrangement.¹¹ Without a quaternary carbon atom β to the leaving mesylate, predominantly eliminations occur (eq 6). In cases of a fully substituted β carbon atom, rearrangement becomes the most favorable reaction course. A seven-center fragmentation is observed as an alternative route (eq 7).



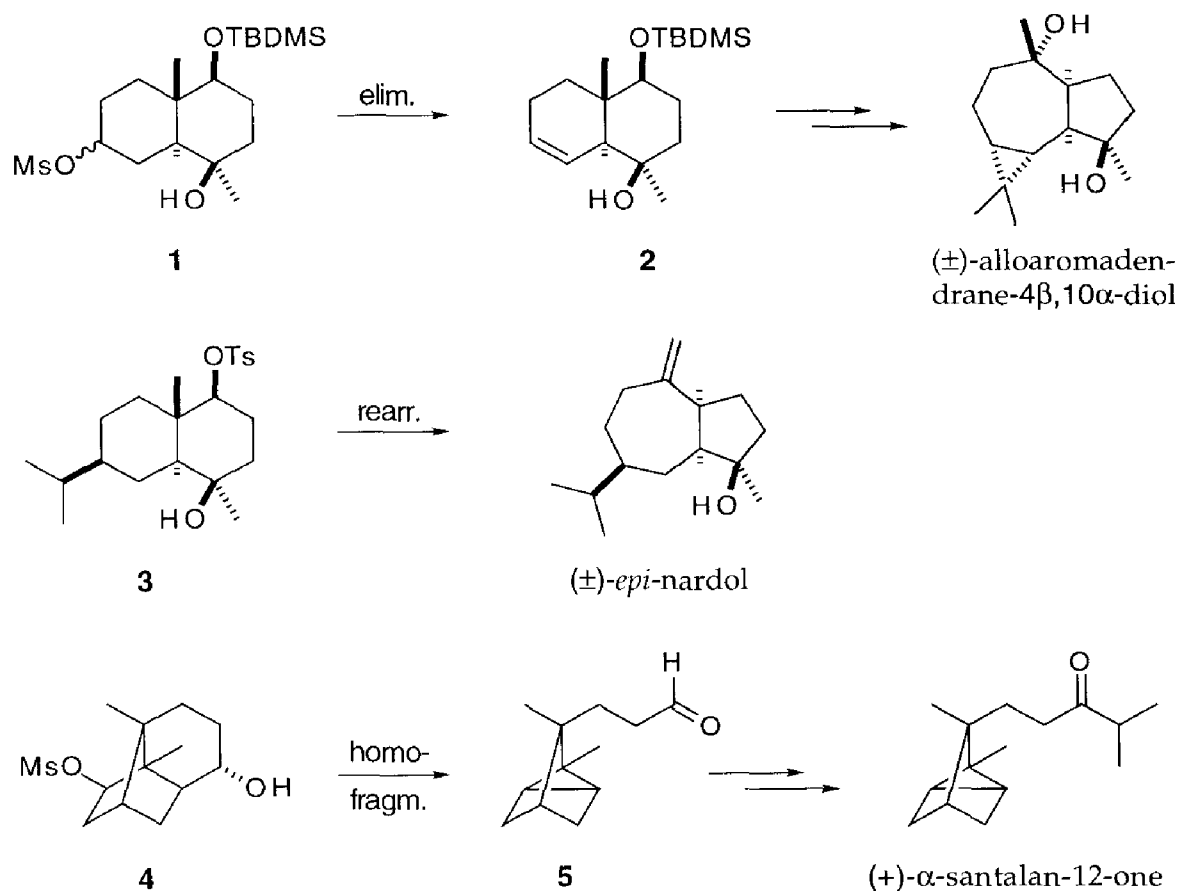
Scheme 7.4

Though, long-range orbital interactions through five σ -bonds still enhance the reaction rate of 1,5-diol monosulfonate esters in comparison with systems that lack these interactions, a dramatic decrease in reaction rate is found with respect to the 1,4-diol monosulfonate esters. In our opinion, the ability of an alcoholate function

to induce intramolecularly the heterolysis of a remote sulfonate ester group in an apolar solvent has reached its limit with the 1,5-diol monosulfonate esters.

7.4 The Selective Elimination, Rearrangement and Homofragmentation of 1,4-Diol Monosulfonate Esters in Natural Product Syntheses

In contrast to the intramolecular base-induced reactions of 1,5-diol monosulfonate esters described in the previous section, the 1,4-analogs react highly predictably and selectively and, consequently, can be used with great confidence in organic syntheses. Dependent on the molecule's architecture, a selective elimination, rearrangement, or homofragmentation can be achieved in high yield. Each of these reactions has been applied successfully in the synthesis of sesquiterpenes. The selective elimination was used in the total synthesis of (\pm)-alloaromadendrane-4 β ,10 α -diol,^{6b} the rearrangement in that of (\pm)-*epi*-nardol,^{6a} and the homofragmentation was used in the synthesis of (+)- α -santalol-12-one (Scheme 7.5).¹²

