Design and Synthesis of New Monoterpenoid Derived Ligands for Asymmetric Catalysis

by

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This one is for my mom,

Margaret Millar

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Abstract

The work to be presented herein illustrates several important facts. First, the synthesis of BIBOL (19), a 1,4-diol derived from the monoterpene camphor has allowed us to demonstrate that oxidative dimerizations of enolates can, and do proceed with nearly complete diastereoselectivity under kinetically controlled conditions. The yield of BIBOL is now 50% on average, with a 10% yield of a second diastereomer, which is likely the result of a non-kinetic hydride reduction, thereby affording the epimeric alcohol, 20, coupled on the *exo* face of camphor. This implies the production of 60% of a single coupling diastereomer. No other diastereomers from the reduction were observed. The utility of BIBOL has been illustrated in early asymmetric additions of diethylzinc to aryl aldehydes, with e.e.'s as high as 25-30%.

To further the oxidative coupling work, the same methodology which gave rise to BIBOL was applied to the chiral pool ketone, menthone. Interestingly, this gave an excellent yield of the α-halohydrin (31), which is the result of a chlorination of menthone. This result clearly indicates the high stereoselectivity of the process regardless of the outcome, and has illustrated an interesting dichotomy between camphor and menthone. The utility of the chlorination product as a precursor other chiral ligands is currently being investigated.

Finally, a new series of 1,3-diols as well as a new aminoalcohol have successfully been synthesized from highly diastereoselective aldol/mannich reactions. Early studies have indicated their potential in asymmetric catalysis, while employing pi-stack interactions as a means of controlling enantioselective aldol reactions.

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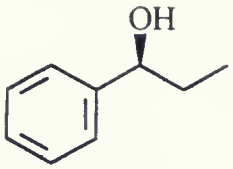
Chapter 1

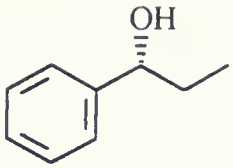
Introduction

1.1 Significance of Stereochemistry

Enantiomers are stereoisomers which display identical chemical functionality and which exhibit the same "relative" configurational arrangement of atoms but differ in the "absolute stereochemistry" about each stereogenic center. For these reasons enantiomers are said to exist as non-superimposable mirror images of one another. Enantiomers display identical chemical properties and most physical properties including spectroscopic properties and even melting point. They differ only in a few areas most notably with the equal but opposite rotation of plane polarized light. A compound which exists in its enantiomerically pure state is said to be optically pure, rotating light to a maximum value either 'levo' or 'dextro' rotatory, designated by *l* or *d* respectively. A rotation of light in the counterclockwise sense is levo (-) while a clockwise or dextro rotation carries with it a positive sign (+). A 50/50 mixture of two enantiomers is said to exist as a racemic mixture, or "racemate" and does not rotate light in either sense due to each enantiomer rotating light equally and oppositely, thereby negating each other. Another important property of enantiomers arising from their lack of chemical individuality is that they can not be separated by conventional methods such as chromatography. This brings about causes devoted to differentiating them, a topic which will be discussed shortly. Stereogenic centers in enantiomers are designated R or S according to the CIP classification system.

Despite their identical chemical nature, enantiomers can have markedly differing interactions with other chiral materials such as biological receptors, and therefore can, and often do exhibit dramatically different activity *in vivo*. One such pair of enantiomers is shown below.



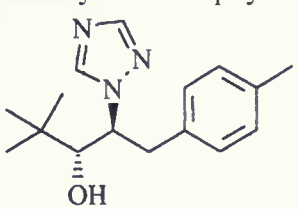


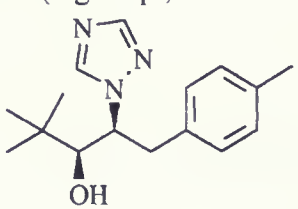
(1S)-1-phenyl-1-propanol (1R)-1-phenyl-1-propanol

Figure 1. A pair of enantiomers

The term "enantioselective transformation" is one which is used to describe the way in which a prochiral molecule is converted synthetically (or biosynthetically) into one which displays a chiral center. This conversion is described as enantioselective if the formation of one enantiomer is favored over the other. However, if the transformation lacks selectivity, and results in the formation of an equal mixture of enantiomers then it is termed "racemic" and the resulting mixture is described as a "racemic mixture".

Diastereomers as opposed to enantiomers, on the other hand, are stereoisomers which exhibit different "relative" stereochemical spaciality and are described as non-superimposable, non-mirror image configurational stereoisomers. Diastereomers exhibit chemical and physical properties which are completely independent of each other and it is therefore not surprising that they behave quite differently in most physical respects (e.g. m.p.,



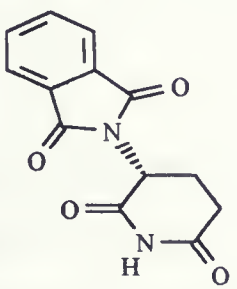


Low Biological Activity Plant Growth Regulator

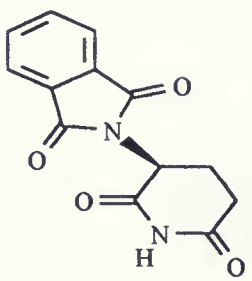
Figure 2. The difference in bio-activity of a diastereomeric pair

spectroscopically, etc), and including *in vivo* effects. Such an example of diasteromers exhibiting differing biological properties is the diastereomeric pair shown in Figure 2.

Until as late as the 1960's, little was known about the harm that administration of a *drug* as a racemate could do from generation to generation. Perhaps one of the most well known cases in which enantiomers mediated dramatically different effects is that of the thalidomide tragedy. This story began in the '60's with a drug that was initially administered to pregnant women as an anti-emetic. While one half (enantiomer) of the drug possessed the desired pharmacological properties, the other enantiomer proved to be teratogenic and severe birth defects were observed in the offspring. It was only later determined why the problem arose, and for those reasons guidelines which greatly restricted the sale of drugs as racemic mixtures were implemented.



(R) Thalidomide
Sedative and hypnotic



(S) Thalidomide
Teratogenic:Fetal death, congenital malformation

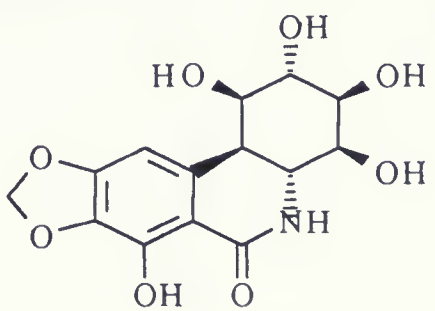
Figure 3. The structures and biological properties of thalidomide

In light of the ramifications posed by thalidomide, it is very surprising that as of 1990 there were 1327 marketed drugs which were totally synthetic. Of these, 528 were chiral with varying numbers of stereocenters while only 61 of these were sold in enantiomerically pure states, the rest as racemates. However, in cases where pharmacological data indicates a difference in biological behavior of the individual enantiomers, the Food and Drug U.S.

administration has made it clear that it will favor sale of drugs with high optical purity. Thus the need and challenge of asymmetric synthesis had now emerged.

In the initial synthesis of a compound that is to be tested for biological activity it is often desirable to obtain the racemate or both enantiomers separately for initial studies. This is so because one enantiomer may exhibit the desirable effects while the other different, or no effects. Once the relationship of absolute structure to bioactivity is known, clearly the introduction of asymmetry during the preparation of the drug is important. The asymmetric total syntheses of natural products and analogues thereof has been a long-standing milestone for the modern day synthetic organic chemist and is now of vital importance to the medicinal chemist. As illustrated above, little was known about the manifestations associated with racemic drug syntheses, but now it has been established that asymmetric syntheses are necessary for the marketing of drugs which exhibit biological activity against cancer, bacteria, viruses such as HIV and other infectious diseases.

Although great advancements have been made with respect to the sale of optically pure compounds obtained from asymmetric syntheses, others with important biological activity, such as pancratistatin [1-3] have yet to reach this stage in their development, due either to inefficient syntheses or those with intolerable optical purities.



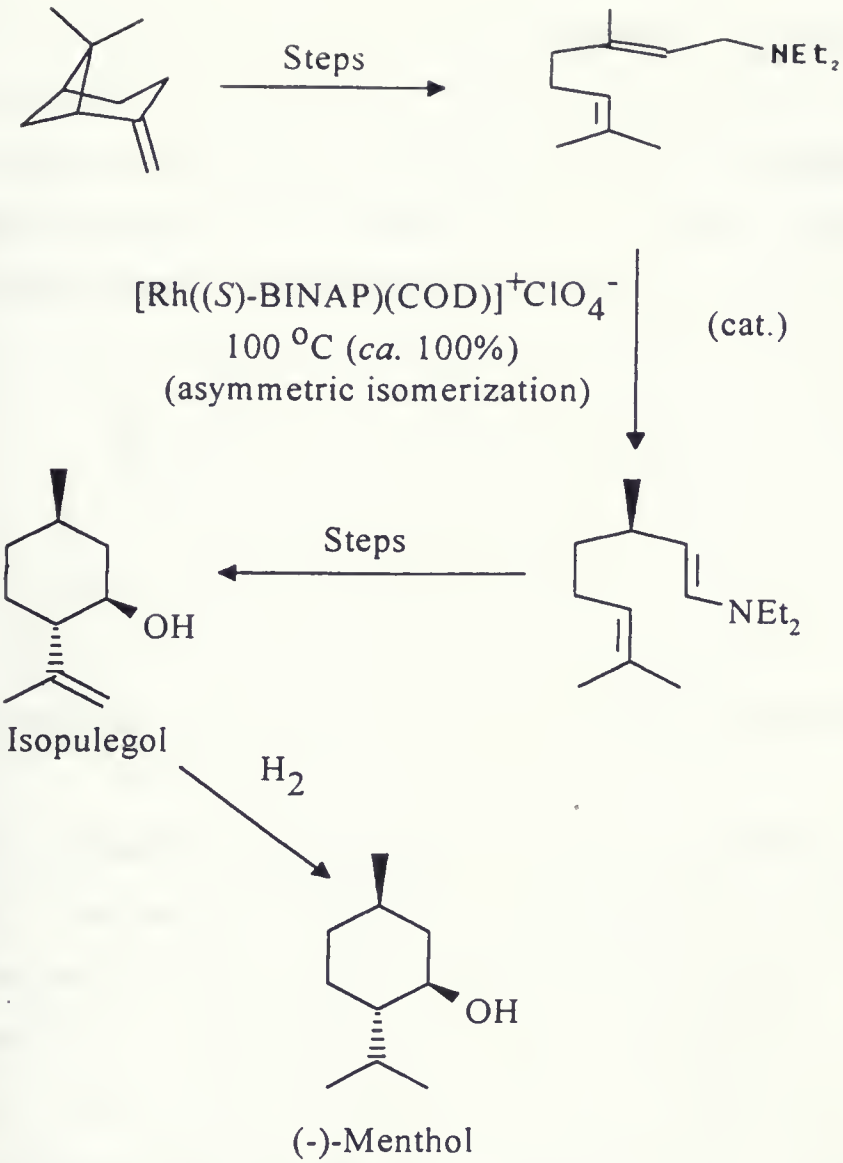
Pancratistatin

Figure 4.

With the rapid discovery of new compounds isolated from marine and terrestrial sources, some of these exhibiting biological importance, the total syntheses of these, and structural analogues thereof is clearly non-trivial and often quite daunting. Thus, the need to develop means to facilitate asymmetric routes is at the forefront of modern day synthetic organic methodology, and a topic addressed herein. Let us now look at some of the classical methods of introducing asymmetry during a synthesis and more modern and synthetically efficient methods.

There are many methods of differentiating one enantiomer from another during the course of a synthesis. Not all are efficient, but each is worthy of mention.

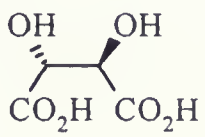
Perhaps the most significant aspect of nature with respect to its chemical make-up is the fact that it is chiral. Of the natural abundance of chemicals that are isolated from both marine and terrestrial sources, most exist in "nearly"optically pure states. The word "nearly" must be used due to the fact that in select cases, the *synthetic* counterpart of a naturally occurring compound exists with greater optical purity than what nature can provide. This fact is true of the monoterpene menthol. This C_{10} compound can actually be synthesized quite efficiently and in greater optical purity than can be isolated, as well as being more abundant *via* synthetic routes than isolation. The synthesis (the Takasago approach) originates from β-pinene and relies on an asymmetric isomerization mediated by a chiral rhodium BINAP complex.



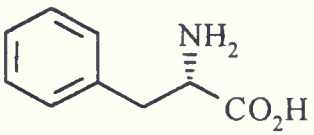
Scheme 1. Takasago Synthesis of Menthol

Before the advent of modern day synthetic methodology, such as that illustrated above, syntheses arising from precursors belonging to the "chiral pool" were by far the most reliable and efficient means of introduction of asymmetry during a synthesis. The chiral pool is a collective term used to describe any synthetic precursor obtained from a natural source, usually available in fairly large and reliable quantities. Chiral pool materials include carbohydrates, amino acids and terpenes such as camphor and menthone. Of the problems that arise with the dependence of chiral pool precursors as a source of chirality is the fact that there simply may not

be a compound with proper functionality which can be incorporated into a synthesis, as well as the fact that the synthesis is limited to only that enantiomer; that is to say that nature generally only provides one form of each compound in question, either the R or the S enantiomer. Most examples of chiral pool compounds including amino acids, carbohydrates, or simple sugars and alkaloids, are only available in the one enantiomeric series from nature.



(+)-tartaric acid

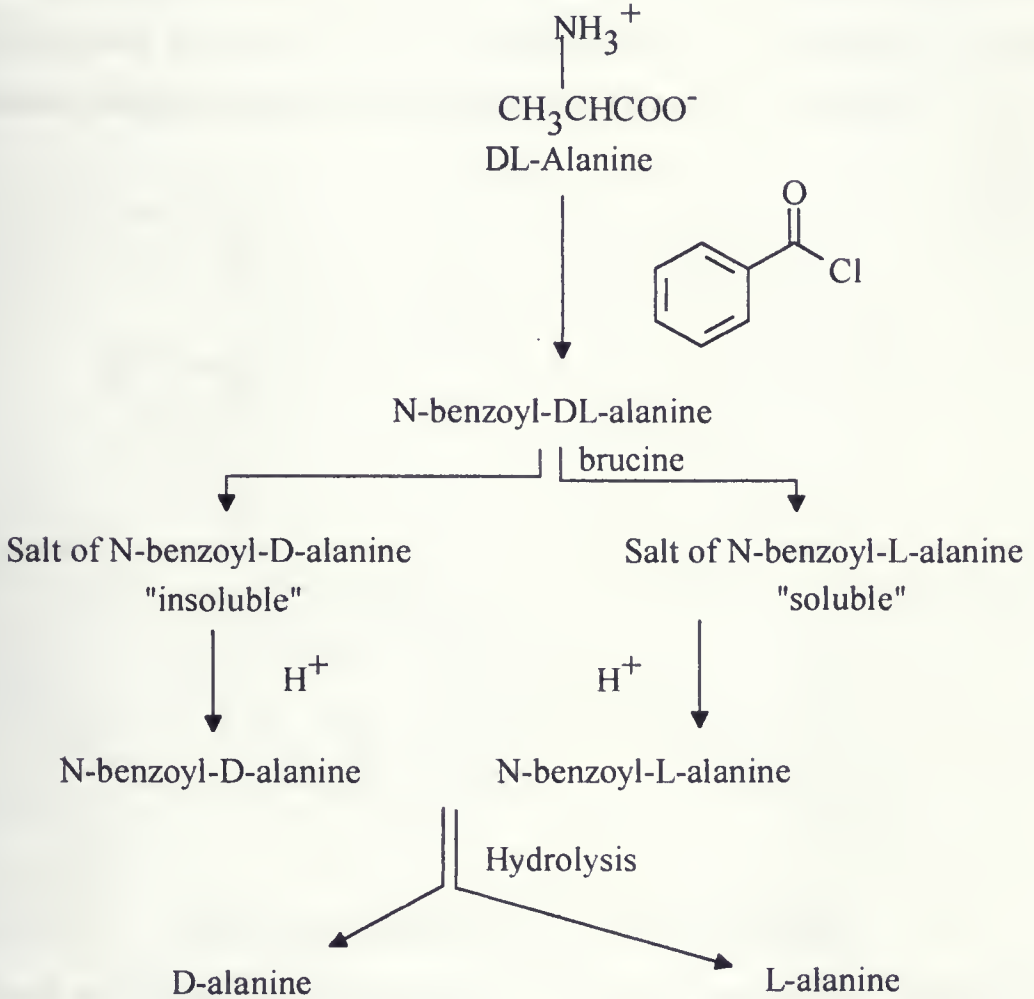


(S)-Phe

Figure 5. Chiral pool compounds L-tartaric acid and the amino acid L-phenylalanine

One of the most classical methods of chiral differentiation is to perform what is termed a chiral resolution. These methods of enantiomeric discrimination can be performed either chemically or enzymatically. In the case of a resolution which is performed chemically, a racemate is treated with a chemical which is capable of converting the mixture to a diastereomeric salt. This is typically followed by a crystallization, hence yielding the salt of one enantiomer while the other diastereomeric complex, having different chemical and physical properties stays in solution and is then filtered off. For example, amino acids synthesized by the Strecker method often lack optical purity, and therefore need to be resolved before being incorporated into synthesis. One method of doing this is to treat the racemic mixture with an acid chloride, typically benzoyl chloride, thereby converting the amine to an amide so that the material is no longer amphoteric. The resulting racemic amide is then treated with a chiral base such as strychnine or brucine, and a typical crystallization is then performed, separating one of the diastereomeric salts. Acidification of the salt then affords one of the optically pure N-protected amino acids, which can then be subjected to standard hydrolysis to yield the

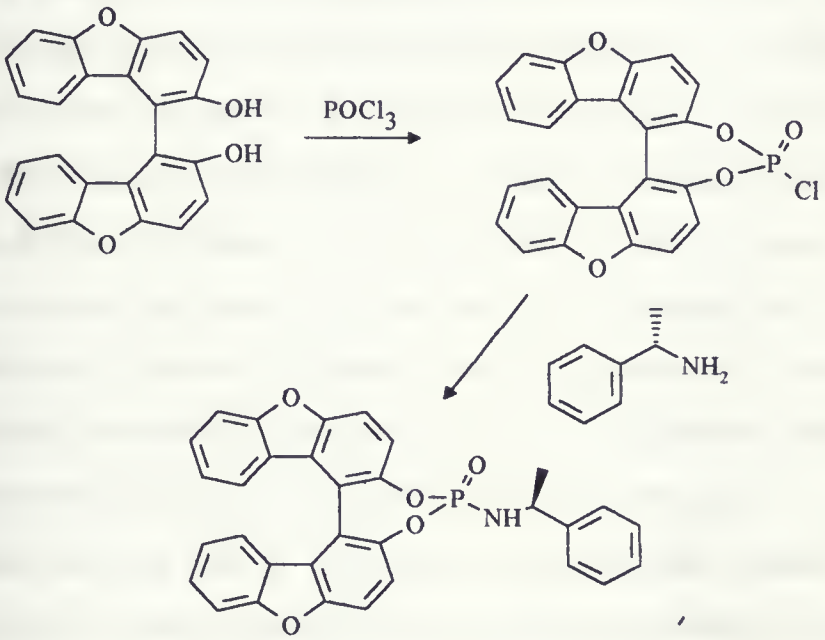
corresponding free amino acid. The scheme outlined below illustrates this process with racemic alanine as an example.



Scheme 2. Resolution of Racemic Alanine *via* Diastereomeric salts.

Other examples of resolving racemates exist. Of them, perhaps the most well known is the method which employs the use of tartaric acid. Many compounds have been resolved as a diastereomeric salt of tartaric acid. The basic idea is the same for that of the DL-alanine example, with the exception that the compounds often do not have to be chemically altered in any way prior to crystallization.

However, the use of salts is not imperative. One can attatch a chiral molecule to the racemate thus converting them to a separable mixture of diastereomers. As an example, racemic (1,1')-Bi(dibenzofuralyl)-2,2'-diol BIFOL [4] was converted to the phosphoric acid chloride with $POCl_3$ which was reacted with chiral phenylethylamine to afford the 1:1 mixture of diastereomers which were separated by fractional crystallization from ethanol.



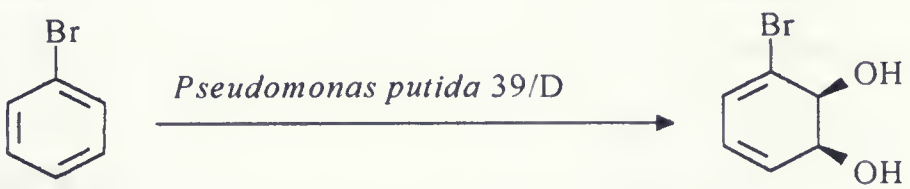
Scheme 3. Chemical Resolution of racemic BIFOL

There are, however obvious limitations to relying on the use of crystallizations as a means of purifying a diastereomeric mixture. The procedure is often non-trivial and can be quite time consuming to develop a protocol which will enable efficient separation. Although crystallization is a common and widespread means of purification of many organic molecules, and when successful can be an excellent method, the former implies that each fraction obtained can have small amounts of the other diastereomer present. There is not always a requirement to separate a mixture of diastereomers *via* crystallization. With sufficient chemical difference, one can often separate them by column chromatography or HPLC. In either case, the conversion of a

racemic mixture to one of diastereomers has obvious detriments due to the fact that a maximum of 50% obtainable yield is associated with such a method. It is, nevertheless, a conventional method for resolution of racemic mixtures.

One may often rely on the employment of an enzyme as a means of performing a resolution. Many examples which work quite well have been documented. The limitation to this method is that enzymes are very specific to individual substrates. It is common to obtain high enantiomeric purity with enzymes on a given racemate, but the optical purities and the effectiveness of the process can drop rapidly as the substrate's chemical functionality is altered. For example, an enzymatic resolution may be highly effective when R = methyl, but changing that to an ethyl or a propyl may render the process obsolete. This is due to the fact that enzymes work on a "lock and key" basis and are therefore not a general method of resolution . Although select examples have proven to be quite widely used, they lack the general usefulness associated with conventional chemical methods of enantiomeric differential resolution.

To expand upon the idea of utilizing an enzyme to induce chirality by resolving enantiomeric mixtures, another method which employs enzymes to impart asymmetry is the field of biotransformations. Unlike a resolution, however, the material which is used in the process is not necessarily chiral at a given site. Instead, the compound is prochiral at that site, and with the enzyme the functional group is altered such that the new compound is chiral. One example of a typical transformation is the whole cell conversion of bromobenzene to the *cis*-diol by *Pseudomonas putida* 39/D. This transformation is widely used and has been incorporated into total syntheses of compounds such as pancratistatin [6].



Scheme 4. Enzymatic conversion of bromobenzene

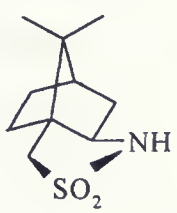
This method of asymmetric induction is much like the employment of enzymes in resolutions. This is due to the "lock and key" specificity of enzymes, and for this reason biotransformations are not considered a general tool for asymmetric induction. They do, however, play an important role in certain respects, such as the example shown above, and for that reason biotransformations will likely be limited to a small number of specific reactions which asymmetric catalysis is incapable of performing.

Bearing in mind that attachment of a compound which originates from the chiral pool such as an amino acid to a racemte can impart the necessary chemical dissimilarity between enantiomers which enables their separation, one such method of stereocontrol in asymmetric synthesis has been well established throughout modern methodology as a very chemically efficient and cost effective means of enantiomeric control. This method is based on the above observation, and that attachment of a chiral subunit at a remote site on a prochiral substrate should be able to induce asymmetry in the form of diastereoselectivity at a given stage in a synthetic route. These attachments, ideally termed "chiral auxiliaries" were developed over the last twenty years or so by researchers such as Wolfgang Oppolzer and David Evans.

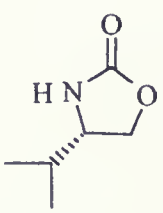
Much like chemical resolutions, chiral auxiliaries are derived from compounds originating from the chiral pool. Unlike resolutions based on diastereomeric salts or compound mixtures, the auxiliary is attatched to the substrate while it lacks chirality. That is, to a compound that is *prochiral*. The way in which auxiliaries work is, the auxiliary is attached to the prochiral compound, the functional group in question is then manipulated in a diastereoselective manner, and then, usually the next step is used to remove the auxiliary. This is more efficient than a resolution due to the fact that the resulting chiral compound is isolated in typically high yields as opposed to a maximum yield of 50%. This is because the auxiliary induces chirality to a prochiral substrate while a resolution follows a step in which configuration is already determined. The only drawback that accompanies the utilization of chiral auxiliaries

is that two additional steps must accompany the synthesis of the target molecule; one for the attachment of the auxiliary and one for its removal,both of which by chemical means, which can bring about for lower overall yields.

As stated above, the more commonly employed chiral auxiliaries originate from chiral pool precursors. One of the most successfully employed chiral auxiliaries used to date is the Oppolzer's camphor sultam [7] which has been used in a wide variety of asymmetric transformations including synthesis of chiral sulfoxides and sulfinimes [10], Diels-Alders [11], hetero Diels-Alder reactions [12] *anti*-aldol reactions [13], osmium tetroxide dihydroxylations [30], radical cyclizations of dienes and diynes [31], Baylis-Hillman reactions [70] and cyclopropanations with diazomethane [32]. The camphor sultam is derived from the monoterpene camphor and it is now available commercially in multi Kg quantities. The second most important class of auxiliary is the Evans' oxazolidinone, typically obtained from either the amino acids valine or phenylalanine. These compounds have been shown to be effective auxiliaries in various reactions such as Michael additions [14], acetalization of alkenes [15], cyclopropanations [16], allylations [17] and Diels-Alder reactions [18], and in the total synthesis of vancomycin [5], which has considerable antibacterial activity against certain drug resistant pathogens such as the methicillin resistant *Staphylococcus aureus* [8,9].



Oppolzer's Camphor Sultam



Evans' Oxazolidinone

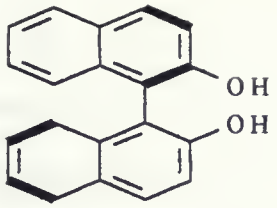
Figure 6. Oppolzer's camphor sultam and Evans' oxazolidinone

Although the chiral auxiliaries just mentioned have been shown to induce high degrees of asymmetry into organic synthesis, while still having industrial applications, they now are

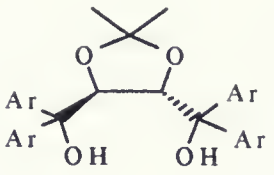
generally considered outdated due to the fact that they lengthen a synthesis by two steps: one for the attachment of the auxiliary and one for its removal. Generally speaking, with lengthening the synthesis of a compound comes an overall reduction in the yield of the final product, and due this increase in length, chiral auxiliaries are now being studied less in place of asymmetric catalysis.

Due to the variety of chemistry that can be studied, the high degree of enantioselectivity and the overall efficiency, asymmetric catalysis is quickly moving to the forefront of organic chemistry. Over the past 20 years or so, the field has taken shape, and is likely the last frontier in modern day methodology. In general, any transformation that can be performed by a metal Lewis acid thereby producing a racemic product could, theoretically be rendered asymmetric using a chiral Lewis acid catalyst.

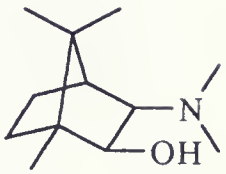
The most common type of ligands which are employed in the growing field of asymmetric catalysis are those which display C_2-symmetry. This term is used to describe a chiral compound containing a axis of symmetry down its central axis, and which when rotated about that axis 180^o maps onto itself. For example, chiral compounds such as TADDOL ($\alpha,\alpha,\alpha\square',\alpha'$-tetraaryl-1,3-dioxolane-4,5-dimethanol) and BINOL (binaphthol) exhibit C_2 symmetry because if "flipped over" they appear identical. Many ligands that have been studied in the field that exhibit C_2 symmetry include the 1,4-diols TADDOL and BINOL, as well as analogues of these compounds. They have clearly established themselves as the benchmark for the field in a host of catalytic asymmetric transformations. They also have limitations in that TADDOL is the result of a 4-step synthesis from tartaric acid while BINOL is prepared in racemic form and later resolved, limiting the overall yield and increasing its cost.



BINOL



TADDOL



N,N-dimethylaminoisoborneol

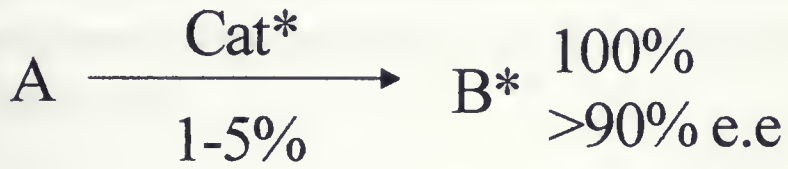
DAIB

Figure 7. The ligands TADDOL, BINOL and DAIB

The way in which chiral catalysis works is first the ligand becomes complexed to a central metal such as copper or titanium (among others), which in turn coordinates to the substrate by virtue of the Lewis acidity of the metal. The substrate is then transformed into a chiral molecule by reaction with another molecule (such as a nucleophile) through a highly diastereoselective transition state due to the C_2symmetry of the complex making one enantioselective reaction more energetically feasible (by a few Kcal), and finally liberation of the product from the catalyst, enabling the catalyst to repeat the cycle. The high degree of turnover possible in these catalytic cycles enables for extensive chiral amplification to the system. Due to it's efficiency and generality, asymmetric catalysis now overshadows the classical methods of chiral induction.

There is a vast array of heteroorganic complexes which are known to promote chiral transformations. The earliest examples of such processes were the transfer of atoms such as hydrogen, nitrogen and oxygen to organic substrates. These earliest examples were the work of the pioneers of the field, and included Noyori, Sharpless and Evans. Much of the earliest work,

including reactions such as asymmetric hydrogenations, epoxidations or dihydroxylations are now used quite routinely in total synthesis of natural and unnatural products and reach extremely high levels of enantioselectivity and efficiency. In most cases a very low loading of the catalyst is required. In many instances enantiomeric excesses (e.e's) greater 98% with yields nearly quantitative can be obtained using less that 2 mol. % of the catalyst! A simplified scheme of the ideal scenario is shown below and as described is quite readily achievable.



Scheme 5. A simplified idealistic representation of an asymmetric transformation

Due to the observed efficiency of asymmtric catalysis, there is no longer the need to rely on chiral pool precursors and be impeded by their limitations to impart asymmetry. As well, the inefficiency of attachment and removal of a chiral auxiliary will no longer be necessary, nor will others derived from pinene, menthol or amino acids, as these methods of chiral induction will become somewhat redundant in future studies. Validation of this statement is supported by the fact that chemists who were important figures in the development of chiral auxiliaries over the past couple decades, such as Evans and Oppolzer have been key researchers in this newly developing methodology. Although the past methods have important applications, achieving e.e.'s as high as 99%, they, much like biotransformations will be limited to a few types of reactions.

Chapter 2

Aspects of the Project

Having discussed with criticism the classical approach to asymmetric induction, the need for development of novel methods for accomplishing enantioselective reactions, as well as some general aspects of asymmetric catalysis and a short discussion of some areas which are specific to this thesis will be discussed.

2.1 Chiral Diols

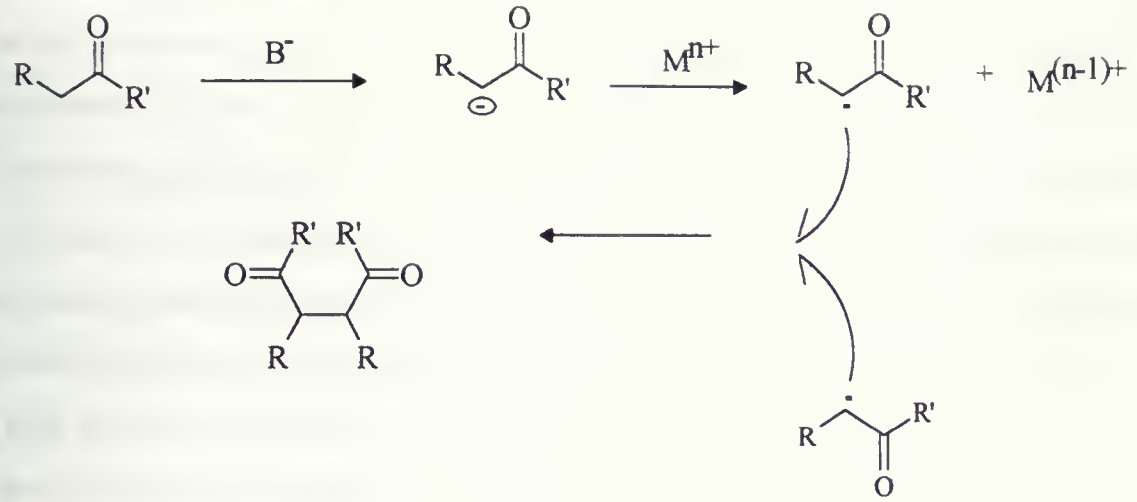
Chiral diols such as the 1,4 diols BINOL and TADDOL derivatives have earned a place in the field of asymmetric catalysis as two of the most commonly studied ligands. Although the aforementioned drawbacks such as length of synthesis (TADDOL) and racemic synthesis (BINOL) are worthy of mention as a rationale for the design and synthesis of new ligands for investigation, these compounds have earned a reputation for excellence in asymmetric studies. TADDOLate complexes of various metals such as titanium have been extensively studdied in a variety of reactions such as nucleophilic additions to aldehydes, ketones and nitroolefins, aldol additions, [2+2] cycloadditions and ene reactions [19], to mention but a few. In addition to these, complexes of TADDOLs have been very extensively studied in Diels-Alder reactions [20-25], all with high degrees of enantioselectivity. Complexes of BINOL and derivatives have also seen extensive study, in reactions such as asymmetric aza Diels-Alder reactions and aldol type reactions [26, 27] as well as in the enantioselective reduction of aromatic ketones by chiral hydrides [28, 29], with optical purities as high as 99%.

