

**CAMPHOR DERIVATIVES IN ASYMMETRIC
SYNTHESIS : A Synthetic, Mechanistic and
Theoretical Study**

THESIS

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Abstract

A series of 3,3-ethylenedioxy-*exo*- and *endo*- bornyl esters have been prepared and subjected to α -benzylation using lithium diisopropylamide and benzyl bromide. In the *exo*-series of esters the diastereofacial selectivity of benzylation was found to improve (up to 34% d.e.) as the steric bulk of the *O*-alkyl group increased, whereas in the *endo*-series, a surprising decrease in stereoselectivity was observed as the steric bulk increased – an observation attributed to flexibility of the metal-coordinated *endo*-enolate system, compared to the relative rigidity of the *exo* analogues. The conformational options for each series was explored at the density functional theory level.

Reductive cyclization of a range of specially prepared *N*-carbobenzyloxy-amino acid esters has been shown to afford the corresponding derivatives, contrary to previous reports that the cyclization is limited to the glycine derivative. The cyclization sequence has been explored in detail, and the yield has been shown to be critically dependent on the stereochemistry of the α -amino acid moiety. Moreover, it seems that reductive cyclization occurs more readily with the *endo*- rather than the *exo*-bornyl *N*-CBZ-amino acid esters. Molecular modelling of relevant transition states at the DFT levels indicates that L-amino acid-derived systems should cyclize preferably in the *exo*-series and D-amino acid-derived systems should cyclize preferably in the *endo* series.

Studies of alkylation of an iminolactone system have reported an interesting anomaly - *exo*-methylation is observed while *endo*-alkylation predominates for larger alkyl groups. This has been studied in detail at the DFT level, and the anomaly is attributed to thermodynamic control in the methyl case, whereas kinetic control is the norm in this system.

Preliminary computer modelling of the intramolecular rearrangement of a 3,3-xylylboryl system at the HF/STO-3G level raised doubts concerning the structure assigned by Evans to one of the rearrangement products, prompting an X-ray crystallographic analysis and leading to the revision of its structure from a pinene to a camphene derivative. The previously elusive spiro[bornane-3,2'-indan]-2-*exo*-tosylate has been successfully isolated, and the kinetics of its ready decomposition to the two camphene products has been followed by ^1H NMR spectroscopy. The *endo*-tosylate analogue, on the other hand, was found to be remarkably stable.

Kinetic data obtained for rearrangement of this *exo*-bornyl tosylate have indicated the op-

eration of tandem autocatalytic and pseudo-first-order transformations leading sequentially to the two isomeric camphene products. An extensive coset analysis of all possible rearrangement processes of the initially-formed cation formed from decomposition of the *exo*-tosylate has afforded a graph containing 336 classical cations (modelled at the AM1 and B3LYP levels) and 526 transition-state complexes (modelled at the AM1 level). This analysis afforded a viable 4-step classical mechanism connecting the first camphene product with the second. A more realistic study, involving non-classical carbocations, has afforded a graph of all possible (classical and non-classical) cations that could be formed by rearrangement of the initially-formed cation. The resulting graph confirms that the only energetically feasible path corresponds to the classical mechanism, but simply involves two steps, including a novel, concerted Wagner-Meerwein – 6,2-hydride shift – Wagner-Meerwein rearrangement.

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1 Introduction

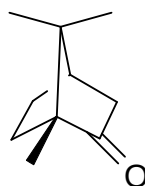
1.1 Preface

Camphor is a remarkable substance with quite a remarkable history. It has been known for seven centuries to the western world, but for a long time before then in Asia.² Obtained from the camphor tree, *cinnamomum camphora* (Figure 1.1),³ camphor has been valued for its medicinal uses, but it is not its medicinal properties that are of concern here. A critical property of natural camphor is its optical activity, and, more importantly its optical purity, for camphor obtained from *cinnamomum camphora* is almost completely pure D-(+)-camphor 1. L-(-)-camphor is also obtainable from natural sources, but is not as prevalent as the D-enantiomer.⁴ Optical purity is an essential consideration in asymmetric synthesis, but the physical properties of camphor are not nearly as controversial or as disputed as its chemical properties.



Figure 1.1: *cinnamomum camphora*.³

While the molecular formula of camphor was determined by Dumas and, independently, by Blanchet and Sell in 1833 but this was but the beginning of the road as far as its structural



1

determination was concerned.⁴ Many structural formulae had been proposed before 1893, when Bredt^{5,6} first suggested what we now know to be the actual structure. Not surprisingly, it took time for this structure to gain acceptance in the scientific world,⁴ since substances like camphor undergo some remarkable transformations. Under certain conditions, it is possible (intentionally or unintentionally) to cause bicyclic systems, such as camphor, to undergo skeletal rearrangements. J. Simonsen stated in 1949,⁴ with regard to camphor and the related camphoric acid:

“It is doubtful if, in the whole range of organic chemistry, any two substances have been the subject of such intensive study, and the difficulties encountered in the determination of their constitution has been due mainly to their tendency to undergo intramolecular rearrangements.”

It is this property to undergo molecular rearrangements that unleashed controversy in the middle of the twentieth century. The nature and mechanism of rearrangement of compounds similar to camphor was subject to much scrutiny. In 1939, Wilson^{7,8} suggested the existence of a 5-coordinated, “non-classical”, carbocation. The late 1940’s saw further exploration of the existence of such systems and, by the 1960’s, a war had begun between two camps supporting and opposing their existence. The main figures in this dispute were Herbert Brown and Saul Winstein; George A. Olah, who by 1969, had experimental evidence confirming the existence of non-classical carbocations, was also drawn into the argument. As late as 1983 the battle was not over, and Olah made the rather exasperated statement:⁹

“Any further continuation of the classical-non-classical ion controversy seems to be a futile exercise of semantics and not of relevant experimental facts.”

In the introduction, which follows, two areas of camphor chemistry will be reviewed.

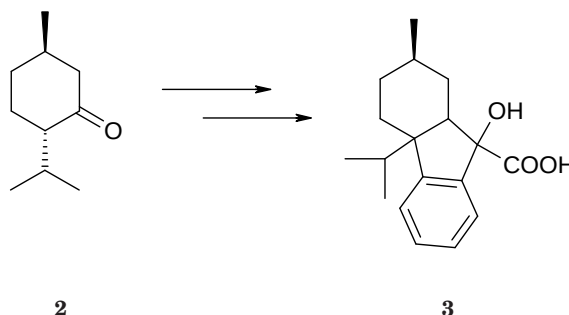
1. The use of camphor-derivatives as a chiral auxiliaries in asymmetric synthesis based on

the very rigid structure of the bicyclic skeleton. This structure remains intact and is elaborated in such a way as to induce asymmetry in subsequent transformations.

2. Situations in which the skeletal structure of camphor derivatives is changed. In this area we examine the conditions conducive to rearrangement, the rearrangement process, and the rearrangement products.

1.2 The importance of asymmetric synthesis

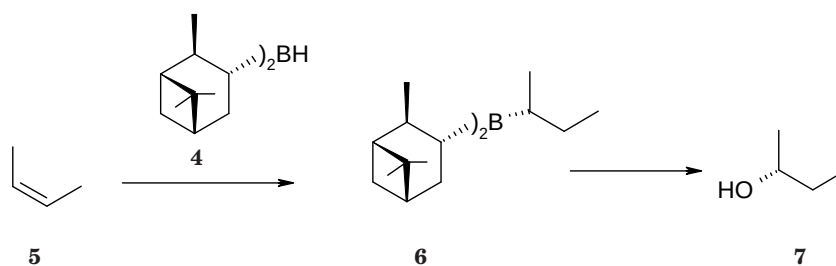
There have been many attempts to induce chirality using purely physical phenomena, such as electrical and magnetic fields, gravitation and polarized light. Although theoretically possible when a combination of fields form a chiral system, these results are often difficult to reproduce, are controversial or produce extremely low enantiomeric excesses.¹⁰ Historically, chemists have been producing products with specific stereochemistry for a long time. These substrate based methods rely on the chirality of the starting material. In the synthesis of the tricyclic compound **3** from L-menthone **2** in 1938,¹¹ for example, retention of stereochemistry at one or perhaps more centres occurs, but was not noted, nor was optical activity reported.



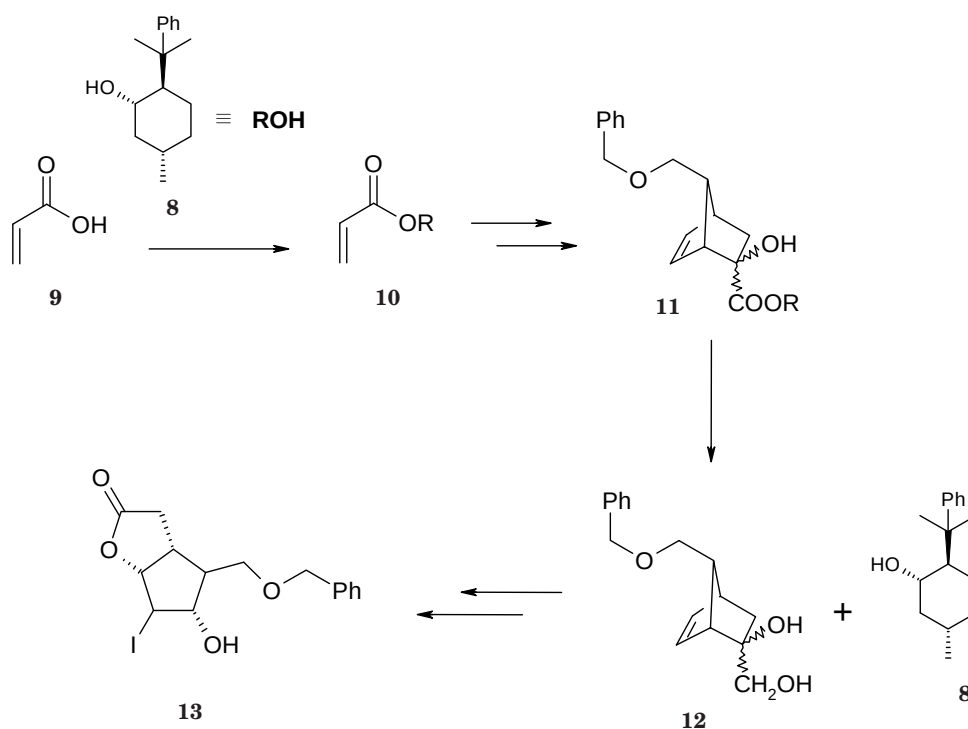
Scheme 1.1: Synthesis of tricyclic compound **3** from L-menthone.

In 1961, H. C. Brown^{12,13} and G. Zweifel synthesized (*R*)-2-butanol **7** from *cis*-2-butene **5** in 87 % enantiomeric excess using the α -pinene-derived chiral reagent, diisopinocampheylborane **4** (Scheme 1.2). This illustrated clearly that chiral reagents were not just of theoretical interest, but could actually produce compounds with acceptable optical purity in good yield. By 1975, E. J. Corey had used what we now term to be a chiral auxiliary to prepare the optically pure iodolactone **13** (Scheme 1.3). The chiral auxiliary **8** was recovered after it had been used to induce chirality in the formation of **11**.¹⁴

The most sophisticated methods for the preparation of optically pure materials involve the

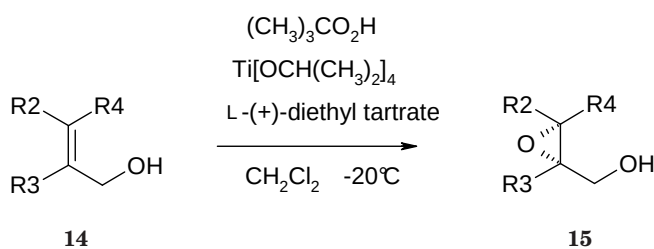


Scheme 1.2: Use of α -pinene as a chiral auxiliary.



Scheme 1.3: Use of 8-phenylmenthol as a chiral auxiliary.

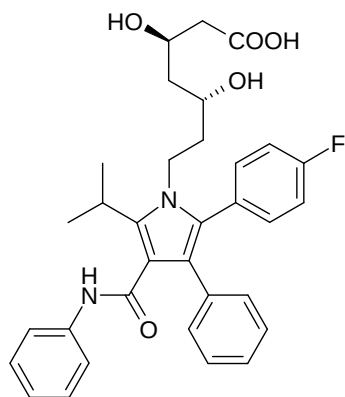
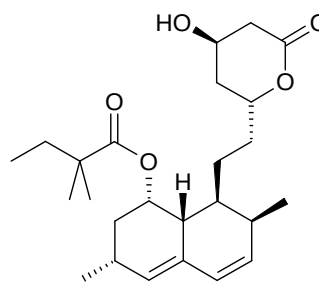
use of chiral catalysts. The award of the 2001 Nobel Prize to W. Knowles, R. Noyori and K. Sharpless emphasizes the importance of these developments to the chemical community.¹⁵ A scheme for the asymmetric Sharpless epoxidation of a generalized allylic alcohol **14** is shown in Scheme 1.4.¹⁶



Scheme 1.4: Sharpless epoxidation.

The stereocontrol of reactions is not simply of interest in the design of elaborate syntheses. There are spectacular examples where one enantiomer of a drug can have adverse side effects while the other has the beneficial properties. Examples include levodopa, which is used to treat Parkinson's disease (the L-enantiomer is active while the D-enantiomer causes a reduction in the white blood cell count) and levamisole, used in cancer therapy (the D-enantiomer causes vomiting in this cancer medication).¹⁷

Perhaps it is easier to see the importance of asymmetric synthesis in economic terms, in particular in the pharmaceutical industry. In 2000, the market for optically pure drugs was of the order of \$123 billion annually.¹⁸ By 2002, it had reached \$159 billion, \$14 billion for the optically pure drugs, atorvastatin **16** and simvastatin **17**, both of which are used to lower blood cholesterol.¹⁹

**16****17**

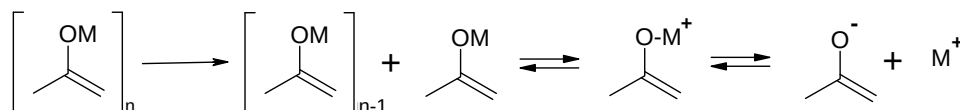
1.3 Factors influencing stereoselectivity in reactions involving enolates

It is important not simply to accept the stereochemical outcomes of reactions, but to rationalize these outcomes. In this section, some of the factors relevant to the stereochemistry of incipient bonds are reviewed.

1.3.1 Stereoselective alkylation of enolates

The alkylation of enolates, and the source of stereocontrol is of particular concern in this study.

Carruthers²⁰ reiterates the point that removal of an acidic α -proton from a ketone (pK_a ca. 19) is a difficult task compared to removal of α -protons from 1,3-dicarbonyl compounds (pK_a ca. 11). Complications following the generation of enolates include aldol condensation with the original ketone²⁰ and proton transfer between the enolate and the original ketone. Moreover the composition of metal enolates formed is considered to be quite complex, ranging from molecular aggregates to free, solvated metal and enolate ions (Scheme 1.5).²¹



Scheme 1.5: Enolate Aggregation.

The equilibrium can be pushed towards the right with additives, such as hexamethylphosphoramide (HMPA), which coordinate the metal cation. Meyers *et al.*,²² for example, have confirmed the structure of a lithium enolate dimer coordinated with tetramethylethylenediamine (TMEDA), while other lithium enolates are known to crystallize as tetramers,^{23,24} hexamers²⁵ (see Figure 1.2) and complex systems involving coordination with solvent, different enolate species or HMPA.^{26–29} The kinetics of alkylation is generally second order (even where aggregation occurs), but more complex behaviour has been observed and attributed to coordination of enolate species with lithium halide product.³⁰ Computer modelling of enolate alkylations has typically been based on free and immediate access to the enolate anion,^{22,31} but a recent study examines the alkylation of an enolate centre within an aggregate.²⁵

Aside from this complicating factor in determining the stereocontrol of alkylations, Evans^{21,23} identifies three sources of chiral induction, *viz.*, “*intra-annular chirality transfer*”, “*extra-*

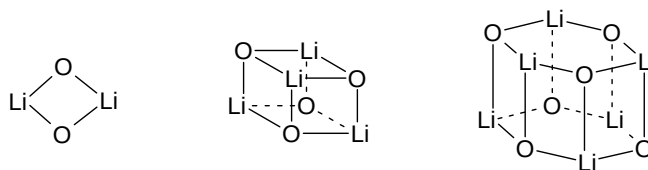


Figure 1.2: Lithium-oxygen geometries in lithium enolate dimers, tetramers and hexamers.²⁵

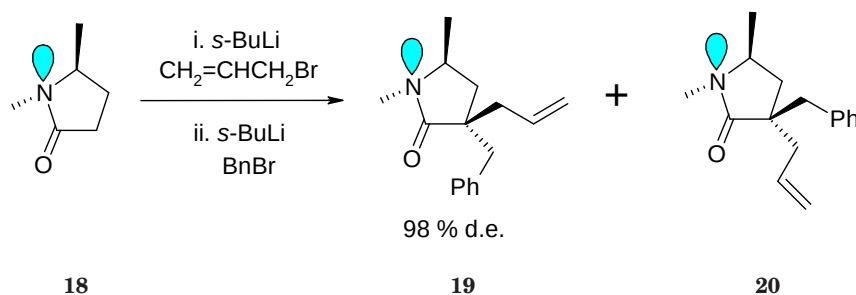
annular chirality transfer” and “*chelate-enforced intra-annular chirality transfer*”. The distinction between these is the position of an existing chiral centre, be it within an enolate-containing ring, external to the ring, or in a position to coordinate a metal ion in order to “lock down” the enolate into a specific geometry prior to alkylation. In all cases stereocontrol can be explained in terms of stereoelectronic and steric effects, although it appears that, in most cases, the latter are more significant.

1.3.2 Electronic influence on stereoselectivity

The type of reaction of interest here involves preferential attack at one face of a π -system, as is present in an enolate, by an electrophile, such as an alkyl halide. Preferential attack at one face of a polarized π -system, such as is present in a carbonyl group, by a nucleophile is treated in a similar manner.³² The traditional methods of analysing π -facial selections involve use of the Felkin-Anh model (which emphasizes reduction of torsional and steric strain in the transition state) or the Cieplak model (where antiperiplanar hyperconjugative effects are predominant).³³

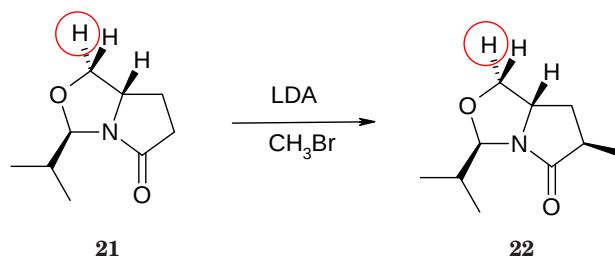
Meyers *et al.*²² report a curious case where a nitrogen lone pair appears to induce diastereoselectivity in alkylation reactions. The dialkylation of the cyclic lactam **18** with allyl bromide followed by benzyl bromide affords product **19** in 98% diastereomeric excess (Scheme 1.6). The stereochemistry shown at the nitrogen atom centre in Scheme 1.6 is, in fact, the one which is present in the lowest energy enolate conformer, and the diastereoselectivity is arguably electronic in origin, since there are no major steric influences.

However, in more complex but similar systems, the substituents could exert steric and, perhaps, even greater electronic effects. Meyers *et al.*²² continued by examining alkylation reactions of, among others, the bicyclic lactam **21** (Scheme 1.7). *Exo*-substituents, for instance the isopropyl substituent on the lactam **21**, only appear to play a small part in determining selectivity in systems such as these. The *exo*-stereoselectivity in this case is essentially steric in origin due to the convex nature of the substrate as a whole and, in particular, the position



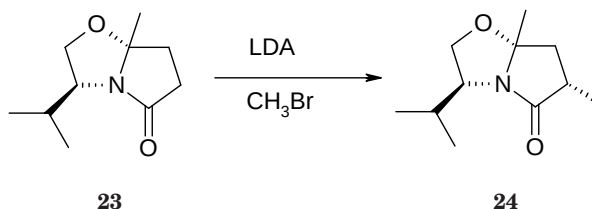
Scheme 1.6: Electronic Influences on Diastereoselectivity.

of the *endo*-hydrogen shown explicitly in Scheme 1.7, rather than the steric influence of *exo*-substituents.



Scheme 1.7: Steric Influences on Diastereoselectivity. The hydrogen indicated is close to the formed enolate centre due to the concave shape of the system.

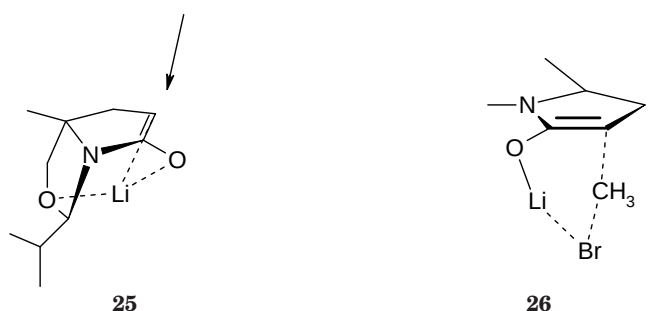
On the other hand, an electronic source of stereoselectivity was strongly suggested by Meyers in the very similar bicyclic lactam system **23**. Alkylation of this system produced mainly the *endo*-isomer **24** (94% d.e., Scheme 1.8), even though the *endo*-face is more hindered (due to the “*endo*” nature of the oxazolidine moiety). The electronic effect due to the nitrogen’s lone pair (Scheme 1.8) was considered to outweigh any steric influence in determining the stereoselectivity.



Scheme 1.8: Electronic Influences on Diastereoselectivity. Although the *endo*-oxazolidine clearly holds a steric influence driving *exo*-attack, the influence from the nitrogen is greater.

The electronic influence on stereoselectivity in the transformations illustrated in Schemes 1.6 and 1.8 is disputed by some. An in-depth RHF/6-31+G(d) and MP3 theoretical study of transition states³⁴ for alkylation of the enolate of the lactam **18** (Scheme 1.6) suggests that

the lone pair determines the most stable conformer of the enolate, but does not influence the stereochemical outcome. Ando *et al.*³⁴ argue that torsional effects render the *endo*-alkylation transition state more stable than the *exo*-alkylation transition state. Tomoda^{35,36} investigated coordination to lithium for both systems (Schemes 1.8 and 1.7). It is suggested that coordination to lithium in **21** in the concave *endo*-region (coordination is to the two oxygens and the enolate π -system) leaves only the *exo*-surface of the enolate open to attack **25** (Scheme 1.9). However, in a simplified version of **23** *endo*-coordination of the lithium (coordination is only to the enolate π -system and oxygen) is also favoured. However, it is in this *endo*-coordinated system that both exterior frontal orbital extension model (EFOE) and π -plane-divided accessible space (PDAS) (see below) analyses at the enolate centre confirm *endo*-stereoselectivity! In the favoured *endo*-transition state **26** there is coordination between the lithium anion and the halide of the incoming alkyl halide, coordination which is not possible with the tricoordinated lithium enolate of **25**.



Scheme 1.9: Tomodo's rationalization of stereoselectivities in Meyer's systems. In **25** the lithium coordination ensures *exo*-attack. In the simplified system **26** used to model the transition state in Scheme 1.8, where the lithium anion coordinates the alkyl halide favouring *endo*-attack.

These, and other in-depth DFT studies of torsional strain indicate serious failures in the use of the Felkin model.³² For instance, in the LAH reduction of cyclohexanone, axial attack incurs greater strain from 1,3-diaxial interactions than the torsional strain involved in equatorial attack in the transition state! The hyperconjugative effect in the Cieplak model is measurable in terms of the bond length of the antiperiplanar bond, and DFT studies have revealed cases where this effect decreases close the transition state. It is clear that neither model holds in complete generality.

Tomoda,³² in looking at carbonyl reactions, proposes a different paradigm, in which stereoselectivity originates from the total difference in energies based on repulsive, electrostatic and donor-acceptor orbital interactions. A number is calculated which gives an indication of

the final term – Tomada calls it the “*exterior frontier orbital electron density*”. For enolates this would translate to the integral of the α -carbon atomic orbital contribution to the HOMO on each face of attack. Liotta³⁷ has yet another perspective. Discounting steric and electronic effects as negligible, he suggests that the root of stereoselectivity lies in the solvation of the enolate species.

1.3.3 Rationalization of steric effects

Oppolzer³⁸ refers to the “*topological bias of a camphor skeleton*” – an elegant way of emphasizing the importance of steric interactions in asymmetric synthesis when camphor is used. Steric interactions arise from repulsion between filled molecular orbitals, but are not termed electronic.

Kinetic stereoselectivity arises from a difference in activation energy for two different reaction pathways, and hence a difference in rate constants.³⁹ The aim of the chiral auxiliary is, of course, to cause such a difference in rates, by raising the activation energy (E_a) of one pathway with respect to the other. The entropy of activation is also significant in diastereoselective reactions since the pathway that requires a more specific orientation of species will exhibit the greatest decrease in entropy in the activated complex. This, however, may not be the full story when looking at diastereoselectivities. There is evidence, for instance, that longer range electrostatic forces may play a role in determining the course of reaction, which may run contrary to both the Cieplak and Felkin-Anh models of π facial stereoselectivity.⁴⁰

Conversely, one could explain the steric effects on selectivity in terms of collision theory.³⁹ Thus, in order to direct facial diastereoselectivity, a chiral auxiliary would be expected to decrease the probability of a successful collision at the unwanted face. Collision theory is somewhat limited, but has been used with success in studying orientational effects in simple substitution reactions,⁴¹ in which the steric bulk of the chiral auxiliary may influence and restrict the orientation for successful collisions.

Tomoda also examined³² the repulsive term and defined a π -plane-divided accessible space (PDAS). This quantifies the steric effect in π -facial stereoselective reactions. Although different to cone angles, which also quantify steric bulk,^{42,43} PDAS also involves integration of the volumes accessible to the reaction centre above and below the plane of the π bond.

1.4 Applications of camphor derivatives, which exhibit skeletal retention, in asymmetric synthesis

Reactions which proceed in high diastereoselectivity are ones in which there is little room for structural flexibility (see, for example, Willis⁴⁴). The structural rigidity of the bicyclic skeleton of camphor is therefore important in its use as a chiral auxiliary.

1.4.1 Camphor-derivatives as chiral auxiliaries

Relative abundance, low cost, high optical purity and structural rigidity all contribute to camphor being an attractive starting material for chiral auxiliaries. A good chiral auxiliary should be easily attached to a prochiral system, and easily removed to afford the chiral product. For this purpose, camphor must be functionalised appropriately. The asymmetric camphor skeleton should be close to the prochiral system in order to direct the asymmetric transformation, and the more rigid the system, the easier it is to predict the stereochemical outcome. These features are illustrated in the following survey of selected systems.

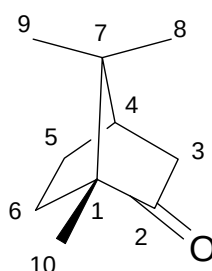
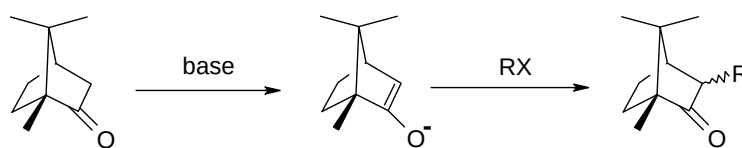


Figure 1.3: Camphor positions.

1.4.1.1 Functionalisation of camphor

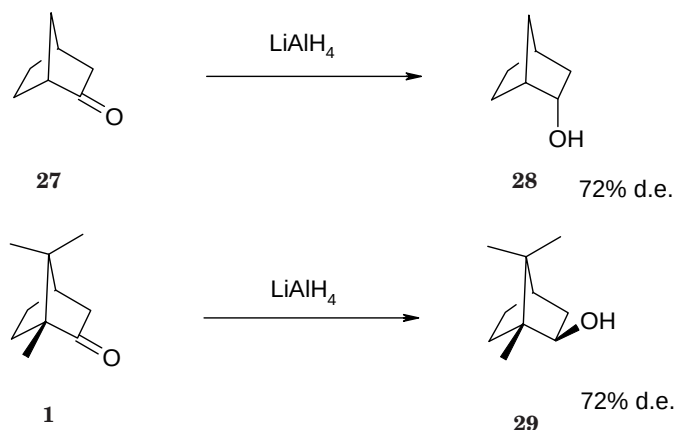
Camphor is quite readily functionalized since it has a reactive ketone moiety and the associated α -methylene group. The ketone moiety at C-2 can be used to direct reactions to the 10-methyl and the 3-methylene groups, (Figure 1.3), and the stereoselectivity of functionalization at these centres is of particular interest. Thus, use of a strong base can abstract a 3-methylene proton and an electrophile, such as an alkyl halide, can be used to introduce functionality at C-3 (Scheme 1.10). However, the stereospecificity of such alkylation has not been fully established.⁴⁵ The second 3-methylene proton may also be abstracted, permitting dialkylation, but stereoselectivity is not an issue here provided the second introduced alkyl

group is the same as the first.



Scheme 1.10: Alkylation of Camphor.

A second method of functionalising C-3, involves oxidation of camphor using selenium (IV) oxide. Formation of the selenite ester directs oxidation specifically toward C-3 resulting in the 2,3-diketone, camphorquinone.⁴⁶ The two carbonyl groups in camphorquinone are readily convertible to a number of different functional groups, but differ in reactivity. The 2-carbonyl group is generally less reactive than the 3-carbonyl group due, it is assumed, to the steric effects of the 10-methyl group. However, π -facial stereoselectivity tends to be greater at position 2, as illustrated by the fact that lithium aluminium hydride (LAH) reduction of norbornanone **27** produces *endo*-norbornanol **28** in 72% diastereomeric excess, while similar reduction of camphor produces isoborneol **29** (the 2-*exo*-hydroxy adduct), also in 72% diastereomeric excess³² (Scheme 1.11).



Scheme 1.11: Stereoselectivities of reduction.

Accounting for the stereoselectivity in these and related reductions of ketones is not easy, and has been somewhat controversial. Figure 1.4 shows the hyperconjugative electron donation from the *endo*-3-hydrogen σ -bond into the σ^* orbital of the incipient bond between the nucleophile and the carbonyl carbon adduced by Cieplak to favour *exo*-attack on the norbornyl enolate. Both the Felkin-Anh model, based on minimizing torsional strain in transition state complexes, and the Cieplak model explain the *exo*-stereoselectivity of LAH reduction of norbornane but, in the related reduction of camphor, the steric effects of the 9- and 10-methyl

groups clearly override any torsional and electronic effects.

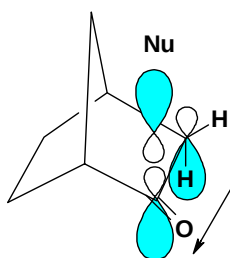
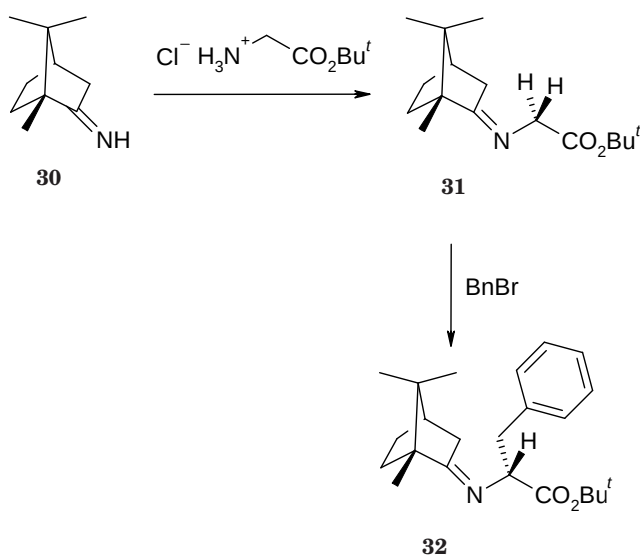


Figure 1.4: Cieplak rationalization of *exo* attack.

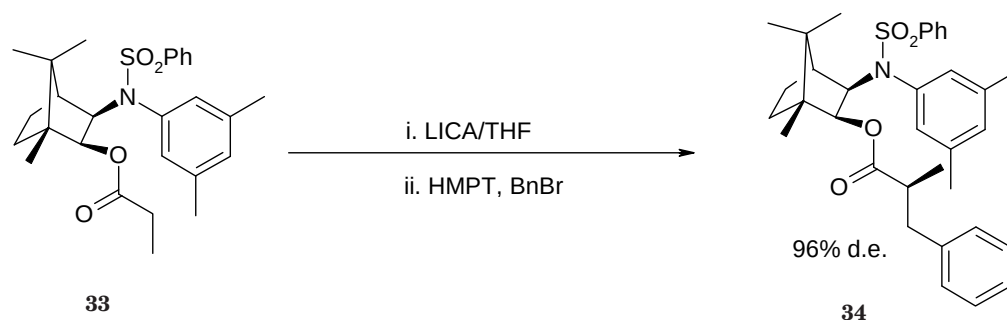
1.4.1.2 Chiral auxiliaries

A highly effective, though simple chiral auxiliary encountered recently in the literature is the camphor imine **30**.⁴⁷ For example, reaction with *t*-butyl glycine hydrochloride affords the camphorylidene derivative **31**, benzylation of which affords product **32** (Scheme 1.12). Although the precise diastereoselectivity is not cited, the product was observed to be spectroscopically identical to the camphorylidene derivative of the (*R*)-phenylalanine ester [the (*S*)-phenylalanine analog was also synthesized, but was different spectroscopically]. Although recovery of the chiral auxiliary is not reported in this paper, the stereo-directing capacity of the camphor skeleton is amply illustrated. In general, however, chiral auxiliaries involving camphor are better designed with functionalization at two centres, C-2–C-3 or C-2–C-10.



Scheme 1.12: Use of camphor imine.

1.4.1.2.1 Improving the efficiency of the chiral auxiliary Bifunctionalizing the camphor skeleton may serve either to improve rigidity or increase steric bulk. Helmchen⁴⁸ has increased the steric bulk of a number of camphor derivatives in an attempt to create a “concave” system. These chiral auxiliaries (illustrated in Figure 1.5) are typically used in the asymmetric alkylation of esters (Scheme 1.13) or in β -additions to acrylate esters. A fascinating change in stereochemistry was observed when HMPT was added in the deprotonating, rather than the alkylating step. In some cases this resulted in a complete reversal of stereochemistry!



Scheme 1.13: Alkylation of camphor-derived propionate.

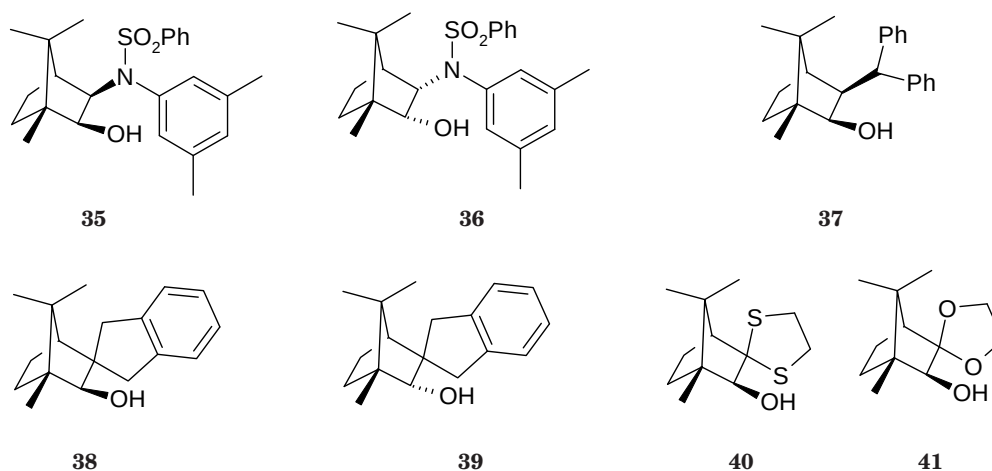
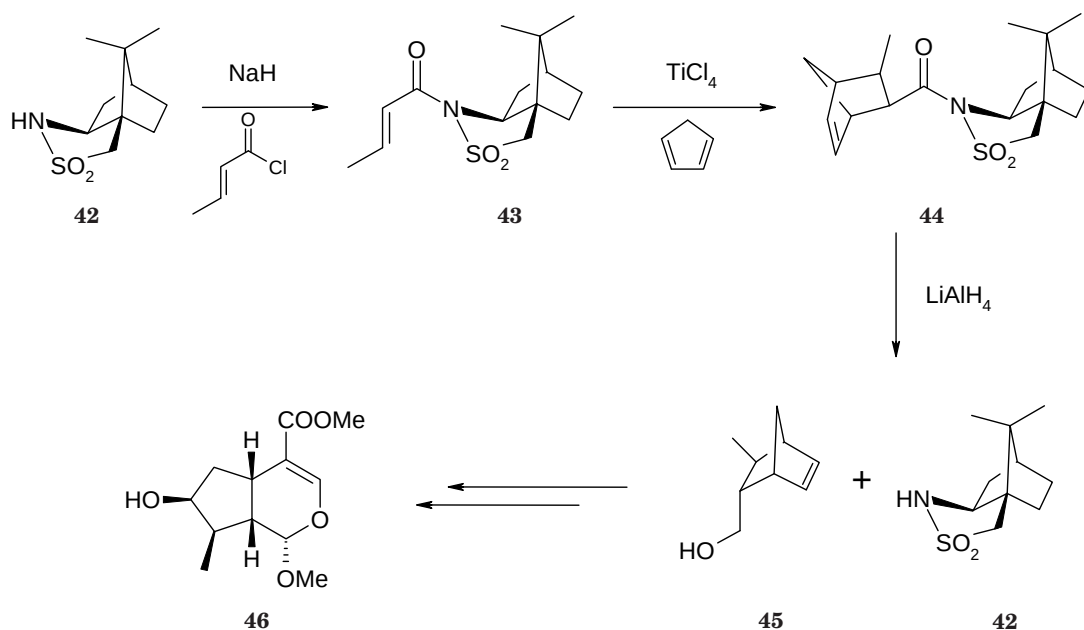


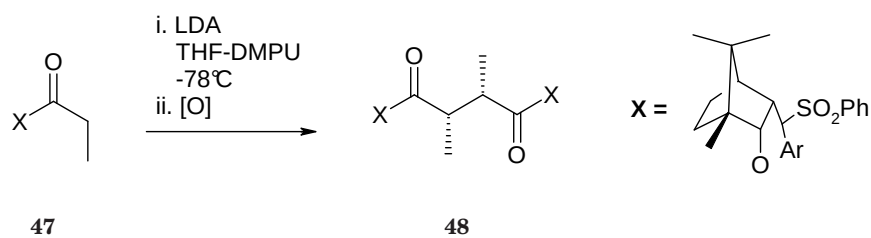
Figure 1.5: Chiral auxiliaries used by Helmchen.

One of the most successful camphor-derived chiral auxiliary is Oppolzer's sultam **42**.³⁸ This is a C-2–C-10 functionalized camphor, which is easily produced from 10-camphorsulfonyl chloride and used in inducing stereochemistry in reactions ranging from bis-hydroxylations to Diels-Alder reactions. An example of its use in a Diels-Alder reaction, is in the synthesis of the aglucone **46** (Scheme 1.14). The chiral auxiliary **42** is recovered in almost quantitative yield by cleavage with LAH.



Scheme 1.14: Use of Oppolzer's sultam **42** as a chiral auxiliary.

1.4.1.2.2 Formation of two chiral centres simultaneously An interesting use of camphor-derived chiral auxiliaries involves the formation of two chiral centres simultaneously as reported by T. Langer *et al.*⁴⁹ The enolate of the chiral propanoic acid ester **47** is dimerized *via* a free radical mechanism, using Cu(II) as the coupling agent, to give the diester, **48**, with (2*S*,3*S*)-configuration, in greater than 99% diastereomeric excess (Scheme 1.15). Although this camphor-derived chiral auxiliary only provides this configuration, other non-camphor-derived chiral auxiliaries have been shown to afford the (*R,R*) and (*R,S*) stereoisomers.⁵⁰



Scheme 1.15: Formation of two chiral centres.

1.5 Rearrangement reactions of camphor derivatives

The often unexpected cationic rearrangements of substituted bicyclo[2.2.1]heptyl (norbornyl) cations have caused much surprise, confusion and discussion (not all of it friendly!) over the past century.⁸ The ease of cationic rearrangement and the many types of rearrangements available to such systems complicate their study. There are two important aspects – the nature of the cations formed and their subsequent rearrangement.

1.5.1 Classical and non-classical carbocations

In 1983, several papers^{9,51–53} were published concerning what were referred to as “non-classical carbocations”. What makes these papers interesting is that they did not contain new experimental results! For more than two decades a war of words had been raging over the concept of “non-classical carbocations”, and the aim of the papers was to try to draw the controversy to a conclusion.

1.5.1.1 The historical perspective

In 1938,⁵⁴ Winstein and Lucas examined the coordination of ethylenic compounds with silver and, as a result of a discussion at a conference with Linus Pauling, proposed the resonance formulation of the coordinative bond illustrated in Figure 1.6.

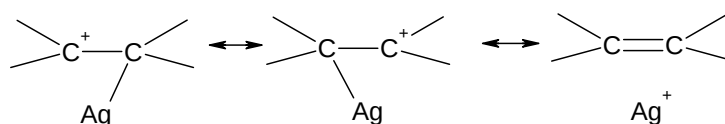


Figure 1.6: Ethylenic coordination to silver.

This, together with his work on neighboring group participation,⁵⁵ influenced Winstein's view of a curious difference in the solvolysis rates⁵⁶ of norbornyl *p*-bromobenzenesulfonates. He reasoned that, since the *exo*-species **50** loses its leaving group more readily than its *endo*-analog **49** (Figure 1.7) (*exo:endo*-rates:350:1), neighbouring group assistance (anchimeric assistance) was involved in the former case. Furthermore, since both enantiomers of norbornyl *exo*-acetate were formed in the presence of acetic acid, he reasoned that the intermediate was the symmetrical non-classical cation **51**. Anchimeric assistance that would aid solvolysis of the *endo*-substrate **49** was not considered, nor was there any need to – the *endo*-solvolysis rate and the lack of appropriate products⁵⁷ rendered this consideration unnecessary.

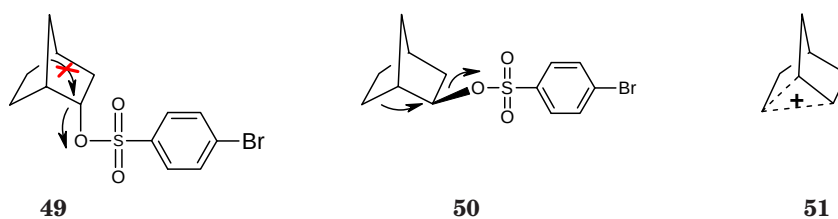
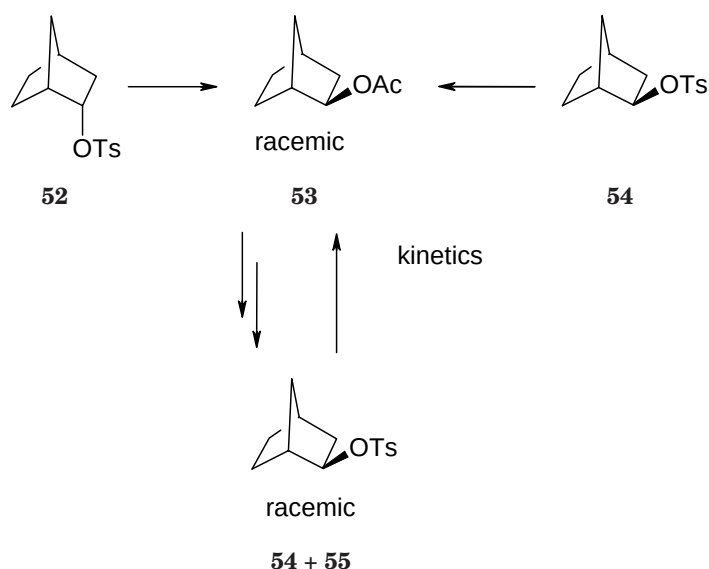


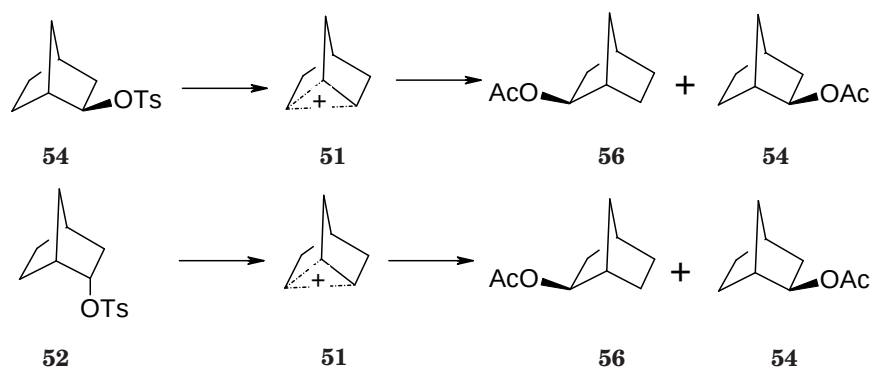
Figure 1.7: *exo* and *endo* norbornyl-*p*-bromobenzenesulfonates.

By May 1952,^{58–60} extensive work had been done by the Winstein group on this solvolysis problem. They provided conclusive proof that *endo* starting material would produce a purely *exo* product. A kinetic study of the recycled racemic product **54** + **55** of solvolysis of the *endo* system **52** afforded data that matched perfectly the kinetic data for solvolysis of the optically pure *exo* product **54** (Scheme 1.16). But there was another problem to address. How was a racemic product produced from an optically pure substrate? Did the solvolysis of optically pure starting material produce an optically pure product, which then racemised, or did the solvolysis itself produce both enantiomers? Although racemization of the *exo* acetate was shown to occur rapidly, solvolysis of (for example) the *endo* brosylate produces a racemic *exo* product directly.



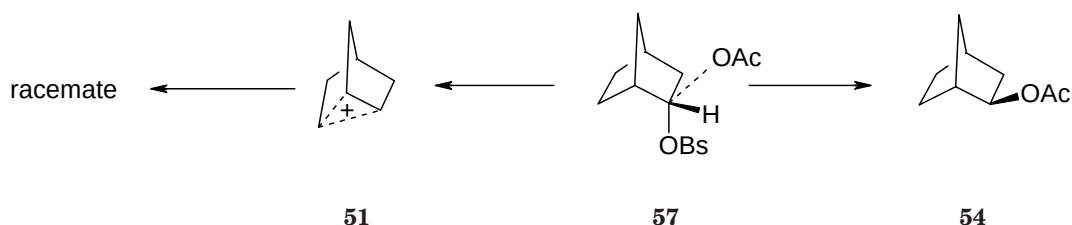
Scheme 1.16: Recycling to prove formation of an *exo* product.

The evidence pointed to a fast ionization, followed by rearrangement to a bridged cation (*i.e.*, the bridged cation does not form in concert with ionization). The phrase, “*bridging lags behind ionization*”, was used often in Winstein’s arguments.⁶¹ However, in solvolysis of the



Scheme 1.17: Solvolysis of exo and endo tosylates.

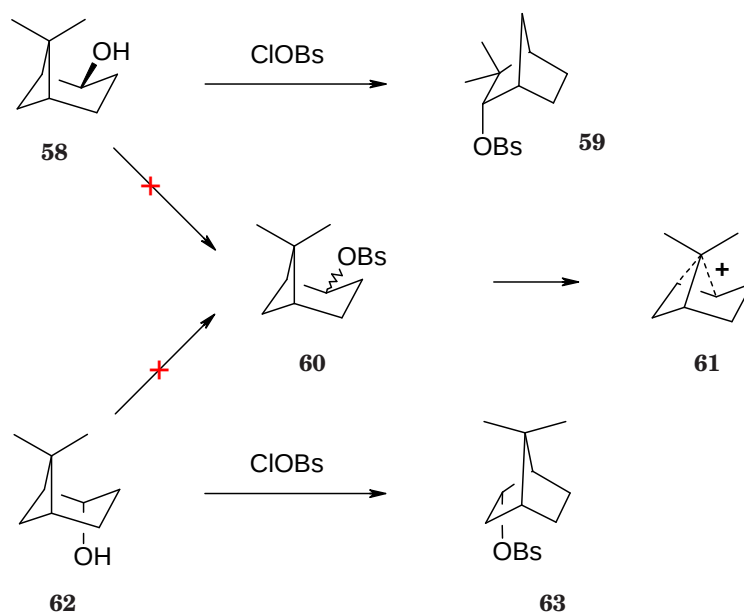
endo-substrates there is a small contribution towards optical activity, attributed to coordination (as in structure **57**) within the solvent sphere (Scheme 1.18).



Scheme 1.18: Coordination leading to the retention of some optical activity.

Anchimeric assistance in all such systems seemed a foregone conclusion, but one system did not provide Winstein with anticipated results.⁶² However, Schleyer⁶³ corrected the interpretation of the results putting them in accordance with Winstein's expectations (Scheme 1.19). Winstein had been looking at solvolyses of norpinyl brosylates **60**, the reported rates of which were well below what should have been anticipated, had anchimeric assistance been involved. Schleyer showed that the brosylates were not, in fact, norpinyl brosylates, but that rearrangement had occurred during their attempted formation and that they were actually the isomeric systems **59** and **63**. The low solvolysis rates could thus be attributed to the fact that solvolysis was that of *endo*-substituted norcamphenyl systems! Winstein later prepared the brosylate **60**, repeated the work, and observed a rate enhancement which he attributed to the bridging shown in the cation **61**.⁶⁴

By 1955 Winstein⁶⁵ had turned his attention to reactions involving position 7 in the norbornyl system and examined anchimeric assistance by a double bond in the loss of leaving groups at that position, which led him to formulate the existence of another non-classical carbocation **65** (Figure 1.8). This accounted for the retention of configuration, and the enhanced



Scheme 1.19: Nopinyl Brosylates.

rate of solvolysis of **66** over **67**.⁶⁶ It seems,⁶⁷ from an orbital perspective, that the double bond π -system donates electron density to the unfilled p -orbital of the sp^2 carbon at position 7, as in structure **71** (Figure 1.9). Solvolysis involving position 2 may be similarly explained (**70**, Figure 1.9).

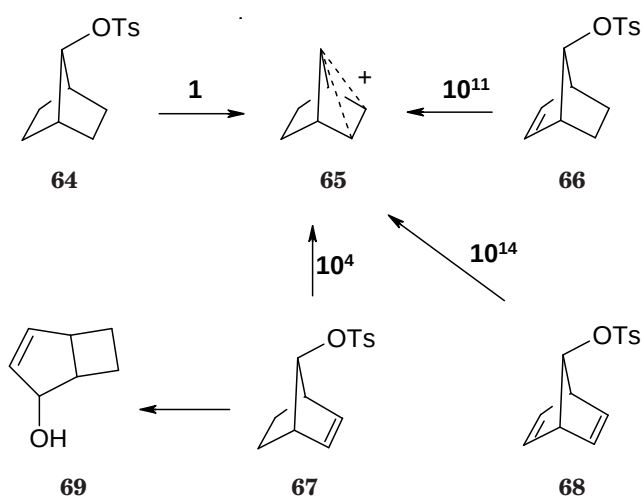


Figure 1.8: Relative rates of non-classical carbocation-formation from loss of a leaving group at position 7.

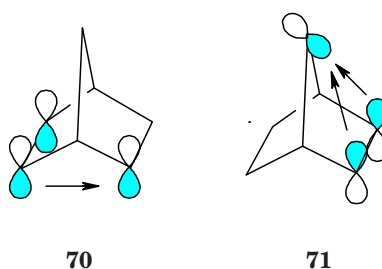
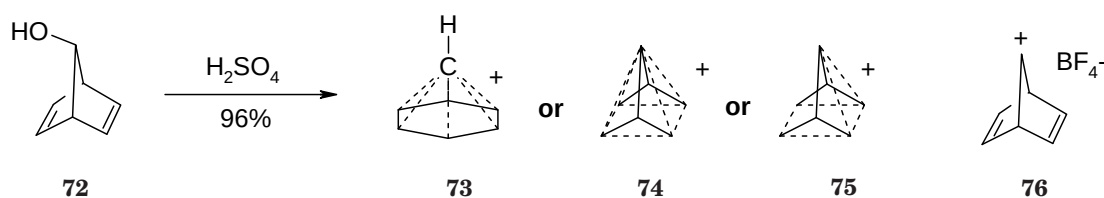


Figure 1.9: Orbital view of anchimeric assistance.

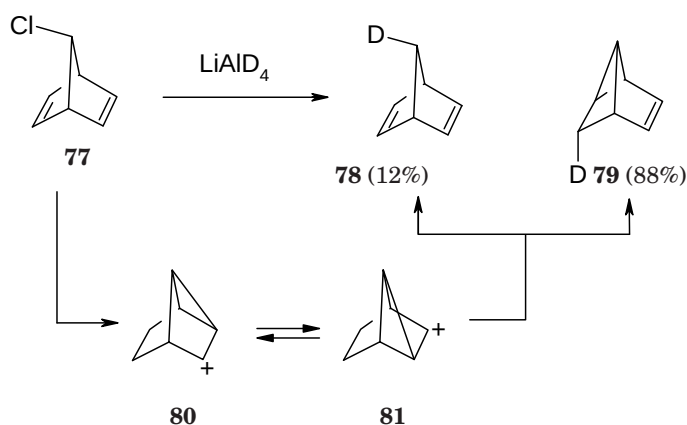
While the 7-*syn*-substituted norbornene **67** also shows accelerated solvolysis rates relative to **64**, the reaction may not, in fact, proceed *via* the non-classical intermediate **65**, since an unexpected rearrangement product **69** is also obtained. Interestingly, the diene **68** exhibited the greatest solvolysis rate,⁶⁸ and it was observed that in concentrated sulfuric acid a cation was produced from the alcohol **72**. This cation, it was suggested, could be represented either as structure **73**, **74** or **75** (Scheme 1.20).



Scheme 1.20: Proposed cations from 7-substituted systems.

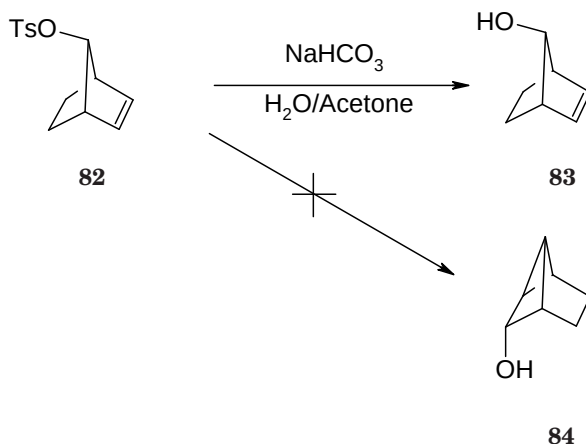
The effect of this rather bold assertion was to prompt further research in the chemical community. Story and Saunders⁶⁹ prepared the fluoborate salt **76** (Scheme 1.20), and showed, using ^1H NMR spectroscopy, that the four olefinic protons were not identical, but rather two pairs of separately identical hydrogens, supporting structure **75** (Story had suggested the existence of a non-classical radical earlier!). This work could not go unnoticed by H. C. Brown, who had been looking at the way in which steric effects determine the course of certain reactions^{70,71} prompting the comment:⁷² *“the possible existence of this intermediate as an equilibrating pair of classical tricyclic carbonium ions cannot be excluded by the available data.”* Brown’s concerns were not just with “non-classical” carbocations but also with anchimeric assistance in general.

It is interesting to note the different types of reaction conditions used in the arguments concerning non-classical carbocations. For instance, the observation by Story^{69,73} that reduction of norbornadienyl chloride **77** with LiAlD_4 (Scheme 1.21) was used by Brown⁷² to support the existence of the equilibrating classical cations **80** and **81** (Brown’s argument related to “trapping” of formed carbocations and analysis of the products formed^{74,75} - a route to examination of steric effects). Winstein, however,⁷⁶ interpreted the results differently. He argued that if that was the case then the tricyclic alcohol **84** should be formed rather than the isolated 7-*anti*-alcohol **83** (Scheme 1.22). Schleyer was also a key player in the controversy, and was unable to find NMR evidence for a single, non-classical carbocation for the disubstituted norbornyl system **85**⁷⁷ (Figure 1.10) - a point enthusiastically received by Brown.⁷⁸



Scheme 1.21: Reduction of nobornadienyl chloride.

While it may be easy to dispute the earlier arguments by Brown contesting the existence



Scheme 1.22: Non-formation of tricyclic products.

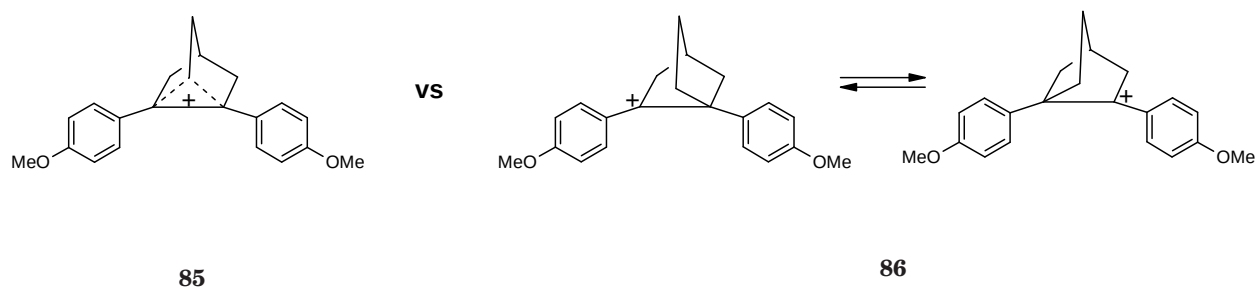


Figure 1.10: Non-classical vs equilibration of dianisyl systems.

of non-classical carbocations, his arguments regarding anchimeric assistance in a series of papers in 1963-1964^{79–82} cannot be readily discarded. According to Brown, careful examination and comparison of cyclic and bicyclic systems reveals the following.

1. 2-Substituted *exo*-norbornyl systems solvolyse at a rate approximately 5 times greater than their monocyclic equivalents due to greater inherent strain in the bicyclic systems.
2. The *exo*-norbornyl brosylate solvolyses at a rate 400 times greater than its *endo* analogue - an observation attributed to anchimeric assistance.
3. The *endo*-analogue solvolyses approximately 5 times faster than the monocyclic equivalent, since in neither case is anchimeric assistance possible, and the difference in rate can be attributed to the extra strain in the bicyclic system.

Brown then argued that the *exo*-norbornyl brosylate, with anchimeric assistance and extra ring strain, should solvolyse at a rate $400 \times 5 = 2000$ times greater than the monocyclic equivalent.

lent. However, since the experimental factor is actually somewhere between 4 and 14, Brown concluded that the solvolysis of *exo*-systems was *not* unusually fast - it was the solvolysis of *endo*- systems that was unusually slow!⁸² There is a flaw in assumption 1., an issue addressed later. The explanation for this discrepancy was steric in origin, involving loss of an *endo*-group *via* a highly hindered transition state. In Figure 1.11, which is similar to the diagram Brown used,⁸² movement of the chlorine atom is hindered, preventing the transition between sp^3 and sp^2 hybridisation at C-2. Schleyer⁸³ suggested similarly that torsional effects involving the 1-substituent could also be involved.

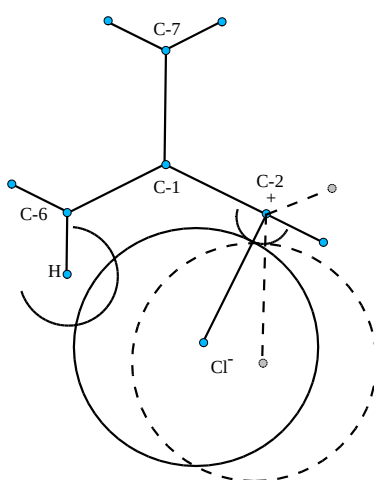


Figure 1.11: Steric problems encountered by the chlorine in norbornyl 2-*endo*-chloride in the transition from bonded (dashed) to nonbonded (solid) for the *endo* transition state.

This interpretation was a serious challenge to neighboring group participation and non-classical carbocation theory, and prompted a flurry of papers on 2-substituted norbornyl systems. Brown followed a different series of arguments. He noted that, if Winstein's original suggestion was correct, variations in substituents at C-1 and C-2 should, in theory, either prevent or promote solvolysis, (by their effect on anchimeric assistance – stabilizing or destabilizing bridging). Experimentally, however, this was not the case, as *exo*- over *endo*- rate enhancement was still apparent in such systems⁸⁴ (Figure 1.12). Thus, according to Brown, anchimeric assistance was not the promoting factor in *exo*-solvolysis, as evidenced by the similar rate ratios between 2-substituted and unsubstituted systems. The problems with this argument will be also addressed later.

A further example⁸⁵ of this type of argument is illustrated in Scheme 1.23. If non-classical carbocations are involved, a methyl group at C-1 should stabilize the transition state for the process **91** → **92**, while the 2-methyl substituent in **93** should destabilize its transition state

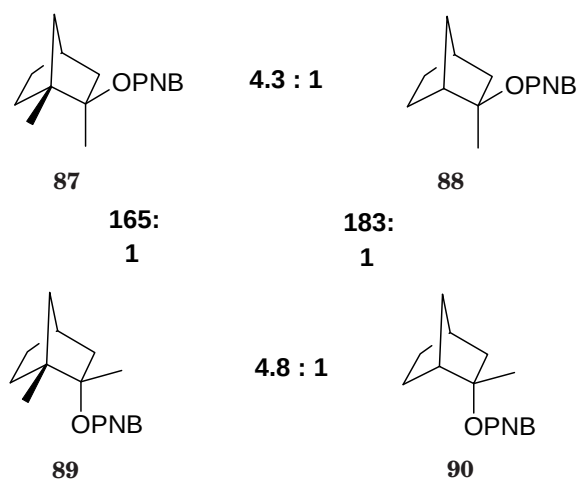
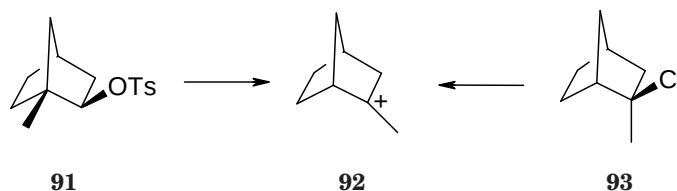


Figure 1.12: Relative rates for *exo*- and *endo*-*p*-nitrobenzoate (OPNB) substituted systems.⁸⁴

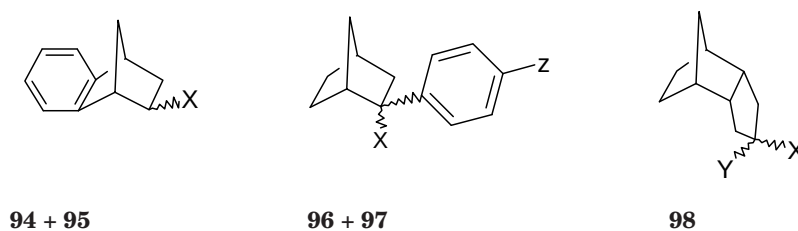
but this is not observed experimentally. It was clear to Brown that there must also be no C-6 participation.



Scheme 1.23: Substitution at positions 1 and 2.⁸⁵

Brown continued by arguing that while the *exo*-tosylate **91** and the *exo*-chloride **93** would involve different carbocations (non-classical or classical, respectively) they behave similarly in terms of *exo/endo* rates under solvolysis conditions. Hence, one should question all "non-classical" cases. Much experimental evidence has been gathered for these and similar 2-substituted systems over the years.⁸⁶ Brown in particular carefully investigated π -participation^{87–89} (in structures such as **94** and **95**), and thoroughly examined the effect at C-2 on σ -participation^{89–94} through the use of aryl substitution (in systems such as **96** and **97**). Convinced as to the lack of σ participation, he searched for steric evidence^{95,96} in support of the slow *endo*-solvolysis model including systems such as **98**.^{97,98}

Schleyer had developed a theoretical method of estimating solvolysis rates based on carbonyl frequencies, dihedral angles and the relief of non-bonded strain.^{63,99,100} Such was the success of this system, Schleyer believed the experimental results of Winstein's anomalous paper⁶² (see Section 1.5.1.1, p18) to be wrong, and he had to investigate why! His system⁹⁹ was based on a semi-empirical approach and used the IR carbonyl frequencies of analogous



Scheme 1.24: Various systems encountered in the search for π -, σ - participation, and steric interactions.

ketones to estimate bond angle strain (the frequency ν_{CO} is sensitive to the C-C-C angle at the carbonyl centre, as is the ease of ionization at the tosylate centre in analogous norbornyl tosylates). Torsional effects were evaluated in terms of the extent to which groups were eclipsed *i.e.*, in terms of the torsion angle, ϕ , the greater the degree of eclipsing the greater the rate of solvolysis. The steric relief associated with the departure of a leaving group was also included in Schleyer's overall theory (Equation 1.1).

$$\log k_{rel} = \frac{(1715 - \nu_{CO})}{8} + 1.32 \sum i(1 + \cos 3\phi_i) + \frac{(GS - TS_{strain})}{1.36} + \text{inductive contribution} \quad (1.1)$$

In Equation 1.1, k_{rel} is the rate constant relative to $C_6H_{11}OTs$, and the parameters which contribute to this rate constant are: i. the carbonyl absorption frequency (ν_{CO}); ii. the torsion angle (ϕ_i); iii. steric relief in the transition state, compared to ground state; and iv. inductive effects due to unsaturated systems in close proximity to the carbonyl group. A more detailed study¹⁰⁰ of norbornyl systems using this method revealed marked discrepancies from the experimental data in cases where anchimeric assistance and bridging had long been suspected. Such discrepancies, Schleyer asserted, clearly supported anchimeric assistance. However, Brown's response⁷⁴ made clear, quite correctly, that rates alone cannot support a non-classical structure (Schleyer was in full agreement as to this point¹⁰¹).

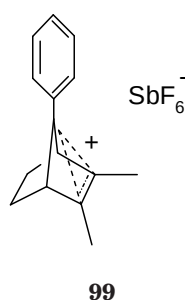
A breakthrough in the controversy, could not come, therefore, from accurate measurements of solvolysis rates, novel substitution of norbornyl systems¹⁰¹ or from theoretical considerations, but from some interesting work on carbocations that was being done at that time.

1.5.2 The evidence for non-classical carbocations

1.5.2.1 Long-lived cations

“Superacids” such as triflic acid ($\text{CF}_3\text{SO}_3\text{H}$) and “magic acid” ($\text{FSO}_3\text{H}\cdot\text{SbF}_5$), are significantly more acidic than conventional acids.⁸ It was with acids such as these that Olah, using NMR spectroscopy, observed the formation of the non-classical norbornyl cation.^{8,102,103} The experiment was conducted in $\text{SbF}_5/\text{SO}_2\text{ClF}/\text{SO}_2\text{F}_2$ at -159°C , at which temperature, no rearrangement process was considered active. It should be noted that at higher temperatures (-78°C) hydride shifts in particular become evident. While the relative slowness of the NMR might be used to challenge his interpretation, Olah also obtained core electron spectroscopic (ESCA) data for the 2-norbornyl system¹⁰⁴ in which all species (even rapidly equilibrating ones) would be evident. Moreover, *ab initio* NMR prediction results indicated the observed NMR chemical shifts of the 2-norbornyl cation to be correct for a single cation rather than for two rapidly equilibrating ones.^{8,9}

Subsequently NMR studies at liquid helium temperatures¹⁰⁵ and crystallographic data (of, for example, the non-classical 2,3-dimethyl-7-phenyl-2-norbornen-7-ylum hexafluoroantimonate(V) salt **99**¹⁰⁶) have confirmed that non-classical carbocations not only exist but, more importantly, that the 2-norbornyl system is a non-classical system. It should be noted that, while many of these studies related specifically to the structures of the 2-norbornyl system, Olah¹⁰⁷ obtained evidence suggesting that at -78° the 1,2-dimethyl-2-norbornyl system, in particular, existed as an equilibrating pair of carbocations (*i.e.* not non-classical).



1.5.2.2 Evidence from solvolyses

Of course, the existence of non-classical carbocations in superacidic media does not prove bridging in normal solvolyses of *exo*-substrates.⁵¹ It has now been established that *endo*-substrates solvolyse at “normal” not “slow” rates,^{53,86} and some experimental data, obtained

in acetic acid, are known to be skewed due to “nucleophilic solvent assistance”.⁸⁶ In summary,⁸⁶ it seems that the following conclusions can be drawn.

1. There is *no* steric interaction on the solvolysis of secondary *endo*-substrates, since accurate experimental data in *non-nucleophilic solvents* suggest these substrates more closely match the solvolysis of monocyclic systems (in contradiction with Brown’s assertions in Section 1.5.1.1). However, there *is still evidence* that retardation of the solvolysis of tertiary substrates is due to steric effects.
2. Even in tertiary systems (*e.g.* 1-hydrogen-2-methyl-norbornyl type systems, in which tertiary to secondary carbocation rearrangements are not favoured) bridging may still aid *exo* solvolysis.
3. Substituents at positions such as 6-*exo* and 5-*exo*- still affect the solvolysis rate remarkably. Since a steric interaction is impossible, electronic effects must be responsible.
4. Electronic effects (from the [C-1–C-6] bond) may stabilize the incipient cation more effectively in the *exo* case where that bond is anti-periplanar to the developing cation orbital, compared to the syn-periplanar arrangement in the *endo* case.
5. Not all situations may be interpreted as strictly “classical” or “non-classical” but rather as existing on a scale between the two.
6. The concept of non-classical or equilibrating classical carbocations is not justified from the solvolysis data.

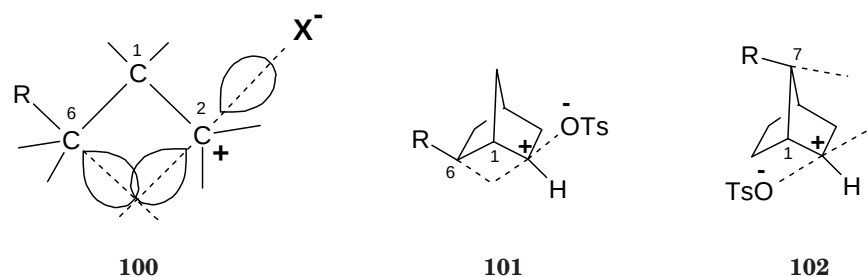


Figure 1.13: Grob’s¹⁰⁸ explanation of anchimeric assistance.

Grob^{108–110} carefully investigated the inductive effect at each position on the norbornyl system. From his diagram **100** (Figure 1.13), it is clear how the 6-*exo*-substituent affects the anchimeric assistance for loss of 2-*exo*-groups. This illustrates why the effect is largely

independent of substitution on C-1 and C-2 (and also why “*bridging lags ionization*” - the geometry of the system at C-6 does not change initially as the system ionizes). Systems **101** and **102** illustrate that anchimeric assistance from position 6 is optimal in solvolysis of *exo*-substrates; that from position 7 is not observed for the corresponding *endo*-systems.

1.5.2.3 Molecular modelling of norbornyl systems

Computational studies on uncharged, substituted norbornyl skeletons give insight into the thermodynamically favoured orientation of, for example, methyl substituents on a norbornyl skeleton. *Exo*-substituents are preferred to *endo* and *trans*-2,3-disubstituted systems are more stable than the *cis*-equivalents.¹¹¹ But molecular modelling has also provided insights into the non-classical carbocation problem. *Ab initio* minimizations of the 2-norbornyl cation produce a symmetrical system, which is clearly non-classical, and it is apparent that the classical 2-norbornyl cation has no existence as a minimum on a potential energy surface.¹¹²

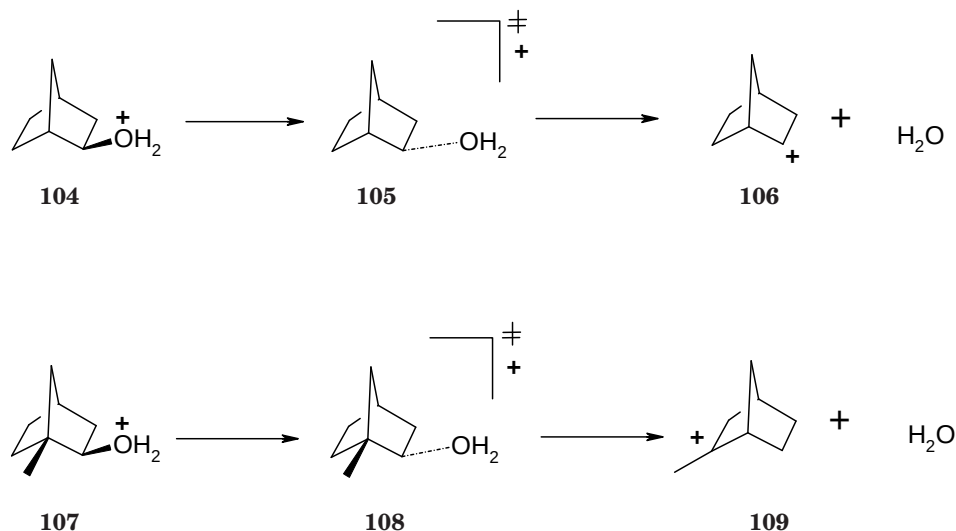
Other theoretical approaches to the non-classical 2-norbornyl carbocation include electron localization function (ELF) studies,¹¹³ in which the stabilization is seen to be electrostatic since no “bond paths” exist between C1, C2 and C6. However, atoms in molecules (AIM) studies show that systems such as the 1,2,4,6-*anti*-tetramethyl-2-norbornyl cation **103** do not exhibit bridging, and as such are more classical in nature.¹¹⁴ However, the insights into these systems provided by theoretical methods run deeper than a simple understanding of static systems. Modelling data also suggests a strong driving force away from the classical 2-norbornyl cation,⁸⁶ affording information on how “bridging” affects the dynamics of real reactions.



103

Schleyer,¹¹⁵ for example, studied the loss of a leaving group from both the norbornyl cationic system and a 1-methyl substituted system, and made some very interesting observations, *viz.*, both *endo*- and *exo*-transition states (**105** shows the *exo* transition state) benefit from “non-classical” stabilization! Scheme 1.25 illustrates the *exo*-transition in each case. Moreover there is no evidence of steric impedance between the leaving group and the 6-*endo*-hydrogen in the *endo* transition state as suggested by Brown, but rather an attractive-

stabilizing interaction. Thus modelling confirms the electronic, rather than steric influence on solvolysis rates.



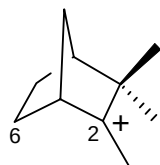
Scheme 1.25: Scheme for the modelling of solvolysis of 2-*exo*-hydroxy derivatives by Schleyer.

Winstein made mention of the idea that “bridging lags ionization”. By this he implied that upon solvolysis a transient, unstable “classical” type system, which formed initially, would give way to a stable, “non-classical” species. He resorted to this argument to explain the lack of increased solvolysis of 1-alkyl-substituted norbornyl type systems [such as 1-(*p*-anisyl)camphene hydrochloride¹¹⁶ and the 2-*exo*-tosylate **91** (Figure 1.23)]. In such systems, the 1-substituent should favour C-6 -participation as this would result in the positive charge moving towards a more favourable C-1 -tertiary carbocation arrangement. However, a change in the electronic distribution requires some accompanying geometrical change, however slight.¹¹⁷ Modelling helps to put some of these issues into perspective. Schleyer¹¹⁵ notes that the pattern of bridging lagging ionization may be apparent geometrically but *not* energetically (*i.e* upon ionization the system is very close energetically to the non-classical arrangement, although geometrically this is not the case)! This insight provides a means to rationalize Winstein’s idea. Only a slight distortion in skeletal structure is sufficient to permit this non-classical stabilization in both transition states (Scheme 1.25). Moreover, Schleyer argues that there is an *exo* over *endo* ionization preference “*in the absence of any bridging*”, but does provide an in-depth rationale for this view.

In the case of the protonated 1-methyl-2-norbornyl 2-*exo*-alcohol¹¹⁵ **107**, modelling reveals that bridging clearly lags loss of the leaving group in all respects. Thus, formation of the

tertiary carbocation is not the major factor in the transition state; hence the very small effect C-1 substitution has on solvolysis. This is in accordance with Grob's explanations (Section 1.5.2.2, p28). The very small *exo vs endo*-rate enhancement due to C-1 substitution is reduced somewhat by the favourable leaving group interactions (leaving group – 1-methyl-2-norbornyl cation interactions) in the *endo* transition state.

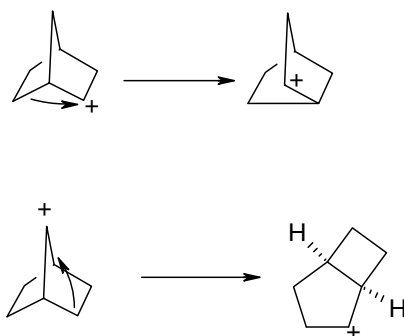
When modelling such systems, the rather flat nature of the potential energy surfaces needs to be borne in mind. Although Schleyer suggested the potential energy well for the non-classical norbornyl cation itself is very steep,⁸⁶ the authors of a transition state study in 1997¹¹⁵ did not take the calculated zero-point vibrational energies (ZPVE) into account specifically because they were aware of the flatness of the potential energy surface (where conditions required for ZPVE do not hold). Sorensen¹¹⁸ also noted that the potential energy surface of the camphenyl cation **110** relating to the C-2–C-6 distance is very flat. Of course, a flat potential energy surface is consistent with the observation above that “bridging lags ionization” geometrically but not energetically.

**110**

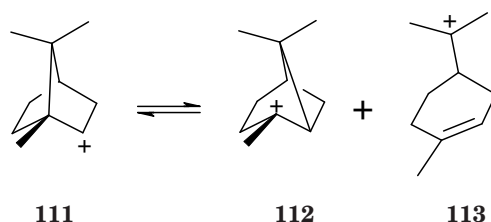
1.5.3 Wagner-Meerwein and Nametkin Rearrangements, and methide- and hydride- Shifts

1.5.3.1 The Wagner-Meerwein rearrangement

In **1875**, Wagner boldly stated that camphor and camphene had different skeletal arrangements, and that the conversion of borneol (obtained from camphor) to camphene involved a skeletal rearrangement.¹¹⁹ Meerwein¹²⁰ proposed the involvement of a carbocation intermediate. This skeletal change became widely known as the Wagner-Meerwein rearrangement. The name refers to a 1,2-skeletal-bond shift in a carbocation skeleton.¹²¹ The most common examples of such shifts involve norbornyl cations and bicyclic systems as illustrated in Scheme 1.26.



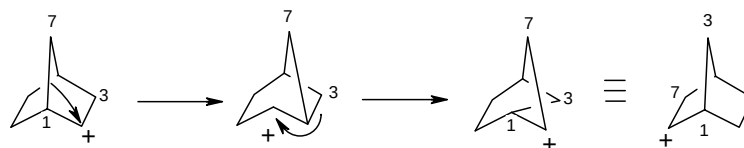
Scheme 1.26: Wagner-Meerwein Rearrangements.



Scheme 1.27: Formation of the pinenyl system.¹²²

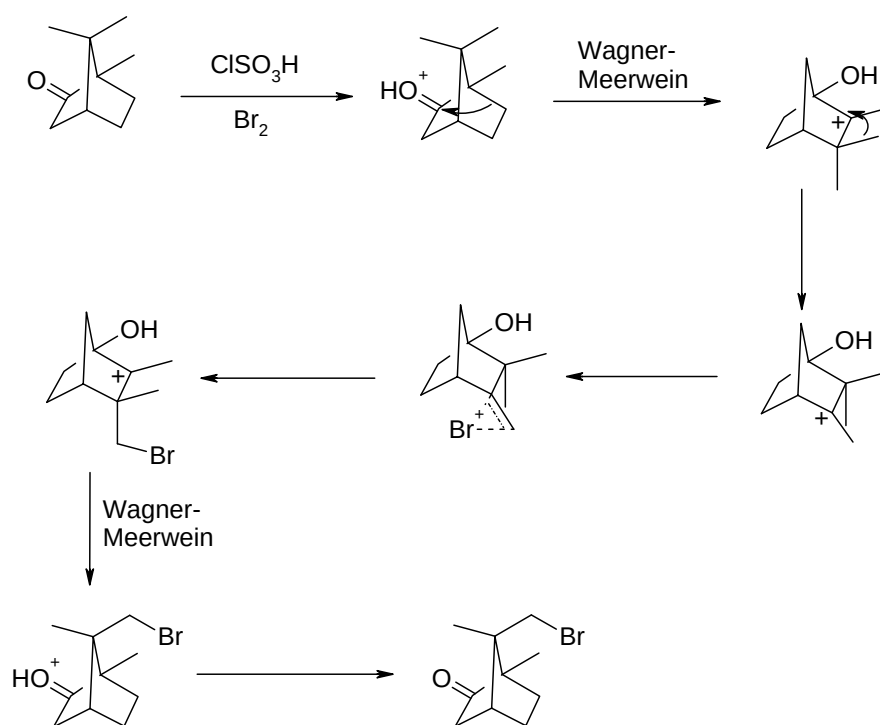
Ebmeyer^{121,122} attributed the formation of the pinenyl system **112** to a Wagner-Meerwein rearrangement (Scheme 1.27), although Hanson¹²¹ has suggested that 3- and 4- membered rings are not generally formed in Wagner-Meerwein transformations. Collins *et al.*,¹²³ on the other hand, defend the “double Wagner-Meerwein” transformation, illustrated in Scheme 1.28, by saying that the 11-step alternative is “too long to be considered seriously”. However, they do not mention any energetic considerations, and references to the double Wagner-Meerwein rearrangement appear to be absent in the more recent literature. It should also be

noted that combinations of more conventional rearrangements can achieve the same result as the double Wagner-Meerwein rearrangement. The double Wagner-Meerwein process can, in fact, be viewed as a combination of two steps (Scheme 1.28).



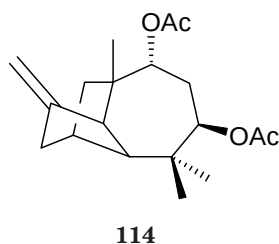
Scheme 1.28: The “double Wagner-Meerwein” transformation.

Wagner-Meerwein transformations are occasionally useful in synthetic pathways. Examples include the C-9 bromination of camphor¹²⁴ (which requires two Wagner-Meerwein steps as illustrated in Scheme 1.29), and the Wagner-Meerwein rearrangement involved in the generation of the novel “uruapane” skeleton in (1*R*,4*S*,5*S*,7*R*,9*R*,10*S*)-7,9-diacetoxyuruap-3(12)-ene **114**.¹²⁵



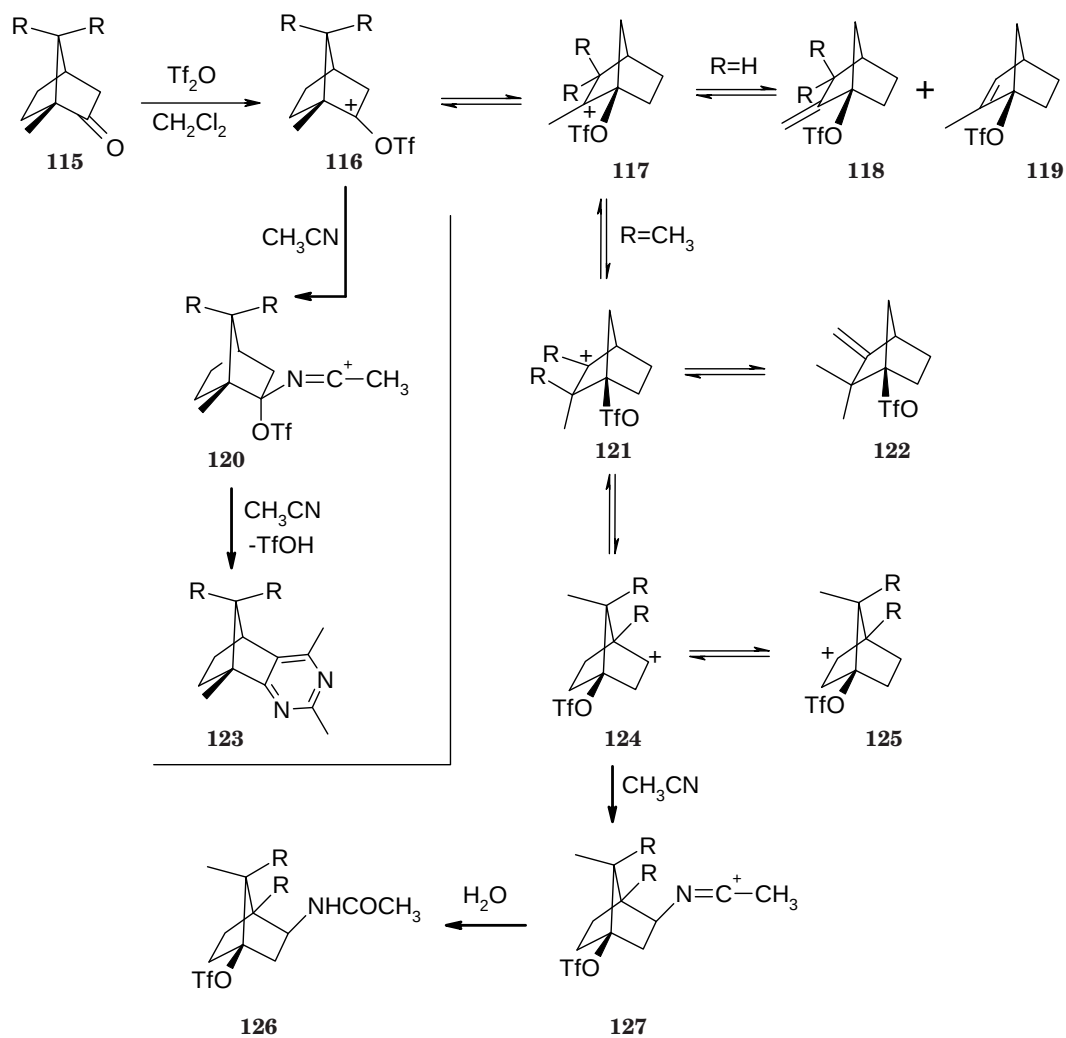
Scheme 1.29: C-9 bromination of camphor.

It seems that Wagner-Meerwein-type rearrangements on substituted norbornyl systems must occur readily - a view supported by the failure to observe equilibrating norbornyl cations in ¹H NMR spectra obtained at liquid helium temperatures.¹⁰⁵ Other transformations, such as hydride shifts are “frozen out” by -159°C.⁸ In an interesting NMR exchange study,¹²⁶ a



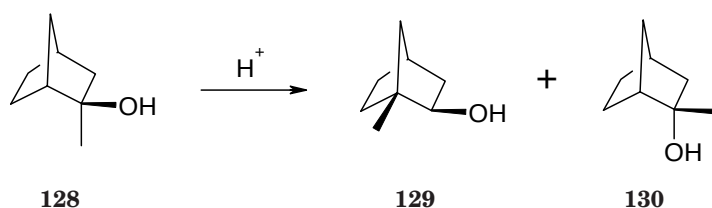
3,2-hydride shift has been calculated to be slower than a 6,2-hydride shift and a Wagner-Meerwein shift by a factor of 10^9 .

The rate of the Wagner-Meerwein and similar rearrangements relative to nucleophilic addition (carbocation trapping),¹²⁷ may be important in determining the outcome of a reaction. Steric effects clearly play a large role. Thus, in Scheme 1.30, when $R = H$ the main product is the pyrimidine derivative **123** (accompanied by smaller quantities of the triflates **118** and **119**), but when $R = CH_3$ the main product is the acetamide **126**, again accompanied by smaller quantities of the isomeric triflates **118** and **122**.

**Scheme 1.30:** Carbocation trapping by CH_3CN .

1.5.3.2 The camphene hydrochloride rearrangement

The hydrogen chloride - catalysed rearrangement of camphene hydrochloride^{128–132} to *iso*-bornyl chloride is an interesting, and well-known, variation on the Wagner-Meerwein theme,¹³³ and the camphene rearrangement may also be involved in the formation of the secondary alcohol **129** observed in the acid catalysed rearrangement of 2-methyl-*exo*-norbornanol (Scheme 1.31).¹²⁹ Brown investigated several routes to camphene hydrochloride in the search for evidence against σ -participation in solvolysis,¹³⁰ while Smith¹³² noticed some shortcomings in the literature regarding the mechanism for this rearrangement. Smith recognized that the two suggested mechanisms, [one involving a purely “classical” carbocation (route I), the other “non-classical” (route II; Scheme 1.32)] failed to account for either the rate enhancement (when catalysed by hydrogen chloride) or stereoselectivity (as in the formation of a *purely* *exo* product).

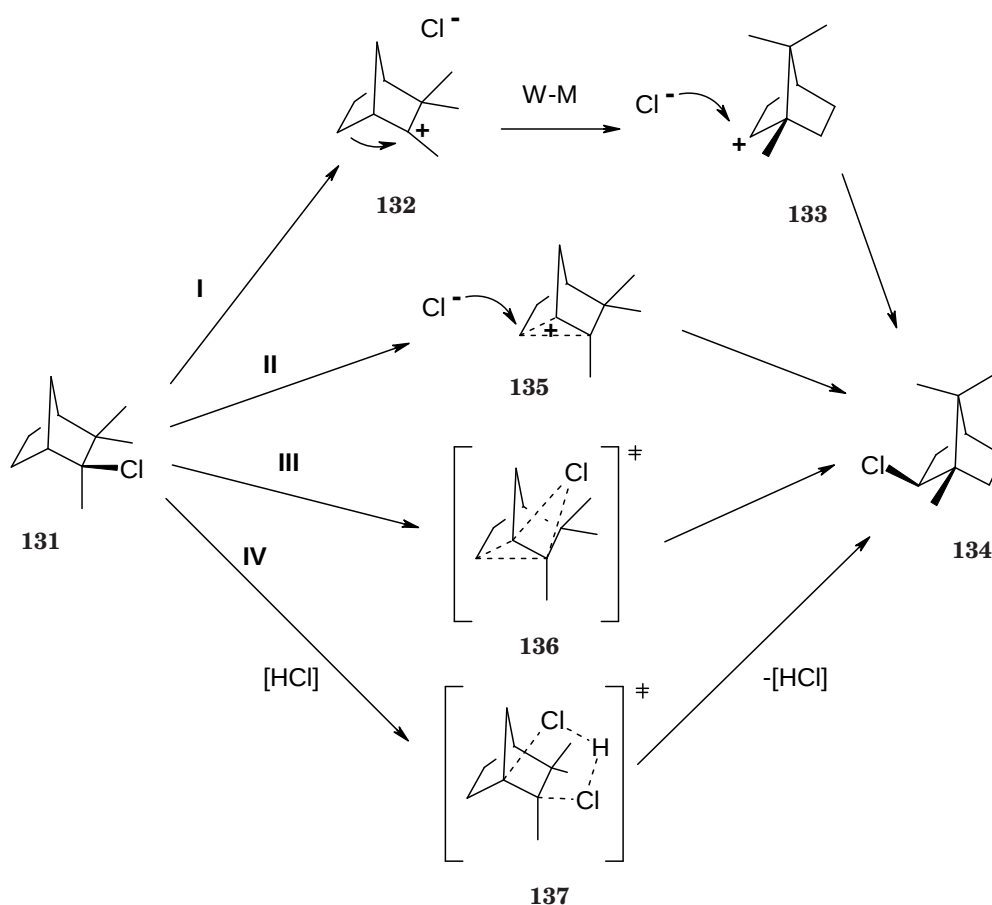


Scheme 1.31: Rearrangement producing a secondary substrate **129**.

Smith¹³² suggested that transition states for this transformation could specifically include the hydrogen chloride. Using computational methods, he located transition states **136** and **137**, respectively, for the uncatalysed rearrangement [which proceeds with the chloride in close proximity and not *via* a carbocation intermediate (route III)] and a hydrogen chloride-catalysed rearrangement [involving a 5-membered ring in the transition state (route IV)]. However, Sorensen¹¹⁸ pointed out some pertinent arguments in favour of ionization. Firstly Smith’s ionization energy for the chloride appeared to be severely limiting (130kcal/mol). Using solution phase calculations, Sorensen corrected this value to about 14kcal/mol, and concluded that the process is a “hybrid” of the two mechanisms (routes I and II) detailed in Scheme 1.32.

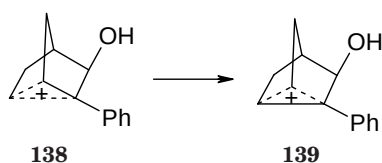
1.5.3.3 Hydride and methide shifts and Nametkin rearrangements

2,3-Hydride and methide shifts are well established and have been studied on the norbornyl cationic skeleton.^{134,135} In terms of rates, it would appear that a 2,3-hydride transfer involves



Scheme 1.32: Proposed routes for the camphene hydrochloride rearrangement.

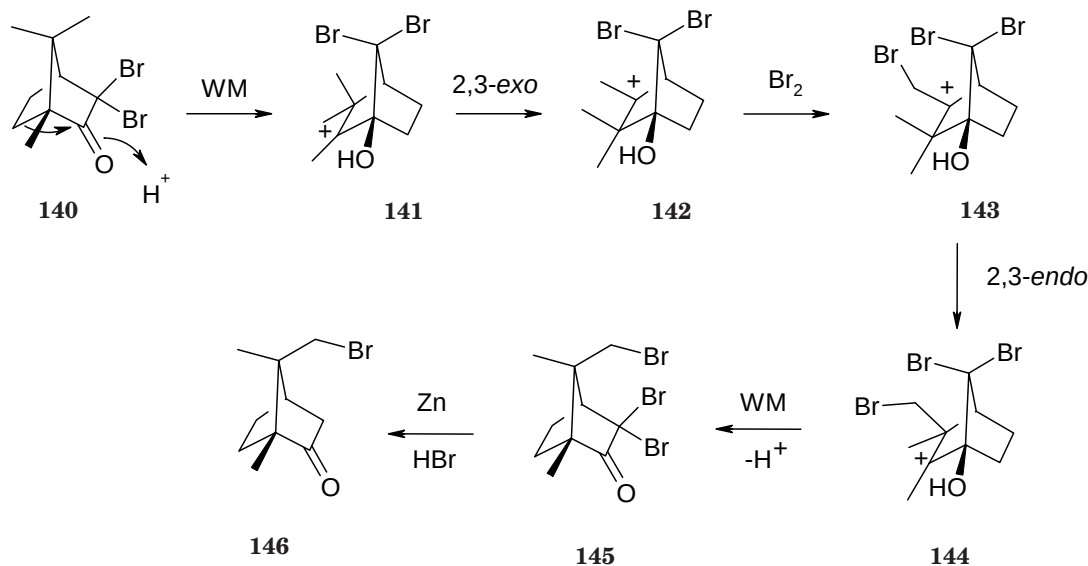
a much larger activation energy than either the 6,2-hydride shift or a Wagner-Meerwein rearrangement.⁷ From a torsional perspective, *exo* groups are better aligned with the empty cationic *p*-orbital than *endo* groups and, consequently, only 2,3-*exo* migrations generally occur.^{136,137} The original rearrangement referred to by Nametkin was essentially a 2,3-*exo*-methide shift on a camphene skeleton.¹³⁶ Roberts¹³⁸ offered evidence from ^{14}C labeling of norbornyl systems that 6,2-hydride shifts also occur on a non-classical carbocation (Scheme 1.33), and both “edge-protonated” and “face-protonated” transition states have been suggested^{134,138–140} *i.e.*, transition states on or off the non-classical face of the non-classical norbornyl cation. However, while the cation **138** may well undergo a hydride shift, the original tertiary carbocation (from which **138** is formed *via* partial rearrangement) is unlikely to undergo that Wagner-Meerwein rearrangement.



Scheme 1.33: Hydride shift on a non-classical carbocation.

1.5.3.4 Steric constraints

Money *et al.*¹⁴¹ cite an example of a reaction which proceeds *via* an *endo*-methide shift, arguing that the severely sterically hindered tribromocamphor cation **143** prevents an *exo*-methide shift from occurring. The *endo*-methide shift, followed by a Wagner-Meerwein transformation, affords the 3,3,8-tribromocamphor **145**, which may be reduced to 8-bromocamphor **146**. Although the steric explanation has been disputed,¹⁴² the fact remains that an *endo*-shift is clearly involved - one of the rare exceptions to the rule. A few other *endo*-2,3-hydride and methide shifts have also been recorded,^{143,144} but these are not the norm.



Scheme 1.34: Formation of 8-bromocamphor *via* a pathway including a 2,3-*endo*-methide shift.

1.5.4 Exploring mechanistic pathways followed by norbornyl carbocations

Substituted norbornyl cationic systems are extremely labile, with the possibility of undergoing multiple step rearrangements. Schemes 1.29 and 1.34 begin to illustrate the complexities of these systems.

1.5.4.1 The complexities of pathways

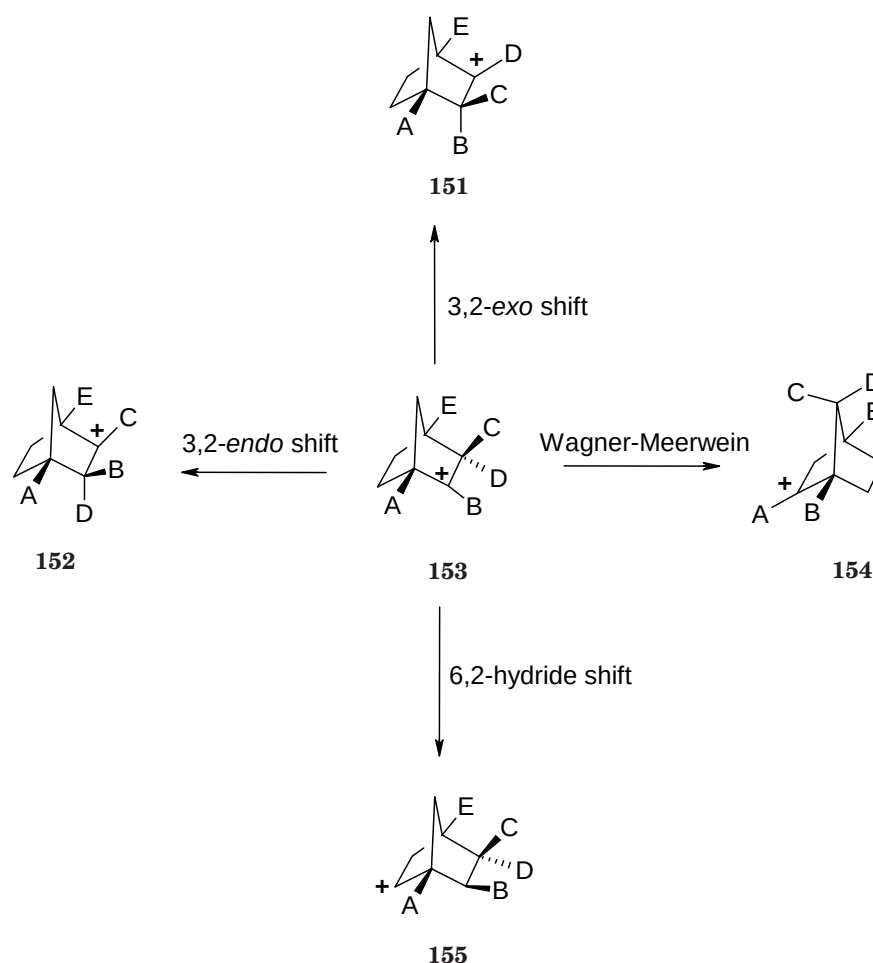
Norbornyl cations may rearrange to afford many different skeletal structures. Kramer¹⁴⁵ has argued that, since so many indistinguishable isomers are accessible *via* rearrangement of the norbornyl cation, in particular, the degeneracy of the system “has an associated entropy” and would therefore be more stable than a similar non-degenerate system. This proposal has provoked intense criticism.^{146,147} However, it is this degeneracy that can make the analysis of rearrangement mechanisms particularly interesting.

1.5.4.2 Computer-assisted analysis

In certain situations the evaluation of mechanistic pathways is impossible by any means other than computerized algebraic methods. Examples include the free-radical pyrolysis of alkanes¹⁴⁸ and the chemistry of planetary atmospheres and interstellar media.¹⁴⁹ More specific to carbocation chemistry is the analysis of rearrangements of substituted norbornyl cations. These cations may undergo Wagner-Meerwein and Nametkin rearrangements, as well as 6,2-hydride and other shifts during the course of a reaction (Scheme 1.35). Any particular substituted norbornyl cation has the option of undergoing any one of a number of these transformations at any time - a situation impossible to follow “manually”! Due to the number of permutations of substitution positions, combined with the number of rearrangements or shifts possible at each step, the only existing way to explore such reaction pathways is to use an appropriate computer programme.

1.5.4.3 Coset analysis of possible pathways

Various stages of a remarkable study by Collins and Johnson on the rearrangement pathways followed by norbornyl systems was published between 1973 and 1974.^{123,150,151} Surprisingly, this study has received very little attention in the literature beyond 1976.¹⁵² In this approach, a mathematical model was developed capable of handling norbornyl cationic systems with as



Scheme 1.35: Possible rearrangement options on a pentasubstituted 2-norbornyl cation.

many as 11 different substituents (*i.e.* a total of $11! = 39916800$ substitution possibilities) down to 1 unique substituent, such as hydrogen only, for the norbornyl cation itself ($11!/11! = 1$ substitution possibility with the associated degeneracy). The number of substitution possibilities may be reduced by only considering one of each pair of enantiomers with a cationic centre at a specified position, as illustrated in the hypothetical transformation detailed in Figure 1.14.

In sequence A, the cation alternates, in each step, between positions 2 and 6. The number of possible cations to be considered can be halved, if one does not consider the 6-cations but only their enantiomers (which happen to be 2-cations!) as shown in Sequence B. It is interesting to note that, in such analyses, no information about chirality is lost, as long as the number of steps is monitored. An odd number of transformations will transpose the cationic centre from position 2 to position 6, while an even number retains the cationic centre at position 2.

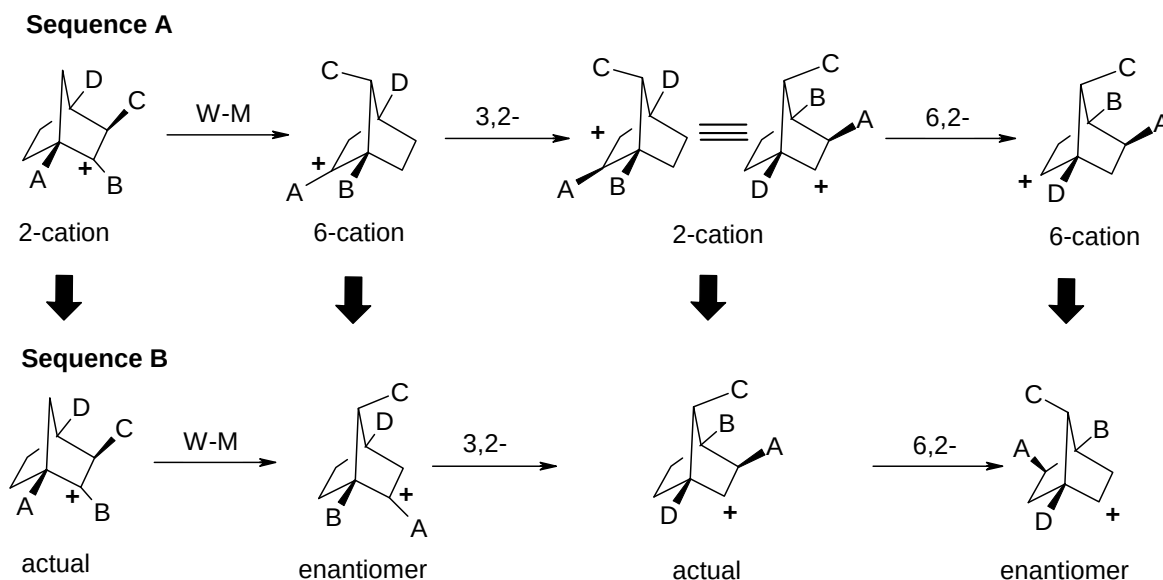


Figure 1.14: Monitoring chirality from an even or odd number of steps.

This is true for all cationic rearrangements in which the norbornyl skeleton is maintained. Thus, in sequence B in Figure 1.14 if a 2-cation is encountered the “actual” cation is drawn, but if a 6-cation, the “enantiomer” is drawn.

In order to create a model that can treat a wide variety of systems, it is perhaps necessary to be pedantic. The model treats each substituted norbornyl system as having 39 916 800 possibilities. This is clearly of no use to a chemist! The algebra then groups together the cations which (to the chemist) are identical. When $a = b = c = \text{Me}$, for example, the 6 cations shown in Figure 1.15 are identical, and must be grouped together.

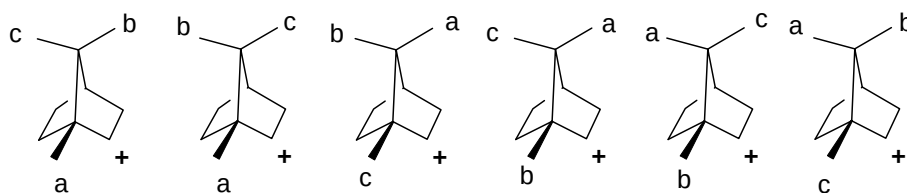


Figure 1.15: The order of substitution does not matter - 6 identical cations.

A set of permutation operators, such as those for Wagner-Meerwein rearrangements and 2,3- and 6,2-shifts, are used to generate a group G (which contains all possible cations from a given starting cation). For the mathematics it is useful to keep track of the subgroup (H) of operators that convert one cation into its indistinguishable isomer (for example combinations of shifts and Wagner-Meerwein transformations which transform one of the cations in Figure 1.15 into another in Figure 1.15!). Then if c is a transformation (such as a Wagner-Meerwein

transformation), then the set of transformations (Hc) will produce a Wagner-Meerwein transformed product from any one of the cations in Figure 1.15; c could, of course, also be a 3,2- or 6,2-shift, or even a combination transformation. Hc is called a right coset of H . In using this approach it is sufficient to look only at the cosets and not the full group (G) of transformations, and these are best examined with the aid of a graph (e.g. Figure 1.17).¹⁵⁰

Having briefly described some of the mathematical principles the graph so obtained is intuitive to the point where a chemist can appreciate its significance *without* actually going into the algebraic details. For instance the graph can be used to track the carbon atoms in the norbornyl system as it undergoes a series of rearrangements (Figures 1.16 and 1.17). However, it is important to note that enantiomers are treated identically in the reduced graph (Figure 1.17). Thus, if a 3- or 6-cation should be formed, its mirror image (which is a 2-cation) can be used in the next transformation. As an example take the carbon at position 1 on a classical 2-norbornyl system (**1**; Figure 1.16). A 6,2-hydride shift will leave that carbon at position 1 (as in **1'**). A Wagner-Meerwein transformation will transform it to position 2, while a 3,2-hydride shift will cause that carbon to end up at position 4 on the 2-norbornyl skeleton as in structures **2'** and **4'** respectively. A “reduced” version of the graph is illustrated in Figure 1.17.

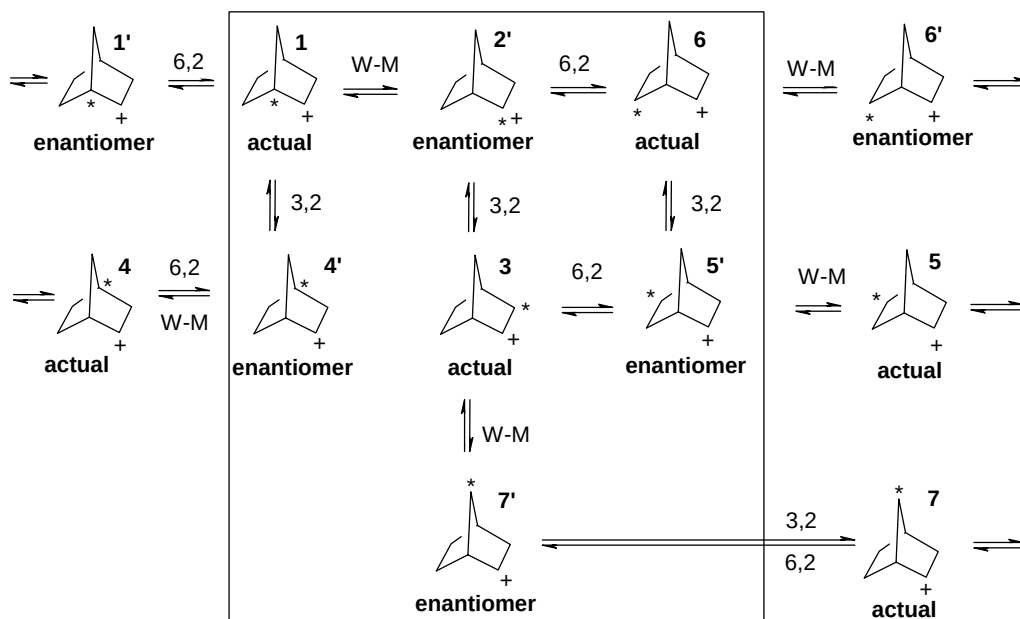


Figure 1.16: Portion of coset graph for skeletal carbon positions; W-M is Wagner-Meerwein, 3,2 is a 3,2-shift and 6,2 is a 6,2-shift. The position of the labelled C atom is indicated by an asterisk and each structure is labelled as being the correct (actual) structure or the enantiomer.

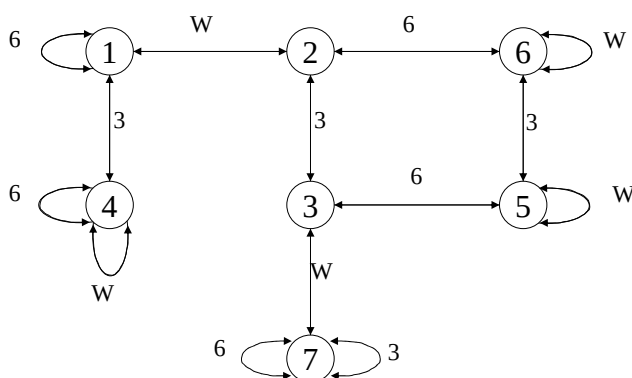
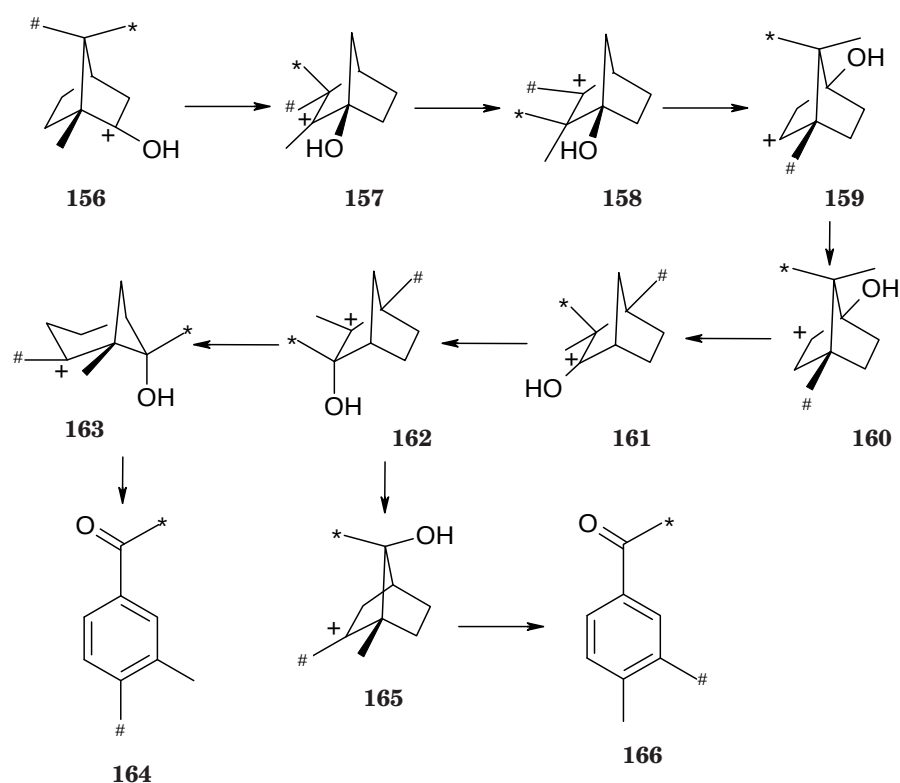


Figure 1.17: The “reduced” version of the graph shown in Figure 1.16, W is Wagner-Meerwein, 3 is a 3,2-shift and 6 is a 6,2-shift, and $1 \equiv 1'$, $2 \equiv 2'$ etc.

The computer programme ORNOCARE developed by C. K. Johnson¹⁵⁰ takes “blocking conditions” into account. For example, 2,6-methide shifts can be excluded and the maximum path length can be limited. The programme locates the simplest loop-free paths between cosets, and was used to locate pathways for the formation of the acetophenones **164** and **166** (Scheme 1.36).¹⁵¹ There was also sufficient proof from this particular result that the *endo*-hydroxyl shift originally proposed by Rodig¹⁵³ was unnecessary.

Of course, when more than one chemical pathway is possible, kinetic analysis becomes



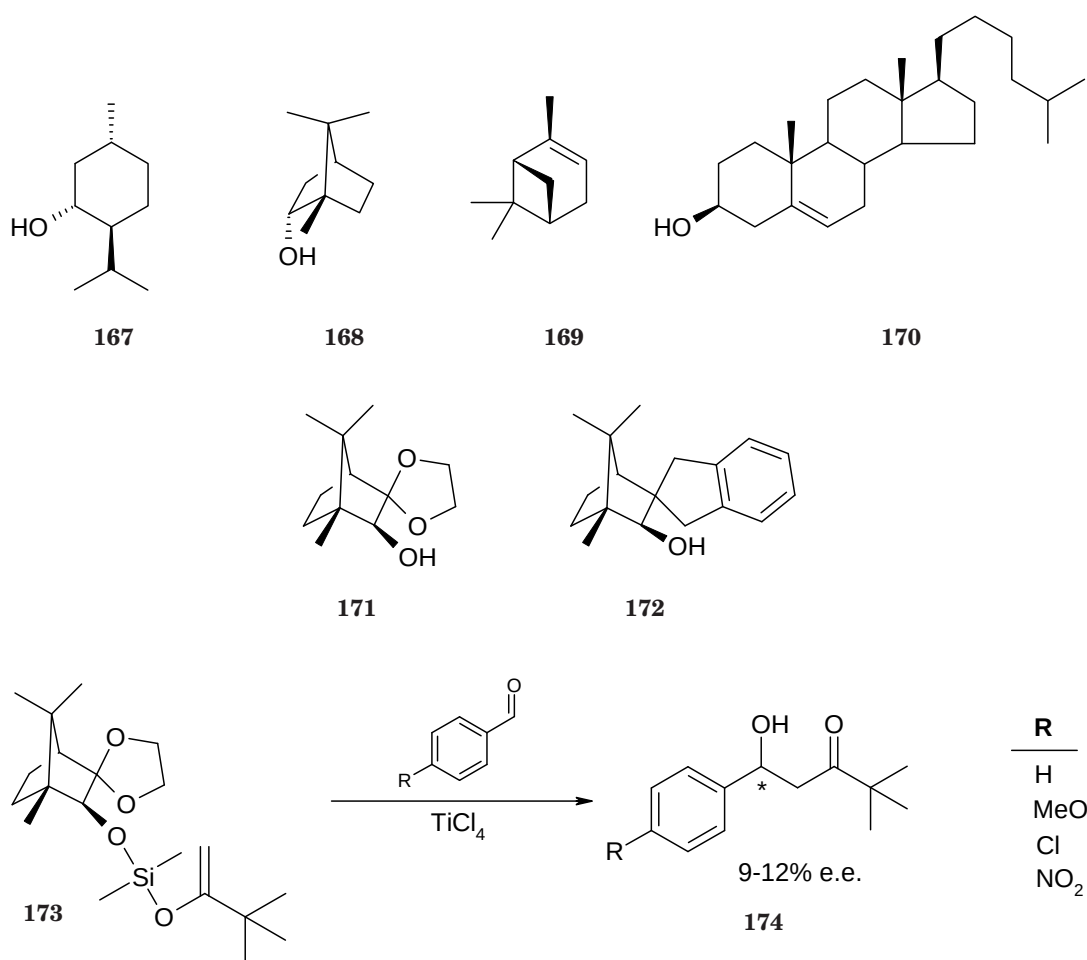
Scheme 1.36: Pathways from computational analysis of the formation of acetophenone derivatives.¹⁵¹

more complicated. The substituted norbornyl case is simpler than most chemical reaction networks, in that there is only a unimolecular transformation at each stage, *i.e.* the number of *complexes* is identical to the number of *species*. However, the rates of reaction will still be governed by a set of differential equations.¹⁵⁴

1.5.5 Previous work in the research group and aims of the present investigation

1.5.5.1 Asymmetric α -alkylation reactions

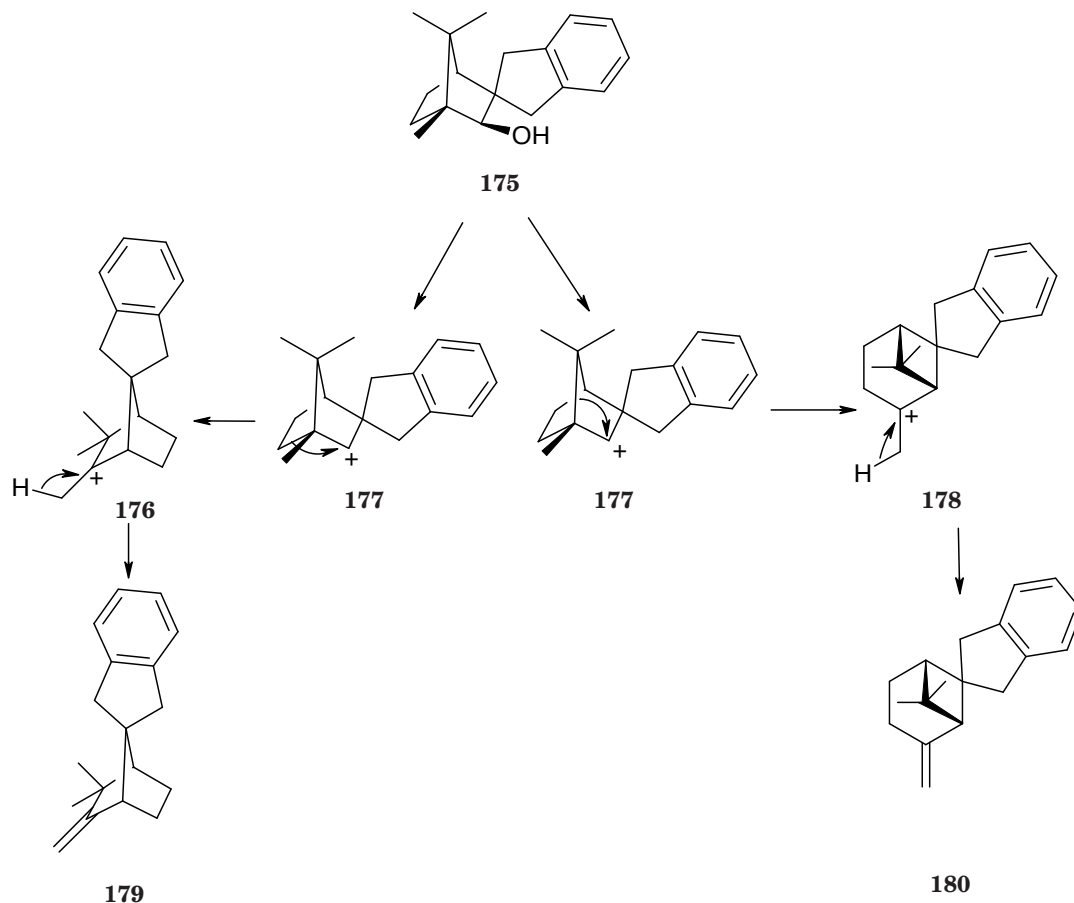
Much work has been done in our research group on the use of chiral auxiliaries for various purposes. Although menthol **167**, borneol **168**, pinene **169** and cholesterol **170** were initially examined as chiral auxiliaries, more recent work has concentrated on the use of camphor-derived systems for asymmetric synthesis. Thus the modified camphor systems **171** and **172** have been used to produce chiral silyl enol ethers for use in asymmetric Mukaiyama reactions with aldehydes (Scheme 1.37).¹⁵⁵



Scheme 1.37: Mukaiyama reaction of a silyl enol ether with aromatic aldehydes.

In order to improve the efficiency of the chiral auxiliary in such a reaction, Evans¹⁵⁶ attempted to locate the substrate moiety (a silyl enol ether) closer to the chiral bornyl skeleton. The result, in one case (illustrated in Scheme 1.38) was an unexpected rearrangement,

which afforded the camphene system **179**. At lower temperatures it appeared that the isomeric pinene system **180** was formed instead.



Scheme 1.38: Rearrangements of a spiroterpenoid system.¹⁵⁶

Chiral α -benzylation reactions have also been studied using chiral auxiliaries such as the ones shown in Figure 1.18.^{157–160} Carboxylic esters of these systems have been subjected to α -benzylation as shown in Scheme 1.39.¹⁵⁷ The diastereoselectivities observed in these reactions were generally rather low (16–47% *d.e.*). The camphor-derived diol **189** has been used very successfully in asymmetric cyclopropanation reactions; an example is shown in Scheme 1.40, where Simmons-Smith cyclopropanation of acetals of several α,β -unsaturated aldehydes affords single diastereomers.¹⁶¹

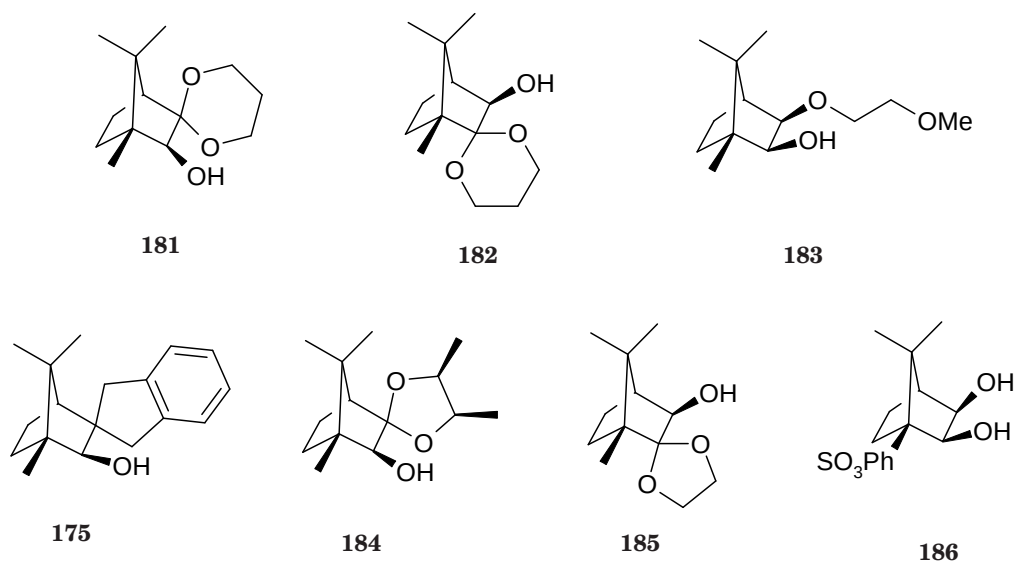
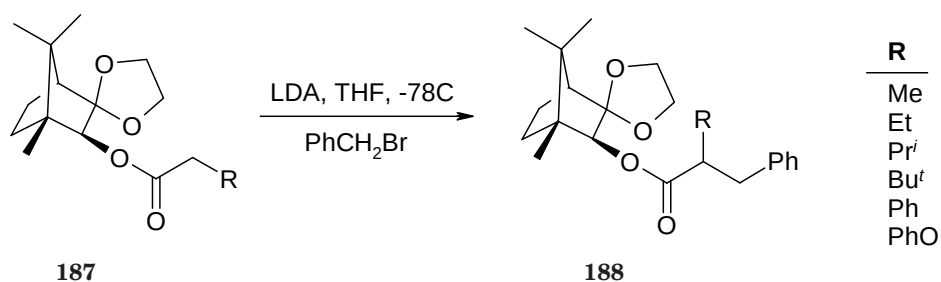
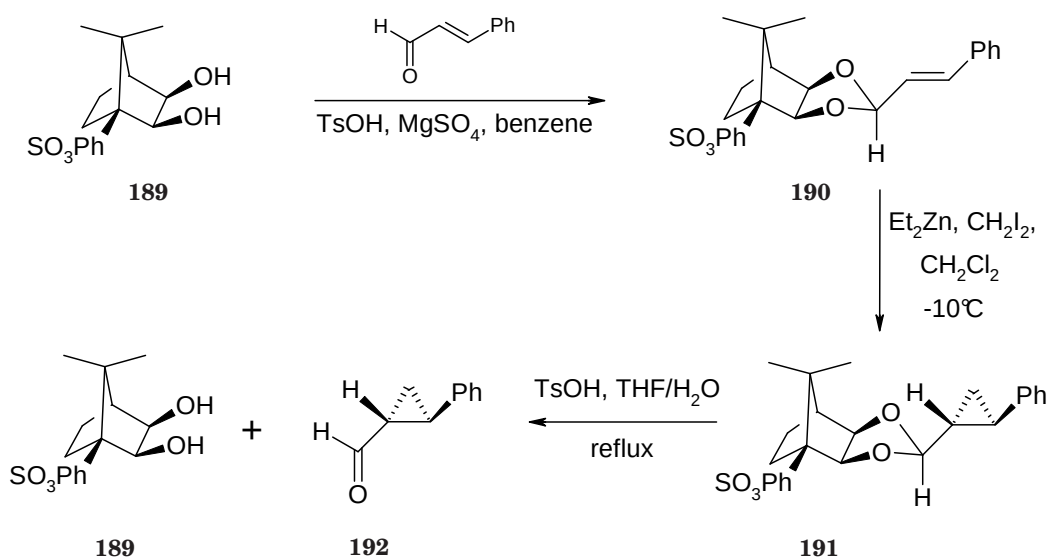


Figure 1.18: Chiral auxiliaries used in asymmetric benzylation studies.^{157–160}

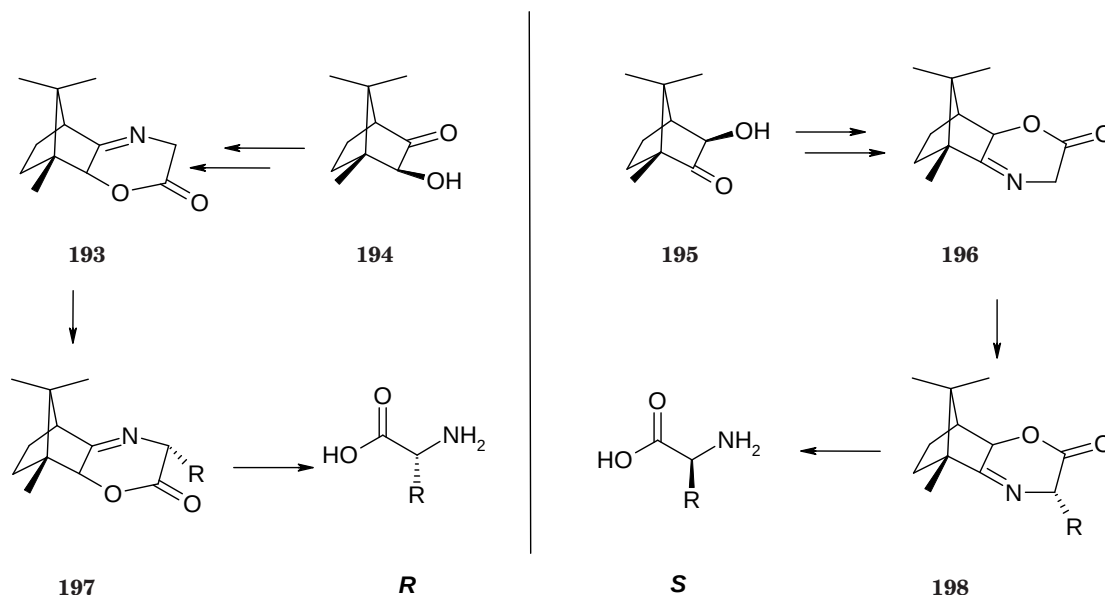


Scheme 1.39: Benzylation of a series of camphor-derived carboxylic esters.¹⁵⁷



Scheme 1.40: Asymmetric cyclopropanation reaction.¹⁶¹

Use has also been made of the ketols **194** and **195** as chiral auxiliaries in α -alkylation reactions. Alkylation studies in which these ketols provide the basis for stereoselectivity have been studied.^{162,163} The general scheme followed in this approach is shown in Scheme 1.41.



