Structural effects on sigmatropic shifts in heteroaromatic allyl ethers †

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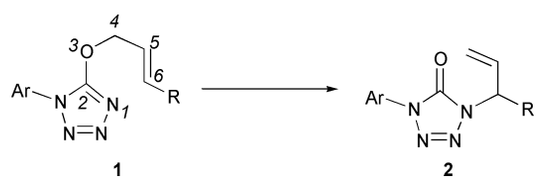
In contrast to the known thermal, exclusively [3,3], *O*- to *N*- rearrangement of allyl groups in phenyltetrazoles (**1**, Scheme 1), the comparable migration of the allyl group in pseudosaccharyl ethers (**3**; Scheme 2) has been shown to proceed through both [1,3]- and [3,3]-mechanisms, **4**, **5**; for the pseudosaccharyl derivative of the natural product myrtenol (**6**; Scheme 3) only the product **7** of a [1,3]-shift has been observed; crystallographic data and theoretical calculations provide an explanation of this ease of [1,3]-isomerization and the observed selectivity as being due to conformational constraints and electronic factors.

Introduction

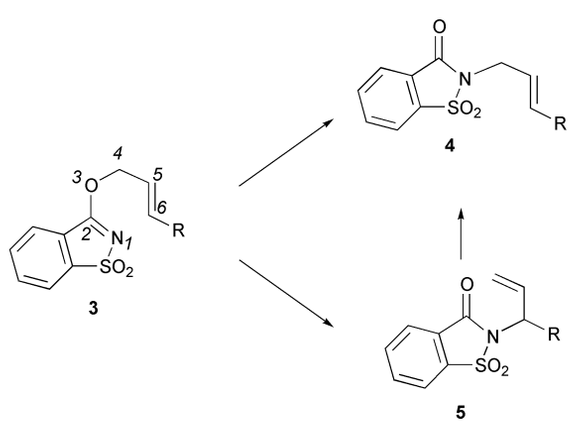
Compounds bearing an allylic alcohol function are often vital structural units of biologically active systems. Allyl alcohols have also attracted widespread attention as key intermediates in synthesis.[1] Previously, we have reported that selective hydrogenolysis of the C–OH bond of allyl alcohols could be achieved conveniently by first reacting the alcohol with a 5-chloro-1-phenyltetrazole to form the heteroaromatic allyl ether, which will then undergo smooth heterogeneously catalysed transfer hydrogenolysis to form the alkene corresponding to the allyl group and phenyltetrazolone.[2] Selective heterogeneous catalytic transfer reduction of such allyl ethers is remarkable, because it competes with hydrogenation of the double bond[2] and also with the relatively easy [3,3]-sigmatropic rearrangement,[3] which is not uncommon in this type of compound.[4] In ethers **1**, the heteroaromatic group together with oxygen from the original allyl alcohol or phenol acts as an excellent leaving group in catalysed *ipso*-substitutions.[5] It has also been found that 3-chloro-1,2-benzisothiazole 1,1-dioxide can be used successfully as an electron-withdrawing derivatizing agent, having an effect similar to that of a tetrazole. Its use presents some economic advantages over the tetrazole since it is made directly from cheap saccharin.[6]

Allyl ethers **1** and **3**, which can be regarded as imidates, are easily synthesised by reaction of allyl alcohols with heteroaromatic halides. In the present work, attention was devoted to the thermal isomerization of imidates formed from the electron-withdrawing heteroaromatic groups, phenyltetrazole (**1**; Scheme 1) and benzisothiazole 1,1-dioxide, (pseudosaccharin, **3**; Scheme 2). Allyloxytetrazoles **1** were obtained by initial reaction of an allyl alcohol with sodium hydride followed by reaction with 5-chloro-1-aryltetrazole.[3] Allyloxypseudosacharins **3** were obtained by direct reaction of an allylic alcohol with 3-chloro-1,2-benzisothiazole 1,1-dioxide in the presence of base.



1 **2**

Scheme 1



Scheme 2

It has been demonstrated that thermal *O*- to *N*- migration of allyl groups in a series of 5-aryltetrazolyl compounds **1** (Scheme 1) proceeds exclusively in a [3,3] sense through a polar chair-like transition state, to give aryltetrazolones **2**.[3] This behaviour is similar to the comparable general Cope rearrangement, which proceeds through an allowed [3,3]-mechanism.[4] Formally analogous thermal *O*- to *N*- rearrangement of an allyl group in pseudosaccharyl derivatives **3** has been shown to proceed through both [1,3] and [3,3] processes, to give the *N*-allyl products **4**, **5** (Scheme 2).[7] Thus, the migration is not exclusively [3,3] and the proportion of [1,3]- and [3,3]-products **4**, **5** depends on temperature, time of reaction and the polarity of the reaction medium. It has also been demonstrated

† Electronic supplementary information (ESI) available: selected crystal data for compound **7**. See http://www.rsc.org/suppdata/p1/b1/b102674g/

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Table 1 Selected structural data obtained from X-ray crystallographic analysis of ethers **1**, **3** (R = Me, Ph)[a]

Structure	R	Bond distances/Å				Angles/°
		O3–C4	C2–O3	C4–C5	(O3–C4)+(C2–O3)	C2–O3–C4
3	Me	1.488	1.314	1.477	2.802	115.9
3	Ph	1.480	1.318	1.493	2.798	116.5
1	Ph	1.489	1.316	1.461	2.800	115.5

[a] Atom numbering as in Schemes 1 and 2.

that, for such allyloxypseudosaccharins, [3,3]-products undergo inversion to the [1,3]-isomers when heated (Scheme 2). Electronic structure calculations[8] have indicated that the process is thermochemically controlled.[7] It is possible that, for ethers **3**, the [1,3]-rearrangement occurs through an allowed concerted pseudopericyclic mechanism, similar to that which has been observed in the rearrangement of allyl esters.[9] Our earlier work on the rearrangement of allyloxypseudosaccharins indicated that a fragmentation–recombination mechanism would not be more favoured than a concerted one.[7]

It has now been observed that, for the pseudosaccharyl derivative of myrtenol **6** (Scheme 3), a natural allylic alcohol, only the [1,3]-isomer **7** is obtained but the phenyltetrazolyl derivative **9** of the same natural product behaves like other allyl tetrazolyl ethers in affording exclusively the [3,3]-isomer **11** (Scheme 4).