Taking into consideration the degree of success achieved by complexes of TADDOLs and BINOL, each still have drawbacks which opens the door for the synthesis of new 1,4-diols with which to study asymmetric transformations.

2.2 Oxidative Couplings

The oxidative dimerizations of phenols by reagents such as manganic tris(acetylacetonate) (MTA) [33] and ferric chloride [34] as a means of creating 1,4-diols such as BINOL and other derivatives has been a longstanding methodological study. Until now, however, the compounds arising from these methods have lacked chirality due to an inability to control enantioselectivity during the coupling of the radical. Oxidative couplings have also been extended to enolizable protons such as ketones, aldehydes and esters by various metal salts such as ferric chloride [35], copper trifluoromethanesulfonate and vanadium [36-37] as a means of generating 1,4-diketones [38-40] and succinic acid derivatives [41-44]. There have also been reports [45-49] which have investigated the control of diastereoselectivity of radical couplings, but to the best of our knowledge there has only been one report [50] of a completely diastereoselective oxidative enolate dimerization, while others fail to clearly define the factors governing such control. This is surprising since it has been reported [41-42] that acyclic enolates bearing chiral auxiliaries dimerize with high stereoselectivity. This implies that cyclic chiral enolates may behave in the same manner and herein these factors are discussed.

The way in which oxidative dimerizations typically work is by the initial deprotonation of an acidic proton. These are typically α to a carbonyl. Then, by using a metal salt such as copper in a higher oxidation state (typically 2+ for copper, 5+ for vanadium) takes an electron from the anion, thereby creating the radical and the cation of the metal becomes reduced by a charge of 1-. The final step in the process is the inter or intramolecular dimerization of two radicals, shown below.



Scheme 6. A general representation of an oxidative coupling

2. 3 Asymmetric Aldol Reactions

The asymmetric aldol reaction is one of the most fundamental and most powerful methods of carbon-carbon bond formation with a high degree of control of relative stereochemistry at new chiral centers known [71]. With its wealth of application this reaction has seen several applications to total synthesis [72-73] as well as fundamental investigations. With so many classes of ligands capable of introducing enantioselectivity, including aminoalcohols such as the camphor derived DAIB [74-75] and other amino alcohols [76], camphor sulfonamides [77], as well as ligands derived from monoterpenoids such as the pinane skeleton [78] and 1,4-diol analogues of BINOL [79], the asymmetric addition of diethylzinc or silyl enol ethers to aryl aldehydes has come to the forefront in terms of asymmetric catalysis and has become the standard method of screening new ligands for asymmetric control. Given that, this reaction will serve as an excellent template for the new ligands which will be discussed herein.

The origin of asymmetric induction in the catalytic enantioselective aldol reaction lies in the ability of an incoming nucleophile to discriminate energetically between the Si and Re faces of the carbonyl compound. In the case of benzaldehyde show below, the aldehyde is activated by coordination to the metal of the Lewis acid in a rapid-reversible process. This is followed by the stereoselective addition of the nucleophile through the now energetically differing diastereomeric transition states (T.S.'s) onto either face. This differentiation is brought about by the nature of the chiral environment around the metal-substrate complex. Now, approach from one face, either the *Si* or the *Re* is blocked (high energy T.S.) by the steric nature of the complex (in the case below the *Si* face is blocked), thereby leaving one face accessible, the low energy T.S. Under properly governed conditions such as temperature, solvent and choice of metal we hope that the new ligands synthesized will impart high degrees of enantioselective control in aldol processes.

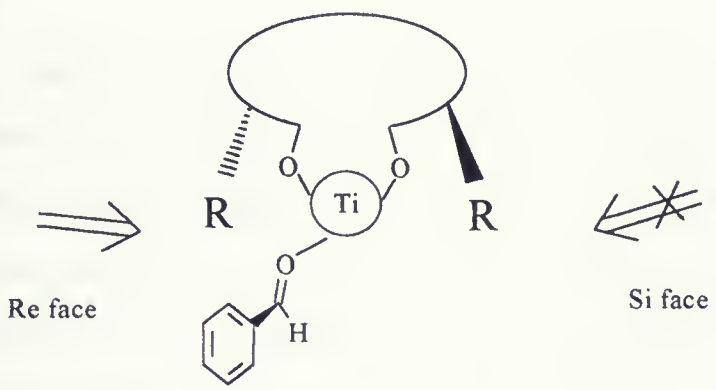
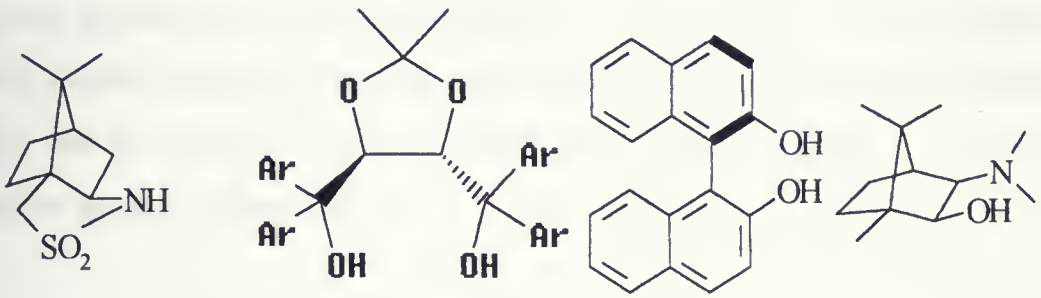


Figure 8. Model depicting the origin of selectivity during catalysis.

Results and Discussion

We began by envisaging a new chiral ligand that contains some of the interesting and well rationalizeded carbon framework that is contained in the well documented ligands such as Oppolzer's camphor sultam **1**, TADDOL **2**, BINOL **3** and DAIB **4**.



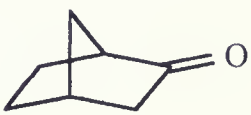
1 2 3 4

Oppolzer's Camphor Sultam TADDOL BINOL DAIB

Figure 9. Representative drawings of interesting ligands

Of these compounds, the functionality that is believed to be important with respect to the documented successes of these (2 and 3), and other compounds like them, is C_2-symmetry, which insures unequal diastereomeric transition states, regardless of how the substrate coordinates to the central metal. The second factor which is thought to play a part in the high degree of enantiomeric discrimination incurred by these compounds is the 1,4-diol functionality displayed in TADDOL and BINOL. This describes how two oxygen atoms are four carbon atoms removed from each other, thereby forming a highly selective seven membered ring when chelating a metal such as titanium. The third element thought to be important to the success not of BINOL or TADDOL, but to compounds such as Oppolzer's camphor sultam and DAIB is the [2.2.1] bicyclic system within the inner structure of the ligand itself. It is not the simple [2.2.1] bicyclic nature alone that plays a crucial role in reactions mediated by these compounds, but it is likely the bridging *gem*-dimethyls which are conveniently located 'atop' the structure.

These methyl groups likely bring about a high degree of steric hindrance to the transition state of the reaction, thereby very greatly differentiating the transition state energies of the individual enantiomeric reactions. This, in turn makes one enantioselective process far more energetically feasible than the other by blocking one face and leaving the other accessible. For example, if one were to take compound such as the unsubstituted bicyclo[2.2.1]heptanone **5** shown below and attempt to use the compound in a manner which was supposed to introduce diastereo or enantioselectivity to the process, the process would likely exhibit low selectivity due to the fact that the bridging methylene is unsubstituted and the difference is only a second methylene on the core cyclohexane.



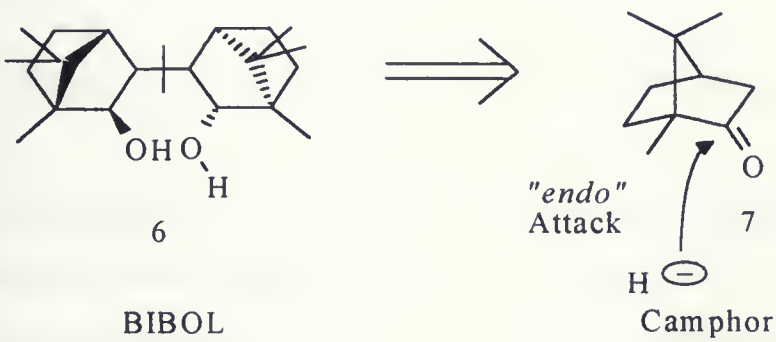
5

bicyclo[2.2.1]heptanone

Figure 10

We postulated that a compound that contains all of the functionality just described would be ideal for studying asymmetric transformations such as additions of diethylzinc to aldehydes. We therefore set out to synthesize a new 1,4-diol with the camphor carbon skeletal subunit and C_2-symmetry. Early modeling studies using AM1 calculations indicated the compound in question would likely contain a camphor dimer coupled on its *exo* face, that is, the same face as the bridging carbon. To accompany this structural feature, the alcohol functionality would likely have to be disposed *exo* as well, that is pointing towards the bridging dimethyls if the compound were to be successful in asymmetric transformations.

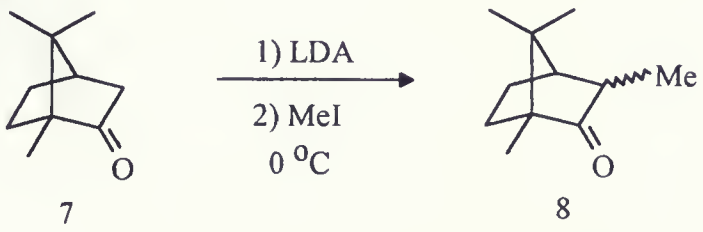
There are very few routes that would enable us to synthesize such a compound [58]. A disconnective approach to a retrosynthetic analysis reveals that the diol functionality must come from a kinetically controlled hydride attack thereby furnishing the *exo* disposed alcohols, as well as a highly stereocontrolled carbon-carbon bond formation reaction. A closer look reveals that the synthetic route would either come from an oxidative coupling of the enolate of camphor, or from an S_N2 type reaction. We named the desired compound "BIBOL", which is simply an abbreviation of biisoborneol. This name came about by virtue of the fact that the compound in question is a simple dimer of *exo*, or isoborneol. It, in turn is merely the epimer of natural borneol, connected at the C (3), show below.



Scheme 7. A retrosynthetic look at BIBOL.

We initially began our quest for BIBOL **6** by approaching the synthesis from an S_N2 manner. This would obviously involve a nucleophilic attack at the C(3) position, by an anion situated at the C(3) counterpart. But in order for the carbon-carbon bond forming reaction to proceed as desired, that is, for the product to be coupled on the *exo* face of both camphor subunits, we would have to insure that at least one half of the stereochemistry be imparted by virtue of the relative stereochemistry of one of the starting materials. The other half of the reaction would therefore be left to proceed knowing that it is well documented [53-56] that nucleophilic substitution proceeds preferentially on the *exo* face of camphor at C(3). This has

been established by many groups over the past decade or so that treatment of camphor **7** with 1.05 eq. of a strong base such as LDA, followed by addition of methyl iodide (excess) leads to about a 75% yield of a 4:1 mixture of 3-*exo*-methylcamphor and 3-*endo*-methylcamphor **8** at O ^{o}C. [53], shown below.



7 8

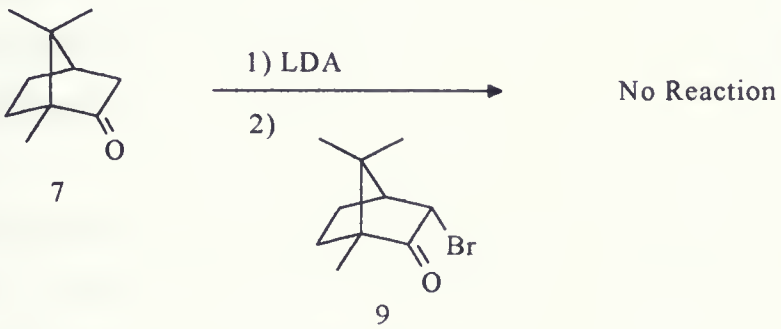
4:1 exo : endo

Scheme 8. Reaction of camphor enolate with methyl iodide.

Bearing in mind the fact that the kinetic product in cases such as this is clearly the *exo* isomer, we postulated that under strictly governing conditions such as choice of solvent and temperature a high degree of kinetic control with respect to orientation from which the nucleophilic attack occurs. That is, we could control the substitution such that the R group, being a second camphor in this case, would indeed be coupled on its *exo* face, especially if substitution were to occur at temperatures below 0 ^{o}C The other half of the stereoselectivity, as mentioned previously would arise by virtue of the stereochemistry of the starting material itself.

Since in this case "R" was another camphor unit, and the desired product is coupled on it's *exo* face as well, we would need to chose an electrophile (in this case at C(3)) that was oriented *endo,* that is, pointing down, or away from the bridging methyls. This would therefore direct the incoming nucleophile in an *exo* attack, being an S_N2 process, thereby inverting the relative stereochemistry at the C(3) position of the electrophile. The choice of reagent that we postulated would afford us the desired *exo-exo* camphor dimer was 3-*endo*-bromocamphor **9**. It

is well known that large halogens such as bromine are typically good leaving groups, and the fact the there was a carbonyl α to the bromine in this case was even more to our advantage, greatly increasing the relative electrophilicity.



7 9

Scheme 9. Initial attempt at BIBOL with an S_N2 reaction

The reaction, shown above, was attempted several times but there were several factors limiting our forward progression. First we were faced with the seemingly trivial, but often frustrating fact that visualization of camphor by TLC could not be done. The bromo compound was faintly visible to staining with anisaldehyde, but the unsubstituted ketone was likely too hindered. It would only stand to reason that the intermediate diketone, should it form, would be even more greatly hindered and less likely to visualize upon staining. For those reasons, it was very difficult to follow the course of the reaction. Secondly, after having gone blind with respect to the progress of the reaction, all compounds isolated were determined to be starting materials. This was likely due to steric hindrance of both the nucleophile and electrophile, coupled with the inability to monitor the course the reaction by TLC.

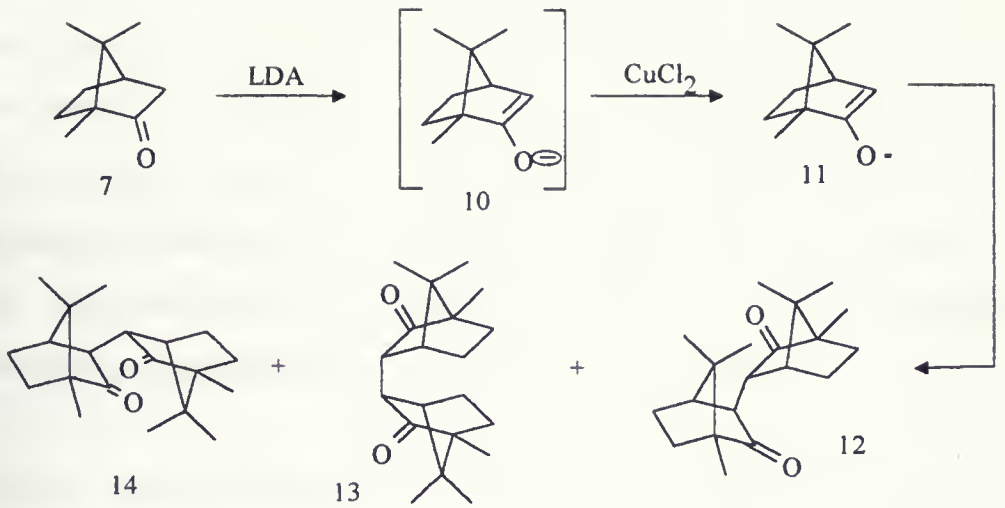
But, strangely, it was noticed that the mass corresponding to the total of both starting materials was not being recovered following work-up. At this time, to add to the fact that the reaction was not proceeding at -78 ^{O}C, it also appeared that upon work-up some of the mass was being lost to sublimation. It is well established that [2.2.1]bicyclic systems sublime readily not

only under reduced pressure, but even at standard temperature and pressure. To accommodate our inability to visualize the formation of a new product, as well as the lack of evidence that supports the formation of one by NMR, we were faced with essentially two options. These options hopefully would a) facilitate the progress of the reaction and b) minimize the potential loss of the new intermediate diketone, since at this stage it was unclear as to whether the diketone would sublime or not.

We then attempted the reaction as in the hitherto mentioned manner, that is, the formation of the enolate of camphor **7** with LDA at 0 ^{o}C followed by addition of α-bromocamphor **9** in dry THF to the enolate at -78 ^{o}C. The exception to the old method was that the reaction would be permitted to quickly equilibrate to 0 ^{o}C, and eventually warm to room temperature. This would hopefully overcome the seemingly sterically crowded nature of both the nucleophile and electrophile, thereby giving product. The only downside to the aforementioned protocol was that it was likely that should the reaction proceed under these conditions, it would, in all probability result in a loss of some of the desired *exo* selectivity of the substitution event, resulting in an undesirable mixture of *exo-exo,* and *exo-endo* diketones. In this case, it was even likely that because of the steric nature of the enolate as a nucleophile, the predominant product would likely be the thermodynamically more stable *exo-endo* coupled product. Further, to accommodate for the speculated volatility of the diketones, it was postulated that by reducing the product *in situ,* hence omitting work-up, the compound would not sublime as readily as the diketone would, due to the increased polarity of the product. But, disappointingly, as before, the reaction failed to give the desired 1,4-diol. The likely product, although not isolated and characterized, was the α-*endo*-bromoisoborneol. This was compared (TLC) to a sample made by reduction of a bit of *endo*-bromocamphor by LAH in THF. With this finding, that is, the failure to promote the synthesis by this method, we were faced with focusing our attention on an alternative method of making BIBOL.

It can be seen that BIBOL, a 1,4-diol, is the final result of the reduction of a 1,4-diketone. With this fact, it was postulated that our now final hopes of making the target molecule BIBOL rested in a oxidative coupling of the camphor. There have been reports that describe the methods by which oxidative coupling of enolates can occur The result of such a process gives directly 1,4-diketones, and in one report [52] the authors describe the oxidative coupling of camphor enolate thereby giving the necessary molecular framework through which our desired 1,4-diol can be made. However, the shortcoming in the previously mentioned report is that the authors claim to have obtained a 60% yield of a mixture of diketones; those being the results of three indiscriminate coupling events to afford the *exo-exo, exo-endo,* and *endo-endo* dimers. Considering the normally high degree of facial selectivity imparted by the bornane skeleton [51] the process in question as well as the aforementioned selectivity of the C(3) substitution on camphor with methyl iodide and other electrophiles such as arylaldehydes [53-56] is quite surprising, It is clearly one which could be improved upon given highly kinetically defining conditions.

As described previously, the factors involved in controlling a highly stereoselective process which promote kinetic control would likely rest in the temperature and solvent. The coupling which was reported previously [52] was performed by oxidizing the enolate, which was prepared by deprotonation of camphor in THF at 0 ^{o}C, by $CuCl_2$ in DMF at -78 ^{o} C with slow warming to room temperature. At this point in our pursuit of BIBOL, we began the second stage of the investigation by attempting to repeat this procedure. Indeed, we confirmed that the coupling event was non facially discriminating, thereby affording a mixture of diketones, **12**, **13** and **14**. This method was quite rapid, requiring only 24h for an apparent consumption of camphor, as determined by the absence of corresponding peaks for camphor in the ^{1}H NMR spectrum.



Scheme 10. A depiction of the non selective couplings of camphor

At this stage, there were several problems which were consistent with the initial attempts at synthesizing BIBOL *via* the S_N2 method previously described. There was once again the inability to visualize the starting material, nor the products. Since the NMR analysis of the mixture of diketones obtained revealed the only traces of camphor, it was thought that camphor was being consumed during the reaction. In other words, a complete coupling of the camphor was occurring. But with this apparent fact arose another difficulty. If camphor is being consumed, but is not visible by TLC, and we were not seeing the intermediate appear on TLC, then there was essentially no method by which the reaction could be monitored. This proved to be somewhat troubling, as it was very difficult in the early trials to come to know whether or not the reaction was complete. Should a reaction be worked up prematurely, the trial would not be qualitative nor quantitative due to the presence of residual camphor. Also, it was essentially impossible to purify the desired diketone due to the fact that a) it was not clearly visible by TLC; b) it would likely have a nearly identical R_f as camphor (this statement is somewhat retrospective as it is now known that BIBOL and synthetic borneols obtained by reduction of uncoupled camphor during the reduction event (description to come) have very similar R_f's on TLC) and c) the coupling step was completely devoid of stereoelectronic control, hence

affording the inseparable mixture of diastereomers; observations consistent with previous reports [59]. As was the case with the S_N2 approach, the mass of the isolated mixture of diastereomers was never in accord with that of the starting material, camphor. The one advantage accompanying all of these associated problems was that camphor is very inexpensive, and a study of the factors involved in governing diastereocontrol during oxidative dimerizations of enolates would likely be, as was later proven, a long and challenging task

Although the method used [52] to obtain the mixture of diketones was by no means worthy of consideration as a viable means to obtain the desired product, it was, however the most time efficient method known to us thus far to promote the formation of the diketone necessary for the production of BIBOL. There has been one other report on the production of the desired *exo-exo* diketone **14** [57], but the synthesis involves a lengthy 5 step process from camphor.

Regardless of the poor selectivity of the coupling to this stage, the desire was to obtain a suitable sample of the diol for analysis. In doing so, a clear understanding of where the desired diol comes on TLC would result, and monitoring for its production by removing small aliquots of each trial, followed by immediate reduction by LAH would be possible. This method would quite easily replace the inefficiency of working up an aliquot at the coupling stage and comparing the ^{13}C spectrum with that of known data [57]. Therefore, the mixture of diketones obtained by nondiscriminate coupling was quickly redissolved in THF immediately following work-up and added to a suspension of LAH in THF at 0 ^{o}C. As expected, the reduction yielded an unimpressive mixture of diastereomers. By TLC, approximately 6 isomers were observed, likely being a complex mixture of *exo-exo, exo-endo,* and *endo-endo* coupled, *exo-exo, exo-endo,* and *endo-endo* diols. In spite of its overwhelming complexity, the mixture was purified on SiO_2 to give approximately 25% of one of two major diastereomers, as well as about 15% of the second.

In order to combat the potential ambiguity that accompanies NMR coupling constants, most notably, the coupling to the C(3) "connecting" proton from the bridgehead proton, we set forth to obtain the respective X-ray crystal structure of each of the two diols. It was determined that crystals suitable for analysis of the major diol were obtained by slow evaporation of AcOEt, while that of the minor were obtained from $CHCl_3$.

Quite surprisingly, the X-ray analysis of the major diol was that of the desired *exo-exo* coupled, *exo-exo* disposed diol, corresponding to what was envisaged as the kinetic product, BIBOL. More surprisingly however, was that the X-ray analysis of the minor diastereomer was determined to be that of the *exo-exo* kinetically coupled, *exo-endo* epimeric diol. The respective crystal structure of each diol is shown below.

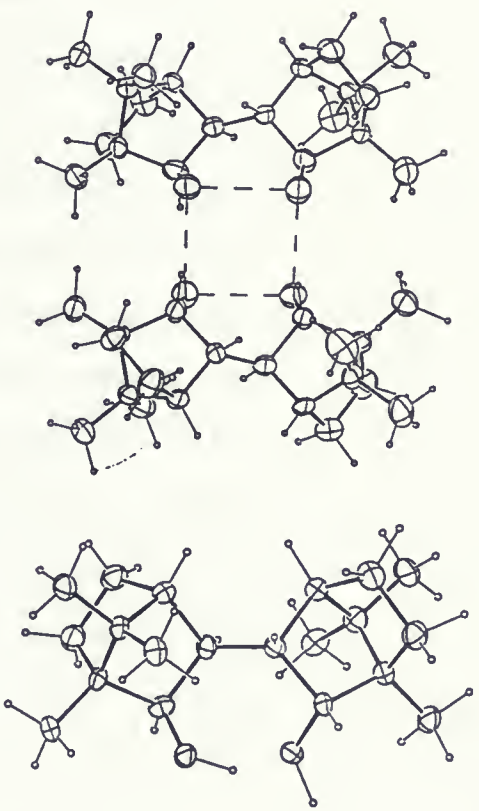


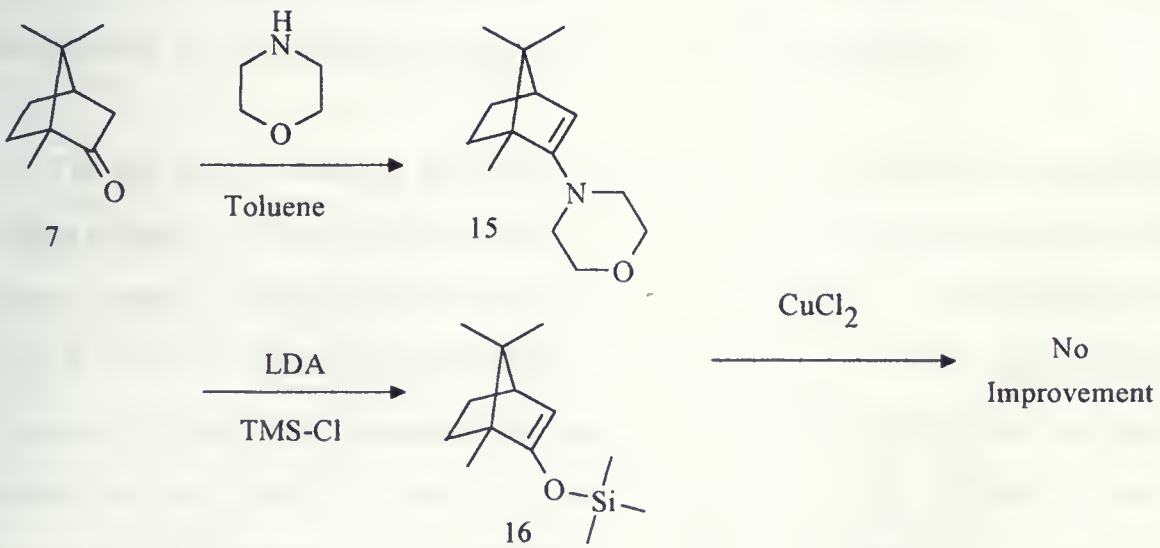
Figure 11. Perspective drawings of the X-ray structures of major isomer BIBOL **19** (bottom) and minor diol **20** (top).

Even though the aforementioned coupling process was thought to, and was proven to lack kinetic control with respect to the process to be described shortly, it is still biased towards production of the kinetic *exo-exo* coupled dimer. This is likely due to the fact that upon oxidation of the enolate **10** to the enoxy radical **11**, the steric repulsions brought forth by the methyl of the bridging carbon on C(7)and the C(3) proton are at a minimum when the *'pseudo-exo'* substituent is the lone electron of the radical, indicating that coupling is a subject of stereoelectronic control

With the desired diol now in hand, efforts which focussed on the improvement of the existing procedure to one which was more diastereoselective with respect to the production of the major diol were now underway. In other words, could conditions be defined which would promote complete stereoelectronic control, hence eliminating the formation of any diketones coupled by their *endo* face? If this could be done it would be a result that is the first of its kind. There were other problems that needed to be addressed at this stage as well. First, the fact that the original procedure gave a 60% yield of a mixture of diketones left a few questions to be answered. The fact that the mass was not being successfully recovered, as in the case of the earliest attempts using α-bromocamphor, suggested that the mixture may be subliming on work-up. Secondly, the fact that a mixture of diketones is observed does not necessarily suggest that the process lacks kinetic control. The mixture may, in fact, be coming from a base mediated epimerizaton event *in situ*, or even without base due to the polar effects of DMF, or even upon work-up. If the lack of stereocontrol was due to an *in situ* base mediated epimerization, or due to work-up, then appropriate reagents would have to be chosen to allow for both a kinetically controlled coupling as well as those which would permit for a (chemoselective) one-pot protocol. These questions would have to be answered slowly over time, with trial and error.

To test if the work-up did in fact promote an epimerization to the *endo* substitution, an attempt at repeating the initial procedure while omitting work-up was performed. The problem was that it was not feasible to perform a LAH reduction in the presence of DMF due to the large consumption of hydride reducing DMF to trimethylamine. The attempt failed to improve the protocol, so it was postulated that a completely different set of parameters must be employed.

The first postulate was that the indiscriminate coupling was the result of rapid and non-kinetic coupling of the enoxy radical. Perhaps by slowing down the rate of the single electron transfer process (SET) the reaction would display an increase in the diastereoselectivity of the coupling step. In order to do so, it was necessary make the enolate less susceptible to oxidation. The initial attempts at doing so involved the production of the enamine, **15** of camphor, and later the silyl enolether, **16** followed by a standard copper II mediated oxidation, shown below.



Scheme 11. Depiction of the production of enamine and silyl enol ether of camphor.

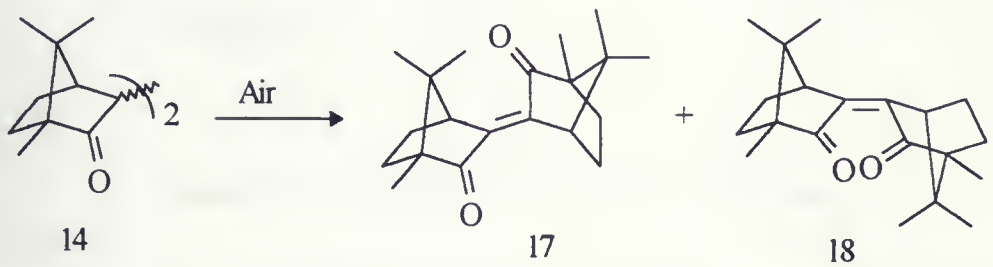
These attempts failed to improve the selectivity of the coupling and even reduced the yield of product. This was likely due to the fact that the rate was too greatly impeded. The

second, and what would eventually be the final method was to change the solvent from THF and DMF to toluene, thereby slowing the SET leading to kinetic control. Even though the enamine was produced in toluene, it may simply not have been susceptible to oxidation.

The rationale behind employing toluene was that changing from a polar solvent such as THF to a non-polar one such as toluene would slow down the rate of the single electron transfer, or SET, thereby mediating a more stereoselective process. The one problem, however, was that $CuCl_2$ is completely insoluble in toluene. It had already been documented [59] that the coupling was ineffective when the choice of cosolvent for $CuCl_2$ was either THF or toluene. This fact is clearly owing to the lack of solubility of the copper salt, thereby negating oxidation. If we were to be successful in our pursuit of BIBOL, we would now have to contend with the choice of reagents which promote kinetic control as well as taking into account the yield of the process, which is a manifestation of factors such as solubility. Therefore, high solubility of the copper salt, especially at -78 ^{o}C would likely be essential for success. We were now faced with many factors which would have to accommodated, all while maintaining stereoselectivity. This lead us to try a series of oxidants that we hoped would promote BIBOL's formation.

The first attempt in the use of toluene was to employ copper trifluoromethanesulfonate, or copper triflate ($Cu(OTf)_2$) as the oxidant [80]. The rationale was that since this copper II salt was more "organic" in nature, due to the presence of the triflate portion, it would likely be more soluble in toluene at depressed temperatures. Initial attempts at dissolution failed, hampering the coupling attempts, but subsequent attempts included the addition of small amounts of pyridine to act as a donor while aiding in the dissolution of the salt. This had a markedly different effect. A dramatic change was observed. It was noticed that the coupling was, as desired, much slower, requiring approximately 48h for the dimerization of about 60% of camphor (by NMR), but more importantly, the coupling was completely stereoselective as only a single bicamphor, that of the *exo-exo* coupled isomer 14 was obtained [60].

