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Five- and six-membered ring formation from the intramolecular reaction of a protonated oxirane and alkene

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ABSTRACT

Computational studies of competing five- and six-membered cyclisation of alkenyloxiranes **1a**–**d** show that intramolecular reaction of a protonated oxirane and alkene is a concerted, single-step, exothermic process. The reactions proceed via reactant-like transition states, but where the oxirane C–O bond is considerably stretched. Two factors are seen to affect the regiochemistry: (1) stabilisation of the transitory positive charge in the transition state favours cyclisation to the more highly substituted oxirane carbon; and (2) there is an inherent stereoelectronic preference for six-membered cyclisation over five-membered cyclisation. The inherent preference for six-membered cyclisation has a parallel in Baldwin's rules for six-membered ring closure of a carbocation with an alkene, rather than Baldwin's rule for intramolecular nucleophilic reaction of three-membered rings, suggesting that the protonated oxirane mimics a carbocation. The electronic and stereoelectronic effects for cyclisation are modified by steric interactions of axial methyl groups. These systems provide a model for the A-ring cyclisation of oxidosqualene.

1. Introduction

In animals and fungi, the four carbocyclic rings and seven stereocentres of the steroid precursor lanosterol are formed from 2,3-(*S*)-oxidosqualene in a remarkable process catalysed by the single enzyme oxidosqualene cyclase (Fig. 1).[1–3] The reaction in the enzyme active site is initiated by complexation of the oxirane oxygen with an acidic aspartic acid residue,[4,5] and ring-opening of the protonated oxirane is considered to occur in concert with the intramolecular attack of the 6,7-double bond to form the six-membered A-ring of lanosterol.[4]

An earlier computational study by Pan et al.[6] investigated the uncatalysed and methanoic acid-catalysed six-membered cyclisation of compound **1a** and found agreement with Corey's conclusions that carbocyclic ring formation and oxirane opening are concerted. The theoretical study (B3LYP/6-31+G(d)//HF/6-31G(d)) showed the transition state for the uncatalysed reaction is reached with an activation energy of 57.0 kcal mol^{-1} and formation of the zwitterion is endothermic by 55.9 kcal mol^{-1}, just 1.1 kcal mol^{-1} below the transition state. Activation by the weakly acidic methanoic acid lowers the activation barrier to 42.9 kcal mol^{-1} and the overall reaction is endothermic by 37.7 kcal mol^{-1}.

Oxidosqualene is stable in glacial acetic acid and stronger acids such as trichloroacetic acid are required to catalyse non-enzymic cyclisation.[4,7] The high activation energy Pan and Gao calculated for methanoic acid-catalysed cyclisation of A-ring model **1a** is consistent with the relative experimental stability of oxidosqualene in acetic acid and trichloroacetic acid. Corey[5] has suggested that the acidity of the catalytic aspartic acid residue in oxidosqualene cyclase is enhanced by a proximate protonated histidine.

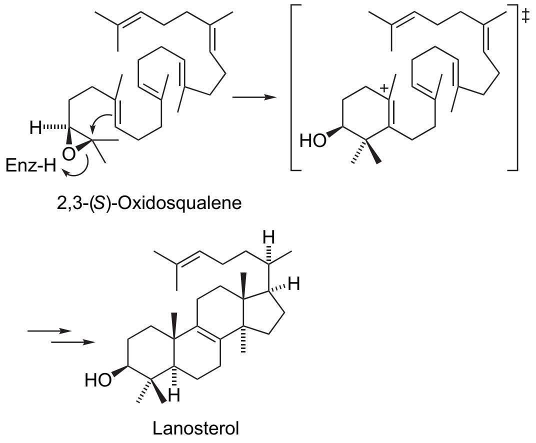

Figure 1. Enzyme-catalysed formation of lanosterol from oxidosqualene showing A-ring formation.

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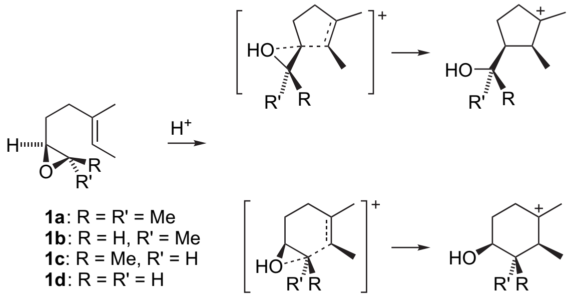

Figure 2. The proton-catalysed six- and five-membered cyclisations of model compounds **1a**–**d**.

Pan and Gao performed calculations on six-membered cyclisation of **1a** with a proton, finding a number of structures between the minima with fixed C2–C7 distances. They did not identify a transition structure, but found a structure ca. 0.6 kcal mol^{-1} above the reactant. Their studies are consistent with cyclisation by oxidosqualene cyclase where the acidity of the catalytic aspartic acid is enhanced. Recently, Hess[8] identified the transition structure using density functional calculations (B3LYP/6-31G(d)//B3LYP/6-31G(d)). The activation barrier was calculated to be low (0.4 kcal mol^{-1}) and the reaction was exothermic ($\Delta E = -13.0$ kcal mol^{-1}).