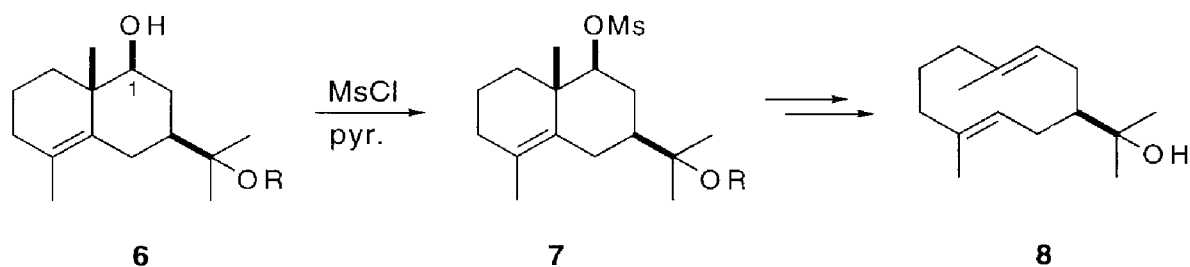


Scheme 7.5

7.5 Other Implications of TBI in Organic Syntheses

The chemical consequences of TBI are not only reflected in the base-induced reactions of 1,4-diol monosulfonate esters and, to a much lesser degree, of 1,5 diol-monosulfonate esters, but also in several other reactions.¹³ For instance, the rate of desilylation of silyl ethers is distinctly influenced by the presence of a remote electron-withdrawing group.¹⁴ Kinetic experiments on a number of sulfonated norbornyl silyl ethers clearly show that the rate of desilylation (and consequently the stability) of these compounds is directly related to the geometry of the σ -relay between the silyl ether function and the sulfonate ester group. The rate of desilylation decrease in the order $W > \text{sickle like} > U$ arrangement. These findings confirm, once again, the validity of the "all-trans rule" in TBI-controlled processes.¹⁵

Very recently, a striking example of compound instability due to TBI has been reported.¹⁶ In the synthetic route towards the germacrane **8**, a hypothetical precursor in the biosynthesis of *cis*-fused eudesmanes, the conversion of **6** ($R = H$) into mesylate **7** ($R = H$) was planned (Scheme 7.6). However, all attempts to mesylate **6** ($R = H$) only led to small amounts of the desired mesylate **7** ($R = H$). The majority of reaction products consisted of alcohols and chlorides, most likely formed via a S_N1 -like replacement of the mesylate group at C(1) of **7** ($R = H$). A tremendous change in reaction behavior was obtained after protection of the tertiary hydroxyl function of **6** as its acetate ($R = Ac$). Treatment of **6** ($R = Ac$) with $MsCl$ in pyridine now gave the mesylate **7** ($R = Ac$) in quantitative yield. This remarkable difference in chemical behavior can be attributed to the occurrence of TBI in mesylate **7** ($R = H$). Under the basic conditions required for effective mesylation of the secondary hydroxyl function of **6** ($R = H$), its tertiary hydroxyl group becomes partially negatively charged which enables the sulfonate ester group to come off more easily