Scheme 1.41: Asymmetric α -alkylation reactions.

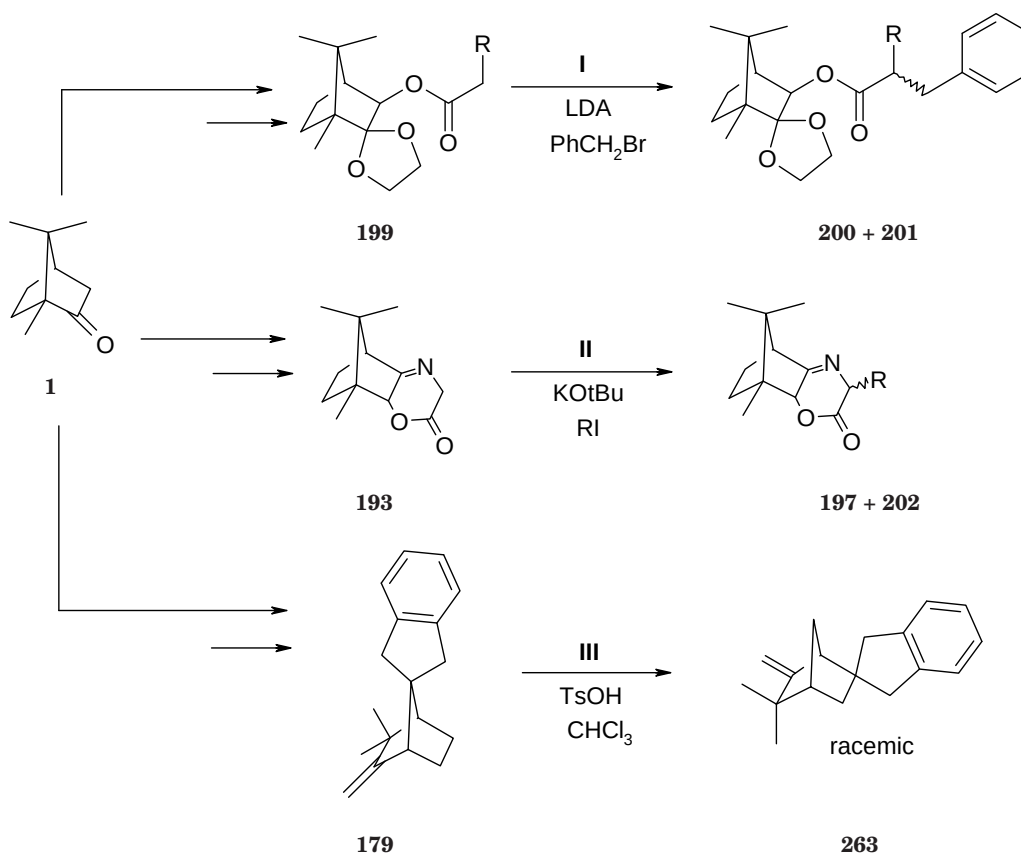
1.6 Aims of the current project

Specific aims of the current project have included the following selected synthetic, kinetic and computational approaches with emphasis on the mechanistic implications.

1. The stereoselective benzylation of camphor-derived esters, following Scheme 2.10, and the modelling of the appropriate lithium enolate intermediates to rationalize the effectiveness of the chiral auxiliary
2. The alkylation of systems such as indicated in Scheme 1.41, and modelling of selected transition states in order to confirm the steric source of stereocontrol.
3. The kinetics of the transformation that gives rise to **180** and **179** in order to obtain energetic data, and theoretical studies of this system in order to deduce the mechanism.

2 Discussion

There is a seemingly endless variety in the ways in which camphor, in particular, can be used in asymmetric synthesis. From a modelling or theoretical perspective, aspects such as rigidity and solvent interaction may play different roles from system to system. Compare the transformations **I-III** in Scheme 2.1.



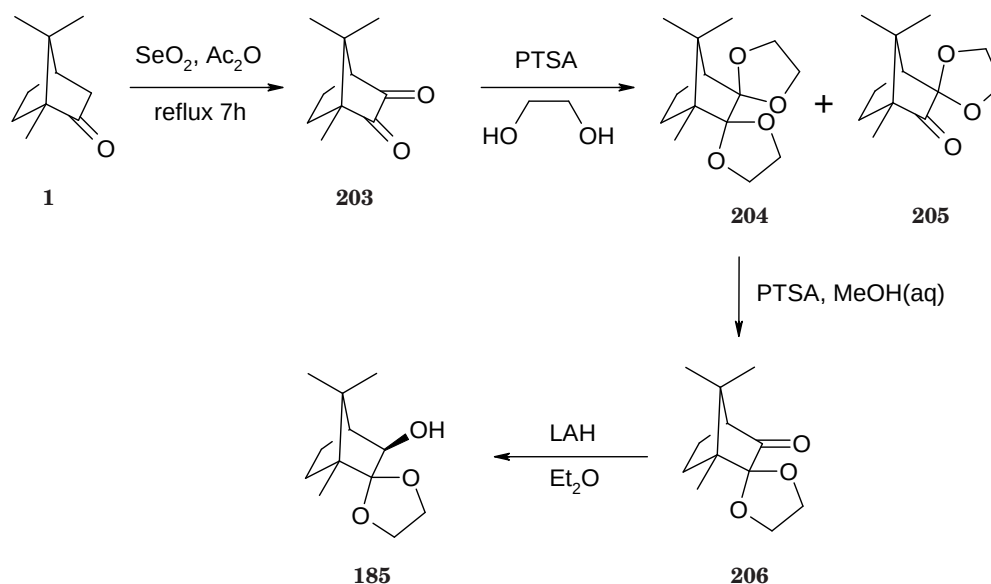
Scheme 2.1: Camphor derivatives in asymmetric reactions.

In each case, two stereoisomeric products are formed, *viz.* two diastereomers or, in the last case, two enantiomers. These three transformations provide the focus for the detailed synthetic, mechanistic and theoretical studies reported in this thesis. The underlying rationale for the expected stereocontrol is different in each case.

In the benzylation step (I) from the ester **199** to the α -benzylated derivatives **200 + 201**, three factors are considered important :- **i**) blocking of attack of the enolate due to the presence of the 2,2-ethylenedioxy group; **ii**) the enolate configuration (*E* or *Z*), quasi-parallel to this 2,2-ethylenedioxy group; and **iii**) preference for the *s-trans* arrangement of the ester moiety.¹⁶⁴ If any one of these expectations is not realized, stereocontrol will be compromised. Alkylation of the iminolactone system **193** to form the series **197** has *endo* stereocontrol that relies on destabilization of the *exo* transition state due to the presence of the 8-methyl group. In the final transformation (III) cascades of rearrangement pathways between starting material **179** and the product **263** can lead to racemization of the product.

2.1 Benzylation of a series of camphor-derived esters

The substrate **185** has been used successfully in the Rhodes group as a chiral auxiliary in the asymmetric benzylation of a series of esters,^{162,163} and is prepared *via* camphorquinone **203** as illustrated in Scheme 2.2. The subsequent benzylation is illustrated in Scheme 2.3. Our interest was not simply to repeat work already done, but rather to carefully examine the mechanistic and structural aspects which may influence stereocontrol throughout the scheme.

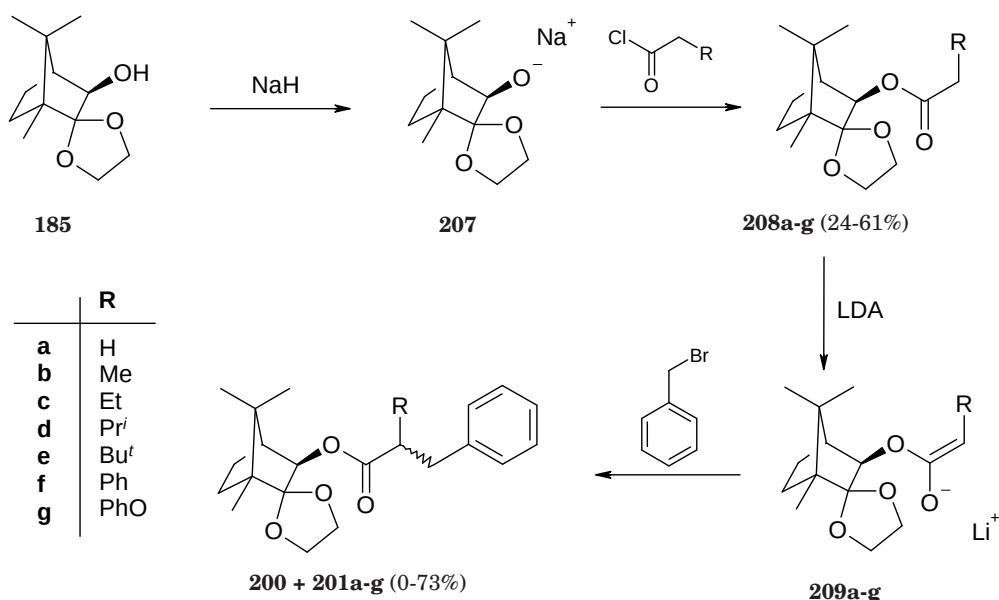


Scheme 2.2: Production of chiral auxiliary **185**.

The alcohol **185** was produced as follows. Oxidation of the ketone, camphor **1**, with selenium dioxide proceeds *via* a selenite ester intermediate to form camphorquinone **203** in moderate yield. Ketalization of camphorquinone **203** produced a mixture of ketals, from which the

diketal **204** was easily separated *via* flash chromatography. Selective deprotection of the less hindered 3-ketone group *via* acid-catalysed hydrolysis gave the ketal **206**, and *endo*-hydride delivery reduced the ketal **206** to the desired chiral auxiliary **185** in 91.5% yield.

For the benzylation studies, the route outlined in Scheme 2.3 was then followed. The series of esters **199** was produced *via* the alkoxide **207**. Deprotonation with lithium diisopropylamide (LDA) to form the enolates, and the subsequent benzylation with benzyl bromide afforded the benzylated systems, for which the stereochemical outcomes were noted. Although these general schemes are not original, some very interesting, previously unreported observations were made during the course of this work.

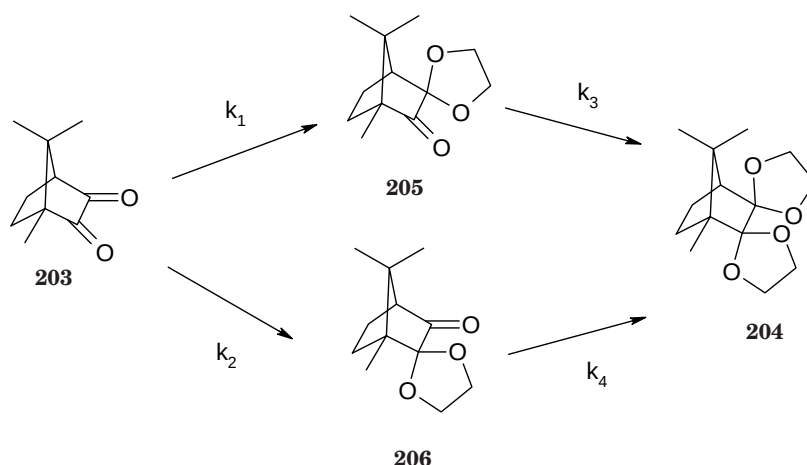


Scheme 2.3: Benzylation reactions.

2.1.1 The order of events in the ketalization step

Firstly, in the production of the ketals **205** and **204** (Scheme 2.2) from camphorquinone **203** (in a Dean-Stark apparatus) we also observed the formation of **206** as reported by Klein¹⁶³ (Scheme 2.4). Of course it would be more correct to represent the scheme as a series of equilibria, but it is the relative rates which are of critical importance. In order to follow the reaction detailed in Scheme 2.4, aliquots were removed at hourly intervals, washed with saturated aqueous sodium hydrogen carbonate solution, dried, and concentrated *in vacuo* and the NMR spectrum was recorded for each sample. Although the monitoring was never undertaken in order to provide a full kinetic analysis for the system, the resulting data (as plotted in Figure

2.1) indicates that there is rapid initial production of both the 2,2-ethylenedioxy- and 3,3-ethylenedioxyketals **206** and **205**, respectively. Analysis of the data reveals that k_1 is three time greater than k_2 , but that k_3 and k_4 are roughly equal and much slower. Each of the two decay pathways of camphorquinone are roughly first order due to the excess ethylene glycol in the reaction mixture. It should, of course, be borne in mind that the reaction is driven by the removal of water, produced during the course of reaction, by means of a Dean-Stark trap.



Scheme 2.4: Acid-catalysed ketalization of camphorquinone with ethylene glycol.

The two “monoketals” **206** and **205** are inseparable *via* column chromatography, although when monoketal **205** is present in excess, selective crystallization may be effected. On elution with a 9:1 mixture of hexane and ethyl acetate, both isomers have an R_f value of 0.42. Reduction of the monoketals affords the corresponding alcohols, which are similarly inseparable, both having an R_f value of 0.37. It seems that the best way to produce pure 3,3-ethylenedioxy ketal **205** is to drive the reaction to the point where none of the 2,2-ethylenedioxy isomer **206** remains, at the expense of some loss of the monoketal **205** and production of the unwanted diketal **204**.

This reaction is interesting in that the regioselectivity is, perhaps, not only dependent on initial access to the less hindered site (C-3), but also on the ease of cyclization at that site. Of course, the hemi-acetal intermediates are not detected on the NMR time-scale, and the equilibria involved are not easily studied.

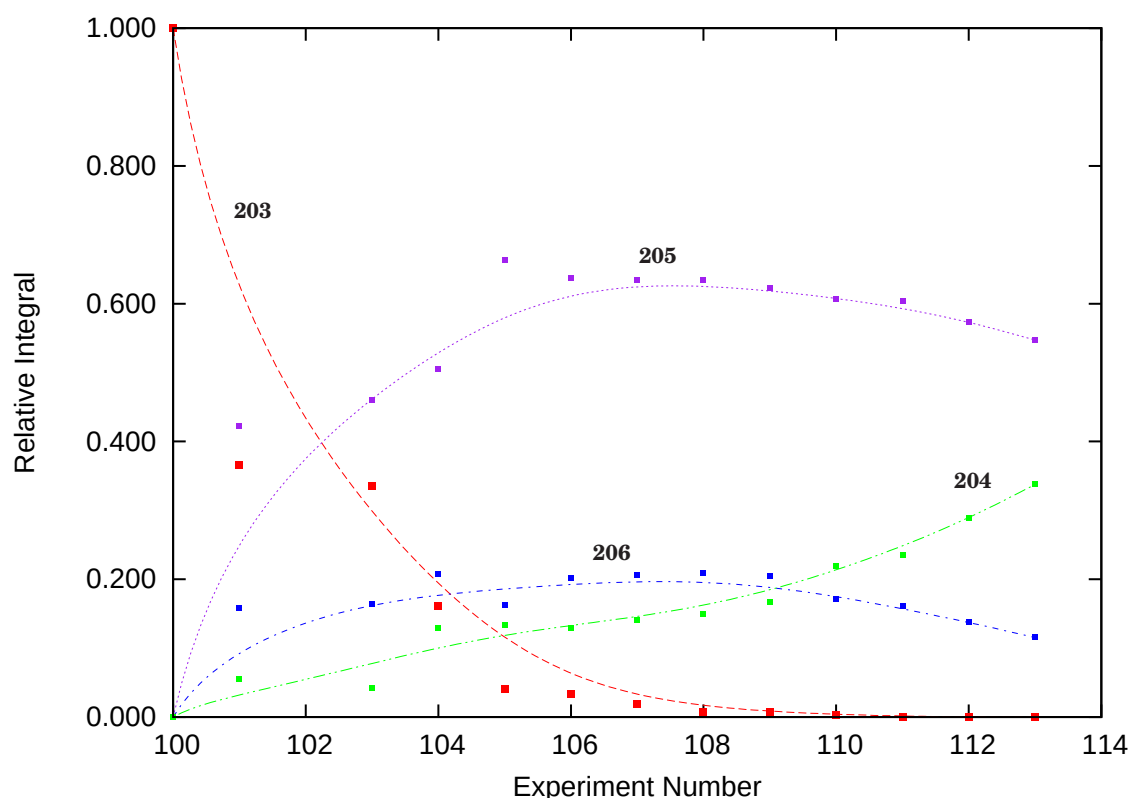
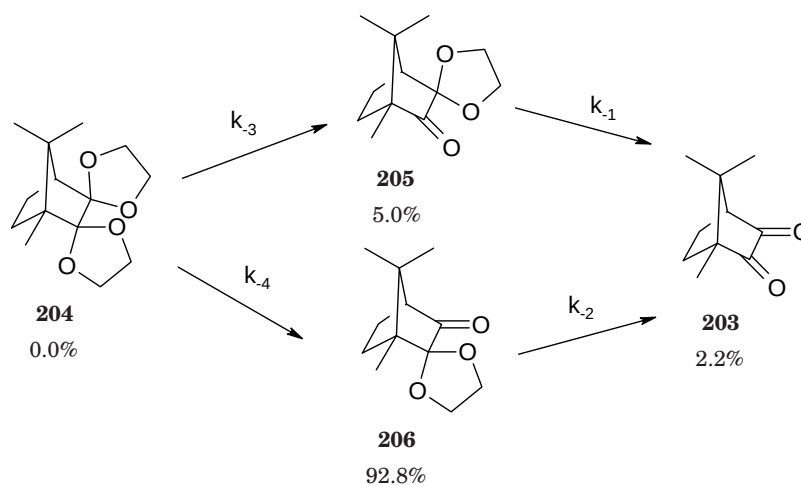


Figure 2.1: Kinetics of the ketalization step **203** $\rightarrow$ **204**.

2.1.2 Deprotection of the diketal **204**

The formation of the monoketal **206** from the diketal **204** is likely to be complicated by competitive formation of the isomeric monoketal **205** and camphorquinone **203** as contaminating species (Scheme 2.5). In the event, regioselectivity during deprotection is better than in the protection step.



Scheme 2.5: Acid-catalysed 2-deprotection of 2,2;3,3-bis(ethylenedioxy)bornane.

The “quantitative” ^{13}C NMR spectrum (Figure 2.2; obtained by acquisition with inverse-gated decoupling and using 9mg of $\text{Cr}(\text{acac})_3$ as relaxation agent¹⁶⁵ and 12mg of the crude deprotection product mixture after 8h, in CDCl_3) illustrates the distribution of products more clearly than the proton NMR spectrum. Thus, from the relative signal integrals, we obtain an indication as to the relative magnitudes of the rates of the deprotection steps, which suggest that $k_{-4}, k_{-1} \gg k_{-3}, k_{-2}$ in Scheme 2.5. After boiling the reaction mixture under reflux for 8h, the starting material **204** could no longer be detected.

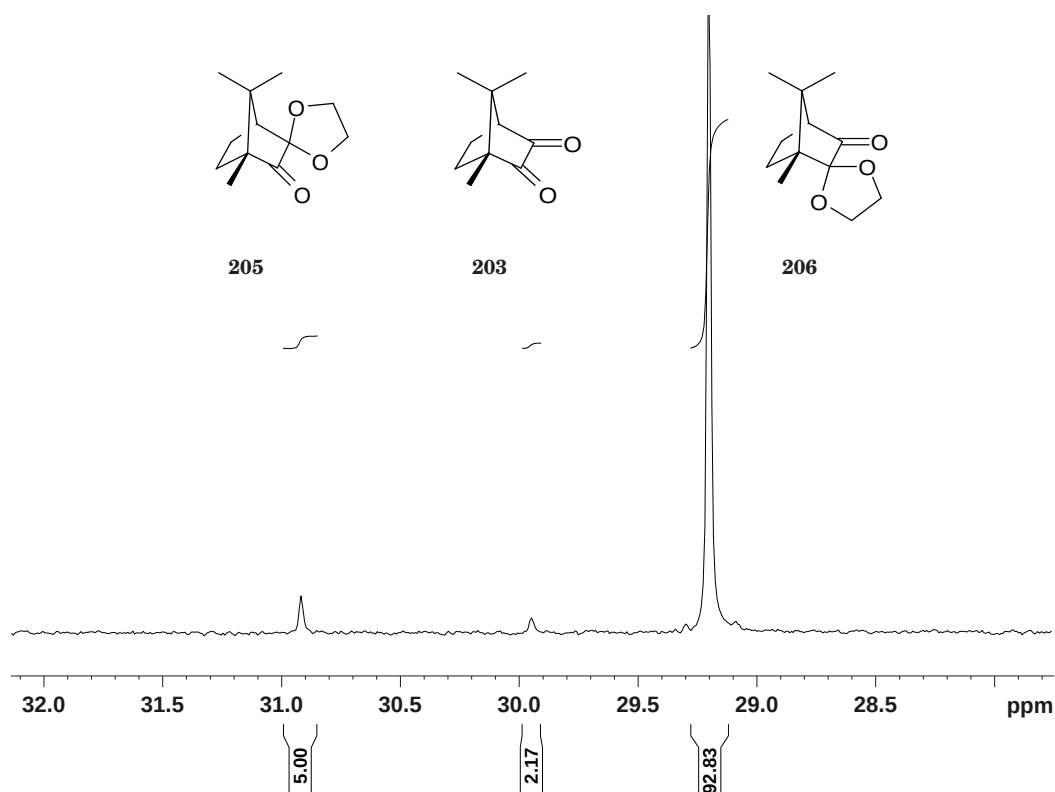
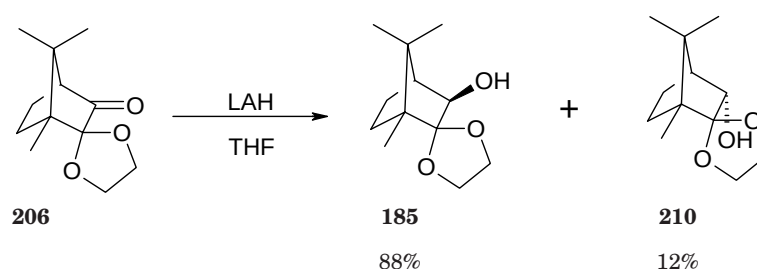


Figure 2.2: Quantitative 150MHz ^{13}C NMR spectrum of crude deprotected product mixture in CDCl_3 .

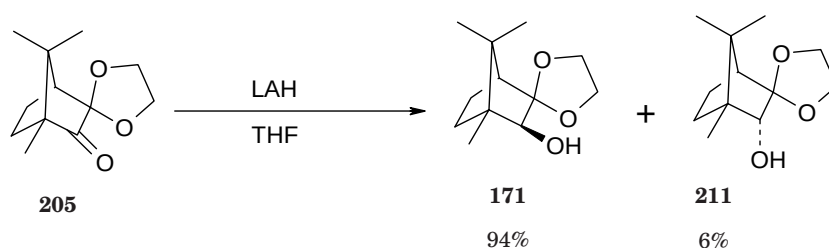
2.1.3 *Endo vs exo* hydride delivery during reduction of the monoketal **206**

Although the potential for contamination by competition products is apparent in Schemes 2.4 and 2.5, the lack of complete dominance of *endo*-hydride delivery during reduction of the ketal **206** (Scheme 2.6) presents a greater problem. In fact, 12% of the *endo* alcohol **210** was isolated together with the desired *exo* alcohol **185** in only 76% d.e. Since the diastereomeric alcohols **210** and **185** were not readily separable on the gram scale, the mixture had to be taken on to the next stage of esterification. This level of stereocontrol is barely better than the diastereoselectivity observed during the reduction of camphor (72% d.e.³² in the *exo*-product). The diastereoselectivities from lithium aluminium hydride (LAH) reduction of camphor systems in tetrahydrofuran (THF) are comparable to those obtained when diethyl ether is used as a solvent.¹⁶⁶



Scheme 2.6: Formation of the *exo*- (**185**) and *endo*-alcohol **210** via *endo*- and *exo*-hydride delivery, respectively.

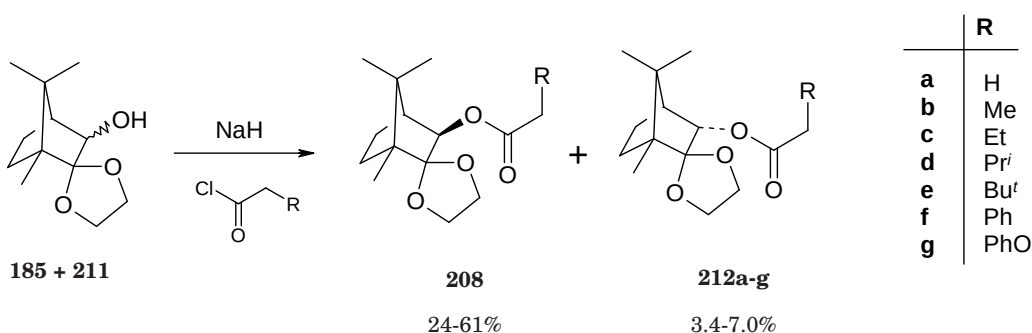
It is noteworthy that in the isomeric monoketal system **205**, in which the free carbonyl group is hindered due to proximity of the 10-methyl group, *exo*-hydride delivery only accounts for 6% of the products, and the *exo*-alcohol **171** is obtained in 88% d.e. (Scheme 2.7).



Scheme 2.7: Formation of the *exo*- (**171**) and *endo*-alcohol **211** via *endo*- and *exo*- hydride delivery, respectively.

Given concomitant formation of the 3-*endo*-alcohol **210**, a series of *endo*-esters **212** was obtained in addition to the *exo*-esters **208** (Scheme 2.8). Unlike their alcohol precursors, some of the pure diastereomeric esters could be isolated following two or three consecutive column

chromatographic separations. The assignment of the stereochemistry at position 3 is readily achieved by inspection of ^1H -NMR spectra. In cases where the 3-H is *endo* (corresponding to the *exo* series of ester!) there is no visible coupling between the 3-H and the 4-H nuclei. However, in the *endo*-ester series (Figure 2.3) coupling constants of *ca* 4.5 Hz are observed. The apparent absence of coupling between the 4-H and the 3-*endo*-H nuclei is attributed to the torsion angle of almost 90° between these vicinal nuclei 4-H-C and the 3-H-C bonds.¹⁶⁷ A longer-range coupling is also evident in the *endo*-series, which is attributed to W-coupling between the 3-*exo*-H and the 5-*exo*-H.



Scheme 2.8: *Exo- vs endo-* hydride delivery.

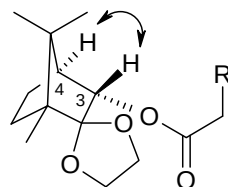
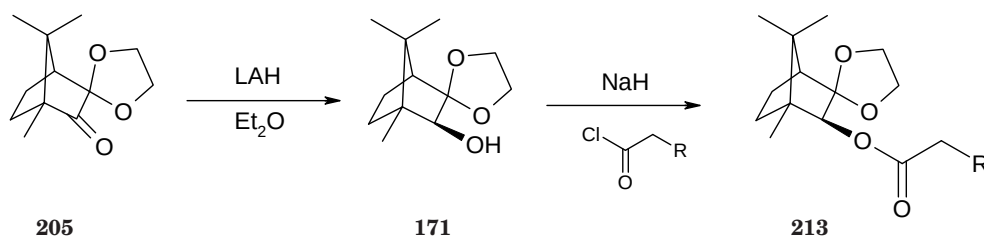
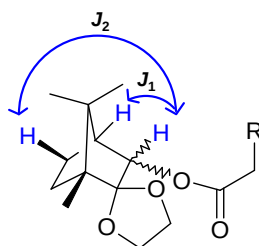


Figure 2.3: Coupling in the *endo*-series of esters.

This coupling not only indicates the stereochemistry at C-3 but also locates the ester group unambiguously at position 3. The isomeric series of esters **213**, in which the ester group is located at C-2, have been produced, characterized and benzylated previously in the research group¹⁵⁷ (Scheme 2.9).



Scheme 2.9: Regio-isomeric system of esters studied by Ravindran.¹⁵⁷

Table 2.1: Characterization of the *exo*-esters **208** and the *endo*-esters **212**.

208 + 212			
compound	R	<i>exo</i> (<i>endo</i> -H δ , ppm)	<i>endo</i> (<i>exo</i> -H δ , ppm)
a	H	4.41	4.97 (dd, $J_1 = 4.7\text{Hz}$, $J_2 = 0.96\text{Hz}$)
b	Me	4.42	4.97 (dd, $J_1 = 4.4\text{Hz}$, $J_2 = 1.2\text{Hz}$)
c	Et	4.41	4.96 (dd, $J_1 = 4.6\text{Hz}$, $J_2 = 1.3\text{Hz}$)
d	<i>i</i> Pr	4.41	4.96 (dd, $J_1 = 4.4\text{Hz}$, $J_2 = 1.1\text{Hz}$)
e	<i>t</i> Bu	4.42	4.96 (dd, $J_1 = 6.6\text{Hz}$, $J_2 = 1.8\text{Hz}$)
f	Ph	4.42	4.96 (d, $J = 4.7\text{Hz}$)
g	PhO	4.49	5.04 (dd, $J_1 = 4.8\text{Hz}$, $J_2 = 1.2\text{Hz}$)

Figures 2.4 and 2.5 illustrate the Heteronuclear Single Quantum Coherence (HSQC) NMR spectra for the *exo-tert*-butyl and the *endo-tert*-butyl esters **208e** and **212e**, respectively. Table 2.1 summarizes relevant chemical shift and corresponding data for the series of *exo*- and *endo*-esters **208** and **212** isolated in the present study.

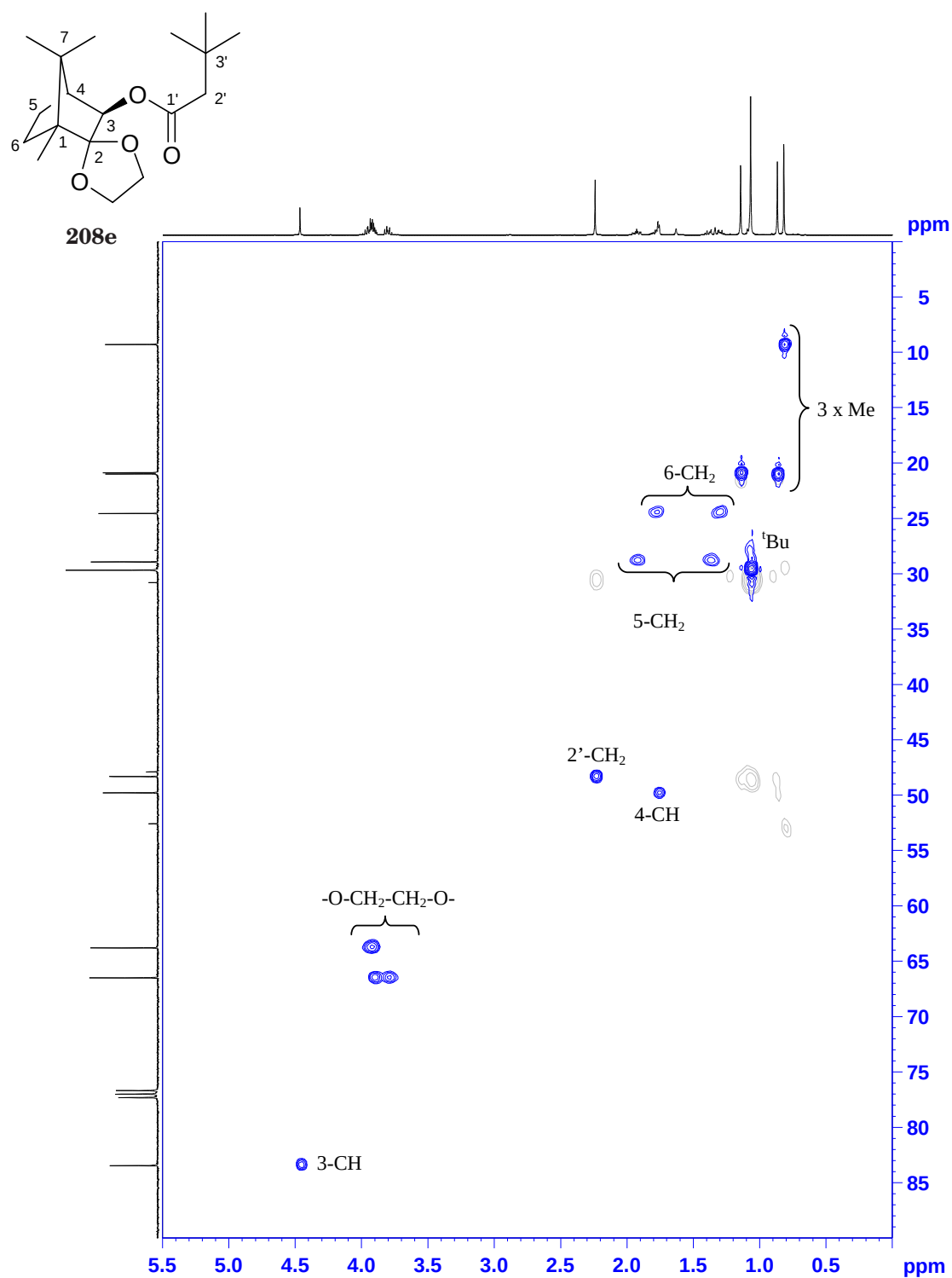


Figure 2.4: HSQC (blue) and HMBC (grey) spectra of the *exo-tert*-butyl ester **208e** in CDCl₃.

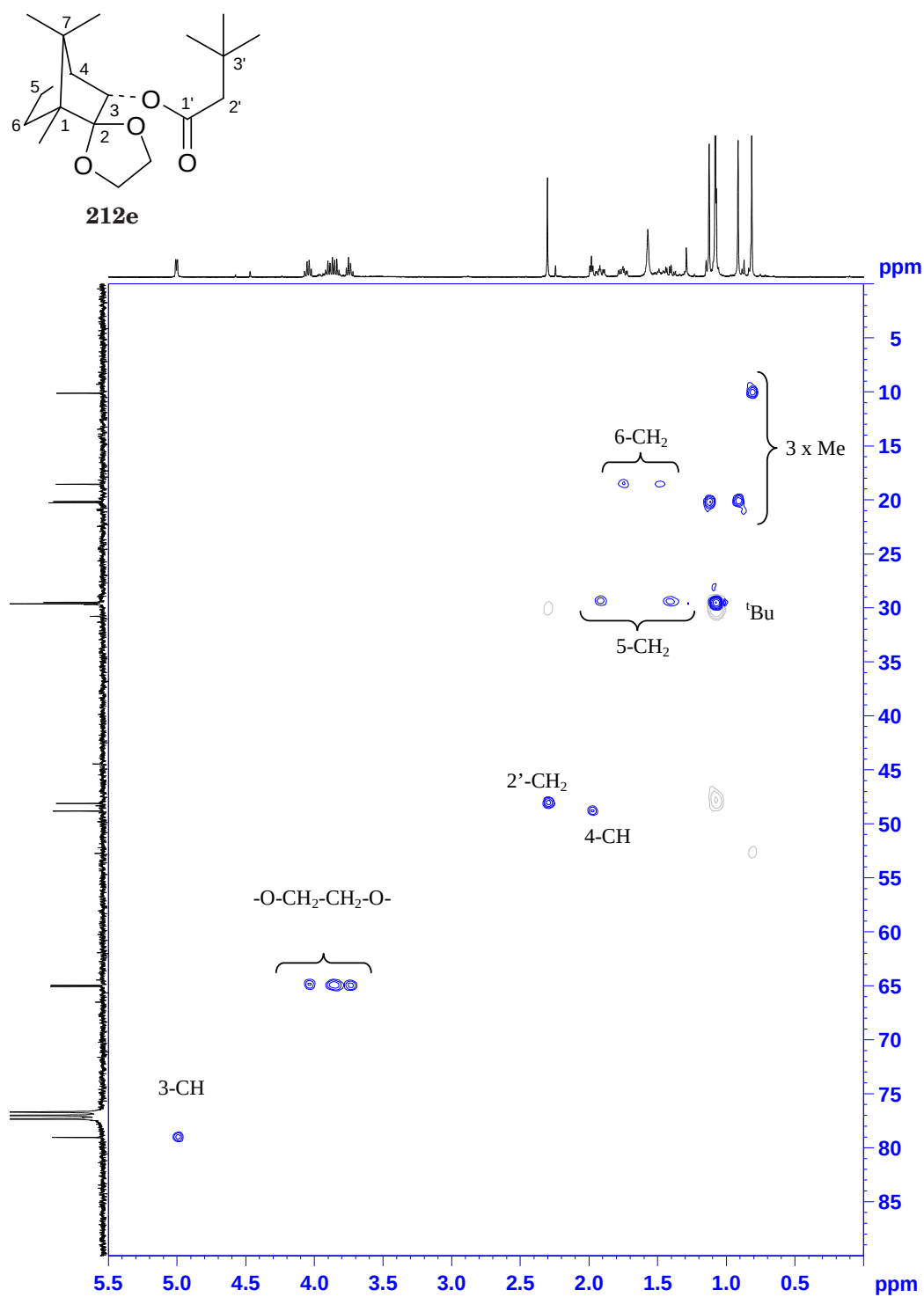
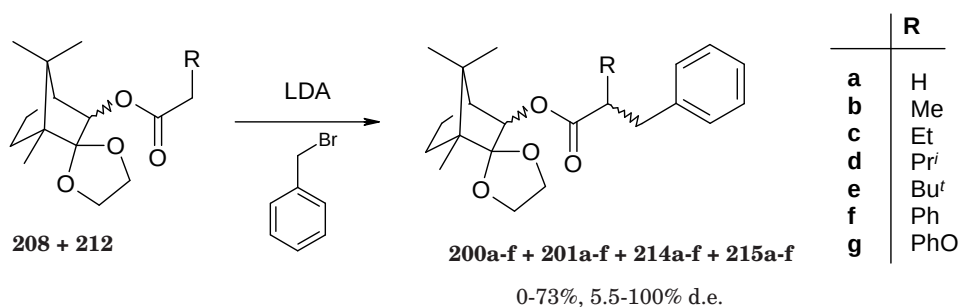


Figure 2.5: HSQC (blue) and HMBC (grey) spectra of the *endo-tert*-butyl ester **212e** in CDCl₃.

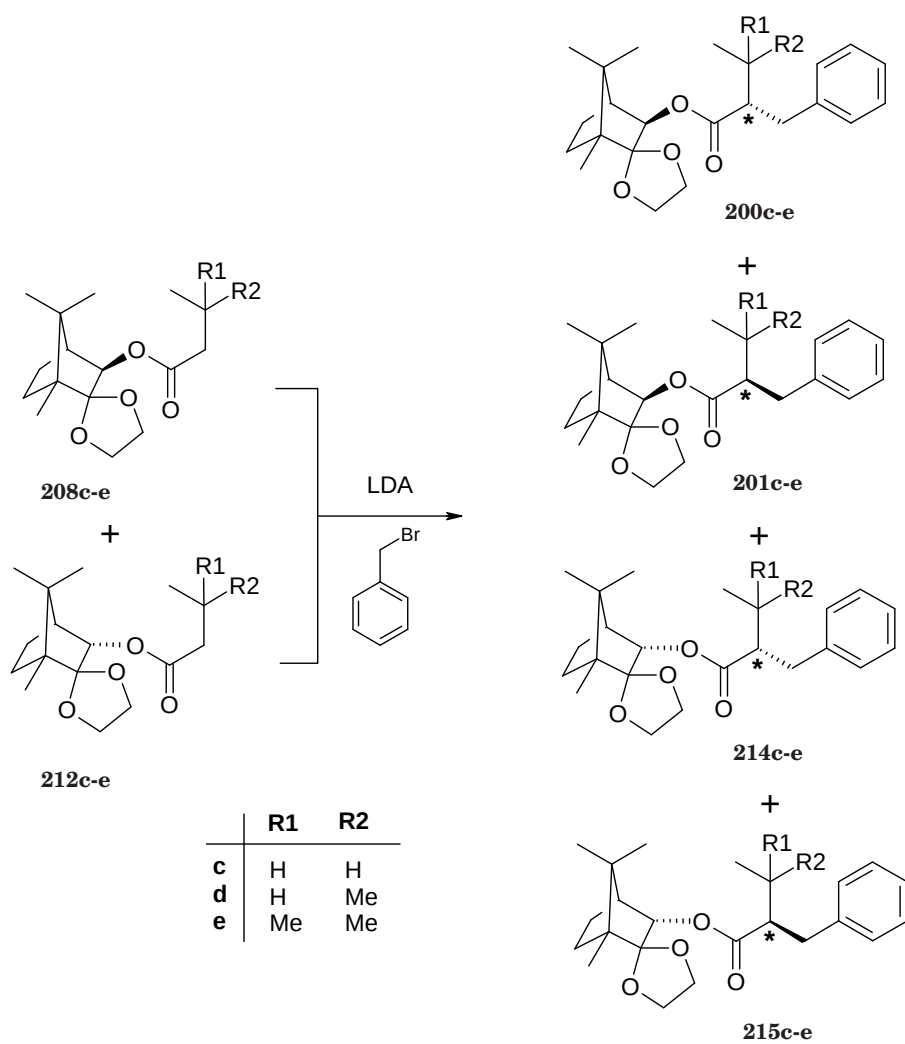
2.1.4 Further observations on the benzylation step

The esters **208** + **212** were benzylated following the method used previously¹⁶³ in the group (Scheme 2.10) to afford the corresponding sets of products – careful study of which has provided useful insights into this reaction.



Scheme 2.10: α -Benzylation of camphor-derived esters.

One of the most interesting results was the observation of *differences* in stereocontrol in the benzylation of the *endo*-esters **212** compared to the *exo*-esters **208**. The unseparated mixtures isolated in the case of the isopropyl- and *tert*-butyl esters gave a wealth of data concerning the benzylation step (Scheme 2.11). In the ¹H NMR spectrum of the crude benzylated *tert*-butyl esters from **208e/212e**, the signals are well separated (Figure 2.6) and it is apparent, from a comparison of the relative integrals, that the diastereoselectivity of benzylation of the *endo*-ester **212e** is 64 % d.e. compared to 67 % d.e. for the benzylation of the *exo*-isomer **208e**. However, the stereochemistry at the new chiral centre has not been assigned absolutely (Scheme 2.11). Figure 2.7 illustrates the ¹H NMR spectra of the *endo*-ester products **215d** and **214d** and the corresponding spectra of the *exo*-ester products **201d** and **200d**, following separation *via* normal phase HPLC.



Scheme 2.11: Benzylation of the *endo*- and *exo*- esters **212c-e** and **208c-e**, respectively.

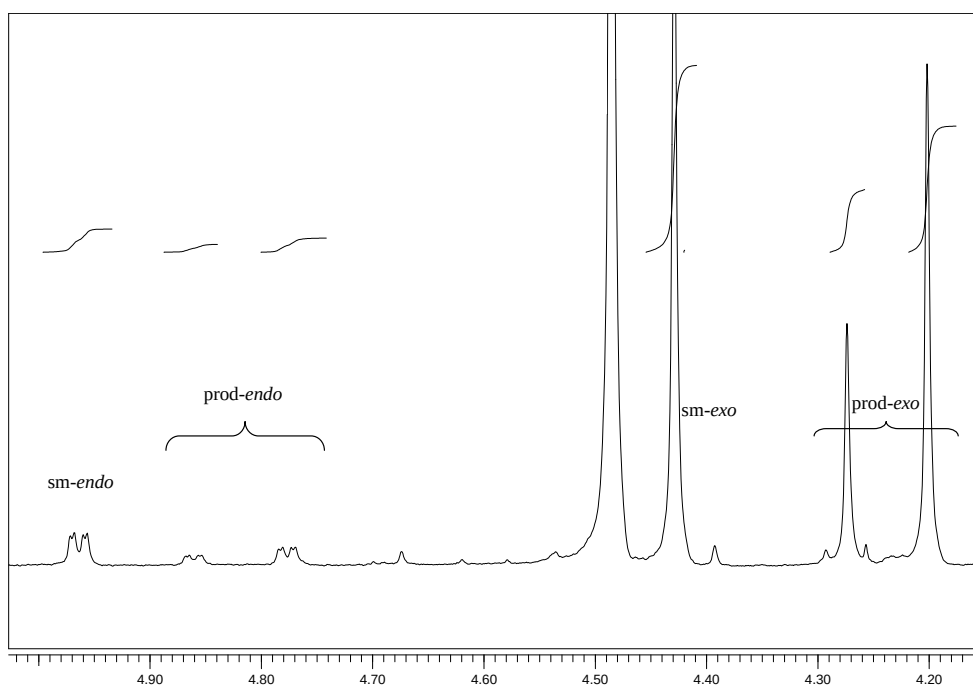


Figure 2.6: ^1H -NMR of crude benzylated product mix of *tert*-butyl ester **208e/212e** showing the C3-H signals; sm = starting material.

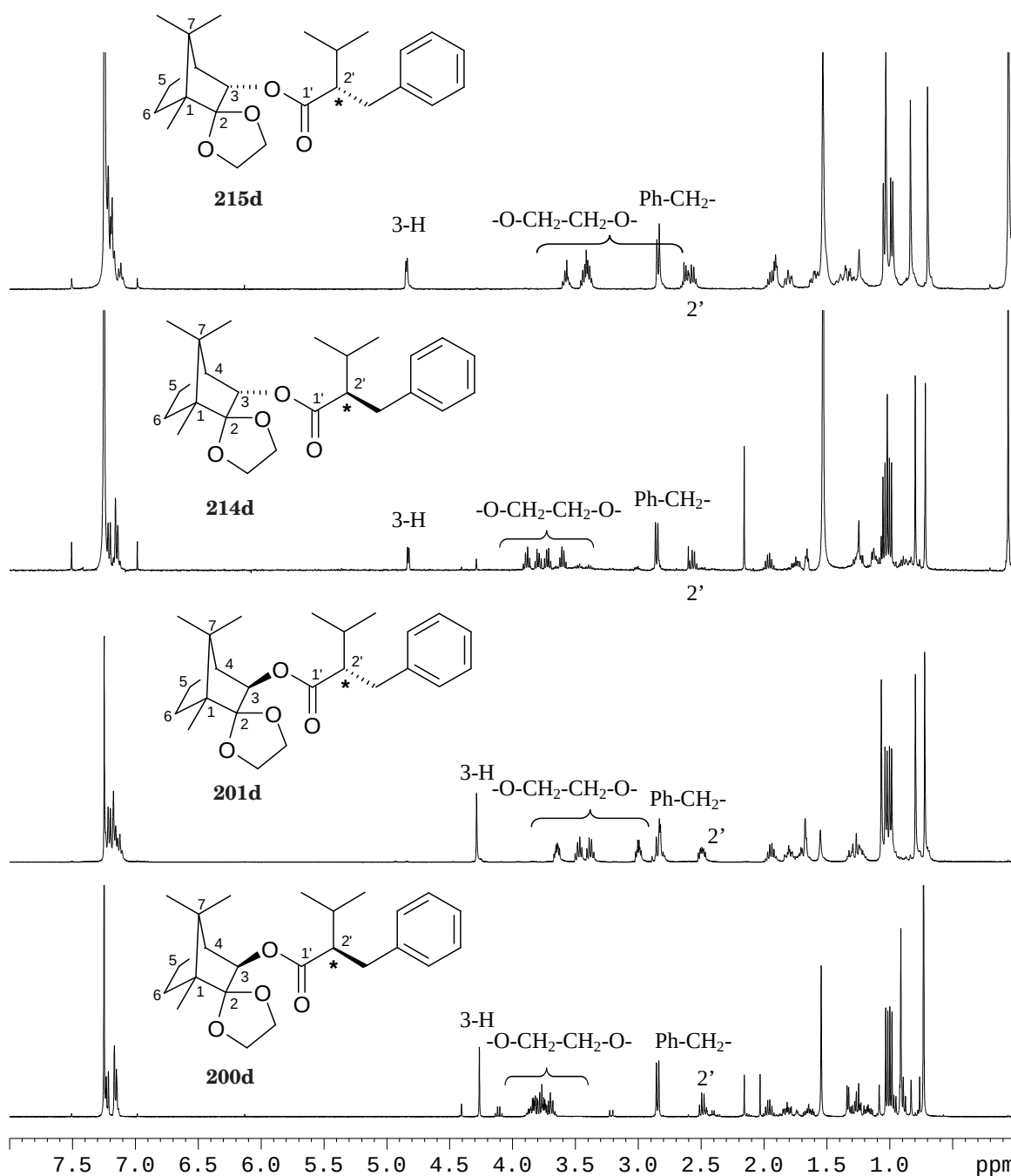


Figure 2.7: ^1H NMR spectra of the four diastereomers obtained following α -benzylation of the *endo*- and *exo*-esters 208d and 212d, respectively, in CDCl_3 .

2.1.5 Mass spectrometric study of the benzylated esters

Not surprisingly, the mass fragmentation patterns exhibited by the four, isomeric α -benzylated isopropyl esters **200d**, **201d**, **214d** and **215d** are virtually identical. Selected pathways proposed for the fragmentation of these systems are shown in Figure 2.9. Of interest is the fragmentation around the new stereogenic centre, which is similar in all cases. The stereochemistry about the ester moiety is not sufficiently limiting in any of the cases to preclude the McLafferty rearrangement. Although the direct McLafferty rearrangement (the radical cation **220**) is not visible in one case, its derivative **222** is. The high-resolution E.I. mass spectrum for the α -benzylated ester **214d** is illustrated in Figure 2.8, while fragmentation data for the four isomeric analogues **200d**, **201d**, **214d** and **215d** are consolidated in Figure 2.9. Thus the initially formed radical cation **217** undergoes: loss of an acyl radical to form the resonance stabilized cation **216**; loss of a carboxylate radical to form the cation **218**; cleavage to form the acylium cation **219**; McLafferty rearrangement to form **220** which forms **222** upon loss of a hydrogen radical; and cleavage of the benzylic system to form the tropylium cation **221**.

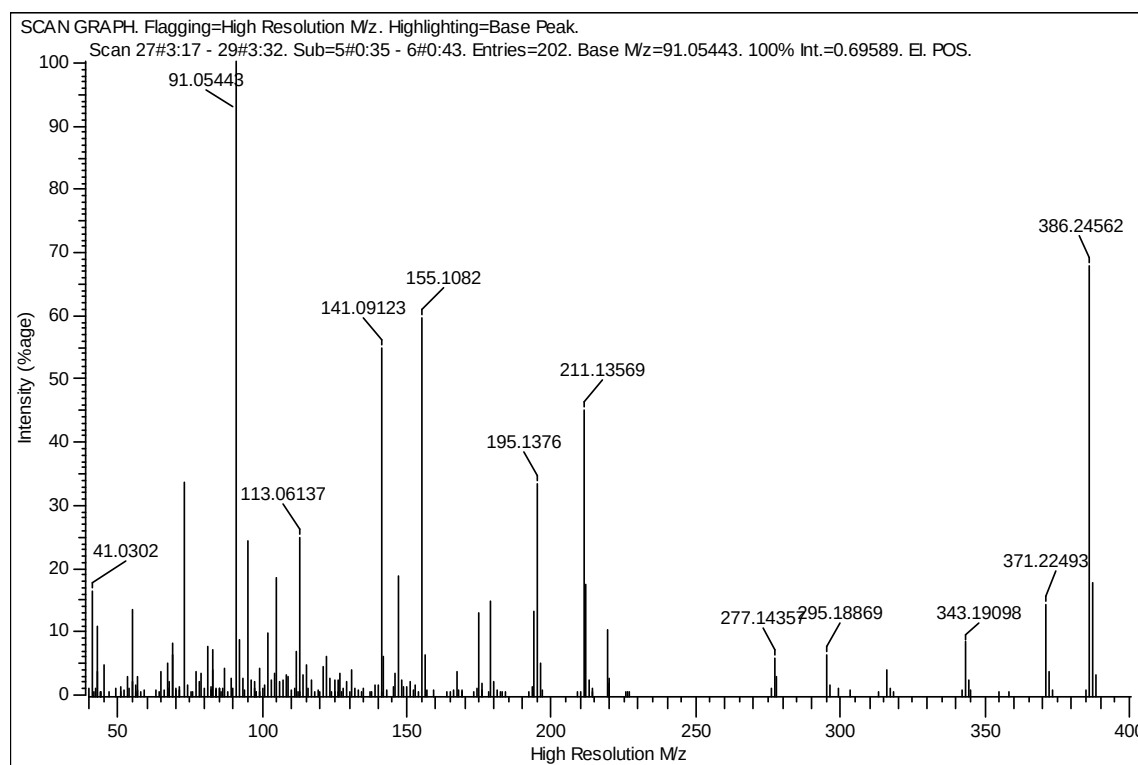


Figure 2.8: High-resolution E.I. mass spectrum of the α -benzylated isopropyl ester **214d**.

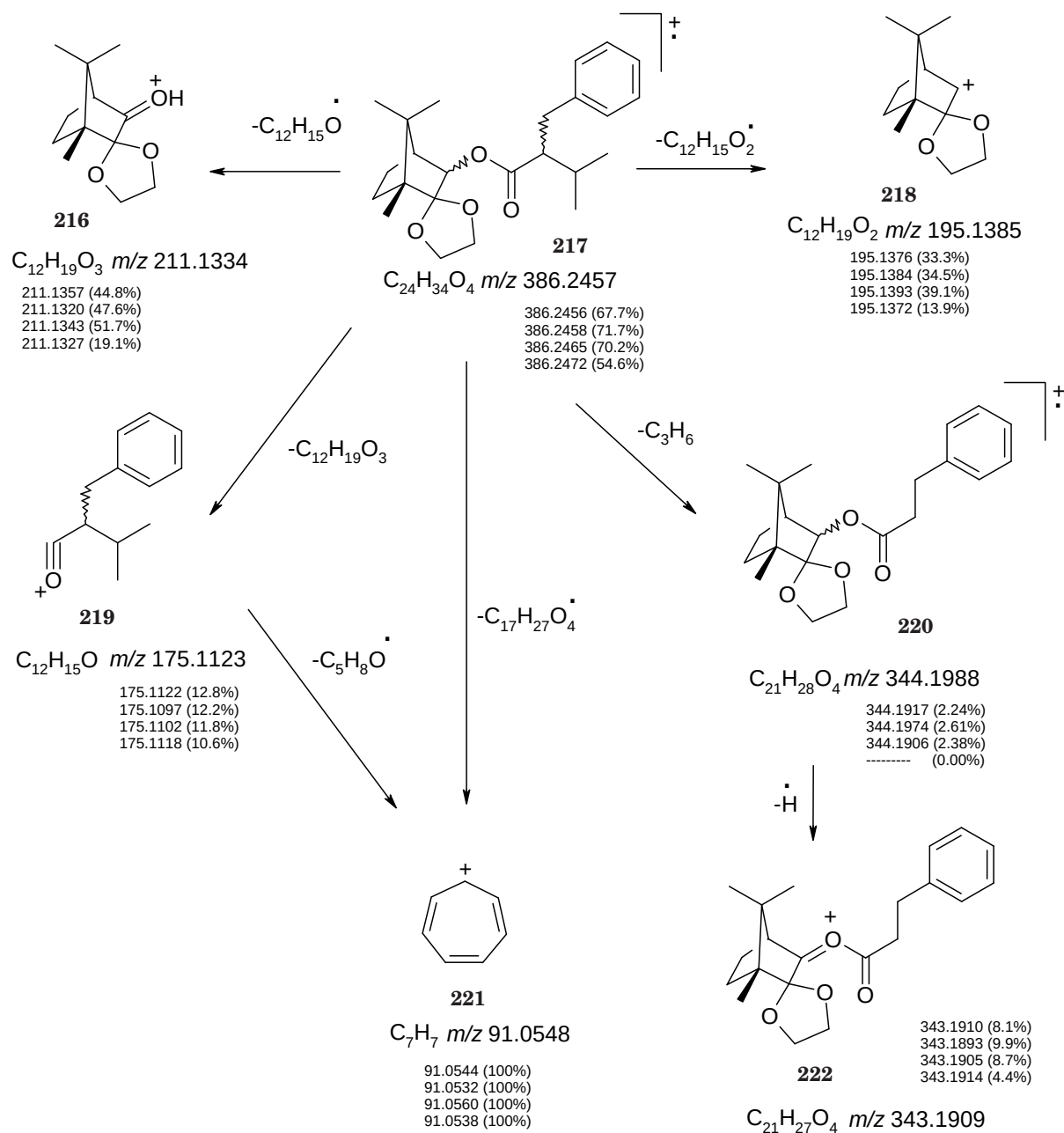
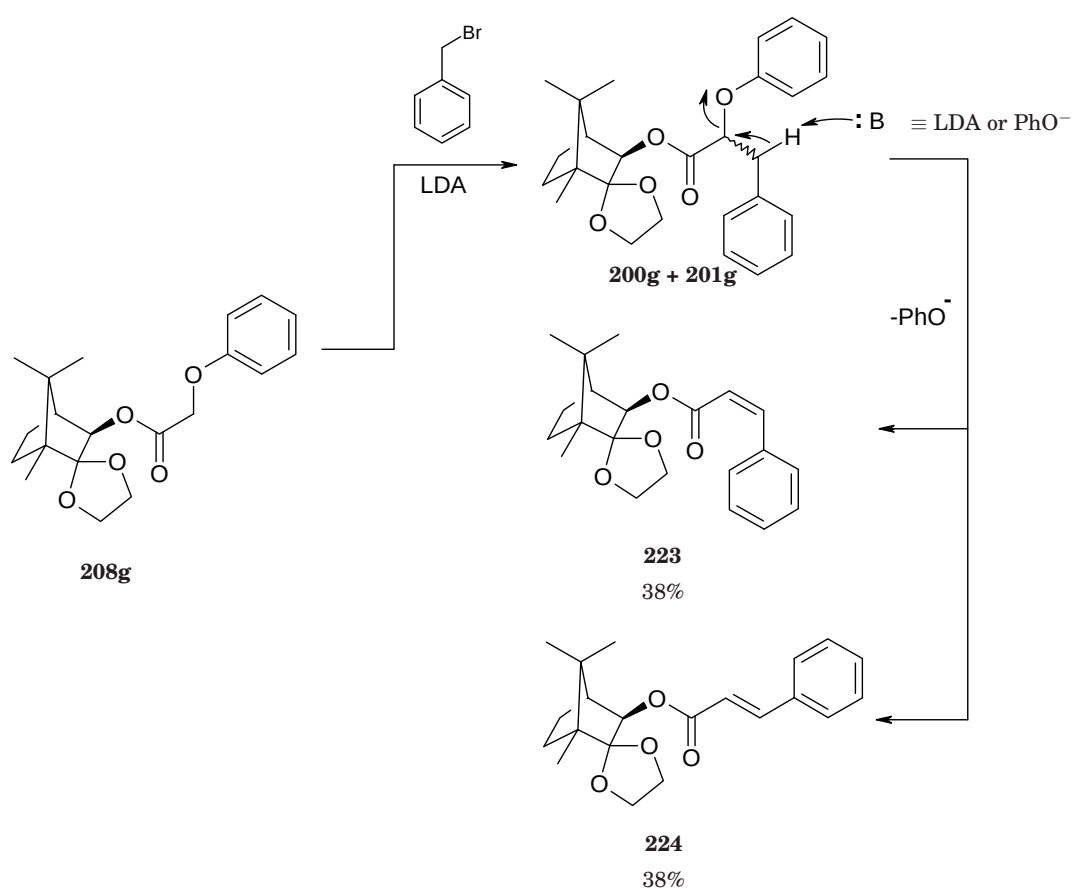


Figure 2.9: Selected EI mass fragmentation pathways proposed for the benzylated isopropyl esters **200d**, **201d**, **214d** and **215d**; calculated data are accompanied by the experimental data for the four diastereomers and their intensities (relative to each base peak).

2.1.6 Competing side reactions

While the benzylation of the phenoxy ester **208g** had already been achieved in the group,¹⁶³ this particular reaction proved to be quite difficult and afforded some interesting products – but not the desired benzylated phenoxy ester! These included a mixture of dephenoxylated geometric isomers **223** and **224**. In the other cases examined (**208b-e**), reactions were “clean” in the sense that only the expected products (or starting materials) were isolated. In these cases, of course, analogous elimination would require the loss of alkylidene anions - poor leaving groups!



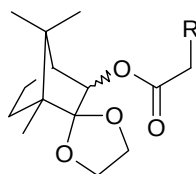
Scheme 2.12: Formation side-products from the benzylation of the phenoxy ester **208g**.

The formation of these products can be rationalized in terms of a base-initiated ($\text{B:} = \text{LDA}$), autocatalytic ($\text{B:} = \text{PhO}^-$) elimination of phenoxide ion, as a good leaving group, to afford the extensively conjugated products **223** and **224**.

2.1.7 Conclusions regarding the experimental benzylation of the camphor derived esters **208a-e** and **212a-e**.

The relative proportions of products isolated from detailed benzylation studies of the *exo*- and *endo*- series of esters **208a-e/212c-e** (i.e. R = Et, ⁱPr and ^tBu) are summarized in Table 2.2.

Table 2.2: Results of the benzylation of the mixture of *exo*-esters **208** and the *endo*-esters **212**.



208 + 212

Compound	R	Overall yield ^a	<i>Exo</i> -isomers 208			<i>Endo</i> -isomers 212		
			<i>exo</i> -R ^b	<i>exo</i> -R ^c	<i>exo</i> -R (d.e.)	<i>endo</i> -R ^b	<i>endo</i> -R ^c	<i>endo</i> -R (d.e.)
a	H	34% (71% ^e)	100% ^f	-	100%	- ^d	- ^d	- ^d
b	Me ^g	23%	70.9%	28.5%	42.4%	0.6%	- ^d	100%
c	Et	73%	50.7%	45.5%	5.5%	3.8%	- ^d	100%
d	Pr ⁱ	-	56%	38%	9%	4.4%	0.44%	82%
e	Bu ^t	49% ^e	30%	15%	34%	3.3%	1.9%	28%

^aCrude yield. ^bMajor isomer as percentage of entire product mix. ^cMinor isomer as percentage of entire product mix. ^dProduct not detected. ^eNMR yield. ^fOnly one possible diastereomer. ^gFor the Me system the accuracy of the experimental data may have been compromised on workup.

It would appear from the data that diastereoselectivity improves (in the *endo*-case) as the bulk of the R group decreases, whereas in the *exo*-ester series, stereoselectivity improves with increased bulk. With R groups such as phenoxy, dephenoxylation prevents observation of the required benzylated esters. This dephenoxylation is accompanied by the loss of the stereocenter. For the case where R = H, no new stereochemical centre is formed. The formation of this product is useful in that it can be alkylated to form the major products of inverse stereochemistry to those observed from benzylation.

The absolute stereochemistry of benzylation at position 2' at this stage in this thesis is not implied. There are major and minor diastereomers for both benzylations of the *endo*- and *exo*-series of esters.

2.1.8 The source of asymmetric induction in the benzylation step

The rationale behind the camphor ketal chiral auxiliary system was that the ester functionality would lie quasi-parallel to the ethylenedioxy group. It was assumed that the geometry of the system would be determined by a preference for an *s-trans*-ester, an *E*-enolate arrangement and an *endo*-orientation of the enolate alkoxide oxygen. Under these circumstances, the enolate would have one side hindered due to the ethylenedioxy group. The unhindered *si*-face would then be exposed to electrophilic attack (Figure 2.10).

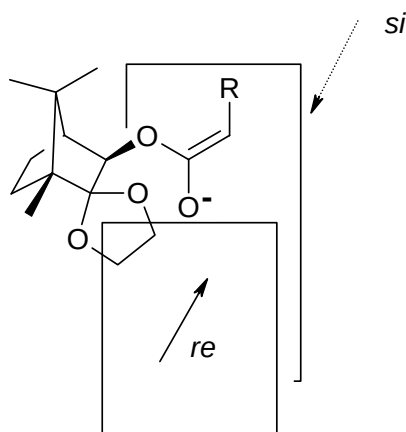


Figure 2.10: *Re* vs. *si* electrophilic attack of the *s-trans-E*-enolate.

Preliminary molecular modelling of the *exo*-system had been carried out in the research group, and there were strong indications of a chelated lithium cation providing rigidity to the enolate system.¹⁶³ It was intended to raise this modelling to the density functional theory (DFT) level in an attempt to predict the stereochemical outcome on the basis of the geometry of the rigid enolate system itself, rather than on the transition states involved. Consequently, a series of *E*- and *Z*-lithium enolate systems were modelled in both the *s-trans*- and *s-cis*-ester conformations at the DFT level. The ground state structures were constructed, DFT calculations were carried out (using DMol³ at the GGA/PW91/DN level) and the results analysed using the Accelrys Materials Studio software package. Equilibrium geometries were confirmed using a full vibrational analysis. Alignment of structures was effected using the alignment module in the Accelrys Cerius² software package. Figure 2.11 shows all the *exo*-enolates modelled for a particular R group.

A variety of conformers for each system were initially evaluated, but only the most reasonable ones were used in this study since there is considerable flexibility in the ethylenedioxy moiety and in the ester side-chain. Most of the conformational changes in the 5-membered

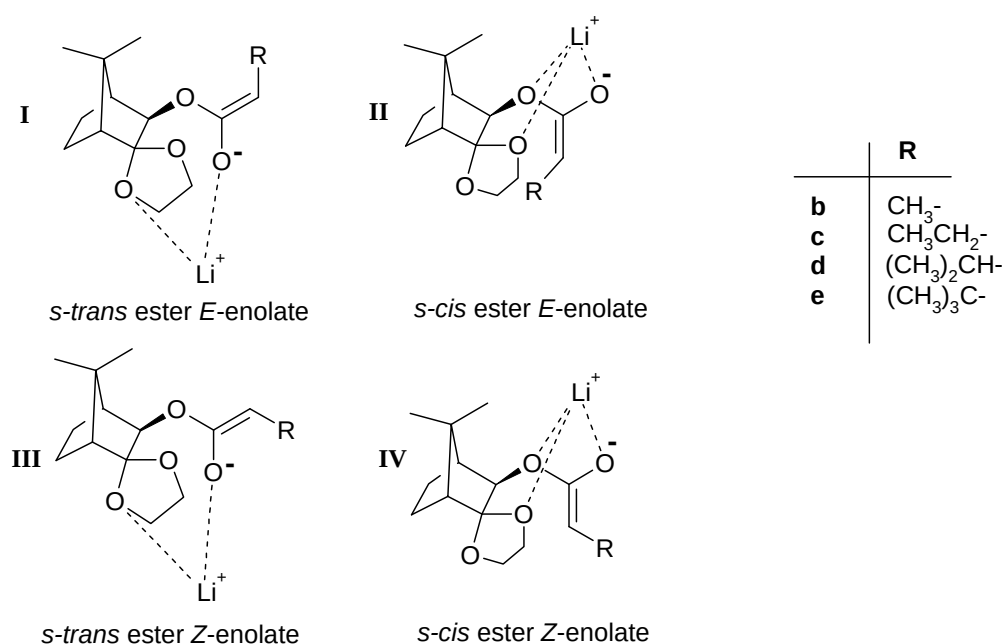


Figure 2.11: Geometric and rotameric options available to the *exo*-enolates.

ring system occur during the DFT minimization itself, and this could diminish the value of any previously determined conformational conclusions based on the molecular dynamics data.

Based on the modelling data, some general observations can be made concerning the coordination of the lithium ion, the preference for *s-cis* or *s-trans*-conformations, the preference for *E* or *Z* enolate configurations, and the conformational rigidity of the enolate systems thus formed. Although the ester moiety does lie quasi-parallel to the ethylenedioxy system in the ester precursors, this is not generally true for those enolates in which the lithium cation exhibits coordination to the ethylenedioxy system (the lithium cation coordinates, depending on the conformation, to one, two or three oxygen atoms). The conformations of enolates with the lithium only in contact with the negative enolate oxygen (a mono-coordinated lithium) were actually not taken any further in this study. In the *exo*-ester series, particular attention was focused on the conformations of the tri-coordinated lithium *s-cis*-ester enolates **II** and **IV** (Figure 2.11) and the di-coordinated lithium *s-trans*-ester enolates **I** and **III**; for the *endo*-series of esters (not shown) the tri-coordinated lithium *endo-s-trans*-ester enolates were examined. Attempts were also made to locate equilibrium geometries for lithium enolates in which the lithium was coordinated to both of the ethylenedioxy oxygens (*i.e.* containing a tri- or tetra-coordinated lithium), but all such attempts failed.

From an examination of the geometrical arrangements and relative energies of the various

lithium enolates, we conclude that :-

1. The *s-cis*-enolates are favoured thermodynamically in the *exo*-series of esters.

Figures 2.12 and 2.13 show overlays of all (*E* and *Z*) *s-cis* and all (*E* and *Z*) *s-trans* - enolates respectively. It is clear from the overlays that neither *E* or *Z* geometry, nor the bulk of the R contribute significantly to the geometry about the lithium centre. However, from Table 2.3 it is apparent that the tri-coordinated lithium systems associated with the *s-cis*-enolate are favoured. This is contrary to the expectation that *s-trans*-ester enolates should be favoured.¹⁶⁸

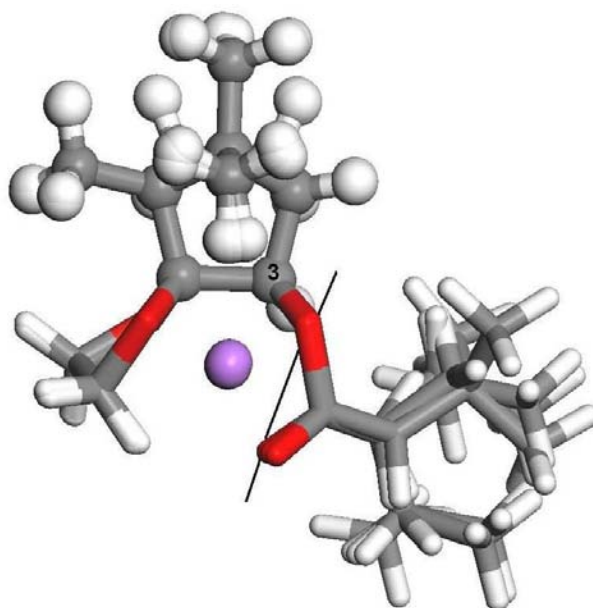


Figure 2.12: Alignment of the tri-coordinated *s-cis*-enolates II and IV (Figure 2.11).

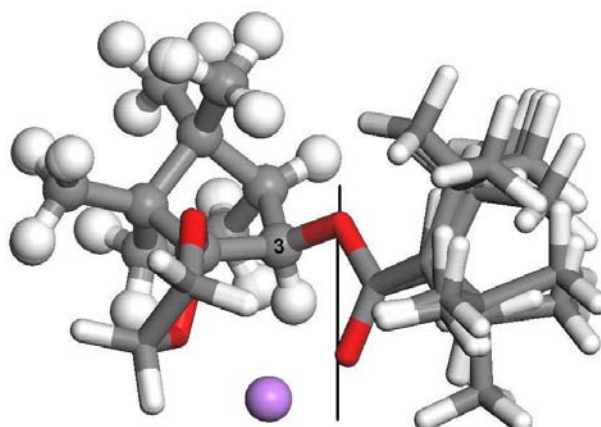


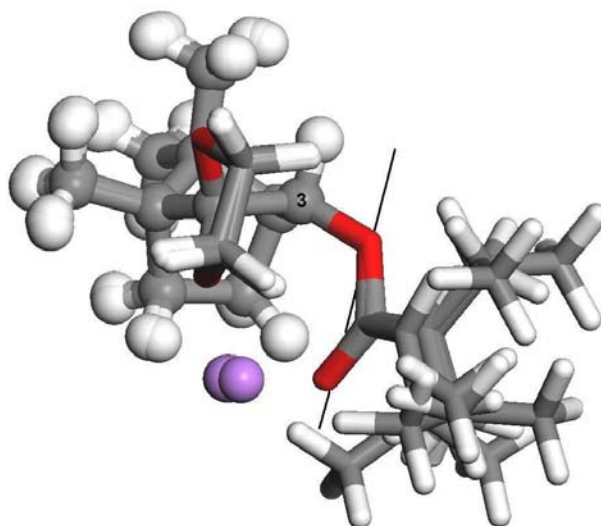
Figure 2.13: Alignment of the di-coordinated *s-trans*-enolates I and III (Figure 2.11).

2. The expected *s-trans*-enolates show two favoured conformations in the *endo*-series of esters.

Table 2.3: Energy differences between di-coordinated *s-trans* and tri-coordinated *s-cis-exo*-ester enolates.

Enolate	R	$G_{cis,200}$ Hartree	$E + ZPVE_{cis}$ Hartree	$E_f(cis)$ Hartree	$\Delta G_{200,trans-cis}$ kcal.mol ⁻¹	$\Delta E_{f,trans-cis}$ kcal.mol ⁻¹
E	methyl	-893.2905	-893.2650	-893.6215	4.528	5.338
E	ethyl	-932.5612	-932.5346	-932.9182	5.274	4.684
E	isopropyl	-971.8324	-971.8050	-972.2158	4.556	4.483
E	<i>tert</i> -butyl	-1011.0967	-1011.0685	-1011.5066	13.152	13.791
Z	methyl	-893.2927	-893.2666	-893.6224	5.183	5.357
Z	ethyl	-932.5640	-932.5372	-932.9204	4.755	5.687
Z	isopropyl	-971.8355	-971.8075	-972.2186	5.089	5.870
Z	<i>tert</i> -butyl	-1011.1058	-1011.0776	-1011.5153	7.842	7.608

In the *endo*-series of esters, two conformations are favoured (termed “closed” and “open”); these are illustrated in Figures 2.14 and 2.15, respectively. It was noted that the lithium enolate geometry in the “closed” conformation alters only slightly with changes in configuration (*E* vs. *Z*) or the bulk of the R group. Table 2.4 illustrates how the “open” conformation is favoured for bulky R groups. The stereoselectivity of attack at the more exposed enolate centre of the “open” conformation is likely to be reduced – a rationalization for the experimentally observed loss of stereoselectivity with increasing of the bulk of R group (Figure 2.15).

**Figure 2.14:** Aligned *endo*-ester enolates in the *s-trans*-conformation (“closed” conformation).

2.1.8.1 Conclusions regarding the theoretical aspects of this system

What has been illustrated in this study is the complexity and conformational mobility of the ester enolate moiety – factors which make meaningful prediction of stereoselectivity difficult,

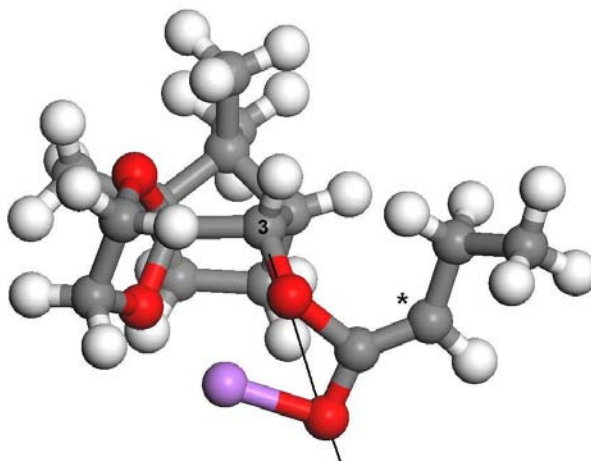


Figure 2.15: *Endo-s-trans* ester (R=Et) enolates with tri-coordinated lithium (“open” conformation with nucleophilic enolate centre marked with an asterisk).

Table 2.4: Differences between “open” and “closed” conformations of the *endo-s-trans*-E systems.

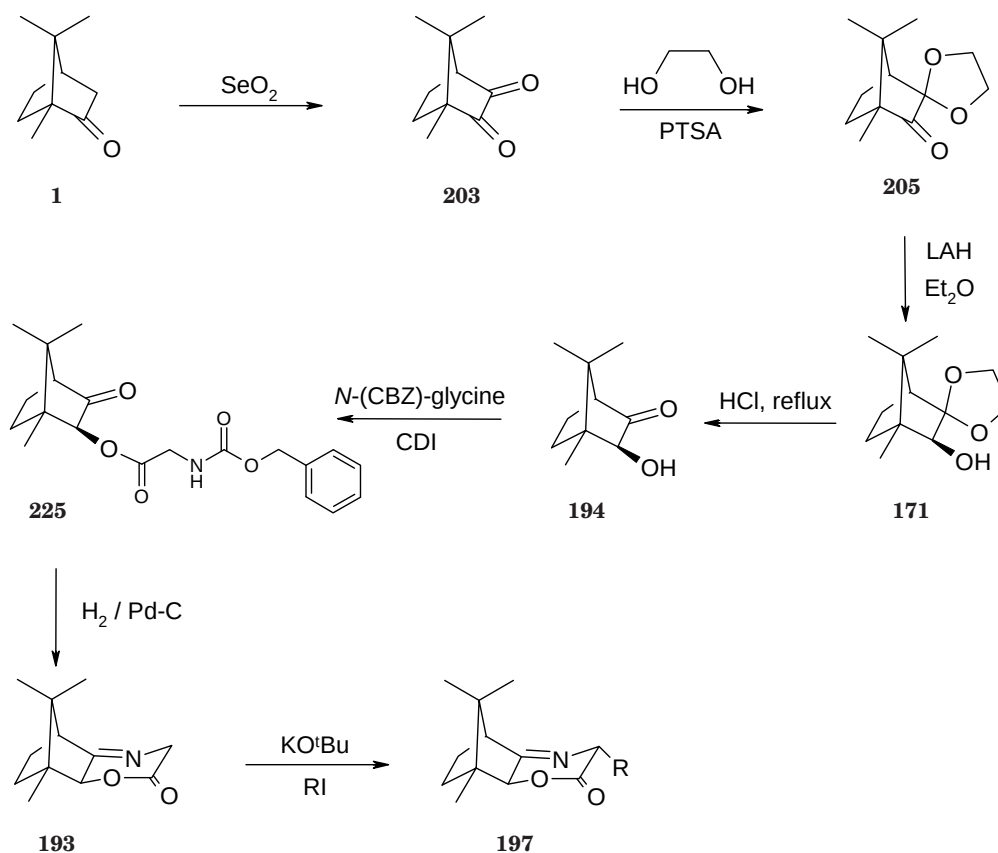
Conformation	R	G ₂₀₀ Hartree	E + ZPVE Hartree	E _f Hartree	$\Delta G_{200,open-closed}$ kcal.mol ⁻¹	$\Delta E_{f,200,open-closed}$ kcal.mol ⁻¹
open	methyl	-893.2905	-893.2645	-893.6202651	10.084	9.908
open	ethyl	-932.5617	-932.5343	-932.9173241	9.228	9.214
open	isopropyl	-971.8200	-971.7919	-972.2039213	0.983	2.081
open	<i>tert</i> -butyl	-1011.0914	-1011.0631	-1011.501809	-	-
closed	methyl	-893.2744	-893.2487	-893.6044749	-	-
closed	ethyl	-932.5470	-932.5192	-932.9026397	-	-
closed	isopropyl	-971.8184	-971.7898	-972.2006044	-	-
closed	<i>tert</i> -butyl ^a	-	-	-	-	-

^a All attempts at obtaining this conformation failed in the *tert*-Bu case.

if not impossible. Unfortunately, time has not permitted an examination of the transition states involved or the development of more accurate theoretical models of these conformationally mobile systems and attention was therefore turned to our studies of rigid tricyclic systems.

2.2 Enantiomer beneficiation of α -amino acids

The camphor iminolactone system was identified as a rigid scaffold ideally suited to the stereoselective synthesis of either L- or D-amino acids as illustrated in Scheme 2.13. Thus, stereoselective production of either the L- or D-series of amino acids could be achieved *via* two routes from either D-(+)- or L-(-)-camphor outlined in Scheme 2.14, the stereochemical outcome in each case depending on the camphor skeleton's capacity for directing alkylation to the *endo* face.

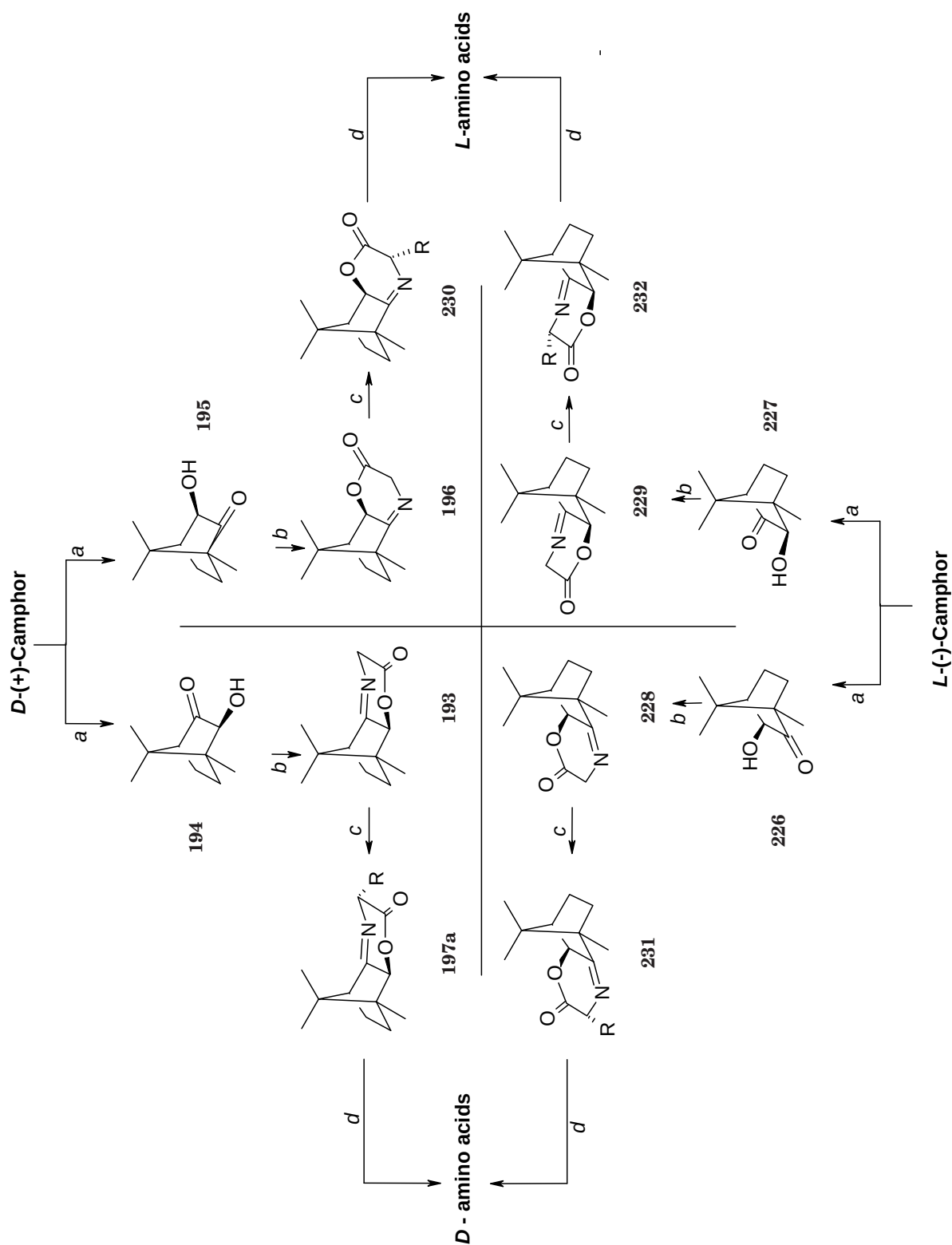


Scheme 2.13: Access to Alkylated Iminolactone Systems.

Earlier studies within the group by Matjila,¹⁶² Ravindran¹⁶⁹ and Klein¹⁶³ had clearly indicated the potential of this approach. However, in the application of this approach certain anomalies had become apparent, and the aim in the present study has been not only to refine the synthetic methodology but also to examine these anomalies.

2.2.1 Construction of the iminolactone scaffold

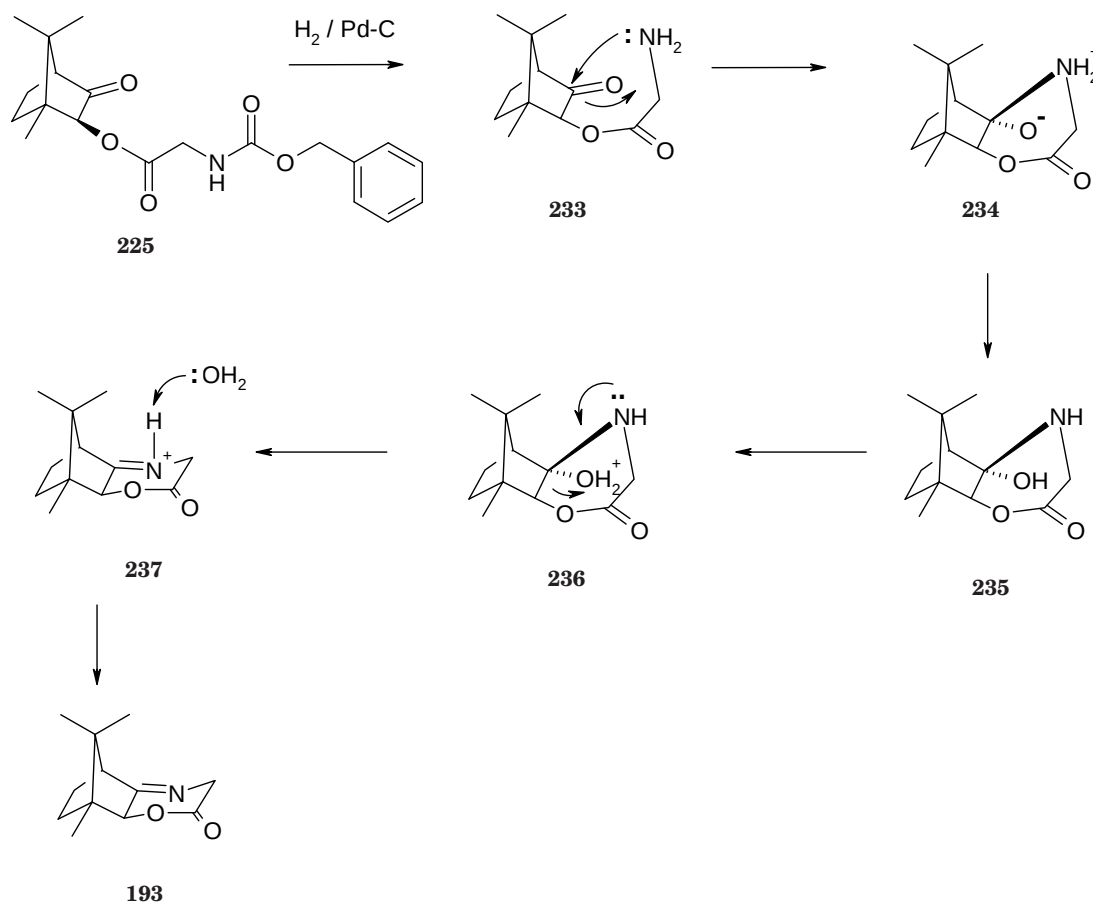
The intention was to focus on the use of 2-*exo*-hydroxy-3-bornanone **194** to generate the 3-iminolactone **193**; the isomeric 2-iminolactone system **196** has been explored in a cognate study by A. R. Duggan.¹⁷⁰ Access to the critical α -ketol **194** from the 2-*exo*-hydroxyketal **171** (Scheme 2.13) was achieved using the methodology discussed in Section 2.1 (p.49). Alkylation of the iminolactone enolate was expected to occur at the less hindered *endo* face. The 2-*exo*-hydroxy ketal **171** was formed in good yield (74%) and good diastereomeric excess (88%) from the ketone **205** by LAH reduction in THF. Hydrolysis of the ketal protecting group was effected by heating in aqueous methanol in the presence of hydrochloric acid. Moderate yields (*ca* 50%) of the ester **225** were obtained by treating the resulting α -ketol **194** with *N*-carbobenzyloxyglycine in the presence of the coupling agent, carbonyl diimidazole (CDI).¹⁷¹ Deprotection *via* hydrogenolysis using a 10% palladium-on-carbon catalyst, led *via* cyclization to the iminolactone **193**, initially in poor yield, but later (by using higher temperature to drive off water) in moderate (*ca* 40%) yield.



Scheme 2.14: General approach to the stereoselective synthesis of α -alkylated amino acids *via* iminolactone scaffolds. *a.* Oxidative functionalization/regiospecific *endo*-hydride delivery. *b.* Attachment of glycine entity. *c.* *Endo*-alkylation. *d.* Hydrolysis of lactone and imine functionalities.

2.2.1.1 Investigation of the imine formation step

In order to optimize yields in the hydrogenolysis-cyclization sequence leading to the imine, it was felt that a more detailed study of the process outlined in Scheme 2.15¹⁷² was warranted. The cyclization is presumed to take place *via* the carbinolamine **235** that is produced by catalytic hydrogenolysis of the glycine ester **225**. Thus, following removal of the CBZ protecting group, the amine lone pair in the acyclic intermediate **233** attacks the carbonyl group (presumably from the *exo*-face) to produce the zwitterion **234**. Proton transfer affords the carbinolamine **235**, which undergoes protonation, and dehydration leads to the iminolactone scaffold **193** *via* the iminium salt **237**.



Scheme 2.15: Expected mechanism for the formation of the iminolactone **193**.

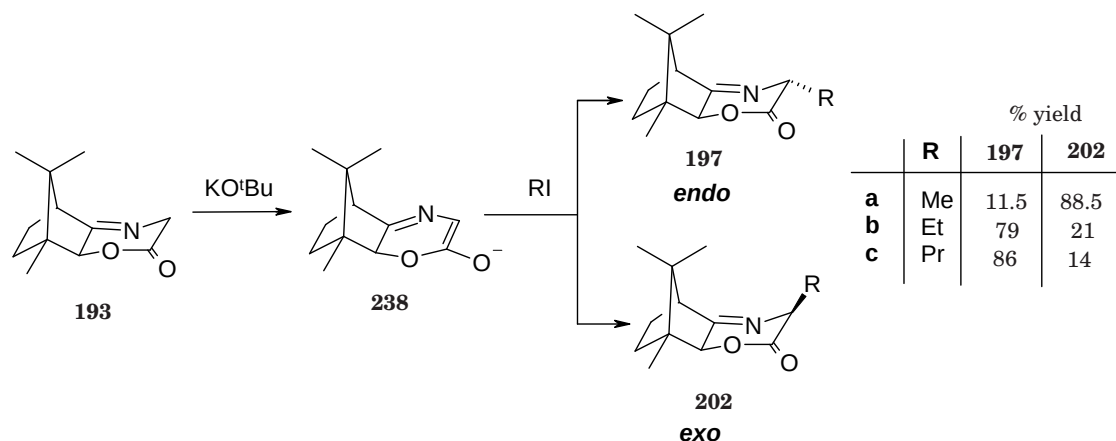
Initially, the reaction was monitored by immersing the hydrogen outlet tube in barium hydroxide solution, the precipitation of barium carbonate indicating loss of carbon dioxide during deprotection. However, it was found that monitoring the reaction by thin layer chromatography (TLC) gave a more accurate indication of what was happening, although this

required cessation of the hydrogen flow, flushing the apparatus with nitrogen prior to removing a sample, evacuation and then resumption of the hydrogen flow. It was clear from the TLC analysis that deprotection of the amino group occurred within 30 minutes at room temperature. However, exactly what followed was far from clear. Essentially, two fractions appeared to be forming, one consistent with the R_f value of the iminolactone **193**, the other more consistent with formation of the hydroxybornanone starting material **194**. At this stage, there was concern about heating the reaction mixture, and increased yields of the iminolactone product were achieved by stirring the reaction mixture overnight. Higher yielding reactions of this type have been reported,¹⁷³ but it is uncertain whether cyclization takes place during the initial reaction, or upon workup when elevated temperatures may accelerate the formation of the imine and/or ensure more complete removal of water present in the solvent from the wet catalyst.

An attempt was made to isolate the deprotected glycine ester **233** and to follow the cyclization in deuterated methanol within an NMR tube. Although not all intermediates have been accounted for, it is clear that, at 27°C, the cyclization **233** $\rightarrow$ **193** requires more than 12h.

2.2.1.2 Alkylation of the glycine-derived iminolactone scaffold

Alkylation of the iminolactone system **193** involves formation of the corresponding iminolactone enolate species **238** using a base such as potassium *tert*-butoxide. Treatment of the enolate with an alkyl halide was expected to produce the alkylated systems **202** or **197**, with preferential formation of the *endo*-series **197a-c** (Scheme 2.16).



Scheme 2.16: Alkylation of the glycine-derived iminolactone (R = Me).

This approach had, in fact, been shown to preferentially afford the *endo*-alkylated derivatives **197** for a wide variety of alkyl groups R^{162,163} but, in the case of methylation (R = Me), anomalous results were obtained. Thus Klein¹⁶³ obtained the *endo*-isomer **197a** as the dominant product, while Matjila¹⁶² isolated the *exo*-isomer **202a** as the dominant product. In order to rationalize these results in the present study, the alkylation reactions for R = Me, Et and Pr were repeated, but methylation of the iminolactone **193** was repeated several times, affording stereoselectivities which differed widely from those reported by Matjila¹⁶² and Klein¹⁶³! (Table 2.5).

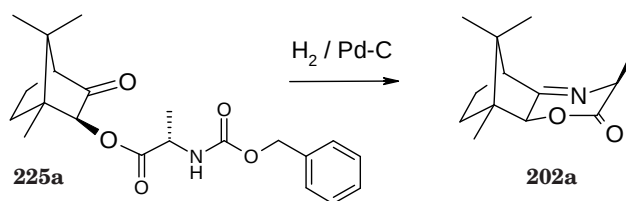
Table 2.5: Varying stereoselectivities for the alkylation of the iminolactone **193**.

R	% d.e.	% d.e. ¹⁶²	% d.e. ¹⁶³
Me	77%, 40% (<i>exo</i>);20%, 44% (<i>endo</i>)	43% (<i>endo</i>)	89% d.e. (<i>exo</i>)
Et	58% (<i>endo</i>)	60% (<i>endo</i>)	69% d.e. (<i>endo</i>)
Pr	72% (<i>endo</i>)	70% (<i>endo</i>)	61% d.e. (<i>endo</i>)

When the methylation of the iminolactone **193** was repeated in the present study, the predominant stereoisomer (77% d.e.) was clearly the *exo*-methyl product **202a**. The HMQC NMR spectrum for the *exo*-methyl product is shown in Figure 2.16. In this spectrum the four upfield methyl signals, the downfield 2-*endo*-H singlet and the 2'-*endo*-H quartet are

all apparent. The 2-D nuclear Overhauser effect (NOESY) spectrum (Figure 2.17) shows an nOe correlation between the 2-*endo*-hydrogen and the 2'-hydrogen but not the 2'-methyl hydrogens, implying that the methyl group is *exo*-orientated. Cyclization of the analogous (CBZ)-L-alanine ester **225b** proceeds similarly (Scheme 2.17) and confirms the *exo* nature of the methyl system in the methylated product **202a** as will be discussed later.

The question to be addressed is: “Why does *exo*-methylation occur while *endo*-alkylation is favoured with higher alkyl groups?”.



Scheme 2.17: Cyclization of the L-alanine derived ester **225a**.

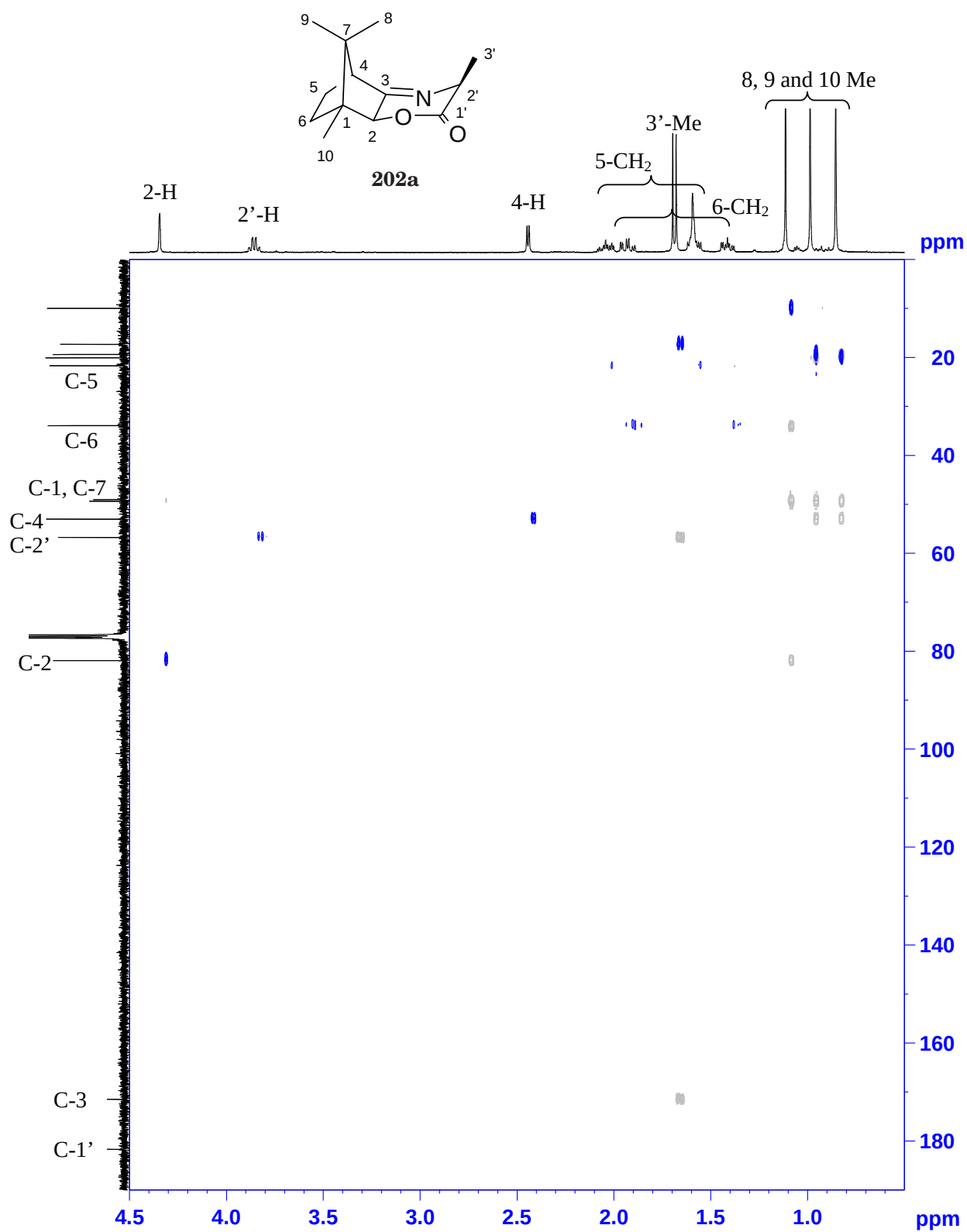


Figure 2.16: HMQC (blue) and HMBC (grey) NMR spectra of the *exo*-methyl iminolactone **202a** in CDCl₃.

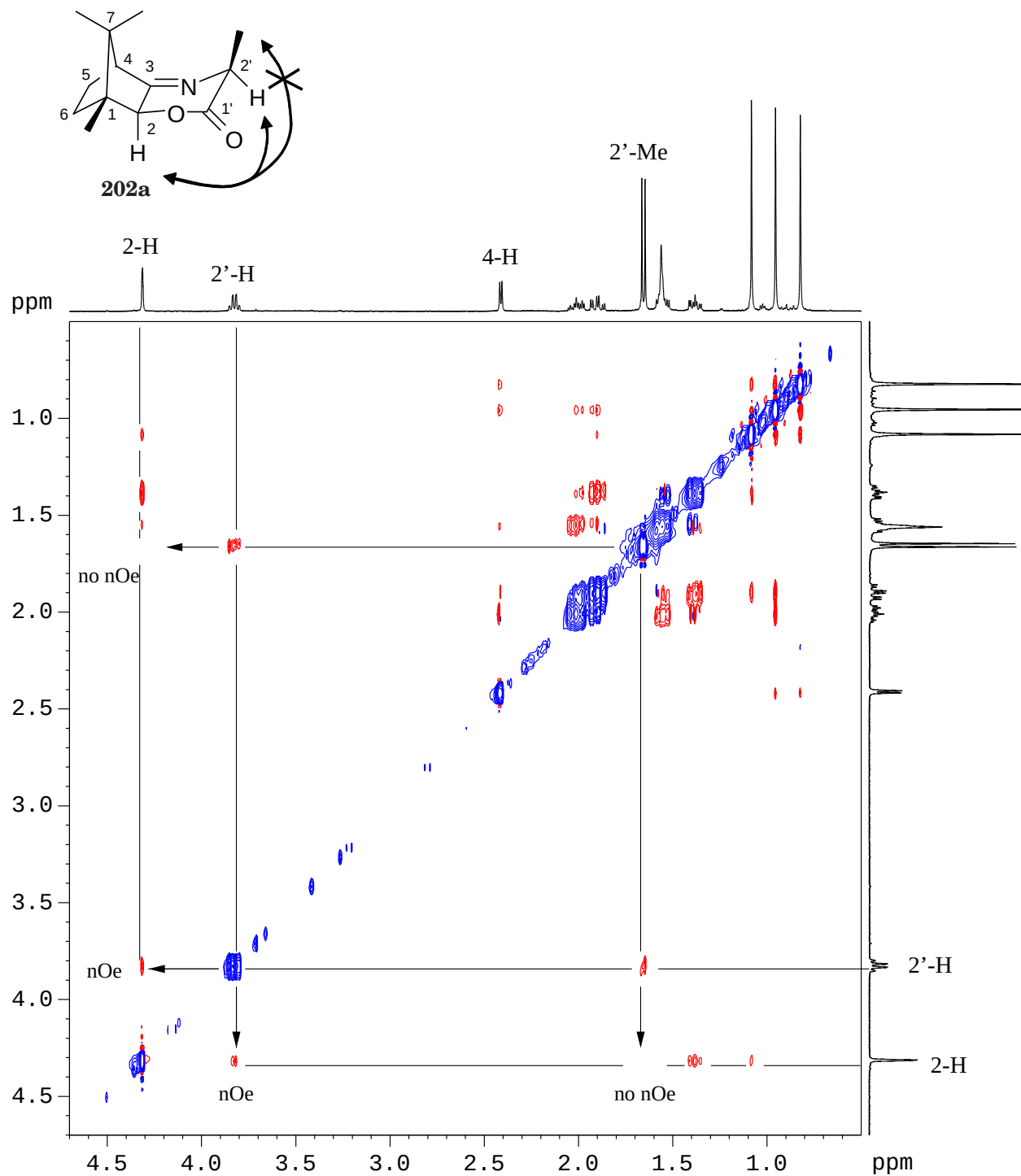
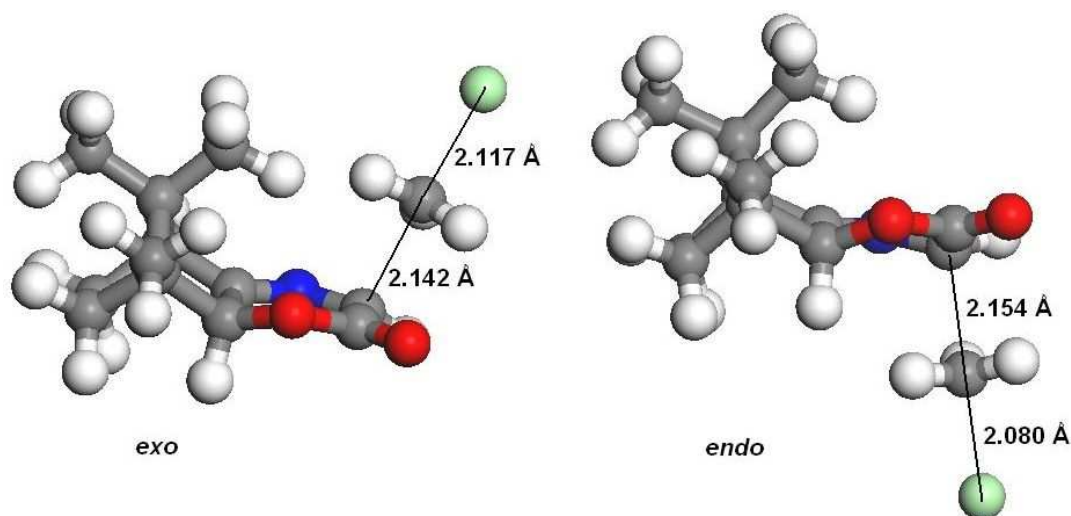


Figure 2.17: 2-D NOESY NMR spectrum of the *exo*-methyl iminolactone **202a** in CDCl_3 .

2.2.1.3 Computer modelling of the alkylated systems

To find answers to these questions we turned to molecular modelling, initially, at the AM1 level in Spartan '02 and the RHF/STO-3G level in GAMESS and, later, at the GGA/PW91/DNP DFT level using DMol³. The AM1 modelling showed that the *endo*-methylation transition state is, as expected, lower in energy (by 3.65 kcal.mol⁻¹) than the *exo*-methylation transition state. Figure 2.18 shows the *exo*- and *endo*-transition states located at this level for methylation of the iminolactone **193** with methyl chloride.



Scheme 2.18: AM1 *Exo*- and *endo*-transition states for alkylation of the enolate of the iminolactone **193** with methyl chloride.

The transition states for attack with methyl bromide (at the DMol³/GGA/PW91/DNP DFT level) also favour the *endo*-transition state ($\Delta G_{exo-endo} = 4.12 \text{ kcal.mol}^{-1}$). This implies that under kinetic conditions, the *endo*-product should predominate; this is supported by the experimental evidence – for all the alkyl groups examined except for the methyl case!

In modelling the *endo*-alkyl products **197a-d** at all levels (AM1, RHF/STO-3G and DFT), it became apparent that the the 1,4-diaxial interaction between the 2'-*endo*-alkyl group and the 2-hydrogen causes a slight puckering of the lactone ring and an increase in energy [$\Delta G_{endo-exo} = 3.4 \text{ kcal.mol}^{-1}$ for the *endo*-methyl product (Figure 2.18)!]. The O-C-C-R torsion angles for the DFT geometries of the isomeric *endo*-(**197a**) and *exo*-methyl product (**202a**) (Figure 2.19; Table 2.6) clearly reflect this, but there appears to be no interaction between the 8-methyl and the *exo*-methyl groups in compound (**202a**). Thus, under thermodynamically controlled conditions, the *exo*-methylated product is expected to predominate.

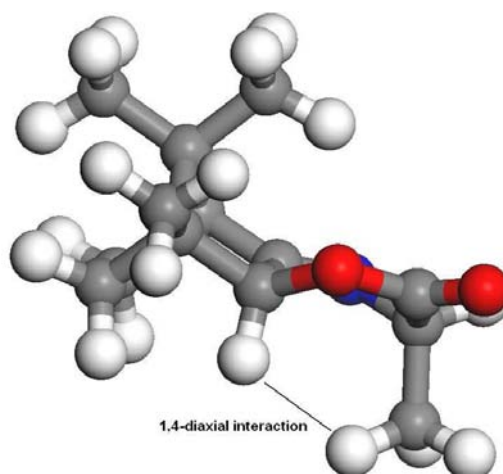


Figure 2.18: DFT model of the *endo*-methyl product **197** indicating the 1,4-diaxial interaction.

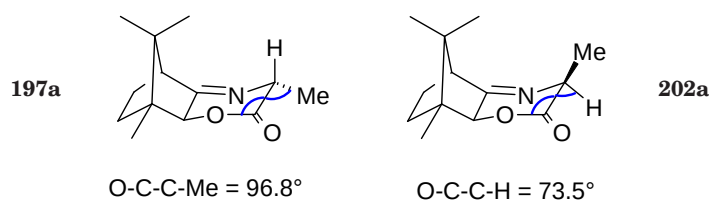


Figure 2.19: Torsion angles in the DMol³/GGA/PW91/DNP geometries of the *endo*-(**197a**) and *exo*-methyl case (**202a**).

For longer chain alkyl groups, the steric interactions between the *exo*-alkyl group and the 8-methyl group were initially presumed to be more significant than the 1,4-diaxial interaction involving the *endo* cases (Figure 2.20). It thus seemed that while the *endo*-systems would be kinetically favoured in all cases, the *exo*-methyl product would be preferred due to thermodynamic considerations. However, a more careful examination showed the above assumption to be incorrect. Systems were subjected to molecular dynamics simulations (quench dynamics in Accelrys Cerius²), providing the lowest energy conformers in which the alkyl group is not twisted. Untwisted alkyl conformers were subjected to *ab initio* RHF calculations using the small basis set STO-3G and, finally at the DFT level. The *exo*-butyl iminolactone **202d** illustrates the lack of interaction with the camphor skeleton (Figure 2.21).

Table 2.6 shows how the energy difference between the *endo*- and *exo*-systems varies with the substituent at the DFT (DMol³/GGA/PW91/DNP) level. It is clear, from the differences that the *exo*-systems are energetically more stable than their *endo*-counterparts in *all cases*. What is evident, however, here is that $\Delta G_{endo-exo}$ is greatest in magnitude in the case of the methylated system (3.0 kcal/mol compared with 0.5-1.9 kcal/mol).

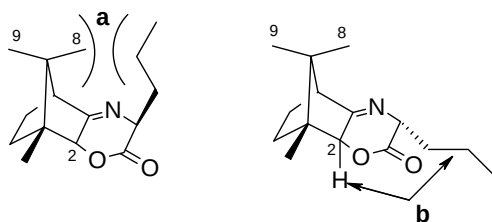


Figure 2.20: Steric interaction (a) between the *exo*-propyl group and the 8-methyl group in compound **202c** and the 1,4-diaxial interaction (b) in the *endo*-isomer **197c**.

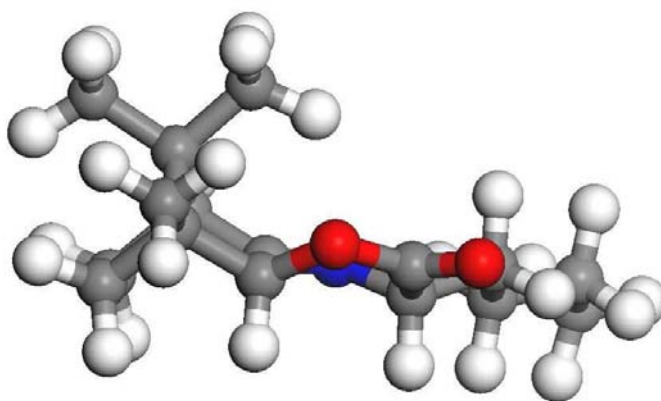
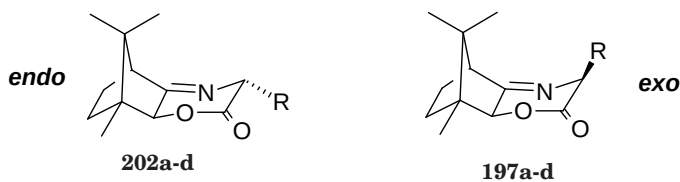


Figure 2.21: The *exo*-butyl iminolactone **202d** geometry at the RHF(STO-3G) level.

Table 2.6: Difference in energy and in torsion angles between *exo*- and *endo*-systems at the DMol³/GGA/PW91/DNP level.



	R	<i>endo</i> O-C-C-R /°	<i>exo</i> O-C-C-H /°	G _{298.15,endo} Hartree	G _{298.15,exo} Hartree	ΔG _{298.15,endo-exo} kcal.mol ⁻¹	G _{200,endo} Hartree	G _{200,exo} Hartree	ΔG _{200,endo-exo} kcal.mol ⁻¹
a	Me	96.8	73.5	-711.7627	-711.7681	3.42	-711.7461	-711.7509	3.03
b	Et	97.7	74.6	-751.0492	-751.0502	0.61	-751.0309	-751.0323	0.83
c	Pr	98.2	75.0	-790.3306	-790.3338	2.00	-790.3117	-790.3147	1.85
d	Bu	95.9	75.3	-829.6139	-829.6163	1.48	-829.5940	-829.5964	1.49

Of course, the side-chain is free to rotate in solution, and as the side-chain increases in length there is more chance of unfavourable steric interaction with the 8-methyl group in the *exo*-case. However, while an overlay of all staggered conformations of the *exo*-butyl side-chain in **202d** supports this argument (Figure 2.23, **B**), it is apparent that the *endo*-case **197d** (Figure 2.23) is even more prone to unfavourable interactions with the bornyl system.

Formation of the 2-*exo*-methylated product **202a** as the *thermodynamically* favoured product presupposes deprotonation and equilibration of the *kinetically* favoured 2-*endo*-isomer. Several factors may account for the apparent equilibration of the 2-methylated system **202a** alone. Thus, increasing the side-chain (Me $\rightarrow$ Et $\rightarrow$ Pr) could be expected to :- i) decrease the acidity of the remaining 2- α -H due to the increasing electron-releasing inductive effects; and ii) inhibit access by KOBu^t and, hence, the formation and stability [the size of the potassium cation being an exacerbating factor (Figure 2.22)] of a second enolate.

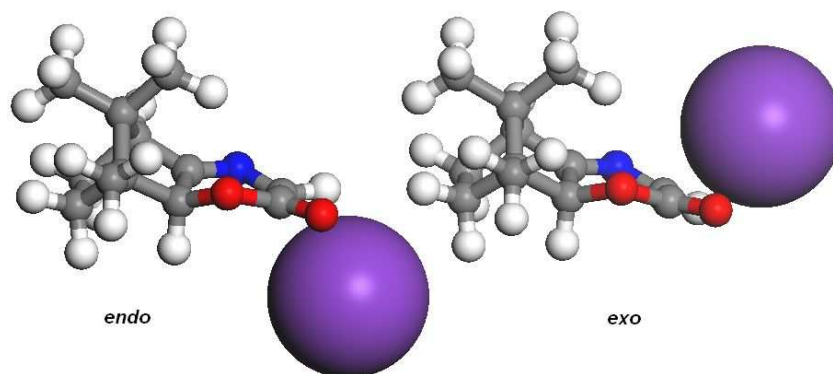
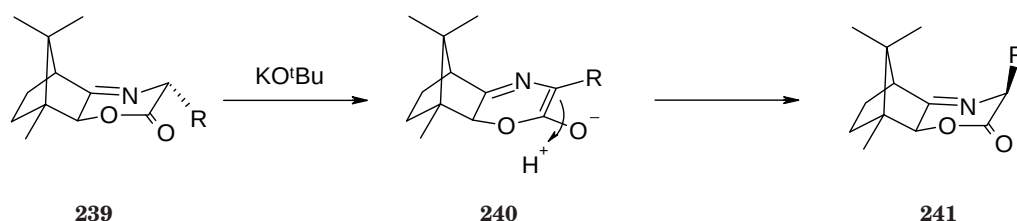


Figure 2.22: “*Endo*”- and “*exo*” potassium enolates.

These possibilities are explored in our explanation of amino acid enantiomer beneficiation *via* the iminolactone systems.



Scheme 2.19: Enolization of the *endo*-system (R = Me).

The schemes encountered in this section (*viz* Schemes 2.13, 2.14 and 2.16) have been in the process of development since 1994 within in our research group, with contributions by Ravindran,¹⁶⁹ Matjila,¹⁶² Klein¹⁶³ and Duggan.¹⁷⁰ While the present study was in progress,

however, papers by Ta-Jung Lu *et al.*^{173–175} have appeared in the literature reporting the approach described in Scheme 2.13 for the production and alkylation of the iminolactone systems **193**. The diastereoselectivities reported¹⁷³ for the production of the alkylated iminolactones **197**, using LDA, were better (up to 98%) than those obtained in our studies using KOBu^t.

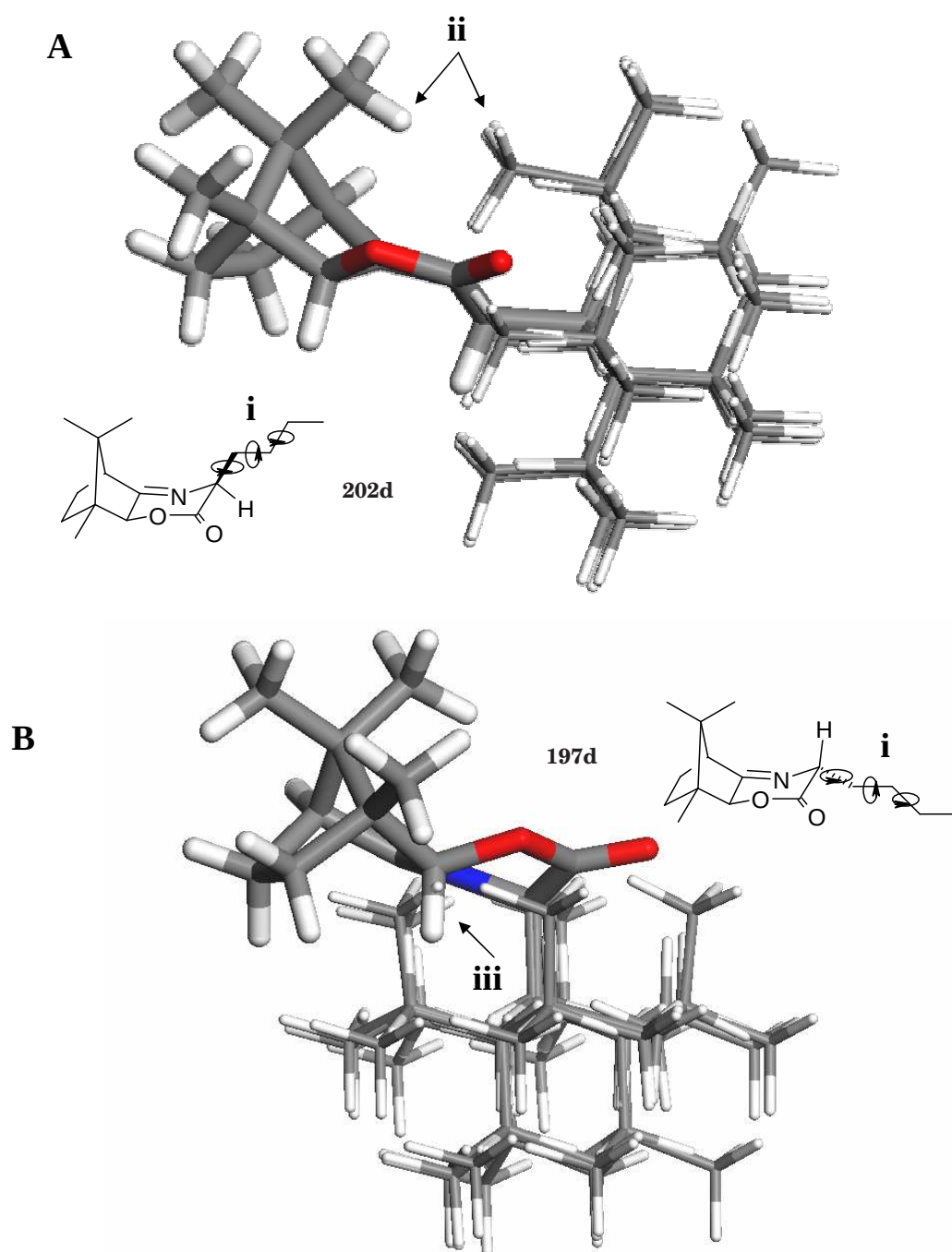


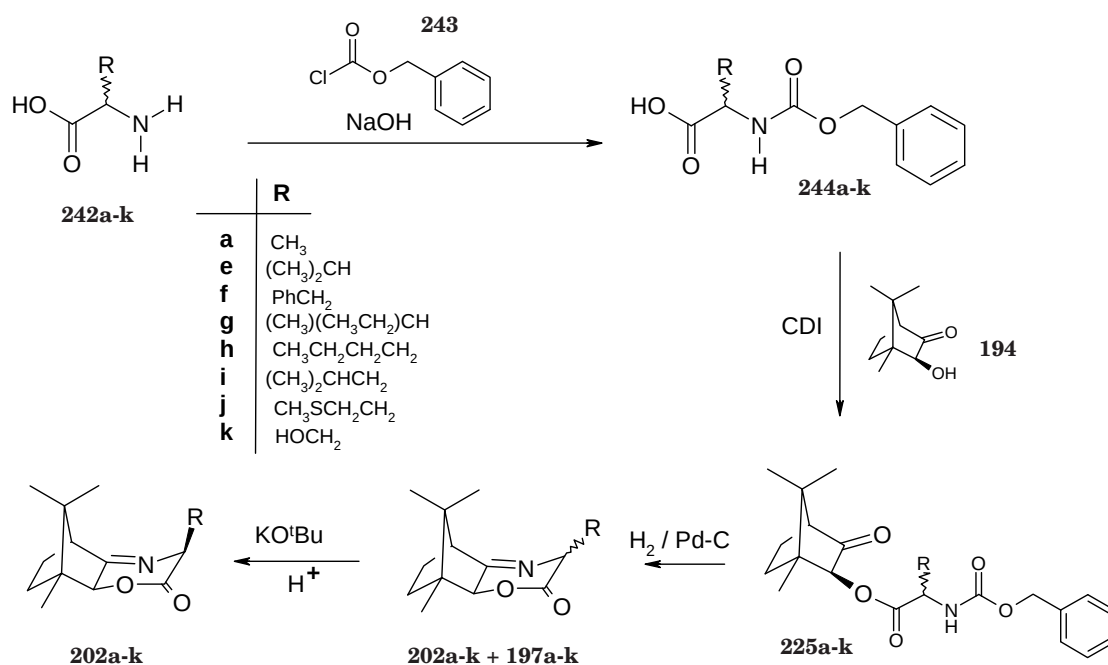
Figure 2.23: Overlay of all staggered conformers of the butyl side chain in **A** the *exo*-system **202d** and **B** the *endo*-system **197d**. **i**. Rotations giving rise to these conformations are indicated. **ii**. Unfavourable interaction in the *exo*-case. **iii**. Unfavourable interaction in the *endo*-case.

