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**π -Stacking As A Control Element
In
Asymmetric Synthesis**

Robert Z. D'Attilio

A thesis submitted to the Faculty of
Graduate Studies in partial fulfillment
of the requirements for the degree of
Master of Science

Department of Chemistry
Carleton University

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April 1991

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The undersigned hereby recommend to the Faculty of Graduate Studies the acceptance of this thesis submitted by Robert Z. D'Attilio, B.Sc. in partial fulfillment of the requirements for the degree of Master of Science.

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Chairman of the Chemistry Department

ABSTRACT

An unusual diastereoselectivity in the addition of an acrolein equivalent to 3-(1',4',4'-trimethyl-3'-vinylcyclohex-2'-enyl)-propanal was investigated. It was postulated that this selectivity resulted from an intramolecular π -stacking interaction between the conjugated diene and carbonyl in solution which shielded one face of the latter from nucleophilic attack. The availability of high field NMR spectra enabled us to determine that the alkylation was not stereoselective after all. However, the isolation of a hetero-Diels-Alder adduct still supports the contention that there is an interaction between the diene and carbonyl in solution.

The importance of selecting the appropriate parameters for adding resolution enhancement to an NMR FID prior to Fourier transformation are also discussed.

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ACRONYMS USED IN THIS THESIS

APT	attached proton test
de	diastereomeric excess
DEPT	distortionless enhancement by polarization transfer
DMSO	dimethyl sulfoxide
EDA	electron donor/electron acceptor
ee	enantiomeric excess
FID	free induction decay
FT	Fourier transformation
HOMO	highest occupied molecular orbital
HPLC	high performance liquid chromatography
IR	infrared
J	coupling constant
LUMO	lowest unoccupied molecular orbital
MM2/MMP2	molecular mechanics programs
MNDO	modified neglect of diatomic overlap
NMR	nuclear magnetic resonance
NOE	nuclear Overhauser effect
PCC	pyridinium chlorochromate
PTSA	<i>p</i> -toluenesulfonic acid
RI	refractive index
THF	tetrahydrofuran
TLC	thin layer chromatography
UV	ultraviolet
VIS	visible

The road of excess leads to the palace of wisdom.

–Blake

INTRODUCTION

GENERAL

π -stacking is a general term used to describe the attractive, non-bonded interactions which occur between π -systems. These inter- or intramolecular associations display a diverse array of geometries, ranging from parallel face-to-face (parallel cofacial) to edge-to-face (edge-on) stacking (see Fig. 1).

The stacking of π -systems has been known for over fifty years and has been used to explain:

- 1) complexation in host guest systems^{1,6,9-15}
- 2) vertical base-base interactions in nucleic acids^{3,4}
- 3) packing of aromatic molecules in crystals^{16,17}
- 4) tertiary structure of proteins^{18,19}
- 5) the selectivity observed in asymmetric reactions^{20-29,31-37}
- 6) intercalation of drugs into DNA^{47,48}
- 7) conformational preferences of polyaromatic macrocycles⁴⁹ and
- 8) porphyrin aggregation^{5,50,51}.

The last decade has seen a resurgence of interest in π -stacking, particularly in the areas of molecular recognition and asymmetric synthesis.

MOLECULAR RECOGNITION

Molecular recognition lies at the heart of most biochemical processes. Much of the effort in research in this area has been devoted to understanding the nature of the associations between receptor and substrate. With this knowledge in hand, it might be possible to improve methods of drug delivery in living organisms, develop new pharmaceuticals and use synthetic receptors as control elements in organic synthesis.

Rebek has done extensive research in the area of molecular recognition. He has

published two excellent reviews^{1a,c} which cover advancements made by his group and contemporaries in this field. Rebek's efforts have essentially been to try to bridge the gap between recognition and catalysis; in other words "bring these two events closer together in space and time"^{1a}. In pursuit of this goal, he developed a

new molecular shape based upon Kemp's triacid² (Fig. 2). Modification of the three axial

carboxylic acids allowed for the selective complexation of an impressive array of substrates ranging from alkaline earth metals to nucleosides. This template permits both hydrogen-bonding and aromatic stacking forces to act simultaneously from perpendicular directions (Fig. 3). For example, the receptor was suitably tailored to complex with the nucleoside adenine as shown in Fig. 4. The amide forms H-bonds in a Watson-Crick fashion to anchor one edge of the nucleoside while the anthracene provides additional stability by π -stacking with the adenine aromatic system. The contribution made by π -stacking in this system was determined to be 1.2 kcal/mol.

The hydrogen-bond edges can be tailored for other nucleosides. For example, appropriate modification of the imide to the carbinolamide or the N-acyl amidine derivative allowed for selective binding of the nucleosides cytosine and guanine respectively (Fig. 5).

Further selectivity can be introduced into Rebek's synthetic receptor by modifying the aryl substituents ie. introducing steric biases.

Thus the modified carboxylic acids in Rebek's receptor provide excellent control and versatility. The H-bonding (base-pairing) controls the directionality in binding and the

ability to tailor this enables one to maximize the interaction between the receptor and substrate. The π -stacking provides an additional platform for selectivity by increasing the overall binding and contributing to the overall orientation of the components. Rebek attributed the π -stacking interactions to either dipole/dipole or dipole/induced dipole attractions in these systems.

The concept of nucleosides associating with heterocyclic amine bases via vertical stacking interactions is not new. During the 1960's, a number of groups³ attempted to define the nature of these non-bonded interactions. Interactions such as van der Waals forces, electrostatic attractions, hydrophobic forces and charge-transfer interactions were proposed. Much of this work has formed a solid foundation upon which modern theories of π - π interactions currently stand⁵.

More recently, Hamilton and co-workers⁶ have tried to explain the structural diversity in the stacking of aromatic rings in the protein recognition of nucleotide bases. The inter-ring geometries are either parallel face-to-face stacking or perpendicular edge-to-face orientations. For example, the guanine-binding site of ribonuclease T₁ contains a tyrosine residue (Tyr 46) which stacks parallel to and at 3.4 Å from the purine plane⁷. In contrast to this, the human c-H-ras oncogene protein binds to guanine via a phenylalanine (Phe 28) whose phenyl ring is positioned almost perpendicular to the nucleotide base⁸.

Hamilton *et al* modelled these nucleoside stacking interactions by preparing two artificial thymine receptors and observing their binding with 1-butylthymine (Fig. 6). By modifying the electronics of the receptor, they could influence the preference of parallel to edge-to-face stacking between the naphthalene and the butylthymine. The x-ray structure of complex 1:2 showed the naphthalene positioned parallel and directly above the pyrimidine ring at an interplanar distance of 3.54 Å. In contrast to this, a crystal of complex 1:3 showed the naphthalene ring to be almost perpendicular to the plane of the thymine-pyridine base-pair plane. These solid state observations were also confirmed in solution by shifts of the relevant protons in the NMR.

Hamilton postulated that these variations in geometry were a consequence of differing electrostatic interactions between the pyrimidine and the substituted naphthalene.

Semi-empirical calculations with MNDO verified this. By calculating the electronic charge on each atom, it was shown that parallel stacking was stabilized by an attractive electrostatic interaction between partial charges of opposite sign on the rings (Fig. 7). However, for complex 1:3, such partial charges were either reduced in magnitude or of opposite sign and thus repulsive

electrostatic interactions forced the face-to-edge interaction. However, as we shall see later, Sanders⁵ points out the inadequacies of this atomic charge model in rationalizing π -stacking interactions.

Zimmerman's research efforts⁹ have resulted in the development of a novel

synthetic receptor, dubbed a molecular tweezer (Fig. 8). Two acridine units held syn cofacially by a rigid spacer were used as the π -surfaces, thus the origin of the term "molecular tweezer". The crystal structure of the tweezer revealed an interaction where there was partial overlap between acridine units of adjacent molecules (Fig. 9).

Incorporation of a carboxylic acid substituent on the tweezer's spacer allowed for H-bonding with a nucleic acid base^{9b}. This receptor is similar to that of Rebek's with respect to the use of π -stacking and H-bonding simultaneously from perpendicular directions. Zimmerman's use of an additional π -stacking surface provided a 60-fold increase in K_{assoc} relative to Rebek's synthetic receptor for the complexation of 9-ethyladenine^{9b}.

PACKING OF AROMATIC MOLECULES IN CRYSTALS

Ishida¹⁶ proposed π - π interactions to explain the vertical stacking in the crystal structure of the sodium salt of PPQ (methoxatin) – a novel coenzyme of quinoproteins (bacterial dehydrogenases) (Fig. 10). X-ray structures showed that PPQ stacks with

itself in a parallel but staggered geometry (Fig. 11). The average interplanar spacing was 3.360 Å for the upper pair and 3.302 Å for the lower pair. This distance is shorter than the normal C-C van der Waals contact distance of 3.4 Å.

Based on MNDO semi-empirical calculations, Ishida postulated that the additional attraction was due to the coupled dipole moments. In addition, many of the short contact pairs between stacked PPQ molecules (<3.4 Å) occurred between atoms capable of forming electron rich/electron deficient pairs. Furthermore, the atomic coefficients of the HOMO and LUMO in the PPQ molecule had mostly the same sign in the short contact

pairs. Evidence of a HOMO-LUMO interaction were the appearance of charge-transfer bands in the UV spectra of complexes of PPQ and aromatic amino acids. Thus Ishida concluded that HOMO-LUMO interactions were also important in the stacking stability.

TERTIARY STRUCTURE OF PROTEINS

Another area of biology/biochemistry where π -stacking interactions have been alluded to is in the area of protein conformation. A number of interactions responsible for the folding of proteins have been identified over the last half century. These are H-bonding, electrostatic interactions (salt bridges) and van der Waals forces (of which hydrophobic forces are included). A fourth is the π - π interactions of aromatic residues of the constituent amino acids.

Burley¹⁸ has surveyed the folding of 34 proteins all containing the aromatic amino acids phenylalanine, tyrosine and tryptophan. His findings indicated that the majority of the aromatic side chains were involved in aromatic pairs. The geometries of these associations were summarized as follows:

- i) the preferential separation between aromatic centroids was between 4.5-7.0 Å
- ii) furthermore, the preferred dihedral angle between pairs was 50–90° ie. edge-to-face stacking

These geometries contrast those observed in DNA between interacting aromatic pairs where the π -surfaces are parallel and separated by a distance of 3.4 Å¹⁸.

Burley's rationalization for the geometries of these aromatic-aromatic interactions is based on electrostatics. In essence there is an attraction between the negatively charged benzene face and the positively charged ring edge on the interacting aromatic ring, thus the preference for edge-to-face interactions (Fig. 12).

There is also evidence that aromatic amino acid side chains also interact with carbonyl oxygen atoms in proteins. In 28 protein crystal structures, Thomas *et al*¹⁹ found a favourable interaction in which the carbonyl oxygen was preferentially in the plane of the benzyl ring of the phenylalanine residue – essentially an edge-on interaction. They also

rationalized this in terms of an attraction between the electronic charge distribution around a benzene ring and the carbonyl oxygen (Fig. 13). Ab-initio calculations on a model system supported this explanation.

ASYMMETRIC SYNTHESIS

The synthesis of natural products in optically active form is desirable for both economic and esthetic reasons. Currently there are four methods for introducing the desired stereogenic centres into a substrate 1) deriving the chirality from the chiral pool 2) optical resolutions 3) enzymes (microbiological processes) and 4) asymmetric synthesis. The latter has witnessed an explosion of interest in the last decade.

π -stacking has been used as a control element in asymmetric synthesis over the past twenty years. The method of implementing such asymmetric induction has been the use of an aromatic surface to stack with the unsaturated prochiral centre of interest thus making only one face of the latter accessible for reaction. The aromatic ring can be either introduced as an auxiliary (chiral) or may be an integral part of the final structure. The use of conjugated unsaturated system leads naturally into the development of asymmetric Diels-Alder reactions. Consequently, a number of synthetic efforts have made use of such a strategy for deriving a number of chiral centres in one step.

A pioneer in the use of π -stacking in asymmetric synthesis was E. J. Corey. His work on the prostaglandins^{20a} led to the development of a highly efficient chiral auxiliary, 8-phenylmenthol^{20b} (Fig. 14).

OPPOLZER **d'ANGELO** **LANGE** **WHITESELL** **SCHARF**

Table 1 Other examples of the use of 8-phenylmenthol as a chiral auxiliary.

A number of groups, Oppolzer²¹, d'Angelo²², Lange²³, Whitesell²⁴, and Scharf²⁵ have made use of Corey's 8-phenylmenthol as a chiral auxiliary. Their efforts are summarized in Table 1.

Unfortunately, most of these groups failed to explore the nature of the selectivity and to what extent π -stacking was important. Whitesell^{24a} performed a number of modifications on the auxiliary to see what effects this would have on the selectivity. Saturation of the phenyl group significantly decreased the selectivity, suggesting that it was

Substrate	de (%)	Substrate	de (%)
99.9:0.1		8:1
2:1		3.5:1
3.9:1		2.3:1
>95:5		99.3:0.7
>95:5		>95:5
1.5:1		1.2:1
4.5:1		

Table 2 The effect of chiral auxiliary modification upon selectivity.

not entirely steric in origin. Table 2 summarizes a number of these modifications.

Note that the aromatic ring is critical for realizing high levels of asymmetric induction. Some property of the phenyl group, be it its' size, shape, or electronic character was responsible for the facial selectivity. Whitesell initially postulated either a phenyl-glyoxylate interaction or the phenyl ring acting as a ligand for the Lewis acid. However a photophysical study^{24c} suggested that there may be a HOMO-LUMO (charge-transfer) interaction between the glyoxylate and phenyl groups. Oppolzer *et al* also proposed a similar π - π orbital overlap^{21a}.

Evans' efforts²⁶ in the asymmetric Diels-Alder cycloaddition reactions of crotonate derivatives resulted in the development of an efficient chiral auxiliary. A number of structural modifications were made to the chiral auxiliary to demonstrate the presence of a transition state π -interaction between the phenyl group and the crotonate. These results are

summarized in Fig. 15. Substitution of the benzyl chain by isopropyl (entry d) or cyclohexylmethyl (entry e) groups resulted in decreased diastereoselectivities even though

both of these saturated species are more sterically demanding. Thus the enhanced facial bias provided by the benzyl substituent had to be due to an electronic interaction between the aromatic π -system and the electron-deficient crotonate. The interaction did not have any charge-transfer character since:

- 1) The benzyl substituted oxazolidone reacts faster than the cyclohexylmethyl derivative and
- 2) Electronically perturbed benzyl substituents (entries g-i) showed little effect in the diastereoselectivity compared with the benzyl derivative.

In a novel experiment, Evans successfully dissected the steric from the electronic contributions responsible for the selectivity. A set of comparison alkylation reactions with gross transition state similarities to the Diels-Alder reactions were performed (Fig. 16). The alkylations should not benefit from π -stacking because of the high electron density in

Fig. 16 Alkylations with the oxazolidone chiral auxiliary.

the enolate intermediate. Therefore, any selectivity would be solely due to steric effects. The comparison of the Diels-Alder and alkylation reactions are plotted in Fig. 17. The straight line represents the steric component responsible for the diastereoselectivity observed in both reaction types. The benzyl substituted oxazolidones (f-i) fall well off the line and indicate an increase in selectivity in the Diels-Alder reaction due to the electronic component. Evans attributed the electronic interaction to dipole-dipole and van der Waals attractions rather than charge-transfer.

Rebek's work^{1a,c} in the area of molecular recognition has resulted in the design and implementation of efficient chiral auxiliaries and catalysts. High selectivities have been obtained with the chiral auxiliary shown in Fig. 18. The large aromatic shelf and the Li

chelate assure electrophilic attack upon the *re* face of the alkene. Similarly, asymmetric alkylations of a complementary sort showed very high diastereoselectivities. This

selectivity has also been extended to protonation with the tricyclic lactam (Fig. 19) as a chiral proton source.