Scheme 7.6

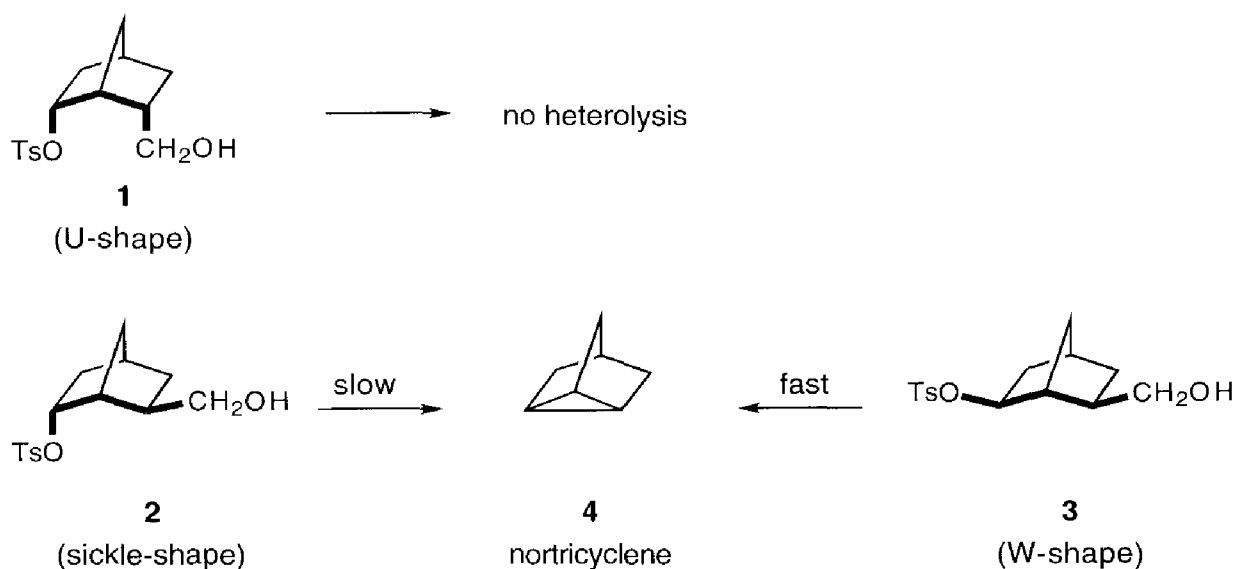
7.6 References and Notes

- 1 (a) Hoffmann, R.; Imamura, A.; Hehre, W. J. *J. Am. Chem. Soc.* **1968**, *90*, 1499. (b) Hoffmann, R. *Acc. Chem. Res.* **1971**, *4*, 1.
- 2 Dewar, M. J. S. *J. Am. Chem. Soc.* **1984**, *106*, 669.
- 3 For example see: (a) Kovac, B.; Novak, I.; Majerski, K. M.; Vinkovic, M.; Kaselj, M. J. *Org. Chem.* **1995**, *53*, 3361. (b) Kroon, J.; Oliver, A. M.; Paddon-Row, M. N.; Verhoeven, J. W. *J. Am. Chem. Soc.* **1990**, *112*, 4868. (c) Krijnen, B.; Beverloo, H. B.; Verhoeven, J. W.; Reiss, C. A.; Goubitz, K.; Heijdenrijk, D. *J. Am. Chem. Soc.* **1989**, *111*, 4433. (d) Schneider, H. J.; Wiegand, E. F.; Becker, N. *J. Org. Chem.* **1988**, *53*, 3361. (e) Closs, G. L.; Calcaterra, L. T.; Green, N. J.; Penfield, K. W.; Miller, J. R. *J. Phys. Chem.* **1986**, *90*, 3673. (f) Snow, L. D.; Williams, F. J. *Chem. Soc., Chem. Commun.* **1983**, 1090. (g) Martin, H. D.; Mayer, B. *Angew. Chem.* **1983**, *95*, 281. (h) Pasman, P.; Rob, F.; Verhoeven, J. W. *J. Am. Chem. Soc.* **1982**, *104*, 5127. (i) Bartetzko, R.; Gleiter, R.; Muthard, J. L.; Paquette, L. A. *J. Am. Chem. Soc.* **1978**, *100*, 5589.
- 4 (a) Grob, C. A. *Angew. Chem.* **1969**, *81*, 543. (b) Gleiter, R.; Stohrer, W.; Hoffmann, R. *Helv. Chim. Acta* **1972**, *55*, 893 and references cited therein.
- 5 For an extensive review of the Wharton reaction, see: Caine, D. *Org. Prep. Proced. Int.* **1988**, *20*, 1.
- 6 (a) Wijnberg, J. B. P. A.; Jenniskens, L. H. D.; Brunekreef, G. A.; de Groot, A. *J. Org. Chem.* **1990**, *55*, 941. (b) Jenniskens, L. H. D.; Wijnberg, J. B. P. A.; de Groot, A. *J. Org. Chem.* **1991**, *56*, 6585. (c) Orrü, R. V. A.; Wijnberg, J. B. P. A.; Jenniskens, L. H. D.; de Groot, A. *J. Org. Chem.* **1993**, *58*, 1199. (d) Orrü, R. V. A.; Wijnberg, J. B. P. A.; Bouwman, C. T.; de Groot, A. *J. Org. Chem.* **1994**, *59*, 374. (e) Orrü, R. V. A.; Wijnberg, J. B. P. A.; de Groot, A. *J. Org. Chem.* **1995**, *60*, 4233.
- 7 When lithium instead of sodium *tert*-amylate is used, 1,3-bridging is reduced and rearrangements are observed.
- 8 (a) Jakupovic, J.; Schuster, A.; Bohlmann, F.; King, R. M.; Haegi, L. *Phytochemistry*, **1989**, *28*, 1943. (b) Ahmed, A. A.; Jakupovic, J.; Bohlmann, F. *Phytochemistry*, **1990**, *29*, 3355. (c) Sakui, N.; Kuroyanagi, M.; Ishitobi, Y.; Sato, M.; Ueno, A. *Phytochemistry*, **1992**, *31*, 143. (d) Piet, D. P.; Schrijvers, R.; Franssen, M. C. R.; de Groot, A. *Tetrahedron*, **1995**, *51*, 6303.
- 9 Attempts to prepare and fragment tertiary sulfonate esters are currently under investigation on our laboratory.
- 10 Tosylate esters can only be prepared in relatively poor yield from tertiary hydroxyl groups
- 11 See chapter 5.
- 12 See chapter 6.
- 13 See also chapter 2 and references cited therein.
- 14 See chapter 4.
- 15 Paddon-Row, M. N. *Acc. Chem. Res.* **1982**, *15*, 245.
- 16 Minnaard, A. J.; Forthcomming Ph.D. Thesis, Wageningen Agricultural University, 1997.