2.2.2 Enantiomer beneficiation studies

In preliminary studies in our group aimed at enhancing the enantiomeric excess of an α -amino acid relative to its enantiomer, Matjila¹⁶² observed that it was possible to deprotonate and then reprotonate the α -methylated iminolactone **197a** (Scheme 2.20) hence increasing the proportion of the *exo*-diastereomer from 43% to 85% d.e.

In the present study, the possibility of using this approach to de-racemize α -amino acids has been explored, the general approach being outlined in Scheme 2.20. Commercially available, enantiopure *N*-carbobenzyloxy-protected amino acids were used, and racemic amino acids were converted to their *N*-carbobenzyloxy-protected derivatives using benzyl chloroformate (Scheme 2.20). Although the protection was effected in poor to moderate yields (3–40%), no attempt was made to optimize these yields, since sufficient material was obtained for a “proof of concept” study. The *N*-protected amino acids **244** were then reacted with the camphor-derived α -ketol **194** to afford the diastereomeric 2-(*exo*)-esters **225a-k** (Scheme 2.20) in applying the same methodology developed for the glycine equivalent **193** (Section 2.2, p.72). Racemic serine (R = CH₂OH) was the only system (of those examined) for which the formation of the corresponding bornyl ester (**225k**) proved unsuccessful. This failure is attributed to competitive intermolecular coupling between the serine hydroxyl and carboxylic acid groups in the presence of carbonyldiimidazole (CDI). The diastereomeric esters **225a-j** were then subjected to the hydrogenolysis-cyclization sequence to afford the corresponding diastereomeric-iminolactones **197a-j** + **202a-j**. In the case of methionine ester **202j** (R = SCH₂CH₃), deprotection under the hydrogenolysis conditions failed to occur due, we suspect, to catalyst poisoning.

The ¹H NMR spectra of the diastereomeric bornyl esters **225a-j** tended to exhibit broad signals with complicated splitting patterns, reflecting the presence of rotamers arising from restricted rotation about the amide group. The bornyl esters **225** derived from the D-amino acids are expected to have different ¹H NMR spectra to those of the diastereomeric esters of the corresponding L-amino acids. In practice, the spectra were too diffuse to realistically assign or quantify signals from diastereomers. Even the ¹H NMR spectrum of the *purified* L-alanine-derived ester **225a** (2'-S, Figure 2.24) reveals complex overlapping of the 8, 9 and 10- methyl signals. Consequently, signals could not be assigned confidently. It is possible, of course, that some kinetic resolution may occur during esterification, thus affecting the diastereomeric ratios of the esters **225** and, concomitantly, the overall efficiency of this approach.

**Scheme 2.20:** Stereoisomeric beneficiation.

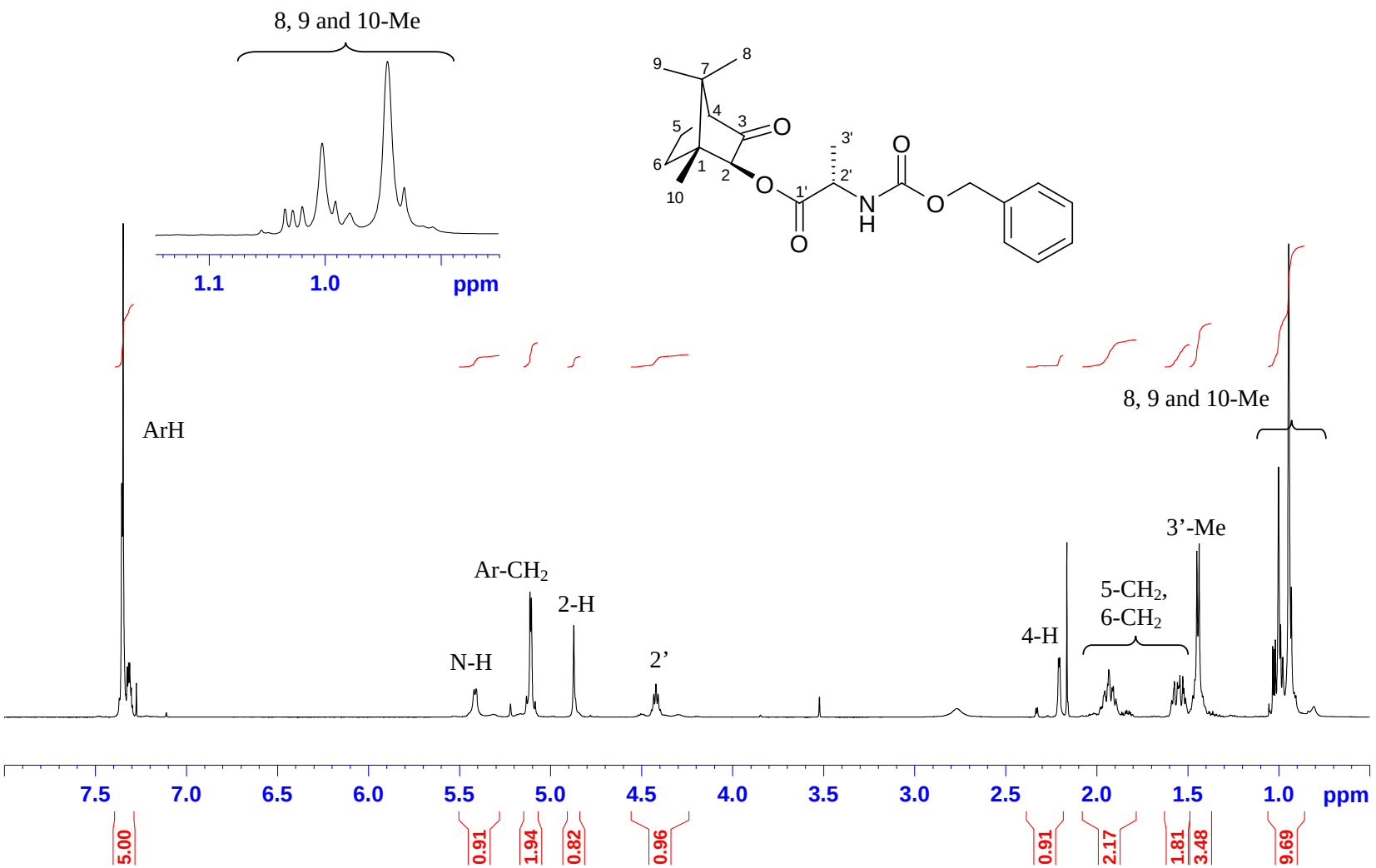
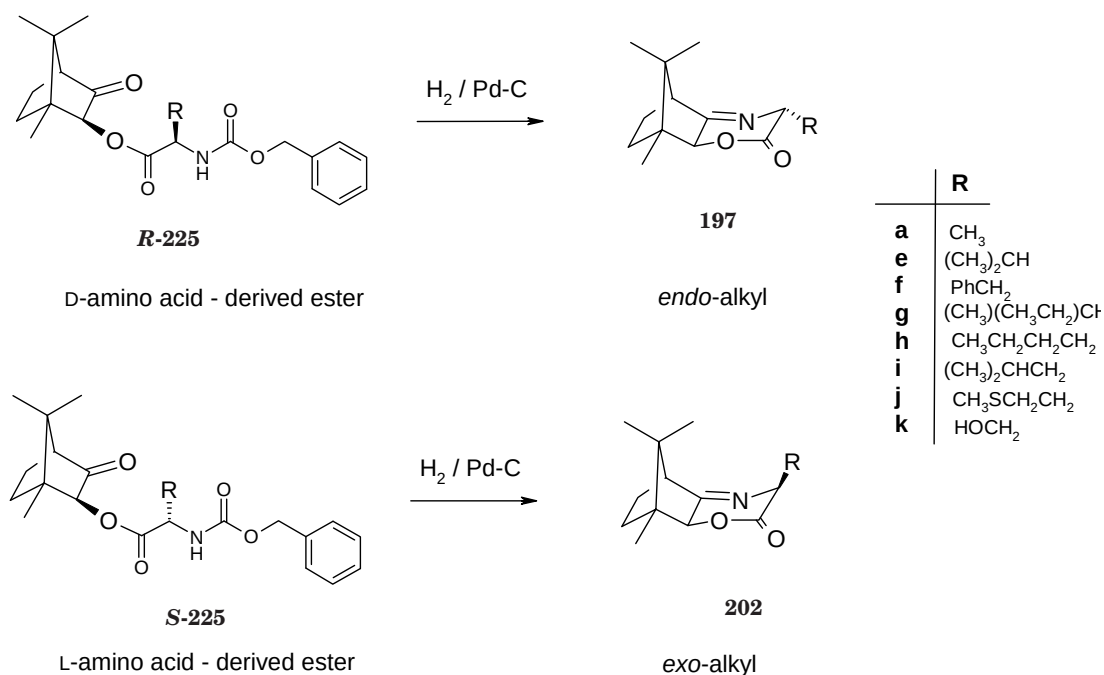


Figure 2.24: 600MHz ^1H NMR spectrum of the CBZ-protected L-alanine-derived ester (*2'S*)-**225a** in CDCl_3 .

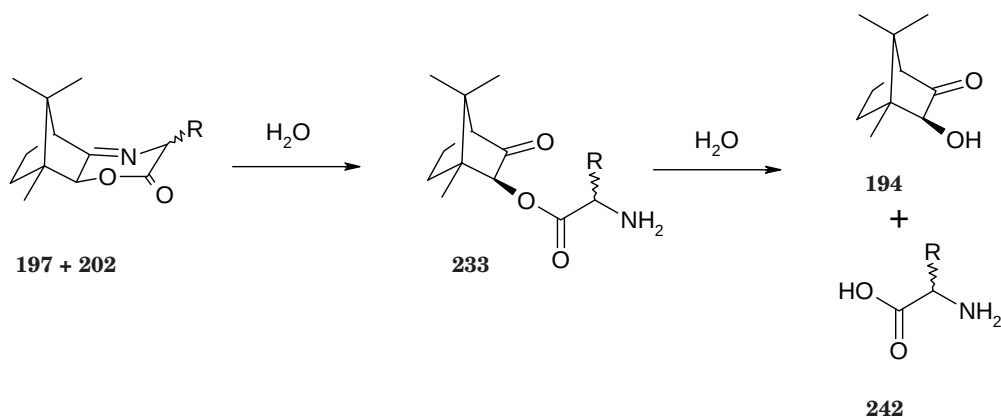
2.2.2.1 Stereoselectivity during reductive cyclization

It was anticipated that cyclization of the diastereomeric 2-*exo*-bornyl esters **225a-j** derived from racemic amino acids would produce equal quantities of (2'*R*)- and (2'*S*)-alkyl iminolactone stereoisomers stereospecifically (Scheme 2.21).



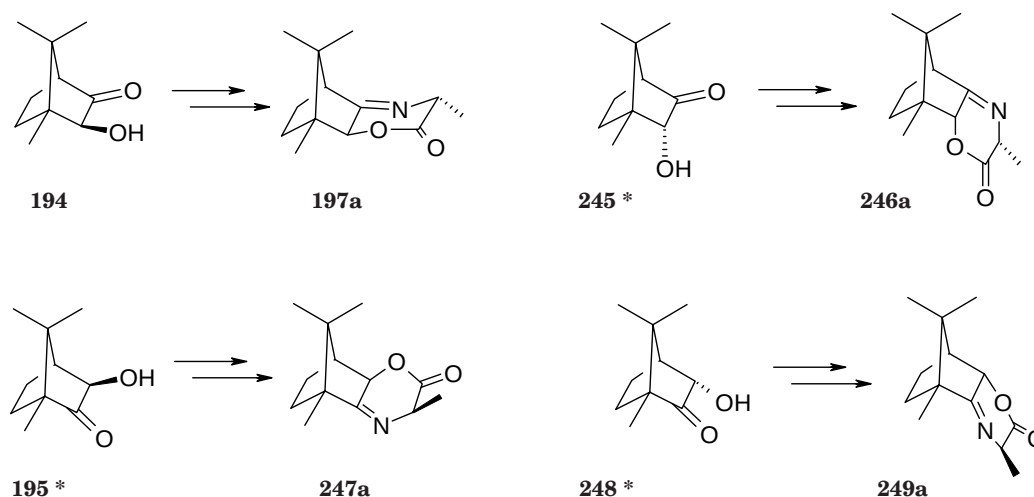
Scheme 2.21: Reductive cyclization of racemic bornyl esters **225**.

However, the concomitant production of water during the cyclization and the presence of water during work-up, permits the formation of the amino ketone **233** and its subsequent hydrolysis to afford the 2-hydroxy-3-bornanone **194** and the amino acid precursor (Scheme 2.22).



Scheme 2.22: Unwanted hydrolyses.

Cyclization of the D-alanine-derived system (2'*R*)-**225a** to afford the iminolactone **197a** was attempted several times under different conditions, but without success. An iminolactone product was obtained, containing the D-alanine moiety and the camphor skeleton, but the ^1H NMR spectrum in CDCl_3 (Figure 2.25) did not correspond to either the 2'*R*- or 2'*S*-methylated products. The NMR spectra clearly indicated the presence of an imine. Further, the HMBC data clearly indicated connectivity between the D-alanine moiety and the camphor skeleton (Figure 2.25). It was assumed that a by-product of an earlier reaction had given rise to this compound. The possible iminolactones fitting this description, and the possible impurities which could give rise to such products are shown in Scheme 2.23.



Scheme 2.23: Possible origin of unwanted D-alanine-derived iminolactone systems from contaminating precursors *.

In order to explore this assumption, the data for this product was compared with the spectroscopic data for the isomeric 2-iminolactone systems **197a**, **202a**, **230a** and **247a** from this study and previous work in the group.^{162,163,170} The ^{13}C NMR chemical shift data are condensed in Figure 2.26 and it is evident that the unidentified by-product, although clearly a similar system, is not one of the known iminolactone systems. The 2-imino analogue with *endo*-ester functionality was not considered since it would exhibit coupling between the 3-*exo*-H and the 4-H nuclei. It was thus concluded (by a process of elimination) that the structure was the (2*R*,2'*R*)-methyl-iminolactone **246a** derivative of the *endo*-hydroxy ketone **245** originating from *exo*-hydride attack during the LAH reduction of the (2*R*)-protected camphor derivative **205** (Scheme 2.7, p. 54); the COSY spectrum for this novel iminolactone is shown in Figure 2.27. Long range coupling between the 2-*exo*-H and the 2'-*exo*-H is evident which

confirms the stereochemistry at this point.¹⁷⁰ A comparison of the experimental *vs* calculated ¹³C NMR chemical shifts for compound **246a** and the isomeric iminolactones is summarized in Figure 2.28. The calculations were conducted on Dmol³ DNP/GGA/PW91 geometries using Gaussian '03/HF/6-311+g(2d,p) on the isomeric systems **246a**, **250a**, **197a** and **202a**. Although there is a general match for the pattern of chemical shifts and C-3 is fairly consistent with the experimental values, the calculated C=O is consistently downfield while the remainder of signals are calculated to be far upfield of the experimental values. The predictive spectra are the best match for the associated experimental signals, in each case.

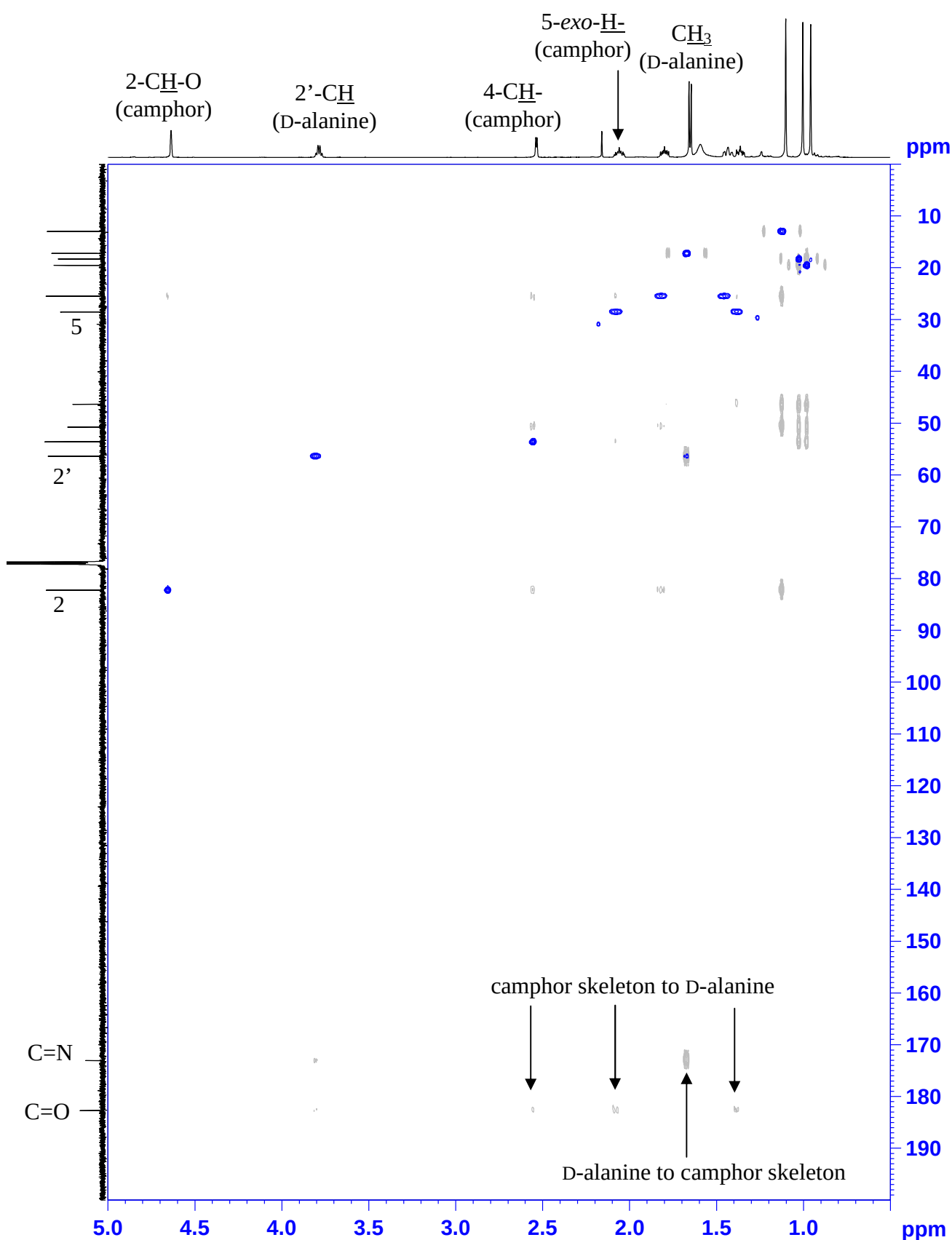


Figure 2.25: 600MHz overlay of HSQC (blue) and HMBC (grey) data for an unexpected iminolactone obtained during hydrogenolysis of the D-alanine derived ester **225a**.

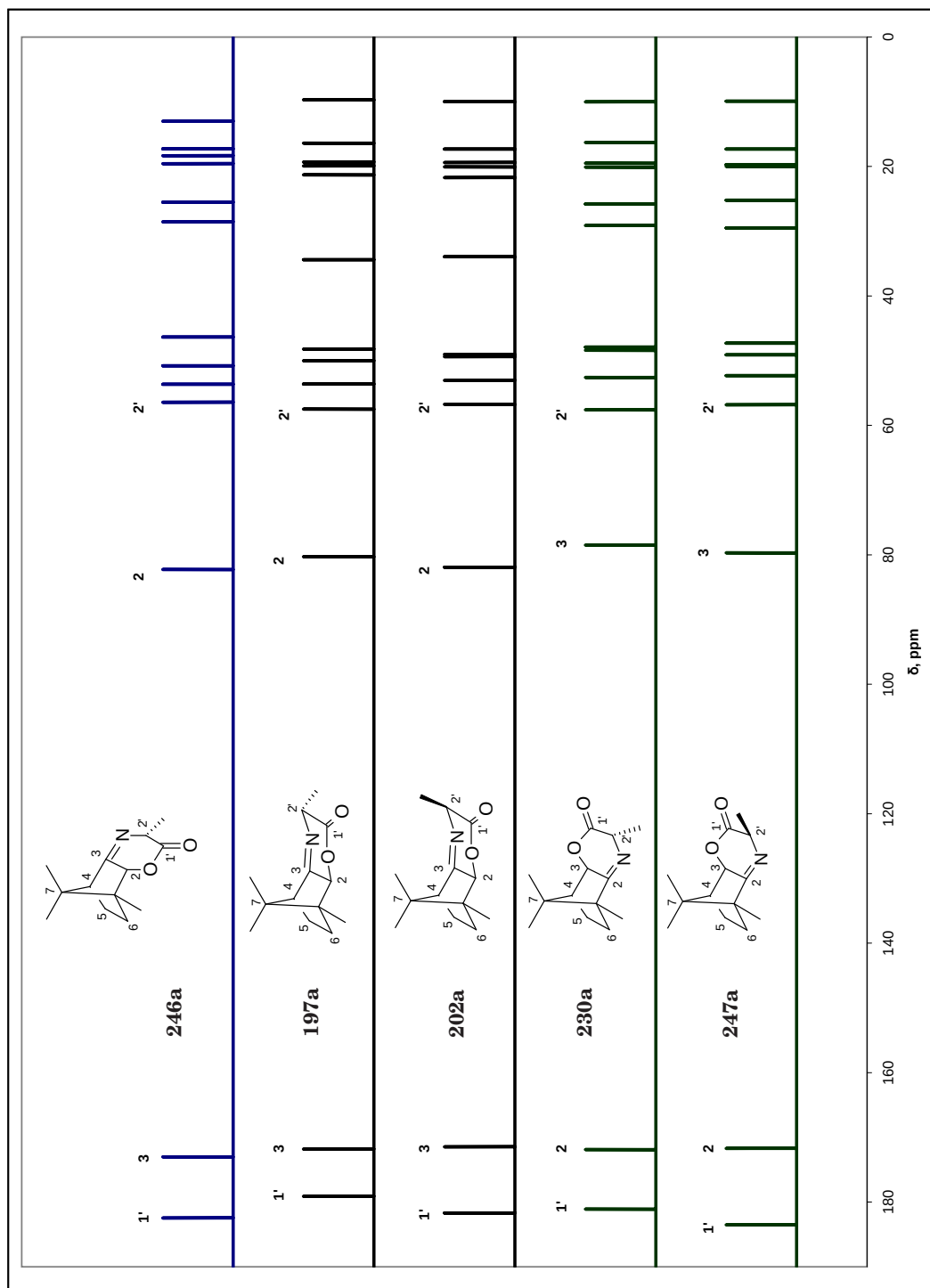


Figure 2.26: Experimental ^{13}C NMR chemical shifts of the proposed iminolactone by-product **246a** and known isomeric iminolactone systems in CDCl_3 .

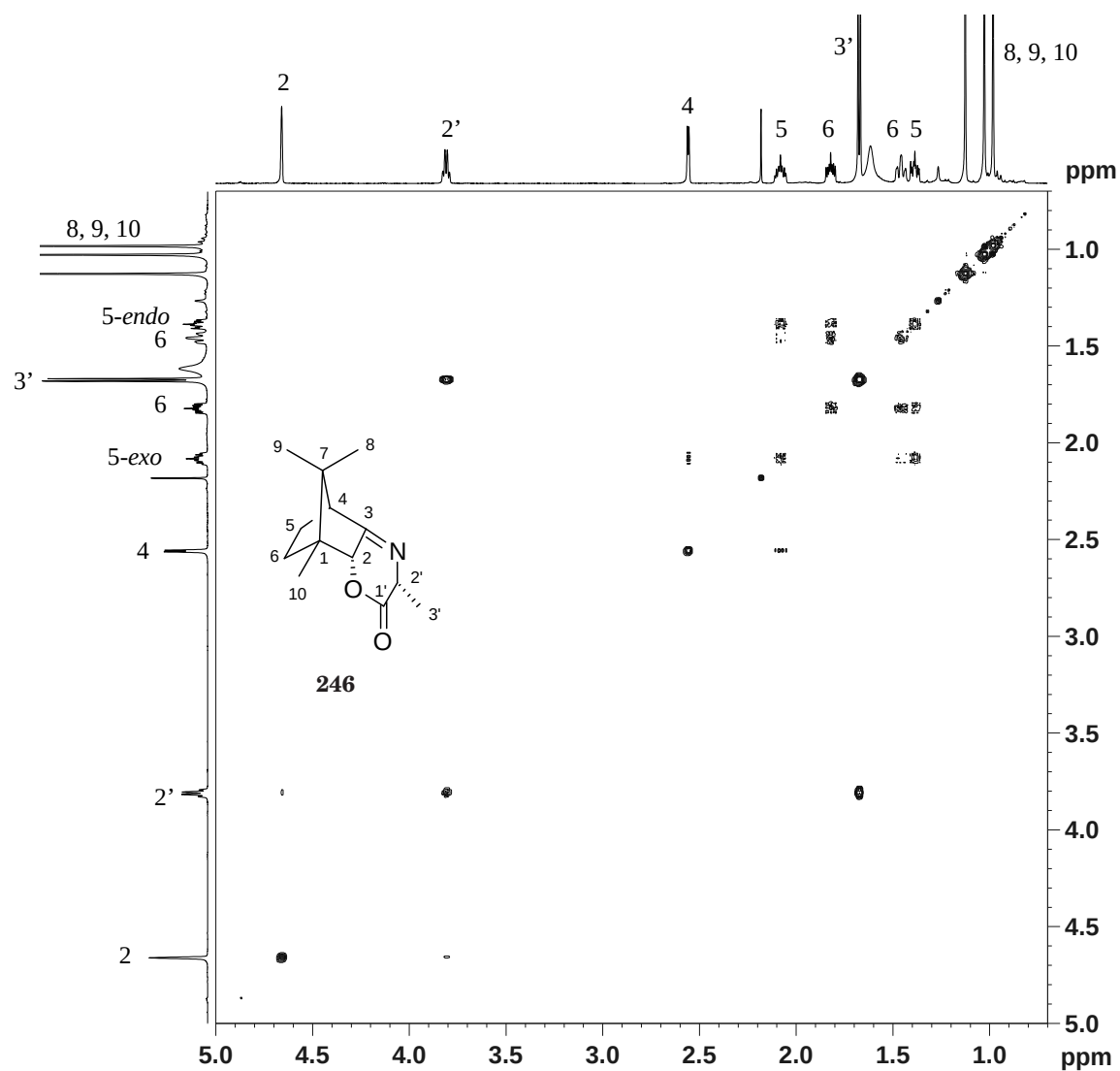


Figure 2.27: 400MHz COSY spectrum of the (2*R*,2'*R*)-3-iminolactone system **246a** derived from D-alanine in CDCl₃.

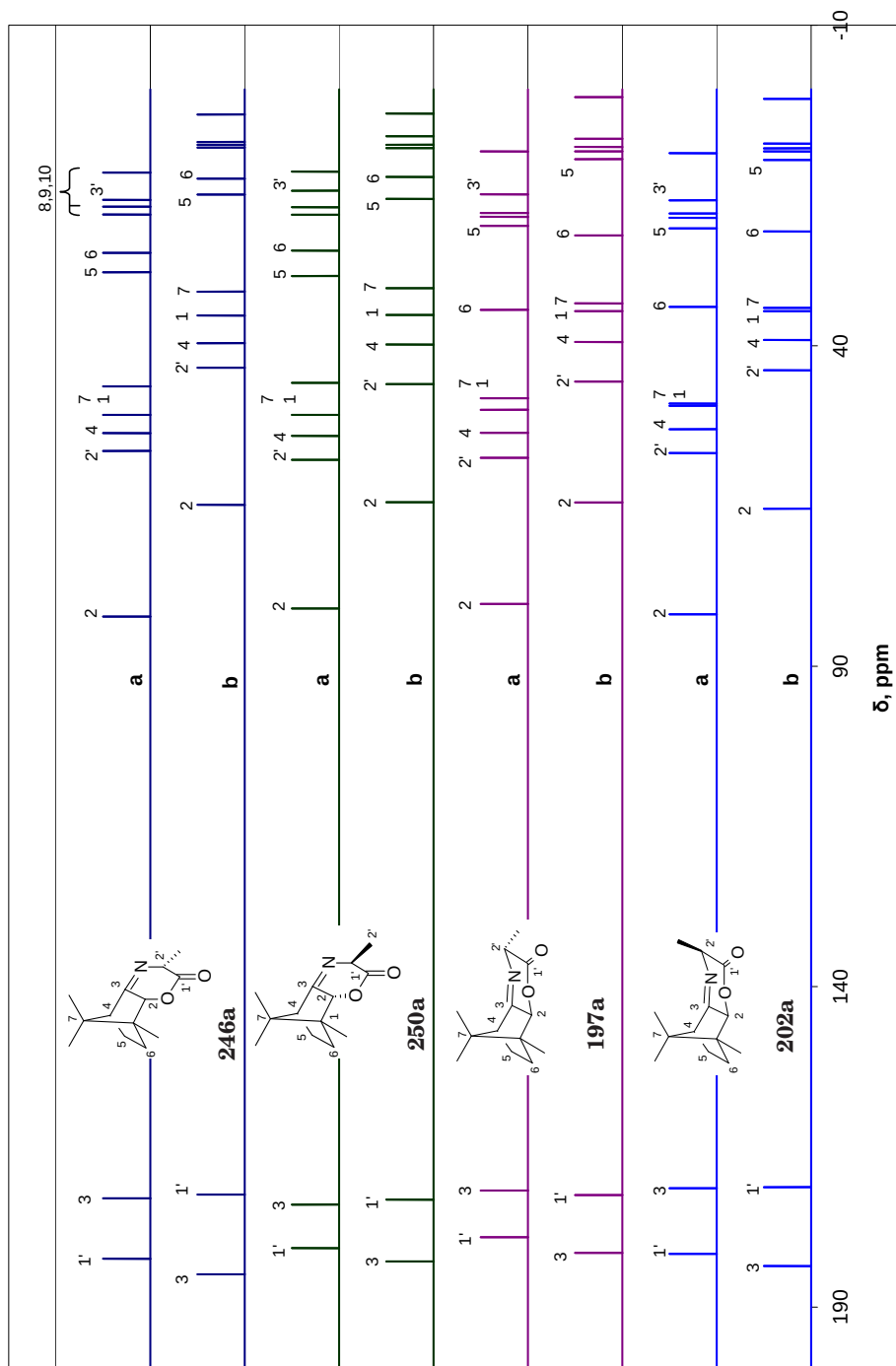
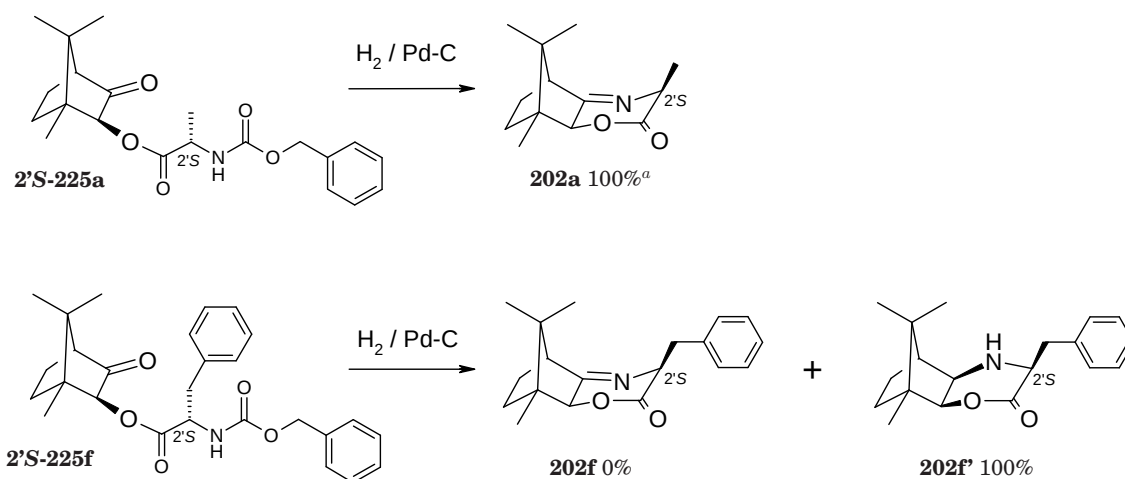


Figure 2.28: Comparison of (a) the experimental ^{13}C chemical shift data for the isomeric iminolactone derivatives **246**, **250**, **197** and **202** with (b) predicted values calculated using Gaussian '03 at the HF/6-311+g(2d,p) level.

The isolation of the (2*R*,2'*R*)-2'-methyliminolactone **246a** raises two interesting issues. Firstly, the fact that the reaction conditions were conducive to cyclization to afford at least some of the (2*R*)-product **246a** from its precursor but *none* of the (2*S*)-*exo*-iminolactone **197a** from its precursor suggests an energetic preference for the former over the latter. Secondly, the L-alanine-derived and L-phenylalanine-derived keto esters **225a** and **225f** have been found to readily undergo deprotection and cyclisation to produce the corresponding 2'-*exo*-alkylated systems **202a** and **202f** (Scheme 2.24). In the latter case, further reduction to the secondary amine **202f'** was observed. Figure 2.29 shows the 400MHz NMR spectra of the benzylated amine system **202f'** - of particular interest are the 2-H and 3-H doublets and the diastereotopic benzylic proton signals.



Scheme 2.24: Cyclizations affording the *exo*-systems. ^a Product as proportion of total cyclized content.

Cyclization of the various keto esters **225** (Scheme 2.26) clearly afforded a variety of products, the range depending, in each case, on the stereochemistry of the precursors. Thus, the keto esters **225a-h** derived from racemic and optically pure L-amino acids all gave the expected 2'-*exo*-alkyl iminolactones **202a-h**, while the two substrates **225e,f** containing the 2*S*,2'*R* system derived from racemic and optically pure D-amino acids also afforded the corresponding 2'-*endo*-alkyl analogues **197e,f** (in poor yield). The product **197a**, as indicated above, was not detected when the D- and DL-alanine substrates were used, due to the low yields expected and/or hydrolysis.

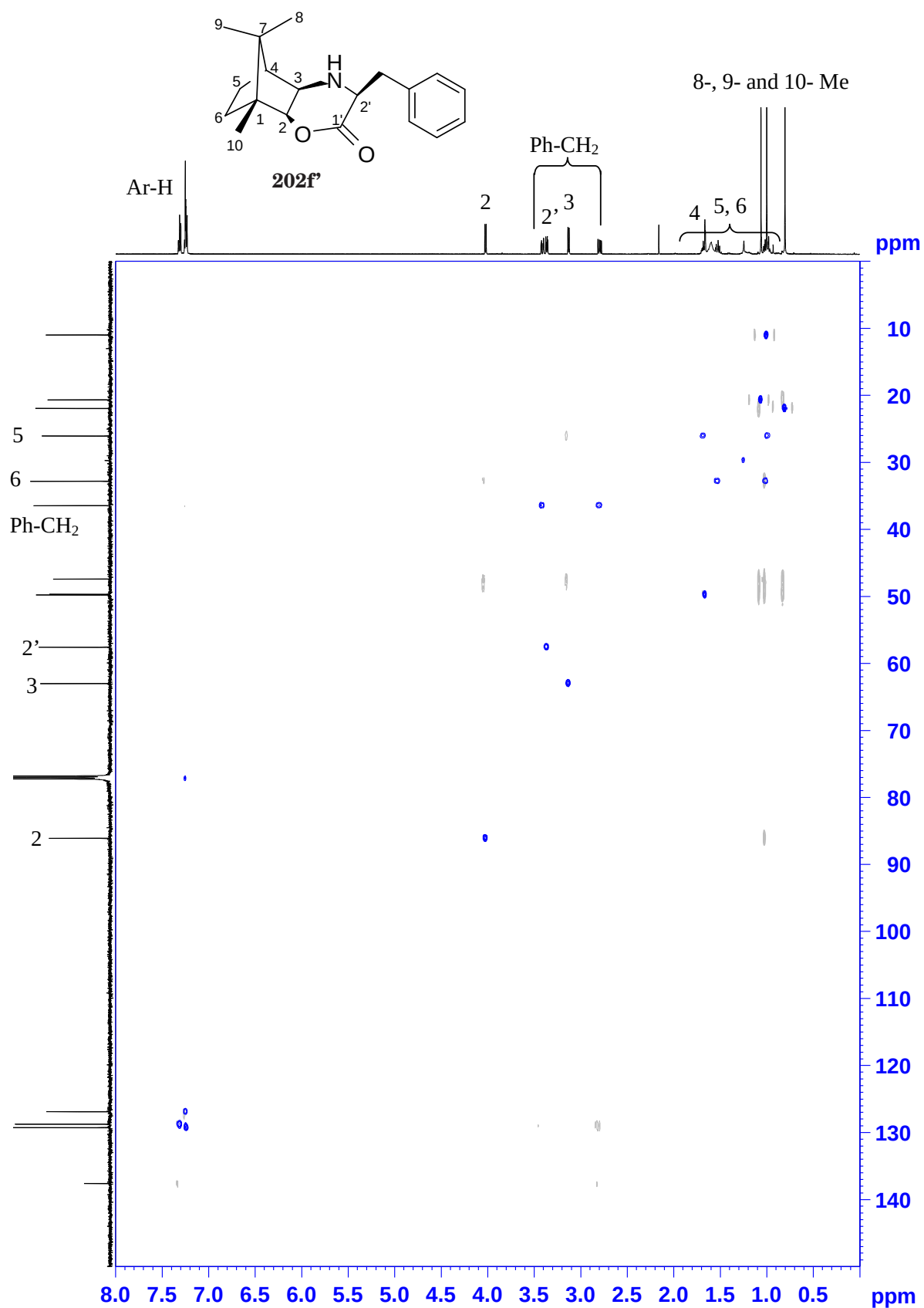
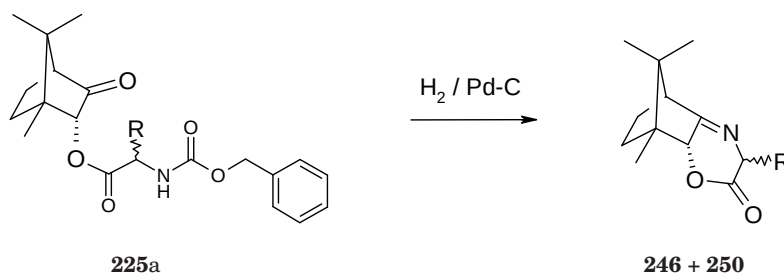
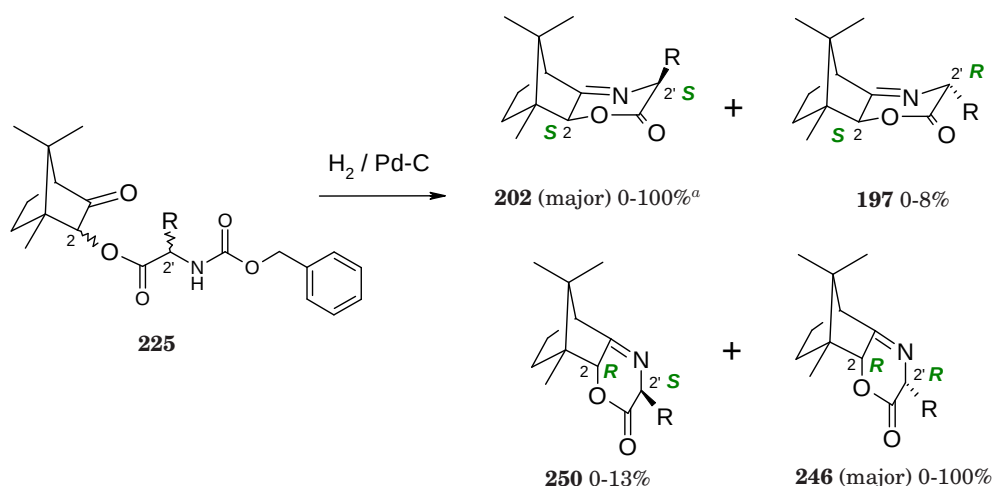


Figure 2.29: 400MHz HMQC (blue) and HMBC (grey) spectra for the amine **202f'** formed by further reduction of the iminolactone **202f** (Scheme 2.24) in CDCl₃.

The CBZ-*endo* ester isomers, present as inseparable impurities (the ratio carried forward from the reduction step is 89:11 (2*S*)-*exo*:(2*R*)-*endo*) in the CBZ-*exo*-ester material, were successfully cyclized under the conditions to the corresponding (2'*R*)-*endo*-alkyl iminolactones **246a-h** and **250a-h**; the only (2'*S*)-*exo*-alkyl analogues that were isolated (with some difficulty) were the D-alanine, D-valine, D-isoleucine and D-norleucine derivatives **250a,e,g,h** (see Table 2.7). The racemic systems **225k** and **225j** failed to provide products, this attributed to catalyst poisoning in the latter case and hydrolysis in the former as described earlier.



Scheme 2.25: Products of cyclizations of 2-*endo* ester systems.



Scheme 2.26: Products of cyclizations. ^a Product as proportion of total iminolactone content.

The chemical shifts of the 8-,9- and 10- methyl groups, and that of the 4-H nucleus on the camphor skeleton give a very good indication of the exact tricyclic structure in question. Alkyl substituents at position 2' (2'-*R* or *S*) have little effect on these chemical shifts, and give rise to recognizable motifs in the NMR spectra in the families of iminolactones. Figure 2.30 illustrates this for the three related systems **246a**, **246e** and **246h** where the three prominent methyl singlets and the 4-H doublet remain virtually unchanged from spectrum to spectrum.

Even using this approach we were still unable to find evidence for the formation of the

Table 2.7: Different groups, stereochemistry and distribution of products formed in the cyclization step. Percentage is as a proportion of desired products (HPLC estimation).

Ester system 225				Product distribution %			
225	R	Amino acid	2'	202 (2 <i>S</i> ,2' <i>S</i>)	197 (2 <i>S</i> ,2' <i>R</i>)	250 (2 <i>R</i> ,2' <i>S</i>)	246 (2 <i>R</i> ,2' <i>R</i>)
a	CH ₃	D-Ala	<i>R</i>	-	-	-	100%, 100%
a	CH ₃	L-Ala	<i>S</i>	100%	-	-	-
a ^a	CH ₃	DL-Ala	<i>RS</i>	31%, 42%	-	13%, 7%	56%, 51% ^e
e	(CH ₃) ₂ CH	DL-Val	<i>RS</i>	33%, 55%	3%, -	11%, -	53%, 45%
f ^a	Ph-CH ₂	D-Phe	<i>R</i>	-	8%	-	92%
f	Ph-CH ₂	L-Phe	<i>S</i>	100% ^b	-	-	- ^d
g	(CH ₃)(CH ₃ CH ₂)CH	DL-Ile	<i>RS</i>	41% ^b	-	4%	55% ^{b,c}
h	CH ₃ CH ₂ CH ₂ CH	DL-Nle	<i>RS</i>	23%	-	2%	75%
i	(CH ₃) ₂ CHCH ₂	DL-Leu	<i>RS</i>	- ^d	-	-	-
j	CH ₃ SCH ₂ CH ₂	DL-Met	<i>RS</i>	- ^f	-	-	-
k	HOCH ₂	DL-Ser	<i>RS</i>	na ^g	na	na	na

^a ¹H NMR estimation. ^bReduction of the imine to a secondary amine has occurred. ^cStereochemistry is assumed, not justified. ^dNot detected. ^eWhere two values are listed, these are the results of two separate experiments. ^fThe methionine-derived system did not react due to catalyst poisoning. ^g Not attempted.

D-alanine-derivative **197a** in the ¹H NMR spectra of the crude product mixture.

A point to note here is that the yields for the cyclization of the 2-(*R*)-*endo*-esters are greater than those of the 2-(*S*)-*exo*-analogues. Considering the unexpected resolution of products obtained from the cyclization, and due to time constraints, beneficiation studies on these products were not carried out.

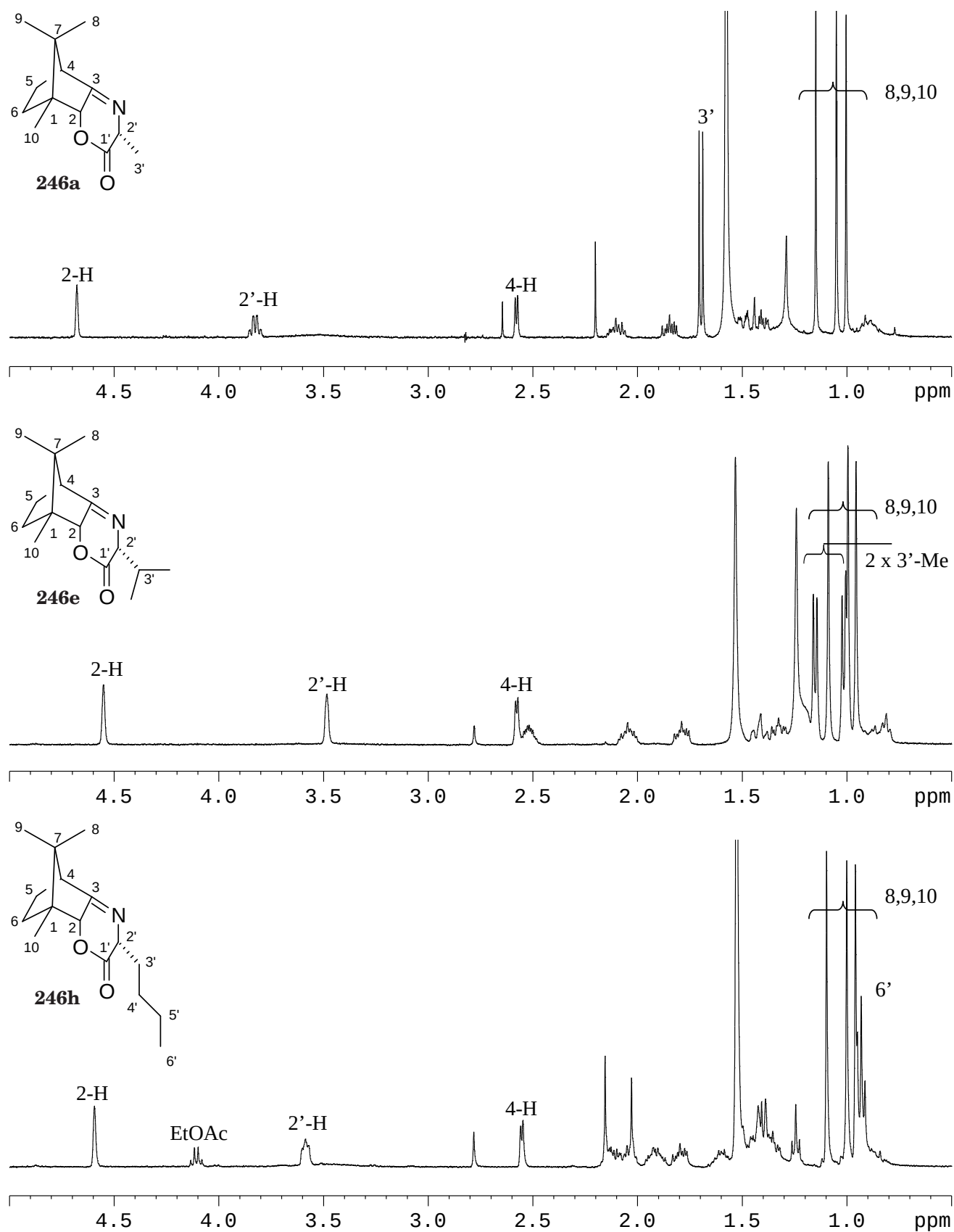
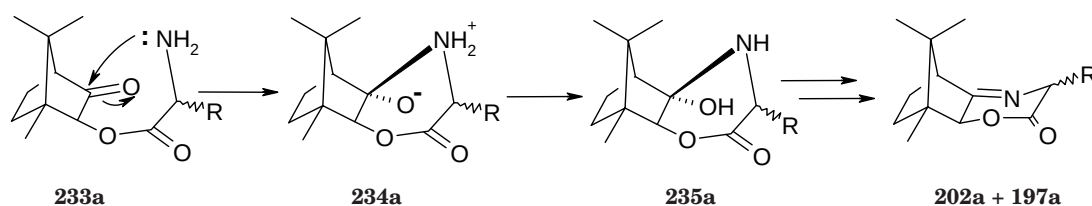


Figure 2.30: Comparison of the 400MHz ^1H NMR spectra of three $(2R)$ -iminolactone systems.

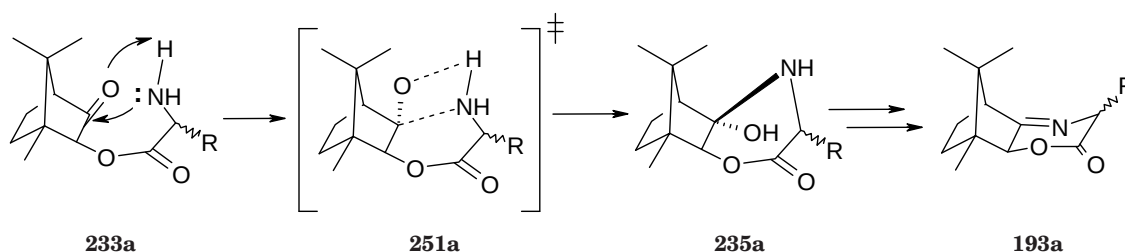
2.2.2.2 Rationalization of the reductive cyclization data

In order to elucidate the observed reactivity patterns, possible intermediates and products involved in the cyclization sequence of D- and L- alanine-derived systems were initially modelled according to Scheme 2.27. The rate-determining step was assumed to involve the cyclization step **233a** $\rightarrow$ **202a** (R = Me), but all attempts to model the zwitterion **234a** failed, geometry optimization leading to the amine precursor **233**.



Scheme 2.27: Cyclization sequence in the formation of the iminolactones **202a + 197a** (R = Me).

The approach was therefore changed and an attempt was made to model the reaction according to the transition state **251** (Scheme 2.28) – an approach which was to prove successful. In order to rationalize all the experimental data obtained for the various D- and L-alanine-derived iminolactones, all of the species shown in Scheme 2.29 were modelled and the corresponding transition states were located.



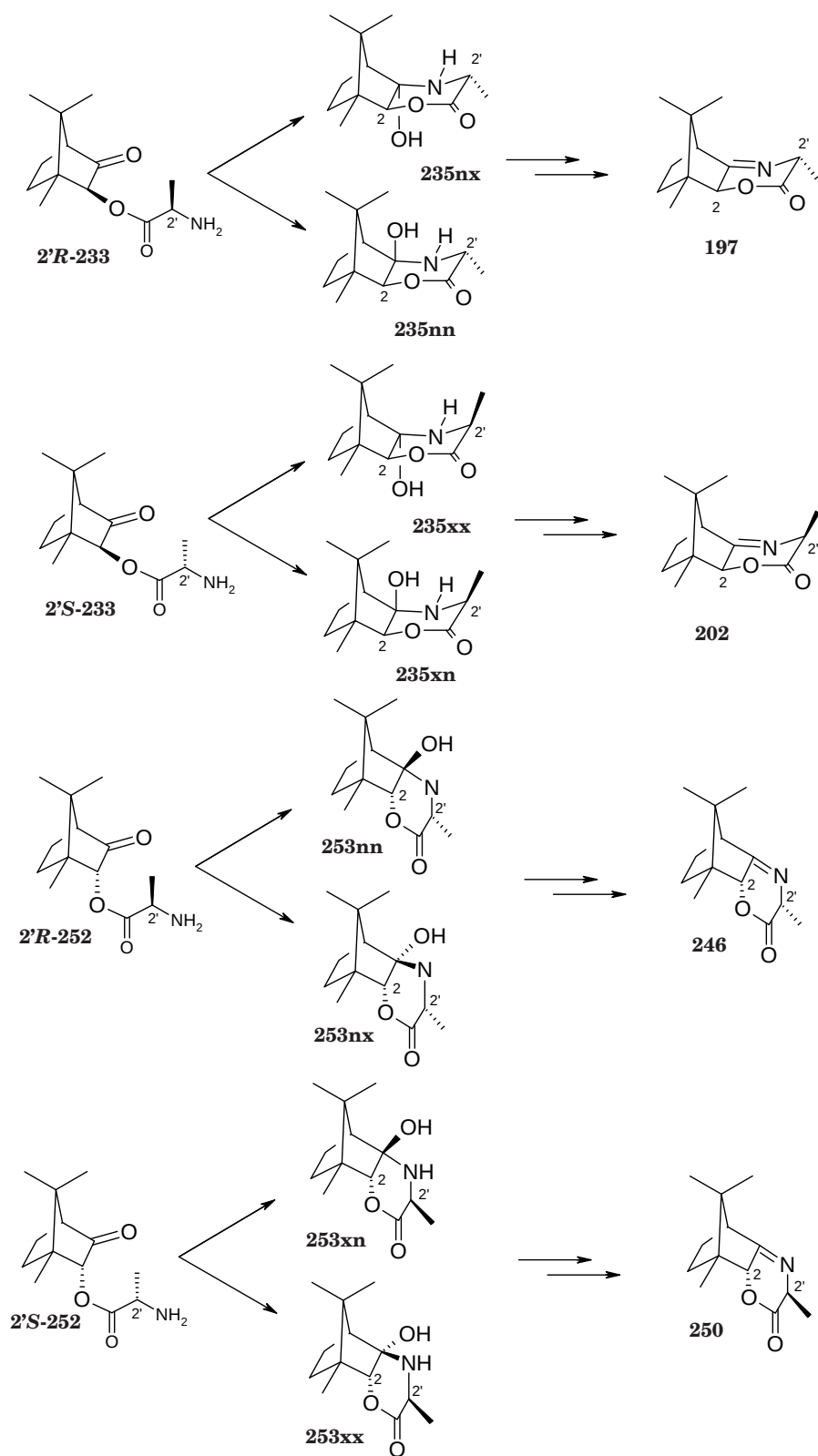
Scheme 2.28: Revised cyclization steps in the formation of the iminolactone **202a** (R = Me).

It was assumed, initially, that for the 2-*exo*-ester systems (2'*R*)-**233** and (2'*S*)-**233**, cyclization *via* *exo*-attack by the amino nitrogen at the 3-carbonyl group would be more favourable than 3-*endo*-attack. On the other hand, for the 2-*endo*-ester systems (2'*R*)-**252** and (2'*S*)-**252**, 3-*endo*-attack was assumed to be favoured. To complete the picture, all eight possible hemiaminal intermediates **235nx**- **253xx** were modelled. (The **n** and **x** refer to *endo* and *exo*, respectively; **nn** refers to *endo* stereocentres at both position 2 and 2', for example). The four iminolactones **197** - **250** were also modelled at the DFT level, using DMol³ and the results are summarized in Table 2.8. It is clear that for the *exo*-ester systems **235x**- and **253x**-, the

intermediates that form as a result of *exo*-attack at the carbonyl centre, in fact, are thermodynamically favoured (Table 2.8); similarly, *endo*-carbonyl attack is favoured in the *endo*-ester systems **253**, supporting the initial assumptions.

Table 2.8: Gas-phase DFT data for the hemiaminal intermediates (Scheme 2.29) involved in the formation of the methylated iminolactones **197,202,246** and **250** at 298.15K.

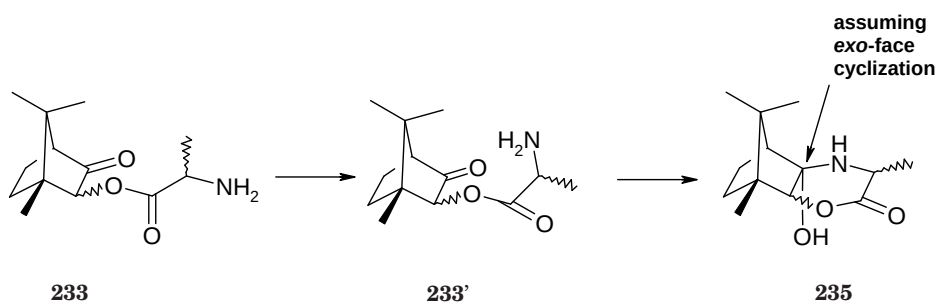
Entry	Molecule	Entropy S [cal/mol.K]	Enthalpy H [Ha]	Free Energy G [Ha]	Electronic Energy E [Ha]	$\Delta G_{rel,253nn}$ kcal.mol ⁻¹
1	235nn	124.455	-788.1037	-788.1628	-788.4442	16.3
2	235nx	124.573	-788.1244	-788.1836	-788.4648	3.2
3	235xn	121.151	-788.1071	-788.1646	-788.4463	15.1
4	235xx	125.120	-788.1274	-788.1869	-788.4687	1.1
5	253nn	122.717	-788.1304	-788.1887	-788.4714	0.0
6	253nx	120.652	-788.1103	-788.1676	-788.4518	13.2
7	253xn	122.564	-788.1265	-788.1848	-788.4680	2.4
8	253xx	121.700	-788.1081	-788.1659	-788.4498	14.3



Scheme 2.29: Modelling of the cyclization of alanine-based systems.

The influence of the 2-proton even in “favourable” situations is illustrated in the geometries of the transition states for cyclization, where transposition of a 2'-*exo*- and 2'-*endo*-substituent consistently changes the geometry dependent on the size of the substituent.

Transition states for the cyclization of each of the imino-ester precursors **233** or **252** were located using the complete Linear Synchronous Transit/Quadratic Synchronous Transit (LST/QST) search implemented in DMol³. Since cyclization involves an initial conformational change (*e.g.* **233** → **233'**; Scheme 2.30) to orientate the nucleophilic amino group appropriately for attack at the electrophilic carbonyl centre, the geometry-optimized uncyclized structures **233** are not good starting structures for the LST/QST method. In some cases a constrained system was used to locate the amino group appropriately relative to the carbonyl group. Regardless of the starting material and product structures, the geometry about the reaction centre in the transition state complex was essentially the same in all cases (Figures 2.31 and 2.32). Transition state confirmations conducted on selected systems verified their identity as the correct transition state between the corresponding amino ketone **233'** and hemi-aminal **235**. The free energy diagram for the cyclization of **2'S-233** is illustrated in Figure 2.31.



Scheme 2.30: Conformational change required for cyclization of the amino ester precursors **233** or **252** to occur.

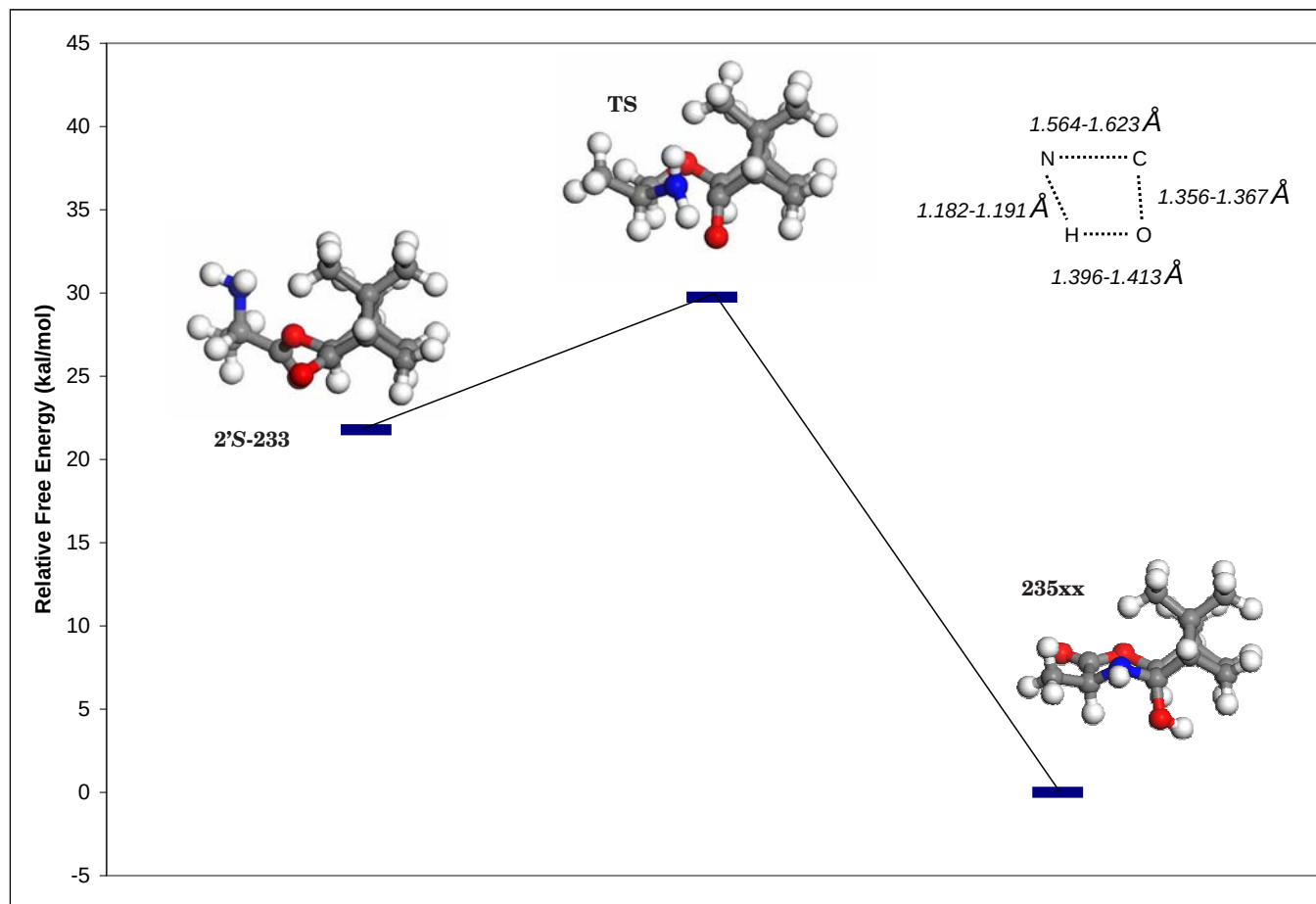


Figure 2.31: Free energy diagram for cyclization of the amino ketone **2'S-233** to the hemi-aminal **235xx**. Transition state dimensions in italics refer to the ranges obtained for transition states of cyclization of **2'S-233**, **2'R-233**, **2'S-252** and **2'R-252**.

Table 2.9: Gas-phase DFT data for the transition states of cyclization step **233** → **235** and **252** → **253** at 298.15K.

Entry	Molecule	Entropy S [cal/mol.K]	Enthalpy H [Ha]	Free Energy G [Ha]	Electronic Energy E [Ha]	$\Delta G^\ddagger$ kcal.mol ⁻¹
1	235nn	121.918	-788.0553	-788.1132	-788.3910	24.5
2	235nx	123.925	-788.0790	-788.1379	-788.4144	9.0
3	235xn	121.290	-788.0601	-788.1177	-788.3960	21.6
4	235xx	121.085	-788.0820	-788.1395	-788.4182	8.0
5	253nn	122.431	-788.0831	-788.1413	-788.4193	8.5
6	253nx	119.402	-788.0628	-788.1195	-788.3993	22.2
7	253xn	122.666	-788.0799	-788.1382	-788.4158	10.5
8	253xx	122.661	-788.0587	-788.1170	-788.3939	23.8

The activation energies for the transition states (Table 2.9) match the thermodynamic stabilities of the hemi-aminal intermediates (Table 2.8) *i.e.* the formation **253nn** is favoured kinetically *and* thermodynamically over **253xn**. Similarly, the formation of **235xx** is favoured over **235nx**. This is in accordance with the experimental distribution of products (Table 2.7). The reason for this appears to be steric. The 2-H will interact sterically with any *cis*-located 2'-alkyl group. Changing the 2'-stereochemistry so that the alkyl group is *trans* to the 2-H atom eases this interaction considerably (Figure 2.32). A comparison of the energies of the isomeric products (Table 2.10) suggests that **246** is favoured slightly over **250**, while the 2-*exo*-2'-*exo* product **202** is favoured slightly over the 2'-*endo*-analog **197**.

Table 2.10: Computational data for iminolactone products **197**, **202**, **246** and **250** at 298.15K.

Molecule	Entropy S [cal/mol.K]	Enthalpy H [Ha]	Free Energy G [Ha]	Electronic Energy E [Ha]	$G_{exo}-G_{endo}$ [kcal/mol]
197	116.566	-711.7073	-711.7627	-712.0206	-
202	120.741	-711.7107	-711.7681	-712.0222	-3.42
246	118.104	-711.7119	-711.7680	-712.0240	-
250	118.247	-711.7097	-711.7659	-712.0223	+1.33

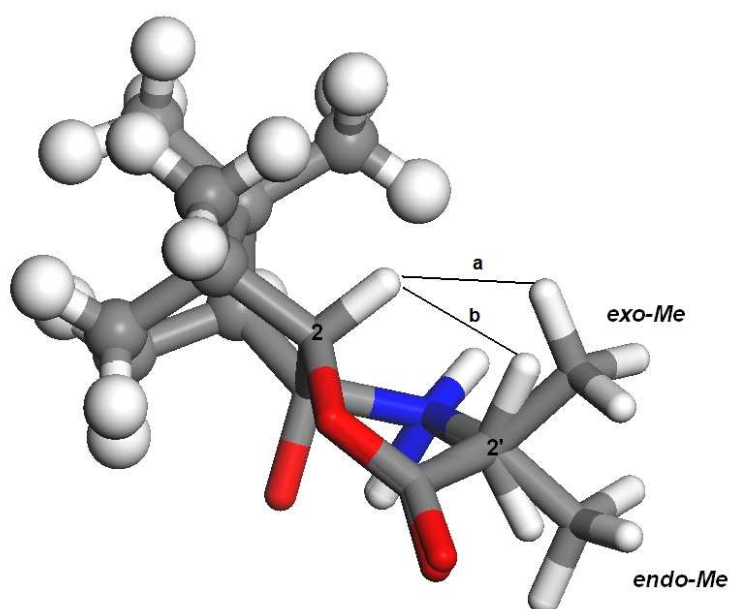


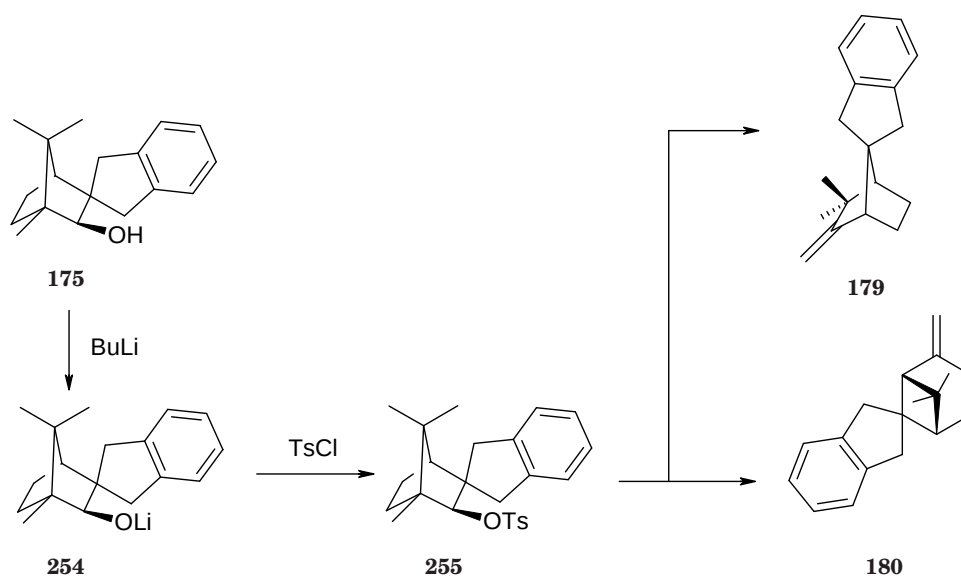
Figure 2.32: Superimposed transition state structures **253xx** and **253nx** illustrating the difference in conformation at position 2' as a result of the severe diaxial interaction **a** with 2-H in the 2'-*exo*-Me case, as compared with the interaction **b** in the 2'-*endo*-Me ($a = 2.69\text{\AA}$ $b = 2.88\text{\AA}$).

2.3 Rearrangements of spiroterpenoid systems

Our initial aims in studying the spiroterpenoid system were to establish the conditions that would permit the chemoselective production of either the camphenyl system **179** or the pinenyl system **180** (Scheme 1.38, Scheme 2.31), and to investigate the kinetics of these transformations. Our initial understanding was that the formation of the pinenyl system **180** was kinetically favoured, while that of the camphenyl system **179** was thermodynamically favoured.

2.3.1 Synthesis of *exo*- and *endo*-tosyl spirocamphor systems

In order to determine at what stage (in the overall transformation) rearrangement actually begins, attempts were made to decrease the rate of tosylation of the *exo*-alcohol **175** (Scheme 2.31), and thus permit the tosylation/rearrangement sequence to be followed. In one approach, 1,8-*bis*-(dimethylamino)naphthalene (Proton Sponge[®]) was used as the base instead of butyllithium to abstract the hydroxylic proton, but the rate was too slow and, even after 12 hours, the reaction had made little progress.

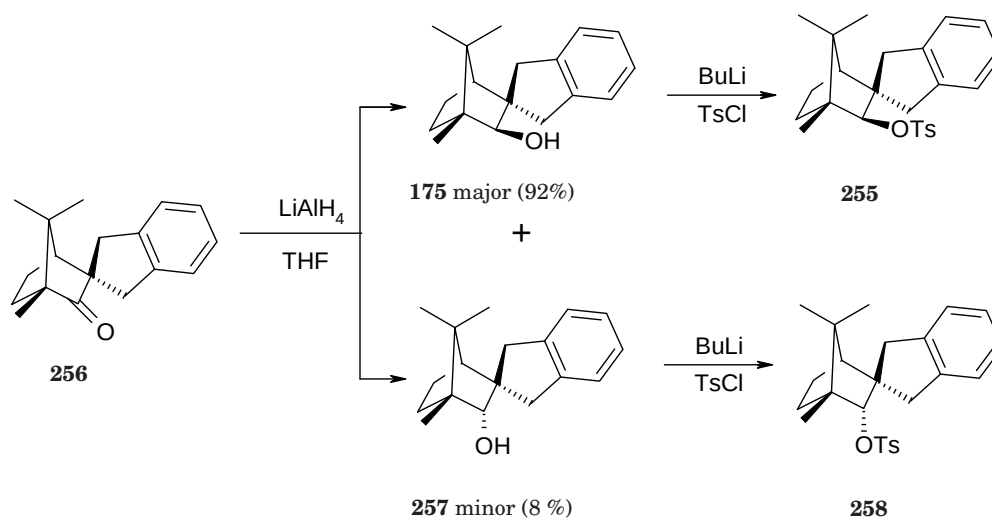


Scheme 2.31: Synthesis and reported rearrangement^{156,176} of the *exo*-tosylate **255**.

In the event, it proved possible to form and isolate the tosylate product **255** at 0 °C, and then monitor its decomposition and the formation of the products **179** and **180** over time. Work-up of the tosylation reaction (**175** $\rightarrow$ **255**) and evaporation of the ethyl acetate extracts at 0 °C afforded material which crystallized readily. NMR analysis revealed, unexpectedly, that the crystalline product was, in fact, the *exo*-tosylate **255** that Evans¹⁵⁶ had unsuccessfully

attempted to produce. The HMQC NMR spectrum, obtained at 0 °C (Figure 2.33), confirmed the presence of the tosyl moiety and, in particular, the 2-*endo*-methine proton - evidenced by the ^1H -signal at δ 4.3ppm. This singlet proved to be an ideal probe to monitor the subsequent transformations.

After further work, the isomeric *endo*-tosylate **258** was also isolated; 2-D NMR spectra for this compound are illustrated in Figure 2.34. In this case, the 2-*exo*-methine singlet appears marginally downfield (at δ 4.7ppm) of the 2-*endo*-methine signal in the isomeric system **255**. Interestingly, during the transformation of the *exo*-tosylate **255** to various terpenoid products the *endo*-isomer **258** remains unchanged and can be separated by flash chromatography. The formation of the *endo*-isomer **258** is attributed to a measure of *exo*-hydride delivery during the LAH reduction of the ketone **256** (Scheme 2.32) – a conclusion supported by the isolation of the *endo*-alcohol **257** by repeated chromatography of the reduction products.



Scheme 2.32: Formation of the *exo*- and *endo*-tosylates **255** and **258**.

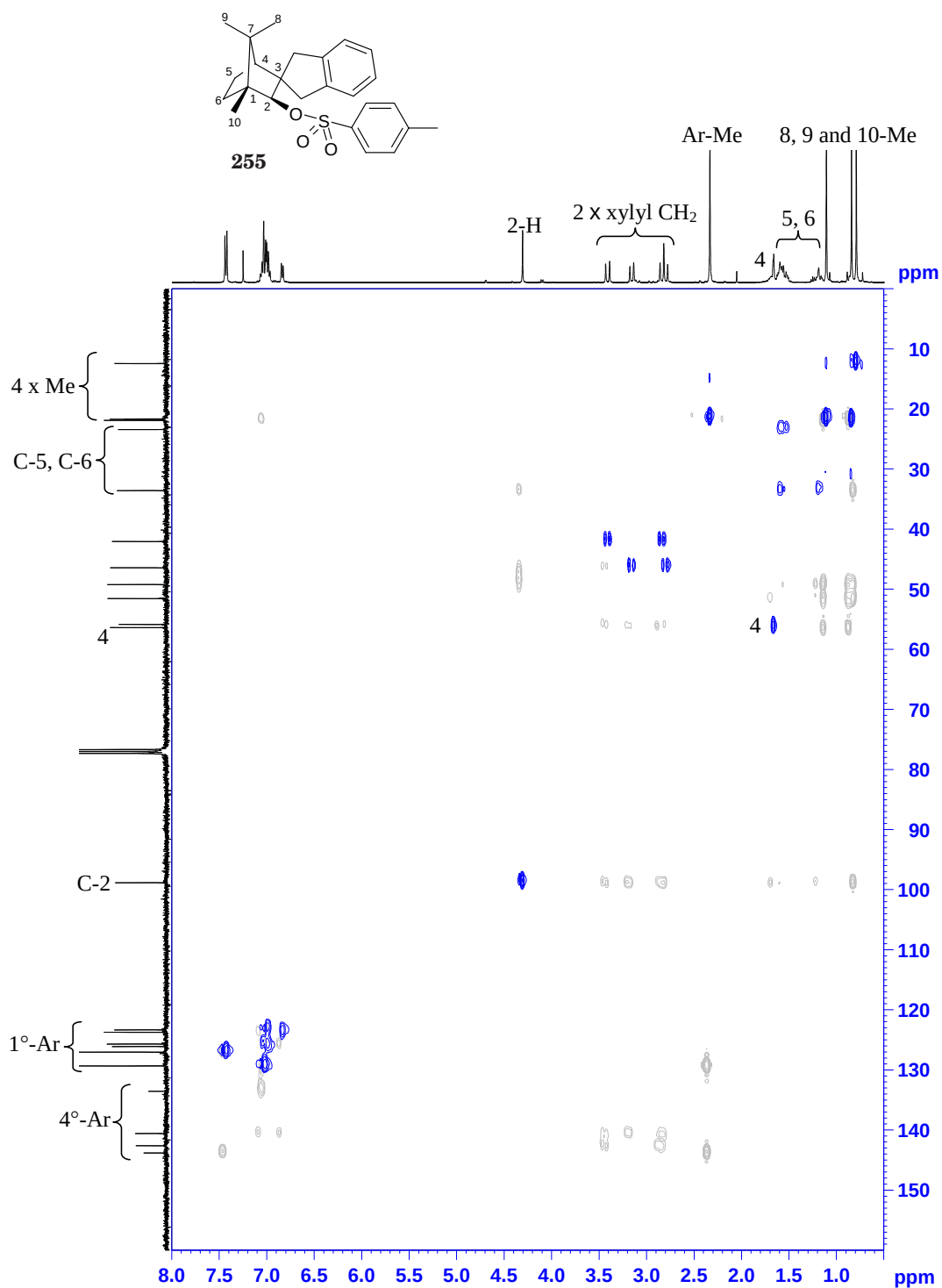


Figure 2.33: 400MHz HMQC (blue) and HMBC (grey) spectra of the *exo*-tosylate **255** in CDCl₃, obtained at 0°C.

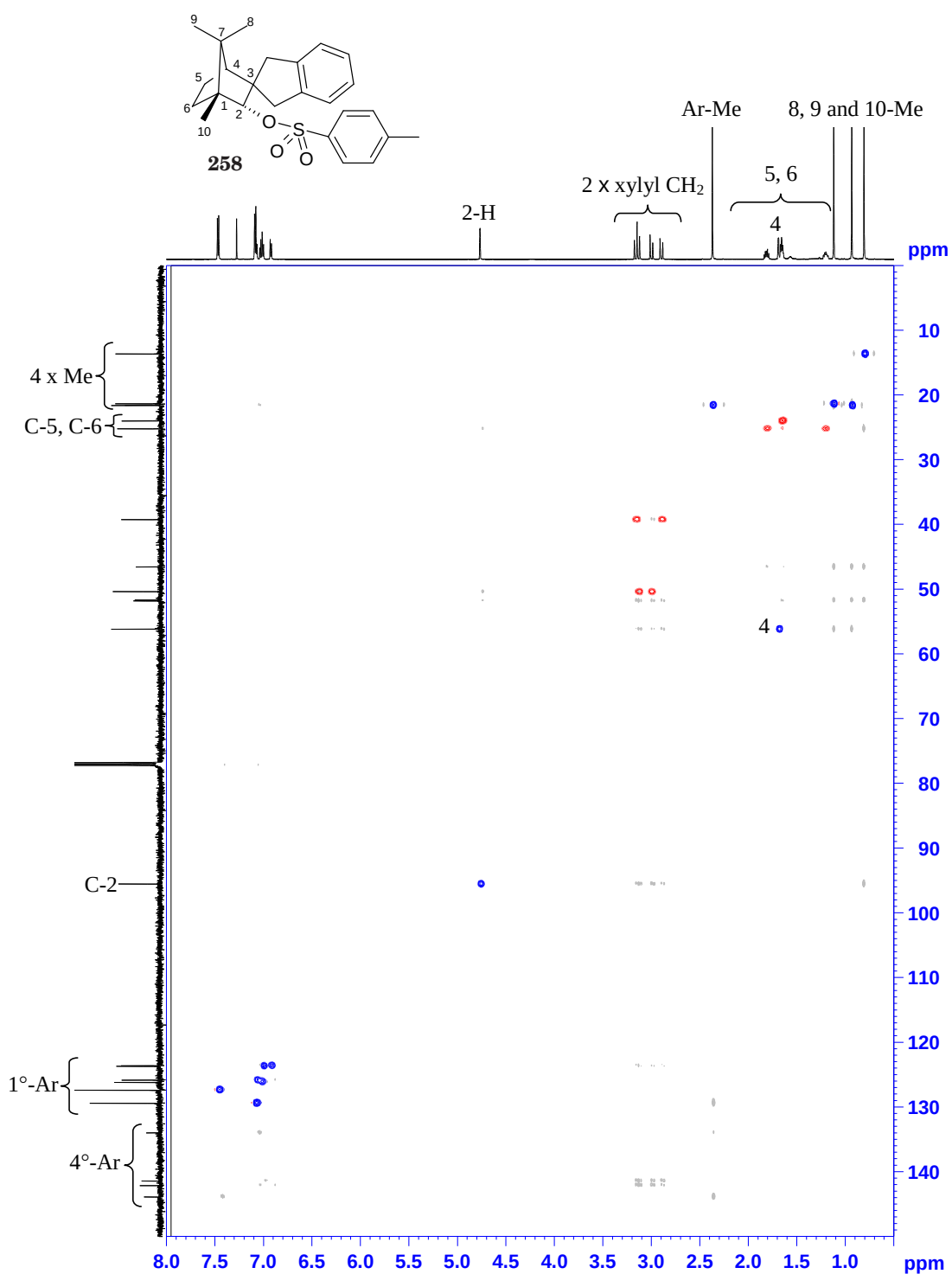
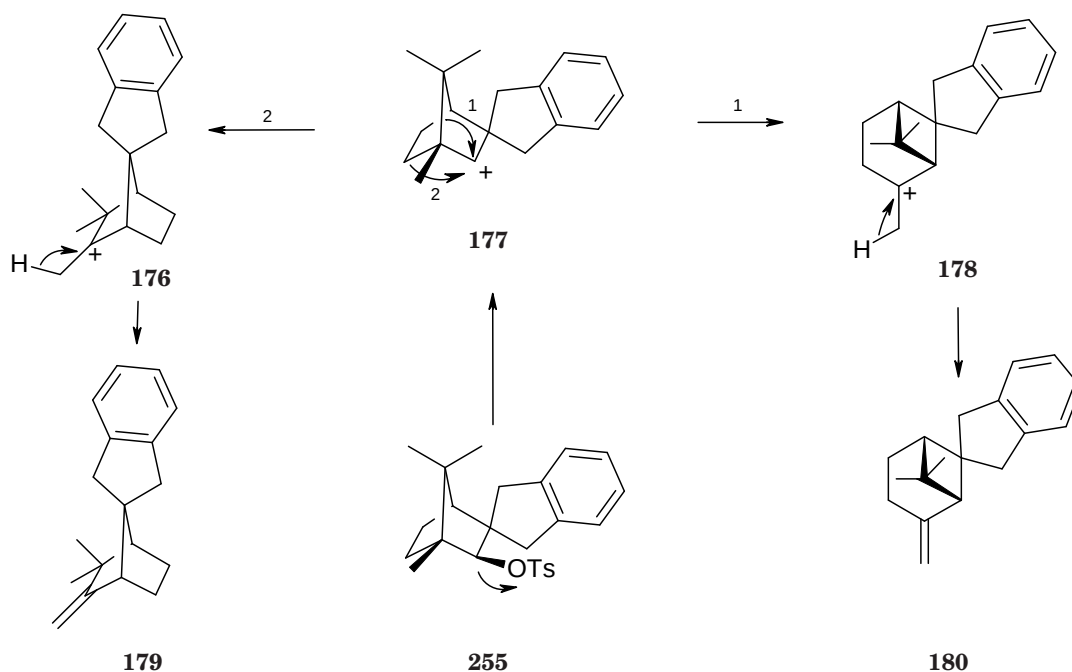


Figure 2.34: 600MHz Multiplicity edited HSQC (red and blue) and HMBC (grey) NMR data for the *endo*-tosylate **258** in CDCl₃ at 24°C.

2.3.2 Decomposition of the tosyl spirocamphor systems

While the *exo*-tosylate **255** could be isolated and characterised, it became apparent that, with time at room temperature, it rearranged not, as expected, to the pinenyl system **180** but, directly to the camphenyl system **179**! The transformation to the pinenyl system occurs subsequently. ^{13}C NMR analysis of the decomposing *exo*-tosylate **255** confirmed the role of the camphenyl system **179** as an intermediate in a subsequent rearrangement. The *endo*-tosylate **258**, unlike its *exo*-analogue **255** is stable, even under refluxing THF (b.p. 66°C) for 1h. The fact that the *endo*-derivative **258** is more stable than the *exo*-derivative **255** is consistent with literature reports on the relative stability of *exo*- and *endo*-tosylates of norbornyl type systems.⁸²

It was initially assumed that the rearrangements proceeded *via* the secondary carbocation **177** formed by the loss of the tosylate anion from the *exo*-tosylate **255**, but preliminary *ab initio* computational studies of putative cationic intermediates provided more questions than answers. Hartree-Fock calculations (GAMESS) using the STO-2G basis set, gave some indication of the relative stability of the expected cationic intermediates and transition states, and the preliminary results are summarized in Figure 2.35.



Scheme 2.33: Initial proposal for the rearrangements of a spiroterpenoid system **255**.¹⁵⁶

The high relative energy of the pinenyl cation **178** (and its deprotonated product **180**),

attributed, largely, to the highly strained cyclobutyl system, posed serious questions. Why would the less stable pinenyl product **180** be formed *after* the more stable camphenyl product **179** and, further, why is the pinenyl product **180** formed *via* a *less stable* transition state (**TS II**) at 0°C , while the camphenyl product is formed *via* a *more stable* transition state (**TS I**) *under reflux*?! Transition state searches failed to afford any transition state or common intermediate (save the starting cation) linking the initially formed camphene **179** and the subsequently formed pinene product **180**.

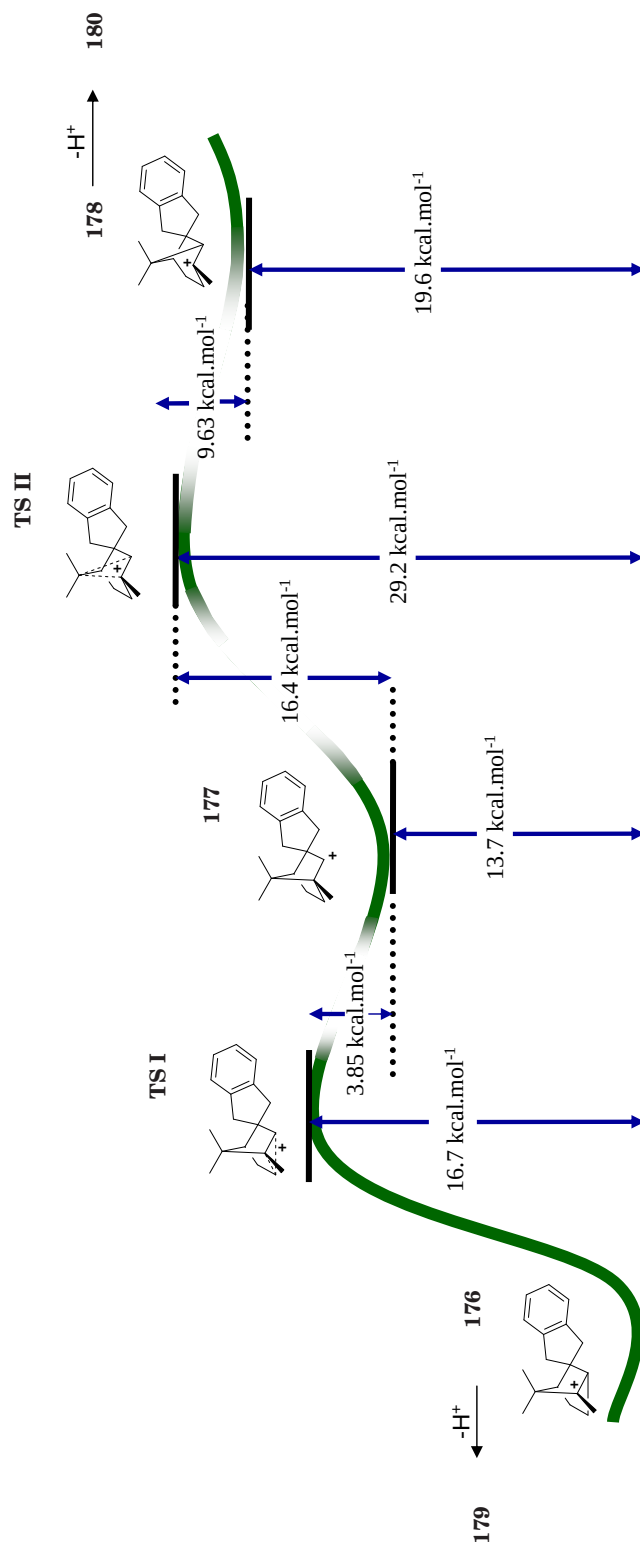
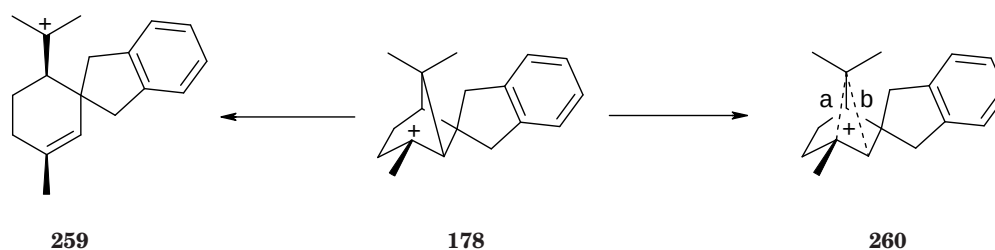


Figure 2.35: Preliminary modelling of putative cations and transition states corresponding to Scheme 2.33, at the RHF/STO-2G level. Electronic energies are quoted in kcal.mol⁻¹ relative to cation **176**.

It is apparent from the literature that the formation of fused cyclobutyl-type systems is not an easy task, and pinene-like compounds tend to undergo ring-enlargement or ring-opening extremely easily.¹⁷⁷ Cyclobutane systems are best formed *via* ring enlargement of cyclopropane systems,^{178,179} pericyclic type reactions¹⁸⁰ and biosynthetically,¹⁸¹ but not under the strongly acidic conditions necessary for cation rearrangement. Moreover, the cyclobutyl system in the pinenyl system **180** is not just strained from a four-membered ring point of view, but also as a result of being highly substituted. Higher level *ab initio* studies of the system (which were undertaken much later in the project), gave a clear indication of the extent of the strain. At the Hartree-Fock 6-31G(d) level, the pinenyl cation **178** undergoes ring-opening to the limonyl cation **259** (Scheme 2.34). The minimization profile for this rearrangement does not show a clear downward trend, suggesting that ring-opening may have resulted from the choice of the step size at each stage in the minimization (the limonyl product **259** is, nevertheless, energetically favourable as a product). However, with larger basis sets [*e.g.* 6-311G(d,p)], the non-classical pinenyl structure **260** was located. This cation is unusual as far as non-classical carbocations go, since its existence is not due to traditional non-classical stabilisation, but from a balance between :- i) resistance to rearrangement to a less stable secondary carbocation, and ii) steric forces driving enlargement to a 5-membered ring. The choice was eventually made to continue work at the B3LYP/6-31G(d) level, since the resulting geometries were the same as those obtained using the higher basis set [6-311G(d,p)].



Scheme 2.34: Structures formed from *ab initio* studies on the pinenyl cation **178**.

The calculated energy values of the relevant cations and molecules are detailed in Tables 2.11 and 2.12. It is important to note that structure **177** does not correspond to a stationary point - an issue that will be addressed later. The only non-classical carbocation observed corresponds to the pinenyl cation **260**.

The inclusion of the second camphenyl cation **261** and the associated camphene II **263** in these tables needs to be explained. The questions raised from the NMR and the initial modelling data prompted a re-examination of the experimentally-based structure assignments

Table 2.11: GAMESS HF and DFT energy data for the modelled cations relative to the most stable carbocation **261**.

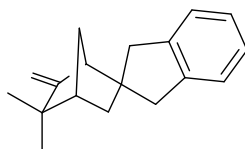
Cation	Ref	HF/6-311G(d)	B3LYP/6-31G(d)			
		ΔE_f [kcal.mol ⁻¹]	ΔE_f [kcal.mol ⁻¹]	$S_{298.15}$ [cal mol ⁻¹ K ⁻¹]	$\Delta H_{298.15}$ [kcal.mol ⁻¹]	$\Delta G_{298.15}$ [kcal.mol ⁻¹]
original ^a	177	3.04	3.95	-	-	-
limonyl	259	6.83	6.70	127.836	4.96	3.26
pinenyl	260	18.47	14.77	124.418	14.50	13.81
camphenyl 1	176	3.04	4.12	121.844	3.77	3.83
camphenyl 2	261	0.00	0.00	122.166	0.00	0.00

^a **177** rearranges *in silico* to **176**.

Table 2.12: GAMESS HF and DFT energetic data for the modelled possible products relative to the most stable system **263**.

Molecule	Ref	HF/6-311G(d)	B3LYP/6-31G(d)			
		ΔE_f [kcal.mol ⁻¹]	ΔE_f [kcal.mol ⁻¹]	$S_{298.15}$ cal mol ⁻¹ K ⁻¹	$\Delta H_{298.15}$ [kcal.mol ⁻¹]	$\Delta G_{298.15}$ [kcal.mol ⁻¹]
pinene	180	21.46	18.64	120.411	19.08	19.20
camphene 1	179	3.82	3.44	118.821	3.89	4.46
camphene 2	263	0.00	0.00	120.769	0.00	0.00
limonene	262	2.99	2.91	126.439	2.91	0.94

for the isolated rearrangement products. Suitable crystals were obtained for x-ray crystallographic analysis, despite the relatively low melting points of both compounds. The resulting x-ray data provided a mixture of fortunes! Firstly, the camphene I structure **179**, as originally assigned,¹⁷⁶ is indeed correct (Figure 2.36). Secondly, it was apparent that the pinenyl structure **260**, originally assigned on the basis of the NMR data,¹⁷⁶ was incorrect; the compound was, in fact, the isomeric camphene II system **263** (Figures 2.37 and 2.38).

**263**

Surprisingly, the x-ray data revealed that the camphene II **263** was actually racemic, with the unit cell containing four molecules – two of each enantiomer (Figure 2.38)! The sample of crystals from which the crystal was obtained for x-ray crystal analysis was shown to be pure by NMR spectroscopy, but polarimetric analysis revealed residual optical activity. Mechanistically, the pathway (**255** → **263**) to both enantiomers from the optically pure [D-(+)-camphor-derived] tosylate **255** was not immediately obvious. The residual optical activity indicated

that the formation of one enantiomer was favoured over the other and, unfortunately, in view of the partial racemization of the camphene II **263**, its intended use to produce chiral reagents was no longer possible.

The electronic- and free-energy data (Table 2.12) clearly indicate that camphene II **263** is more stable than the camphene I **179**, and the theoretical results now fit the experimental observations (Scheme 2.35 shows the sequence; the energetics are apparent from the above Tables 2.12 and 2.11, and illustrated later in the thesis in the free-energy profile Figure 2.101).

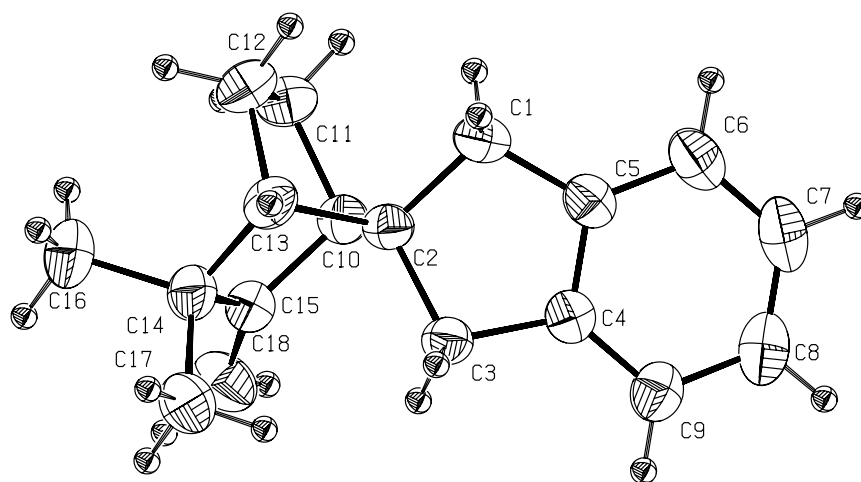


Figure 2.36: Crystal structure of camphene I **179** showing the crystallographic numbering. Thermal ellipsoids are at the 50% probability level.

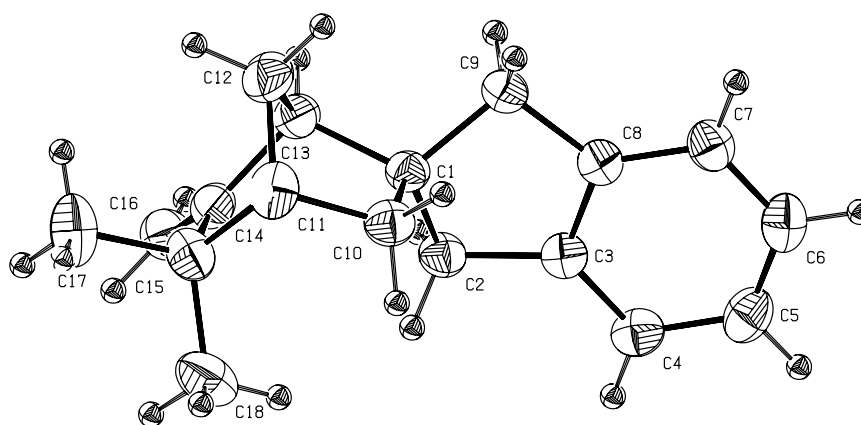


Figure 2.37: Crystal structure of a single enantiomer of camphene II **263** showing the crystallographic numbering. Thermal ellipsoids are at the 50% probability level.

While the original interpretation of the NMR data is consistent with the pinene structure **180** and its formation *via* a Wagner-Meerwein rearrangement of cation **177** is entirely logical, the theoretical and x-ray crystallographic data clearly required a revision of the NMR assign-

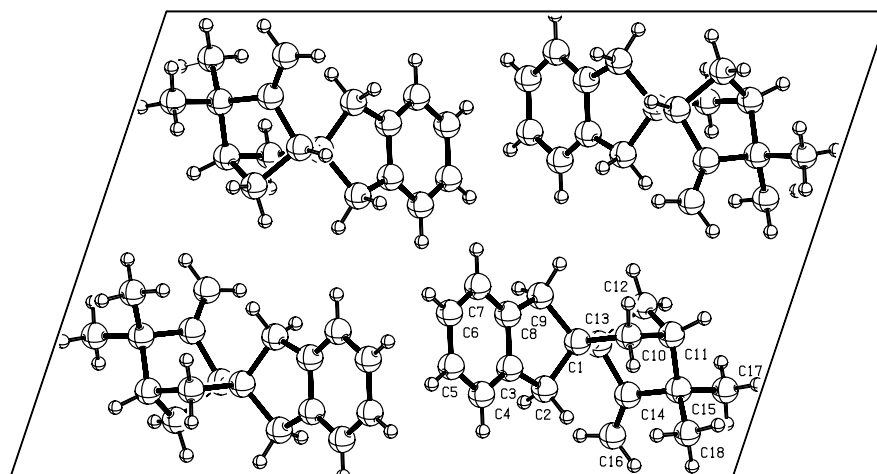
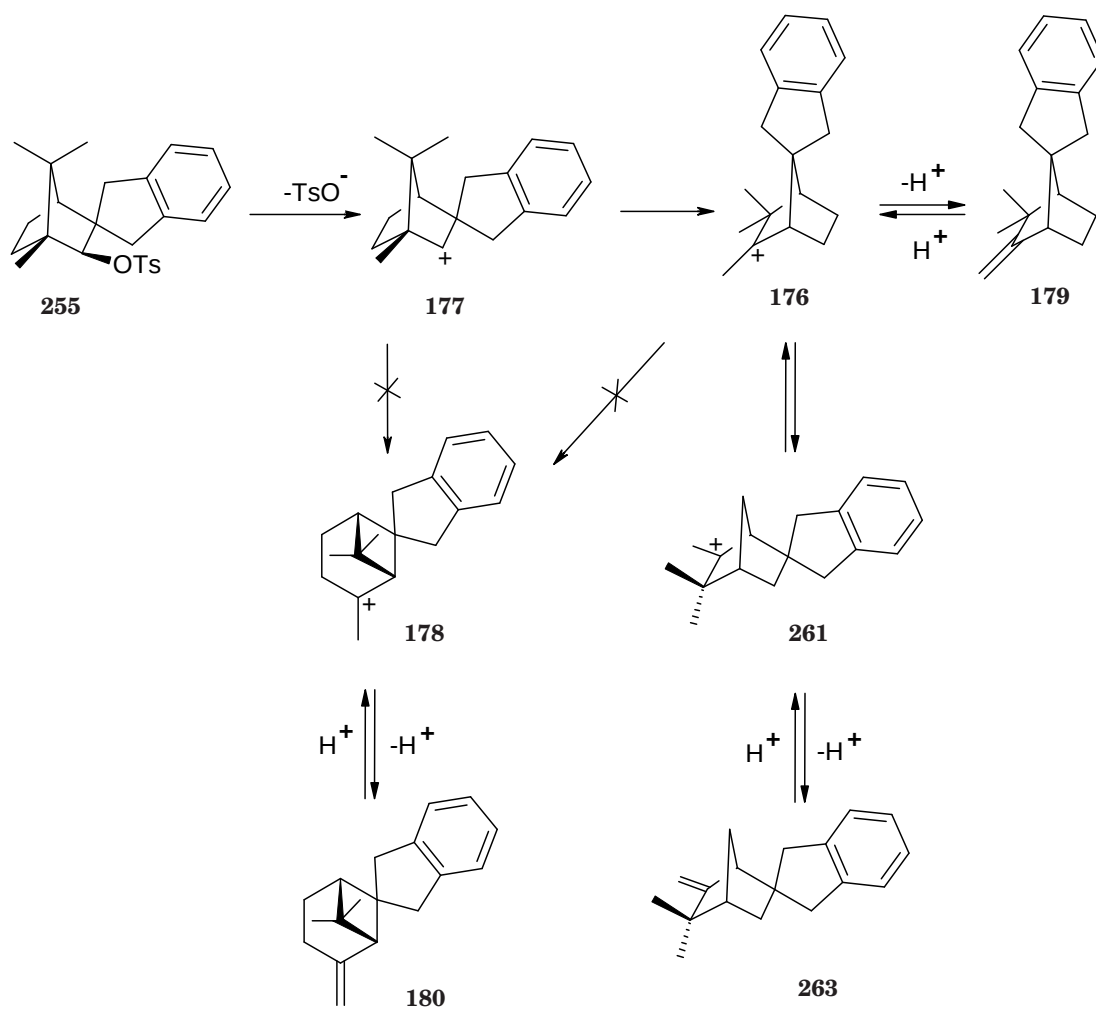


Figure 2.38: Enantiomeric molecules in the unit cell of crystals of camphene II **263**.

ments.¹⁸² The NMR spectra for the re-assigned structure **263** is shown in Figure 2.39 (the data for the camphene I is shown in Figure 2.40 for comparison). In the NMR, differences in the vinylic signals, and in the pattern of the xylyl methylene signals, for the two systems are apparent. The ionization/rearrangement sequence as we now understand it is shown in Scheme 2.35. This scheme makes sense energetically since there is a clear transition from an initial, less stable cation **177** to a more stable kinetically favoured intermediate **176** and its corresponding product **179** and, finally, to an even more stable thermodynamically favoured intermediate **261** and its corresponding product **263**.

What remains to be explained, however, is why the more stable camphene II **263** is obtained following immediate work-up of the tosylation reaction at 0°C (Scheme 2.35), whereas the less stable camphene I **179** is obtained after reflux in THF for 1h. The reason is, in fact, simple since work-up of both reactions includes washing with saturated aqueous NaHCO₃ solution. Thus, immediate work-up of the reaction at 0° affords the tosylate **255**. Washing removes any excess tosic acid but, upon drying, the tosylate **255** decomposes to give the camphene I **179** and tosic acid, the latter providing an acidic environment that catalyses rearrangement of the camphene I **179** to the thermodynamically favoured camphene II **263**. However, in reactions conducted under reflux, complete dissociation of the tosylate to tosic acid and the camphene I product **179** occurs in relatively dilute solution. The dilute tosic acid does not effect rapid transformation to the camphene II **263**, and washing during work-up removes the tosic acid, which might otherwise catalyse further transformation.



Scheme 2.35: Revised scheme for the rearrangements of a spiroterpenoid system in terms of the products **179** and **179** identified by crystal structures. The system **180** is not observed.

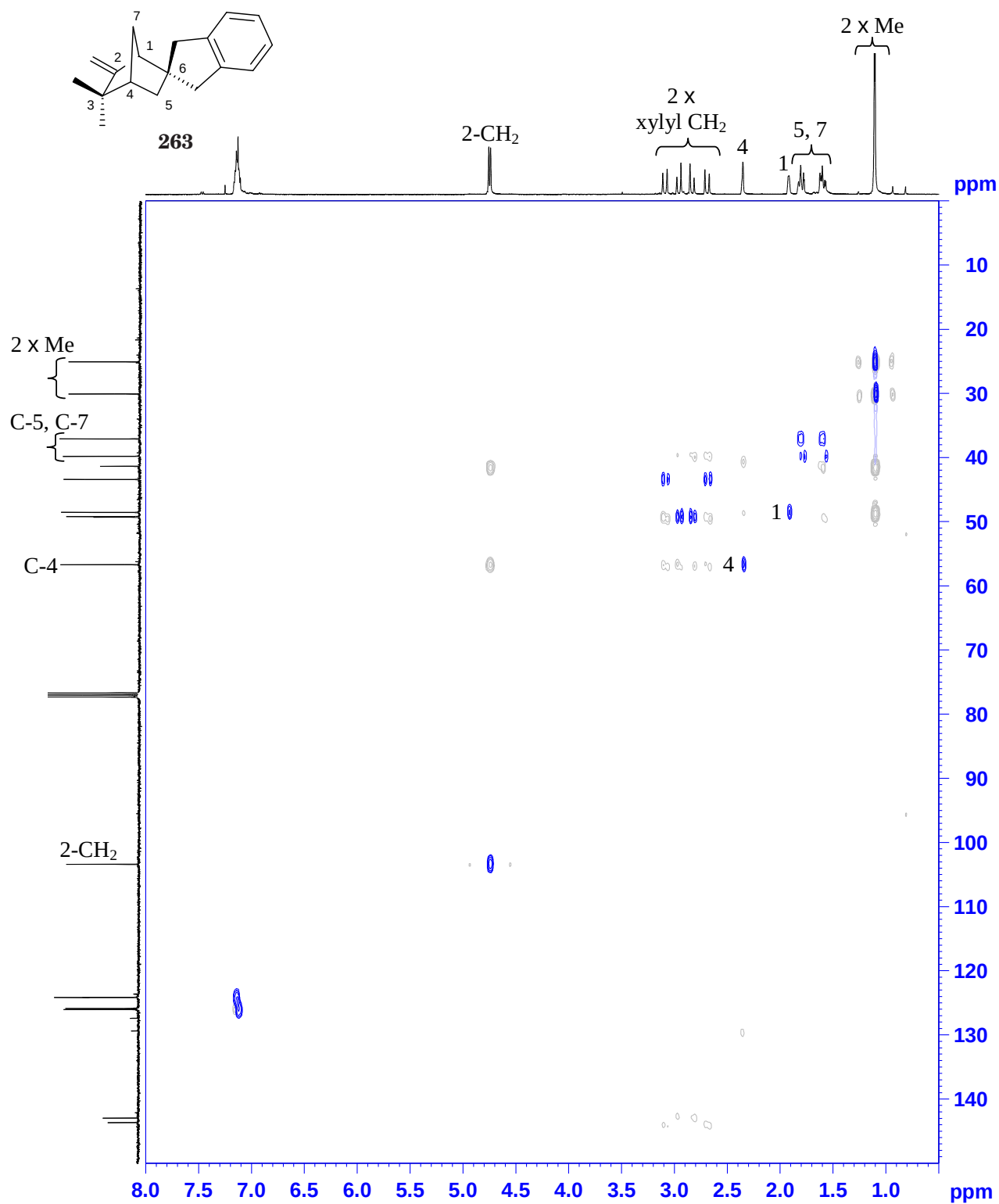


Figure 2.39: 400MHz HSQC (blue) and HMBC (grey) NMR data for camphene II **263** in CDCl₃.

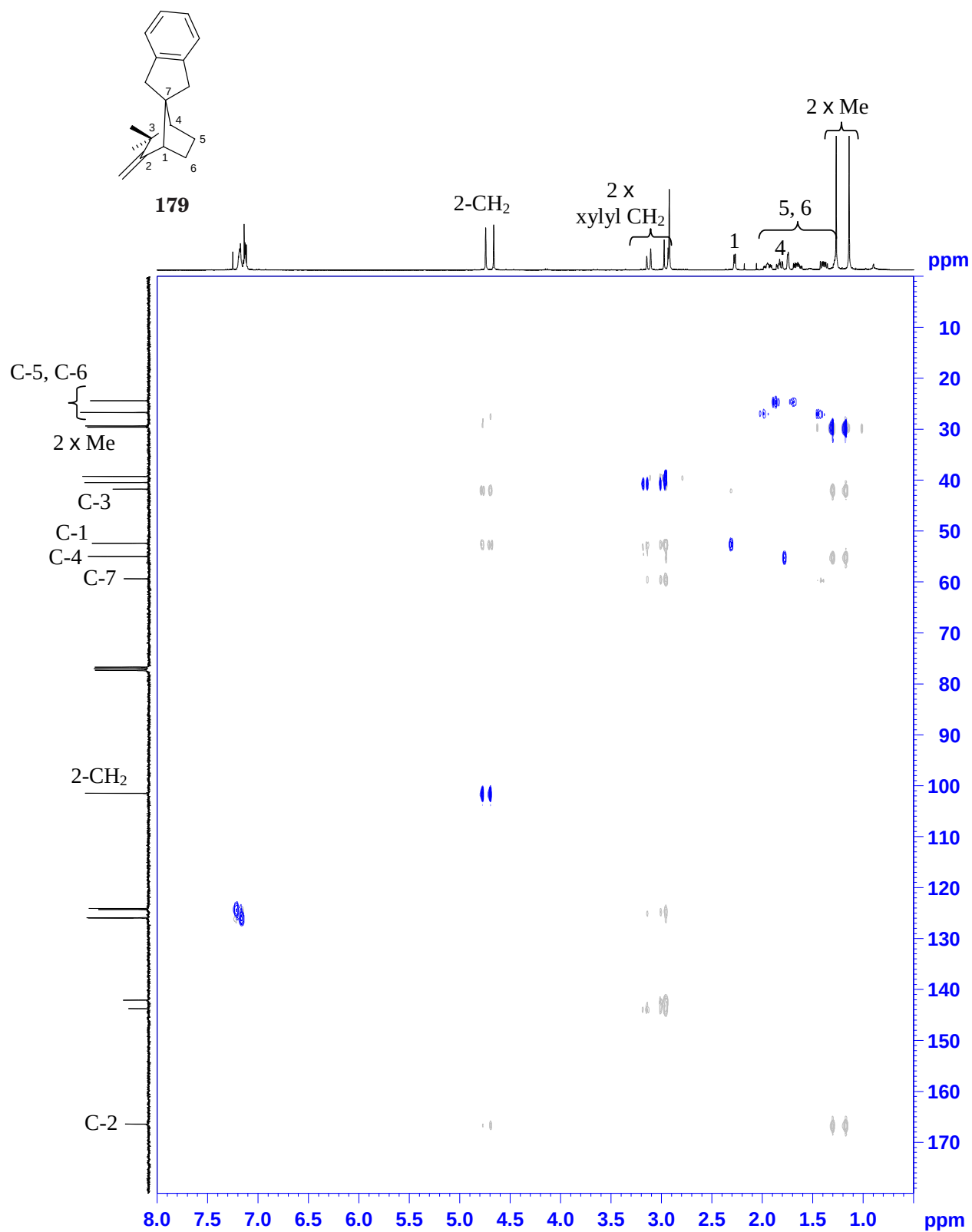
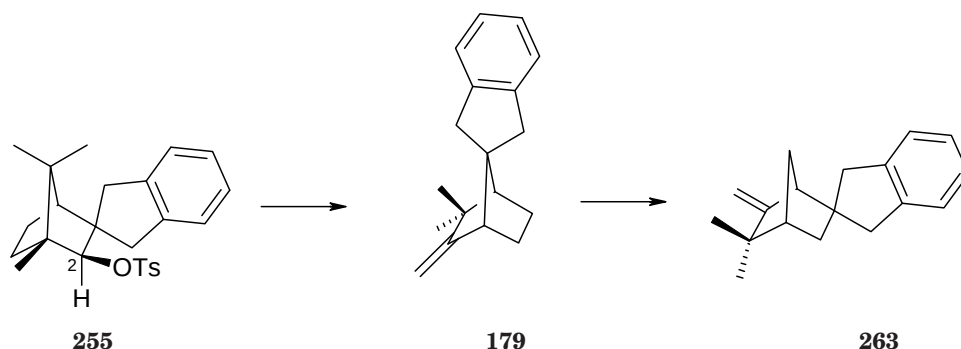


Figure 2.40: 400MHz HSQC (blue) and HMBC (grey) NMR data for camphene I **179** in CDCl₃.

2.3.3 Kinetic studies of the decomposition of the bornyl tosylate **255**



Scheme 2.36: Observed transformation.

The sequential transformation of the tosylate **255** is easily monitored within an NMR tube, and occurs on a manageable timescale between 25°C and 45°C (Scheme 2.36). The decay of the 2-*endo*-proton signal of the tosylate **255** and the appearance of the vinylic proton signals of the camphenes **179** and **263** are readily followed. If the tosylate is freshly synthesized it is possible to prepare the sample in CDCl₃ and store the solution at 0°C until the commencement of the kinetic run with no observable initial degradation. The sample can then be warmed to room temperature rapidly, followed by placement in the NMR probe at the appropriate temperature with a minimum of delay. It is impossible and, in fact, unnecessary to locate an exact time of commencement, but it is necessary to start collecting data as soon as possible since the initial change can be quite rapid, particularly at higher temperatures. Proton NMR spectra are best acquired at short intervals at the start of the experiment, where the change is more rapid, with longer intervals being sufficient later in the process. Figure 2.41 shows the decay of the 2-*endo*-H proton signal of the tosylate **255** at 4.31 ppm, the formation and decay of the two camphene I **179** vinylic proton signals at 4.66 ppm and 4.74 ppm, and the eventual production of the two camphene II **263** vinylic proton signals at 4.74 ppm and 4.76 ppm,

Figure 2.42 shows how the concentrations of all three species change over time in a typical experiment. Analysis of the kinetic data (see Section 2.3.3.2, p. 137) indicated that the original decomposition of the tosylate **255** is autocatalytic in nature, while the decay of the camphene I **179** follows first-order kinetics.

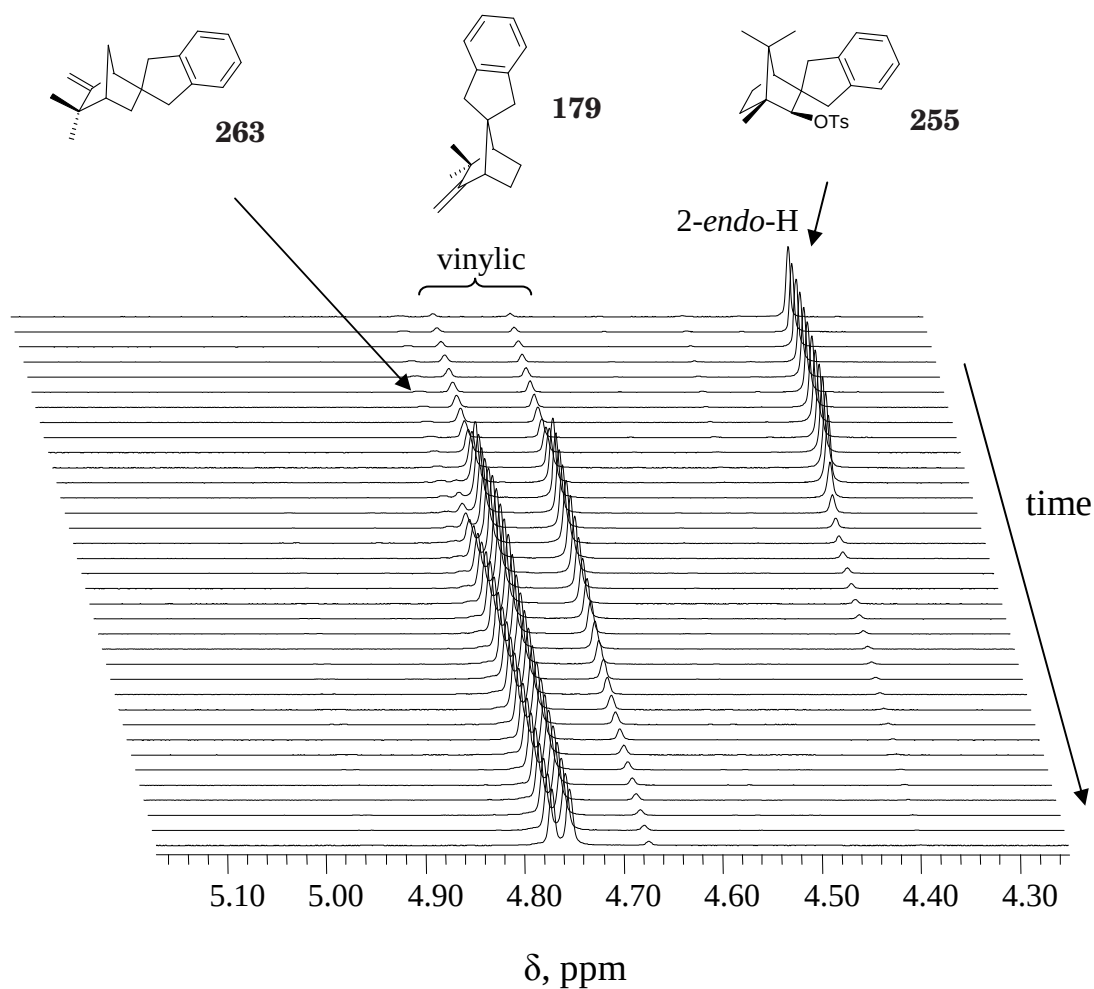


Figure 2.41: Stacked plots of partial ^1H NMR spectra showing the decay and evolution of selected signals during the transformation of the tosylate **255** to the spirocamphene products **179** and **263** in CDCl_3 at 35°C . The time interval between spectra is 300s.

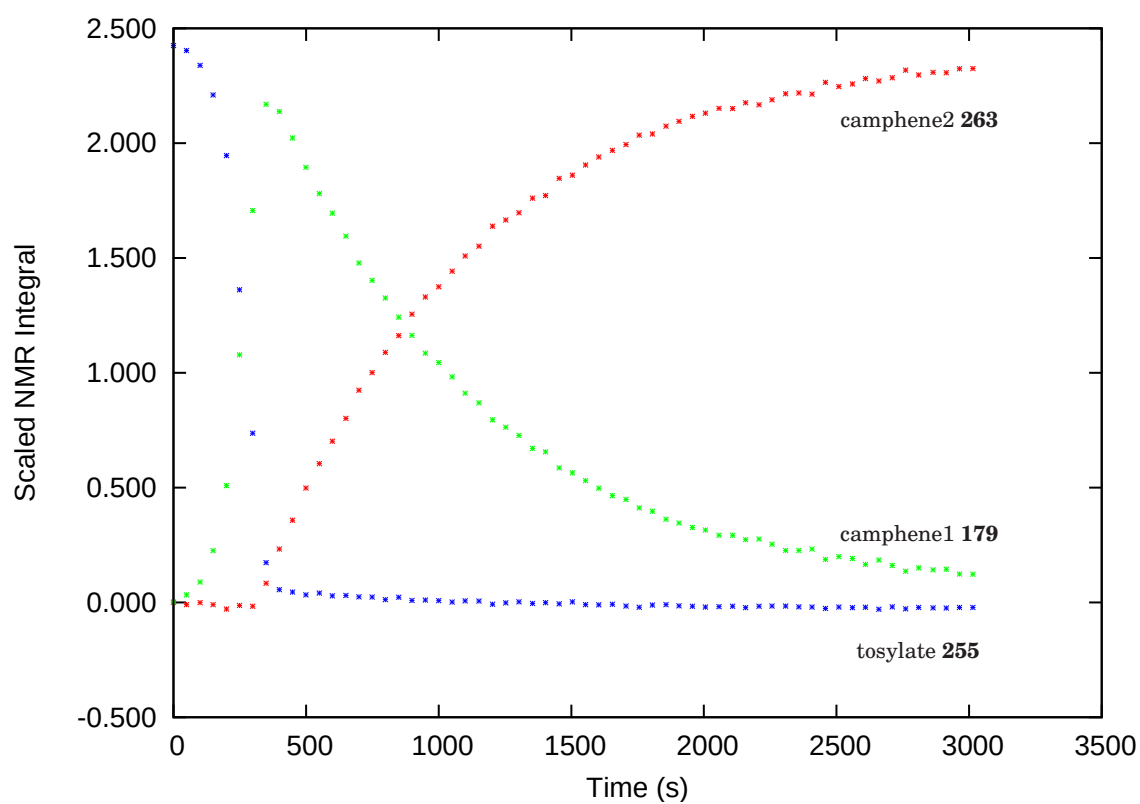


Figure 2.42: Kinetic data for the transformation of the tosylate **255** to the spirocamphene products **179** and **263** at 42°C in CDCl₃.

2.3.3.1 Factors influencing the kinetics

The kinetics of the transformation is dependent on a number of factors, and an awareness of these was necessary in order to obtain reproducible results.

2.3.3.1.1 Determination of concentrations One of the greatest difficulties in obtaining reliable kinetic data, was the crystallization, drying, accurate weighing and dissolution of a substance that decomposes at room temperature! Weighing was possible, but speed and accuracy were problematic from a practical point of view. In addition, variations in the instrument conditions caused variations in the NMR integrals during the course of the experiment. Consequently, it was decided to use an internal calibrant. 1,2,5-Trimethoxybenzene was chosen for this purpose; it could be weighed accurately beforehand, and provides a clear indication of the relative concentrations of all species in the reaction. In order to minimize concentration variations from run to run, a solution of the tosylate **255** and the calibrant in CDCl_3 was prepared in a volumetric flask and placed in ice at 0°C . This solution then provided identical samples for kinetic runs at all temperatures in the range.

2.3.3.1.2 Effect of the solvent Variation of the solvent has a remarkable effect on the kinetics observed in this reaction. Although quantitative data is not available for all solvents in question, it is apparent that the tosylate **255** is more stable in solvents such as ethyl acetate, dimethyl sulfoxide and THF. In fact, storage in ethyl acetate made it possible for the tosylate **255** to be kept for several days at 0°C . In deuterated chloroform and in carbon tetrachloride, however, the change was rapid. A general “rule of thumb”, based on our observations, is that, *the higher the dielectric constant of the solvent:-* i) the lower the interaction between tosic acid and the reacting species; ii) the slower the reactions; and iii) the more dominant the first-order decomposition of the tosylate **255**. This is evident in the reaction in $\text{DMSO}-d_6$ illustrated in Figure 2.43. *For solvents of lower dielectric constant (e.g. CDCl_3)* the converse is true, and the decomposition of the tosylate **255** is autocatalytic in nature.

In order to maintain consistency in the collection of the kinetic data, it was therefore essential to ensure complete removal of solvent impurities known to affect the rate when run in CDCl_3 . Washing the crystalline tosylate with cold hexane followed by rapid drying with filter paper proved an efficient method for removing interfering solvents, in particular THF and ethyl acetate.

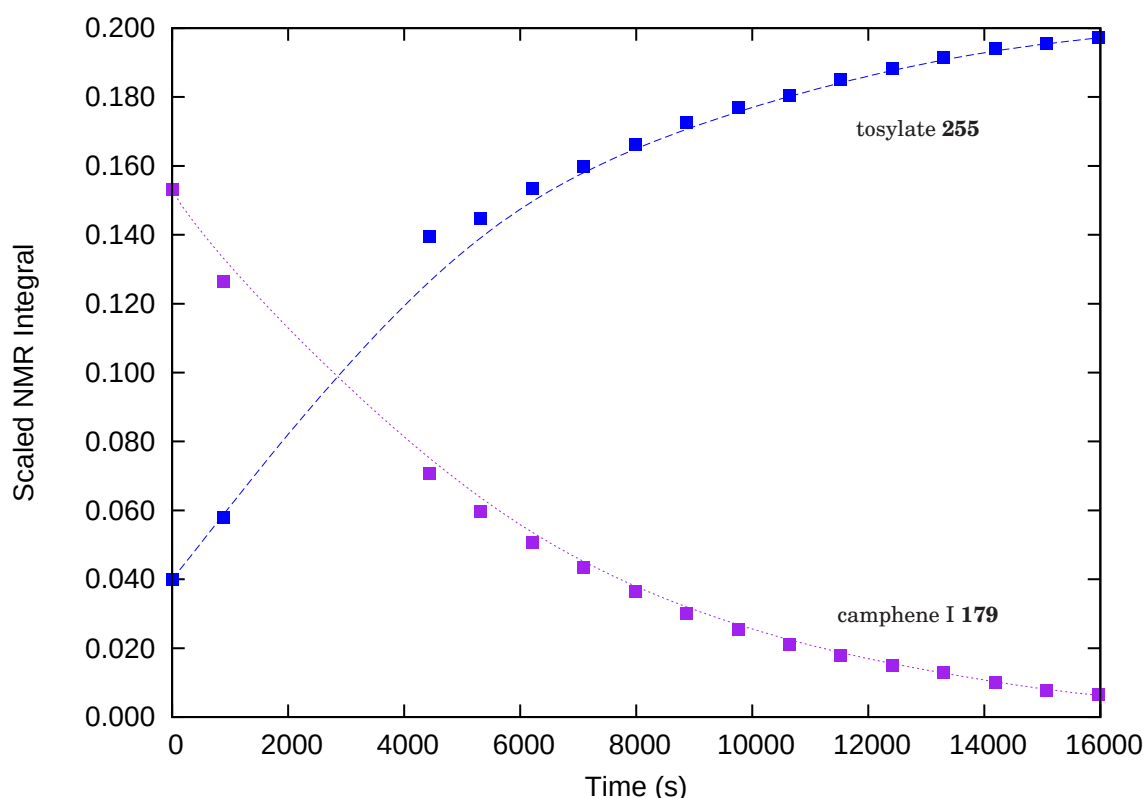


Figure 2.43: Kinetics of the transformation of the tosylate **255** to the spirocamphene product **179** in DMSO- d_6 at 27°C.