The ultimate goal of such endeavors is to achieve the selectivity of enzymes where the organic reagent not only carries out the transformation but actually selects its substrate. Rebek's efforts in asymmetric recognition are now one step closer in realizing this. The triacid represents a tripod upon which large, medium and small groups can be arranged so

as to selectively bind to only one enantiomer of a particular compound (Fig. 20). The acid-base interaction provides one point of contact and the aromatic stacking interactions pin the components together.

A number of individuals have wrongly proposed π -stacking arguments to rationalize the selectivities observed in their systems. Perhaps the most well known example of such is the asymmetric Diels-Alder reaction of Trost's diene^{27a}. In 1980, Trost

Fig. 21 Trost's π -stacked system.

reported moderate to high diastereoselectivity with O-methylmandelic acid as a chiral auxiliary in a Diels-Alder reaction. In order to explain these results, Trost proposed a π -stacking model (Fig. 21) where the aromatic ring shielded one face of the diene. However, Masamune²⁸ observed that replacing the phenyl ring with cyclohexyl did not greatly reduce the stereoselectivity. In view of this result along with their own experimental

observations, Thornton and Siegel²⁹ suggested that π -stacking was not responsible for the facial bias and thus presented another model.

The distinctive characteristics of their model (Fig. 22) are that the diene and carbonyl are coplanar, the Ph-C-C=O dihedral is close to 90° and the methoxy group eclipses the carbonyl³⁰. Thus, the aromatic shields one face of the diene but not because the two are stacked one on top of another.

Fig. 22 Thornton *et al.*'s perpendicular model.

Trost^{27b} has recently verified Thornton's "perpendicular model" using ab-initio/molecular mechanic calculations.

Dauben and Bunce³¹ tried to rationalize the selective addition of dienophiles to chiral butadienes in terms of Trost's original model (Fig. 23). However, in light of the

previous discussion, and the topological similarity between this diene and that of Trost, the selectivity may be a result of a conformational bias which blocks one face of the diene without the need for a π - π interaction.

A similar argument was used by Charlton *et al*³² in their examination of results reported by Ito³³. Ito had proposed that the selectivity observed in cycloadditions of the *o*-quinodimethane (*o*-QDM) in Fig. 24 was due to the π -stacking of the substituent phenyl group with the diene which blocked one face of the *o*-QDM. However, determination of

the absolute configuration of the cycloadduct by Charlton revealed the opposite stereochemistry compared with what Ito predicted from Fig. 24. Thus Charlton hypothesized

the conformation in Fig. 25 as the preferred conformation. The steric bulk of the phenyl group served to block the lower face of the *o*-QDM.

In many of the systems presented so far there is some debate as to the extent π -stacking is responsible for the selectivity being observed. In all the examples cited, there is some conformational bias introduced either sterically or through chelation or base-pairing which forces an interaction between the aromatic ring and the prochiral centre(s). Therefore, these π -stacking interactions are secondary to their steric counterparts.

As far as we know, the only system reported in the literature which comes closest to completely lacking such conformational biases is the Claisen Rearrangement of glycolate esters reported by Kallmerten and Gould³⁴. Kallmerten postulated that a π - π interaction

between the phenyl rings was responsible for the facial selectivity. Further experimental evidence as to the exact nature of the chiral induction remains to be published.

Thus this literature survey of π -stacking in molecular recognition and asymmetric synthesis has revealed a spectrum of examples in which π - π interactions have been used to rationalize various experimental observations. The evidence overwhelmingly supports the

existence of π -stacking. However, the models put forward (which attempt to define the exact nature of these interactions) are too narrow a scope to be applied to all systems. Thus they cannot account for the variations in geometry (parallel face-to-face, to parallel-staggered to edge-to-face interactions) observed. In the next section a general model which appears to satisfy such criteria will be presented.

A NEW MODEL FOR π - π INTERACTIONS

A recent paper by Sanders *et al*⁵ introduces a simple model based on π -system charge distribution for explaining π -stacking interactions. In essence, Sanders' theory is that π -stacking is not due to attractive electronic interactions between two π -systems, but rather an attraction between the π -electrons and the carbon framework which overcomes the π - π electron repulsion. The ideas behind his model are not new. Prior to Sanders' theory, there were three major theories, the hydrophobic model, the electron-donor/electron-acceptor (EDA) model and the atomic charge model which attempted to explain the source of these π - π interactions. As was stated previously, these models could not rationalize all of the physical experimental observations made for π -stacked systems.

PREVIOUS MODELS

HYDROPHOBIC MODEL

The hydrophobic model^{11,38} attempts to rationalize the association of apolar compounds in aqueous solution in terms of thermodynamics. The driving force for complexation has both entropic and enthalpic contributions. The positive entropy change upon desolvation results from reduced solute-solvent interactions and subsequent collapse of the "iceberg-like" water molecules surrounding the solute. The favourable (negative) enthalpic contribution is explained by the enhanced van der Waals interaction between the associated hydrocarbons than between hydrocarbons and water molecules. However, this

model fails to account for π -stacking observed in organic solvents and in addition, maximum π -orbital overlap (parallel face-to-face geometry) is favoured; a situation rarely observed.

THE ELECTRON-DONOR/ACCEPTOR (EDA) MODEL

The term electron-donor/electron-acceptor describes a number of stabilizing interactions which can occur between an electron-rich and electron-deficient species. These interactions range from electrostatic and polarization interactions where electron density is shared, to $\pi \rightarrow \pi^*$ electron-transfer interactions between strong EDA pairs. An example of a charge-transfer complex is the non-bonded association between benzene and iodine. Such interactions are visible in the UV/VIS spectrum as either transition bands or broadened spectra. However, many of the known π -stacking examples show no such absorptions in their UV spectrum.

THE ATOMIC CHARGE MODEL

The atomic charge model states that the attraction between two π -systems arises from uneven charge distributions across them. The positively charged atoms on one π -system line up with the negatively charged atoms in the second system. The problem with this model is that it does not successfully account for the magnitude of the interaction observed in some systems.

SANDERS' MODEL

In general, the energy of interaction between two molecules can be written as:

$$\Delta E = E_{\text{electrostatic}} + E_{\text{induction}} + E_{\text{dispersion}} + E_{\text{exchange}} + E_{\text{charge-transfer}} \quad \text{Eq. 139}$$

Ito *et al*⁴⁰ have measured the enthalpies of the interactions between a phenyl group and a variety of molecules (alkanes, alkenes, substituted benzenes, ethers and carbonyls) and

determined them to range from -0.04 ± 0.02 kcal/mol for cyclohexane to -2.67 ± 0.08 kcal/mol for γ -butyrolactone. The major contributors to the interaction energy are the electrostatic and van der Waals components. The van der Waals term is proportional to the area of π -overlap. Thus, this term would be maximized with the parallel cofacial overlap of two π -systems. However, this geometry is rarely observed because of the large electrostatic barrier due to π - π electron repulsions (see Fig. 27). As one can see, parallel

face-to-face π -stacking is unfavourable because of the repulsion between the two approaching π -clouds. Thus the van der Waals contribution (and hydrophobic effects) control the magnitude of the interaction while the electrostatic term determines the geometry of the interaction. Fig. 28 illustrates how the electrostatic component affects the relative orientation of the two π -systems.

Parallel cofacial geometries have been observed; for example in the crystal structure of some quinones⁴¹. In these cases the π -systems are polarized – the atoms at the site of contact are either both π -electron deficient or a combination of π -rich/ π -deficient. Consequently π - π repulsions are weaker and complete overlap is actually stabilizing. To

illustrate the effect of polarization, Sanders has taken three different π -systems and calculated the electrostatic component of Eq. 1 for all possible π -stacked combinations of the three. Note that the magnitude and conclusions should be considered as qualitative only. The three systems were benzene (non-polar), *p*-phenylenediamine (electron donor) and *p*-benzoquinone (electron acceptor); see Fig. 29.

SUBSTITUENTS		ORIENTATION					
R ₁	R ₂	1	2	3	4	5	6
H	H	14.9	14.8	-2	-2.0	-1.9	-2.0
H	NH ₂	17.8	17.6	-1.4	-1.1	-1.0	-1.4
H	=O	-1.5	-1.7	-5.3	9.1	9.1	-5.3
=O	=O	22.7	-13.6	-0.3	-1.4	0.6	-1.4
=O	NH ₂	3.3	-1.7	-7.6	-7.5	10.9	11.6
NH ₂	NH ₂	25.9	22.2	-0.3	-0.4	-0.6	-0.4

Fig. 29 Effect of π -polarization on π - π interactions (electrostatic contribution only).

Negative values indicate attraction, positive values correspond to repulsion.

From these results the following generalizations can be made:

- offset stacking (orientations 3–6) is attractive.
- parallel face-to-face stacking (orientations 1 and 2) is repulsive; however if the atoms at the site of contact are π -deficient then parallel cofacial stacking is attractive ie. the acceptor-acceptor interaction in orientation 2.
- large repulsive interactions result from interactions where the atoms at the site of contact are π -rich.

In practice though, not all of the orientations illustrated above in Fig. 29 are accessible due to geometric constraints inherent in each molecule.

Sanders has taken these results and formulated a set of qualitative rules for predicting the preferred geometry for systems capable of π -stacking interactions.

For non-polar systems:

- 1) π - π repulsion dominates in a face-to-face π -stacked geometry (Fig. 30a).
- 2) π -carbon framework attraction dominates in an edge-on or T-shaped geometry (Fig. 30b).
- 3) π -carbon framework attraction dominates in an offset π -stacked geometry.

For polarized systems:

- 4) For interactions between highly charged atoms, charge-charge interactions dominate.
- 5) A favourable interaction with a neutral or weakly polarized site requires the following π -polarization:
 - a) a π -deficient atom in a face-to-face geometry (Fig. 30a).
 - b) a π -deficient atom in the vertical T-group in the edge-on geometry (Fig. 30b).

- c) a π -rich atom in the horizontal T-group in the edge on geometry (Fig. 30b).
- 6) A favourable interaction with a neutral or weakly polarized site requires the following carbon framework polarization:
 - a) a positively charged atom in a face-to-face geometry (Fig. 30a).
 - b) a positively charged atom in the vertical T-group in the edge-on geometry (Fig. 30b).
 - c) a negatively charged atom in the horizontal T-group in the edge-on geometry (Fig. 30b).

These rules can now be used to rationalize the array of π -stacking geometries presented earlier. For example, the self-complexation of Zimmerman's molecular tweezers with minimal π -overlap can be accounted for by rules 4 and 5. The offset results from π - π

repulsions due to the π -rich nature of the methoxy substituted acridones. Another example is Hamilton's artificial thymine receptor which shows both parallel face-to-face and edge-to-face orientations depending upon the electronic nature of the naphthalene. Electron-withdrawing substituents such as $-\text{COOR}$ decrease the naphthalene π -electron density and thus the face-to-face orientation is favoured because π - π electron repulsion is reduced. In contrast to this, electron donating substituents, $-\text{OR}$, increase the π -electron density and consequently increased π - π repulsions force the edge-to-face geometry.

Charge-transfer complexes are also accommodated by this simplistic model. However, they are interpreted as a consequence rather than the cause of π - π interactions. In other words they are a special case of the more general π - π interactions. The EDA model presented earlier just considers the overall redox potential of the interacting species and cannot rationalize the geometries observed. The Sanders' model takes into account the electronic character of the atoms at the site of contact and this determines how the π -systems interact.

Another important point which can be drawn from Sanders' model is a problem with the use of molecular mechanic calculations to model such π -stacking interactions^{5,14}. These calculations are unsuccessful if:

- 1) they do not allow for the spatial charge distribution (polarization) of the π -electron system and
- 2) they do not include π -electron repulsion. Consequently energy minimizations are dominated by van der Waals interactions which favour maximum π -orbital overlap.

Unfortunately, one of the more popular and successful energy minimization routines, Allinger's MM2/MMP2⁴², fails to treat successfully non-bonded interactions such as π -stacking. However, Weaver's⁴³ reparameterization of MM2 (MMPEP II) appears to have removed the original's shortcomings and has successfully been applied to the molecular mechanics treatment of peptides and polypeptides.

Thus, Sanders' model for π - π interactions brings together the points developed in previous models and successfully accounts for the variations observed in the geometry of many π -stacking examples.

A NEW π -STACKING EXAMPLE

The major focus of interest in ApSimon's lab a decade ago was the synthesis of the triterpene Friedelin (Fig. 31). David Moir, in his efforts towards its total synthesis, noted a peculiar facial selectivity in the alkylation of the aldehyde depicted in Fig. 32⁴⁴. The

aldehyde is racemic, thus alkylation should result in four stereoisomers, two diastereomers and their respective enantiomers. Each pair (RR,SS and RS,SR) should have different proton and carbon NMR spectra. However, high field ^{13}C NMR (125 MHz) of the crude reaction product showed a single carbinol peak at 72 ppm. Thus, it appeared that only one racemic diastereomer was produced suggesting a facial preference for attack on the carbonyl.

Such cases of 1,4 asymmetric induction are quite rare⁴⁵ and in this instance not likely since the methyl on the chiral centre is too small and too far from the prochiral centre to exert any significant steric influence. Therefore, Moir⁴⁴ postulated that it might be possible for the alkyl side chain to fold in such a manner that the carbonyl lies either above or below the diene (depending upon the stereochemistry at the chiral centre) as shown in **Fig. 33**. The repulsive interactions in such a conformation would be compensated for by a favourable π -orbital interaction (π -stacking) between the diene and carbonyl. Thus one face of the carbonyl was now shielded from nucleophilic attack by the alkylating agent.

There is sufficient evidence in the literature to support such a hypothesis. However this case is unique in that there are no geometric constraints or chelations possible to force a π -orbital interaction. In other words π -stacking is the principal interaction in this system.

Thus an extensive set of experiments were devised⁴⁶ in an attempt to explore the nature of the selectivity and assess its potential in the development of a new chiral auxiliary.

RESULTS AND DISCUSSION

CONFIRMATION OF MOIR'S ORIGINAL OBSERVATION

In order to study the phenomena of this reaction, it was necessary to verify Moir's original observation. The 3-(1', 4', 4'-trimethyl-3'-vinylcyclohex-2'enyl)-propanal **8** (referred to as the diene/aldehyde from now on) was prepared as outlined in Fig. 34⁵².

The alkylating agent, α -lithioacrolein diethyl acetal, was prepared by the metallo-dehalogenation⁵³ of the bromo species with *n*-butyllithium. The solution was allowed to stir for one hour at -78°C to ensure complete formation of the nucleophile. A solution of the diene/aldehyde in THF at room temperature was then added dropwise to the alkylating agent. After two hours, TLC showed no starting substrate so the reaction was quenched. Examination of the crude product by ^{13}C nmr (125 MHz) with resolution enhancement revealed a sharp singlet for the hydroxyl-bearing carbon at 72.75 ppm. Thus Moir's original observation was confirmed (Fig. 35).

Since the carbon bearing the hydroxyl is a chiral centre, one would expect its ^{13}C resonance to be doubled if the compound is a mixture of two diastereomers – each peak of the doublet corresponding to a diastereomer. In addition, the relative intensity of the diastereomeric signals should give a rough idea of the relative amount of each diastereomer. The fact that the carbinol was a sharp singlet suggested that either we did not have a mixture (only one diastereomer was present) or the signal was doubled but not resolvable at this field strength.