Summary

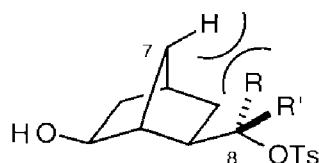
This thesis deals with the reaction behavior of 1,4- and 1,5-diol monosulfonate esters upon basic treatment in apolar solvents and the Through-Bond Interactions (TBI) which are playing a role in these reactions. Furthermore, the influence of TBI on the rate of desilylation of silyl ethers of 1,4-diol monosulfonate esters is shown. Finally, the application of the base-induced homofragmentation is illustrated by the synthesis of a natural product.

In Chapter 1 the historical background of the base-induced reactions of 1,4-diol monosulfonate esters is given. From previous work, it is known that the sulfonate ester bond of 1,4-diol monosulfonates can undergo a facile heterolysis upon treatment with a non-nucleophilic base –sodium *tert*-amylate– in refluxing benzene or toluene. TBI between the oxygen anion, generated by deprotonation of the hydroxyl group, and the sulfonate ester bond are thought to play a dominant role in this heterolysis process. In this thesis all the typical reaction behaviors of the base-treated diol monosulfonates are explained with the concepts of TBI. Furthermore, some examples of chemical consequences of TBI are briefly discussed (Chapter 1).



The studies on the sulfonates 1–3 (Chapter 2) reveal that the magnitude of TBI strongly depends on the geometry of the σ -relay, as is reflected in the rate of heterolysis of the sulfonate ester bond and in the product outcome. For sulfonate

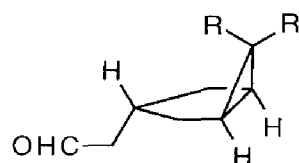
ester **1**, no reaction via heterolysis of the sulfonate ester bond has been found, whereas **2** shows a slow and **3** a fast homofragmentation reaction. The reactivity of these compounds perfectly parallels the increased TBI between two functionalities due to changing the geometry of the relaying σ -bonds from a U-, to a sickle-, and finally, to a W-shape. Though both **2** and **3** show homofragmentation only **3** affords nortricyclene (**4**) in high yields. The stereochemical and stereoelectronic requirements for the homofragmentation can be rationalized similarly to the Grob fragmentation.



5 R = H; R' = H

6 R = H; R' = Me

7 R = Me; R' = H



8 R = H; R' = Me

9 R = Me; R' = H

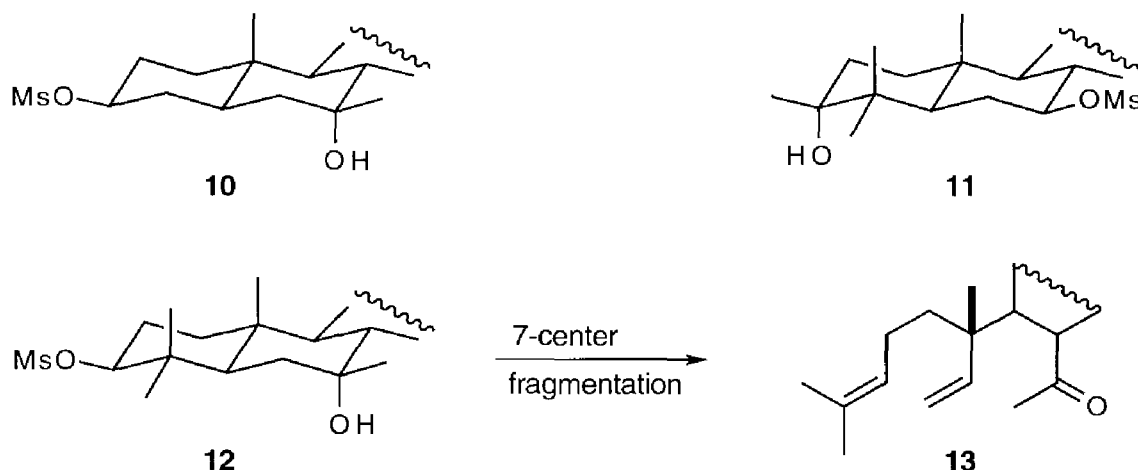
Through-4-bond interactions are not strong enough to split off primary sulfonate esters, as can be concluded from studies on **5**. However, after the introduction of a methyl group at C(8), a selective homofragmentation of **6** to aldehyde **8** has been observed, indicating that the reluctance of the primary sulfonate to heterolyse is most likely due to the instability of the intermediate primary carbocation. The sulfonate ester **7** gives rise to four different products with aldehyde **9** as the main product. The product ratio can be rationalized by using the Curtin-Hammett principle.

In Chapter 3 a simplified Molecular Orbital (MO) description of TBI between an alkoxide function and an (incipient) carbocationic center is given. This description accounts for most of the experimental results obtained from the base-induced heterolyses of 1,4-diol monosulfonate esters. For example, it explains why a "W-shaped" σ -relay between an alkoxide and a sulfonate group results in a relatively facile formation of a carbocation. It also provides insight in the indirect transfer of negative charge from the alkoxide to the (incipient) carbocation center.