The present study extends the work of Pan and Gao and of Hess. We now report a computational study of the proton-catalysed cyclisation of compounds **1b**–**d** along with **1a** (Fig. 2) to elaborate the effect of oxirane substitution on the partition to both five- and six-membered ring compounds. This study is directed to establish the inherent factors underlying the regioselectivity of cyclisation of alkenyloxirane and thereby to extend Baldwin's rules to these systems.[9,†]

2. Results

Stationary points on the potential energy surfaces for formation of a six-membered ring from protonated **1a** were defined by Hess at both B3LYP/6-31G(d) and HF/6-31G(d) levels of theory.[‡] For **1a** we have located the transition structures at B3LYP/6-31+G(d)//HF/6-31G(d) for the five-membered cyclisation as well as the previously described six-membered cyclisation. In addition, we report the potential energy surfaces for the proton-catalysed five- and six-membered cyclisations of compounds **1b**–**d**. All transition states have been confirmed by frequency and intrinsic reaction coordinate (IRC) calculations, and energies have been corrected for zero-point energy from these frequency calculations. All calculations were performed using Gaussian 94W[10] and Gaussian 03W.[11]

Protonation of facially differentiated oxiranes can occur from either face of the ring to give stereoisomeric oxiranium structures. It has been reported[12] that protonation of the least hindered face of methyloxirane to give the *anti* stereoisomer is 0.2 kcal mol^{-1} more stable than the *syn*-protonated stereoisomer (MP2/6-31G(d)//MP2/6-31G(d)). Protonation of **1a**, **1c** and **1d** on the less hindered face of the oxirane *anti* to the 3-methylpent-3-en-1-yl substituent is therefore expected to be favoured over *syn* protonation, and all calculations reported here have been performed on the *anti*-protonated stereoisomers of these molecules. The *trans*-monomethyl oxirane **1b** has more equally hindered faces, however, calculations have been performed only for the stereoisomer protonated *anti* to the 3-methylpent-3-en-1-yl group.

2.1. Dimethyl-substituted oxirane 1a

We confirm the potential energy surface for six-membered cyclisation of protonated **1a** reported by Hess.[8] A cross-section of the potential energy surface for this proton-assisted six-membered cyclisation of **1a** as well as the previously unreported competing five-membered ring closure is shown in Figure 3. The latter parallels the six-membered cyclisation, and both are single-step processes with carbon–oxygen bond cleavage occurring in concert with carbocyclic ring closure in an intramolecular S_N2-like reaction through transition states **3** and **4**, respectively. Intrinsic reaction coordinate (IRC) calculations of both transition states **3** and **4** lead to the same pre-folded conformation of the reactant structure (**2**), and to product structures **5** (six-membered) and **6** (five-membered), respectively.

Pre-folded reactant conformation **2** can be considered as either a chair-like pre-cyclohexyl or a puckered pre-cyclopentyl ring. The double bond is oriented so that the nucleophilic alkene carbon, C7, is available to react with either C2 (six-membered cyclisation) or C3 (five-membered cyclisation); the C2···C7 distance is 3.762 Å and the C3···C7 distance is 3.466 Å. The O–C2 bond distance is 1.575 Å, somewhat longer than the O–C3 distance of 1.511 Å. The difference in oxygen–carbon bond distances can be attributed to the higher degree of substitution of C2 by electron-donating alkyl groups, thereby preferentially stabilising the partial positive charge on that carbon of the oxirane.

Transition state **3** for six-membered cyclisation of **2** (E_A=0.8 kcal mol^{-1})[§] is more favourable than transition state **4** for five-membered cyclisation (E_A=5.6 kcal mol^{-1}). The former must be considered an early transition state even though a carbon–oxygen bond is substantially elongated relieving strain in the three-membered ring. Preference for reaction at the more substituted carbon atom of the oxirane is usual in acid-catalysed reactions and arises from increased stabilisation of the transitory positive charge by the substituent alkyl groups; in basic or neutral conditions oxiranes undergo S_N2 reactions at the less highly substituted, and therefore least hindered, carbon.[13] As well as the strong kinetic preference for six-membered cyclisation via **3**, cyclohexyl product **5** is thermodynamically more stable than the cyclopentyl product **6**; formation of **5** is exothermic by −15.5 kcal mol^{-1}[¶] and formation of cyclopentyl structure **6** is exothermic by −13.8 kcal mol^{-1}.

Carbocationic six-membered cyclisation product **5** is in a chair conformation with two of the methyl groups and the hydroxyl group oriented equatorially (Fig. 3). The optimised structure displays evidence of hyperconjugative stabilisation of the C1 cation similar to that seen in high-level ab initio calculations of 1-methylcyclohexylium **7a**[14,15] (Fig. 4). The C2–C3 bond is elongated (1.607 Å) and the C3–C2–C1$^+$ angle is narrowed to 105.2°; the C1$^+$–CH$_3$ methyl group is rotated so that a carbon–hydrogen bond is aligned with the vacant p-orbital and this carbon–hydrogen bond is elongated and bent towards the carbocation (C7–H distance is 1.096 Å; C1$^+$–C7–H angle is 104.0°). Unlike in **7a**, hyperconjugative stabilisation of **5** by carbon–carbon bonds is not symmetric; the C5–C6 bond is not significantly longer than a normal carbon–carbon bond at 1.558 Å. It is likely that this preference for hyperconjugation from the C2–C3 bond is due to the substituted nature of this bond, i.e., the electron-donating methyl groups on C2 and C3 help to stabilise the loss of electron density from hyperconjugation.