Still, little was known to this point whether work-up was a negatively contributing factor. The total yield of both diols was still not in accord with the mass of the starting material. Also, at this point it had been established that a 3:1 mixture of the major and minor diols was obtained each time. Different hydrides such as DIBALH and L-Selectride were investigated in efforts to increase the selectivity of the reduction, but all hydrides other than LAH failed to deliver the desired product. This fact can likely be attributed to steric hindrance of both the diketone and hydride source. A hitherto unnoticed event was also occurring. Upon attempted isolation and storage of the diketones an oxidation of the diketone 14 to a mixture of alkenes 17 and 18 was occurring. This event is presumably an aerial oxidation, shown below.

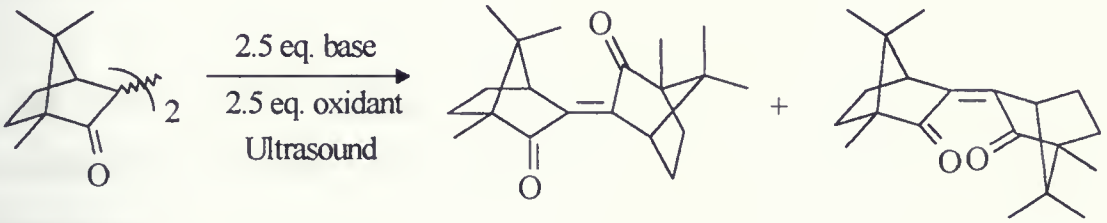


14 17 18

Scheme 12. The aerial oxidation of the isolated diketones.

It was noticed by NMR that a 3:1 mixture of alkenes had developed slowly over time. [68, 69]. At this stage, the intermediate diketone given by the kinetically controlled coupling that was suspected had not been compared to the known NMR data [57]. Interestingly, upon attempted isolation of the individual alkenes by chromatography, each underwent a rapid subsequent isomerization to new 3:1 mixtures. It was also thought that it was beyond coincidental that the 3:1 mixture of diols was in accord with a 3:1 mixture of alkenes. It could be possible that it was not the diketone giving rise to the diols, but a mixture of the alkenes. We therefore attempted to isolate the diketone. NMR data revealed the absence of the peaks which were reported to be the diketone. The most notable peak in the ^{1}H NMR spectrum of the diketone was a doublet at 2.1 with a coupling of 4.13 Hz. Only peaks that corresponded to the

alkenes were noticed. These were peaks at 3.7 and 2.5 ppm, with coupling constants of 4.3 and 4.0 Hz, respectively, with the M+ in the mass spectrum being m/z = 300 instead of 302 for the diketone. In light of this fact, it was now suspected that work-up must be omitted, and proof was in hand that the alkenes were giving rise to the diols. But still, small amounts of the alkenes were being noticed, so attempts using an excess of base (2.5 eq.) with 2.5 eq. of oxidant in ultrasound were shown to promote cleanly the formation of a 3:1 mixture of the alkenes, shown below.



14 17 18

Scheme 13. The facilitated formation of the Alkenes

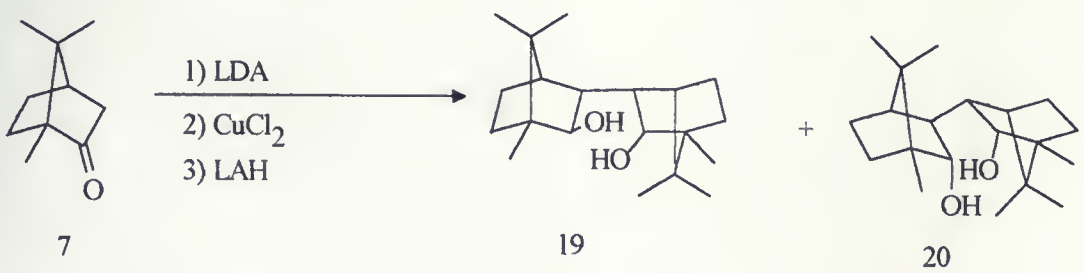
This fact brought to light the notion that strict equivalents of base and oxidant were to be employed to avoid the *in-situ* subsequent oxidation to the alkenes.

Now knowing that equivalents played a crucial role, and being unable to isolate the diketones, and inadvertently avoid product loss by sublimation, we set forth to develop a one pot protocol for the production of BIBOL.

In order to accommodate for the presently poor yield of BIBOL, we tried a series of oxidants that we hoped would promote higher yields. It was suspected that, even with increasing amounts of pyridine, incomplete solubility of the copper salt was the likely factor limiting the yield. A variety of oxidants such as anhydrous copper (II) sulfate, copper (II) acetate, elemental iodine [61] and FeI_3 [62]. All proved to impart deleterious effects on the coupling. For simple

comparison's sake a single trial with the employment of AIBN with α-bromocamphor was attempted, but also proved to be inefficient. The copper (I) salts CuCl and CuI [36] were also tried in a variety of solvents, but clearly do not have the same oxidative strength of the copper (II) salts. A single report [36] illustrated a mixture of copper (I) iodide and TMEDA, which, in light of the economical aspects, prompted us to look at the possible solubility of copper (II) chloride in TMEDA. Initial attempts proved negative until, after numerous trials, it was determined that $CuCl_2$ is fully soluble in a mixture of TMEDA *and* pyridine. With this, the final chapter of the study was near.

We now had the potential of employing toluene, which would ensure high diastereoselectivity, while using a well known oxidant in a cosolvent mixture that would permit for a chemoselective one-pot reduction, and quick synthesis of BIBOL. After several trials, each time an improvement on the yield, it was determined that adding a solution of $CuCl_2$ in pyridine and TMEDA to a cooled solution (-78 ^{o}C) of the enolate of camphor (prepared in toluene with either LDA or LiHMDS at 0 ^{o}C) and allowing to slowly warm to room temperature, followed by a direct reduction by LAH, gave the major diol BIBOL **19** in an excellent and repeatable yield (50% on average) as well as the epimeric alcohol **20** (10%), as shown below.

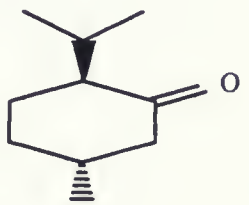


7 19 20

Scheme 14. Final process yielding BIBOL and minor epimer.

This is a great improvement from the 3:1 original mixture reported earlier, considering the known kinetic deliverance of hydride on camphor proceeds from the *endo* face [63] and it should be mentioned that the diastereoselectivity of the coupling step is not lost due to slow warming to room temperature. Also, the fact that a total yield of both diols is approximately 60% of one coupling diastereomer, with four new chiral centers in the new diol is a great improvement upon the previously reported procedure of a 60% yield of mixture of three isomers. This work allowed us to show that oxidative couplings of enolates can and do proceed with complete stereocontrol under kinetically defined conditions [50].

With conditions which promote the highly stereoselective oxidative dimerization of the enolate of camphor now in hand, we set forth to expand the methodology to other chiral ketones of natural origin. The most interesting of the ketones available was clearly menthone, shown below.

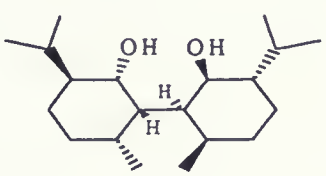


21

Menthone

Figure 12

As can be seen, the compound contains an isopropyl group α to the ketone, which could possibly introduce a high degree of facial selectivity during an asymmetric process. It can also be seen below that once deprotonated by a base and subsequently oxidized to the enoxy radical that the compound would likely couple at the carbon α to the carbonyl and β to the isopropyl group, followed by subsequent reduction to give the bimenthol 22.



22

Bimenthol

Figure 13

If our previously described oxidative dimerization process were to be a general procedure capable of introducing a high degree stereoelectronic control during the dimerization of camphor

then surely it would be capable of the same with menthone to give the desired bimenthol. Once coupled, it was believed that in keeping with the protocol there would be a highly selective, subsequent hydride reduction of the bimenthone to the diol.

It is well established that the ease of interconversion of conformations of the six membered ring, going from chair to chair, shown below, is at it's greatest when the ring lacks substitution.

23 24

Scheme 15. The interconversion of conformers of a substituted cyclohexanone

It is also well known that as the size of the R group increases, the barrier to rotation increases and eventually, as in the case where R = t-Butyl, is too high and the compound exists predominantly in a single conformation. The reason for this is that the compound is minimizing the steric strain brought forth by the interaction of the substituent with axial protons at the three position. These, befittingly are referred to as 1,3-diaxial interactions and are greatly minimized when large groups are in an equatorial orientation, shown below.

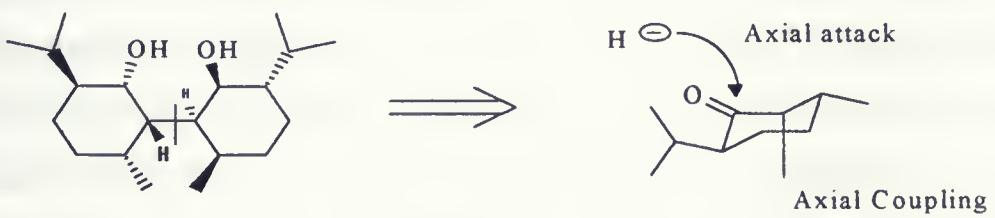
R = Axial R = Equatorial

25 26

Figure 14. Structure depicting axial and equatorial substituents

Because camphor is a bicyclic system its carbon skeleton is rigid enough that the coupling will not be affected by such processes as interconversion of conformations. But it should also be stated that although menthone is, in its simplest form, a substituted cyclohexane ring, it will not interconvert between conformations. This is due to the fact that it possesses large substituents in the methyl and the isopropyl. These groups will preferentially orient themselves equatorially thereby minimizing two sets of 1,3-diaxial destabilizing interactions. With that in mind, menthone would likely serve as an interesting model upon which to study the dimerization methodology. Due to its relative rigidity, any events should be highly stereoselective, similar to camphor.

With any ensuing process being highly stereoselective, a close look at the retrosynthetic analysis will aid in predicting the resulting stereochemistry of the product. Since it is well known that large groups prefer to be equatorial, thereby minimizing strain, we could say that equatorial substituents are thermodynamically more stable. Therefore, based upon our results with camphor, it is likely that coupling will be governed by stereoelectronic control, and likely undergo an axial-axial coupling. Also, since it is our desire to reduce the ensuing intermediate diketone to the diol, we must predict the likely relative stereochemistry of the alcohol groups. Keeping in mind that coupling would likely be axial-axial, and since it is well documented that simple hydrides deliver from an axial approach on substituted cyclohexanones, it can be predicted that the product will be the axial-axial coupled, equatorial-equatorial diol.



22

Bimenthol

21

Scheme 16. A retrosynthetic look at bimenthol

We began by applying the exact same process that was responsible for the highly stereoselective camphor coupling. Much to our delight, the process delivered approximately 80% of a single diastereomer, with virtually no evidence by TLC that others had formed. The first observation was that nearly all of the mass was being recovered just prior to purification on SiO_2. Therefore, it was very likely that the major diastereomer obtained by coupling of camphor was in fact subliming. It was initially thought that the process had very quickly defined parameters for the production, in excellent yield, of a structurally interesting menthone derived diol. The sample obtained had even been subjected to high resolution mass spectral ananlysis, showing a match at m/z = 310 corresponding to the mass of the diol, and since the DEPT spectrum was showing only two negative spikes, corresponding to the presence of two methylenes, the compound in hand was clearly one which was substituted α to the hydroxyl group.

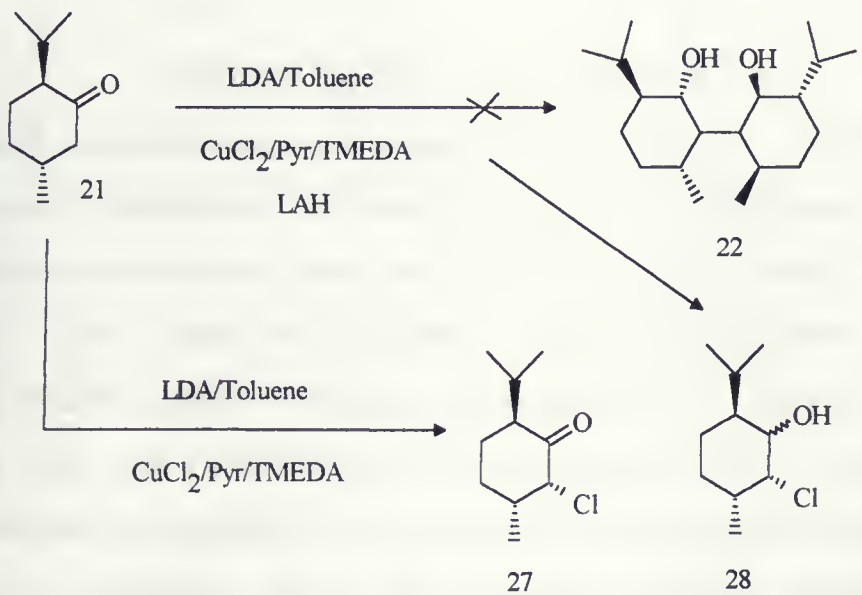
There were two puzzling aspects to the compound however. First was the presence of a peak in the mass spectrum at m/z = 190 that seemingly could not come from the fragmentation of the diol. Secondly, in both the ^{13}C and ^{1}H NMR spectra there were anomalous peaks that did not likely correspond to the structure of the compound. In the ^{13}C spectrum there were two peaks at δ 73.2 and 74.6. It is not surprising that at least one of the peaks is present, corresponding to a carbon which is directly bonded to an oxygen, this being the hydroxy of the alcohol. But the fact there was a second peak in the same region suggested the presence of two carbons that were next to oxygen within the compound. This is indeed the case, as the expected compound does contain two oxygens. But the compound was expected to be C_2-symmetrical, which would imply that there would only be 10 signals in the ^{13}C-spectrum corresponding to the two sets of identical 10 carbons, totalling 20 in all. This reasoning held true for the ^{1}H-spectrum as it exhibited only three doublets in the high field region corresponding to the three methyls: two contained in the isopropyl and the third the final methyl. Certainly a non C_2-symmetrical compound would exhibit two sets of signal in the ^{1}H NMR and ^{13}C but it did not. To

accompany that fact the ^{13}C-spectrum, much like the ^{1}H-spectrum, exhibited only one set of signals, suggesting that, despite the two signals between 70 and 75 ppm, the compound in hand had to be C_2-symmetrical. At this point a few possible explanations were offered as to why there were two signals corresponding to two carbons that were connected to oxygen. One was that there may be intramolecular hydrogen bonding between the alcohols, causing them to be non equivalent. But this theory was quickly dismissed as the X-ray structure of BIBOL indicated that there was a hydrogen bonding phenomenon occurring in it and yet there was only 1 carbon signal downfield. The second hypothesis, which was also used to explain why there were two signals downfield, at approximately 3.5 and 4.4 ppm stated that it was possible that because the compound in question was thought to be a dimer of menthol, joined by a carbon carbon bond, there may be a high degree of steric hindrance within the molecule, which was perhaps forcing the two rings apart, thereby reducing the electron density around that region of the molecule. This, if correct, would explain the reason why there was a second proton downfield. But the theory did not explain why there were a single set of signals in both the ^{13}C spectrum and the ^{1}H spectrum. This theory was quickly dismissed as well, as it can be seen in compounds such as biphenyl that there is no downfield shift at the connecting carbons. To bring matters to light, a similar compound was analyzed by GCMS.

We attempted to do what we were not very successful in doing during the BIBOL project. Due to the fact that we were noticing a great percentage of consumption of the starting material by a suspected coupling, which was contrary to the BIBOL work, it was postulated that it may be possible to isolate the intermediate while omitting reduction. We then set forth to do just that. The reaction was carried out in the hitherto manner, but this time was worked up immediately prior to the reduction. The only concern at this stage was that if the event which was occurring was in fact the coupling to give the kinetic diketone, it may be possible to epimerize the compound during an attempted purification on an acidic medium such as SiO_2. Pleasingly though, the compound believed to be the diketone was isolated with fair purity by SiO_2 and

following that was analyzed by GCMS [64]. The analysis revealed that 75% of the compound tested had a mass of 188, with an isotope pattern consistent with chlorine. No signal at m/z = 310 which exhibited the loss of 28 for the carbonyl was present. Indeed, classical methods of elemental analysis revealed the presence of a halogen, which would explain all of the anomalous peaks in both ^{13}C and ^{1}H spectra.

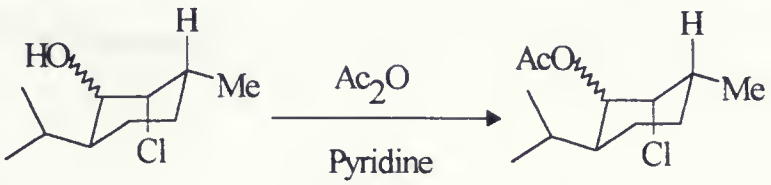
It was clear at this point that the process imparted such a high degree of stereoselectivity in the oxidative dimerization of camphor, was now, under identical conditions affording the α-chloromenthone 27 in a highly diastereoselective and efficient method, shown below.



Scheme 17. Production of the chlorinated products

At this stage, it was still unclear as to the absolute stereochemistry of both the chloroalcohol and the chloroketone. This was due to the fact that the coupling in both ^{1}H NMR spectra was complex due to interferences such as long range couplings, as well as the the fact that the couplings were not first order. The relative stereochemistries were later assigned on the

basis of multidimentional NMR at 500 MHz. In order to reduce the ambiguity introduced by the proton of the hydroxyl group, the acetate derivative 29 was synthesized by reaction of the chloroalcohol 28 in pyridine and acetic anhydride. The acetate, as well was assigned on the basis of two dimentional NMR at 500 MHz, and it's relative stereochemistry would therefore hold true for the chloroalcohol.



28 29

Scheme 18. Acetylating the chloroalcohol.

We initially began the assignments of the relative stereochemistries by obtaining a clean sample of the kinetic chloroketone 27. This would first allow for the assignment of the relative stereochemistry of the chlorination without the introduction of a third coupling from the proton α to the oxygen. Clearly, having the ketone present would enable us to determine weather the chlorine was in an axial or equatorial orientation. Interestingly, the 300 MHz spectrum revealed a doublet at 4.1 ppm. with a coupling constant of approximately 3.0 Hz, while the 500 MHz spectrum revealed that the resonance peak was actually was a doublet of doublets, with *J* values of 3.2 and 1.4 Hz., respectively. This fact was likely an illustration of a long range coupling, since there is only a single proton on the vicinal carbon which explains such a weak coupling of 1.4 Hz

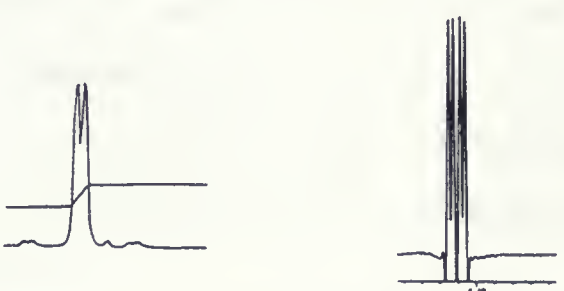


Figure 15. NMR expansions of α-H of 27 at 300 (L) and 500 (R) MHz

Without the aid of 2-D NMR, most notably the COSY and the ROESY spectra, it would stand to reason at the present that since the cyclohexane ring is locked in such a manner by virtue of the presence of the isopropyl and methyl groups in the equatorial orientation that the chlorine was oriented axial, in accord with the model. This statement is made with respect to the Karplus relation, suggesting that a coupling constant of 0-4 Hz corresponds to a dihedral angle of approximately 90^{o}. Clearly, it can be seen that the equatorial proton geminal to the chlorine is about 90^{o} with respect to the proton which is α to the methyl.

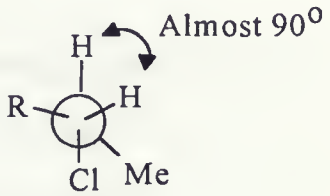


Figure 16 A Newman projection showing the dihedral angle between protons in 27.

The initial sterochemical assignment based on coupling constants was proven to be correct by the ROESY spectrum, which correlates through space interactions of protons that normally do not couple through bonds. It was observed in the spectrum that there is a through space interaction (nOe) between the proton α to the carbonyl at 4.1 ppm and the methyl group. If the chlorine had been oriented equatorial, then there would have likely been an nOe between the same proton at 4.1 ppm and the methyl group as well as the proton α to the isopropyl group or one of the back axial protons. Since there was no correlation to the isopropyl or to a back axial proton, it was clearly concluded that the chlorine is indeed axial. The chlorination process, although a different result than what was initially expected illustrated an interesting dichotomy between camphor and menthone, while holding true that the process gives rise to a high degree of kinetic stereocontrol in either case.

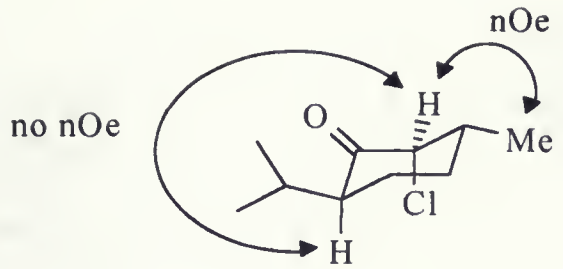
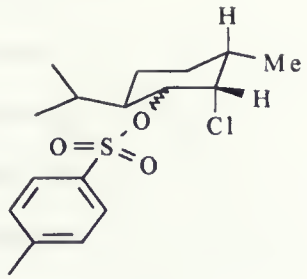
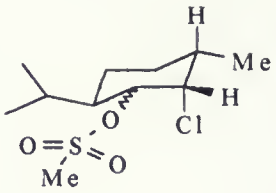


Figure 17. A depiction of the through space couplings observed in 27.

With the relative stereochemistry of the chlorine now securely in hand, we set forth to determine that of the alcohol. As previously stated, it is likely in this case, especially with the ring so rigidly locked, that the hydride would, under kinetic conditions deliver from an axial trajectory, thereby affording the equatorial alcohol. This is an example where the kinetic pathway furnishes the thermodynamic product, unlike that of the chlorination process where both the approach and the product are considered to be kinetic. To begin with, the ^{1}H NMR spectrum was assigned on the basis of multidimensional NMR such as COSY and HETCOR. In order to minimize the ambiguity introduced by the presence of the free alcohol proton, the alcohol was derivatized to the acetate **29** as stated previously. This would in turn enable us to gain a better understanding of the relative sterochemistry of the alcohol. Other derivatives were considered, including the tosylate **58** and the mesylate **59**, which were initially made for possible X-ray analysis, but these compounds introduced ambiguity due to the fact that the methyl group of each was overlapping with other protons in the ^{1}H NMR spectrum. Although these compounds were never considered worthy of full characterization, their structures are verifiable due to the presence of the third 3H singlet at approximately 2.4 for the tosylate methyl and the two 2H doublets at 7.2 and 7.8 ppm corresponding to the aromatic protons, while a 3H singlet at 3.1 ppm for the methyl of the mesylate was observed.



58



59

Figure 18. Representation of the tosylate 58 and mesylate 59.

It was first required that every proton be fully assigned, and this was done with HETCOR, COSY, ROESY and DEPT spectra. Since there were two peaks between 4 and 5 ppm in the ^{1}H spectrum of the acetate, it would first be necessary to determine which was geminal with respect to the chlorine and acetate. On the basis of the COSY spectrum of acetate **29** it was determined that the peak at approximately 4.4 ppm was that which was geminal to the chlorine. This was determined by observation of a correlation to the proton at 1.9 ppm, while it in turn was correlated to the methyl at 1.0 ppm. Should this assignment be correct, the other peak, at about 4.8 ppm should show a correlation to the proton which shows a correlation to the isopropyl. This fact clearly held true, and enabled us to proceed in determining the relative stereochemistry by nOe.

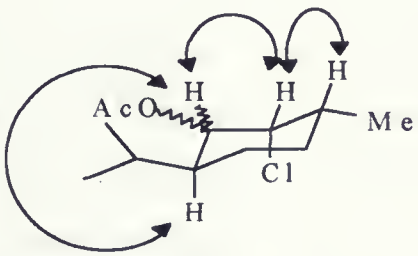
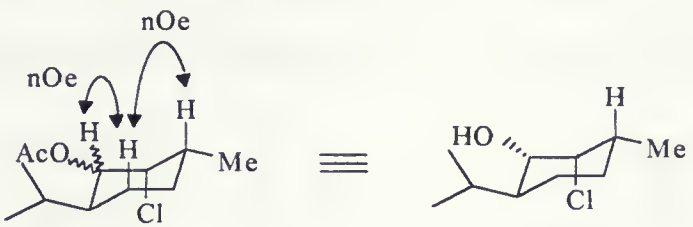


Figure 26. Representation of the observed correlations in acetate 29.

Some of the same rationale held true for the stereochemical assignment of the chloroketone 27. If the alcohol was oriented in an equatorial manner, then it was likely that we would observe an nOe between the proton that also showed a correlation to the proton which is

coupled to the methyl group, likewise with one of the back CH_2 protons. However, if the alcohol was in an axial orientation with the proton being equatorial, then we would have expected not to see an nOe to a proton on one of the back methylenes. But it was observed that there is an nOe between the proton at 4.8 and the axial proton geminal to the methyl. This fact illustrates that the alcohol is indeed equatorial, which is the result of a kinetic hydride reduction.

With the relative stereochemical assignments now secured, it was clear that the chlorination/reduction protocol had allowed for a highly stereoselective and efficient process at approximately 80% yield overall of 28, while introducing two new stereocenters.



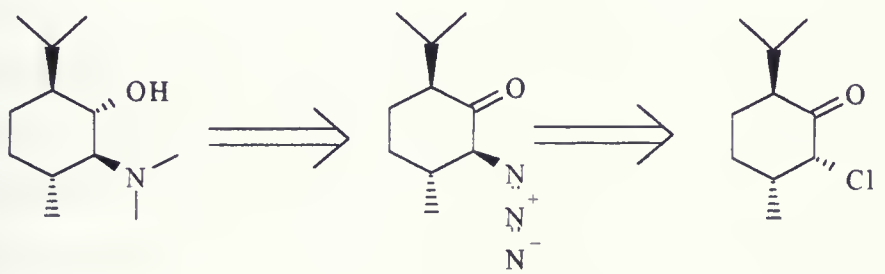
29 31

Figure 19. A representation of the through space interactions and finalized stereochemistry.

With the chlorination process now secure, efforts were taken to promote the coupling of menthone while eliminating the chlorination process. This would likely have to see the elimination of $CuCl_2$ from use. The best oxidant other than $CuCl_2$ was likely $Cu(OTf)_2$, which was shown to promote the coupling of camphor. Several trials were performed including those which saw the immediate allowance of the reaction to warm to room temperature, but all failed to afford the desired product. This was determined on the basis of comparing the DEPT ^{13}C spectrum, which indicated the presence of three negative spikes which in turn is indicative of three methylenes, to that of synthetically prepared menthol. One possible explanation for the failure of menthone to couple is the fact that it may simply be too sterically hindered, since a chlorine imparts less steric encumbrance than does the introduction of a second cyclohexane ring.

Even though efforts to that point failed to deliver the bimenthol, it was worthwhile to investigate the exploitation of the chlorination process to our advantage. Now realizing that the α-chloroketone **27** was stable to silica and could easily be isolated with excellent purity, we attempted several nucleophilic substitutions of the chlorine in effort to synthesize a new amino alcohol that would be analogous to DAIB.

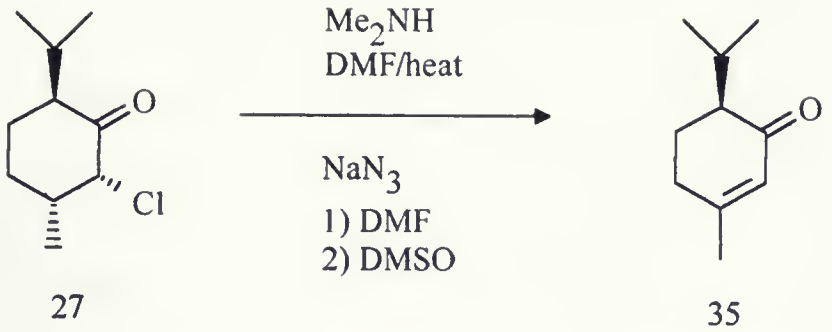
A look at the potential retrosynthetic analysis reveals that chlorine can be displaced by reaction with an azide, followed by reduction of the α-azido group as well as the carbonyl, and finally methylation of the amino-alcohol to the desired dimethylaminomenthol.



33 34 27

Scheme 19. A retrosynthetic look at the amino-alcohol

Several trials which employed the use of reagents such as NaN_3 in DMF or DMSO, including the use of phase transfer catalysts such as triethylbenzylammonium chloride, as well as crown ethers, were attempted but all efforts to displace the chlorine led to either a complex mixture of products or the α,β–unsaturated carbonyl. This product was obtained in highest yield when the reaction was carried out using dimethylamine hydrochloride in DMF, affording a reasonable yield (30-40%) of the unsaturated carbonyl, **35**.

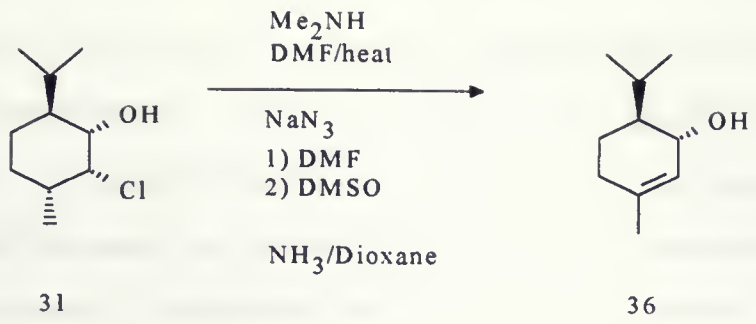


27 35

Scheme 20. Reactions showing the elimination of the chloroketone.

The fact that the elimination product was so easily obtained may be due to the fact that both dimethylamine and sodium azide are acting as weak bases, favoring elimination instead of substitution. This is carried further by the fact that the proton and chlorine are antiperiplanar thereby favoring elimination. In an effort to eliminate the use of a weak conjugate base, a solution of the kinetic chloroketone **27** was added to a solution of the enolate of menthone, but muck like the earlier attempts with camphor and α-bromocamphor, both compounds were likely too hindered for a reaction to occur.

Since the elimination could seemingly not be avoided, we decided to investigate the reactivity of the chloroalcohol. Due to the presence of the methyl, the compound may be far less susceptible to an elimination because the resulting compound would not be conjugated, as is the α,β-unsaturated carbonyl. Many of the same reactions were studied including the reaction of the chloroalcohol **31** with NH_3 in dioxane but, much like those of the chloroketone, the favorable process was that of an elimination, thereby affording the allylic alcohol **36**, as shown below.



Scheme 21. Reaction showing the production of the allylic alcohol, 36.

Quite interestingly though, it was later determined that, under mild conditions using three to five equivalents of NaN_3 in MeOH, the kinetic chloroketone **27** could be very efficiently isomerized to the thermodynamically more stable equatorial chloroketone **57**. This was determined to be correct by ^1H NMR. The peak corresponding to the proton which is α to the carbonyl now has a coupling constant of 11.6 Hz , which is indicative of a dihedral angle between protons of about 180^o.

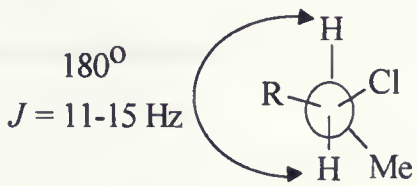
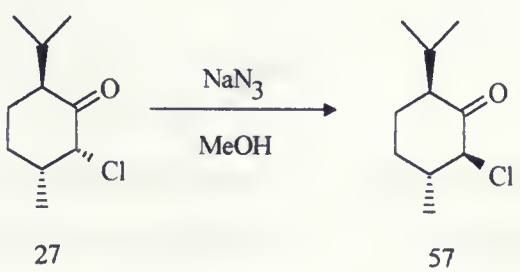


Figure 20. The Newman projection showing the dihedral angle between protons.



Scheme 22. Epimerization of chloroketone

As of now it is unclear what is mediating the epimerization event. Two theories are that N_3^- is acting as a weak base, and under thermal conditions as described above, the process favours elimination. An alternative to that is that NaN_3 is forming a small amount of NaOMe *in situ* and is mediating the event. In any event, we have now described conditions that lead to a highly kinetic chlorination of menthone as well as a base mediated epimerization to the more thermodynamically stable equatorial chloromenthone **57**.