Theoretically, diastereomers should also be observable in the proton spectrum. The digital resolution for a given number of data points is much higher for a ^1H spectrum than a ^{13}C spectrum due to a narrower spectral width in the former. However, in practice ^1H nmr observation of diastereomeric signals is complicated by 1) splitting of chemical shifts by coupled protons 2) the narrow spectral width results in the overlap of signals of interest by other protons 3) ^1H nmr is more sensitive to through space effects while ^{13}C nmr is more sensitive to changes in the carbon skeleton and 4) small $\Delta\delta$ are hard to observe in a narrow spectral width.

IS THE SELECTIVITY PECULIAR TO THE NUCLEOPHILE?

The next set of experiments examined whether this apparent selectivity could be extended to other nucleophiles. Alkylation of the diene/aldehyde was repeated under the same experimental conditions with the following nucleophiles: methyllithium (MeLi), methylmagnesium bromide (MeMgBr), *n*-butyllithium (*n*-butylLi) and vinylmagnesium bromide (vinylMgBr). The choice of the nucleophiles was rationalized as follows: The use of MeLi and MeMgBr tested the effects of changing the metal on the selectivity. The choice

of vinylMgBr (and Me^-) checked if oxygen was a necessary substituent on the nucleophile – was chelation responsible for the selectivity. Finally, the use of *n*-butylli (and also the Me^- nucleophiles) probed whether the double bond in the nucleophile was stacking with the diene prior to alkylation. Fig. 36 summarizes the initial ^{13}C nmr observations made of the alkylation products.

Based on our simplistic π -stacking model, we expected all four nucleophiles to show selectivity in the alkylation of the diene/aldehyde. The fact that the *n*-butylli had access to both faces of the carbonyl suggested that this nucleophile reacted before the diene and aldehyde could stack. *n*-Butylli is the strongest base in this series of nucleophiles ($\text{pK}_\text{a}=50$) and consequently has the greater nucleophilicity (on the assumption that nucleophilicity parallels basicity in the substitution at carbonyl carbons⁵⁴). Since the diene/aldehyde was not cooled to -78°C prior to addition to the nucleophile, it may not have had a chance to form the π -stacked complex and the *n*-butylli reacted immediately with the unstacked carbonyl.

The apparent selectivity shown by MeLi and MeMgBr suggested that oxygen was not a necessary substituent on the nucleophile. These preliminary results also indicated that the selectivity was possibly independent of the character of the metal in the organometallic. Unfortunately, the negative result from the alkylation with vinylMgBr could not be explained.

The results from these alkylations did not provide further proof for the diene π -stacking with the carbonyl. Furthermore, the apparent singularity of the carbinol resonance for the alkylations with MeLi and MeMgBr could reflect the inability of the spectrometer to resolve diastereomeric signals that are extremely close.

IS THE DIENE NECESSARY FOR SELECTIVITY?

Another experiment was devised in order to determine whether π -stacking was responsible for the selectivity in these alkylations. The rationale was that removal of one of

However, the methyl addition product required higher field nmr (125 MHz) to resolve the diastereomeric carbinol signals. The acrolein diethyl acetal and vinyl carbinol doublets were resolved at 50 MHz and 62.5 MHz respectively. These results indicated that the diastereomers could be resolved by ^{13}C nmr and our criterion for selectivity, whether or not the carbinol was doubled, appeared to be valid.

The two sets of alkylations with MeLi and α -lithioacrolein diethyl acetal on the ene and diene/aldehyde are compared below in Table 3. These data appeared to imply that

Substrate	Hydroxyl-Bearing Carbon Resonance (^{13}C)	
	MeLi	α -lithioacrolein diethyl acetal
diene/aldehyde	singlet	singlet
ene/aldehyde	doubled	doubled

Table 3 Comparison between the alkylations with the ene- and diene/aldehyde.

loss of the vinyl double bond resulted in complete loss of selectivity. One might still argue that the carbinol singlets for the diene/aldehyde alkylations were still unresolved doublets. However, there is no apparent reason why hydrogenation of the vinyl double bond should suddenly make the carbinol diastereomers resolvable.

In an attempt to reinforce the ^{13}C nmr data, GC/MS were run on the alkylation products to see if the diastereomers could also be resolved on GC. Unfortunately, a variety of conditions on different machines failed to separate the stereoisomers.

WHAT ROLE DO THE GEM-DIMETHYL GROUPS PLAY?

Another area which was explored was what role the gem-dimethyl groups played in influencing the geometry of the diene. For a maximum π - π interaction, the diene must adopt a cisoid conformation (or as close to it as possible). Molecular mechanics calculations on rotation about the diene dihedral were carried out for both the diene/aldehyde and the diene/aldehyde minus the gem-dimethyl groups. Fig. 39 indicates a preference for the *s*-cis conformation of **8** because of the congestion created by the

Fig. 39 Comparison of steric energy for rotation about the diene dihedral.

methylys. Their removal reduces the steric energy of the *s*-trans conformation. The accuracy of this molecular mechanics calculation of conformational preference for dienes can be illustrated by the following substituted 1,3-butadienes **21a** and **21b**. NOE experiments by Jefford *et al*⁵⁶ confirm that **21a** prefers a fully planar or out-of-plane *s*-cis confirmation to avoid the congestion encountered in the *s*-trans conformation. On the other

hand, diene **21b** prefers a planar or near planar *s*-trans conformation for similar reasons. MM2 calculations of E_{steric} for Jefford's substituted 1,3-butadienes are summarized

in Fig. 41. These calculations support the conclusions drawn from the NOE experiments.

Allylic coupling constants can also be correlated with dihedral angles (ϕ) using the equations developed by Garbisch⁵⁷:

$$^4J = \begin{cases} 1.3\cos^2\phi - 2.6\sin^2\phi & (0^\circ \leq \phi \leq 90^\circ) \\ -2.6\sin^2\phi & (90^\circ \leq \phi \leq 180^\circ) \end{cases}$$

However, since we do not know the sign of the coupling constant ($^4J_{\text{allylic}}$ can be positive or negative), several values of ϕ are possible. Furthermore, small changes in 4J result in large changes in ϕ , making this method suitable only as a crude approximation of the diene dihedral angle. 4J for the diene/aldehyde was measured as 1 Hz and using the Garbisch equation $\phi = \pm 16^\circ$ (for $^4J = +1$ Hz) or $\phi = \pm 50^\circ$ or $\pm 142^\circ$ (for $^4J = -1$ Hz).

Going back to our original substrate, removal of the gem-dimethyl groups should make the *s*-trans conformation just as stable, if not slightly more, than the *s*-cis conformation. Thus, if the π -stacking interaction was not strong enough to keep the diene cisoid, then a significant portion of the transoid conformer would now be populated. This would reduce the diastereoselectivity in subsequent alkylations because the aldehyde cannot stack with the transoid diene. Both *si* and *re* faces of the carbonyl would now be equally accessible to nucleophilic attack. The amount of selectivity lost would depend on the difference in energy between the cisoid/ π -stacked diene and the transoid/unstacked diene.

Fig. 42 outlines the synthesis of the substrate lacking the gem-dimethyl groups.

Fig. 42 Synthesis of the diene/aldehyde lacking the gem-dimethyl groups.

This methodology made available two isomeric dienes, **25a** and **25b**. The 3-(1'-methyl-3'-vinylcyclohex-3'-enyl)-propanal substrate (**25b**) could be used to probe the effect of the cyclic double bond position on the ability to π -stack.

The dehydration reaction was plagued by poor yields. **Table 4** summarizes the reagents and conditions employed along with the corresponding yields. Furthermore, it was impossible to separate the isomeric dienes on TLC (silica gel or aluminum oxide) with any of the standard solvent systems (EtOAc/Hex, CH_2Cl_2 , benzene, pyridine).

Reagent	Overall Yield (%)	Ratio 24a:24b
SOCl_2 ⁵⁸	30	3:4
PTSA/ SiO_2 ⁵⁹	30 [†]	3:1
Molecular Sieves ⁶⁰	42	3:4
PTSA/molecular sieves	38	1:4
DMSO/Δ ⁶¹	30	1:1
PTSA/Dean-Stark ⁵²	18 [†]	5:8

[†] acetal not isolated; reaction conditions cleaved acetal to the aldehyde

Table 4 Summary of the dehydrations of the alcohols to the dienes.

Multiple developments with benzene as the solvent showed some promise on TLC. However, attempts at separation by HPLC (silica column with benzene and a C_{18} column with $\text{H}_2\text{O}/\text{MeOH}$) were unsuccessful. Silver nitrate adsorbed onto silica gel has been used to separate isomeric dienes in certain steroid syntheses⁶². Unfortunately, due to a lack of time this was not pursued any further and this particular experiment was abandoned.

CAN THE SELECTIVITY BE EXTENDED TO KETONES?

Some preliminary work was done to see to what extent the aldehyde was necessary for the selectivity. Thus an alkylation was attempted with a methyl ketone substituted for

THE HETERO-DIELS-ALDER ADDUCT

One of the more significant pieces of evidence to support the π -stacking theory for the diene/aldehyde was the isolation of the tricyclic compound **28** (Fig. 44). The reaction conditions for the hydrolysis of the acetal also catalyzed the Diels-Alder cyclization of the

diene with the carbonyl to give the tricyclic adduct (see Appendix for ^1H and ^{13}C nmr of this product). The reaction conditions were quite mild: stirring at room temperature in a solution of 3M HCl/THF (pH=1).

Isolation of such a product confirmed that there is an interaction between the diene

and carbonyl. The diene must be in the the cisoid conformation in order to form the cyclic six-membered transition state with the carbonyl⁶⁴.

Kanematsu⁶⁵ and Nicolaou⁶⁶ have each exploited a similar intramolecular Diels-Alder of a vinylcyclohexene in the synthesis of a key Forskolin intermediate (Fig. 45). In both syntheses, the tricyclic adducts with the indicated stereochemistry were the sole products.

The relative stereochemistry of compound 28 was determined by comparing dihedral angles derived from coupling constants to dihedral angles calculated for possible structures. Since the aldehyde is racemic, eight stereoisomers (four diastereomers and their respective enantiomers) are theoretically possible (see Fig. 46 – remember that the quaternary chiral centre is racemic. The illustrated geometry was arbitrarily chosen and any results from the ensuing discussion should be applicable to the respective enantiomers).

Drieding models indicated that products 28c and 28d were unlikely to form. The ring has to pucker for the carbonyl to be on top of the diene; a severely strained conformation due to the unfavourable 1,4 non-bonded interaction between the methyl groups. Furthermore, the intramolecular cyclizations of similar structures (Fig. 45) implied that the terminal CH of the diene was oriented "up" upon cyclization. Based on these results, diastereomers 28c and 28d were eliminated.

Observed coupling constants were compared with calculated values in order to differentiate stereoisomers 28a and 28b. A similar approach was successfully used by Peterson *et al* to assign diastereomer configurations of their phenylmyrtanols⁶⁷. The

methine H alpha to the oxygen was coupled to three different protons resulting in a doublet of doublets of doublets at 3.32 ppm. The coupling constants were 5, 9 and 12 Hz. Table 5 summarizes the coupling constants calculated for each diastereomer by PCMODEL. This molecular mechanics program uses a complex elaboration of the Karplus equation for relating dihedral angles and coupling constants. Excellent correlations between observed J values and calculated values have been obtained in the past⁶⁷ using this software package.

Structure	Coupling Constants (Hz)		
	J ₁₂	J ₁₃	J ₁₄
28a	8.9	1.1	8.2
28b	9.3	4.7	10.9
28c	11.3	6.1	10.0
28d	6.2	9.6	4.9
J _{observed}	9.1±0.6	4.9±0.6	11.6±0.6

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Table 5 Coupling constants for the four possible diastereomers of the cycloadduct.

The observed coupling constants almost match exactly those calculated for structure **28b**. The relative stereochemistry of this cycloadduct supports a Diels-Alder cyclization mechanism. This in turn provides evidence for an intramolecular interaction between the diene and carbonyl.

SPECTROSCOPIC ANALYSIS OF THE DIENE/ALDEHYDE

In order to probe the nature of the interaction between the diene and carbonyl, the IR, NMR and UV spectrum of the diene/aldehyde were examined.

The IR stretching frequency and NMR resonance of the carbonyl for both the diene and ene/aldehyde are compared in Table 6. The minor shifts in the IR stretching

frequency were due to solvent effects only. Similarly, the NMR data did not give any indication of a carbonyl/diene interaction.

	IR (cm ⁻¹)	
neat	1726	1727
chloroform	1721	1720
hexane	1733	1734
	NMR (ppm)	
¹ H	9.80	9.75
¹³ C	202.8	203.9

Table 6 UV and IR data for the ene- and diene/aldehyde.

The UV spectra of the diene/aldehyde did not show any charge transfer bands. In light of what was discussed in the introduction, charge transfer bands are a consequence of and not the cause of π -stacking interactions. Thus, depending upon the nature of the interaction, charge transfer bands may or may not be observable in the UV spectrum. The λ_{max} of the diene/aldehyde (230 nm) is characteristic of an *s*-trans diene, opposite to what was predicted from molecular modelling and ¹H nmr coupling constants. However, the molar extinction coefficient is unusually low (8500) and reflects the value expected for *s*-cis dienes ($\epsilon=12\ 000\text{--}28\ 000$ for *s*-trans dienes⁷²). This paradox is characteristic of a number of substituted vinylcyclohexenes as indicated in Fig. 47. These anomalous UV spectra can be explained by the inability of the component double bonds of the diene to achieve complete coplanarity due to steric constraints imposed by substituents on the cyclohexene

ring or twisting of the ring itself. Such effects have been known to induce hypsochromic shifts in $\lambda_{\max}$ and hypochromic shifts in the molar absorptivity⁷³. Molecular modelling calculations confirmed a skew angle of $\pm 30^\circ$ for the diene.

It appears that there is no spectroscopic evidence to support a π - π interaction. However, being that π -interactions can be extremely weak (1 kcal/mol)⁶⁸ and that the alkylations were carried out at -78°C , any such π -stacking interactions may be overcome by thermal motions at room temperature. Thus, any spectroscopic analysis would be observing the diene/aldehyde in a time averaged environment of a number of other conformations.

ARE THESE ALKYLATIONS REALLY STEREOSELECTIVE?

There still remained the possibility that the chemical shift difference between diastereomers was too small to be resolved by the spectrometer. This would imply that these alkylations were not stereoselective at all. Thus, it was proposed that the epimer of

one of the apparently diastereomerically pure alkylation products (compounds 11, 13, 27) be prepared and a ^{13}C nmr of a mix of both diastereomers be run⁴⁶. Ideally, the hydroxyl-bearing carbon resonance would be doubled. If the signal was still a singlet then this method (whether the carbinol resonance was doubled or not) could not be used as a criterion for diastereoselectivity. Any previous statements made about diastereomer purity for the various alkylations would be invalidated because one couldn't differentiate a singlet resonance as resulting from one diastereomer or an unresolved mixture of diastereomers.

The epimer of the alkylation products could easily be prepared by the inversion of configuration of the hydroxyl-bearing carbon via a Mitsunobu reaction⁷⁴. The methyl alkylated diene/aldehyde (13) was chosen as the starting substrate since the other compounds (11 and 27) were too sensitive and racemization is a problem with allylic alcohols⁷⁵. Fig. 48 outlines the procedure. The diene/aldehyde was alkylated with MeLi

as before and the alcohol esterified under the conditions of Mitsunobu⁷⁶ in 1.5 h to give a 91% yield of the desired benzoate. Surprisingly, the ^{13}C nmr of the benzoate revealed the ester bearing carbon at 72.74 ppm to be a doublet of equal intensity. This suggested three

possibilities: 1) the starting material was not diastereomerically pure 2) the inversion was not complete (racemization of the carbinol chiral centre) or 3) the doubling was due to two stable conformations. In this last case, it might be possible for the aromatic ring to associate with the diene resulting in stabilization of two conformations at room temperature. Using dynamic nmr spectroscopy⁷⁷, ^{13}C spectra acquired at 30°, 45°, 60° and 80°C failed to show coalescence or changes in line shape of the doublet. Thus the doubling was due to the presence of diastereomeric carbons. The second possibility was ruled out because these Mitsunobu reactions have been employed on similar simple secondary alcohols with complete inversion of stereochemistry. Therefore, the problem originated in the purity of the starting material, compound 30. A 50 MHz ^{13}C nmr had been run on the alkylation product and it showed a singlet for the carbinol resonance. The instrument was obviously too weak to resolve the diastereomers. This racemization of the carbinol centre was initially taken to be an anomaly since in previous alkylations of the diene/aldehyde with MeLi, the reaction was apparently stereoselective.