Results and discussion

Ground state structural features are frequently used in the interpretation of reactivity.[10] In order to understand the observed difference in thermal behavior between allyloxytetrazolyl- and pseudosaccharyl ethers, X-ray structure determinations and molecular orbital calculations were undertaken. Investigation of structure and reactivity relationships for aryloxytetrazoles and aryloxypseudosaccharins towards catalytic transfer hydrogenolysis[5] and cross-coupling[11] have demonstrated that much of the reactivity of these ethers can be ascribed to changes in bond lengths about the central C–O–C ether bonds, caused by the powerful electron-withdrawing effect of the tetrazolyl or pseudosaccharyl ring systems, *viz*, the originally strong phenolic C–O bond becomes weak and the bond between the oxygen and the carbon of the heteroaromatic ring becomes very strong. The net result of the electronic changes in tetrazolyl or pseudosaccharyl ethers is to provide a molecular structure that lies close to a transition state structure, in which the originally strong phenolic C–O bond in the ether becomes easily cleavable catalytically.[5] Thermal migration of an allyl group from *O*- to -*N* in ethers **1** and **3** involves breaking the ether bond O3–C4 (Schemes 1 and 2) and a shortening of the ether bond C2–O3, as it becomes a formal carbonyl in the leaving group. Therefore, isomerisation should be assisted by ground-state structures of the starting materials if the C–O bonds in the C–O–C ether linkage are already changed advantageously along the reaction co-ordinate.

X-Ray crystallographic data for cinnamyloxytetrazole (**1**; R = Ph; Scheme 1) and cinnamyloxypseudosaccharin (**3**; R = Ph; Scheme 2) indicate that these compounds possess ether linkages having exceptionally short and long C–O bonds (C2–O3 and O3–C4 respectively; Schemes 1 and 2), similar to those found in crotyloxypseudosaccharin (**3**; R = CH_3).[12]

Selected bond lengths and angles for these ethers are presented in Table 1 and show that, for the ether bond O3–C4, bond lengths range from 1.480 to 1.489 Å, which are significantly longer than a normal aliphatic C–O bond (typically 1.43 Å).[13] For the ether bond C2–O3, bond lengths range from 1.314 to 1.318 Å, values that are indicative of partial double bond character. The sum of the bond lengths C2–O3 and O3–C4 for the three ethers is very similar (2.80 ± 0.02 Å). The electron-withdrawing effect of the tetrazolyl and pseudosaccharyl ring extends also into the allyl group. For example, the C4–C5 bond lengths range from 1.461 to 1.493 Å and are significantly shorter than a "standard" single bond (1.53 Å).[13] The considerable degree of sp^2 character at the ether oxygen atom is further confirmed by C2–O3–C4 bond angles of about 116° observed for the tetrazolyl and pseudosaccharyl ethers (Table 1). Therefore, the ground state bond lengths and angles of compounds **1** and **3** are very similar around the central C–O–C linkage.

A search for crystallographic data of other imidates and also for anilides (analogues of the rearranged products of **1** and **3**) has been performed using the Cambridge Crystallographic Database.[14] Structures are presented in Fig. 1 and relevant bond lengths in Table 2.

For compounds **12**–**14** (Table 2, entries 1–3), mean bond lengths C2–O3 are about 1.35 Å (1.32 Å in ethers **1** and **3**) and bond lengths O3–C4 are about 1.44 Å (1.48 Å in ethers **1** and **3**; Table 2).[15] Thus, the bond C2–O3 is shorter than the other ether bond O3–C4 in compounds **12**–**14**, but the difference is not as significant as in compounds **1** and **3**, even for compound **12**, in which there is an electron withdrawing group (CCl_3; entry 1).

For compounds **15**–**22** (analogues to the products of the isomerization in which there is a new C–N bond, N1–C6, and a carbonyl bond that has been formed from the shorter ether bond, C2–O3), no significant differences for the carbonyl bond, and the C–N bond lengths are observed. The spread of values in compounds **15**–**22** (Table 2, entries 4–11)[16] certainly results from the size and the varied nature (presence or absence of heteroatoms) of the ring to which the allyl group is connected. In compounds **2**, **4** and **5**, C–N and C=O bond lengths are not exceptional either. As discussed later, the electron-withdrawing effect of pseudosaccharyl and tetrazolyl groups is not as effective towards the allyl group attached to nitrogen as it is when the allyl group is attached to the oxygen atom.