While attempts at displacement of the chlorine from menthone were underway, we also envisaged a new class of camphor derived 1,3-diols that contain a substituent α to the alcohol of borneol that bear electron rich and deficient aromatic rings. There were three main ligands towards which efforts were focussed; one which is simply benzaldehyde derived [81], one which is derived from *p*-nitrobenzaldehyde and one which is piperonal derived. The main premise behind the idea was that not only would the catalyst introduce asymmetry into reactions by virtue of a chiral Lewis acid/base interaction of the substrate and the metal, but they would also be capable of mediating the process by an interaction known as pi-stacking, as shown below.

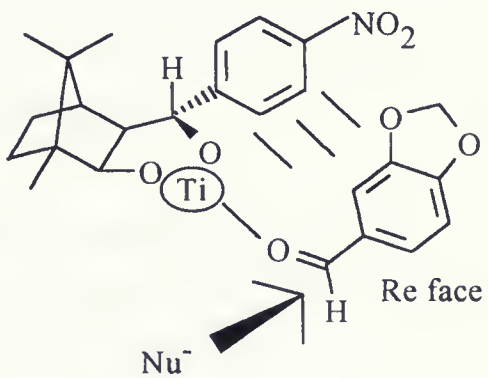
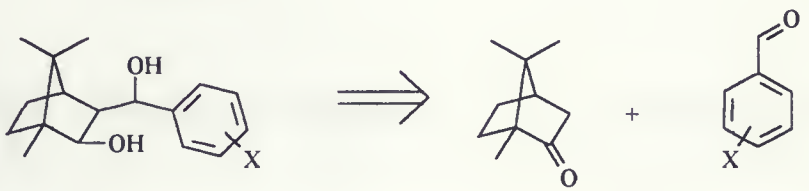


Figure 21. Model depiction of origin of potential stereoselectivity imparted by pi-stack ligands.

The model shows how a substrate such as the electron rich aldehyde piperonal can coordinate to the catalyst in by two interactions. One is by the Lewis acid/base interaction of the aldehyde oxygen with the electropositive titanium atom, while the second is a pi-stack interaction of the rich and deficient aromatic systems. The typical distance of such interactions

are approximately 3.5 Å. It can also be seen that that the Re, or front face is easilyl accessable while the back, or Si face is blocked by the aromatic ring of the catalyst.

From a synthetic standpoint, each of the three ligands could be synthesized from an aldol on each of the aldehydes on the *exo* face of camphor. Following that, a highly selective reduction would complete the synthesis of each and very quickly would the series of ligands be ready for asymmetric studies.

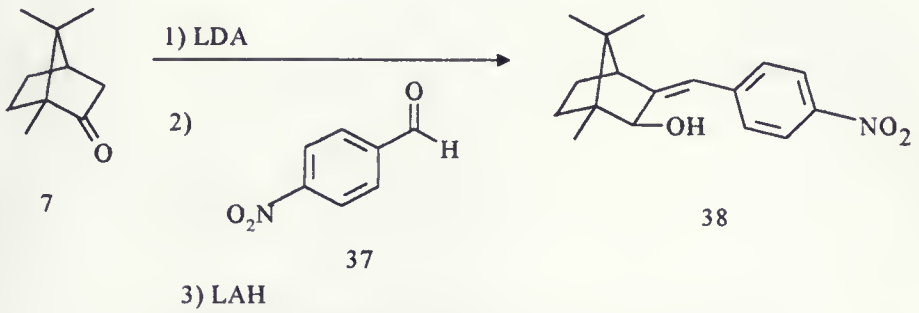


Scheme 23. A retrosynthetic analysis of 1,3-diols

With both of the afforementioned interactions occurring in the transition state, we would hopefully see an increased enantioselectivity at higher temperatures. This implies that the process would be advantageous to their counterparts due to a reduced economical strain due to the lack of need for reduced temperatures.

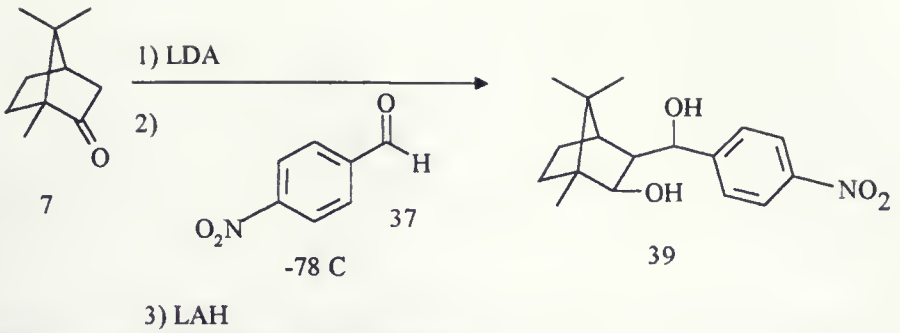
We began the synthesis of the series of ligands by first looking at the reaction of the enolate of camphor with benzoyl chloride. This reaction would hopefully give rise to a new 1,3-diketone which could be kinetically reduced following isolation. But the reaction gave a complex mixture of products and was abandoned. We now focused our attention on the aldol process that would soon give rise to the series of ligands, although this was not originally thought to be a legitimate entry due to the possibility of four new stereocenters; these corresponding to the *exo* or *endo* product as well as the *R* or *S* benzylic alcohol, from addition either the *si* or *re* face of the aldehyde. The first aldehyde to be tried was 4-nitrobenzaldehyde,

because it could conceivably stack with a compound such as piperonal, with the methylenedioxy functionality being common in many natural products such as pancratistatin.



Scheme 24. Reaction of camphor enolate with 4-nitrobenzaldehyde.

Initial attempts involved the addition of the aldehyde **37** to the camphor enolate at -78 ^{o}C, which was then permitted to warm to room temperature overnight. Following the aldol process came what was to be a highly chemoselective reduction of the ketone of camphor in the presence of the nitro group by LAH. The compound then was isolated and determined to be the alkene **38** by ^{1}H and ^{13}C NMR, which slowly isomerized to a 60:40 mixture of alkenes. The compound was determined to be the alkene by the presence of a 1H singlet at 6.6 ppm indicative of a benzylic and sp_2 proton. as well as a fifth signal in the ^{13}C spectrum between 130-150 ppm also indicative of an sp_2 carbon shown above. It was initially thought that in order to prevent the elimination from occurring it would be necessary to trap the aldol alkoxide with a compound such as TMSCl. This may have held true but was not necessary as the reaction was performed a second time while maintaining the -78 ^{o}C conditions. After 24 h the reaction was transferred to a suspension of LAH which gave rise to the desired 1,3-diol **39**. By TLC analysis, this method prevented completely the elimination from occurring thereby preventing the production of 38. The reaction gave a 50% yield, which is quite pleasing considering the introduction of three new stereocenters, along with a chemoselctive reduction of the ketone in the presence of the nitro group.



Scheme 25 The Aldol process used to produce 39

We were now faced with the dilemma of assigning the relative stereochemistry of the product. The model indicated that the aldol reaction should occur on the *exo* face of camphor at C(3), although it has been documented that increasing the size of the aldehyde promotes deliverance on camphor's *endo* face [65]. Also, the hydride should deliver from the *endo* faceof camphor thereby furnishing the *exo* alcohol. But it was not as clear as to whether the enolate had added to the aldehyde from the *si* or *re* face. It has been stated [65] that there is typically a coupling of 0-1 Hz between the C(4) bridgehead proton and that of C(3) when the substituent is in the *exo* orientation and the proton in the *endo* orientation, while there is coupling of about 4 Hz when HA is *exo*. We could conceivably predict the relative stereochemistry of our aldol product **39** by comparing the unreduced product to known coupling constants. Given that, we set forth to synthesize the unreduced aldol product. Considering the fact that the p-nitro derivative underwent the initial elimination we chose a different aldehyde, piperonal, **40** to study. The reaction proceeded cleanly to give an excellent yield of a colorless oil. The NMR was clearly in accord with the model, failing to show a coupling between HA and H4, while HA had a coupling of about 10 Hz from the carbinol proton, HB.

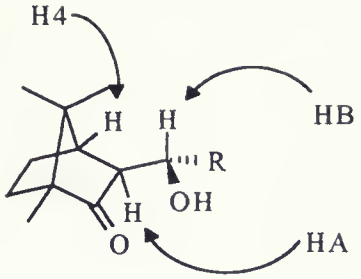


Figure 22. An illustration of the potential couplings in the aldol product, 39.

For the purpose of stereochemical assignment, the elimination product **38** is the quintessential side product. This compound clearly illustrates the coupling to the bridgehead proton without any overlap by other protons. Since the proton is in an allylic position, it is shifted downfield to 2.8 ppm. Also, one can detect clearly the single coupling from one of the back methylene protons due to absence of a substituent α to the carbonyl. The coupling to the bridgehead proton in **38** is about 4.5 Hz, while the coupling to the bridgehead proton in the unreduced aldol product **39** is about 4.0 Hz, without any other splittings. Clearly, this illustrates that the substituents in the aldol products is *exo*.

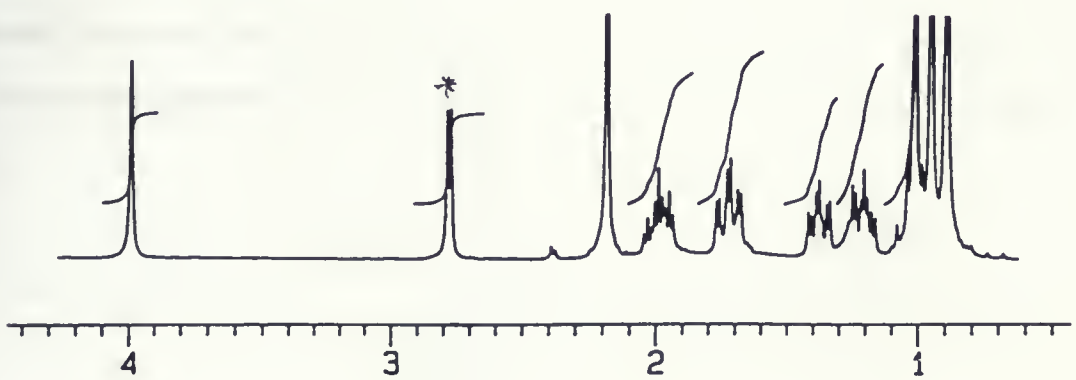


Figure 23. Expansion of the allylic proton of 38

The assignment of stereochemistry at the carbinol was not as easily assigned. The stereochemistry in a carbon-carbon bond of an aldol product is usually assigned on the basis of a cyclic model, such as those shown below.

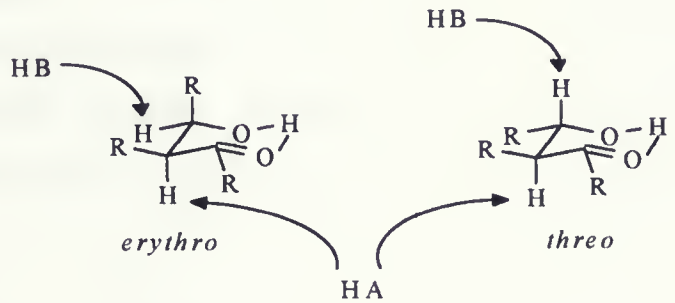
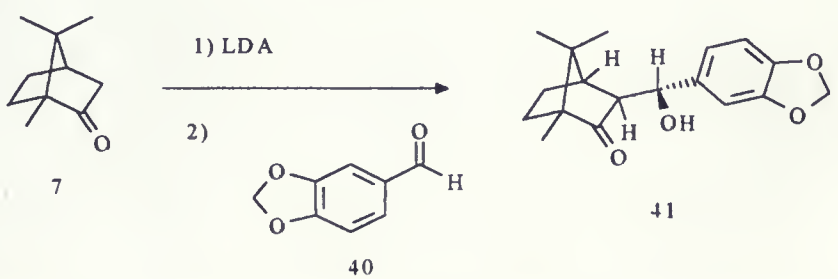


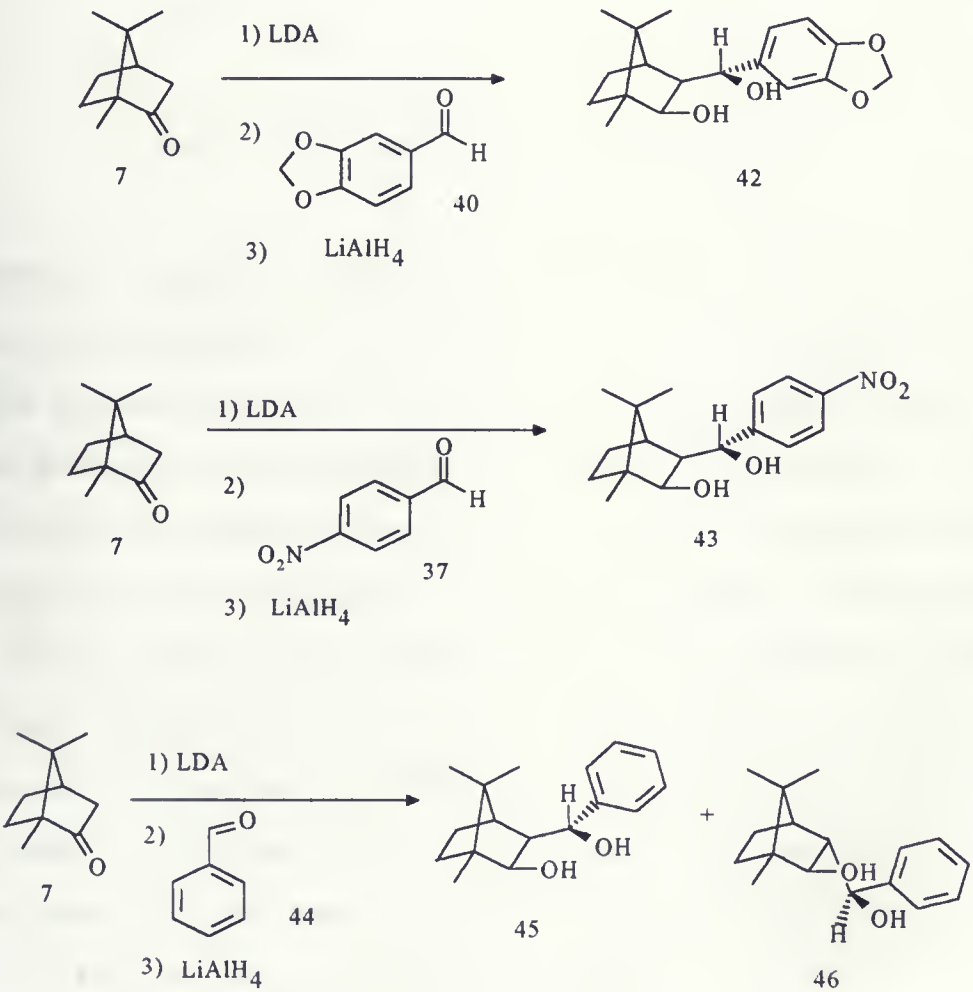
Figure 24. Potential intramolecular hydrogen bonding in the aldol products.

The sterochemistry of the new bond is usually based on the coupling constants of the HA and HB protons, or by the chemical shifts of the A and B carbons [65]. Both methods assume that the product contains intramolecular hydrogen bonding. To assign the relative stereochemistry, it is known that the J_{AB} for the *threo* isomer is usually about 7-12 Hz due to the *anti* relationship of the two protons. The *erythro* isomer, on the other hand is usually accompanied by a J_{AB} of about 0-4 Hz. It can be seen below that the coupling constants for each proton corresponding to A and B in the model couple each other with a J value of about 10 Hz. Based on both models we can say that our compound is the *exo*, and *threo* isomer, shown below.



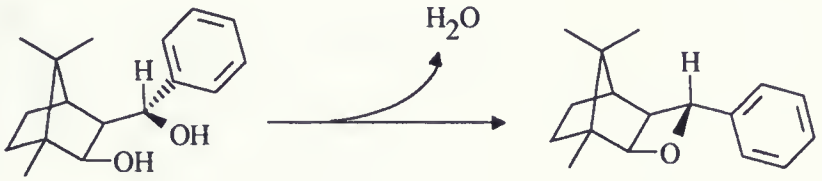
Scheme 26. A final determination of stereochemistry of the aldol product.

To complete the series of ligands, the same protocol that was developed with p-nitrobenzaldehyde was applied to piperonal and benzaldehyde. The reaction with piperonal proceeded with excellent diastereoselectivity affording a 90% yield, while reaction with benzaldehyde was a modest 52% yield of the major diastereomer, whose coupling constants were in accord with the aforementioned stereochemistry, and 20% of a minor diol with couplings indicative of *endo* substitution. We can also conclude the relative stereochemistry of the p-nitro aldol product, as the pertinent couplings are in accord with those of 41.



Scheme 27. Reactions showing outcomes of aldol process

The formation of **45** was later observed to undergo an interesting loss of water. Unlike the aldol products containing the p-nitro and methylenedioxy substituents, the benzaldehyde product slowly lost water on standing in solvent to form the oxatene **47**, shown below.

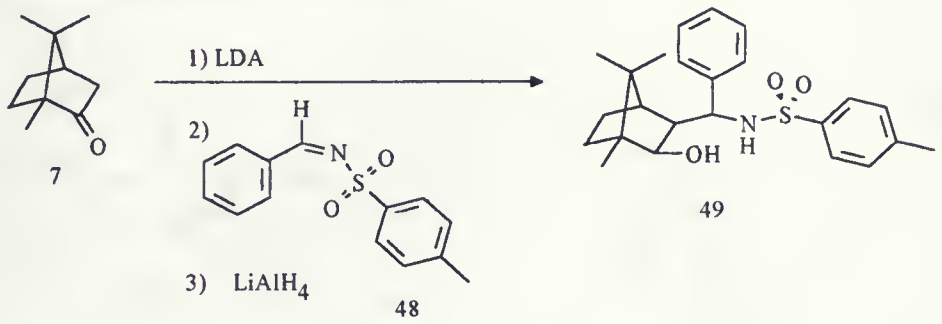


45 47

Scheme 28. The loss of water forming the oxatane

Although the compound first started to show the formation of the oxetane very quickly, the process was never observed to go to completion, even over several days. It would be expected that the p-nitro compound **43** would not undergo such a transformation, due to the withdrawing ability of the nitro, suggesting that a benzylic cation is not stable, but due to the stabilizing ability of the electron releasing methylene dioxy of **42** it would be expected that the rapid formation of an oxetane could occur. At this stage it is unclear as to what is facilitating the reaction depicted in scheme 28. Since benzylic alcohols can be lost to form a benzylic cation is quite well known, and in this case there is a stabilizing factor imparted by the adjacent alcohol, the formation of the oxetane from **45** is not a surprising event. What is surprising is that only one in the series of three underwent such a transformation. This could be attributed to the withdrawing ability of the nitro group, as well as an inductive effect by the methylenedioxy group, both of which acting to destabilize the nascent cation.

With the completion of the new 1,3-diols we turned our attention to the production of new 1,3-aminoalcohols that would be similar to DAIB. The production employed the Mannich type reaction of the enolate of camphor with the N-tosylimine **48**, shown below.



Scheme 29. Mannich type reaction producing the N-tosyl-amino-alcohol

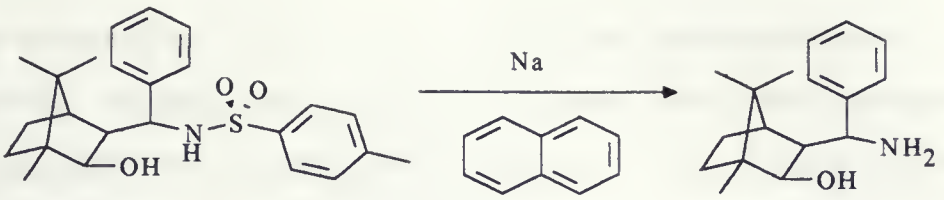
The reaction proceeded smoothly, affording a 60:40 mixture of diastereomers whose stereochemistries have yet to be determined. However, a few conclusion can be made. First, the substituent is in the *exo* orientation. This statement is made due to the fact that the proton at 2.0 ppm that corresponds to HA of the previous model shows couplings of 11.6 and 7.5 Hz from the proton that is α to oxygen (4.0 ppm) and the benzylic proton. There is no coupling of about 4 Hz (from the bridgehead proton) that would indicate that the proton is *exo*. Also, it can be concluded that the alcohol is *exo* due the 7.5 Hz coupling from HA. This coupling is also seen in the 1,3-diols. The only ambiguity left is the relative stereochemistry of the phenyl ring. However, one assumption can possibly be made with regard to determining the stereochemistry at the benzylic site: that is that there is likely a high degree of hydrogen bonding within the molecule between the sulfonamide -NH and the alcohol. If we base an estimate on this notion than it can be seen that there will either be a dihedral angle of about 180^{o} or 60^{o} between HA and HB. By the Karplus relation, we should see a coupling constant of about 10-16 Hz for an angle of about $120\text{-}180^{o}$, while a coupling constant of about 5-8 Hz should be representative of a 60^{o} angle. By

the ^{1}H NMR spectrum a coupling constant of 11.3 Hz was observed, which suggests that there is a large dihedral angle between HA and HB. By this we can hesitantly say that the correct structure is A, shown below, although there is still ambiguity remaining due the close range of coupling constants for theses dihedral angles.

Figure 25. The dihedral angles between HA and HB of A (L) and B (R).

In order to remove the doubt associated with such an unclear stereochemical assignment , several attempts at obtaining a crystal suitable for analysis have failed but efforts are ongoing and a suitable crystal is imminent.

Considering the structure of DAIB, which contains the *N, N'* dimethyl functionality, attempts were made at removing the tosyl derivative from the nitrogen, thereby affording the free amino alcohol 50. These attempts included reaction of 49 with Na and naphthalene in diethoxyethane, with the reaction showing the complete consumption of the starting material by TLC, but complications such as the loss of mass during attempted isolation failed to deliver the product, likely due to its polarity. Clearly, the reaction shows potential to succeed but more efforts are needed at this stage.

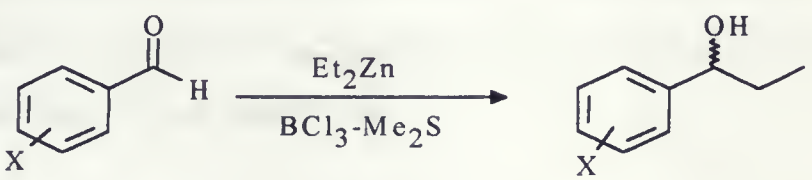


49 50

Scheme 30. Attempted removal of the tosyl group.

As an alternative route to obtaining the dimethylamino alcohol, the ketone from the unreduced piperonal aldol product was reacted with hydroxylamine hydrochloride, but the starting material failed to be consumed likely due to the steric hindrance of the ketone. Attempts at removing the tosyl group and converting the ketone to the oxime are currently underway, and both look to be quite promising.

With the successful synthesis of BIBOL and the new series of pi stack 1,3-diols now complete, we set out to investigate them in a asymmetric transformations, with particular emphasis on the addition of diethylzinc to aryl aldehydes. With two of the 1,3-diol ligands containing aromatic rich and deficient systems the first task in this new chapter was to synthesize the racemate of each of the potentially chiral addition products. This involved the addition of 3 equivalents of diethylzinc to the three aldehydes, p-nitrobenzaldehyde **51**, piperonal **52** and benzaldehyde **53**, shown below.



51: X=p-nitro
52: X=OCH_2O
53: X=H

54: X=p-nitro
55: X=OCH_2O
56: X=H

Scheme 31. Reaction of various aldehydes with diethylzinc

All three reactions proceeded smoothly to afford nearly quantitative yields of each of the three new products. Following this, is was necessary to resolve each of the racemates in order to show that a potentially chiral sample from an asymmetric reaction was in accord with the resolved peaks. The benzaldehyde 56 and p-nitro 54 addition products were readily separated by chiral HPLC (traces shown below) while the piperonal 55 product was not separated. One can notice clearly the 1:1 ratio of the sets of peaks in cases A and B, corresponding to an equal mixture of enantiomers, e.e. = 0%

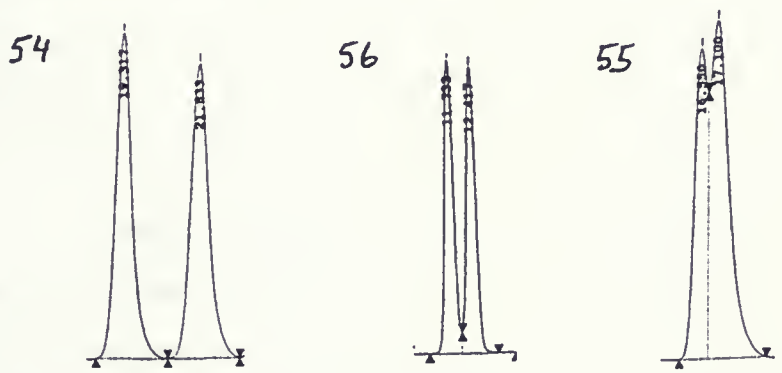


Figure 26. HPLC trace of each of the three Aldol products (region expanded)

The inability to resolve the piperonal derived aldol product **55** proved to be somewhat of a paradox due to the fact that the aldehyde (p-nitro) that was more susceptible to uncatalyzed nucleophilic attack due to the withdrawing ability of the nitro group. Piperonal, on the other hand, contains the electron releasing methylenedioxy portion which makes it a less likely electrophile without the aid of a catalyst. It should be noted that resolution of the three racemats was later achieved chiral GC (see experimental).

In the early stages, there has been modest inference of enatioselectivity imparted by the 1,3-diols, with e.e.'s in the 0-10% range. To test further to see whether there was a pi-stack interaction between the ligands and the substrates, a set of nine reactions, with all three ligands with each of the three aldehyde were carried through with the best method known thus far, regardless of the e.e.. Table 1 shows the results of the study.

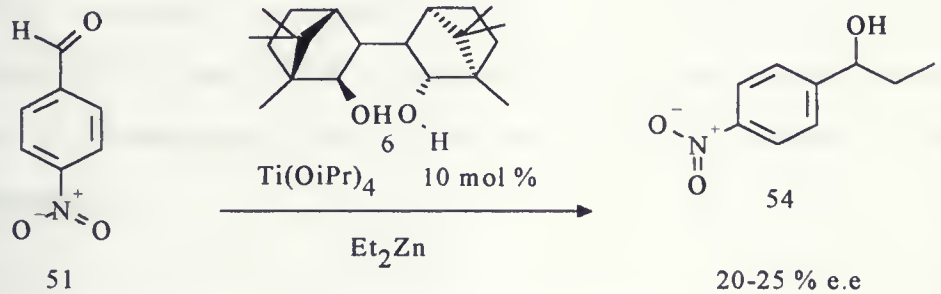
	Aldehyde		
	p-nitro	piperonal	benzaldehyde
Ligand			
p-nitro	3.7	5.4	2.3
piperonal	1.0	3.0	0.8
benzaldehyde	0.9	0.6	2.3

Table 1. Results of study indicating e.e. of reactions.

A few conclusions can be drawn from the table. In spite of the fact that the representative e.e.'s are quite low, one can notice that the greatest e.e. arose when the ligand was the p-nitro ligand and the aldehyde was piperonal. Although only a 5.4% e.e., this is considerably greater than the rest. This could be attributed to the fact that the electron defficient ligand (nitro) may be acting to stack with the less electrophilic electron rich piperonal and pull electron density away from the ring, thereby making it more succeptable to asymmetric nuclueophilic attack. Conversely, the trial with the piperonal derived ligand with the p-nitro aldehyde shows almost no e.e. (1%) which may indicate that although there may be the potential for a pi-stack interaction, the reaction is devoid of asymmetric control due possibly to the fact that this aldehyde is activated by the electron withdrawing ability of the nitro group, which makes it more succeptable to uncatalyzed nucleophilic attack.. This fact clearly illustrates the potential of each in asymmetric catalysis, but also implies that conditions such as choice of metal, solvent and temperature [67] must be optimized. It may also be a possibility that there must be analogues of these ligands synthesized to maximize the interactions of the aromatic systems. Conditions which dictated trials included the use of diethylzinc with and without

titanium in the form of $Ti(OiPr)_4$ and $TiCl_4$, in varying mol percentages, in a variety of solvents such CH_2Cl_2, toluene and THF, and with and without the use of MS 4A

Reactions catalyzed by BIBOL, however, afforded better results. In a manner similar to that of the 1,3-diols, it was determined that first refluxing BIBOL in toluene with an excess of $Ti(OiPr)_4$ followed by cooling to -20 ^oC whereupon diethylzinc was added, followed by p-nitrobenzaldehyde in CH_2Cl_2, afforded the complete conversion of the aldehyde to the alcohol in about 20% e.e., shown below.



Scheme 32. Asymmetric aldol mediated by BIBOL

This result is quite good considering the nature of the aldehyde. As stated previously, since the presence of the electron withdrawing nitro group invites a higher degree of reactivity, and in turn makes it more susceptible to uncatalyzed addition of diethylzinc, the fact that any e.e was observed at all suggests the strong catalytic potential of BIBOL. Reactions to optimize the conditions, including lowering the temperature of the reaction favoring the kinetic approach of the nucleophile, choice of metal, and choice of solvent must be studied to carry forward the investagation of the strong potential of BIBOL.

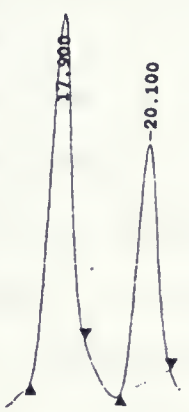


Figure 28. HPLC trace of chiral 54

Conclusions

In summary, several positive conclusions can be drawn from the work presented herein. First, the synthesis of BIBOL has clearly allowed us to show that oxidative dimerizations of enolates can, and do proceed with a high degree of predictable stereoselectivity under strictly governing conditions. This was proven by the isolation of the major diol BIBOL which was obtained from a single diketone of camphor. This result has obvious implications with respect to the production of chiral succinic acid derivatives where stereocontrol has not been achieved thus far and, more importantly, new chiral 1,4-diols. The diol BIBOL has obvious structural similarities with BINOL and TADDOL. The potential effectiveness of BIBOL was shown in the attainment of approximately 20% e.e in an asymmetric addition of diethylzinc to *p*-nitrobenzaldehyde.

Further, an interesting chlorination of menthone was shown to proceed with a high degree of stereoselectivity under the same conditions defined for camphor. This result suggests that the parameters of the process impart a high degree of stereoselectivity in either case. This provided an interesting chlorination/coupling dichotomy between menthone and camphor, and the utilization of the chlorinated menthone derivative is being carried further in the pursuit of new amino-alcohols for asymmetric catalysis.

Also, a new series of 1,3-diols derived from camphor was successfully synthesized which will hopefully govern enantioselective reactions with Lewis acid/base and pi-stack interactions. Although conditions must be optimizes, early results show the promise of the ligands, with particular emphasis on the utilization of pi-stacking in catalysis. To accompany the 1,3-diols, the production of a new 1,3-*N*-tosyl-amino-alcohol was successfully obtained. Efforts now focus on the removal of the tosyl group, followed by *N* alkylation, to produce new 1,3-aminoalcohols analogous to DAIB.

Experimental

General

Unless otherwise noted, all glassware was flame dried under a stream of argon prior to use. All starting materials were obtained from commercial suppliers (Aldrich) unless otherwise noted. All reactions were magnetically stirred. Air sensitive reagents were transferred *via* canula under argon. Low temperature baths were obtained as mixtures of acetone and dry ice (-78 ^{o}C), or ice and water (0 ^{o}C). -30 ^{o}C was obtained by a standard freezer. *In vacuo* refers to the removal of solvent under reduced pressure (Rotovap).

Sodium metal was weighed by placement into a tared beaker of mineral oil. Camphor was purified prior to use by recrystallization from ethanol/water (2:1) and dried under high vacuum, followed by storage over P_2O_5 for a period of no less than 24 h prior to use. Copper (II) chloride was dried at 120 ^{o}C for a 30 minute period prior to use.

Purification on SiO_2 was performed using forced flow with air, on Aldrich reagent silica gel (70-30 mesh). Thin layer chromatography was performed on MACHERY NAGEL POLYGRAM SIL G/UV_{254} precoated plastic plates (0.2mm). Staining was either by ethanolic vanillin or anisaldehyde or 2,4-dinitrophenylhydrazine.

All solvents were distilled prior to use. Tetrahydrofuran, toluene and 1,2-diethoxyethane were distilled from sodium metal / benzophenone while dichloromethane and pyridine were from calcium hydride.