Figure 2.44 shows how the first-order rate constant (for the second transformation **179** → **263** at a single temperature 308K) varies as a function of the concentration of ethyl acetate in the CDCl₃ solution! It is apparent that the larger rate constants *do not occur* at ethyl acetate concentrations above 35mM. This figure illustrates how multi-faceted the kinetics are in this reaction. The autocatalytic rate constant for the transformation **255** → **179** shows trends that are similar, but not as marked.

The presence of trace amounts of water in the reaction presented a further complication. The origin of the water was not fully established, but was attributed to atmospheric condensation on the cold substrate prior to placement in the NMR tube. Surprisingly the effect of the water on the kinetics is actually negligible, but its presence raises another problem. Due to chemical exchange with the tosic acid produced in the reaction, the chemical shift observed for H₂O varies from just above 1.5ppm to well above 5.5ppm during the course of the reaction, and the linewidth of the signal varies between 28Hz and 348Hz in the same period! The result is that at some stage in the reaction, this signal lies *underneath* the signals of interest, causing a resultant *over-estimation* of the corresponding integrals. Consequently, in the

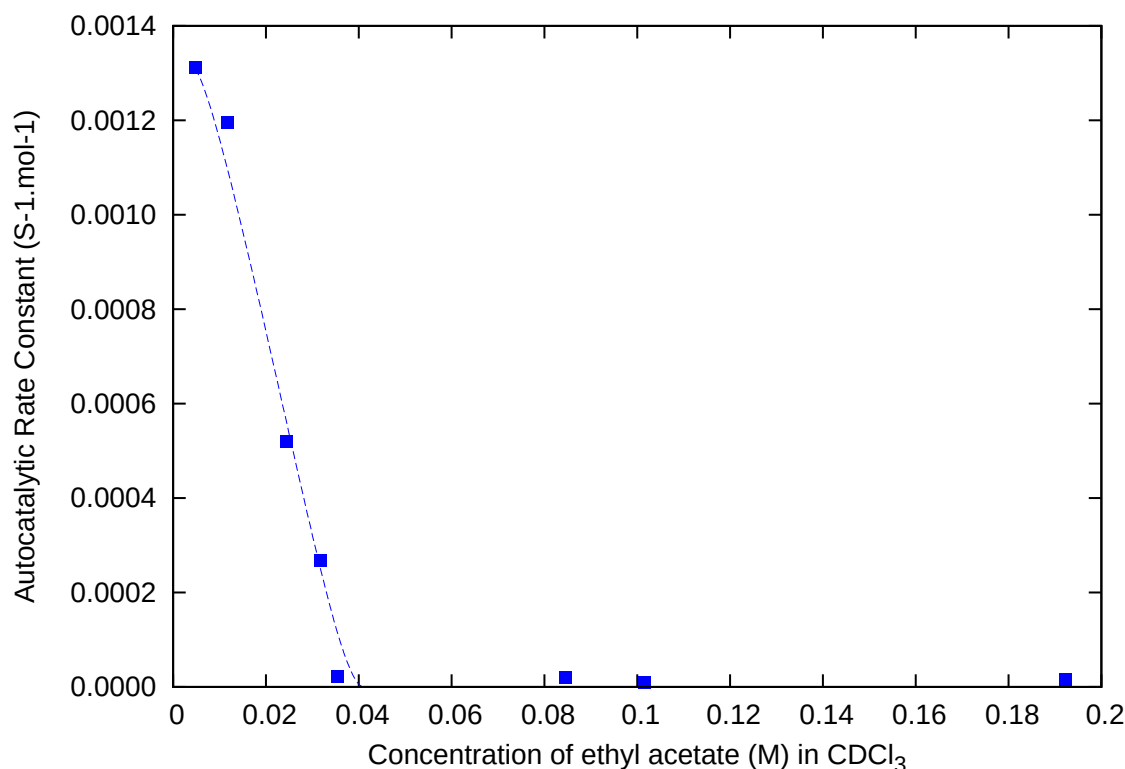


Figure 2.44: Kinetic data for the first-order decomposition of the tosylate **255** in CDCl₃ at 35°C as a function of EtOAc concentration.

kinetic analysis, these points were discarded.

In order to minimize interference by water, the CDCl₃ used in the kinetic runs *was not washed* to remove traces of DCl or HCl. Such traces were judged to have a negligible effect in comparison to the autocatalytic effect of the tosic acid produced in the reaction.

2.3.3.1.3 Effect of the leaving group. Dissociation of the tosylate **255** to afford carbocation **176** (Scheme 2.35) results in the production of tosic acid during the course of reaction. In CDCl₃, the dissociation is, itself, catalysed by tosic acid, thus accounting for the observed autocatalysis (see Figure 2.47 p.132). The tosic acid concentration is also a critical factor in the kinetic analysis of the second transformation (**179** → **263**) but, during most runs, the tosic acid reached saturation levels and began to crystallize out. At higher temperatures, this effect is not as marked but, upon cooling to room temperature, the extent of precipitation is very evident. A further issue to be considered is whether saturation is followed by immediate crystallization of any excess, or whether there is some degree of supersaturation. Figure 2.45 illustrates the crystalline tosic acid present in a NMR tube after a kinetic run.

Insight into this particular issue came from an unexpected source. Figure 2.46 shows that

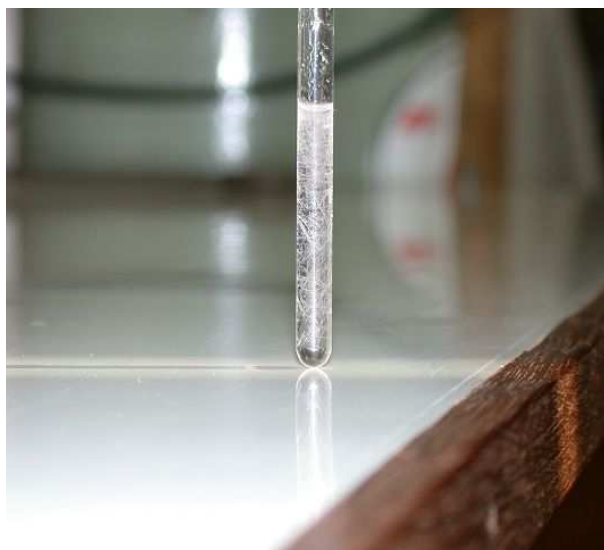


Figure 2.45: Tonic acid produced during course of a kinetic run.

the internal standard, trimethoxybenzene (TMB), and the CHCl_3 (in CDCl_3) signals remain at a virtually constant level, *until the concentration of the tonic acid increases*. The change in the CHCl_3 signal integral is due to interference from neighboring signals. The reason for the change in the TMB signal integral, however, is not so obvious. In the particular case illustrated in Figure 2.46, the intensity of the TMB signal drops to zero after *ca* 2000s. In other cases, with slightly lower starting concentrations of the tosylate **255** and *at lower temperatures*, the signal intensity did not drop to zero but, rather, to a level below the initial value, before returning to a slightly higher level. This anomalous pattern of behaviour may be related to protonation of THB at the supersaturation level of tonic acid and subsequent precipitation of (or co-precipitation with) the released tonic acid.

While the effects could introduce errors, these need not affect the analysis of the first transformation provided the data is discarded once non-linearity of the logarithmic plot is observed. They could, however, affect the kinetic analysis of the second transformation at higher concentrations, given the presumption that the second transformation is first-order with respect to tonic acid.

2.3.3.1.4 An intriguing problem with the rate law Figure 2.46 has another interesting feature. The autocatalysis is only really apparent from about 1700s into the kinetic run (where the familiar “s”-shaped curve is seen); within the region marked **A** in Figure 2.46, the reaction is clearly not autocatalytic. Decomposition of the tosylate **255** may well involve

first-, second- and even third-order components (Figure 2.47). Second-order decomposition does occur (path II), since the tosic acid formed during the reaction clearly accelerates the decomposition of the tosylate **255**. First-order decomposition (ionization) is likely given that the tosylate anion is a the good leaving group and it occupies an *exo*-position on a norbornyl type skeleton;⁸⁶ this could involve two steps (path Ia) or one step (path Ib). In the absence of tosic acid at the start of reaction, ionization is *essential* to initiate the autocatalytic (second-order) decomposition.¹⁸³ Third-order decomposition of the tosylate **255**, involving the concerted process (path III) shown in Figure 2.47 might also be invoked to explain the abnormal curve shape **A** (Figure 2.46).

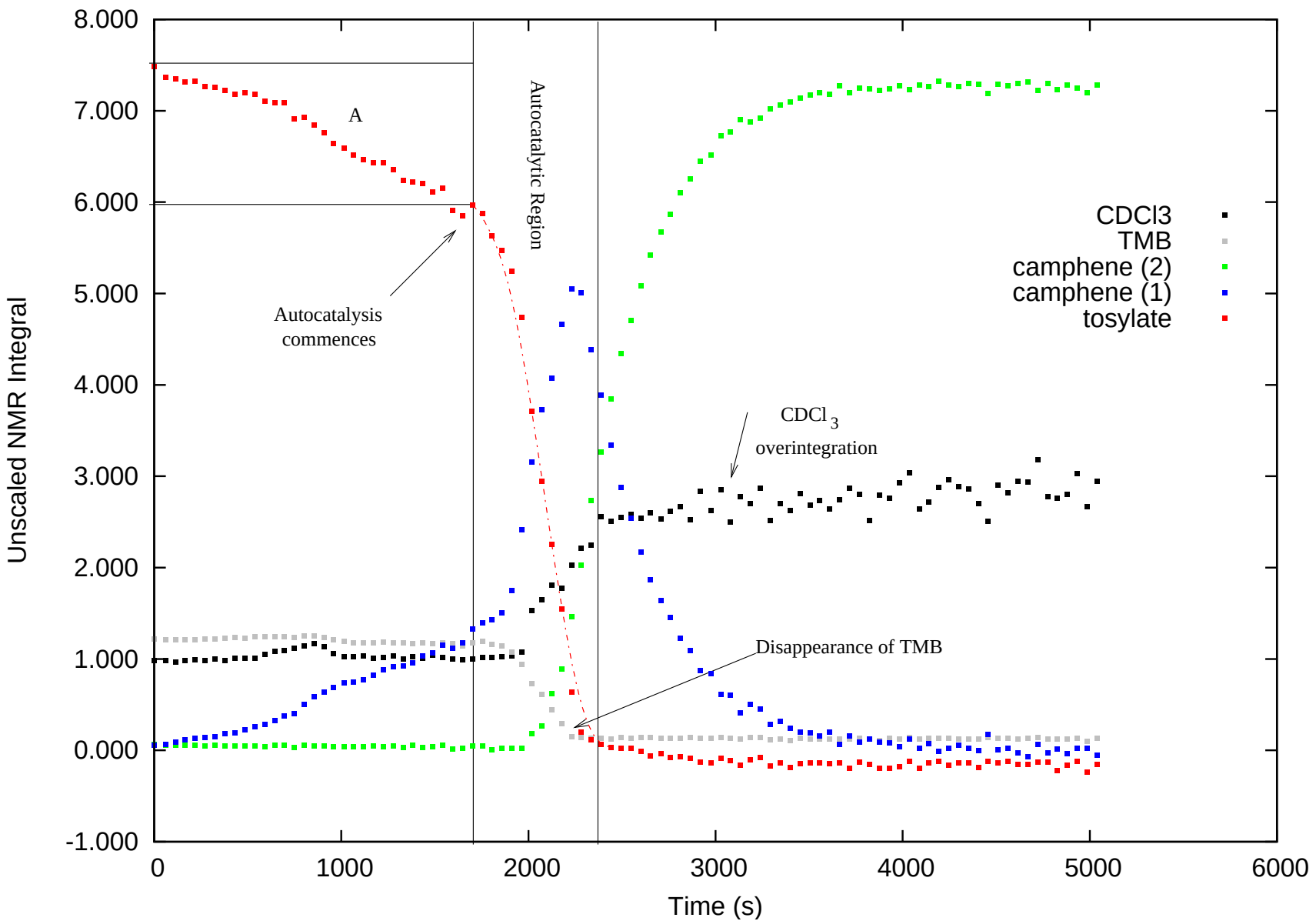


Figure 2.46: Kinetic data for rearrangement of the tosylate **255** in CDCl₃ at 36°C. [TMB]=0.0311M; [Tosylate]₀ ([**255**]₀)=0.185M. 131

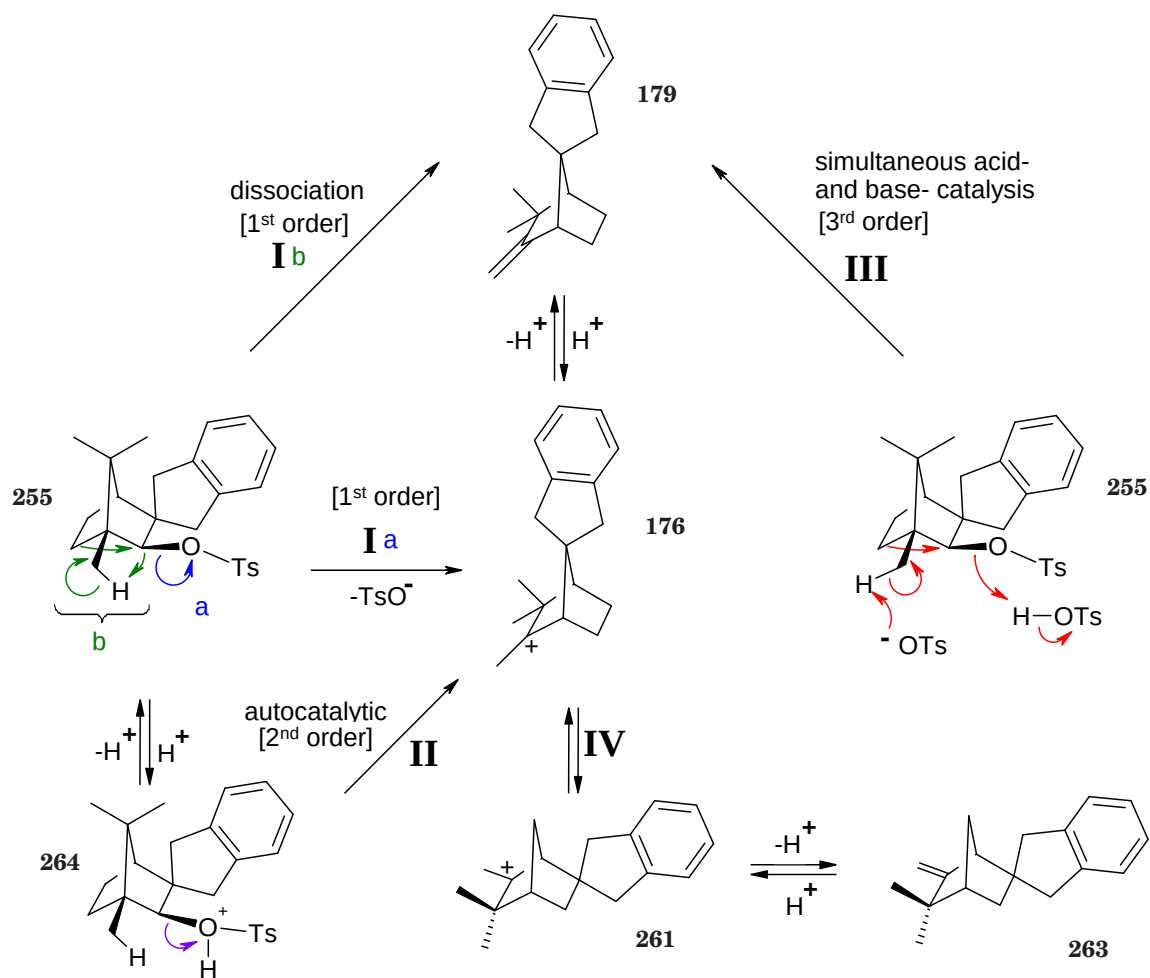


Figure 2.47: Third order decomposition.

The overall reaction scheme is summarized in Figure 2.48, where :- **HAOTs** is the tosylate **255**; **B** is the camphene **I** **179**; **C** is the camphene **II** **263**; k_d is the dissociative rate constant; k_a is the autocatalytic rate constant; and the final step is either first-order or pseudo-first-order.

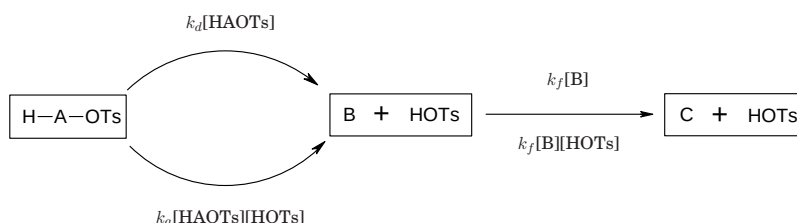


Figure 2.48: Overall kinetic scheme for the transformation of the tosylate **255** (**HAOTs**) to camphenes **179** (**B**) and **263** (**C**).

The concentrations of the reacting species may be represented as follows, where x_0 and z_0 represent the initial concentrations of the tosylate **255** and tosic acid, respectively.

$$[\text{HAOTs}] = x; \quad (2.1)$$

$$[\text{B}] = y; \quad (2.2)$$

$$[\text{C}] = x_0 - x - y; \quad \text{and} \quad (2.3)$$

$$[\text{TsOH}] = z_0 + x_0 - x \quad (2.4)$$

When NMR methods are used to follow the kinetics, it is helpful to introduce a constant (a) relating the integral to the concentration, and then to work with the raw integral data, such that:

$$x = ai, y = aj \text{ and } z_0 = at_0 \quad (2.5)$$

relates the concentrations of the tosylate x , camphene I y and tosic acid z to their respective NMR integrals i , j and t . The first- and second-order components of the overall kinetic scheme are then as shown in equations 2.6 and 2.7, respectively.

$$-\frac{di}{dt} = k_d i \quad (2.6)$$

$$-\frac{di}{dt} = ak_a i(t_0 + i_0 - i) \quad (2.7)$$

Of all the integrated rate equations examined, the most applicable to the paths identified in Figure 2.48 were the pseudo-first-order equation for the second transformation (Equation 2.8); Equation 2.9 for the first, purely autocatalytic reaction; and Equation 2.10 for the autocatalytic/first order combination, corresponding to both paths in Figure 2.48 (see Appendix 4.1 for full details).

$$\ln(j) - \ln(j_0) = k_f x_0 t \quad (2.8)$$

Now x_0 is the total tosic acid present for the second transformation - a molar equivalent of the original tosylate.

$$\ln\left(\frac{i}{(t_0 + i_0) - i}\right) - \ln\left(\frac{i_0}{(t_0 + i_0) - i_0}\right) = -ak_a (t_0 + i_0) t \quad (2.9)$$

$$\ln \left(\frac{k_d + ak_a((t_0 + i_0) - i)}{i} \right) - \ln \left(\frac{k_d + ak_a t_0}{i_0} \right) = (k_d + ak_a(t_0 + i_0)) t \quad (2.10)$$

Figure 2.49 shows how the concentration should vary according to Equation 2.10 with the autocatalytic pathway predominating. The steeper graphs correspond to a larger first-order component. Comparing this graph to Figure 2.46 it seems that the actual mechanism (and the unusual shape of the graph) for the decay of the tosylate **255** is not dominated by simultaneous pathways, but rather by *two distinct pathways* occurring in different stages. However, this pattern was only apparent in the some experiments. A tentative explanation is that washing the tosylate with saturated aqueous NaHCO_3 solution leaves traces of NaHCO_3 on the tosylate crystals. During the kinetic runs, some of the tosic acid produced is neutralized by NaHCO_3 thus inhibiting autocatalysis, and the first-order dissociative pathway predominates initially. Once the available NaHCO_3 is “consumed” autocatalysis may then proceed. Even when this occurs, the data is usable, since autocatalysis is still evident and the quantity of “effective” tosic acid present may be calculated. Fitting Equation 2.10 to a relatively “normal” set of data (Figure 2.50) reveals an initial negative deviation followed by a positive deviation of the experimental data from the theoretical curve, centred around an inflection point at which the H_2O signal (mentioned earlier) moves under the vinylic signal for camphene I **179**. The resultant broadening of the peak, causes an overestimation of signal integral, producing negative or positive errors, depending on which side of the substrate or product signal the interfering H_2O signal appears. The resultant curve is, nevertheless, essentially autocatalytic, and, in fact, the theoretical autocatalytic analysis closely matches the experimental data for the initial decomposition in all cases.

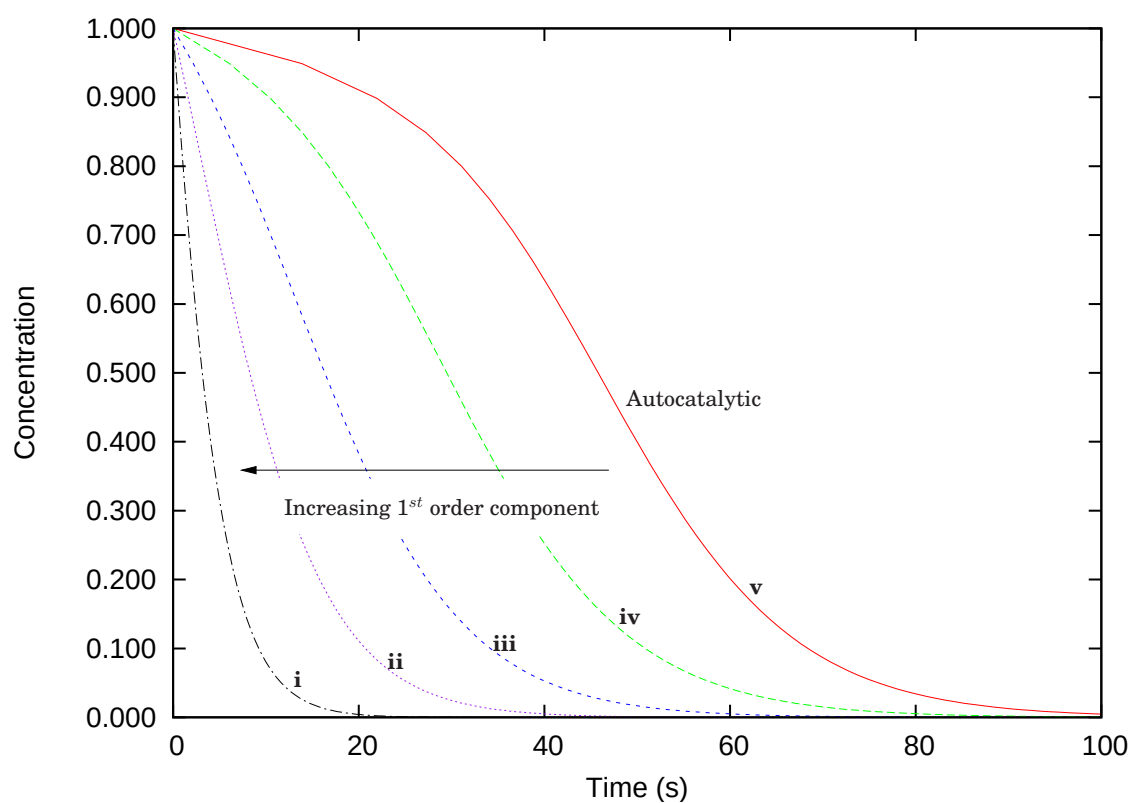


Figure 2.49: Theoretical plots of concentration *vs* time for the simultaneous first-order and autocatalytic decay of the tosylate **255**. Rate constant ratio $k_f : k_a$ is i) 67:33 ii) 38:62 iii) 17:83 iv) 5:95 v) 1:99.

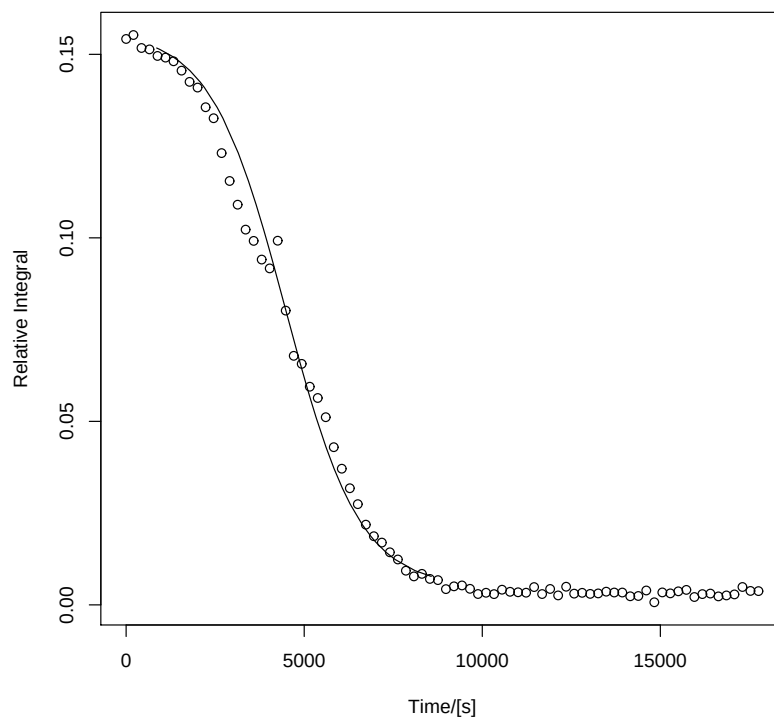


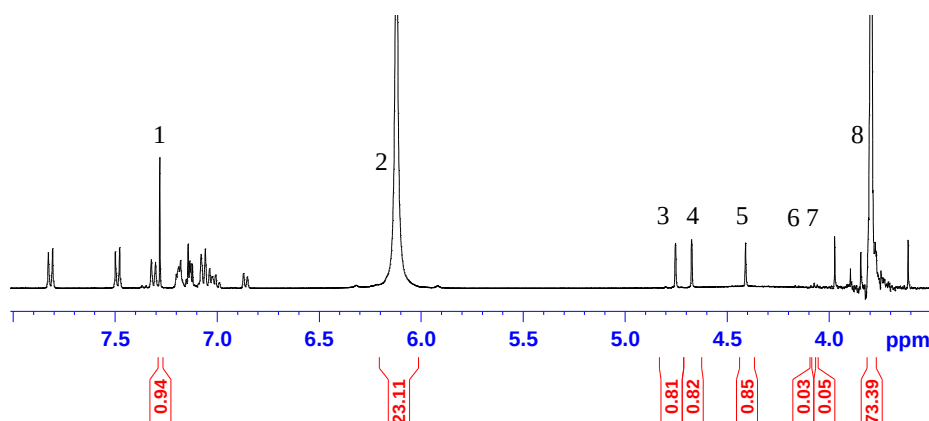
Figure 2.50: Fitting equation 2.10 to a representative set of data, using non-linear regression in the software package R.¹⁸⁴

Table 2.13: Regions of the ^1H NMR spectra (see Figure 2.51) used for integration.

Integration region No.	(δ , ppm)	Assignment
1	7.297-7.259	CDCl_3
2	6.305-5.927	TMB aryl proton (3xH)
3	4.861-4.715	Camphene II 263 (2xH) + Camphene I 179 (1xH)
4	4.715-4.648	Camphene I 179 (1xH)
5	4.461-4.386	Tosylate 255 (1xH)
6	4.206-4.122	Ethyl Acetate (2xH)
7	4.122-4.048	THF (4xH)
8	3.851-3.716	TMB methoxy proton (9xH)

2.3.3.2 Kinetic analysis of the experimental data

The kinetic data were collected for transformations conducted in CDCl_3 . An auxiliary programme was used with XWinNMRTM (Version 2.6, Bruker Spectrospin Ltd.) to automate extraction of the kinetic data. The NMR regions identified as being critical to the study are illustrated in Figure 2.51 and listed in Table 2.13. The integration regions had to be wide enough to accommodate signal drift arising from the significant change in the reaction medium during the course of each experiment, but narrow enough to maintain accuracy. The signals corresponding to the impurities, THF and ethyl acetate, were carefully monitored, since these contaminants may have a marked effect on the results. Regions 3 and 4 (Table 2.13) can be used together to calculate the integral for camphene II **263**.

**Figure 2.51:** Regions of the ^1H NMR spectra used for integration.

2.3.3.2.1 Regression analyses Some difficulties were encountered in applying non-linear regression analysis to the autocatalytic data. The first difficulty stems from the fact that the

concentration (the dependent variable) is an implicit variable, not separable in terms of the time variable. The second difficulty is that the discontinuity at time = 0 in the autocatalytic rate equation and its higher order derivatives, often “misleads” the software during parameter optimization (for example, when a variation results in a negative number under the logarithm). Consequently, it was decided that linear regression would suffice.

There is some redundancy in the data obtained from the NMR analyses since the concentration of any one species is also expressible in terms of the total concentration, and the respective concentrations of the other two species. In many cases it was found convenient to either express the relative concentration of the camphene “*i*” in terms of the reactant (tosylate **255**) concentration and $i_0 - i$ in terms of the sum of the two camphene products, or to invert the equation to base the determination solely on the appearance of camphene I **179** signals. Attempts were also made to minimize noise in the data by choosing to use data from either the reactants or the products. If the initial tosic acid concentration t_0 is very small, then for the first transformation Equation 2.11 from Equation 2.9 holds to a first approximation.

$$\ln \left(\frac{i}{i_0 - i} \right) - \ln \left(\frac{i_0}{t_0} \right) = -ak_a i_0 t \quad (2.11)$$

If j is the relative integral for camphene I **179**, then for the second transformation (Equation 2.9) a plot of $\ln \left(\frac{i}{i_0 - i} \right)$ vs t or the algebraically equivalent plot $\ln \left(\frac{i_0 - j}{j} \right)$ vs t should give a straight line of slope $ak_a i_0$ in the region that autocatalysis takes place, while a plot of $\ln(j)$ vs t should give a straight line of slope $-k_f x_0$ (Equation 2.12). Figure 2.52 shows the correspondence between the experimental and theoretical data in the autocatalytic region, discarding the points after *ca.* 500s. Figure 2.53 shows a good first-order fit, obtained by discarding the initial points in the autocatalytic region. Points were also discarded when judged to suffer from overintegration errors, when lying close to the region of “change” from autocatalytic to first-order, and when the reactions approached completion. In almost all cases, however, there remained a significant number of points to afford reliable best fit lines with high R^2 values. With discontinuous sets of data, preference was given to data points lying well within the autocatalytic region, and distant from the mechanism changeover.

$$\ln(j) - \ln(j_0) = -k_f x_0 t \quad (2.12)$$

Table 2.15 summarizes the final set of experimental data used in the analysis of the auto-

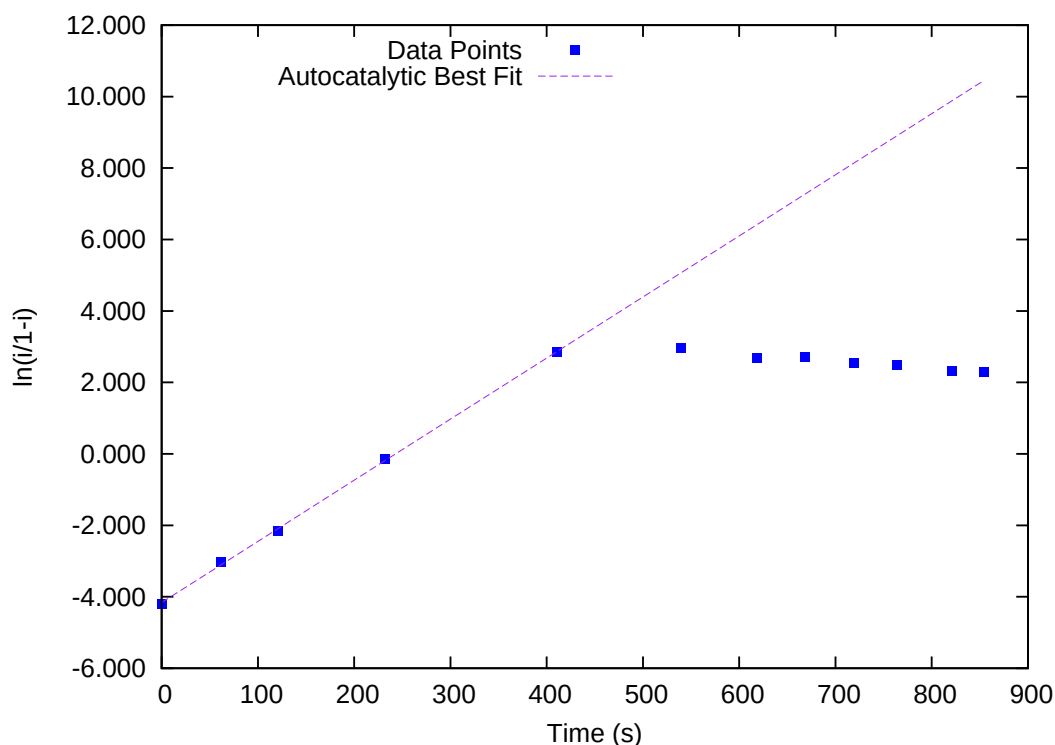


Figure 2.52: Autocatalytic fit for initial data in CDCl_3 at 44°C .

catalytic phase of the reaction. All integrals were scaled relative to the trimethoxybenzene (TMB) calibrant integral (1.00). From the known concentration of the TMB, in each experiment, the initial tosylate **255** (HAOTs) concentration could be calculated and the autocatalytic rate constant k_a obtained from the slope ($k_a = \frac{\text{slope}}{ai_0}$). Experiments were run at different concentrations and temperatures (Table 2.15) and the Arrhenius plot for the autocatalytic phase of the reaction is illustrated in Figure 2.54. The corresponding activation parameters calculated at 298.15K are summarized in Table 2.14.

Kinetic data for the subsequent transformation of camphene I **179** to camphene II **263** was less consistent than for the autocatalytic transformation (**255** $\rightarrow$ **179**). The reasons for this have been discussed above. While good correlations were obtained for data within a batch of runs with identical concentration, it was more difficult to correlate the data between batches of runs with different concentrations. This may well reflect a concentration-dependent interplay between competing first-order and second-order processes; the transformation may of course be pseudo first-order.

It was easier to collect data for the higher concentration runs since, under these conditions, the second transformation proceeds within a reasonable time-frame. Figure 2.55 shows

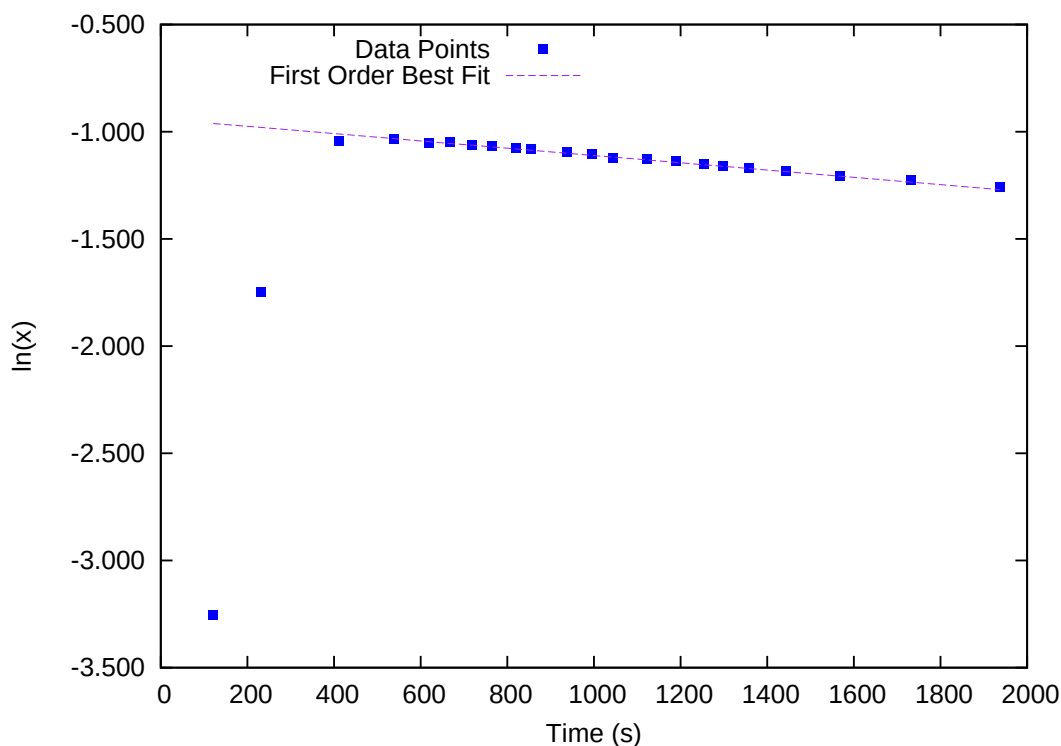


Figure 2.53: First order fit (discarding autocatalytic region) for data in CDCl_3 at 44°C .

Table 2.14: Calculated autocatalytic parameters at 298.15K for the autocatalytic transformation **255** $\rightarrow$ **179**.

R^2	E_a kcal.mol^{-1}	Std Err	$\Delta H^\ddagger$ kcal.mol^{-1}	Std Err	$\Delta S^\ddagger$ cal.mol^{-1}	Std Err	$\Delta G^\ddagger$ kcal.mol^{-1}	Std Err
0.9864	40.13	1.0	39.51	1.0	62.8	3.3	16.84	0.05

the variation in the Arrhenius plots between batches of runs at different concentrations; the change in $\ln |k_f|$ for various higher concentration runs at 308K is also illustrated. The data obtained is illustrated (Table 2.16) for the 0.069M and 0.18M concentration runs.

In summary, we conclude that rearrangement of the camphene I **179** is dependent on proton transfer from the environment, and that the observed gradation in the kinetic data is due to :-

1. the pseudo-first-order nature of the transformation, affected by variations in the tosic acid concentration arising from solubility effects in CDCl_3 , differing initial concentrations of the tosylate **255** and the presence of a neutralizing agent (e.g. NaHCO_3) in the substrate **255**; and
2. the solvent dependence of the reaction, affected by the influence of trace contaminants

Table 2.15: Experimental and calculated data for the autocatalytic period in the transformation **255** $\rightarrow$ **179**.

Experiment Name	T [K]	TMB [M] (<i>a</i>)	AOTs [M] (<i>a</i> <i>i</i> ₀)	$\Sigma^1\text{H}$ <i>i</i> ₀	Intercept <i>c</i>	Error in <i>c</i>	<i>k_a</i> [L/mol ⁻¹ s ⁻¹]	Error in <i>k_a</i>
0404kinetic44b	317.15	0.07241	0.02704	0.37338	-4.15790	0.04936	0.63352	0.00831
0404kinetic46b	319.15	0.07241	0.02732	0.37729	-2.68857	0.12134	0.89119	0.03154
0404kinetics30	303.15	0.17741	0.02724	0.15354	-4.14980	0.14028	0.03314	0.00084
0404kinetics32	305.15	0.17741	0.02650	0.14940	-3.83535	0.08854	0.04480	0.00088
0404kinetics34	307.15	0.17741	0.02705	0.15247	-3.78426	0.13414	0.06576	0.00200
0404kinetics36	309.15	0.17741	0.02653	0.14958	-3.91284	0.06617	0.09085	0.00192
0404kinetics38	311.15	0.17741	0.02629	0.14821	-4.18524	0.07515	0.17498	0.00399
0404kinetics40	313.15	0.17741	0.02693	0.15179	-4.25906	0.09808	0.22759	0.00469
0404kinetics42	315.15	0.17741	0.02626	0.14802	-4.25363	0.20901	0.33154	0.01479
0404kinetics44	317.15	0.17741	0.02637	0.14863	-3.76145	0.09459	0.42840	0.01075
0404kinetics46	319.15	0.17741	0.02565	0.14462	-4.71947	0.81118	0.63836	0.11240
0705kinet32	305.15	0.07241	0.02746	0.37927	-2.44067	0.00941	0.03720	0.00037
0705kinet36	309.15	0.07241	0.02799	0.38657	-2.56402	0.02788	0.09505	0.00191
0705kinet38	311.15	0.07241	0.02795	0.38603	-2.60208	0.14755	0.17418	0.00715
0705kinet40	313.15	0.07241	0.02754	0.38040	-3.01157	0.12997	0.22646	0.00839
0705kinet43	316.15	0.07241	0.02858	0.39474	-2.44166	0.32629	0.41332	0.04441
0705kinet46	319.15	0.07241	0.02746	0.37925	-1.44279	0.23545	0.91257	0.07777
0705kinetb32	305.15	0.04292	0.07027	2.48051	-2.93591	0.06706	0.04206	0.00225
0705kinetb36	309.15	0.04292	0.06815	2.40567	-3.14127	0.10591	0.11819	0.00631
0705kinetb40	313.15	0.04292	0.06933	2.44707	-5.26630	0.11580	0.22267	0.00615
0705kinetb42	315.15	0.04292	0.06874	2.42645	-5.40979	0.09684	0.30742	0.00631
0705kinetb44	317.15	0.04292	0.06966	2.45885	-5.47394	0.21093	0.48509	0.02529

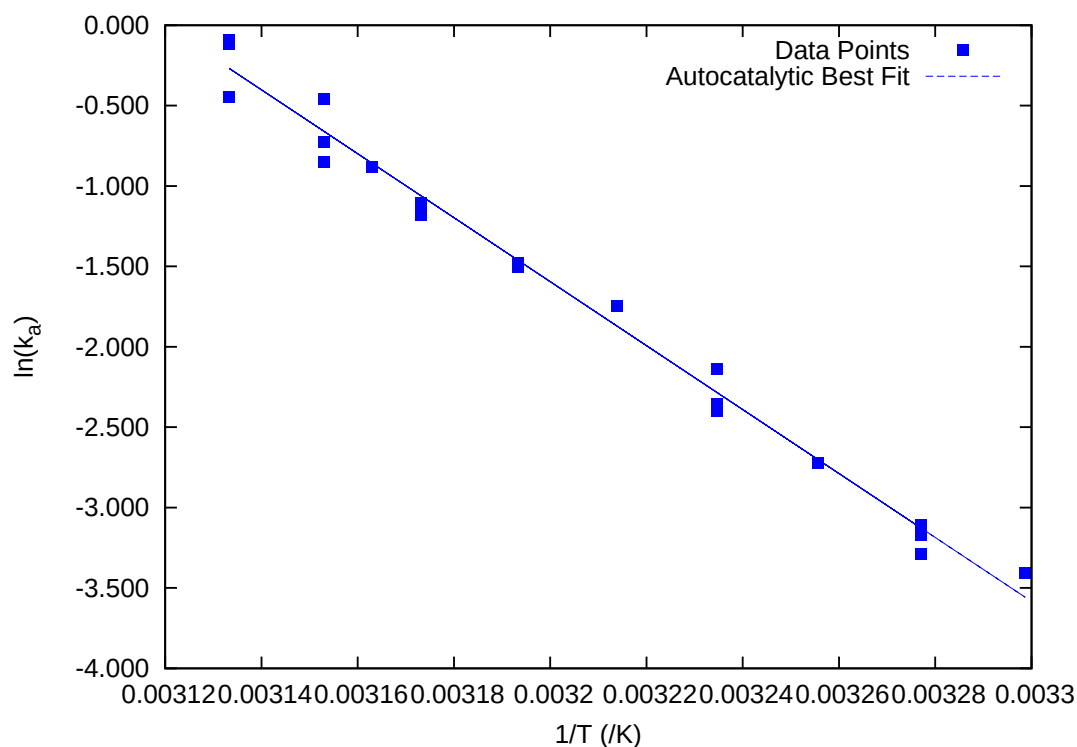


Figure 2.54: Arrhenius Plot of Autocatalytic Reaction.

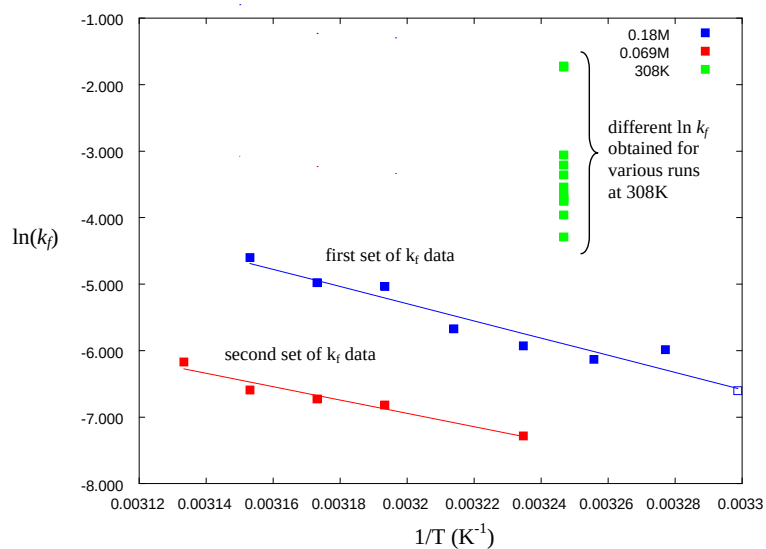


Figure 2.55: Arrhenius plots of first order data. The concentration of TsOH is difficult to determine in the pseudo-first-order transformation.

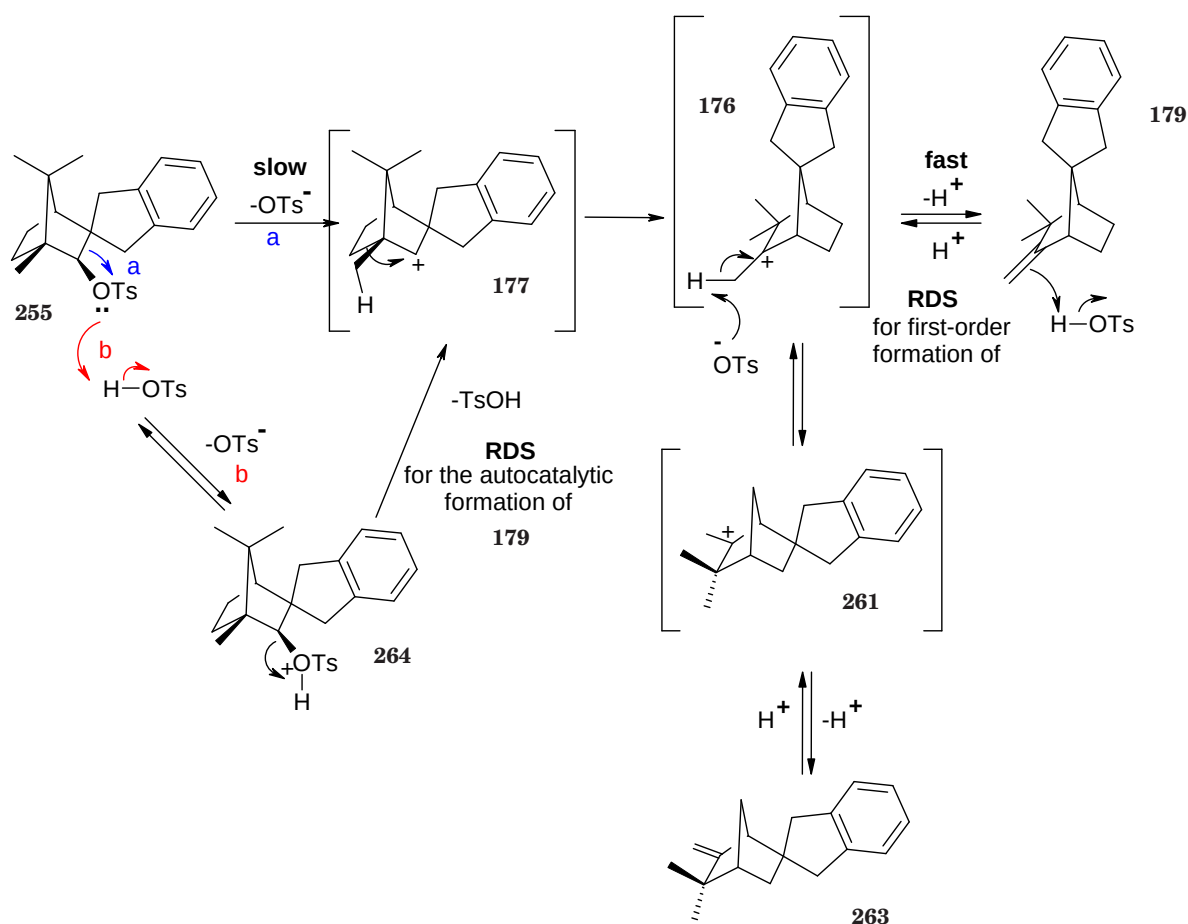
such as THF and/or ethyl acetate, present in the substrate.

Other sources of error, such as temperature inaccuracies within the NMR instrument probe and phasing and integration errors in the NMR spectra are not considered to be significant in comparison with the chemical factors discussed above.

Table 2.16: Calculated activation parameters at 298.15K for the pseudo-first-order transformation **179** $\rightarrow$ **263**.

Π_0 M	R^2	E_a kcal.mol ⁻¹	Std Err	$\Delta H^\ddagger$ kcal.mol ⁻¹	Std Err	$\Delta S^\ddagger$ cal.mol ⁻¹	Std Err	$\Delta G^\ddagger$ kcal.mol ⁻¹	Std Err
0.069	0.9514	20.3	2.6	19.8	2.6	-1.1	8.1	19.1	4.8
0.18	0.9323	26.3	2.9	25.6	2.9	11.1	9.1	18.4	5.5

Based on the experimental kinetic data, the overall mechanism for the transformation (Scheme 2.37) of the tosylate **255** to the camphene I **179** requires an ionization step **a**, but follows second-order kinetics *via* mechanism **b** with the loss of tosylate as the rate-determining step; the large magnitude of $\Delta S^\ddagger$ is attributed to the structural lability of the formed cation **177**. The formation of camphene II **263** from camphene I **179** requires protonation of **179** by tosic acid in the rate-determining step. In the next phase of the mechanistic study, attention was focused on the application of theoretical methods.

**Scheme 2.37:** Proposed mechanistic sequences for the rearrangement reactions **255** $\rightarrow$ **179** $\rightarrow$ **263**.

2.3.4 Theoretical Studies of the decomposition of the tosylate **255**

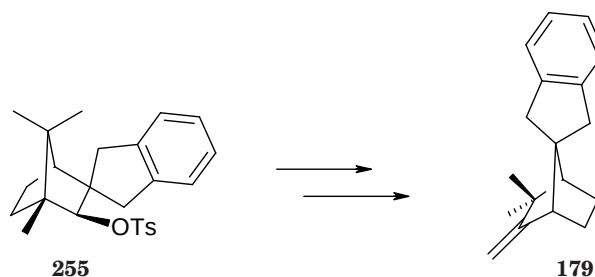
The computational analysis of both phases of the rearrangement of the tosylate **255** (*i.e.* **255** $\rightarrow$ **179** and **179** $\rightarrow$ **263**; Scheme 2.37) involved several studies at increasing levels of theory, *viz.*,

1. calculations at the HF/STO-2G level (followed by HF/6-311G(d,p) minimizations) leading to the re-assignment of the structure of the thermodynamically favoured camphene (see Section 2.3.2, p. 116).
2. geometry optimization at the Hartree-Fock [6-31G(d)] level to explore bridging during carbocation rearrangement **255** $\rightarrow$ **177**;
3. geometry optimisation at the Hartree-Fock [6-31G(d)] level to explore the potential energy surfaces for the rearrangements, **177** $\rightarrow$ **179** and **179** $\rightarrow$ **263**;
4. *Ab initio* molecular dynamics attempts at exploring the transformation **179** $\rightarrow$ **263**;
5. coset analysis of all possible classical rearrangements of the camphenyl I cation **176**;
6. AM1 analysis of 336 intermediates and 526 transition states generated from the coset analysis;
7. conversion of the classical graph to non-classical graph, using DFT; and
8. final analysis of intermediates and transition states in the non-classical pathway for the transformation **176** $\rightarrow$ **261**.

2.3.4.1 Decomposition of the tosylates to the secondary carbocation

There was never really any doubt about the structure assigned to camphene **179** formed initially *via* rearrangement of the tosylate **255** (Scheme 2.38). There are no unusual features, such as the highly strained cyclobutyl system present in the pinenyl structure **260**, and higher level molecular modelling (Hartree-Fock and DFT with basis sets 6-31G and greater) indicated its ready formation.

It appeared from the molecular dynamics data (quench dynamics using the universal force field^{185–187} in the Cerius² software) that the aromatic moieties in the *exo*- and *endo*-systems (Figure 2.56) show π -stacking type interactions, with the π -systems appearing to be better



Scheme 2.38: First transformation **255** $\rightarrow$ **179**.

aligned in the *exo*- than the *endo*-system. Although the interaction between the π -systems appears greater in the *exo* case, B3LYP/6-31G(d) minimizations of these systems show the *exo*- system to be destabilized relative to the *endo*-analog! Although the relative rates for *endo*- and *exo*-decomposition have not been determined, *exo*-decomposition (of **255**) has been observed to occur readily while the *endo*-isomer **258** appears to be remarkably stable (See Section 2.3.2, p. 113).

The direct ionizations of the tosylates **255** and **258** were difficult to work with in DFT packages such as GAMESS¹⁸⁸ due to the attraction *in vacuo* of the positively and negatively charged ions. Since the formation of the cation **177** and its subsequent rearrangement is of interest, the ionization of the protonated tosylate **264** $\rightarrow$ **177** was explored (following the predominant autocatalytic pathway in Scheme 2.37).

Thus the C-OTs bond in each of the protonated tosylates (**264** and **265**) was constrained at increasing lengths, while the C2-C6 internuclear distance was measured for each structure (Figures 2.57 and 2.58), following geometry minimizations at the B3LYP/6-31G(d) level in GAMESS.¹⁸⁸ It was anticipated that this approach, however, would provide a suitable starting point for obtaining transition states for the corresponding ionizations. However, these transition states were not located. Figures 2.57 and 2.58 show the effect of lengthening of the C-O bond on the C2-C6 internuclear distance and on the electronic energy of the system.

Some bridging between C6 and C2 was indicated in the *exo* species **264** in the unconstrained systems (indicated in Figures 2.57 and 2.58), since the C2-C6 distance in the *exo* species **264** is 0.1 Å less than in the *endo*-system **265**. However, in the highest energy structure, corresponding to an approximate transition point for the *exo* substrate ([Figure 2.58), the C2-C6 separation has decreased *very little*, and even when the C-O bond is clearly broken (*e.g* at 2.33 Å), the reduction in the C2-C6 separation is only 0.2 Å. For the *endo* species, even well past the apparent transition state, C6 is only 0.04 Å closer to C2. Certainly from a

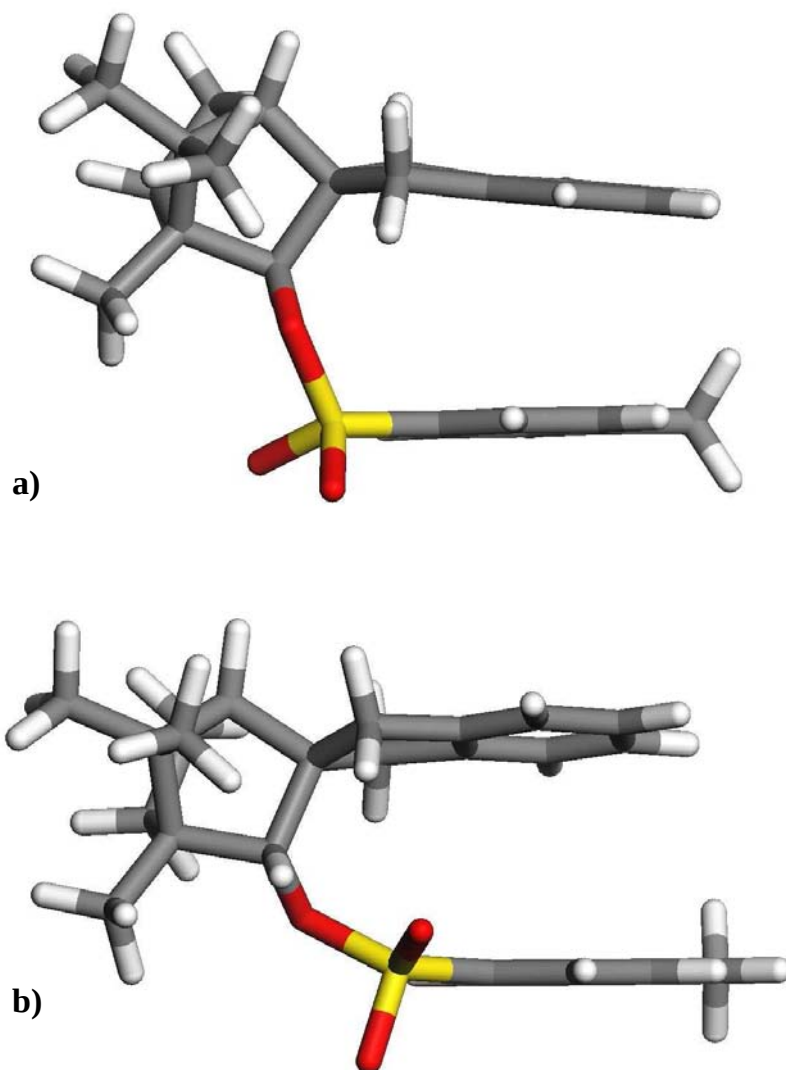


Figure 2.56: Geometry optimized structures of a) the *exo*-tosylate **255**; and b) the *endo*-tosylate **258**.

geometric point of view it seems that bridging, in both the *exo*- and *endo*- cases, largely lags the ionization, *i.e.* rearrangement to the cation **176** does not take place in concert with the ionization.

It is logical, therefore, to consider the fate of this cation **177**. Although medium effects are expected to be important, studying the cation **177** in isolation from the tosic acid produced is not altogether unreasonable.

2.3.4.2 Rearrangement to the optically pure camphene

Figure 2.59 shows how Hartree-Fock [6-31G] minimization quickly “relaxes” the structure of cation **177** obtained from the initial AM1 geometry optimization (**I**). There is, however, a level

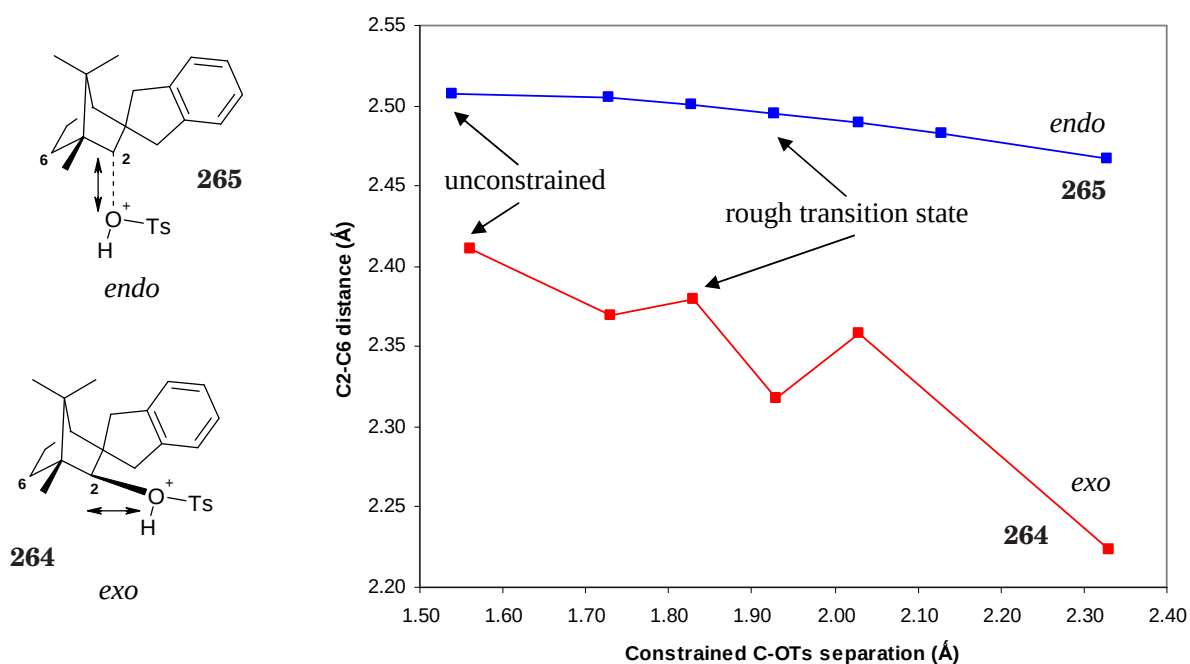


Figure 2.57: Constrained optimizations of protonated tosyl species.

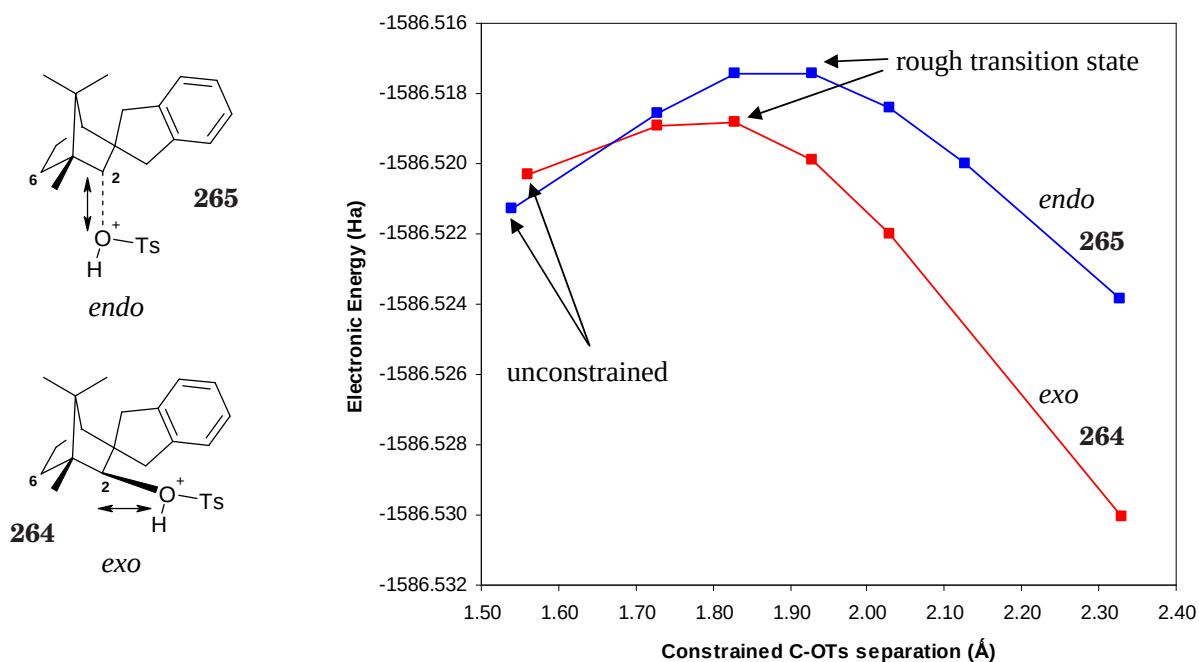


Figure 2.58: Constrained optimizations of protonated tosyl species.

region during which the geometry slowly changes with little change in relative energy until carbon-6 is in a position to bond to carbon-2 (structure **II**). Rearrangement then takes place rapidly, driven by the secondary to tertiary carbocation transformation and producing the cation **176** (structure **III**). Calculations at the DFT level using the 6-31G(d) basis set afford a

slightly less flat energy gradient in the region leading up to structure **II**.

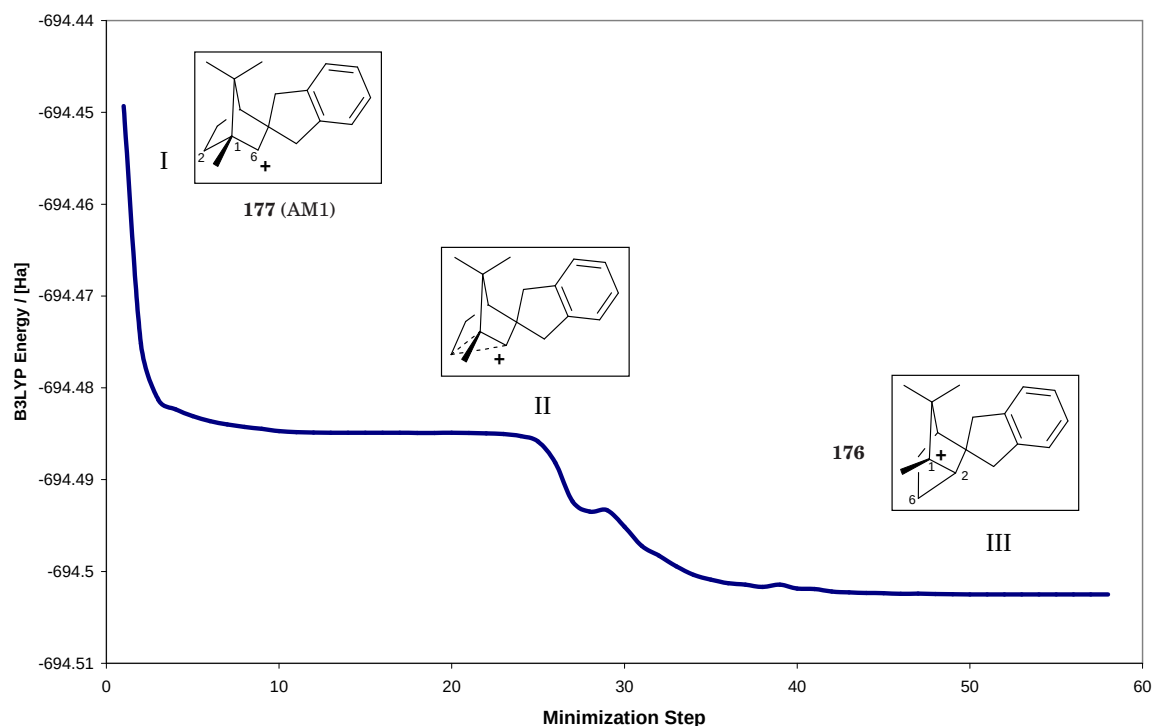


Figure 2.59: HF/6-31G(d) energy minimization and resultant rearrangement of cation **177** to the camphenyl cation **176**.

It was anticipated that the potential energy surface for these transformations would be a valley-ridge inflection point (such as that described by Sadasivam¹⁸⁹), and resemble the surface shown in Figure 2.60. (This figure was generated artificially in Povray¹⁹⁰ by rendering a function of two variables $f(x, y)$, where $f(x, 0)$ has a minimum at a “transition state” $(0, 0)$ and $f(0, y)$ has a maximum at that point). The remarkably flat region **II** in Figure 2.59 was thought, then, to correspond to the “ridge”. Transition state geometry searches from this region failed to produce a transition species (as is expected on the “ridge”). At earlier stages in the study, it was anticipated that this transition state (if it existed) would connect the two assumed products (the pinenyl system **260** and the camphenyl system **176**). This minimization had an added complication: the failure to locate an optimized geometry associated with the initial cation **177** left its existence uncertain.

Varying the C1-C6 and C2-C6 bond lengths in the common cation **177** (Figure 2.61) affords a potential energy surface for the initial reaction **177** $\rightarrow$ **176**. A series of structures with different constraints C1-C6 and C2-C6 bond lengths were initially optimized at the AM1 level, and these optimized systems were then used for constrained optimizations at the Hartree-

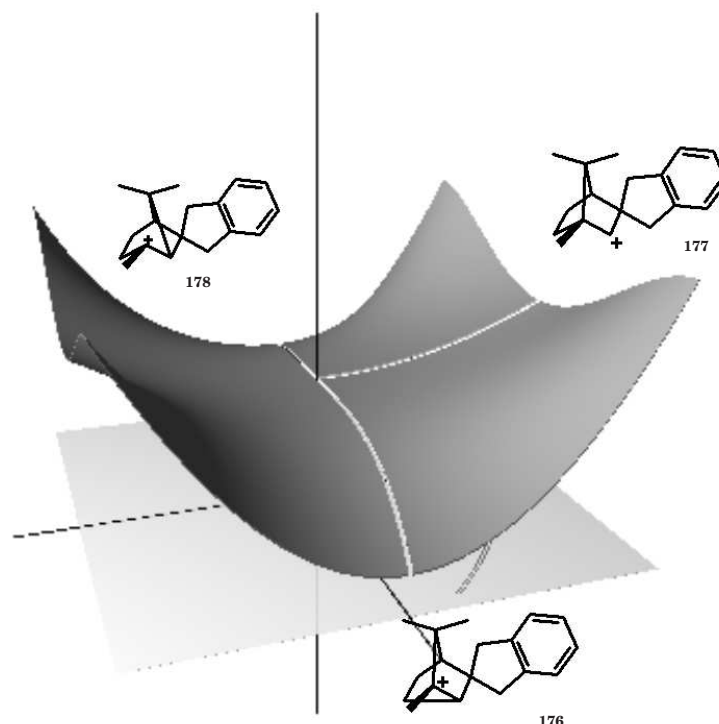


Figure 2.60: Artificially generated potential energy surface illustrating the anticipated energy relationship between starting cation **177** and product cations **176** and **178**.

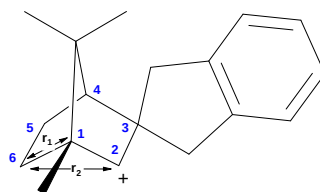


Figure 2.61: Bonds that are varied to generate a potential energy surface in **177**.

Fock and DFT levels. This prevented (in most cases) unwanted rearrangements at the HF and DFT levels. The potential energy surfaces obtained at each of the three levels of theory are shown in Figure 2.63 with r_1 (the C1-C6 distance) and r_2 (the C2-C6 distance) being varied between 1.5 and 2.4 Å. Since the only two constraints are the C1-C6 and C2-C6 distances, highly strained systems at the edges of the potential energy surfaces tended to undergo other rearrangements that relieved the strain. Such rearrangements included a shift of half of the xyllyl group, but no attempt was made to explore these constrained structures further since it was the central region of the surface that was of interest. However, one rearrangement of particular interest was the concerted hydride-shift (**177** → **266**) Wagner-Meerwein (**266** → **267**) rearrangement illustrated in Figure 2.62 - a process later found at the DFT level to be

implicated in the transformation of cation **176** to cation **261**.

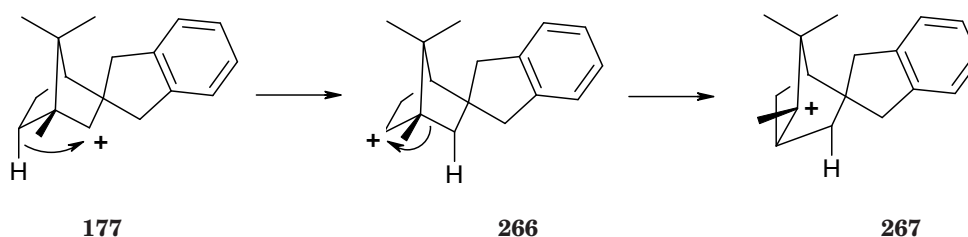


Figure 2.62: Concerted 6,2-hydride shift/Wagner-Meerwein rearrangement.

The semiempirical surface (Figure 2.63 a) differs from the more accurate Hartree-Fock and DFT models (Figure 2.63 b and c) to the extent of suggesting the existence of two classical cations corresponding to the two potential energy wells on the surface. The Hartree-Fock model affords similar results to the more demanding (at least in GAMESS) DFT model, but exhibits a steeper slope on the reactant side of the well relative to the same gradient at B3LYP. B3LYP methods, unlike higher level MP2 calculations, have been found to produce symmetrical norbornyl cations, and unsymmetrical substituted norbornyl cations in accordance with experimental evidence¹¹⁵ (MP2 tends to overestimate the bridging and produce, for example, a symmetric bridged dimethylnorbornyl cation). Regardless of the differences in potential energy surfaces, the stable geometry after minimization is essentially identical for the Hartree-Fock and DFT(B3LYP) cases, and it could be argued that not much is gained by optimizing at the DFT level. Both Hartree-Fock and DFT(B3LYP) methods reveal only one well on the potential energy surface, indicating that the transformation from cation **177** to cation **176** requires no energy of activation. Consequently, steps requiring energy of activation are those involved either in the protonation of the tosylate **255**, direct formation of the transient cation **177** from the protonated tosylate **264** or the loss of a proton from cation **176** to form the neutral camphene **179**.

The theoretically determined structure of the first rearrangement product thus corresponds to the spectroscopically and crystallographically determined structure **179**.

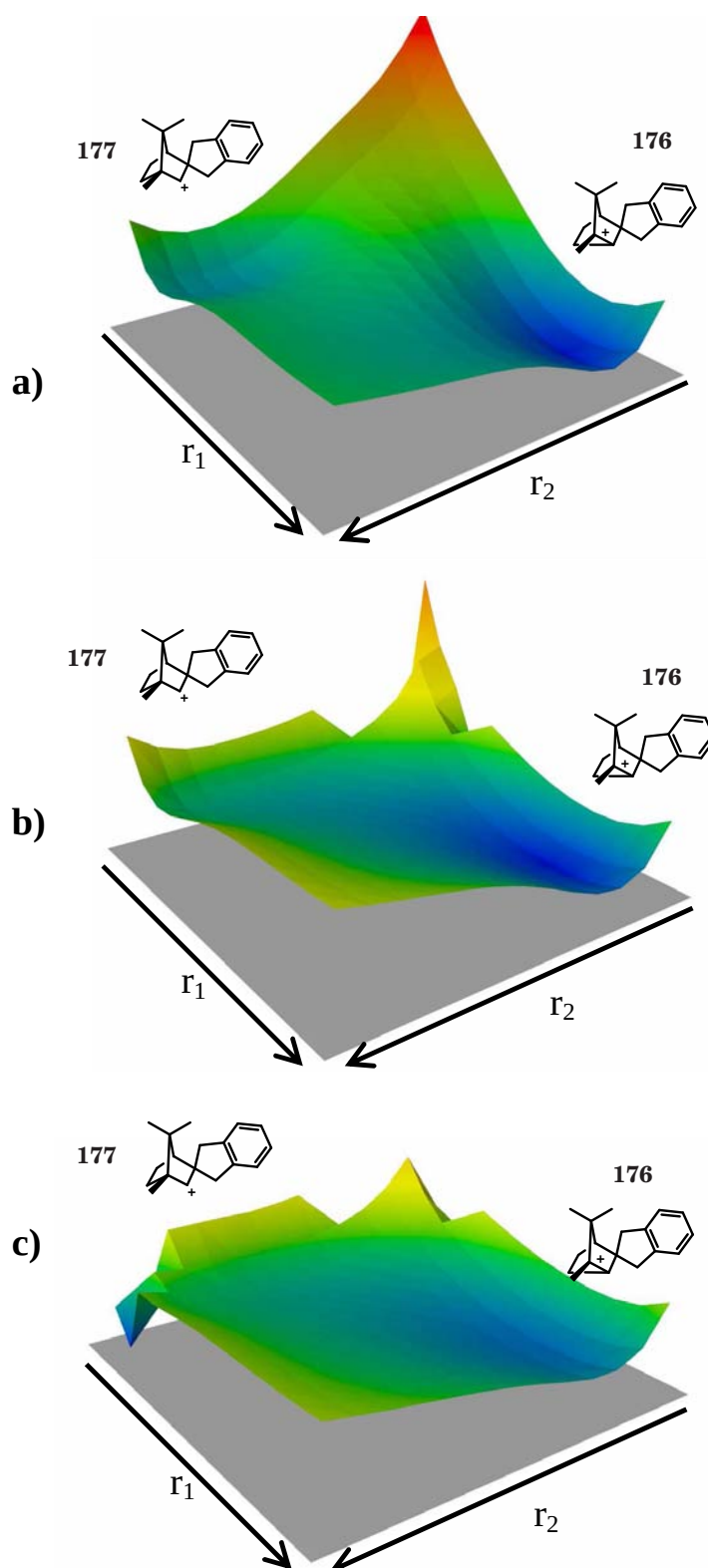
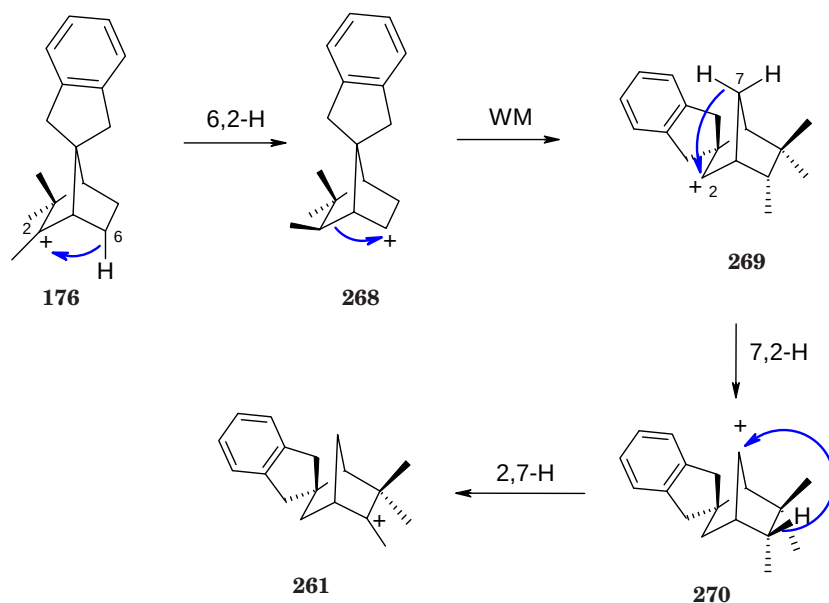


Figure 2.63: Potential energy surfaces for rearrangement of cation **177** to **176** at the :- **a)** AM1; **b)** HF/6-31G(d); and **c)** B3LYP/6-31G(d) levels; r_1 = C1-C6 distance and r_2 = C2-C6 distance.

2.3.4.3 Further rearrangement of camphene 179 to the isomeric camphene 263

A mechanistic pathway for the transformation of camphene **179** to the isomeric camphene **263** is not immediately apparent. After considering common literature rearrangements, such as the 3,2-hydride and methide shifts, the 6,2-hydride shift, and even the double-Wagner-Meerwein rearrangement,¹²³ no obvious pathway became apparent. In desperation, 7,2-migrations, were considered in order to provide the four-step sequence from **176** to **261** (Scheme 2.39). This transformation appears to be feasible, and similar to the established 6,2-hydride shifts; transition states were even located at the AM1 level for this type of transformation (see Figure 2.64 for an example). However, in preliminary studies at the AM1 level of 7,2-migrations of simplified systems it was apparent that the shift required an unfavourable distortion of the norbornyl skeleton. Moreover, there is no precedent for 7,2-hydride migrations in the literature, and attention was therefore turned to other means of solving the problem, *viz.*, Car-Parrinello molecular dynamics and coset analysis of the system.



Scheme 2.39: Possible rearrangement pathways between products involving 7,2-hydride shifts.

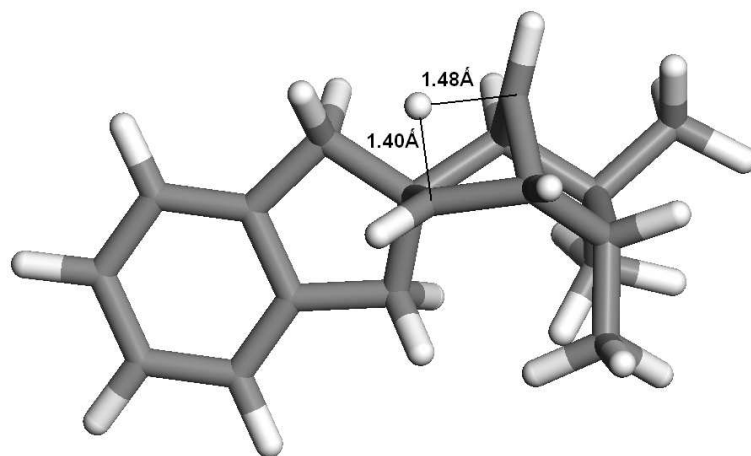


Figure 2.64: AM1 transition state for the first 7,2-shift illustrated in Scheme 2.39.

2.3.4.3.1 Car-Parrinello molecular dynamics A conceptually simple way of examining movement between favourable and unfavourable cations would be an *ab initio* dynamics approach that permitted the formation and breaking of bonds in such systems. The Car-Parrinello Molecular Dynamics¹⁹¹ (CPMD) software package afforded access to such studies, and preliminary B3LYP-level geometry optimizations of a norbornyl cation produced a system with the expected symmetric geometry. Geometry optimization of the camphene cation **176** was similarly effected using the CPMD software before commencing the dynamics study. The resulting structure showed significantly more C2-C6 bridging than the earlier GAMESS [B3LYP/6-31G(d)] structure with contraction of the C2-C6 distance (2.24 from 2.48 Å) and extension of the C1-C6 bond (1.62 from 1.56 Å). Since our approach is to explore the molecular dynamics through the multitude of shift combinations to produce the most stable product, inaccuracies that raise or lower activation energies in comparison to their true values, will speed or slow the dynamics process.

A 50000 step Car-Parrinello molecular dynamics run was effected at 700K. At this temperature rapid rotation of the methyl groups and flipping of the xylyl 5-membered ring are observed. Interestingly, bridging towards the tertiary centre (C-2) does occur (Figure 2.65), but formation of a “pure” secondary cation was not observed. Figures 2.66 and 2.67 show bond distances and hence evidence of bridging at certain points during the run corresponding to structures (c) and (a) in Figure 2.65, respectively.

Our intention was to observe the formation of cation **176**, the precursor of the second camphene product **261**. However, from the graphs, it is evident that during the course of the dynamics run bridging has occurred no more than five times. If 6,2-hydride shifts occur more than order of magnitude slower than this, they would be difficult to observe due to computational requirements. It has been observed that 3,2-hydride shifts occur 10^9 times slower than either of these (Wagner-Meerwein or 6,2-hydride shifts) at -120°C .⁷ It is likely, therefore, that the even slower methide-shifts that are required for the desired transformation will not be observed in a dynamics simulation at a reasonable temperature in a reasonable time-frame!

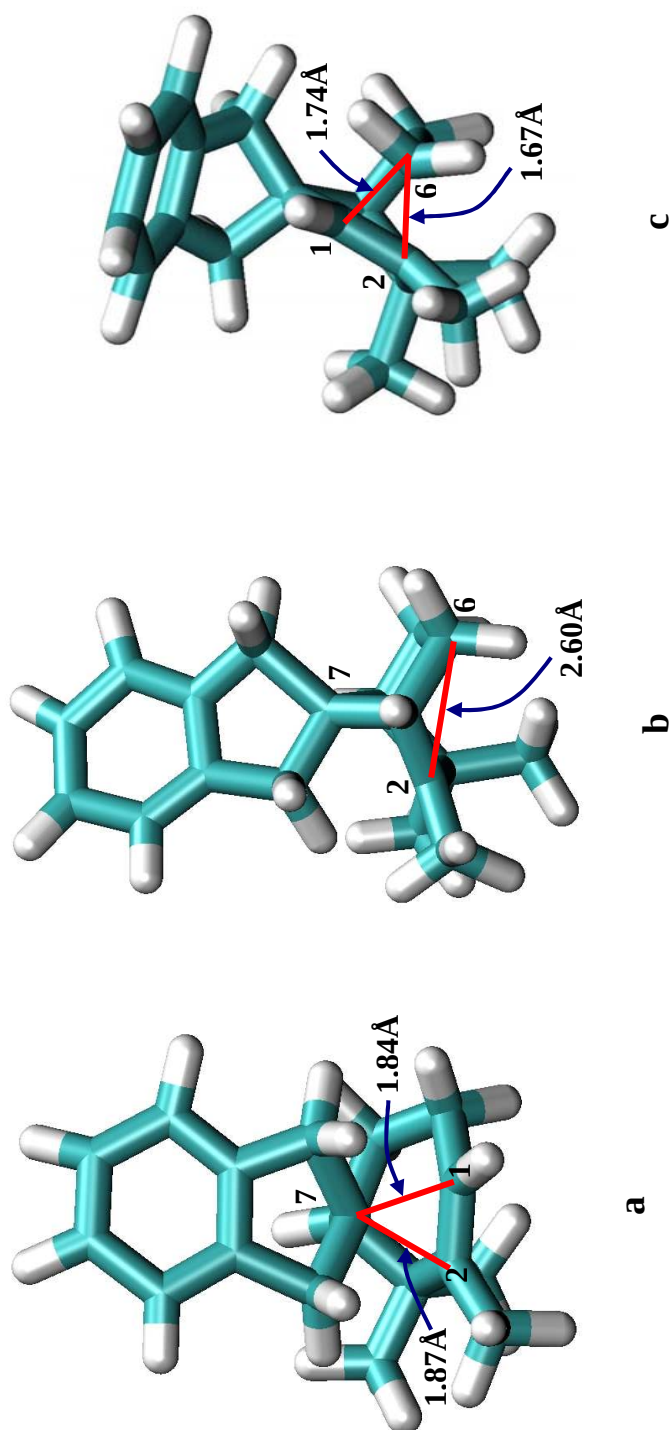


Figure 2.65: Car-Parrinello molecular dynamics of cation **176** at 700K. **a)** Step number 13434 showing C2-C7 bridging; **b)** step number 16155, showing no bridging ; and **c)** step number 20080, C2-C6 bridging.

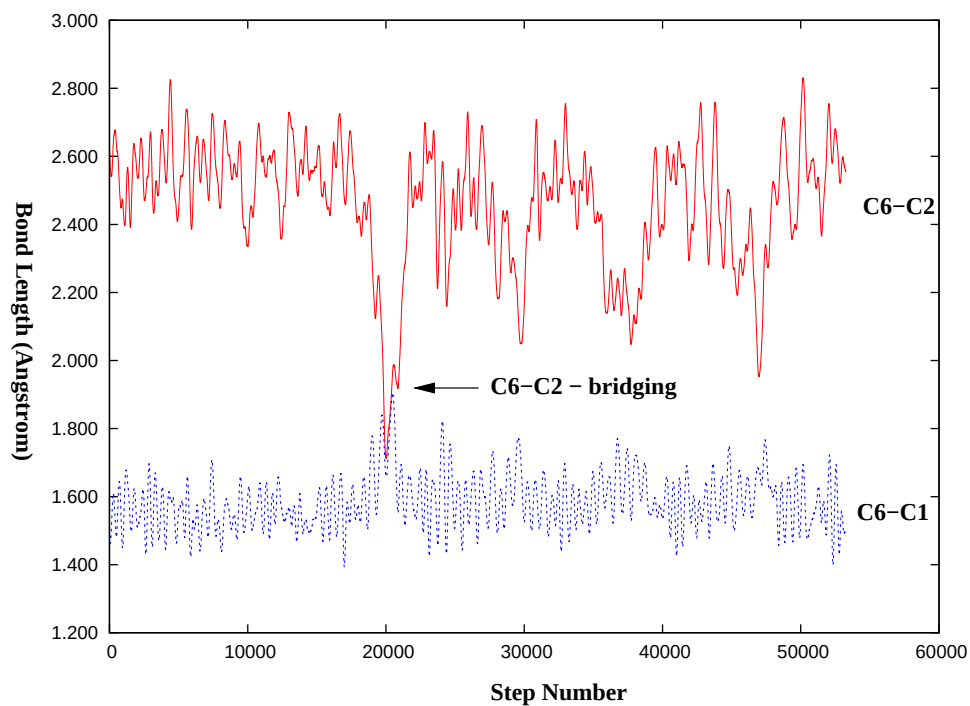


Figure 2.66: Changes in the C6-C2 and C6-C1 bond lengths during the Car-Parrinello dynamics run on cation 176.

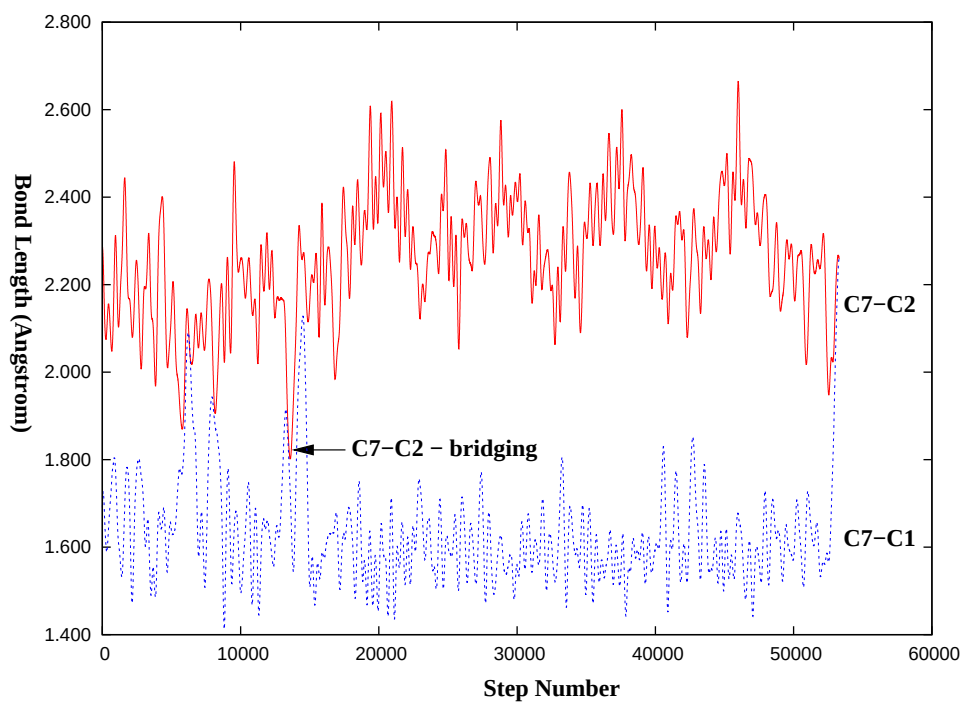


Figure 2.67: Changes in the C7-C2 and C7-C1 bond lengths during the Car-Parrinello dynamics run on cation 176.

2.3.4.3.2 Coset Analysis C. K. Johnson has described a method for evaluating pathways in norbornyl systems with the use of a computer programme he had written (ORNOCARE - Oak Ridge Norbornyl Coset Analysis and Rearrangement¹⁵⁰). Since the original programme was written in PL/1 for an IBM-360 mainframe computer, it seemed wise to recreate the programme using C++ with the wxWindows (recently renamed to wxWidgets) visual library (see Figure 2.68 and Appendix 4.5; p. 304). Testing of the programme involved discovering routes for the formation of acetophenones¹⁵¹ (Scheme 1.36; p. 43). The path obtained was identical to that produced by Johnson's programme.

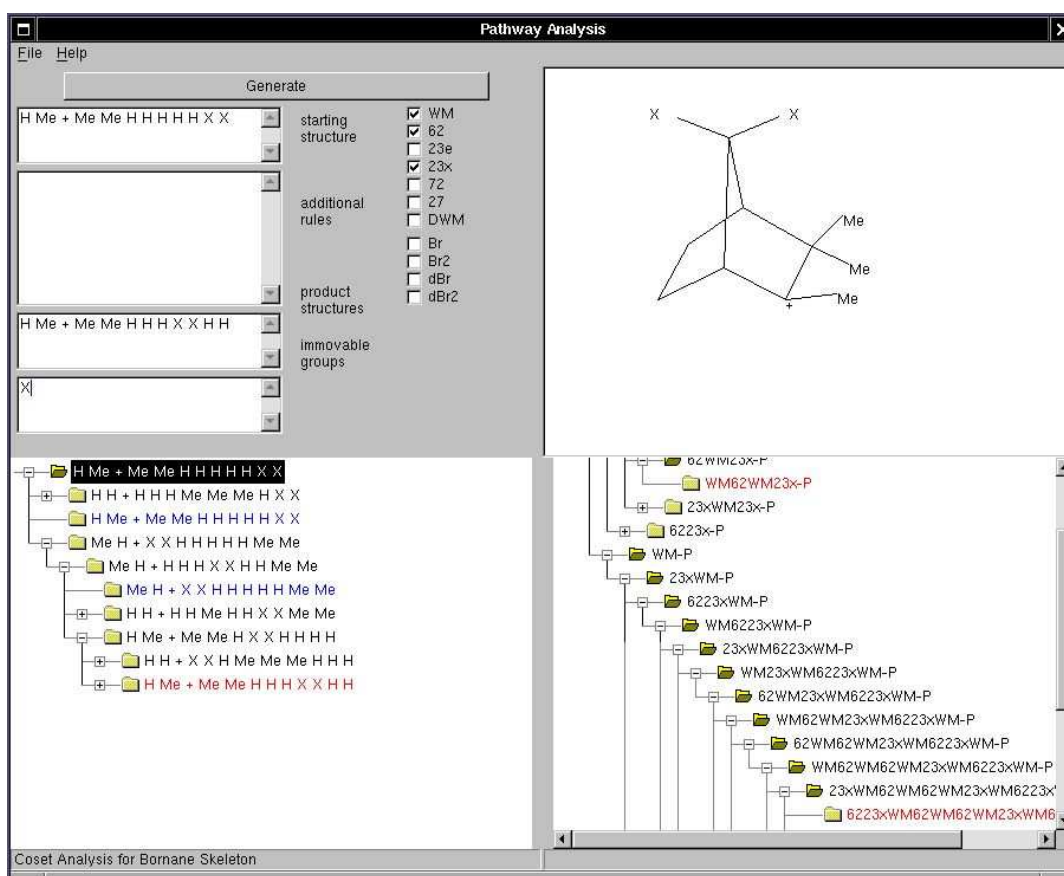


Figure 2.68: Screenshot of Program.

The recreated programme (See Appendix 4.5 p. 304) was implemented as follows:- A class (**Bornane**) was created, with substituted bornane structures being represented as instances of this class. Each bornane object had an associated descriptor, such as “Me H + X X H H H H H Me Me”. There are twelve substituent positions on any norbornyl skeleton (see Figure 2.69 as an example). These are numbered 0,1,2,...,11 referred to as indices due to programming convention. The order of substituents in this descriptor was arbitrarily chosen such that *exo*-

were listed before *endo*-substituents. Thus the 1-position corresponds to index 0; the 2-*exo*-position corresponds to index 1; the 2-*endo* to index 2; and so forth. On the cationic centre, the substituent was written before the positive charge (thus the descriptor is “Me H + X X H H H H H Me Me” for the cation at position C2). The **Bornane** class had procedures for comparing two bornane objects, based on the descriptor, identifying the structures as different, identical or enantiomers. The class always rewrites a given or generated descriptor such that the positive charge is placed at index 2 or 6, never at index 3 or 5. To create the reduced graph the positive charge is always placed at index 2. The underlying assumption is that all structures are classical carbocations, for instance the classical carboaction in Figure 2.69.

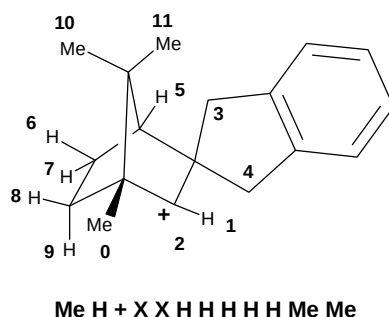


Figure 2.69: Descriptor of substituted bornane systems illustrating the index system used.

For the transformations, a class **RuleList** was created. Each rule in **RuleList** is described in terms of the necessary preconditions (position of positive charge and moving group) and the subsequent rearrangement of substituents. For example, for a 6,2-hydride shift, the preconditions are :- i) a positive charge at either index 2 or index 9 in Figure 2.69 (*i.e.* two rules are necessary) and ii) the group that moves (from index 9 or index 2) must not be defined as immovable (for example, we should never consider a 6,2-methide shift). Once these preconditions are met, the rearrangement rule (*e.g.* “0 1 9 3 4 5 6 7 8 2 10 11”) is applied (Figure 2.70).

The first stage in the execution of the programme is consecutive application of all the transformations in **RuleList** (defining preconditions for type of rearrangement) to the starting **Bornane** object. For example, application of this programme to the rearrangement of the camphenyl cation **176** affords a graph, consisting of nodes (the classical structures) connected by edges (the possible transformations). This is achieved by applying a set of chosen transformations to the starting cation and all subsequently produced transformed cations until no new structures are produced. Figure 2.71 shows the first three generations of structures from

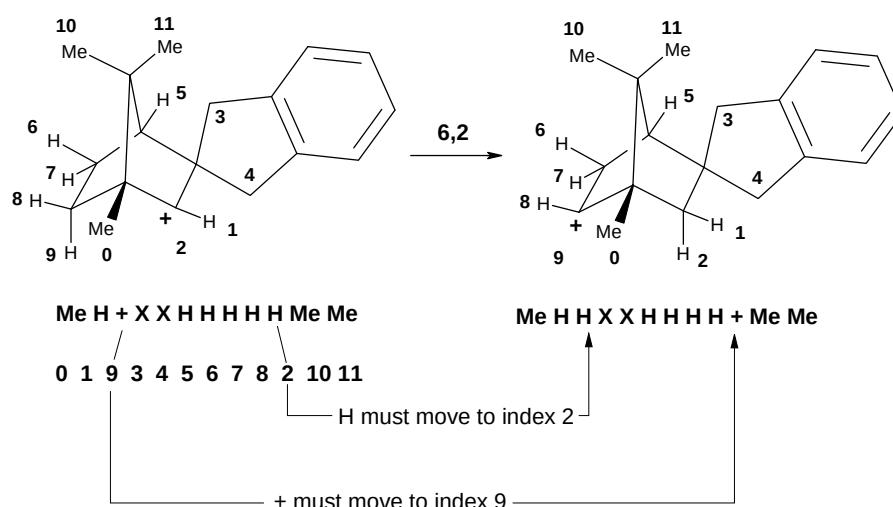


Figure 2.70: The rule “0 1 9 3 4 5 6 7 8 2 10 11” applies a 6,2-hydride shift.

the starting cation (Node **0**) by applying consecutive 6,2-hydride, 3,2-*exo*-hydride and 3,2-methide-shifts and Wagner-Meerwein rearrangements, to provide a total of 5 new, distinct structures. It should be noted that Figure 2.71 is a reduced graph, and the “incorrect” enantiomer is drawn on odd steps. The three rearrangement types are those which are generally recognized as feasible in bornane systems.[?]

In our implementation, the internal representation of this graph is an array of Bornane objects (Figure 2.72). The figure illustrates how Figure 2.71 is generated into three stages (A, B and C) by applying the possible rules to unique structures. The programme continues until no further unique structures are generated. Where necessary enantiomers are used instead of the actual produced cation to maintain the positive charge at index 2.

The reduced graph (Figure 2.73, p.162) obtained as a result of the first 13 sets of transformations from the cation **177** illustrates the process, the colour coding (AM1 energies) and the allowed rearrangement types, *viz.*, 6,2-hydride shifts, 3,2-hydride and methide shifts and Wagner-Meerwein rearrangements. The full graph illustrated in Figure 2.74 (reduced in the sense that enantiomers are not considered) contains 324 different cations, connected by 372 transformations [disallowing the unfavourable 6,2-*endo*-methide shifts, gives a graph with 336 cations, consistent with the fact that there are 336 possible trimethylxylyl-norbornyl cations (discounting enantiomers)].

Once produced, the graph is searched for possible pathways from the starting material to the product. The programme does this search but, in order to prevent cycles in the pathways, a restriction that any given pathway may only contain unique structures is applied. Originally

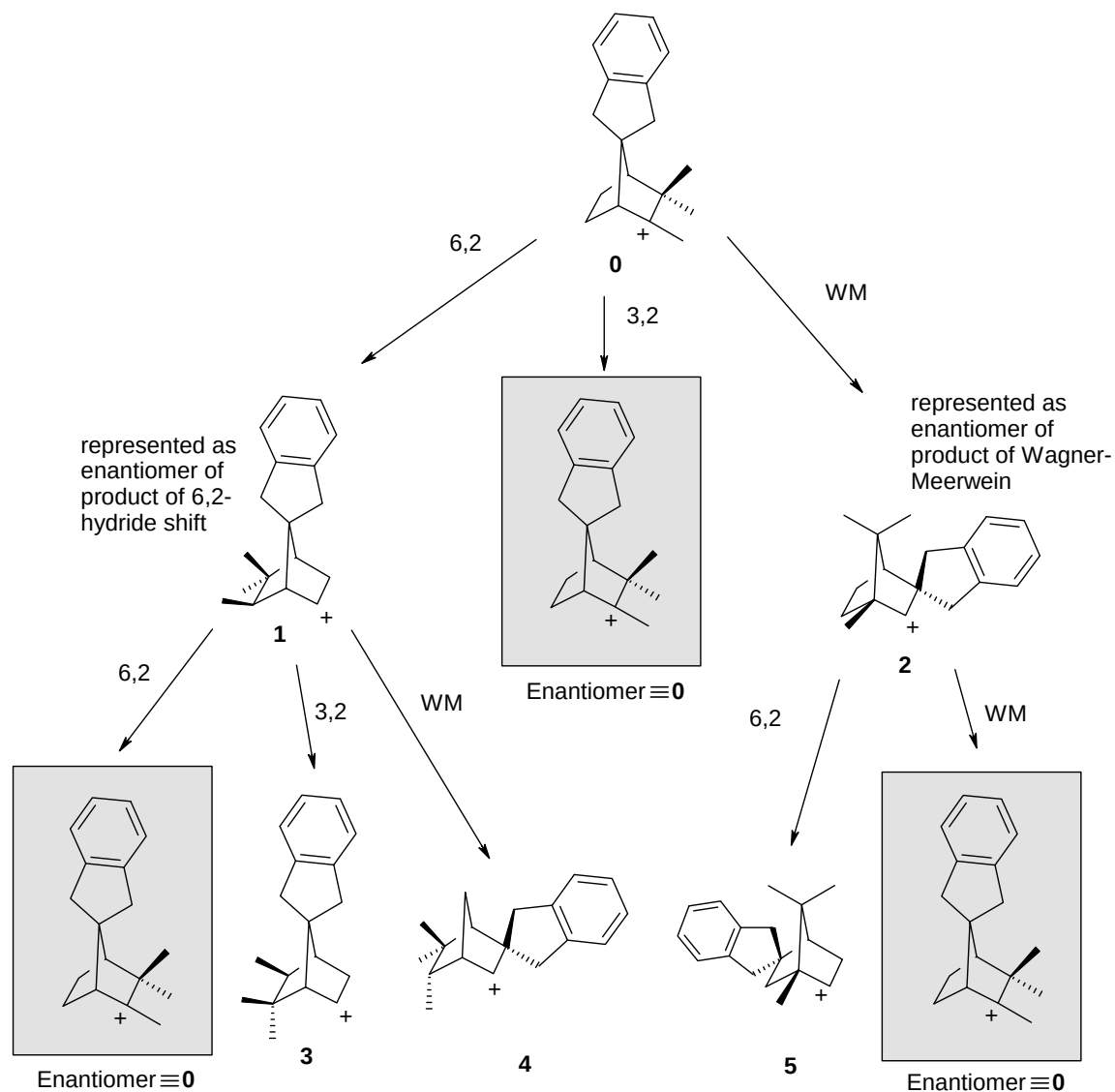


Figure 2.71: Graph generation by successive application of transformations. Structures have been drawn as enantiomers in some cases to place the positive charge at position 2. Greyed structures are not unique and are not used further. No 3,2-shift is possible on node 2.

Johnson *et al.*^{123,150,151} had ignored enantiomers explicitly, but had relied on the number of steps (even or odd) to determine which enantiomer is formed. This approach, however, automatically removes a number of isomerization steps, since enantiomers are not identified as unique structures.

Parent	Duplicate ^a	Unique	Transformation	Descriptor
		0		H Me + Me Me H H H H X X
0		1	62	H H + H H H Me Me Me H X X
0	0		23x	H Me + Me Me H H H H X X
0		2	WM	Me H + X X H H H H Me Me
1	0		62	H Me + Me Me H H H H X X
1		3	23x	H H + H H H Me H Me Me X X
1		4	WM	H H + X X H Me Me H Me H H
2		5	62	Me H + H H H X X H H Me Me
2	0		WM	H Me + Me Me H H H H X X
...	...	...	...	...

^a Includes enantiomers

Figure 2.72: Internal representation of Figure 2.71 as it is generated within the program. 62 denotes a 6,2-shift, 23x denotes 2,3-*exo* shift and WM indicates a Wagner-Meerwein transformation.

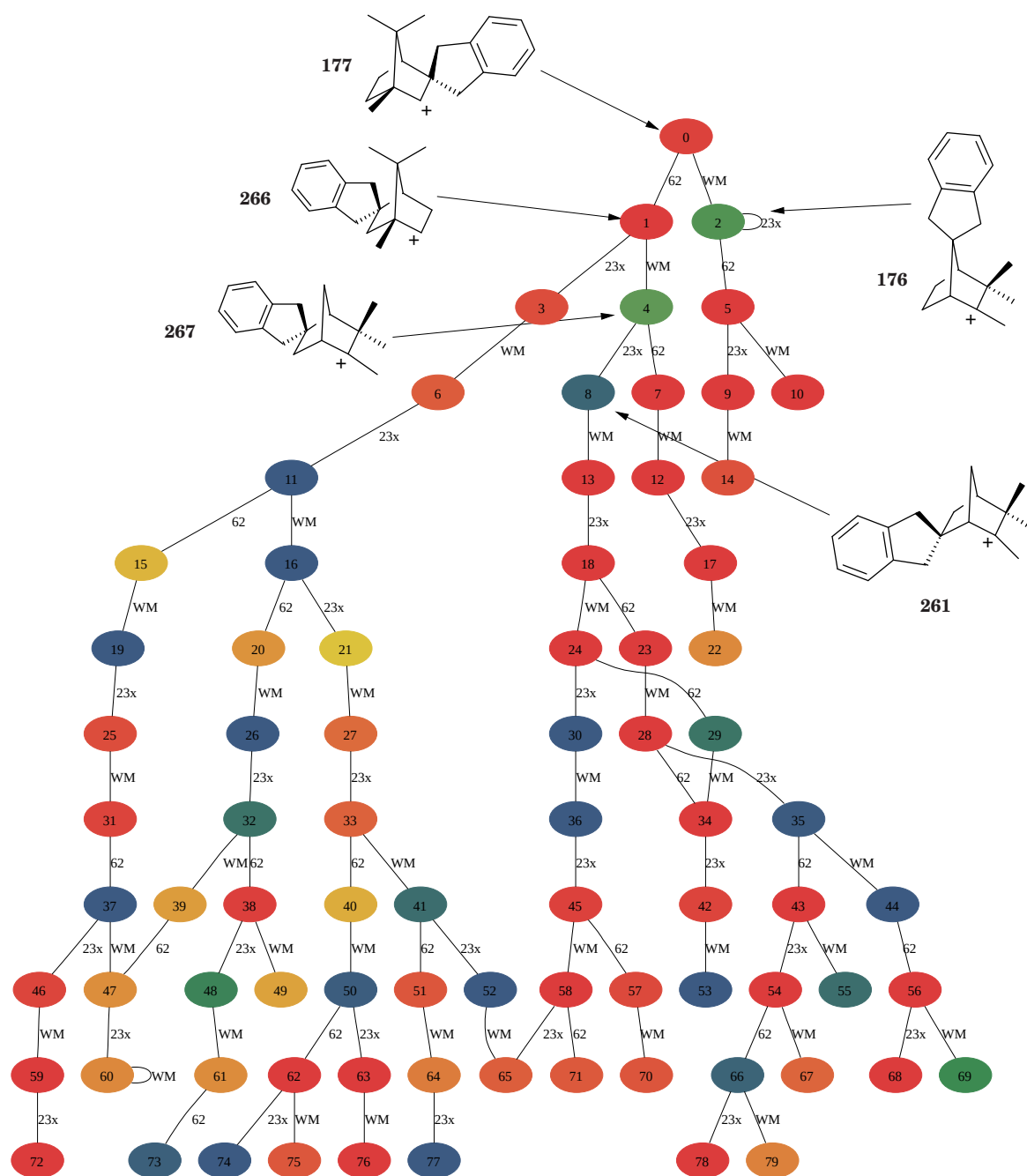


Figure 2.73: Portion of the reduced graph of transformations of the pivotal cation **177**. Of particular interest are the initial camphenyl cation **176** and the final camphenyl cation **261**, corresponding to the two camphene products obtained experimentally. Enantiomeric species are assumed to occupy the same node. The shortest route from **node 2** to **node 8** is clear. The second-shortest route includes **node 65**.

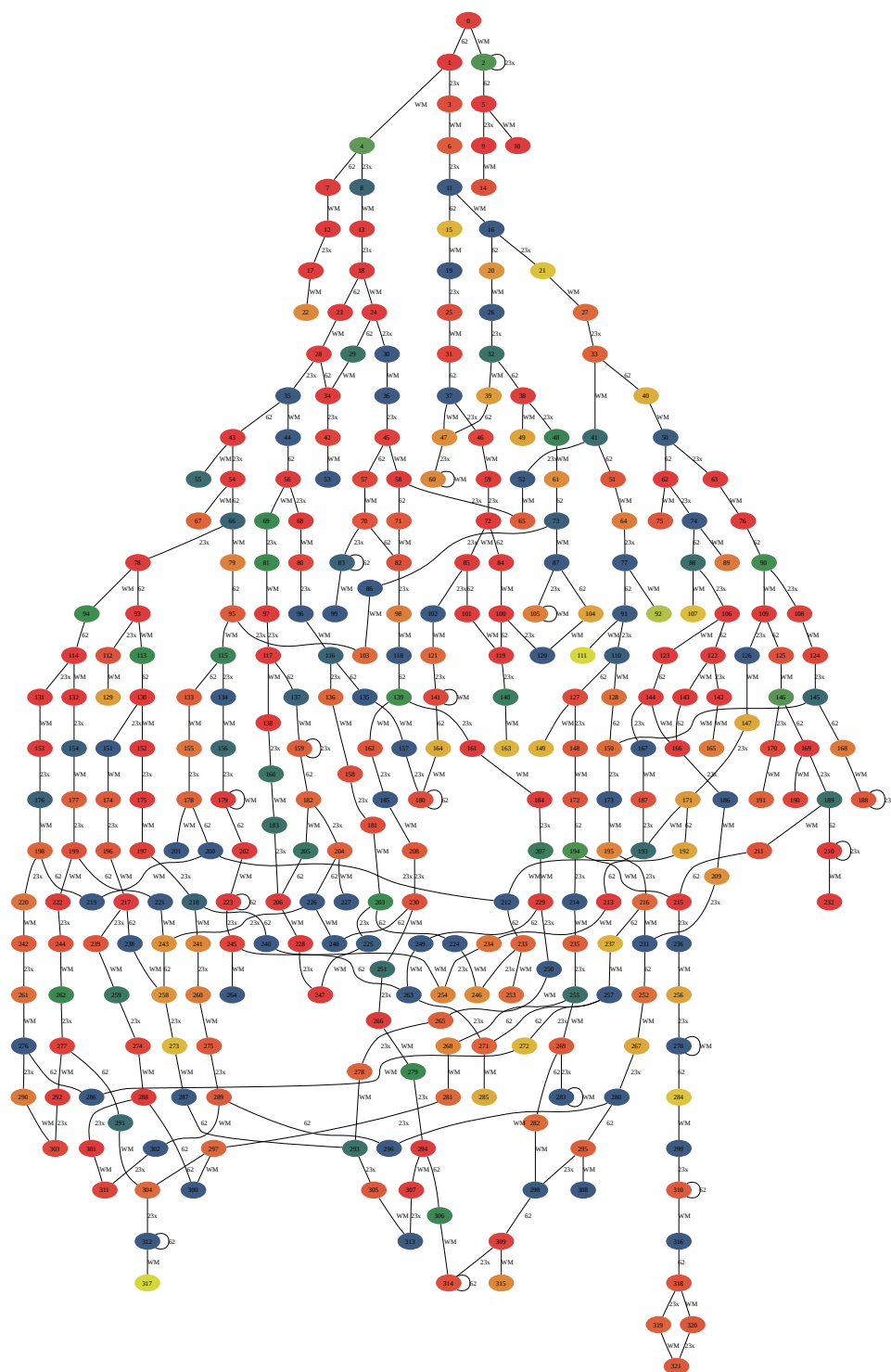


Figure 2.74: Reduced graph of all 372 transformations of the pivotal cation **177**. Of particular interest are the initial camphenyl cation **176** and the final camphenyl cation **261**, corresponding to the two camphene products obtained experimentally. Enantiomeric species are assumed to occupy the same node. The arrangement of nodes is different from Figure 2.73, but the connectivity is the same. AM1 energies of cations [relative to cation **282** (node **280**)] are represented ranging from blue to red.

The graph (Figure 2.74) provided routes (Figure 2.75) from the initial cation **176** (node 2) to its product **261** (node 8) and, in particular, routes that would account for the racemization of the system. Node 2 may transform to itself *via* a 2,3-*exo*-methide shift and, since each node represents a pair of enantiomers, such a single transformation would have to be a racemization step. The routes obtained were entirely unexpected, and it was surprising to find that *all* routes from cation **176** to **261** proceed *via* the common cation **177** (node 0)! It is clear from the graph itself that this is so. Scheme 2.40 illustrates the shortest routes for the transformation of the neutral camphene **179** (*via* cation **176**) to the enantiomeric compounds **263a** and **263b**.

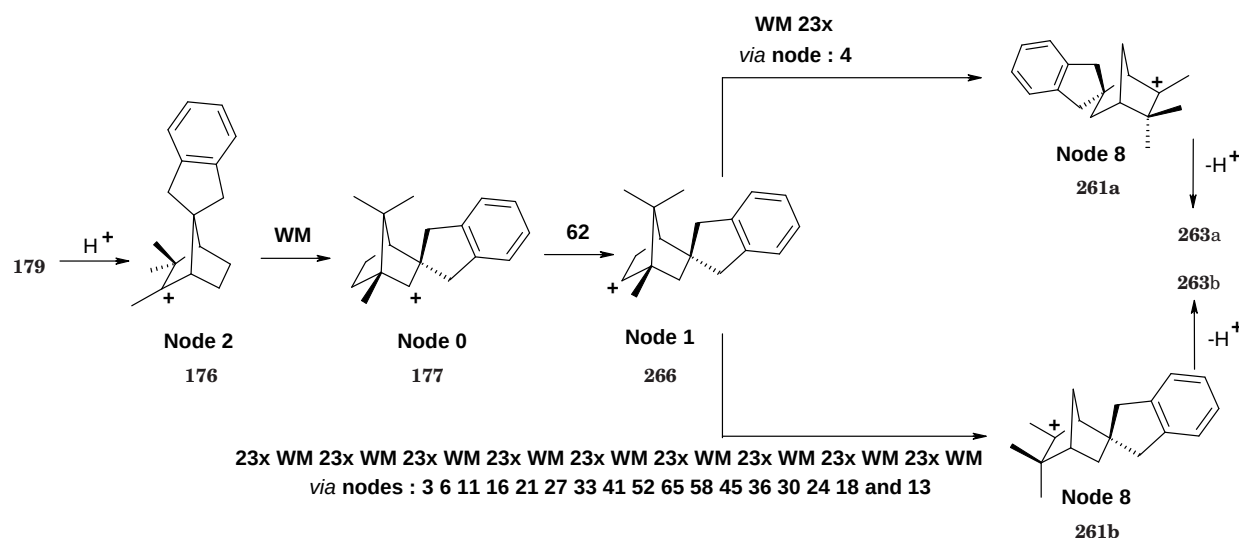
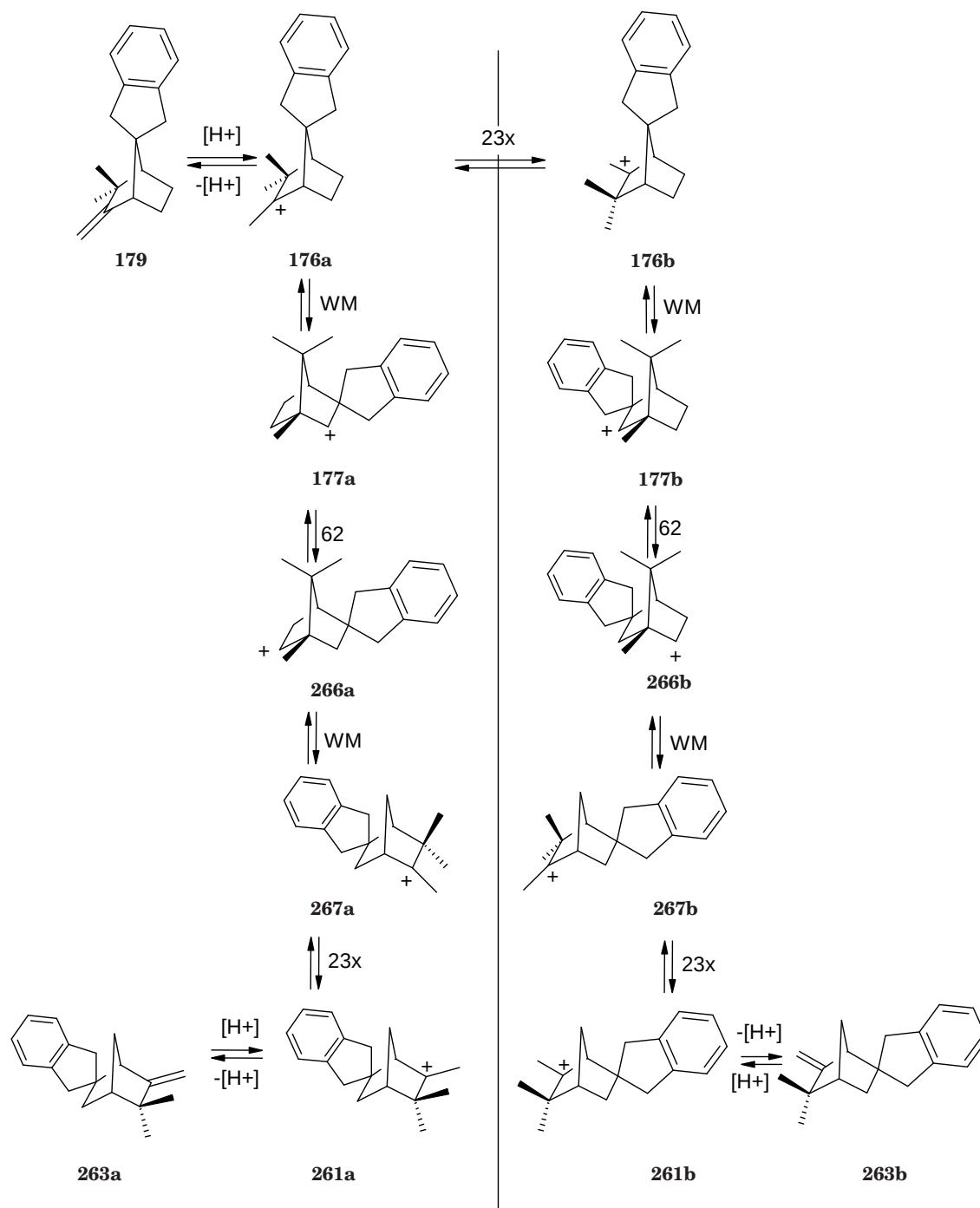


Figure 2.75: The two shortest paths from cation **176** to cation **261** *via* the cation **177**.

It is of passing interest to note that, in the case of the xylyl cations examined in this study, there are no pathways leading to the mutually interrelated set of 12 cations illustrated in Figure 2.76. While there are possible pathways interconnecting these 12 trimethylxylyl cations, *they cannot be produced from the starting cation 176 via a reasonable rearrangement pathway!* The coset analysis thus leads us to propose that the enantiomeric camphenes **263a** and **263b** are produced *via* the mechanistic pathways outlined in Scheme 2.40.



Scheme 2.40: Pathway from camphene I **179** to camphene II **263**.

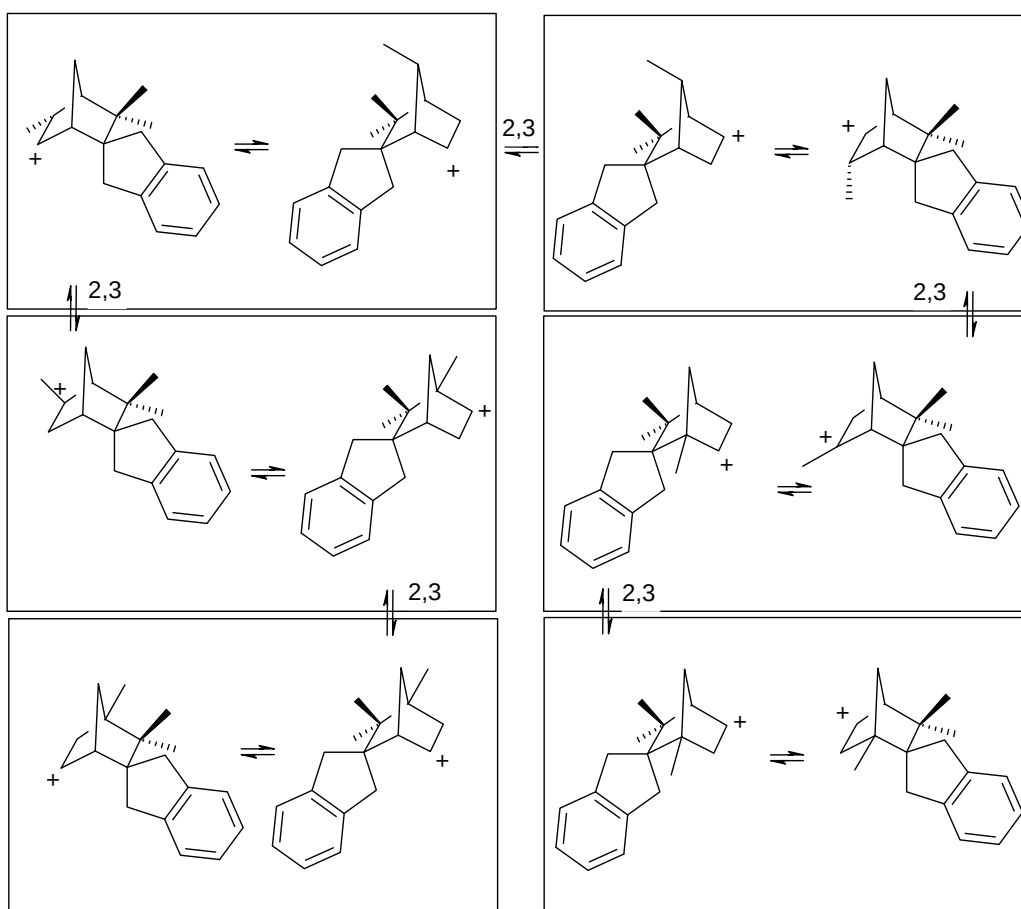


Figure 2.76: Relationship of cations not present in the graph 2.74 and hence not accessible from cation 176.

2.3.4.5 Energetics of the classical route

If we choose the shortest route on the graph (Figure 2.74), the relevant pathways use only 5 nodes or 1.6% of the graph! It may be questioned whether this result justifies the time and effort expended in developing the graph. Although there may be some justification for choosing a shorter pathway over a longer one, based on simplicity, a choice based on the energetic data must be more compelling. (By way of analogy, a yellow 1976 model Ford Escort might manage a 10km journey involving small hills, but 200m of mountain pass might prove impossible!) Two questions that can be addressed by the production of a graph such as Figure 2.74 are:- i) would it be possible to drive the reaction to even more stable products?; and ii) from an asymmetric synthesis point of view, is it possible to prevent racemization? Perhaps the best reason for examining systems like this in such detail is that the analysis reveals a diverse range of pentasubstituted norbornyl cations - secondary and tertiary and with substituents both close to and remote from the cationic centre. This approach clearly affords a comprehensive and, statistically, more accurate view of the rearrangement options than could be obtained from studying a single cation in isolation.

Of course, one problem with obtaining energy data for such a large system is the quantity of data generated. It is pointless to generate energy data for both pairs of enantiomers, but care must be taken to account for racemization: $A \rightleftharpoons A'$, where A' is the *enantiomer* of A [exemplified by the 2,3-*exo*-methide shift which mediates the transformation: **176a** $\rightleftharpoons$ **176b** (Scheme 2.40)]. The challenge was to generate 3-dimensional molecular structures for all 336 unique species, corresponding to *one set of enantiomers* and the following approach was adopted.

The xylyl group may appear as a 3,3'-, 5,5'-, 6,6'- or 7,7'-substituent, and the four associated series of cations constitute the 336 structures. Consequently, four fully methyl-substituted xylyl-norbornyl cations, **271**, **272**, **273** and **274**, and the four corresponding unsubstituted xylyl-norbornyl cations **275**, **276**, **277** and **278** were constructed - both sets representing the possible locations of the xylyl moiety.

Alignment of all eight structures provided three dimensional data for methyl and hydrogen substitution at any position on a xylyl-substituted norbornyl system. A simple programme (See Appendix 4.7, p. 311) was created and used to read in this data and produce the series of 336 trimethyl cations. The programme produces more than one copy of each system (distinguishing between the methyl groups) but computer file-systems disallow duplicate files with

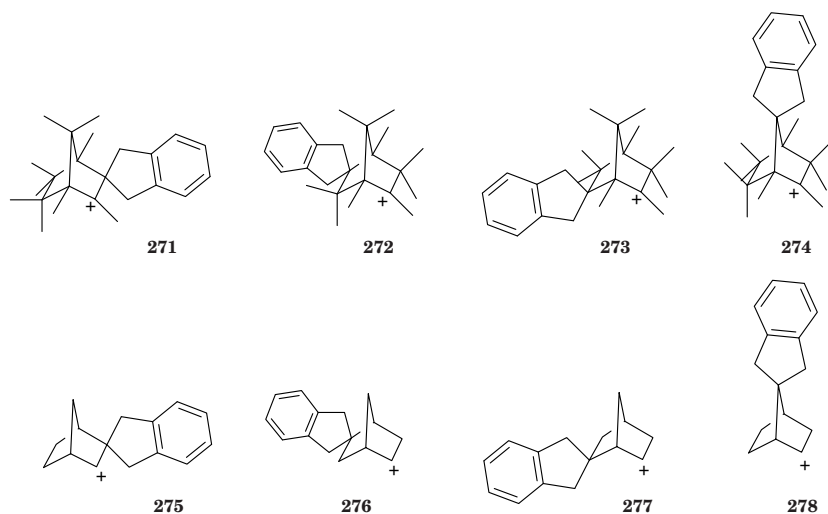


Figure 2.77: Xylyl-substituted norbornyl systems.

identical names, so the correct number of files, one per unique cation, was produced.