Hydrolysis of the benzoate⁷⁸ afforded the desired alcohol (32) as a 50/50 mixture of diastereomers. This compound could still be used in the mixed isomer nmr experiment

Fig. 49 Mixed isomer nmr experiment.

proposed earlier. Addition of the apparently pure diastereomer (13) should result in the increase in intensity of one of the carbinol signals (see Fig. 49). Thus a 1:2 mixture of alcohols 13 (prepared previously in a separate alkylation, purity confirmed by carbinol singlet in 125 MHz ^{13}C nmr) and 32 was analyzed by ^{13}C nmr (125 MHz). Unexpectedly, there was no change in relative intensity of the carbinol doublet. Thus even the apparently diastereomerically pure alcohol, 13, was actually a mixture of its' diastereomers even though previous high field nmr indicated otherwise.

This result casts serious doubts on any of the previous nmrs run where no doubling of the carbinol was used as the criteria for selectivity. The worst case scenario would be that all the carbinols that were singlets (compounds 11, 13, and 27) are actually unresolved doublets. This would imply that alkylations of the diene/aldehyde were not stereoselective after all!

RESOLUTION ENHANCEMENT AND DIASTEREOMERIC SIGNALS

The discrepancy in the diastereomeric purity of alcohol 13 appears to reflect the method in which the FID (Free Induction Decay) was processed prior to Fourier transformation (FT). When looking for doubled signals in an nmr spectrum, one desires the maximum amount of digital resolution so that the signals are characterized as accurately as possible. The FID can be manipulated in two ways to enhance resolution, zero-filling and/or application of an apodization function^{79,80}. An FID is stored in computer memory as a 2^N set of data points ie. 32K. Fourier transformation of 2^N data points in the time domain gives 2^{N-1} points in the frequency domain. Naturally the larger the number of data points, the finer the digital resolution (Hz/point) since there are more data points to characterize each resonance in the spectrum. Zero-filling by adding another 2^N data points (each containing a zero) to the end of the FID doubles the number of data points in the real spectrum from 2^{N-1} to 2^N . Thus no extra information is added to the spectrum, rather the overall appearance is improved by interpolating extra data points in the frequency spectrum.

The FID can also be treated mathematically before FT to improve either the resolution or the sensitivity. This is known as apodization. The best function for resolution enhancement with minimal loss of sensitivity is a Gaussian multiplication. This function biases against the early part of the spectrum to sharpen the lines and against the latter part to improve the signal-to-noise ratio.

Thus, using these two techniques for enhancing resolution, the FID for the methyl-alkylated diene/aldehyde (compound 13) was zero-filled to 128K, multiplied by a Gaussian

function and then transformed into the frequency spectrum. The carbinol resonance at 68.89 ppm, which was previously a singlet, was now resolved into a doublet of equal intensity. In addition, eight other carbon signals were doubled. Similarly, reanalysis of the nmr for the other alkylation products revealed doubling of other signals in addition to the carbinol resonance. Fig. 50 summarizes these results (see Appendix for the actual ^{13}C spectra). Intriguingly, the carbinol resonance for compound 11 was still a singlet; however there were several other signals which were doubled. The bottom line is that each alkylation product is composed of an equal mixture of racemic diastereomers. There is no asymmetric induction at the carbonyl of the diene/aldehyde.

CONCLUSION

An observation by David Moir during other work led to a suggestion that some unusual directing elements were present during the alkylation of the diene/aldehyde 8. Our initial results appeared to support this contention. However, careful reanalysis of the NMR data demonstrated the non-selectivity of this alkylation. Despite this disappointing result we have demonstrated that the diene and aldehyde do interact. The isolation of the hetero-Diels-Alder adduct indicates that in the presence of an acid catalyst, the diene and aldehyde π -orbitals overlap resulting in cyclization.

It is unfortunate that these alkylations are not stereoselective because they would have made an interesting entry for the use of π -stacking in asymmetric synthesis. The majority of examples of asymmetric reactions usually attribute their selectivity to steric or chelation effects. Those cases which attribute their selectivity to π -stacking usually have a geometric constraint or chelation in the molecule that is responsible for bringing the π -systems together. Our π -stacking example would have been unique in that there are no geometric constraints or chelation effects to force the carbonyl and diene to stack.

Thus π -stacking has the potential as a control element in asymmetric synthesis. The formidable task remains of designing a suitable template to exploit this powerful tool. Judging from the incredible amount of interest, effort and preliminary success in the current literature, such goals may not be too far into the future.

FURTHER WORK

It might be worthwhile to repeat the alkylations by reversing the order of addition of the nucleophile to the diene. It is possible that the addition of the room temperature diene/aldehyde results in alkylation before the diene and aldehyde have a chance to associate. Thus by cooling the substrate to -78°C prior to alkylation, the molecular rotations and vibrations may be reduced enough in magnitude to allow the π -stacking between the diene and aldehyde to dominate.

The success of such a modification in the procedure would warrant the investigation of stereoselective additions to other systems where π -stacking is possible as outlined below⁴⁶.

replace the diene with:

furans and thiophenes

acyclic systems

replace the aldehyde with:

Fig. 51 Other substrates which might be worthwhile investigating.

EXPERIMENTAL

GENERAL

All reactions and column chromatography were monitored by thin-layer chromatography (TLC) and/or gas chromatography. TLC's were run on pre-coated silica gel plates (Merck 60 PF-254, 0.25 mm). Plates were analyzed under UV light and/or treated with either a 5% solution of phosphomolybdic acid in ethanol or a 1% ceric ammonium nitrate in 50% sulphuric acid solution. Gas chromatograms were acquired on a Shimadzu GC-9A instrument fitted with a DB-5 Megabore column (30 m x 0.53 mm i.d., 1.5 μ m film thickness) and a flame ionization detector (FID). The temperature program was 100°C for 2 min. then 15°C/min. to 200°C where the temperature was held for 15 min. The carrier (He) flow rate was 10 mL/min.

All solvents used were distilled in glass and purchased from Caledon or Anachemia. Tetrahydrofuran and benzene were distilled from sodium benzophenone ketyl.

All reactions were carried out under argon.

Vinylmagnesium bromide, methyllithium, methylmagnesium bromide and n-butyllithium were purchased from Aldrich and not titrated (standardized) prior to use.

Yields were not reported for any reactions where the products were not purified by chromatography.

PURIFICATIONS

Preparative TLC was carried out on 1 mm or 0.5 mm Merck 60 F-254 precoated silica gel plates. Column chromatography was performed on silica gel (Merck 60, 230-400 mesh).

Medium pressure liquid chromatography (MPLC) separations were carried out on a home built system. The columns were packed dry with silica gel (Merck 60, 230-400 mesh).

Preparative HPLC was done on a Waters Prep 500 HPLC with Prep-pak silica gel columns (Waters Associates) and monitored using an RI detector. Samples were prepared

by passing them through a short column of Florisil or silica and a 0.45 μm filter unit (Millex-HV). Analytical HPLC was conducted on a Waters M-6000A Liquid Chromatograph.

PHYSICAL ANALYSES

Routine ^1H and ^{13}C NMR spectra were run on a Varian EM360, Varian XL 200, Gemini 200, Varian XL 300 (University of Ottawa) or Bruker WM 250 (Agriculture Canada) spectrophotometer. High resolution spectra were acquired with 32K data points on a Bruker AM 500 (Agriculture Canada) instrument. The FID's were zero-filled to 128K and resolution enhanced (Gaussian multiplication) before Fourier transform to give a final digital resolution of 1.4 Hz/point. Chemical shifts were referenced to deuteriochloroform (unless otherwise stated) at 7.24 (^1H) and 77.0 ppm (^{13}C) and reported in units of δ relative to tetramethylsilane (TMS). Confirmation of ^1H chemical shift assignments was made by $^1\text{H}/^1\text{H}$ homonuclear correlation spectra (COSY). ^{13}C assignments were made by using the DEPT or APT pulse sequence and $^1\text{H}/^{13}\text{C}$ heteronuclear correlation spectra (HETCOR). The following abbreviations were used in the NMR descriptions: s (singlet), d (doublet), t (triplet), q (quartet), m (multiplet), br (broad), dd (doublet of doublets), ddd (doublet of doublet of doublets), dq (doublet of quartets), dt (doublet of triplets).

Infrared spectra were recorded on a Perkin-Elmer 683 or Perkin-Elmer 1600 series FT/IR spectrophotometer. The samples were applied as neat films on NaCl cells or dissolved in a solvent and run on 0.1 mm volatile cells. Absorptions are reported in cm^{-1} and are not calibrated. The following abbreviations were used in describing the spectra: s (strong), m (medium), w (weak), br (broad).

UV/VIS spectra were run on a Perkin-Elmer Lambda 4B UV/VIS spectrophotometer. Absorptions are reported in nm and intensity (ϵ).

Mass spectra were obtained on a Finnigan VG707E instrument at 70 eV with the data reported in the form m/z (relative intensity).

GC/MS were run on either: 1) A Varian Vista 5500 gas chromatograph (30 m x 0.32 mm i.d., 0.25 μ m film thickness, DB-5 capillary column) coupled to a Finnigan 700 Ion Trap (Agriculture Canada). The GC temperature program was as follows: 120-280°C at 15°C/min. holding for 12 min. at the final temperature. 2) A Hewlett-Packard 59970C ChemStation with a 5890 Series 2 gas chromatograph (30 m x 0.3 mm o.d., 0.25 μ m film thickness DB-5 capillary column) interfaced to a 5971A Mass Selective Detector (Paracel Laboratories). The GC temperature program was as follows: initial temperature: 50°C, hold time: 2 min.; ramp 1: 7°C/min. to 75°C; ramp 2: 10°C/min. to 120°C; ramp 3: 5°C/min. to 190°C; ramp 4: 10°C/min. to 250°C; ramp 5: 15°C/min. to 290°C 3) A Hewlett-Packard 5890 gas chromatograph (12 m x 0.2 mm i.d., 0.33 μ m film thickness Ultra 1 (OV-101) methylsilicone capillary column) interfaced to a HP 5970 Mass Selective Detector (NRC). The GC temperature program was as follows: 100°C for 2 min. and then ramped at 15°C/min. to 200°C where the final temperature was maintained for 15 min.

MOLECULAR MODELLING

Molecular orbital and energy minimizations were performed on the High Energy Physics VAX running TRIBL (QCPE 529) or on a Macintosh II running PCMODEL (Serena Software).

REACTIONS

3-(3'-Oxo-1',4',4'-trimethylcyclohexyl)-propanal ethylene acetal 5

To a stirred mixture of oven dried magnesium turnings (6.83 g, 0.28 mol) in 25 mL of dry THF was added the 2-(2-bromomethyl)-1,3-dioxolane (50.19 g, 0.28 mol) dropwise over 3 hours so as to maintain an internal temperature of 15-20°C. The Grignard was allowed to form by leaving the mixture stir for 1.5 hours. Afterwards, the Grignard solution was added dropwise over 2 hours to a mixture of the copper (I) catalyst

$\text{CuBr} \cdot \text{Me}_2\text{S}$ (14.43 g, 0.07 mol) in dimethyl sulfide (150 mL) cooled to -78°C . The mixture was left to stir for 1.5 hours then the 3,6,6-trimethyl-2-cyclohexenone (19.78 g, 0.14 mol) dissolved in dry THF/ether (40 mL/60 mL) was added dropwise over 3.5 hours. After 11 hours at -78°C , a TLC showed some residual starting material; so the reaction was allowed to warm to 0°C whereupon another TLC indicated no starting material. The reaction was quenched with a saturated solution of NH_4Cl (120 mL). Then the THF/ether layer was drawn off and the aqueous/precipitate layer was extracted with ether (5x50 mL). The combined ethereal extracts were washed with a saturated NH_4Cl solution and backwashed with ether until the aqueous washings were no longer blue. Drying over anhydrous MgSO_4 and concentration *in vacuo* left 37.39 g of the crude pale yellow oil.

Cleanup on HPLC (25% EtOAc/Hex) afforded 37.25 g of the pure acetal as a pale yellow oil (some residual solvent).

^1H nmr (200 MHz) δ : 0.89, 1.08, 1.11 (s, 3H each, ring methyls), 1.33-1.72 (overlapping multiplets, 8H), 2.16 and 2.31 (AB, $^2J=14$ Hz, 2H, $\text{CH}_2\text{C}=\text{O}$), 3.83-3.98 (overlapping multiplets, 4H, $(\text{CH}_2)_2\text{-O}$), 4.82 (t, $^3J=5$ Hz, 1H, O-CH-O).

^{13}C nmr (50 MHz) δ : 64.93 (O- $(\text{CH}_2)_2\text{-O}$), 104.71 (O-CH-O), 215.97 (C=O).

IR (neat) cm^{-1} : 1705 (s) C=O, loss of C=C and vinylic C-H.

3-(3'-Hydroxy-1',4',4'-trimethyl-3'-vinylcyclohexyl)-propanal ethylene acetal 6

The keto-acetal, 2, (5.70 g, 0.24 mmol) was dissolved in dry THF after which vinylmagnesium bromide (240 mL of 1 M in THF, 240 mmol) was added dropwise over 2.5 hours with stirring. The solution was refluxed for 20 hours at which time an IR showed a broad OH band, a C=C stretch and the absence of the ketone absorption. Quenching with ice-water, followed by extraction with ether (5x100 mL), drying over MgSO_4 and evaporation of the solvent afforded 6.44 g of the crude yellow oil (some residual solvent)

IR (neat) cm^{-1} : 3449 (br. s.) OH, 1644 (m) C=C, loss of ketone absorption.

3-(1',4',4'-Trimethyl-3'-vinylcyclohex-2'-enyl)-propanal ethylene acetal 7

In a flask equipped with a Dean-Stark apparatus was dissolved the crude vinyl cyclohexanone, 3, (6.44 g, .024 mol) and PTSA (0.68 g, 11% by weight) in 200 mL of benzene. The mixture was stirred at reflux for 2 hours after which a TLC revealed no starting material. The ethereal layer was extracted with 10 mL aliquots of a saturated NaHCO_3 solution until the aqueous washings were basic and the latter backwashed with ether. Drying with anhydrous MgSO_4 and removal of baseline material on a short column of flash silica yielded 6.45 g of the crude dark brown oil

IR (neat) cm^{-1} : 1610-1640 (w) diene, 3080 (m) vinylic C-H; 1709 (w) residual ketone; also evidence for the hydrolysis of the acetal on the dienyl acetal -1740 (HC=O) and 2860, 1365 (CHO stretch and bend respectively).

UV nm: λ_{max} =230 nm, ϵ =8300 (methanol)

3-(1',4',4'-Trimethyl-3'-vinylcyclohex-2'-enyl)-propanal 8

To the 3-(1',4',4'-trimethyl-3'-vinylcyclohex-2'-enyl)-propanal ethylene acetal (480 mg, 1.9 mmol) was added THF (30 mL), H_2O (6 mL) and HCl (9.5 mL of 3 M). After stirring for 8 hours at room temperature, the solution was quenched by the addition of a saturated solution of NaHCO_3 until neutral. The THF was removed *in vacuo* and the resulting residue partitioned between equal portions of CH_2Cl_2 and H_2O . The ethereal layer was drawn off and washed with H_2O (1x). The extraction and washing were repeated with another three portions of CH_2Cl_2 . The combined organic extracts were dried over anhydrous Na_2SO_4 and the solvent removed *in vacuo* to yield 414 mg of a yellow oil.