Melting points were obtained on an Electrothermal melting point apparatus and are uncorrected. Optical rotations were obtained in the solvent indicated on a Rudolph Autopol III

polarimeter. NMR (^{1}H and ^{13}C) experiments were performed on a Bruker Avance DPX-300 spectrometer. ^{1}H NMR spectra were obtained at 300 MHz, unless otherwise noted, in $CDCl_3$ with tetramethylsilane as the internal standard. ^{13}C decoupled spectra were obtained in a similar manner with $CDCl_3$ (δ 77.7) as internal standard. ^{1}NMR data are recorded as : chemical shift (ppm) (single = s, doublet = d, triplet = t, quartet = q, multiplet = m, broad = b, followed by number of protons, then *J* vaue(s) in Hz). Infrared spectra were recorded as a thin film on NaCl, and are expressed as either weak (w), medium (m), strong (s) and broad (b).

Mass spectral analysis was performed on a Kratos Concept 1S spectrometer operating in either electron impact (EI) of fast atom bombardment (FAB).

HPLC separations were performed on a Waters 600 Series controller, 600 Series pump and 486 Tanable Absorbance Dtector. Chiral column was a Keystone Chiral β-PM, 250 x 4.6 mm, part number 255 333.

Experimental Procedures

Diols(1R,1'R,2R,2'R,3S,3'S,4R,4'R)-3,3'-Bi(1,7,7,-trimethylbicyclo-[2.2.1]heptan-2-ol) (BIBOL,19) and

(1R,1'R,2R,2'R,3S,3'R,4R,4'R)-Bi(1,7,7-trimethylbicyclo[2.2.1]heptan-2-ol) (20).

Procedure A: Lithium hexamethyldisilylazide (1.0M in toluene, 0.68 mL, 0.68mmol, 1.05 eq.) was added to a solution of (1R)-camphor **7** (0.1g, 0.65 mmol) in toluene (2.0 mL) at O ^{o}C with stirring under Ar over a one minute duration. After 1.5 h, the resulting enolate was cooled to -78 ^{o}C whereupon a solution of $CuCl_2$ (0.093g, 0.69 mmol, 1.05 eq.) in TMEDA (1.0 mL) and pyridine (5.0 mL), which was cooled immediately prior was added dropwise *via* canula under a stream of Ar over a five minute period. It was then permitted to stir for a period of 24h while slowly warming to room temperature. It was transfered *via* canula to a suspension of LAH (0.049g, 1.3 mmol, 2.0 eq.) in dry THF (1.5 mL) at 0 ^{o}C. It was then allowed to stir for 24 h befor excess LAH was quenched by the slow, dropwise addition of H_2O at 0 ^{o}C. This was then followed by dilution with CH_2Cl_2, and treatment with aqueous 1N HCl. The combined organic extracts were then dried over Na_2SO_4, filtered and concentrated *in vacuo* to afford a viscous yellow oil which was subjected to purifcation on SiO_2 with hexane/AcOEt (97.2:2.5). Fractions 30-50 were collected and concentrated to approximately 1 mL, then the remainder of the solvent carefully removed by a gentle stream of air to afford BIBOL, **19**, as white crystals, 50.3 mg., 50%. mp = 176-178 ^{o}C; $[\alpha]_D^{22}$ = +71.1 (c = 0.18, MeOH);

IR : 2883 (m), 2946 (s), 3355, (s, b) cm^{-1};

^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) 0.8 (s, 3H), 0.9 (s, 3H), 0.95 (m, 2H), 1.2 (s, 3H), 1.5 (ddd, 1H, J = 10.2, 10.2, 2.4 Hz), 1.65 (s, 1H), 1.7 (m, 1H), 2.1 (dd, 1H, J = 4.8, 2.2 Hz,), 2.45 (d, 1H, J = 2.98 Hz), 3.75 (m, 1H);

^{13}C NMR, ($CDCl_3$, 125 MHz): δ 83.3, 51.7, 50.1, 49.5. 47.4, 34.3, 30.2, 22.7, 22.2, 12.2;

LREIMS, *m/z*. (% rel): 306 (1.6), 288 (22.7), 152 (41.9);

HREIMS: calc. for $C_{20}H_{34}O_2$ = 306.2558. Found = 306.2574.

TLC with 10% AcOEt in hexane, R_f = 0.4. Dark blue to anisaldehyde. Crystals of 19 which were suitable for X-ray analysis were recrystallized from AcOEt. Elaboration of the column afforded the epimeric alcohol 20 (9.7 mg, 10%) as white crystals, m.p. = 161-163 ^oC; $[\alpha]_D^{22}$ = +99.2 (*c* = 0.14, $CHCl_3$);

IR, thin film, $CHCl_3$: 2871 (m), 2948 (s), 3336 (s,b);

^1H NMR (300 MHz, $CDCl_3$): δ(ppm) 0.8 (s, 3H), 0.85 (s, 3H), 0.9 (s, 3H), 0.91 (m, 1H), 0.95 (s, 3H). 1.0 (s, 3H), 1.05 (m, 1H), 1.1 (s, 3H), 1.2 (m, 2H), 1.5 (m, 2H), 1.6-1.8 (m, 4H), 1.8-2.0 (m, 2H), 3.1 (s, 2H), 3.85 (m, 2H);

^{13}C NMR (125 MHz, $CDCL_3$): δ 83.7, 82.3, 55.5, 53.8, 50.0, 49.9, 49.4, 49.3, 47.7, 47.2, 33.7, 31.4, 30.4, 26.5, 22.8, 22.5, 21.9, 20.8, 13.7, 12.2; ;

LREIMS, *m/z* (% rel): 302 (13.4), 288 (22.0), 152 (36.2);

HREIMS: calc. for $C_{20}H_{34}O_2$ = 306.2558. Found = 306.2575; HREIMS for $M^+ - H_2O$ = 288.2453. Found = 288.2451. Crystals suitable for X-ray analysis were obtained by recrystallization from $CHCl_3$. TLC: 10 AcOEt in hexane, R_f = 0.2, dark blue to Anisaldehyde.

Procedure B: Lithium hexamethyldisilylazide (1.0 M in toluene, 0.68 mL, 0.68 mmol, 1.05 eq.) was added dropwise over a one minute period to a solution of camphor **7** (0.1g, 0.65 mmol) in toluene (2.0 mL) at O ^oC under Ar at 0 ^oC. After 1.5 h, the resulting enolate was cooled to -78 ^oC whereupon a solution of $Cu(OTF)_2$ (0.593g, 1.65 mmol, 2.5 eq.) in toluene (4.0 mL) containing pyridine (0.64mL), which was cooled immediately prior, was added dropwise *via* canula under a stream of Ar over a five minute period. It was then permitted to stir for a period of 48h without warming. After the duration, it was transfered *via* canula to a suspension of LAH (0.049g, 1.3 mmol, 2.0 eq.) in dry THF (1.5 mL) at 0 ^oC. It was then allowed to stir for 24h befor excess LAH was quenched by the slow, dropwise addition of aqueous NH_4Cl at 0 ^oC. The resulting solution was then extracted thoroughly with Et_2O (4 x 20 mL). The combined organic layers were then washed with saturated NaCl, and then dried over Na_2SO_4, filtered and

concentrated *in vacuo* to afford a viscous yellow oil which was subjected to purifcation on SiO_2 with hexane/AcOEt (97.2:2.5). Fractions 30-40 were collected and concentrated to approximately 1 mL, then the remainder of the solvent carefully removed by a gentle stream of air to afford BIBOL, 19 as white crystals, (33 mg, 33%), followed by the minor diol, **20**, (17 mg, 17%). For spectral data, see above. The spectral data obtained *via* this and all other alternative procedures yield samples whose data are in full accord with authentic samples obtained from previously mentioned procedures.

Alkenes (*E*) and (*Z*)-2, 2'-Dioxo-3, 3'-bibornanylidenes, (17 and 18).

The diketone produced by the method described above with the omission of the reduction step was permitted to stand subject to an aerial atmosphere in CH_2Cl_2 for 24h. The mixture of diketones **13** and **14** was purified on SiO_2 with hexane/ AcOEt (95:5) to afford first the *E* isomer **17** as a yellow solid, m.p. 98-100 ^oC;

^1H NMR ($CDCl_3$, 300 MHz): δ (ppm) 0.74 (s, 3H), .094 (s, 6H), .095 (s, 6H), 1.48-1.22 (m, 4H), 1.68 (ddd, 2H, J = 11.4, 11.4, 3.7 Hz), 2.15-2.05 (m, 2H), 3.74 (d, 2H, J = 4.3);

^{13}C NMR ($CDCl_3$, 75 MHz): δ (ppm) 212.4, 141.2, 58.5, 48.8, 46.5, 30.9, 26.3, 21.2, 18.7, 9.6. TLC with CH_2Cl_2, R_f = 0.8, yellow to anisaldehyde, U.V. = 254 nm. Further purification yielded the second *Z* isomer **18** as a yellow solid.

^1H NMR ($CDCl_3$, 300 MHz): δ (ppm) 0.8 (s, 6H), 0.95 (s, 6H), 0.96 (s, 6H), 1.2-1.5 (m, 4H), 1.6-1.8 (m, 2H), 2.0-2.2 (m. 2H), 2.6 (d, J = 4.0, 2H);

^{13}C NMR ($CDCl_3$, 75 MHz): δ (ppm) 203.1, 144.3, 59.1, 51.6, 45.8, 30.2, 26.4, 21.1, 18.8, 9.9. TLC: CH_2Cl_2, R_f = 0.2, yellow to anisaldehyde, U.V. = 254 nm. Immediately following the purification of alkenes 17 and 18, each underwent a subsequent reisomerization to afford a new 3:1 mixture of 17 and 18 as judged by ^1H NMR.

Procedure B) To a solution of camphor **7** (0.1g, 0.65 mmol, 1 eq.) in THF (1.0 mL) at 0^oC under Ar was added LiHMDS (1.0 M in THF, 1.4 mL, 2.05 eq.) dropwise over about one

minute and the solution stirred without warming for a further 1.5h. After this time, a solution of $CuCl_2$ (0.181g, 1.34 mmol, 2.05 eq.) in DMF (1.5 mL) was added *via* canula under a stream of Ar over 2 minutes. The brown solution was then permitted to stir for about 2 minutes while warming to room temperature before it was placed on an ultrasound apparatus at approx. 45 ^oC for 5h. After this time, it was diluted with CH_2Cl_2 and partitioned with aqueous NH_3. The combined organic layers were the dried over Na_2SO_4, filtered and concentrated *in vacuo* to give a viscous yellow oil which was subjected to purification as described above. As an alternative to AcOEt/hexane, it was determined that the mixture can quite easily be purified with CH_2Cl_2 as eluant.

Kinetic α–Chloroketone (2R, 3R, 6S)-2-chloro-6-isopropyl-3-methylcyclohexanone, (27).

To a solution of menthone **21** (0.5g, 3.24mmol, 1 eq.) in dry toluene (3.0 mL) under Ar at 0^oC was added NaHMDS (5.9mL, 3.56mmol, 1.1eq.) and the reaction mixture stirred for a further 60min.,during which time a slight yellow tint developed. The enolate was then lowered to -78^oC whereupon a solution of $CuCl_2$ (1.3g, 9.7mmol, 3.5 eq.) in dry pyridine (11mL) and TMEDA (3.4mL, 7.0eq.) was added *via* canula under a stream of Ar. over a five minute priod. It was permitted to stir for a further 15h while slowly warming to 0^oC, at which time the reaction diluted with water. The mixture was then partitioned between NH_3/DCM, the organic layers combined and dried on Na_2SO_4, filtered and concentrated under reduced pressure to give 0.75g of a brown oil which was purifiied on SiO_2 (hexane) to give **27** (0.458g, 75%) as a clear, colourless oil. $[\alpha]_D20$ = -145.4 (*c* = 0.11, $CHCl_3$);

^1H NMR ($CDCl_3$, 500 MHz), δ (ppm): 4.1 (dd, 1H, *J* = 3.1, 1.8), 2.7 (ddd, 1H, *J* = 12.7, 5.9, 5.9), 2.12 (m, 1H), 2.10-1.95 (m, 2H), 1.76 (m, 1H), 1.6 (dddd, 1H, *J* = 13.8, 7.45, 3.7, 1.3), 1.31 (dddd, 1H, *J* = 12.8, 3.8, 3.8, 3.8), 1.06 (d, 3H, *J* = 6.6), 0.91 (d, 3H, *J* = 6.8), 0.86 (d, 3H, *J* = 6.8);

^{13}C NMR ($CDCl_3$, 125 MHz): 206.9, 68.6, 49.6, 39.3, 28.2, 27.2, 25.9, 21.0, 18.8, 17.7;

IR ($CHCl_3$) 2961 (s,b), 2873 (m), 1718 (s), 1453 (m), 1379 (m), 1164 (m), 1091 (m), 795 (w), 708 (w) cm^{-1};

LREIMS, *m/z* (% rel.): 188 (M^+, 74.7), 173 (70.3) ,153 (20.3), 146 (76.7), 135 (5.4), 124 (9.0), 111 (27.1), 97 (63.2), 86 (28.1), 69 (100.0), 55 (38.2), 43 (16.6);

HREIMS: calc for $C_{10}H_{17}OCl$ = 188.968; found = 188.0967; TLC: 30% CH_2Cl_2/hexane, R_f = 0.5, brown to vanillin. If so desired, the α-haloketone can made by utilizing DMF in place of pyridine/TMEDA. This is done by dissolving the dry $CuCl_2$ in DMF such that the concentration of the $CuCl_2$ in DMF is 1.0 M. Please note that this solution freezes upon cooling to -78 ^oC. Therefore, it is recommended that the sample be added very quickly after cooling, or, if omission of cooling is desired, the solution can be added onto the side of the long neck flask, thereby cooling the solution immediately prior to the addition.

Thermo. α-Chloroketone (2S, 3R, 6S)-2-chloro-6-isopropyl-3-methylcyclohexanone (57).

To a solution of the α-chloroketone 27 (0.250g, 1.32 mmol, 1eq.) in dry MeOH (15 mL) at 0^oC was added NaN_3 (0.86g, 28.6 mmol, 10 eq,) in small proportions over a 10min. duration. It was then stirred without warming for a further 48 h., during which time a white precipitate developed. It was then diluted ***with caution*** with water and extracted with DCM. The organic layers were then combined and concentrated under reduce pressure to give 0.230g of a yellow oil which was purified on SiO_2, first with 7% DCM/Hexane. Fractions 16-30 were combined and concentrated to afford 0.200g (80%) of epimer 57 as a yellow oil which partially crystallized slowly on standing from $CDCl_3$, $[\alpha_d^{20}]$ = -0.018 (*c* = 0.046, $CHCl_3$).

^1H NMR ($CDCl_3$, 300 MHz) δ (ppm): 0.88 (d, 3H, *J* = 6.3), 0.91 (d, 3H, *J* = 6.3), 1.23 (d, 3H, *J* = 6.4), 1.3-1.6 (m, 2H), 1.7-2.2 (m, 5H), 4.1 (d, 1H, *J* = 11.6).

^{13}C NMR ($CDCl_3$, 75 MHz): δ (ppm) 203.2, 72.8, 56.7, 44.8, 34.1, 28.7, 27.0, 21.6, 21.3, 19.2;

IR (thin film, $CDCl_3$): 752.8 (m), 1067 (w, b), 1216 (w), 1273 (w), 1371 (w), 1457 (w, b), 1717 (s, b), 2958 (s) cm^{-1};

LREIMS, *m/z* (% rel.): 188 (M^+, 31.1), 173 (39.2), 153 (11.5), 146 (46.3), 137 (3.1), 124 (6.4), 111 (20.8), 97 (52.1), 86 (25.2), 76 (25.2), 69 (100.0);

HREIMS: Calc for $C_{10}H_{17}ClO$ = 188.0969; Found = 188.0974; TLC: R_f = 0.4, 30% DCM/Hex, brown to vanillin.

Preparation of (1S, 2R, 3R, 6S)-2-chloro-6-isopropyl-3-methylcyclohexanol (28).

Procedure A) To a suspension of LAH (0.04g, 1.05 mmol, 2 eq.) in dry THF (3 mL) under Ar. at -78°C was added a solution of **27** (0.100g, 0.53 mmol, 1 eq.) in dry THF (2 x 1mL) *via* canula under a stream of Ar. It was the permitted to stir for a further 6h before being raised to 0°C whereupon the reaction was quenched by the slow addition of water. The mixture was the partitioned between 1N HCl and DCM, and the organic layers combined, dried on Na_2SO_4, filtered and concentrated under reduced pressure to give 0.121g of a viscous yellow oil which was purified on SiO_2 (3% EtOAc/Hex) to give 0.75g (74%) of **28** as a viscous oil.

Procedure B) As an alternative to the previous procedures, a 'one pot' conversion of menthone to the α-halohydrin was developed whereby the solution obtained by procedure **27** is added directly to a suspension of LAH in dry THF *via* cannula at -78°C. After 24h, the reaction was allowed to warm to 0°C, whereupon excess LAH was quenched by the slow, dropwise addition of water, followed by work-up in the hitherto mentioned manner. This was followed by purification on SiO_2 as described above to give **28** (0.085g, 85%) as a viscous colorless oil directly from menthone. $[\alpha_d^{20}] = -29.2$ ($c = 0.072$, $CHCl_3$);

^1H NMR ($CDCl_3$, 500 MHz) δ (ppm): 4.38 (m, 1H), 3.48 (ddd, 1H, J = 10.6, 10.6, 2.9), 2.13 (sd, 1H, J = 6.9, 2.7), 1.75-1.83 (m, 2H), 1.55-1.63 (m, 2H), 1.38 (m, 2H), 1.03 (d, 3H, J = 6.6), 0.98 (m, 1H), 0.9 (d, 3H, J = 7.0), 0.8 (d, 3H, J = 7.0).

^{13}C NMR ($CDCl_3$, 125 MHz): δ (ppm) 74.6, 73.2, 42.8,36.5, 27.6, 25.8, 22.9, 20.9, 19.2, 16.1;

IR: 525 (w), 617 (w), 682 (w), 1053 (m), 1099 (w), 1385 (m, b), 1453 (m, b), 2873 (s), 2958 (s,b), 3414 (s,b) cm^{-1};

LREIMS, *m/z* (% rel): 190 (11.6), 175 (30.6), 154 (9.2), 137 (41.4), 129 (8.1), 121 (16.7), 112 (16.0), 99 (39.2), 95 (49.3), 85 (100.0), 81 (90.8), 69 (49.1), 55 (49.3), 41 (57.0);

HREIMS: Calc for $C_{10}H_{19}ClO$ = 190.1124. Found = 190.1137; TLC: R_f = 0.3, 10% AcOEt/hexane, brown to vanillin.

Preparation of (1S, 2R, 3R, 6S)-2-chloro-6-isopropyl-3-methylcyclohexyl acetate (29):

A sample of the α-halohydrin, **28**, (0.05g, was dssolved with stirring at room temperature in pyridine (0.5 mL) along with acetic anhydride (0.5 mL). It was then permitted to stir for a further 24 h before the excess pyridine and acetic anhydride were removed by high vac to 0.088g of a viscous yellow oil. The mass was carefully followed during solvent removal to avoid loss of the low boiling acetate derivative. The oil was then partitioned between CH_2Cl_2 and H_2O, and extracted with CH_2Cl_2 (3 x 5 mL). The organic extracts were combined and concentrated *in vacuo* to afford 0.056g of **29** as a viscous off-white oil (90 %).$[\alpha_d^{20}]$ = -152.0 (*c* = 0.98, $CHCl_3$);

^1H NMR ($CDCl_3$, 500 MHz): δ (ppm) 0.74 (d, 3H, *J* = 11.8), 0.9 (d, 3H, *J* = 7.0), 1.0 (d, 3H, *J* = 6.6), 1.1 (m, 1H), 1.4-1.45 (m, 2H), 1.65 (m, 1H), 1.82-1.87 (m, 2H), 1.97 (m, 1H), 2.1 (s, 3H), 4.4 (m, 1H), 4.75 (dd, 1H, *J*= 11.4, 3.1)

^{13}C NMR ($CDCl_3$, 75 MHz): δ (ppm) 171.0, 75.5, 68.5, 39.7, 36.5, 27.2, 26.2, 23.4, 21.5, 20.9, 19.2, 16.5;

IR: 1040 (m), 1239 (s), 1371 (m), 1740 (s), 2960 (s,b) cm^{-1};

LREIMS, *m/z* (% rel): 190 (5.3), 172 (7.3), 154 (4.1), 137 (55.6), 129 (59.8), 121 (4.8), 102 (5.8), 93 (15.2), 81 (20.5), 77 (3.4), 69 (8.9), 55 (11.0), 43 (100.0);

HREIMS: Calc for $C_{12}H_{19}ClO$ = 190.1124; Found = 190.1135; TLC: R_f = 0.6, 10% AcOEt/hexane. Stains brown to vanillin.

(6R)-6-isopropyl-3-methyl-2-cyclohexen-1-one (35):

Procedure A) The α-chloroketone **27** (0.010g, 0.05 mmol, 1 eq.) was dissolved in 0.3 mL of dry DMSO at room temperature along with 0.010g (0.16 mmol, 5 eq.) of NaN_3. The reaction vessel (high pressure cell) was then flushed thoroughly with Ar before being sealed, and the mixture stirred for 12 h at 60 ^oC before being allowed to cool, whereupon the mixture was diluted very carefully with CH_2Cl_2 and then partitioned with H_2O. The combined organic layers were then dried over Na_2SO_4, filtered and concentrated *in vacuo* to afford a viscous oil which was subjected to purification on SiO_2 with 3% AcOEt/hexane. Fractions 16-18 were collected and concentrated to give 0.003g of the α,β-unsaturated carbonyl compound, **35** (38%).

^1H NMR ($CDCl_3$, 300 MHz): δ (ppm) 0.9 (d, 3H, J = 6.8), 0.95 (d, 3H, J = 6.8), 1.75-1.9 (m, 2H), 1.94 (s, 3H), 1.95- 2.1 (m, 2H), 2.25-2.45 (m, 2H), 5.9 (s, 1H);

^{13}C NMR ($CDCl_3$, 75 MHz): δ (ppm) 127 (sp_2);

LREIMS, *m/z* (% rel): 152 (M^+, 46.2), 137 (32.6), 124 (24.3), 110 (86.2), 95 (21.9), 82 (100.0), 71 (47.1), 55 (29.7), 43 (56.2);

HREIMS: Calc for $C_{10}H_{16}O$ = 152.1201; Found = 152.1205; TLC: R_f =0.3, 10%AcOEt/.hexane, orange to anisaldehyde.

Procedure B) It was determined that the α,β-unsaturated carbonyl compound, **35** can be obtained by reaction in a similar manner with the use of DMF in place of DMSO.

(1S, 6R)-6-isopropyl-3-methyl-2-cyclohexen-1-ol (36):

Procedure A) The α-halohydrin 31 (0.010g, 0.05 mmol, 1 eq.) was dissolved in pyridine (0.5 mL) at room temperature in a high pressure vessel and to the solution was added diethylamine hydrochloride (0.020g, 0.25 mmol, 5 eq.) along with DMF (0.5 mL). The reaction

mixture was then heated to approximately 80 ^{o}C and stirred for a further 72 h before being permitted to cool. The reaction was the diluted with H_2O and extracted thoroughly with CH_2Cl_2 (3 x 10 mL). The combined organic extracts were then dried over Na_2SO_4, filtered and concentrated *in vacuo* to give a viscous oil which was purified on SiO_2 with 5% AcOEt/hexane to give 0.045g of the allylic alcohol **36** as a very low boiling colorless oil ***which is quickly lost if not covered***(56%). Representative Data:

^{1}H NMR ($CDCl_3$, 300 MHz): δ (ppm) 1.7 (s, 3H), 4.1 (m,1H), 5.4 (s, 1H);

LREIMS, *m/z* (% rel.): 149 (100.0), 137 (8.4), 111 (7.1), 93 (10.5), 84 (23.5), 69 (24.7), 57 (26.9), 43 (63.9);

HREIMS: Calc. for $C_{10}H_{18}O$ = 154.1358. Found = 154.1344.

Mesylate (59)

The chloroalcohol **31** (0.004g, 0.013 mmol, 1 eq.) was dissolved in dry CH_2Cl_2 (0.5 mL) under Ar at 0^{o}C. To the solution was added dry Et_3N (40 μL, 0.3 mmol, 22 eq.) followed by the slow dropwise addition of methanesulfoylchloride (22 μL, 0.3 mmol, 22 eq.) over a five minute period. After approx. 1h. a yellow coagulant developed, and the reaction permitted to stir while warming to room temp. After approx. 1 h of stirring at room temp. the reaction was diluted with CH_2Cl_2 followed by partitioning with conc. NH_4Cl. The aqueous layer was washed with 3 x 5 mL CH_2Cl_2 and the combined organic layers dried over Na_2SO_4, filtered and concentrated *in vacuo* to give a viscous yellow oil which was placed on high vac to remove extraneous Et_3N, to give 0.005g of the mesylate, **59**, as a clear, colorless oil (quant.) which was studied without further purification.

^{1}H NMR ($CDCl_3$, 300 MHz): δ (ppm) 0.85 (d, 3H, J = 3.4), 0.95 (d, 3H, J = 3.5), 1.05 (d, 3H, J = 2.5), 1.35-1.5 (m, 3H), 1.72 (m, 1H), 1.85 (m, 1H), 1.9-2.1 (m, 2H). 3.1 (s, 3H), 1.55 (m, 1H), 4.65 (m, 1H);

^{13}C NMR ($CDCl_3$, 75 MHz): δ (ppm) 82.5, 68.6, 40.2, 39.8, 36.6, 26.9, 25.9, 23.3, 20.9, 19.1, 15.9.

1,7,7-trimethyl-3-[(z)-1-(4-nitrophenyl)methylidene]bicyclo[2.2.1]heptan-2-ol (38):

To a solution of camphor **7** (0.100g, 0.66 mmol, 1eq.) in dry THF (1.0mL) under Ar at 0 ^{o}C was added lithium diisopropylamide (0.48 mL, 0.72 mmol, 1.1 eq.) dropwise over a one minute duration. The solution was then permitted to stir for a further 1.5h before being lowered to -78 ^{o}C whereupon a solution of P-nitrobenzaldehyde **37** (0.11g, 0.72 mmol, 1.1 eq.) in dry THF (1.0 mL) was added *via* canula under a stream of Ar. over approx. 2 minutes. It was the permitted to stir with slow warming to room temp over a 24h period before the solution was itself transfered *via* canula under a stream of Ar. to a previously cooled suspension of LAH (0.05g, 1.34 mmol, 2 eq.) in dry THF, under Ar at 0^{o}C. It was then permitted to stir for a further 6 h before excess LAH was quenched by the slow, dropwise addition of H_2O at 0 ^{o}C. The organic layer was then thoroughly extracted with CH_2Cl_2 (3 x 15 mL), dried over Na_2SO_4, filtered and concentrated *in vacuo* to give a viscous yellow oil which was purified on SiO_2 with 3% AcOEt/hexane (200 mL), followed by 5%. Fractions 25-35 were collected and concentrated under reduced pressure to give 0.120g of **38** (64%) of the alkene, which rapidly isomerises to a nearly 60:40 mixture of isomers, before *full* spectral interpretation could be achieved. Please note that the individual isomers were not assigned by NMR and are ambiguous to date.

^{1}H NMR ($CDCl_3$, 300 MHz): δ (ppm) (D_2O) 0.85 (s, 3H), 0.9 (s, 3H), 0.95 (s, 3H), 1.2 (m, 1H), 1.35 (ddd, 1H, *J* = 12.3, 12.3, 4.0), 1.95 (m, 1H), 2.8 (d, 1H, *J* = 4.5), 4.0 (s, 1H) 6.65 (s, 1H), 7.4 (d, 2H, *J* = 8.6), 8.2 (d, 1H. *J* = 8.8);

^{13}C NMR ($CDCl_3$, 75 MHz): δ (ppm) 157.7, 145.1, 129.3, 124.1, 121.7, 82.2, 51.1, 49.5, 48.2, 34.2, 31.3, 25.6, 21.5, 19.9, 11.3;

IR (cm^{-1}) not obtained;

LREIMS, *m/z* (% rel): 287 (M^+) (77.3), 272 (100.0), 258 (14.6), 231 (18.7), 212 (22.4), 203 (9.1), 182 (10.0), 165 (20.1), 141 (13.5), 128 (28.3), 112 (56.9), 97 (44.7), 83 (63.5), 69 (21.0), 55 (41.8), 41 (41.9);

HREIMS: Calc. for $C_{17}H_{21}O_3N$ = 287.1521. Found = 287.1527;

TLC: R_f = 0.6, 15 %AcOEt/hexane, green to anisaldehyde; UV = 254.