1-Methylcyclohexylium exists in two distinct chair conformations, termed 'hyperconjomers', linked by a ring-bending transition state[14,15] (Fig. 4); a conformational isomer with the vacant p-orbital

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[†] The present study considers only the reactions *endo* at the alkene. Reactions *exo* at the alkene are not expected to be significant as the products would be secondary carbocations, and in one case the reaction would give a strained cyclobutyl system.

[‡] Hess found little difference between these two levels of theory for this system.

[§] Hess reports a barrier of 0.4 kcal mol^{-1} using both HF and B3LYP methods, in each case corrected for ZPE using the DFT frequencies.

[¶] Hess reports values of −17.0 kcal mol^{-1} at HF and −13.0 kcal mol^{-1} at B3LYP, in each case corrected for ZPE using the DFT frequencies.

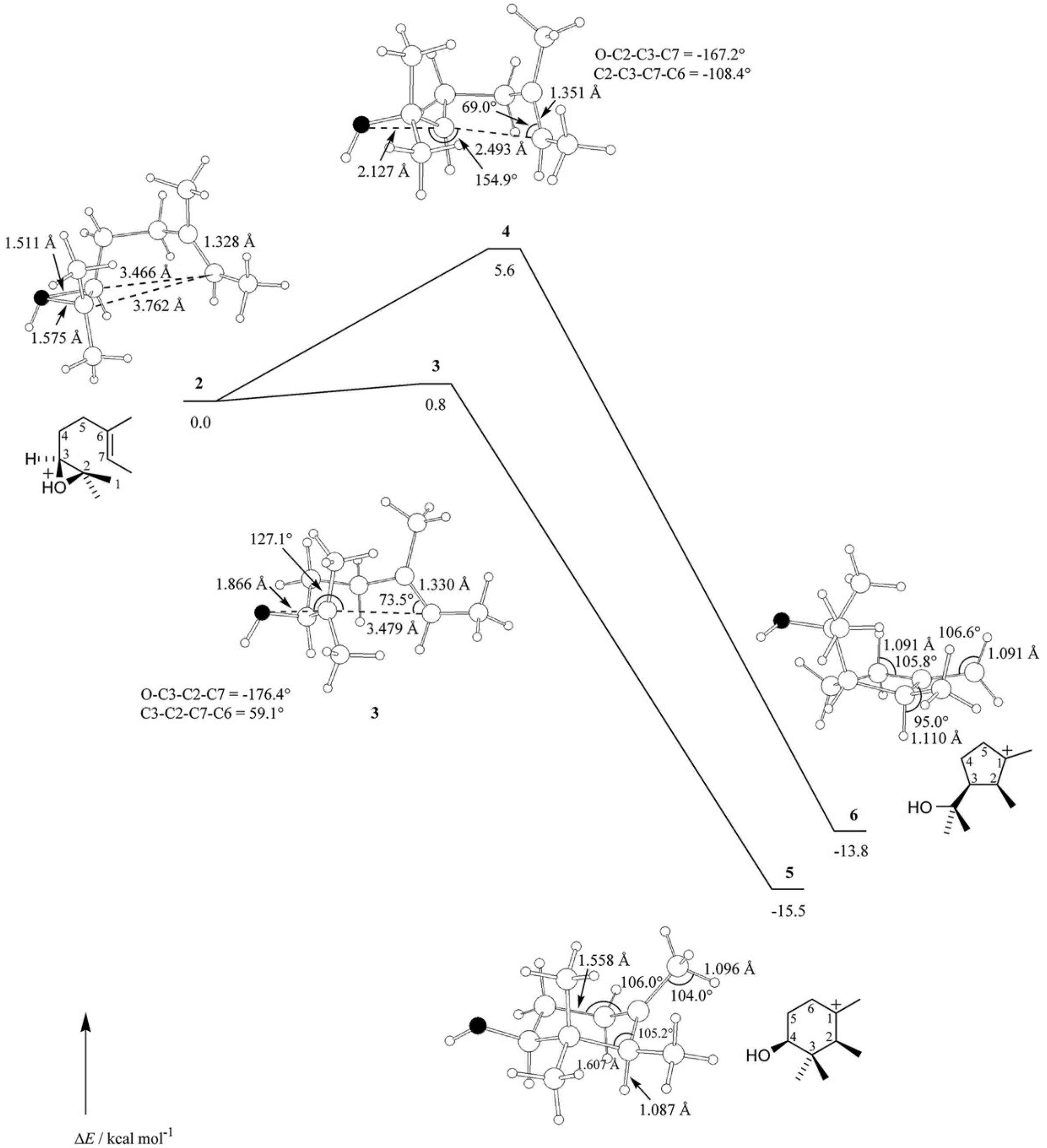

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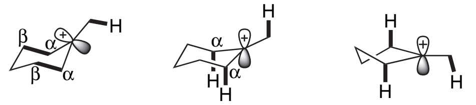
Figure 3. Reaction energy profiles and optimised stationary points for the five- and six-membered cyclisation of protonated **1a** in pre-folded conformation **2** (B3LYP/6-31G(d)//HF/6-31G(d)).