Upon desilylation, the negative charge developed on oxygen of Si-O bonds can be stabilized by remote electron-withdrawing groups (Chapter 4). Desilylation experiments on the silyl ethers of **1-3** and **5-7** demonstrate that the stabilization depends on the strength of the electron-withdrawing group (sulfonate ester vs methyl ether), but also, even to a greater extent, on the geometry of the relaying σ -bonds between the silyl ether and the electron-withdrawing group. The

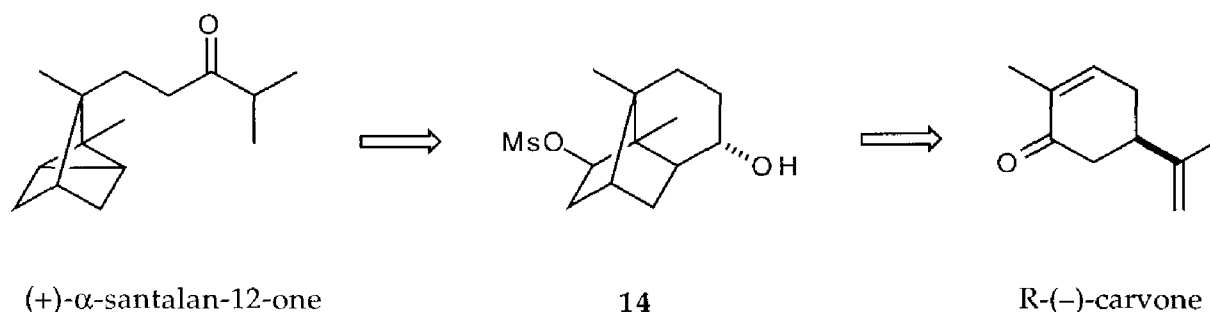
desilylation rate increases upon changing the σ -relay from a U- to a W-shape.

In contrast to 1,4-diol monosulfonate esters with an all-trans σ -relay, their 1,5 analogs **10–12** only exhibit fragmentation as a minor side reaction (Chapter 5).



Dependent on the degree of methyl-substitution no fragmentation product at all (**10**), a trace amount (**11**), or a 20% yield of the seven-center fragmentation product (**12**→**13**) was obtained. It will be clear that the fragmentation of 1,5-diol monosulfonate esters can not effectively be applied in organic syntheses.

Monosulfonated 1,4-diols, on the other hand, react highly predictably and selectively, and consequently they can be applied as intermediates in total synthesis. Previous work on perhydroazulene sesquiterpenes (see Chapter 1) and the work on α -santalene sesquiterpenes described in this thesis (Chapter 6) nicely demonstrates this potential.

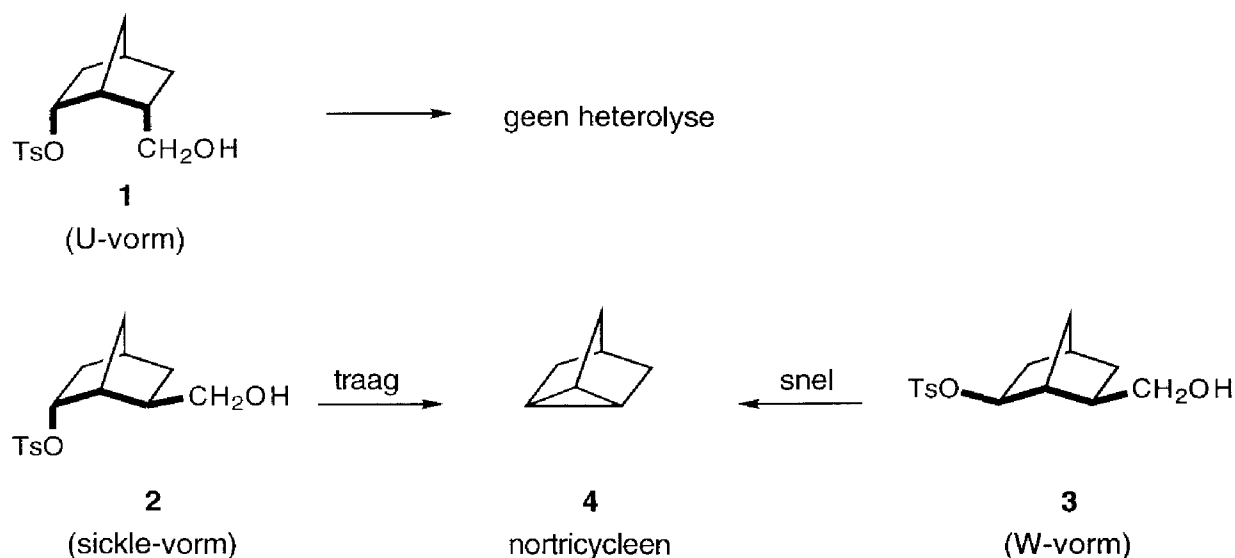


The homofragmentation reaction of monosulfonated 1,4-diols has been used as the key step in the enantiospecific synthesis of an α -santalane. The precursor for this α -santalane, mesylate **14**, was obtained from commercially available (R)-(-)-carvone. With this "Carvone → α -Santalane-route", the homofragmentation reaction has proven its utility in natural product synthesis.