3[(*R*)-1-hydroxymethyl-1-(4-nitrophenyl)methyl]-1,7,7-trimethylbicyclo[2.2.1]heptan-2-ol (39):

To a solution of camphor **7** (0.152g, 1 mmol, 1 eq.), in dry THF (1.0 mL) under Ar at 0 ^{o}C in an extra long neck flask was added lithium diisopropylamide (1.5 M cyclohexane, 0.73 mL, 1.1 eq.) dropwise over approx. 1 minute. It was then stirred for a further 1.5h before being lowered to -78 ^{o} C whereupon a solution of P-nitrobenzaldehyde **37** (0.166g, 1.1 mmol, 1.1 eq.) in dry THF (1.0 mL) was added. It was then permitted to stir without warming for 18h before the aldol product was itself transferred *via* canula under a stream of Ar. to a previously cooled suspension of LAH in dry THF at 0 ^{o}C. It was the permitted to react for a further 2h before excess LAH was quenched by the slow dropwise addition of H_2O at 0 ^{o}C. The organics were then thoroughly extracted with CH_3Cl_2 (3 x 10 mL), dried over Na_2SO_4, filtered and concentrated *in vacuo* to give a viscous yellow oil. Purification on SiO_2 with 15% AcOEt/hexane, with 2% incremental increases in the percentage of AcOEt every 200mL, gave 0.165g (54%) of the major diol **39** as a yellow oil which slowly crystallizes over time to a very hard solid, m.p. = 93-95 ^{o}C; $[\alpha]_D^{20}$ =+63.8, c = 0.108, $CHCl_3$);

^{1}H NMR ($CDCl_3$, 300 MHz): δ (ppm) 0.8 (s, 3H), 0.9 (m, 1H), 1.0 s, 3H), 1.1 (m, 1H), 1.2 (d, 1H, J = 3.9), 1.32 (s, 3H), 1.42-1.62 (m, 2H), 2.05 (dd, 1H, J = 11.0, 8.0), 2.5-3.2 (s, b, 2H), 4.0 (d, 1H, J = 8.0), 5.2 (d, 1H, J = 11.1), 7.5 (d, 2H, J = 8.6), 8.2 (d, 2H, J = 8.5);

^{13}C NMR ($CDCl_3$, 75 MHz): δ (ppm) 151.4, 147.8, 128.4, 124.0, 82.6, 74.7, 58.7, 50.3, 47.6, 47.4, 33.4, 30.1, 22.3, 11.7; (2 C's at 22.3 overlapped)

IR: 755 (m), 863 (w), 1043 (m), 1097 (m), 1348 (s), 1522 (s), 1605 (w), 2953 (s, b), 3395 (s, b) cm^{-1};

LREIMS, *m/z* (% rel.): 287 (1.3), 272 (3.4), 242 (1.1), 229 (2.5), 205 (3.8), 175 (2.6), 153 (25.3), 136 (100.0), 108 (23.1), 95 (84.3), 83 (14.1), 69 (13.3), 55 (16.1), 43 (28.9);

HREIMS: Calc. for M^{+}-H_2O = 287.1521. Found = 287.1530;

TLC: R_f = 0.4, 20% AcOEt/hexane. Blue to vanillin; UV = 254

3-[(*R*)-1-(1,3-benzodioxo-5-yl)-1-hydroxymethyl]-1,7,7-trimethylbicyclo[2.2.1]heptan-2-ol (42)

A solution of camphor **7** (0.100g, 0.66 mmol, 1.0 eq.) in dry THF (0.5 mL) under Ar at 0 ^{o}C was lowered to 0 ^{o}C whereupon lithium diisopropylamide (1.5 M/cyclohexane, 0.48 mL, 1.1 eq.) was added dropwise over about a 1 minute period. It was then permitted to stir for a further 1.5 h before being lowered to -78 ^{o}C whereupon a solution of piperonal **40** (0.108g, 0.73 mmol, 1.1 eq.) in dry THF (0.7 mL) was added dropwise *via* canula over a 2 minute period and the solution was allowed to stir without warming for a further 24 h. It was the warmed to 0 ^{o}C and the added *via* canula to a suspension of LAH (0.050g, 1.3 mmol, 2.0 eq.) in dry THF (1.0 mL). It was allowed to stir without warming for about 3 h before excess LAH was quenched by the slow, dropwise addition of H_2O at 0 ^{o}C. The organics were then extracted with CH_2Cl_2 (3 x15 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure to give a viscous colorless oil which was subjected to purification on SiO_2 with 17% AcOEt/hexane. Fractions 18-22 were collected and concentrated to give 0.187g (90%) of **42** as a clear colorless oil which slowly crystallized on standing, m.p. = 85-87^{o}C; $[\alpha]_D^{20}$ = +41.9, *c* = 0.172, $CHCl_3$);

^{1}H NMR ($CDCl_3$, 300 MHz): δ (ppm) 0.72 (s, 3H), 0.85 (m,1H), 0.94 (s, 3H), 1.05 (m, 1H), 1.2 (d, 1H, *J* = 3.9), 1.25 (s, 3H), 1.42 (ddd, 1H, *J* = 11.7, 11.7, 3.1), 1.55, (m, 1H), 2.0 (dd, 1H, *J* = 11.0, 7.9), 3.05 (s, 1H), 3.5 (bs, 1H), 3.85 (d, 1H, *J* = 7.8), 4.95 (d, 1H, *J* = 11.2), 5.95 (s, 2H), 6.75 (s, 2H), 6.9 (s, 1H);

^{13}C NMR ($CDCl_3$, 75 MHz): δ (ppm) 148.1, 147.3, 138.2, 121.1, 108.3, 107.7, 101.3, 82.2, 75.4, 58.4, 50.1, 47.8, 47.2, 33.8, 30.2, 22.4, 22.2, 11.9;

IR: 739 (s), 811 (s), 866 (m), 932 (m), 1040 (s), 1097 (s), 1249 (s, b), 1443 (s), 1488 (s), 2952 (s, b), 3385 (s, b) cm^{-1};

LREIMS, *m/z* (% rel.): 304 (4.9), 286 (48.2), 268 (4.0), 253 (2.4), 215 (2.2), 187 (9.4), 174 (25.1), 152 (61.9), 148 (100.0), 136 (76.8), 121 (30.9), 108 (18.0), 93 (44.2), 84 (37.1), 77 (13.9), 65 (23.5), 55 (15.0);

HREIMS: Calc. for $C_{18}H_{24}O$ = 304.1675. Found = 304.1682;

TLC: R_f = 0.3, 30% AcOEt/hexane, Dark red to 2,4-dinitrophenylhydrazine; UV = 254

3[(*R*)-1-(1,3-benzodioxol-5-yl)-1-hydroxymethyl]-1,7,7-trimethylbicyclo[2.2.1]heptan-2-one (41)

A solution of camphor **7** (0.250g, 1.6 mmol, 3.0 eq.) in dry THF (1.6 mL) under Ar was lowered to 0°C whereupon Lithium Diisopropyl Amide (1.5 M, cyclohexane, 1.2 mL, 3.3 eq.) was added dropwise over a 2 minute duration and it was then stirred for a further 1.5 h. After this time, th enolate solution was lowered to -78 °C whereupon a solution of Piperonal **40** (0.082g, 0.55 mmol, 1.0 eq.) in dry THF 0.6 mL) was added *via* canula under a stream of Ar . After approx. 18 h of stirring without warming, the reaction was stopped by the addition of NH_4Cl. The organics were then extracted with CH_2Cl_2 (3 x 20 mL) and the combined layers were dried over Na_2SO_4, filtered and concentrated *in vacuo* to give a clear colourless oil which was stored at -30 °C until purification. It was then placed on SiO_2 with CH_2Cl_2/hexane (50:50) to afford 0.127g (77%) of **41** as a clear colorless oil which slowly decomposes if not stored at sub-zero conditions. $[\alpha]_D^{20}$ = 16.6, *c* = 0.108, $CHCl_3$);

^{1}H NMR ($CDCl_3$, 300 MHz): δ (ppm) 0.95 (s, 3H), 0.99 (s, 3H), 1.05 (s, 3H), 1.28 (m, 1H), 1.5-1.75 (m, 3H), 1.9 (m, 1H), 2.2 (d, 1H, *J* = 9.6), 4.8 (d, 1H, *J* = 10.0), 6.0 (s, 2H), 6.78 (s, 2H), 6.88 (s, 1H);

^{13}C NMR ($CDCl_3$, 75 MHz): δ (ppm) 223.4, 148.3, 147.7, 136.3, 120.9, 108.3, 107.4, 101.5, 76.6, 61.5, 58.8, 47.3, 46.1, 29.7, 29.4, 22.6, 20.8, 9.5;

IR 1039 (s), 1248 (s), 1445 (m), 1503 (w), 1721 (s), 2929 (m, b), 3490 (w, b) cm^{-1};

LREIMS, *m* z (% rel.): 302 (9.2), 284 (24.9), 256 (3.6), 241 (7.1), 201 (10.9), 190 (19.6), 175 (18.6), 151 (92.3), 149 (100.0), 137 (25.4), 124 (51.0), 109 (40.3), 95 (62.5), 81 (37.7), 65 (40.3), 55 (37.9), 41 (56.7);

HREIMS: Calc. for $C_{18}H_{22}O_4$ = 302.1518. Found = 302. 1539;

TLC: R_f = 0.3, CH_2Cl_2, Orange to 2,4-dinitrophenylhydrazine; UV =254.

3-dydroxy-4,7,7-trimethyl-2-{(*R*)-1-[(4)-methylphenyl)sulfonamide]1]phenylmethyl}bicyclo[2.2.1]heptane (49 Minor)

To a solution of camphor **7** (0.200g, 1.3 mmol, 1.0eq.), in dry THF (1.5 mL) under Ar at 0^{o}C was added lithium hexamethyldsilylazide (1.0 M/THF, 1.4 mL, 1.4 mmol, 1.1 eq.) dropwise over a 1 minute duration and the resulting solution stirred for a further 1.5 h. It was then lowered to -78 ^{o}C whereupon a solution of the tosylimine, **48**, (0.340g, 1.3 mmol, 1.0 eq.) in dry THF (1.3 mL) was added *via* canula under a stream of Ar over 1 minute. It was then permitted to stir without warming for approx. 24 h before it was transfered to a previously cooled suspension of LAH (0.075g, 1.97 mmol, 1.5 eq.) in dry THF (2.0 mL) under Ar. After about 12 h of stirring with slow warming to room temperature, the reaction was placed back to 0 ^{o}C whereupon excess LAH was quenched by the slow, dropwise addition of H_2O. The mixture was then extracted with CH_2Cl_2 (3 x 15 mL), the organic layers dried on Na_2SO_4, filtered and concentrated *in vacuo* to yield a viscous oil which was purified on SiO_2 with CH_2Cl_2 to afford first 0.181g (32%) of the minor diastereomer **49** a as a clear colorless oil.

Data for minor isomer: $[\alpha]_D^{20} = +16.6$, $c = 0.12$, $CHCl_3$);

^{1}H NMR ($CDCl_3$, 300 MHz): δ (ppm) 0.7 (s, 6H), 1.85-1.15 (m, 2H), 1.2 (s, 3H), 1.49 (m, 1H), 1.7-1.9 (m, 2H), 2.15 (d, 1H, $J = 3.6$), 2.25 (d, 1H, $J = 12.2, 7.7$), 32.35 (s, 3H), 3.4 (d, 1H, $J = 7.6$), 4.59 (dd, 1H, $J = 12.1, 9.0$), 5.2 (d, 1H, $J = 8.9$), 7.05 (m, 7H), 7.45 (d, 2H, $J = 6.5$);

^{13}C NMR ($CDCl_3$, 75 MHz): δ (ppm) 143.8, 143.0, 142.9, 138.4, 129.5, 128.9, 127.6, 127.5, 80.7, 59.4, 57.1, 50.4, 47.8, 47.6, 33.8, 30.3, 22.5, 21.8, 21.6, 12.1; IR: 567 (m), 702 (m), 1057 (m, b), 1157 (s), 1323 (s, b), 1454 (m, b), 1599 (w), 2952 (s, b), 3269 m, b), 3559 (m, b) cm^{-1};

LRFAB; 414 (

HREIMS: Calc. for $C_{24}H_{31}O_3NS$ = Found = ;

TLC: $R_f = 0.4$, 30% AcOEt/hexane, blue to vanillin; UV = 254.

3-dydroxy-4,7,7-trimethyl-2-{(*R*)-1-[(4)-methylphenyl)sulfonamide]1]phenylmethyl}bicyclo[2.2.1]heptane (49 Major)

Further elaboration of the column yielded 0.280g (50%) of the major diastereomer **49b** as an extremely viscous oil which partially crystallises on standing as a viscous, white solid. $[\alpha]_D^{20}$ = 33.2, c = 0.304, $CHCl_3$);

^{1}H NMR ($CDCl_3$, 300 MHz): δ (ppm) 0.68 (s, 3H), 0.8 (m, 1H), 1.0 (s, 3H), 1.01 (d, 1H, J = 3.5), 1.1 (m, 1H), 1.15 (s, 3H), 1.4-1.5 (m, 2H), 1.5-1.7 (s, b, 2H), 2.05 (dd, 1H, J = 11.6, 7.5), 2.33 (s, 3H), 3.98 (d, 1H, J = 7.5), 4.59 (d, 1H, J = 11.7), 6.85-6.92 (m, 2H), 7.02 (d, 2H, J = 8.1), 7.05-7.15 (m, 3H), 7.38 (d, 2H, J = 8.3);

^{13}C NMR ($CDCl_3$, 75 MHz): δ (ppm) 143.3, 140.6, 137.1, 129.4, 128.6, 127.9, 127.8, 127.4, 80.9, 59.7, 57.4, 50.5, 48.1, 47.2, 33.6, 30.4, 22.2, 22.1, 21.8, 12.;

IR: 1156 (m), 1321 (m, b), 1454 (m, b), 2951 (s, b), 3261 (s, b), 3541 (s, b) cm^{-1};

LRFAB, 414

HREIMS: Calc. for $C_{24}H_{31}O_3NS$ = = . Found = ;

TLC: R_f = 0.3, CH_2Cl_2, blue to vanillin

3-[(*R*)-1-hydroxy-1-phenylmethyl]-1,7,7-trimethylbicyclo[2.2.1]heptan-2-ol (45) and 3-[(*R*)-1-hydroxy-1-phenylmethyl]-1,7,7-trimethylbicyclo[2.2.1]heptan-2-ol (46):

To a solution of camphor 7 (0.250g, 1.6 mmol, 1.0 eq.) in dry THF was added lithium hexamethyldsilylazide (1.0 M/THF, 1.8 mL, 1.8 mmol, 1.1 eq.) dropwise over 1 minute under Ar at 0 °C and stirred for a further 1.5 h. The enolate was then lowered to -78 °C whereupon a solution of freshly distilled benzaldehyde (0.174g, 167μL, 1.6 mmol, 1.0 eq.) was added *via* syringe. It was then stirred for a 24 h period before it was permitted to warm to 0 °C whereupon it was added to a previously cooled suspension of LAH (0.124g, 3.3 mmol, 2.0 eq.) in dry THF (30. mL) under Ar. The reduction was then allowed to stir for 6 h before excess LAH was quenched by the slow, dropwise addition of H_2O at 0 °C, followed by extraction of the organics with CH_2Cl_2 (3 x 15 mL). The combined organic layers were then dried over Na_2SO_4, filtered

and concentrated *in vacuo* to give a viscous oil. It was then purified on SiO_2 first with 1% AcOEt/hexane (500 mL), followed by 3% AcOEt/hexane (500 mL) and lastly 10% AcOEt/hexane, to afford first 0.220g (52%) of the major diastereomer **45** as a clear colorless oil, $[\alpha]_D^{20} = 47.6$, $c = 1.12$, $CHCl_3$);

^1H NMR ($CDCl_3$, 300 MHz): δ (ppm) 0.75 (s, 3H), 0.85 (ddd, 1H, J = 8.5, 8.5, 2.3), 0.98 (s, 3H), 1.09 (m, 1H), 1.2 (d, 1H, J = 3.9), 1.32 (s, 3H), 1.4-1.65 (m, 2H), 2.11 (dd, 1H, J = 11.15, 7.9), 2.9 (s,b, 2H), 3.95 (d, 1H, J = 7.9), 5.08 (d, 1H, J = 11.2), 7.2-7.4 (m, 5H);

^{13}C NMR ($CDCl_3$, 75 MHz): δ (ppm) ; 144.0, 128.8, 128.0, 127.6, 82.4, 75.7, 58.5, 50.2, 47.8, 47.3, 33.8, 30.2, 22.4, 22.3, 11.9;

IR: 699 (s), 1044 (m), 1100 (m), 1453 (w), 2951 (s, b), 3386 (s.b) cm^{-1};

LREIMS, *m/z* (% rel.): 242 (8.4), 224 (3.0), 209 (2.6), 181 (2.1), 152 (6.0), 136 (100.0), 130 (21.3), 121 (24.7), 108 (24.8), 95 (51.6), 77 (12.5), 55 (10.3), 41 (14.7);

HREIMS: Calc. for $C_{17}H_{22}O$ (M^+-H_2O) = 242.1671. Found = 242.1671;

TLC: R_f=0.4, 20% AcOEt/Hexane, blue to vanillan; UV = 254

Subsequent fractions gave 0.128g (30%) of the minor diastereomer **46** as a clear colorless oil also.$[\alpha]_D^{20} = 70.2$, $c = 0.188$, $CHCl_3$);

^1H NMR ($CDCl_3$, 300 MHz): δ (ppm) 0.8 (s, 3H), 0.92 (s, 3H), 1.0-1.1 (m, 4H), 1.15-1.3 (m, 2H), 1.55-1.68 (m, 2H), 2.0 (ddd, 1H, J = 13.4, 9.3, 5.0), 3.7-3.9 (s, b, 2H), 4.2 (d, 1H, J = 3.8), 4.65 (d, 1H, J = 11.1), 7.2-7.5 (m, 5H);

^{13}C NMR ($CDCl_3$, 75 MHz): δ (ppm) 144.6, 128.8, 127.9, 127.3, 81.6, 78.6, 61.6, 50.6, 47.9, 47.6, 30.9, 26.3, 21.9, 20.9, 13.6;

IR 700 (m), 1056 (m, b), 1453 (w), 2949 (s, b). 3377 (s, b) cm^{-1};

LREIMS, *m/z* (% rel.): 242 (2.4), 160 (3.4), 136 (36.6), 121 (11.8), 108 (13.5), 95 (23.2), 84 (100.0), 69 (6.1), 55 (12.9), 47 (24.8);

HREIMS: Calc. for $C_{17}H_{22}O$ (M^+-H_2O) = 242.1671. Found = 242.1689;

TLC: R_f = 0.2, 20% AcOEt/Hexane, blue to vanillin; UV = 254

Oxetane (47)

The major diol **45** was permitted to stand in CH_2Cl_2 for 7 days. It was then purified on SiO_2 with CH_2Cl_2 to give **47** as a clear, colorless oil:

^1H NMR ($CDCl_3$, 300 MHz): δ (ppm) 0.89 (s, 3H), 0.9 (m, 1H), 0.95 (s, 3H), 1.12 (m, 1H), 1.45 (s, 3H), 1.5-1.6 (m, 2H), 1.7 (m, 1H), 2.05 (dd, 1H, J = 11.1, 7.4), 3.8 (d, 1H, J = 7.3), 4.8 (d, 1H, J = 11.1), 7.25-7.45 (m, 5H);

^{13}C NMR ($CDCl_3$, 75 MHz): δ (ppm) 142,5, 128.7, 127.8, 127.4, 79.8, 73.0, 57.1, 46.7, 33.9, 30.1, 26.9, 24.3, 23.2, 22.4, 11.9;

LREIMS, *m/z* (% rel.): 242 (M+, 3.3), 225 (2.6), 136 (100.0), 121 (21.6), 108 (20.2), 95 (25.6), 77 (4.7), 55 (4.8), 43 (9.4);

HREIMS: Calc. for $C_{17}H_{22}O$ = 242.1671. Found = 242.2661;

TLC: R_f = 0.9, CH_2Cl_2, blue to vanillin

(+/-)-1-(4-nitrophenyl)-1-propanol (54)

To a cooled (0 ^oC) solution of Et_2Zn (1.0 M/hexane,1.0 mL, 1.1 mmol, 3.5 eq.) along with $BCl_3{\cdot}Me_2S$ (2.0 M/ CH_2Cl_2, 17 μL, 0.03 mmol, 0.1 eq) in dry CH_2Cl_2 under Ar was added a P-nitrobenzaldehyde **51** (0.05g, 0.33 mmol, 1.0 eq.) in dry CH_2Cl_2 (1.0 mL) *via* canula under a stream of Ar. After 1 h, the excess Et_2Zn was quenched by the slow addition of H_2O at 0^oC, and the organics then extracted with CH_3Cl_2 (3 x 10 mL). The combined organic layers were then dried over Na_2SO_4, filtered and concentrated to an oil which was purified on SiO_2 with CH_2Cl_2, to give 0.055g (90%) of **54** as a yellow oil.

^1H NMR ($CDCl_3$, 300 MHz): δ (ppm) 0.95 (dd, 3H, J = 7.5, 7.5), 1.8 (m, 2H), 1.9-2.1 (s, b, 1H). 4.75 (dd, 1H, J = 6.4, 6.4), 7.55 (d, 2H, J = 8.6), 8.22 (d, 2H, J = 8.5);

^{13}C NMR ($CDCl_3$, 75 MHz): δ (ppm) 152.3, 147.7, 127.1, 124.0, 75.2, 32.5, 10.2;

IR 852 (m), 1346 (s), 1518 (s), 2968 (m, b), 3387 (m, b) cm^{-1};

LREIMS, *m/z* (% rel.): 181 (1.4), 163 (1.7), 152 (100.0), 136 (2.5), 115 (2.5), 106 (10.4), 94 (4.8), 77 (7.2), 65 (2.2), 51 (5.0), 43 (2.1);

HREIMS: Calc. for $C_9H_{11}O_3N$ = 181.0739. Found = 181.0740;

TLC: R_f=0.3, CH_2Cl_2, Orange to 2,4-dinitrophenylhydrazine, UV = 254

HPLC: Separated on a β-dex chiral column at a flow rate of 0.5 mL/min, 65% MeOH:35% buffer, with a pressure of approx. 1350 psi. The individual enantiomers elute at approx. 19.5 and 21.5 minutes.

(+/-)-1-(1,3-benzodioxol-5-yl)-1-propanol (55)

The production of the piperonal derived aldol racemate was produced in the exact same manner as for the P-nitro aldol product. The crude product was purified on SiO_2 to give 0.053g (88%) of 55 as a clear colorless oil.

^1H NMR ($CDCl_3$, 300 MHz): δ (ppm) 0.9 (dd, 3H, *J* = 7.2, 7.2), 1.6-1.95 (m, 3H), 4.5 (d,d, 1H, *J* = 6.7, 6.7), 5.95 (s, 2H), 7.8 (s, 2H), 7.9 (s, 1H);

^{13}C NMR ($CDCl_3$, 75 MHz): δ (ppm) 148.1, 147.3, 139.1, 119.8, 108.4, 106.8, 101.4, 76.3, 32.2, 10.6;

IR: 811 (m), 930 (m), 1040 (s), 1248 (s), 1441 (m), 1503 (m), 2932 (m, b), 3377 (m, b) cm^{-1};

LREIMS, *m/z* (% rel.): 180 (M+, 20.9), 162 (100.0), 151 (58.7), 131 (19.0), 121 (3.8), 103 (19.4), 93 (30.9), 81 (5.4), 77 (15.2), 65 (19.5), 57 (2.6), 51 (12.6), 44 (2.0);

HREIMS: Calc. for $C_{10}H_{12}O_3$ = 180.0786. Found = 180.0782;

TLC: R_f = 0.3, CH_2Cl_2, red to 2,4-dinitrophenylhydrazine, UV = 254

(+/-)-1-phenyl-1-propanol (56):

The aldol was performed in the exact same manner as mentioned above, with the exception that benzaldehyde was added neat *via* syringe immediately after being freshly distilled under Ar. All spectra were in accord with literature reports. (Separated on Chiral GC)

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methylene dioxy (racemate)

==========

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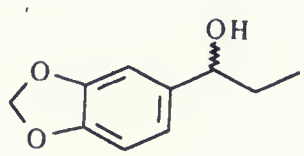
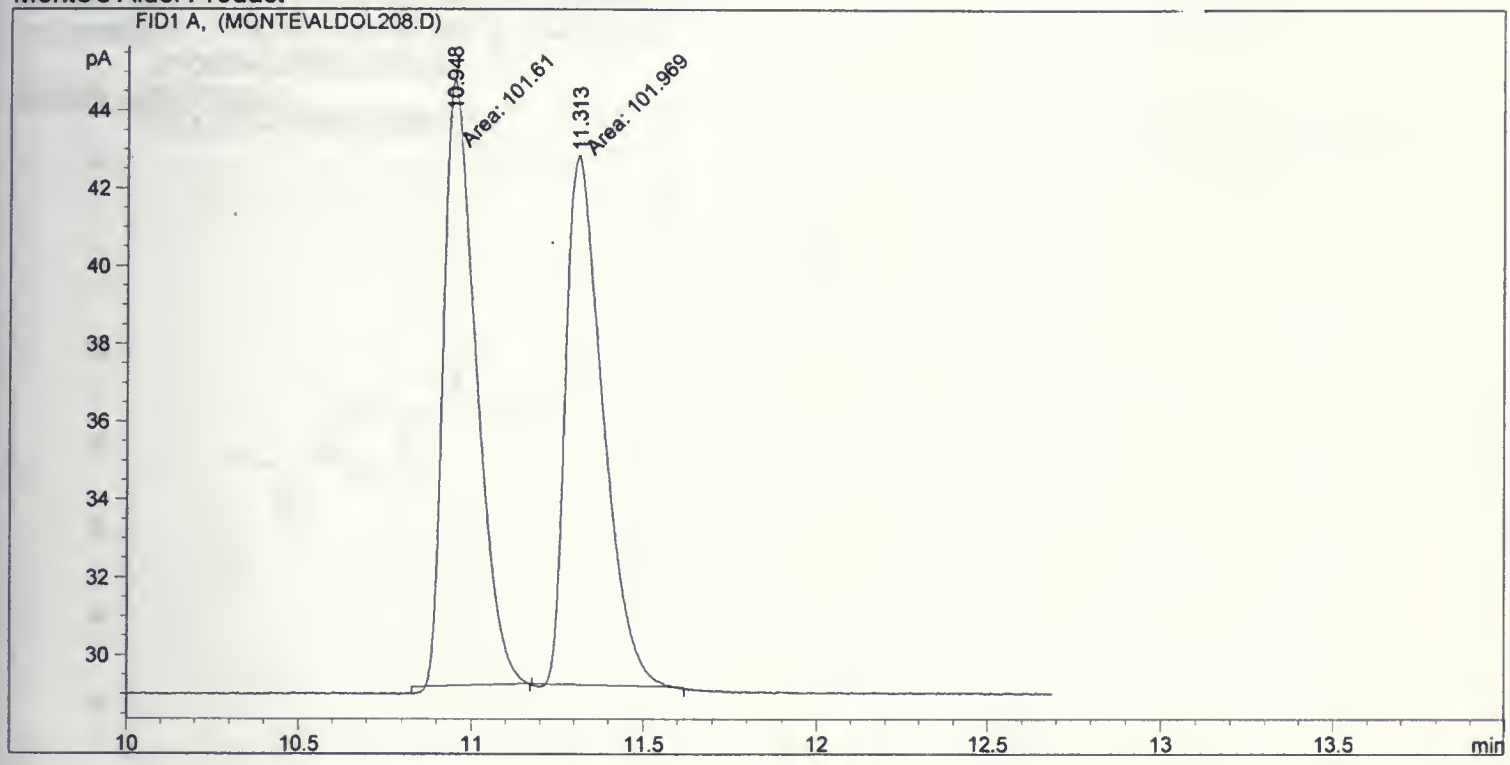


Monte's Aldol Product



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Area Percent Report

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Multiplier : 1.0000
Dilution : 1.0000

Signal 1: FID1 A,

Peak #	RetTime [min]	Type	Width [min]	Area [pA*s]	Height [pA]	Area %
1	0.920	BB S	8.41e-3	2706.46753	5341.19141	92.81058
2	3.525	BB	0.0260	5.97569	3.56937	0.20492
3	5.750	MM	0.0000	9.77116e-2	1.77697e-2	0.00335
4	10.948	MM	0.1089	101.60961	15.55770	3.48441
5	11.313	MM	0.1250	101.96907	13.59146	3.49674

Totals : 2916.11962 5373.92772

nitro (racemic)

==========

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Inj Volume : Manually
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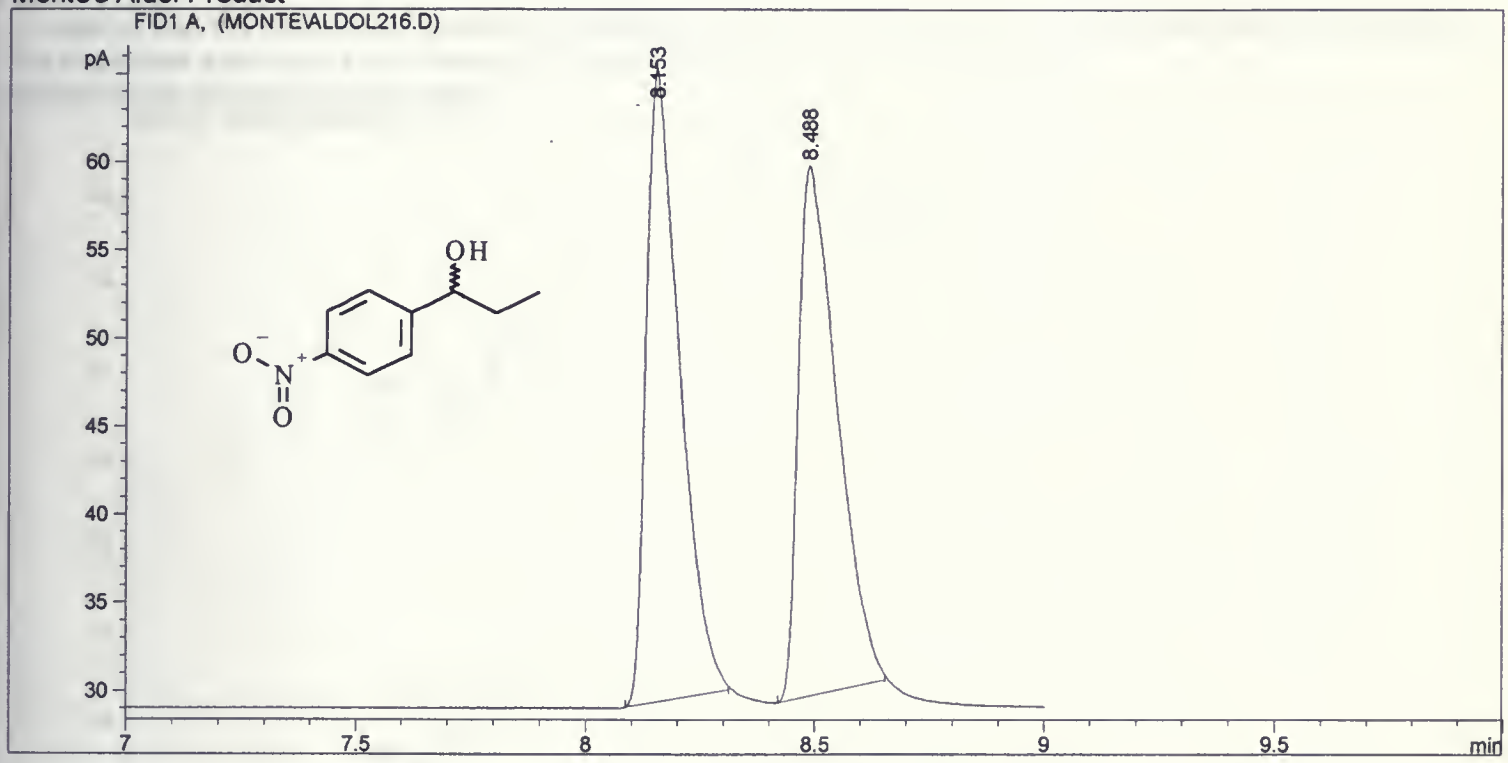
Monte's Aldol Product



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Area Percent Report

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Dilution : 1.0000

Signal 1: FID1 A,

Peak #	RetTime [min]	Type	Width [min]	Area [pA*s]	Height [pA]	Area %
1	0.887	PB S	9.18e-3	1.96815e4	3.09214e4	98.20115
2	1.028	PB	8.00e-3	9.50432e-1	1.77448	0.00474
3	5.785	MM	0.0000	6.06175e-2	6.31092e-2	0.00030
4	8.153	PB	0.0720	183.06752	35.91631	0.91342
5	8.488	PB	0.0799	176.44666	30.07493	0.88039

1-phenyl-1-propanol
Racemic on Chiraldex BPM (30 m)

==========

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Inj Volume : Manually
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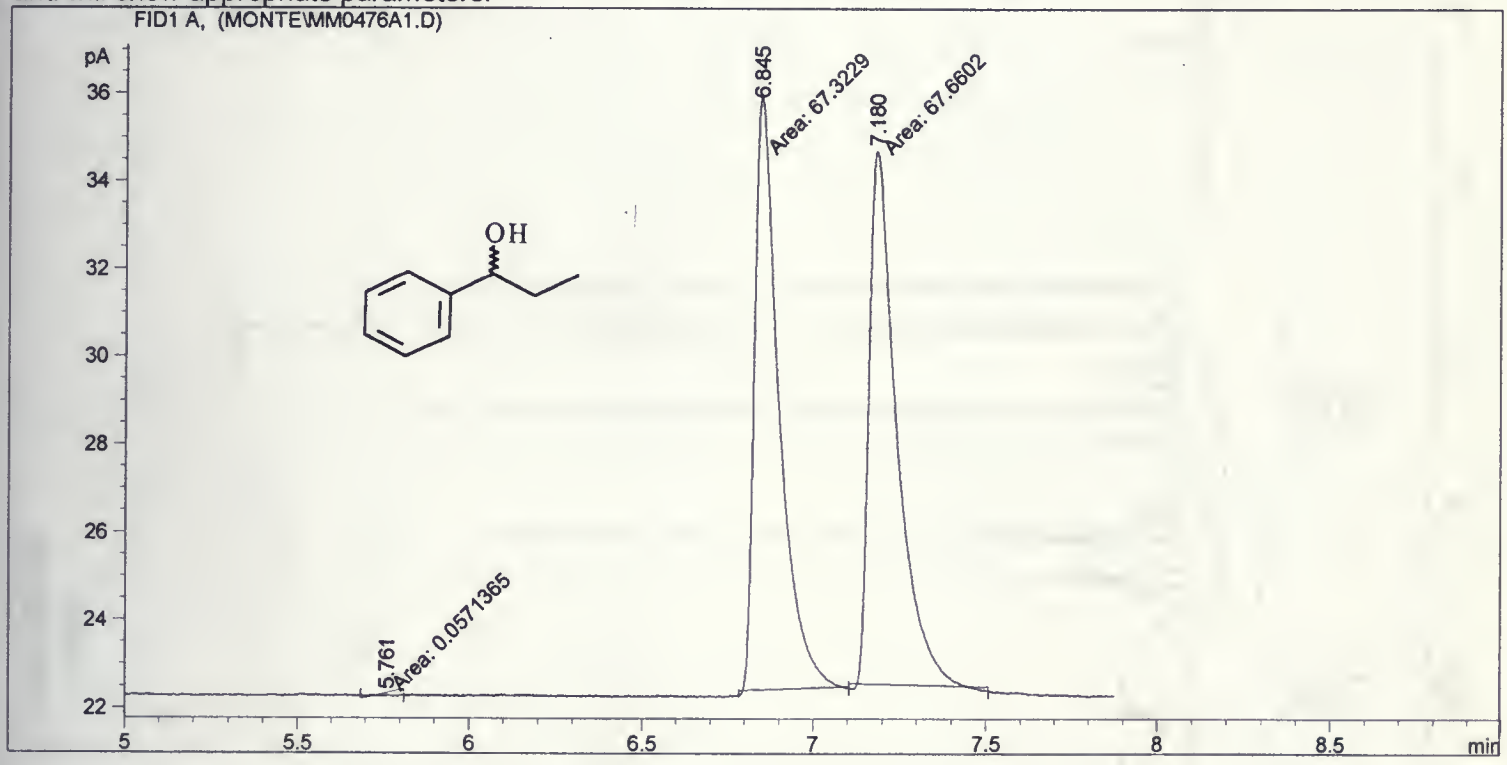
Last changed : 6/29/99 2:05:15 PM by Fred Capretta
(modified after loading)
Method to demo HP 6890 parameter editing for Split/Splitless & Purged Packed inlets plus FID and TCD. This method is the purpose of OFFLINE demos only!

In order to load this method use the macro "6890demo.mac" or copy the file 'IQ1.MTH' from this methods' subdirectory to the instrument subdirectory and rename it 'IQ1.cfg'. The method can then be loaded
and will show appropriate parameters.