7a **7b** **8**

Figure 4. Conformational isomers of 1-methylcyclohexylium (**7a**, **7b**) (Refs. 14–16) and 1-methylcyclopentylium **8** (Ref. 17). Bonds exhibiting hyperconjugation with the cation are shown in bold.

oriented equatorially (**7a**) shows evidence of hyperconjugation from α–β carbon–carbon bonds, and an isomer with the p-orbital oriented axially (**7b**) is stabilised by hyperconjugation from axial carbon–hydrogen bonds α to the carbocation. Hyperconjomer **7a** is calculated to be ca. 1–3 kJ mol^{-1} more stable than **7b** in the gas phase,[14] whereas experimental[16] and theoretical[15] studies show **7b** to be the predominant form in solution. Gas-phase product conformation **5** is the equatorial carbon–carbon stabilised hyperconjomer analogous to **7a**.

In cyclisation product **6**, the five-membered ring is in an envelope conformation with C3 out of the plane of the other four carbon atoms (C2–C1–C5–C4=−0.5°). The methyl groups attached to C1 and C2 lie almost in this plane. The bulky 1-hydroxy-1-methylethyl group on C3 is in a pseudo-axial position similar to the geometry of transition state **4**. A conformational change, so that the C3 substituent moves to a pseudo-equatorial position, is expected to reduce steric interaction between this group and the rest of the molecule resulting in a lower energy structure.

The C_2-symmetrical 1-methylcyclopentylium **8** (Fig. 4) shows evidence of hyperconjugative stabilisation of the C1$^+$ cation by pseudo-axial hydrogen atoms on both intra-annular α-carbon atoms

(C2 and C5) and by a hydrogen atom of the methyl group.[17] Five-membered product **6** displays evidence of hyperconjugation from analogous carbon–hydrogen bonds, but shows a stronger hyperconjugation from the hydrogen on the more substituted C2 carbon atom. The C2–H bond is 1.110 Å and is bent appreciably towards the carbocation, with a $C1^+$–C2–H angle of 95.0°; by contrast, the C5–H and methyl C–H bonds are both 1.091 Å in length and have much larger angles to the carbocation of 105.8° and 106.6°, respectively. As with the asymmetric hyperconjugation of six-membered product **5**, this preference for hyperconjugation from the C2–H bond over the C5–H bond in **6** can be explained by the electron-donating C2 alkyl substituent partially compensating for the loss of electron density arising from donation to the carbocation.

2.2. *trans*- and *cis*-Monomethyloxiranes 1b and 1c

While protonated **1a** is predisposed by electronic considerations to cyclise at the more substituted oxirane carbon to form the six-membered ring, the following structures (**1b** and **1c**) are more equally substituted at each oxirane carbon and the inherent conformational and stereoelectronic preference for partition to five- and six-membered rings becomes more apparent.

The reactive conformation of protonated *trans*-substituted oxirane **9** (Fig. 5) is 1.7 kcal mol^{-1} more stable than the cis isomer **14** (Fig. 6). If the structures of these reactants are considered as pro-chair conformations, the C1 methyl group of **9** can be seen to be in a pseudo-equatorial position, while in the higher energy structure **14** the methyl is in the more sterically hindered pseudo-axial position. This 1.7 kcal mol^{-1} energy difference between the cis and trans isomers is comparable to experimental[18,19] and theoretical[19–21] values for axial and equatorial methylcyclohexane.

The oxirane carbon atoms of **9** and **14** are substituted more equally than those of dimethyl-substituted reactant **2**. The 1,2-disubstitution of **9** and **14** results in a similar degree of positive charge at each carbon in the protonated oxirane and this is reflected in the similar carbon–oxygen bond lengths. The C2···C7 distance of *cis* oxirane **14** is 3.773 Å,