Purification by MPLC (20% CH_2Cl_2 /Hex {500 mL}, 35% CH_2Cl_2 /Hex) yielded 209 mg (53%) of the desired aldehyde and 200 mg of a hetero Diels-Alder adduct.

Aldehyde:

^1H nmr (200 MHz) δ : 0.99, 1.03, (s, 3H each, geminal ring methyls); 1.04 (s, 3H, lone ring methyl); 1.22-1.68 (m, 6H); 2.38-2.48 (m, 2H, $\text{CH}_2\text{-CHO}$); 4.94 (dd, $^3J_{\text{cis}}=11$ Hz, $^2J=2$ Hz, 1H, $\text{CH}_2=\text{CH}$); 5.27 (dd, $^3J_{\text{trans}}=17$ Hz, $^2J=2$ Hz, 1H, $\text{CH}_2=\text{CH}$); 5.38 (s, 1H, $\text{CH}=\text{C}$); 6.23-6.37 (ddd, $^4J=1$ Hz, $^3J_{\text{trans}}=17$ Hz, $^3J_{\text{cis}}=11$ Hz, 1H, $\text{CH}_2=\text{CH}$); 9.79 (t, 1H, $^3J=2$ Hz, CHO).

^{13}C nmr (50 MHz) δ : 27.27, 27.68 ($\text{C}(\text{CH}_3)_2$); 28.44 ($\text{C}(\text{CH}_3)$); 30.70 ($\text{C}(\text{CH}_3)\text{CH}_2$); 33.26 ($\text{C}(\text{CH}_3)_2$); 34.23 ($\text{CH}_2\text{-CHO}$); 34.61 ($\text{C}(\text{CH}_3)$); 35.75 ($\text{C}(\text{CH}_3)_2\text{CH}_2$); 39.55 ($\text{CH}_2\text{CH}_2\text{-CHO}$); 113.45 ($\text{CH}_2=\text{CH}$); 130.72 ($\text{CH}=\text{C}$); 136.83 ($\text{CH}_2=\text{CH}$); 144.32 ($\text{CH}=\text{C}$); 202.82 (CHO).

UV nm: $\lambda_{\text{max}}=230$, $\epsilon=8540$ (hexane); $\lambda_{\text{max}}=231$, $\epsilon=9000$ (methanol).

IR cm^{-1} : $\text{C}=\text{O}$: 1726 (neat), 1721 (CHCl_3), 1732 (hexane), 1728 (CCl_4).

GC/MS m/z : $\text{C}_{14}\text{H}_{22}\text{O}$ (Molec. Wgt.=206): 206 (M^+), 149 (89).

Hetero Diels-Alder adduct 28:

^1H nmr (500 MHz) δ : 1.086, 1.090, 1.14 (s, 3H each, ring Me); 1.2-1.8 (m, br., 9H); 3.30-3.35 (ddd, $^3J=5.0$ Hz, $^3J=9.0$ Hz, $^3J=11.6$ Hz, 1H, O-CH); 4.39 (q, 3J complicated by geminal and long range (5J) coupling, 2H, O- CH_2); 5.23 (q, $^3J=2.9$ Hz, $^3J=2.9$ Hz, $^4J=2.9$ Hz, 1H, $\text{CH}=\text{C}$).

^{13}C nmr (50 MHz) δ : 28.88, 29.25, 30.70 (three ring Me); 32.76 (CH_2); 33.64 ($\text{C}(\text{CH}_3)_2$); 35.22 ($\text{C}(\text{CH}_3)$); 35.58 (CH_2); 36.32 (CH_2); 39.98 (CH_2); 50.12 ($\text{CH-C}=\text{C}$); 68.52 (CH-O); 82.18 ($\text{CH}_2\text{-O}$); 115.70 ($\text{C}=\text{CH}$), 150.26 ($\text{C}=\text{CH}$).

GC/MS m/z : $\text{C}_{14}\text{H}_{22}\text{O}$ (Molec. Wgt.=206): 206 (M^+), 149 (100).

α -Bromoacrolein

Acrolein was distilled (50-53°C) under argon into a receiver containing a small amount of hydroquinone. A stainless steel cannula was used to transfer 35.6 g (0.64 mol) into flask containing ether (250 mL). Bromine (101.5 g, 0.64 mol) was added dropwise with ice-bath cooling, then a further 250 mL of ether was added. The reaction was cooled to 0°C then triethylamine (88.5 mL, 0.64 mol) was added dropwise. After the addition was complete, the reaction was allowed to come to room temperature and stirred for 19 hours. The suspension was filtered through two short Celite pads and concentrated to a volume of approximately 200 mL. The organics were washed with 3 N HCl (aq) (200 mL) and brine (200 mL) and dried over anhydrous MgSO₄. Concentration gave an oil which was distilled at aspirator pressure to give the title compound (34.2 g, 40%).

 α -Bromoacrolein diethyl acetal 9

α -bromoacrolein (26.3 g, 195 mmol) was mixed with triethylorthoformate (40 mL) and a warm solution of ammonium nitrate (740 mg) in ethanol (13 mL) was added. The mixture was put under an inert atmosphere and stirred for 20 hours at room temperature. The mixture was filtered and 980 mg of NaHCO₃ was added. Distillation at aspirator pressure provided the title compound at 50°C (21.5 g, 53%)

¹H NMR (60 MHz) δ : 1.15 (t, 6H, CH₃CH₂); 3.5 (q, 4H, O-CH₂CH₃); 4.82 (s, 1H, acetal H); 5.65, 6.12 (br. s., 1H each, H₂C=C).

3-Hydroxy-2-methylene-5-(1',4',4'-trimethyl-3'-vinylcyclohex-2'-enyl) pentanal diethyl acetal 11

To a flame dried flask was added α -bromoacrolein diethyl acetal (37 mg, 0.18 mmol) and dry THF (1 mL). The contents were cooled to -78°C followed by the dropwise addition of *n*-butyl lithium (0.07 mL of 2.5 M, 0.18 mmol). After stirring for 1.5 hours, a solution of the 3-(1',4',4'-trimethyl-3'-vinylcyclohex-2'-enyl)-propanal (19 mg, 0.09

mmol) in dry THF (1 mL) was added dropwise and left to stir for 2 hours. The reaction was quenched at -60°C with an excess of saturated NH_4Cl (aq). The mixture was extracted with CH_2Cl_2 (4x) and the organics washed with H_2O (1x). Drying over anhydrous Na_2SO_4 and removal of the solvent *in vacuo* yielded 39 mg of a crude oil.

^1H NMR (200 MHz) δ : 0.97, 1.02 (s, 3H each, two geminal ring CH_3); 1.04 (s, 3H, lone ring CH_3); 1.23, 1.24 (overlapping t, $^3J=7$ Hz, 3 H each, $\text{CH}_3\text{-CH}_2\text{O}$); 1.3-1.6 (m.br., 8H); 2.5 (br, 1H, OH), 3.4-3.8 (m, 4H, $\text{CH}_2\text{-O}$); 4.17 (br. q, 1H, HCOH); 4.90 (s, 1H, acetal H); 4.91 (dd, $^2J=2$ Hz, $^3J_{\text{cis}}=11$ Hz, 1H, $\text{CH}_2=\text{CH}$); 5.25 (dd, $^3J_{\text{trans}}=17$ Hz, $^2J=2$ Hz, 1H, $\text{CH}_2=\text{CH}$); 5.25 (s, 1H, terminal methylene H); 5.45 (d, $^4J=1$ Hz, 1H, $\text{CH}=\text{C}$); 5.28 (s, 1H, terminal methylene H); 6.22-6.37 (ddd, $^4J=1\text{Hz}$, $^3J_{\text{trans}}=17$ Hz, $^3J_{\text{cis}}=11$ Hz, 1H, $\text{CH}_2=\text{CH}$).

^{13}C NMR (125 MHz) δ : 15.09 (two $\text{CH}_3\text{CH}_2\text{O}$), 27.20, 27.29 (one $\text{C}(\text{CH}_3)_2$, d); 27.74, 27.79 (one $\text{C}(\text{CH}_3)_2$, d); 28.47, 28.50 ($\text{C}(\text{CH}_3)$, d); 30.25, 30.28 ($\text{C}(\text{OH})\text{CH}_2$, d); 30.86, 31.04 ($\text{C}(\text{CH}_3)\text{-CH}_2$, d); 33.26, 33.27 ($\text{C}(\text{CH}_3)_2$, d); 34.77, 34.83 ($\text{C}(\text{CH}_3)$, d); 36.02, 36.04 ($\text{C}(\text{CH}_3)_2\text{CH}_2$, d); 38.65, 38.68 ($\text{C}(\text{OH})\text{CH}_2\text{CH}_2$, d); 62.15, 62.17 (CH_2O , d); 62.54 (CH_2O); 72.73 (HCOH); 103.16 (O-C-O); 112.89, 112.90 ($\text{CH}_2=\text{CH}$, d); 114.12, 114.14 ($\text{CH}_2=\text{C}$, d); 132.29, 132.34 ($\text{CH}=\text{C}$, d); 137.19 ($\text{CH}_2=\text{CH}$); 143.12, 143.14 ($\text{CH}=\text{C}$, d); 146.93 ($\text{CH}_2=\text{C}$).

3-Hydroxy-5-(1',4',4'-trimethyl-3'-vinylcyclohex-2'-enyl)-prop-1-ene 12

To a flame-dried flask was added vinylmagnesium bromide (0.44 mL of 1 M, 0.44 mmol) and dry THF (1 mL). The solution was cooled to -84°C and a solution of 3-(1',4',4'-trimethyl-3'-vinylcyclohex-2'-enyl)-propanal (65 mg, 0.32 mmol) in dry THF (1

mL) was added dropwise. After 3 hours, TLC still showed starting material, so another aliquot of the Grignard reagent (0.13 mL of 1 M, 0.13 mmol) was added. After another 3 hours, the reaction was left to warm to 0°C over 1 hour and quenched with a saturated NH_4Cl solution (4 mL). The mixture was partitioned between equal portions of CH_2Cl_2 and H_2O . The organic layer was separated and washed with H_2O (1x) followed by brine (1x). The extraction was repeated with another 3 portions of methylene chloride. Drying over anhydrous Na_2SO_4 and removal of the solvent *in vacuo* afforded 78 mg of the crude title compound as an oil.

Purification on a silica gel column (9.2 g, 5% EtOAc/Hex (200 mL)) yielded 34 mg (45%) of the alkylated product and 7 mg of recovered starting material.

^1H NMR (250 MHz) δ : 0.94, 1.00 (s, 3H each, two geminal ring Me); 1.01 (s, 3H, lone ring Me); 1.3-1.7 (br. m., 8H); 4.1 (br, 1H, HCOH); 4.89 (dd, $^2J=2$ Hz, $^3J_{\text{cis}}=11$ Hz, 1H, $\text{CH}_2=\text{CH}$); 5.08 (dd, $^3J_{\text{cis}}=10$ Hz, 1H, $\text{CH}_2=\text{CH-HCOH}$); 5.20 (dd, $^3J_{\text{trans}}=17$ Hz, 1H, $\text{CH}_2=\text{CH-HCOH}$); 5.23 (dd, $^2J=2$ Hz, $^3J_{\text{trans}}=17$ Hz, 1H, $\text{CH}_2=\text{CH}$); 5.40 (s, 1H, $\text{CH}=\text{C}$); 5.77-5.90 (m, 1H, $\text{CH}_2=\text{CH-HCOH}$), 6.21-6.32 (ddd, $^3J_{\text{cis}}=11$ Hz, $^3J_{\text{trans}}=17$ Hz, $^4J=0.9$ Hz, 1H, $\text{CH}_2=\text{CH}$).

^{13}C NMR (125 MHz) δ : 27.20, 27.22 (one $\text{C}(\text{CH}_3)_2$, d); 27.76, 27.77 (one $\text{C}(\text{CH}_3)_2$, d); 28.50 ($\text{C}(\text{CH}_3)$); 30.88, 30.91 ($\text{C}(\text{CH}_3)\text{CH}_2$, d); 31.73, 31.74 ($\text{C}(\text{OH})\text{CH}_2$, d); 33.28 ($\text{C}(\text{CH}_3)_2$); 34.74, 34.76 ($\text{C}(\text{CH}_3)$, d); 36.00 ($\text{C}(\text{CH}_3)_2\text{CH}_2$); 38.12, 38.14 ($\text{C}(\text{OH})\text{CH}_2\text{CH}_2$, d); 73.89, 73.91 (HCOH , d); 112.99 ($\text{CH}_2=\text{CH}$); 114.71, 114.75 ($\text{CH}_2=\text{CHCOH}$, d); 132.14 ($\text{CH}=\text{C}$); 137.16 ($\text{CH}_2=\text{CH}$); 141.24 ($\text{CH}_2=\text{C}$); 143.26 ($\text{CH}=\text{C}$).

GC/MS m/z : $\text{C}_{16}\text{H}_{26}\text{O}$ (Molec. Wgt.=234): 234 (M^+), 149 (100).

2-Hydroxy-6-(1',4',4'-trimethyl-3'-vinylcyclohex-2'-enyl)-butane 13

To a flame-dried flask was added methyllithium (0.39 mL of 1.5 M, 0.59 mmol) and dry THF (1 mL). After cooling to -78°C , a solution of the 3-(1',4',4'-trimethyl-3'-vinylcyclohex-2'-enyl)-propanal (70 mg, 0.34 mmol) in dry THF was added dropwise. The reaction was left to stir for 2.5 hours whereupon TLC showed little starting material. The reaction was then allowed to warm slowly to 0°C over 1.5 hours at which time it was quenched with an excess of saturated NaHCO_3 (aq). The mixture was partitioned between equal portions of CH_2Cl_2 and H_2O . The organic layer was separated, washed with H_2O (1x) and the extraction repeated with another 3 portions of CH_2Cl_2 . Drying over anhydrous Na_2SO_4 and removal of the solvent *in vacuo* left 73 mg of a crude oil.

^{13}C NMR (125 MHz) δ : 23.51 (CH_3COH); 27.19, 27.20 (one $\text{C}(\text{CH}_3)_2$, d); 27.76, 27.78 (one $\text{C}(\text{CH}_3)_2$, d); 28.49, 28.50 ($\text{C}(\text{CH}_3)$, d); 30.89, 30.94 ($\text{C}(\text{CH}_3)\text{CH}_2$, d); 33.28 ($\text{C}(\text{CH}_3)_2$); 33.91 ($\text{C}(\text{OH})\text{CH}_2$); 34.75, 34.76 ($\text{C}(\text{CH}_3)$, d); 36.01 ($\text{C}(\text{CH}_3)_2\text{CH}_2$); 38.66, 38.68 ($\text{C}(\text{OH})\text{CH}_2\text{CH}_2$, d); 68.88, 68.90 (HCOH , d); 112.97 ($\text{CH}_2=\text{CH}$); 132.20, 132.21 ($\text{CH}=\text{C}$, d); 137.17 ($\text{CH}_2=\text{CH}$); 143.21, 143.23 ($\text{CH}=\text{C}$, d).

Purification of 9 mg of the crude oil on a silica prep plate (0.5 mm, 10% EtOAc/Hex) afforded 8 mg of a yellow oil.