Despite ground state structural similarities between compounds **1** and **3**, their reactivity (thermal rearrangement) differs substantially. Cinnamyl and crotyl derivatives of tetrazole (**1**, R = Ph and CH_3 respectively) are converted only to the corresponding [3,3]-isomers when heated neat at 130 °C for 6 and 8 minutes respectively. In contrast, the corresponding pseudosaccharyl derivatives, respectively, require 2 and 3 hours heating under the same experimental conditions and give a mixture of the [1,3]- and [3,3]-migration products.[7] Extended heating times lead to a gradual reduction in the portion of the [3,3]-isomer and an increase in the [1,3]-isomer. The course of the rearrangement was monitored by ^{1}H-NMR spectroscopy, which allows the [3,3]- and [1,3]-products of migration to be distinguished easily and their amounts to be measured quantitatively. Resonances for protons of the allylic system are substantially different in inverted and non-inverted isomers. For instance, for the case of cinnamyloxypseudosaccharin (**3**, R = Ph) analysis of ^{1}H-NMR spectra of the rearranged product reveals two sets of characteristic signals for the [1,3]- and [3,3]-migration products. In particular, signals at δ 4.50 (CH_2), 6.20–6.40 (CH) and 6.80 (CH) for [1,3]-migration and at δ 5.45 (CH_2), 5.80 (CH) and 6.50–6.70 (CH) for [3,3]-migration are particularly prominent and well resolved. No other significant products of reaction were detected.

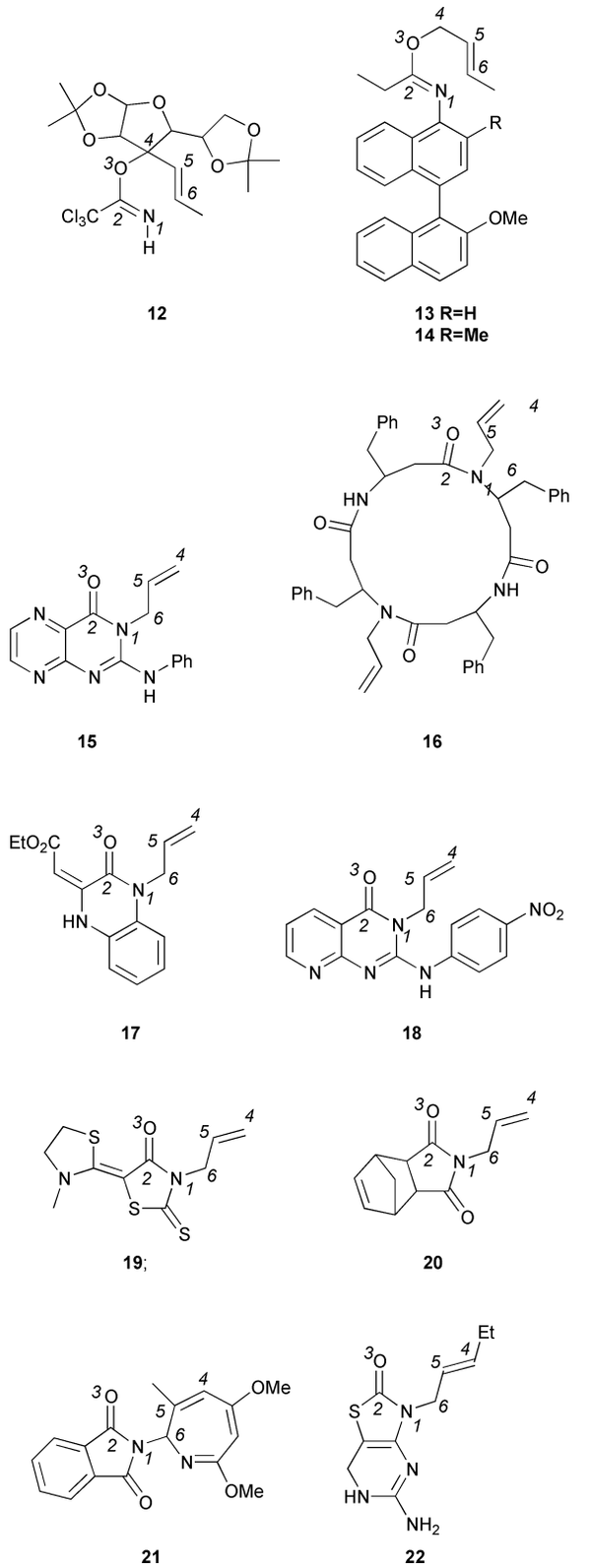


Fig. 1 Structures of imidate and anilide analogues of compounds **1**, **3** and their rearranged products. CCDC references to these compounds can be found in Table 2 and see ref. 15 and 16.

The easy exclusive [3,3]-rearrangement of allyloxy compounds **1** can be ascribed to the ground state structure being already advanced along the reaction coordinate for migration, in agreement with earlier studies of structure and reactivity.[17] However, the observation of mixed [1,3]- and [3,3]- migrations in compounds **3** and the much lower rate of rearrangement, suggests that the structure of the transition state must play an important role.[4]

In order to attempt application of the thermal isomerisation to the transformation of natural products so as to give novel compounds, it was decided to prepare heteroaromatic ethers of some naturally occurring allylic alcohols. Myrtenol falls into this category and has been used as a synthon in organic synthesis.[18] Myrtenol has also been used as a chiral modifier in the enantioselective reduction of ketones.[19] Contrary to results for synthesized ethers **3** (R = H, Me, Ph), during attempted preparation of the pseudosaccharyl ether of myrtenol by its reaction with pseudosaccharyl chloride at 40 °C, following a route that had been used many times before with similar compounds, none of the required myrtenyl ether (**6**, Scheme 3) could be isolated. Instead, as confirmed by X-ray crystallography (Fig. 2), the isomeric *N*-myrtenyl compound **7**, resulting from