Samenvatting

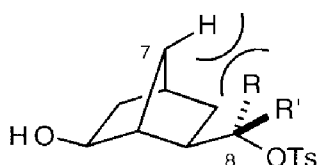
Dit proefschrift behandelt het chemisch gedrag van 1,4- en 1,5-diolmonosulfonaat-esters onder invloed van een niet-nucleofiele base in apolaire oplosmiddelen en de "Through-Bond Interactions" (TBI) die hierbij een rol spelen. Bovendien wordt aangetoond dat TBI ook de desilyleringssnelheid van silylethers kan beïnvloeden. Ten slotte wordt de toepasbaarheid van de base-geïnduceerde homofragmentatie geïllustreerd aan de hand van de synthese van een natuurstof.

In hoofdstuk 1 wordt eerst de geschiedenis van de base-geïnduceerde ionisatie van 1,4-diol monosulfonaten gegeven. Uit voorafgaand onderzoek is gebleken dat de sulfonaatester C–O binding van 1,4-diolmonosulfonaatesters gemakkelijk splitst bij behandeling met de niet-nucleofiele base natrium *tert*-amylaat in benzeen of toluen. TBI tussen het zuurstof anion, ontstaan door het deprotoneren van de hydroxylgroep, en de sulfonaatesterbinding spelen een belangrijke rol bij deze heterolyse. In dit proefschrift worden alle karakteristieke reacties van de met base behandelde diolmonosulfonaatesters verklaard met behulp van TBI. Bovendien worden enkele andere chemische gevolgen van TBI kort besproken (Hoofdstuk 1).

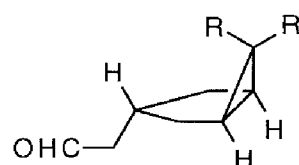


Onderzoek aan de sulfonaten 1–3 (Hoofdstuk 2) geeft aan dat de mate van TBI sterk afhankelijk is van de geometrie van de "σ-relay". Voor sulfonaatester 1 werd geen reactie via heterolyse van de sulfonaatesterbinding gevonden terwijl 2 een

langzame en **3** een snelle homofragmentatie gaven. De reactiviteit van deze verbindingen komt volledig overeen met de toenemende TBI tussen twee functionele groepen wanneer de " σ -relay" tussen deze groepen verandert van een U-, naar een sickle-, en uiteindelijk naar een W-vorm. Alhoewel zowel **2** als **3** een homofragmentatie gaven, werd nortricycleen alleen vanuit **3** in hoge opbrengst gevormd. De stereochemische en stereoelectronische vereisten voor de homofragmentatie kunnen op dezelfde wijze worden beredeneerd als voor de Grob fragmentatie.



- 5** R = H; R' = H
6 R = H; R' = Me
7 R = Me; R' = H



- 8** R = H; R' = Me
9 R = Me; R' = H

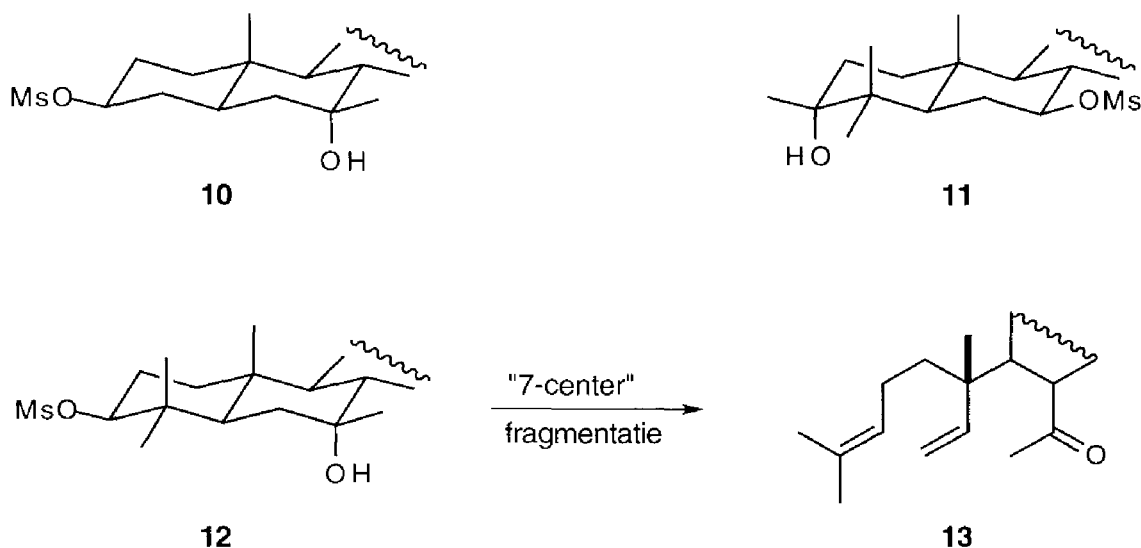
Sulfonaatester **5** geeft aan dat TBI door vier σ -bindingen niet sterk genoeg zijn om primaire sulfonaatesters te laten splitsen. Echter, na de introductie van een methyl groep op C(8) kan een selectieve homofragmentatie van **6** naar aldehyde **8** worden waargenomen. Hieruit blijkt dat het niet heterolysen van primaire sulfonaatesters hoogstwaarschijnlijk wordt veroorzaakt door de instabiliteit van het intermediaire primaire carbocation. Sulfonaatester **7** geeft vier producten met aldehyde **9** als hoofdproduct. De productverhouding kan verklaard worden met behulp van het "Curtin-Hammett" principe.