^1H NMR (250 MHz) δ : 0.94, 1.00 (s, 3H each, two geminal ring Me); 1.02 (s, 3H, lone ring Me); 1.17 (d, $^3J=6$ Hz, 3H, $\text{CH}_3\text{-COH}$); 1.1-1.6 (m. br., 8H); 3.7 (m, 1H, CH-OH); 4.89 (dd, $^2J=2$ Hz, $^3J_{\text{cis}}=11$ Hz, 1H, $\text{CH}_2=\text{CH}$); 5.24 (dd, $^2J=2$ Hz, $^3J_{\text{trans}}=17$ Hz, 1H, $\text{CH}_2=\text{CH}$); 5.41 (s, 1H, $\text{CH}=\text{C}$); 6.27 (ddd, $^3J_{\text{cis}}=11$ Hz, $^3J_{\text{trans}}=17$ Hz, $^4J=1$ Hz, 1H, $\text{CH}_2=\text{CH}$).

GC/MS m/z : ($\text{C}_{15}\text{H}_{26}\text{O}$ (Molec. Wgt.=222): 222 (M^+), 151 (100), 149 (90).

3-Hydroxy-1-(1',4',4'-trimethyl-3'-vinylcyclohex-2'-enyl)-heptane 14

n-butyllithium (0.24 mL of 2.5 M, 0.59 mmol) was added with stirring to dry THF (0.9 mL) in a flame-dried flask. The solution was cooled to -78°C and allowed to stir for an additional 10 minutes before adding dropwise a solution of 3-(1',4',4'-trimethyl-3'-vinylcyclohex-2'-enyl)-propanal (79 mg, 0.38 mmol) in dry THF (0.9 mL). A TLC after 3 hours indicated little starting material and the reaction was allowed to warm to 0°C over 2 hours. The reaction was quenched with an excess of saturated NH₄Cl (aq) and extracted with CH₂Cl₂ (4x). The organics were washed with H₂O (1x), dried and the solvent removed *in vacuo* to give 110 mg of an oil.

¹H NMR (200 MHz) δ : 0.89 (t, ³J=7Hz, 3H, *n*-butyl CH₃); 0.95, 1.01 (s, 3H each, two geminal ring Me); 1.02 (s, 3H, lone ring Me); 1.2-1.5 (br. m., 14H); 3.5 (br, 1H, HCOH); 4.89 (dd, ²J=2 Hz, ³J_{cis}=11 Hz, 1H, CH₂=CH); 5.24 (dd, ²J=2 Hz, ³J_{trans}=17 Hz, 1H, CH₂=CH); 5.42 (s, 1H, CH=C); 6.23-6.33 (ddd, ³J_{trans}=17 Hz, ³J_{cis}=11 Hz, ⁴J=1 Hz, 1H, CH₂=CH).

¹³C NMR (125 MHz) δ : 14.04 (CH₃); 22.75 (CH₂); 27.19, 27.22 (one C(CH₃)₂, d); 27.77, 27.80 (one C(CH₃)₂, d); 27.85 (CH₂); 28.50, 28.51 (C(CH₃), d); 30.91, 31.00 (C(CH₃)CH₂, d); 32.02 (CH₂); 33.30 (C(CH₃)₂); 34.79, 34.83 (C(CH₃), d); 36.05 (C(CH₃)₂CH₂); 37.12 (CH₂); 38.51, 38.54 (C(OH)CH₂CH₂, d); 72.69, 72.73 (HCOH, d); 112.95 (CH₂=CH); 132.29, 132.31 (CH=C, d); 137.20 (CH₂=CH); 143.20 (CH=C).

2-Hydroxy-6-(1',4',4'-trimethyl-3'-vinylcyclohex-2'-enyl)-butane 15

To a flame-dried flask was added methylmagnesium bromide (0.46 mL of 3.0 M, 1.4 mmol) and dry THF (6 mL). The solution was allowed to stir at -78°C for 1 hour after which a solution of 3-(1',4',4'-trimethyl-3'-vinylcyclohex-2'-enyl)-propanal (209 mg, 1.0

mmol) in dry THF (5 mL) was added dropwise over 10 min. After 2 hours, TLC still showed some starting material, so another aliquot of the Grignard reagent (0.15 mL of 3.0 M, 0.45 mmol) was added. After a total reaction time of 5 hours, the reaction was left to warm to 0°C and quenched with a saturated NH₄Cl solution (10 mL). The solvent was removed *in vacuo* and the residue partitioned between equal portions of CH₂Cl₂ and H₂O. The organic layer was drawn off, washed with H₂O (1x) followed by brine (1x), and the extraction repeated with another 3 portions of CH₂Cl₂. Drying over anhydrous Na₂SO₄ and removal of the solvent *in vacuo* afforded 218 mg of a crude oil.

¹³C NMR (62.5 MHz) δ : 23.47 (CH₃-COH); 27.17, 27.74 (two C(CH₃)₂); 28.47 (C(CH₃)); 30.84, 30.89 (C(CH₃)CH₂, d); 33.24 (C(CH₃)₂); 33.85 (C(OH)CH₂); 34.71 (C(CH₃)); 35.95 (C(CH₃)₂CH₂); 38.64 (C(OH)CH₂CH₂); 68.82 (COH); 112.94 (CH₂=CH); 132.18 (CH=C); 137.12 (CH₂=CH); 143.15 (CH=C).

Purification of 115 mg of the crude on silica gel (10 g, 10% EtOAc/Hex {100 mL}, 15% EtOAc/Hex {100 mL}) yielded 102 mg (87%) of the desired alkylated product.

¹H NMR (200 MHz) δ : 0.97, 1.03 (s, 3H each, two geminal ring Me); 1.04 (s, 3H, lone ring Me) 1.20 (d, ³J=6 Hz, 3H, CH₃-COH), 1.3-1.5 (br. m., 8H); 3.73 (m, 1H, H-COH); 4.92 (dd, ²J=2 Hz, ³J_{cis}=11 Hz, 1H, CH₂=CH); 5.26 (dd, ²J=2 Hz, ³J_{trans}=17 Hz, 1H, CH₂=CH); 5.44 (d, ⁴J=0.3 Hz, 1H, CH=C); 6.23-6.37 (ddd, ³J_{cis}=11 Hz, ³J_{trans}=17 Hz, ⁴J=0.9 Hz, 1H, CH₂=CH).

3-(3'-ethyl-1',4',4'-trimethylcyclohex-2'-enyl)-propanal ethylene acetal 16

3-(1',4',4'-Trimethyl-3'-vinylcyclohex-2'-enyl)-propanal ethylene acetal (240 mg, 0.96 mmol) was dissolved in EtOAc (24 mL) and a small amount of 10% Pd on carbon was added. The reaction vessel was attached to a hydrogenation apparatus. The system was then evacuated and filled with hydrogen gas. After stirring for four hours at room

temperature, 22.6 mL of H₂ gas (1.0 mmol) had been consumed. The reaction mixture was filtered and the filtrate concentrated to give a clear dark yellow oil.

Purification of a portion of the crude on a silica gel preparative plate (1 mm, 2% EtOAc/Hex, developed twice) yielded the title compound as an oil.

¹³C NMR (50 MHz) δ : 13.19; 23.24; 27.55; 27.78; 28.30; 28.93; 30.78; 34.23; 34.31; 36.38; 36.99; 64.80 (O-(CH₂)₂-O); 105.26 (acetal C); 128.19 (CH=C); 144.79 (CH=C).

MS (Cl/ether) m/z: C₁₆H₂₈O₂ (Molec. Wgt.=252): 253 (M⁺+1); 191 (100); 151 (37).

3-(3'-ethyl-1',4',4'-trimethylcyclohex-2'-enyl)-propanal 17

The crude 3-(3'-ethyl-1',4',4'-trimethylcyclohex-2'-enyl)-propanal ethylene acetal (2.29 g, 11 mmol) was dissolved in acetone (32 mL) and H₂O (4 mL). Then HCl (7 mL of 1 M) was added dropwise. After stirring for 24 hours at room temperature, the reaction was quenched with an excess of saturated NaHCO₃ (aq). The acetone was removed *in vacuo* and the residue partitioned between equal portions of CH₂Cl₂ and H₂O. The organic layer was separated, washed with H₂O (1x) and the extraction repeated with another 3 portions of methylene chloride. Drying of the combined organic extracts over anhydrous MgSO₄ and concentration *in vacuo* afforded 1.87 g of the crude product.

Purification of 217 mg on a silica gel column (15 g, 35% EtOAc/Hex {200 mL}, 50% {75 mL}, 100 % {75 mL}) afforded 171 mg of the title compound as a colourless oil and 32 mg of recovered starting material.

¹H NMR (300 MHz) δ : 0.93, 0.956, 0.968 (s, 3H each, ring CH₃); 0.962 (t, ³J=7 Hz, 3H, CH₃CH₂); 1.95 (dq, ³J=7 Hz, ⁴J=2 Hz, 2H, CH₃CH₂); 1.2-1.6 (m, 6H); 2.3-2.4 (m, 2H, CH₂CHO); 4.88 (d, ⁴J=1 Hz, 1H, CH=C); 9.75 (t, ³J=2 Hz, 1H, CHO)

^{13}C NMR (50 MHz) δ : 13.13 (CH_3CH_2); 23.27 (CH_3CH_2); 27.51, 27.84, 28.21 (three ring CH_3); 30.74 (CH_2); 34.22 (C quaternary); 34.38 (C quaternary); 34.62 (CH_2); 36.22 (CH_2); 39.69 (CH_2CHO); 127.31 ($\text{CH}=\text{C}$); 145.93 ($\text{CH}=\text{C}$); 203.9 (CHO)

IR cm^{-1} : $\text{C}=\text{O}$: 1727 (neat), 1720 (CHCl_3), 1733 (hexane)

GC/MS m/z : $\text{C}_{14}\text{H}_{24}\text{O}$ (Molec. Wgt.=208): 208 (M^+), 151 (100)

3-Hydroxy-5-(3'-ethyl-1',4',4'-trimethylcyclohex-2'-enyl)-prop-1-ene 18

A solution of vinylmagnesium bromide (0.32 mL of 1.0 M, 0.32 mmol) in dry THF (1 mL) was cooled to -78°C . To this was added, in a dropwise manner, a solution of 3-(3'-ethyl-1',4',4'-trimethylcyclohex-2'-enyl)-propanal (46 mg, 0.22 mmol) in dry THF (1 mL). A TLC 4.5 hours later showed about half of the starting material was left so another aliquot of the Grignard reagent (0.34 mL, 0.34 mmol) was added. The reaction was quenched at -78°C (total reaction time of 12 hours) with an excess of saturated NH_4Cl (aq). The mixture was left to warm overnight to 10°C and extracted the next morning with CH_2Cl_2 (4x). The organics were washed with H_2O (1x), dried over anhydrous Na_2SO_4 and evaporated *in vacuo* to give 54 mg of an oil.

The crude product was purified by column chromatography with silica gel (10 g, 5% EtOAc/Hex {75 mL}, 10% {75 mL}) to give 23 mg (44%) of the desired alkylated product and 14 mg of recovered starting material.

^1H NMR (300 MHz) δ : 0.90, 0.95, 0.96 (s, 3H each, ring CH_3); 0.96 (t, $^3J=7$ Hz, 3H, CH_3CH_2); 1.2-1.6 (br.m., 28H); 1.2-1.6 (1H, OH); 1.94 (dq, $^3J=7$ Hz, 2H, $^3J=1.5$ Hz, CH_3CH_2); 4.02 (q, $^3J=6$ Hz, 1H, CHOH); 4.92 (s, 1H, $\text{CH}=\text{C}$); 5.09 (d, $^3J_{\text{cis}}=10$ Hz, 1H, $\text{CH}_2=\text{CH}$); 5.20 (d, $^3J_{\text{trans}}=18$ Hz, 1H, $\text{CH}_2=\text{CH}$); 5.84 (m, 1H, $\text{CH}_2=\text{CH}$)

^{13}C NMR (75 MHz) δ : 13.28 (CH_3CH_2); 23.31 (CH_3CH_2); 27.67, 27.81 ($\text{C}(\text{CH}_3)_2$); 28.33 ($\text{C}(\text{CH}_3)$); 30.99 ($\text{C}(\text{CH}_3)\text{CH}_2$); 31.83 ($\text{C}(\text{OH})\text{CH}_2$); 34.30 ($\text{C}(\text{CH}_3)_2$); 34.47, 34.50 ($\text{C}(\text{CH}_3)$, d); 36.45 ($(\text{CH}_3)_2\text{CH}_2$); 38.49, 38.53 ($\text{C}(\text{OH})\text{CH}_2\text{CH}_2$, d); 73.98, 74.02 (COH , d); 114.58, 114.62 ($\text{CH}_2=\text{CH}$, d); 128.32 ($\text{CH}=\text{C}$); 141.17 ($\text{CH}_2=\text{CH}$); 144.56 ($\text{CH}=\text{C}$)

GC/MS m/z: $\text{C}_{16}\text{H}_{28}\text{O}$ (Molec. Wgt.=236): 236 (M^+), 151 (100)

2-Hydroxy-6-(3'-ethyl-1',4',4'-trimethylcyclohex-2'-enyl)-butane 19

A solution of methyllithium (0.12 mL of 1.5 M, 0.18 mmol) in dry THF (1 mL) was cooled to -78°C and left to stir for 15 minutes before adding dropwise, a solution of 3-(3'-ethyl-1',4',4'-trimethylcyclohex-2'-enyl)-propanal (21 mg, 0.10 mmol) in dry THF (0.9 mL). After stirring for 2.5 hours, the reaction was allowed to warm to -30°C and quenched with a saturated solution of NH_4Cl . The mixture was diluted with equal portions of CH_2Cl_2 and H_2O . The organic layer was drawn off, washed with H_2O (1x) and the extraction repeated with another 3 portions of CH_2Cl_2 . The combined organics were dried over anhydrous Na_2SO_4 and evaporated *in vacuo* to yield 23 mg of an oil.

^1H NMR (200 MHz) δ : 0.92, 0.97, 0.98 (s, 3H each, ring Me); 0.98 (t, $^3\text{J}=7$ Hz, 3H, CH_3CH_2); 1.19 (d, $^3\text{J}=6$ Hz, 3H, $\text{CH}_3\text{-COH}$); 1.3-1.6 (m. br., 8H); 1.96 (dq, $^3\text{J}=7$ Hz, $^4\text{J}=1$ Hz, 2H, CH_3CH_2); 3.73 (m, 1H, HCOH); 4.95 (s, 1H, $\text{CH}=\text{C}$).

^{13}C NMR (125 MHz) δ : 13.28 (CH_3CH_2); 23.29 (CH_3CH_2); 23.46 ($\text{CH}_3\text{-COH}$); 27.62, 27.63 (one $\text{C}(\text{CH}_3)_2$, d); 27.72 (one $\text{C}(\text{CH}_3)_2$); 28.26 ($\text{C}(\text{CH}_3)$); 31.02, 31.05 ($\text{C}(\text{CH}_3)\text{CH}_2$, d); 34.01 ($\text{C}(\text{OH})\text{CH}_2$); 34.27 ($\text{C}(\text{CH}_3)_2$); 34.44 ($\text{C}(\text{CH}_3)$); 36.46 ($(\text{CH}_3)_2\text{CH}_2$); 39.01, 39.03 ($\text{C}(\text{OH})\text{CH}_2\text{CH}_2$, d); 68.95, 68.97 (HCOH , d); 128.61 ($\text{CH}=\text{C}$); 144.53 ($\text{CH}=\text{C}$).

GC/MS m/z: C₁₅H₂₈O (Molec. Wgt.=224): 224 (M⁺), 151 (100).