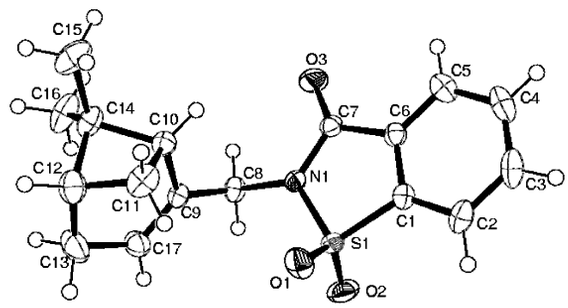


Fig. 2 A perspective view of the structure of ether **7** obtained by X-ray crystallography, showing 50% probability displacement ellipsoids.[20]

[1,3]-sigmatropic rearrangement of the required ether **6**, was the sole crystalline product. When the synthesis was carried out at 20 °C it was possible to isolate the ether **6** and this was found to undergo an exclusive [1,3]-shift to the corresponding *N*-myrtenyl isomer, **7**, when heated at 40 °C for about 30 minutes. This observation was surprising in that the isomerization affords solely the [1,3]-isomer and is much faster than with other pseudosaccharyl derivatives.

X-Ray data for compound **7** are presented here (see supplementary material).† The structure is unexceptional in that the heterocyclic ring is essentially planar (see supplementary material, torsion angles) and its bond angles are similar to those expected for a 1,2-benzisothiazolone 1,1-dioxide. The N1–C8 bond (Fig. 2) is very similar in length to that of a simple aliphatic C–N single bond.[11] There are no exceptional bond lengths or angles in the myrtenyl part of the molecule.[11] However, the very ordinariness of the N1–C8 bond suggests that the saccharyl group is not exerting any electron-withdrawing effect, in contrast to the powerful electron-withdrawing effect found for 3-substituted allyl ethers of saccharin discussed above. The difference may lie in the length of the conjugation systems, since an ether oxygen atom at the 3-position of the benzisothiazole ring can delocalise easily through the heterocycle to the SO_2 group but the heterocyclic nitrogen can only "cross" delocalise to either the carbonyl oxygen at position 3 or to the SO_2 group.

A tetrazolyl derivative of myrtenol, **9**, was also prepared and its thermal behavior studied (Scheme 4). When heated neat at 100 °C this allyl tetrazolyl ether **9** isomerized in two hours to give exclusively the tetrazolone **10**, resulting from a concerted [3,3]-migration of the myrtenyl group. None of the possible product of [1,3]-migration, **11**, was observed. To assess the stability of tetrazolone **10** at higher temperatures, a sample of **10** and (separately) another sample of the precursor ether **9**, were heated at 150 °C for one hour. Analysis of these samples indicated that, again, only the products of [3,3]-isomerization were present. This behavior is in sharp contrast to that observed for pseudosaccharyl derivatives, for which conversion of the [3,3]- into the thermodynamically more stable [1,3]-isomer was observed (Scheme 2).[7]

Table 2 Selected bond lengths, from compounds **12**–**22**[a]

Entry	Structure	Bond distances/Å						Ref.[b]	CCDC reference[c]
		N1–C2	C2–O3	O3–C4	C4–C5	C5–C6	N3–C6		
1	**12**	1.247	1.352	1.435	1.504			15*a*	HAGGOL
2	**13**	1.263	1.347	1.442	1.484	1.311		15*b*	ROKSAL
3	**14**	1.264	1.347	1.451	1.484	1.295		15*b*	ROKSEP
4	**15**	1.394	1.228		1.272	1.461	1.473	16*a*	BAFZUD
5	**16**	1.352	1.240		1.310	1.495	1.479	16*b*	COGGIO
6	**17**	1.366	1.230		1.306	1.498	1.467	16*c*	HIPVUX
7	**18**	1.396	1.225		1.314	1.500	1.490	16*d*	JOYRAQ
8	**19**	1.457	1.235		1.334	1.514	1.479	16*e*	SALAZO
9	**20**	1.376	1.211		1.289	1.494	1.458	16*f*	TEFJUJ
10	**21**	1.403	1.206		1.334	1.520	1.463	16*g*	YONKER
11	**22**	1.358	1.216		1.328	1.485	1.470	16*h*	ZETDAD

[a] Atom numbering as in Fig. 1. [b] As given in the references section. [c] The CCDC reference codes for compounds 12–22 respectively.

Semi-empirical (PM3) molecular orbital calculations were carried out in order to cast light on the mechanism of conversion of heteroaromatic derivatives of myrtenol **6** and **9** into the isomers **7**, **8** and **10**, **11** respectively, *via* possible intermediates (**TS1**, **TS2** and **TS3**, **TS4**; Schemes 3 and 4, respectively). The structures in Figs. 3 and 4 reveal the preferred conformations for