In hoofdstuk 3 wordt een eenvoudige Molecuul-Orbitaal (MO) beschrijving van TBI tussen een alkoxide groep en een carbocation gegeven. Met deze beschrijving is het mogelijk de belangrijkste experimentele waarnemingen van de base-geïnduceerde heterolyse van 1,4-diolmonosulfonaatesters te verklaren. Verklaard wordt waarom een carbocation relatief makkelijk wordt gevormd wanneer de " σ -relay" tussen een alkoxide en een sulfonaatester een "W"-vorm heeft. Bovendien wordt inzicht gegeven in de indirecte ladingsoverdracht van een alkoxide naar een (zich vormend) carbocation.

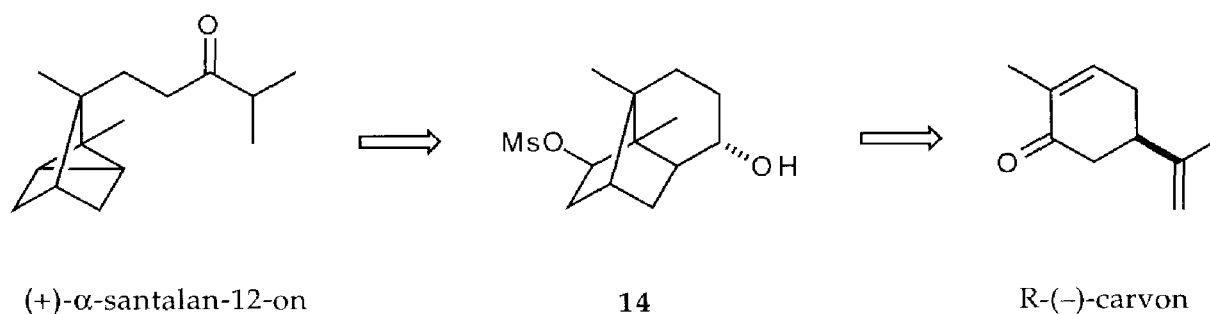
De negatieve lading die ontstaat op het zuurstofatoom van een Si-O binding tijdens de desilylering kan worden gestabiliseerd door electronenzuigende groepen verderop in het molecuul (Hoofdstuk 4). Deze stabilisatie hangt af van de electronenzuigende groep (sulfonaatester vs methylether) maar ook, en zelfs in

sterkere mate, van de geometrie van de " σ -relay". Dit blijkt uit de desilyleringssnelheid van de silylethers 1–3 en 5–7. De snelheid neemt toe wanneer de " σ -relay" verandert van een U- naar een W-vorm.

Omdat 1,4-diolmonosulfonaatesters met een "all-trans" geometrie van de " σ -relay" gemakkelijk een homofragmentatie geven is ook de fragmentatie van de 1,5-diolmonosulfonaatesters 10–12 onderzocht. In tegenstelling tot de 1,4-diolmonosulfonaatesters is de fragmentatiereactie bij deze verbindingen slechts een bijreactie (Hoofdstuk 5).



Afhankelijk van de mate van methylsubstitutie treedt de fragmentatie niet (10), marginaal (11), of in een opbrengst van ca. 20% (12→13) op. Duidelijk is dat de "seven-center" fragmentatie van 1,5-diolmonosulfonaatesters niet effectief toegepast kan worden in de organische synthese. Monosulfonaatesters van 1,4-diolen kunnen daarentegen wel uiterst voorspelbaar en selectief reageren en kunnen dus goed toegepast worden in totaalsynthesen. Eerder werk aan perhydroazuleensesquiterpenen (zie Hoofdstuk 1) en het werk aan α -santalaan sesquiterpenen zoals beschreven in dit proefschrift tonen dit aan.



De homofragmentatie van monogesulfoneerde 1,4-diolen is gebruikt als sleutelstap in de enantiospecifieke synthese van een α -santalaan. De precursor voor deze α -santalaan, mesylaet **14**, is verkregen uit het commercieel verkrijgbare (*R*)-(-)-carvon. Deze nieuwe "Carvon \rightarrow α -Santalaan-route" is een fraaie illustratie van de bruikbaarheid van de homofragmentatie in de synthese van natuurstoffen.

Curriculum Vitae

Petrus Marcus Franciscus Maria Bastiaansen werd geboren op 26 juli 1964 te Oudenbosch. Na het behalen van het MAVO-diploma werd vanaf 1981 gedurende drie jaar de chemische richting van de MLO te Breda gevolgd. Vier jaar later behaalde hij het diploma van de biochemische richting van de HLO eveneens te Breda. Gedurende deze laatste opleiding werd stage gelopen bij Enka Research te Arnhem, Organon International bv te Oss en het laboratorium van de vakgroep microbiologie en enzymologie van de Technische Universiteit te Delft.