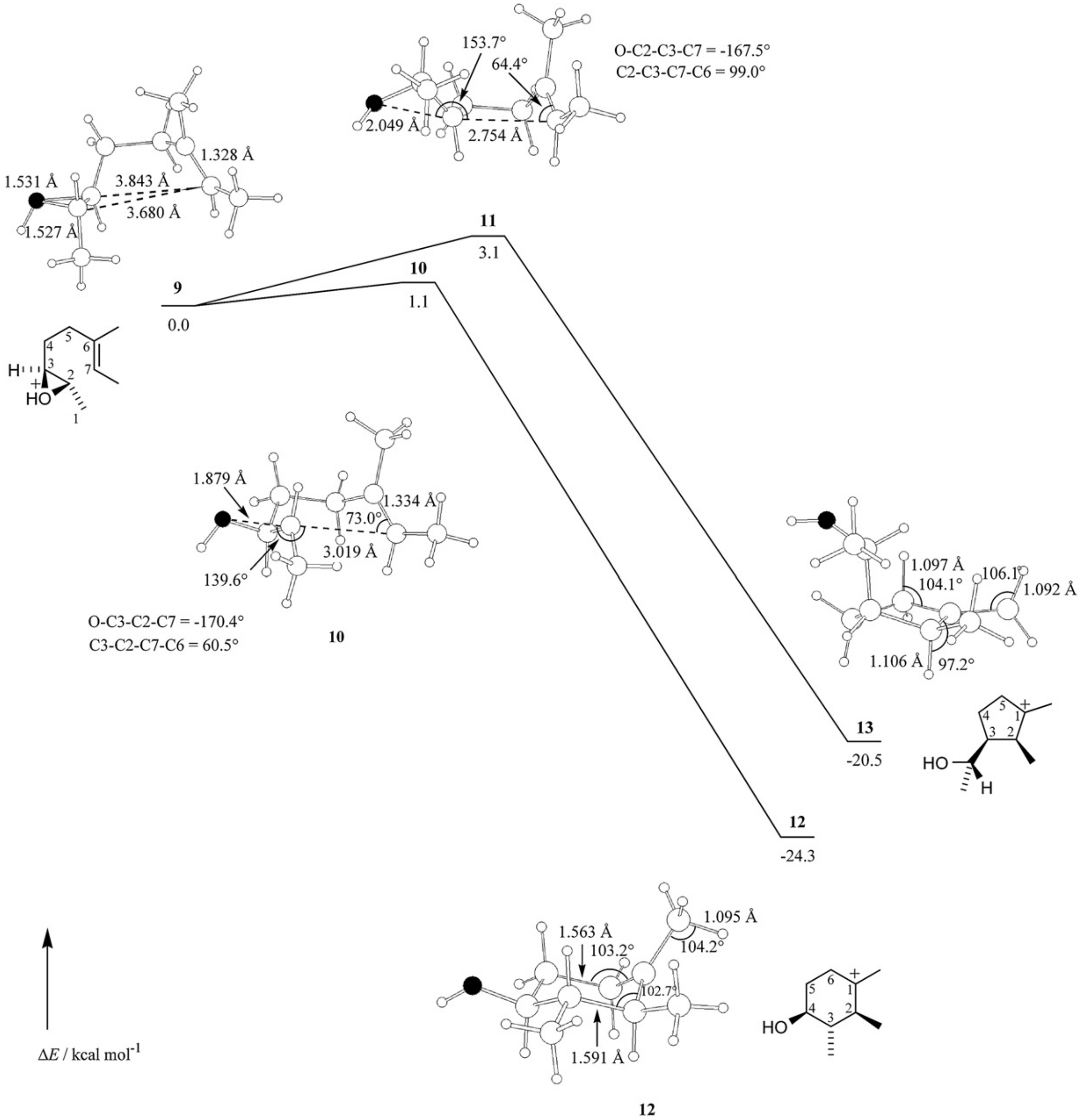


Figure 5. Reaction energy profiles and optimised stationary points for the five- and six-membered cyclisations of protonated **1b** (*trans*-monomethyl-substituted oxirane) in pre-folded conformation **9** (B3LYP/6-31G(d)//HF/6-31G(d)).