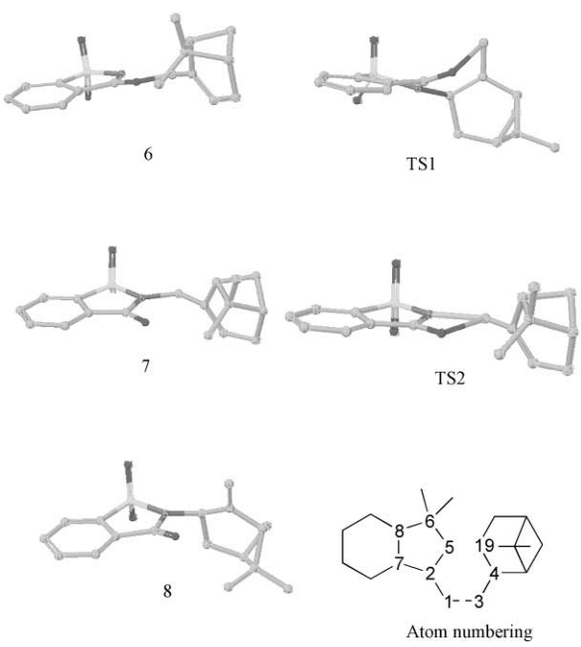
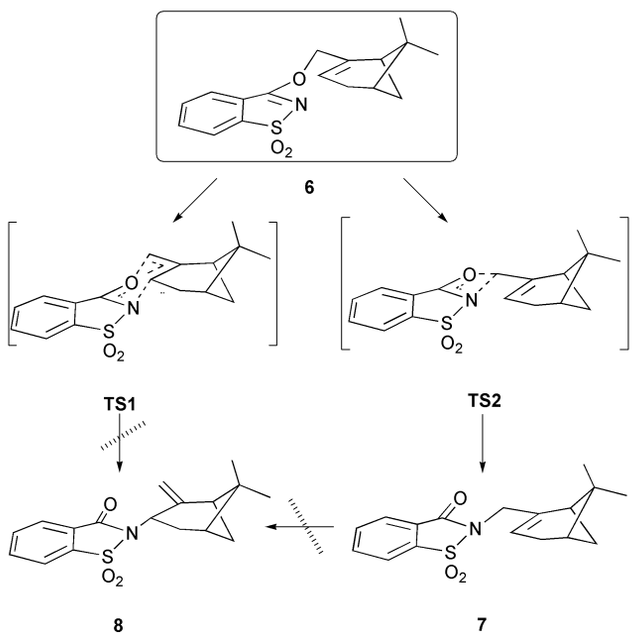


Fig. 3 Calculated minimum energy structures for compounds **6**, **7**, **8** and transition structures **TS1** and **TS2** (Scheme 3).

starting materials **6** and **9**, products **7**, **8**, **10** and **11** and saddle point structures **TS1–TS4**.

For the [3,3]-rearrangement, there are four possible transition state structures, resulting from different possible modes of approach of the double bond in the myrtenyl system to the C=N bond in the heteroaryl system but the one depicted in Schemes 3 and 4 is more favoured because it leads to a less hindred chair-like transition state structure (see supplementary information).

Table 3 lists selected calculated structural data for compounds **6**–**11** and transition states **TS1–TS4**. Minimum energy calculations on the structures of starting materials predict features found in X-ray structural results, such as one short (bond 1–2; 1.34 Å in ether **6** and 1.35 Å in ether **9**), and one long carbon–oxygen ether bond (bond 1–3; 1.44 Å in ethers **6** and **9**) resulting from the electron-withdrawing effect induced by either of the heterocyclic groups. The 5-membered rings are calculated to be planar in both ethers, just as has been observed by X-ray crystallography for other ethers.[5] Similar minimum



Scheme 3

energy calculations on the products of rearrangement predict no extraordinary characteristics. All bond lengths and angles are "standard" and the 5-membered heterocycles are essentially planar. Regarding the transition state structures **TS1** and **TS3**, which were deduced using the algorithms included in the CAChe suite of programs,[8] they show considerable extension of the C–O bond that is about to break. In **TS1**, the 5-membered ring is considerably changed from planarity, as indicated by a dihedral angle of −23.59° (Table 3). In all other transition structures **TS2**, **TS3** and **TS4**, the 5-membered rings are essentially planar.

The values calculated for heats of formation of structures **6**–**11** and transition state structures (saddle point) **TS1–TS4**, at PM3[8] level (Table 3), show that the relative change in enthalpy of formation for conversion of ether **6** into its [3,3]-sigmatropic product **8** *via* **TS1** is 67 kJ mol^{-1} higher than that required for the conversion of ether **6** into the [1,3]-sigmatropic product **7**, as depicted in Fig. 5a. Therefore, it is reasonable to expect that, for the saccharyl ether of myrtenol, the 1,3-rearrangement would be overwhelmingly favoured kinetically over the [3,3]-rearrangement.

It was found also that the [3,3]- and the [1,3]-products **8**, **7** are almost equally stable (*ca.* 167 and 171 kJ mol^{-1} respectively). Thus, the preferential formation of isomer **7** must mostly be due to lower activation energy (Fig. 5a). Analysis of the geometry for structures **TS1** and **TS2** (Fig. 3) shows how differences in their relative energies may arise. **TS1** results from a concerted

Table 3 Enthalpies of formation and selected bond lengths and angles calculated for compounds **6**–**11** and transition states **TS1**–**TS4**[a]

		dihedral angles/°		bond distances /Å						
Structure (Figs.)	ΔH_f kJ mol^{-1}	8–7–2–5	7–8–6–5	1–2	1–3	2–5	3–4	4–19	5–3	5–19
6 (3A)	−136.6	6.32	5.08	1.344	1.439	1.312	1.494	1.346	–	–
7 (3B)	−171.4	0.03	0.43	1.205	–	1.436	1.502	1.350	1.502	–
8 (3C)	−167.2	−5.26	0.98	1.210		1.447	1.334	1.519	–	1.508
TS1 (3D)	158.8	−23.59	8.57	1.214	2.548	1.448	1.382	1.505	–	1.549
TS2 (3E)	92.0	1.70	−0.50	1.240	2.074	1.364	1.462	1.353	1.999	–
9 (4A)	426.4	−0.08	0.03	1.349	1.435	1.363	1.499	1.347	–	–
10 (4B)	384.6	0.80	4.93	1.217	–	1.433	1.335	1.514	–	1.506
11 (4C)	372.0	1.56	0.91	1.221	–	1.437	1.493	1.347	1.493	–
TS3 (4D)	635.4	−4.617	0.30	1.227	2.007	1.433	1.364	1.464	–	1.756
TS4 (4E)	698.1	3.63	3.57	1.248	2.241	1.390	1.432	1.360	2.164	–