3-Hydroxy-2-methylene-5-(3'-ethyl-1',4',4'-trimethylcyclohex-2'-enyl) pentanal diethyl acetal **20**

To a cooled (-78°C) solution of α -bromoacrolein diethyl acetal (58 mg, 0.28 mmol) in dry THF (1 mL) was added dropwise *n*-butyllithium (0.11 ml of 2.5 M, 0.28 mmol). This was left to stir for 1 hour, whereupon a solution of 3-(3'-ethyl-1',4',4'-trimethylcyclohex-2'-enyl)-propanal (32 mg, 0.15 mmol) in dry THF (1 mL) was added dropwise. After 6 hours, the reaction was warmed to 0°C and quenched with an excess of saturated NH₄Cl (aq). The mixture was partitioned between equal portions of CH₂Cl₂ and H₂O. The organic layer was separated, washed with H₂O (1x) and the extraction repeated with another 3 portions of CH₂Cl₂. The combined organics were dried over anhydrous Na₂SO₄ and evaporated *in vacuo* to yield 54 mg of a colourless oil.

¹H NMR (200 MHz) δ : 0.92, 0.97, 0.98 (s, 3H each, ring Me); 0.98 (t, ³J=7 Hz, 3H, CH₃CH₂ allylic); 1.23 (overlapping triplets, ³J=7 Hz, 3H each, CH₃CH₂O); 1.3-1.7 (m. br., 8H); 1.96 (dq, ³J=7 Hz, ⁴J=1 Hz, 2H, CH₃CH₂ allylic); 2.75 (d, 1H, OH); 3.6 (m. br., 4H, CH₂-O); 4.14 (m, 1H, HCOH); 4.90 (s, 1H, acetal H); 4.96 (br. s., 1H, CH=C); 5.24 (s, 1H, CH₂=C); 5.28 (s, 1H, CH₂=C).

¹³C NMR (50 MHz) δ : 13.25 (CH₃ homoallylic); 15.15 (CH₃CH₂O); 23.31 (allylic CH₂); 27.66 (one C(CH₃)₂); 27.84, 27.89 (one C(CH₃)₂, d); 28.32 (C(CH₃)); 30.31 (C(OH)CH₂); 30.98, 31.14 (C(CH₃)CH₂, d); 34.30 (C(CH₃)₂); 34.51, 34.57 (C(CH₃), d); 36.49 (C(CH₃)₂-CH₂); 39.09 (C(OH)CH₂CH₂); 62.16, 62.60 (CH₃CH₂O); 72.86, 72.91 (C-OH, d); 103.14 (O-C-O); 114.24 (CH₂=C); 128.65 (CH=C); 144.63 (CH=C); 146.93 (CH₂=C).

IR cm⁻¹ (neat): 3430 (w. br.) OH; no aldehyde absorption.

GC/MS m/z : $C_{21}H_{38}O_3$ (Molec. Wgt.=338): 292 (M^+ -EtOH), 151 (100).

3-(3'-Oxo-1'-methylcyclohexyl)-propanal ethylene acetal 22

The procedure outlined for the synthesis of 3-(3'-oxo-1',4',4'-trimethylcyclohexyl)-propanal ethylene acetal was repeated with the following modifications:

2-(2-bromomethyl)-1,3-dioxolane	16.44 g	0.091 mol
Mg metal	2.21 g	0.091 mol
THF	30 mL	
 CuBr•Me ₂ S	 4.67 g	 0.023 mol
DMS	40 mL	
 3-methyl-2-cyclohexenone	 5.00 g	 0.045 mol
THF/ether	10 mL/15 mL	

Workup afforded 11.61 g of the crude product as a pale yellow oil

Purification by HPLC (silica columns, 15% EtOAc/Hex) afforded 2.17 g of the pure title compound.

1H NMR (300 MHz) δ : 0.90 (s, 3H, CH₃); 1.3-1.8 (m, 8H); 2.14 (AB, $^2J=13$ Hz, 2H, O=C-CH₂-C); 2.26 (t, $^3J=6$ Hz, 2H, O=C-CH₂-CH₂); 3.8-4.0 (m, 4H, O-(CH₂)₂-O); 4.80 (t, $^3J=5$ Hz, 1H, acetal H).

^{13}C NMR (50 MHz) δ : 21.57; 24.24; 27.59; 34.97; 35.21; 37.63 (C quaternary); 40.52; 53.20; 64.43 (O-(CH₂)₂-O); 104.15 (O-C-O); 211.28 (C=O).

MS (Cl/ether) m/z : $C_{12}H_{20}O_3$ (Molec. Wgt.=212): 213 (M^++1), 195 (100).

3-(3'-Hydroxy-1'-methyl-3'-vinylcyclohexyl)-propanal ethylene acetal 23

The procedure outlined for the synthesis of 3-(3'-hydroxy-1',4',4'-trimethyl-3'-vinylcyclohexyl)-propanal ethylene acetal was repeated with the following modifications:

3-(3'-oxo-1'-methylcyclohexyl)-propanal ethylene acetal	4.00 g	18.8 mmol
vinylmagnesium bromide (1 M)	188 mL	188 mmol
THF	50 mL	

Workup in the usual manner afforded a pale yellow oil (due to the volatility of the product, not all of the solvent was removed *in vacuo* and an accurate crude mass was not determined).

Purification of 2.49 g on a silica gel column (100 g, 5% EtOAc/Hex {100 mL}, 10% {100 mL}, 20% {100 mL}) afforded 888 mg and 651 mg of the diastereomeric alcohols respectively and 233 mg of a mix of the two.

Syn alcohol:

^1H NMR (300 MHz) δ : 1.09 (s, 3H, CH_3); 1.2-1.7 (m. br., 12H); 3.9 (m, 4H, $\text{O}-(\text{CH}_2)_2\text{-O}$); 4.78 (t, $^3J=5$ Hz, 1H, acetal H); 4.96 (dd, $^2J=1$ Hz, $^3J_{\text{cis}}=11$ Hz, 1H, $\text{CH}_2=\text{CH}$); 5.18 (dd, $^2J=1$ Hz, $^3J_{\text{trans}}=17$ Hz, 1H, $\text{CH}_2=\text{CH}$); 5.88 (dd, $^3J_{\text{cis}}=11$ Hz, $^3J_{\text{trans}}=17$ Hz, 1H, $\text{CH}_2=\text{CH}$).

^{13}C NMR (50 MHz) δ : 18.05 (CH_2); 24.21 (CH_3); 27.89 (CH_2); 32.61 (C quaternary); 37.47 (CH_2); 37.60 (CH_2); 40.27 (CH_2); 47.29 (CH_2); 64.85 ($\text{O}-(\text{CH}_2)_2\text{-O}$); 72.77 (COH); 105.23 (O-C-O); 110.66 ($\text{CH}_2=\text{CH}$); 147.64 ($\text{CH}_2=\text{CH}$).

IR cm^{-1} (neat): 3480 (br. m.) OH, 1635 (w) C=C.

GC/MS m/z : $\text{C}_{14}\text{H}_{24}\text{O}_3$ (Molec. Wgt.=240): 240 (M^+), 222 ($\text{M}^+-\text{H}_2\text{O}$), 73 (100).

Anti alcohol:

¹H NMR (300 MHz) δ : 0.82 (s, 3H, CH₃); 1.2-1.8 (m. br., 12H); 3.9 (m, 4H, O-(CH₂)₂-O); 4.82 (t, ³J=5 Hz, 1H, acetal H); 4.96 (dd, ²J=1 Hz, ³J_{cis}=11 Hz, 1H, CH₂=CH); 5.19 (dd, ²J=1 Hz, ³J_{trans}=17 Hz, 1H, CH₂=CH); 5.89 (dd, ³J_{cis}=11 Hz, ³J_{trans}=17 Hz, 1H, CH₂=CH).

GC/MS m/z: C₁₄H₂₄O₃ (Molec. Wgt.=240): 240 (M⁺), 222 (M⁺-H₂O), 73 (100).

Attempts at 3-(1'-Methyl-3'-vinylcyclohex-2'-enyl)-propanal ethylene acetal 24**Thionyl Chloride**

To a flame-dried flask was added 3-(3'-hydroxy-1'-methyl-3'-vinylcyclohexyl)-propanal ethylene acetal (110 mg, 0.46 mmol), CH₂Cl₂ (dried over molecular sieves) (3 mL), and pyridine (distilled over CaH₂) (3 mL). The solution was then cooled to -78°C and thionyl chloride (0.08 mL, 1.10 mmol) was added dropwise. The reaction was left to warm to -2°C over 2 hours. TLC showed no starting material. The reaction was quenched with ice/water and extracted with CH₂Cl₂ (4x). The organic layers were washed with 1% HCl (1x), saturated NaHCO₃ (aq) (1x), and H₂O (1x). Drying over anhydrous Na₂SO₄ and concentration *in vacuo* yielded 96 mg of an oil and sticky solid.

The residue was loaded (the sticky material was insoluble in the solvent system) onto a column of silica gel (10 g, 2% EtOAc/Hex {100 mL}, 5% {100 mL}). Combination of frac 8-10 yielded 31 mg (30%) of the desired diene as a mixture (3:4) of the ring double bond isomers.

GC/MS m/z: 23.87 min.; 222 (M⁺), 121 (24), 99 (100), 73 (20)

24.18 min.; 222 (M⁺), 145 (47), 119 (59), 99 (86), 73 (100).

Combination of Frac 11-13 yielded 30 mg of a colourless oil. NMR identified this compound as the rearranged allylic chloride isomers.

PTSA/SiO₂

To a flame-dried flask was added PTSA adsorbed onto silica (1.49 g) . Then a solution of 3-(3'-hydroxy-1'-methyl-3'-vinylcyclohexyl)-propanal ethylene acetal (69 mg, 0.29 mmol) in dry benzene (20 mL) was rapidly added and the slurry stirred vigorously for 2 hours; TLC showed no starting material. The silica was removed by filtration and rinsed with CH₂Cl₂. The combined organic layers were concentrated *in vacuo* to give a pale yellow solution.

Purification on silica gel (10 g, hexane {30 mL}, 4% EtOAc/Hex {25 mL}, 8% {25 mL}, 16% {50 mL}) yielded 14 mg of an oil that was identified as the hydrolyzed acetal but still a mixture (3:1) of the ring double bond isomers.

IR cm⁻¹ (neat): 1725 (w) CHO.

Molecular Sieves

To an oven-dried flask was added molecular sieves (0.4 g, Linde type 5 Å, 1/16" pellets; dried at 165°C for 4 days then 300°C for 4 hours) followed by a solution of 3-(3'-hydroxy-1'-methyl-3'-vinylcyclohexyl)-propanal ethylene acetal (100 mg, 0.42 mmol) in dry benzene (1 mL). After stirring for 4 hours, a TLC revealed a substantial amount of starting material remaining so another portion of benzene (1 mL) and molecular sieves (0.6 g) was added. 24 hours later there was still starting material so more benzene (3 mL) and sieves (0.5 g) were added and the reaction warmed to 60-68°C. After 51 hours (total reaction time) the sieves were filtered off and rinsed several times with CH₂Cl₂. Concentration *in vacuo* yielded 91 mg of a yellow oil.

Purification on silica gel (10 g, 5% EtOAc/Hex {100 mL}, 10% {50 mL}, 20% {100 mL}) yielded 39 mg (42%) of the isomeric dienes in the ratio of 3:4 and 5 mg of starting material.

^1H NMR (250 MHz) δ : 0.88 (s, 3H, CH_3 for 2',3' double bond isomer); 0.96 (s, 3H, CH_3 for 3',4' double bond isomer); 1.3-2.1 (m. br., 10H); 3.89 (m, 4H, $\text{O}-(\text{CH}_2)_2-\text{O}$); 4.8 (t, 1H, acetal H); 4.8-5.1 (two dd, 1H each, $\text{CH}_2=\text{CH}$ terminal methylene); 5.4 (s, 1H, $\text{CH}=\text{C}$ for 2',3' double bond isomer); 7.7 (br, 1H, $\text{C}=\text{CH}-\text{CH}_2$ for 3',4' double bond isomer); 6.2-6.4 (m, 1H, $\text{CH}_2=\text{CH}$).

GC/MS m/z : 23.92 min.; 222 (M^+), 121 (25), 99 (100), 73 (21)

24.24 min.; 222 (M^+), 145 (48), 119 (59), 99 (82), 73 (100).

PTSA/Molecular Sieves

To a flame-dried flask was added the 3-(3'-hydroxy-1'-methyl-3'-vinylcyclohexyl)-propanal ethylene acetal (104 mg, 0.43 mmol), dry benzene (5 mL), molecular sieves (3 scoops, Linde type 5 Å, 1/16" pellets; dried at 165°C for 4 days then 300°C for 4 hours) and PTSA (1 spatula tip). After stirring for 2 hours at room temperature, TLC indicated that the reaction was complete. The reaction was quenched with an excess of saturated NaHCO_3 (aq) and then centrifuged and filtered to remove the fine particulates. The filtrate was extracted with CH_2Cl_2 (4x) and the organics washed with H_2O (1x). Drying over anhydrous Na_2SO_4 and evaporation yielded 87 mg of a yellow oil.

Purification on silica gel (10 g, 5% EtOAc/Hex {150 mL}) afforded 36 mg (38%) of isomeric dienes in the ratio 1:4.

GC/MS m/z : 23.99 min.; 222 (M^+), 121 (28), 99 (100), 73 (33)

24.32 min.; 222(M^+), 145 (40), 119 (50), 99 (60), 73 (100).

DMSO

In a round bottom flask fitted with a reflux condenser were combined 3-(3'-hydroxy-1'-methyl-3'-vinylcyclohexyl)-propanal ethylene acetal (100 mg, 0.42 mmol) and DMSO (0.20 mL, 2.8 mmol). The reaction was heated with stirring to 160-175°C for 2 hours and then left to cool to room temperature over 1.5 hours. The brown residue was taken up in CH₂Cl₂ and washed with H₂O (1x). The aqueous layer was backwashed with CH₂Cl₂ (2x) and the combined organics were washed once more with H₂O (1x). Drying over anhydrous Na₂SO₄ and concentration *in vacuo* yielded 87 mg of a brown oil.

Purification on silica gel (10 g, 5% EtOAc/Hex) afforded 28 mg (30%) of the isomeric dienes in the ratio 1:1.

PTSA/Benzene (Dean-Stark)

To a simple distillation setup was added 3-(3'-hydroxy-1'-methyl-3'-vinylcyclohexyl)-propanal ethylene acetal (77 mg, 0.32 mmol), dry benzene (10 mL) and PTSA (few crystals). After heating for 3 hours at reflux, the reaction was allowed to cool to room temperature over 0.5 hours. The dark purple solution was quenched by pouring into an excess of saturated NaHCO₃ (aq). The mixture was extracted with CH₂Cl₂ (4x) and washed with brine (1x). Drying over anhydrous Na₂SO₄ and evaporation yielded 64 mg of a brown oil.

Purification on silica gel (10 g, hex {50 mL}, 2% EtOAc/Hex {50 mL}, 5% {50 mL}, 20% {50 mL}) afforded 10 mg (18%) of the isomeric dienes in a 5:8 ratio but with the acetal hydrolyzed to the aldehyde.

GC/MS m/z: 21.75 min.; 160 (M⁺-H₂O), 145 (94), 131 (100)

22.56 min.; 160 (M⁺-H₂O), 145 (100), 131 (57).

Pyridinium chlorochromate (PCC)

Chromium trioxide (25 g, 0.25 mol) was added with stirring to HCl (46 mL of 6 M). The dark brown solution was cooled to 0°C and pyridine (20 g, 0.25 mol) was added dropwise over 20 minutes. An orange solid precipitated after stirring for 25 minutes at 0°C. The solid was collected by filtration, rinsed with one portion of hexane and dried *in vacuo* for 4.5 hours to yield 53.62 g of the granular, orange oxidizing agent.