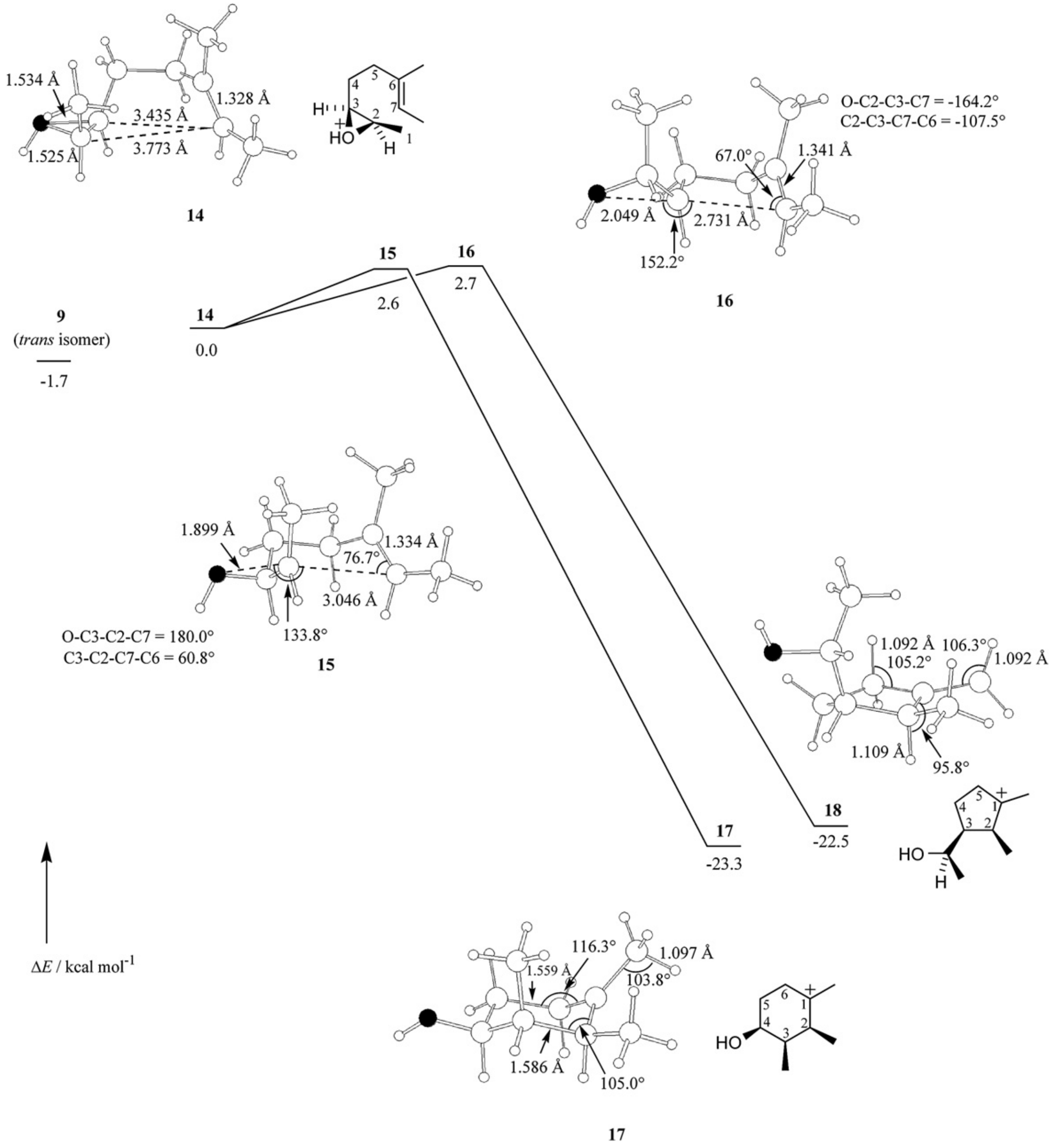


Figure 6. Reaction energy profiles and optimised stationary points for the five- and six-membered cyclisation of protonated **1c** (*cis* monomethyl-substituted oxirane) in pre-folded conformation **14** (B3LYP/6-31G(d)//HF/6-31G(d)).

similar to the analogous distance of **2**, while the C2···C7 distance of *trans*-oxirane **9** is 3.680 Å. It is likely the larger separation of these atoms in **2** and **14** than in **9** is a result of steric interaction between the cis pseudo-axial methyl group and the pro-ring.

Protonated *trans*-oxirane **9** cyclises to six-membered product **12** via transition state **10** with an activation energy of 1.1 kcal mol^{-1}, and to cyclopentyl product **13** via transition state **11** with a barrier of 3.1 kcal mol^{-1} (Fig. 5). The cis isomer **14** requires 2.6 kcal mol^{-1} to reach six-membered transition state **15**, and five-membered transition state **16** is 2.7 kcal mol^{-1} above the protonated oxirane (Fig. 6). The competing reactions of closure to a five- or six-membered product have closer activation barriers in comparison to the competing reactions of dimethyl-substituted **2**, and this can be attributed to the similar stabilisation of the transitory positive charge on both of the oxirane carbon atoms by the substituent alkyl groups.

The activation energy required to reach six-membered cis transition state **15** is 1.5 kcal mol^{-1} higher than that required to reach the isomeric trans structure **10**, and this difference is likely to arise from steric interaction of the C1-methyl group axial to the incipient cyclohexyl ring. In five-membered transition states **11** and **16**, the C1 methyl group is more distant from the rest of the molecule and consequently the barriers to **11** and **16** are more similar. As the transition states for six-membered cyclisation are early and reactant-like, it can be assumed that the energy contribution of the axial methyl group in **15** over the equatorial methyl in **10** is approximately the same as in the reactants at ca. 1.7 kcal mol^{-1}. It can therefore be seen that, after consideration is made for steric interactions and stabilisation of the positive charge, there is an additional preference for six-membered cyclisation over five-membered cyclisation of ca. 1.8–2.0 kcal mol^{-1}.

2.3. Oxirane 1d

The energy profile for competing five- and six-membered cyclisation of protonated **1d** is shown in Figure 7. The reactant in