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Area Percent Report

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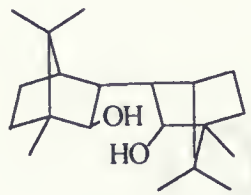
Sorted By : Signal
Multiplier : 1.0000
Dilution : 1.0000

Signal 1: FID1 A,

Peak #	RetTime [min]	Type	Width [min]	Area [pA*s]	Height [pA]	Area %
1	0.921	PV S	8.91e-3	1.77029e4	3.22204e4	47.33045
2	0.949	VB S	0.0148	1.94456e4	2.19598e4	51.98970

Brock DPX300
QSIM

19



19

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PROCNO	1

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NS	16
DS	2
SWH	6172.839 Hz
FIDRES	0.376760 Hz
AQ	1.3271540 sec
RG	1448.2
DW	81.000 usec
DE	4.50 usec
TE	300.0 K
D1	1.00000000 sec
P1	5.30 usec
SFO1	300.1318534 MHz
NUC1	1H
PL1	-4.00 dB

F2 - Processing parameters

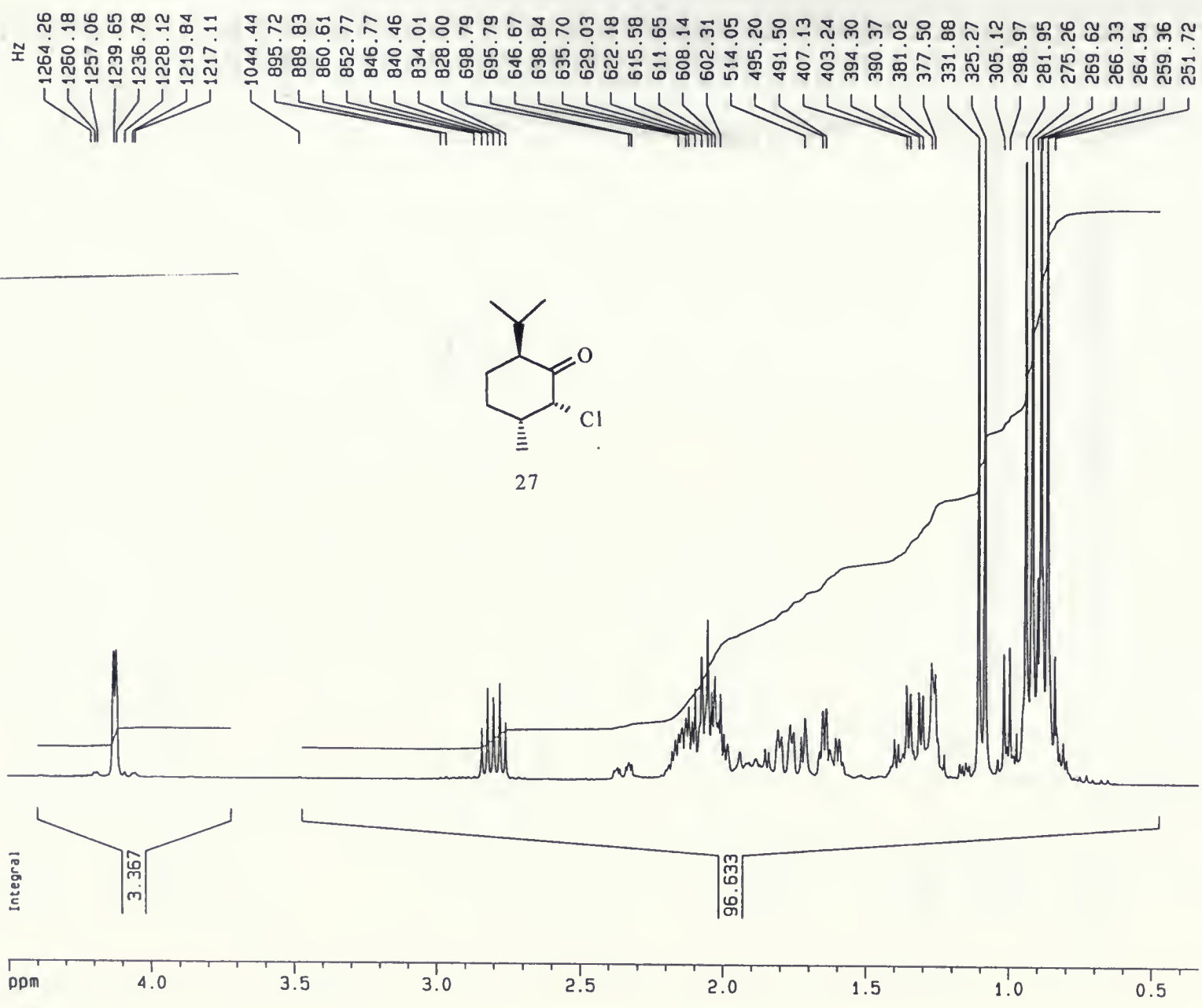
SI	8192
SF	300.1300000 MHz
WDW	EM
SSB	0
LB	0.30 Hz
GB	0
PC	1.00

1D NMR plot parameters

CX	20.00 cm
F1P	4.131 ppm
F1	1239.88 Hz
F2P	-0.414 ppm
F2	-124.25 Hz
PPMCM	0.22726 ppm/cm
HZCM	68.20646 Hz/cm

Brock DPX300
QSIM

27



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PROCNO	1

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SOLVENT	CDCl3
NS	16
DS	2
SWH	6172.839 Hz
FIDRES	0.376760 Hz
AQ	1.3271540 sec
RG	64
DW	81.000 usec
DE	4.50 usec
TE	300.0 K
D1	1.00000000 sec
P1	5.30 usec
SFO1	300.1318534 MHz
NUC1	1H
PL1	-4.00 dB

F2 - Processing parameters

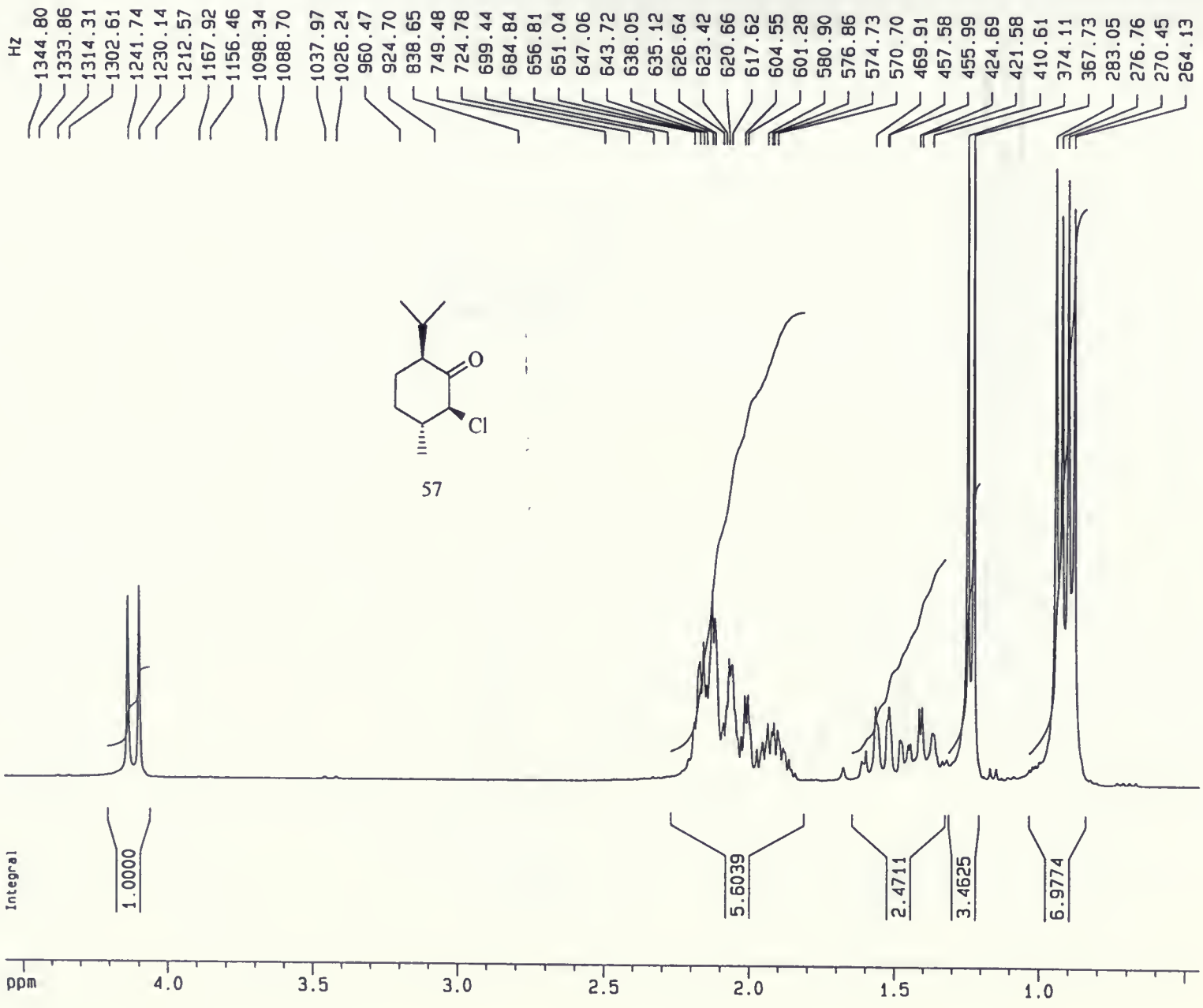
SI	8192
SF	300.1300000 MHz
WDW	EM
SSB	0
LB	0.30 Hz
GB	0
PC	1.00

1D NMR plot parameters

CX	20.00 cm
F1P	4.505 ppm
F1	1352.00 Hz
F2P	0.333 ppm
F2	99.99 Hz
PPMCM	0.20858 ppm/cm
HZCM	62.60044 Hz/cm

57

Brock DPX300
QSIM



57

Current Data Parameters

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NS	16
DS	2
SWH	6172.839 Hz
FIDRES	0.376760 Hz
AQ	1.3271540 sec
RG	80.6
DW	81.000 usec
DE	4.50 usec
TE	300.0 K
D1	1.00000000 sec
P1	5.30 usec
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NUC1	1H
PL1	-4.00 dB

F2 - Processing parameters

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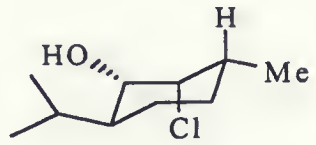
SSB	0
LB	0.30 Hz
GB	0
PC	1.00

1D NMR plot parameters

CX	20.00 cm
F1P	4.564 ppm
F1	1369.67 Hz
F2P	0.449 ppm
F2	134.88 Hz
PPMCM	0.20571 ppm/cm
HZCM	61.73964 Hz/cm

Brock DPX300
QSIM



31

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DS	2
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FIDRES	0.376760 Hz
AQ	1.3271540 sec
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DW	81.000 usec
DE	4.50 usec
TE	300.0 K
D1	1.00000000 sec
P1	5.30 usec
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NUC1	1H
PL1	-4.00 dB

F2 - Processing parameters

SI	8192
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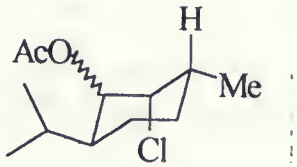
WDW	EM
SSB	0
LB	0.30 Hz
GB	0
PC	1.00

1D NMR plot parameters

CX	20.00 cm
F1P	7.929 ppm
F1	2379.85 Hz
F2P	-0.240 ppm
F2	-71.98 Hz
PPMCM	0.40846 ppm/cm
HZCM	122.59145 Hz/cm

29

Brock DPX300
QSIM



29

Current Data Parameters

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PROCNO	1

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PULPROG	zg30
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SOLVENT	CDCl3
NS	16
DS	2
SWH	6172.839 Hz
FIDRES	0.376760 Hz
AQ	1.3271540 sec
RG	362
DW	81.000 usec
DE	4.50 usec
TE	300.0 K
D1	1.00000000 sec
P1	5.30 usec
SFO1	300.1318534 MHz
NUC1	1H
PL1	-4.00 dB

F2 - Processing parameters

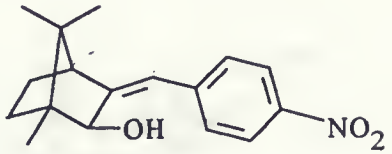
SI	8192
SF	300.1300000 MHz
WDW	EM
SSB	0
LB	0.30 Hz
GB	0
PC	1.00

1D NMR plot parameters

CX	20.00 cm
F1P	8.095 ppm
F1	2429.60 Hz
F2P	0.146 ppm
F2	43.93 Hz
PPMCM	0.39744 ppm/cm
HZCM	119.28342 Hz/cm

Brock DPX300
QSIM

38



38

Current Data Parameters

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PROCNO	1

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DS	2
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FIDRES	0.376760 Hz
AQ	1.3271540 sec
RG	203.2
DW	81.000 usec
DE	4.50 usec
TE	300.0 K
D1	1.00000000 sec
P1	5.30 usec
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NUC1	1H
PL1	-4.00 dB

F2 - Processing parameters

SI	8192
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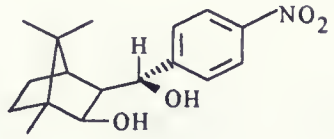
WDW	EM
SSB	0
LB	0.30 Hz
GB	0
PC	1.00

1D NMR plot parameters

CX	20.00 cm
F1P	8.844 ppm
F1	2654.33 Hz
F2P	0.361 ppm
F2	108.36 Hz
PPMCM	0.42414 ppm/cm
HZCM	127.29854 Hz/cm

Brock DPX300
QSIM



43

Current Data Parameters

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PROCNO	1

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SOLVENT	CDCl3
NS	16
DS	2
SWH	6172.839 Hz
FIDRES	0.376760 Hz
AQ	1.3271540 sec
RG	143.7
DW	81.000 usec
DE	4.50 usec
TE	300.0 K
D1	1.00000000 sec
P1	5.30 usec
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NUC1	1H
PL1	-4.00 dB

F2 - Processing parameters

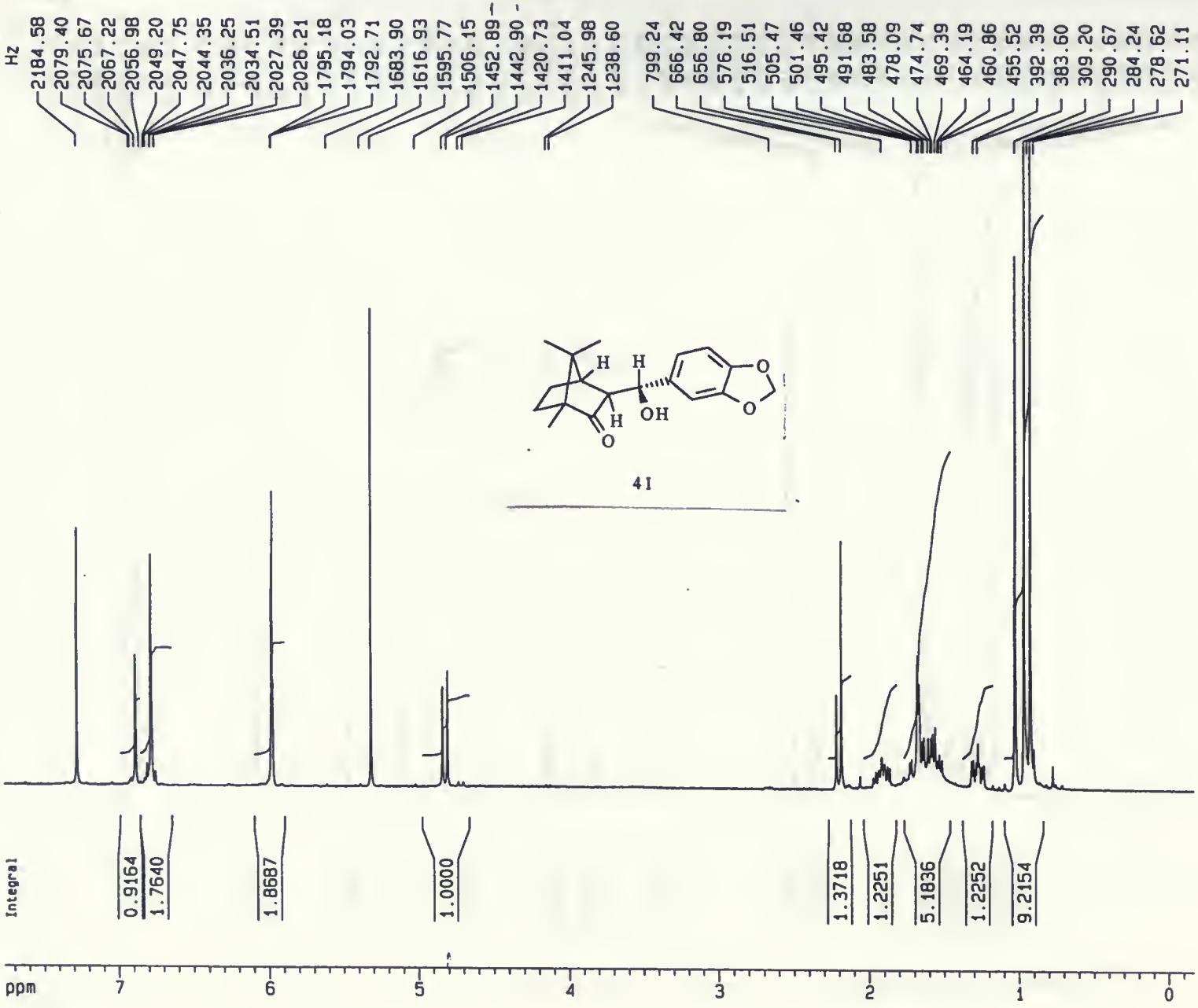
SI	8192
SF	300.1300000 MHz
WDW	EM
SSB	0
LB	0.30 Hz
GB	0
PC	1.00

1D NMR plot parameters

CX	20.00 cm
F1P	8.887 ppm
F1	2667.36 Hz
F2P	-0.312 ppm
F2	-93.49 Hz
PPMCM	0.45994 ppm/cm
HZCM	138.04240 Hz/cm

Brock DPX300
QSIM

41



Current Data Parameters

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PROCNO	1

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DS	2
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RG	1024
DW	81.000 usec
DE	4.50 usec
TE	300.0 K
D1	1.00000000 sec

---------- CHANNEL f1 ---------

NUC1	1H
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PL1	-4.00 dB
SFO1	300.1318534 MHz

F2 - Processing parameters

SI	8192
SF	300.1300000 MHz
WDW	EM
SSB	0
LB	0.30 Hz
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PC	1.00

1D NMR plot parameters

CX	20.00 cm
F1P	7.769 ppm
F1	2331.80 Hz
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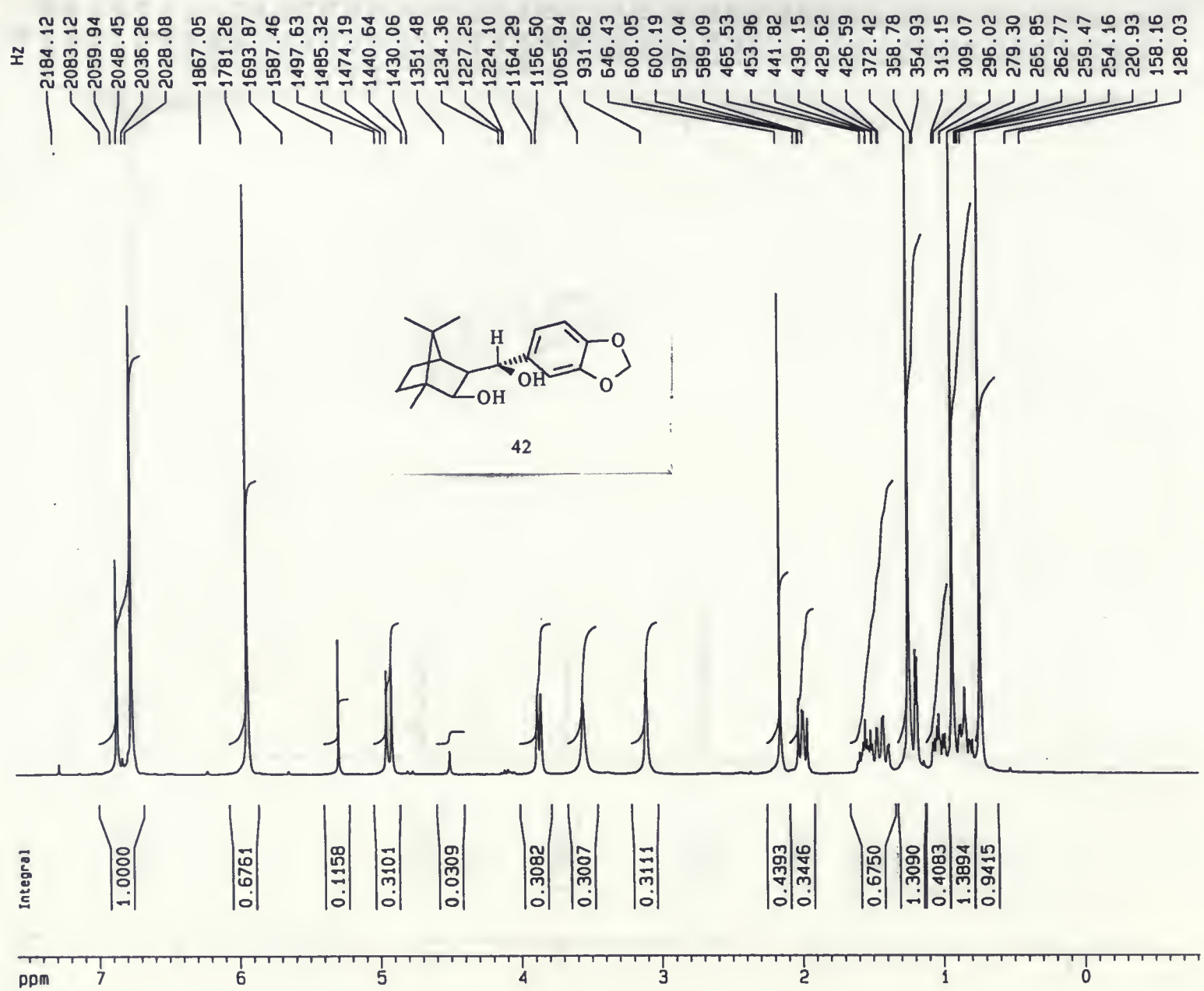
Brock DPX300
QSIM

42



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PULPROG	zg30
TD	16384
SOLVENT	CDCl3
NS	16
DS	2
SWH	6172.839 Hz
FIDRES	0.376760 Hz
AQ	1.3271540 sec
RG	45.3
DW	81.000 usec
DE	4.50 usec
TE	300.0 K
D1	1.00000000 sec
P1	5.30 usec
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NUC1	1H
PL1	-4.00 dB

F2 - Processing parameters

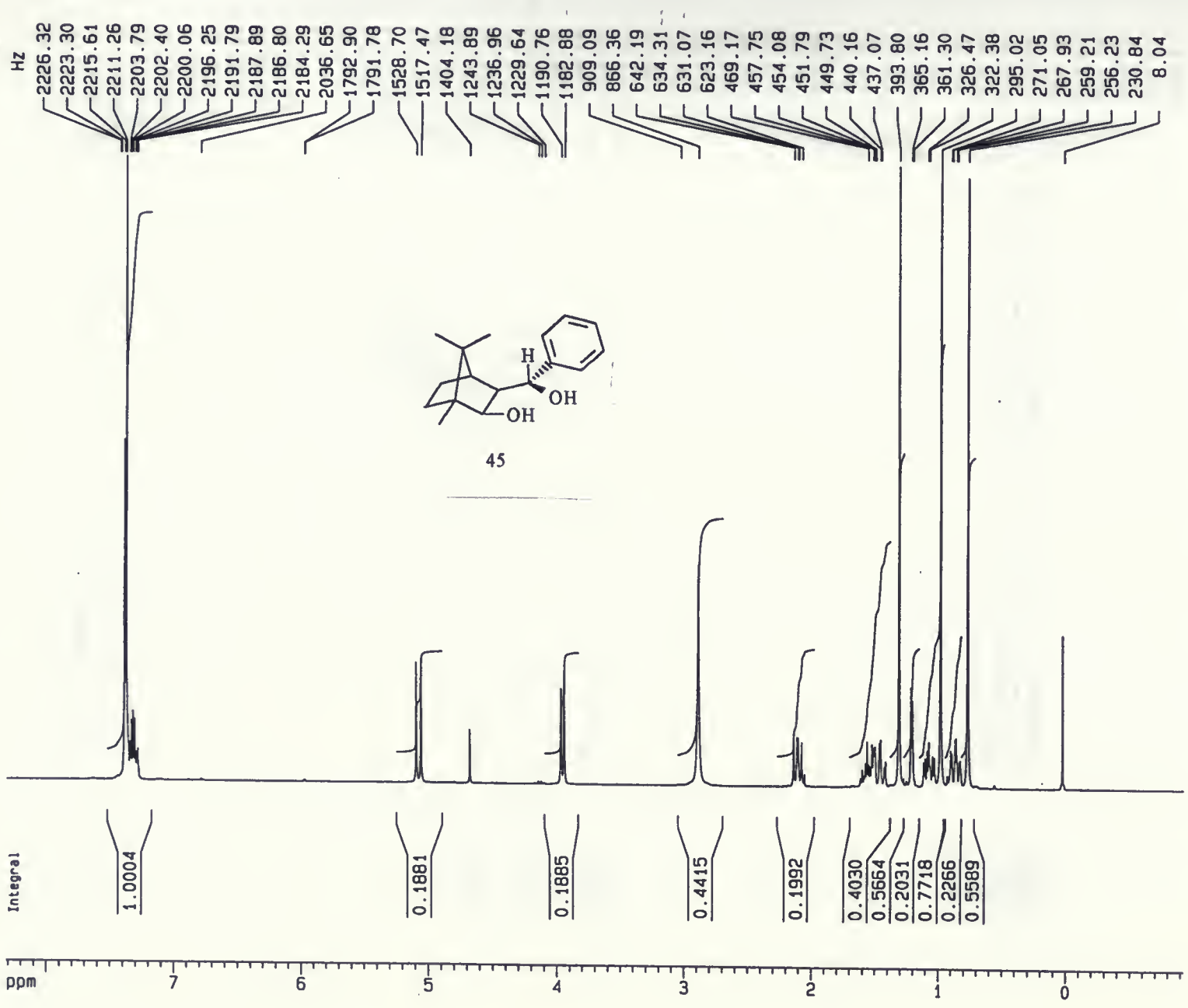
SI	8192
SF	300.1300000 MHz
WDW	EM
SSB	0
LB	0.30 Hz
GB	0
PC	1.00

1D NMR plot parameters

CX	20.00 cm
F1P	7.582 ppm
F1	2275.56 Hz
F2P	-0.811 ppm
F2	-243.40 Hz
PPMCM	0.41965 ppm/cm
HZCM	125.94807 Hz/cm

Brock DPX300
QSIM

45



Current Data Parameters

NAME	mm0481mj
EXPNO	2
PROCNO	1

F2 - Acquisition Parameters

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Time	21.38
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PROBHD	5 mm QNP 1H
PULPROG	zg30
TD	16384
SOLVENT	CDCl3
NS	16
DS	2
SWH	6172.839 Hz
FIDRES	0.376760 Hz
AQ	1.3271540 sec
RG	101.6
DW	81.000 usec
DE	4.50 usec
TE	300.0 K
D1	1.00000000 sec

---------- CHANNEL f1 ---------

NUC1	1H
P1	5.30 usec
PL1	-4.00 dB
SFO1	300.1318534 MHz

F2 - Processing parameters

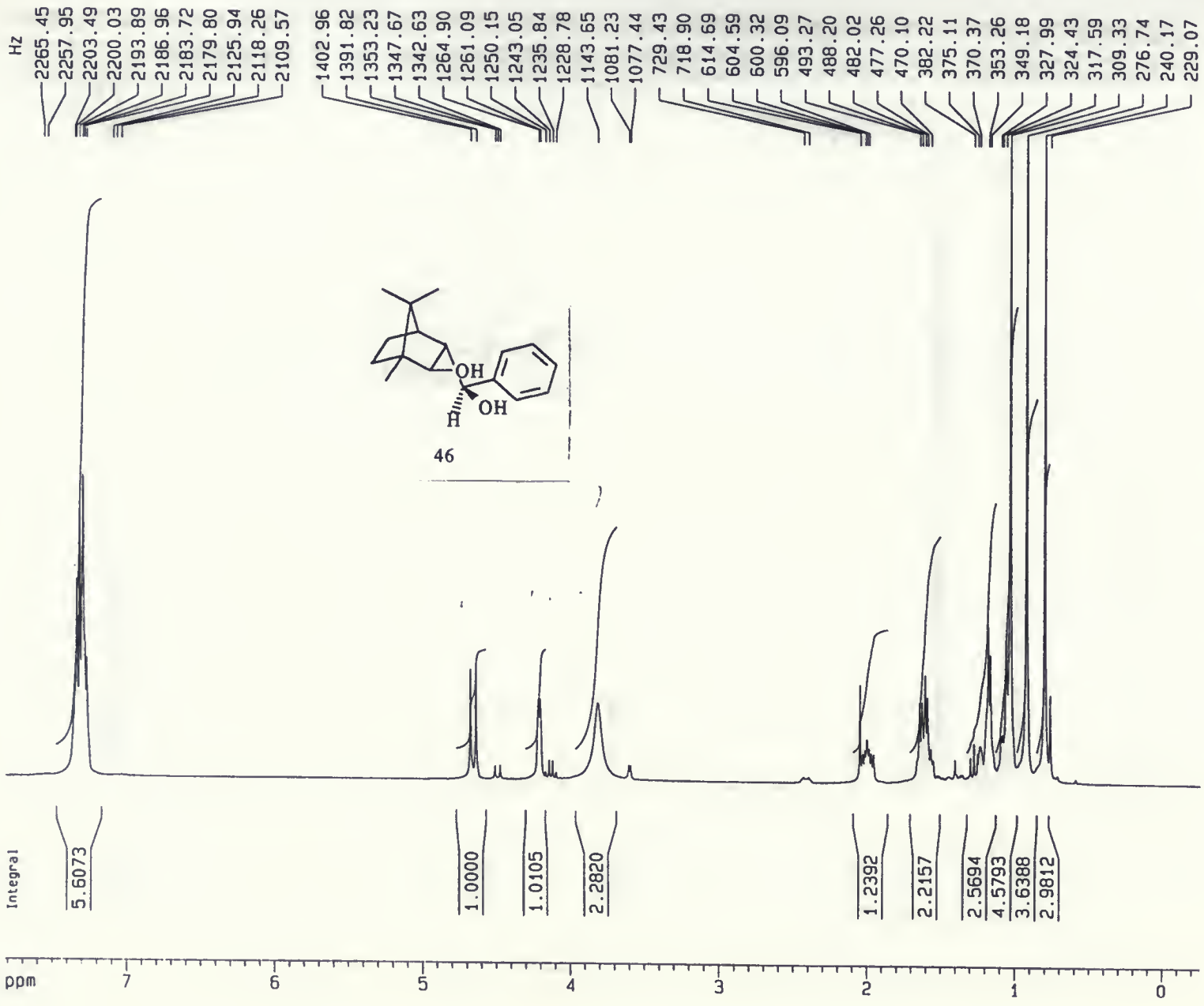
SI	8192
SF	300.1300000 MHz
WDW	EM
SSB	0
LB	0.30 Hz
GB	0
PC	1.00

1D NMR plot parameters

CX	20.00 cm
F1P	8.312 ppm
F1	2494.81 Hz
F2P	-0.920 ppm
F2	-276.24 Hz
PPMCM	0.46164 ppm/cm
HZCM	138.55225 Hz/cm

Brock DPX300
QSIM

46



Current Data Parameters

NAME	mm0481b
EXPNO	1
PROCNO	1

F2 - Acquisition Parameters

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PULPROG	zg30
TD	16384
SOLVENT	CDCl3
NS	16
DS	2
SWH	6172.839 Hz
FIDRES	0.376760 Hz
AQ	1.3271540 sec
RG	35.9
DW	81.000 usec
DE	4.50 usec
TE	300.0 K
D1	1.00000000 sec