[a] Atom numbering as in Figs 3, 4.

pathway, which involves the formation of a chair-like six-membered ring with two partial bonds.[12] **TS2** involves the formation of a partially formed four membered ring (Scheme 3). Analysis of ground state structures (either calculated, Fig. 3 (**6**), or from experimental X-ray determinations[5]) indicates that the benzisothiazole system is always planar and any deviation from planarity must cause a significant increase in energy. Fig. 3 (**TS1**) shows that, for transition state structure **TS1**, the isothiazole 5-membered ring would need to have an "envelope" conformation, giving rise to conformational strain.

Considering that the benzisothiazole ring is highly rigid, the geometry through which a concerted [3,3]-rearrangement would take place is not favoured because it would cause too much distortion to the isothiazole system and hence result in a high energy of activation for [3,3]-rearrangement. This torsional constraint was not observed for other pseudosaccharyl ethers with linear allylic systems such as allyl, crotyl or cinnamyl; in all these cases, the allylic system has no such constraints imposed on the transition state structure and a chair-like conformation can be attained without disrupting the planarity of the benzisothiazole system. With a more rigid allylic system, such as that in myrtenol (which has insufficient flexibility to allow for a chair-like transition structure) [3,3]-migration is difficult to achieve without forcing the benzisothiazole system out of planarity. In contrast, a [1,3]-rearrangement involves a transition state structure, either ionic or concerted,[7] that does not impose any conformational constraint on the benzisothiazole system. Thus, the transition state structure **TS2** is considerably more stable than **TS1** (Fig. 3). One factor that may contribute to this difference in stability is the size of the SO_2 group, which does not cause any significant steric hindrance in the [1,3]-transition state structure but may cause some in the [3,3]. On the other hand, for the [1,3]-rearrangement of **6**, bond formation is at a sterically less demanding primary carbon, making the [1,3]-pathway more competitive.

Isomerization of the tetrazolyl analogue **9** to the [3,3]-product **10** *via* transition structure **TS3** requires an increase in enthalpy of 209 kJ mol^{-1} but conversion into the [1,3]-product **11** would require 272 kJ mol^{-1} (Fig. 5b). Again, this difference explains the preferred [3,3]-isomerization of ether **9** into isomer **10** rather than **11**.

It is notable that the calculated structure **TS3** (Fig. 4) shows a tetrazolyl ring which is essentially planar; this contrasts with the structure calculated for the [3,3]-rearrangement of the benzisothiazolyl ether **TS1**, which would have to be bent (Fig. 3). Since the tetrazolyl system does not bear any bulky substituent group, the less strained 6-membered transition state is naturally more favoured.

Considering the [1,3]-rearrangement, which probably has a considerable degree of ionic character, it seems reasonable to assume that the migration of the allylic "cation" is more easily effected to a more negative nitrogen atom. PM3 calculations

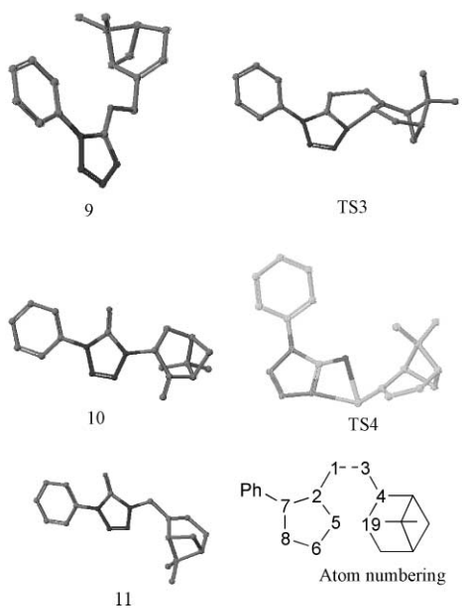


Fig. 4 Calculated minimum energy structures for compounds **9**, **10**, **11** and transition structures **TS3** and **TS4** (Scheme 4).

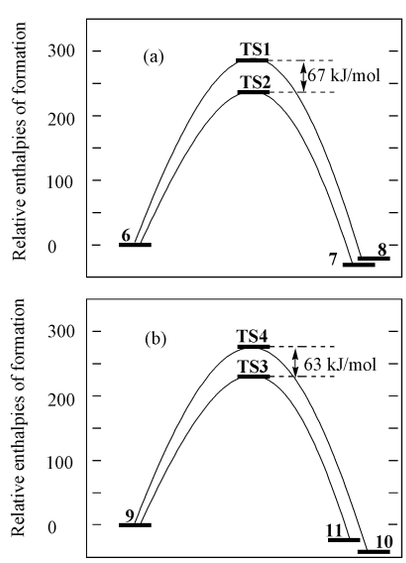
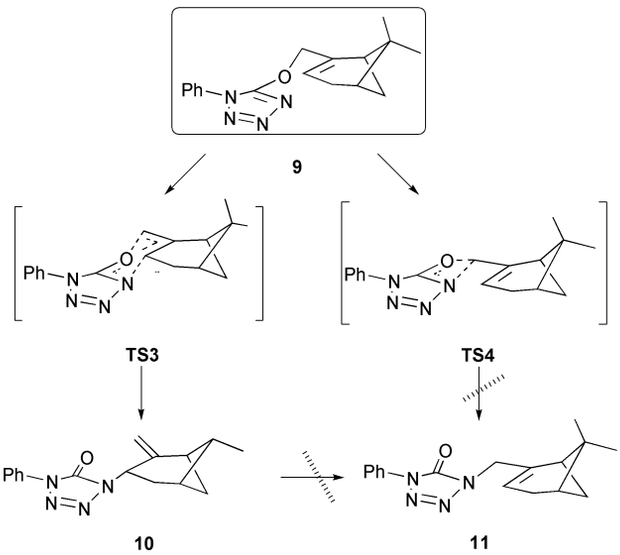