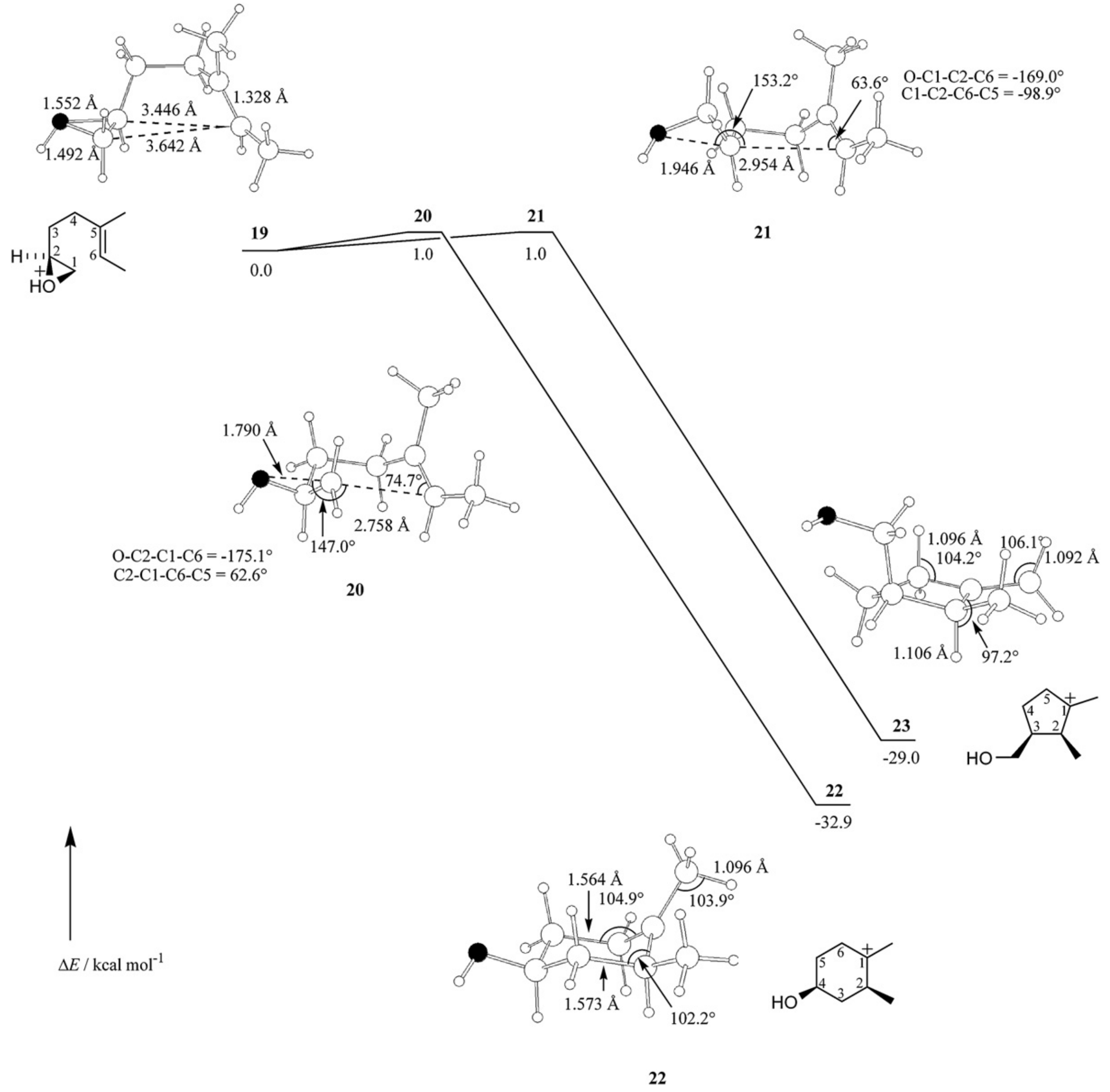


Figure 7. Reaction energy profiles and optimised stationary points for the five- and six-membered cyclisation of protonated **1d** (oxirane with no terminal methyl groups) in pre-folded conformation **19** (B3LYP/6-31G(d)//HF/6-31G(d)).

conformation **19** can be considered as a pro-chair and the C1···C6 distance is 3.642 Å; this distance is similar to the corresponding distance in *trans*-monomethyl oxirane reactant **9**, strengthening the suggestion that the longer distance in **2** and **14** is a result of steric interaction of the cis methyl group 'axial' to the pro-ring. Consistent with the calculated structures **2**, **9** and **14**, the more highly substituted C2–O bond is longer than the C1–O bond, reflecting a higher degree stabilisation of the positive charge.

Protonated alkenyloxirane **19** lacks terminal methyl groups and, as discussed above, it would be expected from considerations of the electronic environment of the protonated oxirane that the preferred cyclisation would occur at the more substituted carbon atom to produce the five-membered product. However, the transition states for both six-membered (**20**) and five-membered (**21**) cyclisations are calculated to require an activation energy of 1.0 kcal mol^{-1}. That the reaction does not occur preferentially at the more substituted carbon atom reflects the inherent conformational preference in six-membered ring formation over-riding the electronic preference for oxirane opening at the more substituted carbon.

3. Discussion

In the acid-catalysed cyclisations of molecules **1a**–**d**, a number of factors are reflected in the activation energies for the competing five- and six-membered transition states. The reactions are all computed to have early transition states, but with the carbon–oxygen bond stretched considerably to relieve oxirane ring strain, with relatively low activation barriers. It is seen that there are three factors, which may reinforce or counteract each other to determine the regioselectivity of cyclisation: (1) stabilisation of the transitory positive charge in the transition state favours cyclisation to the more highly alkyl-substituted oxirane carbon; (2) for structures with a pseudo-axial substituent on the oxirane, intramolecular steric interactions increase the activation barrier; and (3) there is an inherent stereoelectronic preference for six-membered cyclisation over five-membered cyclisation.

Baldwin[6] stated that for intramolecular nucleophilic opening of three-membered rings, the *exo* mode of attack to form the smaller ring is generally favoured (e.g., 5>6; Fig. 8); this generalisation is

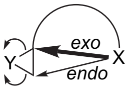


Figure 8. Baldwin's rule for nucleophilic closure at a three-membered ring is a preference for *exo* closure.

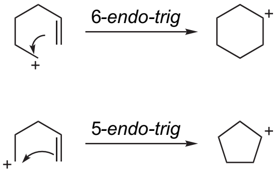


Figure 9. 6-*endo-trig* Cyclisation of a cation and alkene is allowed under Baldwin's rules. Examples of the 5-*endo-trig* reaction mode are also now known.

supported by experimental evidence for epoxynitriles,[22] and experimental[23] and computational[24,25] studies of epoxyalcohols.[‖]

For intramolecular ring closure of a cation and alkene, Baldwin says that the 6-*endo-trig* mode of reaction is well known and that analogous *endo* closure to five-membered rings does not occur for simple cations (Fig. 9); more recent studies have demonstrated that electrophilic 5-*endo-trig* cyclisations can occur.[27]

The inherent preference for six-membered ring formation in the present study is considered to arise from similar stereoelectronic considerations as those that form the basis of Baldwin's rules,[9,**] i.e., as a result of more favourable orbital overlap in the six-membered transition state,[28] however, the preference for six-membered cyclisation conflicts with the regiochemistry predicted by Baldwin's rule for nucleophilic ring closure from three-membered rings. It is thought that the increase in transitory positive charge on the protonated oxirane carbon at the transition state causes reaction characteristics more similar to those of a conventional cation–alkene cyclisation, and thus adherence to Baldwin's rule for closure of a cation and alkene is seen.