Na een onderbreking van één jaar (militaire dienst) zette hij in september 1989 zijn studie voort. De doctoraal studie werd gevolgd aan de Katholieke Universiteit van Nijmegen en omvatte een hoofdvak Organische Chemie onder leiding van prof. dr. B. Zwanenburg. Tijdens deze studie werd in de zomer van 1991 deelgenomen aan een uitwisselingsproject met de Verenigde Staten en werd tien weken onderzoek verricht aan het Carleton College, Northfield, Minnesota (prof. dr. J. R. Mohrig). Het doctoraalexamen werd afgelegd op 16 december 1991.

Vanaf 1 januari 1992 tot 1 januari 1996 was hij als assistent in opleiding (AIO) werkzaam bij de vakgroep Organische Chemie van de Landbouwniversiteit te Wageningen. Het tijdens deze periode uitgevoerde onderzoek, begeleid door dr. J. B. P. A. Wijnberg en prof. dr. Æ. de Groot, staat beschreven in dit proefschrift.

Sinds 1 juni 1996 is hij werkzaam bij Diosynth bv te Oss.



Stellingen

- 1) Ondanks het feit dat 10-O-methyl-alismoxide geïsoleerd is uit een extract van *Alisma orientale* Juzep. is het niet waarschijnlijk dat deze verbinding in deze plant voorkomt.

Nakajima Y., Satoh Y., Katsumata M., Tsujiyama, K., Ida Y., Shoji K. *Phytochemistry*, **1994**, 36, 119.

- 2) Hoewel ook bij Riches *et al.* de solvolysen van een sulfonaat ester wordt beïnvloed door de aanwezigheid van een tin atoom in het molecuul is het door hun onderzochte ϵ -effect niet te vergelijken met eerder onderzochte (β , γ , δ en ζ -) effecten van tin.

Riches B. H., Kitching W. *Chem. Commun.* **1996**, 1907.

- 3) Niet droge tetrabutylammonium fluoride (TBAF.3H₂O) is in reacties vaak droger dan wordt gedacht.

Ko S. Y., Malik M., Dickinson A. F. *J. Org. Chem.* **1994**, 59, 2570.

- 4) Gelet op de discrepantie in de literatuur tussen de donor capaciteit van een C–H vs. een C–C binding is het onverantwoord de selectiviteit in de epoxidatie van een dubbele band in een bicyclisch amide zondermeer toe te schrijven aan de betere donor capaciteit van een C–H binding.

Nukui S., Sodeoka M., Sasai H., Shibasaki M. *J. Org. Chem.* **1995**, 60, 398.

- 5) Bij de structuur-opheldering van podoandin had de alternatieve structuur (**1b**) op grond van de verrichte ¹H-¹³C COSY metingen veel eerder verworpen kunnen worden.

Kubo I., Ying B-P., Castillo M., Brinen L. S., Clardy J. *Phytochemistry*, **1992**, 31, 1545.

- 6) Indien "through-bond interactions" (TBI) uitsluitend een vorm van σ -participatie zijn, dan zijn er geen TBI te verwachten tussen een tertiair carbocation en een alkoxide groep die vier σ -bindingen verwijderd is.

Herrmann R., Kirmse W. *Liebigs Ann.* **1995**, 699.

- 7) De door Koike *et al.* voorgestelde inversie op C(1) en C(7) tijdens de base geïnduceerde omlegging van **19** naar **20** is chemisch niet onderbouwd en in strijd met eerdere publicaties over dit onderwerp.

Koike T., Yamazaki K., Fukumoto N., Yashiro K., Takeuchi N., Tobinaga S. *Chem. Pharm. Bull.* **1996**, 646.

Wijnberg J. B. A., Jenniskens L. H. D., Brunekreef, de Groot A. E. *J. Org. Chem.* **1990** 55, 941.

- 8) Het is niet gemakkelijk in te zien hoe het zetten van een alternatieve "thee" kan leiden tot een goedkope biobrandstof.

Jayaraman K. S. *Nature* **1996**, 383, 112.

- 9) De tekortkoming in de naamgeving van organische moleculen wordt goed geïllustreerd door het verschijnen van steeds meer "graphical abstracts" in de vakliteratuur.
- 10) De gevlekte bosuil dankt zijn voortbestaan aan het grote aantal tuinierende Nederlanders.
- 11) Politieke besluitvorming wordt beïnvloed door de weerbaarheid van de gedupeerde groep.
- 12) De individualisering van de maatschappij treft het verenigingsleven aan twee kanten.
- 13) Onwetendheid is vaak de oorzaak van de veroordeling van de chemische sector.

Stellingen behorende bij het proefschrift **"Through-Bond Interactions in Monosulfonated 1,4- and 1,5-Diols and their Application in Natural Product Synthesis."**

Wageningen, 18 november 1996

P.M.F.M. Bastiaansen