All 336 structures were then minimised using the AM1 semi-empirical model, to obtain AM1 electronic energies for all the cations on the graph. This data is represented in colour in Figure 2.74. Interestingly, examination of the energies of the cations revealed that :- i) the final cation **261**, *i.e.* precursor of the product obtained experimentally, does not correspond to the most stable cation; and ii) the cation energies fall into at least two distinct groups, corresponding to the higher energy, secondary carbocations and the lower-energy, tertiary carbocations. Figure 2.78 shows the energies of the cations, ordered “alphabetically” into substitution groups:- **I**: 6-H,2-H (secondary carbocation); **II**: 6-H,2-Me (tertiary carbocation); **III**: 6-Me,2-H (secondary carbocation); and **IV**: 6-Me,2-Me (tertiary carbocation).

It is interesting to note that the least stable secondary cation **279** (Figure 2.79) is sterically hindered, while the most stable secondary carbocation **280** has an even distribution of groups around the norbornyl skeleton. The least stable tertiary carbocation is the sterically hindered structure **281** while the most stable of all is the tertiary cation **282**. The AM1 model electronic energies are thus consistent with established principles concerning carbocation stability and steric hindrance.

Although examination of the carbocation energies may give a clear indication of which cations are likely to be thermodynamically favoured, the kinetics and, hence, which rearrangements are likely to occur, are dependent on the relative energies of the transition states leading to these cations.

There are 336 possible cations, but the number of edges (*i.e.* the total number of transfor-

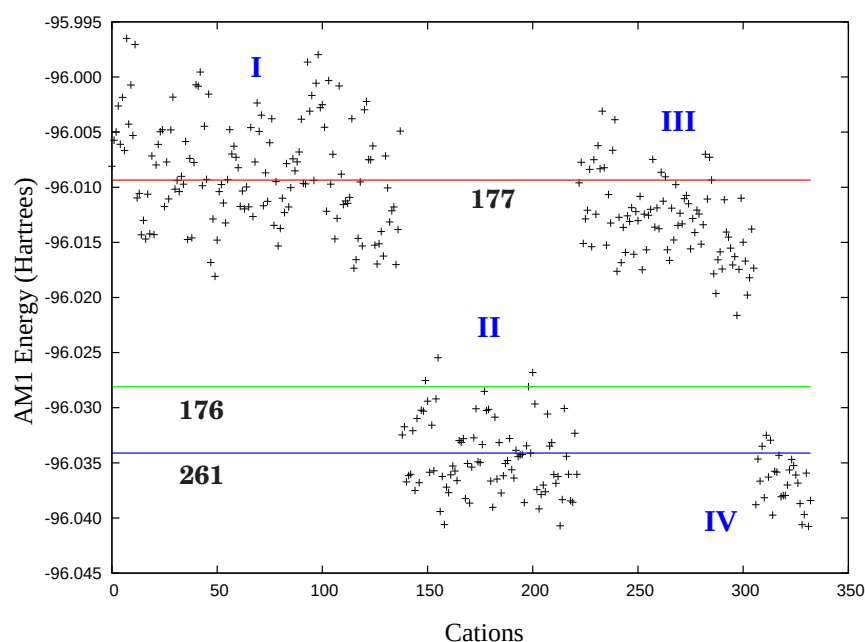


Figure 2.78: AM1 energies of all cations represented in Figure 2.74. The horizontal lines indicate the energy levels of the initial cation **177** (top), the first product cation **176** (middle) and the second product cation **261** (bottom).

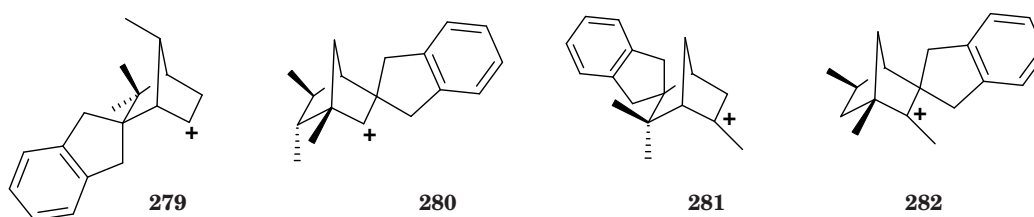


Figure 2.79: Stable and unstable cations located in AM1 calculations.

mations connecting pairs of those 336 cations) is 526 if 6,2-methide and *endo* 3,2-shifts are permitted; this corresponds to 526 transition states! This number includes transition states associated with the conversion of a particular node to itself (each node represents a pair of enantiomeric cations, and the stereochemistry can be tracked by counting the number of steps in a process). For example, if a methide shift in a given structure produces the enantiomer, we cannot lose track of that process simply because the starting node is energetically the same as the product node. Not all transition states are needed. For example, if an *exo*- and an *endo*-hydride shift produce the same product it makes sense to examine the *exo*- transition state, since from literature we know that *exo*-shifts are favoured in these systems.^{136,137} Nevertheless, a strategy was required that would be capable of producing all 526 transition states.

The initial approach involved computation of a linear least motion (LLM) path,¹⁸⁸ based

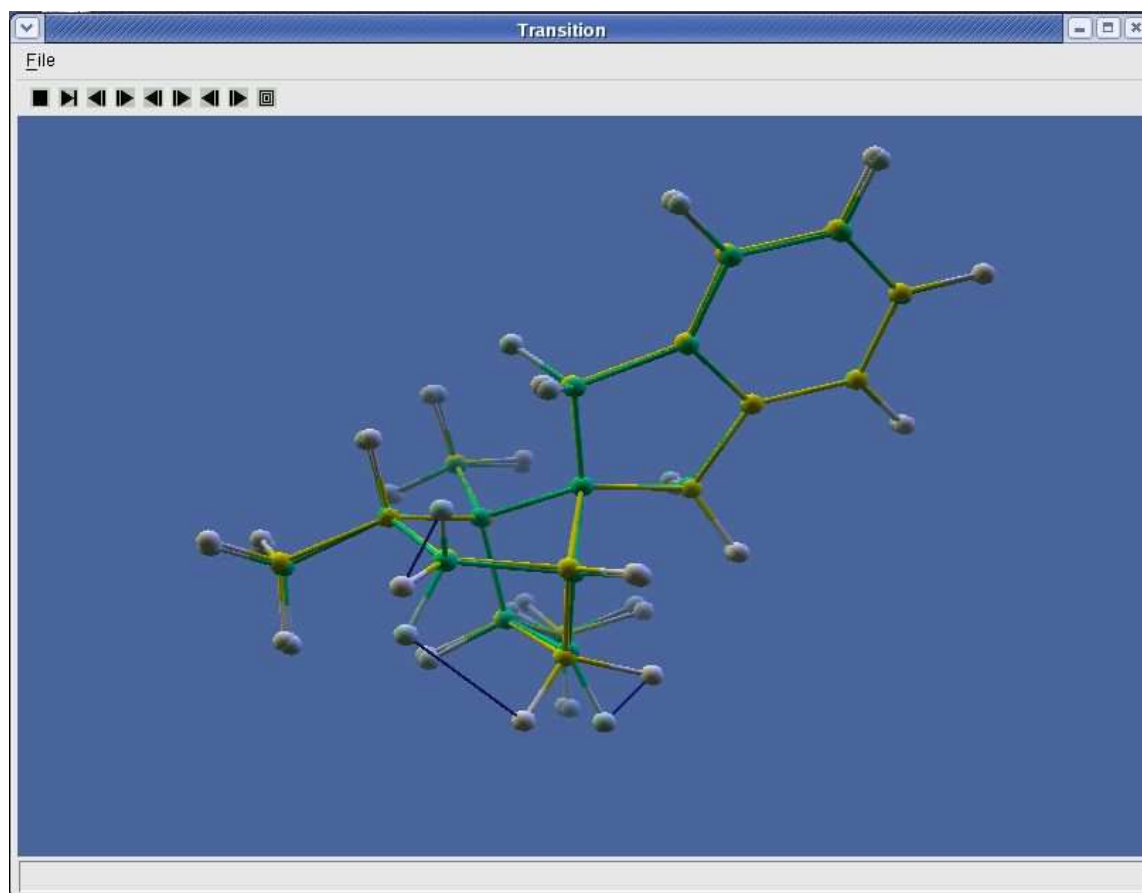


Figure 2.80: Molecular alignment for transition state search using the CINEB method. Reactant structure is yellow; product structure is green. Blue lines connect “matched” atoms from each structure.

on the assumption that individual atoms in the transition state must lie somewhere between their initial and final positions. The problem was to find geometrical averages (of starting and product structures), and a programme (Appendix 4.6; p. 309) was developed to automatically read in pairs of structures that would allow for manual alignment (and enantiomerization of the product structure if necessary). The programme was designed initially to align the structures of starting material and product by superimposing their respective xylyl groups and a series of weighted spatial averages were written to individual files. One in each series of weighted averages was an exact 50% starting material - 50% product average. Unfortunately, this approach was not successful and afforded very few transition structures.

The next attempt to locate the transition structures used an approach similar to the “Climbing Image-Nudged Elastic Band” (CINEB) method.¹⁹³ This involved taking the exact 50:50 average structure in each case, identifying and constraining the “reaction centre”,

and then performing a constrained geometry optimization. The structures obtained had “relaxed” toward the respective transition states and were then used as starting points for transition state searches. A full hessian was calculated at the AM1 level at the start of each run but, in some cases, the exact hessian needed to be recalculated periodically (every 5 steps). This approach was quite successful, permitting 487 of the 526 transition structures to be “located” (93%). Generally, the transition structures involving hydride- and methide- shifts (2,3- and 6,2-) were successfully located, but most of the transition state searches that involved Wagner-Meerwein transition states failed. Moreover, the Wagner-Meerwein transition state searches that had apparently succeeded did not actually produce the required transition structure. The conclusion drawn was that, at the AM1 semi-empirical level, most of the Wagner-Meerwein type transition states had a geometry significantly different from the “average” geometry of their respective cationic precursor and product structures. The few hydride- and methide- shift transition state searches, which failed, failed for good reasons, *viz.*, *exo*-2,3-methide shifts in the presence of a 7,7'-xylyl group require the methide group to be further away due to steric constraints, and any transition state between a secondary and a tertiary carbocation should be closer in geometry to the less stable secondary carbocation. Close examination of the potential energy surfaces of the failed systems afforded some, but not all of the outstanding 2,3-*exo* and 2,3-*endo*-transition states. In particular, no AM1 2,3-*exo* transition state was obtained for the racemization step **176a** $\rightleftharpoons$ **176b** in Scheme 2.40. The corresponding highly symmetric *endo* transition state was located at this level of theory but computation at the HF/STO-2G level was required to locate the *exo* transition state are shown in Figure 2.81.

While all transition states have not been located, sufficient transition state structures were obtained to permit some general observations to be made. Five of the transition states successfully located at the AM1 level are illustrated in Figure 2.82; these are examples of the different transition states obtained. In Figure 2.83, the various transition states are ordered according to their type and energy, while Figure 2.84 shows the relative activation energies for these reversible processes; in each case the smaller energy – either the forward activation energy or the reverse activation energy – is shown. It is commonly accepted that Wagner-Meerwein rearrangements exhibit the lowest activation energy⁷ – a view clearly reflected in the AM1 data. 6,2-Methide shifts do not appear to be mentioned in the literature and, as reflected in Figure 2.84, are energetically unfavourable. Figure 2.84 reveals, on one hand, a seemingly close energy correlation between 3,2-*exo*- and 3,2-*endo*-shifts and a distinct group-

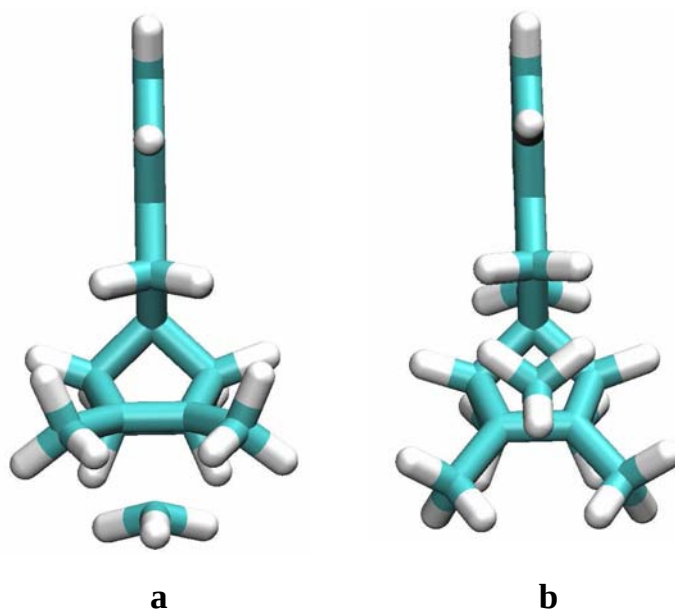


Figure 2.81: **a.** AM1 *Endo* and **b.** HF/STO-2G *exo* transition states for racemization of the camphenyl cation **176**.

ing of unfavourable and favourable 3,2-*exo*- and 3,2-*endo*- transition states on the other. However, the AM1 model clearly fails to explain why the 3,2-*exo*-transitions are typically favoured over the corresponding 3,2-*endo*-transitions.

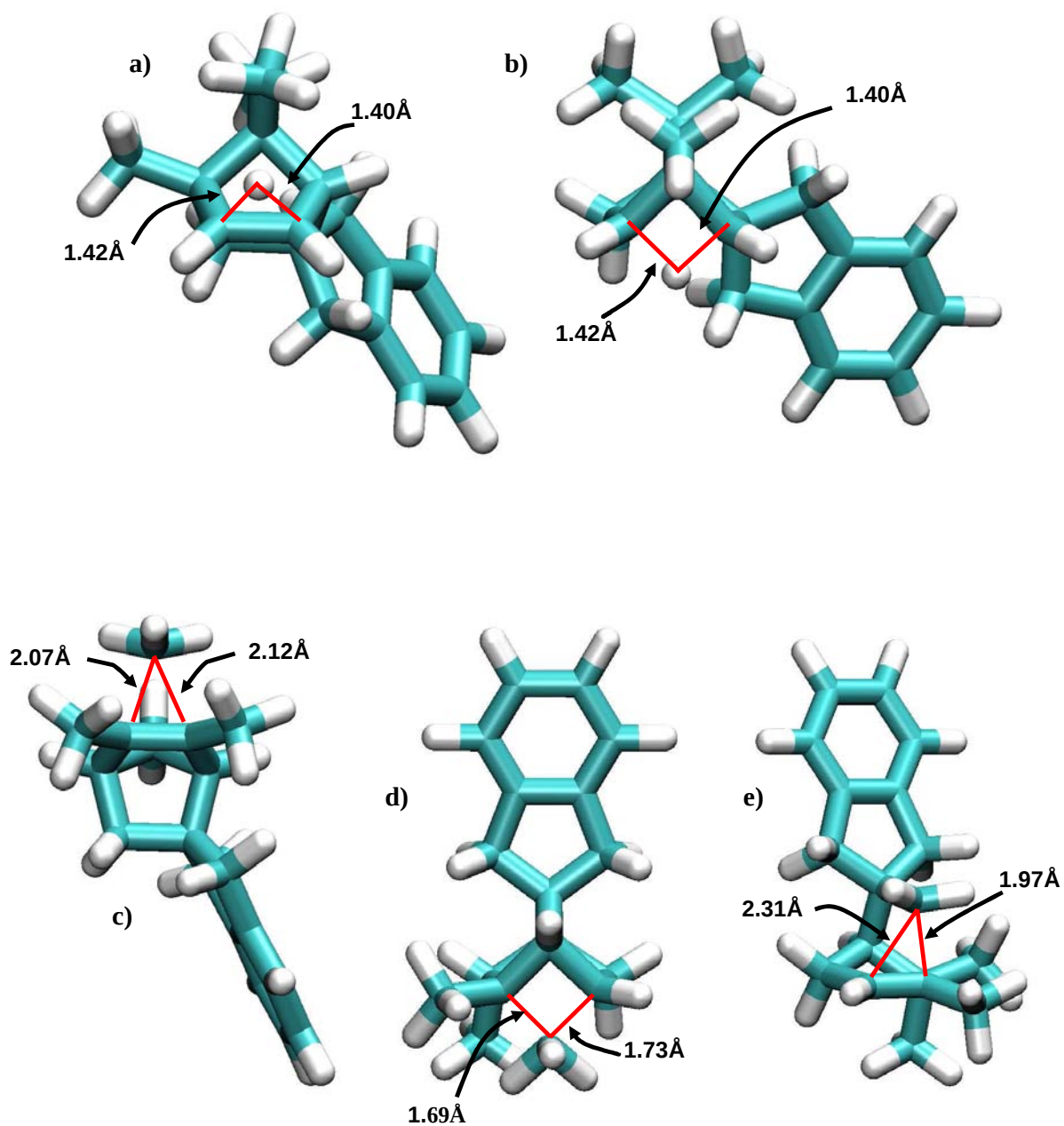


Figure 2.82: Representative AM1 transition states a) 3,2-*exo*-hydride shift; b) 6,2-hydride shift; c) 3,2-*exo*-methide shift; d) 6,2-methide shift; and e) Wagner-Meerwein transition state.

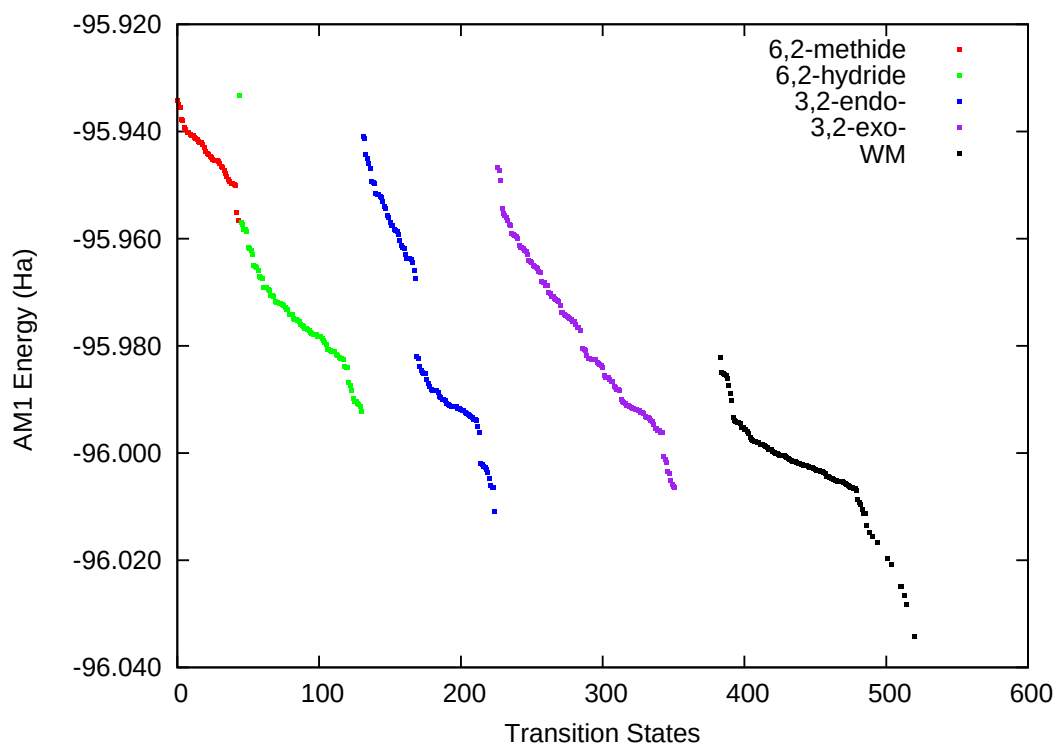


Figure 2.83: AM1 transition states : electronic energy distribution.

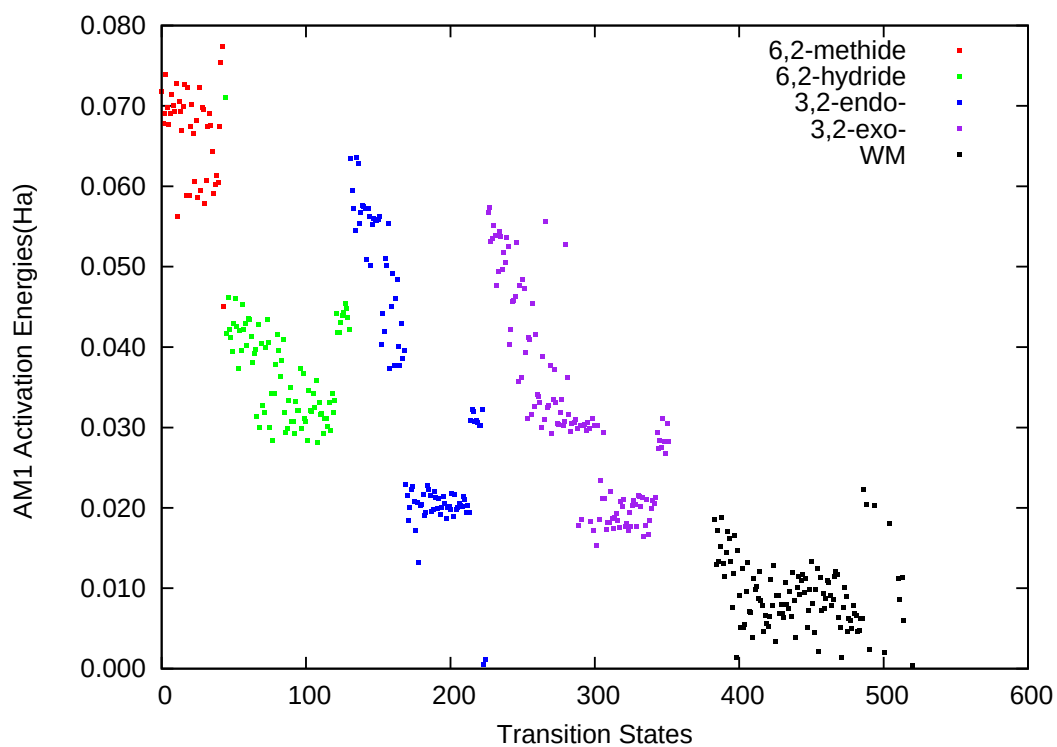
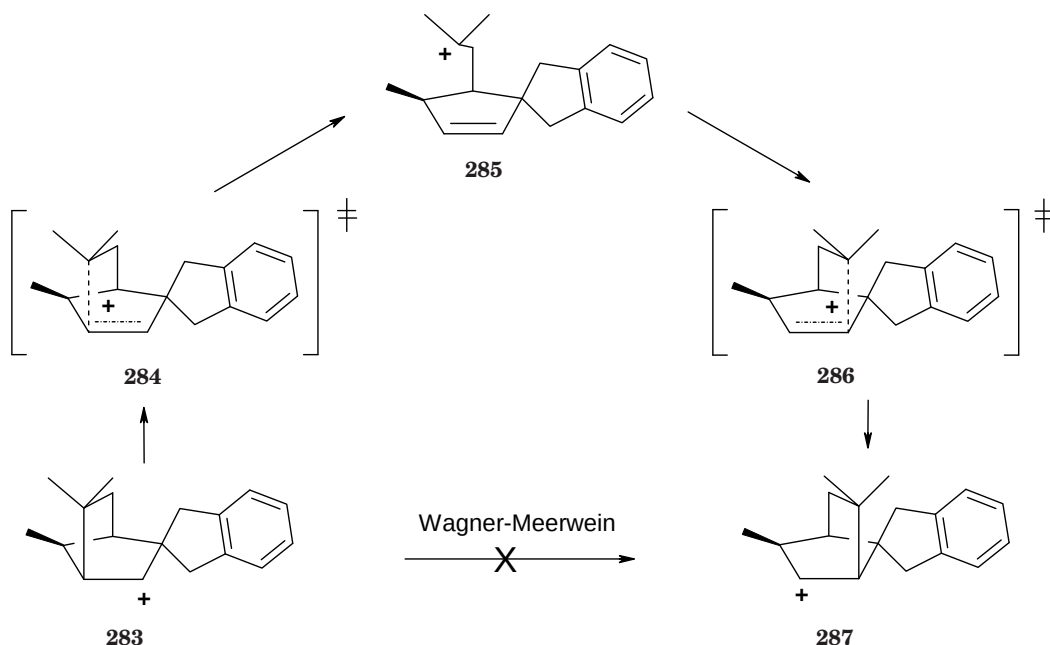


Figure 2.84: AM1 transition states : activation energy distribution.

2.3.4.6 The AM1 semi-empirical Wagner-Meerwein transformation

Many of the Wagner-Meerwein transition states reflected in Figures 2.83 and 2.84 could not be located by the methods described earlier. Consequently, full surface scans were undertaken by varying the forming and breaking bond lengths associated with the Wagner-Meerwein rearrangements in question. From examination of some of the surface scans, however, it soon became clear that *no* semi-empirical transition state structures could be located directly between cations. Instead, in these cases *two* transition states (e.g. **284** and **286**) between the two “ring-closed” structures (e.g. **283** and **287**) and a single “ring-opened” tertiary carbocation (e.g. **285**) were evident (Figure 2.41). The potential energy surface for this particular transformation (**283** $\rightleftharpoons$ **287**) is shown in Figure 2.85.



Scheme 2.41: An example of a system for which a single AM1 Wagner-Meerwein transition state could not be found.

From an examination of the AM1 potential energy surface it is clear why the single Wagner-Meerwein transition state searches failed. The exact centre of the surface corresponds to the original “guess” between the two classical cations located on either side; this guess is far from corresponding to a transition state and actually approximates to an *intermediate* (**285**)! This effectively adds further ring-opened “nodes” to the semi-empirical graph – steps not accommodated in the current study. Similar potential energy surfaces for 27 of the 29 Wagner-Meerwein rearrangements which failed to afford transition state structures at

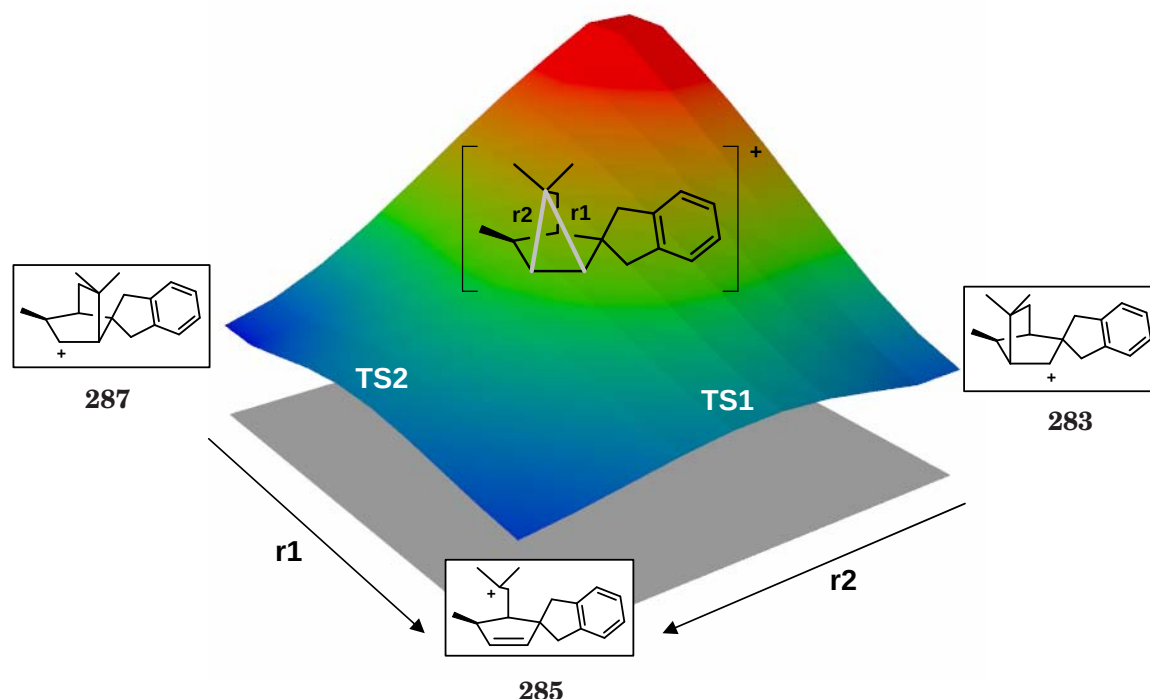


Figure 2.85: AM1 potential energy surface showing the presence of an intermediate in the AM1 Wagner-Meerwein transformation ($283 \rightleftharpoons 287$; Scheme 2.41).

the AM1 level are illustrated in Appendix 4.4 (p. 300). Interestingly, single transition state structures were located at the AM1 level for both of the Wagner-Meerwein rearrangements involved in the shortest pathway for the transformation $176 \rightleftharpoons 261$ as summarized in Scheme 2.40 (p. 165).

2.3.4.7 Conclusions from the classical graph

The graph itself (Figure 2.74) provides a pathway of connected intermediates between the camphene cations **176** and **261** and could be extended to provide energetic data. Due to the consequent increase in complexity the transition state data has not been included in the graph [with an extra node (T) for each edge, $A \rightarrow B$ becomes $A \rightarrow T \rightarrow B$ and the number of edges doubles!]. However the energetic data for the two shortest routes directly between cations **176** and **261** are shown in Figure 2.86.

It is apparent that (at the AM1 level at least) the cation **261** (node 8) does not correspond to the lowest energy species in the second shortest pathway (Figure 2.86). Moreover, the experimentally isolated camphene **263** is by no means the most stable of the 112 exocyclic alkenes arising from deprotonation of the 112 possible tertiary carbocations (Figure 2.87);

the two most stable exocyclic alkenes **288** and **289** are illustrated in Figure 2.88. Of course, the energies are not solvent-corrected and at a higher level of theory the relative energies might be different. Nevertheless, the energy data for the two shortest pathways (Figure 2.86) indicate that access to any of the cations with lower energy than cation **261** would require *much higher* activation energies! On the basis of the foregoing classical analysis, formation of the *racemic* camphene **263** from **179** can be rationalized in terms of the “kinetically feasible” equilibration summarized in Scheme 2.40.

It may not be immediately clear as to why experimentally we observe our final product as one derived from cation **261**, and not perhaps one derived from an even more stable cation on the graph. Even upon construction of the exocyclic alkene products (there are 112 possibilities corresponding to 112 tertiary cations; the two most stable structures are illustrated in Figure 2.88), a simple ordering of these exocyclic alkenes according to stability does not provide us with much information (Figure 2.87).

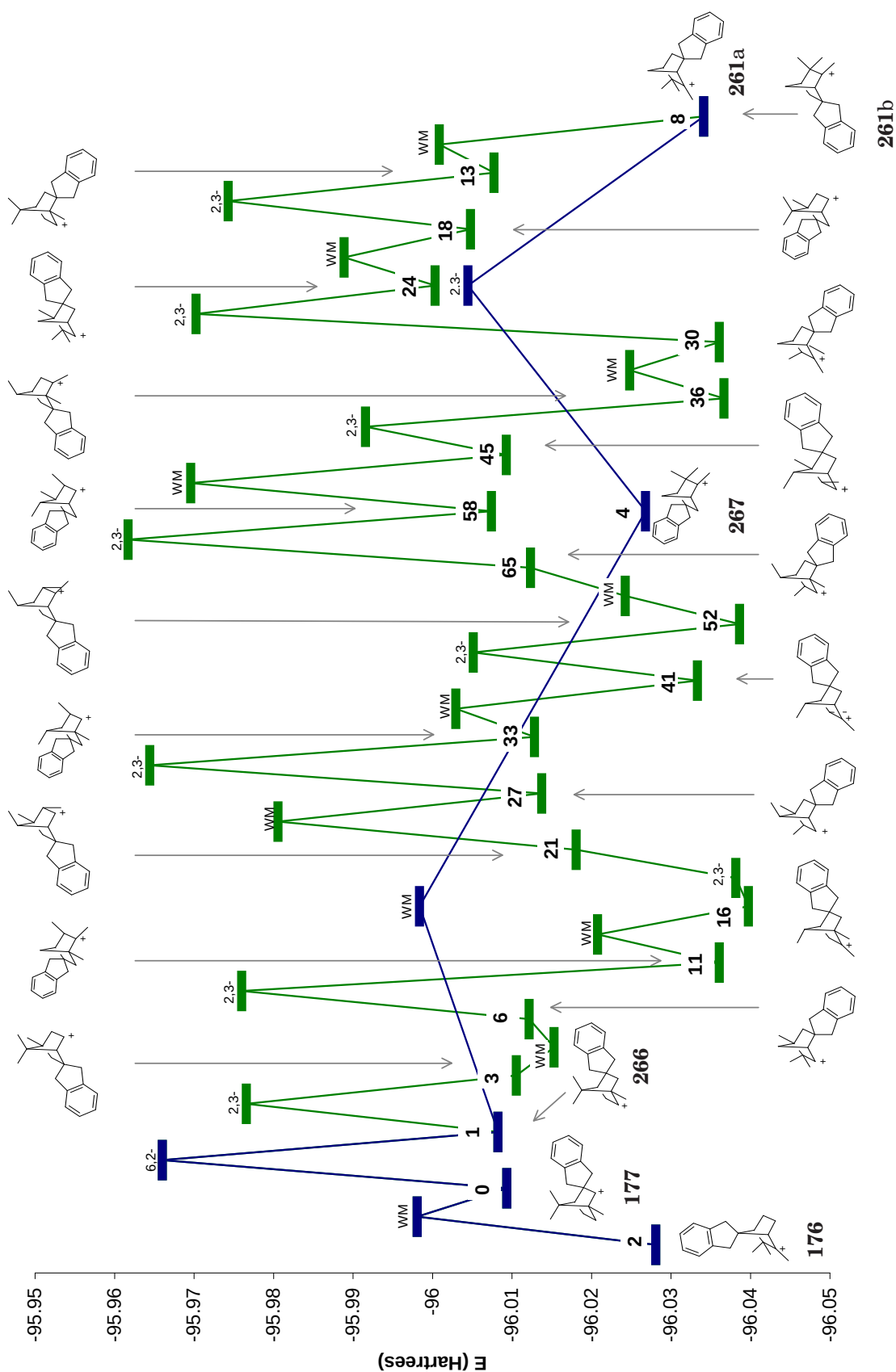


Figure 2.86: AM1 reaction profiles for the two shortest routes (indicated in blue and green) between cations 176 and 261, from the “classical” graph (Figure 2.74). The numbers refer to the nodes in the graph.

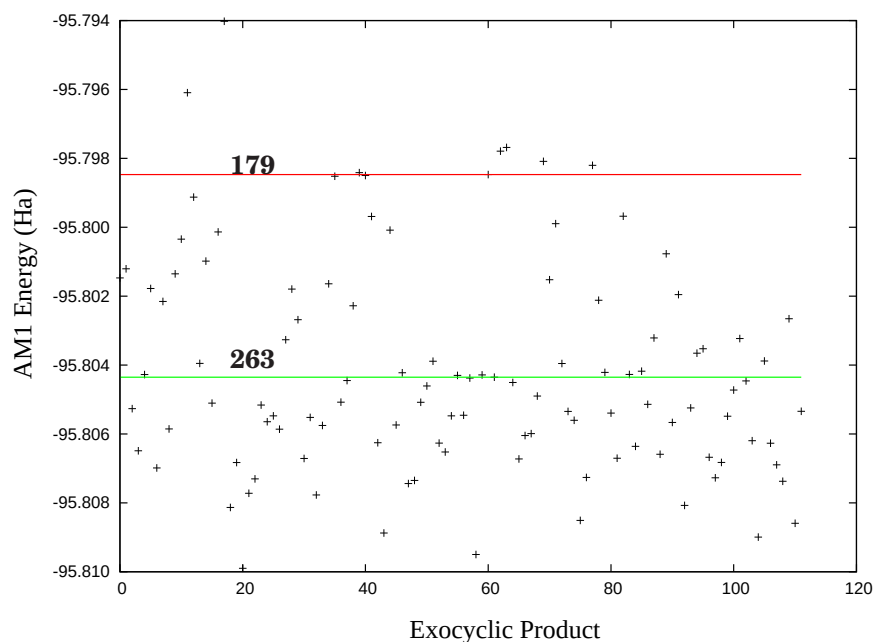


Figure 2.87: AM1 energies of all possible neutral exocyclic products. The lines indicate the energy level of camphene I **179** and camphene II **263**, respectively.

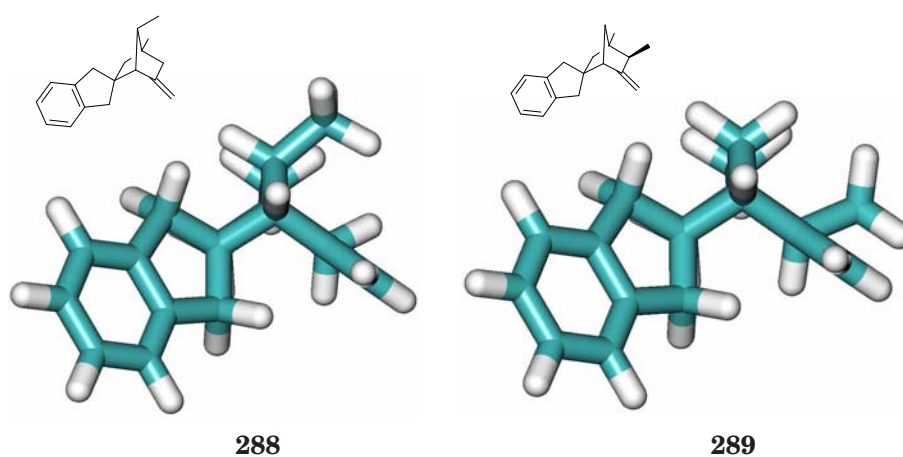


Figure 2.88: Two most stable exocyclic products (formed by loss of a proton from the corresponding tertiary cations) at the AM1 level.

2.3.4.8 Non-classical pathways and the DFT graph

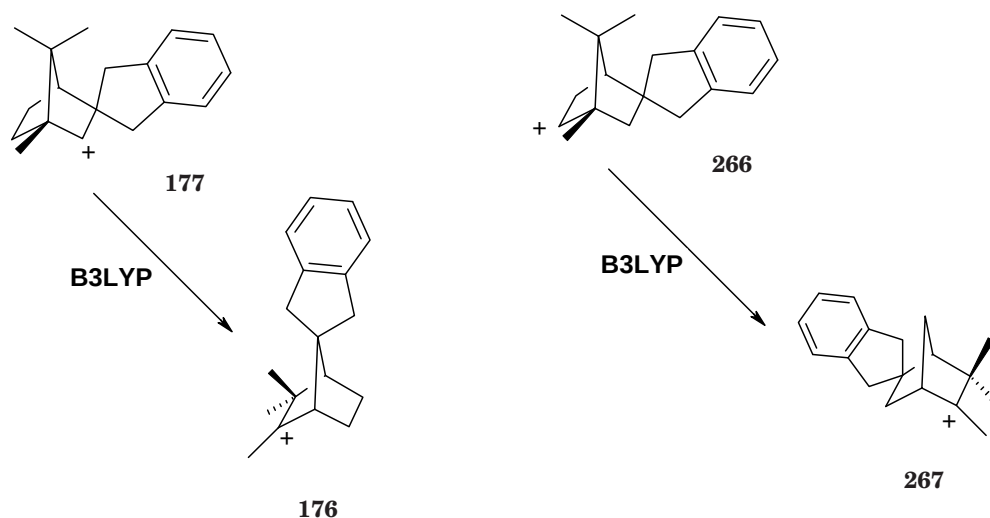
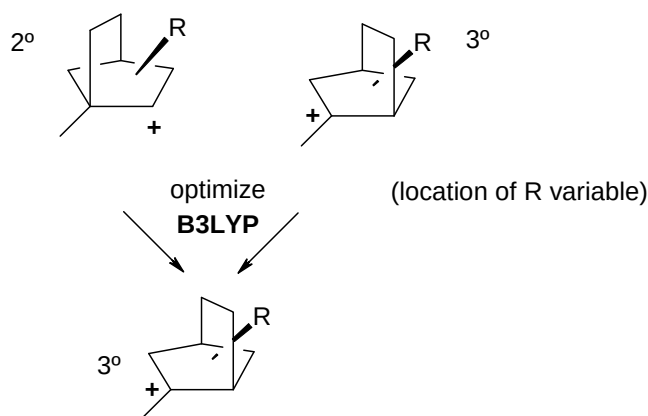


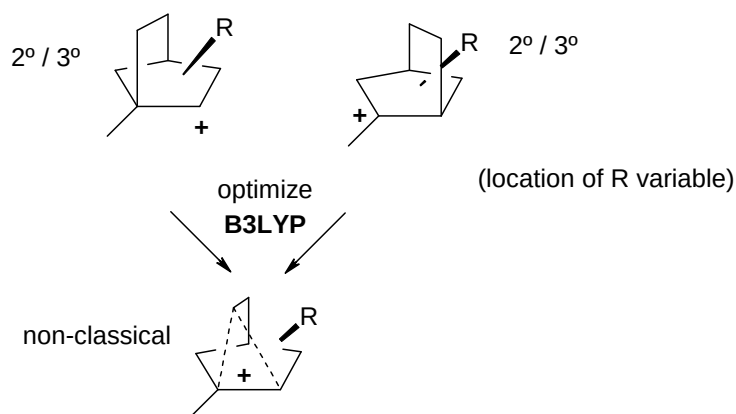
Figure 2.89: The secondary carbocations **177** and **266** rearrange to the tertiary carbocations **176** and **267** under B3LYP/6-31G(d) optimizations.

The AM1 analysis of rearrangements involving classical carbocations furnished a rational route from the camphene cation **176** to the cationic precursor **261** of the final camphene product **263** (Scheme 2.40) – a route which offers an explanation for the partial racemization observed experimentally. The necessary extension of this work to the DFT level, however, posed certain problems. It was apparent, on the basis of the initial HF/6-31G and B3LYP/6-31G(d) calculations (Section 2.3.4.2, p. 146, and Schemes 2.40 and 2.86), that the secondary carbocations **177** and **266** do not represent stationary states but, on geometry optimization rearrange to the corresponding 3° carbocations **176** and **267** (Figure 2.89). Moreover, there was good reason to assume that many pairs of cations (classically separated *via* a Wagner-Meerwein rearrangement) would, in each case, minimize to a single common cation^{112,118,194} - either tertiary (as in the case of cation **176**) or non-classical (similar to what is observed in the norbornyl system¹¹²). The following initial assumptions were consequently made:

1. If a classical secondary and tertiary carbocation are connected *via* a Wagner-Meerwein rearrangement, both will optimize to a common “tertiary” carbocation with little apparent bridging.



2. Pairs of classical secondary carbocations or classical tertiary carbocations will optimize to a common nearly symmetrical non-classical intermediate.



3. “Ring-opened” products would be excluded in the current study, since they are not observed in the system of interest.

Preliminary AM1 and B3LYP/6-31G(d) potential energy surfaces obtained for simple substituted norbornyl systems seemed to support the above assumptions. Thus, the original potential energy surface for the norbornyl cation **51** (Figure 2.90) has two wells corresponding to two nodes on a graph; similarly the methyl substituted norbornyl cation **290** shows three wells at the AM1 level (compare with Section 2.3.4.6; p 175). The two B3LYP potential energy surfaces for these simplified systems show symmetric and unsymmetric single (one

stationary point) wells, respectively. The symmetry of the B3LYP/6-31g(d) norbornyl surface is in agreement with literature reports¹⁹⁴ and was reassuring as, due to time constraints, this was the level of theory used for the DFT calculations on the full systems.

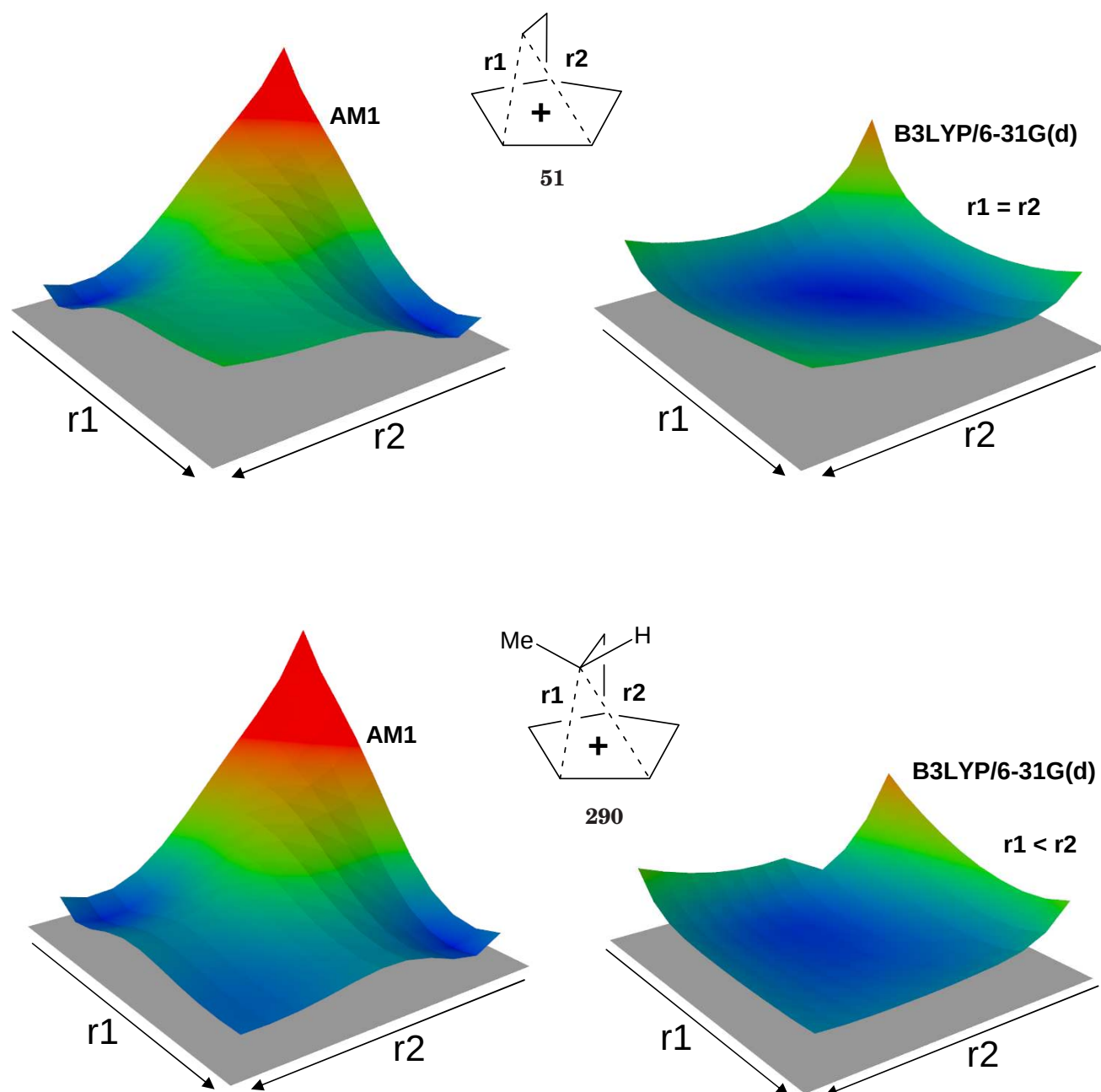


Figure 2.90: Preliminary AM1 and B3LYP surface scans of simple norbornyl and substituted norbornyl systems.

While the foregoing assumptions permit the original graph (Figure 2.74) to be simplified (Figure 2.91) in terms of the number of nodes and edges, the edges, which represent classical 3,2- and 6,2- shifts and Wagner-Meerwein transformations, need to be redefined. Ultimately it is better to view all the edges as either 6,2-shifts or 3,2-shifts, bearing in mind that most involve concerted mechanisms (according to the above assumptions). Thus, in Figure 2.91 a non-classical node (**Node AB**) may transformed to four different products *via* two separate 6,2-shifts and two separate *exo*-3,2-shifts.

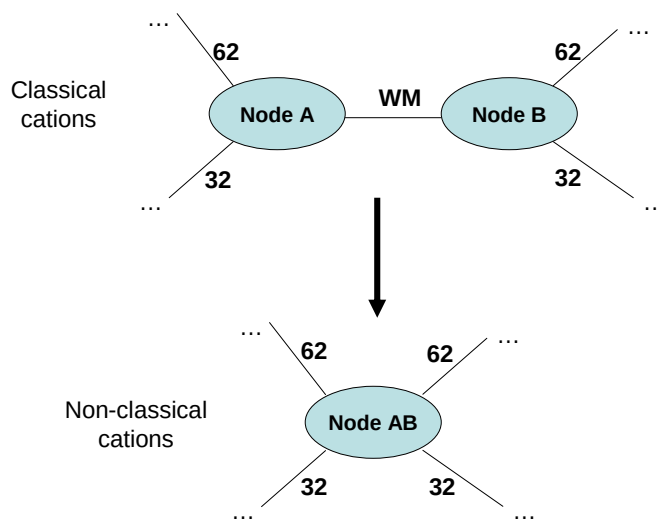


Figure 2.91: Simplification of nodes in graph, going from classical to non-classical carbocations.

In order to be confident of the validity of this approach, each pair of trimethylxyl classical structures was minimized at the B3LYP/6-31G(d) level of theory (Figure 2.92). In the cases where the pair of cations comprised a secondary and a tertiary cation, we were confident of the driving force towards the tertiary carbocation and only the tertiary carbocation was optimized (for reference the different classes of cations have been given the labelling HH-HH, MH-HH, ... according to Figure 2.92). Due to time constraints, B3LYP/6-31G(d) vibrational analyses were conducted on some, but not all B3LYP/6-31G(d) minimized structures. Figure 2.93 indicates the variation in geometry of the B3LYP structures, and Figures 2.97 and 2.98 illustrate the geometry at the cationic centre for the most stable of each “class” of cation (in the 336 modelled systems). In order to confirm that the minimization of each pair leads to a common intermediate, the hydrogens and the aromatic moiety were removed from the optimized non-classical structures for clarity. Keeping the minimized bond geometries intact, the pairs of simplified structures were then aligned using a rigid fit option in the the Cerius2 software suite. In this approach, the RMS differences between atoms is minimized, with

atoms being matched using the Maximum Common Substructure (MCS) search.¹⁹⁵ It was then clear, visually, which pairs had optimized to a common cation. Figure 2.94 illustrates :- (a) one of the lower quality "matched" pairs (where the overlay is not perfect, but where there is a minimization to a common cation skeleton) and (b) a pair which, surprisingly, did not! In the end, most pairs optimized to common intermediates, but Figure 2.95 shows all the pairs of cations which failed to do so. Eight of these pairs (*viz.*, A, E, F, H, I, K, M and P) experience 1,3-diaxial interactions which prevent optimization to a common intermediate.

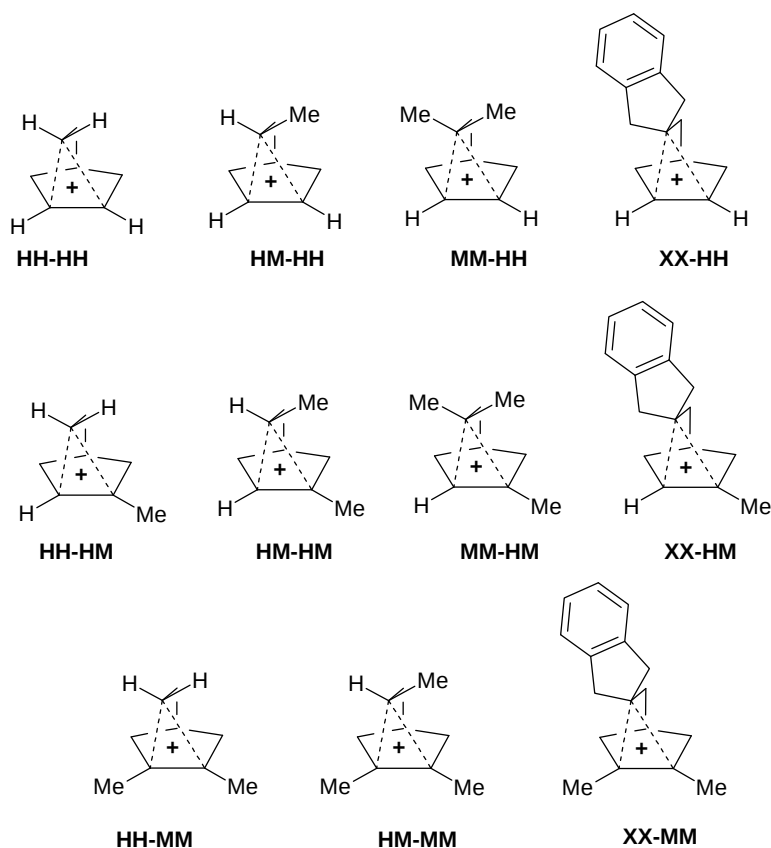


Figure 2.92: Different classes of non-classical cations encountered at the DFT level.

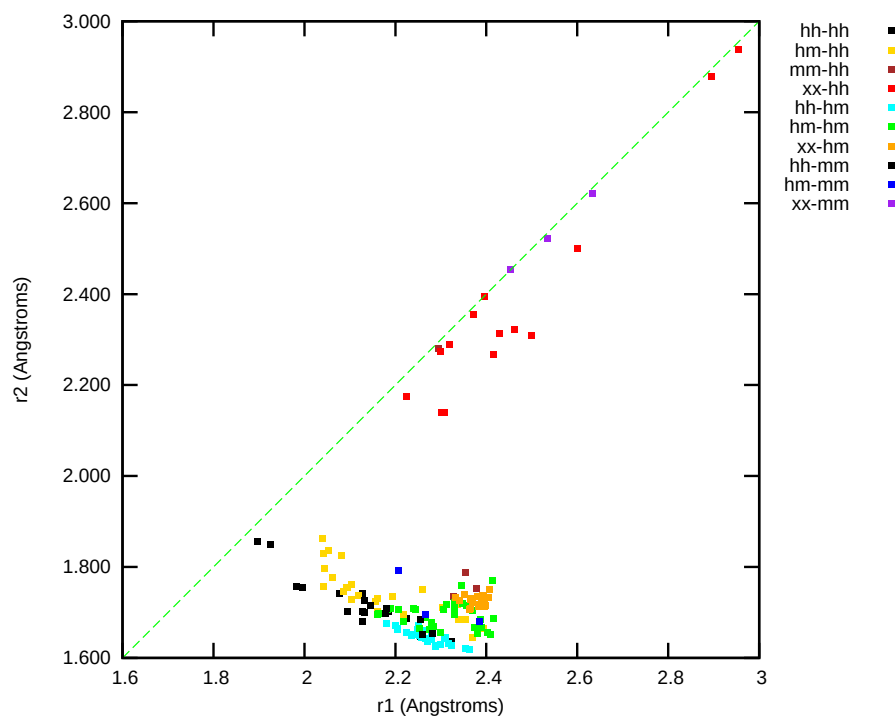


Figure 2.93: Geometry r_1 vs r_2 of the B3LYP/6-31G(d) optimized cations, r_1 and r_2 are labelled such that r_1 is the shorter distance.

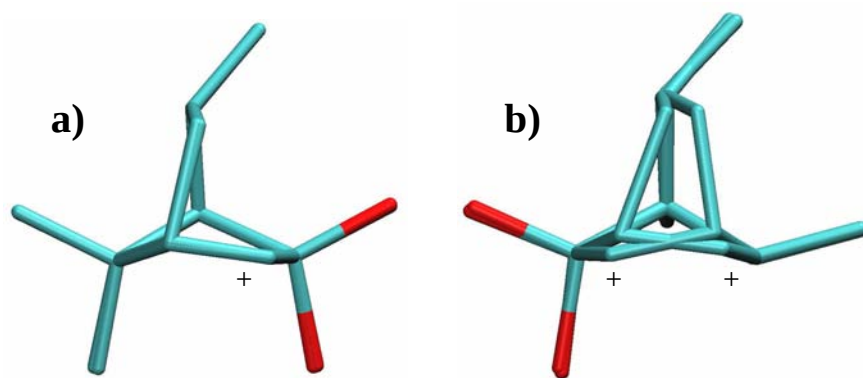


Figure 2.94: a) "Matched" and b) "Unmatched" pairs of B3LYP Structures. "+" indicates the most positive carbon centre; the xylol positions are indicated in red.

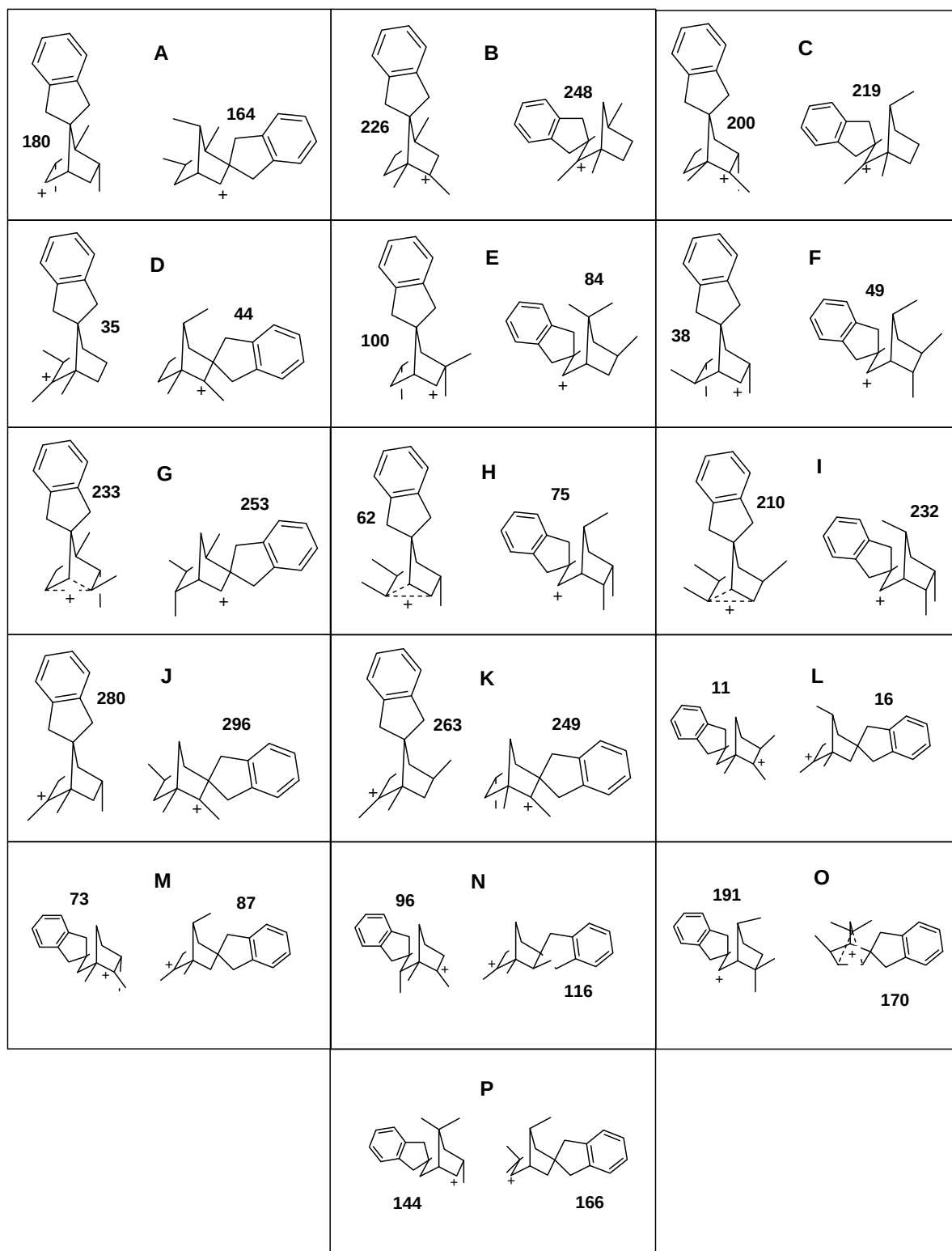
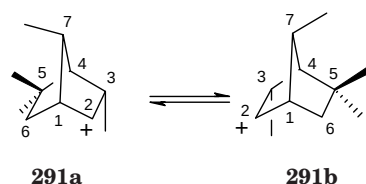


Figure 2.95: Pairs of carbocations with B3LYP-minimized structures which failed to converge to a common intermediate. The numbers indicate the nodes in the graphs in Figures 2.74, 2.73 and 2.99.

This 1,3-diaxial interaction is difficult to illustrate on the systems in Figure 2.95. While the xylyl group introduces important steric interactions, it is not convenient to model due to its sheer bulk. Rotatable methyl groups can, however, be used to illustrate the steric interactions between substituents at positions 3,5 and 7 (Figure 2.96), with the destabilizing 1,3-diaxial interactions driving a change from a single non-classical well into two distinct wells connected by a transition state. Thus, the simple tetramethyl-substituted norbornyl cation **291** was expected to exist as an equilibrating system **291a** $\rightleftharpoons$ **291b** (Scheme 2.42), modelling of which, in fact, afforded the corresponding B3LYP/6-31G(d) potential energy surface shown in Figure 2.96.



Scheme 2.42: Equilibrating carbocations **291a** and **291b**.

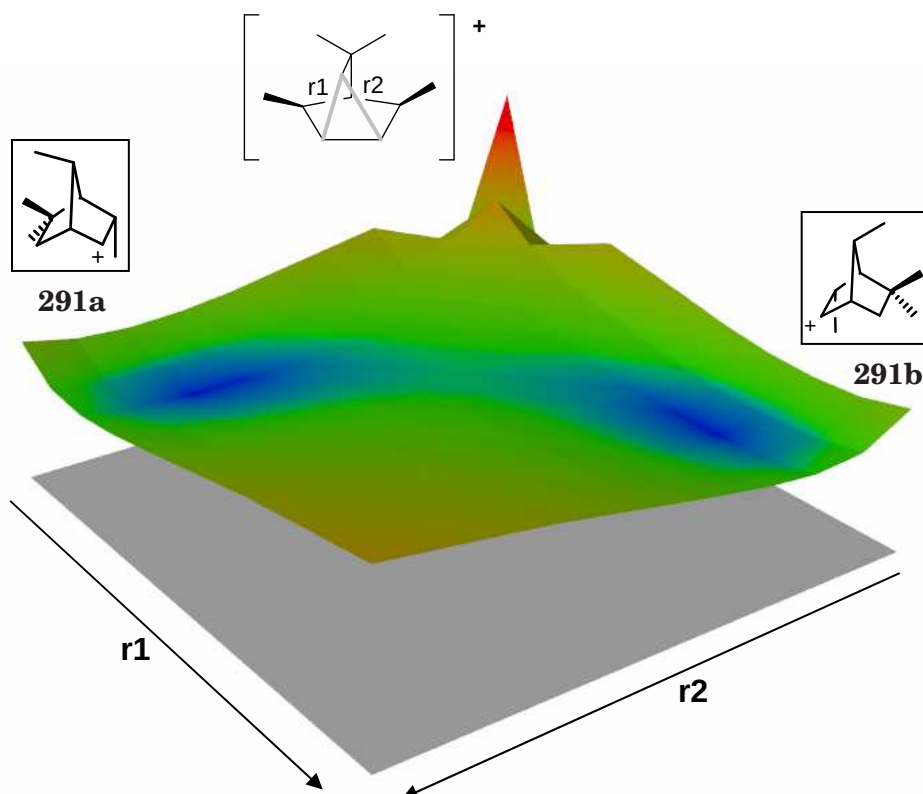


Figure 2.96: B3LYP surface scan of tetramethyl-substituted norbornyl cation **291**.

Ultimately, it seems that the geometry of a particular cation, and the nature of the poten-

tial energy surface (single- or dual-well) will depend on three factors :- *viz* the substituents at positions 1 and 2 on the norbornane skeleton defining either centre as secondary or tertiary; the substitution on the bridging group (primary, secondary or tertiary; symmetrical or unsymmetrical); and the steric influence of groups on the norbornane skeleton itself.

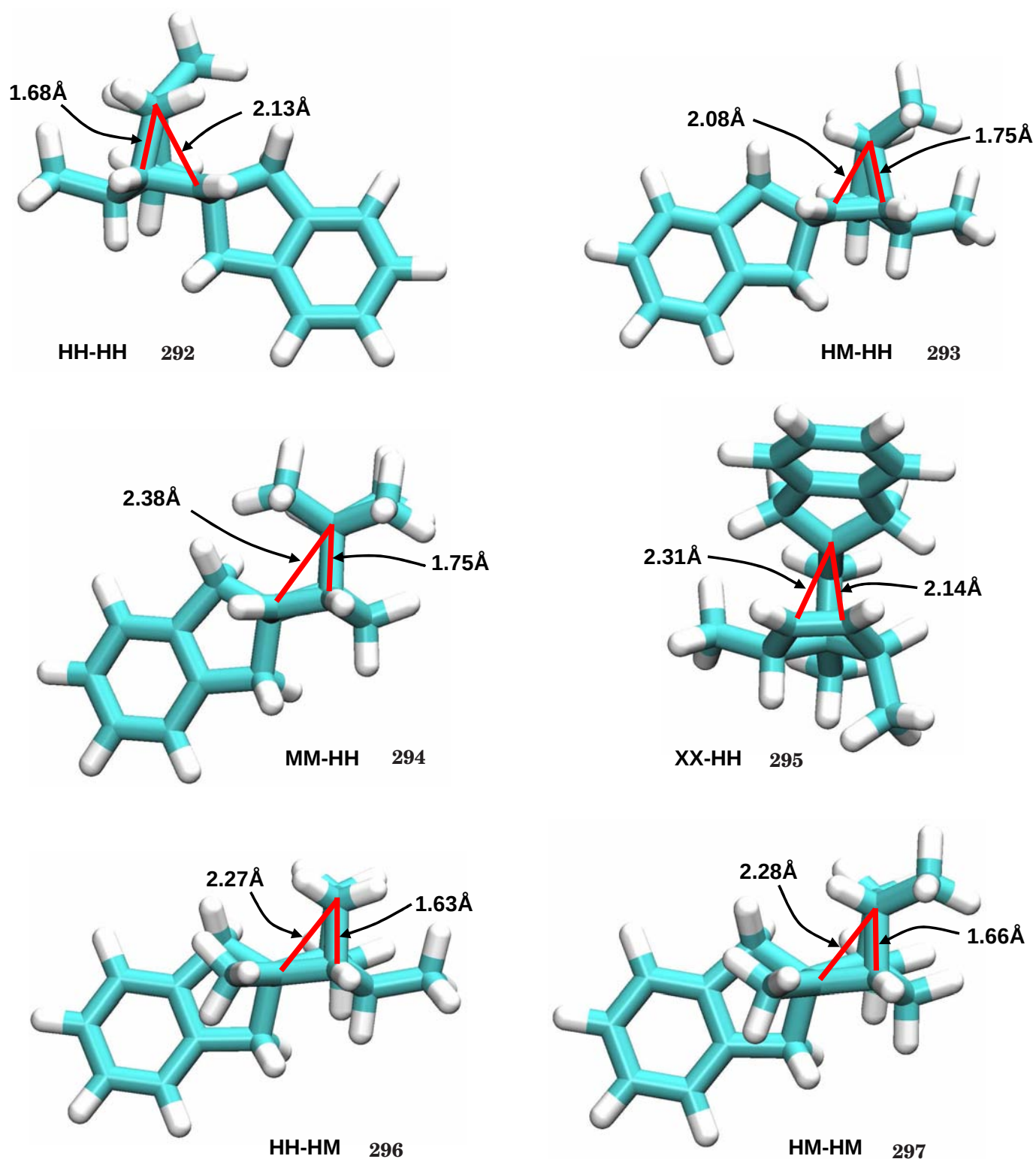


Figure 2.97: Selected B3LYP/6-31G(d) optimized structures.

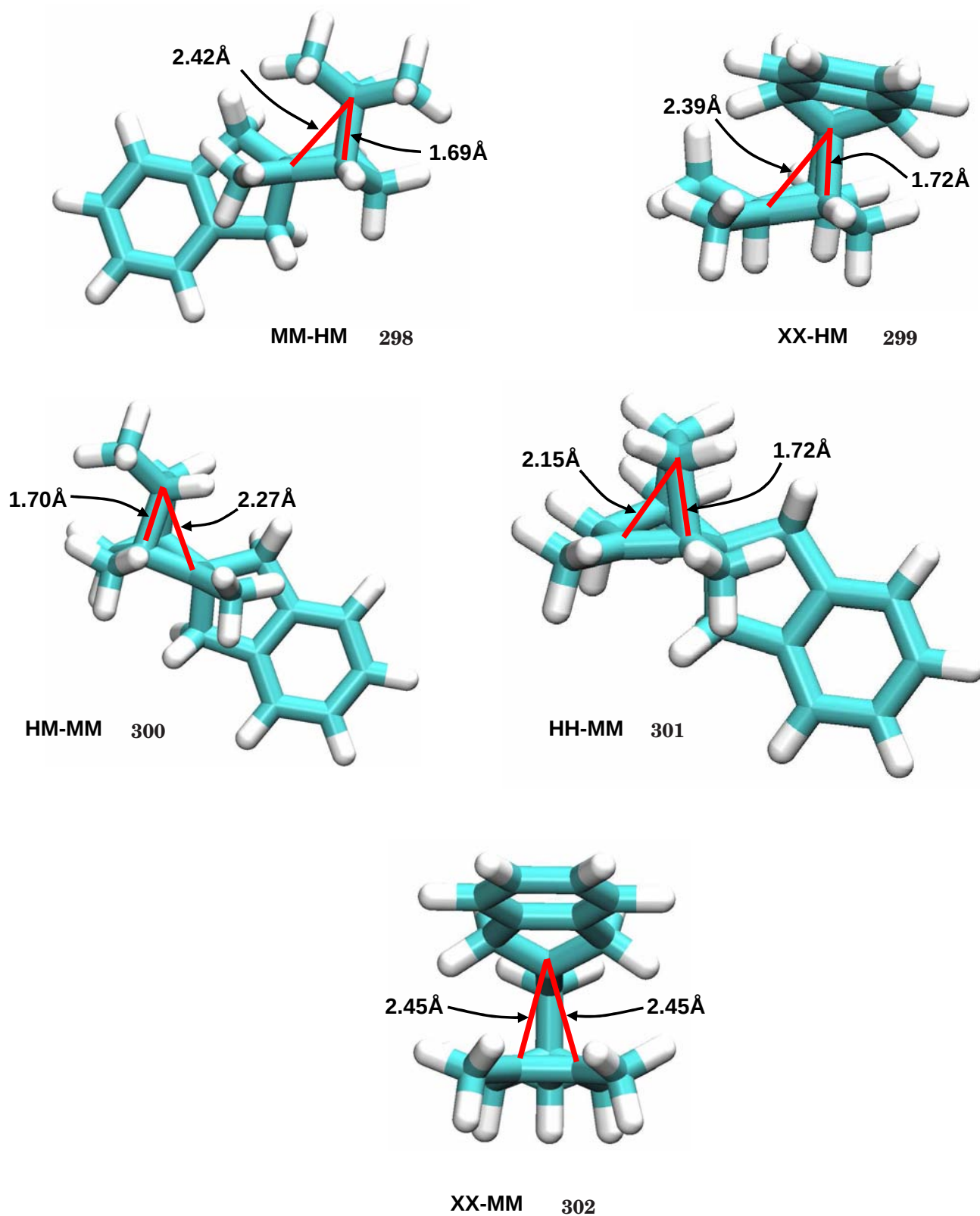
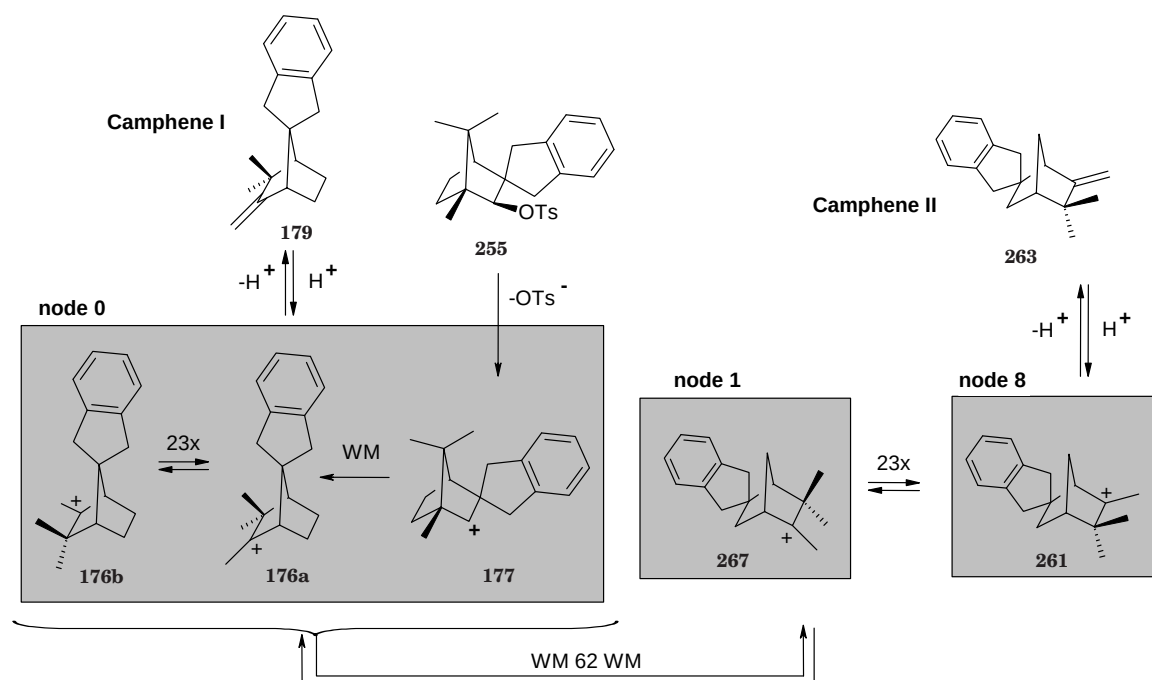


Figure 2.98: Selected B3LYP/6-31G(d) optimized structures.

2.3.4.8.1 The Non-classical Graph In the light of the B3LYP data, it became necessary to amend the classical graph (Figure 2.74). The updated information is summarized in Figure 2.99. The only Wagner-Meerwein transformations remaining in this non-classical graph are for those cation pairs identified as equilibrating pairs and represented as “dual-nodes”. The B3LYP energy is represented by the colour coding: red indicates highest energies relative to the most stable cation **node 135** (31 kcal.mol^{-1}), while blue indicates the lowest energies (0 kcal.mol^{-1}). Since cation **177** (arising from loss of TsOH from the original tosylate **255**) optimizes to cation **176a** on geometry optimization at the B3LYP level, **node 0** on the graph represents *both* **177** and **176a** (or its enantiomer **176b**!). In following transformations, care is necessary. For example, a concerted 6,2-hydride shift (Wagner-Meerwein - 6,2 - Wagner-Meerwein; see Figure 2.44) transforms **node 0** to **node 1** (structure **267**), while a *different* 6,2-hydride shift effects the transformation from **node 0** to the high energy **node 5**.

The theoretical data obtained thus far, permits the identification of low energy intermediates and a likely pathway for the experimentally observed transformation from camphene I to camphene II (**179** $\rightarrow$ **263**). The pathway from the initial camphenyl cation **176** to the final camphenyl system **261** is thus represented by the pathway: **node 0** $\rightarrow$ **node 1** $\rightarrow$ **node 8** *via* two transition states involving 6,2-hydride and a 3,2-methide shifts, respectively (Figure 2.99). The updated scheme of intermediates is illustrated in Scheme 2.43.



Scheme 2.43: Pathway from camphene I **179** to camphene II **263**.

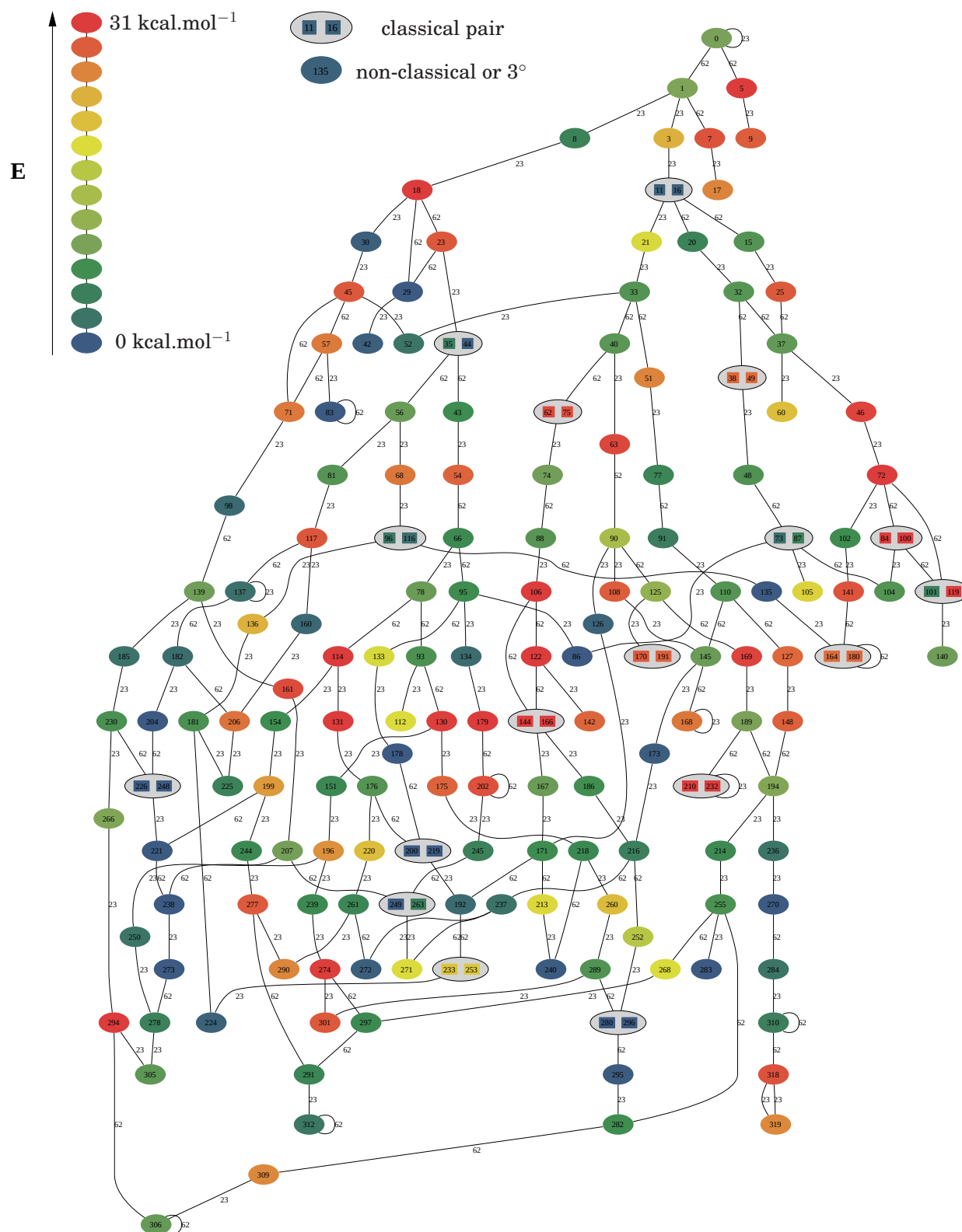
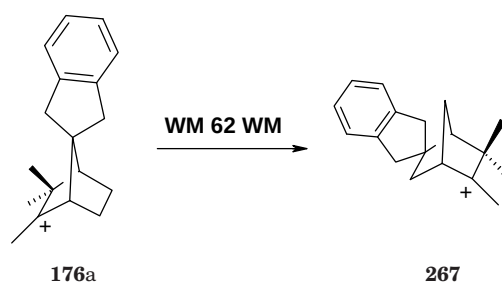


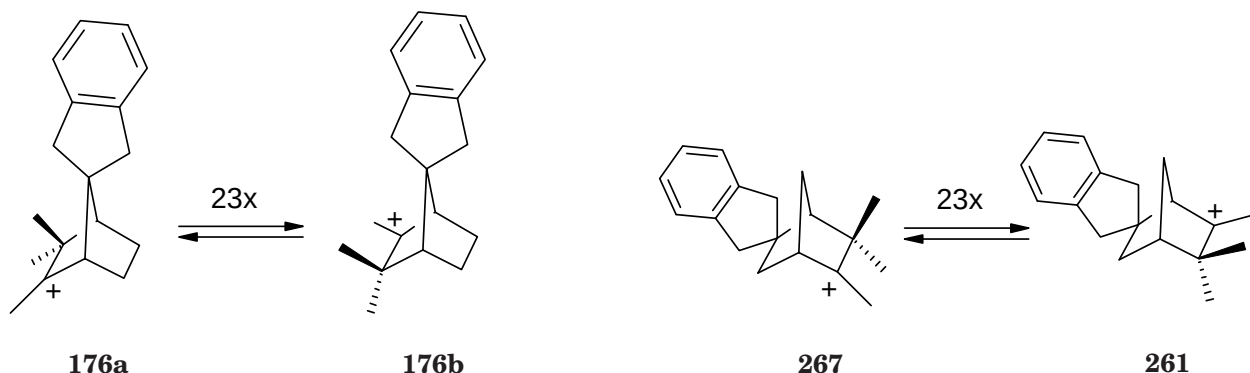
Figure 2.99: Reduced "non-classical" graph of all cationic structures accessible *via* 3,2-; 6,2-; and Wagner-Meerwein transformations from the cation 176 (node 0).¹⁹⁶ Indicated are the B3LYP/6-31G(d) energies relative to the lowest energy node 248.

2.3.4.8.2 The reaction profile from camphene I **179 to camphene II **263**** The evidence is overwhelming that the shortest pathway from the first camphene cation I **176** to the second camphene cation II **261** involves concerted mechanisms and just one intermediate **267**. The next step was then to identify the two transition states connecting this intermediate with the initial product camphene I **179** and the final product camphene II, **263**. Of particular interest was the concerted mechanism (Wagner-Meerwein – 6,2-hydride shift – Wagner-Meerwein) from **179** to **267** (Scheme 2.44).



Scheme 2.44: Concerted rearrangement from cation **176** to cation **267**.

A good starting place to look for the B3LYP/6-31G(d) transition state was the AM1 transition state for the 6,2-hydride shift. The hydride distances (to C2 and C6) were constrained for an optimization at the B3LYP/6-31G(d) level, and the resultant geometry was used as input for a transition state search. The transition state was confirmed using vibrational analysis, and the combined forward and reverse intrinsic reaction coordinate (IRC) runs, illustrated in Figure 2.100 confirm that this is the transition state between tertiary carbocations **176** and **267**. Classical secondary carbocation formation is thus not necessary for this rearrangement to occur.



Scheme 2.45: *Exo*-methide shifts **176a** $\rightarrow$ **176b** and **267** $\rightarrow$ **261**.

The other rearrangements of interest are the “racemization” step (**176a** $\rightarrow$ **176b**) and the

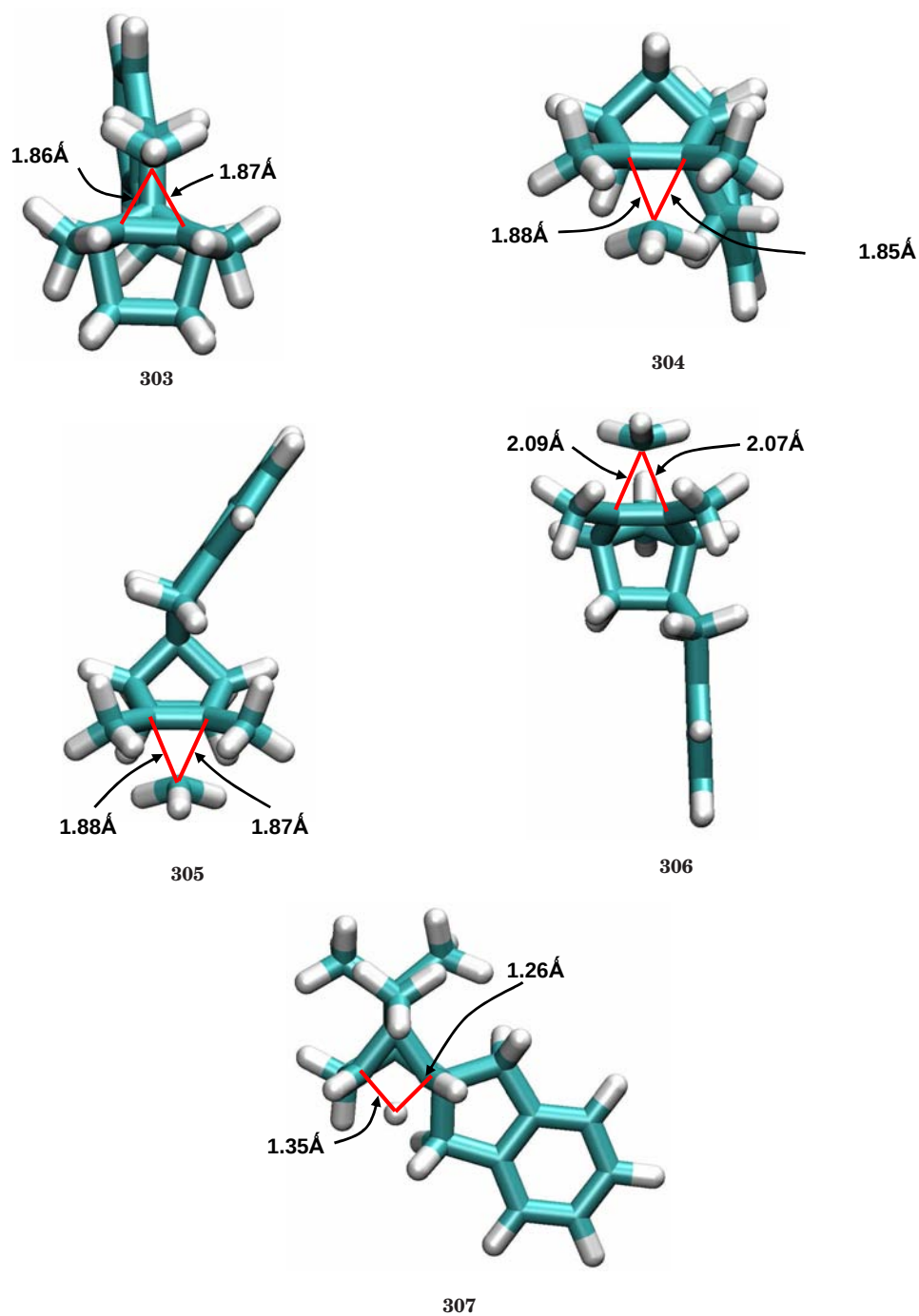
final transformation (**267** $\rightarrow$ **261**), shown in Scheme 2.45. Both of these transformations were expected to occur *via* 3,2-*exo*-methide shifts. Since the 3,2-*endo*-methide shift also effects both transformations, the *endo*-routes were also explored.

The energetic data for all five relevant transition states are summarized in Table 2.17 and the geometries are illustrated in Figure 2.46. It is interesting to note that, while the *endo*-methide shifts are less favoured than the *exo*-equivalents, there is not a large difference. In fact the *endo*-2,3-methide shifts are more favoured than the necessary 6,2-hydride shift!. Moreover, the racemization step (**176a** $\rightleftharpoons$ **176b**) is favoured over the 6,2-hydride shift, suggesting that under no circumstances could we be able to obtain the optically pure camphene II product **263**

Table 2.17: GAMESS B3LYP/6-31G(d) free energy data for the modelled transition states at 298.15K.

Transformation	TS	Cations	B3LYP/6-31G(d)				
			E _f (Ha)	Entropy S (cal.mol ⁻¹ K ⁻¹)	Enthalpy H (Ha)	Free Energy G (Ha)	ΔG (kcal.mol ⁻¹)
<i>exo</i> -methide	303	176a $\rightarrow$ 176b	-698.99520	118.80	-698.61301	-698.66946	18.8
<i>endo</i> -methide	305	176a $\rightarrow$ 176b	-698.99368	118.80	-698.61149	-698.66793	19.8
<i>exo</i> -methide	306	267 $\rightarrow$ 261	-698.99932	119.23	-698.61727	-698.67392	16.0
<i>endo</i> -methide	304	267 $\rightarrow$ 261	-698.98834	119.23	-698.60629	-698.66294	22.9
6,2-hydride	307	176 $\rightarrow$ 267	-698.98600	118.21	-698.60571	-698.66188	23.6

The theoretical evidence is in clear support that Figure 2.101 and Scheme 2.43 represent the best pathway from the camphenyl cation **176a** to **261** accounting for partial racemization of the product.



Scheme 2.46: *Exo*- 3,2-methide shift (**303** and **306**), *endo*- 3,2-methide shift (**305** and **304**) and 6,2-hydride shift (**307**) transition states for Scheme 2.43.

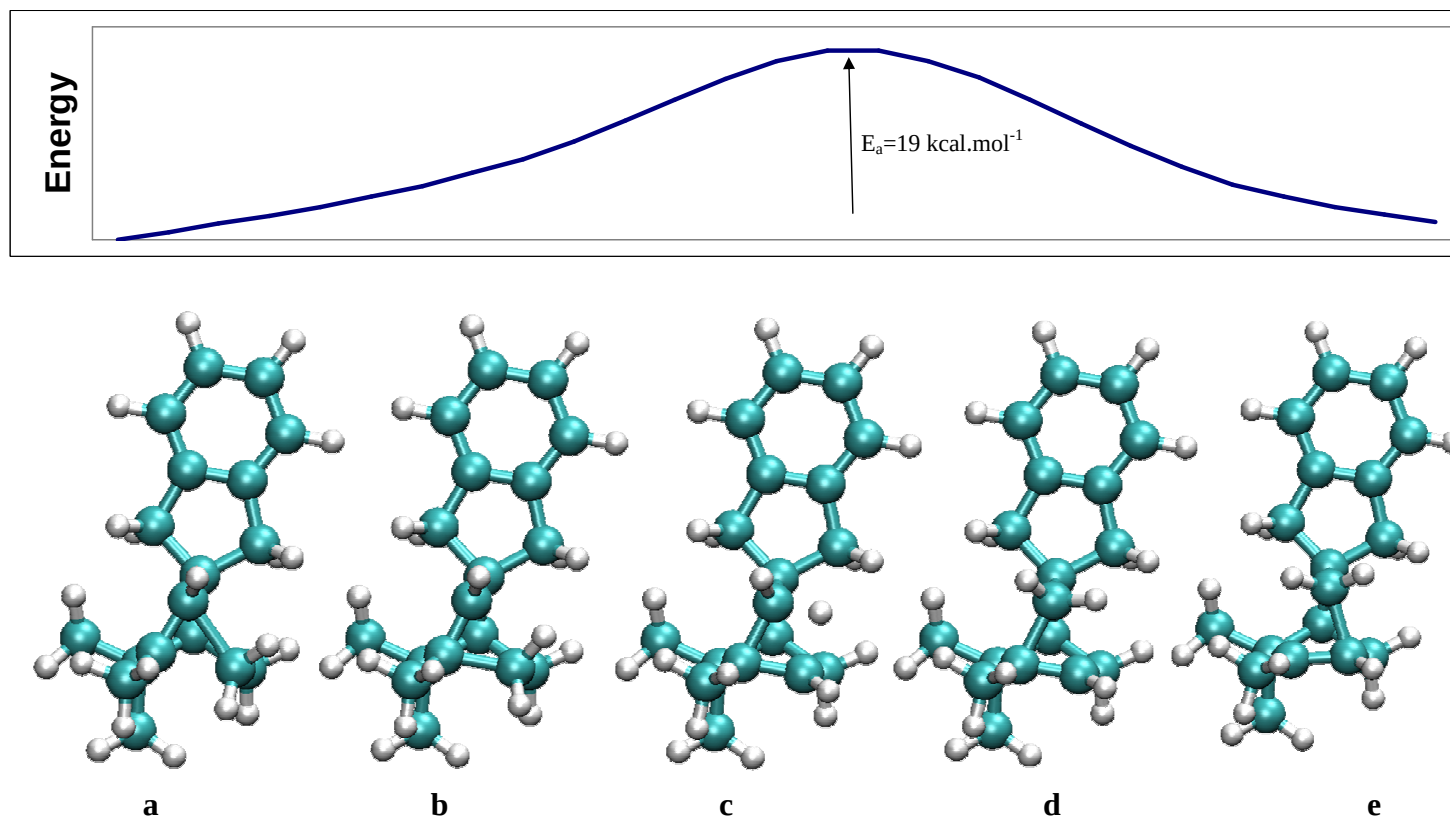


Figure 2.100: Concerted Wagner-Meerwein – 6,2-hydride shift – Wagner-Meerwein transition necessary for the transformation of **176** into **267** from the intrinsic reaction coordinate data. The electronic energy profile has also been extracted. **a.** Partial bridging towards tertiary carbocation centre; **b.** distortion of geometry of bridging group; **c.** hydride shift (transition state); **d.** distorted (not fully classical) secondary carbocation product; and **e.** relaxation of the secondary to the tertiary carbocation.

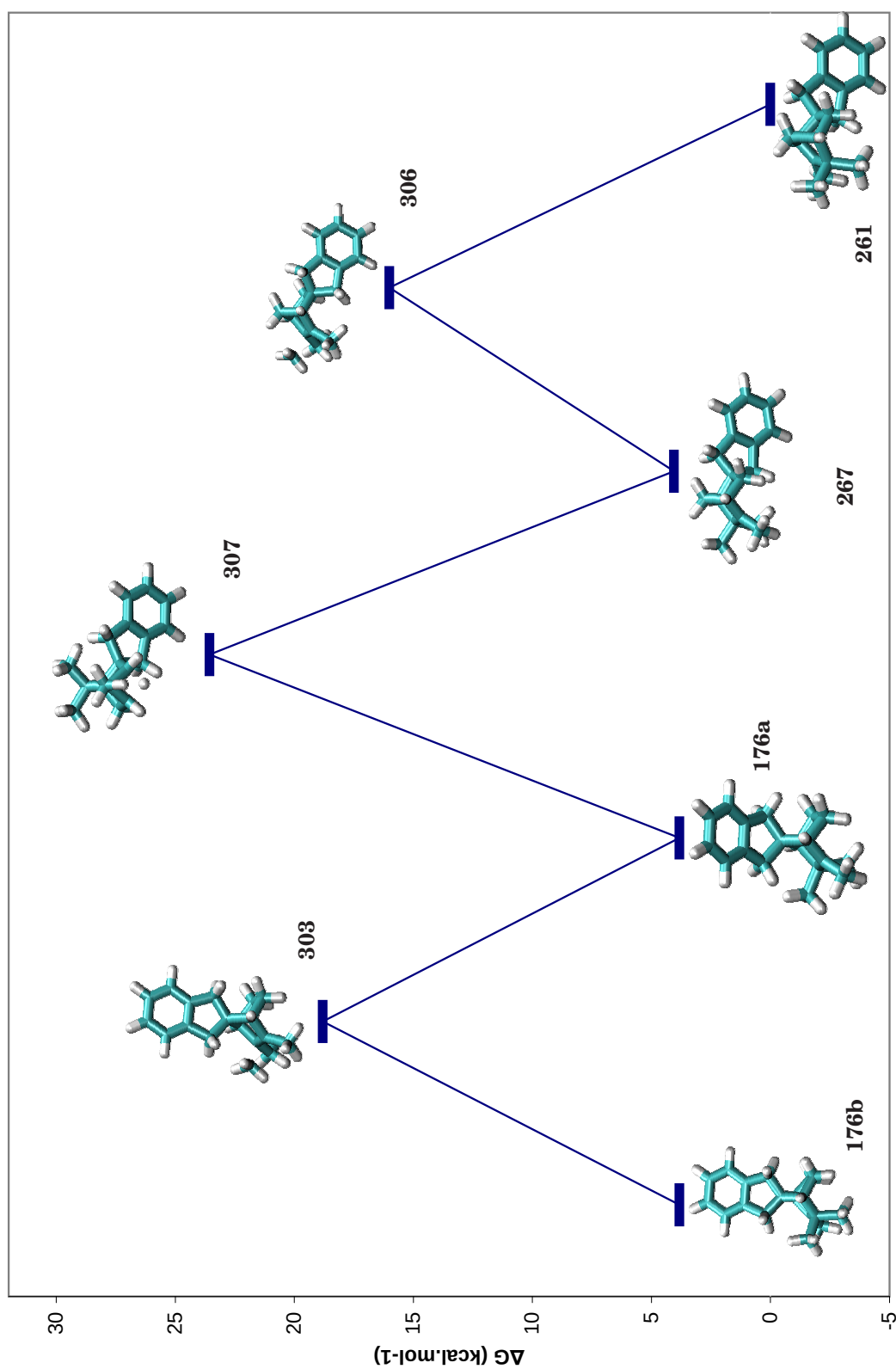


Figure 2.101: B3LYP/6-31G(d) reaction profile for Scheme 2.43 illustrating the racemization step **176a** → **176b**, the concerted transformation **176a** → **267** and the final 3,2-*exo*- shift **267** → **261**.

2.4 Conclusion

The evaluation of the camphor-derived 3,3-ethylenedioxy-2-*exo*- and 2-*endo*-hydroxybornanes as a chiral auxiliaries has led to some unexpected observations. Increasing bulk in the series of ester enolate derivatives results in an increase in the stereoselectivity of α -benzylation in the *exo*-systems, but a decrease in the *endo*-systems. Molecular modelling at the DFT level suggests that these patterns may be attributed to the relative rigidity of the metal-coordinated system in the *exo*-system; accessibility to one face of the enolate appears to decrease as the bulk of the *O*-alkyl moiety increases. In the novel *endo*-systems however, increasing of bulk appears to favour formation of conformers in which both faces of the enolate intermediate are exposed to electrophilic attack.

The source of stereoselectivity in the α -alkylation of camphor-derived iminolactones, previously developed in our group has been examined in detail. It seems that in the case of α -methylation, subsequent enolization of the methylated products, followed by reprotonation results in formation of the *thermodynamically favoured* *exo*-methylated product. For larger alkyl groups, the subsequent enolisation appears to be more difficult and the *kinetically favoured* *endo*-products are obtained. Unfortunately, use of the iminolactone systems to effect enantiomer beneficiation was precluded by the fact that formation of the alkylated systems by direct reductive cyclization of the intermediate prepared with racemic CBZ-amino acids does not provide an equal distribution of products! Rather steric crowding (arising from a single chiral centre) in the transition state appears to determine whether cyclization occurs readily or not. On the other hand, the analogous *endo*-iminolactones have been identified since the yields for these systems is far in excess of their *exo*-counterparts!

The previously elusive spiro[bornane-3,2'-indan]-2-*exo*-tosylate has been successfully isolated and characterized, and shown to decompose readily to form two camphene products. ^1H NMR-based studies of the autocatalytic decomposition of the *exo*-tosylate to an initial camphene-derivative revealed an activation energy of $167.7 \pm 4.3 \text{ kJ mol}^{-1}$; the subsequent pseudo-first-order transformation to the final camphene derivative exhibits an activation energy of the order of 100 kJ mol^{-1} , but uncertainties in the tosic acid concentration prevented determination of the second-order rate constant.

Computational studies of the rearrangement at the HF/STO-3G level prompted the acquisition of X-ray crystal structures, and led the structural revision of the product previously

identified as a pinene derivative **180**. The second rearrangement product was thus shown to be the camphene II **263**. The mechanism for the formation of camphene II **263** from camphene I **179** was finally elucidated by means of a detailed coset analysis. The graph formed from the coset analysis illustrated 336 possible cations that could conceivably be formed by molecular rearrangement of the camphenyl I cation.

Non-classical treatment of the cations revealed that most (but not all) pairs of cations minimized under high-level geometry optimization to a single “non-classical” (or tertiary) species. In some cases steric interactions far from the cationic centre prevented a common minimized structure. Based on the results, the mechanism for the formation of camphene II **263** from camphene I **179** has been shown to be a two step mechanism involving one intermediate (as opposed to the four-step classical mechanism); the first of these steps being a novel, concerted Wagner-Meerwein – 6,2-hydride shift – Wagner-Meerwein rearrangement, the second a traditional 3,2-methide shift.

While the results of these studies have provided fascinating insights into transformations involving the camphor nucleus, other challenges have been uncovered and future research is expected to involve the following.

1. The determination of kinetic parameters for the formation and alkylation of the imino-lactone systems.
2. Application of the optically pure camphene I, in the deployment of new chiral reagents, such as in chiral hydroborating reagents.
3. Following the kinetics of the decomposition of camphene I at known tosic acid concentration levels, to obtain second order kinetic data.
4. A search for the generality of the concerted Wagner-Meerwein – 6,2-hydride shift – Wagner-Meerwein mechanism, in other systems known to undergo numerous rearrangements.

3 Experimental

3.1 General

3.1.1 Analysis

NMR spectra were recorded on Bruker AMX400 or 600 MHz Avance II⁺ spectrometers. Spectra were typically recorded in CDCl₃ and calibrated on the residual CHCl₃ signal at 7.25ppm for proton spectra and the CDCl₃ signal at 77.00ppm for carbon spectra. Melting points were measured on a Kofler hot-stage microscope and are uncorrected. Optical rotations were measured on a Perkin-Elmer 141 polarimeter. Infrared spectra were obtained from thin films on KBr plates using a Perkin-Elmer Spectrum 2000 FT-IR spectrometer, and low resolution mass spectra were recorded on a Finnigan GCQ spectrometer. Diastereomeric excess (d.e.) values were determined using appropriate peaks from the ¹H NMR spectra. In cases of a mixture of diastereomers, the peaks of the major compound are listed first.

3.1.2 Solvents

Tetrahydrofuran (THF), diethyl ether, benzene and toluene were dried over sodium wire, using benzophenone as indicator, and distilled. Dimethylformamide (DMF) was dried over molecular sieves. Methanol and ethanol were purified by reflux over Me(OMg)₂ and Et(OMg)₂, respectively, followed by distillation.

3.1.3 Chromatography

Separations were effected using column chromatography with silica gel 60 PF₂₅₄, HPLC on a Whatman Partisil 10 normal phase column with a Waters RI 410 differential refractometer, and radial chromatography using a "ChromatotronTM" supplied by Harrison Research.

3.1.4 Computational methods

Except where indicated in the discussion, structures were drawn and optimized using the Universal Force Field^{185–187} within Accelrys Cerius² software.¹⁹⁵ The output of DMol³ data was visualized using Accelrys Materials Studio.¹⁹⁷ Car-Parrinello molecular dynamics,¹⁹¹ GAMESS¹⁸⁸ and Gaussian ‘03¹⁹⁸ data required the use of VMD¹⁹⁹ or Molden²⁰⁰ for visualization and analysis.

3.1.4.1 Molecular dynamics

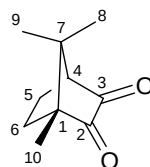
Molecular dynamics were performed in Cerius² using the quenched dynamics method. Conformers were subsequently minimized for analysis. *Ab initio* molecular dynamics required an initial B3LYP optimization of the structure using the CPMD program, followed by a short Car-Parrinello molecular dynamics run (1000 steps, 3 au per step, 0.072ps total) to equilibrate the structure at the required temperature; the run was performed as a continuation of the dynamics at this temperature.

3.1.4.2 Density functional theory calculations

All structures and intermediates (unless indicated otherwise) were subjected to vibrational analysis at the stated level of theory. Transition state confirmations within Materials Studio were conducted for DMol³ transition states, while IRC calculations confirmed the transition states from GAMESS. NMR calculations on equilibrium geometries were conducted using the GIAO method within gaussian using a large basis set [6-311+g(2d,p)] at the Hartree-Fock level of theory.

3.2 Synthesis of chiral auxiliaries

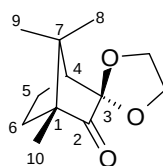
(-)-Camphorquinone **203**



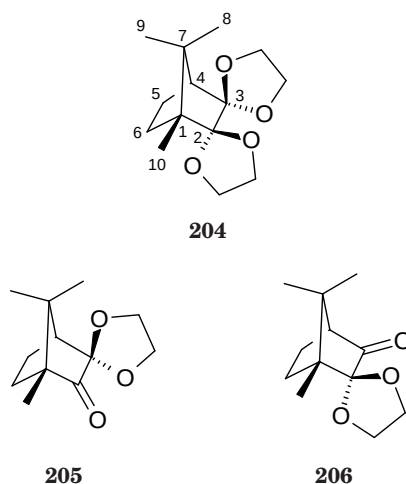
203

To a solution of (+)-camphor (40.0g, 0.27mol) in acetic anhydride (40mL) was added selenium dioxide (48.0g, 0.43mol). The suspension was boiled under reflux for 7h with vigorous stirring to ensure movement of the undissolved selenium dioxide. The fumes were scrubbed using a dilute aqueous NaOH solution. The mixture was allowed to cool to 30°C overnight (to prevent crystallization of product which occurs at room temperature) and the insoluble residue was removed by filtration and washed with glacial acetic acid (40mL). The filtrate and washings were cooled to 0°C and neutralized with 10% aqueous NaOH; the precipitate was filtered off and washed with water at 0°. The yellow solid was recrystallized from hexane to afford (-)-camphorquinone **203** as yellow needles (26.9g, 61.6%), mp. 98-102°C; $[\alpha]_D^{23}$ -109° ($c = 0.86$; CHCl₃); ν_{max}/cm^{-1} (thin film) 1748 (C=O); δ_H (400MHz; CDCl₃) 0.89, 1.02 and 1.06 (9H, 3 x s, 8-, 9-, and 10-Me), 1.55-1.64, 1.83-1.92 and 2.06-2.19 (4H, series of multiplets, 5- and 6-CH₂) and 2.59 (1H, d, J 5.1Hz, 4-H); δ_H (600MHz; CDCl₃) 0.91 (3H, s, 8-Me), 1.04 and 1.08 (6H, 2 x s, 9- and 10-Me), 1.58-1.64 (2H, series of multiplets, 5-*endo*-H and 6-H), 1.90 (1H, m, 6-H), 2.14 (1H, m, 5-*exo*-H) and 2.61 (1H, d, J 5.2Hz, 4-H); δ_C (150MHz; CDCl₃) 8.7 and 17.4 (C-8 and C-9), 21.1 (C-10), 29.9 (C-5), 42.6 (C-7), 57.9 (C-6), 58.6 (C-1), 204.8 (C-3) and 202.8 (C-2).

3,3-(Ethylenedioxy)-2-bornanone **205**, 2,2-(ethylenedioxy)-3-bornanone **206** and 2,2;3,3-bis(ethylenedioxy)bornane **204**



205



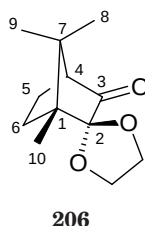
To a solution of (-)-camphorquinone **203** (20.0g, 60.1mmol) in benzene (200mL) was added ethylene glycol (40mL) and *p*-toluenesulfonic acid (1.0g, 6mmol). The mixture was boiled under reflux for 29h; during this time water (5mL) was removed from the system by means of a Dean-Stark apparatus. After cooling the solution was washed with 1M-NaOH (40mL) to remove the *p*-toluenesulfonic acid and with water (40mL) to remove any residual ethylene glycol. The aqueous layer was also extracted with EtOAc (3 x 20mL), and the organic layers were combined, washed with brine, and dried over anhydrous MgSO_4 . The solvent was removed *in vacuo* and the residue was cooled until crystals formed. The crystals were filtered off and washed with hexane to afford 3,3-(ethylenedioxy)-2-bornanone **205** as colourless crystals (5.95g, 25.0%), mp. 89-91°C (lit.,²⁰¹ 88°C); $[\alpha]_D^{23} +61^\circ$ ($c = 1.07$; CHCl_3); $\nu_{\text{max}}/\text{cm}^{-1}$ (thin film) 1642 (C=O); δ_H (600MHz; CDCl_3) 0.89, 0.96 and 1.00 (9H, 3 x s, 8-, 9- and 10-Me); 1.56 (1H, m, 6-*exo*-H), 1.65 (1H, m, 6-*endo*-H), 1.79 (1H, m, 5-*exo*-H), 1.94-1.99 (2H, series of multiplets, 4-H and 5-*endo*-H) and 3.94-4.30 (4H, series of multiplets, $\text{OCH}_2\text{CH}_2\text{O}$); δ_C (150MHz; CDCl_3) 9.1, 19.0 and 21.5 (C-8, C-9 and C-10), 21.4 (C-5), 30.9 (C-6), 43.6 (C-1), 51.5 (C-4), 58.2 (C-7), 64.5 and 66.1 ($\text{OCH}_2\text{-CH}_2\text{O}$), 106.9 (C-3) and 217.3 (C-2).

The filtrate was chromatographed [flash chromatography on silica gel; elution with hexane:EtOAc (9:1)] to afford two fractions: i) 2,2;3,3-bis(ethylene-dioxy)bornane **204** (8.46g, 31%), mp. 63-64 °C (lit.,¹⁶³ 58-59°C); $[\alpha]_D^{23} +3.9^\circ$ ($c = 0.96$; CHCl_3); $\nu_{\text{max}}/\text{cm}^{-1}$ (thin film) 1215 (COC); δ_H (400MHz; CDCl_3) 0.80, 0.87 and 1.18 (9H, 3 x s, 8-, 9- and 10-Me), 1.35 (1H, m, 6-Ha), 1.55 (1H, m, 5-*exo*-H), 1.69 (1H, d, $J=4.6\text{Hz}$, 4-H), 1.80 (1H, m, 5-*endo*-H), 1.95 (1H, m, 6-Hb) and 3.76-3.99 (8H, series of multiplets, 2x $\text{OCH}_2\text{CH}_2\text{O}$); δ_C (100MHz; CDCl_3) 9.8, 20.7 and 21.0 (C-8, C-9 and C-10), 20.9 (C-5), 29.2 (C-6), 44.5 (C-1), 52.7 (C-7), 53.3 (C-4), 64.2,

64.5, 65.0 and 65.9 (OCH₂CH₂O), 113.8 (C-3) and 114.7 (C-2).

ii) a 1:1 mixture of 3,3-(ethylenedioxy)-2-bornanone **205** and 2,2-(ethylenedioxy)-3-bornanone **206** (9.70g, 40.0%).

2,2-(Ethylenedioxy)-3-bornanone **206**



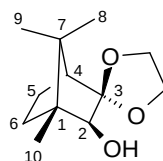
To a solution of 2,2;3,3-bis(ethylenedioxy)bornane **204** (8g, 38mmol) in aqueous methanol (1:1; 100mL) was added *p*-toluenesulfonic acid (4.52g, 43 mmol), and the mixture was boiled under reflux for 8h. (The mixture acquired a yellow tint due to simultaneous formation of camphorquinone **203**.) The mixture was then neutralized with 1M-NaOH (20mL), and the MeOH was removed *in vacuo* at a low temperature. The aqueous residue was extracted with EtOAc (3 x 20mL), and the extracts were washed with brine, dried with anhydrous MgSO₄ and concentrated *in vacuo*. Chromatography of the crude product [flash chromatography on silica gel; elution with hexane:EtOAc (9:1)] afforded 2,2-(ethylenedioxy)-3-bornanone **206** as colourless crystals (4.5g, 65%), mp. 46-48 °C; $[\alpha]_D^{23}$ -79° (*c* = 0.91; CHCl₃); ν_{max}/cm^{-1} (thin film) 1643 (C=O); δ_H (600MHz; CDCl₃) 0.89, 0.94 and 1.03 (9H, 3 x s, 8-, 9- and 10-Me), 1.57 (2H, m, 5-*endo*-H and 6-Ha), 1.91 (1H, m, 5-*exo*-H), 2.05 (1H, m, 6-Hb), 2.16 (1H, d, *J*=5.6Hz, 4-H) and 3.94-4.30 (4H, series of multiplets, OCH₂CH₂O); δ_C (150MHz; CDCl₃) 8.7, 18.2 and 21.5 (C-8, C-9 and C-10), 22.8 (C-5), 29.2 (C-6), 43.7 (C-1), 51.3 (C-7), 59.2 (C-4), 64.9 and 66.4 (OCH₂CH₂O), 107.4 (C-2) and 216.7 (C=O).

0.25g of camphorquinone (4.3%) was also recovered.

3,3-(Ethylenedioxy)-2-*exo*-hydroxybornane **171**

Method 1.

A suspension of lithium aluminium hydride (0.39g, 24mmol) in dry THF (60mL) was heated to 50°C under nitrogen for 30min. A solution of 3,3-(ethylenedioxy)-2-bornanone **205** (5.108g, 24mmol) in THF (10mL) was added slowly and the resulting mixture was heated at

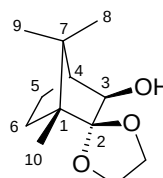
**171**

50°C for 3h and then stirred at room temperature overnight. The reaction was quenched by the addition of 3M-NaOH (2.5mL) and water (2.5mL). The precipitate was filtered off and washed with EtOAc. The aqueous filtrates were extracted with EtOAc (3 x 10mL) and the organic layers combined, dried over MgSO₄ and concentrated *in vacuo*. The crude material was chromatographed [flash chromatography on silica gel; elution with hexane:EtOAc (8:2)] to afford 3,3-(ethylenedioxy)-2-*exo*-hydroxybornane as a colourless oil (3.802 g, 74%); $[\alpha]_D^{23} +11^\circ$ ($c = 0.85$; CHCl₃); ν_{max}/cm^{-1} (thin film) 3424 (OH); δ_H (600MHz; CDCl₃) 0.80, 0.87 and 1.05 (9H, 3 x s, 8-, 9- and 10-Me), 1.14 (1H, m, 6-Ha), 1.47-1.58 (2H, series of multiplets, 5-*exo*- and 6-Hb), 1.67-1.71 (2H, series of multiplets, 4-H, 5-*endo*-H), 2.30 (1H, br s, 2-OH), 3.25 (1H, s, 2-*endo*-H) and 3.79-4.01 (4H, series of multiplets, OCH₂CH₂O); δ_C (150MHz; CDCl₃) 10.9, 21.1 and 21.3 (C-8, C-9 and C-10), 20.8 (C-5), 33.5 (C-6), 47.6 (C-1), 49.7 (C-7), 52.7 (C-4), 63.7 and 65.7 (OCH₂CH₂O), 85.5 (C-2) and 115.2 (C-3).

Method 2. (To establish diastereoselectivity)

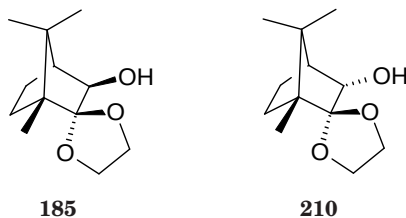
A suspension of lithium aluminium hydride (0.033g, 21mmol) in dry THF (2mL) was heated to 50°C under argon for 30min. 3,3-(Ethylenedioxy)-2-bornanone **205** (0.249g, 12mmol) in THF (2mL) was added slowly and the resulting mixture was heated at 50°C for 3h and then stirred overnight at room temperature. The reaction was quenched by the addition of 3M-NaOH (0.5mL) and water (0.5mL). The precipitate was filtered off and washed with EtOAc (20mL). The organic layer was dried over MgSO₄ and concentrated *in vacuo* to afford 3,3-(ethylenedioxy)-2-*exo*-hydroxybornane **171** and 3,3-(ethylenedioxy)-2-*endo*-hydroxybornane **211**. ¹H NMR analysis indicated 100% conversion and 88% d.e. in the *exo*-product **175**.

2,2-(Ethylenedioxy)-3-*exo*-hydroxybornane 185

**185**

A suspension of lithium aluminium hydride (0.65g, 41mmol) in dry THF (80mL) was heated to 50°C under nitrogen for 30min. 2,2-(Ethylenedioxy)-3-bornanone **206** (9.0g, 43mmol) in THF (15mL) was added slowly and the resulting mixture was heated at 50°C for 3h and then stirred overnight at room temperature. The reaction was quenched by the addition of 3M-NaOH (4mL) and water (4mL). The precipitate was filtered off and washed with EtOAc. The aqueous filtrates were extracted with EtOAc (3 x 20mL) and the organic layers combined, dried over MgSO₄ and concentrated *in vacuo*. The crude material was chromatographed [flash chromatography on silica gel; elution with hexane:EtOAc (9:1)] to afford 2,2-(ethylenedioxy)-3-*exo*-hydroxybornane **185** as a colourless oil (8.32g, 91.5%); $[\alpha]_D^{23} +28.0^\circ$ ($c = 1.15$; CHCl₃); ν_{max}/cm^{-1} (thin film) 3439 (OH); δ_H (600MHz; CDCl₃) 0.78, 0.80 and 1.06 (9H, 3 x s, 8-, 9- and 10-Me), 1.09-1.81 (5H, series of multiplets, 4-H, 5- and 6-CH₂), 2.37 (1H, br s, 3-OH), 3.41 (1H, s, 3-*endo*-H) and 3.71-4.05 (4H, series of multiplets, OCH₂CH₂O); δ_C (150MHz; CDCl₃) 9.3, 21.1 and 21.6 (C-8, C-9 and C-10), 24.5 and 29.1 (C-5 and C-6), 47.7 and 51.8 (C-1 and C-7), 51.5 (C-4), 63.9 and 66.5 (OCH₂CH₂O), 83.0 (C-2) and 116.9 (C-1).

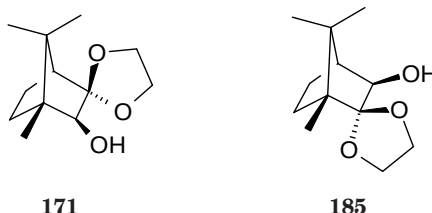
2,2-(Ethylenedioxy)-3-*exo*-hydroxybornane 185 and 2,2-(ethylenedioxy)-3-*endo*-hydroxybornane 210



Method 1. (To establish diastereoselectivity)

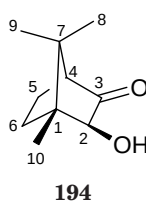
A suspension of lithium aluminium hydride (0.033g, 21mmol) in dry THF (2mL) was heated to 50°C under argon for 30min. 2,2-(Ethylenedioxy)-3-bornanone **206** (0.115g, 0.55mol) in THF (2mL) was added slowly and the resulting mixture was heated at 50°C for 3h and then stirred overnight at room temperature. The reaction was quenched by the addition of 3M-NaOH (0.5mL) and water (0.5mL). The precipitate was filtered off and washed with EtOAc (20mL). The organic layer was dried over MgSO₄ and concentrated *in vacuo*. ¹H NMR analysis indicates 100 % conversion and 76 % d.e. in the *exo*-product **185**.

2,2-(Ethylenedioxy)-3-exo-hydroxybornane 185 and 3,3-(ethylenedioxy)-2-exo-hydroxybornane 171



A suspension of lithium aluminium hydride (0.63g, 39mmol) in dry THF (100mL) was heated to 50°C under nitrogen for 1h. A 1:1 mixture of 3,3-(ethylenedioxy)-2-bornanone and 2,2-(ethylenedioxy)-3-bornanone (9.7g, 46mmol) in THF (10mL) was added slowly and the resulting mixture was heated at 50°C for 3h and then stirred overnight. The reaction was quenched by the addition of 3M-NaOH (5mL) and water (5mL). The precipitate was filtered off and washed with EtOAc. The aqueous filtrates were extracted with EtOAc (3 x 10mL) and the organic layers combined, dried over MgSO₄ and concentrated *in vacuo*. The crude material was chromatographed [flash chromatography on silica gel; elution with hexane:EtOAc (9:1)] to afford the products as an inseparable 1:1 mixture (6.62g, 68%).

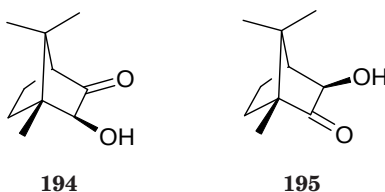
2-Exo-hydroxy-3-bornanone 194



To a solution of 3,3-(ethylenedioxy)-2-exo-hydroxybornane **171** (8g, 38mmol) in THF (20mL) was added 1M HCl (38mL). After heating under reflux at 60°C for 2.5h, the mixture was cooled, neutralized with 3M-NaOH and the THF was removed at reduced pressure. After extraction with EtOAc (3 x 20mL), the organic layer was dried (anhydrous MgSO₄) and the residue concentrated *in vacuo*. Chromatography [flash chromatography on silica gel; elution with hexane:EtOAc (8:2)] afforded 2-exo-hydroxy-3-bornanone **194** as white crystals (5.2g, 77%), mp. 48-51°C (lit.,¹⁶³ 43°C); $[\alpha]_D^{23} +110^\circ$ ($c = 1.18$; CHCl₃); ν_{max}/cm^{-1} (thin film) 1752 (C=O); δ_H (600MHz; CDCl₃) 0.91, 1.00 and 1.01 (9H, 3 x s, 8-, 9- and 10-Me), 1.36 (1H, m, 6-Ha), 1.43 (1H, m, 5-endo-H), 1.83 (1H, m, 6-Hb), 1.91 (1H, m, 5-exo-H), 2.15 (1H, d, $J=4.64$

Hz, 4-H), 2.80 (1H, br s, 2-OH) and 3.52 (1H, s, 2-*endo*-H); δ_C (150MHz; CDCl₃) 10.3, 18.9 and 21.2 (C-8, C-9 and C-10), 20.3 (C-5), 33.9 (C-6), 46.6 (C-7), 49.2 (C-1), 58.7 (C-4), 79.5 (C-2) and 219.1 (C-3).

2-Exo-hydroxy-3-bornanone **194** and 3-exo-hydroxy-2-bornanone **195**



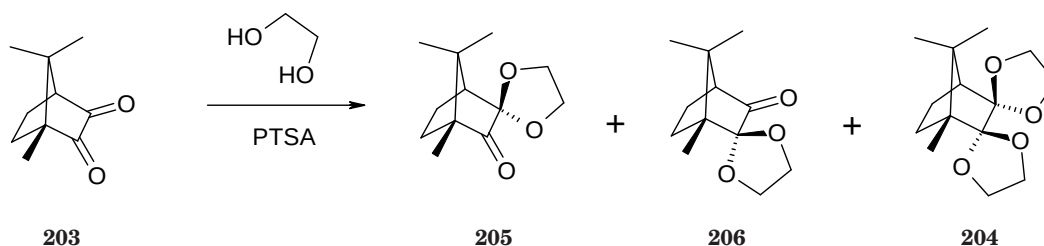
To a solution of a 1:1 mixture of the ketals **185** and **171** (6.62g, 31mmol) in THF (15mL) was added 1M HCl (30mL). After heating under reflux conditions to 60°C for 2.5h, the mixture was cooled, neutralized with 3M-NaOH solution and the THF was removed at reduced pressure. After extraction with EtOAc (4 x 20mL) the organic layer was dried (anhydrous MgSO₄), and the residue concentrated *in vacuo*. Chromatography [flash chromatography on silica gel; elution with hexane:EtOAc (8:2)] afforded the inseparable 1:1 mixture of products **194** and **195** as a white powder (4.53g, 81%). HPLC analysis also failed to effect separation.

Study of the stereoselectivity of deprotection of 2,2;3,3-bis(ethylenedioxy)bornane **204**

To 2,2;3,3-bis(ethylenedioxy)bornane **204** (0.318g, 13mmol) in aqueous methanol (1:1; 5mL) was added *p*-toluenesulfonic acid (0.18g, 1.7mmol). The mixture was boiled under reflux for 8h. After cooling neutralization was effected with 1M-NaOH (2mL), the methanol removed *in vacuo* and the residue extracted with 3x20mL of EtOAc. The organic layer was dried (anhydrous MgSO₄) and the EtOAc was removed *in vacuo*. Stereoselectivities and yields were determined by ¹H and quantitative ¹³C NMR to reveal: 99% overall conversion and formation of the products:

by ¹H:- 83% **206** : 9% **205** : 7% **203**; and

by ¹³C:- 92% **206** : 5% **205** : 2% **203**.

Kinetic study of the ketalization of camphorquinone **203**

To a solution of camphorquinone **203** (5g, 30mmol) in benzene (50mL) was added ethylene glycol (10mL) and *p*-toluenesulfonic acid (0.286g, 2.7mol). The reaction mixture was boiled under reflux in a flask equipped with a Dean-Stark trap. Aliquots (1mL) were removed, washed with 1M-NaOH (1mL) and water (1mL). The organic layer was separated, dried (MgSO₄) and concentrated *in vacuo* and the crude residue was examined by ¹H NMR spectroscopy.