Fig. 5 Diagram showing the variation in relative enthalpies of formation (a) for the conversion of ether **6** into isomers **7**, **8** *via* transition structures **TS1**, **TS2** respectively and, (b) for the conversion of tetrazolyl ether **9** into isomers **10**, **11** *via* transition structures **TS3**, **TS4** respectively.

were performed on the anions of saccharin and tetrazole, starting with a formal negative charge on the oxygen atom. After energy minimization, again at PM3 level of theory, the partial



Scheme 4

charges in the oxygen atom (from which the allyl group departs) were −0.458 for saccharin and −0.464 for the tetrazolone, which are very similar. However, when considering the charges on the nitrogen atom to which the myrtenyl group migrates, the partial charges differ significantly, being −0.794 in the saccharin anion and −0.432 in the tetrazolone anion. Therefore it is expected that the migration of the allylic "cation" will be easier to the more negative nitrogen of the saccharyl "anion". This is again in agreement with the experimental fact that only ether **6** undergoes a [1,3]-sigmatropic shift. If the charges of all the atoms in the heteroaromatic part of neutral molecules **6** and **9** are summed together, it is also found that the charges in the tetrazolyl system (including the oxygen atom) add up to −0.188, whereas they are −0.223 in the saccharyl system; this last effect would increase the possibility of a fragmentation–recombination mechanism for the rearrangement of ether **6**.

In terms of mechanism, if the rearrangements are considered to be pericyclic, only the [3,3] should be observed for both ethers **6** and **9**, since the [1,3]-sigmatropic rearrangement is forbidden by the Woodward–Hoffmann rules. However, this "forbidden" migration is observed exclusively in the pseudosaccharyl ether **6**, possibly *via* a pseudopericyclic mechanism.

Conclusion

It has been observed experimentally that pseudosaccharyl and tetrazolyl ethers of myrtenol undergo different thermal isomerizations despite them having similar bond lengths and angles about the central C–O–C ether bonds. The different reactivities of these ethers may be interpreted in terms of the following criteria. (i) The relative stabilities of the corresponding transition state (saddle point) structures for the [3,3]- and [1,3]-sigmatropic shift. The [3,3]-pathway is less energy demanding for the tetrazolyl ether and the 1,3-pathway is less energy demanding for the pseudosaccharyl ether. (ii) The higher negative charge on the nitrogen atom in the benzisothiazolyl derivative, may explain why ether **6** undergoes exclusively the [1,3]-rearrangement, which has more ionic character. Steric hindrance induced by the bulky SO_2 group, also acts in favour of the less hindered 1,3-pathway. (iii) On the basis of the evidence shown, it seems reasonable to propose that the [1,3]-rearrangement occurs through a pseudopericyclic mechanism.

Experimental

General procedures

Melting points were recorded on a Stuart Scientific SMP3 melting point apparatus and are uncorrected. Mass spectra were obtained on a VG 7070E mass spectrometer by electron ionization (EI) at 70 eV. Proton NMR spectra were obtained on a Varian Gemini 300 FT spectrometer using TMS as the internal standard. All chemicals were used as purchased (Aldrich). Theoretical calculations were performed on an Apple G4 Macintosh using the CAChe WorkSystem 4.1.1 from Oxford Molecular, 1999.[8] Crystallographic data were recorded on a STOE–IPDS diffractometer using graphite monochromated Mo-Kα radiation ($\lambda = 0.71073$ Å, $T = 213$ K). The structure was solved by Direct Methods and were refined by full matrix least squares against F^2 using all data.[21] ‡

3-[(1*R*)-6,6-Dimethylbicyclo[3.1.1]hept-2-en-2-ylmethoxy]- 1,2-benzisothiazole 1,1-dioxide 6

3-Chloro-1,2-benzisothiazole 1,1-dioxide (pseudosaccharyl chloride, 0.71 g, 3.5 mmol) was added to a solution of (1*R*)-6,6-dimethylbicyclo[3.1.1]hept-2-en-2-ylmethanol (myrtenol; 0.5 ml; 3.3 mmol) and triethylamine (5mL) in toluene (50 mL). The mixture was stirred at room temperature until complete disappearance of pseudosaccharyl chloride (TLC, dichloromethane, 2 h). The precipitate of triethylamine hydrochloride was filtered off and the filtrate was washed with brine, and water, and dried (Na_2SO_4). Evaporation of the solvent under vacuum provided the required ether as pale yellow needles (ethyl acetate; 0.46 g; 44% yield; mp 66–67 °C). Analysis: Found C 64.02, H 6.04, N 4.48%, $C_{17}H_{19}NO_3S$ requires C 64.33, H 6.03, N 4.41%. ^{1}H NMR ($CDCl_3$): δ 0.90 (3H, s); 1.19 (1H, d); 1.30 (3H, s); 2.10–2.20 (1H, m); 2.23–2.30 (1H, m); 2.33–2.40 (2H, q); 2.41–2.53 (1H, m); 4.95 (2H, s); 5.82 (1H, t); 7.68–7.73 (2H, m); 7.74–7.80 (1H, q); 7.89 (1H, d, $J = 8.0$ Hz). MS (CI), *m*/*z* 318 ($M + H^+$); 335 ($M + NH_4^+$).