========== CHANNEL f1 ========

NUC1	1H
P1	5.30 usec
PL1	-4.00 dB
SFO1	300.1318534 MHz

F2 - Processing parameters

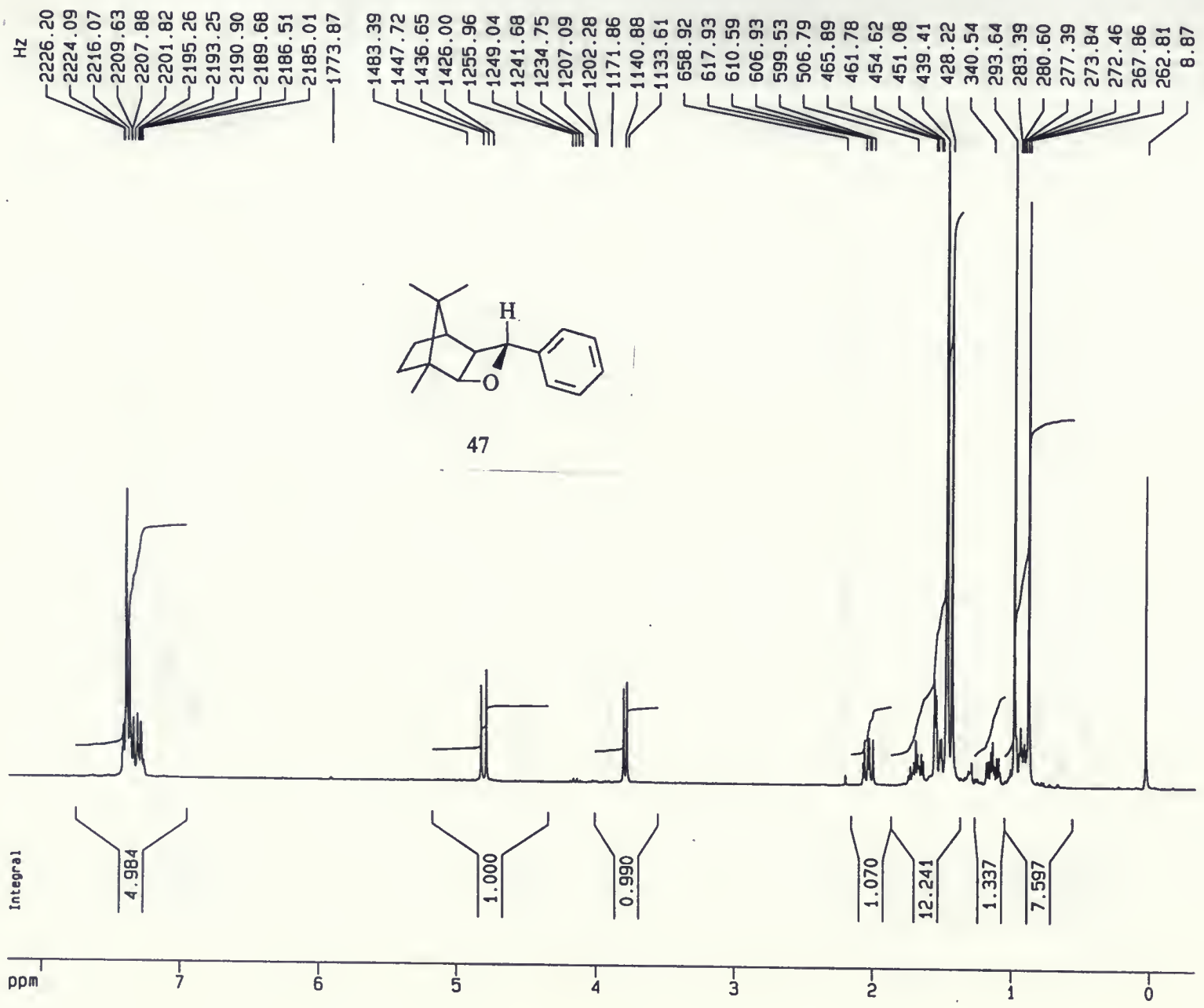
SI	8192
SF	300.1300000 MHz
WDW	EM
SSB	0
LB	0.30 Hz
GB	0
PC	1.00

1D NMR plot parameters

CX	20.00 cm
F1P	7.817 ppm
F1	2345.98 Hz
F2P	-0.259 ppm
F2	-77.80 Hz
PPMCM	0.40379 ppm/cm
HZCM	121.18893 Hz/cm

Brock DPX300
QSIM

47



Current Data Parameters

NAME	oxatane
EXPNO	1
PROCNO	1

F2 - Acquisition Parameters

Date_	990718
Time	21.17
INSTRUM	dpx300
PROBHD	5 mm QNP 1H
PULPROG	zg30
TD	16384
SOLVENT	CDCl3
NS	16
DS	2
SWH	6172.839 Hz
FIDRES	0.376760 Hz
AQ	1.3271540 sec
RG	143.7
DW	81.000 usec
DE	4.50 usec
TE	300.0 K
D1	1.00000000 sec

---------- CHANNEL f1 ---------

NUC1	1H
P1	5.30 usec
PL1	-4.00 dB
SFO1	300.1318534 MHz

F2 - Processing parameters

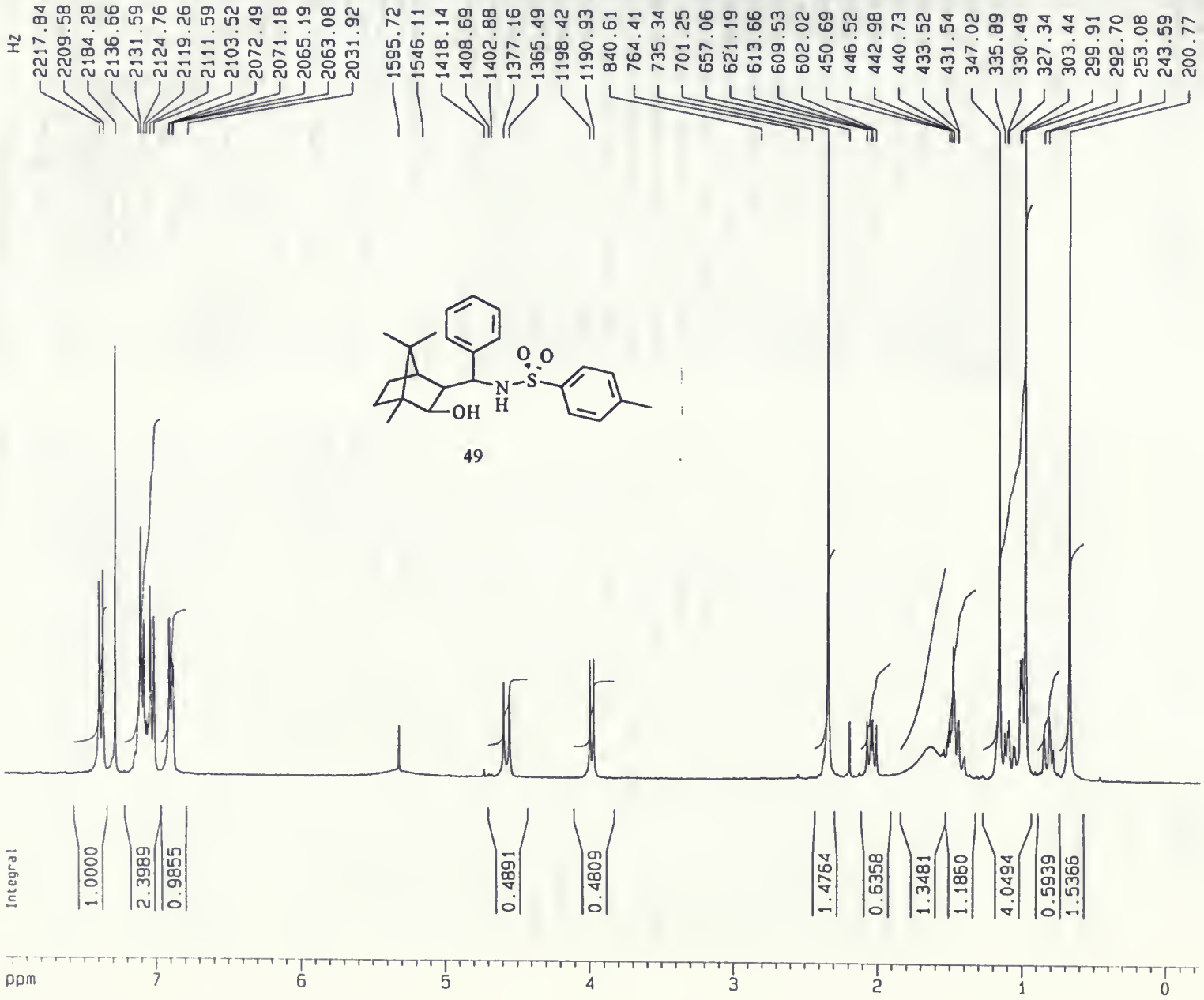
SI	8192
SF	300.1300000 MHz
WDW	EM
SSB	0
LB	0.30 Hz
GB	0
PC	1.00

1D NMR plot parameters

CX	20.00 cm
F1P	8.242 ppm
F1	2473.54 Hz
F2P	-0.330 ppm
F2	-99.06 Hz
PPMCM	0.42858 ppm/cm
HZCM	128.63034 Hz/cm

Brock DPX300
QSIM

49



Current Data Parameters

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PROCNO	1

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PULPROG	zg30
TD	16384
SOLVENT	CDCl3
NS	16
DS	2
SWH	6172.839 Hz
FIDRES	0.376760 Hz
AQ	1.3271540 sec
RG	724.1
DW	81.000 usec
DE	4.50 usec
TE	300.0 K
D1	1.00000000 sec

========== CHANNEL f1 ========

NUC1	1H
P1	5.30 usec
PL1	-4.00 dB
SFO1	300.1318534 MHz

F2 - Processing parameters

SI	8192
SF	300.1300000 MHz
WDW	EM
SSB	0
LB	0.30 Hz
GB	0
PC	1.00

1D NMR plot parameters

CX	20.00 cm
F1P	8.053 ppm
F1	2416.85 Hz
F2P	-0.236 ppm
F2	-70.71 Hz
PPMCM	0.41441 ppm/cm
HZCM	124.37811 Hz/cm

Stereoselective Oxidative Dimerization of (1*R*)-Camphor. A Short Synthesis of *exo,exo*′-3,3′-Biisoborneol

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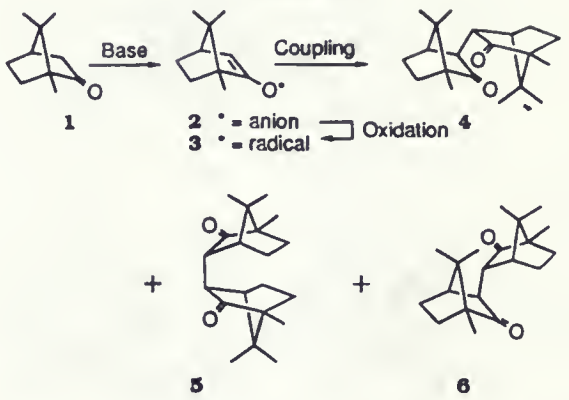
Received March 4, 1999

Introduction

The oxidative dimerization of enolates and their derivatives has been exploited for preparing 1,4-diketones and succinic acid derivatives.[1−4] The reaction has aroused considerable mechanistic interest in view of the nature of the electron-transfer effected by different oxidants, such as Cu(II) salts or elemental iodine, and of its application for synthesizing useful intermediates.[5]

Recently, efforts have focused on improving the diastereoselectivity of the carbon−carbon bond forming step.[5,6] Reports[7] that acyclic enolates bearing chiral auxiliaries dimerize with high stereoselectivity imply that chiral cyclic enolates would behave the same way. However, the oxidation of norbornanone and camphor enolates was stated[2] to give the exo,exo′, endo,endo′, and exo,endo′ 3,3′-dimers **4**, **5**, and **6** as a mixture. This last result is surprising since the bornane skeleton normally confers a high degree of asymmetric induction.[8] In the case of (1*R*)-camphor (**1**), the reaction of the enoxy radical **3** arising by oxidation of the enolate anion **2** should be subject to stereoelectronic or steric control. In other words, coupling of **3** with **2** or **3** is expected to give either *exo,exo*′ (**4**) or *endo,endo*′-3,3′-bicamphor (**5**) (Scheme 1). It therefore seems possible that **4**−**6** could have arisen by base-equilibration of the initial kinetic product or by indiscriminate coupling.[9] Consequently, by choosing the appropriate experimental conditions for kinetic control a single dimer should be obtainable.

Scheme 1



Results and Discussion

We now describe how (1*R*)-camphor (**1**) can be oxidatively dimerized to give exclusively the *exo,exo*′-bicamphor **4** and the C_2-symmetric 1,4-diol *exo,exo*′-3,3′-biisoborneol (**9**) by subsequent reduction in situ. In the original procedure,[2] a solution of **2**, prepared from **1** and LDA in THF at 0 °C, was allowed to react for 30 min with a solution of $CuCl_2$ in dimethyl formamide (DMF) at −78 °C. Repetition of this experiment merely confirmed the previous result; all three bicamphors were obtained. We concluded that the lack of selectivity might be due to the overly rapid formation of radical **3** from **2** and that a less polar solvent would retard electron transfer, thereby favoring kinetic control. However, it had already been noticed[2] that coupling was ineffective when THF or toluene was used as cosolvent for $CuCl_2$. Evidently, oxidation had failed owing to the insolubility of $CuCl_2$. Clearly, high solubility of the copper salt in the cosolvent, especially at −78 °C, is essential for success. Accordingly, $Cu(OTf)_2$ was dissolved in toluene at −78 °C together with a little pyridine to ensure solubility. To it was added a solution of the lithium salt of **2**, prepared in toluene at 0 °C. A dramatic change was observed. Coupling was slower, requiring 48 h to consume 60% of the camphor, and more importantly, it was completely stereoselective. A single bicamphor was formed that was subsequently identified as the exo,exo′ 3,3′-isomer **4**.[10] Attempts at isolating **4** revealed a hitherto-unnoticed event. Partial dehydrogenation occurred, presumably by aerial oxidation, giving (*E*)- and (*Z*)-2,2′-dioxo-3,3′-bibornanylidenes (**7** and **8**) as minor products (Scheme 2).[11]

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(1) Rathke, M.; Lindert, A. *J. Am. Chem. Soc.* **1971**, *93*, 4605.

(2) Ito, Y.; Konoike, T.; Harada, T.; Saegusa, J. *J. Am. Chem. Soc.* **1977**, *99*, 1487.

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(4) Babler, J. H.; Sarussi, S. J. *J. Org. Chem.* **1987**, *52*, 3462.

(5) (a) Belli Paolobelli, A.; Latini, D.; Ruzziconi, R. *Tetrahedron Lett.* **1993**, *34*, 721. (b) Fujii, T.; Hirao, T.; Ohshiro, Y. *Tetrahedron Lett.* **1992**, *33*, 5823. (c) Baciocchi, E.; Casu, A.; Ruzziconi, R. *Tetrahedron Lett.* **1989**, *30*, 3707. (d) Renaud, P.; Fox, M. A. *J. Org. Chem.* **1988**, *53*, 3745. (e) Belletire, J. L.; Spletzer, E. G.; Pinhas, A. R. *Tetrahedron Lett.* **1984**, *25*, 5969. (f) Brocksom, T. J.; Petragnani, N.; Rodrigues, R.; Teixera, H. L. *Synthesis* **1975**, 396.

(6) Schmittel, M.; Burghart, A.; Malisch, W.; Reising, J.; Söllner, R. *J. Org. Chem.* **1998**, *63*, 396 and references therein.

(7) (a) Alvarez-Ibarra, C.; Csáky, A. G.; Colmenero B.; Luz Quiroga, M. *J. Org. Chem.* **1997**, *62*, 2478. (b) Langer, T.; Illich, M.; Helmchen, G. *Tetrahedron Lett.* **1995**, *36*, 4409. (c) Porter, N. A.; Su, Q.; Harp, J. J.; Rosenstein, I. J.; McPhail, A. T. *Tetrahedron Lett.* **1993**, *34*, 4457.

(8) Oppolzer, W. *Tetrahedron* **1987**, *43*, 1969.

(9) The photolysis of *exo*- or *endo*-(1*R*)-3-bromocamphor proceeds through the enoxy radical **3** in its singlet excited state to give a mixture of **4**, **5**, and **6** in a ratio of 1:1:2. A solution of KOH in MeOH readily isomerizes **4** to **5** via **6** (Orita, K.; Yorita, K.; Miyazawa, M.; Suginome, H. *Synlett* **1994**, 937−938).

(10) The configuration of **4** follows from its reduction with LAH (see procedure A, Experimental Section).

(11) Bicamphor **4** on treatment with sodium hydride in DMF followed by addition of $K_3[Fe(CN)_6]$ was reported to give only the *E*-isomer **7** (ref 12). For the formation of **7** as a byproduct from bithiocamphor, see ref 13.

10.1021/jo990394g CCC: $18.00
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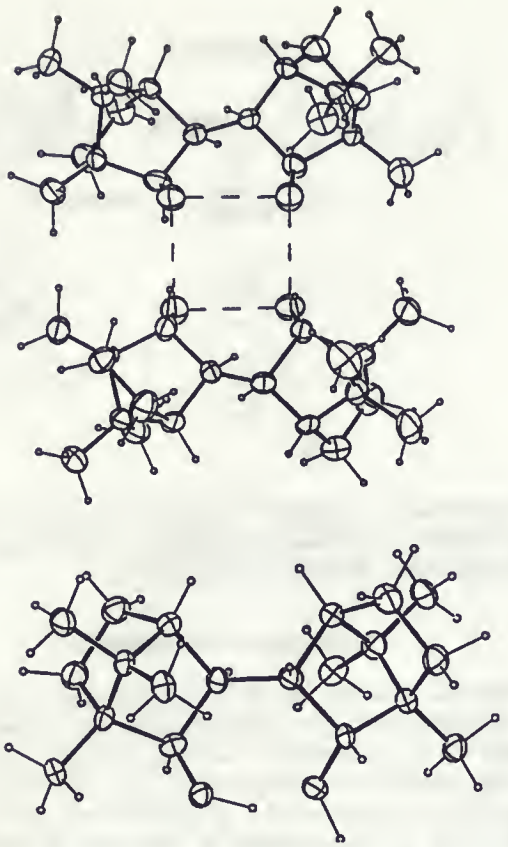
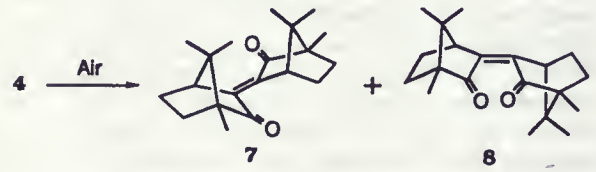
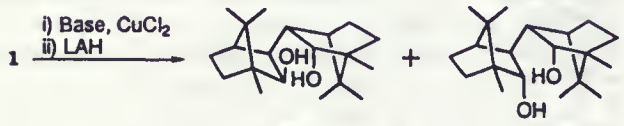


Figure 1. Perspective drawings of the X-ray structures of diols **9** (lower) and **10** (upper).

Scheme 2



Scheme 3



Considering the lability of **4** under the above-described conditions, it was decided to improve the foregoing procedure. The cheaper oxidant, anhydrous $CuCl_2$, was obtained as a homogeneous solution in pyridine by adjunction of tetramethylethylenediamine (TMEDA). Next, the lithium salt of **2** in toluene (Scheme 1) was added at −78 °C. After the coupling stage, the reaction mixture was poured directly into a suspension of lithium aluminum hydride (LAH) in THF. Obviously, **4** was formed as before and subsequently reduced. Instead of a single diol, a second was obtained as well, in yields of 50 and 10%, respectively (Scheme 3). Their structures were determined by X-ray as **9**, the expected *exo,exo'*-2,2'-diol of C_2 symmetry, and **10** the exo,endo' epimer (Figure 1).

The precise mechanism of coupling remains uncertain. A likely possibility is the combination of enoxy radical **3** either with another molecule of **3** or with camphor enolate **2**. In the latter instance, further oxidation of the resulting radical anion affords **4**.[14] In both cases, bond formation occurs on the exo faces of both molecules in a stereoelectronic fashion. As expected, the reduction of **4** by LAH follows a course similar to that of camphor.[15] Attack by hydride ion occurs mainly on the endo face of the carbonyl group owing to steric hindrance by the 7,7-dimethyl substituents and the exo-3 attachment. The yield of both diols in a pure state (60%) may be regarded as satisfactory since some product sublimes on workup. A little isoborneol is also formed from unreacted camphor but is easily removed on purifying the diols.

Conclusion

In conclusion, we have demonstrated that the kinetically controlled oxidation of camphor enolate is entirely feasible and that dimerization occurs stereoselectively on the exo face to give *exo,exo*-3,3'-bicamphor (**4**). The use of toluene as solvent and $Cu(OTf)_2$ in toluene/pyridine or $CuCl_2$ in pyridine/TMEDA as oxidant is of critical importance in ensuring kinetic control. These results have obvious implications for related intermolecular oxidative enolate dimerizations where stereocontrol has not been achieved so far. We also show that the procedure provides convenient access to the potentially valuable C_2-symmetric 1,4-diol **9** or BIBOL,[16] which has obvious features in common with BINOL[17] and TADDOL.[18] Extensions of the coupling methodology to other chiral ketones of natural origin, such as menthone, and the utilization of BIBOL as a chiral ligand are under investigation.[19]

Experimental Section

General Methods. Melting points are uncorrected. Flash chromatography (FC) was performed with 70−230 mesh silica gel. All solvents were distilled from glass prior to use. Toluene and tetrahydrofuran were distilled from sodium metal/benzophenone, while pyridine was distilled from calcium hydride, all under dry nitrogen. (1*R*)-Camphor was recrystallized from ethanol/water (2:1) and dried over P_2O_5 for not less than 24 h prior to use. Cupric chloride was dried in a oven at 150 °C for 15 min and stored (P_2O_5) until used. All glassware was flame-dried under a stream of Ar before use.

Infrared spectra were recorded as thin films on NaCl. ^1H NMR spectra were recorded at 300 MHz in $CDCl_3$, using tetramethylsilane as internal standard. Proton-decoupled ^{13}C spectra were recorded at 75 MHz with $CDCl_3$ (δ 77.7) as internal standard.

(12) Schroth, W.; Hintzsche, E.; Spitzner, R.; Strühl, D.; Schmeiss, K.; Sieler, J. *Tetrahedron* **1995**, *51*, 13261.

(13) Bonnat, M.; Durand, J. O.; Le Corre, M. *Tetrahedron: Asymmetry* **1996**, *7*, 559.

(14) It is possible that dimerization of enoxy radicals **3** is indiscriminate (ref 9). The slow release of **3** may favor its stereoelectronically controlled capture by camphor enolate **2** as the rate-determining step (cf. ref 7a).

(15) Dauben, W. G.; Fonken, G. J.; Noyce, D. S. *J. Am. Chem. Soc.* **1956**, *78*, 2579. Brown, H. C.; Deck, H. R. *J. Am. Chem. Soc.* **1965**, *87*, 5620.

(16) The procedure also provides a one-pot synthesis of **4**, which previously has only been accomplished by a circuitous route from camphor through the intermediacy of (1*R*,1*R'*)-*exo,exo'*-3,3'-bithiocamphor (refs 12 and 13).

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(19) Few methods are presently available for preparing C_2-symmetric 1,4-diols; however, see: P. A. Evans, V. S. Murthy, *J. Org. Chem.* **1998**, *63*, 6768.

(1*R*,1′*R*,2*R*,2′*R*,3*S*,3′*S*,4*R*,4′*R*)-3,3′-Bi(1,7,7-trimethylbicyclo-[2.2.1]heptan-2-ol) (BIBOL, 9) and (1*R*,1′*R*,2*R*,2′*S*,3*S*,3′*S*,4*R*,4′*R*)-3,3′-Bi(1,7,7-trimethylbicyclo[2.2.1]heptan-2-ol) (10). Procedure A. Lithium hexamethyldisilazane (1.0 M in THF, 0.68 mL, 0.68 mmol, 1.05 equiv) was added to a solution of (1*R*)-camphor (1, 0.1 g, 0.65 mmol) in toluene (2 mL) at 0 °C with stirring for 1.5 h. The resulting enolate solution was cooled to −78 °C and transferred to a solution of $Cu(OTf)_2$ (0.593 g, 1.65 mmol, 2.5 equiv) in toluene (4 mL) containing pyridine (0.64 mL), at −78 °C. After the cooled mixture was stirred for 48 h, lithium aluminum hydride (LAH, 0.50 g, 1.31 mmol, 2.0 equiv) was added with further stirring for 12 h at −78 °C. Excess LAH was quenched by slowly adding concentrated aqueous NH_4Cl at 0 °C. The resulting solution was extracted with Et_2O (4 × 15 mL). The combined organic layers were washed (saturated aqueous NaCl), dried (Na_2SO_4), filtered, and evaporated to give 110 mg of solid. Purification over SiO_2 (hexane−AcOEt 97.5:2.5) afforded 9 (33 mg, 33%), followed by 10 (17 mg, 17%). For spectral and other data, see below.

Procedure B. To a solution of 1 (0.1 g., 0.66 mmol) in dry toluene (1.0 mL) under Ar at 0 °C was added dropwise LDA (0.46 mL of 1.5 M in hexane) with stirring for 1 h. To the resulting solution, cooled to −78 °C, was added a solution of $CuCl_2$ (0.093 g, 0.69 mmol) in dry pyridine (5 mL) and TMEDA (1.0 mL) by cannula under Ar. After the mixture was stirred at −78 °C for 24 h, it was allowed to warm to room temperature. Next, the mixture was transferred by syringe to a previously cooled (−78 °C) suspension of LAH (0.049 g, 1.3 mmol) in dry THF (1.5 mL) and stirred at 0 °C for 24 h. Quenching excess LAH by slowly adding H_2O, dilution with CH_2Cl_2, treatment with aqueous 1 N HCl, drying (Na_2SO_4), filtration, and evaporation in vacuo gave a viscous yellow oil. Chromatographic purification (silica gel, hexane/AcOEt 97.5:2.5) furnished 9 (50.3 mg, 50%) as colorless crystals: mp = 176−178 °C; $[\alpha]^{22}_D$ = +71.1 (*c* = 0.18, MeOH); IR 2883 (m), 2946 (s), 3355 (s,b) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 0.8 (s, 3H, CH_3), 0.9 (s, 3H, CH_3), 0.95 (m, 2H, CH_2), 1.2 (s, 3H, CH_3), 1.5 (ddd, *J* = 10.4, 10.4, 2.4 Hz, 1H, CH_2), 1.65 (s, 1H, CH), 1.7 (m, 1H, CH_2), 2.1 (dd, *J* = 4.8, 2.2 Hz, 1H, CH), 2.45 (d, *J* = 2.98 Hz, 1H, OH), 3.75 (m, 1H, *CH*OH); ^{13}C NMR δ 83.3, 51.7, 50.1, 49.5, 47.4, 34.3, 30.2, 22.7, 22.2, 12.2; MS *m/z* (rel) 306 (1.6), 288 (22.7), 152 (41.9); HREIMS calcd for $C_{20}H_{34}O_2$ 306.2558, found 306.2574. Crystals of 9 suitable for X-ray were obtained by slow recrystallization from AcOEt (see below). Subsequent fractions gave the epimeric alcohol 10 (9.7 mg, 10%) as colorless crystals: mp = 161−163 °C; $[\alpha]^{22}_D$ = +99.2 (*c* = 0.14, $CHCl_3$); IR 2871 (m), 2948 (s), 3336 (s,b); ^1H NMR (300 MHz, $CDCl_3$) δ 0.8 (s, 3H, CH_3,), 0.85 (s, 3H, CH_3,), 0.9 (s, 3H, CH_3), 0.91 (m, 1H, CH), 0.95 (s, 3H, CH_3), 1.0 (s, 3H, CH_3), 1.05 (m, 1H, CH_3), 1.1 (s, 3H, CH_3), 1.2 (m, 2H), 1.5 (m, 2H), 1.6−1.8 (m, 4H), 1.8−2.0 (m, 2H), 3.1 (s, 2H, OH), 3.85 (m, 2H, CHOH); ^{13}C NMR: δ 83.7, 82.3, 55.5, 53.8, 50.0, 49.9, 49.4, 49.3, 47.7, 47.2, 33.7, 31.4, 30.4, 26.5, 22.8, 22.5, 21.9, 20.8, 13.7, 12.2; MS *m/z* (rel) 302 (13.4), 288 (22.0), 152 (36.2); HREIMS calcd for $C_{20}H_{34}O_2$ 306.2558, found 306. 2575; HREIMS calcd for $C_{20}H_{32}O$ ($M^+ - H_2O$) = 288.2453, found 288.2451. Crystals of 10 suitable for X-ray were obtained by slow recrystallization from $CHCl_3$ (see below).

Crystal Data for 9: $C_{20}H_{34}O_2$, *M* = 306.5; μ = 0.541 mm^{-1}, *F*(000) = 510, d_x = 1.13 g·cm^{-3}, trigonal, $P3_2$, *Z* = 3, *a* = 11.4149(3) Å, *c* = 11.9304(5) Å, *V* = 1346.26(8) Å^3, crystal from AcOEt solution, colorless prism 0.20 × 0.40 × 0.60 mm. Cell dimensions and intensities measured at 170 K. *R* = 0.049, R_w = 0.048 for 2129 contributing reflections ($|F_o| > 4\sigma(F_o)$). The rotation about the central C(1)−C(1′) bond is precluded by an intramolecular hydrogen bond (O(1)···O(1′) = 2.677(5) Å; O(1)−H(01)···O(1′) = 140(4)°). The molecular packing shows that molecules are associated by hydrogen bonds to form helical chains parallel to the (001) direction (O(1′)···O(1) 1 − *y*, *x* − 1, *z* + 1/3 = 2.812(6) Å; O(1′)−H(01′)···(O1) = 152(5)°).

Crystal Data for 10: $C_{20}H_{34}O_2$, *M* = 306.5; μ = 0.50 mm^{-1}, *F*(000) = 680, d_x = 1.12 g·cm^{-3}, monoclinic, $P2_1$, *Z* = 4, *a* = 10.7203(9) Å, *b* = 12.082(1) Å, *c* = 14.304(1) Å, β = 99.900(5)°, *V* = 1825.1(3) Å^3, crystal from $CHCl_3$ solution, colorless prism 0.25 × 0.28 × 0.32 mm. Cell dimensions and intensities measured at 200 K. *R* = 0.059, R_w = 0.058 for 3817 contributing reflections ($|F_o| > 4\sigma(F_o)$). Both molecules in the asymmetric unit are similar and are associated in pairs by hydrogen bonds through their hydroxyl groups. Intermolecular hydrogen bonds: O(1a)···O(1b) = 2.779(8) Å, O(2a)···O(2b) = 2.720(7) Å. Intramolecular hydrogen bonds: O(1a)···O(2a) = 2.758(6) Å, O(1b)···O(2b) = 2.739(6) Å.

(*E*)- and (*Z*)-2,2′-Dioxo-3,3′-bibornanylidenes (7 and 8). Diketone 4, produced by the above-described procedures with omission of the reduction step, was allowed to stand in the air for 24 h. The formation of a 3:1 mixture of 7 and 8 in a 16% yield was spontaneous. Chromatographic purification of the mixture (silica gel, hexane/AcOEt 95:5) afforded first the *E* isomer 7 as a yellow solid: mp = 98−100 °C; ^1H NMR (300 MHz, $CDCl_3$) δ 0.74 (s, 6H), 0.94 (s, 6H), 0.95 (s, 6H), 1.48−1.22 (m, 4H), 1.68 (ddd, *J* = 11.4, 11.4, 3.7 Hz, 2H), 2.15−2.05 (m, 2H), 3.74 (d, *J* = 4.3 Hz, 2H); ^{13}C NMR δ 212.4, 141.2, 58.5, 48.8, 46.5, 30.9, 26.3, 21.2, 18.7, 9.6. Further purification yielded 8 as a yellow solid, which underwent isomerization over several days to an approximately 3:1 mixture of 7 and 8 (as judged by NMR). *Z* Isomer 8: ^1H NMR δ 0.8 (s, 6H), 0.95 (s, 6H), 0.96 (s, 6H), 1.2−1.5 (m, 4H), 1.6−1.8 (m, 2H), 2.0−2.2 (m, 2H), 2.6 (d, *J* = 4.0 Hz, 2H); ^{13}C NMR δ 203.1, 144.3, 59.1, 51.6, 45.8, 30.2, 26.4, 21.1, 18.8, 9.9.

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Supporting Information Available: Tables of atomic coordinates, displacement parameters, bond lengths, bond angles, dihedral angles, and atomic numbering schemes for 9 and 10. Crystallographic data have been deposited with the Cambridge Crystallographic Data Centre, University Chemical Laboratory, 12 Union Road, Cambridge CB2 1EZ, England (Fax: +44-(1223)-336033. E-mail: deposit@ccdc.cam.ac.uk). This material is available free of charge via the Internet at http://pubs.acs.org.

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