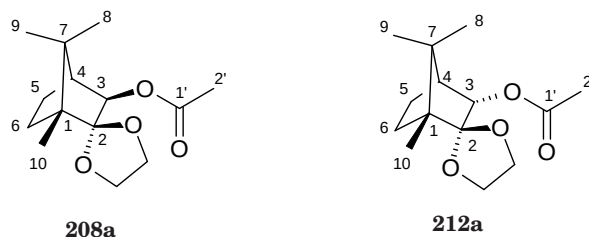
Table 3.1: Relative Integrals in the ketalization of camphorquinone **203**

Time (h)	Camphorquinone	3-ketal	2-ketal	2,3-diketal
0.0	1.00000	0.00000	0.00000	0.00000
1.0	0.36574	0.15803	0.42185	0.05438
2.0	0.33492	0.16416	0.45937	0.04156
3.0	0.16015	0.20670	0.50464	0.12851
4.0	0.04057	0.16198	0.66379	0.13366
5.0	0.03291	0.20113	0.63687	0.12909
6.0	0.01922	0.20533	0.63464	0.14082
7.0	0.00764	0.20882	0.63461	0.14893
8.0	0.00683	0.20372	0.62229	0.16716
9.0	0.00273	0.17135	0.60665	0.21927
10.0	0.00000	0.16070	0.60421	0.23509
11.0	0.00000	0.13791	0.57379	0.28830
12.0	0.00000	0.11530	0.54720	0.33750

3.3 Benzylation of camphor-derived esters

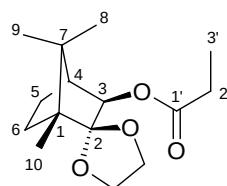
3.3.1 Preparation of esters

2,2-(Ethylenedioxy)-3-exo-bornyl ethanoate 208a and 2,2-(ethylenedioxy)-3-endo-bornyl ethanoate 212a

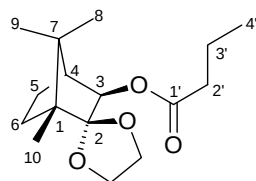
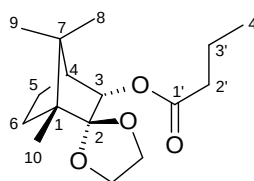


A solution of 2,2-(ethylenedioxy)-3-exo-hydroxybornane **185** (0.606g, 2.4mmol) in dry THF (15mL) was added to a pre-washed suspension of NaH (60% dispersion in oil : 0.266g, 6.7mmol) in dry THF (5mL) under N₂. The mixture was stirred for 1.5h at room temperature, and then under reflux for 30min. The mixture was cooled and acetyl chloride (0.32g, 4mmol) was added dropwise. The mixture was left to stir overnight and the reaction was then quenched by the addition of cold, satd. aq. NaHCO₃ solution (10mL). After the removal of THF *in vacuo*, the aqueous mixture was extracted with EtOAc (3x20mL). The organic layers were combined, dried with anhydrous MgSO₄, concentrated *in vacuo* and chromatographed [radial chromatography; elution with hexane:EtOAc (19:1)] to give two fractions:

- i) 2,2-(ethylenedioxy)-3-exo-bornyl acetate **208a** as an oil (0.306g, 47%); δ_H (400MHz; CDCl₃) 0.77, 0.83 and 1.09 (9H, 3 x s, 8-, 9- and 10-Me), 1.23-1.35, 1.71-1.77 and 1.84-1.91 (5H, series of multiplets, 4-H, 5-CH₂ and 6-CH₂), 2.04 (3H, s, 2'-Me), 3.74-3.92 (4H, series of multiplets, OCH₂CH₂O) and 4.41 (1H, s, 3-H); δ_C (100MHz; CDCl₃) 9.7, 21.1 and 21.4 (C-8, C-9 and C-10), 21.6 (C-2'), 24.8 and 29.3 (C-5 and C-6), 48.3 and 53.0 (C-1 and C-7), 49.9 (C-4), 64.2 and 67.0 (OCH₂CH₂O), 84.1 (C-3), 116.5 (C-2) and 170.6 (C-1').
- ii) 2,2-(Ethylenedioxy)-3-endo-bornyl ethanoate **212a** as an oil (0.047g, 7%); δ_H (400MHz; CDCl₃) 0.77, 0.87 and 1.08 (9H, 3 x s, 8-, 9- and 10-Me), 1.34-1.48, 1.66-1.73, 1.84-1.90 and 1.94-1.96 (5H, series of multiplets, 4-CH, 5-CH₂ and 6-CH₂), 2.10 (3H, s, 2'-Me), 3.64-3.71, 3.80-3.86 and 3.96-4.01 (4H, series of multiplets, OCH₂CH₂O) and 4.97 (1H, d, $J=4.54$ Hz, 3-exo-H); δ_C (100MHz; CDCl₃) 10.4, 20.5 and 20.6 (C-8, C-9 and C-10), 21.6 (C-2'), 44.9 and 49.1 (C-5 and C-6), 53.1 (C-4), 65.3 and 65.5 (OCH₂CH₂O), 79.8 (C-3), 113.3 (C-2) and 171.1 (C-1').

2,2-(Ethylenedioxy)-3-exo-bornyl propanoate 208b**208b**

A solution of 2,2-(ethylenedioxy)-3-exo-hydroxybornane **185** (0.604g, 2.3mmol) in dry THF (15mL) was added to a pre-washed suspension of NaH (60% dispersion in oil; 0.260g, 6.5mmol) in dry THF (5mL) under N₂. The mixture was stirred for 1.5h at room temperature, and then under reflux for 30min. The mixture was cooled and propanoyl chloride (0.355g, 3.8mmol) was added dropwise. The mixture was left to stir overnight and then quenched by the addition of cold, satd. aq. NaHCO₃ (10mL). After the removal of THF *in vacuo*, the aqueous mixture was extracted with EtOAc (3x20mL). The organic layers were combined, dried with anhydrous MgSO₄, concentrated *in vacuo* and chromatographed [radial chromatography; elution with hexane:EtOAc (19:1)] to give 2,2-(ethylenedioxy)-3-exo-bornyl propanoate **208b** as an oil (0.311g, 45%); δ_H (400MHz; CDCl₃) 0.77, 0.83 and 1.08 (9H, 3 x s, 8-, 9- and 10-Me), 1.13 (3H, t, $J=7.63$ Hz, 3'-Me), 2.32 (2H, q, $J=7.57$ Hz, 2'-CH₂), 1.24-1.36, 1.72-1.75 and 1.85-1.91 (5H, series of multiplets, 4-H, 5-CH₂ and 6-CH₂), 3.73-3.95 (4H, series of multiplets, OCH₂CH₂O) and 4.42 (1H, s, 3-H); δ_C (100MHz; CDCl₃) 9.3, 20.8 and 21.0 (C-8, C-9 and C-10), 24.4 and 28.9 (C-5 and C-6), 28.0 (C-2'), 47.9 and 52.6 (C-1 and C-7), 49.5 (C-4), 63.8 and 66.6 (OCH₂CH₂O), 83.5 (C-3), 116.2 (C-2) and 173.5 (C-1').

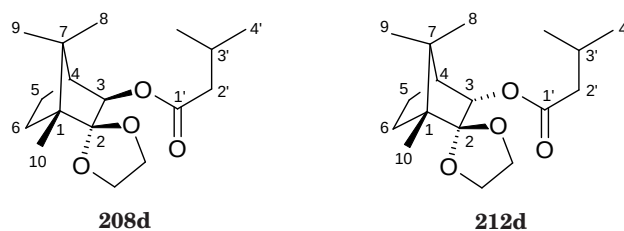
2,2-(Ethylenedioxy)-3-exo-bornyl butanoate 208c and 2,2-(ethylenedioxy)-3-endo-bornyl butanoate 212c**208c****212c**

A solution of 2,2-(ethylenedioxy)-3-exo-hydroxybornane **185** (0.54g, 2.5mmol) in dry THF (15mL) was added to a pre-washed suspension of NaH (60% dispersion in oil; 0.37g, 8mmol) in dry THF (5mL) under N₂. The mixture was stirred for 1.5h at room temperature, and then

under reflux for 30min. The mixture was cooled and butanoyl chloride (0.65g, 6.1mmol) was added dropwise. The mixture was left to stir overnight and then quenched by the addition of cold satd. aq. NaHCO_3 (10mL). After the removal of THF *in vacuo*, the aqueous mixture was extracted with EtOAc (3x20mL). The organic layers were combined, dried with anhydrous MgSO_4 , concentrated *in vacuo* and chromatographed [radial chromatography; elution with hexane:EtOAc (19:1)] to give two fractions:

- i) 2,2-(ethylenedioxy)-3-*exo*-bornyl butanoate **208c** as an oil (0.346g, 38%); δ_H (400MHz; CDCl_3) 0.76, 0.82 and 1.09 (9H, 3 x s, 8-, 9- and 10-Me), 0.94 (3H, t, $J=7.51\text{Hz}$, 4'-Me), 1.64 (2H, m, 3'- CH_2), 2.27 (2H, t, $J=7.26\text{Hz}$, 2'- CH_2), 1.21-1.36, 1.70-1.74 and 1.84-1.91 (5H, series of multiplets, 4-H, 5- CH_2 and 6- CH_2), 3.72-3.94 (4H, series of multiplets, $\text{OCH}_2\text{CH}_2\text{O}$) and 4.41 (1H, s, 3-H); δ_C (100MHz; CDCl_3) 9.2, 20.8 and 21.0 (C-8, C-9 and C-10), 13.7 (C-4'), 18.5 (C-3'), 24.4, 52.6 (C-1 and C-7), 28.9, 47.9 and 49.6 (C-4, C-5 and C-6), 36.6 (C-2'), 63.8 and 66.6 ($\text{OCH}_2\text{CH}_2\text{O}$), 83.4 (C-3), 116.1 (C-2) and 172.7 (C-1').
- ii) 2,2-(Ethylenedioxy)-3-*endo*-bornyl butanoate **212c** as an oil (0.0396g, 5.6%); δ_H (400MHz; CDCl_3) 0.76/0.77, 0.78/0.79 and 1.08/1.07 (9H, 3 x s, 8-, 9- and 10-Me), 0.93 (3H, t, $J=7.33\text{Hz}$, 4'-Me), 2.27 (2H, t, $J=7.9\text{Hz}$, 2'-Me), 1.26-1.38 and 1.61-2.04 (4H, series of multiplets, 4-CH, 2'-, 3'-, 5- and 6- CH_2), 3.81-3.93 (4H, series of multiplets, $\text{OCH}_2\text{CH}_2\text{O}$) and 5.07/5.16 (1H, d, $J=3.85\text{Hz}$, 3-*exo*-H).

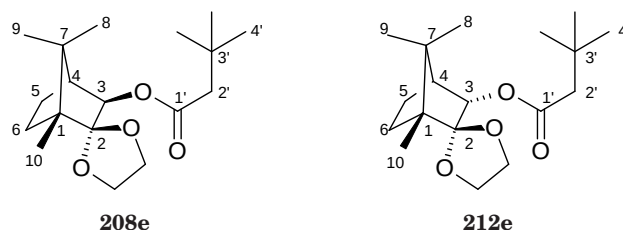
2,2-(Ethylenedioxy)-3-*exo*-bornyl 3-methylbutanoate 208d and 2,2-(ethylenedioxy)-3-*endo*-bornyl 3'-methylbutanoate 212d



A solution of predominantly 2,2-(ethylenedioxy)-3-*exo*-hydroxybornane **185** (0.74g, 3.5mmol) in dry THF (15mL) was added to a prewashed suspension of NaH (60% dispersion in oil; 0.37g, 5.5mmol) in dry THF (5mL) under N_2 . The mixture was stirred for 1.5h at room temperature, and then under reflux for 30min. The mixture was cooled and methylbutanoyl chloride (0.74g, 6.2mmol) was added dropwise. The mixture was left to stir overnight and then quenched by the addition of cold, satd. aq. NaHCO_3 (10mL). After the removal of THF *in vacuo*, the aque-

ous mixture was extracted with EtOAc (3x20mL). The organic layers were combined, dried with anhydrous MgSO_4 , concentrated *in vacuo* and chromatographed [radial chromatography; elution with hexane:EtOAc (19:1)] to give a mixture of 2,2-(ethylenedioxy)-3-*exo*-bornyl 3-methylbutanoate **208d** and 2,2-(ethylenedioxy)-3-*endo*-bornyl 3'-methylbutanoate **212d** as an oil (0.6395g, 61%); δ_H (400MHz; CDCl_3) 0.77, 0.83 and 1.10 (9H, 3 x s, 8-, 9- and 10-Me), 0.94 and 0.96 (6H, 2 x d, $J=3.63\text{Hz}$, $i\text{Pr}$ -methyls), 1.23-1.36, 1.67-1.90, 2.03-2.12 and 2.15-2.18 (9H, series of multiplets, 4-H, 2', 3', 5- and 6- CH_2), 3.71-3.92 (4H, series of multiplets, $\text{OCH}_2\text{CH}_2\text{O}$) and 4.42/4.26[†] (1H, s, 3-*endo/exo*-H, ratio 14:1); δ_C (100MHz; CDCl_3) 9.3/9.5, 20.8 and 21.0 (C-8, C-9 and C-10), 66.5/66.2 and 63.8/63.2 ($\text{OCH}_2\text{CH}_2\text{O}$), 83.4 (C-3), 116.1 (C-2) and 172.1 (C-1').

2,2-(Ethylenedioxy)-3-*exo*-bornyl 3,3-dimethylbutanoate 208e
and 2,2-(ethylenedioxy)-3-*endo*-bornyl 3,3-dimethylbutanoate 212e



A solution of 2,2-(ethylenedioxy)-3-*exo*-hydroxybornane **185** (0.82g, 3.9mmol) in dry THF (15mL) was added to a prewashed suspension of NaH (60% dispersion in oil; 0.41g, 6.1mmol) in dry THF (5mL) under N_2 . The mixture was stirred for 1.5h at room temperature, and then under reflux for 30min. The mixture was cooled and 3,3-dimethylbutanoyl chloride (0.423ml, 6mmol) was added dropwise. The mixture was left to stir overnight and then quenched by the addition of cold, satd. aq. NaHCO_3 (10mL). After the removal of THF *in vacuo*, the aqueous mixture was extracted with EtOAc (3x20mL). The organic layers were combined, dried with anhydrous MgSO_4 , concentrated *in vacuo* and chromatographed [radial chromatography; elution with hexane:EtOAc (19:1)] to give two fractions:

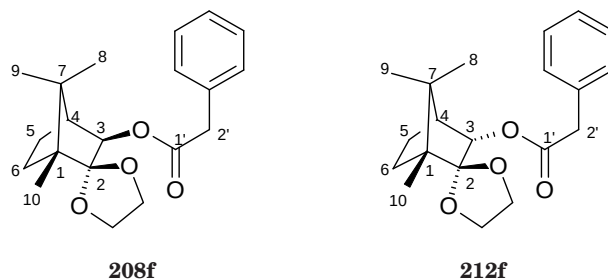
i) 2,2-(Ethylenedioxy)-3-*exo*-bornyl 3,3-dimethylbutanoate **208e** as colourless crystals (0.2929g, 24%); m.p. 46-48°C; δ_H (400MHz; CDCl_3) 0.77, 0.82 and 1.10 (9H, 3 x s, 8-, 9- and 10-Me), 1.02 (9H, s, $t\text{Bu}$ -methyls), 2.19 (2H, s, 2'- CH_2), 1.22-1.36, 1.69-1.74 and 1.86-1.94 (5H, series of multiplets, 4-CH, 5- and 6- CH_2), 3.69-3.78 and 3.84-3.93 (4H, series of multiplets, $\text{OCH}_2\text{CH}_2\text{O}$)

[†]The convention used here and elsewhere indicate corresponding signals for the diastereomeric products.

and 4.42 (1H, s, 3-H); δ_C (100MHz; CDCl_3) 9.3, 20.9 and 21.0 (C-8, C-9 and C-10), 24.6 and 28.9 (C-5 and C-6), 29.7 ($\text{Bu}^t\text{-Me}$), 30.8, 47.9 and 52.6 (C-1, C-7 and C-3'), 48.3 (C-2'), 49.8 (C-4), 66.5 and 63.8 ($\text{OCH}_2\text{CH}_2\text{O}$), 83.5 (C-3), 116.2 (C-2) and 171.5 (C-1').

ii) 2,2-(Ethylenedioxy)-3-endo-bornyl 3,3-dimethylbutanoate **212e** as an oil (0.042g, 3.4%); (Found: M^+ 310.21208. $\text{C}_{18}\text{H}_{30}\text{O}_4$ requires M , 310.21441); δ_H (400MHz; CDCl_3) 0.77, 0.87 and 1.08 (9H, 3 x s, 8-, 9- and 10-Me), 1.04 (9H, s, ^tBu), 1.32-1.48, 1.67-1.75 and 1.85-1.92 (4H, series of multiplets, 5- and 6- CH_2), 1.94 (1H, t, $J=6.6\text{Hz}$, 4-H), 2.26 (2H, s, 2'- CH_2), 3.68-3.71, 3.77-3.89, 3.98-4.04 (4H, series of multiplets, $\text{OCH}_2\text{CH}_2\text{O}$) and 4.96 (1H, dd, $J=6.6$ and 1.8Hz, 3-H); δ_C (100MHz; CDCl_3) 10.1, 20.1 and 20.2 (C-8, C-9 and C-10), 18.6 and 29.4 (C-5 and C-6), 29.6 ($\text{CH}(\text{CH}_3)_3$), 48.1 (C-2'), 48.8 (C-4), 65.0 and 64.9 ($\text{OCH}_2\text{CH}_2\text{O}$), 79.0 (C-3) and 171.9 (C-1').

2,2-(Ethylenedioxy)-3-exo-bornyl phenylethanoate 208f and 2,2-(ethylenedioxy)-3-endo-bornyl phenylethanoate 212f

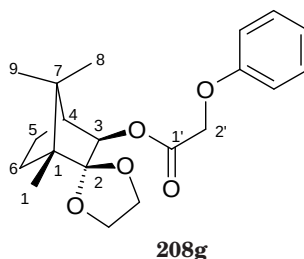


A solution of 2,2-(ethylenedioxy)-3-*exo*-hydroxybornane **185** (0.609g, 1.84mmol) in dry THF (15mL) was added to a pre-washed suspension of NaH (60% dispersion in oil; 0.264g, 4mmol) in dry THF (5mL) under N_2 . The mixture was stirred for 1.5h at room temperature, and then under reflux for 30min. The mixture was cooled and phenylacetyl chloride (0.657g, 4.3mmol) was added dropwise. The mixture was left to stir overnight and then quenched by the addition of cold, satd. aq. NaHCO_3 (10mL). After the removal of THF *in vacuo*, the aqueous mixture was extracted with EtOAc (3x20mL). The organic layers were combined, dried with anhydrous MgSO_4 , concentrated *in vacuo* and chromatographed [radial chromatography; elution with hexane:EtOAc (19:1)] to give two fractions:

i) 2,2-(Ethylenedioxy)-3-*exo*-bornyl phenylethanoate **208f** as an oil (0.279g, 34%); δ_H (400MHz; CDCl_3) 0.76, 0.82 and 1.06 (9H, 3 x s, 8-, 9- and 10-Me), 1.20-1.37, 1.69-1.78 and 1.83-1.89 (5H, series of multiplets, 4-H, 5- and 6- CH_2), 3.54-3.68 and 3.80-3.83 (4H, series of multiplets, $\text{OCH}_2\text{CH}_2\text{O}$), 4.42 (1H, s, 3-H) and 7.20-7.34 (Ar-H).

ii) a 2:1 mixture of the *exo*-product **208f** and 2,2-(ethylenedioxy)-3-*endo*-bornyl phenylacetate **212f** as an oil (0.22g, 22%); δ_H (400MHz; CDCl₃) 0.86, 0.82 and 1.06 (8-, 9- and 10-Me), 3.66 (2H, s, 2'-CH₂), 4.96 (1H, d, J =4.66Hz, 3-H) and 7.21-7.34 (5H, series of multiplets, Ar-H).

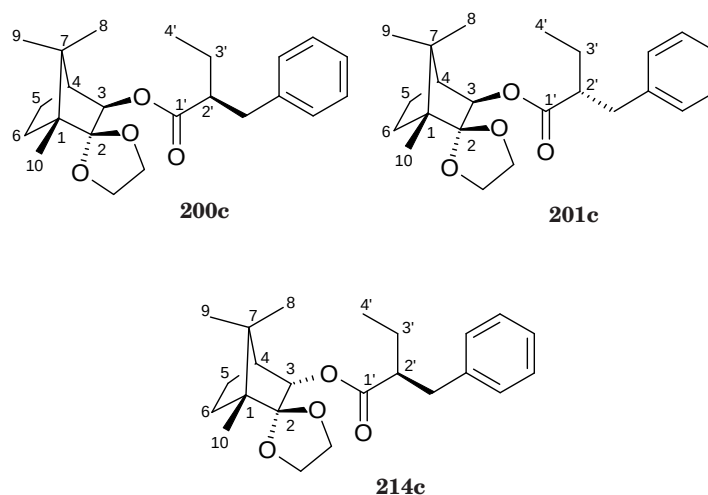
2,2-(Ethylenedioxy)-3-*exo*-bornyl phenoxyethanoate **208g**



A solution of 2,2-(ethylenedioxy)-3-*exo*-hydroxybornane **185** (0.602g, 2.8mmol) in dry THF (15mL) was added to a prewashed suspension of NaH (60% dispersion in oil; 0.262g, 4mmol) in dry THF (5mL) under N₂. The mixture was stirred for 1.5h at room temperature, and then under reflux for 30min. The mixture was cooled and phenoxyethanoyl chloride (0.665g, 4mmol) was added dropwise. The mixture was left to stir overnight and then quenched by the addition of cold, satd. aq. NaHCO₃ (10mL). After the removal of THF *in vacuo*, the aqueous mixture was extracted with EtOAc (3x20mL). The organic layers were combined, dried with anhydrous MgSO₄, concentrated *in vacuo* and chromatographed [radial chromatography; elution with hexane:EtOAc (19:1)] to give 2,2-(ethylenedioxy)-3-*exo*-bornyl phenoxyethanoate **208g** as white crystals (0.429g, 44%); mp. 84-88°C; δ_H (400MHz; CDCl₃) 0.78, 0.84 and 1.07 (9H, 3 x s, 8-, 9- and 10-Me), 1.23-1.37, 1.74-1.80 and 1.86-1.92 (5H, series of multiplets, 4-H, 5- and 6-CH₂), 3.68-3.74, 3.78-3.82 and 3.84-3.94 (4H, series of multiplets, OCH₂CH₂O), 4.62 (2H, s, 2'-CH₂), 4.49 (1H, s, 3-*endo*-H)/5.04 (1H, d, J =4.8Hz, 3-*exo*-H) and 6.70-6.99 and 7.25-7.30 (5H, series of multiplets, Ar-H); δ_C (100MHz; CDCl₃) 9.2, 20.7 and 20.9 (C-8, C-9 and C-10), 24.3 and 28.8 (C-5 and C-6), 47.9 and 52.8 (C-1 and C-7), 49.3 (C-4), 63.9 and 66.6 (OCH₂CH₂O), 65.1 (C-3'), 84.5 (C-3), 114.6, 121.6 and 129.5 (3° Ar-C), 115.9 (4° Ar-C) and 157.8 (C=O).

3.3.2 Benzylation studies on the esters

2,2-(Ethylenedioxy)-3-exo-bornyl 2-benzylbutanoate 200c, 2,2-(Ethylenedioxy)-3-exo-bornyl 2-benzylbutanoate 201c and 2,2-(Ethylenedioxy)-3-endo-bornyl 2-benzylbutanoate 214c¹



A solution of LDA (1.5mmol; generated *in situ* from diisopropylamine and *n*-butyllithium) at -78°C was slowly added to a solution of 2,2-(ethylenedioxy)-3-endo-bornyl butanoate (0.40g, 1.4mmol) in THF(10mL). The mixture was stirred at -78°C for 1h. Benzyl bromide (180μL, 1.5mmol) was added and the mixture was stirred for 2h. The mixture was then stirred overnight, warming to room temperature. The reaction was quenched with saturated NaHCO₃ solution, the THF was removed *in vacuo* and the mixture extracted with EtOAc. The crude product was an oil (0.3868g, 73.3%). Chromatography [HPLC; elution with hexane:EtOAc 3:1] on a portion of the product afforded three fractions:

i) 2,2-(Ethylenedioxy)-3-exo-bornyl 2-benzylbutanoate **200c** as an oil; (Found: M^+ 372.22874. C₂₃H₃₂O₄ requires M , 372.23006); δ_H (400MHz; CDCl₃) 0.76, 0.78 and 1.01 (9H, 3 x s, 8-, 9- and 10-Me), 0.92 (3H, t, J =7.56Hz, 4'-Me), 1.18-1.34, 1.53-1.74 and 1.82-1.89 (9H, series of multiplets, 3'-, 5- and 6-CH₂), 1.50 (1H, t, J =5.19Hz, 4-H), 2.60 (1H, m, 2'-H), 2.73 (1H, dd, J_1 =13.4Hz, J_2 =6.7Hz, Ph-CH₂a), 2.93 (1H, dd, J_1 =14.0Hz, J_2 =8.4Hz, Ph-CH₂b), 3.69-3.78 and 3.84-3.87 (4H, series of multiplets, OCH₂CH₂O), 4.35 (1H, s, 3-H) and 7.15-7.27 (5H, series of multiplets, Ar-H); δ_C (100MHz; CDCl₃) 9.3, 20.8 and 21.0 (C-8, C-9 and C-10), 11.8 (C-4'), 24.4, 24.9 and 28.9 (C-3', C-5 and C-6), 38.1 (PhCH₂), 47.8 and 52.5 (C-1 and C-7), 49.2 (C-2'), 49.8 (C-4), 63.8 and 66.5 (OCH₂CH₂O), 83.4 (C-3), 116.1 (C-2), 126.2, 128.3 and 129.0 (Ar-C),

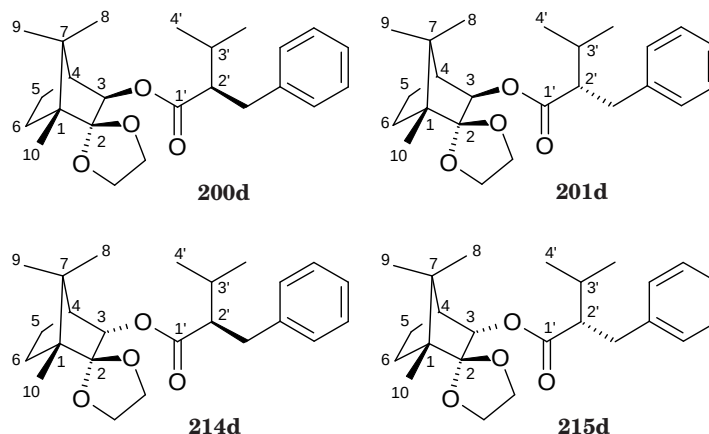
¹The stereochemistry at position 2' in these reactions has not been determined absolutely.

139.6 (4° Ar-C) and 174.7 (C-1').

ii) 2,2-(Ethylenedioxy)-3-exo-bornyl 2-benzylbutanoate **201c** as an oil; (Found: M^+ 372.22854. $C_{23}H_{32}O_4$ requires M , 372.23006); δ_H (400MHz; $CDCl_3$) 0.75, 0.82 and 1.10 (9H, 3 x s, 8-, 9- and 10-Me), 0.92 (3H, t, $J=7.29$ Hz, 4'-Me), 1.22-1.36 and 1.51-1.88 (9H, series of multiplets, 3'-, 4-, 5- and 6- CH_2), 2.60 (1H, m, 2'-H), 2.69 (1H, dd, $J_1=13.6$ Hz, $J_2=6.3$ Hz, Ph- CH_2 a), 2.96 (1H, dd, $J_1=13.6$ Hz, $J_2=8.4$ Hz, Ph- CH_2 b), 3.33-3.39, 3.56-3.66 and 3.72-3.78 (4H, series of multiplets, OCH_2CH_2O), 4.36 (1H, s, 3-H) and 7.13-7.26 (5H, series of multiplets, Ar-H); δ_C (100MHz; $CDCl_3$) 9.2, 20.9 and 21.0 (C-8, C-9 and C-10), 11.8 (C-4'), 24.6, 25.4 and 29.1 (C-3', C-5 and C-6), 38.2 (Ph CH_2), 47.9 and 52.3 (C-1 and C-7), 49.5 (C-2'), 49.9 (C-4), 63.5 and 66.1 (OCH_2CH_2O), 83.3 (C-3), 116.1 (C-2), 126.1, 128.3 and 129.0 (Ar-C), 139.7 (4° Ar-C) and 174.5 (C-1').

iii) 2,2-(Ethylenedioxy)-3-endo-bornyl 2-benzylbutanoate **214c** as an oil; (Found: M^+ 372.23092. $C_{23}H_{32}O_4$ requires M , 372.23006); δ_H (400MHz; $CDCl_3$) 0.73, 0.85 and 1.05 (9H, 3 x s, 8-, 9- and 10-Me), 0.93 (3H, t, $J=7.62$ Hz, 4'-Me), 1.25-1.45, 1.60-1.72, 1.81-1.87, 2.69-2.76 and 2.90-2.92 (9H, series of multiplets, 2'-H, benzylic-, 3'-, 5- and 6- CH_2), 1.94 (1H, t, $J=4.53$ Hz, 4-H), 2.93-2.97, 3.52-3.56 and 3.61-3.68 (4H, series of multiplets, OCH_2CH_2O), 4.88 (1H, d, $J=4.63$ Hz, 3-H) and 7.13-7.25 (5H, series of multiplets, Ar-H); δ_C (100MHz; $CDCl_3$) 9.8, 20.0 and 20.2 (C-8, C-9 and C-10), 11.8 (C-4'), 18.3 and 29.6 (C-5 and C-6), 25.9 (C-3'), 38.4 (Ph CH_2), 48.7 (C-4), 49.7 (C-2'), 64.2 and 64.6 (OCH_2CH_2O), 79.0 (C-3), 126.1, 128.3 and 129.1 (Ar-C) and 175.1 (C-1').

2,2-(Ethylenedioxy)-3-exo-bornyl 2-benzyl-3-methylbutanoate 200d,
2,2-(ethylenedioxy)-3-exo-bornyl 2-benzyl-3-methylbutanoate 201d, 2,2-(ethylenedioxy)-
3-endo-bornyl 2-benzyl-3-methylbutanoate 214d and 2,2-(ethylenedioxy)-3-endo-
bornyl 2-benzyl-3-methylbutanoate 215d



A solution of LDA [11 mmol; generated *in situ* from diisopropylamine (1.54 mL, 11mmol) and *n*-butyllithium (4.6mL of 2.4M solution)] at -78°C was slowly added to a solution of 2,2-(ethylenedioxy)-3-exo-bornyl 3'-methylbutanoate **208d** (0.4031g, 1.31mmol) in THF(10mL). The mixture was stirred at -78°C for 1h. A solution of benzyl bromide (0.187mL, 10 mmol) in THF (5mL) was added and the mixture was stirred for 6h. The mixture was then stirred overnight, warming to room temperature. The reaction was quenched with sat. aq. NaHCO_3 , the THF was removed *in vacuo* and the mixture extracted with EtOAc. Chromatography [HPLC, elution with hexane:EtOAc (3:1)] on a portion of the product afforded four fractions:

i) 2,2-(Ethylenedioxy)-3-exo-bornyl 2-benzyl-3-methylbutanoate **200d** as colourless crystals; (Found: M^+ 386.24719. $\text{C}_{24}\text{H}_{34}\text{O}_4$ requires M , 386.24571); mp. $44\text{--}47^{\circ}\text{C}$; δ_{H} (400MHz; CDCl_3) 0.72, 0.80 and 1.07 (8-, 9- and 10-Me), 0.99 and 1.03 (6H, 2 x d, $J=6.99\text{Hz}$, Pr^i), 1.19-1.34, 1.68-1.75 and 1.77-1.84 (4H, series of multiplets, 5- and 6- CH_2), 1.68 (1H, t, $J=3.0\text{Hz}$, 4-H), 1.95 (1H, m, 3'-H), 2.49 (1H, m, 2'-H), 2.79-2.86 (2H, series of multiplets, benzylic- CH_2), 2.98-3.03, 3.36-3.41, 3.45-3.50 and 3.62-3.66 (4H, series of multiplets, $\text{OCH}_2\text{CH}_2\text{O}$), 4.29 (1H, s, 3-H) and 7.11-7.24 (5H, m, Ar-H); δ_{C} (100MHz; CDCl_3) 9.2, 20.2 and 20.6 (C-8, C-9 and C-10), 20.9 ($\text{C}(\text{CH}_3)_2$), 24.5 and 29.0 (C-5 and C-6), 31.1 (C-3'), 35.9 (PhCH_2), 47.8, 52.0 (C-1 and C-7), 49.9 (C-4), 54.9 (C-2'), 63.3 and 65.8 ($\text{OCH}_2\text{CH}_2\text{O}$), 83.2 (C-3), 126.0, 128.2, 129.0 and 140.3 (Ar-C) and 173.9 (C-1').

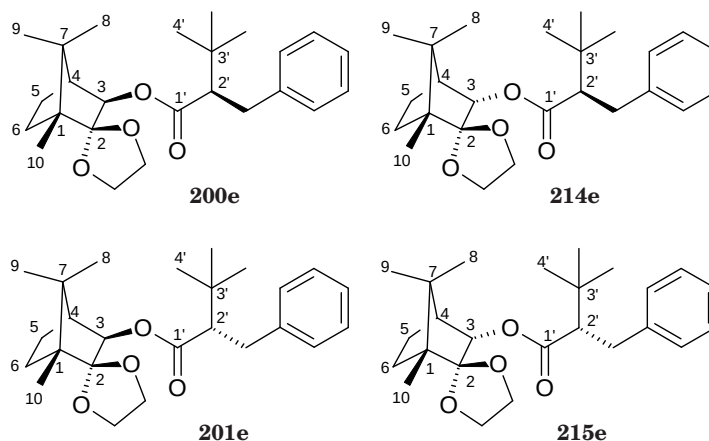
ii) 2,2-(Ethylenedioxy)-3-exo-bornyl 2-benzyl-3-methylbutanoate **201d** as an oil; (Found: M^+

386.24584. $C_{24}H_{34}O_4$ requires M , 386.24571); δ_H (400MHz; $CDCl_3$) 0.73, 0.73 and 0.91 (9H, 3 x s, 8-, 9- and 10-Me), 0.99 and 1.03 (6H, 2 x d, $J=6.73\text{Hz}$, Pr^i), 1.14-1.31, 1.60-1.69 and 1.79-1.86 (4H, series of multiplets, 5- and 6- CH_2), 1.97 (1H, m, 3'-H), 2.48 (1H, m, 2'-H), 2.85 (2H, d 7.91Hz, benzylic- CH_2), 3.66-3.89 (4H, series of multiplets, OCH_2CH_2O), 4.27 (1H, s, 3-H) and 7.13-7.18 and 7.21-7.25 (5H, series of multiplets, Ar-H); δ_C (100MHz; $CDCl_3$) 9.25, 20.2, 20.3, 20.4, 20.6 and 20.8 (C-8, C-9 and C-10, and $C(\underline{CH}_3)_2$), 24.4 and 28.9 (C-5 and C-6), 30.6 (C-3'), 35.8 ($PhCH_2$), 49.7 (C-4), 54.7 (C-2'), 63.7 and 66.3 (OCH_2CH_2O), 83.5 (C-3), 116.1 (C-2), 126.1, 128.3, 128.9 and 140.0 (Ar-C) and 174.2 (C-1').

iii) 2,2-(Ethylenedioxy)-3-endo-bornyl 2-benzyl-3-methylbutanoate **214d** as an oil; (Found: M^+ 386.24645. $C_{24}H_{34}O_4$ requires M , 386.24571); δ_H (400MHz; $CDCl_3$) 0.70, 0.83 and 1.03 (8-, 9- and 10-Me), 0.99 and 1.04 (6H, 2 x d, $J=6.73\text{Hz}$, Pr^i), 1.25-1.39, 1.56-1.63, 1.78-1.83 and 1.90-1.95 (7H, series of multiplets, 2'-, 3'- and 4-H, 5- and 6- CH_2), 2.84 (2H, d, $J=7.57\text{Hz}$, benzylic CH_2), 2.54-2.66, 3.37-3.46 and 3.54-3.60 (4H, series of multiplets, OCH_2CH_2O), 4.84 (1H, dd, $J_1=4.57\text{Hz}$, $J_2=1.28\text{Hz}$, 3-H) and 7.12-7.25 (5H, series of multiplets, Ar-H); δ_C (100MHz; $CDCl_3$) 19.8, 20.0, 20.2 and 20.5 (C-8, C-9 and C-10; $C(\underline{CH}_3)_2$), 18.3 and 29.6 (C-5 and C-6), 31.3 (C-3'), 36.1 ($PhCH_2$), 48.7 (C-4), 55.1 (C-2'), 63.9 and 64.5 (OCH_2CH_2O), 78.8 (C-3), 113.1 (C-2) and 126.0, 128.2, 129.1 and 137.6 (Ar-C).

iv) 2,2-(Ethylenedioxy)-3-endo-bornyl 2-benzyl-3-methylbutanoate **215d** as an oil; (Found: M^+ 386.24571. $C_{24}H_{34}O_4$ requires M , 386.24571); δ_H (400MHz; $CDCl_3$) 0.71, 0.79 and 1.02 (9H, 3 x s, 8-, 9- and 10-Me), 0.99 and 1.05 (6H, 2 x d, $J=6.77\text{Hz}$, Pr^i), 1.08-1.14, 1.22-1.28 and 1.70-1.78 (4H, series of multiplets, 5- and 6- CH_2), 1.66 (1H, t, $J=4.48\text{Hz}$, 4-H), 1.97 (1H, m, 3'-CH), 2.58 (1H, m, 2'-CH), 2.86 (2H, d, $J=7.74\text{Hz}$, benzylic- CH_2), 3.60, 3.72, 3.80 and 3.89 (4H, 4 x d, $J=7.04\text{Hz}$, OCH_2CH_2O), 4.83 (d, $J=4.47\text{Hz}$, 3-H) and 7.12-7.22 (Ar-H); δ_C (100MHz; $CDCl_3$) 9.98, 20.1, 20.2 and 20.3 (C-8, C-9 and C-10, $C(\underline{CH}_3)_2$), 18.12 and 29.4 (C-5 and C-6), 30.9 (C-3'), 36.1 ($PhCH_2$), 48.8 (C-4), 54.6 (C-2'), 64.79 and 64.81 (OCH_2CH_2O), 79.1 (C-3), 114.5 (C-2) and 126.1, 128.3, 128.9 and 140.0 (Ar-C).

2,2-(Ethylenedioxy)-3-exo-bornyl 2-benzyl-3,3-dimethylbutanoate 200e,
2,2-(ethylenedioxy)-3-endo-bornyl 2-benzyl-3,3-dimethylbutanoate 214e,
2,2-(ethylenedioxy)-3-exo-bornyl 2-benzyl-3,3-dimethylbutanoate 201e and 2,2-
(ethylenedioxy)-3-endo-bornyl 2-benzyl-3,3-dimethylbutanoate 215e

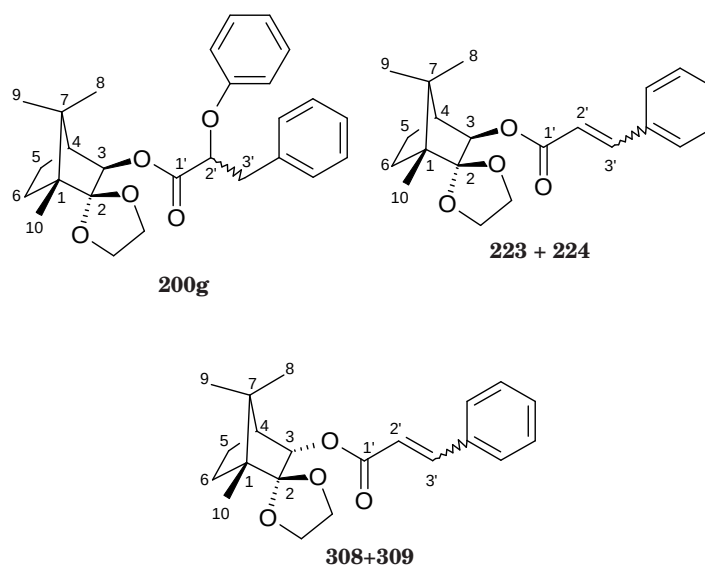


A solution of LDA [11 mmol; generated *in situ* from diisopropylamine (1.54 mL, 11mmol) and *n*-butyllithium (4.6mL of 2.4M solution)] at -78°C was slowly added a solution of 2,2-(ethylenedioxy)-3-exo-bornyl 3',3'-dimethylbutanoate **208e** (0.497g, 1.2mmol) in THF(10mL). The mixture was stirred at -78°C for 1h. Benzyl bromide (0.187mL, 10 mmol in 5mL THF) was added and the mixture was stirred for 2h. The mixture was then stirred overnight, warming to room temperature. The reaction was quenched with saturated NaHCO_3 solution, the THF was removed *in vacuo* and the mixture extracted with EtOAc. Chromatography [HPLC, elution with hexane:EtOAc (3:1)] on a portion of the crude product afforded two fractions:

i) a mixture of 2,2-(ethylenedioxy)-3-exo-bornyl 2-benzyl-3,3-dimethylbutanoate **200e** and 2,2-(ethylenedioxy)-3-endo-bornyl 2-benzyl-3,3-dimethylbutanoate **214e** as an oil; (Found: M^+ 400.26174. $\text{C}_{25}\text{H}_{36}\text{O}_4$ requires M , 400.26136); δ_{H} (400MHz; CDCl_3) 0.68, 0.71 and 0.77 (9H, 3 x s, 8-, 9- and 10-Me), 1.06/1.07 (9H, s, ^tBu -methyls), 1.17-1.34, 1.63-1.70 and 1.80-1.87 (4-H, series of multiplets, 5- and 6- CH_2), 1.61 (1H, s, 4-H), 2.53 (1H, m, 2'-H), 2.86-2.95 (2H, series of multiplets, benzylic CH_2), 3.70-3.91 (4H, series of multiplets, $\text{OCH}_2\text{CH}_2\text{O}$), 4.24 (1H, s, 3-*endo*-H)/4.82 (1H, dd, $J_1=4.69$, $J_2=1.37$, 3-*exo*-H) and 7.15-7.29 (5-H, series of multiplets, Ar-H); δ_{C} (100MHz; CDCl_3) 9.24, 20.3 and 20.7 (C-8, C-9 and C-10), 24.4 and 28.9 (C-5 and C-6), 27.9 (^tBu -Me), 34.2 (benzylic C), 33.24, 47.5 and 52.2 (C-1, C-7 and ^tBu -4 $^{\circ}$ -C), 49.8 (C-4), 58.7 (C-2'), 63.7 and 66.2 ($\text{OCH}_2\text{CH}_2\text{O}$), 83.6 (C-3), 116.1 (C-2), 126.0, 128.2, 128.9 and 140.1 (Ar-C) and 173.9 (C-1').

ii) a mixture of 2,2-(ethylenedioxy)-3-exo-bornyl 2-benzyl-3,3-dimethylbutanoate **201e** and 2,2-(ethylenedioxy)-3-endo-bornyl 2-benzyl-3,3-dimethylbutanoate **215e** as an oil; (Found: M^+ 400.26247. $C_{25}H_{36}O_4$ requires M , 400.26136); δ_H (400MHz; $CDCl_3$) 0.70, 0.78 and 1.05 (18H, 6 x s, 8-, 9-, 10- and t Bu-Me), 1.21-1.33 and 1.65-1.81 (4H, series of multiplets, 5- and 6- CH_2), 1.66 (1H, s, 4-H), 2.50 (1H, dd, $J_1=11.77$, $J_2=3.57$, 2'-H), 2.69-2.73, 3.13-3.19, 3.38-3.43 and 3.54-3.59 (4H, series of multiplets, OCH_2CH_2O), 2.79-2.91 (2H, series of multiplets, benzylic CH_2), 4.27 (1H, s, 3-endo-H)/ 4.86 (1H, dd, $J_1=4.71$, $J_2=1.37$, 3-exo-H) and 7.09-7.23 (5H, series of multiplets, Ar-H); δ_C (100MHz; $CDCl_3$) 9.2, 20.9 and 21.0 (C-8, C-9 and C-10), 28.0 (Bu^t -Me), 24.6 and 29.0 (C-5 and C-6), 34.1 ($PhCH_2$), 50.1 (C-4), 33.5, 47.8 and 51.9 (C-1, C-7 and Bu^t -4°-C), 58.8 (C-2'), 63.1 and 65.5 (OCH_2CH_2O), 83.1 (C-3), 115.8 (C-2), 126.0, 128.3, 129.1 and 140.7 (Ar-C) and 173.5 (C-1').

Attempted preparation of 2,2-(ethylenedioxy)-3-exo-bornyl 2-phenoxy-3-phenylpropanoate and subsequent isolation of 2,2-(ethylenedioxy)-3-exo-bornyl 3-phenylacrylate and 2,2-(ethylenedioxy)-3-endo-bornyl-3 phenylacrylate



A solution of LDA [11 mmol; generated *in situ* from diisopropylamine (1.54 mL, 11mmol) and *n*-butyllithium (4.6mL of 2.4M solution)] at $-78^\circ C$ was slowly added a solution of 2,2-(ethylenedioxy)-3-exo-bornyl phenoxyethanoate **208f** (0.4024g, 1.09mmol) in THF(10mL). The mixture was stirred at $-78^\circ C$ for 1h. Benzyl bromide (230 μ L, 1.31mmol) in THF (10mL) was added and the mixture was stirred for 2h. The mixture was then stirred overnight, warming to room temperature. The reaction was quenched with saturated $NaHCO_3$ solution, the THF was removed *in vacuo* and the mixture extracted with EtOAc. Chromatography [HPLC,

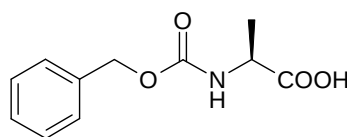
elution with hexane:EtOAc (3:1)] on a portion of the residue afforded two fractions:

- i) a 1:1 mixture of *E* and *Z* 2,2-(ethylenedioxy)-3-exo-bornyl 3-phenylacrylate (**223** and **224**) as a white solid (24.2mg, 6% mass); mp. 134-136 °C; δ_H (400MHz; CDCl₃) 0.94/1.11, 0.67/0.78 and 0.72/0.76 (9H, 3 x s, 8-, 9- and 10-Me), 1.28/1.49 (1H, d, $J=7.2$ Hz, 4-H), 0.81-0.89, 1.14-1.33, 1.50-1.72 and 1.76-1.87 (4H, series of multiplets, 5- and 6-CH₂), 3.45-3.55, 3.63-3.68 and 3.71-3.82 (4H, series of multiplets OCH₂CH₂O), 5.18/5.03 (1H, s, 3-H) and 6.86-6.95 and 7.14-7.27 (5H, series of multiplets, Ar-H); δ_C (100MHz; CDCl₃) 9.20, 20.5/20.7 and 20.9 (C-8, C-9 and C-10), 24.2/24.3 and 28.6/28.7 (C-5 and C-6), 49.2/49.4 (C-4) and 84.8, 85.0 (C-3).
- i) a 1:1 mixture of *E* and *Z* 2,2-(ethylenedioxy)-3-endo-bornyl 3-phenylacrylate (**308** and **309**) as an oil (8.0mg, 2% mass); δ_H (400MHz; CDCl₃) 0.85/0.88, 0.70/0.72 and 0.85/0.88 (9H, 3 x s, 8-, 9- and 10-Me), 1.17-1.29, 1.58-1.61 and 1.81-1.83 (4H, series of multiplets, 5- and 6-CH₂), 1.46/1.56 (1H, d, $J=7.2$ Hz, 4-H), 3.54-3.62 and 3.68-3.77 (4H, series of multiplets, OCH₂CH₂O); 5.20/5.23 (1H, s, 3-H) and 6.87-6.99 and 7.23-7.29 (Ar-H); δ_C (100MHz; CDCl₃) 9.1/9.3, 20.3/20.5 and 20.7/20.8 (C-8, C-9 and C-10), 24.3/24.4 and 28.7 (C-5 and C-6), 49.3/49.6 (C-4), 63.9/64.0 and 66.3/66.4 (OCH₂CH₂O) and 84.7/85.1 (C-3).

3.4 Enantiomer beneficiation of α -amino acids

3.4.1 Carbobenzyloxy protection of amino acids

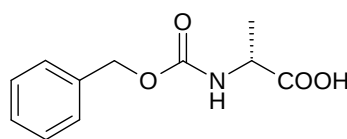
N-(*carbobenzyloxy*)-L-alanine



R-244a

5M-NaOH (4mL) was added to a solution of L-alanine (1.78g, 20mmol) in water (6mL). The solution was stirred and cooled to 10°C. Benzyl chloroformate (3.74g, 0.022mmol) and 2M-NaOH (11mL) were added alternately in 10 portions each while the mixture was maintained at $\leq 10^\circ\text{C}$ for *ca.* 1.5h. The mixture was then allowed to warm to room temperature and stirred for 0.5h. The pH was adjusted to 10 with 2M-NaOH, and the solution was extracted with Et₂O (4x10mL). The aqueous layer was acidified to pH 4 with dil. HCl (5mL), and extracted with diethyl ether (3 x 8mL). The latter diethyl ether fractions were combined, dried (anhydrous MgSO₄) and concentrated *in vacuo*, to afford *N*-(carbobenzyloxy)-L-alanine **R-244a** (0.32g, 7.2%); m.p. 85-88 °C; $[\alpha]_D^{23} +6.8^\circ$ (*c* = 0.62; CHCl₃); $\nu_{\text{max}}/\text{cm}^{-1}$ (thin film) 1651 (C=O); δ_{H} (400MHz; CDCl₃) 1.45 (3H, d, *J*=7.21Hz, α -Me), 5.07-5.14 (2H, series of multiplets, PhCH₂), 7.29-7.37 (5H, series of multiplets, Ar-H) and 7.71 (1H, br s, -COOH).

N-(*carbobenzyloxy*)-D-alanine **S-244a**

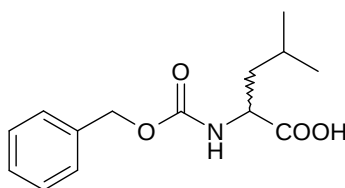


S-244a

5M-NaOH (4mL) was added to a solution of D-alanine (1.78g, 20mmol) in water (6mL). The solution was stirred and cooled to 10°C. Benzyl chloroformate (3.74g, 0.022mmol) and 2M-NaOH (11mL) were added alternately in 10 portions each while the mixture was maintained at $\leq 10^\circ\text{C}$ for *ca.* 1.5h. The mixture was then allowed to warm to room temperature and stirred for 0.5h. The pH was adjusted to 10 with 2M-NaOH, and the solution was extracted with Et₂O (4x10mL). The aqueous layer was acidified to pH 4 with dil. HCl (5mL), and extracted with

diethyl ether (3 x 8mL). The latter diethyl ether fractions were combined, dried (anhydrous MgSO_4) and concentrated *in vacuo*, to afford *N*-(carbobenzyloxy)-D-alanine **S-244a** (0.315g, 7%); m.p. 84-87°C; δ_H (400MHz; CDCl_3) 1.45 (3H, d, $J=7.23\text{Hz}$, $\alpha\text{-Me}$), 4.26-4.45 (1H, m, αCH), 5.07-5.16 (2H, series of multiplets, PhCH_2), 5.84 (2H, br s, NH and OH) and 7.29-7.37 (5H, series of multiplets, Ar-H).

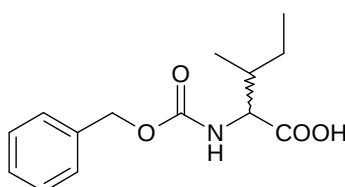
***N*-(carbobenzyloxy)-DL-leucine RS-244i**



RS-244i

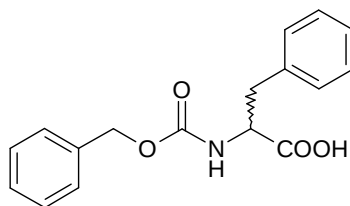
The procedure described for the preparation of *N*-(carbobenzyloxy)-L-alanine **R-244a** was followed using DL-leucine (2.62g, 20mmol). Workup afforded *N*-(carbobenzyloxy)-DL-leucine **RS-244i** as an oil (2.35g, 44%); δ_H (400MHz; CDCl_3) 0.90-0.96 (6H, series of multiplets, 2xMe), 1.58-1.73 (2H, series of multiplets, $\alpha\text{-CH}_2$) and 7.28-7.36 (5H, series of multiplets, Ar-H).

***N*-(carbobenzyloxy)-DL-isoleucine RS-244g**

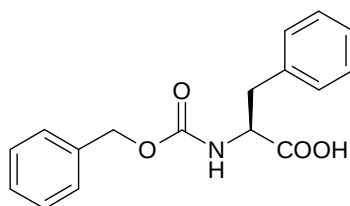


RS-244g

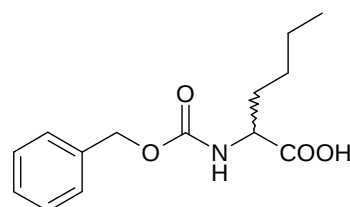
The procedure described for the preparation of *N*-(carbobenzyloxy)-L-alanine **R-244a** was followed using DL-isoleucine (2.62g, 20mmol). Workup afforded *N*-(carbobenzyloxy)-DL-isoleucine **RS-244g** as an oil (0.635g, 25%); δ_H (400MHz; CDCl_3) 0.81-0.99 (6H, series of multiplets, 2 x Me), 1.14-2.02 (3H, series of multiplets, CH and CH_2), 4.46 (1H, m, $\alpha\text{-CH}$), 5.09/5.13 (2H, s, PhCH_2), 5.29-5.41 (1H, br s, NH), 7.07 (1H, br s, COOH) and 7.28-7.38 (5H, series of multiplets, Ar-H).

**RS-244f****N-(carbobenzyloxy)-DL-phenylalanine RS-244f**

The procedure described for the preparation of *N*-(carbobenzyloxy)-L-alanine **R-244a** was followed using DL-phenylalanine (1.51g, 9mmol). Workup afforded *N*-(carbobenzyloxy)-DL-phenylalanine **R-244f** as an oil (0.181g, 6.7%);

N-(carbobenzyloxy)-L-phenylalanine R-244f**R-244f**

The procedure described for the preparation of *N*-(carbobenzyloxy)-L-alanine **R-244a** was followed using L-phenylalanine (1.52g, 10mmol). Workup afforded *N*-(carbobenzyloxy)-L-phenylalanine **R-244f** as an oil (0.5411g, 18%); δ_H (400MHz; CDCl₃) 3.12-3.27 (2H, series of multiplets, PhCH₂), 4.65 (1H, m, α -CH), 5.01-5.16 (2H, m, PhCH₂), 6.35 (2H, br s, NH and OH) and 7.18-7.40 (10H, series of multiplets, Ar-H).

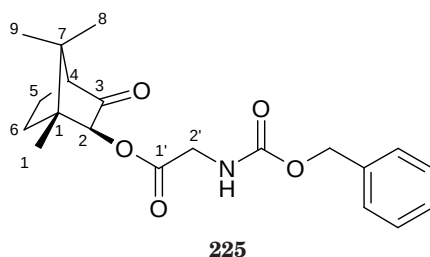
N-(carbobenzyloxy)-DL-norleucine RS-244h**RS-244h**

The procedure described for the preparation of *N*-(carbobenzyloxy)-L-alanine **R-244a** was followed using DL-norleucine (2.62g, 20mmol). Workup afforded *N*-(carbobenzyloxy)-DL-norleucine

RS-244h as an oil (2.13g, 40%); δ_H (400MHz; $CDCl_3$) 0.81-0.93, 1.23-1.40, 1.61-1.72 and 1.81-1.93 (9H, series of multiplets, α -butyl-H), 4.35 (1H, m, α -H), 5.06-5.14 (2H, series of multiplets, Ph-CH₂), 5.23-5.35 (1H, br s, NH) and 7.28-7.37 (5H, series of multiplets, Ar-H).

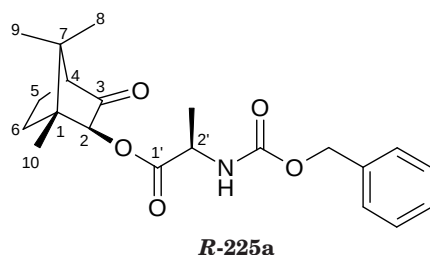
3.4.2 Carbobenzyloxy esters

N-(Carbobenzyloxy)glycine 3-oxo-2-exo-bornyl ester **225**



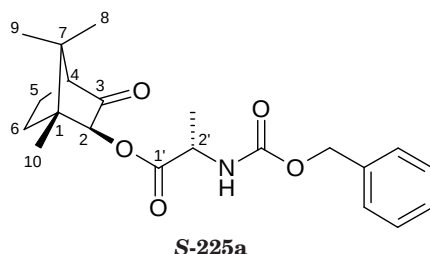
To a solution of *N*-CBZ-glycine (5.89g, 28.2mmol) in anhydrous DMF (9.9mL) was added CDI (4.55g, 28.2mmol). The mixture was stirred at room temperature under N₂ for 30 minutes allowing for the evolution of CO₂. This was followed by the addition of 2-hydroxybornanone (4.55g, 27mmol), and the mixture was stirred overnight. The DMF was distilled off at reduced pressure (35°C). Work-up and flash chromatography, [on silica, elution with hexane:EtOAc (2:3)] afforded **225** as an oil (5.38g, 52%); δ_H (600MHz; $CDCl_3$) 0.90, 0.91 and 0.95 (9H, 3 x s, 8-, 9- and 10-Me), 1.50-1.55 and 1.82-1.94 (4H, series of multiplets, 5-CH₂ and 6-CH₂), 2.19 (1H, s, 4-H), 4.02 (2H, s, 2'-CH₂), 4.88 (1H, s, 2-H), 5.10 (2H, s, Ph-CH₂), 5.38 (1H, br s, NH) and 7.30-7.33 (5H, series of multiplets, Ar-H); δ_C (150MHz; $CDCl_3$) 10.3, 18.3 and 20.7 (C-8, C-9 and C-10), 20.2 and 33.3 (C-5 and C-6), 42.6 (C-2'), 46.6 (C-1), 49.4 (C-7), 58.6 (C-4), 67.0 (Ph-CH₂), 79.1 (C-2), 128.05, 128.4, 128.12 and 136.1 (Ar-C), 156.2 (amide C=O), 169.4 (C-3) and 212.3 (C-1'); *m/z* 359 (0.7%).

N-(Carbobenzyloxy)-D-alanine 3-oxo-2-exo-bornyl ester **R-225a**



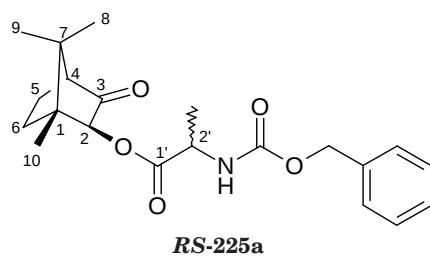
The procedure described for the preparation of *N*-(carbobenzyloxy)glycine 3-oxo-2-*exo*-bornyl ester **225** was followed, using *N*-CBZ-D-alanine (0.105g, 0.45mmol), DMF (1mL), CDI (0.073g, 0.45mmol) and 2-hydroxybornanone (0.076g, 0.45mmol). Work-up and flash chromatography, [hexane:EtOAc 2:3] afforded **R-225a** as an oil (0.054g, 51%); δ_H (400MHz; CDCl₃) 0.89-1.00 (12H, series of multiplets, 8-, 9-, 10- and α -Me), 1.46-1.58 and 1.88-1.95 (4H, series of multiplets, 5- and 6-CH₂), 4.35 (1H, m, α -H), 5.10 (2H, br s, PhCH₂), 5.17-5.29 (1H, br s, NH) and 7.28-7.36 (5H, series of multiplets, Ar-H); m/z 373 (2.4%).

***N*-(Carbobenzyloxy)-L-alanine 3-oxo-2-*exo*-bornyl ester *S*-225a**



The procedure described for the preparation of *N*-(carbobenzyloxy)glycine 3-oxo-2-*exo*-bornyl ester **225** was followed, using *N*-CBZ-L-alanine (0.105g, 0.45mmol), DMF (1mL), CDI (0.073g, 0.45mmol) and 2-hydroxybornanone (0.076g, 0.45mmol). Work-up and flash chromatography, [hexane:EtOAc 2:3] afforded **S-225a** as an oil (0.0342, 34%); δ_H (400MHz; CDCl₃) 0.97-1.08 (9H, series of multiplets, 8-, 9- and 10-Me), 1.48 (3H, d, J =7.74Hz, α -Me), 1.39-1.62 and 1.85-2.01 (4H, series of multiplets, 5- and 6-CH₂), 2.22 (1H, dd, J_1 =12.73, J_2 =3.18, 4H), 4.49 (1H, m, α -H), 5.14 (2H, br s, PhCH₂), 5.33 (1H, br s, NH) and 7.32-7.42 (5H, series of multiplets, Ar-H); m/z 373 (5.5%).

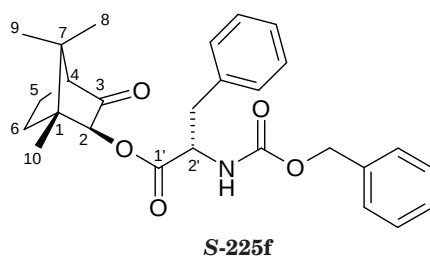
***N*-(Carbobenzyloxy)-DL-alanine 3-oxo-2-*exo*-bornyl ester *RS*-225a**



The procedure described for the preparation of *N*-(carbobenzyloxy)glycine 3-oxo-2-*exo*-bornyl ester **225** was followed, using *N*-CBZ- DL-alanine (1.00g, 4.5mmol, CDI (0.73g, 4.5mmol)

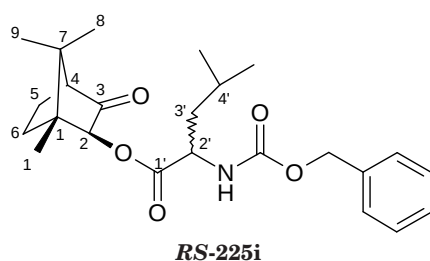
and 2-hydroxybornanone (0.76g, 4.5mmol). Work-up and flash chromatography, [hexane:EtOAc 2:3] afforded **RS-225a** as an oil (0.762g, 43%).

***N*-(Carbobenzyloxy)-L-phenylalanine 3-oxo-2-exo-bornyl ester S-225f**

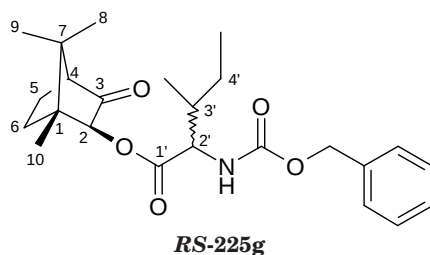


The procedure described for the preparation of *N*-(carbobenzyloxy)glycine 3-oxo-2-exo-bornyl ester **225** was followed, using *N*-CBZ-L-phenylalanine (0.541g, 1.2mmol), CDI (0.29g, 1.8mmol) and 2-hydroxybornanone (0.198 g, 1.2mmol). Work-up and flash chromatography, [hexane:EtOAc 2:3] afforded **S-225f** as an oil (0.24g, 45.4%); (Found: M^+ 449.21708. $C_{27}H_{31}O_5N$ requires M , 449.22022); δ_H (400MHz; $CDCl_3$) 0.90-1.02 (9H, series of multiplets, 8-, 9- and 10-Me), 1.80-1.96 and 1.50-1.58 (4H, series of multiplets, 5- and 6- CH_2), 2.19 (1H, m, 4-CH), 2.98-3.20 (2H, series of multiplets, α - CH_2), 4.00 (1H, m, α -H), 4.86/4.90 (1H, s, 2-H), 5.03-5.08 (2H, series of multiplets, $PhCH_2$) and 7.14-7.35 (5H, series of multiplets, Ar-H).

***N*-(Carbobenzyloxy)-DL-leucine 3-oxo-2-exo-bornyl ester RS-225i**



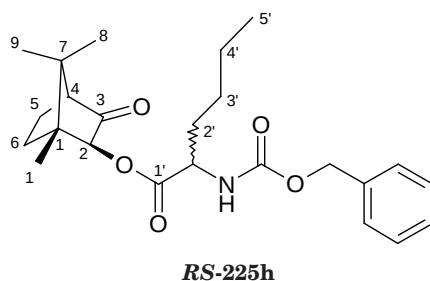
The procedure described for the preparation of *N*-(carbobenzyloxy)glycine 3-oxo-2-exo-bornyl ester **225** was followed, using *N*-CBZ-DL-leucine (1.19g, 4.5mmol), CDI (0.73g, 4.5mmol) and 2-hydroxybornanone (0.76g, 4.5mmol). Work-up and flash chromatography, [hexane:EtOAc 2:3] afforded **RS-225i** as an oil (0.261g, 22%); m/z 415 (1.4%).



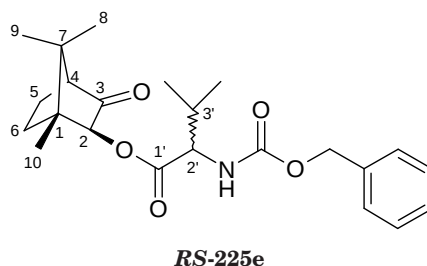
N*-(Carbobenzyloxy)-DL-isoleucine 3-oxo-2-exo-bornyl ester **RS-225g*

The procedure described for the preparation of *N*-(carbobenzyloxy)glycine 3-oxo-2-*exo*-bornyl ester **225** was followed, using *N*-CBZ-DL-isoleucine (1.19g, 4.5mmol), CDI (0.73g, 4.5mmol) and 2-hydroxybornanone (0.76g, 4.5mmol). Work-up and flash chromatography, [hexane:EtOAc 2:3] afforded **RS-225g** as an oil (0.0519g, 4.4%). δ_H (600MHz; $CDCl_3$) 0.88-1.01 (15H, series of multiplets, 3', 4', 8-, 9- and 10-Me), 1.44-1.94 (8H, series of multiplets, 4', 5- and 6- CH_2 , 3'- and 2'-H), 2.15-2.19 (1H, series of multiplets, 4-CH), 4.84-4.90 (1H, series of multiplets, 2-H), 5.09-5.10 (2H, series of multiplets, $PhCH_2$), 5.15-5.22 (1H, series of multiplets, NH) and 7.31-7.34 (5H, series of multiplets, Ar-H).

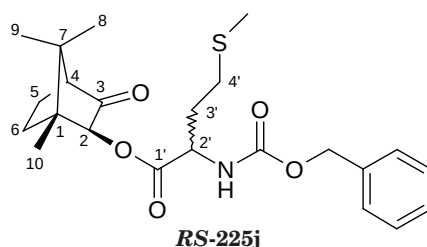
N*-(Carbobenzyloxy)-DL-norleucine 3-oxo-2-exo-bornyl ester **RS-225h*



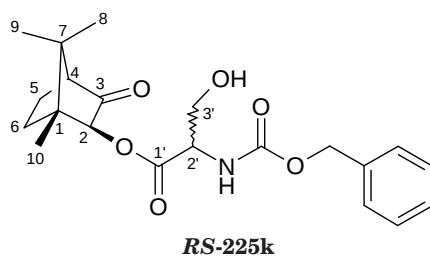
The procedure described for the preparation of *N*-(carbobenzyloxy)glycine 3-oxo-2-*exo*-bornyl ester **225** was followed, using *N*-CBZ-DL-norleucine (1.19g, 4.5mmol), CDI (0.73g, 4.5mmol) and 2-hydroxybornanone (0.76g, 4.5mmol). Work-up and flash chromatography, [hexane:EtOAc 2:3] afforded **RS-225h** as an oil (0.491g, 41%); (Found: M^+ 415.23779. $C_{27}H_{31}O_5N$ requires M , 415.23587); δ_H (400MHz; $CDCl_3$) 0.77-1.01, 1.24-1.40, 1.46-1.59 and 1.62-1.91 (23H, series of multiplets, 4-H, 5- and 6- CH_2 , 8-, 9- and 10-Me, Bu-H's), 4.42 (1H, m, α -H), 4.85/4.87 (1H, s, 2-H), 5.08-5.12 (2H, series of multiplets, $PhCH_2$), 5.14-5.33 (1H, br s, NH) and 7.28-7.37 (5H, series of multiplets, Ar-H).

N-(Carbobenzyloxy)-DL-valine 3-oxo-2-exo-bornyl ester RS-225e

The procedure described for the preparation of *N*-(carbobenzyloxy)glycine 3-oxo-2-*exo*-bornyl ester **225** was followed, using *N*-CBZ-DL-valine (1.13g, 4.5mmol), CDI (0.73g, 4.5mmol) and 2-hydroxybornanone (0.76g, 4.5mmol). Work-up and flash chromatography, [hexane:EtOAc 2:3] afforded **RS-225e** as an oil (0.767g, 41%); δ_H (400MHz; $CDCl_3$) 0.81-1.03 and 1.22-2.21 (11H, series of multiplets, 5 x Me, *i*Pr- and 4-H, 5- and 6- CH_2), 4.34 (1H, m, α -H), 4.87/4.90 (1H, s, 2-H), 5.08-5.11 (2H, series of multiplets, $PhCH_2$), 5.18-5.34 (1H, br s, NH) and 7.28-7.37 (5H, series of multiplets, Ar-H); m/z 401 (2.3%).

N-(Carbobenzyloxy)-DL-methionine 3-oxo-2-exo-bornyl ester RS-225j

The procedure described for the preparation of *N*-(carbobenzyloxy)glycine 3-oxo-2-*exo*-bornyl ester **225** was followed, using *N*-CBZ-DL-methionine (1.27g, 4.5mmol), CDI (0.73g, 4.5mmol) and 2-hydroxybornanone (0.76g, 4.5mmol). Work-up and flash chromatography, [hexane:EtOAc 2:3] afforded **2'RS-225j** as an oil (1.00g, 49%); δ_H (400MHz; $CDCl_3$) 0.89-1.01 (9H, series of multiplets, 8-, 9- and 10-Me), 1.39-1.58 and 1.87-2.18 (4H, series of multiplets, 5- and 6- CH_2), 1.51-1.56 and 2.18 (4H, series of multiplets, α - CH_2 - CH_2 -), 2.03 (1H, s, 4-H), 2.07 (3H, s, S- CH_3), 4.57 (1H, m, α -H), 4.86/4.88 (1H, s, 2-H), 5.10 (2H, br s, $PhCH_2$), 5.38-5.47 (1H, br s, NH) and 7.29-7.36 (5H, series of multiplets, Ar-H); m/z 433 (5.2%).

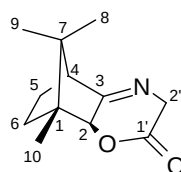


N-(Carbobenzyloxy)-DL-serine 3-oxo-2-exo-bornyl ester *RS-225k*

The procedure described for the preparation of *N*-(carbobenzyloxy)glycine 3-oxo-2-*exo*-bornyl ester **225** was followed, using *N*-CBZ-DL-serine (1.08g, 4.5mmol), CDI (0.73g, 4.5mmol) and 2-hydroxybornanone (0.76g, 4.5mmol). Work-up failed to afford the desired product.

3.4.3 The iminolactones

(2*S*)-Bornyl-3-iminolactone **193**

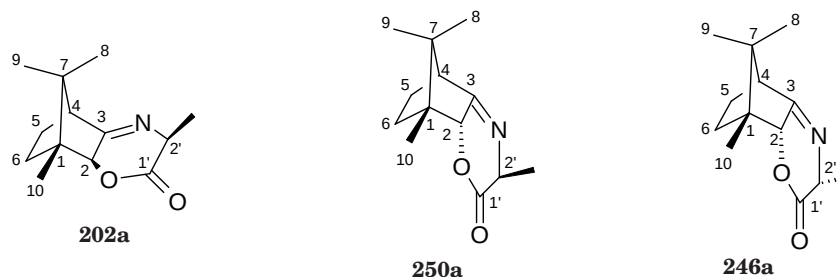
**193**

10% Pd-C catalyst (0.04g) was added to a solution of *N*-(carbobenzyloxy)glycine 3-oxo-2-*exo*-bornyl ester **225** (0.48g, 1.3mmol) in EtOH (5mL). The system was evacuated *in vacuo* and alternately flushed with argon three times. The system was evacuated again, and flushed with H₂, and the mixture was stirred under H₂ at room temperature for 1h, and then at 50° for 3h. After cooling, the catalyst was removed by filtering through Celite, and the solvent was removed at 60° *in vacuo* to ensure removal of any water present. The mixture was purified by chromatography [radial chromatography; elution with hexane:EtOAc (1:1)] to affording two fractions:

i) (2*S*)-bornyl-3-iminolactone **193** as a yellow oil (0.11g, 41%); (Found: M^+ 207.12632. C₁₂H₁₇O₂N requires M , 207.12593); δ_H (600MHz; CDCl₃) 0.82, 0.94, 1.06 (9H, 3 x s, 8-, 9- and 10-Me), 1.33-1.39, 1.49-1.55, 1.84-1.91 and 1.95-2.03 (4H, series of multiplets, 5-CH₂ and 6-CH₂), 2.41 (1H, d, $J=4.59$ Hz, 4-H), 3.86 (2H, dd, $J_1=18.1$ Hz, $J_2=1.89$ Hz, 2'-H), 4.28 (1H, d, $J=1.69$ Hz, 2-H) and 4.47 (1H, d, $J=18.1$ Hz, 2'-H); δ_C (150MHz; CDCl₃) 9.9, 19.3 and 20.0 (C-8, C-9 and C-10), 21.6 and 33.9 (C-5 and C-6), 52.5 (C-2'), 53.2 (C-4), 48.9 and 49.4 (C-1 and C-7) and 81.8 (C-2); and

ii) 2-hydroxybornanone **194** (0.064g, 29.8%).

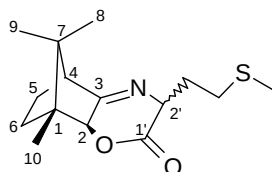
(2*S*,2'*S*)-2'-Methylbornyl-3-iminolactone 202a, (2*R*,2'*S*)-2'-methylbornyl-3-iminolactone 250a and (2*R*,2'*R*)-2'-methylbornyl-3-iminolactone 246a



The procedure described for the preparation of (2*S*)-bornyl-3-iminolactone **193** was followed using the DL-derived alanine ester **2'RS-225a** (0.5g, 2.3mmol) and 0.05g of wet Pd-C catalyst. A portion of the mixture was purified *via* HPLC [elution with hexane:EtOAc 1:1] to give three fractions:

- (i) (2*S*,2'*S*)-2'-methylbornyl-3-iminolactone **202a** as an oil; δ_H (600MHz; CDCl₃) 0.82, 0.95 and 1.08 (9H, 3 x s, 8-, 9- and 10-Me), 1.38 (1H, ddd, $J_1=13.1\text{Hz}$, $J_2=9.3\text{Hz}$, $J_3=3.8\text{Hz}$, 5-*exo*-H), 1.55 (1H, ddd, $J_1=13.5\text{Hz}$, $J_2=9.0\text{Hz}$, $J_3=4.5\text{Hz}$, 4-*endo*-H), 1.88 (1H, td, $J_1=12.5\text{Hz}$, $J_2=4.9\text{Hz}$, 4-*exo*-H), 2.00 (1H, td, $J_1=12.8\text{Hz}$, $J_2=4.2\text{Hz}$, 5-*endo*-H), 1.65 (3H, d, $J_1=7.0\text{Hz}$, 2'-CH₃), 2.41 (1H, d, $J=4.59\text{Hz}$, 4-H), 3.82 (1H, q, $J=7.4\text{Hz}$, 2'-H) and 4.31 (1H, s, 2-H); δ_C (150MHz; CDCl₃) 9.97, 19.4 and 20.0 (C-8, C-9 and C-10), 17.3 (C-3'), 21.7 (C-5), 33.9 (C-6), 49.0 and 49.4 (C-1 and C-7), 53.0 (C-4), 56.8 (C-2'), 81.9 (C-2), 171.5 (C-3) and 181.6 (C-1');
- (ii) (2*R*,2'*S*)-2'-methylbornyl-3-iminolactone **250a** as an oil; δ_H (600MHz; CDCl₃) 0.98, 1.00 and 1.08 (9H, 3 x s, 8-, 9- and 10-Me), 1.18-1.26, 1.39-1.45, 1.78-1.82 and 2.03-2.09 (4H, 4 x m, 5- and 6-CH₂), 1.41 (3H, d, $J_1=7.5\text{Hz}$, 2'-CH₃), 2.53 (1H, br s, 4-H), 4.55 (1H, q, $J=7.3\text{Hz}$, 2'-H) and 4.74 (1H, s, 2-H); δ_C (150MHz; CDCl₃) 12.9, 18.4 and 19.6 (C-8, C-9 and C-10), 15.8 (C-3'), 25.1 (C-6), 29.1 (C-5), 45.8 and 50.8 (C-1 and C-7), 54.0 (C-4), 57.8 (C-2'), 81.0 (C-2), 174.0 (C-3) and 180.7 (C-1');
- (iii) (2*R*,2'*R*)-2'-methylbornyl-3-iminolactone **246a** as an oil; δ_H (600MHz; CDCl₃) 0.96, 1.00 and 1.10 (9H, 3 x s, 8-, 9- and 10-Me), 1.36 (1H, ddd, $J_1=12.9\text{Hz}$, $J_2=9.3\text{Hz}$, $J_3=3.8\text{Hz}$, 5-*exo*-H), 1.41-1.46 (1H, m, 4-*endo*-H), 1.80 (1H, ddd, $J_1=13.7\text{Hz}$, $J_2=9.1\text{Hz}$, $J_3=4.8\text{Hz}$, 4-*exo*-H), 2.05 (1H, ddd, $J_1=17.1\text{Hz}$, $J_2=12.0\text{Hz}$, $J_3=4.8\text{Hz}$, 5-*endo*-H), 1.65 (3H, d, $J_1=6.7\text{Hz}$, 2'-CH₃), 2.54 (1H, d, $J=4.64\text{Hz}$, 4-H), 3.79 (1H, q, $J=7.0\text{Hz}$, 2'-H) and 4.64 (1H, s, 2-H). δ_C (150MHz; CDCl₃) 13.0, 18.3 and 19.5 (C-8, C-9 and C-10), 17.2 (C-3'), 25.5 (C-6), 28.5 (C-5), 46.3 and 50.8 (C-1 and C-7), 53.6 (C-4), 56.4 (C-2'), 82.3 (C-2), 173.0 (C-3) and 182.7 (C-1'); m/z 221 (0.54%).

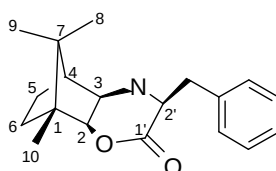
Attempted preparation of (2*S*)-2'-(2-(methylsulfanyl)-ethyl)bornyl-3-iminolactone **193j**

**193j**

Method 1 Bornyl ester **2'RS-225j** (0.5g, 1.2mmol) was placed in dry EtOH (5mL). The system was evacuated and flushed with argon. 10% Pd-C catalyst (0.05g) was added, and the system evacuated and flushed alternately with argon three times. After a final evacuation, H₂ was flushed through the system, and the mixture was left under a H₂ atmosphere for 1h. The mixture was then heated to 60° for 1h. After cooling overnight under H₂, the mixture was filtered through Celite. The solvent was removed completely *in vacuo* at 60° for 1h. NMR analysis indicated no change in the starting material.

Method 2 Bornyl ester **2'RS-225j** (0.5g, 1.2mmol) of the ester was placed in dry EtOH (5mL). The system was evacuated and flushed with argon. A large excess of 10% Pd-C catalyst (0.5g) was added, and the system evacuated and flushed alternately with argon three times. After a final evacuation, H₂ was flushed through the system, and the mixture was left under a H₂ atmosphere for 1h. The mixture was then heated to 60° for 1h. After cooling overnight under H₂, the mixture was filtered through Celite. The solvent was removed completely *in vacuo* at 60° for 1h. NMR analysis indicated no change in the starting material.

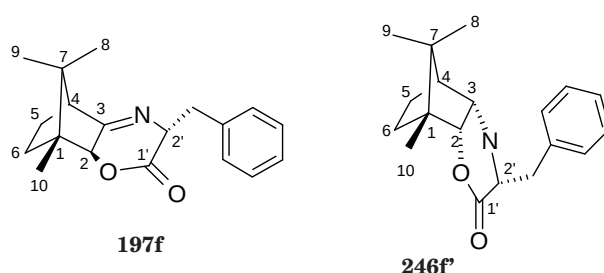
(2*S*,2'*S*,3*R*)-2'-Benzylbornyl-3-aminolactone **202f'**

**202f'**

The procedure described for the preparation of (2*S*)-bornyl-3-iminolactone **193** was followed using L-derived phenylalanine ester **2'S-225f** (0.5g, 1.1mmol). A portion of the mixture was purified *via* HPLC [elution with hexane:EtOAc 1:1] to give the product (2*S*,2'*S*,3*R*)-2'-benzylbornyl-3-aminolactone **202f'** as an oil; δ_H (600MHz; CDCl₃) 0.81, 1.00 and 1.06 (9H, 3 x

s, 8-, 9- and 10-Me), 0.97-1.03, 1.49-1.55 and 1.66-1.70 (5H, series of multiplets, 4-CH, 5- and 6-CH₂), 3.13 (1H, d, $J=7.4$ Hz, 3-H), 3.36 (1H, dd, $J_1=9.2$, $J_2=3.7$, 2'-H), 2.80 and 3.41 (2H, dd, $J_1=14.1$, $J_2=9.2$ and dd, $J_1=14.1$, $J_2=3.7$, PhCH₂), 4.02 (1H, d, $J=7.5$ Hz, 2-H) and 7.23-7.32 (5H, series of multiplets, Ar-H); δ_C (150MHz; CDCl₃) 11.0, 20.6 and 21.9 (C-8, C-9 and C-10), 26.0 and 32.8 (C-5 and C-6), 36.5 (Ph-CH₂), 47.4, 49.7 and 49.8 (C-1, C-4 and C-7), 57.6 (C-2'), 63.0 (C-3), 86.1 (C-2), 126.9, 128.7 and 129.2 (Ar-C), 137.6 (4°-Ar-C) and 171.6 (C-1').

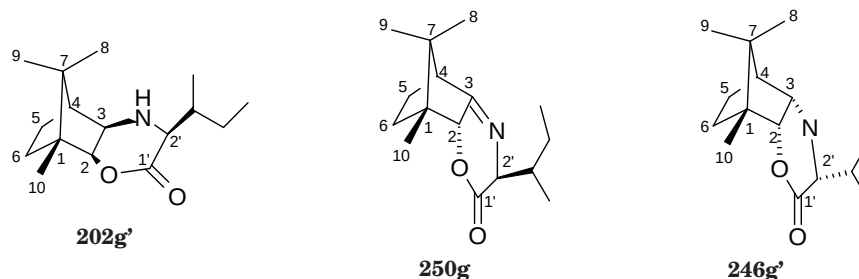
(2*S*,2'*R*)-2'-Benzylbornyl-3-iminolactone



The procedure described for the preparation of (2*S*)-bornyl-3-iminolactone **193** was followed using D-derived phenylalanine ester **2'R-225f** (0.5g, 1.1mmol). A portion of the mixture was purified *via* HPLC [elution with hexane:EtOAc 1:1] to give two fractions:

- i) (2*S*,2'*R*)-2'-benzylbornyl-3-iminolactone **197f** as an oil; δ_H (400MHz; CDCl₃) 0.82, 0.95 and 1.07 (9H, 3 x s, 8-, 9- and 10-Me), 1.17-1.28, 1.34-1.41, 1.86-1.93 and 1.97-2.03 (5H, series of multiplets, 4-H, 5- and 6-CH₂), 1.65 (1H, d, $J=6.2$ Hz, Ph-CH₂), 2.41 (1H, m, 4-H), 3.82 (1H, m, 2'-H), 4.31 (1H, s, 2-H) and 7.22-7.26 (5H, series of multiplets, Ar-H).
- ii) (2*R*,2'*R*,3*R*)-2'-benzylbornyl-3-aminolactone **246f'** as an oil; δ_H (600MHz; CDCl₃) 0.81, 1.00 and 1.06 (9H, 3 x s, 8-, 9- and 10-Me), 0.96-1.04, 1.24-1.26 and 1.47-1.73 (6H, series of multiplets, 4-H, NH, 5- and 6-CH₂), 2.74-2.83 and 3.35-3.43 (3H, series of multiplets, Ph-CH₂ and 2-H), 3.13 (1H, d, $J=7.6$ Hz, 3-H), 4.02 (1H, d, $J=7.4$ Hz, 2-H) and 7.20-7.34 (5H, series of multiplets, Ar-H); δ_C (150MHz; CDCl₃) 11.4, 21.1 and 22.4 (C-8, C-9 and C-10), 26.5 and 33.4 (C-5 and C-6), 36.9 (Ph-CH₂), 47.8, 50.1 and 50.2 (C-1, C-4 and C-7), 68.2 (C-2'), 63.4 (C-3), 86.5 (C-2), 127.3, 129.1 and 129.7 (Ar-C), 138.0 (4°-Ar-C) and 172.0 (C-1').

(2*S*,2'*S*)-2'-(2-butyl)bornyl-3-aminolactone 202g',
(2*R*,2'*S*)-2'-(2-butyl)bornyl-3-iminolactone 250g and
(2*R*,2'*R*)-2'-(2-butyl)bornyl-3-aminolactone 246g'

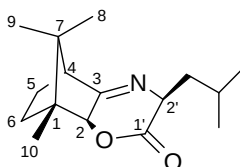


The procedure described for the preparation of (2*S*)-bornyl-3-iminolactone **193** was followed using DL-derived isoleucine ester **2'RS-225g** (0.5g, 1.2mmol). HPLC [elution with hexane:EtOAc (1:1)] on a portion of the product gave three fractions:

- i) (2*S*,2'*S*)-2'-(2-butyl)bornyl-3-iminolactone **202g** as an oil; δ_H (600MHz; CDCl₃) 0.84, 1.00 and 1.12 (9H, 3 x s, 8-, 9- and 10-Me), 0.91 and 1.02 (6H, d, $J=7.7$ Hz and d, $J=7.1$ Hz, 2 x isoleucine CH₃), 1.04-1.10, 1.14-1.19, 1.44-1.50 and 1.52-1.57 (5H, series of multiplets, 5- and 6-CH₂, and 3'-H), 1.76 (1H, m, 3'-H), 1.78 (1H, s, 4-H), 2.08 (1H, m, 4'-H), 3.04 (1H, d, $J=3.03$ Hz, 2'-H), 3.23 (1H, d, $J=9.1$ Hz, 3-H) and 3.97 (1H, d, $J=3.97$, 2-H); δ_C (150MHz; CDCl₃) 16.1, 21.0 and 22.0 (C-8, C-9 and C-10), 11.0 and 12.2 (2 x isoleucine Me), 24.5 and 26.5 (C-5 and C-6), 32.8 (C-3'), 35.3 (C-4'), 47.3 and 49.7 (C-1 and C-7), 49.8 (C-4), 61.3 (C-2'), 63.1 (C-3), 85.9 (C-2) and 171.7 (C-1').
- ii) (2*R*,2'*S*)-2'-(2-butyl)bornyl-3-iminolactone **250g** as an oil; δ_H (600MHz; CDCl₃) 0.91, 0.94 and 1.02 (9H, 3 x s, 8-, 9- and 10-Me), 0.93 and 0.94 (6H, d, $J=6.3$ Hz and d, $J=4.2$ Hz, 2 x leucine CH₃), 1.18-1.20, 1.33-1.39, 1.45-1.55, 1.72-1.78 and 1.97-2.04 (6H, series of multiplets, 3'-, 4'-, 5- and 6-CH₂), 2.47 (1H, d, $J=4.5$ Hz, 4-H), 4.66 (1H, s, 2-H) and 4.47 (1H, dd, $J_1=8.8$ Hz, $J_2=7.0$ Hz, 2'-H).
- iii) (2*R*,2'*R*)-2'-(2-butyl)bornyl-3-iminolactone **246g** as an oil; δ_H (600MHz; CDCl₃) 0.84, 1.01 and 1.12 (9H, 3 x s, 8-, 9- and 10-Me), 0.90 and 0.94 (6H, d, $J=6.5$ Hz and d, $J=6.5$ Hz, 2 x isoleucine CH₃), 1.38-1.43 and 1.84-1.91 (2H, series of multiplets, 3'-H), 1.06-1.10, 1.53-1.59 and 1.73-1.79 (7H, series of multiplets, 4-H, 4'- 5- and 6-CH₂), 3.11 (1H, dd, $J_1=9.2$ Hz, $J_2=4.2$ Hz, 2'-H), 3.27 (1H, d, $J=7.4$ Hz, 3-H) and 4.03 (1H, d, $J=7.4$ Hz, 2-H); δ_C (150MHz; CDCl₃) 11.1, 21.0 and 22.0 (C-8, C-9 and C-10), 21.5 and 23.4 (2 x isoleucine Me), 24.9 (C-4'), 26.6 and 32.8 (C-5 and C-6), 39.3 (C-3'), 49.7 (C-4), 54.7 (C-2'), 63.5 (C-3), 85.9 (C-2) and 172.7 (C-1').

(C-1').

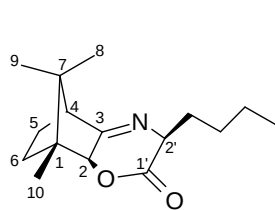
Attempted preparation of (2*S*)-2'-(3-methylpropyl)bornyl-3-iminolactone **202i**



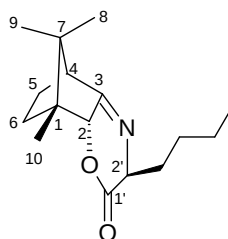
202i

The procedure described for the preparation of (2*S*)-bornyl-3-iminolactone **193** was followed using DL-derived leucine ester **2'RS-225i** (0.5g, 1.2mmol). No imine or amine product was obtained, as determined by NMR analysis.

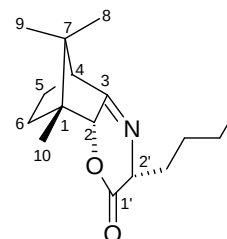
(2*S*,2'*S*)-2'-Butylbornyl-3-iminolactone **202h**, (2*R*,2'*S*)-2'-butylbornyl-3-iminolactone **250h** and (2*R*,2'*R*)-2'-butylbornyl-3-iminolactone **246h**



202h



250h



246h

The procedure described for the preparation of (2*S*)-bornyl-3-iminolactone **193** was followed using DL-derived norleucine ester **2'RS-225h** (0.5g, 1.2mmol). A portion of the mixture was purified *via* HPLC [elution with hexane:EtOAc 1:1] to give three fractions:

- i) (2*S*,2'*S*)-2'-butylbornyl-3-iminolactone **202h** as an oil; δ_H (400MHz; CDCl₃) 0.81, 0.95 and 1.08 (9H, 3 x s, 8-, 9- and 10-Me), 0.93 (3H, t, $J=7.0$ Hz, 6'-CH₃), 1.34-1.44, 1.50-1.61, 1.85-2.04 and 2.08-2.16 (10H, series of multiplets, 3'-, 4'-, 5'-, 5- and 6-CH₂), 2.43 (1H, d, $J=4.4$ Hz, 4-H), 3.64 (1H, m, 2'-H) and 4.27 (1H, s, 2-H); δ_C (100MHz; CDCl₃) 10.5, 19.8 and 20.5 (C-8, C-9 and C-10), 14.4 (C-6'), 22.1 and 34.4 (C-5 and C-6), 23.1, 28.5 and 31.4 (C-3', C-4' and C-5'), 49.4 and 49.8 (C-1 and C-7), 53.5 (C-4), 61.4 (C-2'), 82.0 (C-2), 171.3 (C-3) and 181.9 (C-1'); m/z 263 (47.8%).
- ii) (2*R*,2'*S*)-2'-butylbornyl-3-iminolactone **250h** as an oil; δ_H (400MHz; CDCl₃) 0.88/0.91, 0.93/0.94 and 1.01/1.03 (9H, 3 x s, 8-, 9- and 10-Me), 0.86 (3H, t, $J=8.0$ Hz, 6'-CH₃), 1.17-1.33, 1.41-1.59

and 1.78-1.95 and 2.08-2.16 (10H, series of multiplets, 3'-, 4'-, 5'-, 5- and 6-CH₂), 2.63 (1H, d, $J=4.5\text{Hz}$, 4-H), 3.70 (1H, m, 2'-H) and 4.89 (1H, s, 2-H).

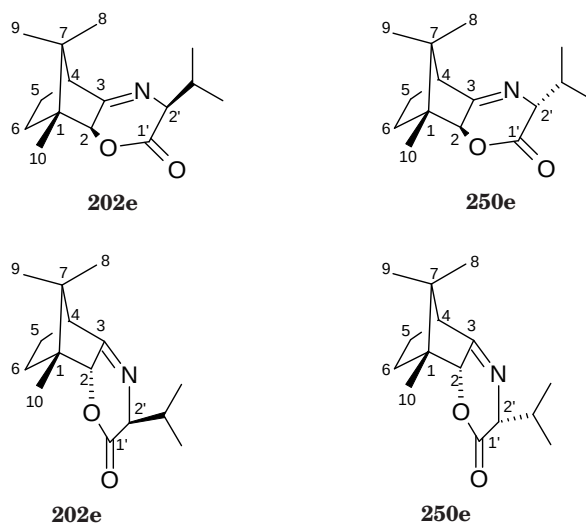
iii) (2*R*,2'*R*)-2'-butylbornyl-3-iminolactone **246h** as an oil; δ_H (400MHz; CDCl₃) 0.96, 1.00 and 1.10 (9H, 3 x s, 8-, 9- and 10-Me) 1.32-1.50, 1.57-1.64, 1.77-1.83, 1.88-1.96 and 2.01-2.14 (10H, series of multiplets, 3'-, 4'-, 5'-, 5- and 6-CH₂), 0.93 (3H, t, $J=7.0\text{Hz}$, 6'-CH₃), 2.55 (1H, d, $J=4.5\text{Hz}$, 4-H), 3.59 (1H, m, 2'-H), 4.59 (1H, s, 2-H); δ_C (100MHz; CDCl₃) 13.1, 18.4 and 19.7 (C-8, C-9 and C-10), 14.1 (C-6'), 25.5, 28.2, 28.6 and 31.0 (C-3', C-4', C-5' and C-5), 22.8 (C-6), 46.3 and 50.7 (C-1 and C-7), 53.7 (C-4), 60.6 (C-2'), 81.9 (C-2), 172.4 (C-3) and 182.6 (C-1'); m/z 263 (27.3%).

(2*S*,2'*S*)-2'-(2-Methylethyl)bornyl-3-iminolactone 202e,

(2*S*,2'*R*)-2'-(2-methylethyl)bornyl-3-iminolactone 250e,

(2*R*,2'*S*)-2'-(2-methylethyl)bornyl-3-iminolactone 202e and

(2*R*,2'*R*)-2'-(2-methylethyl)bornyl-3-iminolactone 250e



The procedure described for the preparation of (2*S*)-bornyl-3-iminolactone **193** was followed using DL-derived valine ester **2'RS-225e** (0.5g, 1.2mmol). A portion of the mixture was purified *via* HPLC [elution with hexane:EtOAc 1:1] to give four fractions:

i) (2*S*,2'*S*)-2'-(2-methylethyl)bornyl-3-iminolactone **202e** as an oil; δ_H (400MHz; CDCl₃) 0.80, 0.95 and 1.07 (9H, 3 x s, 8-, 9- and 10-Me), 1.02 and 1.15 (6H, d, $J=6.7\text{Hz}$ and d, $J=6.9\text{Hz}$, 2 x valine CH₃), 1.36, 1.56, 1.86 and 1.97 (4H, ddd, $J_1=12.8\text{Hz}$, $J_2=9.2\text{Hz}$ and $J_3=3.6\text{Hz}$, ddd, $J_1=12.6\text{Hz}$, $J_2=8.5\text{Hz}$ and $J_3=4.3\text{Hz}$, td, $J_1=6.1\text{Hz}$, $J_2=4.6\text{Hz}$, tt, $J_1=6.3\text{Hz}$, $J_2=4.2\text{Hz}$, 5- and 6-CH₂), 2.45 (1H, d, $J=4.53\text{Hz}$, 3'-H), 2.53 (1H, m, 4'-H), 3.53 (1H, m, 2'-H) and 4.22 (1H, s,

2-H); δ_C (100MHz; $CDCl_3$) 10.4, 17.5 and 19.8 (C-8, C-9 and C-10), 20.1 and 20.4 (2 x valine CH_3), 22.1, 29.3 and 34.4 (C-3', C-5 and C-6), 49.2 and 49.7 (C-1 and C-7), 53.6 (C-4), 65.8 (C-2'), 81.7 (C-2), 170.5 (C-3) and 181.4 (C-1'); m/z 249 (1.7%).

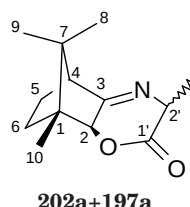
ii) (2S,2'R)-2'-(2-methylethyl)bornyl-3-iminolactone **250e** as an oil; δ_H (400MHz; $CDCl_3$) 0.95, 1.05 and 1.08 (9H, 3 x s, 8-, 9- and 10-Me), 1.05 and 1.09 (6H, d, $J=4.0$ Hz and d, $J=5.6$ Hz, 2 x valine CH_3), 1.19-1.26, 1.32-1.41, 1.84-1.92 and 1.96-2.05 (5H, series of multiplets, 3'-H, 5- and 6- CH_2), 2.41 (1H, d, $J=4.64$ Hz, 4-H), 4.18 (1H, d, $J=9.1$ Hz, 2'-H) and 4.38 (1H, s, 2-H); δ_H (600MHz; $CDCl_3$) 0.84, 0.95 and 1.05 (9H, 3 x s, 8-, 9- and 10-Me), 1.08 and 1.09 (6H, d, $J=7.0$ Hz and d, $J=7.2$ Hz, 2 x valine CH_3), 1.18-1.22, 1.34-1.38, 1.86-1.91 and 1.98-2.04 (5H, series of multiplets, 3'-H, 5- and 6- CH_2), 2.42 (1H, d, $J=4.32$ Hz, 4-H), 4.19 (1H, d, $J=9.1$ Hz, 2'-H) and 4.37 (1H, s, 2-H); δ_C (150MHz; $CDCl_3$) 9.8, 19.4 and 19.9 (C-8, C-9 and C-10), 20.3 (2 x valine CH_3), 21.4 and 34.5 (C-5 and C-6), 31.6 (C-3'), 53.7 (C-4), 68.7 (C-2'), 80.8 (C-2) and 179.7 (C-3).

iii) (2R,2'S)-2'-(2-methylethyl)bornyl-3-iminolactone **202e** as an oil; δ_H (400MHz; $CDCl_3$) 0.98, 0.99 and 1.06 (9H, 3 x s, 8-, 9- and 10-Me), 1.07 and 1.09 (6H, d, $J=6.6$ Hz and d, $J=6.9$ Hz, 2 x valine CH_3), 1.37-1.50 and 1.76-1.83 (3H, series of multiplets, 5-Ha and 6- CH_2), 2.00-2.09 (2H, series of multiplets, 4'-H and 5-Hb), 2.55 (1H, d, $J=4.53$ Hz, 4-H), 4.19 (1H, d, $J=8.8$ Hz, 2'-H) and 4.70 (1H, s, 2-H); δ_H (600MHz; $CDCl_3$) 0.99, 1.00 and 1.07 (9H, 3 x s, 8-, 9- and 10-Me), 1.06 and 1.10 (6H, d, $J=5.7$ Hz and d, $J=6.8$ Hz, 2 x valine CH_3), 1.38-1.44 and 1.77-1.81 (3H, series of multiplets, 5-Ha and 6- CH_2), 2.02-2.08 (2H, series of multiplets, 4'-H and 5-Hb), 2.56 (1H, d, $J=4.3$ Hz, 4-H), 4.19 (1H, d, $J=8.7$ Hz, 2'-H) and 4.70 (1H, s, 2-H); δ_C (150MHz; $CDCl_3$) 12.9, 18.5 and 19.7 (C-8, C-9 and C-10), 20.2 and 20.4 (2 x valine CH_3), 25.2 and 29.3 (C-5 and C-6), 31.5 (C-3'), 45.8 and 51.0 (C-1 and C-7), 54.3 (C-4), 69.1 (C-2'), 81.9 (C-2), 171.8 (C-3) and 181.5 (C-1'); m/z 249 (4.3%).

iv) (2R,2'R)-2'-(2-methylethyl)bornyl-3-iminolactone **250e** as an oil; δ_H (400MHz; $CDCl_3$) 0.96, 1.00 and 1.09 (9H, 3 x s, 8-, 9- and 10-Me), 1.02 and 1.15 (6H, d, $J=6.8$ Hz and d, $J=6.8$ Hz, 2 x valine CH_3), 0.79-0.88 and 1.19-1.26 (2H, series of multiplets, 3'- CH_2), 1.33 (1H, m, 6-Ha), 1.42 (1H, m, 5-endo-H), 1.79 (1H, m, 6-Hb), 2.05 (1H, m, 5-exo-H), 2.52 (1H, m, 4'-H), 2.58 (1H, d, $J=4.36$ Hz, 4-H), 3.49 (1H, m, 2'-H) and 4.55 (1H, s, 2-H); δ_C (100MHz; $CDCl_3$) 13.0, 17.1 and 18.4 (C-8, C-9 and C-10), 19.6 and 19.7 (2 x valine CH_3), 25.5, 28.8 and 29.0 (C-3', C-5 and C-6), 46.2 and 50.7 (C-1 and C-7), 53.8 (C-4), 65.0 (C-2'), 81.7 (C-2), 171.6 (C-3) and 182.3 (C-1').

3.4.4 Alkylation reactions

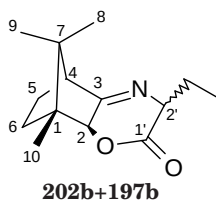
(2'*RS*)-2'-Methylbornyl-3-iminolactone **202a+197a**



KOBu^t (0.038g, 0.34mmol) was added to dry THF (3mL) at -76° under N₂. A solution of the glycine-derived 3-iminolactone **193** (0.05g, 0.24mmol) was added slowly to the stirred solution. After 1 hour, iodomethane (0.037g, 0.26mmol) in dry THF (1mL) was added slowly. The resulting mixture was stirred at -76° for 3h, and warmed to room temperature. Water (1mL) was added immediately and the THF was removed *in vacuo*. The mixture was extracted with EtOAc (4 x 3mL) and the combined extracts dried over anhydrous MgSO₄. The solvent was removed *in vacuo* to give **202a** and **197a** as an oil (0.046g, 77% d.e. *exo*-product); (Found: M⁺ 221.14247. C₁₃H₁₉O₂N requires *M*, 221.14158); δ_H (400MHz; CDCl₃) 0.82, 0.96 and 1.08 (9H, 3 x s, 8-, 9- and 10-Me), 1.38 (1H, ddd, $J_1=12.9$ Hz, $J_2=9.3$ Hz, $J_3=3.6$ Hz, 5-*exo*-H), 1.52-1.59 (1H, m, 6-*endo*-H), 1.90 (1H, td, $J_1=12.5$ Hz, $J_2=4.5$ Hz, 6-*exo*-H), 2.01 (1H, td, $J_1=12.4$ Hz, $J_2=4.1$ Hz, 5-*endo*-H), 1.65 (3H, d, $J_1=7.1$ Hz, 2'-CH₃), 2.41 (1H, d, $J=4.55$ Hz, 4-H), 3.82 (1H, qd, $J_1=6.9$ Hz, $J_2=1.2$ Hz, 2'-H) and 4.31/4.42 (1H, d, $J_1=1.1$ Hz, 2-H); δ_C (100MHz; CDCl₃) 9.97, 19.4 and 20.1 (C-8, C-9 and C-10), 17.3 (C-3'), 21.7 (C-5), 33.9 (C-6), 49.0 and 49.4 (C-1 and C-7), 53.0 (C-4), 56.8 (C-2'), 81.9 (C-2), 171.5 (C-3) and 181.7 (C-1').

The reaction was repeated several times and 40% d.e. (*exo*); 20% d.e. (*endo*); and 44% d.e. (*endo*) ratios were obtained.

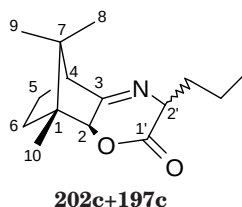
(2'*RS*)-2'-Ethylbornyl-3-iminolactone **202b+197b**



KO^tBu (0.038g, 0.34mmol) was added to dry THF (3mL) at -76° under N₂. A solution of the glycine-derived 3-iminolactone **193** (0.05g, 0.24mmol) was added slowly to the stirred

solution. After 1 hour, iodoethane (0.039g, 0.25mmol) in dry THF (1mL) was added slowly. The resulting mixture was stirred at -76° for 3h, and warmed to room temperature. Water (1mL) was added immediately and the THF was removed *in vacuo*. The mixture was extracted with EtOAc (4 x 3mL) and the combined extracts dried over anhydrous MgSO_4 . The solvent was removed *in vacuo* to give **202b** and **197b** as an oil (72% d.e. *endo*-product); δ_H (400MHz; CDCl_3) 0.84, 1.01 and 1.15 (9H, 3 x s, 8-, 9- and 10-Me), 0.89-0.93 ($3'$ -CH₂ and $4'$ -CH₃) 1.34-1.41 and 1.65-1.96 (4H, series of multiplets, 5- and 6-CH₂), 2.31/2.34 (1h, d, $J=4.4\text{Hz}$, 4-H), 3.41/3.53 (1H, m, $2'$ -H) and 4.34 (1H, s, 2-H).

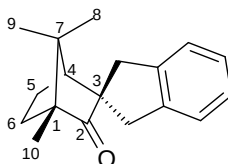
(2'RS)-2'-Propylbornyl-3-iminolactone 202c+197c



KO^tBu (0.038g, 0.34mmol) was added to dry THF (3mL) at -76° under N_2 . A solution of the glycine-derived 3-iminolactone **193** (0.05g, 0.24mmol) was added slowly to the stirred solution. After 1 hour, iodopropane (0.039g, 0.23mmol) in dry THF (1mL) was added slowly. The resulting mixture was stirred at -76° for 3h, and warmed to room temperature. Water (1mL) was added immediately and the THF was removed *in vacuo*. The mixture was extracted with EtOAc (4 x 3mL) and the combined extracts dried over anhydrous MgSO_4 . The solvent was removed *in vacuo* to give **202c** and **197c** as an oil (58% d.e. *endo*-product); δ_H (400MHz; CDCl_3) 0.80, 0.92 and 1.04 (9H, 3 x s, 8-, 9- and 10-Me), 0.96-0.97 (5H, series of multiplets, $4'$ -CH₂ and $5'$ -CH₃), 1.33-1.34 and 1.61-2.01 (5H, series of multiplets, 4-H and 5- and 6-CH₂), 2.22 (2H, m, $3'$ -CH₂), 3.57 (1H, m, $2'$ -H) and 4.21/4.36 (1H, s, 2-H).

3.5 Rearrangements of a Spiroterpenoid System

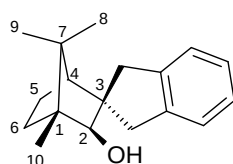
Spiro[bornane-3,2'-indan]-2-one 256



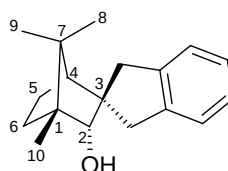
256

(+)-Camphor (30g, 0.20mol) was added to pre-washed NaH (60% dispersion in oil; 18g, 0.45mol) in dry toluene (450mL) and the resulting mixture was stirred for 1h. α,α' -Dichloro-*o*-xylene (34.5g, 0.20mol) was then added and the reaction mixture was boiled under reflux for 18h. Saturated aqueous NaHCO_3 was added and the resulting mixture was extracted with EtOAc (2x300mL). The combined organic layers were dried (anhydrous MgSO_4) and concentrated *in vacuo*. The residue was recrystallized from Et_2O and the crystals were washed with MeOH to afford spiro[bornane-3,2'-indan]-2-one **256** as light yellow crystals (24.4g, 48%); mp. 94-97 °C; δ_H (600MHz; CDCl_3) 0.93, 1.00 and 1.03 (9H, 3 x s, 8-,9- and 10-Me), 1.43-1.48 and 1.64-1.69 (2H, series of multiplets, 6- CH_2), 1.77-1.81 and 1.84-1.90 (2H, series of multiplets, 5- CH_2), 2.00 (1H, d, $J=3.83\text{Hz}$, 4-CH), 2.99 and 3.30 (2H, 2 x d, $J=16.0\text{Hz}$, xylyl- CH_2) and 3.10 and 3.20 (2H, 2 x d, $J=16.3\text{Hz}$, xylyl- CH_2); δ_C (150MHz; CDCl_3) 9.8, 20.9 and 22.7 (C-8, C-9 and C-10), 23.3 (C-5), 30.1 (C-6), 42.4 and 46.1 (2 x xylyl- CH_2), 46.7 (C-1), 53.3 (C-4), 57.7 (C-3), 58.8 (C-7), 123.6, 123.9, 126.4 and 126.5 (Ar-C), 141.9 and 141.0 (4° Ar-C) and 223.9 (C-2).

Spiro[bornane-3,2'-indan]-2-exo-ol 175 and Spiro[bornane-3,2'-indan]-2-endo-ol 257



175



257

Method 1.

Spiro[bornane-3,2'-indan]-2-one **256** (11.5g, 45mmol) in dry Et_2O (50mL) was added dropwise under dry nitrogen to a stirred suspension of LiAlH_4 (1.268g, 80mol) in dry Et_2O at 0°C. The stirred mixture was allowed to warm to room temperature overnight, before quenching

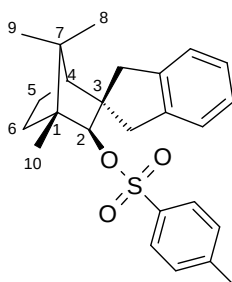
by the successive addition of H₂O (0.1mL), 10% NaOH (0.1mL) and H₂O (0.3mL). The resulting precipitate was collected and extracted by boiling with Et₂O (2x20mL) under reflux. The filtrate and organic extracts were combined, washed with saturated aqueous NaHCO₃ and concentrated *in vacuo*. Flash chromatography afforded two fractions:

i) Spiro[bornane-3,2'-indan]-2-*exo*-ol **175** as a yellow oil (10.396g, 89.7%). Cold finger distillation at reduced pressure (0.1 torr, 124°C-140°C) was used to further obtain the product as a colourless oil; δ_H (600MHz; CDCl₃) 0.87, 0.88 and 1.23 (9H, 3 x s, 8-, 9- and 10-Me), 1.14 (1H, m, 6-Ha), 1.42 (1H, br s, 2-OH), 1.52-1.57 (2H, complex of multiplets, 5-*endo*-H and 6-Hb), 1.66 (1H, m, 5-*exo*-H), 1.73 (1H, d, $J=4.0$ Hz, 4-H), 2.74 and 3.16 (2H, 2 x d, $J=15.4$ Hz, xylyl-CH₂), 2.79 and 3.63 (2H, 2 x d, $J=15.8$ Hz, xylyl-CH₂), 3.32 (1H, s, 2-*endo*-H) and 7.10-7.17 (4-H, complex of multiplets, Ar-H); δ_C (150MHz; CDCl₃) 12.0, 21.9 and 22.2 (C-8, C-9 and C-10), 24.4 (C-5), 34.5 (C-6), 40.9 and 47.5 (xylyl-CH₂), 49.1 (C-1), 51.1 (C-7), 56.2 (C-4), 57.4 (C-3), 89.8 (C-2), 123.7, 124.0, 126.0 and 126.3 (Ar-C) and 141.9 and 144.8 (4° Ar-C); and

ii) spiro[bornane-3,2'-indan]-2-*endo*-ol **257** was obtained as a colourless oil (0.53g, 5%); δ_H (600MHz; CDCl₃) 0.83, 0.92 and 1.08 (9H, 3 x s, 8-, 9- and 10-Me), 1.11-1.15 (1H, m, 6-Ha), 1.58 (1H, br s, 2-OH), 1.58 (1H, m, 5-*endo*-H), 1.64 (1H, m, 5-*exo*-H), 1.71 (1H, d, $J=$, 4-H), 1.85 (1H, m, 6-Hb), 2.77 and 3.27 (2H, 2 x d, $J=15.2$ Hz, xylyl-CH₂), 2.96 and 3.10 (2H, 2 x d, $J=15.7$ Hz, xylyl-CH₂), 3.76 (1H, s, 2-*exo*-H) and 7.07-7.19 (4H, complex of multiplets, Ar-CH); δ_C (150MHz; CDCl₃) 13.9, 21.3 and 21.6 (C-8, C-9 and C-10) 24.5 (C-6), 24.8 (C-5), 46.3 (C-1), 39.1 and 50.0 (2 x xylyl-CH₂), 51.6 (C-7), 53.4 (C-3), 56.1 (C-4), 84.9 (C-2), 123.7, 124.1, 126.0 and 126.2 (Ar-C) and 142.9 and 143.5 (4° Ar-C).

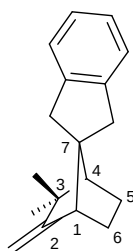
Method 2.

A suspension of lithium aluminium hydride (0.055g, 3.4mmol) in dry THF (2mL) was heated to 50°C under argon for 30min. A solution of spiro[bornane-3,2'-indan]-2-one **256** (0.263g, 1.0mmol) in THF (2mL) was added slowly and the resulting mixture was heated at 50°C for 3h and then stirred overnight at room temperature. The reaction was quenched by the addition of 3M-NaOH (0.5mL) and water (0.5mL). The precipitate was filtered off and washed with EtOAc (20mL). The organic layer was dried over MgSO₄ and concentrated *in vacuo*. ¹H NMR analysis indicated 100% conversion and 84% d.e. in the *exo*-product **175**.

Spiro[bornane-3,2'-indan]-2-exo-tosylate 255**255**

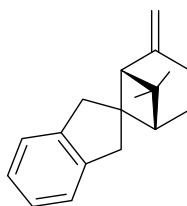
Butyllithium (1.6M solution in hexane; 3.0ml, 4.8mmol) was added dropwise to a stirred solution of spiro[bornane-3,2'-indan]-2-*exo*-ol **175** (1.0g, 4mmol) in dry THF (25mL) under N₂ at 0°C. After 1h, a solution of TsCl (0.9g, 9.6mmol) in a minimal volume of THF was added and the mixture stirred for 1h. The reaction was quenched with satd aq. NaHCO₃ (25mL) and the resulting mixture extracted with EtOAc (3x50mL). The combined organic fractions were dried (anhydrous MgSO₄) and concentrated *in vacuo* at room temperature (but *not* to dryness). Crystals of the product were left in the mother liquor at 0°C until needed.

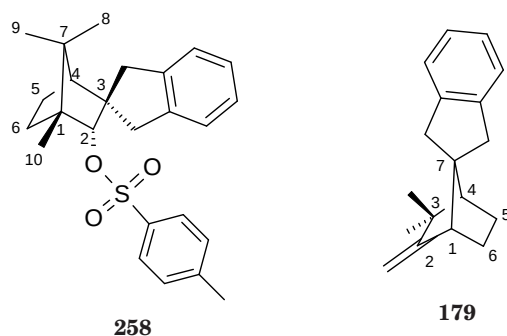
For use in kinetics experiments, the crystals were filtered on a buchner funnel, washed copiously with cold hexane to remove any EtOAc, and dried for *ca.* 1 min before weighing, dissolution for kinetics and cooling on ice. The product *spiro[bornane-3,2'-indan]-2-exo-tosylate 255* as white needles (0.716g, 44%); δ_H (400MHz; CDCl₃) 0.78, 0.84 and 1.11 (9H, 3 x s, 8-, 9- and 10-Me), 1.15-1.27 and 1.51-1.63 (4H, series of multiplets, 5- and 6-CH₂), 1.67 (1H, m, 4-H), 2.33 (3H, s, Ar-CH₃), 2.80 and 3.16 (2H, 2 x d, $J=15.8\text{Hz}$ and 16.0Hz , xylyl-CH₂), 2.84 and 3.41 (2H, 2 x d, $J=16.2\text{Hz}$ and 16.5Hz , xylyl-CH₂), 4.31 (1H, s, 2-H) and 6.64, 6.97-7.07 and 7.43 (8H, d, $J=7.3\text{Hz}$, complex of multiplets and d $J=8.3\text{Hz}$, Ar-CH); δ_C (100MHz; CDCl₃) 12.4, 21.7 and 21.9 (C-8, C-9 and C-10), 21.6 (Ar-CH₃), 23.4 and 33.6 (C-5 and C-6), 42.0 and 46.4 (2 x xylyl-CH₂), 49.2 and 51.6 (C-1 and C-7), 55.9 (C-3), 56.4 (C-4), 98.8 (C-2), 123.3, 123.8, 125.7, 126.1, 127.1 and 129.3 (8 x Ar-C) and 133.6, 140.6, 142.6 and 143.8 (4° Ar-C).

Spiro[camphene-7,2'-indan] 179**179**

Butyllithium (15% solution in hexane, 5.7ml, 9.4mmol) was added dropwise to a stirred solution of spiro[bornane-3,2'-indan]-2-*exo*-ol **175** (2.153g, 8.4mmol) in dry THF (50mL) under N₂ at 0°C. After 1h, TsCl (1.8g, 9.6mmol) was added and the mixture was allowed to warm to room temperature overnight. The mixture was then boiled under reflux for 1h, and cooled to room temperature. The reaction was quenched with satd aq. NaHCO₃ (50mL) and the resulting mixture was extracted with EtOAc (3x50mL). The combined organic fractions were dried (anhydrous MgSO₄) and concentrated *in vacuo*. Flash chromatography [hexane:EtOAc (19:1)] afforded the product. The crystals were further purified *via* distillation (0.2 torr, 118°C) and recrystallization from MeOH to afford spiro[camphene-7,2'-indan] as colourless crystals (1.282g, 81%); m.p. 22-24°; δ_H (400MHz; CDCl₃) 1.12 and 1.25 (6H, 2 x s, 2 x Me), 1.37 (1H, m, 5-*endo*-H), 1.63 (1H, m, 6-*exo*-H), 1.73 (1H, d, $J=2.9$ Hz, 1-H), 1.81 (1H, ddd, $J_1=12.4$ Hz, $J_2=9.5$ Hz, $J_3=2.5$ Hz, 6-*endo*-H), 1.93 (1H, m, 5-*exo*-H), 2.26 (1H, d, $J=4.7$ Hz, 4-H), 2.91 (2H, s, xylyl-CH₂a), 2.93 and 3.11 (2H, 2 x d, $J=14.5$ Hz and 16.3Hz, xylyl-CH₂b), 4.65 and 4.73 (2H, 2 x s, C=CH₂) and 7.10-7.19 (4H, complex of multiplets, Ar-H); δ_C (100MHz; CDCl₃) 24.4 (C-6), 26.7 (C-5), 29.3 and 29.6 (2 x Me), 39.2 and 40.4 (xylyl-CH₂), 41.7 (C-2), 52.3 (C-4), 54.9 (C-1), 59.3 (C-7), 101.4 (C=CH₂), 124.1, 124.3, 125.85 and 125.91 (Ar-C), 142.1 and 143.8 (4° Ar-C) and 166.4 (C-3);

Attempted preparation of spiro[(2(10)pinene-7,2'-indan] 180 and isolation of spiro[camphene-7,2'-indan] 179 and spiro[bornane-3,2'-indan]-2-endo-tosylate
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Method 1.

1,8-Bis(dimethylamino)naphthalene (proton sponge) (0.5g, 2.1mmol) in dry THF (2.5mL) was added. A solution of spiro[bornane-3,2'-indan]-2-*exo*-ol **175** (1.0g, 4.2mmol) in dry THF (25mL) under N₂ at 0°C. After 1h, TsCl (0.9g, 4.8mmol) was added and the stirred mixture was allowed to warm to room temperature overnight. The reaction was quenched with satd aq. NaHCO₃ (50mL), and the resulting mixture extracted with EtOAc (3x25mL). The combined extracts were dried (anhydrous MgSO₄) and concentrated *in vacuo*. After chromatography [hexane:EtOAc (19:1)], starting material (0.84g) was recovered. The remainder was a mixture of unidentified products.

Method 2.

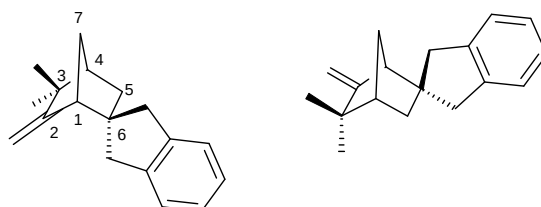
Butyllithium (15% solution in hexane; 5.7ml, 9.4mmol) was added dropwise to a stirred solution of spiro[bornane-3,2'-indan]-2-*exo*-ol **175** (2.153g, 8.4mmol) in dry THF (50mL) under N₂ at 0°C. After 1h, TsCl (1.8g, 9.6mmol) was added, and the stirred mixture was allowed to warm to room temperature overnight. The reaction was quenched with satd aq. NaHCO₃ (50mL) and the resulting mixture was extracted with EtOAc (3x50mL). The combined organic fractions were dried (anhydrous MgSO₄) and concentrated *in vacuo*. Flash chromatography [hexane:EtOAc (19:1)] afforded two fractions (but not the desired product):

i) spiro[camphene-7,2'-indan] **179** as colourless crystals (1.152g, 58%);

ii) *Spiro[bornane-3,2'-indan]-2-endo-tosylate* **258** as light yellow crystals (0.168g, 4.9%); δ_H (600MHz; CDCl₃) 0.78, 0.91 and 1.09 (9H, 3 x s, 8-, 9- and 10-Me), 1.15-1.20, 1.62-1.64 and 1.76-1.81 (4H, series of multiplets, 5- and 6-CH₂), 1.66 (1H, d, $J=2.2$ Hz, 4-H), 2.34 (3H, s, Ar-CH₃), 2.87 and 3.13 (2H, 2 x d, $J=16.3$ Hz and 16.0Hz, xylyl-CH₂a), 2.97 and 3.11 (2H, 2 x d, $J=15.96$ Hz and 15.6Hz, xylyl-CH₂b), 4.74 (1H, d, $J=1.4$ Hz, 2-H), 6.89, 6.97-7.01 and 7.05 (8H, d, $J=7.3$ Hz, complex of multiplets and d $J=6.8$ Hz, xylyl-CH) and 7.06 and 7.44 (4H, 2 x d, $J=7.9$ Hz, $J=8.2$ Hz, tosylate-CH); δ_C (150MHz; CDCl₃) 13.6, 21.3 and 21.6 (C-8, C-9 and C-

10), 21.5 (Ar-CH₃), 24.0 and 25.2 (C-5 and C-6), 39.2 and 50.3 (2 x xylyl CH₂), 46.5 (C-1), 51.6 (C-7), 51.8 (C-3), 56.1 (C-4), 95.5 (C-2), 123.6, 123.6, 125.8 and 126.1 (xylyl Ar-C), 127.3 and 129.3 (tosylate Ar-C), 133.9 and 143.8 (tosylate 4°Ar-C) and 141.4 and 142.0 (xylyl 4°Ar-C).

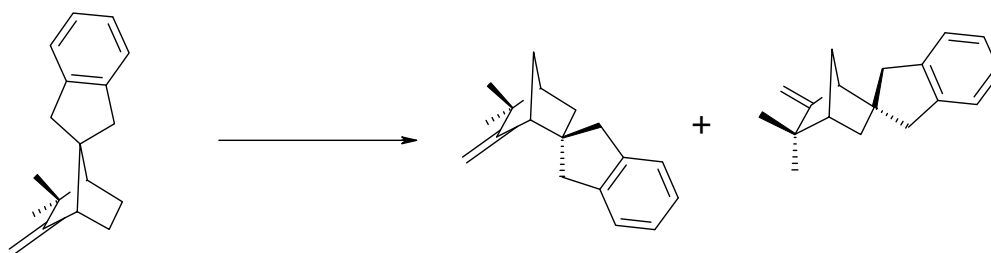
Racemic-spiro[camphene-6,2'-indan] **263**



263

Butyllithium (15% solution in hexane; 5.7ml, 9.4mmol) was added dropwise to a stirred solution of spiro[bornane-3,2'-indan]-2-*exo*-ol **175** (2.153g, 8.4mmol) in dry THF (50mL) under N₂ at 0°C. After 1h, TsCl (1.8g, 9.6mmol) was added, and the stirred mixture was allowed to warm to room temperature. The reaction was quenched with satd aq. NaHCO₃ (50mL) and the resulting mixture was extracted with EtOAc (3x50mL). The combined organic fractions were dried (anhydrous MgSO₄) and concentrated *in vacuo*. After leaving the solid overnight it was apparent that some degradation had occurred. Flash chromatography [elution with hexane:EtOAc (19:1)] afforded *spiro[camphene-6,2'-indan]* **263** as colorless crystals; m.p. 68-70 °C; δ_H (400MHz; CDCl₃) 1.10 and 1.11 (6H, 2 x s, 2 x Me), 1.571.62 and 1.771.83 (4H, series of multiplets, 6- and 7-CH₂), 1.92 (1H, d, $J=2.5$ Hz, 1-H), 2.35 (1H, s, 4-H), 2.69 and 3.09 (2H, 2 x d, $J=15.9$ Hz and 16.0Hz, xylyl-CH₂), 2.83 and 2.96 (2H, 2 x d, $J=15.6$ Hz and 15.6Hz, xylyl-CH₂), 4.74 and 4.75 (2H, 2 x s, C=CH₂) and 7.077.16 (4H, complex of multiplets, Ar-H); δ_C (100MHz; CDCl₃) 25.1 and 30.1 (2 x Me), 37.1 and 39.8 (C-6 and C-7), 41.3 (C-3), 43.4 and 49.2 (2 x xylyl-CH₂), 48.5 (C-1), 49.3 (C-5), 56.7 (C-4), 103.4 (C=CH₂), 124.15, 124.17, 125.9 and 126.0 (Ar-C), 142.9 and 143.6 (4° Ar-C) and 161.7 (C-2).