The stereoelectronic factors that give rise to the inherent preference for six-membered cyclisation of **1a**–**d** can be resolved by consideration of the bond lengths and angles of the transition states in comparison with the transition state for the reaction of methylpropene with protonated oxirane[29] (**24**; Fig. 10). As **24** is a transition state for an intermolecular reaction, and therefore free of the intramolecular conformational constraints of cyclisation, it is likely to adopt the most stereoelectronically favourable conformation.

In **24**, the O–C2–C3 angle of nucleophilic attack at the oxirane is 151.4°. The equivalent O–C_{ep}–C_{alk} angles in the intramolecular transition states for five-membered cyclisation are close to this value in the range 152.2–154.9°. In six-membered transition states **3**, **10** and **15**, the O–C_{ep}–C_{alk} angles are significantly compressed and lie in the range 127.1–139.6°. The angle of nucleophilic attack in **20** is closer to the optimum value at 147.0° and the molecule is able to achieve this more favourable conformation because there are no steric interactions associated with terminal methyl groups. As it is the six-membered transition states, which differ more in this parameter from the value in **24**, it appears that this angle is relatively flexible with a low energy cost for variation.

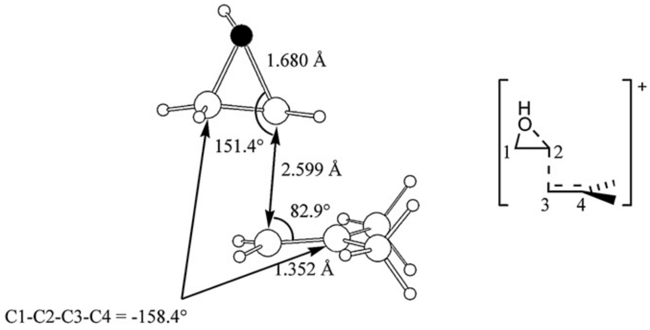


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Figure 10. Optimised transition state for the reaction of protonated oxirane and methylpropene (MP2(Full)/6-31G(d)).

Both the five- and six-membered cyclisation transition states of the present study show significant differences from **24** in the C_{ep}–C_{ep}–C_{alk}–C_{alk} dihedral angle about the forming carbon–carbon bond. In structure **24** this angle (C1–C2–C3–C4) is −158.4° and the deviation from planarity of this angle was ascribed to a steric effect costing less than 0.2 kcal mol^{-1}.[29] This energy cost is considerably lower than the preference for six-membered ring formation seen in the present study, and it is likely that variation of this dihedral angle induces only small energy changes in the transition state and does not significantly affect the regioselectivity of the reaction.

The parameter we consider most important to dictate the stereoelectronic preference for six-membered ring formation in the present study is the C_{ep}–C_{alk}–C_{alk} bond angle, i.e., the angle for electrophilic addition to the alkene. This angle in unlinked transition state **24** (C2–C3–C4) is 82.9°; in the six-membered intramolecular transition states it is in the range 73.0–76.7° and for the five-membered reaction it is compressed to 63.6–69.0°. This greater deviation from the ideal geometry in the cyclopentyl transition states can account for the additional energy cost of these reactions. That the angle of attack of the oxirane carbon at the alkene is the most important parameter affecting transition state energy is consistent with the reaction following Baldwin's rule for cationic cyclisations of alkenes, rather than the rule for nucleophilic cyclisation at three-membered rings.

4. Conclusion

The computational studies of compounds **1a**–**d** show intramolecular reaction of a protonated oxirane and alkene to both the five- and six-membered ring products is a single-step process with carbon–oxygen bond cleavage occurring in concert with intramolecular nucleophilic attack by the proximate double bond to form the carbocyclic ring. These results add further confirmation that oxidosqualene oxirane opening is concerted with A-ring closure. In all cases, the reactions are exothermic and proceed via transition states that are early and reactant-like but where the oxirane C–O bond is considerably stretched.

After consideration of steric interactions and the constraints of a cyclic system, reaction of the alkene: (1) is favoured at the more substituted oxirane carbon; and (2) exhibits an inherent stereoelectronic preference for formation of a six-membered ring. Effects (1) and (2) can counteract or reinforce each other depending on the substitution pattern of the oxirane. The inherent preference for six-membered ring formation has a parallel in Baldwin's rule for intramolecular cyclisation of a carbocation with an alkene, and as such suggests the protonated oxirane mimics a carbocation and overrides the factors underlying Baldwin's rule for three-membered rings.

[‖] An exception to this rule is seen in the preferential formation of the *endo* five-membered cyclic ether in the cyclisation of *cis*- and *trans*-3,4-epoxypentan-1-ol (Refs. 23 and 26). This result reflects the high ring strain of the four-membered *exo* transition states, however, it is to be noted that 3-oxiran-2-ylpropanenitriles readily form four-membered *exo* cyclisation products (Ref. 22).

[**] The cyclisation of enzyme-activated oxidosqualene and the protonated analogues investigated in the present study are not strictly substitutions of oxiranes by the simple nucleophiles discussed by Baldwin, nor are they simple cationic cyclisations of alkenes, but are situations not specifically covered by Baldwin's rules.

In the present study, oxirane **1a** most closely models the oxidosqualene molecule, and the factors leading to a strong preference for six-membered over five-membered cyclisation from **1a** are expected to similarly affect the regiochemistry of A-ring formation from oxidosqualene.

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Supplementary data

Atomic coordinates of all optimised stationary points and calculated energies, zero-point corrections and imaginary frequencies are provided. Supplementary data associated with this article can be found in the online version, at doi:10.1016/j.tet.2008.06.109.

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