2-[(1*R*)-6,6-Dimethylbicyclo[3.1.1]hept-2-en-2-ylmethyl]-3-oxo-1,2-benzisothiazole 1,1-dioxide 7

The procedure was exactly as above but the reaction was carried out at 40 °C to give pale yellow needles (ethyl acetate, 0.90 g; 87% yield; mp 120–121 °C). Analysis: Found C 64.20, H 6.05, N 4.43%, $C_{17}H_{19}NO_3S$ requires C 64.33, H 6.03, N 4.41%. ^{1}H NMR ($CDCl_3$): δ 0.84 (3H, s); 1.28 (3H, s); 2.07–2.10 (1H, m); 2.20–2.25 (1H, q); 2.35–2.42 (2H, m); 4.15–4.20 (2H, q); 4.33–4.39 (2H, d); 5.69 (1H, t); 7.79–7.93 (3H, m); 8.03–8.08 (1H, d, $J = 8.0$ Hz). MS (EI), *m*/*z* 317 (M^+). Experimental data for X-ray diffraction studies of this compound are presented in the supplementary material.

5-[(1*R*)-6,6-Dimethylbicyclo[3.1.1]hept-2-en-2-ylmethoxy]-1-phenyltetrazole 9

3-[(1*R*)-6,6-Dimethylbicyclo[3.1.1]hept-2-en-2-yl]methanol (myrtenol; 0.45 g; 2.9 mmol) in dry THF (10 mL) was added to a slurry of sodium hydride (50.3 g; 60% dispersion in mineral oil; 7.8 mmol) in dry THF (30 mL) under an anhydrous atmosphere. The mixture was stirred at room temperature until no further effervescence was observed (*ca.* 20 min), and then a solution of 5-chloro-1-phenyltetrazole (0.60 g, 2.8 mmol) in dry THF (10 mL) was added all at once. The reaction was monitored by TLC using dichloromethane as eluent. The mixture was stirred overnight at room temperature and then water (30 mL) was added and the organic material was extracted with diethyl ether (3 × 30 mL). The diethyl ether extract was dried (Na_2SO_4), filtered and the filtrate was evaporated to afford the required product as a pale yellow oil that slowly crystallised. Colourless crystals from ethanol (0.40 g; 40% yield; mp 120–122 °C). Analysis: Found C 68.45, H 6.88, N 18.70%, $C_{17}H_{20}N_4O$ requires C 68.89, H 6.80, N 18.90%. ^{1}H NMR ($CDCl_3$): δ 0.84 (3H, s); 1.16–1.26 (2H, m); 1.30 (3H, s); 2.13–2.15 (1H, m); 2.23–2.32 (2H, m); 2.39–2.49 (1H, m); 5.00 (2H,

‡ CCDC reference number 164104.

s); 5.80 (1H, t); 7.44–7.57 (3H, m); 7.70–7.75 (2H, d). MS (EI), *m*/*z* 296 (M^{+}).

4-[(1*R*)-6,6-Dimethylbicyclo[3.1.1]hept-2-en-2-ylmethyl]-1-phenyltetrazol-5-one 11

5-[(1*R*)-6,6-Dimethylbicyclo[3.1.1]hept-2-en-2-ylmethoxy]-1-phenyltetrazole (0.03 g; 0.1 mmol) was placed in an NMR tube and heated neat in an oil bath at 100 °C for 2 hours. The resulting material was dissolved in deuteriated chloroform and examined by ^{1}H NMR spectroscopy. Signals at δ 4.89–4.95 (=CH_2), and 5.30–5.38 (NCH) correspond to [3,3] migration and were particularly prominent and easily resolved. There was no evidence for formation of the [1,3]-product.

^{1}H NMR ($CDCl_3$): δ 0.89 (3H, s); 1.35 (3H, s); 1.57 (1H, m); 2.14–2.28 (2H, m); 2.55–2.57 (1H, d); 2.60–2.68 (2H, q); 4.89–4.95 (2H, d); 5.30–5.38 (1H, m); 7.33–7.61 (3H, m); 7.96–8.01 (2H, d). MS (EI), *m*/*z* 297 $(M + H)^{+}$.

(*E*)-3-(3-Phenylprop-2-enoxy)-1,2-benzisothiazole 1,1-dioxide 3 (R = Ph)

3-Chloro-1,2-benzisothiazole 1,1-dioxide (pseudosaccharyl chloride, 0.92 g, 4.5 mmol) was added to a mixture of (*E*)-3-phenylprop-2-en-1-ol (cinnamyl alcohol; 0.67 g, 5.0 mmol) and triethylamine (5 mL) in toluene (30 mL). The solution was stirred at 40 °C until all of the starting material had disappeared (TLC, about 2 h). The precipitate of triethylamine hydrochloride was filtered off and the filtrate was evaporated to give a yellow solid, which was recrystallised (ethanol; 0.53 g, 40% yield, mp 117–118 °C). Analysis: Found C 64.02, H 4.42, N 4.67%, $C_{16}H_{13}NO_3S$ requires C 64.20, H 4.38, N 4.68%. ^{1}H NMR ($CDCl_3$): δ 5.25 (2H, d, J = 7 Hz); 6.60 (1H, m); 6.85 (1H, d, J = 15.6 Hz); 7.20–7.50 (5H, m); 7.70–7.80 (3H, m); 7.80–7.90 (1H, d, J = 8.0 Hz). MS (EI), *m*/*z* 299 (M^{+}).

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