Racemic-spiro[camphene-6,2'-indan] **263** from *spiro[camphene-7,2'-indan]* **179**



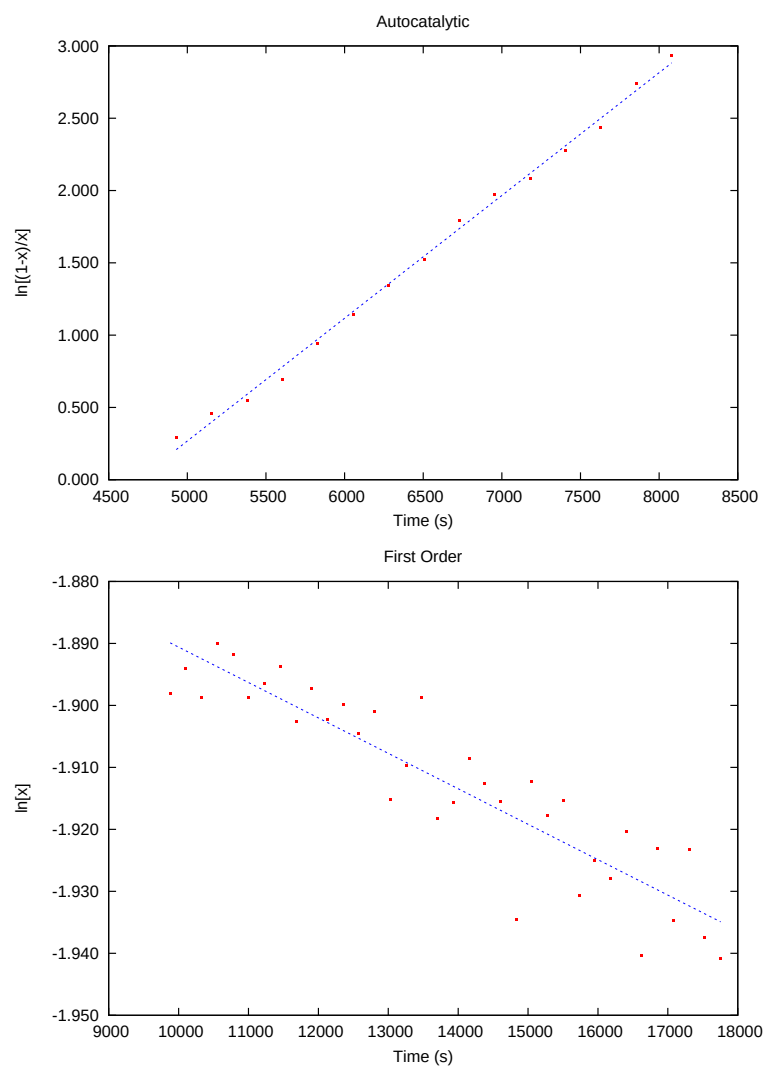
A saturated, dried (anhydrous MgSO_4) solution of TsOH in Et_2O (2mL) was added A solution of spiro[camphene-7,2'-indan] **179** (20mg) in CDCl_3 (2mL). The mixture was warmed to 50°C to permit evaporation of the Et_2O , until the level of the chloroform was approximately 0.6mL. Raising the temperature to 50°C led to the formation of peaks of spiro[camphene-6,2'-indan] **263** in the observed ^1H NMR spectrum.

3.5.1 Kinetic data for the decomposition of the tosylate 255

The tables in each case indicate the concentration and the temperature values for each dataset.

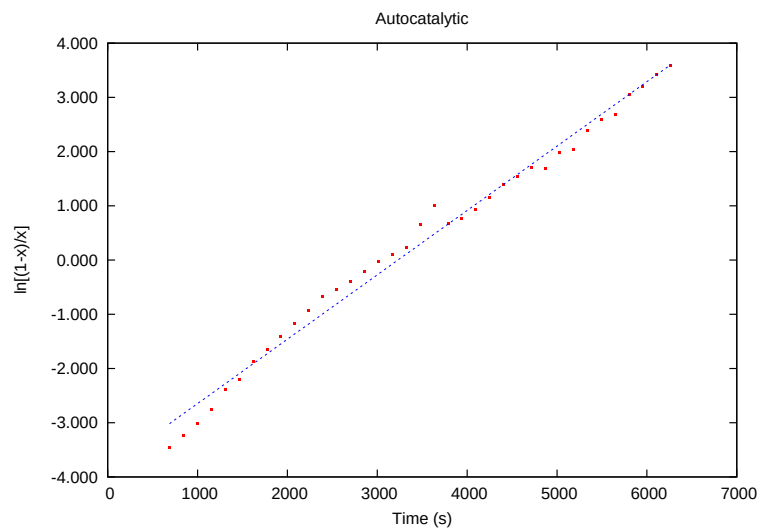
The dataset name refers to the physical NMR data on disk.

DataSet : 0404-30



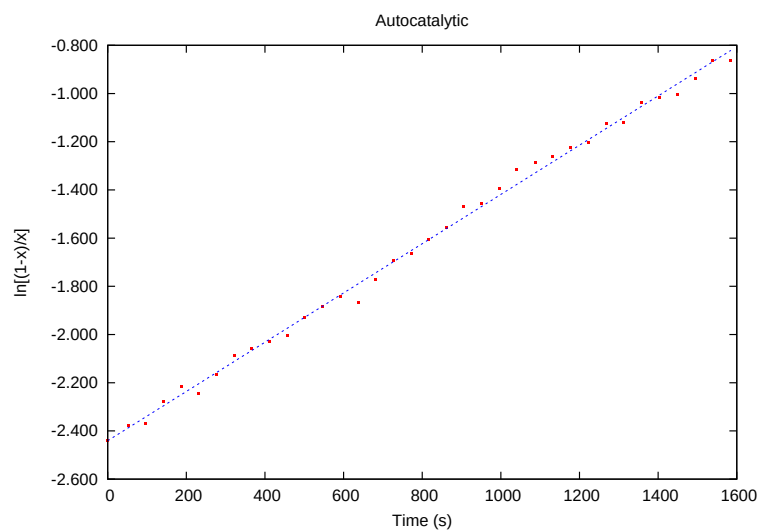
T	[Tosylate]	Autocatalytic				First Order			
/K	M	t_{min}	t_{max}	k_a	R^2	t_{min}	t_{max}	k_f	R^2
303	0.0272	4930s	8080s	$0.0331\text{mol}^{-1}.\text{s}^{-1}$	0.9955	9880s	17755s	0^{-1}	0.8273

DataSet : 0404-32



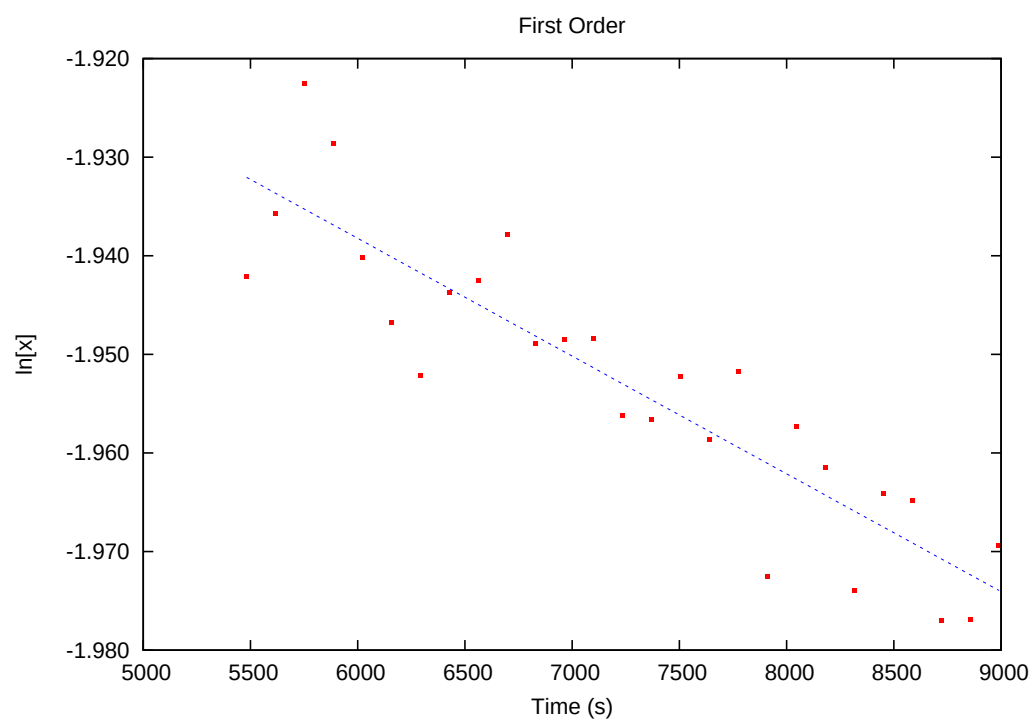
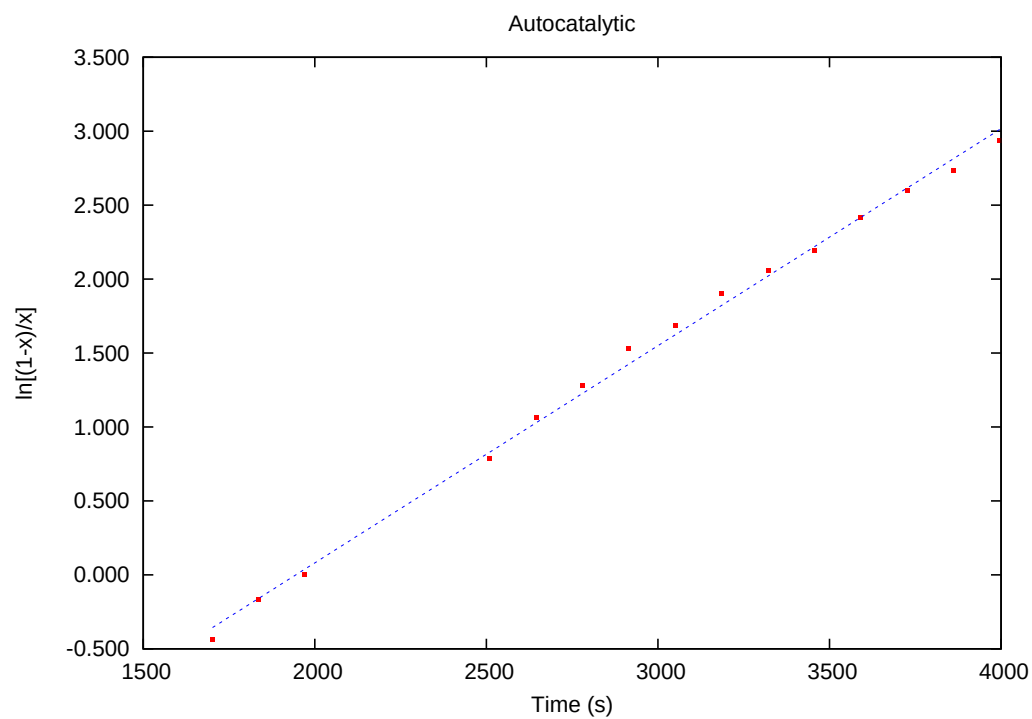
T	[Tosylate]	Autocatalytic				First Order			
/K	M	t_{min}	t_{max}	k_a	R^2	t_{min}	t_{max}	k_f	R^2
305	0.0265	688s	6266s	$0.0448\text{mol}^{-1}.\text{s}^{-1}$	0.9868				

DataSet : 0705-32



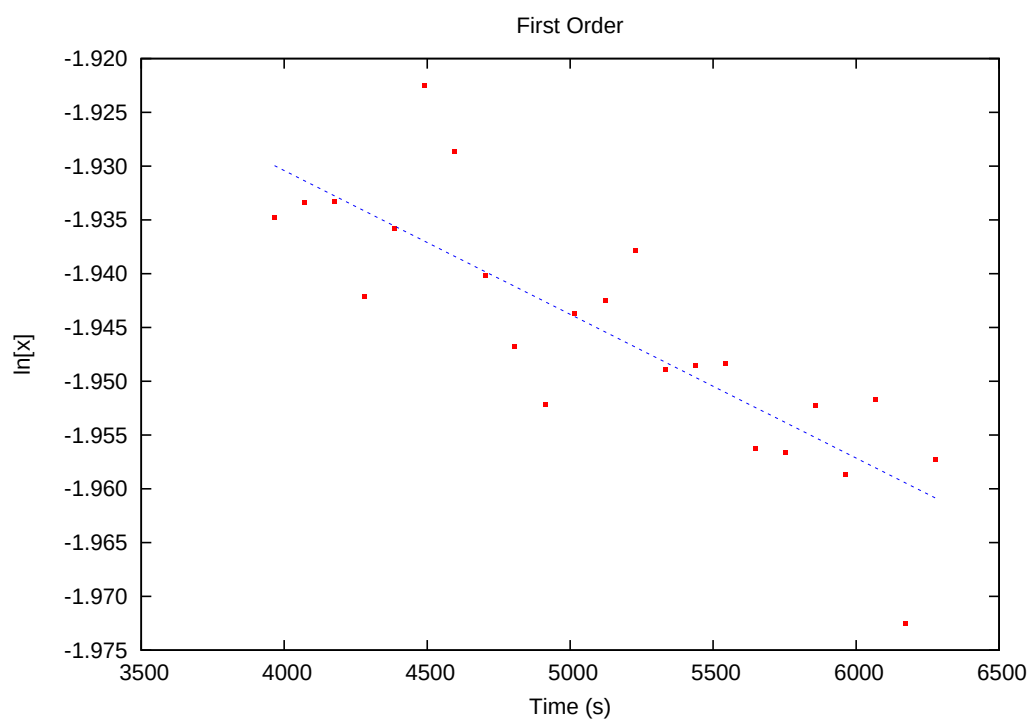
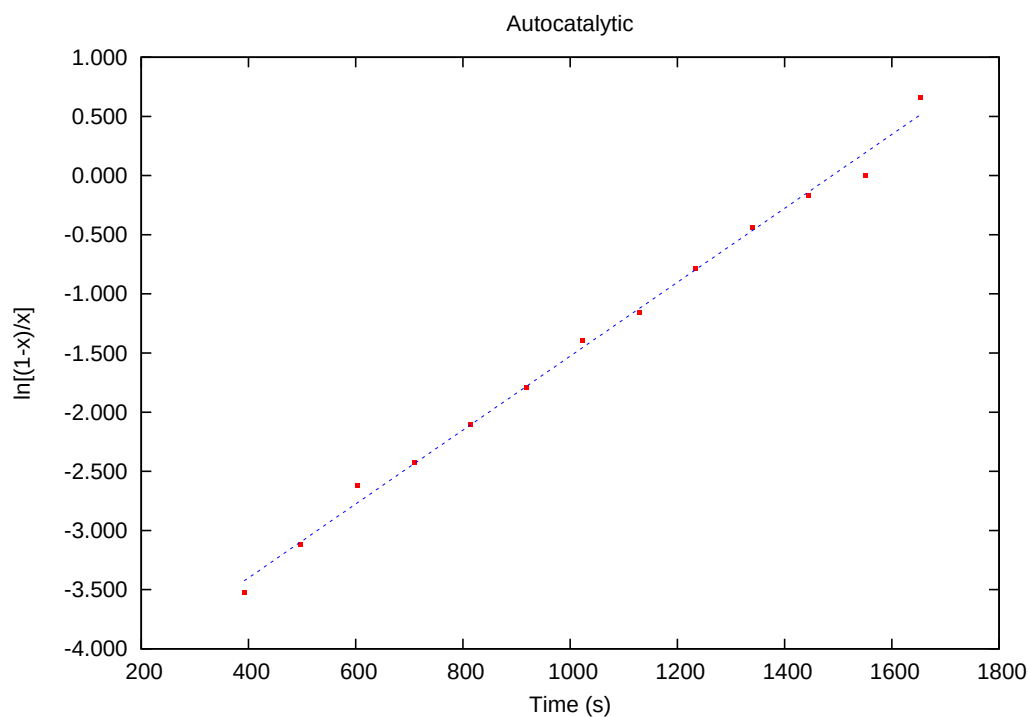
T	[Tosylate]	Autocatalytic				First Order			
/K	M	t_{min}	t_{max}	k_a	R^2	t_{min}	t_{max}	k_f	R^2
305	0.0275	0s	1585s	$0.0372\text{mol}^{-1}.\text{s}^{-1}$	0.9966				

DataSet : 0404-34



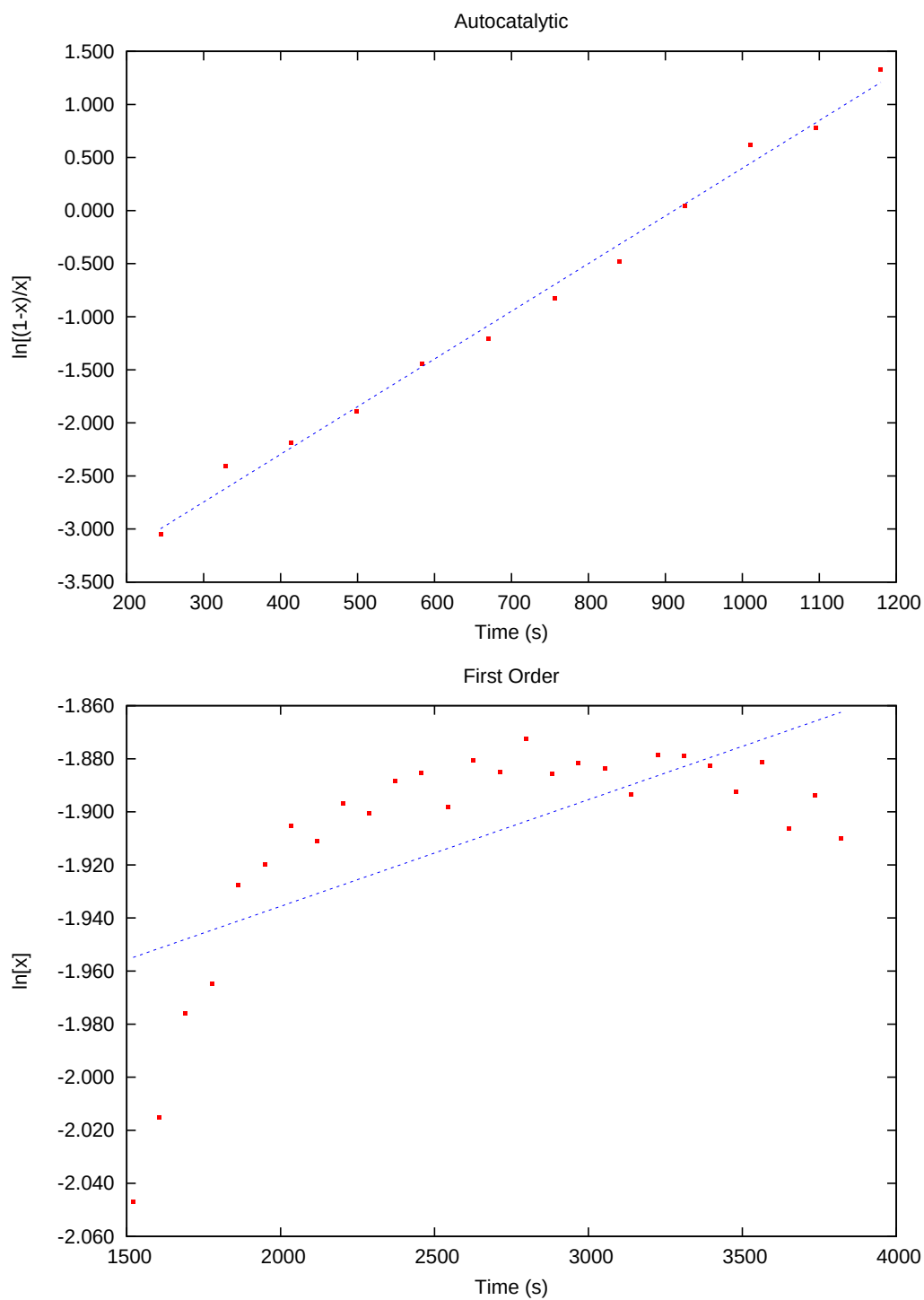
T /K	[Tosylate] M	Autocatalytic				First Order			
		t_{min}	t_{max}	k_a	R^2	t_{min}	t_{max}	k_f	R^2
307	0.0271	1702s	3996s	$0.0658 \text{ mol}^{-1} \cdot \text{s}^{-1}$	0.9773	5482s	8990s	0 s^{-1}	0.8064

DataSet : 0404-36



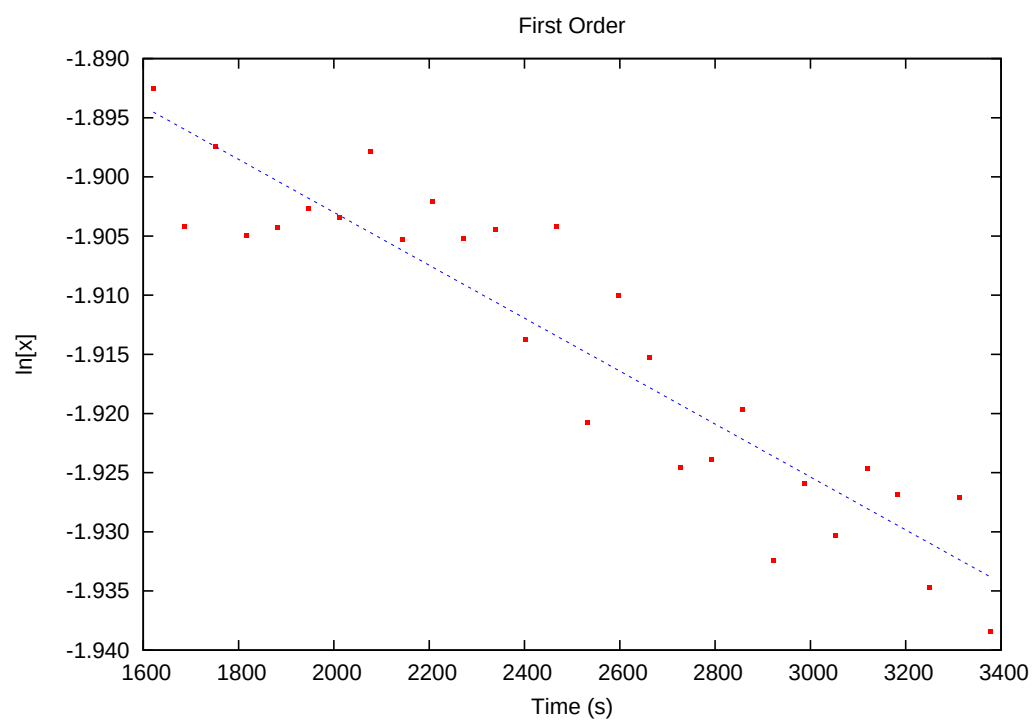
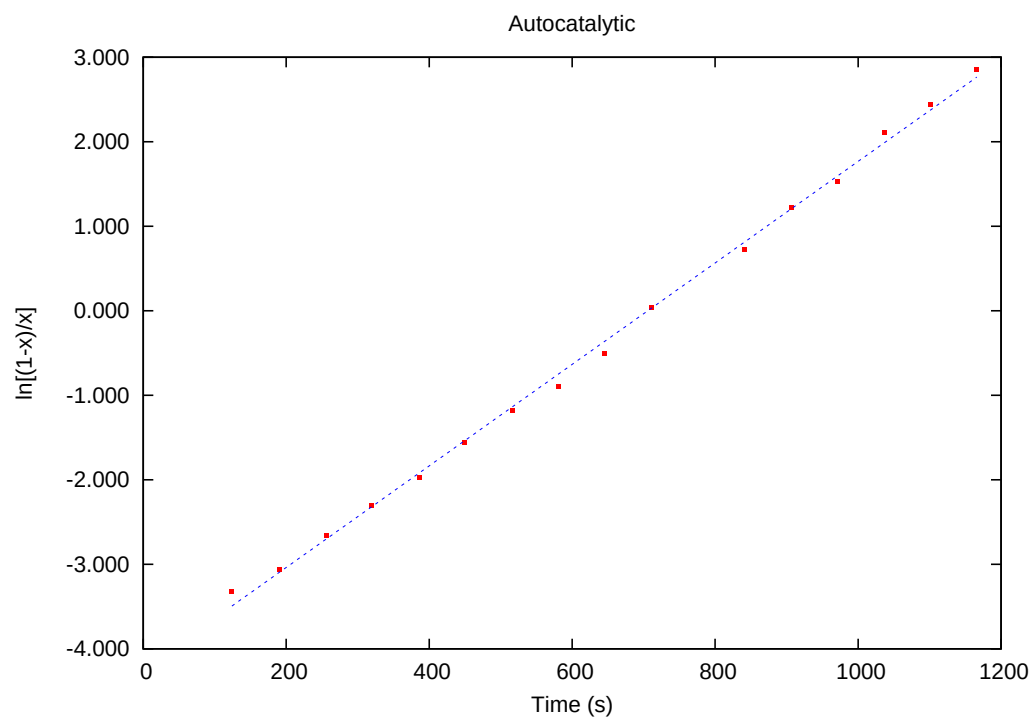
T /K	[Tosylate] M	Autocatalytic				First Order			
		t_{min}	t_{max}	k_a	R^2	t_{min}	t_{max}	k_f	R^2
309	0.0265	392s	1654s	$0.0909 \text{ mol}^{-1} \cdot \text{s}^{-1}$	0.9916	3966s	6278s		0

DataSet : 0404-38



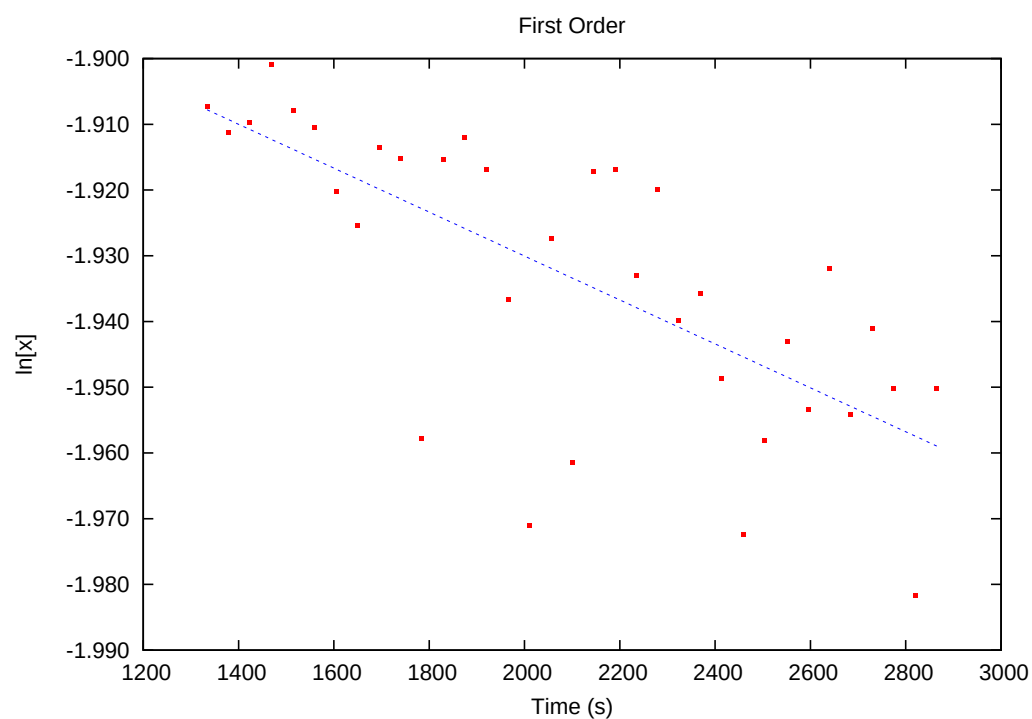
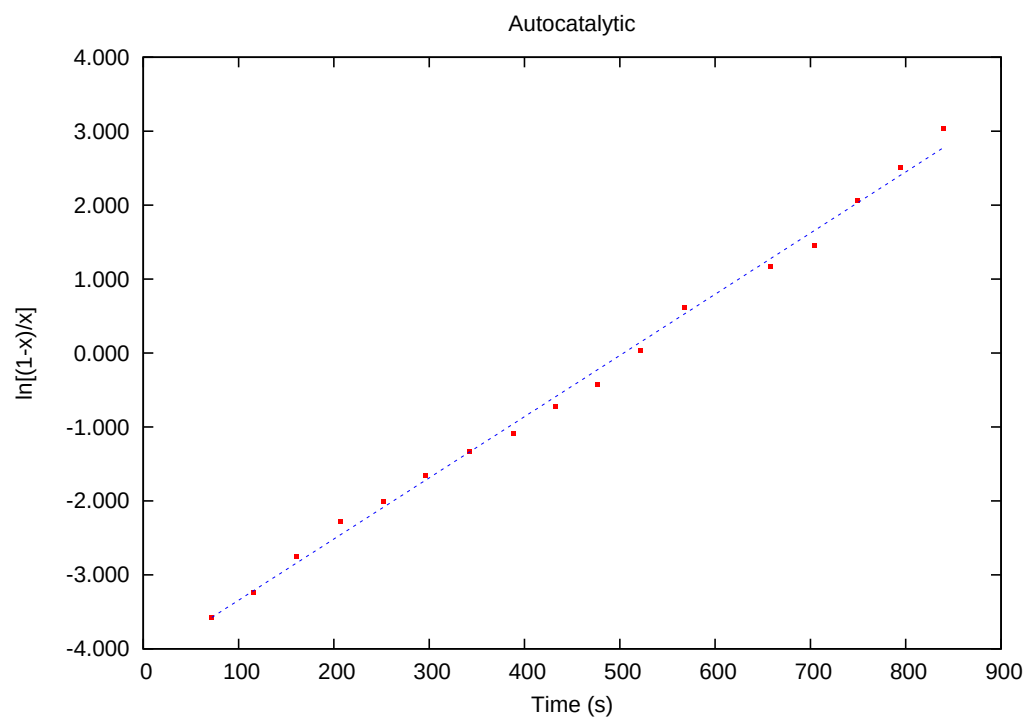
T /K	[Tosylate] M	Autocatalytic				First Order			
		t_{min}	t_{max}	k_a	R^2	t_{min}	t_{max}	k_f	R^2
311	0.0263	244s	1180s	$0.175\text{mol}^{-1}.\text{s}^{-1}$	0.9938				

DataSet : 0404-40



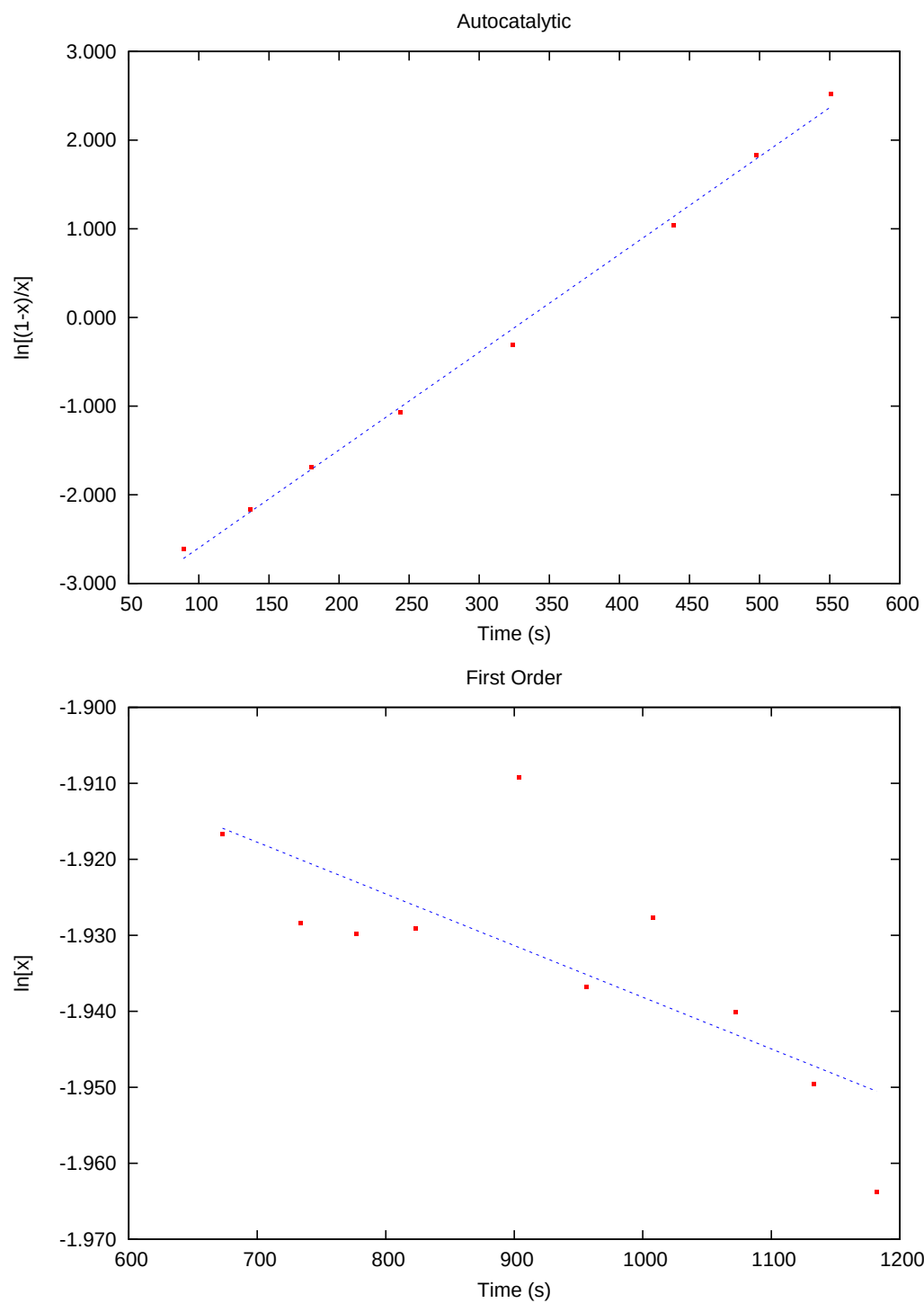
T /K	[Tosylate] M	Autocatalytic				First Order			
		t_{min}	t_{max}	k_a	R^2	t_{min}	t_{max}	k_f	R^2
313	0.0269	124s	1166s	$0.2276 \text{ mol}^{-1} \cdot \text{s}^{-1}$	0.9924	1621s	3377s	0 s^{-1}	0.8661

DataSet : 0404-42



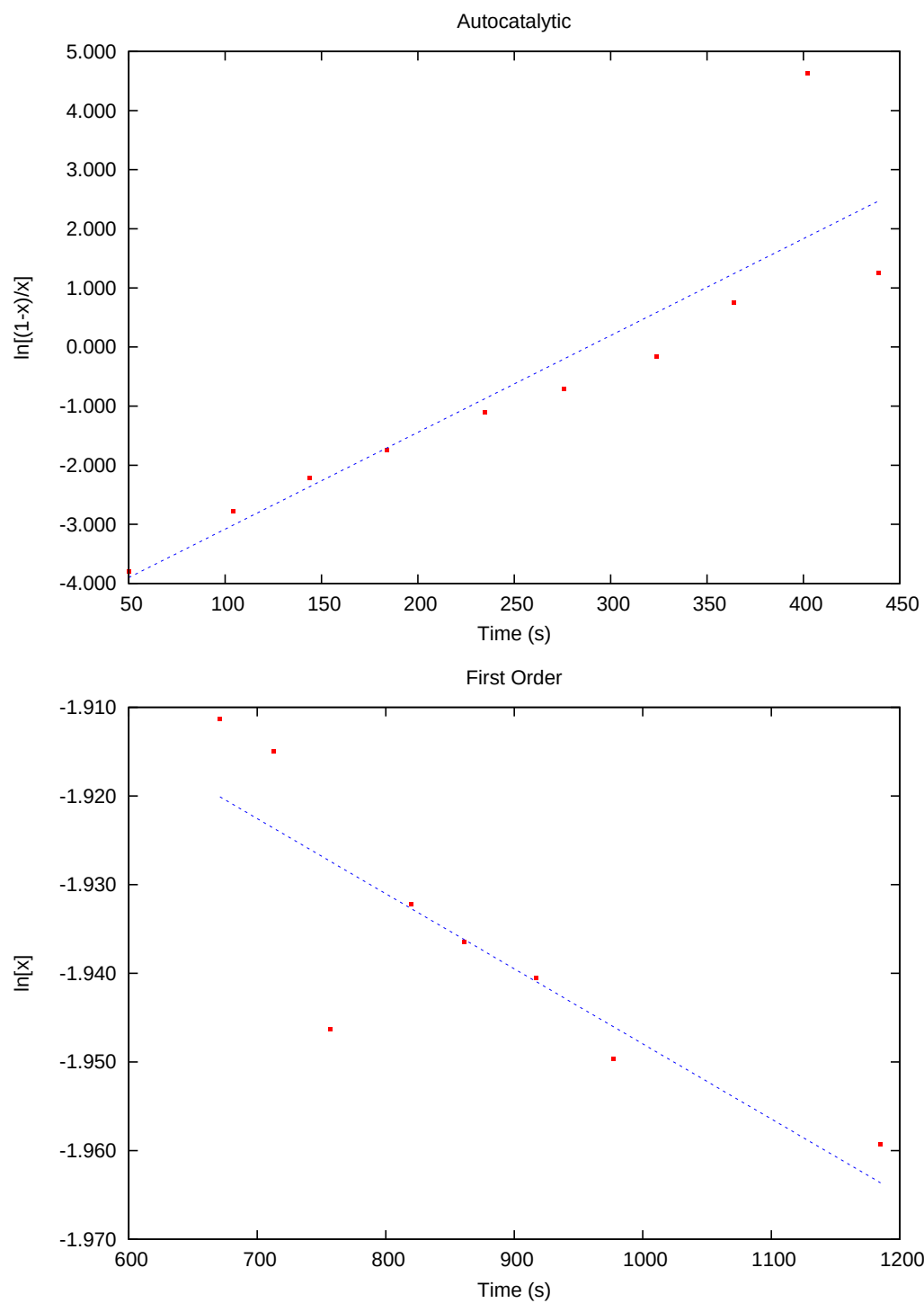
T /K	[Tosylate] M	Autocatalytic				First Order			
		t_{min}	t_{max}	k_a	R^2	t_{min}	t_{max}	k_f	R^2
315	0.0263	72s	840s	$0.3315 \text{ mol}^{-1} \cdot \text{s}^{-1}$	0.9672	1334s	2865s		

DataSet : 0404-44



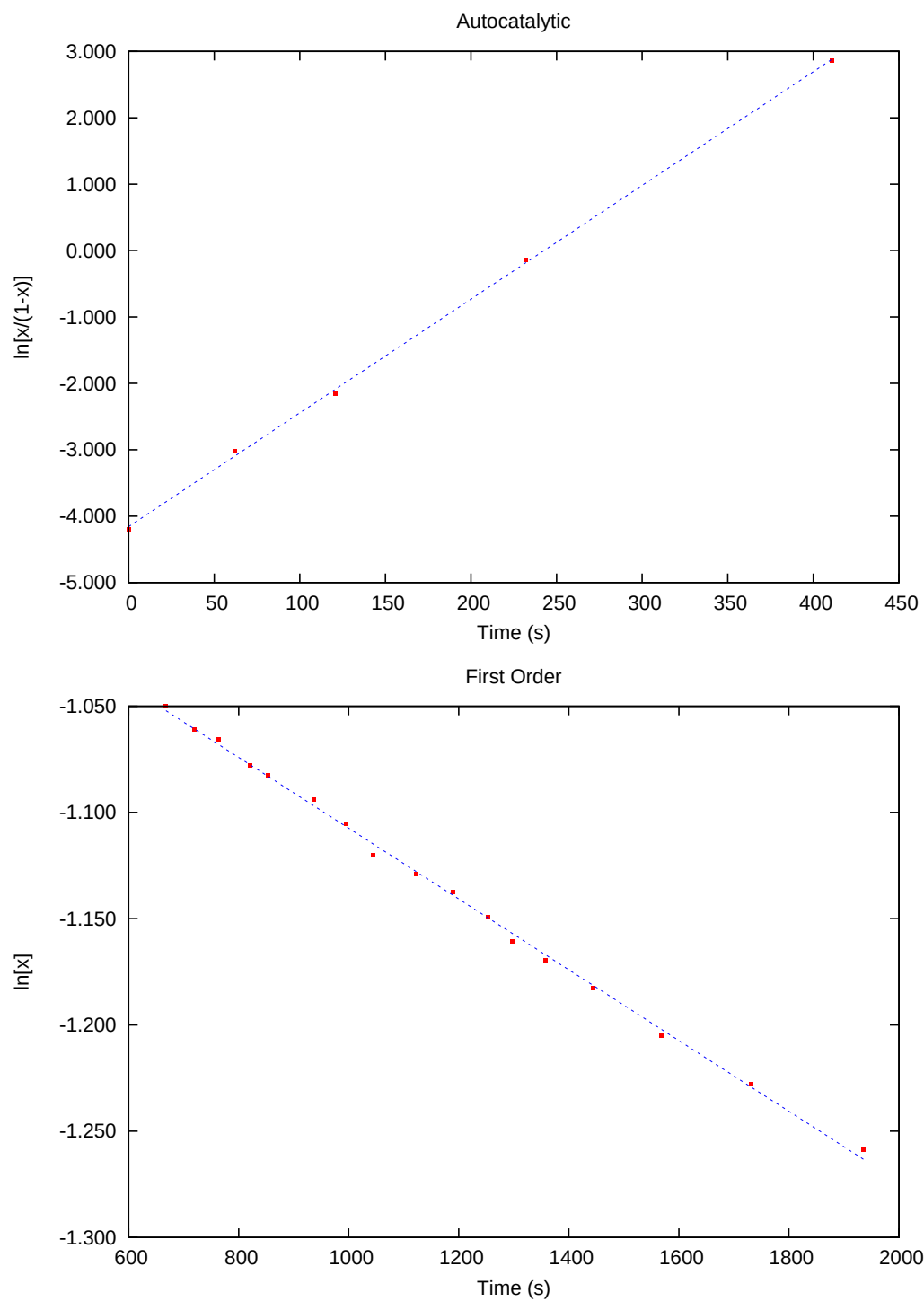
T	[Tosylate]	Autocatalytic				First Order			
/K	M	t_{min}	t_{max}	k_a	R^2	t_{min}	t_{max}	k_f	R^2
317	0.0264	0s	551s	$0.4284 \text{ mol}^{-1} \cdot \text{s}^{-1}$	0.995	673s	1182s		

DataSet : 0404-46



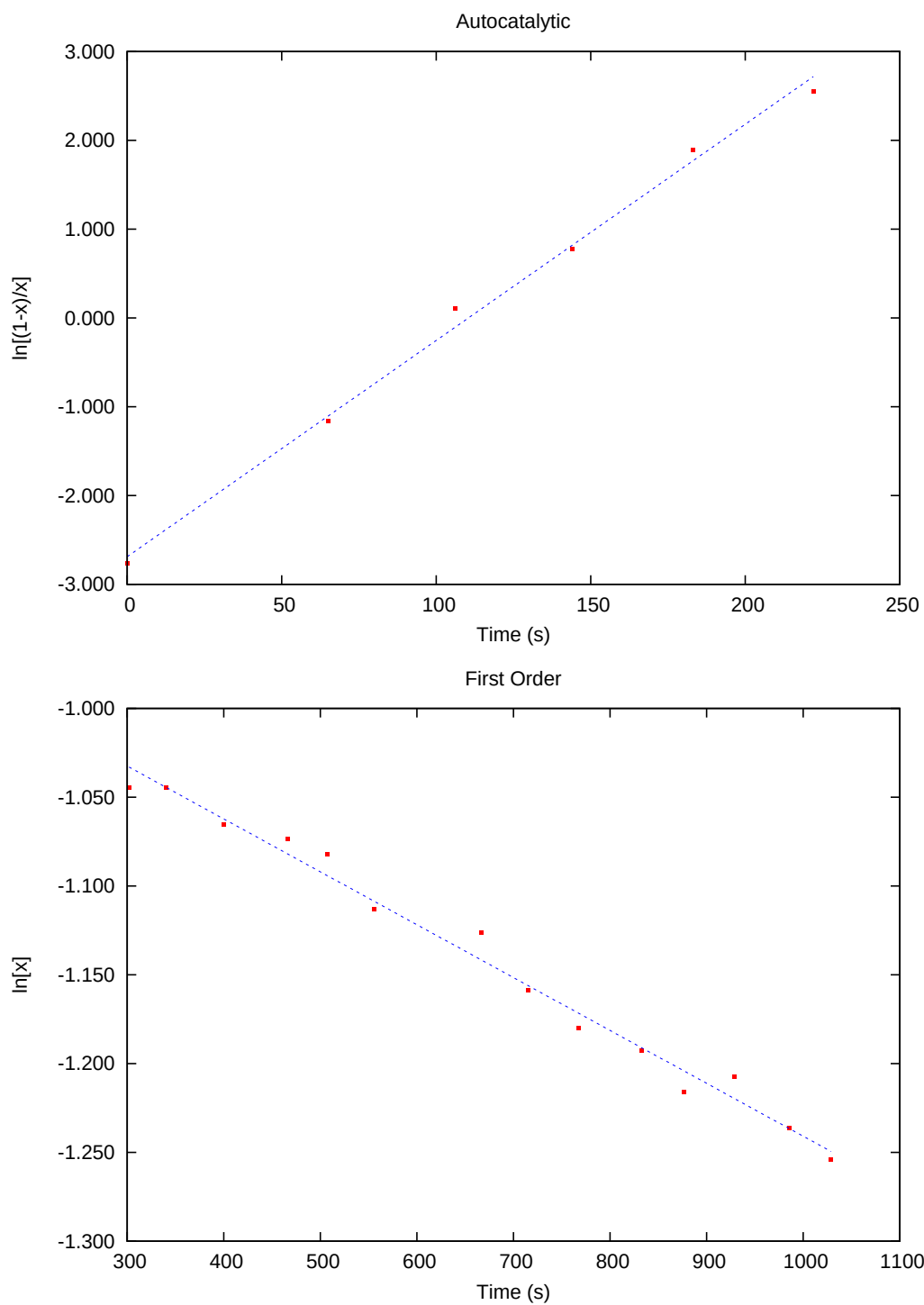
T /K	[Tosylate] M	Autocatalytic				First Order			
		t_{min}	t_{max}	k_a	R^2	t_{min}	t_{max}	k_f	R^2
319	0.0257	50s	439s	$0.6384\text{mol}^{-1}\cdot\text{s}^{-1}$	0.8013	671s	1185s	-0.0001s^{-1}	0.7168

DataSet : 0404-44b



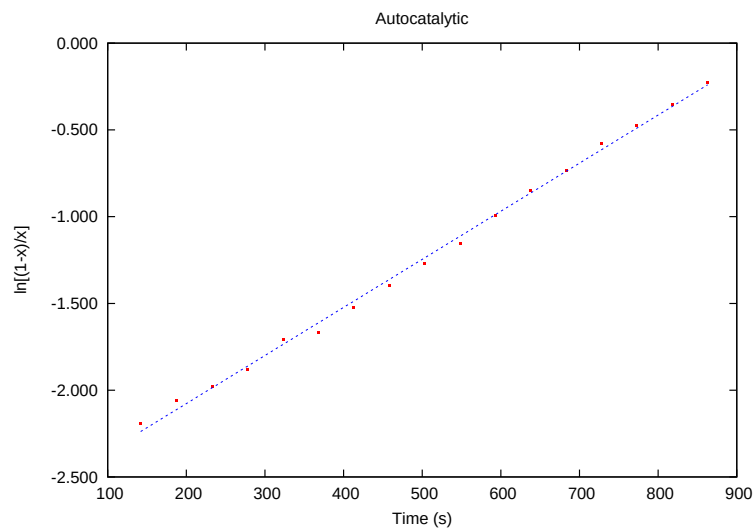
T /K	[Tosylate] M	Autocatalytic				First Order			
		t_{min}	t_{max}	k_a	R^2	t_{min}	t_{max}	k_f	R^2
317	0.027	0s	411s	$0.6335\text{mol}^{-1}\cdot\text{s}^{-1}$	0.9995	668s	1936s	-0.0002s^{-1}	0.9981

DataSet : 0404-46b



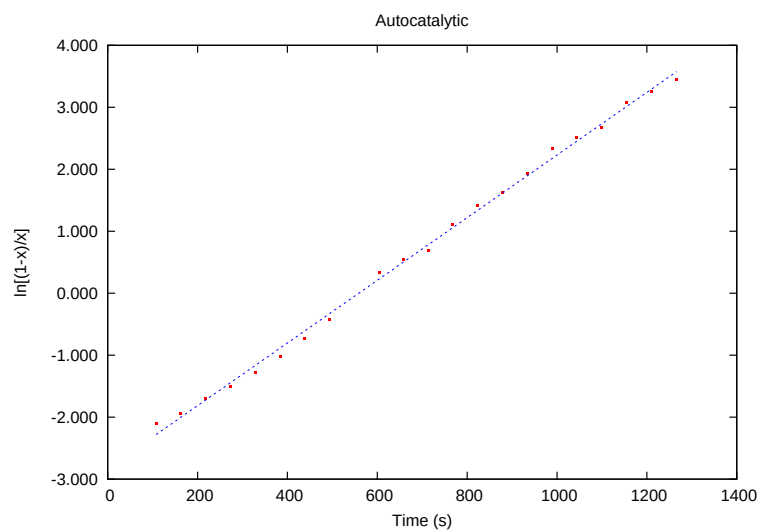
T /K	[Tosylate] M	Autocatalytic				First Order			
		t_{min}	t_{max}	k_a	R^2	t_{min}	t_{max}	k_f	R^2
319	0.0273	0s	222s	$0.8912\text{mol}^{-1}\cdot\text{s}^{-1}$	0.995	302s	1029s	-0.0003s^{-1}	0.9854

DataSet : 0705-36



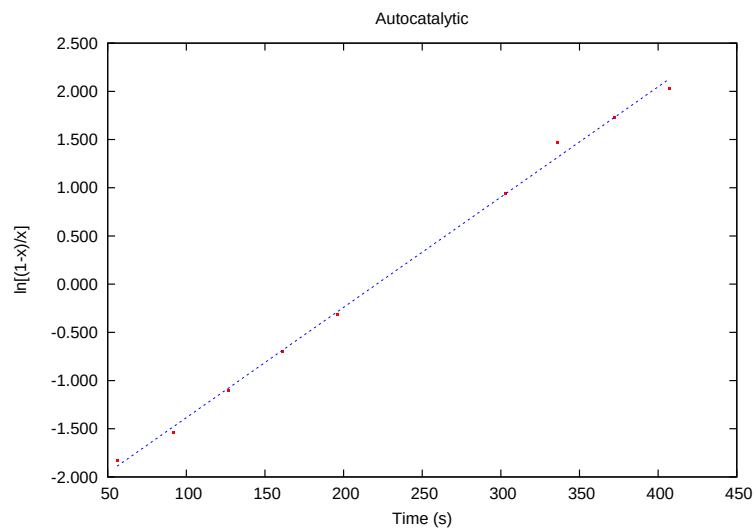
T	[Tosylate]	Autocatalytic				First Order			
/K	M	t_{min}	t_{max}	k_a	R^2	t_{min}	t_{max}	k_f	R^2
309	0.028	142s	863s	$0.0951 \text{mol}^{-1} \cdot \text{s}^{-1}$	0.9931				

DataSet : 0705-38



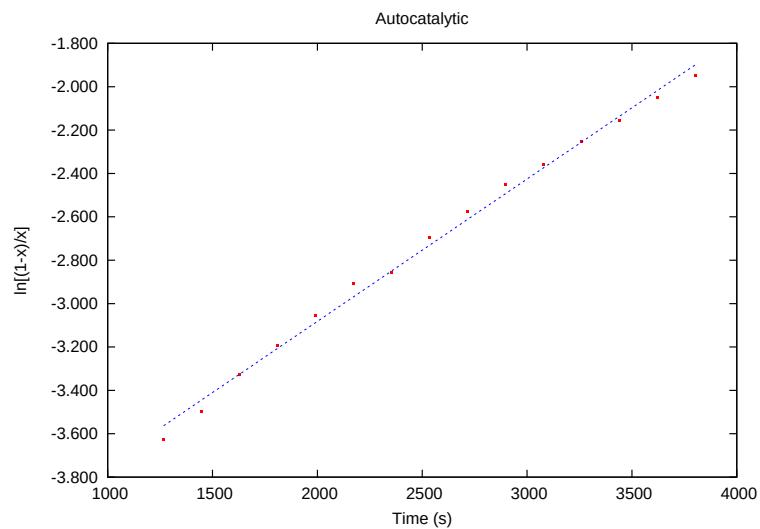
T	[Tosylate]	Autocatalytic				First Order			
/K	M	t_{min}	t_{max}	k_a	R^2	t_{min}	t_{max}	k_f	R^2
311	0.028	108s	1266s	$0.1742 \text{mol}^{-1} \cdot \text{s}^{-1}$	0.9642				

DataSet : 0705-43



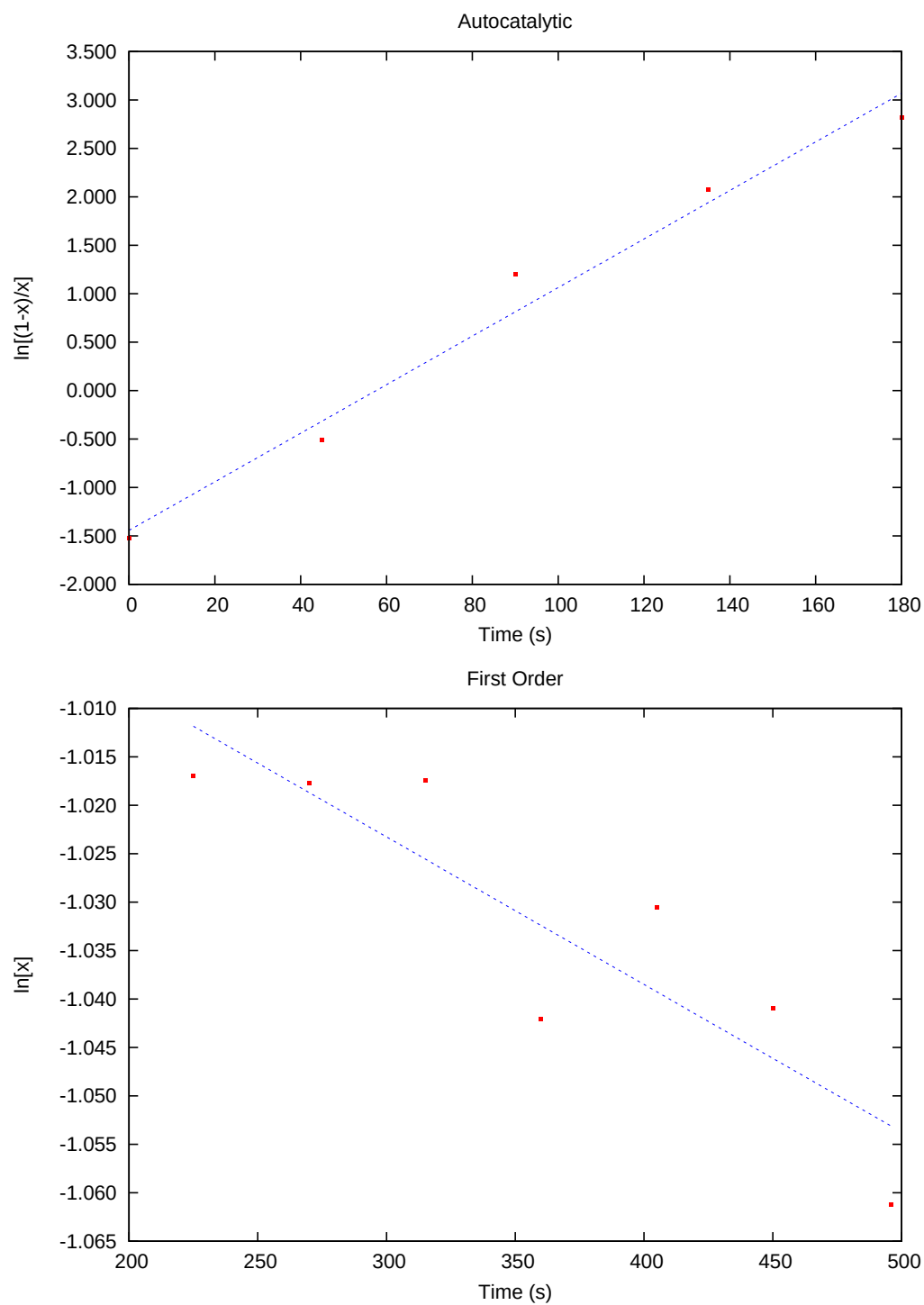
T	[Tosylate]	Autocatalytic				First Order			
/K	M	t_{min}	t_{max}	k_a	R^2	t_{min}	t_{max}	k_f	R^2
316	0.0286	56s	407s	$0.4133\text{mol}^{-1}.\text{s}^{-1}$	0.9058				

DataSet : 0705-30b



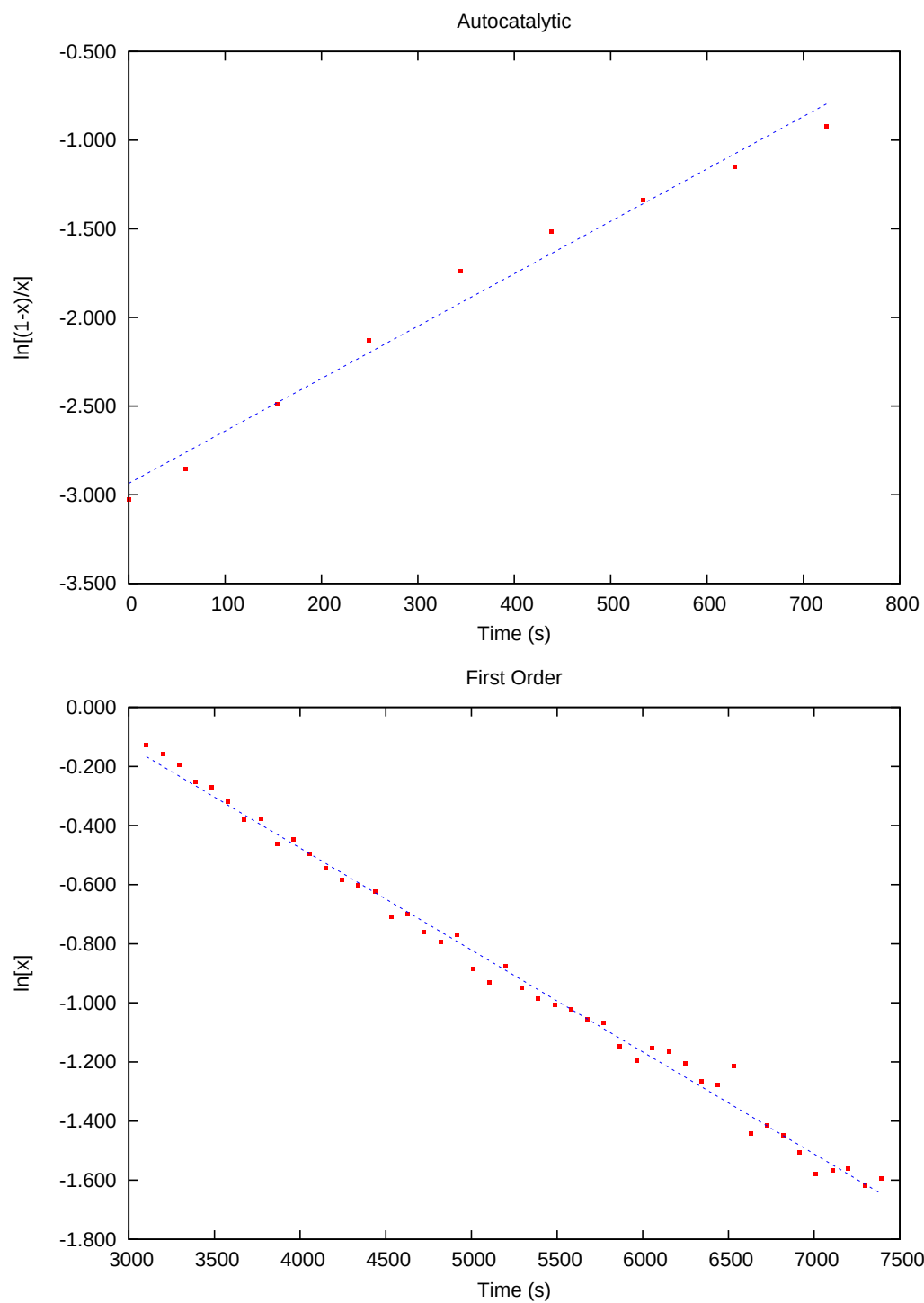
T	[Tosylate]	Autocatalytic				First Order			
/K	M	t_{min}	t_{max}	k_a	R^2	t_{min}	t_{max}	k_f	R^2
303	0.0275	1267s	3804s	$0.9126\text{mol}^{-1}.\text{s}^{-1}$	0.9827				

DataSet : 0705-46



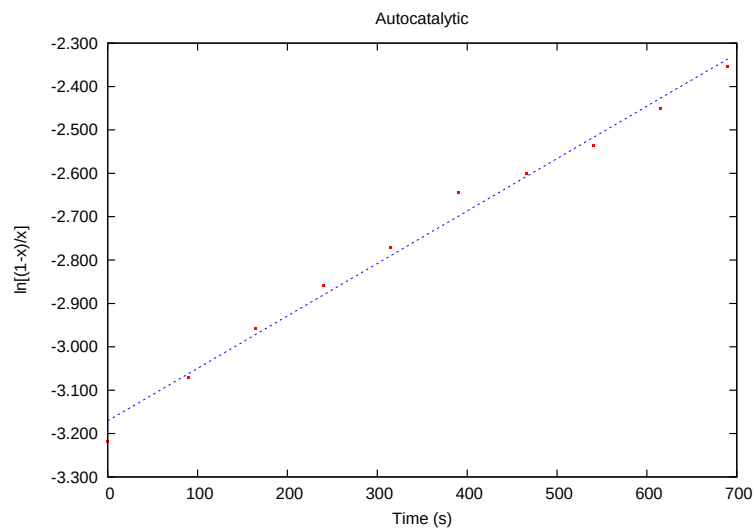
T /K	[Tosylate] M	Autocatalytic				First Order			
		t_{min}	t_{max}	k_a	R^2	t_{min}	t_{max}	k_f	R^2
319	0.0275	0s	180s	$0.9126\text{mol}^{-1}\cdot\text{s}^{-1}$	0.9787	225s	496s	-0.0002s^{-1}	0.7888

DataSet : 0705-32b



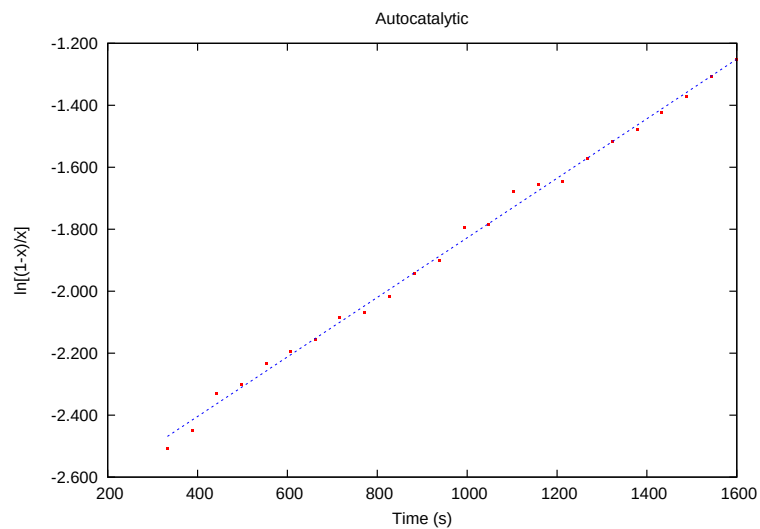
T /K	[Tosylate] M	Autocatalytic				First Order			
		t_{min}	t_{max}	k_a	R^2	t_{min}	t_{max}	k_f	R^2
305	0.0703	0s	724s	$0.0421\text{mol}^{-1}.\text{s}^{-1}$	0.9802	3103s	7391s	0.8182s^{-1}	0.9978

DataSet : 0705-34b



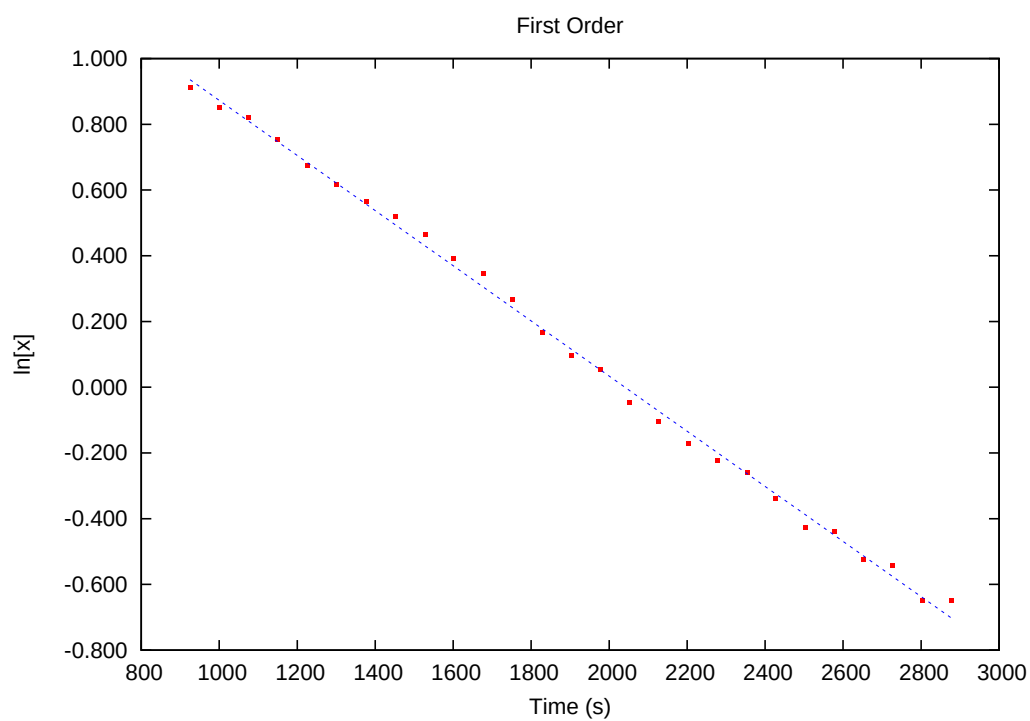
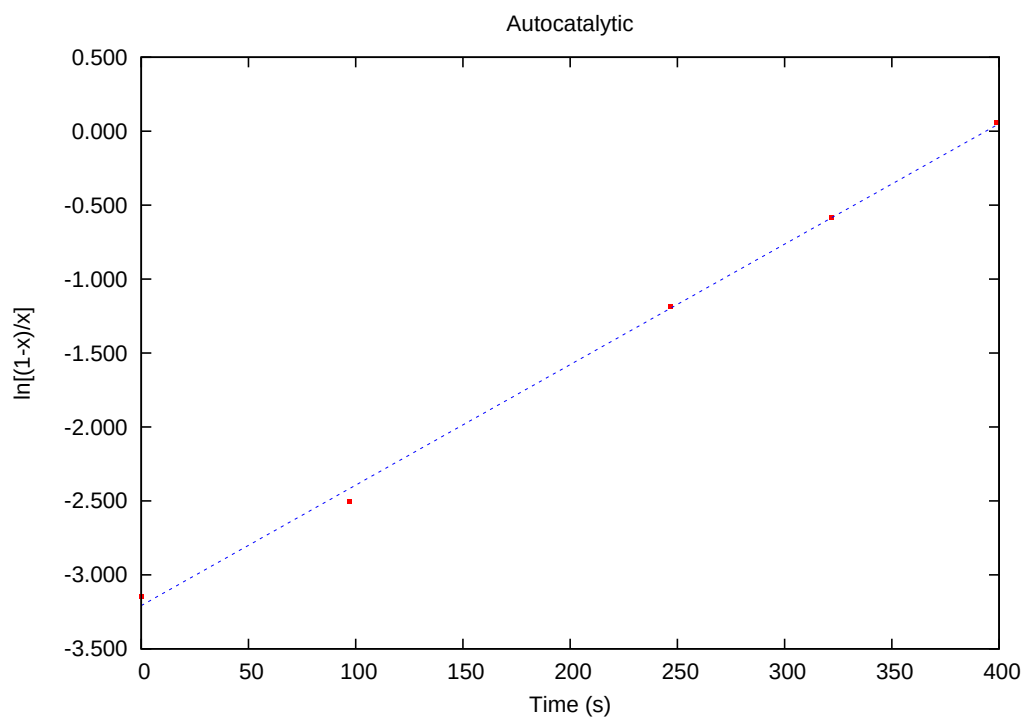
T	[Tosylate]	Autocatalytic				First Order			
/K	M	t_{min}	t_{max}	k_a	R^2	t_{min}	t_{max}	k_f	R^2
307	0.0703	0s	724s	$0.0421 \text{mol}^{-1} \cdot \text{s}^{-1}$	0.9802				

DataSet : 0705-38b



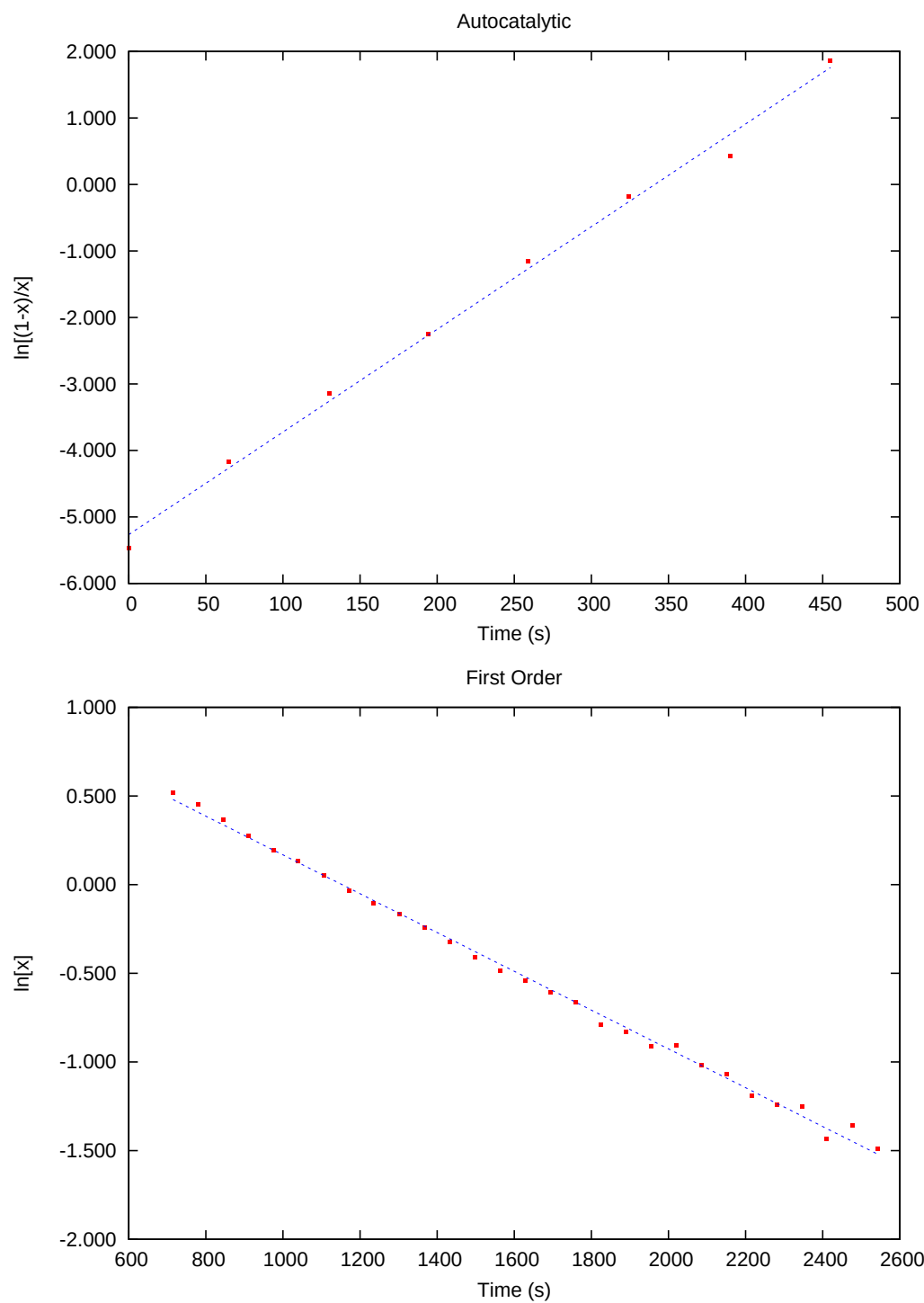
T	[Tosylate]	Autocatalytic				First Order			
/K	M	t_{min}	t_{max}	k_a	R^2	t_{min}	t_{max}	k_f	R^2
311	0.0682	333s	1599s	$0.1182 \text{mol}^{-1} \cdot \text{s}^{-1}$	0.981				

DataSet : 0705-36b



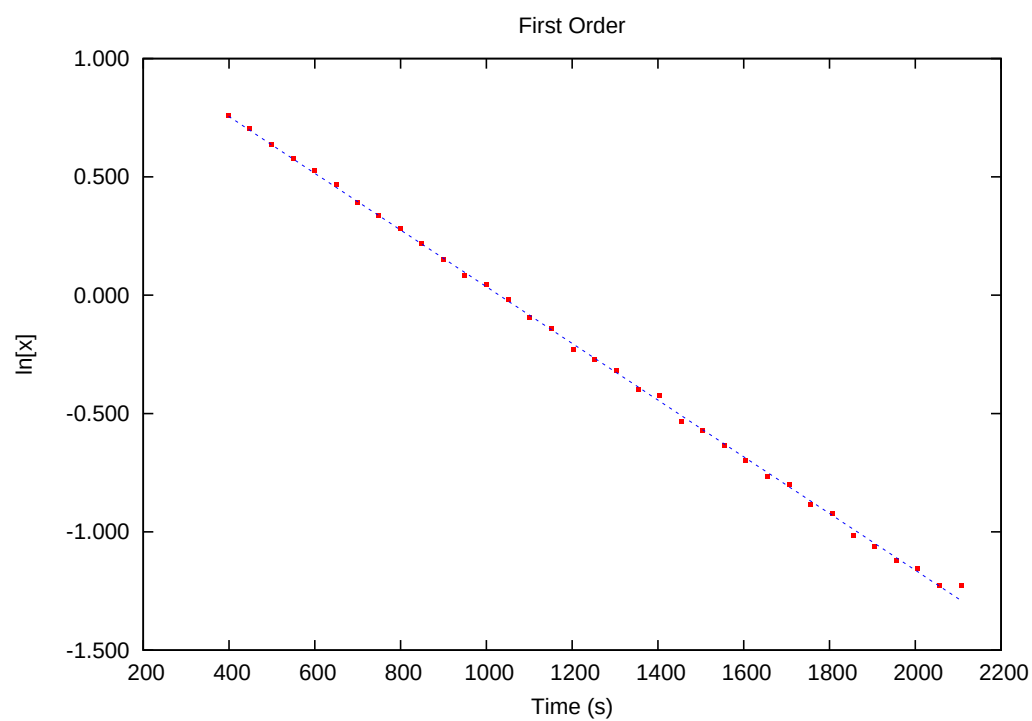
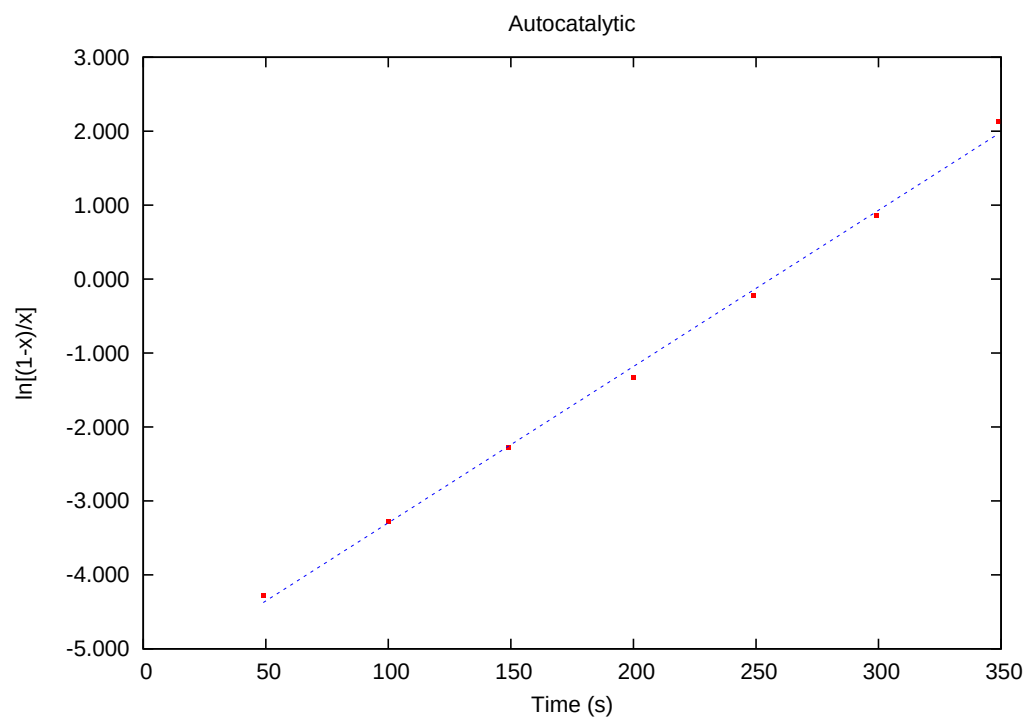
T /K	[Tosylate] M	Autocatalytic				First Order			
		t_{min}	t_{max}	k_a	R^2	t_{min}	t_{max}	k_f	R^2
309	0.0682	0s	399s	$0.1182\text{mol}^{-1}\cdot\text{s}^{-1}$	0.9887	925s	2878s	-0.0007s^{-1}	0.9844

DataSet : 0705-40b



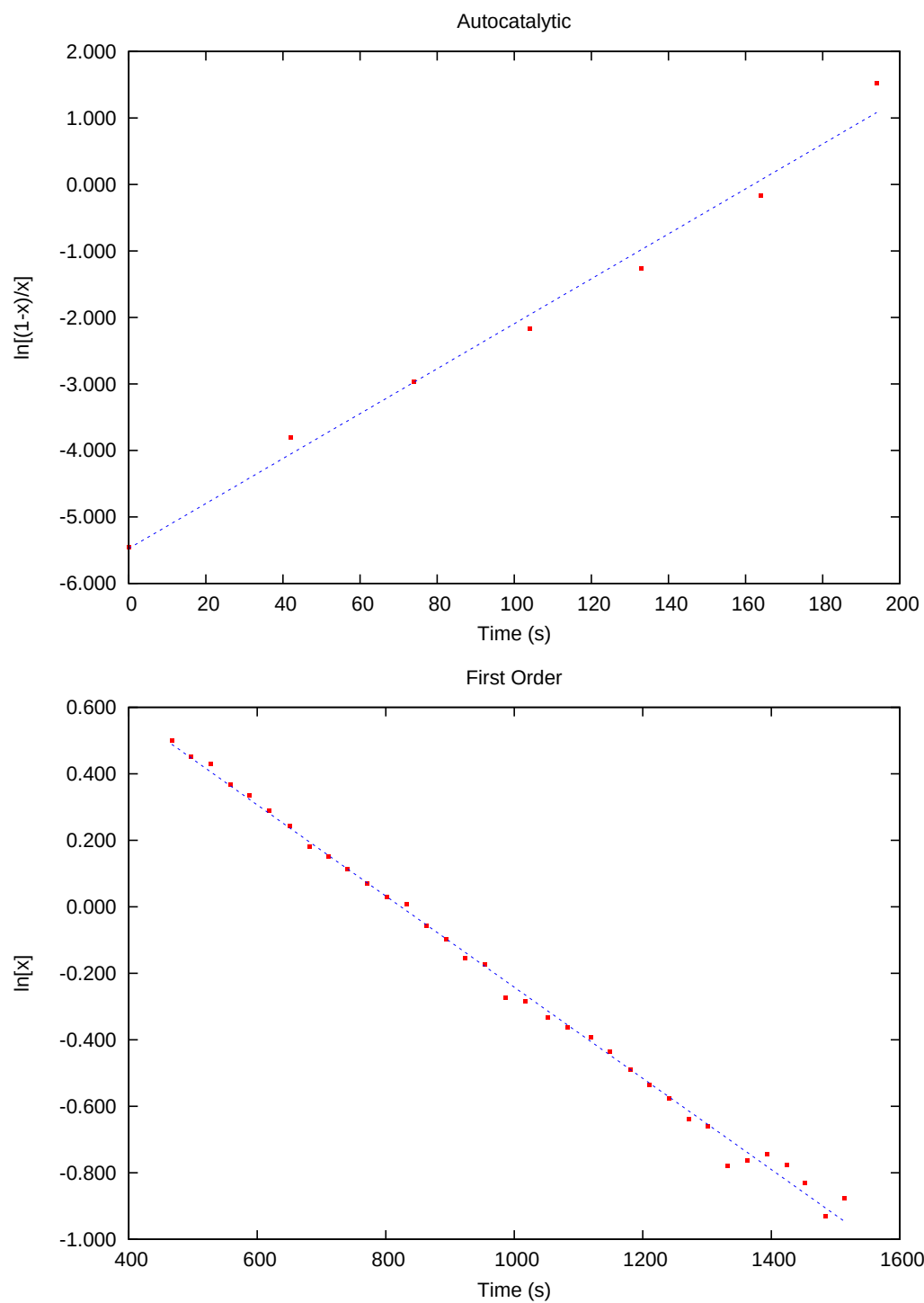
T /K	[Tosylate] M	Autocatalytic				First Order			
		t_{min}	t_{max}	k_a	R^2	t_{min}	t_{max}	k_f	R^2
313	0.0693	0s	455s	$0.2227 \text{ mol}^{-1} \cdot \text{s}^{-1}$	0.9954	715s	2542s	-0.0011 s^{-1}	0.9969

DataSet : 0705-42b



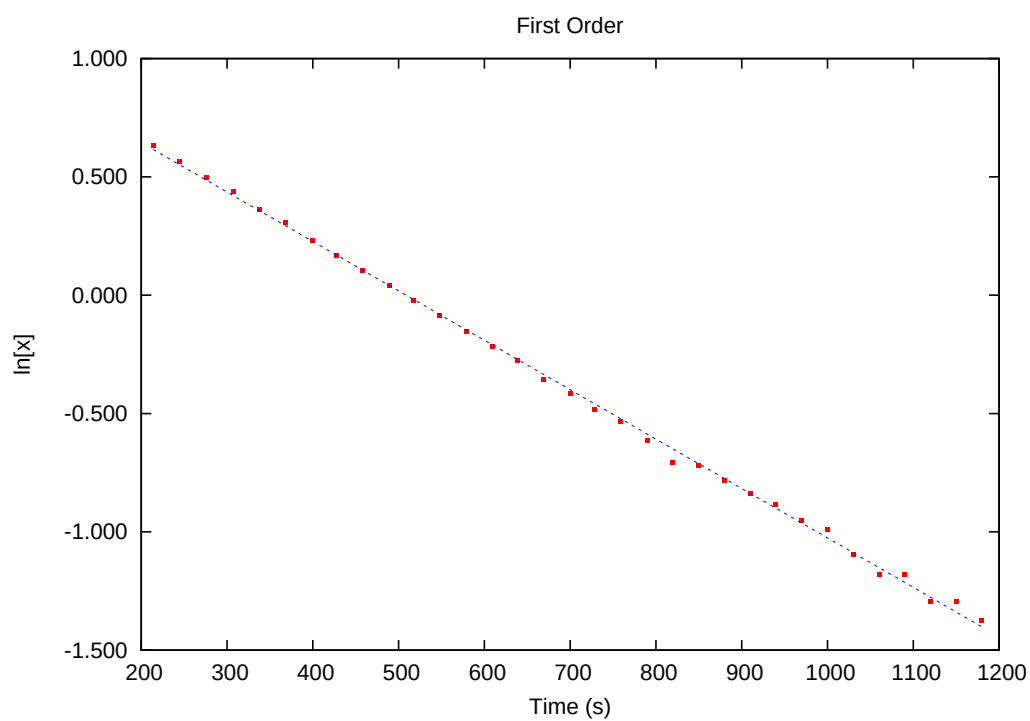
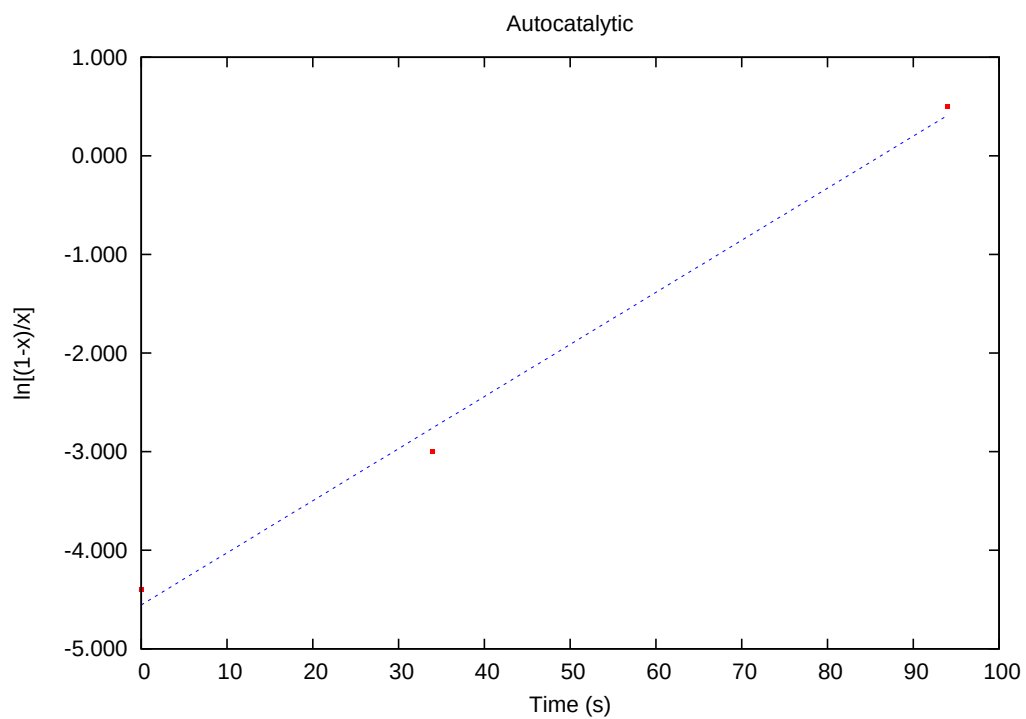
T /K	[Tosylate] M	Autocatalytic				First Order			
		t_{min}	t_{max}	k_a	R^2	t_{min}	t_{max}	k_f	R^2
315	0.0687	49s	349s	$0.3074\text{mol}^{-1}\cdot\text{s}^{-1}$	0.9979	399s	2108s	-0.0012s^{-1}	0.9993

DataSet : 0705-44b



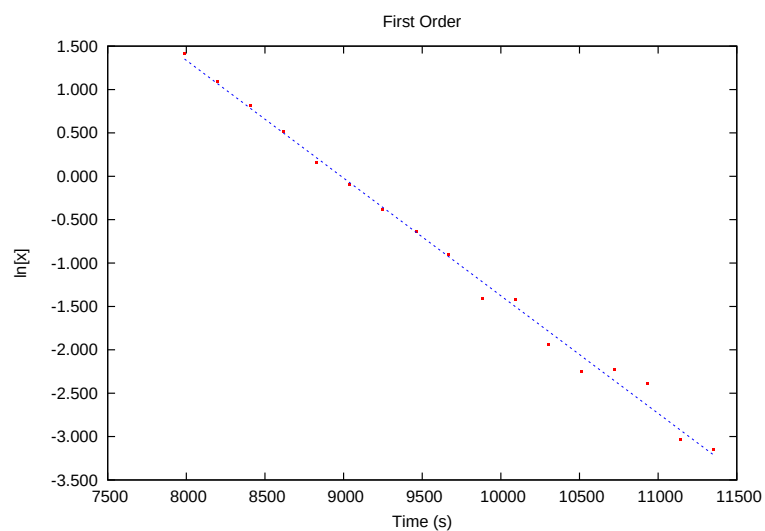
T /K	[Tosylate] M	Autocatalytic				First Order			
		t_{min}	t_{max}	k_a	R^2	t_{min}	t_{max}	k_f	R^2
317	0.0697	0s	194s	$0.4851\text{mol}^{-1}\cdot\text{s}^{-1}$	0.9866	467s	1514s	-0.0014s^{-1}	0.9963

DataSet : 0705-46b



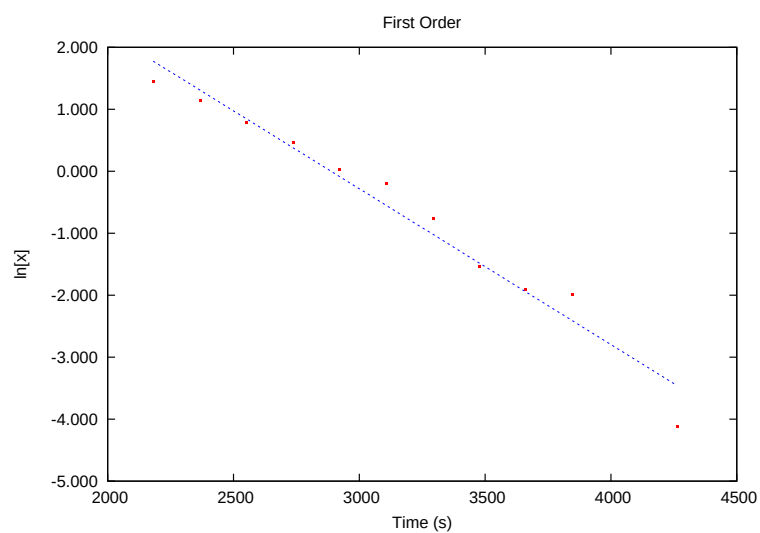
T /K	[Tosylate] M	Autocatalytic				First Order			
		t_{min}	t_{max}	k_a	R^2	t_{min}	t_{max}	k_f	R^2
319	0.0697	0s	94s	$0.4851\text{mol}^{-1}\cdot\text{s}^{-1}$	0.9801	214s	1180s	-0.0021s^{-1}	0.9988

DataSet : 1005-30b



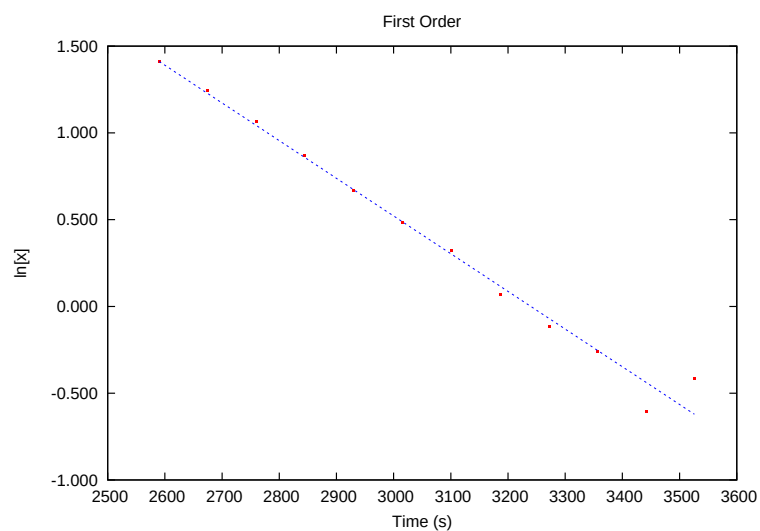
T	[Tosylate]	Autocatalytic				First Order			
/K	M	t_{min}	t_{max}	k_a	R^2	t_{min}	t_{max}	k_f	R^2
303						7989s	11352s	$-0.0014s^{-1}$	0.9939

DataSet : 1005-32b



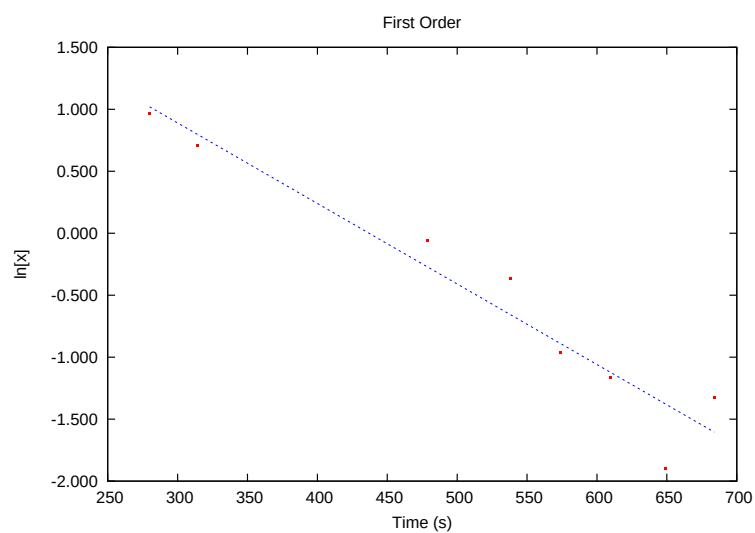
T	[Tosylate]	Autocatalytic				First Order			
/K	M	t_{min}	t_{max}	k_a	R^2	t_{min}	t_{max}	k_f	R^2
305						2181s	4263s	$-0.0025s^{-1}$	0.9647

DataSet : 1005-34b



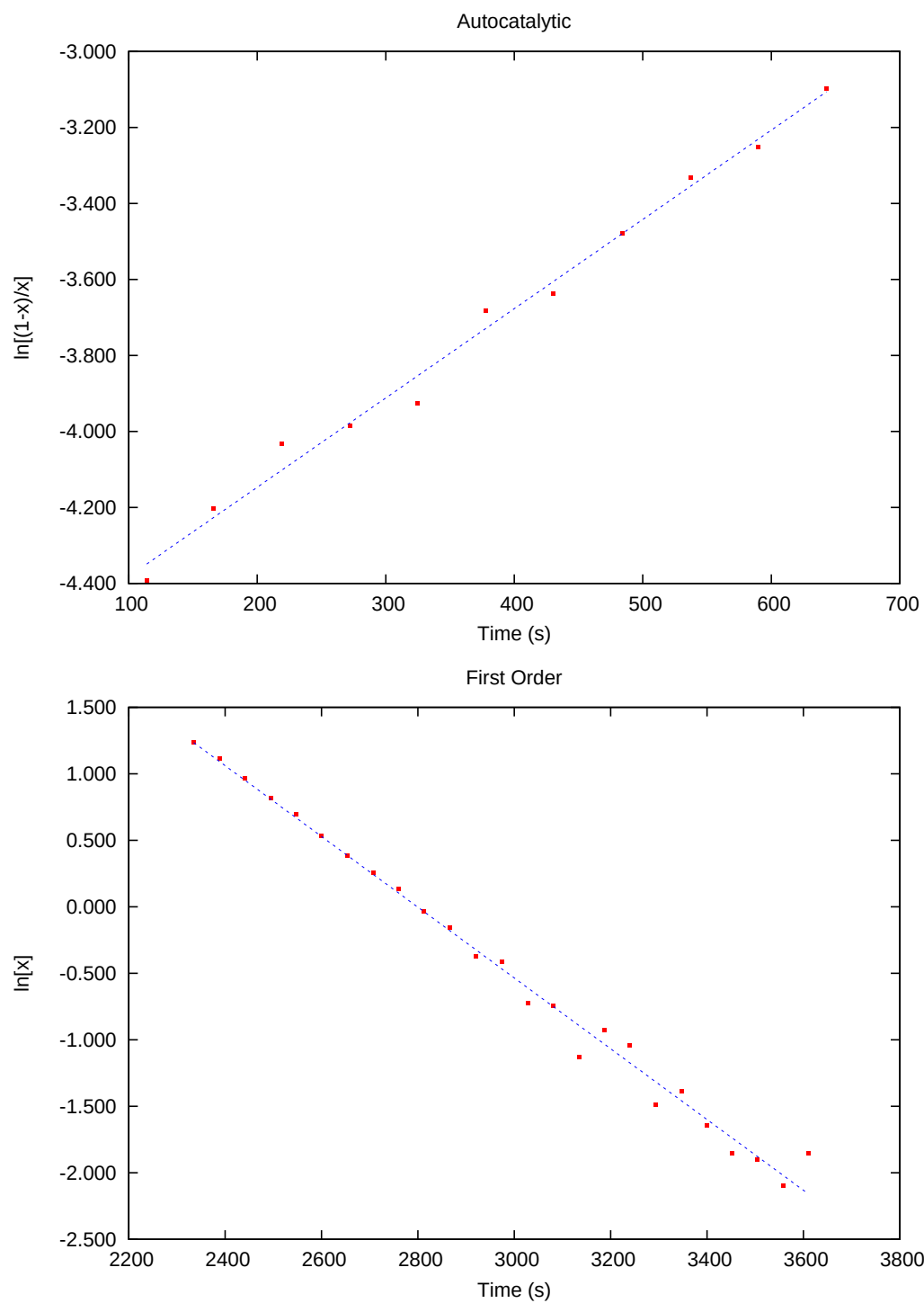
T	[Tosylate]	Autocatalytic				First Order			
/K	M	t_{min}	t_{max}	k_a	R^2	t_{min}	t_{max}	k_f	R^2
307						2590s	3526s	$-0.0022s^{-1}$	0.9845

DataSet : 1005-40b



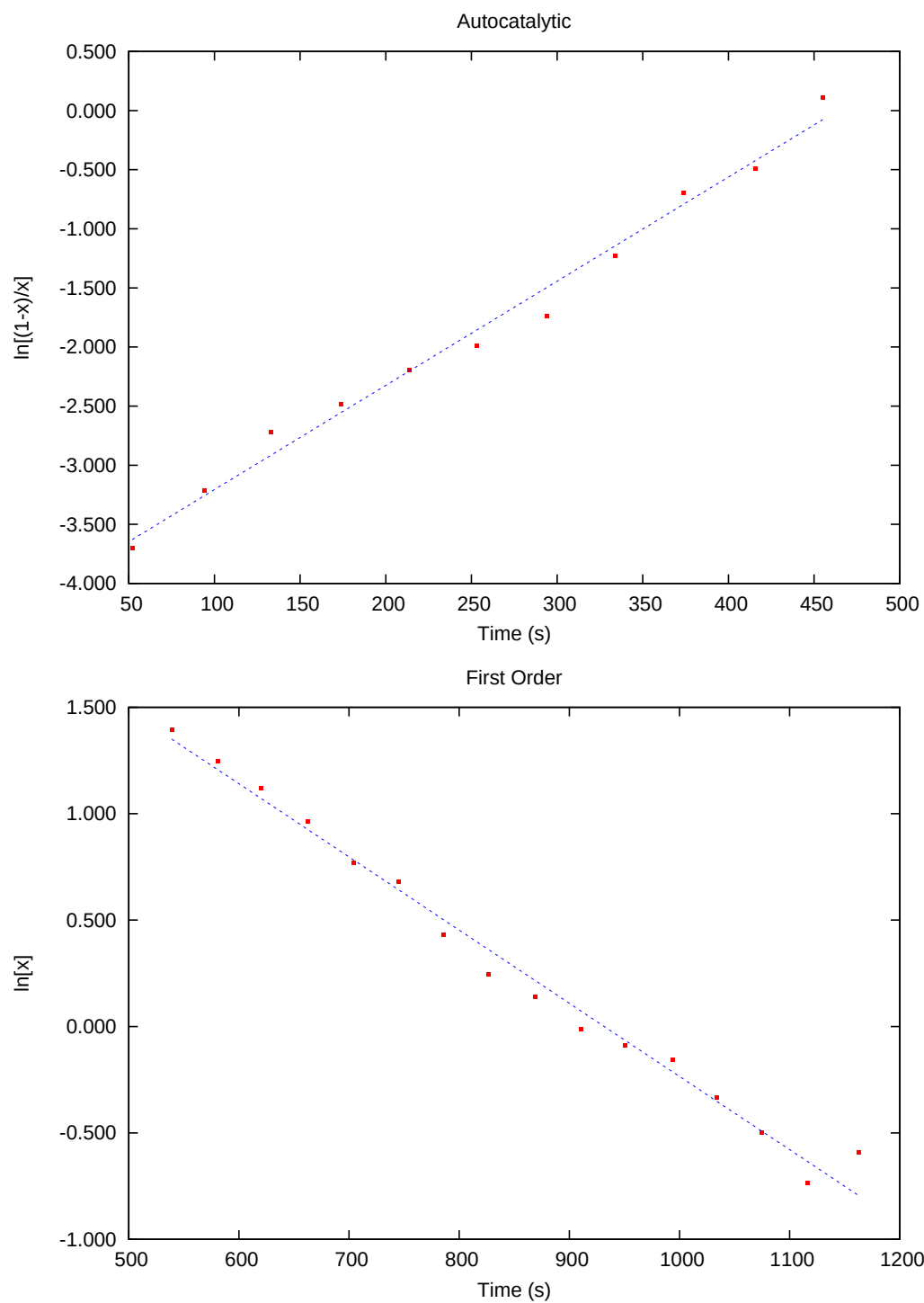
T	[Tosylate]	Autocatalytic				First Order			
/K	M	t_{min}	t_{max}	k_a	R^2	t_{min}	t_{max}	k_f	R^2
313	-1					280s	684s	$-0.0065s^{-1}$	0.9298

DataSet : 1005-36b



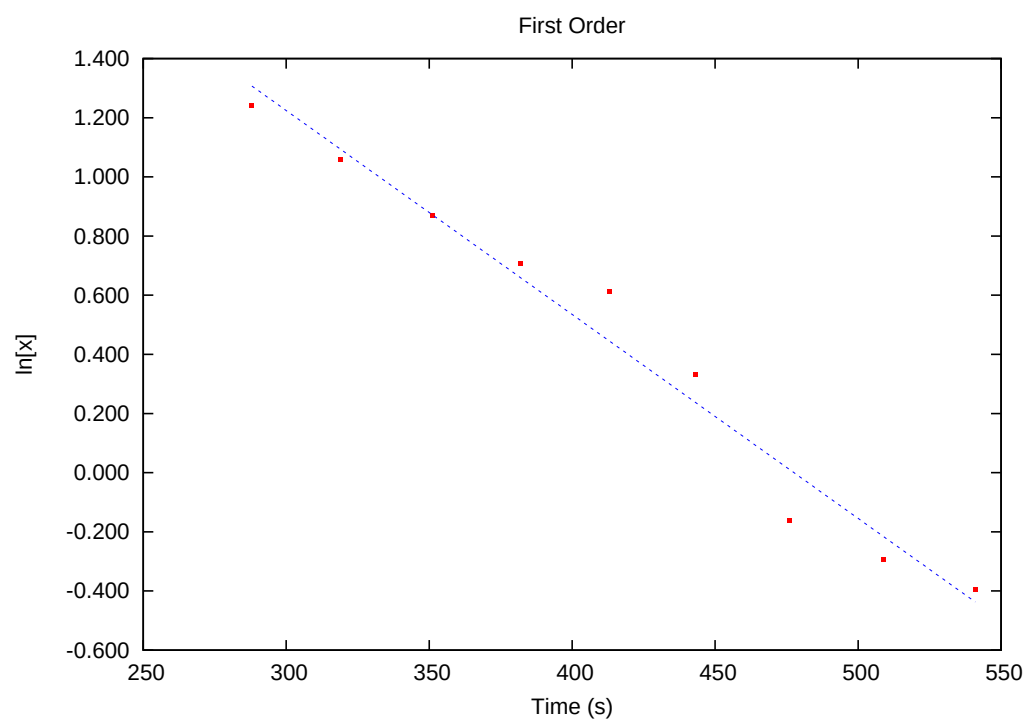
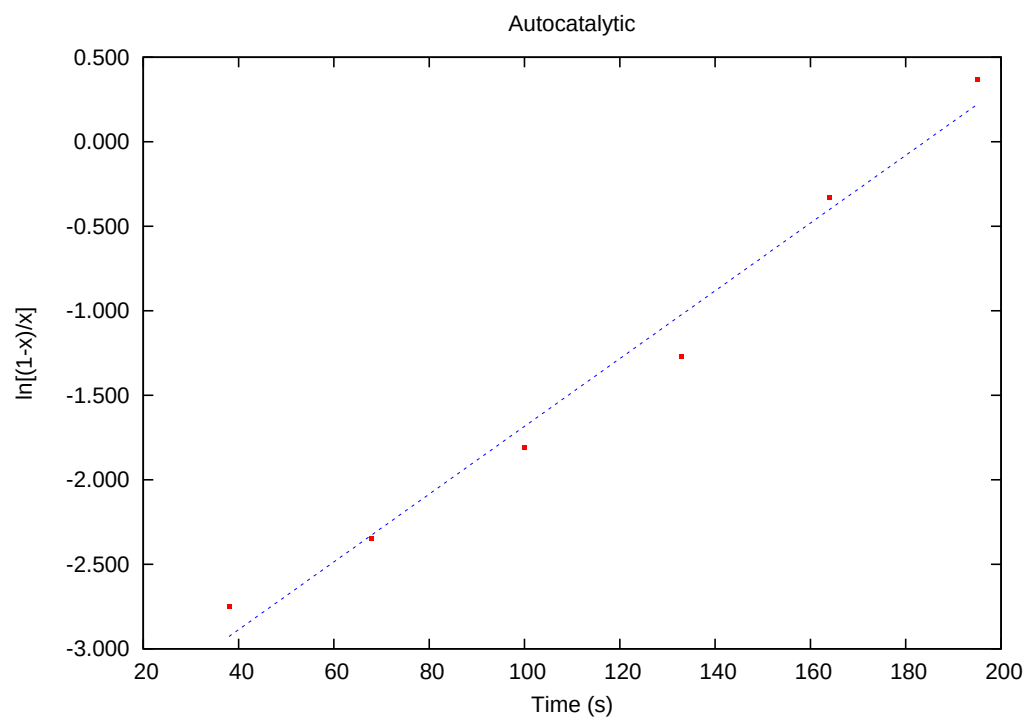
T /K	[Tosylate] M	Autocatalytic				First Order			
		t_{min}	t_{max}	k_a	R^2	t_{min}	t_{max}	k_f	R^2
309	0.0697	114s	643s	$0.4851\text{mol}^{-1}\cdot\text{s}^{-1}$	0.9904	2335s	3610s	-0.0027s^{-1}	0.9903

DataSet : 1005-38b



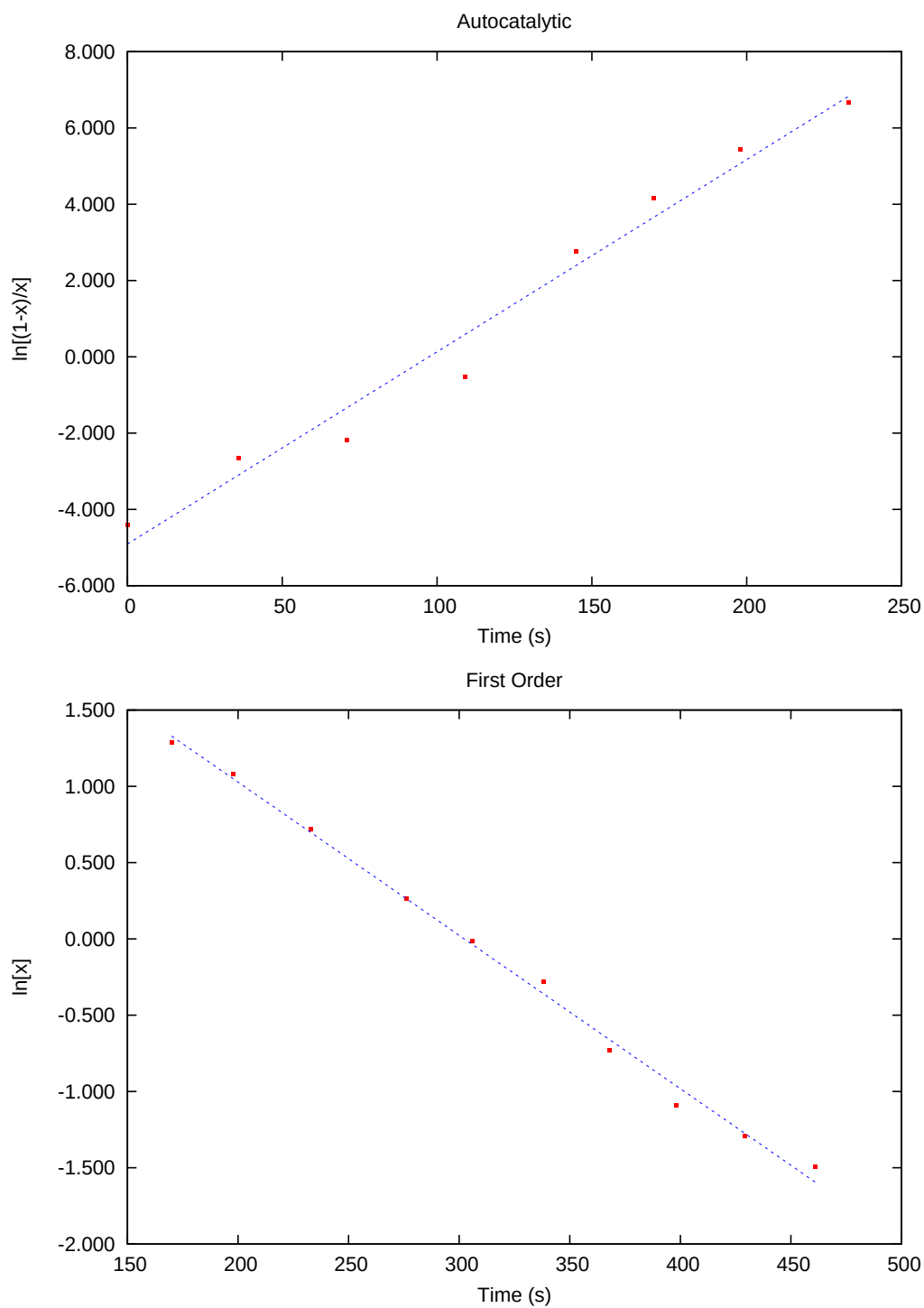
T /K	[Tosylate] M	Autocatalytic				First Order			
		t_{min}	t_{max}	k_a	R^2	t_{min}	t_{max}	k_f	R^2
311	0.0697	52s	455s	$0.4851\text{mol}^{-1}\cdot\text{s}^{-1}$	0.9871	539s	1163s	-0.0034s^{-1}	0.9862

DataSet : 1005-42b



T /K	[Tosylate] M	Autocatalytic				First Order			
		t_{min}	t_{max}	k_a	R^2	t_{min}	t_{max}	k_f	R^2
315	0.0697	38s	195s	$0.4851 \text{mol}^{-1} \cdot \text{s}^{-1}$	0.9808	288s	541s	-0.0069s^{-1}	0.972

DataSet : 1005-44b



T	[Tosylate]	Autocatalytic				First Order			
/K	M	t_{min}	t_{max}	k_a	R^2	t_{min}	t_{max}	k_f	R^2
317	0.0697	0s	233s	$0.4851\text{mol}^{-1}.\text{s}^{-1}$	0.9997	170s	461s	-0.01s^{-1}	0.9953

3.5.2 GAMESS AM1 and B3LYP data.

Table 3.2: GAMESS AM1 energy data for the modelled classical cations from the graph (See Figure 2.74 p163) at 298.15K.