4-(1',4',4'-Trimethyl-3'-vinylcyclohex-2'-enyl)-butan-2-one 26

PCC (122 mg, 0.56 mmol) in CH₂Cl₂ (2 mL) was added rapidly with stirring to a solution of 2-hydroxy-6-(1',4',4'-trimethyl-3'-vinylcyclohex-2'-enyl)-butane (80 mg, 0.36 mmol) in CH₂Cl₂ (2 mL). The reaction immediately turned dark brown. After stirring at room temperature for 3 hours, the reaction contents were diluted with ether and filtered through a pad of Florisil. Evaporation of the solvent yielded 73 mg (92%) of the desired ketone as an oil.

¹H NMR (200 MHz) δ: 0.97, 1.03 (s, 3H each, two geminal ring Me); 1.04 (s, 3H, lone ring Me); 1.4-1.6 (br. m., 6H); 2.15 (s, 3H, CH₃-C=O); 2.42 (dt, 2H, CH₂-C=O); 4.93 (dd, ²J=2 Hz, ³J_{cis}=11 Hz, 1H, CH₂=CH); 5.26 (dd, ²J=2 Hz, ³J_{trans}=17 Hz, 1H, CH₂=CH); 5.39 (s, 1H, CH=C); 6.2-6.4 (ddd, ²J=1 Hz, ³J_{cis}=11 Hz, ³J_{trans}=17 Hz, 1H, CH₂=CH).

¹³C NMR (50 MHz) δ: 27.28, 27.77 (C(CH₃)₂); 28.51 (C(CH₃)); 29.98 (CH₃-C=O); 30.75 (C(CH₃)CH₂); 33.29 (C(CH₃)₂); 34.64 (C(CH₃)); 35.88 (CH₂); 36.08 (C(CH₃)₂CH₂); 39.11 (CH₂); 113.30 (CH₂=CH); 131.17 (CH=C); 136.96 (CH₂=CH); 144.00 (CH=C); 209.30 (C=O).

3-Hydroxy-3-methyl-2-methylene-5-(1',4',4'-trimethyl-3'-vinylcyclohex-2'-enyl) pentanal diethyl acetal 27

A solution of α -bromoacrolein diethyl acetal (44 mg, 0.21 mmol) in dry THF (1.3 mL) was cooled to -78°C and then *n*-butyllithium (0.08 mL of 2.5 M, 0.20 mmol) was added dropwise. After stirring for 1 hour, a solution of 4-(1',4',4'-trimethyl-3'-vinylcyclohex-2'-enyl)-butan-2-one (24 mg, 0.11 mmol) in dry THF (1.3 mL) was added dropwise. The reaction was left to stir overnight and by the next morning had warmed to 6°C (total reaction time = 21.5 hours). The reaction was quenched at 0°C with an excess of saturated NH_4Cl (aq). The mixture was partitioned between equal portions of CH_2Cl_2 and H_2O . The organic layer was separated, washed with H_2O (1x) and the extraction repeated with another 3 portions of CH_2Cl_2 . The combined organics were dried over anhydrous Na_2SO_4 and the solvent removed *in vacuo* to give 44 mg of a crude oil.

Purification of 37 mg of the crude on silica gel (5 g, 10% EtOAc/Hex+3 drops of pyridine) yielded 25 mg (77%) of the alkylated product as a colourless oil and 5 mg of starting material.

^1H NMR (250 MHz) δ : 0.92, 0.99 (s, 3H each, two geminal ring CH_3); 1.01 (s, 3H, lone ring CH_3); 1.21 (t, $^3J=7$ Hz, 6H, two $\text{CH}_3\text{CH}_2\text{O}$); 1.32 (s, 3H, CH_3COH); 1.3-1.6 (br. m., 8H); 3.24 (d, 1H, OH, D_2O exchange); 3.4-3.7 (m. br., 4H, two CH_2O); 4.88 (dd, $^2J=2$ Hz, $^3J_{\text{cis}}=11$ Hz, 1H, $\text{CH}_2=\text{CH}$); 4.95 (s, 1H, acetal H); 5.13 (s, 1H, $\text{CH}_2=\text{C}$); 5.22 (dd, $^2J=2$ Hz, $^3J_{\text{trans}}=17$ Hz, 1H, $\text{CH}_2=\text{CH}$); 5.34 (s, 1H, $\text{CH}_2=\text{C}$); 5.39 (s, 1H, $\text{CH}=\text{C}$); 6.26 (dd, $^3J_{\text{cis}}=11$ Hz, $^3J_{\text{trans}}=17$ Hz, 1H, $\text{CH}_2=\text{CH}$).

^{13}C NMR (125 MHz) δ : 15.07 (two $\text{CH}_3\text{CH}_2\text{O}$); 27.24 (one $\text{C}(\text{CH}_3)_2$); 27.75, 27.77 (one $\text{C}(\text{CH}_3)_2$, d); 28.30 (CH_3COH); 28.48, 28.50 ($\text{C}(\text{CH}_3)$, d); 30.85, 30.96 ($\text{C}(\text{CH}_3)\text{CH}_2$, d); 33.25, 33.26 ($\text{C}(\text{CH}_3)_2$, d); 34.66 ($\text{C}(\text{CH}_3)$); 36.03 ($\text{C}(\text{CH}_3)_2\text{CH}_2$); 36.58, 36.64

(C(OH)CH₂CH₂, d); 36.62 (C(OH)CH₂); 62.33, 62.36, 62.38 (two CH₂O, overlapping doublets); 74.42, 74.43 (COH, d); 101.91, 101.94 (O-C-O, d); 112.86 (CH₂=CH); 112.90, 112.96 (CH₂=C, d); 132.40, 132.42 (CH=C, d); 137.18, 137.19 (CH₂=CH, d); 143.08 (CH=C); 149.24, 149.35 (CH₂=C, d).

GC/MS m/z: C₂₂H₃₈O₃ (Molec. Wgt.=350): 304 (M⁺-EtOH), 149 (100).

3-(1',4',4'-trimethyl-3'-vinylcyclohex-2'-enyl)-propanol 29

A solution of vinylmagnesium bromide (0.25 mL of 1.0 M, 0.25 mmol) in THF (1 mL) was cooled to -78°C. After stirring the rusty brown solution for twenty minutes, a solution of 3-(1',4',4'-trimethyl-3'-vinylcyclohex-2'-enyl)-propanal (37 mg, 0.18 mmol) in THF (1 mL) was added dropwise and the reaction left to stir. Five hours later, another portion of the Grignard reagent (0.05 mL of 1.0 M, 0.05 mmol) was added. A half hour later, the reaction was allowed to warm to 0°C and subsequently quenched with saturated NH₄Cl (aq). The mixture was partitioned between equal portions of CH₂Cl₂ and H₂O. The organic layer was separated, washed with H₂O (1x) and the extraction repeated with another three portions of CH₂Cl₂. Drying over anhydrous Na₂SO₄ and concentration *in vacuo* afforded 50 mg of a pale yellow oil.

Purification on a silica prep plate (1 mm, 15% EtOAc/Hex) yielded 10 mg (27%) of an oil.

¹H NMR (300 MHz) δ: 0.95, 1.01 (s, 3H each, two geminal ring Me); 1.02 (s, 3H, lone ring Me); 1.3-1.6 (m, 8H); 1.5-1.6 (br., 1H, OH, D₂O exchange); 3.61 (t, ³J=7 Hz, 2H, CH₂OH); 4.90 (dd, ³J_{cis}=11 Hz, ²J=2 Hz, 1H, CH₂=CH); 5.24 (dd, ³J_{trans}=17 Hz, ²J=2 Hz, 1H, CH₂=CH); 5.42 (s, 1H, CH=C); 6.23-6.32 (ddd, ⁴J=1 Hz, ³J_{cis}=11 Hz, ³J_{trans}=17 Hz, 1H, CH₂=CH).

^{13}C NMR (50 MHz) δ : 27.25, 27.68 ($\text{C}(\text{CH}_3)_2$); 28.51 ($\text{C}(\text{CH}_3)$); 27.76 (HOCH_2); 30.91 ($\text{C}(\text{CH}_3)\text{CH}_2$); 33.29 ($\text{C}(\text{CH}_3)_2$); 34.80 ($\text{C}(\text{CH}_3)$); 35.99 ($\text{C}(\text{CH}_3)_2\text{CH}_2$); 38.70 (HOCH_2CH_2); 63.82 (CH_2OH); 112.99 ($\text{CH}_2=\text{CH}$); 132.11 ($\text{CH}=\text{C}$); 137.15 ($\text{CH}_2=\text{CH}$); 143.25 ($\text{CH}=\text{C}$).

IR (neat) cm^{-1} : 3350 (s) OH; 1620 (w) C=C.

UV nm: $\lambda_{\text{max}}=231$, $\epsilon=7600$ (hexane); $\lambda_{\text{max}}=231$, $\epsilon=8000$ (methanol).

GC/MS m/z : $\text{C}_{14}\text{H}_{24}\text{O}$ (Molec. Wgt.=208): 208 (M^+), 149 (100).

2-Hydroxybenzoate-6-(1',4',4'-trimethyl-3'-vinylcyclohex-2'-enyl)-butane 31

To a flame-dried flask was added 2-hydroxy-6-(1',4',4'-trimethyl-3'-vinylcyclohex-2'-enyl)-butane (47 mg, 0.21 mmol), dry THF (2 mL), benzoic acid (77 mg, 0.63 mmol), and triphenylphosphine (85 mg, 0.32 mmol). The resulting colourless solution was cooled to 0°C after which diethyl azodicarboxylate (50 μL , 0.32 mmol) was added dropwise over 6 minutes. After stirring at 0°C for 1.5 hours, TLC showed little starting material and a large amount of a higher r_f component. The reaction was worked up by removing most of the THF *in vacuo* and loading the crude onto a column of silica gel (10 g, hexane {30 mL} followed by 5% EtOAc/Hex). This yielded 61 mg (90%) of the desired ester as a colourless, cloudy oil.

^{13}C NMR (125 MHz) δ : 20.07 ($\text{CH}_3\text{-C-O}$); 27.12, 27.16 (one $\text{C}(\text{CH}_3)_2$, d); 27.78, 27.79 (one $\text{C}(\text{CH}_3)_2$, d); 28.46, 28.48 ($\text{C}(\text{CH}_3)$, d); 30.73, 30.90 ($\text{C}(\text{CH}_3)\text{CH}_2$, d); 30.78 ($\text{C}(\text{OBz})\text{CH}_2$); 33.27 ($\text{C}(\text{CH}_3)_2$); 34.72, 34.74 ($\text{C}(\text{CH}_3)$, d); 35.96 ($\text{C}(\text{CH}_3)_2\text{CH}_2$); 38.07, 38.10 ($\text{C}(\text{OBz})\text{CH}_2\text{CH}_2$, d); 72.23, 72.25 (C-OBz , d); 113.07 ($\text{CH}_2=\text{CH}$); 128.26 (two aromatic *m*-CH); 129.50 (two aromatic *o*-CH); 130.93 (C quaternary, aromatic); 131.96, 132.00 ($\text{CH}=\text{C}$, d); 132.65

(aromatic *p*-CH); 137.10, 137.12 (CH₂=CH, d); 143.39 (CH=C);
166.14 (C=O ester).

¹³C NMR (125 MHz, pyridine-d₅) δ: 20.09, 20.11 (CH₃-C-O, d); 27.18, 27.20 (one C(CH₃)₂, d); 27.87, 27.89 (one C(CH₃)₂, d); 28.58, 28.60 (C(CH₃), d); 30.98, 31.01 (C(OBz)CH₂, d); 31.02, 31.12 (C(CH₃)CH₂, d); 33.48 (C(CH₃)₂); 34.99, 35.01 (C(CH₃), d); 36.22 (C(CH₃)₂CH₂); 38.35, 38.38 (C(OBz)CH₂CH₂, d); 72.54, 72.56 (C-OBz, d); 113.46 (CH₂=CH); 128.85 (two aromatic *m*-CH); 129.86 (two aromatic *o*-CH); 131.47 (C quaternary, aromatic); 132.57, 132.61 (CH=C, d); 133.20 (aromatic *p*-CH); 137.52, 137.54 (CH₂=CH, d); 143.61, 143.62 (CH=C, d); 166.17 (C=O ester).

¹³C NMR (125 MHz, pyridine-d₅, 80°C) δ: 20.15 (CH₃-C-O); 27.44, 27.46 (one C(CH₃)₂, d); 28.19, 28.20 (one C(CH₃)₂, d); 28.80, 28.81 (C(CH₃), d); 31.45, 31.48 (C(OBz)CH₂, d); 31.75, 31.81 (C(CH₃)-CH₂, d); 33.77 (C(CH₃)₂); 35.30, 35.32 (C(CH₃), d); 36.86 (C(CH₃)₂CH₂); 38.62, 38.65 (C(OBz)CH₂CH₂, d); 72.81, 72.82 (C-OBz, d); 113.56 (CH₂=CH); 128.89 (two aromatic *m*-CH); 129.99 (two aromatic *o*-CH); 132.14 (C quaternary, aromatic); 132.94, 132.96 (CH=C, d); 133.09 (aromatic *p*-CH); 137.91, 137.93 (CH₂=CH, d); 144.21 (CH=C); 166.41 (C=O ester).

GC/MS m/z: C₂₂H₃₀O₂ (Molec. Wgt.=326): 327 (M⁺+1), 205 (100), 149 (70).

2-Hydroxy-6-(1',4',4'-trimethyl-3'-vinylcyclohex-2'-enyl)-butane 32

2-Hydroxybenzoate-6-(1',4',4'-trimethyl-3'-vinylcyclohex-2'-enyl)-butane (34 mg, 0.10 mmol) was dissolved in methanol (5 ml) and a solution of NaOH (5 mL of an 89 mg in 20% H₂O/MeOH solution) was added dropwise. After stirring for 46 hours at room temperature and 1.5 hours at 35°C, TLC showed no starting material. Most of the MeOH was then removed *in vacuo* and the residue acidified with a few drops of HCl (1.5 M). The reaction contents were then partitioned between equal portions of CH₂Cl₂ and H₂O. The layers were separated and the organic layer was washed with H₂O (1x). The extraction was repeated with another three portions of CH₂Cl₂. Drying over anhydrous Na₂SO₄ and concentration *in vacuo* yielded 38 mg of a solid/oily residue.

Purification on silica gel (10 g, 10% EtOAc/Hex {100 mL}, 15% {100 mL}) yielded 21 mg (95%) of the desired alcohol.

¹³C NMR (125 MHz) δ : 23.50 (CH₃); 27.19, 27.20 (one C(CH₃)₂, d); 27.76, 27.78 (one C(CH₃)₂, d); 28.49, 28.50 (C(CH₃), d); 30.89, 30.94 (C(CH₃)CH₂, d); 33.28 (C(CH₃)₂); 33.91 (C(OH)CH₂); 34.75, 34.76 (C(CH₃), d); 36.00 (C(CH₃)₂CH₂); 38.66, 38.68 (C(OH)-CH₂CH₂, d); 68.88, 68.89 (HCOH, d); 112.96 (CH₂=CH); 132.20, 132.21 (CH=C, d); 137.17 (CH₂=CH); 143.21, 143.22 (CH=C, d).

GC/MS m/z: C₁₅H₂₆O (Molec. Wgt.=222): 205 [(M⁺+1)-H₂O], 151 (98), 149 (85).

2 of/de 2

MICROCOPY RESOLUTION TEST CHART
NATIONAL BUREAU OF STANDARDS
STANDARD REFERENCE MATERIAL 1010a
(ANSI and ISO TEST CHART No. 2)

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APPENDIX

Selected NMR spectra

run at 125 MHz with resolution enhancement added to the expanded regions only

11

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13

14

19

28

28

31

32

13+32

END

04-03-92

FIN