node	Descriptor	E_f Ha	E + ZPVE Ha	H Ha	S cal.mol ⁻¹ K ⁻¹	G Ha	$\Delta G_{relative}$ kcal.mol ⁻¹
17	hhphhhhmmmmxx	-96.0081	-95.6385	-95.6228	118.3	-95.6790	22.1
175	hhphhhhmmxxmm	-96.0057	-95.6361	-95.6212	113.2	-95.6751	24.6
9	hhphhhhmmmmxx	-96.0050	-95.6354	-95.6196	118.6	-95.6759	24.1
131	hhphhhhmmhxxmm	-96.0026	-95.6326	-95.6169	118.5	-95.6732	25.8
12	hhphhhhmmhmmxx	-96.0061	-95.6366	-95.6208	118.9	-95.6773	23.2
5	hhphhhhmmmmhxx	-96.0018	-95.6324	-95.6165	119.2	-95.6731	25.8
-	hhphhhhmmxxhm	-96.0067	-95.6368	-95.6212	117.0	-95.6768	23.5
-	hhphhhhmmxxmh	-95.9965	-95.6260	-95.6106	116.1	-95.6658	30.4
152	hhphhhhxxhmmmm	-96.0043	-95.6344	-95.6187	117.9	-95.6748	24.8
114	hhphhhhxxmhmm	-96.0007	-95.6311	-95.6152	119.1	-95.6718	26.7
-	hhphhhhxxmmhm	-96.0053	-95.6352	-95.6197	117.4	-95.6754	24.4
-	hhphhhhxxmmmh	-95.9970	-95.6270	-95.6115	117.6	-95.6674	29.4
112	hhphhmmhmmmmxx	-96.0110	-95.6421	-95.6261	119.3	-95.6828	19.8
3	hhphhmmhxxmm	-96.0106	-95.6415	-95.6256	119.2	-95.6822	20.1
234	hhphhmmhmmmmxx	-96.0143	-95.6459	-95.6297	120.4	-95.6869	17.2
233	hhphhmmhmmhxx	-96.0130	-95.6445	-95.6282	121.3	-95.6859	17.8
260	hhphhmmhmmxxhm	-96.0147	-95.6462	-95.6308	115.6	-95.6858	17.9
158	hhphhmmhmmxxmh	-96.0106	-95.6414	-95.6256	118.5	-95.6819	20.3
155	hhphhmmhmmmmxx	-96.0142	-95.6457	-95.6295	120.1	-95.6866	17.4
54	hhphhmmhmmhxx	-96.0072	-95.6380	-95.6221	118.8	-95.6786	22.4
220	hhphhmmhxxhm	-96.0143	-95.6454	-95.6294	119.8	-95.6863	17.6
68	hhphhmmhxxmh	-96.0080	-95.6387	-95.6228	118.8	-95.6792	22.0
34	hhphhmmmmhxx	-96.0061	-95.6371	-95.6213	118.1	-95.6774	23.2
-	hhphhmmmmxxhh	-96.0050	-95.6352	-95.6198	116.2	-95.6750	24.6
18	hhphhmmxxhhmm	-96.0048	-95.6356	-95.6197	118.6	-95.6761	24.0
196	hhphhmmxxhmhm	-96.0117	-95.6429	-95.6277	115.1	-95.6824	20.0
228	hhphhmmxxhmmh	-96.0077	-95.6384	-95.6225	119.2	-95.6791	22.1
199	hhphhmmxxmhmm	-96.0111	-95.6422	-95.6261	120.2	-95.6832	19.5
117	hhphhmmxxmhmh	-96.0048	-95.6351	-95.6193	118.1	-95.6754	24.4
-	hhphhmmxxmmhh	-96.0018	-95.6321	-95.6166	116.9	-95.6721	26.4
170	hhphmhhmmmmxx	-96.0102	-95.6404	-95.6246	118.6	-95.6809	20.9
108	hhphmhhhhxxmm	-96.0094	-95.6395	-95.6237	119.3	-95.6804	21.3
25	hhphmhhmmmmxx	-96.0104	-95.6409	-95.6250	119.2	-95.6816	20.5
38	hhphmhhmmhxx	-96.0090	-95.6396	-95.6235	120.8	-95.6809	21.0
311	hhphmhhmmxxhm	-96.0097	-95.6399	-95.6240	119.6	-95.6809	21.0
184	hhphmhhmmxxmh	-96.0058	-95.6358	-95.6201	118.6	-95.6765	23.7
64	hhphmhmhmmmmxx	-96.0147	-95.6455	-95.6293	120.8	-95.6867	17.3

node	Descriptor	E_f Ha	E + ZPVE Ha	H Ha	S cal.mol ⁻¹ K ⁻¹	G Ha	$\Delta G_{relative}$ kcal.mol ⁻¹
62	hhphmhmhmhxx	-96.0074	-95.6380	-95.6219	120.9	-95.6793	21.9
290	hhphmhmhxxhm	-96.0146	-95.6451	-95.6290	120.5	-95.6863	17.6
161	hhphmhmhxxmh	-96.0078	-95.6377	-95.6219	119.6	-95.6787	22.3
119	hhphmhmhmhxx	-96.0007	-95.6307	-95.6150	117.6	-95.6709	27.2
-	hhphmhmhxxhh	-96.0008	-95.6303	-95.6150	116.3	-95.6702	27.6
144	hhphmhmhxxhmm	-95.9995	-95.6293	-95.6137	117.6	-95.6696	28.0
274	hhphmhmhxxhmm	-96.0099	-95.6401	-95.6243	118.7	-95.6807	21.1
307	hhphmhmhxxhmmh	-96.0045	-95.6344	-95.6187	117.9	-95.6748	24.8
277	hhphmhmhxxhmmh	-96.0093	-95.6393	-95.6235	119.1	-95.6800	21.5
294	hhphmhmhxxhmmh	-96.0016	-95.6314	-95.6156	118.3	-95.6718	26.6
-	hhphmhmhxxmmhh	-96.0010	-95.6307	-95.6153	116.4	-95.6706	27.4
267	hhphmhmhxxhmmh	-96.0168	-95.6484	-95.6330	115.9	-95.6881	16.4
271	hhphmhmhxxhmmh	-96.0129	-95.6442	-95.6279	121.5	-95.6856	18.0
21	hhphmhmhxxhmmh	-96.0181	-95.6493	-95.6330	122.1	-95.6910	14.6
105	hhphmhmhxxhmmh	-96.0148	-95.6456	-95.6296	120.4	-95.6868	17.3
180	hhphmhmhxxhmmh	-96.0104	-95.6416	-95.6254	120.0	-95.6824	20.0
80	hhphmhmhxxhmmh	-96.0097	-95.6404	-95.6245	119.3	-95.6812	20.8
70	hhphmhmhxxhmmh	-96.0114	-95.6427	-95.6265	120.3	-95.6836	19.2
136	hhphmhmhxxhmmh	-96.0132	-95.6440	-95.6281	119.9	-95.6850	18.4
45	hhphmhmhxxhmmh	-96.0093	-95.6402	-95.6242	119.6	-95.6811	20.8
179	hhphmhmhxxhmmh	-96.0048	-95.6353	-95.6195	118.6	-95.6758	24.1
138	hhphmhmhxxhmmh	-96.0070	-95.6374	-95.6216	118.6	-95.6780	22.8
206	hhphmhmhxxhmmh	-96.0063	-95.6367	-95.6209	118.9	-95.6774	23.2
142	hhphmhmhxxhmmh	-96.0073	-95.6375	-95.6215	119.7	-95.6784	22.5
59	hhphmhmhxxhmmh	-96.0082	-95.6384	-95.6225	119.9	-95.6794	21.9
188	hhphmhmhxxhmmh	-96.0117	-95.6424	-95.6263	120.6	-95.6836	19.3
127	hhphmhmhxxhmmh	-96.0103	-95.6413	-95.6249	122.7	-95.6832	19.5
321	hhphmhmhxxhmmh	-96.0120	-95.6421	-95.6261	120.1	-95.6832	19.5
303	hhphmhmhxxhmmh	-96.0100	-95.6400	-95.6241	119.7	-95.6809	20.9
148	hhphmhmhxxhmmh	-96.0118	-95.6425	-95.6262	121.5	-95.6840	19.0
210	hhphmhmhxxhmmh	-96.0046	-95.6353	-95.6190	121.6	-95.6768	23.5
319	hhphmhmhxxhmmh	-96.0127	-95.6428	-95.6268	120.0	-95.6838	19.1
301	hhphmhmhxxhmmh	-96.0077	-95.6376	-95.6216	120.0	-95.6786	22.4
122	hhphmhmhxxhmmh	-96.0024	-95.6325	-95.6166	119.8	-95.6735	25.6
-	hhphmhmhxxhmmh	-96.0049	-95.6342	-95.6187	116.8	-95.6742	25.1
72	hhphmhmhxxhmmh	-96.0035	-95.6335	-95.6177	118.8	-95.6742	25.2
320	hhphmhmhxxhmmh	-96.0117	-95.6421	-95.6260	120.5	-95.6833	19.5
292	hhphmhmhxxhmmh	-96.0087	-95.6389	-95.6229	120.3	-95.6800	21.5
318	hhphmhmhxxhmmh	-96.0113	-95.6417	-95.6256	120.7	-95.6830	19.7
288	hhphmhmhxxhmmh	-96.0060	-95.6361	-95.6201	119.9	-95.6770	23.4

node	Descriptor	E_f Ha	E + ZPVE Ha	H Ha	S cal.mol ⁻¹ K ⁻¹	G Ha	$\Delta G_{relative}$ kcal.mol ⁻¹
-	hhpmhxxmmhh	-96.0038	-95.6337	-95.6189	113.0	-95.6726	26.2
281	hhpmhmhhhmxx	-96.0134	-95.6447	-95.6285	120.6	-95.6858	17.9
309	hhpmhmhhmhhxx	-96.0095	-95.6407	-95.6244	121.2	-95.6820	20.3
60	hhpmhmhhxxhm	-96.0153	-95.6464	-95.6302	121.7	-95.6880	16.5
27	hhpmhmhhxxmh	-96.0137	-95.6445	-95.6284	120.6	-95.6857	17.9
82	hhpmhmhmhhxx	-96.0110	-95.6422	-95.6260	120.2	-95.6831	19.6
242	hhpmhmhmxxhh	-96.0123	-95.6429	-95.6269	119.8	-95.6838	19.1
223	hhpmhmhmhhxx	-96.0078	-95.6386	-95.6226	118.6	-95.6790	22.1
275	hhpmhmhmxxhh	-96.0118	-95.6422	-95.6272	114.3	-95.6815	20.6
141	hhpmhmxxhhhm	-96.0100	-95.6409	-95.6247	120.5	-95.6820	20.3
58	hhpmhmxxhhmh	-96.0074	-95.6379	-95.6219	120.0	-95.6789	22.2
222	hhpmhmxxhmhh	-96.0085	-95.6388	-95.6229	120.1	-95.6799	21.5
217	hhpmhmxxmhhh	-96.0077	-95.6376	-95.6218	118.8	-95.6782	22.6
63	hhpmmhhhhmxx	-96.0068	-95.6367	-95.6208	119.1	-95.6774	23.1
169	hhpmmhhhhmhhxx	-96.0038	-95.6338	-95.6178	120.1	-95.6749	24.7
46	hhpmmhhhhxxhm	-96.0096	-95.6391	-95.6233	119.2	-95.6800	21.5
124	hhpmmhhhhxxmh	-96.0097	-95.6396	-95.6237	119.4	-95.6804	21.3
100	hhpmmhhhmhhxx	-95.9986	-95.6284	-95.6125	118.6	-95.6689	28.5
153	hhpmmhhmxxhh	-96.0031	-95.6327	-95.6170	118.7	-95.6734	25.7
106	hhpmmhmhhhhxx	-96.0017	-95.6313	-95.6155	118.7	-95.6719	26.6
197	hhpmmhmhxxhh	-96.0094	-95.6391	-95.6233	118.9	-95.6798	21.7
85	hhpmmhxxhhhm	-96.0006	-95.6299	-95.6142	118.0	-95.6703	27.6
166	hhpmmhxxhhmh	-95.9980	-95.6274	-95.6117	118.9	-95.6682	28.9
132	hhpmmhxxhmhh	-96.0028	-95.6319	-95.6164	117.1	-95.6720	26.5
130	hhpmmhxxmhhh	-96.0025	-95.6320	-95.6163	118.3	-95.6725	26.2
28	hhpmmmhhhhhxx	-96.0046	-95.6351	-95.6191	118.9	-95.6756	24.3
6	hhpmmmhxxhh	-96.0122	-95.6427	-95.6267	120.2	-95.6838	19.1
24	hhpmmmxhhhhh	-96.0003	-95.6299	-95.6143	118.1	-95.6704	27.6
190	hhpxxhhhhmmm	-96.0097	-95.6394	-95.6236	118.8	-95.6800	21.5
76	hhpxxhhhmhmm	-96.0070	-95.6366	-95.6208	119.1	-95.6773	23.2
165	hhpxxhhhmhm	-96.0147	-95.6445	-95.6286	119.2	-95.6853	18.2
191	hhpxxhhhmhmh	-96.0128	-95.6426	-95.6268	118.8	-95.6832	19.5
123	hhpxxhhmmhmm	-96.0008	-95.6303	-95.6146	118.3	-95.6708	27.3
232	hhpxxhhmhmhm	-96.0088	-95.6384	-95.6226	118.6	-95.6790	22.1
75	hhpxxhhmmhmh	-96.0116	-95.6412	-95.6254	118.5	-95.6817	20.4
172	hhpxxhhmmhmm	-96.0112	-95.6410	-95.6250	119.9	-95.6820	20.3
51	hhpxxhhmmhmh	-96.0115	-95.6411	-95.6252	118.8	-95.6817	20.5
14	hhpxxhhmmhhh	-96.0109	-95.6404	-95.6248	117.5	-95.6807	21.1
84	hhpxxhmhhmm	-96.0038	-95.6332	-95.6174	118.6	-95.6738	25.4
149	hhpxxhmhhmm	-96.0173	-95.6475	-95.6313	121.0	-95.6887	16.0

node	Descriptor	E_f Ha	E + ZPVE Ha	H Ha	S cal.mol ⁻¹ K ⁻¹	G Ha	$\Delta G_{relative}$ kcal.mol ⁻¹
49	hhpxxhmhhmmh	-96.0166	-95.6466	-95.6305	120.3	-95.6876	16.7
168	hhpxxhmhmhmm	-96.0146	-95.6446	-95.6285	121.0	-95.6860	17.7
31	hhpxxhmhmhmm	-96.0095	-95.6395	-95.6234	120.4	-95.6807	21.1
22	hhpxxhmhmmhh	-96.0153	-95.6451	-95.6293	118.5	-95.6856	18.0
143	hhpxxhmmhhhm	-96.0030	-95.6325	-95.6167	118.7	-95.6731	25.8
101	hhpxxhmmhhmh	-96.0022	-95.6314	-95.6158	117.6	-95.6717	26.7
10	hhpxxhmmhmhh	-96.0075	-95.6369	-95.6213	117.9	-95.6773	23.2
7	hhpxxhmmhbbb	-96.0075	-95.6368	-95.6212	117.6	-95.6771	23.3
23	hhpxxmhhhhmm	-96.0062	-95.6367	-95.6207	119.6	-95.6775	23.1
315	hhpxxmhhhhmm	-96.0152	-95.6458	-95.6296	120.7	-95.6870	17.1
285	hhpxxmhhhhmmh	-96.0170	-95.6476	-95.6314	120.3	-95.6886	16.1
268	hhpxxmhhmhmm	-96.0151	-95.6457	-95.6295	121.5	-95.6872	17.0
252	hhpxxmhhmhmmh	-96.0140	-95.6447	-95.6285	120.8	-95.6859	17.8
129	hhpxxmhhmmhh	-96.0162	-95.6468	-95.6308	119.7	-95.6877	16.7
202	hhpxxmhmhhhm	-96.0072	-95.6376	-95.6215	120.7	-95.6788	22.2
57	hhpxxmhmhhmh	-96.0101	-95.6407	-95.6245	120.4	-95.6817	20.4
67	hhpxxmhmhmhh	-96.0109	-95.6410	-95.6252	119.1	-95.6817	20.4
133	hhpxxmhmhbbb	-96.0131	-95.6435	-95.6274	120.5	-95.6846	18.6
71	hhpxxmmhhhhm	-96.0121	-95.6427	-95.6265	120.9	-95.6839	19.0
164	hhpxxmmhhhhmh	-96.0118	-95.6423	-95.6262	120.3	-95.6833	19.4
253	hhpxxmmhhmhmm	-96.0170	-95.6473	-95.6313	119.8	-95.6882	16.3
213	hhpxxmmhmhbbb	-96.0138	-95.6441	-95.6290	114.8	-95.6835	19.3
29	hhpxxmmhbbb	-96.0049	-95.6347	-95.6190	117.6	-95.6749	24.7
140	hmphhhhmmxx	-96.0324	-95.6634	-95.6473	120.3	-95.7045	6.1
167	hmphhhhhxxmm	-96.0317	-95.6624	-95.6464	120.3	-95.7036	6.7
19	hmphhhhmmhxx	-96.0367	-95.6682	-95.6520	121.9	-95.7099	2.8
77	hmphhhhmmhxx	-96.0362	-95.6677	-95.6512	123.0	-95.7097	2.9
259	hmphhhhmxxhm	-96.0360	-95.6671	-95.6509	121.5	-95.7086	3.5
313	hmphhhhmxxmh	-96.0321	-95.6627	-95.6467	120.1	-95.7038	6.6
48	hmphhhmhmmxx	-96.0375	-95.6690	-95.6526	122.6	-95.7109	2.1
74	hmphhhmhmhxx	-96.0310	-95.6623	-95.6459	122.7	-95.7042	6.3
262	hmphhhmhxxhm	-96.0368	-95.6678	-95.6525	115.7	-95.7075	4.2
279	hmphhhmhxxmh	-96.0302	-95.6608	-95.6457	115.1	-95.7004	8.7
146	hmphhhmmhxxx	-96.0303	-95.6615	-95.6453	121.9	-95.7032	6.9
-	hmphhhmmxxhh	-96.0275	-95.6578	-95.6422	117.5	-95.6980	10.2
90	hmphhhxxhhmm	-96.0294	-95.6605	-95.6443	121.9	-95.7023	7.5
302	hmphhhxxhmhm	-96.0358	-95.6669	-95.6507	122.0	-95.7086	3.5
207	hmphhhxxhmmh	-96.0316	-95.6624	-95.6463	121.3	-95.7040	6.5
276	hmphhhxxmhmm	-96.0357	-95.6668	-95.6505	122.0	-95.7085	3.6
139	hmphhhxxmhmmh	-96.0292	-95.6599	-95.6438	121.5	-95.7015	8.0

node	Descriptor Ha	E_f Ha	E + ZPVE Ha	H cal.mol ⁻¹ K ⁻¹	S Ha	G kcal.mol ⁻¹	$\Delta G_{relative}$
-	hmpphhxxmmhh	-96.0255	-95.6556	-95.6400	118.5	-95.6963	11.3
299	hmpphmhhhhmxx	-96.0394	-95.6717	-95.6552	123.0	-95.7136	0.4
312	hmpphmhhhmhxx	-96.0362	-95.6683	-95.6517	123.2	-95.7102	2.5
173	hmpphmhhxxhm	-96.0406	-95.6724	-95.6560	122.7	-95.7143	0.0
236	hmpphmhhxxmh	-96.0372	-95.6690	-95.6526	122.8	-95.7109	2.1
257	hmpphmhmhhxx	-96.0377	-95.6698	-95.6533	122.9	-95.7117	1.6
185	hmpphmhmxxhh	-96.0361	-95.6675	-95.6522	115.7	-95.7072	4.5
298	hmpphmmhhhhxx	-96.0353	-95.6671	-95.6508	121.3	-95.7084	3.7
250	hmpphmmhxxhh	-96.0357	-95.6669	-95.6518	115.1	-95.7064	4.9
231	hmpphmxxhhhm	-96.0366	-95.6682	-95.6518	122.7	-95.7101	2.6
255	hmpphmxxhhmh	-96.0330	-95.6646	-95.6482	123.1	-95.7067	4.8
251	hmpphmxxhmhh	-96.0331	-95.6644	-95.6482	121.1	-95.7058	5.3
293	hmpphmxxmhhh	-96.0328	-95.6640	-95.6478	121.9	-95.7057	5.4
26	hmpmhnhhhmxx	-96.0382	-95.6697	-95.6532	122.5	-95.7114	1.8
91	hmpmhnhhhmxx	-96.0351	-95.6663	-95.6498	123.3	-95.7084	3.7
52	hmpmhnhhhxxhm	-96.0386	-95.6696	-95.6533	122.9	-95.7117	1.6
214	hmpmhnhhhxxmh	-96.0354	-95.6660	-95.6498	121.6	-95.7076	4.2
32	hmpmhnhhhmhhxx	-96.0327	-95.6639	-95.6476	121.9	-95.7055	5.5
81	hmpmhnhhmxxhh	-96.0301	-95.6603	-95.6445	119.5	-95.7013	8.2
110	hmpmhnmhhhhxx	-96.0349	-95.6662	-95.6498	122.8	-95.7081	3.9
225	hmpmhnmhxxhh	-96.0350	-95.6655	-95.6503	115.4	-95.7052	5.7
41	hmpmhnhxxhhhm	-96.0333	-95.6643	-95.6481	121.9	-95.7060	5.2
194	hmpmhnhxxhhmh	-96.0285	-95.6592	-95.6431	121.0	-95.7006	8.6
69	hmpmhnhxxhmhh	-96.0302	-95.6605	-95.6447	119.6	-95.7015	8.0
203	hmpmhnhxxmhhh	-96.0301	-95.6606	-95.6445	121.3	-95.7021	7.6
212	hmpmhmmhhhhxx	-96.0366	-95.6685	-95.6520	122.1	-95.7101	2.6
86	hmpmhmmhxxhh	-96.0390	-95.6703	-95.6540	122.4	-95.7121	1.4
115	hmpmhmmxxhhhh	-96.0309	-95.6617	-95.6456	120.9	-95.7031	7.0
120	hmpmhnhhhhhmxx	-96.0365	-95.6679	-95.6514	123.3	-95.7100	2.7
88	hmpmhnhhhhmxx	-96.0332	-95.6645	-95.6480	124.2	-95.7070	4.6
102	hmpmhnhhhxxhm	-96.0377	-95.6688	-95.6524	123.3	-95.7109	2.1
186	hmpmhnhhhxxmh	-96.0362	-95.6670	-95.6507	122.7	-95.7090	3.3
50	hmpmhnhhhmhhxx	-96.0351	-95.6665	-95.6500	123.3	-95.7085	3.6
154	hmpmhnhhhmxxhh	-96.0348	-95.6653	-95.6492	121.1	-95.7067	4.7
189	hmpmhnhmhhhhxx	-96.0328	-95.6640	-95.6475	123.1	-95.7060	5.2
151	hmpmhnhmhhxxhh	-96.0356	-95.6663	-95.6501	122.0	-95.7081	3.9
37	hmpmhnhxxhhhm	-96.0364	-95.6673	-95.6509	122.7	-95.7092	3.2
145	hmpmhnhxxhhmh	-96.0339	-95.6646	-95.6483	123.0	-95.7067	4.8
176	hmpmhnhxxhmhh	-96.0344	-95.6648	-95.6488	121.0	-95.7063	5.0
218	hmpmhnhxxmhhh	-96.0343	-95.6649	-95.6487	121.8	-95.7066	4.8

node	Descriptor	E_f Ha	E + ZPVE Ha	H Ha	S cal.mol ⁻¹ K ⁻¹	G Ha	$\Delta G_{relative}$ kcal.mol ⁻¹
66	hmpmhmhhhhxx	-96.0342	-95.6659	-95.6495	121.8	-95.7074	4.3
126	hmpmhmhhxxhh	-96.0386	-95.6703	-95.6538	124.6	-95.7130	0.8
193	hmpmhmxxhhhh	-96.0335	-95.6644	-95.6481	122.2	-95.7062	5.1
2	hmpmmhhhhhhxx	-96.0281	-95.6587	-95.6426	121.0	-95.7001	8.9
8	hmpmmhhhhxxhh	-96.0341	-95.6646	-95.6485	121.6	-95.7063	5.0
4	hmpmmhxxhhhh	-96.0268	-95.6570	-95.6410	120.3	-95.6982	10.1
94	hmpxxhhhhhhmm	-96.0296	-95.6603	-95.6441	121.5	-95.7018	7.8
264	hmpxxhhhhhmhm	-96.0374	-95.6682	-95.6518	122.8	-95.7101	2.6
308	hmpxxhhhhmmhm	-96.0392	-95.6699	-95.6535	122.2	-95.7116	1.7
118	hmpxxhhhmhmhm	-96.0379	-95.6687	-95.6522	123.9	-95.7111	2.0
286	hmpxxhhhmhmhm	-96.0370	-95.6679	-95.6523	118.7	-95.7087	3.5
53	hmpxxhhhmhmhm	-96.0376	-95.6683	-95.6521	122.3	-95.7102	2.6
306	hmpxxhhmhhhmhm	-96.0306	-95.6613	-95.6450	122.1	-95.7030	7.1
291	hmpxxhhmhhhmhm	-96.0335	-95.6642	-95.6479	122.4	-95.7061	5.1
55	hmpxxhhmhmhmhm	-96.0332	-95.6636	-95.6475	121.4	-95.7052	5.7
224	hmpxxhhmmhhhh	-96.0361	-95.6665	-95.6503	121.3	-95.7080	4.0
300	hmpxxhmhhhhhm	-96.0368	-95.6679	-95.6523	118.3	-95.7085	3.6
316	hmpxxhmhhhhhm	-96.0362	-95.6671	-95.6516	117.4	-95.7074	4.3
201	hmpxxhmhhhmhm	-96.0407	-95.6716	-95.6552	122.7	-95.7134	0.5
240	hmpxxhmhmhhhh	-96.0383	-95.6688	-95.6526	121.7	-95.7104	2.4
113	hmpxxhmmhhhhh	-96.0301	-95.6602	-95.6443	119.8	-95.7012	8.2
137	hmpxxmhhhhhhm	-96.0344	-95.6658	-95.6492	123.4	-95.7079	4.0
221	hmpxxmhhhhhmhm	-96.0360	-95.6677	-95.6520	117.4	-95.7078	4.1
227	hmpxxmhhhhmhmhm	-96.0384	-95.6700	-95.6544	117.5	-95.7102	2.5
287	hmpxxmhhmhhhh	-96.0386	-95.6698	-95.6534	122.1	-95.7114	1.8
205	hmpxxmhmhhhhh	-96.0323	-95.6630	-95.6468	120.7	-95.7042	6.3
238	hmpxxmmhhhhhh	-96.0360	-95.6669	-95.6507	121.4	-95.7083	3.7
42	mhpshhhhhmmxx	-96.0096	-95.6405	-95.6247	118.2	-95.6808	21.0
13	mhpshhhhhxxmm	-96.0077	-95.6389	-95.6228	120.1	-95.6799	21.6
254	mhpshhhhmhmxx	-96.0151	-95.6468	-95.6306	121.1	-95.6881	16.4
178	mhpshhhhmhmhm	-96.0129	-95.6444	-95.6281	120.6	-95.6854	18.1
174	mhpshhhhmxxhm	-96.0121	-95.6435	-95.6282	115.4	-95.6830	19.6
247	mhpshhhhmxxmh	-96.0084	-95.6390	-95.6232	118.9	-95.6796	21.7
246	mhpshhhmhmhmxx	-96.0154	-95.6472	-95.6307	122.1	-95.6887	16.0
43	mhpshhhmhmhmhm	-96.0075	-95.6388	-95.6227	119.6	-95.6795	21.8
177	mhpshhhmhmhmhm	-96.0124	-95.6436	-95.6275	120.1	-95.6846	18.6
97	mhpshhhmhmhmhm	-96.0062	-95.6369	-95.6210	119.4	-95.6777	22.9
93	mhpshhhmmhhxxx	-96.0083	-95.6395	-95.6235	119.1	-95.6801	21.4
-	mhpshhhmmxxhh	-96.0031	-95.6337	-95.6181	117.1	-95.6737	25.5
1	mhpshhhxxhhmm	-96.0082	-95.6393	-95.6233	119.4	-95.6800	21.5

node	Descriptor	E_f Ha	E + ZPVE Ha	H Ha	S cal.mol ⁻¹ K ⁻¹	G Ha	$\Delta G_{relative}$ kcal.mol ⁻¹
241	mhpshhxxhmhm	-96.0152	-95.6464	-95.6312	114.9	-95.6857	17.9
181	mhpshhxxhmmh	-96.0107	-95.6416	-95.6256	119.7	-95.6825	20.0
198	mhpshhxxmhhm	-96.0132	-95.6444	-95.6283	120.1	-95.6854	18.1
56	mhpshhxxmhmh	-96.0066	-95.6373	-95.6214	119.1	-95.6780	22.8
-	mhpshhxxmmhh	-96.0039	-95.6344	-95.6188	117.2	-95.6745	24.9
273	mhpshmhmmhxx	-96.0176	-95.6500	-95.6336	121.0	-95.6911	14.6
204	mhpshmhmmhxx	-96.0127	-95.6447	-95.6285	120.4	-95.6857	18.0
147	mhpshmhxxhm	-96.0168	-95.6490	-95.6334	116.9	-95.6889	15.9
103	mhpshmhxxmh	-96.0136	-95.6453	-95.6300	115.1	-95.6847	18.6
258	mhpshmhmmhxx	-96.0159	-95.6482	-95.6318	120.8	-95.6892	15.7
265	mhpshmhmmxhh	-96.0126	-95.6443	-95.6281	120.8	-95.6855	18.1
182	mhpshmmhmmhxx	-96.0131	-95.6448	-95.6286	119.3	-95.6853	18.2
208	mhpshmmhxxhh	-96.0119	-95.6432	-95.6272	119.3	-95.6839	19.1
171	mhpshmmxxhmm	-96.0161	-95.6480	-95.6316	121.5	-95.6894	15.6
95	mhpshmmxxhmm	-96.0122	-95.6438	-95.6276	120.8	-95.6850	18.4
278	mhpshmmxxmhh	-96.0130	-95.6448	-95.6294	115.6	-95.6843	18.8
230	mhpshmmxxmhh	-96.0108	-95.6420	-95.6260	119.1	-95.6826	19.9
272	mhpshmmhmmhxx	-96.0175	-95.6490	-95.6327	121.1	-95.6902	15.1
295	mhpshmmhmmhxx	-96.0124	-95.6437	-95.6275	120.7	-95.6848	18.5
209	mhpshmmhxxhm	-96.0157	-95.6468	-95.6314	116.6	-95.6868	17.3
235	mhpshmmhxxmh	-96.0125	-95.6434	-95.6273	121.1	-95.6848	18.5
310	mhpshmmhmmhxx	-96.0120	-95.6435	-95.6272	120.8	-95.6846	18.6
266	mhpshmmhmmxhh	-96.0075	-95.6380	-95.6221	119.8	-95.6790	22.1
304	mhpshmmhmmhxx	-96.0136	-95.6451	-95.6287	121.8	-95.6865	17.4
305	mhpshmmhmmxhh	-96.0119	-95.6427	-95.6266	120.7	-95.6840	19.0
150	mhpshmmhmmhmm	-96.0138	-95.6448	-95.6286	120.7	-95.6859	17.8
215	mhpshmmhmmhmm	-96.0086	-95.6394	-95.6234	119.3	-95.6801	21.4
162	mhpshmmhmmhmm	-96.0113	-95.6417	-95.6258	119.0	-95.6824	20.0
229	mhpshmmhmmhmm	-96.0090	-95.6395	-95.6237	118.7	-95.6801	21.4
243	mhpshmmhmmhmm	-96.0157	-95.6476	-95.6313	120.6	-95.6886	16.1
256	mhpshmmhmmhmm	-96.0166	-95.6483	-95.6328	116.5	-95.6882	16.4
269	mhpshmmhmmhmm	-96.0119	-95.6432	-95.6271	120.4	-95.6843	18.8
98	mhpshmmhmmhmm	-96.0148	-95.6463	-95.6298	122.0	-95.6878	16.6
245	mhpshmmhmmhmm	-96.0098	-95.6410	-95.6247	121.5	-95.6824	20.0
121	mhpshmmhmmhmm	-96.0135	-95.6448	-95.6283	123.0	-95.6867	17.3
65	mhpshmmhmmhmm	-96.0123	-95.6432	-95.6278	116.0	-95.6830	19.7
297	mhpshmmhmmhmm	-96.0133	-95.6450	-95.6285	122.2	-95.6865	17.4
244	mhpshmmhmmhmm	-96.0110	-95.6416	-95.6255	120.8	-95.6829	19.7
314	mhpshmmhmmhmm	-96.0107	-95.6419	-95.6256	121.0	-95.6831	19.6
239	mhpshmmhmmhmm	-96.0115	-95.6421	-95.6269	115.1	-95.6816	20.5

node	Descriptor	E_f Ha	E + ZPVE Ha	H Ha	S cal.mol ⁻¹ K ⁻¹	G Ha	$\Delta G_{relative}$ kcal.mol ⁻¹
47	mhpmhxxhxxhmm	-96.0156	-95.6469	-95.6305	122.0	-95.6884	16.2
33	mhpmhxxhxxhmmh	-96.0128	-95.6436	-95.6273	120.8	-95.6847	18.5
261	mhpmhxxhxxhmmh	-96.0141	-95.6449	-95.6296	115.4	-95.6844	18.7
289	mhpmhxxhxxhmmh	-96.0121	-95.6425	-95.6265	120.1	-95.6836	19.3
159	mhpmhxxhxxhmmh	-96.0124	-95.6442	-95.6279	120.9	-95.6853	18.2
195	mhpmhxxhxxhmmh	-96.0152	-95.6469	-95.6314	117.1	-95.6870	17.1
216	mhpmhxxhxxhmmh	-96.0134	-95.6444	-95.6282	121.0	-95.6857	17.9
78	mhpmmhxxhxxhmm	-96.0070	-95.6376	-95.6215	119.8	-95.6784	22.5
187	mhpmmhxxhxxhmm	-96.0111	-95.6421	-95.6267	116.4	-95.6819	20.3
109	mhpmmhxxhxxhmm	-96.0073	-95.6376	-95.6216	119.6	-95.6784	22.5
0	mhpmmhxxhxxhmm	-96.0093	-95.6401	-95.6239	120.7	-95.6813	20.7
107	mhpmmhxxhxxhmm	-96.0178	-95.6487	-95.6324	121.5	-95.6901	15.2
111	mhpmmhxxhxxhmm	-96.0196	-95.6504	-95.6342	120.7	-95.6915	14.3
104	mhpmmhxxhxxhmm	-96.0166	-95.6473	-95.6310	121.8	-95.6889	15.9
20	mhpmmhxxhxxhmm	-96.0159	-95.6463	-95.6303	120.1	-95.6873	16.9
163	mhpmmhxxhxxhmm	-96.0174	-95.6479	-95.6320	119.3	-95.6887	16.1
211	mhpmmhxxhxxhmm	-96.0111	-95.6419	-95.6256	120.9	-95.6831	19.6
128	mhpmmhxxhxxhmm	-96.0141	-95.6449	-95.6287	120.9	-95.6861	17.7
89	mhpmmhxxhxxhmm	-96.0145	-95.6449	-95.6289	119.5	-95.6857	17.9
61	mhpmmhxxhxxhmm	-96.0155	-95.6457	-95.6298	119.6	-95.6866	17.4
40	mhpmmhxxhxxhmm	-96.0170	-95.6481	-95.6316	122.5	-95.6898	15.4
39	mhpmmhxxhxxhmm	-96.0163	-95.6471	-95.6308	121.2	-95.6884	16.3
92	mhpmmhxxhxxhmm	-96.0216	-95.6524	-95.6362	121.4	-95.6938	12.8
15	mhpmmhxxhxxhmm	-96.0174	-95.6477	-95.6317	120.0	-95.6887	16.0
125	mhpmmhxxhxxhmm	-96.0110	-95.6412	-95.6253	119.1	-95.6819	20.3
79	mhpmmhxxhxxhmm	-96.0150	-95.6467	-95.6301	123.0	-95.6885	16.2
192	mhpmmhxxhxxhmm	-96.0167	-95.6480	-95.6317	121.0	-95.6892	15.8
317	mhpmmhxxhxxhmm	-96.0198	-95.6511	-95.6347	121.1	-95.6923	13.8
284	mhpmmhxxhxxhmm	-96.0182	-95.6491	-95.6330	120.5	-95.6902	15.1
282	mhpmmhxxhxxhmm	-96.0138	-95.6449	-95.6286	121.3	-95.6862	17.6
237	mhpmmhxxhxxhmm	-96.0173	-95.6481	-95.6319	120.2	-95.6891	15.8
157	mmpmhhxxhxxhmm	-96.0388	-95.6711	-95.6545	122.8	-95.7129	0.9
83	mmpmhhxxhxxhmm	-96.0347	-95.6665	-95.6501	121.8	-95.7080	3.9
36	mmpmhhxxhxxhmm	-96.0367	-95.6683	-95.6528	116.6	-95.7082	3.8
156	mmpmhhxxhxxhmm	-96.0335	-95.6647	-95.6495	115.3	-95.7042	6.3
280	mmpmhhxxhxxhmm	-96.0382	-95.6705	-95.6539	123.3	-95.7124	1.2
160	mmpmhhxxhxxhmm	-96.0325	-95.6636	-95.6476	120.3	-95.7047	6.0
263	mmpmhhxxhxxhmm	-96.0363	-95.6683	-95.6518	122.6	-95.7101	2.6
183	mmpmhhxxhxxhmm	-96.0329	-95.6643	-95.6482	120.7	-95.7055	5.5
16	mmpmhhxxhxxhmm	-96.0397	-95.6716	-95.6551	123.2	-95.7136	0.4

node	Descriptor	E_f Ha	E + ZPVE Ha	H Ha	S cal.mol ⁻¹ K ⁻¹	G Ha	$\Delta G_{relative}$ kcal.mol ⁻¹
87	mmphhxhxxhhmh	-96.0358	-95.6674	-95.6510	122.5	-95.7092	3.2
96	mmphhxhxxhmhh	-96.0358	-95.6671	-95.6510	121.2	-95.7085	3.6
116	mmphhxhxxmhhh	-96.0343	-95.6655	-95.6494	121.2	-95.7070	4.6
226	mmphhmhhhhx	-96.0381	-95.6708	-95.6551	117.3	-95.7108	2.2
283	mmphhmhhxxhh	-96.0380	-95.6707	-95.6549	118.4	-95.7112	1.9
270	mmphhmxxhhhh	-96.0379	-95.6702	-95.6536	123.3	-95.7122	1.3
200	mmphmhhhhx	-96.0370	-95.6691	-95.6525	123.4	-95.7111	2.0
134	mmphmhhxxhh	-96.0356	-95.6667	-95.6514	116.2	-95.7066	4.8
73	mmphmhxxhhhh	-96.0347	-95.6660	-95.6497	121.9	-95.7076	4.2
35	mmpmhhhhhhx	-96.0352	-95.6673	-95.6507	123.4	-95.7094	3.1
30	mmpmhhhhxxhh	-96.0361	-95.6677	-95.6521	117.9	-95.7081	3.9
11	mmpmhhxxhhhh	-96.0388	-95.6703	-95.6538	123.0	-95.7122	1.3
44	mmpxxhhhhhhm	-96.0368	-95.6687	-95.6520	124.3	-95.7110	2.0
219	mmpxxhhhhhhmh	-96.0387	-95.6701	-95.6537	122.4	-95.7118	1.5
99	mmpxxhhhhmhh	-96.0406	-95.6722	-95.6557	122.6	-95.7139	0.2
135	mmpxxhhhmhhh	-96.0397	-95.6710	-95.6555	116.9	-95.7110	2.1
249	mmpxxhhmhhhh	-96.0359	-95.6668	-95.6505	121.6	-95.7083	3.7
296	mmpxxhmhhhhh	-96.0408	-95.6720	-95.6555	122.9	-95.7139	0.3
248	mmpxxmhhhhhh	-96.0384	-95.6704	-95.6538	122.8	-95.7121	1.3

Table 3.3: GAMESS B3LYP thermodynamic data for selected nodes in the non-classical graph (Figure 2.99 p.192).

node	Descriptor	E_f Ha	E + ZPVE Ha	H Ha	S cal.mol ⁻¹ K ⁻¹	G Ha	$\Delta E_{f,node8}$ kcal.mol ⁻¹	ΔG_{node8} kcal.mol ⁻¹
0	hmpmmhhhhhhxx	-699.0181	-698.6520	-698.6364	121.84	-698.6354	4.1	3.7
1	hmpmmhxxhhhh	-699.0181	-698.6512	-698.6354	123.06	-698.6345	4.1	4.3
3	hhpmmmhxxhh	-699.0095	-698.6441	-698.6281	122.50	-698.6272	9.5	8.9
5	hhpxxhmmhmmh	-698.9991	-698.6325	-698.6169	122.34	-698.6159	16.1	16.0
7	hhpxxhmmhmmh	-699.0018	-698.6355	-698.6197	123.40	-698.6187	14.3	14.2
8	hmpmmhhhhxxhh	-699.0247	-698.6580	-698.6423	122.17	-698.6414	0.0	0.0
9	hhpxxhmmhmmh	-699.0034	-698.6373	-698.6216	122.27	-698.6206	13.4	13.0
11	mmpmhxxhhhhh	-699.0296	-698.6650	-698.6487	125.61	-698.6478	-3.1	-4.0
15	hmphhhhmhmxx	-699.0218	-698.6564	-698.6406	122.58	-698.6396	1.8	1.1
16	mmphhxxhhhhm	-699.0300	-698.6646	-698.6488	122.95	-698.6478	-3.3	-4.0
17	hhpxxhmhmmhh	-699.0067	-698.6403	-698.6247	121.99	-698.6237	11.3	11.1
18	hhpmmmxhhhhh	-698.9992	-698.6329	-698.6173	121.71	-698.6163	16.0	15.7
20	hmpmhhhhhmxx	-699.0255	-698.6596	-698.6438	122.50	-698.6429	-0.5	-0.9
23	hhpmmmhbbhxx	-699.0029	-698.6360	-698.6203	121.48	-698.6194	13.6	13.8
25	hhphmhhmhmxx	-699.0029	-698.6379	-698.6216	125.39	-698.6207	13.7	13.0
29	hhphhmmmhbbx	-699.0331	-698.6667	-698.6510	121.81	-698.6501	-5.3	-5.5
30	mmphhhhhhxxhm	-699.0303	-698.6662	-698.6498	125.16	-698.6489	-3.5	-4.7
33	hmpmhxxhhhhm	-699.0220	-698.6566	-698.6408	123.32	-698.6399	1.7	0.9
35	mmpmhbbhhbbx	-699.0268	-698.6615	-698.6454	123.68	-698.6445	-1.3	-1.9
40	hmpmhbbhbbx	-699.0213	-698.6559	-698.6401	122.93	-698.6391	2.1	1.4
44	mmpxxhhhhhhm	-699.0303	-698.6655	-698.6492	125.14	-698.6483	-3.5	-4.3
45	hhphmmxxhhhm	-699.0027	-698.6379	-698.6219	123.14	-698.6210	13.8	12.8
52	hmpmhbbhxxhm	-699.0278	-698.6626	-698.6466	123.87	-698.6457	-1.9	-2.7

Table 3.4: GAMESS B3LYP optimizations for Wagner-Meerwein-separated pairs of cations, for the creation of the non-classical graph (Figure 2.99 p.192). The geometry at C-1, C-2 and C-6 is indicated. Energy values are in Hartrees, distances are in Å.

node	Descriptor	r_{12}	r_{16}	r_{26}	E_f	node	Descriptor	r_{12}	r_{16}	r_{26}	E_f
0	mhpxxhhhhmm					2	hmpmmhhhhxx	1.44	1.65	2.26	-699.0180
1	mhpshhxxhhmm					4	hmpmmhxxhhhh	1.45	1.65	2.28	-699.0177
3	hhphhmhxxmm	1.37	2.32	2.14	-699.0092	6	hhpmmhxxhh	1.38	2.11	2.31	-699.0094
5	hhphhmmmhxx	1.44	2.41	1.66	-698.9987	10	hhpxxhmmhmmh	1.44	1.67	2.39	-698.9991
7	hhpxxhmmhmmh	1.43	1.70	2.22	-699.0018	12	hhphhmmhmmxx	1.42	2.21	1.70	-699.0022
8	hmpmmhxxhh	1.43	1.71	2.40	-699.0257	13	mhpshhxxmm				
9	hhphhmmhmmxx	1.42	2.36	1.73	-699.0034	14	hhpxxhmmhmmh	1.42	1.74	2.36	-699.0033
11	mmpmhxxhhhh	1.43	1.71	2.18	-699.0299	16	mmpshhxxhhm	1.43	1.71	2.18	-699.0300
15	mhpxxhmmhmmh					19	hmpshhmmhmmxx	1.42	1.72	2.31	-699.0220
17	hhphhmmhmmxx	1.41	2.35	1.77	-699.0068	22	hhpxxhmmhmmh	1.42	1.75	2.38	-699.0068
18	hhphmmxxhhmm	1.40	2.00	1.76	-698.9989	24	hhpmmmmxxhhhh	1.40	1.75	1.99	-698.9989
20	mhpxxhhmmhmmh					26	hmpshhmmhmmxx	1.43	1.70	2.33	-699.0256
21	hhphmmhxxhm	1.37	2.14	2.31	-699.0120	27	hhpmhmmhxxmh	1.37	2.31	2.12	-699.0122
23	hhpxxmhhhhmm	1.39	1.85	1.92	-699.0026	28	hhpmmmmhhhhxx	1.40	1.97	1.80	-699.0029
25	hhphmmhmmhmmxx	1.42	2.16	1.72	-699.0030	31	hhpxxhmmhmmh	1.41	1.73	2.15	-699.0029
29	hhpxxmmhmmh	1.55	1.54	2.48		34	hhphhmmhmmhxx	1.54	2.48	1.54	-699.0329
30	mmpmhmmhxxhh	1.38	2.48	2.47	-699.0302	36	mmpshhmmhxxhm	1.38	2.52	2.53	-699.0302
32	hmpshmmhmmhxx	1.44	1.65	2.24	-699.0217	39	mhpxxhmmhmmh				
33	mhpshmmhmmh					41	hmpshmmhxxhhm	1.44	1.65	2.28	-699.0221
35	mmpmhmmhmmhxx	1.44	1.68	2.22	-699.0267	44	mmpxxhmmhmmh	1.46	1.65	2.28	-699.0304
37	hmpshmmhmmh	1.44	1.66	2.26	-699.0203	47	mhpshmmhmmh				
38	hhphmmhmmhxx	1.41	1.76	2.06	-699.0047	49	hhpxxhmmhmmh	1.43	1.68	2.35	-699.0052
40	mhpxxhmmhmmh					50	hmpshmmhmmhxx	1.44	1.64	2.28	-699.0213
42	mhpshmmhmmhxx					53	hmpxxhmmhmmh	1.45	1.69	2.42	-699.0302
43	mhpshmmhmmhxx					55	hmpxxhmmhmmh	1.45	1.66	2.40	-699.0242
45	hhphmmhmmhmmh	1.40	1.75	2.00	-699.0028	58	hhpmhmmhmmh	1.40	1.98	1.76	-699.0028
46	hhpmhmmhmmh	1.37	2.29	2.42	-699.0003	59	hhpmhmmhmmh	1.37	2.42	2.27	-699.0001
48	hmpshmmhmmhxx	1.43	1.71	2.33	-699.0223	61	mhpxxhmmhmmh				
51	hhpxxhmmhmmh	1.41	1.73	2.10	-699.0068	64	hhphmmhmmhmmxx	1.41	2.10	1.73	-699.0067
52	hmpshmmhmmh	1.43	1.71	2.38	-699.0274	65	mhpshmmhmmh				
54	hhphmmhmmhxx	1.39	1.91	2.00	-699.0034	67	hhpxxhmmhmmh	1.45	1.64	2.37	-699.0051
56	mhpshmmhmmh					69	hmpshmmhmmh	1.44	1.68	2.39	-699.0197
57	hhpxxhmmhmmh	1.44	1.64	2.23	-699.0060	70	hhphmmhmmhmmh	1.42	2.13	1.68	-699.0062

node	Descriptor	r_{12}	r_{16}	r_{26}	E_f	node	Descriptor	r_{12}	r_{16}	r_{26}	E_f
60	hhpmhmbhxxhm	1.36	2.40	2.40	-699.0101	60	hhpmhmbhxxhm	1.36	2.40	2.40	-699.0101
62	hhphmbhmhxx	1.40	1.82	2.05	-699.0008	75	hhpxxhhmhmhm	1.43	1.69	2.34	-699.0013
63	hhpmmhbbhmxx	1.41	2.10	1.75	-699.0005	76	hhpxxhhbmhm	1.41	1.75	2.09	-699.0008
66	hmpmbmhhhhxx	1.44	1.66	2.23	-699.0247	79	mhpxxmhhhhhm				
68	hhphhmmhxxmh	1.37	2.32	2.16	-699.0059	80	hhphmmhmxxhh	1.37	2.11	2.30	-699.0061
71	hhpxxmmhbbhm	1.42	1.70	2.13	-699.0059	82	hhpmhmbmhhxx	1.41	2.07	1.74	-699.0063
72	hhpmhbxhbmhm	1.41	2.08	1.74	-698.9882	85	hhpmmhbxhbbhm	1.41	1.74	2.10	-698.9883
73	mmphmbxxhbbh	1.45	1.67	2.25	-699.0282	87	mmphhbxhbmhm	1.44	1.68	2.25	-699.0258
74	hmpbbbmhmhxx	1.43	1.71	2.18	-699.0187	89	mhpxxhbmhmhb				
77	hmpbbbmhmhxx	1.43	1.70	2.16	-699.0254	92	mhpxxbmhbmb				
78	mhpmmhbbhhxx					94	hmpxxbbbmhm	1.45	1.64	2.27	-699.0197
81	hmpmbbmhmxxh	1.43	1.71	2.40	-699.0218	97	mhpbbbmhmxxm				
83	mmphbbbmhmxx	1.45	2.36	1.69	-699.0348	99	mmpxxbbbmhb	1.45	1.68	2.39	-699.0345
84	hhpxxmbbmhm	1.42	1.70	2.19	-698.9898	100	hhpmmhbmhhxx	1.40	1.76	2.05	-698.9892
86	hmpmbbmhmxxh	1.43	1.72	2.39	-699.0313	103	mhpbbbmhmxxm				
88	hmpmbbbbmhmxx	1.44	1.68	2.22	-699.0215	107	mhpxxbbbmhm				
90	hmpbbbxhbmhm	1.43	1.67	2.25	-699.0152	109	mhpmmhbxhbbh				
91	hmpmbbmhmhxx	1.43	1.70	2.16	-699.0264	111	mhpxxbbbmhm				
93	mhpbbbmhmhxx					113	hmpxxbmhbhh	1.46	1.62	2.36	-699.0227
95	mhpbbmxxhbmh					115	hmpmbmxxbbhh	1.44	1.65	2.24	-699.0243
96	mmphhbxhbmhb	1.42	1.78	2.33	-699.0274	116	mmphhbxmhbhh	1.43	1.79	2.21	-699.0282
98	mhpmbbbbmhmxx					118	hmpxxbbbmhm	1.44	1.68	2.28	-699.0287
101	hhpxxmbbmhmh	1.55	1.55	2.50	-699.0264	119	hhphmbmmhxx	1.42	1.69	2.23	-698.9876
102	hmpmbbbbmhm	1.43	1.72	2.40	-699.0243	121	mhpmbbbbmhm				
104	mhpxxbbbmhm					120	hmpmbbbbmhmxx	1.44	1.67	2.37	-699.0221
105	hhphmmhbmxxm	1.37	2.21	2.21	-699.0113	105	hhphmmhbmxxm	1.37	2.21	2.21	-699.0113
106	hhpmbbmhbhhxx	1.41	2.10	1.73	-698.9898	123	hhpxxhbmhbmm	1.42	1.70	2.13	-698.9893
108	hhphmbbhxxmm	1.38	2.24	2.17	-699.0033	124	hhpmbbhbmxxm	1.38	2.17	2.22	-699.0032
110	hmpmbbmhbhhxx	1.44	1.65	2.26	-699.0218	128	mhpxxhbmhbhm				
112	hhphbmhbmmxx	1.43	2.35	1.72	-699.0116	129	hhpxxmbbmhb	1.43	1.72	2.35	-699.0121
114	hhphbbxmhm	1.39	1.86	2.05	-698.9951	132	hhpmbbmxxbmhb	1.39	2.03	1.88	-698.9949
117	hhphbmxxbmhm	1.39	1.83	2.04	-699.0025	138	hhphmmxxbmhb	1.39	2.03	1.83	-699.0024
122	hhpmbbmhbhhxx	1.45	2.29	1.64	-698.9915	143	hhpxxmbbmhb	1.45	1.64	2.32	-698.9917

Experimental

node	Descriptor	r_{12}	r_{16}	r_{26}	E_f	node	Descriptor	r_{12}	r_{16}	r_{26}	E_f
125	mhpxxhmmhxxxh					146	hmpghhmmhxxxh	1.44	1.64	2.31	-699.0164
126	hmpmhmmhxxxhh	1.43	1.73	2.37	-699.0297	147	mhpghmmhxxxhm				
127	hhpmhhmmhxxxh	1.42	2.33	1.73	-699.0048	149	hhpxxhmmhmmhm	1.42	1.72	2.34	-699.0047
130	hhpmhmmhxxxhh	1.41	1.76	2.10	-698.9995	152	hhphhmmhxxxmm	1.41	2.11	1.77	-698.9997
131	hhphhmmhxxxmm	1.37	2.47	2.33	-698.9986	153	hhpmmhmmhxxxh	1.37	2.33	2.49	-698.9990
133	hhpxxmmhmmhxx	1.42	1.70	2.16	-699.0121	155	hhphhmmhmmhxx	1.42	2.17	1.69	-699.0122
134	mmpmhmmhxxxhh	1.39	2.40	2.51	-699.0287	156	mmpghhmmhxxxm	1.38	2.51	2.42	-699.0285
135	mmpxxhmmhmmhxx	1.45	1.71	2.27	-699.0361	157	mmpghhmmhmmhxx	1.45	2.27	1.70	-699.0361
136	hhphmmhmmhxxxh	1.37	2.16	2.32	-699.0093	158	hhphhmmhmmhxx	1.37	2.30	2.14	-699.0095
137	hmpxxmmhmmhmm	1.45	1.65	2.26	-699.0280	159	mhpmmhmmhmmhxx				
139	hmpghhmmhmmhm	1.43	1.71	2.22	-699.0190	162	mhpmmhmmhmmhm				
140	hmpghhmmhmmhxx	1.42	1.76	2.35	-699.0191	163	mhpmmhmmhmmhm				
141	hhpmhmmhmmhmm	1.39	1.86	1.90	-699.0022	141	hhpmhmmhmmhmm	1.39	1.86	1.90	-699.0022
142	hhpmhmmhmmhmm	1.42	2.36	1.78	-699.0044	165	hhpmmhmmhmmhm	1.41	1.79	2.35	-699.0047
144	hhphmmhmmhmmhm	1.41	1.74	2.13	-698.9865	166	hhpmmhmmhmmhm	1.41	1.75	2.07	-698.9864
145	hmpmhmmhmmhmm	1.44	1.66	2.28	-699.0196	150	mhpmmhmmhmmhm				
148	hhpmhmmhmmhmm	1.41	2.12	1.74	-699.0034	172	hhpmmhmmhmmhm	1.42	1.73	2.16	-699.0042
151	hmpmhmmhmmhmm	1.43	1.74	2.39	-699.0250	174	mhpmmhmmhmmhm				
154	hmpmhmmhmmhmm	1.43	1.73	2.39	-699.0244	177	mhpmmhmmhmmhm				
160	mmpghhmmhmmhmm	1.38	2.62	2.63	-699.0291	183	mmpghhmmhmmhmm	1.38	2.59	2.60	-699.0294
161	hhphmmhmmhmmhm	1.37	2.28	2.30	-699.0012	184	hhphmmhmmhmmhm	1.37	2.27	2.30	-699.0011
164	hhpmmhmmhmmhm	1.43	1.65	2.26	-699.0053	180	hhphmmhmmhmmhm	1.40	1.77	1.99	-699.0046
167	hmpghhmmhmmhmm	1.43	1.73	2.33	-699.0196	187	mhpmmhmmhmmhmm				
168	hhpmmhmmhmmhm	1.41	1.74	2.17	-699.0061	188	hhpmhmmhmmhmm	1.41	2.19	1.73	-699.0059
169	hhpmhmmhmmhmm	1.41	1.77	2.06	-699.0003	190	hhpmmhmmhmmhm	1.40	2.06	1.78	-698.9998
170	hhphmmhmmhmmhm	1.38	2.26	2.17	-699.0030	191	hhpmmhmmhmmhm	1.42	1.74	2.33	-699.0038
171	mhpmmhmmhmmhm					193	hmpmmhmmhmmhm	1.43	1.68	2.18	-699.0243
173	hmpghmmhmmhmmhm	1.43	1.73	2.36	-699.0305	195	mhpmmhmmhmmhm				
175	hhphmmhmmhmmhm	1.37	2.39	2.20	-699.0045	197	hhpmhmmhmmhmm	1.37	2.31	2.50	-699.0041
176	hmpmhmmhmmhmmhm	1.43	1.72	2.35	-699.0217	198	mhpmmhmmhmmhm				
178	mhpmmhmmhmmhm					201	hmpmmhmmhmmhm	1.45	1.65	2.41	-699.0312
179	hhphmmhmmhmmhm	1.41	1.74	2.08	-698.9976	179	hhphmmhmmhmmhm	1.41	1.74	2.08	-698.9976
181	mhpmmhmmhmmhm					203	hmpmmhmmhmmhm	1.43	1.69	2.27	-699.0230

Experimental

node	Descriptor	r_{12}	r_{16}	r_{26}	E_f	node	Descriptor	r_{12}	r_{16}	r_{26}	E_f
182	mhpqhmmhbbhxx					205	hmpxxmhmbhhh	1.46	1.63	2.29	-699.0285
185	hmpqhmbmxxhh	1.43	1.73	2.38	-699.0278	208	mhpqhmbmxxhh				
186	hmpmhbbhxxmh	1.43	1.71	2.36	-699.0238	209	mhpqhmbbxxhm				
189	hmpmhbmhbbhxx	1.45	1.62	2.35	-699.0179	211	mhpqxbhmbbhhm				
192	mhpqxbmbbhhmh					212	hmpqhmbbhhbxx	1.43	1.66	2.21	-699.0288
194	hmpqhmbxxhhmh	1.44	1.65	2.31	-699.0175	215	mhpqhmbxxhhmh				
196	hhpqbmbxxmhbm	1.40	2.03	1.81	-699.0076	217	hhpqbmbxxmbhh	1.40	1.80	2.03	-699.0074
199	hhpqbmbxxmbhm	1.40	1.80	2.04	-699.0079	222	hhpqbmbxxmbhh	1.40	2.03	1.79	-699.0081
200	mmpqhmbbhhbxx	1.44	1.70	2.18	-699.0313	219	mmpqxbhbbhhmh	1.46	1.65	2.28	
202	hhpqbmbmbbhhm	1.42	1.69	2.12	-699.0018	223	hhpqbmbmbbhhx	1.42	2.10	1.70	-699.0018
204	mhpqhmbbhmhxx					227	hmpqxbmbbhmhh	1.45	1.65	2.38	-699.0324
206	hhpqbmbxxmbhh	1.41	1.76	2.04	-699.0057	228	hhpqbmbxxmbmh	1.40	2.06	1.76	-699.0058
207	hmpqbhbxxhmbh	1.43	1.72	2.36	-699.0184	229	mhpqhmbxxmbhh				
210	hhpqbmbmbmhxx	1.39	1.86	2.04	-698.9955	232	hhpqbxbhmbmhbm	1.42	1.72	2.31	-698.9965
213	hhpqbmbmbmbhh	1.41	1.73	2.11	-699.0114	234	hhpqbmbmbbmxx	1.42	2.15	1.71	-699.0118
214	hmpqhmbbhhxxmh	1.43	1.71	2.36	-699.0247	235	mhpqhmbbhhxxmh				
216	mhpqbmbxxbhhhh					231	hmpqhmbxxbhhm	1.43	1.67	2.20	-699.0261
218	hmpqbhbxxmbhh	1.43	1.71	2.24	-699.0250	241	mhpqbhbxxmbhm				
220	hhpqbmbmbxxhm	1.37	2.32	2.29	-699.0100	242	hhpqbmbmbxxhh	1.37	2.26	2.27	-699.0102
221	hmpqxbmbbhhmh	1.45	1.64	2.27	-699.0323	243	mhpqhmbbhhbxx				
224	hmpqxbhmbbhh	1.45	1.66	2.30	-699.0298	246	mhpqbhbmbbmxx				
225	hmpqbmbmbxxhh	1.43	1.73	2.40	-699.0259	247	mhpqbhbmbxxmh				
226	mmpqbmbbhhbxx	1.43	1.72	2.15	-699.0333	248	mmpqxbmbbhhhh	1.45	1.66	2.24	-699.0372
230	mhpqbmbxxmbhh					251	hmpqbmbxxmbhh	1.42	1.72	2.33	-699.0231
233	hhpqbmbmbmhxx	1.39	1.83	2.00	-699.0105	253	hhpqbmbbhhmbh	1.43	1.68	2.33	-699.0107
236	hmpqbmbbhhxxmh	1.43	1.73	2.34	-699.0275	256	mhpqhmbbhhxhh				
237	mhpqxbmbbhhhh					257	hmpqbmbmbbhhx	1.43	1.66	2.20	-699.0276
238	hmpqxbmbbhhhh	1.45	1.63	2.29	-699.0315	258	mhpqbmbmbbhhx				
239	mhpqbmbmbxxhh					259	hmpqbhbmbxxhm	1.43	1.73	2.38	-699.0247
240	hmpqxbmbmbhh	1.44	1.67	2.28	-699.0307	254	mhpqbhbmbbmxx				
244	mhpqbhbmbxxhh					262	hmpqbhbmbxxhm	1.42	1.74	2.39	-699.0249
245	mhpqbhbhbmbhh					264	hmpqxbhbhbmbhm	1.44	1.67	2.39	-699.0259
249	mmpqxbhbhbhhh	1.46	1.65	2.26	-699.0319	263	mmpqbhbhbhbhh	1.44	1.70	2.20	-699.0263

Experimental

node	Descriptor	r_{12}	r_{16}	r_{26}	E_f	node	Descriptor	r_{12}	r_{16}	r_{26}	E_f
250	hmpfhmmhxxhh	1.42	1.73	2.38	-699.0273	265	mhpfhmmhxxhh				
252	hhpxxmhhmhmh	1.41	1.75	2.09	-699.0140	267	hhphmmhhhmxx	1.41	2.09	1.75	-699.0141
255	hmpfhmxxhhmh	1.43	1.66	2.25	-699.0228	269	mhpfhmmxxhhhh				
260	hhphhmhmxxhm	1.37	2.26	2.27	-699.0099	275	hhpmhmhmxxhh	1.37	2.28	2.29	-699.0098
261	mhpmmhxxhmhh					276	hmpfhmxxmhhm	1.43	1.71	2.25	-699.0252
266	mhpmmhmmxxhh					279	hmpfhmmhxxmh	1.43	1.72	2.37	-699.0176
268	hhpxxmhhmhhm	1.41	1.75	2.13	-699.0121	281	hhpmhmhhhmxx	1.41	2.12	1.74	-699.0118
270	mmphhmxxhhhh	1.43	1.70	2.18		270	mmphhmxxhhhh	1.43	1.70	2.18	
271	hhphmmhhmhxx	1.40	1.81	2.02	-699.0119	285	hhpxxmhhhmhm	1.42	1.71	2.30	-699.0117
272	mhpmmhhhhmxx					286	hmpxxhhhmhmh	1.44	1.66	2.25	-699.0301
273	mhpmmhhhhmxx					287	hmpxxmhhmhhh	1.44	1.66	2.28	-699.0352
274	hhphmxxhmhm	1.39	2.05	1.84	-698.9992	288	hhpmhxxmhmh	1.40	1.84	2.05	-698.9997
277	hhphmxxmhhm	1.41	1.76	2.08	-699.0030	292	hhpmhxxhmmh	1.41	2.10	1.76	-699.0031
278	mhpmmxxhmhh					293	hmpfhmxxmhhh	1.42	1.71	2.21	-699.0259
280	mmphhhhmhhxx	1.43	1.73	2.13	-699.0300	296	mmpxxhmhhhhh	1.46	1.65	2.28	-699.0357
282	mhpxxmhmhhhh					298	hmpfhmmhhhhxx	1.44	1.65	2.25	-699.0240
283	mmphhmhhxxhh	1.38	2.45	2.45	-699.0338	283	mmphhmhhxxhh	1.38	2.45	2.45	-699.0338
284	mhpxxmhhmhhh					299	hmpfhmhhhmxx	1.42	1.71	2.31	-699.0275
289	mhpmmhxxmhhh					302	hmpfhmxxhmhm	1.43	1.70	2.37	-699.0223
290	hhphmhmhmxxm	1.37	2.32	2.46	-699.0069	303	hhpmhhhmxxmh	1.37	2.43	2.26	-699.0069
291	hmpxxhmmhmmh	1.45	1.63	2.30	-699.0254	304	mhpmmhmhhhhxx				
294	hhphmhmhmhmh	1.41	1.76	2.10	-698.9960	307	hhphmhmhmhmh	1.41	2.12	1.76	-698.9959
295	mhpmmhhhmhmxx					308	hmpxxhhhhmmh	1.45	1.66	2.38	-699.0305
297	mhpmmhhhmhhxx					300	hmpxxmhhhhhm	1.45	1.63	2.32	-699.0249
310	mhpmmhhhmhhxx					316	hmpxxmhhhhmh	1.45	1.63	2.32	-699.0263
312	hmpmmhhhmhmxx	1.43	1.71	2.19	-699.0272	317	mhpmmhhhmhmh				
318	hhpmhxxmhhm	1.40	1.83	2.08	-699.0022	320	hhpmhxxhmhm	1.40	2.07	1.81	-699.0019
319	hhpmhmmhmxxm	1.35	2.86	2.86	-699.0072	321	hhpmhmmhmxxm	1.35	2.95	2.94	-699.0069
301	hhpmhmmhmxxm	1.37	2.43	2.31	-699.0027	311	hhphmhhmxxhm	1.37	2.35	2.46	-699.0030
305	mhpmmhmhmxxhh					313	hmpfhmmhmxxmh	1.42	1.74	2.35	-699.0210
306	hmpxxhmmhhhm	1.45	1.64	2.28	-699.0200	314	mhpmmhmhhhhxx				
309	hhpmhmhhmhmxx	1.41	2.26	1.75	-699.0069	315	hhpxxmhhhmhm	1.42	1.72	2.31	-699.0071

4 Appendix

4.1 Rate analysis for the decomposition of the tosylate¹

$$\text{AOTs} = x, \text{B} = y, \text{C} = x_0 - x - y, \text{OTs}^- = t_0 + x_0 - x$$

For The Decomposition of the Starting Material AOTs:

Zeroth order

$$\frac{dx}{dt} = -k_0$$

First order

$$\frac{dx}{dt} = -k_1 x$$

Second order

$$\frac{dx}{dt} = -k_2 x(t_0 + x_0 - x)$$

Third order

$$\frac{dx}{dt} = -k_3 x(t_0 + x_0 - x)^2$$

For the purposes of using nmr to follow the kinetics, it is easier to introduce a constant relating the integral to the concentration, and then to work with the raw integral data produced. Thus we have:

$$x = ai, \quad x_0 = ai_0, \quad t_0 = at_0$$

$$dx = a di$$

And the four rates become

Zeroth order

$$-\frac{di}{dt} = \frac{k_0}{a}$$

First order

$$-\frac{di}{dt} = k_1 i$$

Second order

$$-\frac{di}{dt} = ak_2 i(t_0 + i_0 - k_t i), \quad k_t = 1$$

Third order

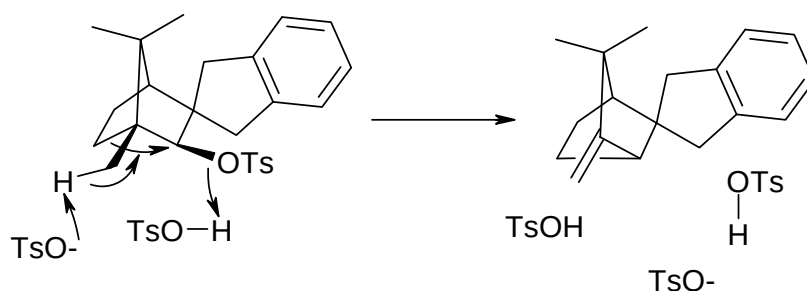
$$-\frac{di}{dt} = a^2 k_3 i(t_0 + i_0 - i)^2$$

It is clear from the experimental data that autocatalysis plays a major role, *i.e.* the second order contribution to the rate is the most significant. It is possible, however to explain the presence of other order components in the rate equation.

Due to the nature of the preparation of the starting material, there possibility exists for there to be an excess of PTSA. PTSA is sparingly soluble in chloroform and may therefore form a fine suspension. This highly acidic suspension would catalyse the decomposition of the starting material. While the concentration of the PTSA produced remained low enough to not have a significant effect, the rate of decomposition would be proportional to the surface area of PTSA originally present. Thus we could have a zeroth order component.

The first order dissociative mechanism is an even more likely component of the rate equation. A very well studied system, good leaving groups need little persuasion to dissociate from the *exo*- position on any norbornyl skeleton. Further, in the absence of starting PTSA, it is essential to have dissociation for initiation of the autocatalysis.

A third order mechanism is of low probability, but one can suggest a plausible pathway. TsOH protonation of the starting material.



The combinations of contributions to the overall rate that were examined were

1. Purely autocatalytic

$$-\frac{di}{dt} = ak_2 i(t_0 + i_0 - k_t i)$$

$$\frac{di}{i(t_0 + i_0 - k_t i)} = -ak_2 dt$$

$$\frac{\ln(i)}{(t_0 + i_0)} - \frac{\ln((t_0 + i_0) - k_t i)}{(t_0 + i_0)} = -ak_2 t + C'$$

$$\ln(i) - \ln((t_0 + i_0) - k_t i) = -ak_2 (t_0 + i_0) t + C'$$

$$\ln\left(\frac{i}{(t_0 + i_0) - k_t i}\right) = -ak_2 (t_0 + i_0) t + C'$$

$$\ln\left(\frac{i_0}{(t_0 + i_0) - k_t i_0}\right) = C'$$

$$\ln\left(\frac{i}{(t_0 + i_0) - k_t i}\right) - \ln\left(\frac{i_0}{(t_0 + i_0) - k_t i_0}\right) = -ak_2 (t_0 + i_0) t$$

At the point of maximum rate, i_i :

$$\left[\frac{d^2 a}{dt^2} \right]_{i_i} = ak_2((t_0 + i_0) - k_t i_i) - ak_2 k_t i_i = 0$$

$$(t_0 + i_0) = 2k_t i_i$$

$$k_t = \frac{(t_0 + i_0)}{2i_i}$$

And the equation reduces to

$$\ln\left(\frac{i}{1 - \frac{i}{2i_i}}\right) - \ln\left(\frac{i_0}{1 - \frac{i_0}{2i_i}}\right) = -ak_2(t_0 + i_0) t$$

2. Autocatalytic and zeroth order

$$-\frac{di}{dt} = \frac{k_0}{a} + ak_2 i((t_0 + i_0) - i)$$

$$\frac{di}{\frac{k_0}{a} + ak_2 i((t_0 + i_0) - i)} = -dt$$

$$\text{let } A = k_0/a, B = ak_2, C = (t_0 + i_0)$$

$$\frac{di}{A + Bi(C - i)} = -dt$$

$$\frac{di}{A + BCi - Bi^2} = -dt$$

$$\text{let } q = -4AB - (BC)^2$$

$$\frac{-2}{\sqrt{-q}} \tanh^{-1}\left(\frac{BC - 2Bi}{\sqrt{-q}}\right) = -t + C'$$

$$\frac{-2}{\sqrt{-q}} \tanh^{-1}\left(\frac{BC - 2Bi}{\sqrt{-q}}\right) - \frac{-2}{\sqrt{-q}} \tanh^{-1}\left(\frac{BC - 2Bi_0}{\sqrt{-q}}\right) = -t$$

$$\tanh^{-1}\left(\frac{BC - 2Bi}{\sqrt{-q}}\right) - \tanh^{-1}\left(\frac{BC - 2Bi_0}{\sqrt{-q}}\right) = \frac{\sqrt{-q}}{2}t$$

$$\tanh^{-1}\left(\frac{ak_2(t_0 + i_0) - 2ak_0i}{\sqrt{a^2k_2^2(t_0 + i_0)^2 + 4k_0k_2}}\right) - \tanh^{-1}\left(\frac{ak_2(t_0 + i_0) - 2ak_0i_0}{\sqrt{a^2k_2^2(t_0 + i_0)^2 + 4k_0k_2}}\right) = \frac{\sqrt{a^2k_2^2(t_0 + i_0)^2 + 4k_0k_2}}{2}t$$

3. Autocatalytic and first order

$$-\frac{di}{dt} = k_1i + ak_2i((t_0 + i_0) - i)$$

$$\frac{di}{k_1i + ak_2i((t_0 + i_0) - i)} = -dt$$

$$\frac{\ln(i)}{k_1 + ak_2(t_0 + i_0)} - \frac{\ln(k_1 + ak_2((t_0 + i_0) - i))}{k_1 + ak_2(t_0 + i_0)} = -t + C'$$

$$\ln\left(\frac{k_1 + ak_2((t_0 + i_0) - i)}{i}\right) = (k_1 + ak_2(t_0 + i_0))t + C'$$

$$\ln\left(\frac{k_1 + ak_2((t_0 + i_0) - i)}{i}\right) - \ln\left(\frac{k_1 + ak_2t_0}{i_0}\right) = (k_1 + ak_2(t_0 + i_0))t$$

At the point of maximum rate, i_i :

$$\left[\frac{d^2a}{dt^2}\right]_{i_i} = k_1 + ak_2((t_0 + i_0) - i_i) - ak_2i_i = 0$$

$$k_1 + ak_2((t_0 + i_0) - 2i_i) = 0$$

$$\frac{k_1}{ak_2} + (t_0 + i_0) - 2i_i = 0$$

$$\frac{k_1}{ak_2} + (t_0 + i_0) = 2i_i$$

$$\ln\left(\frac{2i_i - i}{i}\right) - \ln\left(\frac{\frac{k_1}{ak_2} + t_0}{i_0}\right) = (k_1 + ak_2(t_0 + i_0))t$$

4. Autocatalytic and third order

$$-\frac{di}{dt} = ak_2i((t_0 + i_0) - i) + a^2k_3i((t_0 + i_0) - i)^2$$

$$\frac{di}{k_2i((t_0 + i_0) - i) + ak_3((t_0 + i_0) - i)^2} = -a dt$$

let $A=k_2$, $B=ak_3$, and $C=(t_0+i_0)$

$$\frac{di}{Ai(C - i) + Bi(C - i)^2} = -adt$$

$$\frac{di}{ACi - Ai^2 + C^2Bi - 2BCi^2 + Bi^3} = -adt$$

$$\frac{di}{(AC + C^2B)i - (A + 2BC)i^2 + Bi^3} = -adt$$

$$\frac{di}{i[(AC + C^2B) - (A + 2BC)i + Bi^2]} = -adt$$

$$\frac{di}{C(A + BC)i} + \frac{di}{AC(C - i)} - \frac{B^2di}{A(A + BC)(A + BC - Bi)} = -adt$$

$$\frac{\ln(i)}{C(A + BC)} + \frac{\ln(C - i)}{AC} + \frac{B \ln(A + BC - Bi)}{A(A + BC)} = -at + C'$$

$$\frac{\ln(i)}{C} + \frac{(A + BC)\ln(C - i)}{AC} + \frac{B \ln(A + BC - Bi)}{A} = -a(A + BC)t + C''$$

$$A \ln(i) + (A + BC) \ln(C - i) + BC \ln(A + BC - Bi) = -aAC(A + BC)t + C''$$

4.2 Crystallographic data for spiro[camphene-5,2-indan] 263

Empirical Formula	C ₁₈ H ₂₂
Formula Weight	238.36
Temperature	193K
Wavelength	0.71073 Å
Crystal System	monoclinic
Space Group	<i>P</i> 2 ₁ / <i>c</i>
Unit Cell Dimensions	<i>a</i> = 18.641(4) Å
	<i>b</i> = 6.1420(12) Å
	<i>c</i> = 12.756(3) Å
	α = 90.00°
	β = 108.53(3)°
	γ = 90.00°
V	1384.7 (5) Å ³
Z	5
D _c	1.143g.m ⁻³
F(000)	520
Crystal Size	0.05 x 0.11 x 0.3 mm ³
θ range	3.20 to 27.47°
Index ranges	$-24 \leq h \leq 23, -7 \leq k \leq 7, -16 \leq l \leq 16$
Reflections collected	5859
Unique reflections	3144
Refinement method	Full-matrix, least squares on F ²
Goodness-of-fit on F ²	1.038
μ	0.064 mm ⁻¹
R ₁	0.0519
wR2	0.1227

Table 4.1: Bond lengths [Å] and angles [°] for spiro[camphene-5,2-indan] **263**

C(3)-C(4)	1.388(2)	C(4)-C(3)-C(8)	120.61(14)
C(3)-C(8)	1.390(2)	C(4)-C(3)-C(2)	129.54(13)
C(3)-C(2)	1.504(2)	C(8)-C(3)-C(2)	109.85(13)
C(8)-C(7)	1.393(2)	C(3)-C(8)-C(7)	120.04(14)
C(8)-C(9)	1.508(2)	C(3)-C(8)-C(9)	109.97(13)
C(2)-C(1)	1.544(2)	C(7)-C(8)-C(9)	129.97(14)
C(1)-C(13)	1.545(2)	C(3)-C(2)-C(1)	103.99(11)
C(1)-C(9)	1.553(2)	C(2)-C(1)-C(13)	114.73(12)
C(1)-C(10)	1.565(2)	C(2)-C(1)-C(9)	102.49(12)
C(14)-C(16)	1.317(2)	C(13)-C(1)-C(9)	113.79(12)
C(14)-C(15)	1.520(2)	C(2)-C(1)-C(10)	113.21(12)
C(14)-C(13)	1.527(2)	C(13)-C(1)-C(10)	102.01(12)
C(10)-C(11)	1.526(2)	C(9)-C(1)-C(10)	111.00(12)
C(6)-C(5)	1.381(2)	C(16)-C(14)-C(15)	126.14(15)
C(6)-C(7)	1.390(2)	C(16)-C(14)-C(13)	126.69(15)
C(13)-C(12)	1.540(2)	C(15)-C(14)-C(13)	107.15(13)
C(4)-C(5)	1.389(2)	C(11)-C(10)-C(1)	104.12(12)
C(15)-C(17)	1.539(2)	C(5)-C(6)-C(7)	120.73(15)
C(15)-C(18)	1.545(2)	C(8)-C(9)-C(1)	103.27(11)
C(15)-C(11)	1.562(2)	C(6)-C(7)-C(8)	119.06(15)
C(12)-C(11)	1.530(2)	C(14)-C(13)-C(12)	100.58(13)
		C(14)-C(13)-C(1)	107.57(12)
		C(12)-C(13)-C(1)	100.63(12)
		C(3)-C(4)-C(5)	119.14(15)
		C(14)-C(15)-C(17)	111.08(15)
		C(14)-C(15)-C(18)	113.27(14)
		C(17)-C(15)-C(18)	107.74(15)
		C(14)-C(15)-C(11)	100.55(13)
		C(17)-C(15)-C(11)	110.47(14)
		C(18)-C(15)-C(11)	113.68(15)
		C(6)-C(5)-C(4)	120.41(15)
		C(11)-C(12)-C(13)	94.78(12)
		C(10)-C(11)-C(12)	100.75(13)
		C(10)-C(11)-C(15)	110.12(13)

4.3 Crystallographic data for spiro[camphene-7,2-indan] 179

Empirical Formula	C ₁₈ H ₂₂
Formula Weight	238.36
Temperature	198K
Wavelength	0.71073 Å
Crystal System	orthorhombic
Space Group	
Unit Cell Dimensions	$a = 8.8355(18) \text{ Å}$
	$b = 10.042(2) \text{ Å}$
	$c = 15.924(3) \text{ Å}$
	$\alpha = 90.00^\circ$
	$\beta = 90.00^\circ$
	$\gamma = 90.00^\circ$
V	1412.9 (5) Å ³
Z	4
D _c	1.121 Mg.cm ⁻³
F(000)	520
Crystal Size	0.10 x 0.25 x 0.40 mm ³
θ range	4.26 to 27.10°
Index ranges	$-11 \leq h \leq 11, -12 \leq k \leq 12, -20 \leq l \leq 20$
Reflections collected	3107
Unique reflections	3107
Refinement method	Full-matrix, least squares on F ²
Goodness-of-fit on F ²	1.042
μ	0.062 mm ⁻¹
R ₁	0.0348
wR2	0.0760

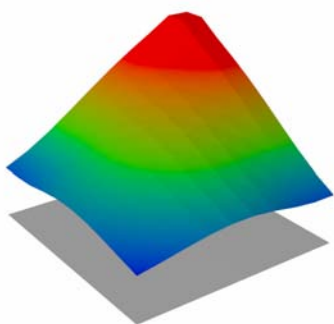
Table 4.2: Bond lengths [Å] and angles [°] for spiro[camphene-7,2-indan] **263**

C(3)-C(4)	1.5086(17)	C(4)-C(3)-C(2)	103.75(9)
C(3)-C(2)	1.5477(16)	C(12)-C(13)-C(2)	99.76(10)
C(13)-C(12)	1.5416(18)	C(12)-C(13)-C(14)	109.34(11)
C(13)-C(2)	1.5518(16)	C(2)-C(13)-C(14)	103.86(9)
C(13)-C(14)	1.5639(19)	C(18)-C(15)-C(10)	127.16(13)
C(15)-C(18)	1.3200(19)	C(18)-C(15)-C(14)	126.37(12)
C(15)-C(10)	1.5085(17)	C(10)-C(15)-C(14)	106.46(10)
C(15)-C(14)	1.5361(18)	C(9)-C(4)-C(5)	120.87(12)
C(4)-C(9)	1.3837(18)	C(9)-C(4)-C(3)	129.07(12)
C(4)-C(5)	1.3900(18)	C(5)-C(4)-C(3)	110.05(11)
C(6)-C(7)	1.385(2)	C(7)-C(6)-C(5)	118.93(14)
C(6)-C(5)	1.3878(19)	C(4)-C(9)-C(8)	118.66(14)
C(9)-C(8)	1.392(2)	C(6)-C(5)-C(4)	120.10(13)
C(5)-C(1)	1.5021(18)	C(6)-C(5)-C(1)	129.67(13)
C(2)-C(10)	1.5520(17)	C(4)-C(5)-C(1)	110.23(11)
C(2)-C(1)	1.5549(17)	C(3)-C(2)-C(13)	119.61(10)
C(8)-C(7)	1.377(2)	C(3)-C(2)-C(10)	111.99(9)
C(11)-C(10)	1.5495(17)	C(13)-C(2)-C(10)	93.15(9)
C(11)-C(12)	1.5570(19)	C(3)-C(2)-C(1)	102.91(10)
C(17)-C(14)	1.540(2)	C(13)-C(2)-C(1)	115.76(10)
C(14)-C(16)	1.5410(19)	C(10)-C(2)-C(1)	113.84(10)
		C(5)-C(1)-C(2)	103.71(10)
		C(7)-C(8)-C(9)	120.50(14)
		C(10)-C(11)-C(12)	103.10(10)
		C(15)-C(10)-C(11)	107.74(10)
		C(15)-C(10)-C(2)	100.51(9)
		C(11)-C(10)-C(2)	102.07(9)
		C(13)-C(12)-C(11)	102.66(10)
		C(8)-C(7)-C(6)	120.93(13)
		C(15)-C(14)-C(17)	113.34(11)
		C(15)-C(14)-C(16)	110.32(12)
		C(17)-C(14)-C(16)	106.54(12)
		C(15)-C(14)-C(13)	100.45(10)
		C(17)-C(14)-C(13)	112.08(12)
		C(16)-C(14)-C(13)	114.25(11)

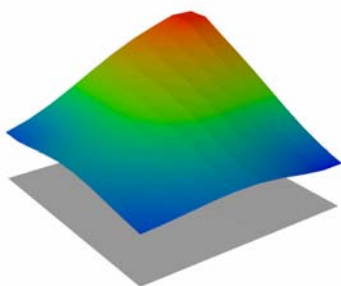
4.4 AM1 Wagner-Meerwein potential energy surfaces

In these potential energy surfaces, the descriptor given is that of the classical structure corresponding to the left-hand-most part of the potential energy surface.

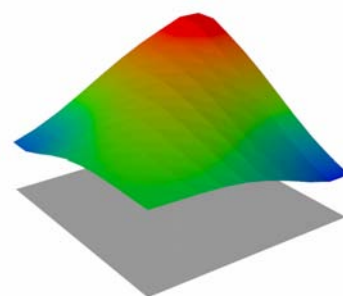
AM1 potential energy surfaces for Wagner-Meerwein transition states that failed.



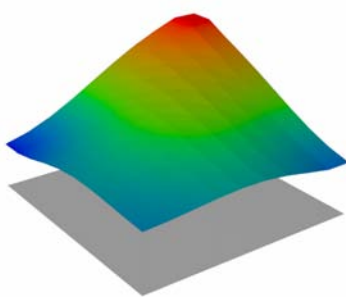
hhphhmmhxxhm



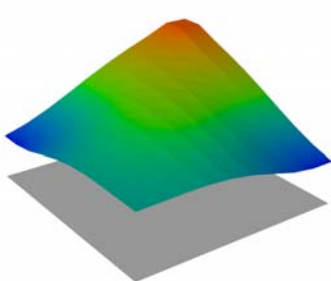
hhphhmxxmhbm



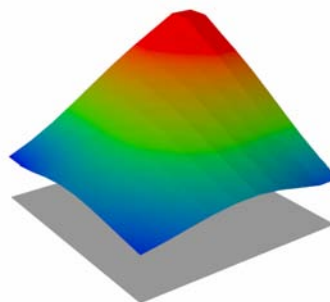
mmpxxhmhhhhh



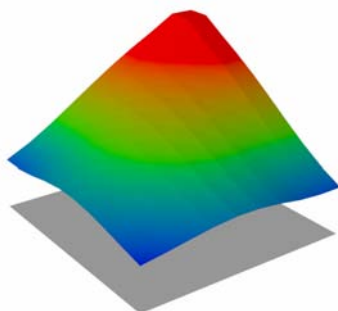
hhphmmhbmhxx



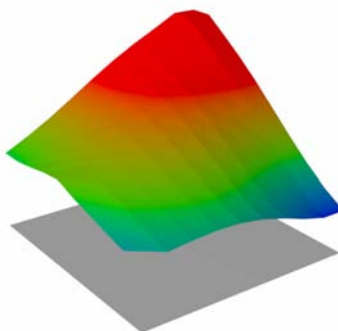
hhphmmxxhbmh



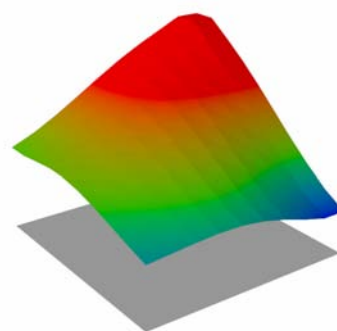
hhpmhhhhxxmm



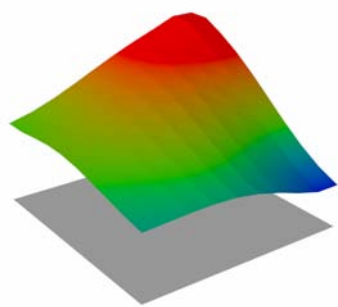
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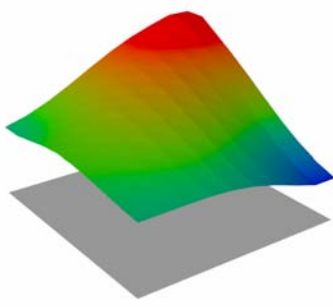
hmphhhhhxxmm



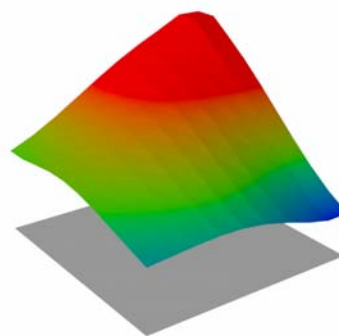
hmphhhhbmxxhm



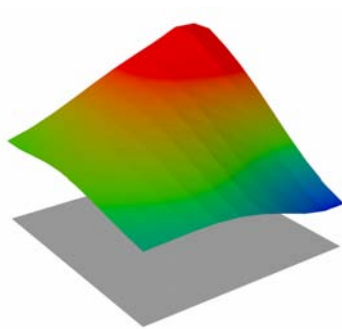
hmphhhxxhmhm



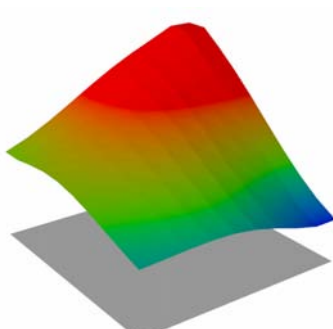
hmphhmhhmhxx



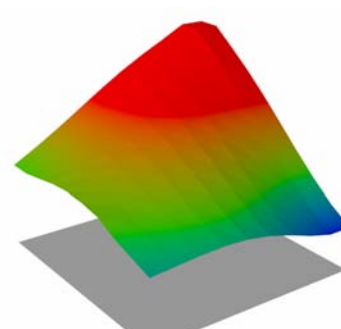
hmphhmmhxxhh



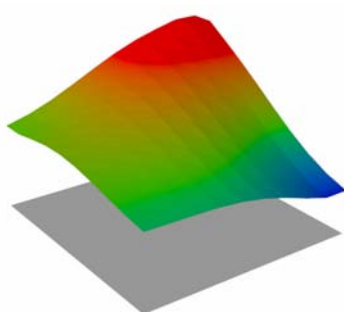
hmphhmxxhmhh



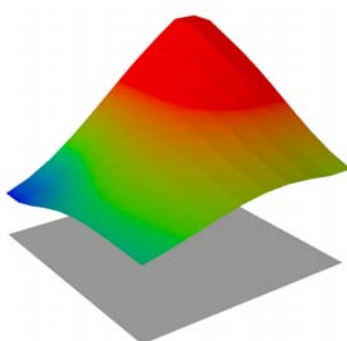
hmpmhmmhxxhh



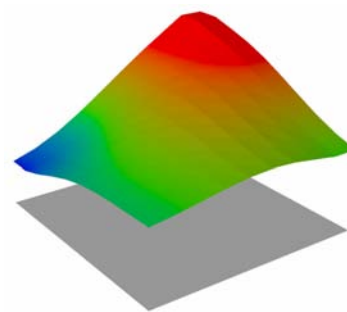
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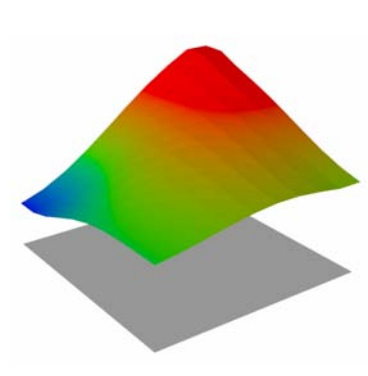
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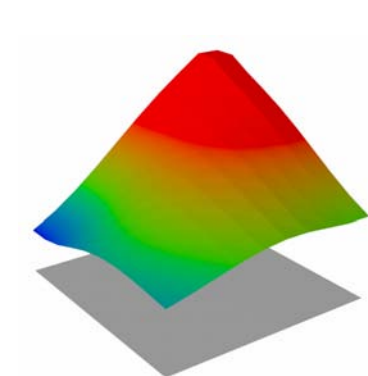
mhphhhhhmmxx



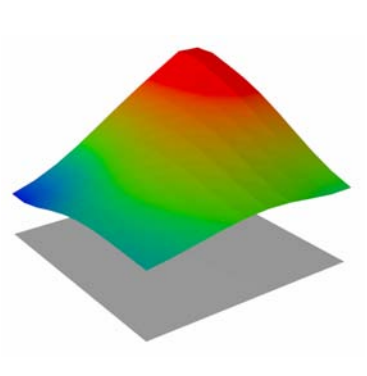
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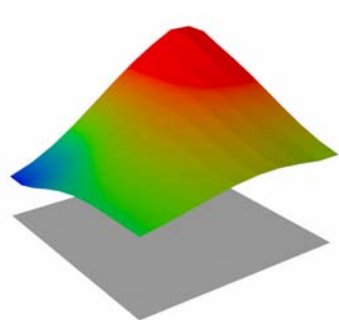
mhphmhhhmhxx



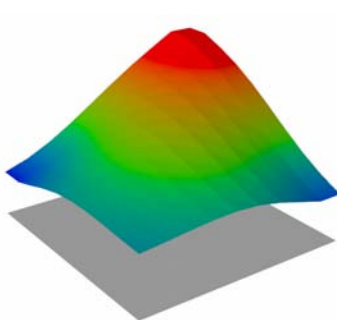
mhphmhhmxxhh



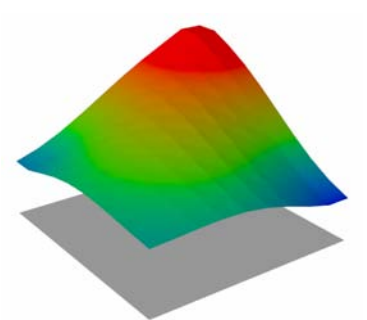
mhphmxxxhmmh



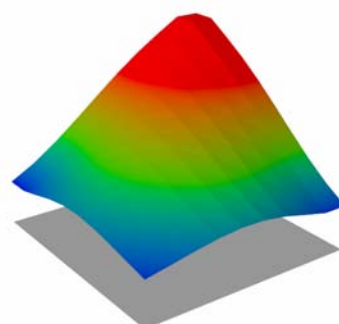
mhpmmhhhhmxx



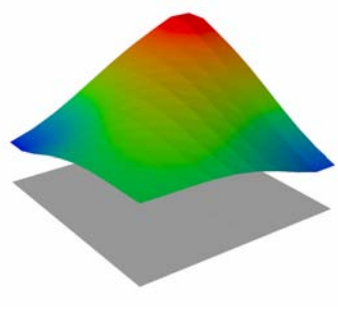
mmphhhhhhmxx



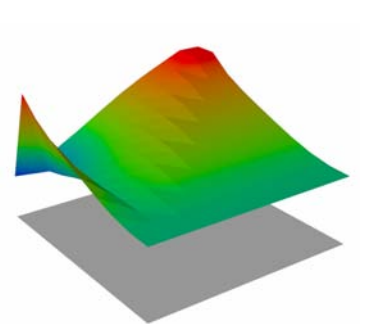
mmphhhhhmxx



mmphhhhmxxhh



mmphhmhhhhxx



mmphmxxhhhh

4.5 Coset Analysis Program

4.5.1 Procedure for generation of array

Code Fragment 1:

```

void FindAllStructures(wxString desc, wxString cons, RuleList rules, int level,
                      wxString immovable)
{
    if(debug)printf("FindAllStructures().entry\n");
    //  What happens here is this:
    //  we have an array that goes up to number level, say 2000 or 3000 so
    //  we start with one element in that array at position [0]
    //  the counters i and k move along the array, k faster than i because
    //  the structure at position i creates several new structures, k keeps track
    //  with each one as they are generated.
    //  if a duplicate structure is generated it is flagged - enanti or dupli
    //  a duplicate is not used to generate any further structures.
    //  the rules are used to create these new structures

    output_t output_type = t_class_dotty;
    wxProgressDialog * progressdlg = new wxProgressDialog
                                   ("Progress", "generating list",1000,NULL,
                                   wxPD_CAN_ABORT | wxPD_ELAPSED_TIME | wxPD_AUTO_HIDE);

    wxString tempstr;
    //local declarations
    wxString tmpdesc=wxString(desc); //Descriptor of substitutions
    wxString tmpcons=wxString(cons); //Constructor ie path to substitution pattern
    Bornane newnode;
    int current=0, //parent position
        generated=0, //child position
        total=1, //number of unique structures
        totalmeer=0, //total of unique nonclassical structures
        totalenant=0; //number of unique (by enantiomer) structures

    //Set current bornane to have current descriptor and constructor
    all[current].Set(desc,cons);
    if(debug)kprint(all[current].descriptor);
    if(debug)printf("rule number is %d\n",rules.ruleno);
    while(generated<level && current<level && current <= generated)
    {
        //current is the position of the parent
        //generating children at position generated
        //create new node identical to current one
        newnode=all[current];
        //we only use the current structure to create children if it is not already
        //a duplicate. Else we doubly duplicate children
        //if(all[current].dupli<0)
        if(all[current].duporenanti<0)
        {
            bool containsx;
            //If the current is not a duplicate we use each appropriate rule to create
            //a child for the current
            for(int j=0;j<rules.ruleno;j++)
            {
                containsx=false; //check inappropriate rule
                ///////////////////////////////////////////////////
                //FOR THIS RULE IS IT APPROPRIATE TO MOVE THIS GROUP?
                if(rules.movpos[j]<0); //no moving groups (eg WM) therefore rule will apply
                else if(immovable.Contains(newnode.p[rules.movpos[j]]))
                //these are positions X than do not move on any rule
                //The rule j defines the position that will move rules.movpos[j].
            }
        }
    }
}

```



```

//The actual moving group will be newnode.p[this position]
//If this actual group should be immovable then the group will
//be contained in the immovable string (eg Br X) and
containsx=true;
else if(rules.immovable[j].Contains(newnode.p[rules.movpos[j]]))
//these are groups that do not move with this particular rule
containsx=true;
////////////////////////////////////////////////////////////////////////////////////////////////////////////////////////////////
////////////////////////////////////////////////////////////////////////////////////////////////////////////////////////////////
//HAVE WE JUST USED THIS RULE?
//eg WMWM=1, 6262=1, 23e23e=1;
if(all[current].finalrule>0)
{
    if(rules.names[all[current].finalrule]==rules.names[j])containsx=true;
    //contains immovable group because double appl of single rule is unity
}
////////////////////////////////////////////////////////////////////////////////////////////////////////////////////////////////
////////////////////////////////////////////////////////////////////////////////////////////////////////////////////////////////
//
tmpdesc.Empty();tmpcons.Empty();
////////////////////////////////////////////////////////////////////////////////////////////////////////////////////////////////
//If the rule matches the parent and not immovable ito groups + prev rule
//we can generate a child
if((newnode.pospos==rules.pospos[j]) && !containsx)
{
    //printf("Matching rule %d for molecule %d\n",j,i);
    int l;
    //To construct the child construct the parent and add the rule
    //for the child eg parent WM23ewM rule 62 child is WM23ewM62
    tmpcons=newnode.construct+rules.names[j];
    //Create the child descriptor using the rules
    for(l=0;l<12;l++)
    {
        tmpdesc=tmpdesc+newnode.p[rules.rules[j][l]];
        //Split the groups in the descriptor with a space
        if(l<11){tmpdesc=tmpdesc+" ";}
    }
    //We are ready to create the actual child
    generated++;
    //create the child
    all[generated].Set(tmpdesc,tmpcons);
    //NOTE: we record the final rule to create this child
    all[generated].finalrule=j;
    //compare the child against all generated children
    //to mark it if it is a duplicate or an enantiomer
    for(l=0;l<generated;l++)
    {
        if(all[generated]==all[l])
        {all[generated].dupli=l;all[generated].duporenanti=1;l=generated;}
    }
    if(all[generated].dupli<0)
    {
        //Have checked right through and are happy it is not a duplicate
        //but it could still be an enantiomer
        for(l=0;l<generated;l++)
        {
            if(all[generated].isenantiomer(all[l]))
            {all[generated].enanti=l;all[generated].duporenanti=1;l=generated;}
        }
    }
    if(all[generated].dupli<0)
    {
        //Have checked right through and are happy it is not a duplicate
        //but it could also be a meer
        for(l=0;l<=generated;l++)
        {
            if(all[generated].ismeer(all[l]))

```

```

        {
            all[generated].meer=l;
            printf("meer : ");printf(all[generated].descriptor);printf("-");
            printf(all[l].descriptor);
            if(l==generated)printf(" ***");
            printf("\n");
            l=generated;
        }
    }
}
//Update the totals
if(all[generated].dupli<0){all[generated].uniqueseq=total;total++;}
if(all[generated].enanti>=0)totalenant++;
if(all[generated].meer>=0)totalmeer++;
//mark the current child's parent as the current
all[generated].parent=current;
}
}
}
for(int j=0;j<rules.ruleno;j++)
for(int n=0;n<rules.substno;n++)
{
    //////////////////////////////////////
    //
    tmpdesc.Empty();tmpcons.Empty();
    //////////////////////////////////////
    //If the rule matches the parent and not immovable ito groups + prev rule
    //we can generate a child
    tmpdesc=newnode.descriptor;
    if((newnode.descriptor).Contains(rules.substitutions[n][0]))
    {
        //printf("Matching rule %d for molecule %d\n",j,i);
        int l;
        //To construct the child construct the parent and add the rule
        //for the child eg parent WM23ewM rule 62 child is WM23ewM62
        tmpcons=newnode.construct+rules.substnames[n];
        tmpdesc=newnode.descriptor;
        //Create the child descriptor using the rules and a enantiomer descriptor
        tmpdesc.Replace(rules.substitutions[n][0],rules.substitutions[n][1]);
        //We are ready to create the actual child
        generated++;
        //create the child
        all[generated].Set(tmpdesc,tmpcons);
        //NOTE: we record the final rule to create this child
        all[generated].finalrule=n+rules.ruleno;
        //make it out of ruleno range to hint to look at subst
        //compare the child against all generated children
        //to mark it if it is a duplicate or an enantiomer
        for(l=0;l<generated;l++)
        {
            if(all[generated]==all[l])
            {all[generated].dupli=l;all[generated].duporenanti=1;l=generated;}
        }
        if(all[generated].dupli<0)
        {
            //Have checked right through and are happy it is not a duplicate
            //but it could still be an enantiomer
            for(l=0;l<generated;l++)
            {
                if(all[generated].isenantiomer(all[l]))
                {all[generated].enanti=l;all[generated].duporenanti=1;l=generated;}
            }
        }
        if(all[generated].dupli<0)
        {
            //Have checked right through and are happy it is not a duplicate
            //but it could also be a meer
            for(l=0;l<=generated;l++)
            {

```

```

        if(all[generated].ismeer(all[l]))
        {
            all[generated].meer=l;
            printf("meer : ");printf(all[generated].descriptor);printf("-");
            printf(all[l].descriptor);
            if(l==generated)printf(" ***");
            printf("\n");
            l=generated;
        }
    }
}
//Update the totals
if(all[generated].dupli<0){all[generated].uniqueseq=total;total++;}
if(all[generated].enanti>=0)totalenant++;
if(all[generated].meer>=0)totalmeer++;
//mark the current child's parent as the current
all[generated].parent=current;
}
}
}
all[current].duporenanti=0;
//Create all children for the next structure
current++;
tempstr.sprintf("current: %7d generated: %7d \nunique: %7d enantiomers : %7d\n",
current,generated,total,totalenant);
if(!progressdlg->Update((int)(1000.0*(float)current/(float)generated),tempstr))
{progressdlg->Destroy();return;}
}
printf("current was %d, generated was %d \n",current,generated);
printf("total is %d of which %d are enantiomers of others\n",total,totalenant);
printf("and total of meers is %d\n",totalmeer);
progressdlg->Destroy();
for(int n=0;n<=generated;n++)
{
    printf("%d\tp %d\td %d\te %d\tu %d\t", n , all[n].parent, all[n].dupli,
all[n].enanti, all[n].uniqueseq );
    if(all[n].finalrule>=0) printf(rules.names[all[n].finalrule]);
    printf("\t\t");
    printf(all[n].descriptor);
    printf("\n");
}
int intfirst,intsecond,intrule,inttemp;
for(int n=0;n<=generated;n++)
{
    if(all[n].dupli>=0)
    {
        intfirst=all[n].parent;intsecond=all[n].dupli;intrule=all[n].finalrule;
    }
    else if(all[n].enanti>=0)
    {
        intfirst=all[n].parent;intsecond=all[n].enanti;intrule=all[n].finalrule;
    }
    else
    {
        intfirst=all[n].parent;intsecond=n;intrule=all[n].finalrule;
    }
    if(intfirst>intsecond){inttemp=intfirst;intfirst=intsecond;intsecond=inttemp;}
    bool dupconnection=false;
    for(int m=0;m<n;m++)
    {
        if((connectors[0][m]==intfirst)&&(connectors[1][m]==intsecond))
            dupconnection=true;
    }
    //note this will not take into account different connectors for exo/endo shifts
    //but when there is a choice of endo/exo leading to identical products exo should
    //prevail unless it is obvious
    if(!dupconnection)
    {

```


4.6 Transition State Searching Program

4.6.1 Procedures for generation of transition state guesses

Code Fragment 2:

```

void MyCanvas::OnMouse(wxMouseEvent& event)
{
    ...
    if (event.Dragging())
        //click and drag to rotate both molecules for easy accessibility
        {
            ...
        }
    if(event.RightUp())
    {
        //retrieve the closest atom id
        //convert to an atom number on the second molecule
        //match this to the last selected atom from the first molecule
        ...
    }
    if(event.LeftDClick())
    {
        //retrieve the closest atom id
        //convert to an atom number on the first molecule
        //i.e select an atom from the first molecule to be matched
        //with the second
        {}
    }
    info.beginx = event.GetX();
    info.beginy = event.GetY();
}

static int GetSpiroNo(int firstmol,wxString filename)
//return the atom number of the spiro carbon.
{
    ...
}

static int RotateMol(double theta,point vector)
//rotate the product molecule
{
    ...
}

static void FlipMol()
//enantiomerize the product molecule (for if the wrong enantiomer is drawn)
{
    ...
}

void AlignMolecules()
//make a good attempt at aligning the two structures to start with
//and save time with manual rotation etc for the 526 transition states
{
    ...
}

void MatchAtoms()
{
    //do the best to create an initial atom match
    //that will minimize manual work
    //best way to start is to match atoms on the
    //xylyl group. Not a very general procedure
    //just to solve this particular problem
    ...
}

void LoadMolecules()

```

```

//read in the next pair of molecules for processing
{
    ...
}

void WriteAverages()
//write a series of 21 weighted averages as GAMESS input files
{
    for(i=0;i<21;i++)
    {
        weight=(double)i;
        weight/=20.0;
        num.sprintf("%d",i);
        if(i<10)num="0"+num;
        molfile=
            fopen("energies/"+filenames[currentselection].Left(25)+"-"+num+".inp","w");
            fprintf(molfile," $contrl coord=cart units=angs\n");
            fprintf(molfile,"          scftyp=rhf runtyp=energy\n");
            fprintf(molfile,"          icharg=1 exetyp=run maxit=100\n");
            fprintf(molfile," $end\n\n");
            fprintf(molfile," $scf dirscf=.true. $end\n");
            fprintf(molfile," $system memory=14000000 timlim=1200000\n");
            fprintf(molfile," $end\n");
            fprintf(molfile," $statpt opttol=1.0E-6 nstep=500 $end\n");
            fprintf(molfile," $basis gbasis=AM1 $end\n");
            fprintf(molfile," $guess guess=huckel $end\n\n");
            fprintf(molfile," $data\n\n");
            fprintf(molfile,"C1\n");

            for(j=0;j<NUMBER_ATOMS;j++)
            {
                x1=molecule1[j].x;y1=molecule1[j].y;
                z1=molecule1[j].z;
                x2=molecule2[atommatch[j]].x;
                y2=molecule2[atommatch[j]].y;
                z2=molecule2[atommatch[j]].z;
                dx=x2-x1;dy=y2-y1;dz=z2-z1;
                fprintf(molfile," %c      %2.1f %2.8f %2.8f %2.8f\n",
                    molecule1[j].type,molecule1[j].mass,
                    x1+weight*dx,
                    y1+weight*dy,
                    z1+weight*dz);
            }
            fprintf(molfile," $end\n");
            fclose(molfile);
        }
    }
}

bool MyApp::OnInit()
{
    ...
    LoadMolecules();
    ...
}

//enantiomerize the second of the pair
void MyFrame::OnFlip(wxCommandEvent& WXUNUSED(event)){pcanvas->OnFlip();}
//write averages and move to the next pair
void MyFrame::OnNextMol(wxCommandEvent& WXUNUSED(event)){pcanvas->OnNextMol();}
//rotate backwards (x,y or z) the second of the pair
void MyFrame::OnXBack(wxCommandEvent& WXUNUSED(event)){pcanvas->OnXBack();}
void MyFrame::OnYBack(wxCommandEvent& WXUNUSED(event)){pcanvas->OnYBack();}
void MyFrame::OnZBack(wxCommandEvent& WXUNUSED(event)){pcanvas->OnZBack();}
//rotate forward (x,y or z) the second of the pair
void MyFrame::OnXForward(wxCommandEvent& WXUNUSED(event)){pcanvas->OnXForward();}
void MyFrame::OnYForward(wxCommandEvent& WXUNUSED(event)){pcanvas->OnYForward();}
void MyFrame::OnZForward(wxCommandEvent& WXUNUSED(event)){pcanvas->OnZForward();}
void MyFrame::OnMatch(wxCommandEvent& WXUNUSED(event)){pcanvas->OnMatch();}

```

4.7 Generation of structures for computational analysis

Code Fragment 3:

```

// 9 possible places to put 3 methyl groups, so
for(i=2;i<9;i++){
  for(j=1;j<i;j++){
    for(k=0;k<j;k++){
      // generate filename
      ...
      // open file with filename
      ...
      // write out header information (gamess input)
      ...
      // write base carbon skeleton (norbornyl carbons)
      ...
      // write base carbon skeleton (xylyl group carbons and hydrogens)
      for(l=0;l<9;l++){
        if(l==i || l==j || l==k){
          // print methyls i,j,k
          ...
        }
        else{
          // print all hydrogens not i,j,k
          ...
        }
      }
    }
  }
  // close file
} // for(k ...
} // for(j ...
} // for(i ...

```

References

1. P. W. M. Jacobs, *J. Phys. Chem. B*, 1997, **101**, 10086–10093.
2. W. A. Durham, *Pacific Affairs*, 1932, **5**, 797–801.
3. R. P. Ellis, *Ecoport Picture Databank - Cinnamomum camphora*, online: <http://ecoport.org/ep?SearchType=pdb&PdbID=16632>, Accessed: 13 Nov 2007.
4. J. L. Simonsen, In *The Terpenes, The Dicyclic Terpenes and their Derivatives*, Cambridge University Press, 1949, Chapter V, Vol 2, 372–373.
5. J. Bredt, *Ber.*, 1893, **26**, 3047.
6. J. Bredt and J. W. H. Perkin, *J. Chem. Soc., Trans.*, 1913, **103**, 2182–2225.
7. T. P. Nevell, E. deSalas and C. L. Wilson, *J. Chem. Soc.*, 1939, 1188–1199.
8. G. A. Olah, *J. Org. Chem.*, 2001, **66**, 5943–5957.
9. G. A. Olah, G. K. S. Prakash and M. Saunders, *Acc. Chem. Res.*, 1983, **16**, 440–448.
10. M. Avalos, R. Babiano, P. Cintas, J. L. Jimenez, J. C. Palacios and L. D. Barron, *Chem. Rev.*, 1991, **63**, 2391–2404.
11. R. M. Orcutt and M. T. Bogert, *J. Org. Chem.*, 1939, **4**, 543–547.
12. H. C. Brown and G. Zweifel, *J. Am. Chem. Soc.*, 1961, **83**, 486–487.
13. H. C. Brown and P. V. Ramachandran, *Pure & Appl. Chem.*, 1991, **63**, 307–316.
14. E. J. Corey and H. E. Ensley, *J. Am. Chem. Soc.*, 1968, **97**, 6908–6909.
15. The Royal Swedish Academy of Sciences, *The Nobel Prize in Chemistry 2001 - Information for the Public*, online: <http://nobelprize.org/chemistry/laureates/2001/public.html>, Accessed: 11 Nov 2007.
16. T. Katsuki and K. B. Sharpless, *J. Am. Chem. Soc.*, 1980, **102**, 5974–5976.
17. FDA, *FDA's policy statement for the development of new stereoisomeric drugs*, online: <http://www.fda.gov/cder/guidance/stereo.htm>, Accessed : 13 Nov 2007.
18. S. C. Stinson, *Chem. Eng. News*, 2001, **79**, 45–47.
19. A. M. Rouhi, *Chem. Eng. News*, 2003, **81**, 45–55.
20. W. Carruthers, In *Some Modern Methods of Organic Synthesis*, ed. 3, Cambridge University Press, 1986.
21. D. Cain, *Alkylations of Enols and Enolates*, In *Comprehensive Organic Synthesis*, Pergamon, New York, 1991, Vol 3.
22. A. I. Meyers, M. A. Seefeld, B. A. Lefker, J. F. Blake and P. G. Williard, *J. Am. Chem. Soc.*, 1998, **120**, 7429–7438.

-
23. D. A. Evans, *Stereoselective Alkylation Reactions of Chiral Metal Enolates In Asymmetric Synthesis*, Academic Press, 1984, Vol 3.
24. A. Streitwieser, *J. Mol. Model.*, 2006, **12**, 673–680.
25. A. J. McNeil, G. E. S. Toombes, S. M. Gruner, E. Lobkovsky, D. B. Collum, S. V. Chandramouli, B. J. Vanasse and T. A. Ayers, *J. Am. Chem. Soc.*, 1963, **85**, 16559–16568.
26. A. V. Yakimansky and A. H. E. Müller, *J. Am. Chem. Soc.*, 2001, **123**, 4932–4937.
27. L. M. Pratt and A. Streitweiser, *J. Am. Chem. Soc.*, 2003, **68**, 2830–2838.
28. P. G. Williard and G. J. MacEwan, *J. Am. Chem. Soc.*, 1989, **111**, 7671–7672.
29. M. Suzuki, H. Koyama and R. Noyori, *Tetrahedron*, 2004, **60**, 1571–1579.
30. J. A. Miller and H. D. Zook, *J. Org. Chem.*, 1977, **42**, 2629–2631.
31. C. S. Pomelli, A. M. Bianucci, P. Crotti and L. Favero, *J. Org. Chem.*, 2004, **69**, 150–157.
32. S. Tomoda, *Chem. Rev.*, 1999, **99**, 1243–1263.
33. B. W. Gung, *Tetrahedron*, 1996, **52**, 5263–5301.
34. K. Ando, N. S. Green, Y. Li and K. N. Houk, *J. Am. Chem. Soc.*, 1999, **121**, 5334–5335.
35. Y. Ikuta and S. Tomoda, *Org. Lett.*, 2003, **6**, 189–192.
36. Y. Ikuta and S. Tomoda, *Tetrahedron Lett.*, 2003, **44**, 5931–5934.
37. K. A. Durkin and D. Liotta, *J. Am. Chem. Soc.*, 1990, **112**, 8162–8163.
38. W. Oppolzer, *Tetrahedron*, 1987, **43**, 1969–2004.
39. *Comprehensive Chemical Kinetics*, Elsevier, 1969, Vol 2.
40. B. W. Gung, *Tetrahedron*, 1996, **52**, 5263–5301.
41. K. M. Ervin, *Int. J. Mass. Spect.*, 1999, **120**, 343–350.
42. C. A. Tolman, *Chem. Rev.*, 1977, **77**, 313–348.
43. D. White, B. Taverner, P. Leach and N. Coville, *Adv. Organomet. Chem.*, 1994, **205**, 478.
44. M. Willis, M. Palmer, A. Smith, J. Kenny and T. Walsgrove, *Molecules*, 2000, **5**, 4–18.
45. T. Money, *Natural Product Reports*, 1985, **2**, 253–290.
46. J. March, In *Advanced Organic Chemistry*, ed. 4, John Wiley & Sons, 1188–1189.
47. D. L. Gamble, W. P. Hems and B. Ridge, *J. Chem. Soc. Perkin Trans. 1*, 2001, **1**, 248–260.
48. G. Helmchen, A. Selim, D. Dorsch and I. Taufer, *Tetrahedron Lett.*, 1983, **24**, 3213–3216.

-
49. T. Langer, M. Illich and G. Helmchen, *Tetrahedron Lett.*, 1995, **36**, 4409.
 50. A. G. Csákÿ and J. Plumet, *Chem. Soc. Rev.*, 2001, **30**, 313–320.
 51. H. C. Brown, *Acc. Chem. Res.*, 1983, **16**, 432–440.
 52. K. Raghavachari, R. C. Haddon, P. von R. Schleyer and H. F. Schaefer III, *J. Am. Chem. Soc.*, 1983, **105**, 5915–5917.
 53. C. Walling, *J. Am. Chem. Soc.*, 1983, **16**, 448–454.
 54. S. Winstein and H. J. Lucas, *J. Am. Chem. Soc.*, 1938, **60**, 836–847.
 55. S. Winstein and E. Grunwald, *J. Am. Chem. Soc.*, 1948, **70**, 828–837.
 56. S. Winstein and D. S. Trifan, *J. Am. Chem. Soc.*, 1949, **71**, 2953.
 57. S. Winstein, E. Clippinger, R. Howe and E. Vogelfanger, *J. Am. Chem. Soc.*, 1965, **87**, 376–377.
 58. S. Winstein and D. S. Trifan, *J. Am. Chem. Soc.*, 1952, **74**, 1147–1154.
 59. S. Winstein and D. S. Trifan, *J. Am. Chem. Soc.*, 1952, **74**, 1154–1160.
 60. S. Winstein and K. C. Schreiber, *J. Am. Chem. Soc.*, 1952, **74**, 2165–2170.
 61. S. Winstein, *J. Am. Chem. Soc.*, 1965, **87**, 381–382.
 62. S. Winstein and N. J. Holness, *J. Am. Chem. Soc.*, 1955, **77**, 3054–3061.
 63. P. von R. Schleyer, W. E. Watts and C. Cupas, *J. Am. Chem. Soc.*, 1964, **86**, 2722–2723.
 64. E. C. Friedrich and S. Winstein, *J. Am. Chem. Soc.*, 1964, **86**, 2721–2722.
 65. S. Winstein, M. Shatavsky, C. Norton and R. B. Woodward, *J. Am. Chem. Soc.*, 1955, **77**, 4183–4184.
 66. S. Winstein and E. T. Stafford, *J. Am. Chem. Soc.*, 1957, **79**, 505–506.
 67. S. Winstein, M. Shatavsky, C. Norton and R. B. Woodward, *J. Am. Chem. Soc.*, 1956, **78**, 592–597.
 68. S. Winstein and C. Ordronneau, *J. Am. Chem. Soc.*, 1960, **82**, 2084–2085.
 69. P. R. Story and M. Saunders, *J. Am. Chem. Soc.*, 1962, **84**, 4876–4882.
 70. H. C. Brown and R. B. Kornblum, *J. Am. Chem. Soc.*, 1954, **76**, 4510–4515.
 71. H. C. Brown and M. Nakagawa, *J. Am. Chem. Soc.*, 1955, **77**, 3614–3619.
 72. H. C. Brown and H. M. Bell, *J. Am. Chem. Soc.*, 1963, **85**, 2324.
 73. P. R. Story, *J. Am. Chem. Soc.*, 1961, **83**, 3347–3349.
 74. H. M. Bell and H. C. Brown, *J. Am. Chem. Soc.*, 1964, **86**, 5007–5008.
 75. R. Howe, E. C. Friedrich and S. Winstein, *J. Am. Chem. Soc.*, 1965, **87**, 379–381.

-
76. S. Winstein, A. H. Lewin and K. C. Pande, *J. Am. Chem. Soc.*, 1963, **85**, 2324–2326.
77. P. von R. Schleyer, D. C. Kleinfelter and H. G. Richey, *J. Am. Chem. Soc.*, 1963, **85**, 479–481.
78. H. C. Brown and H. M. Bell, *J. Am. Chem. Soc.*, 1964, **86**, 5003–5004.
79. H. C. Brown and F. J. Chloupek, *J. Am. Chem. Soc.*, 1963, **85**, 2322–2324.
80. H. C. Brown, F. J. Chloupek and M. H. Rei, *J. Am. Chem. Soc.*, 1964, **86**, 1246–1247.
81. H. C. Brown, F. J. Chloupek and M. H. Rei, *J. Am. Chem. Soc.*, 1964, **86**, 1247–1248.
82. H. C. Brown, F. J. Chloupek and M. H. Rei, *J. Am. Chem. Soc.*, 1964, **86**, 1248–1250.
83. P. von R. Schleyer, *J. Am. Chem. Soc.*, 1967, **89**, 701 – 703.
84. H. C. Brown and M. H. Rei, *J. Am. Chem. Soc.*, 1964, **86**, 5004–5005.
85. H. C. Brown and H. M. Bell, *J. Am. Chem. Soc.*, 1964, **86**, 5006–5007.
86. D. Lenoir, Y. Apeliog, D. Arad and P. von R. Schleyer, *J. Am. Chem. Soc.*, 1988, **53**, 661–675.
87. H. C. Brown and G. L. Tritle, *J. Am. Chem. Soc.*, 1966, **88**, 1320–1322.
88. H. C. Brown and G. L. Tritle, *J. Am. Chem. Soc.*, 1968, **90**, 2689–2691.
89. H. C. Brown and K. T. Liu, *J. Am. Chem. Soc.*, 1969, **91**, 5909–5911.
90. H. C. Brown and K. Takeuchi, *J. Am. Chem. Soc.*, 1966, **88**, 5336–5338.
91. H. C. Brown and K. Takeuchi, *J. Am. Chem. Soc.*, 1968, **90**, 2691–2693.
92. K. Takeuchi and H. C. Brown, *J. Am. Chem. Soc.*, 1968, **90**, 2693–2694.
93. H. C. Brown and K. Takeuchi, *J. Am. Chem. Soc.*, 1968, **90**, 5268–5270.
94. K. Takeuchi and H. C. Brown, *J. Am. Chem. Soc.*, 1968, **90**, 5270–5272.
95. H. C. Brown and S. Ikegami, *J. Am. Chem. Soc.*, 1968, **90**, 7122–7124.
96. S. Ikegami, D. L. van der Jagt and H. C. Brown, *J. Am. Chem. Soc.*, 1968, **90**, 7124–7126.
97. H. C. Brown and W. J. Hammar, *J. Am. Chem. Soc.*, 1967, **89**, 6378–6380.
98. H. C. Brown, I. Rothberg and D. L. van der Jagt, *J. Am. Chem. Soc.*, 1967, **89**, 6380–6381.
99. P. von R. Schleyer, *J. Am. Chem. Soc.*, 1964, **86**, 1854–1856.
100. P. von R. Schleyer, *J. Am. Chem. Soc.*, 1964, **86**, 1856–1857.
101. P. von R. Schleyer, M. M. Donaldson and W. E. Watts, *J. Am. Chem. Soc.*, 1965, **87**, 375–376.

-
102. P. von R. Schleyer, W. E. Watts, R. C. Fort, M. B. Comisarow and G. A. Olah, *J. Am. Chem. Soc.*, 1964, **86**, 5679–5680.
103. G. A. Olah, A. M. White, J. R. de Member, A. Commeyras and C. Y. Lui, *J. Am. Chem. Soc.*, 1970, **92**, 4627–4640.
104. G. A. Olah, G. Liang, G. D. Mateescu and J. L. Riemenschneider, *J. Am. Chem. Soc.*, 1973, **95**, 8698–8702.
105. C. S. Yannoni, V. Macho and P. C. Myhre, *J. Am. Chem. Soc.*, 1982, **104**, 7380–7381.
106. L. Thomas, *J. Am. Chem. Soc.*, 1989, **111**, 9224–9232.
107. G. A. Olah, J. R. de Member, C. Y. Lui and R. D. Porter, *J. Am. Chem. Soc.*, 1971, **93**, 1442 – 1446.
108. P. Flury and C. A. Grob, *Tetrahedron Lett.*, 1983, **24**, 3195–3198.
109. F. Fuso, C. A. Grob, P. Sawlewicz and Y. Guo-Wei, *Tetrahedron Lett.*, 1985, **26**, 3083–3086.
110. C. A. Grob and P. Sawlewicz, *Tetrahedron Lett.*, 1984, **25**, 2973–2976.
111. Y. Brunel and A. Rassat, *Tetrahedron*, 1978, **34**, 1343–1347.
112. P. R. Schreiner, P. von R. Schleyer and H. F. Schaefer III, *J. Org. Chem.*, 1997, **62**, 4216–4228.
113. N. H. Werstiuk, H. M. Muchall and S. Noury, *J. Phys. Chem. A*, 2000, **104**, 11601–11605.
114. H. M. Muchall and N. H. Werstiuk, *J. Phys. Chem. A*, 1999, **103**, 6599–6602.
115. P. R. Schreiner, P. von R. Schleyer and H. F. Schaefer III, *J. Org. Chem.*, 1997, **62**, 4216–4228.
116. H. C. Brown and H. M. Bell, *J. Am. Chem. Soc.*, 1964, **86**, 5003–5004.
117. L. Radom, J. A. Pople, V. Buss and P. von R. Schleyer, *J. Am. Chem. Soc.*, 1972, **94**, 311–321.
118. P. Brunelle, T. S. Sorensen and C. Taeschler, *J. Org. Chem.*, 2001, **66**, 7294 – 7302.
119. L. Birladeanu, *J. Chem. Ed.*, 2000, **77**, 858–863.
120. H. Meerwein, *Ann. Chem.*, 1914, **405**, 129.
121. J. R. Hanson, In *Wagner-Meerwein Rearrangements in Asymmetric Synthesis*, Academic Press, New York, 1984, Vol 3.
122. F. Ebmeyer, *Theochem*, 2002, **582**, 251–255.
123. C. J. Collins, C. K. Johnson and V. F. Raaen, *J. Am. Chem. Soc.*, 1974, **96**, 2524–2531.
124. C. R. Eck, R. W. Mills and T. Money, *J. Chem. Soc. Perkin Trans. 1*, 1975, 251–254.
125. C. Cerda-García-Rojas, C. A. Flores-Sandoval, L. U. Román, J. D. Hernández and P. Joseph-Nathan, *Tetrahedron*, 2002, **58**, 1061–1068.

-
126. M. Saunders, P. von R. Schleyer and G. A. Olah, *J. Am. Chem. Soc.*, 1964, **86**, 5680–5681.
127. A. G. Martínez, E. T. Vilar, A. G. Fraile, A. H. Fernández, C. S. de La Moya and F. M. Jiménez, *Tetrahedron*, 1998, **54**, 4607–4614.
128. M. H. Rei and H. C. Brown, *J. Am. Chem. Soc.*, 1966, **88**, 5335–5336.
129. H. C. Brown and K. T. Liu, *J. Am. Chem. Soc.*, 1967, **89**, 466–467.
130. H. C. Brown and K. T. Liu, *J. Am. Chem. Soc.*, 1967, **89**, 3898–3900.
131. H. C. Brown and K. T. Liu, *J. Am. Chem. Soc.*, 1967, **89**, 3900–3901.
132. W. B. Smith, *J. Org. Chem.*, 1999, **64**, 60–64.
133. M.-H. Rei and H. C. Brown, *J. Am. Chem. Soc.*, 1966, **88**, 5335–5336.
134. B. M. Benjamin and C. J. Collins, *Tetrahedron Lett.*, 1966, **45**, 5477–5481.
135. V. F. Raaen, B. M. Benjamin and C. J. Collins, *Tetrahedron Lett.*, 1971, **28**, 2613–2616.
136. P. C. Moews, J. R. Knox and W. R. Vaughan, *J. Am. Chem. Soc.*, 1978, **100**, 260–264.
137. P. von R. Schleyer, *J. Am. Chem. Soc.*, 1967, **89**, 699 – 701.
138. J. D. Roberts and C. C. Lee, *J. Am. Chem. Soc.*, 1951, **73**, 5009–5010.
139. C. J. Collins, Z. K. Cheema, R. G. Werth and B. M. Benjamin, *J. Am. Chem. Soc.*, 1964, **86**, 4913–4917.
140. A. Colter, E. C. Friedrich, N. J. Holness and S. Winstein, *J. Am. Chem. Soc.*, 1965, **87**, 378–379.
141. P. Cachia, N. Darby, C. R. Eck and T. Money, *J. Chem. Soc. Perkin Trans. 1*, 1976, 359–362.
142. R. Antkowiak and W. Z. Antkowiak, *Polish J. Chem*, 1994, **68**, 2297.
143. A. W. Bushell and J. Pelham Wilder, *J. Am. Chem. Soc.*, 1967, **89**, 5721–5722.
144. H. J. E. Baldwin and T. C. Barden, *J. Am. Chem. Soc.*, 1983, **105**, 6656–6662.
145. G. M. Kramer, C. G. Scouten, R. V. Kastrup, E. R. Ernst and C. F. Pictroski, *J. Phys. Chem.*, 1989, **93**, 6257–6260.
146. M. Saunders, *J. Phys. Chem.*, 1990, **94**, 6509–6511.
147. E. Spohr and M. Wolfsberg, *J. Phys. Chem.*, 1990, **94**, 6511–6512.
148. E. Ranzi, T. Faravelli, P. Gaffuri, E. Garavaglia and A. Goldaniga, *Ind. Eng. Chem. Res.*, 1997, **36**, 3336–3344.
149. R. V. Sole and A. Munteanu, *Europhys. Lett.*, 2004, **68**, 170–176.
150. C. K. Johnson and C. J. Collins, *J. Am. Chem. Soc.*, 1974, **96**, 2514–2523.

151. C. J. Collins and C. K. Johnson, *J. Am. Chem. Soc.*, 1973, **95**, 4766–4768.
152. T. S. Sorensen, *Acc. Chem. Res.*, 1976, **9**, 257–265.
153. O. R. Rodig and R. J. Sysko, *J. Am. Chem. Soc.*, 1972, **94**, 6475–6479.
154. J. Gunawardena, *Chemical reaction network theory for in-silico biologists*, online: <http://vcp.med.harvard.edu/papers/crnt.pdf>, 2003, Accessed 11 Nov 2007.
155. P. T. Kaye and R. A. Learmonth, *S. Afr. J. Chem.*, 1990, **43**, 114–116.
156. M. D. Evans *Asymmetric Induction in Reactions of Chiral Carboxylic Esters and Silyl Enol Ethers*, Ph.D. Thesis, Rhodes University, 1997.
157. P. T. Kaye and S. S. Ravindran, *S. Afr. J. Chem.*, 1994, **47**, 17–20.
158. P. T. Kaye and S. S. Ravindran, *S. Afr. J. Chem.*, 1995, **48**, 64–70.
159. M. D. Evans and P. T. Kaye, *Synth. Comm.*, 1998, **28**, 4485–4494.
160. M. D. Evans and P. T. Kaye, *Synth. Comm.*, 2001, **31**, 805–815.
161. P. T. Kaye and W. E. Molema, *Chem. Commun.*, 1998, 2479–2480.
162. J. M. Matjila *Applications of Camphor-Derived Chiral Auxiliaries in the Asymmetric Synthesis of α -amino acids and other systems*, Ph.D. Thesis, Rhodes University, 1998.
163. R. Klein “Asymmetric α -alkylation reactions”, M.Sc. Thesis, Rhodes University, 1999.
164. W. Oppolzer, G. Poli, C. Starkemann and G. Bernardinelli, *Tetrahedron Lett.*, 1988, **29**, 3559–3562.
165. J. N. Shoolery, *Prog. NMR Spec.*, 1977, **11**, 79–93.
166. J. S. Cha, S. J. Moon, O. O. Kwon and Y. R. Lee, *Bull. Korean Chem. Soc.*, 2000, **21**, 128–130.
167. M. Karplus, *J. Am. Chem. Soc.*, 1963, **85**, 2870–2871.
168. E. J. Corey and R. A. Sneed, *J. Am. Chem. Soc.*, 1956, **78**, 6269–6269.
169. S. S. Ravindran *Studies in Asymmetric Synthesis*, Ph.D. Thesis, Rhodes University, 1994.
170. A. R. Duggan *Camphor-Derived Chiral Auxiliaries: A Synthetic, Mechanistic and Computational Study*, Ph.D. Thesis, Rhodes University, 2006.
171. H. Staab and K. Wendel, *Organic Syntheses*, 1968, **48**, 44.
172. J. McMurray, In *Organic Chemistry*, ed. 3, Brooks/Cole, 1992.
173. P.-F. Xu, Y.-S. Chen, S.-I. Lin and T.-J. Lu, *J. Org. Chem.*, 2002, **67**, 2309–2314.
174. P.-F. Xu and T.-J. Lu, *J. Org. Chem.*, 2003, **68**, 658–661.
175. P.-F. Xu, S. Li, T.-J. Lu, C.-C. Wu, B. Fan and G. Golfis, *J. Org. Chem.*, 2006, **71**, 4364–4373.

-
176. M. D. Evans and P. T. Kaye, *S. Afr. J. Chem.*, 1998, **51**, 160–161.
177. W. A. Mosher, *J. Am. Chem. Soc.*, 1947, **69**, 2139–2141.
178. C. M. Alam, S. Hisanori and T. Masao, *Tetrahedron Lett.*, 2003, **44**, 3329–3332.
179. M. Miyashita and A. Yoshikoshi, *J. Am. Chem. Soc.*, 1974, **96**, 1917–1925.
180. C. Hardouin, T. Frédéric and D. Eric, *J. Org. Chem.*, 2001, **66**, 4450–4452.
181. M. H. Shastri and S. Dev, *Tetrahedron*, 1992, **48**, 4905–4918.
182. K. A. Lobb and P. T. Kaye, *S. Afr. J. Chem.*, 2003, **56**, 60–62.
183. M. E. Brown, *Thermochim. Acta*, 1997, **300**, 93–106.
184. R Development Core Team “R: A Language and Environment for Statistical Computing”, R Foundation for Statistical Computing, Vienna, Austria, 2007 ISBN 3-900051-07-0.
185. A. Rappe, C. Casewit, K. Colwell, W. Goddard-III and W. Skiff, *J. Am. Chem. Soc.*, 1992, **114**, 10024–10035.
186. L. Castonguay and A. Rappe, *J. Am. Chem. Soc.*, 1992, **114**, 5832–5842.
187. A. Rappe and K. Colwell, *Inorg. Chem.*, 1993, **32**, 3438–3450.
188. M. W. Schmidt, K. K. Baldridge, J. A. Boatz, S.T.Elbert, M. S. Gordon, J. J. Jensen, S. Koseki, N. Matsunaga, K. A. Nguyen, S. Su, T. L. Windus, M. Dupuis and J. A. Montgomery, *J. Comp. Chem.*, 1993, **14**, 1347–1363.
189. D. V. Sadasivam, E. Prasad, I. R. A. Flowers and D. M. Birney, *J. Phys. Chem. A*, 2006, **110**, 1288–1294.
190. Persistence of Vision Raytracer (Version 3.6), Copyright Persistence of Vision Pty. Ltd. (2004).
191. CPMD V3.11 ©IBM Corp 1990-2006, Copyright MPI fuer Festkoerperforschung Stuttgart 1997-2001.
192. E. R. Gansner and S. C. North, *Softw. Pract. Exper.*, 2000, **30**, 1203–1233.
193. K. J. Caspersen and E. A. Carter, *Proc. Nat. Acad. Sci.*, 2005, **102**, 6738–6743.
194. W. Koch and B. Liu, *J. Am. Chem. Soc.*, 1989, **111**, 1527–1530.
195. Cerius², V.4.0, BIOSYMM/Molecular Simulations Inc.
196. *Note that the node containing 101 and 119 is a discrepancy - run 101 actually failed and has not been repeated, and the energy is that of a xylyl shifted cation.*, .
197. Materials StudioTM, V.2.2, Accelrys Inc.

-
198. M. J. Frisch, G. W. Trucks, H. B. Schlegel, G. E. Scuseria and M. A. Robb, J. R. Cheeseman, Montgomery, Jr., J. A., T. Vreven and K. N. Kudin, J. C. Burant, J. M. Millam, S. S. Iyengar, J. Tomasi and V. Barone, B. Mennucci, M. Cossi, G. Scalmani, N. Rega and G. A. Petersson, H. Nakatsuji, M. Hada, M. Ehara, K. Toyota and R. Fukuda, J. Hasegawa, M. Ishida, T. Nakajima, Y. Honda, O. Kitao and H. Nakai, M. Klene, X. Li, J. E. Knox, H. P. Hratchian, J. B. Cross and V. Bakken, C. Adamo, J. Jaramillo, R. Gomperts, R. E. Stratmann, O. Yazyev, A. J. Austin, R. Cammi, C. Pomelli, J. W. Ochterski, P. Y. Ayala, K. Morokuma, G. A. Voth, P. Salvador, J. J. Dannenberg and V. G. Zakrzewski, S. Dapprich, A. D. Daniels, M. C. Strain and O. Farkas, D. K. Malick, A. D. Rabuck, K. Raghavachari and J. B. Foresman, J. V. Ortiz, Q. Cui, A. G. Baboul, S. Clifford and J. Cioslowski, B. B. Stefanov, G. Liu, A. Liashenko, P. Piskorz and I. Komaromi, R. L. Martin, D. J. Fox, T. Keith, M. A. Al-Laham and C. Y. Peng, A. Nanayakkara, M. Challacombe, P. M. W. Gill and B. Johnson, W. Chen, M. W. Wong, C. Gonzalez and J. A. Pople, Gaussian 03, Revision B.05, Gaussian, Inc., Wallingford, CT, 2004.
199. W. Humphrey, A. Dalke and K. Schulten, *J. Mol. Graph.*, 1996, **14**, 33-38.
200. G. Schaftenaar and J. Noordik, *J. Comput.-Aided Mol. Design*, 2000, **14**, 123-134.
201. I. Fleming and R. B. Woodward, *J. Chem. Soc., C*, 1968, 1289–1289.